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Iridium-Catalyzed Hydrocarbonation of Unsaturated Systems: Enantioselective Synthesis of Heteropolycyclic Scaffolds

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DOCTORAL THESIS

IRIDIUM-CATALYZED HYDROCARBONATION OF UNSATURATED SYSTEMS: ENANTIOSELECTIVE SYNTHESIS OF HETEROPOLYCYCLIC SCAFFOLDS

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SANTIAGO DE COMPOSTELA

Acknowledgments / Agradecimientos

Este manuscrito cierra un capítulo fundamental en mi vida, uno que me ha permitido crecer como científico y como persona. Dado que esta será la parte de mi tesis que más lectores tendrá, quiero aprovechar la oportunidad para expresar mi más sincero agradecimiento a todas aquellas personas que han contribuido a mi formación y me han acompañado en este camino.

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Abbreviations and acronyms

Ac	Acetyl (-COMe)
acac	Acetylacetone
AMLA	Ambiphilic Metal Ligand Activation
Ar	Aryl
BARF	tetrakis[3,5-bis(trifluoromethyl)phenyl] borate
σ-BM	σ-Bond Metathesis
Bn	Benzyl (-CH_2Ph)
br	Broad
BTFM	3,5-bis(trifluoromethyl) phenyl
Bu	Butyl
CA	Chiral Auxiliary
CCDC	Cambridge Crystallographic Data Centre
CMD	Concerted Metallation Deprotonation
COD	1,5-cyclooctadiene
COE	Cyclooctene
Cp	Cyclopentadienyl
Cp*	Pentamethylcyclopentadienyl
d	Doublet
DAD	Diode Array Detector
DBU	1,8-diazabicyclo[5.4.0] undec-7-ene
DCE	1,2-dichloroethane
dd	Double doublet
ddd	Doublet of doublet of doublets
DFT	Density Functional Theory
Dioxane	1,4-Dioxane
DG	Directing Group
DM	3,5-dimethylphenyl / Xylyl
DMM	3,5-dimethyl-4-methoxyphenyl
DMA	Dimethylacetamide
DMAP	4-dimethylaminopyridine
DME	Dimethoxyethane
DMF	*N,N*-dimethylformamide
DMSO	Dimethylsulfoxide
dq	Doublet of quartet
dr	Diastereomeric ratio
dt	Doublet of triplets
DTBM	3,5-di-tert-butyl-4-methoxyphenyl
DTMS	3,5-bis(trimethylsilyl) phenyl
E	Electron-withdrawing group
ee	Enantiomeric excess
equiv	Equivalents
er	Enantiomeric ratio
Et	Ethyl
Fur	Furyl
GC-MS	Gas Chromatography Mass Spectrometry
β-HE	β-Hydride Elimination
Hex	Hexyl
HPLC	High Performance Liquid Chromatography
HRMS	High Resolution Mass Spectra

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I	Intermediate
Int	Intermediate computed through DFT
J	Coupling constant
KIE	Kinetic Isotope Effect
L	Ligand
LLHT	Ligand-to-Ligand Hydrogen atom Tranfer
[M]	Metal complex
m	*meta*
m	Multiplet
***m*CPBA**	*m*-Chloroperoxybenzoic acid
Me	Methyl
MI	Migratory insertion
min	Minute/s
MPS	Methylphenylsulfoximine
Ms	Methanesulfonyl/Mesyl
MS	Molecular sieves
2-MeTHF	2-Methyltetrahydrofuran
MOM	Methoxymethyl
MTBE	Methyl-*tert*butylether
n.d.	Not determined or not measured
NMR	Nuclear Magnetic Resonance
nOe	Nuclear Overhauser Effect
o	*ortho*
OA	Oxidative addition
p	*para*
p	Pentet
PG	Protecting group
Ph	Phenyl
Pin	Pinacol
Piv	Pivaloyl (-CO*t*Bu)
PPTS	Pyridinium *p*-toluenesulfonate
Pr	Propyl
q	Quartet
qd	Quartet of doublets
RE	Reductive Elimination
rt	Room Temperature
SM	Starting Material
t	Triplet
t	Time
T	Temperature
***t*-AmOH**	2-Methyl-2-butanol
TBAF	Tetrabutylammonium fluoride
TBAOH	Tetrabutylammonium hydroxide
TBS	*tert*-butyldimethylsilyl
td	Triple doublet
TDI	TOF-determining transition state
THF	Tetrahydrofuran
TLC	Thin Layer Chromatography
TMC	Transition Metal -Catalyzed
TMS	Trimethylsilyl
TOF	Turnover Frequency
Tol	Tolyl
Ts	*p*-Toluenesulfonyl/Tosyl
TS	Transition State
Xyl	Xylyl

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1

Summary / Resumo

1.1. Summary

Introduction

Throughout the history of synthetic chemistry, the pursuit of more efficient and sustainable processes has become progressively significant. Modern organic synthesis not only seeks the preparation of target molecules but also designing processes that maximize resource efficiency. This involves conserving the maximum number of atoms from starting materials (atom economy), reducing the number of synthetic steps (step economy), and minimizing the need for intermediate purification (pot economy).

While these concepts initially emerged from economic motivations, such as saving time, effort, and costs, they closely align with the principles of green chemistry.[15] Guided by these principles, organic chemists aim to generate complex molecules from safe, simple, and readily available starting materials with minimal waste, while striving for environmental sustainability. In this context, the discovery and development of catalytic methods is especially timely.

Transition metal catalyzed reactions have emerged as powerful tools in modern organic synthesis, driving advancements in fields like pharmaceuticals, materials science, and fine chemicals. These reactions offer significant advantages in terms of sustainability and efficiency. By employing catalytic amounts of transition metals, they enable the formation of complex molecules with high selectivity and atom economy. Additionally, many of these reactions proceed under mild conditions, reducing energy consumption and the need for harsh reagents. This focus on efficiency and reduced environmental impact aligns well with the principles of green chemistry, making transition metal catalysis a cornerstone of sustainable chemical synthesis.

Despite the advancements in transition metal catalysis, many reactions rely on pre-functionalized substrates (e.g., organic halides), which compromise the atom economy. In this context, the development of C–H activation/functionalization strategies has emerged as a promising approach to address the pre-elaboration problem and directly convert simple precursors into advanced products with full-atom economy.

A major challenge in the C–H activation field is related to controlling the site selectivity, namely, the activation of the desired the bond in the presence of others. For this reason, the use of a directing group is a very applied strategy to selectively direct the activation of a given C–H bond within complex molecules. The directing group, commonly a Lewis base, coordinates the metal center and guides its approach toward the specific C–H

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bond that will be activated**,** lowering entropic barriers and, in many cases, accelerating the reaction.

This doctoral thesis focuses on the activation of aromatic C–H bonds using directing groups and their addition across alkenes and other unsaturated systems, to formally yield hydrocarbonation process. These reactions constitute an attractive synthetic approach to generate highly complex molecules quickly and efficiently, and with full atom economy.

During the last decades, there has been significant progress in the field; however, there are still many challenges to tackle, and limitations that need to be overcome, to be able to extend the scope and potential of this chemistry, especially for the assembly of structurally complex molecules in an asymmetric fashion. Intramolecular hydroarylation processes of alkenes are mostly limited to those that provide tertiary stereocenters, while the construction of quaternary centers is still a major restriction of most of the reported methods. Additionally, these cycloisomerizations are generally restricted to forming five- or six-membered rings, but not larger systems.

Curiously, intramolecular hydroarylations of partners like allenes or carbonyls, that could open highly relevant synthetic doors, are still an uncharted area.

On these bases, the general objectives of this PhD thesis were:

- **The development of highly enantioselective hydroarylations of alkenes for assembling fused heteropolycyclic systems**, **including those equipped with all-carbon quaternary stereocenters.**
  Moreover, we also aimed at the building of cycles beyond the most common five and six membered rings, as well as the construction of polycycles equipped with multiple stereocenters in an enantio- and diastereoselective manner.

- **The development of methodologies for intramolecular C–H additions across allenes, including enantioselective variants**.
  Allenes, despite their peculiar structure and reactivity potential, have barely been investigated in hydrocarbonation reactions. A thorough study of their reactivity in hydroarylation processes should provide new, highly relevant synthetic methods.

- **Discovery of cascade processes involving additional C=C bonds**.
  This would allow a faster increase in skeletal complexity.

- **Development of methodologies for intramolecular C–H addition across carbonyls, including enantioselective variants**.
  Similarly to allenes, the use of ketones and aldehydes as partners in hydrocarbonation reactions has been very scarce, particularly in an enantioselective fashion. However,

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we hypothesize that, if appropriately controlled, these methods hold a great synthetic potential.

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Enantioselective Intramolecular Iridium(I)-Catalyzed Hydroarylations of Alkenes. Access to Polycyclic Systems Bearing Quaternary Stereocenters

Quaternary carbon stereocenters are ubiquitously present in numerous natural products, which exhibit significant and diverse bioactivities. **Figure 1** shows some natural products bearing chiral quaternary carbon centers embedded in heteropolycyclic skeletons. Despite significant advances in the past few decades, the number of catalytic methodologies for their bond-forming assembly is relatively low, particularly in an asymmetric fashion.

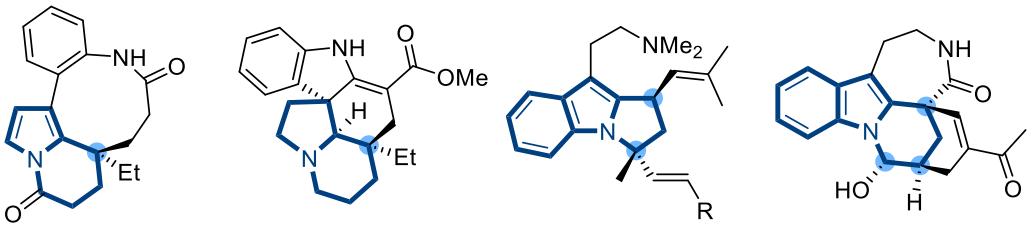


***Figure 1**: Natural products with heteropolycyclic skeletons bearing all-carbon quaternary stereocenters.*

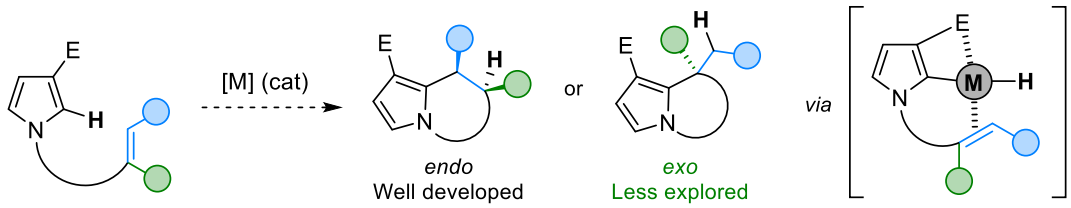
Most precedents on TMC hydroarylations that generate all-carbon quaternary centers typically rely on processes involving C–H activations via a CMD (Concerted Metallation-Deprotonation) mechanism, followed by migratory insertion and protodemetallation. But very few of them have been developed in an asymmetric fashion.

On the other hand, processes wherein the C–H bond is added across the unsaturated system through an oxidative addition/migratory insertion/reductive elimination manifold are rare.

When we started our investigation, the only examples that had been reported based on the oxidative insertion of a metal catalyst into an aromatic C–H bond had been developed in our own group and were carried out in a racemic fashion.

Our initial objectives focused on the development of an intramolecular enantioselective hydrocarbonation process that allows the asymmetric assembly of heteropolycyclic systems, including those containing all-carbon quaternary centers though an *exo*-selective hydroarylation (see **Scheme 1**). We specially focused on pyrrole precursors, owing to the relevance of the resulting products.

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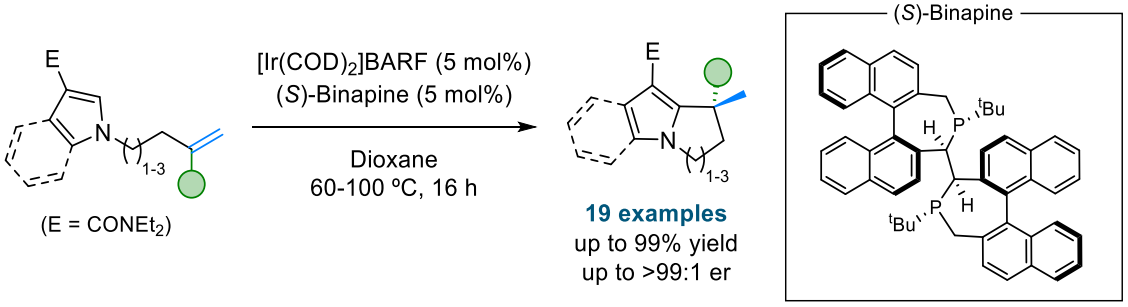


***Scheme 1**: TM-catalyzed direct addition of C–H bonds across alkenes.*

The formation of different ring sizes, by using precursors with diverse lengths at the connecting tether, was also a major goal, as this could increase the synthetic utility of the method.

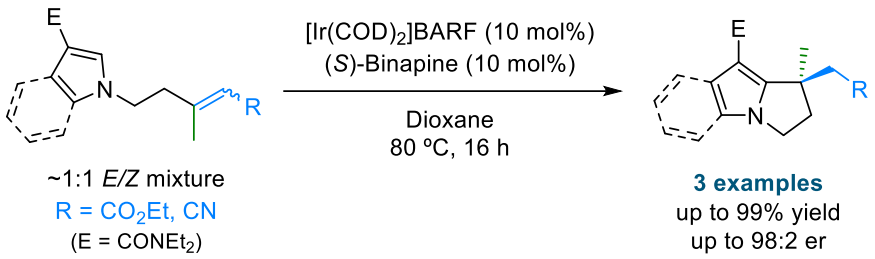
We used as model substrate an alkenyl-tethered pyrrole equipped with a diethylamide at C3, which works as directing group. After testing different ligands in combination with [Ir(COD)$_2$]BARF, Binapine was found to be the most effective, allowing *exo*-selective hydroarylations with enantiomeric ratios (er) higher than 99:1. Additionally, other directing groups, solvents, iridium and rhodium precatalysts and temperatures were evaluated.

With the optimal conditions in hand, the scope of the process for the generation of dihydro-1*H*-pyrrolizines and related heteropolycycles was explored. To our delight, our method represents the first enantioselective metal-catalyzed cycloisomerization based on a C–H activation that allows to build either five-, six- or seven-membered rings, with excellent er's. The method allows the construction of molecules bearing quaternary and tertiary stereocenters embedded in indole- and pyrrole-based heteropolycyclic systems. In all cases with excellent yields and enantioselectivities (see **Scheme 2**).



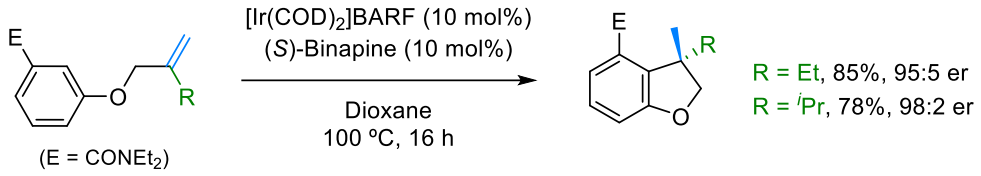
***Scheme 2**: Highly enantioselective Ir-catalyzed hydroarylation of alkenes.*

In addition, the methodology tolerates the use of trisubstituted alkenes as ~1:1 *E*/*Z* mixture of isomers, with good yields and excellent er's. To the best of our knowledge, the possibility of obtaining these products with high er, regardless of the configuration of the parent trisubstituted alkene, lacks precedents in C–H hydrocarbonation protocols (**Scheme 3**).



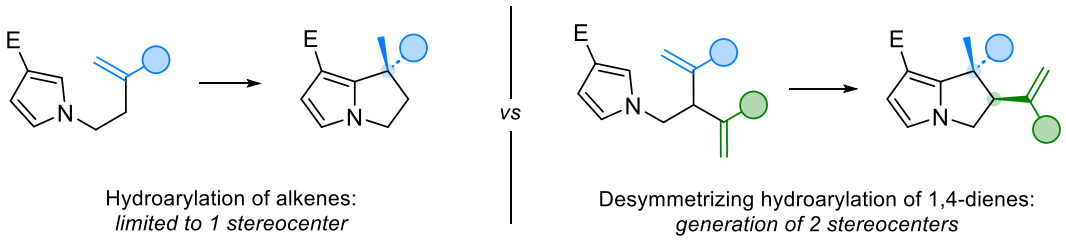
Scheme 3: *Ir-catalyzed cycloisomerization of trisubstituted alkene-tethered pyrroles.*

Encouragingly, the catalyst derived from [Ir(COD)$_2$]BARF and (*S*)-Binapine also facilitated the cyclization of *O*-alkenyl tether carboxamides, furnishing the desired dihydrobenzofurans in good yields and enantiomeric ratios up to 98:2 (**Scheme 4**).



Scheme 4: *Ir-catalyzed cycloisomerization for the synthesis of dihydrobenzofurans.*

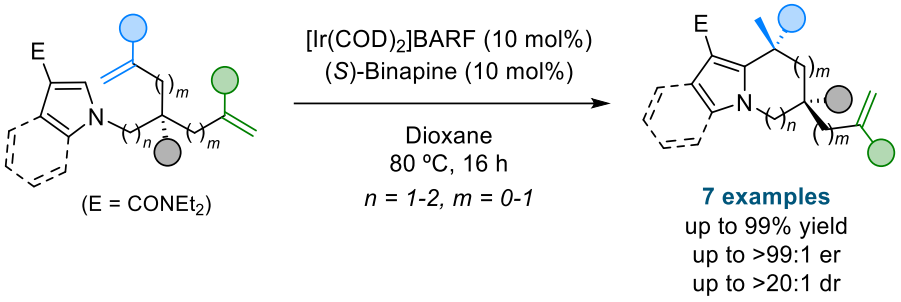
The above-described methodology is very versatile; however, its *exo*-selective nature impedes, *a priori*, the generation of more than one stereocenter within the newly generated ring (**Scheme 5**, left). To overcome this limitation, we successfully developed a novel protocol that combines the hydroarylation process with a concomitant desymmetrization of a prochiral center, which is conveniently located at the connecting tether. Thus, related heterocyclic products containing multiple stereocenters within the newly formed ring were obtained with excellent stereoselectivities (**Scheme 5**, right).



Scheme 5*: General strategy for the generation of 2 stereocenters by desymmetrization of pyrrole-dienyl substrates.*

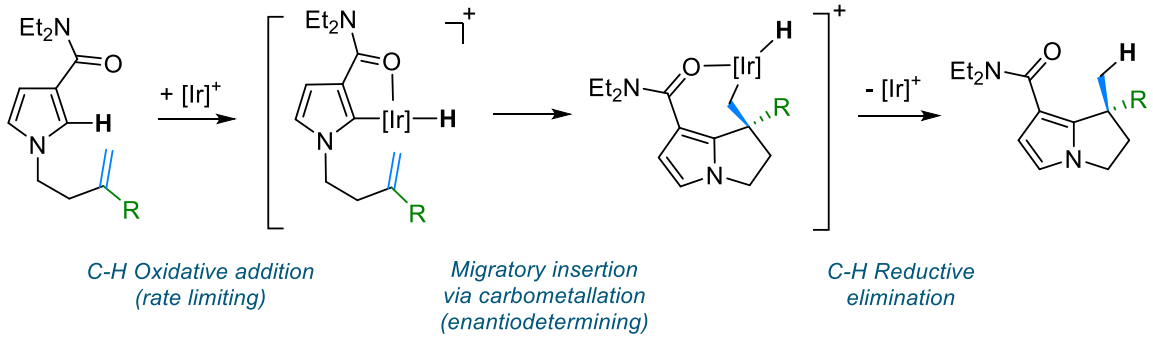
We found that the chiral catalyst can distinguish between enantiotopic alkenes of the prochiral center, while maintaining an excellent facial selectivity of the alkene insertion. Thus, an array of tetrahydroindolizine and dihydropyrrolizine derivatives, featuring vicinal or skipped stereocenters can be obtained with good yields, diastereoselectivities and enantioselectivities (higher than 8:2 dr, and up to 99:1 er, **Scheme 6**).

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***Scheme 6**: Enantioselective desymmetrization of prochiral diene precursors.*

Regarding the mechanism, we propose an initial oxidative addition, followed by carbometallation and a final reductive elimination (see **Scheme 7**). To shed light on the factors contributing to the observed reactivity, and high enantioselectivity, Dr. Martín Calvelo conducted computational mechanistic studies. Overall, the theoretical results align well with our experimental data and the experimentally calculated KIE, confirming that the C–H oxidative addition to the Ir(I) complex is turnover-determining. Additionally, the calculated energetic profile supports the alkene migratory insertion as the enantiodetermining step, and is consistent with the high enantiomeric ratios experimentally obtained, as well as with the absolute configuration of the major enantiomer.



***Scheme 7**: Proposed mechanism based on deuterium labelling experiments and DFT studies.*

Regioselective Iridium(I)-Catalyzed Intramolecular Hydroarylations of Allene-Tethered Pyrroles and Indoles

Allenes, a class of C–C unsaturated molecule that holds two consecutive C–C double bonds, have emerged as highly versatile reactants in organic synthesis. Their unique structural configuration imparts higher reactivity compared to alkenes, with the additional advantage that their resulting products usually retain one of the two double bonds, enabling convenient further elaboration. However, this structural features of allenes conveys severe chemo- and regioselectivity issues, which complicate their reactivity and, overall, the development of efficient and highly selective methods (see **Figure 2**).

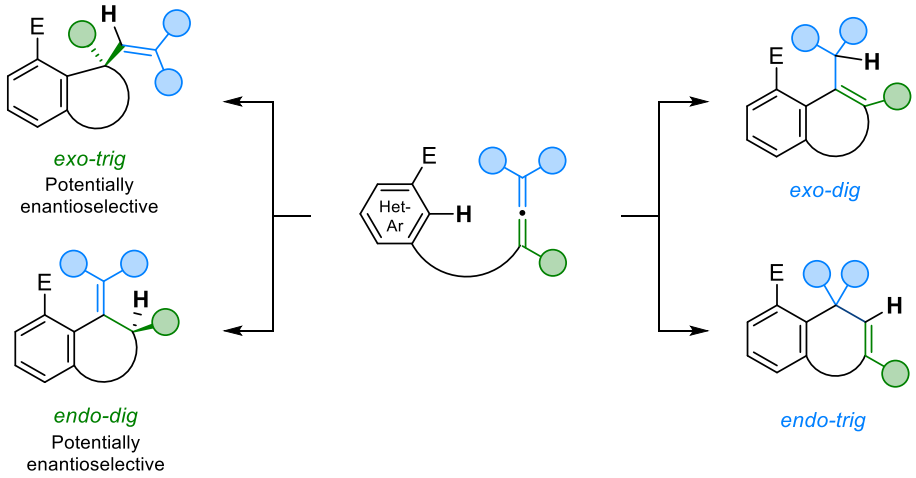


***Figure 2**: Potential regioisomers result of an intramolecular hydroarylation of allenes.*

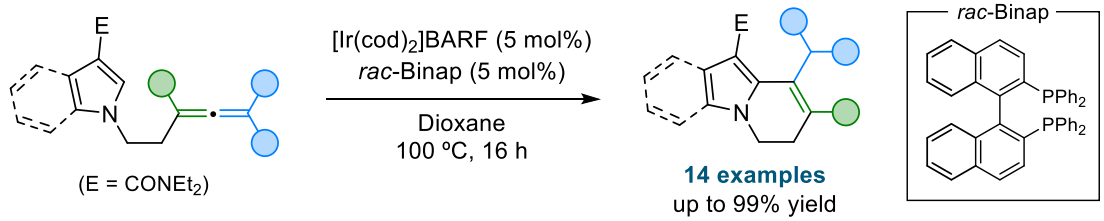
In recent years, a diverse array of hydroarylation reactions involving allenes has been developed. Among these methodologies, those that proceed via electrophilic aromatic substitution or C–H activation through concerted metalation-deprotonation (CMD) processes are particularly prevalent. Curiously, hydroarylation processes of allenes based on a C-H oxidative addition/migratory insertion/reductive elimination manifold are extremely scarce. Indeed, only few intermolecular examples that provide access to achiral linear adducts has been published before we started our research.

Our objective consisted on the development of new intramolecular transition metal catalyzed hydroarylations of allenes, based on activation of C–H bonds of heteroaromatic precursors. Hypothetically, these processes could yield diverse types of products, depending on whether the cyclization occurs in an *endo* or *exo* fashion and on which of the allene's double bonds participates in the reaction. In addition to the study of the chemo- and regioselectivity in these cycloisomerizations, potential asymmetric variants using chiral iridium(I) catalysts were also explored, owing to the lack of precedents to build the expected products in an enantioselective fashion.

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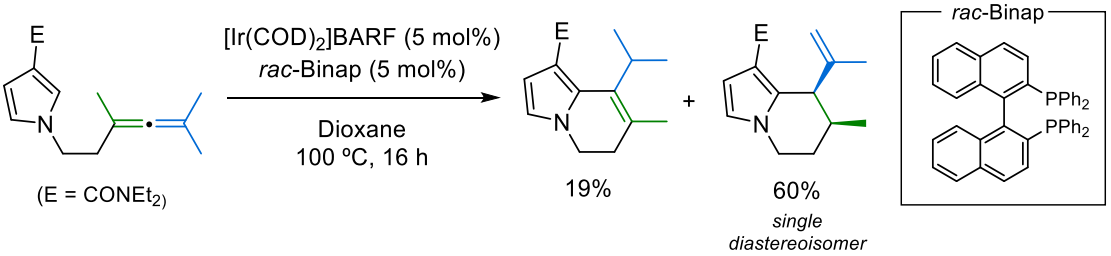
A model substrate bearing two methylene units between the pyrrole and the allene was prepared to evaluate the viability of the reaction. During the optimization process, different ligands, iridium sources, solvents, temperatures and directing groups were evaluated. By employing Binap as ligand, together with [Ir(COD)$_2$]BARF, we found the selective formation of a product that results from an *exo*-selective hydroarylation of the distal C–C double bond of the allene (**Scheme 8**). Noteworthy, this class of products cannot be accessed through analogous hydrocarbonations of pyrrole-tethered alkynes, which usually yield products with exocyclic alkenes.

The generality of the method with other allenyl-pyrrole substrates was explored. Thus, we found that the reaction tolerates mono- di- and tri-substituted allenes, yielding dihydroindolizines with excellent performance. Precursors bearing an indole, instead of the pyrrole moiety also proved to be viable substrates for the reaction. Consequently, the dihydropyrido[1,2-a]indoles were obtained with full selectivity and good yields.



***Scheme 8**. Scope of exo-selective hydrocarbonation of allene-tethered indoles.*

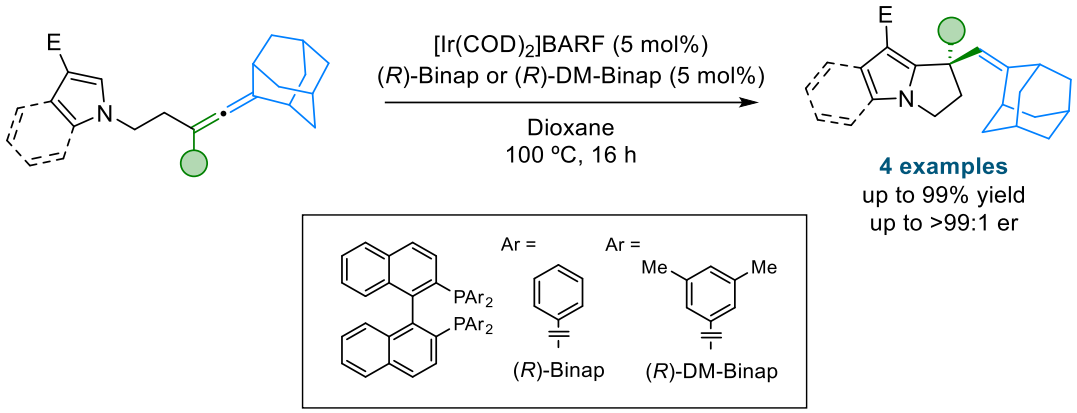
Surprisingly, when tetrasubstituted allenes were submitted to the standard reaction conditions, we observed the formation of unexpected chiral tetrahydroindolizines as predominant products, as single diastereoisomers (see **Scheme 9**). Given the significance of this novel transformation from a synthetic and mechanistic perspective, the exploration of this unique reactivity of tetrasubstituted allenyl precursors was specifically addressed in a separate chapter of this thesis.



***Scheme 9**: Outcome of the reaction of a precursor bearing a tetrasubstituted allene with a two-methylene linker.*

Additionally, when testing allene precursors with increased steric hindrance by introducing vinylidene-adamantanes, we found a shift in selectivity. In this case the

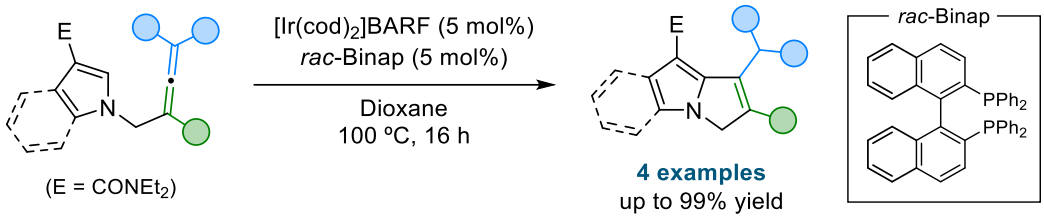
selective *exo* addition across the internal double bond provided access to chiral 2,3-dihydropyrrolizines with excellent enantioselectivities by employing (*R*)-Binap or (*R*)-DM-Binap as ligands (**Scheme 10**).



Scheme 10: *Scope of enantioselective hydroarylation of adamantane-containing substrates.*

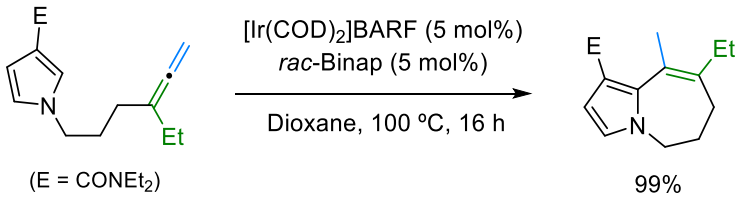
We then analyzed the influence of the chain length that connects the pyrrole and the allene, we prepared different precursors with either one or three methylene units.

In the case of substrates with one methylene unit, we observed the selective formation of products result of the *exo* addition to the distal double bond, regardless of the substitution pattern of the allene (**Scheme 11**).



Scheme 11*. Exo-selective hydrocarbonation of allene-tethered pyrroles and indoles to form 5-membered rings.*

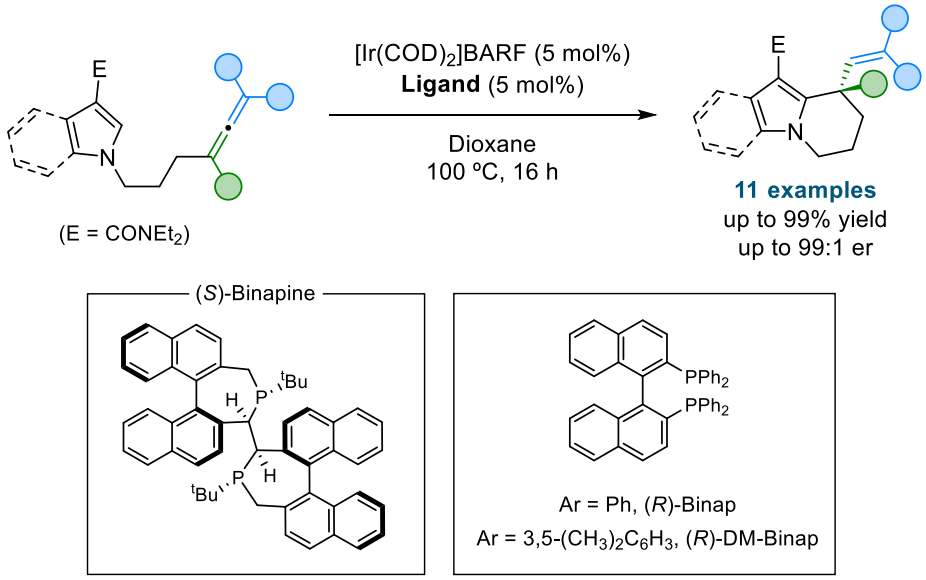
With a substrate lacking substituents in the distal carbon of the allene and bearing three methylene units, we also observed the addition across the distal double bond (**Scheme 12**).



Scheme 12*. Hydrocarbonation of allene-tethered pyrroles with three methylene units .*

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However, when employing substrates with substituents at the terminal position of the allene, the reaction proceeds again though the *exo*-selective addition across the internal double bond to yield chiral tetrahydroindolizine products bearing vinyl-substituted stereocenters. Gratefully, by employing chiral ligands like Binapine or Binap, these can be obtained with good yields and very high enantioselectivities (**Scheme 13**).



***Scheme 13**. Exo-selective hydrocarbonation of allene-tethered pyrroles and indoles. Some results were obtained in collaboration with Alejandro Rey.*

To shed light on the factors contributing to the selectivity in these reactions, Dr. Martín Calvelo conducted computational mechanistic studies. The calculations align well with the experimental findings and allow us to rationalize the factors governing selectivity.

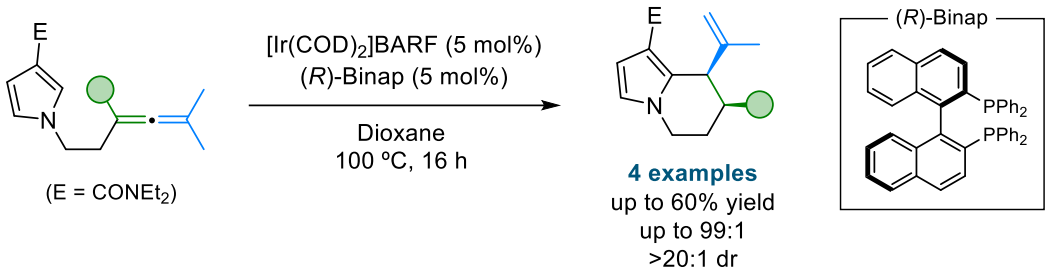
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Iridium(I)-Catalyzed Cascade Reactions of Allene-Tethered Pyrroles and Indoles

As indicated before, substrates bearing tetrasubstituted allenes and two methylene units in the connection tether, in presence of the Ir(I)/Binap catalyst at 100 ºC, produce chiral adducts with multiple stereocenters with high er and dr. This process might involve cascade hydrogenation and dehydrogenation steps after the initial cyclization.

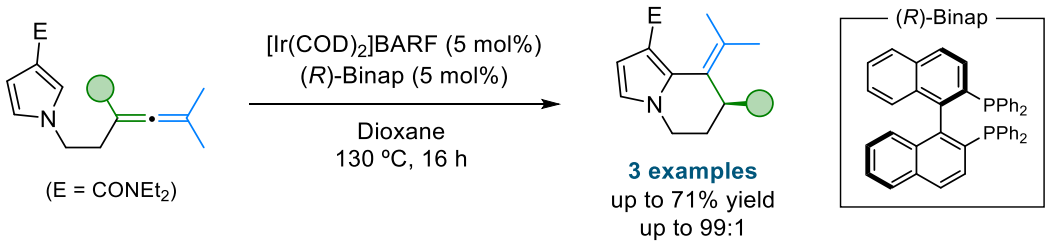
The relevance of the products, diastereoselectivity of the reaction and intriguing mechanistic aspects of the transformation encouraged us to develop a general catalytic method based on this hypothetic cascade process.

Other substrates with tetrasubstituted allenes were evaluated to assess the generality of the reaction. When the reactions were carried out at 100 ºC, the expected chiral tetrahydroindolizines bearing two stereocenters were obtained with moderate yields but excellent selectivity (**Scheme 14**).



Scheme 14: *Ir-catalyzed reaction at 100 ºC of tetrasubstituted allenyl-pyrroles to give chiral tetrahydroindolizines.*

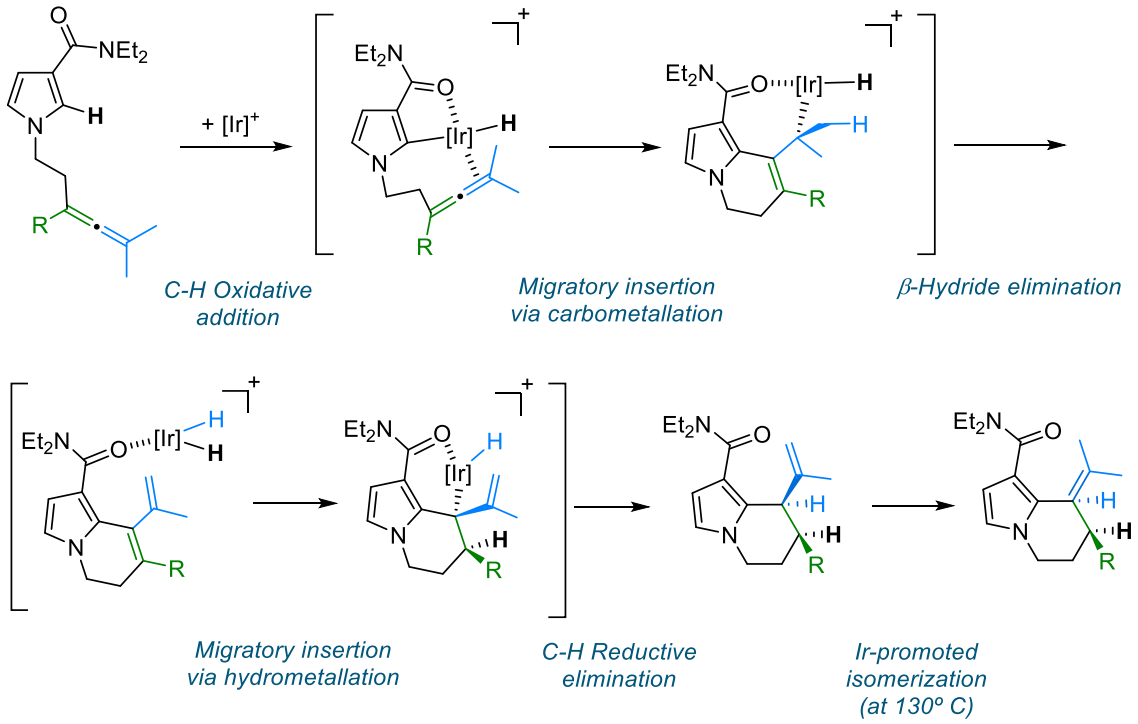
Additionally, when the reaction was conducted at 130 °C, the major products obtained were chiral tetrahydroindolizine bearing *exo*-alkenes (**Scheme 15**). Control experiments support that these products arise from a double bond isomerization of the previously formed products (**Scheme 13**).



Scheme 15: *Ir-catalyzed reaction at 130 ºC of tetrasubstituted allenyl-pyrroles to give chiral tetrahydroindolizines.*

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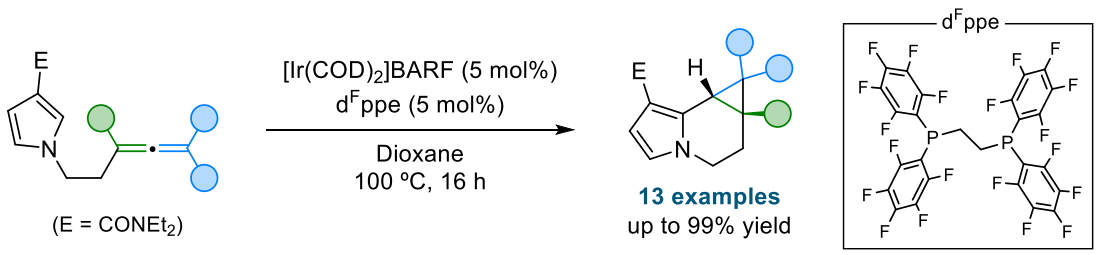
DFT calculations and deuteration labelling experiments supported the hypothesized cascade, namely a mechanism involving a C–H oxidative addition followed by an *exo*-selective carbometallation into the distal double bond of the allene. Then, a β-hydride elimination could generate an Ir-bishydride intermediate that keeps the iridium coordinated to the carbonyl moiety. This bishydride species could then transfer the hydrogen atoms to the double bond of the dihydroindolizine core, through an hydrometallation/C–H reductive elimination sequence, ultimately releasing the observed product (**Scheme 16**).



***Scheme 16**: Proposed mechanism for the tandem hydroarylation-transfer hydrogenation reaction of allenyl-pyrroles.*

During the optimization of this tandem reaction, we unexpectedly discovered that when the same tetrasubstituted precursors were treated under standard iridium-promoted hydrocarbonation conditions, but using the fluorinated biphosphine d^Fppe as ligand, cyclopropane-fused tetrahydroindolizines were selectively formed. The reaction tolerates a carbocycle at their distal carbon, allowing the construction of different spirocyclic architectures (**Scheme 17**).

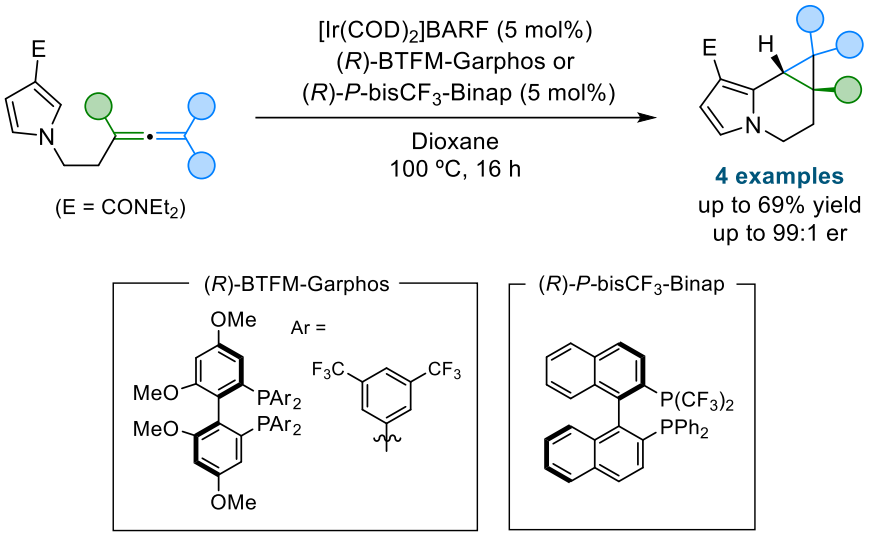
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***Scheme 17**: Ir-catalyzed tandem hydroarylation/cyclopropanation of tetrasubstituted allenyl-substituted pyrroles.*

Motivated by the prevalence of chiral cyclopropane-fused heterocycles in biorelevant compounds, a preliminary assessment of the feasibility of an enantioselective variation of this transformation using chiral electron-deficient phosphine ligands was conducted.

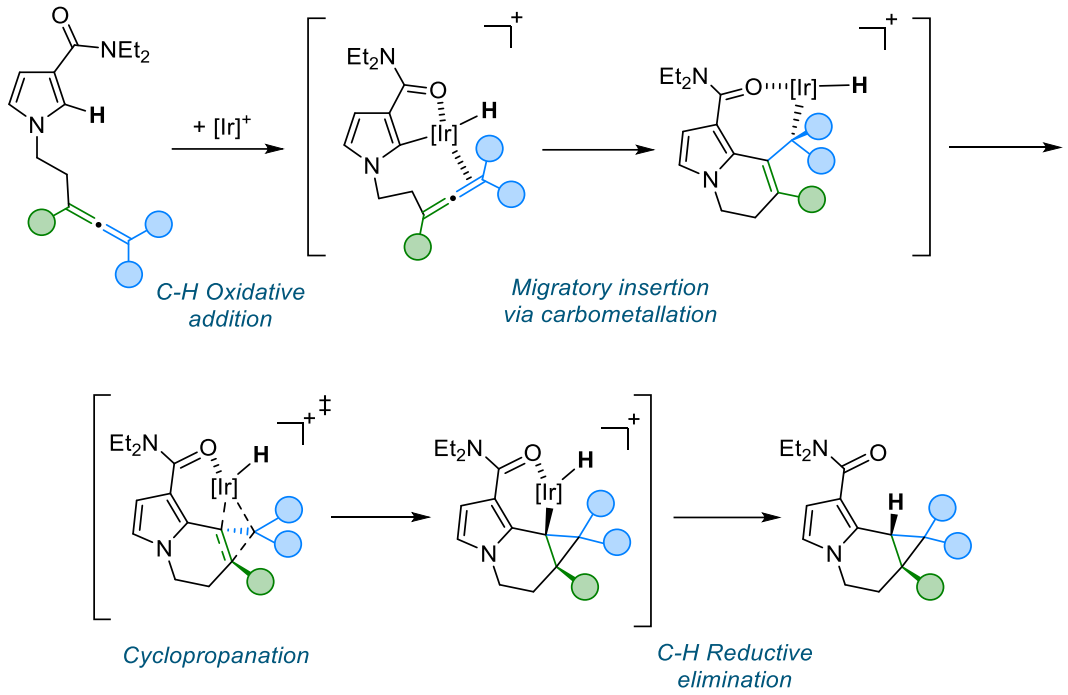
By employing electron-deficient ligands such as (*R*)-BTFM-Garphos, or the chiral ligand (*R*)-*P*-bisCF$_3$-Binap, initially developed by Togni, different tetrasubstituted allenyl pyrroles were converted into the desired cyclopropane-fused tetrahydroindolizines yielding moderate to good yields and enantiomeric ratios of up to 99:1



***Scheme 18**: Enantioselective Ir-catalyzed tandem hydroarylation/cyclopropanation of tetrasubstituted allenyl-substituted pyrroles.*

Regarding the mechanism, we propose that, after the oxidative addition and carbometallation of the distal double bond of the allene, there is an intramolecular carboiridation with formation of a cyclopropyl ring. After a final reductive elimination, the observed products are released (see **Scheme 19**). Computational studies supported this scenario and confirmed the crucial role of the fluorinated ligand in this process.

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***Scheme 19**: Proposed mechanism for the tandem hydroarylation-cyclopropanation reaction of allenyl-pyrroles.*

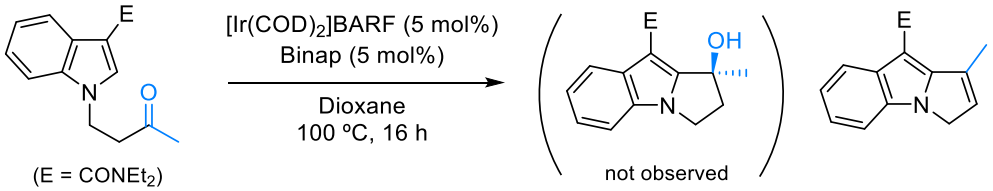
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Intramolecular Iridium(I)-Catalyzed Hydroarylation of Carbonyl Systems

The direct hydroarylation of ketones represent a highly atom economical manner to build tertiary alcohols, although the number of methodologies involving an initial C(sp^2)–H activation is surprisingly low and those reported methods hold very narrow scopes. Moreover, the development of enantioselective variants is essentially unknown.

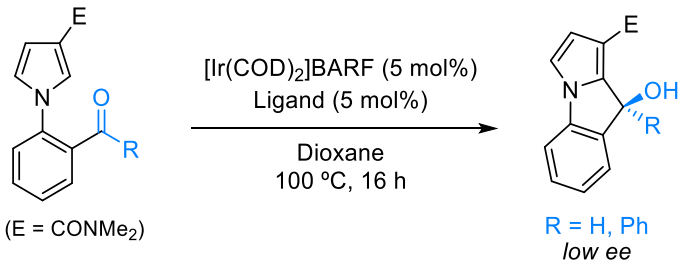
Therefore, we decided to explore the use of pyrrole-carbonyl precursors as probes to evaluate the viability of these reactions, using iridium catalysis. This approach could potentially yield chiral heterocyclic systems containing tertiary and secondary alcohols, , a structural motif prevalent in natural products.

Our studies commenced with the preparation of a precursor related to those described in previous chapters, but featuring a methyl ketone, instead of the alkene or allene. Unfortunately, catalysts formed *in situ* from [Ir(COD)$_2$]BARF and Binap, previously used to promote *exo*-selective intermolecular hydroarylations of C–C unsaturated systems, quantitatively yielded an achiral pyrroloindole product, instead of the initially expected chiral tertiary alcohol (see **Scheme 20**). This result is consonant with previously reported reactions and confirms the challenge of avoiding dehydration of the desired products.



***Scheme 20**: Ir-catalyzed cyclodehydration of an indole-ketone precursor.*

Given this selectivity toward the dehydrated products, we also tested the reaction with precursors that would prevent this dehydration to the *endo*-alkene. Unfortunately, although the desired cyclic alcohols were formed in good yields, these were obtained in a racemic fashion (**Scheme 21**).

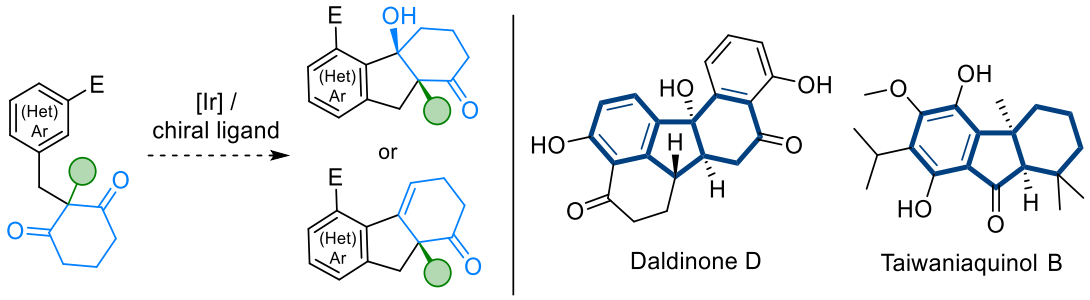


***Scheme 21**: Ir-catalyzed intramolecular hydroarylation of carbonyls.*

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On these bases, we decided to explore a desymmetrization strategy with 1,3-diketones. Our previous work with alkenes demonstrated the viability of desymmetrizing protocols, and its successful application to carbonyls could potentially lead to the enantioselective synthesis of polycyclic structures bearing quaternary stereocenters, as depicted in **Scheme 22**.

Our research in this endeavor was focused on aryl, instead of heteroaryl donor sources of C–H bonds. Gratifyingly, using cyclic 1,3-diketones as partners, we could easily obtain chiral tricyclic systems that are present in several biologically relevant molecules such as Daldinone C and Taiwaniaquinol B, depicted in **Scheme 22**.

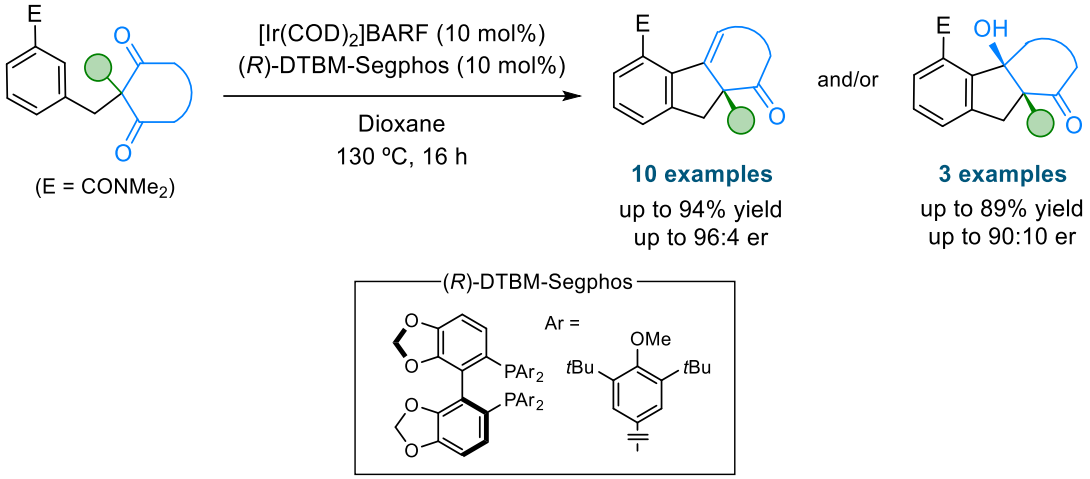


***Scheme 22**: General scheme of the desymmetrizing hydroarylation strategy and representative natural products bearing similar scaffolds.*

Although preliminary experiments employing diethylamide as directing group provided very low yields; by changing the directing group from diethylamide to dimethylamide, we were able to reach full conversions. Moreover, we found that by employing DTBM-Segphos in combination with $[Ir(COD)_2]BARF$, at 130 ºC in dioxane, we could reach up to 94% yield and 90:10 er. With these conditions, we explored the generality of the method, which allowed the synthesis of a variety of hexahydrofluorenes bearing quaternary carbon centers, from their corresponding diketones, in excellent yields and high stereoselectivities (**Scheme 23**).

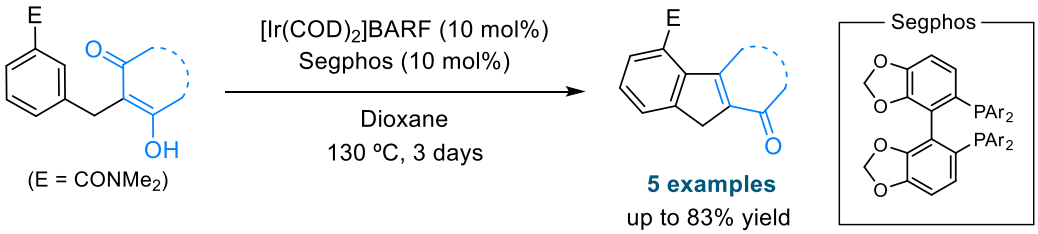
Curiously, when employing some cyclic diketones, especially those with 5-membered rings, the dehydration does not take place, allowing the formation of products bearing multiple stereocenters with full diastereoselectivity. Overall, this method constitutes the first Ir-catalyzed hydroarylation of carbonyl moieties, which is additionally coupled to a desymmetrization of a prochiral center.

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***Scheme 23**: Ir-catalyzed desymmetrizing hydroarylation of 1,3-diketones.*

Finally, we also examined various substrates lacking substituents at the 2-position of the 1,3-diketone. In these cases, the concomitant dehydration takes place to yield achiral indenes (**Scheme 24**).



***Scheme 24**: Achiral indenes through Ir-catalyzed cyclodehydration.*

These results pave the way for additional improvements of the method, as well as for its application to the synthesis of biorelevant products that hold these tricyclic scaffolds.

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1.2. Resumo

Introdución

Ao longo da historia da química sintética, a procura de procesos máis eficientes e sostibles foi adquirindo progresivamente maior relevancia. A síntese orgánica moderna non só busca a preparación de moléculas obxectivo, senón tamén deseñar procesos que maximicen a eficiencia dos recursos. Isto inclúe conservar o máximo número de átomos dos materiais de partida (economía atómica), reducir o número de pasos sintéticos, e minimizar a necesidade de purificación de intermedios.

Aínda que estes conceptos inicialmente xurdiron por motivacións económicas, como o aforro de tempo, esforzo e custos, están estreitamente relacionados cos principios da química verde. Guiados por estes principios, os químicos orgánicos procuran xerar moléculas complexas a partir de materiais de partida seguros, simples e facilmente dispoñibles, con residuos mínimos e promovendo a sustentabilidade ambiental. Neste contexto, o descubrimento e desenvolvemento de métodos catalíticos é especialmente oportuno.

As reaccións catalizadas por metais de transición convertéronse en ferramentas poderosas na síntese orgánica moderna, impulsando avances en campos como a farmacéutica ou a ciencia de materiais. Estas reaccións ofrecen vantaxes significativas en termos de sustentabilidade e eficiencia. Empregando cantidades catalíticas de metais de transición, facilítase a formación de moléculas complexas cunha alta selectividade e economía atómica. Ademais, moitas destas reaccións levan a cabo en condicións suaves, reducindo o consumo de enerxía e a necesidade de reactivos agresivos. Este enfoque na eficiencia e no menor impacto ambiental aliñase ben cos principios da química verde, facendo da catálise por metais de transición un piar da síntese química sostible.

A pesar dos avances na catálise por metais de transición, moitas reaccións dependen de substratos prefuncionalizados (como haluros orgánicos), o que compromete a economía atómica. Neste contexto, o desenvolvemento de estratexias de activación/funcionalización de enlaces C–H emerxeu como un enfoque prometedor para abordar o problema da preelaboración e converter directamente precursores simples en produtos avanzados con economía atómica total.

Un dos principais retos no campo da activación de enlaces C–H está relacionado co control da selectividade de sitio, é dicir, a activación do enlace desexado na presenza doutros. Por esta razón, o uso dun grupo director é unha estratexia amplamente aplicada

para dirixir selectivamente a activación dun enlace C–H nunha molécula complexa. O grupo director, comunmente unha base de Lewis, coordínase co centro metálico, guiando o enlace C–H específico que debe activarse, reducindo barreiras entrópicas e, en moitos casos, acelerando a reacción.

Esta tese de doutoramento céntrase na activación de enlaces aromáticos C–H empregando grupos directores e a súa adición a alquenos e outros sistemas insaturados, para dar lugar a procesos de hidrocarbonación. Estas reaccións constitúen un enfoque sintético atractivo para xerar moléculas altamente complexas de forma rápida e eficiente, e con economía atómica total.

Nas últimas décadas houbo avances significativos neste campo. Porén, aínda existen moitos retos que afrontar e limitacións que superar para ampliar o alcance e o potencial desta química, especialmente para a ensamblaxe de moléculas estruturalmente complexas. Os procesos de hidroarilación intramolecular de alquenos están maioritariamente limitados a aqueles nos que se xera un centro estereoxénico terciario, mentres a construción de centros cuaternarios aínda supón unha importante limitación da maioría dos métodos descritos. Ademais, estas cicloisomerizacións xeralmente restrinxe á formación de ciclos de cinco ou seis membros, pero non aneis máis grandes.

Curiosamente, as hidroarilacións intramoleculares doutros sistemas como os alenos ou carbonilos, que poderían abrir portas sintéticas moi relevantes, aínda son unha área pouco explorada.

Por conseguinte, os obxectivos xerais desta tese de doutoramento foron:

- **O desenvolvemento de hidroarilacións intramoleculares altamente enantioselectivas de alquenos para ensamblar sistemas heteropolicíclicos fusionados, incluíndo aqueles equipados con centros estereoxénicos cuaternarios.**
  Ademais, buscouse a construción de ciclos diferentes aos máis comúns de cinco ou seis membros, así como a construción de policiclos equipados con múltiples centros estereoxénicos de forma enantio- e diastereoselectiva.

- **O desenvolvemento de metodoloxías para adicións intramoleculares de enlaces C–H a alenos, incluíndo variantes enantioselectivas.**
  Os alenos, a pesar da súa estrutura peculiar e do seu potencial reactivo, apenas se investigaron en reaccións de hidroarilación intramolecular. Sen dúbida, un estudo exhaustivo da súa reactividade en procesos de hidroarilación debería proporcionar novos e relevantes métodos sintéticos.

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- **O descubrimento de procesos en cascada que impliquen enlaces C=C adicionais.**
  Isto permitiría un aumento máis rápido da complexidade esquelética.
- **O desenvolvemento de metodoloxías para adicións intramoleculares de enlaces C–H a carbonilos, incluíndo variantes enantioselectivas.**
  De maneira similar aos alenos, o uso de cetonas e aldehidos en reaccións de hidrocarbonación foi moi escaso, especialmente dun xeito enantioselectivo Con todo, hipotetizamos que, se se controlan adecuadamente, estes métodos deberían ter un gran potencial sintético.

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Hidroarilacións intramoleculares enantioselectivas catalizadas por Iridio(I). Acceso a sistemas policíclicos con centros estereoxénicos cuaternarios

Os centros estereoxénicos de carbono cuaternario están presentes, de maneira ubicua, en numerosos produtos naturais, que presentan bioactividades significativas e diversas. A **Figura 3** mostra algúns produtos naturais que conteñen centros quirais de carbono cuaternario incrustados en andamiaxes heteropolicíclicos. A pesar dos avances significativos nas últimas décadas, o número de metodoloxías catalíticas para a súa ensamblaxe é relativamente baixo.

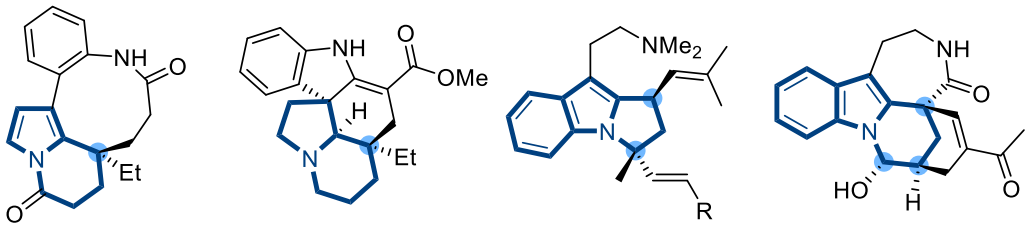


***Figura 3**: Produtos naturais con andamiaxes heteropolicíclicos que conteñen centros estereoxénicos cuaternarios totalmente de carbono.*

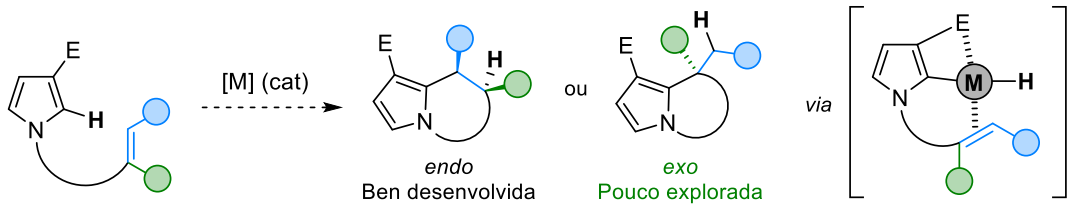
A maioría dos precedentes sobre hidroarilacións catalizadas por metais de transición (TMC) que xeran centros cuaternarios totalmente de carbono dependen de procesos que implican activacións de enlaces C–H mediante un mecanismo de Metalación-Desprotonación Concertada (CMD, polas súas siglas en inglés), seguido de inserción migratoria e protodemetalación. Porén, moi poucos deles foron desenvolvidos de maneira asimétrica.

Por outra banda, os procesos nos que o enlace C–H se engade a través dun sistema insaturado mediante un mecanismo de adición oxidativa–inserción migratoria–eliminación redutora son moi raros.

Cando comezamos a nosa investigación, os únicos exemplos reportados baseados na inserción oxidativa dun catalizador metálico nun enlace C–H aromático foron desenvolvidos polo noso propio grupo e realizáronse de xeito racémico.

Os nosos obxectivos iniciais centráronse no desenvolvemento dun proceso de hidrocarbonación intramolecular enantioselectivo que permitise a ensamblaxe asimétrica de sistemas heteropolicíclicos, incluíndo aqueles que conteñen centros cuaternarios totalmente carbonados (ver **Esquema 25**). Prestamos especial atención aos precursores baseados en pirrois, debido á relevancia dos produtos resultantes.

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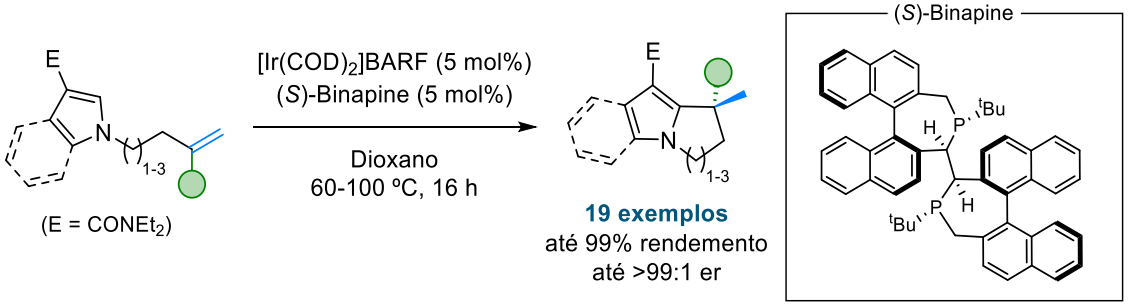


***Esquema 25**: Adición directa de enlaces C–H a alquenos catalizada por metais de transición.*

A formación de aneis de diferentes tamaños, empregando precursores con lonxitudes diversas na cadea conectora, tamén é un obxectivo importante, xa que podería aumentar a utilidade sintética do método.

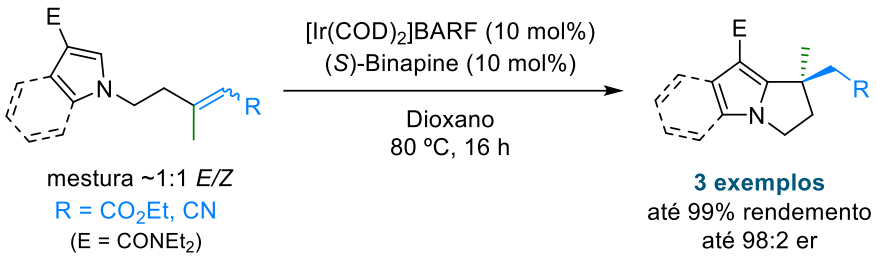
Utilizamos, como substratos modelos, pirrois unidos a alquenos, equipados cunha dietilamida no C3 que actúa como grupo director. Despois de probar diferentes ligandos en combinación con [Ir(COD)$_2$]BARF, encontrouse que Binapine era o máis efectivo, permitindo hidroarilacións *exo*-selectivas con máis do 99:1 er. Ademais, probáronse outros grupos directores, disolventes, temperaturas e precatalizadores de iridio e rodio.

Coas condicións óptimas en man, explorouse o alcance do proceso para a xeración de dihidro-1H-pirrolizinas e policiclos relacionados. Para a nosa satisfacción, o noso método representa a primeira cicloisomerización enantioselectiva catalizada por metais baseada nunha activación C–H que permite construír aneis de cinco, seis ou sete membros, con excelentes valores de er. O método permite a construción de moléculas con centros estereoxénicos cuaternarios e terciarios incrustados en sistemas heteropolicíclicos fusionados con indois e pirrois. En todos os casos, obtivéronse rendementos e enantioselectividades excelentes (ver **Esquema 26**).



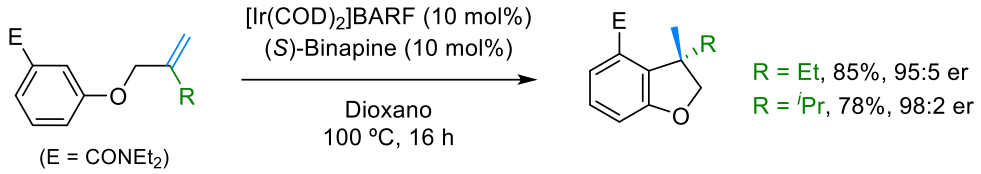
***Esquema 26**: Hidroarilación altamente enantioselectiva de alquenos catalizada por Ir.*

Ademais, a metodoloxía tolera o uso de alquenos trisubstituídos como mestura ~1:1 de isómeros *E/Z*, con bos rendementos e excelentes valores de er. Polo que sabemos, a posibilidade de obter estes produtos con alta ee, independentemente da configuración do alqueno trisubstituído inicial, carece de precedentes en protocolos de hidrocarbonación relacionados (**Esquema 27**).



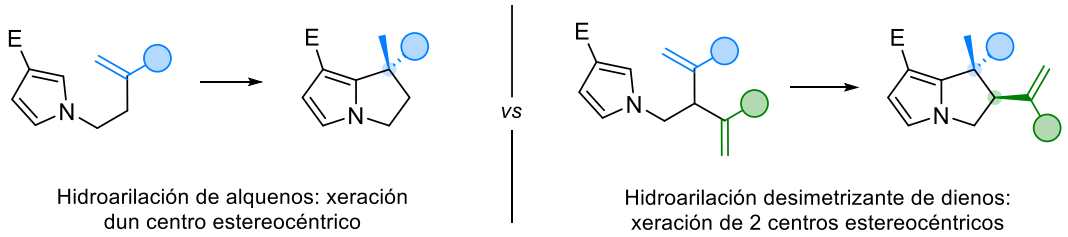
Esquema 27: *Cicloisomerización catalizada por Ir de pirrois unidos a alquenos trisubstituídos.*

De xeito alentador, o catalizador derivado de [Ir(COD)$_2$]BARF e Binapine tamén facilitou a ciclización de sistemas aromáticos unidos a alquenos, obtendo os desexados dihidrobenzofuranos con bos rendementos e relacións enantioméricas de até 98:2 (**Esquema 28**).



Esquema 28: *Cicloisomerización catalizada por Ir para a síntese de dihidrobenzofuranos.*

A metodoloxía descrita anteriormente é moi versátil; porén, a súa natureza *exo*-selectiva impide, *a priori*, a xeración de máis dun centro estereoxénico dentro do anel recentemente xerado. Para superar esta limitación, preguntámonos se esta tecnoloxía podería adaptarse aínda máis para construír produtos que contivesen múltiples centros estereoxénicos dentro do anel formado, combinando a cicloisomerización cun proceso concomitante de desimetrización dun centro proquiral (**Esquema 29**).

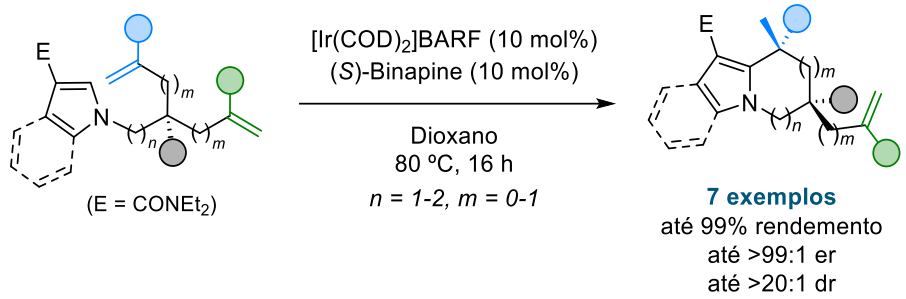


Esquema 29*: Estratexia xeral para a xeración de 2 centros estereoxénicos mediante desimetrización de substratos dienilo-pirrol.*

Descubrimos que o catalizador quiral pode distinguir entre os dous alquenos do precursor proquiral mantendo unha excelente selectividade facial na inserción do alqueno. Así, pódese obter un conxunto de derivados de tetrahidroindolizina e dihidropirrolizina, con estereocentros contiguos ou non contiguos, con bos rendementos,

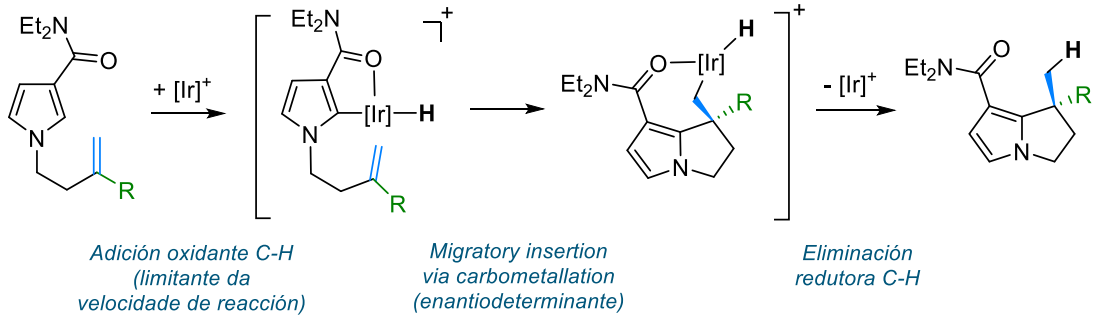
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diastereoselectividades e enantioselectividades (maiores a 8:2 dr e ata 99:1 er, **Esquema 30**).



Esquema 30 *Desimetrización enantioselectiva de precursores de dienos proquirais*

En canto ao mecanismo, propoñemos unha adición oxidante inicial, seguida dunha carbometalación e unha eliminación redutora final (ver **Esquema 31**). Para aclarar os factores que contribúen á reactividade observada e á alta enantioselectividade, o Dr. Martín Calvelo realizou estudos mecanísticos computacionais. En xeral, os resultados teóricos aliñáronse coas condicións experimentais e co efecto isotópico cinético (KIE, polas súas siglas en inglés) observado experimentalmente, confirmando que a adición oxidante do enlace C–H ao complexo de Ir(I) é o paso determinante da velocidade da reacción. Ademais, o perfil enerxético calculado apoia a inserción migratoria do alqueno como o paso determinante da enantioselectividade, consistente cos altos valores enantioméricos obtidos experimentalmente e coa configuración absoluta do enantiómero maioritario.



Esquema 31*: Mecanismo proposto baseado en experimentos de marcaxe con deuterio e estudos computacionais DFT.*

Hidroarilacións intramoleculares rexioselectivas catalizadas por Iridio(I) en pirrois e indois unidos a alenos

Os alenos son unha clase de moléculas insaturadas que posúen dous dobres enlaces C–C adxacentes e que emerxeron como reactivos altamente versátiles na síntese orgánica. A súa configuración estrutural única confírelles unha reactividade superior aos alquenos, coa vantaxe adicional de que os produtos adoitan conservar un dobre enlace para unha posterior elaboración. Porén, os alenos presentan problemas de quimoselectividade e regioselectividade que poden complicar a súa reactividade (ver **Figura 4**).

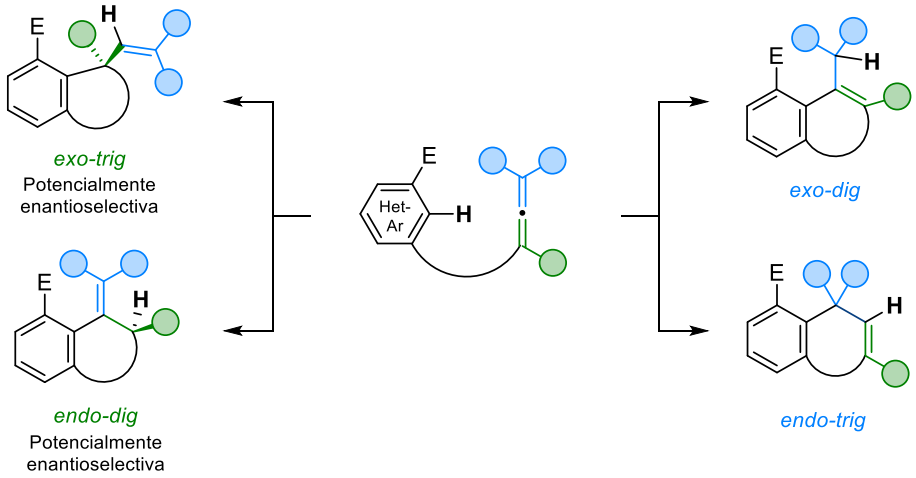


***Figura 4**: Posibles rexioisómeros resultantes dunha hidroarilación intramolecular de alenos.*

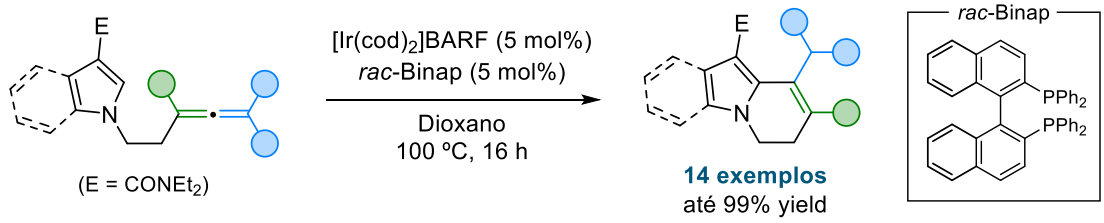
Nos últimos anos desenvolveuse unha ampla variedade de reaccións de hidroarilación que implican alenos. Entre estas metodoloxías, aquelas que proceden a través de substitucións aromáticas electrofílicas ou activacións de enlaces C–H mediante procesos de metalación-desprotonación concertada (CMD) son particularmente prevalentes. Os procesos de hidroarilación de alenos baseados en secuencias de adición oxidante/inserción migratoria/eliminación redutora son extremadamente escasos. Antes de comezar a nosa investigación só se publicaron algúns exemplos intermoleculares que permiten acceder a produtos lineais aquirais.

Estabelecemos como obxectivo o desenvolvemento dunha nova hidroarilación intramolecular catalizada por metais de transición baseada na activación de enlaces C–H de precursores heteroaromáticos a alenos. Esta reacción podería xerar diferentes tipos de produtos, dependendo de se a ciclación ocorre nunha forma *endo* ou *exo* e de cal dos dobres enlaces do aleno sofre a adición. Ademais do estudo da quimoselectividade e rexioselectividade nestas cicloisomerizacións, tamén se exploraron posíbeis variantes asimétricas empregando catalizadores quirais de iridio(I),

debido á falta de precedentes para construír os produtos esperados de maneira enantioselectiva.

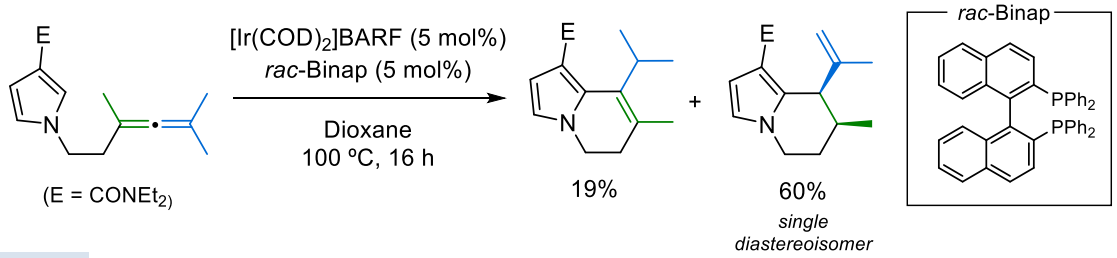
Preparouse un substrato modelo que contiña dúas unidades de metileno entre o pirrol e o aleno para avaliar a viabilidade da cicloisomerización. Durante o proceso de optimización, probáronse diferentes ligandos, precatalizadores de iridio, disolventes, temperaturas e grupos directores. Empregando Binap como ligando, xunto con [Ir(COD)$_2$]BARF, atopamos a formación selectiva dun produto que resulta dunha hidroarilación *exo* do dobre enlace distal do aleno. Isto é relevante porque esta clase de produtos non se pode obter mediante hidrocarbonacións análogas de pirrois unidos a alquinos, que adoitan xerar produtos con alquenos exocíclicos (**Esquema 32**).

Explorouse a xeneralidade do método con outros substratos de pirrol-aleno. Descubrimos que a reacción tolera alenos mono-, di- e trisubstituídos, xerando dihidroindolizinas cun excelente rendemento. Os precursores que conteñen un indol no canto do pirrol demostraron ser substratos viables para a reacción. Como resultado, obtivéronse dihidropirido[1,2-a]indois con plena selectividade e bos rendementos.



***Esquema 32**. Alcance da hidrocarbonación exo-selectiva de indois unidos a alenos.*

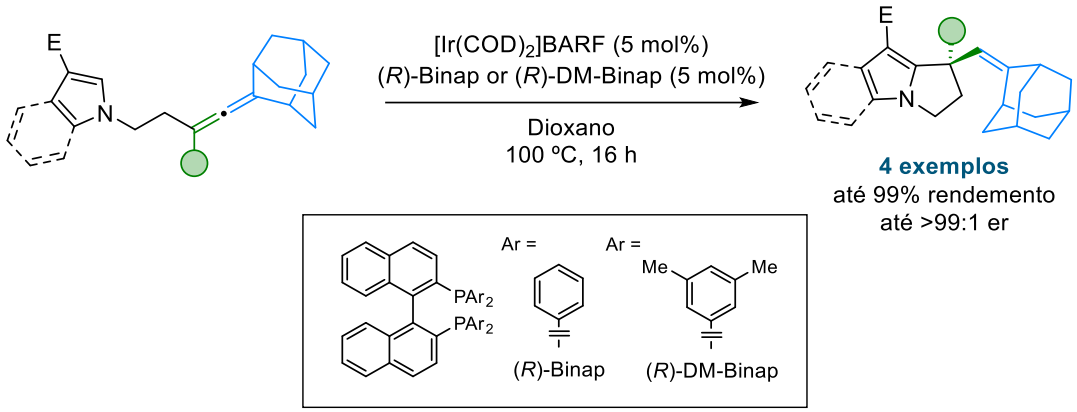
Sorprendentemente, cando os alenos tetrasubstituídos foron sometidos ás condicións estándar de reacción con Binap, observouse a formación de tetrahidroindolizinas quirais inesperadas como produtos predominantes e como únicos diastereoisómeros (**Esquema 33**). Dada a relevancia desta nova transformación desde unha perspectiva sintética e mecanística, a exploración desta reactividade de precursores de alenos tetrasubstituídos foi abordada nun capítulo separado desta tese.



***Esquema 33**: Resultado da reacción dun precursor que contén un aleno tetrasubstituído cun enlazador de dous metilenos.*

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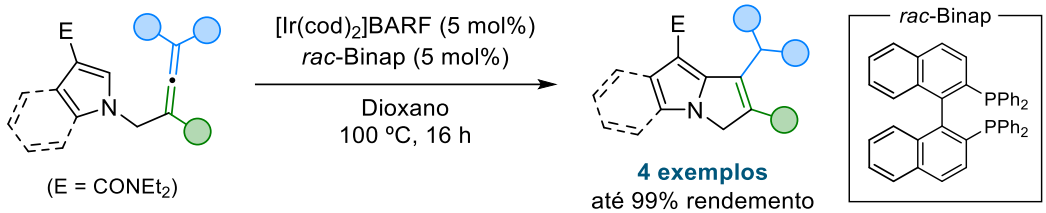
Alén disto, ao probar precursores de alenos con maior impedimento estérico mediante a introdución de viniliden-adamantanos, observamos un cambio na selectividade. Neste caso, a adición *exo* selectiva a través do dobre enlace interno permitiu acceder a 2,3-dihidropirrolizinas quirais con excelentes enantioselectividades empregando (*R*)-Binap ou (*R*)-DM-Binap como ligandos (**Esquema 34**).



Esquema 34: *Alcance da hidroarilación enantioselectiva de substratos que conteñen adamantano.*

A continuación, analizouse a influencia da lonxitude da cadea que conecta o pirrol co aleno. Preparáronse diferentes precursores con unha ou tres unidades de metileno.

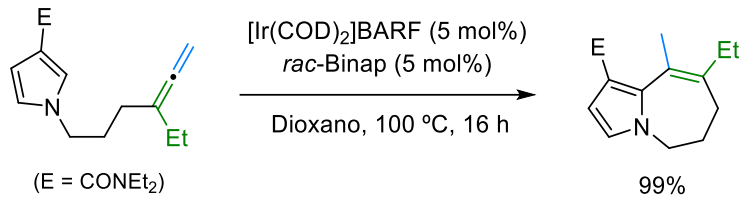
No caso de substratos cunha unidade de metileno, observouse a formación selectiva de produtos resultantes da adición *exo* ao dobre enlace distal, independentemente do patrón de substitución do aleno (**Esquema 35**).



Esquema 35*. Hidrocarbonación exo-selectiva de pirrois e indois unidos a alenos para formar aneis de 5 membros.*

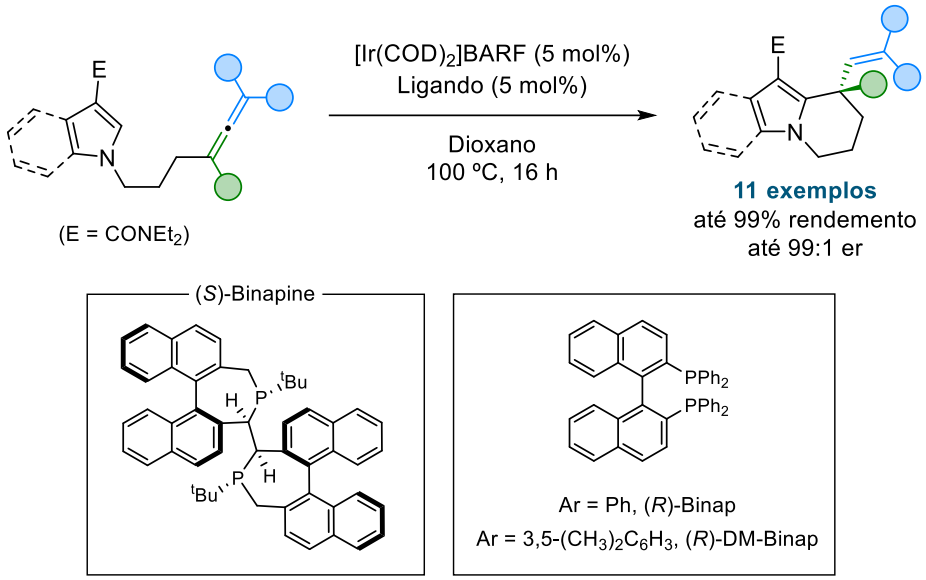
Con substratos que carecen de substituíntes no carbono distal do aleno e que conteñen tres unidades de metileno, tamén se observou a adición a través do dobre enlace distal (**Esquema 36**).

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***Esquema 36**. Hidrocarbonación de pirrois unidos a alenos con tres unidades de metileno.*

Porén, cando se empregaron substratos con substituíntes na posición terminal do aleno, a reacción procede mediante a adición *exo*-selectiva a través do dobre enlace interno. Empregando ligandos quirais como Binapine ou derivados de Binap, pódense obter tetrahidroindolizinas quirais con centros estereoxénicos vinil-substituídos cunha boa enantioselectividade (**Esquema 37**).



***Esquema 37**. Hidrocarbonación exo-selectiva de pirrois e indois unidos a alenos. Algúns resultados foron obtidos en colaboración con Alejandro Rey.*

Para aclarar os factores que contribúen á selectividade nestas reaccións, o Dr. Martín Calvelo realizou estudos mecanísticos computacionais. Os cálculos aliñáronse cos achados experimentais e permitíronnos racionalizar os factores que gobernan a selectividade.

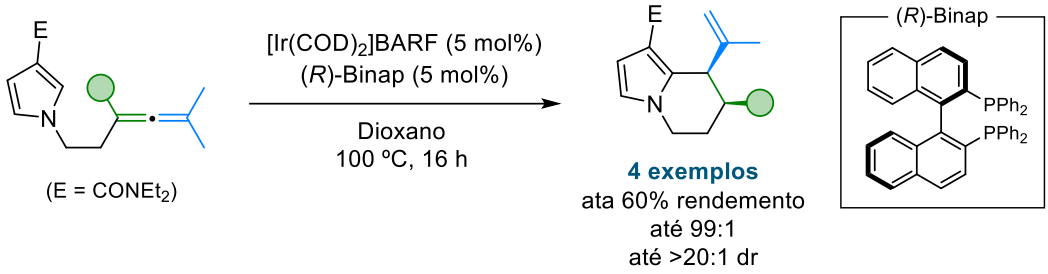
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Reaccións en cascada catalizadas por Iridio(I) en pirrois e indois unidos a alenos

Como se indicou anteriormente, os substratos que conteñen alenos tetrasubstituídos e dúas unidades de metileno na cadea conectora, en presenza do catalizador Ir/Binap a 100 ºC, producen produtos quirais con múltiples centros estereoxénicos e moi bos valores de ratios enantioméricos e diastereoméricos. Este proceso pode implicar pasos de hidroxenación e deshidroxenación en cascada despois da ciclación inicial.

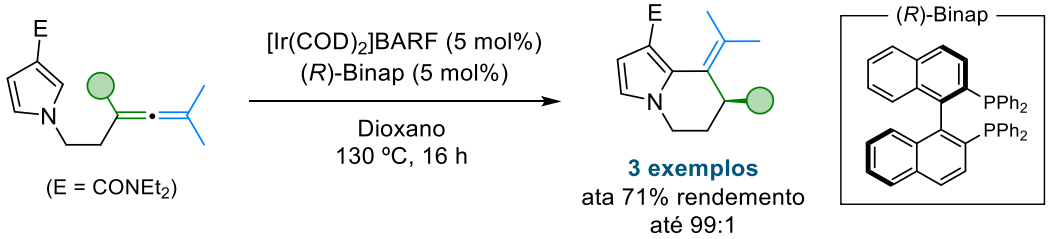
A relevancia dos produtos, a diastereoselectividade da reacción e os intrigantes aspectos mecanísticos da transformación levaron a profundar neste fenómeno e tentar desenvolver un método catalítico xeral baseado neste hipotético proceso en cascada.

Probáronse outros substratos con alenos tetrasubstituídos para avaliar a xeneralidade da reacción. Cando as reaccións se levaron a cabo a 100 ºC, obtivéronse as esperadas tetrahidroindolizinas quirais con dous centros estereoxénicos, con rendementos moderados pero excelente estereoselectividade (**Esquema 38**).



Esquema 38: *Reacción catalizada por Ir a 100 ºC de pirrois-alenos tetrasubstituídos para obter tetrahidroindolizinas quirais.*

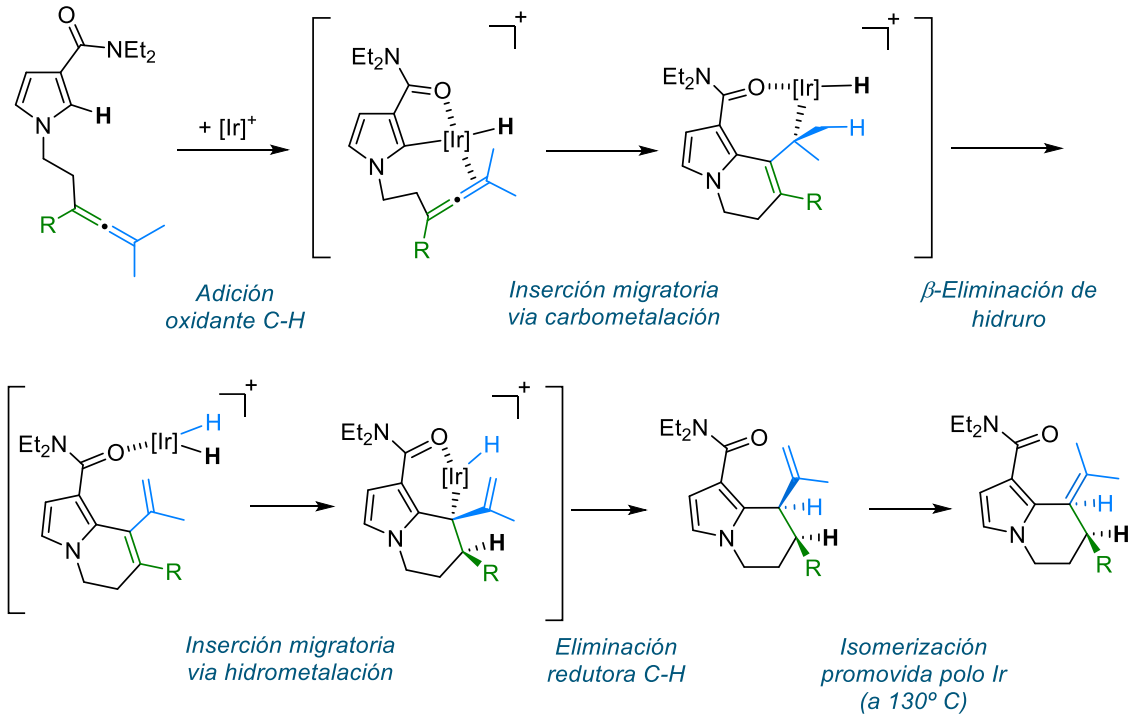
Ademais, cando a reacción se levou a cabo a 130 ºC, os principais produtos obtidos foron tetrahidroindolizinas quirais que conteñen alquenos *exo* (**Esquema 39**). Experimentos de control apoian que estes produtos xorden dunha isomerización do dobre enlace dos produtos mostrados no **Esquema 39**.



Esquema 39: *Reacción catalizada por Ir a 130 ºC de pirrois-alenos tetrasubstituídos para obter tetrahidroindolizinas quirais.*

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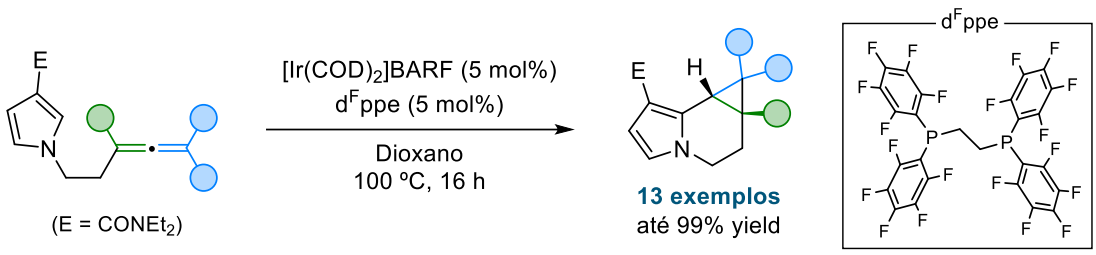
Os cálculos DFT e experimentos de marcaxe con deuterio apoian un mecanismo que implica unha adición oxidante do enlace C–H, seguida dunha carbometalación *exo*-selectiva no dobre enlace distal do aleno. Posteriormente, hai unha β-eliminación de hidruro que xera un intermedio de bis-hidruro de Ir que mantén o iridio coordinado ao carbonilo. Esta especie de bis-hidruro podería transferir os átomos de hidróxeno ao dobre enlace do núcleo da dihidroindolizina mediante unha secuencia de hidrometalación/eliminación redutora do enlace C–H, liberando finalmente o produto observado (**Esquema 40**).



***Esquema 40**: Mecanismo proposto para a reacción en cascada hidroarilación-transferencia de hidróxeno de pirrois-alenos.*

Durante a optimización desta reacción en cascada, descubrimos inesperadamente que, cando os mesmos precursores tetrasubstituídos se trataron baixo as condicións estándar de hidrocarbonación promovida por iridio, pero empregando o ligando bisfosfina fluorada d^Fppe, formáronse de maneira selectiva tetrahidroindolizinas fusionadas con ciclopropanos. A reacción tolera un carbociclo no carbono distal do aleno, permitindo a construción de diferentes arquitecturas espirocíclicas (**Esquema 41**).

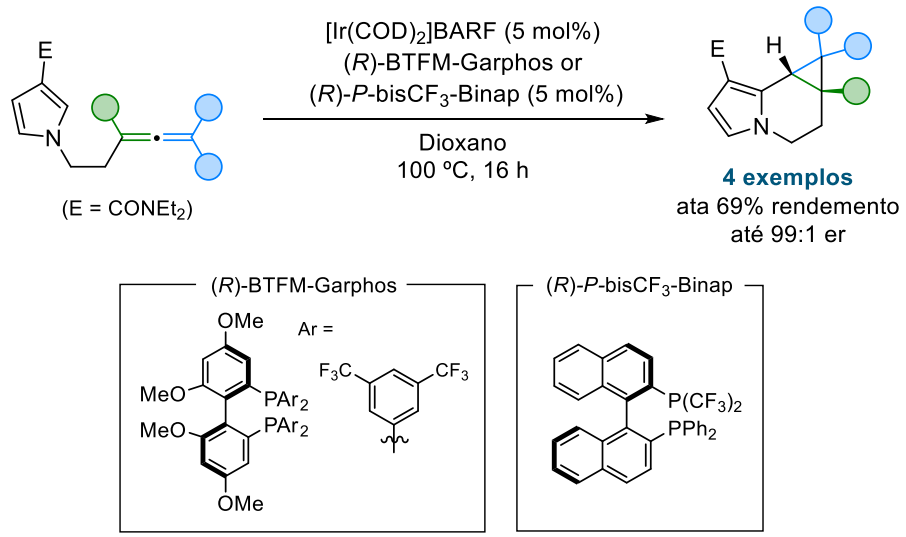
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***Esquema 41**: Reacción en cascada hidroarilación/ciclopropanación catalizada por Ir de pirrois-alenos tetrasubstituídos.*

Motivados pola prevalencia de heterociclos quirais fusionados con ciclopropanos en compostos biorelevantes, realizouse unha avaliación preliminar da viabilidade dunha variante enantioselectiva desta transformación empregando ligandos fosfina quirais electrónicamente deficientes.

Empregando ligandos electrónicamente deficientes como (*R*)-BTFM-Garphos ou o ligando quiral (*R*)-*P*-bisCF$_3$-Binap, inicialmente desenvolvido por Togni, diferentes pirrois-alenos tetrasubstituídos convertéronse nas desexadas tetrahidroindolizinas fusionadas con ciclopropano, obtendo rendementos de moderados a bos, e proporcións enantioméricas de ata 99:1 (**Esquema 42**).

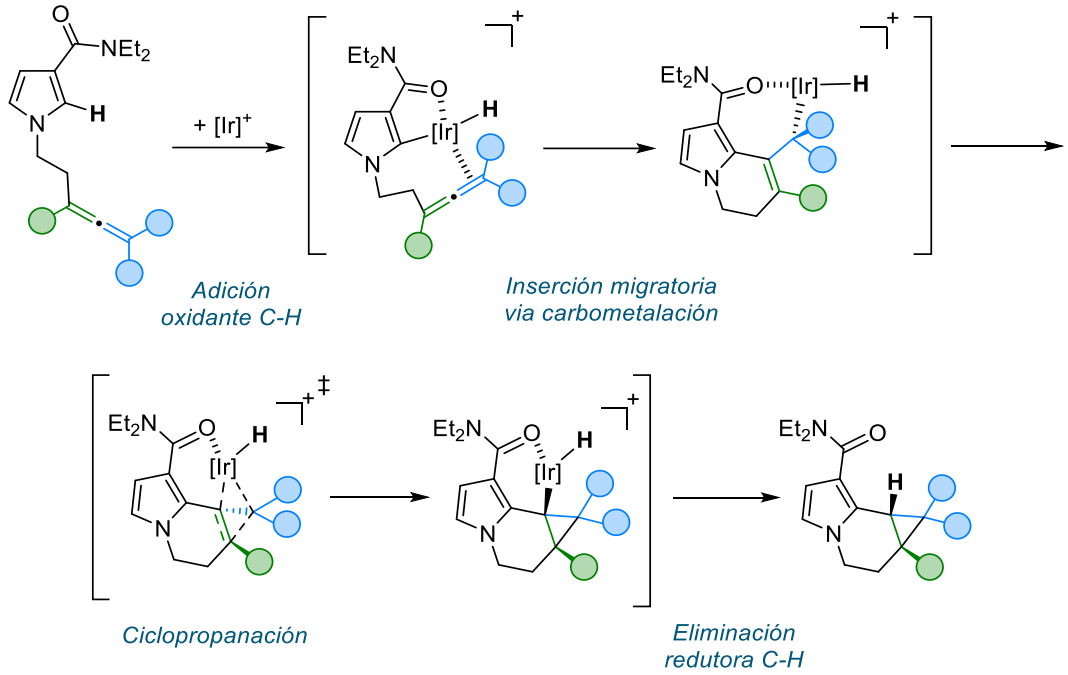


***Esquema 42**: Hidroarilación/ciclopropanación enantioselectiva catalizada por Ir de pirrois-alenos tetrasubstituídos.*

En canto ao mecanismo, propoñemos que despois da adición oxidante e carbometalación no dobre enlace distal do aleno, o centro de iridio podería migrar desde o carbono terminal do antigo aleno ao central, coa formación concomitante dun anel de ciclopropano. Tras unha eliminación redutora final, os produtos observados son

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liberados (ver **Esquema 43**). Os estudos computacionais apoiaron este escenario e confirmaron o papel crucial do ligando fluorado neste proceso.



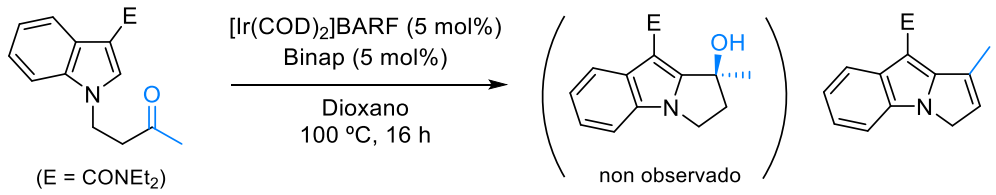
***Esquema 43**: Mecanismo proposto para a reacción en cascada hidroarilación-ciclopropanación de pirrois-alenos.*

Hidroarilación intramolecular de sistemas carbonílicos catalizada por Iridio(I)

A hidroarilación directa de cetonas representa unha estratexia altamente económica en termos atómicos para construír alcois terciarios, aínda que o número de metodoloxías que implican unha activación inicial de enlaces C(sp^2)–H é moi baixo e adoitan presentar un alcance moi restrinxido. Ademais, o desenvolvemento de variantes enantioselectivas é esencialmente descoñecido.

Por iso, decidimos explorar o uso de precursores pirrol-cetona ou aldehido como sondas para probar a viabilidade destas reaccións empregando catálise por iridio. Este enfoque podería xerar sistemas heterocíclicos quirais que contivesen alcois terciarios e secundarios de maneira enantioselectiva, un motivo estrutural prevalente en produtos naturais.

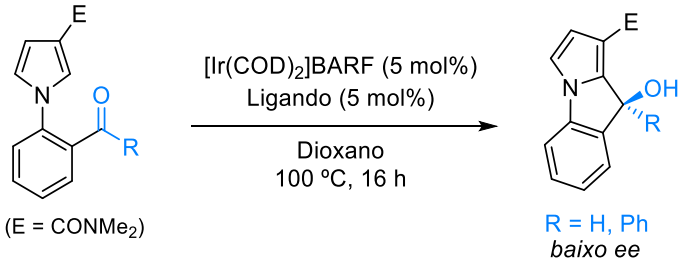
Os nosos estudos comezaron coa preparación dun precursor relacionado cos descritos en capítulos anteriores, pero que contiña unha cetona no canto dun alqueno ou aleno. Os catalizadores formados *in situ* entre [Ir(COD)$_2$]BARF e Binap, previamente empregados para promover hidroarilacións intermoleculares *exo*-selectivas doutros sistemas insaturados, renderon cuantitativamente un pirroloindol aquiral en lugar do inicialmente esperado alcol terciario (ver **Esquema 44**). Este resultado é coherente coas reaccións previamente reportadas que destacan a facilidade do paso de deshidratación.



***Esquema 44**: Ciclo-deshidratación catalizada por Ir dun precursor indol-cetona.*

Dada a aparente selectividade da reacción cara á formación de produtos deshidratados, buscouse preparar un substrato que impedise a deshidratación cara o alqueno *endo*. Desafortunadamente, aínda que se formaron os alcohois cíclicos desexados con bos rendementos, estes obtivéronse de forma racémica (**Esquema 45**).

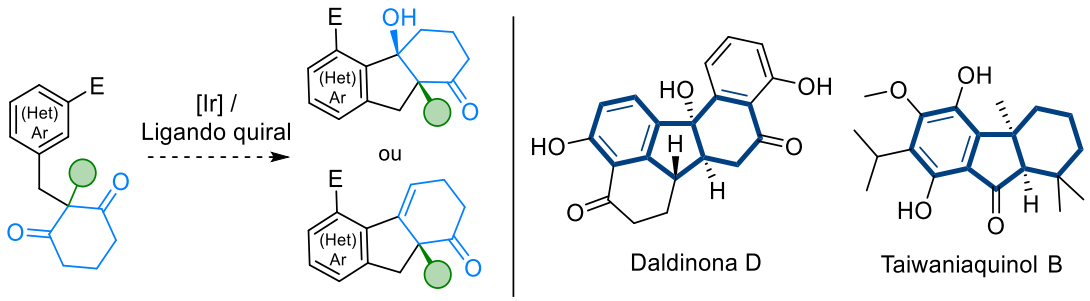
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***Esquema 45**: Hidroarilación intramolecular de carbonilos catalizada por Ir.*

Dados estes resultados, nos que ou ben se perden os centros estereoxénicos ou se obteñen produtos cunha enantioselectividade moi baixa, decidimos explorar unha estratexia de desimetrización con 1,3-dicetonas. O noso traballo previo con alquenos demostrou a viabilidade deste enfoque, e a súa aplicación xeitosa a carbonilos podería levar potencialmente á síntese enantioselectiva de estruturas policíclicas que conteñen centros estereoxénicos cuaternarios, como se representa no **Esquema 46**.

Considerando a prevalencia natural destes motivos e a facilidade de preparación dos precursores necesarios, a nosa investigación neste empeño centrouse en precursores con arilos no canto de heteroarilos. De feito, empregando 1,3-dicetonas cíclicas, puidemos obter facilmente núcleos estruturais presentes en moléculas bioloxicamente relevantes como a Daldinona C e o Taiwaniaquinol B, representadas no **Esquema 46**.

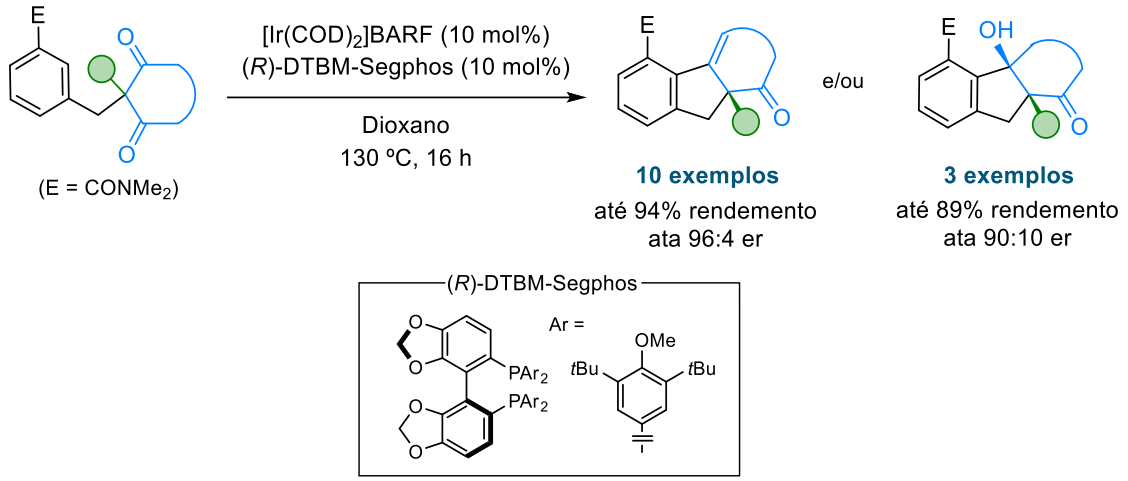


***Esquema 46**: Esquema xeral da estratexia de hidroarilación desimetrizante e produtos naturais representativos que conteñen andamiaxes similares.*

Aínda que os experimentos preliminares empregando dietilamida como grupo director proporcionaron rendementos moi baixos; ao cambiar o grupo director de dietilamida a dimetilamida, logramos alcanzar conversións completas. Atopamos que, empregando DTBM-Segphos en combinación con [Ir(COD)$_2$]BARF, a 130 ºC en dioxano, puidemos alcanzar ata un 94% de rendemento e un 90:10 er. Con estas condicións, decidimos explorar a xeneralidade do proceso. Illáronse varios hexahidrofluorenos que conteñen centros carbonados cuaternarios a partir das correspondentes dicetonas con diferentes patróns de substitución (**Esquema 47**).

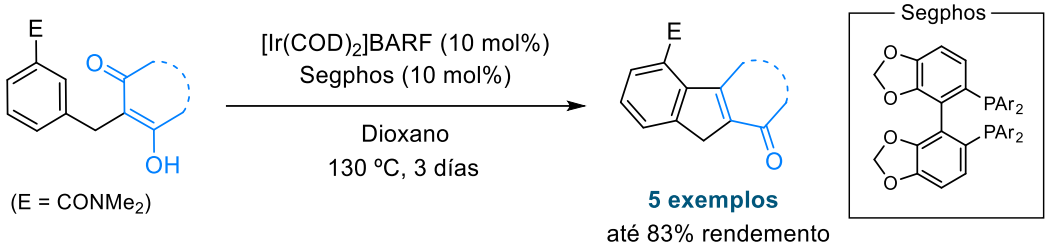
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Curiosamente, cando se empregaron dicetonas específicas, especialmente as de 5 membros, non se produciu a deshidratación, permitindo illar produtos que contiñan múltiples centros estereoxénicos con diastereoselectividade completa. Este método constitúe a primeira hidroarilación de sistemas carbonílicos catalizada por iridio acoplada a un proceso de desimetrización dun centro proquiral.



***Esquema 47**: Hidroarilación desimetrizante catalizada por Ir de 1,3-dicetonas.*

Tamén examinamos varios substratos que carecen de substituíntes na posición 2 da 1,3-dicetona. Nestes casos, a deshidratación concomitante ten lugar, xerando indenos aquirais (**Esquema 48**).



***Esquema 48**: Indenos aquirais mediante ciclo-deshidratación catalizada por Ir.*

Os esforzos actuais céntranse na expansión da xeneralidade deste método e na súa aplicabilidade na síntese de moléculas biorelevantes que conteñen estes andamiaxes tricíclicos.

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2

Introduction



2.1. Organic synthesis

The discovery of fire, humanity's first controlled chemical process, ignited a spark of curiosity that continues to fuel our exploration of the world. Rooted in our cultural and genetic heritage is the desire to explain the phenomena around us. The development of science has allowed us not only to understand these processes but also to harness their power for human benefit.

Synthetic chemistry is the art and science of constructing molecules, whether natural or designed, from simpler or more accessible atoms and molecules. The first organic synthesis is often traced back to Wöhler's discovery in 1828, who synthesized urea from inorganic precursors.[1] This milestone challenged the prevailing vitalism theory and demonstrated that organic molecules could be synthesized from inorganic precursors.

Organic synthesis has been a cornerstone of modern chemistry, enabling us to replicate, modify, and even improve the molecules found in nature. From pharmaceuticals to dyes, countless substances essential to our lives have been produced through synthetic methods. Moreover, organic synthesis plays a crucial role in confirming or revising the structures of natural products, providing valuable insights into their biological functions and potential applications.[2]

Over the last two centuries, chemists have developed a vast arsenal of techniques and strategies to create molecules that were once thought to be exclusively natural, many of which hold significant pharmaceutical or industrial value.[3] Notable milestones include Fischer's synthesis of glucose in 1890, and the synthesis of camphor by Komppa and Perkin between 1903 and 1904. These achievements not only expanded our chemical repertoire but also paved the way for future innovations.

Beyond its practical applications, the synthesis of natural products has served as a fertile ground for the development of new chemical methods. The challenges posed by complex natural molecules have driven chemists to devise more efficient, selective, and sustainable synthetic strategies.

Today, organic chemistry goes far beyond replicating nature. Many compounds are designed to fulfil specific functions. However, the total synthesis of natural products constitutes the perfect playground to showcase the power and versatility of modern synthetic chemistry.

[1] F. Wöhler, *Ann. Phys. Chem.*, **1828**, *88*, 253–256.
[2] K. C. Nicolaou, S. Rigol, R. Yu, *CCS Chem.*, **2019**, *1*, 3–37.
[3] K. C. Nicolaou, *Angew. Chem. Int. Ed.*, **2013**, *52*, 131–146.

R. B. Woodward, who was awarded the Nobel Prize in 1965, made great contributions to the synthesis of complex natural products such as quinine,[4] cholesterol,[5] strychnine,[6] lysergic acid,[7] chlorophyll,[8] and vitamin B_{12}.[9] Woodward's syntheses were often described as having an element of art, and since then, synthetic chemists have always sought elegance as well as utility in synthesis. Other remarkable examples include the total synthesis of the anticancer drug Taxol in 1994,[10] and the synthesis of antibiotic Vancomycin in 1999 by Nicolaou.[11]

Throughout the development of synthetic chemistry, the pursuit of more efficient and sustainable processes has become increasingly important. This new perspective in organic chemistry emphasizes not just achieving target molecules at any cost but also striving for processes that conserve the maximum number of atoms from the starting materials (atom economy),[12] reduce the number of synthetic steps (step economy)[13] and minimize the need for isolation or purification of intermediates (pot economy).[14]

While these concepts are related to economic interests like saving time, effort, and cost, they also align well with the principles of **green chemistry**.[15] These principles include waste reduction, maximizing **atom economy**, designing safer chemical syntheses and products, improving energy efficiency, using renewable feedstocks, avoiding protecting groups, employing **catalysts** instead of stoichiometric reagents, creating biodegradable chemicals, preventing pollution, and minimizing the risk of accidents. In line with these principles, we, as organic chemists, aim to generate high molecular complexity from safe, simple, and readily available starting materials, with minimal waste, while being as environmentally friendly as possible.

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[4] R. B. Woodward, W. V. E. Doering, *J. Am. Chem. Soc.*, **1945**, *67*, 860–874.

[5] R. B. Woodward, K. Bloch, *J. Am. Chem. Soc.*, **1953**, *75*, 2023–2024.

[6] R. B. Woodward, M. P. Cava, W. D. Ollis, A. Hunger, H. U. Daeniker, K. Schenker, *J. Am. Chem. Soc.*, **1954**, *76*, 4749–4751.

[7] E. C. Kornfeld, E. J. Fornefeld, G. B. Kline, M. J. Mann, D. E. Morrison, R. G. Jones, R. B. Woodward, *J. Am. Chem. Soc.* 1956, **78**, 3087–3114.

[8] R. B. Woodward, W. A. Ayer, J. M. Beaton, F. Bickelhaupt, R. Bonnett, P. Buchschacher, H. Volz *et al.*, *J. Am. Chem. Soc.*, **1960**, *82*, 3800–3802.

[9] R. B. Woodward, *Pure Appl. Chem.*, **1973**, *33*, 145–178.

[10] K. C. Nicolaou, Z. Yang, J. J. Liu, H. Ueno, P. G. Nantermet, R. K. Guy, C. F. Claiborne, J. Renaud, E. A. Couladouros, K. Paulvannan, E. J. Sorensen, *Nature*, **1994**, *367*, 630–634.

[11] K. C. Nicolaou, H. J. Mitchell, N. F. Jain, N. Winssinger, R. Hughes, T. Bando, *Angew. Chem. Int. Ed.*, **1999**, *38*, 240–244.

[12] B. M. Trost, *Science*, **1991**, *254*, 1471–1477.

[13] P. A. Wender, M. P. Croatt, B. Witulski, *Tetrahedron*, **2006**, *62*, 7505–7511.

[14] Y. Hayashi, *Chem. Sci.*, **2016**, *7*, 866–880.

[15] H. C. Erythropel, J. B. Zimmerman, T. M. de Winter, L. Petitjean, F. Melnikov, C. H. Lam, A. W. Lounsbury, K. E. Mellor, N. Z. Janković, Q. Tu, L. N. Pincus, M. M. Falinski, W. Shi, P. Coish, D. L. Plata, P. T. Anastas, *Green Chem.*, **2018**, *20*, 1929–1961.

2.2. Catalysis

Some substances called catalysts accelerate a chemical reaction by providing an alternative reaction pathway with a lower activation energy, without being consumed in the process and without changing the thermodynamic properties of the reaction (see **Figure 5**).

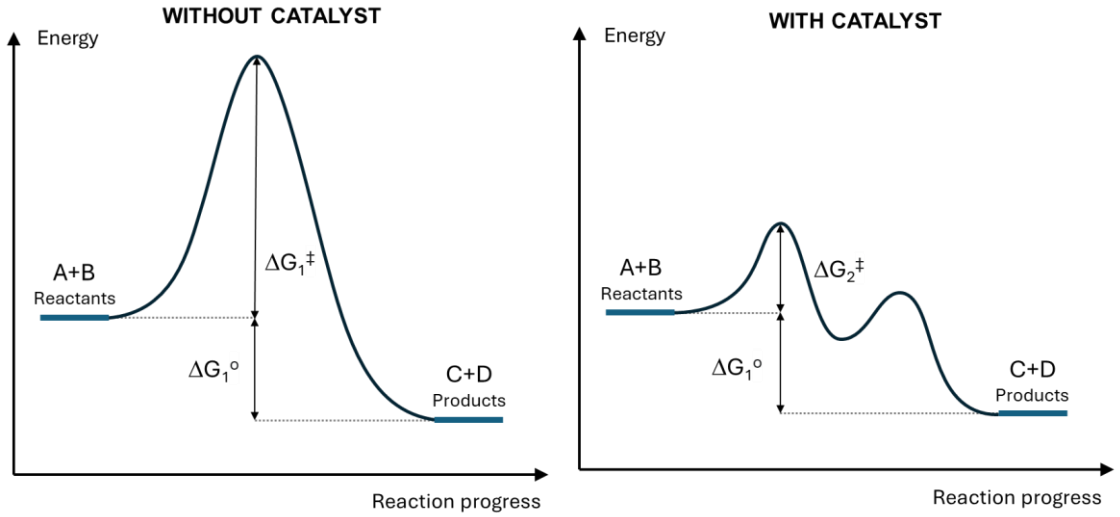


***Figure 5**: Example of a reaction energy profile without catalyst (left), and in the presence of a catalyst (right).*

Catalysis is broadly classified as homogeneous, when the catalyst and the reactants are in the same phase, or heterogeneous, when the catalyst is in a different phase than the reactants. However, catalysis can also be divided into subcategories depending on the nature of the catalyst:

- Biocatalysis: Involves enzymes as catalysts and is crucial in biological processes. Enzymes are highly specific and efficient, operating under mild conditions and in a complex environment.[16]
- Organocatalysis: Based on the use of organic molecules as catalysts.[17]
- Organometallic Catalysis: Involves organometallic compounds, particularly those containing transition metals, as catalysts.[18]

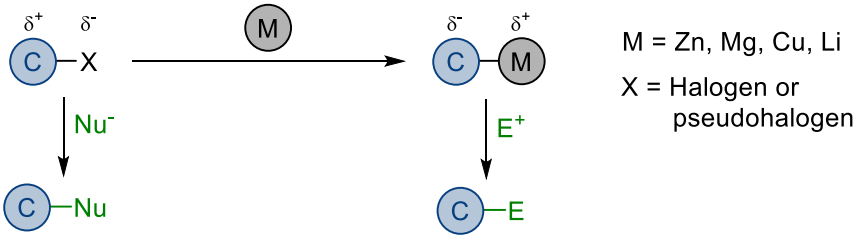
[16] K. Drauz, H. Waldmann. *Enzyme Catalysis in Organic Synthesis*. Wiley-VCH, Weinheim, **2002**.
[17] M. T. Reetz, B. List, B. S. Jaroch, H. Weinmann. *Organocatalysis*. Springer-Verlag, Berlin, **2008**.
[18] R. H. Crabtree, *The Organometallic Chemistry of Transition Metals*. Wiley-Interscience, New Jersey, **2005**.

2.2.1. Organometallic chemistry and synthetic relevance

Organometallic chemistry is formally described as the study of compounds that contain metal-carbon bonds. However, advances in this field are in close relationship with other metal-based compounds formed by hydrides or alkoxides, so it is difficult to trace a define line between inorganic and organometallic chemistry.

The platinum complex $K[PtCl_3(C_2H_4)]$, prepared in 1827, is considered as the first organometallic compound.[19] This discovery occurred almost simultaneously to the urea synthesis by Wöhler. However, the use of organometallic compounds in organic chemistry just started in 1849, when Frankland discovered organozinc compounds and their reactivity towards organic molecules.[20]

Incorporating metals into organic molecules introduces new reactivity patterns that can be exploited in synthesis. For example, by its ability to reverse the polarity (*umpolung*) of a bond in an electrophilic molecule by forming an organometallic derivative (see **Scheme 49**). A pioneer example is the formation of organomagnesium compounds, discovered by Grignard in the early 20th century,[21] followed by the discovery of organocopper and organolithium compounds.



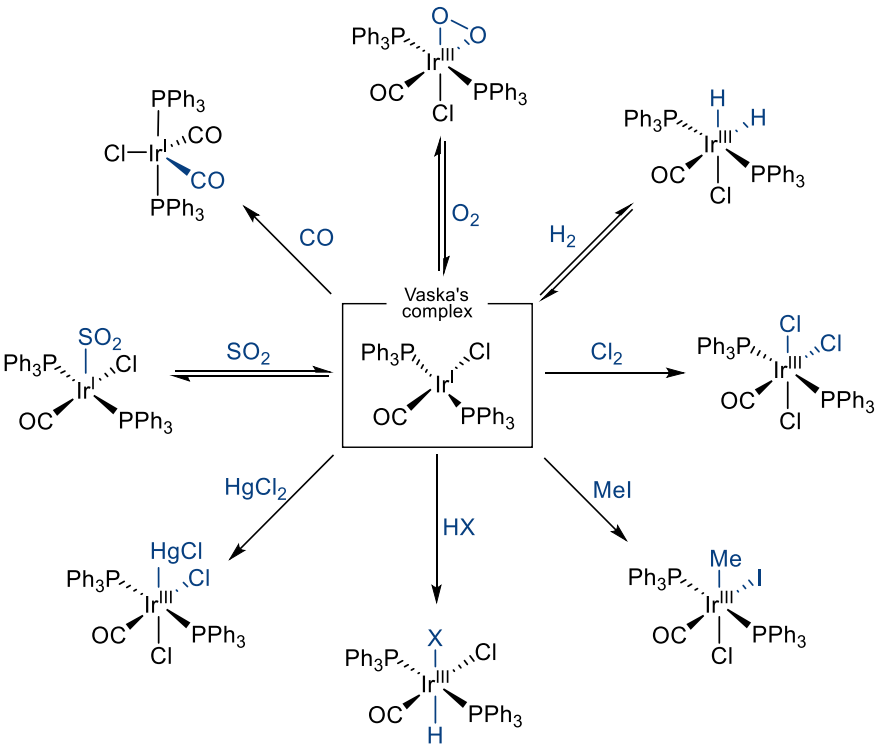
***Scheme 49**: Polarity inversion of organohalides through formation of organometallic species.*

As organometallic chemistry developed, the significant utility of metal complexes in synthetic chemistry became increasingly understood. Transition metals, with their ability to change between different oxidation states, enable oxidation-reduction processes in a wide range of transformations. The properties of the metal center within a complex can be modulated by changing its ancillary ligands, allowing the design of new reagents and catalysts for specific reactions. The following section provides a brief overview of the key historical milestones of transition metal complexes and their synthetic applications as catalysts.

[19] W. C. Zeise, *Ann. Phys. Chem.*, **1831**, *97*, 497–541.
[20] E. Frankland, *Liebigs Ann. Chem.*, **1849**, *71*, 171
[21] V. Grignard, *Compt. Rend. Hebd. Séances Acad. Sci.*, **1900**, *130*, 1322–1324.

2.2.2. Organometallic catalysis, brief historical perspective

During the 20th century, the foundations of organometallic catalysis were established. In addition to the previously mentioned contributions of Grignard and Ziegler, some other key chemists deserve a special mention. For instance, in the sixties, Vaska developed the conceptual framework for homogeneous catalysis, with the discovery of the iridium complex $IrCl(CO)(PPh_3)_2$, which is still known as Vaska's complex. This 16-electron species can activate and promote reactions with various species like oxygen or hydrogen, (see **Scheme 50**), which undergo oxidative additions to generate new iridium(III) complexes. These studies defined the bases of this elementary step in organometallic chemistry.[22]



***Scheme 50**: Activation of small molecules by Vaska's complex.*

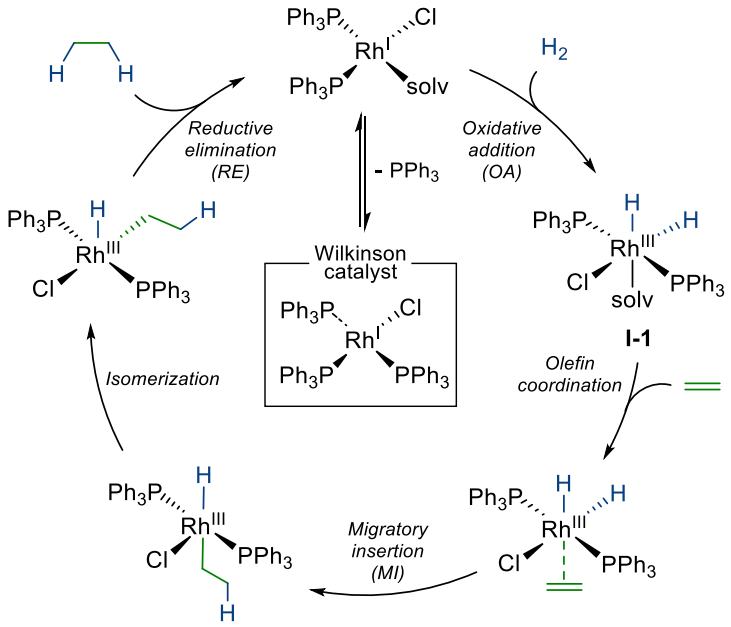
The same year, Wilkinson, Osborn and Coffey independently discovered the complex $RhCl(PPh_3)_3$, which turned out to be an excellent catalyst for the hydrogenation of alkenes and alkynes.[23] The mechanism of hydrogenation was elucidated by Halpern,[24] who proposed an initial oxidative addition (OA) of hydrogen, leading to bishydride rhodium (III) species **I-1**. This intermediate then undergoes migratory insertion (*MI*) of

[22] (a) L. Vaska, *Science*, **1963**, *140*, 809–810. (b) S. J. Laplaca, L. A. Ibers, *J. Am. Chem. Soc.*, **1965**, *87*, 2581–2586. (c) L. Vaska, J. W. DiLuzio, *J. Am. Chem. Soc.*, **1962**, *84*, 679–680. (d) F. DeMartin, N. Mascioccini, *Acta Cryst.*, **1983**, *39*, 1225–1226. (e) L. Vaska, *Science*, **1966**, *152*, 769–771. (f) P. R. Chock, J. Halpern, *J. Am. Chem. Soc.*, **1966**, *88*, 3511–3514.

[23] J. A. Osborn, G. Wilkinson, J. J. Mrowca, *Inorg. Synth.*, **1967**, *10*, 67, *Inorganic Syntheses*, E. L. Muetterties (Ed.).

[24] J. Halpern, *Inorg. Chim. Acta*, **1981**, *50*, 11–19.

the olefin into the M–H bond, ultimately resulting in the formation of the corresponding alkane through a reductive elimination (*RE*) (**Scheme 51**).



***Scheme 51**: Catalytic cycle of olefin hydrogenation catalyzed by Wilkinson complex.*

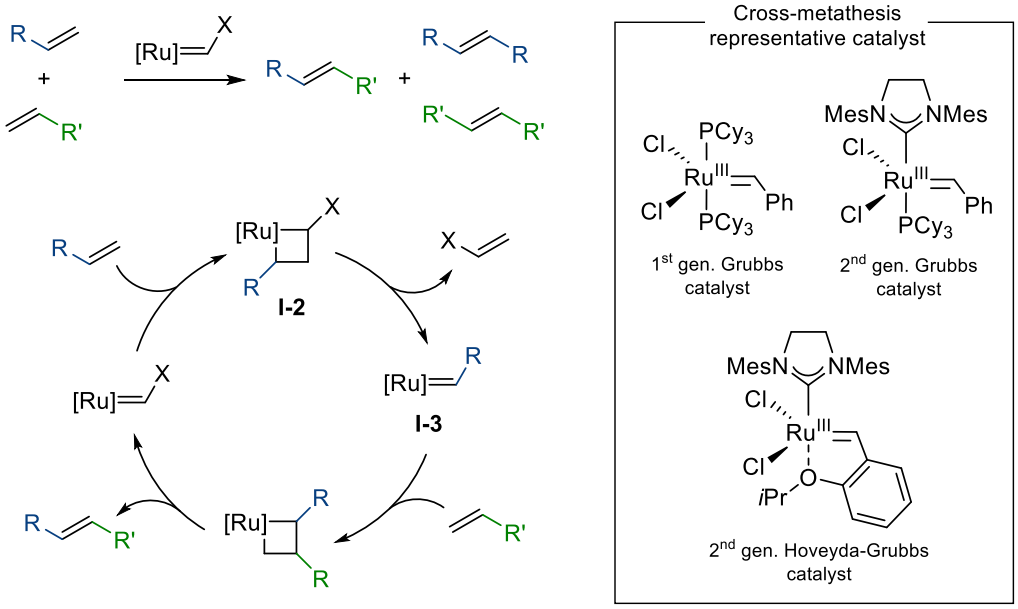
These advancements made by Vaska and Wilkinson highlighted the potential of organometallic catalysis, not only to enhance existing processes but also to develop new transformations that would be impossible with the tools of classical organic chemistry.

The development of metathesis reactions, for which Chauvin, Grubbs and Schrock were awarded the Nobel Prize in Chemistry in 2005, was a key milestone in the history of organometallic catalysis.[25] In this process, an initial metal-carbene species undergoes a [2+2] cycloaddition with an olefin to provide a metallacyclobutane **I-2** that can then evolve to afford a new olefin and another alkylidene species **I-3**. The latter can react with the second olefin through the same process, ultimately producing the final cross-metathesis alkene product (see **Scheme 52**). Molybdenum and especially ruthenium catalysts are widely used in these reactions due to their versatility, efficiency, and stability.[26]

[25] https://www.nobelprize.org/prizes/chemistry/2005/summary/

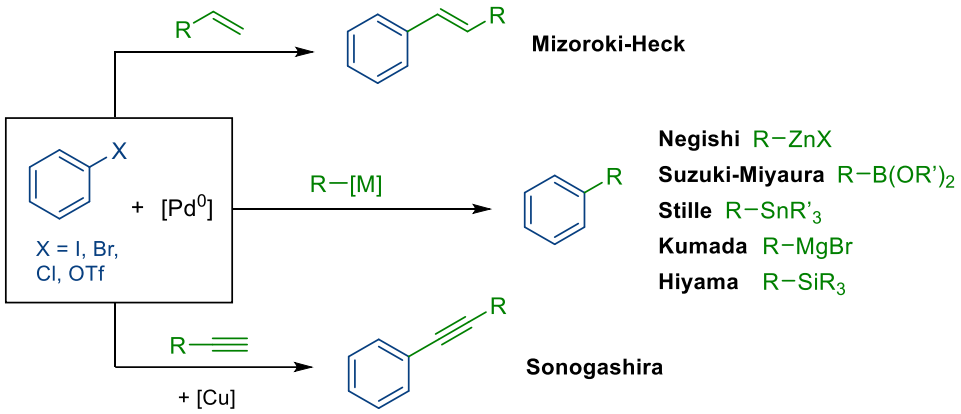
[26] (a) T. M. Trnka, R. H. Grubbs, *Acc. Chem. Res.*, **2001**, *34*, 18–29. (b) S. J. Connon, S. Blechert, *Angew. Chem. Int. Ed.*, **2003**, *42*, 1900–1923. (c) R. Schrock, A. H. Hoveyda, *Angew. Chem. Int. Ed.*, **2003**, *42*, 4592–4633. (d) K. C. Nicolaou, P. G. Bulger, D. Sarlah, *Angew. Chem. Int. Ed.*, **2005**, *44*, 4490–4527. (e) A. Fürstner, *Science*, **2013**, *341*, 1357–1365.

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***Scheme 52**: General mechanism of alkene cross-metathesis and representative catalysts.*

Another milestone in this area was the development of palladium-catalyzed cross-coupling reactions (**Scheme 53**). Heck, Negishi, and Suzuki were awarded the Nobel Prize in Chemistry in 2010 for their contributions in this field.[27]



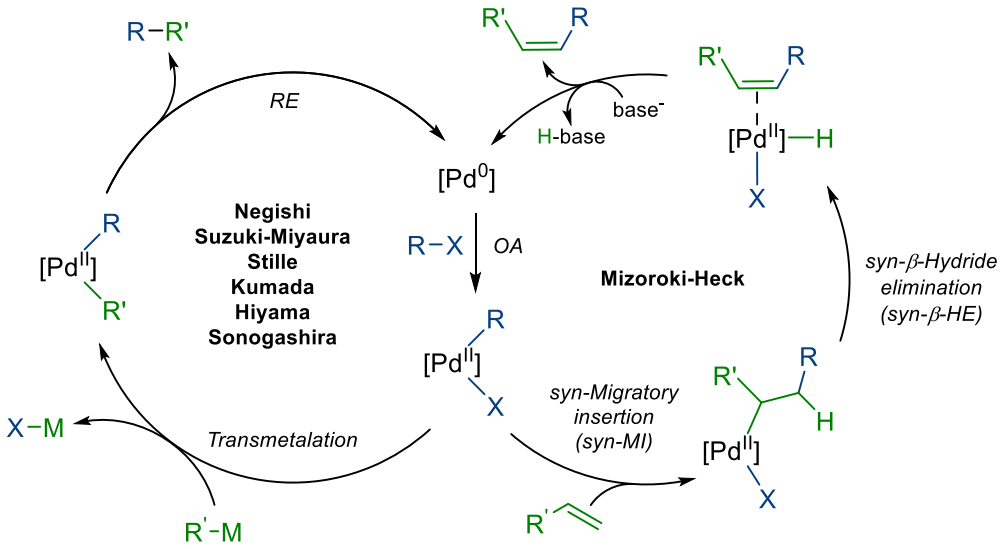
***Scheme 53**: Representative Pd-catalyzed C–C cross couplings reactions.*

The mechanism of the Heck type reactions typically involves the oxidative addition of an aryl halide or pseudohalide to a palladium(0) species. This is followed by the coordination and subsequent insertion of an olefin into the Pd–C bond, and a subsequent β-hydride elimination that enables product formation and the regeneration of the catalytically active species (see **Scheme 54**).

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[27] C. C. C. Johansson Seechurn, M. O. Kitching, T. J. Colacot, V. Snieckus, *Angew. Chem. Int. Ed.*, **2012**, *51*, 5062–5085.

In other palladium-catalyzed couplings, after oxidative addition, a transmetallation step occurs using different organometallic species, before releasing the cross-coupling product by a reductive elimination. Notable examples include the Suzuki-Miyaura cross-coupling (using boron species), as well as the Negishi (M = [Zr]), Kumada (M = [Mg]), Stille (M = [Sn]), Hiyama (M = [Si], and Sonogashira M = [Cu]) reactions (**Scheme 54**).



***Scheme 54**: General mechanisms for the Pd-catalyzed cross-coupling reactions.*

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2.3. Asymmetric synthesis

2.3.1. Chirality and asymmetric synthesis strategies

Molecular chirality refers to a property of certain molecules that have a non-superimposable mirror image. This concept is crucial in chemistry and biology, as the two mirror images, or enantiomers, of a chiral molecule can exhibit dramatically opposite properties. For instance, both enantiomers can have very different smells or, even more crucially, one can have therapeutic effects while the other might be ineffective or even toxic (**Figure 6**). Therefore, controlling enantioselectivity is of primary importance in the preparation of active chiral products.

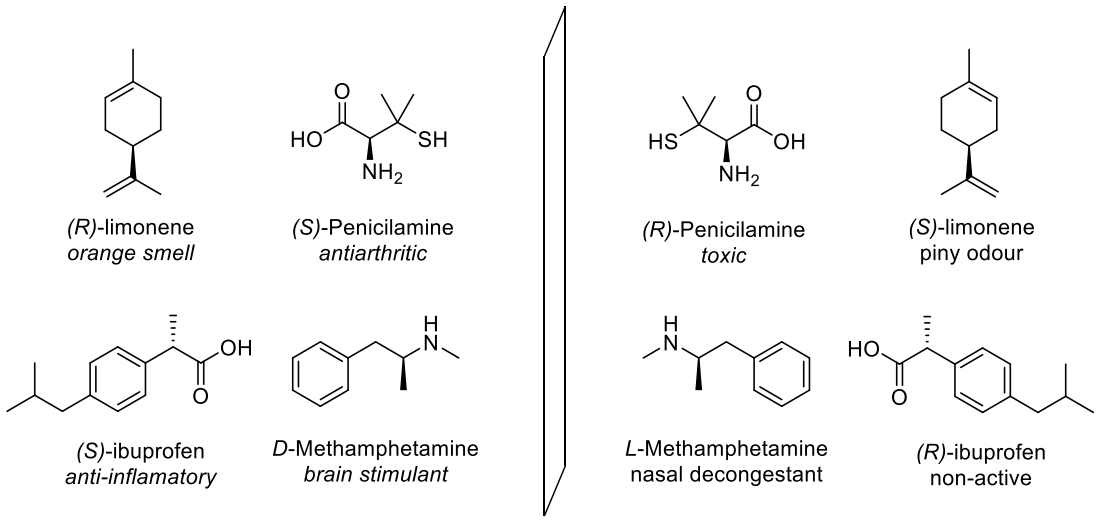
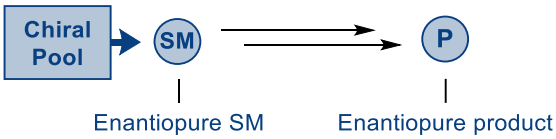


***Figure 6**: Examples of enantiomers possessing different biological properties.*

To achieve this goal, different strategies might be used depending on the complexity of the target molecule and the availability of starting materials.

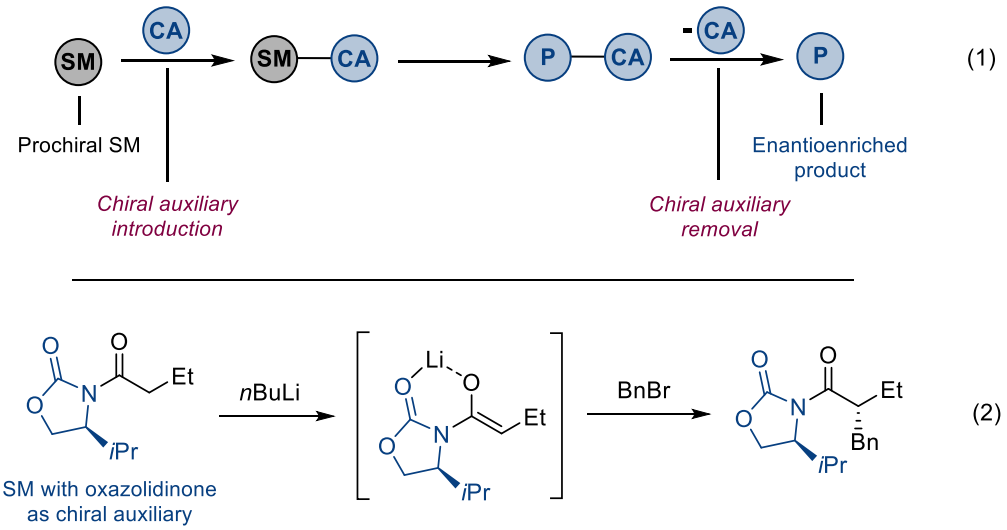
One approach is to use the chiral pool, which refers to several naturally occurring chiral molecules that can be employed as starting materials (amino acids, sugars, or alkaloids). These chiral resources are transformed into more complex compounds in a stereoselective manner (**Scheme 55**). While this method is advantageous for producing molecules structurally related to the starting materials, it is rather limited by the availability of the required natural sources.



***Scheme 55**: Chiral poll strategy for asymmetric synthesis.*

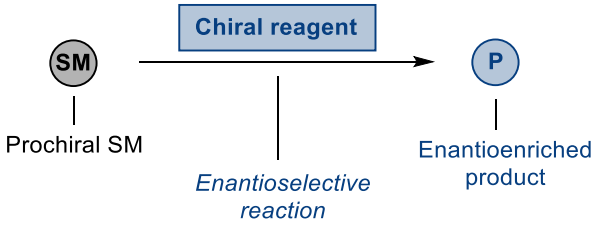
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Another strategy involves the use of chiral auxiliaries, which are temporarily linked to the substrate to introduce chirality during subsequent processes. Although this approach is highly effective for achieving stereoselectivity, it involves additional steps to attach and detach the auxiliary, which reduces the overall efficiency and increase costs (see **Scheme 56**, equation 1). Evans oxazolidinones are one of the most prominent examples, which have been widely employed in stereoselective transformations such as aldol reactions, alkylations, and Diels-Alder cycloadditions (see example at equation 2).[28]



***Scheme 56**: Chiral auxiliary strategy for asymmetric synthesis (1), and stereoselective alkylation of carbonyl compounds with oxazolidinones as chiral auxiliar (2).*

The third strategy involves the use of enantiopure chiral reagents that can introduce asymmetry in prochiral substrates (**Scheme 57**). This method offers the benefit of achieving the desired stereoselectivity without altering the substrate. In recent years, there have been significant strides in the development of enantiopure chiral reagents, and particularly in those that work in a catalytic fashion (asymmetric catalysts).[29]



***Scheme 57**: Asymmetric reactions using chiral reagents.*

[28] (a) D. A. Evans, J. Bartroli, T. L. Shih, *J. Am. Chem. Soc.*, **1981**, *103*, 2127–2129. (b) D. A. Evans, M. D. Ennis, D. J. Mathre, *J. Am. Chem. Soc.*, **1982**, *104*, 1737–1739. (c) D. A. Evans, K. T. Chapman, J. Bisaha, *J. Am. Chem. Soc.*, **1984**, *106*, 4261–4263.

[29] D.M. Huryn, 'Carbanions of alkali and alkaline-earth cations: (II) selectivity of carbonyl addition reactions', *Comprehensive Organic Synthesis II*, **2014**, 1–26.

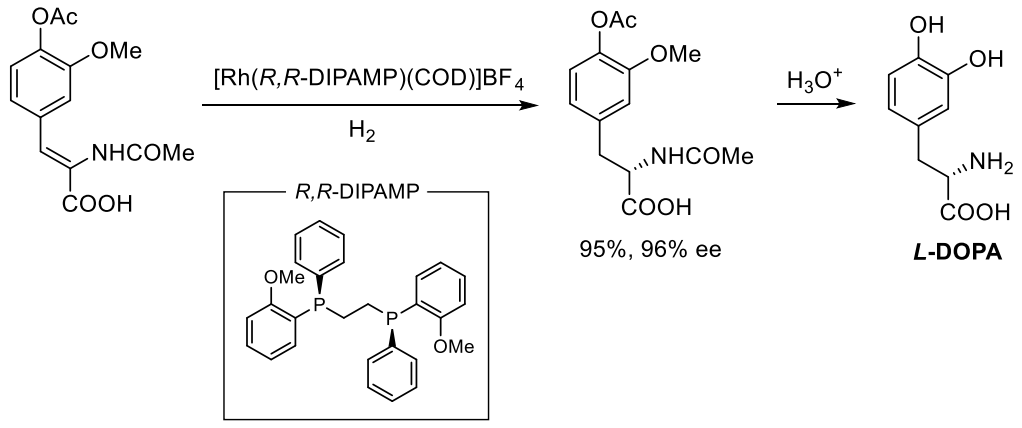
2.3.2. Asymmetric catalysis

In contrast to chiral auxiliaries or reagents, chiral catalysts are added in sub-stoichiometric amounts, are not consumed during the process and, therefore, lead to much more efficient and atom economical processes. During the last decades, asymmetric catalysis evolved from a simple curiosity, applied to few hydrogenations and C–C bond formation reactions, to one of the most prominent fields of catalysis. Indeed, it has revolutionized synthetic chemistry, facilitating the efficient production of enantiopure compounds on an industrial scale.

Depending on the nature of the catalyst, asymmetric catalysis can be divided into biocatalysis, organocatalysis and organometallic catalysis. These three areas are both exciting and complementary.

2.3.3. Asymmetric organometallic catalysis

In 1968, Knowles, a scientist at Monsanto, made a ground-breaking discovery by combining the Schrock-Osborn catalyst with a chiral biphosphine ligand, (*R,R*)-DIPAMP (**Scheme 58**). This modification allowed the asymmetric synthesis of *L*-DOPA, which was used for the treatment for Parkinson's disease, and constituted the first example of asymmetric TM-catalysis applied to an industrial process.[30]



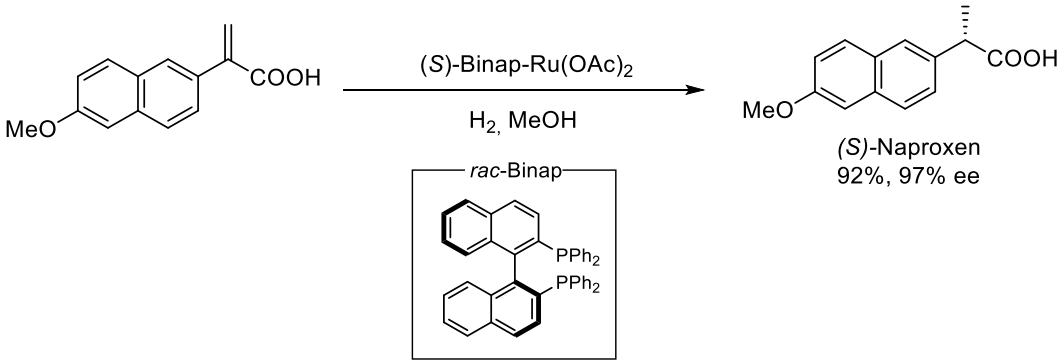
***Scheme 58**: Monsanto's synthesis of L-DOPA.*

Despite the advantages of asymmetric catalysis, its development requires an often-complicated synthesis of chiral ligands. Some of them, often termed as "privileged ligands", have shown effectiveness across a wide spectrum of reactions.

For instance, Noyori contributed to the field with the first examples of an axially chiral ligand, Binap, which is by far the most employed ligand in organometallic catalysis. In

[30] W. S. Knowles, *Acc. Chem. Res.*, **1983**, *16*, 106–112.

one of the pioneering examples, Noyori showed that in combination with ruthenium, Binap is particularly effective for the asymmetric hydrogenation of olefins and β-ketoesters. As shown in **Scheme 59**, the synthesis of the anti-inflammatory drug (*S*)-Naproxen is achieved through enantioselective hydrogenation of an achiral precursor with excellent enantioselectivity.[31]



***Scheme 59**: Enantioselective synthesis of (S)-Naproxen by hydrogenation catalyzed by Binap-Ru complexes.*

Owing to these and other developments, Knowles and Noyori received the Nobel Prize in 2001, along with Sharpless, who had introduced enantioselective epoxidation reactions of olefins with chiral titanium catalysts.[32] More recently, List and MacMillan received the Nobel Prize in 2021 for their pioneer work in asymmetric organocatalysis. Both prices, with only 20 years of difference, clearly highlight how asymmetric catalysis has impacted science and our society.[33]

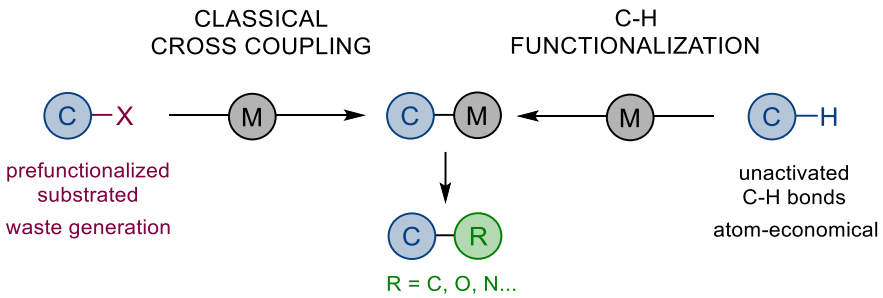
[31] (a) T. Ohta, H. Takaya, R. Noyori, *Inorg. Chem.*, **1988**, *27*, 566–569. (b) T. Ohkuma, H. Ooka, S. Hashiguchi, T. Ikariya, R. Noyori, *J. Am. Chem. Soc.*, **1995**, *117*, 2675–2676.

[32] https://www.nobelprize.org/prizes/chemistry/2001/summary/

[33] https://www.nobelprize.org/prizes/chemistry/2021/summary/

2.4. TM-promoted C–H functionalization reactions

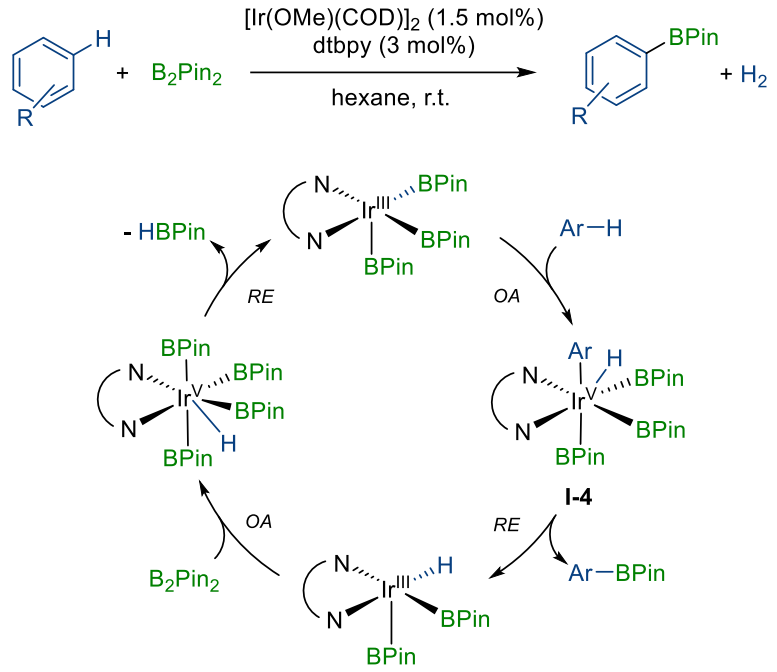
As discussed in the previous section, many transition metal-catalyzed reactions involve the use of pre-functionalized substrates (organic halides and/ or organometallic reagents), which compromises the atom economy of the overall process. To solve these limitations, C–H activation/functionalization methods have emerged as alternative, much more appealing approaches (**Scheme 60**).[34]



***Scheme 60**: Classical cross-coupling vs C–H functionalization.*

At the beginning of this century, Hartwig and Malezcka independently introduced one of the most representative examples of this type of catalysis, the iridium-catalyzed C–H borylation of aromatic systems. The proposed mechanism, illustrated in **Scheme 61**, typically begins with the oxidative addition of a diboron species like PinB–BPin to an iridium(I) complex, followed by an oxidative addition of the C–H bond, to generate Ir(V) hydride species **I-4**. Then, a C–B reductive elimination yields the borylated arene product and restores a Ir(III) active intermediate species.

[34] For selected reviews on C–H activation, see: (a) R. G. Bergman, *Nature*, **2007**, *446*, 391–393. (b) T. Gensch, M. N. Hopkinson, F. Glorius, J. Wencel-Delord, *Chem. Soc. Rev.*, **2016**, *45*, 2900–2936. (c) J. F. Hartwig, *J. Am. Chem. Soc.*, **2015**, *138*, 2–24. (d) T. Dalton, T. Faber, F. Glorius, *ACS Cent. Sci.*, **2021**, *7*, 245–261. (e) T. Rogge, N. Kaplaneris, N. Chatani, J. Kim, S. Chang, B. Punji, L. L. Schafer, D. G. Musaev, J. Wencel-Delord, C. A. Roberts, R. Sarpong, Z. E. Wilson, M. A. Brimble, M. J. Johansson, L. Ackermann, *Nat. Rev. Methods Primers*, **2021**, *1*, 43.



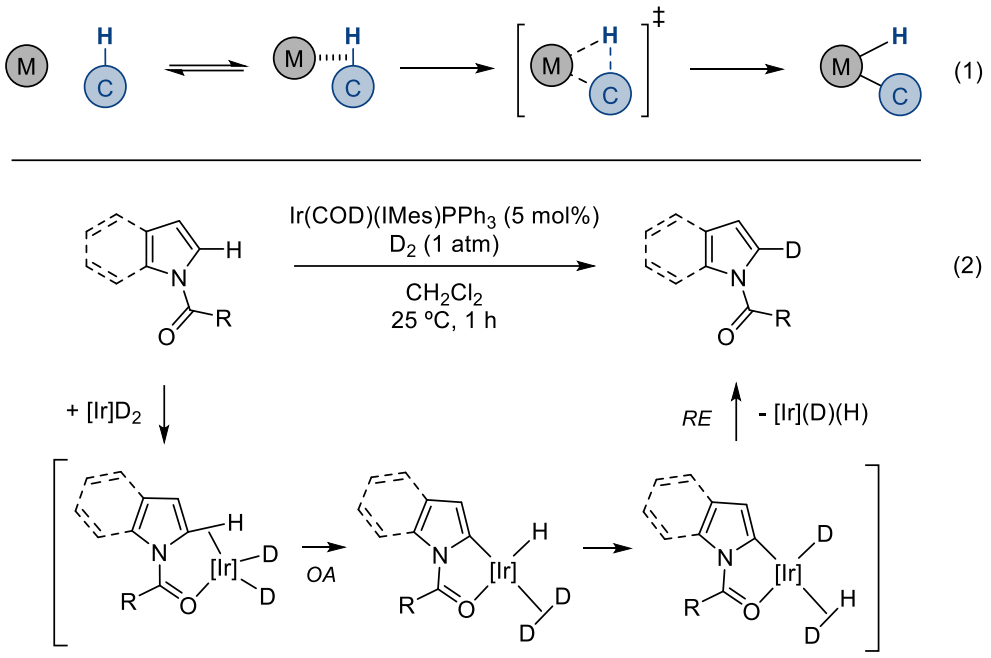
***Scheme 61**: C–H borylation catalyzed by iridium complexes and proposed mechanism.*

2.4.1. C–H activation mechanisms

In the previous example, the C–H activation occurs through the oxidative addition of a C–H bond to the metal center (as depicted in **Scheme 62**, equation 1). This type of activation is typical for electron-rich, low-valent metal complexes, such as those of ruthenium, palladium, osmium, rhodium, platinum, and iridium, which tend to be oxidized in the process.

Oxidative addition of C–H bonds to organometallic species is exemplified in the equation 2 of **Scheme 62**, where selective deuteration of pyrroles and indoles occurs using an iridium catalyst.[35] Besides this mechanistic scenario, which generates a "C–M–H" species, there are other alternatives that will be briefly discussed below.[36]

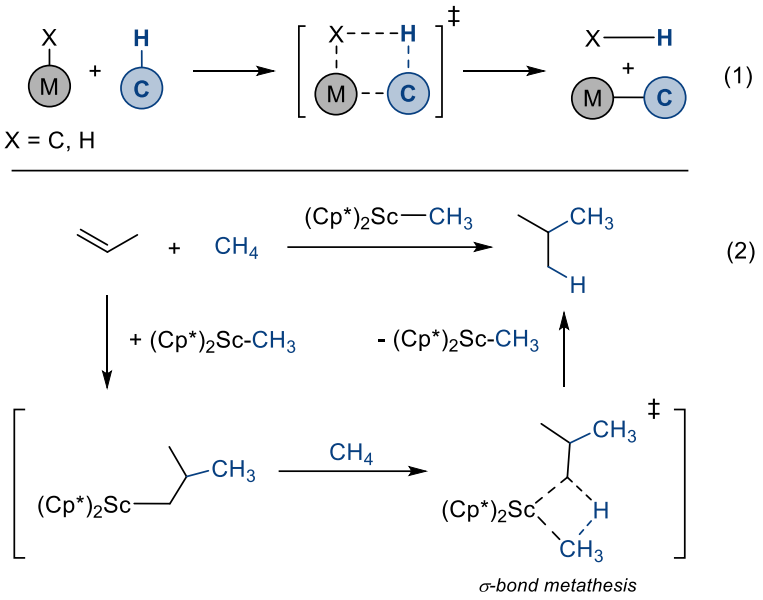
[35] W. J. Kerr, D. M. Lindsay, P. K. Owens, M. Reid, T. Tuttle, S. Campos, *ACS Catal.*, **2017**, *7*, 7182–7186.
[36] Y.-H. Cheng, Y.-S. Ho, C.-J. Yang, C.-Y. Chen, C.-T. Hsieh, M.-J. Cheng, *J. Phys. Chem. A*, **2024**, *128*, 4638–4650.



***Scheme 62**: General scheme of C–H activation by oxidative addition (1) and an example of this process in Ir-catalyzed deuteration of indoles (2).*

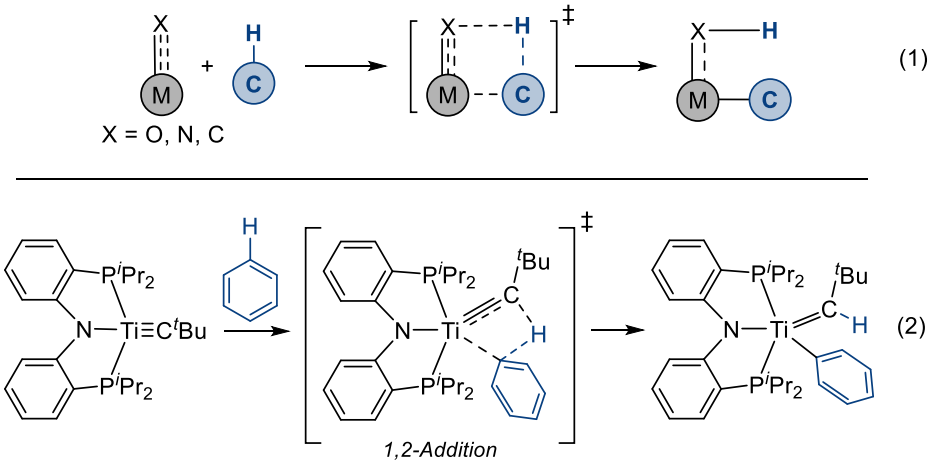
When employing early d⁰ transition metals in a high oxidation state (e.g. Sc^{III}, Zr^{IV}, Nb^{IV}, Ta^{V}), oxidative additions are not feasible due to the lack of available *d* electrons. Instead, these metals can interact with C–H bonds through a process known as σ-bond metathesis (σ-BM). This mechanism involves a concerted four-center transition state, similar to a [2σ + 2σ] cycloaddition and occurs without altering the metal's oxidation state (see **Scheme 63**, equation 1).[37] For example, Tilley and coworkers reported a hydromethylation of propene catalyzed by a scandium catalyst (equation 2).[38]

[37] F. Roudesly, J. Oble, G. Poli, *J. Mol. Catal. A: Chem.*, **2017**, *426*, 275–296.
[38] A. D. Sadow, T. D. Tilley, *J. Am. Chem. Soc.* **2003**, *125*, 7971–7977.



***Scheme 63**: General mechanism for C–H activation via σ-bond metathesis (1) and an example reported by Tilley (2).*

On the other hand, C–H bonds can also be activated in a concerted four-center 1,2-addition across metal-ligand multiple bonds. The mechanism differs from the σ-BM scheme in that the newly formed X–H bond remains attached to the metal. Amido, alkylidene, alkoxy and alkylidyne complexes of early and middle transition metals (e.g. Ti, Zr) frequently participate via this mechanism, depicted in **Scheme 64**, equation 1. Mindiola and coworkers reported an example of this type of C–H bond activation with Ti-alkylidyne complexes, as shown in equation 2.[39]

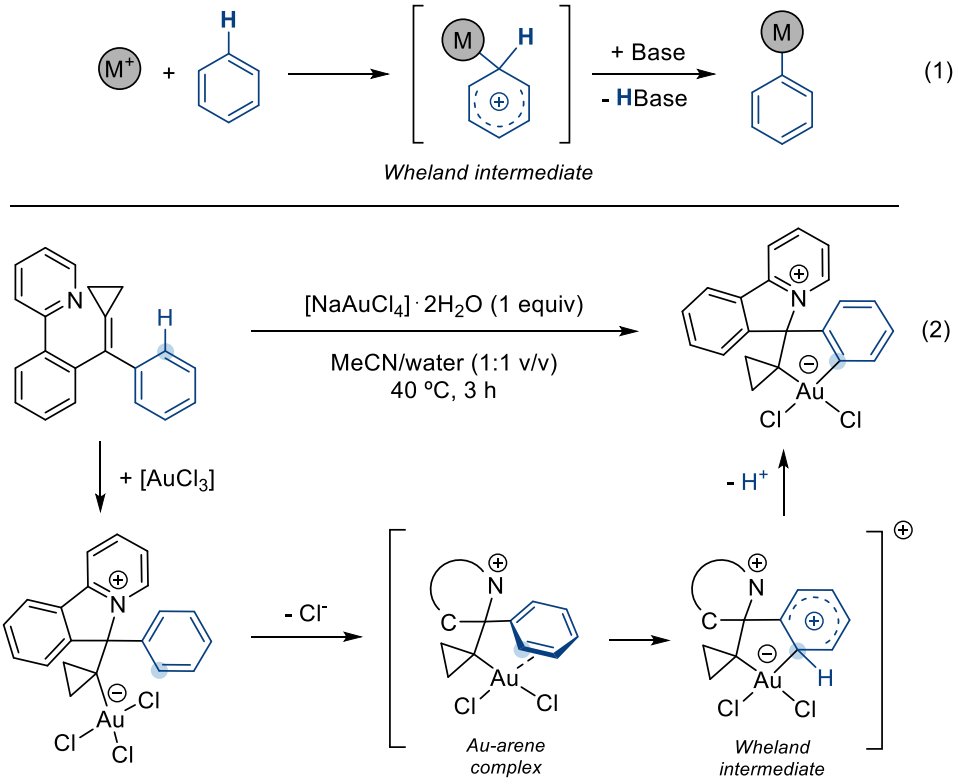


***Scheme 64**: General mechanism for C–H activation via 1,2-addition (1) and example reported by the group of Mindiola (2).*

[39] B. C. Bailey, H. Fan, E. W. Baum, J. C. Huffman, M.-H. Baik, D. J. Mindiola, *J. Am. Chem. Soc.* **2005**, *127*, 16016–16017.

When employing metals at high oxidation states and electron-rich substrates, metalation can take place through electrophilic substitution. The nucleophilic hydrocarbon attacks the metal center, forming cationic species (often called Wheland intermediates in the case of aromatic systems). The new M–C bond increases the acidity of the vicinal C(aryl)–H bond, which can be easily deprotonated by a base (**Scheme 65**, equation 1). When the base is located within the coordination sphere of the metal center, this mechanism is also referred to as a base-assisted intramolecular electrophilic substitution.[40]

During my predoctoral stay at Prof. Nevado's group, and as part of a collaboration with my group in Santiago, we discovered new zwitterionic gold(III) complexes that evolve upon heating to cyclic Au(III) complexes bearing C(sp^3)–Au–C(sp^2) bonds. The preparation of a series of zwitterionic acyclic Au(III) complexes and the study their evolution to their cyclic counterpart allowed us to determine that the mechanism consists on an intramolecular S_EAr in which the coordination of the C–H bond, rather than the formation of the Wheland intermediate is the rate determining step (equation 2).[41]

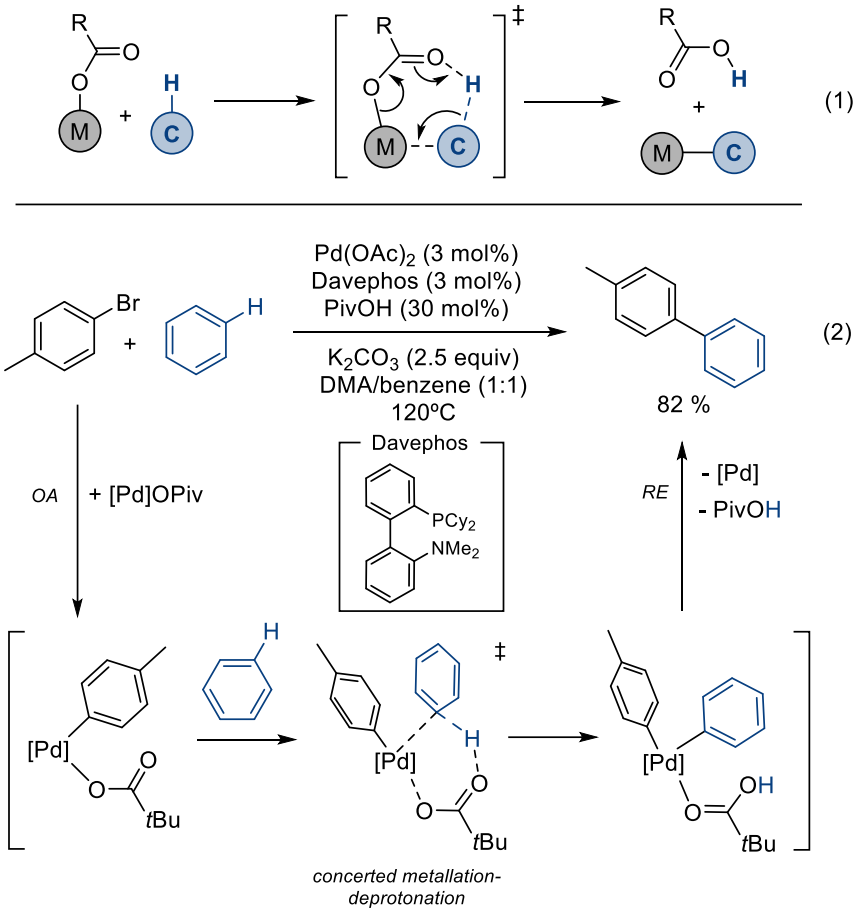


***Scheme 65**: General scheme of C–H activation by electrophilic aromatic substitution (1), and an example of C–H auration of this type developed in collaboration with Nevado's group (2).*

[40] K. M. Altus and J. A. Love, *Commun. Chem.*, **2021**, *4*, 173.

[41] J. A. González, A. Arribas, P. Tian, S. Díaz-Alonso, J. L. Mascareñas, F. López, C. Nevado, *Angew. Chem. Int. Ed.* **2024**, e202402798.

In addition to the previously mentioned mechanisms, there is another process that holds significant synthetic relevance. In certain cases, an anionic ligand of the metal acts as an internal base to facilitate the cleavage of the C–H bond, simultaneously enabling the formation of the C–Metal bond. Ligands that facilitate this mechanism are often carboxylates, operating through what is known as a Concerted Metallation-Deprotonation (CMD) process (**Scheme 66**, equation 1). This mechanism is categorized under the broader concept of Ambiphilic Metal-Ligand Activation (AMLA), where the ligand plays a dual role in both cleaving the C–H bond and promoting the subsequent metallation.[37] In 2006, Fagnou published a pioneer example of this type of C–H activation, applied in the Pd-catalyzed cross-coupling between aryl bromides and benzene promoted by pivalic acid (equation 2).



***Scheme 66**: General mechanism of CMD process for C–H activation.*

Beyond the previously mentioned inner sphere mechanisms, C–H activation can also occur through an outer-sphere mechanisms. Some processes involve the activation of C–H bonds by metal-oxo, metal-nitrene, or metal-carbene species, leading to the

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formation of M–X–H intermediates, which are coupled with the creation of a new X–C bond in a concerted or stepwise manner (**Scheme 67**, equation 1).

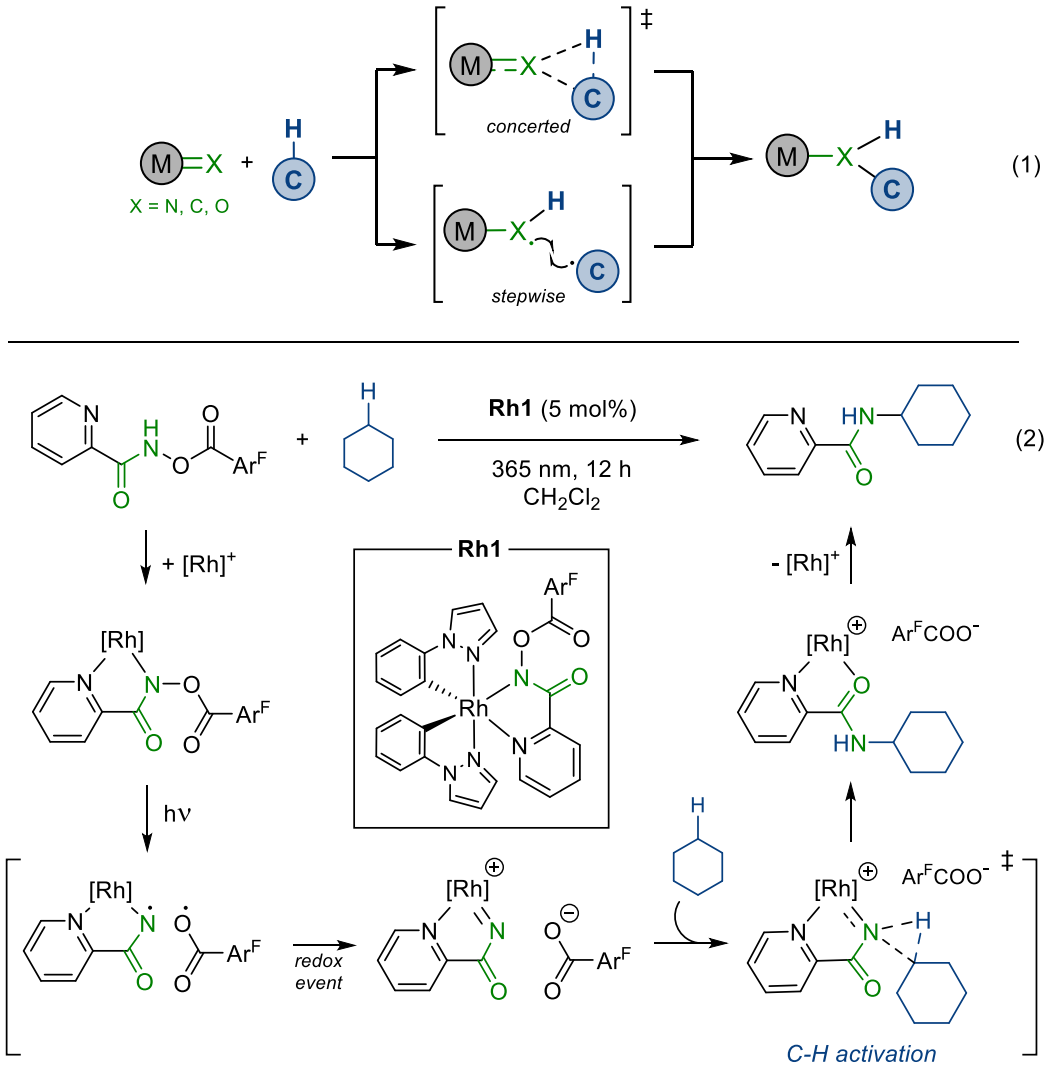
These outer-sphere mechanisms have demonstrated significant versatility in both intramolecular and intermolecular C–H functionalization reactions, especially in the activation of C(sp^3)–H bonds.[37] The study of these processes is challenging due to the high reactivity of organometallic species, particularly in the case of metal-nitrenes, which are highly elusive.[42]

During my predoctoral research stay at Professor Chang's group in South Korea, we synthetized and explored the reactivity of new rhodium-hydroxamate complexes, shown in equation 2. Upon photoexcitation**,** these complexes release acylnitrene species and acyloxy radicals to eventually provide a Rh-acylnitrenoid that can insert into C(sp^2)–H and C(sp^3)–H bonds, even catalytically. Furthermore, we have demonstrated that these species can also react with nucleophiles, resulting in the formation of new N–N and N–O bonds.

Working on this project provided me with valuable insights into the catalytic activation of C–H bonds and the discovery of novel mechanisms, distinct from those explored in this doctoral thesis.

[42] (a) K. M. Carsch, I. M. DiMucci, D. A. Iovan, A. Li, S.-L. Zheng, C. J. Titus, S. J. Lee, K. D. Irwin, D. Nordlund, K. M. Lancaster, T. A. Betley, *Science*, **2019**, *365*, 1138–1143. (b) A. Grünwald, N. Orth, A. Scheurer, F. W. Heinemann, A. Pöthig, D. Munz, *Angew. Chem. Int. Ed.*, **2018**, *57*, 16228–16232. n(c) A. Grünwald, B. Goswami, K. Breitwieser, B. Morgenstern, M. Gimferrer, F. W. Heinemann, D. M. Momper, C. W. M. Kay, D. Munz, *J. Am. Chem. Soc.*, **2022**, *144*, 8897–8901. (d) A. Das, Y.-S. Chen, J. H. Reibenspies, D. C. Powers, *J. Am. Chem. Soc.*, **2019**, *141*, 16232–16236. (e) A. Das, C.-H. Wang, G. P. Van Trieste III, C.-J. Sun, Y.-S. Chen, J. H. Reibenspies, D. C. Powers, *J. Am. Chem. Soc.*, **2020**, *142*, 19862–19867. (f) J. Sun, J. Abbenseth, H. Verplancke, M. Diefenbach, B. de Bruin, D. Hunger, C. Würtele, J. van Slageren, M. C. Holthausen, S. Schneider, *Nat. Chem.*, **2020**, *12*, 1054–1059. (g) T. Schmidt-Räntsch, H. Verplancke, J. N. Lienert, S. Demeshko, M. Otte, G. P. Van Trieste III, K. A. Reid, J. H. Reibenspies, D. C. Powers, M. C. Holthausen, S. Schneider, *Angew. Chem. Int. Ed.*, **2022**, *61*, e202115626.

[37] F. Roudesly, J. Oble, G. Poli, *J. Mol. Catal. A: Chem.*, **2017**, *426*, 275–296.

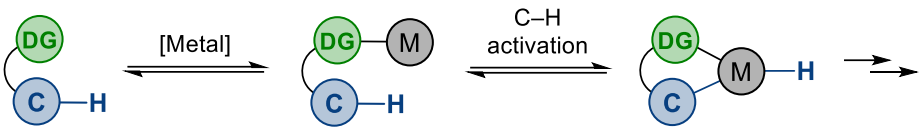


***Scheme 67**: General scheme for outer-sphere C–H activation (1), and studies developed by Chang to isolate Rh-nitrenoid species and its application in catalytic C–H amidation processes (2).*

2.4.2. Selectivity of the C–H activation. Directing group strategy

A major challenge in the C–H activation field is related to controlling the site selectivity, namely the activation of the desired bond in the presence of others. For this reason, the use of a directing group (DG) is a very broadly applied strategy that helps to direct the activation of a given C–H bond within complex molecules. The directing group, commonly a Lewis Base, coordinates to the metal center, guiding to the specific C–H bond that needs to be activated, lowering entropic barriers and, in many cases, accelerating the reaction (see **Scheme 68**). The choice of an appropriate directing group depends on the type of C–H bond targeted for activation, as well as on the metal and the mechanism involved in each specific case.[43]

[43] Y.-H. Cheng, Y.-S. Ho, C.-J. Yang, C.-Y. Chen, C.-T. Hsieh, M.-J. Cheng, *J. Phys. Chem. A*, **2024**, *128* (23), 4638–4650.



***Scheme 68**: Directing group strategy to enable site selective C–H activation.*

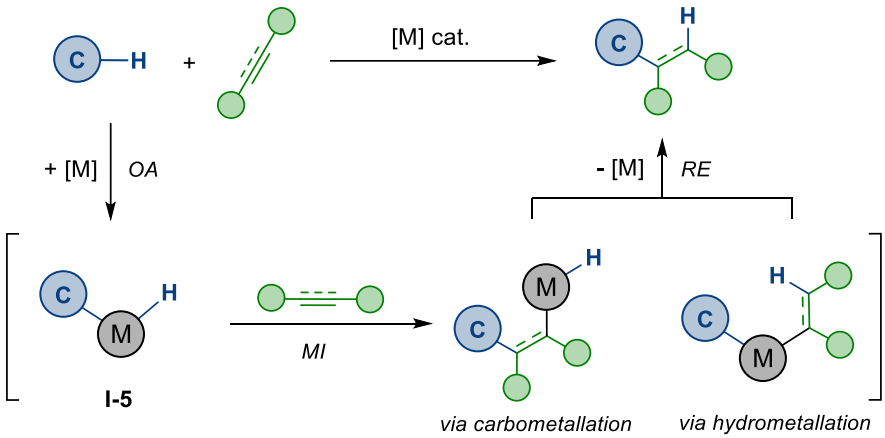
This doctoral thesis focuses on the activation of aromatic C–H bonds using directing groups and their addition to C–C and C–O unsaturated bonds, to formally deliver hydrocarbonation products. Mechanistically, the developed methods are based on C–H activations via oxidative addition to low valent metal (M) catalysts, to form C–M–H species, followed by migratory insertion and reductive elimination steps. A more detailed overview of the existing precedents for these methodologies will be presented in the following section.

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2.5. TM-catalyzed addition of C–H bonds across unsaturated systems

The addition of C–H bonds across alkenes, alkynes and other unsaturated systems constitutes an attractive synthetic approach to construct highly complex molecules quickly and efficiently, with full atom economy. These reactions are globally named as hydrocarbonations and include processes in which both carbon and hydrogen atoms are directly transferred to the final products, thus excluding reactions based on CMD or S_EAr C–H activation modes (see section 2.4.1).

The general mechanism of these processes is depicted in **Scheme 69**. The first step is the C–H bond activation by oxidative addition, to generate a key metal hydride intermediate **I-5**. Coordination of the unsaturated system to the metal center, followed by migratory insertion into either the C–M (carbometallation) or the M–H (hydrometallation) bond, delivers new organometallic species, which eventually provide a common product, via either a C–C or a C–H reductive elimination (this mechanism will be hereafter abbreviated as *OA/MI/RE*).



***Scheme 69**. General mechanism of TM-catalyzed insertions of C–H bonds to unsaturated partners.*

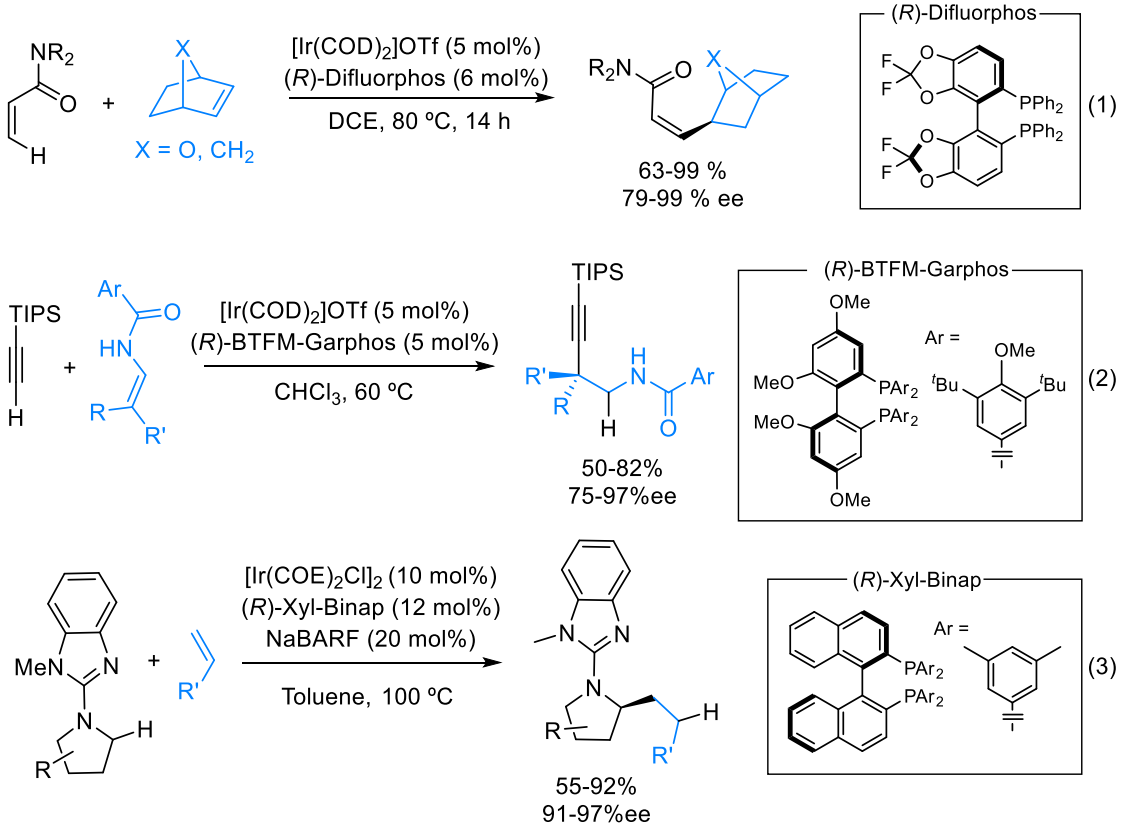
The C–H bond addition across double or triple bonds is a particularly attractive transformation that allows the formation of C–C bonds with complete atom economy. During the last decades, there has been significant progress in the field; however, there are still many challenges to tackle and important limitations that need to be overcome to be able to extend the scope and potential of this chemistry, especially for the assembly of structurally complex molecules.

The following sections will review the most significant advancements in the field of aromatic C(sp_2)–H bond addition across unsaturated systems, organized by addition to alkenes, alkynes and other unsaturated systems.

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In addition to processes involving the activation of aromatic C(sp²)–H bonds, there are reactions that involve the activation of olefinic C(sp²)–H bonds, exemplified with the work of Li and coworkers (**Scheme 70**, equation 1).[44] Similarly, several C(sp)–H bond activation processes have been described, as exemplified with the Ir(I)-catalyzed reaction reported by Li (equation 2).[45]

Similar addition reactions involving the activation of C(sp³)–H bonds are more challenging, and only a few examples have been reported, such as that shown in equation 3.



***Scheme 70**: Examples of Ir(I)-catalyzed additions of C(sp²)-H, C(sp)-H and C(sp³)-H bonds across unsaturated systems.*

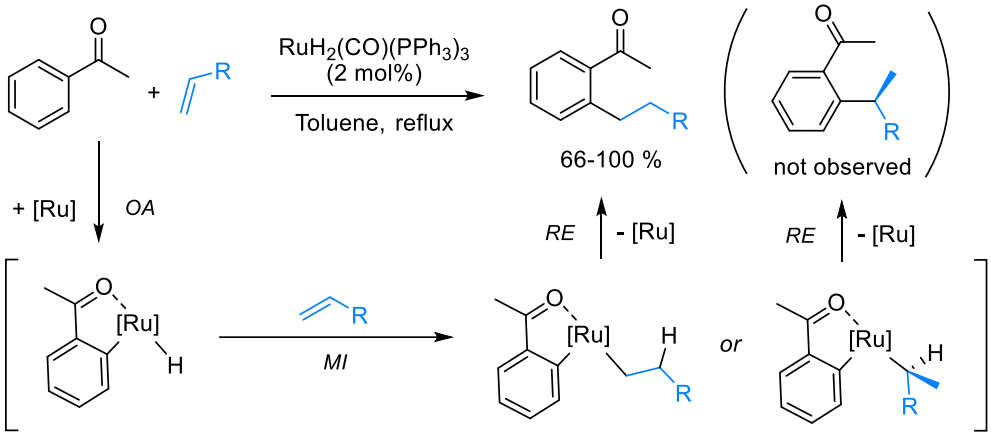
2.5.1. TM-catalyzed intermolecular additions of aromatic C–H bonds to alkenes

In 1993, Murai and colleagues reported ruthenium complexes that can catalyze the hydroarylation of alkenes using aromatic ketones (see **Scheme 71**). Specifically, $RuH_2(CO)(PPh_3)_3$ evolves in situ into a catalytically active Ru(0) species, which coordinates the carbonyl group of the ketone, thus facilitating the oxidative addition of its

[44] X. Sun, X.-Y. Bai, A.-Z. Li, and B.-J. Li, *Organometallics*, **2021**, *40*, 2182–2187.

[45] W. Zhao, H. X. Lu, W. W. Zhang, and B. J. Li, *Acc. Chem. Res.*, **2023**, *56*, 308–321. For a review of the existing methods of this type, see: A. Arribas, C. Lázaro-Milla, J. L. Mascareñas, and F. López, *Catalytic Addition of C–H Bonds Across C–C π-Bonds*, in *Reference Module in Chemistry, Molecular Sciences and Chemical Engineering*, Elsevier, **2023**..

ortho C–H bond to the metal center. Therefore, the ketone serves as a directing group, determining the regioselectivity of the activation. The resulting ruthenium-hydride species evolves to the experimentally observed linear hydroarylation product via regioselective alkene migratory insertion into the Ru–H bond and a final C–C reductive elimination.[46] Steric reasons were proposed to determine the formation of the achiral linear product, rather that its potentially competitive chiral branched regioisomer.



***Scheme 71**: Ruthenium-catalyzed hydroarylation of alkenes, developed by Murai.*

In addition to aryl ketones, Murai and coworkers also introduced the use of aromatic systems with directing groups such as imines, oxazolines, nitriles, hydrazones, esters, and aldehydes[47] in a series of reports disclosing hydroarylation of olefins. These reactions employed either $Ru_3(CO)_{12}$ or $Ru(H)_2(CO)(PPh_3)_3$ as precatalysts.

These studies triggered the development of new methods using different metal catalysts. For instance, Kang reported a rhodium-catalyzed hydroarylation of alkenes that provides linear adducts in a selective manner (**Scheme 72**, equation 1).[48] A later work by Yoshikai demonstrated that by selecting appropriate ligands for a cobalt catalyst, this type of hydrocarbonations could either provide linear or branched products (equation 2).[49]

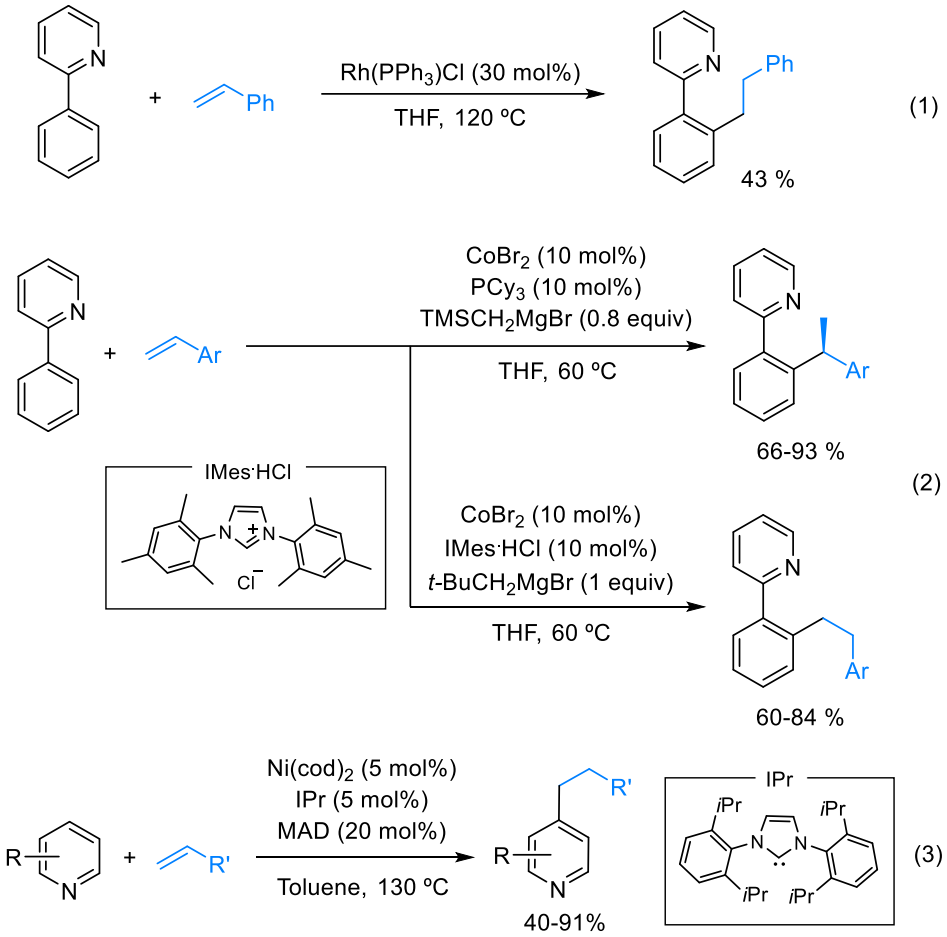
[46] S. Murai, F. Kakiuchi, S. Sekine, Y. Tanaka, A. Kamatani, M. Sonoda, N. Chatani. *Nature* **1993**, *366*, 529-531.

[47] (a) F. Kakiuchi, T. Sato, M. Yamauchi, N. Chatani, S. Murai. *Chem. Lett.* **1999**, *28*, 19-20. (b) F. Kakiuchi, M. Sonoda, T. Tsujimoto, N. Chatani, S. Murai. *Chem. Lett.* **1999**, *28*, 1083-1084. (c) F. Kakiuchi, T. Tsujimoto, M. Sonoda, N. Chatani, S. Murai. *Synlett* **2001**, 0948-0951. (d) F. Kakiuchi, H. Ohtaki, M. Sonoda, N. Chatani, S. Murai. *Chem. Lett.* **2001**, *30*, 918-919. (e) M. Sonoda, F. Kakiuchi, A. Kamatani, N. Chatani, S. Murai *Chem. Lett.* **1996**, 109-110. (f) F. Kakiuchi, T. Sato, K. Igi, N. Chatani, S. Murai. *Chem. Lett.* **2001**, *30*, 386-387.

[48] Y.-G. Lim, Y. H. Kim, and J.-B. Kang, *J. Chem. Soc., Chem. Commun.*, **1994**, *2267*–2268. For other examples employing rhodium catalysis, see: (a) Y.-G. Lim, Y. H. Kim, J.-B. Kang, *J. Chem. Soc., Chem. Commun.*, **1994**, 2267-2268. (b) C. P. Lenges, M. Brookhart, *J. Am. Chem. Soc.*, **1999**, *121*, 6616-6623. (c) Y.-G. Lim, J.-S. Han, S.-S. Yang, J. H. Chun, *Tetrahedron Lett.*, **2001**, *42*, 4853-4856. (d) K. L. Tan, R. G. Bergman, J. A. Ellman, *J. Am. Chem. Soc.*, **2002**, *124*, 13964-13965. (e) K. L. Tan, S. Park, J. A. Ellman, R. G. Bergman, *J. Org. Chem.*, **2004**, *69*, 7329-7335. (f) S. H. Wiedemann, R. G. Bergman, J. A. Ellman, *Org. Lett.*, **2004**, *6*, 1685-1687. (g) Y.-G. Lim, B. T. Koo, *Tetrahedron Lett.*, **2005**, *46*, 7997-8001. (h) Y.-G. Lim, J. H. Lee, J. Yoo, C. H. Jun, *Org. Lett.*, **2005**, *7*, 2889-2892.

[49] K. Gao and N. Yoshikai, *J. Am. Chem. Soc.*, **2011**, *133*, 400–402. and *Acc. Chem. Res.*, **2014**, *47*, 1208–1219. For other examples employing cobalt catalysis, see: (a) K. Gao, N. Yoshikai, *J. Am. Chem. Soc.*, **2011**, *133*, 400-402. (b) L. Ilies, Q. Chen, X. Zeng, E. Nakamura, *J. Am. Chem. Soc.*, **2011**, *133*, 5221-5223. (c) P. S. Lee, N. Yoshikai, *Angew. Chem. Int. Ed.*, **2013**, *52*, 1240-1244. (d) B. A. Suslick, T. D. Tilley, *J. Am. Chem. Soc.*, **2020**, *142*, 11203-11218. (e) A. Whyte, A. Torelli, B. Mirabi, L. Prieto, J. F. Rodriguez, M. Lautens, *J. Am. Chem. Soc.*, **2020**, *142*, 9510-9517.

Another important group of reactions involve nickel catalysts, which are particularly efficient for the activation of pyridines and related systems. An example of this methodology is the work of Hiyama, depicted in equation 3.[50]

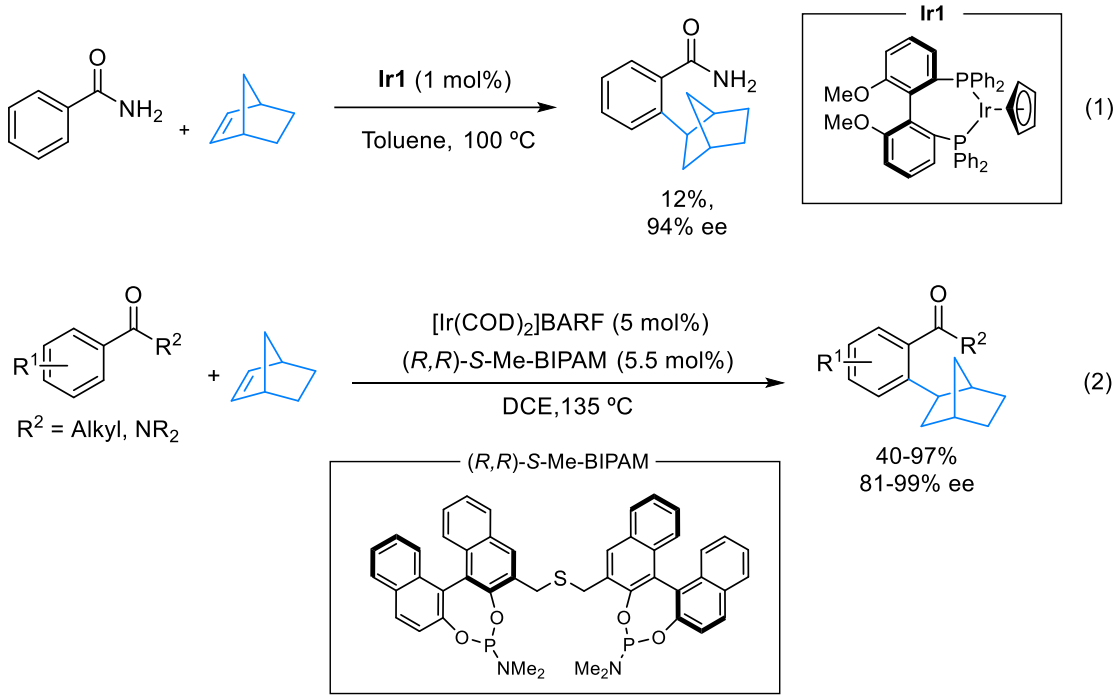


***Scheme 72**: Examples of hydroarylations employing rhodium (1), cobalt (2) and nickel (3) catalysis.*

Besides these metals, iridium has also been successfully employed. Thus, in the early 2000s, Togni and colleagues pioneered the use of iridium catalysts for the hydroarylation of norbornenes with benzamides. Using complex **Ir1** as catalyst resulted in the exclusive formation of the hydrocarbonation product with high enantiomeric excess, but in low yield

[50] Y. Nakao, Y. Yamada, N. Kashihara, and T. Hiyama, *J. Am. Chem. Soc.*, **2010**, *132*, 13666–13668. For other examples employing nickel catalysis, see: (a) N. D. Clement, K. J. Cavell, *Angew. Chem. Int. Ed.*, **2004**, *43*, 3845-3847. (b) A. T. Normand, K. J. Hawkes, N. D. Clement, K. J. Cavell, B. F. Yates, *Organometallics*, **2007**, *26*, 5352-5363. (c) Y. Nakao, N. Kashihara, K. S. Kanyiva, T. Hiyama, *J. Am. Chem. Soc.*, **2008**, *130*, 16170-16171. (d) Y. Nakao, H. Idei, K. S. Kanyiva, T. Hiyama, *J. Am. Chem. Soc.*, **2009**, *131*, 15996-15997. (e) Y. Nakao, Y. Yamada, N. Kashihara, T. Hiyama, *J. Am. Chem. Soc.*, **2010**, *132*, 13666-13668. (f) Y. Nakao, N. Kashihara, K. S. Kanyiva, T. Hiyama, *Angew. Chem. Int. Ed.*, **2010**, *49*, 4451-4454. (g) R. Tamura, Y. Yamada, Y. Nakao, T. Hiyama, *Angew. Chem. Int. Ed.*, **2012**, *51*, 5679-5682. (h) J. S. Bair, Y. Schramm, A. G. Sergeev, E. Clot, O. Eisenstein, J. F. Hartwig, *J. Am. Chem. Soc.*, **2014**, *136*, 13098-13101. (i) Y. Schramm, M. Takeuchi, K. Semba, Y. Nakao, J. F. Hartwig, *J. Am. Chem. Soc.*, **2015**, *137*, 12215-12218. (j) S. Okumura, S. Tang, T. Saito, K. Semba, S. Sakaki, Y. Nakao, *J. Am. Chem. Soc.*, **2016**, *138*, 14699-14704.

(**Scheme 73**, equation 1).[51] In 2015, Yamamoto and colleagues reported a highly enantioselective variant of this reaction, using a chiral catalyst formed in situ from [Ir(COD)$_2$]BARF and the bidentate phosphoramidite ligand (*R,R*)-*S*-Me-BIPAM. The corresponding *o*-alkylated benzophenones were obtained with enantioselectivities exceeding 90% (equation 2).[52]



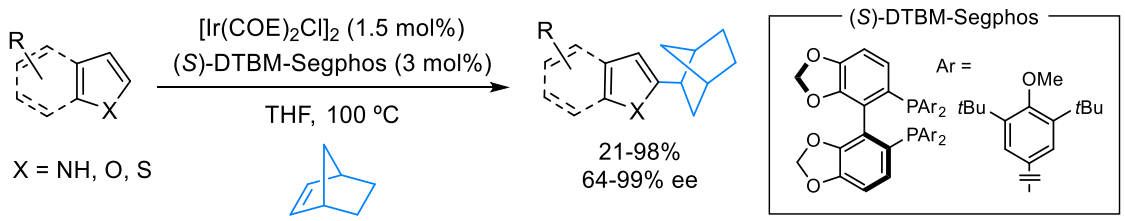
***Scheme 73**: Ir-catalyzed hydroarylations of 2-norbornene.*

The enantioselective hydroarylation of strained olefins like norbornene can also be achieved using electron-rich heteroaromatic rings as substrates, without the need of a directing group, as demonstrated by Hartwig and coworkers in 2013. The catalyst used in this case is generated in situ from [Ir(COE)$_2$Cl]$_2$ and the chiral ligand (*S*)-DTBM-Segphos (**Scheme 74**).[53]

[51] R. Aufdenblatten, S. Diezi, A. Togni. *Monatsh. Chem.* **2000**, *131*, 1345-1350. For related examples see: (a) R. Dorta, A. Togni. *Chem. Commun.* **2003**, 760-761. (b) R. Dorta, A. Togni. *Organometallics,* **1998**, *17*, 3423-3428. (b) K. Tsuchikama, M. Kasagawa, Y. K. Hashimoto, K. *Endo*, T. Shibata. *J. Organomet. Chem.,* **2008**, *693*, 3939-3942.

[52] T. Shirai, Y. Yamamoto. *Angew. Chem. Int. Ed.,* **2015**, *54*, 9894-9897.

[53] C. S. Sevov, J. F. Hartwig. *J. Am. Chem. Soc.,* **2013**, *135*, 2116-2119. For another example of DG-free heteroaromatic C-H bond activation, see: W. Zhao, B.-J. Li. *J. Am. Chem. Soc.,* **2023**, *145*, 12, 6861–6870.



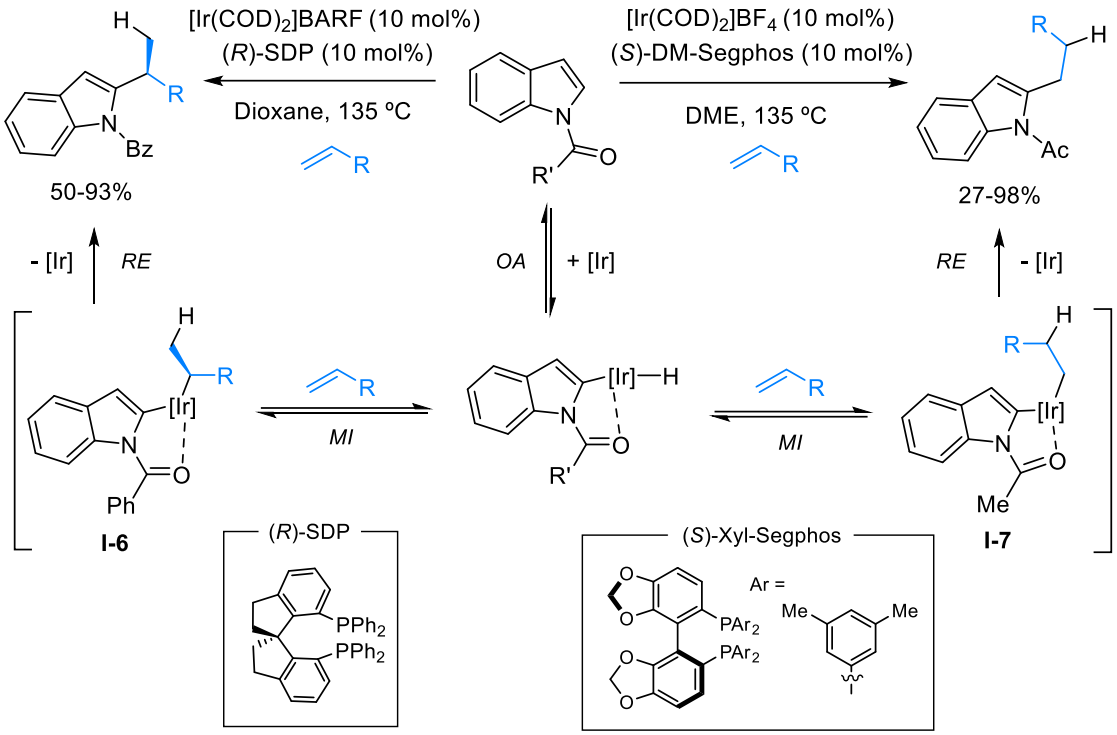
***Scheme 74**: Directing group-free Ir-catalyzed enantioselective hydrocarbonation of norbornenes using heteroarenes, reported by Hartwig.*

Although the reactions of norbornenes and similar strained alkenes highlight the potential of iridium catalysts for hydroarylation reactions, the synthetic applications of the resulting products are limited. Indeed, extending this methodology to synthetically more relevant non-strained alkenes is challenging, due to their lower reactivity, and the regioselectivity issues encountered when they are not symmetrical.

In this regard, Shibata and colleagues showed in 2012 that cationic iridium(I)-biphosphine catalysts can selectively *C2*-alkylate *N*-substituted indoles with styrenes. Interestingly, the choice of the catalyst, alkene and directing group determined whether branched or linear products were formed. For example, *N*-acetyl indoles reacted with $[Ir(COD)_2]BF_4$/DM-Segphos to produce the linear product with high selectivity. In contrast, the chiral catalyst from $[Ir(COD)_2]$BARF and spirobiphosphine SDP yielded branched products from *N*-benzoyl indoles, with moderate to good regioselectivities (**Scheme 75**).[54] Mechanistically, the authors proposed an initial oxidative addition of the C–H bond to the metal, followed by a hydroiridation of the alkene to form either the branched or the linear intermediate (**I-6** and **I-7,** respectively). Deuterium labelling experiments indicated that both steps are reversible. Eventually, a C–C reductive elimination would deliver the corresponding products.

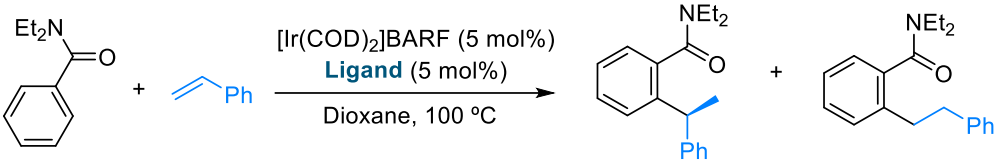
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[54] S. Pan, N. Ryu, T. Shibata. *J. Am. Chem. Soc.,* **2012**, *134*, 17474-17477.



***Scheme 75**: Iridium promoted alkylation at the C2-position of indoles developed by Shibata and coworkers.*

In 2014, Bower reported an intermolecular, iridium-catalyzed hydroarylation of alkenes that selectively generates branched products. The method, which uses aryl dialkylamides and related aryl ketones, is effective with both styrenes and non-activated olefins (**Scheme 76**).[55] The use of an iridium(I) catalyst bearing electron-deficient biphosphines of wide bite angles, such as d^{F}ppb was critical for achieving good yields and high regioselectivity. The non-fluorinated variant, dppb, resulted in lower yields but maintained branched selectivity. On the other hand, electronically similar biphosphines with narrower bite angles, like d^{F}ppe, produced lower branched-to-linear ratios.

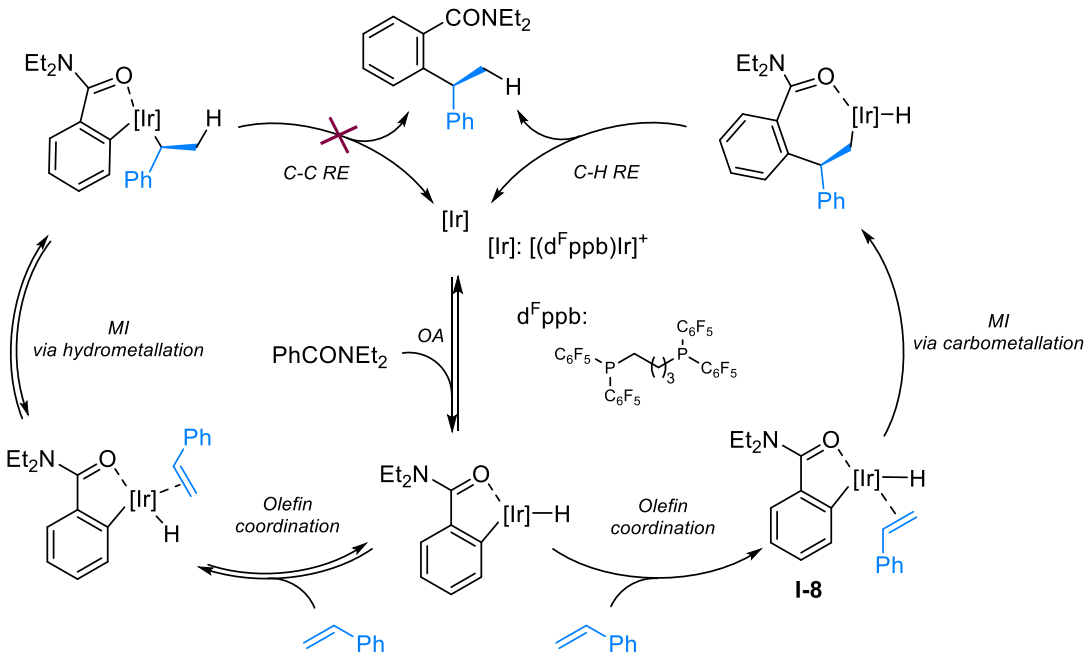


	yield	*branched* : *linear*
d^{F}ppb (*n* = 4, Ar = C_6F_5)	100%	100 : 0
dppb (*n* = 4, Ar = Ph)	100%	100 : 0
d^{F}ppe (*n* = 2, Ar = C_6F_5)	100%	36 : 64

***Scheme 76**: Iridium-catalyzed branched-selective hydroarylation developed by Bower and co-workers.*

[55] G. E. Crisenza, N. G. McCreanor, J. F. Bower. *J. Am. Chem. Soc.*, **2014**, *136*, 10258-10261.

On the bases of deuterium labelling studies, Bower suggested a mechanistic pathway wherein the initially generated iridium hydride intermediate evolves through a hydrometallation and an eventual C–C reductive elimination to form the product, with both, the oxidative addition and the alkene hydrometallation being reversible. The C–C reductive elimination was proposed to be the product-determining step (see **Scheme 77**). However, subsequent DFT calculations by Huang and Liu revealed that, while oxidative addition and hydrometallation are indeed reversible, the C–C reductive elimination has a very high energy barrier.[56] Thus, an alternative pathway involving the migratory insertion of the olefin into the C(sp_2)–Ir bond of **I-8** (carbometallation), followed by a C–H reductive elimination, was found to be energetically more favorable, as shown in **Scheme 77**.



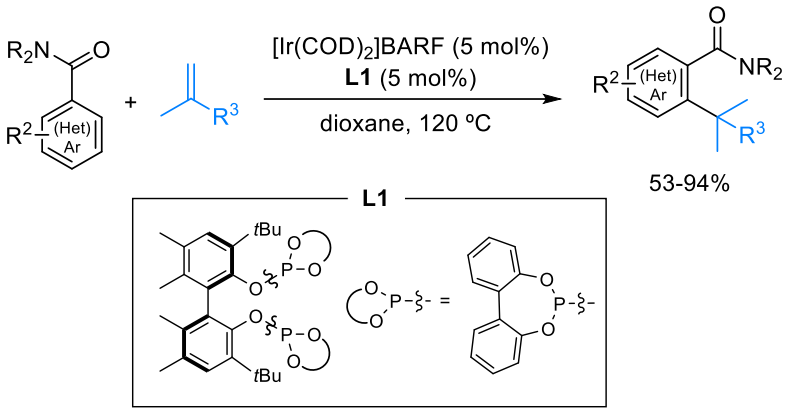
***Scheme 77**: Mechanistic pathways studied by Huang for the branched-selective hydroarylation of benzamides reported by Bower.*

Although considerable developments of intermolecular branch-selective methodologies have been achieved,[57] the use of 1,1-disubstituted alkenes to yield quaternary stereocenters still remains as a major challenge. In this context, in 2022, after the publication of some of our results (i.e. section 5.1), Bower and co-workers demonstrated

[56] G. Huang, P. Liu. *ACS Catal.*, **2016**, *6*, 809-820.

[57] Examples of branch-selective Ir-catalyzed hydroarylations: (a) Y. Ebe, T. Nishimura, *J. Am. Chem. Soc.*, **2015**, *137*, 5899-5902. (b) M. Zhang, G. Huang, *Dalton Trans.*, **2016**, *45*, 3552-3557. (c) M. Hatano, Y. Ebe, T. Nishimura, H. Yorimitsu, *J. Am. Chem. Soc.*, **2016**, *138*, 4010-4013. (d) D. Yamauchi, T. Nishimura, H. Yorimitsu, *Chem. Commun.*, **2017**, *53*, 2760-2763. (e) G. E. Crisenza, O. O. Sokolova, J. F. Bower, *Angew. Chem. Int. Ed.*, **2015**, *54*, 14866-14870. (f) T. Shibata, M. Michino, H. Kurita, Y. K. Tahara, K. S. Kanyiva, *Chem. Eur. J.*, **2017**, *23*, 88-91. (g) T. Shirai, T. Okamoto, Y. Yamamoto, *Asian J. Org. Chem.*, **2018**, *7*, 1054-1056. (h) S. Grelaud, P. Cooper, L. J. Feron, J. F. Bower, *J. Am. Chem. Soc.*, **2018**, *140*, 9351-9356. (g) M. Xiong, Y. Shu, J. Tang, F. Yang, D. Xing, *Molecules*, **2022**, *27*.

that iridium catalysts featuring the bisphosphite ligand **L1** enables the intermolecular hydroarylation of 1,1-disubstituted alkenes, producing products with quaternary carbon centers. Although the reaction has only been reported in racemic form (despite the use of chiral ligands), it is worth to note that it allows the synthesis of the sterically most hindered regioisomers, a unique feature that so far has only been achieved with tailored Ir catalysts (**Scheme 78**).[58]



***Scheme 78**: Bower's branched selective Iridium catalyzed hydroarylations of 1,1-disubstituted alkenes.*

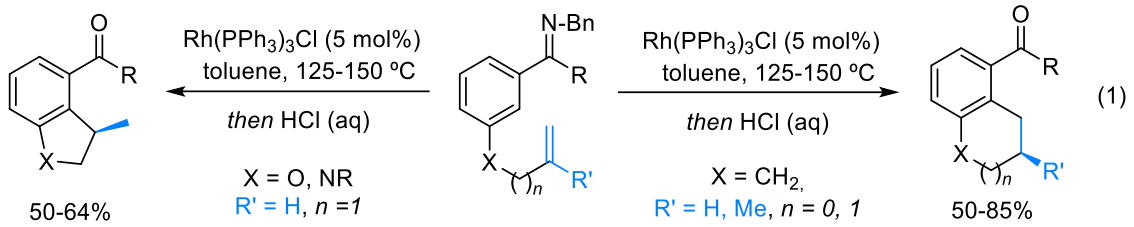
2.5.2. TM-catalyzed intramolecular additions of aromatic C–H bonds to alkenes

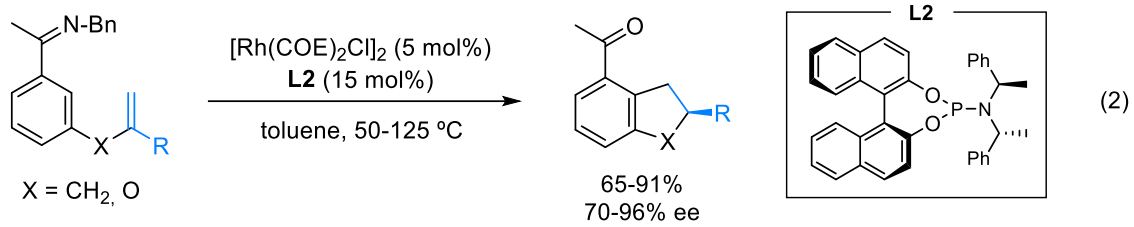
The intramolecular versions of these hydrocarbonation reactions are particularly appealing from a synthetic perspective, as they offer the opportunity to construct rings through a C–C bond-forming process. Remarkably, although these processes enable the generation of high structural complexity with complete atom economy, the number of examples is still scarce.

In 2001, Bergman and Ellman pioneered these synthetic methodologies by disclosing a Rh-catalyzed intramolecular hydroarylation of alkenes, using imines as directing groups.[59] This strategy enables the formation of various carbo- and heterocycles, such as indanes, dihydrobenzofurans, and indolines. Depending on the substrate, the cyclization proceeds via *exo*- or *endo-cyclization* pathways (**Scheme 79**, equation 1).

[58] P. Cooper, A. G. Dalling, E. H. E. Farrar, T. P. Aldhous, S. Grelaud, E. Lester, L. J. Feron, P. D. Kemmitt, M. N. Grayson, J. F. Bower. *Chem. Sci.,* **2022**, *13*, 11183-11189.
[59] R. K. Thalji, K. A. Ahrendt, R. G. Bergman, J. A. Ellman, *J. Am. Chem. Soc.*, **2001**, *123*, 9692-9693.

In 2004, the same group reported an enantioselective variant of the imine-directed alkylation using rhodium catalysts bearing chiral phosphoramidites, like **L2** (equation 2).[60]



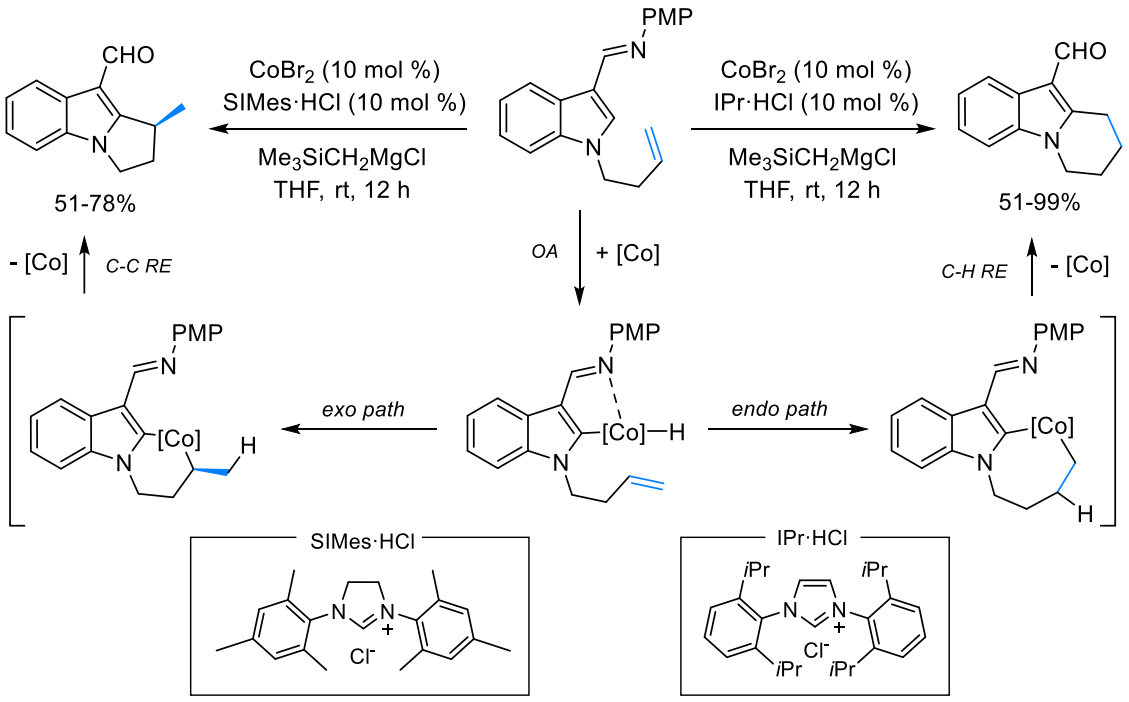


***Scheme 79**: Diverse Rh-catalyzed intramolecular hydroarylation of alkenes developed by Shibata and co-workers.*

Intramolecular hydroarylations can also be promoted by other metal catalysts. In 2013, Yoshikai reported the first intramolecular hydroarylation catalyzed by cobalt.[61] The catalytically active species were generated by combining $CoBr_2$ with a *N*-heterocyclic carbene ligand (such as SIMes or IPr) and using the Grignard reagent Me_3SiCH_2MgCl as reducing agent. The selectivity varied depending on the ancillary ligand used. With SIMes, the 5-membered *exo*-adducts featuring a tertiary carbon center were selectively formed. Conversely, the IPr ligand favored 6-membered rings through an *endo* cyclization, as shown in **Scheme 80**. Deuterium labeling experiments supported a hydrometallation-based mechanism.

[60] R. K. Thalji, J. A. Ellman, R. G. Bergman, *J. Am. Chem. Soc.*, **2004**, *126*, 7192-7193. For other related enantioselective examples,, see: (a) H. Harada, R. K. Thalji, R. G. Bergman, J. A. Ellman, *J. Org. Chem.*, **2008**, *73*, 6772-6779. (b) A. S. Tsai, R. M. Wilson, H. Harada, R. G. Bergman, J. A. Ellman, *Chem. Commun.*, **2009**, 3910-3912. (c) K. A. Ahrendt, R. G. Bergman, J. A. Ellman, *Org. Lett.*, **2003**, *5*, 1301-1303. (d) R. M. Wilson, R. K. Thalji, R. G. Bergman, J. A. Ellman, *Org. Lett.*, **2006**, *8*, 1745-1747

[61] Z. Ding, N. Yoshikai, *Angew. Chem. Int. Ed.*, **2013**, *52*, 8574-8578.



***Scheme 80**: Cobalt catalyzed intramolecular cyclization of indoles developed by Yoshikai.*

Nickel catalysts can also promote hydroarylations of alkenes, both inter- and intramolecularly. However, the success of these reactions is usually restricted to pyridines,[62] and imidazole-based systems.[63] Cramer made significant advances in the development of enantioselective versions in intramolecular *endo*-selective C–H annulation of *N*-tethered alkenyl indoles and pyrroles, without the requirement of any directing group.[64] This method enabled the access to a wide variety of tetrahydropyridoindoles and tetrahydroindolizines with excellent yields and selectivities; however, it is limited to the generation of 6-membered rings (**Scheme 81**).

Using computational studies, [65] Zhang proposed that the nickel-promoted C–H activation occurs via a Ligand-to-Ligand Hydrogen Transfer (*LLHT*) step, a type of process that can be interpreted as a concerted C–H activation/migratory insertion (Scheme 79). [66] Due to the relatively small atomic radius of Ni(0), this process is favored over the typical standard oxidative addition and migratory insertion of the resulting metal hydride species.

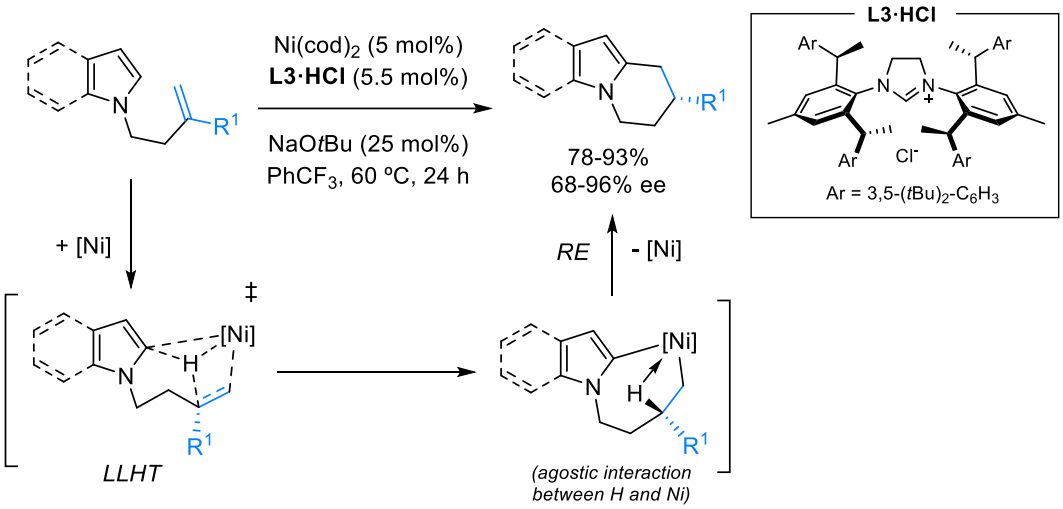
[62] (a) Y. Nakao, H. Idei, K. S. Kanyiva, T. Hiyama, *J. Am. Chem. Soc.*, **2009**, *131*, 15996–15997. (b) P. A. Donets, N. Cramer, *Angew. Chem. Int. Ed.*, **2015**, *54*, 633–637. (c) J. Diesel, A. M. Finogenova, N. Cramer, *J. Am. Chem. Soc.*, **2018**, *140*, 4489–4493. (d) D. Shen, W.-B. Zhang, Z. Li, S.-L. Shi, Y. Xu, *Adv. Synth. Catal.*, **2020**, *362*, 1125–1130.

[63] (a) A. T. Normand, S. K. Yen, H. V. Huynh, T. S. A. Hor, K. J. Cavell, *Organometallics*, **2008**, *27*, 3153–3160. (b) Y. X. Wang, S. L. Qi, Y. X. Luan, X. W. Han, S. Wang, H. Chen, M. Ye, *J. Am. Chem. Soc.*, **2018**, *140*, 5360–5364. (c) Z. J. Liu, J. F. Li, F. P. Zhang, X. T. Xu, M. Ye, *Org. Lett.*, **2023**, *25*, 353–357. (d) . F. Li, W. W. Xu, R. H. Wang, Y. Li, G. Yin, M. Ye, *Nat. Commun.*, **2021**, *12*, 3070.

[64] J. Diesel, D. Grosheva, S. Kodama, N. Cramer, *Angew. Chem. Int. Ed.*, **2019**, *58*, 11044–11048.

[65] X. Zhao, X. Ma, R. Zhu, D. Zhang, *Chem. Eur. J.*, **2020**, *26*, 5459-5468.

[66] S. Tang, O. Eisenstein, Y. Nakao, S. Sakaki, *Organometallics*, **2017**, *36*, 2761-2771.

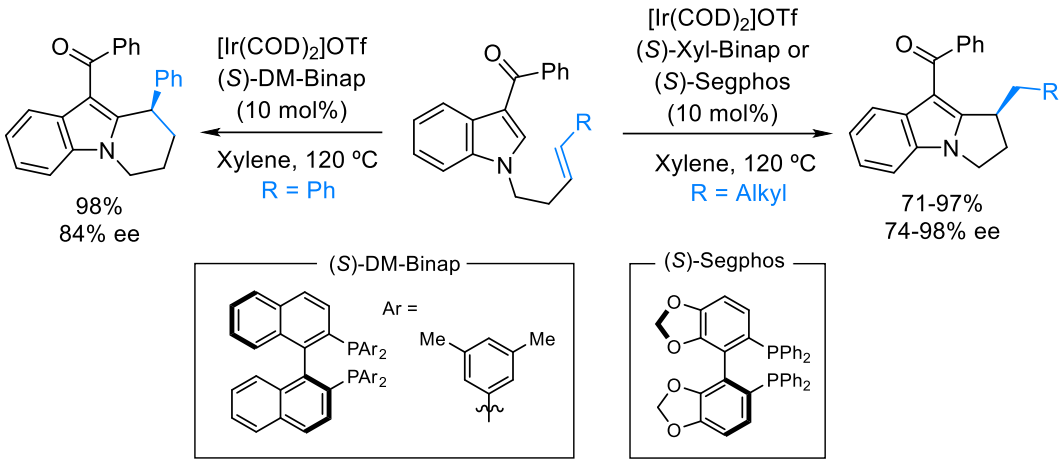


***Scheme 81**: Ni-catalyzed intramolecular endo-selective C–H annulation of N-tethered alkenyl indoles and pyrroles by Cramer.*

Despite the variety of intermolecular methodologies developed with iridium catalysts (section 2.5.1), when we started our investigations the intramolecular variants promoted by complexes this metal were extremely scarce. Thus, in 2015, Shibata and coworkers had reported an iridium-promoted intramolecular enantioselective hydroarylation of *N*-tethered alkenyl indoles. The catalyst, generated in situ from $[Ir(COD)_2]OTf$ and a chiral biphosphine affords either 5-*exo* or 6-*endo* cyclization products, depending on the substitution pattern of the alkene and the specific biphosphine used (e.g. DM-Binap or Segphos). Unsubstituted and alkyl-substituted olefins tend to follow an *exo* pathway, producing dihydropyrroloindoles with tertiary stereocenters. In contrast, when the terminal substituent of the alkene is an aryl group, and DM-Binap is employed as ligand, a 6-*endo*-selective cyclization is favored, yielding chiral tetrahydropyridoindoles (see **Scheme 82**).[67] Unfortunately, the methodology was limited to indoles and to a few substituted alkene partners, and didn't include the generation of products with quaternary stereocenters.

