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Transition Metal Catalyzed Annulations Based On The Activation Of C–H Bonds

David Fernández Fernández

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D. David Fernández Fernández

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Que a presente tese, titulada ***Transition Metal-Catalyzed Annulations Based On The Activation Of C–H Bonds*** correspóndese co traballo realizado por David Fernández Fernández baixo a nosa dirección, nos laboratorios do Centro Singular de Investigación en Química Biolóxica e Materiais Moleculares (CIQUS) de la USC.

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To my parents and sister

To B

"I estonces… estonces, cumpreuse a xusticia:
eu, neles; i as leises, na man que os ferira."

A xustiza pola man
Rosalía de Castro

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Abbreviations and acronyms

In this manuscript, the abbreviations and acronyms wide used in organic and organometallic chemistry have been used following the recommendations found in the on-line *Guidelines for authors* of the *Journal Of Organic Chemistry*.

(https://pubs.acs.org/paragonplus/submission/joceah/joceah_abbreviations.pdf)

Additionally, we have also included the following abbreviations and acronyms.

AcOH	Acetic acid
Ar	Aryl
BDE	Bond dissociation energy
Boc	*tert*-Butyloxycarbonyl
Bu	Butyl
cat	Catalyst / catalytic
CMD	Concerted metalation deprotonation
cod	1,5-cyclooctadiene
Cp*	Pentamethylcyclopentadienyl
CW	Coworkers
Cy	Cyclohexyl
d	Doublet
DCE	1,2-dichloroethane
DCM	Dichloromethane
DFT	Density functional theory
DG	Directing group
DME	Dimethoxyethane
DMF	*N*,*N*-dimethyl formamide
DMSO	Dimethyl sulfoxide
dmpe	1,2-Bis(dimethylphosphino)ethane
dppb	1,4-bis(diphenylphosphino)butane
ee	Enantiomeric excess
equiv.	Equivalent
HOMO	Highest occupied molecular orbital
HRMS	High resolution mass spectroscopy
Ind	Indenyl
IPr	1,3-Bis(2,6-diisopropylphenyl) imidazol-2-ylidene
J	Coupling constant
KIE	Kinetic isotopic effect
L	Ligand
LRMS	Low resolution mass spectroscopy
[M]	Metal complex
M	Molarity
m	Multiplet
Me	Methyl
MPS	Methyl phenyl sulfoximine
NMR	Nuclear magnetic resonance
nOe	Nuclear Overhauser effect
Nu	Nucleophile
o	*ortho*
p-cymene	4-isopropyltoluene
Ph	Phenyl
Pin	Pinacol group
Pr	Propyl
q	Quadruplet
rt	Room temperature

T	Temperature	TM	Transition metal
t	Triplet	TMS	Trimethylsilane
t-AmOH	2-methyl-2-butanol	TS	Transition state

Introduction

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1. Organic Synthesis: Relevance and challenges

Organic synthesis has been defined by Nicolaou as "*the art and science of replicating the molecules of living nature and creating others like them in the laboratory*".[1,2] From the beginning of the history, humans have developed methods to transform matter, with the invention of fire as a cornerstone for the initial application of chemical reactions. After the discovery that matter is made of atoms and molecules, and the crescent understanding of their behaviors, Alchemy became Chemistry. Today we can state that Chemistry is likely the discipline that has contributed most to the evolution of society. Thanks to the ability to understand, transform and make molecules and molecular materials, in the last centuries there have been impressive advances in chemical technologies and in new materials that are key to the wellbeing of modern society.

The twentieth century was clearly the century of chemical synthesis. While initial work before the fifties was more methodological, subsequent efforts were more focused on the synthesis of complex molecules, especially on the total synthesis of natural products (Figure 1). Mental-brilliance together with dedication, persistence and hard work, were the pillars for success. Woodward and Corey, described with the following words the heart and soul of the matter:

"There is excitement, adventure, and challenge, and there can be great art in organic synthesis." R. B. Woodward[3]

"The organic chemist is more than a logician and strategist; he is an explorer strongly influenced to speculate, to imagine, and even to create. These added elements provide the touch of artistry which can be included in a cataloguing of the basic principles of synthesis but are very real and extremely important." E. J. Corey[4]

The relevance of synthesis is not exclusively limited to the preparation of natural products. Frequently, subtle modifications on the core of these natural products, or entirely new designed molecules, can lead to better properties and fascinating novel functions.

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[1] a) K. C. Nicolaou, E. J. Sorensen, *Classics in total synthesis: targets, strategies, methods.* Weinheim New York: VCH, **1996**. b) K. C. Nicolaou, S. A. Snyder, *Classics in total synthesis II: more targets, strategies, methods,* Wiley-VCH, **2003**. b) K. C. Nicolaou, J. S. Chen. *Classics in total synthesis III: further targets, strategies, methods*, Wiley-VCH, **2011**.
[2] K. C. Nicolaou, *Proc. R. Soc. A,* **2014**, *470*, 20130690–20130690.
[3] R. B. Woodward, *Perspectives in Organic Chemistry*, A. R. Todd, Interscience: New York, **1956**, pp 155-184.
[4] E. J. Corey, *Pure & Appl. Chem.,* **1967**, *14*, 19.

The ultimate goal of organic synthesis is to assemble a targeted organic product from readily available starting materials and reagents in the most efficient way. The process starts with the planning of a disconnection strategy, and the proposal of a sequence of reactions. In many cases, the more rapid approach involves transformations that have not been previously described, and hence opportunities arise for the discovery of new methodologies. Despite the huge amount of synthetic methods and reactions discovered by chemists, one can imagine many chemical transformations for which there is not yet a solution. In this context, the discovery of rapid and practical methodologies that allow the assembly of structurally-challenging products from readily accessible starting materials, in a sustainable and efficient manner, is highly demanded.[5]

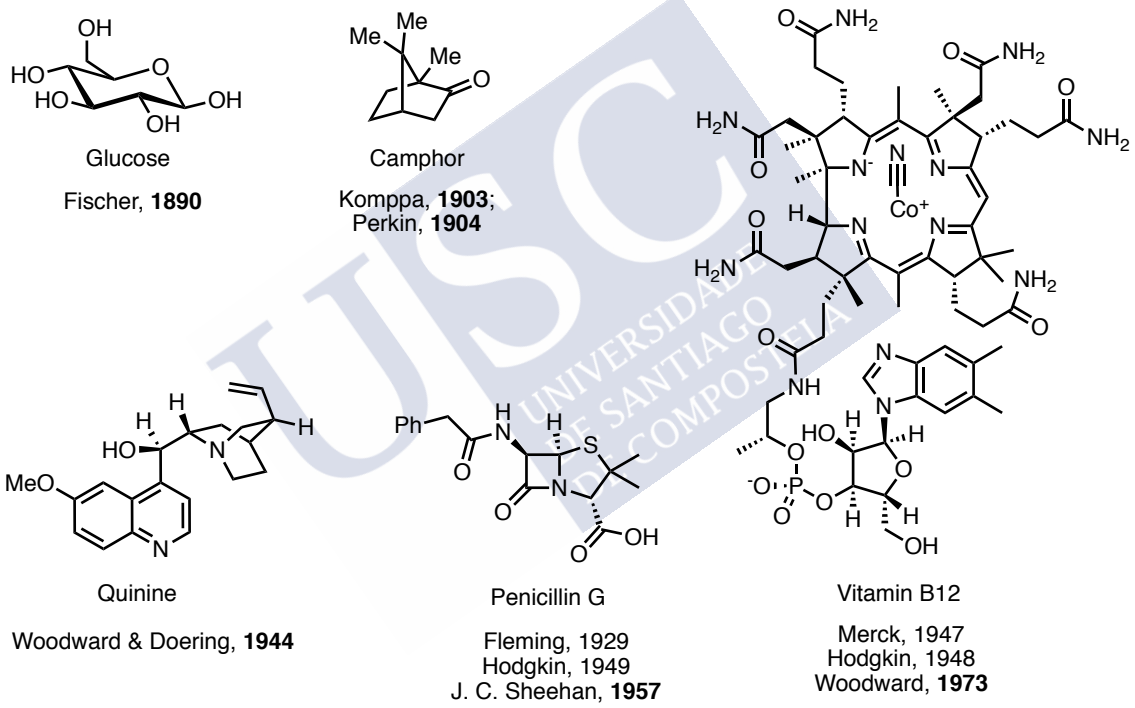


Figure 1. Selected milestone total syntheses achievements in last centuries.

This new perspective of synthesis has led to the establishment of several new concepts: **atom economy**,[6] which refers to the maximization in the atoms of the reactants that are incorporated to the final product; **Step economy**,[7] seeks the minimization of the number of single reactions involved in a synthetic route; **Redox economy**,[8] seeks to reduce non-

[5] A) P. A. Wender, B.L. Miller, *Nature*, **2009**, *460*, 197–201; b) T. Newhouse; P. S. Baran, R. W. Hoffmann, *Chem. Soc. Rev.* **2009**, *38*, 3010–3021.
[6] B. M. Trost, *Science*, **1991**, *254*, 1471–1477.
[7] P. A. Wender, M. P. Croatt, B. Witulski, *Tetrahedron*, **2006**, *62*, 7505–7511.
[8] N. Z. Burns, P. S. Baran, R. W. Hoffmann, *Angew. Chem. Int. Ed.,* **2009**, *48*, 2854–2867

strategic reductive and oxidative steps that lower the efficiency of a synthesis and are difficult to implement in industrial scenarios; **Pot economy,**[9] that relies on the capability to perform several reactions in the minimal amount of *pots* possible, avoiding unnecessary workups and isolation techniques; and **Green chemistry,** [10] whose principles are particularly critical in typical large-scale operations of industries: prevention of waste, atom economy, non-hazardous synthesis, benign chemicals, solvents and auxiliaries, design for energy efficiency, use of renewable feedstocks, reduction of derivatives, catalysis, design for degradation, analysis for pollution prevention and accident prevention.

Taking all of these concepts in consideration, a definition of ideal synthesis could be formulated as *"the production of a target molecule in a single synthetic operation from readily available starting materials, in 100% yield and without side-product formation. The synthesis should be simple, safe, economically acceptable and environmentally friendly."* P. A. Wender[5a]

2. Transition metal catalysis (TMC). A brief historical perspective

Despite the great amount of synthetic methods and reactions discovered by chemists over the last century, organic synthesis still faces many challenges. The need for significant amounts of the targeted molecules (whether natural or not) is one of the forces that constantly drives the discovery and development of new efficient synthetic methodologies that can allow a rapid and versatile access to complex molecular targets from easily accessible starting materials.

In this context, the development of new chemical reactions promoted by catalysts is particularly important.[11] A chemical reaction is accelerated by a catalyst through interaction with the reacting molecules. After the products are generated, the catalyst detaches from the complex, so that it is again available for the next reacting molecules. Therefore, catalysis can be understood as a cyclic event in which the promoter species (the catalyst) participates and is retrieved unchanged at the end of the cycle.[12]

[9] Y. Hayashi, *Chem. Sci.,* **2016**, *7*, 866–880.
[10] 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, et al., *Green Chemistry* **2018**, *20*, 1929–1961.
[11] M. C. Caserio, *J. Chem. Educ.* **1999**, *76*, 901.
[12] I. Chorkendorff, J. W. Niemantsverdriet, *Concepts of Modern Catalysis and Kinetics*, Wiley-VCH Verlag GmbH & Co. KGaA, **2003**.

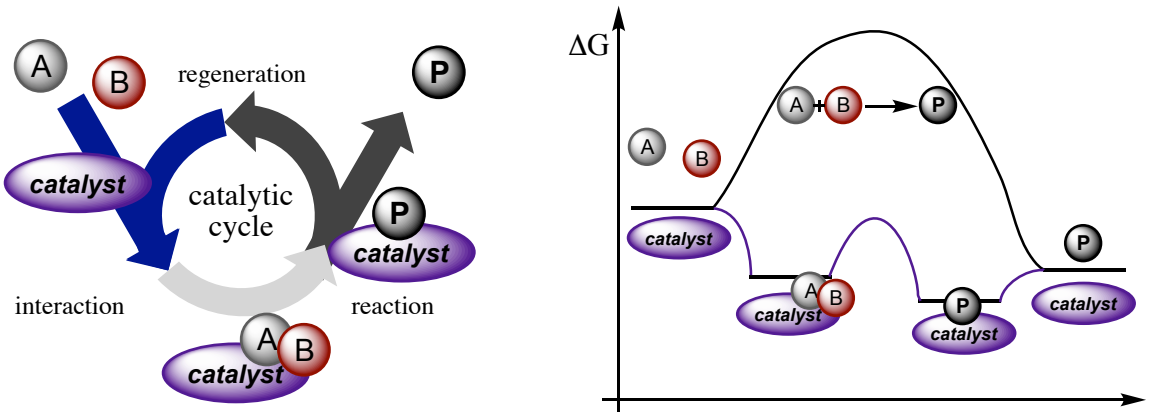


Figure 2. Catalytic cycle of a bimolecular reaction.

Depending on the phase of the reactants and the catalyst, it is possible to distinguish between two types of catalysis: homogeneous and heterogeneous catalysis. In homogeneous catalysis, the catalyst and the reactants are in the same phase, usually liquid. On the other hand, heterogeneous catalysis refers to those processes in which the catalysts and the reagents are in different phase; most of them involving a solid catalyst.

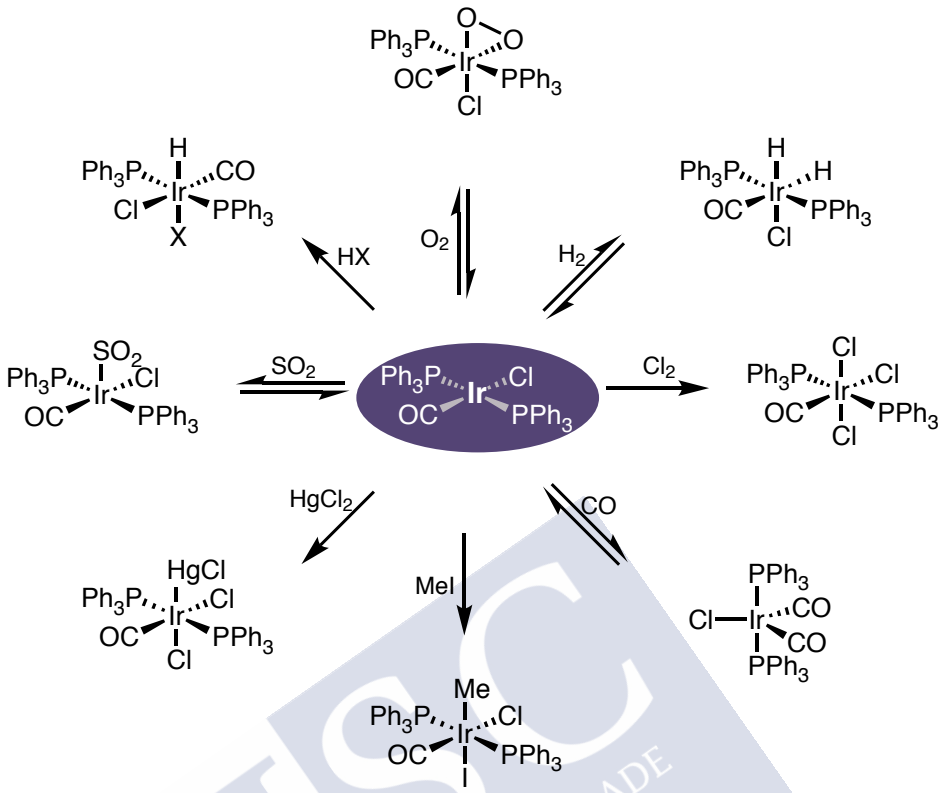
Homogeneous catalysis can be further classified according to the type of catalyst as biocatalysis, organocatalysis (use of non-metal catalysts such as phosphines, amines or *N*-heterocyclic carbenes) and transition metal catalysis. The latter is particularly powerful, not only because of the variety of transition metals with different coordination abilities, but mainly because their reactivity can be tuned by the use of ancillary ligands.

The origins of transition metal catalysis can be traced back to the XIX century, with the discovery of the first π-complex, trichloro(ethene) platinate (II), now known as Zeise's salt. During the twentieth century, their pillars were settled, with essential contributions in the first decades from Grignard, Fischer and Tropsch, Pope, or Ziegler and Natta. Already in the sixties, critical contributions by Vaska (iridium complexes), Wilkinson (rhodium complexes and ferrocenes), Fisher (metal carbenes) and Noyori (chiral copper complexes), paved the way for a myriad of incoming developments in homogeneous organometallic catalysis, including enantioselective processes.

In this regard, the pioneering work of Vaska with the iridium complex $IrCl(CO)(PPh_3)_2$ (commonly named as Vaska's complex) was groundbreaking (Scheme 1).[13] This

[13] a) L. Vaska, J. W. DiLuzio, *J. Am. Chem. Soc.* **1961**, *83*, 2784–2785; b) L. Vaska, *Acc. Chem. Res.* **1968**, *1*, 335–344.

unsaturated 16 electron iridium species was found to activate and promote the reactivity of different species, including oxygen and hydrogen.[14]



Scheme 1. Reactivity of Vaska's complex

All these preliminary works defined the foundations of homogeneous organometallic catalysis and helped to determine the different steps of an organometallic catalytic cycle, such as oxidative additions or reductive eliminations. Moreover, a large number of chemists started to pay attention to the organometallic field, which experimented an exponential expansion.

In this regard, a major breakthrough was the synthesis and characterization of the rhodium complex $RhCl(PPh_3)_3$, by Wilkinson.[15] This complex resulted to be an excellent catalyst for the hydrogenation of triple and double bonds, even at room temperature and with just 1 atmosphere of hydrogen gas.[16] A cornerstone in the success of the Wilkinson catalyst is its selectivity towards alkene C–C unsaturated bonds versus aryl rings, carbonyls, carboxylic

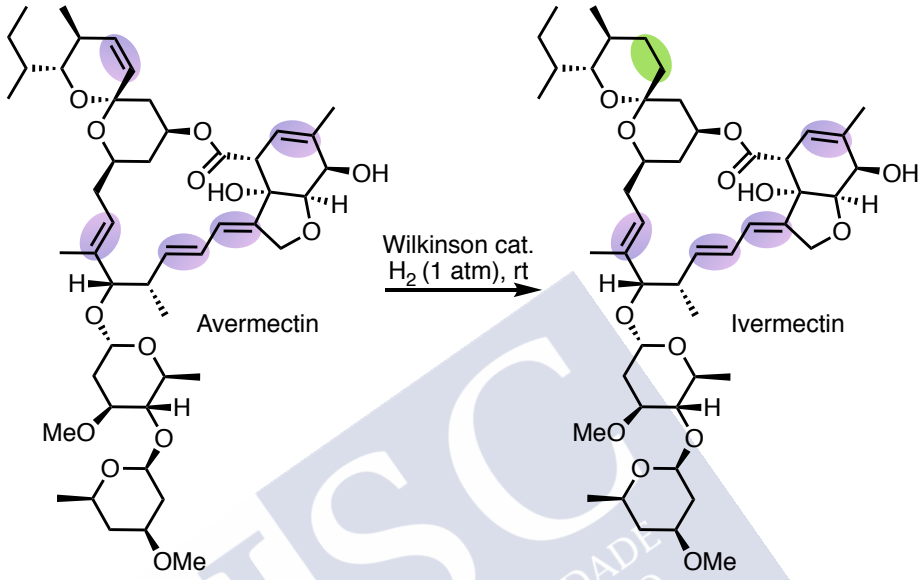
[14] a) L. Vaska, *Science* **1963**, *140*, 809–810; b) S.J. Laplaca, J.A. Ibers, *J. Am. Chem. Soc.*, **1965**, *87*, 2581-2586; c) L. Vaska, J.W. DiLuzio, *J. Am. Chem. Soc.*, **1962**, *84*, 679-680; d) F. DeMartin, N. Mascioccini, *Acta Cryst.*, **1983**, *39*, 1225-1226; e) L. Vaska, *Science*.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

[15] a) J. A. Osborn, G. Wilkinson, J. F. Young, *Chem. Commun.*, **1965**, 17; b) J. F. Young, J. A. Osborn, F. H. Jardine, G. Wilkinson, *Chem. Comm.*, **1965**, 131-132.

[16] a) F. H. Jardine, J. A. Osbron, G. Wilkinson, *J. Chem. Soc.* (A), **1967**, 1574–1578. b) F. H. Jardine, in *Progress in Inorganic Chemistry*, John Wiley & Sons, Inc., **2007**, pp. 63–202.

derivatives, nitro or nitrile groups. A beautiful example of its selectivity can be seen in the synthesis of the Ivermectin (Scheme 2), a drug used against *river blindness* and also active against *Nemathelminthes* and the *Arthropoda*.[17]

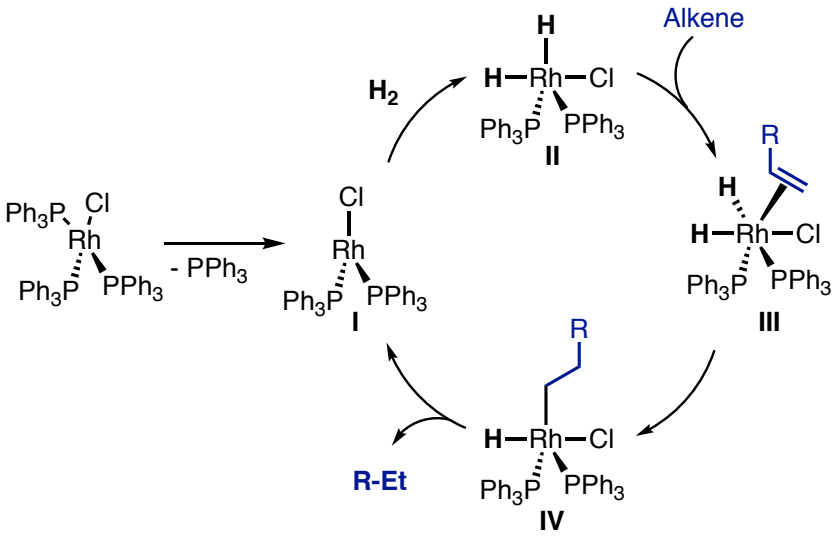
Its precursor, Avermectin, has five double bonds but the Wilkinson catalyst allows a very selective hydrogenation of the less hindered and more reactive cis-alkene (Scheme 2).



Scheme 2. Wilkinson catalyst in the synthesis of complex molecules.

The mechanism of the hydrogenation reaction was originally proposed by Halpern in the eighties (Scheme 3).[18] It starts with replacement of one of the phosphines of the Wilkinson catalyst with a weakly-bounded molecule of solvent, to give a 14 electrons rhodium intermediate (**I**) that can oxidatively insert a molecule of hydrogen and yield a pentacoordinate rhodium III species (**II**), still with a vacant coordination site. Then, an alkene molecule can be added to form an octahedral 18-electron rhodium complex (**III**). The next step is a hydrometalation of this alkene to form an alkyl rhodium complex (**IV**) that delivers the product through a reductive elimination, thus regenerating the catalyst.

[17] W. Campbell, M. Fisher, E. Stapley, G. Albers-Schonberg, T. Jacob, *Science* **1983**, *221*, 823–828.
[18] J. Halpern, *Inorganica Chim. Acta* **1981**, *50*, 11–19.



Scheme 3. Hydrogenation mechanism with Wilkinson catalyst

Besides hydrogenations, the Wilkinson complex was widely used during the last decades for a variety of transformations including decarbonylations,[19] cyclotrimerizations[20] and alkylation reactions,[21] among others.

Overall, the progress derived from the Vaska's and Wilkinson's complexes helped to highlight the potential of organometallic catalysis in synthetic chemistry, not only to improve the efficiency of current methodologies, but also for unveiling new transformations that were not possible by conventional synthetic procedures.

Nowadays, the utility of transition metal catalysis can be exemplified with a myriad of elegant methods.[22] A representative precedent is the Reppe's cyclization of acetylene to cyclooctatetraene, a process that allows to dramatically decrease in the number of steps required to synthesize this challenging small molecule (Scheme 4, A).[23] In other areas such as materials chemistry, the use of transition metal catalysis is also important and, for instance, rhodium catalysts have been used for the assembly of polymeric molecules from its monomers (Scheme 4, B).[24]

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[19] a) T. Matsuda, M. Shigeno, M. Murakami, *Chem. Lett.* **2006**, *35*, 288–289. b) Y. Wang, Y.-C. Luo, H.-B. Zhang, P.-F. Xu, *Org. Biomol. Chem.*, **2012**, *10*, 8211–8215.

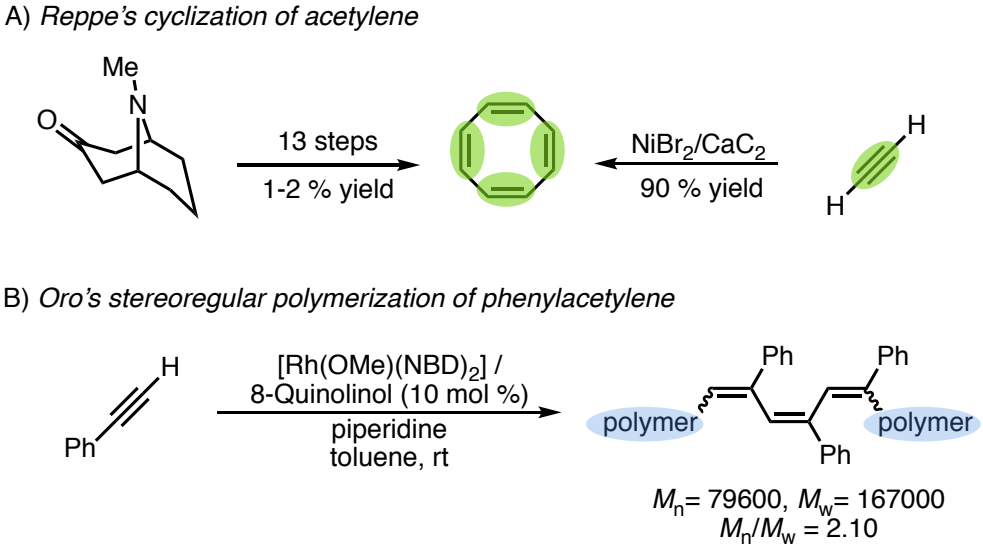
[20] a) S. Kotha, E. Brahmachary, *Tetrahedron Lett.* **1997**, *38*, 3561–3564. b) Q. Sun, X. Zhou, K. Islam, D. J. Kyle, *Tetrahedron Lett.* **2001**, *42*, 6495–6497.

[21] a) Y.-G. Lim, J.-S. Han, B. Koo, J.-B. Kang, *Bull. Korean Chem. Soc.* **1999**, *9,* 1097–1100. b) T. Muraoka, I. Matsuda, K. Itoh, *Tetrahedron Lett.* **1998**, *39*, 7325–7328.

[22] Crabtree, R. *The Organometallic Chemistry of the Transition Metals*, 4th ed. John Wiley & Sons, **2005**.

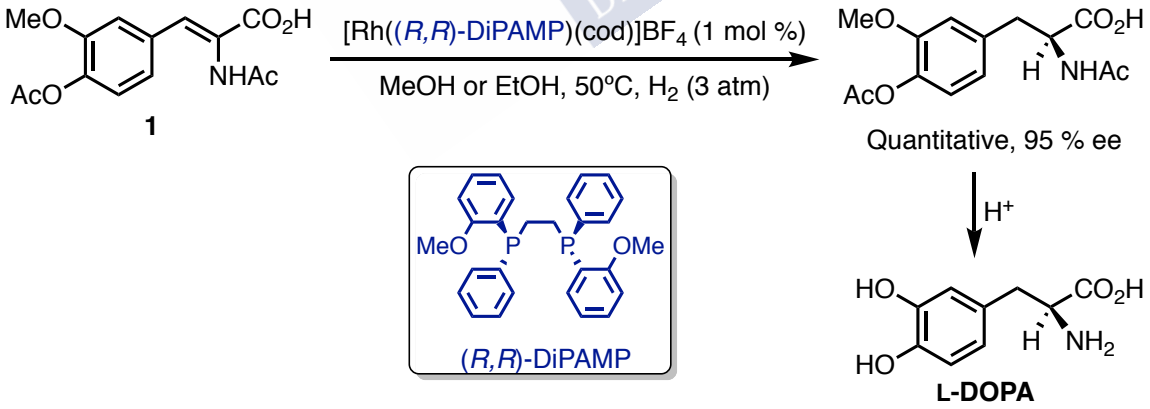
[23] W. Reppe, O. Schlichting, K. Klager, T. Toepel, *Justus Liebigs Ann. Chem.* **1948**, *560*, 1-92.

[24] a) E. A. Jaseer, M. A. Casado, A. A. Al-Saadi, L. A. Oro, *Inorg. Chem. Commun.* **2014**, *40*, 78–81. b) F. Kakiuchi, S. Takano, T. Kochi, *ACS Catal.* **2018**, *8*, 6127–6137. c) R. F. T. Stepto, *Pure Appl. Chem.* **2009**, *81*, 351–353.



Scheme 4. Transition metal-mediated trasformations.

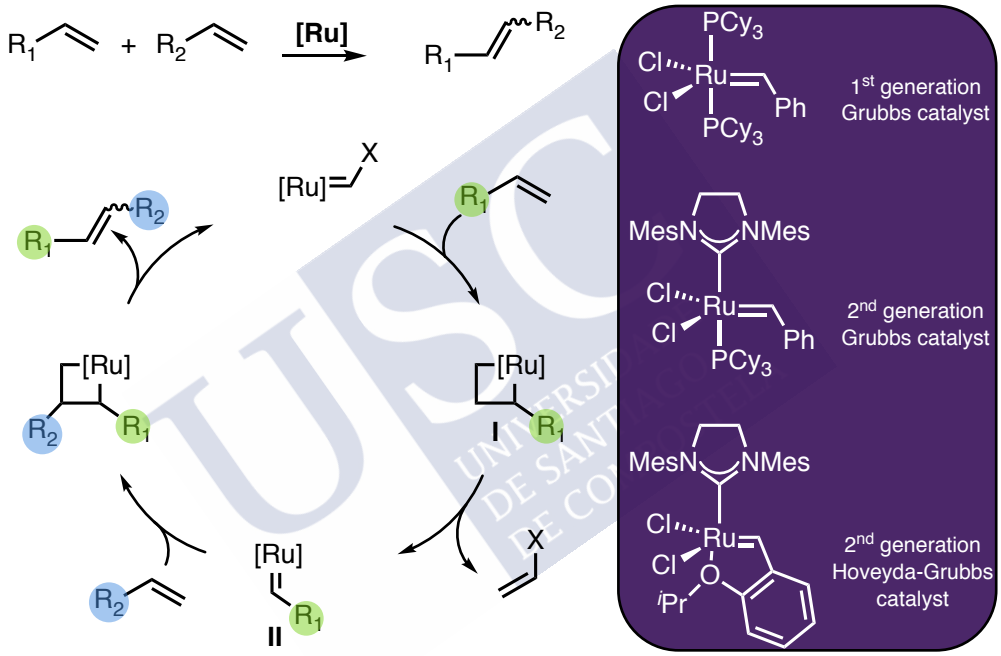
A number of Nobel Prizes have been associated to discoveries in the area of transition metal catalysis. In 2001, Willian S. Knowles, Ryoji Noyori and K. Barry Sharpless shared the prize for the work on asymmetric catalysis mediated by chiral transition metal complexes.[25] An early illustrative example of the synthetic power of asymmetric transition metal catalysis was reported in 1977 by Knowles at Monsanto in the preparation of L-DOPA by means of an enantioselective hydrogenation of the enamide precursor **1** using a chiral bisphosphine rhodium complex (Scheme 5).



Scheme 5. Synthesis of L-DOPA using Rh catalyzed asymmetric hydrogenation

[25] a) W. S. Knowles, *Angew. Chem. Int. Ed.* **2002**, *41*, 1999–2007; b) R. Noyori, *Angew. Chem. Int. Ed.* **2002**, *41*, 2008–2022; c) K. B. Sharpless, *Angew. Chem. Int. Ed.* **2002**, *41*, 2024–2042.

On the other hand, in 2005, Yves Chauvin, Robert H. Grubbs and Richard R. Schrock were also awarded for the development of transition-metal catalyzed metathesis reactions.[26] The mechanism of alkene cross-metathesis is illustrated in scheme 6. The initial step is a (2+2) cycloaddition reaction between an olefin and a transition-metal carbene to give a metallacyclobutane intermediate (**I**). Then, a retro (2+2) cycloaddition takes place to afford an alkene and a new alkylidene (**II**), that can react with another olefin through a (2+2), retro (2+2) process. Molybdenum and particularly ruthenium complexes are the most employed catalysts, and most of them are easy to handle, stable to air and with a remarkable functional group tolerance.[27]



Scheme 6. General mechanism of alkene cross-metathesis and representative catalysts.

One of the major breakthroughs in organometallic catalysis deals with development of palladium mediated cross-coupling reactions. Indeed, Richard Heck, Ei-ichi Negishi and Akira Suzuki received the Nobel prize of chemistry in 2010, for their discoveries in this field. The relevance of these transformations relied on their ability to construct carbon-

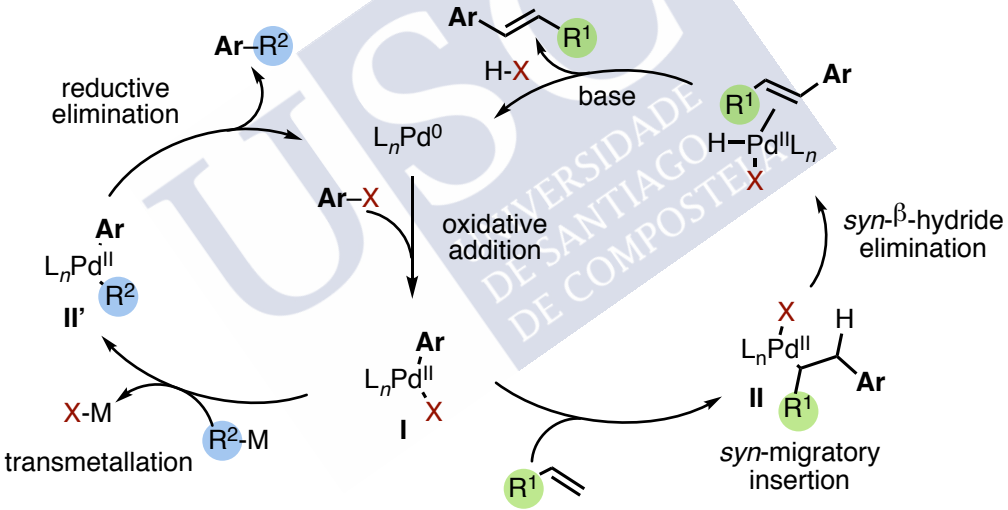
[26] a) P. Jean-Louis Hérisson, Y. Chauvin, *Die Makromolekulare Chem.* **1971**, *141*, 161–176; b) R. H. Grubbs, T. K. Brunck, *J. Am. Chem. Soc.* **1972**, *94*, 2538–2540; c) R. H. Grubbs, P. L. Burk, D. D. Carr, *J. Am. Chem. Soc.* **1975**, *97*, 3265–3267; d) R. R. Schrock, P. Meakin, *J. Am. Chem. Soc.* **1974**, *96*, 5288–5290. For selected reviews see e) G. C. Vougioukalakis, R. H. Grubbs, *Chem. Rev.* **2010**, *110*, 1746–1787; f) R. R. Schrock, *Acc. Chem. Res.* **1990**, *23*, 158–165.

[27] 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. 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.

carbon bonds in a completely novel manner, thus triggering a revolution in academia and industry.

The general mechanistic picture of these Pd-catalyzed cross-coupling reactions is illustrated in scheme 7. These coupling reactions share the oxidative addition step of the aryl halide, or pseudohalide, to the palladium(0) species, which initiates the catalytic cycle. For the Mizoroki-Heck coupling, the reaction proceeds by coordination of the alkene to the Pd-aryl species, followed by its *syn* migratory insertion (**II**). The final step of the process consists of a β-hydride elimination to afford the product. The catalyst is restored due to the base-assisted elimination of the H-X.

In the case of the Negishi, Suzuki–Miyaura, Kumada, Stille and Hiyama cross coupling, transmetallation steps with organometallic species follows the oxidative addition to generate a high valent Pd intermediate (**II'**), bearing the two coupling partners. Successive reductive elimination results in C–C bond formation and regenerates the catalyst (Scheme 7Scheme 7).[28]

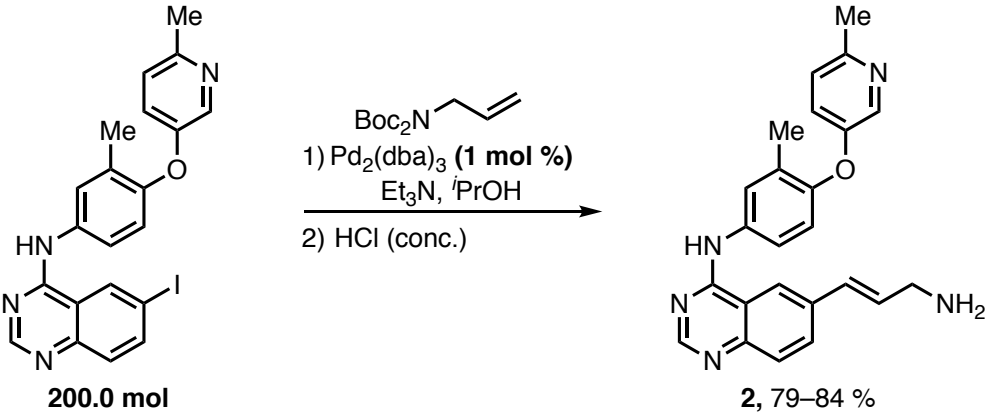


Scheme 7. Palladium-catalyzed cross-coupling mechanisms

Since the late 20th century, these transformations are considered among the most powerful tools to assemble carbon-carbon bonds and have found many applications in the pharma

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

industry. As an illustrative example, a very efficient Heck coupling that was used as key step in the synthesis of the oncology candidate **2** is presented in Scheme 8.[29,30]



Scheme 8. Heck reaction performed at kilogram-scale

3. Transition metal-catalyzed annulations of unsaturated partners

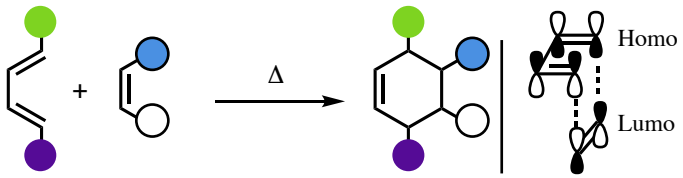
Among the repertoire of transition metal catalyzed transformations that allow a significant increase in molecular complexity, formal cycloadditions and cycloisomerization processes occupy a prominent position, owing to the generation of cyclic products from acyclic precursors.

While cycloaddition reactions allow the construction of cyclic adducts by the simple addition of two or more unsaturated molecules, and involve the formation of at least two new bonds, cycloisomerization reaction conveys the generation of a cyclic structure through a cyclization process and involves a reorganization of some of their unsaturated bonds.[31]

Classical cycloadditions, which do not involve TM catalysis, can be classified as allowed or forbidden by the Woodward-Hoffmann rules, [32] or the frontier molecular orbital theory by Fukui.[33] Those forbidden under thermal conditions may need photochemical activation or radical initiators. The most remarkable cycloaddition is the Diels-Alder (DA) reaction,[34]

[29] D. H. B. Ripin, D. E. Bourassa, T. Brandt, M. J. Castaldi, H. N. Frost, J. Hawkins, P. J. Johnson, S. S. Massett, K. Neumann, J. Phillips, et al., *Org. Process Res. Dev.* **2005**, *9*, 440–450.
[30] C. Capello, U. Fischer, K. Hungerbühler, *Green Chem.* **2007**, *9*, 927.
[31] P. Muller, *Pure Appl. Chem.* **1994**, *66*, 1077–1184.
[32] (a) R. B. Woodward, R. Hoffmann, *J. Am. Chem. Soc.* **1965**, *87*, 395–397. (b) R. B. Woodward, R. Hoffmann, *J. Am. Chem. Soc.* **1965**, *87*, 2046–2048. (c) R. B. Woodward, R. Hoffmann, *J. Am. Chem. Soc.* **1965**, *87*, 2511–2513; d) R. B. Woodward, R. Hoffmann, *Angew. Chem. Int. Ed.,* **1969**, *8*, 781–853.
[33] S. Inagaki, H. Fujimoto, K. Fukui, *J. Am. Chem. Soc.,* **1976**, *98*, 4693–4701.
[34] O. Diels, K. Alder, *Justus Liebig's Ann. Chem.* **1928**, *460*, 98–122.

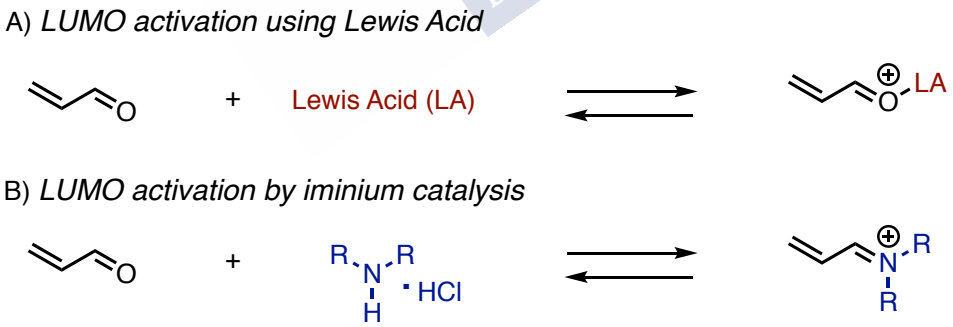
a process wherein a six-membered ring is assembled from a diene and a dienophile, enabling the generation of up to four contiguous stereogenic centers in a single step, in most of the cases with excellent levels of stereoselectivity (Scheme 9Scheme 9).[35]



Scheme 9. Diels-Alder reaction

Despite the versatility of this annulation, in many cases the reaction requires special activating functional groups at the diene and/or dienophile, or the use Lewis acid catalysts, for facilitating an effective HOMO-LUMO interaction of the two reacting partners (Scheme 10, A).[36]

In recent times, organocatalysis and transition metal catalysis have emerged as attractive tools for the development of novel types of formal cycloaddition reactions. With respect to the former, the introduction of MacMillan's imidazolidinone organocatalysts for inducing enantioselective Diels-Alder reactions, meant a revolution in organic synthesis, establishing the concept of LUMO activation by a chiral amine catalyst, commonly named since then as *iminium* catalysis (Scheme 10, B).[37]



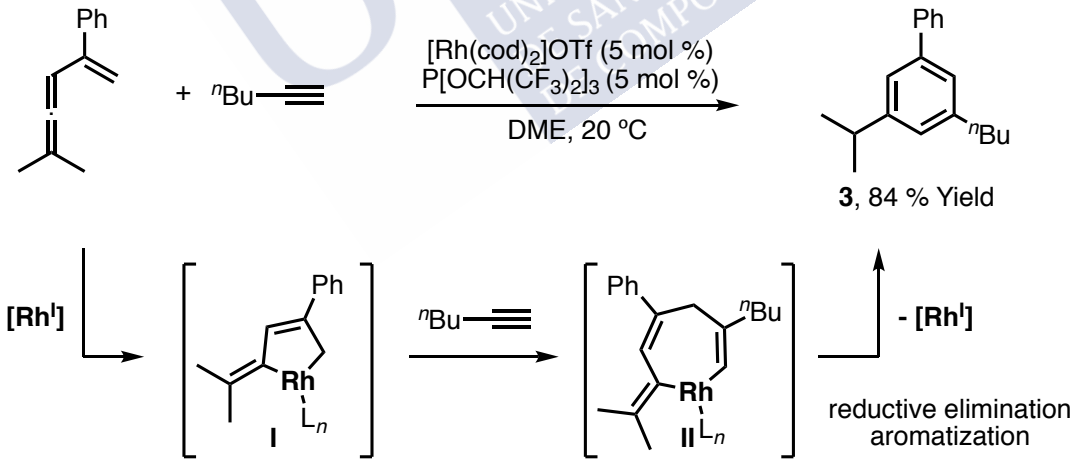
Scheme 10. Activation mechanisms based on decreasing the LUMO energy

[35] a) F. A. Corey, R. J. Sundberg, *"Advanced Organic Chemistry"* fifth edition; b) K. C. Nicolaou, S. A. Snyder, T. Montagnon, G. Vassilikogiannakis, *Angew. Chem. Int. Ed.* **2002**, *41*, 1668–1698. c) I. Coldham, R. Hufton, *Chem. Rev.* **2005**, *105*, 2765–2810.

[36] B. H. Kagan, O. Riant, *Chem. Rev.*, **1992**, *92*, 1007–1019.

[37] a) K. A. Ahrendt, C. J. Borths, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2000**, *122*, 4243–4244; b) A. B. Northrup, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2002**, *124*, 2458–2460; c) R. M. Wilson, W. S. Jen, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2005**, *127*, 11616–11617; d) S. A. Selka¨la¨, A. M. P. Koskinen, *Eur. J. Org. Chem.* **2005**, 1620–1624.

The ability of transition metals to activate C–C unsaturated systems such as olefins, alkynes, allenes or dienes enabled the development of cycloadditions that otherwise require very high temperatures.[38] But even more importantly, transition metal catalysis has also allowed the discovery of novel types of formal cycloadditions.[39] Most of the developed processes use rhodium, iridium, ruthenium, cobalt, nickel, or palladium catalysts. These metals are prone to experiment redox events, often involving metalacyclic intermediates which deliver the product through reductive elimination steps. Volhardt, Wender, Trost, Murakami and many others contributed to this field employing different type of metal complexes.[40] Thus, Murakami's rhodium-catalyzed intermolecular (4+2) cycloaddition reaction between vinylallenes and alkynes could exemplify the potential of the transition metal mediated cycloadditions, as the reaction cannot be achieved under thermal conditions (Scheme 11). The reaction, which operates under very mild conditions using the catalyst resulting from $[Rh(cod)_2]OTf$ and $P[OCH(CF_3)_2]_3$, allows the generation of highly functionalized aromatic rings. The authors suggested a mechanistic pathway involving a five-membered rhodacyclic intermediate (**I**) that subsequently undergoes alkyne insertion to afford the seven-membered intermediate **II**. Successive reductive elimination and isomerization to the more stable aromatic product **3** close the catalytic cycle.



Scheme 11. Rh catalyzed formal [4+2] cycloaddition of non-activated substrates.

[38] A) K. R. Flower, H. Wan, A. Whiting, A. P. Lightfoot, *Chem.Commun.* **2001**, 1812–1813. B) S. Iwasa, A. Fakhruddin, Y. Tsukamoto, M. Kameyama, H. Nishiyama, *Tetrahedron Lett.* **2002**, *43*, 6159–6161. C) C. P. Chow, K. J. Shea, *J. Am. Chem. Soc.* **2005**, *127*, 3678–3679.

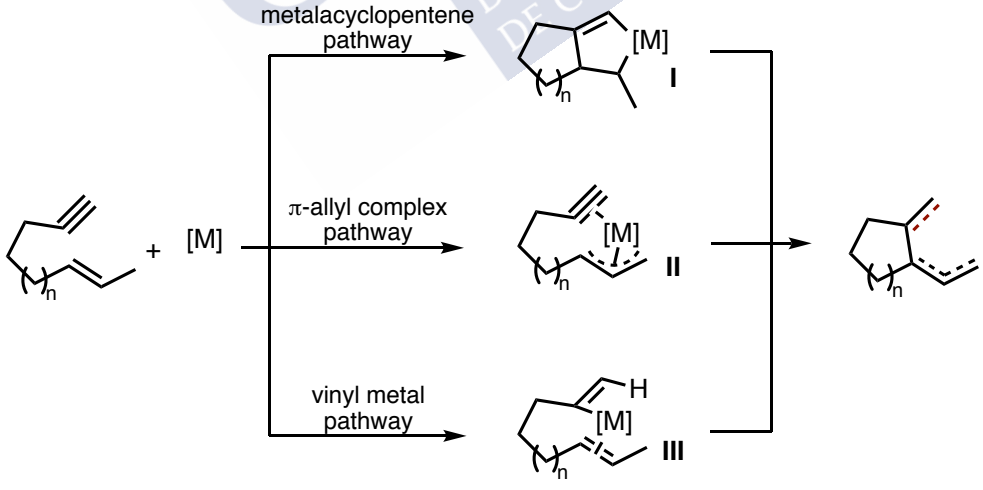
[39] M. Lautens, W. Klute, W. Tam, *Chem. Rev.* **1996**, *96*, 49–92.

[40] A) P. A. Wender, T. E. Jenkins, *J. Am. Chem. Soc.* **1989**, *111*, 6432–6434. B) P. A. Wender, J. P. Christy, *J. Am. Chem. Soc.* **2006**, *128*, 5354–5355. C) J. Montgomery, E. Oblinger, A. V. Savchenko, *J. Am. Chem. Soc.* **1997**, *119*, 4911-4920. D) M. Murakami, H. Amii, K. Itami, Y. Ito, *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 1476–1477. E) M. Murakami, K. Itami, Y. Ito, *Angew. Chem. Int. Ed. Engl.* **1996**, *34*, 2691–2694.