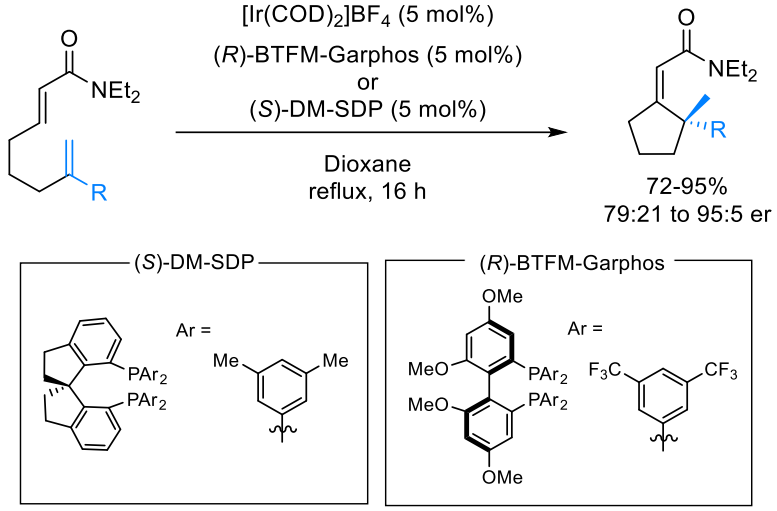
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[67] Shibata, T.; Ryu, N.; Takano, H. *Adv. Synth. Catal.*, **2015**, *357*, 1131–1135.



***Scheme 82**: Iridium catalyzed exo and endo selective intramolecular hydroarylations developed by Shibata and coworkers.*

In this context, our group described in 2017 an iridium(I)-catalyzed intramolecular hydrocarbonation based on the activation of olefinic C–H bonds. This methodology constitutes one of the very scarce examples that provides an asymmetric access to cyclic systems with quaternary carbon centers, although enantioselectivities were generally moderate (typically 80:20 er) and only in very few cases reached er's > 95:5 (**Scheme 83**).[68]

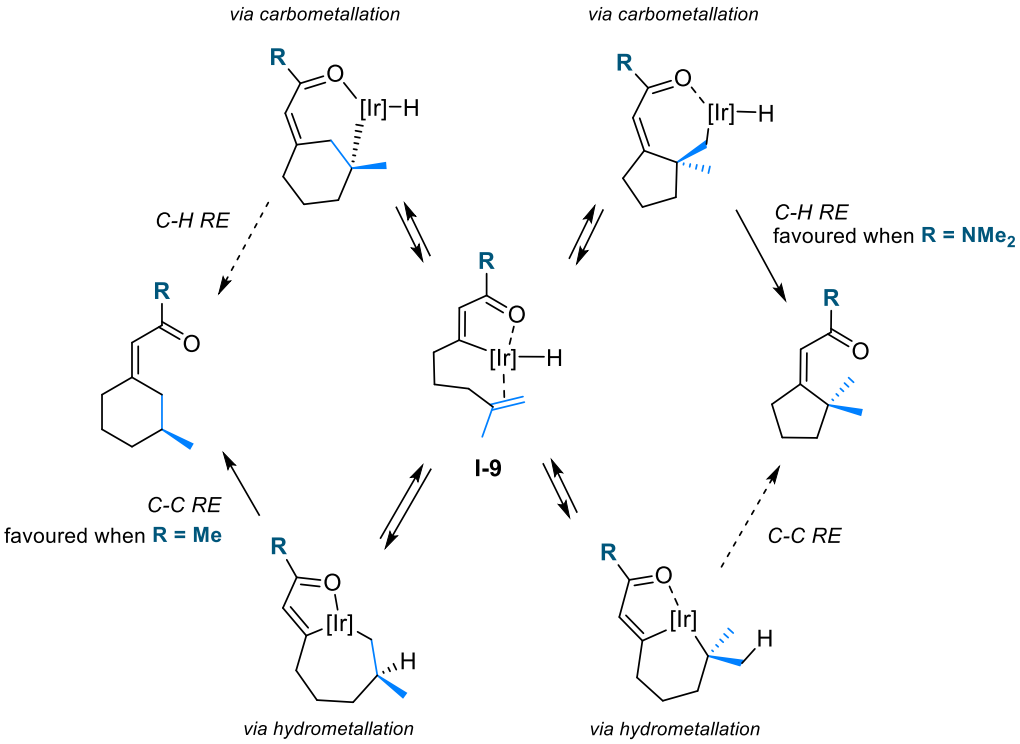


***Scheme 83**: Iridium catalyzed intramolecular hydroarylation of alkenes to access quaternary carbon centers developed by our group.*

Subsequent computational studies conducted by Huang and coworkers, indicate that the *exo*-cyclization products are formed through a migratory insertion of the alkene into the iridium-carbon bond of intermediate **I-9** (carbometallation), followed by a C–H reductive elimination (**Scheme 84**), in line with previous computational studies on intermolecular

[68] D. F. Fernández, M. Gulías, J. L. Mascareñas, F. López, *Angew. Chem. Int. Ed.*, **2017**, *56*, 9541–9545.

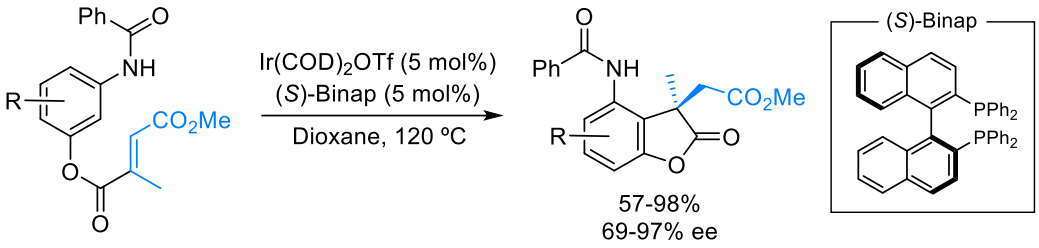
hydroarylations (see **Scheme 77**, page 85).[69] The alternative path, which involves *exo*-migratory insertion of the alkene into the Ir–H bond, followed by C–C reductive elimination, entails higher activation barriers. Furthermore, the study concludes that the *exo* selectivity of this process is favored by the use of a dialkylamide as a directing group. When employing ketones as directing group, the *endo*-migratory insertion followed by C–C reductive elimination is computationally favored. Indeed, the C–C reductive elimination step is highly influenced by the coordinating strength of the directing group; the weaker coordination of the ketone group, compared to the amide, results in a more electron-deficient Ir center, which favors the C–C reductive elimination, leading to the observed *endo*-selectivity.



***Scheme 84**: Proposed mechanism for Ir-catalyzed hydrocarbonation of alkenes by Huang.*

A year later, Shibata reported an intramolecular hydroarylation of α,β-unsaturated acrylates with acetanilides to produce compounds that feature quaternary carbon stereocenters (**Scheme 85**).[70] The reaction uses a catalyst generated from [Ir(COD)$_2$OTf] and Binap, delivering the products in good yields and with moderate to good enantioselectivities, although the scope is limited to the generation of 5-membered γ-lactones.

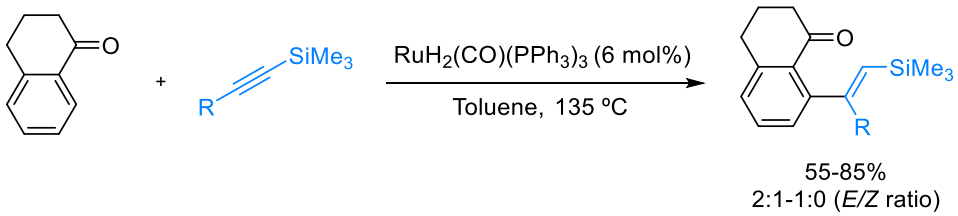
[69] Y. Lang, M. Zhang, Y. Cao, G. Huang, *Chem. Commun.*, **2018**, *54*, 2678–2681.
[70] T. Shibata, H. Kurita, S. Onoda, K. S. Kanyiva, *Asian J. Org. Chem.*, **2018**, *7*, 1411–1418.



***Scheme 85**: Shibata's intramolecular hydroarylation of α,β-unsaturated acrylates with acetanilides catalyzed by iridium(I).*

2.5.3. TM-catalyzed additions of aromatic C–H bonds to alkynes

In 1995, following his work on the hydrocarbonation of alkenes, Murai reported a ruthenium-catalyzed intermolecular hydroarylation of alkynes with aromatic systems bearing a ketone, to direct the C–H activation (**Scheme 86**).[71] Conducted at 135 ºC, the reaction provides access to a variety of β-vinyl substituted ketones with good yields and notable *E/Z* selectivities.



***Scheme 86**: Ru-catalyzed hydroarylation of alkynes developed by Murai.*

Similarly to the hydroarylation of alkenes, numerous synthetic methodologies with alkynes were developed since then using ruthenium,[72] and other transition metals like rhodium,[73] nickel,[74] or cobalt complexes.[75]

Regarding iridium, Miura reported in 1999 a pioneering example with 1-naphthols, using a catalyst generated in situ from $[Ir(COD)Cl]_2$, P(*t*-Bu)$_3$, and catalytic amounts of

[71] F. Kakiuchi, Y. Yamamoto, N. Chatani, S. Murai. *Chem. Lett.,* **1995**, *24*, 681-682.

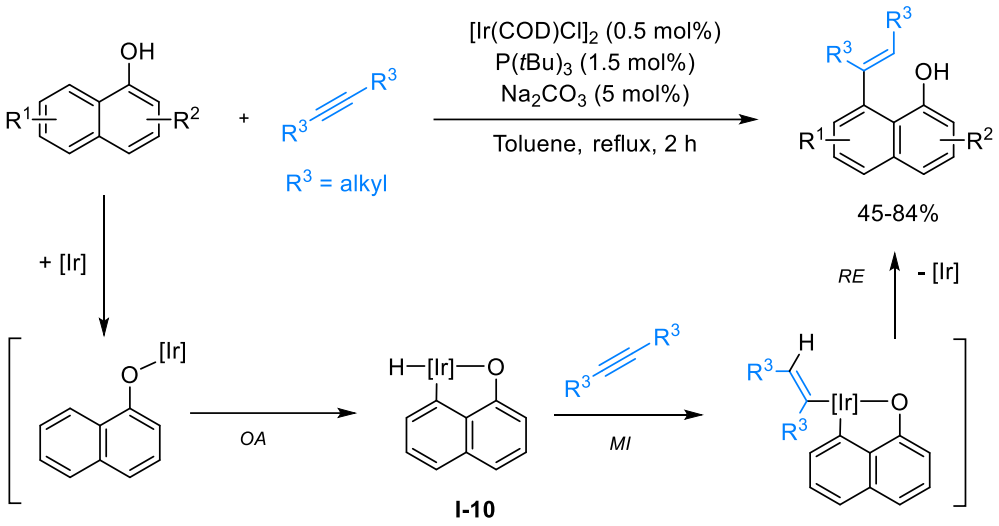
[72] Examples employing ruthenium catalysis: (a) N. M. Neisius, B. Plietker, *Angew. Chem. Int. Ed.*, **2009**, *48*, 5752-5755. (b) K. Meng, J. Zhang, F. Li, Z. Lin, K. Zhang, G. Zhong, *Org. Lett.*, **2017**, *19*, 2498-2501.

[73] Examples employing rhodium catalysis: (a) D. A. Colby, R. G. Bergman, J. A. Ellman, *J. Am. Chem. Soc.*, **2006**, *128*, 5604-5605. (b) C. Aissa, A. Furstner, *J. Am. Chem. Soc.*, **2007**, *129*, 14836-14837. (c) D. A. Colby, R. G. Bergman, J. A. Ellman, *J. Am. Chem. Soc.*, **2008**, *130*, 3645-3651. (d) S. Duttwyler, S. Chen, M. K. Takase, K. B. Wiberg, R. G. Bergman, J. A. Ellman, *Science*, **2013**, *339*, 678-682. (e) F. Mo, G. Dong, *Science*, **2014**, *345*, 68-72. (f) X. Sun, E.-Z. Lin, B.-J. Li, *J. Am. Chem. Soc.*, **2022**, *144*, 17351-17358.

[74] Examples employing nickel catalysis: (a) Y. Nakao, K. S. Kanyiva, S. Oda, T. Hiyama, *J. Am. Chem. Soc.*, **2006**, *128*, 8146-8147. (b) Y. Nakao, K. S. Kanyiva, T. Hiyama, *J. Am. Chem. Soc.*, **2008**, *130*, 2448-2449. (c) C. C. Tsai, W. C. Shih, C. H. Fang, C. Y. Li, T. G. Ong, G. P. Yap, *J. Am. Chem. Soc.*, **2010**, *132*, 11887-11889.

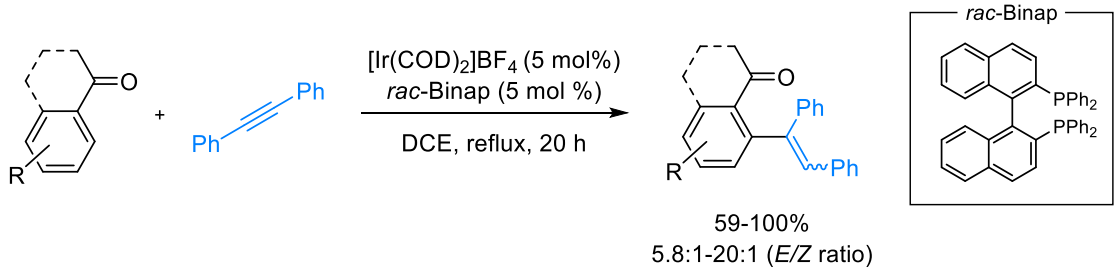
[75] Examples employing cobalt catalysis: (a) K. Gao, P. S. Lee, T. Fujita, N. Yoshikai, *J. Am. Chem. Soc.*, **2010**, *132*, 12249-12251. (b) P. S. Lee, T. Fujita, N. Yoshikai, *J. Am. Chem. Soc.*, **2011**, *133*, 17283-17295. (c) Y. Saito, J. Kikuchi, C. Wang, N. Yoshikai, *Angew. Chem. Int. Ed.*, **2023**, *62*, e202301006.

Na_2CO_3.[76] The reaction is proposed to proceed via an iridium naphtholate complex, which undergoes oxidative insertion of the C(8)–H bond of the naphthol. The resulting intermediate **I-10** undergoes alkyne hydrometallation followed by C–C reductive elimination to deliver the *cis*-hydroarylated product (see **Scheme 87**).



***Scheme 87**: Iridium-catalyzed hydroarylation of alkynes with naphthols.*

The iridium catalyst formed from $[Ir(COD)_2]BF_4$ and *rac*-Binap, which Shibata demonstrated to promote the hydroarylation of alkenes with aryl ketones, is also effective for alkynes such as diphenylacetylene.[77] This catalyst yields the expected *o*-alkenylated products in moderate to excellent yields (**Scheme 88**).



***Scheme 88**: Ir-catalyzed hydroarylation of alkynes with aryl ketones developed by Shibata.*

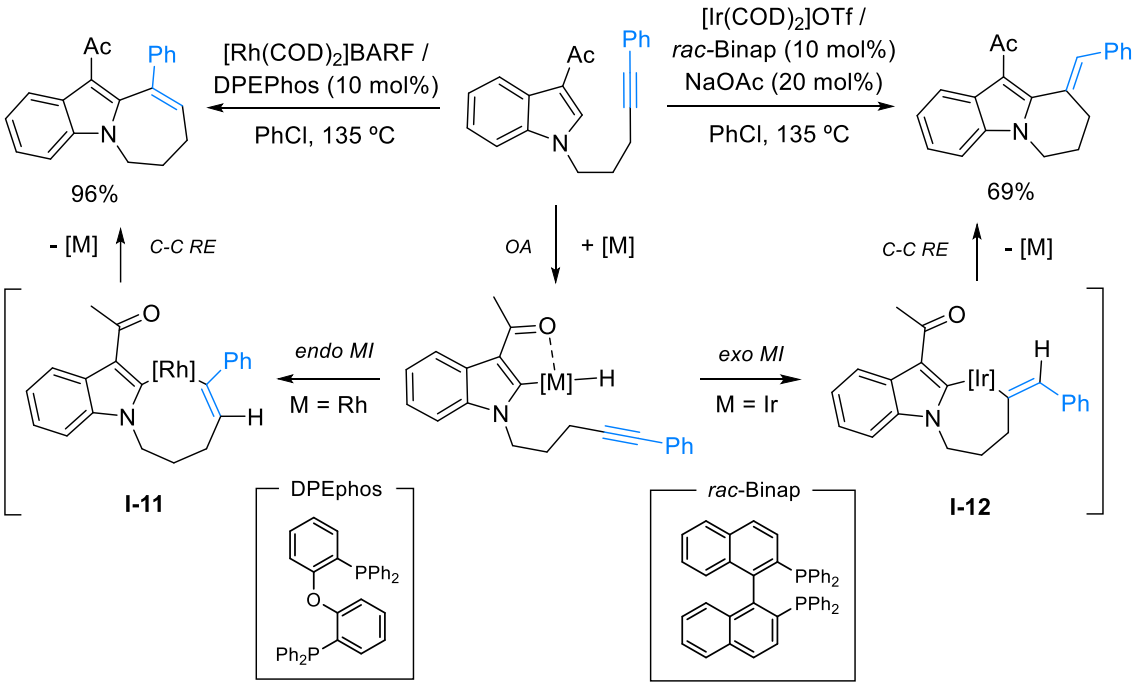
Examples of metal-catalyzed intramolecular hydrocarbonations of alkynes, based on C−H bond activations, are rare, regardless of the metal used. In 2017, Shibata reported the use of rhodium and iridium catalysts for a regiodivergent intramolecular

[76] T. Satoh, Y. Nishinaka, M. Miura, M. Nomura. *Chem. Lett.,* **1999**, *28*, 615-616. The method was later extended to include *N*-(1-naphthyl)sulfonamides: Y. Nishinaka, T. Satoh, M. Miura, H. Morisaka, M. Nomura, H. Matsui, C. Yamaguchi. *Bull. Chem. Soc. Jpn.,* **2001**, *74*, 1727-1735.

[77] K. Tsuchikama, M. Kasagawa,Y. K. Hashimoto, K. *Endo*, T. Shibata. *J. Organomet. Chem.,* **2008**, *693*, 3939-3942.

hydroarylation of *N*-tethered alkynyl indoles.[78] The iridium catalyst, derived from $[Ir(COD)_2]OTf$ and Binap, facilitated a 6-*exo*-dig cyclization. Conversely, a rhodium catalyst, generated in situ from $[Rh(COD)_2]BARF$ and the biphosphine ligand DPEPhos, promoted a 7-*endo*-dig cyclization to produce an adduct with a seven-membered ring (**Scheme 89**).

The authors proposed that with the rhodium catalyst, an initial chelation-assisted C−H activation is followed by *trans* hydrometallation, forming an eight-membered rhodacyclic intermediate (**I-11**). In contrast, the iridium catalyst would undergo an *exo*-selective hydrometallation to form **I-12**. Subsequent C−C reductive eliminations would then produce the six- and seven-membered fused rings. The authors did not exclude an alternative mechanism involving carbometallations and C−H reductive eliminations.

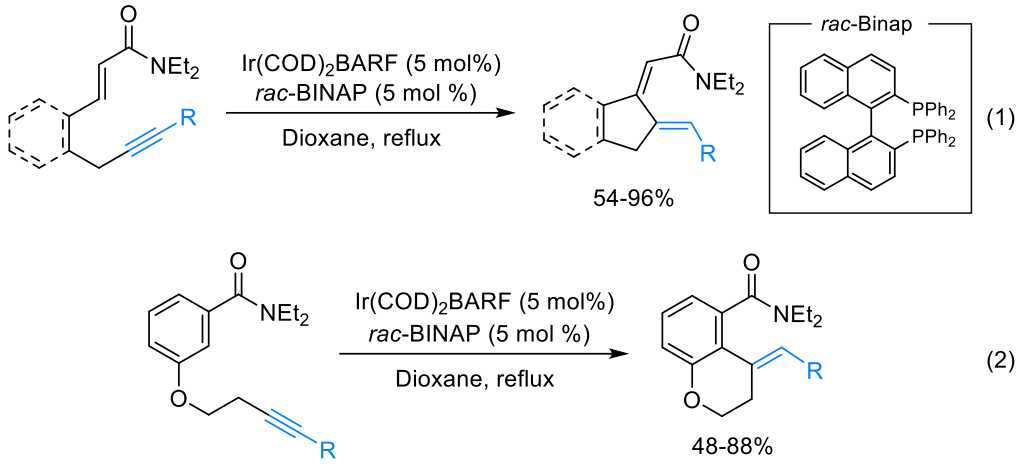


***Scheme 89**: Metal-dependent intramolecular hydroarylation of alkynes developed by Shibata and co-workers.*

In 2018, our group introduced a more versatile intramolecular Ir-catalyzed *exo* cyclization that extends beyond the activation of (hetero)aromatic C–H bonds to include more challenging C–H bonds of alkenes. This approach generates *exo*-alkylidene systems with complete stereoselectivity (**Scheme 90**, equations 1 and 2).[79] The use of a

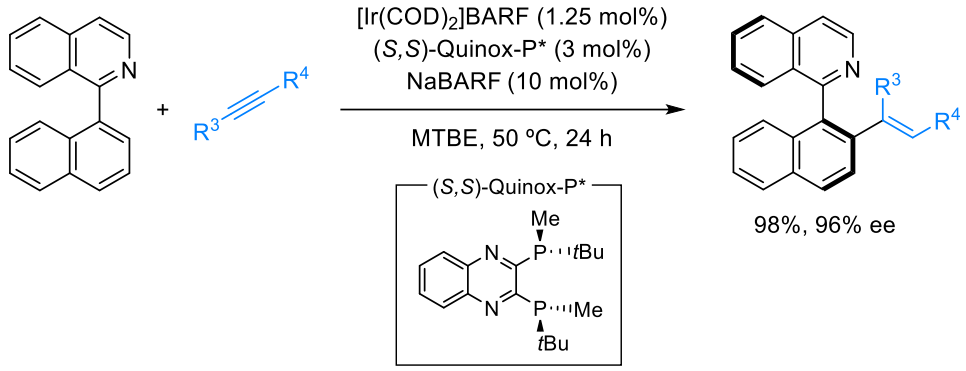
[78] T. Shibata, T. Baba, H. Takano, K. S. Kanyiva, *Adv. Synth. Catal.*, **2017**, *359*, 1849–1853.
[79] D. F. Fernández, C. A. B. Rodrigues, M. Calvelo, M. Gulías, J. L. Mascareñas, F. López, *ACS Catal.*, **2018**, *8*, 7397–7402.

diethylcarboxamide as a directing group is crucial for the process's efficiency, as ketones or carboxylic esters fail to participate in the reaction.



***Scheme 90**: Ir-catalyzed intramolecular hydrocarbonation of alkynes developed by our group.*

These methodologies do not generate new stereocenters, but there are a few examples of asymmetric versions. Notably, Lassaletta and colleagues developed an atroposelective alkenylation of 2-phenylpyridines, yielding axially chiral styrenes with good yields and high enantioselectivities, by employing the chiral iridium(I) catalyst formed from $[Ir(COD)_2Cl]_2$, Quinox-P* and NaBARF (**Scheme 91**).[80]



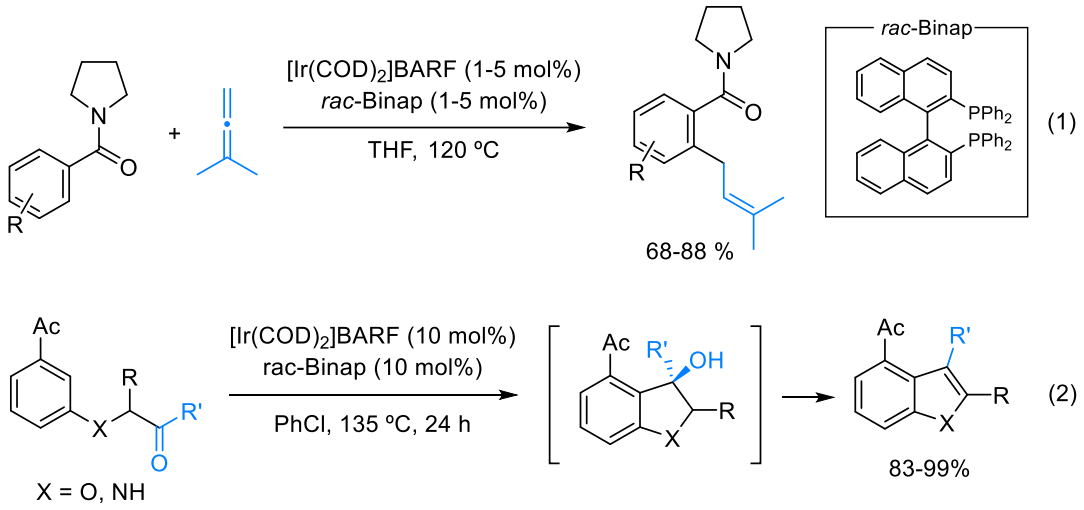
***Scheme 91**: Ir-catalyzed asymmetric hydroarylation of alkynes towards axially chiral heterobiaryls, developed by Lassaletta and coworkers.*

2.5.4. *TM-catalyzed additions of aromatic C–H bonds to other C=C and C=X unsaturated systems*

Aside from the abovementioned examples of C(sp^2)–H additions to alkenes and alkynes, there are a few cases of hydrocarbonation reactions using other unsaturated systems

[80] P. Vázquez-Domínguez, A. Romero-Arenas, R. Fernández, J. M. Lassaletta, A. Ros. *ACS Catal.*, **2022**, *13*, 42-48. For a related work, see: S.-L. You, Q. Gu, Q. Zhou, S.-Y. Yin, D.-S. Zheng, W.-W. Zhang, S.-Z. Zhang. *Synlett*, **2023**, *34*, 1442-1446.

such as allenes. The scarcity is even more evident considering the additions to heterounsaturated systems, like carbonyls or imines. In pioneering independent works, Krische[81] and Shibata[82] published examples of hydroarylations of allenes and ketones, both leading to achiral products (**Scheme 92**, equations 1 and 2 respectively). These methodologies will be discussed in detail in the corresponding chapters of this thesis.



***Scheme 92**: Examples of Ir-catalyzed hydroarylations of allenes and ketones*

As shown throughout the precedents described in this introduction, intramolecular hydroarylation processes are mostly limited to those cases where a tertiary stereocenter is generated. Additionally, they are generally restricted to forming five- or six-membered rings from very standard aromatic precursors. Intramolecular examples using allenes as partners are completely unprecedented.

Moreover, in the case of the addition to carbonyls, the examples of these processes are still scarce and limited to the synthesis of specific types of products.

Therefore, there are still many important problems and limitations that need to be addressed in this area of hydrocarbonation reactions.

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[81] Y. J. Zhang, E. Skucas, M. J. Krische, *Org. Lett.,* **2009**, *11*, 4248-4250.
[82] K. Tsuchikama, Y.-K. Hashimoto, K. *Endo*, T. Shibata, *Adv. Synth. Catal.*, **2009**, *351*, 2850–2854.

3

Objectives



As outlined in the introduction of this PhD thesis, intramolecular hydroarylation methodologies based on transition metal catalyzed C–H bond insertion into unsaturated systems have garnered significant attention due to their inherent atom economy and potential for constructing fused carbo- and hetero-polycyclic systems. Despite intensive efforts in this field, there are still major challenges that need to be addressed.

In this PhD thesis we have focused our efforts on:

- **The development of highly enantioselective hydroarylations of alkenes for the assembly of fused heterocyclic systems**, **including those bearing all-carbon quaternary stereocenters.**
  Moreover, we aimed to construct not only products with the more common five- and six-membered rings, but also higher cycles, as well as polycycles containing multiple stereocenters, in an enantio- and diastereoselective manner.

- **The development of methodologies for intramolecular C–H addition across allenes, including enantioselective variants**.
  As deduced from the introduction, allenes, despite their peculiar structure, and reactivity potential, have barely been investigated in hydrocarbonation reactions. We are convinced of their unique potential to unveil novel reactivity patterns.

- **Discovery of cascade processes involving additional C=C bonds**.
  This would allow a faster increase in skeletal complexity.

- **Development of methodologies for intramolecular C–H addition across carbonyls, including enantioselective variants**.
  Similarly to allenes, the use of ketones and aldehydes as partners in hydrocarbonation reactions has been very scarce, and, if appropriately controlled, they hold a great synthetic potential.

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4

Methodology



4.1. Materials employed

Bis(cyclooctadiene)iridium(I) tetrakis(3,5-bis(trifluoromethyl) phenyl) borate (abbreviated as [Ir(COD)$_2$]BARF) and Bis(1,5-cyclooctadiene) Iridium(I) tetrafluoroborate (abbreviated as [Ir(COD)$_2$]BF$_4$) were purchased from Aldrich and Strem Chemicals. Other bisphosphines were purchased from Aldrich or Strem-Chemicals. All other reagents used were bought from Aldrich, Alfa Aesar, TCI or Acros and used without further purification.

4.2. General experimental information

All reactions dealing with air- and moisture-sensitive compounds were carried out in oven-dried reaction flask under argon atmosphere with dry solvents. The abbreviation "*rt*" refers to reactions carried out at a temperature between 20-25°C. Reaction mixtures were stirred using Teflon-coated magnetic stirring bars. Reaction temperatures were maintained using Thermowatch-controlled silicone oil baths or aluminum heating blocks.

Thin-layer chromatography (TLC) was performed on silica gel plates and components were visualized by observation under UV light, and by treating the plates with p-anisaldehyde or phosphomolybdic acid solutions, followed by heating. Flash chromatography was carried out on silica gel unless otherwise stated. Dryings were performed with anhydrous Na_2SO_4.

Concentration refers to the removal of volatile solvents via distillation using a Büchi rotary evaporator followed by residual solvent removal under high vacuum.

4.3. General information about characterization of compounds

NMR spectra were recorded in $CDCl_3$, at 300 MHz (Varian) or 500 MHz (Varian). Carbon types and structure assignments were determined from DEPT-NMR. NMR spectra were analyzed using MestreNova© NMR data processing software (www.mestrelab.com). ^{1}H-NMR spectral data are reported as follows: chemical shift (δ ppm), integration and multiplicity. The following abbreviations are used to indicate signal multiplicity: s, singlet; d, doublet; t, triplet; q, quartet; dd, double doublet; ddd, doublet of doublet of doublets; td, triple doublet; dt, doublet of triplets; dq, doublet of quartet; m, multiplet; br, broad. 1,3,5-Trimethoxybenzene or dibromomethane was used as internal standard. NMR spectra of the precursors and products of this thesis can be downloaded using this link: https://2ly.link/21fpK (password: FURXmRnw).

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Mass spectra (ESI-MS) were acquired using IT-MS Bruker AmaZon SL at CIQUS and using chemical ionization (CI) electron impact (EI), or electrospray ionization (ESI) at the CACTUS facility of the University of Santiago de Compostela.

Melting points were measured on a Büchi Melting Point B-560 apparatus.

Enantiomeric ratios (er) were determined on an Agilent HPLC 1100 Series or on a Jasco SFC 4000 series by using commercially available chiral columns.

X-ray crystallographic analysis was conducted at the CACTUS facility of the University of Santiago de Compostela. The measurements were performed with a Bruker D8 Venture Photon III-14 using a microfocus sealed tube as diffraction source. CIF data can be downloaded using this link: https://2ly.link/21fpK (password: FURXmRnw).

4.4. General procedure for Ir(I)-catalyzed reactions

$[Ir(COD)_2]$BARF or other iridium source (cat), ligand (cat), substrate (typically 0.1 mmol) and solvent (typically 0.125 M) were sequentially added to a sealed tube under argon atmosphere and the reaction mixture was then stirred at the indicated temperature for the indicated time. The mixture was concentrated, and the crude residue was purified by flash chromatography. The specific experimental details of each reaction developed in this doctoral thesis are provided in section 7, pages 249.

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5

Results and discussion



5.1

Enantioselective intramolecular Iridium(I)-catalyzed hydroarylations of alkenes: Access to polycyclic systems bearing quaternary stereocenters

Part of the results of this section were published:

Highly Enantioselective Iridium(I)-Catalyzed Hydrocarbonation of Alkenes: A Versatile Approach to Heterocyclic Systems Bearing Quaternary Stereocenters

A. Arribas,[1] M. Calvelo,[1] D.F. Fernández,[1] C. A. B. Rodrigues,[1] J. L. Mascareñas,[1] F. López[1,2]
Angew. Chem. Int. Ed., **2021**, *60*, 19297–19305.

[1] Centro Singular de Investigación en Química Biolóxica e Materiais Moleculares (CiQUS) and Departamento de Química Orgánica, Universidade de Santiago de Compostela, 15782 Santiago de Compostela (Spain)

[2] Misión Biológica de Galicia, Consejo Superior de InvestigacionesCientíficas (CSIC)36080 Pontevedra (Spain)

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5.1.1. Precedents

Polycyclic systems bearing all carbon quaternary carbon centers

Quaternary carbon stereocenters are ubiquitously present in numerous natural products, which exhibit significant and diverse bioactivities. **Figure 7** shows some natural products bearing chiral quaternary carbon centers embedded in heteropolycyclic skeletons. Despite significant advances in the past few decades, the number of enantioselective catalytic methodologies for the preparation of these motifs is very low, so that the development of new asymmetric protocols is of major relevance.[83]

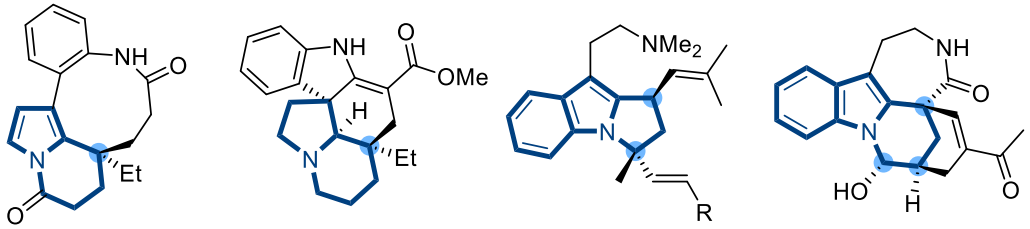
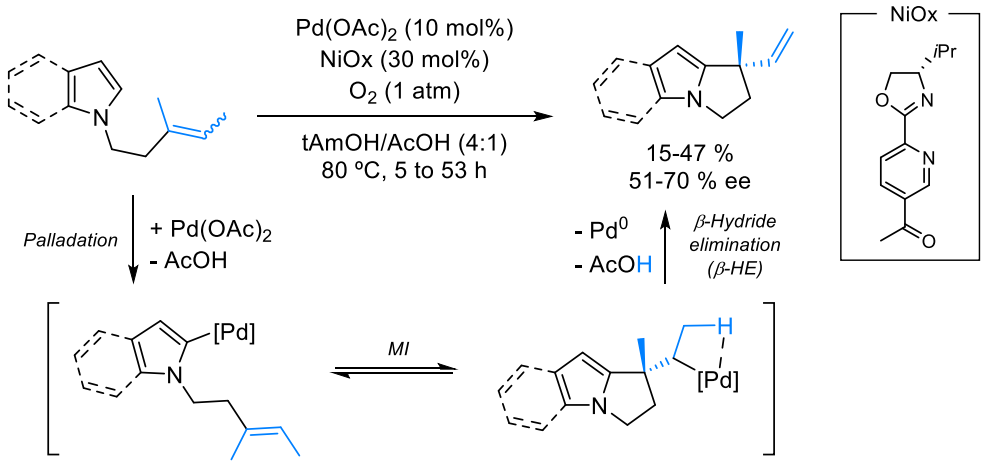


***Figure 7**: Natural products with heteropolycyclic skeletons bearing all-carbon quaternary stereocenters.*

In 2003, Stoltz reported an elegant example of an intramolecular Fujiwara-Moritani reaction that enables the generation of fused heterocyclic systems bearing all-carbon quaternary stereocenters.[84] In 2009, Oestreich reported the enantioselective variant of this process,[85] which mechanistically involves the C–H activation of a heterocycle with a Pd catalyst, via a CMD mechanism, a subsequent migratory insertion and a β-hydride elimination, resulting in the formation of the indole-containing polycycles with modest enantioselectivities (**Scheme 93**).

[83] C. Li, S. S. Ragab, G. Liu, and W. Tang, *Nat. Prod. Rep.*, **2020**, *37*, 276–292.
[84] E. M. Ferreira and B. M. Stoltz, *J. Am. Chem. Soc.*, **2003**, *125*, 9578–9579.
[85] J. A. Schiffner, T. H. Wöste, and M. Oestreich, *Eur. J. Org. Chem.*, **2010**, *174*, 174–182.



***Scheme 93**: Pd-catalyzed intramolecular Fujiwara-Moritani developed by Stoltz.*

The following section reviews alternative intramolecular hydroarylations of alkenes that facilitate the asymmetric construction of cyclic systems with quaternary stereocenters, involving processes mediated by C–H activations via oxidative addition or CMD-like mechanisms.

TM catalyzed intramolecular hydroarylations of alkenes leading polycyclic systems bearing all-carbon quaternary centers: Asymmetric variants

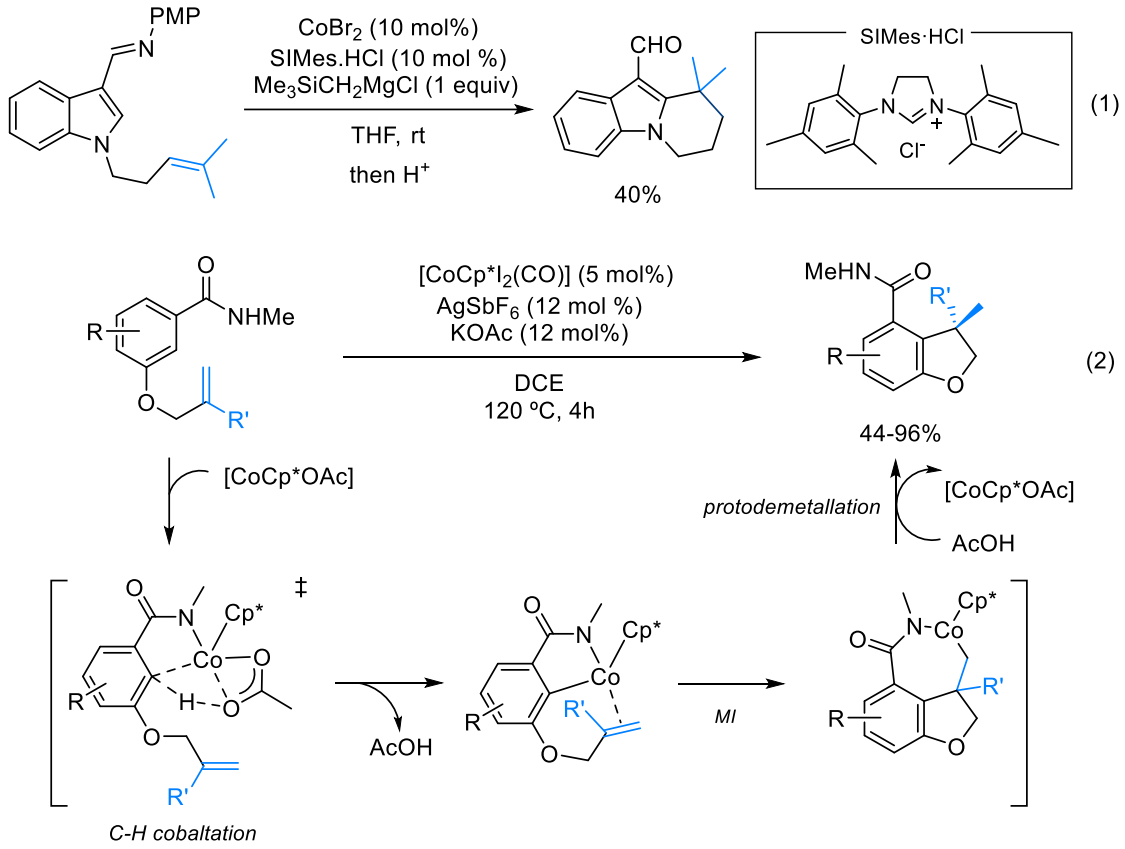
Most precedents on TMC hydroarylations that generate all-carbon quaternary centers typically rely on processes involving C–H activations via a CMD (Concerted Metallation-Deprotonation) mechanism, followed by migratory insertion and protodemetallation. But very few of them have been developed in an asymmetric fashion.

On the other hand, processes wherein the C–H bond is added across the unsaturated system through an oxidative addition/migratory insertion/reductive elimination manifold are rare and, particularly, those entailing enantioselective versions were unknown when this PhD work was initiated. Therefore, in this section we will include precedents of non-enantioselective examples leading to cyclic systems bearing all-carbon stereocenters, as well as those enantioselective variants that were published during our own studies.

In 2013, Yoshikai reported, a single example of a low valent cobalt catalyst that is able to promote an *endo*-selective hydroarylation that yields a product with a quaternary center (**Scheme 94**, equation 1).[61] The authors proposed a mechanism based on C–H oxidative addition, followed by migratory insertion and reductive elimination. In 2020, Lete and coworkers reported Co(III)-catalyzed intramolecular hydroarylation that

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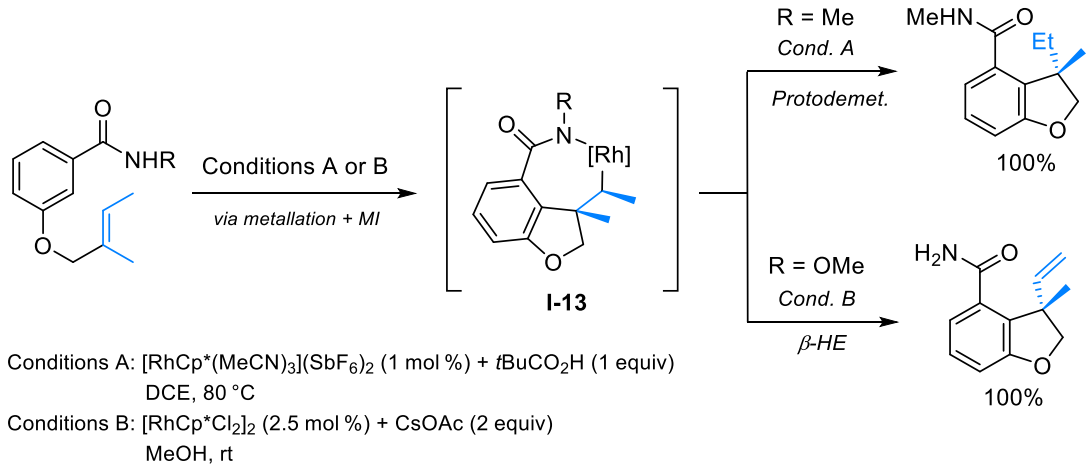
generates benzohydrofuranes bearing quaternary centers (equation 2).[86] The authors proposed a CMD process for the C–H activation, which is facilitated by coordination of the cobalt to the amide group. Both methods were only reported in a racemic variant and limited to the formation of a specific type of skeleton.



***Scheme 94**: Low valent Cobalt-catalyzed hydroarylation example generating a quaternary carbon center (1), and Co(III)-catalyzed intramolecular hydroarylation (2).*

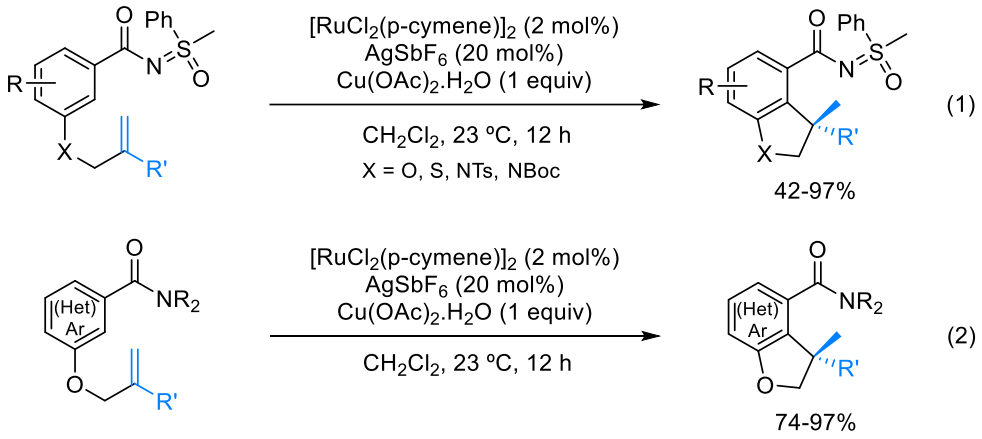
In 2013, Rovis reported a Rh(III)-catalyzed intramolecular process that generates a variety of dihydrobenzofurans bearing carbon quaternary centers in a racemic manner.[87] A common intermediate, **I-13,** is formed through a CMD process, followed by a migratory insertion. Depending on the amide used as directing group and the catalyst employed, the reaction leads to different products such as those resulting from a protonation or a β-hydride elimination (see **Scheme 95**).

[61] Z. Ding, N. Yoshikai, *Angew. Chem. Int. Ed.*, **2013**, *52*, 8574-8578.
[86] A. Carral-Menoyo, N. Sotomayor, E. Lete, *J. Org. Chem.*, **2020**, *85*, 10261–10270.
[87] T. A. Davis, T. K. Hyster, T. Rovis, *Angew. Chem. Int. Ed.*, **2013**, *52*, 14181–14185.



***Scheme 95**: Skeletal diversity on intramolecular hydroarylations employing Rh(III) catalysis, developed by Rovis and coworkers.*

In 2016, Sahoo developed a variant of this type of process using a cationic ruthenium catalyst, generated in situ from $[RuCl_2(p\text{-cymene})]_2$ and $AgSbF_6$.[88] They employed methyl phenyl sulfoximine (MPS) as directing group (**Scheme 96**, equation 1). Worth noting, in 2016, Sahoo and coworkers developed similar reactions using commercially available amides as directing groups (equation 2).[89] In both cases the processes are limited to the synthesis of dihydrobenzofurans and related 5-membered heterocycles in a racemic manner.

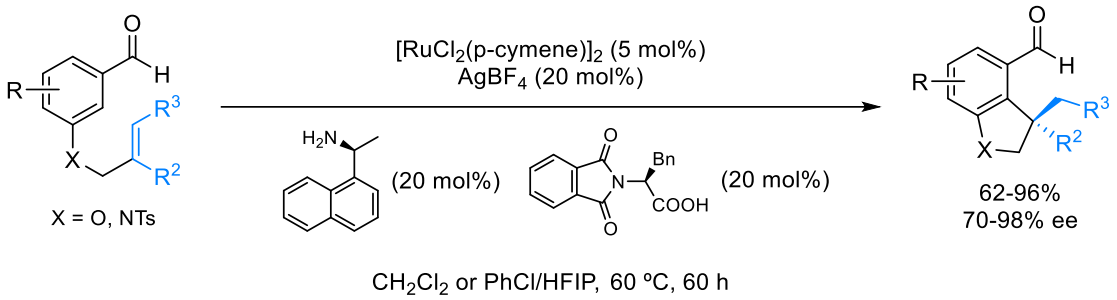


***Scheme 96**: Ru(II)-catalyzed intramolecular cyclizations developed by Sahoo group.*

In 2019, Cui published an enantioselective ruthenium-catalyzed hydroarylation of alkene-tethered benzaldehydes using a chiral transient directing group, which is formed

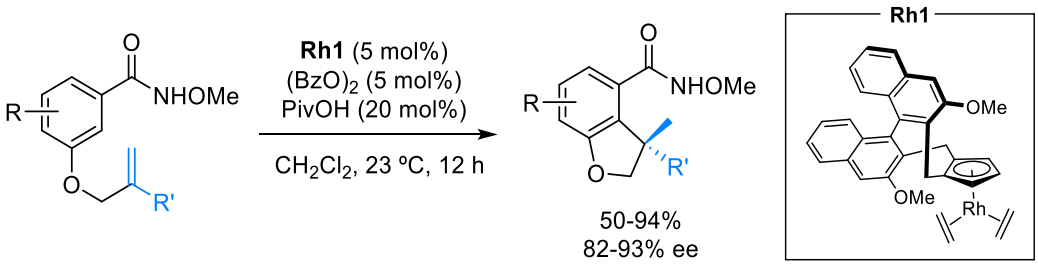
[88] K. Ghosh, R. K. Rit, E. Ramesh, A. K. Sahoo, *Angew. Chem. Int. Ed.*, **2016**, *55*, 7821–7825.
[89] R. K. Rit, K. Ghosh, R. Mandal, A. K. Sahoo, *J. Org. Chem.*, **2016**, *81*, 8552–8560.

in situ by condensation of the benzaldehyde and a chiral amine. The method provides good yields and ee's of up to 98% ee (**Scheme 97**).[90]



***Scheme 97**: Ru(II)-catalyzed enantioselective cyclization enabled by chiral transient directing group strategy.*

One of the common limitations of using transition metals in high oxidation states, which are required for CMD-like processes, is the lack of compatibility between their required reaction conditions and standard chiral ligands such as phosphines, phosphites, phosphoramidites, bipyridines, or NHCs. This limitation was overcome in 2014 by Cramer, who reported Rh(III) catalysts bearing chiral cyclopentadienyl ligands, for the enantioselective synthesis of dihydrobenzofurans with quaternary stereocenters (**Scheme 98**).[91] Despite the novelty, the hydroarylation method was still limited to build dihydrobenzofurans from allyl phenol ethers, and to the exclusive generation of methyl-substituted stereocenters (from terminally unsubstituted alkenes).



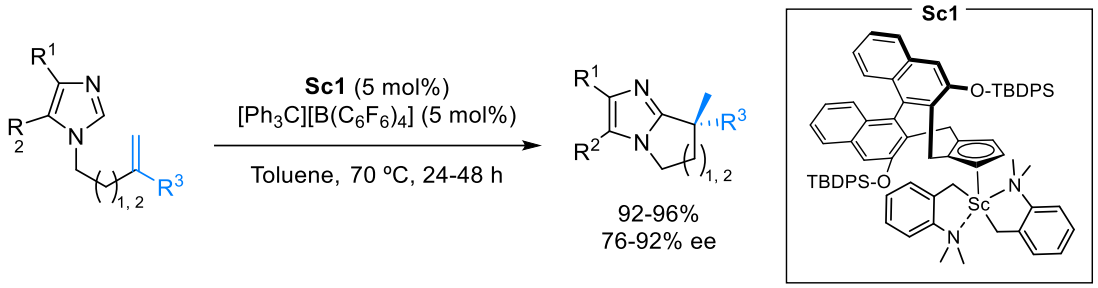
***Scheme 98**: Enantioselective intramolecular cyclization using chiral Rh(III) complexes developed by Cramer.*

It is important to note that most processes discussed up to this point have been exclusively focused on the assembly of 5-membered rings (and almost exclusively dihydrobenzofurans). In 2020, Hou published a related methodology based on the use of chiral scandium catalysts that enables the intramolecular hydroarylation of 1,1-

[90] Z. Y. Li, H. H. C. Lakmal, X. Qian, Z. Zhu, B. Donnadieu, S. J. McClain, X. Xu, X. Cui, *J. Am. Chem. Soc.*, **2019**, *141*, 15730–15736. A few months later, the Wang group published a very similar study, using the same catalyst and chiral amine in their process, reaching enantiomeric excesses of up to 99%: G. Li, Q. Liu, L. Vasamsetty, W. Guo, J. Wang, *Angew. Chem. Int. Ed.*, **2020**, *59*, 3475–3479.

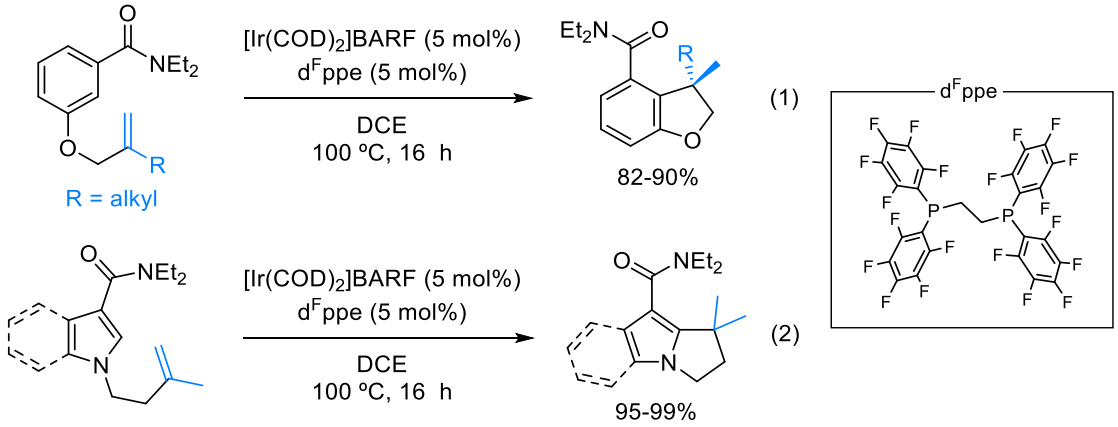
[91] B. Ye, P. A. Donets, N. Cramer, *Angew. Chem. Int. Ed.*, **2013**, *53*, 507–511.

disubstituted alkenes using imidazoles and benzimidazoles, allowing the formation of 5 and 6-membered rings bearing quaternary stereocenters with high enantioselectivities (**Scheme 99**).[92] A computational study conducted by Wang in 2021 supported that the C–H activation occurs through a deprotonative process which resembles those CMD-like mechanims based on rhodium(III), ruthenium(II), or cobalt(III) catalysts.[93]



***Scheme 99**: Enantioselective cyclization of alkenyl-imidazoles though scandium-catalysis.*

All these previous examples for building quaternary centers are based on CMD or related activation modes, so that the final stage of the catalytic cycle is a protonation process. At the moment we started our investigation, the only reported examples that were based on the insertion of a metal catalyst into a C–H bond, to eventually transfer these two atoms to a C–C unsaturated moiety, had been developed by own group, as shown in the **Scheme 83** of the general introduction (page 90), and in **Scheme 100**. These latter reactions were conducted in a racemic fashion.[94]

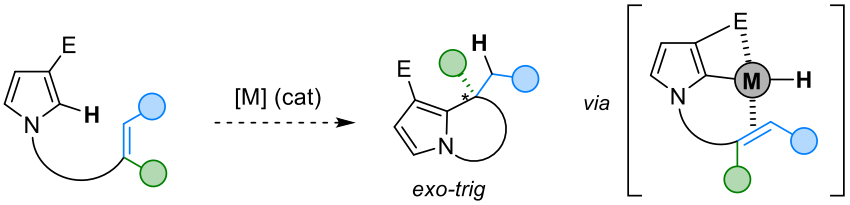


***Scheme 100**: Iridium catalyzed intramolecular hydroarylation of alkenes to access quaternary carbon centers developed by our group.*

[92] S. J. Lou, Z. Mo, M. Nishiura, Z. Hou, *J. Am. Chem. Soc.*, **2020**, *142*, 1200–1205.
[93] J. Guo, W. Yang, D. Zhang, S. G. Wang, X. Wang, *J. Org. Chem.*, **2021**, *86*, 4598–4606.

5.1.2. Objectives

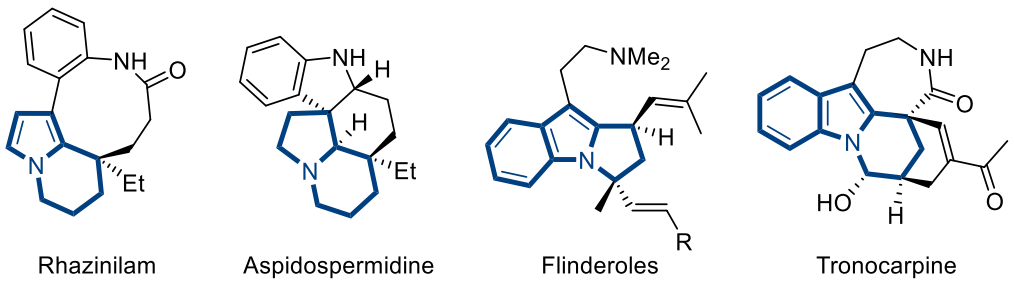
Due to the limited precedents of intramolecular C–H additions across alkenes, specially to build quaternary stereocenters, and the lack of asymmetric approaches, our initial objective consisted on the development of intramolecular enantioselective hydrocarbonation processes that allow the asymmetric assembly of heteropolycyclic systems, including those containing all-carbon quaternary centers (see **Scheme 101**). We specially focused on pyrrole precursors, owing to the relevance of the resulting products.



***Scheme 101**: TM-catalyzed direct addition of C–H bonds into alkenes.*

The formation of different ring sizes, by using precursors with diverse lengths of the connecting tether is also a major goal, as this could increase the synthetic utility of the method.

The resulting methodology should be useful to build dihydro-pyrrolizine and tetrahydro-indolizine scaffolds, which are present in many natural products. Some alkaloids of this type are shown in **Scheme 102**, like Rhazinilam, Aspidospermidine, Tronocarpine, and the anti-malarial family of Flinderoles.



Rhazinilam Aspidospermidine Flinderoles Tronocarpine

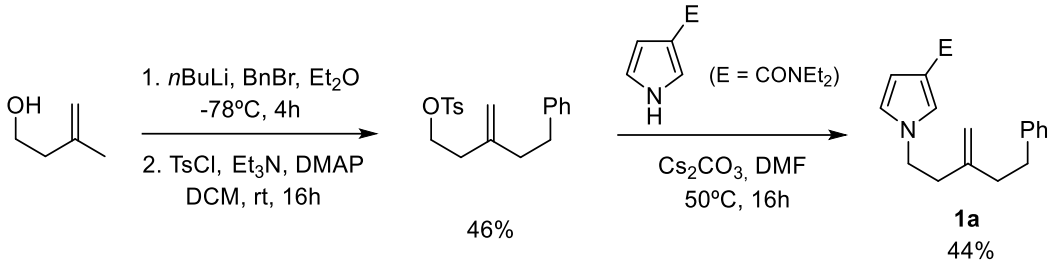
***Scheme 102**: Related natural products bearing quaternary and tertiary stereocenters.*

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5.1.3. Development of enantioselective intramolecular hydroarylations of alkenes with pyrroles and other heteroaromatic systems

Reaction development

In order to study the feasibility of the reaction, the model precursor **1a** was initially synthesized. As illustrated in **Scheme 103**, starting from 3-methyl-3-buten-1-ol, a double deprotonation of the alcohol and the terminal methyl group, allowed the allylic position to be alkylated with benzyl bromide. Then, activation of the alcohol as a tosylate and its final reaction with the *N,N*-diethyl-1*H*-pyrrole-3-carboxamide led to the desired precursor in an overall yield of 20% (3 steps).



***Scheme 103**: Synthesis of model substrate **1a**.*

The performance of different chiral iridium(I) complexes was initially assessed using the iridium catalyst previously used to promote *exo*-selective intermolecular hydroarylations (see section 2.5.1). Unfortunately, heating a dioxane solution of **1a** in the presence of the Ir(I) complex generated *in situ* from [Ir(COD)$_2$]BARF and (*R,R*)-Quinox-P* or (*S*)-DTBM-Segphos, at 60 ºC, led to the full recovery starting material, after 16 hours (**Table 1**, entries 1 and 2). Other chiral ligands like (*S*)-SDP which had shown to provide moderate enantioselectivities in our recently developed intramolecular *exo*-selective hydroalkenylation reactions (see **Scheme 82** and **Scheme 100**, pages 90 and 114 respectively), provided the 2,3-dihydropyrrolizine **2a** in 44% yield, with a moderate enantiomeric ratio of 71:29 (entry 3).[94]

The use of (*R,R,S,S*)-Duanphos improved the yield of **2a**, although the er remained modest (entry 4). Neither the *endo* regioisomer nor any other cyclized product were observed in these crude mixtures, which highlights the tendency of these precursors, under Ir catalysis, to provide the desired *exo*-hydroarylated products.

Remarkably, the use of BTFM-Garphos or Binap led to more efficient processes, providing good yields of **2a** and er's up to 97:3 (entries 5 and 6). When employing (*S*)-

[94] D. F. Fernández, M. Gulías, J. L. Mascareñas, F. López, *Angew. Chem. Int. Ed.,* **2017**, *56*, 9541-9545; *Angew. Chem.,* **2017**, *129*, 9669-9673.

DM-Binap, a lower yield was obtained (entry 7). Notably, during the screening, we found that the Ir complex derived from [Ir(COD)$_2$]BARF and (*S*)-Binapine, a chiral biphosphine with axial and central chirality (both at carbon and phosphorus),[95] was even more effective, delivering **2a** in a 95% yield and with an almost perfect enantiomeric ratio, > 99.5:0.5 (entry 8). Moreover, this model reaction could be conducted in 2 hours or with just 1 mol% of the Ir/Binapine catalyst, without deterring the yield or the enantiomeric ratio of the product, **2a** (entries 9 and 10).

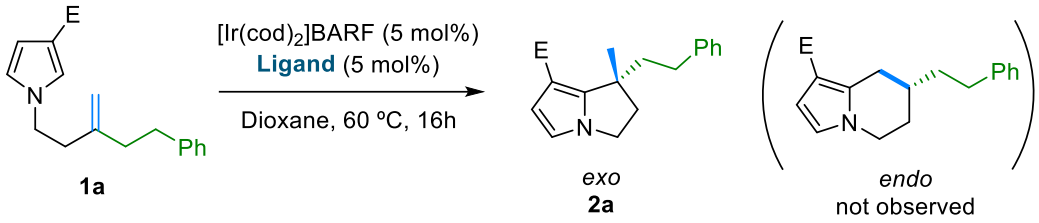
Interestingly, this chiral ligand (*S*)-Binapine had been previously used in enantioselective hydrogenation reactions;[96] but we have observed that in some cases the relative configuration of the stereocenters within this molecule has been incorrectly depicted in the literature.[97] This issue has also been noted in some commercial sources (e.g. Strem Chemicals). Consequently, we have communicated these errors.

[95] For its development, see: (a) W. Tang, W. Wang, Y. Chi, X. Zhang, *Angew. Chem. Int. Ed.,* **2003**, *42*, 3509-3511. (b) *Encyclopedia of Reagents for Organic Synthesis*. (doi.org/10.1002/047084289X.rn01362).

[96] (a) P. Yang, H. Xu, J. (S.) Zhou, *Angew. Chem. Int. Ed.*, **2014**, *53*, 12210–12213. (b) H. Yang, N. Huo, P. Yang, H. Pei, H. Lv, X. Zhang, *Org. Lett.*, **2015**, *17*, 4144–4147. (c) P. Yang, C. Zhang, Y. Ma, C. Zhang, A. Li, B. Tang, J. S. Zhou, *Angew. Chem. Int. Ed.*, **2017**, *56*, 14702–14706. (d) X. Zhao, H. Xu, X. Huang, J. S. Zhou, *J. Am. Chem. Soc.*, **2019**, *131*, 298–302.

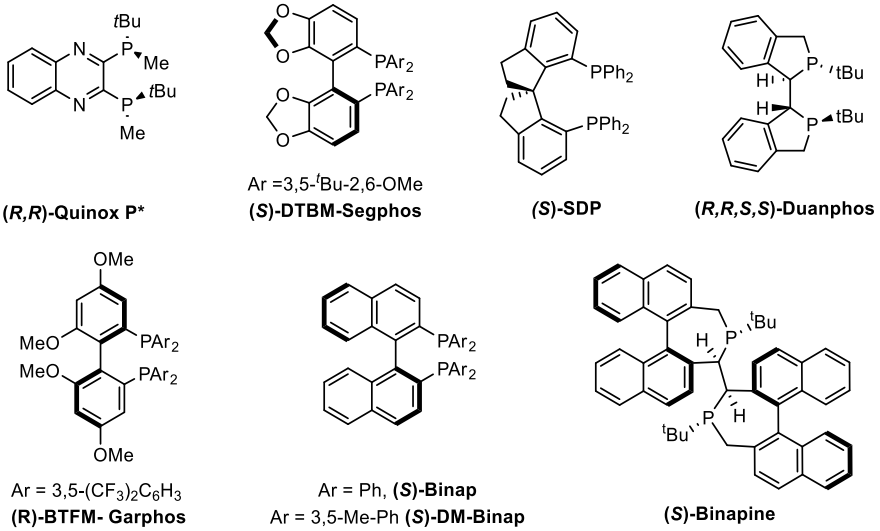
[97] (a) A. T. Axtell, J. Klosin, K. A. Abboud, *Organometallics*, **2006**, *25*, 5003–5009. (b) X. Li, C. You, H. Yang, J. Che, P. Chen, Y. Yang, H. Lv, X. Zhang, *Chem. Eur. J.*, **2017**, *359*, 597–602. (c) X. Li, C. You, S. Li, H. Lv, X. Zhang, *Org. Lett.*, **2017**, *19*, 5130–5133. (d) J. Long, W. Gao, Y. Guan, H. Lv, X. Zhang, *Org. Lett.*, **2018**, *20*, 5914–5917.

Table 1: *Evaluation of different asymmetric ligands for the cycloisomerization of* ***1a****, and structure of the chiral ligands evaluated.*



Entry	Ligand	Yield (%)	er
1	(*R,R*)-Quinox-P*	0	n.d.
2	(*S*)-DTBM-Segphos	0	n.d.
3	(*S*)-SDP	44	71:29
4	(*R,R,S,S*)-Duanphos	81	71:29
5	(*S*)-Binap	83	97:3
6	(*R*)-BTFM-Garphos	94	96:4
7	(*S*)-DM-Binap	17	93:7
8	(*S*)-Binapine	99	>99.5:0.5
9[a]	(*S*)-Binapine	95	>99.5:0.5
10[b]	(*S*)-Binapine	99	>99.5:0.5

[a]2 hours of reaction time. [b]1 mol% of catalyst.

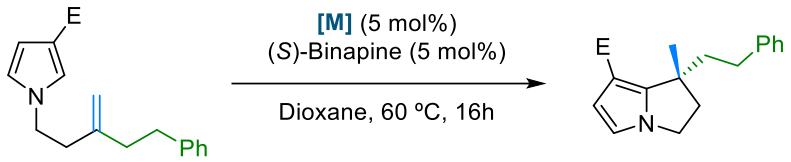


When employing other iridium(I) sources such as $[Ir(COD)_2]BF_4$ or $[Ir(COD)_2]OTf$, the expected product **2a** was also obtained, but in lower yields, as shown in **Table 2**, entries 2 and 3. Notably, the Rh(I) complex analogous to the aforementioned iridium catalyst did not yield any product at 60 °C (entry 4), and only traces of **2a** were detected after

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prolonged heating at 120 ºC (entry 5). These results highlight the exclusive potential of the iridium reagents.

Table 2: *Evaluation of different metal sources for the cycloisomerization of* ***1a****.* [a] *Conducted at 120 ºC.*



1a (E = $CONEt_2$) **2a**

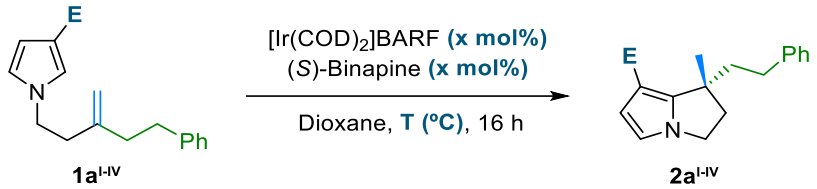
Entry	[M]	Yield (%)	er
1	[Ir(COD)$_2$]**BARF**	99	>99.5:0.5
2	[Ir(COD)$_2$]**BF_4**	24	99.6:0.4
3	[Ir(COD)$_2$]**OTf**	34	99.6:0.4
4	[**Rh**(COD)$_2$]BARF	0	n.d.
5[a]	[**Rh**(COD)$_2$]BARF	4	n.d.

The importance of the directing group was clearly evidenced from the failure of the C-3 unsubstituted pyrrole **1a'** to yield any product, even after several hours at elevated temperatures (**Table 3**, entries 2 and 3). Moreover, the use of a dialkyl carboxamide as directing group is also important, since the cyclization of the pyrrole **1a''**, featuring a methyl ketone at C-3 instead of the diethyl carboxamide, required heating at 120 °C and a higher catalyst loading to achieve complete conversion, whereas the corresponding product (**2a'**) was obtained with a moderate yield and poor er (65:35 er, entry 6). On the other hand, the use of related precursors bearing alternative directing groups, like an ethyl ester (**1a'''**) or carboxylic acid (**1a^{IV}**), did not allow to obtain any product (entries 4-7).

Overall, these findings underscore the superiority of the Ir/Binapine catalyst, coupled with the carboxamide directing group, for facilitating the enantioselective cyclization of the alkenyl pyrrole **1a** in an *exo*-selective fashion.

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Table 3: *Evaluation of different directing groups for the cycloisomerization of* ***1a****.*



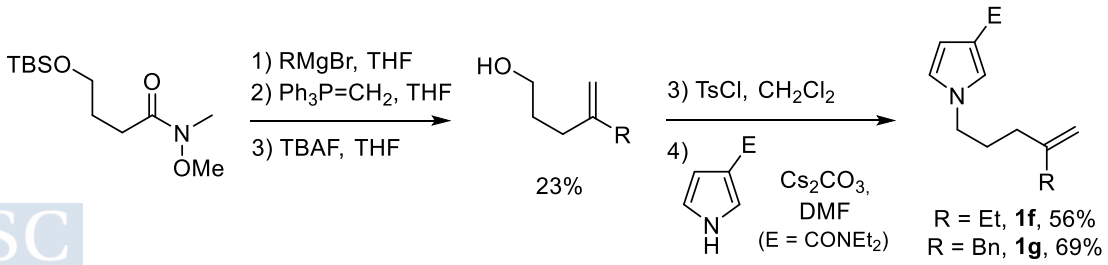
1a^{I-IV} **2a^{I-IV}**

Entry	E	mol% cat.	T (ºC)	Yield (%)	er
1	$CONEt_2$ (**1a**)	5	60	99	99.8:0.2
2	H (**1a'**)	5	60	0	n.d.
3	H (**1a'**)	10	120	0	n.d.
4	$COCH_3$ (**1a''**)	5	60	0	n.d.
3	$COCH_3$ (**1a''**)	10	120	49	65:35
4	CO_2Et (**1a'''**)	5	60	0	n.d.
5	CO_2Et (**1a'''**)	10	120	0	n.d.
6	COOH (**1a^{IV}**)	5	60	0	n.d.
7	COOH (**1a^{IV}**)	10	120	0	n.d.

Scope

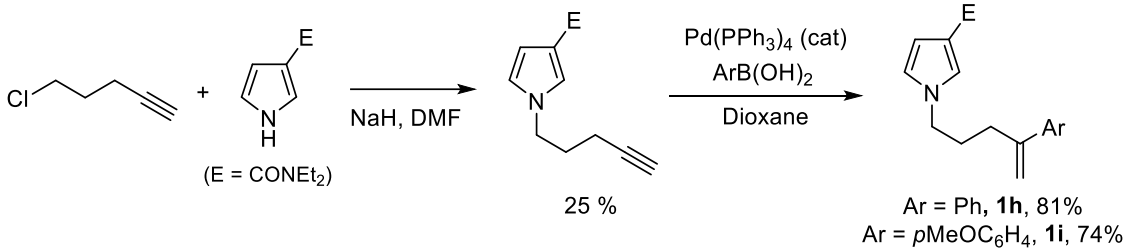
With the optimal conditions in hand, the scope of the process for the generation of dihydro-1*H*-pyrrolizines and related polycycles was explored. To this end, various precursors were synthesized. Substrates **1b-e**, bearing two methylene units between the pyrrole and the alkene, with different alkyl substituents at the alkene, were prepared following a route analogous to that shown in **Scheme 103**.

We also prepared substrates **1f-g,** with three methylene units at the linker and different alkyl substituents at the alkene, which were synthesized via the pathway illustrated in **Scheme 104**. Thus, different Grignard reagents were added to the TBS-protected γ-hydroxybutyric Weinreb amide, to afford the corresponding ketones. After a Wittig olefination and TBS removal, the desired alkenyl alcohols were obtained. Subsequent tosylation and coupling to the pyrrole, afford the precursors **1f-g**.

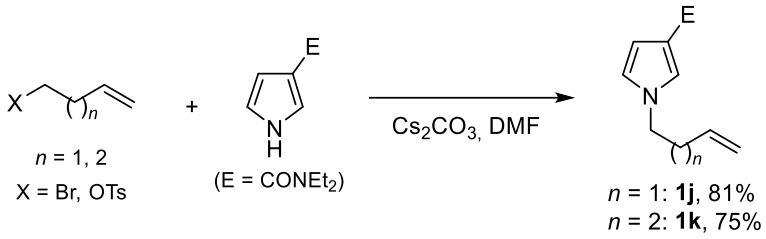


Scheme 104*: General synthesis of starting materials* ***1f-g****.*

Substrates **1h-i**, featuring an aryl substituent at the alkene, were obtained as described in **Scheme 105**, following a strategy that is based on a Pd-catalyzed arylation of the terminal alkyne moiety of a common alkynyl-pyrrole precursor. The use of different aryl boronic acids led us to obtain the desired precursors in good yields. Finally, substrates with unsubstituted alkenes were prepared from commercially available bromides or alcohols, as outlined in **Scheme 106**.



***Scheme 105**: General synthesis of starting materials **1h-i**.*



***Scheme 106**: General synthesis of precursors with unsubstituted alkenes **1j-k**.*

Although the model cyclization reaction of **1a** is very efficient with just 1 mol% of Ir catalyst, to ensure generality of the process when employing potentially more challenging substrates, we used 5 mol% of the Ir-Binapine catalyst and a standard reaction time of 16 hours.

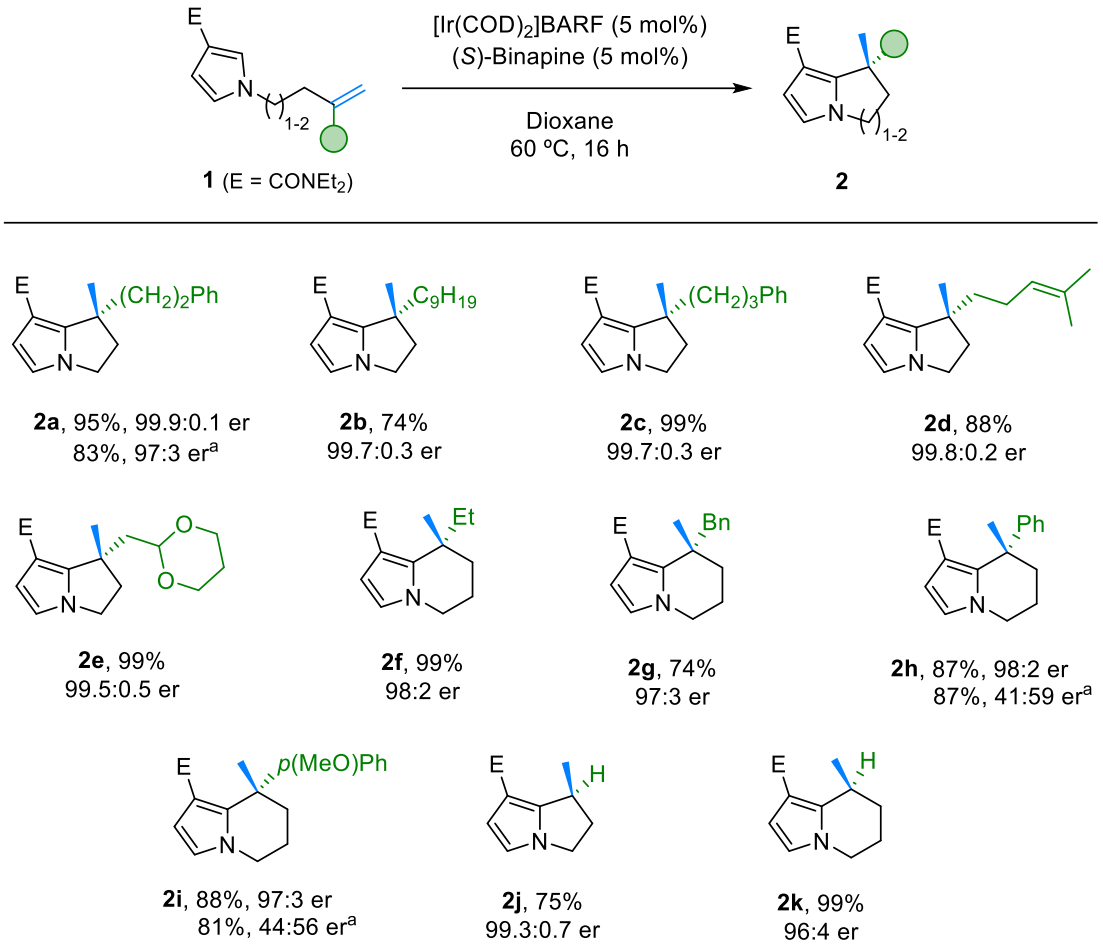
The cycloisomerizations of pyrroles **1b-1e**, bearing different types of substituents at the internal position of the alkene, was successful, providing the corresponding dihydro-1*H*-pyrrolizine products **2b-2e**, resulting from a completely selective 5-*exo* cyclization, in very good yields and with er's above 99.5:0.5 (**Scheme 107**). No traces of the corresponding 6-*endo* cyclization product were detected.

Precursors with longer linkers, with three methylene units between the alkene and the pyrrole, were then examined. Pleasingly, products **2f-2i**, bearing all-carbon quaternary stereocenters, either with aryl or alkyl substituents, were obtained in good yields (74-99%) and with excellent enantiomeric ratios that range from 97:3 to 98:2. In these cases, the use of Binapine is critical to obtain good er's, as other chiral ligands that were

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effective with **1a**, such as Binap, probed to be inefficient (er's < 60:40, **2a** and **2h-i**, see **Scheme 107**).

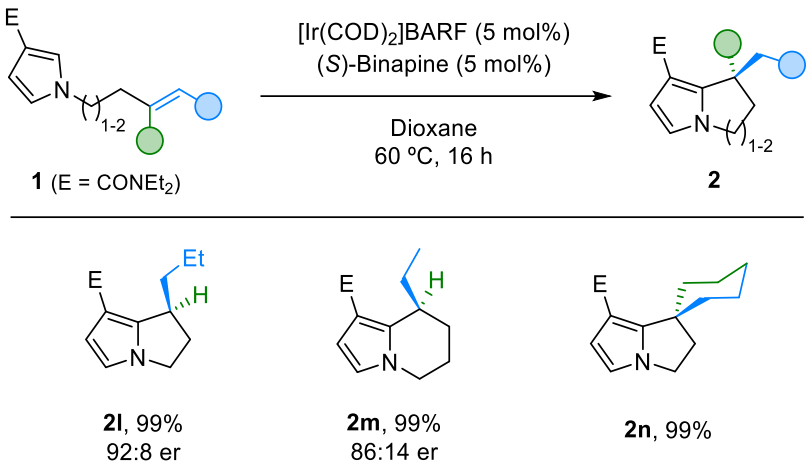
We next explored the cyclization of precursors **1j** and **1k**, bearing alkenes without substituents. Using Ir/Binapine catalyst, the expected products were selectively obtained with tertiary stereocenters (**2j-k**), in high yields and excellent er's (up to 99.3:0.7).



Scheme 107: *Exo-selective enantioselective hydrocarbonation of alkene-tethered pyrroles. [a] Carried out using (R)-Binap instead of (S)-Binapine*

We next explored substrates with (*E*)-1,2-disubstituted alkenes, which were prepared using commercially available precursors through the strategy shown in **Scheme 106**. Thus, when employing (*E*)-**1l** and (*E*)-**1m**, the corresponding adducts, **2l** and **2m** were obtained in quantitative yields and with high er's. Additionally, when employing precursor **1n**, bearing a cyclic alkene, the achiral spirocyclic compound **2n** was obtained in a 99% yield.

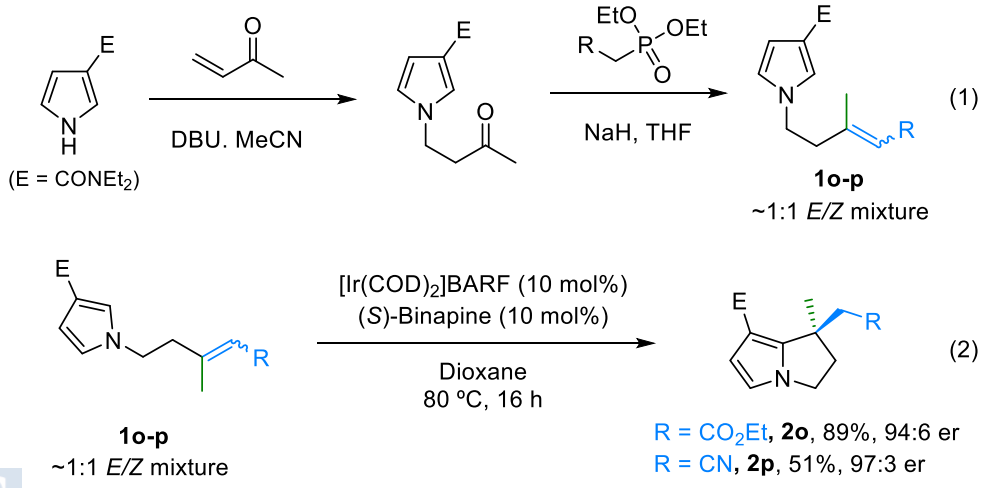
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Scheme 108: *Hydrocarbonation of 1,2-disubtituted and cyclic alkene-tethered pyrroles.*

The use of trisubstituted alkenes has very few precedents in intramolecular hydrocarbonation processes. To check whether our method can promote the cyclization over this type of alkenes, precursors **1o** and **1p**, were prepared through a Wittig-Horner reaction which delivers a ~1:1 *E*/*Z* mixture of isomers, as depicted in **Scheme 109**, equation 1.

These precursors were both tested as 1:1 *E/Z* mixtures, resulting from the Wittig reactions. Gratifyingly, the cycloadditions of **1o** and **1p** respectively afforded the products **2o** and **2p** with good yields and excellent er, despite of being *E/Z* mixtures (equation 2). To the best of our knowledge, the possibility of obtaining the desired products with high ee, regardless of the configuration of the parent trisubstituted alkene, lacks precedents in related C–H hydrocarbonation protocols. This further increases the synthetic utility of the method, since avoids the many times difficult separation of the alkene isomers.



Scheme 109: *Synthesis of substrates of trisubstituted alkene-tethered pyrroles* ***1o-p*** *(1) and its Ir-catalyzed cycloisomerization (2).*

With these results in hand, we then checked if indoles could also be employed as substrates. Several precursors were prepared by adapting the synthetic protocols previously used to prepare the analogous pyrrole-alkene precursors. Therefore, alkene-tethered indoles **1q** and **1s** were prepared using the strategy shown in **Scheme 103** (page 116), whereas substrates **1r** and **1u** were obtained through the strategies shown in **Scheme 104** and **Scheme 105** (page 121).

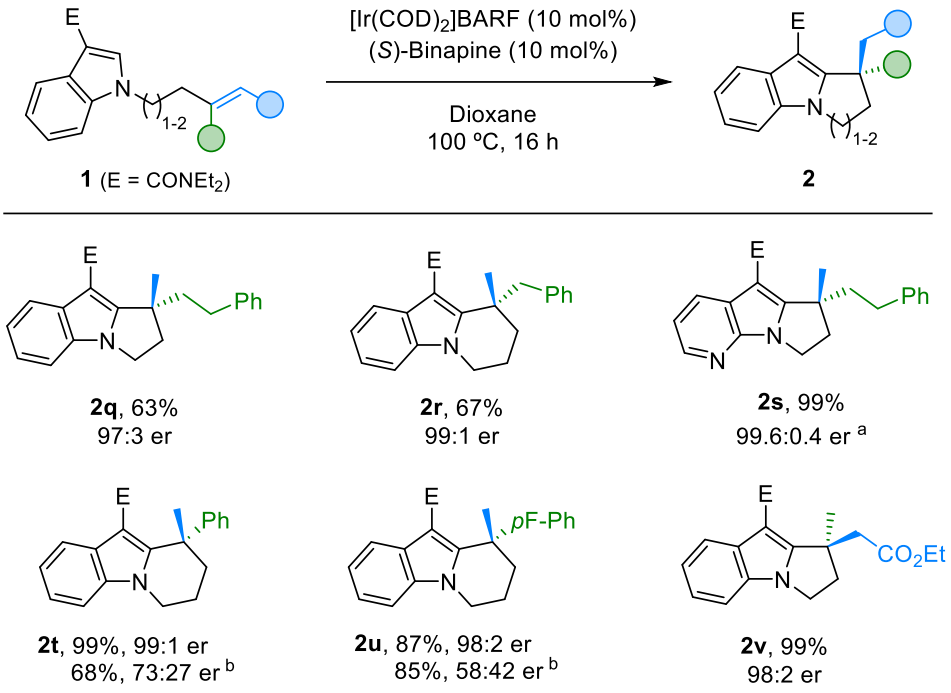
As can be seen in **Scheme 110**, the hydroarylation of **1q** and **1r** proceeds very well, although a slightly higher temperature was usually required to achieve full conversions. Dihydropyrrolo[1,2-a]indole and tetrahydropyrido[1,2-a]indole products **2q** and **2r** were both obtained in good yields and with er's above 97:3.

The 7-azaindole precursor **1s** also participated in the process to afford the corresponding dihydropyridopyrrolizine derivate **2s** in 99% yield and 99.6:0.4 er. Likewise, indole precursors with aryl substituents at the internal position of the alkene moiety were also good substrates for the Ir/Binapine catalyst, so that the tricyclic products **2t** and **2u** were obtained with high yields and er's ≥ 98:2.

An equally high enantiomeric ratio was also obtained in the cyclization of an indole precursor bearing a trisubstituted alkene (**1v**, *E*/*Z* ~ 1:1),[98] which afforded **2v** in 99% yield. Gratifyingly, the absolute configuration of **2r** (99:1 er) could be determined by X-ray crystallographic analysis (**Figure 8**). Again, (*R*)-Binap fails to provide good enantioselectivity, as shown in the reactions leading to **2t** and **2u** (**Scheme 110**). These results highlight again the unique generality of the Ir-Binapine catalysts, which exceeds the performance of any other type of metal catalyst previously use for promoting related hydroarylation reactions.

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[98] Synthetized following strategy shown in **Scheme 109** (page 131). See the experimental procedures for further details.



Scheme 110: *Exo-selective enantioselective hydrocarbonation of 1,2-disubtituted alkene-tethered indoles.* [a] *Reaction time 48h.* [b] *Carried out using (R)-Binap instead of (S)-Binapine.*

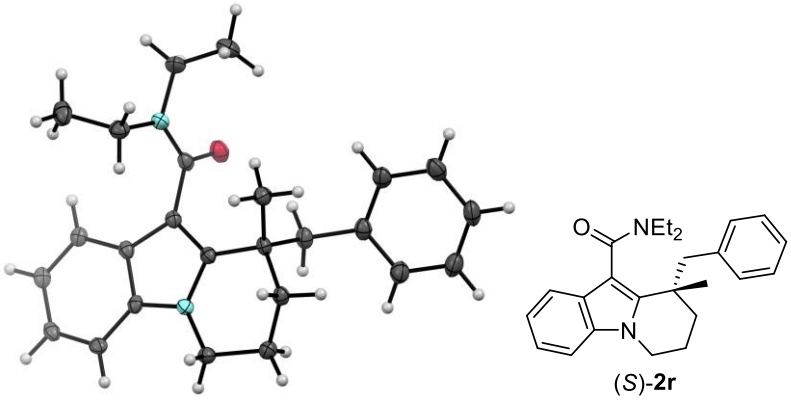


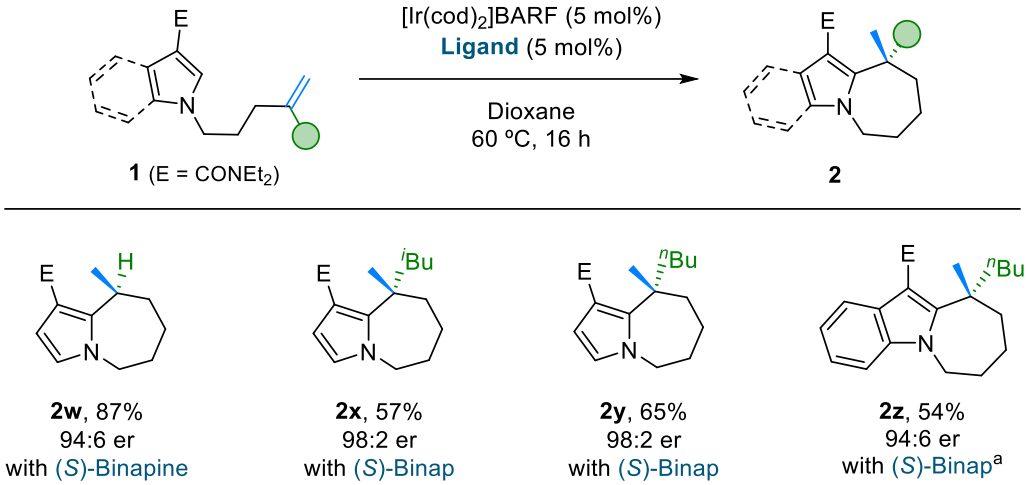
Figure 8: *X-ray structure of (S)-**2r** (CCDC deposition number 2062632)*

The unprecedented versatility of this method, which allows us to generate both five- and six-membered rings with excellent er's, regardless of the type of substituent at the alkene internal position, led us to investigate whether larger rings could also be formed. Therefore, we prepared precursor **1w**, bearing four methylene units between the pyrrole and the alkene, following the same strategy employed for **1j** and **1k**. The synthesis of substrates **1x-z** was adapted from **Scheme 105**, equation 1 (page 116).

The cyclization of **1w** resulted in the formation of the tetrahydropyrrolo[1,2-*a*]azepine **2w** (**Scheme 111**). This process was only found effective using Binapine as ligand (87% yield and 94:6 er). However, the formation of related products with all-carbon quaternary

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stereocenters, such as **2x-z**, through a 7-*exo* cyclization of the corresponding precursors, proceeded in better yields with Binap (er's from 94:6 to 98:2), instead of (*S*)-Binapine.



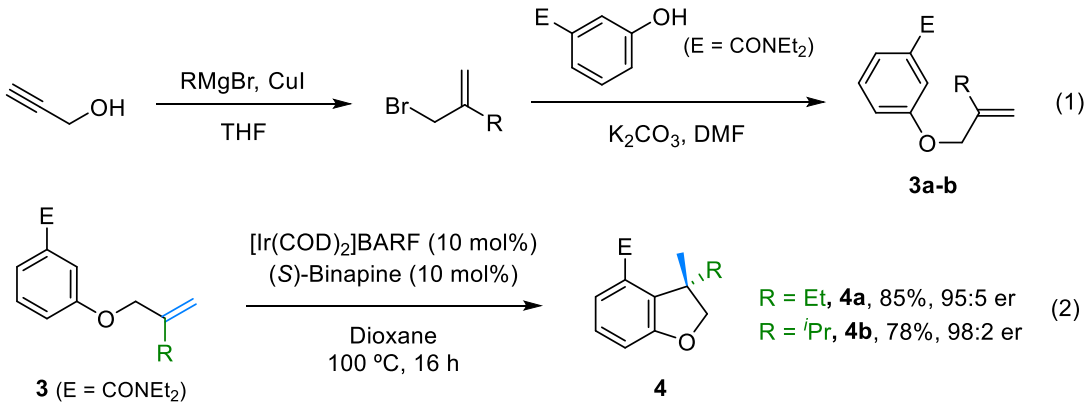
Scheme 111: *Exo-selective enantioselective hydrocarbonation of alkene-tethered pyrroles to form 7-membered rings.* [a] *Reaction time 48h.*

Overall, our method represents the first enantioselective metal-catalyzed cycloisomerization based on a C–H activation that allows to build either five-, six- or seven-membered rings, with excellent er's, regardless of the nature of the generated stereocenters.

Given the method's versatility, its applicability to the hydroarylation of other precursors was also analyzed. In particular, we checked its performance in the hydroarylation reactions leading to dihydrobenzofurans, for which few other methods had been described (see introduction, pages 111-114), but are typically restricted to the generation of tertiary stereocenters.[99] The substrates were prepared as depicted in **Scheme 112**, equation 1.

Encouragingly, the catalyst derived from [Ir(COD)$_2$]BARF and (*S*)-Binapine facilitated the cyclization of *O*-alkenyl tether carboxamides **3a-b**, to obtain the desired dihydrobenzofurans (**4a-b**) in good yields with enantiomeric ratios up to 98:2 (equation 2). Consequently, our methodology can be ranked among the most versatile enantioselective approaches for synthesizing various types of polyheterocyclic systems featuring all-carbon quaternary stereocenters.

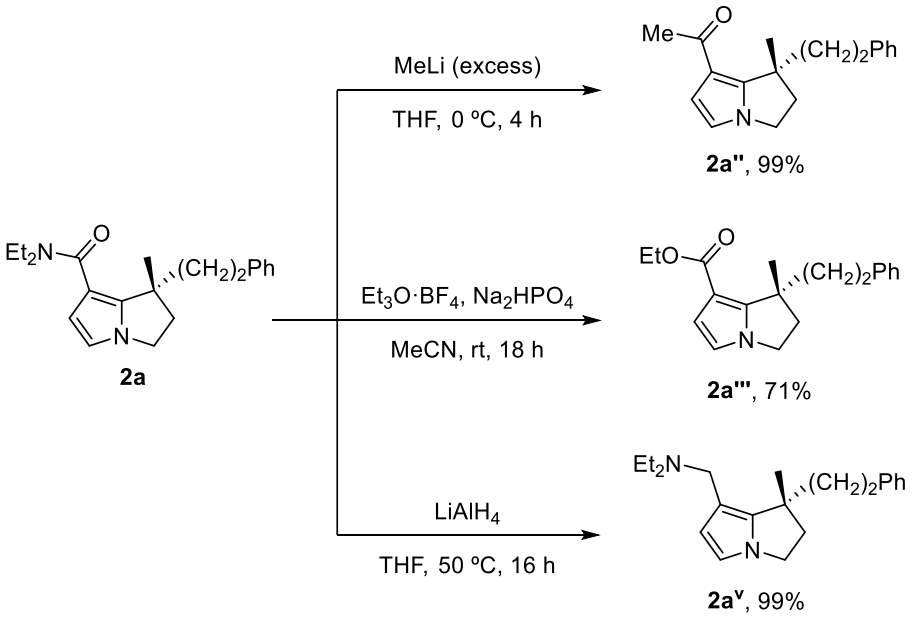
[99] For two exceptions with high valent transition metal catalysts, see: (a) B. Ye, P. A. Donets, N. Cramer, *Angew. Chem. Int. Ed.,* **2014**, *53*, 507-511. (b) G. Li, Q. Liu, L. Vasamsetty, W. Guo, J. Wang, *Angew. Chem. Int. Ed.,* **2020**, *59*, 3475-3479.



Scheme 112: *Synthesis of substrates **3a-b** (1), and its Ir-catalyzed cycloisomerization for the synthesis of dihydrobenzofurans (2).*

Derivatization of the products

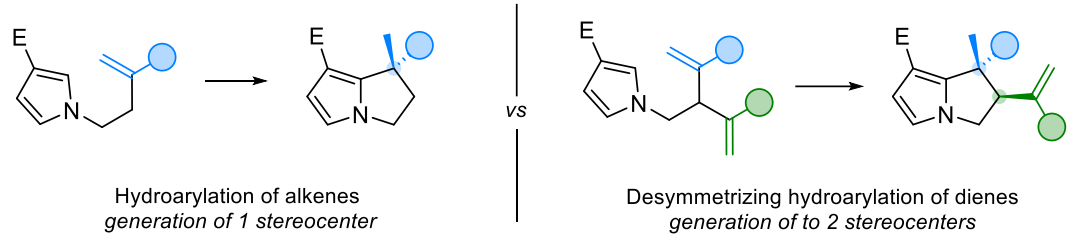
We then analyzed whether the dialkylcarboxamide moiety of the products could be used as aa versatile functional group for subsequent modifications. Illustrated with a model product (**2a**), proved that it can be readily transformed into a ketone (**2a'**), a carboxylic ester (**2a'''**), or an amine (**2a^{v}**), in all cases with high yields (**Scheme 113**). This underscores its utility as a platform for diverse further elaborations.



Scheme 113: *Synthetic manipulations of the diethylamide directing group.*

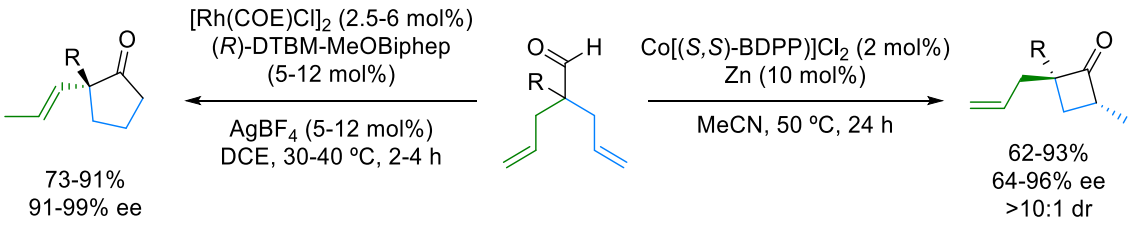
5.1.4. Development of a desymmetrizing hydrocarbonation reaction: access to heterocyclic systems bearing two quaternary stereocenters

The above-described methodology is very versatile; however, its *exo*-selective nature impedes, *a priori*, the generation of more than one stereocenter within the newly generated ring. To overcome this limitation, we wondered whether this technology could be further adapted to construct products containing multiple stereocenters within the newly formed ring, by combining the cycloisomerization with a concomitant desymmetrization of a prochiral center (**Scheme 114**).



***Scheme 114**: General strategy for the generation of two stereocenters by desymmetrization of pyrrole-dienyl substrates.*

Related strategies had been previously reported by Dong in the context of hydroformylation reactions. Some examples are depicted in **Scheme 115**, employing Rh(I) and Co(I) catalysis. Depending on the catalyst *endo*- (with Rh) and *exo*-selective (using Co) desymmetrization can be achieved with high enantioselectivities.[100] However, in the context of asymmetric hydroarylation reactions, there were no precedents.

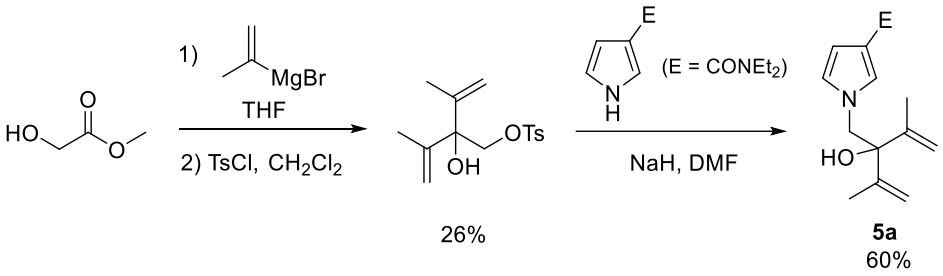


***Scheme 115**: Rh-catalyzed desymmetrizing hydroformylation of dienes developed by Breit and coworkers.*

[100] (a) J. W. Park, K. G. Kou, D. K. Kim, V. M. Dong, *Chem. Sci.*, **2015**, *6*, 4479–4483. (b) D. K. Kim, J. Riedel, R. S. Kim, V. M. Dong, *J. Am. Chem. Soc.*, **2017**, *139*, 10208–10211. For reviews covering desymmetrizing TM-catalyzed methodologies, see: (a) X. P. Zeng, Z. Y. Cao, Y. H. Wang, F. Zhou, J. Zhou, *Chem. Rev.*, **2016**, *116*, 7330–96. (b) D. Pierrot, I. Marek, *Angew. Chem. Int. Ed.*, **2020**, *59*, 36–49. (c) C. Nájera, F. Foubelo, J. M. Sansano, M. Yus, *Tetrahedron*, **2022**, *106–107*, 132629.

Reaction development

To evaluate the viability of the reaction, the prochiral diene **5a** synthesized in a few steps starting from unexpensive ethyl glycolate, as shown in **Scheme 116**. Although this reaction would only generate one stereocenter from the desymmetrization of the prochiral diene, this would allow us to independently study the viability of the desymmetrization.

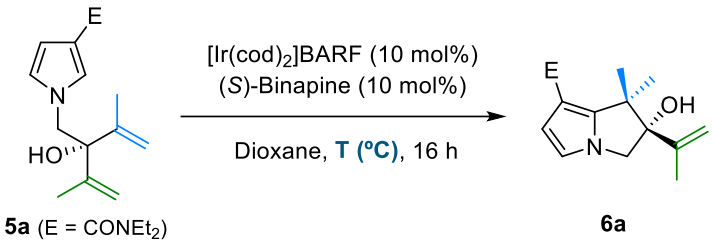


***Scheme 116**: Synthesis of model substrate **5a**.*

The investigation started by testing the conditions previously used in the hydroarylation of alkenes. When carrying out the reaction with **5a** using a 10 mol% Ir/Binapine catalyst at 60 °C, a 75% of product **6a** with 95:5 er was obtained (**Table 4**, entry 1). Increasing the reaction temperature to 80 °C, resulted in a higher 90% yield, without any detrimental effect on the enantiomeric ratio (entry 2). Higher temperatures, of 100 and 120 °C, further increased the yield, although enantioselectivity was slightly affected (entries 3 and 4). In order to achieve good results with more complex substrates, 10 mol% Ir/Binapine at 80 °C were chosen as general conditions.

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Table 4: *Screening of the desymmetrizing hydrocarbonation of prochiral diene* ***5a****.*

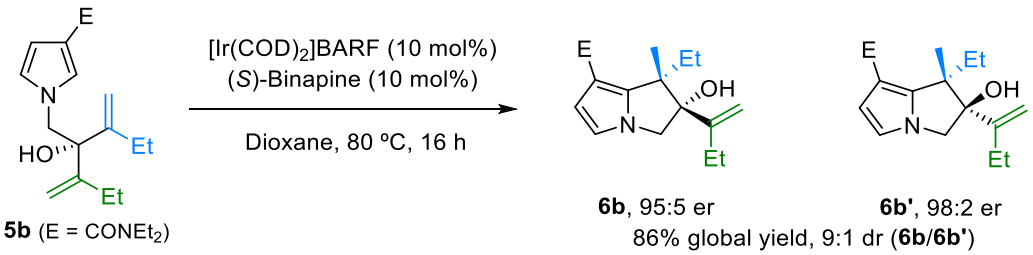


5a (E = $CONEt_2$) **6a**

Entry	T (ºC)	Yield (%)	er
1	60	75	95:5
2	80	90	95:5
3	100	93	94:6
4	120	95	93:7

Scope of the process

With these conditions at hand, the generality of the method was explored with other substrates. The analogous precursor **5b**, featuring an ethyl instead of a methyl group at the internal position of the alkene, was prepared following the same strategy (**Scheme 116**), but using but-1-en-2-ylmagnesium bromide as Grignard reagent. Gratifyingly, when **5b** was treated with the Ir(I)/(*S*)-Binapine catalyst, the desired hydroarylation product, bearing two consecutive stereocenters was obtained, as a 9:1 mixture of diastereoisomers. Interestingly, both the major (**6b**) and minor (**6b'**) isomers were obtained with excellent enantiomeric ratios, of 98:2 and 95:5, respectively (**Scheme 117**). The relative configuration of both isomers was confirmed with nOe experiments.



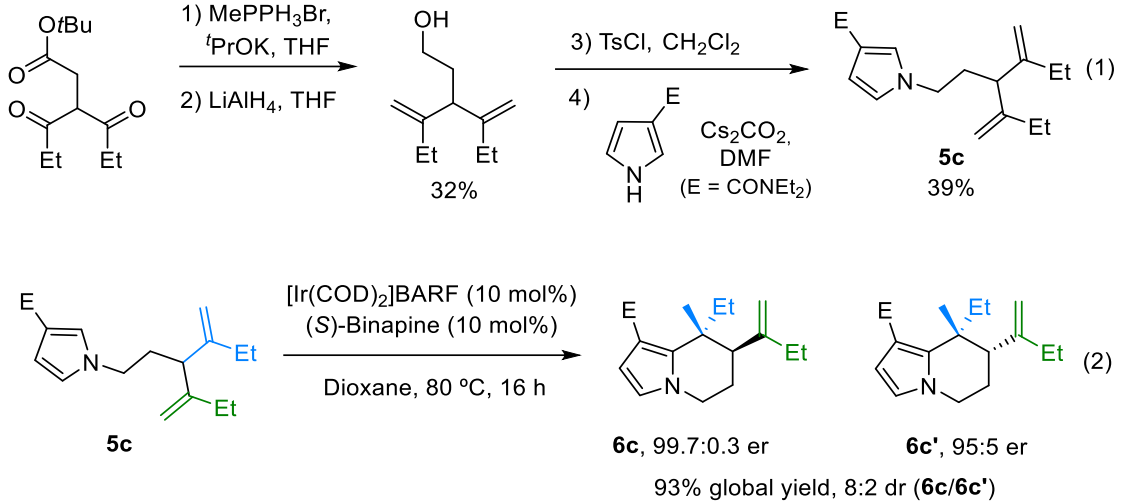
5b (E = $CONEt_2$)

6b, 95:5 er **6b'**, 98:2 er
86% global yield, 9:1 dr (**6b**/**6b'**)

Scheme 117*: Ir-catalyzed desymmetrization of prochiral precursor* ***5c****.*

This outcome demonstrates that the chiral catalyst can distinguish between enantiotopic alkenes of the prochiral center while maintaining an excellent facial selectivity at the alkene insertion. Moreover, it was also interesting to confirm that the hydroxyl group is tolerated, without the requirement of being masked by a protecting group. Based on these results, we prepared the hydroxyl-free precursor **5c**, following the strategy depicted in **Scheme 118**, equation 1. Using the optimal conditions, **5c** yielded the desired

tetrahydroindolizine product bearing two vicinal stereocenters with a good diastereomeric ratio (**6c**:**6c'** = 8:2) and excellent enantiomeric ratios (99.7:0.3 and 95:5, respectively; equation 2).



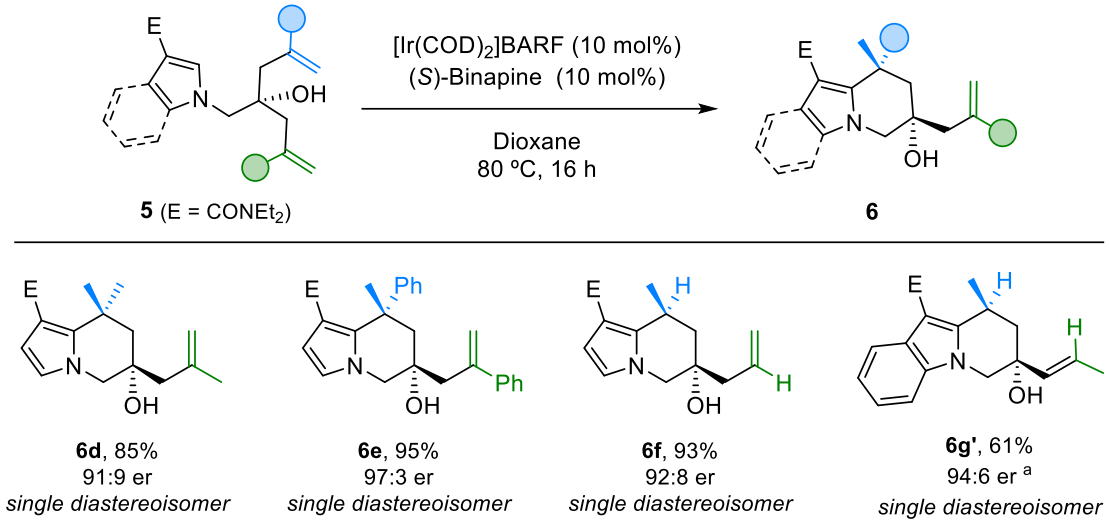
***Scheme 118**: Synthesis of prochiral precursor **5c** (1), and its Ir-catalyzed desymmetrization (2).*

Next, we studied the viability of a desymmetrizing hydrocarbonation of pyrroles bearing a prochiral 1,6-diene like **5d.** The synthesis of the precursors was carried out following an analogous strategy to that described in **Scheme 116**, but using allyl magnesium bromide as Grignard reagent.

Gratifyingly, when **5d** was treated with Ir(I)-Binapine catalyst, the reaction afforded the tetrahydroindolizine derivative **6d**, which was isolated in 85% yield. The enantiomeric ratio of 91:9 confirmed the excellent capacity of the catalyst to promote the desymmetrization (**Scheme 119**). Moreover, the cyclization of pyrrole **5e**, possessing a phenyl substituent at the internal position of the alkene, resulted in the formation of the desired product, **6e**, bearing two fully substituted stereocenters in relative 1,3-positions, with complete diastereoselectivity, excellent yield and a 97:3 enantiomeric ratio.

Notably, the generation of tertiary stereocenters is also possible. The tetrahydroindolizine derivative **5f** was obtained in 93% yield, exhibiting complete diastereoselectivity and an enantiomeric ratio of 92:8. Furthermore, the desymmetrizing hydroarylation can also be extended to indole precursors, by increasing the reaction temperature to 100 ºC. The precursor **5g** yielded the product **6g'**, in which the non-reactive allyl moiety isomerizes towards the observed internal alkene, with excellent stereoselectivities (dr = 1:0; er = 94:6). The relative and absolute stereochemistry of this product was elucidated via X-ray crystallography, as shown in **Figure 9**.

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Scheme 119: *Enantioselective desymmetrization of prochiral 1,6-diene precursors.*
[a] Conducted at 100 ºC.

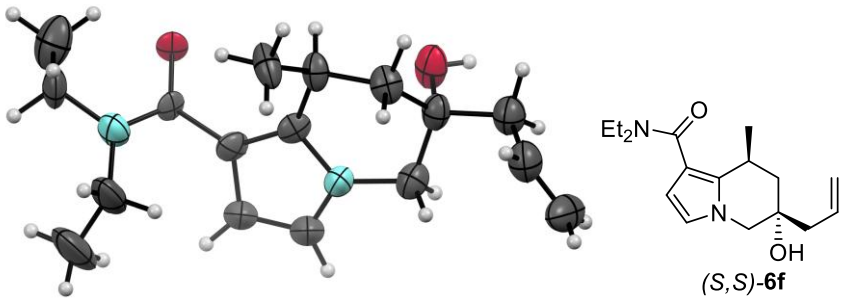
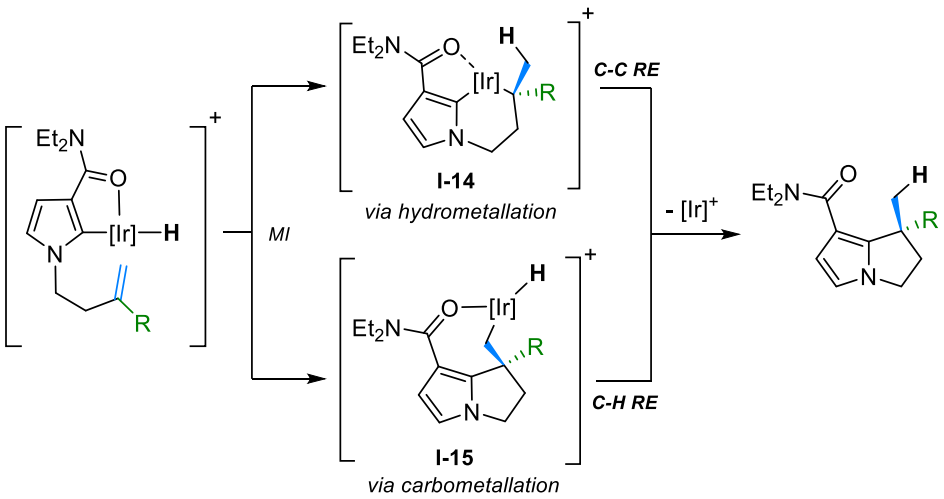


Figure 9: *X-ray structure of* ***6f*** *(CCDC deposition number 2062633)*

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5.1.5. Mechanistic studies

Two different scenarios have been usually postulated for this general type of hydroarylation reactions (see **Scheme 107**, page 122). After the C–H insertion into the low valent metal catalyst, a hydrometallation or a carbometallation of the olefin can occur. The former sequence, frequently proposed, requires a C–C reductive elimination from **I-14** to close the cycle, whereas the latter would involve a C–H reductive elimination from **I-15**. In the case of iridium catalysts, it has been postulated that the high barriers associated to an eventual C–Ir–C reductive elimination[69] makes more plausible a carbometallation/C–H reductive elimination, regardless the higher energetic cost associated to carbometallation process, in comparison to the hydrometallation (**Scheme 120**).



***Scheme 120**: Hydrometallation/C-C RE vs carbometallation/C–H RE pathways in the Ir-catalyzed exo-hydroarylation.*

Nonetheless, to confirm that hypothesis, and in order to shed further light on the mechanism and distinguish between these two options, we carried out both experimental and theoretical studies.

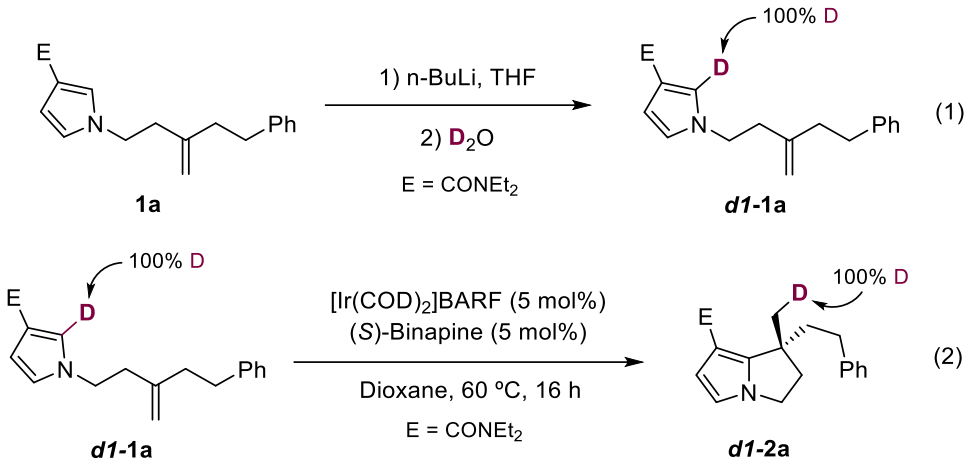
Deuterium labelling experiments

A precursor incorporating deuterium at the C2 position of the pyrrole was prepared by deprotonating the C2 position of **1a** with *n*-BuLi, followed by protonation with excess D_2O, as depicted in see **Scheme 121**, equation 1.

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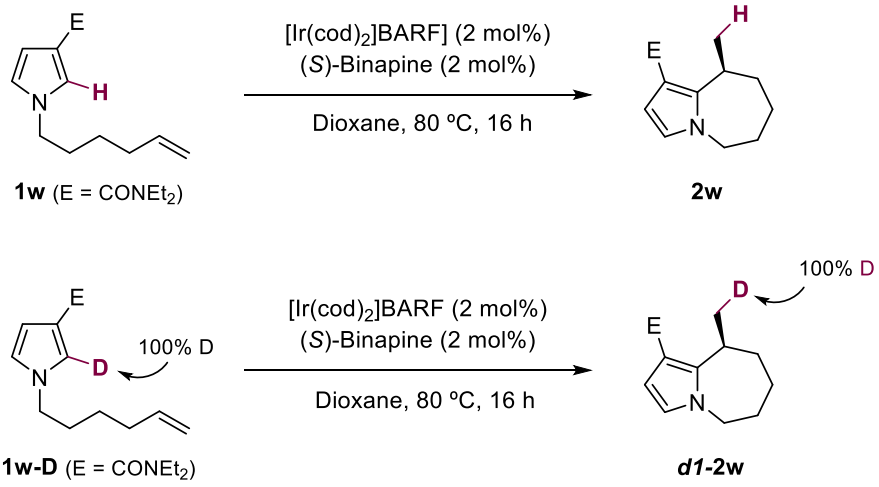
[69] Y. Lang, M. Zhang, Y. Cao, G. Huang, *Chem. Commun.*, **2018**, *54*, 2678–2681.

Running the cycloisomerization with ***d1*-1a**, results in the selective formation of the deuterated product ***d1*-2a**, isotopically labelled at the methyl position (equation 2).



Scheme 121: *Preparation of deuterated substrate* ***d1-1a*** *(1) and its cycloisomerization towards* ***d1-2a*** *(2).*

The deuterated substrate ***d1*-1w** was selected for measuring the kinetic isotope effect (KIE), because its reaction is slower, making its kinetics easier to be determined. Nevertheless, it was necessary to slightly modify the reaction conditions (80 °C and 2 mol% of catalyst, **Scheme 122**). Two parallel reactions were conducted on a scale of 0.4 mmol with both **1w** and ***d1*-1w**, and aliquots were taken every 2.5 minutes, immediately filtered through Florisil®, and analyzed by GC-MS chromatography.



Scheme 122: *Parallel cycloisomerization reactions with* ***1w*** *and* ***d1-1w****.*

The obtained ratios of products and starting materials were plotted to calculate the gradient of the straight line by least squares regression (**Figure 10**). The KIE value,

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obtained by dividing both gradients, was 4.2, which is consistent with a primary kinetic isotope effect.

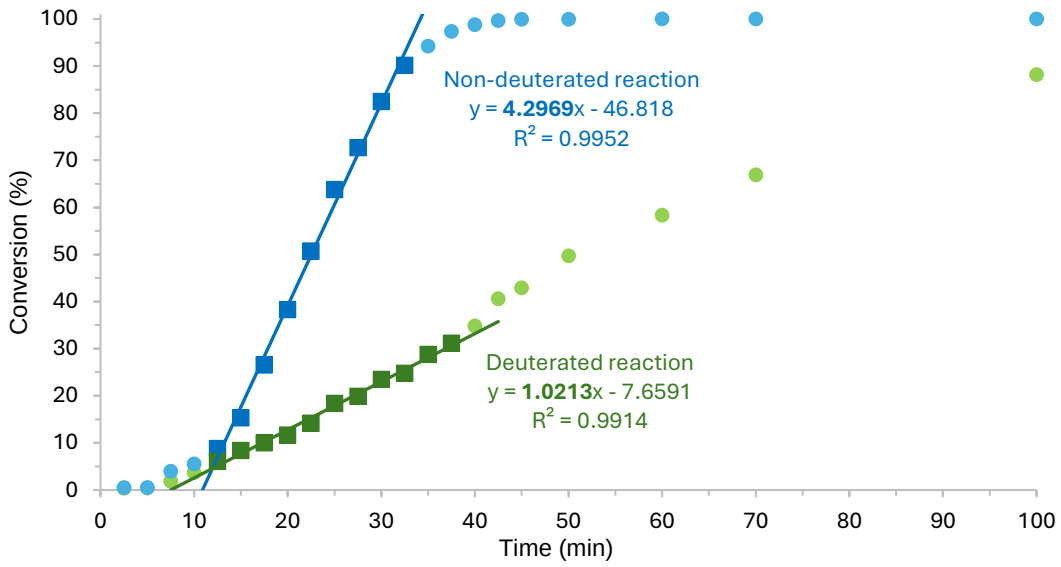


Figure 10: *Plot of the quotient between the integral of the product and the remaining starting material at various times, the lines were calculated by least squares regression. Blue line: Reaction with* ***1w****. Green line: Reaction with* ***d1-1w****.*

These results are compatible with a scenario in which the C–H activation would be turnover limiting. However, it does not allow to distinguish between a carbometallation or hydrometallation pathway (see **Scheme 120**), since the former might also involve a C–H reductive elimination as rate limiting step.

DFT computational analysis

To shed light on the factors contributing to the observed reactivity and especially high enantioselectivity, Dr. Martín Calvelo conducted computational mechanistic studies. For the DFT analysis, he used the Ir/(*S*)-Binapine complex and the model precursor **1g'**, with a dimethylamide group instead of the diethylamide, to reduce computational costs.

The calculations reveal that upon coordination of the Ir/Binapine complex to the amide carbonyl moiety (**Int-A**), there is an oxidative addition of the pyrrole C(2)–H bond to the Ir(I) center via an accessible energy barrier of 18.5 kcal/mol (**TS-AB**). This process leads to a distorted square-pyramidal iridium(III)-hydride species, **Int-B** (**Figure 11**).

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In consonance with previous studies by Huang,[69] our preliminary computations also confirmed the preference of a carbometallation / C–H reductive elimination sequence. Therefore, this route will be exclusively discussed from now on.

Coordination of the olefin to the iridium center can result in two octahedral diastereoisomers with significantly different energies. Species ***S*-Int-C**, leading to the experimentally observed enantiomer ***S*-2g'**, was found to be 5.8 kcal/mol more stable than its counterpart ***R*-Int-C**.

Further examination of the carbometallations reveals that the *exo*-selective migratory insertion from ***S*-Int-C** proceeds through transition state ***S*-TS-CD**, which is 3.1 kcal/mol more stable than ***R*-TS-CD**. The resulting iridium(III) hydride intermediate ***S*-Int-D** is also notably more stable than ***R*-Int-D**, by 3.6 kcal/mol.

Ultimately, the C–H reductive elimination that closes the catalytic cycle requires an initial isomerization to a square-pyramidal isomer (from **Int-D** to **Int-D'**), facilitating the subsequent C–H bond forming process via transition state **TS-DE**. In the case of the reductive elimination, the one yielding the experimentally observed enantiomer (***S*-I-E**) is favored by 4.5 kcal/mol.

TS-AB is identified as the TOF-determining transition state (TDTS), and **Int-A** as the TOF-determining intermediate (TDI), resulting in an energetic barrier of 18.5 kcal/mol. Overall, the theoretical results align with experimental conditions and the experimentally observed KIE, confirming that the C–H oxidative addition to the Ir(I) complex is turnover-determining.

Additionally, the calculated energetic profile supports the alkene migratory insertion as the enantiodetermining step and is consistent with the high enantiomeric ratios experimentally obtained and the absolute configuration of the major enantiomer (e.g., ***S*-2g'**).

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[69] Y. Lang, M. Zhang, Y. Cao, G. Huang, *Chem. Commun.*, **2018**, *54*, 2678–2681.

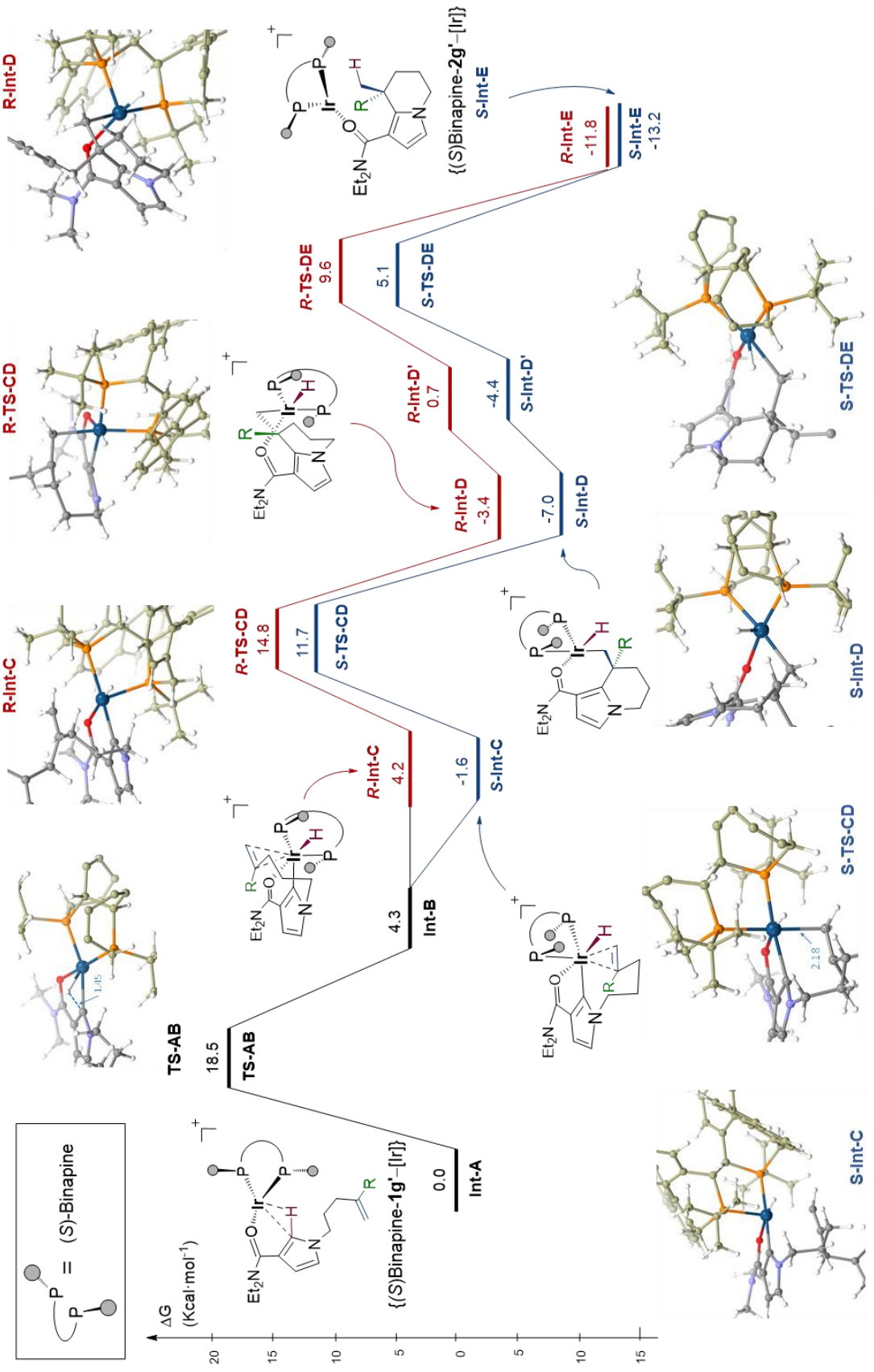


Figure 11: *Energy Profile ΔG^{solv} (kcal·mol^{-1}) for the Hydrocarbonation of **1g'** (R = Bn). B3LYP/6-31G(d) (LANL2DZ for Ir) // M06/6-311++g(d,p) (SDD for Ir). Binap ligand is mostly simplified in the 3D representations.*

To elucidate the origins of the observed high enantiofacial selectivity, Dr. Calvelo conducted a detailed analysis of the non-covalent interactions (NCIs) involved in the enantiodetermining carbometallation step. Employing the NCI-index based on electron density (NCIPLOT program) and the atoms in molecule (AIM) formalism, he identified the bond paths of these interactions and their associated bond critical points.

Initial analysis of intermediates ***S*-Int-C** and ***R*-Int-C** revealed that ***S*-Int-C** exhibits a greater number of stabilizing non-covalent interactions (13 vs. 10 NCIs) compared to ***R*-Int-C**. While several of these NCIs are comparable between the two intermediates (e.g., a C–H···π interaction between a *t*Bu group of the ligand and the pyrrole ring), key differences emerge (**Figure 12**).

Specifically, ***S*-Int-C** displays three unique interactions between the carboxamide group at C-3 and the chiral ligand: two C–H···O contacts involving the carbonyl oxygen and a *t*Bu group of Binapine, and a C–H···N interaction with the amide nitrogen. In contrast, the less stable isomer, ***R*-Int-C**, exhibits only two of these interactions.

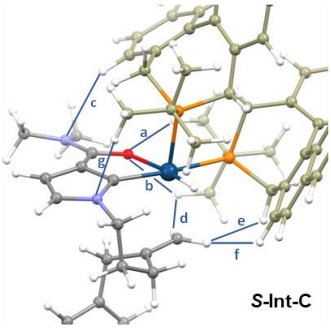
Additionally, a second type of weak non-covalent attractive interaction, namely hydrogen-hydrogen bonding of the C–H···H–C type,[103] was detected between the terminal hydrogen atoms of the alkene moiety and specific hydrogens of the ligand. ***S*-Int-C** exhibits a C–H···H–C interaction between one of the olefinic hydrogens and a *t*Bu group of Binapine, as well as two such interactions between the other alkenyl hydrogen and two different ligand hydrogens. In contrast, ***R*-Int-C** displays only one C–H···H–C interaction involving an alkene hydrogen, resulting in reduced stabilization.

Regarding the ensuing transition states, the more stable ***S*-TS-CD** retains a slightly reduced number of NCIs compared to its precursor intermediate, ***S*-Int-C**. However, all the C–H···O and C–H···H-C contacts identified in ***S*-Int-C** are preserved in ***S*-TS-CD**. Similarly, ***R*-TS-CD** retains the same key interactions as ***R*-Int-C**.

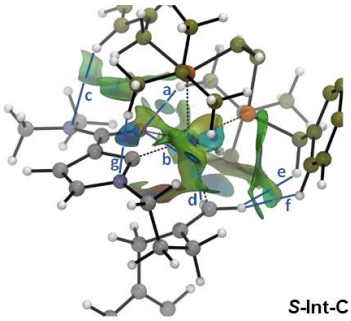
Collectively, these findings suggest that the observed high facial selectivity arises from additive and synergistic effects of multiple weak non-covalent attractive interactions. These interactions, particularly those involving the carboxamide moiety and specific hydrogens of Binapine (C–H···O interactions), as well as those between hydrogens of the olefin and the ligand (C–H···H–C dihydrogen interactions), should be playing a crucial role in the enantiodiscrimination process.

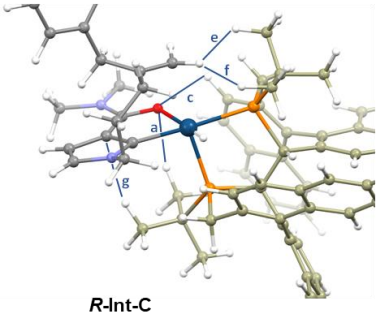
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[103] (a) C. F. Matta, J. Hernandez-Trujillo, T. H. Tang, and R. F. Bader, *Chem. Eur. J.* **2003**, *9*, 1940–1951. (b) J. Echeverría, G. Aullon, D. Danovich, S. Shaik, and S. Alvarez, *Nat. Chem.* **2011**, *3*, 323–330. (c) M. P. Mitoraj, F. Sagan, M. G. Babashkina, A. Y. Isaev, Y. M. Chichigina, and D. A. Safin, *Eur. J. Org. Chem.* **2019**, 493–503.

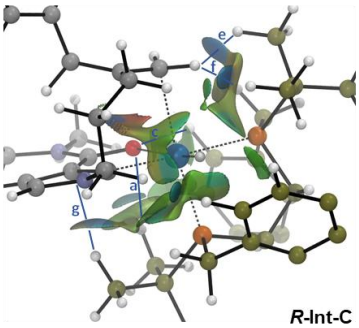


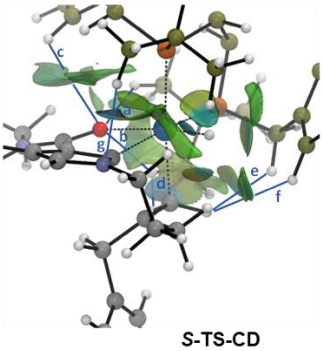
Interaction	type	***S*-Int-C** d (Å)
a	C-H···O	2.43
b	C-H···O	2.82
c	C-H···N/O	2.70
d	C-H···H-C	2.01
e	C-H···H-C	2.18
f	C-H···H-C	2.48
g	C-H···N(p)	2.34





Interaction	type	***R*-Int-C** d (Å)
a	C-H···O	2.32
c	C-H···O	2.94
e	C-H···H-C	2.00
f	C-H···H-C	1.95
g	C-H···p	2.47





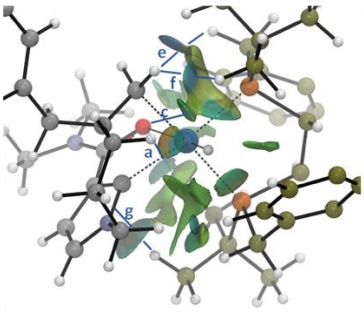


***Figure 12**: Optimized geometries of **S-Int-C**, **R-Int-C**, **S-TS-CD** and **R-TS-CD** highlighting key interatomic contacts (blue lines a–g), which correspond to non-covalent interactions. The type of interatomic interaction and the distance (Å) associated to them at **S-Int-C**, **R-Int-C** are tabulated. Only selected fractions of the whole stationary points are shown.*

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5.1.6. Conclusions

In summary, we have developed a highly enantioselective iridium-catalyzed intramolecular hydrocarbonation method capable of furnishing five-, six-, and seven-membered fused heterocyclic scaffolds bearing either tertiary or all-carbon quaternary stereocenters.

This methodology exhibits broad substrate scope, even tolerating the use of disubstituted and trisubstituted alkenes, and enabling the synthesis of products bearing diverse stereocenters and substituents. Remarkably, the use of trisubstituted alkenes as *E/Z* mixtures is also possible, providing pyrrole and indole fused to 5-membered rings with high enantioselectivity.

Furthermore, alkenyl pyrrole precursors which bear a prochiral center at the tether that links the pyrrole/indole with the alkene, can efficiently undergo a concomitant desymmetrization process. Thus, an array of tetrahydroindolizine and dihydropyrrolizine derivatives, featuring vicinal or skipped stereocenters can be obtained with good yields as well as excellent, diastereo- and enantio-selectivities (higher than 8:2 dr, and up to 99:1 er).

These results open new avenues for the application of this methodology to the asymmetric synthesis of biorelevant indole alkaloids, which bear several stereocenters. It is noteworthy that the use of Binapine, a chiral ligand that has been mostly overlooked,[96] proved indispensable for achieving high levels of both diastereo- and enantiocontrol.

Additionally, DFT computational studies validate carbometallation as the enantiodetermining step of the reaction, aligning closely with the experimental observations.

These findings not only advance our understanding of intramolecular hydrocarbonation processes but also pave the way for the development of novel methodologies employing similar chiral iridium catalysts.

[96] (a) P. Yang, H. Xu, J. S. Zhou, *Angew. Chem. Int. Ed.*, **2014**, *53*, 12210–12213. (b) H. Yang, N. Huo, P. Yang, H. Pei, H. Lv, X. Zhang, *Org. Lett.*, **2015**, *17*, 4144–4147. (c) P. Yang, C. Zhang, Y. Ma, C. Zhang, A. Li, B. Tang, J. S. Zhou, *Angew. Chem. Int. Ed.*, **2017**, *56*, 14702–14706. (d) X. Zhao, H. Xu, X. Huang, J. S. Zhou, *J. Am. Chem. Soc.*, **2019**, *131*, 298–302.

5.1.7. Later work based on related Ir(I) catalysis

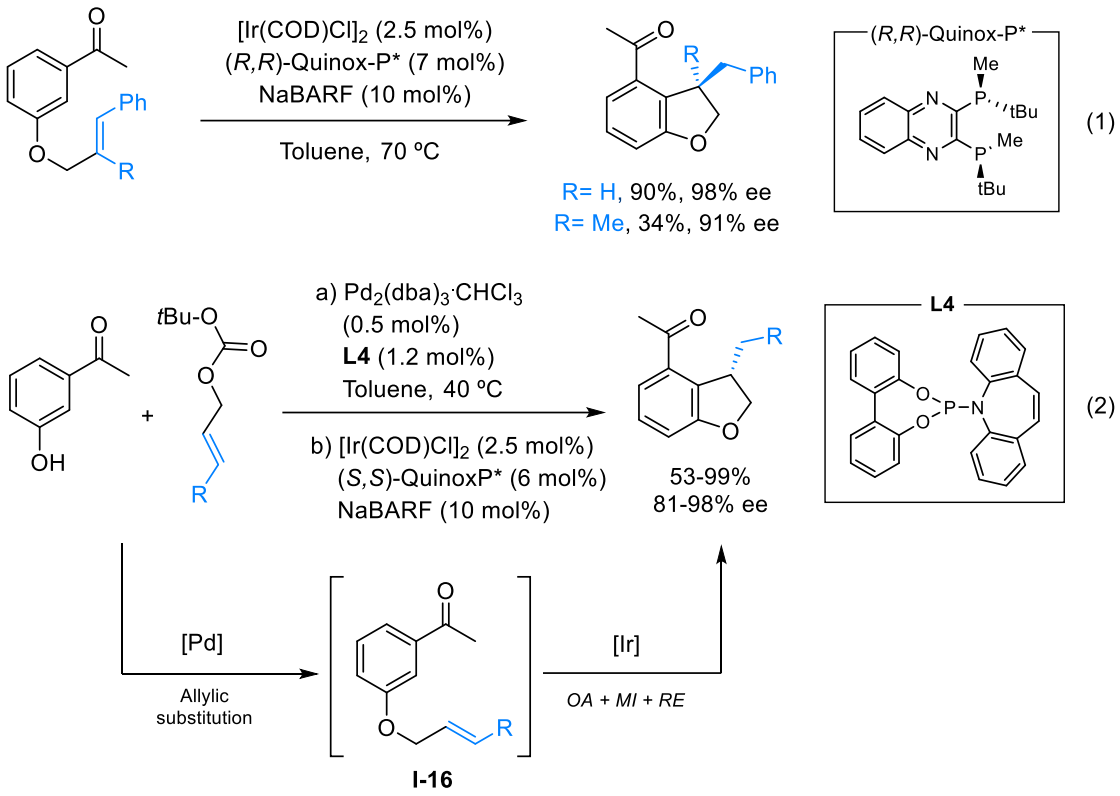
After the publication of the results presented in this chapter, several groups have developed related methodologies based on the use of Iridium(I) catalysts which also allows the generation of quaternary stereocenters.

In 2020, Rueping and Cavallo introduced an intramolecular enantioselective hydroarylation method for internal alkenes, which efficiently produces chiral dihydrofurans under mild conditions with high yields and excellent selectivities for tertiary stereocenters. The Iridium(I)/QuinoxP* cationic complex catalyzes the reaction using ketones and alkyl carboxamides as directing groups (**Scheme 123**, equation 1).[104] Although examples building quaternary carbon stereocenters were included, they were low yielding compared to those obtained when tertiary centers are generated.

Around the same time, Nishimura and colleagues developed a similar asymmetric hydroarylation that yields 3-substituted dihydrobenzofurans, using the same chiral catalyst. They also combined this with a one-pot synthesis of the hydroarylation precursor **I-16** via a Pd-catalyzed reaction between 3-acetylphenols and allylic carbonates, achieving good yields and high enantioselectivities (equation 2).[105] Unfortunately, the method is very limited in terms of scope, as it only delivers 5-members rings.

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[104] V. S. Shinde, M. V. Mane, L. Cavallo, M. Rueping, *Chem. Eur. J.*, **2020**, *26*, 8308–8313.
[105] K. Sakamoto, T. Nishimura, *Org. Biomol. Chem.*, **2021**, *19*, 684–690.



Scheme 123: *Enantioselective Iridium-catalyzed hydroarylations for the construction of chiral dihydrobenzofurans.*

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5.2

Regioselective Iridium(I)-Catalyzed Intramolecular Hydroarylations of Allene-Tethered Pyrroles and Indoles

Part of the results of this section were published:

Skeletal and Mechanistic Diversity in Ir-Catalyzed Cycloisomerizations of Allene-Tethered Pyrroles and Indoles

A. Arribas,[1] M. Calvelo,[1] A. Rey,[1] J. L. Mascareñas,[1] F. López [1,2]
Angew. Chem. Int. Ed., **2023**, *63*, e202408258.

[1] Centro Singular de Investigación en Química Biolóxica e Materiais Moleculares (CiQUS) and Departamento de Química Orgánica, Universidade de Santiago de Compostela, 15782 Santiago de Compostela (Spain)

[2] Misión Biológica de Galicia, Consejo Superior de InvestigacionesCientíficas (CSIC)36080 Pontevedra (Spain)

5.2.1. *Allenes as partners in TM-catalyzed functionalizations involving the activation of C–H bonds*

Allenes, a class of C–C unsaturated molecule that holds two consecutive C–C double bonds, have emerged as highly versatile reactants in organic synthesis.[106] Their unique structural configuration imparts higher reactivity compared to alkenes, with the additional advantage that their resulting products usually retain one of the two double bonds, enabling convenient further elaboration. These properties can be leveraged for the assembly of complex molecules.[107]

However, allenes present chemo- and regioselectivity issues, which complicate their reactivity and, overall, the development of efficient and highly selective methods. Furthermore, allenes can be chiral due to the perpendicular orientation of the two double bonds, which can raise additional challenges.

Numerous hydrofunctionalizations of allenes have been developed, primarily for the formation of C–N, C–O, and C–C bonds, often catalyzed by transition metals. When these processes are selective, they facilitate the efficient construction of skeletons bearing versatile allyl or vinyl motifs (see **Figure 13**), which can be converted into other functional groups, en route to the synthesis bioactive compounds and pharmaceuticals.

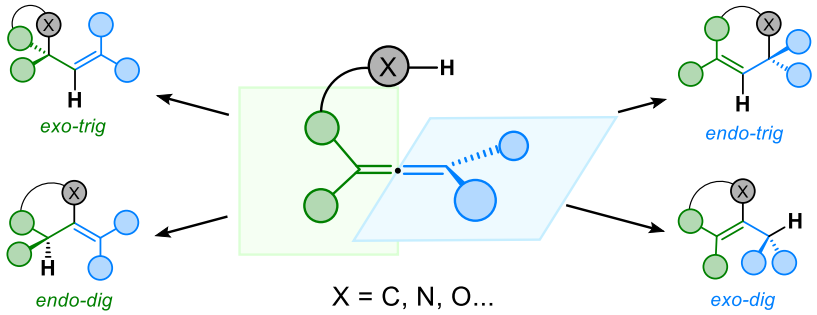


***Figure 13**: Diversity of regioisomers result of intramolecular hydrofunctionalizations of allenes.*

[106] D.R. Taylor, *Chem. Rev.*, **1967**, *67*, 317–359.

[107] (a) R. Santhoshkumar, C.-H. Cheng, *Asian J. Org. Chem.*, **2018**, *7*, 1151–1163. (b) J. L. Mascareñas, I. Varela, F. López, *Acc. Chem. Res.*, **2019**, *52*, 465–479. (c) F. López, J. L. Mascareñas, *Chem. Soc. Rev.*, **2014**, *43*, 2904–2915.

5.2.2. TM-Catalyzed hydroarylations of allenes

In recent years, a few hydroarylation reactions involving allenes has been developed. Among these methodologies, those that proceed via either electrophilic aromatic substitutions or C–H activations based on concerted metalation-deprotonations (CMD) are particularly prevalent.

The subsequent sections will highlight key precedents in this topic, alongside with the few examples involving the C–H addition across the allene partners.

Allene hydroarylations through S_EAr processes

In 2006, Widenhoefer reported an Au(I) catalyzed cyclization of allenyl precursors bearing a tethered nucleophile, including indole moieties.[108] In another work, the same authors developed a highly enantioselective variant of this hydroindolations using [(*S*)-DTBM-Biphep]Au_2Cl_2 as catalyst (**Scheme 124**, equation 1).[109]

The intermolecular versions of the above-mentioned processes have been widely explored with both Au(I) and Au(III) catalysts.[110] In 2018, Lee developed an intermolecular hydroindolation with high chirality transfer from enantioenriched 1,3-disubstituted allenes (equation 2),[111] whereas mechanistically similar intramolecular processes have also been developed with other metals such as palladium,[112] platinum[113] and cooper.[114]

These processes are based on the nucleophilic attack of arenes to π-activated allenes of type **I-17**, and a final protodemetallation of intermediates of type **I-18** (exemplified in equation 2). Most of these intermolecular reactions are selective towards products resulting from attack to the less-substituted site of the allene.

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[108] Z. Zhang, C. Liu, R. E. Kinder, X. Han, Q. Hua, R. A. Widenhoefer, *J. Am. Chem. Soc.,* 2006, **128**, 9066–9073.

[109] C. Liu, R. A. Widenhoefer, *Org. Lett.,* 2007, **9**, 1935–1938. For other intramolecular examples, see: (a) T. Watanabe, S. Oishi, N. Fujii, H. Ohno, *Org. Lett.,* **2007**, *9*, 4821–4824. (b) M. A. Tarselli, M. R. Gagné, *J. Org. Chem.,* **2008,** *73*, 2439–2441. (c) D. Weber, M. R. Gagné, *Org. Lett.,* **2009**, *11*, 4962–4965. (d) B. Chen, W. Fan, G. Chai, S. Ma, *Org. Lett.*, **2012**, *14*, 3616–3619.

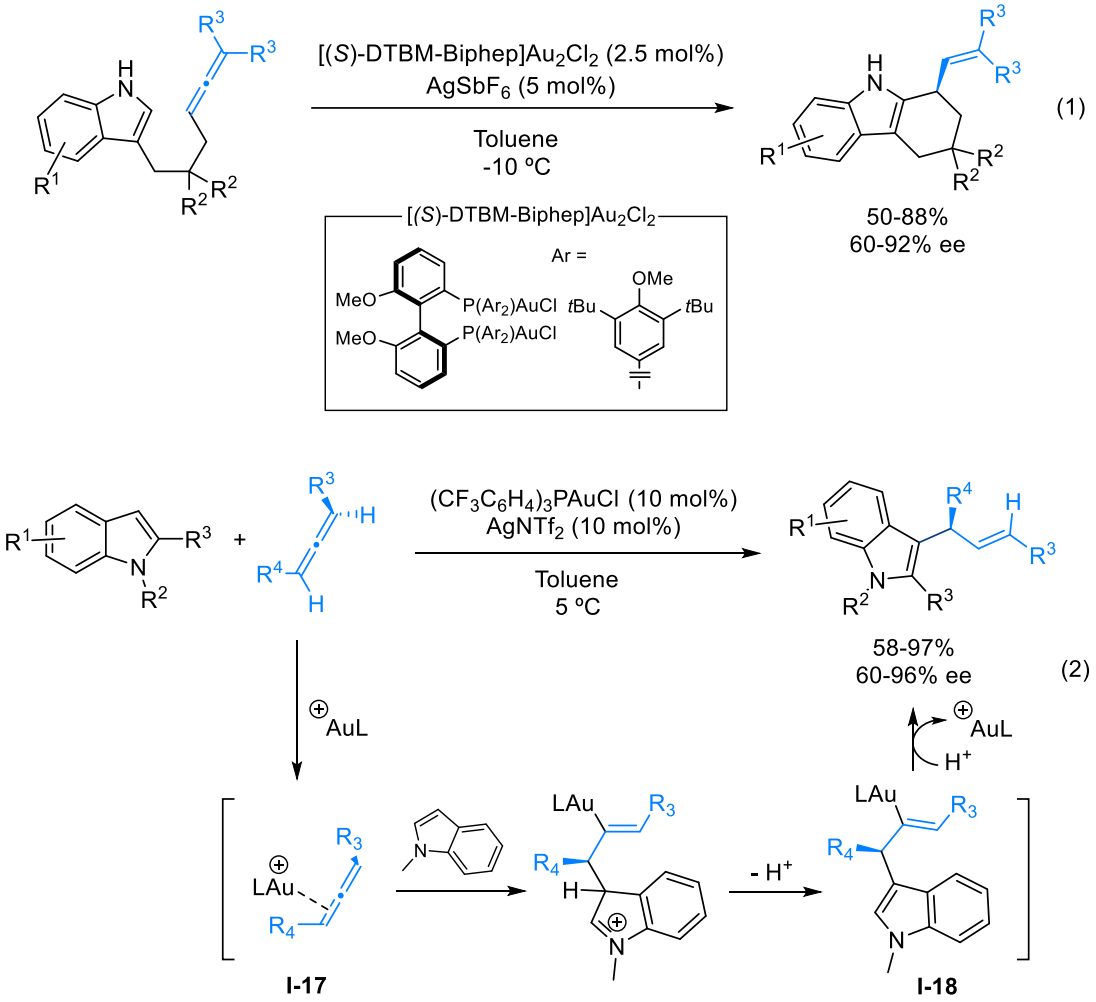
[110] R. Skouta, C.-J. Li, *Canadian Journal of Chemistry,* **2008**, *86*, 616-620. (b) K. L. Toups, G. T. Liu, R. A. Widenhoefer, *J. Organomet. Chem.,* **2009**, *694*, 571-575. (c) M. A. Tarselli, A. Liu, M. R. Gagne, *Tetrahedron* **2009**, *65*, 1785-1789. (d) M. C. Kimber, *Org. Lett.,* **2010**, *12*, 1128–1131. (e) M. Z. Wang, C. Y. Zhou, Z. Guo, E. L. Wong, M. K. Wong, C. M. Che, *Chem. Asian J.,* **2011**, *6*, 812-824. (f) C. N. Kona, M. H. Shinde, C. V. Ramana, *Org. Biomol. Chem.,* **2015**, *13*, 5358-5362.

[111] D. R. Sutherland, L. Kinsman, S. M. Angiolini, G. M. Rosair, A.-L. Lee, *Chemistry* **2018**, *24*, 7002-7009.

[112] Z. Fang, C. Fu, S. Ma, *Chemistry* **2010**, *16*, 3910-3913.

[113] J. Mo, P. H. Lee, *Org. Lett.*, **2010**, *12*, 2570–2573.

[114] R. Abed Ali Abdine, L. Pagès, M. Taillefer, F. Monnier, *Eur. J. Org. Chem.,* **2020**, *48*, 7466-7469.



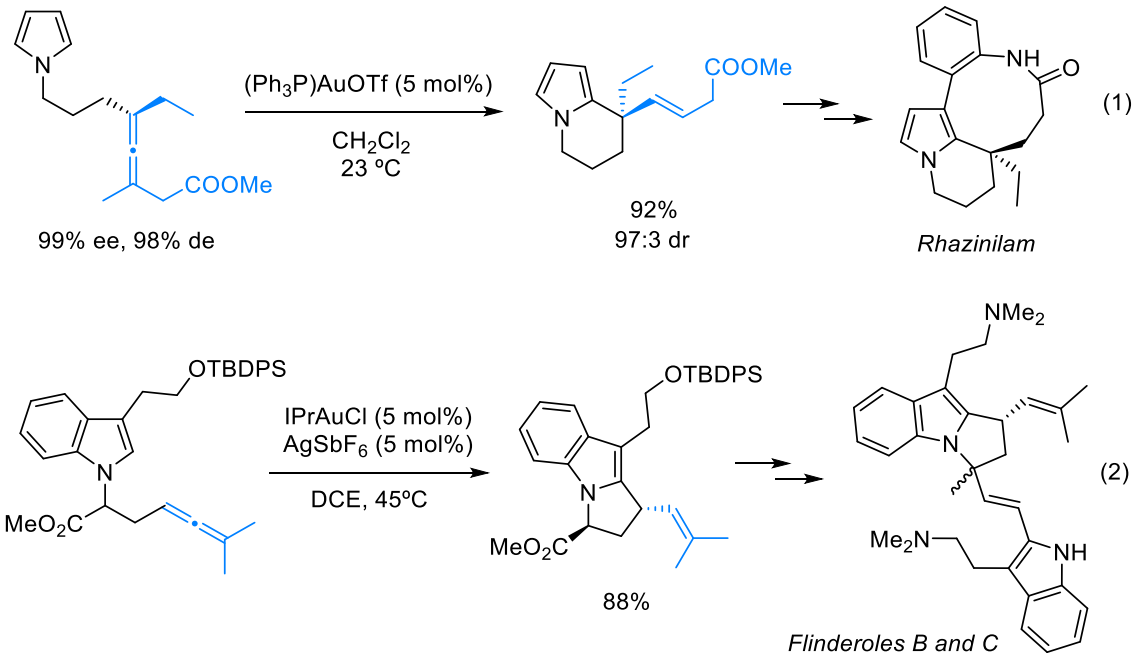
***Scheme 124**: Au-catalyzed hydroarylations of allenes*

This type of gold-catalyzed methodologies, particularly the intramolecular ones, have been applied to the synthesis of some natural products. For instance, Nelson and coworkers developed an intramolecular hydroarylation of allenyl-pyrrole systems and successfully applied it to the first asymmetric synthesis of Rhazinilam.[115] Rhazinilam.[116] In the process, chirality was transferred from the initially synthesized enantioenriched allene to the cyclized product (**Scheme 125**, equation 1). On the other hand, in 2011, Toste and coworkers adapted this strategy to the total synthesis of Flinderoles B and C, in this case, in a racemic fashion (equation 2).[117]

[115] For racemic synthesis: (a) A. H. Ratcliffe, G. F. Smith, G. N. Smith, *Tetrahedron Lett.*, **1973**, *14*, 5179–5184. (b) P. Magnus, T. Rainey, *Tetrahedron*, **2001**, *57*, 8647–8651. (c) M. G. Banwell, A. J. Edwards, K. A. Jolliffe, J. A. Smith, E. Hamel, P. Verdier-Pinard, *Org. Biomol. Chem.*, **2003**, *1*, 296–305. (d) A. L. Bowie, C. C. Hughes, D. Trauner, *Org. Lett.*, **2005**, *7*, 5207–5209. (e) J. A. Johnson, N. Li, D. Sames, *J. Am. Chem. Soc.*, **2002**, *124*, 6900–6903. (f) M. G. Banwell, D. A. S. Beck, A. C. Willis, *ARKIVOC*, **2006**, 163–174.

[116] Z. Liu, A. S. Wasmuth, S. G. Nelson, *J. Am. Chem. Soc.*, **2006**, *128*, 10352–10353.

[117] R. M. Zeldina, F. D. Toste, *Chem. Sci.*, **2011**, *2*, 1706–1709.



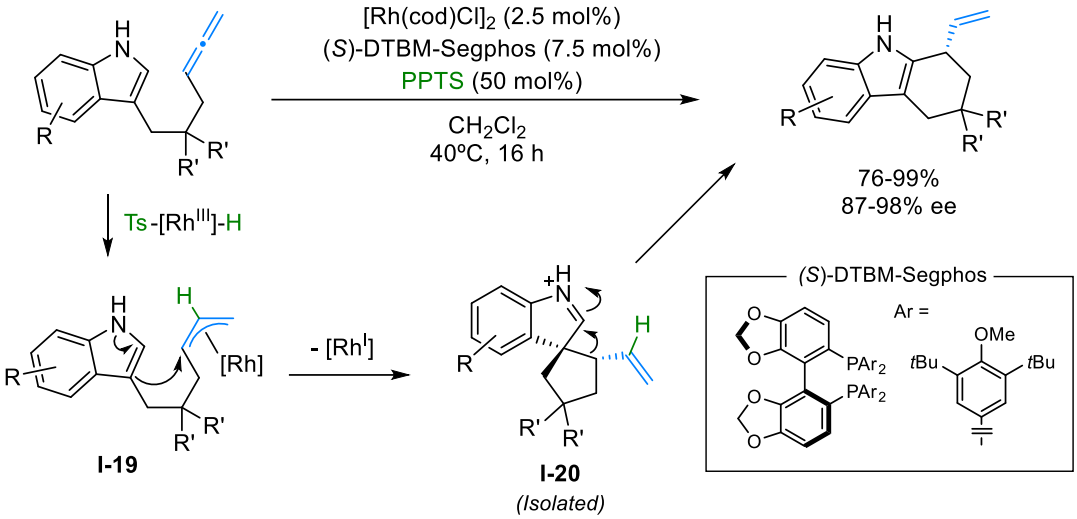
***Scheme 125**: Au-catalyzed intramolecular cyclization of allenyl-pyrroles and indoles with application in natural product synthesis.*

Hydroarylation reactions initiated by activation of allenes with external metal-hydrides

In 2015, Breit reported an interesting intramolecular reaction of allenyl indoles, catalyzed by Rh(I). The authors propose the formation of a rhodium hydride from the reaction of the Rh(I) complex generated from $[Rh(COD)Cl]_2$ and (*R*)-DTBM-Segphos and a proton source (pyridinium *p*-toluenesulfonate, PPTS). Then, this metal-hydride inserts into the allene, leading to an electrophilic π-allyl Rh intermediate (**I-19**), which undergoes a nucleophilic attack of the indole through its C3 position. Consequently, the spiroindolenine **I-20** is generated and ultimately isomerizes to the observed product (**Scheme 126**).[118]

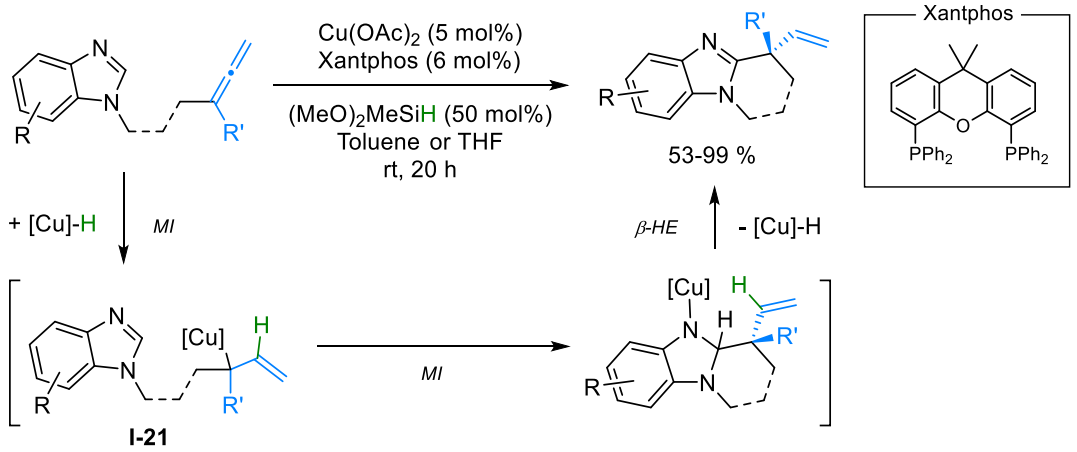
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[118] C. P. Grugel, B. Breit, *Org. Lett.*, **2019**, *21*, 5798–5802.



***Scheme 126**: Rh(I)-catalyzed hydroarylation of allenes reported by Breit.*

The same group published in 2020 a hydrocarbonation reaction that works both intra- and intermolecularly.[119] In this case, a copper-hydride, generated from a silane and a copper(I)-biphosphine precatalyst was proposed as the key catalytic species. The allene inserts into this metal-hydride, and the resulting allyl copper species **I-21** adds to the C=N bond of the benzimidazole. The regeneration of the LCuH species occurs through a β-hydride elimination (β-HE) that also releases the product (see **Scheme 127**).



***Scheme 127**: Hydroarylation of allenes employing cooper-hydride species reported by Breit.*

Allene hydroarylations based on TMC C–H activations

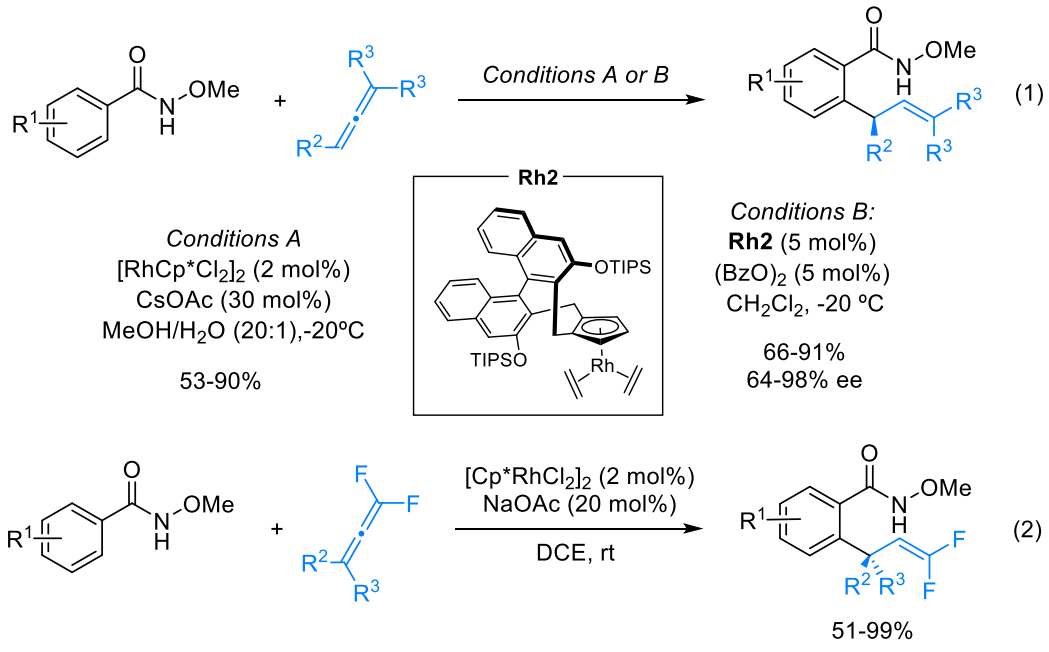
While most of these processes have been optimized for the hydroarylation of alkenes and alkynes, some intermolecular processes with allenes have also been reported.[120]

[119] Y. Dong, B. Breit, *Org. Lett.*, **2021**, *23*, 6765-6769.
[120] L. Pagès, R. Abed Ali Abdine, F. Monnier, M. Taillefer, *Eur. J. Org. Chem.*, **2022**, e202200724.

In most of the reported allene hydroarylation methods based on C–H activations, this step takes place through concerted metallation-deprotonation processes, followed by migratory insertions and an eventual protodemetallation. Indeed, very few examples are based on C–H oxidative additions to low valent transition metal complexes, to eventually transfer this bond to a C–C unsaturated partner (following a migratory insertion–reductive elimination sequence).

In 2012, Ma reported a Rh(III) catalyzed hydroarylation of *N*-methoxybenzamides that affords allyl-substituted products. The reaction proceeds via an initial C–H activation through a CMD-type process, followed by the regioselective allene insertion and the final protodemetallation (see **Scheme 128**, equation 1, conditions A).[121] The following year, Cramer developed the enantioselective variant, using the chiral Rh(III) catalysts previously employed in similar hydroarylation reactions with alkenes and alkynes.[122] In both cases, only tertiary stereocenters were constructed (equation 1, conditions B).

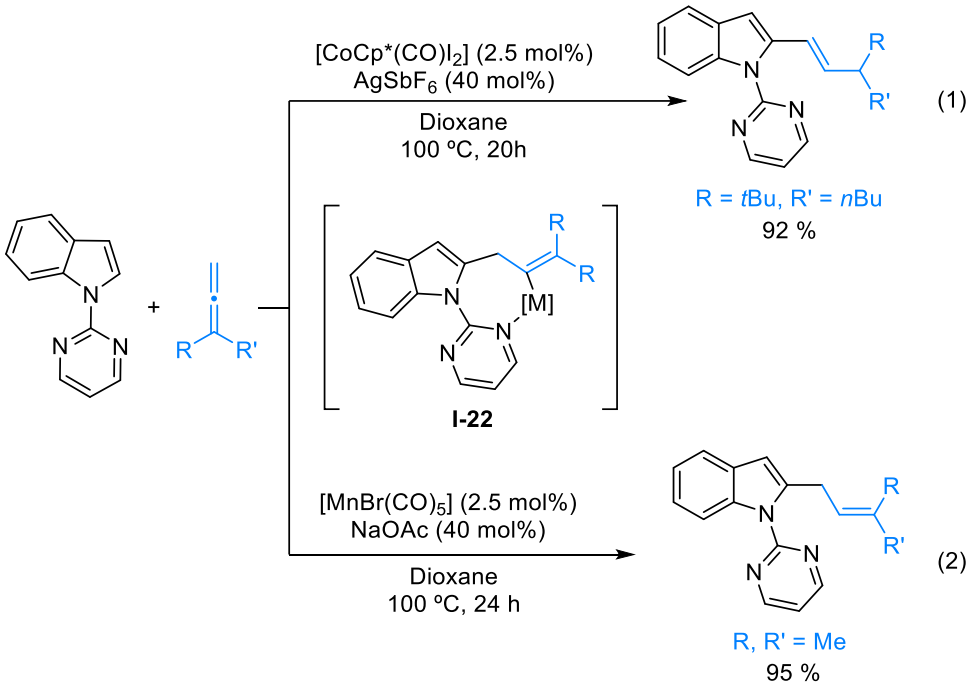
More recently, in 2022, Feng published a Rh(III)-catalyzed hydroarylation of 1,1-difluoroallenes. Although racemic, the process constitutes one of the few examples leading to carbon quaternary centers, in a regioselective fashion (equation 2).[123]



***Scheme 128**: Enantioselective Rh-catalyzed hydroarylation developed by Cramer (1), and Rh-catalyzed hydroarylation of 1,1-difluoroallenes (2).*

[121] R. Zeng, C. Fu, S. Ma, *J. Am. Chem. Soc.*, **2012**, *134*, 9597-9600
[122] B. Ye, N. Cramer, *J. Am. Chem. Soc.*, **2013**, *135*, 636-639.
[123] C.-Q. Wang, Z.-Q. Li, L. Tian, P. J. Walsh, C. Feng, *Cell Rep. Phys. Sci.*, **2022**, 3, 101117.

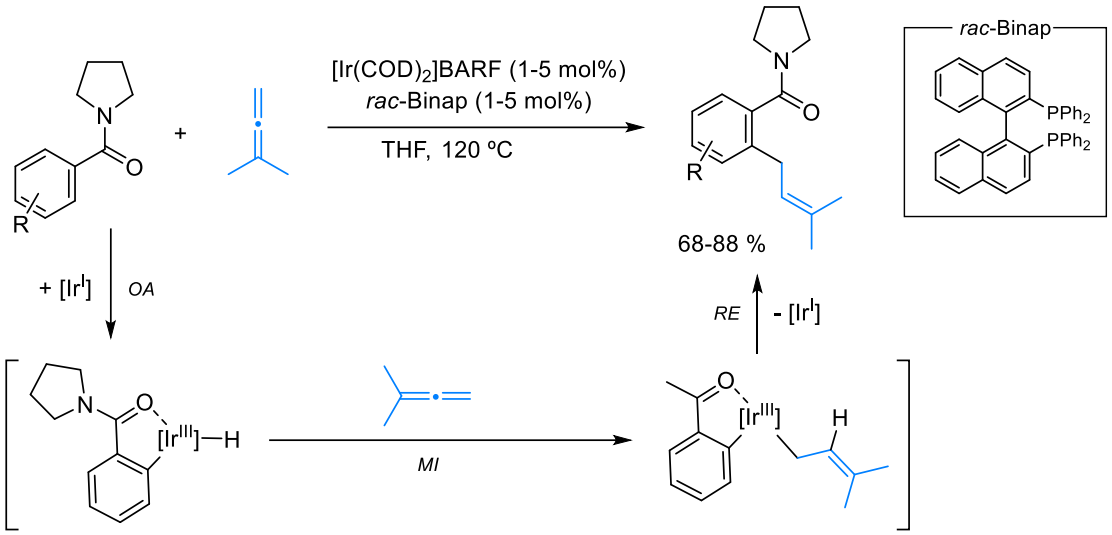
In 2017, Ackermann developed a cobalt (III) catalyzed hydroindolation reaction of allenes, by which selectively delivers alkenylated indoles (**Scheme 129**, equation 1).[124] The same year, Wang and coworkers developed a similar methodology catalyzed by manganese, to selectively access vinylated adducts (equation 2).[125] In both processes, they propose analogous intermediates of type **I-22** resulting from the selective insertion of the unsubstituted double bond into the C–M bond.



***Scheme 129**: Hydroarylations based on base-assisted C–H activation process.*

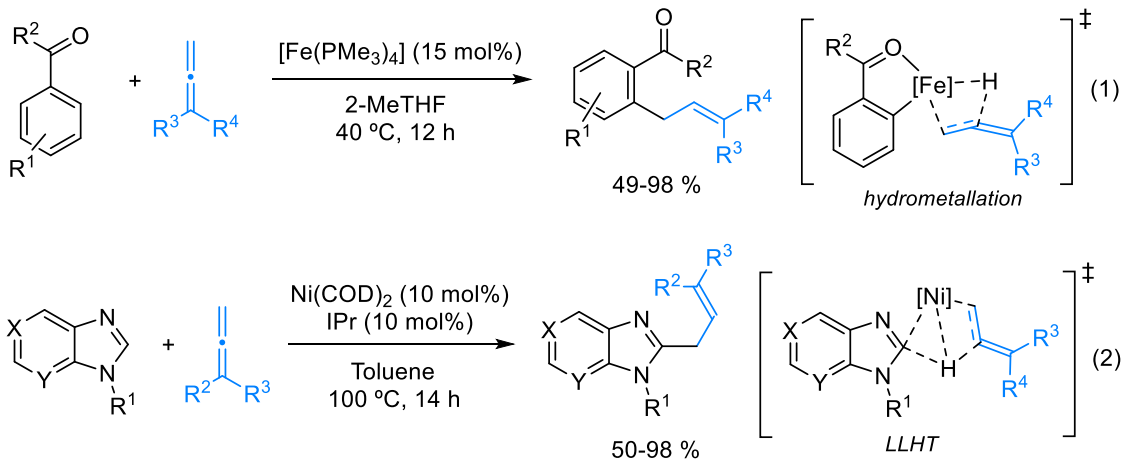
As commented, hydroarylation processes of allenes, based on a C–H oxidative addition/migratory insertion/reductive elimination sequence, are extremely scarce. In 2009, Krische developed a pioneered example, an iridium(I)-catalyzed intermolecular hydroarylation of 1,1-dimethyl allene with benzamides, that efficiently delivers prenylated benzamides with moderate to good yields. Curiously, the method is strictly restricted to 1,1-dimethyl allene and the linear, achiral product is selectively obtained in all the reported cases. The authors proposed a hydrometallation pathway as probable mechanism for the reaction (**Scheme 130**).[81]

[124] S. Nakanowatari, R. Mei, M. Feldt, L. Ackermann, *ACS Catal.,* **2017**, 7, 2511-2515 (in this case, another molecule of substrate acts as an external base for C–H activation).
[125] (a) S. Y. Chen, Q. Li, H. Wang, *J. Org. Chem.,* **2017**, *82*, 11173-11181. (b) C. Wang, A. Wang, M. Rueping, *Angew. Chem. Int. Ed.,* **2017**, *56*, 9935.
[81] Y. J. Zhang, E. Skucas, M. J. Krische, *Org. Lett.,* **2009**, *11*, 4248-4250.



***Scheme 130**: Ir(I)-catalyzed Intermolecular addition of C–H bonds across 1,1-dimethylallene developed by Krische.*

In addition to these methods, Ackermann disclosed two recent studies in which intermolecular C–H bond additions across 1,1-disubstitued allenes also lead to achiral linear products (**Scheme 131**). One of these studies, involving low valent iron catalysts, proposes the insertion of the metal center into the C–H bond, to generate an iron hydride intermediate (equation 1).[127] The other method (equation 2), based on a nickel(0) catalyst, is proposed to involve a ligand to ligand hydrogen atom transfer, similar to that indicated in some Ni-catalyzed hydroarylation of alkenes (see **Scheme 81**, page 60).[128]



***Scheme 131**: Iron- and nickel-catalyzed C–H bond additions across allenes and proposed key transition states.*

[127] (a) A. M. Messinis, L. H. Finger, L. Hu, L. Ackermann, *J. Am. Chem. Soc.*, **2020**, *142*, 13102-13111. (b) A. M. Messinis, J. C. A. Oliveira, A. C. Stückl, L. Ackermann, *ACS Catal.*, **2022**, *12*, 4947-4960.
[128] S. Nakanowatari, T. Muller, J. C. A. Oliveira, L. Ackermann, *Angew. Chem.*, **2017**, *129*, 16107-16111.

In summary, there are very few precedents on transition metal-catalyzed hydrocarbonations of allenes based on C–H bond activation processes, and many of them are restricted to intermolecular processes. Therefore, the intramolecular hydrocarbonation of allenes represents a yet uncharted field, especially when referring to real additions of C–H bonds across one of the allene double bonds.

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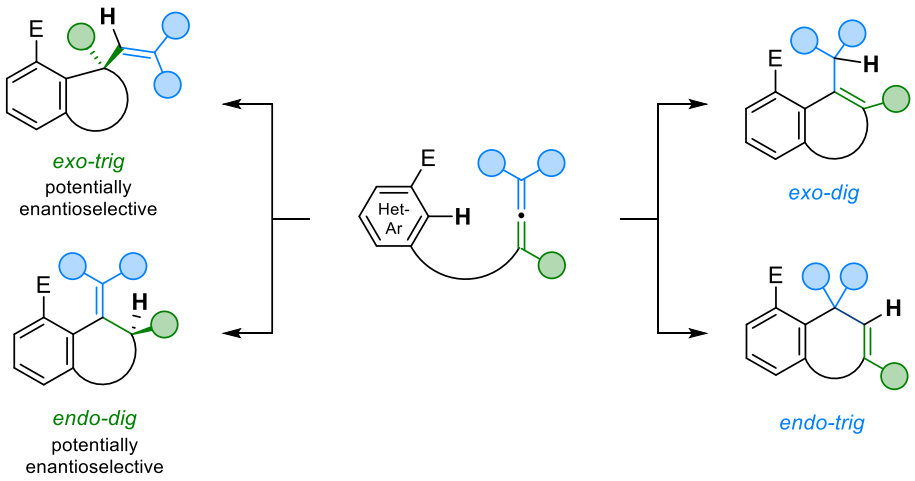
5.2.3. Objectives

Our objective consisted on the development of new intramolecular transition metal catalyzed hydroarylations of allenes, based on activation of C–H bonds of heteroaromatic precursors. A priori, these processes could yield different types of products, depending on whether the cyclization occurs in an *endo* or *exo* fashion (regioselectivity), and on which of the allene's double bonds undergoes addition (chemoselectivity, **Scheme 132**).

Among the diverse types of products, those resulting from *exo*-trig cyclization would be particularly appealing since the products could hold chiral tertiary and quaternary stereocenters with a vinyl substituent, very useful for subsequent synthetic manipulations.

On the other hand, *exo*-dig cyclizations offer a promising route to compounds that could not be obtained using our previously reported alkyne addition methodologies (see **Scheme 90**, page 95).[79]

In addition to the study of the chemo- and regioselectivity of the envisioned cycloisomerizations, potential asymmetric variants using chiral iridium(I) catalysts would also be explored, owing to the lack of precedents to build the expected products in an enantioselective fashion.



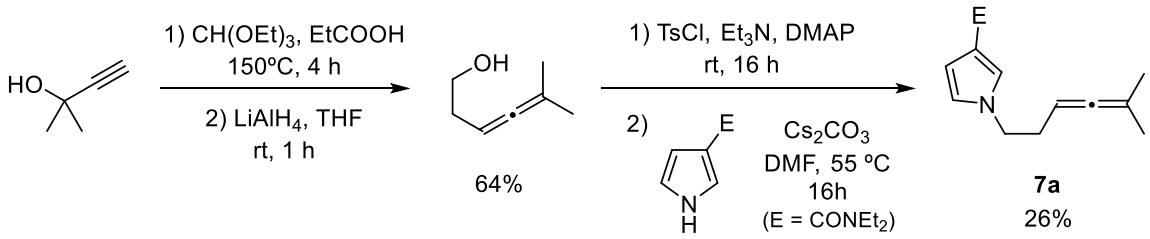
***Scheme 132**: Possible hydroarylation regioisomers that could be eventually formed.*

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[79] D. F. Fernández, C. A. B. Rodrigues, M. Calvelo, M. Gulías, J. L. Mascareñas, F. López, *ACS Catal.*, **2018**, *8*, 7397–7402.

5.2.4. Preliminary studies on the hydroarylation of allenyl-pyrroles

To evaluate the viability of the cycloisomerization, we prepared the model substrate **7a**, which bears two methylene units between the pyrrole and the allene, (**Scheme 133**). Its synthesis involved a Claisen condensation between 2-methylbut-3-yn-2-ol and triethylorthoacetate and a subsequent reduction of the resulting compound with $LiAlH_4$, to afford the corresponding allenyl alcohol in 64% global yield. Its tosylation and subsequent alkylation with 1H-pyrrole-3-diethylcarboxamide, led to **7a** in 26% yield.



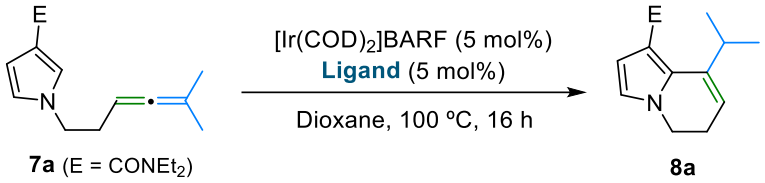
***Scheme 133**: Synthetic route to prepare substrate **7a**.*

We then evaluated iridium catalysis with different ligands that provided satisfactory results in our previously reported intramolecular hydroarylation of alkenes and alkynes.[129] The utilization of d^Fppe, previously successful in intramolecular hydrocarbonations of alkenes, proved futile (**Table 5**, entry 2), along with its derivatives dppe and (*R,R*)-Duphos (entries 3 and 4). Similarly, (*S*)-Binapine, known for its efficacy in the hydroarylation of alkenyl pyrroles, yielded a complex mixture of products (entry 5).

Gratifyingly, (*R*)-Segphos, and particularly (*R*)-BTFM-Garphos, facilitated a selective conversion toward the dihydroindolizine product **8a** (with yields of 26% and 82% respectively, entries 6 and 7). The use of *rac*-Binap resulted in the isolation of 83% of the achiral dihydroindolizine **8a**, without detecting any other cyclization byproduct (entry 8).

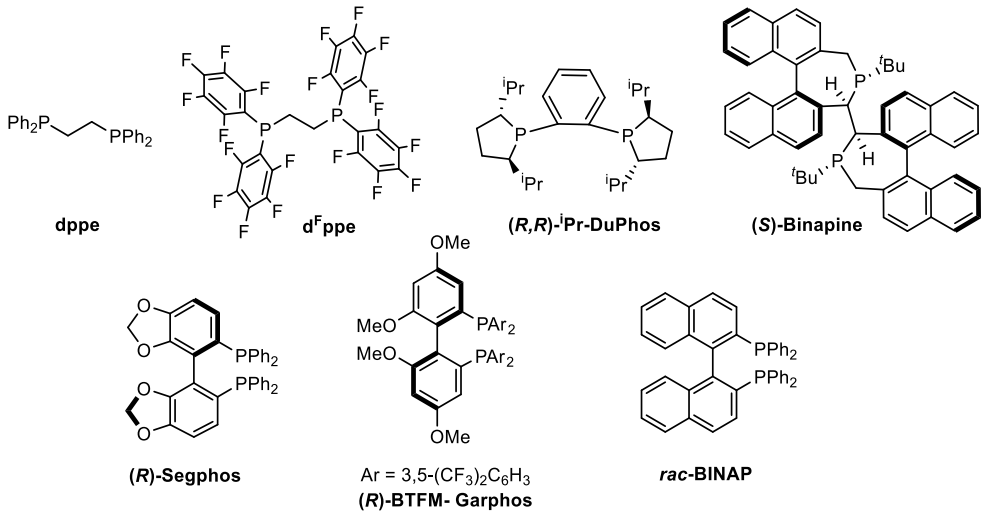
[129] (a) D. F. Fernández, M. Gulías, J. L. Mascareñas, F. López, *Angew. Chem. Int. Ed.,* **2017**, *56*, 9541–9545. (b) D. F. Fernández, C. A. B. Rodrigues, M. Calvelo, M. Gulías, J. L. Mascareñas, F. López, *ACS Catal.,* **2018**, *8*, 7397–7402. (c) A. Arribas, M. Calvelo, D. F. Fernández, C. A. B. Rodrigues, J. L. Mascareñas, F. López, *Angew. Chem. Int. Ed.,* **2021**, *60*, 19297–19305.

Table 5: *Evaluation of different ligands for the cycloisomerization of* ***7a****, and structure of the ligands evaluated.*



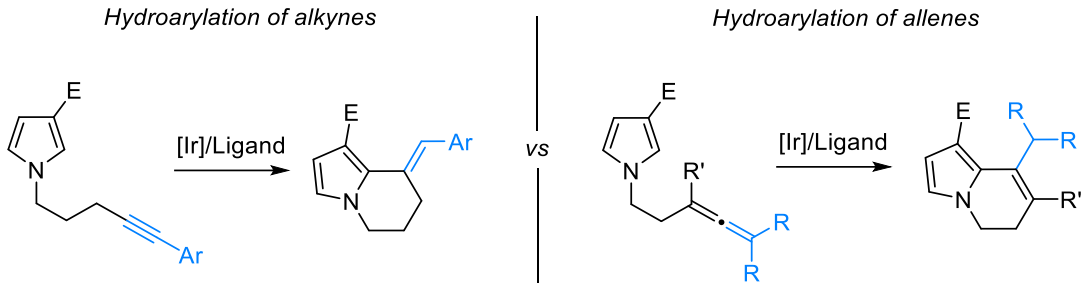
7a (E = $CONEt_2$) **8a**

Entry	Ligand	Yield (%)
1	d^Fppe	0
2	dppe	0
3	(*R,R*)-Duphos	<5
4	(*S*)-Binapine	0
5	(*R*)-Segphos	26
6	(*R*)-BTFM-Garphos	82
7	*rac*-Binap	83



Product **8a** results from an *exo*-hydroarylation of the distal C–C double bond of the allene. The presence of an endocyclic double bond within the newly formed ring is appealing from a synthetic standpoint, because this class of products is typically obtained via harsh reductions of the corresponding aromatic indolizine. Moreover, they cannot be obtained through analogous hydrocarbonations of pyrrole-tethered alkynes, which usually yield products with exocyclic alkenes (see **Scheme 134**).[130]

[130] D. F. Fernández, C. A. B. Rodrigues, M. Calvelo, M. Gulías, J. L. Mascareñas, F. López, *ACS Catal.*, **2018**, *8*, 7397–7402. See Scheme 90, page 50.



***Scheme 134**: Iridium catalyzed hydroarylation of allenes vs analogous reaction with alkynes.*

It is relevant to highlight that similar indolizine scaffolds are common in a variety of products with anti-inflammatory, anticancer, and antimicrobial properties, among others.[131] Additionally, indolizine-containing compounds have been described in electroluminescent materials, dyes, sensors, and biomarkers.[132] Therefore, the full exploration of this methodology was warranted.

Accordingly, we then checked the robustness of the conditions by reducing the catalyst loading to 1 mol%, observing a detrimental effect on the yield (15%, **Table 6**, entry 2). A similar outcome was observed when the reaction time was reduced to 4 hours (20% yield, entry 3), or when the reaction was performed at 60 ºC (<5% yield, entry 4,).

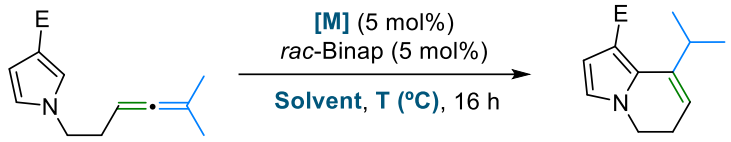
Other solvents like toluene of 1,2-DCE, which worked on previously reported Ir-catalyzed hydroarylations, were effective but led to lower yields (79 and 62% yield respectively, entries 5 and 6).

When employing other iridium(I) sources like $[Ir(COD)_2]BF_4$ or $[Ir(COD)_2]OTf$, the expected product **8a** was also obtained, but again in lower yields (entries 7 and 8). Notably, with $[Rh(COD)_2]BARF$, no product was obtained at 100 or 120 ºC (entries 9 and 10), highlighting the unique capacity of Ir(I) to promote these reactions.

[131] (a) K. M. Dawood, H. Abdel-Gawad, M. Ellithey, H. A. Mohamed, and B. Hegazi, *Arch. Pharm. Chem. Life Sci.*, **2006**, *339*, 133–140. (b) S. Chen, Z. Xia, M. Nagai, R. Lu, E. Kostik, T. Przewloka, M. Song, D. Chimmanamada, D. James, S. Zhang, J. Jiang, M. Ono, K. Koya, and L. Sun, *Med. Chem. Comm.*, **2011**, *2*, 176–180. (c) S. Teklu, L. L. Gundersen, T. Larsen, and K. E. Malterud, *Bioorg. Med. Chem.*, **2005**, *13*, 3127–3139. (d) W. Chai, J. G. Breitenbucher, A. Kwok, X. Li, V. Wong, N. I. Carruthers, T. W. Lovenberg, C. Mazur, S. J. Wilson, F. U. Axe, and T. K. Jones, *Bioorg. Med. Chem. Lett.*, **2003**, *13*, 1767–1770. (e) S. Medda, P. Jaisankar, R. K. Manna, B. Pal, V. S. Giri, and M. K. Basu, *J. Drug Target.*, **2003**, *11*, 123–128.

[132] (a) J. Wan, C.-J. Zheng, M.-K. Fung, X.-K. Liu, C.-S. Lee, and X.-H. Zhang, *J. Mater. Chem.*, **2012**, *22*, 4502–4510. (b) F. Delattre, P. Woisel, G. Surpateanu, F. Cazier, and P. Blach, *Tetrahedron*, **2005**, *61*, 3939–3945. (c) B. Liu, Z. Wang, N. Wu, M. Li, J. You, and J. Lan, *Chem. Eur. J.*, **2012**, *18*, 1599–1603.

Table 6. *Evaluation of different asymmetric ligands for the cycloisomerization of* ***7a****.* [a] *1 mol% of catalyst.* [b] *Reaction time = 4 hours.*



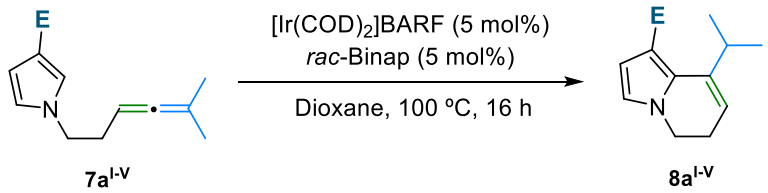
7a (E = $CONEt_2$) **8a**

Entry	[M]	Solvent	T (ºC)	Yield (%)
1	[Ir(COD_2]BARF	Dioxane	100	83
2[a]	[Ir(COD_2]BARF	Dioxane	100	15
3[b]	[Ir(COD_2]BARF	Dioxane	100	20
4	[Ir(COD_2]BARF	Dioxane	**60**	<5
5	[Ir(COD_2]BARF	**Toluene**	100	79
6	[Ir(COD_2]BARF	**DCE**	100	62
7	[Ir(COD_2]**BF_4**	Dioxane	100	23
8	[Ir(COD_2]**OTf**	Dioxane	100	37
9	[**Rh**(COD_2]BARF	Dioxane	100	<5
10	[**Rh**(COD_2]BARF	Dioxane	120	0

The importance of the diethylamide directing group was next explored. When precursor **7a'**, without the diethylamide moiety at the pyrrole C3 position, was treated under Ir/Binap catalysis, there was almost no conversion (**Table 7**, entry 2). On the other hand, alternative directing groups previously evaluated in the intramolecular hydroarylation of alkenes, such as methyl ketone **7a"**(entry 3), ester **7a'"**(entry 4), or carboxylic acid **7a^{IV}** (entry 5), were equally unsuccessful. The aldehyde **7a^{V}** also failed to give any cyclization product (entry 6). Only the Weinreb amide precursor **7a^{VI}** could be partially converted into its product **8a^{VI}**, which was isolated in a very low 14% yield (entry 7).

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Table 7. *Evaluation of different directing groups for the cycloisomerization of compounds of type* ***7****.*



7a^{I-V} **8a^{I-V}**

Entry	E	Yield (%)
1	$CONEt_2$ (**7a**)	83
2	H (**7a^{I}**)	0
3	COMe (**7a^{II}**)	0
4	COOEt (**7a^{III}**)	0
5	COOH (**7a^{IV}**)	0
6	COH (**7a^{V}**)	0
7	CON(Me)OMe (**7a^{VI}**)	14

Curiously, the regioselectivity in the hydroarylation of **7a** remained unaltered regardless of the type of bisphosphine ligand used, the reaction temperature, iridium precatalyst, solvent, or amide directing group. To sum up, the best conditions involve the use of $[Ir(COD)_2]BARF$ as Ir(I) source and Binap as ligand, in dioxane at 100 ºC.

5.2.5. Scope

Taking as standard conditions the catalyst generated from equimolar amounts of $[Ir(COD)_2]BARF$ and Binap, the generality of the method with other allenyl-pyrrole substrates was explored. These precursors were prepared following the synthetic strategy already depicted in **Scheme 133**, but using propargylic alcohols with different substituents (alkyl, aryl or hydrogens) at their propargylic center.

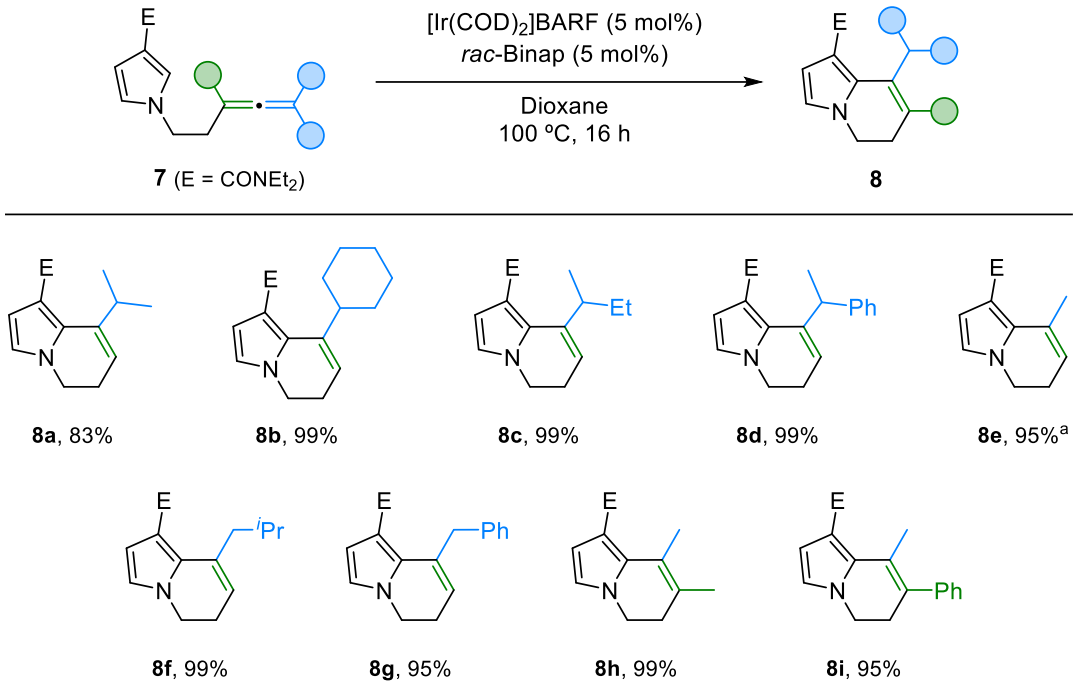
Satisfyingly, a *N*-allenyl pyrrole bearing a vinylidenecyclohexane yielded the expected product **8b** in quantitative yield. When employing other unsymmetrical terminal allenes such as **7c** and **7d**, the corresponding dihydroindolizines **8c** and **8d** were obtained in almost quantitative yields (**Scheme 135**)

The precursor bearing an allene without substituents at both internal and distal positions produced the expected product, **8e,** in 68% yield. Interestingly, in this specific case, employing the bulkier ligand Binapine, instead of Binap, led to a faster and cleaner reaction (99% yield).

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Substrates containing terminally monosubstituted allenes, either with alkyl or aryl groups, also participated in the process, to give the desired products, such as **8f** and **8g**, with excellent yields, at 80 °C (95-99% yield). The structure of **8g** was further confirmed via single-crystal X-ray diffraction analysis (**Figure 14**).

Moreover, internally substituted allenyl systems, both with alkyl (**7h**) and aryl (**7i**) substituents, proved to be excellent substrates, yielding the expected dihydroindolizines **8h** and **8i** in nearly quantitative yields (**Scheme 135**).



***Scheme 135**. Scope of exo-selective hydrocarbonation of allene-tethered pyrroles. [a] Carried out using Binapine as ligand.*

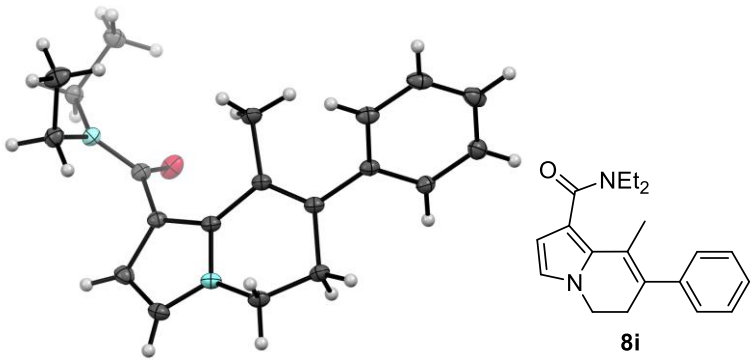
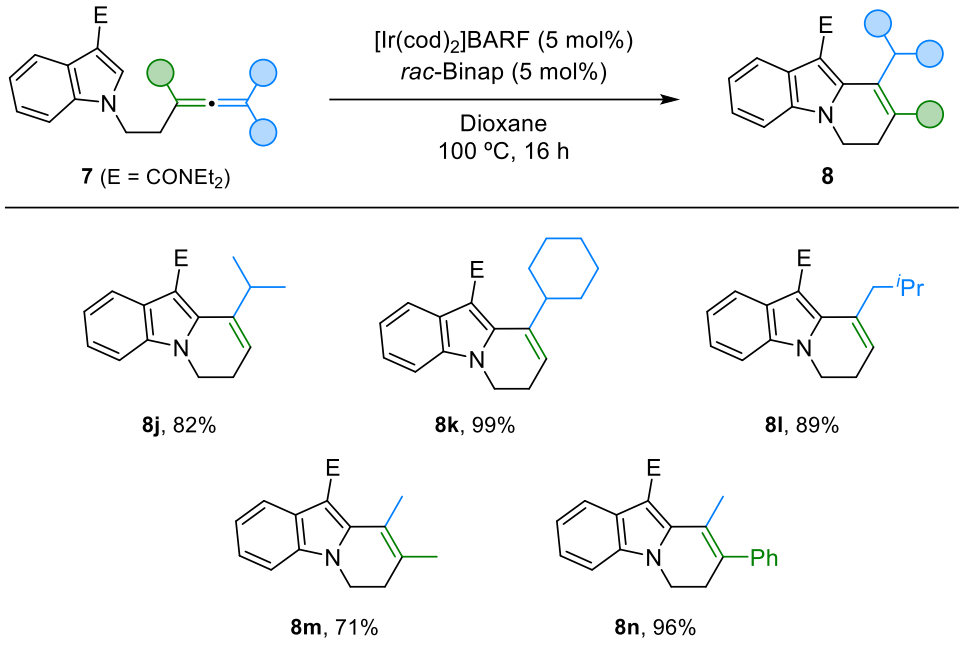


***Figure 14:** X-ray structure of **8i** (CCDC deposition number 2329797).*

Precursors related to **7a** and **7b** but bearing an indole, instead of the pyrrole moiety, also proved to be viable substrates. Consequently, the dihydropyrido[1,2-a]indoles **9j-k** were obtained with full selectivity and yields ranging from good to excellent (82 and 99%,

Scheme 136). Likewise, indole precursors containing either 1,3- or 1,1-disubstituted allenes also yielded their respective products (**8l-n**) in high yields. The structure of **8l** was confirmed via single-crystal X-ray diffraction (**Figure 15**).



***Scheme 136**. Scope of exo-selective hydrocarbonation of allene-tethered indoles.*

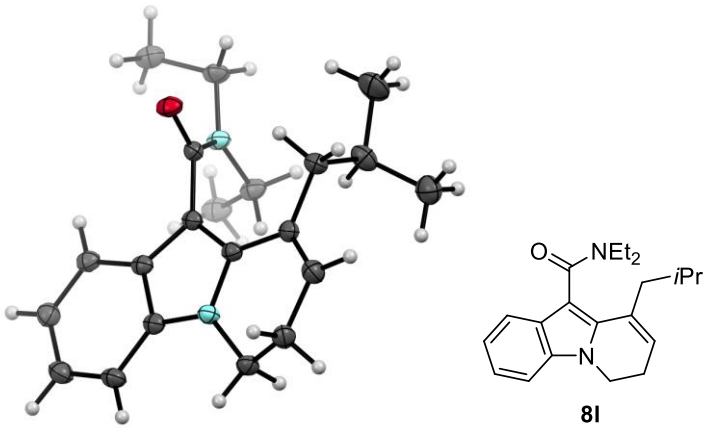
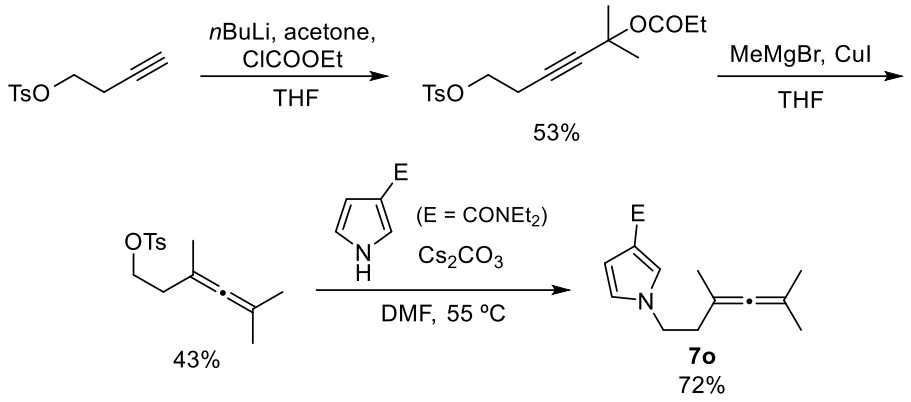


***Figure 15:** X-ray structure of **8l** (CCDC deposition number 2329798)*

After testing reaction precursors with mono-, and disubstituted allenes, we prepared **7o**, a substrate bearing a fully substituted allene partner (three methyl groups). Its synthesis started with the multigram-scale tosylation of commercially available but-3-yn-1-ol. The resulting tosylate was then converted into its lithium alkynylide, which was then trapped by addition of acetone. The resulting alkoxide was captured with ethyl chloroformate and the resulting propargylic carbonate was purified and subsequently transformed into the desired allene by the addition of methyl cuprate (generated from MeMgBr and CuI).

Alkylation of the pyrrole with the obtained allenyl tosylate yielded the desired product, **7o**, in 72% yield (**Scheme 137**).

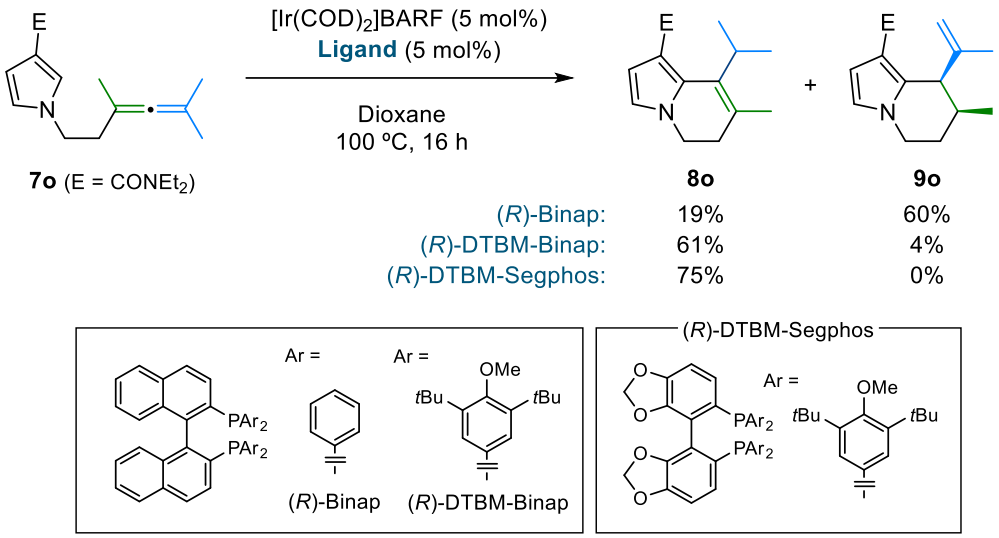


***Scheme 137**: General synthetic route to prepare substrates with tetrasubstituted allenes.*

Surprisingly, when the tetrasubstituted allene **7o** was submitted to the standard reaction conditions with Ir(I)/Binap, we observed the unexpected tetrahydroindolizine **9o** as major product (60% yield) alongside a 19% yield of the canonical **8o** (**Scheme 138**). However, with an electron-donating ligand such as DTBM-Binap or DTBM-Segphos the regioselectivity towards the dihydroindolizine **8o** was restored (61 and 75% yield respectively).

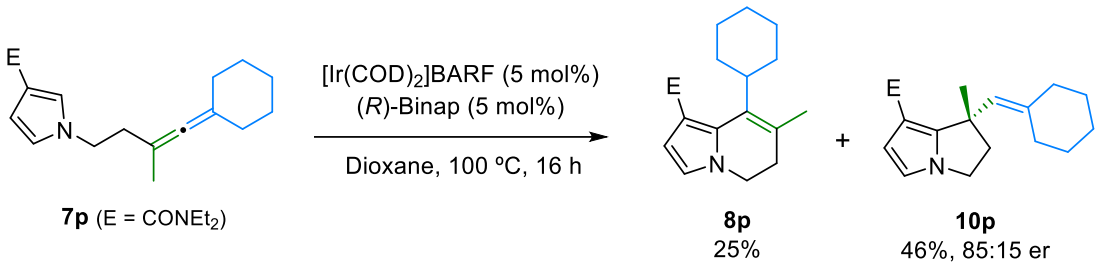
The compound **9o** contains two chiral centers and is obtained as a sole diastereoisomer. Given the significance of this novel transformation, both from a synthetic and mechanistic perspective, the exploration of this unexpected reactivity of tetrasubstituted allenyl precursors was specifically addressed in a separate chapter of this thesis (see section 5.3, page 185).

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***Scheme 138**. Results of hydrocarbonation of allene-tethered pyrrole **7o**.*

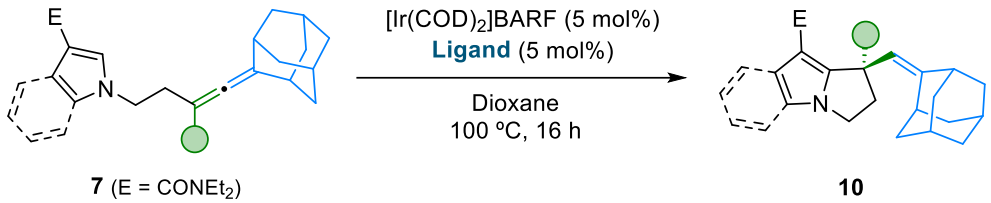
Curiously, the reaction of the related precursor **7p** with the Ir(I)/Binap catalyst led to the 2,3-dihydropyrrolizine **10p** in a 46% yield and 85:15 er, along with 25% of the canonical **8p** (**Scheme 139**). The product of type **9** was not detected in this case. On the other hand, using DTBM-Segphos as ligand, which had allowed to switch the selectivity towards the selective formation of **8p** (from **7p**), in this case just led to a complex mixture of products, as observed by NMR of the reaction crude.

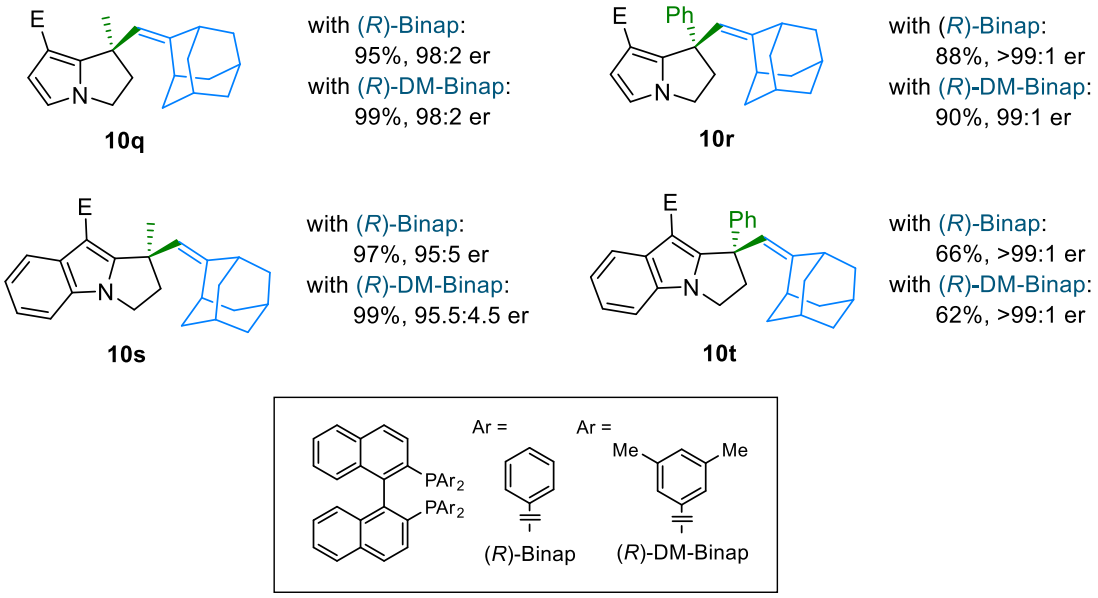


***Scheme 139:** Outcome of the intramolecular hydroarylation of compound **7p**.*

The majoritarian formation of product **10p** might be explained in terms of the steric hindrance imposed by the cyclohexane moiety, which could impede the coordination of the iridium catalyst to the distal position of the allene (see mechanistic analysis in page 177). This hypothesis was confirmed when testing precursors **7q-t,** which bear an even more bulky vinylidene-adamantane, since the corresponding 2,3-dihydropyrrolizines **10q-t** were all obtained in high yields and with good enantiomeric ratios (even >99:1 er), both using (*R*)-Binap and (*R*)-DM-Binap as ligands (**Scheme 140**). The structure of compound **10t** was confirmed by X-ray diffractometry (**Figure 16**).

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Scheme 140: *Scope of enantioselective hydroarylation of adamantane-containing substrates* ***7q-t****.*

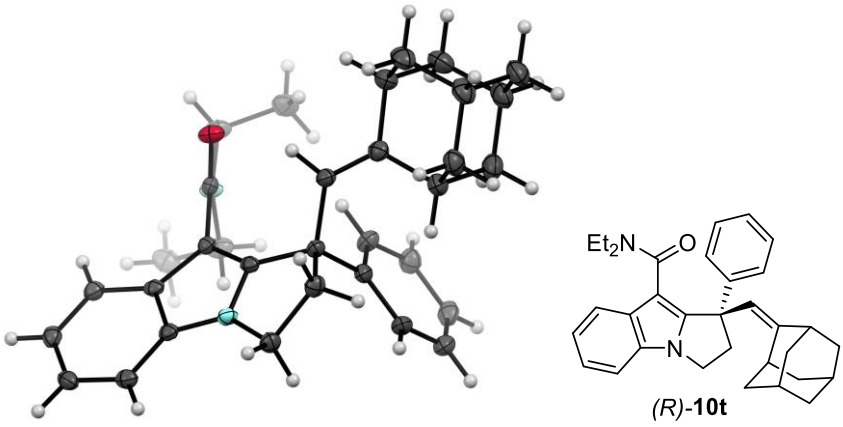


Figure 16*: X-Ray structure of* ***10t.***

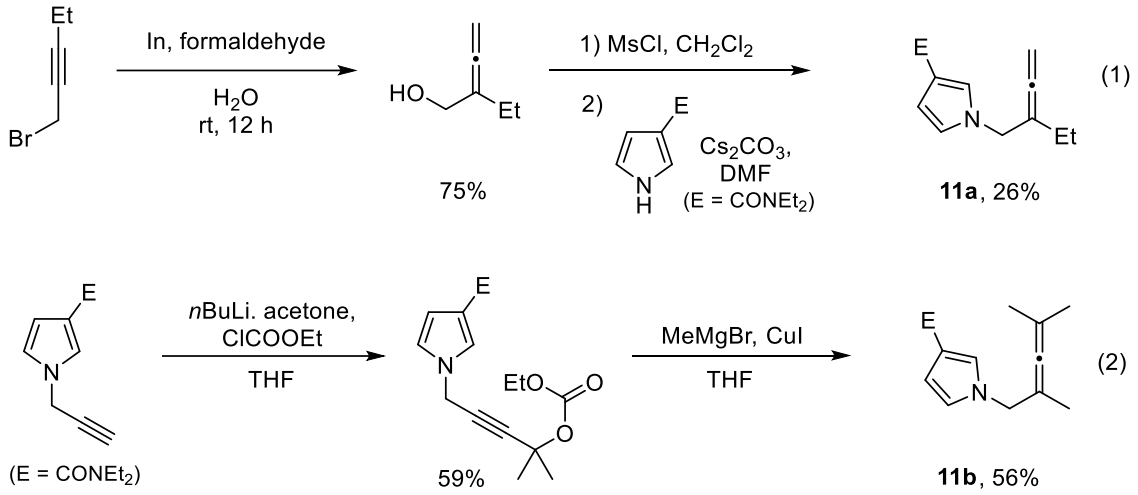
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5.2.6. Influence of the connecting tether length

In order to analyze the influence of the chain length that connects the pyrrole and the allene, we prepared different precursors with either one or three methylene units.

Precursors **11**, with one methylene unit in the linker, were prepared through different strategies depending on the substitution pattern of the allene. The allenol used to prepare **11a** was synthesized using a Barbier-type reaction between 1-bromo-2-pentyne and formaldehyde (see **Scheme 141**, equation 1).

The tetrasubstituted allene **11b** was prepared as indicated in equation 2. First, addition of a pyrrole-alkynylide to acetone and trapping of the corresponding alkoxide with ethyl chloroformate. The resulting carbonate was transformed into **11b** by addition of methyl cuprate (equation 2). Other substrates of this type, such as **11c-d,** were synthesized in an analogous manner.



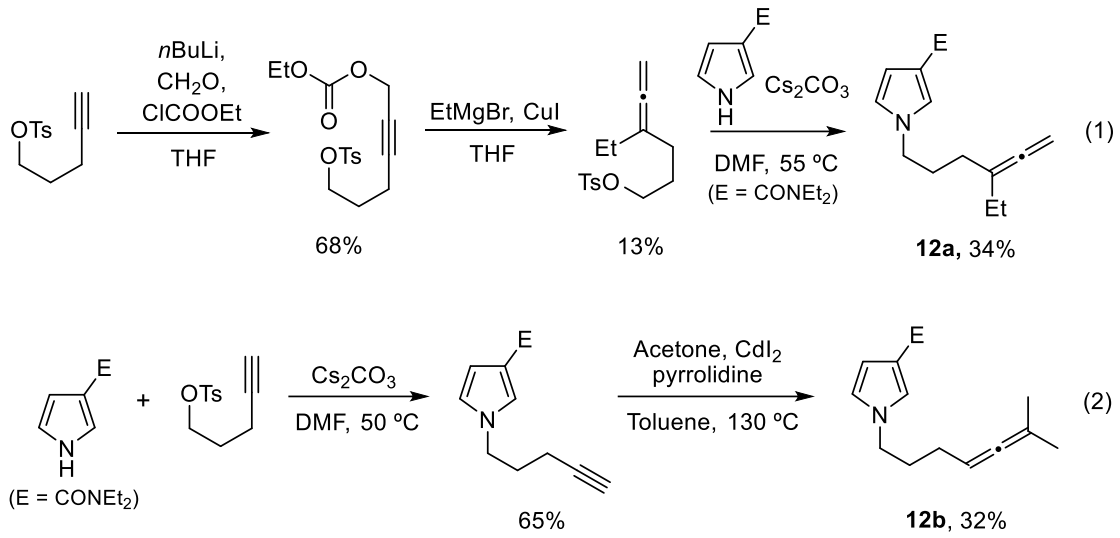
***Scheme 141**: Synthesis of precursors of type **11**.*

The precursor with a longer tether, **12a**, without any substituent at the terminal position of the allene, was prepared following a synthetic route analogous to that shown in **Scheme 137** (page 162), as depicted in **Scheme 142**, equation 1. The same synthetic strategy was also employed for the preparation of related substrates with substituents at the allene proximal position.

In the case of the terminally disubstituted precursor **12b**, the allene was obtained from the corresponding terminal alkyne, using a methodology reported by Ma and coworkers, consisting of a modified Crabbé procedure, using CdI_2 and pyrrolidine as base (equation 2).[133]

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[133] *X. Tang, C. Zhu, T. Cao, J. Kuang, W. Lin, S. Ni, J. Zhang, S. Ma. Nat. Commun.*, **2013**, *4*, 2450.

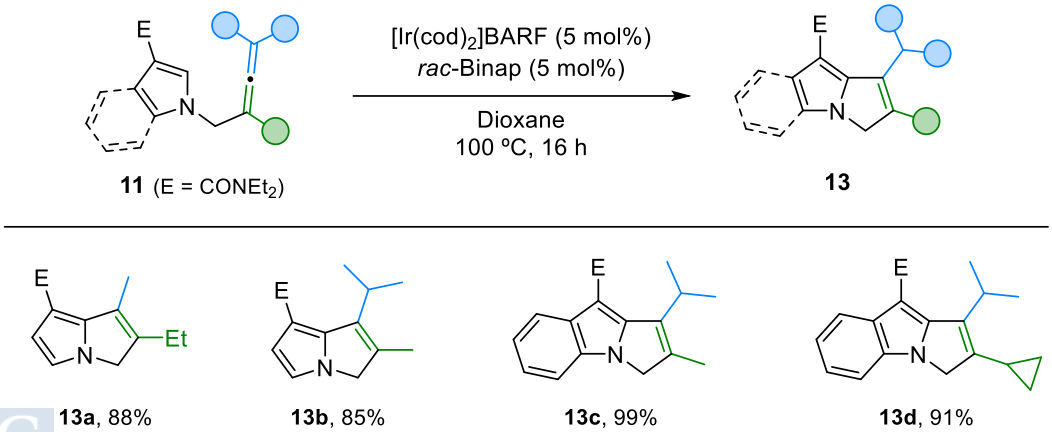


Scheme 142: *Synthetic routes to prepare substrates of type* ***12****.*

Results with substrates equipped with a one-carbon linker

Submitting the precursor **11a** to the Ir/Binap catalyst led to the achiral product **13a**, arising from an *exo* addition to the distal allene double bond, in 88% yield. When substrate **11b** (bearing a tetrasubstituted allene) was treated under the same reaction conditions, the analogous product, **13b,** was obtained selectively (**Scheme 143**). This outcome is different from that previously observed with the precursors with a two-carbon linker (**7o**), which also bears a tetrasubstituted allene (see **Scheme 138**, page 163), as well as from that of precursors **7p-t**. However, it is important to note that an *exo*-cyclization to the proximal double bond in precursors **11** would result in the formation of a strained four-membered ring.

Similarly to **11b**, indoles **11c** and **11d** also yielded the expected five-membered products **13c** and **13d**, resulting from the *exo* addition to the distal double bond (**Scheme 143**).



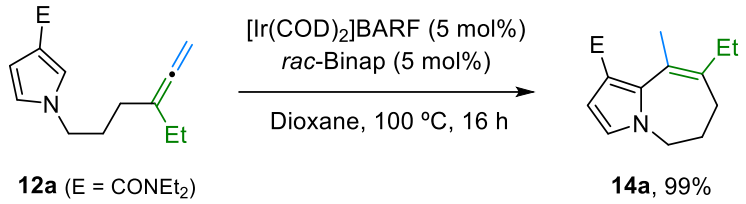
Scheme 143*. Scope of exo-selective hydrocarbonation of allene-tethered pyrroles and indoles of type* ***11*** *to form 5-membered rings.*

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Results with substrates with three-carbon tethers

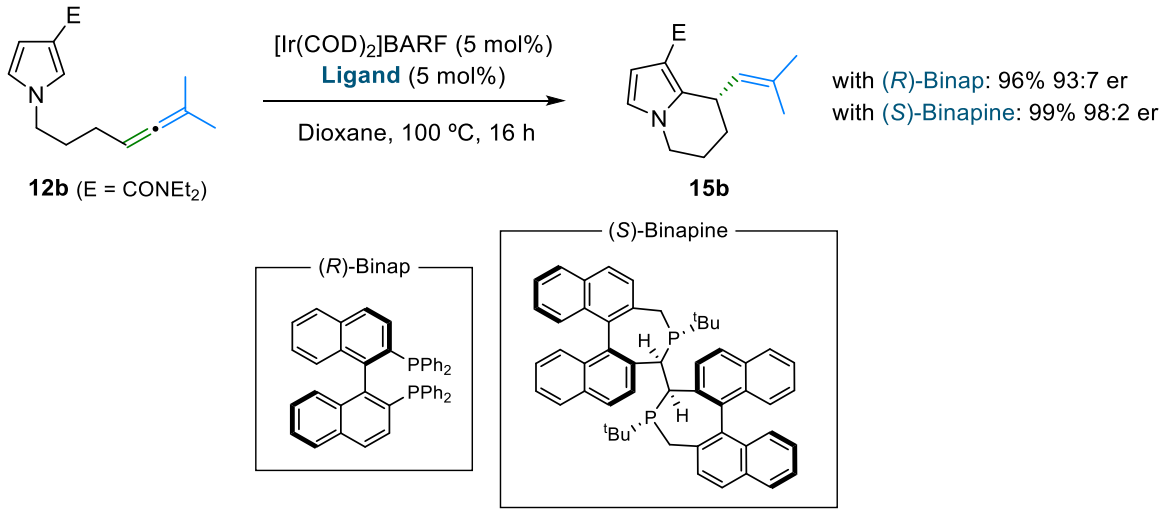
In the case of precursors holding a three-methylene carbon tether between the reactants, we expected selectivity issues as the hydroarylation reaction might equally lead to five, six or even seven-membered rings.

However, the reaction of **12a**, lacking substituents at the distal carbon of the allene, exclusively afforded the 7-membered fused heterocycle **14a** (99% yield, **Scheme 144**). Curiously, using Binapine as ligand, we observed a mixture of isomers (^{1}H-NMR of the crude mixture).



***Scheme 144**. Hydrocarbonation of allene-tethered pyrrole **12a**.*

In contrast, the reaction of the terminally disubstituted allene **12b,** under otherwise identical conditions, gave the unexpected product **15b,** bearing a vinyl-substituted tertiary stereocenter, in 96% yield and with 93:7 er. Gratifyingly, with Binapine as ligand, the reaction also gave **15b** in 99% yield, with a higher 98:2 er (see **Scheme 145**).

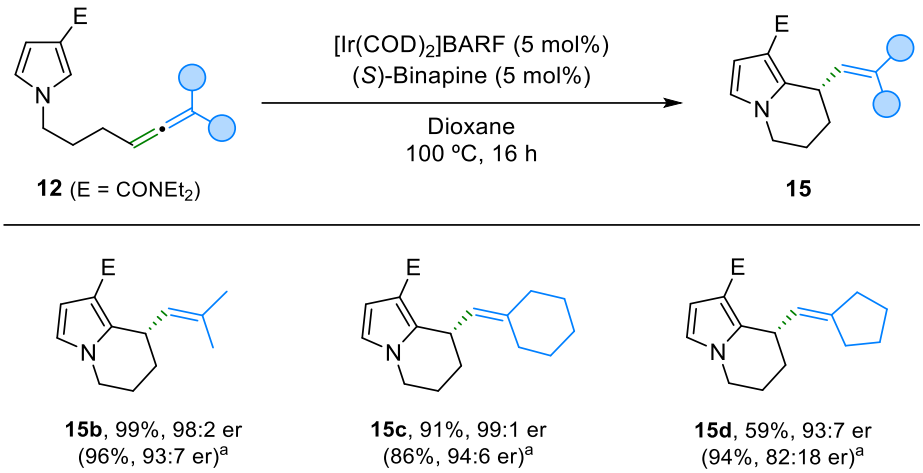


***Scheme 145:** Enantioselective hydroarylation of allenyl-pyrrole **12b**.*

Other substrates of type **12** were prepared following the synthetic route used for **12a** (as shown in **Scheme 142**, equation 2; page 166), but using other ketones instead of acetone..

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The cycloisomerization reactions of vinylidenecyclohexane **12c**, when employing Binapine as ligand at 100 ºC, gave the expected product with a six-member ring **15c**, with an exceptional 99:1 er (see **Scheme 146**). The X-ray structure obtained of *rac*-**15c** is shown in **Figure 17**. The related substrate **12d**, which holds a vinylidenecyclopentane, yielded **15d** in moderate yield but with an exceptional 97:3 er. Employing Binap, instead of Binapine, also resulted in good yields and high enantiomeric ratios, just slightly lower than those obtained with Binapine.



***Scheme 146**. Scope of enantioselective intramolecular hydroarylation of allene-tethered pyrroles **15**.*
[a] (R)-Binap instead of (S)-Binapine was employed as ligand

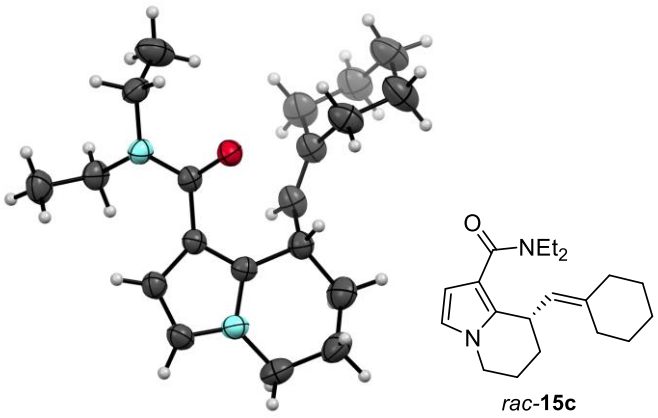
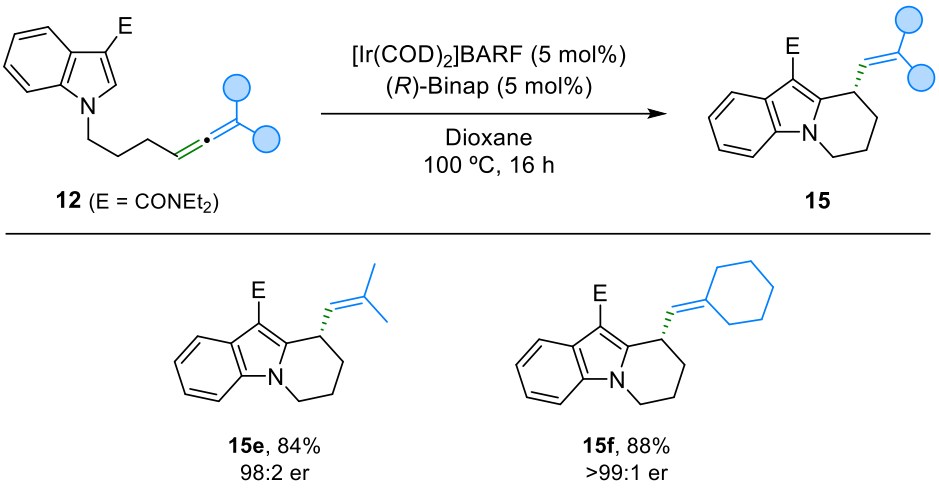


***Figure 17**: X-ray structure of **16b**.*

The same reactions can also be performed using indole precursors although the use of Binapine resulted in low conversions, so the ligand of choice was Binap. Thus, the hydroarylation of precursor **12e** (prepared in a similar fashion to **12a**) led to **15e** in 84% yield and 98:2 er. Likewise, the tetrahydroindolizine **15f** was obtained in 88% yield and an excellent er > 99:1 (**Scheme 147**). .