The most widely-known cycloisomerization reaction is the Alder-ene reaction, a process that usually requires high temperatures and its application to complex-molecule synthesis is rather limited.[41]

Trost pioneering work on the palladium-catalyzed cycloisomerization of 1,6-enynes to 1,3- or 1,4-dienes, developed in 1985, set the basis for the development of novel types of mild cycloisomerization reactions.[42] Indeed, cycloisomerization processes have become very powerful synthetic tools and found applications in the production of many clinically relevant molecules.[43]

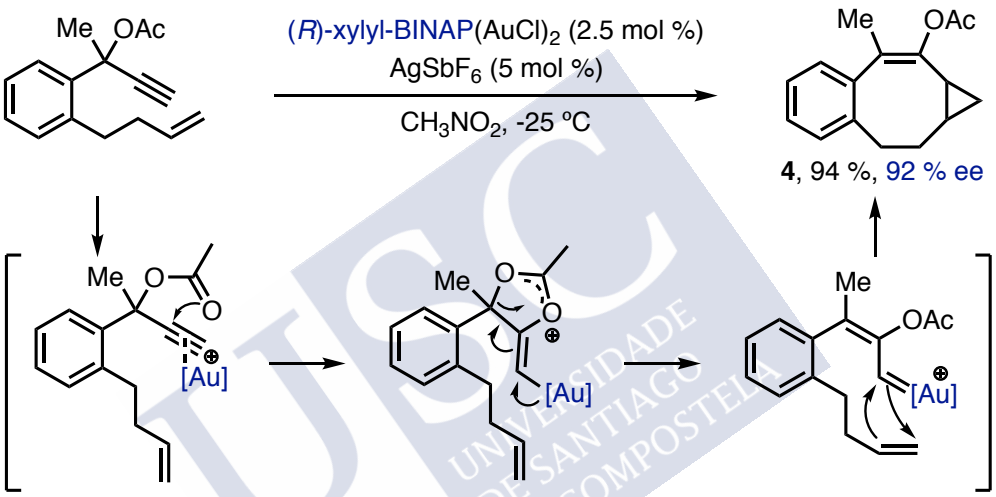
With regard to the cycloisomerization of 1, *n*-enynes, a topic relevant in the context of this PhD thesis, it is commonly accepted that the reaction may proceed through three different mechanistic pathways. In a very simplified manner, and depending on which unsaturated position is reacting first, it is possible to distinguish between a **metalacycloalkene pathway**, wherein both unsaturations are oxidatively coupled to give metalacyclic intermediates (**I**, Scheme 12, top); a **π-allyl complex pathway**, which relies on initial allylic activation processes to give intermediates of type **II**, favored by specific substituents at the allylic position (Scheme 12, middle); and a **vinyl metal pathway**, which is the result of a hydrometallation of the alkyne moiety to yield an intermediate of type **III** that subsequently undergoes carbometalation of the double bond (Scheme 12, bottom).



Scheme 12. Mechanistic pathways in enyne cycloisomerization

[41] K. Alder, F. Pascher, A. Schmitz, *Ber. Dtsch. Chem. Ges. B*, **1943**, *76*, 27–53.
[42] B. M. Trost, M. Lautens, *J. Am. Chem. Soc.*, **1985**, *107*, 1781–1783
[43] C. I. Stathakis, P. L. Gkizis, A. L. Zografos, *Nat. Prod. Rep.* **2016**, *33*, 1093–1117.

Besides these processes, which generally can be promoted using palladium, nickel, rhodium or ruthenium catalysts, alternative cycloisomerizations relying on other mechanistic pathways have also been developed in recent years. On one hand, cycloisomerizations governed by electrophilic gold (I) and platinum (II) metal complexes, which are able to selectively activate alkynes in the presence of alkenes, have emerged as powerful tools to promote cycloisomerizations conveying complex skeletal rearrangements.[44] As a representative case, Toste reported in 2009 an asymmetric cycloisomerization cascade which involves the generation of a gold carbene species which reacts with the pendant alkene to give the cyclopropanated product **4** (Scheme 13) .[45]



Scheme 13. Gold-catalyzed cascade cycloisomerization

In recent years, with the advent of a number of methods to activate relatively inert **carbon-hydrogen bonds** by transition metal catalysts, a number of cycloisomerization and formal cycloaddition involving such C–H activations have been developed. Before detailing some examples, we present in the next sections some precedents on C–H functionalization processes.

[44] M. García-Mota, N. Cabello, F. Maseras, A. M. Echavarren, J. Pérez-Ramírez, N. Lopez, *ChemPhysChem* **2008**, *9*, 1624–1629.

[45] a) I. D. G. Watson, S. Ritter, F. D. Toste, *J. Am. Chem. Soc.* **2009**, *131*, 2056–2057; b) S. G. Sethofer, T. Mayer, F. D. Toste, *J. Am. Chem. Soc.* **2010**, *132*, 8276–8277; c) I. D. G. Watson, F. D. Toste, *Chem. Sci.* **2012**, 3, 2899–2920.

4. C–H Functionalizations based on the transition metal catalysis

As indicated in the previous chapters, most TM-catalyzed reactions so far described involve unsaturated partners and/or precursors with specific functional groups, as it is the case in Suzuki-Miyaura or similar cross-coupling reactions. Recently, C–H activation has emerged as bright approach to functionalize simple carbon-hydrogen bonds.

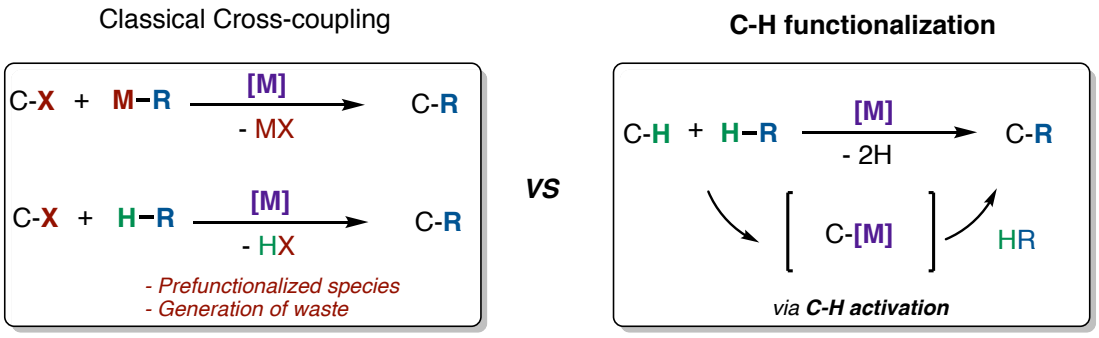
The omnipresence of C–H bonds in organic molecules suggests that discovering TM-mediated methods for their selective activation can open innumerable possibilities for regioselective functionalizations. [46] The catalytic functionalization of inert C–H bonds emerged as the *ideal strategy* to manipulate organic compounds, because it avoids the need to pre-install halogens or other functional groups, which are usually required in many processes, such as in Heck or Suzuki cross-couplings. In this more atom-economic strategy, the key organometallic intermediates are generated though a suitable play of the metal-ligand complex with the substrate which allows the cleavage of the C–H bond and formation of a metalated derivative (Scheme 14, right).

Regardless the of the type transformation, transition metal catalyzed (TMC) C–H activations face numerous challenges. The bond dissociation energy (BDE) already sheds some light into the strength of a typical C–H bond: the BDE of a C–H bond, strong and weakly polarized, is much higher than that of C-X bond (the bond dissociation energy of benzene (Csp^2-H) is 472.2 $\pm$ 2.2 kJ mol^{-1} while the corresponding for the iodobenzene (Csp^2-I) is 272.0 $\pm$ 4.2 kJ mol^{-1}).[47] Most of the TMC C–H functionalization reports deal with the activation of C(sp^2)–H s of aryl rings, while the cleavage of C(sp^3)–H bonds being much more difficult.

On the other hand, the above-mentioned ubiquity of carbon-hydrogen bonds demands highly regioselective approaches, to avoid undesired side pathways.

[46] a) A. E. Shilov, G. B. Shul'pin, *Chem. Rev.* **1997**, *97*, 2879–2932; b) R. G. Bergman, *Nature* **2007**, *446*, 391–393; c) J. F. Hartwig, *J. Am. Chem. Soc.* **2015**, *138*, 2–24.

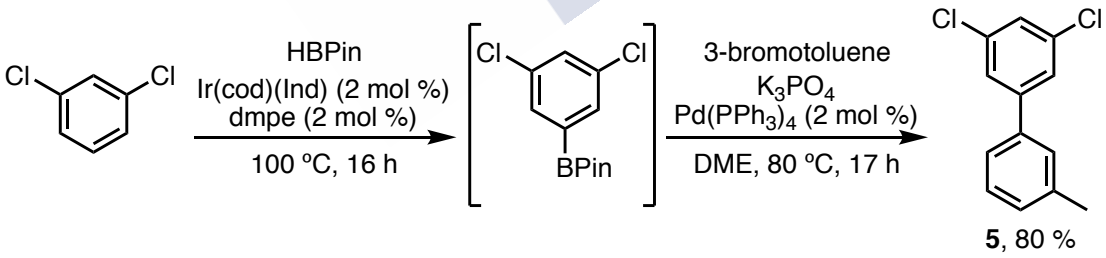
[47] Y. R. Luo, *Comprehensive Handbook of Chemical Bond Energies*, CRC Press, Boca Raton, FL, **2007**



Scheme 14. C-H functionalization vs Classical Cross-coupling methodologies

During the last decades, the number of C–H activation reactions promoted by transition metal catalysis have grown exponentially.[48] In most of the cases, the metal-mediated C–H activation has been linked to a functionalization processes, for instance the introduction of halogens, boron species or oxygen containing functional groups.

For instance, Hartwig [49] and Maleczka [50] research groups have developed pioneering iridium-catalyzed C–H borylations of aromatic compounds based on the selective activation of one of the C–H bonds of the aromatic system. Overall, the process represents a very practical C–H borylation which can be coupled in a one pot process with a Pd-catalyzed *cross-coupling* as shown in scheme 15. The remarkable selectivity of the iridium-catalyzed borylation towards the *meta* position allowed the selective formation of the biaryl product **5**, with a notable yield.



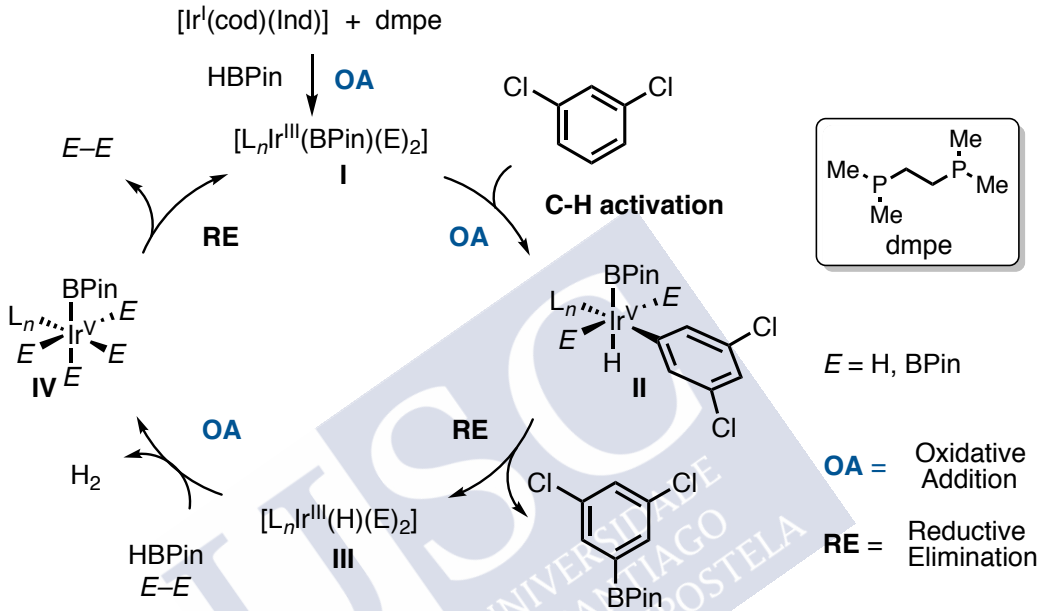
Scheme 15. One-pot C-H borylation and cross-coupling reaction.

[48] P. H. Dixneuf, H. Doucet, *C-H Bond Activation and Catalytic Functionalization I*, Springer Int. Publishing, **2016**.

[49] a) H. Chen, S. Schlecht, T. C. Semple, J. F. Hartwig, *Science* **2000**, *287*, 1995–1997; b) T. Ishiyama, Y. Nobuta, J. F. Hartwig, N. Miyaura, *Chem. Commun.* **2003**, 2924–2925; c) T. M. Boller, J. M. Murphy, M. Hapke, T. Ishiyama, N. Miyaura, J. F. Hartwig, *J. Am. Chem. Soc.* **2005**, *127*, 14263–14278.

[50] a) J.-Y. Cho, M. K. Tse, D. Holmes, R. E. Maleczka Jr., M. R. Smith III, *Science* **2001**, *295*, 305–308; b) P. C. Roosen, V. A. Kallepalli, B. Chattopadhyay, D. A. Singleton, R. E. Maleczka Jr., M. R. Smith III, *J. Am. Chem. Soc.* **2012**, *134*, 11350–11353; c) S. M. Preshlock, B. Ghaffari, P. E. Maligres, S. W. Krska, R. E. Maleczka Jr., M. R. Smith III, *J. Am. Chem. Soc.* **2013**, *135*, 7572–7582.

Regarding the mechanism, the iridium complex formed from [Ir(cod)(Ind)] and dmpe undergoes an oxidative addition of HBpin leading to an Ir(III) intermediate **I** that also undergoes an oxidative addition of the arene C_{sp^2}–H bond to form a new Ir^V species (**II**) . This intermediate, can easily experience a reductive elimination to yield the borylated product. The iridium (III) complex resulting from the reductive elimination suffers an oxidative addition of H–BPin and a subsequent reductive elimination of H_2 to regenerate the catalyst (Scheme 16).

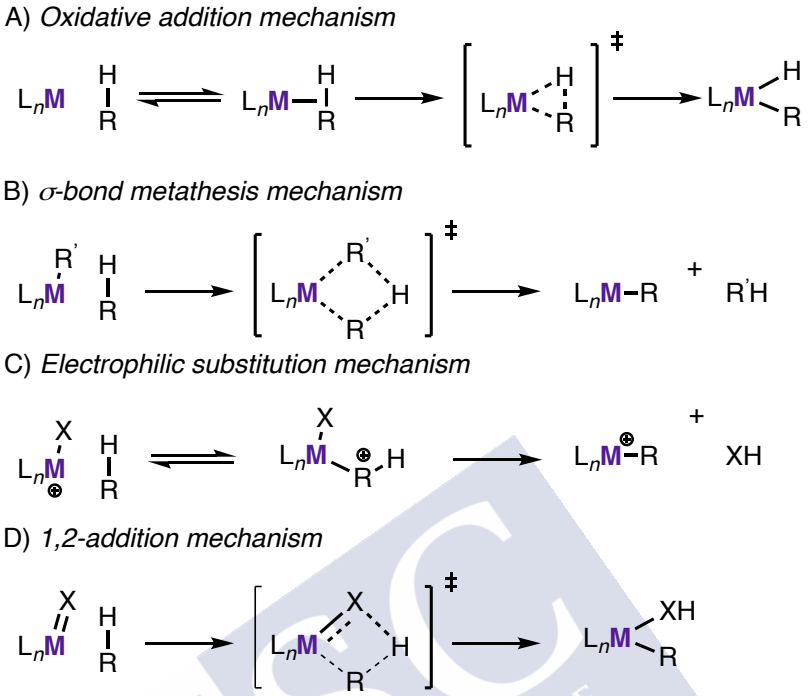


Scheme 16. Mechanistic proposal for the borylation involving an Iridium-mediated C-H activation

Importantly, the activation/functionalization of C–H bonds using transition metal catalysis is not limited to the formation of carbon-heteroatom bonds but can also be used to make C–C bonds. Therefore, it is possible to perform formal C–C *cross-coupling* reactions, like in the examples that will be described below.

The previous C–H activation mechanism involves an **oxidative addition**, with the metal complex inserting into the C–H bond leading to C-[M]-H species. This is typical of electron-rich, low-valent complexes of the late transition metals (ruthenium, osmium, rhodium, iridium, platinum), which are oxidized in the process. A change in the coordination geometry of the metal complex is mandatory, in order to accommodate two new bonds.

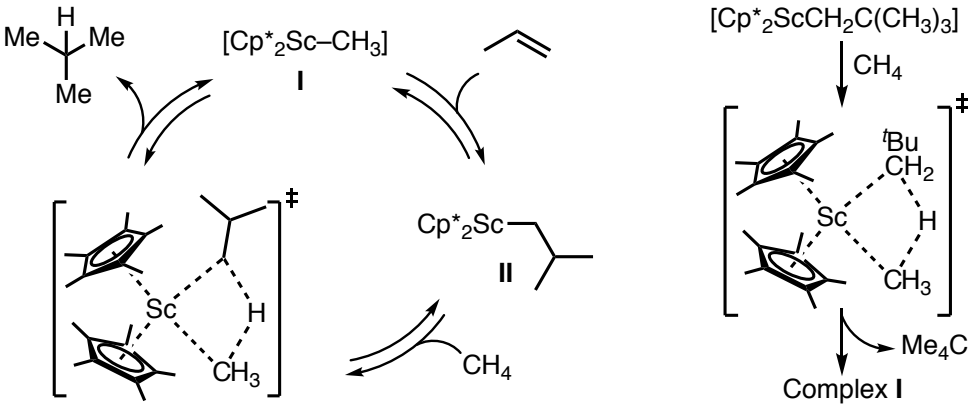
In addition to this oxidative insertion process (Scheme 17, A), the activation of "inert" C–H bonds can be accomplished through alternative mechanisms (Scheme 17, B-D).[51]



Scheme 17. General mechanistic pathways in C-H activation

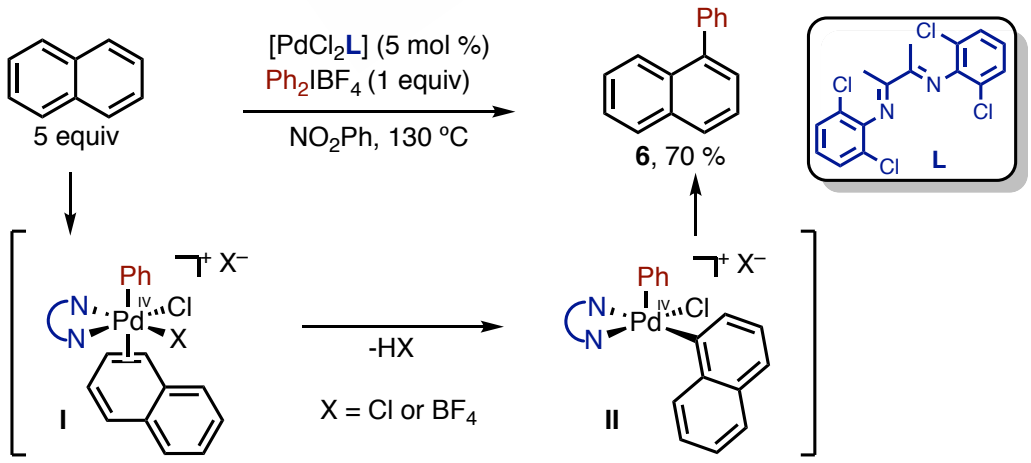
The **σ-bond metathesis** mechanism relies on a concerted exchange of a sigma bond between the metal and the ligand with one carbon-hydrogen bond of the substrate, in a formal [2σ + 2σ] cycloaddition.[52] As an example, the group of Tilley reported a hydromethylation of propene catalyzed by a scandium catalyst.[53] The mechanism was determined to involve the formation of the complex **I** via sigma bond metathesis between methane and the precursor [$Cp^*_2ScCH_2C(CH_3)_3$]. Then, the alkene inserts into the Sc–C bond and the resulting complex (**II**) suffers another σ-bond metathesis with methane to regenerate **I** and isobutane as product (Scheme 18).

[51] a) X. Qi, Y. Li, R. Bai, Y. Lan, *Acc. Chem. Res.* **2017**, *50*, 2799–2808; b) J. A. Labinger, J. E. Bercaw, *Nature* **2002**, *417*, 507–514; c) D. Lapointe, K. Fagnou, *Chem. Lett.* **2010**, *39*, 1118–1126; d) D. Balcells, E. Clot, O. Eisenstein, *Chem. Rev.* **2010**, *110*, 749–823.
[52] R. Waterman, *Organometallics* **2013**, *32*, 7249–7263.
[53] A. D. Sadow, T. D. Tilley, *J. Am. Chem. Soc.* **2003**, *125*, 7971–7977.



Scheme 18. Mechanism for the Hydromethylation of Alkenes and C-H activation via σ-bond metathesis

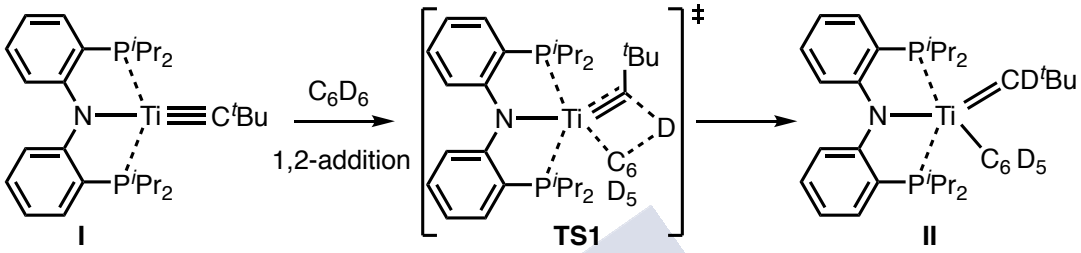
An **electrophilic substitution** mechanism is plausible for late or post transition metals in higher oxidation states. In this pathway, the nucleophilic C–H of an aromatic compound *attacks* the transition metal producing a delocalized cationic species, a sort of Wheeland intermediate, that is able to rearomatize creating the metalated species. For instance, the palladium-catalyzed naphthalene arylation developed by Sanford and Hickman is presented in scheme 19.[54] After the oxidative addition of the iodonium species into the palladium catalyst, the naphthalene coordinates to yield the intermediate **I**. Subsequent C–H activation and reductive elimination steps generate the 1-substituted naphthalene derivative **6**. The authors proposed an electrophilic substitution mechanism based on the KIE value of 1.0 ± 0.1. This value, significantly smaller than typical Pd^{II}-catalyzed C–H arylations, suggest that the C–H bond cleavage is not involved in the rate-determining step of the cycle.



Scheme 19. Electrophilic substitution proposal for the Sanford naphthalene arylation.

[54] A. J. Hick man, M. S. Sanford, *ACS Catal.* **2011**, *1*, 170–174.

Finally, alkylidene or alkylidyne complexes can activate C–H bonds by facilitating the transference of the hydrogen to the carbene, likely through a concerted process (Scheme 20). An example of this mechanism was reported by Mindiola and coworkers.[55] Combined experimental and theoretical studies confirmed that the initial alkynylidene complex **I** undergoes the 1, 2-addition of C-D bond of d^6-benzene, through the transition state **TS1**, leading to the alkylidene titanium complex **II**.



Scheme 20. 1,2-addition key step in the Intramolecular C-H Bond Activation by a Titanium Alkylidene

Besides these main mechanisms, it is possible to describe another, highly relevant alternative related to the abovementioned electrophilic substitution, that is named as concerted metalation-deprotonation process (CMD), although some authors have referred to this mechanism with other names, such as internal electrophilic substitution (IES)[56] or ambiphilic metal-ligand activation (AMLA)[57]. It could be defined as a process in which an anionic ligand of the metal, generally a carboxylate, withdraws the hydrogen atom of the C–H bond, while the corresponding carbon-metal bond is simultaneously formed in a cyclic transition state (Scheme 21).

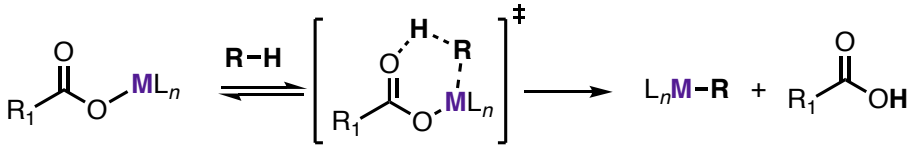
It was proposed to rationalize several experimental data that electrophilic substitution cannot entirely explain. Fagnou contributed to this field extensively, being one of the main architects of this new concept in C–H bond activation catalysis.[58]

[55] 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.

[56] J. Oxgaard, W. J. Tenn, R. J. Nielsen, R. A. Periana, W. A. Goddard, *Organometallics* **2007**, *26*, 1565–1567.

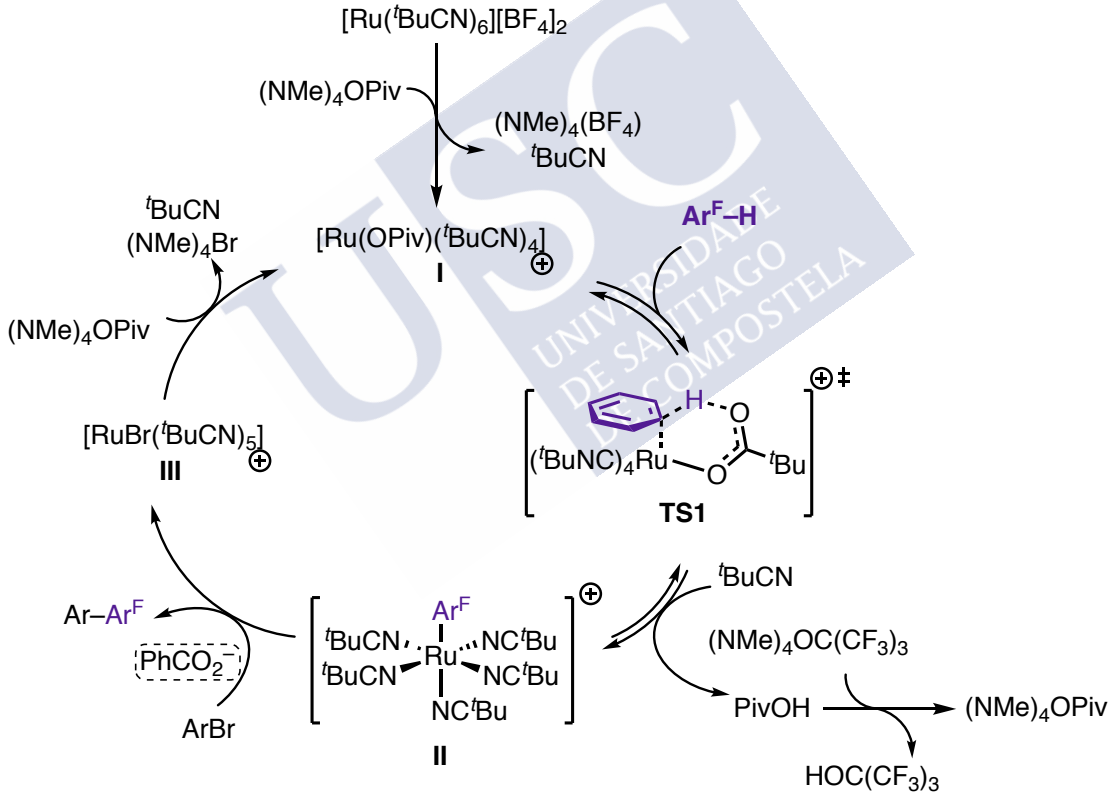
[57] Y. Boutadla, D. L. Davies, S. A. Macgregor, A. I. Poblador-Bahamonde, *Dalton Trans.* **2009**, 5820–5831.