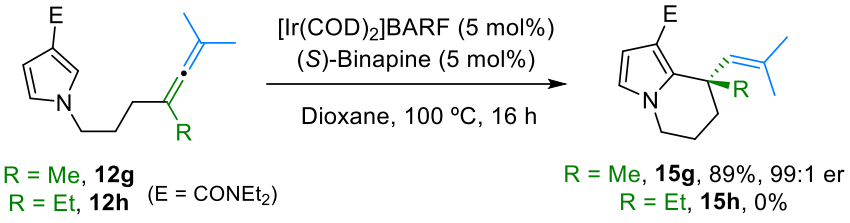
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***Scheme 147**. Scope of enantioselective intramolecular hydroarylation of allene-tethered indoles **12e-f**. Carried out by Alejandro Rey.*

Given the prevalence of naturally occurring products containing tetrahydroindolizine skeletons bearing all-carbon quaternary stereocenters, the reactivity of precursors of type **12**, but bearing tetrasubstituted allenes was next explored. These substrates were prepared following a synthetic route analogous to that of **12a**, shown in **Scheme 142** (page 166).

Gratifyingly, the reaction of the trimethyl-substituted allenyl precursor **12g**, promoted by the Ir(I)/Binapine catalyst, led to of the selective formation of the expected tetrahydroindolizine product **15g** with excellent yield and an almost perfect enantioselectivity (**Scheme 148a**).Curiously, despite this excellent result, the reaction of precursors bearing substituents other than methyl at the proximal position of the allene (e.g. **12h**, R = Et) led to full recovery of the allene precursor when Ir/Binapine was used as catalyst. (**Scheme 148b**).



***Scheme 148:** Enantioselective hydroarylation of allenyl-pyrroles **12g** and **12h** employing (S)-Binapine as ligand.*

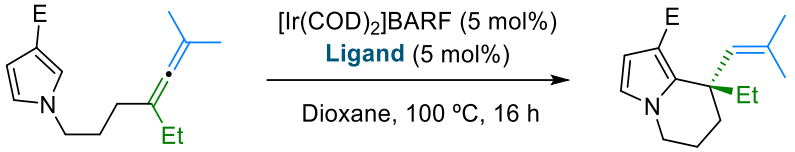
However, less bulky bisphosphines like Binap enabled the reaction of **12h** to give **15h** with perfect selectivity, 88% isolated yield, and an excellent 94:6 er (**Table 8**, entry 2). Moreover, the use of DM-Garphos allowed to slightly improve the er of **15h** up to 96:4 (entry 3). With the analogous fluorinated bisphosphine BTFM-Garphos, we observed a

higher yield, although the enantioselectivity was affected (75:25, entry 4). On the other hand, the use of Binap derivatives such as Tol-Binap and DM-Binap also led to **15h** with excellent levels of enantioselectivity (95:5 and 98:2 respectively), and high yields (85% and 93%, entries 5 and 6).

Finally, we also carried out the reaction at lower temperature using DM-Garphos, aiming to further increase the *ee*. As can be seen in entry 7, although the *ee* could be slightly improved up to 99:1, the yield was significantly lower. The absolute configuration of the product was assigned by X-ray diffractometry (see **Figure 18**).

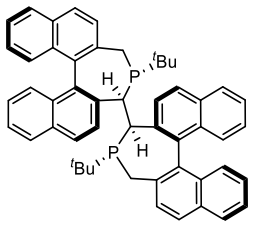
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Table 8: *Evaluation of ligands for the enantioselective intramolecular hydroarylation of precursor* ***12h****, and structure of the ligands evaluated. Results obtained in collaboration with Alejandro Rey.*
[a] Conducted at 80 ºC.

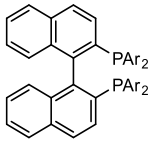


12h (E = $CONEt_2$) **15h**

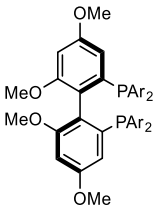
Entry	Ligand	Yield (%)	er
1	(*S*)-Binapine	0	n.d.
2	(*R*)-Binap	88	94:6
3	(*R*)-DM-Garphos	83	96:4
4	(*R*)-BTFM-Garphos	98	75:25
5	(*R*)-Tol-Binap	85	95:5
6	(*R*)-DM-Binap	93	98:2
7[a]	(*R*)-DM-Binap	52	99:1



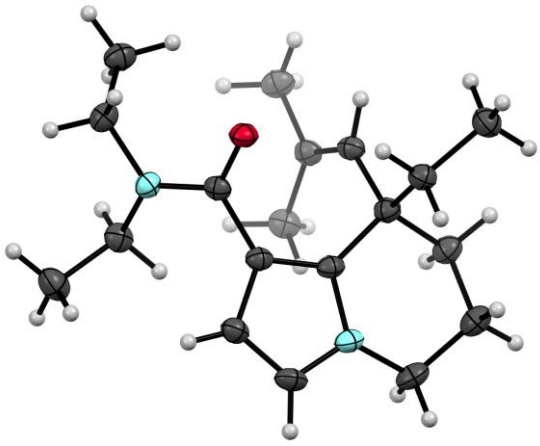
(*S*)-Binapine

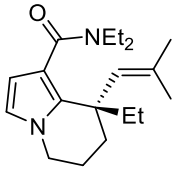


Ar = Ph, **(*R*)-Binap**
Ar = 4-(CH_3)-C_6H_4, **(*R*)-Tol-Binap**
Ar = 3,5-$(CH_3)_2C_6H_3$, **(*R*)-DM-Binap**



Ar = 3,5-$(CF_3)_2C_6H_3$, **(*R*)-BTFM-Garphos**
Ar = 3,5-$(CH_3)_2C_6H_3$, **(*R*)-DM-Garphos**





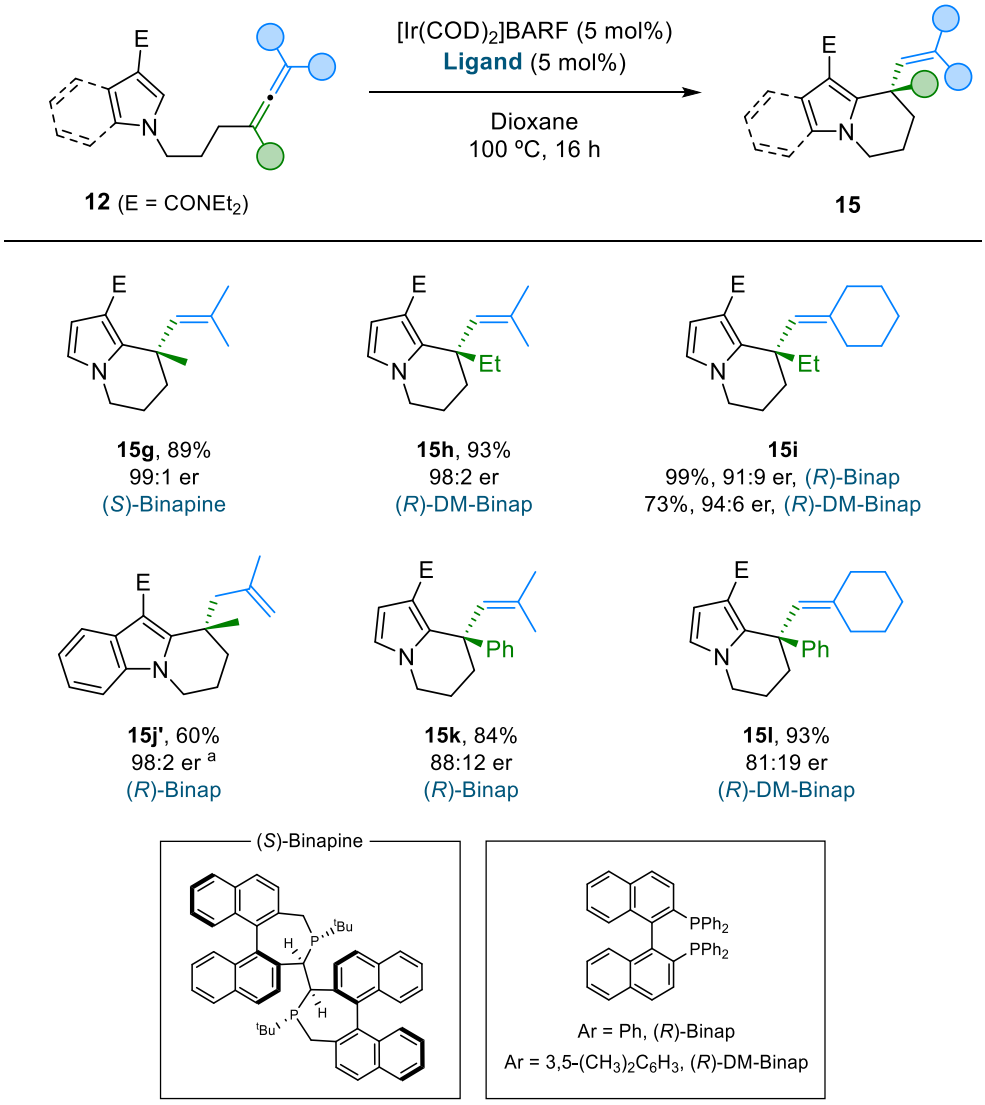
(*S*)-**15h**

Figure 18*: X-ray structure of* ***15h****.*

Other precursors similar to **12h** can also undergo similar cycloisomerizations. Therefore, the reaction of **12i**, promoted by Ir(I)/Binap, led to the tetrahydroindolizine **15i** was

isolated in 99% yield and an enantiomeric ratio of 91:9. In this case, the use (*R*)-DM-Binap allowed to increase the enantiomeric ratio up to 94:6 (see **Scheme 149**).

The reaction also works with indole precursors, such as **12j,** to give the isomerized product **15j'**, which holds its double bond at the terminal position (60% yield and an excellent 98:2 er). When employing allenes substituted with aromatic groups at their proximal position (**12k** and **12l**), the levels of enantioselectivity were slightly lower (88:12 and 81:19 er respectively), although yields were equally high.



***Scheme 149**. Exo-selective hydrocarbonation of allene-tethered pyrroles and indoles **12**. Some examples were carried out in collaboration with Alejandro Rey.(S)-Binapine was only effective for **15g**. [a] Conducted at 80 ºC.*

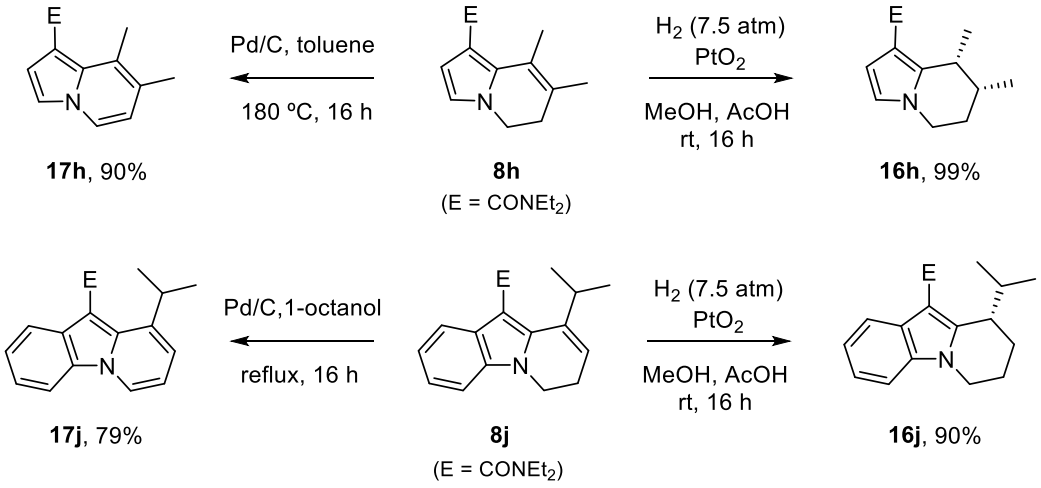
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5.2.7. Derivatization of the products

Given that the pyrido[1,2-a]indole or pyrrolo[1,2-a]indole structures of type **8** constitute the main core of many compounds with anticancer, anti-inflammatory, and/or fluorescent properties,[134] an initial investigation of their synthetic potential was conducted.

Thus, using straightforward dehydrogenation conditions, **8h** could be readily converted into the fluorescent aromatic indolizine product **16h** (90% yield). Utilizing the same approach, indole **8j** underwent conversion into the corresponding dehydrogenated product **16j**, which was isolated with 79% yield (**Scheme 150**).

Additionally, subjecting **8h** or **8j** to hydrogenation conditions (H_2, 7.5 atm) with PtO_2 as catalyst, we observed with complete stereoselectivity, the formation of tetrahydroindolizine **12h** and tetrahydropyridoindole **17j**, respectively (**Scheme 150**). The relative configuration of their stereocenters was verified via single-crystal X-ray diffraction structure of **17h** (**Figure 19**).



***Scheme 150**. Some synthetic manipulations on products of type **8**.*

[134] (a) Y. Yao, M. Alami, A. Hamze, O. Provot, *Org. Biomol. Chem.* **2021**, *19*, 3509–3526. (b) Y. G. Shelke, P. E. Hande, S. J. Gharpure, *Org. Biomol. Chem.* **2021**, *19*, 7544–7574. (c) G. A. Cordell, *The Alkaloids: Chemistry and Biology*, Vol. 60, Elsevier Science, San Diego, **2003**, pp.1 –404.

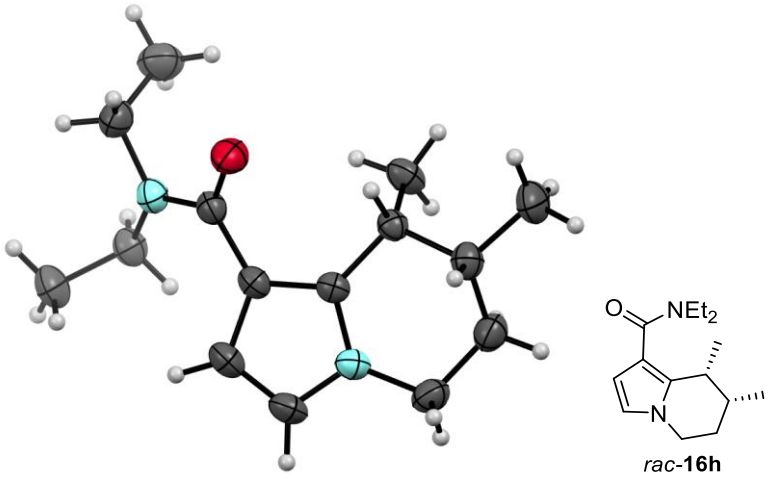
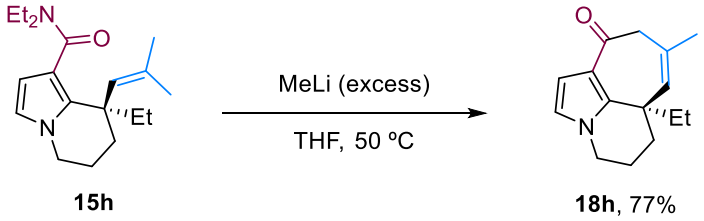


Figure 19: *X-ray structure of* ***16h*** *(CCDC deposition number 2329802).*

Considering that the tetrahydroindolizine and pyrido[1,2-a]indole skeletons of type **15**, which result of an *exo*-trig hydroarylation, constitute the central core of numerous natural products, the manipulation of these adducts was also explored. In this case, we undertook more ambitious transformations, including modifications of the diethylamide, the pyrrole core as well as the vinyl group of these types of products.

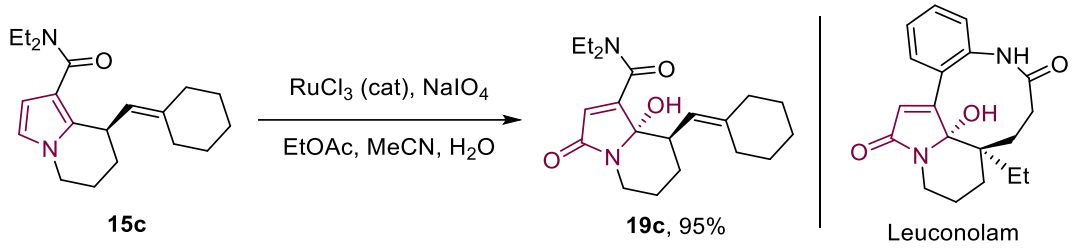
Surprisingly, treating compound **15h** with an excess of MeLi, the polycyclic product **18h** was isolated in a 77% yield (**Scheme 151**). This reaction is assumed to proceed through an allylic deprotonation and addition of the resulting carbanion to the diethylamide, instead of the originally expected addition of MeLi to the carboxamide. Nonetheless, the reaction is appealing, as it enables straightforward access to this type of rare triple-fused heterocyclic scaffolds.



Scheme 151: *Formation of compound* ***18i****, by cyclization of* ***10i****.*

On the other hand, the pyrrole ring of **15c** can be selectively oxidized to yield the compound **19c**, which holds the central core of several alkaloids, such as Leuconolam (**Scheme 152**). The structure was confirmed by X-ray diffractometry (**Figure 20**).

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Scheme 152: *Synthesis of **19c** by oxidation of compound **15c** (left), and structure of natural compound Leuconolam (right).*

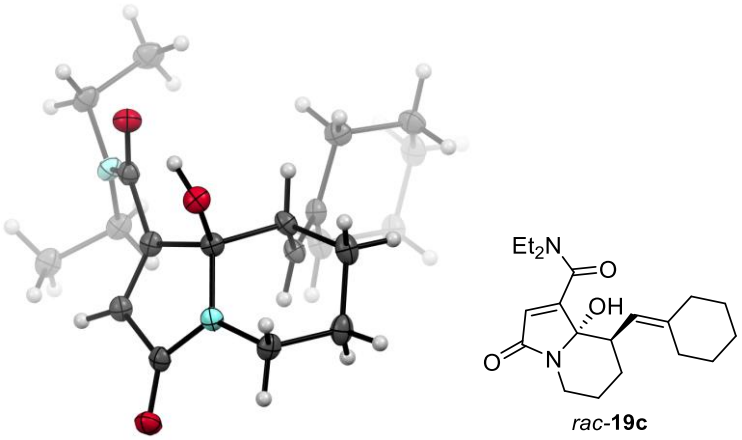
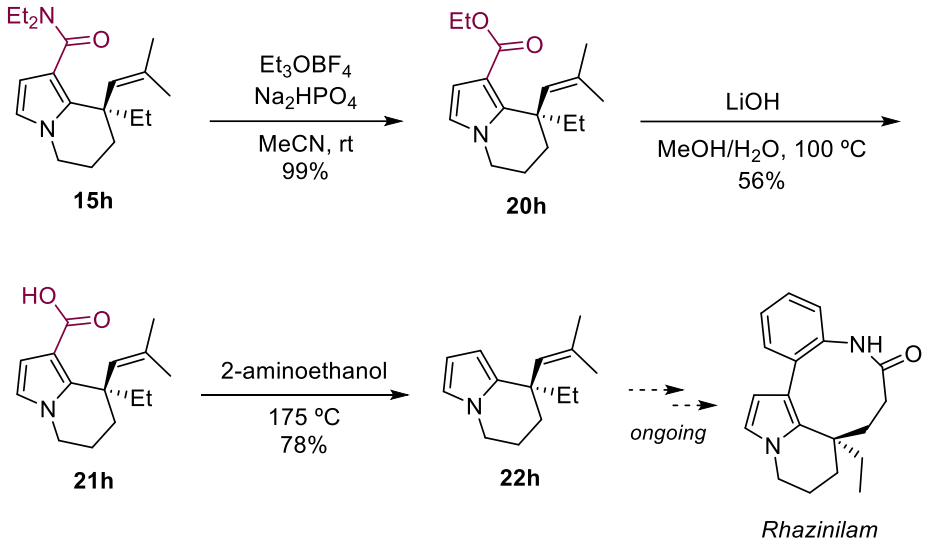


***Figure 20**: X-Ray structure of **19c**.*

Another useful transformation involved the removal of the diethyl amide unit, which was carried out by transforming the amide into the corresponding ethyl ester by treatment with Et_3OBF_4 (99% yield). Subsequent hydrolysis with LiOH led to the carboxylic acid **21h** in 56% yield. Finally, a thermal decarboxylation in aminoethanol at 175 ºC, yielded the pyrrole **22h** in 78% yield (see **Scheme 153**). Current efforts by Alejandro Rey are focused on the transformation of **22h** into a reported precursor of Rhazinilam.[116]

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[116] Z. Liu, A. S. Wasmuth, S. G. Nelson, *J. Am. Chem. Soc.,* **2006**, *128*, 10352–10353.

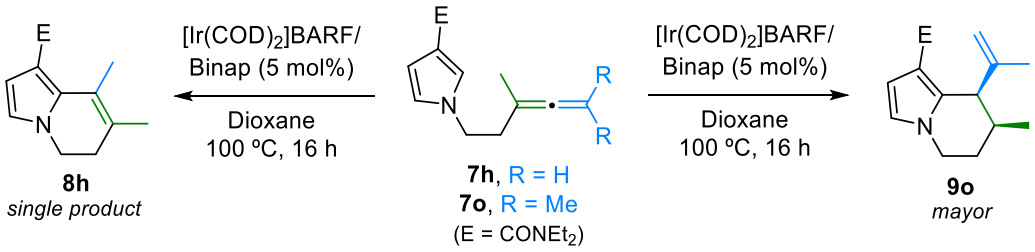


Scheme 153**: Directing group removal of **15h

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5.2.8. Computational studies

As showed in page 160, the allenyl-pyrrole **7h** reacted to give exclusively the dihydroindolizine **8h**, result of the addition of the C–H bond across the distal double bond of the allene (**Scheme 154**). However, the same reaction using the precursor **7o**, which has three methyl substituents at the allene leads to a mixture of the initially expected product **8o**, together with the hydrogenated product **9o** (see **Scheme 138**, page 163).



***Scheme 154**: Outcome of the reaction of allenyl-pyrroles **7h** and **7o**.*

To shed some light on the mechanism of the reaction and reasons behind this different behavior, Dr. Martín Calvelo conducted DFT calculations. Results are summarized in **Figure 21** and **Figure 22**.

We use model substrates like **7h'**, containing a dimethyl amide instead of the experimentally used diethyl derivative, to somehow reduce the overall computational cost. Similarly to previous DFT calculations with precursors containing alkenes or alkynes, the insertion of the C–H bond of the model **7h'** into the Ir(I) complex was found to involve a low energy barrier (17.7 kcal/mol), via **TS-FG**, to give the Ir(III) intermediate **Int-G**, which holds a vacant site. This allows the allene to coordinate the Ir(III) center, either through its proximal or distal double bond, leading to intermediates **Int-G$_P$** and **Int-G$_D$**, respectively. From these intermediates, various carbo- and hydrometallation processes were examined, and the two possible *exo*-carbometallations of either allene double bond were found to be the most energetically accessible.

Intermediate **Int-G$_P$**, resulting from the coordination of the internal C=C bond of the allene, presents a suitable orientation for a carbometallation step, which yields the chiral dihydropyrrolizine iridium(III) species **Int-H$_P$**. However, this intermediate is the precursor of products of type **10**, which are not observed experimentally when employing **7h** as precursor.

Alternatively, when the allene coordinates to the iridium center through its distal C=C bond, the resulting intermediate **Int-G$_D$** is more stable, probably due to a lower steric strain. The subsequent carbometallation also proceeds through a low energy barrier,

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forming a dihydroindolizine intermediate **Int-H$_D$**. This intermediate is significantly more stable than **Int-H$_P$**. Therefore, the carbometallation of the distal C=C bond of the allene is both kinetically and thermodynamically favored. From **Int-H$_D$**, a subsequent C–H reductive elimination to form **Int-I** is relatively easy and proceeds via the square-pyramidal isomer **Int-H'$_D$**, through an energy barrier of 12.6 kcal/mol.

Thus, the migratory insertion (via **TS-GH$_D$** or **TS-GH$_P$**) determines the selectivity of the process towards the experimentally observed products of type **8**, with an energy difference of 7.6 kcal/mol.

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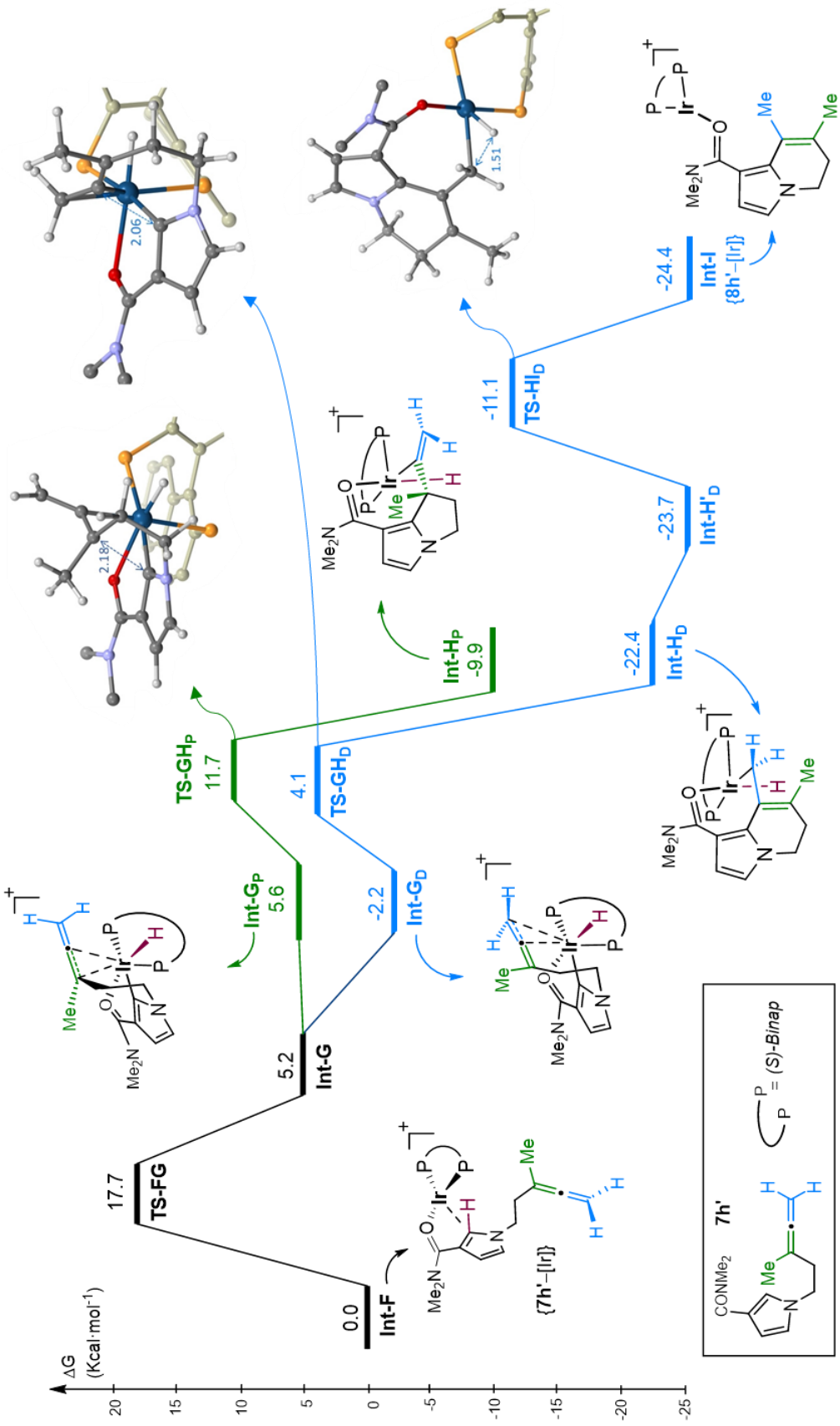


***Figure 21**: Energy Profile ΔGsolv (kcal·mol-1) for the Hydrocarbonation of **7h'**. B3LYP/6-31G(d) (LANL2DZ for Ir) // M06/6-311++g(d,p) (SDD for Ir). Binap ligand is mostly simplified in the 3D representations.*

Using as precursor the tetrasubstituted allene **7o'**, the initial coordination of the distal double bond is disfavored, probably due to the steric hinderance imposed by the methyl groups at the allene distal position. However, the subsequent carbometallation of the proximal double bond, through **TS-JK$_D$**, still lies above the analogous carbometallation of the distal one (**TS-JK$_P$**).

Also interesting, in this case, the reductive elimination towards the product of type **8** is energetically more costly compared with the analogous step computed for substrate **7o'** ($\Delta\Delta G$ = 3.8 kcal /Mol see **Figure 21**). This higher barrier could be behind the low selectivity of the reaction toward **8o**, which is obtained as minor product with the Ir/Binap catalyst (see **Scheme 138**, page 163), whereas the unconventional product **9o** is majoritarily formed. Only by varying the ligand (to DTBM-Segphos), product **8o** became the major one (see **Scheme 138**). In the next chapter of this thesis, in which we explore this divergent reactivity, we will also detail computational studies on other pathways from **Int-K$_D$** , which might explain the observed change in selectivity.

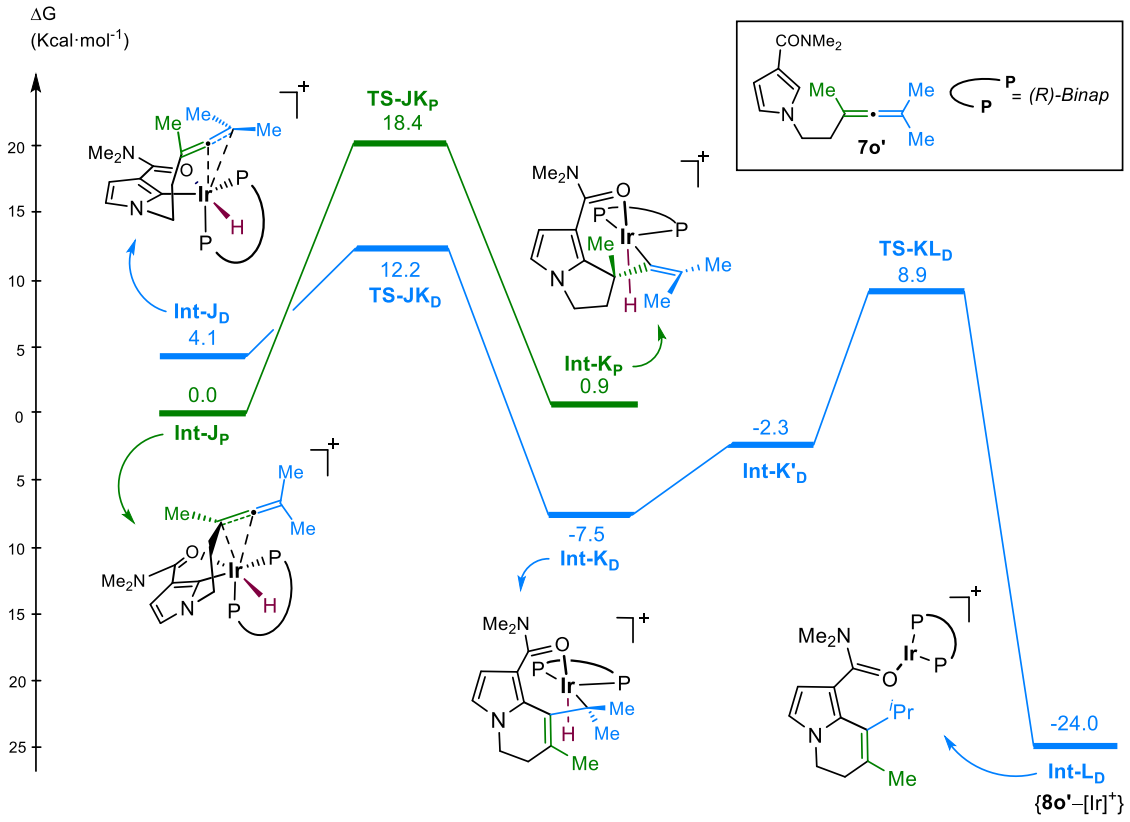
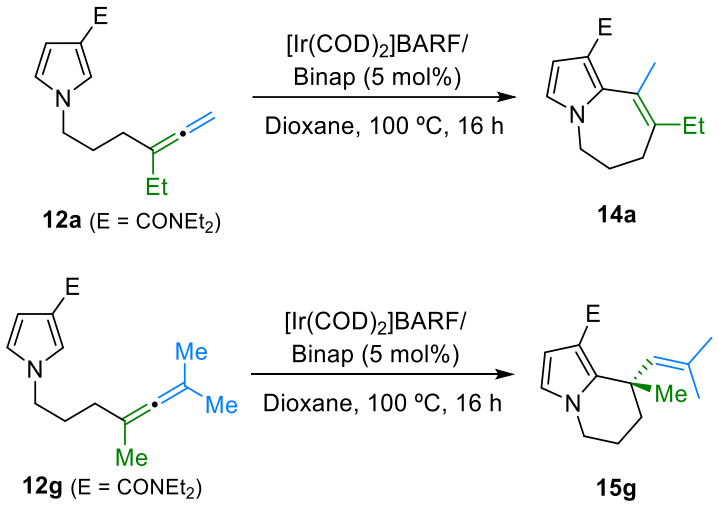


***Figure 22**: Energy Profile ΔGsolv (kcal·mol-1) for the Hydrocarbonation of **7o'**. B3LYP/6-31G(d) (LANL2DZ for Ir) // M06/6-311++g(d,p) (SDD for Ir). Binap ligand is mostly simplified in the 3D representations.*

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Finally, Dr. Martín Calvelo also conducted DFT calculations to try to understand the factors influencing the selectivity when employing substrates with a larger, three-methylene tether between the pyrrole and the allene (**Figure 23**). As indicated in page 167, the reaction of **12a** with only one methyl group at the internal position of the allene, gave exclusively **14a**, resulting from an *exo*-addition of the pyrrole C(2)–H bond across the distal double bond of the allene. However, the reaction of the terminally disubstituted allene **12g** (see page 169), gave the chiral tetrahydroindolizine **15g,** in which this C–H bond is transferred to the internal double bond (**Scheme 155**).



***Scheme 155**: Outcome of the reaction of substrates **12a** and **12g**.*

According to the computational studies, the allene of **12a'** can coordinate to the Ir(III) intermediate through either its proximal or distal double bond, leading to intermediates **Int-M$_P$** and **Int-M$_D$**, respectively. From these intermediates, *exo*-carbometallations of both allene double bonds were modelled. Intermediate **Int-M$_P$**, resulting from the coordination of the proximal C=C bond of the allene, is 3.9 kcal/mol less stable than **Int-M$_D$**. The energy barrier for the subsequent carbometallation through **TS-MN$_P$**, towards **Int-N$_P$**, was found to be slightly above the carbometallation of the distal double bond through **TS-MN$_D$**.

Even though transition states **TS-MN$_P$** and **TS-MN$_D$** have nearly the same energy, calculations were carried out in a model system, with -CONMe$_2$ as a directing group, which might also influence the result. In any case, we also analyze these carbometallation steps with a terminally demethylated allene precursor, like **12g'**. As can be seen in **Figure 23** (bottom), the effect of terminal substitution of the allene is clearly reproduced in the calculations.

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Specifically, precursor **12g'**, can coordinate to the Ir(III) intermediate through its proximal or distal double bond, leading to intermediates **Int-O$_P$** and **Int-O$_D$**. Intermediate **Int-O$_P$**, resulting from the coordination of the internal C=C bond of the allene, is suitably oriented for carbometallation, yielding the chiral dihydropyrrolizine iridium(III) species **Int-P$_P$**, through an energy barrier of 9.8 kcal/mol. Alternatively, when the allene coordinates the iridium through its distal C=C bond, the resulting intermediate, **Int-O$_D$**, became less stable, 2.4 kcal/ mol above its proximal isomer. The subsequent carbometallation, to form intermediate **Int-P$_D$** also proceeds through a more energetic transition state (**TS-OP$_D$**, $\Delta\Delta G$ = 6.3 kcal /mol). Therefore, steric reasons probably determine that the carbometallation of the proximal C=C bond of the allene becomes favored when employing substrates that bear substituents at the distal position of the allene (e.g. **12g**), which is consistent with the experimental observations.

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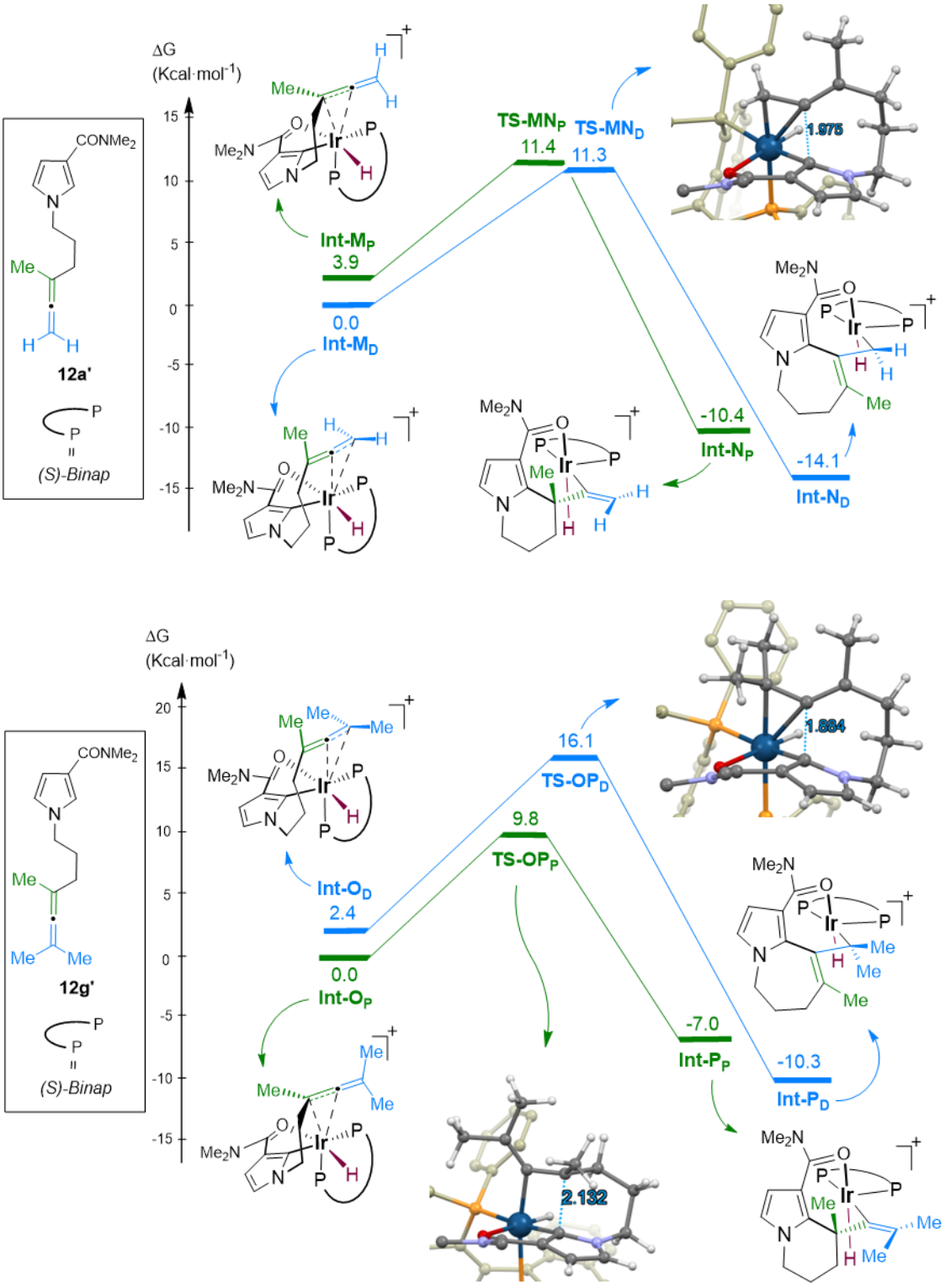


***Figure 23**: Energy Profile ΔGsolv (kcal·mol-1) for the Hydrocarbonation of **12a'** and **12g'**. B3LYP/6-31G(d) (LANL2DZ for Ir) // M06/6-311++g(d,p) (SDD for Ir). Binap ligand is mostly simplified in the 3D representations.*

5.2.9. Conclusions

We have developed a variety of intramolecular cycloisomerizations of allenyl-pyrrole precursors under iridium (I) catalysis. The reactivity and selectivity of the processes depend on the substitution pattern of the allene, the tether length, and the choice of ligand, but we have found clear reactivity patterns.

The methodology proposes a practical and direct approach to dihydroindolizine-skeletons, which can be easily manipulated to give diverse types of heteropolycyclic products.

In some cases, in reactions of substrates with three methylene units between the arene and the allene, we observed that the addition occurs at the proximal instead of the distal allene bond, yielding chiral vinyl-substituted products with high enantioselectivity. Some transformations of these products were developed, opening the door to their potential application to the synthesis of natural products.

DFT computational studies supported the experimental findings and provide insights for further developments.

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5.3

Iridium(I)-Catalyzed Cascade Reactions of Allene-Tethered Pyrroles and Indoles

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Part of the results of this section were published:

Skeletal and Mechanistic Diversity in Ir-Catalyzed Cycloisomerizations of Allene-Tethered Pyrroles and Indoles

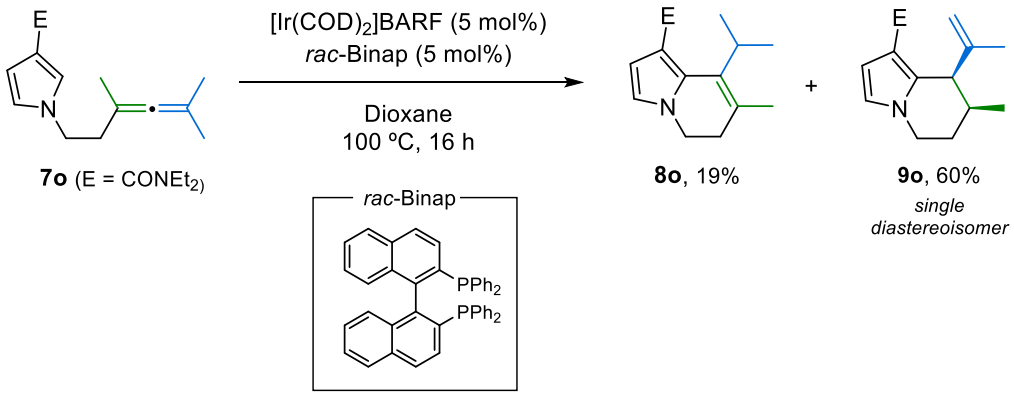
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Angew. Chem. Int. Ed., **2024** *63*, e202408258.

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5.3.1. Anomalous result in the reaction of the tetramethylated allene precursor 7o

As commented in the previous chapter, when exploring the iridium-catalyzed cycloisomerization of tetrasubstituted allenylpyrrole **7o**, the major product was not the expected adduct **8o**, but the chiral isomer **9o**. This product seems to result from a rearrangement that entails a formal migration of a double bond (**Scheme 156**). This suggests a mechanistic pathway that extends beyond the conventional oxidative addition/migratory insertion/reductive elimination sequence (abbreviated as *OA/MI/RE*), potentially involving more complex cascade processes.



***Scheme 156**: Outcome of the reaction of allenyl-pyrrole **7o**.*

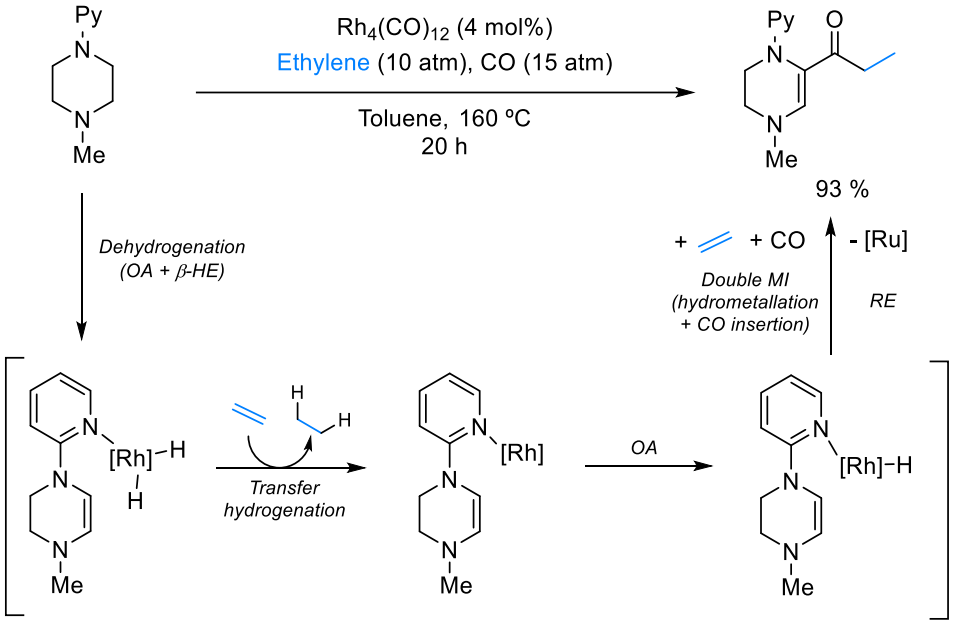
In the following sections, we provide a literature review that covers potentially related cascade processes initiated by a C–H oxidative addition into a metal catalyst, to generate a “C–M–H” species.

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5.3.2. Precedents of cascade reactions initiated by a transition metal promoted C–H oxidative addition

Cascade reactions involving C–H activation/dehydrogenation processes

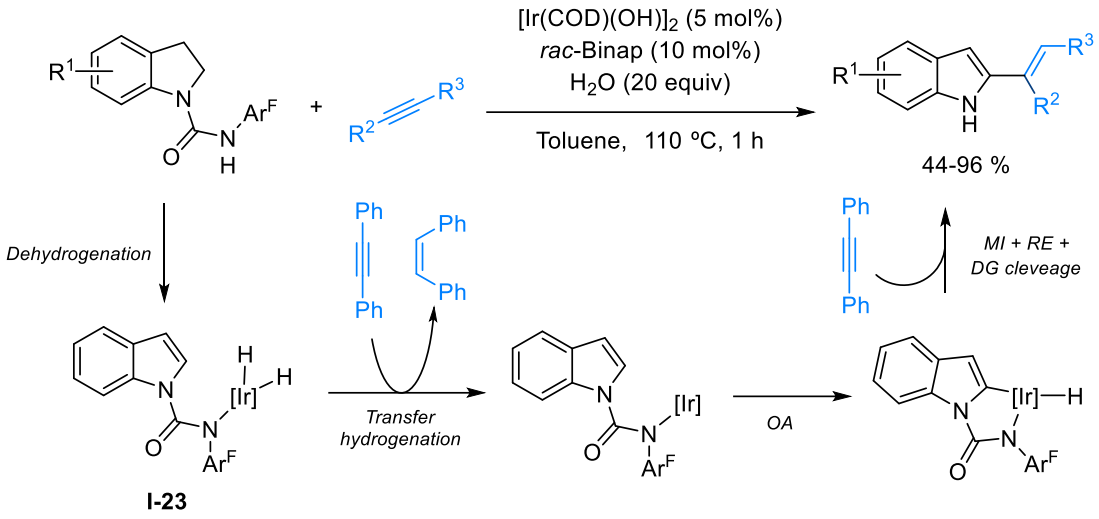
In 1997, Murai developed a ruthenium-catalyzed methodology that couples an initial dehydrogenation of piperidine, with a double insertion of CO and ethylene, to access carbonylated tetrahydropyrazines (see **Scheme 157**). In this process, an excess of ethylene acts as the hydrogen acceptor (through an *MI/RE* sequence).[135] Besides this work, other related methodologies utilizing iridium catalysis have also been published.[136]



***Scheme 157**: Murai's cascade process involving Ru-catalyzed dehydration.*

Our group recently reported an Iridium(I)-catalyzed dehydrogenation/hydrocarbonation tandem process between indolines and alkynes, to yield 2-alkenylindoles in good yields (**Scheme 158**). In this process, a bis-hydride iridium species **I-23** is postulated to be formed through a C–H oxidative addition/β-hydride elimination sequence. The excess of alkyne acts as a hydrogen acceptor, and then the generated indole undergoes a new oxidative addition followed by migratory insertion of a new alkyne unit and an RE. Eventually, a directing group cleavage takes place, to deliver the *N*-unsubstituted 2-alkenylindoles.[137]

[135] Y. Ishii, N. Chatani, F. Kakiuchi, S. Murai, *Organometallics*, **1997**, *16*, 3615–3622.
[136] T. Ohmura, K. Yagi, S. Kusaka, M. Suginome, *ACS Catal.*, **2020**, *10*, 3152–3157.
[137] C. Lázaro-Milla, J. L. Mascareñas, F. López, *ACS Catal.*, **2024**, *14*, 2872–2882.



***Scheme 158**: Iridium-catalyzed tandem dehydrogenation/alkenylation developed by our group.*

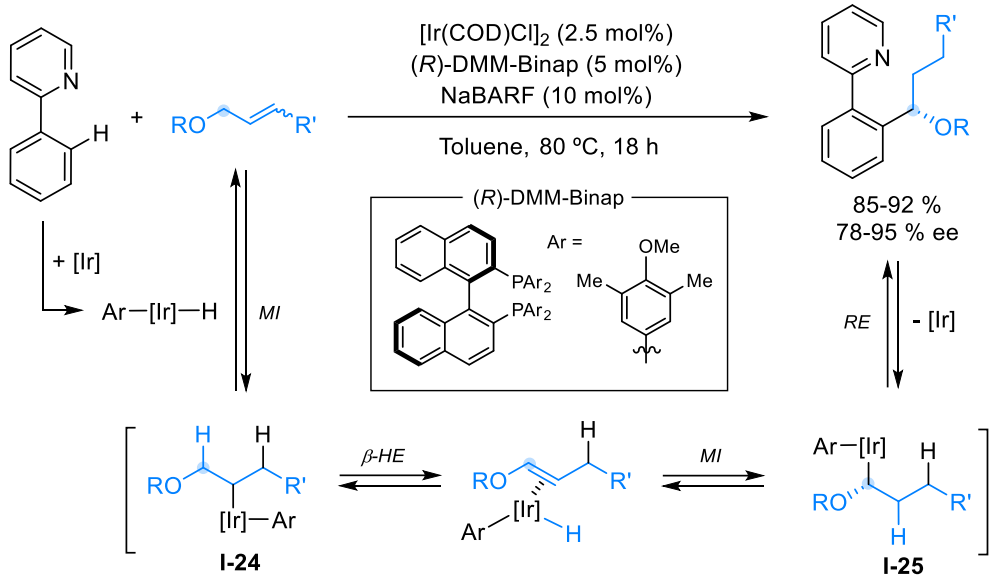
Cascade reactions involving alkene chain walking after the C–H activation

Chain walking processes enable the functionalization of hydrocarbons at positions different from where the initial activation occurs. A significant advantage of this approach is that it permits the use of isomeric mixtures as starting materials since bonds are formed only at the specific locations selected by the catalyst.[138]

The chain walking of alkenes can occur through various mechanisms, such as 1,2-hydride shifts, 1,3-hydride shifts, or 1,3-proton shifts. However, for the sake of conciseness, in this section we only cover chain walking processes embedded in hydrocarbonations reactions that involve metal hydrides intermediates, resulting from C–H activation steps.

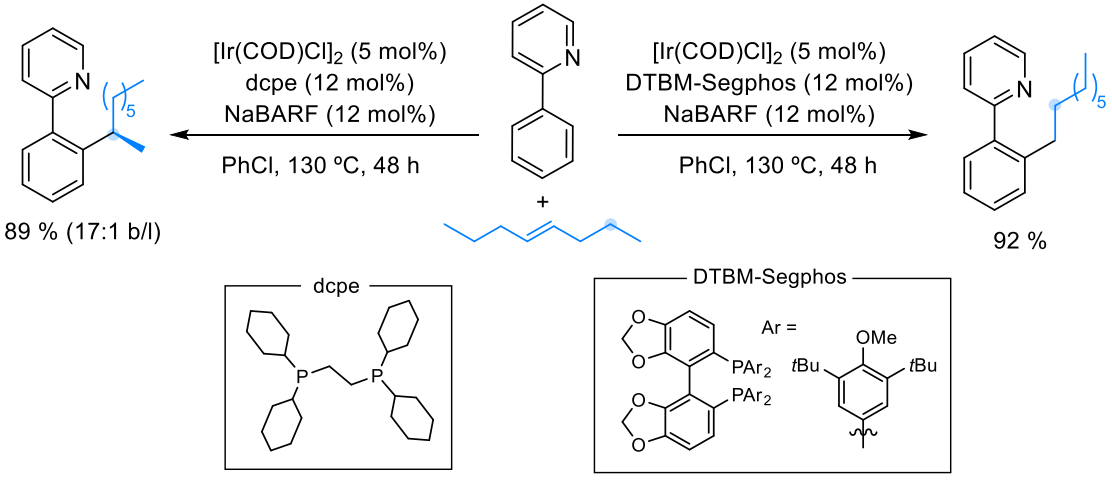
In 2017, Nishimura and Yorimitsu published the first example of this type, which involved the formation of a metal hydride through the oxidative addition of an aromatic C–H bond to a low valent Ir(I)/Binap catalyst, and the subsequent insertion of an olefin to form **I-24**. Then, a β-hydride elimination regenerates the metal hydride, shifting the double bond one position away within the alkyl chain. An additional hydrometallation allow the metal to reach the adjacent position of the terminal ether (**I-25**), and a final reductive elimination leads to the alkylated product, which is obtained with high levels of enantioselectivity (**Scheme 159**).[139] Subsequent works by Shi and Shibata extended these methodologies to other types of alkenyl precursors, and involving lengthier chain walking events.[140]

[138] S. Ghosh, S. Patel, and I. Chatterjee, *Chem. Commun.*, **2021**, *57*, 11110–11130.
[139] Y. Ebe, M. Onoda, T. Nishimura, H. Yorimitsu, *Angew. Chem. Int. Ed.*, **2017**, *56*, 5607–5611.
[140] (a) A. J. Borah and Z. Shi, *J. Am. Chem. Soc.*, **2018**, *140*, 6062–6066. (b) K. H. N. Tang, K. Uchida, K. Nishihara, M. Ito, and T. Shibata, *Org. Lett.*, **2022**, *24*, 1313–1317.



***Scheme 159**: Chain-walking hydroarylation reported by Nishimura.*

In a recent work, Zhang developed a related chain-walking protocol in which the final hydrofunctionalization can be either linear- or branched-selective, depending on the phosphine ligand employed (**Scheme 160**).[141] In particular, while dcpe provides branched products, the use of DTBM-Segphos provides linear adducts in high yields.



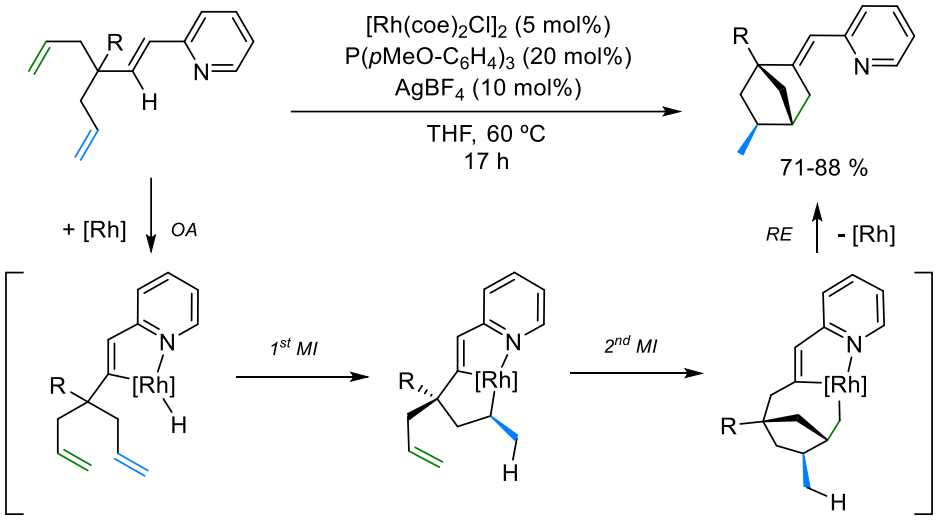
***Scheme 160**: Examples of Ir(I)-catalyzed chain-walking processes.*

Processes involving double migratory insertion after the C–H activation

In 2014, Aïssa published an example of a cascade process in which, after the C–H activation of an alkenyl C–H bond, two consecutive migratory insertions occur before the reductive elimination takes place.[142] This system enables the efficient construction of

[141] F. Li, Y. Luo, J. Ren, Q. Yuan, D. Yan, W. Zhang, Angew. Chem. Int. Ed., **2023**, 62, e202309859.
[142] C. Aïssa, K. Y. T. Ho, D. J. Tetlow, and M. Pin-Nó, *Angew. Chem. Int. Ed.*, **2014**, *53*, 4209–4212.

bicyclic structures from simple 1,6-heptadiene precursors (see **Scheme 161**). Despite the synthetic potential of such tandem reactions, no further examples, neither enantioselective variant of this type of processes have been reported.



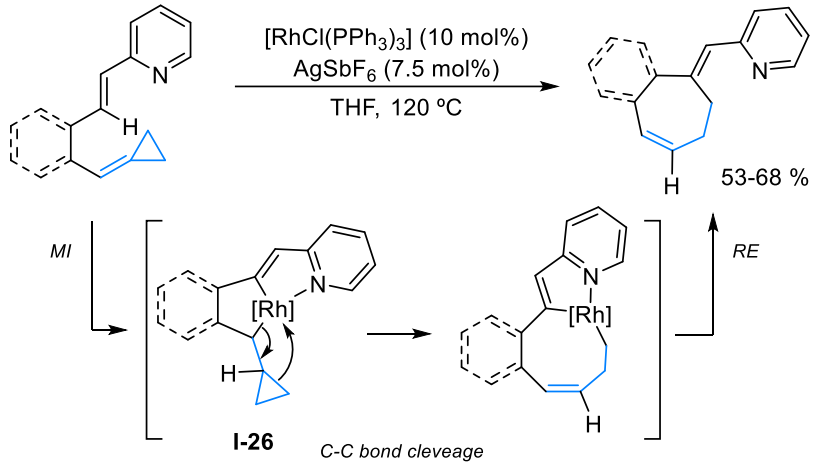
***Scheme 161**: Aïssa's tandem carbocyclization of 1,6-heptadienes.*

Reactions involving C–C bond cleavage after the migratory insertion

Another type of cascade reaction involves the ring opening of a strained ring after the migratory insertion step. In particular, Fürstner developed a rhodium(I)-catalyzed tandem process that involves an initial oxidative addition of an alkenyl C–H bond to a Rh(I) catalyst, and it is followed by a migratory insertion of a tethered ACP and a subsequent ring expansion of the cyclopropane (**I-26)** through a β-carboelimination process (**Scheme 162**).[143] An eventual C-C reductive elimination in the generated rhodacyclooctene intermediate generates the observed seven-membered carbocycle. Despite the potential of these type of processes, this is the only example in which a C–C bond cleavage is combined within the standard *OA/MI/RE* sequence.

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[143] C. Aïssa, A. Fürstner, *J. Am. Chem. Soc.*, **2007**, *129*, 14836–14837.



***Scheme 162**: Rh-catalyzed tandem hydrocarbonation-ring expansion.*

Finally, it is worth to highlight that this type of cascade methods has also been studied in processes wherein the C–H activation occurs via a CMD mechanism, both for the opening of heterocyclic systems such as oxabenzonorbornadienes or epoxides,[144] as well as for that of strained carbocyclic systems like ACPs,[145] VCPs,[146] or cyclopropenes.[147] However, since the initial carbon and hydrogen atoms are not conserved in the product, these are not compiled in this section.

In summary, the use of TM-catalysis in C–H functionalization processes that entail additional steps beyond the canonical *OA/MI/RE* (oxidative addition, migratory insertion, and reductive elimination) sequence, has so far been limited to the previously mentioned cases, which include dehydrogenation, chain walking, and double migratory insertions. As discussed in this and previous section 5.2, developing new cascade methodologies involving different and/or additional steps in the mechanism would be of great interest, due to the high level of structural complexity that can be achieved in a single synthetic step.

[144] (a) Z. Qi, X. Li, *Angew. Chem. Int. Ed.*, **2013**, *52*, 8995–9000. (b) S. Yu and X. Li, *Org. Lett.*, **2014**, *16*, 1200–1203. (c) S.-S. Zhang, J.-Q. Wu, Y.-X. Lao, X.-G. Liu, Y. Liu, W.-X. Lv, D.-H. Tan, Y.-F. Zeng, and H. Wang, *Org. Lett.*, **2014**, *16*, 6412–6415. (d) Y. Hara, S. Onodera, T. Kochi, and F. Kakiuchi, *Org. Lett.*, **2015**, *17*, 4850–4853.

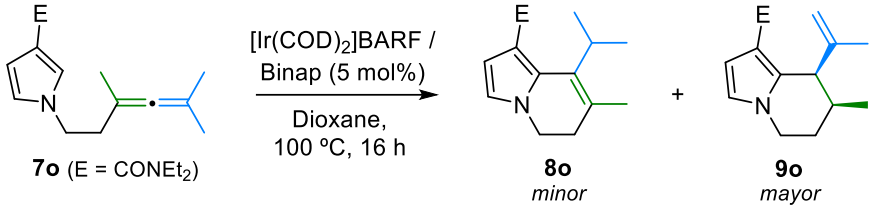
[145] (a) S. Cui, Y. Zhang, and Q. Wu, *Chem. Sci.*, **2013**, *4*, 3421–3426. (b) Y.-F. Liang, V. Müller, W. Liu, A. Münch, D. Stalke, L. Ackermann, *Angew. Chem.*, **2017**, *129*, 9543–9547. (c) M. Li, F. Y. Kwong, *Angew. Chem. Int. Ed.*, **2018**, *57*, 6512–6516. (d) Q. Li, X. Yuan, B. Li, and B. Wang, *Chem. Commun.*, **2020**, *56*, 1835.

[146] J.-Q. Wu, Z.-P. Qiu, S.-S. Zhang, J.-G. Liu, Y.-X. Lao, L.-Q. Gu, Z.-S. Huang, J. Li, H. Wang, *Chem. Commun.*, **2015**, *51*, 77–80.

[147] H. Zhang , K. Wang , B. Wang , H. Yi , F. Hu , C. Li , Y. Zhang and J. Wang , *Angew. Chem. Int. Ed.*, **2014**, *53*, 13234 –13238

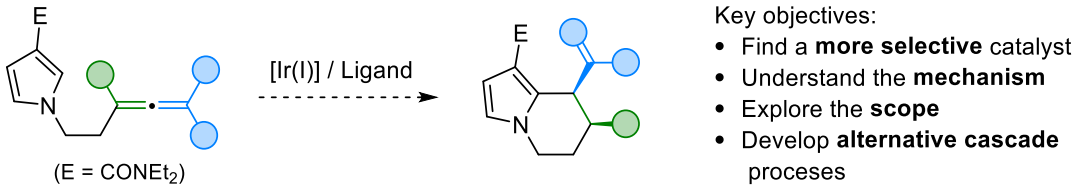
5.3.3. Objectives

As indicated before (**Scheme 156**, page187), the reaction of allenyl-pyrrole substrates of type **7o** with an Ir/Binap catalyst lead to the relevant tetrahydroindolizine product **9o** as major product. This compound might be the result of a cascade process involving additional steps beyond the initially expected *OA/MI/RE* mechanism (**Scheme 163**).



***Scheme 163**: Selective tandem hydrometallation/dehydrogenation/hydrogenation process of allenyl-pyrrole substrates*

The relevance of this product, the diastereoselectivity of the reaction and the intriguing mechanistic aspects of the transformation prompted us further explore this reactivity, aiming to eventually develop a general and enantioselective catalytic method.



***Scheme 164:** Explore the novel reactivity of allenyl-pyrrole substrates of type **7**.*

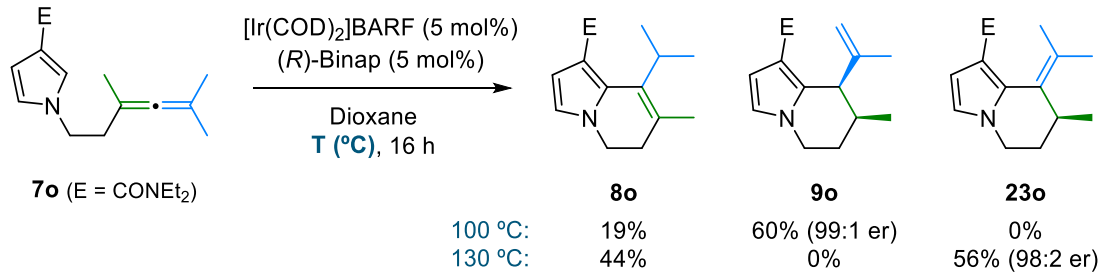
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5.3.4. Cascade conversion of allenyl-pyrroles like 7o into enantioenriched tetrahydroindolizines

Influence of the reaction conditions in the hydrocarbonation of 7o

As previously indicated in section 5.2, when performing the reaction of allenyl-pyrrole **7o** with Ir(I)/(*R*)-Binap as catalyst, at 100 °C, an unexpected tetrahydroindolizine, **9o**, bearing two new chiral stereocenters was obtained in a good yield and an excellent 99:1 er (**Scheme 165**). The initially expected product, **8o**, resulting from a simple hydroarylation of distal bond of the allene was obtained, as minor product, in 19% yield.

To gain insights into the reaction, we first studied the influence of the temperature. When the reaction was performed at 80 ºC some unreacted starting material was recovered, along with other minor undistinguishable byproducts. However, when it was conducted at 130 °C, the major product obtained was the chiral tetrahydroindolizine **23o**, which was isolated in 56% yield and with an almost identical enantiomeric ratio of 98:2 er.



Scheme 165: *Outcome of the reaction of* ***7o*** *using Ir/(R)-Binap as catalyst at different temperatures.*

We evaluated different solvents and iridium sources, with no significant changes. However, the use of different biphosphines led to different selectivities. Indeed, as previously indicated in **Scheme 138** (page 163), when the DBTM-Segphos ligand, featuring several electron-donating groups, was employed, the major product observed was the canonical dihydroindolizine **8o**.

Scope

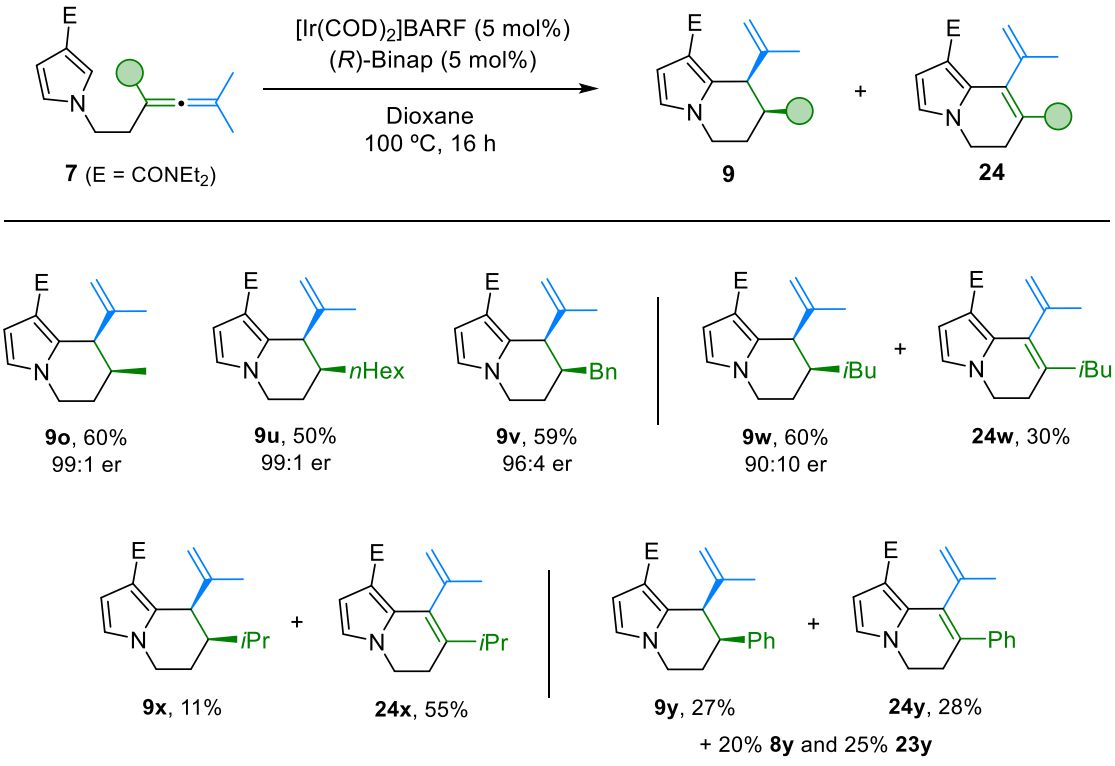
In addition to **7o**, other substrates with tetrasubstituted allenes were evaluated to assess the generality of the above reaction. The precursor **7u**, featuring an *n*-hexyl group at the internal position of the allene, yielded the expected chiral tetrahydroindolizine **9u** (50% yield) as major product, with an excellent 99:1 enantiomeric ratio. Similarly, the reaction of a precursor bearing a benzyl group (**7v**) at the internal position of the allene provided

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the corresponding chiral tetrahydroindolizine **9v** (59% yield) with a high enantiomeric ratio of 96:4 (**Scheme 166**).

In all these cases, minor amounts of the initially anticipated dihydroindolizine products of type **8** and traces (<5%) of the dehydrogenated derivatives **24** were also observed (see **Scheme 166**). In this regard, a substrate with a bulkier group (*iso*-butyl) at the internal position of the allene (**7w**), resulted in a higher proportion of the dehydrogenated side-product **24w**.

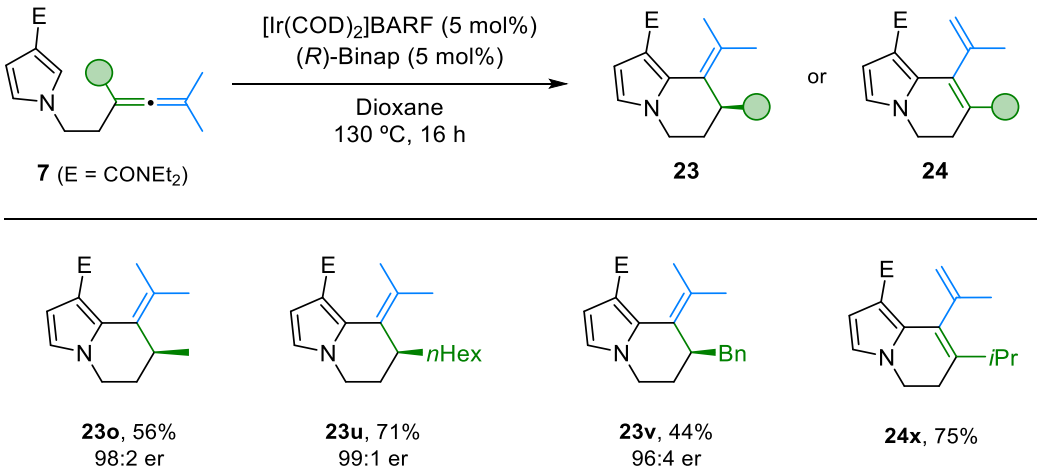
When employing a substrate with an even bulkier substituent, **7x**, the chiral product **9x** was detected only in an 11% yield, and the major product of the reaction was the dihydroindolizine derivative **24x**. These results suggest that compounds **24** could be intermediates in the formation of products **9**. The increase in the steric bulkiness at the former internal position of the allene could indeed hamper the hydrogenation of the endocyclic double bond of **24**, diminishing the proportion of products **9**. On the other hand, the use of a phenyl-substituted allene like **7y** led to a mixture of products in which **9y** (27%) and **23y** (28%) are the major ones. However, important amounts of **8y** (20%) and **24y** (25%) were also identified by NMR of the reaction mixture.



Scheme 166: *Scope of the reaction of allenyl-pyrroles **7** at 100 ºC to give tetrahydroindolizines **9**.*

Finally, when these reactions were performed at 130 °C, the formation of isomeric products of type **23** was observed in moderate to good yields and with equally high

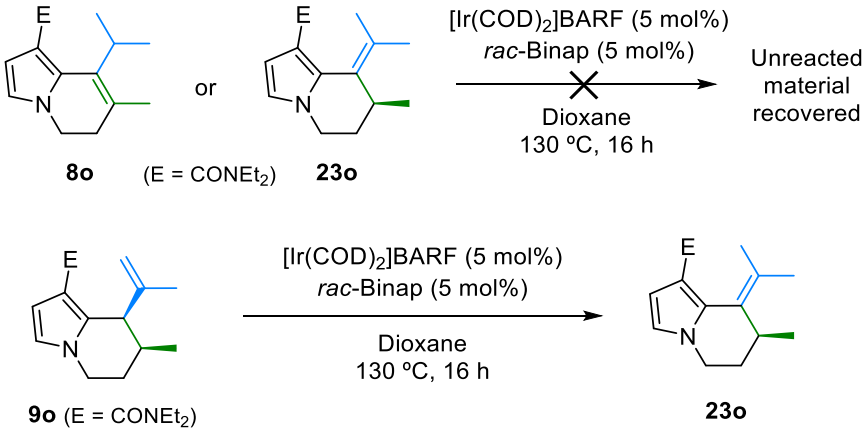
enantiomeric ratios. This is exemplified by the formation of **23u**, **23v**, or **23w,** with yields ranging from 44% to 71% and with enantiomeric ratios between 96:4 and 99:1. In the case of **7x**, the major product was again **24x**, which was obtained in 75% yield (**Scheme 167**).



Scheme 167: *Scope of the reaction at 130 ºC of allenyl-pyrroles **7** to give tetrahydroindolizines **23** or the dihydroindolizine **24x**.*

Mechanistic insights

A series of control experiments were first conducted. Each of the products was subjected to the reaction conditions leading to **23o** (Ir/Binap catalyst at 130 °C). Compounds **8o** and **23o** remained intact after 16 hours, but in the case of **9o**, complete conversion to **23o** was observed (**Scheme 168**). This result suggests that the formation of **23o** occurs via an Ir-promoted alkene isomerization.



Scheme 168*: Control experiments by subjecting **8o**, **9o** and **23o** to standard reaction conditions at 130 ºC.*

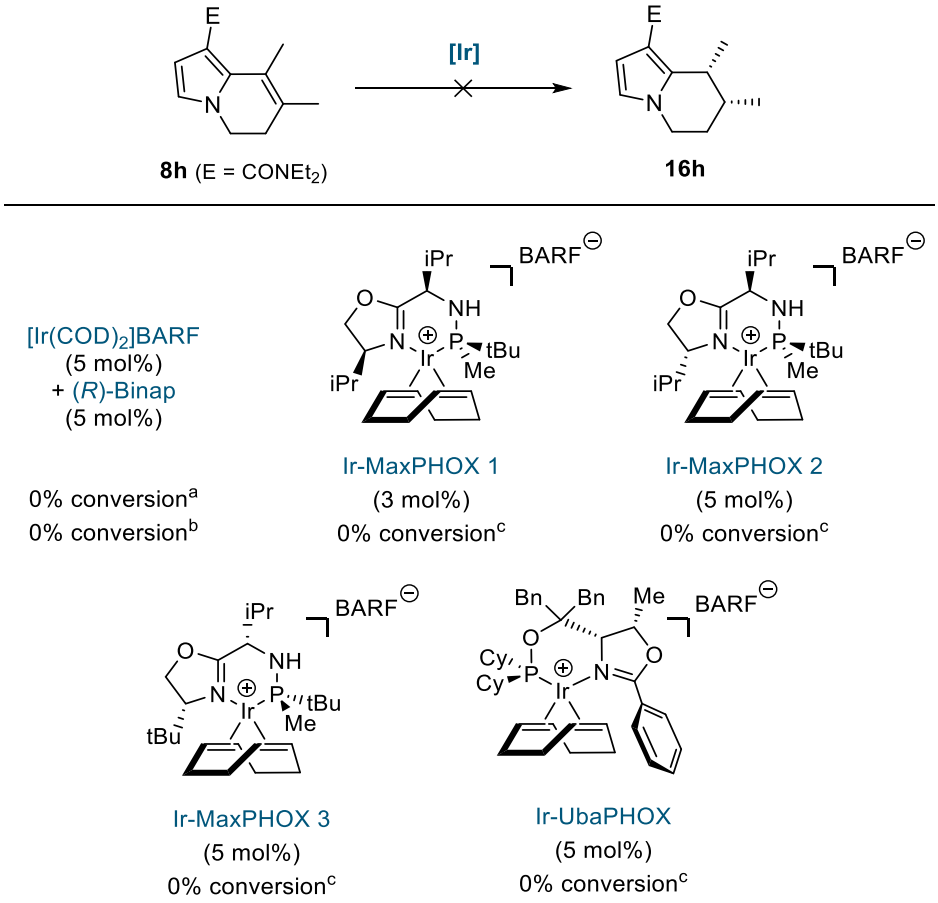
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To investigate whether dienes **24** could be intermediates in the formation of products **9**, via an intramolecular hydrogenation process, we independently study the feasibility of hydrogenating **8h**, with an Ir(I) catalyst and external hydrogen. Indeed, the asymmetric hydrogenation of the tetrasubstituted olefin of **8** is a relevant challenge, which could provide a new entry to chiral tetrahydroindolizines like **9**. These experiments were carried out by the group of Xavier Verdaguer and Antoni Riera, experts in Ir-catalyzed hydrogenation of alkenes.

They tested the potential hydrogenation of product **8h** with Ir/Binap and other iridium catalysts developed by his group for the hydrogenation of highly substituted olefins.[148] In all trials, unreacted starting material was observed (**Scheme 169**). These results suggest that the catalytic species responsible for the formation of **9** are different from those that are generated in standard Ir-catalyzed hydrogenations with molecular hydrogen. Indeed, it is worth to note that the hydrogenation of alkenes with Ir(I) catalysts has been proposed to proceed through a Ir(IV)-Ir(III) cycle, rather than a Ir(III)-Ir(I) path,[149] which could explain the observed divergent results. Additionally, these results highlight the challenge of performing enantioselective hydrogenations of this type of fully-substituted endocyclic olefins.

[148] (a) E. Salomó, S. Orgué, A. Riera, X. Verdaguer, *Angew. Chem. Int. Ed.*, **2016**, *55*, 7988–7992. (b) M. Biosca, E. Salomó, P. de la Cruz-Sánchez, A. Riera, X. Verdaguer, O. Pàmies, M. Diéguez, *Org. Lett.*, **2019**, *21*, 807–811. (c) M. Biosca, P. de la Cruz-Sánchez, J. Faiges, J. Margalef, E. Salomó, A. Riera, X. Verdaguer, J. Ferré, F. Maseras, M. Besora, O. Pàmies, M. Diéguez, *ACS Catal.*, **2023**, *13*, 3020–3035.

[149] S. Kraft, K. Ryan, and R. B. Kargbo, *J. Am. Chem. Soc.* **2017**, *139*, 34, 11630–11641.

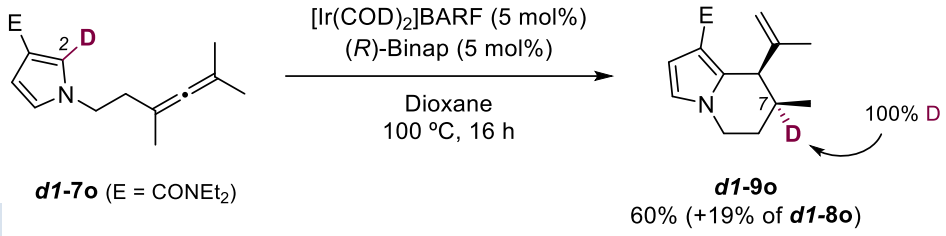


Scheme 169: *Attempted hydrogenation of* ***8h*** *using Ir-catalysts. [a] Conducted under 9 bars of H_2 in CH_2Cl_2. [b] Conducted under 9 bars of H_2 in dioxane. [c] Conducted under 50 bars of H_2 in CH_2Cl_2..*

Deuteration experiments

In order to gain further mechanistic insights, we made ***d1*-7o**, a precursor that is deuterated at the C-2 position of pyrrole. Its synthesis was carried out using the same method as for ***d1*-1a**, as depicted in **Scheme 121**, page 134.

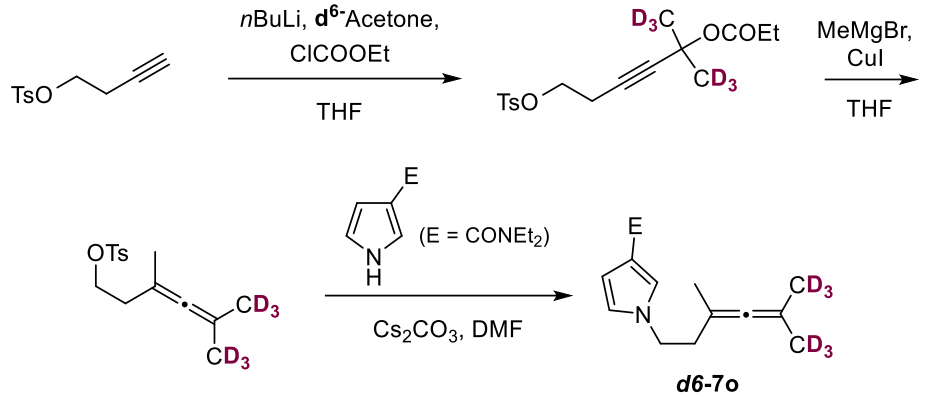
When subjecting the deuterated allene-pyrrole ***d1*-7o** to the standard reaction conditions (Ir/(*R*)-Binap catalyst, at 100 °C, the selective deuteration at a single C-2 position of ***d1*-9o** was observed. This deuteration pattern was deduced from ^{1}H- and ^{2}D-NMR spectra, with no other isotopomers detected (**Scheme 170**).



Scheme 170*: Hydroarylation of deuterated precursor* ***d1*-7o***.*

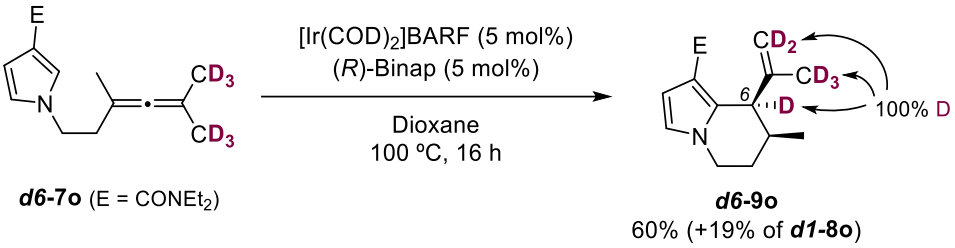
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Next, we interrogated the origin of the hydrogen atom located at the vinyl-substituted stereocenter C-7. To do so, a labelled substrate, bearing two deuterated methyl groups at the terminal position of the allene (***d6*-7o**) was prepared, as depicted in **Scheme 171**.



***Scheme 171**: Synthesis of the deuterated substrate **d6-7o**.*

Treatment of the precursor ***d6*-7o** under standard conditions led to the product ***d6*-9o** (^{1}H- and ^{2}D-NMR spectroscopy, **Scheme 172**), again as a single isotopomer with the deuterium atom exclusively located at C-6.



***d6*-7o** (E = $CONEt_2$)

***d6*-9o**
60% (+19% of ***d1*-8o**)

***Scheme 172**: Hydroarylation of deuterated precursor **d6-7o**.*

Interestingly, the hexadeuterated product ***d6*-9o** turned out to be solid, unlike its non-deuterated isotopomer. After obtaining crystals of the compound, the absolute configuration of its two stereocenters was determined (see **Figure 24**).

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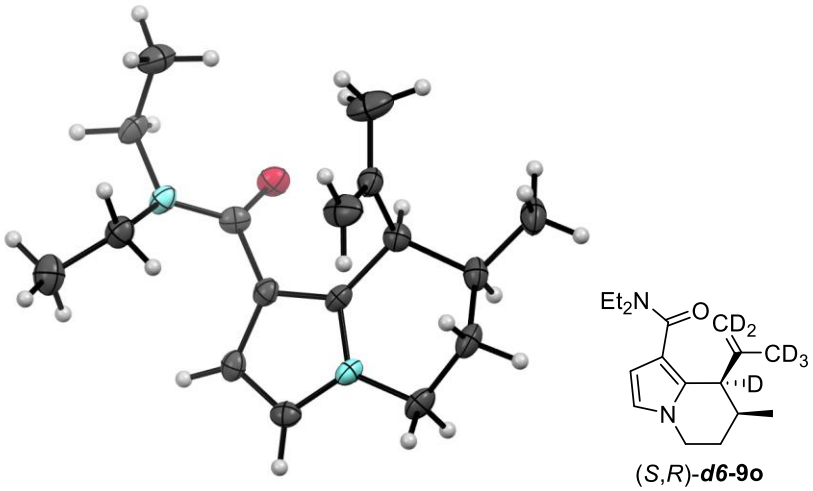
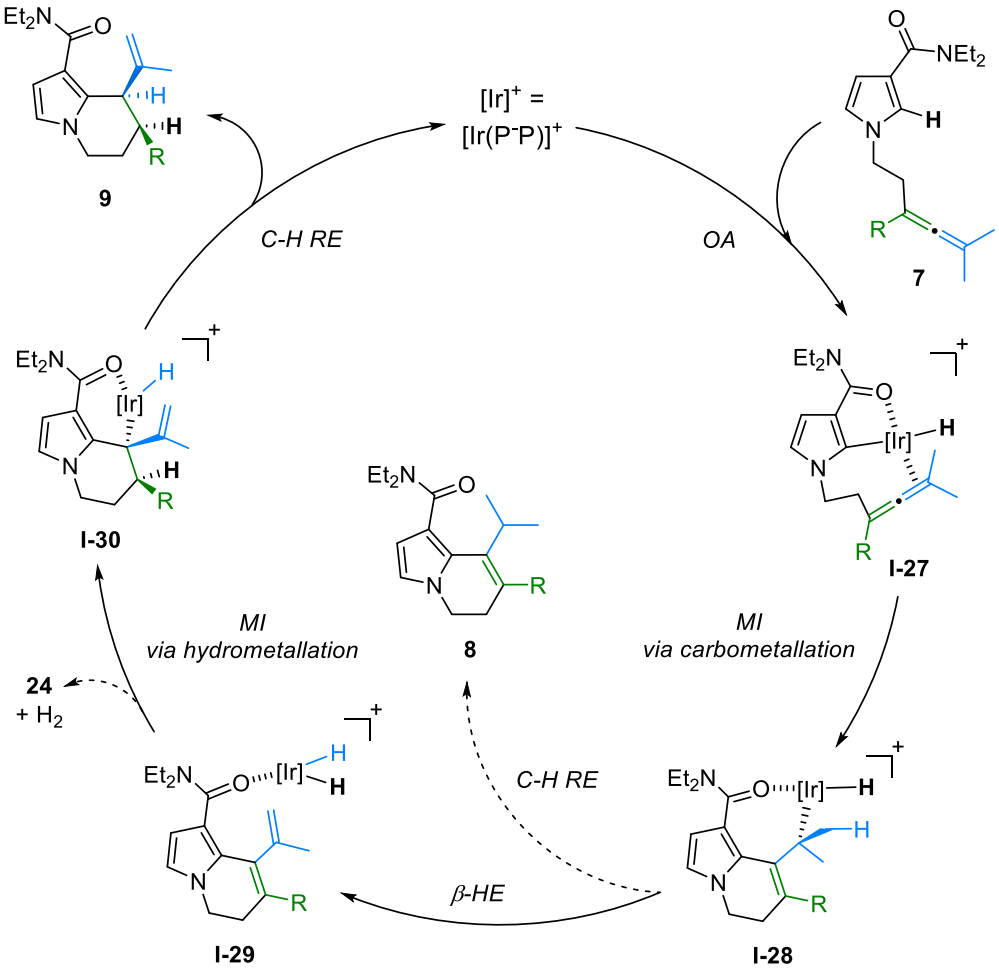


***Figure 24**: X-Ray structure of compound **d6-9o** (CCDC deposition number 2338733)*

These deuteration results led us to propose the mechanism shown in **Scheme 173**. After an oxidative addition of the C–H bond to form the iridium hydride **I-27** and a subsequent carbometallation towards **I-28**, this intermediate could then evolve through C–H reductive elimination to form compound **8o**. However, in this scenario, a β-hydride elimination to yield an iridium bishydride **I-29** could be more favorable. Through a hydrometallation, **I-30** is formed, and the final product **9o** would be delivered through a final C–H reductive elimination. Curiously, the hydrometallation step from the bis-hydride **I-29**, should be completely regio-and stereoselective, as the deuterated product **d6-9o** only holds a deuterium atom at the C-6 position, while the product **9o** is obtained with excellent enantiomeric ratio.

When this intramolecular transfer hydrogenation cannot take place (e.g. by steric reasons), H_2 might be released from **I-29** or, alternatively, this species could also transfer its hydrogens to an alternative hydrogen acceptor (such as COD), in a less hindered intermolecular fashion. This process would eventually release the side products of type **24**, which are major when bulky groups are present at former internal position of the allene (e.g. **24x**).

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***Scheme 173**: Proposed catalytic cycle for the formation of products **8, 9** and **24** from allenyl pyrroles **7**.*

Computational studies

To gain further insights into this process, DFT calculations were conducted by Dr. Martín Calvelo. The energy landscape was studied using the model precursor **7o'**, featuring three methyl groups at the allene (see **Figure 25**).

Different pathways from the intermediate **Int-K$_D$** (resulting from carbometallation of **Int-J$_D$**) were explored. The anticipated C–H reductive elimination towards the product **Int-L$_D$**, occurring via its square-pyramidal isomer **Int-K$_D$'**, comprises an overall energy barrier of 16.4 kcal/mol.

Interestingly, the calculations confirm that the presence of the three methyl groups introduces a new, and energetically more favorable β-hydride elimination pathway, leading to an iridium bis-hydride-diene complex **Int-R** (analog of the previously proposed species **I-29**). This intermediate would evolve to the observed hydrogenated product **9o'** through a stereoselective hydrogenation process. Initial computations qualitatively support an intramolecular nature for this transfer hydrogenation, but further work should

be carried out to eventually close the overall catalytic cycle. This mechanism also supports the formation of products of type **24**, when employing substrates with bulky substituents in the internal position of the allene, that impedes the hydrogenation of the internal double bond from **Int-R**.

In summary, this computational study allows us to confidentially propose a new type of cascade cycloisomerization reaction that is based on an initial C-H activation step. Indeed, to the best of our knowledge, the dehydrogenative generation of an iridium bis-hydride intermediate, followed by an intramolecular, enantioselective transfer hydrogenation to an alkene, had never been reported.[150]

[150] For a related racemic case, in which the substrate rather than the product is hydrogenated, in low yield, see: B. DeBoef, S. J. Pastine, D. Sames, *J. Am. Chem. Soc.,* **2004**, *126*, 6556-6557. For selected examples of cascade hydroarylation processes that involve alternative coupled steps (e.g. chain walking, migratory insertions, opening of strained rings or dehydrogenations), see: (a) Y. Ebe, M. Onoda, T. Nishimura, H. Yorimitsu, *Angew. Chem. Int. Ed.*, **2017**, *56*, 5607-5611. (b) F. Li, Y. Luo, J. Ren, Q. Yuan, D. Yan, W. Zhang, *Angew. Chem. Int. Ed.*, **2023**, *62*, e202309859. (c) C. Aissa, A. Furstner, *J. Am. Chem. Soc.,* **2007**, *129*, 14836-14837. (d) C. Aissa, K. Y. Ho, D. J. Tetlow, M. Pin-No, *Angew. Chem. Int. Ed.,* **2014**, *53*, 4209-4212. (e) Y. Ishii, N. Chatani, F. Kakiuchi, S. Murai, *Organometallics,* **1997**, *16*, 3615-3622. (f) T. Ohmura, K. Yagi, S. Kusaka, M. Suginome, *ACS Catal.,* **2020**, *10*, 3152-3157.

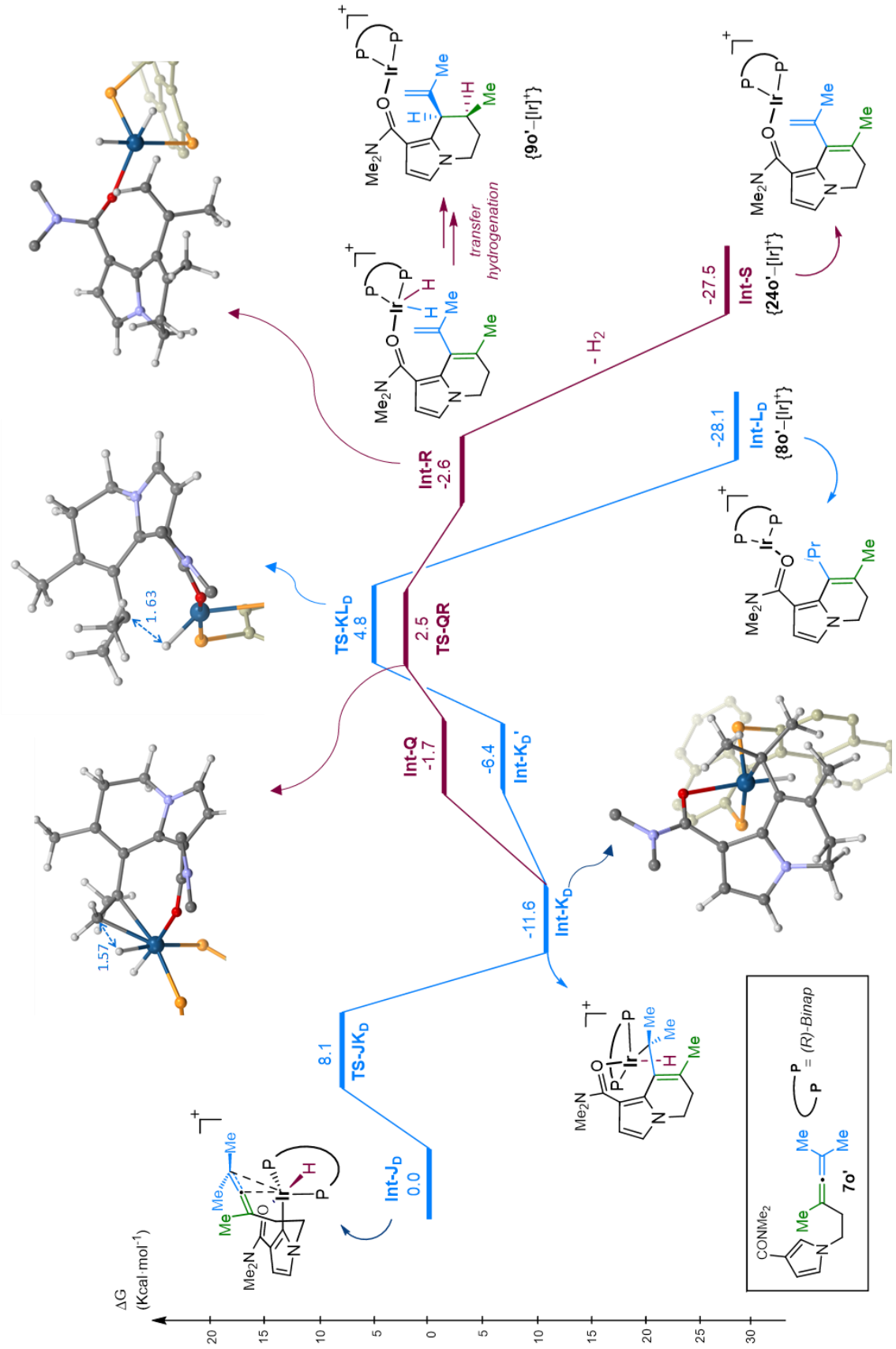


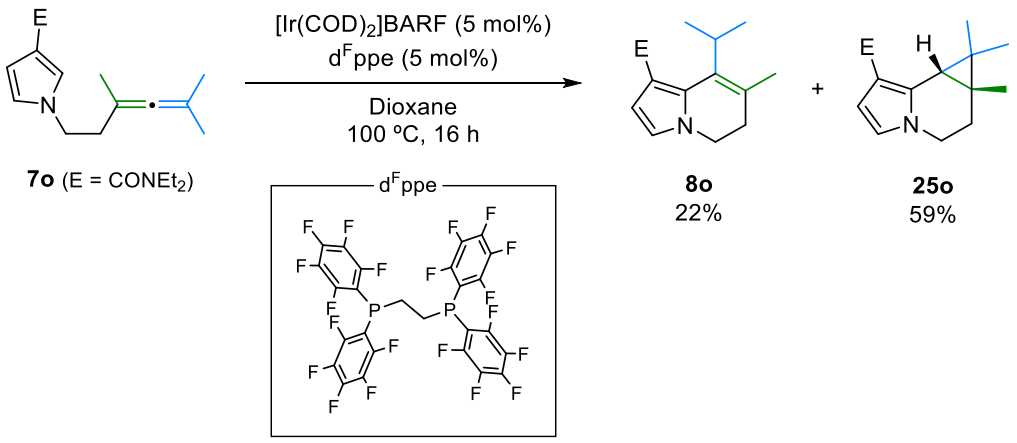
Figure 25: *Energy profile ΔGsolv (kcal/mol) for the hydrocarbonation of* ***7o'****. B3LYP/6-31G(d) (LANL2DZ for Ir) // M06/6-311++g(d,p) (SDD for Ir). Binap ligand is mostly simplified in the 3D representations.*

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5.3.5. Direct assembly of chiral cyclopropane-fused heterocycles from allenyl-pyrroles

Discovery of a cyclization/cyclopropanation cascade: Importance of d^{F}ppe

During the optimization of the tandem reaction presented in the preceding section 5.2, we unexpected discovered that when precursor **7o** was treated under standard iridium-promoted hydrocarbonation conditions, but using the fluorinated biphosphine d^{F}ppe as ligand, the cyclopropane-fused tetrahydroindolizine **25o** was formed in 59% yield, along with a 22% of the initially expected product **8o** (**Scheme 174**). In contrast, the use of dppe, under otherwise identical conditions, resulted in the recovery of the starting material (**7o**), whereas performing the reaction at higher temperatures led to a complex mixture of products. Therefore, the electron-deficient character of d^{F}ppe proved crucial for this outcome, which we anticipate to entail a complex mechanistic cascade.



Scheme 174: *Reaction of* ***7o*** *when employing d^{F}ppe as ligand.*

Relevance of cyclopropane-fused heteropolycyclic scaffolds

This anomalous result is of major interest, as this type of cyclopropane containing cyclic structures are common in different natural products[151] and drug molecules (see **Figure 26**).[152] Incorporating cyclopropanes into bioactive compounds has been shown to increase their stability, molecular rigidity, and pharmacological potency.

[151] Cyclopropane in natural molecules: (a) J. Tan, Z. Dong, J. Liu, *Helv. Chim. Acta*, **2000**, *83*, 3191–3197. (b) A. Kasali, O. Ekundayo, C. Paul, W. König, *Phytochem.*, **2002**, *59*, 805–810. (c) W. Chou, I. Fanizza, T. Uchiyama, M. Komatsu, H. Ikeda, D. Cane, *J. Am. Chem. Soc.*, **2010**, *132*, 8850–8851. (d) B. Zhai, J. Clark, T. Ling, M. Connelly, F. Medina, F. Rivas, *Molecules*, **2014**, *19*, 756–766. (e) Y. Aoyagi, A. Yamazaki, C. Nakatsugawa, H. Fukaya, K. Takeya, S. Kawauchi, H. Izumi, *Org. Lett.*, **2008**, *10*, 4429–4432. (f) S. Sherif, S. Barbara, W. Victor, T. Frank, H. Michael, E. Werner, H. Alexandra, K. Matthias, W. Lin, P. Peter, *Bioorg. Med. Chem.*, **2011**, *19*, 4644–4651.

[152] Cyclopropanes in drugs and bioactive molecules: (a) T. Talele, *J. Med. Chem.*, **2016**, *59*, 8712–8756. (b) K. A. Jacobson, J.-M. Boeynaems, *Drug Discov. Today*, **2010**, *15*, 570–578.

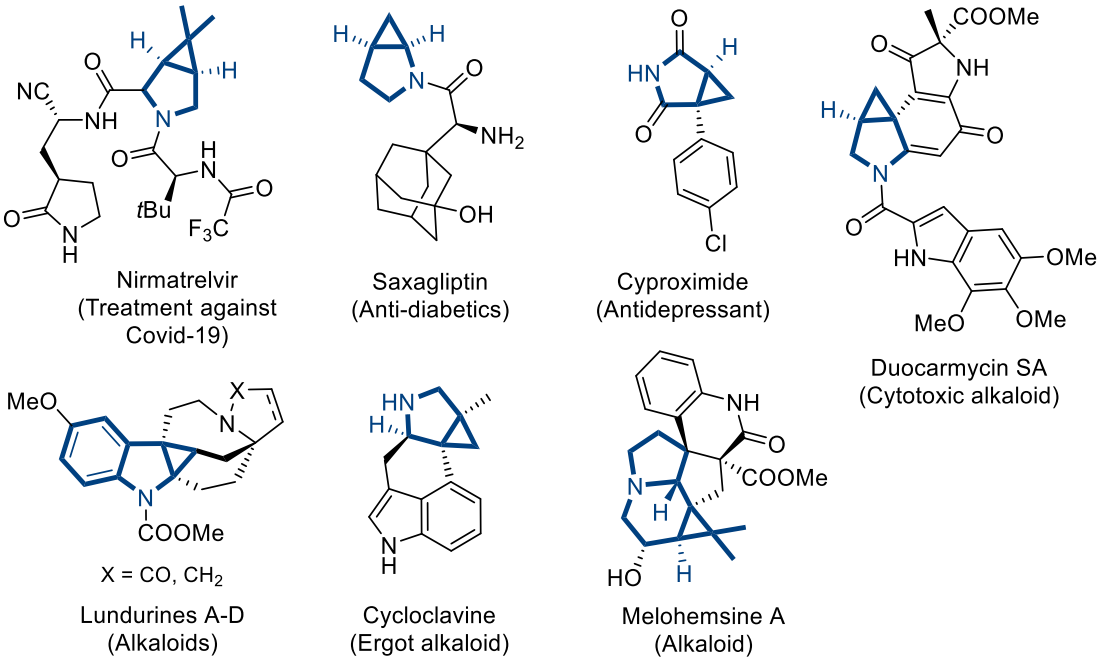


***Figure 26**: Relevant drugs and alkaloids bearing cyclopropanes fused to heterocycles.*

Consequently, a vast arsenal of cyclopropanation methods have been developed; some of which are enantioselective, as many molecules containing cyclopropanes are chiral. On the other hand, most of these methods rely on metal carbenes or carbenoid intermediates, while methodologies that do not use these reagents remain quite underdeveloped.[153]

Furthermore, examples where cyclopropanation occurs concurrently with the construction of polycyclic structures are even rarer. The structural significance of cyclopropane-fused heterocyclic systems, which are present in various biologically relevant products, along with the intriguing mechanistic aspects associated with this transformation, prompted us to further explore the generality of this unconventional cyclization/cyclopropanation cascade.[154]

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[153] For reviews of cyclopropane synthesis: (a) H. Lebel, J. Marcoux, C. Molinaro, A. Charette, *Chem. Rev.*, **2003**, *103*, 977–1050. (b) W. Wu, Z. Lin, H. Jiang, *Org. Biomol. Chem.*, **2018**, *16*, 7315–7329. (c) E. M. D. Allouche, A. B. Charette, *Synthesis*, **2019**, *51*, 3947–3963. (d) M. Mato, A. Franchino, C. García-Morales, A. M. Echavarren, *Chem. Rev.* **2021**, *121*, 14, 8613–8684.

[154] (a) P. Keglevich, A. Keglevich, L. Hazai, G. Kalaus, C. Szantay, *Curr. Org. Chem.,* **2014**, *18*, 2037-2042. (b) T. T. Talele, *J. Med. Chem.,* **2016**, *59*, 8712-8756. (c) L. A. Wessjohann, W. Brandt, T. Thiemann, *Chem. Rev.,* **2003**, *103*, 1625-1648. (d) M. J. R. Richter, F. J. Zécri, K. Briner, S. L. Schreiber, *Angew. Chem. Int. Ed.,* **2022**, *61*, e202203221. *(*e) D. Ellis, K. L. Kuhen, B. Anaclerio, B. Wu, K. Wolff, H. Yin, B. Bursulaya, J. Caldwell, D. Karanewsky, Y. He, *Bioorg. Med. Chem. Lett.,* **2006**, *16*, 4246-4251. (f) M. A. M. Subbaiah, *J. Med. Chem.,* **2018**, *61*, 2133-2165. (g) T. Wirth, K. Schmuck, L. F. Tietze, S. A. Sieber, *Angew. Chem. Int. Ed.,* **2012**, *51*, 2874-2877. (h) F. G. Njoroge, K. X. Chen, N.-Y. Shih, J. J. Piwinski, *Acc. Chem. Res.,* **2008**, *41*, 50-59. (i) D. Y. K. Chen, R. H. Pouwer, J.-A. Richard, *Chem. Soc. Rev.,* **2012**, *41*, 4631-4642. (j) Z.-H. Wang, L.-W. Shen, K.-X. Xie, Y. You, J.-Q. Zhao, W.-C. Yuan, *Org. Lett.,* **2020**, *22*, 3114-3118.

Scope of the process

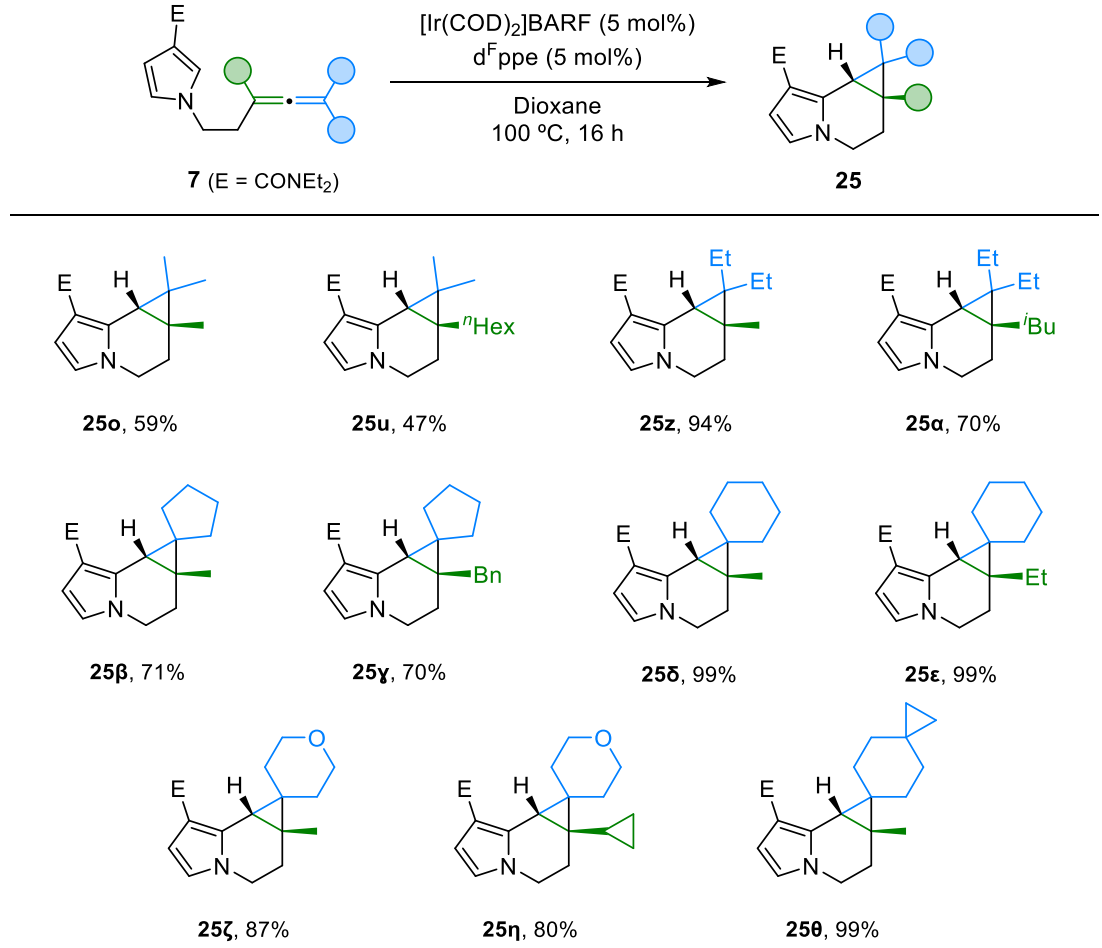
Once the importance of using the electron-deficient ligand d^Fppe was established, the generality of the reaction with other substrates was explored. These compounds were prepared through the same synthetic sequence used to obtain other tetrasubstituted allene-containing precursors (as depicted in **Scheme 137**, page 162).

As showed in **Scheme 175**, the reaction tolerates other substituents at the internal position of the allene. For example, the cyclopropane-fused tetrahydroindolizine **25u**, containing an *n*-hexyl chain at the ring-fusion, was efficiently obtained. Additionally, products like **25z**, bearing ethyl groups at the cyclopropyl ring, were formed in an excellent 94% yield, with complete chemoselectivity. Similarly, **25α** was obtained from its corresponding precursor **7α** in a good yield.

Unfortunately, the use of tri- or di-substituted allenes, like those employed in section 5.2 of this thesis (e.g. **7a**, page 160), did not lead to cyclopropanated products. Instead, they resulted in mixtures of products and decomposition of the starting materials.

However, allenes bearing a carbocycle at their distal carbon, such as cyclopentylidene or cyclohexylidene groups, proved to be excellent substrates. Thus, chiral tetrahydroindolizines bearing a five- or a six-membered spirocyclopropane-fused moiety were obtained in yields up to 99% (**Scheme 175**, **25β**–**25ε**). The structure of **25δ** was further confirmed by X-ray diffraction analysis (**Figure 27**). By following this approach, other cyclopropane-fused tetrahydroindolizines bearing diverse spirocyclic architectures (e.g., **25ζ**–**25η**) were synthesized from their corresponding tetrasubstituted allenyl precursors in good to excellent yields.

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***Scheme 175**: Scope of the Ir-catalyzed tandem hydroarylation/cyclopropanation of allenyl-substituted pyrroles **7**.*

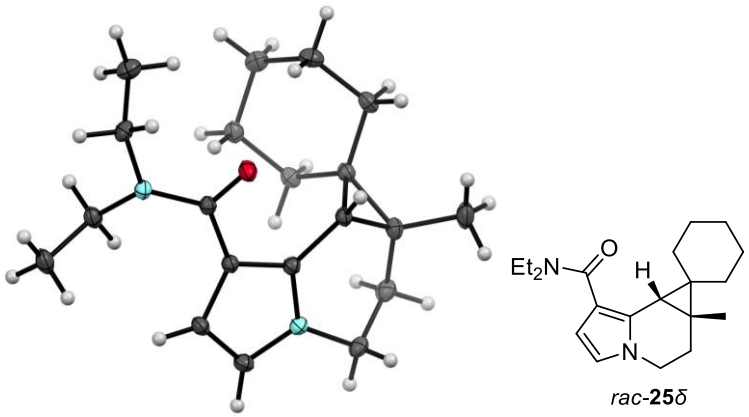
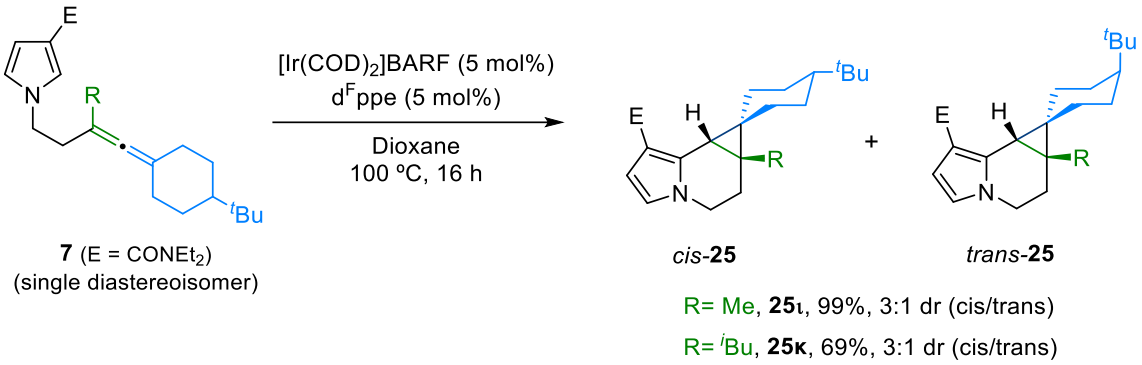


***Figure 27**: X-Ray structure of compound **25δ** (CCDC deposition number 2329799).*

Additionally, substrates **7ι** and **7κ**, which feature a 4-*t*Bu-substituted cyclohexylidene group, led to the expected products as mixture of two isomers (*cis* and *trans*), separable by flash chromatography, in a 3:1 ratio (**Scheme 176**). The X-ray structure of the major

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isomer from the reaction of **7ι** was also obtained, revealing it to be the *cis* isomer of **25ι** (**Figure 28**).



***Scheme 176**: Scope of the Ir-catalyzed tandem hydroarylation/cyclopropanation of allenyl-substituted pyrroles **7**, bearing 4-tBu-substituted cyclohexylidene group.*

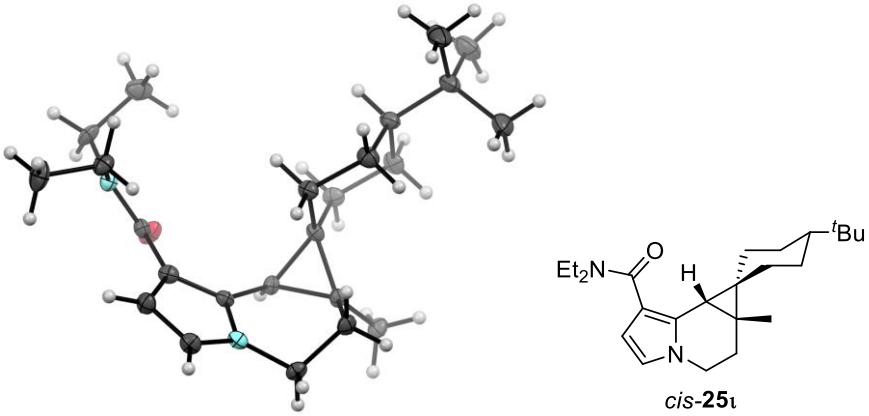


***Figure 28**: X-Ray structure of compound cis-**25ι** (CCDC deposition number 2329801).*

Development of an asymmetric variant

Motivated by the prevalence of chiral cyclopropane-fused heterocycles in biorelevant compounds, a preliminary assessment of the feasibility of an enantioselective variation of this transformation using chiral electron-deficient phosphine ligands was conducted.

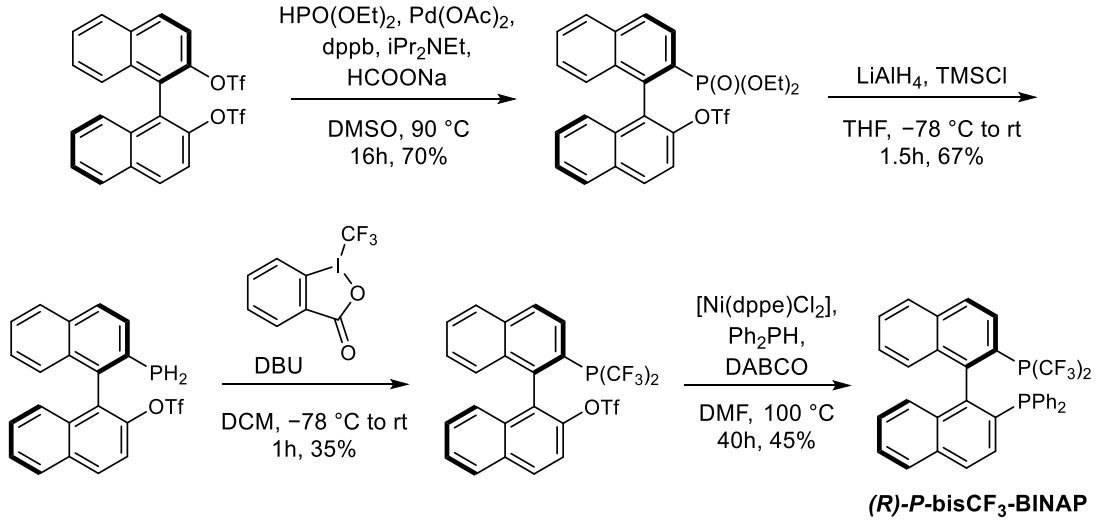
Our initial approach involved the use of chiral analogues of d^{F}ppe, such as (*R*)-Biphop^F, a chiral bidentate pentafluoroaryl-phosphinite, originally developed by Kundig and coworkers in the context of chiral Lewis acid metal catalysts.[155] This endeavor led to the isolation of compound **25o** in 63%, with a moderate enantiomeric excess of 63:37 (**Table 9**, entry 2).

[155] J. Rickerby, M. Vallet, G. Bernardinelli, F. Viton, E. P. Kündig, *Chem. Eur. J.*; **2007**, *13*, 3354-3368. Ligand synthesis was carried out by Alejandro Rey.

By employing the ferrocenylbisphosphine (*R*)-BTFM-Walphos, featuring a single bis(3,5-trifluoromethylphenyl) phosphine, the reaction yielded a 1:1 mixture of the standard cycloisomerization product **8o** (41% yield) and the desired cyclopropane-fused derivative **25o**, which was isolated in 42% yield and with a moderate 70:30 er (entry 3).

Significantly, (*R*)-BTFM-Garphos, incorporating two bis(3,5-trifluoromethylphenyl) phosphines, exhibited a notably higher selectivity (**8o**:**25o** ratio = 1:2), furnishing **25o** in a good 58% yield and an excellent 94:6 er (entry 4). The crucial role of the electron-deficient character of phosphine ligand to direct the chemoselectivity towards **25** was again evident, as the use of analogous ligands bearing methyl groups [i.e. (*R*)-Xyl-Garphos] or hydrogen atoms [i.e. (*R*)-Garphos], instead of the CF_3 groups, resulted exclusively in mixtures of other standard products like **8o** and **9o**, no the cyclopropane derivatives (entries 5 and 6).

Bis-trifluoromethyl phosphine derivatives are recognized as highly proficient π-acceptor ligands, although chiral variants are rare.[156] In this context, the chiral ligand (*R*)-*P*-bisCF_3-Binap, initially developed by Togni,[157] (synthesis showcased on **Scheme 177**) was prepared, and tested to see its behavior in our process.

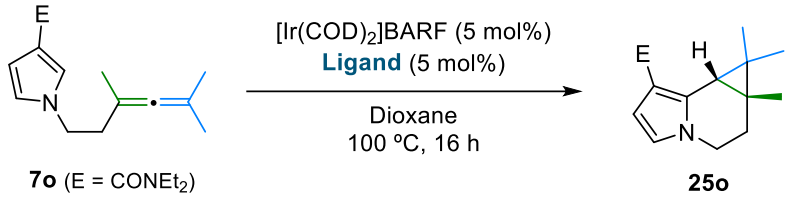


***Scheme 177**: Synthesis of reported by (R)-P-bisCF3-Binap by Togni and coworkers.*

[156] (a) S. Lauzon, T. Ollevier, *Chem. Sci.,* **2022**, *13*, 10985-11008. (b) Z. Hu, Y. Li, K. Liu, Q. Shen, *J. Org. Chem.,* **2012**, *77*, 7957-7967.
[157] N. Armanino, R. Koller, A. Togni, *Organometallics,* **2010**, *29*, 1771-1777.

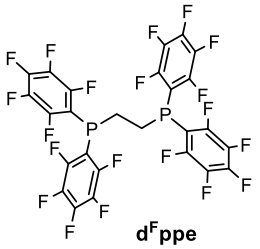
Surprisingly, despite this nonsymmetric biphosphine had never been employed in enantioselective transformations, its corresponding Ir(I) complex facilitated the cycloisomerization reaction of **7o**, yielding **25o** in a remarkable 69% yield and with an excellent 97:3 er (entry 7).

Table 9: *Evaluation of different ligands for the cycloisomerization of* ***7o*** *towards* ***25o****.*

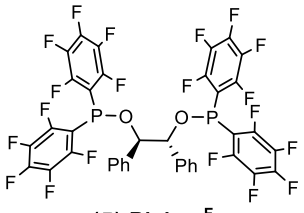


7o (E = $CONEt_2$) **25o**

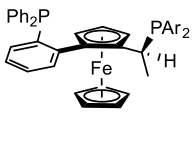
Entry	Ligand	Yield (%)	er
1	d^Fppe	83	-
2	(*R*)-Biphop^F	63	63:37
3	(*R*)-BTFM-Walphos	42	70:30
4	(*R*)-BTFM-Garphos	49	93:7
5	(*R*)-Xyl-Garphos	0	-
6	(*R*)-Garphos	0	-
7	(*R*)-*P*-bisCF_3-Binap	69	97:3



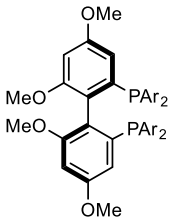
d^Fppe



(*R*)-Biphop^F



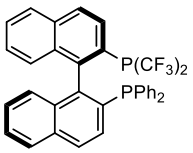
Ar = 3,5-$(CF_3)_2C_6H_3$
(*R*)-BTFM-Walphos



Ar = 3,5-$(CF_3)_2C_6H_3$
(*R*)-BTFM-Garphos

Ar = 3,5-$(CH_3)_2C_6H_3$
(*R*)-Xyl- Garphos

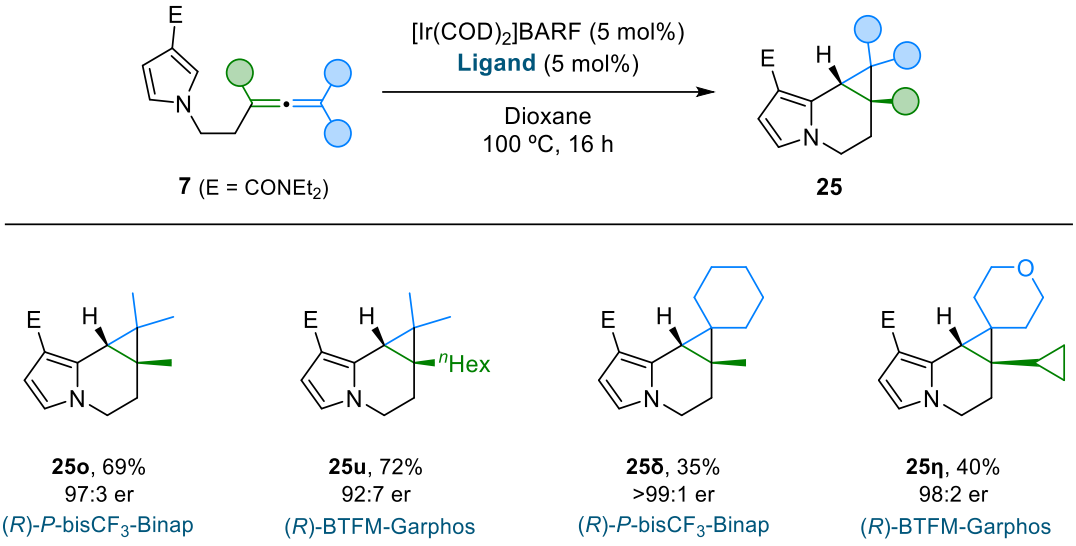
Ar = Ph
(*R*)-Garphos



(*R*)-*P*-bisCF_3-Binap

Therefore, by employing either this ligand or (*R*)-BTFM-Garphos, different tetrasubstituted allenyl pyrroles of type **7** were converted into the desired cyclopropane-fused tetrahydroindolizines **25**, yielding moderate to good yields and enantiomeric ratios of up to 99:1 (**Scheme 178**). X-ray diffraction analysis of a crystalline sample of **25η** (98:2 er) allowed to confirm its absolute stereochemistry (**Figure 29**).

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***Scheme 178**: Preliminary asymmetric tandem hydrocarbonation/cyclopropanation of allenyl-pyrroles **7**.*

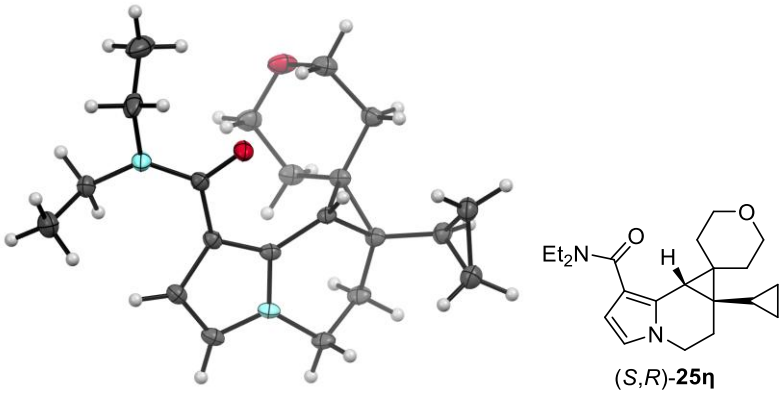


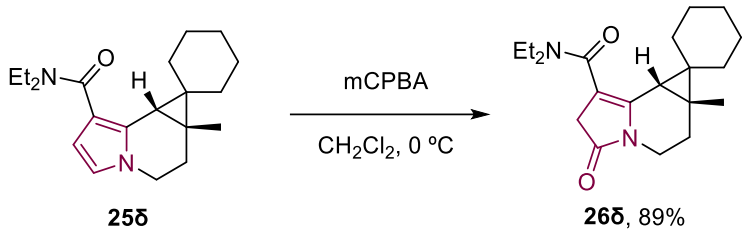
***Figure 29**: X-Ray structure of compound **25η** (CCDC deposition number 233873).*

Synthetic versatility of the products

In section 5.1 of this thesis, various synthetic possibilities for transforming the diethylamide group of the adducts were demonstrated. Additionally, in section 5.2.7, the scope was expanded by identifying conditions to remove the directing group, along with other reactions showcasing the synthetic utility of the pyrrole ring and other substituents of the products.

To reach products with even greater structural complexity, we attempted to oxidize the pyrrole moiety of compounds **25**. Curiously, although the conditions previously used for the oxidation of **16c** (see **Scheme 152**), did not lead to any identifiable product, by employing *m*CPBA, compound **26δ** was successfully obtained from **25δ**, in an excellent 89% yield (**Scheme 179**).

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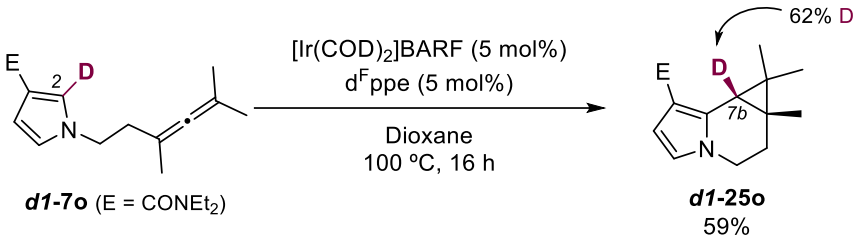
25δ **26δ**, 89%

***Scheme 179**: Oxidation of compound **25δ** using mCPBA.*

Mechanistic insights of the cascade cyclopropanation

The above transformations lack precedents in literature and raise intriguing mechanistic insights, which we wanted to tackle.

Analogously to the experiments with ***d1*-7o** (page 198), we carried out its reaction by using d^{F}ppe instead Binap. As expected, the deuterium located at the C-2 position of the pyrrole in ***d1*-7o** is selectively transferred to the cyclopropane carbon C-7b, of ***d1*-25o**, as illustrated in **Scheme 180**.



***d1*-7o** (E = CONEt$_2$) ***d1*-25o** 59%

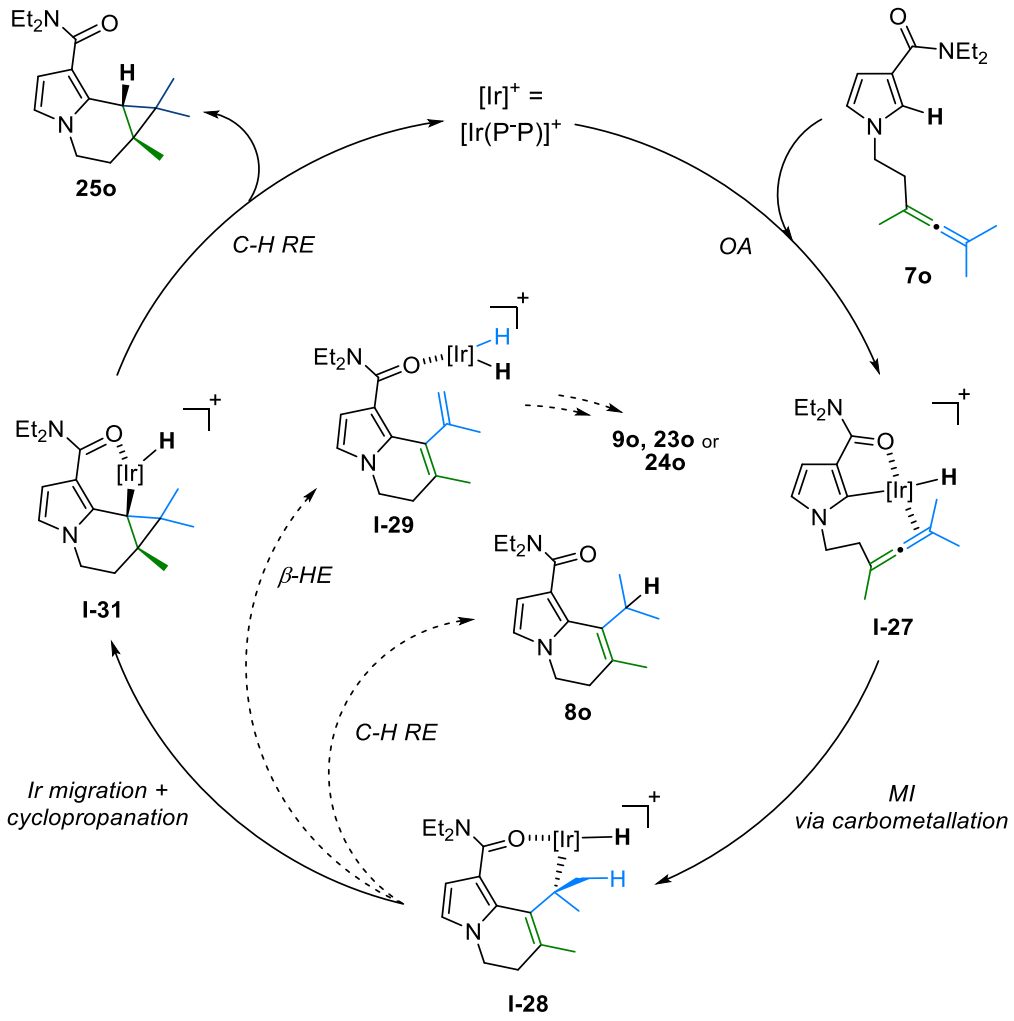
***Scheme 180**: Reaction of deuterated substrate **d1-7o** using d^{F}ppe as ligand.*

In consonance with these results, we propose the mechanism shown in **Scheme 181**. After the insertion of the C–H bond of **7o** into the iridium center to form **I-27**, a carbometallation of the distal double bond of the allene would lead to intermediate **I-28**.

Then, instead of a standard reductive elimination towards **8o**, a carbometallation of the internal double bond takes place, with the formation of a new C–C bond, resulting in intermediate **I-31**. After an eventual reductive elimination, it provides the product **25o**.

The use of an electron deficient biphosphine seems crucial to favor the cyclopropanation, over the reductive elimination to yield **8o**, as well as over β-hydride elimination, which would lead to products **9o**, **23o**, or **24o**.

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***Scheme 181**: Proposed catalytic cycle for the formation of cyclopropane fused product **25o**.*

Computational studies

To try to better understand why these cyclopropane-fused adducts **25** are formed from tetrasubstituted allene precursors, when electron-deficient bisphosphines are used (like d^Fppe, BTFM-Garphos, or *P*-bisCF$_3$-Binap), Dr. Martín Calvelo carried out DFT calculations on a model system, using (*R*)-BTFM-Binap as model ligand.

The analysis included the possible formation of both enantiomers (**Int-U^R** and **Int-U^S**), which would be the result of the approach of the Ir center from the top (**Int-T^R**) or bottom (**Int-T^S**) face of the alkene moiety in intermediates **Int-T** (analogs of **I-28**, in **Scheme 181**). Both transition states (**TS-TU^R** and **TS-TU^R**) were located and led to the desired stereoisomers, validating the initially proposed mechanistic path. **Figure 30** shows that the most favorable TS (**TS-TU^R**), corresponds to the formation of the experimentally observed product (1a*R*,7b*R*)-**25o'** (as determined by X-ray crystallographic analysis of **25γ**), when (*R*)-BTFM-Garphos or (*R*)-*P*-bisCF$_3$-Binap are used as ligands. The

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alternative transition state, **TS-TU^S**, leading to the opposite enantiomer (1a*S*,7b*S*)-**25o'** was located 4.9 kcal/moll above **TS-TU^R**, a result which is in full agreement with the high enantiomeric ratios and the absolute configuration of the isolated products. Overall, the step from **Int-T^R** to **Int-U^R** has a barrier of 19.9 kcal/mol. The potentially competitive C–H reductive elimination from this intermediate was also located, but its TS lies 2.9 kcal/mol above **TS-TU^R**, which is also in full agreement with experimental results.

On the other hand, alternative mechanistic hypothesis, such as those involving π-allyl iridium hydride intermediates, could not be computationally located.

It is worth noting that when DM-Binap was used as model ligand for the calculations, instead of BTFM-Binap, the transition state leading to the cyclopropanated product could not be located. The same failure occurred when testing Binap or dppe as ligands. This shows how the use of fluorinated, electron-deficient biphosphine ligands is crucial to activate this new process leading to the cyclopropanated product, which is fully consistent with the experimental observations.

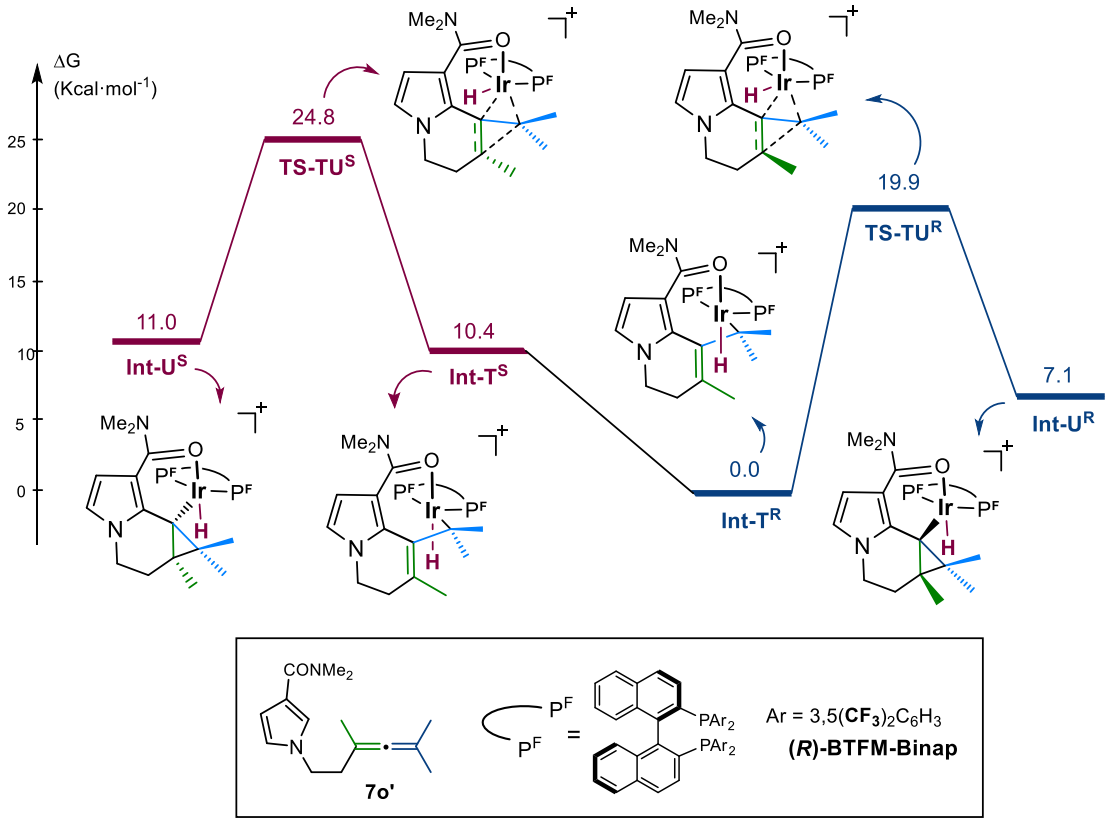


***Figure 30**: Key step of the energy profile (ΔG^{solv}, kcal/mol) of the tandem hydrocarbonation/cyclopropanation of **7o'** using (R)-3,5-(CF$_3$)$_2$-Binap as model ligand; B3LYP/6-31G(d) (LANL2DZ for Ir) // M06/6-311++g(d,p) (SDD for Ir). NOTE: Int-T is equivalent to Int-K but with BTFM-Binap instead of Binap.*

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Finally, Dr. Calvelo carried out an analysis of the non-covalent interactions of **TS-TU^{R}** , which revealed several non-covalent interactions that might be responsible for the unique outcome of the reactions with these ligands. Calculations identified several stabilizing interactions between the CF_3 groups of the ligand and the dihydroindolizine moiety, including C-F···H-C and C-F···N-amide contacts (**Figure 31**). These interactions, alongside potential electronic effects that the electron deficient ligand should impart on the iridium center, likely determines to the preference for the cyclopropanation step over standard C–H reductive and β-hydride eliminations.

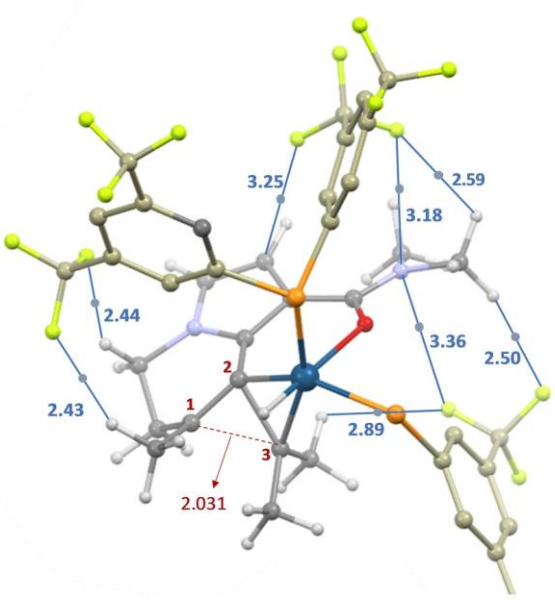


***Figure 31**: Non-covalent interactions found in **TS-TU^{R}** (blue lines correspond to non-covalent interactions (NCI's) for which bond paths and bond critical points were found by AIM formalism) Only key hydrogens are shown for clarity.*

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5.3.6. Conclusions

In conclusion, we have discovered two iridium promoted cascade processes triggered by an initial intramolecular addition of a “C–Ir–H” species across specific allenes. Key for these reaction pathways is the structure of the allene and the use of specific ancillary ligands.

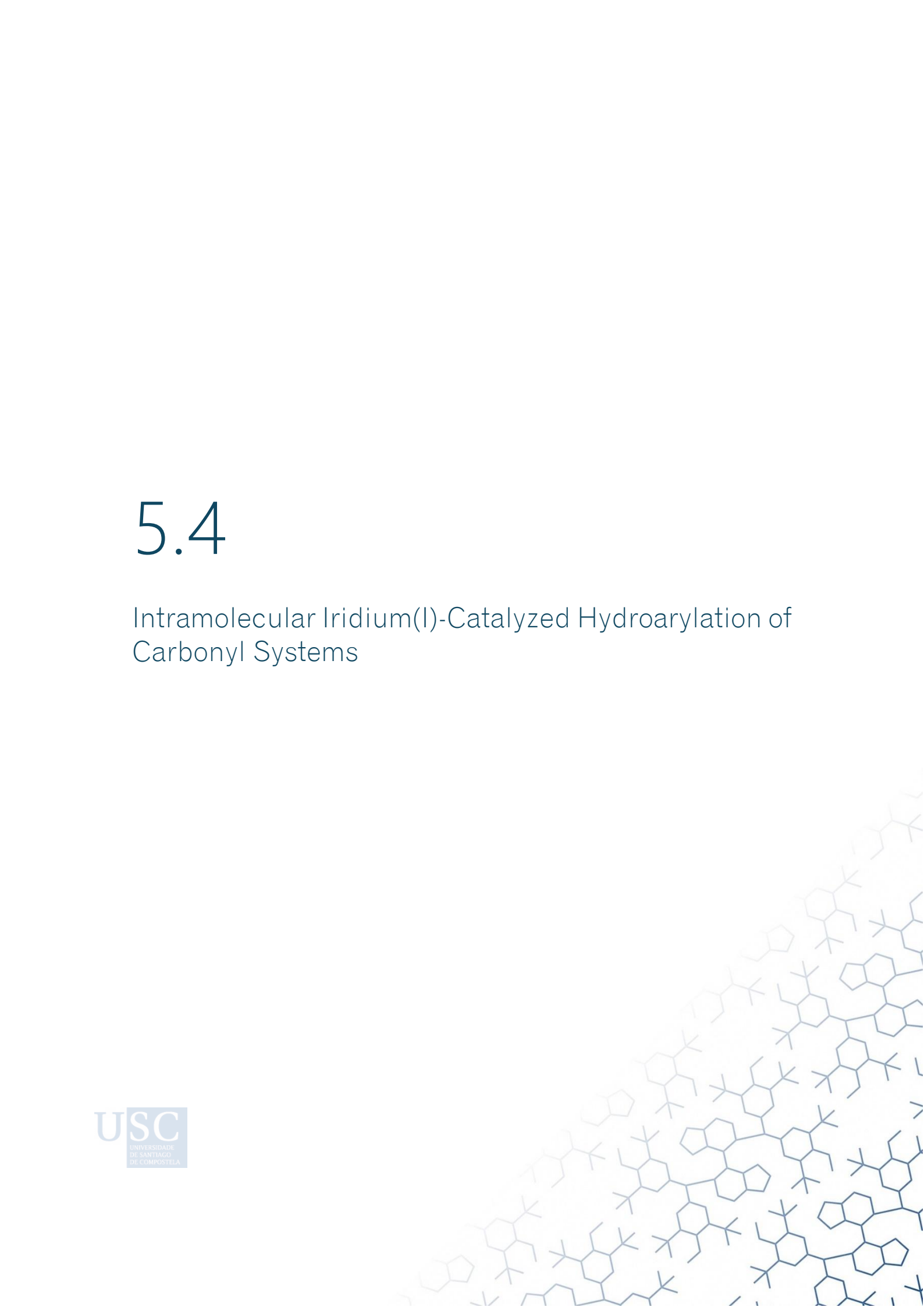
Specifically, when employing substrates bearing tetrasubstituted allenes, a cyclization followed by an intramolecular dehydrogenation-hydrogenation sequence occurs, enabling the isolation of compounds with up to two stereocenters in a highly diastereo- and enantioselective manner. Although this reaction seems limited to specific substrates, these findings pave the way for the development of new reactions that incorporate these types of cascade processes.

Additionally, it was found that when using electron-deficient bisphosphine ligands, a tandem hydrocarbonation/cyclopropanation takes place, a process that had not previously been described with iridium or any other metal catalysts. This sequence allowed the formation of various fused polycyclic products containing cyclopropanes, which are challenging to obtain via other methodologies. Furthermore, an enantioselective variant of this process was developed by using chiral electron-deficient ligands. Future work will focus on extending this cyclopropanation to other systems, aiming to expand the synthetic potential of this newly discovered process.

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5.4

Intramolecular Iridium(I)-Catalyzed Hydroarylation of Carbonyl Systems



5.4.1. Precedents of hydroarylations of carbonyl systems

Examples of TM-catalyzed additions to ketones using prefunctionalized substrates

Optically active tertiary alcohols are prevalent motifs in various pharmaceuticals, agrochemicals, and natural products (see **Figure 32**). Consequently, the development of direct and efficient bond-forming reactions for creating these motifs has been a longstanding challenge in organic chemistry.

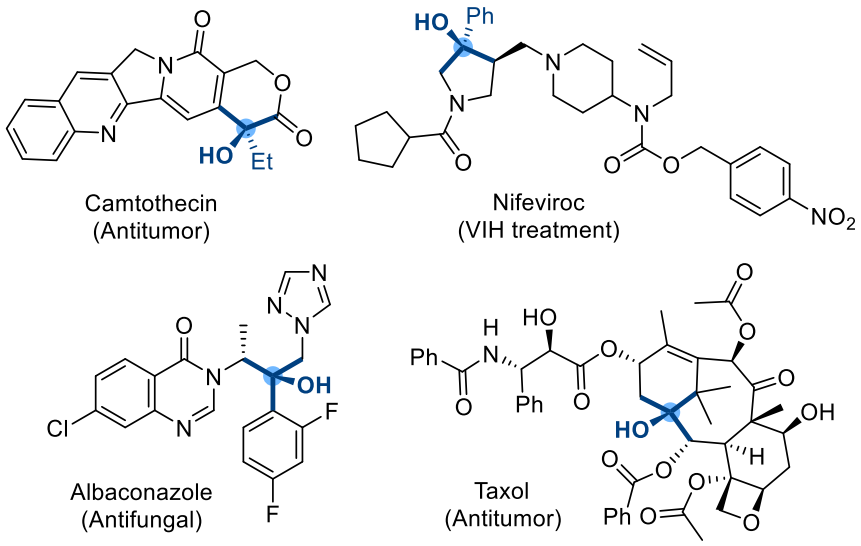


***Figure 32**: Relevant molecules bearing chiral tertiary alcohols.*

Historically, the Grignard reaction has been a popular approach for building tertiary alcohols. However, they require the use of highly reactive and basic organometallic reagents, such as organomagnesium, organozinc, or organoaluminium compounds, which often lack tolerance for functional groups, hindering their applicability in complex molecules.

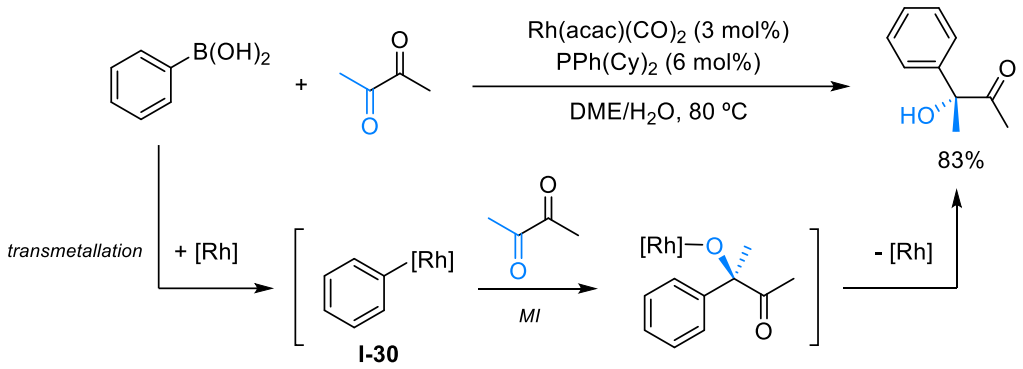
Furthermore, the sensitivity of these organometallic reagents to moisture and air complicates their handling and purification. This makes them impractical for transforming highly functionalized compounds or for late-stage modifications of bioactive molecules.

An attractive alternative to the use of stoichiometric organometallic reagents relies on the transition metal-catalyzed addition of arylboron compounds to ketones. Pioneering work by Feringa[158] and Chisholm[159] demonstrated the feasibility of this approach; by

[158] P. Y. Toullec, R. B. C. Jagt, J. G. de Vries, B. L. Feringa, A. J. Minnaard, *Org. Lett.*, **2006**, *8*, 2715–2718.
[159] G. R. Ganci, J. D. Chisholm, *Tetrahedron Lett*., **2007**, *48*, 8266–8269.

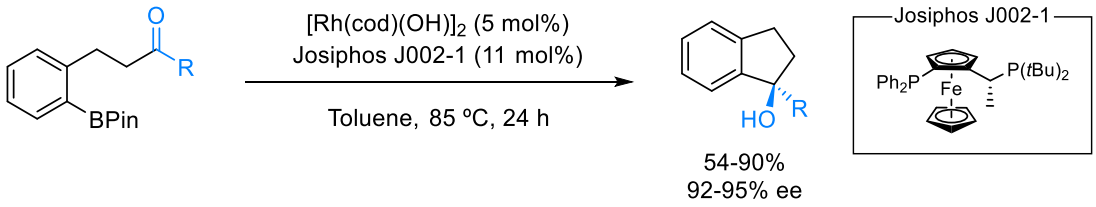
employing rhodium catalysis in the intermolecular addition of aryl boronic acids to highly activated carbonyls like in 1,2-diketones and 1,2-ketoesters.

In these reactions, the catalytic cycle begins with the transmetallation of the arylboron compound, forming an aryl-rhodium species **I-32**. This intermediate then undergoes migratory insertion of the ketone, followed by hydrolysis to produce the desired tertiary alcohol (see **Scheme 182**).



***Scheme 182**: Rh-catalyzed addition of arylboronic acids to ketones developed by Chisholm.*

During recent years, numerous methodologies based on this reactivity have been developed, especially in enantioselective variants.[160] An example of this is the work was published in 2016 by Sarpong's group, in which they carry out an intramolecular asymmetric addition using a chiral Rh catalyst bearing a Josiphos ligand (**Scheme 183**).[161]



***Scheme 183**: Enantioselective hydroarylation of ketones developed by Sarpong's group.*

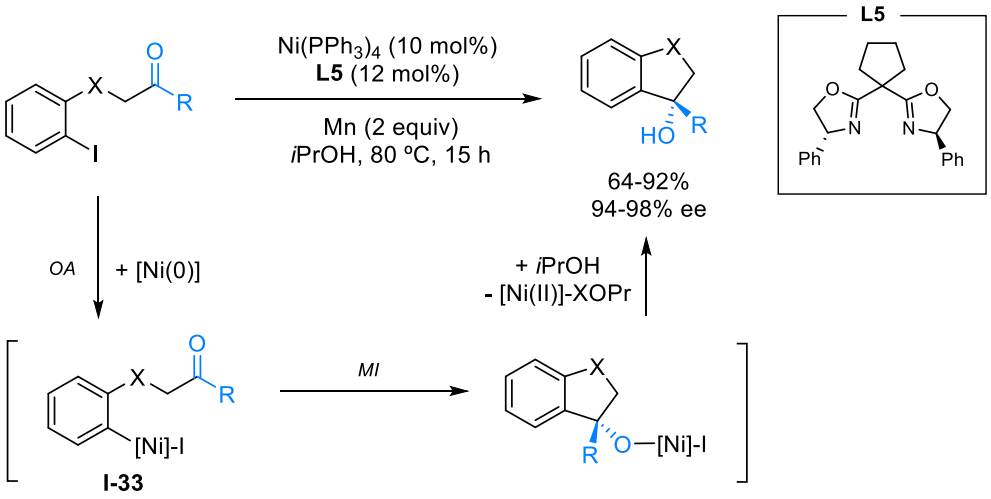
While this approach offers the benefit of using stable and less toxic arylboron compounds, it requires additional steps to introduce the boron functionality to the

[160] See examples: (a) L. Huang, J. Zhu, G. Jiao, Z. Wang, X. Yu, W.-P. Deng, W. Tang, *Angew. Chem. Int. Ed.*, **2016**, *55*, 4527–4531. (b) Y. Cai, L.-X. Ruan, A. Rahman, S.-L. Shi, *Angew. Chem. Int. Ed.*, **2021**, *60*, 5262–5267. (c) J. Zhu, Z. Li, J. Li, D. Tian, R. Xu, Z. Tan, Z. Chen, W. Tang, *Chem. Sci.*, **2023**, *14*, 1606–1612.

[161] G. M. Gallego, R. Sarpong, *Chem. Sci.*, **2012**, *3*, 1338–1342. For other intramolecular examples of this type, see: (a) G. Liu, X. Lu, *J. Am. Chem. Soc.*, **2006**, *128*, 16504–16505. (b) G. Liu, X. Lu, *Tetrahedron*, **2008**, *64*, 7324–7330. (c) J. Bouffard, K. Itami, *Org. Lett.*, **2009**, *11*, 4410–4413. (d) C. Nib, J. Gao, X. Fang, *Chem. Commun.*, **2020**, *56*, 2654–2657.

substrates. Moreover, the low atom economy of these reactions can limit their overall efficiency.

Another common strategy for hydroarylation involves the addition of aryl halides to carbonyls. Most of these processes employ nickel catalysts in conjunction with stoichiometric reducing agents.[162] As illustrated in **Scheme 184**, Lv and coworkers reported an asymmetric intramolecular addition of organohalides to ketones.[163] The mechanism involves the formation of **I-33** through oxidative addition of the C–I bond to a nickel(0) species, followed by migratory insertion of the ketone and protolysis, to release the product and a Ni(II) species, which is regenerated to Ni(0) by manganese.



***Scheme 184**: Ni-catalyzed enantioselective hydroarylation of ketones based on C–I oxidative addition.*

Precedents of hydroarylations of ketones based on C–H bond activation

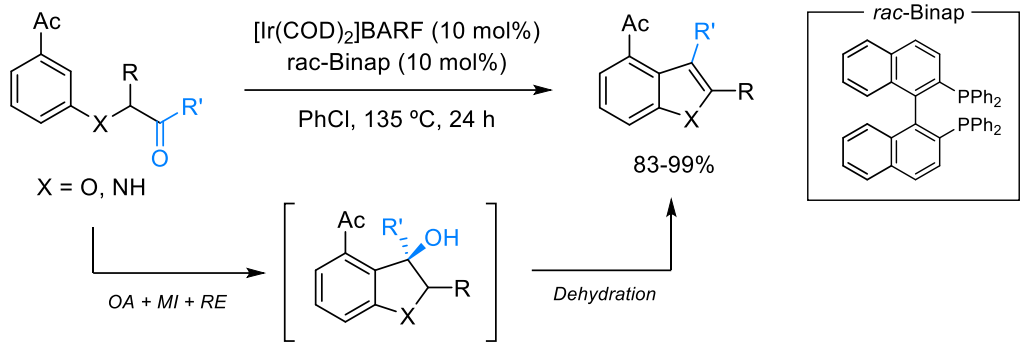
The direct hydroarylation of ketones would represent a highly atom economical manner to build tertiary alcohols, although precedents in this type of processes are scarce.

In 2009, Shibata reported an iridium(I)-catalyzed methodology for the construction of benzofurans and indoles based on C–H activation and addition to ketones, followed by a dehydration process. Although this approach does not produce chiral molecules, it represented the first example of C–H insertion into ketones (**Scheme 185**).[82]

[162] See examples: (a) J.-X. Hu, H. Wu, C.-Y. Li, W.-J. Sheng, Y.-X. Jia, J.-R. Gao, *Chem. Eur. J.*, **2011**, *17*, 5234–5237. (b) S. Huang, J. S. Zhou, *J. Am. Chem. Soc.*, **2024**, *146*, 12895–12900. (c) Z. Zhu, J. Xiao, M. Li, Z. Shi, *Angew. Chem. Int. Ed.*, **2022**, *61*, e202201370.

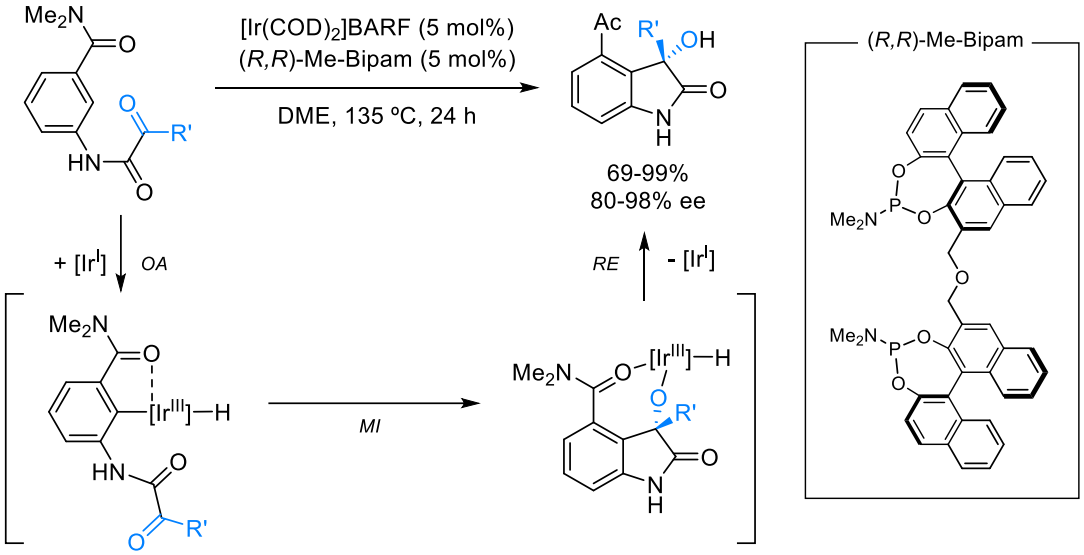
[163] Y. Li, W. Li, J. Tian, G. Huang, H. Lv, *Org. Lett.*, **2020**, *22*, 5353–5357.

[82] K. Tsuchikama, Y.-K. Hashimoto, K. *Endo*, T. Shibata, *Adv. Synth. Catal.*, **2009**, *351*, 2850–2854.



***Scheme 185**: Construction of benzofurans and indoles by Ir-catalyzed cyclodehydration reported by Shibata.*

Inspired by Shibata's pioneering efforts, Yamamoto introduced in 2014 a novel asymmetric synthesis of oxindoles, using an Iridium catalyst comprising a new bisphosphoramidite ligand (Me-Bipam). The strategic use of α-ketoamides as coupling partners allows to avoid any dehydration process, so the products hold the chiral center. Although the method provides excellent enantioselectivities, the substrate scope is rather narrow, very much limited to the synthesis of 3-hydroxyindolones (**Scheme 186**).[164]



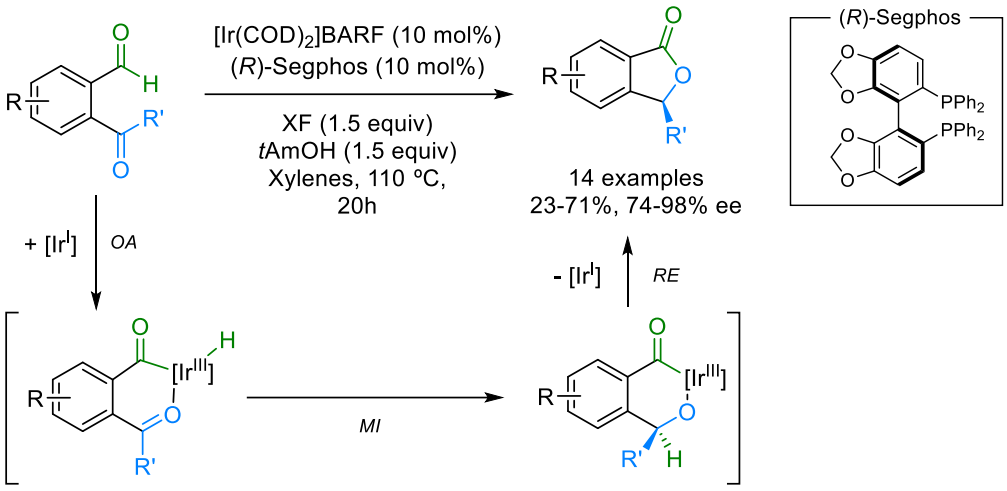
***Scheme 186**: Ir-catalyzed intramolecular hydroarylation of ketones developed by Yamamoto.*

In 2019, the same group reported a mechanistically related intramolecular hydroformylation of ketones, obtaining excellent enantiomeric excesses when using the chiral biphosphine I-Segphos, as depicted in **Scheme 187**.[165] This reaction starts with

[164] (a) T. Shirai, H. Ito, Y. Yamamoto, *Angew. Chem. Int. Ed.*, **2014**, *53*, 2658–2661. (b) T. Shirai, Y. Yamamoto, *Organometallics*, **2015**, *34*, 3459–3463.

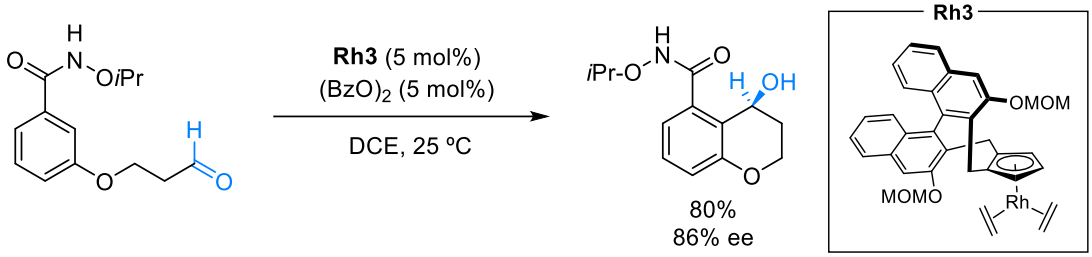
[165] T. Shirai, K. Sugimoto, M. Iwasaki, R. Sumida, H. Fujita, Y. Yamamoto, *Synlett*, **2019**, *30*, 972–976.

an oxidative addition of the iridium into the C–H bond of the aldehyde, its addition to the ketone, and a final C–O reductive elimination to give the observed lactones.



***Scheme 187**: Ir-catalyzed hydroformylation of ketones developed by Yamamoto.*

Cramer and co-workers reported in 2015 that a chiral cyclopentadienyl rhodium (III) catalyst (**Rh3**), related to **Rh1** and **Rh2** (pages 113 and 150, respectively), could also be used to promote intramolecular hydroarylations of aldehydes. The proposed mechanism entails a CMD type of C–H activation, followed by the addition of the resulting aryl Rh(III) species to the linked aldehyde. Eventually, a protolysis delivers the product (**Scheme 188**).[166] The enantioselectivities are generally modest, and the scope of the process limited to building chiral 5-hydroxychromanes.



***Scheme 188**: Rh(III)-catalyzed hydroarylation of aldehydes by Cramer.*

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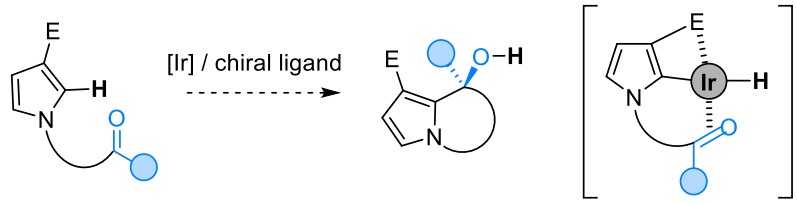
[166] B. Ye, N. Cramer, *Synlett*, **2015**, *26*, 1490–1495.

In summary, the number of hydroarylation processes of carbonyl moieties involving an initial C(sp^2)–H activation is very low and the methods present very narrow scopes. Moreover, the development of enantioselective variants is essentially unknown. In consequence, uncovering new catalytic hydroarylations of ketones, particularly in asymmetric fashion, remains an attractive goal.

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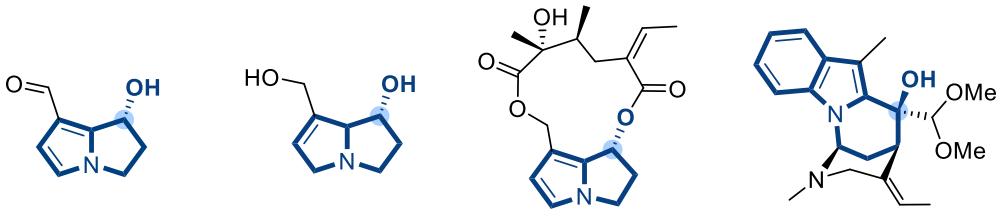
5.4.2. Objectives

Given the lack of methodologies for ketone hydroarylations based on C–H bond activation processes, we decided to explore the use of pyrrole-ketone or aldehyde precursors as probes to test the viability of these reactions, using iridium catalysis (**Scheme 189**).



***Scheme 189**: TM-catalyzed addition of heteroaromatic C–H bonds into ketones or aldehydes.*

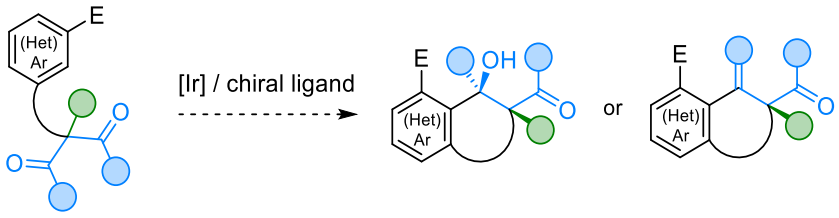
This approach could potentially yield chiral heterocyclic systems containing tertiary and secondary alcohols in an enantioselective manner, a structural motif prevalent in natural products, like those shown in **Scheme 190**.



Hydroxydadaidal | Retronecine | Dehydrosenecionine | Alstoscholarisine J

***Scheme 190**: Related heteropolycyclic natural products bearing oxygen-containing stereocenters.*

Considering that the reported precedents suggest that concomitant dehydration processes are highly favored, thus eroding the newly generated stereocenters, the viability of a desymmetrizing hydroarylation, wherein at least one of the two stereocenters initially generated is conserved, will also be explored (**Scheme 191**).

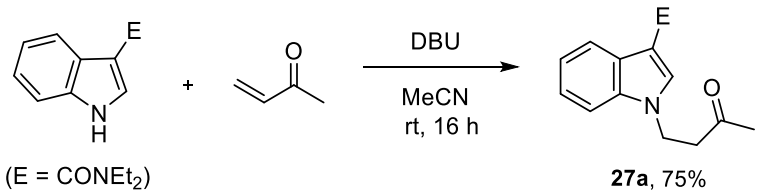


***Scheme 191**: General scheme of an intramolecular desymmetrizing hydroarylation of diketones.*

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5.4.3. Preliminary studies

Our studies commenced with the preparation of a precursor related to those described in previous chapters, but featuring a ketone instead of an alkene or allene. Thus, the synthesis of the 4-indolyl-butan-2-one **27a** was achieved in a single step via the 1,4-addition to 3-buten-2-one depicted in **Scheme 183**.



Scheme 192: *General synthesis of model substrate* ***27a****.*

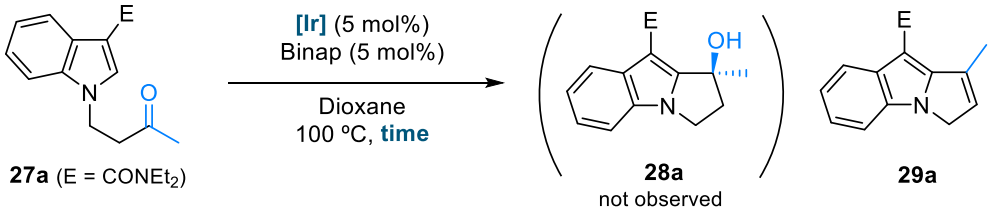
We then tested the catalyst formed in situ from $[Ir(COD)_2]BARF$ and Binap, previously used to promote *exo*-selective intermolecular hydroarylations of other unsaturated systems, observing the quantitative formations of the achiral pyrroloindole **29a**, instead of the initially expected dihydropyrroloindole **28a** (**Table 10**, entry 1). This result is consistent with the cases previously reported by Shibata (see **Scheme 185**).[82]

Reducing the reaction time to 2 hours also gave **29a** (detected by NMR in the crude mixture, entry 2). The use of $[Ir(COD)_2]BF_4$ as precatalyst also provided the same outcome (entry 3). Other bisphosphines were evaluated, but mixtures of starting material and **29a** were obtained, without any trace of **28a** (based on NMR and GS-MS).

Trying to trap the desired product, **28a**, we repeated the reaction with the addition of trimethylsilyl chloride and acetyl chloride. However, in these cases, only starting material was recovered (entries 4 and 5).

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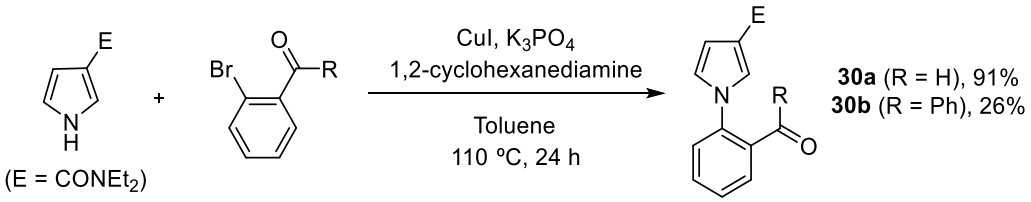
***Table 10**: Preliminary experiments about hydroarylation of precursor **27a**.*



27a (E = $CONEt_2$) **28a** not observed **29a**

Entry	[Ir]	Time (h)	Additive	Outcome
1	$[Ir(COD)_2]$BARF	16	-	**29a**, full conv.
2	$[Ir(COD)_2]$BARF	**2**	-	**29a**, full conv.
3	$[Ir(COD)_2]$**BF_4**	16	-	**29a**, full conv.
4	$[Ir(COD)_2]$BARF	16	**TMSCl**	**27a** recovered
5	$[Ir(COD)_2]$BARF	16	**AcCl**	**27a** recovered

Given the reaction's apparent selectivity toward the formation of dehydrated products **29**, we prepared new substrates that would impede the dehydration, with an *o*-substituted phenyl linker between the pyrrole and the ketone. These precursors of type **30** were synthesized in a single step via an Ullmann coupling between the corresponding N-H pyrrole and the aryl bromide, as outlined in **Scheme 193**.



(E = $CONEt_2$)

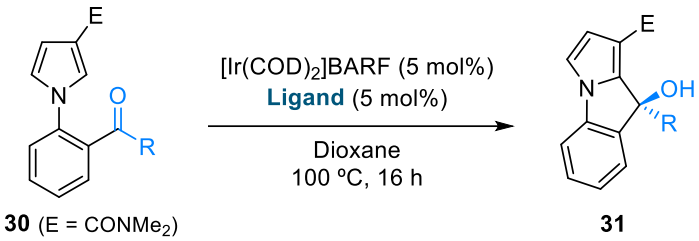
***Scheme 193**: General synthesis of precursors of type **30**.*

When aldehyde **30a** was reacted with $[Ir(COD)_2]$BARF/(*S*)-Binap, the desired alcohol **31a** was obtained in an excellent 89% yield. Unfortunately, analysis by chiral HPLC revealed very low enantioselectivity (53:47 er, **Table 11**, entry 1). In an effort to improve this enantiomeric ratio, we explored other chiral ligands, instead of Binap. While (*S*)-Binapine and I-DTBM-Segphos afforded **31a** in moderate yields as a racemic mixture (entries 2 and 3), I-BTFM-Garphos provided the product with a modest 60:40 enantiomeric ratio, and a yield of 41% (entry 4).

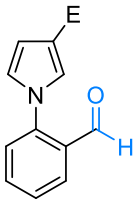
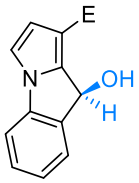
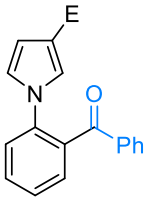
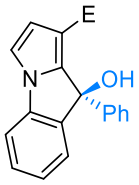
Related results were obtained when employing the analogous phenyl ketone **30b**. Both (*S*)-Binap and (*S*)-Binapine led to the quantitative formation of racemic **31b** (**Table 11**, entries 5 and 6). However, in this case, the use of I-BTFM-Garphos did not lead to any product (entry 7).

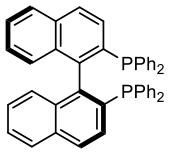
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***Table 11**: Reactions of different precursors of type **30** with different Ir(I)-bisphosphine catalysts.*

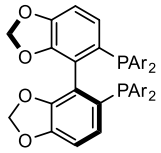


30 (E = $CONMe_2$) **31**

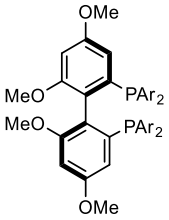
Entry	Substrate	Ligand	Product	Yield (%)	er
1	 **30a**	*(S)*-Binap	 **31a**	89	53:47
2		*(S)*-Binapine		38	50:50
3		*l*-DBTM-Segphos		64	50:50
4		*l*-BTFM-Garphos		41	60:40
5	 **30b**	*(S)*-Binap	 **31b**	99	50:50
6		*(S)*-Binapine		99	50:50
7		*l*-BTFM-Garphos		0	-



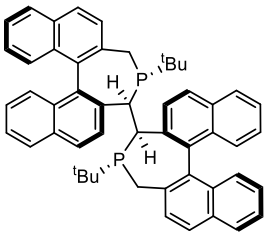
(*S*)-Binap



Ar =3,5-^{t}Bu-2,6-OMe
(*S*)-DTBM-Segphos



Ar = 3,5-$(CF_3)_2C_6H_3$
(R)-BTFM- Garphos



(*S*)-Binapine

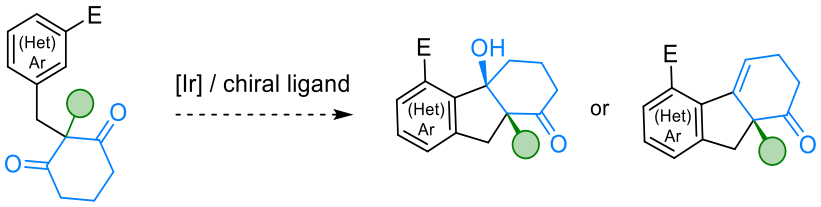
Although the alcohols **31** were not formed in an enantioselective manner, we do not rule out that this could be eventually achieved by finding the appropriate chiral ligand.

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5.4.4. Desymmetrizing hydrocarbonation of 1,3-diketones

Given the results obtained in section 5.4.3, where either the stereocenters are lost or products were obtained with very low enantioselectivity, we decided to explore a desymmetrization strategy with 1,3-diketones.

Our previous work with alkenes demonstrated the viability of this approach,[167] and its successful application to carbonyls could potentially lead to the enantioselective synthesis of polycyclic structures bearing at least one carbon quaternary stereocenter, as depicted in **Scheme 194**.



***Scheme 194**: General scheme of the desymmetrizing hydroarylation strategy.*

Considering the natural prevalence of these motifs, and the facility of the preparation of the required precursors, our research in this endeavor was focused on aryl instead of heteroaryl C–H donors. Indeed, using cyclic prochiral 1,3-diketones as acceptors, we could easily obtain structural cores that are present in some biologically relevant molecules such as Daldinone C, Taiwaniaquinol B and Lecanindole D, depicted in **Figure 33**.

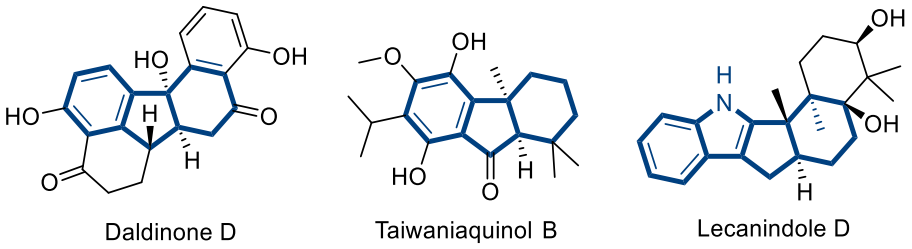


***Figure 33**: Natural products with a decahydrofluorene skeleton.*

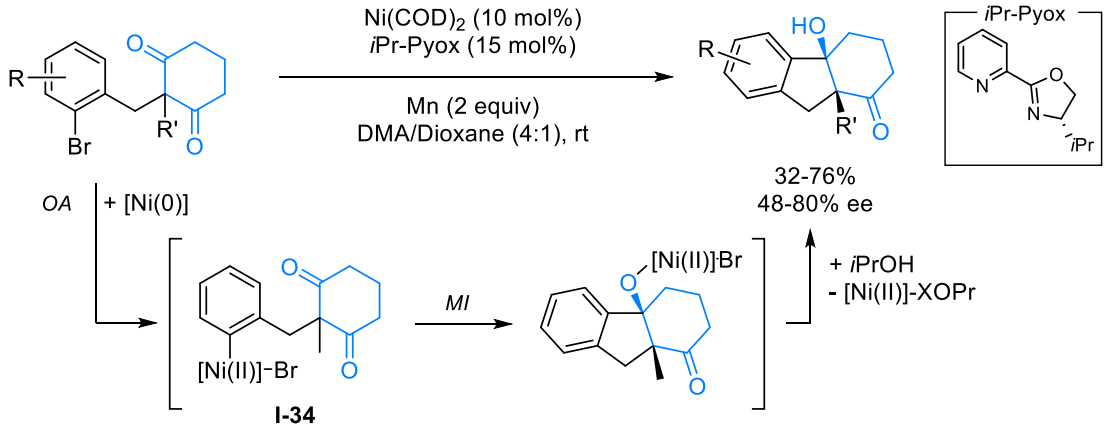
The following section will provide an overview of several related catalytic desymmetrization processes of substrates bearing prochiral 1,3-diketones, with a particular focus on those processes that involve additions of transient aryl-metal species to carbonyl moieties.

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[167] A. Arribas, M. Calvelo, D. F. Fernández, C. A. B. Rodrigues, J. L. Mascareñas, F. López, *Angew. Chem. Int. Ed.*, **2021**, *60*, 19297–19305.

Precedents about TM-catalyzed desymmetrization reactions of 1,3-diketones

In 2020, Zhou and Xu reported a desymmetrizing hydroarylation of diketones that yields tricyclic compounds with high diastereo- and enantioselectivities, by employing the nickel catalyst generated in situ from $Ni(COD)_2$ and *i*Pr-Pyox ligand. The process is initiated with the oxidative addition of the aromatic C–Br bond to the Ni(0) complex, to form aryl-metal species like **I-34**. This is followed by the migratory insertion of one of the carbonyls of the pendant 1,3-diketone. A subsequent hydrolysis step affords the final product (**Scheme 195**).[168] The ee's remained generally modest (up to 80%).

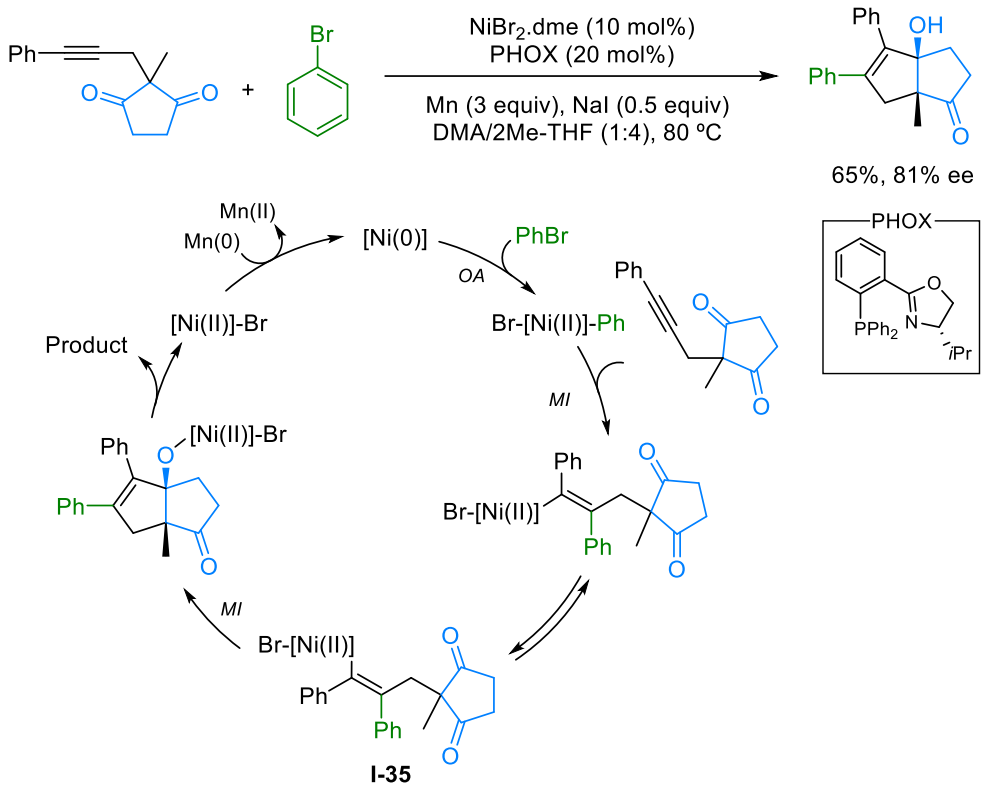


***Scheme 195**: Ni-catalyzed desymmetrizing hydroarylation of cyclic 1,3-diketones.*

In the same year, Kong's group reported a related process that yields polycyclic compounds with two stereocenters with high enantio- and diastereo-selectivity. The reaction begins with the oxidative addition of an aryl bromide to a Ni(0) catalyst (generated in situ by reduction of a Ni(II) precatalyst with Mn). This is followed by the migratory insertion of an alkyne into the Ar–Ni bond. Subsequent cis/trans isomerization yields **I-35**, which evolves via a second migratory insertion of one of the diketone carbonyls into its Ni–C bond (**Scheme 196**).[169]

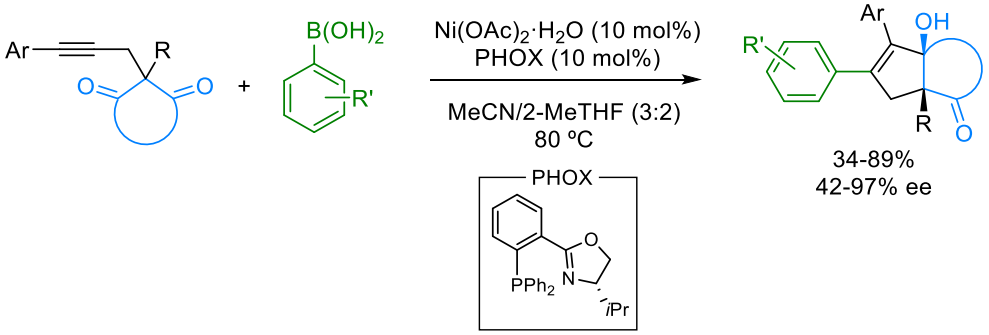
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[168] P. Zhou, T. Xu, *Chem. Commun.*, **2020**, *56*, 8194–8197.
[169] Z. Zhou, W. Liu, W. Kong, *Org. Lett.*, **2020**, *22*, 6982–6987.



***Scheme 196**: Ni-catalyzed desymmetrizing process involving double migratory insertion developed by Kong and coworkers.*

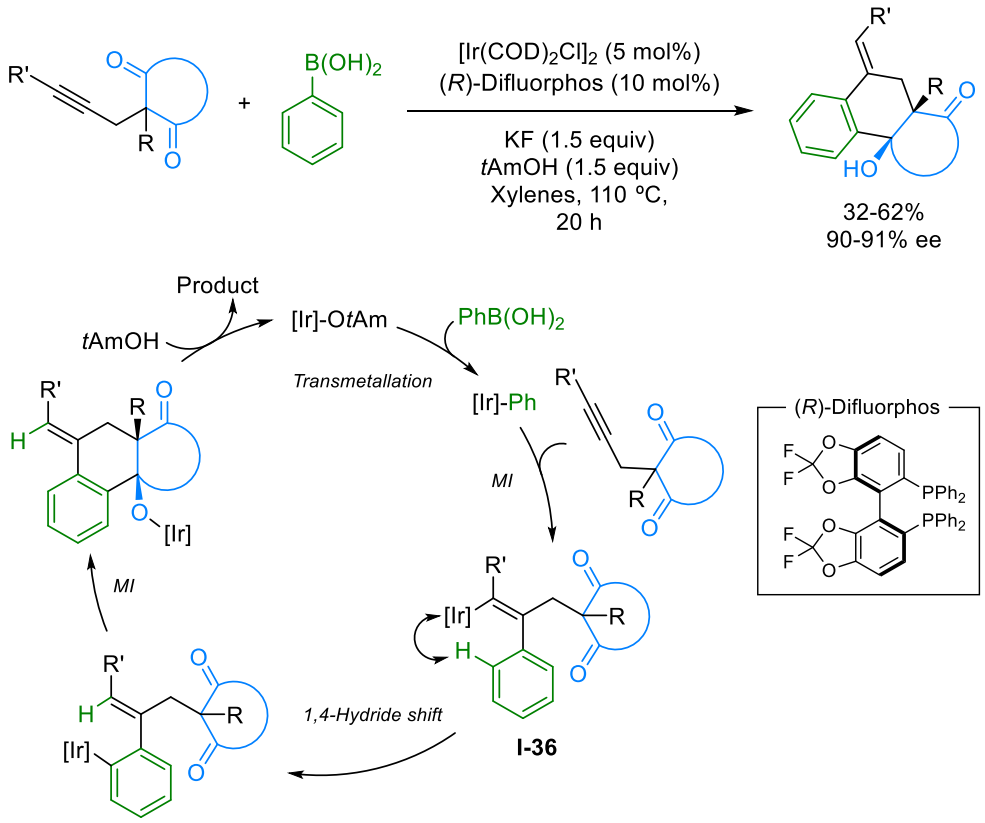
In 2016, Lam and colleagues reported a similar process. However, in this case, aryl-nickel species are generated through a transmetallation using aryl boronic acids as starting materials, as opposed to the oxidative addition pathway of the preceding examples (**Scheme 197**).[170]



***Scheme 197**: Ni-catalyzed desymmetrizing process initiated by transmetallation, developed by Lam.*

[170] C. Clarke, C. A. Incerti-Pradillos, H. W. Lam, *J. Am. Chem. Soc.*, ***2016**, 138,* 8068–8071. See also: B. M. Bocknack, L.-C. Wang, M. J. Krische, *Proc. Natl. Acad. Sci. USA **2004**, 101,* 5421–5424.

Lam and coworkers also reported an interesting tandem process catalyzed by iridium (I) to yield tricyclic compounds bearing multiple stereocenters with high er and dr.[171] The reaction begins with a transmetallation step using phenylboronic acid to form an aryl–iridium species, which then undergoes migratory insertion of an alkyne to generate intermediate **I-36**. This is followed by a 1,4-hydrogen shift between the metal center and the aromatic hydrogen, to generate an aryl-iridium species that adds to one of the carbonyls of the 1,3-diketone, through a very effective desymmetrization step (see **Scheme 198**). In the following years, numerous processes similar to Lam's examples were reported employing Rh(I) catalysis instead of iridium.[172]



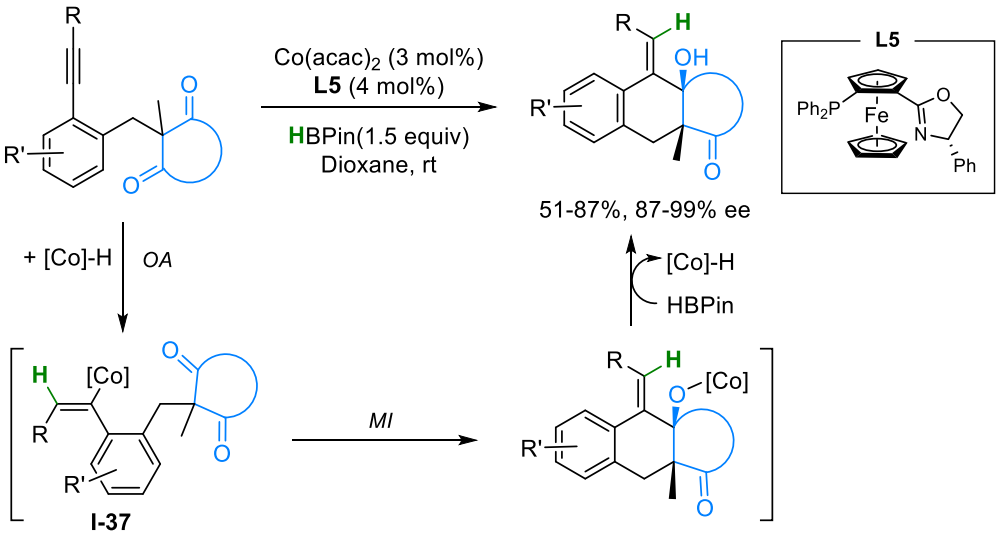
***Scheme 198**: Lam's Ir-catalyzed arylative cyclization of alkynones by 1,4-Iridium migration.*

These cascade processes are not limited to the initial generation of aryl-metal species. For instance, in 2013, Jia reported that the in situ generated cobalt hydride species, from $Co(acac)_2$ and HBPin, undergoes a migratory insertion of an alkyne to form the alkenyl cobalt species **I-37**. Addition of this nucleophilic moiety to the prochiral diketone, followed

[171] B. M. Partridge, J. S. González, and H. W. Lam, *Angew. Chem. Int. Ed.*, **2014**, *53*, 6523–6527.

[172] Related Rh(I) catalyzed processes involving 1,4-hydride shift: (a) B. M. Partridge, M. Callingham, W. Lewis, H. W. Lam, *Angew. Chem. Int. Ed.,* **2017**, *56*, 7227–7232. (b) A. Groves, J. Sun, H. R. I. Parke, M. Callingham, S. P. Argent, L. J. Taylor, H. W. Lam, *Chem. Sci.,* **2020**, *11*, 2759–2764. (c) A. Selmani, S. Darses, *Org. Lett.*, **2020**, *22*, 2681–2686.

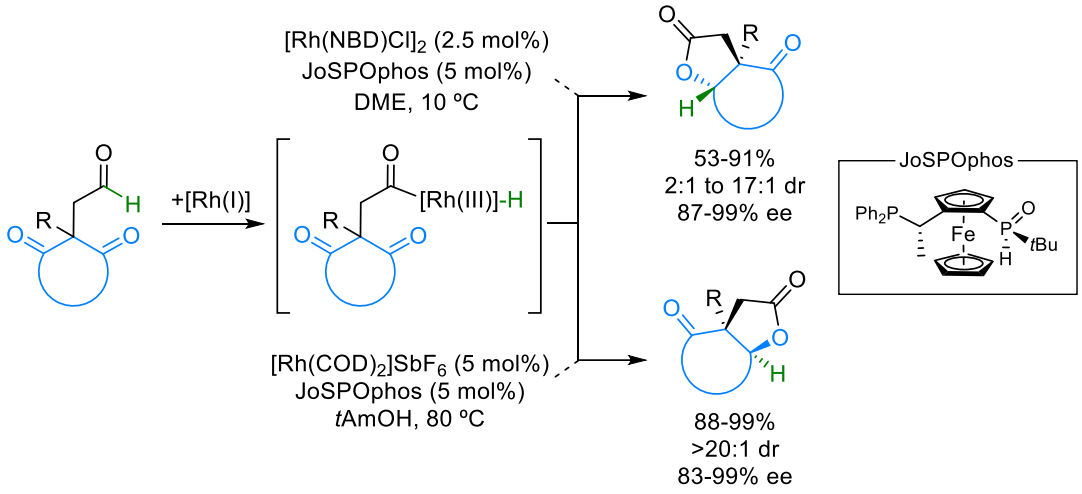
by the catalyst regeneration mediated by HBPin, yields the observed product (**Scheme 199**).[173] Similar strategies utilizing metal-boron species have also been studied.[174]



***Scheme 199**: Co-hydride-catalyzed desymmetrizing hydrocarbonation of diketones developed by Jia.*

Aldehydes have also been used to perform desymmetrizing hydroacylation processes. Dong and colleagues reported in 2016 an innovative process involving the intramolecular C–H insertion of aldehydes into 1,3-diketones.[175] This asymmetric hydroformylation reaction, catalyzed by Rh(I)/JoSPOphos complexes, exhibits remarkable selectivity toward both *syn* or *anti* γ-lactones. Thus, the selectivity is adjusted by appropriate selection of the rhodium precatalyst and reaction conditions (**Scheme 200**). Importantly, this study provides the only documented case of a diketone desymmetrization through a TMC C–H bond activation.

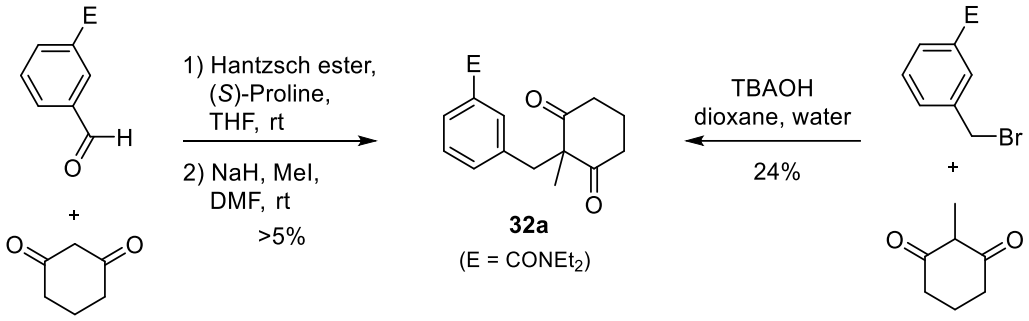
[173] R.-X. Liang, H.-W. Tang, J.-L. Liu, J.-F. Xu, L.-J. Chen, Y.-X. Jia, *Chem. Sci.*, **2023**, *14*, 6393–6398. See also: (a) J. Deschamp, O. Riant, *Org. Lett.*, **2009**, *11*, 1217–1220. (b) J. Ou, W.-T. Wong, P. Chiu, *Tetrahedron*, **2012**, *68*, 3450–3456.
[174] (a) A. R. Burns, J. S. González, H. W. Lam, *Angew. Chem. Int. Ed.*, **2012**, *51*, 10827–10831. (b) P. Zheng, X. Han, J. Hu, X. Zhao, T. Xu, *Org. Lett.*, **2019**, *21*, 6040–6044. (c) Y.-S. Zhao, X.-Q. Tang, J.-C. Tao, P. Tian, G.-Q. Lin, *Org. Biomol. Chem.*, **2016**, *14*, 4400–4404.
[175] X. Wu, Z. Chen, Y.-B. Bai, V. M. Dong, *J. Am. Chem. Soc.*, **2016**, *138*, 12013–12016.



***Scheme 200**: Rh(I)-catalyzed desymmetrizing hydroacylation of diketones developed by Dong.*

Initial studies

To investigate the feasibility of our strategy using iridium catalysts, we selected compound **32a**, bearing a cyclic 2-substituted-1,3-diketone, as a model precursor. Initially, we attempted to synthesize this substrate through an organocatalytic reaction between 3-formyl-diethylbenzamide and 1,3-cyclohexanedione,[176] followed by methylation with MeI. However, due to the low yields and reproducibility problems observed, we opted for an alternative approach consisting of the alkylation of 2-methyl-1,3-cyclohexanedione with 3-bromomethyl-diethylbenzamide, as outlined in **Scheme 201**.



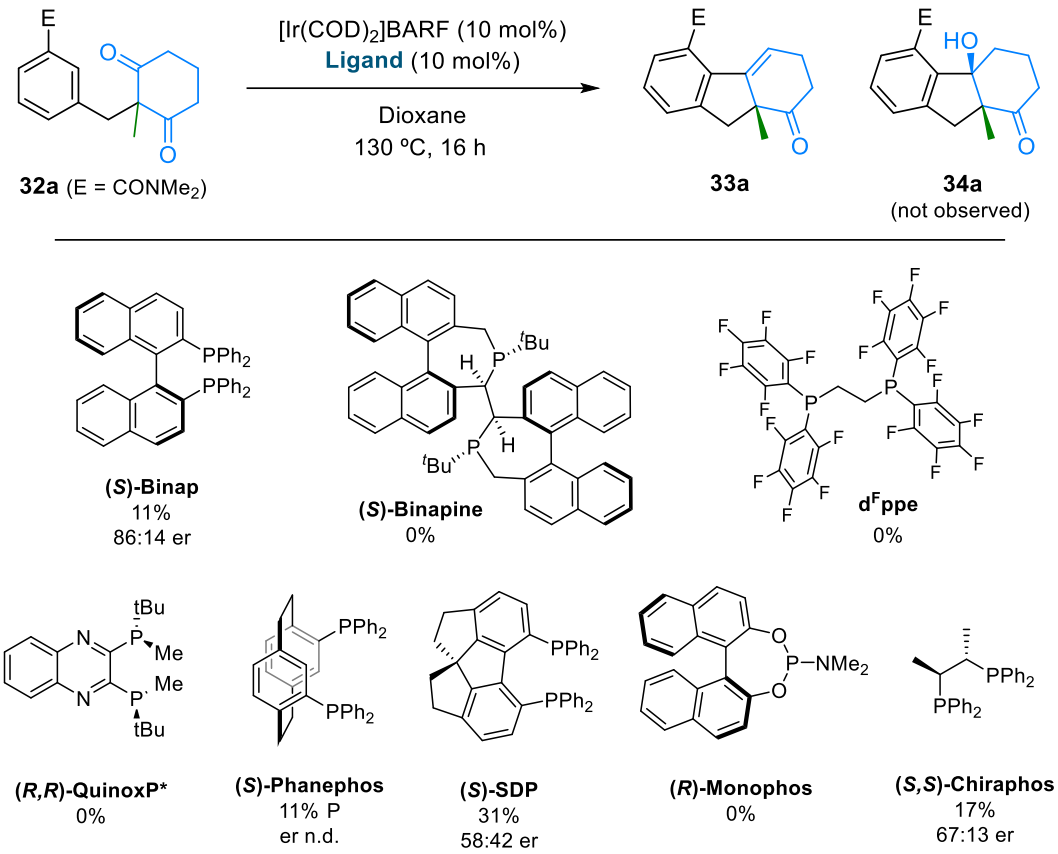
***Scheme 201**: General synthesis of substrate **32a**.*

Then, we evaluated the performance of various chiral iridium(I) complexes, previously utilized for *exo*-selective intermolecular hydroarylations of alkenes and allenes. Heating a dioxane solution of **32a** in the presence of 10 mol% of the complex in situ generated from [Ir(COD)$_2$]BARF and (*S*)-Binap, at 130 ºC, resulted in the formation of product **33a** in low yield, although with a promising 86:14 er. The use of the bulky biphosphine (S)-

[176] D. B. Ramachary and M. Kishor, *J. Org. Chem.* **2007**, *72*, 14, 5056–5068.

Binapine, or the electron-deficient d^{F}ppe led to recovery of the starting material. Same outcome was obtained with QuinoxP* and Phanephos or even I-Monophos, which worked in the hydroarylation of ketones of Yamamoto.[164]

With the spirobisphosphine (*S*)-SDP, previously used by our group in Ir-catalyzed hydrocarbonations , we obtained a 32% yield, but low enantioinduction (58:42 er). On the other hand, a simple ligand like (*S,S*)-Chiraphos, was able to promote this transformation with a moderate er (67:13), but low yield (**Scheme 202**).

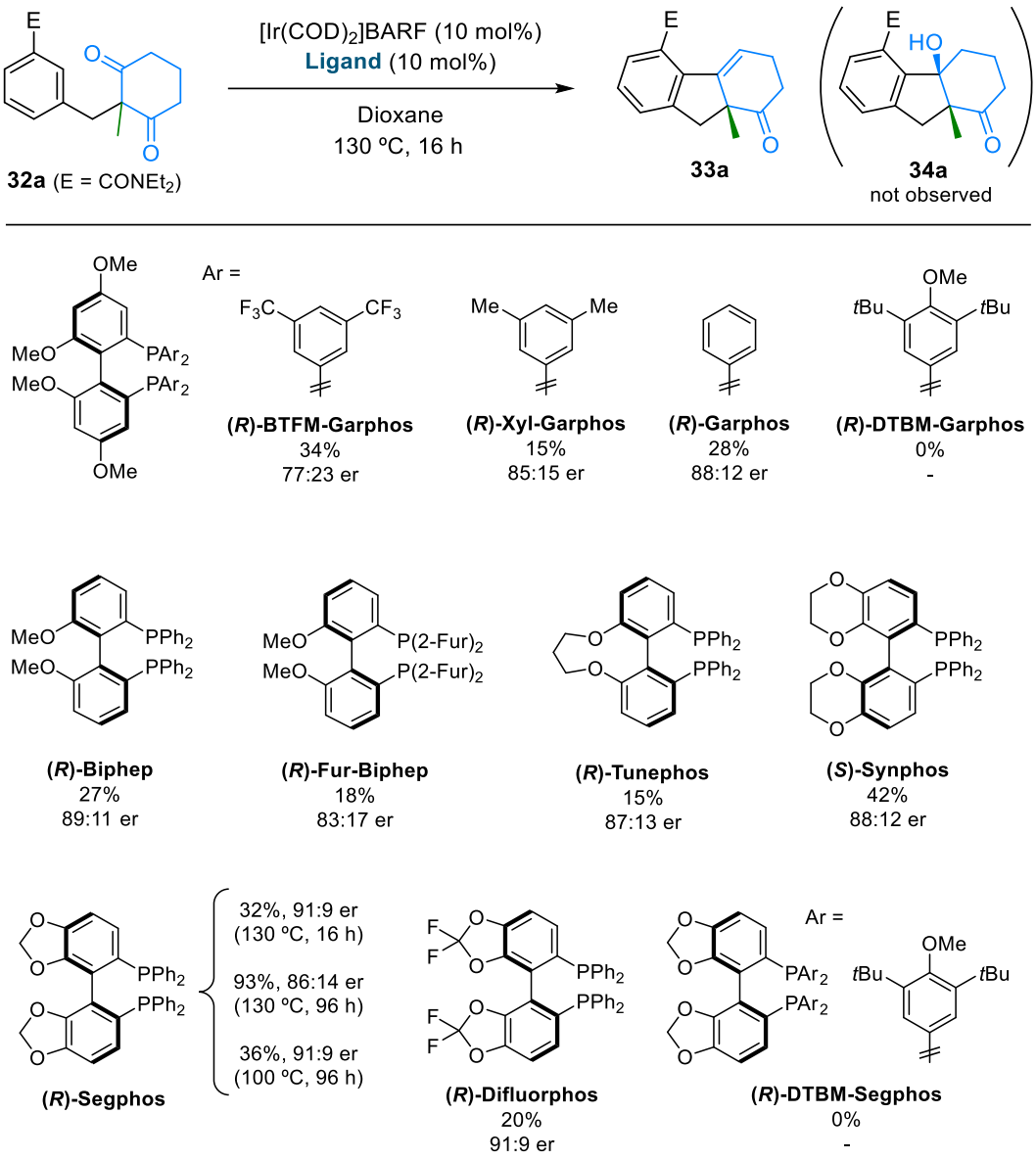


***Scheme 202**: Initial screening of ligands for the Ir-catalyzed hydroarylative desymmetrization of **32a**.*

On these bases, we next explored other C2-symmetric bisphosphines, related to Binap. Using I-BTFM-Garphos, we obtained the dehydrated product **33a** in a modest 34% yield, with a moderate enantiomeric ratio of 77:23. The analogous I-DM-Garphos promoted higher enantioselectivity (85:15 er) yet led to a diminished yield of 15%. The unsubstituted I-Garphos afforded a 28% yield with an improved enantiomeric ratio of 88:12. Conversely, the sterically hindered I-DTBM-Garphos ligand failed to catalyze the transformation, even under prolonged reaction times (see **Scheme 203**).

Building upon the successful results with Garphos ligands, we investigated a series of related analogues. I-Biphep displayed comparable performance to I-Garphos, whereas its derivatives I-Fur-Biphep and I-Tunephos exhibited diminished yields and enantioselectivities. The sterically hindered I-DTBM-Segphos resulted ineffective. In contrast, I-Synphos, I-Segphos, and I-Difluorphos proved to be efficient catalysts for the cyclodehydration of **32a**, affording generally better yields and enantioselectivities. Optimization studies with I-Segphos revealed that extending the reaction time to 96 hours improved the yield to 96% at the expense of enantioselectivity (83:17 er). Conversely, lowering the reaction temperature to 100 °C for 96 hours provided 36% of **33a** in 91:1 er (see **Scheme 203**).

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***Scheme 203**: Screening of oxygenated chiral ligands for the Ir-catalyzed hydroarylative desymmetrization of **32a**.*

In these optimization experiments, we observed promising enantioselectivities but consistently low conversions. We initially attributed the low yields to potential catalyst inhibition by water generated during the reaction. Nevertheless, when substrates with other directing groups such as 1-pyrrolidinylmethanone (**32b**) and dimethylamide (**32c**) were tested under the same conditions we observed significantly improved yields, exceeding 96%; however, enantiomeric ratios slightly dropped to 86:14 and 87:13, respectively (**Table 12**, entries 3 and 5).

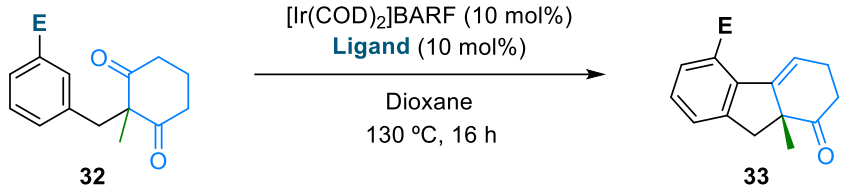
These results prompted us to re-evaluate the I-DTBM-Segphos ligand, which had been unsuccessful with precursor **32a** (entry 2). Interestingly, the corresponding Ir(I) was able to promote the reaction of **32b**, to afford **33b** in 90% yield and an 88:12 er (entry 4). This

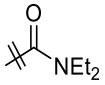
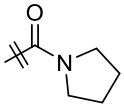
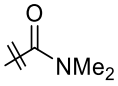
result was further improved using the dimethyl carboxamide precursors **32c** , which afforded **33c** in 94% yield and 90:10 er (entry 6).

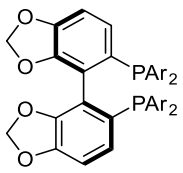
Comparable results were obtained with I-DTMS-Segphos and I-DTMS-Garphos, affording **33c** in high yields but with 86:14 and 85:15 er, respectively (entries 10-11). However, reactions with other ligands like I-BTFM-Garphos, I-BTFM-Binap, and I-BTFM-Synphos did not reach the 85:15 er (entries 7-9). When employing the I-Sunphos ligand, the product was formed in 91% yield, but a modest 71:29 er, a result that suggest the relevance of fine tuning the bisphosphine bite angle for the enantioinduction process.

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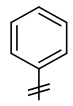
***Table 12**: Optimization of cyclodehydration of precursors **32a-c**. Carried out in collaboration with Dr. Carlos Lázaro.*



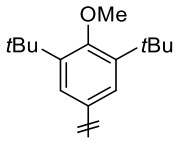
Entry	E		Ligand	Yield (%)	er
1		(**32a**)	I-Segphos	32	90:10
2			I-DTBM-Segphos	0	-
3		(**32b**)	I-Segphos	99	86:14
4			I-DTBM-Segphos	90	88:12
5		(**32c**)	I-Segphos	96	85:15
6			I-DTBM-Segphos	94	90:10
7			I-DTBM-Garphos	34	84:16
8			I-DTBM-Binap	75	85:15
9			I-DTBM-Synphos	27	85:15
10			I-DTMS-Segphos	98	86:14
11			I-DTMS-Garphos	88	85:15
12			I-Sunphos	91	71:29



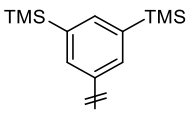
Ar =



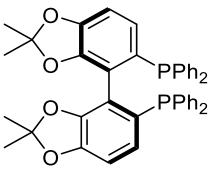
(*R*)-Segphos



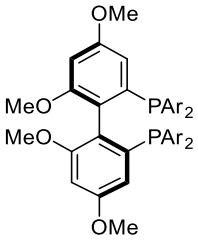
(*R*)-DTBM-Segphos



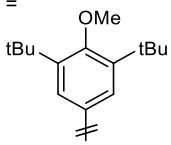
(*R*)-DTMS-Segphos



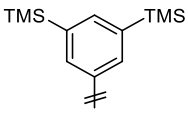
(*R*)-Sunphos



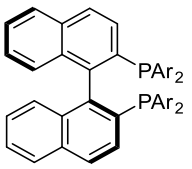
Ar =



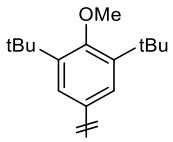
(*R*)-DTBM-Garphos



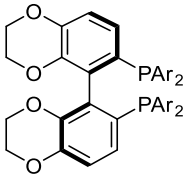
(*R*)-DTMS-Garphos



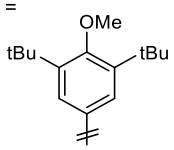
Ar =



(*R*)-DTBM-Binap



Ar =

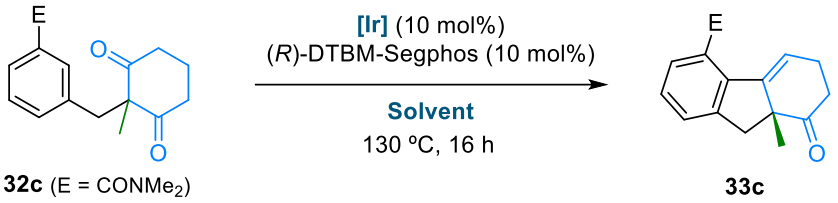


(*S*)-DTBM-Synphos

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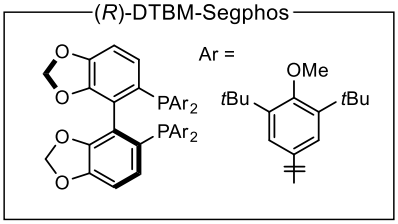
Then, the influence of the iridium precursor and the solvent was assessed. With iridium complexes like $[Ir(COD)_2]BF_4$ or $[Ir(COD)_2]Otf$, we observed negligible conversions (**Table 13**, entries 2 and 3). When using other solvents like toluene, fluorobenzene or 1,2-dichloroethane, instead of dioxane, there are low conversions, as deduced from NMR analysis of the crude mixtures (entries 4-6). On the other hand, solvents like dimethoxyethane and 2-methyltetrahydrofuran also resulted in complete inhibition of the reaction (entries 7 and 8). These results confirmed $[Ir(COD)_2]BARF$ and dioxane as the best combination to promote the transformation of **32c**.

***Table 13**: Influence of iridium precatalysts and solvents in the cyclodehydration of **32c**.*



32c (E = $CONMe_2$) **33c**

Entry	[Ir]	Solvent	Yield (%)	er
1	$[Ir(COD)_2]BARF$	Dioxane	94	90:10
2	$[Ir(COD)_2]\mathbf{BF_4}$	Dioxane	<5	nd
3	$[Ir(COD)_2]\mathbf{Otf}$	Dioxane	<5	nd
4	$[Ir(COD)_2]BARF$	**Toluene**	<5	nd
5	$[Ir(COD)_2]BARF$	**Fluorobenzene**	<5	nd
6	$[Ir(COD)_2]BARF$	**DCE**	<5	nd
7	$[Ir(COD)_2]BARF$	**DME**	<5	nd
8	$[Ir(COD)_2]BARF$	**2-MeTHF**	<5	nd

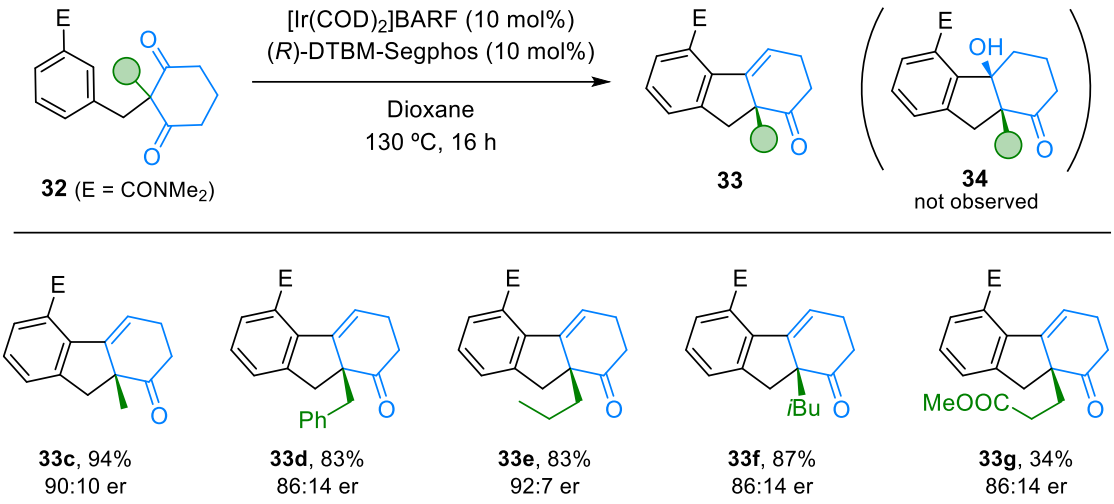


Scope

With the optimized reaction conditions, a series of substrates bearing different substituents at the 2-position of the diketone were evaluated. Substrates **32d**, **32e** and **32f** afforded the corresponding dehydration products **33** in good yields and with acceptable enantiomeric ratios. The structure of **33d** was established by X-ray

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crystallography (**Figure 34**). Introducing an ester functionality into the substrate led to the formation of **33g** with a comparable enantiomeric ratio, albeit in a lower yield of 34% (see **Scheme 204**).



***Scheme 204**: Scope of products **33** bearing different substituents at the quaternary carbon center. Carried out in collaboration with Dr. Carlos Lázaro.*

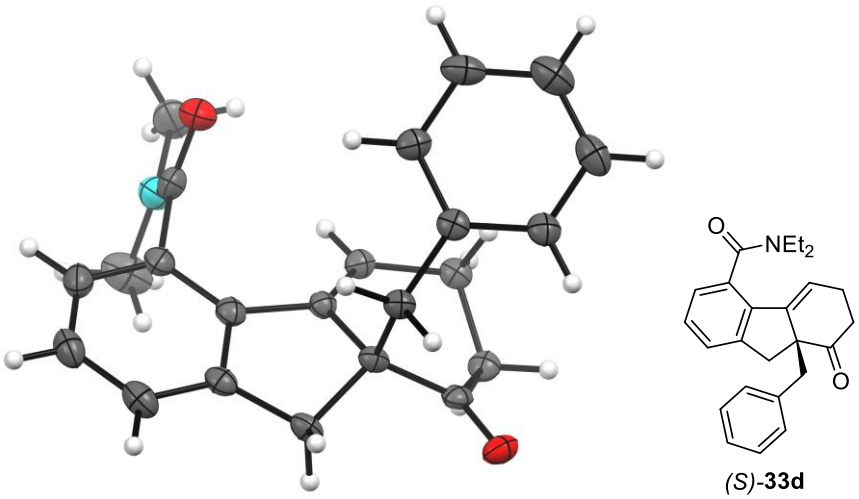
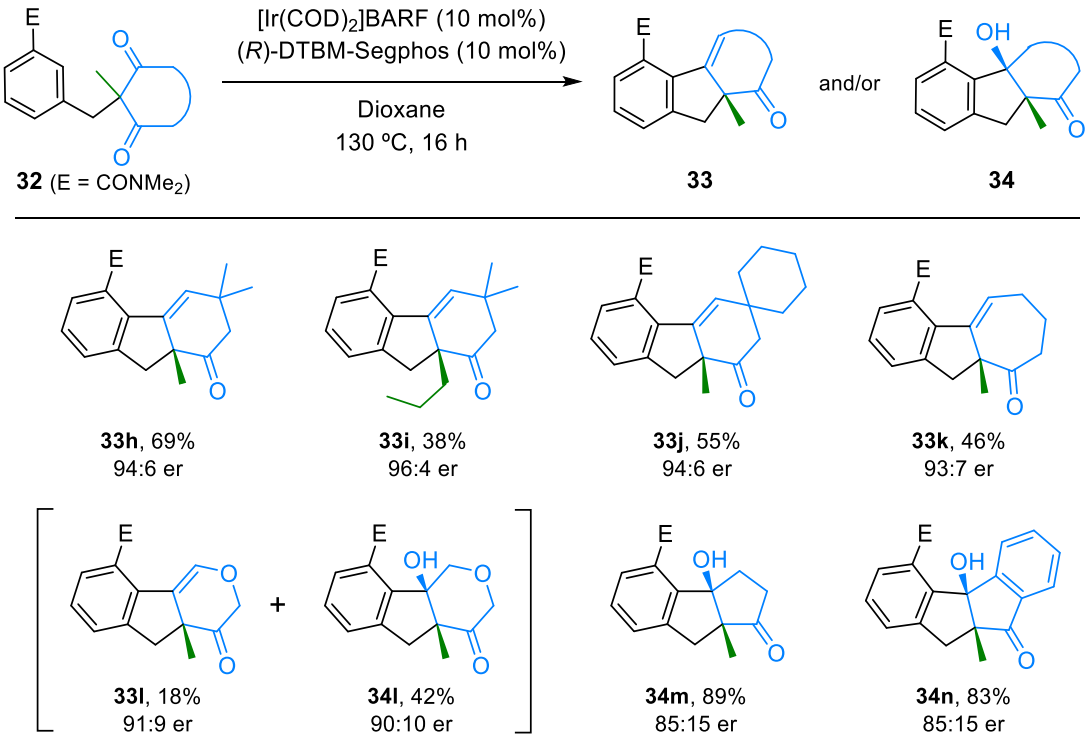


***Figure 34**: X-Ray structure of compound **33d**.*

Next, various precursors with different cyclic diketone moieties were examined. Substrates **32h** and **32j**, featuring two methyl groups at the 4-position of the diketone, afforded the dehydrated products **33h** and **33i** with enantioselectivities exceeding 94:6 er. The use of spirocyclic diketones like **32j** is also tolerated, providing the corresponding product **33j** in 55% yield and 94:6 er. Similarly, the substrate **32k**, bearing a 1,3-cycloheptanedione, was employed, compound **33h** was obtained in a 46% yield and 93:7 er.

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Curiously, substrate **32l**, containing a tetrahydropyran-1,2-dione, gave a mixture of 18% of the dehydrated product **33l** and 42% of alcohol **34l**, both with er values exceeding 90:10 (**Scheme 205**). And when 1,3-cyclopentanedione **32m** was used as the precursor, the alcohol **34m** was obtained in an 89% yield and an 85:15 er. It is possible that in this case, dehydration to the highly strained product **33m** is disfavored. Similarly, 1,2-indanedione **32n** selectively afforded **34n** in an 83% yield with an 85:15 er (**Scheme 205**). Gratifyingly, the structure of **34n** was obtained through X-Ray analysis of a racemic crystal (**Figure 35**).



***Scheme 205**: Scope of desymmetrizing hydroarylation of different 1,3-diketones. Carried out in collaboration with Dr. Carlos Lázaro.*

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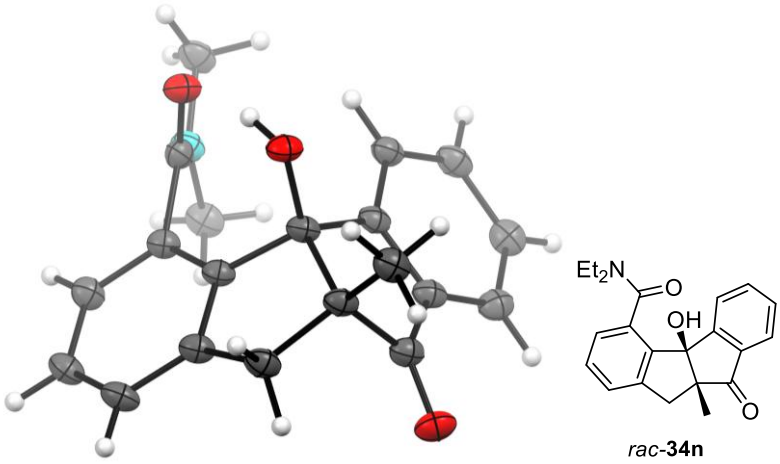


***Figure 35**: X-Ray structure of compound **34n**.*

The reaction presented some limitations, illustrated in **Figure 36**. Compounds **32o** and **32p** mainly decomposed under the reaction conditions. Additionally, acetylacetone **33q** did not react, and the starting material was recovered intact after the standard treatment.

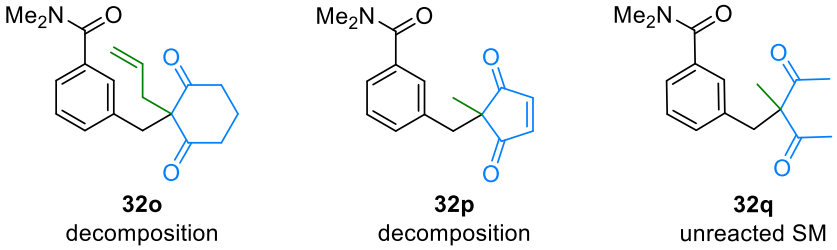
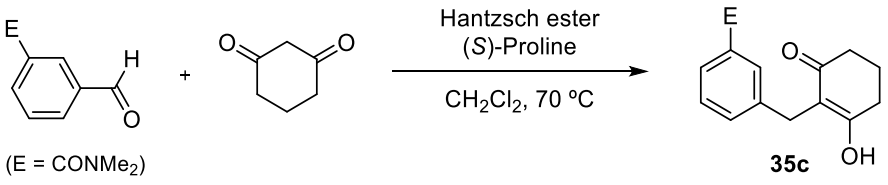


***Figure 36**: Unsuccessful starting materials evaluated in the desymmetrizing hydroarylation of diketones.*

We also examined various substrates lacking substituents at the 2-position of the 1,3-diketone, that were prepared using an organocatalytic reaction between the corresponding 3-formylbenzamide and the diketone, as exemplified for **35c** in **Scheme 206**.

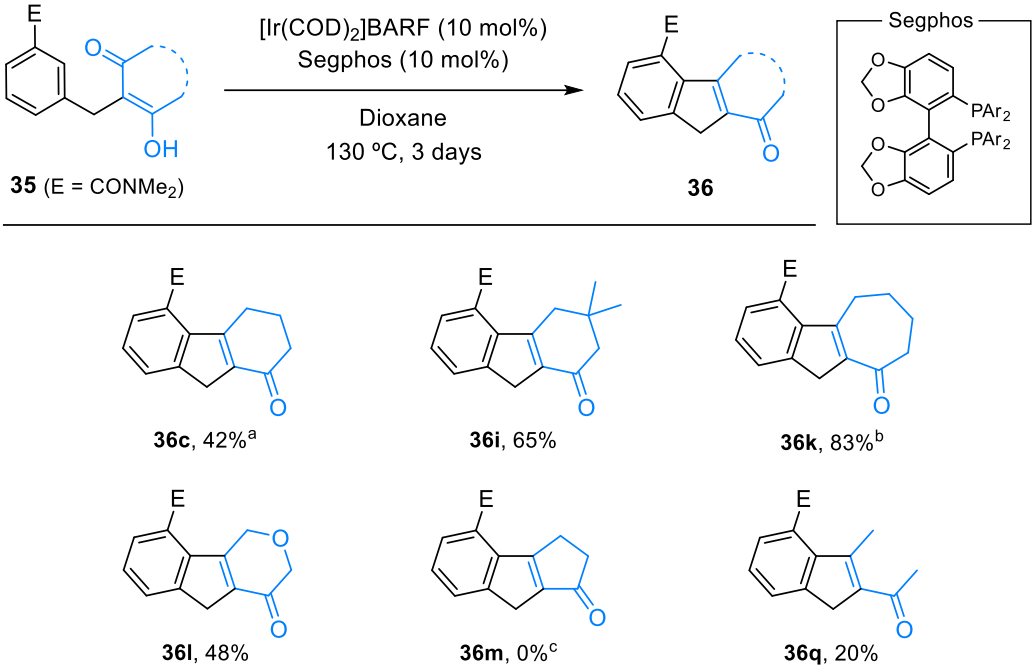


***Scheme 206**: Synthesis of precursor **35c**.*

By using Segphos as a ligand in dioxane at 130 °C, indenes **36h**, with fused 6- and 7-membered rings, were obtained in moderate yields after 3 days of reaction time.

Gratifyingly, product **36i** was crystallized and analyzed through X-ray diffractometry (**Figure 37**).

The cyclopentanedione **35m** did not produce the expected adduct, even when increasing the reaction time or using other ligands instead of Segphos. However, in this case, the use of the acyclic diketone **35q** allowed the isolation of 20% of indene **36q**.



***Scheme 207**: Scope of achiral products **36** through Ir-catalyzed cyclodehydration. Results obtained in collaboration with Dr. Carlos Lázaro. [a] 16 h of reaction time. [b] 20 h of reaction time. [c] Unreacted SM was obtained even with prolonged reaction times and other ligands.*

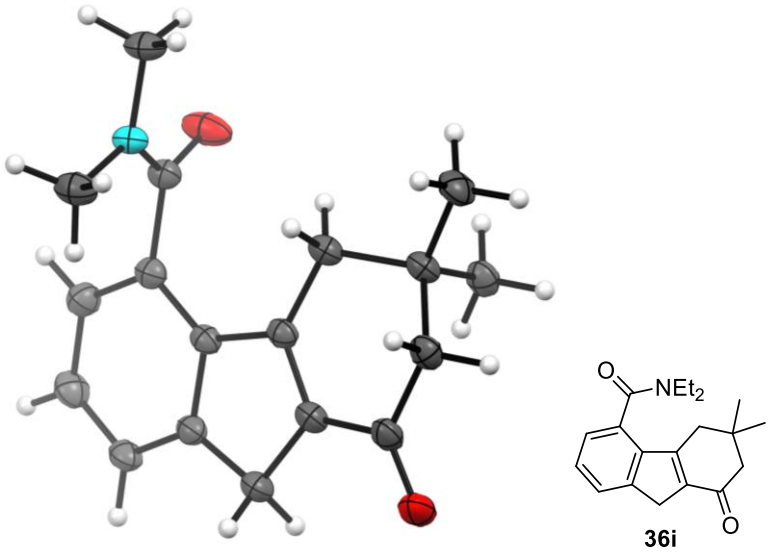
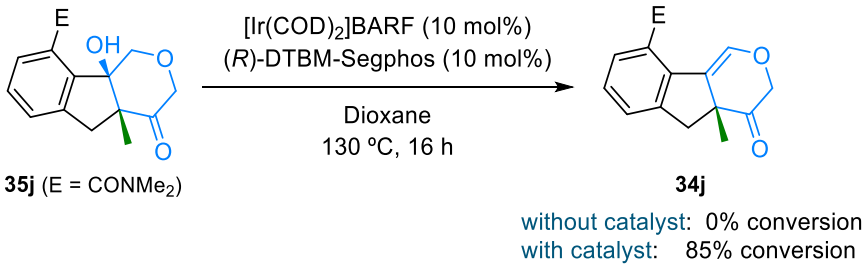


***Figure 37**: X-Ray structure of compound **36i**.*

Control experiments and mechanistic insights

During our analysis of the reaction scope, in addition to products **34** resulting from hydroarylation/dehydration processes, we also observed in some cases products where the alcohol is retained. To determine whether this dehydration step is spontaneous or if the catalyst is involved, we analyzed the process with alcohol **35j**.

When a solution of **35j** in dioxane was heated to 130 °C for 16 hours, no conversion to **34j** was observed (**Scheme 208**). However, upon addition of the Ir/DTBM-Segphos catalyst, conversion to **34j** was observed by NMR analysis of the crude mixture. This confirms that the iridium catalyst is essential for this dehydration. Further studies on this project are ongoing, in collaboration with Dr. Carlos Lázaro.



***Scheme 208**: Control experiments in the formation of **34j** from **34j**.*

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5.4.5. Conclusions

We have demonstrated the viability of intramolecular hydroarylation of ketones under Iridium(I) catalysis. In most cases, hydrocarbonation is followed by concomitant dehydration to the alkenes, under the reaction conditions. In some case the alcohol products can be isolated.

The asymmetric process is better implemented in desymmetrization reactions of cyclic 1,3-diketone-tethered aromatic systems, which lead to hexahydrofluorenes bearing quaternary carbon centers. By carefully selecting appropriate ligands, we successfully developed the first Ir-catalyzed hydroarylation for the desymmetrization of these systems, with moderate to good enantioselectivities.

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General conclusions

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This Ph.D. thesis explores the development of novel iridium-catalyzed intramolecular hydroarylation reactions.

In several studies, we investigated the hydroarylation of alkenes, allenes, and carbonyls. For alkenes, we developed a highly enantioselective method for constructing heteropolycyclic scaffolds with excellent stereochemical control, including compounds with multiple stereocenters. Mechanistic studies, supported by computational analysis, revealed a pathway involving C–H oxidative addition, carbometallation (the enantiodetermining step), and reductive elimination.

We also investigated the hydroarylation of allenyl-tethered pyrroles, demonstrating that chemo-, regio-, and enantioselectivity can be tuned by varying substrate structure and ligand choice. Combined experimental and computational studies provided valuable insights into reaction pathways and selectivity trends.

Furthermore, we discovered a novel cascade process involving cyclization, dehydrogenation, and hydrogenation steps, enabling the diastereo- and enantioselective synthesis of complex chiral products, including those containing cyclopropanes. The use of fluorinated ligands proved crucial for accessing to these singular products.

Finally, we explored the hydroarylation of carbonyls, which often proceeds with concomitant dehydration. This approach was successfully applied to the desymmetrization of cyclic 1,3-diketones, affording hexahydrofluorenes with quaternary carbon centers and moderate to good enantioselectivities.

This work demonstrates the versatility of iridium catalysis for the enantioselective construction of diverse and complex molecular architectures, providing valuable insights into reaction mechanisms and selectivity control.

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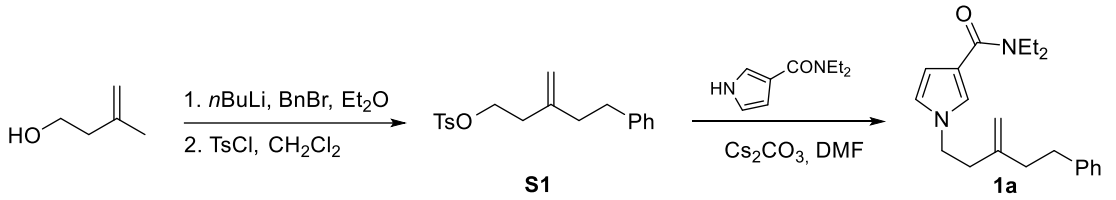
Experimental procedures and characterization of compounds



7.1. Experimental data of section 5.1

Synthesis of precursors 1a-a[IV], 1b-e, 1q and 1s

*(exemplified for **1a**).*



n-BuLi (21.9 mL, 35.08 mmol, 2.5 M in hexanes) was added to a solution of TMEDA (6.8 mL, 45.6 mmol) and Et_2O (29 mL) at 0 °C, and the resulting solution was stirred at *rt* for 1 h. The solution was then cooled (0 °C), and 3-methylbut-3-en-1-ol (0.95 g, 13.1 mmol) was added slowly. The resulting solution was stirred at *rt* for 6 h, leading to a heterogeneous brown suspension. This slurry was cooled to -78 °C and benzyl bromide (1.0 mL, 8.77 mmol) was slowly added. The reaction was then allowed to slowly warm up to *rt* overnight, quenched with aqueous saturated solution of NH_4Cl (45 mL) and the layers were separated. The aqueous layer was extracted with Et_2O (3× 60 mL) and the combined organic layers were dried and concentrated *in vacuo* to give a crude residue which was purified by column chromatography (1:9 to 2:8 EtOAc/hexanes) to give 3-methylene-5-phenylpentan-1-ol (3.70 g, 71% yield) as a colorless oil.[177]

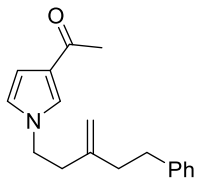
Tosyl chloride (2.38 g, 12.5 mmol), DMAP (0.21 g, 1.70 mmol) and Et_3N (3.2 mL, 22.7 mmol) were added to a solution of 3-methylene-5-phenylpentan-1-ol (2.0 g, 11.3 mmol) in CH_2Cl_2 (57 mL). The resulting solution turned cloudy after 5-10 minutes and was allowed to stir at *rt* for 3 h. The reaction was quenched with H_2O (70 mL), the phases were separated and the organic phase was washed twice with NH_4Cl (sat), dried and concentrated to yield a crude yellow residue that was purified by flash column chromatography to afford 3-methylene-5-phenylpentyl 4-methylbenzenesulfonate (**S1**, 2.51 g, 67% yield), as a colorless oil.[178] **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.69 (d, *J* = 6.9 Hz, 2H), 7.31 – 6.98 (m, 7H), 4.75 (s, 1H), 4.66 (s, 1H), 4.03 (t, *J* = 6.2 Hz, 2H), 2.58 (t, *J* = 7.7 Hz, 2H), 2.33 (s, 3H), 2.29 (t, *J* = 6.9 Hz, 2H), 2.13 (t, *J* = 8.1 Hz, 2H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 144.88 (C), 143.59 (C), 141.64 (C), 133.16 (C), 129.95 (CH), 128.40 (CH), 128.34 (CH), 127.93 (CH), 125.97 (CH), 112.51 (CH_2), 68.75 (CH_2), 37.65 (CH_2), 35.35 (CH_2), 34.09 (CH_2), 21.62 (CH_3).

[177] K. Y. Yong, J. A. Lotoski, and J. M. Chong, *J. Org. Chem.* **2001**, *66*, 8248-8251.

[178] C. J. Gerry, B. K. Hua, M. J. Wawer, J. P. Knowles, S. D. Nelson, O. Verho, S. Dandapani, B. K. Wagner, P. A. Clemons, K. I. Booker-Milburn, Z. V. Boskovic, and S. L. Schreiner, *J. Am. Chem. Soc.* **2016**, *138*, 8920.

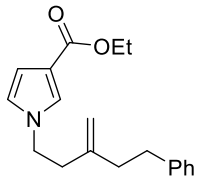
3-Methylene-5-phenylpentyl 4-methylbenzenesulfonate (**S1**, 735.3 mg, 2.23 mmol) was added to a solution of *N,N*-diethyl-1H-pyrrole-3-carboxamide (231.9 mg, 1.40 mmol) and Cs_2CO_3 (1.04 g, 3.18 mmol) in DMF (9 mL). The reaction mixture was stirred at 55 ºC for 16 h, allowed to cool to *rt* and water (20 mL) was added. The mixture was extracted with Et_2O (5 x 20 mL). The organic phase was dried, concentrated and the crude residue was purified by flash chromatography to yield *N,N*-diethyl-1-(3-methylene-5-phenylpentyl)-1H-pyrrole-3-carboxamide (**1a**, 320.0 mg, 44% yield) as yellow oil. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.29 (t, *J* = 7.5 Hz, 2H), 7.22 – 7.17 (m, 3H), 7.08 (s, 1H), 6.57 (s, 1H), 6.34 (s, 1H), 4.90 (s, 1H), 4.81 (s, 1H), 3.98 (t, *J* = 7.5 Hz, 2H), 3.54 (q, *J* = 7.1 Hz, 4H), 2.77 (t, *J* = 8.0 Hz, 2H), 2.52 (t, *J* = 7.5 Hz, 2H), 2.34 (t, *J* = 8.1 Hz, 2H), 1.23 (t, *J* = 7.1 Hz, 6H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 166.28 (CO), 144.99 (C), 141.33 (C), 128.07 (CH), 128.07 (CH), 125.98 (CH), 123.33 (CH), 120.03 (CH), 119.15 (C), 111.66 (CH_2), 108.53 (CH), 48.37 (CH_2), 41.24 (CH_2), 37.62 (CH_2), 37.50 (CH_2), 34.05 (CH_2), 13.745 (CH_3). **HRMS** [APCI]: *m/z* calculated for $C_{21}H_{29}N_2O$ $[M+H]^+$: 325.2274, found 325.2277. **NMR spectra at page 457.**

1-(3-Methylene-5-phenylpentyl)-1H-pyrrole-3-carboxylic acid (1a')



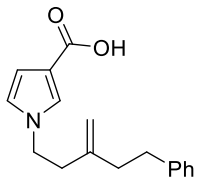
Synthesized by following the procedure used for **1a**, using 1-(1H-pyrrol-3-yl)ethan-1-one instead of *N,N*-diethyl-1H-pyrrole-3-carboxamide. Obtained as yellow oil (64% yield). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.37 – 7.16 (m, 6H), 6.64 – 6.56 (m, 2H), 4.92 (s, 1H), 4.80 (s, 1H), 4.01 (t, *J* = 9.8 Hz, 2H), 2.78 (t, *J* = 8.1 Hz, 2H), 2.52 (t, *J* = 8.7 Hz, 3H), 2.41 (s, 4H), 2.40 – 2.28 (m, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 144.50 (C), 141.22 (C), 128.12 (CH), 127.99 (CH), 125.72 (CH), 125.33 (CH), 121.79 (CH), 111.95 (CH_2), 109.02 (CH), 48.55 (CH_2), 37.52 (CH_2), 37.42 (CH_2), 33.93 (CH_2), 26.77 (CH_3). **HRMS** [APCI]: *m/z* calculated for $C_{18}H_{21}NO$ $[M+H]^+$: 268.1696, found 268.1694.

Ethyl 1-(3-methylene-5-phenylpentyl)-1H-pyrrole-3-carboxylate (1a''')



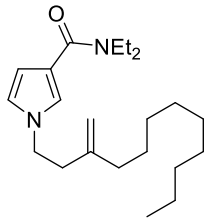
Synthesized by following the procedure used for **1a**, using ethyl-1H-pyrrole-3-carboxylate, instead of *N,N*-diethyl-1H-pyrrole-3-carboxamide. Obtained as yellow oil (78% yield). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.36 – 7.24 (m, 3H), 7.24 – 7.13 (m, 3H), 6.59 (s, 1H), 6.54 (s, 1H), 4.88 (s, 1H), 4.76 (s, 1H), 4.26 (q, *J* = 7.1 Hz, 2H), 3.92 (t, *J* = 7.4 Hz, 2H), 2.80 – 2.67 (m, 2H), 2.45 (t, *J* = 7.4 Hz, 2H), 2.37 – 2.23 (m, 2H), 1.33 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 164.64 (CO), 144.79 (C), 141.44 (C), 128.24 (CH), 128.17 (CH), 125.83 (CH), 125.63 (CH), 121.35 (CH), 115.92 (C), 111.93 (CH_2), 109.86 (CH), 59.33 (CH_2), 48.60 (CH_2), 37.65 (CH_2), 37.58 (CH_2), 34.08 (CH_2), 14.39 (CH_3). **HRMS** [APCI]: *m/z* calculated for $C_{19}H_{24}NO_2$ $[M+H]^+$: 298.1802, found 298.1801.

1-(3-Methylene-5-phenylpentyl)-1H-pyrrole-3-carboxylic acid (1a^{IV})



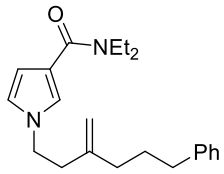
Synthesized by following the procedure used for **1a**, using 1H-pyrrole-3-carboxylic acid instead of *N,N*-diethyl-1H-pyrrole-3-carboxamide. Obtained as yellow oil (42% yield). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 9.46 (s, 1H), 7.46 (s, 1H), 7.35 (t, *J* = 7.4 Hz, 2H), 7.30 – 7.22 (m, 3H), 6.78 (d, *J* = 2.8 Hz, 1H), 6.72 (d, *J* = 3.2 Hz, 1H), 4.95 (s, 2H), 4.44 (t, *J* = 6.8 Hz, 2H), 2.98 – 2.77 (m, 2H), 2.55 (t, *J* = 6.9 Hz, 2H), 2.46 (t, *J* = 7.8 Hz, 2H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 165.63 (CO), 145.18 (C), 141.88 (C), 128.32 (CH), 128.32 (CH), 125.83 (CH), 123.83 (CH), 119.10 (CH), 115.95 (C), 111.64 (CH_2), 109.54 (CH), 62.42 (CH_2), 37.98 (CH_2), 35.32 (CH_2), 34.20 (CH_3). **HRMS** [APCI]: *m/z* calculated for $C_{17}H_{20}NO_2$ $[M+H]^+$: 270.1489, found 270.1488.

***N,N*-Diethyl-1-(3-methylenedodecyl)-1H-pyrrole-3-carboxamide (1b)**



Synthesized by following the procedure used for **1a**. Obtained in 76% yield, as yellow oil. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.05 (s, 1H), 6.55 (s, 1H), 6.30 (s, 1H), 4.80 (s, 1H), 4.71 (s, 1H), 3.94 (t, *J* = 7.6 Hz, 2H), 3.52 (q, *J* = 7.1 Hz, 4H), 2.45 (t, *J* = 7.4 Hz, 2H), 1.99 (t, *J* = 7.6 Hz, 2H), 1.47 – 1.35 (m, 2H), 1.34 – 1.22 (m, 12H), 1.20 (t, *J* = 7.1 Hz, 6H), 0.87 (t, *J* = 6.9 Hz, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 166.57 (CO), 145.99 (CH), 123.59 (CH), 120.28 (CH), 119.35 (C), 111.20 (CH), 108.73 (CH), 48.66 (CH_2), 41.51 (CH_2), 37.68 (CH_2), 36.1 (CH_2), 31.82 (CH_2), 29.49 (CH_2), 29.43 (CH_2), 29.27 (CH_2), 29.22 (CH_2), 27.72 (CH_2), 22.58 (CH_2), 13.95 (CH_3), 13.71 (CH_3). **HRMS** [APCI]: *m/z* calculated for $C_{22}H_{39}N_2O$ $[M+H]^+$: 347.3057, found 347.3058.

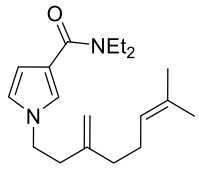
***N,N*-Diethyl-1-(3-methylene-6-phenylhexyl)-1H-pyrrole-3-carboxamide (1c)**



Synthesized by following the procedure used for **1a**. Obtained in 71% yield, as yellow oil. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.27 (t, *J* = 7.5 Hz, 2H), 7.16 (d, *J* = 7.5 Hz, 3H), 7.04 (s, 1H), 6.54 (s, 1H), 6.30 (s, 1H), 4.85 (s, 1H), 4.76 (s, 1H), 3.93 (t, *J* = 7.5 Hz, 2H), 3.52 (q, *J* = 7.1 Hz, 4H), 2.61 (t, *J* = 7.6 Hz, 2H), 2.47 (t, *J* = 7.5 Hz, 2H), 2.05 (t, *J* = 7.8 Hz, 2H), 1.77 (p, *J* = 7.9, 7.2 Hz, 2H), 1.21 (t, *J* = 7.1 Hz, 6H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 166.50 (CO), 145.45 (C), 142.03 (C), 128.30 (CH), 128.25 (CH), 125.74 (CH), 123.48 (CH), 120.23 (CH), 119.43 (C), 111.58 (CH_2), 108.74 (CH), 48.55 (CH_2), 41.46 (CH_2), 37.64 (CH_2), 35.53 (CH_2), 35.38 (CH_2), 29.27 (CH_2), 13.69 (CH_3). **HRMS** [APCI]: *m/z* calculated for $C_{22}H_{31}N_2O$ $[M+H]^+$: 339.2431, found 339.2430.

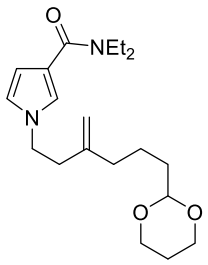
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***N,N*-Diethyl-1-(7-methyl-3-methyleneoct-6-en-1-yl)-1H-pyrrole-3-carboxamide (1d)**



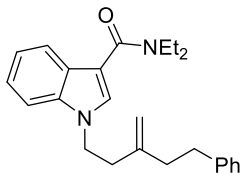
Synthesized by following the procedure used for **1a**. Obtained in 46% yield, as yellow oil. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.04 (t, *J* = 2.2 Hz, 1H), 6.56 (t, *J* = 2.5 Hz, 1H), 6.31 (dd, *J* = 2.8, 1.8 Hz, 1H), 5.14 – 5.05 (m, 1H), 4.83 (d, *J* = 1.4 Hz, 1H), 4.76 – 4.72 (m, 1H), 3.96 (t, *J* = 7.7 Hz, 2H), 3.52 (q, *J* = 7.1 Hz, 4H), 2.48 (t, *J* = 6.9 Hz, 2H), 2.17 – 2.07 (m, 2H), 2.07 – 2.00 (m, 2H), 1.69 (d, *J* = 1.3 Hz, 3H), 1.61 (s, 3H), 1.21 (t, *J* = 7.1 Hz, 6H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 166.49 (CO), 145.57 (C), 131.81 (C), 123.60 (CH), 123.39 (CH), 120.21 (CH), 119.41 (C), 111.41 (CH_2), 108.69 (CH), 48.58 (CH_2), 41.41 (CH_2), 37.75 (CH_2), 36.04 (CH_2), 26.31 (CH_2), 25.46 (CH_2), 17.56 (CH_2), 13.66 (CH_3). **HRMS** [APCI]: *m/z* calculated for $C_{19}H_{31}N_2O$ $[M+H]^+$: 303.2431 , found 303.2428.

1-(5-(1,3-Dioxan-2-yl)-3-methylenepentyl)-*N,N*-diethyl-1H-pyrrole-3-carboxamide (1e)



Synthesized by following the procedure used for **1a**. Obtained in 41% yield, as yellow oil. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.01 (t, *J* = 2.1 Hz, 1H), 6.53 (t, *J* = 2.6 Hz, 1H), 6.28 (t, *J* = 2.6, 2.1 Hz, 1H), 4.80 (s, 1H), 4.70 (s, 1H), 4.49 (t, *J* = 4.7 Hz, 1H), 4.06 (dd, *J* = 10.5, 5.0 Hz, 2H), 3.92 (t, *J* = 7.6 Hz, 2H), 3.72 (td, *J* = 12.3, 2.7 Hz, 2H), 3.50 (q, *J* = 7.1 Hz, 4H), 2.44 (t, *J* = 7.5 Hz, 2H), 2.08 – 1.96 (m, 2H), 1.60 – 1.48 (m, 4H), 1.18 (t, *J* = 7.1 Hz, 6H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 166.26 (CO), 145.14 (CH), 123.14 (CH), 119.98 (CH), 119.13 (C), 111.36 (CH_2), 108.45 (CH), 101.77 (CH), 48.30 (CH_2), 41.18 (CH_2), 37.26 (CH_2), 35.60 (CH_2), 34.42 (CH_2), 25.54 (CH_2), 21.64 (CH_2), 13.42 (CH_3). **HRMS** [APCI]: *m/z* calculated for $C_{20}H_{33}N_2O_3$ $[M+H]^+$: 349.2486, found 349.2486.

***N,N*-Diethyl-1-(3-methylene-5-phenylpentyl)-1H-indole-3-carboxamide (1q)**

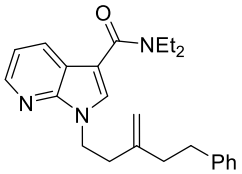


Synthesized by following the procedure used for **1a**, using *N,N*-diethyl-1H-indole-3-carboxamide instead of *N,N*-diethyl-1-(3-methylene-5-phenylpentyl)-1H-pyrrole-3-carboxamide. Obtained as yellow oil (154 mg, 63% yield). **^{1}H NMR** (750 MHz, $CDCl_3$) δ 7.68 (d, *J* = 7.9 Hz, 1H), 7.20 (d, *J* = 8.1 Hz, 1H), 7.18 – 7.10 (m, 4H), 7.09 – 7.03 (m, 2H), 7.01 (d, *J* = 7.2 Hz, 2H), 4.77 (s, 1H), 4.66 (s, 1H), 4.08 (t, *J* = 7.4 Hz, 2H), 3.43 (q, *J* = 7.1 Hz, 4H), 2.62 (t, *J* = 7.6 Hz, 2H), 2.44 (t, *J* = 7.4 Hz, 2H), 2.21 (t, *J* = 8.0 Hz, 2H), 1.09 (t, *J* = 7.1 Hz, 6H). **^{13}C NMR** (189 MHz, $CDCl_3$) δ 166.62 (CO), 145.29 (C), 141.41 (C), 135.52 (C), 128.22 (CH), 128.12 (CH), 128.02 (CH), 126.91 (C), 125.82 (CH), 122.17 (CH), 120.97 (CH), 120.45 (CH), 112.06 (CH_2), 111.35 (C), 109.36

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(CH), 45.27 (CH_2), 41.19 (CH_2), 37.68 (CH_2), 36.30 (CH_2), 34.23 (CH_2), 13.73 (CH_3). **HRMS** [APCI]: *m/z* calculated for $C_{25}H_{31}N_2O$ $[M+H]^+$: 375.2431, found 375.2429.

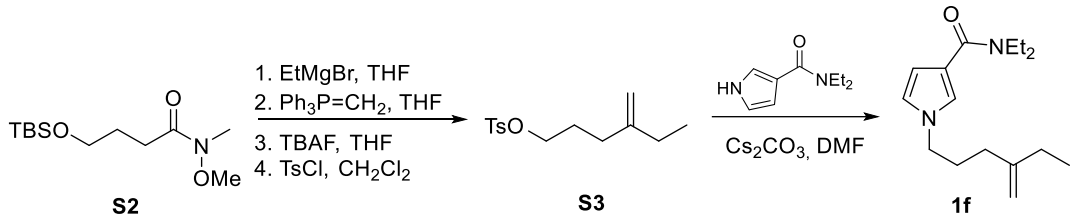
N,N-Diethyl-1-(3-methylene-5-phenylpentyl)-1H-pyrrolo[2,3-b]pyridine-3-carboxamide (1s)



Synthesized by following the procedure used for **1a**, using *N,N*-diethyl-1H-pyrrolo[2,3-b]pyridine-3-carboxamide instead of *N,N*-diethyl-1-(3-methylene-5-phenylpentyl)-1H-pyrrole-3-carboxamide. Obtained as yellow oil (71% yield). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.28 (d, *J* = 4.6 Hz, 1H), 8.10 (d, *J* = 7.8 Hz, 1H), 7.31 (s, 1H), 7.18 (t, *J* = 7.5 Hz, 2H), 7.12 – 7.03 (m, 4H), 4.76 (s, 1H), 4.68 (s, 1H), 4.38 (t, *J* = 7.2 Hz, 2H), 3.48 (q, *J* = 7.1 Hz, 4H), 2.71 – 2.63 (m, 2H), 2.55 (t, *J* = 7.2 Hz, 2H), 2.34 – 2.25 (m, 2H), 1.15 (t, *J* = 7.1 Hz, 6H). **^{13}C NMR** (189 MHz, $CDCl_3$) δ 165.94 (CO), 146.94 (C), 145.61 (C), 143.57 (CH), 141.86 (C), 129.95 (CH), 128.50 (CH), 128.45 (CH), 128.37 (CH), 126.07 (CH), 120.08 (C), 117.06 (CH), 112.30 (CH_2), 109.74 (C), 43.68 (CH_2), 41.64 (CH_2), 37.86 (CH_2), 36.78 (CH_2), 34.45 (CH_2), 14.02 (CH_3). **HRMS** [APCI]: *m/z* calculated for $C_{24}H_{30}N_3O$ $[M+H]^+$: 376.2383, found 376.2395. **NMR spectra at page 460.**

Synthesis of precursors 1f-g, 1r and 1x-z

*(exemplified for **1f**).*



EtMgBr (11.5 mL, 0.034 mol, 3 M) was added dropwise to a solution of 4-((tert-butyldimethylsilyl)oxy)-N-methoxy-N-methylbutanamide[179] (3.0 g, 0.011 mol) in THF at 0 ºC, and the mixture was stirred overnight at *rt*. Then, 30 mL of a saturated solution of Rochelle salt were added at 0 ºC. The reaction was extracted with Et_2O (3 x 50 mL) and the combined organic phases were dried, filtered, concentrated and the resulting residue purified by flash column chromatography (1:9 to 3:7 EtOAc/hexanes) to give **6-((*tert*-butyldimethylsilyl)oxy)hexan-3-one** (**S2**), obtained as colorless oil (2.13 g, 80% yield). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 3.61 (t, *J* = 6.1 Hz, 2H), 2.58 – 2.35 (m, 4H), 1.78 (p, *J* = 6.3 Hz, 2H), 1.05 (t, *J* = 7.3 Hz, 3H), 0.88 (s, 9H), 0.03 (s, 6H). **^{13}C NMR** (75 MHz, $CDCl_3$)

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[179] W. J. Kerr, A. J. Morrison, and L. C. Paterson, *Tetrahedron* **2015**, *71*, 5356-5361.

δ 211.73 (CO), 62.35 (CH_2), 38.78 (CH_2), 36.08 (CH_2), 27.04 (CH_2), 26.06 (CH_3), 18.45 (C), 8.00 (CH_3), -5.22 (CH_3).

Sodium *tert*-Butoxide (1.93 g, 20.1 mmol) was added in 3 portions to a solution of methyltriphenylphosphonium bromide (7.81 g, 21.9 mmol) in benzene (46 mL) at 0 ºC. The mixture was refluxed for 6 h, 6-((tert-butyldimethylsilyl)oxy)hexan-3-one (2.1 g, 9.1 mmol) was added, and the resulting mixture was refluxed overnight. Water (50 mL) was added and the mixture was extracted with Et_2O (3x 25 mL). The combined organic phases were dried, filtered, concentrated and the resulting residue purified by column chromatography (1:9 to 2:8 EtOAc/hexanes) to give *t*-butyldimethyl((4-methylenehexyl)oxy)silane (1.33 g, 64% yield) as colorless oil.

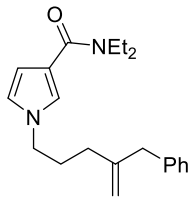
TBAF (8.5 mL, 8.53 mmol) was added dropwise to a solution of this alkene (1.30 g, 5.7 mmol) in THF (14 mL) at 0 ºC. The mixture was stirred for 2 h at that temperature and for another 2 h at *rt*. Then, water (25 mL) and Et_2O (50 mL) were sequentially added. The organic phase was dried, filtered, concentrated and the resulting alcohol was tosylated, without further purification, using the conditions described for the synthesis of 3-methylene-5-phenylpentyl-4-methylbenzenesulfonate (**S1**). Thus, **4-methylenehexyl 4-methylbenzenesulfonate** (**S3**) was obtained as colorless oil (680 mg, 45% yield). The following data is in agreement with that reported in literature.[180] **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.79 (d, 2H, *J* = 8.2), 7.34 (d, 2H, *J* = 8.2), 4.70 (br s, 1H), 4.60 (br s, 1H), 4.02 (t, 2H, *J* = 7.3), 2.45 (s, 3H), 2.04 (m, 2H), 1.93 (q, 2H, *J* = 7.4), 1.78 (m, 2H), 0.98 (t, 3H, *J* = 7.4). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 149.4 (C), 144.7 (C), 129.8 (CH), 127.9 (CH), 108.6 (CH_2), 70.2 (CH_2), 31.7 (CH_2), 28.6 (CH_2), 26.9 (CH_2), 26.9 (CH_2), 21.6 (CH_2), 12.2 (CH_2).

The assembly of **1f** was performed following the alkylation procedure described for **1a**. ***N,N*-Diethyl-1-(4-methylenehexyl)-1H-pyrrole-3-carboxamide** (**1f**) was obtained in 56% yield as yellow oil. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.04 (s, 1H), 6.54 (s, 1H), 6.30 (s, 1H), 4.76 (s, 1H), 4.70 (s, 1H), 3.83 (t, *J* = 6.9 Hz, 2H), 3.52 (q, *J* = 7.1 Hz, 4H), 2.07 – 1.83 (m, 6H), 1.20 (t, *J* = 7.1 Hz, 6H), 1.00 (t, *J* = 7.4 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) 166.55 (C), 149.72 (C), 123.59 (CH), 120.31 (CH), 119.40 (C), 108.72 (CH), 108.57 (CH_2), 49.26 (CH_2), 41.48 (CH_2), 32.91 (CH_2), 29.14 (CH_2), 28.66 (CH_2), 13.69 (CH_3), 12.24 (CH_3). **HRMS** [APCI]: *m/z* calculated for $C_{16}H_{27}N_2O$ $[M+H]^+$: 263.2118, found 263.2116.

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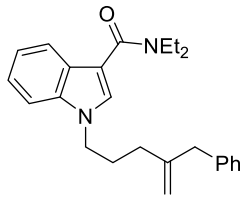
[180] M. G. Banwell, A. J. Edwards, K. A. Jolliffe, J. A. Smith, E. Hamel, and P. Verdier-Pinard, *Org. Biomol. Chem.* **2003**, *1*, 296–305.

1-(4-Benzylpent-4-en-1-yl)-*N,N*-diethyl-1H-pyrrole-3-carboxamide (1g)



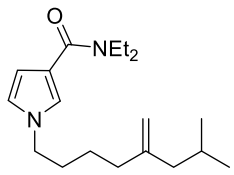
Synthesized by following the procedure used for **1f**. Obtained as yellow oil in 69% yield. **^{1}H NMR** (750 MHz, $CDCl_3$) δ 7.19 (t, *J* = 7.4 Hz, 2H), 7.12 (t, *J* = 7.4 Hz, 1H), 7.08 (d, *J* = 6.7 Hz, 2H), 6.93 (t, *J* = 2.0 Hz, 1H), 6.42 (t, *J* = 2.6 Hz, 1H), 6.22 (dd, *J* = 2.8, 1.8 Hz, 1H), 4.76 (s, 1H), 4.75 (s, 1H), 3.72 (t, *J* = 7.0 Hz, 2H), 3.45 (q, *J* = 7.1 Hz, 4H), 3.25 (s, 2H), 1.90 (d, *J* = 7.1 Hz, 2H), 1.86 – 1.77 (m, 2H), 1.14 (t, *J* = 7.1 Hz, 6H). **^{13}C NMR** (189 MHz, $CDCl_3$) δ 166.51 (CO), 147.23 (C), 139.21 (C), 128.78 (CH), 128.22 (CH), 126.08 (CH), 123.78 (CH), 120.27 (CH), 118.98 (C), 111.95 (CH_2), 108.66 (CH), 49.15 (CH_2), 42.96 (CH_2), 41.50 (CH_2), 32.16 (CH_2), 28.96 (CH_2), 13.56 (CH_3). **HRMS** [APCI]: *m/z* calculated for $C_{21}H_{29}N_2O$ $[M+H]^+$: 325.2274, found 325.2274.

1-(4-Benzylpent-4-en-1-yl)-*N,N*-diethyl-1H-indole-3-carboxamide (1r)



Synthesized by following the procedure used for **1f** (38% yield, yellow oil). **^{1}H NMR** (750 MHz, $CDCl_3$) 7.86 (d, *J* = 7.9 Hz, 1H), 7.35 – 7.25 (m, 4H), 7.25 – 7.20 (m, 2H), 7.18 (d, *J* = 7.2 Hz, 2H), 4.89 (d, *J* = 7.6 Hz, 2H), 4.08 (t, *J* = 7.0 Hz, 2H), 3.60 (q, *J* = 7.1 Hz, 4H), 3.36 (s, 2H), 2.13 – 1.95 (m, 4H), 1.26 (t, *J* = 7.1 Hz, 6H). **^{13}C NMR** (189 MHz, $CDCl_3$) δ 166.51 (CO), 147.13 (C), 139.02 (C), 135.60 (C), 128.65, 128.11, 127.89, 126.85 (C), 125.98 (CH), 122.03 (CH), 120.84 (CH), 120.30 (CH), 111.80 (CH_2), 111.25 (C), 109.37 (CH), 45.77 (CH_2), 42.88 (CH_2), 41.11 (CH_2), 32.27 (CH_2), 27.64 (CH_2), 13.65 (CH_3). **HRMS** [APCI]: *m/z* calculated for $C_{25}H_{31}N_2O$ $[M+H]^+$: 375.2431, found 375.2427.

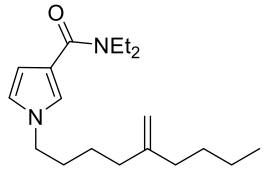
***N,N*-Diethyl-1-(7-methyl-5-methyleneoctyl)-1H-pyrrole-3-carboxamide (1x)**



Synthesized by following the procedure used for **1f** (87% yield, yellow oil). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.02 (dd, *J* = 2.3, 1.8 Hz, 1H), 6.53 (dd, *J* = 2.8, 2.3 Hz, 1H), 6.29 (dd, *J* = 2.8, 1.8 Hz, 1H), 4.68 (d, *J* = 8.1 Hz, 2H), 3.82 (t, *J* = 7.1 Hz, 2H), 3.50 (q, *J* = 7.1 Hz, 4H), 1.97 (t, *J* = 7.6 Hz, 2H), 1.83 (d, *J* = 7.4 Hz, 2H), 1.79 – 1.64 (m, 3H), 1.41 (p, *J* = 7.6 Hz, 2H), 1.19 (t, *J* = 7.1 Hz, 6H), 0.84 (d, *J* = 6.6 Hz, 6H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 166.66 (C), 147.89 (C), 123.66 (CH), 120.39 (CH), 119.51 (C), 110.65 (CH_2), 108.78 (CH), 49.80 (CH_2), 45.84 (CH_2), 41.58 (CH_2), 35.27 (CH_2), 30.91 (CH_2), 26.15 (CH), 24.75 (CH_2), 22.51 (CH_3), 13.81 (CH_3). **HRMS** [APCI]: *m/z* calculated for $C_{19}H_{33}N_2O$ $[M+H]^+$: 305.2587, found 305.2588. **NMR spectra at page 461**

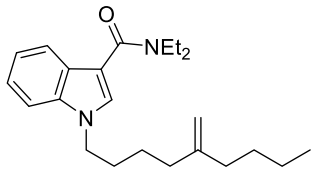
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N,N-Diethyl-1-(5-methylenenonyl)-1H-pyrrole-3-carboxamide (1y)



Synthesized by following the procedure used for **1f**, (45% yield, yellow oil). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.01 (t, *J* = 2.1 Hz, 1H), 6.52 (t, *J* = 2.6 Hz, 1H), 6.28 (dd, *J* = 2.8, 1.8 Hz, 1H), 4.68 (s, 1H), 4.64 (s, 1H), 3.82 (t, *J* = 7.1 Hz, 2H), 3.50 (q, *J* = 7.1 Hz, 4H), 1.96 (dt, *J* = 25.3, 7.6 Hz, 4H), 1.74 (p, *J* = 7.3 Hz, 2H), 1.45 – 1.31 (m, 4H), 1.33 – 1.22 (m, 2H), 1.18 (t, *J* = 7.1 Hz, 6H), 0.87 (t, *J* = 7.2 Hz, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 166.47 (CO), 149.02 (C), 123.47 (CH), 120.23 (CH), 119.35 (C), 109.08 (CH_2), 108.61 (CH), 49.62 (CH_2), 41.42 (CH_2), 35.48 (CH_2), 35.33 (CH_2), 30.72 (CH_2), 29.91 (CH_2), 24.63 (CH_2), 22.29 (CH_2), 13.75 (CH_3), 13.64 (CH_3). **HRMS** [APCI]: *m/z* calculated for $C_{19}H_{33}N_2O$ $[M+H]^+$: 305.2587, found 305.2584.

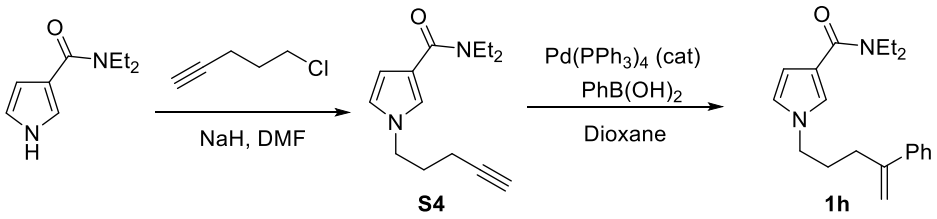
N,N-Diethyl-1-(5-methylenenonyl)-1H-indole-3-carboxamide (1z)



Synthesized by following the procedure used for **1f** (51% yield, yellow oil). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.69 (d, *J* = 7.8 Hz, 1H), 7.26 – 7.23 (m, 1H), 7.24 (s, 1H), 7.15 (t, *J* = 7.6 Hz, 1H), 7.09 (t, *J* = 7.5 Hz, 1H), 4.64 (d, *J* = 1.8 Hz, 1H), 4.60 (d, *J* = 1.9 Hz, 1H), 4.05 (t, *J* = 7.1 Hz, 2H), 3.50 (q, *J* = 7.1 Hz, 4H), 1.97 (t, *J* = 6.9 Hz, 2H), 1.89 (t, *J* = 7.6 Hz, 2H), 1.79 (p, *J* = 7.3 Hz, 2H), 1.41 (p, *J* = 7.7 Hz, 2H), 1.32 – 1.28 (m, 2H), 1.24 – 1.20 (m, 2H), 1.14 (t, *J* = 7.1 Hz, 6H), 0.81 (d, *J* = 7.2 Hz, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 166.84 (C), 149.04 (C), 135.79 (C), 128.29 (CH), 126.85 (C), 122.18 (CH), 120.95 (CH), 120.48 (CH), 111.26 (C), 109.54 (CH), 109.13 (CH_2), 46.44 (CH_2), 41.32 (CH_2), 35.52 (CH_2), 35.41 (CH_2), 29.94 (CH_2), 29.61 (CH_2), 24.97 (CH_2), 22.32 (CH_2), 13.77 (CH_3). **HRMS** [APCI]: *m/z* calculated for $C_{23}H_{35}N_2O$ $[M+H]^+$: 355.2744, found 355.2744.

Synthesis of precursors 1h-l and 1t-u

*(exemplified for **1h**).*



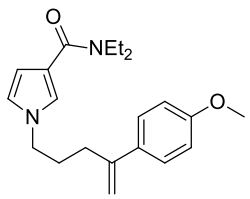
5-Chloropent-1-yne (648 mg, 6.32 mmol) was added to a solution of *N,N*-diethyl-1H-pyrrole-3-carboxamide (700 mg, 4.21 mmol), NaI (947 mg, 6.32 mmol) and Cs_2CO_3 (2.06 g, 6.32 mmol) in DMF (6.1 mL). The reaction mixture was stirred at 80 ºC for 72 h under Ar atmosphere, allowed to cool to *rt* and water (20 mL) was added. The mixture was

extracted with Et_2O (5 x 25 mL). The organic phase was dried, concentrated and the crude residue was purified by flash chromatography to yield 221 mg, 25% yield) as yellow oil.

Under argon atmosphere ***N,N*-diethyl-1-(pent-4-yn-1-yl)-1H-pyrrole-3-carboxamide** (**S4**, 100 mg, 0.43 mmol), $Pd(PPh_3)_4$ (24.9 mg, 0.022 mmol) and phenylboronic acid (57.7 mg, 0.47 mmol) were placed in a Schlenk tube. Dry 1,4-Dioxane (2 mL) and AcOH (5 μL, 0.09 mmol) were added and the solution was stirred at *rt* for 15 min, then at 80 ºC for 24h. The reaction was cooled to *rt* and the solvent was removed in vacuo. The resulting crude product was purified by flash column chromatography (20:80 EtOAc/hexanes) to afford ***N,N*-diethyl-1-(4-phenylpent-4-en-1-yl)-1H-pyrrole-3-carboxamide** (**1h**, 108.2 mg, 81% yield), obtained as yellow oil. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.35 – 7.13 (m, 5H), 6.95 (s, 1H), 6.45 (s, 1H), 6.24 (s, 1H), 5.23 (d, *J* = 1.5 Hz, 1H), 4.99 (d, *J* = 1.4 Hz, 1H), 3.77 (t, *J* = 7.1 Hz, 2H), 3.45 (q, *J* = 7.1 Hz, 4H), 2.46 – 2.40 (m, 2H), 1.85 (p, *J* = 7.2 Hz, 2H), 1.14 (t, *J* = 7.1 Hz, 6H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 166.72 (C), 147.42 (C), 140.92 (C), 128.53 (CH), 127.71 (CH), 126.24 (CH), 123.77 (CH), 120.51 (CH), 119.67 (C), 113.28 (CH_2), 108.96 (CH), 49.23 (CH_2), 41.66 (CH_2), 32.41 (CH_2), 29.70 (CH_2), 13.88 (CH_3). **HRMS** [APCI]: *m/z* calculated for $C_{20}H_{27}N_2O$ $[M+H]^+$: 311.2118, found 311.2117.

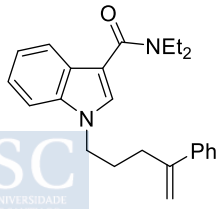
NMR spectra at page 459.

***N,N*-Diethyl-1-(4-(4-methoxyphenyl)pent-4-en-1-yl)-1H-pyrrole-3-carboxamide (1i)**



Synthesized by following the same procedure used for **1h**, using *p*-methoxyphenyl boronic acid (74% yield, yellow oil). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.20 (d, *J* = 8.6 Hz, 2H), 6.96 (s, 1H), 6.78 (d, *J* = 8.6 Hz, 2H), 6.45 (s, 1H), 6.24 (s, 1H), 5.15 (s, 1H), 4.90 (s, 1H), 3.77 (t, *J* = 7.1 Hz, 2H), 3.73 (s, 3H), 3.45 (q, *J* = 7.1 Hz, 4H), 2.40 (d, *J* = 7.4 Hz, 2H), 1.84 (t, *J* = 7.3 Hz, 2H), 1.14 (t, *J* = 7.0 Hz, 6H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 166.50 (C), 159.24 (C), 146.44 (C), 133.06 (C), 127.09 (CH), 123.66 (CH), 120.31 (CH), 119.29 (C), 113.79 (CH), 111.56 (CH_2), 108.72 (CH), 55.18 (CH_3), 49.02 (CH_2), 41.47 (CH_2), 32.21 (CH_2), 29.51 (CH_2), 13.65 (CH_3). **HRMS** [APCI]: *m/z* calculated for $C_{21}H_{20}N_2O_2$ $[M+H]^+$: 341.2224, found 341.2223.

***N,N*-Diethyl-1-(4-phenylpent-4-en-1-yl)-1H-indole-3-carboxamide (1t)**

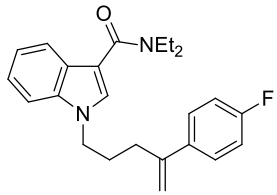


Synthesized by following the same procedure used for **1h**, using *N,N*-diethyl-1H-indole-3-carboxamide (54% yield). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.82 (dd, *J* = 7.4, 1.5 Hz, 1H), 7.40 – 7.30 (m, 6H), 7.28 – 7.19 (m, 3H), 5.37 (s, 1H), 5.13 (s, 1H), 4.16 (t, *J* = 7.2 Hz, 2H), 3.65 – 3.59 (m, 4H), 2.60 (t, *J* = 7.4 Hz, 2H), 2.07 (p, *J* = 7.3 Hz, 2H), 1.26

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(t, *J* = 7.1 Hz, 6H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 166.96 (C), 147.35 (C), 140.83 (C), 135.95 (C), 128.55 (CH), 128.44 (CH), 127.74 (CH), 127.09 (C), 126.26 (CH), 122.41 (CH), 121.16 (CH), 120.71 (CH), 113.35 (CH_2), 111.60 (C), 109.74 (CH), 46.02 (CH_2), 41.48 (CH_2), 32.61 (CH_2), 28.40 (CH_2), 13.98 (CH_3). **HRMS** [APCI]: *m/z* calculated for $C_{24}H_{27}N_2O$ [M+H]$^+$: 361.2274, found 361.2274.

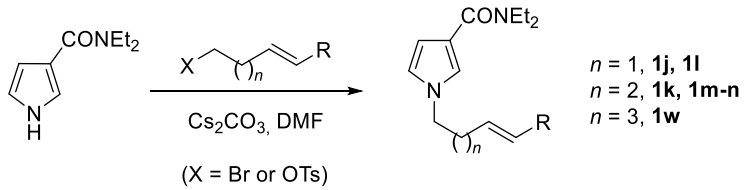
N,N-Diethyl-1-(4-(4-fluorophenyl)pent-4-en-1-yl)-1H-indole-3-carboxamide (1u)



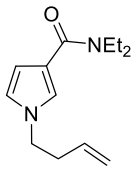
Synthesized by following the same procedure used for **1h**, using *p*-fluorophenyl boronic acid and *N,N*-diethyl-1H-indole-3-carboxamide (35% yield, brown oil). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.70 (d, *J* = 7.8 Hz, 1H), 7.26 – 7.10 (m, 6H), 6.93 (t, *J* = 8.6 Hz, 2H), 5.21 (s, 1H), 5.01 (s, 1H), 4.07 (t, *J* = 7.1 Hz, 2H), 3.51 (q, *J* = 7.1 Hz, 4H), 2.46 (t, *J* = 7.4 Hz, 2H), 1.96 (q, *J* = 7.6 Hz, 2H), 1.16 (t, *J* = 7.0 Hz, 6H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 166.75 (C), 162.36 (C, d, J_F = 247.0 Hz), 146.09 (C), 136.66 (C, d, J_F = 3.5 Hz), 135.73 (C), 128.35 (CH), 127.63 (CH, d, J_F = 7.8 Hz), 126.83 (C), 122.25 (CH), 120.96 (CH), 120.58 (CH), 115.17 (CH, d, J_F = 21.4 Hz), 113.10 (CH_2), 111.39 (C), 109.50 (CH), 45.80 (CH_2), 41.31 (CH_2), 32.49 (CH_2), 28.13 (CH_2), 13.75 (CH_3). **HRMS** [APCI]: *m/z* calculated for $C_{24}H_{28}N_2OF$ [M+H]$^+$: 379.2180, found 379.2179.

Synthesis of precursors 1j-n and 1w

*(exemplified for **1j**).*



1-(But-3-en-1-yl)-*N,N*-diethyl-1H-pyrrole-3-carboxamide (1j)

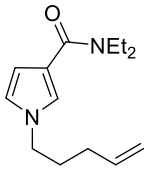


4-Br-buten-1-ene (205 mg, 1.52 mmol) was added to a solution of *N,N*-diethyl-1H-pyrrole-3-carboxamide (200 mg, 1.20 mmol) and Cs_2CO_3 (989 mg, 3.03 mmol) in DMF (4.3 mL). The reaction mixture was stirred at 80 ºC for 16 h, allowed to cool to *rt* and water (15 mL) was added. The mixture was extracted with Et_2O (3 x 20 mL/mmol). The organic phase was dried, concentrated and the resulting crude residue was purified by flash chromatography to obtain **1-(but-3-en-1-yl)-*N,N*-diethyl-1H-pyrrole-3-carboxamide** (**1j**, 430 mg, 81% yield) as brown oil. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.12 (t, *J* = 2.0 Hz, 1H), 6.58 (t, *J* = 2.7 Hz, 1H), 6.32 (dd, *J* = 2.8, 1.8 Hz, 1H), 5.82 – 5.66 (m, 1H), 5.14 – 5.02 (m, 2H), 3.92 (t, *J* = 7.2 Hz, 2H), 3.54 (q, *J* = 7.1 Hz, 4H), 2.52 (q, *J* = 7.1 Hz, 2H), 1.23 (t, *J* = 7.1 Hz, 6H). **^{13}C NMR**

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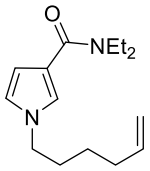
(126 MHz, $CDCl_3$) δ 166.66 (CO), 134.07 (CH), 124.02 (CH), 120.44 (CH), 118.90 (C), 117.52 (CH_2), 108.84 (CH), 49.42 (CH_2), 41.68 (CH_2), 35.44 (CH_2), 13.67 (CH_3). **HRMS** [APCI]: *m/z* calculated for $C_{13}H_{21}N_2O$ $[M+H]^+$: 221.1648, found 221.1648.

***N,N*-Diethyl-1-(pent-4-en-1-yl)-1H-pyrrole-3-carboxamide (1k)**



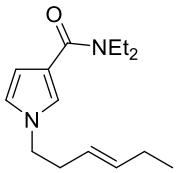
Synthesized by following the same procedure used for **1j**, obtained as yellow oil in 75% yield. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 6.97 (t, *J* = 2.0 Hz, 1H), 6.48 (t, *J* = 2.6 Hz, 1H), 6.25 (dd, *J* = 2.9, 1.8 Hz, 1H), 5.77 – 5.62 (m, 1H), 5.00 – 4.90 (m, 2H), 3.78 (t, *J* = 7.0 Hz, 2H), 3.46 (q, *J* = 7.1 Hz, 4H), 1.98 (q, *J* = 7.3 Hz, 2H), 1.79 (p, *J* = 7.3 Hz, 2H), 1.14 (t, *J* = 7.1 Hz, 6H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 166.28 (CO), 136.79 (CH), 123.24 (CH), 120.12 (CH), 119.23 (C), 115.40 (CH_2), 108.55 (CH), 48.72 (CH_2), 41.26 (CH_2), 30.22 (CH_2), 29.98 (CH_2), 13.50 (CH_3). **HRMS** [APCI]: *m/z* calculated for $C_{14}H_{23}N_2O$ $[M+H]^+$: 235.1805, found 235.1805.

***N,N*-Diethyl-1-(hex-5-en-1-yl)-1H-pyrrole-3-carboxamide (1w)**



Synthesized by following the same procedure used for **1j**, obtained as yellow oil in 45 % yield. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 6.99 (t, *J* = 2.0 Hz, 1H), 6.50 (t, *J* = 2.6 Hz, 1H), 6.26 (dd, *J* = 2.8, 1.7 Hz, 1H), 5.76 – 5.64 (m, 1H), 4.99 – 4.86 (m, 2H), 3.79 (t, *J* = 7.1 Hz, 2H), 3.48 (q, *J* = 7.1 Hz, 4H), 2.01 (q, *J* = 7.2 Hz, 2H), 1.72 (p, *J* = 7.3 Hz, 2H), 1.34 (p, *J* = 7.5 Hz, 2H), 1.16 (t, *J* = 7.1 Hz, 6H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 166.38 (CO), 137.80 (CH), 123.35 (CH), 120.15 (CH), 119.25 (C), 114.76 (CH_2), 108.54 (CH), 49.47 (CH_2), 41.32 (CH_2), 32.89 (CH_2), 30.38 (CH_2), 25.67 (CH_2), 13.55 (CH_3). **HRMS** [APCI]: *m/z* calculated for $C_{15}H_{25}N_2O$ $[M+H]^+$: 249.1961, found 249.1958.

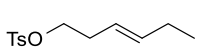
(*E*)-*N,N*-diethyl-1-(hex-3-en-1-yl)-1H-pyrrole-3-carboxamide (1l)



Alkylation performed using the same procedure than **1a** using **S5**, obtained as yellow oil (0.31 g, 91% yield). **^{1}H NMR** (750 MHz, $CDCl_3$) δ 6.97 (t, *J* = 2.0 Hz, 1H), 6.49 (t, *J* = 2.6 Hz, 1H), 6.24 (dd, *J* = 2.8, 1.7 Hz, 1H), 5.50 – 5.38 (m, 1H), 5.33 – 5.19 (m, 1H), 3.79 (t, *J* = 7.2 Hz, 2H), 3.46 (q, *J* = 7.1 Hz, 4H), 2.36 (q, *J* = 7.0 Hz, 2H), 1.91 (p, *J* = 7.4 Hz, 2H), 1.15 (t, *J* = 7.1 Hz, 6H), 0.87 (t, *J* = 7.5 Hz, 3H) ppm. **^{13}C NMR** (189 MHz, $CDCl_3$) δ 166.48 (CO), 135.24 (CH), 124.26 (CH), 123.42 (CH), 120.31 (CH), 119.05 (C), 108.61 (CH), 49.88 (CH_2), 41.36 (CH_2), 34.42 (CH_2), 25.44 (CH_2), 13.66 (CH_3), 13.51 (CH_3) ppm. **HRMS** [APCI]: *m/z* calculated for $C_{15}H_{25}N_2O$ $[M+H]^+$: 249.1961, found 249.1959.

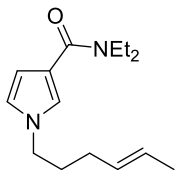
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(*E*)-hex-3-en-1-yl 4-methylbenzenesulfonate (S5)



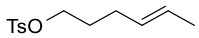
Tosylation of commercially available (*E*)-hex-3-en-1-ol performed using the same conditions than 3-methylene-5-phenylpentyl 4-methylbenzenesulfonate (S1), obtained as transparent oil (1.60 g, 65% yield). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.78 (d, *J* = 8.3 Hz, 2H), 7.33 (d, *J* = 7.9 Hz, 2H), 5.59 – 5.44 (m, 1H), 5.37 – 5.17 (m, 1H), 4.01 (t, *J* = 6.9 Hz, 2H), 2.44 (s, 3H), 2.32 (qd, *J* = 6.8, 1.2 Hz, 2H), 2.08 – 1.86 (m, 2H), 0.92 (t, *J* = 7.4 Hz, 3H) ppm. **^{13}C NMR** (75 MHz, $CDCl_3$) δ 144.17 (C), 136.07 (CH), 129.78 (CH), 127.90 (CH), 122.54 (CH), 70.15 (CH_2), 32.08 (CH_2), 25.52 (CH_2), 21.61 (CH_3), 13.49 (CH_3) ppm (one quaternary carbon signal overlapped).

(*E*)-*N,N*-diethyl-1-(hex-4-en-1-yl)-1H-pyrrole-3-carboxamide (1m)



Alkylation performed using the same procedure than **1a** using **S6**, obtained as yellow oil (0.34 g, 88% yield). **^{1}H NMR** (750 MHz, $CDCl_3$) δ 6.97 (s, 1H), 6.49 (s, 1H), 6.25 (s, 1H), 5.49 – 5.21 (m, 2H), 3.77 (t, *J* = 7.1 Hz, 2H), 3.47 (q, *J* = 7.1 Hz, 4H), 1.91 (q, *J* = 7.1 Hz, 2H), 1.75 (p, *J* = 7.2 Hz, 2H), 1.58 (dd, *J* = 6.0, 1.5 Hz, 3H), 1.15 (t, *J* = 7.1 Hz, 7H) ppm. **^{13}C NMR** (189 MHz, $CDCl_3$) δ 166.52 (CO), 129.53 (C), 126.16 (CH), 123.50 (CH), 120.30 (CH), 119.28 (C), 108.68 (CH), 48.98 (CH_2), 41.45 (CH_2), 30.79 (CH_2), 29.28 (CH_2), 17.66 (CH_3), 13.67 (CH_3) ppm. **HRMS** [APCI]: *m/z* calculated for $C_{15}H_{25}N_2O$ $[M+H]^+$: 249.1961, found 249.1959.

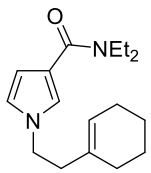
(*E*)-hex-4-en-1-yl 4-methylbenzenesulfonate (S6)



Tosylation of commercially available (*E*)-hex-4-en-1-ol performed using the same conditions than 3-methylene-5-phenylpentyl 4-methylbenzenesulfonate, obtained as transparent oil (1.02 g, 80% yield). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.79 (d, *J* = 8.3 Hz, 2H), 7.34 (d, *J* = 8.2 Hz, 2H), 5.46 – 5.12 (m, 2H), 4.01 (t, *J* = 6.4 Hz, 2H), 2.45 (s, 3H), 2.05 – 1.91 (m, 2H), 1.68 (p, *J* = 6.5 Hz, 2H), 1.58 (d, *J* = 4.8 Hz, 3H) ppm. **^{13}C NMR** (75 MHz, $CDCl_3$) δ 144.88 (C), 133.29 (C), 129.92 (CH), 129.18 (CH), 128.04 (CH), 126.64 (CH), 70.02 (CH_2), 28.69 (CH_2), 28.30 (CH_2), 21.76 (CH_3), 17.96 (CH_3) ppm.

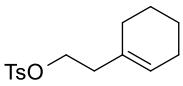
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1-(2-(cyclohex-1-en-1-yl)ethyl)-*N,N*-diethyl-1H-pyrrole-3-carboxamide (1n)



Alkylation performed using the same procedure than **1a**, using **S7**. Obtained as yellow oil (0.87 g, 47 % yield). **^{1}H NMR** (750 MHz, $CDCl_3$) δ 7.00 (t, *J* = 2.1 Hz, 1H), 6.52 (t, *J* = 2.6 Hz, 1H), 6.27 (dd, *J* = 2.8, 1.8 Hz, 1H), 5.38 – 5.31 (m, 1H), 3.87 (t, *J* = 7.4 Hz, 2H), 3.48 (q, *J* = 7.1 Hz, 4H), 2.32 (t, *J* = 7.4 Hz, 2H), 1.89 (dt, *J* = 12.5, 5.3 Hz, 4H), 1.62 – 1.44 (m, 4H), 1.18 (t, *J* = 7.1 Hz, 6H) ppm. **^{13}C NMR** (189 MHz, $CDCl_3$) δ 166.60 (CO), 133.82 (C), 123.91 (CH), 123.58 (CH), 120.39 (CH), 118.98 (C), 108.64 (CH), 48.65 (CH_2), 41.45 (CH_2 amide), 39.81 (CH_2), 28.23 (CH_2), 25.20 (CH_2), 22.83 (CH_2), 22.21 (CH_2), 13.75 (CH_3 amide) ppm. **HRMS** [APCI]: *m/z* calculated for $[M+H]^+$: 274.2045, found 274.2045.

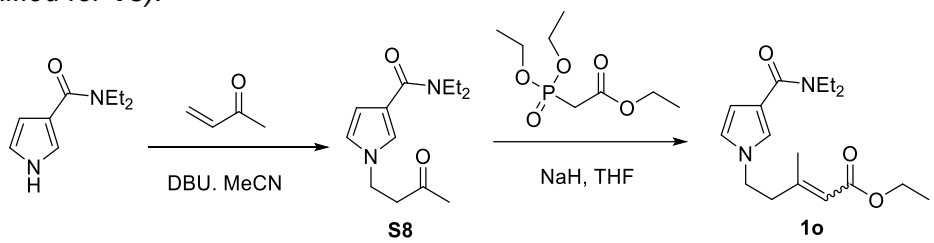
2-(cyclohex-1-en-1-yl)ethyl 4-methylbenzenesulfonate (S7)



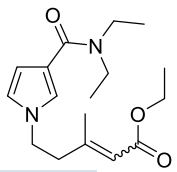
Commercially available ethyl 2-(cyclohex-1-en-1-yl)acetate was reduced using $LiAlH_4$, then tosylation was performed using the same conditions than 3-methylene-5-phenylpentyl 4-methylbenzenesulfonate (**S1**), obtained as transparent oil (1.6 g, 80% combined yield). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.73 (d, *J* = 8.1 Hz, 2H), 7.30 (d, *J* = 8.2 Hz, 2H), 5.41 – 5.27 (m, 1H), 4.03 (t, *J* = 6.8 Hz, 2H), 2.39 (s, 3H), 2.26 – 2.14 (m, 2H), 1.93 – 1.84 (m, 2H), 1.81 – 1.71 (m, 2H), 1.55 – 1.39 (m, 4H) ppm. **^{13}C NMR** (75 MHz, $CDCl_3$) δ 144.56 (C), 133.17 (C), 132.15 (C), 129.68 (CH), 127.68 (CH), 124.24 (CH), 68.93 (CH_2), 36.95 (CH_2), 28.05 (CH_2), 25.02 (CH_2), 22.57 (CH_2), 21.98 (CH_2), 21.40 (CH_3) ppm.

Synthesis of precursors 1o-p and 1v

*(exemplified for **1o**).*



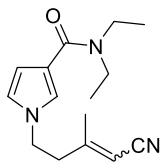
ethyl 5-(3-(diethylcarbamoyl)-1H-pyrrol-1-yl)-3-methylpent-2-enoate (1o)



Methylvinylketone (0.73 mL, 9.02 mmol) was added to a solution of *N,N*-diethyl-1H-pyrrole-3-carboxamide (1 g, 6.01 mmol) and DBU (0.45 mL, 3.00 mmol) in MeCN (12 mL). The reaction was stirred at 50 ºC for 16h under Ar atmosphere, allowed to cool to *rt* and water (100 mL) was added. The mixture was extracted with Et_2O (5 x 25 mL). The organic phase was dried, concentrated and the crude residue was purified by flash chromatography to obtain ***N,N***-

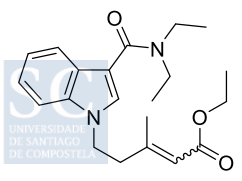
diethyl-1-(3-oxobutyl)-1H-pyrrole-3-carboxamide (**S8**, 1.24 g, 87% yield) as yellow oil. Under argon atmosphere, NaH (63.5 mg, 1.59 mmol, 60% suspension) was added to a solution of triethylphosphonoacetate (0.32 mL, 1.59 mmol) in THF (4.6 mL). After 30 minutes of vigorous stirring, *N,N*-diethyl-1-(3-oxobutyl)-1H-pyrrole-3-carboxamide **S7** (0.25 g, 1.06 mmol) in THF (0.9 mL) was added to the reaction. The reaction was stirred for 16 h at 50 ºC under Ar atmosphere, allowed to cool to *rt* and water (50 mL) was added. The mixture was extracted with AcOEt (5 x 25 mL). The organic phase was dried, concentrated and the crude residue was purified by flash chromatography (156 mg, 48% yield), obtained an inseparable 6:4 mixture of E/Z isomers as yellow oil. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.09 (s, 0.42H), 7.04 (d, *J* = 2.1 Hz, 0.58H), 6.63 (s, 0.42H), 6.55 (t, *J* = 2.6 Hz, 0.58H), 6.32 (t, *J* = 2.3 Hz, 1H), 5.77 (s, 0.42H), 5.62 (s, 0.58H), 4.15 (tt, *J* = 7.3, 3.6 Hz, 2H), 4.03 (q, *J* = 7.8 Hz, 2H), 3.57 – 3.47 (m, 4H), 3.02 (t, *J* = 7.3 Hz, 0.84H), 2.59 (t, *J* = 7.3 Hz, 1.16H), 2.17 (s, 1.74H), 1.75 (s, 1.26H), 1.33 – 1.21 (m, 9H) ppm. **^{13}C NMR** (75 MHz, $CDCl_3$) δ 166.15 (CO), 163.75 (CO), 156.07 (C), 154.54 (C), 123.77 (CH), 123.41 (CH), 120.58 (CH), 120.33 (CH), 119.61 (C), 119.24 (C), 118.24 (CH), 118.08 (CH), 109.09 (CH), 108.95 (CH), 59.72 (CH_2), 48.61 (CH_2), 47.90 (CH_2), 42.42 (CH_2), 41.25 (CH_2), 35.76 (CH_2), 25.87 (CH_3), 18.64 (CH_3), 14.26 (CH_3), 13.73 (CH_3) ppm. **HRMS** [APCI]: *m/z* calculated for $C_{17}H_{27}N_2O_3$ $[M+H]^+$: 307.2016, found 307.2020.

1-(4-cyano-3-methylbut-3-en-1-yl)-*N,N*-diethyl-1H-pyrrole-3-carboxamide (1p)



Synthesized by following the procedure used for **1o**, using diethyl (cyanomethyl)phosphonate instead of triethylphosphonoacetate. Obtained as an inseparable 6:4 mixture of *E/Z* isomers as a yellow oil in 57% of global yield. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.03 – 6.86 (m, 1H), 6.54 (t, *J* = 2.6 Hz, 0.4H), 6.48 (t, *J* = 2.6 Hz, 0.6H), 6.25 (dd, *J* = 5.5, 3.1 Hz, 1H), 5.15 (s, 0.4H), 4.98 (s, 0.6H), 3.98 (dt, *J* = 16.3, 7.0 Hz, 2H), 3.44 (q, *J* = 7.1 Hz, 4H), 2.76 (t, *J* = 7.0 Hz, 0.8H), 2.56 (t, *J* = 6.9 Hz, 1.2H), 1.98 (s, 1.8H), 1.77 (s, 1.2H), 1.14 (t, *J* = 7.1 Hz, 6H) ppm. **^{13}C NMR** (75 MHz, $CDCl_3$) δ 166.20 (CO), 161.04 (CN), 160.49 (CN), 123.17 (CH), 123.05 (CH), 120.34 (CH), 120.26 (CH), 119.76 (C), 116.34 (C), 116.16 (C), 109.30 (CH), 109.15 (CH), 98.25 (CH), 97.70 (CH), 47.43 (CH_2), 47.25 (CH_2), 42.09 (CH_2), 39.97 (CH_2), 37.71 (CH_2), 23.08 (CH_3), 20.76 (CH_3), 13.80 (CH_3) ppm. **HRMS** [APCI]: *m/z* calculated for $C_{15}H_{22}N_3O$ $[M+H]^+$: 260.1757, found 260.1759.

ethyl 5-(3-(diethylcarbamoyl)-1H-indol-1-yl)-3-methylpent-2-enoate (1v)

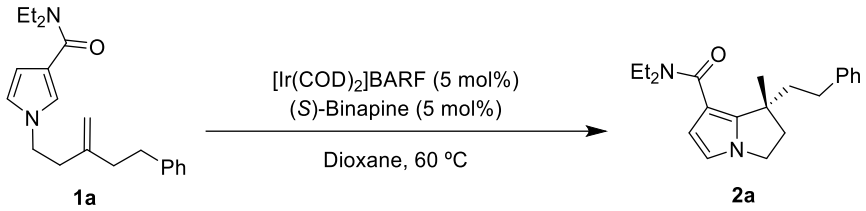


Synthesized by following the procedure used for **1o**, using diethyl *N,N*-diethyl-1H-indole-3-carboxamide instead of *N,N*-diethyl-1H-pyrrole-3-carboxamide. Obtained as an inseparable 1:1 mixture of *E/Z* isomers as yellow oil in 66% of global yield. **^{1}H NMR** (300 MHz,

$CDCl_3$) δ 7.78 (d, *J* = 7.9 Hz, 1H), 7.49 – 7.17 (m, 4H), 5.78 (s, 0.46H), 5.59 (s, 0.54H), 4.29 (dt, *J* = 14.3, 7.3 Hz, 2H), 4.22 – 4.04 (m, 2H), 3.55 (t, *J* = 7.1 Hz, 4H), 3.08 (t, *J* = 7.4 Hz, 1.08H), 2.64 (t, *J* = 7.2 Hz, 0.92H), 2.20 (s, 1.38H), 1.75 (s, 1.62H), 1.42 – 1.09 (m, 9H) ppm. **^{13}C NMR** (75 MHz, $CDCl_3$) δ 166.75 (CO), 166.61 (CO), 166.04 (CO), 165.94 (CO), 155.77 (C), 154.71 (C), 135.68 (C), 135.53 (C), 128.37 (CH), 127.92 (CH), 126.99 (C), 126.92 (C), 122.55 (CH), 122.43 (CH), 121.17 (CH), 120.99 (CH), 120.79 (CH), 120.65 (CH), 118.47 (CH), 118.27 (CH), 111.59 (C), 111.41 (C), 109.75 (CH), 109.33 (CH), 59.79 (CH_2), 59.71 (CH_2), 45.18 (CH_2), 44.68 (CH_2), 41.33 (CH_2), 40.93 (CH_2), 34.49 (CH_2), 25.99 (CH_3), 18.75 (CH_3), 14.27 (CH_3), 13.88 (CH_3) ppm. **HRMS** [APCI]: *m/z* calculated for $C_{21}H_{29}N_3O$ [M+H]$^+$: 339.2305, found 339.2305.

Synthesis of compounds 2 by hydroarylation of precursors 1

*(exemplified for **2a**).*



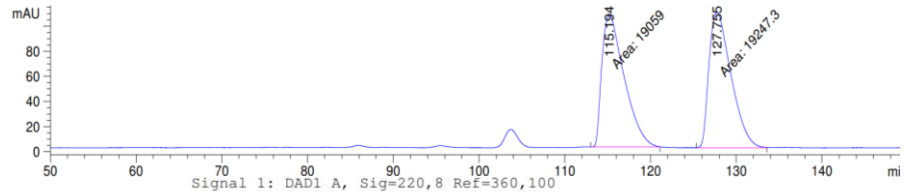
1a **2a**

Prepared following general procedure for catalytic reactions (page 104), using **1a** (50 mg, 0.154 mmol), $[Ir(COD)_2]$BARF (9.8 mg, 0.008 mmol) and (*S*)-Binapine (9.8 mg, 0.008 mmol) in dioxane (1.2 mL) at 60 ºC for 16 h. Obtained as yellow oil (47.5 mg, 95% yield). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.16 – 7.01 (m, 5H), 6.35 (d, *J* = 2.8 Hz, 1H), 6.14 (d, *J* = 2.8 Hz, 1H), 3.95 – 3.79 (m, 2H), 3.55 – 3.29 (m, 4H), 2.56 – 2.46 (m, 1H), 2.46 – 2.34 (m, 2H), 2.21 – 2.13 (m, 1H), 2.13 – 2.04 (m, 1H), 1.99 – 1.90 (m, 1H), 1.40 (s, 3H), 1.10 (t, *J* = 7.1 Hz, 6H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 167.88 (CO), 145.78 (C), 142.91 (C), 128.56 (CH), 128.39 (CH), 125.71 (CH), 112.41 (CH), 111.70 (CH), 110.54 (C), 45.45 (CH_2), 43.62 (C), 41.72 (CH_2), 41.60 (CH_2), 41.43 (CH_2), 31.97 (CH_2), 26.94 (CH_2), 25.97 (CH_3), 13.90 (CH_3). **HRMS** [APCI]: *m/z* calculated for $C_{21}H_{29}N_2O$ [M+H]$^+$: 325.2274, found 325.2278. **NMR spectra at page 462.**

Enantioselectivity was determined by chiral HPLC analysis on a Chiralpack IE-3 column at *rt* (Hexane:iPrOH = 98:02, 1mL/min).

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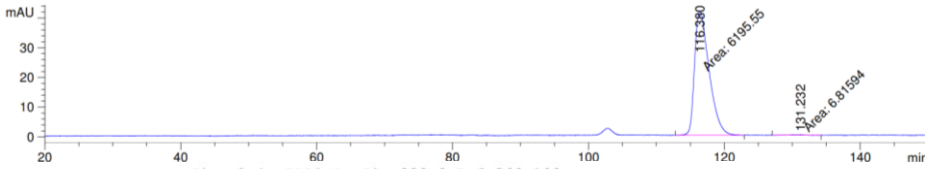
- Racemic sample prepared using [Ir(COD)$_2$]BARF / *rac*-BINAP (5 mol%) at 100 ºC.



Signal 1: DAD1 A, Sig=220,8 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	115.194	MM	3.0125	1.90590e4	105.44257	49.7542
2	127.755	MM	2.9684	1.92473e4	108.06902	50.2458
Totals :				3.83063e4	213.51158	

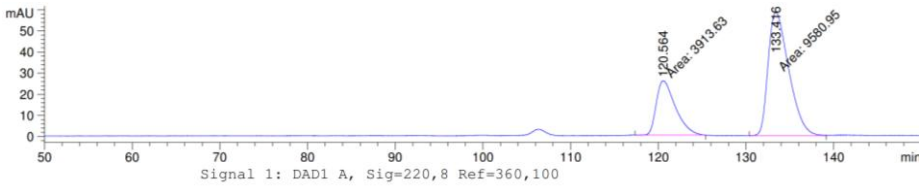
- Asymmetric sample prepared using [Ir(COD)$_2$]BARF / *(S)*-Binapine (5 mol%) at 60 ºC (95% yield, 99.9: 0.1 er).



Signal 1: DAD1 A, Sig=220,8 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	116.380	MM	2.4736	6195.54639	41.74466	99.8901
2	131.232	MM	0.9341	6.81594	1.21617e-1	0.1099
Totals :				6202.36232	41.86628	

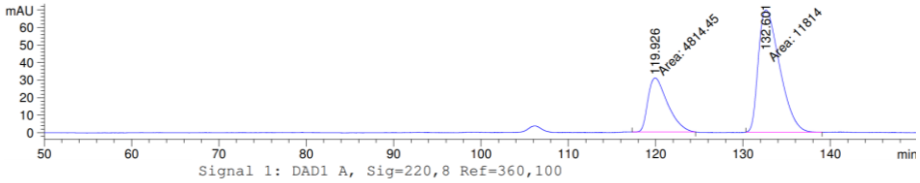
- Asymmetric sample prepared using [Ir(COD)$_2$]BARF / *(S)*-SDP (5 mol%) at 60 ºC (44% yield, 71: 29 er).



Signal 1: DAD1 A, Sig=220,8 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	120.564	MM	2.5344	3913.63086	25.73623	29.0015
2	133.416	MM	2.7324	9580.95312	58.43945	70.9985
Totals :				1.34946e4	84.17568	

- Asymmetric sample prepared using [Ir(COD)$_2$]BARF / (*R,R,S,S*)-DuanPhos (5 mol%) at 60 ºC (81% yield, 71: 29 er).

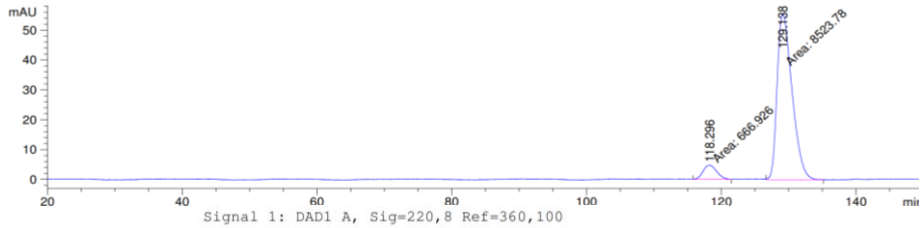


Signal 1: DAD1 A, Sig=220,8 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	119.926	MM	2.6047	4814.45117	30.80593	28.9531
2	132.601	MM	2.8240	1.18140e4	69.72458	71.0469
Totals :				1.66285e4	100.53050	

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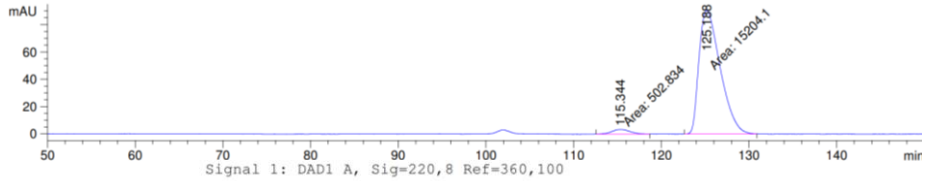
- Asymmetric sample prepared using [Ir(COD)$_2$]BARF / *(S)*-DM-BINAP (5 mol%) at 60 ºC (17% yield, 93: 7 er).



Signal 1: DAD1 A, Sig=220,8 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	118.296	MM	2.3358	666.92554	4.75875	7.2565
2	129.138	MM	2.5585	8523.78418	55.52687	92.7435
Totals :				9190.70972	60.28562	

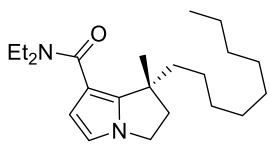
- Asymmetric sample prepared using [Ir(COD)$_2$]BARF / *(S)*-BINAP (5 mol%) at 60 ºC (83% yield, 97: 3 er).



Signal 1: DAD1 A, Sig=220,8 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	115.344	MM	2.4212	502.83386	3.46132	3.2013
2	125.188	MM	2.7977	1.52041e4	90.57454	96.7987
Totals :				1.57070e4	94.03586	

***(R)*-*N,N*-Diethyl-1-methyl-1-nonyl-2,3-dihydro-1H-pyrrolizine-7-carboxamide (2b)**

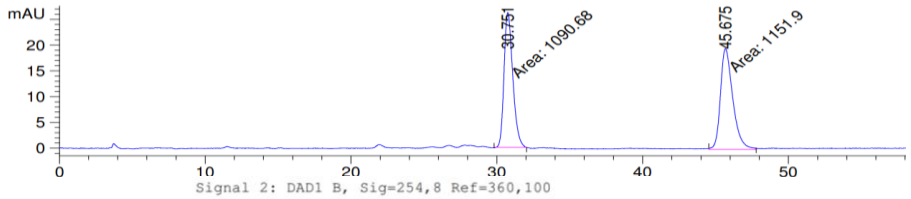


Prepared following general procedure for catalytic reactions (page 104), using **1b** Isolated by flash chromatography (1:3 to 3:1 EtOAc/Hexanes) as orange oil. **^{1}H NMR** (500 MHz, $CDCl_3$) δ ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.39 (d, *J* = 2.7 Hz, 1H), 6.18 (d, *J* = 2.7 Hz, 1H), 3.98 – 3.85 (m, 2H), 3.57 – 3.40 (m, 4H), 2.48 – 2.35 (m, 1H), 2.21 – 2.14 (m, 1H), 1.79 – 1.68 (m, 2H), 1.40 (s, 3H), 1.35 – 1.20 (m, 14H), 1.18 (t, *J* = 7.1 Hz, 6H), 0.87 (t, *J* = 7.0 Hz, 3H) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$) δ 167.57 (CO), 145.91 (C), 111.69 (CH), 111.06 (CH), 109.75 (C), 53.06 (CH_2), 45.04 (CH_2), 43.02 (C), 41.04 (CH_2), 39.51 (CH_2), 31.62 (CH_2), 29.98 (CH_2), 29.45 (CH_2), 29.37 (CH_2), 29.02 (CH_2), 25.38 (CH_3), 24.96 (CH_2), 22.37 (CH_2), 13.73 (CH_3), 13.42 (CH_3). **HRMS** [APCI]: *m/z* calculated for $C_{22}H_{39}N_2O$ $[M+H]^+$: 347.3057, found 347.3059.

Enantioselectivity was determined by chiral HPLC analysis on a Chiralpack IF-3 column at *rt* (Hexane:iPrOH = 98:02, 1mL/min).

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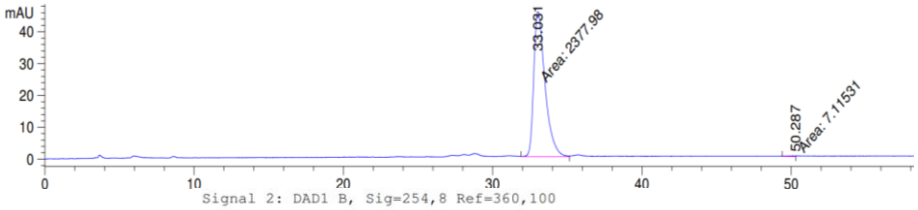
- Racemic sample prepared using [Ir(COD)$_2$]BARF / *rac*-BINAP (5 mol%) at 100 ºC.



Signal 2: DAD1 B, Sig=254,8 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	30.751	MM	0.6944	1090.68298	26.17857	48.6351
2	45.675	MM	0.9813	1151.89966	19.56469	51.3649
Totals :				2242.58264	45.74326	

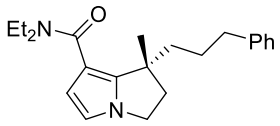
- Asymmetric sample prepared using [Ir(COD)$_2$]BARF / *(S)*-Binapine at 60 ºC (74% yield, 99.7:0.3 er).



Signal 2: DAD1 B, Sig=254,8 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	33.031	MM	0.8705	2377.97607	45.52933	99.7017
2	50.287	MM	0.4769	7.11531	2.48660e-1	0.2983
Totals :				2385.09138	45.77799	

(*R*)-*N*,*N*-Diethyl-1-methyl-1-(3-phenylpropyl)-2,3-dihydro-1H-pyrrolizine-7-carboxamide (2c)

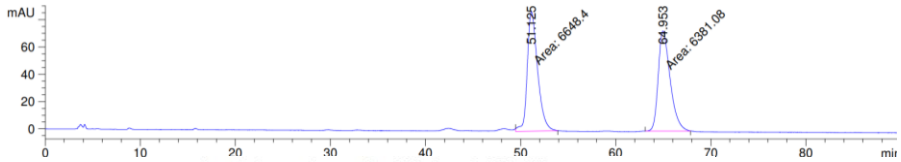


Prepared following general procedure for catalytic reactions (page 104), using **1c.** Isolated by flash chromatography (1:3 to 3:1 EtOAc/Hexanes) as brown oil. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.29 – 7.05 (m, 5H), 6.39 (d, *J* = 2.8 Hz, 1H), 6.18 (d, *J* = 2.6 Hz, 1H), 4.00 – 3.76 (m, 2H), 3.63 – 3.32 (m, 4H), 2.57 (t, *J* = 7.8 Hz, 2H), 2.46 – 2.28 (m, 1H), 2.27 – 2.08 (m, 1H), 1.94 – 1.73 (m, 2H), 1.72 – 1.50 (m, 1H), 1.49 – 1.44 (m, 1H), 1.41 (s, 3H), 1.18 (t, *J* = 7.1 Hz, 6H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 167.93 (CO), 146.19 (C), 142.96 (C), 128.53 (CH), 128.36 (CH), 125.74 (CH), 112.24 (CH), 111.55 (CH), 110.22 (C), 45.42 (CH_2), 43.35 (C), 41.46 (CH_2), 41.37 (CH_2), 39.68 (CH_2), 36.67 (CH_2), 27.51 (CH_2), 25.75 (CH_3), 13.87 (CH_3). **HRMS** [APCI]: *m/z* calculated for $C_{22}H_{31}N_2O$ $[M+H]^+$: 339.2431, found 339.2432.

Enantioselectivity was determined by chiral HPLC analysis on a Chiralpack IF-3 column at *rt* (Hexane:iPrOH = 98:02, 1mL/min).

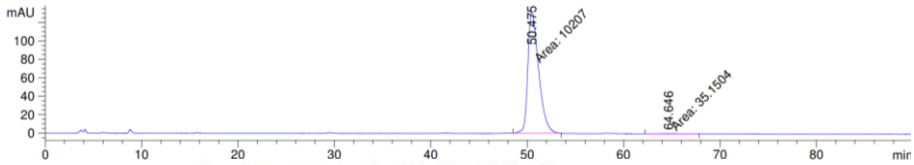
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- Racemic sample prepared using [Ir(COD)$_2$]BARF / *rac*-BINAP (5 mol%) at 100 ºC.



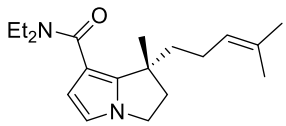
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	51.125	MM	1.2658	6648.40137	87.53709	51.0259
2	64.953	MM	1.4526	6381.07520	73.21513	48.9741
Totals :				1.30295e4	160.75222	

- Asymmetric sample prepared using [Ir(COD)$_2$]BARF / *(S)*-Binapine (5 mol%) at 60 ºC (99% yield, 99.7:0.7 er).



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	50.475	MM	1.2902	1.02070e4	131.84760	99.6568
2	64.646	MM	1.7528	35.15036	3.34230e-1	0.3432
Totals :				1.02421e4	132.18183	

_(R)_-_N,N_-Diethyl-1-methyl-1-(4-methylpent-3-en-1-yl)-2,3-dihydro-1H-pyrrolizine-7-carboxamide (2d)

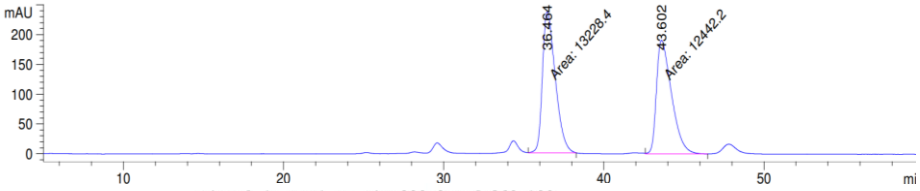


Prepared following general procedure for catalytic reactions (page 104), using **1d.** The product was isolated by flash chromatography (1:3 to 3:1 EtOAc/Hexanes) as brown oil. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 6.39 (d, *J* = 2.8 Hz, 1H), 6.18 (d, *J* = 2.8 Hz, 1H), 5.11 – 5.03 (m, 1H), 3.96 – 3.86 (m, 2H), 3.57 – 3.39 (m, 4H), 2.45 (ddd, *J* = 12.5, 7.9, 6.4 Hz, 1H), 2.20 (ddd, *J* = 12.6, 7.8, 6.0 Hz, 1H), 2.02 – 1.91 (m, 1H), 1.85 – 1.70 (m, 3H), 1.63 (s, 3H), 1.54 (s, 3H), 1.41 (s, 3H), 1.18 (t, *J* = 7.1 Hz, 6H) ppm.**^{13}C NMR** (126 MHz, $CDCl_3$) δ 13C NMR (126 MHz, $CDCl_3$) δ 167.87 (CO), 146.05 (C), 131.00 (C), 124.91 (CH), 112.19 (CH), 111.55 (CH), 110.26 (C), 45.41 (CH_2), 43.41 (C), 41.47 (C), 41.45 (CH_2), 39.79 (CH_2), 25.72 (CH_3), 25.68 (CH_2), 24.10 (CH_2), 17.69 (CH_3), 13.82 (CH_3). **HRMS** [APCI]: *m/z* calculated for $C_{19}H_{31}N_2O$ $[M+H]^+$: 303.2431, found 303.2429.

Enantioselectivity was determined by chiral HPLC analysis on a Chiralpack IF-3 column at *rt* (Hexane:iPrOH = 98:02, 1mL/min).

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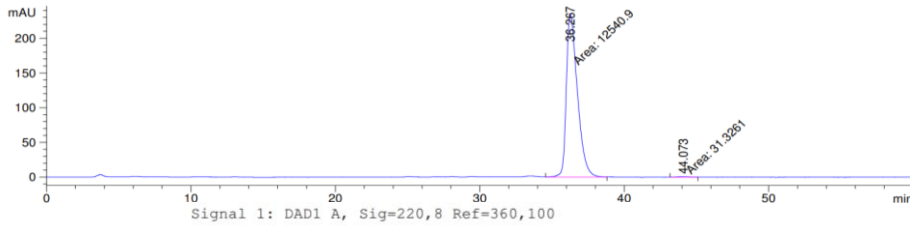
- Racemic sample prepared using [Ir(COD)$_2$]BARF / *rac*-BINAP (5 mol%) at 100 ºC.



Signal 1: DAD1 A, Sig=220,8 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	36.464	MM	0.9301	1.32284e4	237.03780	51.5313
2	43.602	MM	1.0878	1.24422e4	190.63158	48.4687
Totals :				2.56706e4	427.66937	

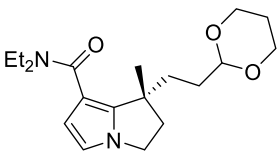
- Asymmetric sample prepared using [Ir(COD)$_2$]BARF / *(S)*-Binapine (5 mol%) at 60 ºC (88% yield, 99.8:0.2 er).



Signal 1: DAD1 A, Sig=220,8 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	36.267	MM	0.8907	1.25409e4	234.66106	99.7508
2	44.073	MM	0.8380	31.32609	6.23063e-1	0.2492
Totals :				1.25722e4	235.28412	

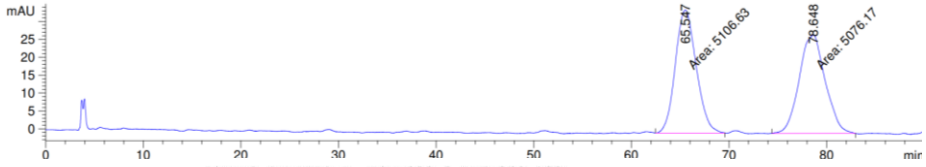
_(R)_-1-(2-(1,3-Dioxan-2-yl)ethyl)-_N,N_-diethyl-1-methyl-2,3-dihydro-1H-pyrrolizine-7-carboxamide (2e)



Prepared following general procedure for catalytic reactions (page 104), using **1e.** The product was isolated by flash chromatography (1:3 to 3:1 EtOAc/Hexanes) as orange oi. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 6.39 (d, *J* = 2.6 Hz, 1H), 6.16 (d, *J* = 2.7 Hz, 1H), 4.45 (t, *J* = 5.1 Hz, 1H), 4.04 (dd, *J* = 11.5, 4.9 Hz, 2H), 3.90 (t, *J* = 7.0 Hz, 2H), 3.70 (t, *J* = 12.1 Hz, 2H), 3.60 – 3.31 (m, 4H), 2.50 – 2.33 (m, 1H), 2.24 – 2.10 (m, 1H), 2.10 – 1.90 (m, 1H), 1.74 (t, *J* = 8.9 Hz, 2H), 1.53 (q, *J* = 7.7 Hz, 2H), 1.38 (s, 3H), 1.34 – 1.24 (m, 1H), 1.16 (t, *J* = 7.0 Hz, 6H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 167.94 (CO), 146.09 (C), 112.20 (CH), 111.47 (CH), 110.18 (C), 102.47 (CH), 66.95 (CH_2), 45.38 (CH_2), 43.37 (C), 41.35 (CH_2), 39.59 (CH_2), 35.88 (CH_2), 26.08 (CH_2), 25.63 (CH_3), 19.76 (CH_2), 13.82 (CH_3). **HRMS** [APCI]: *m/z* calculated for $C_{20}H_{33}N_2O_3$ $[M+H]^+$: 349.2486, found 349.2486. Enantioselectivity was determined by HPLC on a Chiralpack IA column at *rt* (Hexane:iPrOH = 98:02, 1mL/min).

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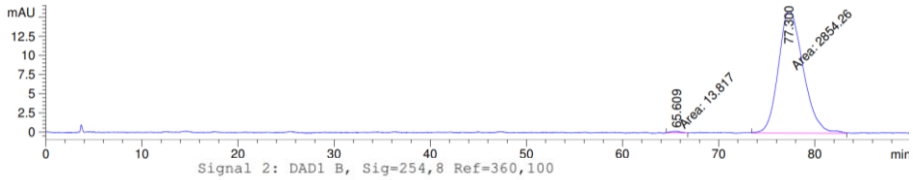
- Racemic sample prepared using [Ir(COD)$_2$]BARF / *rac*-BINAP (5 mol%) at 100 ºC.



Signal 1: DAD1 A, Sig=220,8 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	65.547	MM	2.4799	5106.63428	34.32022	50.1496
2	78.648	MM	3.0833	5076.17188	27.43931	49.8504
Totals :				1.01828e4	61.75953	

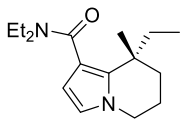
- Asymmetric sample prepared using [Ir(COD)$_2$]BARF / *(S)*-Binapine (5 mol%) at 60 ºC (99% yield, 99.5:0.5 er).



Signal 2: DAD1 B, Sig=254,8 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	65.609	MM	1.1145	13.81701	2.06625e-1	0.4818
2	77.300	MM	2.9943	2854.25610	15.88723	99.5182
Totals :				2868.07311	16.09386	

_(R)-N,N_,8-Triethyl-8-methyl-5,6,7,8-tetrahydroindolizine-1-carboxamide (2f)

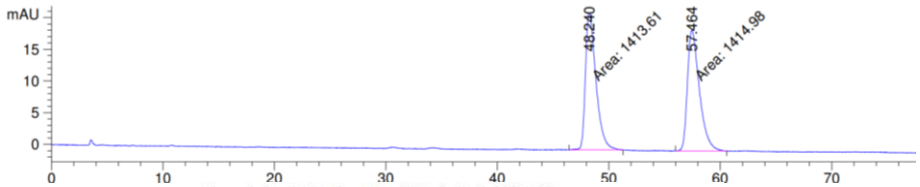


Prepared following general procedure for catalytic reactions (page 104), using **1a**. The product was isolated by flash chromatography (1:3 to 3:1 EtOAc/Hexanes) as brown oil. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 6.36 (d, *J* = 2.8 Hz, 1H), 6.00 (d, *J* = 2.7 Hz, 1H), 3.95 – 3.75 (m, 2H), 3.55 – 3.30 (m, 4H), 2.04 – 1.87 (m, 2H), 1.87 – 1.62 (m, 4H), 1.33 (s, 3H), 1.15 (t, *J* = 7.1 Hz, 6H), 0.78 (t, *J* = 7.5 Hz, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 170.01 (CO), 135.90 (C), 117.75 (CH), 114.70 (C), 107.39 (CH), 46.10 (CH_2), 40.79 (CH_2), 36.11 (C), 33.27 (CH_2), 33.11 (CH_2), 27.13 (CH_3), 20.15 (CH_2), 13.42 (CH_3), 8.80 (CH_3). **HRMS** [APCI]: *m/z* calculated for $C_{16}H_{27}N_2O$ $[M+H]^+$: 263.2118, found 263.2118.

Enantioselectivity was determined by chiral HPLC analysis on a Chiralpack IF-3 column at *rt* (Hexane:iPrOH = 97:03, 1mL/min).

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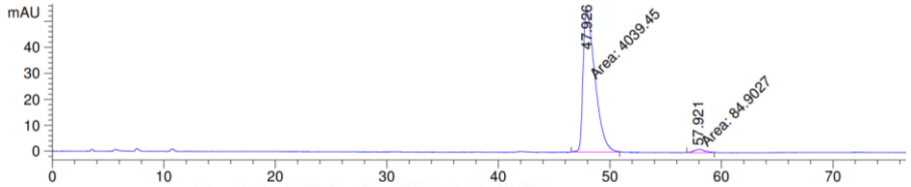
- Racemic sample prepared using [Ir(COD)$_2$]BARF / *rac*-BINAP (5 mol%) at 100 ºC.



Signal 2: DAD1 B, Sig=254,8 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	48.240	MM	1.0916	1413.61230	21.58357	49.9759
2	57.464	MM	1.2386	1414.97815	19.03972	50.0241
Totals :				2828.59045	40.62329	

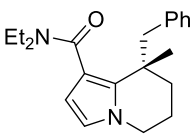
- Asymmetric sample prepared using [Ir(COD)$_2$]BARF / *(S)*-Binapine (5 mol%) at 60 ºC (99% yield, 98 :2 er).



Signal 2: DAD1 B, Sig=254,8 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	47.926	MM	1.2429	4039.45386	54.16912	97.9414
2	57.921	MM	1.1819	84.90269	1.19723	2.0586
Totals :				4124.35654	55.36635	

_(S)_-8-Benzyl-_N,N_-diethyl-8-methyl-5,6,7,8-tetrahydroindolizine-1-carboxamide (2g)

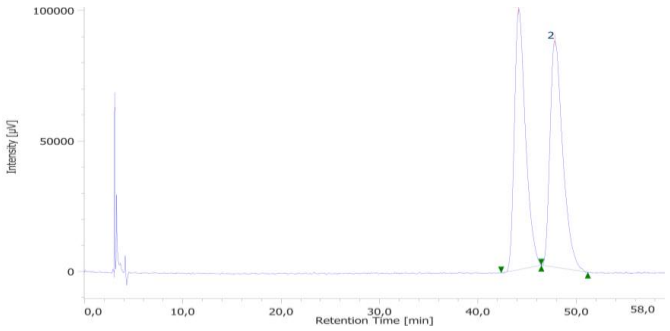


Prepared following general procedure for catalytic reactions (page 104), using **1a**. The product was isolated by flash chromatography (1:3 to 3:1 EtOAc/Hexanes) as orange oil.**^{1}H NMR** (750 MHz, $CDCl_3$) δ 7.21 (t, *J* = 7.8 Hz, 2H), 7.16 (t, *J* = 7.2 Hz, 1H), 7.12 (d, *J* = 6.6 Hz, 2H), 6.39 (d, *J* = 2.8 Hz, 1H), 6.08 (d, *J* = 2.8 Hz, 1H), 3.88 – 3.74 (m, 2H), 3.48 (q, *J* = 7.1 Hz, 4H), 3.19 (d, *J* = 2.4 Hz, 2H), 1.95 – 1.76 (m, 3H), 1.44 – 1.37 (m, 1H), 1.34 (s, 3H), 1.20 (t, *J* = 7.1 Hz, 6H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 170.14 (CO), 139.28 (C), 135.81 (C), 130.87 (CH), 127.82 (CH), 126.03 (CH), 117.92 (CH), 115.26 (C), 107.69 (CH), 46.89 (CH_2), 46.10 (CH_2), 41.13 (CH_2), 36.69 (C), 33.90 (CH_2), 27.47 (CH_3), 20.19 (CH_2), 13.58 (CH_3). **HRMS** [APCI]: *m/z* calculated for $C_{21}H_{29}N_2O$ $[M+H]^+$: 325.2274, found 325.2275.

Enantioselectivity was determined by chiral SFC analysis on Lux 5μm Amylose-2 column at *rt* (CO_2:MeOH = 95:05, 1mL/min).

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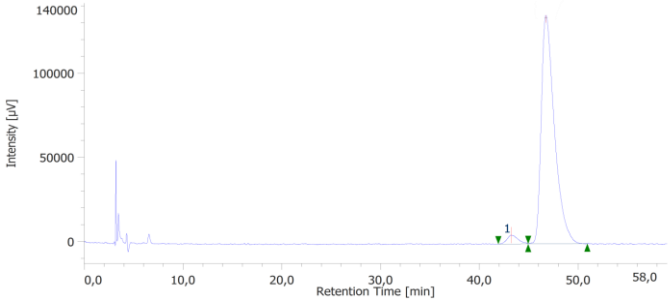
- Racemic sample prepared using [Ir(COD)$_2$]BARF / *rac*-BINAP (5 mol%) at 100 ºC.



Channel Name 220,0nm

#	Peak Name	CH	tR [min]	Area [μV·sec]	Height [μV]	Area%
1	Unknown	5	44,140	7823677	99894	50,019
2	Unknown	5	47,803	7817733	86752	49,981

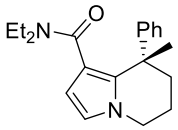
- Asymmetric sample prepared using [Ir(COD)$_2$]BARF / *(S)*-Binapine (5 mol%) at 60 ºC (74% yield, 97:3 er).



Channel Name 220,0nm

#	Peak Name	CH	tR [min]	Area [μV·sec]	Height [μV]	Area%
1	Unknown	5	43,203	418916	5310	3,230
2	Unknown	5	46,730	12550317	135938	96,770

_(S)-N,N_-Diethyl-8-methyl-8-phenyl-5,6,7,8-tetrahydroindolizine-1-carboxamide (2h)

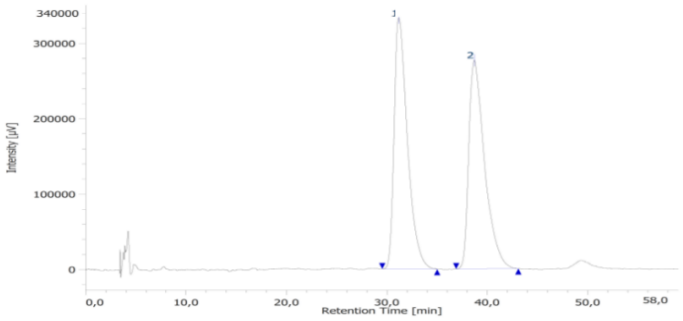


Prepared following general procedure for catalytic reactions (page 104), using **1a.** The product was isolated by flash chromatography (1:3 to 3:1 EtOAc/Hexanes) as orange oil. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.29 – 6.90 (m, 5H), 6.41 (d, *J* = 2.8 Hz, 1H), 5.99 (d, *J* = 2.8 Hz, 1H), 3.91 (t, *J* = 6.0 Hz, 2H), 3.30 – 3.15 (m, 2H), 2.97 – 2.82 (m, 2H), 2.00 – 1.86 (m, 2H), 1.83 – 1.75 (m, 5H), 0.83 (t, *J* = 6.6 Hz, 6H). **^{13}C NMR** (126 MHz, $CDCl_3$) 168.84 (C), 149.19 (C), 135.39 (C), 127.76 (CH), 127.16 (CH), 125.82 (CH), 118.02 (CH), 116.15 (C), 107.61 (CH), 45.87 (CH_2), 41.12 (C), 41.0 (br, CH_2), 40.28 (CH_2), 27.13 (CH_3), 20.22 (CH_2), 13.83 (CH_3). **HRMS** [APCI]: *m/z* calculated for $C_{20}H_{27}N_2O$ $[M+H]^+$: 311.2118, found 311.2118. **NMR spectra at page 463.**

Enantioselectivity was determined by chiral SFC analysis on Lux 5μm Amylose-2 at *rt* (CO_2:MeOH = 95:05, 1mL/min).

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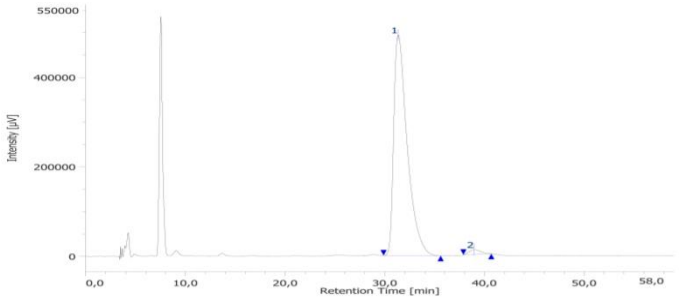
- Racemic sample prepared using [Ir(COD)$_2$]BARF / *rac*-BINAP (5 mol%) at 100 ºC.



Channel Name 220.0nm

#	Peak Name	CH	tR [min]	Area [μV·sec]	Height [μV]	Area%
1	Unknown	5	31.170	30785288	332700	50.407
2	Unknown	5	38.703	30287601	276611	49.593

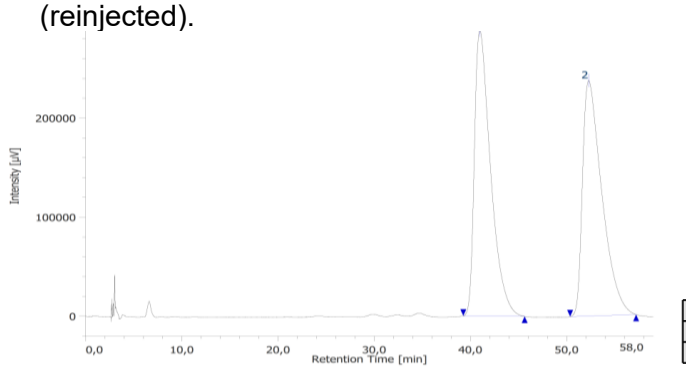
- Asymmetric sample prepared using [Ir(COD)$_2$]BARF / *(S)*-Binapine (5 mol%) at 60 ºC (87% yield, 98:2 er).



Channel Name 220.0nm

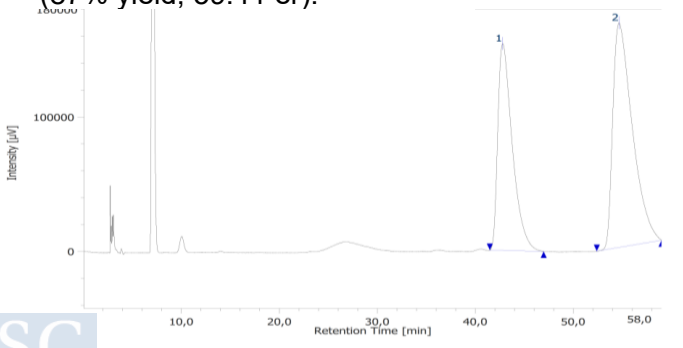
#	Peak Name	CH	tR [min]	Area [μV·sec]	Height [μV]	Area%
1	Unknown	5	31.337	46461911	492706	98.184
2	Unknown	5	38.967	859390	10547	1.816

- Racemic sample prepared using [Ir(COD)$_2$]BARF / rac-BINAP (5 mol%) at 100 ºC (reinjected).



#	Peak Name	CH	tR [min]	Area [μV·sec]	Height [μV]	Area%
1	Unknown	10	40.963	33804833	288450	50.385
2	Unknown	10	52.270	33287799	237619	49.615

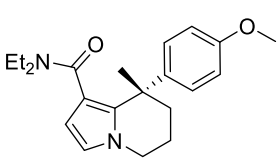
- Asymmetric sample prepared using [Ir(COD)$_2$]BARF / *(S)*-BINAP (5 mol%) at 60 ºC (87% yield, 59:41 er).



#	Peak Name	CH	tR [min]	Area [μV·sec]	Height [μV]	Area%
1	Unknown	10	42.790	15822644	153834	40.633
2	Unknown	10	54.673	23117517	167050	59.367

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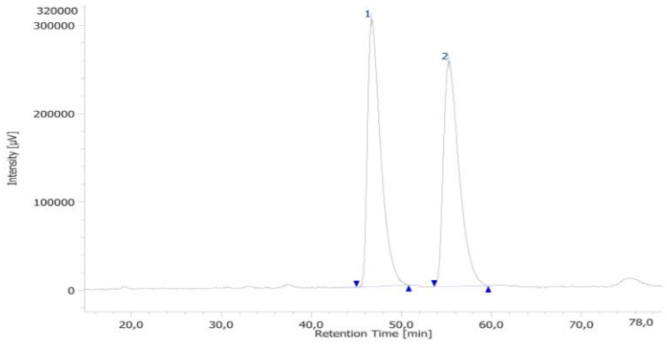
***(S)-N,N*-Diethyl-8-(4-methoxyphenyl)-8-methyl-5,6,7,8-tetrahydroindolizine-1-carboxamide (2i)**



Prepared following general procedure for catalytic reactions (page 104), using **1i.** The product was isolated by flash chromatography (1:3 to 3:1 EtOAc/Hexanes) as orange oil.[1] **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.07 (d, *J* = 8.8 Hz, 2H), 6.76 (d, *J* = 8.8 Hz, 2H), 6.48 (d, *J* = 2.8 Hz, 1H), 6.07 (d, *J* = 2.5 Hz, 1H), 4.02 – 3.92 (m, 2H), 3.75 (s, 3H), 3.38 – 3.26 (m, 2H), 3.07 – 2.96 (m, 2H), 2.07 – 1.93 (m, 2H), 1.87 – 1.82 (m, 5H), 0.93 (t, *J* = 7.1 Hz, 6H). **^{13}C NMR** (126 MHz, $CDCl_3$) 168.99 (C), 157.84 (C), 141.37 (C), 135.64 (C), 128.16 (CH), 118.02 (CH), 115.91 (C), 113.24 (CH), 107.58 (CH), 55.39 (CH_3), 45.86 (CH_2), 40.6 (br CH_2), 40.49 (C), 40.19 (CH_2), 27.36 (CH_3), 20.20 (CH_2), 13.33 (CH_3). **HRMS** [APCI]: *m/z* calculated for $C_{21}H_{28}N_2O_2$ $[M+H]^+$: 341.2224, found 341.2226.

Enantioselectivity was determined by chiral SFC analysis on Lux 5□m Amylose-2 at *rt* (CO_2:MeOH = 95:05, 1mL/min).

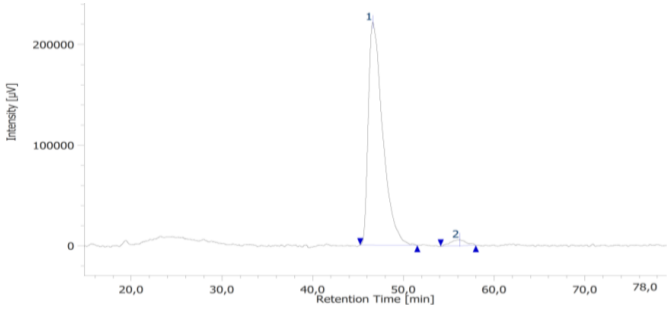
- Racemic sample prepared using $[Ir(COD)_2]$BARF / *rac*-BINAP (5 mol%) at 100 ºC.



Channel Name 222.0nm

#	Peak Name	CH	tR [min]	Area [μV*sec]	Height [μV]	Area%
1	Unknown	6	46.687	30749333	302871	49.961
2	Unknown	6	55.280	30797049	254616	50.039

- Asymmetric sample prepared using $[Ir(COD)_2]$BARF / *(S)*-Binapine (5 mol%) at 60 ºC (87% yield, 97:3 er).

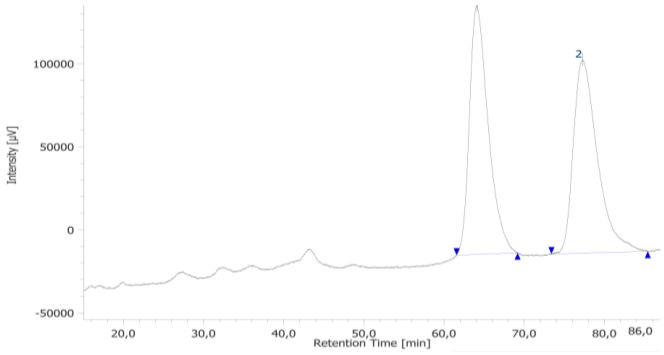


Channel Name 222.0nm

#	Peak Name	CH	tR [min]	Area [μV*sec]	Height [μV]	Area%
1	Unknown	6	46.613	24385365	221296	97.115
2	Unknown	6	56.180	724466	5974	2.885

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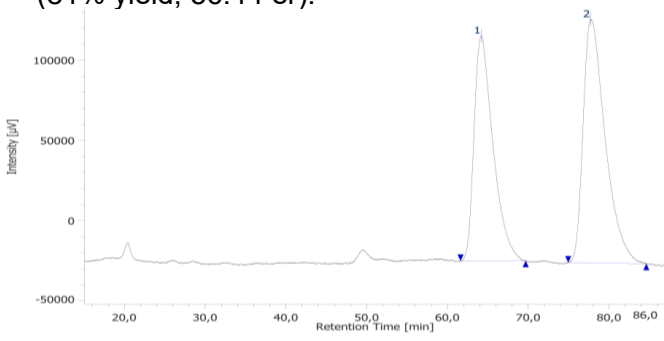
- Racemic sample prepared using [Ir(COD)$_2$]BARF / rac-BINAP (5 mol%) at 100 ºC (reinjected).



Channel Name 200,0nm

#	Peak Name	CH	tR [min]	Area [μV·sec]	Height [μV]	Area%
1	Unknown	5	64,097	24358509	149615	50,147
2	Unknown	5	77,257	24215734	116312	49,853

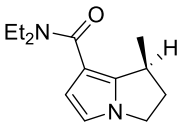
- Asymmetric sample prepared using [Ir(COD)$_2$]BARF / *(S)*-BINAP (5 mol%) at 60 ºC (81% yield, 56:44 er).



Channel Name 200,0nm

#	Peak Name	CH	tR [min]	Area [μV·sec]	Height [μV]	Area%
1	Unknown	5	64,157	22876337	140295	44,292
2	Unknown	5	77,667	28772595	151697	55,708

***(S)*-*N,N*-Diethyl-1-methyl-2,3-dihydro-1H-pyrrolizine-7-carboxamide (2j)**

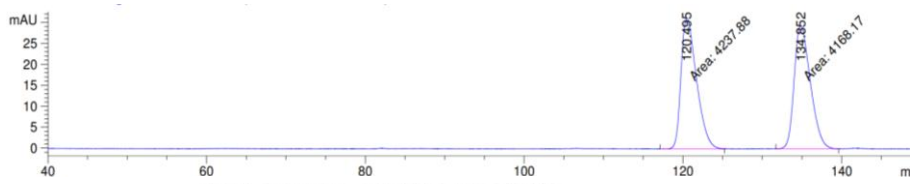


Prepared following general procedure for catalytic reactions (page 104), using **1j.** The product was isolated by flash chromatography (1:3 to 3:1 EtOAc/Hexanes) as brown oil. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 6.44 (d, *J* = 2.8 Hz, 1H), 6.25 (d, *J* = 2.8 Hz, 1H), 4.03 – 3.90 (m, 1H), 3.90 – 3.75 (m, 1H), 3.58 – 3.49 (m, 4H), 3.49 – 3.41 (m, 1H), 2.75 – 2.61 (m, 1H), 2.12 – 2.00 (m, 1H), 1.29 (d, *J* = 6.9 Hz, 3H), 1.19 (t, *J* = 7.1 Hz, 6H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 167.40 (CO), 145.59 (C), 112.84 (CH), 111.80 (CH), 110.35 (C), 45.74 (CH_2), 41.48 (CH_2), 36.55 (CH_2), 33.04 (CH_3), 19.31 (CH_3), 13.90 (CH_3). **HRMS** [APCI]: *m/z* calculated for $C_{13}H_{21}N_2O$ $[M+H]^+$: 221.1648, found 221.1647.

Enantioselectivity was determined by chiral HPLC analysis on a Chiralpack IE-3 column at *rt* (Hexane:iPrOH = 97:03, 1mL/min).

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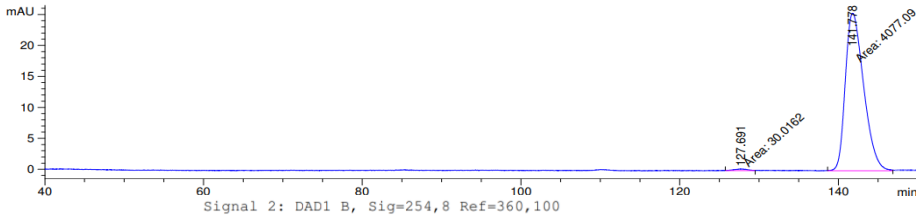
- Racemic sample prepared using [Ir(COD)$_2$]BARF / *rac*-BINAP (5 mol%) at 100 ºC.



Signal 2: DAD1 B, Sig=254,8 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	120.495	MM	2.2659	4237.87500	31.17087	50.4146
2	134.852	MM	2.3571	4168.16992	29.47280	49.5854
Totals :				8406.04492	60.64367	

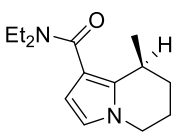
- Asymmetric sample prepared using [Ir(COD)$_2$]BARF / *(S)*-Binapine (5 mol%) at 60 ºC (75% yield, 99:1 er).



Signal 2: DAD1 B, Sig=254,8 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	127.691	MM	1.8204	30.01622	2.74809e-1	0.7308
2	141.778	MM	2.6722	4077.08765	25.42950	99.2692
Totals :				4107.10387	25.70431	

_(S)-N,N_-Diethyl-8-methyl-5,6,7,8-tetrahydroindolizine-1-carboxamide (2k)

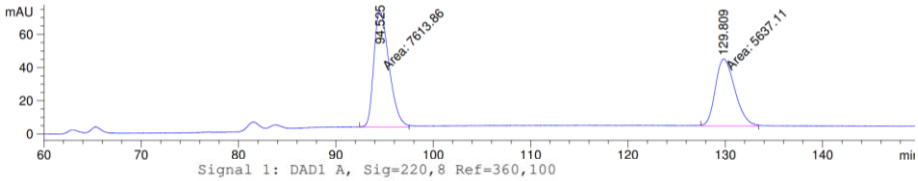


Prepared following general procedure for catalytic reactions (page 104), using **1k.** [Ir(COD)$_2$]BARF and the chiral ligand were dissolved in dioxane and stirred for 30 minutes before adding the substrate. The product was isolated by flash chromatography (1:3 to 3:1 EtOAc/Hexanes) as brown oil. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 6.38 (d, *J* = 2.8 Hz, 1H), 6.09 (d, *J* = 2.8 Hz, 1H), 3.86 (t, *J* = 4.9 Hz, 2H), 3.47 (dp, *J* = 27.8, 6.9 Hz, 4H), 3.39 – 3.25 (m, 1H), 2.06 – 1.77 (m, 3H), 1.56 – 1.40 (m, 1H), 1.26 – 1.11 (m, 9H) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$) δ 167.82 (CO), 134.29 (C), 116.58 (CH), 113.50 (C), 106.28 (CH), 44.66 (CH_2), 28.61 (CH_2), 28.36 (CH_2), 26.55 (CH), 20.22 (CH_3), 20.02 (CH_2), 12.52 (CH_3). **HRMS** [APCI]: *m/z* calculated for $C_{14}H_{23}N_2O$ $[M+H]^+$: 235.1805, found 235.1814.

Enantioselectivity was determined by chiral HPLC analysis on a Chiralpack IE-3 column at *rt* (Hexane:iPrOH = 95:05, 1mL/min).

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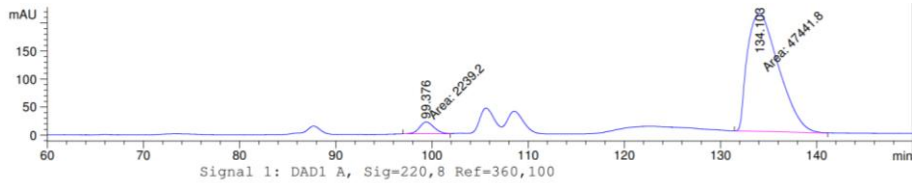
- Racemic sample prepared using [Ir(COD)$_2$]BARF / *rac*-BINAP (5 mol%), at 100 ºC.



Signal 1: DAD1 A, Sig=220,8 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	94.525	MM	1.8164	7613.85938	69.86070	57.4589
2	129.809	MM	2.3248	5637.11475	40.41278	42.5411
Totals :				1.32510e4	110.27348	

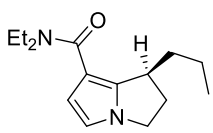
- Asymmetric sample prepared using [Ir(COD)$_2$]BARF / *(S)*-Binapine (5 mol%) at 60 ºC (99% yield, 95.5:0.5 er).



Signal 1: DAD1 A, Sig=220,8 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area	Height	Area %
1	99.376	MM	1.7707	2239.20337	21.07598	4.5072
2	134.103	MM	3.7566	4.74418e4	210.48383	95.4928
Totals :				4.96810e4	231.55980	

(S)-*N*,*N*-diethyl-1-propyl-2,3-dihydro-1H-pyrrolizine-7-carboxamide (2l)

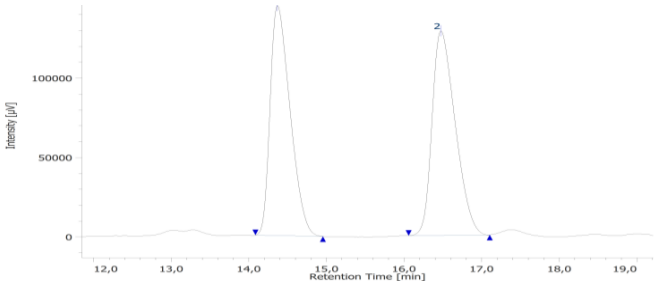


Prepared following general procedure for catalytic reactions (page 104), using **1l.** The product was isolated by flash chromatography (1:3 to 3:1 Ethyl acetate/Hexanes) as orange oil. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 6.45 (d, *J* = 2.8 Hz, 1H), 6.25 (d, *J* = 2.8 Hz, 1H), 3.95 (ddd, *J* = 10.5, 8.1, 6.3 Hz, 1H), 3.85 (ddd, *J* = 10.4, 8.5, 5.4 Hz, 1H), 3.59 – 3.45 (m, 4H), 3.37 (td, *J* = 8.3, 4.4 Hz, 1H), 2.65 (ddt, *J* = 12.7, 8.4, 6.3 Hz, 1H), 2.15 (ddt, *J* = 13.1, 8.1, 5.2 Hz, 1H), 1.88 – 1.77 (m, 1H), 1.47 – 1.37 (m, 1H), 1.37 – 1.28 (m, 2H), 1.19 (t, *J* = 7.1 Hz, 6H), 0.90 (t, *J* = 7.2 Hz, 3H) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$) δ 167.50 (CO), 143.81 (C), 112.63 (CH), 111.56 (CH), 110.47 (CH), 45.58 (CH_2), 41.09 (CH_2), 37.81 (CH), 35.99 (CH_2), 33.79 (CH_2), 20.37 (CH_2), 13.97 (CH_3), 13.61 (CH_3) ppm. **HRMS** [APCI]: *m/z* calculated for $C_{15}H_{25}N_2O$ $[M+H]^+$: 249.1961, found 249.1961.

Enantioselectivity was determined by chiral SFC analysis on Lux i-Cellulose-5 column at *rt* (CO_2:MeOH = 80:20, 1mL/min).

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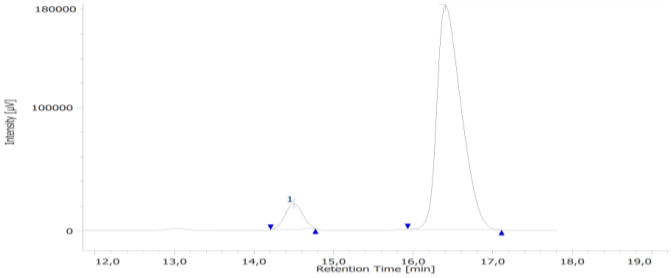
- Racemic sample: Prepared using 5 mol% $[Ir(COD)_2]BARF$ / rac-Binap as catalyst, at 100 ºC, in dioxane.



Channel Name 275,0nm

#	Peak Name	CH	tR [min]	Area [μV·sec]	Height [μV]	Area%
1	Unknown	6	14,367	2588258	144606	49,273
2	Unknown	6	16,473	2664685	128635	50,727

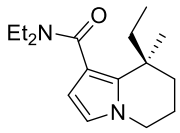
- Asymmetric sample: Prepared using 5 mol% $[Ir(COD)_2]BARF$ / *(S)*-Binapine (99% yield, 92:8 er), at 60 ºC in dioxane.



Channel Name 275,0nm

#	Peak Name	CH	tR [min]	Area [μV·sec]	Height [μV]	Area%
1	Unknown	6	14,497	322353	20799	7,719
2	Unknown	6	16,403	3853565	181618	92,281

_(S)-N,N_,8-triethyl-5,6,7,8-tetrahydroindolizine-1-carboxamide (2m)

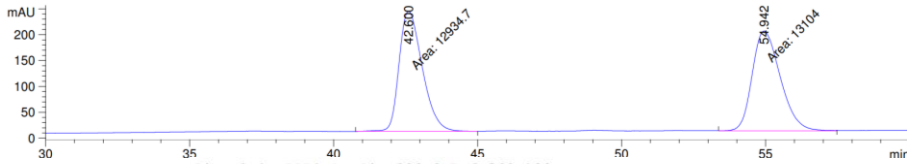


Prepared following general procedure for catalytic reactions (page 104), using **1m.** The product was isolated by flash chromatography (1:3 to 3:1 Ethyl acetate/Hexanes) as orange oil. **^{1}H NMR** (750 MHz, $CDCl_3$) δ 6.38 (d, *J* = 2.8 Hz, 1H), 6.10 (d, *J* = 2.9 Hz, 1H), 3.92 – 3.80 (m, 2H), 3.47 (ddq, *J* = 58.8, 14.0, 7.1 Hz, 4H), 3.23 – 3.15 (m, 1H), 2.04 – 1.96 (m, 1H), 1.96 – 1.87 (m, 1H), 1.86 – 1.77 (m, 1H), 1.78 – 1.68 (m, 1H), 1.68 – 1.60 (m, 1H), 1.51 – 1.42 (m, 1H), 1.17 (t, *J* = 7.1 Hz, 6H), 0.89 (t, *J* = 7.4 Hz, 3H) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$) δ 169.10 (CO), 134.83 (C), 117.86 (CH), 114.73 (C), 107.48 (CH), 45.89 (CH_2), 41.04 (CH_2), 33.81 (CH), 28.15 (CH_2), 25.19 (CH_2), 20.96 (CH_2), 13.66 (CH_3), 11.53 (CH_3) ppm. **HRMS** [APCI]: *m/z* calculated for $C_{15}H_{25}N_2O$ $[M+H]^+$: 249.1961, found 249.1961.

Enantioselectivity was determined by chiral HPLC analysis on IE3 column at *rt* (Hexane:iPrOH = 90:10, 1mL/min).

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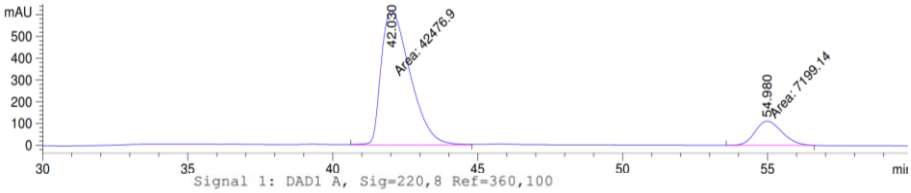
- Racemic sample: Prepared using 5 mol% $[Ir(COD)_2]BARF$ / rac-Binap as catalyst, at 100 ºC, in dioxane.



Signal 1: DAD1 A, Sig=220,8 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	42.600	MM	0.9305	1.29347e4	231.69078	49.6750
2	54.942	MM	1.1333	1.31040e4	192.71481	50.3250
Totals :				2.60387e4	424.40559	

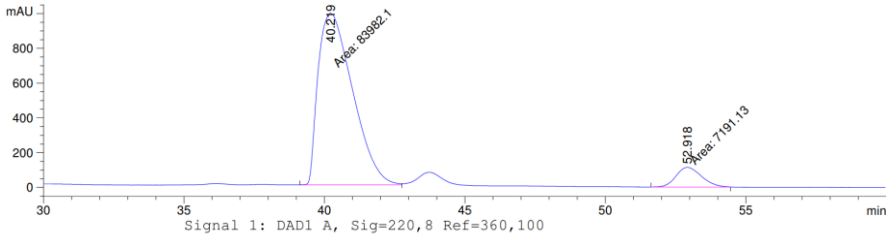
- Asymmetric sample prepared using $[Ir(COD)_2]BARF$ / *(S)*-Binapine (5 mol%) at 60 ºC (99% yield, 86:15 er)



Signal 1: DAD1 A, Sig=220,8 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	42.030	MM	1.1512	4.24769e4	614.97351	85.5078
2	54.980	MM	1.0797	7199.13525	111.12690	14.4922
Totals :				4.96760e4	726.10041	

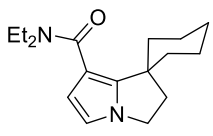
- Asymmetric sample prepared using $[Ir(COD)_2]BARF$ / *(S)*-Segphos (5 mol%) at 100 ºC (99% yield, 92:8 er).



Signal 1: DAD1 A, Sig=220,8 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	40.219	MM	1.4181	8.39821e4	987.01794	92.1127
2	52.918	MM	1.0562	7191.13184	113.47227	7.8873
Totals :				9.11733e4	1100.49022	

_N,N_-diethyl-2',3'-dihydrospiro[cyclohexane-1,1'-pyrrolizine]-7'-carboxamide (2n)

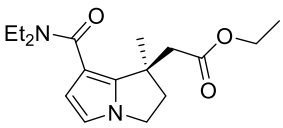


Prepared following general procedure for catalytic reactions (page 104), using **1n.** The product was isolated by flash chromatography (3:1 to 9:1 Ethyl acetate/Hexanes) as yellowish oil in 99% yield . **^{1}H NMR** (500 MHz, $CDCl_3$) δ 6.40 (d, *J* = 2.7 Hz, 1H), 6.16 (d, *J* = 2.4 Hz, 1H), 3.92 (t, *J* = 7.0 Hz, 2H), 3.49 (q, *J* = 7.1 Hz, 4H), 2.38 (t, *J* = 7.0 Hz, 2H), 2.11 (td, *J* = 12.9, 3.9 Hz, 2H), 1.78 – 1.62 (m, 4H), 1.60 – 1.52 (m, 2H), 1.36 (d, *J* = 10.2 Hz, 2H), 1.18 (t, *J* = 7.1 Hz, 6H) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$) δ 168.36 (CO), 146.50 (C), 112.26 (CH), 111.56 (CH), 110.08 (C), 45.17 (CH_2), 44.09 (C), 41.50 (CH_2 amide), 38.34

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(CH_2), 34.96 (CH_2), 25.59 (CH_2), 23.61 (CH_2), 13.88 (CH_3 amide) ppm. **HRMS** [APCI]: *m/z* calculated for $C_{17}H_{26}N_2O$ [M+H]$^+$: 274.2045, found 274.2041.

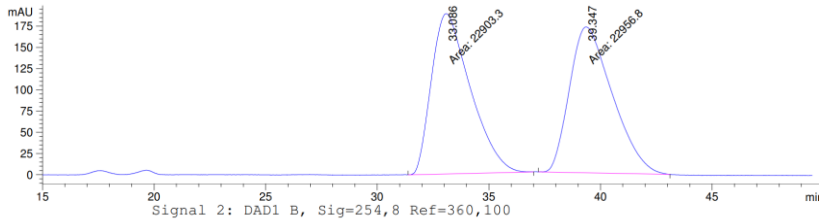
***(S)-E*thyl *(R)*-2-(7-(diethylcarbamoyl)-1-methyl-2,3-dihydro-1H-pyrrolizin-1-yl)acetate (2o)**



Prepared following general procedure for catalytic reactions (page 104), using **1o.** The product was isolated by flash chromatography (3:1 to 9:1 Ethyl acetate/Hexanes) as yellowish oil. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 6.42 (d, *J* = 2.5 Hz, 1H), 6.21 (d, *J* = 2.8 Hz, 1H), 4.11 – 4.01 (m, 2H), 4.01 – 3.93 (m, 2H), 3.59 – 3.42 (m, 4H), 3.02 (d, *J* = 1.1 Hz, 1H), 2.81 (d, *J* = 15.3 Hz, 1H), 2.79 – 2.74 (m, 1H), 2.40 – 2.33 (m, 1H), 1.50 (s, 3H), 1.23 – 1.15 (m, 9H) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$) δ 171.91 (CO), 167.30 (CO), 145.75 (C), 112.30 (CH), 111.51 (CH), 109.97 (C), 59.79 (CH_2), 45.14 (CH_2), 42.98 (CH_2), 41.38 (C), 41.08 (CH_2), 40.08 (CH_2), 25.13 (CH_3), 14.12 (CH_3), 13.64 (CH_3) ppm. **HRMS** [APCI]: *m/z* calculated for $C_{17}H_{27}N_2O_3$ [M+H]$^+$: 307.2016, found 307.2022.

Enantioselectivity was determined by chiral DAD analysis on IA column at *rt* (Hexane:iPrOH = 97:3, 1mL/min).

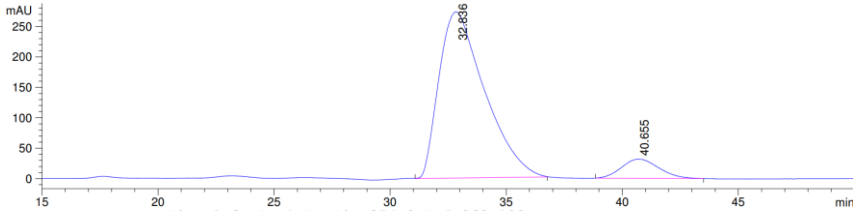
- <u>Racemic sample:</u> Prepared using 5 mol% [Ir(COD)$_2$]BARF / rac-Binap as catalyst, at 100 ºC, in dioxane.



Signal 2: DAD1 B, Sig=254,8 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	33.086	MM	2.0204	2.29033e4	188.93639	49.9416
2	39.347	MM	2.2258	2.29568e4	171.90274	50.0584
Totals :				4.58601e4	360.83913	

- <u>Asymmetric sample</u> prepared using [Ir(COD)$_2$]BARF / *(S)*-Binapine (10 mol%) at 100 ºC (96% yield, 91:9 er).

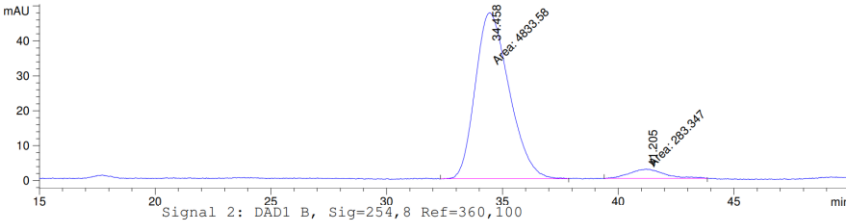


Signal 2: DAD1 B, Sig=254,8 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	32.836	BB	1.6356	3.73492e4	273.08978	91.3942
2	40.655	BB	1.3201	3516.83813	31.51105	8.6058
Totals :				4.08660e4	304.60084	

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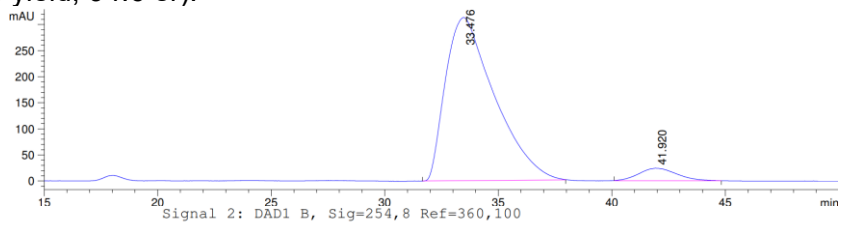
- Asymmetric sample prepared using [Ir(COD)$_2$]BARF / *(S)*-Binapine (5 mol%) at 60 ºC (15% yield, 94:6 er).



Signal 2: DAD1 B, Sig=254,8 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	34.458	MM	1.6927	4833.57764	47.59365	94.4625
2	41.205	MM	1.7719	283.34735	2.66515	5.5375
Totals :				5116.92499	50.25880	

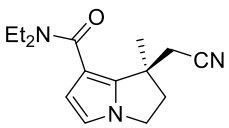
- Asymmetric sample prepared using [Ir(COD)$_2$]BARF / *(S)*-Binapine (10 mol%) at 80 ºC (89% yield, 94:6 er).



Signal 2: DAD1 B, Sig=254,8 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	33.476	PB	1.7890	4.69171e4	312.95877	94.3466
2	41.920	BB	1.3761	2811.34717	24.15085	5.6534
Totals :				4.97284e4	337.10962	

_(R)_-1-(cyanomethyl)-_N,N_-diethyl-1-methyl-2,3-dihydro-1H-pyrrolizine-7-carboxamide (2p)

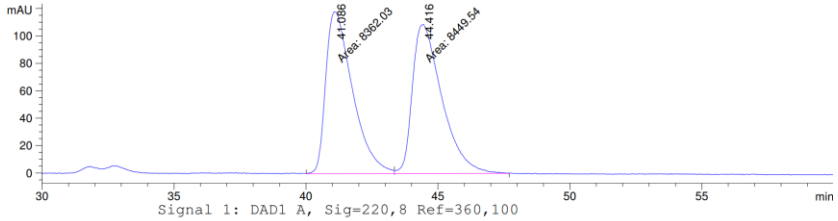


Prepared following general procedure for catalytic reactions (page 104), using **1p.** The product was isolated by flash chromatography (3:1 to 9:1 Ethyl acetate/Hexanes) as yellowish oil. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 6.48 (d, *J* = 2.9 Hz, 1H), 6.27 (d, *J* = 2.8 Hz, 1H), 4.13 – 3.97 (m, 2H), 3.52 (q, *J* = 7.1 Hz, 4H), 3.15 – 2.95 (m, 2H), 2.68 (ddd, *J* = 13.6, 8.2, 5.9 Hz, 1H), 2.44 (ddd, *J* = 13.4, 8.2, 5.7 Hz, 1H), 1.59 – 1.47 (m, 3H), 1.22 (t, *J* = 7.0 Hz, 6H) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$) δ 165.75 (CO), 142.87 (CN), 117.39 (C), 112.19 (CH), 110.92 (CH), 109.78 (C), 43.98 (CH_2), 40.59 (CH_2), 40.54 (C), 39.59 (CH_2), 26.78 (CH_2), 23.57 (CH_3), 12.64 (CH_3) ppm. **HRMS** [APCI]: *m/z* calculated for $C_{15}H_{22}N_3O$ $[M+H]^+$: 260.1757, found 260.1751.

Enantioselectivity was determined by chiral DAD analysis on IF3 column at *rt* (Hexane:iPrOH = 95:5, 1mL/min).

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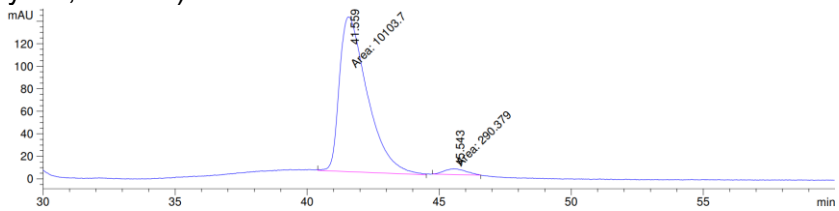
- Racemic sample: Prepared using 5 mol% $[Ir(COD)_2]BARF$ / *rac*-Binap as catalyst, at 100 ºC, in dioxane.



Signal 1: DAD1 A, Sig=220,8 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	41.086	MF	1.1800	8362.02832	118.10485	49.7397
2	44.416	FM	1.2952	8449.54102	108.73125	50.2603
Totals :				1.68116e4	226.83611	

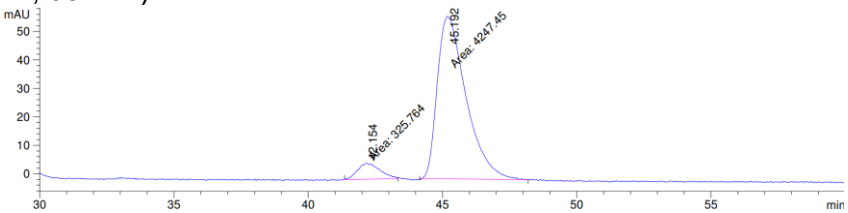
- Asymmetric sample prepared using $[Ir(COD)_2]BARF$ / *(S)*-Binapine (10 mol%) at 100 ºC (51% yield, 97:3 er).



Signal 1: DAD1 A, Sig=220,8 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	41.559	MM	1.2259	1.01037e4	137.36801	97.2063
2	45.543	MM	0.9332	290.37851	5.18597	2.7937
Totals :				1.03941e4	142.55398	

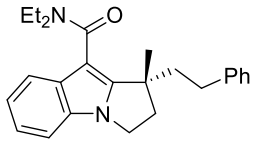
- Asymmetric sample prepared using $[Ir(COD)_2]BARF$ / *(S)*-Binap (5 mol%) at 100 ºC (64% yield, 93:7 er).



Signal 1: DAD1 A, Sig=220,8 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	42.154	MM	0.9584	325.76358	5.66523	7.1233
2	45.192	MM	1.2388	4247.45410	57.14469	92.8767
Totals :				4573.21768	62.80993	

_(R)_-_N,N_-Diethyl-1-methyl-1-phenethyl-2,3-dihydro-1H-pyrrolo[1,2-a]indole-9-carboxamide (2v)

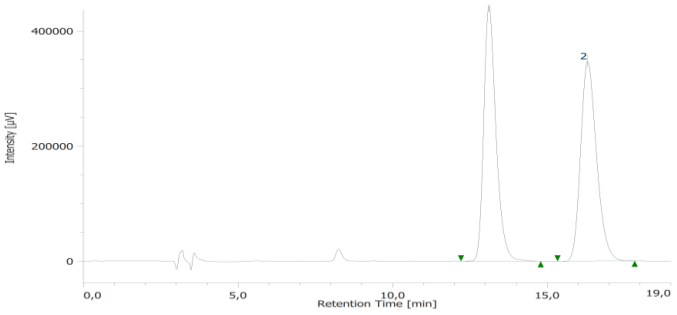


Prepared following general procedure for catalytic reactions (page 104), using **1v.** The product was isolated by flash chromatography (1:3 to 3:1 EtOAc/Hexanes) as brown oil.**^{1}H NMR** (750 MHz, $CDCl_3$) δ 7.35 (d, *J* = 7.9 Hz, 1H), 7.18 – 7.11 (m, 3H), 7.11 – 6.97 (m, 5H), 4.03 (t, *J* = 8.6 Hz, 2H), 3.53 – 3.40 (m, 4H), 2.58 (ddt, *J* = 26.1, 13.0, 7.2 Hz, 2H), 2.48 (td, *J* = 12.9, 4.9 Hz, 1H), 2.32 (dt, *J* = 12.5, 6.9 Hz, 1H), 2.15 (td, *J* = 12.9, 4.3

Hz, 1H), 2.08 (td, *J* = 12.8, 5.2 Hz, 1H), 1.47 (s, 3H), 1.08 (t, *J* = 7.2 Hz, 6H). **^{13}C NMR** (189 MHz, $CDCl_3$) δ 167.50 (CO), 151.87 (C), 142.49 (C), 131.61 (C), 130.46 (C), 128.57 (CH), 128.50 (CH), 125.89 (CH), 121.25 (CH), 120.31 (CH), 120.02 (CH), 109.90 (CH), 103.69 (C), 43.61 (C), 43.05 (CH_2), 41.95 (CH_2), 41.42 (CH_2), 41.19 (br CH_2), 31.87 (CH_2), 26.09 (CH_3), 13.96 (CH_3). **HRMS** [APCI]: *m/z* calculated for $C_{25}H_{31}N_2O$ $[M+H]^+$: 375.2431, found 375.2427.

Enantioselectivity was determined by chiral SFC analysis on Lux 5μm Amylose-2 at *rt* (CO_2:MeOH = 80:20, 1mL/min).

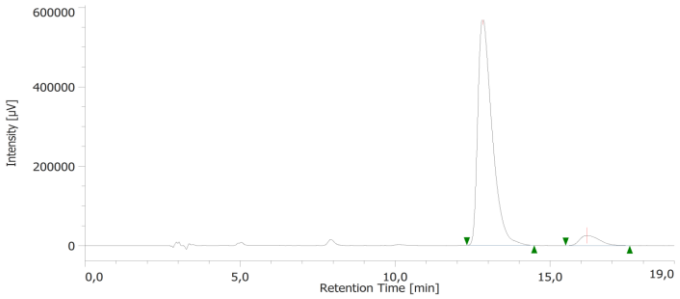
- Racemic sample prepared using [Ir(COD)$_2$]BARF / *rac*-BINAP (5 mol%), at 60 ºC.



Channel Name 200,0nm

#	Peak Name	CH	tR [min]	Area [μV·sec]	Height [μV]	Area%
1	Unknown	5	12,857	20480410	766522	50,370
2	Unknown	5	16,033	20179700	553792	49,630

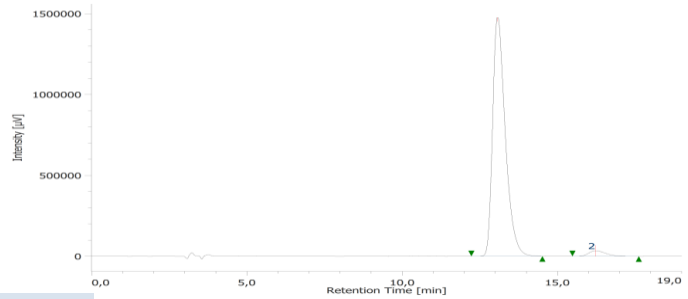
- Asymmetric sample prepared using [Ir(COD)$_2$]BARF / *(R)*-BINAP (5 mol%) at 100 ºC (61% yield, 94:6 er).



Channel Name 200,0nm

#	Peak Name	CH	tR [min]	Area [μV·sec]	Height [μV]	Area%
1	Unknown	6	12,820	18295375	575269	94,169
2	Unknown	6	16,173	1132935	25567	5,831

- Asymmetric sample prepared using [Ir(COD)$_2$]BARF / *(S)*-Binapine (10 mol%) at 100 ºC (63% yield, 97:3 er).

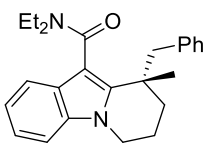


Channel Name 200,0nm

#	Peak Name	CH	tR [min]	Area [μV·sec]	Height [μV]	Area%
1	Unknown	5	13,070	41853446	1483789	96,968
2	Unknown	5	16,227	1308513	34274	3,032

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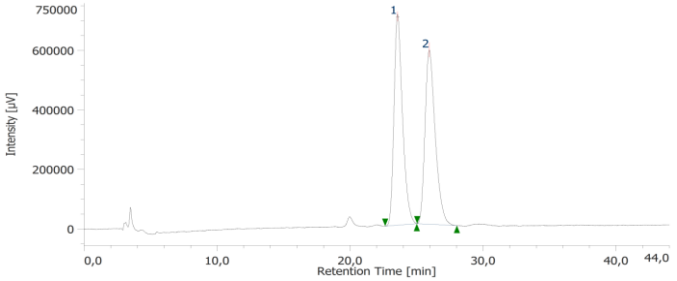
_(S)_-9-Benzyl-_N,N_-diethyl-9-methyl-6,7,8,9-tetrahydropyrido[1,2-a]indole-10-carboxamide (2r)



Prepared following general procedure for catalytic reactions (page 104), using **1r.** Obtained as brown oil. **^{1}H NMR** (500 MHz, DMSO-d) δ 7.30 (d, *J* = 9.0 Hz, 1H), 7.25 (d, *J* = 7.8 Hz, 1H), 7.17 (t, *J* = 7.2 Hz, 2H), 7.12 (t, *J* = 7.2 Hz, 1H), 7.07 (d, *J* = 6.8 Hz, 3H), 7.01 (t, *J* = 7.0 Hz, 1H), 4.04 – 3.83 (m, 2H), 3.51 – 3.25 (m, 4H), 3.18 (s, 2H), 2.06 – 1.93 (m, 1H), 1.93 – 1.82 (m, 1H), 1.83 – 1.72 (m, 1H), 1.48 – 1.36 (m, 1H), 1.28 (s, 3H), 1.14 – 0.99 (m, 6H). **^{13}C NMR** (126 MHz, DMSO-d) δ 168.23 (CO), 142.97 (C), 138.76 (C), 135.06 (C), 130.82 (CH), 128.18 (CH), 126.54 (CH), 126.12 (C), 121.39 (CH), 120.44 (CH), 118.47 (CH), 110.12 (CH), 108.19 (C), 46.26 (CH_2), 42.62 (CH_2), 37.12 (C), 33.17 (CH_2), 27.42 (CH_3), 19.27 (CH_2), 13.91 (CH_3), 13.56 (CH_3). **HRMS** [APCI]: *m/z* calculated for $C_{25}H_{31}N_2O$ $[M+H]^+$: 375.2431, found 375.2427.

Enantioselectivity was determined by chiral SFC analysis on Lux 5um Amylose-2 at *rt* (CO_2:MeOH = 80:20, 1mL/min).

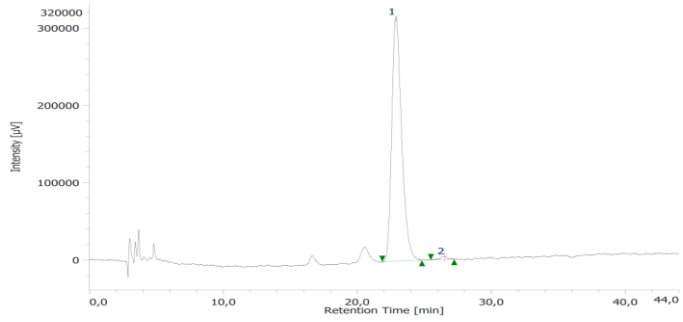
- Racemic sample prepared using [Ir(COD)$_2$]BARF / *rac*-BINAP (5 mol%), at 100 ºC.



Channel Name 200,0nm

#	Peak Name	CH	tR [min]	Area [μV·sec]	Height [μV]	Area%
1	Unknown	5	23,550	31506599	709160	50,226
2	Unknown	5	25,960	31223052	585949	49,774

- Asymmetric sample prepared using [Ir(COD)$_2$]BARF / *(S)*-Binapine (5 mol%) at 60 ºC (32% yield, 99:1 er).

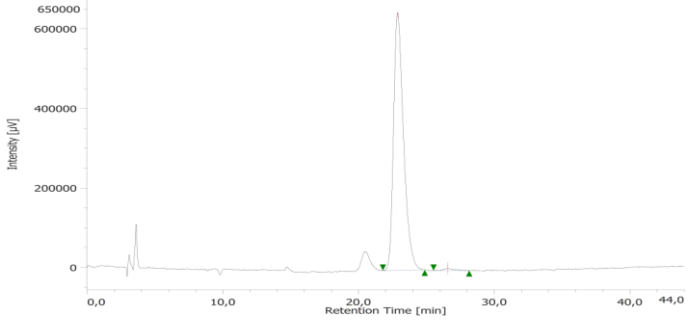


Channel Name 200,0nm

#	Peak Name	CH	tR [min]	Area [μV·sec]	Height [μV]	Area%
1	Unknown	5	22,867	16163629	316174	98,986
2	Unknown	5	26,527	165567	4363	1,014

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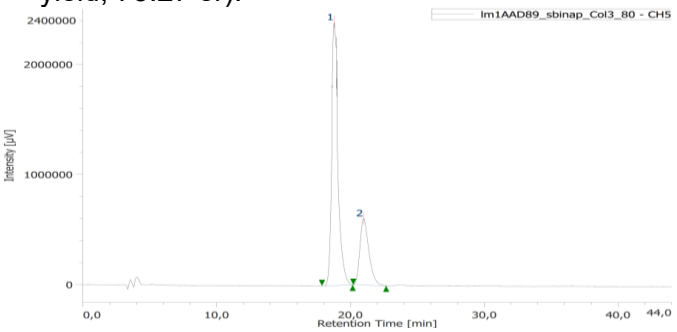
- Asymmetric sample prepared using [Ir(COD)$_2$]BARF / *(S)*-Binapine (10 mol%) at 100 ºC (67% yield, 99:1 er).



Channel Name 200,0nm

#	Peak Name	CH	tR [min]	Area [μV·sec]	Height [μV]	Area%
1	Unknown	5	22,877	33147726	649475	99,122
2	Unknown	5	26,587	293650	5843	0,878

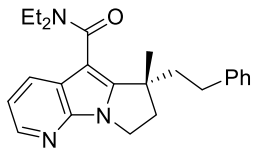
- Asymmetric sample prepared using [Ir(COD)$_2$]BARF / BINAP (5 mol%) at 100 ºC (68% yield, 73:27 er).



Channel Name 200,0nm

#	Peak Name	CH	tR [min]	Area [μV·sec]	Height [μV]	Area%
1	Unknown	5	18,770	78070162	2392430	73,538
2	Unknown	5	20,970	28092976	606438	26,462

_N,N_-Diethyl-6-methyl-6-phenethyl-7,8-dihydro-6H-pyrido[3,2-b]pyrrolizine-5-carboxamide (2s)

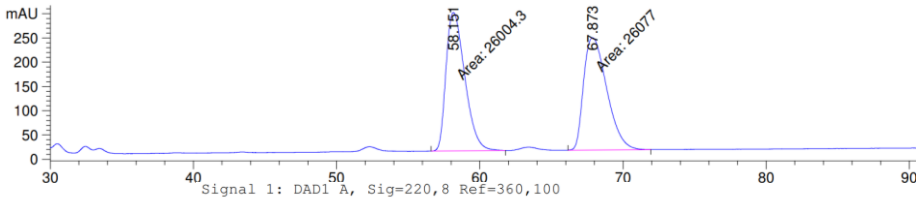


Prepared following general procedure for catalytic reactions (page 104), using **1s.** The product was isolated by flash chromatography (1:3 to 9:1 EtOAc/Hexanes) as brown oil.**^{1}H NMR** (750 MHz, $CDCl_3$) δ 8.33 (dd, *J* = 4.8, 1.5 Hz, 1H), 7.80 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.32 (dd, *J* = 14.4, 6.8 Hz, 2H), 7.27 – 7.18 (m, 3H), 7.14 (dd, *J* = 7.9, 4.7 Hz, 1H), 4.42 – 4.31 (m, 2H), 3.67 – 3.52 (m, 4H), 2.85 – 2.69 (m, 2H), 2.69 – 2.57 (m, 1H), 2.54 – 2.43 (m, 1H), 2.36 – 2.18 (m, 2H), 1.64 (s, 3H), 1.24 (t, *J* = 7.1 Hz, 6H). **^{13}C NMR** (189 MHz, $CDCl_3$) δ 166.43 (CO), 152.44 (C), 142.93 (C), 142.18 (CH), 142.03 (C), 128.46 (CH), 128.43 (CH), 127.75 (CH), 125.90 (CH), 123.04 (C), 116.34 (CH), 102.02 (C), 43.73 (C), 42.42 (CH_2), 41.56 (CH_2), 41.02 (CH_2), 31.65 (CH_2), 25.71 (CH_3), 13.90 (CH_3) ppm. **HRMS** [APCI]: *m/z* calculated for $C_{24}H_{30}N_3O$ $[M+H]^+$: 376.2383, found 376.2392. **NMR spectra at page 465.**

Enantioselectivity was determined by chiral HPLC analysis on a Chiralpack IE-3 column at *rt* (Hexane:iPrOH = 80:20, 1mL/min).

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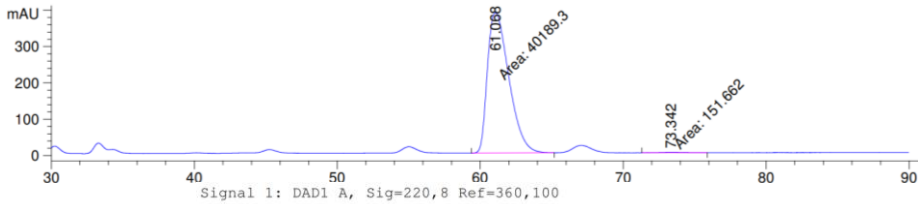
- Racemic sample prepared using [Ir(COD)$_2$]BARF / *rac*-BINAP (5 mol%), at 100 ºC.



Signal 1: DAD1 A, Sig=220,8 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	58.151	MM	1.5181	2.60043e4	285.49393	49.9302
2	67.873	MM	1.8747	2.60770e4	231.83774	50.0698
Totals :				5.20813e4	517.33167	

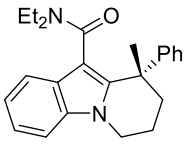
- Asymmetric sample prepared using [Ir(COD)$_2$]BARF / *(S)*-Binapine (10 mol%) at 100 ºC (99% yield, 99.6:0.4 er).



Signal 1: DAD1 A, Sig=220,8 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	61.068	MM	1.7333	4.01893e4	386.44177	99.6240
2	73.342	MM	1.7756	151.66240	1.42360	0.3760
Totals :				4.03410e4	387.86537	

_(S)_-_N,N_-Diethyl-9-methyl-9-phenyl-6,7,8,9-tetrahydropyrido[1,2-a]indole-10-carboxamide (2t)

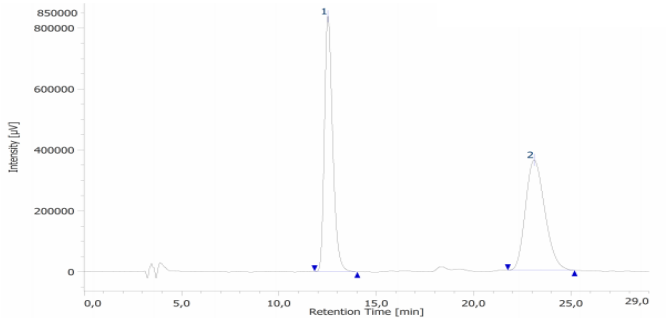


Prepared following general procedure for catalytic reactions (page 104), using **1t.** The product was isolated by flash chromatography (1:3 to 3:1 EtOAc/Hexanes) as orange oil. **^{1}H NMR** (500 MHz, DMSOd) δ 7.41 (d, *J* = 8.2 Hz, 1H), 7.29 (d, *J* = 7.8 Hz, 1H), 7.25 – 7.10 (m, 6H), 7.10 – 7.05 (m, 1H), 4.19 – 4.03 (m, 2H), 3.33 – 3.09 (m, 4H), 2.25 – 2.14 (m, 1H), 2.07 – 1.98 (m, 1H), 1.96 – 1.89 (m, 1H), 1.82 (s, 4H), 0.93 (t, *J* = 7.1 Hz, 6H). **^{13}C NMR** (126 MHz, DMSOd) δ 166.08 (C), 147.01 (C), 140.57 (C), 134.40 (C), 126.99 (CH), 126.19 (CH), 125.12 (C), 125.04 (CH), 120.56 (CH), 119.38 (CH), 117.65 (CH), 109.10 (CH), 108.46 (C), 41.29 (CH_2), 40.82 (C), 37.81(CH_2), 26.55 (CH_3), 18.21 (CH_2), 12.45 (CH_3). **HRMS** [APCI]: *m/z* calculated for $C_{24}H_{29}N_2O$ $[M+H]^+$: 361.2274, found 361.2274.

Enantioselectivity was determined by chiral SFC analysis on Lux 5um Amylose-2 at *rt* (CO_2:MeOH = 80:20, 1mL/min).

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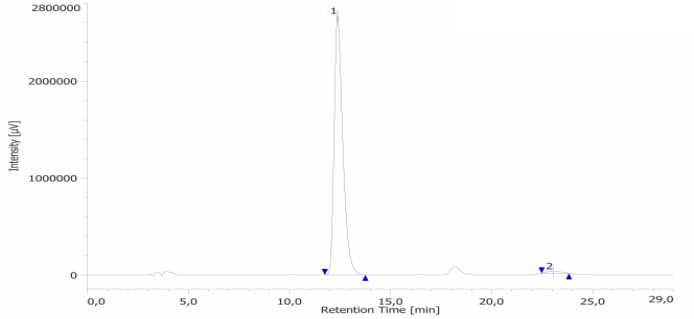
- Racemic sample prepared using [Ir(COD)$_2$]BARF / *rac*-BINAP (5 mol %) at 100 ºC.



Channel Name 220,0nm

#	Peak Name	CH	tR [min]	Area [μV·sec]	Height [μV]	Area%
1	Unknown	5	12.513	24702092	836893	49.693
2	Unknown	5	23.097	25006873	361831	50.307

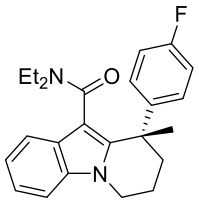
- Asymmetric sample prepared using [Ir(COD)$_2$]BARF / *(S)*-Binapine (10 mol%) at 100 ºC (99% yield, 99:1 er).



Channel Name 220,0nm

#	Peak Name	CH	tR [min]	Area [μV·sec]	Height [μV]	Area%
1	Unknown	5	12.373	79334745	2671567	98.678
2	Unknown	5	23.047	1062781	21613	1.322

_(S)-N,N_-Diethyl-9-(4-fluorophenyl)-9-methyl-6,7,8,9-tetrahydropyrido[1,2-a]indole-10-carboxamide (2u)

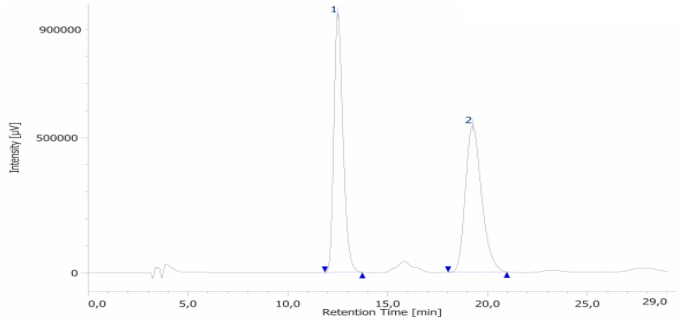


Prepared following general procedure for catalytic reactions (page 104), using **1u.** The product was isolated by flash chromatography (1:3 to 3:1 EtOAc/Hexanes) as orange oil. 87% yield.**^{1}H NMR** (500 MHz, DMSO-d) δ 7.45 – 7.40 (m, 1H), 7.33 – 7.28 (m, 1H), 7.22 – 7.14 (m, 3H), 7.12 – 7.06 (m, 1H), 7.03 – 6.97 (m, 2H), 4.20 – 4.07 (m, 2H), 3.37 – 3.01 (m, 4H), 2.24 – 2.14 (m, 1H), 2.12 – 1.99 (m, 1H), 1.98 – 1.90 (m, 1H), 1.82 (s, 4H), 0.96 (t, *J* = 6.9, 6.4 Hz, 6H). **^{13}C NMR** (126 MHz, DMSO-d) δ 166.03 (C), 160.03 (C, d, *J* = 242.6 Hz), 43.1 (C), 140.5 (C), 34.41 (C), 128.16 (CH, d, *J* = 8.0 Hz), 125.01 (C), 120.64 (CH), 119.45 (CH), 117.68 (CH), 113.48 (CH, d, *J* = 21.0 Hz), 109.15 (CH), 108.38 (C), 41.30 (CH_2), 40.41 (C), 37.80 (CH_2), 26.67 (CH_3), 18.19 (CH_2), 12.43 (CH_3). **HRMS** [APCI]: *m/z* calculated for $C_{24}H_{28}N_2OF$ $[M+H]^+$: 379.2180, found 379.2180.

Enantioselectivity was determined by chiral SFC analysis on Lux 5um Amylose-2 at *rt* (CO_2:MeOH = 80:20, 1mL/min).

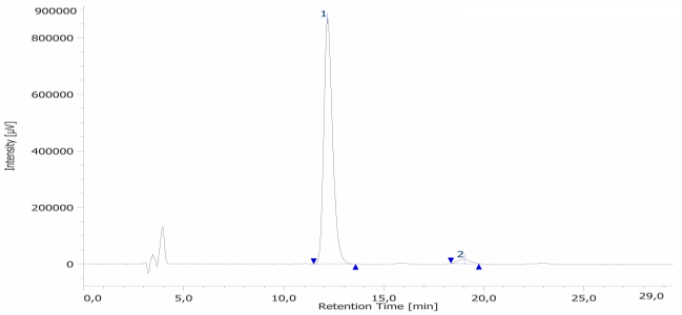
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- Racemic sample prepared using [Ir(COD)$_2$]BARF / *rac*-BINAP (10 mol%) at 100 ºC.



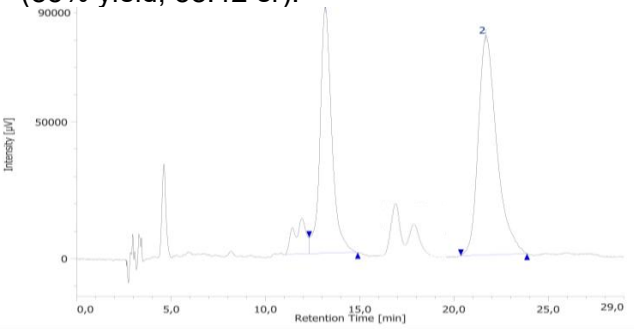
#	Peak Name	CH	tR [min]	Area [μV·sec]	Height [μV]	Area%
1	Unknown	5	12.497	30621555	956909	49.972
2	Unknown	5	19.243	30656447	543624	50.028

- Asymmetric sample prepared using [Ir(COD)$_2$]BARF / *(S)*-Binapine (10 mol%) at 100 ºC (87% yield, 97.5:2.5 er).



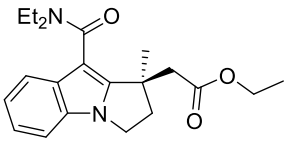
#	Peak Name	CH	tR [min]	Area [μV·sec]	Height [μV]	Area%
1	Unknown	5	12.183	26468495	868655	97.513
2	Unknown	5	19.017	675156	15665	2.487

- Asymmetric sample prepared using [Ir(COD)$_2$]BARF / *(S)*-BINAP (10 mol%) at 100 ºC (85% yield, 58:42 er).



#	Peak Name	CH	tR [min]	Area [μV·sec]	Height [μV]	Area%
1	Unknown	10	13.163	3896215	90290	41.567
2	Unknown	10	21.680	5477069	80198	58.433

_(S)_-Ethyl-_(R)_-2-(9-(diethylcarbamoyl)-1-methyl-2,3-dihydro-1H-pyrrolo[1,2-a]indol-1-yl)acetate (2v)



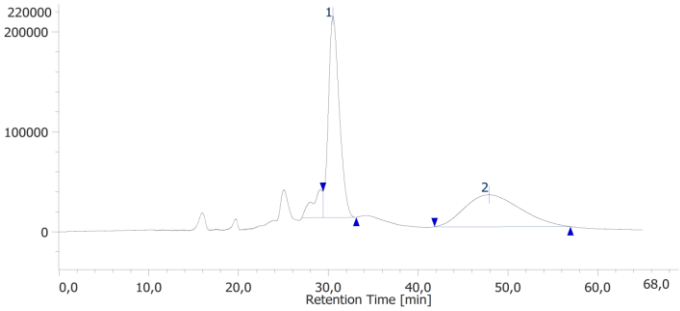
Prepared following general procedure for catalytic reactions (page 104), using **1v.** The product was isolated by flash chromatography (3:1 to 9:1 Ethyl acetate/Hexanes) as yellowish oil. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.45 – 7.39 (m, 1H), 7.23 (dt, *J* = 8.2, 1.0 Hz, 1H), 7.18 – 7.13 (m, 1H), 7.13 – 7.09 (m, 1H), 4.19 – 4.05 (m, 4H), 3.55 (m, 4H), 3.07 (d, *J* = 15.5 Hz, 1H), 2.94 – 2.88 (m, 1H), 2.86 (d, *J* = 15.4 Hz, 1H), 2.56 – 2.44 (m, 1H), 1.58 (s, 3H), 1.25 – 1.12 (m, 9H) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$) δ 171.41 (CO), 167.19 (CO), 151.65 (C), 131.25 (C), 129.88 (C), 121.12 (CH), 120.14 (CH), 119.80 (CH), 109.78 (CH), 103.03 (C), 60.03 (CH_2), 43.13 (CH_2), 42.70 (CH_2), 41.28 (C),

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40.81 (CH_2), 25.32 (CH_3), 14.06 (CH_3), 13.70 (CH_3) ppm. **HRMS** [APCI]: *m/z* calculated for $C_{21}H_{29}N_3O$ $[M+H]^+$: 339.2305, found 339.2301.

Enantioselectivity was determined by chiral SFC analysis on Lux Amylose-2 column at *rt* (CO_2:MeOH = 85:15, 1mL/min).

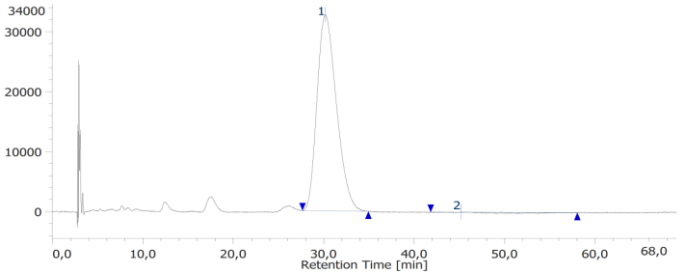
- Racemic sample: Prepared using 5 mol% $[Ir(COD)_2]BARF$ / rac-Binap as catalyst, at 100 ºC, in dioxane.



Channel Name 220,0nm

#	Peak Name	CH	tR [min]	Area [μV·sec]	Height [μV]	Area%
1	Unknown	7	30,503	111626233	1335251	52,559
2	Unknown	7	47,873	100758033	223720	47,441

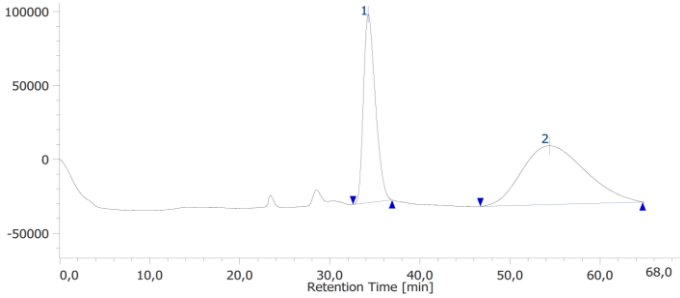
- Asymmetric sample prepared using $[Ir(COD)_2]BARF$ / *(S)*-Binapine (5 mol%) at 60 ºC (72% yield, 98:2 er).



Channel Name 254,0nm

#	Peak Name	CH	tR [min]	Area [μV·sec]	Height [μV]	Area%
1	Unknown	5	30,170	4894014	32725	99,930
2	Unknown	5	45,167	3422	72	0,070

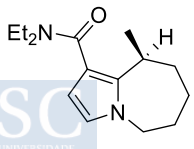
- Asymmetric sample prepared using $[Ir(COD)_2]BARF$ / *(S)*-Segphos (5 mol%) at 60 ºC (89% yield, 68:38 er).



Channel Name 254,0nm

#	Peak Name	CH	tR [min]	Area [μV·sec]	Height [μV]	Area%
1	Unknown	5	34,253	11761644	127424	37,744
2	Unknown	5	54,343	19399592	39767	62,256

_(S)-N,N_-Diethyl-9-methyl-6,7,8,9-tetrahydro-5H-pyrrolo[1,2-a]azepine-1-carboxamide (2w)



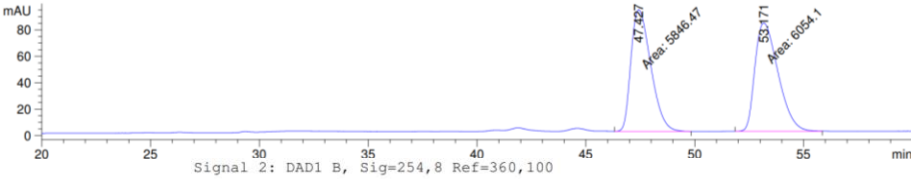
Prepared following general procedure for catalytic reactions (page 104), using **1w.** The product was isolated by flash chromatography (3:7 to 7:3 EtOAc/Hexanes) as brown oil. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 6.35 (d, *J* = 2.9 Hz, 1H), 5.93 (d, *J* = 2.8 Hz, 1H), 4.03 – 3.88 (m, 2H), 3.47 (q, *J*

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= 7.1 Hz, 5H), 1.94 – 1.84 (m, 2H), 1.84 – 1.74 (m, 2H), 1.74 – 1.54 (m, 2H), 1.27 (d, *J* = 2.8 Hz, 3H), 1.16 (t, *J* = 7.1 Hz, 6H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 169.23 (CO), 138.21 (C), 120.74 (CH), 117.07 (C), 105.55 (CH), 50.87 (CH_2), 33.92 (CH_2), 30.51 (CH), 29.94 (CH_2), 29.86 (CH_2), 25.52 (CH_2), 18.18 (CH_3), 13.84 (CH_3). **HRMS** [APCI]: *m/z* calculated for $C_{15}H_{25}N_2O$ $[M+H]^+$: 249.1961, found 249.1960.

Enantioselectivity was determined by chiral HPLC analysis on a Chiralpack IE-3 column at *rt* (Hexane:iPrOH = 95:5, 1mL/min).

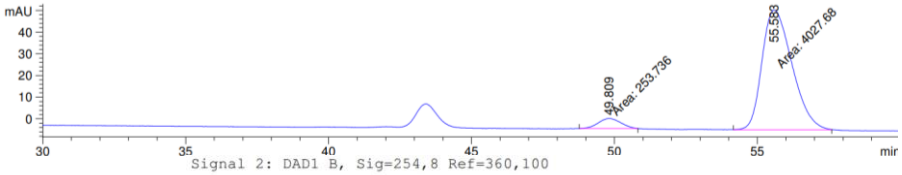
- Racemic sample prepared using $[Ir(COD)_2]BARF$ / *rac*-BINAP (5 mol%), at 100 ºC.



Signal 2: DAD1 B, Sig=254,8 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	47.427	MM	1.0571	5846.46777	92.17535	49.1276
2	53.171	MM	1.2297	6054.09912	82.05271	50.8724
Totals :				1.19006e4	174.22806	

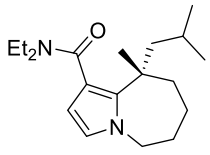
- Asymmetric sample prepared using $[Ir(COD)_2]BARF$ / *(S)*-Binapine (5 mol%) at 60 ºC (87% yield, 94:6 er).



Signal 2: DAD1 B, Sig=254,8 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	49.809	MM	0.9130	253.73634	4.63199	5.9265
2	55.583	MM	1.2173	4027.67554	55.14415	94.0735
Totals :				4281.41188	59.77614	

_(S)-N,N_-Diethyl-9-isobutyl-9-methyl-6,7,8,9-tetrahydro-5H-pyrrolo[1,2-a]azepine-1-carboxamide (2x)



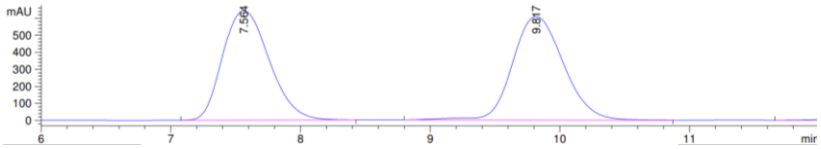
Prepared following general procedure for catalytic reactions (page 104), using **1x.** The product was isolated by flash chromatography (1:3 to 3:1 EtOAc/Hexanes) as orange oil.**^{1}H NMR** (500 MHz, DMSO) δ 6.51 (d, *J* = 2.8 Hz, 1H), 5.67 (d, *J* = 2.7 Hz, 1H), 4.07 – 3.99 (m, 2H), 3.51 – 3.19 (m, 4H), 1.98 – 1.92 (m, 1H), 1.92 – 1.82 (m, 2H), 1.80 – 1.72 (m, 1H), 1.72 – 1.65 (m, 2H), 1.59 – 1.51 (m, 1H), 1.50 – 1.39 (m, 1H), 1.30 (s, 3H), 1.26 (dd, *J* = 14.0, 3.8 Hz, 1H), 1.07 (t, *J* = 7.1 Hz, 6H), 0.88 (d, *J* = 6.7 Hz, 3H), 0.58 (d, *J* = 6.5 Hz, 3H). **^{13}C NMR** (126 MHz, DMSOd) δ 169.06 (CO), 133.75 (C), 121.38 (CH), 118.31 (C), 104.61 (CH), 49.48 (CH_2), 46.44 (CH_2), 41.04 (CH_2), 38.82 (C), 28.51 (CH_2), 27.04 (CH),

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24.77 (CH_3), 23.33 (CH_2), 23.19 (CH_3), 22.93 (CH_3), 12.34 (CH_3) **HRMS** [APCI]: *m/z* calculated for $C_{19}H_{33}N_2O$ $[M+H]^+$: 305.2587, found 305.2587. **NMR spectra at page 464.**

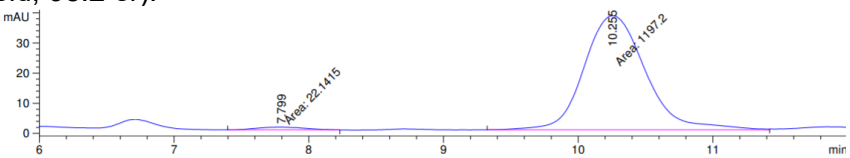
Enantioselectivity was determined by chiral HPLC analysis on a Chiralpack IA-3 column at *rt* (Hexane:iPrOH = 95:5, 1mL/min).

- Racemic sample prepared using [Ir(COD)$_2$]BARF / *rac*-BINAP (5 mol%), at 100 ºC.



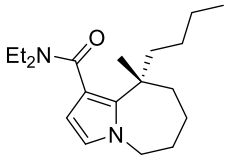
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	7.564	MM	0.4159	1.60562e4	643.50555	50.4660
2	9.817	MM	0.4375	1.57596e4	600.39514	49.5340
Totals :				3.18158e4	1243.90070	

- Asymmetric sample prepared using [Ir(COD)$_2$]BARF / *(S)*-BINAP (5 mol%) at 100 ºC (57% yield, 98:2 er).



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	7.799	MM	0.4085	22.14152	9.03416e-1	1.8159
2	10.255	MM	0.5283	1197.19519	37.76752	98.1841
Totals :				1219.33671	38.67094	

9-Butyl-*N,N*-diethyl-9-methyl-6,7,8,9-tetrahydro-5H-pyrrolo[1,2-a]azepine-1-carboxamide (2y)

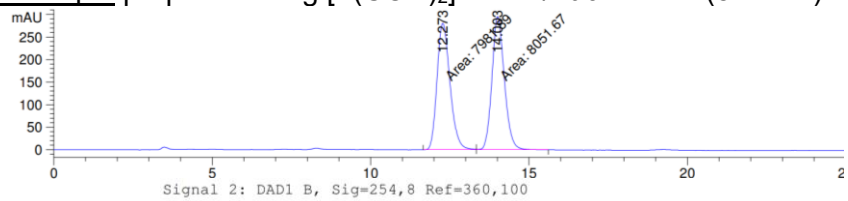


Prepared following general procedure for catalytic reactions (page 104), using **1y.** The product was isolated by flash chromatography (1:3 to 3:1 EtOAc/Hexanes) as orange oil.**^{1}H NMR** (500 MHz, DMSO) δ 6.51 (d, *J* = 2.8 Hz, 1H), 5.69 (d, *J* = 2.7 Hz, 1H), 4.09 – 3.98 (m, 2H), 3.45 – 3.23 (m, 4H), 1.89 – 1.77 (m, 3H), 1.76 – 1.68 (m, 2H), 1.59 – 1.48 (m, 3H), 1.32 – 1.20 (m, 7H), 1.08 (t, *J* = 7.1 Hz, 6H), 0.86 (t, *J* = 7.1 Hz, 3H) ppm. **^{13}C NMR** (126 MHz, DMSOd) δ 170.04 (CO), 135.46 (C), 122.45 (CH), 119.14 (C), 105.55 (CH), 50.44 (CH_2), 40.96 (CH_2), 40.08 (CH_2), 39.70 (C), 38.69 (CH_2), 29.34 (CH_2), 27.25 (CH_3), 26.46 (CH_2), 24.30 (CH_2), 23.13 (CH_2), 14.17 (CH_3), 13.33 (CH_3). **HRMS** [APCI]: *m/z* calculated for $C_{19}H_{33}N_2O$ $[M+H]^+$: 305.2587, found 305.2587.

Enantioselectivity was determined by chiral HPLC analysis on a Chiralpack IA-3 column at *rt* (Hexane:iPrOH = 95:05, 1mL/min).

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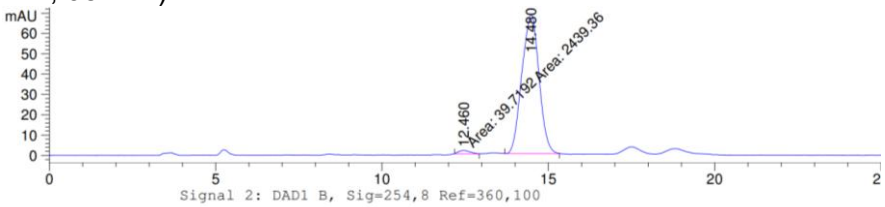
- Racemic sample prepared using [Ir(COD)$_2$]BARF / *rac*-BINAP (5 mol%) at 100 ºC.



Signal 2: DAD1 B, Sig=254,8 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	12.272	MM	0.4768	975.79376	34.10858	49.9841
2	14.001	MM	0.4508	976.41339	36.10172	50.0159
Totals :				1952.20715	70.21030	

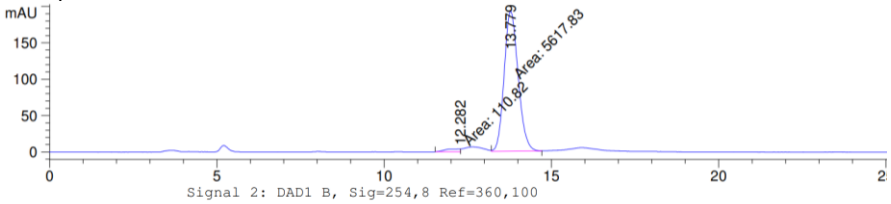
- Asymmetric sample prepared using [Ir(COD)$_2$]BARF / *(S)*-BINAP (5 mol%) at 100 ºC (65% yield, 98:2 er).



Signal 2: DAD1 B, Sig=254,8 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	12.460	MM	0.4010	39.71915	1.65077	1.6022
2	14.480	MM	0.5953	2439.35693	68.29777	98.3978
Totals :				2479.07609	69.94854	

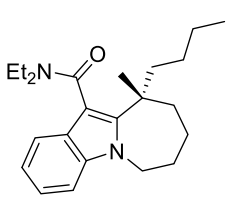
- Asymmetric sample prepared using [Ir(COD)$_2$]BARF / *(S)*-Binapine (5 mol%) at 120 ºC (94:6 er).



Signal 2: DAD1 B, Sig=254,8 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	11.934	MF	0.4983	777.74371	26.01580	6.2213
2	13.779	FM	0.4900	1.17235e4	398.72516	93.7787
Totals :				1.25013e4	424.74096	

_(R)_-10-Butyl-_N,N_-diethyl-10-methyl-7,8,9,10-tetrahydro-6H-azepino[1,2-a]indole-11-carboxamide (2z)



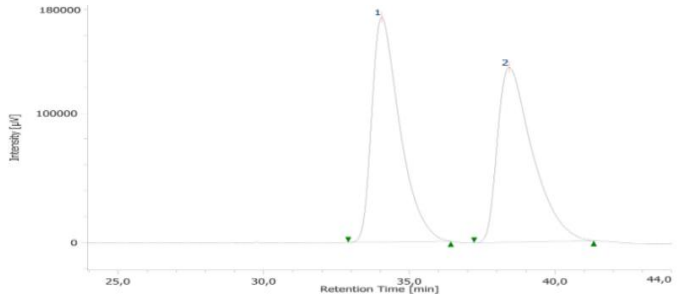
Prepared following general procedure for catalytic reactions (page 104), using **1z.** The product was isolated by flash chromatography (1:3 to 3:1 EtOAc/Hexanes) as orange oil. **^{1}H NMR** (500 MHz, DMSOd) δ 7.45 (d, *J* = 8.3 Hz, 1H), 7.25 – 7.03 (m, 2H), 7.03 – 6.92 (m, 1H), 3.67 – 3.51 (m, 1H), 3.50 – 3.38 (m, 1H), 3.32 – 3.00 (m, 4H), 2.07 – 1.45 (m, 8H), 1.38 (s, 3H), 1.31 – 1.20 (m, 3H), 1.20 – 1.14 (m, 3H), 1.07 – 0.90 (m, 4H), 0.81 (t, *J* = 7.0 Hz, 3H) ppm. **^{13}C NMR** (126 MHz, DMSOd) δ 167.47 (C), 142.42 (C), 135.48 (C), 125.07 (C), 120.73 (CH), 118.57 (CH), 117.37 (CH), 110.42 (C),

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108.76 (CH), 43.75 (CH_2), 42.28 (CH_2), 38.41 (C), 37.40 (CH_2), 27.87 (CH_2), 26.41 (CH_3), 25.44 (CH_2), 23.38 (CH_2), 22.10 (CH_2), 13.11 (CH_3), 11.81 (CH_3) **HRMS** [APCI]: *m/z* calculated for $C_{23}H_{35}N_2O$ $[M+H]^+$: 355.2744, found 355.2741.

Enantioselectivity was determined by chiral SFC analysis on Lux 5um Amylose-2 column at *rt* (CO_2:MeOH = 95:05, 1mL/min).

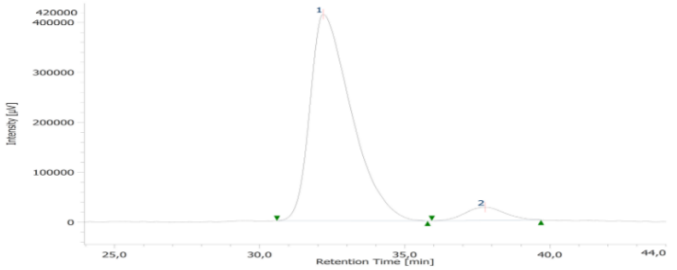
- Racemic sample prepared using [Ir(COD)$_2$]BARF / *rac*-BINAP (5 mol%), at 100 ºC.



Channel Name 222.0nm

#	Peak Name	CH	tR [min]	Area [μV·sec]	Height [μV]	Area%
1	Unknown	6	34.047	11667087	173888	50.744
2	Unknown	6	38.420	11324889	135333	49.256

- Asymmetric sample prepared using [Ir(COD)$_2$]BARF / *(S)*-BINAP (10 mol%) at 100 ºC (54% yield, 94:6 er).

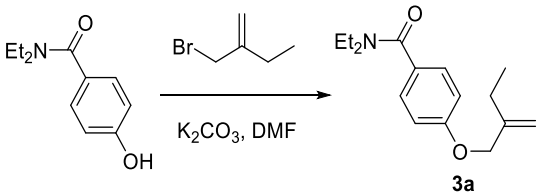


Channel Name 222.0nm

#	Peak Name	CH	tR [min]	Area [μV·sec]	Height [μV]	Area%
1	Unknown	6	32.183	41082559	413618	94.245
2	Unknown	6	37.763	2508547	26346	5.755

Synthesis of precursors 3a-b

*(exemplified for **3a**)*

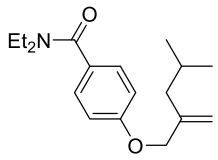


3a

2-(Bromomethyl)but-1-ene (463 mg, 3.1 mmol) was added dropwise to a solution of *N,N*-diethyl-3-hydroxybenzamide (500 mg, 2.59 mmol) and K_2CO_3 (430 mg, 3.1 mmol) in DMF (3 mL). The mixture was stirred 20 *h* at *rt*, diluted with Et_2O(10 mL) and washed with water (3 x 15 mL). The organic phase was dried, concentrated and chromatographed to yield ***N,N*,3-triethyl-3-methyl-2,3-dihydrobenzofuran-4-carboxamide** (**3a**) as colorless oil (278 mg, 41% yield) **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.28 – 7.21 (m, 1H), 6.93 – 6.86 (m, 3H), 5.02 (d, J = 37.6 Hz, 2H), 4.45 (s, 2H), 3.58 – 3.11 (m, 4H), 2.12 (q, J = 7.4 Hz, 2H), 1.25 – 1.01 (m, 9H). **^{13}C NMR** (126 MHz, $CDCl_3$)

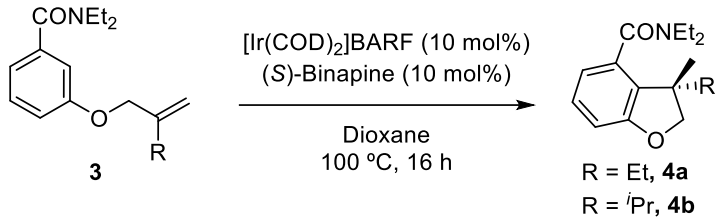
δ 170.98 (C), 158.80 (C), 146.20 (C), 138.56 (C), 129.52 (CH), 118.53 (CH), 115.76 (CH), 112.61 (CH), 110.98 (CH_2), 71.03 (CH_2), 43.22 (CH_2), 39.15 (CH_2), 25.85 (CH_2), 14.20 (CH_3), 12.90 (CH_3), 12.02 (CH_3). **HRMS** [APCI]: *m/z* calculated for $C_{16}H_{24}NO_2$ $[M+H]^+$: 248.1645, found 248.1645. Data in agreement with that reported in literature.[5]

***N,N*-Diethyl-4-((4-methyl-2-methylenepentyl)oxy)benzamide (3b)**

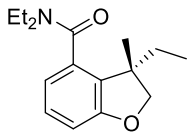


Synthetized using the abovementioned procedure using 4-methyl-2-methylenepentyl 4-methylbenzenesulfonate as alkylating agent, (68% yield, colorless oil). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.25 – 7.16 (m, 1H), 6.92 – 6.81 (m, 3H), 5.09 (s, 1H), 4.90 (s, 1H), 4.37 (s, 2H), 3.33 (s, 4H), 1.95 (d, *J* = 7.3 Hz, 2H), 1.74 (dt, *J* = 13.6, 6.8 Hz, 1H), 1.10 (s, 6H), 0.84 (d, *J* = 6.5 Hz, 6H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 158.91 (CO), 148.99 (C), 143.54 (C), 138.10 (C), 129.64 (CH), 118.63 (CH), 115.90 (CH), 113.45 (CH_2), 112.73 (CH), 70.89 (CH_2), 43.07 (CH_2), 26.33 (CH), 22.64 (CH_3). **HRMS** [APCI]: *m/z* calculated for $C_{18}H_{28}NO_2$ $[M+H]^+$: 290.2115, found 290.2116. **NMR spectra at page 466.**

Synthesis of compounds 3 by hydroarylation of precursors 4



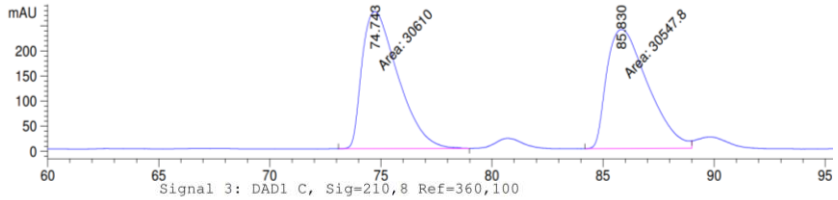
***(S)-N,N*,3-Triethyl-3-methyl-2,3-dihydrobenzofuran-4-carboxamide (4a)**



Prepared following general procedure for catalytic reactions (page 104), using **3a**, and 10mol% of catalyst. The product was isolated by flash chromatography (1:5 to 3:1 EtOAc/Hexanes) as a yellow transparent oil.**^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.09 (td, *J* = 7.8, 1.6 Hz, 1H), 6.75 (dd, *J* = 8.1, 0.7 Hz, 1H), 6.65 (dd, *J* = 7.6, 0.8 Hz, 1H), 4.34 (d, *J* = 8.5 Hz, 1H), 4.08 (d, *J* = 8.5 Hz, 1H), 3.54 (br, 2H), 3.23 – 3.09 (m, 2H), 1.89 – 1.60 (m, 2H), 1.34 (s, 3H), 1.28 – 1.21 (m, 3H), 1.15 – 1.06 (m, 3H), 0.81 (t, *J* = 7.5 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 169.59 (C), 160.89 (C), 134.02 (C), 131.07 (C), 128.23 (CH), 118.27 (CH), 110.16 (CH), 82.06 (CH_2), 46.98 (C), 43.25 (CH), 38.67 (CH_2), 32.37 (CH_2), 24.55 (CH_2), 13.94 (CH_3), 12.64 (CH_3), 9.04 (CH_3). **HRMS** [ESI-TOF]: m/z calculated for $C_{16}H_{24}NO_2$ ($[M+H]^+$) 262.1799, found 262.1802. Data in agreement with those reported in literature.[5]

Enantioselectivity was determined by chiral HPLC analysis on a Chiralpack IE-3 column at *rt* (Hexane:iPrOH = 98:02, 1mL/min).

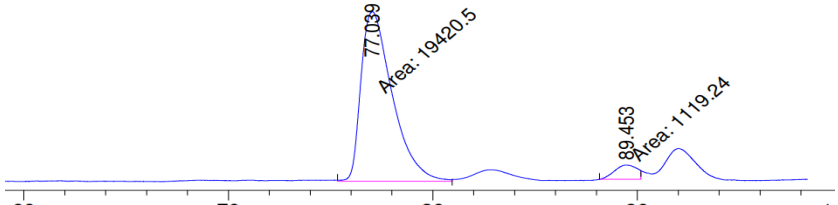
- Racemic sample prepared using [Ir(COD)$_2$]BARF / *rac*-BINAP (10 mol%) at 100 ºC.



Signal 3: DAD1 C, Sig=210,8 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	74.743	MM	1.8700	3.06100e4	272.81390	50.0509
2	85.830	MF	2.1465	3.05478e4	237.18533	49.9491
Totals :				6.11578e4	509.99924	

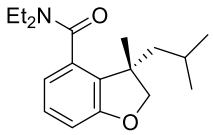
- Asymmetric sample prepared using [Ir(COD)$_2$]BARF / *(S)*-Binapine (10 mol%) at 100 ºC (85 % yield, 94:6 er).



Signal 3: DAD1 C, Sig=210,8 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	77.039	MM	1.7797	1.94205e4	181.86565	94.5508
2	89.453	MF	1.2747	1119.24304	14.63445	5.4492
Totals :				2.05397e4	196.50009	

(*S*)-*N*,*N*-Diethyl-3-isobutyl-3-methyl-2,3-dihydrobenzofuran-4-carboxamide (4b)

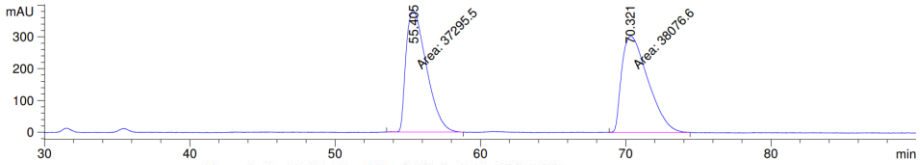


Prepared following general procedure for catalytic reactions (page 104), using **3b** and 10 mol% of catalyst The product was isolated by flash chromatography (1:5 to 3:1 EtOAc/Hexanes) as a yellow transparent oil.**^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.10 (t, *J* = 7.8 Hz, 1H), 6.78 (dd, *J* = 8.0, 0.9 Hz, 1H), 6.66 (dd, *J* = 7.5, 1.0 Hz, 1H), 4.40 (d, *J* = 8.8 Hz, 1H), 4.16 (d, *J* = 11.3 Hz, 1H), 3.55 (br m, 2H), 3.17 (d, *J* = 7.3 Hz, 2H), 1.69 (br m, 2H), 1.56 (s, 1H), 1.37 (s, 3H), 1.26 (t, *J* = 7.1 Hz, 3H), 1.11 (t, *J* = 7.1 Hz, 3H), 0.95 (d, *J* = 6.4 Hz, 3H), 0.85 – 0.75 (m, 3H) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$) δ 169.72 (CO), 160.42 (C), 133.87 (C), 128.27 (CH), 118.40 (CH), 110.31 (CH), 83.21 (CH_2), 46.85 (C), 43.25 (CH_2), 38.69 (CH_2), 25.47 (CH_3), 24.98 (CH), 24.08 (C), 13.93 (CH_3), 12.67 (CH_3) ppm. **HRMS** [APCI]: *m/z* calculated for $C_{18}H_{28}NO_2$ $[M+H]^+$: 290.2115, found 290.2108. **NMR spectra at page 467.**

Enantioselectivity was determined by chiral HPLC analysis on a Chiralpack IE-3 column at *rt* (Hexane:iPrOH = 98:02, 1mL/min).

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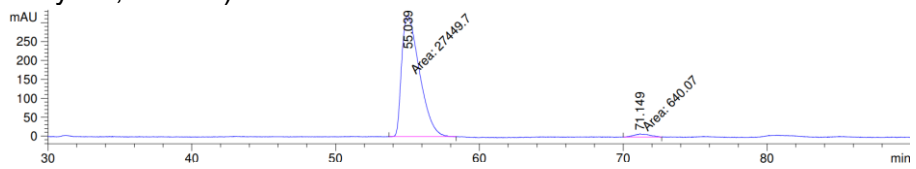
- Racemic sample prepared using [Ir(COD)$_2$]BARF / *rac*-BINAP (10 mol%) at 100 ºC.



Signal 3: DAD1 C, Sig=210,8 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	55.405	MM	1.6246	3.72955e4	382.60724	49.4819
2	70.321	MM	2.0952	3.80766e4	302.88556	50.5181
Totals :				7.53720e4	685.49280	

- Asymmetric sample prepared using [Ir(COD)$_2$]BARF / *(S)*-Binapine (10 mol%) at 100 ºC (76 % yield, 98:2 er).

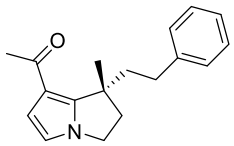


Signal 3: DAD1 C, Sig=210,8 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	55.039	MM	1.4338	2.74497e4	319.08923	97.7213
2	71.149	MM	1.2466	640.07031	8.55789	2.2787
Totals :				2.80898e4	327.64712	

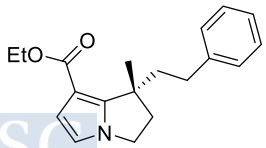
Transformations of compound 2a

(S)-1-(1-methyl-1-phenethyl-2,3-dihydro-1H-pyrrolizin-7-yl)ethan-1-one (2a^{II})



La(OTf)$_3$ (108.4 mg, 0.182 mmol) in THF (0.77 mL) was added to a solution of MeLi-LiBr (0.132 mL, 0.185 mmol, 1.5 M) at -78 ºC. After 5 minutes of stirring, **2a** (50 mg, 0.182 mmol) was added diluted in THF (0.31 mL) and the mixture was stirred at *rt* overnight. The product was isolated by flash chromatography (1:5 to 3:1 EtOAc/Hexanes) as a yellow transparent oil. 64% yield. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.24 – 6.99 (m, 5H), 6.49 (d, *J* = 2.9 Hz, 1H), 6.37 (d, *J* = 2.9 Hz, 1H), 3.95 – 3.84 (m, 2H), 2.58 – 2.42 (m, 2H), 2.36 – 2.27 (m, 5H), 2.21 (ddd, *J* = 12.8, 8.4, 6.1 Hz, 1H), 1.97 (ddd, *J* = 14.9, 12.7, 5.1 Hz, 1H), 1.40 (s, 3H) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$) δ 193.42 (CO), 149.11 (C), 142.73 (C), 128.55 (CH), 46.14 (CH_2), 44.43 (C), 42.20 (CH_2), 40.27 (C), 32.00 (CH_2), 25.21 (CH_3), 14.29 (CH_3) ppm. **HRMS** [APCI]: *m/z* calculated for $C_{18}H_{22}NO$ $[M+H]^+$: 268.1696, found 268.1690.

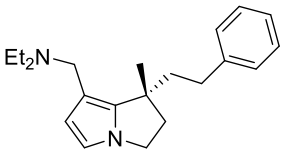
(S)-Ethyl 1-methyl-1-phenethyl-2,3-dihydro-1H-pyrrolizine-7-carboxylate (2a^{III})



To a stirring solution of **2a** (18.5 mg, 0.057 mmol) in CH_3CN (0.285 mL) at rt, was added Na_2HPO_4 (6.6 mg, 0.047 mmol), followed by $(CH_3)_3OBF_4$ (17.6 mg, 0.093 mmol). After consumption of the amide was complete, as indicated by TLC analysis (18 h), a saturated solution of $NaHCO_3$ (10 mL) was slowly added. The resulting mixture was

stirred for 18 h and then extracted with EtOAc (3 x 50 mL). The combined organic phases were concentrated, and the product was isolated by flash chromatography (1:8 to 1:1 EtOAc/Hexanes) as a yellow transparent oil, 71% yield. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.31 – 7.19 (m, 2H), 7.19 – 7.06 (m, 3H), 6.66 (d, *J* = 2.9 Hz, 1H), 6.47 (d, *J* = 2.9 Hz, 1H), 4.26 (q, *J* = 7.1 Hz, 2H), 3.98 (t, *J* = 7.3 Hz, 2H), 2.66 – 2.48 (m, 2H), 2.35 (ddt, *J* = 23.3, 13.4, 7.4 Hz, 3H), 2.04 (dt, *J* = 13.2, 6.8 Hz, 1H), 1.49 (s, 3H), 1.33 (t, *J* = 7.1 Hz, 3H) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$) δ 164.96 (CO), 148.76 (C), 142.67 (C), 128.47 (CH), 128.43 (CH), 125.77 (CH), 115.07 (CH), 113.96 (CH), 107.30 (C), 59.50 (CH_2), 45.82 (CH_2), 44.16 (C), 41.53 (CH_2), 40.95 (CH_2), 31.91 (CH_2), 25.82 (CH_3), 14.71 (CH_3) ppm. **HRMS** [APCI]: *m/z* calculated for $C_{19}H_{24}NO_2$ $[M+H]^+$: 298.18016, found 298.18014.

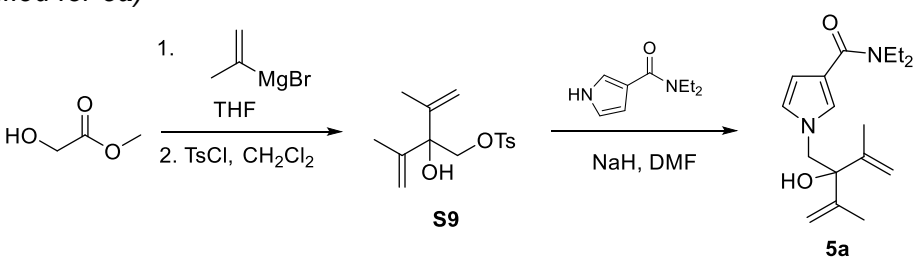
(S)-N-ethyl-*N*-((1-methyl-1-phenethyl-2,3-dihydro-1H-pyrrolizin-7-yl)methyl)ethanamine (2a^{v})



To a solution of **2a** (25 mg, 0.077 mmol) in THF (1.5 mL), $LiAlH_4$ (17.5 mg, 0.462 mmol) was added at 0 ºC. After 15 minutes of stirring, the reaction was heated at 50 ºC and stirred overnight. Sat. NH_4Cl solution (10mL) was carefully added and then extracted (3 x 25mL). The combined organic layers were concentrated under vacuum and the product was characterized without further purification with 99% yield. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.16 (t, *J* = 7.6 Hz, 2H), 7.11 – 7.00 (m, 3H), 6.36 (d, *J* = 2.7 Hz, 1H), 6.10 (d, *J* = 2.7 Hz, 1H), 3.85 (t, *J* = 7.0 Hz, 2H), 3.39 (d, *J* = 3.9 Hz, 2H), 2.60 – 2.51 (m, 1H), 2.47 (q, *J* = 7.2 Hz, 4H), 2.39 (dt, *J* = 13.7, 7.1 Hz, 2H), 2.20 – 2.14 (m, 1H), 1.94 (dt, *J* = 10.9, 5.0 Hz, 2H), 1.33 (s, 3H), 0.95 (t, *J* = 7.1 Hz, 6H) ppm. **^{13}C NMR** (75 MHz, $CDCl_3$) δ 142.74 (C), 140.61 (C), 128.29 (2xCH + C), 125.63 (CH), 113.72 (CH), 112.15 (CH), 49.45 (CH_2), 46.37 (CH_2), 45.01 (CH_2), 42.78 (CH_2), 42.46 (C), 41.57 (CH_2), 31.80 (CH_2), 26.16 (CH_3), 11.62 (CH_3) ppm. **HRMS** [APCI]: *m/z* calculated for $C_{21}H_{31}N_2$ $[M+H]^+$: 311.2482, found 311.2490.

Synthesis of precursors 5a-b and 5d-g

*(exemplified for **5a**)*



S9 **5a**

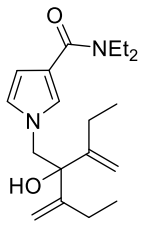
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Methyl vinylmagnesium bromide (15.4 mL, 0.5 M) was added dropwise to a solution of ethyl glycolate (0.182 mL, 0.20 g, 1.92 mmol) in THF (12.8 mL, 0.15 M) at 0 ºC. The reaction was stirred at *rt for* 6 h, quenched with $NH_4Cl_{(sat)}$ (50 mL) and extracted with Et_2O (3 x 25 mL). The combined organic phases were dried, filtered and evaporated at reduced pressure to give **3-methyl-2-(prop-1-en-2-yl)but-3-ene-1,2-diol** (1.07 g, 54% yield) as a colorless oil, which was used without further purification. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 5.05 (s, 4H), 3.81 (s, 2H), 2.37 (s, 2H), 1.71 (s, 6H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 145.12 (CH_2), 112.50 (CH_2), 108.80 (CH), 79.87 (C), 65.76 (CH_2), 18.88 (CH_2). Tosyl chloride (1.29 g, 6.77 mmol), DMAP (137.9 mg, 1.13 mmol) and Et_3N (2.1 mL, 15.0 mmol) were added to a solution of this alcohol (1.07 g, 6.44 mmol) in CH_2Cl_2 (38 mL) and the mixture was allowed to stir at *rt* for 3 *h* before being quenched with water (50 mL). The phases were separated, and the organic phase was washed twice with $NH_4Cl_{(sat)}$, dried and concentrated under reduced pressure. The crude yellow oil was purified by flash column chromatography (1:9 to 2:8 EtOAc/hexanes) to afford **2-hydroxy-3-methyl-2-(prop-1-en-2-yl)but-3-en-1-yl 4-methylbenzenesulfonate** (**S9**) as a yellowish solid (1.10 g, 49% yield).[2] **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.81 (d, *J* = 8.0 Hz, 2H), 7.37 (d, *J* = 8.0 Hz, 2H), 5.00 (d, *J* = 6.7 Hz, 4H), 4.24 (s, 2H), 2.47 (s, 3H), 2,35 (br, 1H), 1.65 (s, 6H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 145.27 (C), 143.72 (C), 132.60 (C), 130.09 (CH), 128.13 (CH), 113.26 (CH_2), 78.27 (C), 72.95 (CH_2), 21.81 (CH_3), 18.58 (CH_3).

2-hydroxy-3-methyl-2-(prop-1-en-2-yl)but-3-en-1-yl 4-methylbenzenesulfonate (**S9**, 1.1 g, 3.71 mmol) was added to a solution of *N,N*-diethyl-1H-pyrrole-3-carboxamide (616.9 mg, 3.71 mmol), and NaH (212.2 mg, 5.31 mmol, 60%) in DMF (14.8 mL). The reaction mixture was stirred at *rt* overnight and water (75 mL) was added. The mixture was extracted with Et_2O (5 x 25 mL). The organic phase was dried, concentrated and the crude residue was purified by flash chromatography, obtaining ***N,N*-diethyl-1-(2-hydroxy-3-methyl-2-(prop-1-en-2-yl)but-3-en-1-yl)-1H-pyrrole-3-carboxamide** (**5a**) as a white solid. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.05 (t, *J* = 2.0 Hz, 1H), 6.59 (dd, *J* = 2.9, 2.2 Hz, 1H), 6.30 (dd, *J* = 2.9, 1.8 Hz, 1H), 5.01 (dd, *J* = 1.5, 0.8 Hz, 2H), 4.98 (t, *J* = 0.8 Hz, 2H), 4.23 (s, 2H), 3.51 (q, *J* = 7.1 Hz, 4H), 2.35 (br, 1H), 1.72 (dd, *J* = 1.5, 0.7 Hz, 6H), 1.20 (t, *J* = 7.1 Hz, 6H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 166.66 (CO), 145.25 (C), 125.01 (CH), 122.35 (CH), 119.17 (C), 112.67 (CH_2), 108.80 (C), 78.91 (C), 55.46 (CH_2), 41.60 (CH_2), 18.88 (CH_3), 13.73 (CH_3). **HRMS** [APCI]: *m/z* calculated for $C_{17}H_{27}N_2O_2$ $[M+H]^+$: 291.2067, found 291.2063.

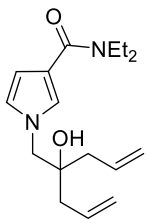
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1-(2-(But-1-en-2-yl)-2-hydroxy-3-methylenepentyl)-*N,N*-diethyl-1H-pyrrole-3-carboxamide (5b)



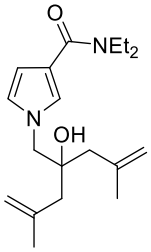
Synthesized by following the procedure used for **5a**, using 1-ethylvinylmagnesium bromide as Grignard reagent. Obtained as white solid (110 mg, 88% yield). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 6.95 (t, *J* = 2.0 Hz, 1H), 6.48 (t, *J* = 2.5 Hz, 1H), 6.20 (dd, *J* = 2.9, 1.8 Hz, 1H), 4.99 (s, 2H), 4.92 (s, 2H), 4.15 (s, 2H), 3.42 (q, *J* = 7.1 Hz, 4H), 2.45 (s, 1H), 2.03 – 1.77 (m, 4H), 1.11 (t, *J* = 7.1 Hz, 6H), 0.95 (t, *J* = 7.4 Hz, 6H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 166.65 (CO), 151.40 (C), 124.97 (CH), 122.34 (CH), 118.94 (C), 109.72 (CH_2), 108.51 (CH), 79.40 (C), 56.31 (CH_2), 41.47 (CH_2), 23.62 (CH_2), 13.64 (CH_3), 12.25 (CH_3). **HRMS** [APCI]: *m/z* calculated for $C_{19}H_{31}N_2O_2$ $[M+H]^+$: 319.2380, found 319.2379. **NMR spectra at page 468.**

1-(2-Allyl-2-hydroxypent-4-en-1-yl)-*N,N*-diethyl-1H-pyrrole-3-carboxamide (5d)



Synthesized by following the procedure used for **5a**, using allylmagnesium bromide as Grignard reagent. Obtained as colorless oil (120 mg, 15% global yield). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.08 (s, 1H), 6.62 (s, 1H), 6.33 (s, 1H), 5.81 (dd, *J* = 17.5, 9.0 Hz, 2H), 5.21 – 5.08 (m, 4H), 3.82 (s, 2H), 3.56 – 3.49 (m, 4H), 2.34 – 2.06 (m, 6H), 1.24 – 1.18 (m, 6H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 166.73 (C), 132.77 (CH), 125.20 (CH), 122.42 (CH), 119,64 (C), 119.62 (CH_2), 108.98 (CH), 73.35 (CH_2), 57.38 (CH_2), 41.86 (CH_2), 41.42 (CH_2), 13.87 (CH_3). **HRMS** [APCI]: *m/z* calculated for $C_{17}H_{26}N_2O_2$ $[M+H]^+$: 291.2067, found 291.2068.

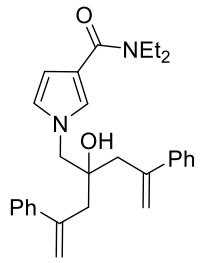
***N,N*-Diethyl-1-(2-hydroxy-4-methyl-2-(2-methylallyl)pent-4-en-1-yl)-1H-pyrrole-3-carboxamide (5e)**



Synthesized by following the procedure used for **5a**, using methylallylmagnesium bromide as Grignard reagent. Obtained as white solid (71 mg, 13% global yield). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.09 (s, 1H), 6.62 (s, 1H), 6.33 (d, J = 1.3 Hz, 1H), 4.94 (s, 2H), 4.74 (s, 2H), 3.87 (s, 2H), 3.51 (q, J = 7.1 Hz, 4H), 2.25 – 2.04 (m, 4H), 1.82 (s, 6H), 1.20 (t, J = 7.1 Hz, 6H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 166.76 (CO), 141.95 (C), 125.40 (C), 122.50 (CH), 119.25 (CH), 115.73 (CH_2), 108.86 (CH), 73.38 (C), 58.33 (CH_2), 45.89 (CH_2), 40.82 (CH_2), 24.94 (CH_3), 13.80 (CH_3). **HRMS** [APCI]: *m/z* calculated for $C_{19}H_{31}N_2O_2$ $[M+H]^+$: 319.2380, found 319.2377.

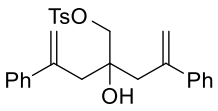
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***N,N*-Diethyl-1-(2-hydroxy-4-phenyl-2-(2-phenylallyl)pent-4-en-1-yl)-1H-pyrrole-3-carboxamide (5f)**



Synthetized following a similar procedure than **5a** using 2-hydroxy-4-phenyl-2-(2-phenylallyl)pent-4-en-1-yl 4-methylbenzenesulfonate (**S10**, see its synthesis and data below) instead of **S9**. **^{1}H NMR** (500 MHz, DMSO) 7.44 – 7.12 (m, 10H), 7.02 (d, *J* = 2.5 Hz, 1H), 6.65 (d, *J* = 2.6 Hz, 1H), 6.18 (d, *J* = 2.5 Hz, 1H), 5.36 (s, 2H), 5.19 (s, 2H), 3.78 (s, 2H), 3.48 – 3.36 (m, 4H), 2.65 (d, *J* = 16.4 Hz, 2H), 2.55 (d, *J* = 16.4 Hz, 2H), 1.14 – 1.05 (m, 6H). **^{13}C NMR** (126 MHz, DMSO) δ 164.91 (CO), 143.62 (C), 142.11 (C), 127.49 (CH), 126.49 (CH), 125.60 (CH), 124.35 (CH), 121.99 (CH), 117.92 (C), 116.83 (CH_2), 107.49 (CH), 73.45 (COH), 56.86 (CH_2), 41.58 (CH_2), 40.33 (CH_2), 13.09 (CH_3). **HRMS** [APCI]: *m/z* calculated for $C_{29}H_{35}N_2O_2$ $[M+H]^+$: 443.2693, found 443.2691.

2-Hydroxy-4-phenyl-2-(2-phenylallyl)pent-4-en-1-yl 4-methylbenzenesulfonate (S10).

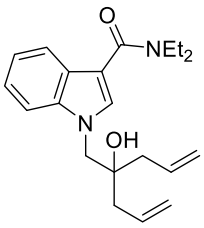


Ethyl 2-((tert-butyldimethylsilyl)oxy)acetate (1.0 g, 4.58 mmol) was added to a mixture of (3-bromoprop-1-en-2-yl)benzene (3.6 g, 18.31 mmol) and indium powder (1.08 g, 9.16 mmol) in THF (4.6 mL) and the resulting mixture was refluxed for 16 h. Water (30 mL) was added, the phases were separated, and the organic phase was washed twice with NH_4Cl(sat), dried and concentrated to yield the corresponding 4-(((tert-butyldimethylsilyl)oxy)methyl)-2,6-diphenylhepta-1,6-dien-4-ol which was submitted to standard OTBS deprotection using TBAF, without further purification. Thus, **4-phenyl-2-(2-phenylallyl)pent-4-ene-1,2-diol** was obtained as a white solid. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.44 – 7.24 (m, 10H), 5.38 (d, *J* = 1.8 Hz, 2H), 5.17 (d, *J* = 1.8 Hz, 2H), 3.19 (s, 2H), 2.78 (s, 4H), 1.87 (s, 2H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 144.94 (C), 142.38 (C), 128.52 (CH), 127.66 (CH), 126.39 (CH), 117.95 (CH_2), 74.72 (C), 66.94 (CH_2), 42.51 (CH_2). Tosylation of this diol was performed using the abovementioned conditions described for **S9**, to yield **2-Hydroxy-4-phenyl-2-(2-phenylallyl)pent-4-en-1-yl 4-methylbenzenesulfonate** (**S10**) as yellowish solid (530 mg, 26% global yield, 3 steps) **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.60 (d, *J* = 8.4 Hz, 2H), 7.28 (d, *J* = 3.5 Hz, 13H), 5.31 (d, *J* = 1.6 Hz, 2H), 5.09 (d, *J* = 3.3 Hz, 2H), 3.60 (s, 2H), 2.82 – 2.65 (m, 4H), 2.45 (s, 4H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 144.43 (C), 143.49

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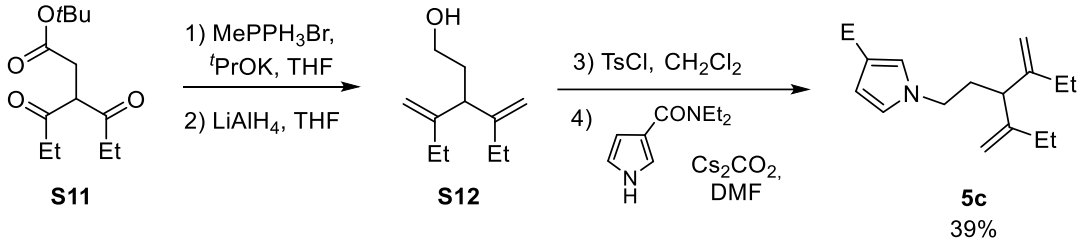
(C), 141.63 (C), 132.18 (C), 129.45 (CH), 128.19 (CH), 127.68 (CH), 127.36 (CH), 126.05 (CH), 118.32 (CH_2), 72.74 (CH_2), 72.49 (CH_2), 42.15 (CH_2), 21.36 (CH_3).

1-(2-allyl-2-hydroxypent-4-en-1-yl)-*N,N*-diethyl-1H-indole-3-carboxamide (5g)



Synthesized by following the procedure used for **5d**, using *N,N*-diethyl-1H-indole-3-carboxamide. Obtained as colorless oil (105 mg, 21% global yield). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.70 (d, *J* = 7.9 Hz, 1H), 7.40 (s, 1H), 7.29 (d, *J* = 8.3 Hz, 1H), 7.19 – 7.06 (m, 2H), 5.81 – 5.69 (m, 2H), 5.14 – 4.95 (m, 4H), 4.03 (s, 2H), 3.49 (q, *J* = 7.1 Hz, 4H), 2.22 (dd, *J* = 14.2, 7.3 Hz, 2H), 2.11 (dd, *J* = 14.2, 7.4 Hz, 2H), 1.14 (t, *J* = 7.2 Hz, 6H) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$) δ 166.97 (CO), 137.26 (C), 132.65 (CH), 129.88 (CH), 126.83 (C), 122.54 (CH), 121.01 (CH), 120.75 (CH), 119.79 (CH_2), 111.89 (C), 110.34 (CH), 74.35 (COH), 53.79 (CH_2), 42.10 (CH_3), 13.99 (CH_3) ppm. **HRMS** [APCI]: *m/z* calculated for $C_{21}H_{29}N_2O_2$ $[M+H]^+$: 341.2224, found 341.2223.

Synthesis of precursors 5a-b and 5d-g



tert-butyl 4-oxo-3-propionylhexanoate (**S11**) was prepared according to reported procedures.[181] A mixture of methyltriphenylphosphonium bromide (14.08 g, 39.4 mmol) and t-BuOK (4.42 g, 39.4 mmol) in toluene (130 mL) was refluxed for 1 h. Then, a solution of **tert-butyl 4-oxo-3-propionylhexanoate** (3.0 g, 13.1 mmol) in toluene (30 mL) was added to the mixture at room temperature, and then the whole was refluxed for 3 h. After being cooled to room temperature, the mixture was diluted with saturated aqueous NH_4Cl and extracted with ether. The extract was washed with brine and dried over $MgSO_4$. Removal of the solvent in vacuo gave an oily residue, which was purified by column chromatography on silica gel. **tert-butyl 3-(but-1-en-2-yl)-4-methylenehexanoate** was obtained in 62% yield as a yellow oil and was used in the next step without further purification.

To a suspension of $LiAlH_4$ (288 Mg, 7.58 mmol) in Et_2O (60 mL), a solution of **tert-butyl 3-(but-1-en-2-yl)-4-methylenehexanoate** (1.81 g, 7.58 mmol) was added at 0 ºC, and the mixture was allowed to stir at r.t. for 1h. Then, water (50 mL) was slowly added at 0

[181] Glaxo Group Ltd, M. A. Duval, W. D. Simon, Patent WO2009074519A1, **2009**.

ºC. The mixture was extracted with Et_2O (3 x 100 mL).The organic phase was dried, concentrated and the crude residue was purified by flash chromatography using 5% Et_2O in hexanes as eluent, obtaining **3-(but-1-en-2-yl)-4-methylenehexan-1-ol** (**S12**) in 49% yield as a yellow oil**. ^{1}H NMR** (300 MHz, $CDCl_3$) δ 4.88 – 4.81 (m, 4H), 3.62 (td, *J* = 6.5, 1.1 Hz, 2H), 2.86 (t, *J* = 7.6 Hz, 1H), 1.96 – 1.77 (m, 6H), 1.00 (td, *J* = 7.4, 1.0 Hz, 6H) ppm. **^{13}C NMR** (75 MHz, $CDCl_3$) δ 152.11 (C), 109.03 (CH_2), 61.82 (CH_2), 49.73 (CH), 34.07 (CH_2), 26.27 (CH_2), 12.38 (CH_3) ppm.

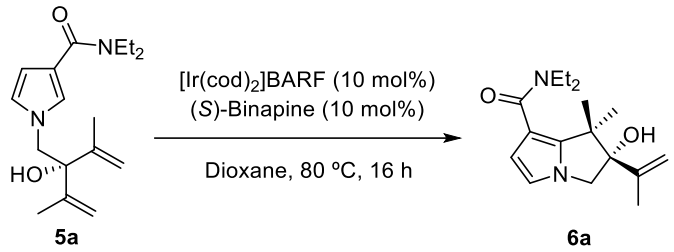
To a solution of **3-(but-1-en-2-yl)-4-methylenehexan-1-ol** (**S12**, 748 mg, 3.9 mmol), DMAP (4.4 mg, 0.036 mmol) and triethylamine (0.65 mL, 4.63 mmol) in CH_2Cl_2 (2.5 ml) at 0 °C was added *p*-toluenesulfonyl chloride (600 mg, 3.57 mmol) and the reaction mixture was stirred for 4 hours at *rt*. The reaction was quenched with water (30 mL) and extracted with CH_2Cl_2 (3 x 40 mL). The organic phase was dried, concentrated and the crude residue was purified by flash chromatography using 5% Et_2O in hexanes as eluent, obtaining **3-(but-1-en-2-yl)-4-methylenehexyl 4-methylbenzenesulfonate** in a quantitative yield as a brown oil. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.77 (d, *J* = 8.3 Hz, 2H), 7.33 (d, *J* = 8.1 Hz, 2H), 4.80 (s, 2H), 4.71 (s, 2H), 4.00 (t, *J* = 6.6 Hz, 2H), 2.75 (t, *J* = 7.7 Hz, 1H), 2.44 (s, 3H), 1.94 – 1.77 (m, 6H), 0.94 (t, *J* = 7.4 Hz, 6H) ppm. **^{13}C NMR** (75 MHz, $CDCl_3$) δ 150.67 (C), 144.77 (C), 133.33 (C), 129.89 (CH), 128.02 (CH), 109.54 (CH_2), 69.35 (CH_2), 48.64 (CH), 30.27 (CH_2), 26.21 (CH_2), 21.74 (CH_2), 12.29 (CH_3) ppm.