[58] a) M. Lafrance, C. N. Rowley, T. K. Woo, K. Fagnou, *J. Am. Chem. Soc.* **2006**, *128*, 8754–8756; b) M. Lafrance, S. I. Gorelsky, K. Fagnou, *J. Am. Chem. Soc.* **2007**, *129*, 14570–14571; c) S. I. Gorelsky, D. Lapointe, K. Fagnou, *J. Am. Chem. Soc.* **2008**, *130*, 10848–10849



Scheme 21. General mechanism of the CMD

As a recent example, this type of mechanism has been suggested to be involved in the ruthenium catalyzed arylation of fluoroarenes with arylhalides.[59] Based on experimental and DFT calculations, Larrosa and coworkers have proposed the initial formation of the active catalyst **I** that undergoes a concerted metalation-deprotonation process (**TS1**) to yield the arylruthenium complex **II**. A subsequent oxidative addition of the bromoarene and reductive elimination step leads to the complex **III**, that can easily regenerate the catalyst **I** by a halide to pivalate ligand exchange (Scheme 22).



Scheme 22. Mechanistic proposal to explain the Ru-catalyzed arylation of fluoroarenes

While in the above example the C–H activation could be easily achieved owing to the intrinsic activated nature of the perfluorinated substrate, in most of the cases performing regioselective C–H activations require the presence of a directing group. Designing metal-

[59] M. Simonetti, G. J. P. Perry, X. C. Cambeiro, F. Juliá-Hernández, J. N. Arokianathar, I. Larrosa, *J. Am. Chem. Soc.* **2016**, *138*, 3596–3606.

chelating directing groups solves regioselectivity issues, bringing the metal in close proximity to the carbon-hydrogen bond to be activated.[60] This tactic not only improves selectivity, but also lowers the entropic barrier of the C–H activation and accelerates the process. A diversity of heteroatom-based directing groups, with different properties such as coordinating strength or denticity, have been successfully developed for this purpose (Figure 3).[61]

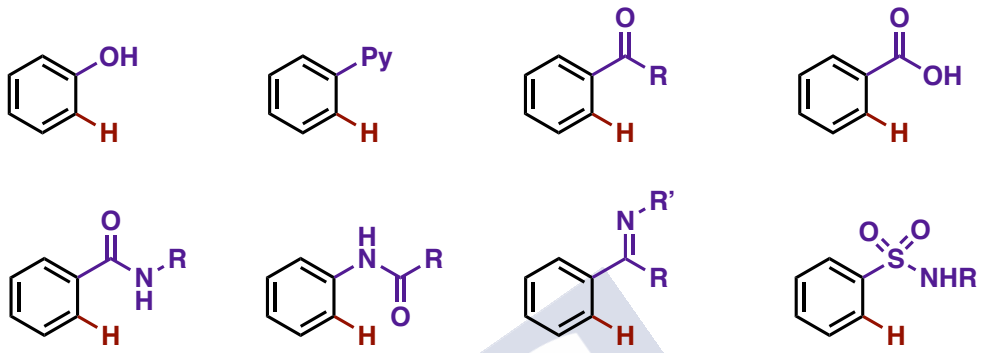


Figure 3. Representative monodentate directing groups for *ortho* C-H activation.

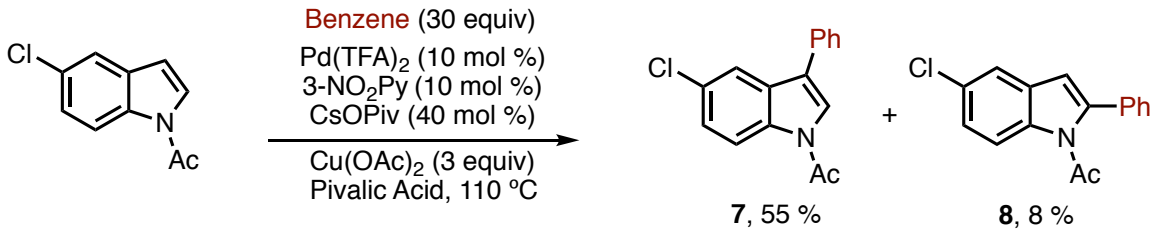
The choice of the directing group usually obeys to different aspects: the nature of the transformation that is carried out, the precise transition metal used for the reaction, the kind of C–H bond to be activated, and the potential mechanism involved in the process. Moreover, the opportunity to select an appropriate directing group also allows additional modulation of the reactivity of the metal center, in a similar way as ancillary ligands do.

In some cases, the method does not require the use of directing groups, as the electronics of the system warrants a selective C-H insertion of the metal complex. This is the case of the work described by Fagnou in 2007,[62] consisting of a Pd-catalyzed cross coupling between indole precursors and simple arenes. The catalytic optimal conditions were achieved by using $Pd(TFA)_2$, 3-nitropyridine, cesium pivalate and copper acetate as oxidant. The pyridine additive might stabilize the palladium (0) species generated in the reaction, preventing the formation of palladium black. The methodology is regioselective, preferentially giving the 3-substituted indole derivatives like **7** (Scheme 23).

[60] a) K. M. Engle, T.-S. Mei, M. Wasa, J.-Q. Yu, *Acc. Chem. Res.* **2011**, 45, 788–802; b) Z. Chen, B. Wang, J. Zhang, W. Yu, Z. Liu, Y. Zhang, *Org. Chem. Front.* **2015**, *2*, 1107–1295; c) R. K. Rit, M. R. Yadav, K. Ghosh, A. K. Sahoo, *Tetrahedron* **2015**, *71*, 4450–4459.

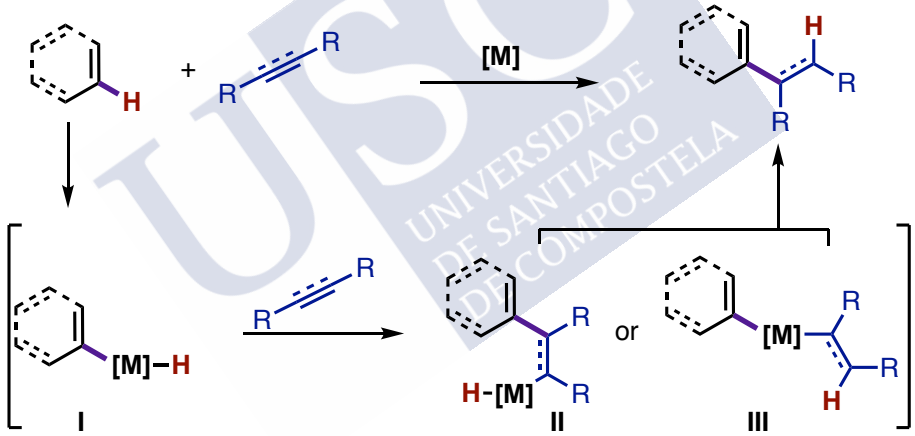
[61] C. Sambiagio, D. Schönbauer, R. Blieck, T. Dao-Huy, G. Pototschnig, P. Schaaf, T. Wiesinger, M. F. Zia, J. Wencel-Delord, T. Besset, et al., *Chem. Soc. Rev.* **2018**, *47*, 6603–6743.

[62] D. R. Stuart, K. Fagnou, *Science* **2007**, *316*, 1172–1175.



Scheme 23. C−C cross-coupling reactions by C−H bond functionalization described by Fagnou.

A particularly appealing way of making C–C carbon bonds using C–H activation processes consists of the hydrocarbonation of unsaturated partners, as they usually involve a total atom economy. The general mechanism is illustrated in scheme 24. First the C–H bond is activated by oxidative addition of the metal catalyst to generate an intermediate **I**. Subsequently insertion of the unsaturated partner leads to the formation of intermediates **II** or **III**, by a carbometallation or hydrometallation pathway, respectively. Finally, a reductive elimination of these intermediates regenerates the catalyst and yields the product.



Scheme 24. General mechanism of TM-mediated hydrocarbonation reactions

This type of transformation forms the basis of chapters 1 and 2 of this thesis, and therefore in the next section we describe further details.

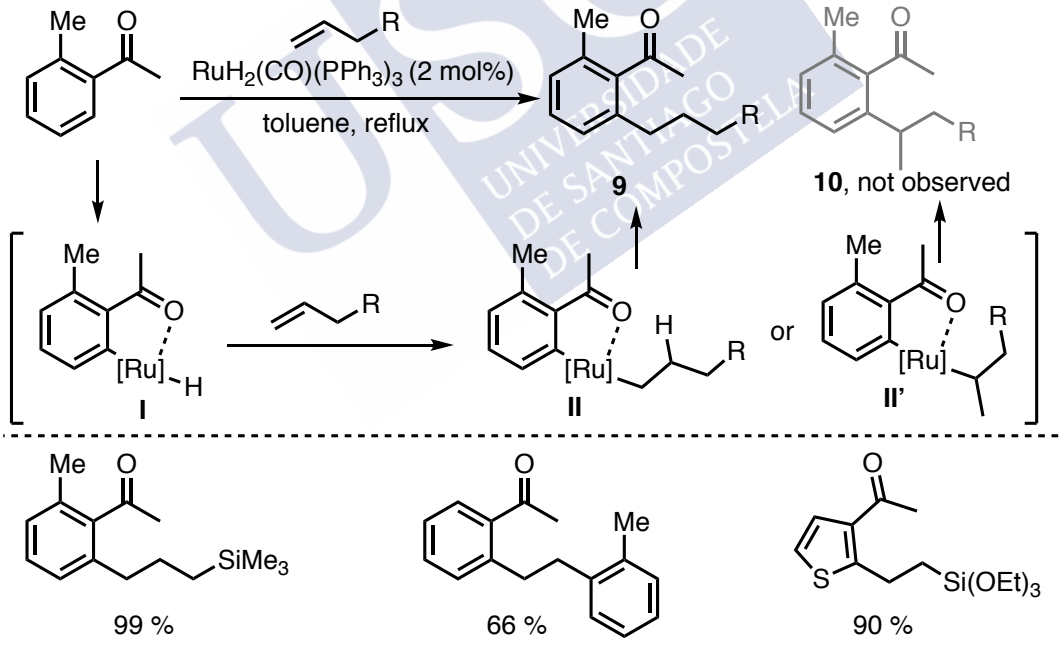
5. Intermolecular alkene and alkyne hydroarylation & hydroalkenylation reactions using TMC

5.1 Alkene hydrocarbonation reactions: Emphasis on iridium-promoted processes and asymmetric additions

The TMC addition of C–H bonds across the double bond of an alkene is a very attractive transformation for many reasons that go from the formation of a C–C bond in a very clean

way (atom economy), to the possibility of creating new carbon sterocenters. In recent years, a number of alkene or alkyne hydrocarbonation methods have been described. Not surprisingly, most of them rely on the activation of arene and heteroarene Csp^2-H bonds, due to the easier C–H activation.[63]

In this context, it is first mandatory to mention the seminal discoveries of Lewis[64] and Murai,[65] using ruthenium catalysts. In 1993, Murai and co-workers demonstrated that the ruthenium complex $RuH_2(CO)(PPh_3)_3$ is able of selectively insert into the $C(sp^2)$–H bond of arenes to generate precise ruthenated intermediates of type **I** (Scheme 25). A vital point to this step is the presence of a ketone at the arene precursor that directs the insertion of the Ru at its *ortho* position, based on a chelation assistance control. Then, intermediate **I** evolves to the linear hydroarylation product **9** through a regioselective alkene migratory insertion into the Ru-H bond and a subsequent reductive elimination. The branched hydroarylated product of type **10** is not observed in this transformation; indeed, this linear selectivity is the most common for most of the subsequently developed transition-metal catalyzed hydrocarbonation reactions.



Scheme 25. Pioneering Ruthenium-Catalyzed hydroarylation of alkenes developed by Murai.

[63] a) C. G. Newton, S.-G. Wang, C. C. Oliveira, N. Cramer, *Chem. Rev.* **2017**, *117*, 8908–8976; b) Z. Dong, Z. Ren, S. J. Thompson, Y. Xu, G. Dong, *Chem. Rev.* **2017**, *117*, 9333–9403.

[64] L. N. Lewis and J. F. Smith, *J. Am. Chem. Soc.* **1986**, *108*, 2728–2735.

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

This groundbreaking discovery paved the way for many other related hydrocarbonations,[66] using different ruthenium,[67] cobalt,[68] and rhodium catalysts.[69] Curiously, the use of iridium complexes, which can present several advantages from a reactivity and mechanistic perspective, was less explored.[70] Since this thesis deals mainly with iridium complexes, in this section we will mainly comment the use of iridium complexes in alkene hydroarylation processes. Furthermore, we will mainly discuss the addition of substrates with aromatic C(sp^2)–H bonds, which are the widest described in the literature; albeit we will comment the few relevant reported examples in which alkene C–H bonds are activated.

In this regard, Togni and coworkers reported in 2003 the first example using an iridium catalyst, namely a hydroarylation reaction of norbornene with phenols. The process, which is catalyzed by an Ir(I) bisphosphine complex provides the *ortho*-monoalkylated product **11**, together with minor amounts of the *ortho*-dialkylated side product **12** (Scheme 26, A).[71]

In 2008, Shibata reported a related hydroarylation of 2-norbornene with acetophenone. The process, which is catalyzed by the chiral catalyst resulting from the combination of $[Ir(cod)_2]BF_4$ and the bisphosphine (*R*)-MeO-BIPHEP, provides the product **13** with moderate enantioselectivity (Scheme 26, B).[72] Interestingly, they reported an analogous iridium catalyst that also promotes the hydrocarbonation of acetophenes with styrenes, albeit with poor regioselectivity, so mixtures of linear and branched products (**14** and **15**) are typically obtained with moderate yields (Scheme 26, C).

[66] a) P. W. R. Harris, P. D. Woodgate, *J. Organomet. Chem.*, **1997**, *530*, 211–223; b) Y.-G. Lim, J.-B. Kang, B. Tak Koo, *Tetrahedron Lett.*, **1999**, *40*, 7691–7694; c) Y.-G. Lim, J.-S. Han, S.-S. Yang, J. H. Chun, *Tetrahedron Lett.*, **2001**, *42*, 4853–4856.

[67] a) M. Hirano, N. Kurata, T. Marumo, S. Komiya, *Organometallics*, **1998**, *17*, 501–503; b) M. Hirano, N. Kurata, S. Komiya, *J. Organomet. Chem.*, **2000**, *607*, 18–26; c) R. F. R. Jazzar, M. Varrone, A. D. Burrows, S. A. Macgregor, M. F. Mahon, M. K. Whittlesey, *Inorg. Chim. Acta*, **2006**, *359*, 815–820; d) L. Benhamou, V. César, N. Lugan, G. Lavigne, *Organometallics*, **2007**, *26*, 4673–4676; e) T. Lundrigan, C. L. M. Jackson, M. I. Uddin, L. A. Tucker, A. A.-S. Ali, A. Linden, T. S. Cameron, A. Thompson, *Can. J. Chem.*, **2012**, *90*, 693–700; f) S. Busch, W. Leitner, *Adv. Synth. Catal.*, **2001**, *343*, 192–195; g) T. Matsubara, N. Koga, D. G. Musaev, K. Morokuma, *J. Am. Chem. Soc.*, **1998**, *120*, 12692–12693.

[68] a) K. Gao, N. Yoshikai, *Chem. Commun.*, **2012**, *48*, 4305–4307; b) K. Gao, R. Paira, N. Yoshikai, *Adv. Synth. Catal.*, **2014**, *356*, 1486–1490. c) C. Suzuki, K. Hirano, T. Satoh, M. Miura, *Org. Lett.*, **2013**, *15*, 3990–3993.

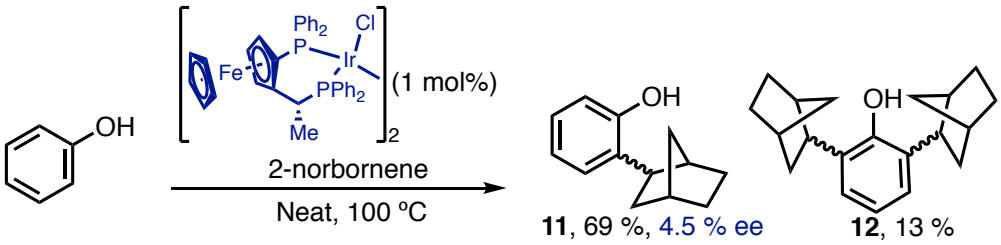
[69] a) D. A. Colby, R. G. Bergman, J. A. Ellman, *J. Am. Chem. Soc.*, **2006**, *128*, 5604–5605. b) C. Aïssa, A. Fürstner, *J. Am. Chem. Soc.*, **2007**, *129*, 14836–14837.

[70] Y. Nishinaka, T. Satoh, M. Miura, H. Morisaka, M. Nomura, H. Matsui, C. Yamaguchi, *Bull. Chem. Soc. Jpn.*, **2001**, *74*, 1727–1735.

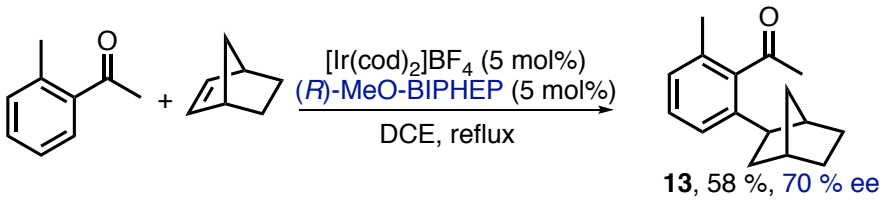
[71] R. Dorta, A. Togni, *Chem. Commun.*, **2003**, *0*, 760–761.

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

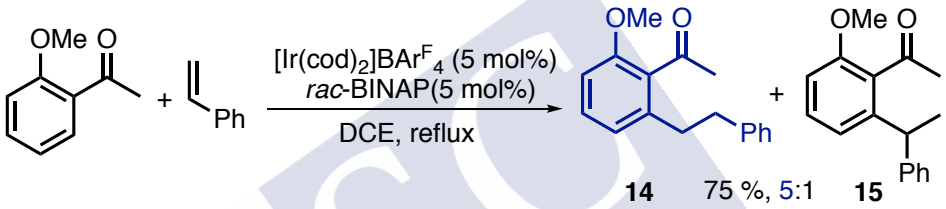
A) *Togni's pioneering Ir-catalyzed 2-norbornene hydroarylation*



B) *Shibata's enantioselective Ir-catalyzed 2-norbornene hydroarylation*



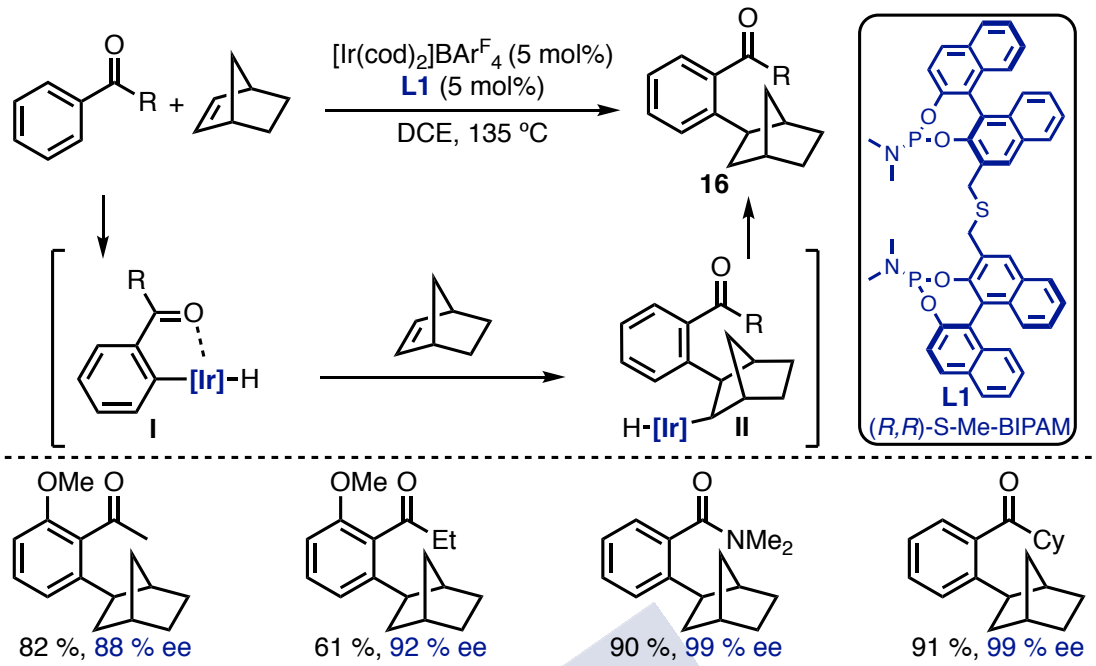
C) *Shibata's Ir-catalyzed styrene hydrocarbonation*



Scheme 26. Initial efforts in the Ir-catalyzed hydrocarbonation of alkenes

In 2015, Yamamoto described an iridium-catalyzed highly enantioselective protocol for the intermolecular hydroarylation of norbornene (Scheme 27).[73] The best results were observed by using $[Ir(cod)_2]BAr^F_4$ and *(R,R)-S*-Me-BIPAM as ligand. From a mechanistic perspective the authors suggested that the reaction starts with the *ortho* C–H activation to generate the intermediate **I**. After coordination of norbornene, a migratory insertion into the iridium-carbon bond, followed by a subsequent C–H reductive elimination would yield the product **16** and regenerate the catalyst. A KIE value of 2.08 and D_2O exchange experiments indicated that the C–H bond cleavage is involved in the turnover-limiting step.

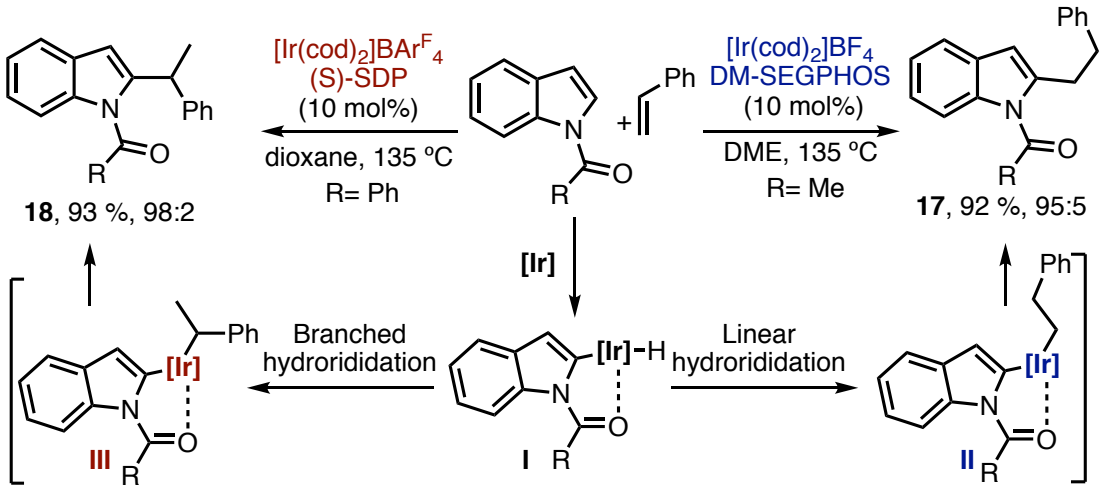
[73] T. Shirai, Y. Yamamoto, *Angew. Chem. Int. Ed.* **2015**, *54*, 9894–9897.



Scheme 27. Ir-catalyzed enantioselective hydroarylation with norbornene developed by Yamamoto.

In 2012, Shibata reported an alkene addition at the C2-position of indoles mediated by an iridium(I)-bisphosphine cationic catalyst.[74] Importantly, depending on the nature of the catalyst and of the directing group tethered to the indolic nitrogen, linear or branched products **17** and **18** could be obtained (Scheme 28). Thus, the use of an acetyl directing group in combination with the catalyst resulting from $[Ir(cod)_2]BF_4$ and DM-SEGPHOS provided the linear product **17** (branched: linear ratio of 5:95). In contrast, the chiral catalyst generated from $[Ir(cod)_2]BAr^F_4$ and the spirobisphosphine ligand SDP, in combination with a benzoyl directing group at the indolic nitrogen, promoted the formation of the branched product **18** (branched : linear ratios around 98:2) with moderate to good enantio-selectivities. Despite the relevance of this strategy to control the regioselectivity, the methodology is essentially limited to indoles and styrenes. The authors suggested a mechanistic pathway involving an initial C–H activation by oxidative addition (**I**), followed by a hydroiridation of the alkene to provide the regioisomeric intermediates **II** *or* **III**. Subsequent reductive eliminations afford the corresponding linear (**17**) or branched (**18**) product. The reasons behind the ligand dependent regioselectivity were not detailed.