3-(but-1-en-2-yl)-4-methylenehexyl 4-methylbenzenesulfonate (582 mg, 3.71 mmol) was added to a solution of *N,N*-diethyl-1H-pyrrole-3-carboxamide (616.9 mg, 3.71 mmol), and NaH (212.2 mg, 5.31 mmol, 60%) in DMF (14.8 mL). The reaction mixture was stirred at *rt* overnight and water (75 mL) was added. The mixture was extracted with Et_2O (5 x 25 mL). The organic phase was dried, concentrated and the crude residue was purified by flash chromatography, obtaining **1-(3-(But-1-en-2-yl)-4-methylenehexyl)-*N,N*-diethyl-1H-pyrrole-3-carboxamide** (**5c**). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.01 (t, *J* = 2.0 Hz, 1H), 6.51 (t, *J* = 2.6 Hz, 1H), 6.27 (dd, *J* = 2.9, 1.8 Hz, 1H), 4.85 (d, *J* = 1.5 Hz, 2H), 4.80 (d, *J* = 1.1 Hz, 2H), 3.77 (t, *J* = 7.2 Hz, 2H), 3.48 (q, *J* = 7.1 Hz, 4H), 2.59 (t, *J* = 7.6 Hz, 1H), 1.97 (q, *J* = 7.5 Hz, 3H), 1.94 – 1.78 (m, 4H), 1.17 (t, *J* = 7.1 Hz, 6H), 0.95 (t, *J* = 7.4 Hz, 6H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 166.60 (CO), 150.86 (C), 123.65 (CH), 120.42 (CH), 119.06 (C), 109.44 (CH_2), 108.69 (CH), 49.86 (CH), 48.09 (CH_2), 41.49 (CH_2), 32.50 (CH_2), 26.08 (CH_2), 13.76 (CH_3), 12.21 (CH_3). **HRMS** [APCI]: *m/z* calculated for $C_{20}H_{33}N_2O$ $[M+H]^+$: 317.2587, found 217.2585. **NMR spectra at page 469.**

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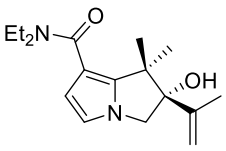
Synthesis of compounds 6 by hydroarylation of precursors 5

*(exemplified for **6a**)*



5a **6a**

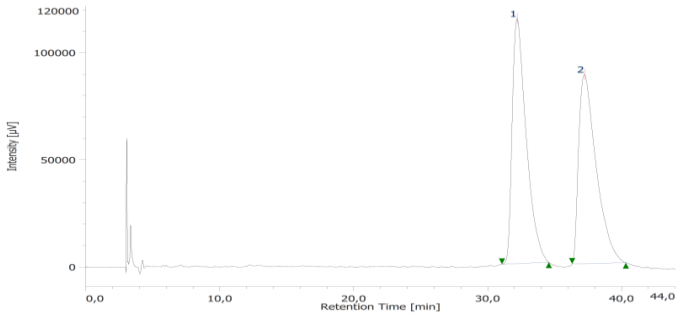
N,N-Diethyl-2-hydroxy-1,1-dimethyl-2-(prop-1-en-2-yl)-2,3-dihydro-1H-pyrrolizine-7-carboxamide (6a)



Prepared following general procedure for catalytic reactions (page 104), using **5a** and 10 mol% of catalyst**.** The product was isolated by flash chromatography (1:3 to 3:1 EtOAc/Hexanes) as a yellow oil.**^{1}H NMR** (500 MHz, $CDCl_3$) δ 6.45 (d, *J* = 2.8 Hz, 1H), 6.15 (d, *J* = 2.8 Hz, 1H), 5.08 – 4.99 (m, 2H), 4.32 (d, *J* = 11.0 Hz, 1H), 3.88 (d, *J* = 11.0 Hz, 1H), 3.57 – 3.39 (m, 4H), 1.77 (dd, *J* = 1.5, 0.7 Hz, 3H), 1.44 (s, 3H), 1.23 (s, 3H), 1.17 (t, *J* = 7.1 Hz, 6H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 167.54 (CO), 145.03 (C), 144.31 (C), 113.17 (CH_2), 112.78 (CH), 111.30 (C), 110.62 (CH), 89.18 (C), 56.11 (CH_2), 46.70 (C), 40.96 (CH_2), 23.16 (CH_3), 20.12 (CH_3), 20.03 (CH_3), 13.62 (CH_3). **HRMS** [APCI]: *m/z* calculated for $C_{17}H_{27}N_2O_2$ $[M+H]^+$: 291.2067, found 291.2069.

Enantioselectivity was determined by chiral SFC analysis on Lux 5um Amylose-2 column at *rt* (CO_2:MeOH = 95:05, 1mL/min).

- Racemic sample prepared using $[Ir(COD)_2]$BARF / *rac*-BINAP (5 mol%) at 100 ºC (88% yield).

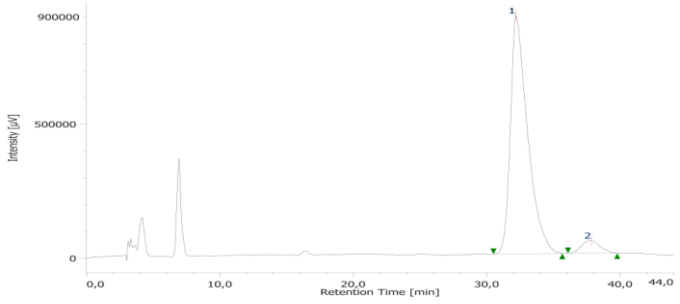


Channel Name 254,0nm

#	Peak Name	CH	tR [min]	Area [μV·sec]	Height [μV]	Area%
1	Unknown	7	32.193	8332284	114214	50.868
2	Unknown	7	37.223	8047770	88146	49.132

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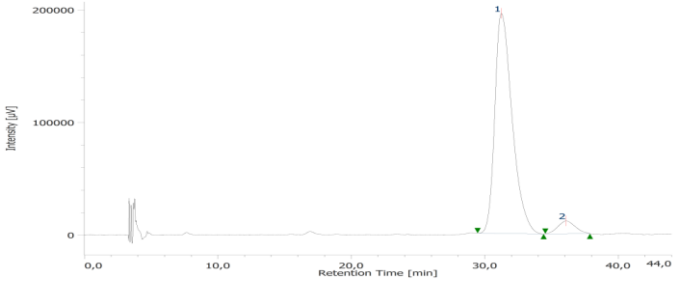
- Asymmetric sample prepared using [Ir(COD)$_2$]BARF / *(S)*-Binapine (10 mol%) at 80 ºC (90% yield, 95:5 er).



Channel Name 254,0nm

#	Peak Name	CH	tR [min]	Area [μV·sec]	Height [μV]	Area%
1	Unknown	5	32,167	79470094	888735	94,529
2	Unknown	5	37,850	4599135	47975	5,471

- Asymmetric sample prepared using [Ir(COD)$_2$]BARF / *(S)*-Binapine (10 mol%) at 60 ºC (75% yield, 95:5 er).



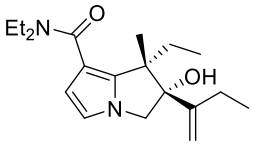
Channel Name 254,0nm

#	Peak Name	CH	tR [min]	Area [μV·sec]	Height [μV]	Area%
1	Unknown	7	31,240	17726745	195493	94,541
2	Unknown	7	36,093	1023503	11471	5,459

2-(But-1-en-2-yl)-*N,N*,1-triethyl-2-hydroxy-1-methyl-2,3-dihydro-1H-pyrrolizine-7-carboxamide (6b and 6b')

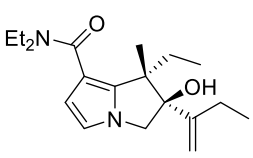
Prepared following general procedure for catalytic reactions (page 104), using **5b** and 10 mol% of catalyst. The products were independently isolated by flash chromatography (1:3 to 3:1 EtOAc/Hexanes) as yellow oils. Diastereoselectivity was determined by ^{1}H-NMR (crude reaction residue) and enantioselectivity by chiral HPLC analysis on a Chiralpack IE-3 column at *rt* (Hexane:iPrOH = 90:10, 1mL/min).

(*1S,2S*)-2-(but-1-en-2-yl)-*N,N*,1-triethyl-2-hydroxy-1-methyl-2,3-dihydro-1H-pyrrolizine-7-carboxamide (6b).



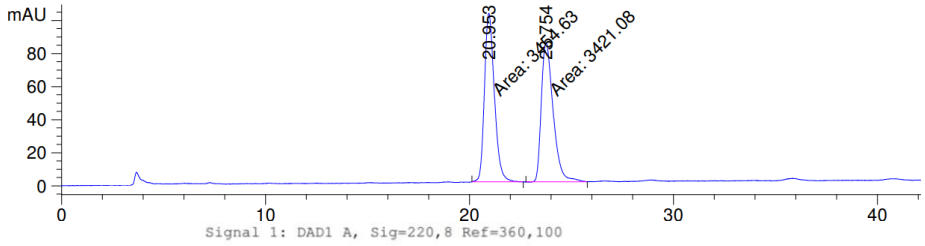
^{1}H NMR (500 MHz, $CDCl_3$) δ 6.45 (d, *J* = 2.8 Hz, 1H), 6.16 (d, *J* = 2.8 Hz, 1H), 5.01 (s, 1H), 4.98 (s, 1H), 4.14 (d, *J* = 10.7 Hz, 1H), 3.97 (d, *J* = 10.7 Hz, 1H), 3.53 – 3.37 (m, 4H), 1.94 – 1.87 (m, 1H), 1.87 – 1.80 (m, 3H), 1.17 (d, *J* = 7.0 Hz, 6H), 1.16 (s, 3H), 1.02 (t, *J* = 7.3 Hz, 3H), 0.92 (t, *J* = 7.4 Hz, 3H) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$) δ 167.91 (CO), 153.48 (C), 142.65 (C), 112.85 (CH), 111.00 (CH), 109.26 (CH_2), 89.64 (C), 57.34 (CH_2), 50.33 (C), 41.06 (CH_2), 29.82 (CH_2), 23.98 (CH_2), 20.02 (CH_3), 13.70 (CH_3), 12.77 (CH_3), 10.34 (CH_3). **HRMS** [APCI]: *m/z* calculated for $C_{19}H_{31}N_2O_2$ $[M+H]^+$: 319.2377, found 319.2380. **NMR spectra at page 471.**

(1S,2R)-2-(but-1-en-2-yl)-*N,N*,1-triethyl-2-hydroxy-1-methyl-2,3-dihydro-1H-pyrrolizine-7-carboxamide (6b')



^{1}H NMR (500 MHz, $CDCl_3$) δ 6.49 (d, *J* = 2.8 Hz, 1H), 6.15 (d, *J* = 2.7 Hz, 1H), 5.19 (s, 1H), 5.09 (s, 1H), 4.39 (d, *J* = 10.9 Hz, 1H), 3.84 (d, *J* = 10.9 Hz, 1H), 3.54 – 3.40 (m, 4H), 2.31 – 2.12 (m, 1H), 2.13 – 2.00 (m, 1H), 1.57 – 1.48 (m, 2H), 1.46 (s, 3H), 1.17 (t, *J* = 7.0 Hz, 6H), 1.10 (t, *J* = 7.2 Hz, 3H), 0.81 (t, *J* = 7.4 Hz, 3H) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$) δ 168.12 (CO), 150.49 (C), 141.82 (C), 113.37 (CH), 111.30 (CH_2), 110.89 (CH), 90.23 (C), 56.84 (CH_2), 51.95 (C), 40.99 (CH_2), 30.37 (CH_2), 4.90 (CH_2), 17.07 (CH_3), 13.69 (CH_3), 12.87 (CH_3), 9.49 (CH_3). **HRMS** [APCI]: *m/z* calculated for $C_{19}H_{31}N_2O_2$ $[M+H]^+$: 319.2380, found 319.2380. **NMR spectra at page 472.**

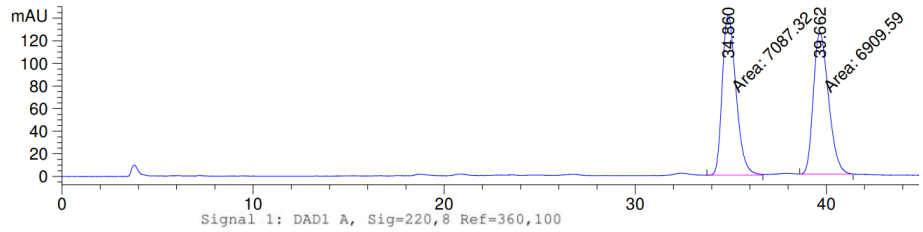
- Racemic sample of **6b'** prepared using $[Ir(COD)_2]BARF$ / *rac*-BINAP (10 mol%) at 100 ºC.



Signal 1: DAD1 A, Sig=220,8 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	20.953	MM	0.5647	3454.63257	101.96333	50.2440
2	23.754	MM	0.6775	3421.07935	84.16113	49.7560
Totals :				6875.71191	186.12446	

- Racemic sample of **6b** prepared using $[Ir(COD)_2]BARF$ / *rac*-BINAP (10 mol%), at 100 ºC.

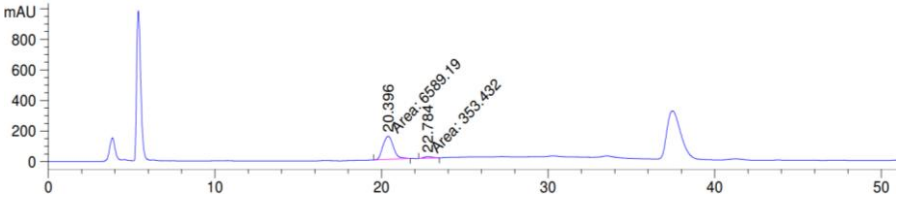


Signal 1: DAD1 A, Sig=220,8 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	34.860	MM	0.8320	7087.32227	141.97357	50.6349
2	39.662	MM	0.9228	6909.58643	124.79570	49.3651
Totals :				1.39969e4	266.76927	

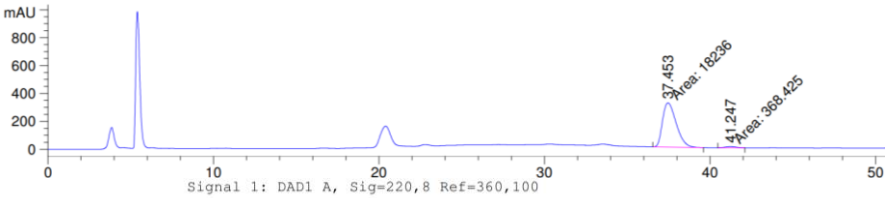
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- Asymmetric sample prepared using [Ir(COD)$_2$]BARF / *(S)*-Binapine (10 mol%) at 80 ºC (86% global yield, dr (**6b**:**6b'**) = 9:1, **6b'**: 95:5 er, **6b**: 98.2 er).



Signal 1: DAD1 A, Sig=220,8 Ref=360,100

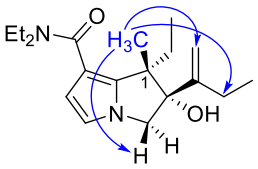
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	20.396	MM	0.7265	6589.19336	151.16190	94.9092
2	22.784	MM	0.5776	353.43225	10.19841	5.0908
Totals :				6942.62561	161.36030	



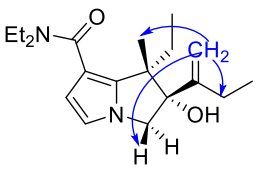
Signal 1: DAD1 A, Sig=220,8 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	37.453	MM	0.9590	1.82360e4	316.94119	98.0197
2	41.247	MM	0.8092	368.42465	7.58806	1.9803
Totals :				1.86044e4	324.52925	

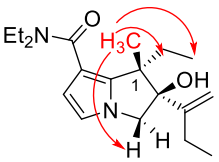
The relative configuration of the isomers was determined by nOe analysis (see spectra at page 473):



6b: Irradiation at methyl of C-1



6b: Irradiation at alkenyl CH_2



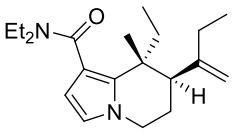
6b': Irradiation at methyl of C-1

7-(But-1-en-2-yl)-*N,N*,8-triethyl-8-methyl-5,6,7,8-tetrahydroindolizine-1-carboxamide (6c and 6c')

Prepared following general procedure for catalytic reactions (page 104), using **5c** and 10 mol% of catalyst. The products were partially separated by flash chromatography (1:3 to 3:1 EtOAc/Hexanes) as yellow oils. 93% global yield, dr (**4c**:**4c'**) =8:2. Small portions of each isomer were isolated for characterization. Diastereoselectivity was determined by ^{1}H-NMR (crude reaction residue) and enantioselectivity was determined by chiral HPLC analysis on a Chiralpack IE-3 column at *rt* (Hexane:iPrOH =95:05, 1mL/min).

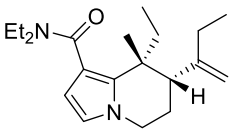
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(*7S*,*8R*)-7-(But-1-en-2-yl)-*N,N*,8-triethyl-8-methyl-5,6,7,8-tetrahydroindolizine-1-carboxamide (**6c**)



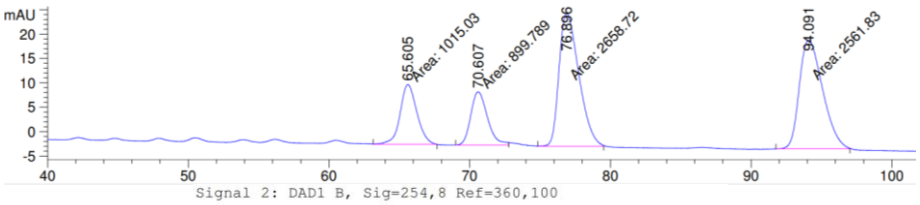
^{1}H NMR (500 MHz, $CDCl_3$) δ 6.40 (d, *J* = 2.9 Hz, 1H), 6.01 (d, *J* = 2.1 Hz, 1H), 4.91 (s, 1H), 4.31 (s, 1H), 3.96 – 3.83 (m, 2H), 3.39 (br m, 4H), 2.33 – 2.30 (m, 1H), 2.13 – 2.07 (m, 2H), 1.97 – 1.86 (m, 3H), 1.84 – 1.78 (m, 1H), 1.43 (s, 3H), 1.15 (t, *J* = 7.1 Hz, 6H), 1.07 (t, *J* = 7.4 Hz, 3H), 0.78 (t, *J* = 7.4 Hz, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 170.54 (CO), 149.26 (C), 136.03 (C), 118.00 (CH), 114.34 (C), 110.12 (CH_2), 107.75 (CH), 46.70 (CH), 42.30 (CH_2), 38.43 (C), 30.43 (CH_2), 28.66 (CH_2), 27.78 (CH_3), 23.29 (CH_2), 14.4 (CH_3), 12.60 (CH_3), 8.56 (CH_3). **HRMS** [APCI]: *m/z* calculated for $C_{20}H_{33}N_2O$ $[M+H]^+$: 317.2587, found 317.2586. **NMR spectra at page 475.**

(*7R*, *8R*)-7-(but-1-en-2-yl)-*N,N*,8-triethyl-8-methyl-5,6,7,8-tetrahydroindolizine-1-carboxa-mide (**6c'**)



^{1}H NMR (500 MHz, $CDCl_3$) δ 6.40 (s, 1H), 6.04 (s, 1H), 4.94 (s, 1H), 4.49 (s, 1H), 4.03 – 3.86 (m, 2H), 3.56 – 3.28 (m, 4H), 2.57 – 2.49 (m, 1H), 2.14 – 1.98 (m, 4H), 1.91 (dt, *J* = 14.5, 7.2 Hz, 1H), 1.79 (dd, *J* = 14.5, 7.3 Hz, 1H), 1.32 (s, 3H), 1.16 (t, *J* = 7.0 Hz, 6H), 1.06 (t, *J* = 7.4 Hz, 3H), 0.81 (t, *J* = 7.4 Hz, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 170.09 (CO), 151.01 (C), 135.97 (C), 117.79 (CH), 114.47 (C), 111.24 (CH_2), 107.93 (CH), 44.28 (CH_2), 43.88 (CH), 39.86 (C), 32.50 (CH_2), 30.50 (CH_2), 24.65 (CH_2), 23.37 (CH_3), 14.0 (CH_3), 12.99 (CH_3), 9.18 (CH_3) (ethyl amide signals are not visible due to the presence of rotamers). **HRMS** [APCI]: *m/z* calculated for $C_{20}H_{33}N_2O$ $[M+H]^+$: 317.2587, found 317.2586. **NMR spectra at page 476.**

- Racemic sample of **6c** and **6c'** prepared using $[Ir(COD)_2]$BARF / *rac*-BINAP (10 mol%) at 100 ºC, (**6c**:**6c'**) =3:7.

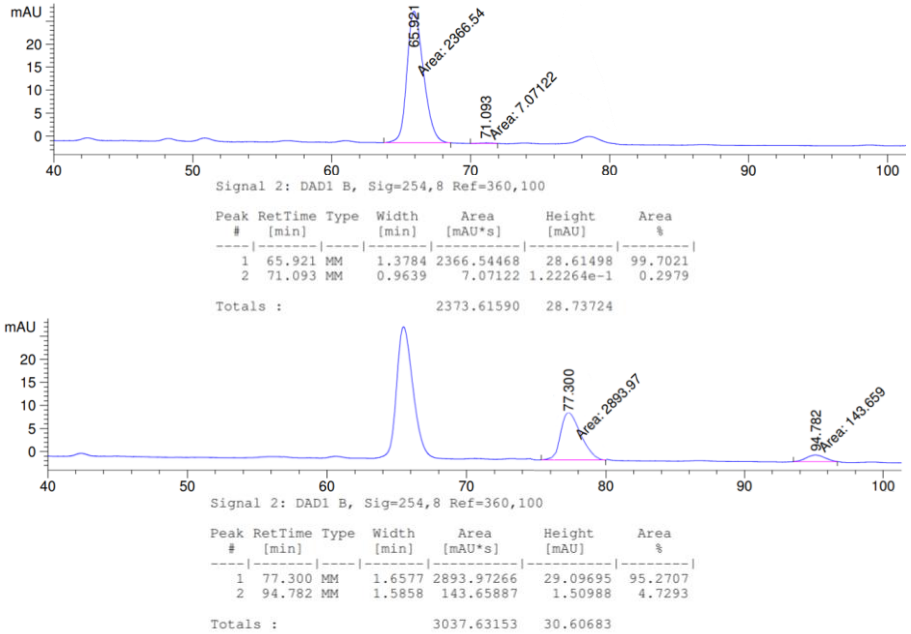


Signal 2: DAD1 B, Sig=254,8 Ref=360,100

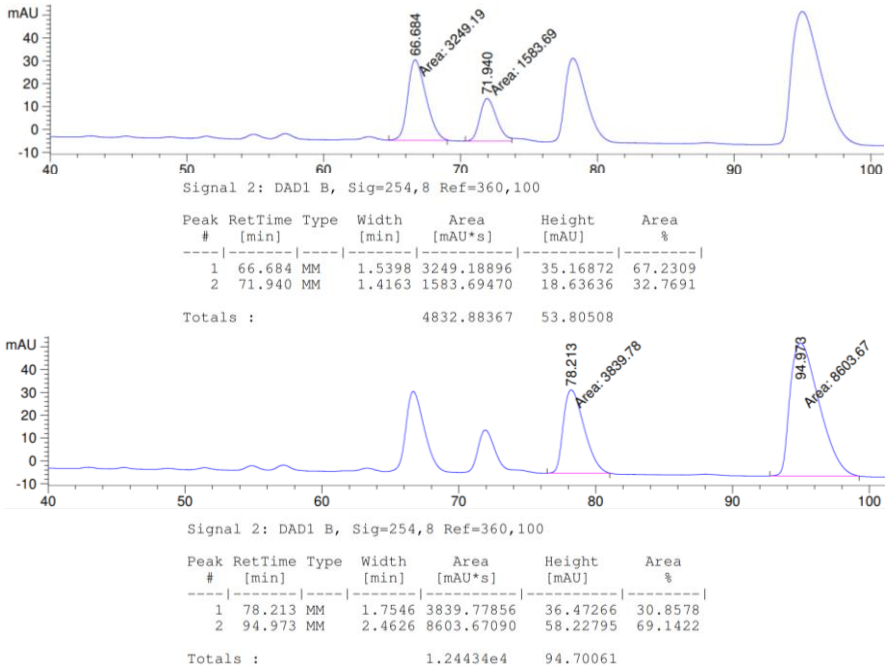
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	65.605	MM	1.3838	1015.03168	12.22551	14.2253
2	70.607	MM	1.3718	899.78894	10.93236	12.6103
3	76.896	MM	1.6280	2658.72046	27.21852	37.2611
4	94.091	MM	1.9162	2561.83423	22.28237	35.9033
Totals :				7135.37531	72.65875	

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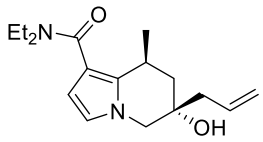
- Asymmetric sample prepared using [Ir(COD)$_2$]BARF / *(S)*-Binapine (10 mol%) at 80 ºC (93% global yield, dr (**6c**:**6c'**) =8:2; **6c**: 99.7:0.3 er and **6c'**: 95:5 er).



- Asymmetric sample prepared using [Ir(COD)$_2$]BARF / *(S)*-BINAP (10 mol%) at 80 ºC (93% global yield, dr (**6c**:**6c'**)= 2:8, **6c**: 67:33 er, **6c':** 31:69 er).



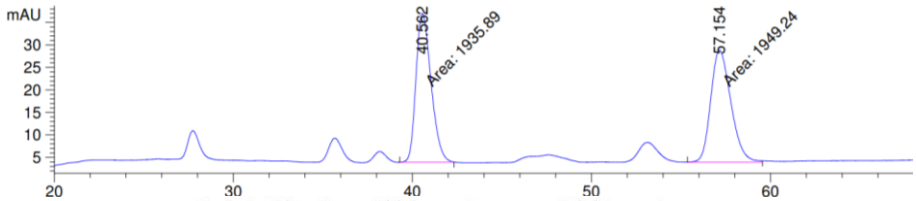
(*6S*,*8S*)-6-Allyl-*N*,*N*-diethyl-6-hydroxy-8-methyl-5,6,7,8-tetrahydroindolizine-1-carboxamide (6d)



Prepared following general procedure for catalytic reactions (page 104), using **5d** and 10 mol% of catalyst. The product was isolated by flash chromatography (1:3 to 3:1 EtOAc/Hexanes) as white solid. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 6.41 (d, *J* = 2.9 Hz, 1H), 6.14 (d, *J* = 2.7 Hz, 1H), 6.02 – 5.87 (m, 1H), 5.29 – 5.11 (m, 2H), 3.84 – 3.76 (m, 2H), 3.60 – 3.45 (m, 4H), 3.44 – 3.36 (m, 1H), 2.38 (t, *J* = 7.3 Hz, 2H), 2.07 – 1.99 (m, 1H), 1.48 – 1.41 (m, 1H), 1.25 (d, *J* = 6.7 Hz, 3H), 1.20 (t, *J* = 7.1 Hz, 6H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 169.62 (CO), 135.32 (C), 132.54 (CH), 125.90 (C), 119.52 (CH_2), 118.72 (CH), 108.31 (CH), 70.06 (C), 55.50 (CH_2), 45.14 (CH_2), 42.40 (CH_2), 41.63 (CH_2), 25.28 (CH), 20.69 (CH_3), 13.20 (CH_3). **HRMS** [APCI]: *m/z* calculated for $C_{17}H_{26}N_2O_2$ $[M+H]^+$: 291.2067, found 291.2057.

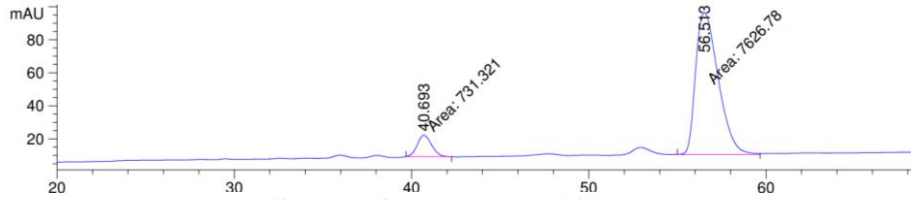
Enantioselectivity was determined by chiral HPLC analysis on a Chiralpack IE-3 column at *rt* (Hexane:iPrOH = 90:10, 1mL/min).

- Racemic sample prepared using $[Ir(COD)_2]$BARF / *rac*-BINAP (5 mol%) at 100 ºC.



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	40.562	MM	0.9759	1935.88904	33.06186	49.8282
2	57.154	MM	1.3061	1949.23828	24.87390	50.1718
Totals :				3885.12732	57.93575	

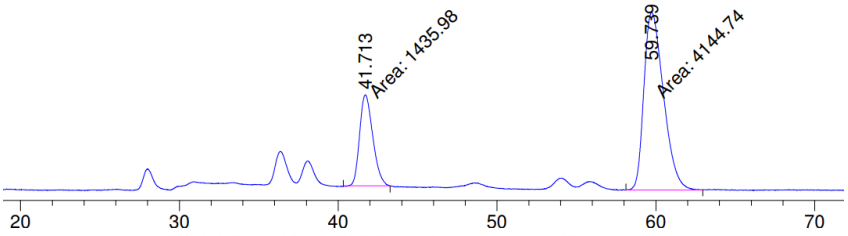
- Asymmetric sample prepared using $[Ir(COD)_2]$BARF / *(S)*-Binapine (10 mol%) at 80 ºC (93% yield, 92:8 er).



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	40.693	MM	0.9386	731.32141	12.98656	8.7499
2	56.513	MM	1.4779	7626.77783	86.01084	91.2501
Totals :				8358.09924	98.99740	

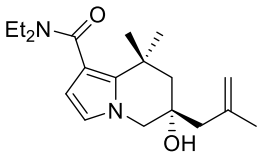
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- Asymmetric sample prepared using [Ir(COD)$_2$]BARF / *(S)*-BINAP (10 mol%) at 80 ºC (80% yield, 74:26 er).



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	41.713	MM	0.9647	1435.98352	24.80984	25.7312
2	59.739	MM	1.4284	4144.73584	48.36060	74.2688
Totals :				5580.71936	73.17045	

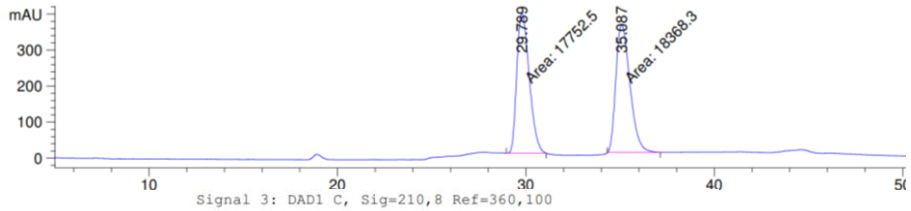
_(S)_-_N,N_-Diethyl-6-hydroxy-8,8-dimethyl-6-(2-methylallyl)-5,6,7,8-tetrahydroindolizine-1-carboxamide (6e)



Prepared following general procedure for catalytic reactions (page 104), using **5e** and 10 mol% of catalyst. The product was isolated by flash chromatography (1:3 to 3:1 EtOAc/Hexanes) as white solid. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 6.39 (d, *J* = 2.8 Hz, 1H), 6.07 (d, *J* = 2.7 Hz, 1H), 5.01 (s, 1H), 4.82 (s, 1H), 3.87 – 3.76 (m, 2H), 3.53 – 3.30 (m, 4H), 2.36 – 2.27 (m, 2H), 1.89 (s, 3H), 1.87 – 1.71 (m, 2H), 1.50 (s, 3H), 1.37 (s, 3H), 1.16 (t, *J* = 7.1 Hz, 6H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 169.66 (CO), 141.11 (C), 133.87 (C), 118.07 (CH), 115.80 (CH_2), 115.18 (C), 107.87 (CH), 70.87 (C), 55.39 (CH_2), 49.82 (CH_2), 48.52 (CH_2), 40.40 (CH_2), 32.34 (C), 32.02 (CH_3), 31.51 (CH_3), 24.86 (CH_3), 13.29 (CH_3). **HRMS** [APCI]: *m/z* calculated for $C_{19}H_{31}N_2O_2$ $[M+H]^+$: 319.2380, found 319.2375.

Enantioselectivity was determined by chiral HPLC analysis on a Chiralpack IE-3 column at *rt* (Hexane:iPrOH = 90:10, 1mL/min).

- Racemic sample prepared using [Ir(COD)$_2$]BARF / *rac*-BINAP (5 mol%) at 100 ºC.

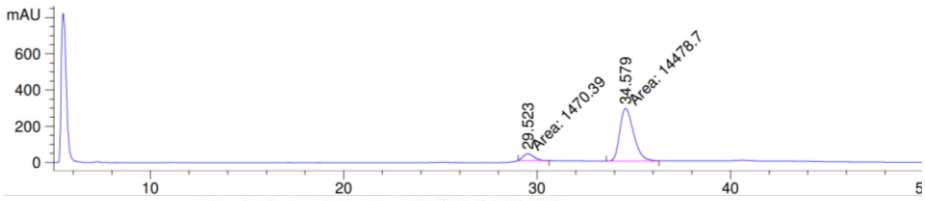


Signal 3: DAD1 C, Sig=210,8 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	29.789	MM	0.7628	1.77525e4	387.89624	49.1476
2	35.087	MM	0.8653	1.83683e4	353.80756	50.8524
Totals :				3.61207e4	741.70380	

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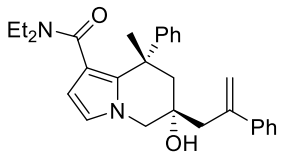
- Asymmetric sample prepared using [Ir(COD)$_2$]BARF / *(S)*-Binapine (10 mol%) at 80 ºC (85% yield, 91:9 er).



Signal 3: DAD1 C, Sig=210,8 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	29.523	MM	0.6498	1470.38916	37.71147	9.2193
2	34.579	MM	0.8296	1.44787e4	290.88257	90.7807
Totals :				1.59491e4	328.59404	

(*6S*,*8S*)-*N*,*N*-Diethyl-6-hydroxy-8-methyl-8-phenyl-6-(2-phenylallyl)-5,6,7,8-tetrahydroindolizine-1-carboxamide (6f)

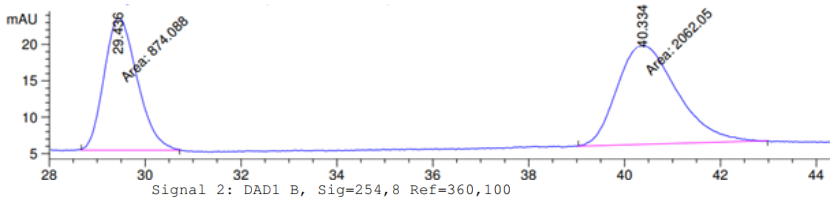


Prepared following general procedure for catalytic reactions (page 104), using **5f** and 10 mol% of catalyst. The product was isolated by flash chromatography (1:3 to 3:1 EtOAc/Hexanes) as white solid. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.38 – 7.31 (m, 5H), 7.21 – 7.11 (m, 5H), 6.32 (d, *J* = 2.7 Hz, 1H), 6.10 (d, *J* = 2.4 Hz, 1H), 5.41 (d, *J* = 1.9 Hz, 1H), 5.18 (s, 1H), 3.71 (d, *J* = 12.8 Hz, 1H), 3.56 (d, *J* = 12.8 Hz, 1H), 3.28 (ddd, *J* = 27.2, 13.7, 6.8 Hz, 4H), 2.78 (d, *J* = 6.6 Hz, 2H), 2.41 (d, *J* = 14.5 Hz, 1H), 2.25 (br s, 1H), 2.02 (s, 1H), 1.68 (s, 3H), 0.99 (d, *J* = 7.1 Hz, 6H). **^{13}C signals** obtained using **HSQC (^{1}H-^{13}C) NMR** and **HMBC (^{1}H-^{13}C) NMR** (175 MHz, $CDCl_3$) δ 169.7 (CO), 148.6 (C), 142.5 (C), 133.3 (C), 129.2 (CH), 129.0 (CH), 128.7 (CH), 128.7 (CH), 128.1 (CH), 127.6 (CH), 119.2 (CH_2), 118.6 (C), 118.5 (CH), 117.2 (C), 108.3 (CH), 71.9 (COH), 54.2 (CH_2), 51.7 (CH_2), 47.2 (CH_2), 41.2 (C), 40.0 (CH_2 amide), 30.3 (CH_3), 14.4 (CH_3 amide). **HRMS** [APCI]: *m/z* calculated for $C_{29}H_{35}N_2O_2$ $[M+H]^+$: 443.2693, found 443.2692. **NMR spectra at page 477.**

Enantioselectivity was determined by chiral HPLC analysis on a Chiralpack IE-3 column at *rt* (Hexane:iPrOH = 85:15, 1mL/min).

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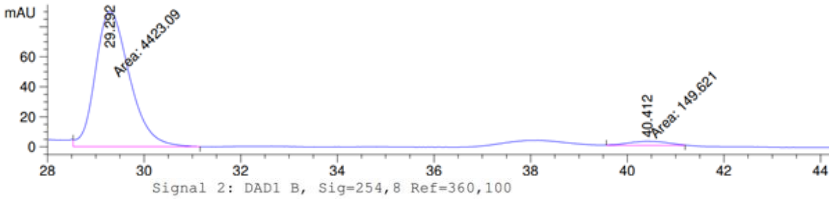
- Racemic sample prepared using [Ir(COD)$_2$]BARF / *rac*-BINAP (10 mol%) at 100 ºC.



Signal 2: DAD1 B, Sig=254,8 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	29.450	MM	0.7980	2128.11914	44.44935	50.7884
2	40.334	MM	1.2077	2062.04541	28.45647	49.2116
Totals :				4190.16455	72.90582	

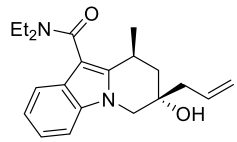
- Asymmetric sample prepared using [Ir(COD)$_2$]BARF / *(S)*-Binapine (10 mol%) at 80 ºC (95% yield, 97:3 er).



Signal 2: DAD1 B, Sig=254,8 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	29.292	FM	0.8190	4423.08740	90.01463	96.7280
2	40.412	MM	0.9313	149.62083	2.67761	3.2720
Totals :				4572.70824	92.69223	

(7R,9S)-*N,N*-diethyl-7-hydroxy-9-methyl-7-(propa-1,2-dien-1-yl)-6,7,8,9-tetrahydropyrido[1,2-a]indole-10-carboxamide (6g)

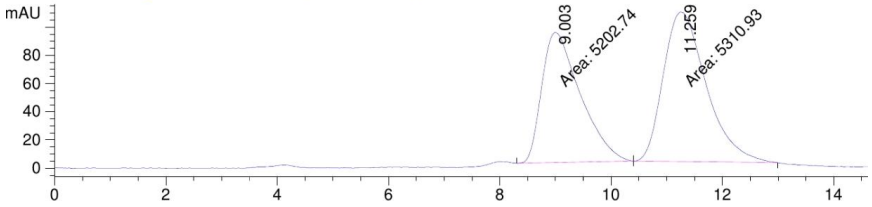


Prepared following general procedure for catalytic reactions (page 104), using **5g** and 10 mol% of catalyst. The product was isolated by flash chromatography (1:3 to 3:1 EtOAc/Hexanes) as a white solid. **^{1}H NMR** (500 MHz, DMSO) δ 7.38 – 7.26 (m, 2H), 7.16 – 7.03 (m, 2H), 5.93 – 5.60 (m, 2H), 4.07 (dd, *J* = 12.4, 2.1 Hz, 1H), 3.85 (d, *J* = 12.5 Hz, 1H), 3.59 – 3.49 (m, 2H), 3.47 – 3.40 (m, 1H), 3.39 – 3.33 (m, 2H), 2.02 – 1.96 (m, 1H), 1.75 (dd, *J* = 6.4, 1.6 Hz, 3H), 1.66 – 1.61 (m, 1H), 1.30 (d, *J* = 6.9 Hz, 3H), 1.12 (t, *J* = 6.9 Hz, 6H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ13C NMR (126 MHz, DMSO) δ 166.77 (CO), 136.34 (CH), 134.80 (C), 134.26 (C), 125.50 (C), 123.08 (CH), 120.01 (CH), 119.30 (CH), 117.35 (CH), 108.71 (CH), 106.80 (C), 68.03 (COH), 51.49 (CH_2), 41.04 (CH_2), 24.93 (CH_2), 19.01 (CH_3), 16.65 (CH_3), 12.91 (CH_3) ppm. **HRMS** [APCI]: *m/z* calculated for $C_{21}H_{29}N_2O_2$ $[M+H]^+$: 341.2224, found 341.2226.

Enantioselectivity was determined by chiral HPLC analysis on a Chiralpack IA column at *rt* (Hexane:iPrOH = 90:10, 1mL/min).

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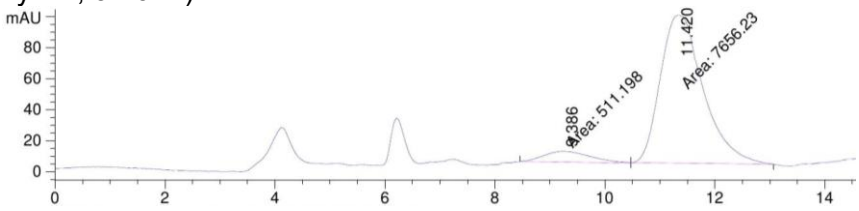
- Racemic sample prepared using [Ir(COD)$_2$]BARF / *rac*-BINAP (10 mol%) at 100 ºC.



Signal 2: DAD1 B, Sig=254,8 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	9.003	MM	0.8847	5202.74463	98.01669	49.4855
2	11.259	MM	0.8542	5310.92822	103.62795	50.5145

- Asymmetric sample prepared using [Ir(COD)$_2$]BARF / *(S)*-Binapine (10 mol%) at 100 ºC (61% yield, 94:6 er).

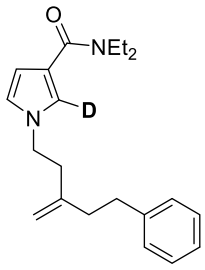


Signal 2: DAD1 B, Sig=254,8 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	9.386	MM	0.8224	511.19760	10.35938	6.2590
2	11.420	MM	1.3777	7656.22607	92.62019	93.7410
Totals :				8167.42368	102.97958	

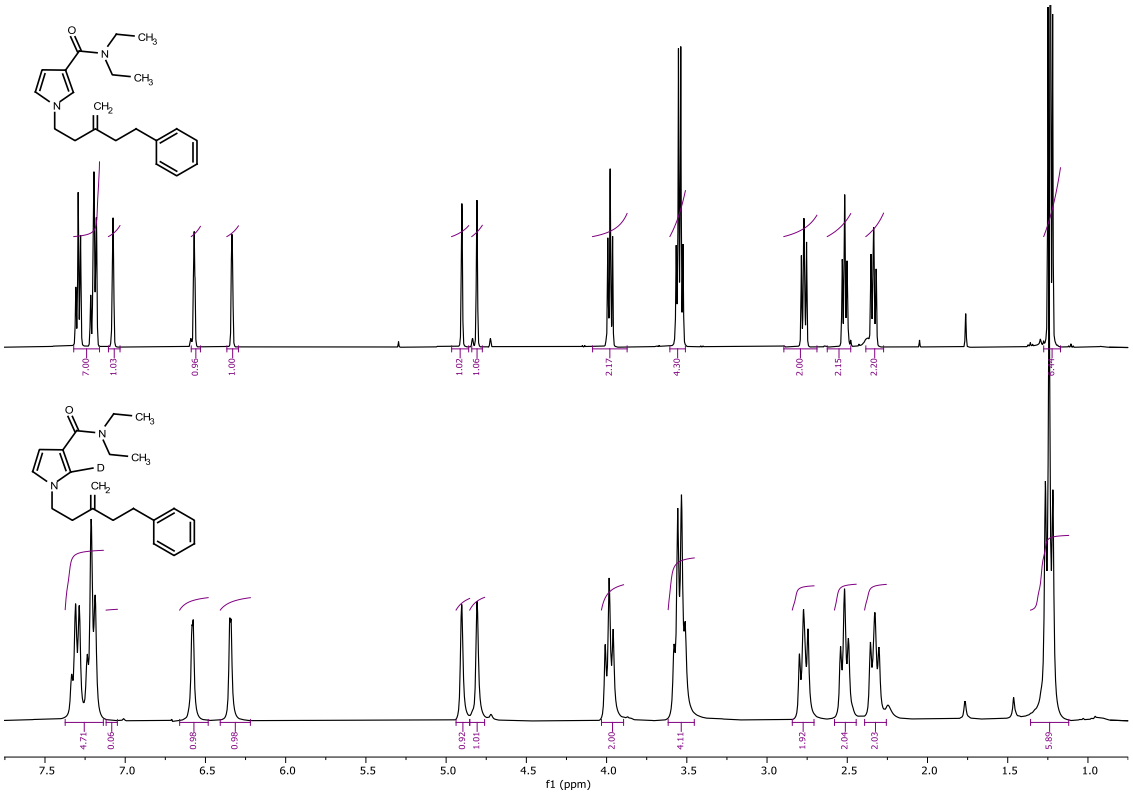
Synthesis of deuterated precursors d1-1a and d1-1w

Preparation of the deuterated substrate d1-1a



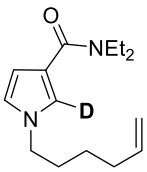
n-BuLi (0.102 mL, 0.254 mmol, 2.5 M solution in hexanes) was added to a solution of **1a** (75 mg, 0.231 mmol) in THF at 0 ºC. After 30 minutes, D_2O (5 mL) was added dropwise. The mixture was extracted with Et_2O (3 x 20 mL/mmol). The organic phase was dried, concentrated and the crude residue was purified by flash chromatography, obtaining ***N,N*-diethyl-1-(3-methylene-5-phenylpentyl)-1H-pyrrole-3-carboxamide-2-d**, ***d1*-1a** as a yellow oil (71 mg, 94.4 % yield, > 95% D content). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.23 (dt, *J* = 29.7, 7.6 Hz, 5H), 6.54 (s, 1H), 6.31 (s, 1H), 4.87 (s, 1H), 4.77 (s, 1H), 3.95 (t, *J* = 7.5 Hz, 2H), 3.51 (q, *J* = 7.1 Hz, 4H), 2.84 – 2.61 (m, 2H), 2.48 (t, *J* = 7.5 Hz, 2H), 2.29 (t, *J* = 8.1 Hz, 2H), 1.21 (t, *J* = 7.1 Hz, 6H) ppm. **^{2}H NMR** (300 MHz, $CDCl_3$) 7.08 (D). **HRMS** [APCI]: *m/z* calculated for $C_{21}H_{27}N_2OD$ $[M+H]^+$: 326.2337, found 326.2339.

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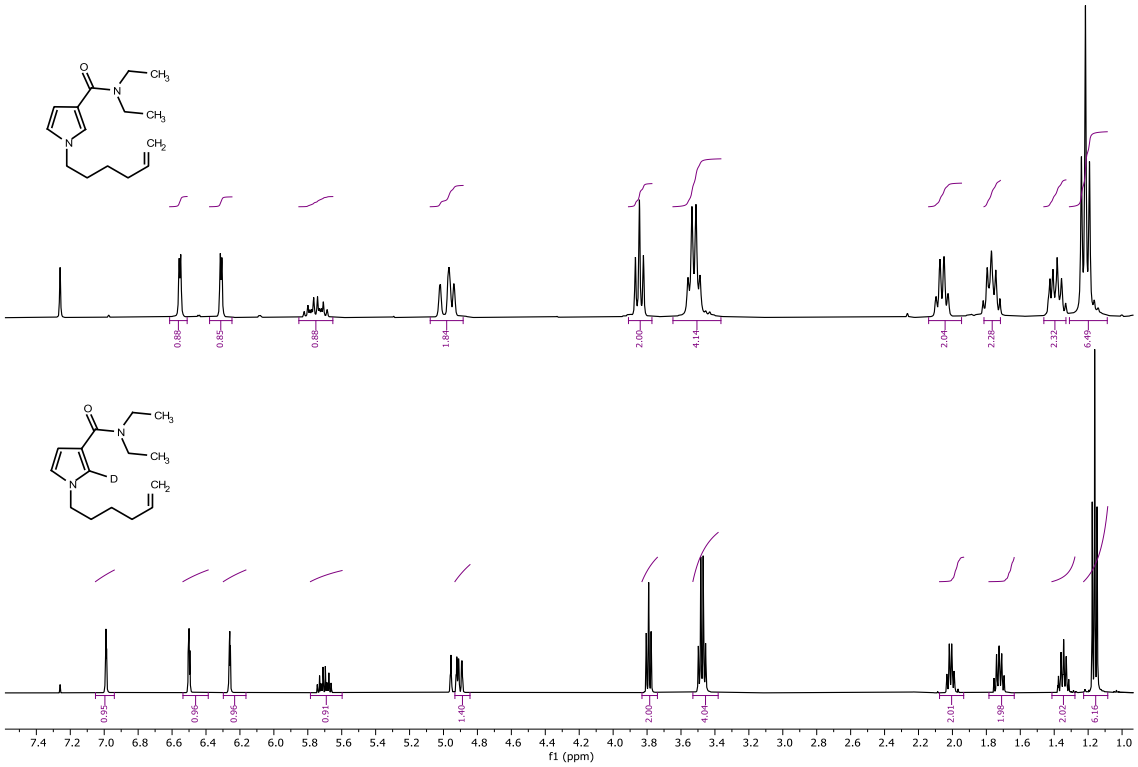
***Scheme 209**: [1]H-NMR Spectra of **1a** and **d1-1a**.*

Preparation of the deuterated substrate d1-1w



Synthetized following the same procedure than ***d1-1a***, obtaining ***N,N*-diethyl-1-(hex-5-en-1-yl)-1H-pyrrole-3-carboxamide-2-D** as a yellow oil (***d1*-1w**, 135.1 mg, 91.5 % yield, > 95% deuterium content). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 6.55 (d, *J* = 2.8 Hz, 1H), 6.31 (d, *J* = 2.8 Hz, 1H), 5.85 – 5.65 (m, 1H), 5.08 – 4.88 (m, 2H), 3.85 (t, *J* = 7.1 Hz, 2H), 3.52 (q, *J* = 7.1 Hz, 4H), 2.06 (q, *J* = 7.1 Hz, 2H), 1.76 (q, *J* = 7.4 Hz, 2H), 1.46 – 1.33 (m, 2H), 1.22 (t, *J* = 7.1 Hz, 6H). **^{2}H NMR** (300 MHz, $CDCl_3$) 6.99 (D). **HRMS** [APCI]: *m/z* calculated for $C_{15}H_{24}N_2OD$ $[M+H]^+$: 250.2024, found 250.2020.

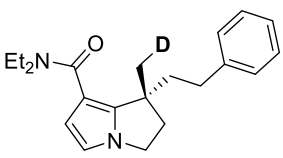
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***Scheme 210**: [1]H-NMR Spectra of **1w** and **d1-1w**.*

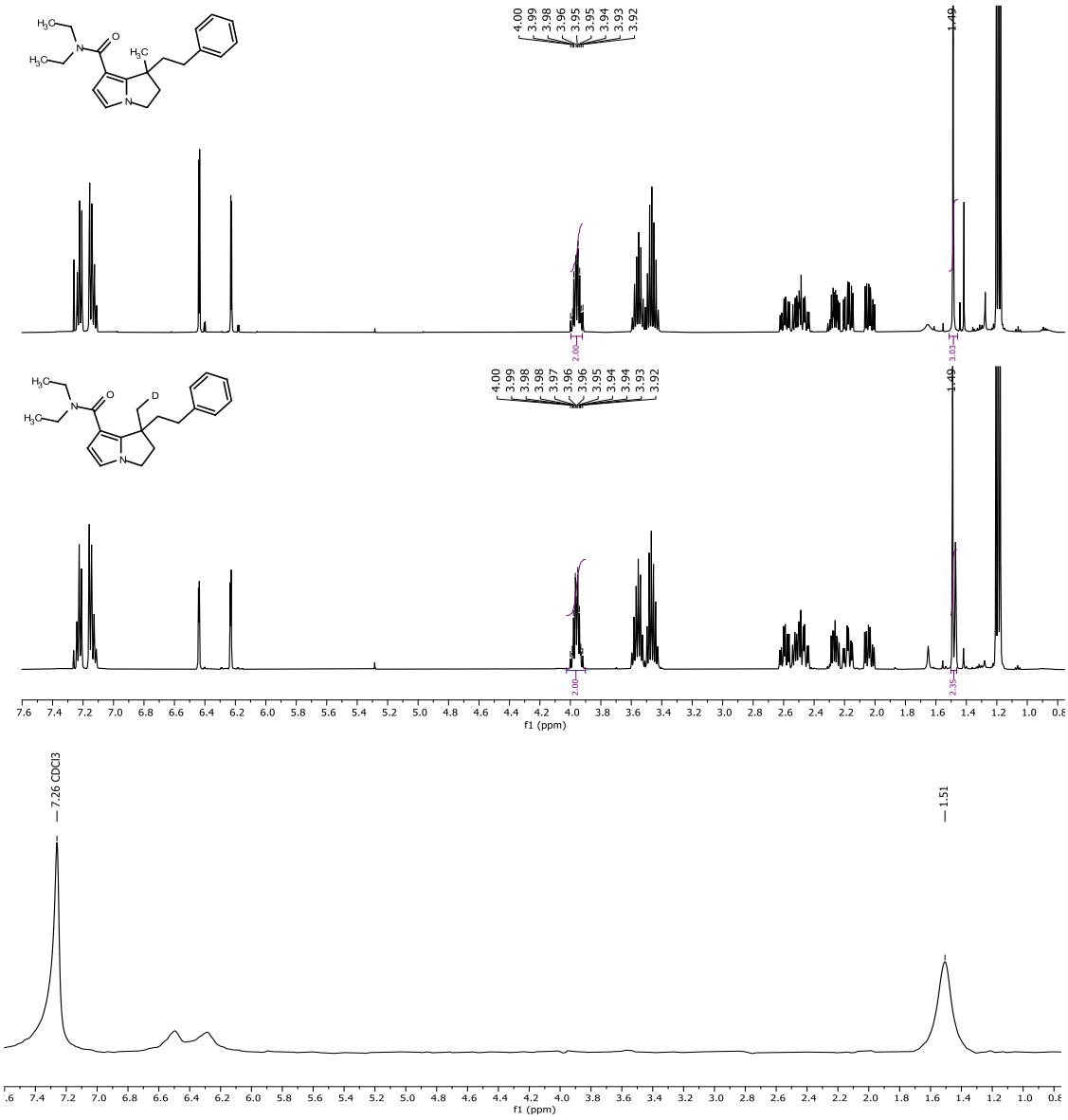
Synthesis of deuterated products d1-2a and d1-2w

N,N-Diethyl-1-(methyl-d)-1-phenethyl-2,3-dihydro-1H-pyrrolizine-7-carboxamide (*d1*-2a)



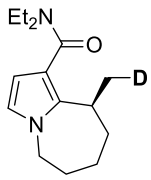
Prepared following general procedure for catalytic reactions (page 104), using ***d1*-1a**. Carried out at 100 ºC (reaction time: 2 h) under otherwise identical standard conditions. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.33 – 7.04 (m, 5H), 6.44 (d, *J* = 2.7 Hz, 1H), 6.23 (d, *J* = 2.7 Hz, 1H), 3.96 (dt, *J* = 8.0, 5.6 Hz, 2H), 3.62 – 3.50 (m, 2H), 3.51 – 3.40 (m, 2H), 2.65 – 2.55 (m, 1H), 2.55 – 2.41 (m, 2H), 2.31 – 2.23 (m, 1H), 2.23 – 2.13 (m, 1H), 2.09 – 1.99 (m, 1H), 1.48 (d, *J* = 9.5 Hz, 2H), 1.19 (t, *J* = 7.1 Hz, 6H) ppm. **^{2}H NMR** (300 MHz, $CDCl_3$) 1.50 (D). **HRMS** [APCI]: *m/z* calculated for $C_{21}H_{27}N_2OD$ $[M+H]^+$: 326.2337, found 326.2340.

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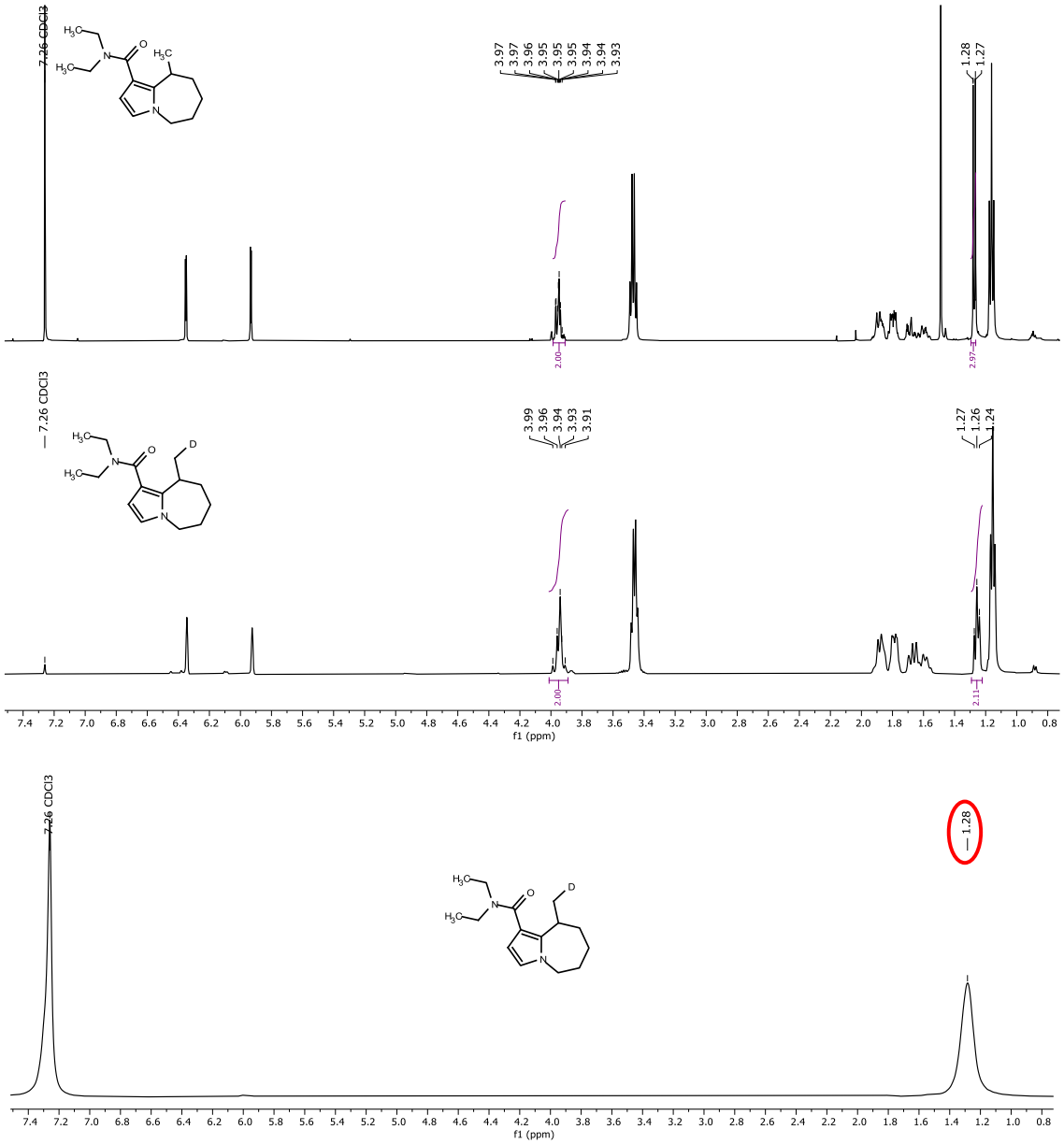
***Scheme 211**: [1]H-NMR Spectra **of 2a** and **d1-2a**, and [2]H-NMR Spectra **d1-2a**.*

N,N-Diethyl-9-(methyl-d)-6,7,8,9-tetrahydro-5H-pyrrolo[1,2-a]azepine-1-carboxamide (*d1*-2w)

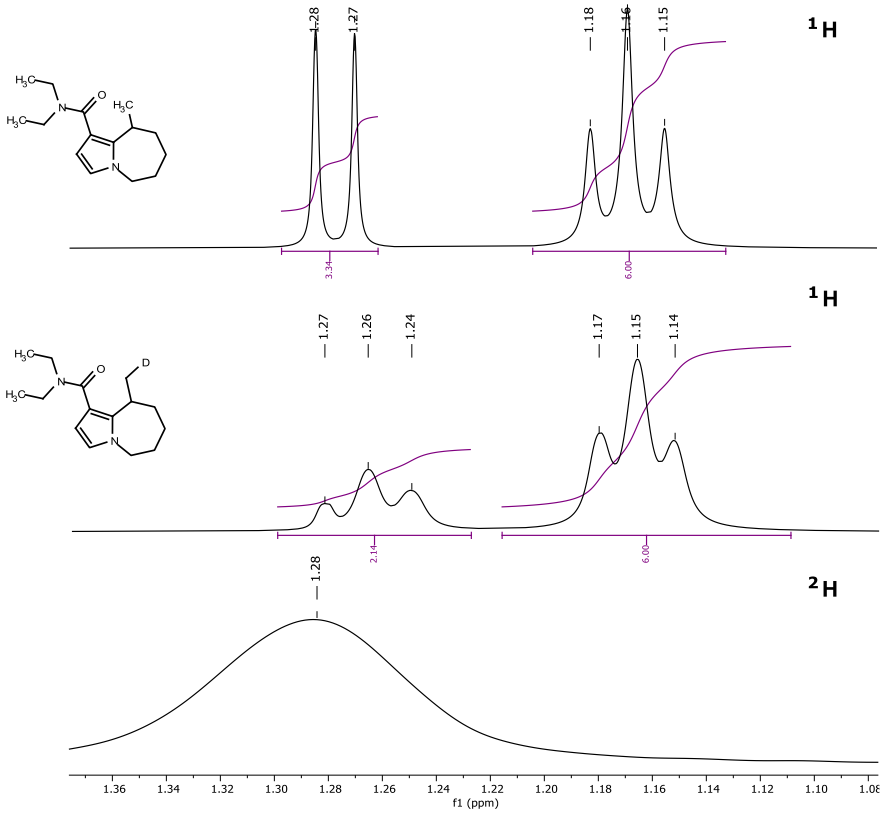


Prepared following general procedure for catalytic reactions (page 104), using ***d1*-1w**. Carried out at 100 ºC (reaction time: 2 h) under otherwise identical standard conditions. ^{1}**H NMR** (500 MHz, $CDCl_3$) δ 6.35 (s, 1H), 5.92 (d, *J* = 2.6 Hz, 1H), 4.01 – 3.89 (m, 2H), 3.46 (q, *J* = 7.1 Hz, 5H), 1.99 – 1.75 (m, 4H), 1.73 – 1.56 (m, 2H), 1.26 (t, *J* = 8.3 Hz, 2H), 1.15 (t, *J* = 7.2 Hz, 6H). **HRMS** [APCI]: *m/z* calculated for 250.2024, found 250.2021.

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***Scheme 212**: [1]H-NMR Spectra of **2w** and **d1-2w**, and [2]H-NMR Spectra **d1-2w**.*



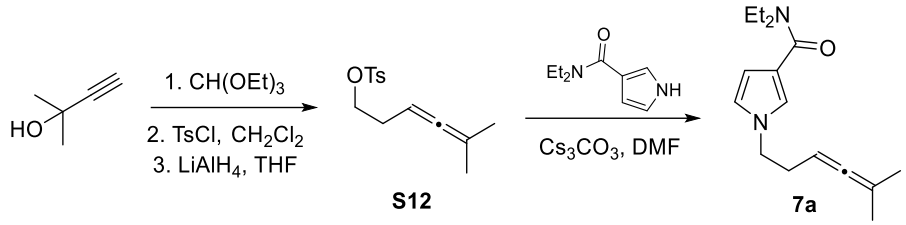
Scheme 213: *^{1}H-NMR Spectra of **2w** and **d1-2w**, and ^{2}H-NMR Spectra **d1-2w**.*

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7.2. Experimental data of section 5.2

Synthesis of precursors 7a-a[VI], 7b-n

*(exemplified for **7a**)*



A mixture of 2-Methyl-3-butyn-2-ol (5.0 mL, 59.0 mmol), triethylothoacetate (32.0 mL, 0.176 mol) and a few drops of propionic acid was heated to 140-150 ºC for 2 hours with continuous removal of ethanol by distillation. When the distillation ceased, the reaction was cooled to room temperature, and the reaction was poured into HCl (0.1 M, 250 mL). Then the mixture was extracted with Et_2O (3 x 100 mL), and the combined organic phases were dried with Na_2SO_4 and concentrated under vacuum. The crude oil was purified by flash chromatography (10:1 Hexanes/Et_2O) to afford ethyl 5-methylhexa-3,4-dienoate (6.70 g, 73%), as a colorless oil. The following data is in agreement with that reported in literature.[182] **^{1}H NMR** (300 MHz, $CDCl_3$) δ 5.05 (m, 1H), 4.11 (q, J = 7.2 Hz, 2H), 2.93 (d, J = 7.2 Hz, 2H), 2.93 (d, J = 2H), 1.64 (s, 6H), 1.23 (t, J = 7.5 Hz, 3H) ppm. **^{13}C NMR** (75< MHz, $CDCl_3$) δ 202.8 (C), 171.9 (CO), 96.2 (C), 81.9 (CH), 60.5 (CH_2), 35.2 (CH_2), 20.3 (CH_3), 14.1 (CH_3) ppm.

To a suspension of $LiAlH_4$ (0.295 g, 7.78 mmol) in Et_2O (73.0 mL), a solution of ethyl 5-methylhexa-3,4-dienoate (1.20 g, 7.78 mmol) was added at 0 ºC, and the mixture was allowed to stir at r.t. for 1h. Then, water slowly added at 0 ºC. The mixture was extracted with Et_2O (3 x 75 mL), and the combined organic phases were dried, concentrated and the crude residue was used without further purification in the next step (0.76 g, 87%). The following data is in agreement with that reported in literature.[183] **^{1}H NMR** (300 MHz, $CDCl_3$) δ 4.94 (m, 1H), 3.67 (t, *J* = 6.3 Hz, 2H), 2.20 (dt, *J* = 3.0, 6.3 Hz, 2H), 1.71 (br s, OH), 1.68 (d, 5 J = 2.9 Hz, 6 H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 202.7 (C), 95.8 (C), 85.2 (CH), 62.2 (CH_2), 32.6 (CH_2), 20.8 (CH_3) ppm.

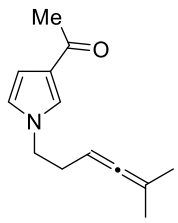
Tosyl chloride (1.30 g, 6.78 mmol), DMAP (124 mg, 1.02 mmol) and Et_3N (1.90 mL, 13.6 mmol) were added to a solution of 5-methylhexa-3,4-dien-1-ol (0.76 g, 6.78 mmol) in CH_2Cl_2 (34.0 mL). The resulting solution turned cloudy after 5-10 minutes and was allowed to stir at *rt* for 3 h. The reaction was quenched with H_2O (70 mL), the phases

[182] Procedure adapted from: B. M. Trost, A. B. Pinkerton, and M. Seidel, *J. Am. Chem. Soc.* **2001**, *123*, 50, 12466 -12476.
[183] Procedure adapted from: J. Naapuri, J. D. Rolfes, J. Keil, C. Manzana Sapu, and J. Deska, *Green Chem.* **2017**, *19*, 447-452.

were separated, and the organic phase was washed twice with NaCl (sat), dried and concentrated to yield a crude yellow residue that was purified by flash column chromatography to afford **5-methylhexa-3,4-dien-1-yl 4-methylbenzenesulfonate** (**S13**, 0.67 g, 37% yield), as a colorless oil.[184] **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.78 (d, *J* = 8.4 Hz, 2H), 7.33 (d, *J* = 8.0 Hz, 2H), 4.82 (dq, *J* = 6.6, 3.4 Hz, 1H), 4.12 – 3.97 (m, 2H), 2.44 (s, 3H), 2.27 (q, *J* = 6.6 Hz, 2H), 1.62 (d, *J* = 2.9 Hz, 6H) ppm. **^{13}C NMR** (75 MHz, $CDCl_3$) δ 202.78 (C), 144.77 (C), 133.40 (C), 129.90 (CH), 127.98 (CH), 96.60 (C), 83.44 (CH), 69.89 (CH_2), 28.94 (CH_2), 21.72 (CH_3), 20.55 (CH_3) ppm. **HRMS** [APCI]: *m/z* calculated for $C_{14}H_{19}SO_3$ $[M+H]^+$: 267.1049, found 267.1052.

5-methylhexa-3,4-dien-1-yl 4-methylbenzenesulfonate (**S13**, 600 mg, 2.25 mmol) was added to a solution of *N,N*-diethyl-1H-pyrrole-3-carboxamide (374 mg, 2.25 mmol) and Cs_2CO_3 (1.47 g, 4.51 mmol) in DMF (6.40 mL). The reaction mixture was stirred at 55 ºC for 16 h, allowed to cool to *rt* and water (20 mL) was added. The mixture was extracted with EtOAc (5 x 50 mL). The organic phase was dried, concentrated and the crude residue was purified by flash chromatography to yield ***N,N*-diethyl-1-(5-methylhexa-3,4-dien-1-yl)-1H-pyrrole-3-carboxamide** (**7a**) (407 mg, 69% yield) as a yellow oil. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.06 (t, *J* = 2.0 Hz, 1H), 6.57 (t, *J* = 2.6 Hz, 1H), 6.30 (dd, *J* = 2.8, 1.8 Hz, 1H), 4.95 – 4.84 (m, 1H), 3.89 (t, *J* = 7.1 Hz, 2H), 3.51 (q, *J* = 7.1 Hz, 4H), 2.38 (q, *J* = 6.9 Hz, 2H), 1.63 (d, *J* = 2.9 Hz, 6H), 1.20 (t, *J* = 7.1 Hz, 6H) ppm. **^{13}C NMR** (75 MHz, $CDCl_3$) δ 202.60 (C), 166.46 (CO), 123.97 (CH), 120.56 (CH), 119.36 (C), 108.77 (CH), 96.48 (C), 85.09 (CH), 49.57 (CH_2), 41.65 (CH_2 amide), 31.16 (CH_2), 20.62 (CH_3), 13.90 (CH_3 amide) ppm. **HRMS** [APCI]: *m/z* calculated for $C_{16}H_{25}N_2O$ $[M+H]^+$: 261.1961, found 261.1960. **NMR spectra at page 478.**

1-(1-(5-Methylhexa-3,4-dien-1-yl)-1H-pyrrol-3-yl)ethan-1-one (7a'')

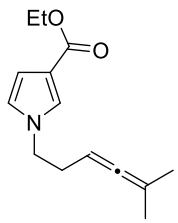


Synthesized by following the procedure used for **7a** but using 1-(1H-pyrrol-3-yl)ethan-1-one. Obtained in 81% yield, as a yellow oil. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.28 (t, *J* = 2.0 Hz, 1H), 6.61 (t, *J* = 2.5 Hz, 1H), 6.56 (dd, *J* = 2.9, 1.8 Hz, 1H), 4.90 (tp, *J* = 5.9, 2.7 Hz, 1H), 3.93 (t, *J* = 6.9 Hz, 2H), 2.47 – 2.35 (m, 5H), 1.62 (d, *J* = 2.9 Hz, 6H) ppm. **^{13}C NMR** (75 MHz, $CDCl_3$) δ 202.68 (C), 193.52 (CO), 125.98 (CH), 125.98 (C), 122.34 (CH), 109.32 (CH), 96.72 (C), 84.73 (CH), 49.72 (CH_2), 30.98 (CH_2), 27.15 (CH_3), 20.54 (CH_3) ppm (one quaternary carbon signal overlapped). **HRMS** [APCI]: *m/z* calculated for $C_{13}H_{18}NO$ $[M+H]^+$: 204.1383, found 204.1378.

USC

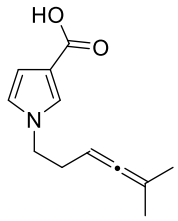
184 Procedure adapted from: A. Arribas, M. Calvelo, D. F. Fernández, C. A. B. Rodrigues, J. L. Mascareñas and F. López, *Angew. Chem. Int. Ed.* **2021**, *60*, 19297-19305.

Ethyl 1-(5-methylhexa-3,4-dien-1-yl)-1H-pyrrole-3-carboxylate (7a'")



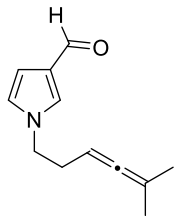
Synthesized by following the procedure used for **7a** but using ethyl 1H-pyrrole-3-carboxylate. Obtained in 47% yield, as yellow oil. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.25 (t, *J* = 2.0 Hz, 1H), 6.55 (t, *J* = 2.6 Hz, 1H), 6.52 (dd, *J* = 2.9, 1.7 Hz, 1H), 4.91 – 4.79 (m, 1H), 4.22 (q, *J* = 7.1 Hz, 2H), 3.87 (t, *J* = 6.9 Hz, 2H), 2.35 (q, *J* = 6.8 Hz, 2H), 1.59 (d, *J* = 2.9 Hz, 6H), 1.28 (t, *J* = 7.1 Hz, 3H) ppm. **^{13}C NMR** (75 MHz, $CDCl_3$) δ 202.49 (C), 164.81 (CO), 125.91 (CH), 121.48 (CH), 115.82 (C), 109.82 (CH), 96.37 (C), 84.72 (C), 59.37 (CH_2), 49.43 (CH_2), 30.83 (CH_2), 20.33 (CH_3), 14.44 (CH_3) ppm. **HRMS** [APCI]: *m/z* calculated for $C_{14}H_{20}NO_2$ $[M+H]^+$: 234.1489, found 234.1488.

1-(5-Methylhexa-3,4-dien-1-yl)-1H-pyrrole-3-carboxylic acid (7a^{IV})



Synthesized after hydrolysis with LiOH of compound **7a'"**. Obtained in 87% yield, as yellow oil. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 10.77 (br, 1H), 7.38 (s, 1H), 6.61 (d, *J* = 1.9 Hz, 2H), 4.90 (dt, *J* = 6.2, 3.2 Hz, 1H), 3.94 (t, *J* = 6.9 Hz, 2H), 2.41 (q, *J* = 6.7 Hz, 2H), 1.63 (d, *J* = 2.9 Hz, 6H) ppm. **^{13}C NMR** (75 MHz, $CDCl_3$) δ 202.60 (C), 170.69 (CO), 127.39 (CH), 121.99 (CH), 114.85 (C), 110.50 (CH), 96.55 (C), 84.70 (CH) , 49.59 (CH_2), 30.78 (CH_2), 20.38 (CH_3) ppm. **HRMS** [APCI]: *m/z* calculated for $C_{12}H_{16}NO_2$ $[M+H]^+$: 206.1176, found 206.1171.

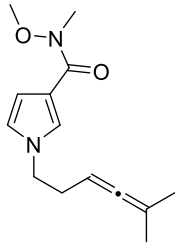
1-(5-Methylhexa-3,4-dien-1-yl)-1H-pyrrole-3-carbaldehyde (7a^{V})



Synthesized by following the procedure used for **7a** but using 1H-pyrrole-3-carboxaldehyde. Obtained in 43% yield, as yellow oil. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 9.70 (s, 1H), 7.28 (t, *J* = 1.9 Hz, 1H), 6.66 (t, *J* = 2.5 Hz, 1H), 6.59 (dd, *J* = 2.9, 1.6 Hz, 1H), 4.89 (tp, *J* = 5.9, 2.9 Hz, 1H), 3.95 (t, *J* = 6.9 Hz, 2H), 2.41 (q, *J* = 6.8 Hz, 2H), 1.59 (d, *J* = 2.9 Hz, 6H) ppm. **^{13}C NMR** (75 MHz, $CDCl_3$) δ 202.72 (C), 185.33 (CHO), 129.04 (CH), 126.54 (C), 123.36 (CH), 108.30 (CH), 96.76 (C), 84.61 (CH), 49.79 (CH_2), 30.84 (CH_2), 20.48 (CH_3) ppm. **HRMS** [APCI]: *m/z* calculated for $C_{12}H_{16}NO$ $[M+H]^+$: 190.1226, found 190.1221.

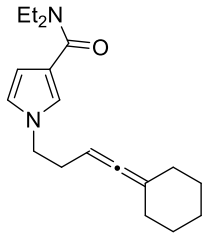
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***N*-methoxy-*N*-methyl-1-(5-methylhexa-3,4-dien-1-yl)-1H-pyrrole-3-carboxamide (7a^{v}')**



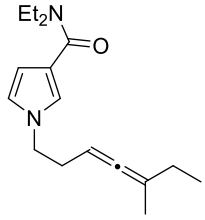
Synthesized from compound **7a'''** by treatment with *i*PrMgCl and NHMeOMe. Obtained in 68% yield, as yellow oil. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.29 (t, *J* = 2.0 Hz, 1H), 6.60 (dd, *J* = 2.9, 1.7 Hz, 1H), 6.55 (d, *J* = 2.4 Hz, 1H), 4.84 (tq, *J* = 6.0, 3.0 Hz, 1H), 3.87 (t, *J* = 7.0 Hz, 2H), 3.65 (s, 3H), 3.25 (s, 3H), 2.34 (q, *J* = 6.9 Hz, 2H), 1.57 (d, *J* = 2.9 Hz, 6H) ppm. **^{13}C NMR** (75 MHz, $CDCl_3$) δ 202.43 (C), 165.28 (CO), 126.03 (CH), 120.75 (CH), 116.50 (C), 110.79 (CH), 96.23 (C), 84.77 (CH), 60.67 (CH), 49.43 (CH_2), 33.01 (CH_3), 30.92 (CH_2), 20.37 (CH_3) ppm. **HRMS** [APCI]: *m/z* calculated for $[M+H]^+$: 234.1489, found 234.1490.

1-(4-Cyclohexylidenebut-3-en-1-yl)-*N,N*-diethyl-1H-pyrrole-3-carboxamide (7b)



Synthesized by following the procedure used for **7a**. Obtained in 69% yield, as yellow oil. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.07 (t, *J* = 2.1 Hz, 1H), 6.58 (t, *J* = 2.6 Hz, 1H), 6.30 (t, *J* = 2.3 Hz, 1H), 4.95 – 4.86 (m, 1H), 3.90 (t, *J* = 7.1 Hz, 2H), 3.52 (q, *J* = 7.1 Hz, 4H), 2.40 (q, *J* = 6.9 Hz, 2H), 2.11 – 1.96 (m, 4H), 1.62 – 1.42 (m, 6H), 1.21 (t, *J* = 7.1 Hz, 6H) ppm. **^{13}C NMR** (75 MHz, $CDCl_3$) δ 199.18 (C), 166.67 (CO), 123.97 (CH), 120.53 (CH), 119.30 (C), 108.71 (CH), 103.79 (C), 84.90 (CH), 49.57 (CH_2), 41.60 (CH_2 amide), 31.57 (CH_2), 31.30 (CH_2), 27.50 (CH_2), 26.17 (CH_2), 13.88 (CH_3 amide) ppm. **HRMS** [APCI]: *m/z* calculated for $C_{19}H_{29}N_2O$ $[M+H]^+$: 301.2274, found 301.2263.

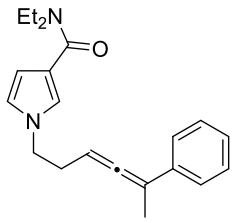
***N,N*-diethyl-1-(5-methylhepta-3,4-dien-1-yl)-1H-pyrrole-3-carboxamide (7c)**



Synthesized by following the procedure used for **7a**. Obtained in 99% yield, as yellow oil. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.07 (t, J = 2.0 Hz, 1H), 6.57 (t, J = 2.6 Hz, 1H), 6.31 (dd, J = 2.9, 1.8 Hz, 1H), 5.01 (dq, J = 6.3, 3.2 Hz, 1H), 3.90 (t, J = 7.2 Hz, 2H), 3.53 (q, J = 7.1 Hz, 4H), 2.42 (q, J = 6.9 Hz, 2H), 1.97 – 1.88 (m, 2H), 1.65 (d, J = 2.9 Hz, 3H), 1.21 (t, J = 7.1 Hz, 6H), 0.96 (t, J = 7.4 Hz, 3H) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$) δ 201.89 (C), 166.76 (CO), 123.91 (CH), 120.52 (CH), 119.65 (C), 108.88 (CH), 102.77 (C), 87.02 (CH), 49.76 (CH_2), 41.65 (CH_2), 31.35 (CH_2), 27.11 (CH_2), 19.03 (CH_3), 13.93 (CH_3), 12.37 (CH_3) ppm. **HRMS** [APCI]: *m/z* calculated for $C_{17}H_{27}N_2O$ $[M+H]^+$: 275.2118, found. 275.2123.

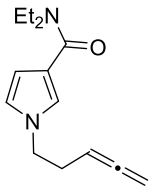
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***N,N*-diethyl-1-(5-phenylhexa-3,4-dien-1-yl)-1H-pyrrole-3-carboxamide (7d)**



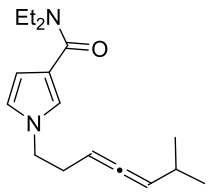
Synthesized by following the procedure used for **7a**. Obtained in 59% yield, as yellow oil. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.34 – 7.29 (m, 3H), 7.19 (dq, *J* = 7.8, 2.8 Hz, 1H), 7.09 (t, *J* = 2.0 Hz, 1H), 6.60 (t, *J* = 2.6 Hz, 1H), 6.33 (dd, *J* = 2.9, 1.8 Hz, 1H), 5.39 (tt, *J* = 6.3, 3.1 Hz, 1H), 3.98 (t, *J* = 7.0 Hz, 2H), 3.56 – 3.37 (m, 5H), 2.56 (q, *J* = 6.9 Hz, 2H), 2.04 (d, *J* = 2.9 Hz, 3H), 1.21 (t, *J* = 7.1 Hz, 6H) ppm. **^{13}C NMR** (75 MHz, $CDCl_3$) δ 204.86 (C), 166.58 (CO), 136.95 (C), 128.43 (CH), 126.83 (CH), 125.79 (CH), 123.78 (CH), 120.57 (CH), 119.49 (C), 109.06 (CH), 101.80 (C), 89.23 (CH), 49.41 (CH_2), 41.82 (CH_2 amide), 30.95 (CH_2), 17.09 (CH_3), 13.90 (CH_3 amide) ppm. **HRMS** [APCI]: *m/z* calculated for $C_{21}H_{27}N_2O$ $[M+H]^+$: 323.2118, found 323.2116.

***N,N*-Diethyl-1-(penta-3,4-dien-1-yl)-1H-pyrrole-3-carboxamide (7e)**



Synthesized by following the procedure used for **7a**. Obtained in 33% yield, as yellow oil. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.09 (t, *J* = 2.1 Hz, 1H), 6.59 (t, *J* = 2.7 Hz, 1H), 6.32 (t, *J* = 2.4 Hz, 1H), 5.06 (p, *J* = 6.8 Hz, 1H), 4.71 (dt, *J* = 6.5, 3.1 Hz, 2H), 3.94 (t, *J* = 7.2 Hz, 2H), 3.53 (q, *J* = 7.1 Hz, 4H), 2.44 (ddt, *J* = 10.2, 7.0, 3.6 Hz, 2H), 1.22 (t, *J* = 7.1 Hz, 6H) ppm. **^{13}C NMR** (75 MHz, $CDCl_3$) δ 208.86 (C), 166.48 (CO), 123.52 (CH), 120.41 (CH), 119.33 (C), 108.78 (CH), 86.17 (CH), 75.70 (CH_2), 49.09 (CH_2), 41.43 (CH_2 amide), 30.07 (CH_2), 13.71 (CH_3 amide) ppm. **HRMS** [APCI]: *m/z* calculated for $C_{14}H_{21}N_2O$ $[M+H]^+$: 233.1648, found 233.1647.

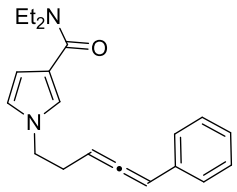
***N,N*-Diethyl-1-(6-methylhepta-3,4-dien-1-yl)-1H-pyrrole-3-carboxamide (7f)**



Synthesized by following the procedure used for **7a**. Obtained in 54% yield, as yellow oil. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.06 (t, *J* = 2.0 Hz, 1H), 6.57 (t, *J* = 2.6 Hz, 1H), 6.30 (dd, *J* = 2.9, 1.7 Hz, 1H), 5.12 (m, 2H), 3.91 (t, *J* = 7.3 Hz, 2H), 3.52 (q, *J* = 7.1 Hz, 4H), 2.43 (m, 2H), 2.25 (m, 1H), 1.21 (t, *J* = 7.1 Hz, 6H), 0.97 (d, *J* = 6.8 Hz, 6H) ppm. **^{13}C NMR** (75 MHz, $CDCl_3$) δ 203.06 (C), 166.64 (CO), 123.84 (CH), 120.51 (CH), 108.86 (CH), 99.79 (CH), 88.33 (CH), 49.52 (CH_2), 41.56 (CH_2 amide), 31.04 (CH_2), 27.92 (CH), 22.55 (CH_3), 13.89 (CH_3 amide) ppm. **HRMS** [APCI]: *m/z* calculated for $C_{17}H_{27}N_2O$ $[M+H]^+$: 275.2118, found 275.2121. **NMR spectra at page 479.**

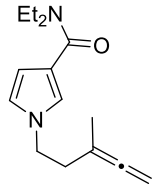
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***N,N*-Diethyl-1-(5-phenylpenta-3,4-dien-1-yl)-1H-pyrrole-3-carboxamide (7g)**



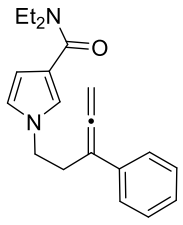
Synthesized by following the procedure used for **7a**. Obtained in 75% yield, as yellow oil. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.24 – 7.07 (m, 5H), 7.00 (s, 1H), 6.51 (s, 1H), 6.26 (s, 1H), 6.09 (dt, *J* = 6.1, 2.9 Hz, 1H), 5.44 (q, *J* = 6.7 Hz, 1H), 3.92 (t, *J* = 7.1 Hz, 2H), 3.45 (t, *J* = 7.1 Hz, 4H), 2.51 (m, 2H), 1.13 (t, *J* = 7.1 Hz, 6H) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$) δ 205.93 (C), 166.62 (CO), 134.29 (C), 128.75 (CH), 127.20 (CH), 126.92 (CH), 123.66 (CH), 120.58 (CH), 119.88 (C), 109.23 (C), 95.88 (CH), 91.21 (CH), 49.34 (CH_2), 41.65 (CH_2), 30.73 (CH_2), 13.90 (CH_3) ppm. **HRMS** [APCI]: *m/z* calculated for $C_{20}H_{25}N_2O$ $[M+H]^+$: 309.1961, found 309.1962.

***N,N*-Diethyl-1-(3-methylpenta-3,4-dien-1-yl)-1H-pyrrole-3-carboxamide (7h)**



Synthesized by following the procedure used for **7a**. Obtained in 53% yield, as yellow oil. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.05 (d, *J* = 1.9 Hz, 1H), 6.56 (t, *J* = 3.0 Hz, 1H), 6.34 – 6.25 (m, 1H), 4.62 (m, 2H), 3.97 – 3.89 (m, 2H), 3.51 (q, *J* = 7.1 Hz, 4H), 2.35 (tt, *J* = 7.1, 3.2 Hz, 2H), 1.67 (s, 3H), 1.27 – 1.14 (m, 6H) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$) δ ^{13}C NMR (75 MHz, $CDCl_3$) δ 206.14 (C), 166.63 (CO), 123.74 (CH), 120.49 (CH), 119.35 (C), 108.81 (CH), 95.26 (C), 75.51 (CH_2), 47.97 (CH_2), 41.85 (CH_2 amide), 35.05 (CH_2), 18.94 (CH_3), 13.83 (CH_3 amide) ppm. **HRMS** [APCI]: *m/z* calculated for $C_{15}H_{23}N_2O$ $[M+H]^+$: 247.1805, found 247.1805. **NMR spectra at page 480.**

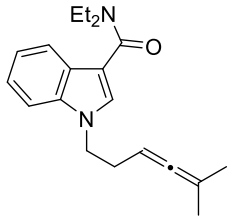
***N,N*-Diethyl-1-(3-phenylpenta-3,4-dien-1-yl)-1H-pyrrole-3-carboxamide (7i)**



Synthesized by following the procedure used for **7a**. Obtained in 69% yield, as yellow oil. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.32 – 7.21 (m, 4H), 7.19 – 7.12 (m, 1H), 7.00 (t, *J* = 2.0 Hz, 1H), 6.52 (t, *J* = 2.6 Hz, 1H), 6.26 (dd, *J* = 2.9, 1.8 Hz, 1H), 5.02 (t, *J* = 3.2 Hz, 2H), 4.02 – 3.97 (m, 2H), 3.45 (q, *J* = 7.1 Hz, 4H), 2.83 – 2.78 (m, 2H), 1.14 (t, *J* = 7.1 Hz, 6H) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$) δ 208.41 (C), 166.67 (CO), 135.33 (C), 128.75 (CH), 127.20 (CH), 125.94 (CH), 123.81 (CH), 120.61 (CH), 119.57 (C), 108.97 (CH), 101.74 (C), 79.26 (CH_2), 48.30 (CH_2), 40.62 (CH_2 amide) 31.75 (CH_2), 13.13 (CH_3 amide) ppm. **HRMS** [APCI]: *m/z* calculated for $C_{20}H_{25}N_2O$ $[M+H]^+$: 309.1961, found 309.1973.

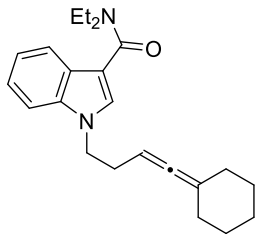
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N,N-Diethyl-1-(5-methylhexa-3,4-dien-1-yl)-1H-indole-3-carboxamide (7j)



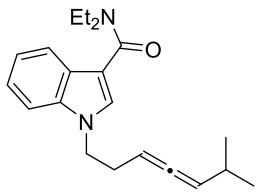
Synthesized by following the procedure used for **7a**. Obtained in 76% yield, as yellow oil. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.80 – 7.73 (m, 1H), 7.39 – 7.30 (m, 2H), 7.27 – 7.12 (m, 2H), 4.95 (tt, *J* = 6.4, 3.1 Hz, 1H), 4.18 (t, *J* = 7.1 Hz, 2H), 3.58 (q, *J* = 7.1 Hz, 4H), 2.49 (q, *J* = 6.9 Hz, 2H), 1.60 (s, 3H), 1.59 (s, 3H), 1.22 (t, *J* = 7.1 Hz, 6H) ppm. **^{13}C NMR** (75 MHz, $CDCl_3$) δ 202.62 (C), 167.00 (CO), 135.93 (C), 128.55 (CH), 127.02 (C), 122.32 (CH), 121.11 (CH), 120.67 (CH), 111.43 (C), 109.81 (CH), 96.63 (C), 85.17 (CH), 46.30 (CH_2), 41.38 (CH_2 amide), 29.92 (CH_2), 20.59 (2x CH_3), 14.04 (CH_3 amide) ppm. **HRMS** [APCI]: *m/z* calculated for $C_{20}H_{27}N_2O$ $[M+H]^+$: 311.2118, found 311.2117.

1-(4-Cyclohexylidenebut-3-en-1-yl)-*N,N*-diethyl-1H-indole-3-carboxamide (7k)



Synthesized by following the procedure used for **7a**. Obtained in 61% yield, as yellow oil. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.76 (d, *J* = 7.1 Hz, 1H), 7.38 – 7.32 (m, 2H), 7.23 (t, *J* = 7.9 Hz, 0H), 7.17 (t, *J* = 7.2 Hz, 1H), 5.01 – 4.89 (m, 1H), 4.18 (t, *J* = 7.2 Hz, 2H), 3.57 (q, *J* = 7.1 Hz, 4H), 2.50 (q, *J* = 7.0 Hz, 2H), 2.10 – 1.90 (m, 4H), 1.62 – 1.42 (m, 6H), 1.22 (t, *J* = 7.1 Hz, 6H) ppm. **^{13}C NMR** (75 MHz, $CDCl_3$) δ 199.21 (C), 166.98 (CO), 135.88 (C), 128.59 (CH), 127.01 (C), 122.29 (CH), 121.09 (CH), 120.65 (CH), 111.30 (C), 109.79 (CH), 103.96 (C), 84.97 (CH), 46.34 (CH_2), 41.37 (CH_2 amide), 31.57 (CH_2), 29.94 (CH_2), 27.47 (CH_2), 26.15 (CH_2), 14.00 (CH_3 amide) ppm. **HRMS** [APCI]: *m/z* calculated for $C_{23}H_{31}N_2O$ $[M+H]^+$: 351.2431, found 351.2431.

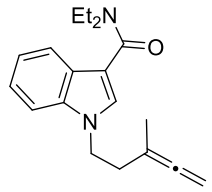
N,N-Diethyl-1-(6-methylhepta-3,4-dien-1-yl)-1H-indole-3-carboxamide (7l)



Synthesized by following the procedure used for **7a**. Obtained in 51% yield, as yellow oil. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.86 – 7.76 (m, 1H), 7.36 (d, *J* = 9.1 Hz, 2H), 7.22 (m, 2H), 5.22 – 5.10 (m, 2H), 4.21 (t, *J* = 7.3 Hz, 2H), 3.59 (q, *J* = 7.1 Hz, 4H), 2.60 – 2.47 (m, 2H), 2.27 (m, 1H), 1.24 (t, *J* = 7.1 Hz, 6H), 0.99 (dd, *J* = 6.8, 1.3 Hz, 6H) ppm. **^{13}C NMR** (75 MHz, $CDCl_3$) δ 203.05 (C), 166.82 (C), 135.75 (C), 128.35 (CH), 127.00 (C), 122.30 (CH), 121.07 (CH), 120.62 (CH), 111.36 (C), 109.64 (CH), 99.79 (CH), 88.36 (CH), 46.22 (CH_2), 41.32 (CH_2 amide), 29.65 (CH_2), 27.82 (CH), 22.48 (CH_3), 13.94 (CH_3) ppm. **HRMS** [APCI]: *m/z* calculated for $C_{21}H_{29}N_2O$ $[M+H]^+$: 325.2274, found 325.2272.

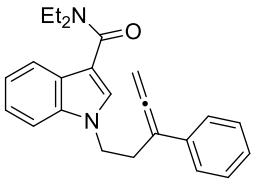
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N,N-Diethyl-1-(3-methylpenta-3,4-dien-1-yl)-1H-indole-3-carboxamide (7m)



Synthesized by following the procedure used for **7a**. Obtained in 46% yield, as yellow oil. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.79 (d, *J* = 7.7 Hz, 1H), 7.33 (d+s, *J* = 6.9 Hz, 2H), 7.23 (t, *J* = 7.3 Hz, 1H), 7.17 (t, *J* = 7.1 Hz, 1H), 4.64 (q, *J* = 3.2 Hz, 2H), 4.22 (t, *J* = 7.3 Hz, 2H), 3.57 (q, *J* = 7.1 Hz, 4H), 2.50 – 2.39 (m, 2H), 1.70 (t, *J* = 3.2 Hz, 3H), 1.22 (t, *J* = 7.1 Hz, 6H) ppm. **^{13}C NMR** (75 MHz, $CDCl_3$) δ 206.17 (C), 166.84 (CO), 135.71 (C), 128.35 (CH), 126.98 (C), 122.27 (CH), 121.06 (CH), 120.61 (CH), 111.23 (C), 109.56 (CH), 95.32 (C), 75.54 (CH_2), 44.71 (CH_2), 41.32 (CH_2 amide), 33.55 (CH_2), 18.97 (CH_3), 13.93 (CH_3) ppm. **HRMS** [APCI]: *m/z* calculated for $C_{19}H_{25}N_2O$ $[M+H]^+$: 297.1961, found 297.1963.

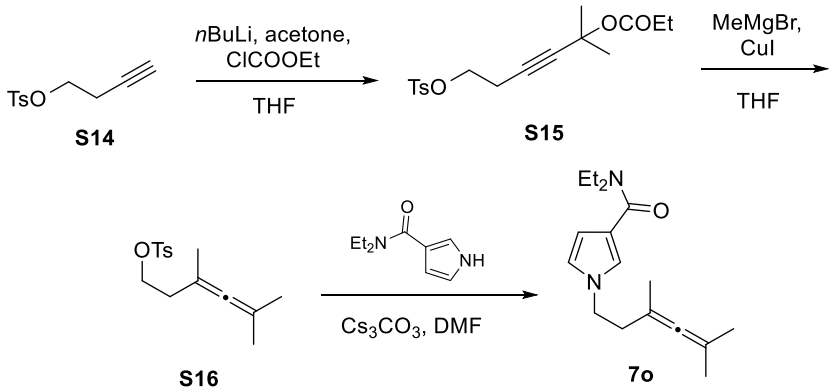
N,N-Diethyl-1-(3-phenylpenta-3,4-dien-1-yl)-1H-indole-3-carboxamide (7n)



Synthesized by following the procedure used for **7a**. Obtained in 56% yield, as yellow oil. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.74 (dd, *J* = 7.9, 0.9 Hz, 1H), 7.36 – 7.25 (m, 6H), 7.19 (td, *J* = 6.9, 1.3 Hz, 2H), 7.13 (m, 1H), 4.99 (t, *J* = 3.1 Hz, 2H), 4.34 – 4.22 (m, 2H), 3.50 (q, *J* = 7.1 Hz, 4H), 2.95 – 2.83 (m, 2H), 1.15 (t, *J* = 7.1 Hz, 6H) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$) δ 208.46 (C), 166.85 (CO), 135.79 (C), 135.24 (C), 128.77 (CH), 128.49 (CH), 127.24 (CH), 127.07 (C), 125.92 (CH), 122.44 (CH), 121.18 (CH), 120.75 (CH), 111.50 (C), 109.66 (CH), 101.79 (C), 79.22 (CH_2), 45.15 (CH_2), 40.84 (CH_2 amide), 30.26 (CH_3), 15.39 (CH_3 amide), 14.02 (CH_3 amide) ppm. **HRMS** [APCI]: *m/z* calculated for $C_{24}H_{27}N_2O$ $[M+H]^+$: 359.2118, found 359.2127. **NMR spectra at page 481.**

Synthesis of precursors 7o-t

*(exemplified for **7o**)*



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But-3-yn-1-yl 4-methylbenzenesulfonate (**S14**, prepared following previously reported procedures,[185] 3.00 g, 13.4 mmol) was dissolved in THF (90 mL) and cooled to -78 ºC, then *n*BuLi was added (5.60 mL, 2.5 M in THF). After 10 minutes, acetone was added (1.50 mL, 20.1 mmol) and the reaction was gradually warmed to *rt.* The reaction was followed by TLC so, when all the starting material was consumed, ethylchloroformate (2.60 mL, 26.7 mmol) was added. After 1-2h, the reaction was quenched with H_2O (70 mL), and the reaction was extracted with Et_2O (3 x 75 mL) and the combined organic phases were washed with NaCl (sat.), dried and concentrated to yield a crude yellow residue that was purified by flash column chromatography (from 9:1 to 8:2 hexanes/EtOAc) to afford **5-((ethoxycarbonyl)oxy)-5-methylhex-3-yn-1-yl 4-methylbenzenesulfonate** (**S15**, 2.51 g, 53% yield), as yellow oil.

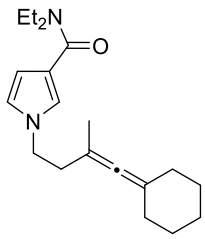
CuI (1.61 g, 8.47 mmol) was suspended in anhydrous THF (56.0 mL) and cooled to 0 ºC, then MeMgBr (5.60 mL, 3 M in THF) was added. After 10 minutes, **5-((ethoxycarbonyl)oxy)-5-methylhex-3-yn-1-yl 4-methylbenzenesulfonate** (**S15**, 2.00 g, 5.64 mmol) dissolved in 5.60 mL of THF were added to the mixture. When TLC indicates that the reaction is finished (typically after 20 minutes), 40 mL of a saturated solution of NH_4Cl were added. The mixture was extracted with Et_2O (3 x 75 mL), and the combined organic phases were washed with NaCl (sat.), dried and concentrated to yield a crude yellow residue that was purified by flash column chromatography (from 19:1 to 9:1 hexanes/EtOAc) to afford **3,5-dimethylhexa-3,4-dien-1-yl 4-methylbenzenesulfonate** (**S16**, 687 mg, 43%), as yellow oil.[186] **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.07 (d, *J* = 8.0 Hz, 2H), 7.62 (d, *J* = 7.9 Hz, 2H), 4.37 (t, *J* = 6.9 Hz, 2H), 2.73 (s, 3H), 2.51 (t, *J* = 6.9 Hz, 2H), 1.89 (s, 6H), 1.87 (s, 3H) ppm. **^{13}C NMR** (75 MHz, $CDCl_3$) δ 199.10 (C), 144.69 (C), 129.83 (CH), 127.91 (CH), 95.95 (C), 92.19 (C), 68.99 (CH_2), 33.47 (CH_2), 30.38 (CH_3), 20.79 (CH_3), 19.61 (CH_3) ppm.

3,5-dimethylhexa-3,4-dien-1-yl 4-methylbenzenesulfonate (**S16,** 412 mg, 1.47 mmol) was added to a solution of *N,N*-diethyl-1H-pyrrole-3-carboxamide (269 mg, 1.61 mmol) and Cs_2CO_3 (0.96 g, 2.94 mmol) in DMF (4.20 mL). The reaction mixture was stirred at 55 ºC for 16 h, allowed to cool to *rt* and water (20 mL) was added. The mixture was extracted with EtOAc (5 x 50 mL). The organic phase was dried, concentrated and the crude residue was purified by flash chromatography to give **1-(3,5-dimethylhexa-3,4-dien-1-yl)-*N,N*-diethyl-1H-pyrrole-3-carboxamide** (**7o**, 292 mg, 72% yield) as yellow oil. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.02 (t, *J* = 2.0 Hz, 1H), 6.53 (t, *J* = 2.6 Hz, 1H), 6.26 (dd, *J* = 2.8, 1.8 Hz, 1H), 3.88 (t, *J* = 7.2 Hz, 2H), 3.50 (q, *J* = 7.1 Hz, 4H), 2.32 (t, *J* = 7.2

[185] X.-F. Ren, E. Turos, C.H. Lake, and M.R. Churchill, *J. Org. Chem.* **1995**, *60*, 6468-6483.
[186] Procedure adapted from: C.-H. Ting, Y.-L. Hsu, and R.-S. Liu, *Chem. Commun.* **2012**, *48*, 6577-6579.

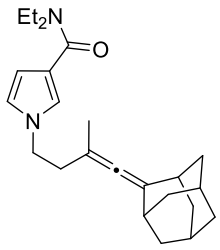
Hz, 2H), 1.61 (s, 3H), 1.59 (s, 6H), 1.18 (t, *J* = 7.1 Hz, 6H) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$) δ 199.28 (C), 166.66 (CO), 123.76 (CH), 120.40 (CH), 119.37 (C), 108.65 (CH), 95.67 (C), 93.68 (C), 48.29 (CH_2), 41.52 (CH_2 amide), 35.85 (CH_2), 20.72 (CH_3), 19.51 (CH_3), 13.80 (CH_3 amide) ppm. **HRMS** [APCI]: *m/z* calculated for $C_{17}H_{27}N_2O$ $[M+H]^+$: 275.2118, found 275.2126. **NMR spectra at page 482.**

1-(4-Cyclohexylidene-3-methylbut-3-en-1-yl)-*N,N*-diethyl-1H-pyrrole-3-carboxamide (7p)



Synthesized by following the procedure used for **7o**, using cyclohexanone instead of acetone. Obtained in 46% yield as yellow oil. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.07 (t, *J* = 2.0 Hz, 1H), 6.57 (t, *J* = 2.6 Hz, 1H), 6.29 (dd, *J* = 2.8, 1.8 Hz, 1H), 3.91 (t, *J* = 7.3 Hz, 2H), 3.52 (q, *J* = 7.1 Hz, 4H), 2.35 (t, *J* = 7.3 Hz, 2H), 2.08 – 1.94 (m, 4H), 1.66 (s, 3H), 1.60 – 1.43 (m, 6H), 1.21 (t, *J* = 7.1 Hz, 6H) ppm. **^{13}C NMR** (75 MHz, $CDCl_3$) δ 195.52 (C), 166.60 (CO), 123.89 (CH), 120.38 (CH), 119.11 (C), 108.52 (CH), 103.31 (C), 93.35 (C), 48.30 (CH_2), 41.51 (CH_2 amide), 35.85 (CH_2), 31.86 (CH_2), 27.76 (CH_2), 26.20 (CH_2), 19.92 (CH_3), 13.80 (CH_3 amide) ppm. **HRMS** [APCI]: *m/z* calculated for $C_{20}H_{31}N_2O$ $[M+H]^+$: 315.2431, found 315.2427.

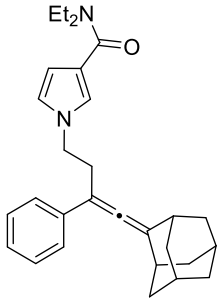
1-(4-((1R,5S)-adamantan-2-ylidene)-3-methylbut-3-en-1-yl)-*N,N*-diethyl-1H-pyrrole-3-carboxamide (7q)



Synthesized by following the procedure used for **7o**, using adamantanone instead of acetone. Obtained in 32% yield as yellow oil. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.08 (q, *J* = 1.7 Hz, 1H), 6.58 (q, *J* = 1.9 Hz, 1H), 6.29 (dt, *J* = 2.9, 1.4 Hz, 1H), 3.93 (t, *J* = 7.5 Hz, 2H), 3.52 (q, *J* = 7.0 Hz, 4H), 2.46 – 2.28 (m, 4H), 2.00 – 1.90 (m, 2H), 1.90 – 1.74 (m, 10H), 1.68 (s, 3H), 1.21 (t, *J* = 7.3 Hz, 6H) ppm. **^{13}C NMR** (75 MHz, $CDCl_3$) δ 191.41 (C), 166.70 (CO), 124.04 (CH), 120.47 (CH), 119.28 (C), 111.08 (C), 108.67 (CH), 94.28 (C), 48.56 (CH_2), 41.55 (CH_2 amide), 39.31 (CH_2), 39.02 (CH_2), 37.24 (CH_2), 36.18 (CH_2), 35.41 (CH_3), 28.28 (CH), 28.25 (CH), 20.50 (CH), 13.90 (CH_3 amide) ppm. **HRMS** [APCI]: *m/z* calculated for $C_{24}H_{35}N_2O$ $[M+H]^+$: 367.2744, found 367.2743. **NMR spectra at page 483.**

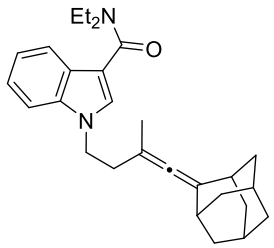
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1-(4-((1r,3r,5r,7r)-adamantan-2-ylidene)-3-phenylbut-3-en-1-yl)-*N,N*-diethyl-1H-pyrrole-3-carboxamide (7r)



Synthesized by following the procedure used for **7o**, using adamantanone instead of acetone, and PhMgBr instead of MeMgBr. Obtained in 29% yield as yellow oil. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.43 – 7.26 (m, 4H), 7.22 – 7.14 (m, 1H), 7.10 (d, *J* = 2.0 Hz, 1H), 6.60 (t, *J* = 2.6 Hz, 1H), 6.32 (dd, *J* = 2.8, 1.6 Hz, 1H), 4.07 (t, *J* = 7.5 Hz, 2H), 3.53 (q, *J* = 7.1 Hz, 4H), 2.88 (t, *J* = 7.5 Hz, 2H), 2.55 (s, 2H), 2.16 – 1.70 (m, 15H), 1.21 (t, *J* = 7.1 Hz, 6H) ppm. **^{13}C NMR** (75 MHz, $CDCl_3$) δ 194.04 (C), 166.63 (CO), 137.63 (C), 128.59 (CH), 126.51 (CH), 125.69 (CH), 124.03 (CH), 120.55 (CH), 119.41 (C), 114.60 (C), 108.85 (CH), 100.52 (C), 48.77 (CH_2), 41.58 (CH_2 amide), 39.29 (CH_2), 39.08 (CH_2), 37.04 (CH_2), 35.02 (CH), 32.39 (CH_2), 28.16 (CH), 28.11 (CH), 13.88 (CH_3 amide) ppm. **HRMS** [APCI]: *m/z* calculated for $C_{29}H_{37}N_2O$ $[M+H]^+$: 429.2900, found 429.2903.

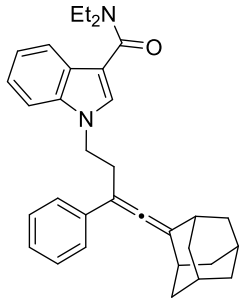
1-(4-((1R,5S)-adamantan-2-ylidene)-3-methylbut-3-en-1-yl)-*N,N*-diethyl-1H-indole-3-carboxamide (7s)



Synthesized by following the procedure used for **7o**, using adamantanone instead of acetone, and *N,N*-diethyl-1H-indole-3-carboxamide instead of *N,N*-diethyl-1H-pyrrole-3-carboxamide. Obtained in 41% yield as yellow oil. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.77 (d, *J* = 8.0 Hz, 1H), 7.37 (s, 1H), 7.33 (d, *J* = 7.7 Hz, 1H), 7.22 (t, *J* = 7.5 Hz, 1H), 7.19 – 7.12 (m, 1H), 4.20 (t, *J* = 7.5 Hz, 2H), 3.57 (q, *J* = 7.1 Hz, 4H), 2.46 (t, *J* = 7.5 Hz, 2H), 2.36 (t, *J* = 3.1 Hz, 2H), 1.96 – 1.69 (m, 15H), 1.22 (t, *J* = 7.1 Hz, 6H) ppm. **^{13}C NMR** (75 MHz, $CDCl_3$) δ 191.33 (C), 166.87 (CO), 135.74 (C), 128.40 (CH), 126.91 (C), 122.15 (CH), 120.98 (CH), 120.51 (CH), 111.14 (C), 111.08 (C), 109.56 (CH), 94.21 (CH), 45.21 (CH_2), 41.23 (CH_2 amide), 39.11 (CH_2), 38.87 (CH_2), 37.07 (CH_2), 35.31 (CH), 34.41 (CH_2), 28.10 (CH), 20.42 (CH_3), 13.89 (CH_3 amide) ppm. **HRMS** [APCI]: *m/z* calculated for $C_{28}H_{37}N_2O$ $[M+H]^+$: 417.2900, found 417.2908.

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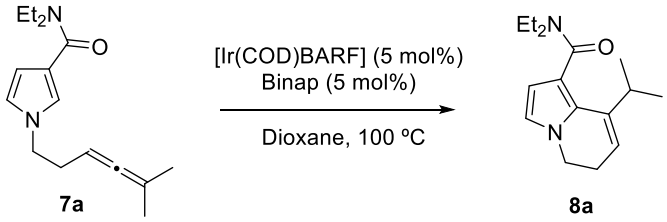
1-(4-((1r,3r,5r,7r)-adamantan-2-ylidene)-3-phenylbut-3-en-1-yl)-*N,N*-diethyl-1H-indole-3-carboxamide (7t)



Synthesized by following the procedure used for **7o**, using adamantanone instead of acetone, and PhMgBr instead of MeMgBr, and *N,N*-diethyl-1H-indole-3-carboxamide instead of *N,N*-diethyl-1H-pyrrole-3-carboxamide. Obtained in 35% yield as yellow oil. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.75 (d, *J* = 7.4 Hz, 1H), 7.37 – 7.07 (m, 9H), 4.29 (t, *J* = 7.4 Hz, 2H), 3.51 (q, *J* = 7.1 Hz, 4H), 2.92 (t, *J* = 7.4 Hz, 2H), 2.41 (t, *J* = 3.2 Hz, 2H), 1.96 – 1.62 (m, 12H), 1.15 (t, *J* = 7.1 Hz, 6H) 194.13 (C), 166.85 (CO), 137.49 (C), 135.79 (C), 128.61 (CH), 127.14 (C), 126.54 (CH), 125.66 (CH), 122.36 (CH), 121.21 (CH), 120.70 (CH), 114.64 (C), 111.22 (C), 109.65 (CH), 100.43 (C), 45.59 (CH_2), 41.32 (CH_2 amide), 39.25 (CH_2), 38.93 (CH_2), 36.96 (CH_2), 34.97 (CH), 30.74 (CH_2), 28.10 (CH), 28.02 (CH), 13.97 (CH_3 amide) (one aromatic CH signal is overlapped) ppm. **^{13}C NMR** (75 MHz, $CDCl_3$) δ ppm. **HRMS** [APCI]: *m/z* calculated for C33H39N2O $[M+H]^+$: 479.3057, found 479.3064.

Synthesis of compounds 8 by hydroarylation of precursors 7

*(exemplified for **8a**)*

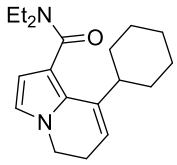


Prepared following general procedure for catalytic reactions (page 104), using ***7a***. $[Ir(COD)_2]$BARF (6.40 mg, 0.005 mmol), Binap (2.50 mg, 0.005 mmol), **7a** (26.0 mg, 0.10 mmol) and dioxane (0.80 mL) were sequentially added to a sealed tube under Argon atmosphere and stirred at 100 ºC for 16 h. The mixture was concentrated, and the crude residue was purified by flash chromatography (1:3 to 3:1 EtOAc/Hexanes). ***N,N*-diethyl-8-isopropyl-5,6-dihydroindolizine-1-carboxamide** (**8a**) obtained in 82% yield, as yellow oil. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 6.52 (d, *J* = 2.8 Hz, 1H), 6.05 (d, *J* = 2.7 Hz, 1H), 5.58 (t, *J* = 4.8 Hz, 1H), 3.83 (t, *J* = 7.1 Hz, 2H), 3.59 – 3.43 (m, 2H), 3.43 – 3.22 (m, 2H), 2.94 – 2.82 (m, 1H), 2.46 – 2.35 (m, 2H), 1.26 – 1.00 (m, 12H) ppm. **^{13}C NMR** (75 MHz, $CDCl_3$) δ 169.13 (CO), 139.71 (C), 120.06 (CH), 115.34 (C), 113.89 (CH), 106.88 (CH), 44.43 (CH_2), 41.69 (CH_2 amide), 37.48 (CH_2 amide), 30.61 (CH), 24.85 (CH_2), 22.57 (CH_3), 14.21 (CH_3 amide), 11.99 (CH_3 amide) ppm (1 quat. C signal missed or

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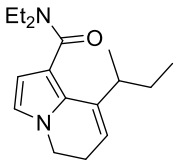
overlapped). **HRMS** [APCI]: *m/z* calculated for $C_{16}H_{25}N_2O$ $[M+H]^+$: 261.1961, found 261.1966. **NMR spectra at page 488.**

8-Cyclohexyl-*N,N*-diethyl-5,6-dihydroindolizine-1-carboxamide (8b)



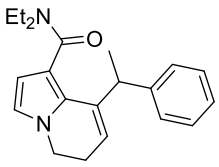
Prepared following general procedure for catalytic reactions (page 104), using ***7b*** and *rac*-Binap (5 mol%) as ligand. Obtained in 99% yield as yellow oil. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 6.50 (d, *J* = 2.7 Hz, 1H), 6.03 (d, *J* = 2.7 Hz, 1H), 5.55 (t, *J* = 4.8 Hz, 1H), 3.81 (t, *J* = 7.0 Hz, 2H), 3.53 (q, *J* = 7.0 Hz, 2H), 3.33 (q, *J* = 7.2 Hz, 2H), 2.45 – 2.35 (m, 3H), 1.91 – 1.78 (m, 2H), 1.78 – 1.62 (m, 3H), 1.33 – 1.01 (m, 11H) ppm. **^{13}C NMR** (75 MHz, $CDCl_3$) δ 169.30 (CO), 139.13 (C), 127.25 (C), 120.16 (CH), 115.46 (C), 114.50 (CH), 107.09 (CH), 44.15 (CH_2), 43.34 (CH_2 amide), 39.11 (CH_2 amide), 38.55 (CH), 33.56 (CH_2), 26.91 (CH_2), 26.57 (CH_2), 24.30 (CH_2), 14.13 (CH_3 amide), 13.23 (CH_3 amide) ppm. **HRMS** [APCI]: *m/z* calculated for $C_{19}H_{29}N_2O$ $[M+H]^+$: 301.2274, found 301.2280.

8-(sec-butyl)-*N,N*-diethyl-5,6-dihydroindolizine-1-carboxamide (8c)



Prepared following general procedure for catalytic reactions (page 104), using ***7c*** and *rac*-Binap (5 mol%) as ligand. Obtained in 99% yield as yellow oil. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 6.43 (d, J = 2.7 Hz, 1H), 5.97 (d, J = 2.7 Hz, 1H), 5.48 (m, 1H), 3.83 – 3.70 (m, 2H), 3.44 (s, 2H), 3.25 (s, 2H), 2.56 (m, J = 7.8, 6.7, 5.7, 1.1 Hz, 1H), 2.43 – 2.28 (m, 2H), 1.53 – 1.46 (m, 1H), 1.25 (dt, J = 13.4, 7.4 Hz, 1H), 1.13 (br, 3H), 0.99 (br, 3H), 0.98 (d, 3H), 0.77 (t, J = 7.4 Hz, 3H) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$) δ 13C NMR (126 MHz, $CDCl_3$) δ 169.36 (CO), 139.01 (C), 127.60 (C), 120.25 (CH), 115.86 (C), 114.52 (CH), 107.20 (CH), 44.27 (CH_2), 43.35 (CH_2 amide), 38.98 (CH_2 amide), 34.93 (CH), 29.60 (CH_3), 24.40 (CH_2), 19.91 (CH_2), 14.21 (CH_3), 12.71 (CH_3 amide), 11.67 (CH_3) ppm. **HRMS** [APCI]: *m/z* calculated for $C_{17}H_{27}N_2O$ $[M+H]^+$: 275.2118, found 275.2125.

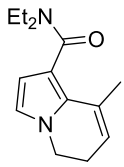
***N,N*-diethyl-8-(1-phenylethyl)-5,6-dihydroindolizine-1-carboxamide (8d)**



Prepared following general procedure for catalytic reactions (page 104), using ***7d*** and *rac*-Binap (5 mol%) as ligand. Obtained in 99% yield as yellow oil. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.23 – 7.15 (m, 4H), 7.15 – 7.07 (m, 1H), 6.48 (d, *J* = 2.7 Hz, 1H), 5.97 (d, *J* = 2.7 Hz, 1H), 5.70 – 5.62 (m, 1H), 4.38 (q, *J* = 7.1 Hz, 1H), 3.97 – 3.82 (m, 2H), 3.59 (dq, *J* = 14.1, 7.1 Hz, 1H), 3.22 (dq, *J* = 14.1, 7.1 Hz, 1H), 2.94 (dq, *J* = 14.3, 7.2 Hz, 1H), 2.60 – 2.40 (m, 3H), 1.37 (d, *J* = 7.1 Hz, 3H), 1.19 (t, *J* = 7.1 Hz, 3H), 0.93 (t, *J* = 7.1 Hz, 3H) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$) δ 169.24 (CO), 146.20 (C), 136.72 (C), 128.15 (CH), 127.90 (C), 127.80 (CH), 125.91 (CH), 119.88 (CH), 117.76 (CH), 116.52 (C), 107.31 (CH), 44.19

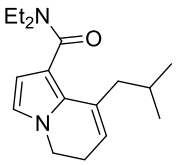
(CH_2), 43.61 (CH_2), 39.66 (CH_2 amide), 39.18 (CH_2 amide), 24.50 (CH), 22.12 (CH_3), 14.25 (CH_3 amide), 13.22 (CH_3 amide) ppm. **HRMS** [APCI]: *m/z* calculated for $C_{21}H_{27}N_2O$ $[M+H]^+$: 323.2118, found 323.2116.

***N,N*-Diethyl-8-methyl-5,6-dihydroindolizine-1-carboxamide (8e)**



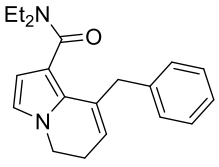
Prepared following general procedure for catalytic reactions (page 104), using ***7e*** and Binapine (5 mol%) as ligand. Obtained in 99% yield as yellow oil. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 6.51 (d, *J* = 2.8 Hz, 1H), 6.05 (d, *J* = 2.7 Hz, 1H), 5.51 – 5.42 (m, 1H), 3.87 (t, *J* = 7.2 Hz, 2H), 3.59 – 3.42 (m, 3H), 3.42 – 3.24 (m, 2H), 2.47 – 2.36 (m, 2H), 1.96 (d, *J* = 1.8 Hz, 3H), 1.20 (t, *J* = 7.1 Hz, 4H), 1.08 (t, *J* = 7.1 Hz, 3H) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$) δ 169.29 (CO), 128.24 (C), 127.84 (C), 120.27 (CH), 117.52 (CH), 116.29 (C), 106.85 (CH), 44.08 (CH_2), 43.36 (CH_2 amide), 39.00 (CH_2 amide), 24.37 (CH_2), 18.89 (CH_3), 14.07 (CH_3 amide), 12.70 (CH_3 amide) ppm. **HRMS** [APCI]: *m/z* calculated for $C_{14}H_{21}N_2O$ $[M+H]^+$: 233.1648, found 233.1647.

***N,N*-Diethyl-8-isobutyl-5,6-dihydroindolizine-1-carboxamide (8f)**



Prepared following general procedure for catalytic reactions (page 104), using ***7f*** and *rac*-Binap (5 mol%) as ligand. Synthesized by following the procedure used for **8a**, but heating at 80 ºC instead of 100 ºC, and using **7f** instead. Obtained in 99% yield as yellow oil. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 6.50 (d, *J* = 2.7 Hz, 1H), 6.05 (d, *J* = 2.7 Hz, 1H), 5.50 (td, *J* = 4.1, 3.4, 2.3 Hz, 1H), 3.85 (t, *J* = 7.1 Hz, 2H), 3.48 (br m, 4H), 2.45 – 2.39 (m, 2H), 2.24 – 2.19 (m, 2H), 1.75 (dq, *J* = 13.5, 6.7 Hz, 1H), 1.26 – 1.06 (m, 6H), 0.85 (d, *J* = 6.6 Hz, 6H) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$) δ 157.10 (CO), 120.28 (C), 115.77 (C), 108.14 (CH), 106.27 (CH), 104.18 (C), 95.30 (CH), 32.27 (CH_2), 31.38 (CH_2 amide), 29.85 (CH_2), 27.07 (CH_2 amide), 14.79 (CH), 12.54 (CH_2), 10.57 (CH_3), 2.22 (CH_3 amide), 0.91 (CH_3 amide) ppm. **HRMS** [APCI]: *m/z* calculated for $C_{17}H_{27}N_2O$ $[M+H]^+$: 275.2118, found 275.2119. **NMR spectra at page 489.**

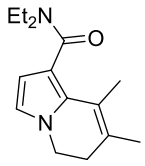
8-Benzyl-*N,N*-diethyl-5,6-dihydroindolizine-1-carboxamide (8g)



Prepared following general procedure for catalytic reactions (page 104), using ***7g*** and *rac*-Binap (5 mol%) as ligand, at 80 ºC instead of 100 ºC. Obtained in 95% yield as yellow oil. **^{1}H NMR** (500 MHz, CD_2Cl_2) δ 7.22 (dd, J = 8.1, 6.9 Hz, 2H), 7.19 – 7.09 (m, 3H), 6.54 (d, J = 2.7 Hz, 1H), 5.98 (d, J = 2.7 Hz, 1H), 5.41 (td, J = 4.0, 3.3, 2.3 Hz, 1H), 3.90 (t, J = 7.1 Hz, 2H), 3.72 (d, J = 1.7 Hz, 2H), 3.37 (q, J = 7.0 Hz, 2H), 2.97 (q, J = 7.1 Hz, 2H), 2.49 – 2.41 (m, 2H), 1.12 (t, J = 7.2 Hz, 3H), 0.95 (t, J = 7.1 Hz, 3H) ppm. **^{13}C NMR** (126

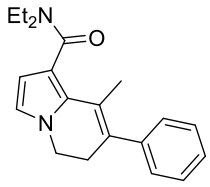
MHz, CD_2Cl_2) δ 168.98 (CO), 140.34 (C), 132.28 (C), 129.54 (CH), 128.56 (CH), 128.03 (C), 126.43 (CH), 120.55 (CH), 120.38 (CH), 117.19 (C), 107.32 (CH), 44.52 (CH_2), 43.91 (CH_2 amide), 39.78 (CH_2 amide), 38.26 (CH_2), 24.97 (CH_2), 14.49 (CH_3 amide), 13.23 (CH_3 amide) ppm. **HRMS** [APCI]: *m/z* calculated for $C_{20}H_{25}N_2O$ $[M+H]^+$: 309.1961, found 309.1958.

***N,N*-Diethyl-7,8-dimethyl-5,6-dihydroindolizine-1-carboxamide (8h)**



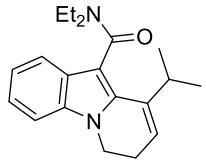
Prepared following general procedure for catalytic reactions (page 104), using ***7h*** and *rac*-Binap (5 mol%) as ligand. Obtained in 99% yield as yellow oil. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 6.44 (d, *J* = 2.8 Hz, 1H), 6.02 (d, *J* = 2.7 Hz, 1H), 3.85 (t, *J* = 7.1 Hz, 2H), 3.59 – 3.28 (m, 4H), 2.41 – 2.35 (m, 2H), 1.91 (s, 3H), 1.84 (s, 3H), 1.23 – 1.03 (m, 6H) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$) δ 169.72 (CO), 129.06 (C), 124.79 (C), 121.15 (C), 119.16 (CH), 114.96 (C), 107.10 (CH), 43.82 (CH_2), 43.32 (CH_2 amide), 38.91 (CH_2 amide), 31.22 (CH_2), 19.24 (CH_3), 14.26 (CH_3 amide), 14.13 (CH_3), 12.64 (CH_3 amide) ppm. **HRMS** [APCI]: *m/z* calculated for $C_{15}H_{23}N_2O$ $[M+H]^+$: 247.1805, found 247.1806. **NMR spectra at page 490.**

***N,N*-Diethyl-9-methyl-8-phenyl-6,7-dihydropyrido[1,2-a]indole-10-carboxamide (8i)**



Prepared following general procedure for catalytic reactions (page 104), using ***7i*** and *rac*-Binap (5 mol%) as ligand. Obtained in 99% yield as yellow solid. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.41 – 7.31 (m, 2H), 7.30 – 7.20 (m, 3H), 6.57 (d, *J* = 2.7 Hz, 1H), 6.12 (d, *J* = 2.7 Hz, 1H), 4.03 (t, *J* = 7.1 Hz, 2H), 3.55 (q, *J* = 7.1 Hz, 2H), 3.39 (q, *J* = 7.1 Hz, 2H), 2.79 (td, *J* = 7.1, 1.7 Hz, 2H), 1.97 (s, 3H), 1.21 (t, *J* = 7.1 Hz, 3H), 1.13 (t, *J* = 7.1 Hz, 3H) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$) ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.49 (CO), 141.99 (C), 129.09 (C), 128.86 (CH), 128.59 (C), 128.24 (CH), 126.70 (CH), 123.53 (C), 119.83 (CH), 117.04 (C), 107.51 (CH), 44.38 (CH_2), 43.37 (CH_2), 38.95 (CH_2 amide), 31.43 (CH_2 amide), 15.67 (CH_2), 14.27 (CH_3 amide), 12.55 (CH_3 amide) ppm. **HRMS** [APCI]: *m/z* calculated for $C_{20}H_{25}N_2O$ $[M+H]^+$: 309.1961, found 309.1963.

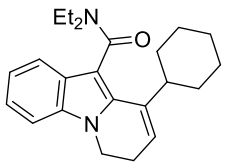
***N,N*-Diethyl-9-isopropyl-6,7-dihydropyrido[1,2-a]indole-10-carboxamide (8j)**



Prepared following general procedure for catalytic reactions (page 104), using ***7j*** and *rac*-Binap (5 mol%) as ligand. Obtained in 82% yield, yellow oil. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.48 (d, *J* = 7.9 Hz, 1H), 7.31 – 7.19 (m, 2H), 7.10 (t, *J* = 7.3 Hz, 1H), 5.95 (t, *J* = 4.8 Hz, 1H), 4.07 (q, *J* = 6.7 Hz, 2H), 3.81 (dt, *J* = 14.1, 7.0 Hz, 1H), 3.59 (dt, *J* = 13.5, 7.0 Hz, 1H), 3.44 – 3.24 (m, 2H), 3.03 (p, *J* = 6.8 Hz, 1H), 2.60 (q, *J* = 6.4 Hz, 2H), 1.33 (t, *J* = 7.1 Hz, 3H), 1.21 (d, *J* = 6.7 Hz, 3H), 1.16 (d, *J* = 6.8 Hz, 3H), 1.05 (t, *J* = 7.1 Hz, 3H) ppm. **^{13}C**

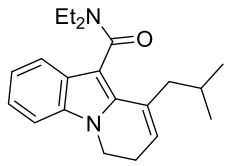
NMR (75 MHz, $CDCl_3$) δ 168.07 (CO), 139.69 (C), 135.69 (C), 132.46 (C), 126.54 (C), 122.57 (CH), 120.04 (CH), 119.46 (CH), 119.36 (CH), 108.77 (CH), 107.84 (C), 43.47 (CH_2), 39.69 (CH_2 amide), 38.84 (CH_2 amide), 28.58 (CH), 24.07 (CH_2), 23.25 (CH_3), 22.84 (CH_3 amide), 14.29 (CH_3 amide), 12.76 (CH_3 amide) ppm. **HRMS** [APCI]: *m/z* calculated for $C_{20}H_{27}N_2O$ $[M+H]^+$: 311.2118, found 311.2128.

9-Cyclohexyl-*N,N*-diethyl-6,7-dihydropyrido[1,2-a]indole-10-carboxamide (8k)



Prepared following general procedure for catalytic reactions (page 104), using ***7k*** and *rac*-Binap (5 mol%) as ligand. Obtained in 99% yield as yellow oil. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.42 (d, *J* = 7.9 Hz, 1H), 7.26 – 7.14 (m, 2H), 7.06 (t, *J* = 7.3 Hz, 1H), 5.88 (t, *J* = 4.8 Hz, 1H), 4.02 (t, *J* = 7.0 Hz, 2H), 3.68 (d, *J* = 7.0 Hz, 2H), 3.32 (q, *J* = 7.1 Hz, 2H), 2.56 (q, *J* = 6.8 Hz, 3H), 2.08 (d, *J* = 12.6 Hz, 1H), 1.83 – 1.68 (m, 4H), 1.37 (t, *J* = 7.1 Hz, 3H), 1.31 – 1.10 (m, 5H), 1.01 (t, *J* = 7.1 Hz, 3H) ppm. **^{13}C NMR** (75 MHz, $CDCl_3$) δ 167.97 (CO), 138.99 (C), 135.75 (C), 132.63 (C), 126.64 (C), 122.52 (CH), 120.04 (CH), 119.86 (CH), 119.42 (CH), 108.74 (CH), 107.87 (C), 43.68 (CH_2), 39.73 (CH_2 amide), 39.36 (CH_2 amide), 38.98 (CH), 34.08 (CH_2), 33.52 (CH_2), 27.12 (CH_2), 26.85 (CH_2), 26.48 (CH_2), 24.17 (CH_2), 14.29 (CH_3 amide), 13.51 (CH_3 amide) ppm (some cyclohexyl and amide signals are duplicated due to rotamerism). **HRMS** [APCI]: *m/z* calculated for $C_{23}H_{31}N_2O$ $[M+H]^+$: 351.2431, found 351.2428.

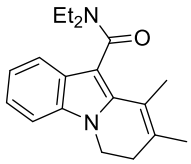
***N,N*-Diethyl-9-isobutyl-6,7-dihydropyrido[1,2-a]indole-10-carboxamide (8l)**



Prepared following general procedure for catalytic reactions (page 104), using ***7l*** and *rac*-Binap (5 mol%) as ligand. Obtained in 89% yield as yellow solid. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.46 (d, *J* = 8.0 Hz, 1H), 7.30 – 7.21 (m, 2H), 7.10 (m, 1H), 5.86 (t, *J* = 4.7 Hz, 1H), 4.14 – 4.01 (m, 2H), 3.70 (m, 2H), 3.34 (m, 2H), 2.61 (td, *J* = 7.5, 7.0, 4.9 Hz, 2H), 2.43 – 2.30 (m, 2H), 1.90 (dt, *J* = 13.3, 6.6 Hz, 1H), 1.37 (t, *J* = 7.1 Hz, 3H), 1.05 (t, *J* = 7.1 Hz, 3H), 0.93 (t, *J* = 6.2 Hz, 6H) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$) δ 167.80 (CO), 135.66 (C), 132.75 (C), 131.77 (C), 123.42 (CH), 122.59 (CH), 120.08 (CH), 119.53 (CH), 108.77 (CH), 108.32 (C), 43.62 (CH_2), 41.83 (CH_2), 39.74 (CH_2 amide), 39.04 (CH_2 amide), 26.76 (CH), 24.26 (CH_2), 22.52 (CH_3), 14.24 (CH_3 amide), 13.19 (CH_3 amide) ppm. **HRMS** [APCI]: *m/z* calculated for $C_{21}H_{29}N_2O$ $[M+H]^+$: 325.2274, found 325.2273.

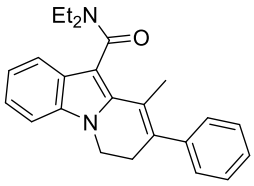
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N,N-Diethyl-8,9-dimethyl-6,7-dihydropyrido[1,2-a]indole-10-carboxamide (8m)



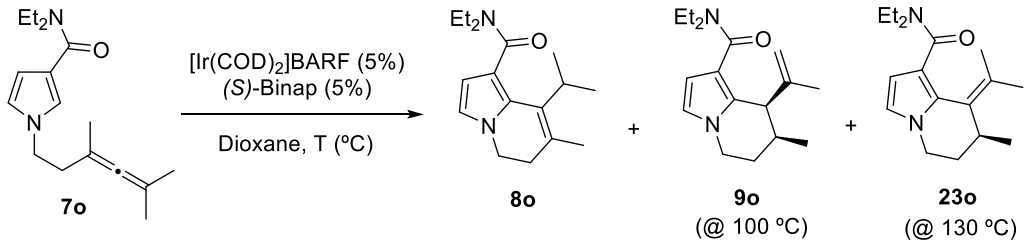
Prepared following general procedure for catalytic reactions (page 104), using ***7m*** and *rac*-Binap (5 mol%) as ligand. Obtained in 71% yield as yellow oil. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.40 (d, *J* = 8.0 Hz, 1H), 7.24 – 7.13 (m, 2H), 7.05 (m, 1H), 4.13 – 3.96 (m, 2H), 3.75 – 3.55 (m, 2H), 3.33 (q, *J* = 7.2 Hz, 2H), 2.66 – 2.44 (m, 2H), 2.05 (s, 3H), 1.94 (s, 3H), 1.31 (t, *J* = 7.1 Hz, 3H), 1.02 (t, *J* = 7.1 Hz, 3H) ppm. **^{13}C NMR** (75 MHz, $CDCl_3$) δ 168.50 (CO), 135.42 (C), 134.54 (C), 130.55 (C), 126.96 (C), 122.14 (CH), 121.18 (C), 120.02 (CH), 119.13 (CH), 108.55 (CH), 107.46 (C), 43.56 (CH_2), 39.65 (CH_2 amide), 39.12 (CH_2 amide), 31.05 (CH_2), 19.82 (CH_3), 14.48 (CH_3), 14.42 (CH_3 amide), 12.98 (CH_3 amide) ppm. **HRMS** [APCI]: *m/z* calculated for $C_{19}H_{25}N_2O$ $[M+H]^+$: 297.1961, found 297.1962.

N,N-Diethyl-8-methyl-7-phenyl-5,6-dihydroindolizine-1-carboxamide (8n)



Prepared following general procedure for catalytic reactions (page 104), using ***7n*** and *rac*-Binap (5 mol%) as ligand. Synthesized by following the procedure used for **8a**, using **7n** instead. Obtained in 96% yield as yellow oil. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.44 – 7.31 (m, 3H), 7.30 – 7.16 (m, 5H), 7.06 (m, 1H), 4.17 (dt, *J* = 8.1, 6.4 Hz, 2H), 3.64 (m, 2H), 3.34 (q, *J* = 7.1 Hz, 2H), 2.88 (m, 2H), 2.05 (s, 3H), 1.27 (t, *J* = 7.1 Hz, 3H), 1.02 (t, *J* = 7.1 Hz, 3H) ppm. **^{13}C NMR** (75 MHz, $CDCl_3$) δ 168.26 (CO), 141.67 (C), 135.52 (C), 134.30 (C), 134.01 (C), 128.69 (CH), 128.41 (CH), 127.21 (CH), 126.90 (C), 123.39 (C), 122.74 (CH), 120.27 (CH), 119.36 (CH), 109.42 (C), 108.82 (CH), 43.60 (CH_2), 40.20 (CH_2), 39.11 (CH_2), 31.32 (CH_2), 15.99 (CH_3), 14.48 (CH_3), 12.89 (CH_3) ppm (ethyl groups from amide not equivalent due to rotamers). **HRMS** [APCI]: *m/z* calculated for $C_{24}H_{27}N_2O$ $[M+H]^+$: 359.2118, found 359.2129. **NMR spectra at page 491.**

Hydroarylation of precursors 7o

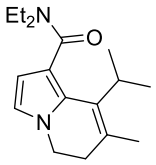


Prepared following general procedure for catalytic reactions (page 104), using ***7o.*** $[Ir(COD)_2]BARF$ (6.40 mg, 0.005 mmol), Binap (3.80 mg, 0.005 mmol), **7o** (27.4 mg, 0.10 mmol) and dioxane (0.80 mL) were sequentially added to a sealed tube under Argon atmosphere and stirred at 100 ºC for 16 h. The mixture was concentrated, and the crude

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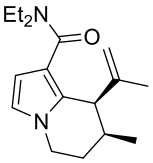
residue was purified by flash chromatography (1:3 to 3:1 EtOAc/Hexanes) to yield **9o** (60% yield, 99:1 er) together with **8o** (19%). When the same reaction was carried out at 130 ºC, under otherwise identical reaction conditions, **23o** was obtained (56% yield, 99:1 er).

***N,N*-Diethyl-8-isopropyl-7-methyl-5,6-dihydroindolizine-1-carboxamide (8o)**



Prepared following general procedure for catalytic reactions (page 104), using ***7o*** and *(R)*-DTBM-Segphos (5 mol%) as ligand. Obtained in 62% yield as yellow oil. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 6.44 (d, *J* = 2.8 Hz, 1H), 6.00 (d, *J* = 2.7 Hz, 1H), 3.80 (t, *J* = 7.0 Hz, 2H), 3.51 (br m, 2H), 3.35 (br m, 2H), 2.83 (p, *J* = 7.2 Hz, 1H), 2.32 (t, *J* = 7.0 Hz, 2H), 1.95 (s, 3H), 1.23 (d, *J* = 7.2 Hz, 6H), 1.21 – 1.02 (m, 6H) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$) δ 169.86 (CO), 132.05 (C), 129.28 (C), 125.58 (C), 119.29 (CH), 115.07 (C), 107.17 (CH), 43.79 (CH_2), 43.41 (CH_2 amide), 39.08 (CH_2 amide), 32.74 (CH_2), 29.54 (CH), 21.58 (CH_2), 20.80 (CH_3), 14.27 (CH_3 amide), 12.70 (CH_3 amide) ppm. **HRMS** [APCI]: *m/z* calculated for $C_{17}H_{27}N_2O$ $[M+H]^+$: 275.2118, found 275.2119. **NMR spectra at page 492.**

(7S,8R)-*N,N*-Diethyl-7-methyl-8-(prop-1-en-2-yl)-5,6,7,8-tetrahydroindolizine-1-carboxamide (9o)

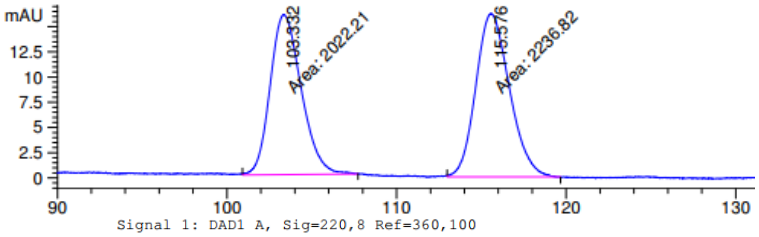


Prepared following general procedure for catalytic reactions (page 104), using ***7o*** at 100 ºC*.* Obtained in 60% yield as yellow oil. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 6.42 (d, *J* = 2.9 Hz, 1H), 6.13 (d, *J* = 2.8 Hz, 1H), 4.83 – 4.75 (m, 1H), 4.56 – 4.48 (m, 1H), 4.09 – 3.97 (m, 2H), 3.92 – 3.81 (m, 1H), 3.48 (dt, *J* = 14.2, 7.1 Hz, 2H), 3.28 (dq, *J* = 14.0, 7.0 Hz, 2H), 2.19 – 2-15 (m, 1H), 2.08 – 1.97 (m, 1H), 1.74 – 1.68 (m, 2H), 1.67 (s, 3H), 1.13 (t, *J* = 7.1 Hz, 6H), 1.02 (d, *J* = 7.0 Hz, 3H) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$) δ 171.73 (CO), 145.79 (C), 117.57 (CH), 114.30 (CH_2), 107.81 (CH), 45.01 (CH_2), 44.28 (CH), 30.30 (CH), 27.61 (CH_2), 23.99 (CH_3), 18.83 (CH_3) ppm [NOTE: ethyl amide signals are not visible due to rotamerism]. **HRMS** [APCI]: *m/z* calculated for $C_{17}H_{27}N_2O$ $[M+H]^+$: 275.2118, found 275.2125. **NMR spectra at page 493.**

Enantioselectivity was determined by chiral HPLC analysis on a Chiralpack IE3 column at *rt* (Hexane:iPrOH = 95:5, 1mL/min).

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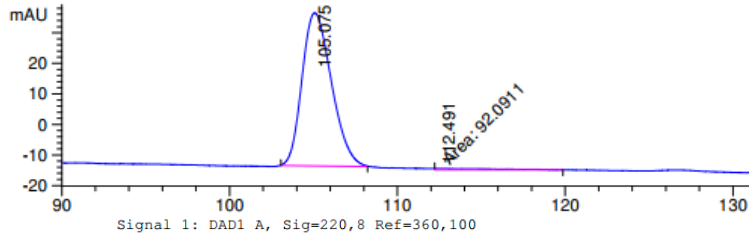
- Racemic sample prepared using [Ir(COD)$_2$]BARF / *rac*-Binap (5 mol%) at 100 ºC.



Signal 1: DAD1 A, Sig=220,8 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	103.332	MM	2.1248	2022.21179	15.86168	47.4806
2	115.576	MM	2.3036	2236.81738	16.18329	52.5194
Totals :				4259.02917	32.04498	

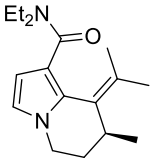
- Asymmetric sample prepared using [Ir(COD)$_2$]BARF / *(S)*-Binap (5 mol%) at 100 ºC (60% yield, 99:1 er).



Signal 1: DAD1 A, Sig=220,8 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	105.075	BB	1.4320	6092.06836	50.05326	98.5109
2	112.491	MM	3.7327	92.09114	4.11191e-1	1.4891
Totals :				6184.15950	50.46445	

_N,N_-Diethyl-7-methyl-8-(propan-2-ylidene)-5,6,7,8-tetrahydroindolizine-1-carboxamide (23o)

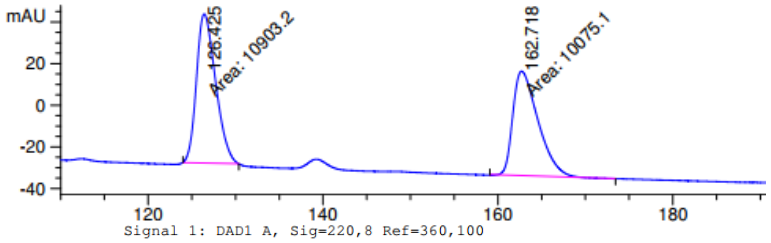


Prepared following general procedure for catalytic reactions (page 104), using ***7o*** at 130 ºC. Obtained in 56% yield as yellow oil. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 6.55 (d, *J* = 2.8 Hz, 1H), 6.23 (d, *J* = 2.8 Hz, 1H), 3.99 – 3.86 (m, 1H), 3.79 – 3.67 (m, 1H), 3.52 – 3.36 (m, 3H), 3.13 (q, *J* = 6.8 Hz, 1H), 2.24 – 2.11 (m, 1H), 1.82 (s, 3H), 1.70 (s, 3H), 1.64 – 1.51 (m, 2H), 1.20 – 1.10 (m, 6H), 1.05 (d, *J* = 6.9 Hz, 3H) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$) δ 169.16 (CO), 129.78 (C), 129.31 (C), 126.37 (C), 118.48 (CH), 118.11 (C), 108.66 (CH), 43.33 (CH_2), 43.18 (CH_2 amide), 38.69 (CH_2 amide), 32.31 (CH_2), 31.40 (CH), 22.81 (CH_3), 20.93 (CH_3), 19.54 (CH_3), 14.17 (CH_3 amide), 12.75 (CH_3 amide). **HRMS** [APCI]: *m/z* calculated for $C_{17}H_{27}N_2O$ $[M+H]^+$: 275.2118, found 275.2114. **NMR spectra at page 513.**

Enantioselectivity was determined by chiral HPLC analysis on a Chiralpack IE3 column at *rt* (Hexane:iPrOH = 95:5, 1mL/min).

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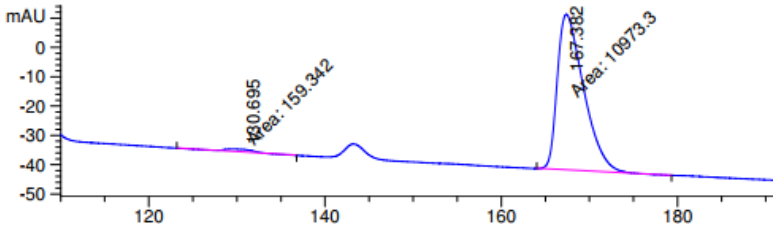
- Racemic sample prepared using [Ir(COD)$_2$]BARF / *rac*-Binap (5 mol%) at **130 ºC**.



Signal 1: DAD1 A, Sig=220,8 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	126.425	MM	2.5378	1.09032e4	71.60541	51.9737
2	162.718	MM	3.3466	1.00751e4	50.17562	48.0263
Totals :				2.09783e4	121.78103	

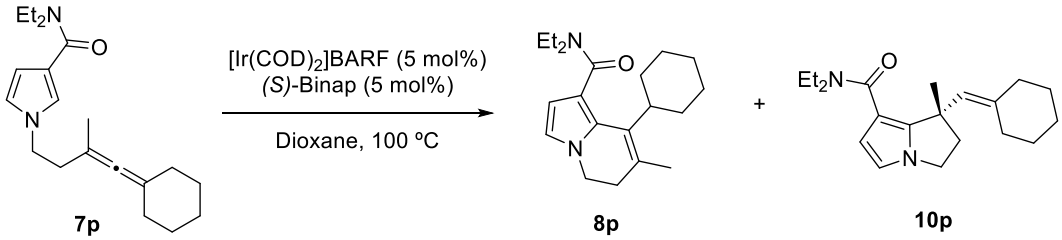
- Asymmetric sample prepared using [Ir(COD)$_2$]BARF / *(S)*-Binap (5 mol%) at **130 ºC** (56% yield, 99:1 er).



Signal 1: DAD1 A, Sig=220,8 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	130.695	MM	3.0573	159.34245	8.68636e-1	1.4313
2	167.382	MM	3.4481	1.09733e4	53.03979	98.5687
Totals :				1.11327e4	53.90842	

Hydroarylation of precursor 7p

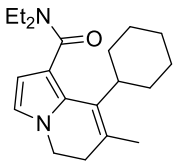


7p **8p** **10p**

Prepared following general procedure for catalytic reactions (page 104), using ***7p.*** [Ir(COD)$_2$]BARF (6.4 mg, 0.005 mmol), *(S)*-Binap (3.1 mg, 0.005 mmol), **7p** (31.4 mg, 0.1 mmol) and dioxane (0.8 mL) were sequentially added to a sealed tube under Argon atmosphere and stirred at 100 ºC for 16 h. The mixture was concentrated, and the crude residue was purified by flash chromatography (1:3 to 3:1 EtOAc/Hexanes) to yield 25% of **8p** and 46% of **10p** (85:15 er).

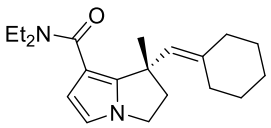
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8-cyclohexyl-*N,N*-diethyl-7-methyl-5,6-dihydroindolizine-1-carboxamide (8p)



Obtained in 25% yield. A small portion was isolated for purification as yellow oil. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 6.43 (d, *J* = 2.8 Hz, 1H), 5.99 (d, *J* = 2.7 Hz, 1H), 3.78 (t, *J* = 7.0 Hz, 2H), 3.55 (q, *J* = 7.1 Hz, 2H), 3.41 (q, *J* = 7.1 Hz, 2H), 2.41 – 2.29 (m, 3H), 1.98 (s, 3H), 1.78 – 1.72 (m, 4H), 1.67 – 1.63 (m, 1H), 1.27 (t, *J* = 6.6 Hz, 3H), 1.23 – 1.16 (m, 5H), 1.09 (t, *J* = 7.1 Hz, 3H) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$) δ 169.79 (CO), 130.62 (C), 129.79 (C), 126.15 (C), 119.05 (CH), 114.83 (C), 107.16 (CH), 43.71 (CH_2), 43.47 (CH_2 amide), 40.96 (CH), 39.31 (CH_2 amide), 32.73 (CH_2), 30.95 (CH_2), 27.55 (CH_2), 26.38 (CH_2), 21.47 (CH_3), 14.36 (CH_3 amide), 13.38 (CH_3 amide). **HRMS** [APCI]: *m/z* calculated for $C_{20}H_{31}N_2O$ $[M+H]^+$: 315-2431, found 315.2429.

***(S)*-1-(cyclohexylidenemethyl)-*N,N*-diethyl-1-methyl-2,3-dihydro-1H-pyrrolizine-7-carboxamide (10p)**

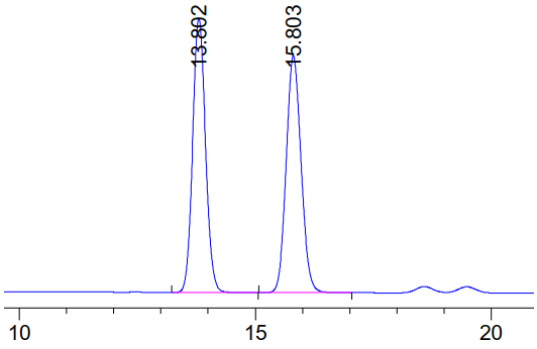


Obtained in 56% yield as yellow oil. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 6.35 (d, *J* = 2.8 Hz, 1H), 6.13 (d, *J* = 2.8 Hz, 1H), 5.46 (s, 1H), 3.92 – 3.83 (m, 2H), 3.62 – 3.53 (m, 2H), 3.22 (dq, *J* = 14.0, 7.0 Hz, 2H), 2.57 – 2.51 (m, 1H), 2.40 – 2.32 (m, 1H), 1.99 – 1.88 (m, 2H), 1.73 (q, *J* = 6.0 Hz, 2H), 1.49 (s, 3H), 1.44 – 1.28 (m, 6H), 1.12 (t, *J* = 7.1 Hz, 6H) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$) δ 167.31 (CO), 147.56 (C), 140.32 (C), 128.58 (CH), 111.97 (CH), 111.39 (CH), 109.43 (C), 45.20 (CH_2), 45.06 (CH_2), 42.96 (C), 40.09 (CH_2 amide), 37.90 (CH_2), 29.67 (CH_2), 28.85 (CH_2), 27.77 (CH_3), 27.53 (CH_2), 26.74 (CH_2), 13.76 (CH_3 amide). **HRMS** [APCI]: *m/z* calculated for $C_{20}H_{31}N_2O$ $[M+H]^+$: 315-2431, found 315.2427.

Enantioselectivity was determined by chiral HPLC analysis on a Chiralpack IE3 column at *rt* (Hexane:iPrOH = 95:5, 1mL/min).

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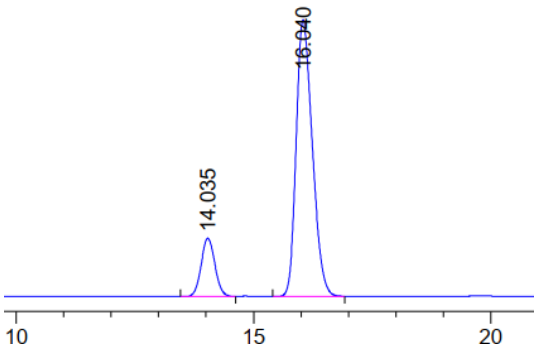
- Racemic sample prepared using [Ir(COD)$_2$]BARF / *rac*-Binap (5 mol%) at 100 ºC.



Signal 1: DAD1 A, Sig=220,4 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	13.802	BB	0.2950	3002.62158	158.47360	49.9704
2	15.803	BB	0.3416	3006.17700	137.23285	50.0296
Totals :				6008.79858	295.70645	

- Asymmetric sample prepared using [Ir(COD)$_2$]BARF / *(S)*-Binap (5 mol%) at 100 ºC (46% yield, 85:15 er).

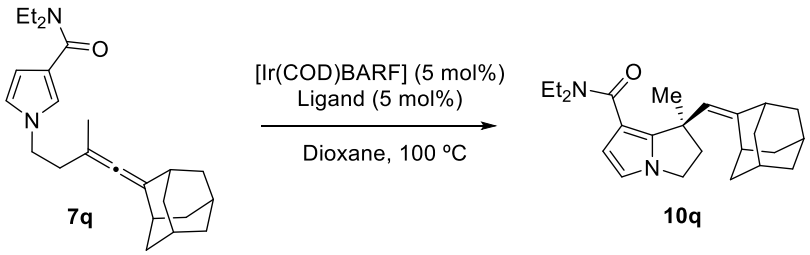


Signal 1: DAD1 A, Sig=220,4 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	14.035	BB	0.3130	3053.66602	151.59013	15.2182
2	16.040	BB	0.3657	1.70123e4	719.89124	84.7818
Totals :				2.00659e4	871.48137	

Synthesis of compounds 10 by hydroarylation of precursors 7

*(exemplified for **10q**)*

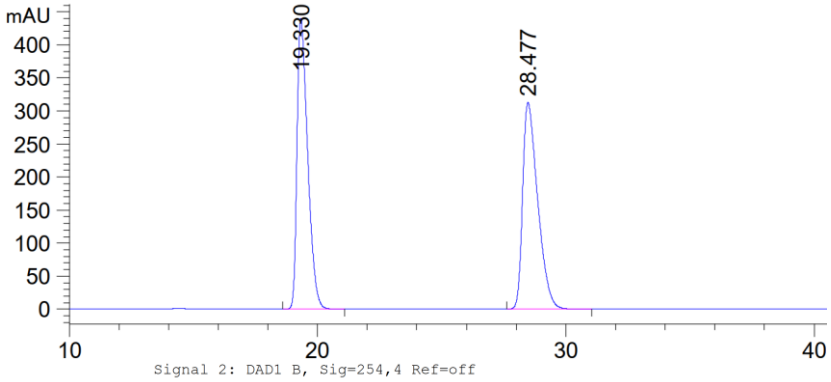


Prepared following general procedure for catalytic reactions using ***7q.*** [Ir(COD)$_2$]BARF (6.4 mg, 0.005 mmol), *(S)*-Binap (3.1 mg, 0.005 mmol), **7q** (36.7 mg, 0.1 mmol) and

dioxane (0.8 mL) were sequentially added to a sealed tube under Argon atmosphere and stirred at 100 ºC for 16 h. The mixture was concentrated, and the crude residue was purified by flash chromatography (1:3 to 3:1 EtOAc/Hexanes) to yield ***(R)*-1-(((1*R*,3*R*,5*R*,7*S*)-adamantan-2-ylidene)methyl)-*N,N*-diethyl-1-methyl-2,3-dihydro-1H-pyrrolizine-7-carboxamide** (**10q**) as yellow oil. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 6.41 (d, *J* = 2.9 Hz, 1H), 6.20 (d, *J* = 2.8 Hz, 1H), 5.51 (s, 1H), 4.00 – 3.86 (m, 2H), 3.74 – 3.62 (m, 2H), 3.29 (dq, *J* = 14.0, 7.0 Hz, 2H), 2.62 – 2.54 (m, 1H), 2.48 – 2.41 (m, 1H), 2.41 – 2.32 (m, 1H), 2.32 – 2.24 (m, 1H), 1.92 – 1.80 (m, 2H), 1.80 – 1.66 (m, 9H), 1.66 – 1.58 (m, 1H), 1.55 (s, 3H), 1.19 (t, *J* = 7.1 Hz, 6H) ppm. **^{13}C NMR** (75 MHz, $CDCl_3$) δ 167.08 (CO), 148.10 (C), 148.00 (C), 123.82 (CH), 111.98 (CH), 111.51 (CH), 109.13 (C), 45.15 (CH_2), 44.89 (CH_2), 43.04 (C), 40.75 (CH), 40.00 (CH_2), 39.89 (CH_2), 38.71 (CH_2), 37.98 (CH_2), 37.30 (CH_2), 32.68 (CH_3), 28.33 (CH), 28.29 (CH), 27.66 (CH), 13.82 (CH_3 amide) [NOTE: CH_2 amide signals are not visible due to rotamerism] ppm. **HRMS** [APCI]: *m/z* calculated for $C_{24}H_{35}N_2O$ $[M+H]^+$: 367.2744, found 367.2750. **NMR spectra at page 494.**

Enantioselectivity was determined by chiral HPLC analysis on a Chiralpack IG3 column at *rt* (Hexane:iPrOH = 95:5, 1mL/min).

- Racemic sample prepared using $[Ir(COD)_2]$BARF / *rac*-Binap (5 mol%) at 100 ºC.

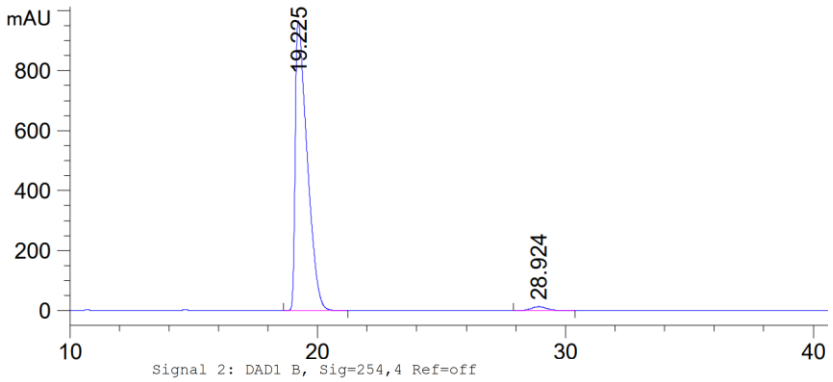


Signal 2: DAD1 B, Sig=254,4 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	19.330	BB	0.4575	1.30999e4	439.77292	49.9219
2	28.477	BB	0.6364	1.31409e4	312.64761	50.0781
Totals :				2.62408e4	752.42053	

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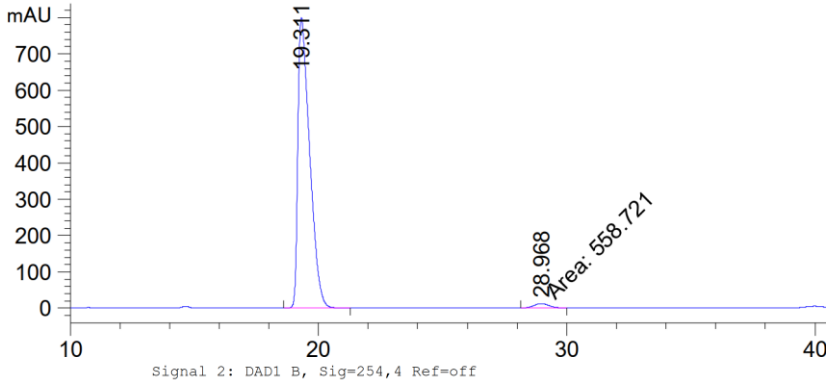
- Asymmetric sample prepared using [Ir(COD)$_2$]BARF / *(R)*-Binap (5 mol%) at 100 ºC (95% yield, 98:2 er).



Signal 2: DAD1 B, Sig=254,4 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	19.225	BB	0.4960	3.21143e4	965.66974	98.3671
2	28.924	BB	0.6360	533.10052	12.69251	1.6329
Totals :				3.26474e4	978.36225	

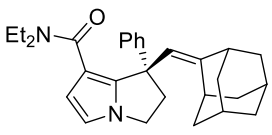
- Asymmetric sample prepared using [Ir(COD)$_2$]BARF / *(R)*-DM-Binap (5 mol%) at 100 ºC (99% yield, 98:2 er).



Signal 2: DAD1 B, Sig=254,4 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	19.311	BB	0.4944	2.63330e4	799.17767	97.9223
2	28.968	MM	0.7397	558.72070	12.58938	2.0777
Totals :				2.68917e4	811.76705	

_(R)_-1-(((1_R_,3_R_,5_R_,7_S_)-adamantan-2-ylidene)methyl)-_N,N_-diethyl-1-phenyl-2,3-dihydro-1H-pyrrolizine-7-carboxamide (**10r**)

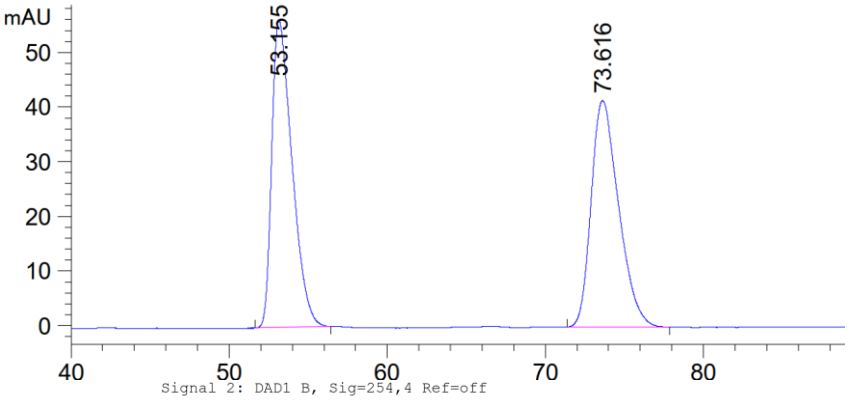


Prepared following general procedure for catalytic reactions (page 104), using ***7r***. Obtained as yellow oil. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.29 (d, *J* = 6.9 Hz, 2H), 7.21 (t, *J* = 7.7 Hz, 2H), 7.10 (t, *J* = 7.3 Hz, 1H), 6.50 (d, *J* = 2.7 Hz, 1H), 6.19 (d, *J* = 2.7 Hz, 1H), 6.10 (s, 1H), 4.08 – 4.03 (m, 1H), 4.01 – 3.95 (m, 1H), 3.13 (br m, *J* = 45.8 Hz, 4H), 3.09 – 3.04 (m, 1H), 2.99 – 2.92 (m, 1H), 2.46 (t, *J* = 3.3 Hz, 1H), 2.41 (t, *J* = 3.3 Hz, 1H), 1.92 – 1.69 (m, 10H), 1.66 – 1.59 (m, 2H), 0.99 (t, *J* = 7.0 Hz, 6H) ppm. **^{13}C NMR** (126

MHz, $CDCl_3$) δ 167.43 (CO), 149.25 (C), 147.09 (C), 144.38 (C), 128.03 (CH), 126.93 (CH), 125.91 (CH), 123.24 (CH), 112.48 (CH), 111.65 (CH), 111.01 (C), 51.66 (C), 45.97 (CH_2), 45.73 (CH_2), 40.69 (CH), 40.18 (CH_2), 39.67 (CH_2), 38.49 (CH_2), 37.83 (CH_2), 37.35 (CH_2), 33.29 (CH), 28.35 (CH), 28.21 (CH), 13.18 (CH_3 amide) [NOTE: CH_2 amide signals are not visible due to rotamerism]. **HRMS** [APCI]: *m/z* calculated for $C_{29}H_{37}N_2O$ $[M+H]^+$: 429.2900, found 429.2911.

Enantioselectivity was determined by chiral HPLC analysis on a Chiralpack IG3 column at *rt* (Hexane:iPrOH = 95:5, 1mL/min).

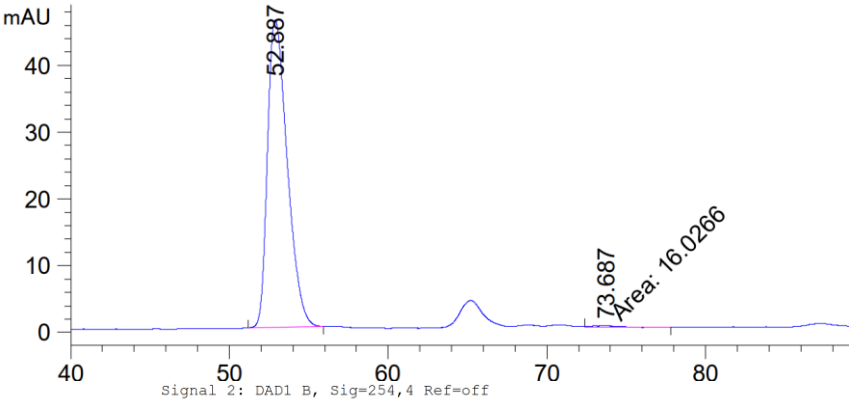
- Racemic sample prepared using [Ir(COD)$_2$]BARF / *rac*-Binap (5 mol%) at 100 ºC.



Signal 2: DAD1 B, Sig=254,4 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	53.155	BB	1.2936	5005.47461	56.28304	49.9844
2	73.616	BB	1.6832	5008.60889	41.46523	50.0156
Totals :				1.00141e4	97.74827	

- Asymmetric sample prepared using [Ir(COD)$_2$]BARF / *(R)*-Binap (5 mol%) at 100 ºC (88% yield, >99:1 er).

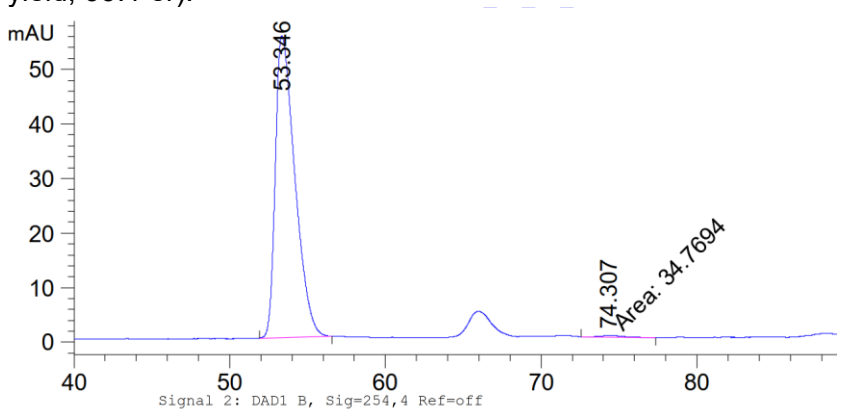


Signal 2: DAD1 B, Sig=254,4 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	52.887	BB	1.3011	3982.91699	46.04792	99.5992
2	73.687	MM	1.5891	16.02655	1.68085e-1	0.4008
Totals :				3998.94354	46.21600	

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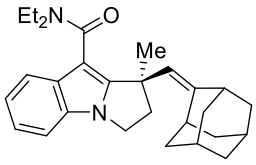
- Asymmetric sample prepared using [Ir(COD)$_2$]BARF / *(R)*-DM-Binap (5 mol%) at 100 ºC (90% yield, 99:1 er).



Signal 2: DAD1 B, Sig=254,4 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	53.346	BB	1.2707	4807.15039	55.27149	99.2819
2	74.307	MM	1.7732	34.76944	3.26797e-1	0.7181
Totals :				4841.91983	55.59829	

***(R)*-1-(((1*R*,3*R*,5*R*,7*S*)-adamantan-2-ylidene)methyl)-*N,N*-diethyl-1-methyl-2,3-dihydro-1H-pyrrolo[1,2-a]indole-9-carboxamide** (**10s**)

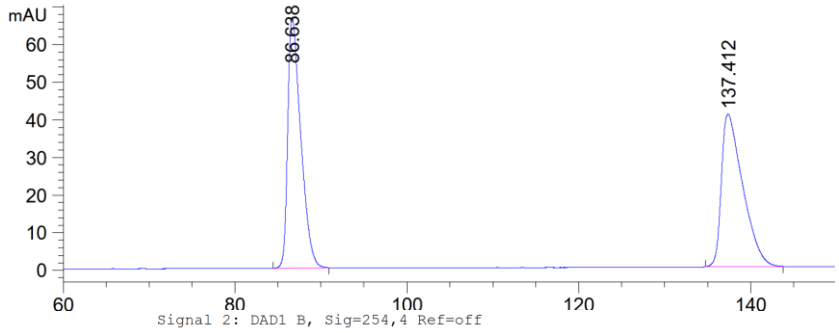


Prepared following general procedure for catalytic reactions (page 104), using ***7s.*** Obtained as white solid. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.42 (d, *J* = 7.8 Hz, 1H), 7.22 (d, *J* = 7.9 Hz, 1H), 7.14 (t, *J* = 7.1 Hz, 1H), 7.09 (t, *J* = 7.3 Hz, 1H), 5.69 (s, 1H), 4.15 (td, *J* = 9.4, 3.9 Hz, 1H), 4.05 (dt, *J* = 9.9, 7.6 Hz, 1H), 3.62 – 3.48 (m, 4H), 2.83 – 2.74 (m, 2H), 2.71 – 2.62 (m, 1H), 2.28 (t, *J* = 3.3 Hz, 1H), 1.97 – 1.88 (m, 2H), 1.87 – 1.70 (m, 11H), 1.63 (s, 3H), 1.24 – 1.13 (m, 6H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 167.34 (CO), 153.53 (C), 149.10 (C), 131.28 (C), 130.31 (C), 122.78 (CH), 120.98 (CH), 120.05 (CH), 119.81 (CH), 109.77 (CH), 102.62 (C), 43.88 (CH_2), 43.55 (C), 42.94 (CH_2), 41.02 (CH), 40.04 (CH_2), 39.84 (CH_2), 38.79 (CH_2), 38.50 (CH_2), 37.28 (CH_2), 33.28 (CH), 28.29 (CH), 27.58 (CH_3), 13.94 (CH_3 amide) ppm [NOTE: CH_2 amide signals are not visible due to rotamerism]. **HRMS** [APCI]: *m/z* calculated for $C_{28}H_{37}N_2O$ $[M+H]^+$: 417.2900, found 417.2909.

Enantioselectivity was determined by chiral HPLC analysis on a Chiralpack IF3 column at *rt* (Hexane:iPrOH = 95:5, 1mL/min).

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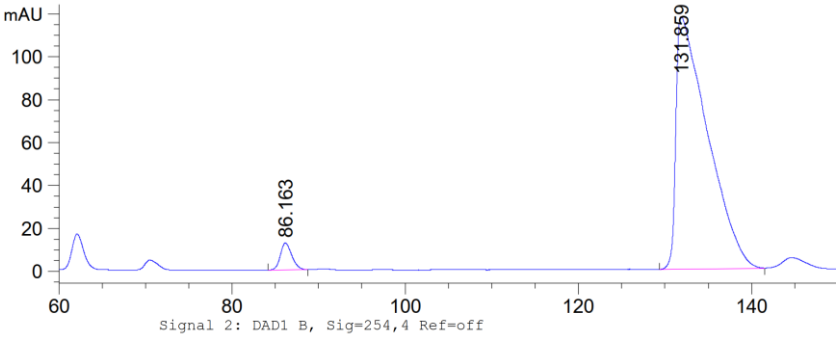
- Racemic sample prepared using [Ir(COD)$_2$]BARF / *rac*-Binap (5 mol%) at 100 ºC.



Signal 2: DAD1 B, Sig=254,4 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	86.638	BB	1.4831	7006.37744	66.61270	50.0512
2	137.412	BB	2.0776	6992.03027	40.55066	49.9488
Totals :				1.39984e4	107.16336	

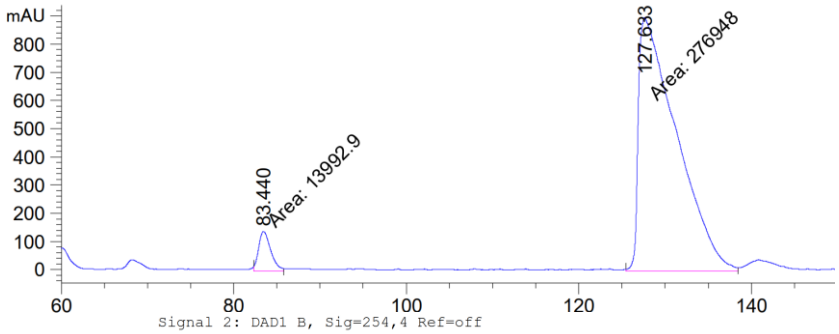
- Asymmetric sample prepared using [Ir(COD)$_2$]BARF / *(R)*-Binap (5 mol%) at 100 ºC (97% yield, 95:5 er).



Signal 2: DAD1 B, Sig=254,4 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	86.163	BB	1.1900	1145.21558	12.55724	3.6903
2	131.859	BB	3.1639	2.98882e4	117.56827	96.3097
Totals :				3.10334e4	130.12551	

- Asymmetric sample prepared using [Ir(COD)$_2$]BARF / *(R)*-DM-Binap (5 mol%) at 100 ºC (99% yield, 96:4 er).

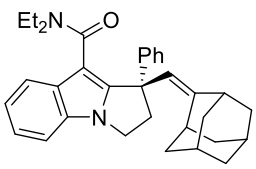


Signal 2: DAD1 B, Sig=254,4 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	83.436	BB	1.3229	2229.14600	23.79547	4.4160
2	127.635	BB	3.7844	4.82499e4	161.64424	95.5840
Totals :				5.04790e4	185.43971	

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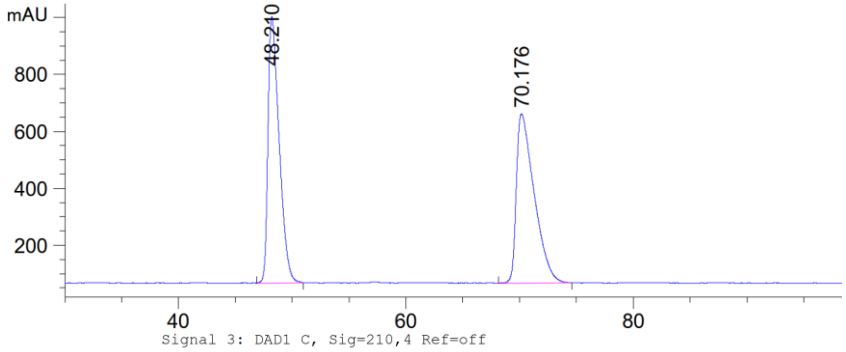
***(R)*-1-(((1*R*,3*R*,5*R*,7*S*)-adamantan-2-ylidene)methyl)-*N,N*-diethyl-1-phenyl-2,3-dihydro-1H-pyrrolo[1,2-a]indole-9-carboxamide** (**10t**)



Prepared following general procedure for catalytic reactions (page 104), using ***7t.*** Obtained as white solid. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.45 (td, *J* = 8.2, 4.2 Hz, 3H), 7.34 – 7.04 (m, 6H), 6.28 (s, 1H), 4.38 – 4.22 (m, 2H), 3.59 – 2.82 (m, 6H), 2.58 – 2.46 (m, 2H), 2.04 – 1.75 (m, 10H), 1.74 – 1.58 (m, 2H), 0.96 (br m, 6H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 166.88 (CO), 150.59 (C), 150.24 (C), 146.01 (C), 131.43 (C), 130.68 (C), 128.27 (CH), 127.16 (CH), 126.36 (CH), 122.62 (CH), 121.37 (CH), 120.16 (CH), 120.01 (CH), 109.83 (CH), 104.20 (C), 51.89 (C), 45.28 (CH_2), 43.60 (CH_2), 40.88 (CH), 40.40 (CH_2), 39.64 (CH_2), 38.88 (CH_2), 37.66 (CH_2), 37.42 (CH_2), 33.66 (CH), 28.48 (CH), 28.26 (CH), 13.61 (CH_3 amide) ppm [NOTE: CH_2 amide signals are not visible due to rotamerism]. **HRMS** [APCI]: *m/z* calculated for $C_{33}H_{39}N_2O$ $[M+H]^+$: 479.3057, found 479.3048.

Enantioselectivity was determined by chiral HPLC analysis on a Chiralpack IF3 column at *rt* (Hexane:iPrOH = 85:15, 1mL/min).

- Racemic sample prepared using $[Ir(COD)_2]BARF$ / *rac*-Binap (5 mol%) at 100 ºC.

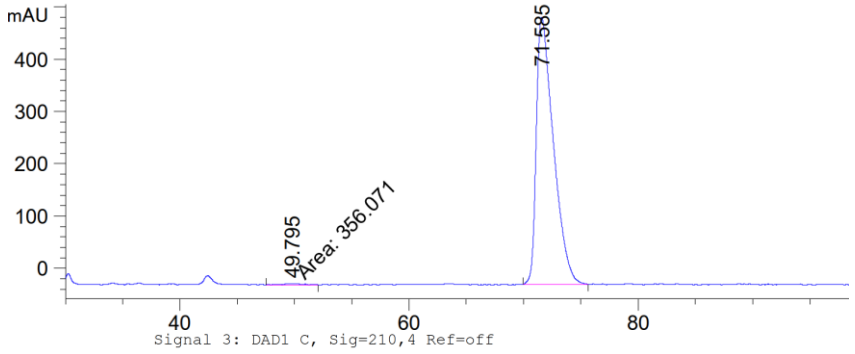


Signal 3: DAD1 C, Sig=210,4 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	48.210	BB	1.0338	6.37981e4	935.30951	49.5805
2	70.176	BB	1.5717	6.48776e4	595.21320	50.4195
Totals :				1.28676e5	1530.52271	

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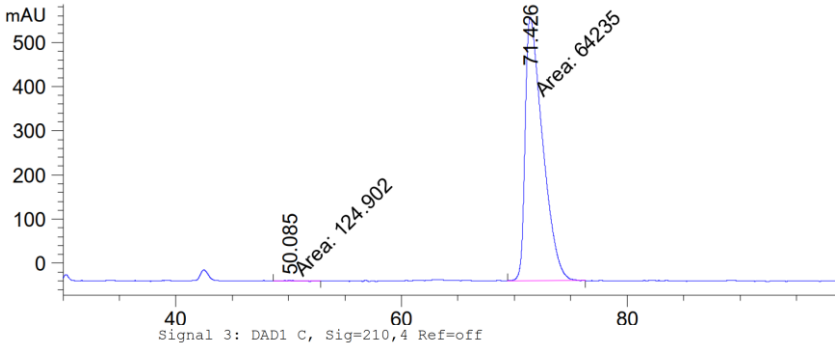
- Asymmetric sample prepared using [Ir(COD)$_2$]BARF / *(R)*-Binap (5 mol%) at 100 ºC (66% yield, >99:1 er).



Signal 3: DAD1 C, Sig=210,4 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	49.795	MM	2.0871	356.07083	2.84347	0.6674
2	71.585	BB	1.4564	5.29995e4	510.85599	99.3326
Totals :				5.33555e4	513.69946	

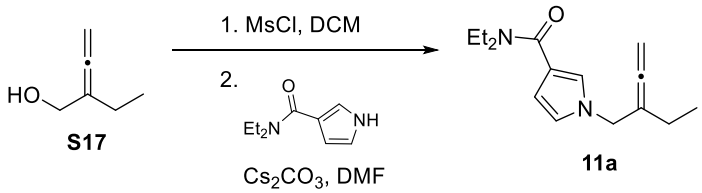
- Asymmetric sample prepared using [Ir(COD)$_2$]BARF / *(R)*-DM-Binap (5 mol%) at 100 ºC (62% yield, >99:1 er).



Signal 3: DAD1 C, Sig=210,4 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	50.085	MM	1.6451	124.90231	1.26539	0.1941
2	71.426	MM	1.7941	6.42350e4	596.71594	99.8059
Totals :				6.43599e4	597.98133	

Synthesis of precursor 11a



2-ethylbuta-2,3-dien-1-ol (**S17**) were synthetized following reported procedures from literature.[187] **2-ethylbuta-2,3-dien-1-ol** (**S17**, 3.00 mmol) was dissolved in CH_2Cl_2 (6.50 mL) and cooled to 0 ºC. Triethylamine (0.54 mL, 3.90 mmol) and MsCl (0.28 mL, 3.60 mmol) were added sequentially. The reaction was allowed to warm to r.t and after 1,5 h

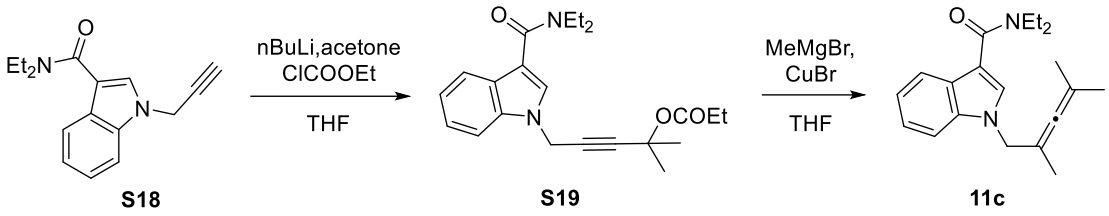
[187] N. Lumbroso-Bader, E. Michel, and C. Troyanowsky, *Bull. Soc. Chim. Fr.* **1967**, 189-195.

was quenched with 30 mL of water and extracted with CH_2Cl_2 (3 x 20mL). The combined organic phases were dried with Na_2SO_4, filtered and the solvent was removed under reduced pressure.[188]

The resulting yellow oil was dissolved in DMF (8.60 mL), and Cs_2CO_3 (1.46 g, 4.50 mmol) and *N,N*-diethyl-1H-pyrrole-3-carboxamide (549 mg, 3.30 mmol) were added. The mixture was stirred at 55 ºC for 16h, and water (100 mL) was added. The mixture was extracted with EtOAc (3 x 50 mL), and the combined organic phases was dried, concentrated and the crude residue was purified by flash chromatography (7:3 to 3:7 hexanes/EtOAc) to yield ***N,N*-diethyl-1-(2-ethylbuta-2,3-dien-1-yl)-1H-pyrrole-3-carboxamide** (**11a**) as yellow oil in 26% yield. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.04 (t, *J* = 2.0 Hz, 1H), 6.56 (t, *J* = 2.6 Hz, 1H), 6.31 (dd, *J* = 2.9, 1.7 Hz, 1H), 4.84 – 4.79 (m, 2H), 4.40 (t, *J* = 2.3 Hz, 2H), 3.51 (q, *J* = 7.1 Hz, 4H), 1.91 – 1.81 (m, 2H), 1.20 (t, *J* = 7.1 Hz, 6H), 0.98 (t, *J* = 7.4 Hz, 3H) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$) δ 206.56 (C), 166.70 (CO), 123.99 (CH), 120.88 (CH), 119.80 (C), 109.04 (CH), 102.50 (C), 77.47 (CH_2), 52.60 (CH_2), 41.66 (CH_2 amide), 22.44 (CH_2), 13.86 (CH_3 amide), 11.91 (CH_3) ppm. **HRMS** [APCI]: *m/z* calculated for $C_{15}H_{23}N_2O$ $[M+H]^+$: 247.1805, found 247.1804. **NMR spectra at page 495.**

Synthesis of precursors 11b-d

*(exemplified for **11c**)*



S18 **S19** **11c**

***N,N*-diethyl-1-(prop-2-yn-1-yl)-1H-indole-3-carboxamide** (**S18,** 0.95 mg, 3.74 mmol) was dissolved in THF (12.5 mL) and cooled to -78 ºC, then n-BuLi was added (1.90 mL, 4.86 mmol, 2.5 M in THF). After 10 minutes, acetone was added (0.30 mL, 4.11 mmol) and the reaction was gradually warmed to r.t. The reaction was followed by TLC and, when all the starting material was consumed, ethylchloroformate (0.71 mL, 7.47 mmol) was added. After 1-2h, the reaction was quenched with H_2O (40 mL), and the reaction was extracted with Et_2O (3 x 50 mL) and the combined organic phases were washed with NaCl (sat.), dried and concentrated to yield a crude yellow residue that was purified by flash column chromatography (from 3:1 to 1:3 hexanes/EtOAc) to afford **5-(3-**

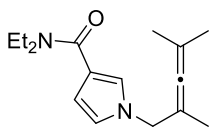
USC

[188] Procedure adapted from: J. Barluenga, F. J. Fañanás, R. Sanz, C. Marcos, and J. M. Ignacio, *Chem. Commun.* **2005**, 933–935.

(diethylcarbamoyl)-1H-indol-1-yl)-2-methylpent-3-yn-2-yl ethyl carbonate (**S19**) as yellow oil in 60% yield. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.73 – 7.64 (m, 1H), 7.38 (s, 1H), 7.27 – 7.20 (m, 1H), 7.16 – 7.02 (m, 2H), 4.78 (s, 2H), 4.04 (q, *J* = 7.1 Hz, 2H), 3.49 – 3.37 (m, 5H), 1.56 (s, 6H), 1.21 – 1.05 (m, 9H) ppm. **^{13}C NMR** (75 MHz, $CDCl_3$) δ 166.53 (CO), 152.89 (CO), 135.56 (C), 127.46 (CH), 127.33 (C), 122.63 (CH), 121.12 (CH), 121.03 (C), 111.69 (C), 109.60 (CH), 86.83 (C), 74.43 (C), 73.70 (C), 63.68 (CH_2), 41.32 (CH_2 amide), 36.37 (CH_2), 28.71 (CH_3), 14.23 (CH_3), 13.90 (CH_3 amide) ppm.

CuBr (97.0 mg, 0.68 mmol) was suspended in anhydrous THF (7.80 mL) and cooled to 0 ºC, then MeMgCl (0.54 mL, 1.35 mmol, 2.5 M in THF) was added. After 10 minutes, **5-(3-(diethylcarbamoyl)-1H-indol-1-yl)-2-methylpent-3-yn-2-yl ethyl carbonate** (**S19**, 0.20 g, 0.52 mmol) dissolved in 7.80 mL of THF were slowly added to the mixture. When TLC indicates that the reaction is finished (typically after 20 minutes), 40 mL of a saturated solution of NH_4Cl were added. The mixture was extracted with Et_2O (3 x 75 mL), and the combined organic phases were washed with NaCl (sat), dried and concentrated to yield a crude yellow residue that was purified by flash column chromatography (from 3:1 to 1:3 hexanes/EtOAc) to afford **1-(2,4-dimethylpenta-2,3-dien-1-yl)-*N,N*-diethyl-1H-indole-3-carboxamide** (**11c**) as yellow oil in 56% yield. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.77 (d, *J* = 7.9 Hz, 1H), 7.36 – 7.29 (m, 2H), 7.26 – 7.13 (m, 2H), 4.60 (s, 2H), 3.58 (q, *J* = 7.1 Hz, 4H), 1.60 (s, 3H), 1.56 (s, 6H), 1.23 (t, *J* = 7.1 Hz, 6H) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$) δ 200.08 (C), 167.07 (CO), 136.38 (C), 128.84 (CH), 127.29 (C), 122.34 (CH), 121.12 (CH), 120.69 (CH), 111.61 (C), 110.34 (CH), 97.10 (C), 93.70 (C), 51.17 (CH_2), 41.51 (CH_2 amide), 20.53 (CH_3), 16.83 (CH_3), 14.06 (CH_3 amide) ppm. **HRMS** [APCI]: *m/z* calculated for $C_{20}H_{27}N_2O$ $[M+H]^+$: 311.2118, found 311.2118.

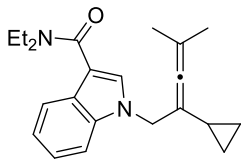
1-(2,4-Dimethylpenta-2,3-dien-1-yl)-*N,N*-diethyl-1H-pyrrole-3-carboxamide (11b)



Synthesized by following an analogous procedure to the one used for **11c.** Obtained in 40% yield as yellow oil. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.00 (t, *J* = 1.9 Hz, 1H), 6.52 (t, *J* = 2.4 Hz, 1H), 6.32 – 6.26 (m, 1H), 4.27 (s, 2H), 3.48 (q, *J* = 7.1 Hz, 4H), 1.60 (s, 6H), 1.51 (s, 3H), 1.17 (t, *J* = 7.9 Hz, 6H) ppm. **^{13}C NMR** (75 MHz, $CDCl_3$) δ 200.11 (C), 166.55 (CO), 123.78 (CH), 120.76 (CH), 119.12 (C), 108.72 (CH), 96.18 (C), 94.02 (C), 54.27 (CH_2), 41.50 (CH_2 amide), 20.59 (CH_3), 16.55 (CH_3), 13.75 (CH_3 amide) ppm. **HRMS** [APCI]: *m/z* calculated for $C_{16}H_{25}N_2O$ $[M+H]^+$: 261.1961, found 261.1951.

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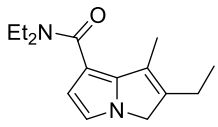
1-(2-Cyclopropyl-4-methylpenta-2,3-dien-1-yl)-*N,N*-diethyl-1H-indole-3-carboxamide (11d)



Synthesized by following an analogous procedure to the one used for **11c.** Obtained in 55% yield as yellow oil. **^{1}H NMR** (300 MHz, $CDCl_3$) δ ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.77 (d, *J* = 7.0 Hz, 1H), 7.38 – 7.31 (m, 2H), 7.24 – 7.11 (m, 2H), 4.72 (s, 2H), 3.57 (q, *J* = 7.1 Hz, 4H), 1.54 (s, 6H), 1.22 (t, *J* = 7.1 Hz, 6H), 1.03 – 0.95 (m, 1H), 0.60 – 0.51 (m, 2H), 0.27 – 0.17 (m, 2H) ppm. **^{13}C NMR** (75 MHz, $CDCl_3$) δ 198.05 (C), 166.99 (CO), 136.20 (C), 128.94 (CH), 127.13 (C), 122.17 (CH), 120.97 (CH), 120.56 (CH), 111.17 (C), 110.28 (CH), 102.09 (C), 99.78 (C), 50.17 (CH_2), 41.38 (CH_2 amide), 20.57 (CH_3), 14.00 (CH_3 amide), 10.82 (CH), 6.74 (CH_2) ppm. **HRMS** [APCI]: *m/z* calculated for $C_{22}H_{29}N_2O$ $[M+H]^+$: 337.2274, found 337.2274. **NMR spectra at page 496.**

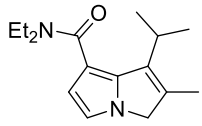
Synthesis of compounds 13 by hydroarylation of precursors 11

N,N,2-Triethyl-1-methyl-3H-pyrrolizine-7-carboxamide (13a)



Prepared following general procedure for catalytic reactions (page 104), using ***11a.*** Obtained in 88% yield as yellow oil. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 6.73 (dd, *J* = 2.8, 0.9 Hz, 1H), 6.20 (d, *J* = 2.8 Hz, 1H), 4.29 (dq, *J* = 2.0, 1.0 Hz, 2H), 3.52 (q, *J* = 7.1 Hz, 4H), 2.37 (q, *J* = 7.6 Hz, 2H), 2.05 – 2.00 (m, 3H), 1.19 (t, *J* = 7.1 Hz, 6H), 1.10 (t, *J* = 7.6 Hz, 3H) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$) δ 167.74 (CO), 144.89 (C), 139.73 (C), 126.34 (C), 115.31 (CH), 110.73 (CH), 108.15 (C), 52.92 (CH_2), 41.42 (CH_2 amide), 20.13 (CH_2), 14.18 (CH_3 amide), 13.93 (CH_3), 10.58 (CH_3) ppm. **HRMS** [APCI]: *m/z* calculated for $C_{15}H_{23}N_2O$ $[M+H]^+$: 247.1805, found 247.1813. **NMR spectra at page 500.**

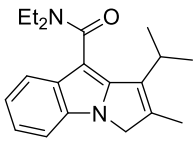
N,N-Diethyl-1-isopropyl-2-methyl-3H-pyrrolizine-7-carboxamide (13b)



Prepared following general procedure for catalytic reactions (page 104), using ***11b.*** Obtained in 85% yield as yellow oil. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 6.74 (d, *J* = 2.7 Hz, 1H), 6.12 (d, *J* = 2.7 Hz, 1H), 4.21 (s, 2H), 3.47 (q, *J* = 7.0 Hz, 4H), 3.05 (p, *J* = 7.1 Hz, 1H), 1.97 (s, 3H), 1.22 (d, *J* = 7.1 Hz, 6H), 1.16 (t, *J* = 7.1 Hz, 6H) ppm. **^{13}C NMR** (75 MHz, $CDCl_3$) δ 168.93 (CO), 140.90 (C), 136.84 (C), 131.30 (C), 115.30 (CH), 110.42 (CH), 108.01 (C), 54.85 (CH_2), 43.57 (CH_2 amide), 39.97 (CH_2 amide), 25.85 (CH), 20.92 (CH_3), 13.47 (CH_3 amide), 12.66 (CH_3) ppm. **HRMS** [APCI]: *m/z* calculated for $C_{16}H_{25}N_2O$ $[M+H]^+$: 261.1961, found 261.1955.

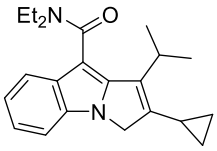
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N,N-Diethyl-1-isopropyl-2-methyl-3H-pyrrolo[1,2-a]indole-9-carboxamide (13c)



Prepared following general procedure for catalytic reactions (page 104), using ***11c***. Obtained in 99% yield as yellow oil. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.45 – 7.39 (m, 1H), 7.19 (dd, *J* = 8.1, 2.2 Hz, 1H), 7.11 (dt, *J* = 8.9, 4.5 Hz, 1H), 7.08 – 7.01 (m, 1H), 4.39 (s, 2H), 3.54 (s, 4H), 3.14 (pd, *J* = 7.2, 2.2 Hz, 1H), 2.11 (s, 3H), 1.30 (d, *J* = 2.4 Hz, 6H), 1.25 – 1.08 (m, 6H) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$) δ 167.95 (CO), 146.94 (C), 137.20 (C), 137.12 (C), 133.29 (C), 130.36 (C), 121.47 (CH), 120.33 (CH), 119.69 (CH), 108.59 (CH), 101.47 (C), 53.29 (CH_2), 40.95 (CH_2 amide), 26.12 (CH), 21.21 (CH_3), 14.20 (CH_3 amide), 13.45 (CH_3) ppm. **HRMS** [APCI]: *m/z* calculated for $C_{20}H_{27}N_2O$ $[M+H]^+$: 311.2118, found 311.2117.

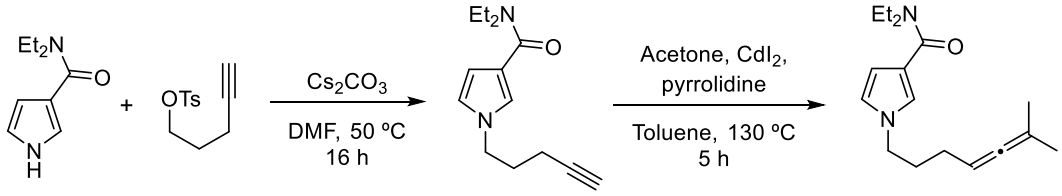
2-Cyclopropyl-*N,N*-diethyl-1-isopropyl-3H-pyrrolo[1,2-a]indole-9-carboxamide (13d)



Prepared following general procedure for catalytic reactions (page 104), using ***11d.*** Obtained in 91% yield as yellow oil. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.41 (d, *J* = 7.8 Hz, 1H), 7.21 – 6.99 (m, 3H), 4.19 (s, 2H), 3.75 – 3.36 (m, 4H), 3.27 (p, *J* = 7.1 Hz, 1H), 2.05 – 1.94 (m, 1H), 1.36 (d, *J* = 7.1 Hz, 6H), 1.31 – 1.02 (m, 6H), 1.01 – 0.92 (m, 2H), 0.71 – 0.61 (m, 2H) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$) δ 167.92 (CO), 146.98 (C), 142.96 (C), 137.65 (C), 133.13 (C), 130.26 (C), 121.34 (CH), 120.14 (CH), 119.60 (CH), 108.41 (CH), 100.83 (C), 48.90 (CH_2), 43.62 (CH_2 amide), 39.01 (CH_2 amide), 26.10 (CH), 21.22 (CH_3), 14.47 (CH_3 amide), 13.21 (CH_3 amide), 10.30 (CH_3), 7.75 (CH_2) ppm. **HRMS** [APCI]: *m/z* calculated for $C_{22}H_{29}N_2O$ $[M+H]^+$: 337.2274, found 337.2272. **NMR spectra at page 501.**

Synthesis of precursors 12b-e

*(exemplified for **12b**)*

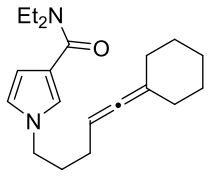


***N,N*-diethyl-1-(pent-4-yn-1-yl)-1H-pyrrole-3-carboxamide** (**S20**) was prepared using standard alkylation conditions. A sealed tube containing CdI_2 (378 mg, 1.03 mmol) was heated under vacuum until the white CdI_2 turned to yellow-green. Then, compound **S20** (0.3 g, 1.30 mmol), pyrrolidine (117 mL, 1.42 mmol) and acetone (104 mL, 1.42 mmol) and toluene (6.4 mL) were sequentially added and heated to 130 ºC. After 5 hours, was

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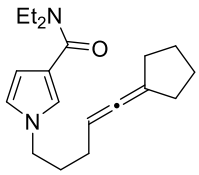
gradually warmed to r.t. and the crude mixture was filtrated through a short pad of silica gel eluted with Et_2O (100 ml).[189] The solution was concentrated to yield a crude residue that was purified by flash column chromatography (from 3:1 to 1:3 hexanes/EtOAc) to afford ***N,N*-diethyl-1-(6-methylhepta-4,5-dien-1-yl)-1H-pyrrole-3-carboxamide** (**12b**) in 32% yield as yellow oil. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.05 (t, *J* = 2.0 Hz, 1H), 6.56 (t, *J* = 2.6 Hz, 1H), 6.32 (t, *J* = 2.2 Hz, 1H), 4.94 (m, 1H), 3.88 (t, *J* = 7.0 Hz, 2H), 3.53 (q, *J* = 7.1 Hz, 4H), 1.95 (q, *J* = 6.7 Hz, 2H), 1.86 (p, *J* = 7.0 Hz, 2H), 1.70 (d, *J* = 2.9 Hz, 6H), 1.23 (d, *J* = 7.1 Hz, 6H) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$) δ 202.28 (C), 166.80 (CO), 123.85 (CH), 120.60 (CH), 119.65 (C), 108.89 (CH), 96.02 (C), 87.60 (CH), 49.14 (CH_2), 41.69 (CH_2 amide), 30.64 (CH_2), 26.03 (CH_2), 20.80 (CH_3), 13.92 (CH_3 amide). ppm. **HRMS** [APCI]: *m/z* calculated for $C_{17}H_{27}N_2O$ $[M+H]^+$: 275.2118, found 275.2119. **NMR spectra at page 498.**

1-(5-cyclohexylidenepent-4-en-1-yl)-*N,N*-diethyl-1H-pyrrole-3-carboxamide (12c)



Synthesized by following the procedure used for **12b,** using cyclohexanone instead of acetone. Obtained in 38% yield as yellow oil. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.05 (t, *J* = 2.0 Hz, 1H), 6.56 (t, *J* = 2.6 Hz, 1H), 6.31 (dd, *J* = 2.8, 1.7 Hz, 1H), 4.99 – 4.90 (m, 1H), 3.88 (t, *J* = 6.8 Hz, 2H), 3.52 (q, *J* = 7.1 Hz, 4H), 2.16 – 2.05 (m, 4H), 2.01 – 1.90 (m, 2H), 1.90 – 1.80 (m, 2H), 1.63 – 1.43 (m, 6H), 1.21 (t, *J* = 7.1 Hz, 6H) ppm. **^{13}C NMR** (75 MHz, $CDCl_3$) δ 198.70 (C), 166.69 (CO), 123.81 (CH), 120.60 (CH), 119.39 (C), 108.75 (CH), 103.41 (C), 87.34 (CH), 48.97 (CH_2), 41.61 (CH_2 amide), 31.85 (CH_2), 30.44 (CH_2), 27.56 (CH_2), 26.22 (CH_2), 26.01 (CH_2), 13.88 (CH_3 amide) ppm. **HRMS** [APCI]: *m/z* calculated for $C_{20}H_{31}N_2O$ $[M+H]^+$: 315.2431, found 315.2432.

1-(5-cyclopentylidenepent-4-en-1-yl)-*N,N*-diethyl-1H-pyrrole-3-carboxamide (12d)

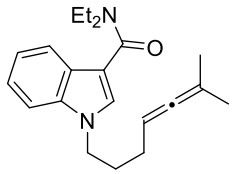


Synthesized by following the procedure used for **12b,** using cyclopentanone instead of acetone. Obtained in 64% yield as yellow oil. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.06 (t, *J* = 2.0 Hz, 1H), 6.55 (t, *J* = 2.6 Hz, 1H), 6.31 (dd, *J* = 2.8, 1.8 Hz, 1H), 5.05 (tt, *J* = 6.0, 4.0 Hz, 1H), 3.88 (t, *J* = 6.9 Hz, 2H), 3.53 (q, *J* = 7.1 Hz, 4H), 2.39 – 2.27 (m, 4H), 2.01 – 1.91 (m, 2H), 1.91 – 1.81 (m, 2H), 1.70 – 1.62 (m, 4H), 1.21 (t, *J* = 7.1 Hz, 6H) ppm. **^{13}C NMR** (75 MHz, $CDCl_3$) δ 197.48 (C), 166.77 (CO), 123.92 (CH), 120.62 (CH), 119.34 (C), 108.77 (CH), 104.71 (C), 90.05 (CH), 49.07 (CH_2), 41.58 (CH_2 amide), 31.40 (CH_2), 30.50 (CH_2), 27.15 (CH_2), 26.09 (CH_2), 13.90 (CH_3 amide) ppm. **HRMS** [APCI]: *m/z* calculated for $C_{19}H_{29}N_2O$ $[M+H]^+$: 301.2274, found 301.2280.

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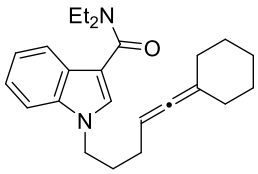
[189] X. Tang, C. Zhu, T. Cao, et al., *Nat. Commun.* **2013**, *4*, 2450.

N,N-diethyl-1-(6-methylhepta-4,5-dien-1-yl)-1H-indole-3-carboxamide (12e)



Synthesized by following the procedure used for **12b,** using *N,N*-diethyl-1H-indole-3-carboxamide instead of *N,N*-diethyl-1H-pyrrole-3-carboxamide. Obtained in 32% yield as yellow oil. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.77 (ddd, *J* = 7.7, 1.5, 0.8 Hz, 1H), 7.39 – 7.31 (m, 2H), 7.20 – 7.14 (m, 1H), 4.97 (td, *J* = 5.9, 2.9 Hz, 1H), 4.17 (t, *J* = 6.7 Hz, 2H), 3.57 (q, *J* = 7.1 Hz, 4H), 2.05 – 1.89 (m, 4H), 1.71 (d, *J* = 3.0 Hz, 6H), 1.22 (t, *J* = 7.1 Hz, 6H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 202.02 (C), 166.88 (CO), 135.78 (C), 128.37 (CH), 126.87 (C), 122.20 (CH), 120.99 (CH), 120.51 (CH), 111.26 (C),109.66 (CH), 96.02 (C), 87.44 (CH), 45.72 (CH_2), 41.28 (CH_2 amide), 29.14 (CH_2), 26.06 (CH_2), 20.73 (CH_3), 13.89 (CH_3 amide). **HRMS** [APCI]: *m/z* calculated for $C_{21}H_{29}N_2O$ [M+H]+: 325.2274, found 325.2274.

1-(5-cyclohexylidenepent-4-en-1-yl)-*N,N*-diethyl-1H-indole-3-carboxamide (12f)

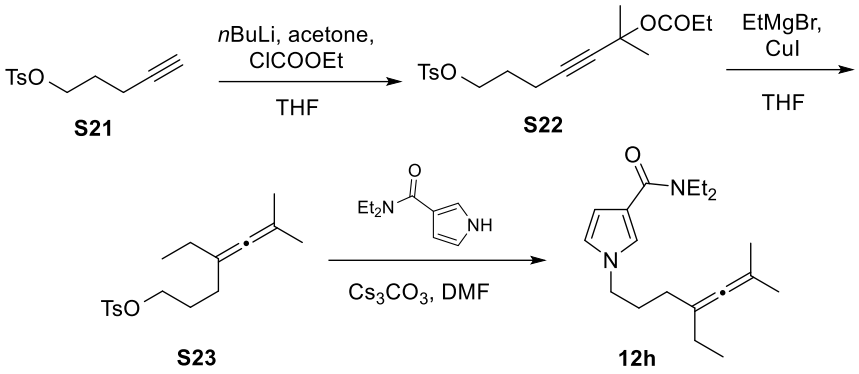


Synthesized by following the procedure used for **12b,** using cyclohexanone instead of acetone and *N,N*-diethyl-1H-indole-3-carboxamide instead of *N,N*-diethyl-1H-pyrrole-3-carboxamide. Obtained in 34% yield as yellow oil. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.70 (d, *J* = 7.9 Hz, 1H), 7.30 – 7.25 (m, 2H), 7.17 (t, *J* = 7.7 Hz, 1H), 7.10 (t, *J* = 7.5 Hz, 1H), 4.91 (dq, *J* = 6.2, 2.9 Hz, 1H), 4.09 (t, *J* = 6.5 Hz, 2H), 3.49 (q, *J* = 7.1 Hz, 4H), 2.05 (m, 4H), 1.96 – 1.84 (m, 4H), 1.51 (m, 4H), 1.45 (m, 2H), 1.14 (t, *J* = 7.1 Hz, 6H) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$) δ 197.69 (C), 165.85 (CO), 134.86 (C), 127.24 (CH), 125.92 (C), 121.17 (CH), 119.97 (CH), 119.46 (CH), 110.42 (C), 108.61 (CH), 102.43 (C), 86.23 (CH), 44.62 (CH_2), 40.28 (CH_2 amide), 30.74 (CH_2), 28.11 (CH_2), 26.43 (CH_2), 25.17 (CH_2), 25.08 (CH_2), 12.83 (CH_3 amide) ppm. **HRMS** [APCI]: *m/z* calculated for $C_{24}H_{33}N_2O$ [M+H]+: 365.2587, found 365.2590.

Synthesis of precursors 12a and 12g-l

Precursors bearing tetrasubstituted allenes of this type were prepared following analogous procedures employed for the synthesis of compound **7o** (page 327). Exemplified for **12h**.

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Pent-4-yn-1-yl 4-methylbenzenesulfonate (**S21**, prepared following previously reported procedures, 3.07 g, 12.7 mmol) was dissolved in THF (113 mL) and cooled to -78 ºC, then *n*BuLi was added (5.3 mL, 2.5 M in THF, 13.4 mmol). After 10 minutes, acetone was added (1.1 mL, 15.2 mmol) and the reaction was gradually warmed to *rt.* The reaction was followed by TLC, when all the starting material was consumed, ethylchloroformate (3.6 mL, 38.1 mmol) was added. After 1-2h, the reaction was quenched with water (500 mL), and the reaction was extracted with Et_2O (3 x 300 mL) and the combined organic phases were washed with NaCl (sat.), dried and concentrated to yield a crude yellow residue that was purified by flash column chromatography (from 9:1 to 8:2 hexanes/EtOAc) to afford **2-methyl-7-(tosyloxy)hept-3-yn-2-yl propionate** (**S22**, 3.42 g, 73 % yield), as yellow oil. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.84 – 7.75 (d, 2H), 7.39 – 7.30 (d, 2H), 4.21 – 4.08 (m, 4H), 2.44 (s, 3H), 2.27 (t, *J* = 6.9 Hz, 2H), 1.83 (m, 2H), 1.61 (s, 6H), 1.29 (t, *J* = 7.1 Hz, 3H) ppm. **^{13}C NMR** (75 MHz, $CDCl_3$) δ 152.86 (CO), 144.69 (C), 133.18 (C), 129.84 (CH), 127.88 (CH), 82.78 (C), 82.08 (C), 74.23 (C), 68.92 (CH_2), 63.39 (CH_2), 28.99 (CH_3), 27.87 (CH_2), 21.59 (CH_3), 14.98 (CH_2), 14.22 (CH_3) ppm.

CuI (1.78 g, 9.3 mmol) was suspended in anhydrous THF (93 mL) and cooled to 0 ºC, then EtMgBr (6.2 mL, 3 M in THF, 18.6 mmol) was added. After 10 minutes, **2-methyl-7-(tosyloxy)hept-3-yn-2-yl propionate** (**S22**, 3.42 g, 9.3 mmol) dissolved in 20 mL of THF was added to the mixture. When TLC indicates that the reaction is finished (typically after 20 minutes), 300 mL of saturated solution of NH_4Cl were added. The mixture was extracted with Et_2O (3 x 300 mL), and the combined organic phases were washed with NaCl (sat.), dried and concentrated to yield a crude yellow residue that was purified by flash column chromatography (from 19:1 to 9:1 hexanes/EtOAc) to afford **4-ethyl-6-methylhepta-4,5-dien-1-yl 4-methylbenzenesulfonate** (**S23**, 2.13 g, 74%), as yellow oil.[190] **^{1}H NMR** (300 MHz), ^{13}C NMR (75 MHz, $CDCl_3$) δ 197.96 (C), 144.70 (C), 133.55

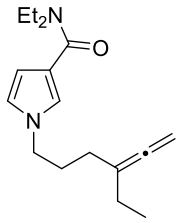
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[190] Procedure adapted from: C.-H. Ting, Y.-L. Hsu, and R.-S. Liu, *Chem. Commun.* **2012**, *48*, 6577–6579.

(C), 129.91 (CH), 128.04 (CH), 102.66 (C), 97.56 (C), 70.59 (CH_2), 28.44 (CH_2), 27.17 (CH_2), 26.38 (CH_2), 21.74 (CH_3), 21.00 (CH_3), 12.43 (CH_3) ppm.

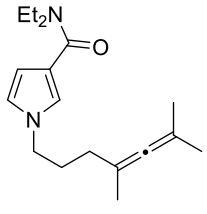
4-ethyl-6-methylhepta-4,5-dien-1-yl 4-methylbenzenesulfonate (**S23**, 1.89 g, 6.2 mmol) was added to a solution of *N,N*-diethyl-1H-pyrrole-3-carboxamide (1.23 g, 7.4 mmol) and Cs_2CO_3 (3.65 g, 11.2 mmol) in DMF (17.6 mL). The reaction mixture was stirred at 55 ºC for 16 h, allowed to cool to *rt* and water (400 mL) was added. The mixture was extracted with EtOAc (5 x 200 mL). The organic phase was dried, concentrated and the crude residue was purified by flash chromatography to give ***N,N*-diethyl-1-(4-ethyl-6-methylhepta-4,5-dien-1-yl)-1H-pyrrole-3-carboxamide** (**12h**) as yellow oil in 59% yield. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.07 – 7.02 (m, 1H), 6.55 (dd, *J* = 2.8, 2.3 Hz, 1H), 6.32 (dd, *J* = 2.8, 1.8 Hz, 1H), 3.86 (t, *J* = 6.9 Hz, 2H), 3.54 (q, *J* = 7.1 Hz, 4H), 1.94 – 1.85 (m, 6H), 1.70 (s, 6H), 1.22 (t, *J* = 7.1 Hz, 6H), 0.96 (t, *J* = 7.4 Hz, 3H) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$) δ 198.18 (C), 166.60 (CO), 123.65 (CH), 120.38 (CH), 119.37 (C), 108.65 (CH), 102.70 (C), 97.10 (C), 49.22 (CH_2), 41.48 (CH_2 amide), 29.50 (CH_2), 29.31 (CH_2), 26.30 (CH_2), 20.93 (CH_3), 13.73 (CH_3 amide), 12.29 (CH_3) ppm. **HRMS** [APCI]: *m/z* calculated for $C_{19}H_{31}N_2O$ [M+H]+: 303.2431, found 303.2434.

***N,N*-Diethyl-1-(4-ethylhexa-4,5-dien-1-yl)-1H-pyrrole-3-carboxamide (12a)**



Synthesized by following an analogous procedure to the one used for **12h.** Obtained in 34% yield as yellow oil. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.07 (t, *J* = 2.0 Hz, 1H), 6.56 (t, *J* = 2.6 Hz, 1H), 6.32 (dd, *J* = 2.8, 1.8 Hz, 1H), 4.79 – 4.69 (m, 2H), 3.93 – 3.84 (m, 2H), 3.53 (q, *J* = 7.1 Hz, 4H), 1.97 – 1.86 (m, 6H), 1.22 (t, *J* = 7.1 Hz, 6H), 1.00 (t, *J* = 7.4 Hz, 3H) ppm. **^{13}C NMR** (75 MHz, $CDCl_3$) δ 205.37 (C), 166.75 (CO), 124.09 (CH), 120.67 (CH), 119.23 (C), 108.85 (CH), 104.04 (C), 77.36 (CH_2), 49.75 (CH_2), 42.59 (CH_2 amide), 29.12 (CH_2), 28.71 (CH_2), 25.42 (CH_2), 13.03 (CH_3 amide), 12.22 (CH_3) ppm. **HRMS** [APCI]: *m/z* calculated for $C_{17}H_{27}N_2O$ [M+H]$^+$: 275.2118, found 275.2126. **NMR spectra at page 497.**

1-(4,6-dimethylhepta-4,5-dien-1-yl)-*N,N*-diethyl-1H-pyrrole-3-carboxamide (12g)

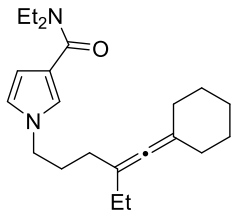


Synthesized by following an analogous procedure to the used for **12h**. Obtained in 45% yield as a yellow oil. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.26 (s, 1H), 6.77 (t, *J* = 2.5 Hz, 1H), 6.53 (dd, *J* = 2.9, 1.8 Hz, 1H), 4.08 (t, *J* = 6.9 Hz, 2H), 3.75 (q, *J* = 7.1 Hz, 4H), 2.13 – 2.05 (m, 4H), 1.89 (s, 6H), 1.84 (s, 3H), 1.43 (t, *J* = 7.1 Hz, 6H) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$) δ 199.06 (C), 166.79 (CO), 123.82 (CH), 120.57 (CH), 119.53 (C), 108.84 (CH), 95.94 (C), 95.11 (C), 49.32 (CH_2), 41.70 (CH_2 amide), 31.08 (CH_2), 29.35 (CH_2),

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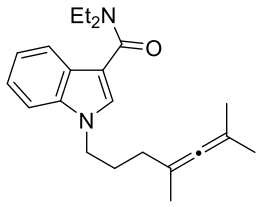
21.02 (CH_3), 19.72 (CH_3), 13.92 (CH_3 amide) ppm. **HRMS** [APCI]: *m/z* calculated for $C_{18}H_{29}CHN_2O$ [M+H]+: 289.2274, found 289.2273.

1-(4-(cyclohexylidenemethylene)hexyl)-*N,N*-diethyl-1H-pyrrole-3-carboxamide (12i)



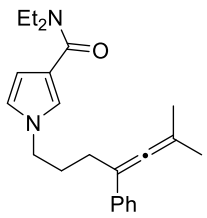
Synthesized by following an analogous procedure to the used for **12h**. Obtained in 60% yield as yellow oil. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.09 – 6.96 (m, 1H), 6.55 (d, *J* = 2.9 Hz, 1H), 6.31 (d, *J* = 2.6 Hz, 1H), 3.86 (q, *J* = 4.0 Hz, 2H), 3.60 – 3.48 (m, 4H), 2.19 – 2.01 (m, 4H), 1.95 – 1.80 (m, 6H), 1.65 – 1.46 (m, 6H), 1.21 (dt, *J* = 7.2, 3.6 Hz, 6H), 0.96 (td, *J* = 7.5, 2.9 Hz, 3H) ppm. **^{13}C NMR** (75 MHz, $CDCl_3$) δ 194.59 (C), 166.75 (CO), 123.89 (CH), 120.62 (CH), 119.30 (C), 108.76 (CH), 105.22 (C), 102.59 (C), 49.27 (CH_2), 41.70 (CH_2 amide), 32.41 (CH_2), 29.66 (CH_2), 29.34 (CH_2), 28.11 (CH_2), 26.44 (CH_2), 26.38 (CH_2), 13.91 (CH_3 amide), 12.54 (CH_3) ppm. **HRMS** [APCI]: *m/z* calculated for $C_{22}H_{35}N_2O$ $[M+H]^+$: 343.2740, found 343.2740. **NMR spectra at page 499.**

1-(4,6-dimethylhepta-4,5-dien-1-yl)-*N,N*-diethyl-1H-indole-3-carboxamide (12j)



Synthesized by following an analogous procedure to the used for **12h**. Obtained in 55% yield as yellow oil. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.77 (d, *J* = 7.8 Hz, 1H), 7.34 (d, *J* = 10.8 Hz, 2H), 7.27 – 7.21 (m, 1H), 7.17 (t, *J* = 7.4 Hz, 1H), 4.14 (t, *J* = 6.8 Hz, 2H), 3.57 (q, *J* = 7.1 Hz, 4H), 1.93 (d, *J* = 9.1 Hz, 4H), 1.70 (d, *J* = 1.2 Hz, 6H), 1.63 (s, 3H), 1.22 (t, *J* = 7.1 Hz, 6H) ppm. **^{13}C NMR** (75 MHz, $CDCl_3$) δ 198.85 (C), 166.90 (CO), 135.84 (C), 128.42 (CH), 126.87 (C), 122.19 (CH), 120.98 (CH), 120.49 (CH), 111.19 (C), 109.67 (CH), 95.81 (C), 95.16 (C), 45.92 (CH_2), 41.29 (CH_2 amide), 31.06 (CH_2), 27.87 (CH_2), 21.02 (CH_3), 19.77 (CH_3), 13.90 (CH_3 amide), ppm. **HRMS** [APCI]: *m/z* calculated for $C_{22}H_{31}N_2O$ [M+H]+: 339.2431, found 339.2434.

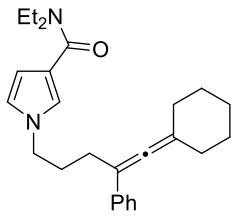
***N,N*-diethyl-1-(6-methyl-4-phenylhepta-4,5-dien-1-yl)-1H-pyrrole-3-carboxamide (12k)**



Synthesized by following an analogous procedure to the used for **12h**. Obtained in 56% yield as yellow oil. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.37 – 7.27 (m, 4H), 7.23 – 7.16 (m, 1H), 7.09 (t, *J* = 2.0 Hz, 1H), 6.60 (t, *J* = 2.5 Hz, 1H), 6.35 (dd, *J* = 2.8, 1.7 Hz, 1H), 3.95 (t, *J* = 7.1 Hz, 2H), 3.55 (q, *J* = 7.1 Hz, 4H), 2.41 (t, *J* = 7.1 Hz, 2H), 2.02 (p, *J* = 7.2 Hz, 2H), 1.85 (s, 6H), 1.24 (t, *J* = 7.1 Hz, 6H) ppm. **^{13}C NMR** (75 MHz, $CDCl_3$) δ 201.58 (C), 166.58 (CO), 137.88 (C), 128.32 (CH), 128.23 (CH), 126.40 (CH), 125.93 (CH), 123.71 (CH), 120.49 (CH), 119.33 (C), 108.77 (CH), 102.30 (C), 99.25 (C), 49.25 (CH_2), 41.49

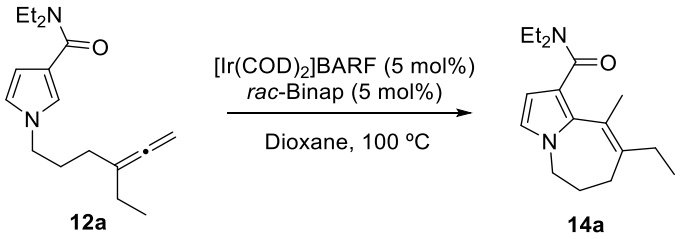
(CH_2 amide), 29.50 (CH_2), 26.85 (CH_2), 20.48 (CH_3), 13.77 (CH_3 amide) ppm. **HRMS** [APCI]: *m/z* calculated for $C_{23}H_{31}N_2O$ [M+H]+: 351.2431, found 351.2426.

1-(5-cyclohexylidene-4-phenylpent-4-en-1-yl)-*N,N*-diethyl-1H-pyrrole-3-carboxamide (12l)



Synthesized by following an analogous procedure to the used for **12h**. Obtained in 51% yield as yellow oil. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.40 – 7.34 (m, 2H), 7.31 (dd, *J* = 8.6, 7.0 Hz, 2H), 7.19 (ddt, *J* = 7.3, 5.5, 1.3 Hz, 1H), 7.08 (t, *J* = 2.0 Hz, 1H), 6.60 (t, *J* = 2.6 Hz, 1H), 6.36 (dd, *J* = 2.8, 1.7 Hz, 1H), 3.96 (t, *J* = 7.1 Hz, 2H), 3.55 (q, *J* = 7.1 Hz, 4H), 2.42 (t, *J* = 7.1 Hz, 2H), 2.34 – 2.18 (m, 4H), 2.04 (p, *J* = 7.1 Hz, 2H), 1.71 (p, *J* = 5.9 Hz, 4H), 1.67 – 1.54 (m, 2H), 1.23 (t, *J* = 7.1 Hz, 6H) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$) δ 197.01 (C), 165.58 (CO), 137.02 (C), 127.27 (CH), 125.25(CH), 124.80 (CH), 122.56 (CH), 119.42 (CH), 118.45 (C), 107.78 (CH), 105.60 (C), 101.11 (C), 48.15 (CH_2), 40.49 (CH_2 amide), 30.57 (CH_2), 28.45 (CH_2), 26.79 (CH_2), 25.88 (CH_2), 25.12 (CH_2), 12.71 (CH_3 amide) ppm. **HRMS** [APCI]: *m/z* calculated for $C_{26}H_{35}N_2O$ [M+H]+: 391.2744, found 391.2746.

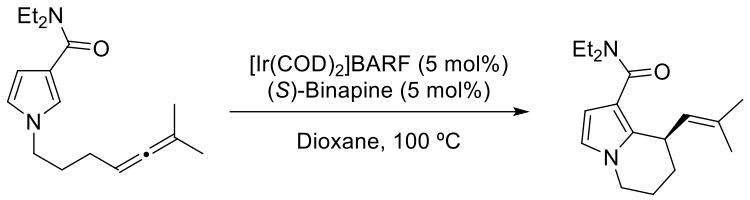
Synthesis of compound 14a by hydroarylation of precursor 12a



Prepared following general procedure for catalytic reactions (page 104)**.** $[Ir(COD)_2]BARF$ (4.5 mg, 0.004 mmol), *rac*-Binap (2.2 mg, 0.004 mmol), **12a** (19.2 mg, 0.07 mmol) and dioxane (0.56 mL) were sequentially added to a sealed tube under Argon atmosphere and stirred at 100 ºC for 16 h. The mixture was concentrated, and the crude residue was purified by flash chromatography (1:3 to 3:1 EtOAc/Hexanes) to yield ***N,N*,8-Triethyl-9-methyl-6,7-dihydro-5H-pyrrolo[1,2-a]azepine-1-carboxamide** (**14a**) in 99% yield as yellow oil. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 6.54 (d, *J* = 2.8 Hz, 1H), 6.16 (d, *J* = 2.8 Hz, 1H), 3.83 (t, *J* = 6.3 Hz, 2H), 3.56 – 3.34 (m, 4H), 2.25 (q, *J* = 7.6 Hz, 2H), 2.15 – 2.04 (m, 4H), 1.89 (s, 3H), 1.13 (s, 6H), 1.07 (t, *J* = 7.5 Hz, 3H) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$) δ 168.96 (CO), 138.61 (C), 134.55 (C), 123.81 (C), 119.54 (CH), 117.06 (C), 107.36 (CH), 46.11 (CH_2), 32.57 (CH_2), 29.75 (CH_2), 27.26 (CH_2), 17.25 (CH_3), 13.17 (CH_3) ppm. **HRMS** [APCI]: *m/z* calculated for $C_{17}H_{27}N_2O$ [M+H]$^+$: 275.2118, found 275.2125. **NMR spectra at page 502.**

Synthesis of compounds 15 by hydroarylation of 12

*(exemplified for **15b**)*

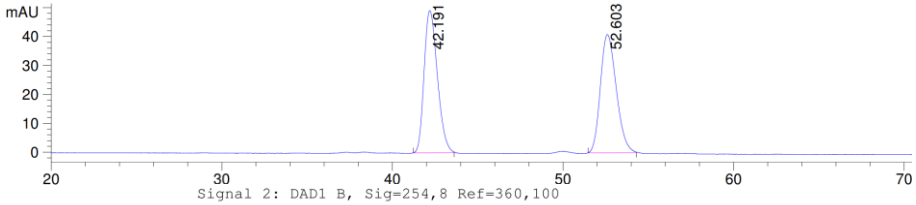


12b **15b**

Prepared following general procedure for catalytic reactions using ***7q.*** $[Ir(COD)_2]BARF$ (6.4 mg, 0.005 mmol), *(S)*-Binapine (3.7 mg, 0.005 mmol), **12b** (27.4 mg, 0.1 mmol) and dioxane (0.8 mL) were sequentially added to a sealed tube under Argon atmosphere and stirred at 100 ºC for 16 h. The mixture was concentrated, and the crude residue was purified by flash chromatography (1:3 to 3:1 EtOAc/Hexanes) to yield ***(R)-N,N*-diethyl-8-(2-methylprop-1-en-1-yl)-5,6,7,8-tetrahydroindolizine-1-carboxamide** (**15b**) in 99% yield as yellow oil. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 6.40 (t, *J* = 2.3 Hz, 1H), 6.06 (t, *J* = 2.3 Hz, 1H), 5.11 (d, *J* = 9.5 Hz, 1H), 4.02 – 3.95 (m, 1H), 3.89 (t, *J* = 5.8 Hz, 2H), 3.48 – 3.29 (m, 4H), 2.07 – 1.93 (m, 2H), 1.93 – 1.83 (m, 1H), 1.64 (s, 3H), 1.61 – 1.50 (m, 2H), 1.11 (t, *J* = 7.1 Hz, 6H) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$) δ 168.84 (CO), 132.00 (C), 131.17 (C), 127.33 (CH), 117.99 (CH), 116.17 (C), 107.30 (CH), 45.69 (CH_2), 41.54 (CH_2 amide), 32.60 (CH), 28.60 (CH_2), 25.89 (CH_3), 21.85 (CH_2), 17.92 (CH_3), 13.80 (CH_3 amide) ppm. **HRMS** [APCI]: *m/z* calculated for $C_{17}H_{27}N_2O$ $[M+H]^+$: 275.2118, found 275.2119. **NMR spectra at page 503.**

Enantioselectivity was determined by chiral HPLC analysis on a Chiralpack IE3 column at *rt* (Hexane:iPrOH = 90:10, 1mL/min).

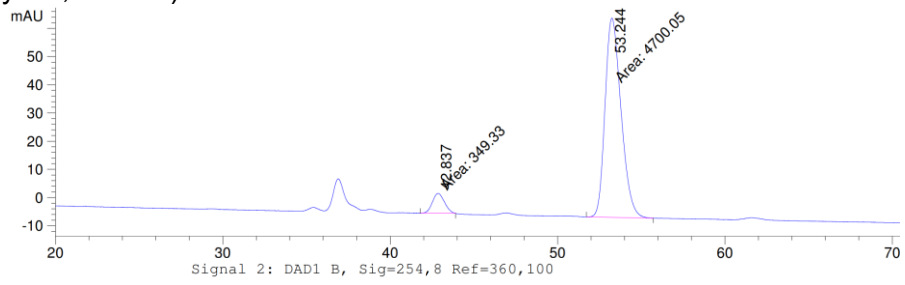
- Racemic sample prepared using $[Ir(COD)_2]BARF$ / *rac*-Binap (5 mol%) at 100 ºC.



Signal 2: DAD1 B, Sig=254,8 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	42.191	BB	0.8087	2659.39819	49.18980	50.1501
2	52.603	BB	0.9439	2643.48267	40.90613	49.8499
Totals :				5302.88086	90.09593	

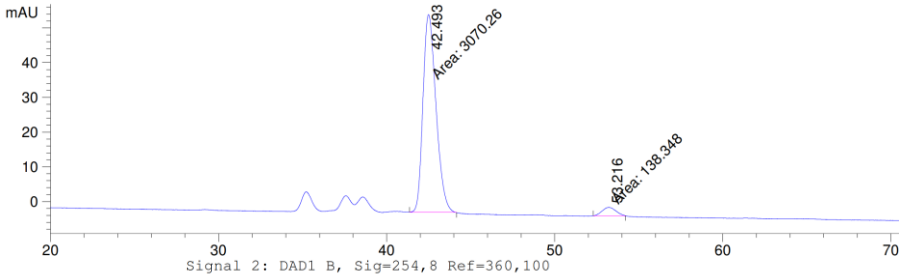
- Asymmetric sample prepared using [Ir(COD)$_2$]BARF / *(S)*-Binap (5 mol%) at 100 ºC (96% yield, 93:7 er).



Signal 2: DAD1 B, Sig=254,8 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	42.837	MM	0.8301	349.32996	7.01377	6.9183
2	53.244	MM	1.1084	4700.04834	70.67555	93.0817

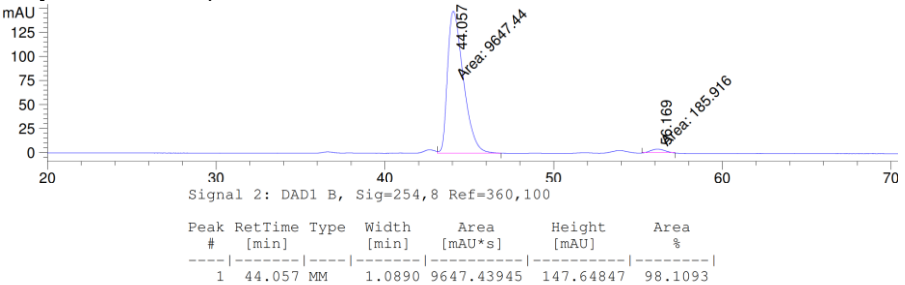
- Asymmetric sample prepared using [Ir(COD)$_2$]BARF / *(R)*-DM-Binap (5 mol%) at 100 ºC (94% yield, 96:4 er).



Signal 2: DAD1 B, Sig=254,8 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	42.493	MM	0.8985	3070.26416	56.95118	95.6882
2	53.216	MM	0.9311	138.34799	2.47648	4.3118

- Asymmetric sample prepared using [Ir(COD)$_2$]BARF / *(S)*-Binapine (5 mol%) at 100 ºC (99% yield, 98:2 er).

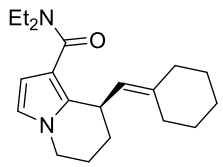


Signal 2: DAD1 B, Sig=254,8 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	44.057	MM	1.0890	9647.43945	147.64847	98.1093
2	56.169	MM	0.8747	185.91643	3.54261	1.8907

Totals : 9833.35588 151.19108

_(R)_-8-(cyclohexylidenemethyl)-_N,N_-diethyl-5,6,7,8-tetrahydroindolizine-1-carboxamide (15c)

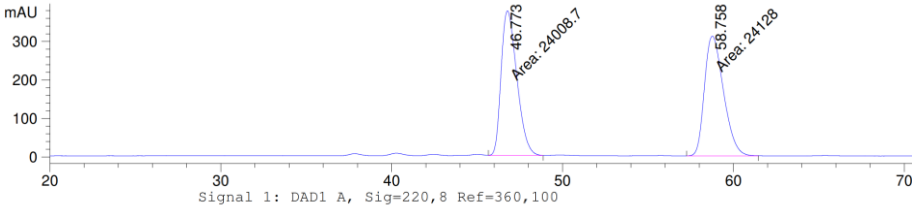


Prepared following general procedure for catalytic reactions (page 104), using ***12c***. Synthesized by following the procedure used for **15b**, using **12c**. Obtained as white solid. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 6.40 (d, *J* = 2.8 Hz, 1H), 6.07 (d, *J* = 2.7 Hz, 1H), 5.08 (d, *J* = 9.3 Hz, 1H), 4.07 (dt, *J* = 9.2, 6.5 Hz, 1H), 3.89 (t, *J* = 6.1 Hz, 2H), 3.49 – 3.32 (m, 4H), 2.33 – 2.24 (m, 1H), 2.18 – 2.07 (m, 1H), 2.07 – 1.81 (m, 6H), 1.69 – 1.60 (m, 1H), 1.60 –

1.37 (m, 6H), 1.13 (t, *J* = 7.1 Hz, 6H) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$) δ 168.75 (CO), 139.29 (C), 132.69 (C), 124.05 (CH), 118.00 (CH), 115.83 (C), 107.46 (CH), 45.70 (CH_2), 42.02 (CH_2 amide), 37.34 (CH_2), 31.49 (CH), 29.28 (CH_2), 29.15 (CH_2), 28.80 (CH_2), 28.18 (CH_2), 27.11 (CH_2), 21.66 (CH_2), 13.92 (CH_3 amide) ppm. **HRMS** [APCI]: *m/z* calculated for $C_{20}H_{31}N_2O$ $[M+H]^+$: 315.2431, found 315.2433.

Enantioselectivity was determined by chiral HPLC analysis on a Chiralpack IE3 column at *rt* (Hexane:iPrOH = 90:10, 1mL/min).

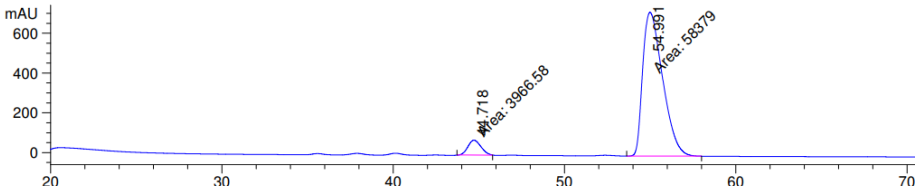
- Racemic sample prepared using [Ir(COD)$_2$]BARF / *rac*-Binap (5 mol%) at 100 ºC.



Signal 1: DAD1 A, Sig=220,8 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	46.773	MM	1.0653	2.40087e4	375.61053	49.8761
2	58.758	MM	1.2914	2.41280e4	311.39484	50.1239
Totals :				4.81366e4	687.00537	

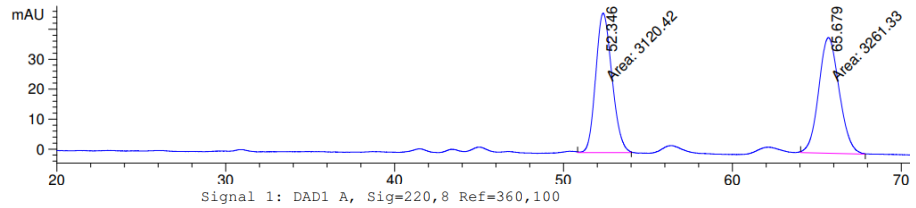
- Asymmetric sample prepared using [Ir(COD)$_2$]BARF / *(R)*-Binap (5 mol%) at 100 ºC (86% yield, 94:6 er).



Signal 1: DAD1 A, Sig=220,8 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	44.718	MM	0.8824	3966.57593	74.92372	6.3622
2	54.991	MM	1.3458	5.83790e4	722.99127	93.6378
Totals :				6.23456e4	797.91499	

- Racemic sample prepared using [Ir(COD)$_2$]BARF / *rac*-Binap (5 mol%) at 100 ºC (reinjected)

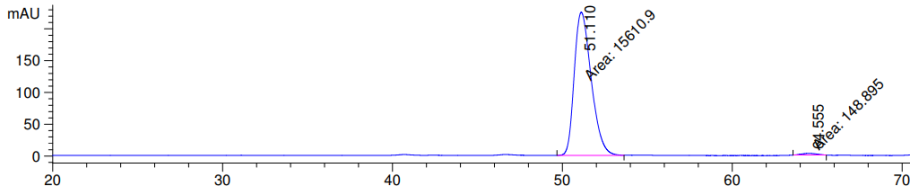


Signal 1: DAD1 A, Sig=220,8 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	52.346	MM	1.1176	3120.42432	46.53654	48.8960
2	65.679	MM	1.4073	3261.33496	38.62499	51.1040
Totals :				6381.75928	85.16153	

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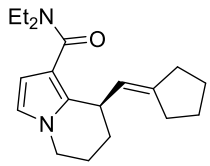
- Asymmetric sample prepared using [Ir(COD)$_2$]BARF / *(S)*-Binapine (5 mol%) at 100 ºC (91% yield, 99:1 er).



Signal 1: DAD1 A, Sig=220,8 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	51.110	MM	1.1554	1.56109e4	225.18304	99.0552
2	64.555	MM	0.9975	148.89497	2.48789	0.9448
Totals :				1.57598e4	227.67094	

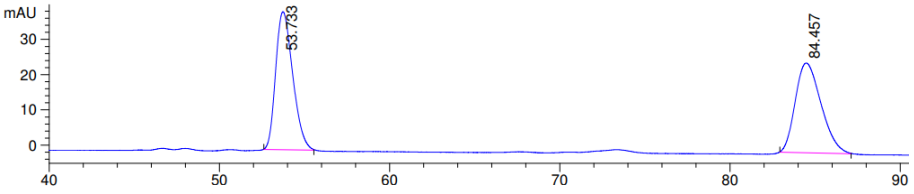
_(R)_-8-(cyclopentylidenemethyl)-_N,N_-diethyl-5,6,7,8-tetrahydroindolizine-1-carboxamide (15d)



Prepared following general procedure for catalytic reactions (page 104), using ***12d.*** Obtained as brown oil. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 6.39 (d, *J* = 2.8 Hz, 1H), 6.05 (d, *J* = 2.8 Hz, 1H), 5.23 (dp, *J* = 9.3, 2.4 Hz, 1H), 3.95 – 3.83 (m, 3H), 3.39 (qd, *J* = 7.0, 4.8 Hz, 4H), 2.48 (m, 1H), 2.21 – 2.14 (m, 3H), 2.05 – 1.93 (m, 2H), 1.90 – 1.81 (m, 1H), 1.69 – 1.63 (m, 2H), 1.60 – 1.52 (m, 3H), 1.11 (t, *J* = 7.1 Hz, 6H) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$) δ 168.88 (CO), 143.18 (C), 132.12 (C), 122.62 (CH), 117.93 (CH), 116.09 (C), 107.29 (CH), 45.69 (CH_2), 40.67 (CH_2 amide), 34.08 (CH), 33.89 (CH_2), 28.44 (CH_2), 28.32 (CH_2), 26.60 (CH_2), 26.45 (CH_2), 21.78 (CH_2), 13.88 (CH_3 amide) ppm. **HRMS** [APCI]: *m/z* calculated for $C_{19}H_{29}N_2O$ $[M+H]^+$: 301.2274, found 301.2263.

Enantioselectivity was determined by chiral HPLC analysis on a Chiralpack IE3 column at *rt* (Hexane:iPrOH = 90:10, 1mL/min).

- Racemic sample prepared using [Ir(COD)$_2$]BARF / *rac*-Binap (5 mol%) at 100 ºC.

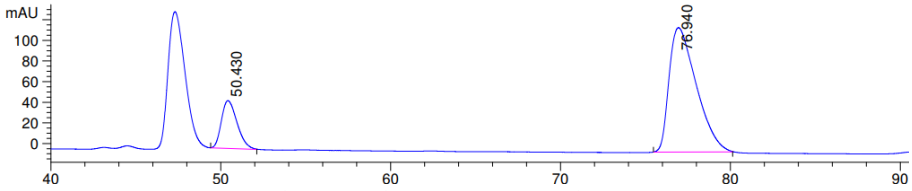


Signal 2: DAD1 B, Sig=254,8 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	53.733	BB	0.9865	2724.95166	39.12566	50.4135
2	84.457	BB	1.2405	2680.25049	25.45273	49.5865
Totals :				5405.20215	64.57839	

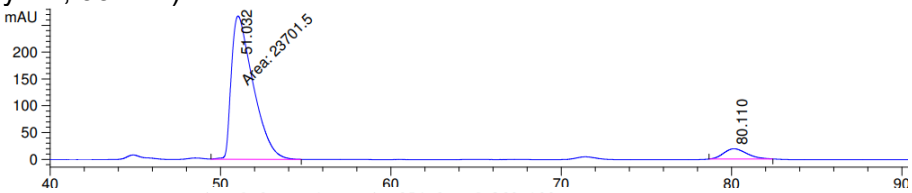
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- Asymmetric sample prepared using [Ir(COD)$_2$]BARF / *(R)*-Binap (5 mol%) at 100 ºC (94% yield, 82:18 er).



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	50.430	PB	0.9196	2959.62329	46.31308	18.0613
2	76.940	BB	1.5598	1.34269e4	120.70349	81.9387
Totals :				1.63865e4	167.01657	

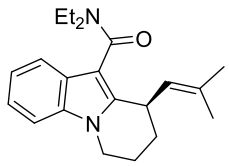
- Asymmetric sample prepared using [Ir(COD)$_2$]BARF / *(S)*-Binapine(5 mol%) at 100 ºC (59% yield, 93:7 er).



Signal 2: DAD1 B, Sig=254,8 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	51.032	MM	1.4784	2.37015e4	267.19449	92.8821
2	80.110	BB	1.1158	1816.33472	19.12859	7.1179
Totals :				2.55178e4	286.32308	

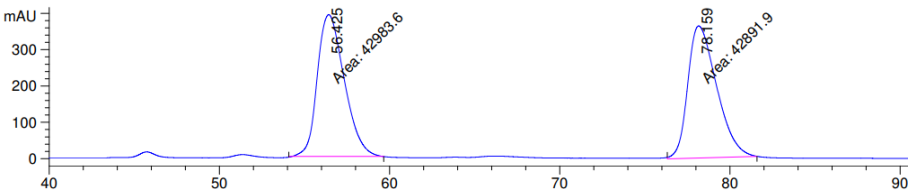
_(R)-N,N_-diethyl-9-(2-methylprop-1-en-1-yl)-6,7,8,9-tetrahydropyrido[1,2-a]indole-10-carboxamide (15e)



Prepared following general procedure for catalytic reactions (page 104), using ***12e.*** Obtained as yellow oil. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.39 (d, *J* = 7.7 Hz, 1H), 7.26 – 7.23 (m, 2H), 7.15 (ddd, *J* = 8.2, 7.1, 1.3 Hz, 1H), 7.10 (ddd, *J* = 8.0, 7.0, 1.2 Hz, 1H), 5.24 (d, *J* = 9.6 Hz, 1H), 4.21 (s, 1H), 4.05 (t, *J* = 6.2 Hz, 2H), 3.76 – 3.24 (m, 4H), 2.25 – 1.96 (m, 4H), 1.77 (s, *J* = 1.4 Hz, 3H), 1.71 – 1.64 (m, 3H), 1.31 – 0.99 (m, 6H) ppm. **HRMS** [APCI]: *m/z* calculated for $C_{21}H_{29}N_2O_1$ $[M+H]^+$: 325.2274, found 325.2274.

Enantioselectivity was determined by chiral HPLC analysis on a Chiralpack IA3 column at *rt* (Hexane:iPrOH = 80:20, 1mL/min).

Racemic sample prepared using [Ir(COD)$_2$]BARF / *rac*-Binap (5 mol%) at 100 ºC.

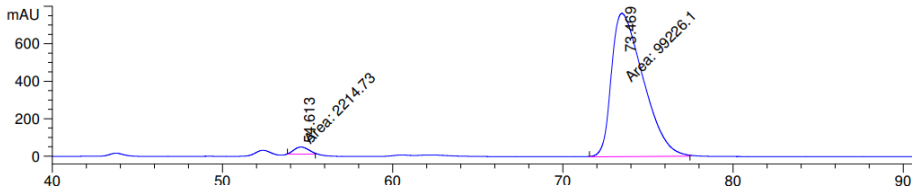


Signal 1: DAD1 A, Sig=220,8 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	56.425	MM	1.8335	4.29836e4	390.72498	50.0534
2	78.159	MM	1.9641	4.28919e4	363.96140	49.9466
Totals :				8.58755e4	754.68637	

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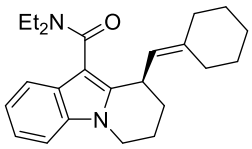
- Asymmetric sample prepared using [Ir(COD)$_2$]BARF / *(R)*-Binap (5 mol%) at 100 ºC (84% yield, 98:2 er).



Signal 1: DAD1 A, Sig=220,8 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	54.613	MM	0.9779	2214.72681	37.74796	2.1833
2	73.469	MM	2.1617	9.92261e4	765.03772	97.8167
Totals :				1.01441e5	802.78568	

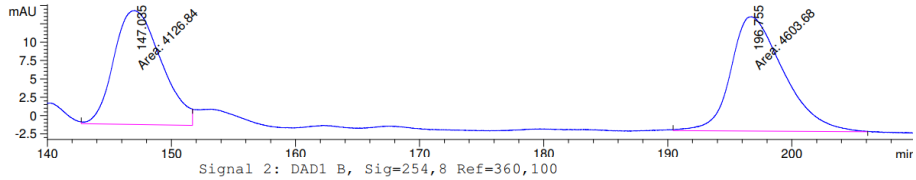
(*R*)-9-(cyclohexylidenemethyl)-*N,N*-diethyl-6,7,8,9-tetrahydropyrido[1,2-a]indole-10-carboxamide (15f)



Prepared following general procedure for catalytic reactions (page 104), using ***12f.*** Synthesized by following the procedure used for **15b**, using **12e**. Obtained as yellow oil. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.44 – 7.39 (m, 1H), 7.29 – 7.25 (m, 1H), 7.17 (ddd, *J* = 8.1, 7.0, 1.3 Hz, 1H), 7.13 (ddd, *J* = 8.2, 7.0, 1.2 Hz, 1H), 5.22 (d, *J* = 9.4 Hz, 1H), 4.31 (s, 1H), 4.18 – 3.18 (m, 6H), 2.42 – 2.17 (m, 4H), 2.14 – 1.96 (m, 4H), 1.81 – 1.41 (m, 6H), 1.31 – 1.01 (m, 6H) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$) δ 166.37 (CO), 138.87 (C), 134.15 (C), 149.95 (C), 122.04 (CH), 119.84 (CH), 119.26 (CH), 117.69 (CH), 107.79 (CH), 107.70 (C), 41.29 (CH_2), 36.13 (CH_2), 30.70 (CH_2 amide) 28.00 (CH_2), 27.77 (CH_2), 27.47 (CH_2), 26.91 (CH_2), 25.85 (CH_2), 19.82 (CH_2), 12.84 (CH_3 amide) ppm. **HRMS** [APCI]: *m/z* calculated for $C_{24}H_{33}N_2O$ [M+H]+: 365.2587, found 365.2591.

Enantioselectivity was determined by chiral HPLC analysis on a Chiralpack IF3 column at *rt* (Hexane:iPrOH = 95:5, 1mL/min).

- Racemic sample prepared using [Ir(COD)$_2$]BARF / *rac*-Binap (5 mol%) at 100 ºC.

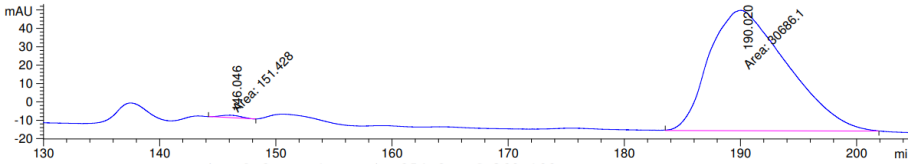


Signal 2: DAD1 B, Sig=254,8 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	147.035	MF	4.4338	4126.84473	15.51278	47.2691
2	196.755	MM	4.9253	4603.68066	15.57831	52.7309
Totals :				8730.52539	31.09109	

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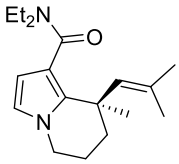
- Asymmetric sample prepared using [Ir(COD)$_2$]BARF / *(R)*-Binap (5 mol%) at 100 ºC (88% yield, 99:1 er).



Signal 2: DAD1 B, Sig=254,8 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	146.046	MM	1.8979	151.42764	1.32980	0.4911
2	190.020	MM	7.8078	3.06861e4	65.50294	99.5089
Totals :				3.08375e4	66.83274	

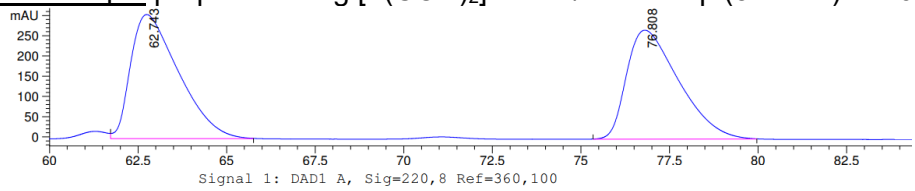
_(R)-N,N_-diethyl-8-methyl-8-(2-methylprop-1-en-1-yl)-5,6,7,8-tetrahydroindolizine-1-carboxamide (15g)



Prepared following general procedure for catalytic reactions (page 104), using ***12g.*** Obtained as yellow oil. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 6.48 – 6.27 (m, 1H), 5.97 (dd, *J* = 2.9, 1.0 Hz, 1H), 5.33 (dt, *J* = 2.8, 1.5 Hz, 1H), 3.97 – 3.70 (m, 2H), 3.31 (ddt, *J* = 154.7, 14.0, 7.0 Hz, 4H), 2.03 – 1.77 (m, 3H), 1.65 – 1.59 (m, 1H), 1.58 (s, 3H) 1.54 (s, 3H), 1.16 (d, *J* = 1.4 Hz, 3H), 1.09 (t, *J* = 7.0 Hz, 6H) δ ppm. **^{13}C NMR** (126 MHz, $CDCl_3$) δ 169.00 (CO), 136.30 (C), 134.26 (CH), 131.01 (C), 117.00 (CH), 114.70 (C), 107.43 (CH), 45.70 (CH_2), 36.61 (C), 36.24 (CH_2), 29.87 (CH_3), 27.11 (CH_3), 20.17 (CH_2), 18.38 (CH_3), 13.36 (CH_3 amide) ppm. **HRMS** [APCI]: *m/z* calculated for $C_{18}H_{29}N_2O$ [M+H]+: 289.2274, found 289.2280.

Enantioselectivity was determined by chiral HPLC analysis on a Chiralpack IE3 column at *rt* (Hexane:iPrOH = 95:5, 1mL/min).

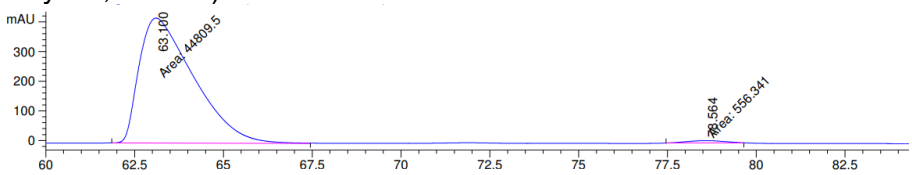
- Racemic sample prepared using [Ir(COD)$_2$]BARF / rac-Binap (5 mol%) at 100 ºC.



Signal 1: DAD1 A, Sig=220,8 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	62.743	VB	1.3930	2.88781e4	307.10840	51.1959
2	76.808	BB	1.4883	2.75290e4	269.37021	48.8041
Totals :				5.64070e4	576.47861	

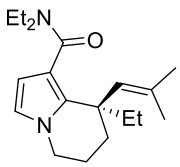
- Asymmetric sample prepared using [Ir(COD)$_2$]BARF / *(S)*-Binapine (5 mol%) at 100 ºC (89% yield, 99:1 er).



Signal 1: DAD1 A, Sig=220,8 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	63.100	MM	1.7711	4.48095e4	421.66492	98.7737
2	78.564	MM	1.2049	556.34082	7.69535	1.2263
Totals :				4.53658e4	429.36027	

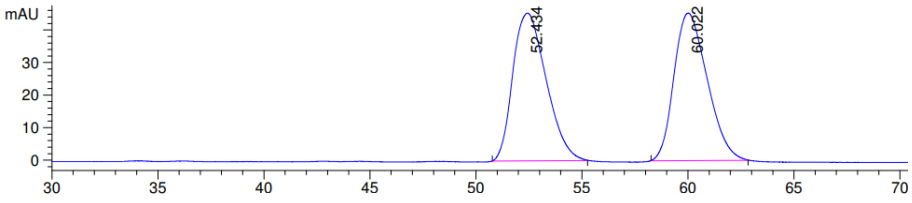
***(R)-N,N,8*-triethyl-8-(2-methylprop-1-en-1-yl)-5,6,7,8-tetrahydroindolizine-1-carboxamide (15h)**



Prepared following general procedure for catalytic reactions (page 104), using ***12h.*** Obtained as white solid. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 6.32 (d, *J* = 2.8 Hz, 1H), 5.96 (d, *J* = 2.9 Hz, 1H), 5.35 (p, *J* = 1.4 Hz, 1H), 3.99 – 3.69 (m, 2H), 3.46 – 3.10 (m, 4H), 2.19 (dq, *J* = 14.7, 7.4 Hz, 1H), 1.94 – 1.61 (m, 5H), 1.58 (d, *J* = 1.4 Hz, 3H), 1.13 (d, *J* = 1.3 Hz, 3H), 1.07 (t, *J* = 7.1 Hz, 6H), 0.78 (t, *J* = 7.4 Hz, 3H) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$) δ 169.00 (CO), 136.34 (C), 132.16 (CH), 131.15 (C), 117.08 (CH), 114.60 (C), 107.46 (CH), 45.76 (CH_2), 40.09 (C), 32.68 (CH_2), 30.18 (CH_2), 27.40 (CH_3), 19.79 (CH_2), 18.63 (CH_3), 13.36 (CH_3 amide), 8.83 (CH_3) ppm. **HRMS** [APCI]: *m/z* calculated for $C_{19}H_{31}N_2O$ [M+H]+: 303.2431, found 303.2428.

Enantioselectivity was determined by chiral HPLC analysis on a Chiralpack IF3 column at *rt* (Hexane:iPrOH = 98:2, 1mL/min).

- Racemic sample prepared using [Ir(COD)$_2$]BARF / *rac*-Binap (5 mol%) at 100 ºC.

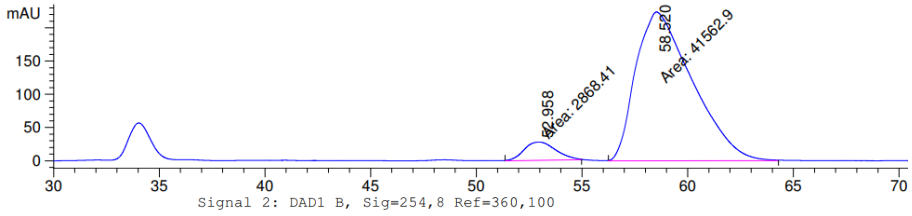


Signal 2: DAD1 B, Sig=254,8 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	52.434	BB	1.3521	4973.46045	45.39774	50.1660
2	60.022	BB	1.3074	4940.54980	45.33421	49.8340
Totals :				9914.01025	90.73196	

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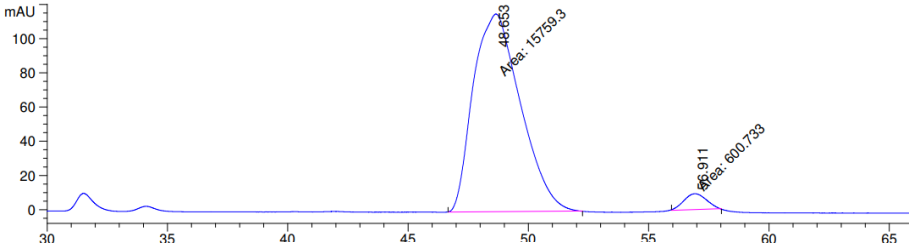
- Asymmetric sample prepared using [Ir(COD)$_2$]BARF / *(S)*-Binap (5 mol%) at 100 ºC (88% yield, 94:6 er).



Signal 2: DAD1 B, Sig=254,8 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	52.958	MM	1.7399	2868.41113	27.47628	6.4558
2	58.520	MM	3.0951	4.15629e4	223.80704	93.5442

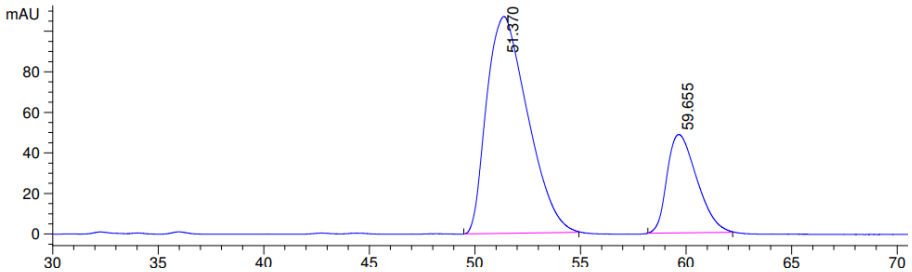
- Asymmetric sample prepared using [Ir(COD)$_2$]BARF / *(R)*-DM-Garphos (5 mol%) at 100 ºC (83% yield, 96:4 er).



Signal 2: DAD1 B, Sig=254,8 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	48.653	MM	2.2713	1.57593e4	115.64205	96.3280
2	56.911	MM	1.0820	600.73254	9.25376	3.6720

- Asymmetric sample prepared using [Ir(COD)$_2$]BARF / *(R)*-BTFM-Garphos (5 mol%) at 100 ºC (98% yield, 75:15 er).

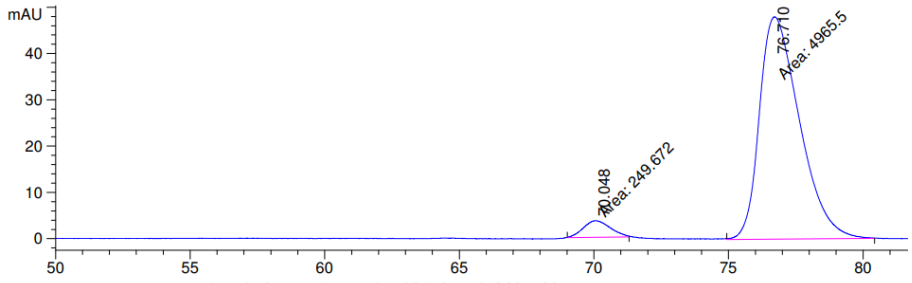


Signal 2: DAD1 B, Sig=254,8 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	51.370	PB	1.7157	1.44323e4	106.99685	75.1563
2	59.655	BB	1.2087	4770.73389	48.53700	24.8437

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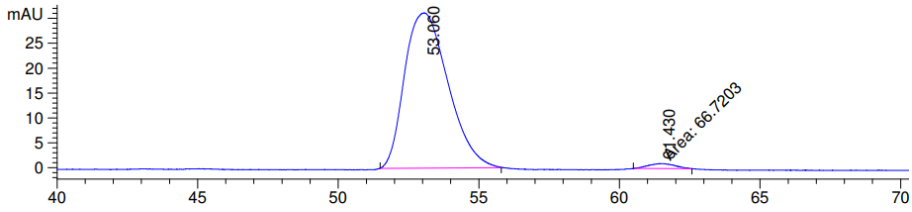
- Asymmetric sample prepared using [Ir(COD)$_2$]BARF / *(S)*-Tol-Binap (5 mol%) at 100 ºC (85% yield, 95:5 er).



Signal 2: DAD1 B, Sig=254,8 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	70.048	MM	1.1647	249.67151	3.57276	4.7874
2	76.710	MM	1.7231	4965.49512	48.02765	95.2126

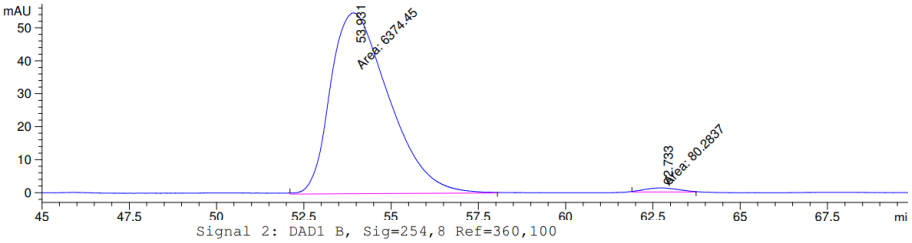
- Asymmetric sample prepared using [Ir(COD)$_2$]BARF / *(R)*-DM-Binap (5 mol%) at 100 ºC (93% yield, 98:2 er).



Signal 2: DAD1 B, Sig=254,8 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	53.060	BB	1.2735	3356.23950	31.18677	98.0508
2	61.430	MM	1.0973	66.72029	1.01342	1.9492
Totals :				3422.95979	32.20019	

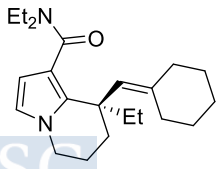
- Asymmetric sample prepared using [Ir(COD)$_2$]BARF / *(R)*-DM-Binap (5 mol%) at 80 ºC (52% yield, 99:1 er).



Signal 2: DAD1 B, Sig=254,8 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	53.931	MM	1.9384	6374.45459	54.80994	98.7562
2	62.733	MM	1.0966	80.28365	1.22020	1.2438
Totals :				6454.73824	56.03015	

_(R)_-8-(cyclohexylidenemethyl)-_N,N_,8-triethyl-5,6,7,8-tetrahydroindolizine-1-carboxamide (15i)

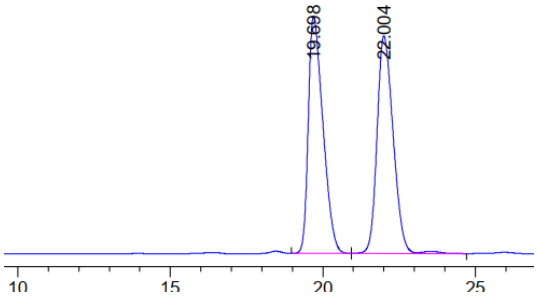


Prepared following general procedure for catalytic reactions (page 104), using ***12i.*** Obtained as white solid. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 6.38 (d, *J* = 2.8 Hz, 1H), 6.03 (d, *J* = 3.0 Hz, 1H), 5.38 (s, 1H), 3.97 – 3.86 (m, 2H), 3.50 (dq, *J* = 14.2, 7.1 Hz, 2H), 3.26 (dd, *J* = 13.9, 7.0 Hz, 2H), 2.28 (dq, *J* = 14.7, 7.4 Hz, 1H), 2.11 – 2.04 (m, 1H), 1.97 – 1.84 (m, 5H), 1.78

– 1.64 (m, 3H), 1.61 – 1.51 (m, 2H), 1.48 – 1.41 (m, 1H), 1.39 – 1.31 (m, 2H), 1.23 (dd, *J* = 8.1, 4.3 Hz, 1H), 1.15 (t, *J* = 7.1 Hz, 6H), 0.87 – 0.82 (m, 3H) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$) δ 169.07 (CO), 139.46 (C), 137.18 (C), 129.39 (CH), 117.24 (CH), 114.53 (C), 107.69 (CH), 45.97 (CH_2), 40.73 (CH_2 amide), 40.09 (C), 38.78 (CH_2), 32.88 (CH_2), 31.23 (CH_2), 30.14 (CH_2), 29.16 (CH_2), 27.81 (CH_2), 27.00 (CH_2), 20.04 (CH_2), 13.58 (CH_3 amide), 9.10 (CH_3) ppm. **HRMS** [APCI]: *m/z* calculated for $C_{22}H_{35}N_2O$ [M+H]+: 343.2744, found 343.2740. **NMR spectra at page 504.**

Enantioselectivity was determined by chiral HPLC analysis on a Chiralpack IG3 column at *rt* (Hexane:iPrOH = 95:5, 1mL/min).

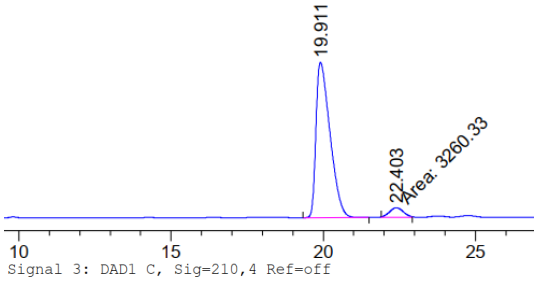
- Racemic sample prepared using [Ir(COD)$_2$]BARF / *rac*-Binap (5 mol%) at 100 ºC.



Signal 3: DAD1 C, Sig=210,4 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	19.698	BB	0.5083	4.67443e4	1404.46521	49.5968
2	22.004	BV R	0.5679	4.75042e4	1287.45947	50.4032
Totals :				9.42485e4	2691.92468	

- Asymmetric sample prepared using [Ir(COD)$_2$]BARF / *(R)*-DM-Binap (5 mol%) at 100 ºC (73% yield, 94:6 er)

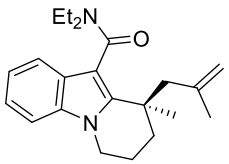


Signal 3: DAD1 C, Sig=210,4 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	19.911	BB	0.4952	5.34849e4	1671.87854	94.2544
2	22.403	MM	0.5266	3260.33276	103.18930	5.7456
Totals :				5.67453e4	1775.06784	

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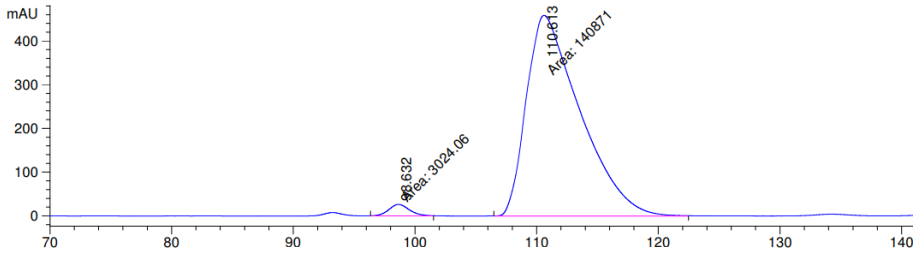
(R)-*N,N*-diethyl-9-methyl-9-(2-methylallyl)-6,7,8,9-tetrahydropyrido[1,2-a]indole-10-carboxamide (15j')



Prepared following general procedure for catalytic reactions (page 104), using ***12r.*** Obtained as yellow oil. **^{1}H NMR** (500 MHz, DMSOd, 100 ºC) δ 7.77 – 7.72 (d, *J* = 7.8 Hz, 1H), 7.66 (d, *J* = 7.8 Hz, 1H), 7.51 (ddt, *J* = 8.1, 7.0, 1.0 Hz, 1H), 7.44 (t, *J* = 7.4 Hz, 1H), 5.23 (dd, *J* = 2.6, 1.4 Hz, 1H), 5.05 (d, *J* = 2.5 Hz, 1H), 4.44 (t, *J* = 5.9 Hz, 2H), 3.80 (d, *J* = 42.0 Hz, 4H), 3.15 – 2.96 (m, 2H), 2.60 – 2.33 (m, 4H), 2.03 (s, 3H), 1.80 (s, 3H), 1.51 (dt, *J* = 35.1, 7.4 Hz, 6H) ppm. **^{13}C NMR** (126 MHz, DMSOd, 100 ºC) δ 167.02 (CO), 142.23 (C), 141.97 (C), 133.96 (C), 125.13 (C), 120.28 (CH), 119.34 (CH), 117.40 (CH), 113.85 (CH_2), 109.03 (CH), 107.07 (C), 47.53 (CH_2), 41.60 (CH_2), 35.48 (C), 32.61 (CH_2), 27.25 (CH_3), 23.56 (CH_3), 18.48 (CH_2), 12.83 (CH_3 amide) ppm. **HRMS** [APCI]: *m/z* calculated for $C_{22}H_{31}N_2O$ [M+H]+: 339.2431, found 339.2429.

Enantioselectivity was determined by chiral HPLC analysis on a Chiralpack IF3 column at *rt* (Hexane:iPrOH = 95:5, 1mL/min).

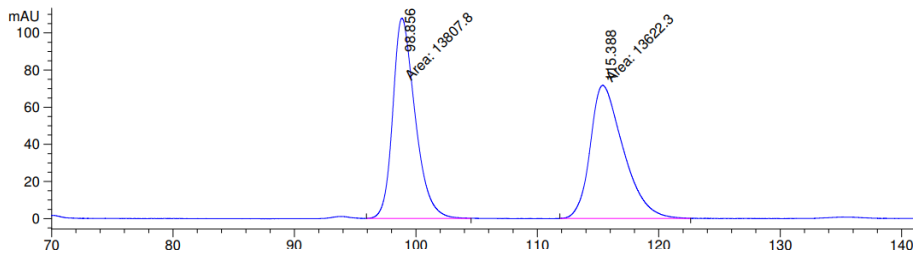
- Racemic sample prepared using [Ir(COD)$_2$]BARF / *rac*-Binap (5 mol%) at 100 ºC.



Signal 1: DAD1 A, Sig=220,8 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	98.632	MM	1.9323	3024.06201	26.08400	2.1016
2	110.613	MM	5.1199	1.40871e5	458.57755	97.8984
Totals :				1.43895e5	484.66155	

- Asymmetric sample prepared using [Ir(COD)$_2$]BARF / *(R)*-DM-Binap (5 mol%) at 100 ºC (60% yield, 98:2 er).

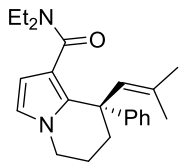


Signal 1: DAD1 A, Sig=220,8 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	98.856	MM	2.1315	1.38078e4	107.96615	50.3381
2	115.388	MM	3.1620	1.36223e4	71.80082	49.6619
Totals :				2.74300e4	179.76697	

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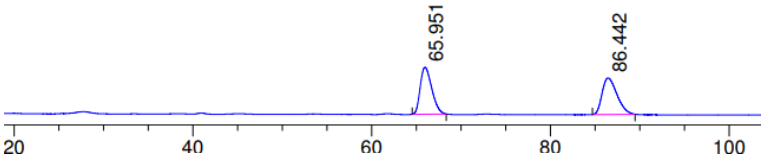
***(R)-N,N*-diethyl-8-(2-methylprop-1-en-1-yl)-8-phenyl-5,6,7,8-tetrahydroindolizine-1-carboxamide (15k)**



Prepared following general procedure for catalytic reactions (page 104), using ***12k.*** Obtained as yellow oil. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.18 – 7.13 (m, 2H), 7.08 – 7.03 (m, 3H), 6.47 (d, *J* = 2.8 Hz, 1H), 6.06 (d, *J* = 2.9 Hz, 1H), 5.78 (p, *J* = 1.5 Hz, 1H), 4.02 – 3.83 (m, 2H), 3.12 (ddq, *J* = 76.1, 14.0, 7.1 Hz, 4H), 2.22 – 2.03 (m, 2H), 1.81 – 1.72 (m, 1H), 1.68 (d, *J* = 1.5 Hz, 3H), 1.67 – 1.57 (m, 1H), 1.26 (d, *J* = 1.4 Hz, 3H), 0.95 (t, *J* = 7.0 Hz, 6H) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$) δ 166.90 (CO), 147.78 (C), 133.48 (C), 131.61 (CH), 131.25 (C), 126.99 (CH), 126.32 (CH), 124.53 (CH), 116.65 (CH), 115.45 (C), 106.62 (CH), 45.45 (C), 44.59 (CH_2), 36.74 (CH_2), 26.55 (CH_2), 18.64 (CH_2), 18.09 (CH_3), 12.44 (CH_3 amide) ppm. **HRMS** [APCI]: *m/z* calculated for $C_{23}H_{31}N_2O$ [M+H]+: 351.2431, found 351.2428.

Enantioselectivity was determined by chiral HPLC analysis on a Chiralpack IE3 column at *rt* (Hexane:iPrOH = 95:5, 1mL/min).

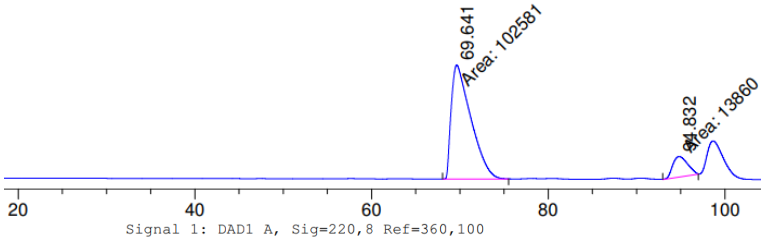
- Racemic sample prepared using [Ir(COD)$_2$]BARF / *rac*-Binap (5 mol%) at 100 ºC.



Signal 1: DAD1 A, Sig=220,8 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	65.951	BB	1.2914	7957.63965	88.13541	50.1057
2	86.442	BB	1.3878	7924.05371	68.48857	49.8943
Totals :				1.58817e4	156.62399	

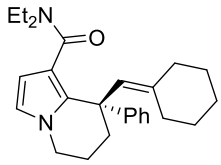
- Asymmetric sample prepared using [Ir(COD)$_2$]BARF / *(S)*-Binap (5 mol%) at 100 ºC (84% yield, 88:12 er).



Signal 1: DAD1 A, Sig=220,8 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	69.641	MM	2.5736	1.02581e5	664.31775	88.0970
2	94.832	MM	1.9387	1.38600e4	119.15489	11.9030
Totals :				1.16441e5	783.47264	

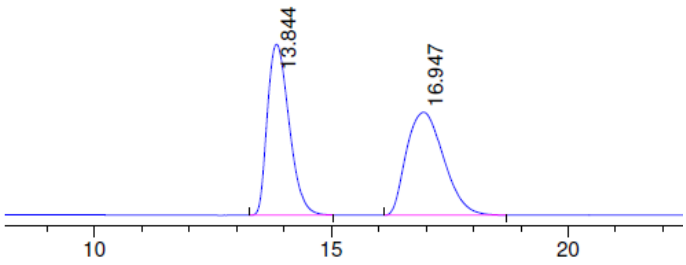
(R)-8-(cyclohexylidenemethyl)-*N,N*-diethyl-8-phenyl-5,6,7,8-tetrahydroindolizine-1-carboxamide (15l)



Prepared following general procedure for catalytic reactions (page 104), using ***12l***. Obtained as yellow oil. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.13 (dd, *J* = 8.3, 7.0 Hz, 2H), 7.08 – 7.04 (m, 2H), 7.04 – 6.99 (m, 1H), 6.42 (d, *J* = 2.8 Hz, 1H), 6.02 (d, *J* = 2.8 Hz, 1H), 5.73 (s, 1H), 4.00 – 3.79 (m, 2H), 3.09 (ddq, *J* = 80.9, 14.0, 7.1 Hz, 4H), 2.13 – 2.03 (m, 3H), 2.00 – 1.91 (m, 1H), 1.85 – 1.72 (m, 2H), 1.67 – 1.56 (m, 2H), 1.52 (m, 2H), 1.49 – 1.39 (m, 2H), 1.38 – 1.21 (m, 2H), 0.92 (t, *J* = 7.1 Hz, 6H) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$) δ 166.73 (CO), 147.70 (C), 139.30 (C), 134.30 (C), 128.70 (CH), 127.02 (CH), 126.26 (CH), 124.48 (CH), 116.55 (CH), 115.21 (C), 106.62 (CH), 45.17 (C), 44.63 (CH_2), 37.60 (CH_2), 37.46 (CH_2), 29.36 (CH_2), 28.00 (CH_2), 26.39 (CH_2), 25.72 (CH_2), 18.80 (CH_2), 12.45 (CH_3 amide) ppm. **HRMS** [APCI]: *m/z* calculated for $C_{26}H_{35}N_2O$ [M+H]+: 391.2744, found 391.2743.

Enantioselectivity was determined by chiral HPLC analysis on a Chiralpack IF3 column at *rt* (Hexane:iPrOH = 90:10, 1mL/min).

- <u>Racemic sample</u> prepared using $[Ir(COD)_2]$BARF / *rac*-Binap (5 mol%) at 100 ºC.

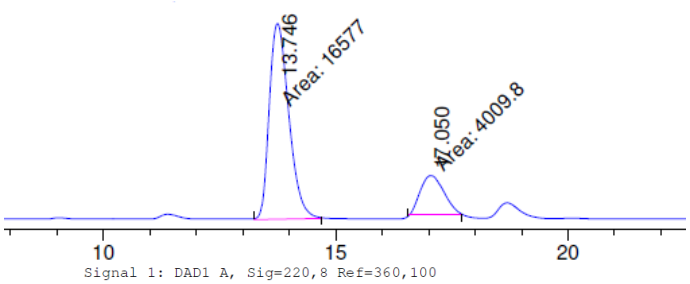


Signal 1: DAD1 A, Sig=220,8 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	13.844	PB	0.5104	2.80586e4	874.38867	49.3240
2	16.947	BB	0.8770	2.88278e4	526.33429	50.6760

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- Asymmetric sample prepared using [Ir(COD)$_2$]BARF / *(R)*-DM-Binap (5 mol%) at 100 ºC (93% yield, 81:19 er).

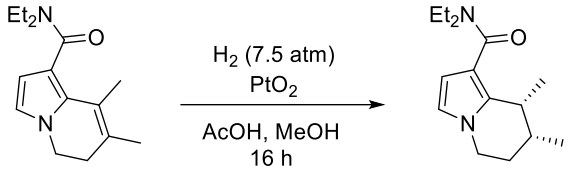


Signal 1: DAD1 A, Sig=220,8 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	13.746	MM	0.4900	1.65770e4	563.82050	80.5224
2	17.050	MM	0.5888	4009.79883	113.49632	19.4776

Transformations of compounds 8h and 8j

Synthesis of 16h by hydrogenation of 8h

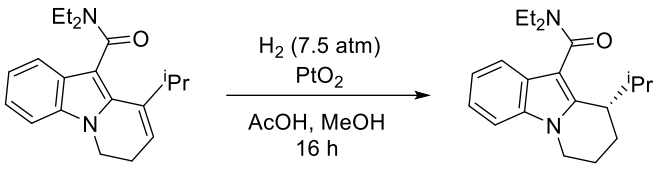


8h **16h**

PtO_2 (3.10 mg, 0.01 mmol) was added to a solution of compound **8h** (25 mg, 0.101 mmol) in MeOH (1.00 mL) and AcOH (1.00 mL, 0.01 mmol). The solution was submitted to hydrogenation using a pressured reactor at 7.50 bar for 16 h. The mixture was filtered through Celite®, the filtrate was concentrated, and the obtained residue was purified by column chromatography on silica gel (from 3:1 to 1:3 hexanes/EtOAc) to afford **(*7S*,8S**)-*N,N*-Diethyl-7,8-dimethyl-5,6,7,8-tetrahydroindolizine-1-carboxamide** (**16h**) as white solid in a quantitative yield.[191] **^{1}H NMR** (300 MHz, $CDCl_3$) δ 6.38 (d, *J* = 2.9 Hz, 1H), 6.12 (d, *J* = 2.9 Hz, 1H), 3.98 m, 1H), 3.84 (m, 1H), 3.60 – 3.34 (m, 4H), 2.13 – 1.99 (m, 1H), 1.88 (m, 1H), 1.78 – 1.62 (m, 2H), 1.18 (t, *J* = 7.1 Hz, 6H), 1.07 (d, *J* = 7.1 Hz, 3H), 1.01 (d, *J* = 6.9 Hz, 3H) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$) δ 168.62 (CO), 137.74 (C), 117.53 (CH), 113.66 (C), 107.77 (CH), 45.22 (CH_2), 31.46 (CH), 30.50 (CH), 26.24 (CH_2), 18.08 (CH_3), 15.41 (CH_3) ppm (amide signals don't appear due to rotamerism). **HRMS** [APCI]: *m/z* calculated for $C_{15}H_{25}N_2O$ $[M+H]^+$: 249.1961, found 249.1962. **NMR spectra at page 505.**

191 Procedure adapted from: B. V. M. Teodoro, J. T. M. Correia, and F. Coelho, *J. Org. Chem.* **2015**, *80*, 2529–2538.

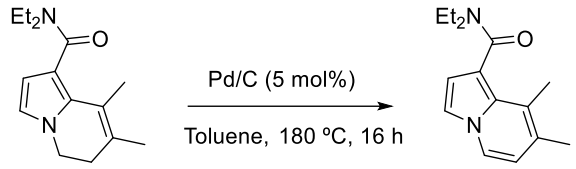
Synthesis of 16j by hydrogenation of 8j



8j **16j**

Obtained using the same reaction conditions used for **16h** but using **8j** as starting material, to obtain ***(S*)-N,N*-Diethyl-9-isopropyl-6,7,8,9-tetrahydropyrido[1,2-a]indole-10-carboxamide** (**11j**) as yellow oil in 90% yield. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.51 – 7.39 (m, 1H), 7.34 – 7.24 (m, 1H), 7.24 – 7.10 (m, 2H), 4.20 – 4.10 (m, 1H), 4.02 – 3.92 (m, 1H), 3.71 (s, 2H), 3.47 (dt, *J* = 14.1, 7.1 Hz, 3H), 2.43 – 2.27 (m, 1H), 2.27 – 2.14 (m, 1H), 2.06 – 1.85 (m, 2H), 1.85 – 1.74 (m, 1H), 1.21 (br m, 6H), 1.06 (d, *J* = 6.9 Hz, 3H), 0.82 (d, *J* = 6.9 Hz, 3H) ppm. **^{13}C NMR** (75 MHz, $CDCl_3$) δ 168.49 (CO), 135.26 (C), 126.39 (C), 120.94 (CH), 120.46 (CH), 118.95 (CH), 109.01 (CH), 107.84 (C), 42.63 (CH_2), 38.83 (CH_2 amide), 31.33 (CH), 21.66 (CH_2), 20.95 (CH), 20.49 (CH_2), 17.95 (CH_3), 13.54 (CH_3 amide) ppm. **HRMS** [APCI]: *m/z* calculated for $C_{20}H_{29}N_2O$ $[M+H]^+$: 313.2274, found 313.2276.

Synthesis of 17h by dehydrogenation of 8h



8h **17h**

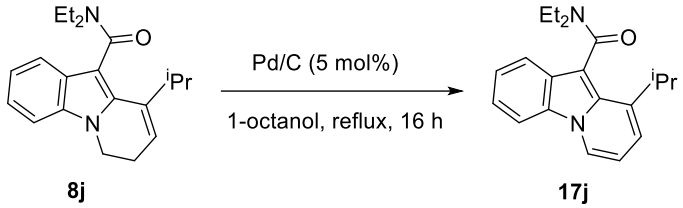
In a sealed tube was added Pd/C (10.6 mg, 0.01 mmol, 10 wt. % Pd loading) over a solution of compound **8h** (24.6 mg, 0.10 mmol), in toluene (1 mL). The reaction mixture was heated to 180 ºC for 16h. The mixture was filtered through Celite®, the filtrate was concentrated, and the obtained residue was purified by column chromatography on silica gel (from 3:1 to 1:3 hexanes/EtOAc) to afford ***N,N*-diethyl-7,8-dimethylindolizine-1-carboxamide** (**17h**) as brown oil in 90% yield.[192] **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.69 (d, *J* = 7.0 Hz, 1H), 7.18 – 7.08 (m, 1H), 6.72 – 6.60 (m, 1H), 6.34 (d, *J* = 7.0 Hz, 1H), 3.58 – 3.49 (br s, 2H), 3.34 3.25 (br s, 2H), 2.29 (s, 3H), 2.22 (s, 3H), 1.26 (br m, *J* = 6.1, 5.0 Hz, 3H), 1.41 - 1.06 (br m, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 169.60 (CO), 130.82 (C), 125.80 (C), 124.97 (C), 122.68 (CH), 115.03 (CH), 112.86 (CH), 111.58 (CH), 108.20 (C), 43.61 (CH_2 amide), 39.22 (CH_2 amide), 18.68 (CH_3), 14.63 (CH_3), 12.77 (CH_3 amide),

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[192] Procedure adapted from: O. V. Baranova, M. E. Zhidkov, and S. V. Dubovitskii, *Tetrahedron Lett.* **2011**, *52*, 2397–2398.

10.71 (CH_3 amide). **HRMS** [APCI]: *m/z* calculated for $C_{15}H_{21}N_2O$ $[M+H]^+$: 245.1648, found 245.1649. **NMR spectra at page 505**

Synthesis of 17j by dehydrogenation of 8j

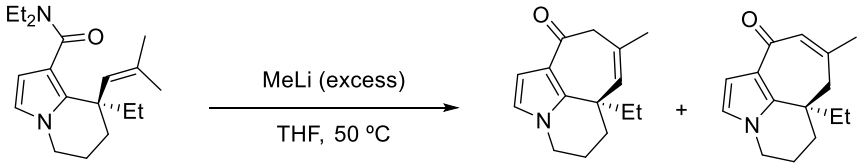


8j **17j**

Obtained using the same reaction conditions used for **17h** but using **8j** as starting material and 1-octanol (reflux) as solvent, to afford ***N,N*-diethyl-9-isopropylpyrido[1,2-a]indole-10-carboxamide** (**17j**) as brown oil in 79% yield. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.24 (d, *J* = 7.0 Hz, 1H), 7.85 (d, *J* = 8.2 Hz, 1H), 7.66 (d, *J* = 8.0 Hz, 1H), 7.37 (t, *J* = 6.9 Hz, 1H), 7.29 (d, *J* = 7.0 Hz, 2H), 6.91 (d, *J* = 6.8 Hz, 1H), 6.57 (t, *J* = 6.9 Hz, 1H), 3.91 – 3.77 (m, 1H), 3.74 – 3.60 (m, 1H), 3.60 – 3.48 (m, 1H), 3.41 – 3.30 (m, 2H), 1.39 – 1.37 (m, 6H), 1.26 (d, *J* = 6.8 Hz, 3H), 1.02 (t, *J* = 7.1 Hz, 3H) ppm. **^{13}C NMR** (75 MHz, $CDCl_3$) δ 168.19 (CO), 139.82 (C), 134.27 (C), 127.11 (C), 123.44 (CH), 121.99 (CH), 120.32 (CH), 119.11 (CH), 118.98 (CH), 110.26 (CH), 108.73 (CH), 100.36 (C), 43.60 (CH_2 amide), 38.94 (CH_2 amide), 28.47 (CH), 23.04 (CH_3), 14.31 (CH_3 amide), 12.83 (CH_3 amide) ppm. **HRMS** [APCI]: *m/z* calculated for $C_{20}H_{25}N_2O$ $[M+H]^+$: 309.1961, found 309.1954.

Transformations of compound 15h

MeLi-mediated cyclization of compound 15h

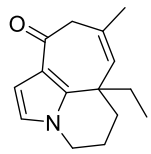


15h **18h** **18h'**

MeLi (0.46 mL, 0.74 mmol, 1.6 M in Et_2O) was slowly added to a solution of compound **15h** (45.0 mg, 0.15 mmol) in THF (0.74 mL) at 0 ºC and the mixture was stirred at 50 ºC for 16 h. The reaction was quenched with the addition of 5 mL of water, and the mixture was extracted with Et_2O (3 x 20 mL). The combined organic phases were concentrated under vacuum and the residue was purified by flash chromatography (1:10 to 1:1 EtOAc/Hexanes) to yield a 77% of **18h** together with 21% of isomerized product **18h'**, both as yellow oils.

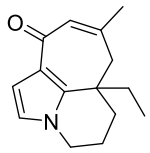
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6a-ethyl-8-methyl-5,6,6a,9-tetrahydrocyclohepta[hi]indolizin-10(4H)-one (18h)



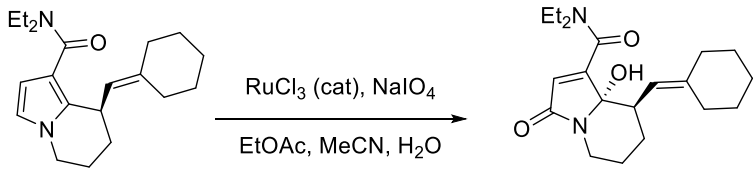
^{1}H NMR (300 MHz, $CDCl_3$) δ 6.66 (d, *J* = 3.1 Hz, 1H), 6.42 (d, *J* = 3.1 Hz, 1H), 5.39 (s, 1H), 4.06 – 3.93 (m, 1H), 3.88 – 3.73 (m, 2H), 3.05 (d, *J* = 17.0 Hz, 1H), 2.21 – 2.04 (m, 3H), 1.93 (br m, *J* = 4.8 Hz, 1H), 1.87 (s, 3H), 1.77 – 1.61 (m, 2H), 0.89 (t, *J* = 7.4 Hz, 3H) ppm. **^{13}C NMR** (75 MHz, $CDCl_3$) δ 191.55 (CO), 139.50 (C), 132.82 (C), 131.97 (CH), 120.35 (C), 120.15 (CH), 109.31 (CH), 48.83 (CH_2), 45.19 (CH_2), 39.02 (C), 30.91 (CH_2), 28.67 (CH_2), 27.02 (CH_3), 18.45 (CH_2), 9.73 (CH_3) ppm. **HRMS** [APCI]: *m/z* calculated for $C_{15}H_{20}NO$ $[M+H]^+$: 230.1539, found 230.1529. **NMR spectra at page 507.**

6a-ethyl-8-methyl-5,6,6a,7-tetrahydrocyclohepta[hi]indolizin-10(4H)-one (18h')



^{1}H NMR (300 MHz, $CDCl_3$) δ 6.70 (d, *J* = 3.0 Hz, 1H), 6.44 (d, *J* = 3.0 Hz, 1H), 6.20 (s, 1H), 4.01 (dd, *J* = 12.3, 6.0 Hz, 1H), 3.90 – 3.76 (m, 1H), 2.70 (d, *J* = 17.2 Hz, 1H), 2.25 (d, *J* = 16.4 Hz, 1H), 2.10 (dd, *J* = 13.4, 6.2 Hz, 2H), 2.03 (s, 3H), 2.01 – 1.85 (m, 3H), 1.64 (td, *J* = 14.8, 13.3, 5.9 Hz, 2H), 1.50 – 1.35 (m, 1H), 0.81 (t, *J* = 7.5 Hz, 3H) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$) δ 185.65 (CO), 148.57 (C), 143.06 (C), 131.25 (CH), 121.38 (C), 120.20 (CH), 109.98 (CH), 45.30 (CH_2), 43.41 (CH_2), 37.15 (C), 30.26 (CH_2), 29.07 (CH_3), 27.62 (CH_2), 19.30 (CH_2), 8.89 (CH_3) ppm. **HRMS** [APCI]: *m/z* calculated for $C_{15}H_{20}NO$ $[M+H]^+$: 230.1539, found 230.1540. **NMR spectra at page 509.**

Oxidation of compound 15c



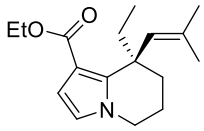
15c **19c**

To a stirred solution of $NaIO_4$ (11.2 mg, 0.05 mmol) in water (0.9 mL) was added $RuCl_3.3H_2O$ (5.1 mg, 0.023 mmol) dissolved in MeCN (1.2 mL). The resulting mixture was stirred at *rt* for 2 min and then a solution of compound **15c** (47.2 mg, 0.15 mmol) in EtOAc (1.2 mL). The reaction was monitored by TLC and when completed, the reaction was passed through a pad of celite using EtOAc (50 mL). The mixture was concentrated under vacuum and the residue was purified by flash chromatography (1:10 to 4:1 EtOAc/Hexanes) to yield **(8R,8aS)-8-(cyclohexylidenemethyl)-*N,N*-diethyl-8a-hydroxy-3-oxo-3,5,6,7,8,8a-hexahydroindolizine-1-carboxamide (19c)** in a quantitative yield as white solid. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 6.13 (s, 1H), 5.98 (s, 1H), 4.76 (d, *J* = 10.1 Hz, 1H), 4.12 (dd, *J* = 12.9, 4.6 Hz, 1H), 3.58 (tq, *J* = 14.4, 7.2 Hz, 2H), 3.29 (dq, *J* = 13.9, 7.1 Hz, 1H), 3.16 – 2.99 (m, 2H), 2.99 – 2.85 (m, 1H), 2.40 – 2.15 (m,

2H), 2.06 – 1.97 (m, 1H), 1.94 – 1.77 (m, 2H), 1.62 – 1.37 (m, 9H), 1.24 (t, *J* = 7.1 Hz, 3H), 1.18 (t, *J* = 7.1 Hz, 3H) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$) δ 166.58 (CO), 165.03 (CO), 149.99 (C), 142.38 (C), 125.81 (CH), 118.72 (CH), 91.42 (COH), 42.95 (CH_2 amide), 40.30 (CH_2 amide), 39.70 (CH), 37.52 (CH_2), 36.63 (CH_2), 29.35 (CH_2), 28.77 (CH_2), 28.10 (CH_2), 26.89 (CH_2), 26.51 (CH_2), 19.87 (CH_2), 14.76 (CH_3 amide), 12.76 (CH_3 amide) ppm. **HRMS** [APCI]: *m/z* calculated for $C_{20}H_{29}N_2O_2$ $[M-H_2O+H]^+$: 329.2224, found 329.2214. **NMR spectra at page 510.**

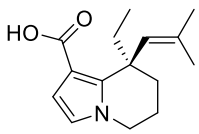
Directing group removal of compound 15h

Ethyl (R)-8-ethyl-8-(2-methylprop-1-en-1-yl)-5,6,7,8-tetrahydroindolizine-1-carboxylate (20h)



To a stirring solution of **15h** (300 mg, 0.99 mmol) in CH_3CN (7.9 mL) at rt, was added Na_2HPO_4 (352 mg, 2.48 mmol), followed by $(CH_3)_3OBF_4$ (753 mg, 3.97 mmol). After consumption of the amide was complete, as indicated by TLC analysis (2 h), a 1M NaOH solution (10 mL) was slowly added. The resulting mixture was stirred for 1 h and then extracted with EtOAc (3 x 100 mL). The combined organic phases were concentrated, and the product was isolated by flash chromatography (1:8 to 1:1 EtOAc/Hexanes). Obtained in 99% yield as pale-yellow oil. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 6.58 (d, *J* = 3.0 Hz, 1H), 6.40 (d, *J* = 3.0 Hz, 1H), 5.50 (p, *J* = 1.4 Hz, 1H), 4.16 (q, *J* = 7.1 Hz, 2H), 3.99 – 3.85 (m, 2H), 2.08 (qd, *J* = 7.5, 0.9 Hz, 2H), 2.02 – 1.79 (m, 3H), 1.71 – 1.59 (m, 4H), 1.28 (t, *J* = 7.1 Hz, 3H), 0.99 (d, *J* = 1.3 Hz, 3H), 0.83 (t, *J* = 7.5 Hz, 3H) ppm. **^{13}C NMR** (75 MHz, $CDCl_3$) δ 164.62 (CO), 141.73 (C), 132.25 (CH), 129.42 (C), 118.41 (CH), 111.59 (CH), 111.32 (C), 59.20 (CH_2), 46.62 (CH_2), 40.31 (C), 31.75 (CH_2), 31.53 (CH_2), 27.28 (C), 19.87 (CH_2), 18.24 (CH_3), 14.55 (CH_3), 9.03 (CH_3) ppm. **HRMS** [APCI]: *m/z* calculated for $C_{17}H_{26}NO_2$ $[M+H]^+$: 276.1958, found 276.1953.

***(R)*-8-ethyl-8-(2-methylprop-1-en-1-yl)-5,6,7,8-tetrahydroindolizine-1-carboxylic acid (21h)**

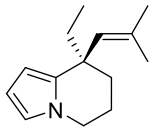


A solution of LiOH (1.89 g, 79 mmol) in water (5.2 mL) was added to a solution of **20h** (272 mg, 0.98 mmol) in MeOH (5.2 mL). The mixture was refluxed for 7 days. Then, HCl was added until pH < 2, and then extracted with EtOAc (3 x 100 mL). The combined organic phases were concentrated, and the product was isolated by flash chromatography (2:8 to 6:4 EtOAc/Hexanes). Obtained in 56% yield as yellow oil. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 6.66 (d, *J* = 3.0 Hz, 1H), 6.43 (d, *J* = 3.1 Hz, 1H), 5.51 (s, 1H), 3.94 (q, *J* = 5.5 Hz, 2H), 2.13 – 1.85 (m, 4H), 1.66 (s, 3H), 1.36 – 1.20 (m, 2H), 1.03 (s, 3H), 0.83 (t, *J* = 7.5 Hz, 3H)

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ppm. **^{13}C NMR** (75 MHz, $CDCl_3$) δ 168.88 (CO), 142.90 (C), 132.17 (CH), 130.10 (C), 118.76 (CH), 112.46 (CH), 110.42 (C), 46.70 (CH_2), 40.37 (C), 31.80 (CH_2), 31.59 (CH_2), 27.19 (CH_3), 19.88 (CH_2), 18.31 (CH_3), 9.12 (CH_3) ppm. **HRMS** [APCI]: *m/z* calculated for $C_{15}H_{22}NO_2$ [M+H]+: 248.1645 , found 248.1640. **NMR spectra at page 512.**

***(R)*-8-ethyl-8-(2-methylprop-1-en-1-yl)-5,6,7,8-tetrahydroindolizine (22h)**



A suspension of **21h** (82 mg, 0.33 mmol) and 2-aminoethanol (0.43 mL) was heated to 175 °C under a nitrogen atmosphere for 30 min. The mixture was allowed to cool to room temperature, diluted with water (5 mL) and extracted with ethyl acetate (3 x 40 mL). The combined organic phases were washed with brine, concentrated, and the product was isolated by flash chromatography (1:9 to 3:7 EtOAc/Hexanes). Obtained in 78% yield as brown oil. **^{1}H NMR** (300 MHz, CD_2Cl_2) δ 6.47 (dd, *J* = 2.7, 1.7 Hz, 1H), 6.03 (t, *J* = 3.1 Hz, 1H), 5.75 (dd, *J* = 3.6, 1.8 Hz, 1H), 5.25 (dt, *J* = 2.8, 1.4 Hz, 1H), 3.97 – 3.76 (m, 2H), 1.96 – 1.81 (m, 2H), 1.75 – 1.63 (m, 7H), 1.00 (d, *J* = 1.4 Hz, 3H), 0.89 (t, *J* = 7.4 Hz, 3H) ppm. **^{13}C NMR** (75 MHz, CD_2Cl_2) δ 135.45 (C), 133.06 (CH), 132.28 (C), 118.00 (CH), 107.81 (CH), 105.13 (CH), 45.69 (CH_2), 40.66 (C), 35.48 (CH_2), 33.16 (CH_2), 28.09 (CH_3), 20.60 (CH_2), 17.76 (CH_3), 9.29 (CH_3) ppm. **HRMS** [APCI]: *m/z* calculated for $C_{14}H_{22}N$ [M+H]+: 204.1747, found 204.1739.

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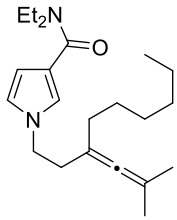
7.3. Experimental data of section 5.3

Synthesis of precursors 7o and 7p

Experimental procedures for the synthesis of precursors **7o** and **7p** are detailed in page 327.

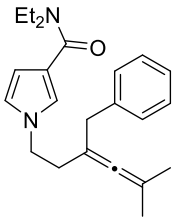
Synthesis of precursors 7p and 7u-j

_N,N_-Diethyl-1-(3-(2-methylprop-1-en-1-ylidene)nonyl)-1H-pyrrole-3-carboxamide (7u)



Synthesized by following an analogous procedure used for **7o**, using *n*HexylMgBr instead of MeMgBr. Obtained in 42% yield as yellow oil. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.05 (t, *J* = 2.0 Hz, 1H), 6.55 (t, *J* = 2.6 Hz, 1H), 6.28 (dd, *J* = 2.9, 1.8 Hz, 1H), 3.88 (t, *J* = 7.3 Hz, 2H), 3.51 (q, *J* = 7.1 Hz, 4H), 2.33 (t, *J* = 7.4 Hz, 2H), 1.87 (t, *J* = 7.0 Hz, 2H), 1.62 (s, 6H), 1.23 (dt, *J* = 20.5, 6.6 Hz, 14H), 0.92 – 0.80 (m, 3H) ppm. **^{13}C NMR** (75 MHz, $CDCl_3$) δ 198.68 (C), 166.70 (CO), 123.89 (CH), 120.48 (CH), 119.16 (C), 108.61 (CH), 98.63 (C), 97.16 (C), 48.47 (CH_2), 41.56 (CH_2 amide), 34.51 (CH_2), 33.22 (CH_2), 31.86 (CH_2), 28.94 (CH_2), 27.62 (CH_2), 22.74 (CH_2), 20.87 (CH_3), 14.16 (CH_3), 13.85 (CH_3 amide) ppm. **HRMS** [APCI]: *m/z* calculated for $C_{22}H_{37}N_2O$ $[M+H]^+$: 345.2900, found 345.2901.

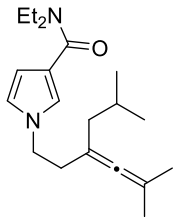
1-(3-Benzyl-5-methylhexa-3,4-dien-1-yl)-_N,N_-diethyl-1H-pyrrole-3-carboxamide (7v)



Synthesized by following an analogous procedure used for **7o**, using BnMgBr instead of MeMgBr. Obtained in 57% yield as yellow oil. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.35 – 7.17 (m, 5H), 7.06 (d, *J* = 2.2 Hz, 1H), 6.55 (d, *J* = 2.7 Hz, 1H), 6.36 – 6.27 (m, 1H), 3.90 (t, *J* = 7.3 Hz, 2H), 3.57 (q, *J* = 7.1 Hz, 4H), 3.28 (s, 2H), 2.36 (t, *J* = 7.3 Hz, 2H), 1.68 (s, 6H), 1.26 (t, *J* = 7.1 Hz, 6H) ppm. **^{13}C NMR** (75 MHz, $CDCl_3$) δ 200.04 (C), 166.69 (CO), 139.84 (C), 128.95 (CH), 128.37 (CH), 126.30 (CH), 123.91 (CH), 120.50 (CH), 119.25 (C), 108.65 (CH), 98.22 (CH), 97.28 (CH), 48.46 (CH_2), 41.57 (CH_2 amide), 40.84 (CH_2), 33.52 (CH_2), 20.82 (CH_3), 13.89 (CH_3 amide) ppm. **HRMS** [APCI]: *m/z* calculated for $C_{23}H_{31}N_2O$ $[M+H]^+$: 351.2431, found 351.2430.

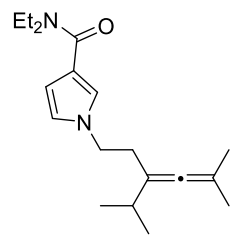
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***N,N*-Diethyl-1-(3-isobutyl-5-methylhexa-3,4-dien-1-yl)-1H-pyrrole-3-carboxamide (7w)**



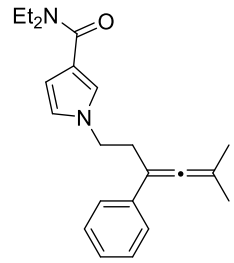
Synthesized by following an analogous procedure used for **7o**, using *i*BuMgBr instead of MeMgBr. Obtained in 51% yield as yellow oil. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.05 (t, *J* = 2.0 Hz, 1H), 6.55 (t, *J* = 2.5 Hz, 1H), 6.28 (t, *J* = 2.4 Hz, 1H), 3.89 (t, *J* = 7.5 Hz, 2H), 3.51 (q, *J* = 7.2 Hz, 4H), 2.31 (t, *J* = 7.4 Hz, 2H), 1.76 (d, *J* = 6.8 Hz, 2H), 1.63 (s, 7H), 1.20 (t, *J* = 7.1 Hz, 6H), 0.87 (d, *J* = 6.3 Hz, 6H) ppm. **^{13}C NMR** (75 MHz, $CDCl_3$) δ 199.31 (C), 166.71 (CO), 123.89 (CH), 120.48 (CH), 119.20 (C), 108.60 (CH), 97.42 (C), 96.57 (C), 48.44 (CH_2), 42.98 (CH_2), 41.53 (CH_2 amide), 34.55 (CH_2), 26.62 (CH), 22.61 (CH_3), 20.80 (CH_3), 13.86 (CH_3 amide) ppm. **HRMS** [APCI]: *m/z* calculated for $C_{20}H_{33}N_2O$ $[M+H]^+$: 317.2587, found 317.2587. **NMR spectra at page 484.**

***N,N*-Diethyl-1-(3-isopropyl-5-methylhexa-3,4-dien-1-yl)-1H-pyrrole-3-carboxamide (7x)**



Synthesized by following an analogous procedure used for **7o**, using *i*PrMgBr instead of MeMgBr. Obtained in 76% yield as yellow oil. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.07 (d, *J* = 2.3 Hz, 1H), 6.57 (t, *J* = 2.7 Hz, 1H), 6.29 (t, *J* = 2.4 Hz, 1H), 3.88 (t, *J* = 7.5 Hz, 2H), 3.52 (q, *J* = 7.1 Hz, 4H), 2.37 (t, *J* = 7.5 Hz, 2H), 2.02 (p, *J* = 6.7 Hz, 1H), 1.65 (s, 6H), 1.21 (t, *J* = 7.0 Hz, 6H), 0.96 (d, *J* = 6.7 Hz, 6H) ppm. **^{13}C NMR** (75 MHz, $CDCl_3$) δ 197.55 (C), 166.73 (CO), 123.88 (CH), 120.53 (CH), 119.25 (C), 108.64 (CH), 105.41 (C), 98.59 (C), 48.75 (CH_2), 41.57 (CH_2 amide), 32.73 (CH_2 amide), 31.94 (CH), 21.88 (CH_3), 21.01 (CH_3), 13.89 (CH_3 amide) ppm. **HRMS** [APCI]: *m/z* calculated for $C_{19}H_{31}N_2O$ $[M+H]^+$: 303.2431, found 303.2431.

***N,N*-Diethyl-1-(5-methyl-3-phenylhexa-3,4-dien-1-yl)-1H-pyrrole-3-carboxamide (7y)**

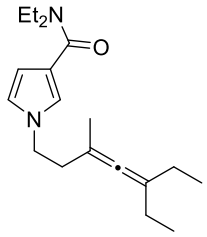


Synthesized by following an analogous procedure used for **7o**, using PhMgBr instead of MeMgBr. Obtained in 49% yield as yellow oil. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.31 – 7.26 (m, 4H), 7.19 (dd, *J* = 5.7, 3.1 Hz, 1H), 7.08 (t, *J* = 2.1 Hz, 1H), 6.59 (t, *J* = 2.6 Hz, 1H), 6.32 (dd, *J* = 2.8, 1.8 Hz, 1H), 5.39 (dq, *J* = 6.6, 3.3 Hz, 1H), 3.98 (t, *J* = 7.0 Hz, 2H), 3.53 – 3.46 (m, 4H), 2.56 (q, *J* = 6.9 Hz, 2H), 2.04 (d, *J* = 2.9 Hz, 3H), 1.24 – 1.18 (m, 6H) ppm. **^{13}C NMR** (75 MHz, $CDCl_3$) δ 204.85 (C), 166.62 (CO), 136.93 (C), 128.67 (CH), 128.42 (C), 127.24 (CH), 126.82 (C), 125.78 (CH), 123.81 (CH), 120.59 (CH), 109.06 (CH), 89.22 (CH), 49.40 (CH_2), 43.17

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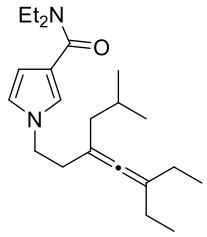
(CH_2 amide), 30.94 (CH_2), 17.08 (CH_3), 13.93 (CH_3 amide) ppm. **HRMS** [APCI]: *m/z* calculated for $C_{22}H_{29}N_2O$ $[M+H]^+$: 337.2274, found 337.2280.

***N,N*-Diethyl-1-(5-ethyl-3-methylhepta-3,4-dien-1-yl)-1H-pyrrole-3-carboxamide (7z)**



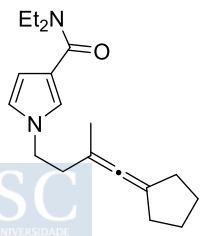
Synthesized by following an analogous procedure used for **7o**, using 3-pentanone instead of acetone. Obtained in 37% yield as yellow oil. **^{1}H NMR** (300 MHz, CD_2Cl_2) δ 7.02 (t, *J* = 2.0 Hz, 1H), 6.61 (t, *J* = 2.6 Hz, 1H), 6.28 (dd, *J* = 2.9, 1.8 Hz, 1H), 3.93 (t, *J* = 7.5 Hz, 2H), 3.49 (q, *J* = 7.1 Hz, 4H), 2.41 (t, *J* = 7.5 Hz, 2H), 1.93 (q, *J* = 7.4 Hz, 4H), 1.69 (s, 3H), 1.19 (t, *J* = 7.1 Hz, 6H), 0.94 (t, *J* = 7.4 Hz, 6H) ppm. **^{13}C NMR** (75 MHz, CD_2Cl_2) δ 197.90 (C), 166.57 (CO), 123.72 (CH), 120.72 (CH), 119.77 (C), 109.29 (C), 108.99 (CH), 98.33 (C), 48.92 (CH_2), 41.81 (CH_2 amide), 36.36 (CH_2), 26.34 (CH_2), 19.98 (CH_3), 13.99 (CH_3 amide), 12.70 (CH_3) ppm. **HRMS** [APCI]: *m/z* calculated for $C_{19}H_{31}N_2O$ $[M+H]^+$: 303.2431, found 303.2434.

***N,N*-Diethyl-1-(5-ethyl-3-isobutylhepta-3,4-dien-1-yl)-1H-pyrrole-3-carboxamide (7α)**



Synthesized by following an analogous procedure used for **7o**, using *i*PrMgBr instead of MeMgBr, and 3-pentanone instead of acetone. Obtained in 43% yield as yellow oil. **^{1}H NMR** (300 MHz, CD_2Cl_2) δ 7.07 (t, *J* = 2.0 Hz, 1H), 6.56 (t, *J* = 2.6 Hz, 1H), 6.29 (dd, *J* = 2.9, 1.8 Hz, 1H), 3.89 (t, 2H), 3.52 (q, *J* = 7.1 Hz, 4H), 2.36 (t, *J* = 7.9 Hz, 2H), 1.94 (q, *J* = 7.7 Hz, 4H), 1.82 (d, *J* = 7.0 Hz, 2H), 1.70 (dt, *J* = 13.7, 6.6 Hz, 1H), 1.21 (t, *J* = 7.1 Hz, 6H), 0.95 (t, *J* = 7.4 Hz, 6H), 0.89 (d, *J* = 6.5 Hz, 6H) ppm. **^{13}C NMR** (75 MHz, CD_2Cl_2) δ 197.58 (C), 166.72 (CO), 123.97 (CH), 120.44 (CH), 119.27 (C), 109.60 (C), 108.66 (CH), 101.44 (C), 48.73 (CH_2), 43.42 (CH_2), 41.50 (CH_2 amide), 34.64 (CH_2), 26.77 (CH), 26.13 (CH_2), 22.80 (CH_3), 14.70 (CH_3 amide), 12.78 (CH_3) ppm. **HRMS** [APCI]: *m/z* calculated for $C_{22}H_{37}N_2O$ $[M+H]^+$: 345.2900, found 345.2900. **NMR spectra at page 485.**

1-(4-Cyclopentylidene-3-methylbut-3-en-1-yl)-*N,N*-diethyl-1H-pyrrole-3-carboxamide (7β)

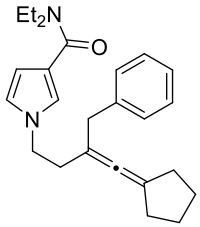


Synthesized by following an analogous procedure used for **7o**, using cyclopentanone instead of acetone. Obtained in 67% yield as yellow oil. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.06 (t, *J* = 2.0 Hz, 1H), 6.56 (t, *J* = 2.5 Hz, 1H), 6.28 (dd, *J* = 2.9, 1.7 Hz, 1H), 3.90 (t, *J* = 7.2 Hz, 2H), 3.51 (q, *J* = 7.1 Hz, 4H), 2.36 (t, *J* = 7.3 Hz, 2H), 2.31 – 2.14 (m, 4H), 1.65 (s, 3H), 1.65 – 1.55 (m, 4H), 1.20 (t, *J* = 7.1 Hz, 6H) ppm. **^{13}C**

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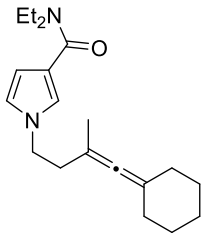
NMR (75 MHz, $CDCl_3$) δ 194.59 (C), 166.71 (CO), 123.95 (CH), 120.50 (CH), 108.89 (C), 108.67 (CH), 104.62 (C), 96.46 (C), 48.37 (CH_2), 41.58 (CH_2 amide), 35.99 (CH_2), 31.24 (CH_2), 27.07 (CH_2), 19.87 (CH_3), 13.86 (CH_3 amide) ppm. **HRMS** [APCI]: *m/z* calculated for $C_{19}H_{29}N_2O$ $[M+H]^+$: 301.2274, found 301.2280.

1-(3-Benzyl-4-cyclopentylidenebut-3-en-1-yl)-*N,N*-diethyl-1H-pyrrole-3-carboxamide (7ɣ)



Synthesized by following an analogous procedure used for **7o**, using BnMgBr instead of MeMgBr, and cyclopentanone instead of acetone. Obtained in 30% yield as yellow oil. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.33 – 7.13 (m, 5H), 7.04 (t, *J* = 2.0 Hz, 1H), 6.54 (t, *J* = 2.6 Hz, 1H), 6.31 (dd, *J* = 2.9, 1.7 Hz, 1H), 3.90 (t, *J* = 7.3 Hz, 2H), 3.57 – 3.50 (m, 4H), 3.26 (s, 2H), 2.37 (t, *J* = 7.3 Hz, 2H), 2.31 – 2.18 (m, 4H), 1.70 – 1.52 (m, 4H), 1.23 (t, *J* = 7.1 Hz, 6H) ppm. **^{13}C NMR** (75 MHz, $CDCl_3$) δ 195.48 (C), 166.69 (CO), 139.85 (C), 129.02 (CH), 128.68 (C), 128.31 (CH), 126.25 (CH), 123.92 (CH), 120.53 (CH), 119.23 (C), 108.66 (CH), 106.27 (C), 101.10 (C), 48.52 (CH_2), 41.65 (CH_2 amide), 41.00 (CH_2), 33.78 (CH_2), 31.28 (CH_2), 27.03 (CH_2), 13.87 (CH_3 amide) ppm. **HRMS** [APCI]: *m/z* calculated for $C_{25}H_{33}N_2O$ $[M+H]^+$: 377.2587, found 377.2592.

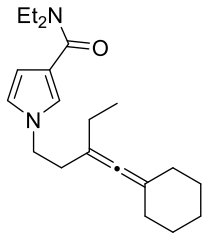
1-(4-Cyclohexylidene-3-methylbut-3-en-1-yl)-*N,N*-diethyl-1H-pyrrole-3-carboxamide (7δ)



Synthesized by following an analogous procedure used for **7o**, using cyclohexanone instead of acetone. Obtained in 46% yield as yellow oil. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.07 (t, *J* = 2.0 Hz, 1H), 6.57 (t, *J* = 2.6 Hz, 1H), 6.29 (dd, *J* = 2.8, 1.8 Hz, 1H), 3.91 (t, *J* = 7.3 Hz, 2H), 3.52 (q, *J* = 7.1 Hz, 4H), 2.35 (t, *J* = 7.3 Hz, 2H), 2.08 – 1.94 (m, 4H), 1.66 (s, 3H), 1.60 – 1.43 (m, 6H), 1.21 (t, *J* = 7.1 Hz, 6H) ppm. **^{13}C NMR** (75 MHz, $CDCl_3$) δ 195.52 (C), 166.60 (CO), 123.89 (CH), 120.38 (CH), 119.11 (C), 108.52 (CH), 103.31 (C), 93.35 (C), 48.30 (CH_2), 41.51 (CH_2 amide), 35.85 (CH_2), 31.86 (CH_2), 27.76 (CH_2), 26.20 (CH_2), 19.92 (CH_3), 13.80 (CH_3 amide) ppm. **HRMS** [APCI]: *m/z* calculated for $C_{20}H_{31}N_2O$ $[M+H]^+$: 315.2431, found 315.2427. **NMR spectra at page 486.**

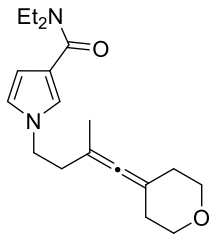
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1-(3-(Cyclohexylidenemethylene)pentyl)-*N,N*-diethyl-1H-pyrrole-3-carboxamide (7ε)



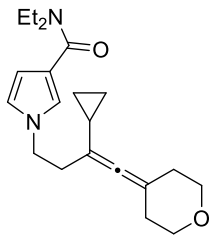
Synthesized by following an analogous procedure used for **7o**, using EtMgBr instead of MeMgBr, and cyclohexanone instead of acetone. Obtained in 73% yield as yellow oil. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.05 (t, *J* = 2.1 Hz, 1H), 6.55 (t, *J* = 2.6 Hz, 1H), 6.27 (dd, *J* = 2.9, 1.7 Hz, 1H), 3.90 (t, *J* = 7.4 Hz, 2H), 3.50 (q, *J* = 7.1 Hz, 4H), 2.34 (t, *J* = 7.4 Hz, 2H), 2.02 (t, *J* = 5.3 Hz, 4H), 1.87 (q, *J* = 7.3 Hz, 2H), 1.61 – 1.41 (m, 6H), 1.19 (t, *J* = 7.1 Hz, 6H), 0.94 (t, *J* = 7.3 Hz, 3H) ppm. **^{13}C NMR** (75 MHz, $CDCl_3$) δ 194.66 (C), 166.65 (CO), 123.88 (CH), 120.47 (CH), 119.09 (C), 108.56 (CH), 105.75 (C), 100.36 (C), 48.51 (CH_2), 41.67 (CH_2 amide), 34.67 (CH_2), 32.10 (CH_2), 27.96 (CH_2), 26.31 (CH_2), 26.18 (CH_2), 13.82 (CH_3 amide), 12.36 (CH_3) ppm. **HRMS** [APCI]: *m/z* calculated for $C_{21}H_{33}N_2O$ $[M+H]^+$: 329.2587, found 329.2595.

***N,N*-Diethyl-1-(3-methyl-4-(tetrahydro-4H-pyran-4-ylidene)but-3-en-1-yl)-1H-pyrrole-3-carboxamide (7ζ)**



Synthesized by following an analogous procedure used for **7o**, using tetrahydro-4H-pyran-4-one instead of acetone. Obtained in 70% yield as yellow oil. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.07 (t, *J* = 2.0 Hz, 1H), 6.55 (t, *J* = 2.6 Hz, 1H), 6.28 (dd, *J* = 2.9, 1.8 Hz, 1H), 3.92 (t, *J* = 7.1 Hz, 2H), 3.74 – 3.57 (m, 4H), 3.51 (q, *J* = 7.1 Hz, 4H), 2.38 (t, *J* = 7.1 Hz, 2H), 2.20 – 2.03 (m, 4H), 1.68 (s, 3H), 1.20 (t, *J* = 7.1 Hz, 6H) ppm. **^{13}C NMR** (75 MHz, $CDCl_3$) δ 196.14 (C), 166.56 (CO), 124.02 (CH), 120.47 (CH), 119.27 (C), 108.65 (CH), 98.58 (C), 95.02 (C), 69.01 (CH_2), 48.16 (CH_2), 41.68 (CH_2 amide), 35.86 (CH_2), 31.94 (CH_2), 19.82 (CH_3), 13.83 (CH_3 amide) ppm. **HRMS** [APCI]: *m/z* calculated for $C_{19}H_{29}N_2O_2$ $[M+H]^+$: 317.2223, found 317.2224.

1-(3-Cyclopropyl-4-(tetrahydro-4H-pyran-4-ylidene)but-3-en-1-yl)-*N,N*-diethyl-1H-pyrrole-3-carboxamide (7η)

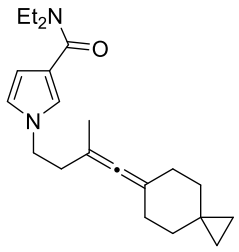


Synthesized by following an analogous procedure used for **7o**, using cyclopropyl magnesium bromide instead of MeMgBr, and tetrahydro-4H-pyran-4-one instead of acetone. Obtained in 22% yield as yellow oil. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.04 (t, *J* = 2.1 Hz, 1H), 6.54 (t, *J* = 2.6 Hz, 1H), 6.25 (t, *J* = 2.3 Hz, 1H), 3.94 (t, *J* = 7.1 Hz, 2H), 3.62 (qt, *J* = 11.1, 5.4 Hz, 4H), 3.48 (q, *J* = 7.1 Hz, 4H), 2.47 (t, *J* = 7.1 Hz, 2H), 2.06 (t, *J* = 5.5 Hz, 4H), 1.17 (t, *J* = 7.1 Hz, 6H), 1.10 – 0.98 (m, 1H), 0.67 – 0.57 (m, 2H), 0.31 – 0.20 (m, 2H) ppm. **^{13}C NMR** (75 MHz, $CDCl_3$) δ 194.15 (C), 166.46 (CO), 123.87

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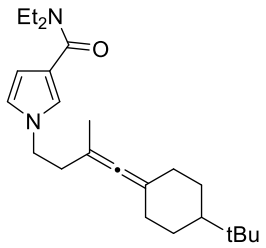
(CH), 120.41 (CH), 119.15 (C), 108.56 (CH), 103.44 (C), 101.70 (C), 69.13 (CH_2), 48.35 (CH_2), 41.44 (CH_2 amide), 34.80 (CH_2), 32.06 (CH_2), 13.78 (CH_3 amide), 12.65 (CH), 7.05 (CH_2) ppm. **HRMS** [APCI]: *m/z* calculated for $C_{21}H_{31}N_2O_2$ $[M+H]^+$:343.2380, found 343.2387.

_N,N_-Diethyl-1-(3-methyl-4-(spiro[2.5]octan-6-ylidene)but-3-en-1-yl)-1H-pyrrole-3-carboxamide (7θ)



Synthesized by following an analogous procedure used for **7o**, using spiro[2.5]octan-6-one instead of acetone. Obtained in 37% yield as yellow oil. **^{1}H NMR** (300 MHz, $CDCl_3$) 7.04 (t, *J* = 2.1 Hz, 1H), 6.54 (t, *J* = 2.6 Hz, 1H), 6.25 (t, *J* = 2.3 Hz, 1H), 3.89 (t, *J* = 7.3 Hz, 2H), 3.48 (q, *J* = 7.1 Hz, 4H), 2.33 (t, *J* = 7.3 Hz, 2H), 2.05 (t, *J* = 6.0 Hz, 4H), 1.63 (s, 3H), 1.31 (h, *J* = 6.8 Hz, 4H), 1.17 (t, *J* = 7.1 Hz, 6H), 0.22 (s, 4H) ppm. **^{13}C NMR** (75 MHz, $CDCl_3$) δ 195.93 (C), 166.54 (CO), 123.79 (CH), 120.38 (CH), 119.09 (C), 108.54 (CH), 102.64 (C), 93.42 (C), 48.24 (CH_2), 41.43 (CH_2 amide), 36.57 (CH_2), 35.80 (CH_2), 30.73 (CH_2), 19.89 (CH_3), 18.58 (C), 13.75 (CH_3 amide), 11.82 (CH_2) ppm. **HRMS** [APCI]: *m/z* calculated for $C_{22}H_{33}N_2O$ $[M+H]^+$: 341.2587, found 341.2597.

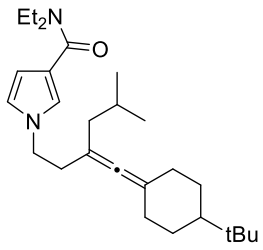
1-(4-(4-(Tert-butyl)cyclohexylidene)-3-methylbut-3-en-1-yl)-_N,N_-diethyl-1H-pyrrole-3-carboxamide (7ι)



Synthesized by following an analogous procedure used for **7o**, using 4-(tert-butyl)cyclohexan-1-one instead of acetone. Obtained in 73% yield as a mixture of isomers in a 3:1 ratio. The major isomer obtained was purified and isolated in 11% yield as yellow oil. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.06 (t, *J* = 2.0 Hz, 1H), 6.56 (t, *J* = 2.6 Hz, 1H), 6.29 (dd, *J* = 2.8, 1.8 Hz, 1H), 3.89 (t, *J* = 7.2 Hz, 2H), 3.52 (q, *J* = 7.1 Hz, 4H), 2.34 (t, *J* = 7.2 Hz, 2H), 2.24 – 2.17 (m, 2H), 1.95 – 1.87 (m, 2H), 1.87 – 1.80 (m, 2H), 1.67 (s, 3H), 1.21 (t, *J* = 7.1 Hz, 6H), 1.12 – 1.00 (m, 3H), 0.84 (s, 9H) ppm. **^{13}C NMR** (75 MHz, $CDCl_3$) δ 195.45 (C), 166.75 (CO), 123.99 (CH), 120.56 (CH), 119.18 (C), 108.62 (CH), 103.20 (C), 93.58 (C), 48.42 (CH_2), 47.97 (CH), 40.82 (CH_2 amide), 35.95 (CH_2), 32.61 (C), 31.99 (CH_2), 28.56 (CH_2), 27.72 (CH_3), 20.38 (CH_3), 13.46 (CH_3 amide) ppm. **HRMS** [APCI]: *m/z* calculated for $C_{24}H_{39}N_2O$ $[M+H]^+$: 371.3057, found 371.3064. **NMR spectra at page 487.**

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1-(3-((4-(*tert*-butyl)cyclohexylidene)methylene)-5-methylhexyl)-*N,N*-diethyl-1H-pyrrole-3-carboxamide (7κ)

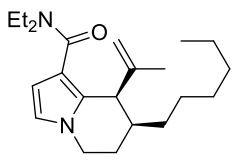


Synthesized by following an analogous procedure used for **7o**, using *i*-PrMgBr instead of MeMgBr, and 4-(*tert*-butyl)cyclohexan-1-one instead of acetone. Obtained in 81% yield as a mixture of isomers in a 3:1 ratio. The major isomer obtained was purified and isolated in a 13% yield as yellow oil. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.05 (t, *J* = 2.0 Hz, 1H), 6.55 (t, *J* = 2.6 Hz, 1H), 6.28 (dd, *J* = 2.9, 1.8 Hz, 1H), 3.88 (t, *J* = 7.3 Hz, 2H), 3.52 (q, *J* = 7.1 Hz, 4H), 2.31 (t, *J* = 7.3 Hz, 2H), 2.28 – 2.17 (m, 2H), 1.99 – 1.62 (m, 8H), 1.21 (t, *J* = 7.1 Hz, 6H), 1.09 – 1.02 (m, 2H), 0.89 (d, *J* = 6.4 Hz, 6H), 0.84 (s, 9H) ppm. **^{13}C NMR** (75 MHz, $CDCl_3$) δ 195.40 (C), 166.77 (CO), 123.94 (CH), 120.57 (CH), 119.20 (C), 108.60 (CH), 104.25 (C), 97.41 (C), 48.55 (CH_2), 47.98 (CH), 43.29 (CH_2), 41.53 (CH_2 amide), 34.82 (CH_2), 32.59 (C), 32.09 (CH_2), 28.65 (CH_2), 27.70 (CH_3), 26.63 (CH), 22.73 (CH_3), 13.90 (CH_3 amide) ppm. **HRMS** [APCI]: *m/z* calculated for $C_{23}H_{31}N_2O$ $[M+H]^+$: 413.3526, found 413.3525.

Synthesis of compounds 8, 9, and 23 from precursors 7

Experimental procedures and characterization of products **8o**, **9o** and **23o**, result of the cycloisomerization of **7o**, are detailed in page 336.

***(7S,8R)*-*N,N*-Diethyl-7-hexyl-8-(prop-1-en-2-yl)-5,6,7,8-tetrahydroindolizine-1-carboxamide (9u)**

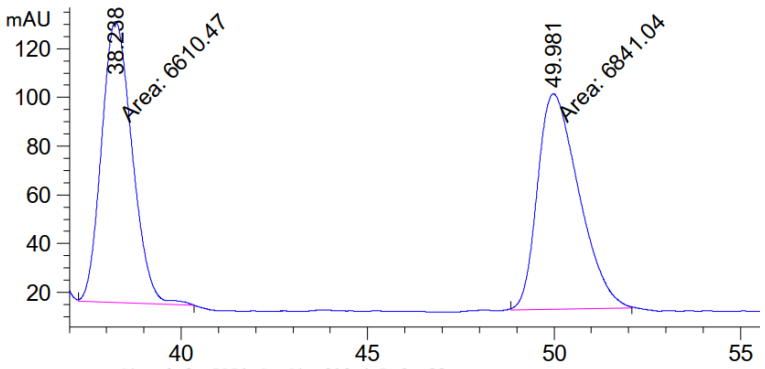


Prepared following general procedure for catalytic reactions (page 104), using ***7u.*** Obtained as yellow oil. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 6.42 (d, *J* = 3.2 Hz, 1H), 6.12 (d, *J* = 3.3 Hz, 1H), 4.76 (s, 1H), 4.60 (s, 1H), 4.15 – 4.02 (m, 2H), 3.84 (td, *J* = 11.9, 5.2 Hz, 1H), 3.48 (dd, *J* = 13.7, 7.1 Hz, 2H), 3.29 (dq, *J* = 13.9, 6.9 Hz, 2H), 2.08 – 1.93 (m, 2H), 1.83 – 1.75 (m, 1H), 1.63 (s, 3H), 1.36 – 1.21 (m, 12H), 1.13 (t, *J* = 7.0 Hz, 3H), 0.88 (dt, *J* = 10.8, 6.0 Hz, 3H) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$) δ 168.71 (CO), 145.47 (C), 133.59 (C), 117.56 (CH), 115.53 (C), 114.78 (CH_2), 107.86 (CH), 45.43 (CH_2), 43.29 (CH), 40.88 (CH_2 amide), 35.95 (CH), 33.14 (CH_2), 29.86 (CH_2), 29.62 (CH_2), 27.69 (CH_2), 25.53 (CH_3), 23.56 (CH_2), 14.16 (CH_3), 13.67 (CH_3 amide) ppm. **HRMS** [APCI]: *m/z* calculated for $C_{12}H_{37}N_2O$ $[M+H]^+$: 345.2900, found 345.2904.

Enantioselectivity was determined by chiral HPLC analysis on a Chiralpack IG3 column at *rt* (Hexane:iPrOH = 95:5, 1mL/min).

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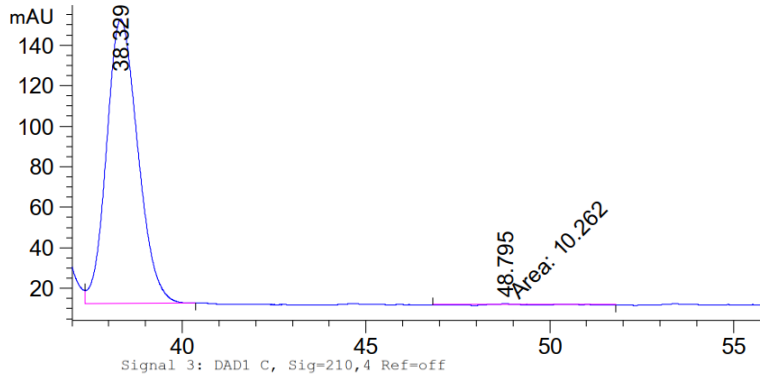
- Racemic sample prepared using [Ir(COD)$_2$]BARF / *rac*-Binap (5 mol%) at 100 ºC.



Signal 3: DAD1 C, Sig=210,4 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	38.238	MM	0.9549	6610.47070	115.37387	49.1430
2	49.981	MM	1.2888	6841.03809	88.47007	50.8570
Totals :				1.34515e4	203.84394	

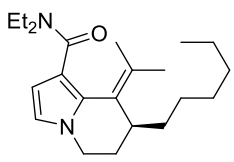
- Asymmetric sample prepared using [Ir(COD)$_2$]BARF / *(S)*-Binap (5 mol%) at 100 ºC (50% yield, >99:1 er)



Signal 3: DAD1 C, Sig=210,4 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	38.329	VB	0.9234	8287.46875	140.24428	99.8763
2	48.795	MM	0.4847	10.26201	3.52865e-1	0.1237
Totals :				8297.73076	140.59714	

_(S)-N,N_-Diethyl-7-hexyl-8-(propan-2-ylidene)-5,6,7,8-tetrahydroindolizine-1-carboxamide (23u)

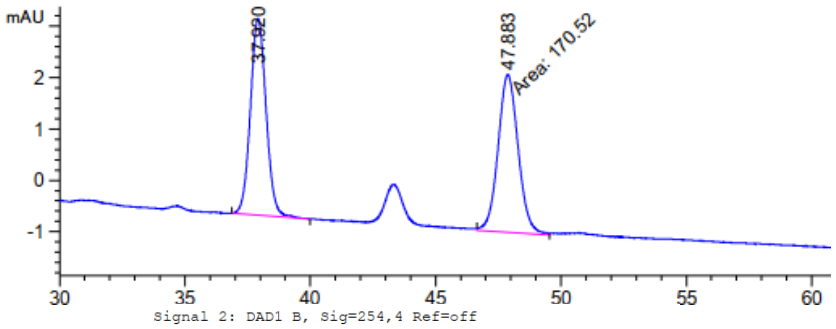


Prepared following general procedure for catalytic reactions (page 104), using ***7u***. Obtained as yellow oil. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 6.52 (d, *J* = 2.8 Hz, 1H), 6.22 (d, *J* = 2.7 Hz, 1H), 3.97 – 3.88 (m, 1H), 3.82 – 3.73 (m, 1H), 3.55 – 3.41 (m, 4H), 2.18 – 2.10 (m, 1H), 1.82 (s, 3H), 1.75 – 1.68 (m, 4H), 1.47 – 1.42 (m, 1H), 1.37 – 1.23 (m, 10H), 1.16 (t, *J* = 7.1 Hz, 6H), 0.87 (td, *J* = 6.6, 4.0 Hz, 3H) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$) δ 169.14 (CO), 130.40 (C), 129.11 (C), 126.30 (C) , 118.38 (CH), 118.10 (C), 108.79 (CH), 44.09

(CH_2 amide), 43.11 (CH_2), 36.68 (CH), 34.00 (CH_2), 32.04 (CH_2), 29.80 (CH_2), 29.58 (CH_2), 27.59 (CH_2), 22.92 (CH_3), 22.83 (CH_2), 21.15 (CH_3), 14.16 (CH_3), 13.73 (CH_3 amide) ppm. **HRMS** [APCI]: *m/z* calculated for $C_{12}H_{37}N_2O$ $[M+H]^+$: 345.2900, found 345.2908.

Enantioselectivity was determined by chiral HPLC analysis on a Chiralpack IE3 column at *rt* (Hexane:iPrOH = 90:10, 1mL/min).

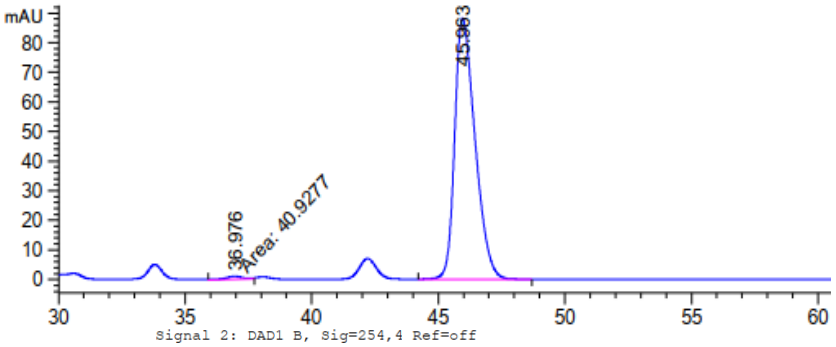
- Racemic sample prepared using $[Ir(COD)_2]BARF$ / *rac*-Binap (5 mol%) at **130 ºC**.



Signal 2: DAD1 B, Sig=254,4 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	37.920	BB	0.5985	166.96379	3.83062	49.4732
2	47.883	MM	0.9275	170.51985	3.06427	50.5268
Totals :				337.48364	6.89488	

- Asymmetric sample prepared using $[Ir(COD)_2]BARF$ / *(S)*-Binap (5 mol%) at **130 ºC** (71% yield, 99: 1 er)

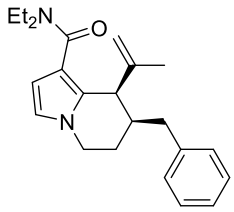


Signal 2: DAD1 B, Sig=254,4 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	36.976	MM	0.7405	40.92773	9.21228e-1	0.8231
2	45.963	BB	0.8502	4931.21387	88.21017	99.1769
Totals :				4972.14160	89.13140	

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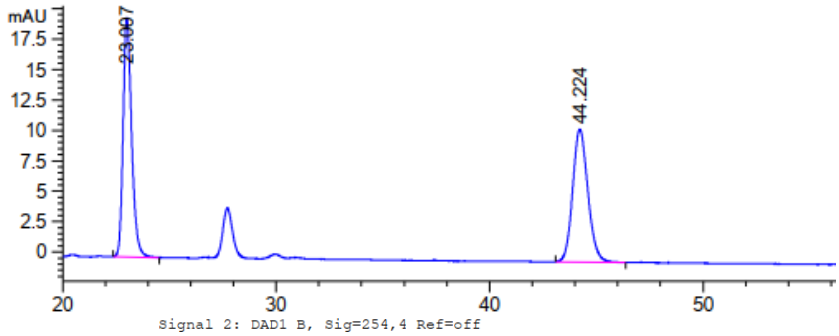
(7S,8R)-7-Benzyl-*N,N*-diethyl-8-(prop-1-en-2-yl)-5,6,7,8-tetrahydroindolizine-1-carboxamide (9v)



Prepared following general procedure for catalytic reactions (page 104), using ***7v.*** Obtained as yellow oil. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.28 (t, *J* = 7.4 Hz, 2H), 7.21 – 7.15 (m, 3H), 6.41 (d, *J* = 2.8 Hz, 1H), 6.14 (d, *J* = 2.8 Hz, 1H), 4.85 (t, *J* = 1.8 Hz, 1H), 4.64 (d, *J* = 2.0 Hz, 1H), 4.24 (d, *J* = 5.2 Hz, 1H), 4.02 (ddd, *J* = 12.3, 5.9, 2.3 Hz, 1H), 3.76 – 3.68 (m, 1H), 3.50 (dq, *J* = 14.2, 7.2 Hz, 2H), 3.30 (dq, *J* = 14.0, 7.0 Hz, 2H), 2.97 – 2.89 (m, 1H), 2.39 – 2.28 (m, 2H), 2.03 – 1.93 (m, 1H), 1.72 (s, 3H), 1.70 – 1.65 (m, 1H), 1.14 (t, *J* = 7.1 Hz, 6H) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$) δ 168.59 (CO), 145.40 (C), 140.87 (C), 133.34 (C), 129.30 (CH), 128.56 (CH), 126.21 (CH), 117.70 (CH), 115.59 (C), 115.18 (CH_2), 107.93 (CH), 45.28 (CH_2), 44.13 (CH), 40.84 (CH_2 amide), 39.65 (CH_2), 37.784 (CH), 23.84 (CH_2), 23.72 (CH_3), 13.70 (CH_3) ppm. **HRMS** [APCI]: *m/z* calculated for $C_{23}H_{31}N_2O$ $[M+H]^+$: 351.2431, found 351.2431.

Enantioselectivity was determined by chiral HPLC analysis on a Chiralpack IF3 column at *rt* (Hexane:iPrOH =90:10, 1mL/min).

- Racemic sample prepared using $[Ir(COD)_2]BARF$ / *rac*-Binap (5 mol%) at 100 ºC.

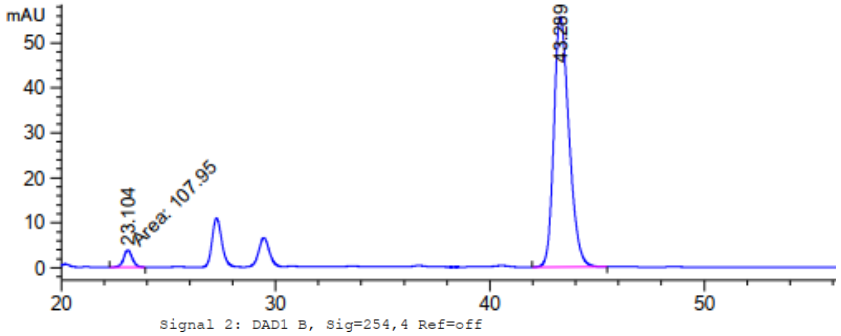


Signal 2: DAD1 B, Sig=254,4 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	23.007	BB	0.4230	543.47675	19.62722	50.1407
2	44.224	BB	0.7205	540.42664	10.89884	49.8593
Totals :				1083.90338	30.52606	

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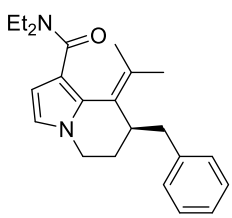
- Asymmetric sample prepared using [Ir(COD)$_2$]BARF / *(S)*-Binap (5 mol%) at 100 ºC (59% yield, 96:4 er)



Signal 2: DAD1 B, Sig=254,4 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	23.104	MM	0.4686	107.94975	3.83970	3.7906
2	43.289	BB	0.7602	2739.86694	55.66597	96.2094
Totals :				2847.81669	59.50567	

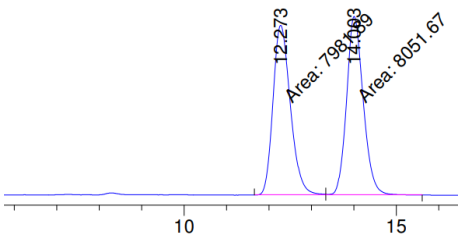
_(S)_-7-Benzyl-_N,N_-diethyl-8-(propan-2-ylidene)-5,6,7,8-tetrahydroindolizine-1-carboxamide (23v)



Prepared following general procedure for catalytic reactions (page 104), using ***7v***. Obtained as yellow oil. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.28 (t, 2H), 7.25 – 7.17 (m, 3H), 6.57 (d, *J* = 2.8 Hz, 1H), 6.25 (d, *J* = 2.8 Hz, 1H), 3.94 (ddd, *J* = 12.5, 7.1, 5.2 Hz, 1H), 3.73 (ddd, *J* = 12.5, 7.6, 4.9 Hz, 1H), 3.75 – 3.40 (br m, 4H), 3.28 (td, *J* = 11.2, 6.3 Hz, 1H), 2.95 (dd, *J* = 13.7, 4.9 Hz, 1H), 2.40 (dd, *J* = 13.7, 10.6 Hz, 1H), 1.98 – 1.90 (m, 1H), 1.84 (s, 3H), 1.73 (s, 3H), 1.65 – 1.59 (m, 1H), 1.19 (br m, 6H) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$) δ 169.00 (CO), 140.71 (C), 130.34 (C), 129.92 (C), 129.13 (CH), 128.50 (CH), 126.10 (CH), 125.16 (C), 118.41 (CH), 118.15 (C), 108.47 (CH), 43.23 (CH_2), 42.85 (CH_2 amide), 40.23 (CH_2), 39.07 (CH_2 amide), 38.59 (CH), 29.15 (CH_2), 22.82 (CH_3), 20.99 (CH_3), 14.04 (CH_3 amide), 13.28 (CH_3 amide) ppm. **HRMS** [APCI]: *m/z* calculated for $C_{23}H_{31}N_2O$ $[M+H]^+$: 351.2431, found 351.2431.

Enantioselectivity was determined by chiral HPLC analysis on a Chiralpack IG3 column at *rt* (Hexane:iPrOH =85:15, 1mL/min).

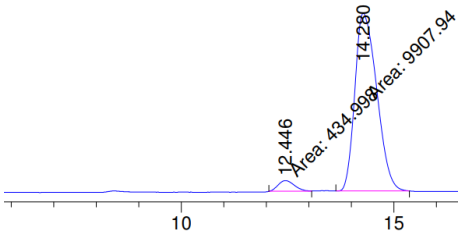
- Racemic sample prepared using [Ir(COD)$_2$]BARF / *rac*-Binap (5 mol%) at **130 ºC**.



Signal 1: DAD1 A, Sig=220,8 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	12.273	MM	0.4742	7981.89307	280.51941	49.7824
2	14.003	MM	0.4546	8051.66699	295.20190	50.2176
Totals :				1.60336e4	575.72131	

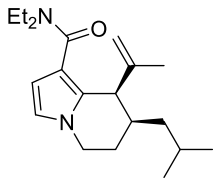
- Asymmetric sample prepared using [Ir(COD)$_2$]BARF / *(S)*-Binap (5 mol%) at **130 ºC** (44% yield, 96:4 er)



Signal 1: DAD1 A, Sig=220,8 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	12.446	MM	0.4410	434.99780	16.43886	4.2057
2	14.280	MM	0.5945	9907.93555	277.78339	95.7943
Totals :				1.03429e4	294.22225	

(7S,8R)-N,N-Diethyl-7-isobutyl-8-(prop-1-en-2-yl)-5,6,7,8-tetrahydroindolizine-1-carboxamide (9w)

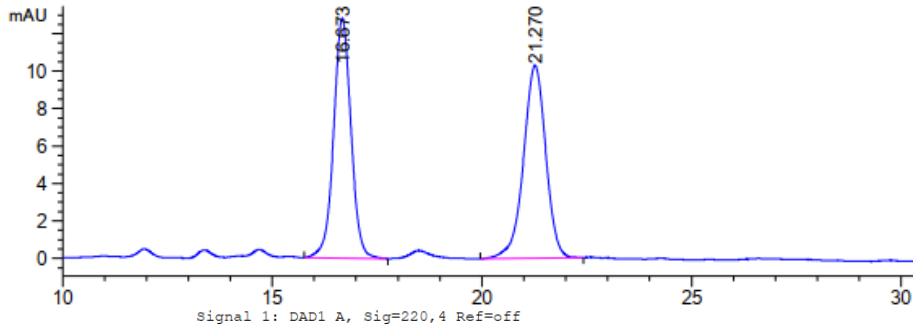


Prepared following general procedure for catalytic reactions (page 104), using ***7w***. Obtained together with **25w**, as pale yellow oil. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 6.42 (d, *J* = 2.8 Hz, 1H), 6.12 (d, *J* = 2.8 Hz, 1H), 4.75 (s, 1H), 4.60 (s, 1H), 4.14 – 3.98 (m, 2H), 3.85 (td, *J* = 11.9, 5.0 Hz, 1H), 3.48 (s, 3H), 3.25 (dq, *J* = 14.0, 7.0 Hz, 2H), 2.19 – 1.87 (m, 2H), 1.79 – 1.67 (m, 2H), 1.61 (s, 3H), 1.35 – 1.21 (m, 2H), 1.12 (t, *J* = 7.1 Hz, 6H), 0.91 (d, *J* = 6.6 Hz, 3H), 0.86 (d, *J* = 6.6 Hz, 3H) ppm. **^{13}C NMR** (75 MHz, $CDCl_3$) δ 168.68 (CO), 145.32 (C), 133.36 (C), 117.57 (CH), 115.38 (C), 114.84 (CH_2), 107.71 (CH), 45.36 (CH_2), 43.25 (CH), 42.29 (CH_2), 40.36 (CH_2 amide), 33.09 (CH), 25.54 (CH), 25.12 (CH_2), 23.50 (CH_3), 23.33 (CH_3), 22.55 (CH_3), 13.64 (CH_3 amide) ppm. **HRMS** [APCI]: *m/z* calculated for $C_{20}H_{33}N_2O$ $[M+H]^+$: 317.2587, found 317.2599.

Enantioselectivity was determined by chiral HPLC analysis on a Chiralpack IG3 column at *rt* (Hexane:iPrOH = 90:10, 1mL/min).

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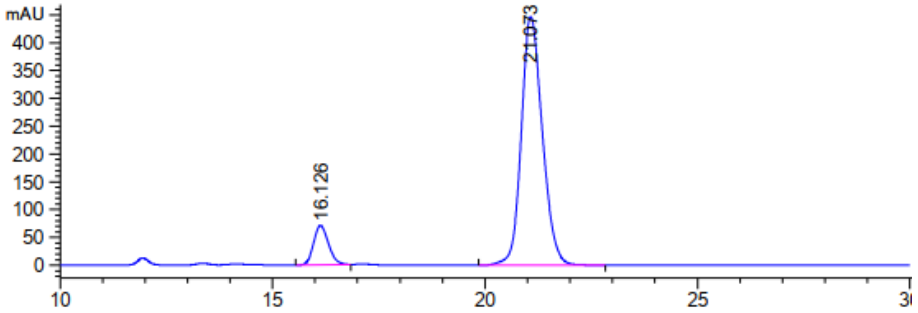
- Racemic sample prepared using [Ir(COD)$_2$]BARF / *rac*-Binap (5 mol%) at 100 ºC.



Signal 1: DAD1 A, Sig=220,4 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	16.673	BB	0.4403	369.60992	12.82153	49.2246
2	21.270	BB	0.5635	381.25430	10.30817	50.7754
Totals :				750.86423	23.12970	

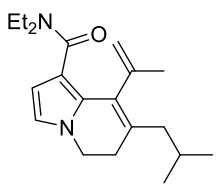
- Asymmetric sample prepared using [Ir(COD)$_2$]BARF / *(S)*-Binap (5 mol%) at 100 ºC (34% yield, 90:10 er).



Signal 1: DAD1 A, Sig=220,4 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	16.126	BB	0.3751	1707.21545	70.84903	9.9886
2	21.073	BB	0.5298	1.53843e4	446.70663	90.0114
Totals :				1.70916e4	517.55566	

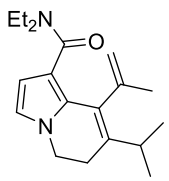
_N,N_-Diethyl-7-isobutyl-8-(prop-1-en-2-yl)-5,6-dihydroindolizine-1-carboxamide (24w)



Prepared following general procedure for catalytic reactions (page 104), using ***7w*** and Binap (5 mol%) as ligand at **130 ºC**. Obtained in a 75% yield as yellow oil. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 6.49 (d, *J* = 2.7 Hz, 1H), 6.03 (d, *J* = 2.7 Hz, 1H), 5.02 (dd, *J* = 2.6, 1.5 Hz, 1H), 4.78 (dd, *J* = 2.5, 1.2 Hz, 1H), 3.87 (t, *J* = 7.0 Hz, 2H), 3.59 – 3.35 (m, 2H), 3.25 – 3.09 (m, 2H), 2.40 (t, *J* = 7.0 Hz, 2H), 2.10 (d, *J* = 7.4 Hz, 2H), 1.90 (s, 3H), 1.85 – 1.79 (m, 1H), 1.16 (t, *J* = 7.1 Hz, 3H), 1.04 (t, *J* = 7.1 Hz, 3H), 0.89 (d, *J* = 6.6 Hz, 6H) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$) δ 168.91 (CO), 130.51 (C), 127.98 (C), 126.50 (C), 119.62 (CH), 116.76 (CH_2), 116.11 (C), 107.42 (CH), 44.06 (CH_2 amide), 43.26 (CH_2), 42.06 (CH_2 amide), 38.74 (CH_2), 28.20 (CH_2), 26.99 (CH_3), 24.60 (CH_3), 22.79

(CH_3), 14.15 (CH_3 amide), 12.55 (CH_3 amide) ppm. **HRMS** [APCI]: *m/z* calculated for $C_{20}H_{31}N_2O$ $[M+H]^+$: 315.2431, found 315.2430. **NMR spectra at page 514**.

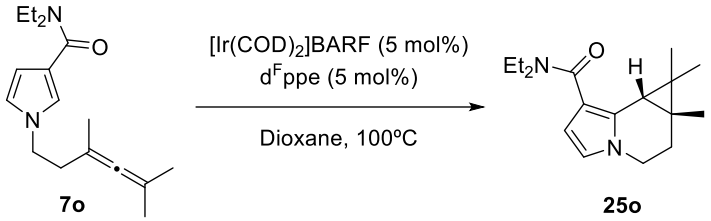
***N,N*-Diethyl-7-isopropyl-8-(prop-1-en-2-yl)-5,6-dihydroindolizine-1-carboxamide (24x)**



Prepared following general procedure for catalytic reactions (page 104), using ***7x*** and Binap (5 mol%) as ligand at **130 ºC**. Obtained in 75% yield as yellow oil. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 6.48 (d, *J* = 2.7 Hz, 1H), 6.02 (dd, *J* = 2.7, 0.9 Hz, 1H), 5.00 (dd, *J* = 2.6, 1.4 Hz, 1H), 4.77 (dd, *J* = 2.6, 1.3 Hz, 1H), 3.85 (t, *J* = 7.0 Hz, 2H), 3.44 (br s, 2H), 3.20 (br m, *J* = 7.4 Hz, 2H), 2.96 (p, *J* = 6.8 Hz, 1H), 2.37 (t, *J* = 7.0 Hz, 2H), 1.93 (d, *J* = 1.4 Hz, 3H), 1.16 (t, *J* = 7.1 Hz, 3H), 1.05 (t, *J* = 7.1 Hz, 3H), 0.99 (d, *J* = 6.8 Hz, 6H) ppm. **^{13}C NMR** (75 MHz, $CDCl_3$) δ 168.91 (CO), 142.07 (C), 133.86 (C), 128.36 (C),126.60 (C), 119.50 (CH), 116.23 (C), 115.94 (CH_2), 107.33 (CH), 44.46 (CH_2), 43.21 (CH_2 amide), 38.65 (CH_2 amide), 29.92 (CH), 24.71 (CH_3), 22.87 (CH_2), 21.03 (CH_3), 14.13 (CH_3 amide), 12.52 (CH_3 amide) ppm. **HRMS** [APCI]: *m/z* calculated for $C_{19}H_{29}N_2O$ $[M+H]^+$: 301.2274, found 301.2275.

Synthesis of compounds 25 by hydroarylation/cyclopropanation of precursors 7

*(exemplified for **7o**).*

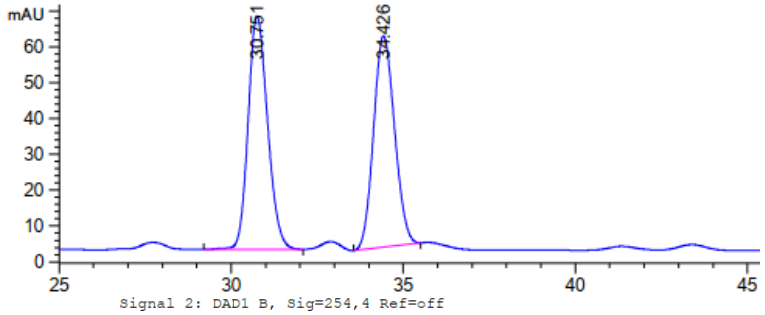


Prepared following general procedure for catalytic reactions (page 104), using ***7o*** and d^Fppe (5 mol%) as ligand. $[Ir(COD)_2]BARF$ (6.4 mg, 0.005 mmol), d^Fppe (3.8 mg, 0.005 mmol), **7o** (27.4 mg, 0.1 mmol) and dioxane (0.8 mL) were sequentially added to a sealed tube under Argon atmosphere and stirred at 100 ºC for 16 h. The mixture was concentrated, and the crude residue was purified by flash chromatography (1:3 to 3:1 EtOAc/Hexanes). (***1aR,7bR*)-*N,N*-diethyl-1,1,1a-trimethyl-1a,2,3,7b-tetrahydro-1H-cyclopropa[g]indolizine-7-carboxamide** (**25o**) obtained in 59% yield as yellow oil. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 6.40 (d, *J* = 2.8 Hz, 1H), 6.11 (d, *J* = 2.8 Hz, 1H), 3.80 – 3.65 (m, 2H), 3.60 – 3.39 (m, 4H), 1.97 – 1.78 (m, 2H), 1.62 (s, 1H), 1.29 (s, 3H), 1.23 (s, 3H), 1.18 (t, *J* = 7.0 Hz, 6H), 0.71 (s, 3H) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$) δ 168.21 (CO), 130.72 (C), 117.17 (CH), 117.06 (C), 106.48 (CH), 42.75 (CH_2), 41.19 (CH_2 amide), 29.73 (CH_2), 28.15 (C), 26.69 (CH), 22.51 (CH_3), 22.13 (CH_3), 21.69 (C), 18.78 (CH_3), 13.92

(CH_3 amide) ppm. **HRMS** [APCI]: *m/z* calculated for $C_{17}H_{27}N_2O$ $[M+H]^+$: 275.2118, found 275.2113. **NMR spectra at page 515**.

The enantioselective variant is performed using BTFM-Garphos or **L5** as optimal ligands, instead of d^Fppe. Enantioselectivity was determined by chiral HPLC analysis on a Chiralpack IG3 column at *rt* (Hexane:iPrOH = 95:5, 1mL/min).

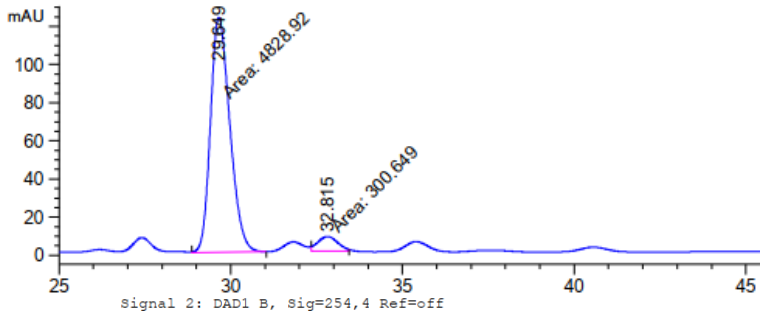
- Racemic sample prepared using $[Ir(COD)_2]BARF$ / d^Fppe (5 mol%) at 100 ºC.



Signal 2: DAD1 B, Sig=254,4 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	30.751	BB	0.6096	2564.56470	65.09927	50.6773
2	34.426	BB	0.6621	2496.01489	58.93935	49.3227
Totals :				5060.57959	124.03862	

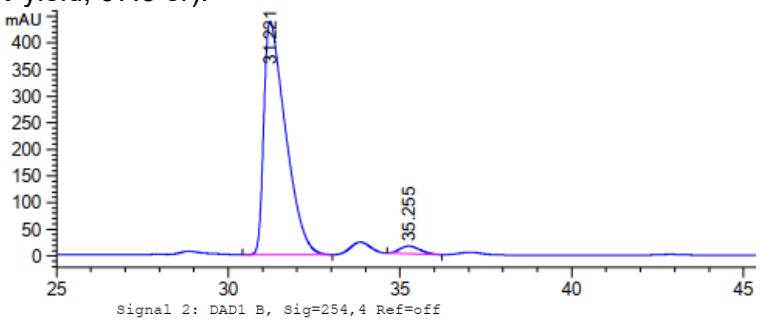
- Asymmetric sample prepared using $[Ir(COD)_2]BARF$ / *(R)*-BTFM-Garphos (5 mol%) at 100 ºC (49% yield, 94:6 er).



Signal 2: DAD1 B, Sig=254,4 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	29.649	MM	0.6543	4828.92383	122.99636	94.1389
2	32.815	MM	0.6664	300.64886	7.51869	5.8611
Totals :				5129.57269	130.51505	

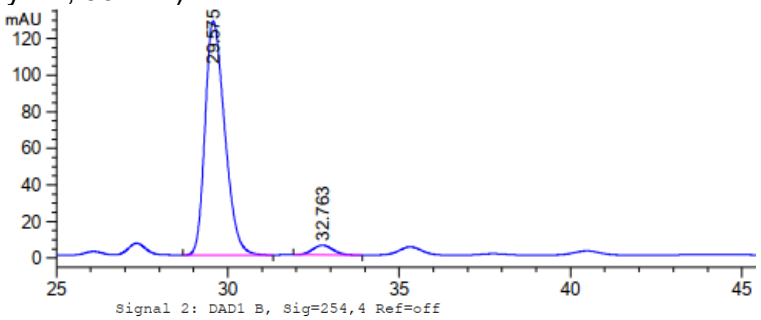
- Asymmetric sample prepared using [Ir(COD)$_2$]BARF / *(R)*-*P*-bisCF$_3$-Binap (5 mol%) at 100 ºC (69% yield, 97:3 er).



Signal 2: DAD1 B, Sig=254,4 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	31.221	BB	0.6568	1.92554e4	438.10498	97.0632
2	35.255	BB	0.6359	582.60974	14.34192	2.9368
Totals :				1.98381e4	452.44690	

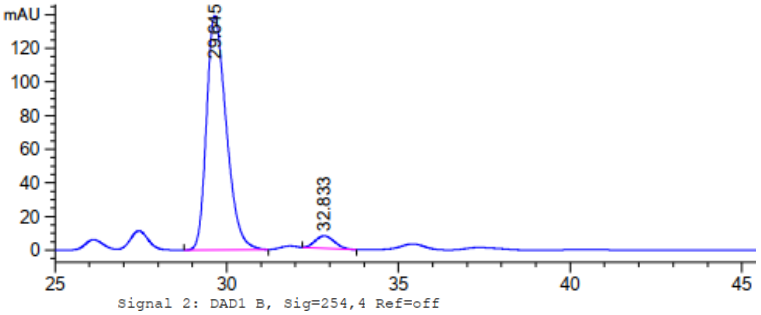
- Asymmetric sample prepared using [Ir(COD)$_2$]BARF / *(R)*-BTFM-Garphos (5 mol%) at 60 ºC (37% yield, 96:4 er).



Signal 2: DAD1 B, Sig=254,4 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	29.575	BB	0.6166	5104.44434	128.17934	95.8893
2	32.763	BB	0.6175	218.82286	5.32398	4.1107
Totals :				5323.26720	133.50331	

- Asymmetric sample prepared using [Ir(COD)$_2$]BARF / *(R)*-BTFM-Garphos (5 mol%) at 100 ºC in toluene (46% yield, 94:6 er).

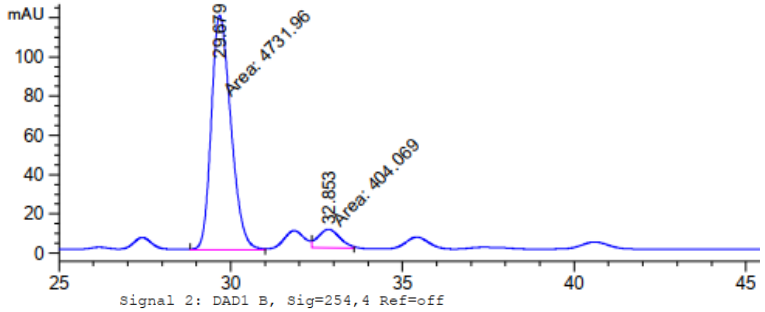


Signal 2: DAD1 B, Sig=254,4 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	29.645	BB	0.6147	5568.25879	139.19133	95.1199
2	32.833	BB	0.5844	285.67810	7.39961	4.8801
Totals :				5853.93689	146.59094	

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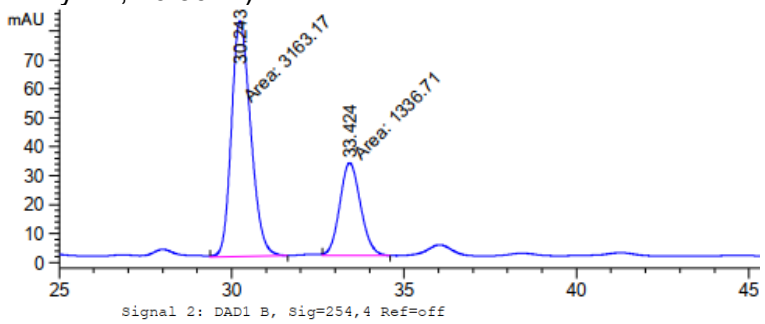
- Asymmetric sample prepared using [Ir(COD)$_2$]BARF / *(R)*-BTFM-Garphos (5 mol%) at 120 ºC (47% yield, 92:8 er).



Signal 2: DAD1 B, Sig=254,4 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	29.679	MM	0.6605	4731.96191	119.40114	92.1327
2	32.853	MM	0.7189	404.06946	9.36718	7.8673
Totals :				5136.03137	128.76832	

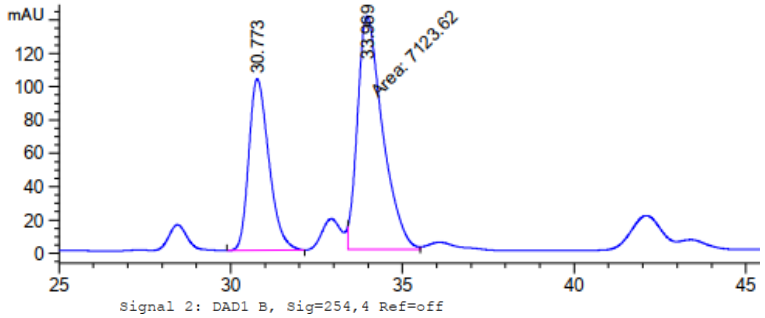
- Asymmetric sample prepared using [Ir(COD)$_2$]BARF / *(R)*-BTFM-Walphos (5 mol%) at 100 ºC (42% yield, 70:30 er).



Signal 2: DAD1 B, Sig=254,4 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	30.243	MM	0.6476	3163.16748	81.40766	70.2945
2	33.424	MM	0.6967	1336.71252	31.97562	29.7055
Totals :				4499.88000	113.38328	

- Asymmetric sample prepared using [Ir(COD)$_2$]BARF / (*R,R*)-Biphep-F (5 mol%) at 100 ºC (65% yield, 63:37 er).

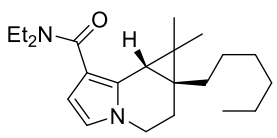


Signal 2: DAD1 B, Sig=254,4 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	30.773	BB	0.6279	4200.98291	102.98278	37.0961
2	33.969	FM	0.8473	7123.61523	140.12094	62.9039
Totals :				1.13246e4	243.10372	

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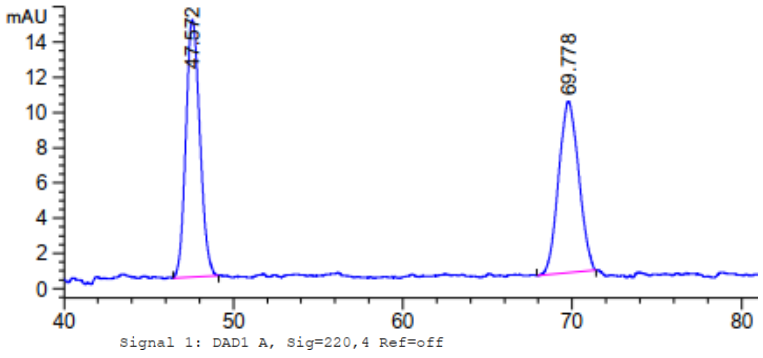
***(1aR,7bR)-N,N*-Diethyl-1a-hexyl-1,1-dimethyl-1a,2,3,7b-tetrahydro-1H-cyclopropa[g]indolizine-7-carboxa-mide (25u)**



Prepared following general procedure for catalytic reactions (page 104), using **7u**. Obtained in 47% yield as yellow oil. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 6.38 (d, *J* = 2.8 Hz, 1H), 6.11 (d, *J* = 2.7 Hz, 1H), 3.72 – 3.66 (m, 2H), 3.56 (dq, *J* = 14.2, 7.1 Hz, 2H), 3.42 (dq, *J* = 14.0, 7.0 Hz, 2H), 1.98 (dt, *J* = 14.6, 3.1 Hz, 1H), 1.88 – 1.80 (m, 1H), 1.66 (s, 1H), 1.62 – 1.58 (m, 1H), 1.51 – 1.26 (m, 9H), 1.25 (s, 3H), 1.18 (t, *J* = 7.0 Hz, 6H), 0.88 (t, *J* = 6.7 Hz, 3H), 0.68 (s, 3H) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$) δ 168.20 (CO), 130.77 (C), 117.04 (CH), 116.91 (C), 106.50 (CH), 43.27 (CH_2), 39.85 (CH_2 amide), 36.71 (CH_2), 32.04 (CH_2), 29.99 (CH_2), 28.44 (C), 27.05 (CH_2), 26.75 (CH_2), 26.29 (CH), 26.03 (C), 22.79 (CH_2), 22.52 (CH_3), 19.18 (CH_3), 14.23 (CH_3), 13.90 (CH_3 amide) ppm. **HRMS** [APCI]: *m/z* calculated for $C_{22}H_{37}N_2O$ $[M+H]^+$: 345.2900, found 345.2900.

Enantioselectivity was determined by chiral HPLC analysis on a Chiralpack IG3 column at *rt* (Hexane:iPrOH = 98:2, 1mL/min).

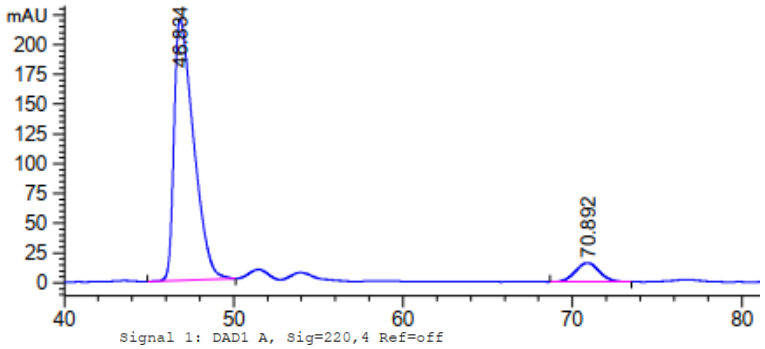
- Racemic sample prepared using $[Ir(COD)_2]$BARF / d^Fppe (5 mol%) at 100 ºC (47% yield).



Signal 1: DAD1 A, Sig=220,4 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	47.572	BB	0.8652	840.76776	14.61407	51.0314
2	69.778	BB	1.0529	806.78284	9.75509	48.9686
Totals :				1647.55060	24.36916	

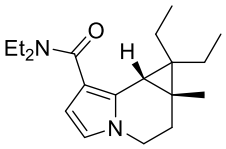
- Asymmetric sample prepared using [Ir(COD)$_2$]BARF / *(R)*-BTFM-Garphos (5 mol%) at 100 ºC (72% yield, 92:8 er)



Signal 1: DAD1 A, Sig=220,4 Ref=off

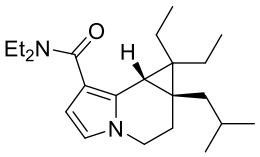
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	46.834	BB	1.1874	1.75818e4	219.74757	91.7801
2	70.892	BB	1.2963	1574.65283	15.99795	8.2199
Totals :				1.91565e4	235.74553	

***(1aR*,7bS*)*-*N*,*N*,1,1-Tetraethyl-1a-methyl-1a,2,3,7b-tetrahydro-1H-cyclopropa[g]indolizine-7-carboxamide (25z)**



Prepared following general procedure for catalytic reactions (page 104), using **7z** and d^{F}ppe (5 mol%) as ligand at 100 ºC. Obtained in 94% yield as yellow oil. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 6.43 (d, *J* = 2.9 Hz, 1H), 6.11 (d, *J* = 2.7 Hz, 1H), 3.81 – 3.56 (m, 4H), 3.33 (dq, *J* = 14.1, 7.0 Hz, 2H), 1.94 – 1.84 (m, 2H), 1.73 (s, 1H), 1.64 – 1.43 (m, 3H), 1.34 (s, 3H), 1.21 (t, *J* = 7.0 Hz, 6H), 1.15 – 1.07 (m, 1H), 0.97 (t, *J* = 7.3 Hz, 3H), 0.81 – 0.75 (m, 3H) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$) δ 168.28 (CO), 130.54 (C), 117.02 (C), 116.99 (CH), 106.21 (CH), 42.62 (CH_2), 40.83 (CH_2 amide), 37.88 (C), 29.87 (CH_2), 26.14 (CH), 23.76 (CH_2), 22.54 (C), 22.08 (CH_3), 20.13 (CH_2), 13.85 (CH_3 amide), 11.49 (CH_3), 10.10 (CH_3) ppm. **HRMS** [APCI]: *m/z* calculated for $C_{19}H_{31}N_2O$ [M+H]$^+$: 303.2431, found 303.2434.

***(1aR*,7bR*)*-*N*,*N*,1,1-Tetraethyl-1a-isobutyl-1a,2,3,7b-tetrahydro-1H-cyclopropa[g]indolizine-7-carboxamide (25α)**

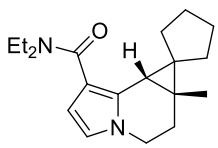


Prepared following general procedure for catalytic reactions (page 104), using **7α** and d^{F}ppe (5 mol%) as ligand at 100 ºC. Obtained in 70% yield as yellow oil. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 6.39 (d, *J* = 2.8 Hz, 1H), 6.09 (d, *J* = 2.9 Hz, 1H), 3.76 – 3.66 (m, 2H), 3.60 (dq, *J* = 14.1, 7.1 Hz, 2H), 3.32 (dq, *J* = 14.0, 7.0 Hz, 2H), 2.08 (ddd, *J* = 14.8, 3.9, 2.2 Hz, 1H), 1.93 – 1.78 (m, 2H), 1.75 (s, 1H), 1.67 – 1.58 (m, 2H), 1.47 – 1.40 (m, 1H), 1.30 – 1.21 (m, 2H), 1.18 (t, *J* = 7.1 Hz, 6H), 1.00 – 0.93 (m, 6H), 0.91 (d, *J* = 6.7 Hz, 3H), 0.77 (t, *J* = 7.4 Hz, 3H), 0.57 (dq, *J* = 14.7, 7.3 Hz, 1H) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$)

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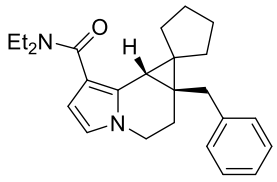
δ 168.33 (CO), 130.19 (C), 117.12 (C), 116.89 (CH), 106.34 (CH), 44.08 (CH_2), 43.03 (CH_2), 40.92 (CH_2 amide), 38.05 (C), 26.92 (C), 26.26 (CH), 25.94 (CH), 24.09 (CH_2), 23.50 (CH_3), 23.35 (CH_3), 20.01 (CH_2), 13.89 (CH_3 amide), 11.68 (CH_3), 9.89 (CH_3) ppm. **HRMS** [APCI]: *m/z* calculated for $C_{22}H_{37}N_2O$ $[M+H]^+$: 345.2900, found 345.2904. **NMR spectra at page 518.**

***(1a'R*,7b'S*)-,N*-Diethyl-1a'-methyl-1a',2',3',7b'-tetrahydrospiro[cyclopentane-1,1'-cyclopropa[g]indolizi-ne]-7'-carboxamide (25β)**



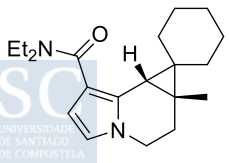
Prepared following general procedure for catalytic reactions (page 104), using **7β** and d^Fppe (5 mol%) as ligand at 100 ºC. Obtained in 71% yield as yellow oil. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 6.39 (d, *J* = 2.9 Hz, 1H), 6.12 (d, *J* = 2.8 Hz, 1H), 3.83 – 3.74 (m, 1H), 3.66 – 3.54 (m, 3H), 3.38 (dq, *J* = 14.2, 7.1 Hz, 2H), 1.93 (dt, *J* = 14.3, 5.2 Hz, 1H), 1.88 – 1.79 (m, 3H), 1.75 – 1.67 (m, 1H), 1.66 – 1.48 (m, 5H), 1.42 (dt, *J* = 12.6, 8.1 Hz, 1H), 1.27 (s, 3H), 1.18 (t, *J* = 7.1 Hz, 6H) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$) δ 168.29 (CO), 131.32 (C), 117.26 (CH), 116.62 (C), 106.69 (CH), 106.69 (CH), 42.67 (CH_2), 40.83 (C), 33.82 (CH_2), 30.14 (CH_2), 28.41 (CH_2), 28.16 (CH), 26.33 (CH_2), 26.17 (CH_2), 23.04 (C), 20.87 (CH_3), 13.83 (CH_3 amide) ppm. **HRMS** [APCI]: *m/z* calculated for $C_{19}H_{29}N_2O$ $[M+H]^+$: 301.2274, found 301.2263.

(*1a'R*,7b'R)-1a'-Benzyl-*N,N*-diethyl-1a',2',3',7b'-tetrahydrospiro[cyclopentane-1,1'-cyclopropa[g]indolizi-ne]-7'-carboxamide (25ɣ)**



Prepared following general procedure for catalytic reactions (page 104), using **7ɣ** and d^Fppe (5 mol%) as ligand at 100 ºC. Obtained in 70% yield as yellow oil. **^{1}H NMR** (500 MHz, $CDCl_3$) δ ppm. **^{13}C NMR** (75 MHz, $CDCl_3$) δ 168.20 (CO), 140.09 (C), 129.18 (CH), 128.57 (CH), 128.53 (CH), 126.27 (CH), 117.30 (CH), 116.92 (C), 106.66 (CH), 43.08 (CH_2), 42.73 (CH_2 amide), 41.38 (C), 40.57 (CH_2), 33.90 (CH_2), 29.03 (CH_2), 27.79 (CH), 27.62 (CH_2), 26.39 (CH_2), 26.09 (CH_2), 24.97 (C), 13.87 (CH_3 amide) ppm. **HRMS** [APCI]: *m/z* calculated for $C_{25}H_{33}N_2O$ $[M+H]^+$: 377.2587, found 377.2596.

***(1a'R,7b'S)-N,N*-Diethyl-1a'-methyl-1a',2',3',7b'-tetrahydrospiro[cyclohexane-1,1'-cyclopropa[g]indolizine]-7'-carboxamide (25δ)**



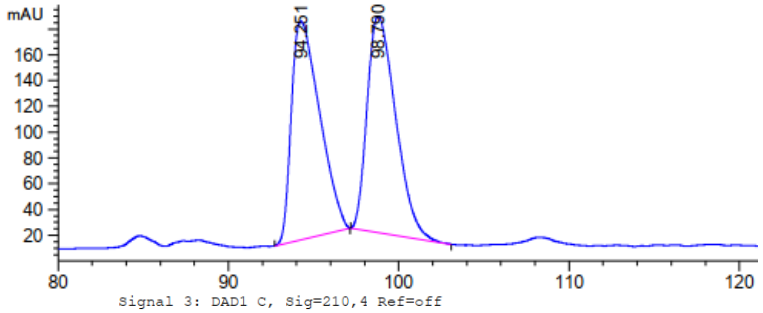
Prepared following general procedure for catalytic reactions (page 104), using **7δ**. Obtained in 99% yield as white solid. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 6.39 (d, *J* = 2.9 Hz, 1H), 6.11 (d, *J* = 2.9 Hz, 1H), 3.76 (td, *J* = 12.4, 4.0 Hz, 1H), 3.73 – 3.64 (m, 3H), 3.29 (dq, *J* = 14.0, 7.0

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Hz, 2H), 1.92 (ddd, *J* = 14.3, 12.6, 5.2 Hz, 1H), 1.81 (dd, *J* = 4.0, 2.2 Hz, 1H), 1.77 (s, 1H), 1.63 – 1.44 (m, 7H), 1.35 – 1.25 (m, 3H), 1.30 (s, 3H), 1.20 (t, *J* = 7.0 Hz, 7H) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$) δ 168.22 (CO), 131.23 (C), 117.03 (CH), 117.01 (C), 106.45 (CH), 42.69 (CH_2), 40.89 (CH_2 amide), 35.02 (C), 32.44 (CH_2), 29.27 (CH_2), 28.55 (CH_2), 26.45 (CH_2), 26.25 (CH_2), 25.98 (CH), 24.97 (CH_2), 21.89 (C), 21.54 (CH_3), 13.72 (CH_3 amide) ppm. **HRMS** [APCI]: *m/z* calculated for $C_{20}H_{31}N_2O$ $[M+H]^+$: 315.2431, found 315.2442. **NMR spectra at page 519.**

Enantioselectivity was determined by chiral HPLC analysis on a Chiralpack IG3 column at *rt* (Hexane:iPrOH = 90:10, 1mL/min).

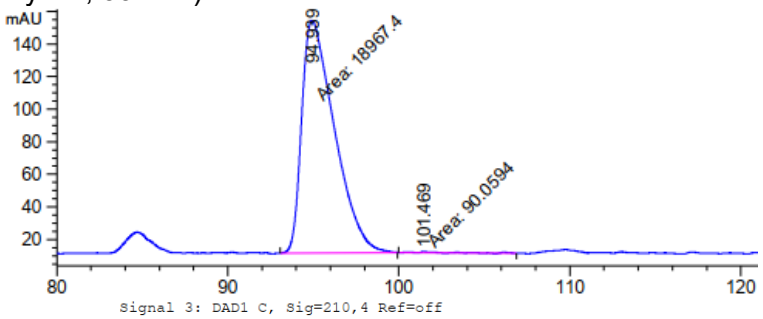
- Racemic sample prepared using [Ir(COD)$_2$]BARF / *rac*-Binap (5 mol%) at 100 ºC (99% yield).



Signal 3: DAD1 C, Sig=210,4 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	94.251	BB	1.6721	1.95861e4	169.49797	49.9490
2	98.790	BB	1.8195	1.96260e4	167.92493	50.0510
Totals :				3.92121e4	337.42290	

- Asymmetric sample prepared using [Ir(COD)$_2$]BARF / *(R)*-*P*-bisCF$_3$-Binap (5 mol%) at 100 ºC (35% yield, 99:1 er)

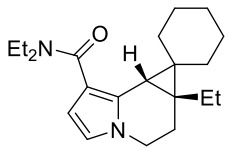


Signal 3: DAD1 C, Sig=210,4 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	94.939	MM	2.2165	1.89674e4	142.62123	99.5274
2	101.469	MM	2.1467	90.05936	6.99204e-1	0.4726
Totals :				1.90575e4	143.32044	

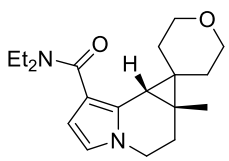
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***(1a'R*,7b'R*)-N,N*,1a'-triethyl-1a',2',3',7b'-tetrahydrospiro[cyclohexane-1,1'-cyclopropa[g]indolizine]-7'-carboxamide (25ε)**



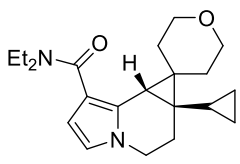
Prepared following general procedure for catalytic reactions (page 104), using **7ε** and d^{F}ppe (5 mol%) as ligand at 100 ºC. Obtained in 99% yield as white solid. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 6.37 (d, *J* = 2.9 Hz, 1H), 6.11 (d, *J* = 2.9 Hz, 1H), 3.77 – 3.67 (m, 4H), 3.25 (dq, *J* = 14.0, 7.0 Hz, 2H), 1.98 – 1.85 (m, 2H), 1.88 (s, 1H) 1.68 (dq, *J* = 14.8, 7.4 Hz, 1H), 1.63 – 1.49 (m, 7H), 1.33 (m, 1H), 1.21 (t, *J* = 7.1 Hz, 6H), 1.12 – 1.06 (m, 2H), 1.01 (t, *J* = 7.4 Hz, 3H), 0.91 – 0.82 (m, 1H) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$) δ 168.19 (CO), 131.54 (C), 116.91 (CH), 116.81 (C), 106.51 (CH), 43.35 (CH_2), 40.83 (CH_2 amide), 35.44 (C), 32.24 (CH_2), 28.84 (CH_2), 28.54 (CH_2), 27.14 (C), 26.48 (CH_2), 26.20 (CH_2), 25.63 (CH_2), 25.32 (CH), 24.79 (CH_2), 13.69 (CH_3 amide), 11.22 (CH_3) ppm. **HRMS** [APCI]: *m/z* calculated for $C_{21}H_{33}N_2O$ $[M+H]^+$: 329.2587, found 329.2591.

***(1aR*,7bS*)-N,N*,1a'-Triethyl-1a',2',3',7b'-tetrahydrospiro[cyclohexane-1,1'-cyclopropa[g]indolizine]-7'-carboxa-mide (25ζ)**



Prepared following general procedure for catalytic reactions (page 104), using **7ζ** and d^{F}ppe (5 mol%) as ligand at 100 ºC. Obtained in 87% yield as white solid. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 6.41 (d, *J* = 2.9 Hz, 1H), 6.12 (d, *J* = 2.9 Hz, 1H), 3.93 – 3.86 (m, 1H), 3.79 – 3.62 (m, 6H), 3.27 (h, *J* = 7.0 Hz, 2H), 3.15 (td, *J* = 11.3, 2.6 Hz, 1H), 1.98 (s, 1H), 1.89 (m), 1.86 – 1.80 (m, 2H), 1.50 (m), 1.31 (dd, *J* = 13.7, 2.6 Hz, 1H), 1.28 (s, 3H), 1.23 (t, *J* = 7.1 Hz, 6H), 0.64 (dd, *J* = 13.4, 2.5 Hz, 1H) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$) δ 167.83 (CO), 131.13 (C), 117.38 (CH), 116.87 (C), 106.52 (CH), 67.79 (CH_2), 66.66 (CH_2), 42.53 (CH_2), 40.04 (CH_2 amide), 32.41 (CH_2), 32.40 (CH_2), 28.89 (CH_2), 28.73 (CH_2), 25.33 (CH), 21.47 (C), 20.97 (CH_3), 14.70 (CH_3 amide) ppm. **HRMS** [APCI]: *m/z* calculated for $C_{19}H_{29}N_2O_2$ $[M+H]^+$: 317.2223, found 317.2226.

***(1a'R,7b'R)*-1a-Cyclopropyl-*N,N*-diethyl-1a,2',3,3',5',6',7b-octahydrospiro[cyclopropa[g]indolizine-1,4'-pyran]-7-carboxamide (25η)**



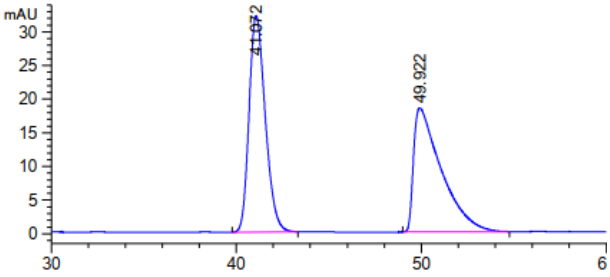
Prepared following general procedure for catalytic reactions (page 104), using **7η**. Obtained in 80% yield as white solid. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 6.36 (d, *J* = 2.9 Hz, 1H), 6.12 (d, *J* = 2.9 Hz, 1H), 3.90 – 3.82 (m, 1H), 3.73 – 3.63 (m, 6H), 3.31 (dq, *J* = 14.0, 7.0 Hz, 2H), 3.22 (td, *J* = 11.1, 2.7 Hz, 1H), 2.20 – 2.15 (m, 1H), 2.08 (s, 1H), 1.97 – 1.85 (m, 2H), 1.59 – 1.55 (m, 1H), 1.53 – 1.45 (m, 1H), 1.24 (t, *J* = 7.1 Hz, 6H), 1.17 – 1.10 (m, 1H), 0.70 – 0.62 (m, 1H), 0.57 – 0.50 (m, 1H), 0.49 – 0.43 (m, 1H), 0.41 – 0.32 (m, 2H)

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ppm. **^{13}C NMR** (126 MHz, $CDCl_3$) δ 167.80 (CO), 130.94 (C), 117.34 (CH), 116.93 (C), 106.78 (CH), 67.90 (CH_2), 66.81 (CH_2), 43.78 (CH_2), 41.19 (CH_2 amide), 33.53 (C), 32.45 (CH_2), 29.25 (CH_2), 28.08 (CH_2), 26.38 (C), 21.58 (CH), 15.97 (CH), 13.90 (CH_3 amide), 4.73 (CH_2), 1.47 (CH_2) ppm. **HRMS** [APCI]: *m/z* calculated for $C_{21}H_{31}N_2O_2$ $[M+H]^+$: 343.2380, found 343.2387.

Enantioselectivity was determined by chiral HPLC analysis on a Chiralpack IG3 column at *rt* (Hexane:iPrOH =90:10, 1mL/min).

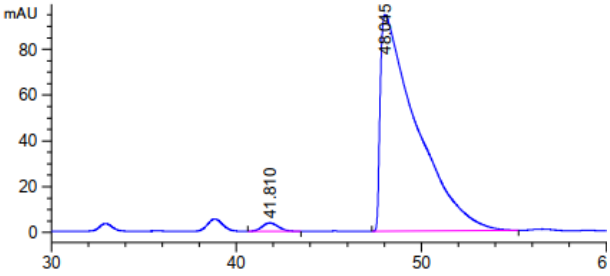
- Racemic sample prepared using [Ir(COD)$_2$]BARF / *rac*-Binap (5 mol%) at 100 ºC (80% yield).



Signal 2: DAD1 B, Sig=254,4 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	41.072	BB	0.9286	1953.56714	32.16628	50.4535
2	49.922	BB	1.3630	1918.44519	18.45156	49.5465
Totals :				3872.01233	50.61783	

- Asymmetric sample prepared using [Ir(COD)$_2$]BARF / *(R)*-BTFM-Garphos (5 mol%) at 100 ºC (40% yield, 98:2 er).

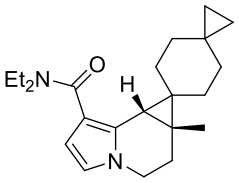


Signal 2: DAD1 B, Sig=254,4 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	41.810	BB	0.7307	221.13838	3.67155	1.6831
2	48.045	BB	1.7516	1.29176e4	94.56882	98.3169
Totals :				1.31388e4	98.24037	

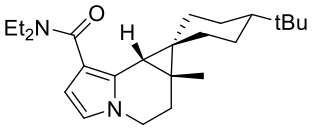
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***(1a'R*,7b'R*)*-*N,N*-Diethyl-1a''-methyl-1a'',2'',3'',7b''-tetrahydrodispiro[cyclopropane-1,1'-cyclohexane-4',1''-cyclopropa[g]indolizine]-7''-carboxamide (25θ)**



Prepared following general procedure for catalytic reactions (page 104), using **7θ** and d^{F}ppe (5 mol%) as ligand at 100 ºC. Obtained in 99% yield as white solid. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 6.40 (d, *J* = 2.8 Hz, 1H), 6.10 (d, *J* = 2.8 Hz, 1H), 3.79 – 3.66 (m, 4H), 3.21 (dq, *J* = 13.8, 6.9 Hz, 2H), 1.94 (m), 1.84 – 1.78 (m, 2H), 1.76 – 1.69 (m, 1H), 1.65 (m), 1.55 – 1.48 (m, 1H), 1.31 (s, 3H), 1.26 – 1.15 (m, 8H), 1.11 – 1.03 (m, 1H), 0.94 – 0.87 (m, 1H), 0.84 – 0.77 (m, 1H), 0.25 – 0.11 (m, 4H) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$) δ 168.15 (CO), 131.28 (C), 116.98 (CH), 116.82 (C), 106.25 (CH), 42.61 (CH_2), 41.23 (CH_2 amide), 35.09 (CH_2), 34.57 (C), 33.76 (CH_2), 31.11 (CH_2), 29.32 (CH_2), 27.40 (CH_2), 25.45 (CH), 21.72 (C), 21.69 (CH_3), 18.77 (C), 13.69 (CH_3 amide), 11.90 (CH_2), 11.36 (CH_2) ppm. **HRMS** [APCI]: *m/z* calculated for $C_{22}H_{33}N_2O$ $[M+H]^+$: 241.2587, found 241.2597.

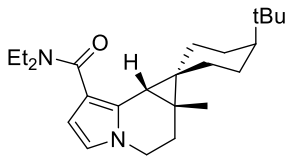
***(1s*,1a'R*,4S*,7b'S*)*-4-(*tert*-butyl)-*N,N*-diethyl-1a'-methyl-1a',2',3',7b'-tetrahydrospiro[cyclohexane-1,1'-cyclopropa[g]indolizine]-7'-carboxamide (*cis*-24ι)**



Prepared following general procedure for catalytic reactions (page 104), using **7ι** and d^{F}ppe (5 mol%) as ligand at 100 ºC. Obtained in 99% yield, as a white solid mixture of isomers in a 3:1 ratio (cis/trans-**25ι**). A small portion was purified to characterization. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 6.40 (d, *J* = 2.8 Hz, 1H), 6.10 (d, *J* = 2.9 Hz, 1H), 3.80 – 3.73 (m, 1H), 3.72 – 3.66 (m, 1H), 3.60 – 3.51 (m, 2H), 3.48 – 3.40 (m, 2H), 1.91 – 1.84 (m, 2H), 1.79 – 1.69 (m, 2H), 1.66 – 1.56 (m, 3H), 1.35 (s, 3H), 1.22 – 1.16 (m, 7H), 1.04 – 0.95 (m, 1H), 0.87 – 0.80 (m, 12H) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$) δ 168.21 (CO), 130.45 (C), 117.11 (CH), 117.06 (C), 106.52 (CH), 48.48 (CH), 42.78 (CH_2), 35.27 (CH_2 amide), 33.03 (CH_2), 32.56 (C), 29.84 (CH_2), 29.11 (CH_2), 27.76 (CH_3), 27.58 (CH_2), 26.28 (CH_2), 26.10 (CH), 21.91 (C), 21.89 (CH_3), 13.95 (CH_3 amide) ppm. **HRMS** [APCI]: *m/z* calculated for $C_{24}H_{39}N_2O$ $[M+H]^+$: 371.3057, found 371.3063. **NMR spectra at page 520.**

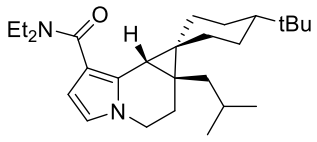
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***(1r,1a'R*,4R*,7b'S*)*-4-(*tert*-butyl)-*N,N*-diethyl-1a'-methyl-1a',2',3',7b'-tetrahydrospiro[cyclohexane-1,1'-cyclopropa[g]indolizine]-7'-carboxamide (*trans*-25ι)**



Prepared following general procedure for catalytic reactions (page 104), using **7ι** and d^Fppe (5 mol%) as ligand at 100 ºC. Obtained in 99% yield, as a white solid mixture of isomers in a 3:1 ratio (cis/trans-**25ι**). A small portion was purified to characterization. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 6.39 (d, *J* = 2.9 Hz, 1H), 6.13 (d, *J* = 2.9 Hz, 1H), 3.75 (td, *J* = 12.4, 4.1 Hz, 1H), 3.67 (m, *J* = 12.1, 5.5, 2.2 Hz, 1H), 3.61 (br m, 2H), 3.39 (br m, 2H), 1.98 (m, *J* = 14.5, 12.6, 5.6 Hz, 1H), 1.92 (s, 1H), 1.76 (m, *J* = 14.2, 3.9, 2.0 Hz, 2H), 1.55 (dd, *J* = 12.9, 3.6 Hz, 1H), 1.51 – 1.46 (m, 2H), 1.31 – 1.26 (m, 4H), 1.23 (t, *J* = 7.1 Hz, 6H), 1.21 – 1.17 (m, 1H), 0.89 – 0.84 (m, 2H), 0.82 (s, 9H), 0.77 (td, *J* = 12.4, 3.7 Hz, 1H) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$) δ 168.09 (CO), 132.27 (C), 117.18 (CH), 117.01 (C), 106.94 (CH), 48.51 (CH), 42.70 (CH_2), 42.18 (CH_2 amide), 34.63 (C), 32.69 (CH_2), 32.47 (C), 28.90 (CH_2), 27.88 (CH_3), 26.98 (CH_2), 26.22 (CH), 26.03 (CH_2), 21.56 (CH_3), 21.52 (C), 14.49 (CH_3 amide) ppm (one CH_2 signal is overlapped). **HRMS** [APCI]: *m/z* calculated for $C_{24}H_{39}N_2O$ $[M+H]^+$: 371.3057, found 371.3063. **NMR spectra at page 521.**

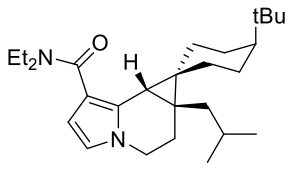
***(1s*,1a'R*,4S*,7b'S*)*-4-(*tert*-butyl)-*N,N*-diethyl-1a'-isobutyl-*1a',2',3',7b'*-tetrahydrospiro[cyclohexane-*1,1'*-cyclopropa[g]indolizine]-*7'*-carboxamide (*cis*-25κ)**



Prepared following general procedure for catalytic reactions (page 104), using **7κ** and d^Fppe (5 mol%) as ligand at 100 ºC. Obtained in 69% yield, as a white solid mixture of isomers in a 3:1 ratio (cis/trans-**25κ**). A small portion was purified to characterization. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 6.38 (d, *J* = 2.9 Hz, 1H), 6.11 (d, *J* = 2.8 Hz, 1H), 3.78 – 3.70 (m, 2H), 3.55 (dq, *J* = 14.1, 7.1 Hz, 2H), 3.45 (m, *J* = 20.9, 7.0 Hz, 2H), 2.04 (dt, *J* = 14.7, 3.1 Hz, 1H), 1.98 – 1.86 (m, 2H), 1.85 – 1.77 (m, 2H), 1.75 – 1.68 (m, 2H), 1.66 – 1.60 (m, 2H), 1.28 – 1.23 (m, 2H), 1.22 – 1.16 (m, 8H), 0.96 (2 x d, *J* = 8.0, 6H), 0.82 (s, 9H), 0.80 – 0.73 (m, 2H) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$) δ 168.07 (CO), 130.48 (C), 117.07 (CH), 116.78 (C), 106.62 (CH), 48.29 (CH), 44.72 (CH_2), 43.83 (CH_2), 41.11 (CH_2 amide), 33.34 (C), 32.77 (CH_2), 32.55 (C), 28.97 (CH_2), 27.73 (CH_3), 27.16 (CH_2), 27.02 (CH_2), 26.68 (CH), 25.92 (CH_2), 25.84 (CH_2), 25.03 (CH), 23.97 (C), 22.69 (CH_3), 13.96 (CH_3 amide) ppm. **HRMS** [APCI]: *m/z* calculated for $C_{23}H_{31}N_2O$ $[M+H]^+$: 413.3526, found 413.3526.

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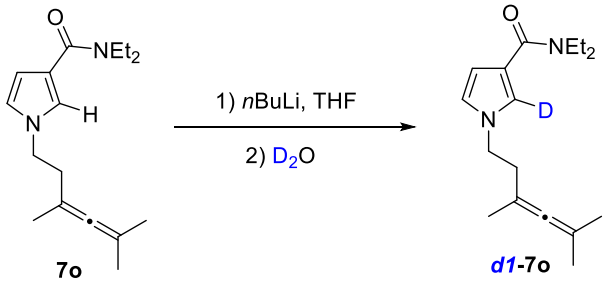
***(1r,1a'R,4R*,7b'S*)*-4-(*tert*-butyl)-*N,N*-diethyl-*1a'*-isobutyl-*1a',2',3',7b'*-tetrahydrospiro[cyclohexane-*1,1'*-cyclopropa[g]indolizine]-*7'*-carboxamide (*trans*-25κ)**



Prepared following general procedure for catalytic reactions (page 104), using **7κ** and d^{F}ppe (5 mol%) as ligand at 100 ºC. Obtained in 69% yield, as a white solid mixture of isomers in a 3:1 ratio (cis/trans-**25κ**). A small portion was purified to characterization. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 6.39 (d, *J* = 2.9 Hz, 1H), 6.14 (d, *J* = 2.9 Hz, 1H), 3.96 – 3.07 (m, 6H), 2.01 (s, 1H), 1.99 – 1.92 (m, 1H), 1.92 – 1.86 (m, 1H), 1.75 (dt, *J* = 12.5, 3.0 Hz, 1H), 1.61 – 1.53 (m, 5H), 1.47 (dt, *J* = 12.4, 3.2 Hz, 1H), 1.42 (dd, *J* = 14.4, 6.8 Hz, 1H), 1.26 – 1.22 (m, 6H), 1.19 (dd, *J* = 13.1, 3.9 Hz, 1H), 0.94 (d, *J* = 6.6 Hz, 3H), 0.89 (d, *J* = 6.7 Hz, 3H), 0.87 – 0.84 (m, 2H), 0.80 (s, 9H), 0.72 (td, *J* = 12.5, 3.8 Hz, 1H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 168.03 (CO), 132.13 (C), 117.09 (CH), 116.77 (C), 107.01 (CH), 48.46 (CH), 43.52 (CH_2 amide), 43.06 (CH_2 amide), 34.63 (C), 33.53 (CH_2), 32.42 (C), 29.85 (CH_2), 28.98 (CH_2), 27.82 (CH_3), 27.08 (CH_2), 25.98 (CH), 25.90 (CH), 25.38 (CH_2), 24.57 (CH), 23.38 (CH_3), 23.29 (CH_3), 14.58 (CH_3 amide). **HRMS** [APCI]: *m/z* calculated for $C_{23}H_{31}N_2O$ $[M+H]^+$: 413.3526, found 413.3525.

Deuterium labelling experiments

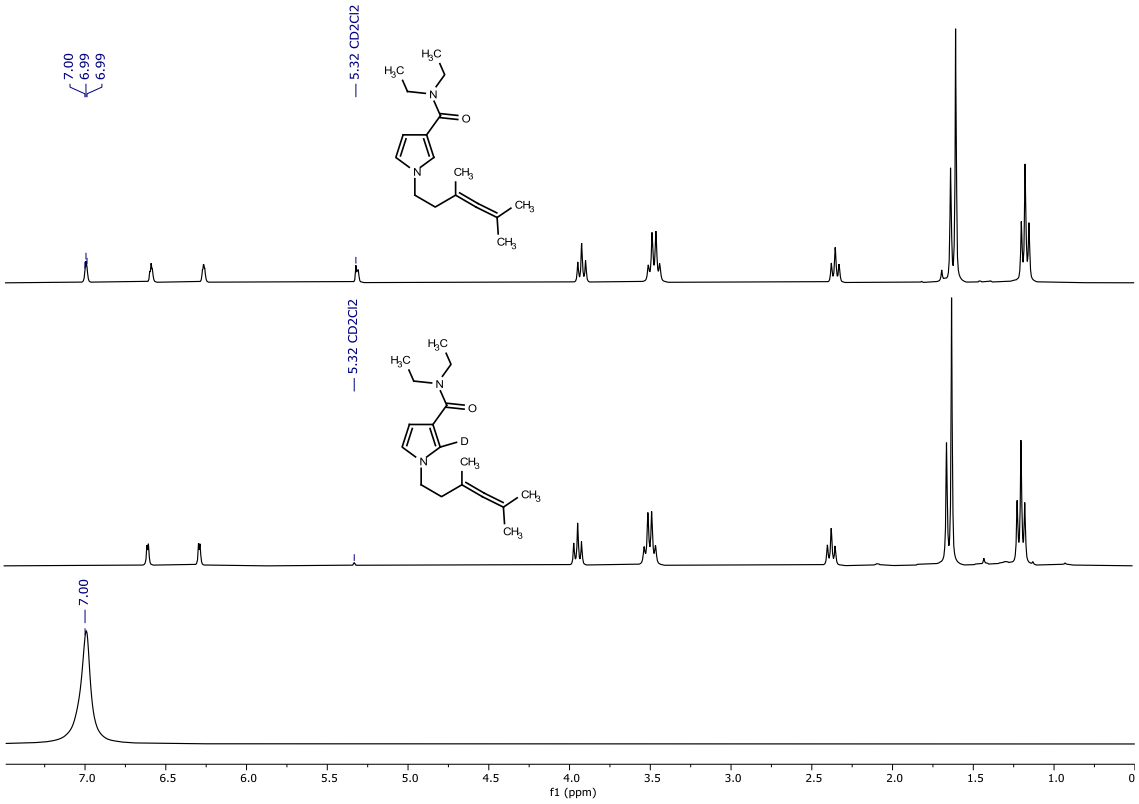
Synthesis of deuterated precursors d1-7o



7o ***d1*-7o**

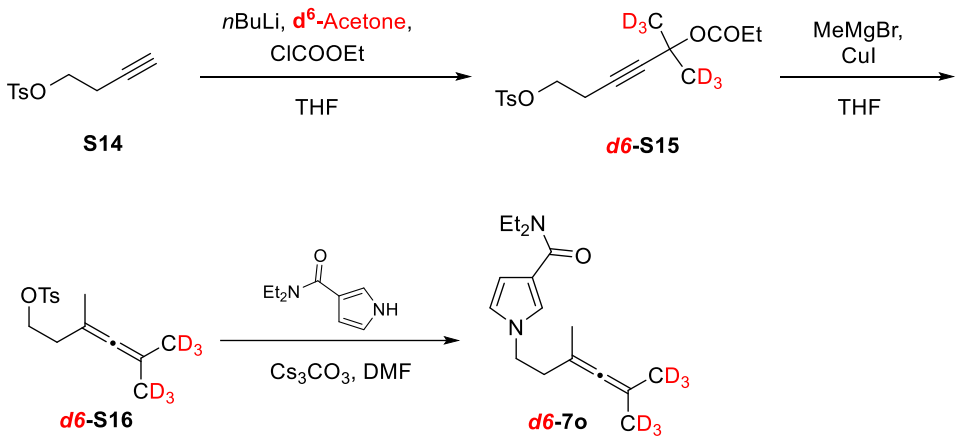
*n*BuLi (0.10 mL, 0.25 mmol, 2.5 M solution in hexanes) was added to a solution of **7o** (150 mg, 0.574 mmol) in THF (2.70 mL) at 0 ºC. After 10 minutes, D_2O (1 mL, 49.9 mmol) was added, and the mixture was extracted with Et_2O (3 x 10 mL). The organic phase was dried, concentrated and the crude residue was purified by flash chromatography, obtaining **1-(3,5-dimethylhexa-3,4-dien-1-yl)-*N,N*-diethyl-1H-pyrrole-3-carboxamide-2-d** (***d1*-7o**) as yellow oil (135 mg, 90% yield, 100% D content). **^{1}H NMR** (300 MHz, CD_2Cl_2) δ 6.60 (d, *J* = 2.8 Hz, 1H), 6.28 (d, *J* = 2.8 Hz, 1H), 3.93 (dd, *J* = 8.0, 6.4 Hz, 2H), 3.49 (q, *J* = 7.1 Hz, 4H), 2.36 (t, *J* = 7.2 Hz, 2H), 1.65 (s, 3H), 1.62 (s, 6H), 1.19 (t, *J* = 7.1 Hz, 6H) ppm. **^{2}H NMR** (77 MHz, CH_2Cl_2) δ 7.00 (s, 1H). **HRMS** [APCI]: *m/z* calculated for $C_{17}H_{26}DN_2O$ $[M+H]^+$: 276.2181, found 276.2186.

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Scheme 214**: [1]H-NMR of **7o**, [1]H-NMR of **d1-7o** and [2]H-NMR of **d1-7o.

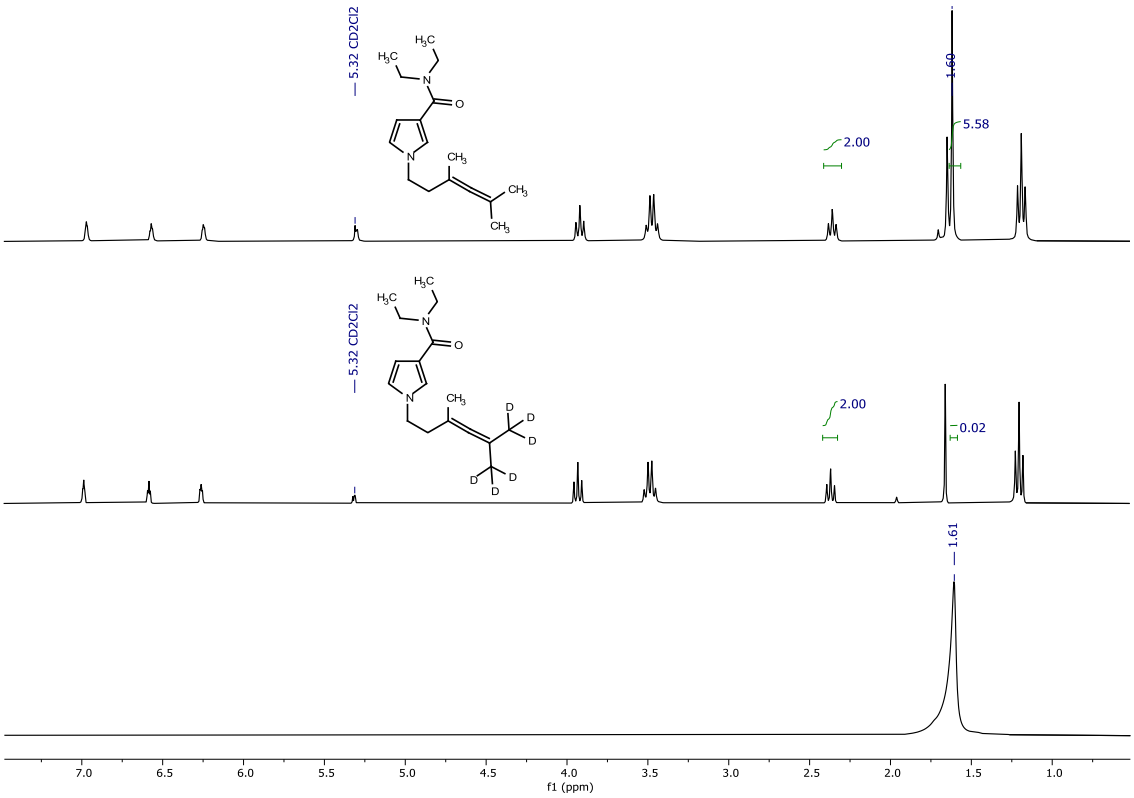
Synthesis of deuterated precursor d6-7o



Compound ***d6*-7o** was prepared following the same procedure used for **7o**, but d^6-acetone was used instead of acetone in the preparation of precursor ***d6*-S16**. ***N,N*-diethyl-1-(3-methyl-5-(methyl-d^3)hexa-3,4-dien-1-yl-6,6,6-d^3)-1H-pyrrole-3-carboxamide** (***d6*-7o**) was obtained as yellow oil (100% D content). **^{1}H NMR** (300 MHz, CD_2Cl_2) δ 7.01 (t, *J* = 2.1 Hz, 1H), 6.60 (t, *J* = 2.6 Hz, 1H), 6.28 (dd, *J* = 2.8, 1.8 Hz, 1H), 3.93 (t, *J* = 7.2 Hz, 2H), 3.48 (q, *J* = 7.1 Hz, 4H), 2.36 (t, *J* = 7.2 Hz, 2H), 1.64 (s, 3H),

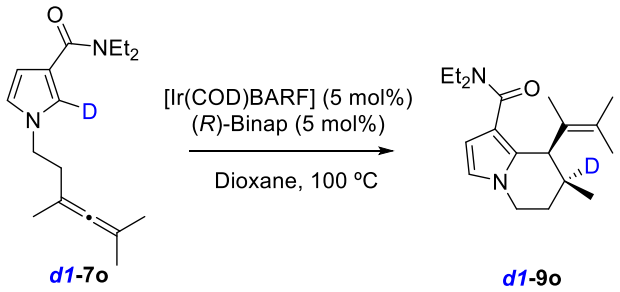
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1.19 (t, *J* = 7.1 Hz, 6H) ppm. **^{2}H NMR** (77 MHz, CH_2Cl_2) δ 1.57 (s, 6H). **HRMS** [APCI]: *m/z* calculated for $C_{17}H_{21}D_6N_2O$ $[M+H]^+$: 281.2495, found 281.2499.



***Scheme 215**: ^{1}H-NMR of **7o**, ^{1}H-NMR of **d6-7o** and ^{2}H-NMR of **d6-7o**.*

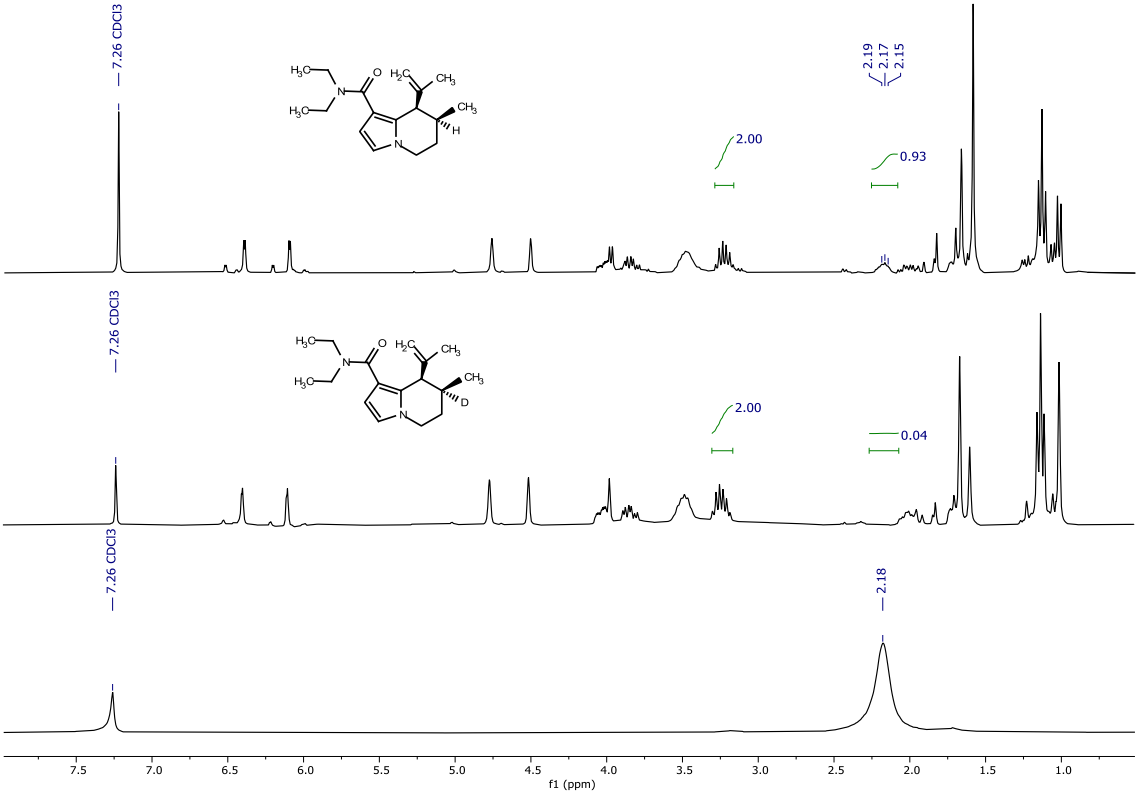
Hydroarylation of d1-7o



***d1*-7o** **d1-9o**

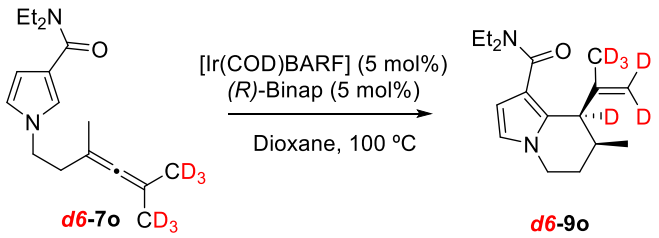
Prepared following general procedure for catalytic reactions (page 104), using ***d1*-7o** and Binap (5 mol%) as ligand at 100 ºC **(*7S,8R*)-*N,N*-Diethyl-7-methyl-8-(3-methylbut-2-en-2-yl)-5,6,7,8-tetrahydroindolizine-1-carboxamide-7-d** (***d1*-9o**) was obtained as colorless oil. **^{1}H-NMR** (300 MHz, $CDCl_3$) δ 6.42 (d, *J* = 2.7 Hz, 1H), 6.12 (d, *J* = 2.7 Hz, 1H), 4.78 (s, 1H), 4.52 (s, 1H), 4.04 (m), 3.99 (s, 1H), 3.85 (td, *J* = 12.1, 5.4 Hz, 1H), 3.50 (dd, *J* = 14.2, 7.1 Hz, 2H), 3.24 (dq, *J* = 14.0, 7.1 Hz, 2H), 2.00 (m), 1.75 – 1.68 (m, 1H), 1.66 (s, 3H), 1.12 (t, *J* = 7.0 Hz, 6H), 1.00 (s, 3H) ppm. **^{2}H-NMR** (77 MHz, $CHCl_3$) δ

2.18 (s, 1H). **HRMS** [APCI]: *m/z* calculated for $C_{17}H_{26}DN_2O$ $[M+H]^+$: 276.2181, found 276.2170. **Note**: Deuterium labelling experiments confirmed that the hydrogen atom at C2 position of the pyrrole is directly transferred to the carbon atom attached to the proximal methyl of the former allene, suggesting that the reaction may consist of a regioselective cascade hydroarylation/ dehydrogenation/ hydrogenation sequence.



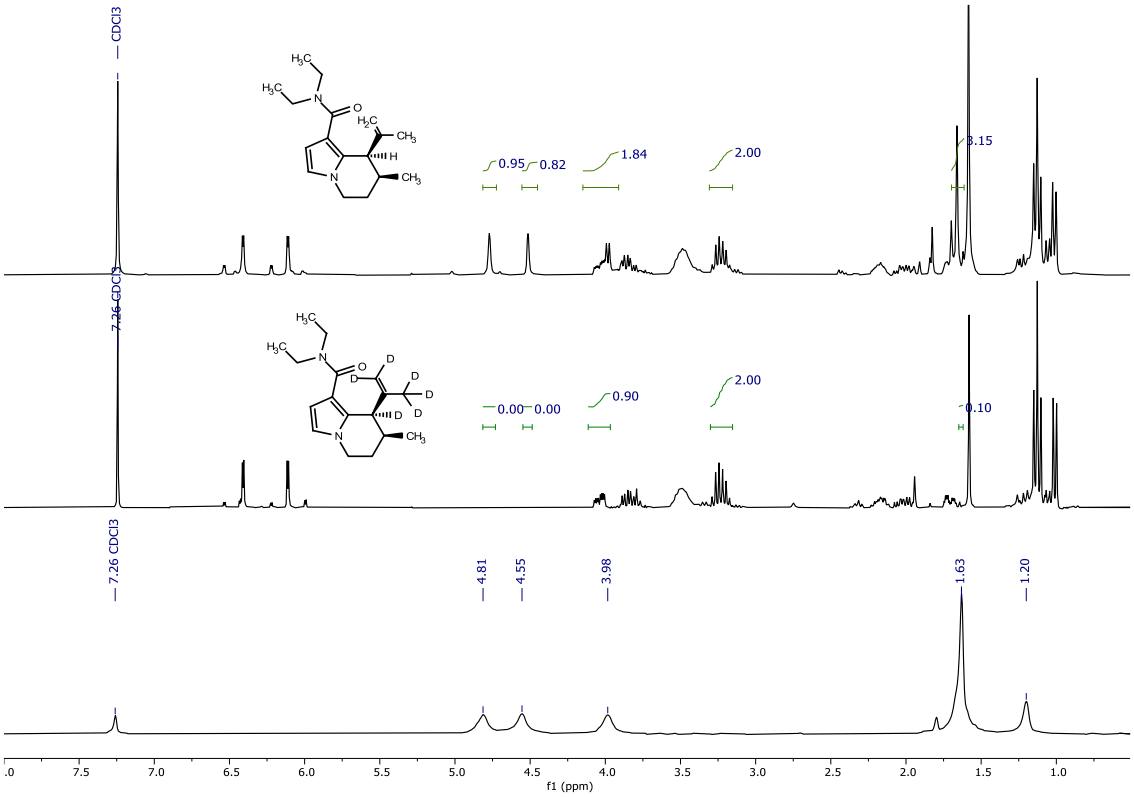
***Scheme 216**: ^{1}H-NMR of **9o**, ^{1}H-NMR of **d1-9o** and ^{2}H-NMR of **d1-9o**.*

Hydroarylation of d6-7o



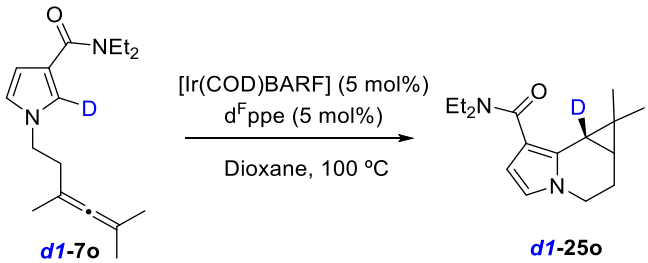
Prepared following general procedure for catalytic reactions (page 104), using ***d6*-7o** and Binap (5 mol%) as ligand at 100 ºC **(*7S,8R*)-*N,N*-diethyl-7-methyl-8-(prop-1-en-2-yl-d5)-5,6,7,8-tetrahydroindolizine-1-carboxamide-8-d** (***d6*-9o**) obtained as white solid as a single isopotomer. **^{1}H-NMR** (300 MHz, $CDCl_3$) δ 6.42 (d, *J* = 2.8 Hz, 1H), 6.12 (d, *J* = 2.8 Hz, 1H), 4.05 (m), 3.85 (td, *J* = 11.9, 5.4 Hz, 1H), 3.49 (s, 2H), 3.23 (dq, *J* = 14.0, 7.0 Hz, 2H), 2.24 – 2.10 (m, 1H), 2.08 – 1.97 (m, 1H), 1.76 – 1.65 (m, 1H), 1.12 (t, *J* =

7.1 Hz, 6H), 1.01 (d, *J* = 6.9 Hz, 3H) ppm. **^{2}H-NMR** (77 MHz, $CHCl_3$) δ 4.81 (s, 1H), 4.55 (s, 1H), 3.98 (s, 1H), 1.63 (s, 3H). **HRMS** [APCI]: *m/z* calculated for $C_{17}H_{21}D_6N_2O$ $[M+H]^+$: 281.2495, found 281.2494. **Note**: Deuterium labelling experiments confirmed that one of the hydrogen atoms at the terminal methyls of the allene is directly transferred to the carbon atom attached to the pyrrole, suggesting that the reaction may consist of a regioselective cascade hydroarylation/ dehydrogenation/ hydrogenation sequence.



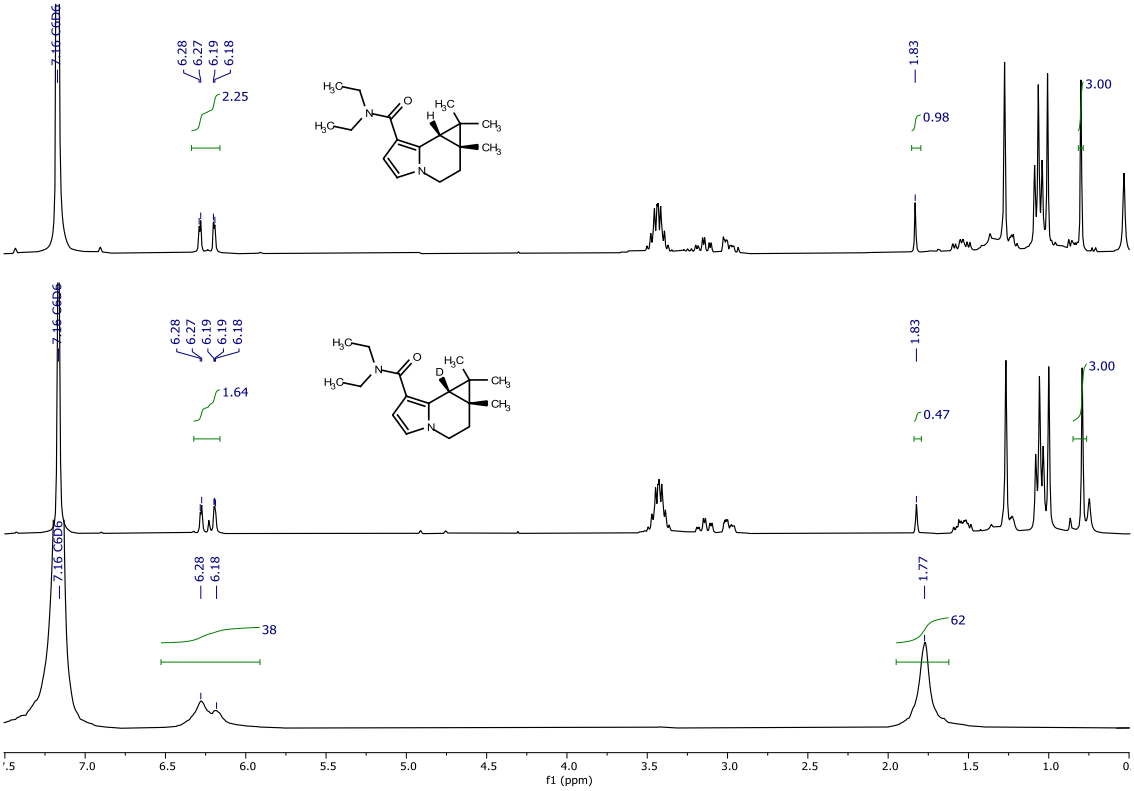
***Scheme 217**: ^{1}H-NMR of **9o**, ^{1}H-NMR of **d6-9o** and ^{2}H-NMR of **d6-9o**.*

Cyclopropanation of d1-7o



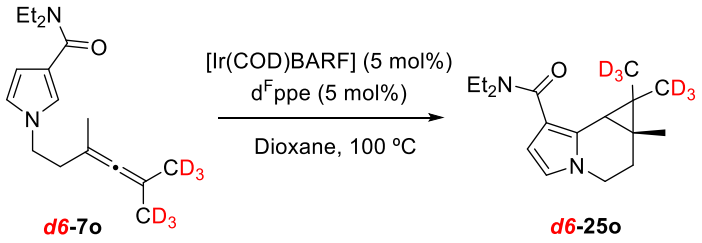
Prepared following general procedure for catalytic reactions (page 104), using ***d1*-7o** and d^{F}ppe (5 mol%) as ligand at 100 ºC **(*7S,8R*)-*N,N*-Diethyl-7-methyl-8-(prop-1-en-2-yl-d5)-5,6,7,8-tetrahydroindolizine-1-carboxamide-8-d** (***d1*-25o**) obtained as white solid. **^{1}H NMR** (300 MHz, C_6D_6) δ 6.26 (d, *J* = 2.8 Hz, 0.66H), 6.18 (d, *J* = 2.4 Hz, 0.79H), 3.42 (m), 3.13 (td, *J* = 12.3, 4.0 Hz, 1H), 2.98 (m), 1.83 (s, 0.56H), 1.60 – 1.33 (m, 2H), 1.26

(s, 3H), 1.05 (t, *J* = 7.0 Hz, 6H), 0.99 (s, 3H), 0.78 (s, 3H) ppm. **^{2}H NMR** (77 MHz, C_6D_6) δ 6.27 (s, 0.22H), 6.20 (s, 0.13H), 1.77 (s, 0.66H). **HRMS** [APCI]: *m/z* calculated for $C_{17}H_{26}DN_2O$ $[M+H]^+$: 276.2181, found 276.2184. Partial deuteration of pyrrolic protons was observed. **Note**: Deuterium labelling experiments confirmed that the hydrogen atom at the C2 position of the pyrrole is directly transferred to the cyclopropyl ring fusion, suggesting that the reaction may consist of a cascade hydroarylation/ cyclopropanation sequence.



***Scheme 218**: ^{1}H-NMR of **25o**, ^{1}H-NMR of **d1-25o** and ^{2}H-NMR of **d1-25o**.*

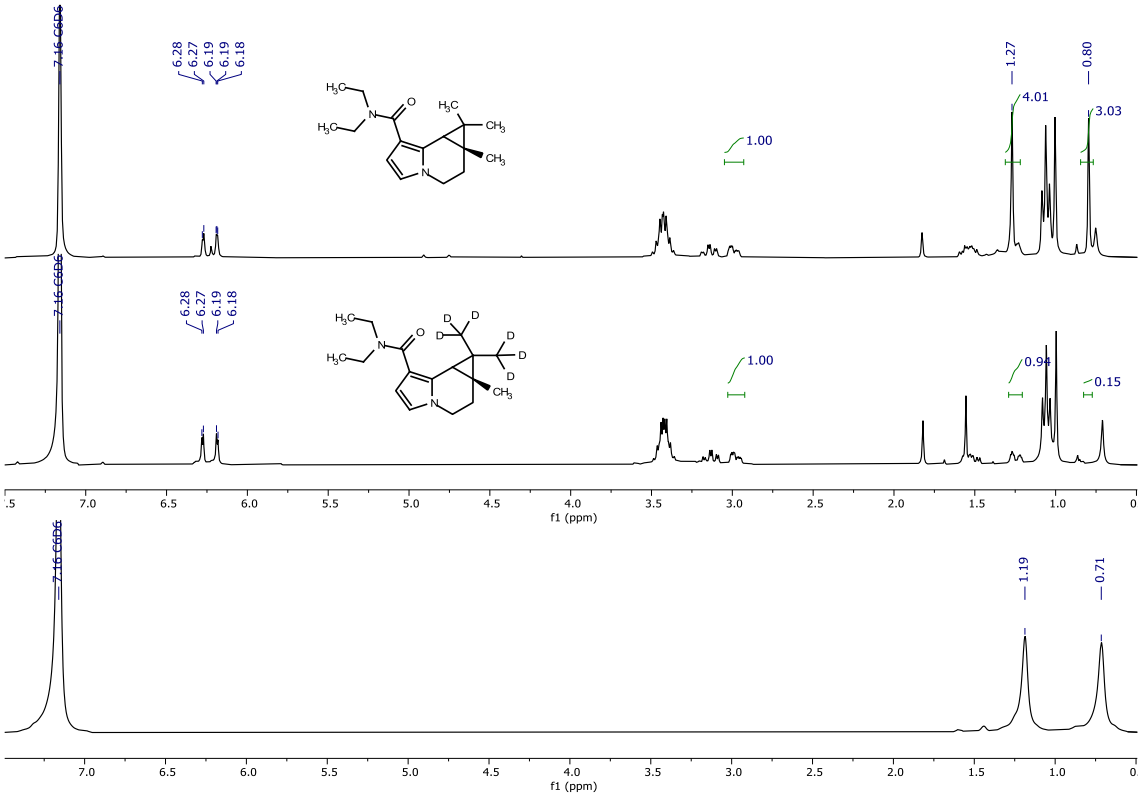
Cyclopropanation of d6-7o



***d6*-7o** ***d6*-25o**

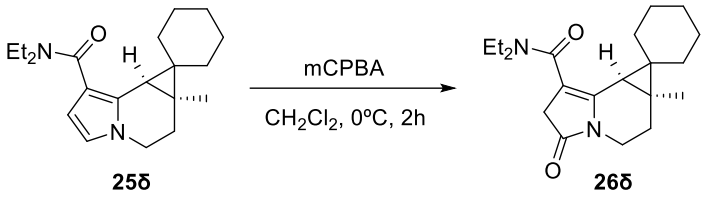
Prepared following general procedure for catalytic reactions (page 104), using ***d6*-7o** and d^{F}ppe (5 mol%) as ligand at 100 ºC. **(*7S,8R*)-*N,N*-Diethyl-7-methyl-8-(prop-1-en-2-yl-d5)-5,6,7,8-tetrahydroindolizine-1-carboxamide-8-d** (***d6*-25o**) obtained as white solid. **^{1}H NMR** (300 MHz, C_6D_6) δ 6.23 (d, *J* = 2.8 Hz, 1H), 6.14 (d, *J* = 2.8 Hz, 1H), 3.38 (m), 3.09 (td, *J* = 12.4, 4.0 Hz, 1H), 2.93 (m), 1.78 (s, 1H), 1.50 – 1.40 (m, 1H), 1.25 – 1.14

(m, 1H), 1.01 (t, *J* = 7.0 Hz, 6H), 0.95 (s, 3H) ppm. **^{2}H NMR** (77 MHz, C_6H_6) δ 1.19 (s, 3H), 0.71 (s, 3H). **HRMS** [APCI]: *m/z* calculated for $C_{17}H_{21}D_6N_2O$ $[M+H]^+$: 281.2495, found 281.2502.



***Scheme 219**: ^{1}H-NMR of **25o**, ^{1}H-NMR of **d6-25o** and ^{2}H-NMR of **d6-25o**.*

Synthesis of compound 26δ by oxidation of compound 25δ



m-CPBA (31.4 mg, 0.14 mmol) was added to an ice-cooled solution of compound **25δ** (40.0 mg, 0.127 mmol) in CH_2Cl_2 (1.5 mL). The mixture was stirred for 2h, water was added (25 mL), and the crude was extracted using CH_2Cl_2 (3 x 15 mL). The combined organic phases were dried and evaporated under reduced pressure. The obtained residue was purified by column chromatography on silica gel (from 3:1 to 1:3 hexanes/EtOAc) to afford ***(1a'S*,7b'R*)-N,N*-diethyl-1a'-methyl-5'-oxo-1a',2',3',5',6',7b'-hexahydrospiro[cyclohexane-1,1'-cyclopropa[g]indolizine]-7'-carboxamide** (**26δ**) as colorless oil in 89% yield. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 3.83 (m), 3.46 (dt, *J* = 14.3, 6.9 Hz, 2H), 3.41 – 3.24 (m, 4H), 2.98 (td, *J* = 12.5, 4.8 Hz, 1H), 1.79

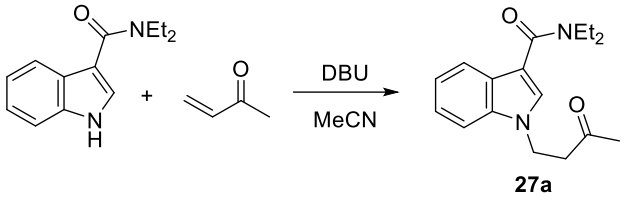
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– 1.66 (m, 2H), 1.64 (s, 1H), 1.56 – 1.44 (m, 5H), 1.43 – 1.34 (m, 2H), 1.33 – 1.28 (m, 1H), 1.27 (s, 3H), 1.25 – 1.19 (m, 2H), 1.17 (t, *J* = 7.1 Hz, 6H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 175.20 (CO), 166.25 (CO), 144.80 (C), 108.83 (C), 40.92 (CH_2 amide), 39.71 (CH_2), 35.99 (CH_2), 34.74 (C), 32.64 (CH_2), 28.91 (CH_2), 27.01 (CH_2), 26.25 (CH), 26.14 (CH_2), 24.83 (CH_2), 23.80 (C), 21.29 (CH_3), 13.78 (CH_3). **HRMS** [APCI]: *m/z* calculated for $C_{20}H_{31}N_2O_2$ $[M+H]^+$: 331.2380, found 331.2379. **NMR spectra at page 522.**

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7.4. Experimental data of section 5.4

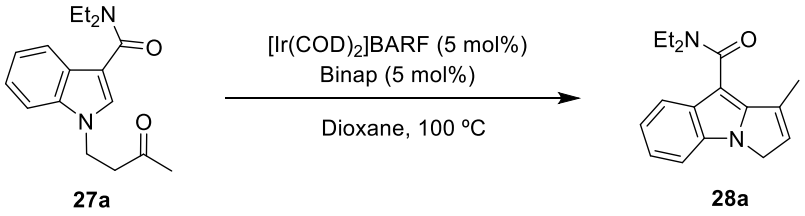
Synthesis of precursor 27a



27a

Methylvinylketone (0.56 mL, 6.94 mmol) was added to a solution of *N,N*-diethyl-1H-indole-3-carboxamide (750 mg, 3.47 mmol) and DBU (0.25 mL, 1.73 mmol) in MeCN (6.9 mL). The reaction was stirred at 50 ºC for 16 h under Ar atmosphere, allowed to cool to *rt* and water (100 mL) was added. The mixture was extracted with Et_2O (5 x 25 mL). The organic phase was dried, concentrated and the crude residue was purified by flash chromatography to obtain ***N,N*-diethyl-1-(3-oxobutyl)-1H-indole-3-carboxamide (27a)** as yellow oil in 75% yield. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.80 – 7.72 (m, 1H), 7.35 (s, 1H), 7.30 – 7.23 (m, 1H), 7.17 (m, 2H), 4.35 (t, *J* = 6.4 Hz, 2H), 3.51 (q, *J* = 7.1 Hz, 4H), 2.89 (t, *J* = 6.3 Hz, 2H), 2.05 (s, 3H), 1.19 (t, *J* = 7.1 Hz, 6H) ppm. **^{13}C NMR** (75 MHz, $CDCl_3$) δ 205.87 (CO), 166.52 (CO), 135.26 (C), 128.80 (CH), 127.12 (C), 122.40 (CH), 121.13 (CH), 120.69 (CH), 110.97 (C), 109.29 (CH), 43.00 (CH_2), 41.27 (CH_2 amide), 40.49 (CH_2), 30.23 (CH_3), 13.85 (CH_3 amide) ppm. **HRMS** [APCI]: *m/z* calculated for $C_{17}H2_3N_2O_2$ $[M+H]^+$: 287.1754, found 287.1758.

Synthesis of compounds 29a by cyclodehydration of 27a



27a **28a**

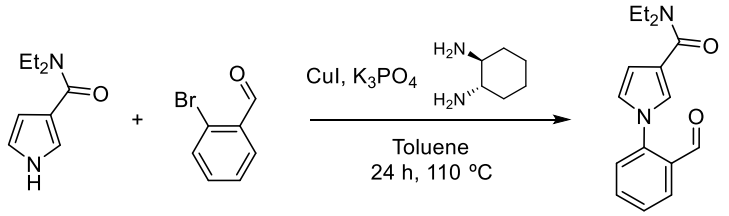
Prepared following general procedure for catalytic reactions (page 104), using **27a** (28.6 mg, 0.1 mmol), $[Ir(COD)_2]BARF$ (6.4 mg, 0.005 mmol) and *rac*-Binap (3.1 mg, 0.005 mmol) in dioxane (0.8 mL) at 100 ºC for 16 h. Purified by flash chromatography (3:1 to 1:3 hexanes/EtOAc). ***N,N*-diethyl-1-methyl-3H-pyrrolo[1,2-a]indole-9-carboxamide (28a)** was obtained as brown oil (26.6 mg, 99% yield). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.51 (dt, *J* = 7.9, 1.0 Hz, 1H), 7.28 (dt, *J* = 7.9, 0.9 Hz, 1H), 7.17 (ddd, *J* = 8.1, 7.1, 1.2 Hz, 1H), 7.10 (ddd, *J* = 8.1, 7.0, 1.1 Hz, 1H), 6.24 (q, *J* = 1.8 Hz, 1H), 4.52 (t, *J* = 2.1 Hz, 2H), 3.56 (br s, 4H), 2.19 (d, *J* = 1.8 Hz, 3H), 1.17 (br, 7H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 167.03 (CO), 147.84 (C), 133.82 (C), 133.35 (C), 130.05 (C), 129.03 (CH), 121.77 (CH),

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120.72 (CH), 120.04 (CH), 109.13 (CH), 101.96 (C), 49.69 (CH_2), 40.49 (CH_2 amide), 14.13 (CH_3 amide), 13.35 (CH_3) ppm. **HRMS** [APCI]: *m/z* calculated for $C_{17}H_{20}N_2O$ $[M+H]^+$: 269.1648, found 269.1643.

Synthesis of precursor 30a-c

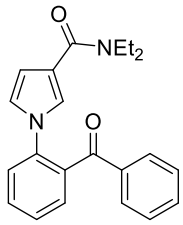
*(exemplified for **30a**).*



30a

A mixture of 2-bromobenzaldehyde (300 mg, 1.62 mmol), *N,N*-diethyl-1H-pyrrole-3-carboxamide (269 mg, 1.62 mmol), (±)-trans-1,2- cyclohexanediamine (18 mg, 0.16 mmol), CuI (31 mg, 0.16 mmol), and K_3PO_4 (1.03 g, 4.86 mmol) was degassed and the flask filled with Argon. After the addition of Toluene (5.4 mL) under a stream of argon, the reaction was stirred for 24 h at 110 ℃ in oil bath under argon atmosphere. The reaction mixture was cooled to ambient temperature, diluted with ethyl acetate (20-30 mL), filtered through a plug of celite, eluting with additional ethyl acetate (50-100 mL). The filtrate was concentrated, and the resulting residue was purified by column chromatography (1:3 to 3:1 hexanes/EtOAc) to obtain ***N,N*-diethyl-1-(2-formylphenyl)-1H-pyrrole-3-carboxamide (30a)** as pale-yellow solid in 91% yield. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 9.81 (s, 1H), 7.97 (d, *J* = 7.8 Hz, 1H), 7.67 (t, *J* = 7.7 Hz, 1H), 7.50 (t, *J* = 7.6 Hz, 1H), 7.41 (d, *J* = 7.9 Hz, 1H), 7.26 (s, 1H), 6.84 (s, 1H), 6.55 (s, 1H), 3.53 (q, *J* = 7.2 Hz, 4H), 1.22 (t, *J* = 7.1 Hz, 6H) ppm. **^{13}C NMR** (75 MHz, $CDCl_3$) δ 189.32 (CO), 165.92 (CO), 142.88 (C), 134.95 (CH), 130.71 (C), 128.53 (CH), 128.37 (CH), 126.63 (CH), 125.31 (CH), 123.77 (CH), 121.82 (C), 110.79 (CH), 40.83 (CH_2 amide), 14.08 (CH_3 amide) ppm. **HRMS** [APCI]: *m/z* calculated for $C_{16}H_{19}N_2O_2$ $[M+H]^+$: 271.1441, found 271.1431.

1-(2-benzoylphenyl)-*N,N*-diethyl-1H-pyrrole-3-carboxamide (30b)



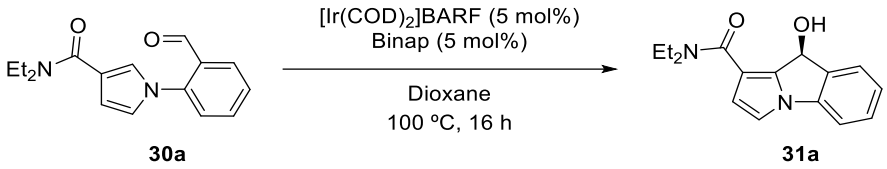
Synthesized by following the procedure used for **30a** but employing (2-bromophenyl)(phenyl)methanone instead of 2-bromobenzaldehyde. Obtained as yellow solid in 26% yield. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.69 – 7.59 (m, 4H), 7.48 (dd, *J* = 10.4, 7.8 Hz, 3H), 7.32 (t, *J* = 7.6 Hz, 2H), 7.03 (s, 1H), 6.71 (s, 1H), 6.25 (s, 1H), 3.31 (br m, 4H), 1.11 (br t, *J* = 7.0 Hz, 6H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 196.06 (CO), 166.06 (CO), 138.45 (C), 136.25 (C), 134.79 (C), 133.32 (CH), 131.70 (CH), 129.73 (CH), 129.12 (CH), 128.23 (CH), 127.59 (CH), 125.12 (CH), 123.03 (CH), 122.04 (CH), 121.50 (C),

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110.78 (CH), 41.62 (CH_2 amide), 13.72 (CH_3 amide) ppm. **HRMS** [APCI]: *m/z* calculated for $C_{22}H_{23}N_2O_2$ $[M+H]^+$: 347.1754, found 347.1750. **NMR spectra at page 523.**

Synthesis of compounds 32a-b from precursors 30a-b

*(exemplified for **31a**).*

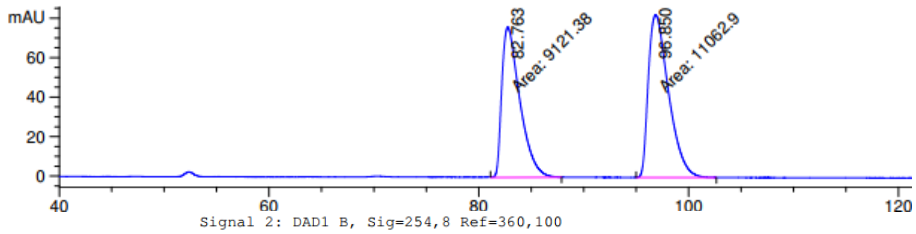


30a **31a**

Prepared following general procedure for catalytic reactions (page 104), using **30a** (27.0 mg, 0.1 mmol), $[Ir(COD)_2]BARF$ (6.4 mg, 0.005 mmol) and Binap (3.1 mg, 0.005 mmol) at 100 ºC for 16 h. The mixture was concentrated, and the crude residue was purified by flash chromatography (1:2 to 0:1 Hexanes/EtOAc) to obtain ***N,N*-diethyl-9-hydroxy-9H-pyrrolo[1,2-a]indole-1-carboxamide (31a)** as pale-yellow solid. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.65 (dq, *J* = 7.4, 0.7 Hz, 1H), 7.35 (td, *J* = 7.7, 1.2 Hz, 1H), 7.22 (d, *J* = 7.8 Hz, 1H), 7.19 (td, *J* = 7.5, 1.0 Hz, 1H), 6.97 (d, *J* = 3.0 Hz, 1H), 6.44 (d, *J* = 3.0 Hz, 1H), 5.91 (d, *J* = 0.7 Hz, 1H), 5.83 (s, 1H), 3.74 (s, 2H), 3.52 (dq, *J* = 14.2, 7.1 Hz, 2H), 1.31 (t, *J* = 7.1 Hz, 6H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 166.51 (CO), 145.70 (C), 140.29 (C), 137.51 (C), 129.25 (CH), 126.82 (CH), 125.03 (CH), 115.37 (C), 112.14 (CH), 111.06 (CH), 110.31 (CH), 42.30 (CH_2 amide), 13.97 (CH_3 amide) ppm. **HRMS** [APCI]: *m/z* calculated for $C_{16}H_{19}N_2O_2$ $[M+H]^+$: 271.1441, found 271.1449.

Enantioselectivity was determined by chiral HPLC analysis on a Chiralpack IE3 column at *rt* (Hexane:iPrOH = 90:10, 1mL/min).

- Racemic sample prepared using $[Ir(COD)_2]BARF$ / *rac*-Binap (5 mol%) at 100 ºC.

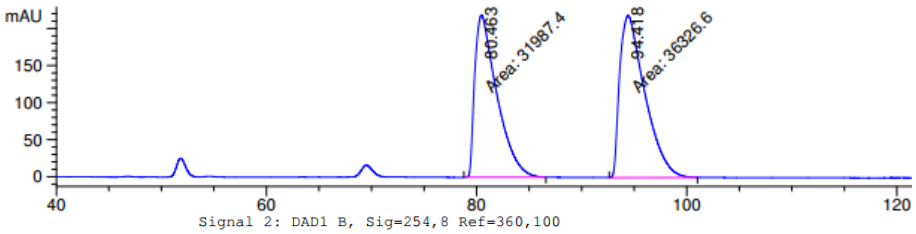


Signal 2: DAD1 B, Sig=254,8 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	82.763	MM	1.9969	9121.38086	76.13032	45.1906
2	96.850	MM	2.2389	1.10629e4	82.35287	54.8094
Totals :				2.01842e4	158.48319	

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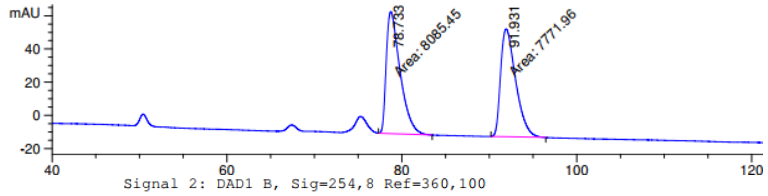
- Asymmetric sample prepared using [Ir(COD)$_2$]BARF / *(S)*-Binap (5 mol%) at 100 ºC (89% yield, 53:47 er).