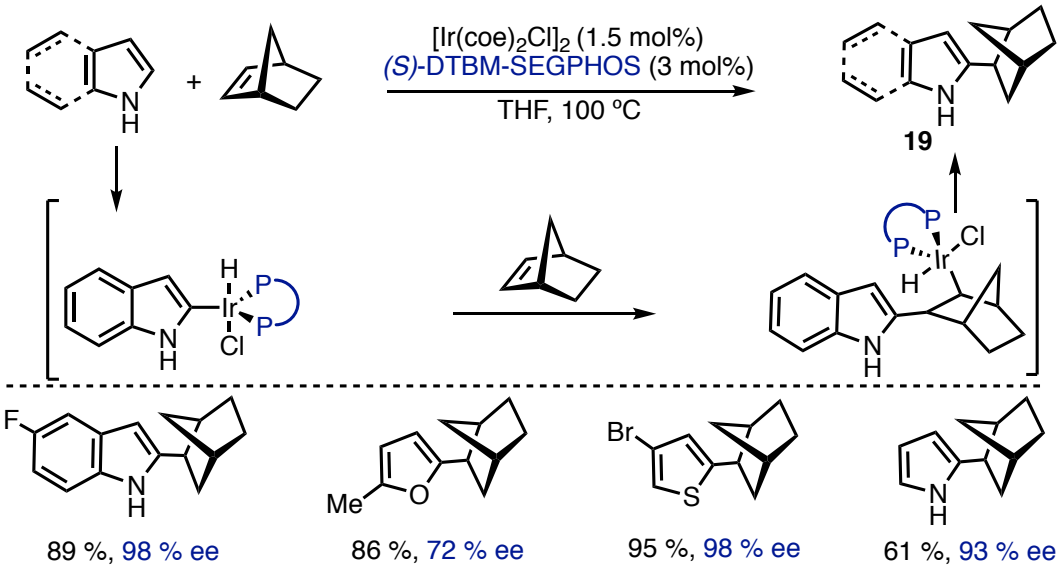
[74] S. Pan, N. Ryu, T. Shibata, *J. Am. Chem. Soc.*, **2012**, *134*, 17474–17477.



Scheme 28. Iridium promoted alkylation of C2-Position of Indoles developed by Shibata.

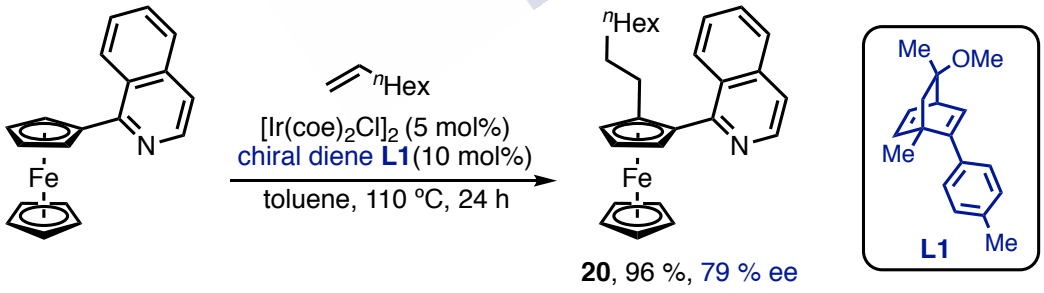
In 2013, Hartwig and coworkers reported an iridium promoted enantioselective hydroarylation of norbornene and related bicycloalkenes with heteroaromatic systems such as indoles, furans, pyrrols or thiophenes.[75] In this case, the method does not require the use of directing groups, as the electronics of the heteroaromatic system warrants a selective C–H insertion of the metal complex. The optimal conditions involved a neutral iridium complex $[Ir(coe)_2Cl]_2$ and the chiral bisphosphine (*S*)-DTBM-Segphos, in THF at 100 ºC. The corresponding products of type **19** are obtained in good yields and excellent enantioselectivities of up to 98% (Scheme 29). The process follows the standard mechanism: oxidative addition, carbometalation and subsequent C–H reductive elimination. Mechanistic experiments using deuterated probes indicated that the C–H activation is not the turnover-limiting step, since an Ir-deuteride resonance was detected at room temperature; thus, a turnover-limiting carbometallation step was proposed.

[75] C. S. Sevov, J. F. Hartwig, *J. Am. Chem. Soc.*, **2013**, *135*, 2116–2119.



Scheme 29. Ir-catalyzed enantioselective hydroarylation with norbornene developed by Hartwig.

In 2014, Shibata and coworkers reported an iridium catalyzed enantioselective hydrocarbonation of alkenes with quinoline-substituted ferrocenes (Scheme 30).[76] The method constitutes the first example of an enantioselective C(sp^2)–H alkylation of ferrocenes and it is promoted by the iridium catalyst resulting from the combination of the neutral precursor $[Ir(coe)_2Cl]_2$ and a chiral diene **L1**. Curiously, this methodology is compatible with different types of alkenes, such as styrene derivatives, acrylates and unactivated alkenes like 1-octene, and takes place with almost complete selectivity towards the linear isomer **20**.

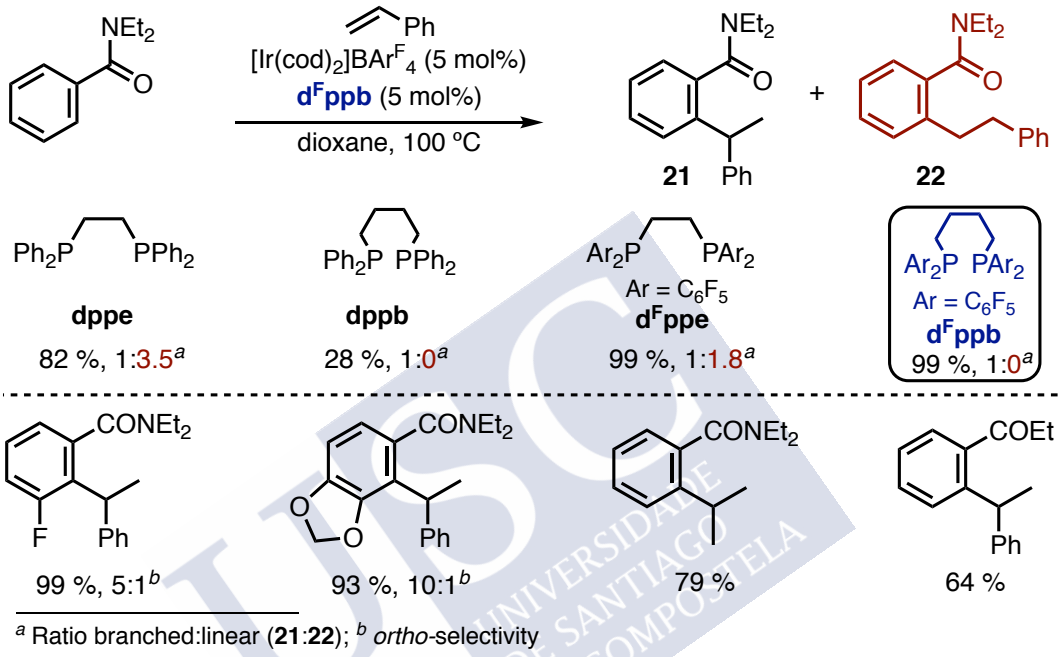


Scheme 30. Ir-promoted alkylation of ferrocenes developed by Shibata.

Also in 2014, Bower and coworkers described a branched-selective, iridium-catalyzed hydroarylation reaction of alkenes with benzamides.[77] Key for the efficiency and selectivity of the reaction is the use of a dialkyl carboxamide or a ketone as directing group in

[76] T. Shibata, T. Shizuno, *Angew. Chem. Int. Ed.*, **2014**, *53*, 5410–5413.
[77] G. E. M. Crisenza, N. G. McCreanor, J. F. Bower, *J. Am. Chem. Soc.*, **2014**, *136*, 10258–10261.

combination with the iridium catalyst generated from the cationic complex $[Ir(cod)_2]BAr^F_4$ and the electron-deficient bisphosphine d^Fppb. Curiously, the use of related bisphosphines with narrower bite angles, like d^Fppe, led to lower branched (**21**) to linear (**22**) ratios, whereas the use of the homologous non-fluorinated phosphine ligand dppb led to a drastic reduction in the reaction yield, while keeping the branched-selectivity. The reaction proceeds smoothly for a variety of styrenes, as well as for few unactivated olefins.



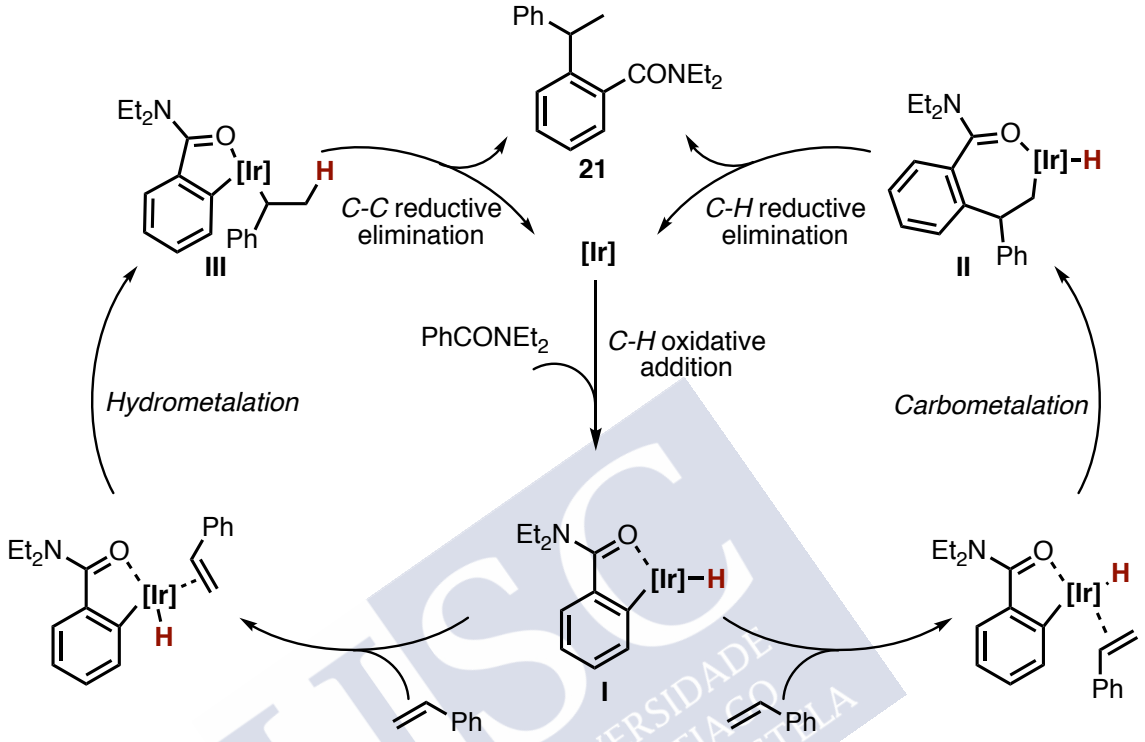
Scheme 31. Ir-catalyzed branch-selective hydroarylation developed by Bower.

Initially, the authors proposed a mechanistic pathway (Scheme 32) in which the iridium hydride intermediate **I** evolves through a hydrometallation. Indeed, deuterium labeling experiments revealed that both the oxidative addition and the alkene hydrometallation are reversible, so the C–C reductive elimination was suggested as the product-determining step.

However, subsequent DFT calculations performed by Huang and Liu suggested that, although the hydrometalation step might occur and be reversible, the C–C reductive elimination has an exceedingly high energy barrier.[78] Indeed, calculations indicate that the productive pathway of the reaction should involve a migratory insertion of the olefin into the Ir–C(sp^2) bond of **I**, a carbometalation process that yields the iridium hydride species **II**. An ensuing C–H reductive elimination would yield the product **21**. According to these

[78] G. Huang, P. Liu, *ACS Catal.*, **2016**, *6*, 809–820.

DFT studies, the carbometalation constitutes the rate and regioselectivity-determining step of the overall reaction. The computational study also concludes that large bite angle ligands like dppb disfavor the linear selectivity due to highly unfavorable steric repulsions between the substrate and the aryl rings of the phosphine during the migratory insertion step.

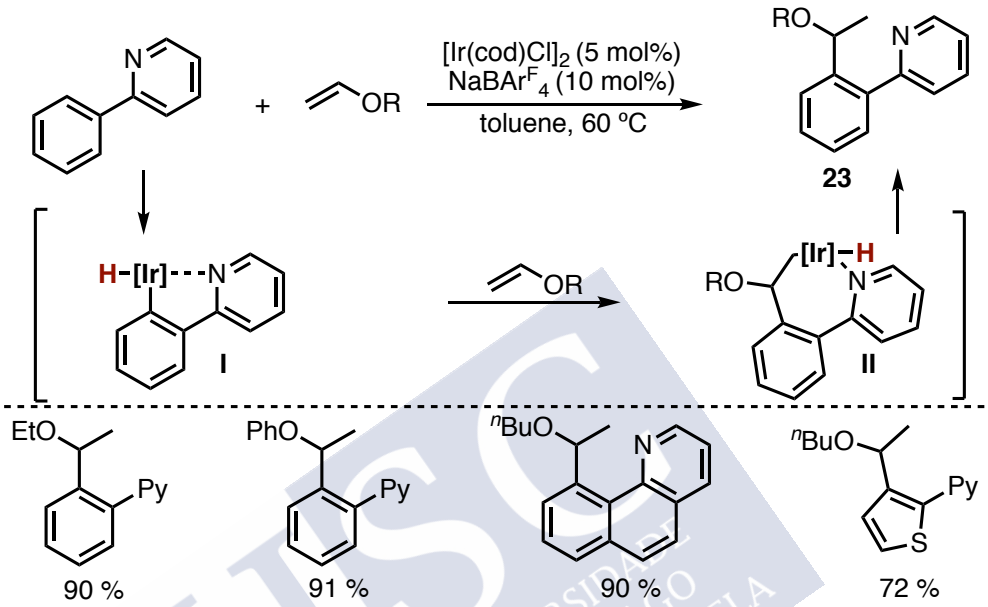


Scheme 32. Mechanistic proposal by Huang.

In 2015, Nishimura reported an iridium-catalyzed hydroarylation of vinyl ethers using a pyridine directing group.[79] The reaction proceeds very efficiently under mild conditions for a variety of *ortho*-aryl pyridine precursors and provides the *ortho*-alkylated products **23** with complete branched selectivity. Remarkably, the optimal catalyst, $[IrCl(cod)]_2$ / $NaBAr^F{}_4$, does not involve the use of added bisphosphines, like in previous cases. Thus, a preliminary enantioselective version was explored using an iridium complex wherein the cyclooctadiene ligand was replaced by the chiral diene (*S*,*S*)-Fc-tfb*, achieving a 76% ee (92% yield) for a model case.[80] Mechanistic experiments with deuterium-labeled substrates indicated that the C–H activation assisted by the pyridine is reversible. Moreover, further computational studies by Huang[81] suggested that, similarly to the previous reaction by

[79] a) Y. Ebe, T. Nishimura, *J. Am. Chem. Soc.*, **2015**, *137*, 5899–5902. b) M. Nagamoto, T. Nishimura, *Chem. Commun.*, **2014**, *50*, 6274–6277.
[80] For a comprehensive review on enantioselective chiral diene-iridium catalysis, see: M. Nagamoto, T. Nishimura, *ACS Catal.*, **2016**, *7*, 833–847.
[81] M. Zhang, G. Huang, *Dalton Trans.*, **2016**, *45*, 3552–3557.

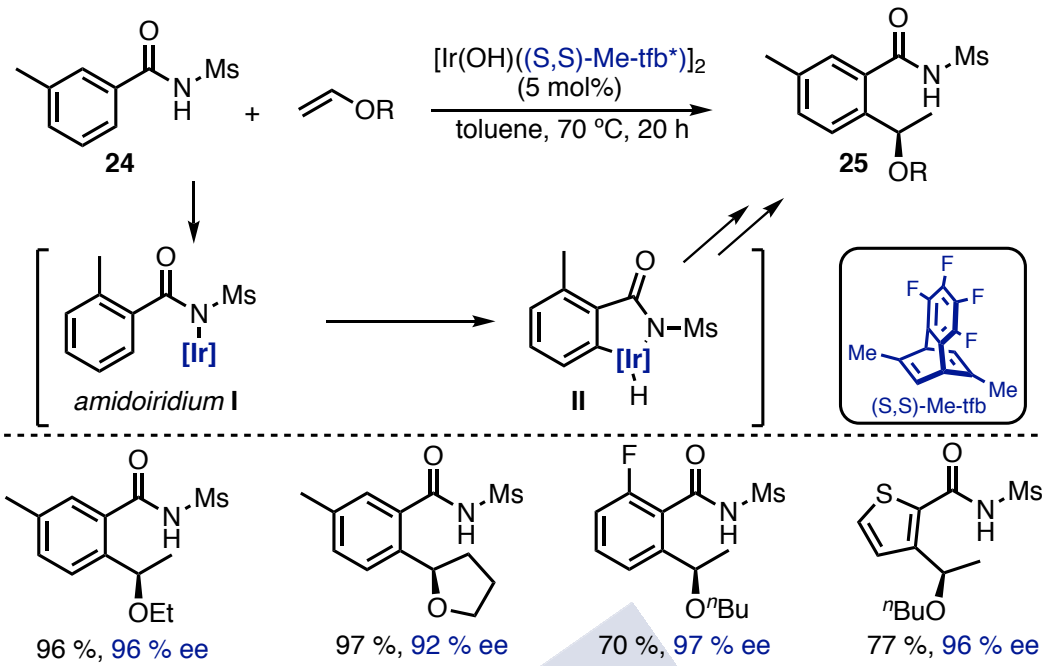
Bower (see Scheme 32), the productive pathway involves a carbometalation process, being this the rate and selectivity determining step. The C–H reductive elimination provides the observed product (Scheme 33). The authors indicate that the good regioselectivity of the process is related to the electron-donating character of the alkoxy group in the alkene reacting partner.



Scheme 33. Iridium-Catalyzed hydroarylation of vinyl ethers developed by Nishimura.

In 2016, Nishimura and coworkers described an alternative hydroarylation reaction of enol ethers using mesitylbenzamides of type **24** as substrates.[82] The reaction is catalyzed by a hydroxoiridium(I) complex featuring the chiral diene (*S,S*)-Me-tfb*, and provided the corresponding products with complete branched selectivity, good yields and excellent enantioselectivities. The mechanistic proposal considers that the reaction starts by deprotonation of the amide by the hydroxoiridium catalyst followed by reversible oxidative addition of the C–H bond to yield intermediate **II**. Subsequent carbometalation and C–H reductive elimination would yield the *ortho*-alkylated amide **25** (Scheme 34). In consonance with the proposal, the complex $[Ir(cod)Cl]_2$ / $NaBAr^F_4$, is not able of promote the reaction. Interestingly, the rhodium analogue $[Rh(OH)(cod)]_2$ was also ineffective.

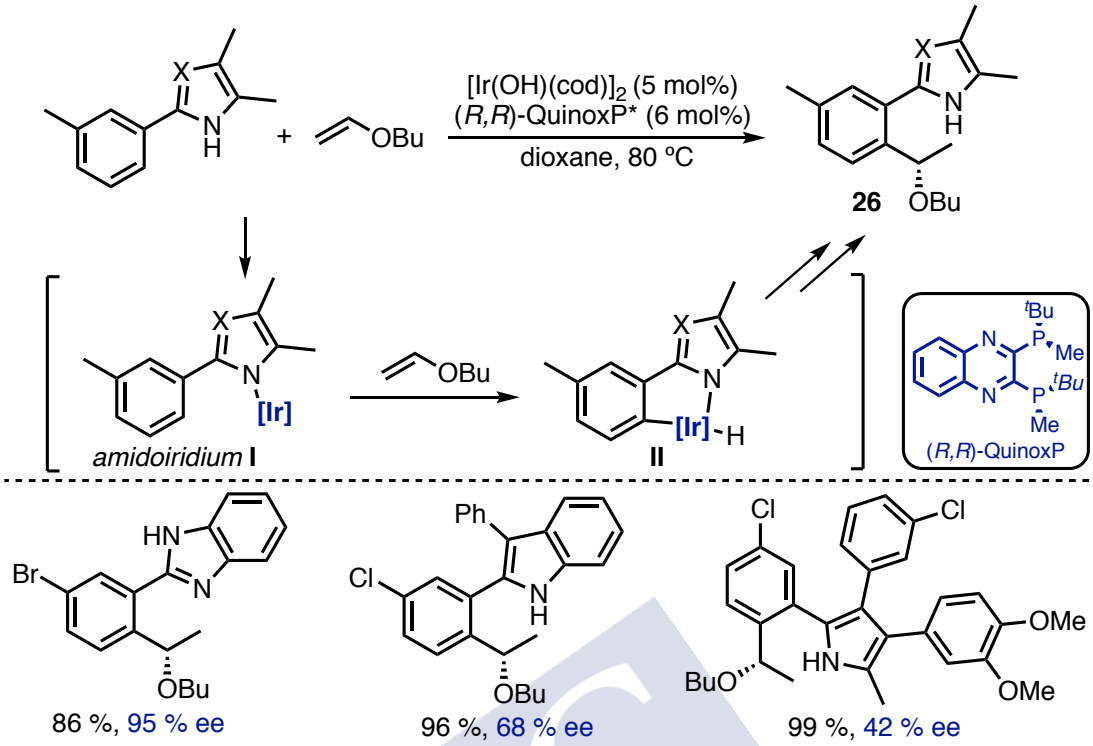
[82] M. Hatano, Y. Ebe, T. Nishimura, H. Yorimitsu, *J. Am.Chem. Soc.*, **2016**, *138*, 4010–4013.



Scheme 34. Hydroxoiridium mediated enantioselective hydroarylation developed by Nishimura.

In a related strategy, the same group reported a highly enantioselective hydroarylation of enol ethers using heteroaromatic directing groups that contain an acidic N-H bond, such as azoles, pyrroles, imidazoles, indoles or benzimidazoles (Scheme 35).[83] In this case, the optimal catalyst consisted of an hydroxyiridium(I) complex prepared from $[Ir(OH)(cod)]_2$ and (*R*,*R*)-QuinoxP*. Thus, after the initial N-H deprotonation of the heteroaromatic directing group, the resulting neutral amidoiridium complex **I** evolves towards the branched selective product **26**, putatively, through the same steps previously proposed for the hydroarylation of vinyl ethers with benzamides (Scheme 34).

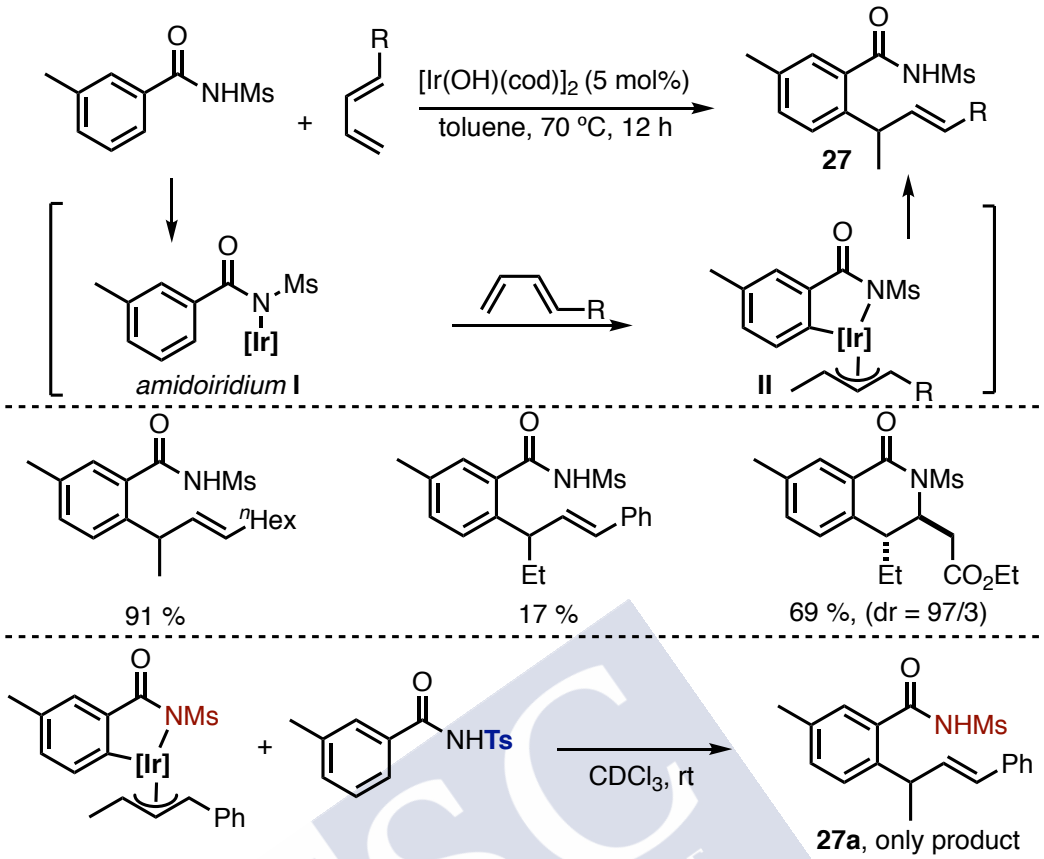
[83] D. Yamauchi, T. Nishimura, H. Yorimitsu, *Chem. Commun.*, **2017**, *53*, 2760–2763.