Signal 2: DAD1 B, Sig=254,8 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	80.463	MM	2.4330	3.19874e4	219.12234	46.8241
2	94.418	MM	2.7667	3.63266e4	218.83029	53.1759

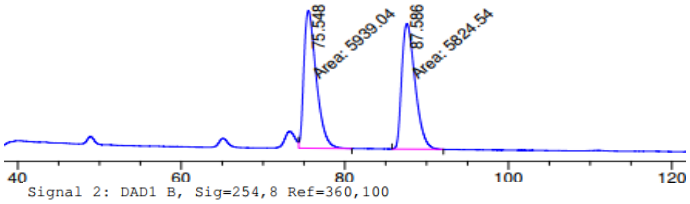
- Asymmetric sample prepared using [Ir(COD)$_2$]BARF / *(R)*-DTBM-Segphos (5 mol%) at 100 ºC (64% yield, 50:50 er).



Signal 2: DAD1 B, Sig=254,8 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	78.733	MM	1.8325	8085.45264	73.53698	50.9885
2	91.931	MM	1.9949	7771.96484	64.93113	49.0115
Totals :				1.58574e4	138.46811	

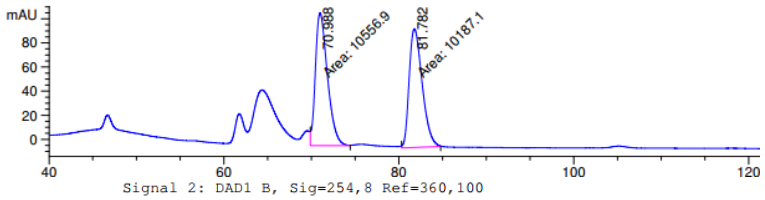
- Racemic sample prepared using [Ir(COD)$_2$]BARF / *rac*-Binap (5 mol%) at 100 ºC (reinjected).



Signal 2: DAD1 B, Sig=254,8 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	75.548	FM	1.7602	5939.03760	56.23354	50.4867
2	87.586	MM	1.8938	5824.53857	51.25848	49.5133
Totals :				1.17636e4	107.49202	

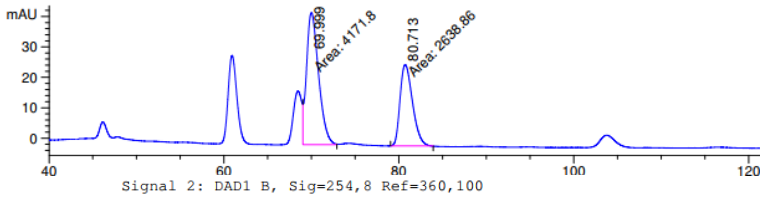
- Asymmetric sample prepared using [Ir(COD)$_2$]BARF / *(S)*-Binapine (5 mol%) at 100 ºC (38% yield, 50:50 er).



Signal 2: DAD1 B, Sig=254,8 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	70.981	MM	1.5970	4647.75342	48.50506	50.9831
2	81.774	MM	1.7206	4468.51758	43.28327	49.0169
Totals :				9116.27100	91.78833	

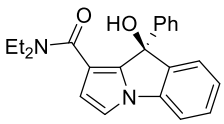
- Asymmetric sample prepared using [Ir(COD)$_2$]BARF / *(R)*-BTFM-Garphos (5 mol%) at 100 ºC (41% yield, approx.. 60:40 er).



Signal 2: DAD1 B, Sig=254,8 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	69.999	FM	1.6021	4171.80322	43.39827	61.2540
2	80.713	MM	1.6468	2638.85840	26.70664	38.7460
Totals :				6810.66162	70.10491	

_N,N_-diethyl-9-hydroxy-9-phenyl-9H-pyrrolo[1,2-a]indole-1-carboxamide (31b)

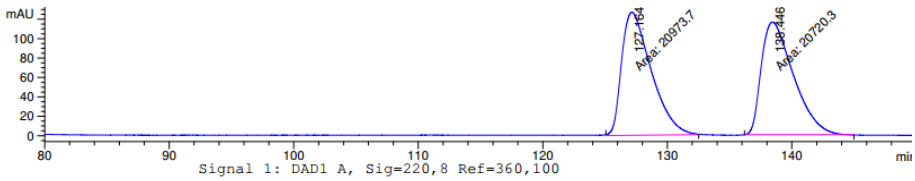


Prepared following general procedure for catalytic reactions (page 104), using **30b.** Obtained as pale yellow solid. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.43 – 7.40 (m, 2H), 7.34 (d, *J* = 7.6 Hz, 1H), 7.30 (td, *J* = 7.6, 1.2 Hz, 1H), 7.25 – 7.20 (m, 3H), 7.21 – 7.14 (m, 1H), 7.09 (td, *J* = 7.5, 1.2 Hz, 1H), 7.00 (d, *J* = 3.0 Hz, 1H), 6.71 (s, 1H), 6.42 (d, *J* = 3.0 Hz, 1H), 3.59 (br, 2H), 3.34 (br m, *J* = 7.1 Hz, 2H), 1.10 (br, 6H) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$) δ 166.49 (CO), 148.37 (C), 144.14 (C), 142.71 (C), 139.36 (C), 129.01 (CH), 128.06 (CH), 127.22 (CH), 126.05 (CH), 125.44 (CH), 125.42 (CH), 114.79 (C), 112.12 (CH), 110.87 (CH), 110.35 (CH), 77.91 (C), 42.21 (CH_2 amide), 13.78 (CH_3 amide) ppm. **HRMS** [APCI]: *m/z* calculated for $C_{22}H_{23}N_2O_2$ $[M+H]^+$: 347.1754, found 347.1754. **NMR spectra at page 524.**

Enantioselectivity was determined by chiral HPLC analysis on a Chiralpack IE3 column at *rt* (Hexane:iPrOH = 95:5, 1mL/min).

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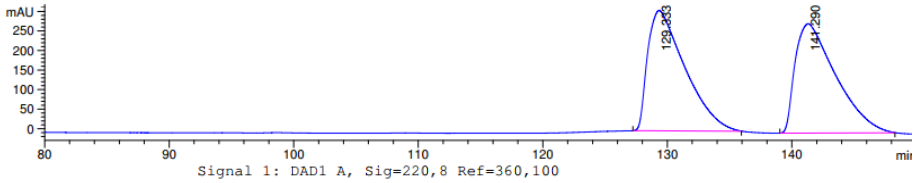
- Racemic sample prepared using [Ir(COD)$_2$]BARF / *rac*-Binap (5 mol%) at 100 ºC.



Signal 1: DAD1 A, Sig=220,8 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	127.164	MM	2.7564	2.09737e4	126.81770	50.3038
2	138.446	MM	2.9806	2.07203e4	115.86071	49.6962
Totals :				4.16940e4	242.67841	

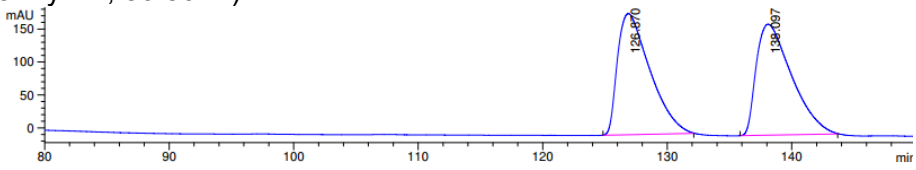
- Asymmetric sample prepared using [Ir(COD)$_2$]BARF / *(S)*-Binap (5 mol%) at 100 ºC (99% yield, 50:50 er).



Signal 1: DAD1 A, Sig=220,8 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	129.333	BB	2.4907	6.39927e4	307.64932	50.2343
2	141.290	PB	2.7201	6.33957e4	279.72601	49.7657
Totals :				1.27388e5	587.37534	

- Asymmetric sample prepared using [Ir(COD)$_2$]BARF / *(S)*-Binapine (5 mol%) at 100 ºC (99% yield, 50:50 er).

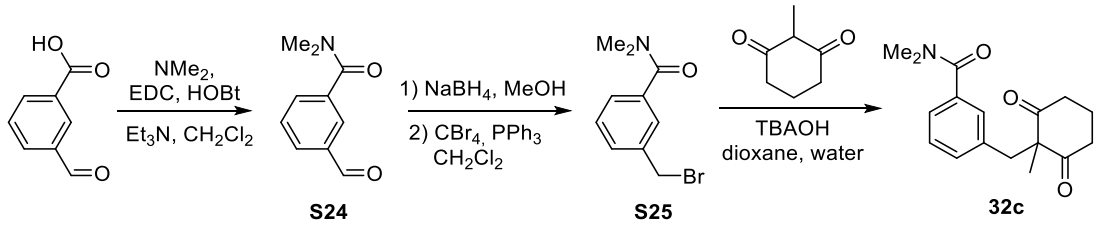


Signal 1: DAD1 A, Sig=220,8 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	126.870	BB	2.1194	3.32266e4	183.94009	50.0109
2	138.097	BB	2.3598	3.32122e4	168.48148	49.9891
Totals :				6.64388e4	352.42157	

Synthesis of precursors 32a-n

*(exemplified for **32c**).*



Me_2NH (19.1 mL, 38.3 mmol, 2 M in THF) was added to a solution of 3-Formyl-benzoic acid (5.0 g, 33.3 mmol), EDC·HCl (9.6 g, 49.6 mmol), HOBt (5.3 g, 33.3 mmol) and Et_3N

(27.8 mL, 0.2 mol) in CH_2Cl_2 (133 mL). The resulting mixture was stirred overnight and then quenched with water (1 L). The layers were separated, and the aqueous phase was extracted twice with CH_2Cl_2 (2 x 300 mL). The combined organic layers were washed with brine (400 mL) dried, and the solvent was evaporated to afford **3-Formyl-*N,N*-dimethylbenzamide** (**S24**, 5.9 g, 86% yield) as pale-yellow oil, that was used without further purification.

$NaBH_4$ (1.05 g, 27.8 mmol) was added to a solution of **3-Formyl-*N,N*-dimethylbenzamide** (**S24**, 3.28 g, 18.5) in MeOH (74 mL) at 0 ºC. The reaction was stirred at the same temperature until full conversion of the starting material (TLC). The reaction was quenched with a saturated solution of NH_4Cl in water (100 mL). The reaction mixture was extracted with AcOEt (3 x 200 mL). The combined organic layers were washed with brine (200 mL) dried, and the solvent was evaporated to afford **3-(hydroxymethyl)-*N,N*-dimethylbenzamide** (3.15 g, 95 % yield) that was used without further purification.

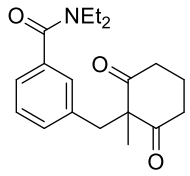
To a solution of PPh_3 (3.51 g, 13.4 mmol) and **3-(hydroxymethyl)-*N,N*-dimethylbenzamide** (2.0 g, 11.2 mmol) in CH_2Cl_2 (56 mL) at rt, CBr_4 (1.3 mL, 13.4 mmol) was added portionwise. When TLC showed the reaction was complete, reaction mixture was concentrated, and the resulting crude was purified by column chromatography (100% EtOAc) to deliver **3-(bromomethyl)-*N,N*-dimethylbenzamide** (**S25**, 2.0 g, 74% yield) as yellow oil.

To a stirred solution of 2-methylcyclohexane-1,3-dione (200 mg, 1.59 mmol) in dioxane (0.8 mL) was added aqueous TBAOH (0.59 mL, 1.59 mmol, 1.54 M in water). The mixture was stirred for 20 min at rt. Then a solution of **3-(bromomethyl)-*N,N*-dimethylbenzamide** (**S25**, 461 mg g, 1.90 mmol) in dioxane (0.8 mL) was added and the reaction mixture was stirred for another 12-36 h. Upon completion, the reaction was quenched with saturated aqueous solution of NH_4Cl (20 mL) and extracted with EtOAc (3 x 100 mL). The organics were combined, dried over anhydrous Na_2SO_4, and evaporated under reduced pressure.[193] The crude mixture was purified by column chromatography (0 to 100% EtOAc/hexanes) to give **3-(bromomethyl)-*N,N*-dimethylbenzamide** (**32c**) as white solid in 36% yield. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.20 – 7.07 (m, 2H), 7.04 – 6.88 (m, 2H), 3.04 (s, 2H), 2.97 (br s, 3H), 2.83 (br s, 3H), 2.55 – 2.40 (m, 2H), 2.34 – 2.19 (m, 2H), 1.76 – 1.61 (m, 1H), 1.56 – 1.41 (m, 1H), 1.18 (s, 3H) ppm. **^{13}C NMR** (75 MHz, $CDCl_3$) δ 210.72 (CO), 171.09 (CO), 136.74 (C), 136.38 (C), 131.06 (CH), 128.40 (CH), 128.33 (CH), 125.63 (CH), 65.22 (C), 42.53 (CH_2), 39.37 (CH_3

[193] Procedure adapted from P. Zhou, T. Xu, *Chem. Commun.,* **2020**, *56*, 8194-8197.

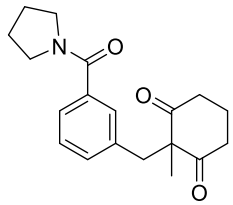
amide), 38.89 (CH_2), 35.18 (CH_3 amide), 22.20 (CH_3), 16.61 (CH_2) ppm. **HRMS** [APCI]: *m/z* calculated for $C_{17}H_{22}NO_3$ $[M+H]^+$: 288.1594, found 288.1597.

***N,N*-diethyl-3-((1-methyl-2,6-dioxocyclohexyl)methyl)benzamide (32a)**



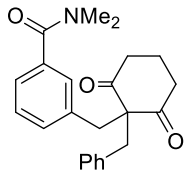
Synthesized by following the procedure used for **32c**. Obtained as pale-yellow solid in 24% yield. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.31 – 7.17 (m, 2H), 7.09 – 7.02 (m, 1H), 3.52 (br m, 2H), 3.22 (br m, 2H), 3.15 (s, 2H), 2.65 – 2.49 (m, 2H), 2.44 – 2.28 (m, 2H), 1.88 – 1.70 (m, 1H), 1.67 – 1.50 (m, 1H), 1.30 (s, 3H), 1.17 (br m, *J* = 31.0 Hz, 6H) ppm. **^{13}C NMR** (75 MHz, $CDCl_3$) δ 210.99 (CO), 170.96 (CO), 137.62 (C), 137.06 (C), 130.89 (CH), 128.63 (CH), 127.84 (CH), 125.23 (CH), 65.41 (C), 43.00 (CH_2), 39.20 (CH_2), 22.50 (CH_3), 16.82 (CH_2) ppm [NOTE: amide signals are not visible due to rotamerism]. **HRMS** [APCI]: *m/z* calculated for $C_{19}H_{26}NO_3$ $[M+H]^+$: 316.1907, found 316.1909.

2-methyl-2-(3-(pyrrolidine-1-carbonyl)benzyl)cyclohexane-1,3-dione (32b)



Synthesized by following the procedure used for **32c**. Obtained as colourless solid in 17% yield. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.36 (d, *J* = 7.6 Hz, 1H), 7.26 (t, *J* = 7.6 Hz, 1H), 7.16 (s, 1H), 7.09 (d, *J* = 7.5 Hz, 1H), 3.61 (t, *J* = 6.8 Hz, 2H), 3.36 (t, *J* = 6.5 Hz, 2H), 3.15 (s, 2H), 2.63 – 2.48 (m, 2H), 2.41 – 2.29 (m, 2H), 2.00 – 1.74 (m, 5H), 1.65 – 1.49 (m, 1H), 1.29 (s, 3H) ppm. **^{13}C NMR** (75 MHz, $CDCl_3$) δ 210.95 (CO), 169.32 (CO), 137.46 (C), 136.73 (C), 131.43 (CH), 128.47 (CH), 125.91 (CH), 65.32 (C), 49.47 (CH_2), 46.16 (CH_2), 42.79 (CH_2), 39.10 (CH_2), 26.41 (CH_2), 24.44 (CH_2), 22.49 (CH_3), 16.71 (CH_2) δ ppm. **HRMS** [APCI]: *m/z* calculated for $C_{19}H_{24}NO_3$ $[M+H]^+$: 314.1751, found 314.1753.

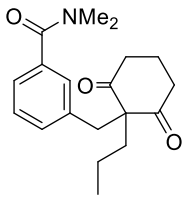
3-((1-benzyl-2,6-dioxocyclohexyl)methyl)-*N,N*-dimethylbenzamide (32d)



Synthesized by following the procedure used for **32c**. Obtained as white solid in 61% yield. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.23 – 7.07 (m, 5H), 7.07 – 6.85 (m, 4H), 3.18 (dd, *J* = 11.7, 3.8 Hz, 4H), 3.01 (br s, 3H), 2.85 (br s, 3H), 1.93 – 1.69 (m, 4H), 0.89 – 0.72 (m, 2H) ppm. **^{13}C NMR** (75 MHz, $CDCl_3$) δ 212.62 (CO), 171.00 (CO), 136.78 (C), 136.54 (C), 136.08 (C), 131.05 (CH), 129.86 (CH), 128.73 (CH), 128.58 (CH), 128.30 (CH_2), 127.13 (CH_2), 125.90 (CH_2), 70.58 (C), 45.39 (CH_2), 44.37 (CH_2), 41.47 (CH_2), 39.38 (CH_3 amide), 35.25 (CH_3 amide), 14.64 (CH_2) ppm. **HRMS** [APCI]: *m/z* calculated for $C_{23}H_{26}NO_3$ $[M+H]^+$: 364.1907, found 364.1908. **NMR spectra at page 525.**

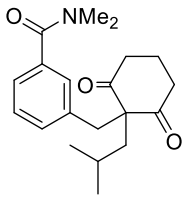
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3-((2,6-dioxo-1-propylcyclohexyl)methyl)-*N,N*-dimethylbenzamide (32e)



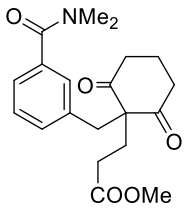
Synthesized by following the procedure used for **32c**. Obtained as white solid in 93% yield. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.18 – 7.04 (m, 2H), 6.97 – 6.84 (m, 2H), 2.95 (br s, *J* = 4.9 Hz, 6H), 2.79 (br s, 3H), 2.30 (ddd, *J* = 17.2, 8.5, 4.9 Hz, 2H), 2.01 (ddd, *J* = 17.2, 8.3, 4.9 Hz, 2H), 1.76 – 1.66 (m, 2H), 1.66 – 1.50 (m, 1H), 1.24 – 1.10 (m, 1H), 0.96 (dq, *J* = 14.7, 7.3 Hz, 2H), 0.71 (t, *J* = 7.2 Hz, 3H) ppm. **^{13}C NMR** (75 MHz, $CDCl_3$) δ 212.00 (CO), 170.94 (CO), 136.81 (C), 136.54 (C), 130.88 (CH), 128.47 (CH), 128.15 (CH), 125.63 (CH), 69.15 (C), 43.75 (CH_2), 41.03 (CH_2), 40.69 (CH_2), 39.27 (CH_3 amide), 35.10 (CH_3 amide), 18.64 (CH_2), 15.64 (C)H2, 14.33 (CH_3) ppm. **HRMS** [APCI]: *m/z* calculated for $C_{19}H_{26}NO_3$ $[M+H]^+$: 316.1907, found 316.1905.

3-((1-isobutyl-2,6-dioxocyclohexyl)methyl)-*N,N*-dimethylbenzamide (32f)



Synthesized by following the procedure used for **32c**. Obtained as white solid in 66% yield. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.23 – 7.10 (m, 2H), 6.99 – 6.86 (m, 2H), 2.97 (br m, 5H), 2.83 (br s, 3H), 2.47 – 2.32 (m, 2H), 2.07 – 1.94 (m, 2H), 1.90 – 1.75 (m, 2H), 1.75 – 1.57 (m, 1H), 1.45 – 1.28 (m, 1H), 1.28 – 1.09 (m, 1H), 0.81 – 0.62 (m, 6H) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$) δ ^{13}C NMR (75 MHz, $CDCl_3$) δ 212.19 (CO), 170.98 (CO), 136.69 (C), 136.57 (C), 131.01 (CH), 128.62 (CH), 128.26 (CH), 125.87 (CH), 68.56 (C), 47.78 (CH_2), 45.95 (CH_2), 40.74 (CH_2), 39.36 (CH_3 amide), 35.20 (CH_3 amide), 25.43 (CH), 24.04 (CH_3), 15.77 (CH_2) ppm. **HRMS** [APCI]: *m/z* calculated for $C_{20}H_{28}NO_3$ $[M+H]^+$: 330.2064, found 330.2064.

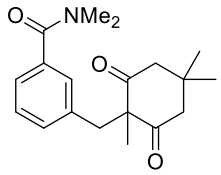
methyl 3-(1-(3-(dimethylcarbamoyl)benzyl)-2,6-dioxocyclohexyl)propanoate (32g)



Synthesized by following the procedure used for **32c**. Obtained as pale-yellow solid. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.31 – 7.21 (m, 2H), 7.06 – 6.96 (m, 2H), 3.61 (s, 2H), 3.07 (br s, 5H), 2.91 (br s, 3H), 2.58 – 2.40 (m, 3H), 2.32 – 2.18 (m, 2H), 2.16 (s, 3H), 1.83 – 1.66 (m, 1H), 1.53 – 1.33 (m, 1H) ppm. **^{13}C NMR** (75 MHz, $CDCl_3$) δ 210.87 (CO), 172.84 (CO), 171.15 (C), 136.80 (C), 136.12 (CH), 131.23 (CH), 128.78 (CH), 128.48 (CH), 126.11 (CH), 68.26 (C), 51.78 (CH_3), 43.73 (CH_2), 40.20 (CH_2), 39.54 (CH_3 amide), 35.36 (CH_3 amide), 31.44 (CH_2), 29.63 (CH_2), 16.15 (CH_2) ppm. **HRMS** [APCI]: *m/z* calculated for $C_{20}H_{26}NO_5$ $[M+H]^+$: 360.1805, found 360.1808.

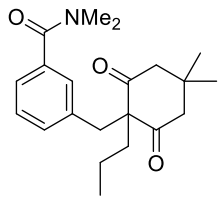
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***N,N*-dimethyl-3-((1,4,4-trimethyl-2,6-dioxocyclohexyl)methyl)benzamide (32h)**



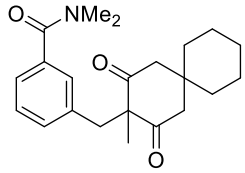
Synthesized by following the procedure used for **32c**. Obtained as pale-yellow solid in 72% yield. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.21 – 7.10 (m, 2H), 7.09 – 6.97 (m, 2H), 3.01 (br m, 5H), 2.84 (s, 3H), 2.42 (d, *J* = 2.5 Hz, 4H), 1.16 (d, *J* = 3.8 Hz, 3H), 0.81 (d, *J* = 3.2 Hz, 3H), 0.67 (d, *J* = 3.1 Hz, 3H) ppm. **^{13}C NMR** (75 MHz, $CDCl_3$) δ 209.97 (CO), 171.08 (CO), 136.23 (C), 131.59 (CH), 128.88 (CH), 128.18 (CH), 125.66 (CH), 64.75 (C), 52.08 (CH_2), 42.35 (CH_2), 39.35 (CH_3 amide), 35.15 (CH_3 amide), 30.24 (C), 28.50 (CH_3), 28.27 (CH_3), 20.96 (CH_3) ppm. **HRMS** [APCI]: *m/z* calculated for $C_{19}H_{26}NO_3$ $[M+H]^+$: 316.1907, found 316.1907.

3-((4,4-dimethyl-2,6-dioxo-1-propylcyclohexyl)methyl)-*N,N*-diethylbenzamide (32i)



Synthesized by following the procedure used for **32c**. Obtained as white solid in 80% yield. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.20 – 7.04 (m, 4H), 3.03 (d, *J* = 4.1 Hz, 2H), 2.98 (br s, 3H), 2.83 (br s, 3H), 2.44 (dd, *J* = 15.5, 3.6 Hz, 2H), 2.29 (dd, *J* = 15.4, 3.4 Hz, 2H), 1.67 – 1.58 (m, 2H), 1.19 – 1.03 (m, 2H), 0.92 – 0.71 (m, 6H), 0.40 (d, *J* = 4.0 Hz, 3H) ppm. **^{13}C NMR** (75 MHz, $CDCl_3$) δ 209.50 (CO), 209.48 (CO), 171.26 (C), 136.80 (C), 135.89 (C), 132.36 (CH), 129.74 (CH), 127.93 (CH), 125.42 (CH), 69.32 (C), 52.18 (CH_2), 39.38 (CH_2), 39.34 (CH_2), 35.16 (CH_3 amide), 30.11 (C), 29.20 (CH_3), 27.50 (CH_3), 17.83 (CH_2), 14.26 (CH_3) ppm. **HRMS** [APCI]: *m/z* calculated for $C_{21}H_{30}NO_3$ $[M+H]^+$: 344.2220, found 344.2221. **NMR spectra at page 526.**

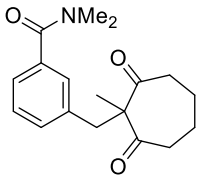
***N,N*-dimethyl-3-((3-methyl-2,4-dioxospiro[5.5]undecan-3-yl)methyl)benzamide (32j)**



Synthesized by following the procedure used for **32c**. Obtained as colourless oil in 90% yield. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.20 – 7.07 (m, 2H), 7.05 – 6.93 (m, 2H), 2.96 (br m, 5H), 2.81 (br s, 3H), 2.49 (dd, *J* = 15.0, 2.7 Hz, 2H), 2.37 (dd, *J* = 15.0, 1.9 Hz, 2H), 1.38 – 1.14 (m, 6H), 1.14 – 1.00 (m, 5H), 0.97 – 0.79 (m, 2H) ppm. **^{13}C NMR** (75 MHz, $CDCl_3$) δ 209.90 (CO), 170.95 (CO), 136.15 (C), 131.44 (CH), 128.79 (CH), 128.03 (CH), 125.55 (CH), 65.14 (C), 49.75 (CH_2), 42.40 (CH_2), 39.28 (CH_3 amide), 36.65 (CH_2), 36.26 (CH_2), 35.06 (CH_3 amide), 33.00 (C), 25.01 (CH_2), 20.98 (CH_2), 20.95 (CH_2), 20.70 (CH_3) ppm. **HRMS** [APCI]: *m/z* calculated for $C_{22}H_{30}NO_3$ $[M+H]^+$: 356.2220, found 356.2222.

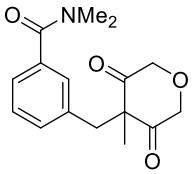
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***N,N*-dimethyl-3-((1-methyl-2,7-dioxocycloheptyl)methyl)benzamide (32k)**



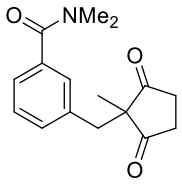
Synthesized by following the procedure used for **32c**. Obtained as white solid in 48% yield. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.25 – 7.14 (m, 2H), 7.07 – 6.93 (m, 2H), 3.08 (br s, *J* = 2.2 Hz, 2H), 3.02 (br s, 3H), 2.88 (br s, 3H), 2.45 – 2.32 (m, 4H), 1.89 – 1.72 (m, 4H), 1.10 (br d, *J* = 2.1 Hz, 3H) ppm. **^{13}C NMR** (75 MHz, $CDCl_3$) δ 211.66 (CO), 171.26 (CO), 136.43 (C), 136.35 (C), 131.26 (CH), 128.53 (CH), 128.32 (CH), 125.59 (CH), 65.89 (C), 41.75 (CH_2), 39.69 (CH_2), 39.47 (CH_3 amide), 35.26 (CH_3 amide), 27.87 (CH_2), 18.92 (CH_3) ppm. **HRMS** [APCI]: *m/z* calculated for $C_{18}H_{24}NO_3$ $[M+H]^+$: 302.1751, found 302.1755.

***N,N*-dimethyl-3-((4-methyl-3,5-dioxotetrahydro-2H-pyran-4-yl)methyl)benzamide (32l)**



Synthesized by following the procedure used for **32c**. Obtained as colourless oil in 75% yield. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.33 – 7.22 (m, 2H), 7.14 – 7.03 (m, 2H), 4.18 (d, *J* = 3.5 Hz, 4H), 3.24 (d, *J* = 4.3 Hz, 2H), 3.06 (br s, 3H), 2.92 (br s, 3H), 1.28 (d, *J* = 5.2 Hz, 3H) ppm. **^{13}C NMR** (75 MHz, $CDCl_3$) δ 207.49 (CO), 171.11 (CO), 136.52 (C), 135.69 (C), 131.24 (CH), 128.58 (CH), 128.50 (CH), 125.91 (CH), 73.52 (C), 64.69 (CH_2), 40.90 (CH_2), 39.43 (CH_3 amide), 35.26 (CH_3 amide), 18.37 (CH_3) ppm. **HRMS** [APCI]: *m/z* calculated for $C_{16}H_{20}NO_4$ $[M+H]^+$: 290.1387, found 290.1392. **NMR spectra at page 527.**

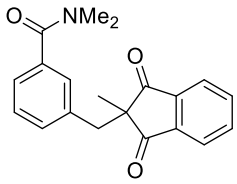
***N,N*-dimethyl-3-((1-methyl-2,5-dioxocyclopentyl)methyl)benzamide (32m)**



Synthesized by following the procedure used for **33c**. Obtained as colourless oil in 50% yield. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.27 – 7.16 (m, 2H), 7.06 – 6.97 (m, 2H), 3.02 (br s, 3H), 2.89 (br d, *J* = 12.9 Hz, 5H), 2.63 – 2.49 (m, 2H), 2.16 – 2.05 (m, 2H), 1.14 (s, 3H) ppm. **^{13}C NMR** (75 MHz, $CDCl_3$) δ 216.65 (CO), 170.98 (CO), 136.68 (C), 135.90 (C), 130.81 (CH), 128.73 (CH), 128.10 (CH), 126.06 (CH), 58.06 (C), 41.92 (CH_2), 39.41 (CH_3 amide), 35.63 (CH_2), 35.28 (CH_3 amide), 20.24 (CH_3) ppm. **HRMS** [APCI]: *m/z* calculated for $C_{16}H_{20}NO_3$ $[M+H]^+$: 274.1438, found 274.1442.

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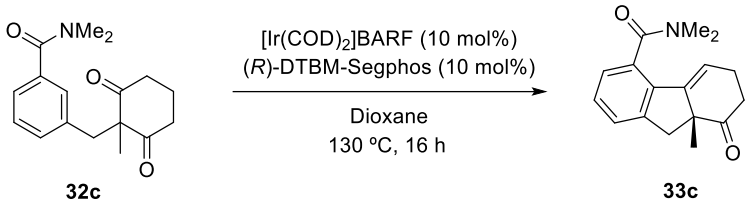
***N,N*-dimethyl-3-((2-methyl-1,3-dioxo-2,3-dihydro-1H-inden-2-yl)methyl)benzamide (32n)**



Synthesized by following the procedure used for **32c**. Obtained as pale-yellow solid in 77% yield. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.82 – 7.72 (m, 2H), 7.68 (ddd, *J* = 4.8, 3.2, 1.5 Hz, 2H), 7.07 – 6.94 (m, 3H), 3.14 (s, 2H), 3.01 (br s, 3H), 2.68 (br s, 3H), 1.36 (s, 3H) ppm. **^{13}C NMR** (300 MHz, $CDCl_3$) δ 7.82 – 7.72 (m, 2H), 7.68 (ddd, *J* = 4.8, 3.2, 1.5 Hz, 2H), 7.07 – 6.94 (m, 3H), 3.14 (s, 2H), 3.01 (br s, 3H), 2.68 (br s, 3H), 1.36 (s, 3H) ppm. **HRMS** [APCI]: *m/z* calculated for $C_{20}H_{20}NO_3$ $[M+H]^+$: 322.1438, found 322.1437. **NMR spectra at page 528.**

Synthesis of compounds 33 and/or 34 from precursors 33

*(exemplified for **33c**).*

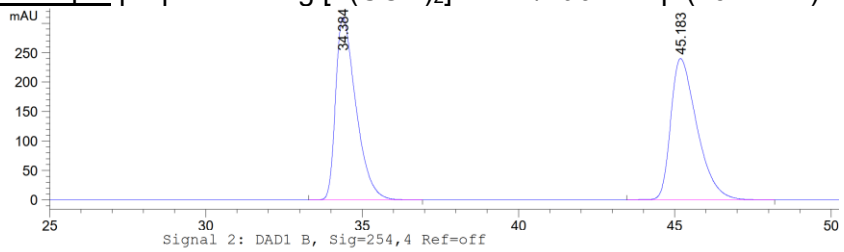


32c **33c**

Prepared following general procedure for catalytic reactions (page 104), using **32c** (28.7 mg, 0.1 mmol), $[Ir(COD)_2]BARF$ (12.7 mg, 0.01 mmol) and (*R*)-DTBM-Segphos (11.8 mg, 0.01 mmol) at 100 ºC for 16 h. The mixture was concentrated, and the crude residue was purified by flash chromatography (1:3 to 3:1 Hexanes/CH_2Cl_2, then 1:10 hexanes/EtOAc to 100% EtOAc). ***(R)-N,N*,9a-trimethyl-1-oxo-2,3,9,9a-tetrahydro-1H-fluorene-5-carboxamide (33c)** was obtained as pale yellow oil **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.26 – 7.14 (m, 2H), 7.08 – 6.95 (m, 1H), 6.05 (d x2, *J* = 88.4, 6.8, 2.8 Hz, 1H), 3.29 (d x2, *J* = 41.4, 16.6 Hz, 1H), 3.11 (s x2, 3H), 2.78 (d, *J* = 3.0 Hz, 3H), 2.75 – 2.60 (m, 3H), 2.57 – 2.48 (m, 1H), 2.32 – 2.23 (m, 1H), 1.25 (s x2, 3H) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$) δ 215.15 (CO), 170.72 (CO), 145.43 (C), 145.27 (C), 143.49 (C), 142.79 (C), 133.37 (C), 133.25 (C), 131.80 (C), 131.53 (C), 128.82 (CH), 128.51 (CH), 126.42 (CH), 126.34 (CH), 124.88 (CH), 124.54 (CH), 119.64 (CH), 118.97 (CH), 55.28 (C), 54.99 (C), 40.17 (CH_2), 40.00 (CH_2), 38.49 (CH_3 amide), 38.28 (CH_3 amide), 35.62 (CH_2), 35.27 (CH_2), 34.90 (CH_3 amide), 34.63 (CH_3 amide), 24.58 (CH_3), 24.08 (CH_3), 23.88 (CH_2) ppm [NOTE: Most carbon signals are duplicated due to rotamerism]. **HRMS** [APCI]: *m/z* calculated for $C_{17}H_{20}NO_2$ $[M+H]^+$: 270.1489, found 270.1492. **NMR spectra at page 529.**

Enantioselectivity was determined by chiral HPLC analysis on a Chiralpack IG3 column at *rt* (Hexane:iPrOH = 90:10, 1mL/min).

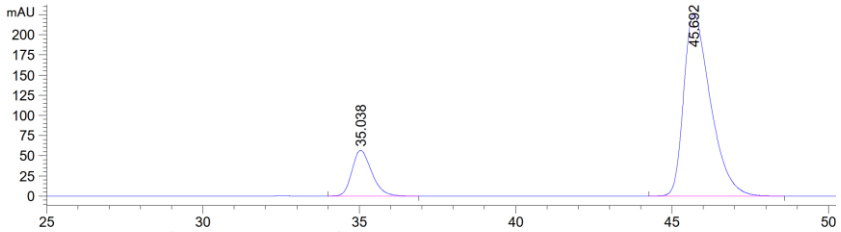
- Racemic sample prepared using [Ir(COD)$_2$]BARF / *rac*-Binap (10 mol%) at 130 ºC.



Signal 2: DAD1 B, Sig=254,4 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	34.384	BB	0.6841	1.39710e4	309.82864	49.9253
2	45.183	BB	0.8859	1.40129e4	239.74489	50.0747
Totals :				2.79839e4	549.57353	

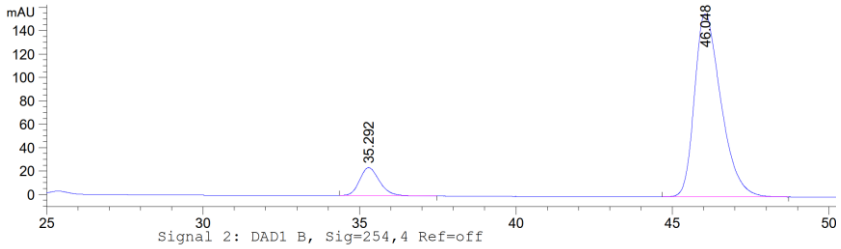
- Asymmetric sample prepared using [Ir(COD)$_2$]BARF / *(R)*-Segphos (10 mol%) at 130 ºC (96% yield, 85:15 er).



Signal 2: DAD1 B, Sig=254,4 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	35.038	BB	0.6669	2477.19238	56.56292	15.5466
2	45.692	BB	0.9019	1.34568e4	226.25812	84.4534
Totals :				1.59340e4	282.82104	

- Asymmetric sample prepared using [Ir(COD)$_2$]BARF / *(R)*-DTBM-Segphos (10 mol%) at 130 ºC (94% yield, 90:10 er).

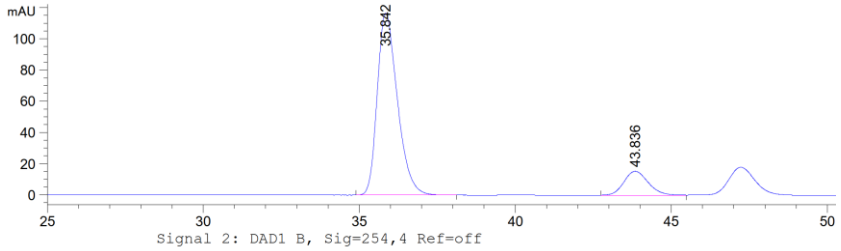


Signal 2: DAD1 B, Sig=254,4 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	35.292	BB	0.6694	1044.03687	23.81981	10.1981
2	46.048	BB	0.9013	9193.52148	156.50128	89.8019
Totals :				1.02376e4	180.32109	

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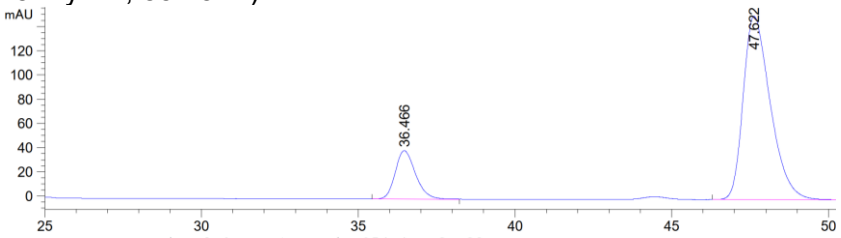
- Asymmetric sample prepared using [Ir(COD)$_2$]BARF / *(S)*-DTBM-Garphos (10 mol%) at 130 ºC (34% yield, 84:16 er).



Signal 2: DAD1 B, Sig=254,4 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	35.842	BB	0.6892	5233.57715	116.70697	86.4011
2	43.836	BB	0.7880	823.72748	15.35051	13.5989
Totals :				6057.30463	132.05748	

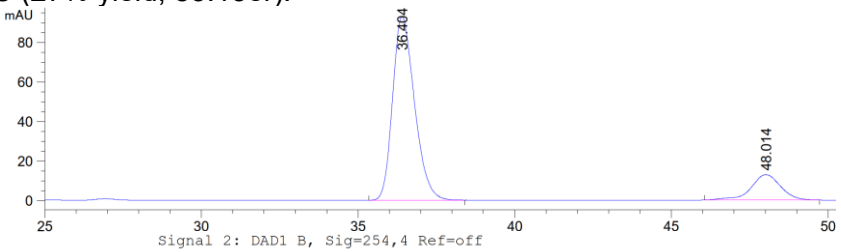
- Asymmetric sample prepared using [Ir(COD)$_2$]BARF / *(R)*-DTBM-Binap (10 mol%) at 130 ºC (75% yield, 85:15 er).



Signal 2: DAD1 B, Sig=254,4 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	36.466	BB	0.6826	1789.56519	39.95393	16.4475
2	47.622	BB	0.9063	9090.91504	151.44569	83.5525
Totals :				1.08805e4	191.39962	

- Asymmetric sample prepared using [Ir(COD)$_2$]BARF / *(S)*-DTBM-Synphos (10 mol%) at 130 ºC (27% yield, 85:15er).

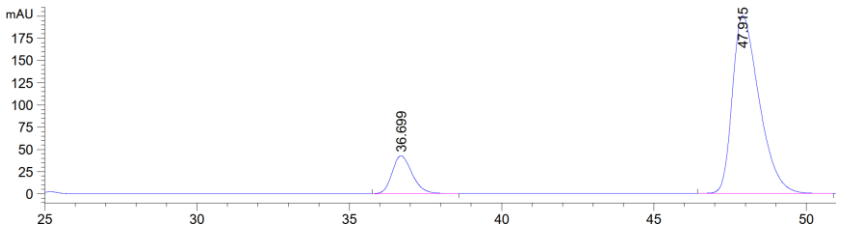


Signal 2: DAD1 B, Sig=254,4 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	36.404	BB	0.7567	4513.62988	92.91423	84.2187
2	48.014	BB	0.8087	845.78650	12.83587	15.7813
Totals :				5359.41638	105.75010	

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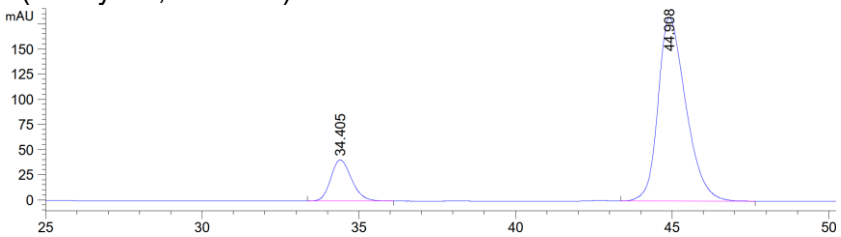
- Asymmetric sample prepared using [Ir(COD)$_2$]BARF / *(R)*-DTMS-Segphos (10 mol%) at 130 ºC (98% yield, 86:14 er).



Signal 2: DAD1 B, Sig=254,4 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	36.699	BB	0.7039	1946.85693	42.53896	13.7417
2	47.915	BB	0.9309	1.22206e4	199.99457	86.2583
Totals :				1.41675e4	242.53353	

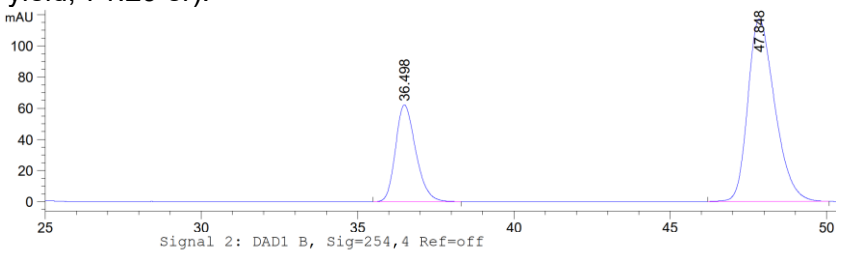
- Asymmetric sample prepared using [Ir(COD)$_2$]BARF / *(R)*-DTMS-Garphos (10 mol%) at 130 ºC (88% yield, 85:15 er).



Signal 2: DAD1 B, Sig=254,4 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	34.405	BB	0.7096	1883.53687	40.87844	14.3572
2	44.908	BB	0.9351	1.12356e4	182.28778	85.6428
Totals :				1.31191e4	223.16622	

- Asymmetric sample prepared using [Ir(COD)$_2$]BARF / *(R)*-Sunphos (10 mol%) at 130 ºC (91% yield, 71:29 er).

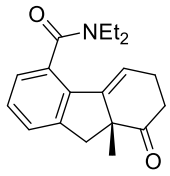


Signal 2: DAD1 B, Sig=254,4 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	36.498	BB	0.6881	2791.11890	62.13311	28.4429
2	47.848	BB	0.9097	7021.92773	117.08994	71.5571
Totals :				9813.04663	179.22304	

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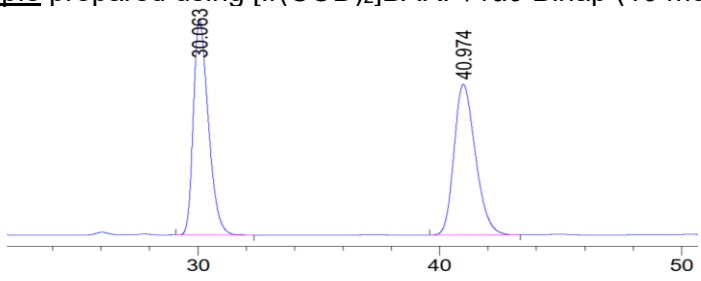
(*R*)-*N*,*N*-diethyl-9a-methyl-1-oxo-2,3,9,9a-tetrahydro-1H-fluorene-5-carboxamide (33a)



Prepared following general procedure for catalytic reactions (page 104), using **32a**. Obtained as colourless oil. **^{1}H NMR** (500 MHz, $CDCl_3$, 0 ºC) δ 7.30 – 7.22 (m, 2H), 7.10 – 7.04 (m, 1H), 6.34 – 6.14 (m, 1H), 3.85 – 3.65 (m, 1H), 3.59 – 3.43 (m, 1H), 3.36 (2 x d, *J* = 16.6 Hz, 1H), 3.22 – 3.08 (m, 2H), 2.85 – 2.65 (m, 3H), 2.64 – 2.50 (m, 1H), 2.42 – 2.29 (m, 1H), 1.35 – 1.27 (m, 6H), 1.06 – 1.00 (m, 3H) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$) δ 215.24 (CO), 170.18 (CO), 170.13 (CO), 145.31 (C), 145.06 (C), 143.41 (C), 142.96 (C), 133.24 (C), 133.09 (C), 132.31 (C), 132.05 (C), 128.55 (CH), 128.25 (CH), 126.16 (CH), 126.13 (CH), 124.69 (CH), 124.54 (CH), 120.27 (CH), 119.29 (CH), 55.18 (C), 54.99 (C), 42.91 (CH_2), 42.69 (CH_2), 40.22 (CH_2), 40.01 (CH_2), 38.91 (CH_2), 38.85 (CH_2), 35.56 (CH_2), 35.28 (CH_2), 24.35 (CH_3), 24.09 (CH_3), 23.75 (CH_2), 23.66 (CH_2), 14.07 (CH_3 amide), 13.93 (CH_3 amide), 12.85 (CH_3 amide), 12.74 (CH_3 amide) ppm [NOTE: Most of the signals are duplicated due to rotamerism]. **HRMS** [APCI]: *m/z* calculated for $C_{19}H_{24}NO_2$ $[M+H]^+$: 298.1802, found 298.1801.

Enantioselectivity was determined by chiral HPLC analysis on a Chiralpack IG3 column at *rt* (Hexane:iPrOH = 85:15, 1mL/min).

- <u>Racemic sample</u> prepared using $[Ir(COD)_2]BARF$ / *rac*-Binap (10 mol%) at 130 ºC.

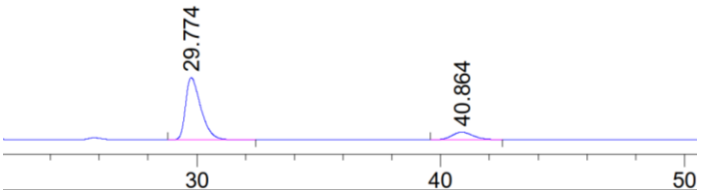


Signal 2: DAD1 B, Sig=254,4 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	30.063	BB	0.6568	9070.25098	211.32121	49.9914
2	40.974	BB	0.9391	9073.36230	147.61282	50.0086
Totals :				1.81436e4	358.93404	

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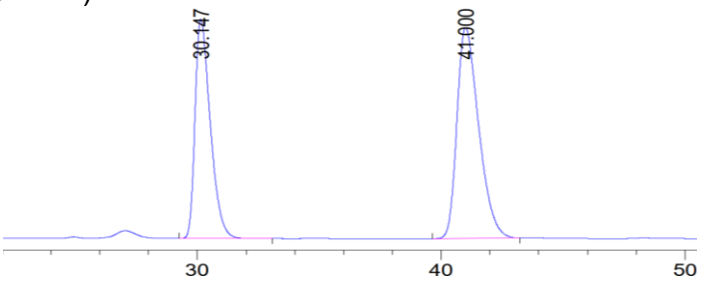
- Asymmetric sample prepared using [Ir(COD)$_2$]BARF / *(S)*-Binap (10 mol%) at 130 ºC (11% yield, 86:14 er).



Signal 2: DAD1 B, Sig=254,4 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	29.774	BB	0.6569	1.60965e4	371.95630	85.9019
2	40.864	BB	0.9004	2641.71826	44.38205	14.0981
Totals :				1.87382e4	416.33835	

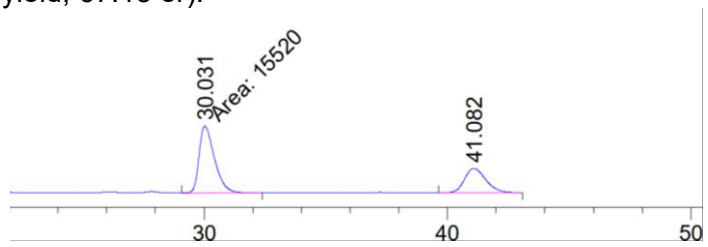
- Asymmetric sample prepared using [Ir(COD)$_2$]BARF / *(S)*-SDP (10 mol%) at 130 ºC (31% yield, 58:42 er).



Signal 2: DAD1 B, Sig=254,4 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	30.147	BB	0.6646	1.40568e4	323.69339	42.2042
2	41.000	BB	0.9445	1.92498e4	310.82568	57.7958
Totals :				3.33066e4	634.51907	

- Asymmetric sample prepared using [Ir(COD)$_2$]BARF / *(S,S)*-Chiraphos (10 mol%) at 130 ºC (17% yield, 67:13 er).

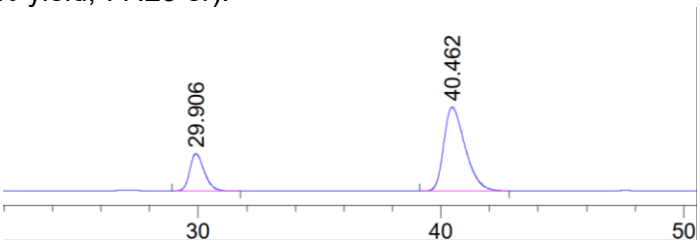


Signal 2: DAD1 B, Sig=254,4 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	30.031	MM	0.7349	1.55200e4	351.95459	66.8506
2	41.082	BBA	0.9233	7695.95605	127.29644	33.1494
Totals :				2.32160e4	479.25103	

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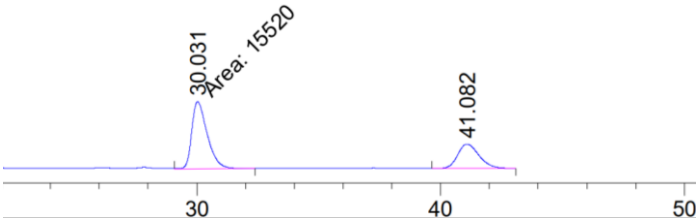
- Asymmetric sample prepared using [Ir(COD)$_2$]BARF / *(R)*-BTFM-Garphos (10 mol%) at 130 ºC (34% yield, 77:23 er).



Signal 2: DAD1 B, Sig=254,4 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	29.906	BB	0.6364	5643.30176	136.48903	23.2501
2	40.462	BB	0.9319	1.86288e4	306.13339	76.7499
Totals :				2.42721e4	442.62242	

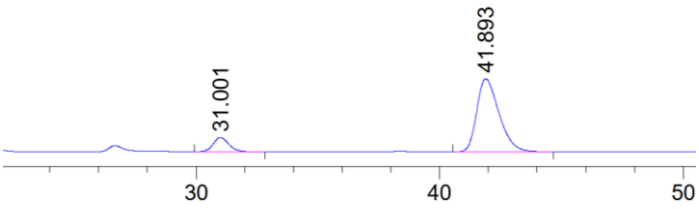
- Asymmetric sample prepared using [Ir(COD)$_2$]BARF / *(R)*-Xyl-Garphos (10 mol%) at 130 ºC (15% yield, 85:15 er).



Signal 2: DAD1 B, Sig=254,4 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	30.031	MM	0.7349	1.55200e4	351.95459	66.8506
2	41.082	BBA	0.9233	7695.95605	127.29644	33.1494
Totals :				2.32160e4	479.25103	

- Asymmetric sample prepared using [Ir(COD)$_2$]BARF / *(R)*-Garphos (10 mol%) at 130 ºC (28% yield, 88:12 er).

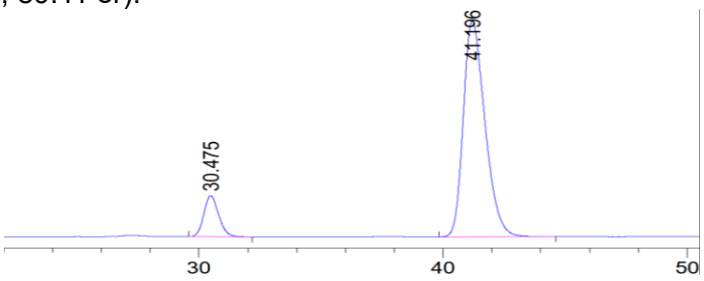


Signal 2: DAD1 B, Sig=254,4 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	31.001	BB	0.6696	2142.04834	48.09890	12.0759
2	41.893	BB	0.9764	1.55962e4	245.75458	87.9241
Totals :				1.77382e4	293.85348	

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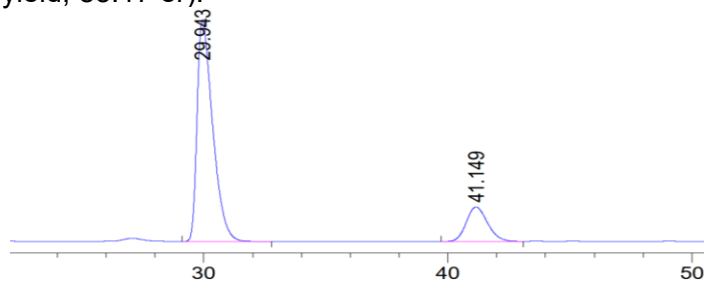
- Asymmetric sample prepared using [Ir(COD)$_2$]BARF / *(R)*-Biphep (10 mol%) at 130 ºC (27% yield, 89:11 er).



Signal 2: DAD1 B, Sig=254,4 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	30.475	BB	0.6493	1874.00647	44.50229	11.4669
2	41.196	BB	0.9499	1.44688e4	235.13129	88.5331
Totals :				1.63428e4	279.63357	

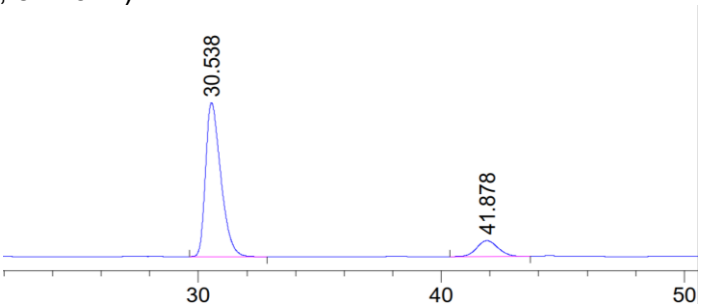
- Asymmetric sample prepared using [Ir(COD)$_2$]BARF / *(R)*-Fur-Biphep (10 mol%) at 130 ºC (18% yield, 83:17 er).



Signal 2: DAD1 B, Sig=254,4 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	29.943	BB	0.6710	2.27459e4	513.33368	82.5609
2	41.149	BB	0.9118	4804.55176	79.64384	17.4391
Totals :				2.75505e4	592.97752	

- Asymmetric sample prepared using [Ir(COD)$_2$]BARF / *(R)*-Tunephos (10 mol%) at 130 ºC (15% yield, 87:13 er).

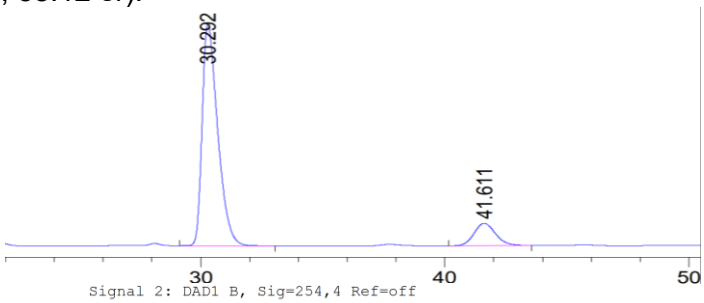


Signal 2: DAD1 B, Sig=254,4 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	30.538	BB	0.6695	1.19513e4	274.73361	87.3839
2	41.878	BB	0.9181	1725.47815	28.26974	12.6161
Totals :				1.36768e4	303.00335	

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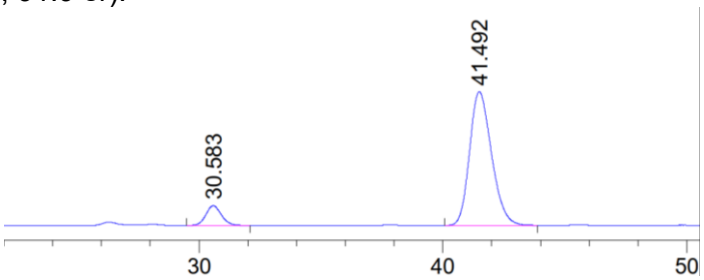
- Asymmetric sample prepared using [Ir(COD)$_2$]BARF / *(S)*-Synphos (10 mol%) at 130 ºC (42% yield, 88:12 er).



Signal 2: DAD1 B, Sig=254,4 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	30.292	BB	0.6701	1.64804e4	373.99960	87.8005
2	41.611	BB	0.9090	2289.87793	37.57164	12.1995
Totals :				1.87702e4	411.57124	

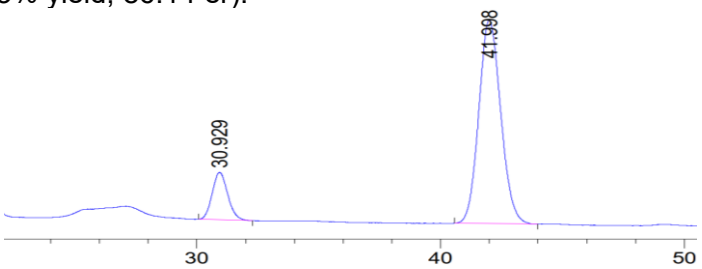
- Asymmetric sample prepared using [Ir(COD)$_2$]BARF / *(R)*-Segphos (10 mol%) at 130 ºC (32% yield, 91:9 er).



Signal 2: DAD1 B, Sig=254,4 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	30.583	BB	0.6567	877.47595	19.81256	9.4351
2	41.492	BB	0.9621	8422.65625	134.59262	90.5649
Totals :				9300.13220	154.40518	

- Asymmetric sample prepared using [Ir(COD)$_2$]BARF / *(R)*-Segphos (10 mol%) at 130 ºC for 96 h (93% yield, 86:14 er).

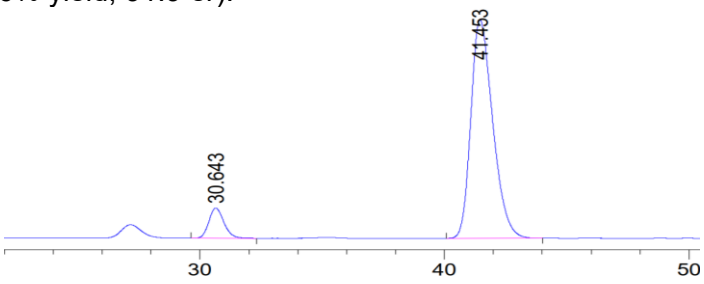


Signal 1: DAD1 A, Sig=220,4 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	30.928	BB	0.6223	420.58707	9.46682	14.2089
2	41.998	BB	0.9368	2539.43555	40.53845	85.7911
Totals :				2960.02261	50.00527	

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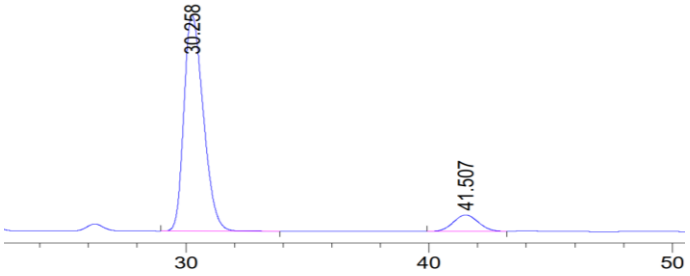
- Asymmetric sample prepared using [Ir(COD)$_2$]BARF / *(R)*-Segphos (10 mol%) at 100 ºC for 96 h (36% yield, 91:9 er).



Signal 2: DAD1 B, Sig=254,4 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	30.643	BB	0.6487	1210.91858	28.44452	8.6409
2	41.453	BB	0.9533	1.28029e4	205.93584	91.3591
Totals :				1.40138e4	234.38036	

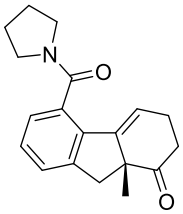
- Asymmetric sample prepared using [Ir(COD)$_2$]BARF / *(R)*-Difluorphos (10 mol%) at 130 ºC (20% yield, 91:9 er).



Signal 2: DAD1 B, Sig=254,4 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	30.258	BB	0.8660	1.79027e4	323.32187	91.1247
2	41.507	BB	1.0517	1743.67542	24.45950	8.8753
Totals :				1.96464e4	347.78137	

_(R)_-9a-methyl-5-(pyrrolidine-1-carbonyl)-2,3,9,9a-tetrahydro-1H-fluoren-1-one (33b)

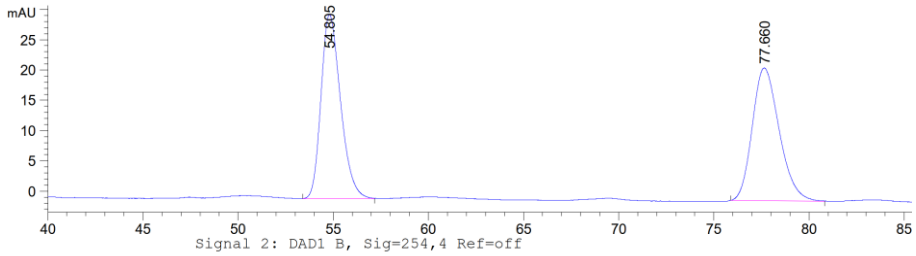


Prepared following general procedure for catalytic reactions (page 104), using **32b.** Obtained as yellow oil. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.28 – 7.19 (m, 2H), 7.15 – 7.05 (m, 1H), 6.20 (dd, *J* = 6.9, 2.8 Hz, 1H), 3.66 (hept, *J* = 6.2 Hz, 2H), 3.34 (d, *J* = 16.7 Hz, 1H), 3.13 (t, *J* = 6.3 Hz, 2H), 2.79 – 2.65 (m, 3H), 2.61 – 2.49 (m, 1H), 2.40 – 2.26 (m, 1H), 1.92 (dp, *J* = 25.3, 6.5 Hz, 4H), 1.31 (s, 3H) ppm. **^{13}C NMR** (300 MHz, $CDCl_3$) δ 7.28 – 7.19 (m, 2H), 7.15 – 7.05 (m, 1H), 6.20 (dd, *J* = 6.9, 2.8 Hz, 1H), 3.66 (hept, *J* = 6.2 Hz, 2H), 3.34 (d, *J* = 16.7 Hz, 1H), 3.13 (t, *J* = 6.3 Hz, 2H), 2.79 – 2.65 (m, 3H), 2.61 – 2.49 (m, 1H), 2.40 – 2.26 (m, 1H), 1.92 (dp, *J* = 25.3, 6.5 Hz, 4H), 1.31 (s, 3H) ppm. **HRMS** [APCI]: *m/z* calculated for $C_{19}H_{22}NO_2$ [M+H]$^+$: 296.1645, found 296.1654.

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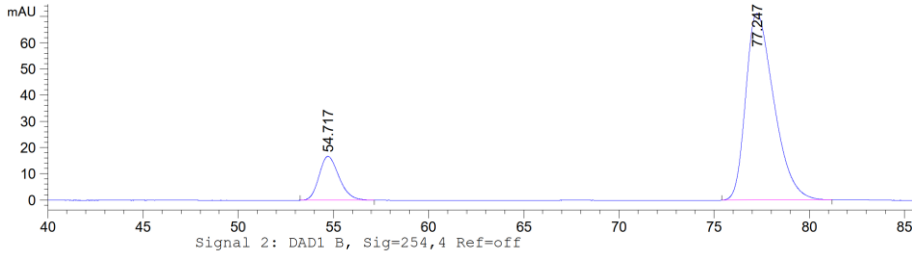
Enantioselectivity was determined by chiral HPLC analysis on a Chiralpack IG3 column at *rt* (Hexane:iPrOH = 85:15, 1mL/min).

- Racemic sample prepared using [Ir(COD)$_2$]BARF / *rac*-Binap (10 mol%) at 130 ºC.



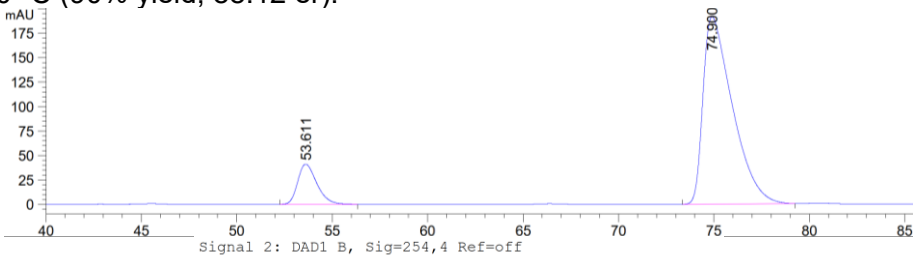
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	54.805	BB	1.0133	2163.95337	30.36803	50.1148
2	77.660	BB	1.1650	2154.04321	21.90953	49.8852
Totals :				4317.99658	52.27755	

- Asymmetric sample prepared using [Ir(COD)$_2$]BARF / *(R)*-Segphos (10 mol%) at 130 ºC (99% yield, 86:14 er).



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	54.717	BB	1.0390	1225.31812	16.75934	14.3093
2	77.247	BB	1.4367	7337.76758	71.29932	85.6907
Totals :				8563.08569	88.05866	

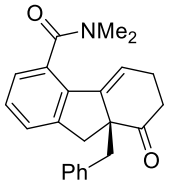
- Asymmetric sample prepared using [Ir(COD)$_2$]BARF / *(R)*-DTBM-Segphos (10 mol%) at 130 ºC (90% yield, 88:12 er).



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	53.611	BB	1.0422	2852.89722	41.08267	12.2058
2	74.900	BB	1.5488	2.05204e4	191.70538	87.7942
Totals :				2.33733e4	232.78805	

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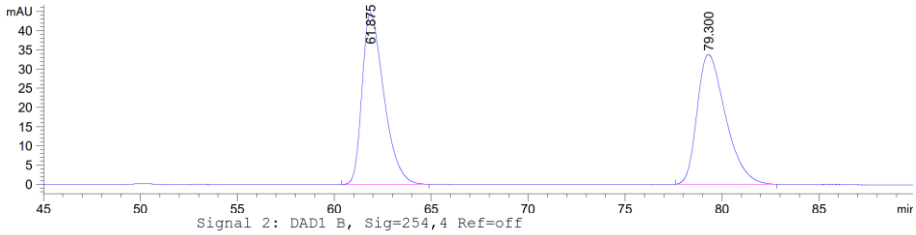
(*R*)-9a-benzyl-*N,N*-dimethyl-1-oxo-2,3,9,9a-tetrahydro-1H-fluorene-5-carboxamide (33d)



Prepared following general procedure for catalytic reactions (page 104), using **32d.** Obtained as white solid. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.24 – 7.09 (m, 5H), 7.05 – 6.94 (m, 3H), 6.14 (d x2, *J* = 149.9, 6.6, 2.7 Hz, 1H), 3.17 – 2.75 (m, 10H), 2.54 – 2.38 (m, 1H), 2.32 – 2.13 (m, 2H), 1.88 – 1.63 (m, 2H), 1.25 – 1.15 (m, 1H) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$) δ 215.44 (CO), 215.05 (CO), 170.67 (CO), 142.99 (C), 142.93 (C), 136.27 (C), 134.82 (C), 134.19 (C), 133.77 (C), 131.80 (C), 131.36 (C), 130.32 (CH), 130.02 (CH), 128.58 (CH), 128.35 (CH), 128.14 (CH), 127.02 (CH), 126.87 (CH), 126.12 (CH), 126.04 (CH), 124.78 (CH), 124.57 (CH), 122.33 (CH), 121.23 (CH), 60.46 (C), 43.90 (CH_2), 43.61 (CH_2), 38.98 (CH_2), 38.85 (CH_3 amide + CH_2), 38.60 (CH_3 amide), 36.83 (CH_2), 36.61 (CH_2), 34.86 (CH_3 amide), 34.68 (CH_3 amide), 31.72 (CH_2), 23.23 (CH_2), 22.80 (CH_2) ppm [NOTE: Most signals are duplicated due to rotamerism]. **HRMS** [APCI]: *m/z* calculated for $C_{23}H_{24}NO_2$ $[M+H]^+$: 346.1802, found 346.1800.

Enantioselectivity was determined by chiral HPLC analysis on a Chiralpack IE3 column at *rt* (Hexane:iPrOH = 85:15, 1mL/min).

- <u>Racemic sample</u> prepared using $[Ir(COD)_2]$BARF / *rac*-Binap (10 mol%) at 130 ºC.

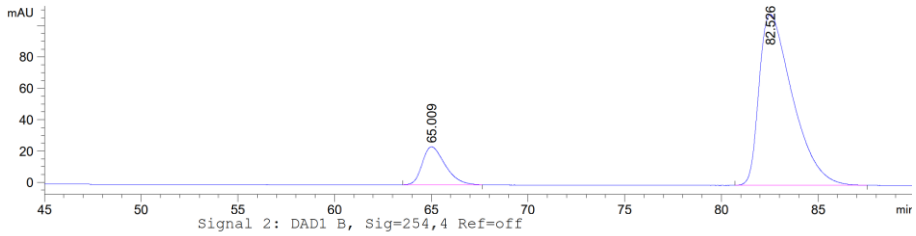


Signal 2: DAD1 B, Sig=254,4 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	61.875	BB	1.1522	3485.56543	44.57793	50.2446
2	79.300	BB	1.4140	3451.63477	33.78318	49.7554
Totals :				6937.20020	78.36112	

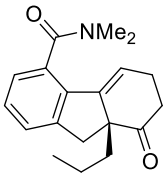
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- Asymmetric sample prepared using [Ir(COD)$_2$]BARF / *(R)*-DTBM-Segphos (10 mol%) at 130 ºC (83% yield, 88:12 er).



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	65.009	BB	1.1586	1983.33972	24.18972	13.1489
2	82.526	BB	1.6980	1.31003e4	109.16790	86.8511
Totals :				1.50836e4	133.35762	

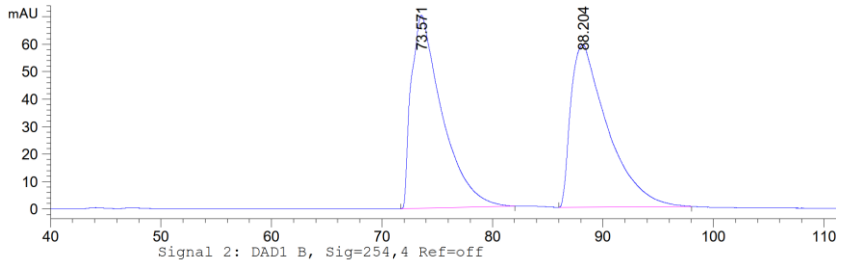
_(R)_-_N,N_-dimethyl-1-oxo-9a-propyl-2,3,9,9a-tetrahydro-1H-fluorene-5-carboxamide (33e)



Prepared following general procedure for catalytic reactions (page 104), using **32c**. Obtained as yellow oil. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.31 – 7.17 (m, 2H), 7.06 (s, 1H), 6.14 (br d, *J* = 51.1 Hz, 1H), 3.33 (br d, *J* = 16.9 Hz, 1H), 3.17 (d, *J* = 1.4 Hz, 3H), 2.96 – 2.50 (m, 8H), 2.45 – 2.27 (m, 1H), 1.79 – 1.54 (m, 3H), 1.38 – 1.07 (m, 2H), 0.83 (t, *J* = 7.3 Hz, 3H) ppm. **^{13}C NMR** (75 MHz, $CDCl_3$) δ 213.74 (CO), 170.77 (CO), 145.07 (C), 134.28 (C), 131.57 (C), 128.58 (CH), 125.96 (CH), 124.79 (CH), 120.33 (CH), 59.60 (C), 40.00 (CH_2), 38.36 (CH_3 amide), 37.60 (CH_2), 35.30 (CH_2), 34.82 (CH_3 amide), 24.29 (CH_2), 18.14 (CH_2), 14.46 (CH_3) ppm. **HRMS** [APCI]: *m/z* calculated for $C_{19}H_{24}NO_2$ [M+H]$^+$: 298.1802, found 298.1808.

Enantioselectivity was determined by chiral HPLC analysis on a Chiralpack IA3 column at *rt* (Hexane:iPrOH = 98:2, 1mL/min).

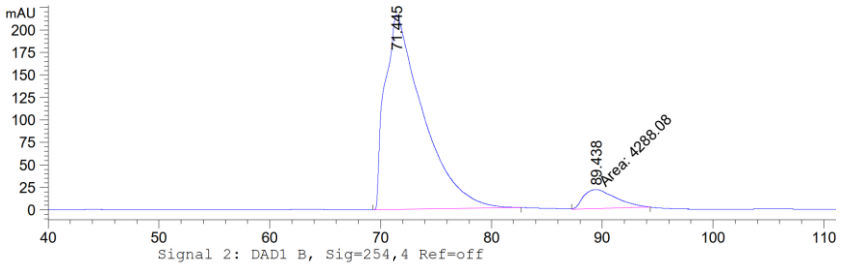
- Racemic sample prepared using [Ir(COD)$_2$]BARF / *rac*-Binap (10 mol%) at 130 ºC.



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	73.571	BB	2.4031	1.36043e4	70.25624	49.8985
2	88.204	BB	2.6951	1.36597e4	59.26249	50.1015
Totals :				2.72640e4	129.51873	

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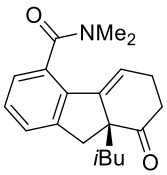
- Asymmetric sample prepared using [Ir(COD)$_2$]BARF / *(R)*-DTBM-Segphos (10 mol%) at 130 ºC (83% yield, 92:7 er).



Signal 2: DAD1 B, Sig=254,4 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	71.445	BB	2.9823	5.14544e4	216.07074	92.3073
2	89.438	MM	3.3635	4288.08203	21.24780	7.6927
Totals :				5.57425e4	237.31854	

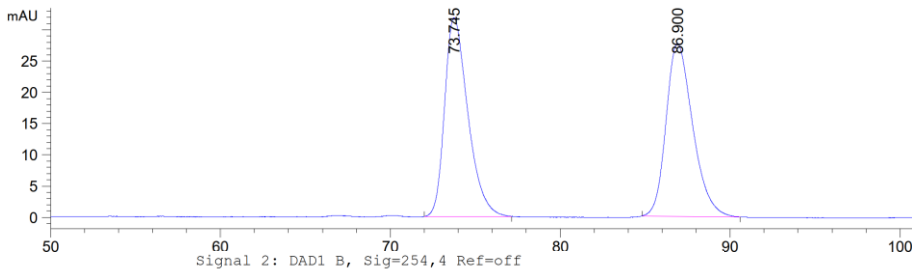
_(R)_-9a-isobutyl-_N,N_-dimethyl-1-oxo-2,3,9,9a-tetrahydro-1H-fluorene-5-carboxamide (33f)



Prepared following general procedure for catalytic reactions (page 104), using **32f.** Obtained as yellow oil. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.32 – 7.17 (m, 2H), 7.07 (br m, 1H), 6.13 (br d, *J* = 54.8 Hz, 1H), 3.46 – 3.31 (m, 1H), 3.17 (d, *J* = 1.1 Hz, 3H), 2.92 (d, *J* = 16.9 Hz, 1H), 2.85 (s, 3H), 2.82 – 2.67 (m, 2H), 2.65 – 2.48 (m, 1H), 2.45 – 2.31 (m, 1H), 1.66 (m, 4H), 0.86 (dd, *J* = 17.1, 6.3 Hz, 6H) ppm. **^{13}C NMR** (75 MHz, $CDCl_3$) δ 213.79 (CO), 170.78 (CO), 145.88 (C), 143.50 (C), 134.12 (C), 131.69 (C), 128.60 (CH), 126.12 (CH), 124.82 (CH), 120.58 (CH), 59.85 (C), 46.31 (CH_3), 38.42 (CH_2), 37.82 (CH_3), 35.54 (CH), 34.84 (CH_2), 25.29 (CH_2), 24.49 (CH_3), 23.96 (CH_2) ppm. **HRMS** [APCI]: *m/z* calculated for $C_{20}H_{26}NO_2$ $[M+H]^+$: 312.1958, found 312.1961.

Enantioselectivity was determined by chiral HPLC analysis on a Chiralpack IE3 column at *rt* (Hexane:iPrOH = 85:15, 1mL/min).

- Racemic sample prepared using [Ir(COD)$_2$]BARF / *rac*-Binap (10 mol%) at 130 ºC.

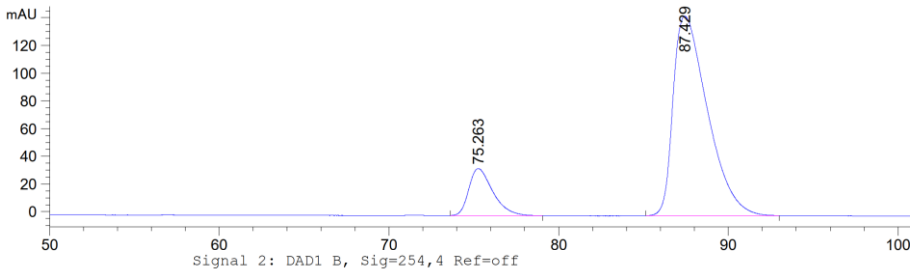


Signal 2: DAD1 B, Sig=254,4 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	73.745	BB	1.2353	3036.65112	31.82165	50.1676
2	86.900	BB	1.3160	3016.36035	27.66604	49.8324
Totals :				6053.01147	59.48769	

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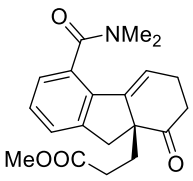
- Asymmetric sample prepared using [Ir(COD)$_2$]BARF / *(R)*-DTBM-Segphos (10 mol%) at 130 ºC (83% yield, 92:7 er).



Signal 2: DAD1 B, Sig=254,4 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	75.263	BB	1.2579	3332.41870	33.92892	14.1122
2	87.429	BB	1.9546	2.02813e4	144.05305	85.8878
Totals :				2.36137e4	177.98198	

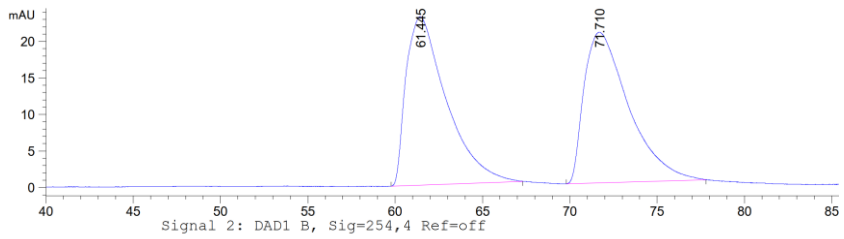
Methyl-*(R)*-3-(4-(dimethylcarbamoyl)-8-oxo-6,7,8,9-tetrahydro-8aH-fluoren-8a-yl)propanoate (33g)



Prepared following general procedure for catalytic reactions (page 104), using **32g.** Obtained as yellow oil. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.28 – 7.21 (m, 2H), 7.19 – 6.97 (m, 1H), 6.22 (br s, *J* = 40.7 Hz, 1H), 3.62 (s, 3H), 3.38 – 3.26 (m, 1H), 3.17 (s, 3H), 2.84 (s + m, 5H), 2.68 – 2.51 (m, 2H), 2.43 – 2.20 (m, 3H), 2.11 – 1.90 (m, 2H). ppm. **^{13}C NMR** (126 MHz, $CDCl_3$) δ 213.32 (CO), 173.41 (CO), 170.60 (CO), 144.36 (C), 142.81 (C), 133.89 (C), 131.71 (C), 128.89 (CH), 126.12 (CH), 125.09 (CH), 121.27 (CH), 58.51 (C), 51.87 (CH_3), 38.44 (CH_3 amide), 35.56 (CH_2), 34.89 (CH_2), 31.68 (CH_3 amide), 29.49 (CH_2), 23.92 (CH_2) ppm. **HRMS** [APCI]: *m/z* calculated for $C_{20}H_{24}NO_4$ $[M+H]^+$: 342.1700, found 342.1696.

Enantioselectivity was determined by chiral HPLC analysis on a Chiralpack IA3 column at *rt* (Hexane:iPrOH = 95:5, 1mL/min).

- Racemic sample prepared using [Ir(COD)$_2$]BARF / *rac*-Binap (10 mol%) at 130 ºC.

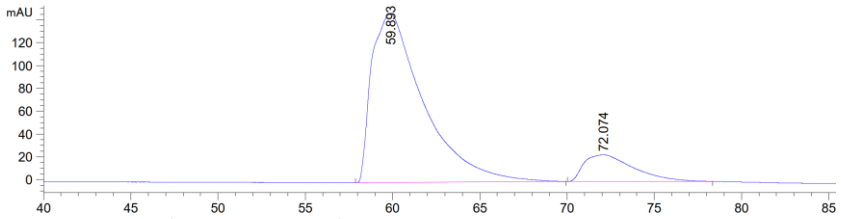


Signal 2: DAD1 B, Sig=254,4 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	61.445	BB	1.9013	3710.27759	23.08197	50.3530
2	71.710	BB	2.0800	3658.25049	20.61841	49.6470
Totals :				7368.52808	43.70038	

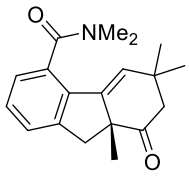
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- Asymmetric sample prepared using [Ir(COD)$_2$]BARF / *(R)*-DTBM-Segphos (10 mol%) at 130 ºC (34% yield, 86:14 er).



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	59.893	BB	2.5692	3.06300e4	147.83817	86.9404
2	72.074	BB	2.3013	4601.02979	23.44714	13.0596
Totals :				3.52310e4	171.28531	

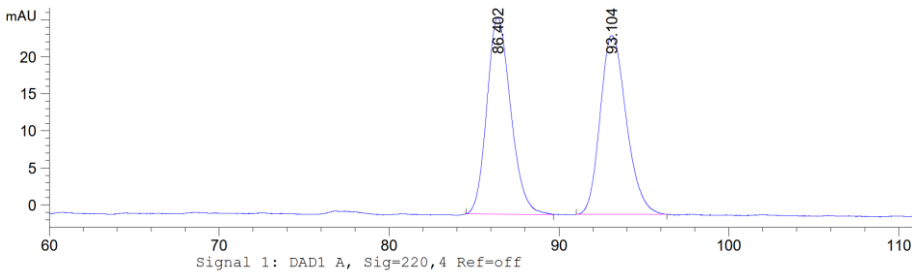
_(R)-N,N_,3,3,9a-pentamethyl-1-oxo-2,3,9,9a-tetrahydro-1H-fluorene-5-carboxamide (33h)



Prepared following general procedure for catalytic reactions (page 104), using **32h.** Obtained as white solid. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.33 – 7.20 (m, 2H), 7.19 – 7.08 (m, 1H), 5.78 (s, 1H), 3.24 (d, *J* = 15.9 Hz, 1H), 3.15 (s, 3H), 2.94 – 2.77 (m, 4H), 2.68 (d, *J* = 15.8 Hz, 1H), 2.28 (d, *J* = 14.2 Hz, 1H), 1.39 (s, 3H), 1.27 (s, 3H), 1.08 (s, 3H) ppm. **^{13}C NMR** (75 MHz, $CDCl_3$) δ 212.65 (CO), 170.54 (CO), 142.43 (C), 134.57 (C), 131.79 (C), 131.10 (CH), 128.61 (CH), 126.60 (CH), 125.30 (CH), 54.65 (C), 49.85 (CH_2), 39.52 (CH_2), 39.24 (C), 38.20 (CH_3), 34.83 (CH_3), 30.92 (CH_3 amide), 30.70 (CH_3), 27.78 (CH_3 amide) ppm. **HRMS** [APCI]: *m/z* calculated for $C_{19}H_{24}NO_2$ $[M+H]^+$: 298.1802, found 298.1807.

Enantioselectivity was determined by chiral HPLC analysis on a Chiralpack IG3 column at *rt* (Hexane:iPrOH = 95:5, 1mL/min).

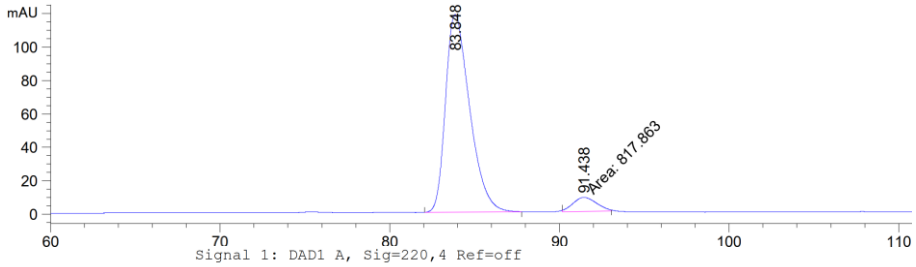
- Racemic sample prepared using [Ir(COD)$_2$]BARF / *rac*-Binap (10 mol%) at 130 ºC.



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	86.402	BB	1.1796	2592.83154	26.54327	50.0611
2	93.104	BB	1.2658	2586.50684	24.14364	49.9389
Totals :				5179.33838	50.68691	

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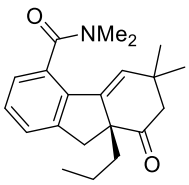
- Asymmetric sample prepared using [Ir(COD)$_2$]BARF / *(R)*-DTBM-Segphos (10 mol%) at 130 ºC (69% yield, 93:7 er).



Signal 1: DAD1 A, Sig=220,4 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	83.848	BB	1.4196	1.17279e4	118.40192	93.4810
2	91.438	MM	1.6126	817.86310	8.45300	6.5190
Totals :				1.25458e4	126.85491	

(*R*)-*N*,*N*,3,3-tetramethyl-1-oxo-9a-propyl-2,3,9,9a-tetrahydro-1H-fluorene-5-carboxamide (33i)

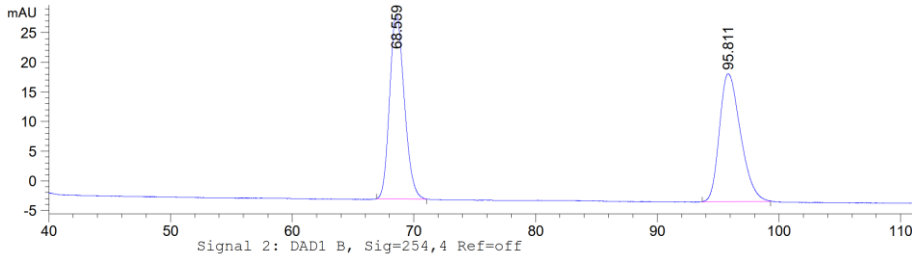


Prepared following general procedure for catalytic reactions (page 104), using **32i** Obtained as white solid. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.36 – 7.05 (m, 3H), 5.71 (br s, 1H), 3.20 (d, *J* = 16.5 Hz, 1H), 3.13 (s, 3H), 2.89 – 2.69 (m, 5H), 2.25 (dd, *J* = 13.5, 1.5 Hz, 1H), 1.73 – 1.60 (m, 2H), 1.43 – 1.31 (m, 1H), 1.28 (d, *J* = 1.8 Hz, 3H), 1.12 (d, *J* = 6.9 Hz, 1H), 1.04 (d, *J* = 1.8 Hz, 3H), 0.83 (dd, *J* = 8.1, 6.3 Hz, 3H) ppm. **^{13}C NMR** (75 MHz, $CDCl_3$) δ 211.41 (CO), 170.59 (CO), 142.62 (C), 134.83 (C), 131.65 (C), 130.97 (CH), 128.56 (CH), 126.50 (CH), 125.22 (CH), 59.37 (C), 49.62 (CH_2), 43.56 (CH_2), 40.18 (C), 38.32 (CH_3), 35.62 (CH_2), 34.85 (CH_3 amide), 31.11 (CH_3 + CH_3 amide), 18.33 (CH_2), 14.49 (CH_3) ppm. **HRMS** [APCI]: *m/z* calculated for $C_{21}H_{28}NO_2$ $[M+H]^+$: 326.2115, found 326.2113. **NMR spectra at page 530.**

Enantioselectivity was determined by chiral HPLC analysis on a Chiralpack IG3 column at *rt* (Hexane:iPrOH = 95:5, 1mL/min).

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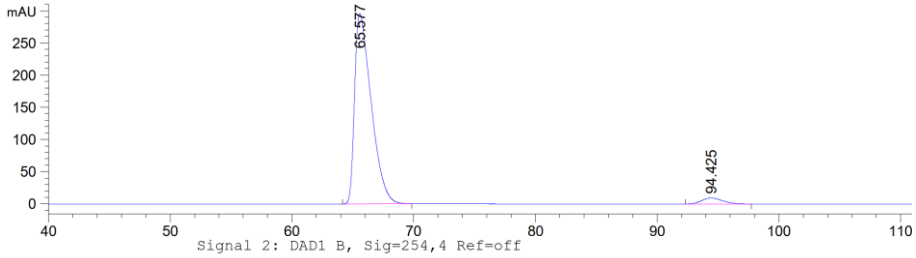
- Racemic sample prepared using [Ir(COD)$_2$]BARF / *rac*-Binap (10 mol%) at 130 ºC.



Signal 2: DAD1 B, Sig=254,4 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	68.559	BB	1.1949	2610.06348	31.17161	50.1357
2	95.811	BB	1.4158	2595.93213	21.54314	49.8643
Totals :				5205.99561	52.71475	

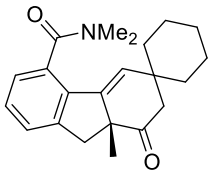
- Asymmetric sample prepared using [Ir(COD)$_2$]BARF / *(R)*-DTBM-Segphos (10 mol%) at 130 ºC (38% yield, 96:4 er).



Signal 2: DAD1 B, Sig=254,4 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	65.577	BB	1.3565	2.79504e4	295.77328	96.1442
2	94.425	BB	1.4128	1120.93506	9.38970	3.8558
Totals :				2.90714e4	305.16298	

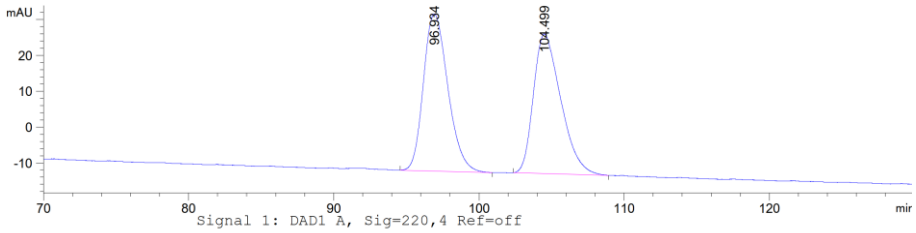
(*R*)-*N*,*N*,9a'-trimethyl-1'-oxo-1',2',9',9a'-tetrahydrospiro[cyclohexane-1,3'-fluorene]-5'-carboxamide (33j)



Prepared following general procedure for catalytic reactions (page 104), using **32j.** Obtained as white solid. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.34 – 7.20 (m, 2H), 7.17 (br m, 1H), 6.01 (br s, 1H), 3.28 – 3.07 (m, 4H), 2.85 (s, 3H), 2.69 (d, *J* = 15.9 Hz, 2H), 2.45 (d, *J* = 14.8 Hz, 1H), 1.76 – 1.40 (m, 10H), 1.39 (s, 3H) ppm. **^{13}C NMR** (75 MHz, $CDCl_3$) δ 213.29 (CO), 170.59 (CO), 143.04 (C), 142.33 (C), 134.78 (C), 131.74 (C), 130.12 (CH), 128.62 (CH), 126.56 (CH), 125.39 (CH), 55.10 (C), 47.86 (CH_2), 41.79 (C), 39.99 (CH_2), 39.76 (CH_2), 38.18 (CH_3 amide), 34.92 (CH_3 amide), 27.63 (CH_3), 25.67 (CH_2), 22.19 (CH_2), 21.94 (CH_2) ppm. **HRMS** [APCI]: *m/z* calculated for $C_{22}H_{28}NO_2$ $[M+H]^+$: 338.2115, found 38.2112.

Enantioselectivity was determined by chiral HPLC analysis on a Chiralpack IG3 column at *rt* (Hexane:iPrOH = 95:5, 1mL/min).

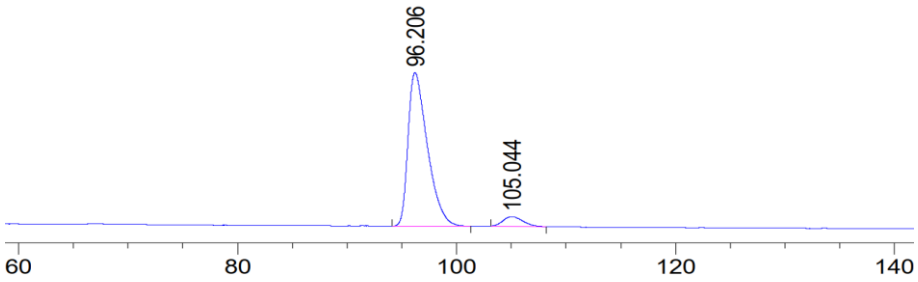
- Racemic sample prepared using [Ir(COD)$_2$]BARF / *rac*-Binap (10 mol%) at 130 ºC.



Signal 1: DAD1 A, Sig=220,4 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	96.934	BB	1.4283	5141.37842	43.90170	50.1871
2	104.499	BB	1.5709	5103.04639	38.99007	49.8129
Totals :				1.02444e4	82.89177	

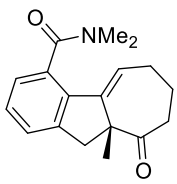
- Asymmetric sample prepared using [Ir(COD)$_2$]BARF / *(R)*-DTBM-Segphos (10 mol%) at 130 ºC (55% yield, 94:6 er).



Signal 1: DAD1 A, Sig=220,4 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	96.206	BB	1.7405	1.82147e4	148.14220	93.9355
2	105.044	BB	1.4678	1175.95276	9.38545	6.0645
Totals :				1.93907e4	157.52765	

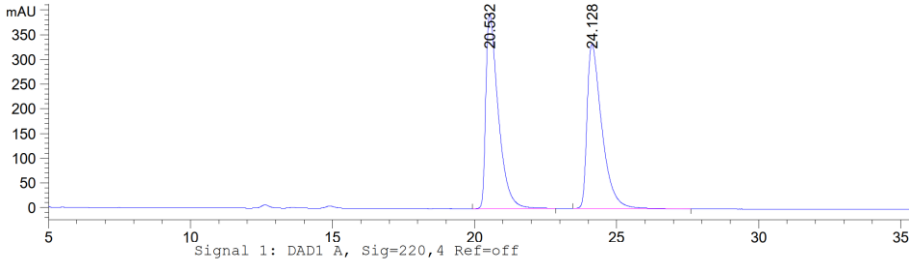
(*R*)-*N*,*N*,9a-trimethyl-9-oxo-6,7,8,9,9a,10-hexahydrobenzo[a]azulene-4-carboxamide (33k)



Prepared following general procedure for catalytic reactions (page 104), using **32k.** Obtained as colourless oil. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.21 – 7.19 (m, 2H), 7.05 (t, *J* = 4.4 Hz, 1H), 6.07 (t, *J* = 7.3 Hz, 1H), 3.19 (d, *J* = 16.1 Hz, 1H), 3.06 (s, 3H), 2.94 (td, *J* = 11.0, 8.1 Hz, 1H), 2.69 (s, 3H), 2.57 (d, *J* = 16.1 Hz, 1H), 2.34 – 2.28 (m, 1H), 2.24 – 2.15 (m, 2H), 2.03 – 1.95 (m, 1H), 1.81 – 1.71 (m, 1H), 1.27 (s, 3H) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$) δ 215.06 (CO), 171.01 (CO), 147.51 (C), 142.64 (C), 135.29 (C), 131.80 (C), 128.54 (CH), 126.17 (CH), 125.40 (CH), 120.84 (CH), 59.63 (C), 42.72 (CH_2), 38.01 (CH_3 amide), 37.80 (CH_2), 34.94 (CH_3 amide), 25.10 (CH_2), 24.56 (CH_2), 21.56 (CH_3) ppm. [NOTE: 2 rotamers are observed by NMR, only the major one was assigned for simplicity]. **HRMS** [APCI]: *m/z* calculated for $C_{18}H_{22}NO_2$ $[M+H]^+$: 284.1645, found 284.1649.

Enantioselectivity was determined by chiral HPLC analysis on a Chiralpack IF3 column at *rt* (Hexane:iPrOH = 85:15, 1mL/min).

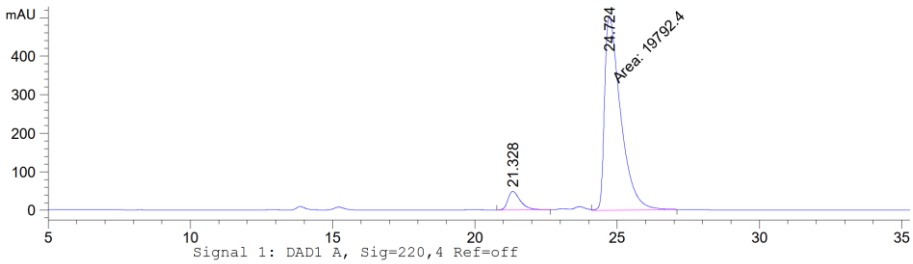
- Racemic sample prepared using [Ir(COD)$_2$]BARF / *rac*-Binap (10 mol%) at 130 ºC.



Signal 1: DAD1 A, Sig=220,4 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	20.532	BB	0.4516	1.19683e4	394.91968	49.9386
2	24.128	BB	0.5392	1.19977e4	332.31760	50.0614
Totals :				2.39660e4	727.23727	

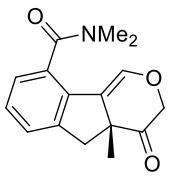
- Asymmetric sample prepared using [Ir(COD)$_2$]BARF / *(R)*-DTBM-Segphos (10 mol%) at 130 ºC (46% yield, 93:7 er).



Signal 1: DAD1 A, Sig=220,4 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	21.328	BB	0.4583	1445.44751	47.86138	6.8060
2	24.724	MM	0.6535	1.97924e4	504.76437	93.1940
Totals :				2.12379e4	552.62576	

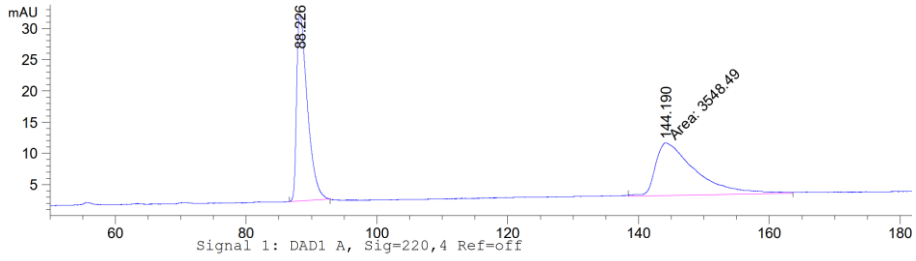
_(R)_-_N,N_,4a-trimethyl-4-oxo-3,4,4a,5-tetrahydroindeno[1,2-c]pyran-9-carboxamide (33l)



Prepared following general procedure for catalytic reactions (page 104), using **32l.** Obtained as colourless oil. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.33 – 7.20 (m, 2H), 7.10 (d, *J* = 7.2 Hz, 1H), 6.99 (br s, 1H), 4.66 (d, *J* = 18.2 Hz, 1H), 4.17 (d, *J* = 18.1 Hz, 1H), 3.49 (d, *J* = 17.0 Hz, 1H), 3.17 (d, *J* = 1.6 Hz, 3H), 2.88 (s, 3H), 2.81 (d, *J* = 17.2 Hz, 1H), 1.40 (d, *J* = 1.7 Hz, 3H) ppm. **^{13}C NMR** (75 MHz, $CDCl_3$) δ 211.37 (CO), 170.71 (CO), 141.99 (C), 139.88 (CH), 131.70 (C), 131.08 (C), 128.08 (CH), 126.24 (CH), 125.07 (CH), 71.50 (CH_2), 52.59 (C), 39.35 (CH_2), 38.35 (CH_3 amide), 34.89 (CH_3 amide), 23.85 (CH_3) ppm. **HRMS** [APCI]: *m/z* calculated for $C_{16}H_{18}NO_3$ $[M+H]^+$: 272.1281, found 272.1283. **NMR spectra at page 531.**

Enantioselectivity was determined by chiral HPLC analysis on a Chiralpack IF3 column at *rt* (Hexane:iPrOH = 95:5, 1mL/min).

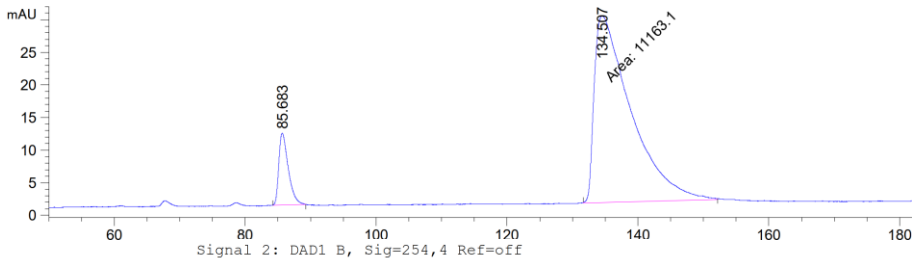
- Racemic sample prepared using [Ir(COD)$_2$]BARF / *rac*-Binap (5 mol%) at 130 ºC.



Signal 1: DAD1 A, Sig=220,4 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	88.232	BB	1.3894	6120.70459	52.99802	51.3319
2	144.080	MM	6.6160	5803.07031	14.61870	48.6681
Totals :				1.19238e4	67.61672	

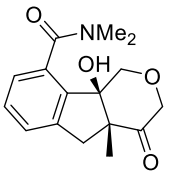
- Asymmetric sample prepared using [Ir(COD)$_2$]BARF / *(R)*-DTBM-Segphos (5 mol%) at 130 ºC (18% yield, 91:9 er).



Signal 2: DAD1 B, Sig=254,4 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	85.683	BB	1.1838	1111.04907	11.06162	9.0519
2	134.507	MM	6.5069	1.11631e4	28.59300	90.9481

(4aR,9bR)-9b-hydroxy-*N,N*,4a-trimethyl-4-oxo-1,3,4,4a,5,9b-hexahydroindeno[1,2-c]pyran-9-carboxamide (34l)

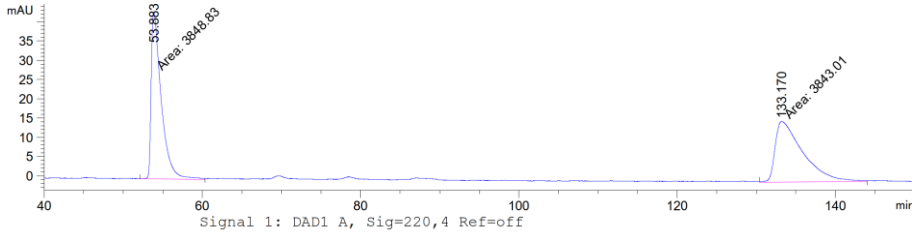


Prepared following general procedure for catalytic reactions (page 104), using **32l.** Obtained as colourless oil. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.33 – 7.25 (m, 2H), 7.17 – 7.08 (m, 1H), 4.22 – 3.94 (m, 5H), 3.56 (d, *J* = 16.1 Hz, 1H), 3.17 (s, 3H), 3.05 (s, 3H), 2.88 (d, *J* = 16.2 Hz, 1H), 1.40 (s, 3H) ppm. **^{13}C NMR** (75 MHz, $CDCl_3$) δ 211.71 (CO), 171.59 (CO), 143.31 (C), 141.97 (C), 132.63 (C), 128.54 (CH), 126.52 (CH), 125.34 (CH), 82.28 (COH), 72.79 (CH_2), 71.99 (CH_2), 59.44 (C), 40.71 (CH_2), 39.85 (CH_3 amide), 35.33 (CH_3 amide), 17.75 (CH_3) ppm. **HRMS** [APCI]: *m/z* calculated for $C_{16}H_{20}NO_3$ $[M+H]^+$: 274.1438, found 274.1439. **NMR spectra at page 532.**

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Enantioselectivity was determined by chiral HPLC analysis on a Chiralpack IF3 column at *rt* (Hexane:iPrOH = 95:5, 1mL/min).

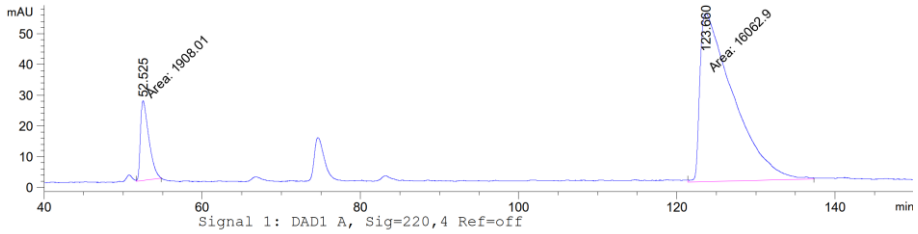
- Racemic sample prepared using [Ir(COD)$_2$]BARF / *rac*-Binap (10 mol%) at 130 ºC.



Signal 1: DAD1 A, Sig=220,4 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	53.883	MM	1.4776	3848.82739	43.41310	50.0378
2	133.170	MM	4.0703	3843.01343	15.73593	49.9622
Totals :				7691.84082	59.14903	

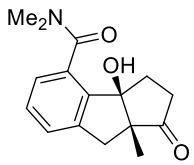
- Asymmetric sample prepared using [Ir(COD)$_2$]BARF / *(R)*-DTBM-Segphos (10 mol%) at 130 ºC (42% yield, 90:10 er).



Signal 1: DAD1 A, Sig=220,4 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	52.525	MM	1.2315	1908.00769	25.82290	10.6172
2	123.660	MM	4.8944	1.60629e4	54.69849	89.3828
Totals :				1.79710e4	80.52139	

(3aR,8aR)-3a-hydroxy-*N,N*,8a-trimethyl-1-oxo-1,2,3,3a,8,8a-hexahydrocyclopenta[a]indene-4-carboxamide (34m)

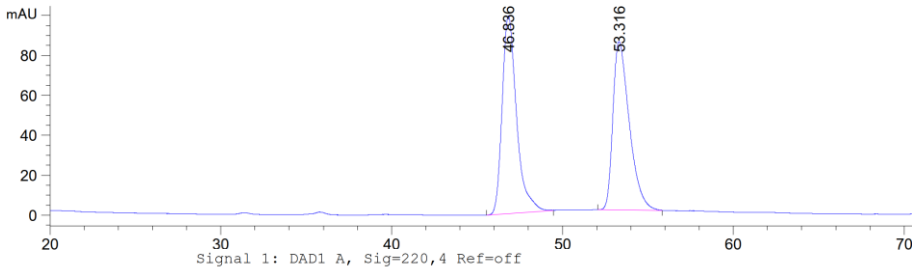


Prepared following general procedure for catalytic reactions (page 104), using **32m.** Obtained as colourless oil. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.29 – 7.24 (m, 2H), 7.16 (dd, *J* = 6.1, 1.7 Hz, 1H), 5.05 (s, 1H), 3.28 (d, *J* = 16.4 Hz, 1H), 3.21 (s, 3H), 3.11 (s, 3H), 2.95 (d, *J* = 16.4 Hz, 1H), 2.54 (ddd, *J* = 18.6, 8.7, 2.6 Hz, 1H), 2.42 – 2.27 (m, 2H), 1.85 (ddd, *J* = 18.6, 11.3, 9.4 Hz, 1H), 1.27 (s, 3H) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$) δ 221.86 (CO), 171.90 (CO), 144.42 (C), 144.25 (C), 131.53 (C), 128.39 (CH), 126.84 (CH), 125.88 (CH), 87.58 (COH), 59.12 (C), 41.57 (CH_2), 39.83 (CH_3 amide), 37.35 (CH_2), 35.50 (CH_3 amide), 32.38 (CH_2), 15.52 (CH_3) ppm. **HRMS** [APCI]: *m/z* calculated for $C_{16}H_{20}NO_3$ $[M+H]^+$: 274.1438, found 274.1439.

Enantioselectivity was determined by chiral HPLC analysis on a Chiralpack IG3 column at *rt* (Hexane:iPrOH = 90:10, 1mL/min).

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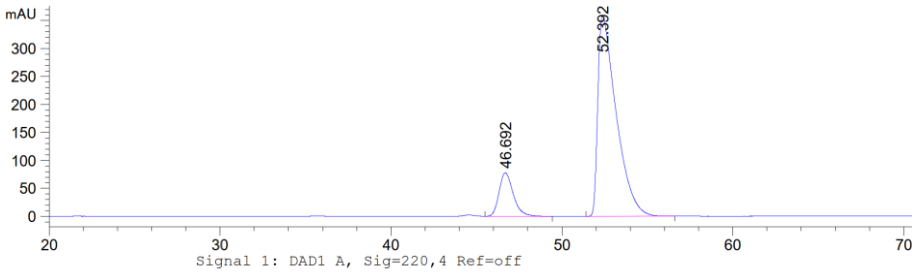
- Racemic sample prepared using [Ir(COD)$_2$]BARF / *rac*-Binap (10 mol%) at 130 ºC.



Signal 1: DAD1 A, Sig=220,4 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	46.836	BB	0.8911	5817.60791	99.07535	50.8700
2	53.316	BB	0.9791	5618.61816	84.35500	49.1300
Totals :				1.14362e4	183.43035	

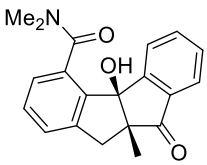
- Asymmetric sample prepared using [Ir(COD)$_2$]BARF / *(R)*-DTBM-Segphos (10 mol%) at 130 ºC (89% yield, 86:14 er).



Signal 1: DAD1 A, Sig=220,4 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	46.692	BB	0.8802	4507.39014	77.76432	14.4007
2	52.392	BB	1.0829	2.67925e4	358.90402	85.5993
Totals :				3.12999e4	436.66834	

(4bR,9aR)-4b-hydroxy-*N,N*,9a-trimethyl-9-oxo-4b,9,9a,10-tetrahydroindeno[1,2-a]indene-4-carboxamide (34n)

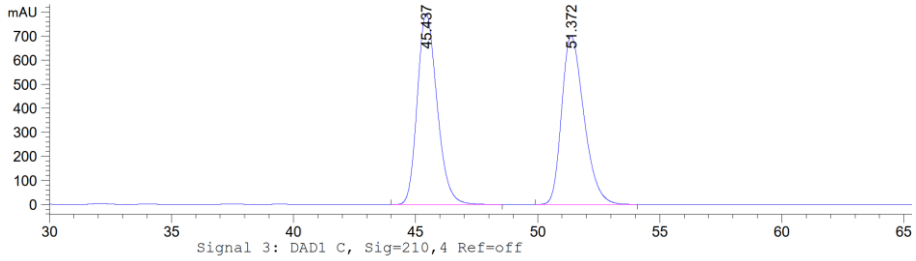


Prepared following general procedure for catalytic reactions (page 104), using **32n.** Obtained as pale yellow solid. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.84 (d, *J* = 7.8 Hz, 1H), 7.67 (d, *J* = 7.6 Hz, 1H), 7.62 (t, *J* = 7.5 Hz, 1H), 7.40 (t, *J* = 7.4 Hz, 1H), 7.25 – 7.19 (m, 2H), 7.01 (d, *J* = 7.1 Hz, 1H), 5.87 (s, 1H), 3.60 (d, *J* = 16.8 Hz, 1H), 3.19 (s, 3H), 3.04 (d, *J* = 16.8 Hz, 1H), 2.55 (s, 3H), 1.39 (s, 3H) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$) δ 208.25 (CO), 172.75 (CO), 156.37 (C), 144.59 (C), 143.74 (C), 134.89 (C), 134.47 (CH), 132.91 (C), 129.02 (CH), 128.47 (CH), 127.40 (CH), 125.41 (CH), 124.76 (CH), 123.87 (CH), 87.82 (COH), 62.72 (C), 39.48 (CH_3 amide), 39.41 (CH_2), 35.35 (CH_3 amide), 18.37 (CH_3) ppm. **HRMS** [APCI]: *m/z* calculated for $C_{20}H_{20}NO_3$ [M+H]$^+$: 322.1438, found 322.1435. **NMR spectra at page 533.**

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Enantioselectivity was determined by chiral HPLC analysis on a Chiralpack IG3 column at *rt* (Hexane:iPrOH = 90:10, 1mL/min).

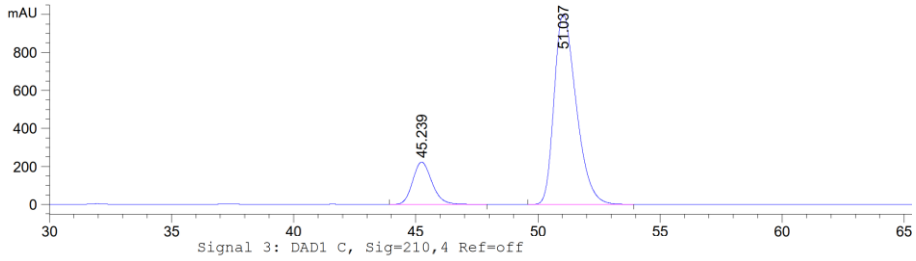
- Racemic sample prepared using [Ir(COD)$_2$]BARF / *rac*-Binap (10 mol%) at 130 ºC.



Signal 3: DAD1 C, Sig=210,4 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	45.437	BB	0.8754	4.47011e4	793.34485	50.1578
2	51.372	BB	0.9838	4.44198e4	700.51093	49.8422
Totals :				8.91209e4	1493.85577	

- Asymmetric sample prepared using [Ir(COD)$_2$]BARF / *(R)*-DTBM-Segphos(10 mol%) at 130 ºC (83% yield, 85:15 er).

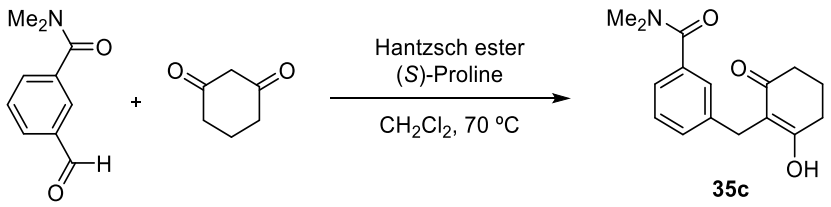


Signal 3: DAD1 C, Sig=210,4 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	45.239	BB	0.8474	1.22725e4	223.24045	16.3050
2	51.037	BB	0.9682	6.29959e4	1001.01520	83.6950
Totals :				7.52684e4	1224.25565	

Synthesis of substrates 35

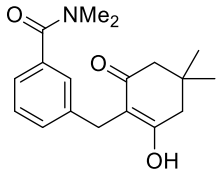
*(exemplified for **35c**).*



3-Formyl-*N,N*-dimethylamide (300 mg, 2.68 mmol), cyclohexane-1,3-dione (521 mg, 2.94 mmol), Hantzsch ester (745 mg, 2.94 mmol), (*S*)-Proline (62 mg, 0.53 mmol) were added to a sealed tube, then CH_2Cl_2 (5.4 mL) is added. The reaction was stirred for 16 h. The mixture was transferred to a separatory funnel and water (100 mL) was added. The mixture was extracted with AcOEt (5 x 100 mL). The organic phase was dried,

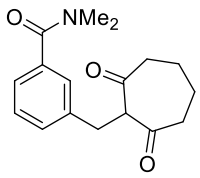
concentrated and the crude residue was purified by flash chromatography using 0% to 100% of EtOAc/hexanes, and then eluted with EtOAc/MeOH (9:1). **3-((2,6-dioxocyclohexyl)methyl)-*N,N*-dimethylbenzamide** (**35c**) was obtained as pale brown solid in 61% yield. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 10.61 (s, 1H), 7.27 (d, *J* = 8.4 Hz, 2H), 7.18 (t, *J* = 7.5 Hz, 1H), 7.09 (d, *J* = 7.5 Hz, 1H), 3.58 (s, 2H), 3.05 (s, 3H), 2.92 (s, 3H), 2.28 (t, *J* = 6.3 Hz, 4H), 1.91 – 1.66 (m, 2H) ppm. **^{13}C NMR** (75 MHz, $CDCl_3$) δ 172.39 (CO), 142.19 (C), 134.66 (C), 130.16 (CH), 127.79 (CH), 127.03 (CH), 123.73 (CH), 114.77 (C), 39.52 (CH_3 amide), 35.30 (CH_3 amide), 32.59 (CH_2), 27.34 (CH_2), 20.57 (CH_2) ppm. **HRMS** [APCI]: *m/z* calculated for $C_{16}H_{20}NO_3$ $[M+H]^+$: 274.1438, found 274.1438. **NMR spectra at page 534.**

3-((4,4-dimethyl-2,6-dioxocyclohexyl)methyl)-*N,N*-dimethylbenzamide (35i)



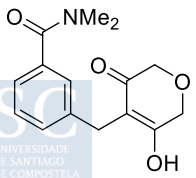
Synthesized by following the procedure used for **35c**. Obtained as colourless oil in 89% yield. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.30 – 7.18 (m, 2H), 7.14 (t, *J* = 7.5 Hz, 1H), 7.04 (d, *J* = 7.6 Hz, 1H), 3.53 (s, 2H), 3.02 (br s, 3H), 2.87 (br s, 3H), 2.06 (s, 4H), 0.84 (s, 6H) ppm. **^{13}C NMR** (75 MHz, $CDCl_3$) δ 172.72 (CO), 142.60 (C), 134.85 (C), 130.41 (CH), 128.01 (CH), 127.20 (CH), 123.80 (CH), 113.59 (C), 39.71 (CH_3 amide), 35.49 (CH_3 amide), 31.82 (C), 28.26 (CH_3), 27.43 (CH_2) ppm (one CH_2 signal is missing probably due to rotamerism and/or tautomerism). **HRMS** [APCI]: *m/z* calculated for $C_{18}H_{24}NO_3$ $[M+H]^+$: 302.1751, found 302.1753.

3-((2,7-dioxocycloheptyl)methyl)-*N,N*-dimethylbenzamide (35k)



Synthesized by following the procedure used for **35c**. Obtained as white solid in 52% yield. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.24 – 7.05 (m, 4H), 4.19 (t, *J* = 6.8 Hz, 1H), 3.07 (dd, *J* = 6.7, 2.2 Hz, 2H), 3.01 (br s, 3H), 2.87 (br s, 3H), 2.56 – 2.31 (m, 4H), 2.11 – 1.93 (m, 2H), 1.85 – 1.66 (m, 2H) ppm. **^{13}C NMR** (75 MHz, $CDCl_3$) δ 204.89 (CO), 171.37 (CO), 139.36 (C), 136.37 (C), 130.12 (CH), 128.39 (CH), 127.43 (CH), 124.99 (CH), 68.00 (CH), 44.34 (CH_2), 39.43 (CH_3 amide), 35.19 (CH_3 amide), 31.50 (CH_2), 24.73 (CH_2) ppm. **HRMS** [APCI]: *m/z* calculated for $C_{17}H_{22}NO_3$ $[M+H]^+$: 288.1594, found 288.1594. **NMR spectra at page 535.**

3-((3,5-dioxotetrahydro-2H-pyran-4-yl)methyl)-*N,N*-dimethylbenzamide (35l)

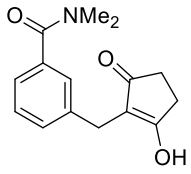


Synthesized by following the procedure used for **35c**. Obtained as a white solid in 32% yield. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.38 – 7.29 (m, 1H), 7.28 – 7.22 (m, 2H), 7.12 (d, *J* = 7.5 Hz, 1H), 4.06 (s, 4H), 3.61 (s, 2H), 3.13 (s, 3H), 3.00 (s, 3H) ppm. **^{13}C NMR** (75 MHz, $CDCl_3$) δ 173.13

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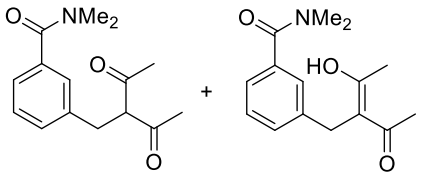
(CO), 142.06 (C), 134.47 (C), 130.93 (CH), 128.24 (CH), 127.15 (CH), 123.95 (CH), 112.50 (C), 68.38 (CH_2), 39.96 (CH_3 amide), 35.73 (CH_3 amide), 26.45 (CH_2) ppm. **HRMS** [APCI]: *m/z* calculated for $C_{15}H_{18}NO_4$ $[M+H]^+$: 276.1230, found 276.1233.

3-((2,5-dioxocyclopentyl)methyl)-*N,N*-dimethylbenzamide (35m)



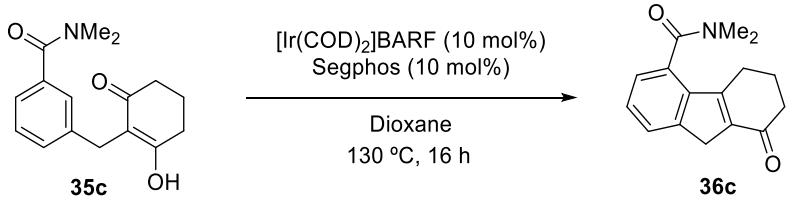
Synthesized by following the procedure used for **35c**. Obtained as a white solid. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.36 – 7.30 (m, 1H), 7.30 – 7.22 (m, 2H), 7.15 (dd, *J* = 7.6, 1.5 Hz, 1H), 3.48 (s, 2H), 3.14 (s, 3H), 3.00 (s, 3H), 2.32 (s, 4H) ppm. **^{13}C NMR** (75 MHz, $CDCl_3$) δ 172.90 (CO), 141.37 (C), 135.04 (C), 130.60 (CH), 128.34 (CH), 127.02 (CH), 124.21 (CH), 116.47 (C), 39.91 (CH_3 amide), 35.71 (CH_3 amide), 30.47 (CH_2), 26.90 (CH_2) ppm. **HRMS** [APCI]: *m/z* calculated for C15H18NO3 $[M+H]^+$: 260.1281, found 260.1280.

3-(2-acetyl-3-oxobutyl)-*N,N*-dimethylbenzamide (35q)



Synthesized by following the procedure used for **35c**. Obtained as colourless oil. [NOTE: Both tautomers are visible by NMR] Ketone: **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.70 – 7.58 (m, 1H), 7.53 – 7.40 (m, 1H), 7.33 – 7.15 (m, 2H), 3.99 (t, *J* = 7.4 Hz, 1H), 3.14 (d, *J* = 7.4 Hz, 2H), 3.07 (s, 3H), 2.92 (s, 3H), 2.11 (s, 3H), 2.04 (s, 3H) ppm. Enol: **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.70 – 7.60 (m, 1H), 7.55 – 7.39 (m, 1H), 7.33 – 7.13 (m, 2H), 3.66 (s, 2H), 3.07 (s, 3H), 2.92 (s, 3H), 2.11 (s, 3H), 2.04 (s, 3H) ppm. Ketone + enol: **^{13}C NMR** (75 MHz, $CDCl_3$) δ 203.13 (CO), 191.94 (CO), 171.48 (CO), 140.12 (C), 138.42 (C), 136.87 (C), 132.14 (CH), 132.01 (CH), 131.96 (CH), 131.93 (CH), 129.85 (CH), 128.79 (CH), 128.73 (CH), 128.59 (CH), 128.50 (CH), 128.43 (CH), 127.30 (CH), 126.04 (CH), 125.52 (CH), 125.04 (CH), 107.84 (C), 69.61 (CH), 39.52 (CH_3 amide), 35.33 (CH_3 amide), 33.85 (CH_2), 32.80 (CH_2), 29.77 (CH_3), 23.32 (CH_3) ppm [NOTE: Many carbon signals are duplicated due to tautomerism and rotamerism]. **HRMS** [APCI]: *m/z* calculated for $C_{15}H_{20}NO_3$ $[M+H]^+$: 262.1438, found 262.1439.

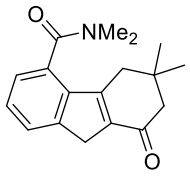
Ir-catalyzed reactions of substrates 35



Prepared following general procedure for catalytic reactions (page 104), using **35c** (27.3 mg, 0.1 mmol), $[Ir(COD)_2]BARF$ (12.7 mg, 0.01 mmol) and (*R*)-Segphos (11.8 mg, 0.01

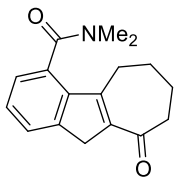
mmol) at 130 ºC. The mixture was concentrated, and the crude residue was purified by flash chromatography (1:10 hexanes/EtOAc to 100% EtOAc, then 100% EtOAc to 9:1 EtOAc/MeOH). ***N,N*-dimethyl-1-oxo-2,3,4,9-tetrahydro-1H-fluorene-5-carboxamide (36c)** was obtained as colourless oil in 42% yield. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.55 (d, *J* = 7.6 Hz, 1H), 7.40 (t, *J* = 7.5 Hz, 1H), 7.21 (d, *J* = 7.6 Hz, 1H), 3.61 (q, *J* = 2.8 Hz, 2H), 3.19 (s, 3H), 2.95 (br m, *J* = 18.5 Hz, 1H), 2.87 (s, 3H), 2.57 – 2.44 (m, 3H), 2.21 – 2.13 (m, 2H) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$) δ 197.00 (CO), 170.39 (CO), 158.67 (C), 146.06 (C), 140.15 (C), 139.06 (C), 132.39 (C), 128.69 (CH), 125.40 (CH), 124.76 (CH), 39.28 (CH_3 amide), 38.03 (CH_2), 35.17 (CH_2), 34.93 (CH_3 amide), 24.04 (CH_2), 23.87 (CH_2) ppm. **HRMS** [APCI]: *m/z* calculated for $C_{16}H_{18}NO_2$ $[M+H]^+$: 256.1332, found 256.1332. **NMR spectra at page 536.**

***N,N*,3,3-tetramethyl-1-oxo-2,3,4,9-tetrahydro-1H-fluorene-5-carboxamide (36i)**



Prepared following general procedure for catalytic reactions (page 104), using **35i** and (*R*)-Segphos (5 mol%) as ligand at 130 ºC for 3 days. Obtained as white solid in 65% yield. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.55 (d, *J* = 8.6 Hz, 1H), 7.39 (t, *J* = 7.5 Hz, 1H), 7.20 (d, *J* = 7.5 Hz, 1H), 3.65 – 3.57 (m, 2H), 3.18 (d, *J* = 1.0 Hz, 3H), 2.84 (s + m, 4H), 2.40 (s + m, 3H), 1.11 (s, 6H) ppm. **^{13}C NMR** (75 MHz, $CDCl_3$) δ 196.64 (CO), 170.40 (CO), 156.75 (C), 146.34 (C), 139.26 (C), 139.06 (C), 132.37 (C), 128.64 (CH), 125.39 (CH), 124.72 (CH), 51.96 (CH_2), 39.19 (CH_3 amide), 38.13 (CH_2), 34.91 (CH_2), 34.87 (CH_3 amide), 28.82 (CH_3) ppm. **HRMS** [APCI]: *m/z* calculated for $C_{18}H_{22}NO_2$ $[M+H]^+$: 284.1645, found 284.1650.

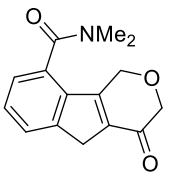
***N,N*-dimethyl-9-oxo-5,6,7,8,9,10-hexahydrobenzo[a]azulene-4-carboxamide (36k)**



Prepared following general procedure for catalytic reactions (page 104), using **35k** and (*R*)-Segphos (5 mol%) as ligand at 130 ºC for 20 h. Obtained as a colourless oil in 83% yield. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.49 (d, *J* = 7.4 Hz, 1H), 7.35 (t, *J* = 7.6 Hz, 1H), 7.15 (d, *J* = 7.6 Hz, 1H), 3.72 – 3.62 (m, 2H), 3.17 (s, 3H), 3.12 – 2.99 (m, 1H), 2.85 (s, 3H), 2.78 – 2.57 (m, 3H), 2.03 – 1.80 (m, 4H) ppm. **^{13}C NMR** (75 MHz, $CDCl_3$) δ (75 MHz, $CDCl_3$) δ 200.81 (CO), 171.07 (CO), 153.50 (C), 145.26 (C), 142.87 (C), 140.51 (C), 132.45 (C), 127.98 (C), 124.95 (CH), 124.85 (CH), 43.60 (CH_2), 39.19 (CH_3 amide), 38.73 (CH_2), 34.89 (CH_3 amide), 28.20 (CH_2), 26.18 (CH_2), 22.12 (CH_2) ppm. **HRMS** [APCI]: *m/z* calculated for $C_{17}H_{20}NO_2$ $[M+H]^+$: 270.1489, found 270.1488. **NMR spectra at page 537.**

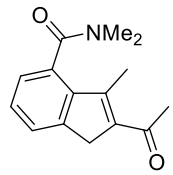
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N,N-dimethyl-4-oxo-1,3,4,5-tetrahydroindeno[1,2-c]pyran-9-carboxamide (36l)



Prepared following general procedure for catalytic reactions (page 104), using **35l** and (*R*)-Segphos (5 mol%) as ligand at 130 ºC for 3 days Obtained as white solid in 48% yield. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.61 (dd, *J* = 7.7, 1.2 Hz, 1H), 7.44 (t, *J* = 7.6 Hz, 1H), 7.25 (d, *J* = 6.8 Hz, 1H), 4.77 (br s, 2H), 4.24 (s, 2H), 3.69 (s, 2H), 3.18 (d, *J* = 1.2 Hz, 3H), 2.93 (d, *J* = 1.2 Hz, 3H) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$) δ 192.55 (CO), 169.97 (CO), 157.70 (C), 146.25 (C), 137.30 (C), 132.10 (C), 129.13 (CH), 125.85 (CH), 125.03 (CH), 72.16 (CH_2), 64.66 (CH_2), 39.43 (CH_3 amide), 35.13 (CH_3 amide), 34.82 (CH_2) ppm. **HRMS** [APCI]: *m/z* calculated for $C_{15}H_{16}NO_3$ $[M+H]^+$: 258.1125, found 258.1127.

2-acetyl-*N,N*,3-trimethyl-1H-indene-4-carboxamide (36q)



Prepared following general procedure for catalytic reactions (page 104), using **35q** and (*R*)-Segphos (5 mol%) as ligand at 130 ºC for 3 days. Obtained as pale-yellow oil in 20% yield. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.50 (dq, *J* = 7.5, 0.8 Hz, 1H), 7.38 (t, *J* = 7.5 Hz, 1H), 7.20 – 7.17 (m, 1H), 3.71 (q, *J* = 2.5 Hz, 2H), 3.17 (s, 3H), 2.82 (s, 3H), 2.48 (t, *J* = 2.5 Hz, 3H), 2.45 (s, 3H) ppm. **^{13}C NMR** (75 MHz, $CDCl_3$) δ 197.25 (CO), 170.79 (C), 149.47 (C), 144.25 (C), 140.82 (C), 138.98 (C), 132.76 (C), 128.12 (CH), 125.05 (CH), 124.59 (CH), 39.51 (CH_2), 39.09 (CH_3 amide), 34.83 (CH_3 amide), 30.64 (CH_3), 13.66 (CH_3) ppm. **HRMS** [APCI]: *m/z* calculated for $C_{15}H_{18}NO_2$ $[M+H]^+$: 244.1332, found 244.1335.

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8

Bibliography

The bibliographic references in this doctoral thesis are presented as footnotes to facilitate reading.

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Appendices

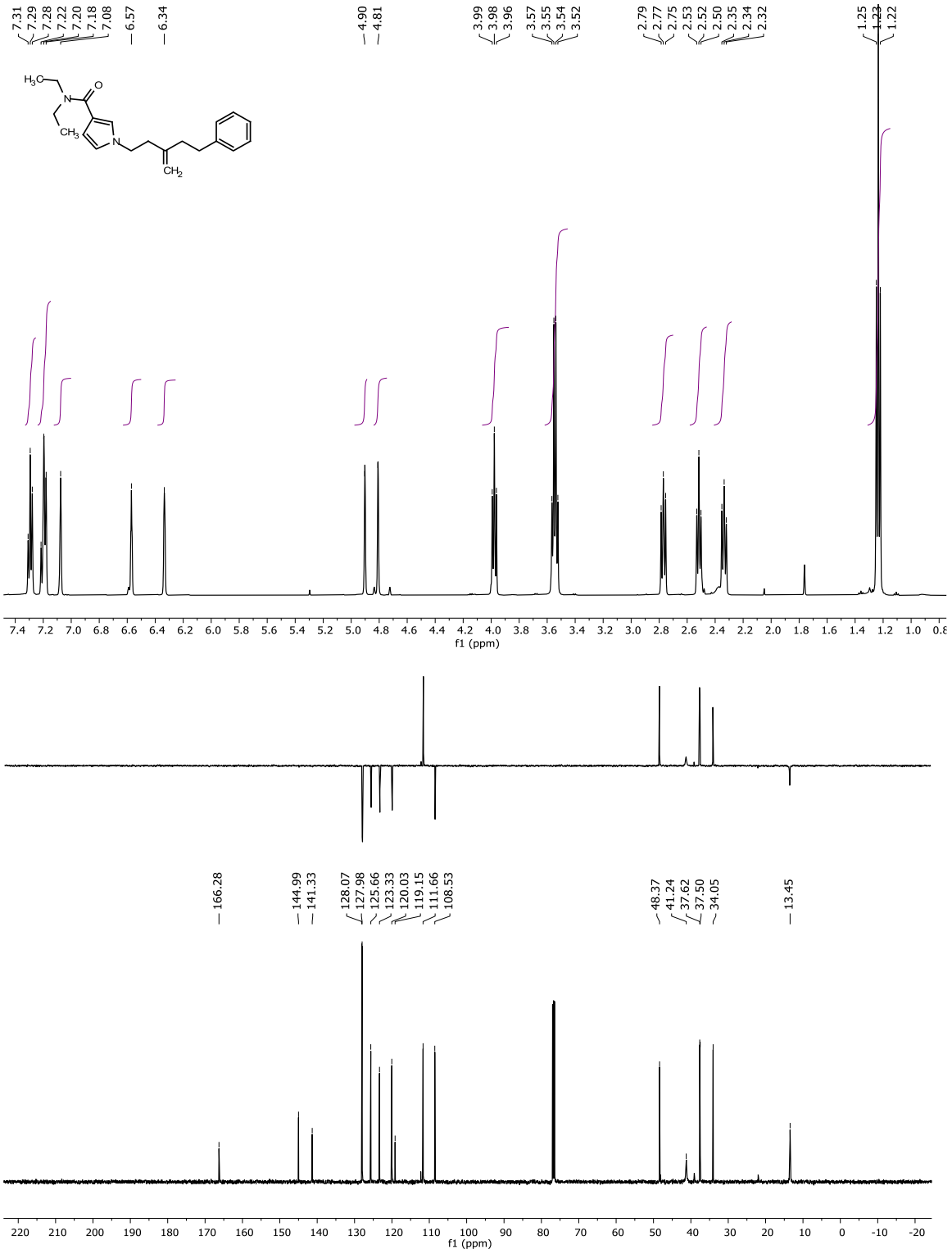


Appendix I: Selected NMR spectra

The following pages contain representative NMR spectra for the compounds synthesized and characterized in this work.

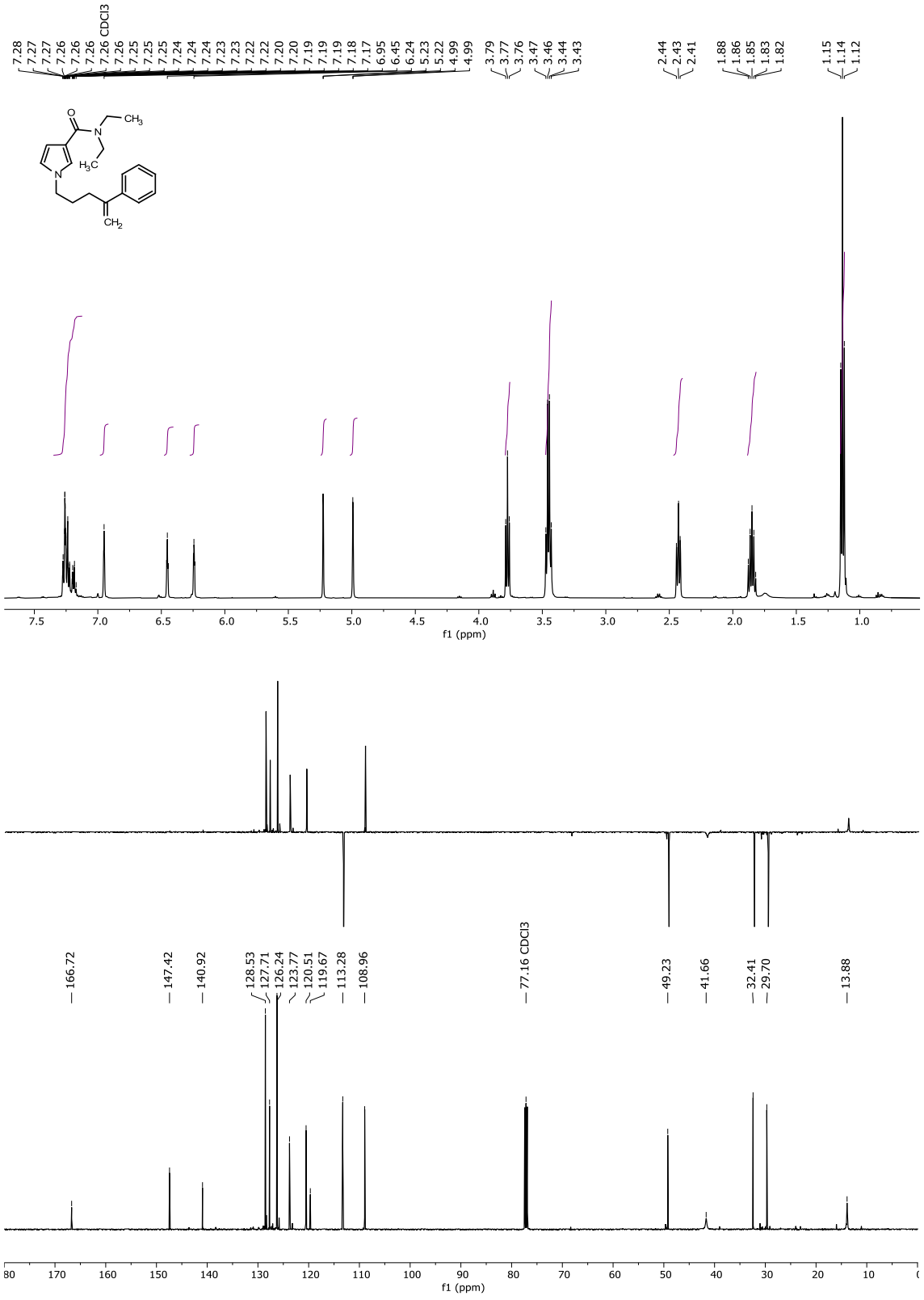
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*^{1}H and ^{13}C NMR of **1a***



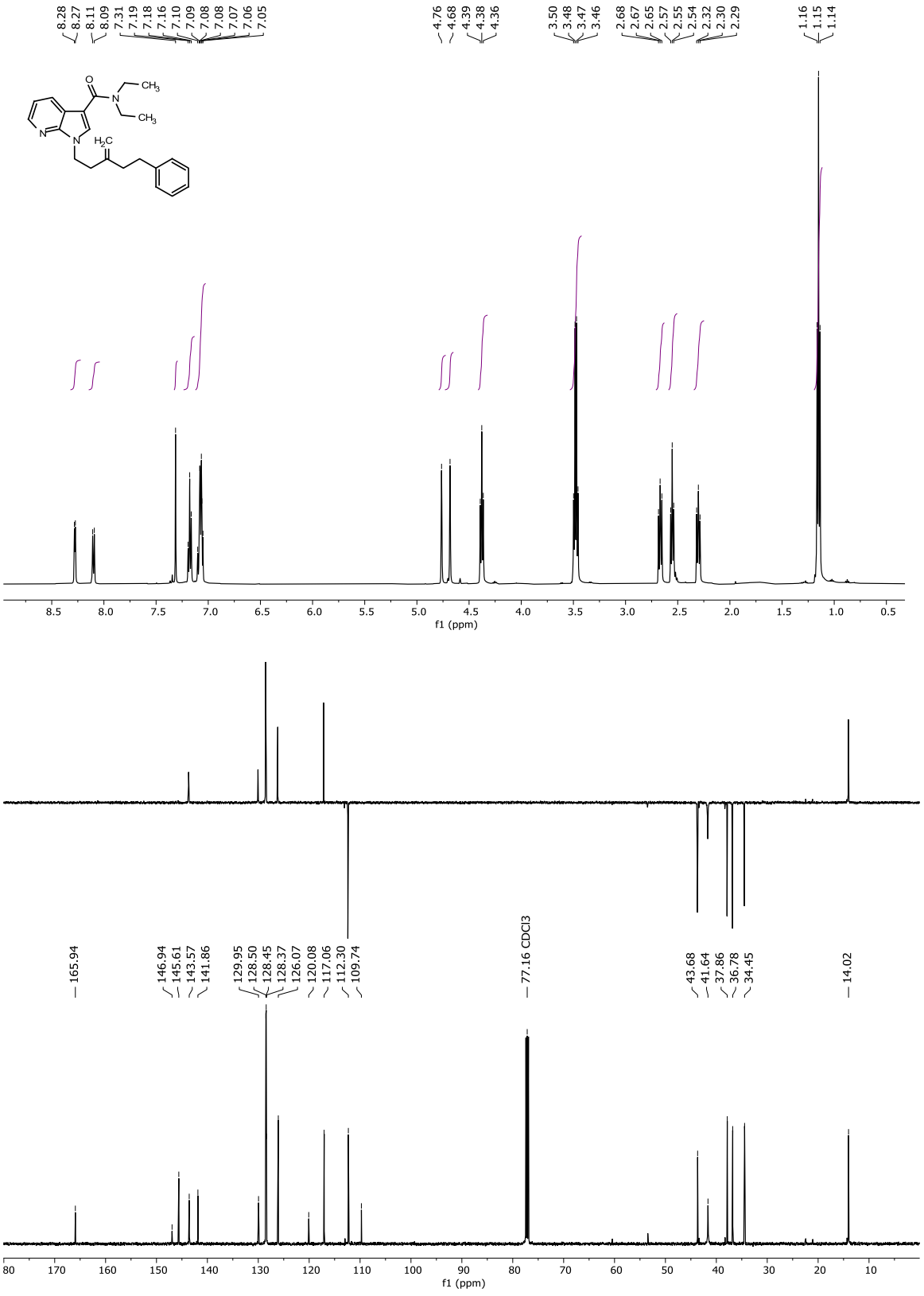
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*^{1}H and ^{13}C NMR of **1h***



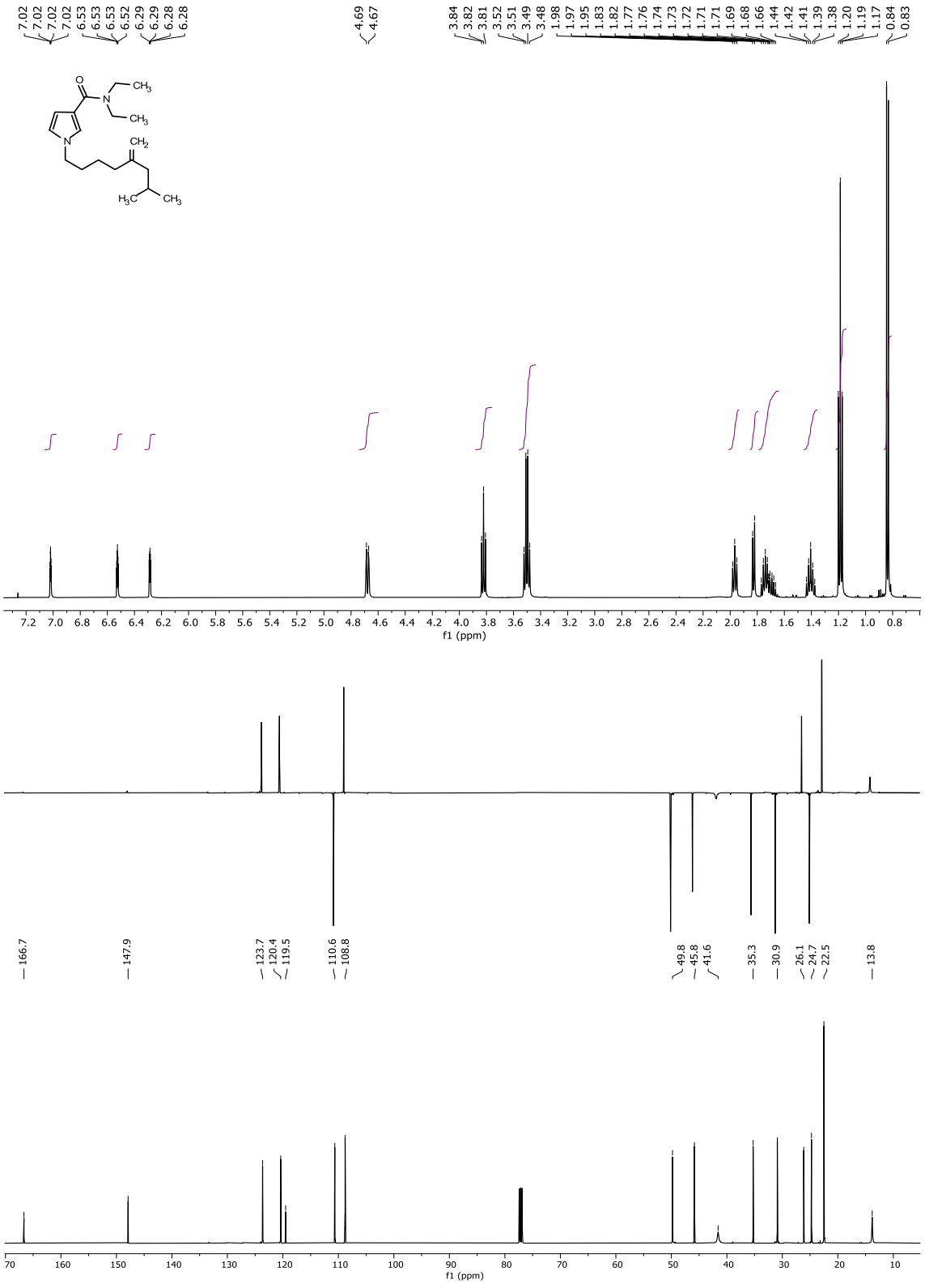
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*^{1}H and ^{13}C NMR of **1s***

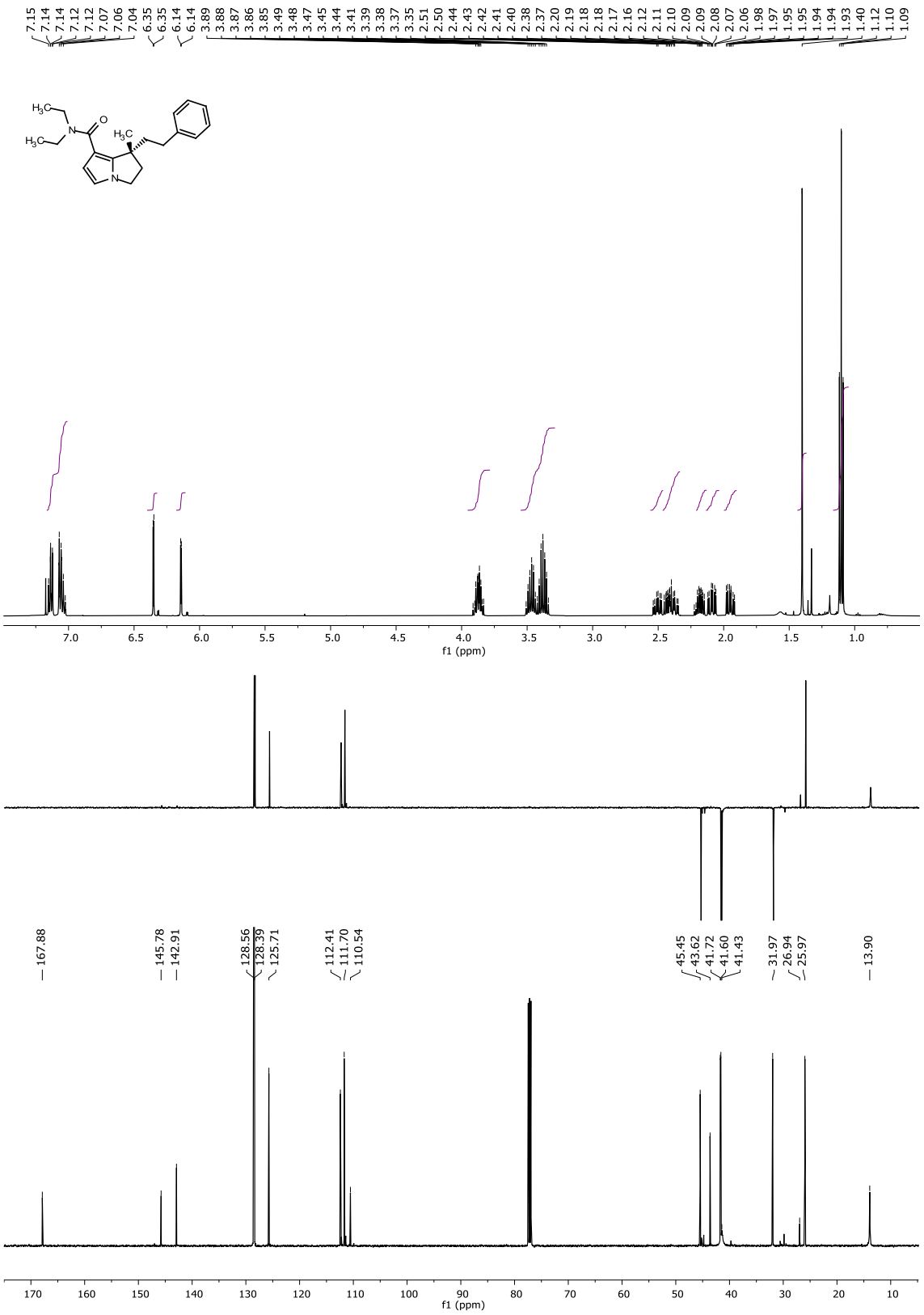


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*^{1}H and ^{13}C NMR of **1x***

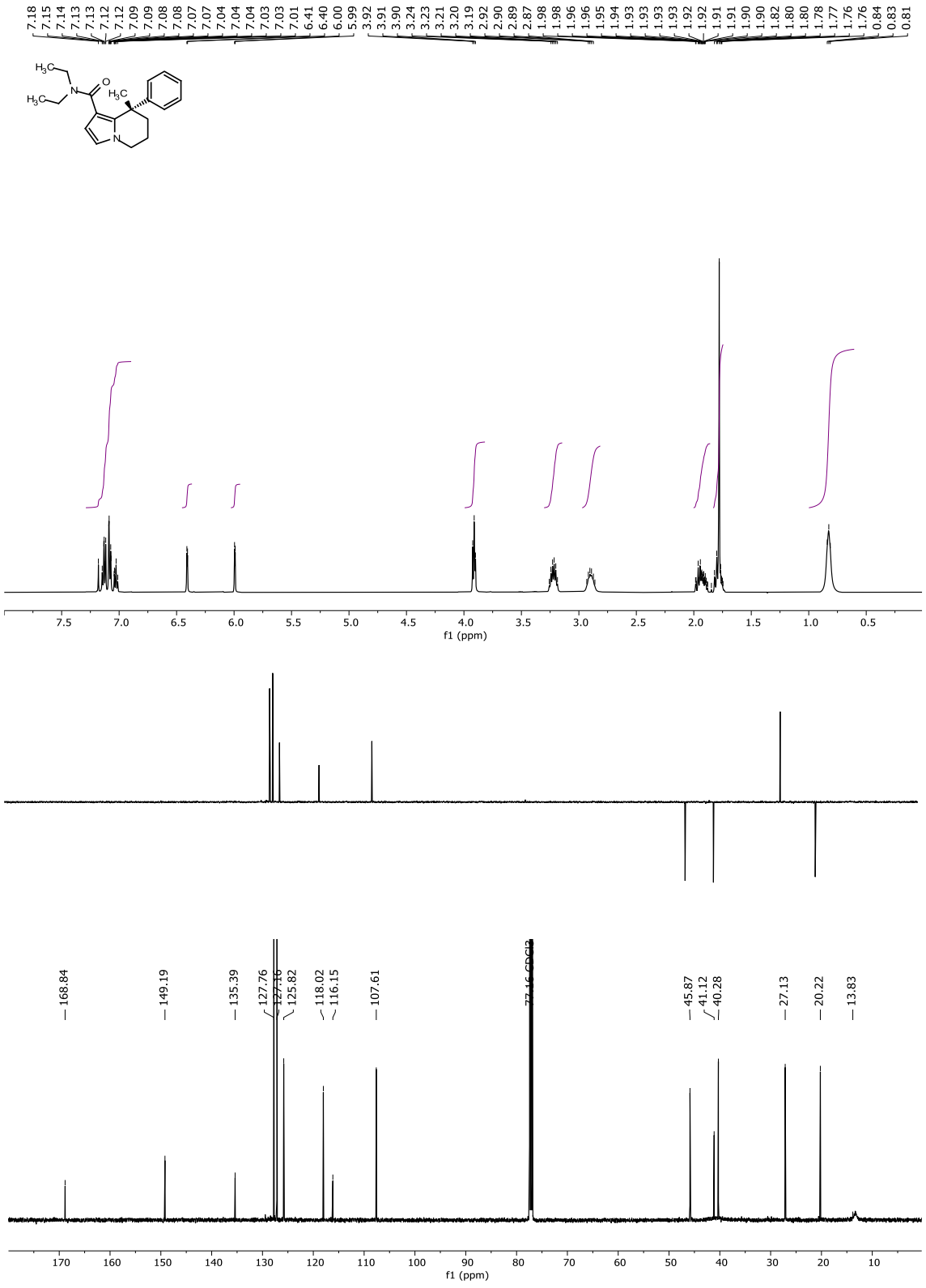


*^{1}H and ^{13}C NMR of **2a***



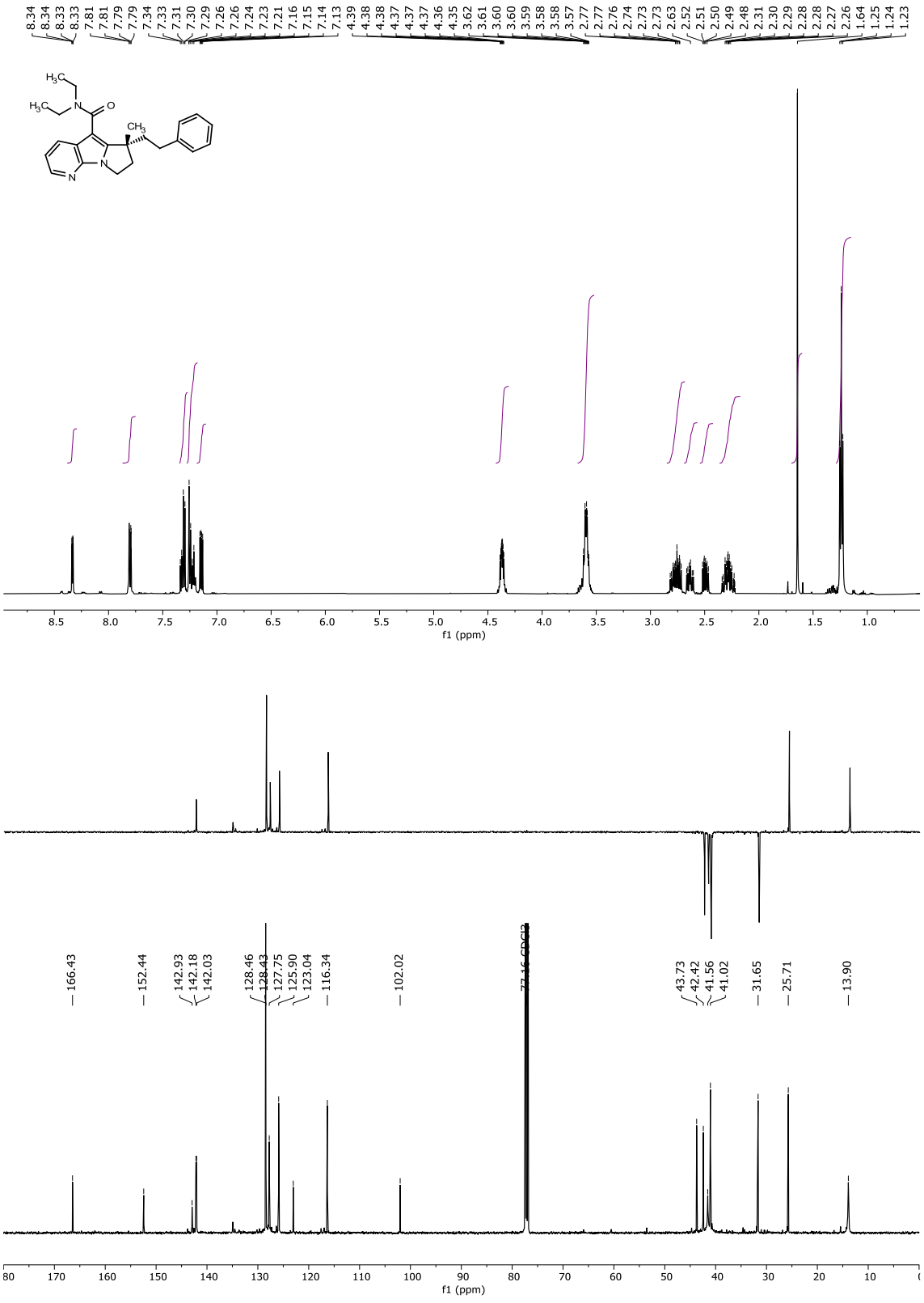
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*^{1}H and ^{13}C NMR of **2h***



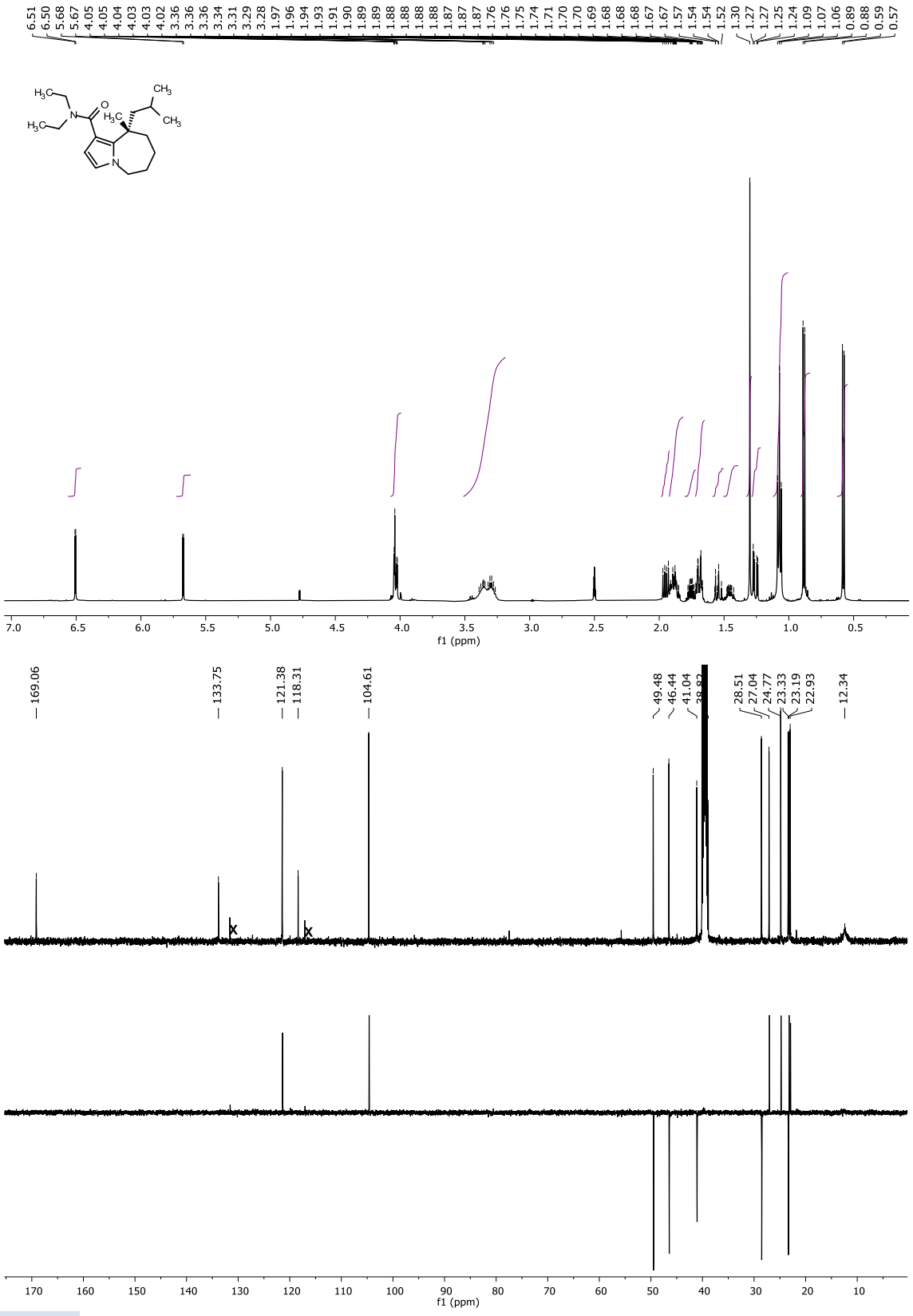
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*^{1}H and ^{13}C NMR of **2x***



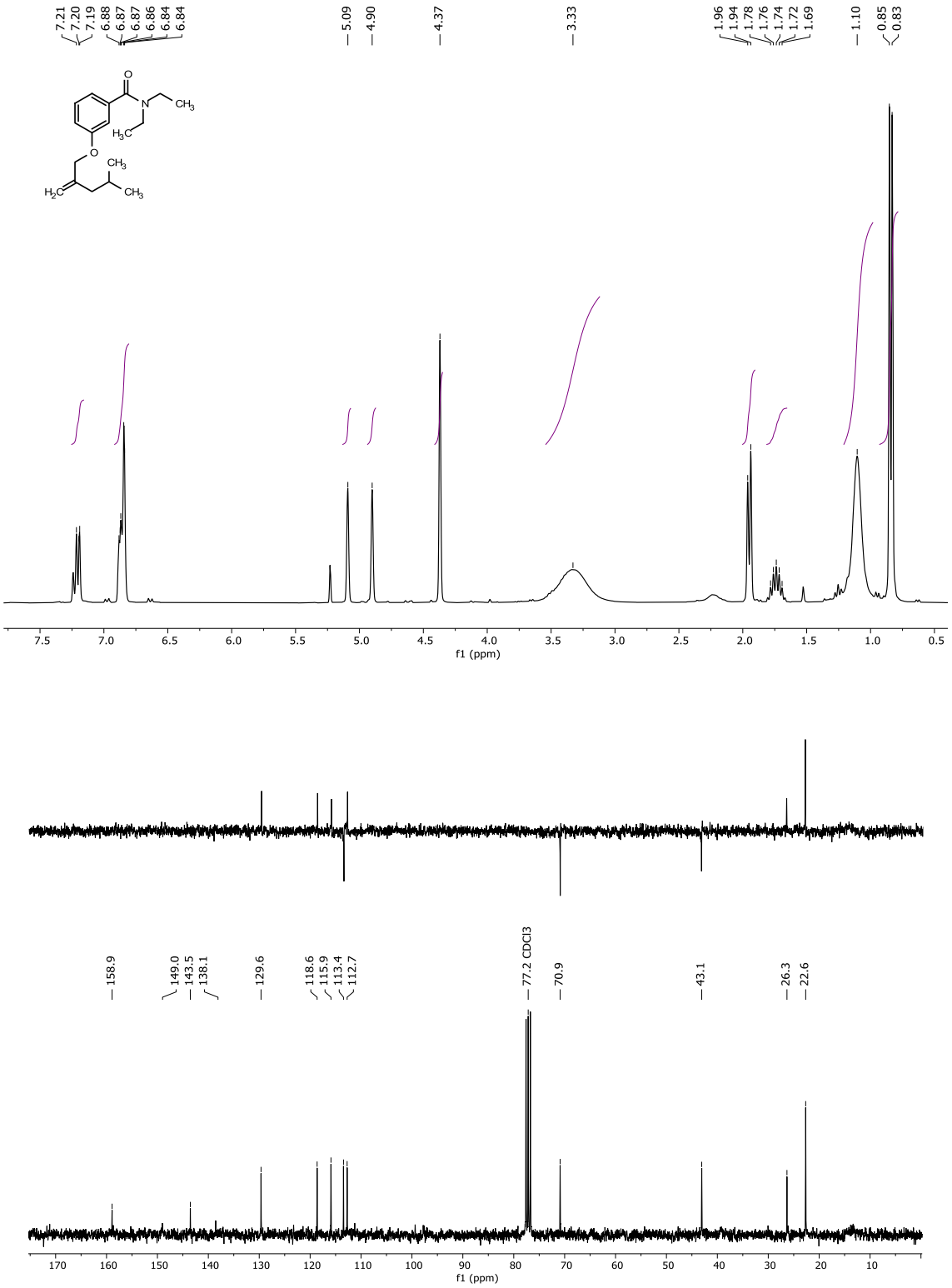
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*^{1}H and ^{13}C NMR of **2s***



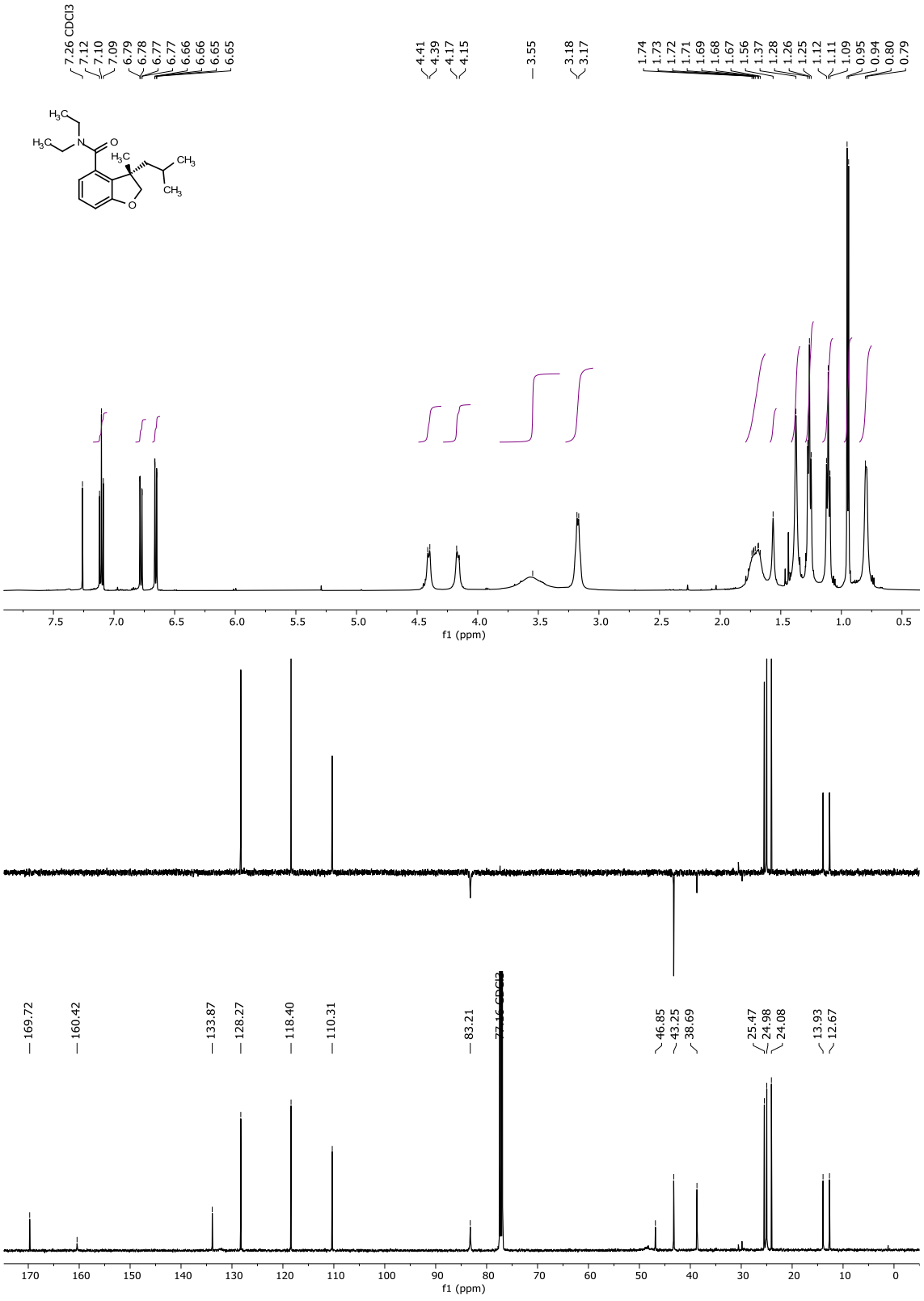
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*^{1}H and ^{13}C NMR of **3b***



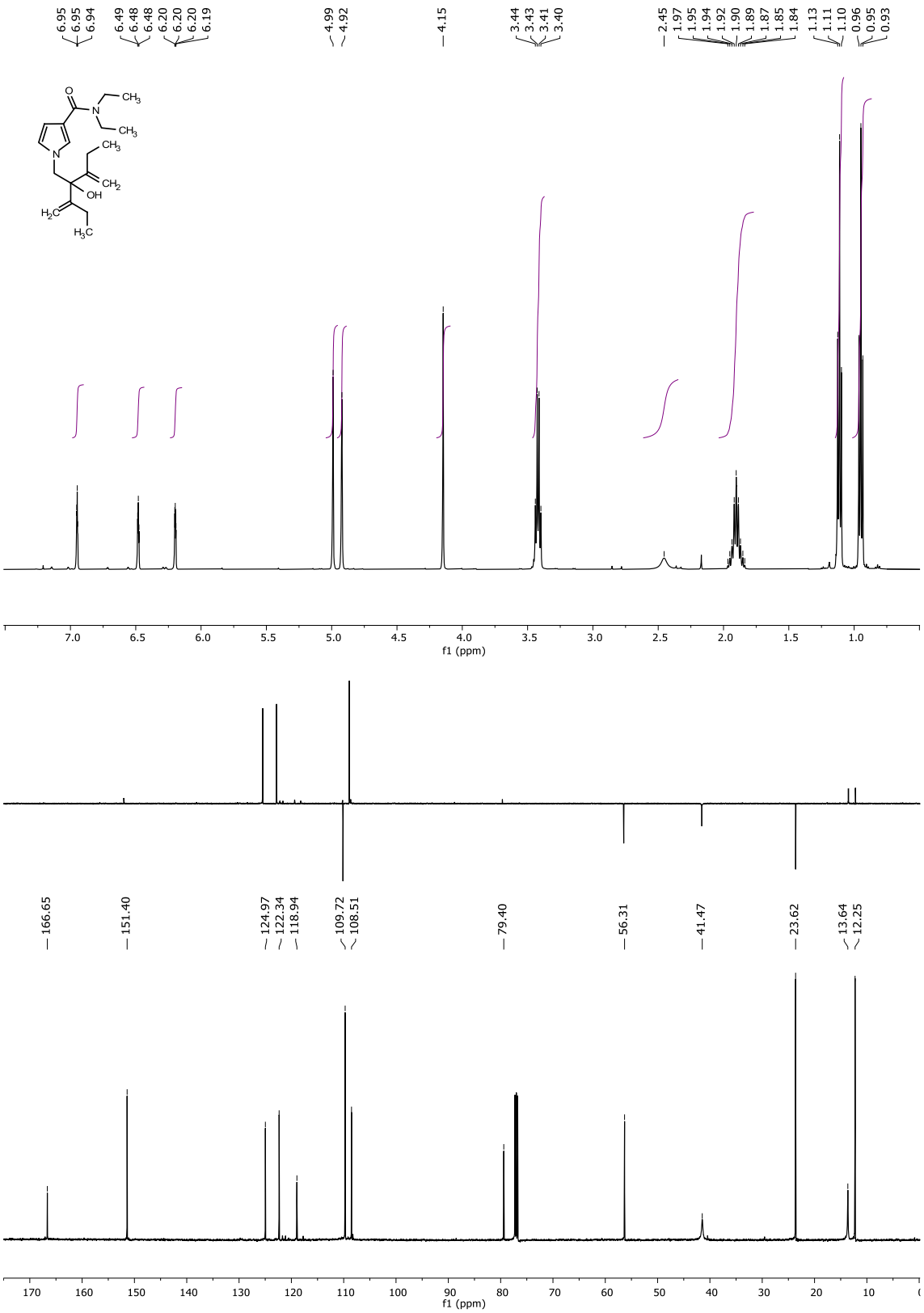
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*^{1}H and ^{13}C NMR of **4b***



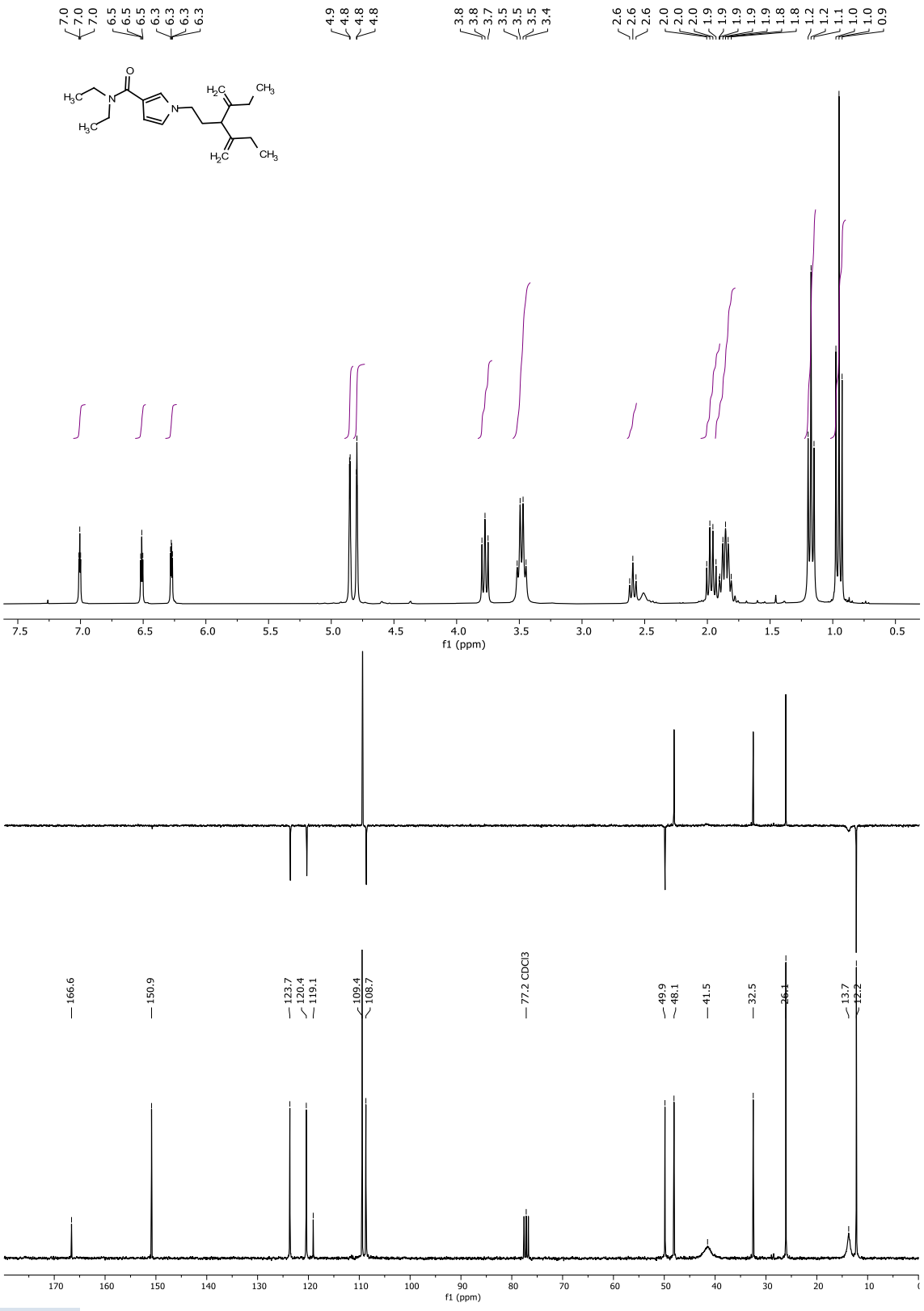
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*^{1}H and ^{13}C NMR of **5b***



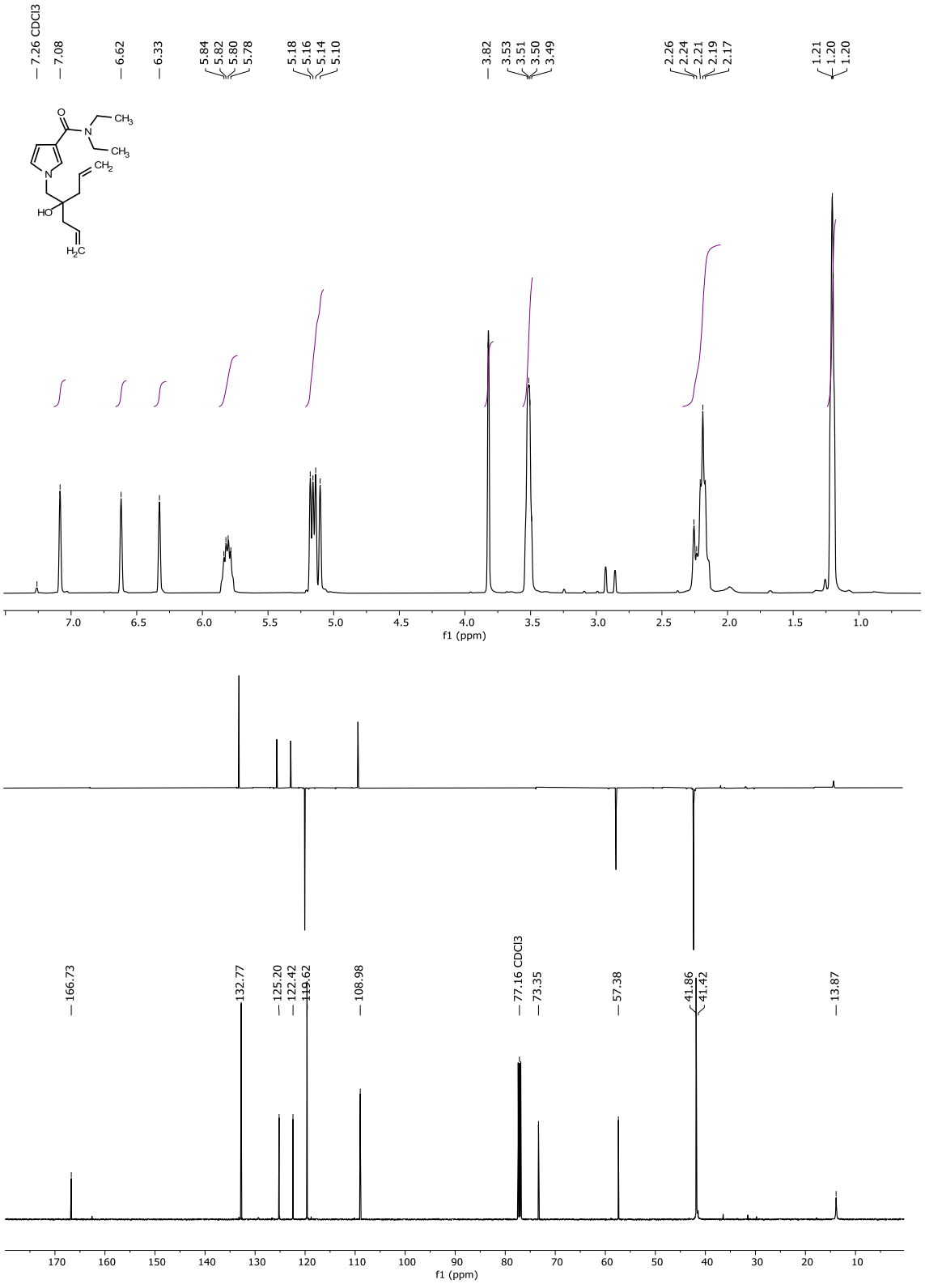
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*^{1}H and ^{13}C NMR of **5c***



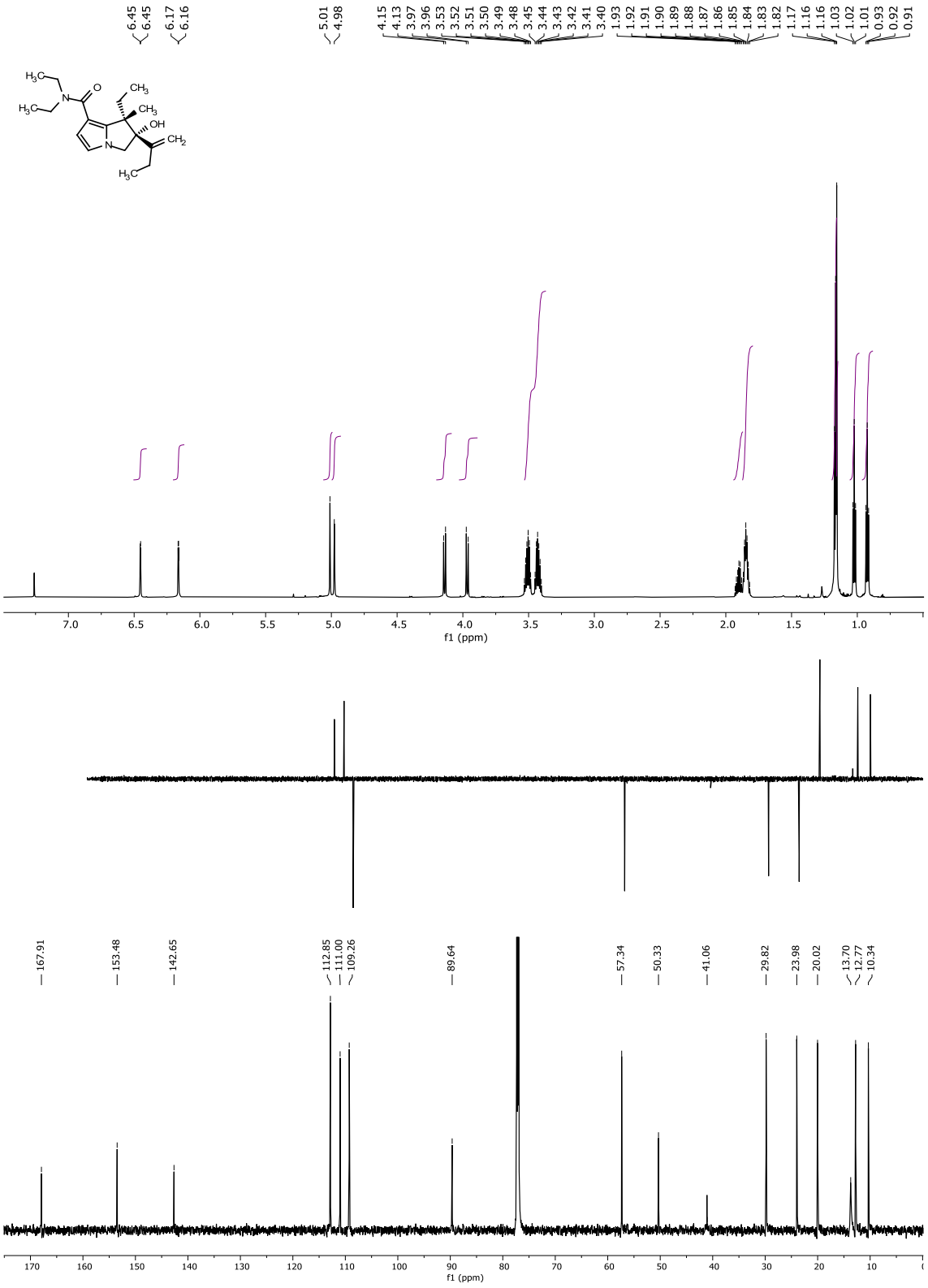
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*^{1}H and ^{13}C NMR of **5f***



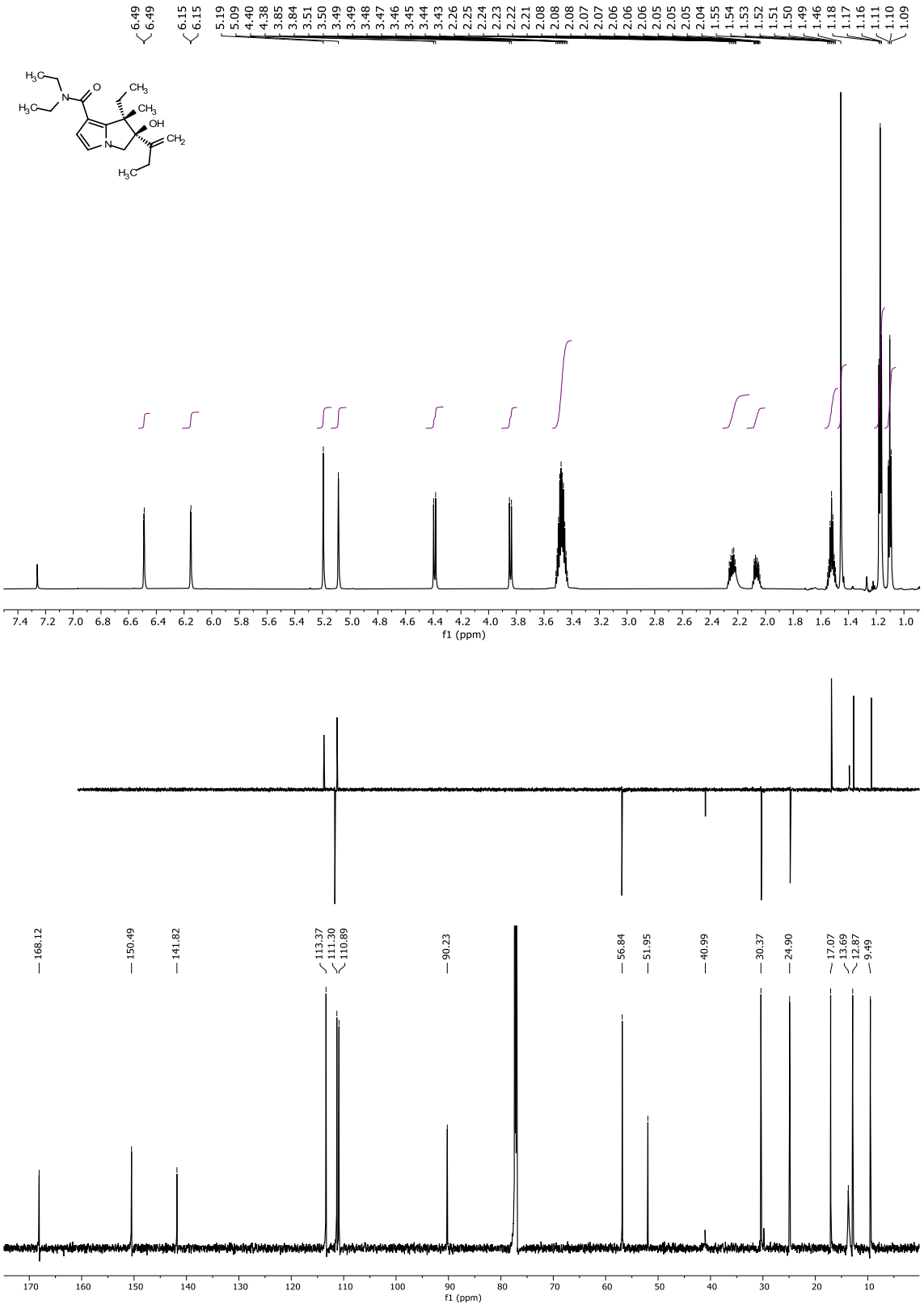
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*^{1}H and ^{13}C NMR of **6b***



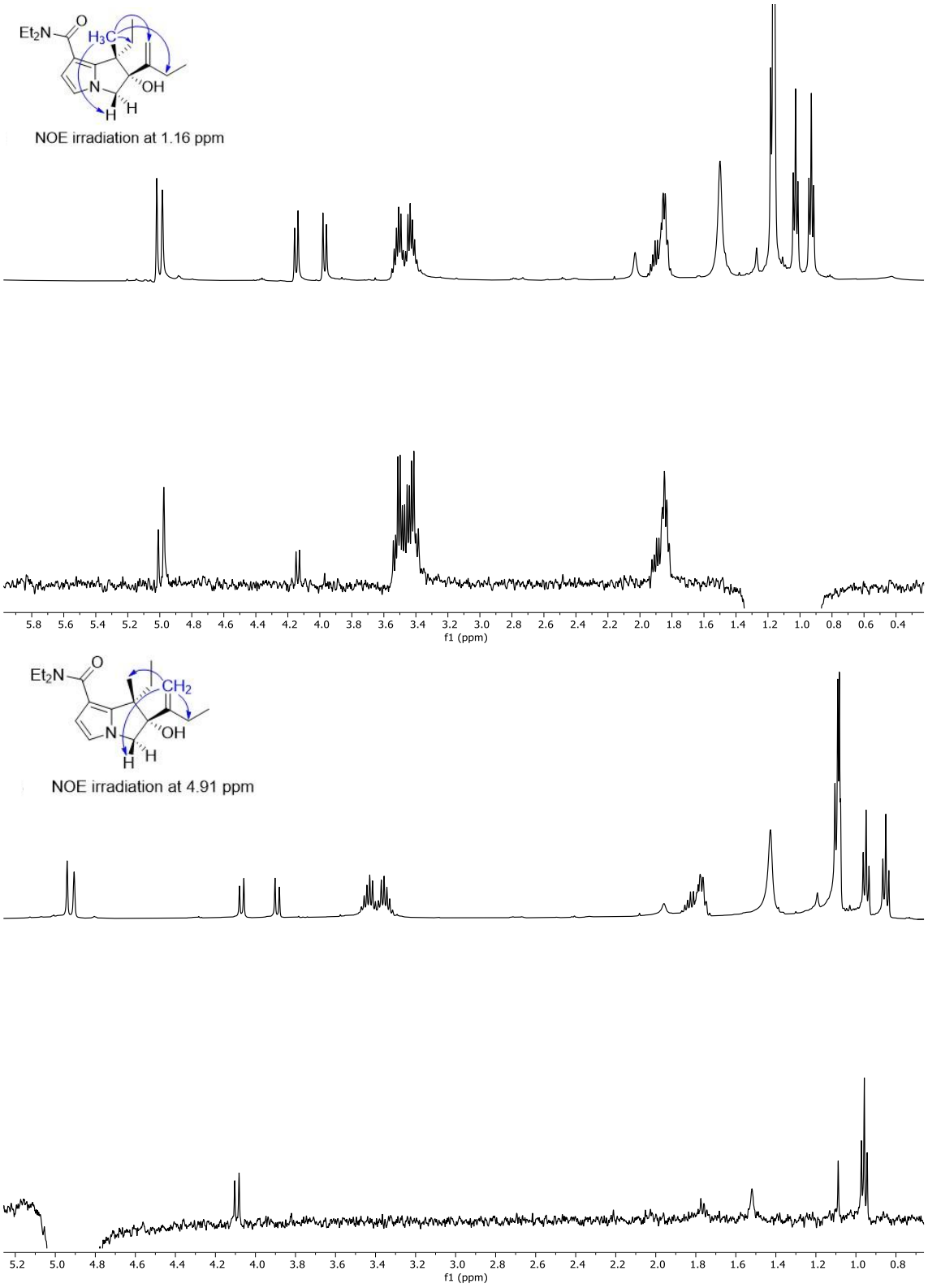
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*^{1}H and ^{13}C NMR of **6b'***

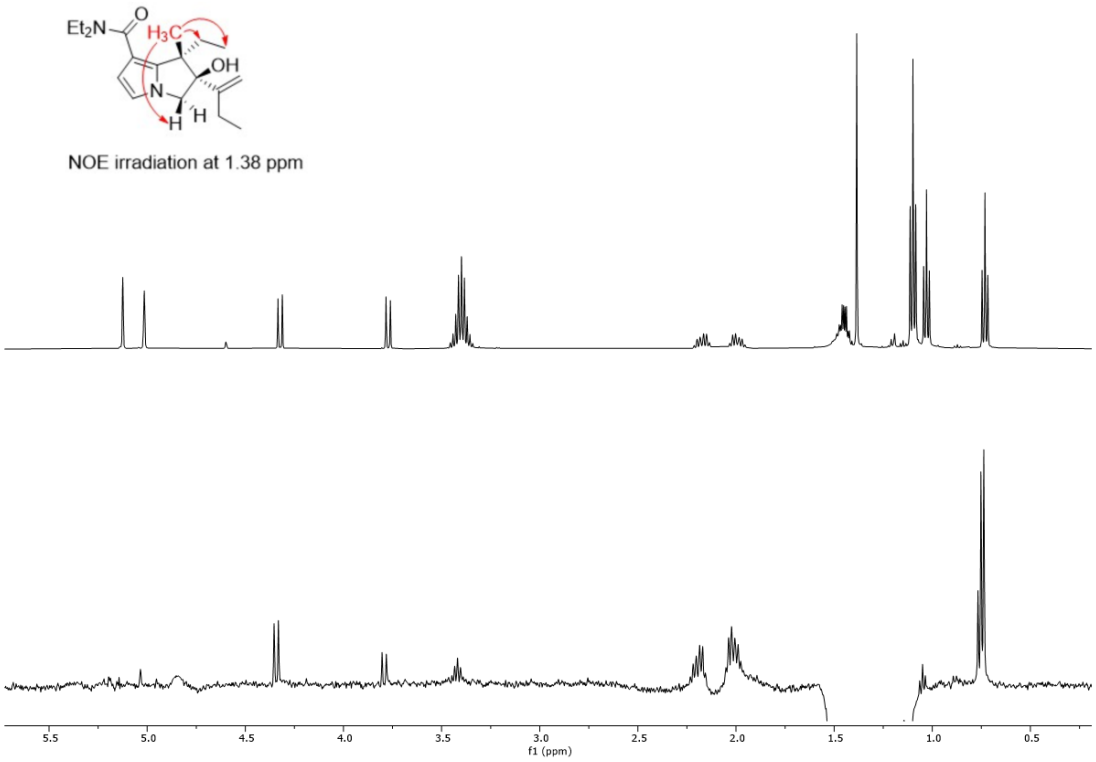


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*NOE irradiations of **6b** and **6b'***

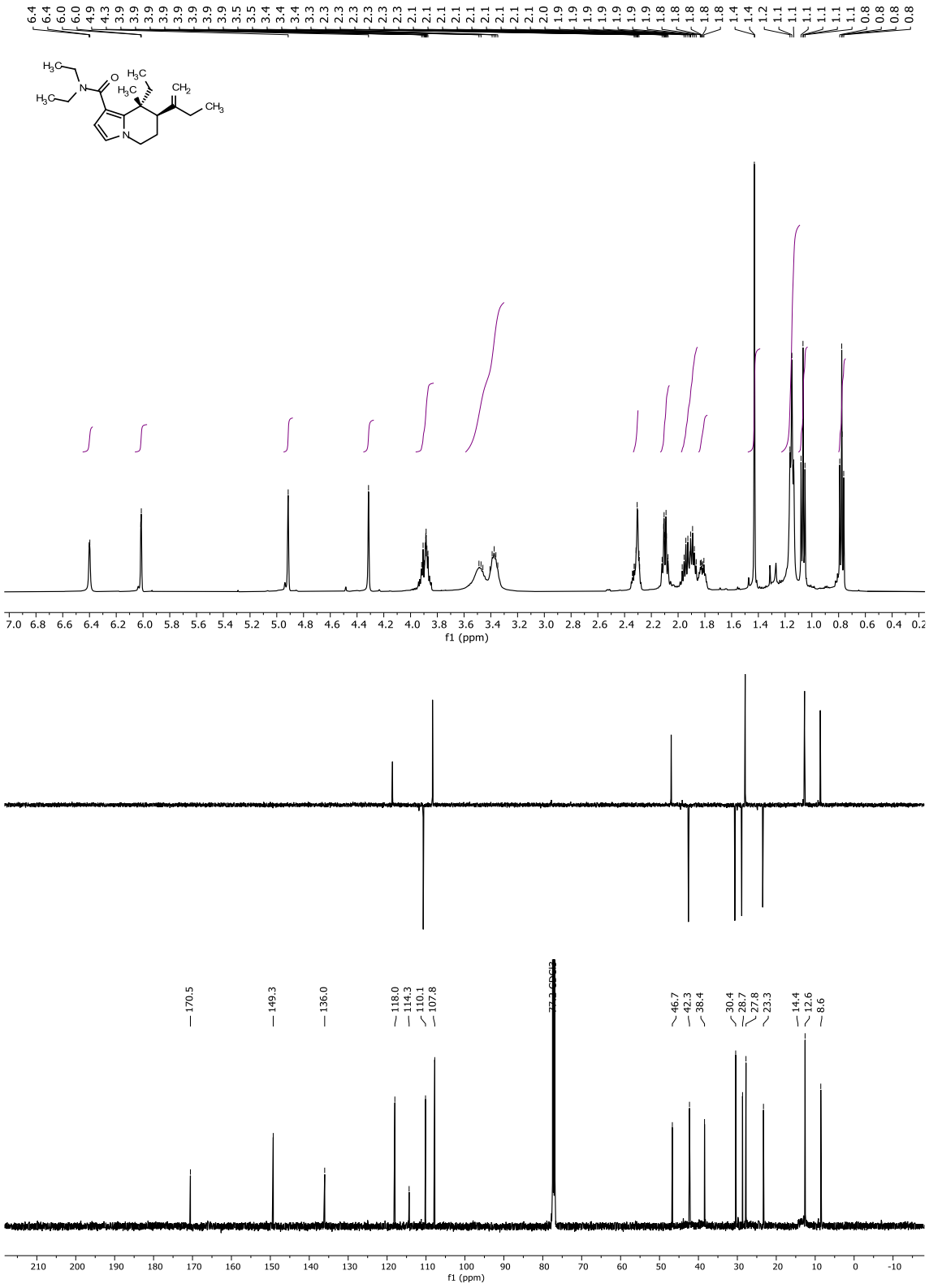


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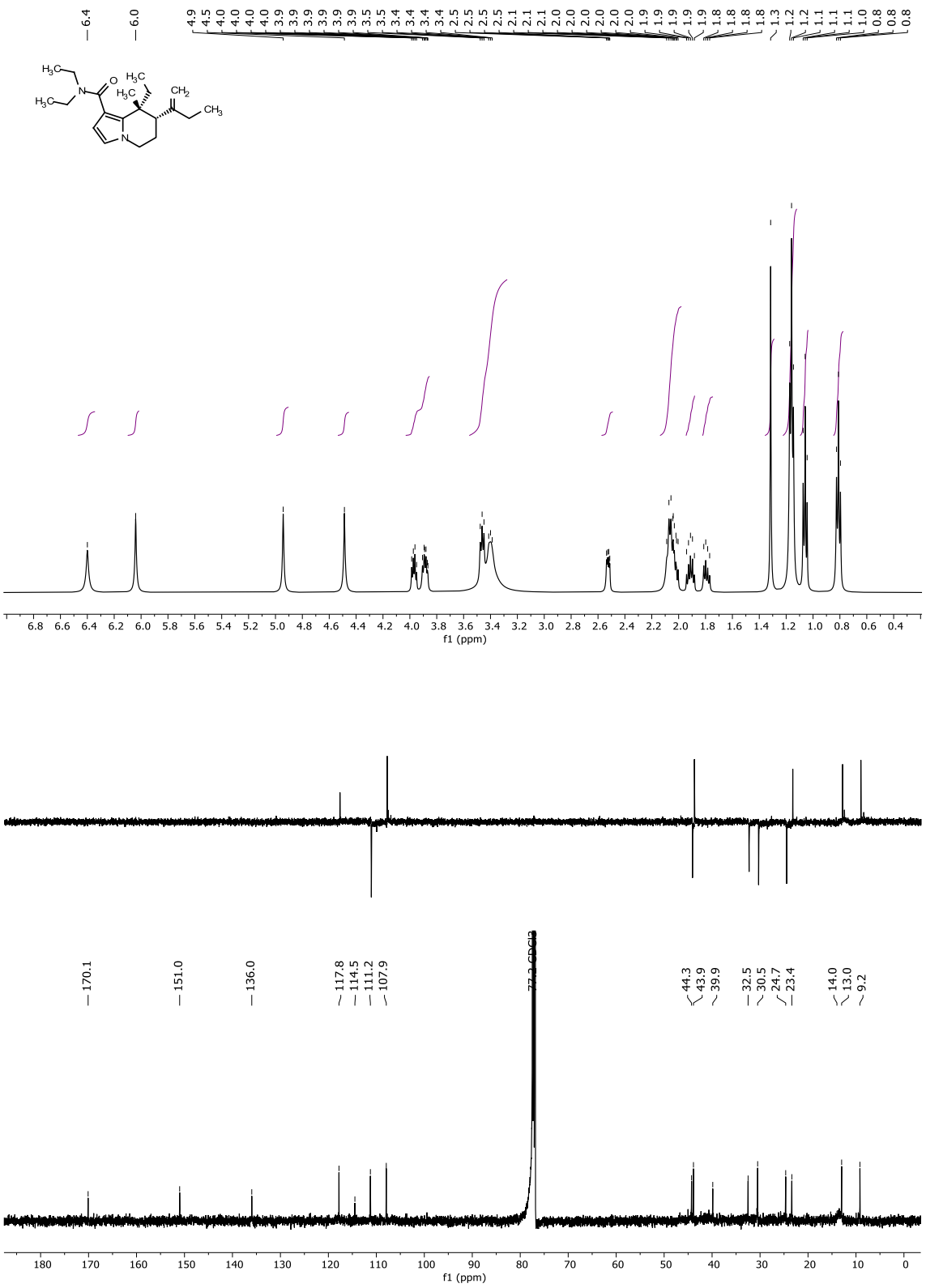
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*^{1}H and ^{13}C NMR of **6c***



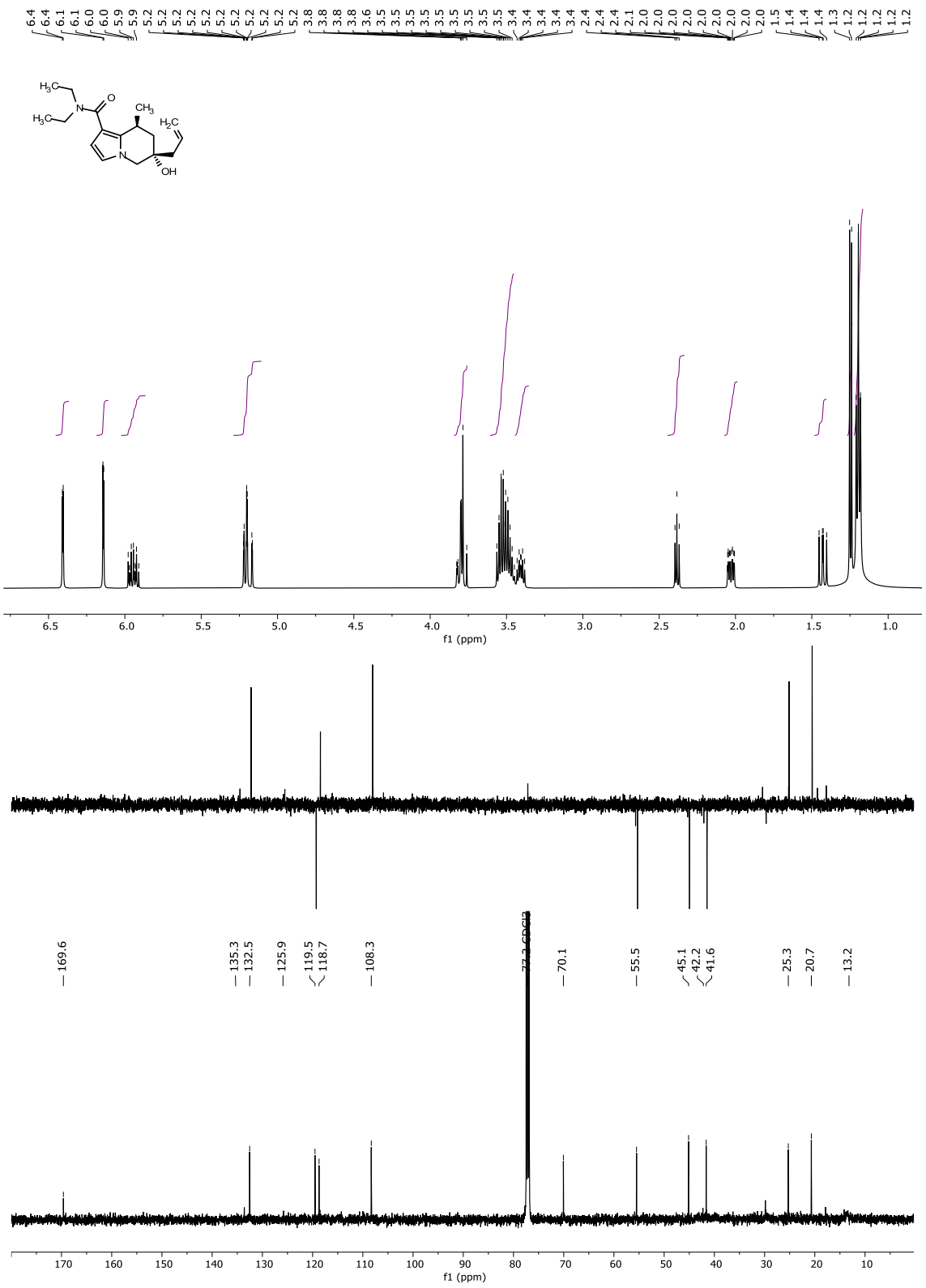
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*^{1}H and ^{13}C NMR of **6c'***



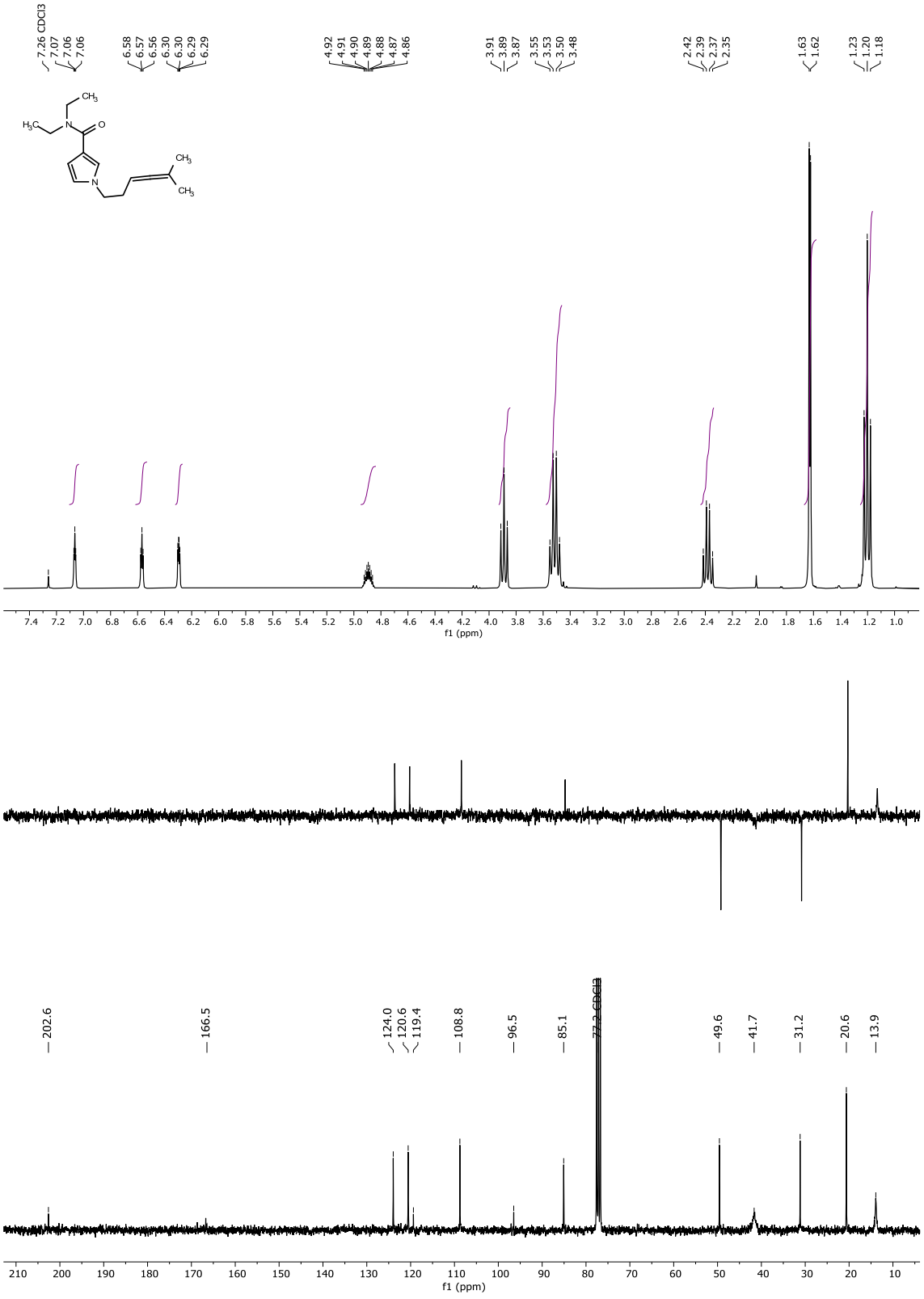
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*^{1}H and ^{13}C NMR of **6f***

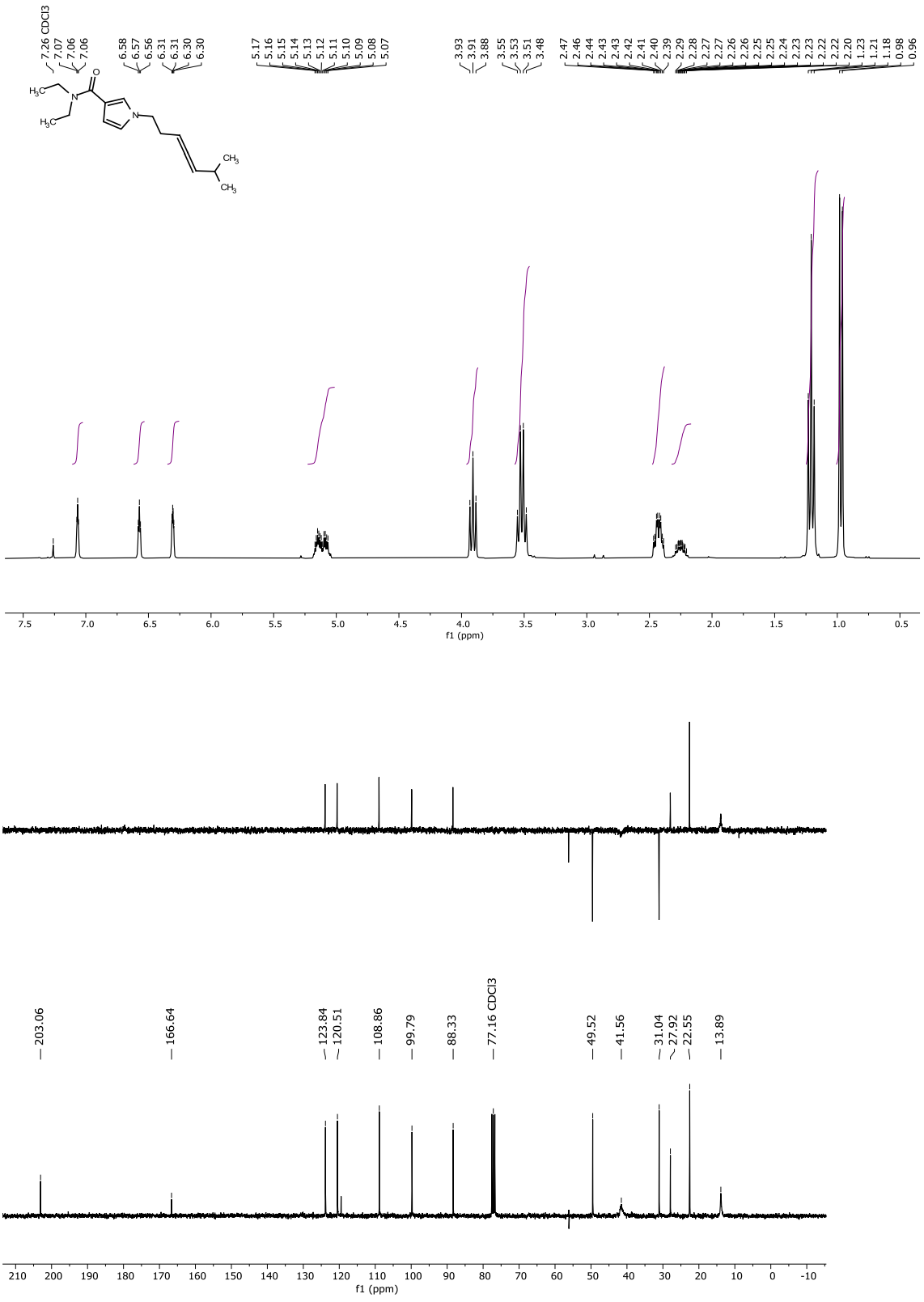


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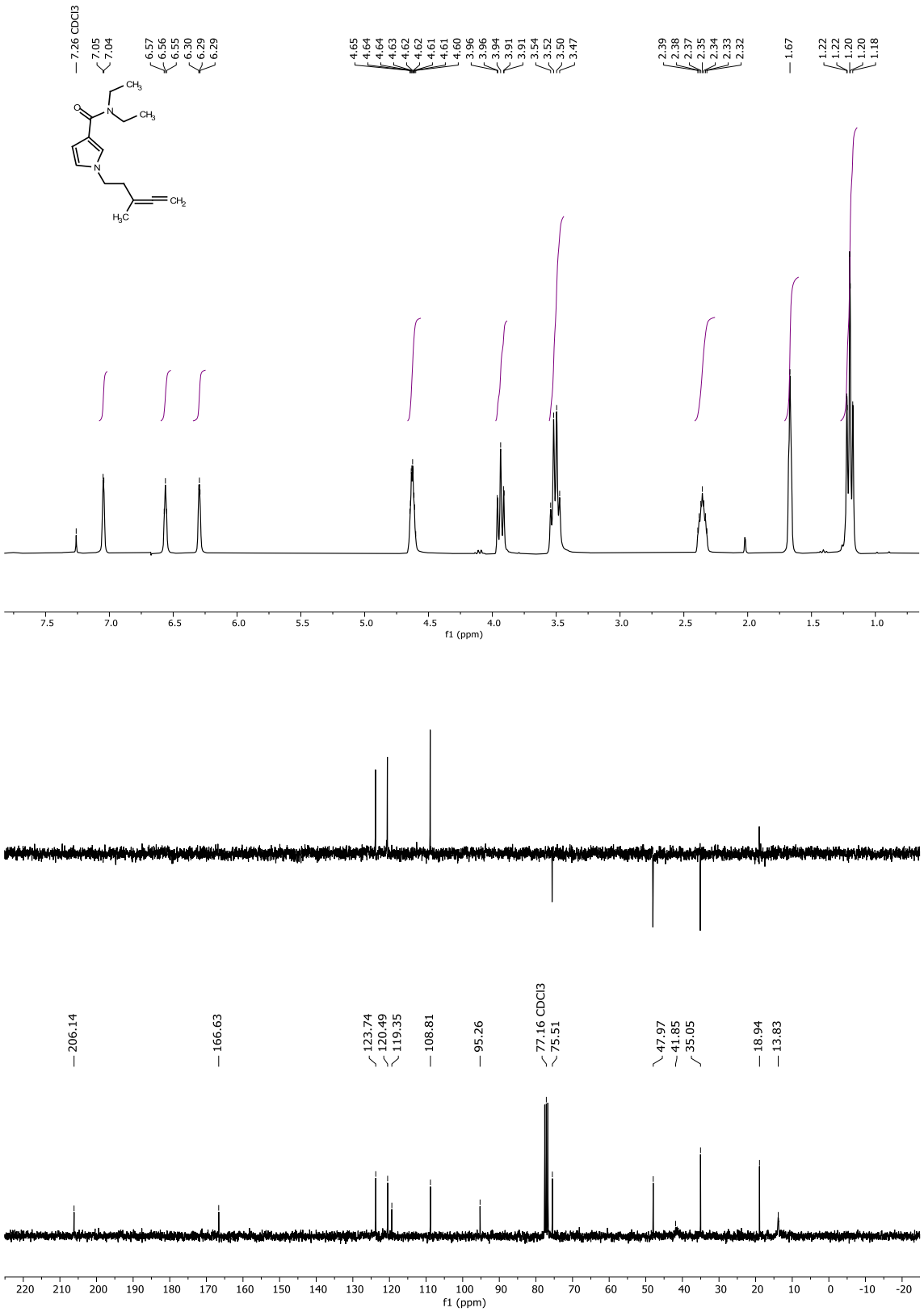
*^{1}H and ^{13}C NMR of **7a***



*^{1}H and ^{13}C NMR of **7f***

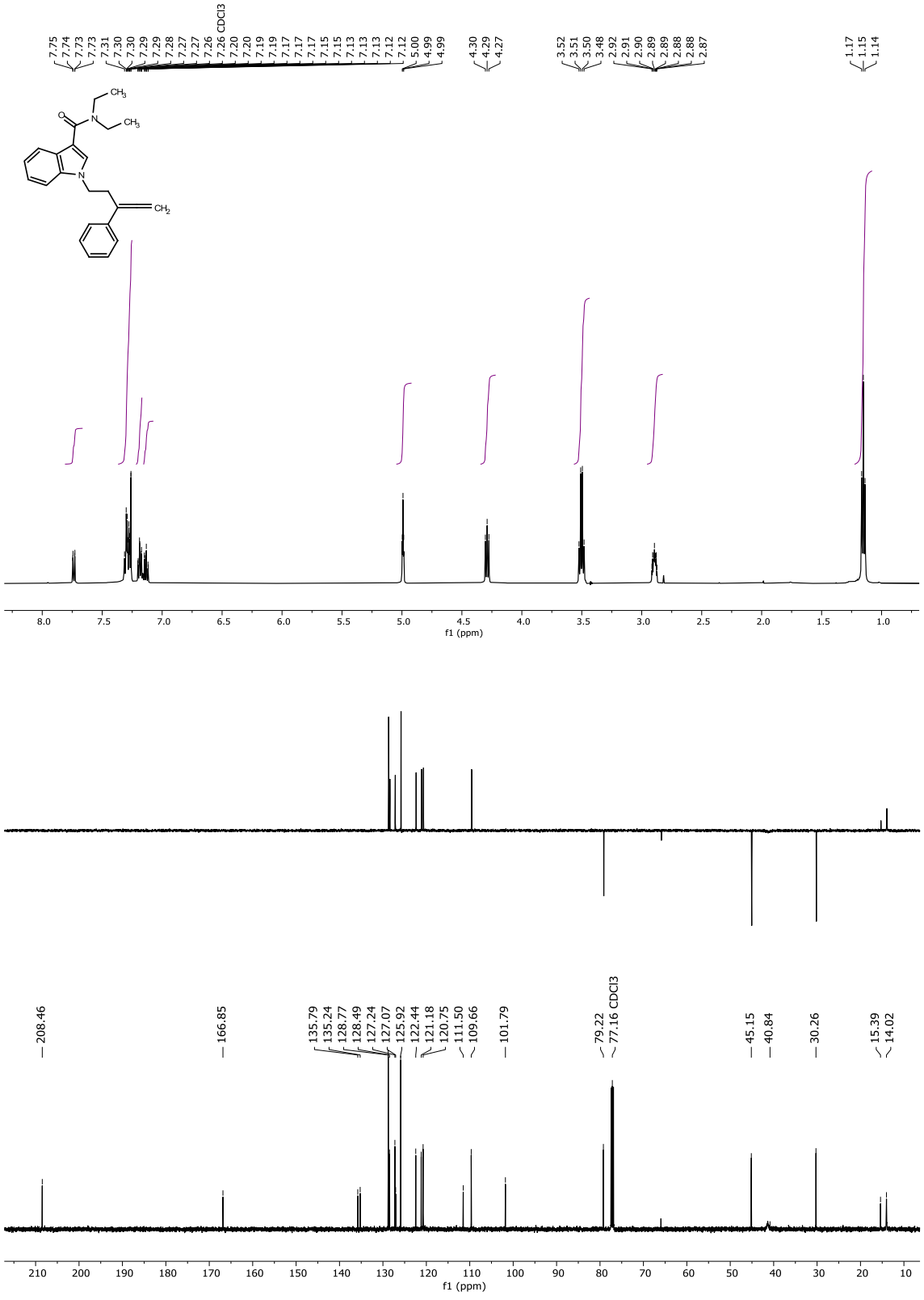


*^{1}H and ^{13}C NMR of **7h***



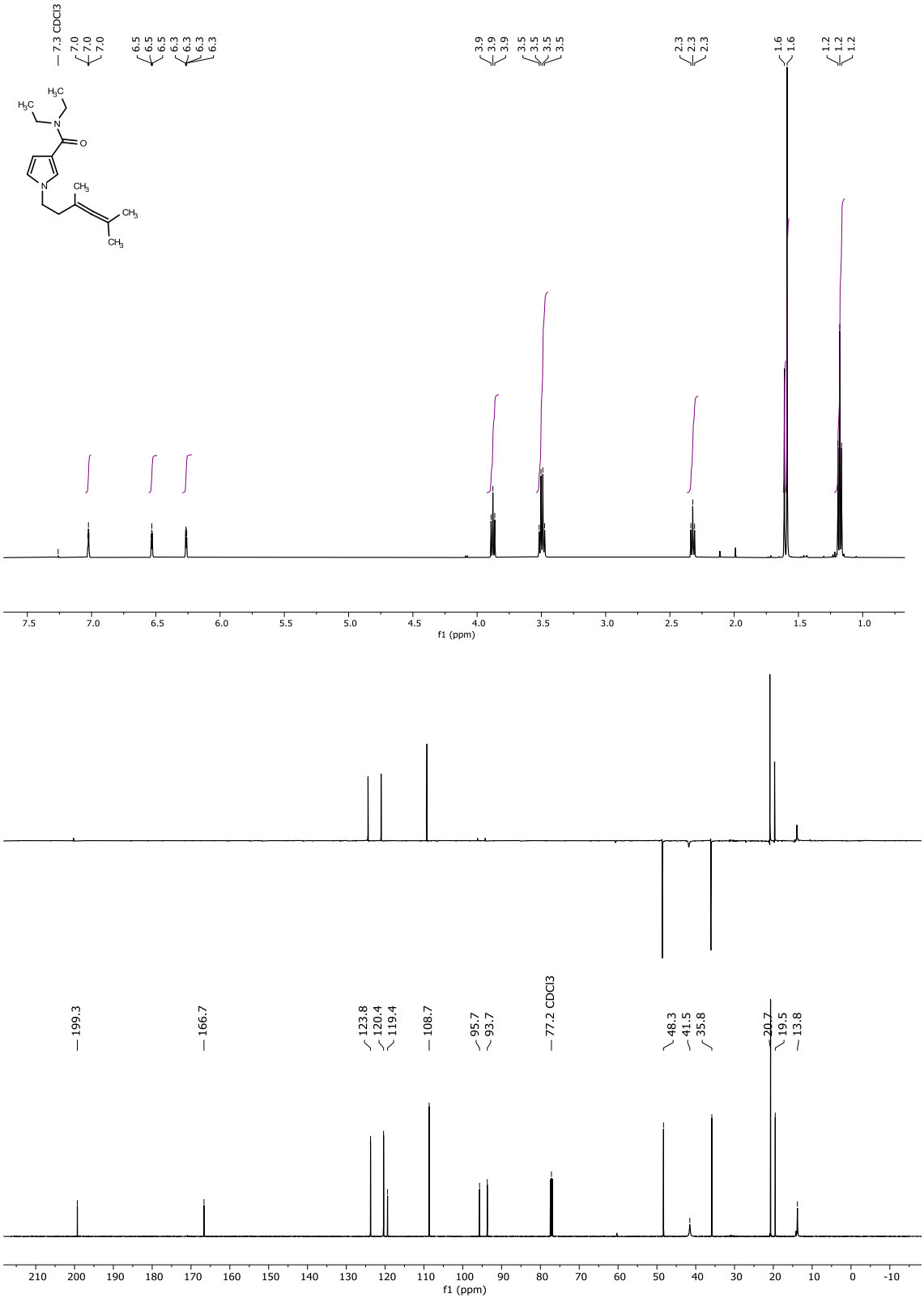
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*^{1}H and ^{13}C NMR of **7n***



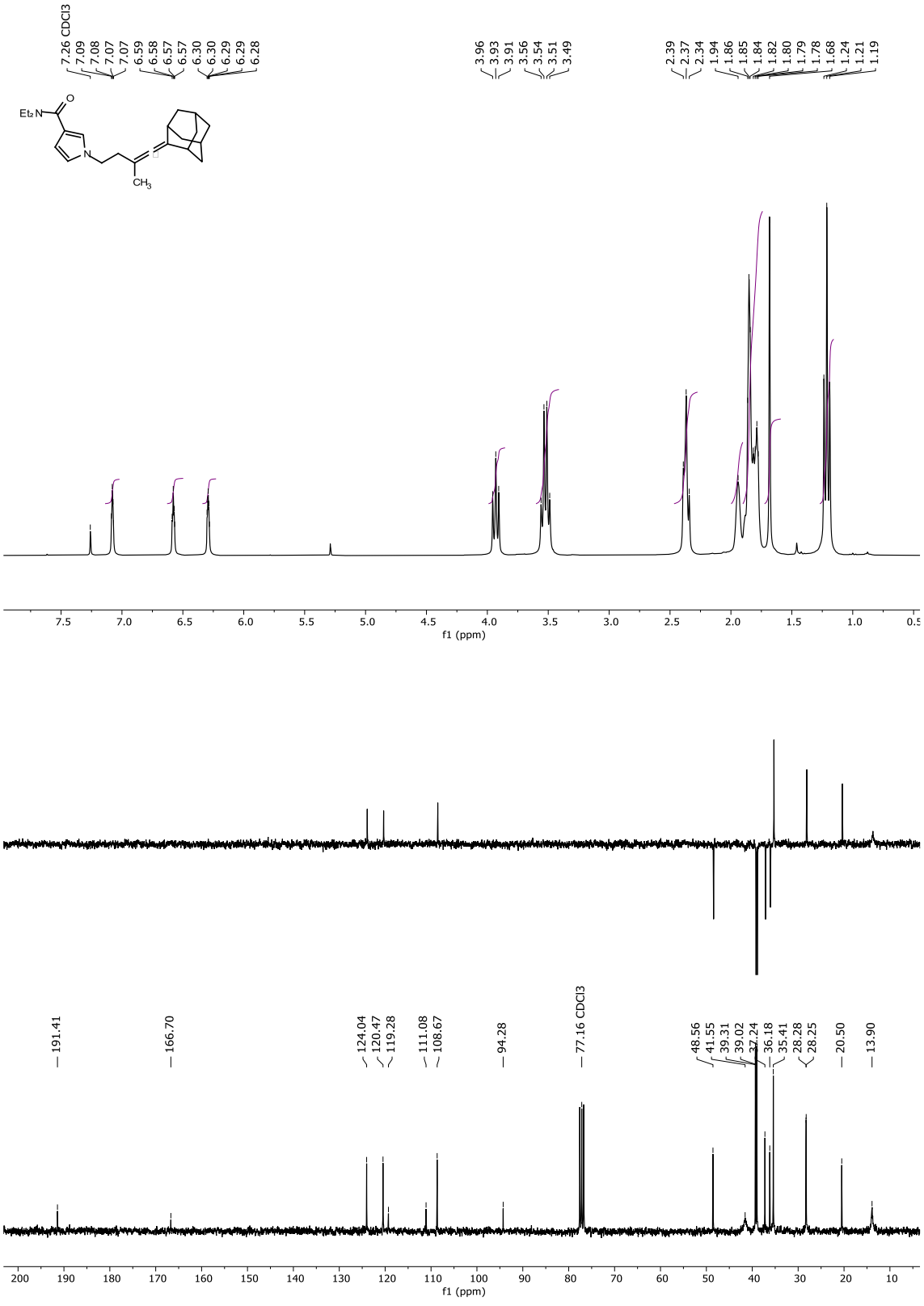
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*^{1}H and ^{13}C NMR of **7o***



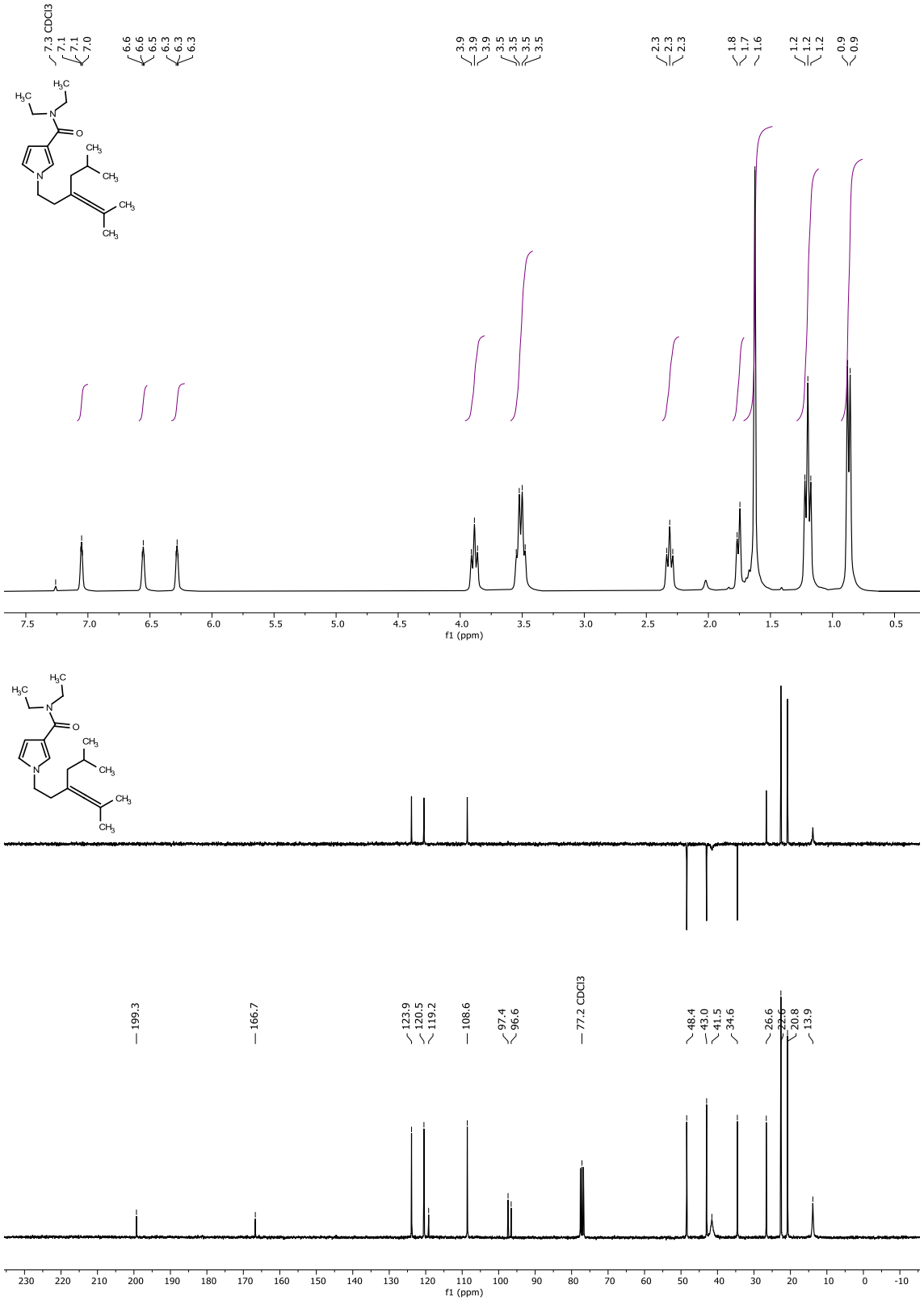
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*^{1}H and ^{13}C NMR of **7q***



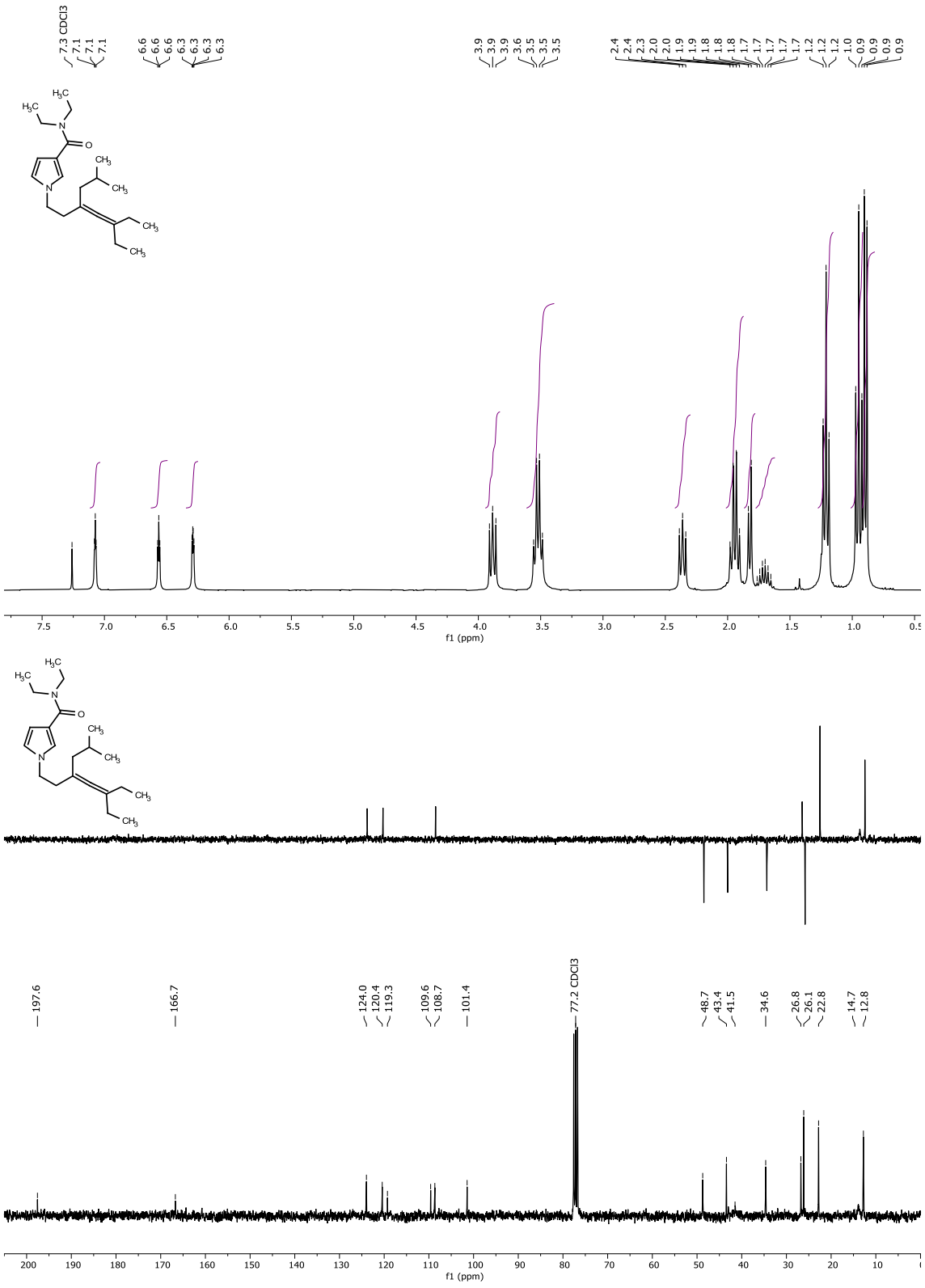
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*^{1}H and ^{13}C NMR of **7w***



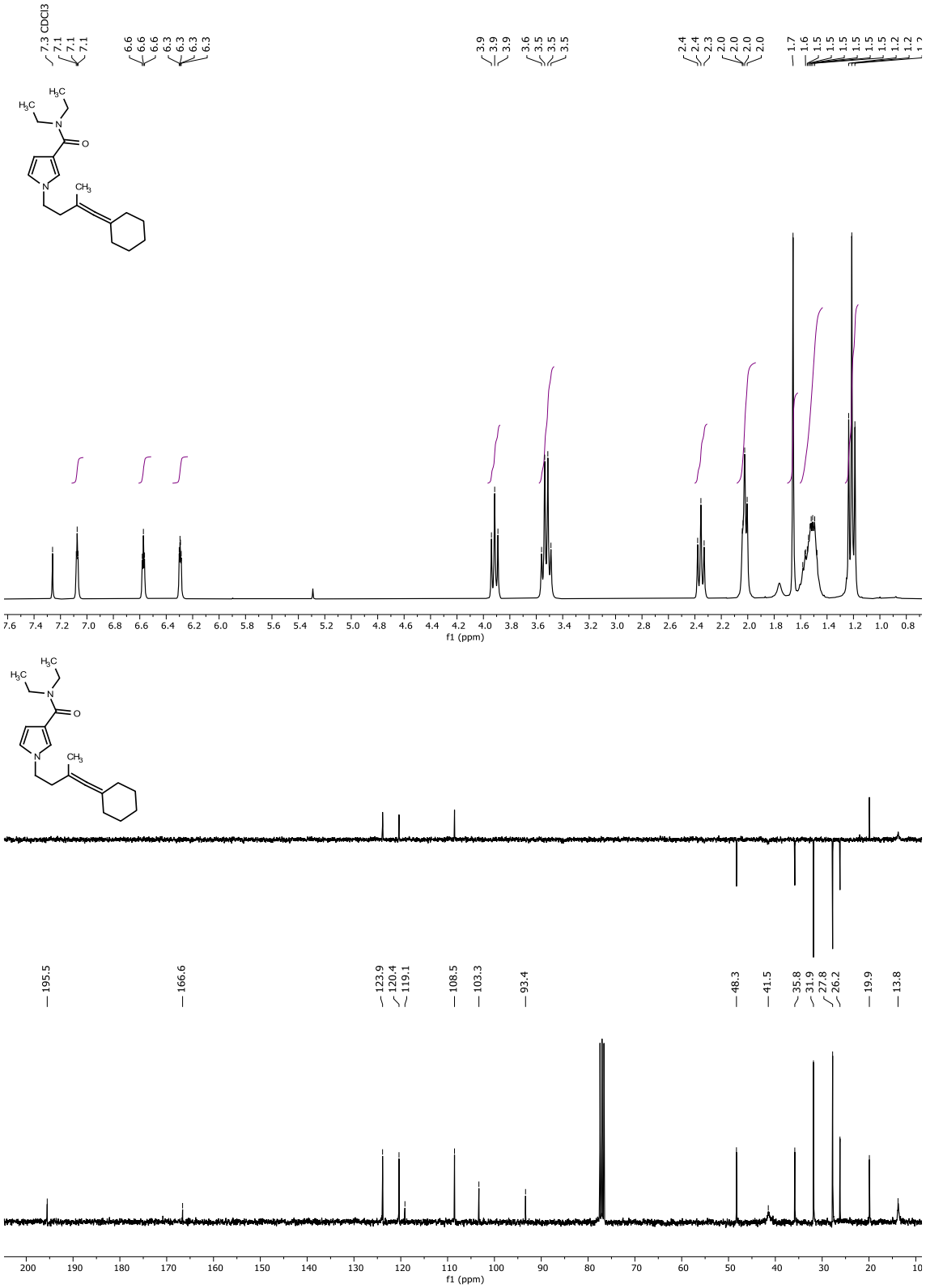
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*^{1}H and ^{13}C NMR of **7α***



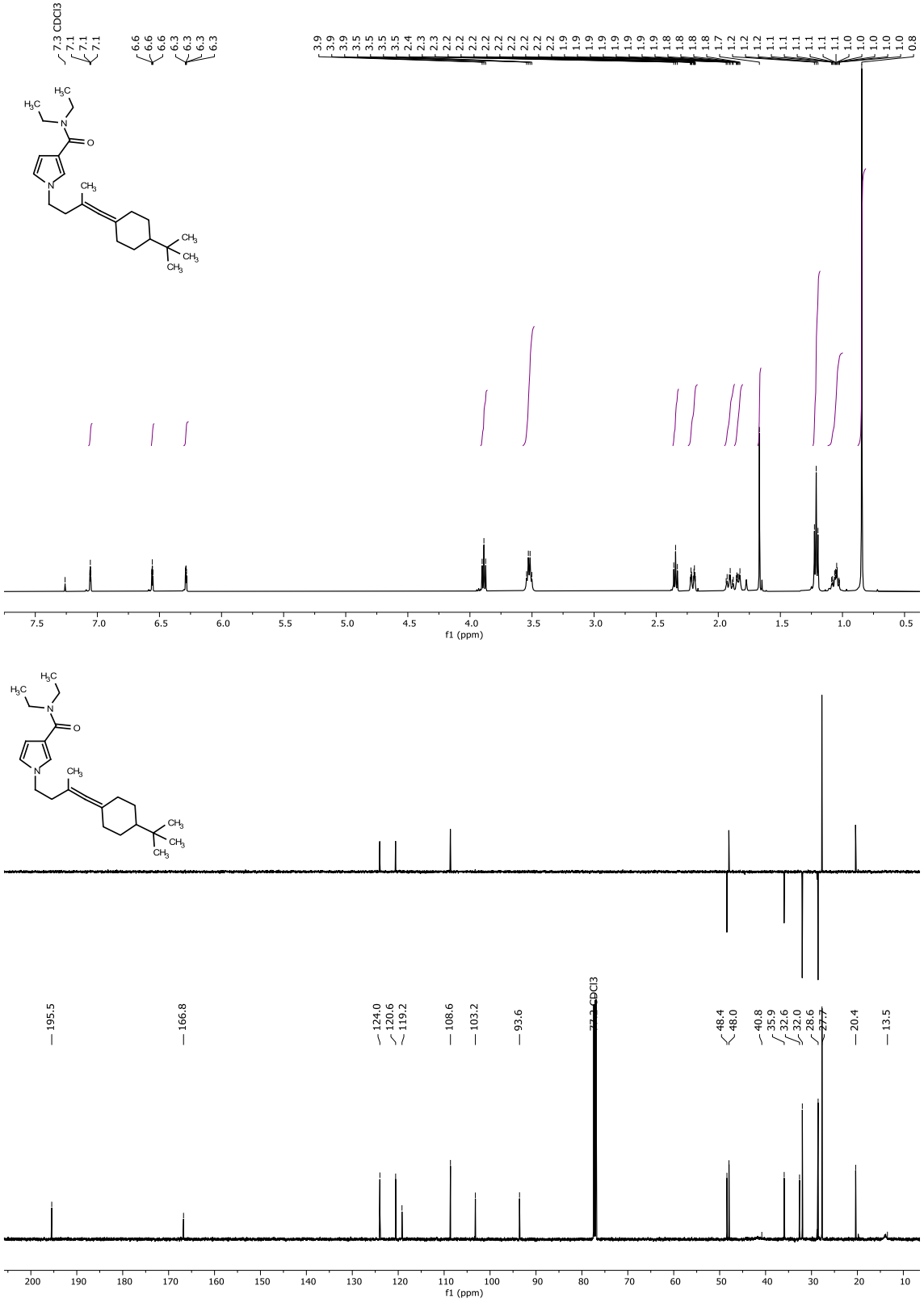
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*^{1}H and ^{13}C NMR of **7δ***



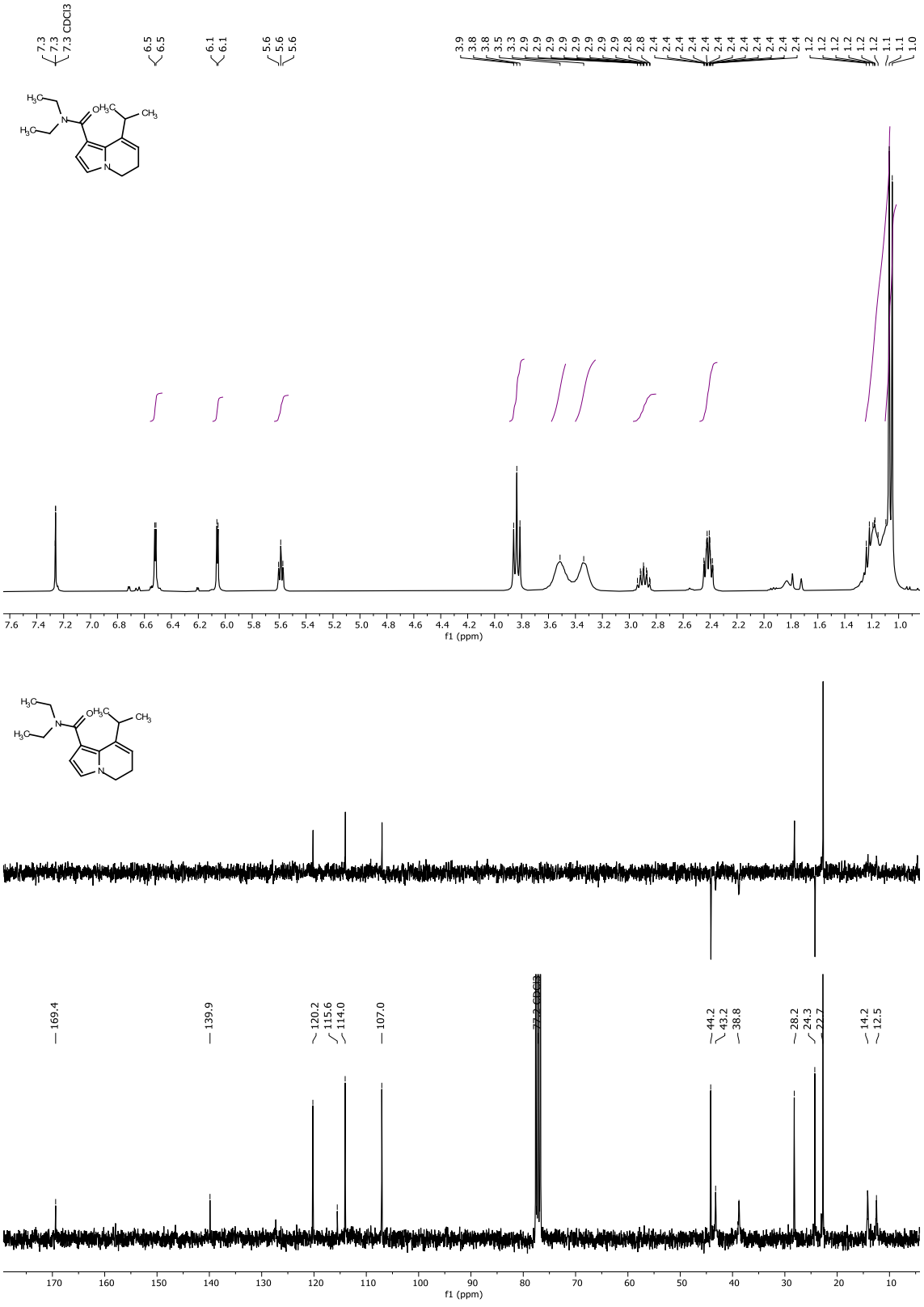
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*^{1}H and ^{13}C NMR of **7ι***

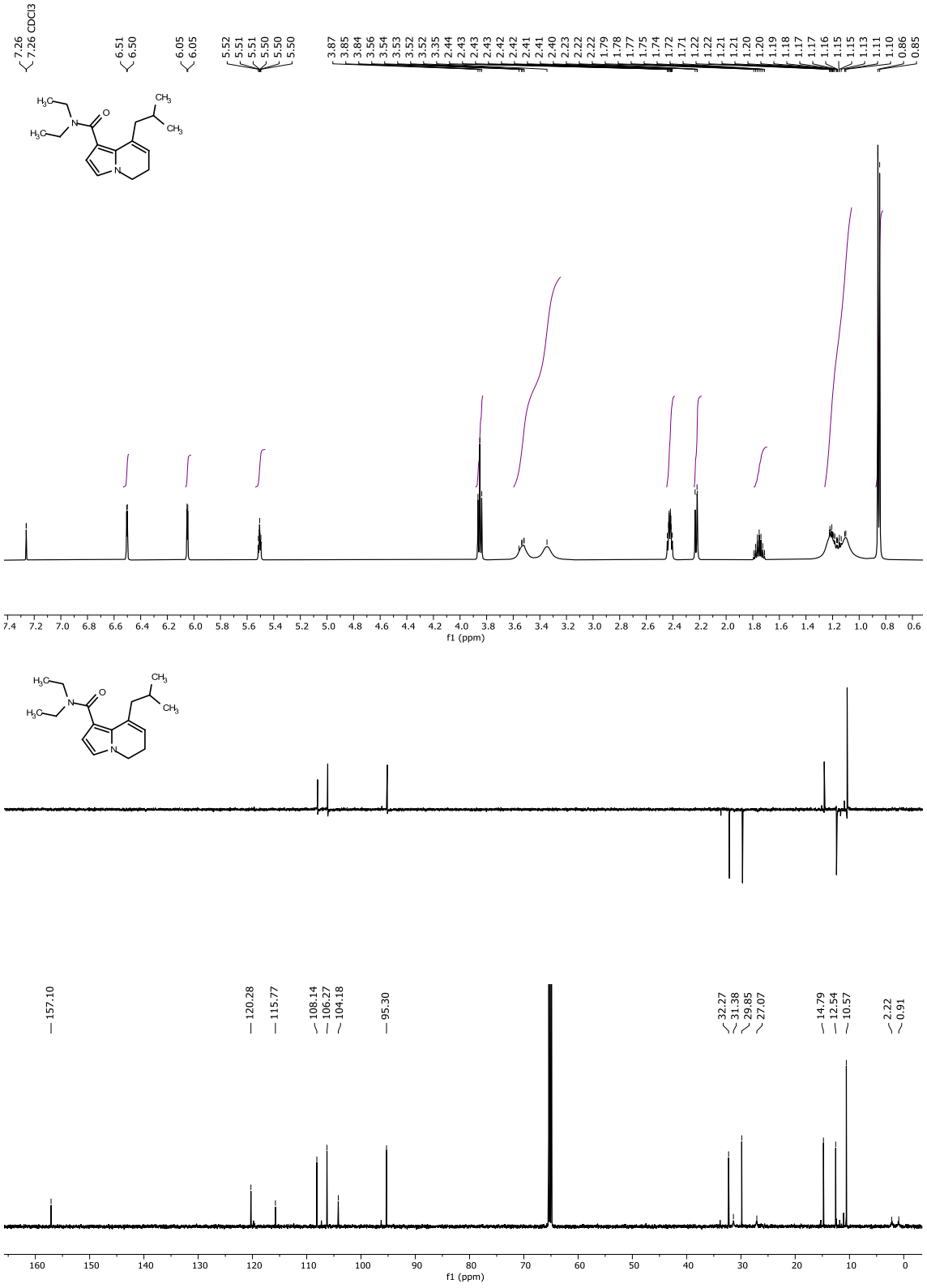


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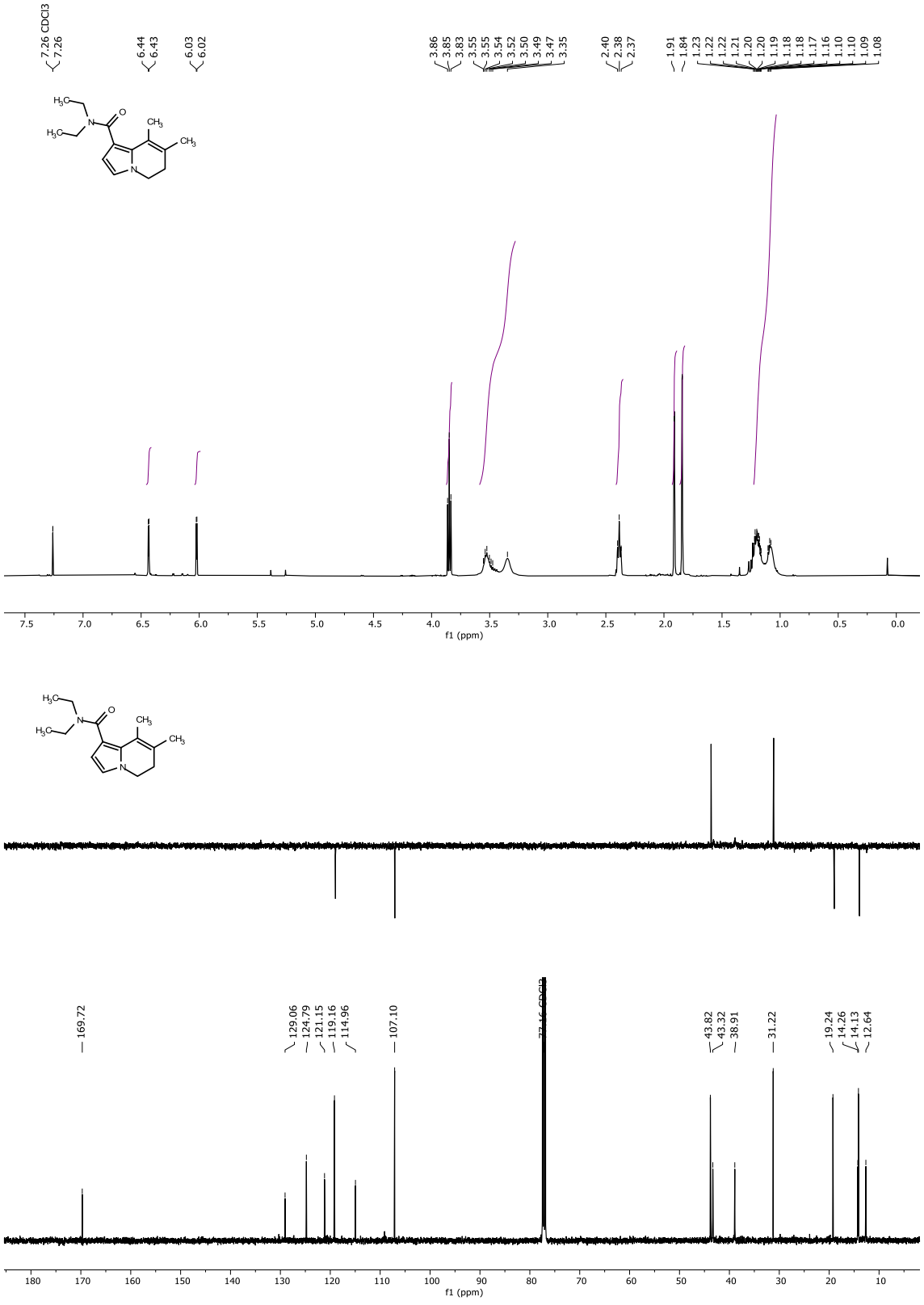
*^{1}H and ^{13}C NMR of **8a***



*^{1}H and ^{13}C NMR of **8f***

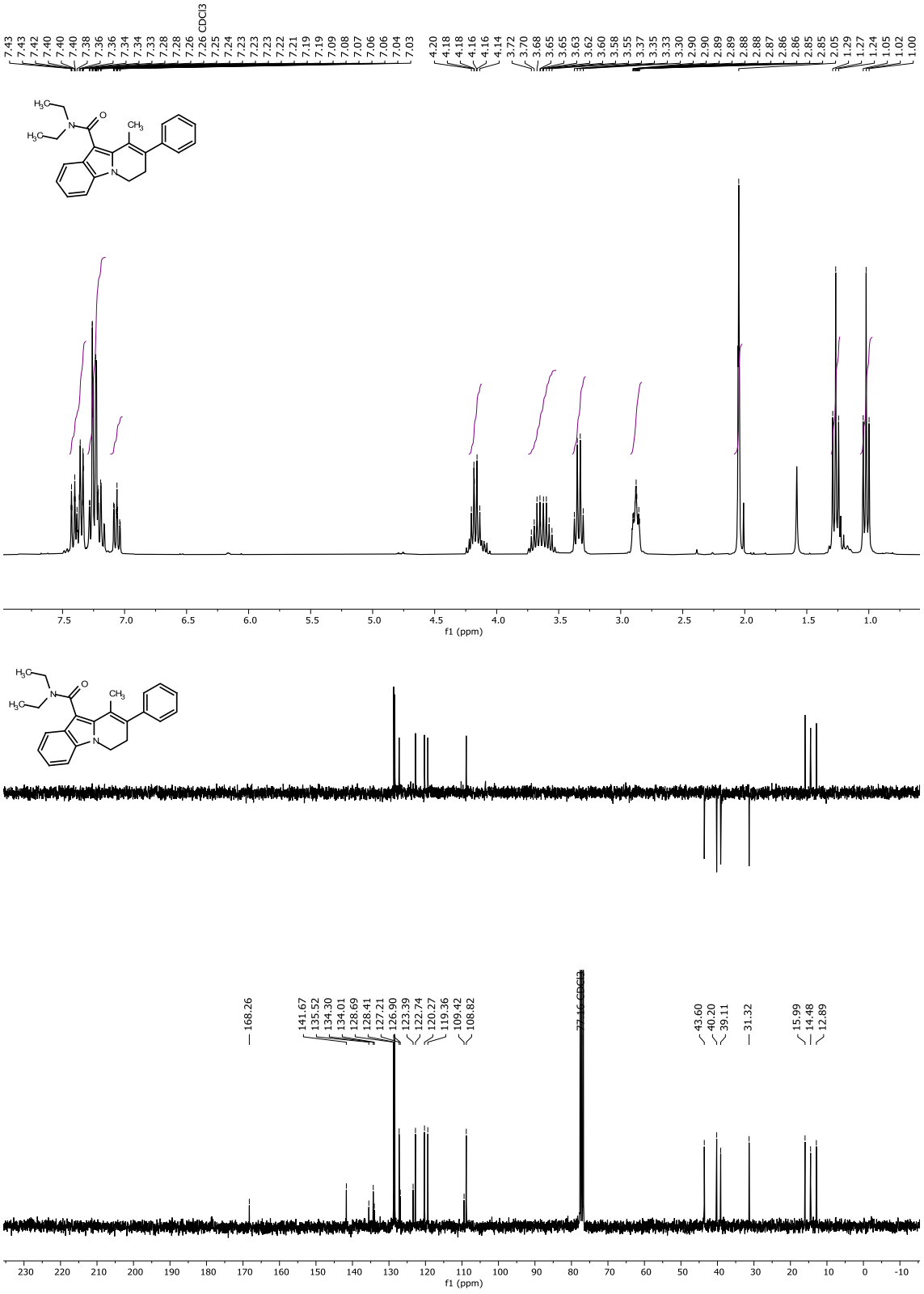


*^{1}H and ^{13}C NMR of **8h***



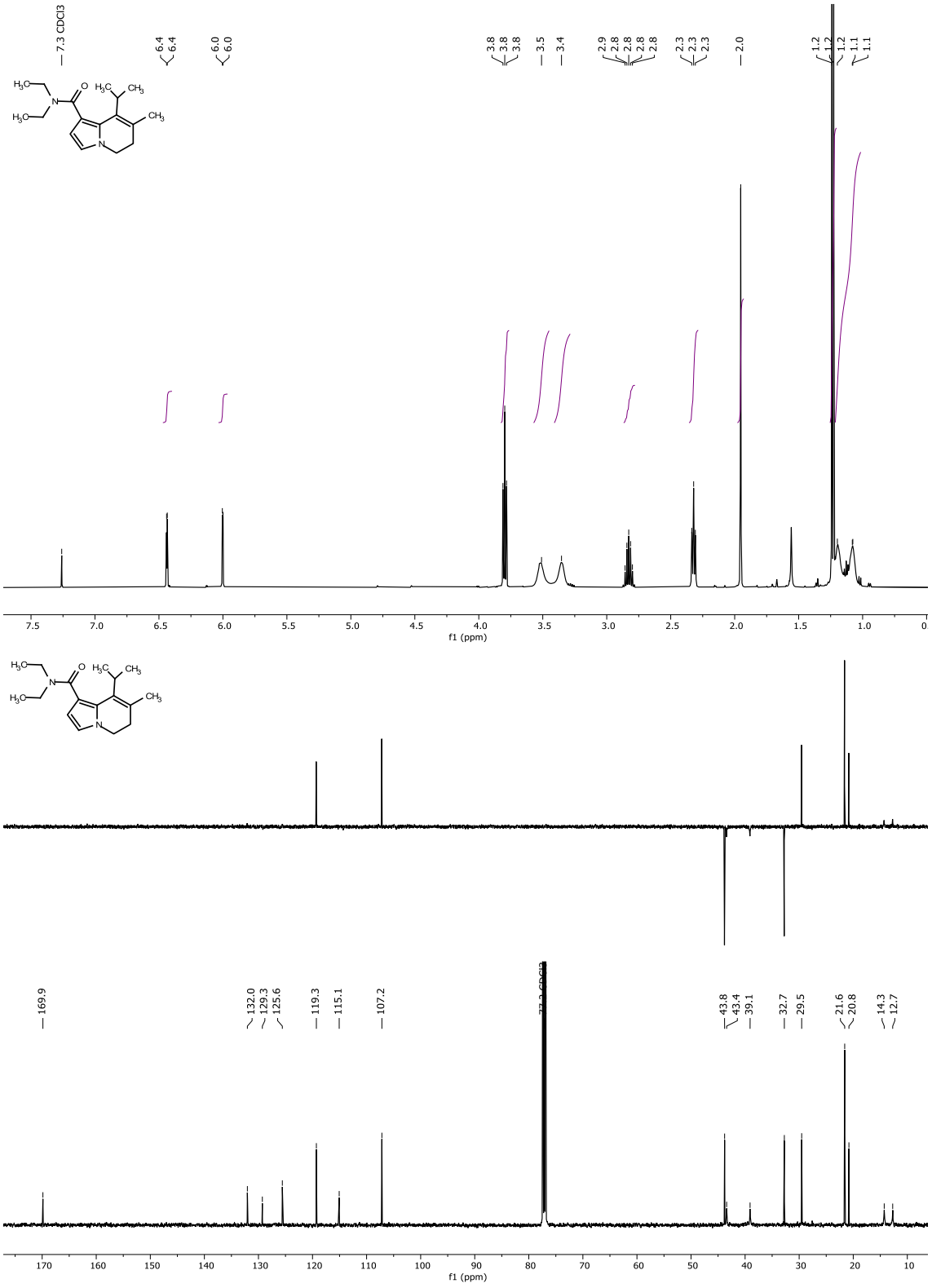
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*^{1}H and ^{13}C NMR of **8n***



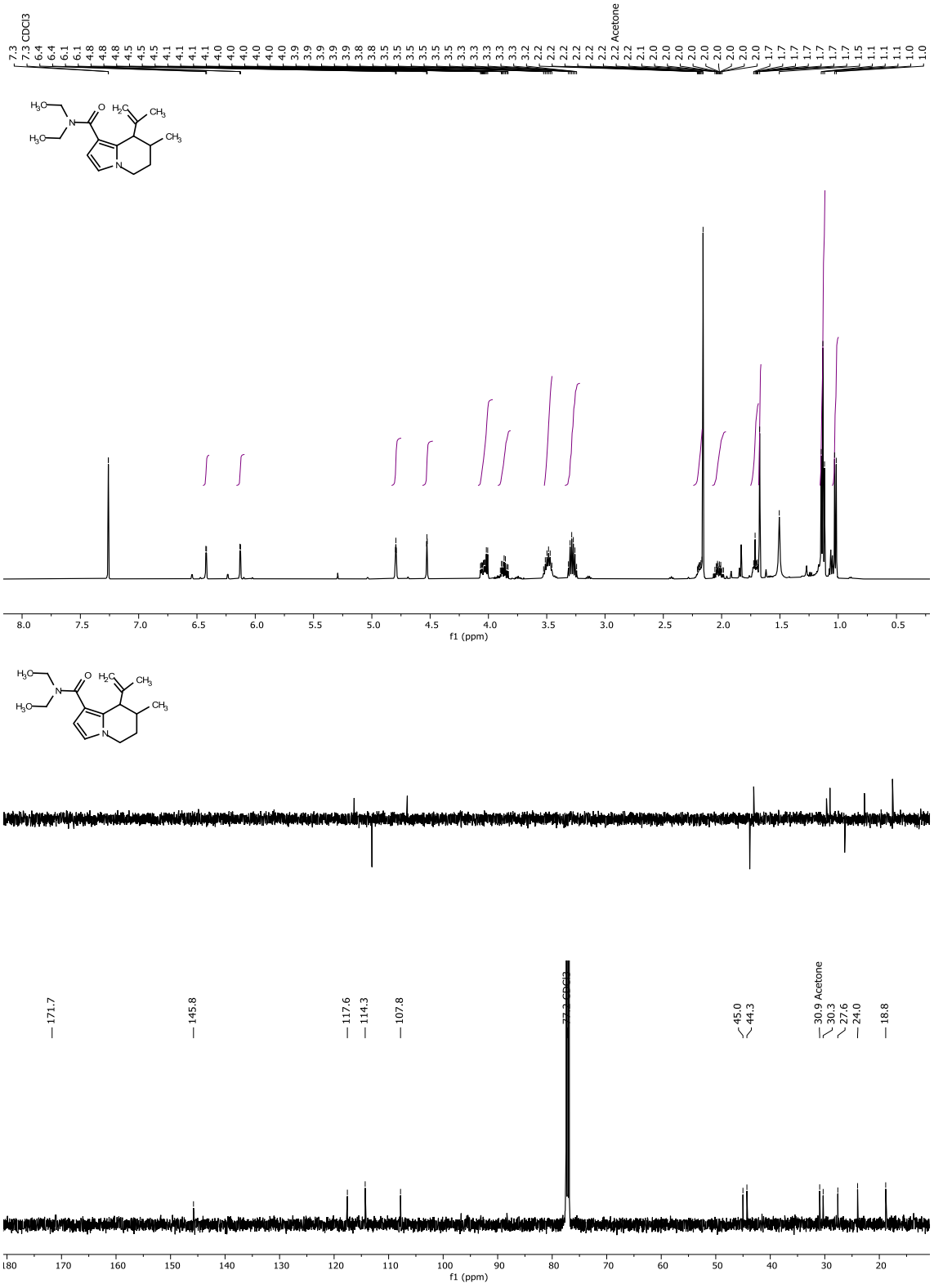
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*^{1}H and ^{13}C NMR of **8o***



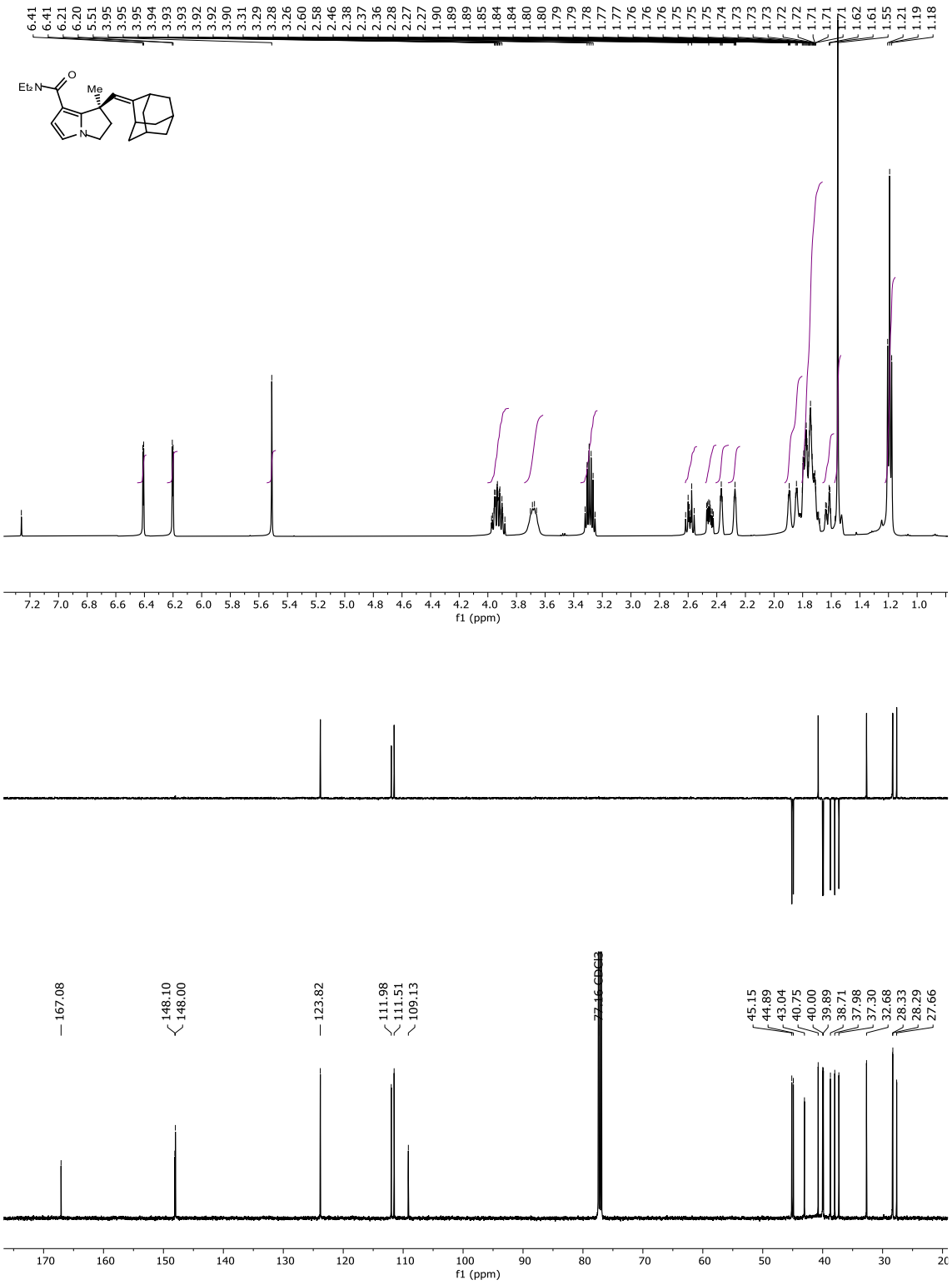
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*^{1}H and ^{13}C NMR of **9o***



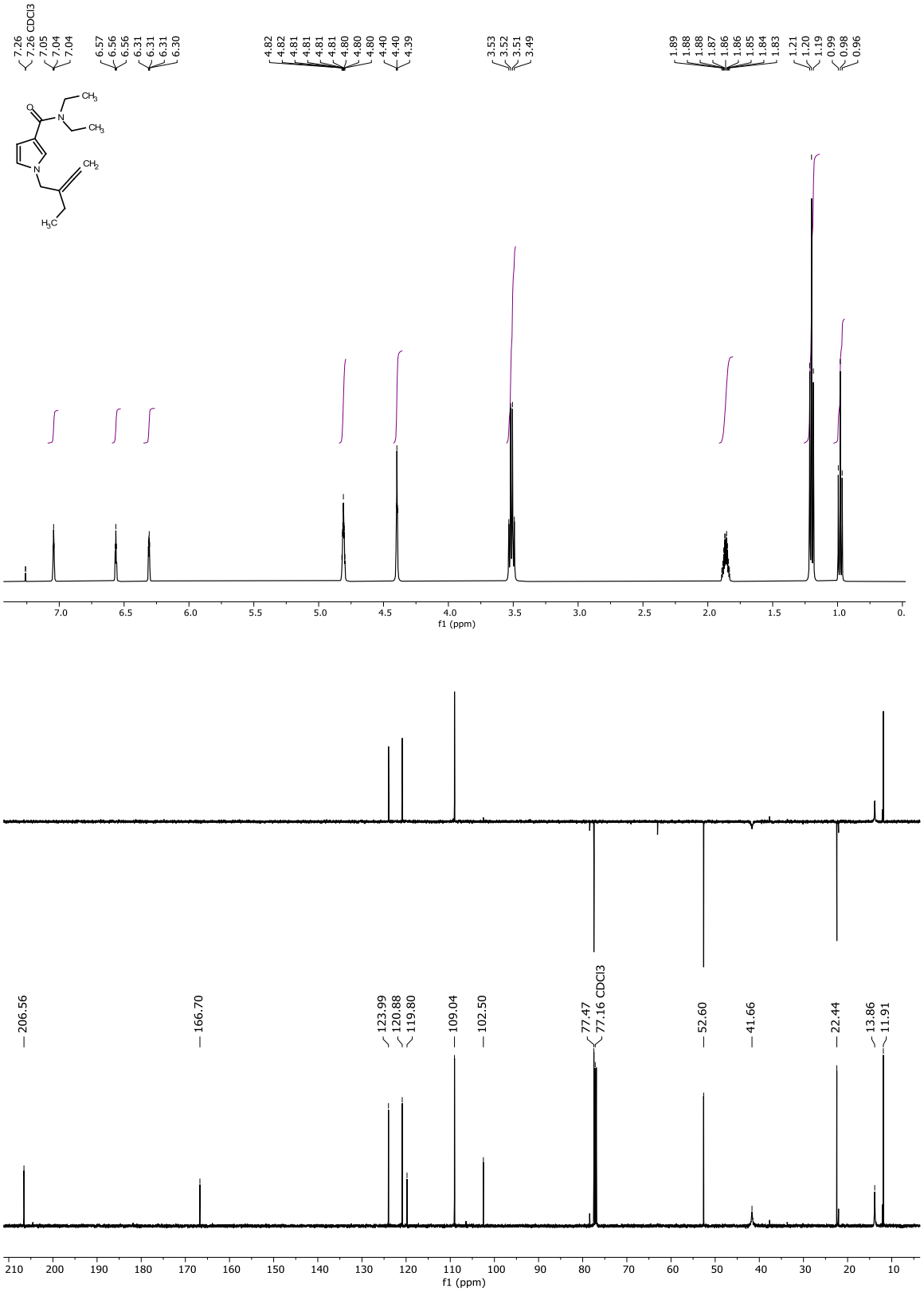
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*^{1}H and ^{13}C NMR of **10q***

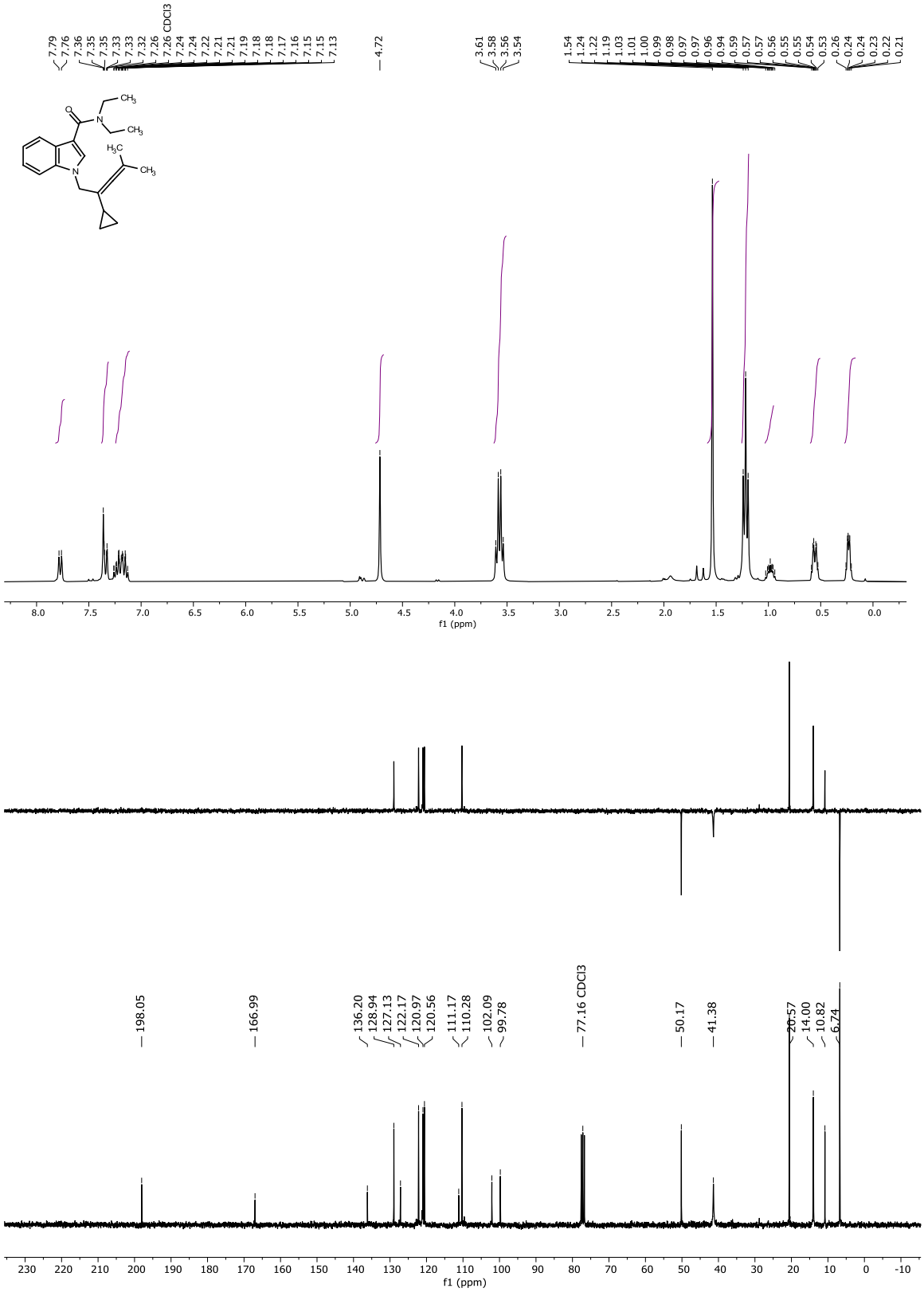


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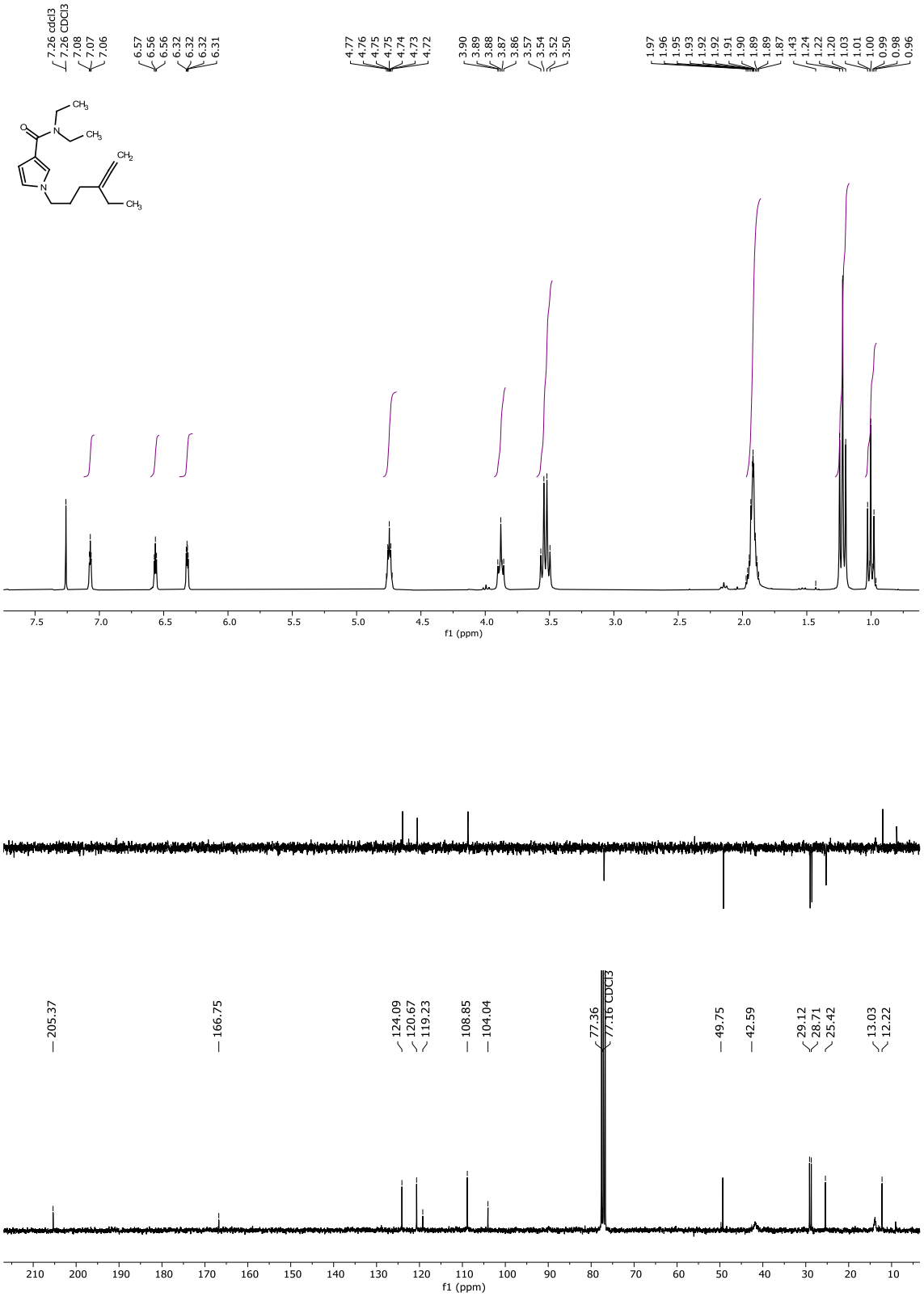
*^{1}H and ^{13}C NMR of **11a***



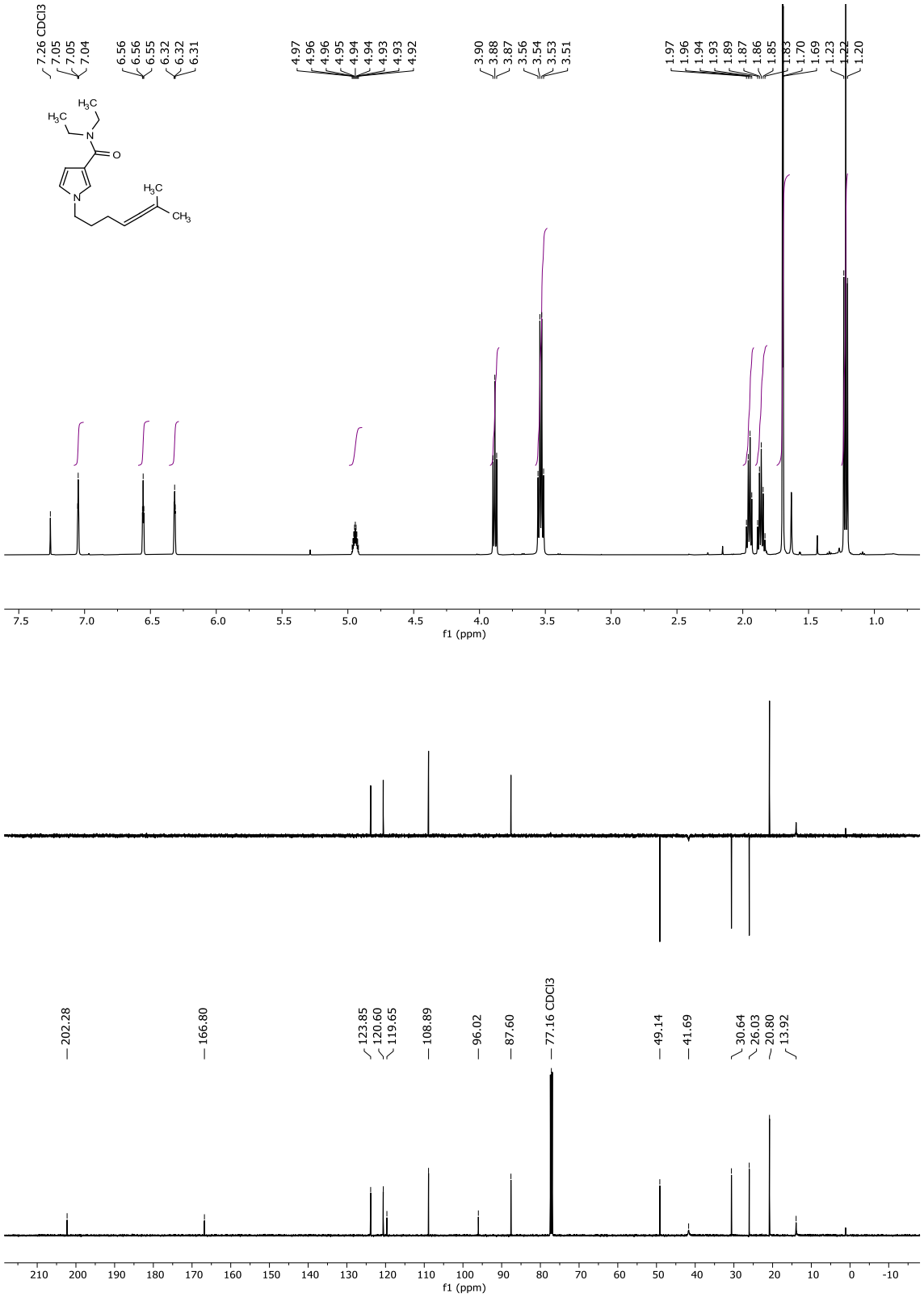
*^{1}H and ^{13}C NMR of **11d***



*^{1}H and ^{13}C NMR of **12a***

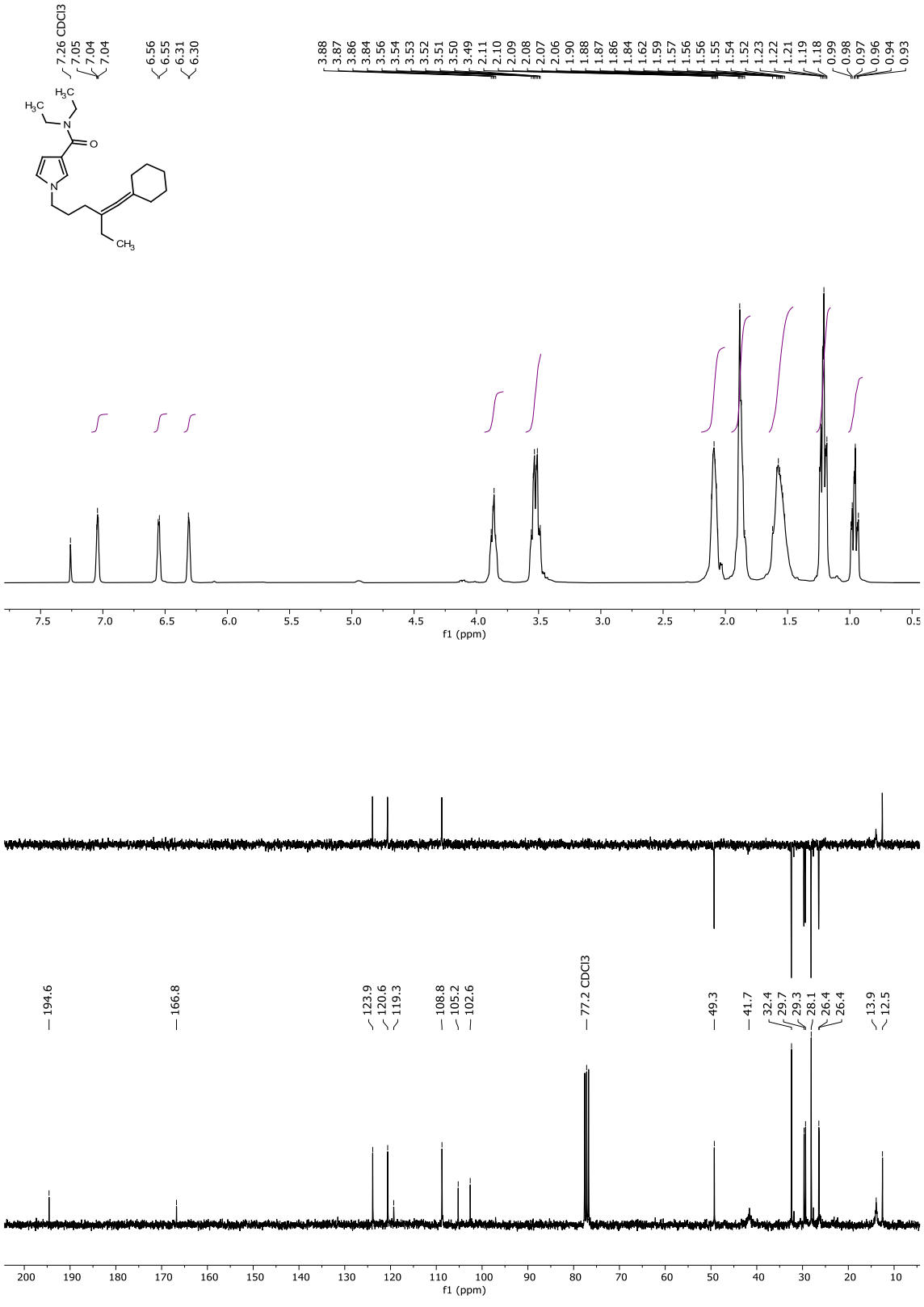


*^{1}H and ^{13}C NMR of **12b***



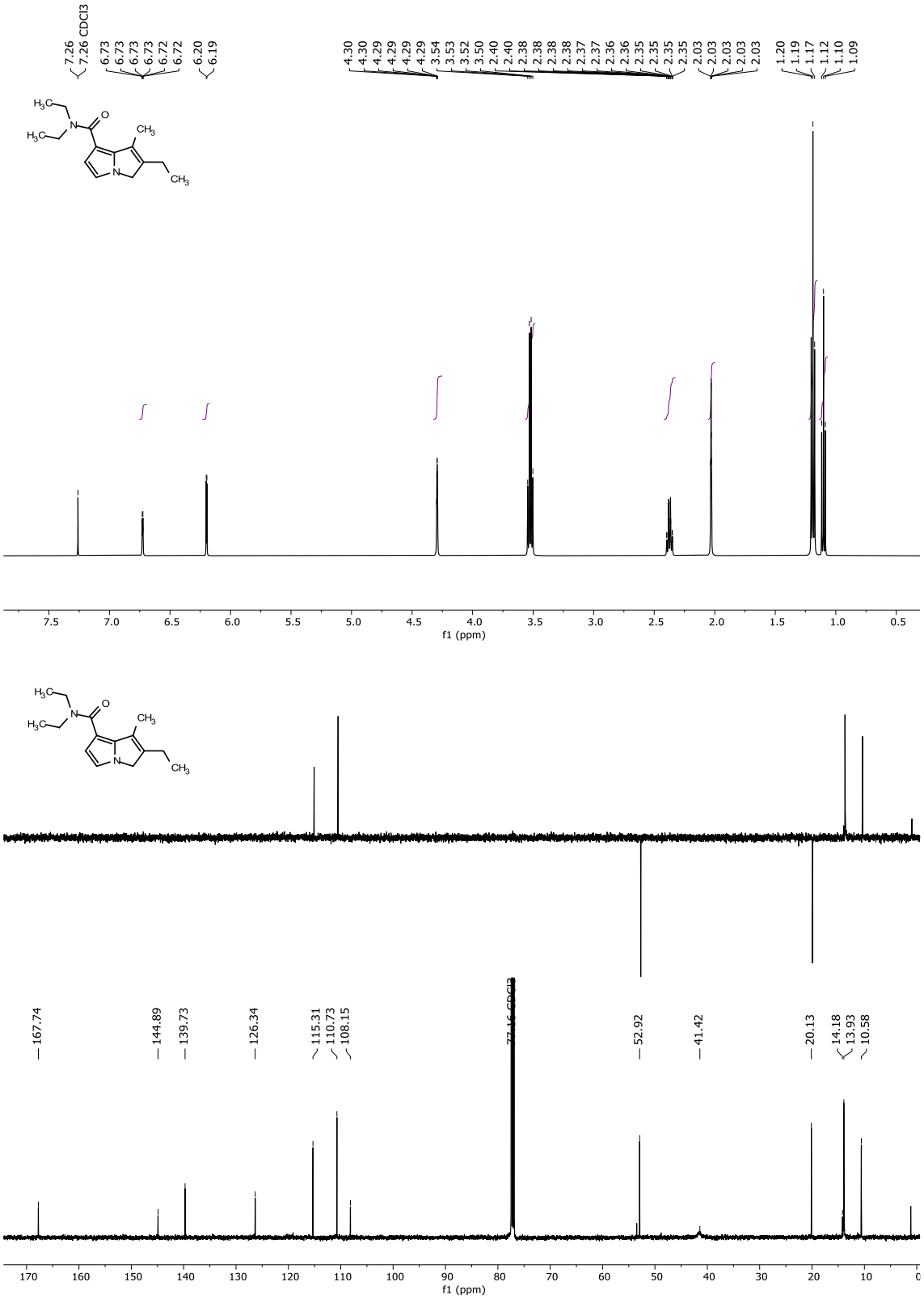
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*^{1}H and ^{13}C NMR of **12i***



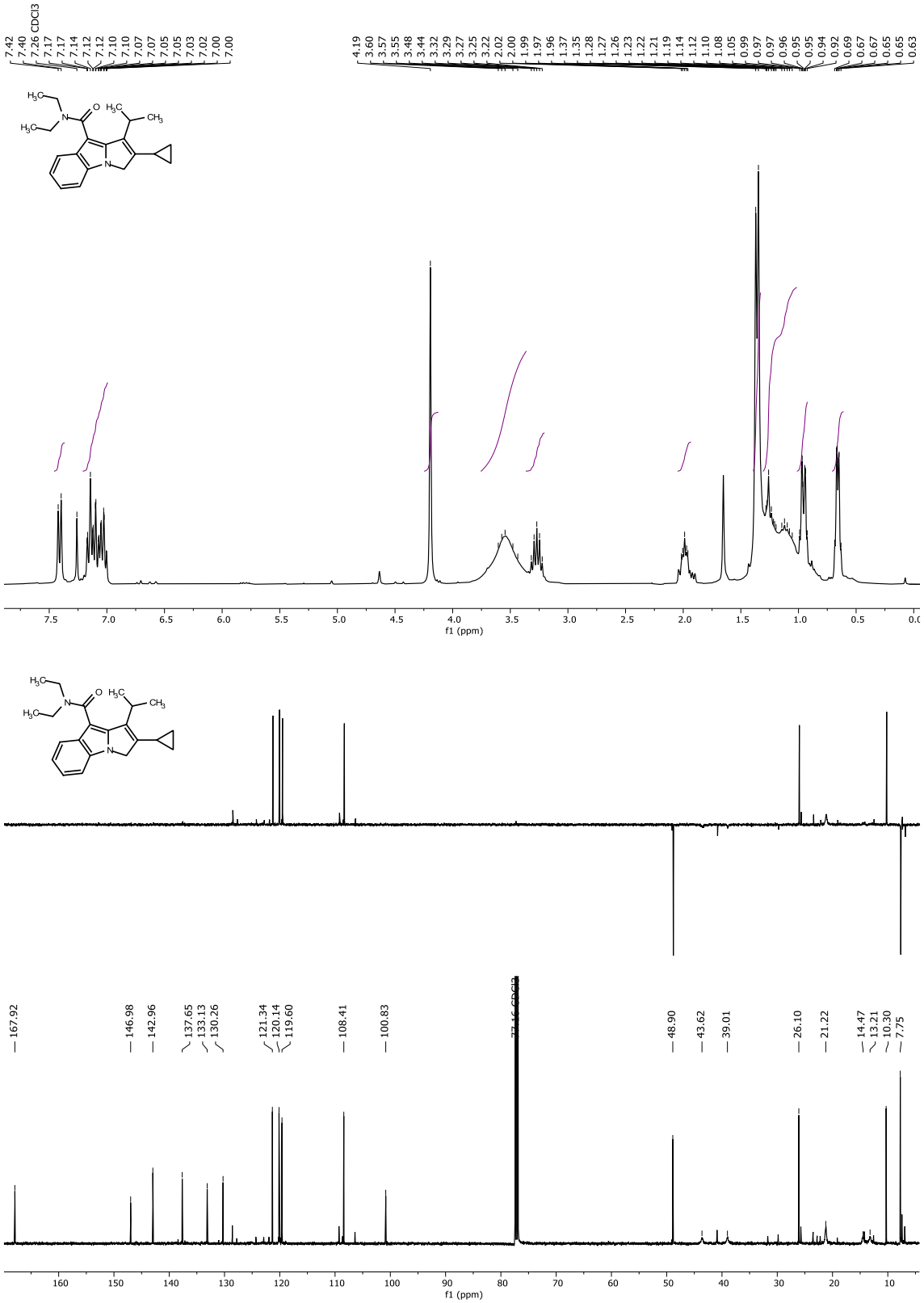
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*^{1}H and ^{13}C NMR of **13a***



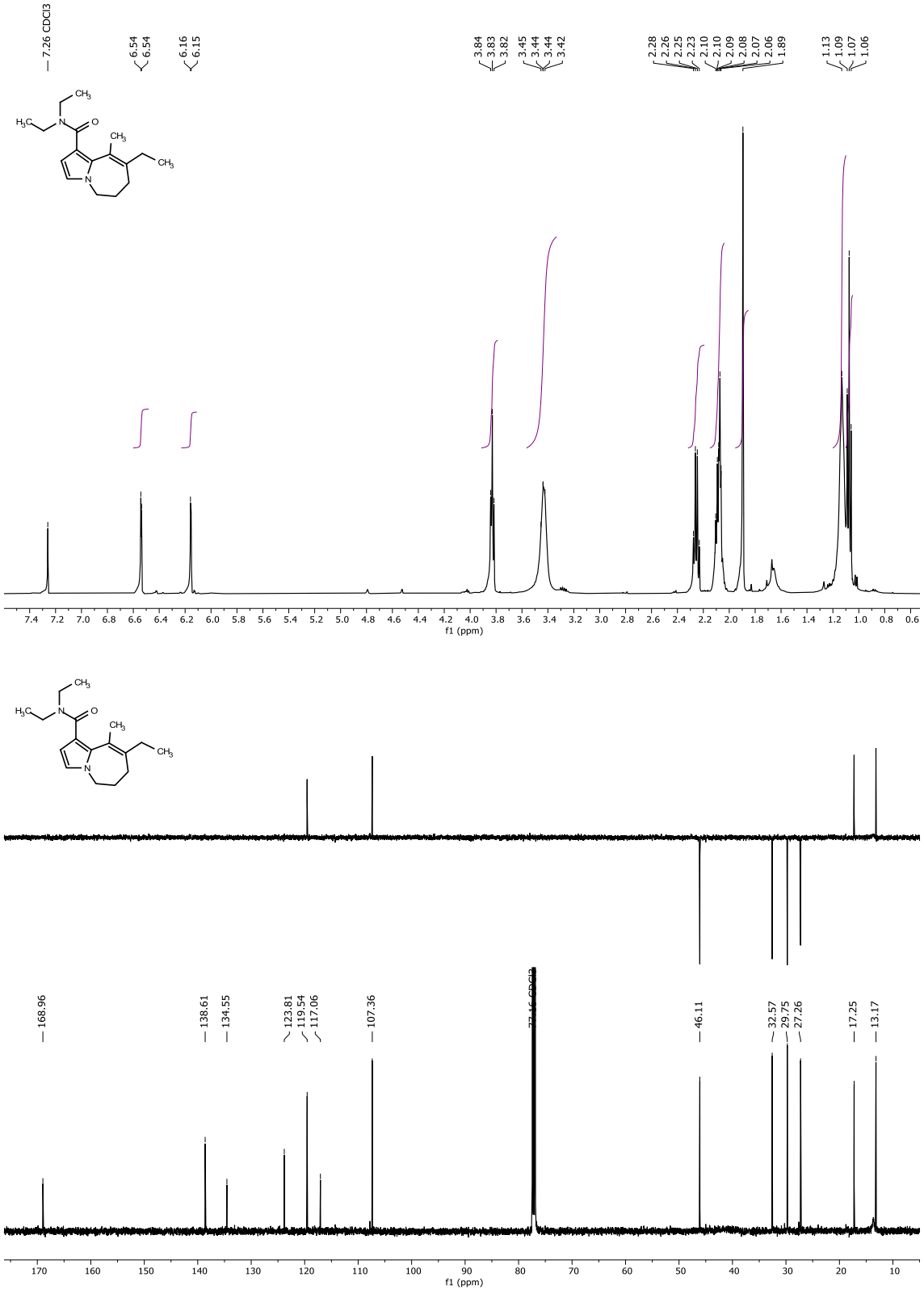
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*^{1}H and ^{13}C NMR of **13d***



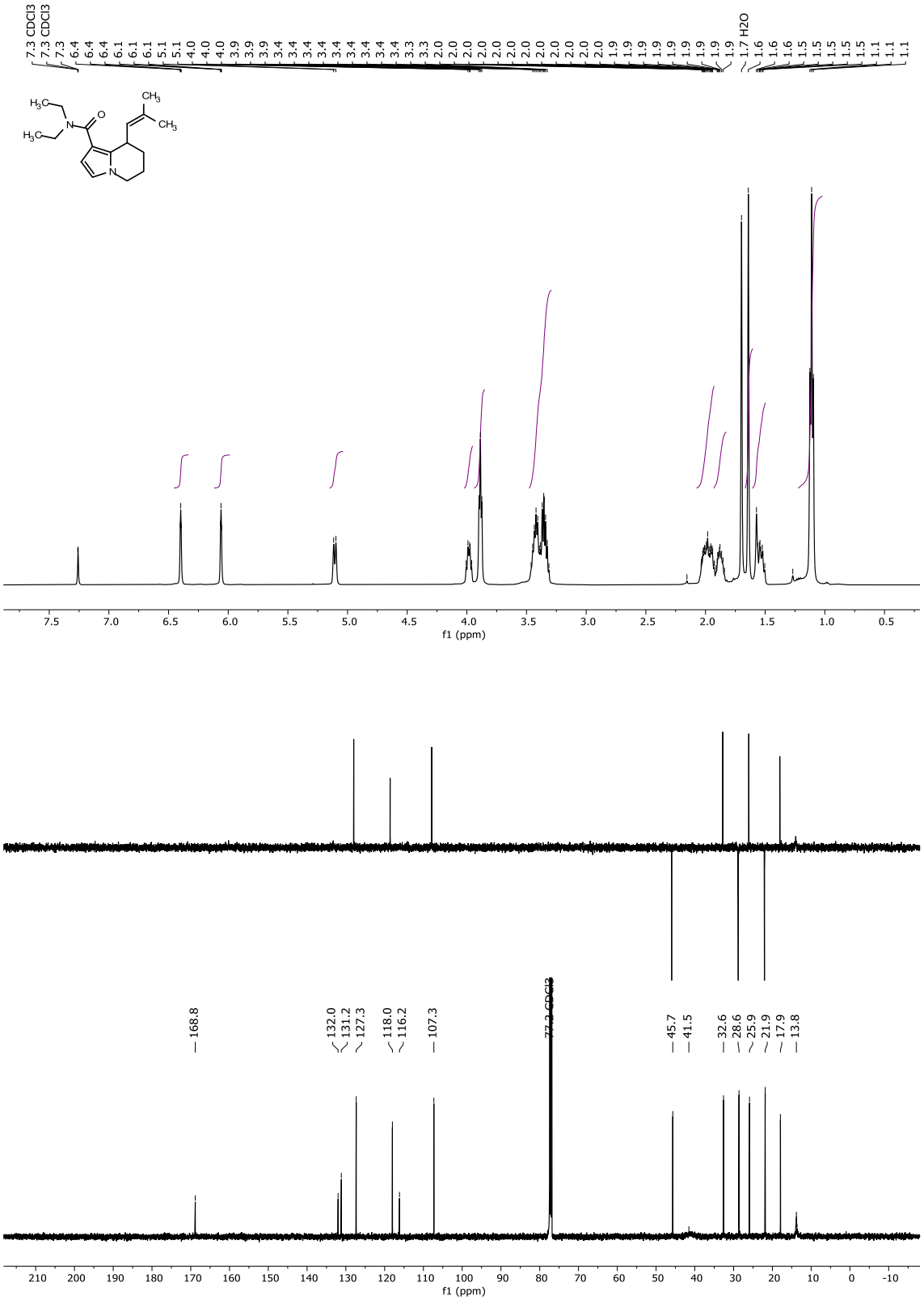
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*^{1}H and ^{13}C NMR of **14a***



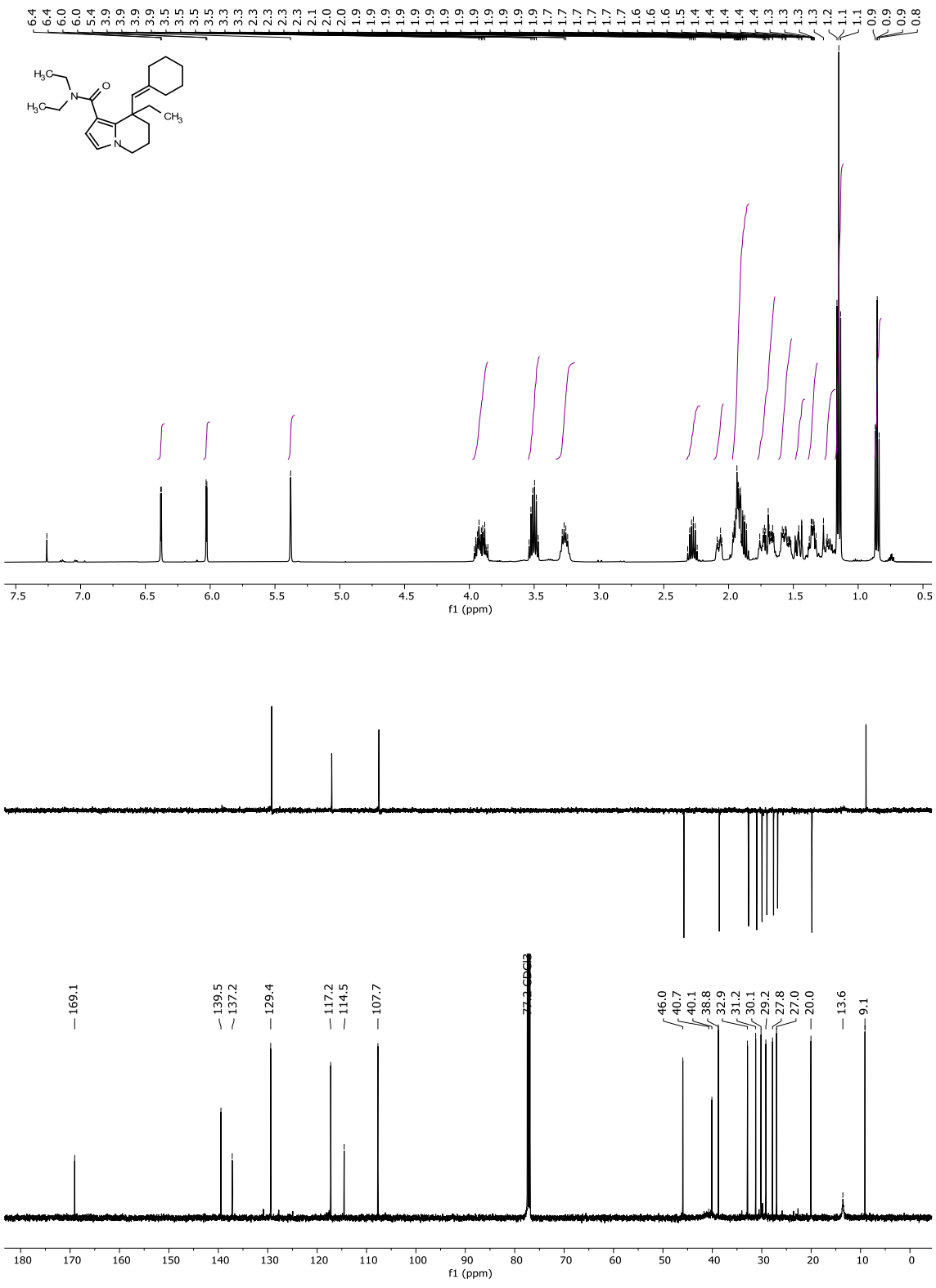
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*^{1}H and ^{13}C NMR of **15a***



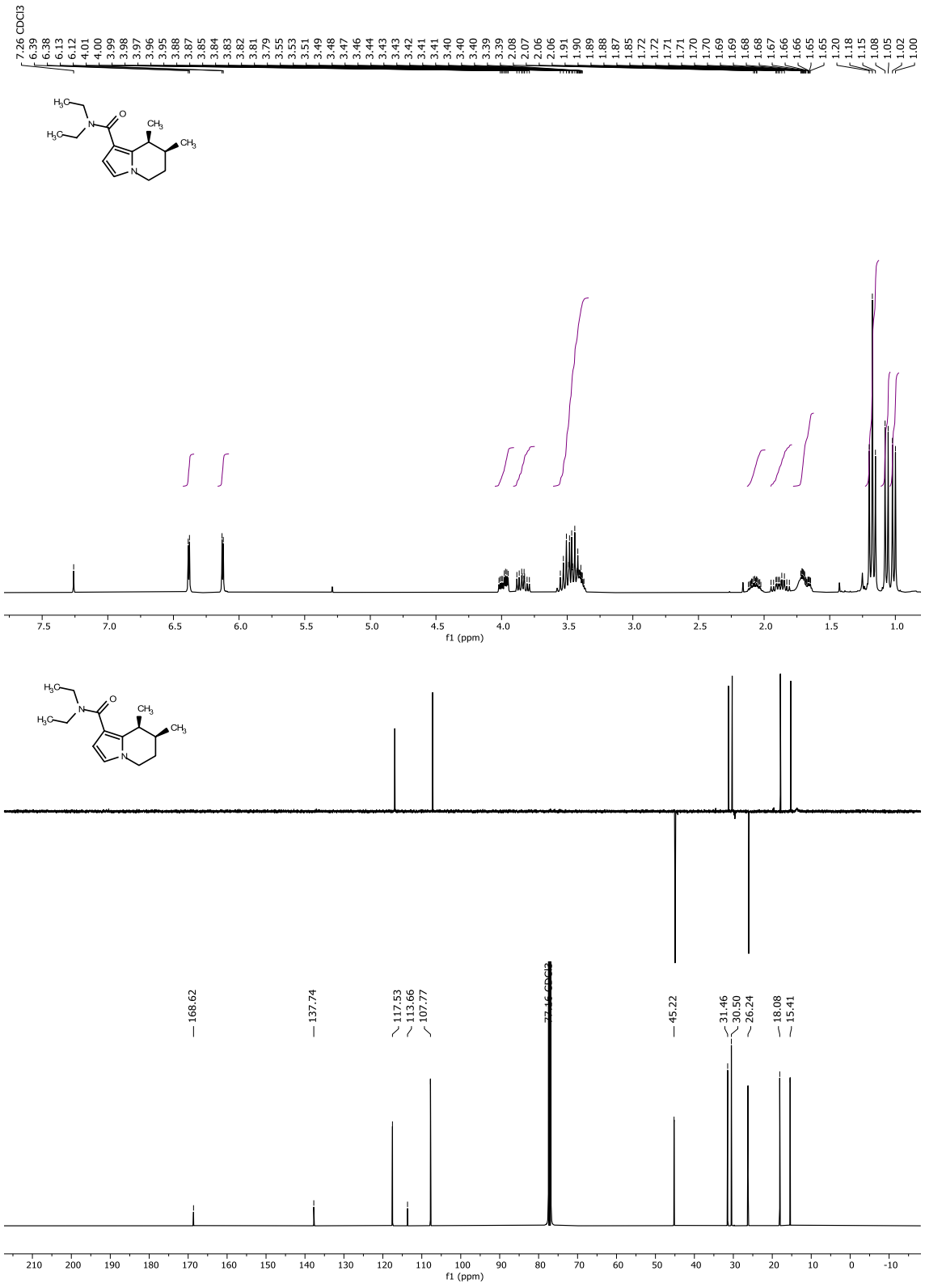
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*^{1}H and ^{13}C NMR of **15i***

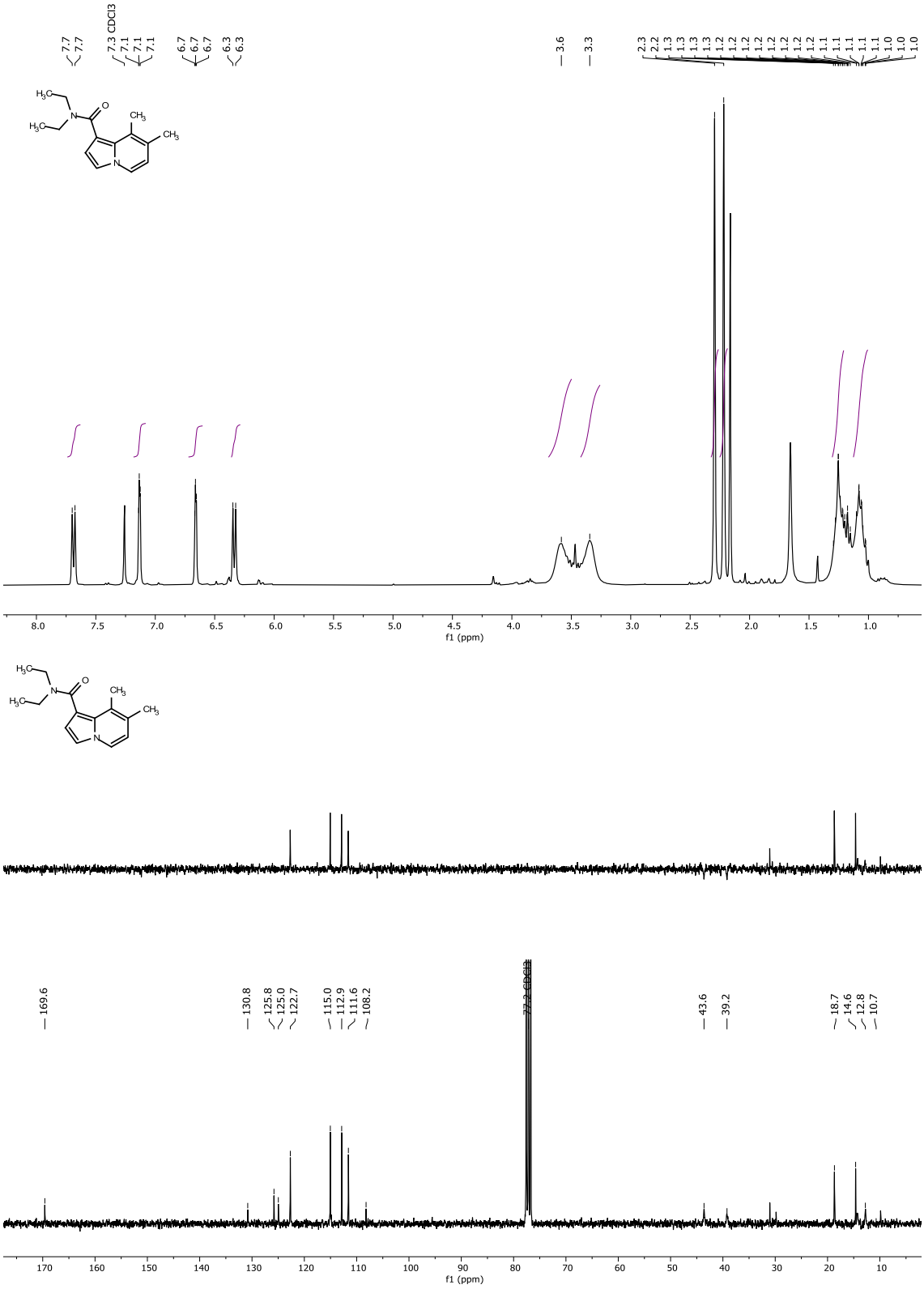


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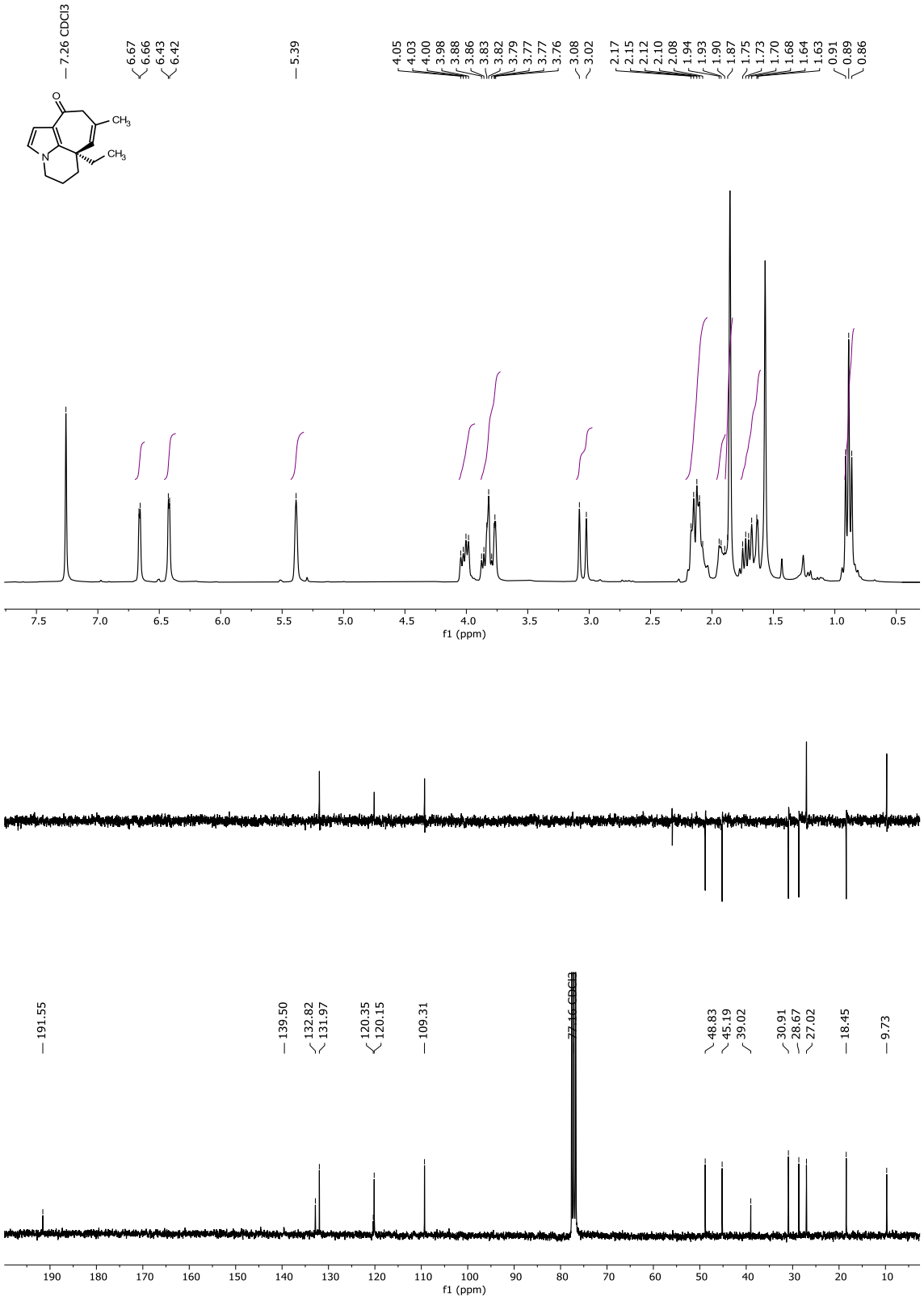
*^{1}H and ^{13}C NMR of **16h***



*^{1}H and ^{13}C NMR of **17h***

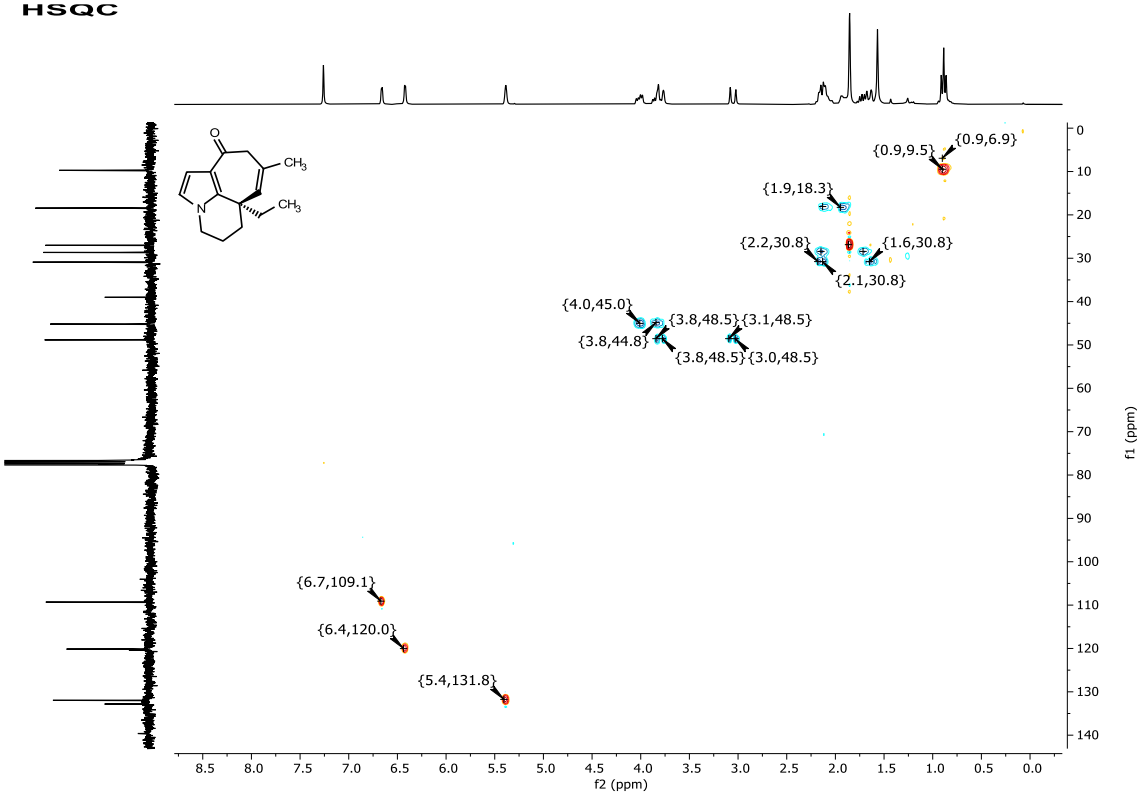


*^{1}H and ^{13}C NMR, HSQC and HMBC of **18h***

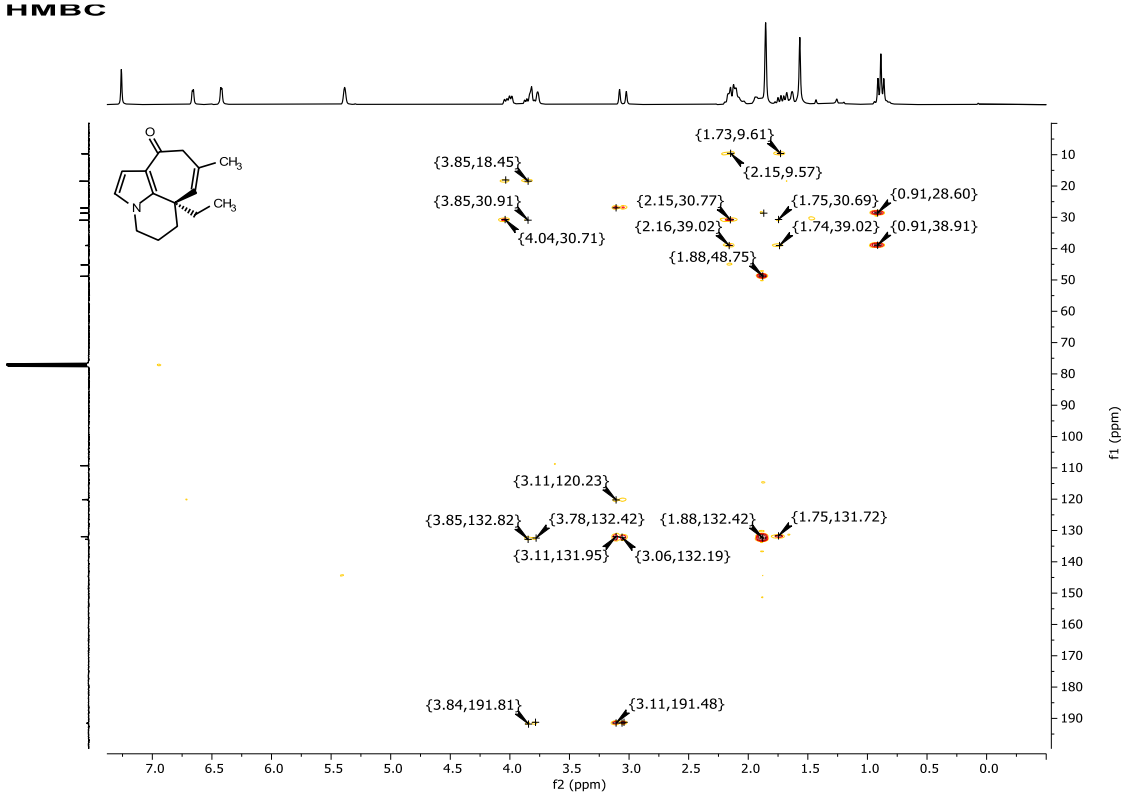


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HSQC

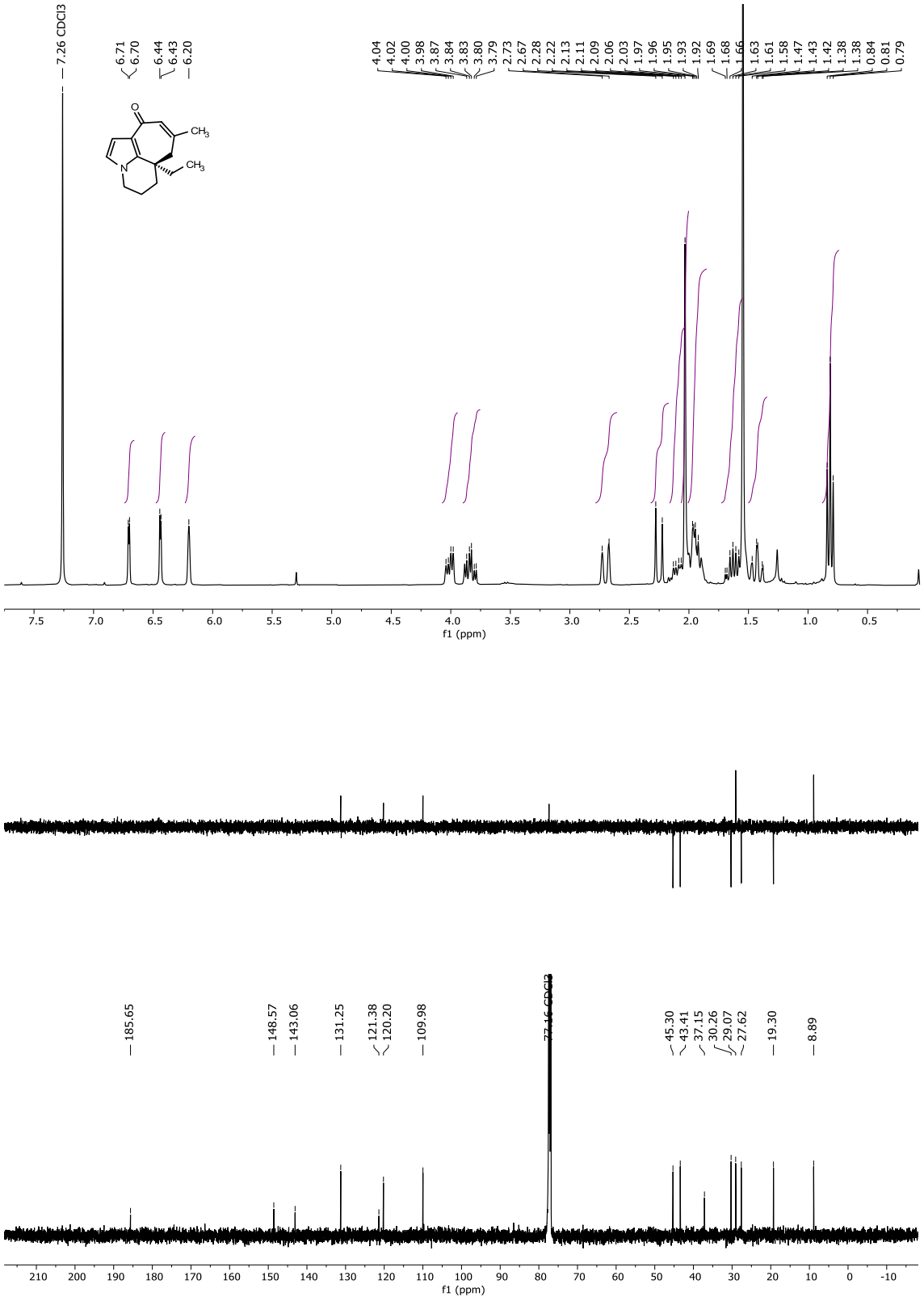


HMBC

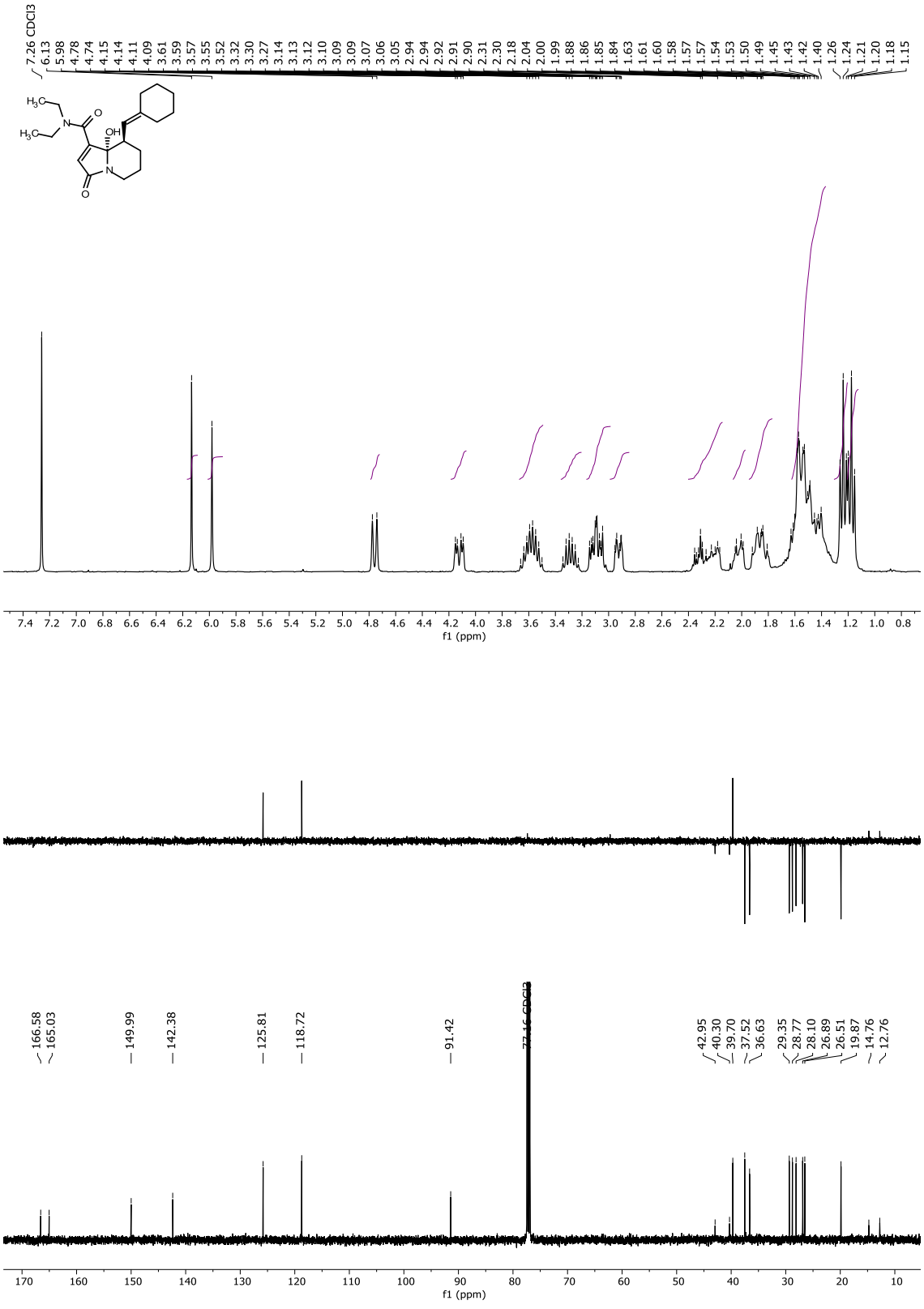


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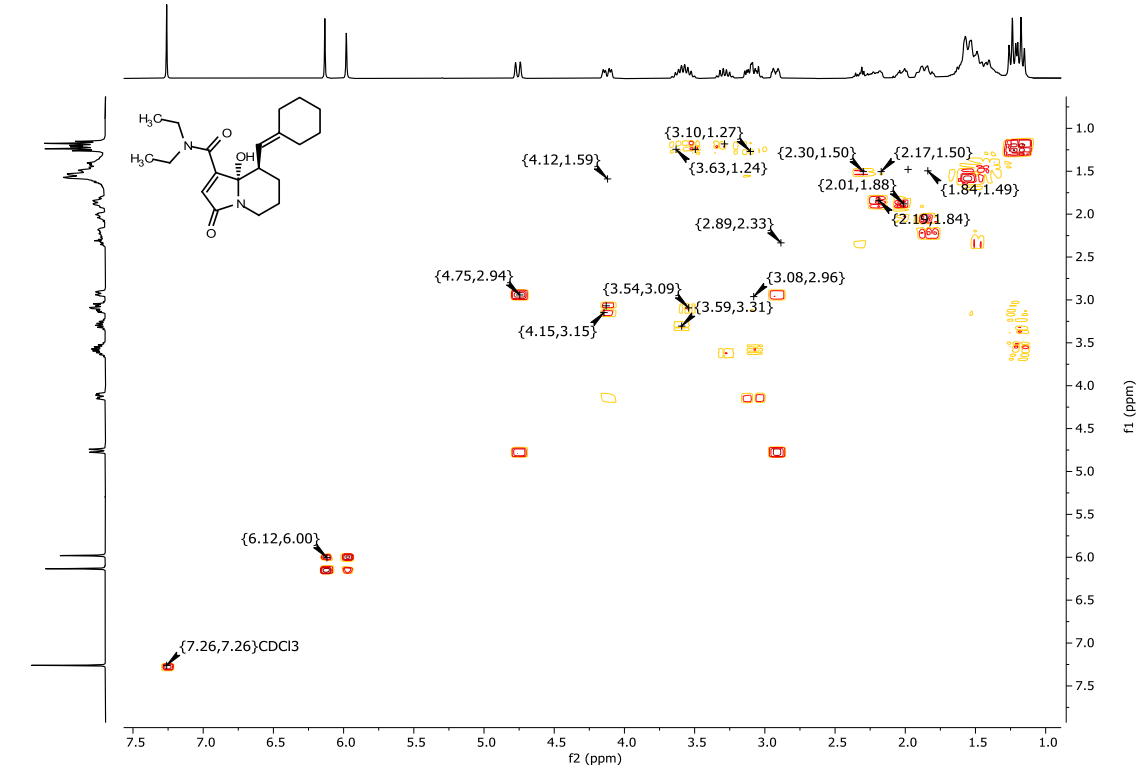
*^{1}H and ^{13}C NMR of **18h'***

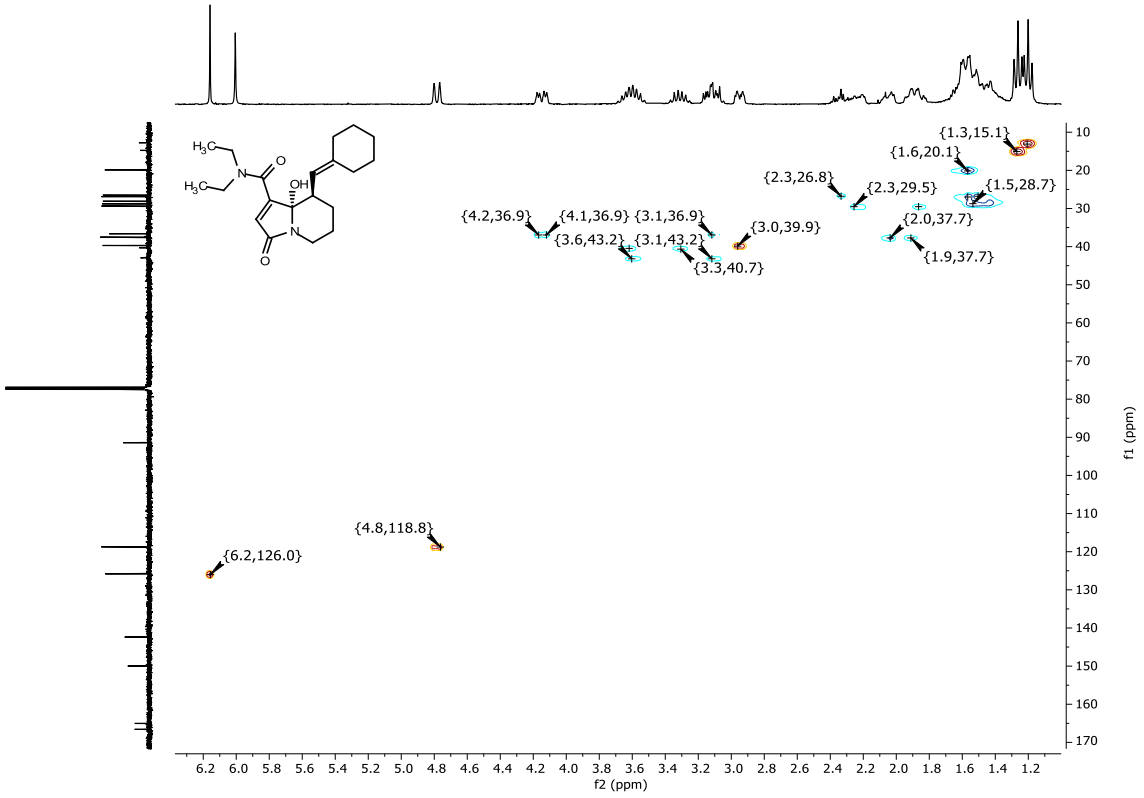


*^{1}H and ^{13}C NMR, HSQC and HMBC of **19c***

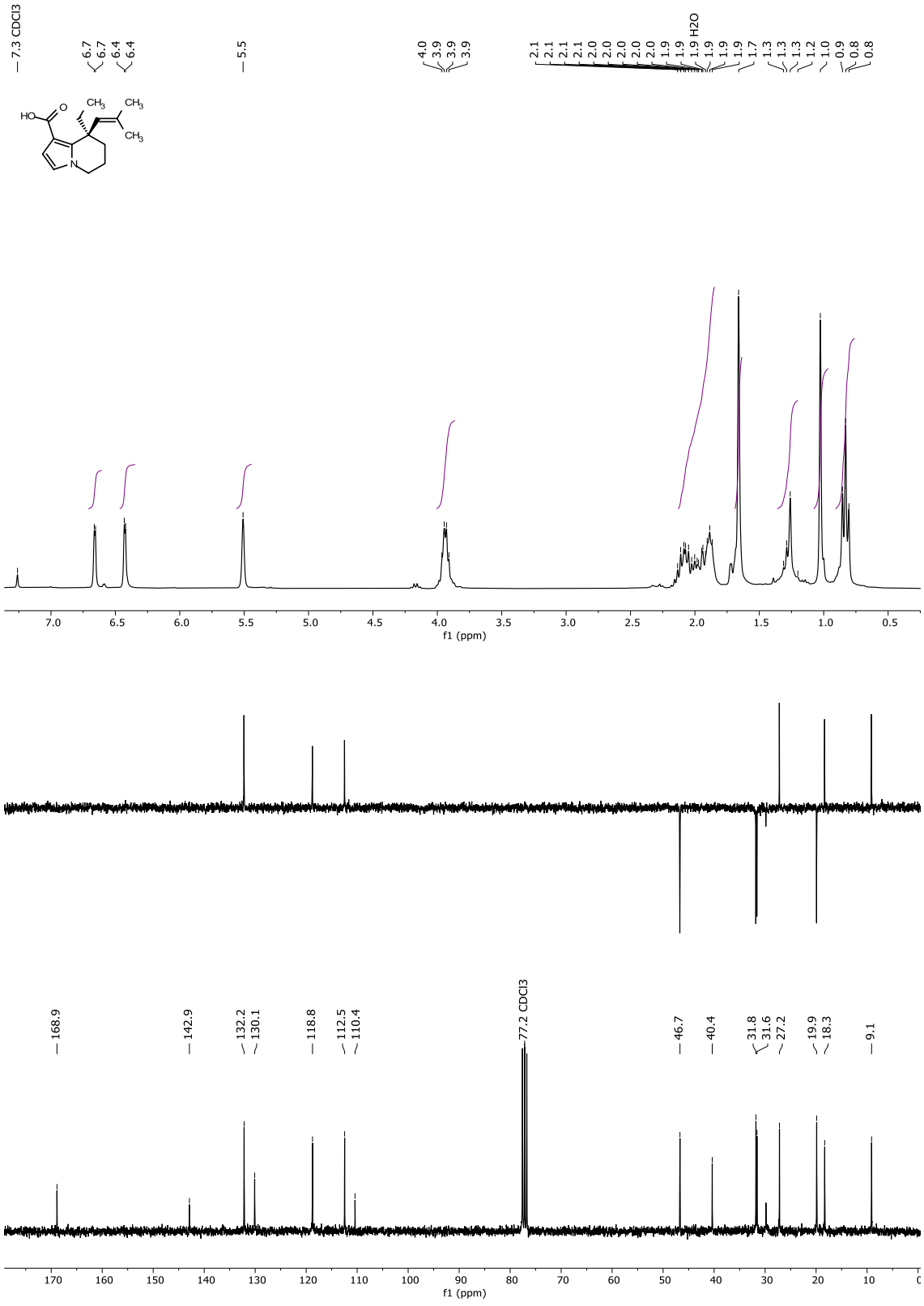


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{3.10,1.27}
{3.63,1.24}
{4.12,1.59}
{2.30,1.50}
{2.17,1.50}
{2.01,1.88}
{1.84,1.49}
{2.89,2.33}
{4.75,2.94}
{3.54,3.09}
{3.08,2.96}
{3.59,3.31}
{4.15,3.15}
{6.12,6.00}
{7.26,7.26}CDCl3
f2 (ppm)
f1 (ppm)

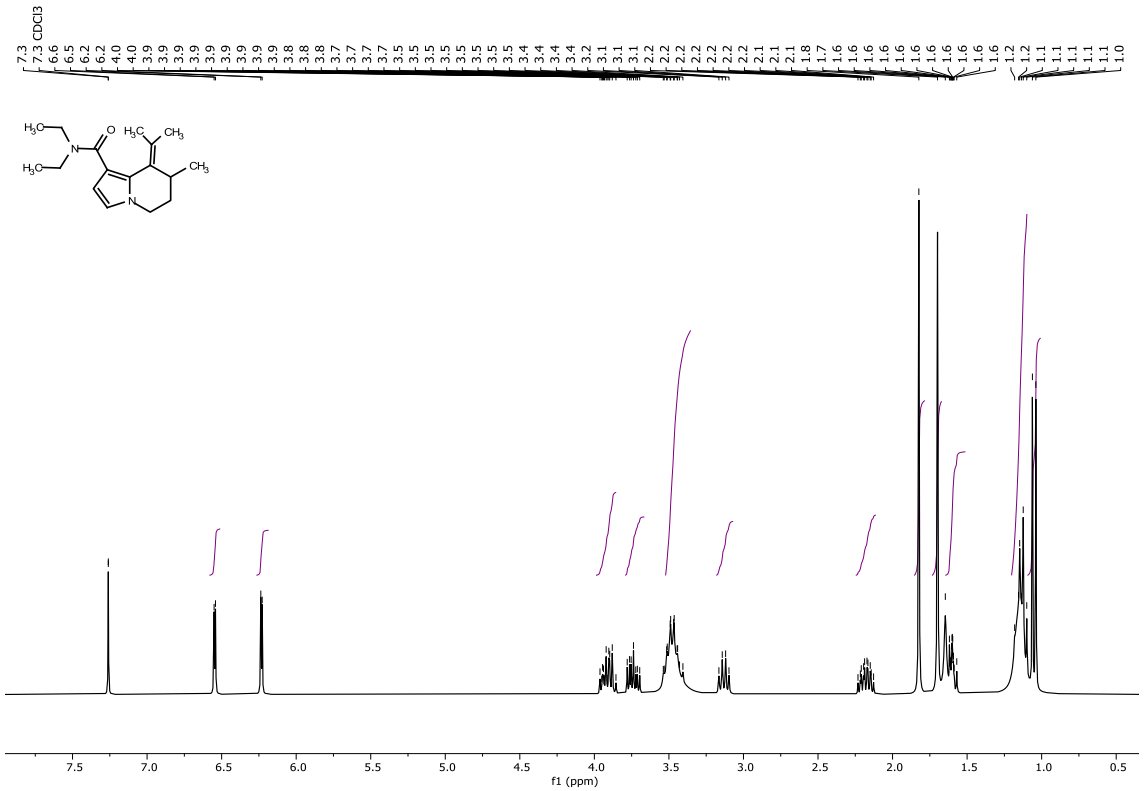

{1.3,15.1}
{1.6,20.1}
{2.3,26.8}
{2.3,29.5}
{1.5,28.7}
{4.2,36.9}
{4.1,36.9}
{3.1,36.9}
{3.0,39.9}
{2.0,37.7}
{3.6,43.2}
{3.1,43.2}
{1.9,37.7}
{3.3,40.7}
{4.8,118.8}
{6.2,126.0}
f2 (ppm)
f1 (ppm)

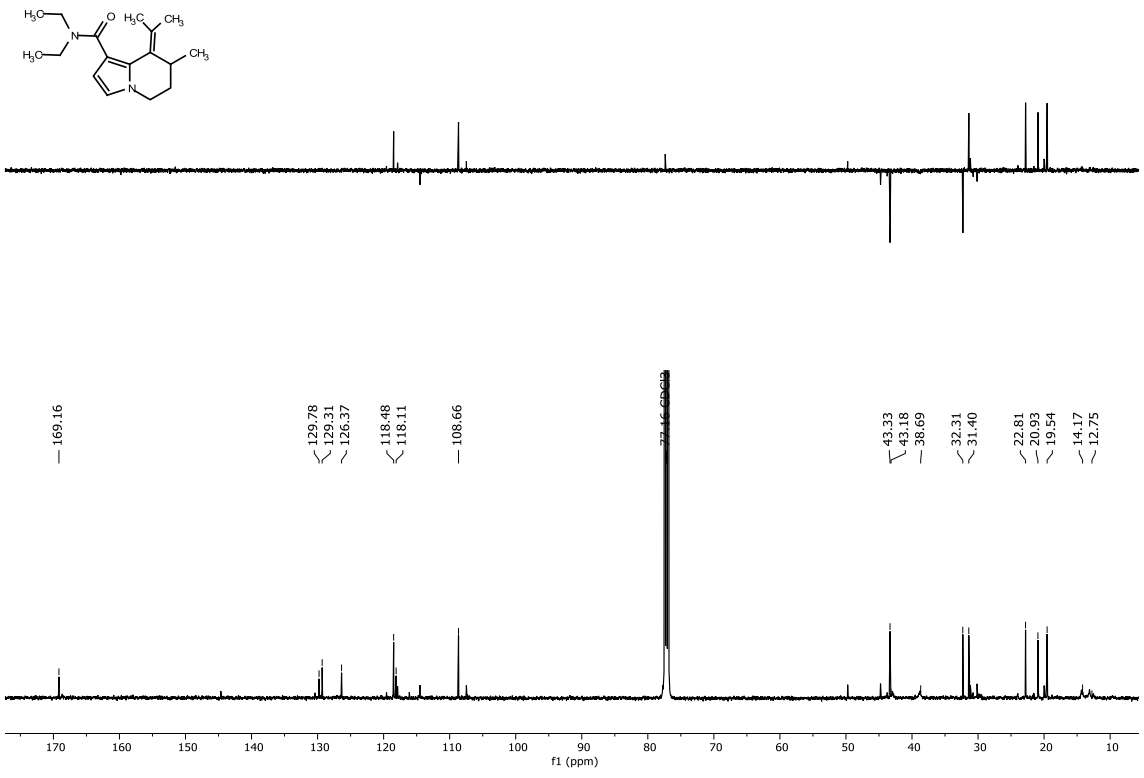
*^{1}H and ^{13}C NMR of **21h***



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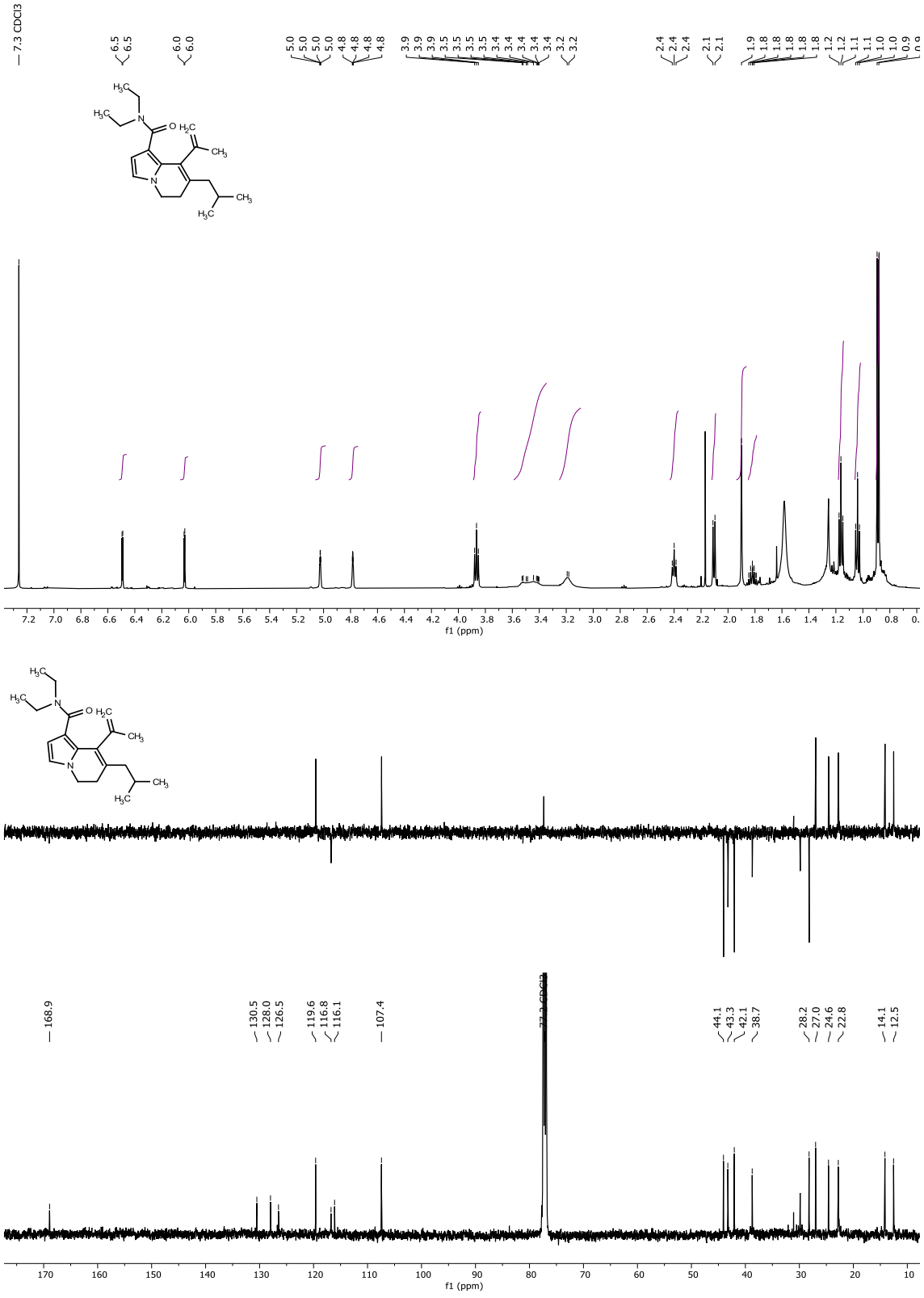
*^{1}H and ^{13}C NMR of **23o***





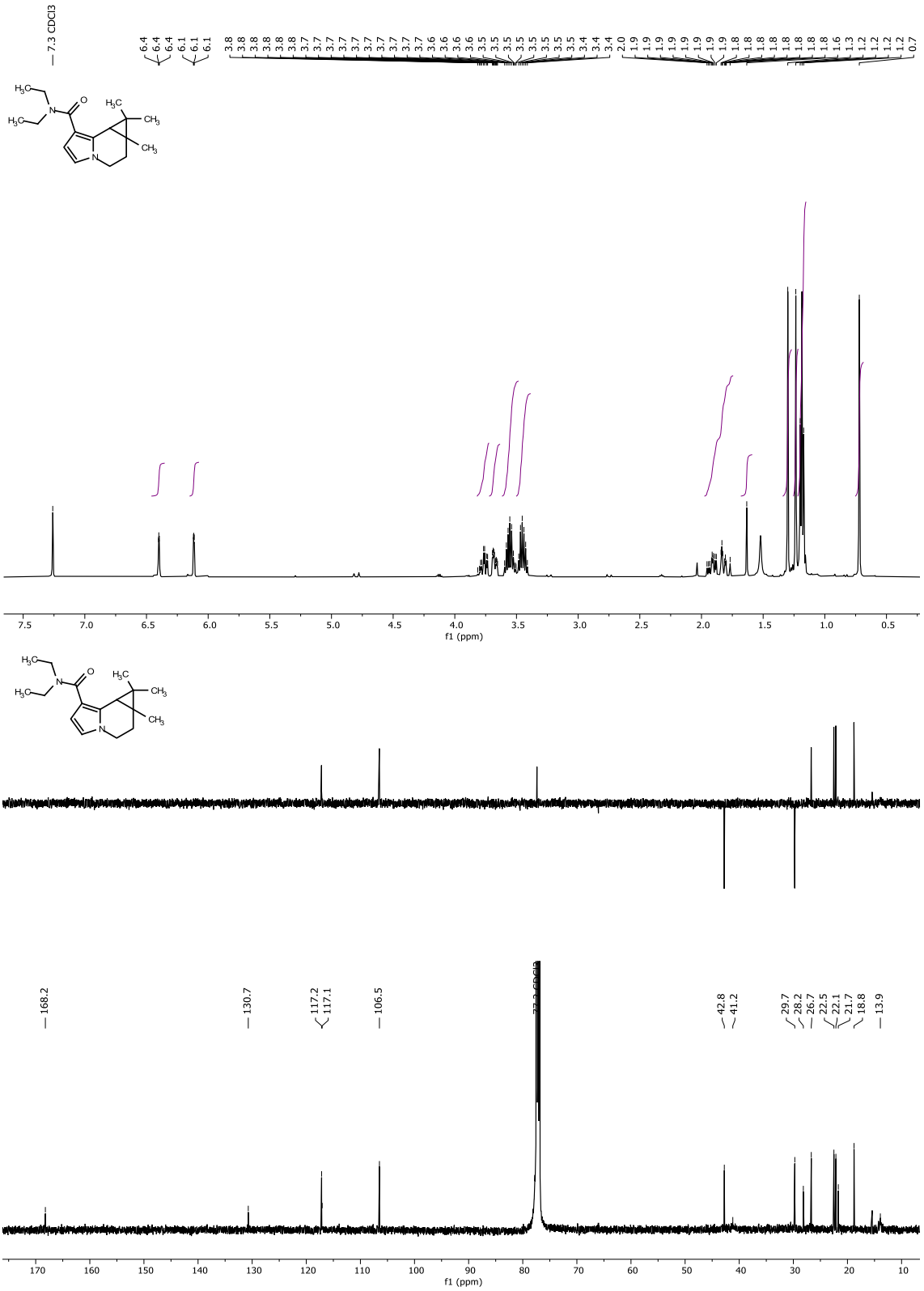
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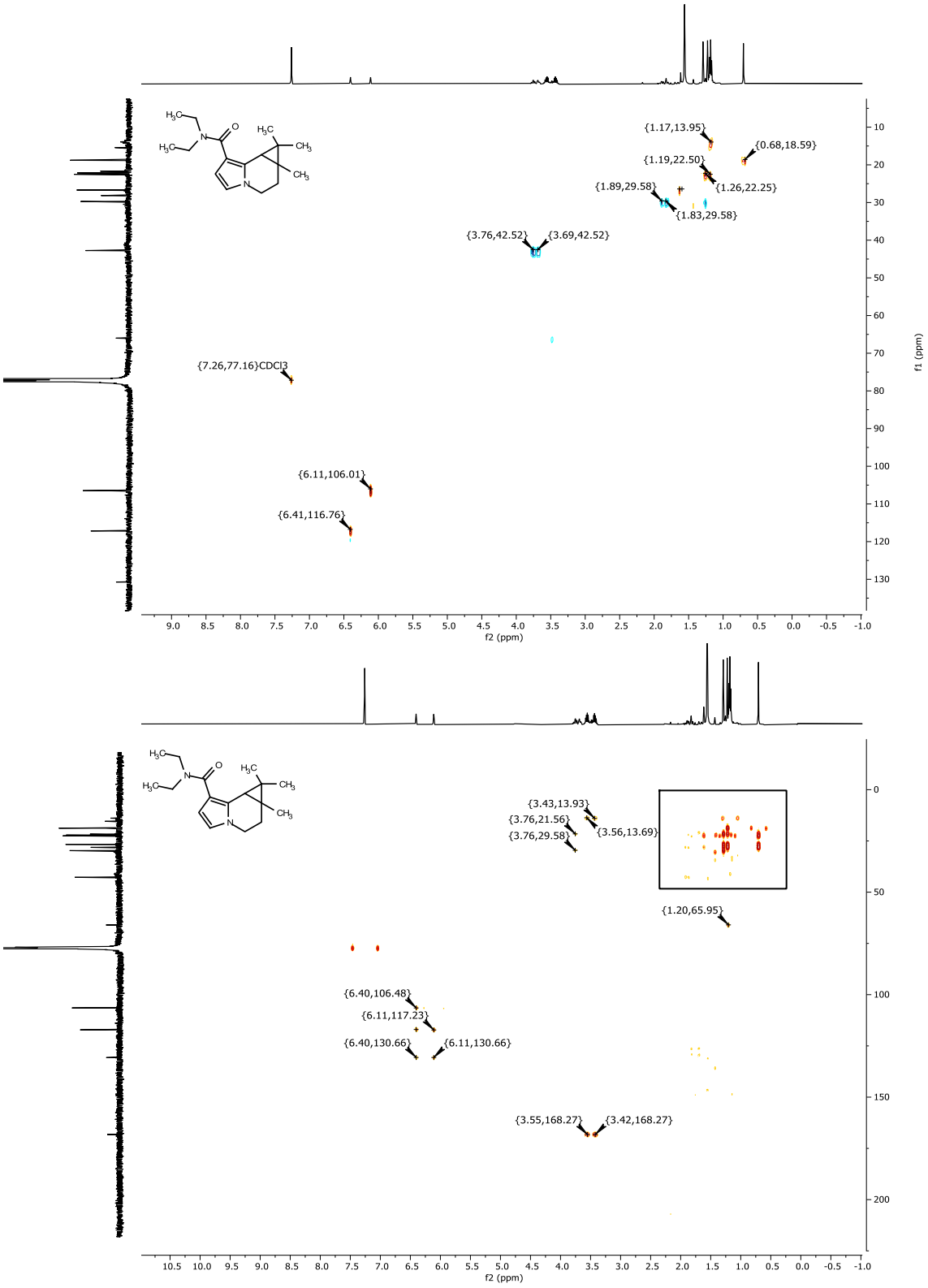
*^{1}H and ^{13}C NMR of **24w***



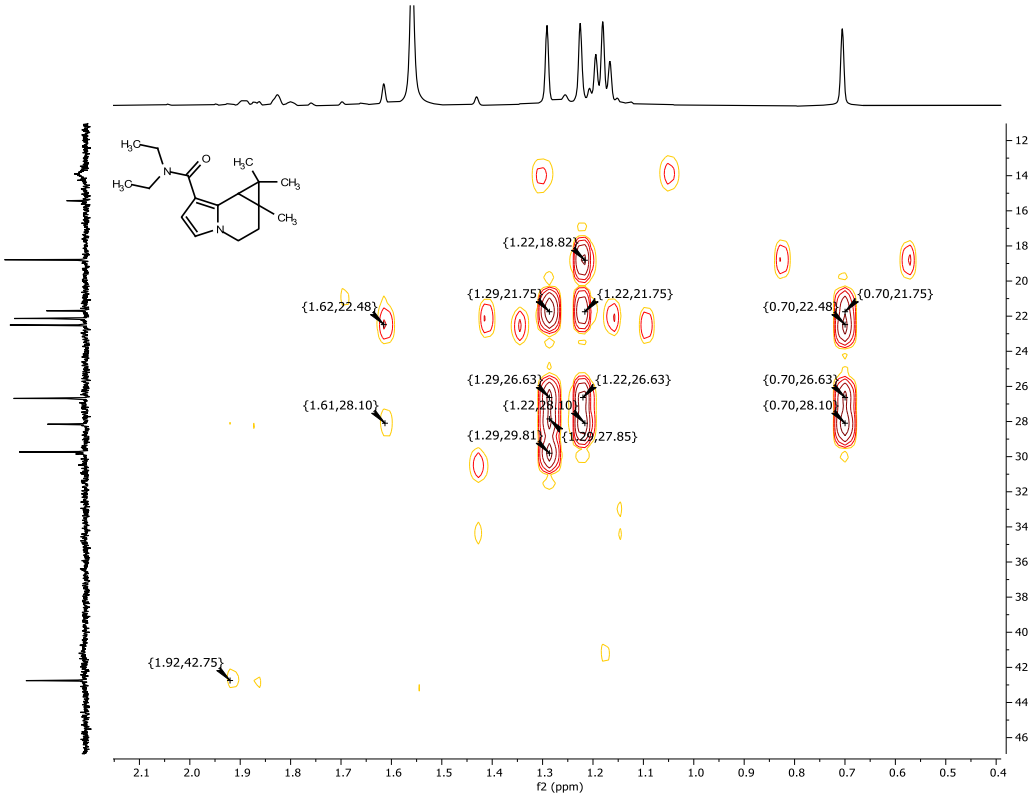
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*^{1}H and ^{13}C NMR, HSQC and HMBC of **25o***



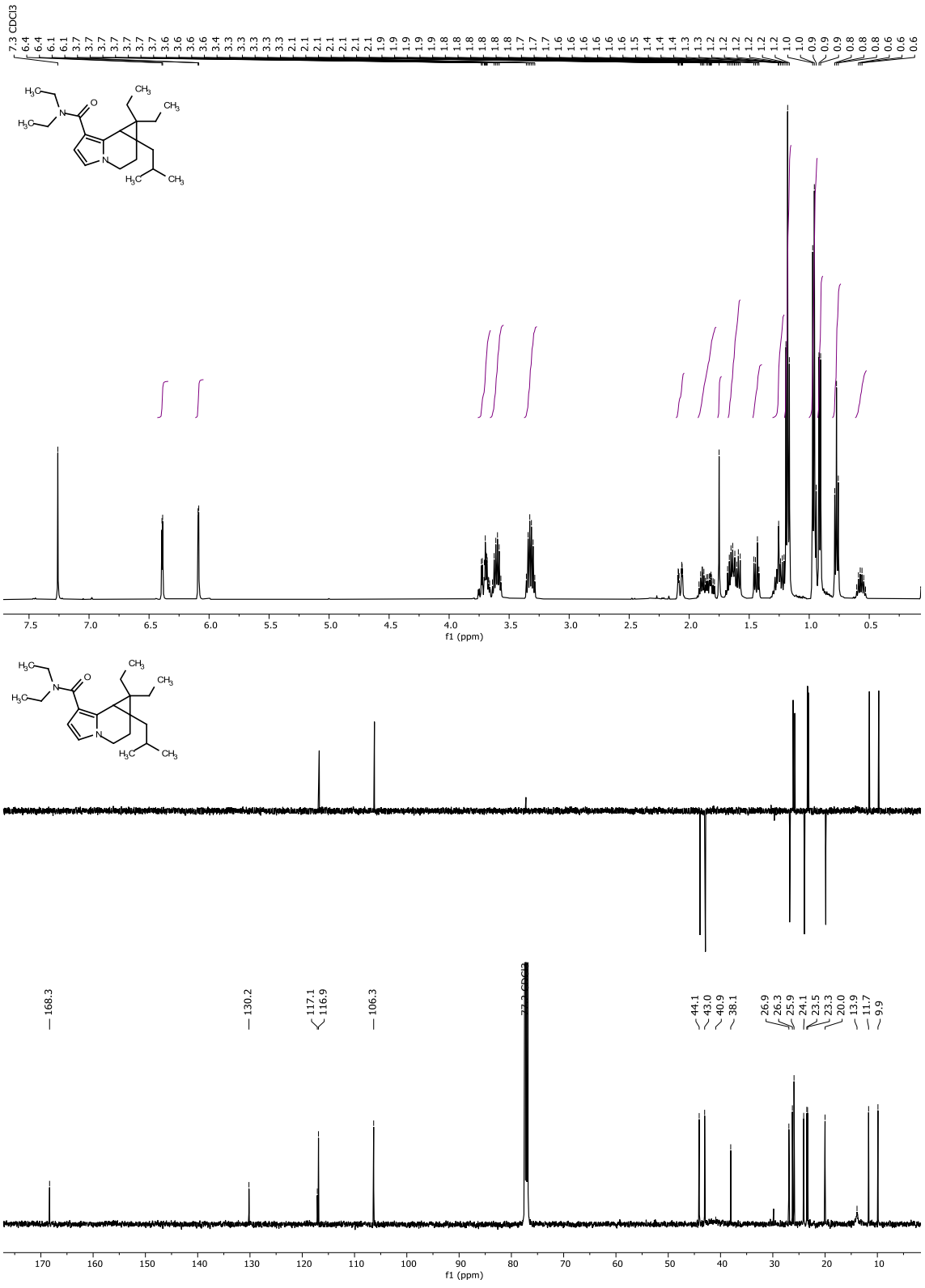


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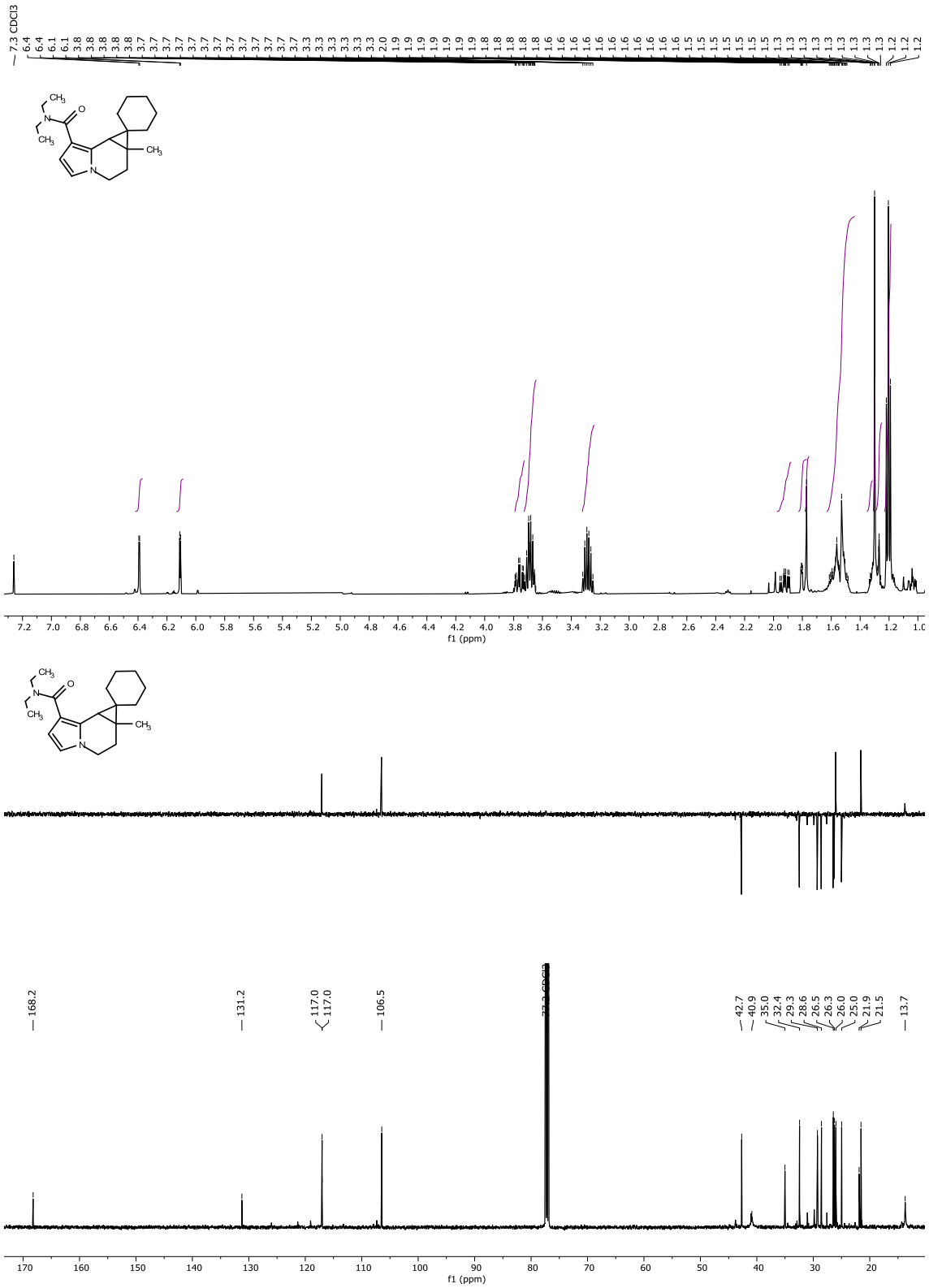
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*^{1}H and ^{13}C NMR of **25α***

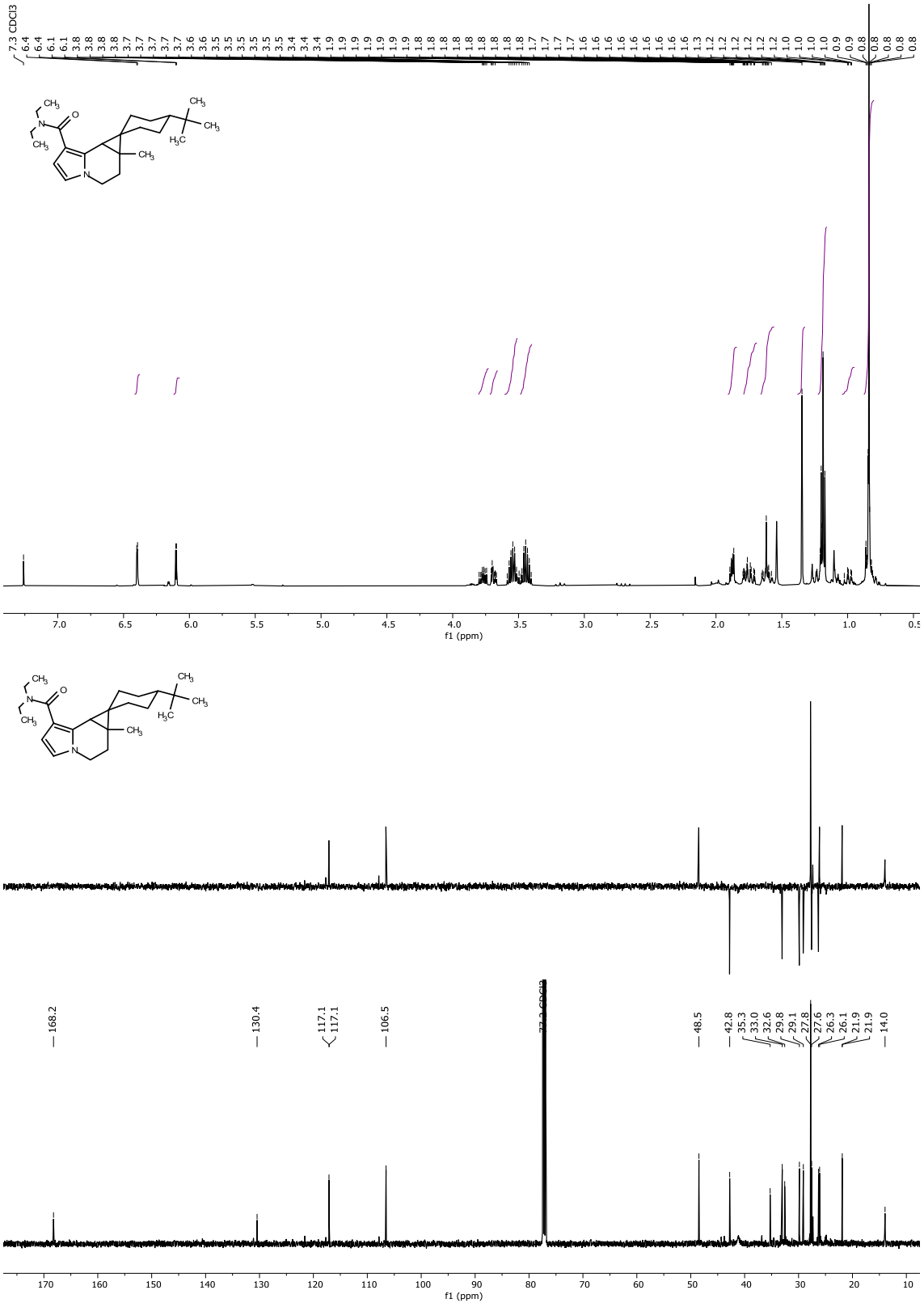


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^{1}H and ^{13}C NMR of ***25δ***

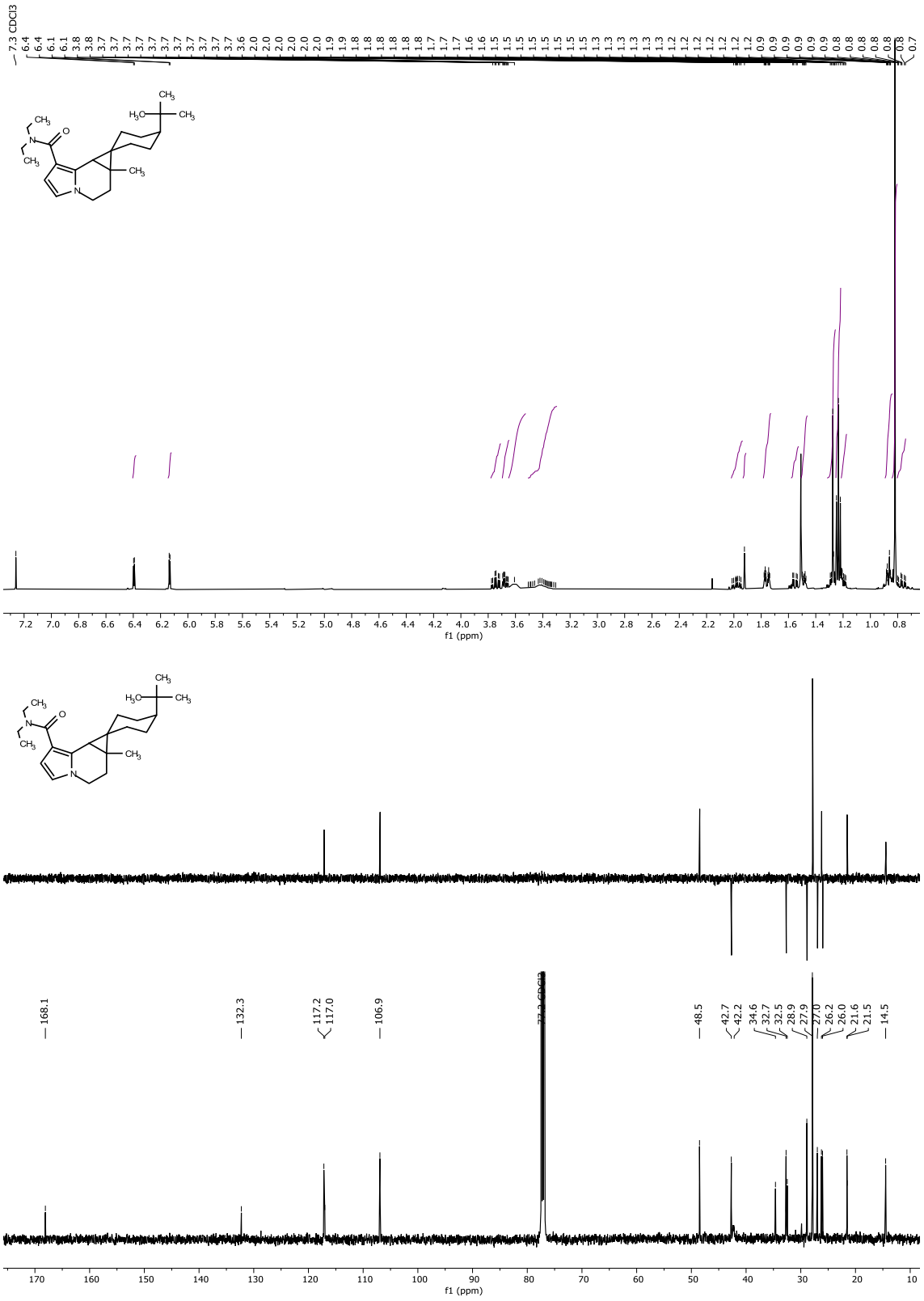


*^{1}H and ^{13}C NMR of **25ι***



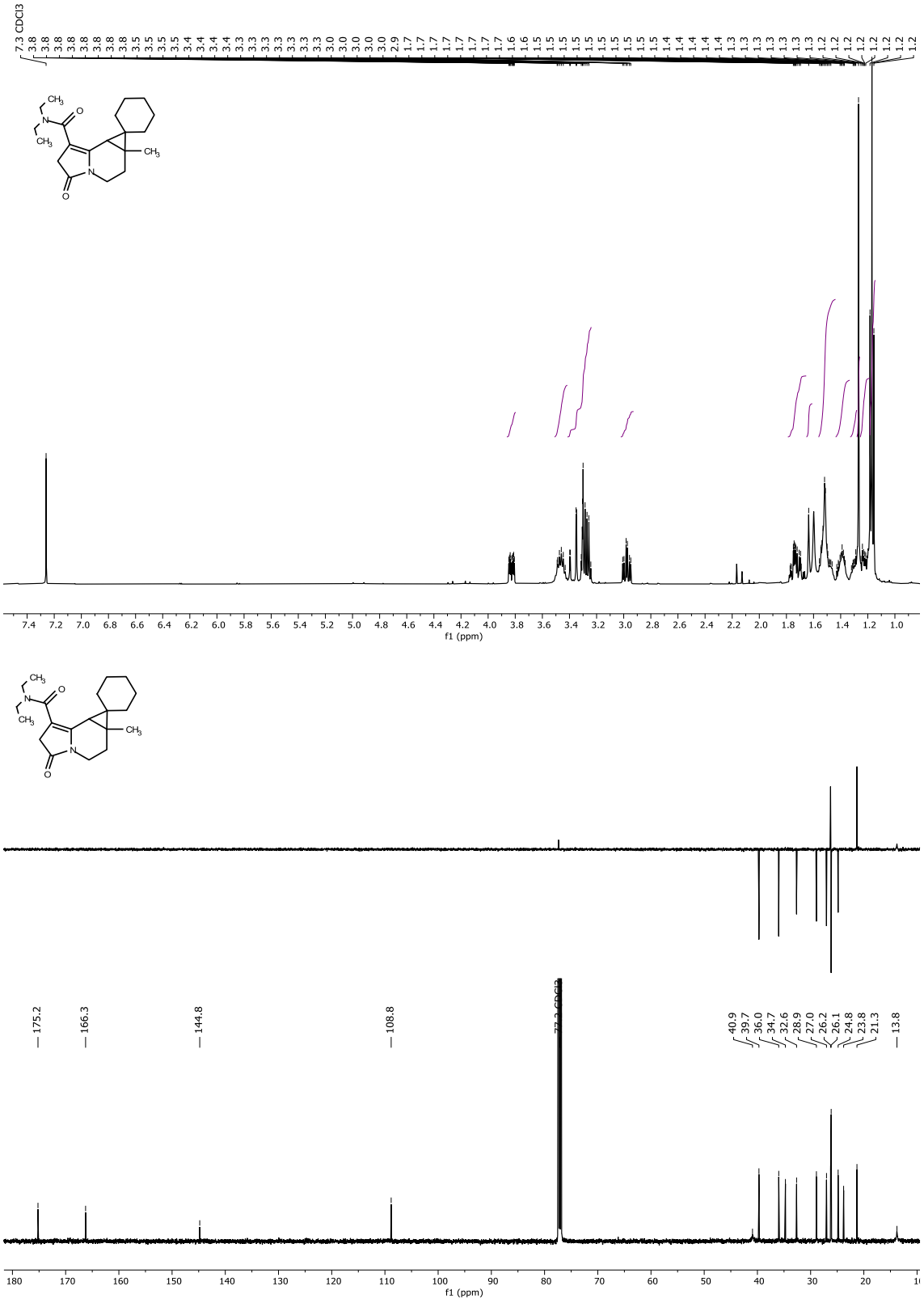
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*^{1}H and ^{13}C NMR of **25ι'***



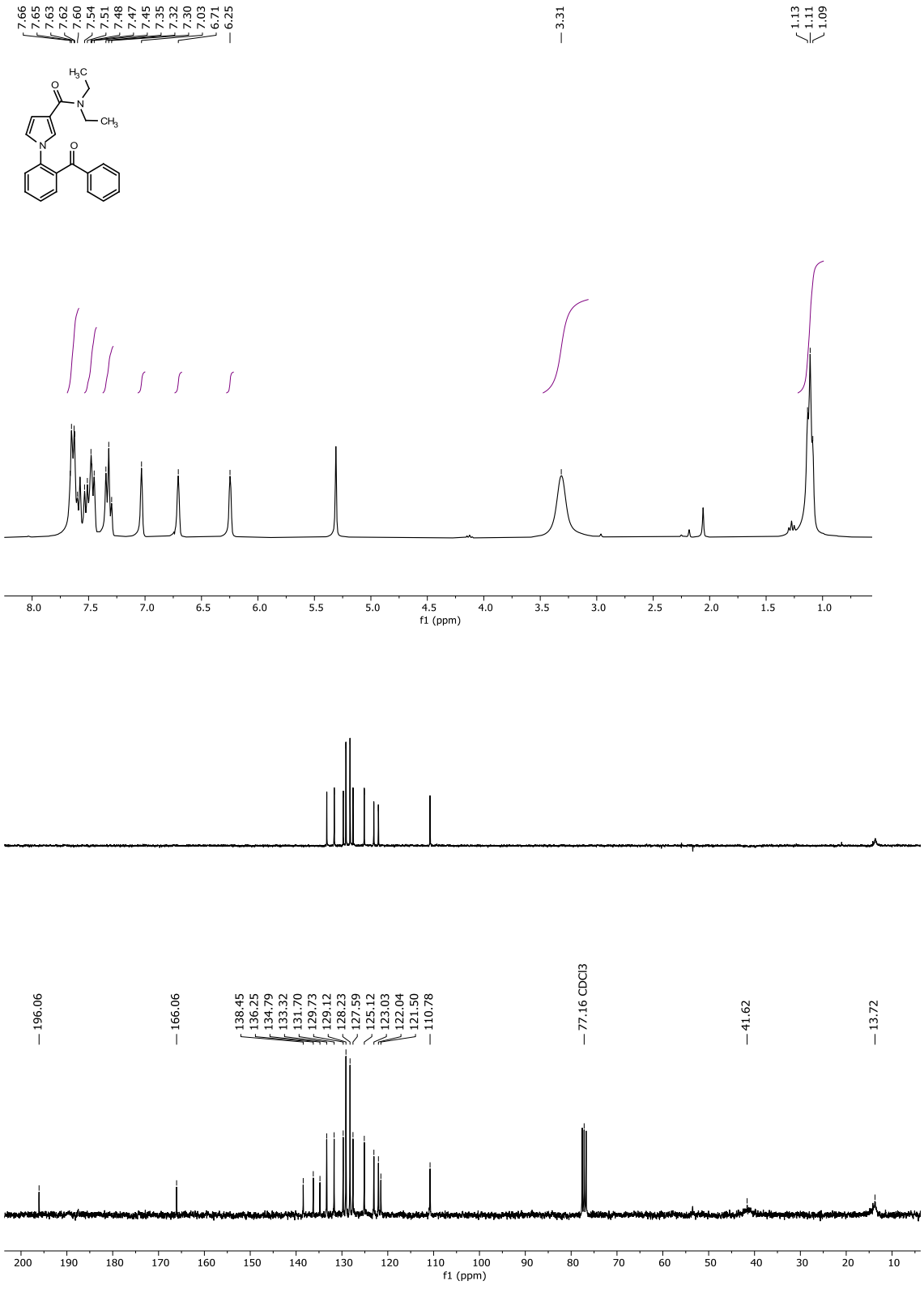
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*^{1}H and ^{13}C NMR of **26δ***

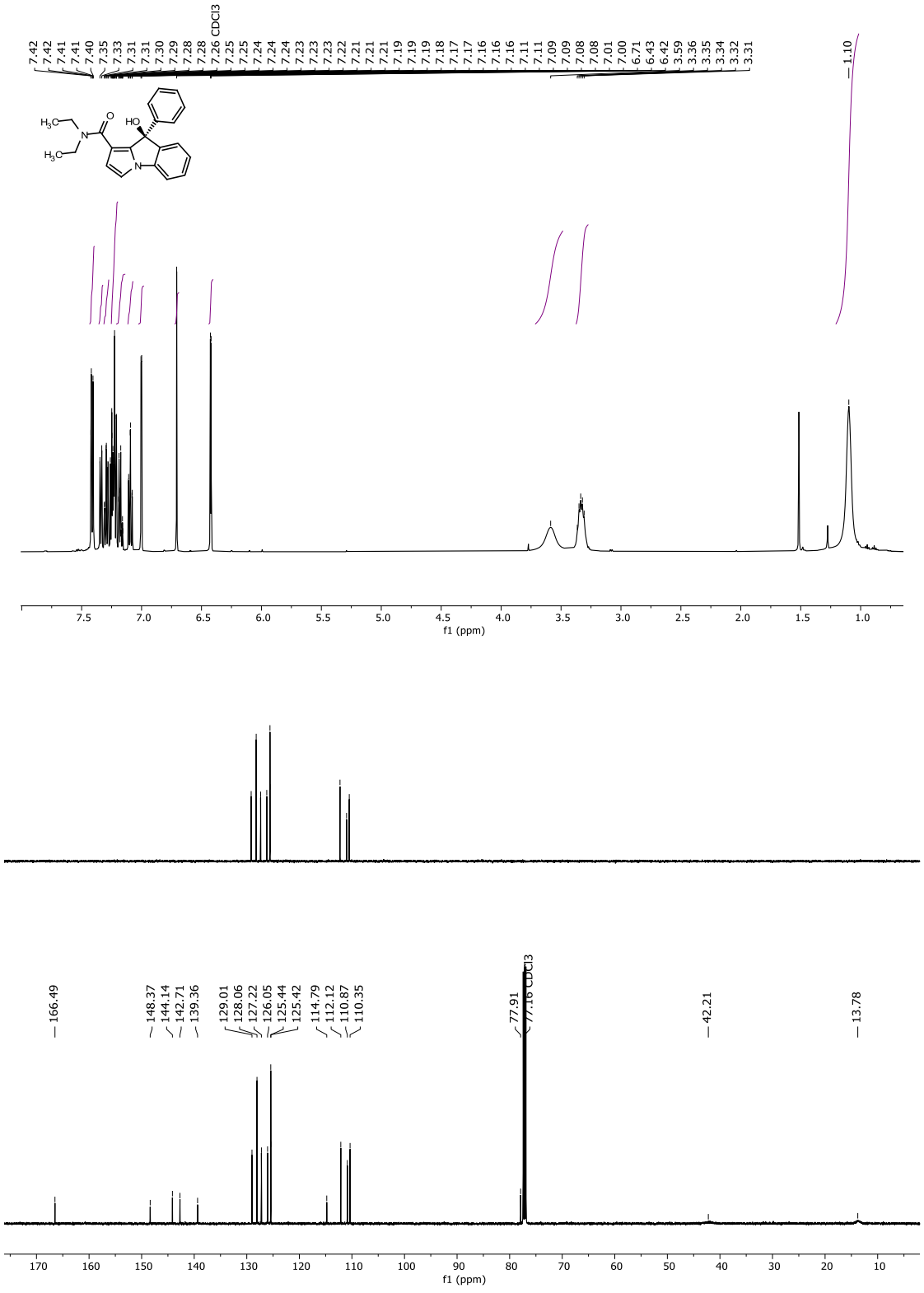


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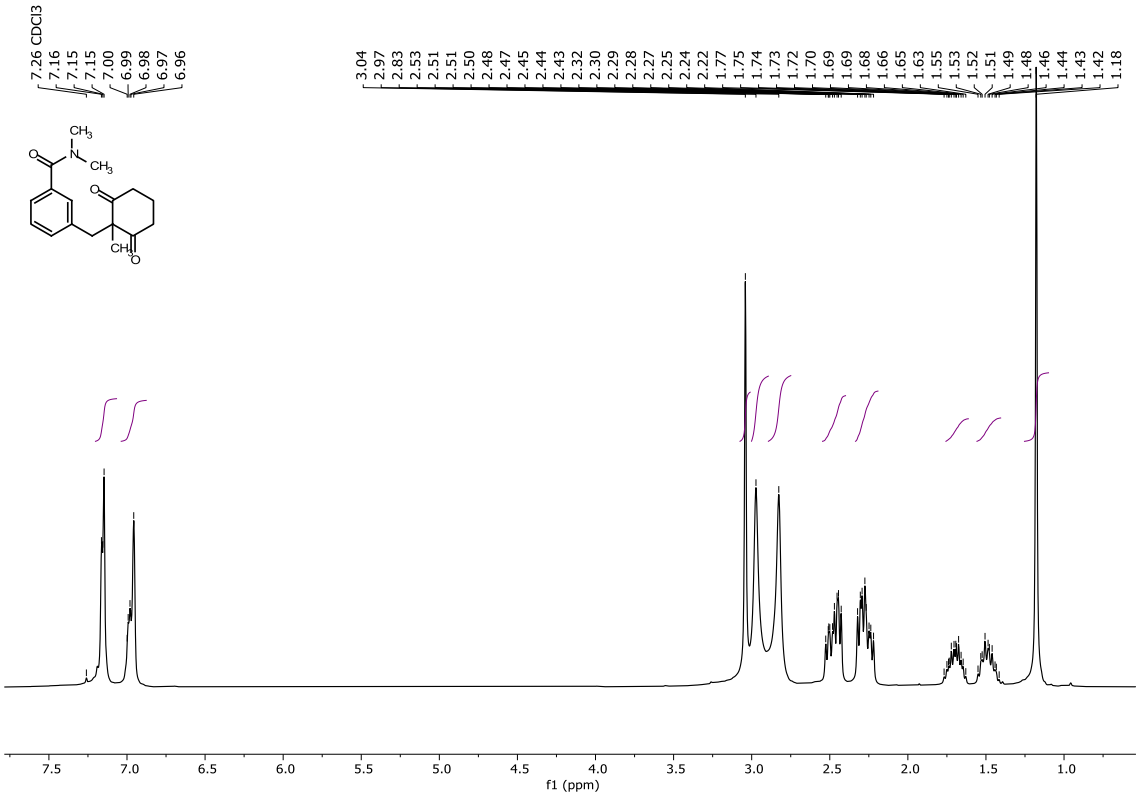
*^{1}H and ^{13}C NMR of **30b***

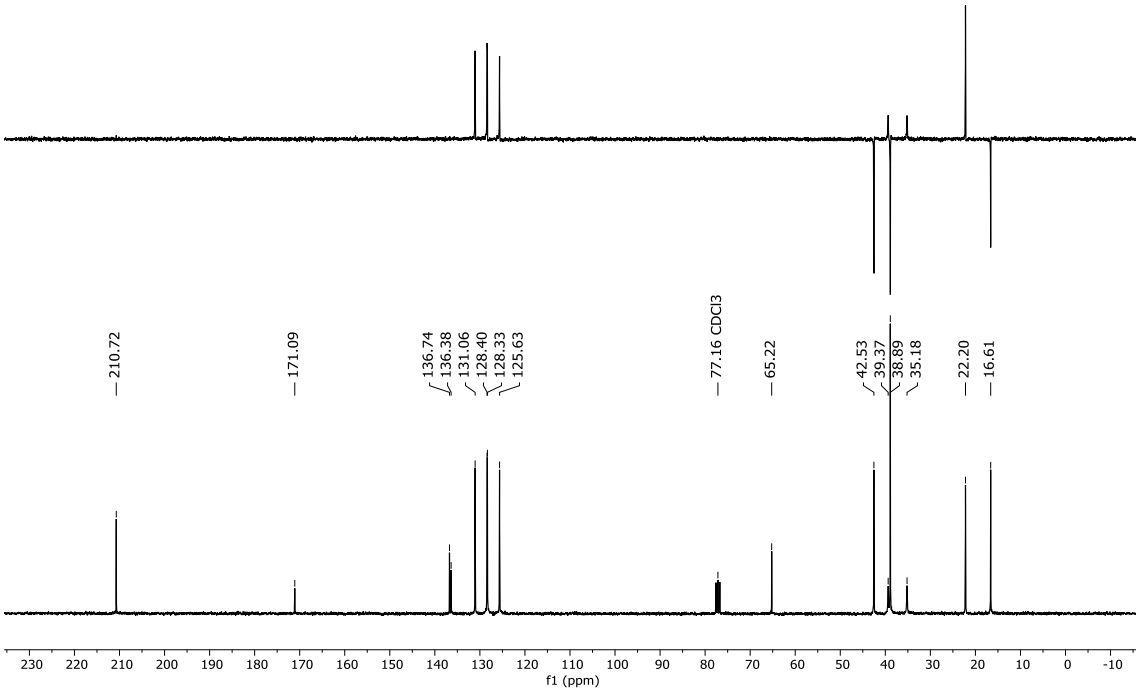


*^{1}H and ^{13}C NMR of **31b***



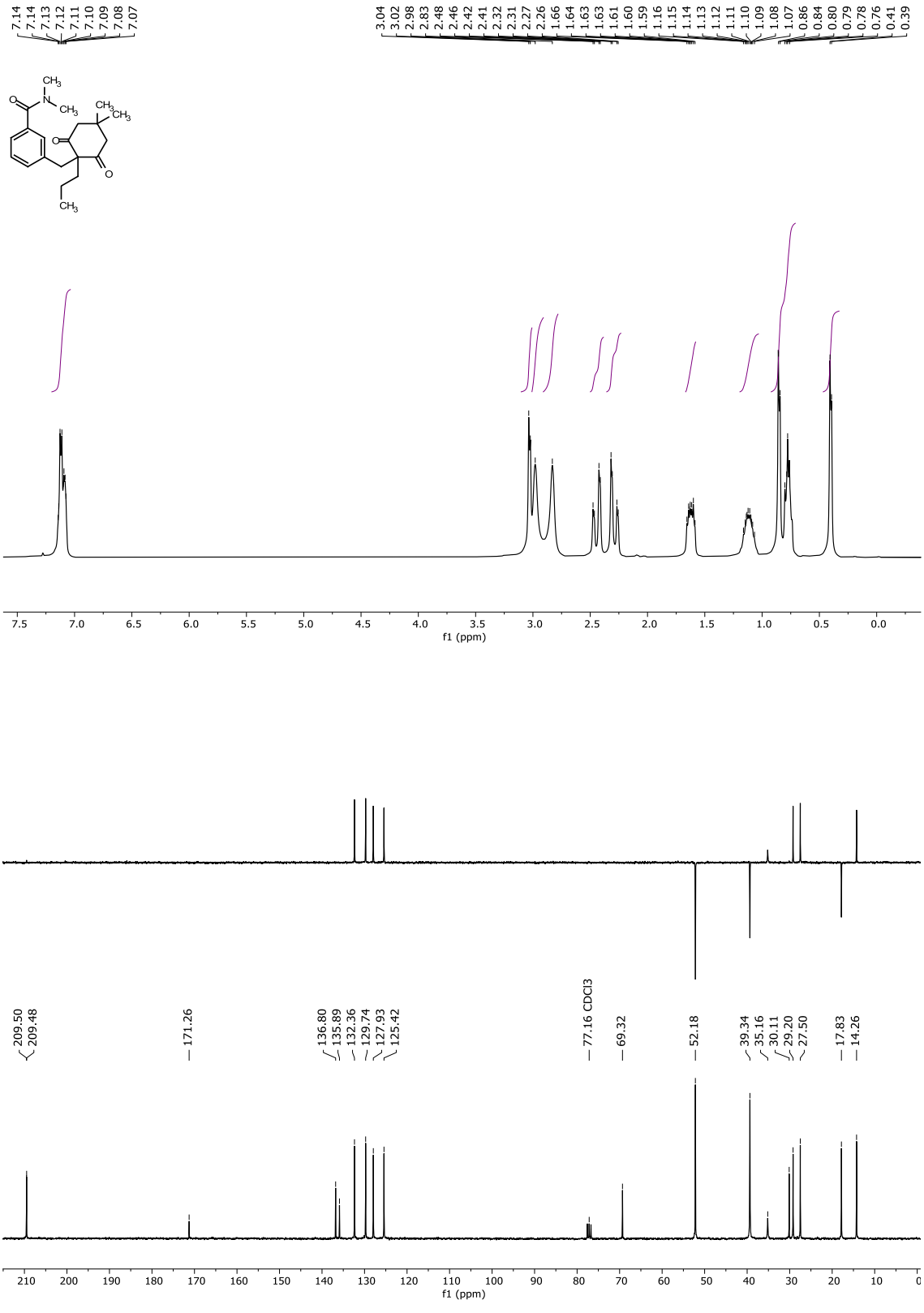
*^{1}H and ^{13}C NMR of **32c***





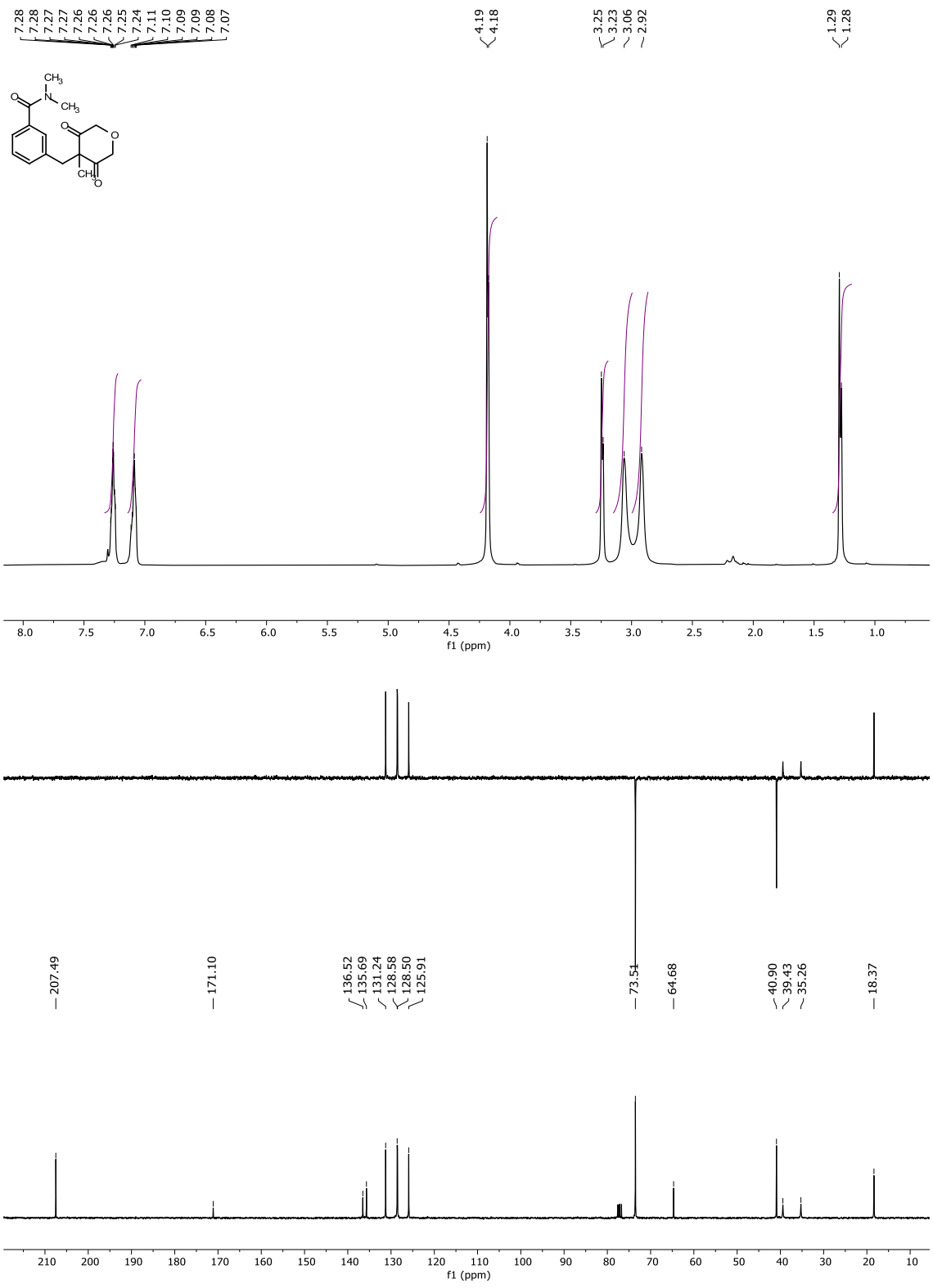
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*^{1}H and ^{13}C NMR of **32i***

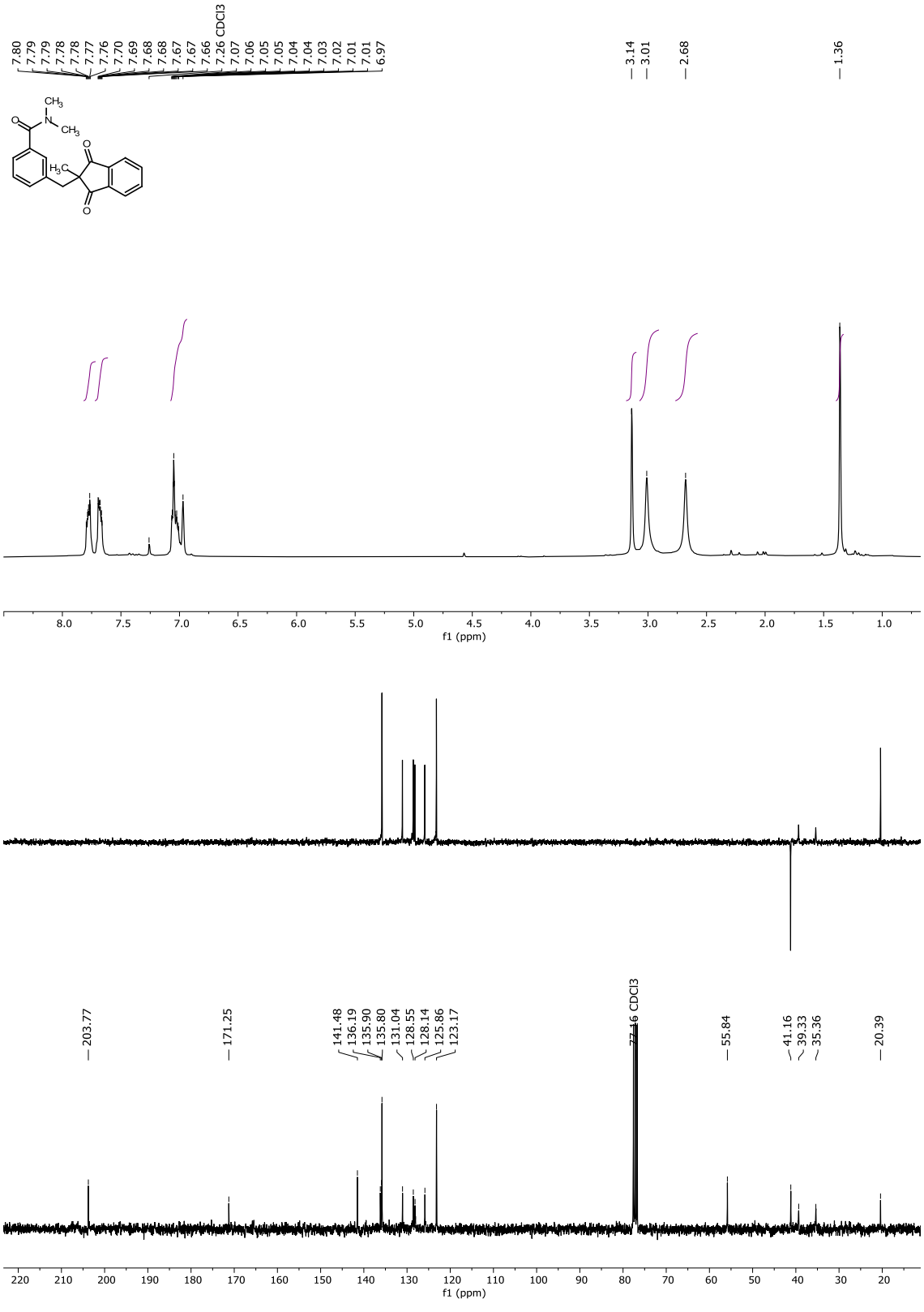


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*^{1}H and ^{13}C NMR of **32l***

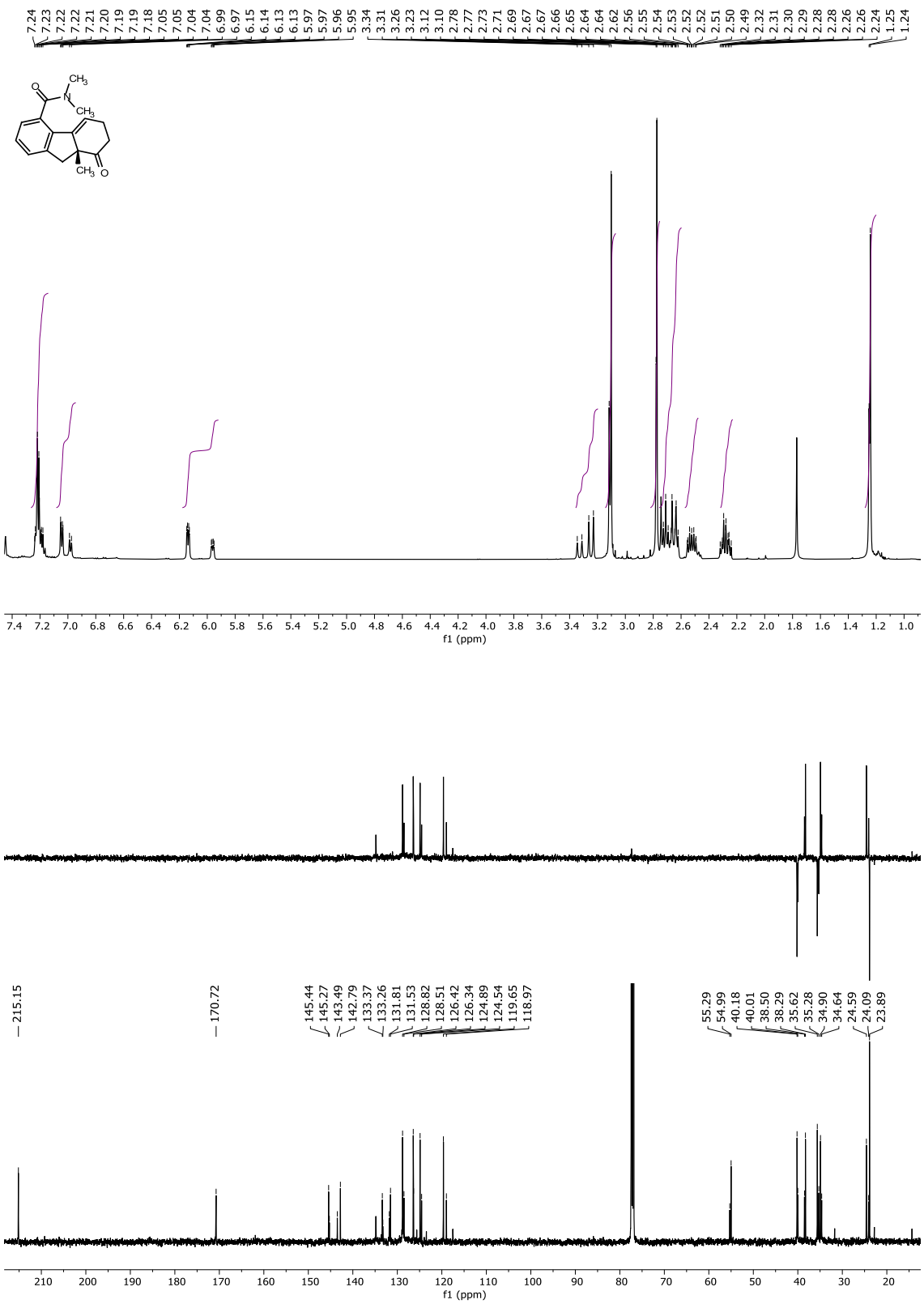


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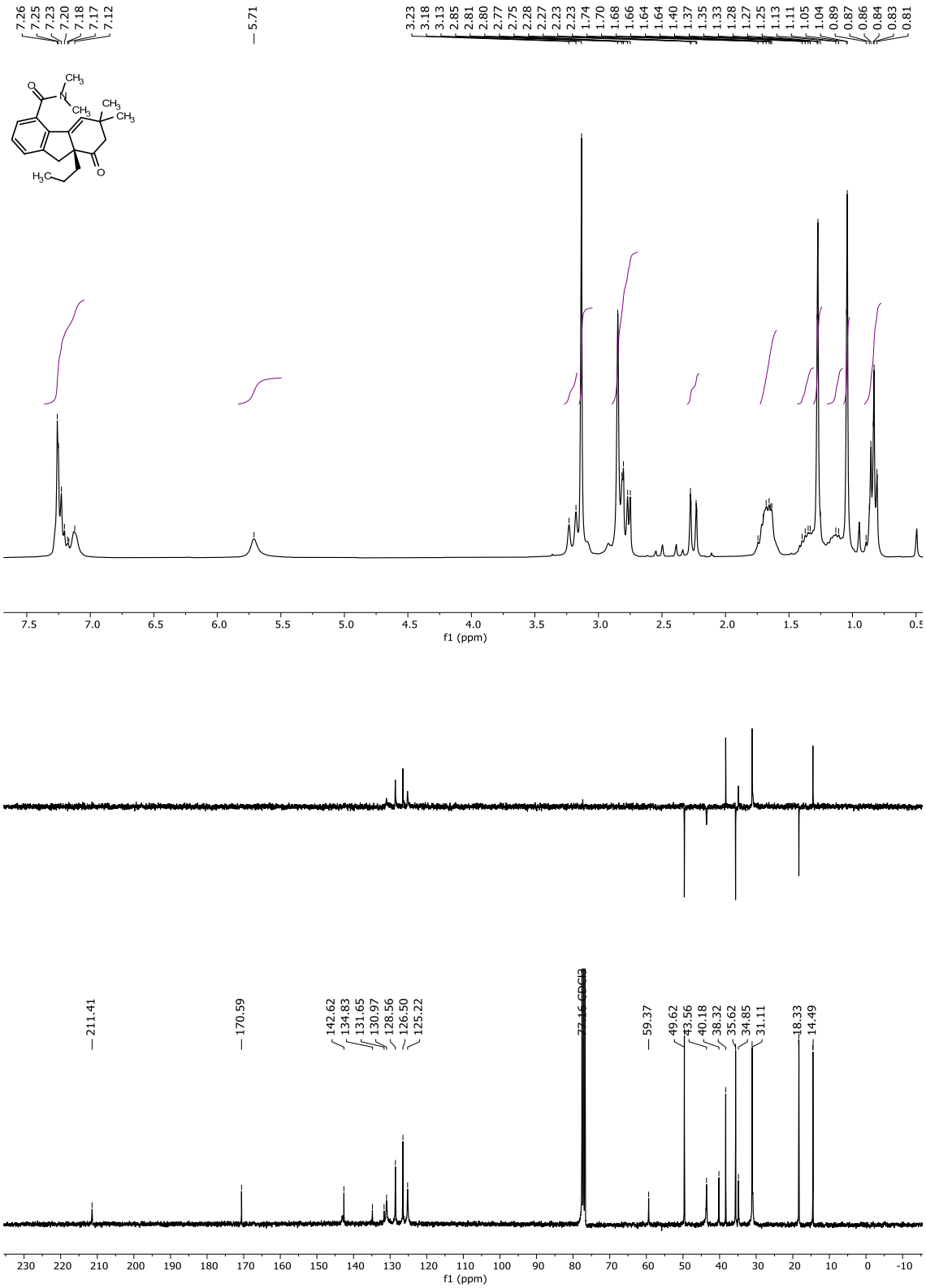
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*^{1}H and ^{13}C NMR of **33c***

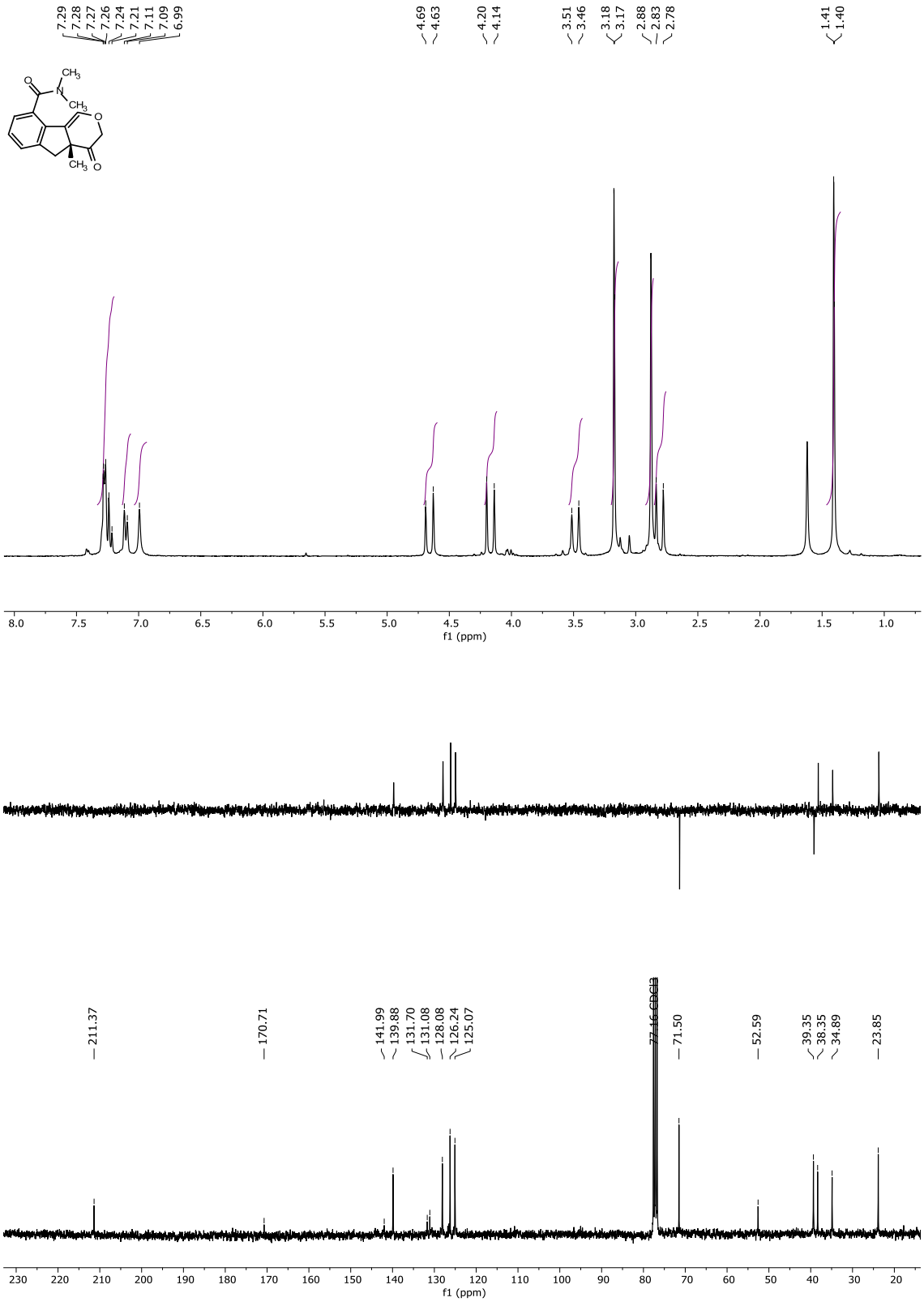


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*^{1}H and ^{13}C NMR of **33i***

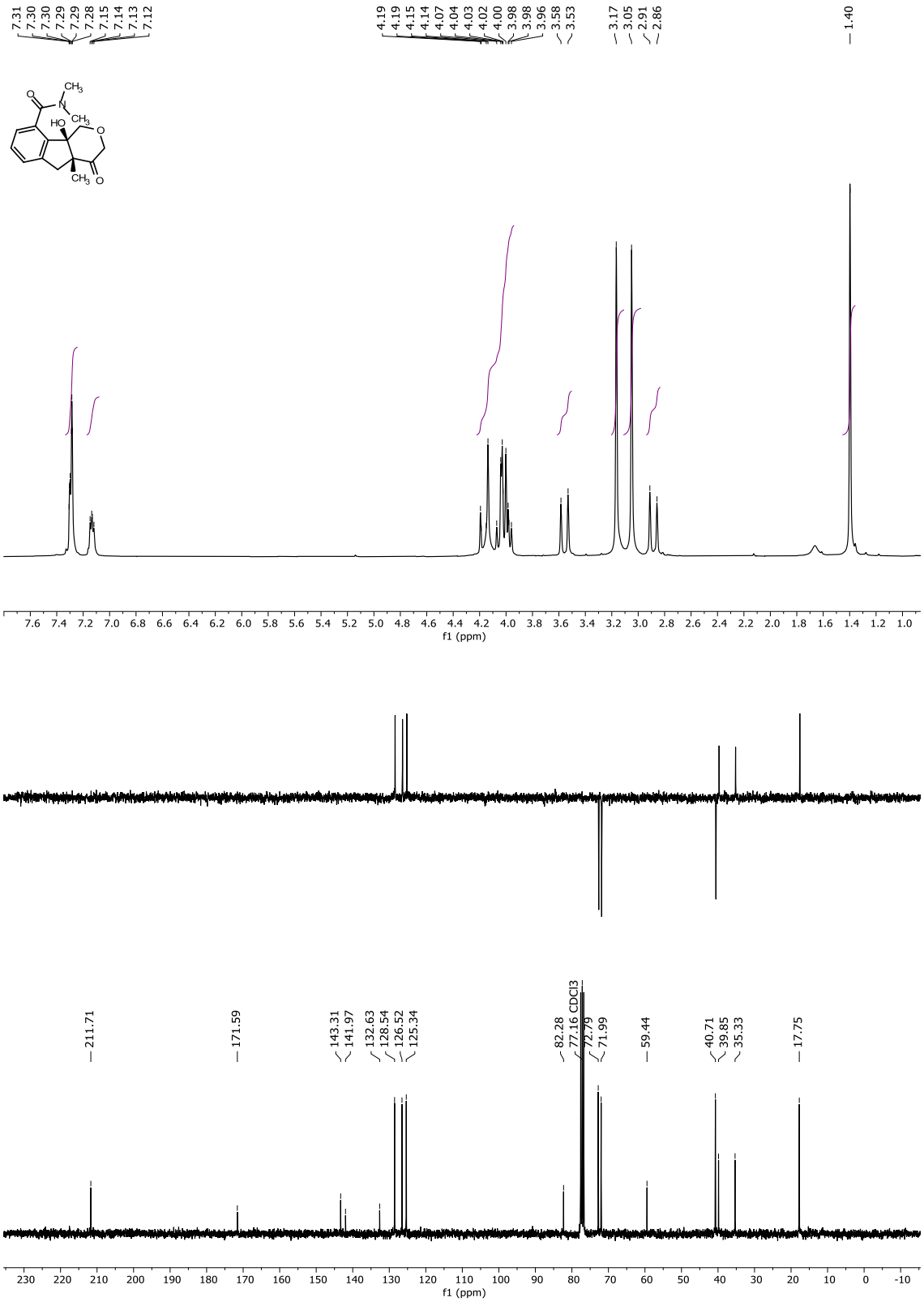


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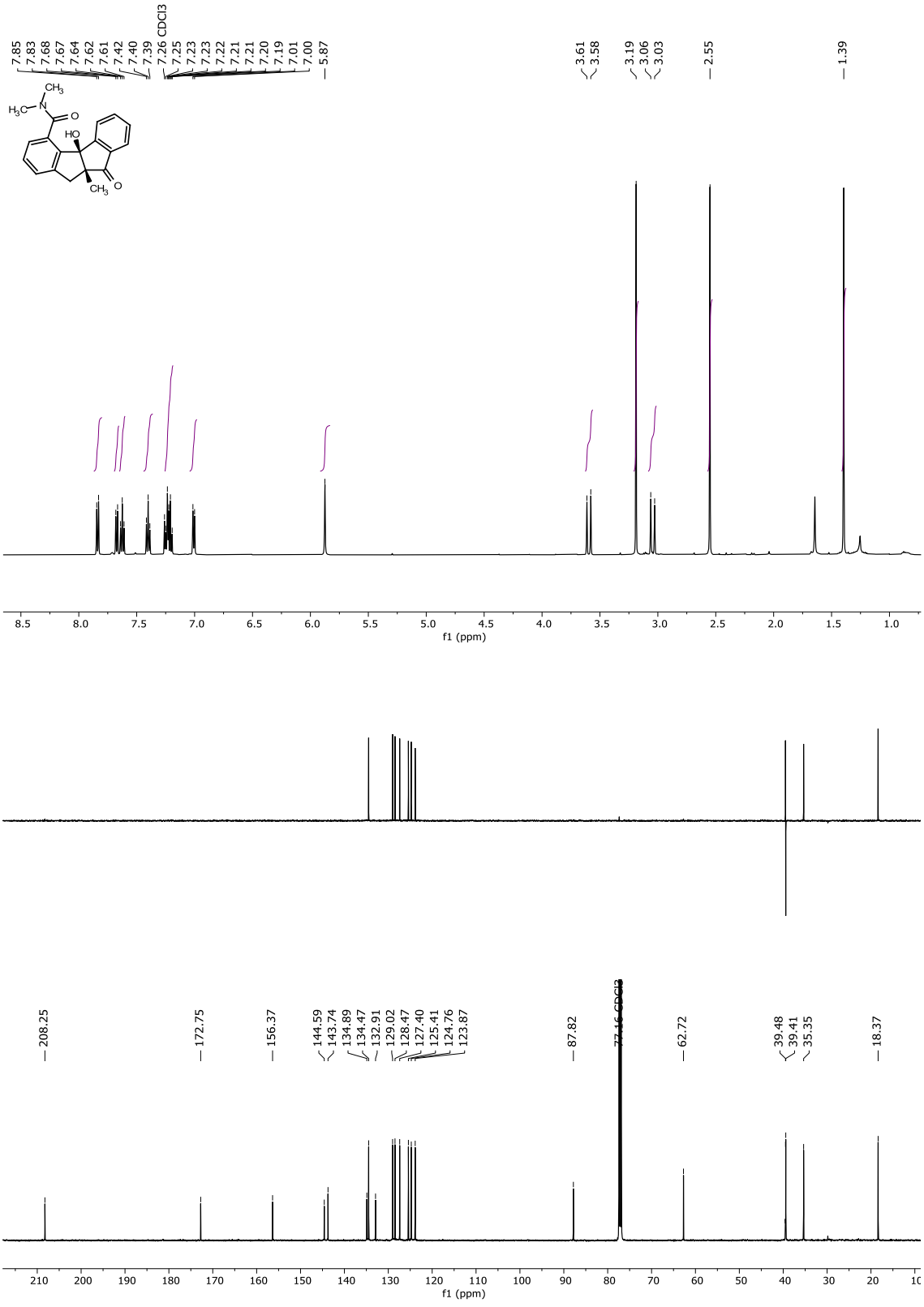
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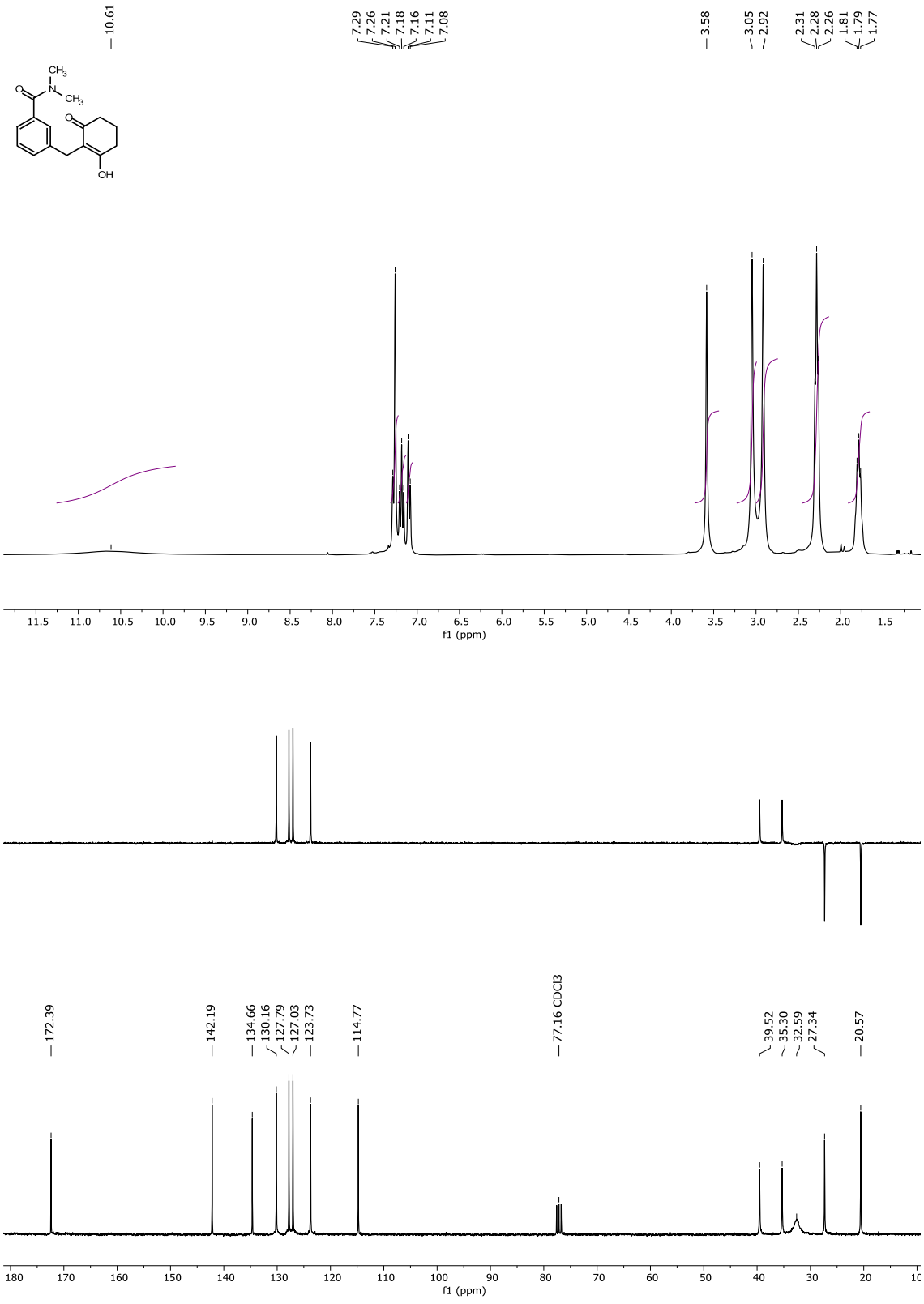
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*^{1}H and ^{13}C NMR of **34n***



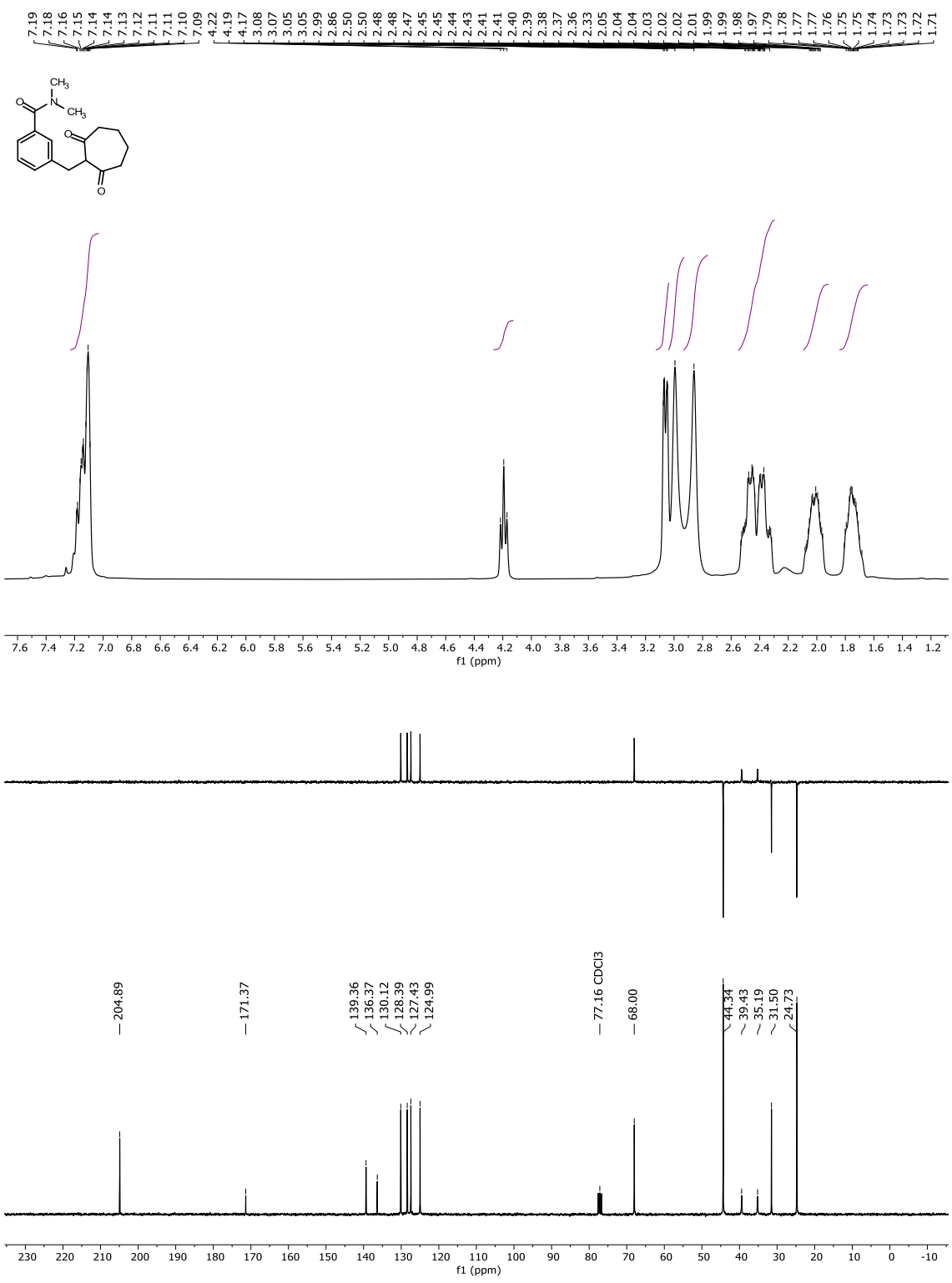
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*^{1}H and ^{13}C NMR of **35c***



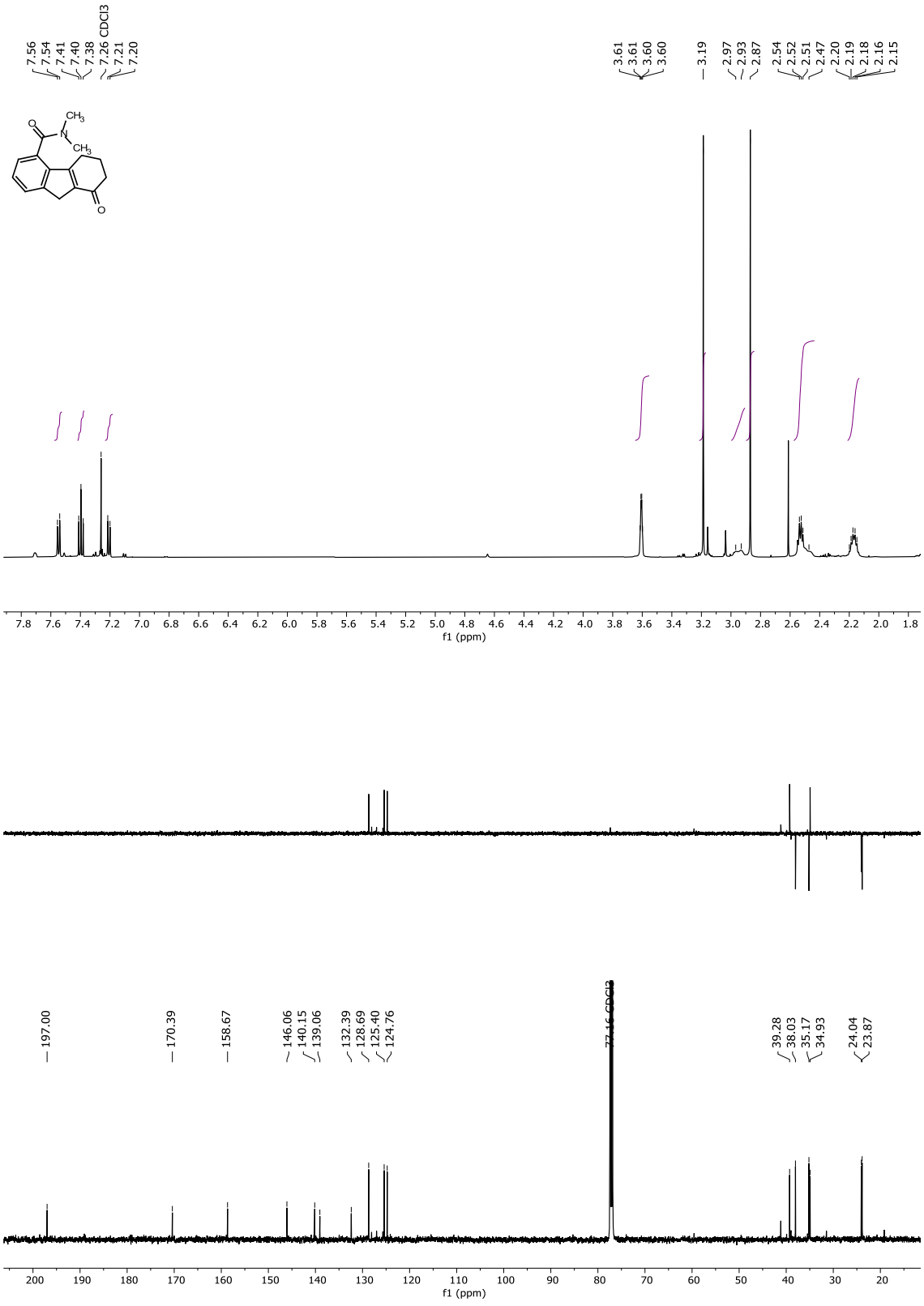
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*^{1}H and ^{13}C NMR of **35k***



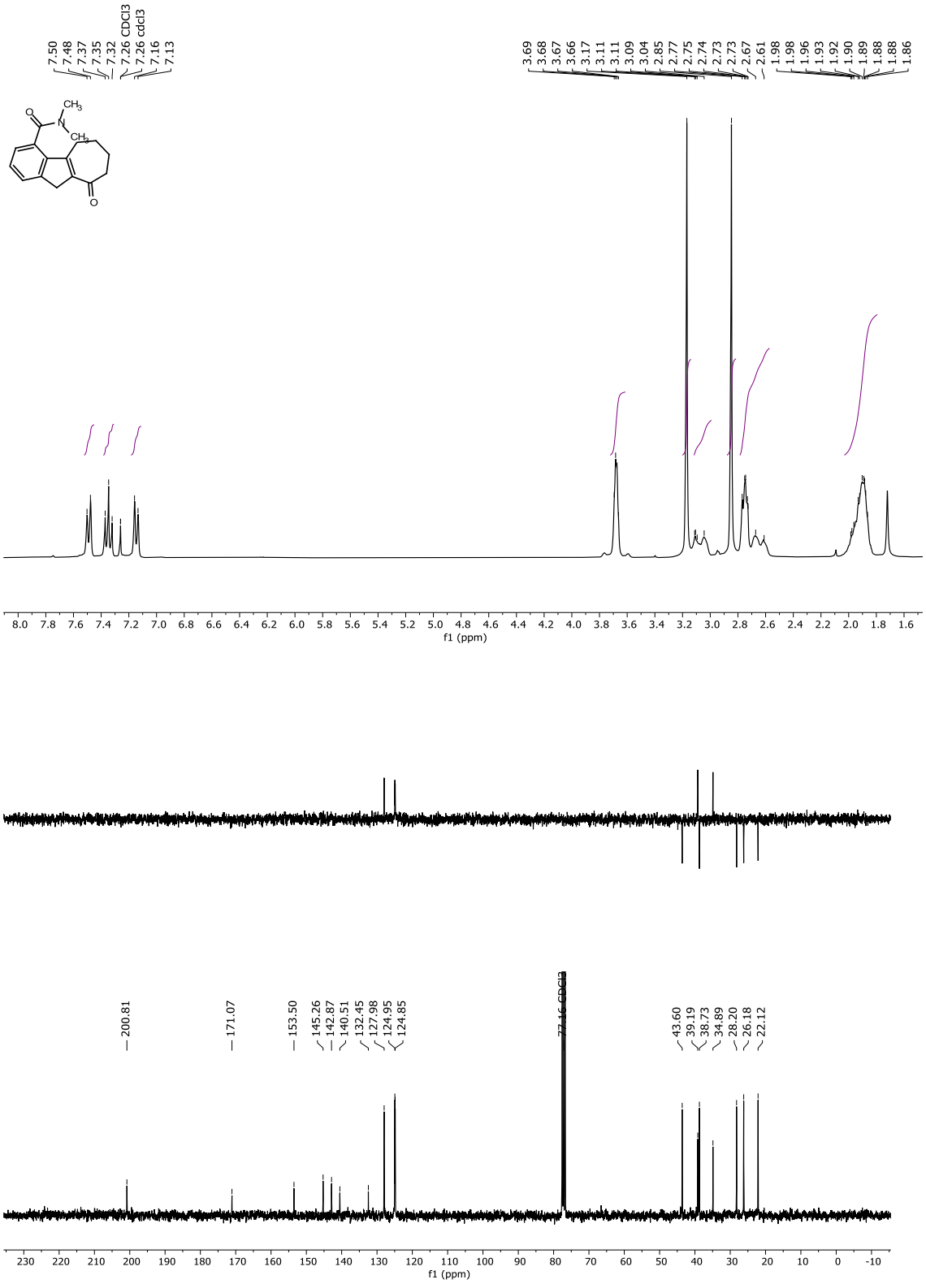
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*: ^{1}H and ^{13}C NMR of **36c***



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*^{1}H and ^{13}C NMR of **36k***



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Appendix II: List of publications

Title: **Highly Enantioselective Iridium(I)-Catalyzed Hydrocarbonation of Alkenes: A Versatile Approach to Heterocyclic Systems Bearing Quaternary Stereocenters**

Authors: Andrés Arribas, Martín Calvelo, David F. Fernández, Catarina A. B. Rodrigues, Prof. José L. Mascareñas, Dr. Fernando López

Affiliation: Centro Singular de Investigación en Química Biolóxica e Materiais Moleculares (CIQUS) and Departamento de Química Orgánica, Universidade de Santiago de Compostela, 15782 Santiago de Compostela (Spain)

Journal: Angewandte Chemie International Edition

Year: 2021

Volume, pages: 60, 19297-19305

Impact factor: 26.6 (2023)

PhD student contribution: Discovery of the reaction; Synthesis of starting materials; Screening of conditions; Synthesis and characterization of all compounds; Manipulation of the products; Discussion of the results and revision of the manuscript

Title: **Skeletal and Mechanistic Diversity in Ir-Catalyzed Cycloisomerizations of Allene-Tethered Pyrroles and Indoles**

Authors: Andrés Arribas, Dr. Martín Calvelo, Alejandro Rey, Prof. Dr. José L. Mascareñas, Dr. Fernando López

Affiliation: Centro Singular de Investigación en Química Biolóxica e Materiais Moleculares (CIQUS) and Departamento de Química Orgánica, Universidade de Santiago de Compostela, 15782 Santiago de Compostela (Spain)

Journal: Angewandte Chemie International Edition

Year: 2023

Volume, pages: 63, e202408258

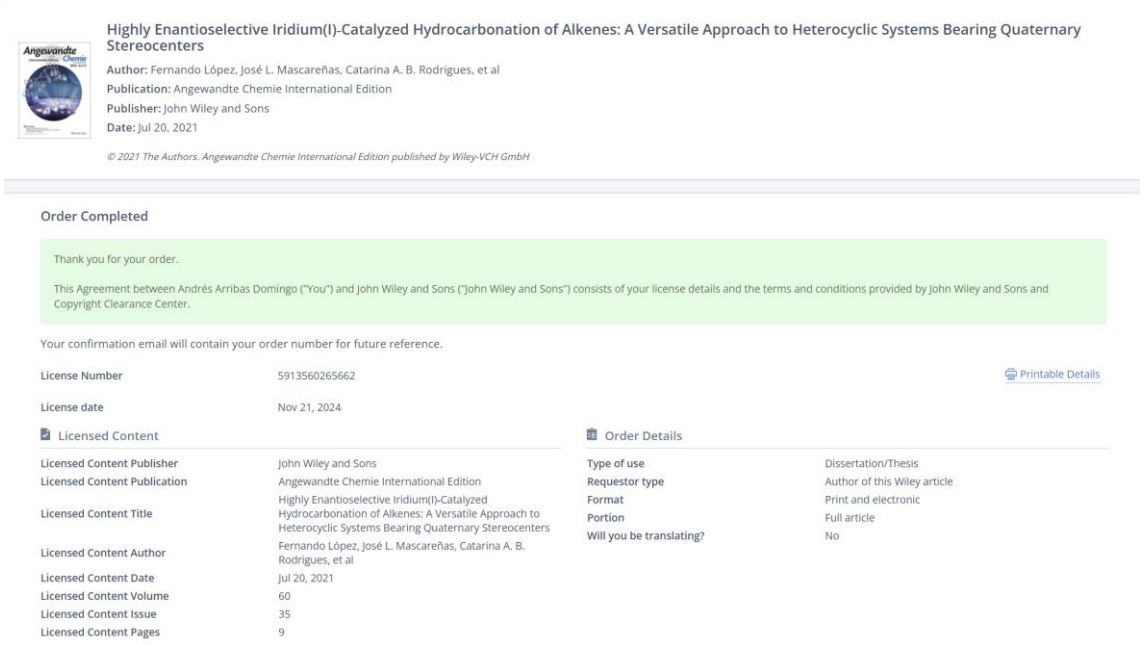
Impact factor: 26.6 (2023)

PhD student contribution: Discovery of the reaction; Synthesis of starting materials; Screening of conditions; Synthesis and characterization of all compounds; Manipulation of the products; Discussion of the results and revision of the manuscript

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Highly Enantioselective Iridium(I)-Catalyzed Hydrocarbonation of Alkenes: A Versatile Approach to Heterocyclic Systems Bearing Quaternary Stereocenters

Author: Fernando López, José L. Mascareñas, Catarina A. B. Rodrigues, et al
Publication: Angewandte Chemie International Edition
Publisher: John Wiley and Sons
Date: Jul 20, 2021

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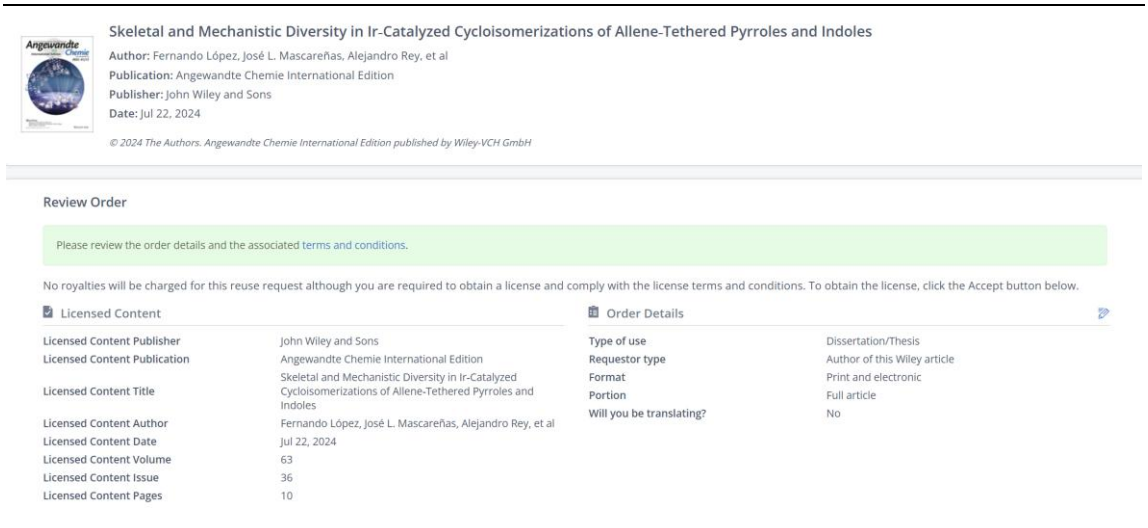
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Skeletal and Mechanistic Diversity in Ir-Catalyzed Cycloisomerizations of Allene-Tethered Pyrroles and Indoles

Author: Fernando López, José L. Mascareñas, Alejandro Rey, et al
Publication: Angewandte Chemie International Edition
Publisher: John Wiley and Sons
Date: Jul 22, 2024

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This PhD thesis descrives our efforts in the development of several Iridium-catalyzed methodologies involving the activation of aromatic and heteroaromatic C-H bonds, and their intramolecular addition across different unsaturated partners like alkenes, allenes and ketones. These transformations allowed us to build polycyclic scaffolds that are present in several natural products and biologically relevant molecules. Additionally, asymmetric versions of most of these transformations have also been developed, achieving the corresponding adducts with very high enantioselectivities.