Scheme 35. Hydroxoiridium mediated Hydroarylation using heteroaromatic DGs developed by Nishimura.

Very recently Nishimura extended this method to the hydroarylation of conjugated dienes.[84] The optimal catalyst involved the use of $[Ir(OH)(cod)]_2$, without any additional phosphine ligand, which apparently inhibited the process. As in the above reaction, $[Rh(OH)(cod)]_2$ displayed no catalytic activity. Importantly, the species **II**, generated after C–H insertion and hydrometallation, could be isolated and determined to be an intermediate rather than an off-cycle resting state of the process due to the exclusive formation of **27a** (Scheme 36, bottom) in a crossover experiment. Therefore, the proposed mechanistic pathway involves the reaction of the hydridoiridium(III) intermediate **I** with the diene to afford the observed π-allyliridium(III) species **II**, which evolves to the product **27** through a C–C reductive elimination.

[84] M. Nagamoto, H. Yorimitsu, T. Nishimura, *Org. Lett.*, **2018**, *20*, 828–831.



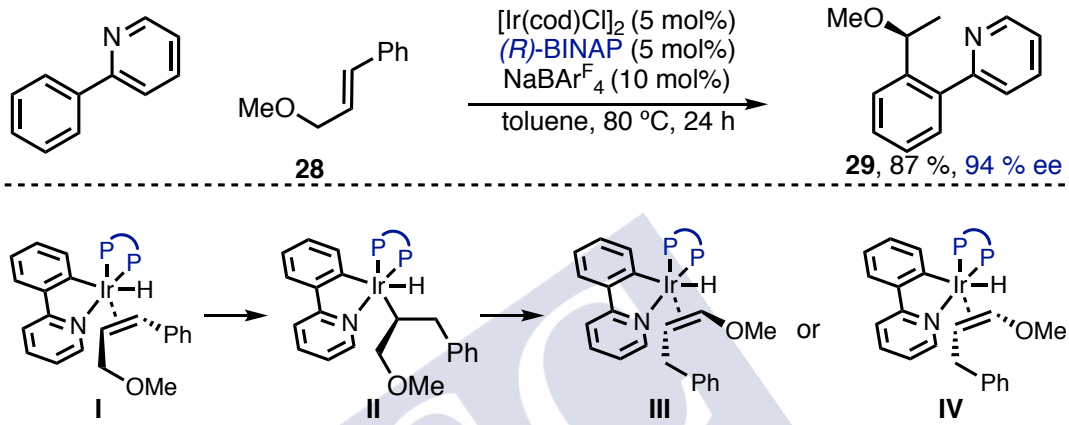
Scheme 36. Hydroxoiridium mediated Hydroarylation of Conjugated Dienes developed by Nishimura.

Besides vinyl ethers and conjugated dienes, Nishimura and coworkers also demonstrated that this chemistry could be extended to the hydroarylation of alkenes like **28**, bearing an ether at a remote position (Scheme 37).[85] In particular, the catalyst generated in situ from $[IrCl(cod)]_2$, *(R)*-BINAP and $NaBAr^F_4$ promotes very efficiently the reaction of 2-aryl pyridines and alkenyl ethers **28**, generating the enantioriched hydroarylation products of type **29** with good yields, complete regioselectivities and enantioselectivities typically above the 90% level. The reaction involves an initial isomerization of the alkenyl ethers **28** into the related vinylethers by a chain walking type of mechanism that is promoted by the aryl(hydrido)iridium (III) species **I** (bottom-left). The authors observed H/D scrambling in both reagents, the phenylpyridine and the alkenyl ether **28**, indicating that the C–H activation and insertion steps are reversible.

Computational studies more recently performed by Huang, confirmed that the reaction involves the isomerization of the alkenyl ethers by the aryl(hydrido)iridium (III) intermediate **I**, through a sequence of migratory insertions / β-hydride eliminations, to

[85] Y. Ebe, M. Onoda, T. Nishimura, H. Yorimitsu, *Angew. Chem. Int. Ed.*, **2017**, *56*, 5607–5611.

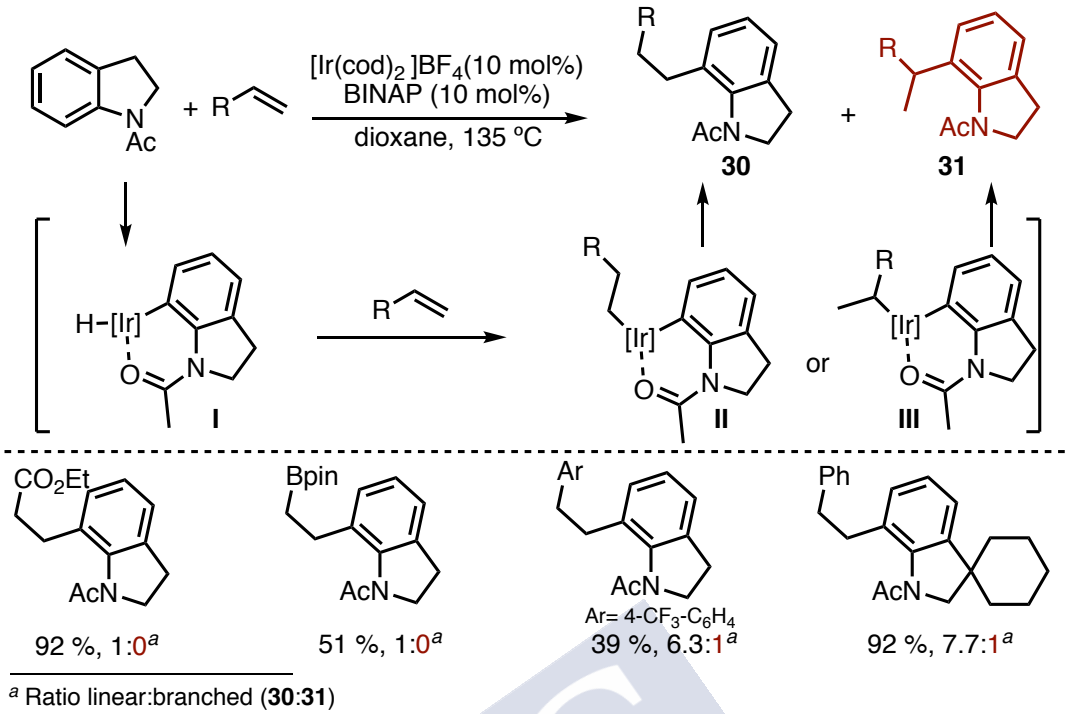
eventually provide both the *Z*- and *E*-1-alkenyl ethers. Interestingly, computational data indicate that these isomers, which can be interconverted following the same mechanism, lead to opposite enantiomers of the observed product **29**. Accordingly, DFT calculations suggest that the high enantioselectivities experimentally observed by Nishimura are the consequence of highly unfavorable steric interactions that are exclusively observed in the migratory insertion (carboiridation) of the Z-alkenyl isomer (Scheme 37).[86]



Scheme 37. Ir-catalyzed enantioselective hydroarylation of alkenes bearing an ether at remote position developed by Nishimura.

Besides carboxamides, pyridines and related heteroaromatic moieties, as well as tertiary acetamides have also been shown to be excellent directing groups for iridium-catalyzed hydrocarbonation reactions. Indeed, already in 2014, Shibata reported an Ir (I)-catalyzed direct C-7 alkylation of *N*-acetyl indolines with electron deficient alkenes like acrylates.[87] The catalyst generated from $[Ir(cod)_2]BF_4$ and BINAP afforded preferentially the corresponding linear products of type **30** with good yields, albeit harsh reaction conditions were typically required (e.g. heating at 135 ºC for 24 h). The use of other alkenes such as styrene is tolerated, although mixtures of linear (**30**) and branched (**31**) isomers were obtained in these cases. From a mechanistic perspective, the authors assumed a hydroiridation /C–C reductive elimination pathway but neither mechanistic data nor computational investigations have been reported to validate this proposal.

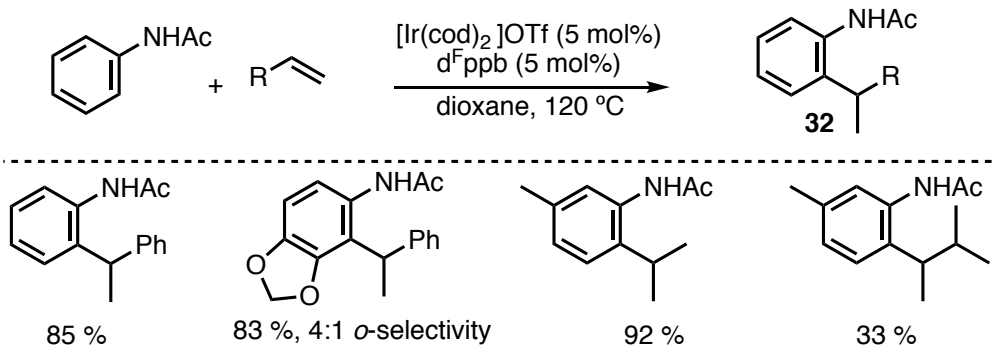
[86] M. Zhang, L. Hu, Y. Lang, Y. Cao, G. Huang, *J. Org. Chem.*, **2018**, *83*, 2937–2947.
[87] S. Pan, N. Ryu, T. Shibata, *Adv. Synth. Catal.*, **2014**, *356*, 929–933.



Scheme 38. Ir-catalyzed hydrocarbonation of acetamides developed by Shibata.

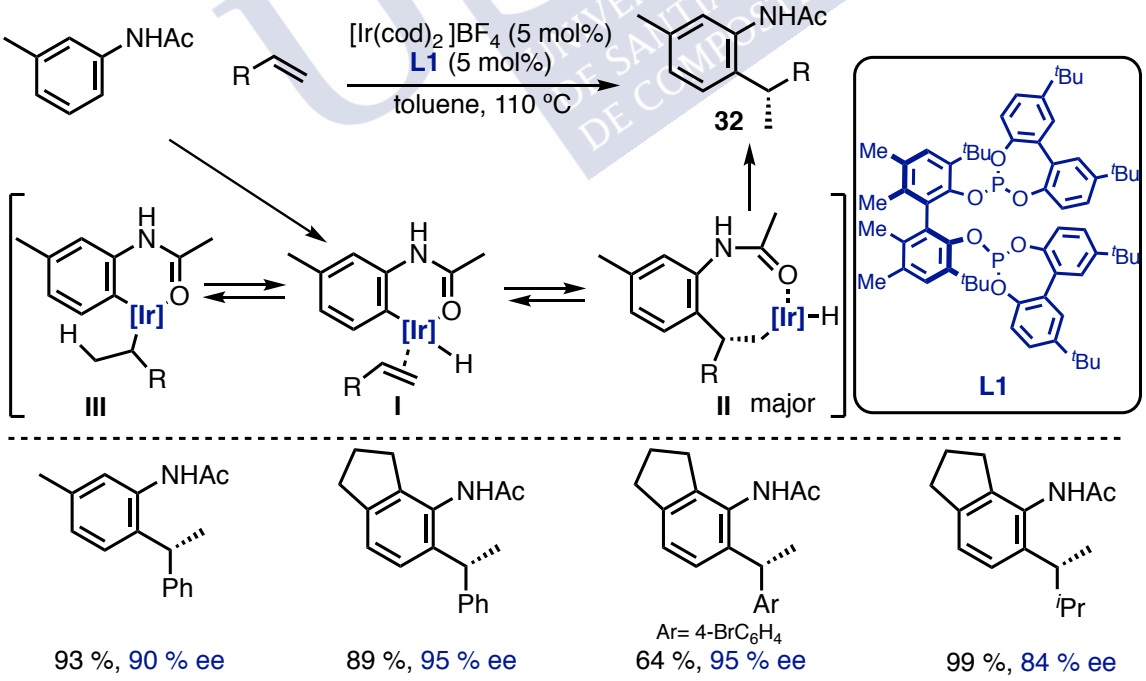
In this context, Bower and coworkers also described the use of acetamides as directing groups in iridium-catalyzed hydrocarbonations.[88] In particular, these authors described in 2015 an iridium-mediated branched-selective *ortho*-alkylation of acetanilides with aryl- or alkyl-substituted alkenes. Like in the hydroarylation of alkenes with benzamides (see Scheme 31), the best results were achieved with the iridium complex generated *in situ* from $[Ir(cod)_2]OTf$ and the wide-bite-angle and electron-deficient bisphosphine d^Fppb. Interestingly, a progression from low to high branched to linear selectivity was observed as the ligand varied from a narrow to a more wide-bite angle. The use of pentafluorinated aryl phosphines was also is key to obtain high conversions and improved selectivity towards the branched products of type **32** (Scheme 39).

[88] G. E. M. Crisenza, O. O. Sokolova, J. F. Bower, *Angew. Chem. Int. Ed.*, **2015**, *54*, 14866–14870.



Scheme 39. Ir-catalyzed branched-selective hydrocarbonation developed by Bower.

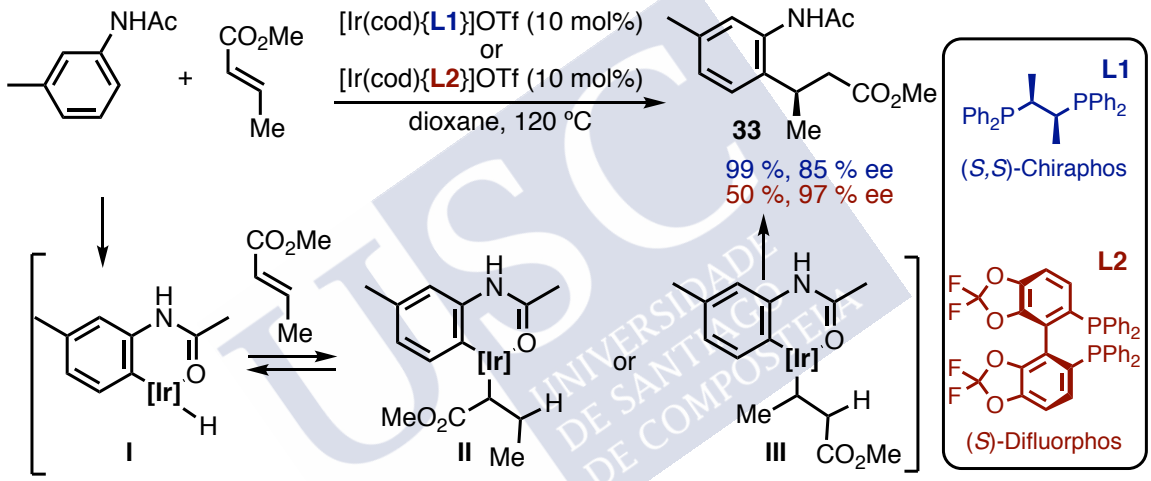
Very recently, Bower and collaborators reported the enantioselective variant of this hydroarylation process.[89] The optimal conditions were achieved by the combination of $[Ir(cod)_2]BF_4$ and the chiral bisphosphite ligand **L1** (scheme 40). Albeit deuterium labeling experiments revealed that a reversible hydroiridation towards **III** could operate, natural abundance ^{13}C KIE experiments allowed to discard the possibility of a C–C reductive elimination. Thus, a selective facial carbometalation to yield the intermediate **II** followed by an irreversible and turnover-limiting C–H reductive elimination is the most plausible pathway.



Scheme 40. Ir-catalyzed Branched and Enantioselective Hydrocarbonation developed by Bower.

[89] S. Grélaud, P. Cooper, L. J. Feron, J. F. Bower, *J. Am. Chem. Soc.*, **2018**, *140*, 9351–9356.

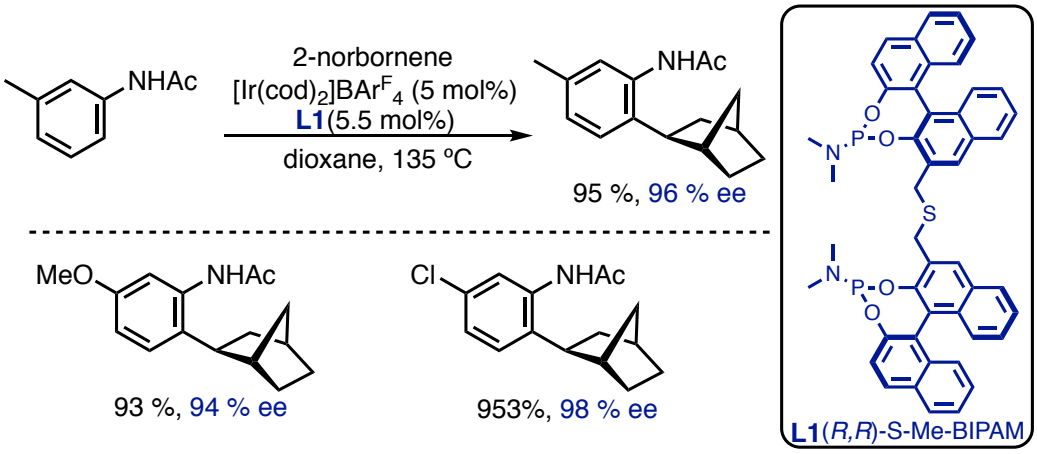
In 2017, Shibata and coworkers further contributed to this field by developing an enantioselective hydroarylation of acetanilides with α,β-unsaturated carbonyl compounds.[90] Using an iridium cationic catalyst featuring the chiral bisphosphines Chiraphos or Difluorophos, led to excellent enantioselectivities in favor of the β-arylated carbonyl product **33**. Interestingly, and contrary to most iridium-catalyzed hydroarylations, this method only works with β-substituted olefins, and proceeds in a completely regioselective manner. From the mechanistic point of view, the authors proposed that, after the initial C–H oxidative addition, a reversible hydrometallation could take place to yield regioisomeric intermediates **II** and **III**. Then, an irreversible reductive elimination would exclusively occur at **III**, delivering the observed product **33** (Scheme 41).



Scheme 41. Ir-catalyzed enantioselective hydrocarbonation of α, β unsaturated carbonyl compounds developed by Shibata.

Very recently, Yamamoto demonstrated that the chiral iridium catalyst derived from the bisphosphoramidite ligand (*R*,*R*)-S-Me-BIPAM, previously used for the enantioselective hydroarylation of norbornene with benzamides (Scheme 27), was also able to promote the hydroarylation of this alkene with acetanilides (Scheme 42).[91] Unfortunately, despite the high yields and enantioselectivities achieved for several acetanilides, the reaction seems to be limited to the use of norbornene as alkene partner.

[90] T. Shibata, M. Michino, H. Kurita, Y. Tahara, K. S. Kanyiva, *Chem. Eur. J.*, **2016**, *23*, 88–91.
[91] T. Shirai, T. Okamoto, Y. Yamamoto, *Asian J. Org. Chem.*, **2018**, *7*, 1054–1056.

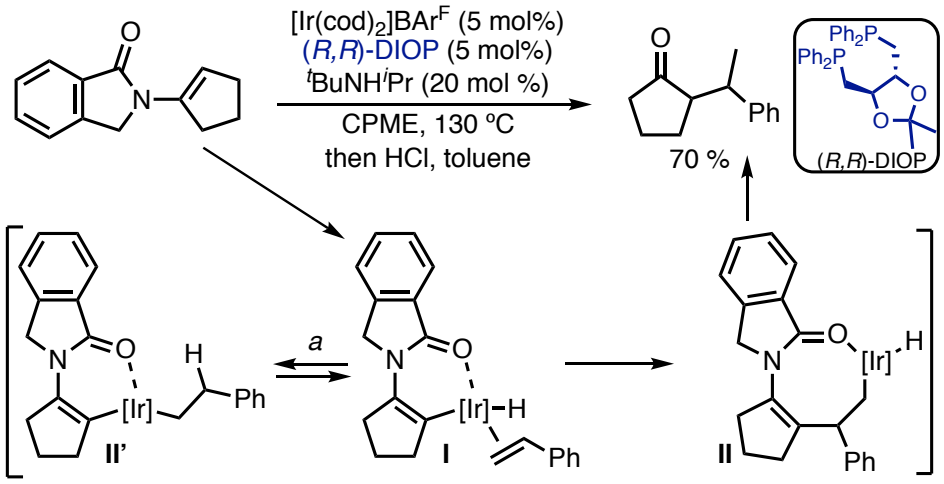


Scheme 42. Ir-BIPAM system for the enantioseletive hydroarylation of norbornene developed by Yamamoto.

Dong and collaborators described an intermolecular branched-selective α-alkylation of ketones with simple alkenes, based on the initial pre-installation of an enamide by condensation between the ketone and isoindolin-1-one. Thus, the carbonyl moiety of the resulting enamide acts as directing group, enabling the activation of the C–H bond at the enamide β-position by the cationic iridium-bisphosphine complex $[Ir(cod)_2]BAr^F_4$ / DIOP.[92] Besides styrenes, monoalkyl substituted alkenes are also suitable coupling partners for the transformation. Unfortunately, the isoindolin-1-one partner could not be used as a catalytic directing group, so the stoichiometric generation of the corresponding enamide is required before the Ir catalysis. On the other hand, neither the absolute or relative stereochemistry could be controlled by this catalyst, so diastereoselectivites were typically close to a 1:1 ratio and the enantioselectivity observed in a model reaction was very low.

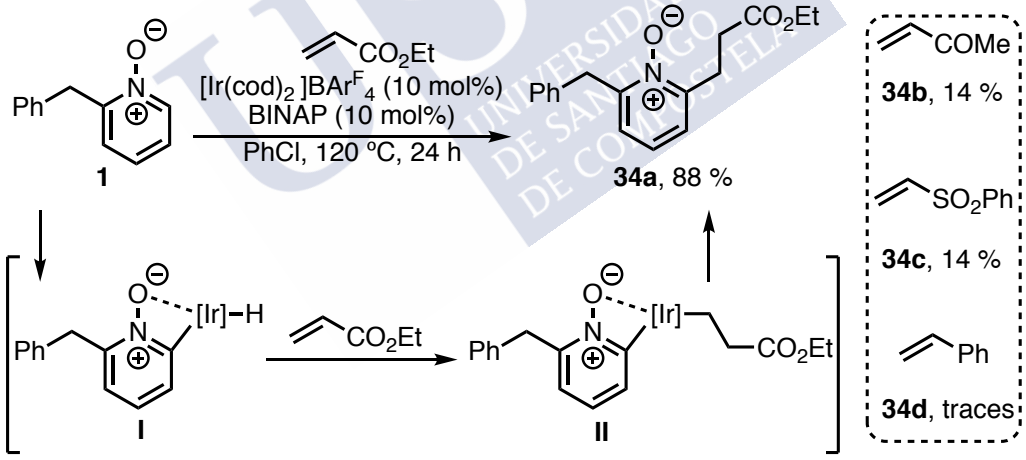
Finally, deuterium labeling experiments suggested that a hydroiridation process can occur (path *a*, scheme 43) but the absence of linear selectivity suggests that the productive pathway might involve a carboiridation step to afford the hydridoiridium(III) species **II**, similarly to what has been previously proposed for the hydrocarbonation with acetanilides (see Scheme 41).

[92] D. Xing, G. Dong, *J. Am. Chem. Soc.*, **2017**, *139*, 13664–13667.



Scheme 43. Ir-catalyzed Branched-Selective enamide α-alkylation developed by Dong.

Besides amides, ketones and heteroaromatic directing groups, Shibata and coworkers introduced in 2015 the use of pyridine *N*-oxides as directing groups for iridium-catalyzed hydrocarbonation reactions.[93] The cationic complex derived from $[Ir(cod)_2]BAr^F_4$ and BINAP afforded the best results when ethyl acrylate are used (**34a**). Other alkenes such as methyl vinyl ketone, phenyl vinyl sulfone and styrene gave poor results (**34b, c** & **d**).

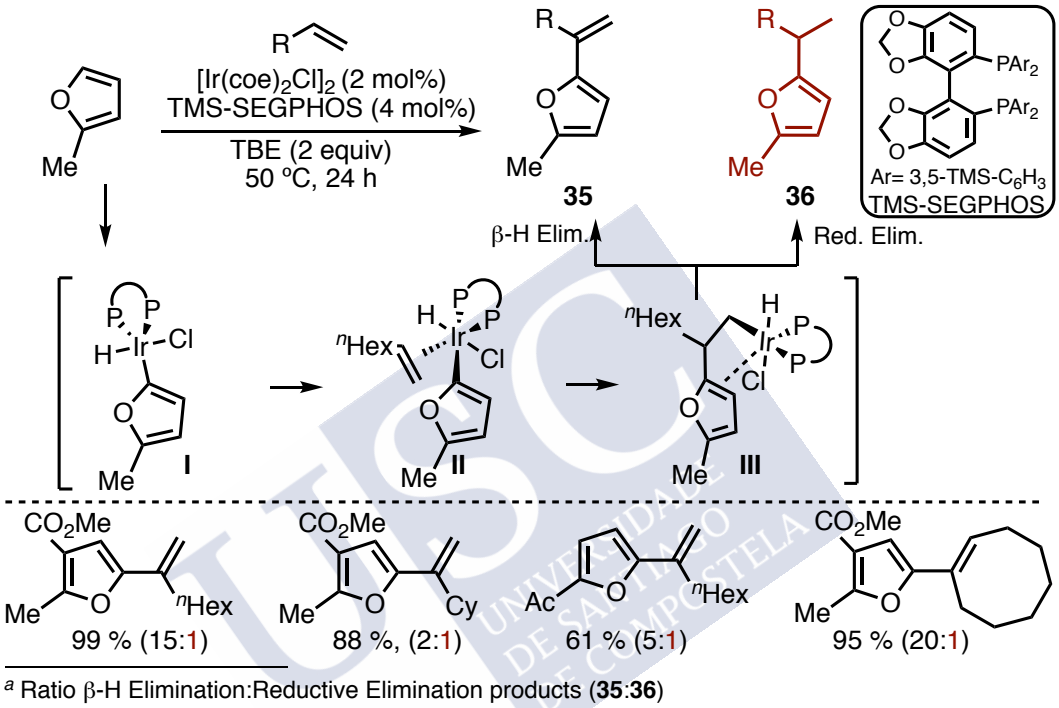


Scheme 44. Ir-catalyzed hydroarylation of pyridine N-oxides developed by Shibata

In addition to the abovementioned examples of hydrocarbonations, some examples have been reported in which the final reductive elimination is substituted by a β-H elimination, thus delivering an oxidative alkenylation. The initial example was reported in 2014 by Hartwig and coworkers, employing the neutral iridium catalyst resulting from the combination of $[Ir(coe)_2Cl]_2$ and TMS-SEGPHOS.[94] Remarkably, this strategy allows the

[93] T. Shibata, H. Takano, *Org. Chem. Front.* **2015**, *2*, 383–387.
[94] C. S. Sevov, J. F. Hartwig, *J. Am. Chem. Soc.*, **2014**, *136*, 10625–10631.

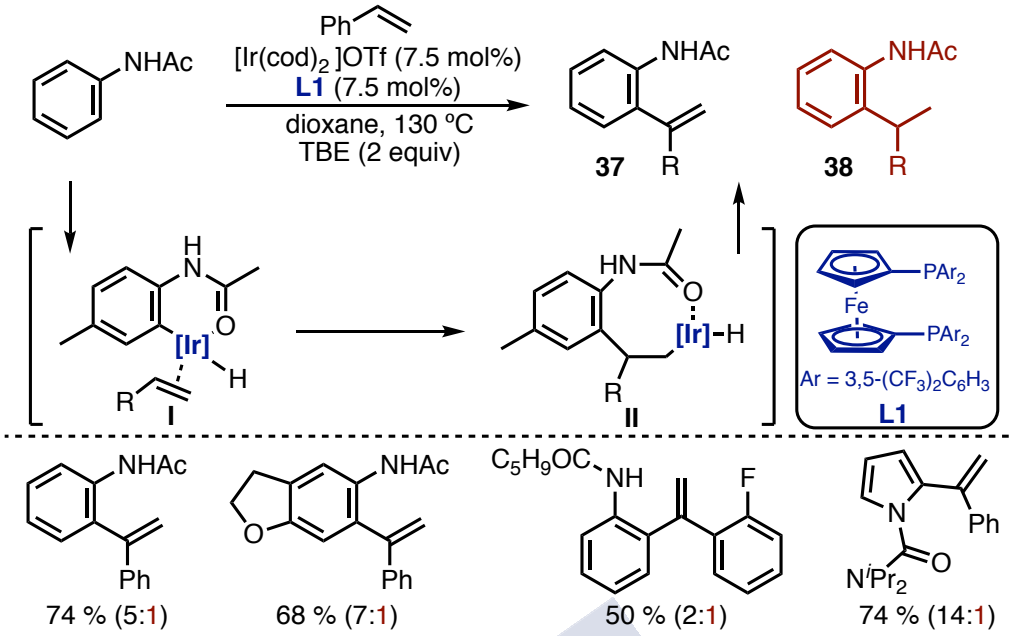
preferential generation of branched vinylfuran products (**35**) over the alkylfurans of type **36**, and proceeds without directing groups and under mild conditions. From a mechanistic point of view, the authors suggested an oxidative addition of the furan (**I**) followed by a coordination of the alkene and a carboiridation process, to yield the intermediate **III** (Scheme 45). A final β-H elimination and dissociation would deliver the vinylfuran **35** while the *tert*-butylethylene (TBE) acts as sacrificial hydrogen acceptor to regenerate the iridium catalyst.



Scheme 45. Ir-catalyzed alkenylation of furans developed by Hartwig.

More recently, Bower disclosed a related oxidative hydrorylation process that allows to install styrene moieties at the *ortho* position of anilides.[95] The catalyst generated from [Ir(cod)$_2$OTf] and the bisphosphine-ferrocenyl ligand **L1** affords the desired products **37** in good yields and with excellent regioselectivities, albeit variable amounts of hydroarylated products of type **38** were typically observed [**37** : **38** ratio from 2:1 to >20: 1, depending on the properties of the acetanilide and alkene (Scheme 46)]. On the other hand, the use of heteroaromatic systems such as pyrrole-1-carboximides was also tolerated, providing the desired C-2 vinylic pyrroles in moderate to good yields. As indicated in the above example, the TBE is used as a hydrogen acceptor to increase the catalyst turnover.

[95] P. Cooper, G. E. M. Crisenza, L. J. Feron, J. F. Bower, *Angew. Chem. Int. Ed.*, **2018**, *57*, 14198–14202.



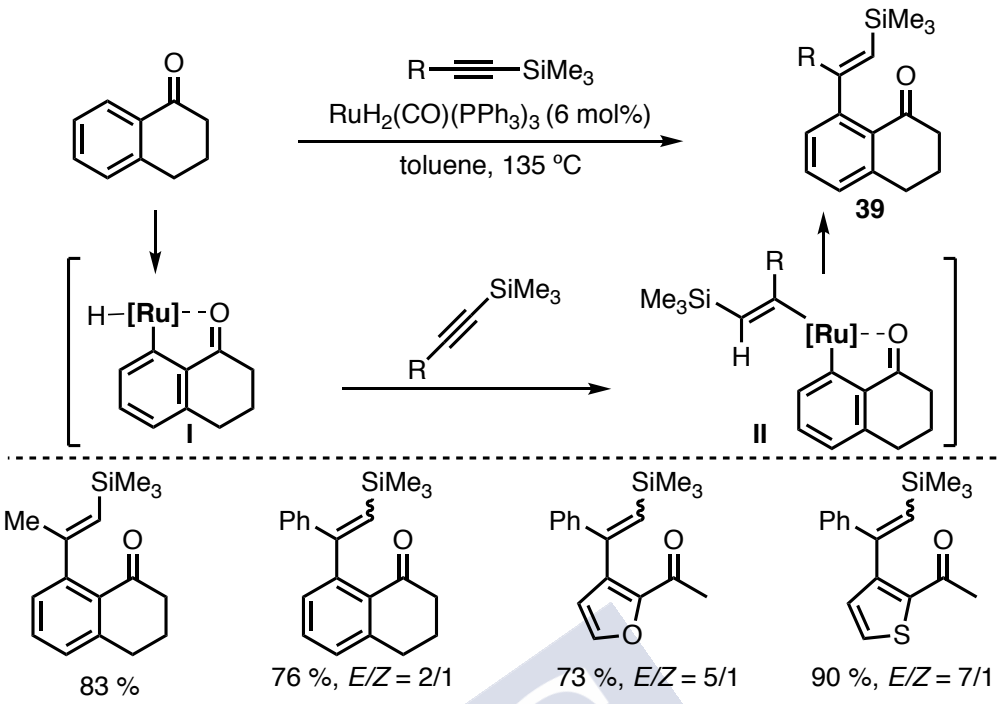
[a] Ratio β-H Elimination:Reductive Elimination products (**37**:**38**)

Scheme 46. Ir-catalyzed oxidative hydroarylation of anilides developed by Bower

5.2 Alkyne hydrocarbonation reactions. Emphasis on iridium catalysis.

As indicated above, the addition of C–H bonds to alkenes is synthetically appealing. While the addition to alkynes doesn't generate new stereocenters in the alkyne carbons, it produces alkenyl products which could be further manipulated, and thus are also synthetically very attractive.[96] However, these processes have been much less studied, compared to those involving the addition to alkenes. In 1995, Murai described a ruthenium catalyzed intermolecular hydroarylation of alkynes with arenes and heteroarenes in a regioselective manner (Scheme 47).[97] Although the reaction requires high temperatures, it allows the access to a variety of β vinyl-substituted ketones (**39**) in good yields.

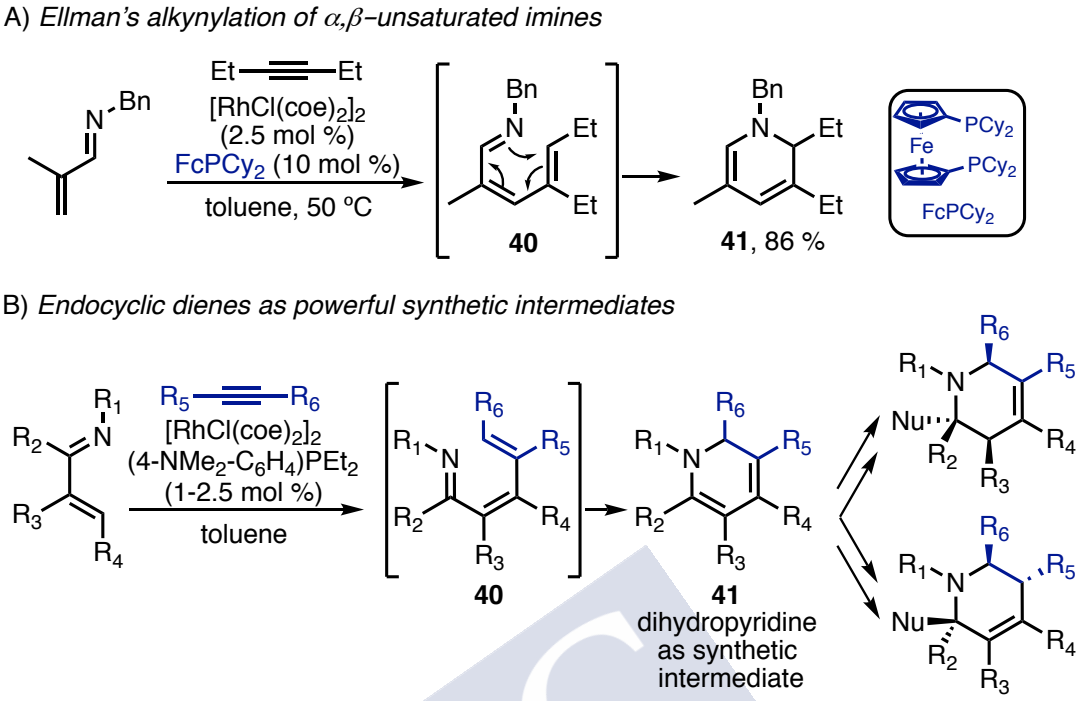
[96] a) K. Kokubo, K. Matsumasa, M. Miura, M. Nomura, *J. Org. Chem.*, **1997**, *62*, 4564–4565; b) M. Mori, Y. Kozawa, M. Nishida, M. Kanamaru, K. Onozuka, M. Takimoto, *Org. Lett.*, **2000**, *2*, 3245–3247.
[97] F. Kakiuchi, Y. Yamamoto, N. Chatani, S. Murai, *Chem.Lett.*, **1995**, *24*, 681–682.



Scheme 47. Ru-catalyzed regioselective hydroarylation of alkynes developed by Murai.

A fully atom-economical approach towards endocyclic dienes was reported by Ellman in 2006. The stereoselective alkynylation of α,β-unsaturated imines with alkynes follows also a related mechanistic pathway.[98] Curiously, when disubstituted alkynes were used, the resulting hydrocarbonated products (**40**) further reacted in situ through an electrocyclic ring closure to afford dihydropyridine products of type **41** (Scheme 48, A). Later, the same authors demonstrated that the *in situ* generated dienes of type **41** is the synthetic intermediate of a variety of highly diastereomeric complex piperidines (Scheme 48, B).[99]

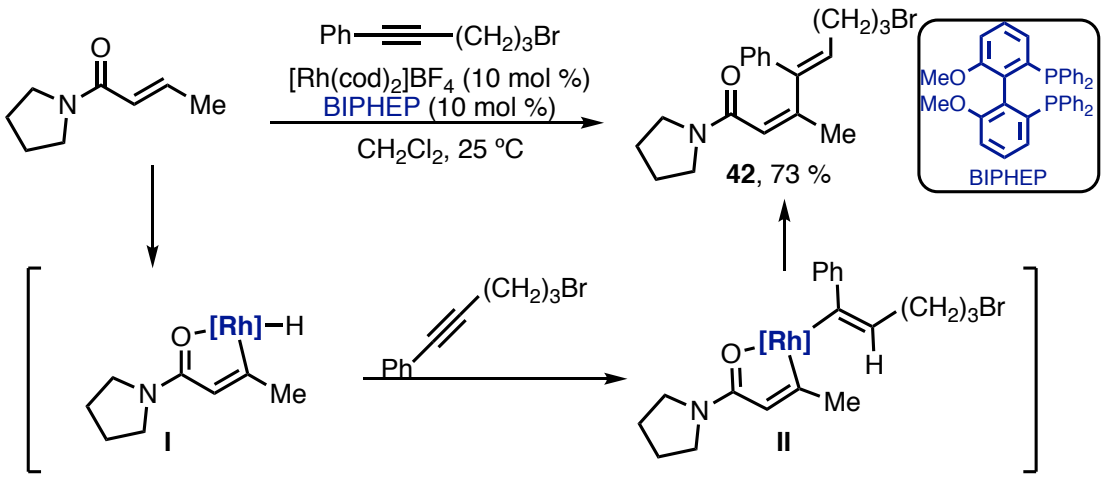
[98] D. A. Colby, R. G. Bergman, J. A. Ellman, *J. Am. Chem. Soc.*, **2006**, *128*, 5604–5605.
[99] S. Duttwyler, S. Chen, M. K. Takase, K. B. Wiberg, R. G. Bergman, J. A. Ellman, *Science,* **2013**, *339*, 678–682.



Scheme 48. Rh-catalyzed alkynylation and electrocyclic ring closure developed by Ellman.

Related intermolecular processes using Ru and Rh catalysts have also been described by Plietker, Tanaka and Zhong using carboxyl esters or carboxamides as directing group for the C–H activation.[100] Tanaka and coworkers have developed a rhodium-catalyzed hydroalkenylation to obtain the diene **42** with almost complete selectivity. The optimal conditions involved $[Rh(cod)_2]BF_4$ and BIPHEP in dichloromethane at room temperature (Scheme 49). Curiously, the use of the 1-pyrrolidinecarbonyl group seems essential for this transformation, whereas dimethyl amides, ester or ketones shut down the reactivity.

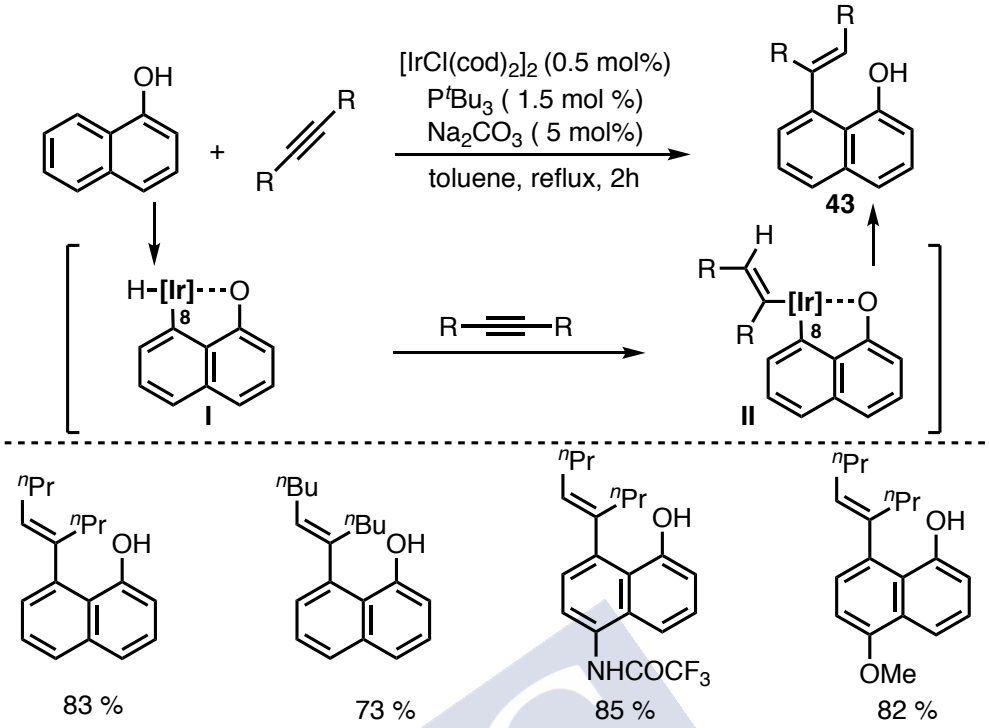
[100] a) Y. Shibata, Y. Otake, M. Hirano, K. Tanaka, *Org. Lett.*, **2009**, *11*, 689–692; b) N. M. Neisius, B. Plietker, *Angew. Chem. Int. Ed.*, **2009**, *48*, 5752–5755; c) K. Meng, J. Zhang, F. Li, Z. Lin, K. Zhang, G. Zhong, *Org. Lett.*, **2017**, *19*, 2498–2501.



Scheme 49. Rh-catalyzed hydroalkynylation developed by Tanaka.

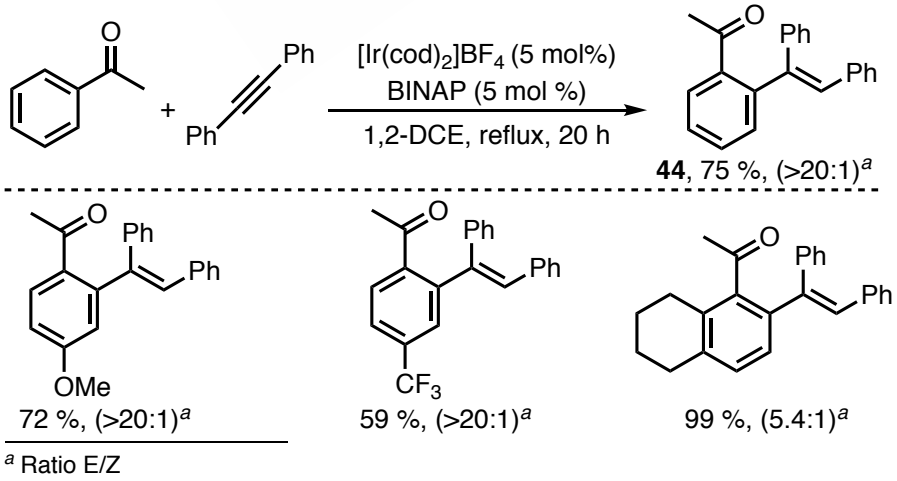
While iridium has been extensively used in C–H bond activation/functionalization processes, the application of this transition metal for the catalytic construction of C–C bonds via hydrocarbonation reactions of alkynes has been scarce. In 1999, Satoh and Miura reported a pioneering example, namely an iridium-catalyzed hydroarylation reaction of alkynes with 1-naphthols, mediated by a catalyst that is generated in situ by combination of $[IrCl(cod)_2]_2$ and tri-*tert*-butylphosphine, with catalytic amounts of Na_2CO_3. The authors suggested a mechanistic pathway that involves the initial coordination of naphthol to the iridium species to form a naphtolate complex by liberation of HCl. Then, an oxidative addition of the C_8-H bond to the iridium center generates **I** which undergoes the alkyne hydrometallation followed by carbon-carbon reductive elimination to afford the hydroarylated product with *cis* stereochemistry.[101]

[101] T. Satoh, Y. Nishinaka, M. Miura, M. Nomura, *Chem. Lett.*, **1999**, *28*, 615–616.



Scheme 50. Pioneering Iridium-catalyzed hydroarylation of naphtols with alkynes developed by Miura.

In 2008, Shibata and coworkers contributed to this field by describing an Ir-catalyzed hydroarylation of alkynes with aryl ketones to give the corresponding *ortho*-alkenylated products **44** with good yields.[102] The best results were achieved with the Ir catalyst generated from $[Ir(cod)_2]BF_4$ and BINAP. The analogous rhodium complexes provided the same products but with lower efficiency. Contrary to the conditions previously found by Miura, monodentate ligands such as PPh_3 or PCy_3 are not suitable for this transformation.

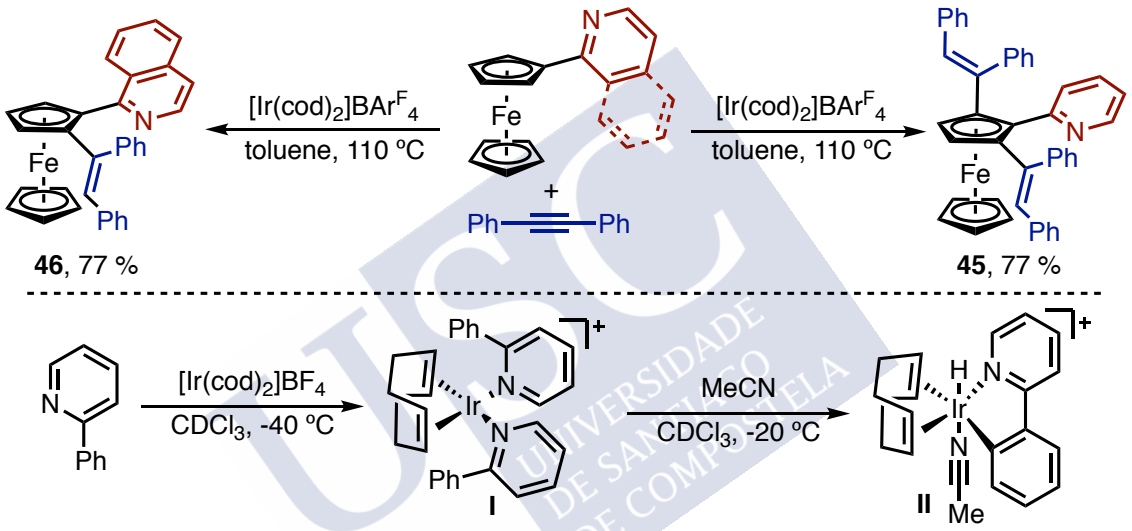


Scheme 51. Ir-catalyzed hydroarylation of aryl ketones with alkynes developed by Shibata.

[102] K. Tsuchikama, M. Kasagawa, Yu-Ki Hashimoto, K. Endo, T. Shibata, *J. Organomet. Chem.*, **2008**, *693*, 3939–3942.

In 2012, Shibata described a catalytic alkenylation of ferrocenes, promoted by $[Ir(cod)_2]BAr^F$ in refluxing chlorobenzene.[103] Curiously, the reaction can give mono- or dialkenylated products depending on the bulkiness of the directing group. Thus, while a pyridine moiety makes the reaction selective towards the *ortho*-dialkylated product **45** (Scheme 52, right), a quinoline directing group yields almost exclusively the monoalkylated ferrocene **46** (Scheme 52, left).

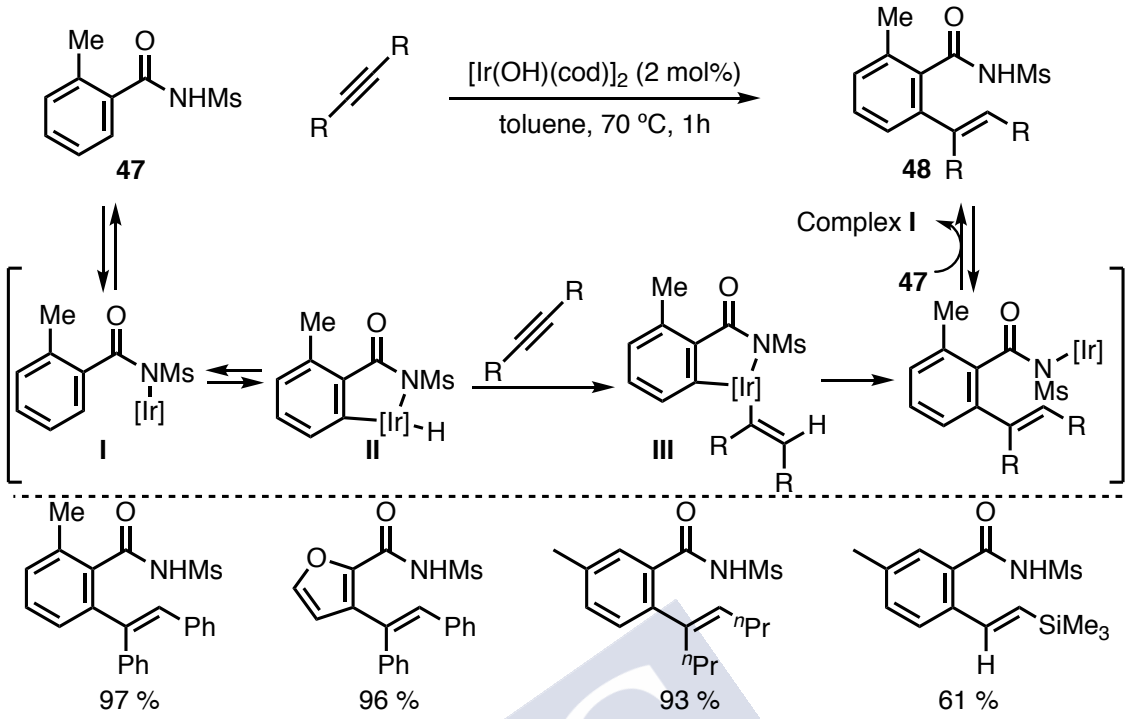
As expected, the reaction is initiated by chelation-assisted oxidative addition of a C–H bond of the cyclopenadienyl (Cp) ring to the iridium(I) complex. Indeed, by using ortho-phenyl pyridine instead of the ferrocenyl analog, the authors were able to detect and trap an Ir(III)–H complex **II** that is generated by adding MeCN to the initially formed complex **I**.



Scheme 52. Ir-catalyzed alkenylation and alkylation of ferrocenes developed by Shibata.

In 2017 Nishimura reported a hydroarylation of alkynes with *N*-sulfonylbenzamides catalyzed by the hydroxoiridium complex $[Ir(OH)(cod)]_2$ (Scheme 53).[104] It is worth to mention that this methodology does not require the use of phosphines or basic additives. The proposed catalytic cycle starts with the deprotonation of the benzamide **47** by the iridium-hydroxide species to generate an amidoiridium species **I**. This intermediate evolves through ortho C–H activation to yield an hydridoiridium metallacycle **II** that undergoes an alkyne migratory insertion by hydrometallation to generate species **III**. Reductive elimination gives the amide **48** and regenerates the amidoiridium **I** upon coordination to **47**.

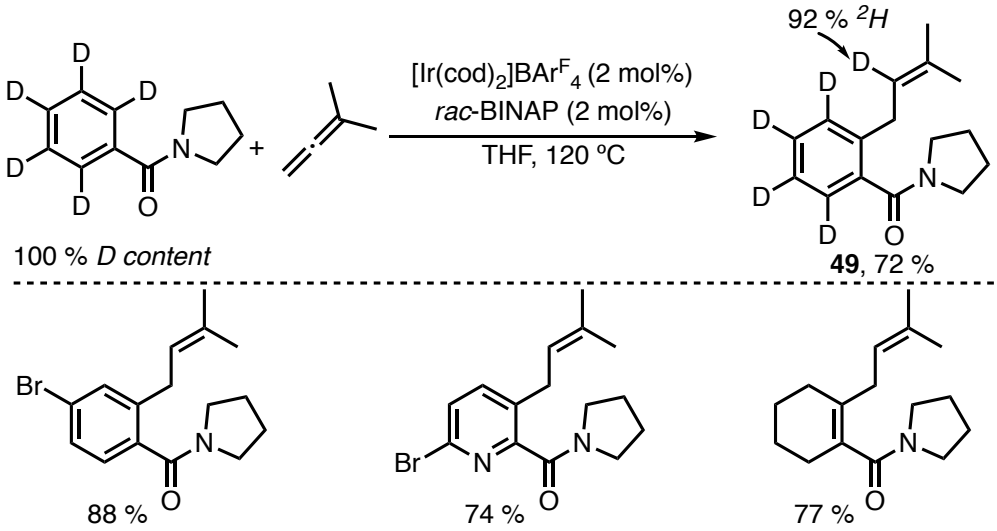
[103] S. Takebayashi, T. Shibata, *Organometallics*, **2012**, *31*, 4114–4117.
[104] M. Nagamoto, J. Fukuda, M. Hatano, H. Yorimitsu, T. Nishimura, *Org. Lett.*, **2017**, *19*, 5952–5955.



Scheme 53. Hydroarylation of Alkynes by a Hydroxoiridium complex developed by Nishimura.

Iridium catalysis is also able to promote the hydrocarbonation of allenes. In particular, in 2009, Krische demonstrated aromatic carboxamides as well as α,β-unsaturated carboxamides react with 1,1-dimethyl allene, in the presence of a cationic iridium complex derived from $[Ir(cod)_2]BAr^F{}_4$ and BINAP to give the corresponding prenylated product in excellent yield, as a single regioisomer (Scheme 54).[105] Deuteration labeling experiments corroborate the *ortho*-C–H oxidative addition. Subsequent allene insertion and reductive elimination steps deliver the product of prenylation **49**, with regeneration of cationic iridium(I).

[105] Y. J. Zhang, E. Skucas, M. J. Krische, *Org. Lett.*, **2009**, *11*, 4248–4250.



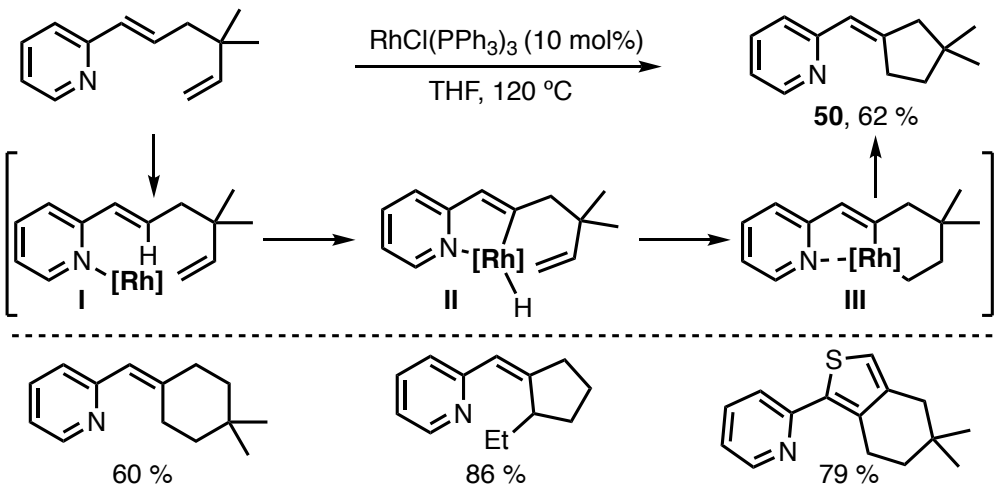
Scheme 54. Iridium-catalyzed hydroarylation of Carboxamides with allenes developed by Krische.

6. Intramolecular alkene and alkyne hydroarylation & hydroalkenylation reactions using TMC

6.1. Intramolecular alkene hydrocarbonation reactions

Regardless of the type of transition-metal catalyst used, intramolecular versions of the above hydrocarbonation transformations are extremely appealing from a synthetic perspective, owing to the possibility of building a ring while there is a concomitant formation of a C–C bond. Therefore, the increase in synthetic complexity in an atom economical way is highly relevant. Murai has also pioneered such intramolecular reactions, using substrates containing pyridines as directing groups (Scheme 55).[106] Both ruthenium and rhodium complexes are competent catalysts for this transformation, albeit the best results were achieved using the Wilkinson catalyst, in THF at 120 ºC. The authors proposed an initial activation of the C(sp^2)–H bond of the alkene, assisted by the coordination of the nitrogen atom of the pyridine to the transition metal (**I**), to give a metalacyclic intermediate of type **II**. The olefin insertion can then take place (**III**) through a hydrometallation process. A subsequent reductive elimination step would yield the intramolecular hydroalkenylated product **50**.

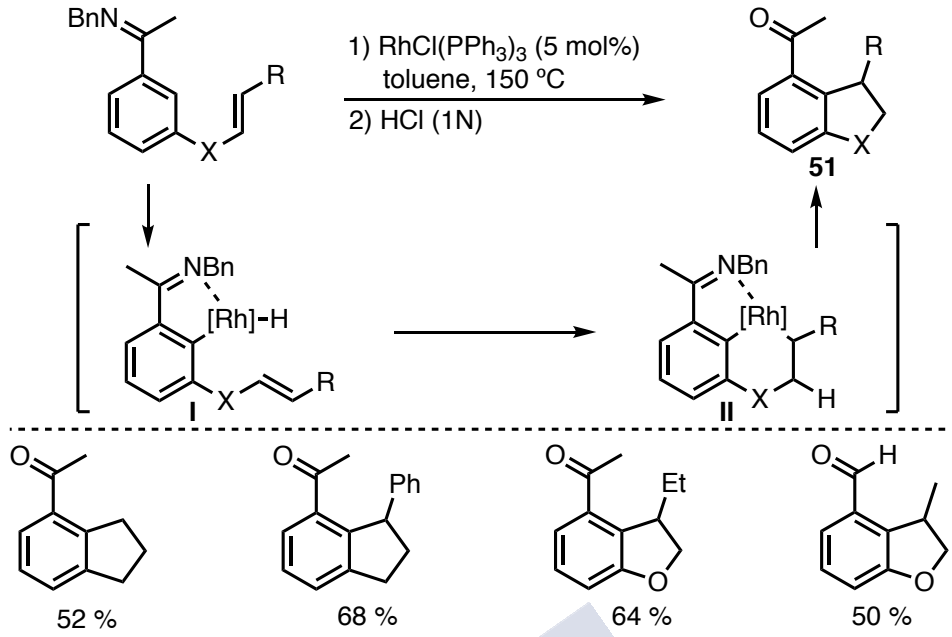
[106] a) F. Kakiuchi, M. Yamauchi, N. Chatani, S. Murai, *Chem. Lett.*, **1996**, *25*, 111–112; b) N. Fujii, F. Kakiuchi, A. Yamada, N. Chatani, S. Murai, *Chem. Lett.*, **1997**, *26*, 425–426; c) Fujii, F. Kakiuchi, A. Yamada, N. Chatani, S. Murai, *Bull. Chem. Soc. Jpn.*, **1998**, *71*, 285–298.



Scheme 55. Rhodium-catalyzed intramolecular hydroalkenylation developed by Murai.

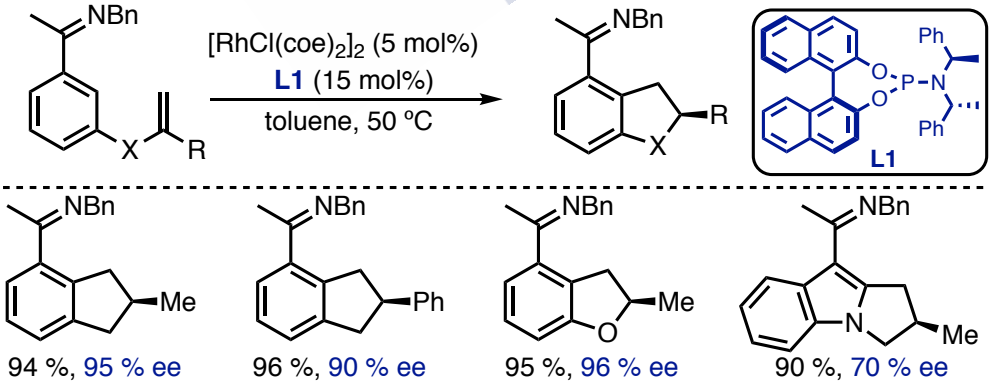
In 2001, Ellman and Bergman reported a rhodium-catalyzed intramolecular cyclization of aromatic ketimines bearing a pendant alkene at the *ortho* position.[107] The reaction provides an expedient access to useful indane, tetralane, dihydrobenzofuran and dihydroindole derivatives (Scheme 56). The optimal conditions involved the use of the Wilkinson catalyst in toluene at 150 ºC, and a benzyl imine as directing group.[108] From a mechanistic point of view, the authors proposed the coordination of the imine to the rhodium complex, followed by C–H bond insertion at the imine *ortho* position, to the generate a rhodium hydride intermediate of type **I**. After the coordination of the olefin to the metal, an *endo*-selective migratory insertion into the Rh-H bond provides a metalacyclic complex (**II**) that undergoes reductive elimination to afford the product **51**.[109] Despite its relevance, the method is basically limited to the use of α-monosubstituted alkenes which, considering the *endo*-selective cyclization, limits the versatility of the process and doesn't permit to build quaternary stereocenters.

[107] a) K. L. Tan, R. G. Bergman, J. A. Ellman, *J. Am. Chem. Soc.*, **2001**, *123*, 2685–2686; b) R. K. Thalji, K. A. Ahrendt, R. G. Bergman, J. A. Ellman, *J. Am. Chem. Soc.*, **2001**, *123*, 9692–9693.
[108] C.-H. Jun, J.-B. Hong, Y.-H. Kim, K.-Y. Chung, *Angew. Chem. Int. Ed.* **2000**, *39*, 3440–3442.
[109] a) R. K. Thalji, K. A. Ahrendt, R. G. Bergman, J. A. Ellman, *J. Org. Chem.* **2005**, *70*, 6775–6781; b) C.-H. Jun, C. W. Moon, J.-B. Hong, S.-G. Lim, K.-Y. Chung, Y.-H. Kim, *Chem. Eur. J.*, **2002**, *8*, 485–492.



Scheme 56. Rhodium-catalyzed intramolecular hydroarylation of imines developed by Ellman.

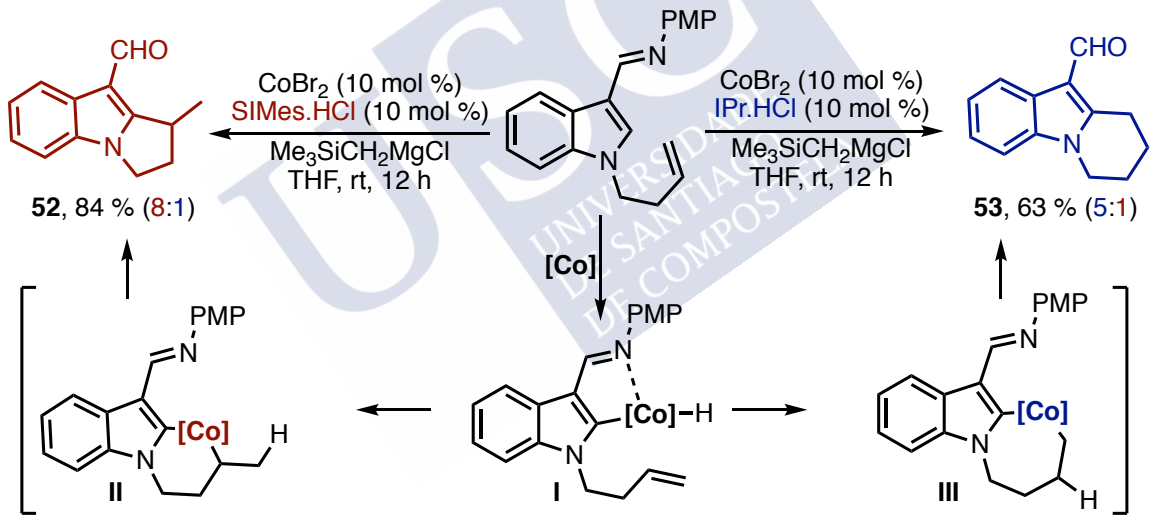
Interestingly, the same group disclosed an enantioselective variant of this process, at milder temperatures, promoted by a rhodium catalyst prepared in situ from $[RhCl(coe)_2]_2$ and a chiral phosphoramidite ligand (Scheme 57).[110] Enantioselectivities of up to 96% were achieved with the binol phosphoramidite (*S*,*R*,*R*)-**L1**. It is proposed that the effectiveness of this catalyst is based on the characteristic binding properties of the ligand, which include reduced σ–donation to rhodium and enhanced π–acceptor ability compared to phosphines.



Scheme 57. Enantioselective cyclization of aromatic imines developed by Ellman.

[110] a) R. K. Thalji, J. A. Ellman, R. G. Bergman, *J. Am. Chem. Soc.*, **2004**, *126*, 7192–7193; b) S. J. O'Malley, K. L. Tan, A. Watzke, R. G. Bergman, J. A. Ellman, *J. Am. Chem. Soc.*, **2005**, *127*, 13496–13497; c) H. Harada, R. K. Thalji, R. G. Bergman, J. A. Ellman, *J. Org. Chem.*, **2008**, *73*, 6772–6779.

An increasing number of examples on cyclization processes relying on C–H activations are being described in more recent years. In 2013, Yoshikai and collaborators reported a cobalt-catalyzed intramolecular olefin hydroarylation of indole derivatives.[111] The optimal conditions for the reaction were found to involve $CoBr_2$ in combination with a N-heterocyclic carbene and the Grignard reagent Me_3SiCH_2MgCl in THF. Different selectivity is obtained depending on the carbene choice: using SIMes.HCl an *exo*-adduct **52** containing a tertiary carbon center is generated, while with IPr·HCl an *endo*-type cyclization to form a derivative **53** is observed (Scheme 58). Unfortunately, the transformation is limited to indole precursors. From a mechanistic point of view, the authors propose an initial C–H oxidative addition of the metal at the C_2-H of the indole derivative (intermediate **I**). Subsequent hydrometallation leads to the six-membered (**II**) or seven-membered cobaltacycle intermediates (**III**), a final reductive elimination step affords the *exo* (**52**) or the *endo* (**53**) product.



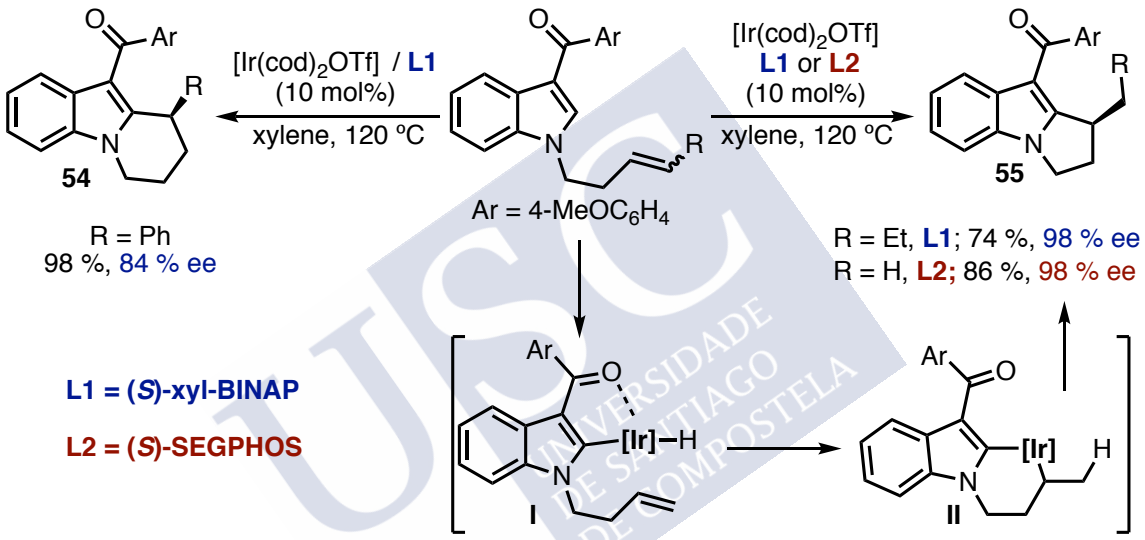
Scheme 58. Cobalt catalyzed intramolecular cyclization of indole derivatives

With regard to the use of iridium catalysts, in contrast to the important number of intermolecular examples (sections 5.1 and 5.2), related intramolecular transformations remained much less studied.

In 2015, Shibata reported a catalytic intramolecular enantioselective C–H hydroarylation of N-tethered alkenyl indoles using a catalyst generated *in situ* from $[Ir(cod)_2]OTf$ and a chiral bisphosphine (**L1** or **L2**).[112] Interestingly, depending on the substitution pattern of

[111] Z. Ding, N. Yoshikai, *Angew. Chem. Int. Ed.* **2013**, *52*, 8574–8578.
[112] T. Shibata, N. Ryu, H. Takano, *Adv. Synth. Catal.*, **2015**, *357*, 1131–1135.

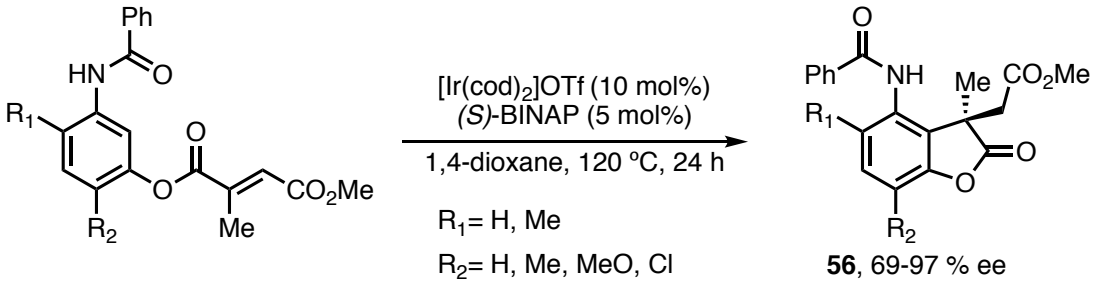
the alkene moiety, 5-*exo* or 6-*endo* products are obtained. Thus, monosubstituted and alkyl disubstituted olefins favor an *exo* pathway to create a dihydropyrroloindole derivative bearing a tertiary stereocenter, **55** (Scheme 59, right). On the contrary, when the terminal substituent of the alkene is an aryl moiety (Scheme 59, left), a 6-*endo*-selective cyclization occurs, delivering the tetrahydropyridoindole derivative (**54**). Despite this versatility, it is worth to highlight that this method has not been proven successful for the generation of quaternary carbon stereocenters. As for the intermolecular hydrocarbonation indoles, the authors proposed a catalytic cycle based on the iridium insertion at the indole C_2-H bond (**I**), followed by a reversible hydroridation and a C–C reductive elimination.



Scheme 59. Ir-catalyzed selective ligand-dependent cyclization developed by Shibata.

Already in 2018, Shibata and coworkers demonstrated that the hydrocarbonation of α,β-unsaturated acrylates with acetanilides (see scheme 60) could also be successfully developed in an intramolecular fashion, to yield chiral γ-lactones of type **56**, with chiral quaternary carbon stereocenters.[113] The optimal conditions were achieved by using the iridium complex resulting from [Ir(cod)$_2$OTf] and (*S*)-BINAP. Albeit the scope is modest, the chiral γ-lactones can be obtained with moderate to good enantioselectivities.

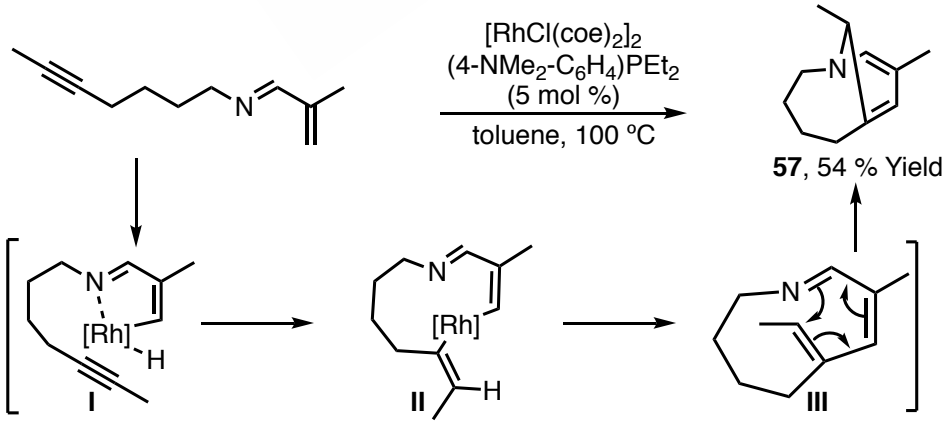
[113] T. Shibata, H. Kurita, S. Onoda, K. S. Kanyiva, *Asian J. Org. Chem.* **2018**, *7*, 1411–1418.



Scheme 60. Ir-catalyzed intramolecular hydrocarbonation of acrylates developed by Shibata.

6.2. Intramolecular Alkyne hydrocarbonation reactions

Examples on metal-catalyzed intramolecular hydrocarbonations of alkynes based on the activation of inert C–H bonds are scarce, regardless of the type of metal used. In 2008, Ellman and coworkers disclosed a rhodium catalyzed intramolecular alkenylation of α,β-unsaturated imines bearing a *N*-tethered alkyne moiety, to yield bridgehead azabicycles **57**.[114] The optimal conditions to generate the dienic product consist of using $[RhCl(coe)_2]_2$ and [4-(dimethylamino)phenyl]diethylphosphine, in toluene at 100 ºC. From a mechanistic point of view, the authors propose a first imine-directed C–H activation at the β-position of the alkene to form the vinyl rhodium intermediate **I**. A regioselective hydrometalation of the alkyne to yield a rhodacyclic intermediate **II**, which evolves through reductive eliminations to yield **III**. Finally, the bridgehead enamide **57** is produced by a subsequent electrocyclization process (Scheme 61).



Scheme 61. Rh-catalyzed bridgehead azabicycles based on Rh-catalyzed intramolecular hydroalkenylation .

[114] a) S. Yotphan, R. G. Bergman, J. A. Ellman, *J. Am. Chem. Soc.,* **2008**, *130*, 2452–2453. b) D. A. Colby, R. G. Bergman, J. A. Ellman, *J. Am. Chem. Soc.,* **2008**, *130*, 3645–3651.

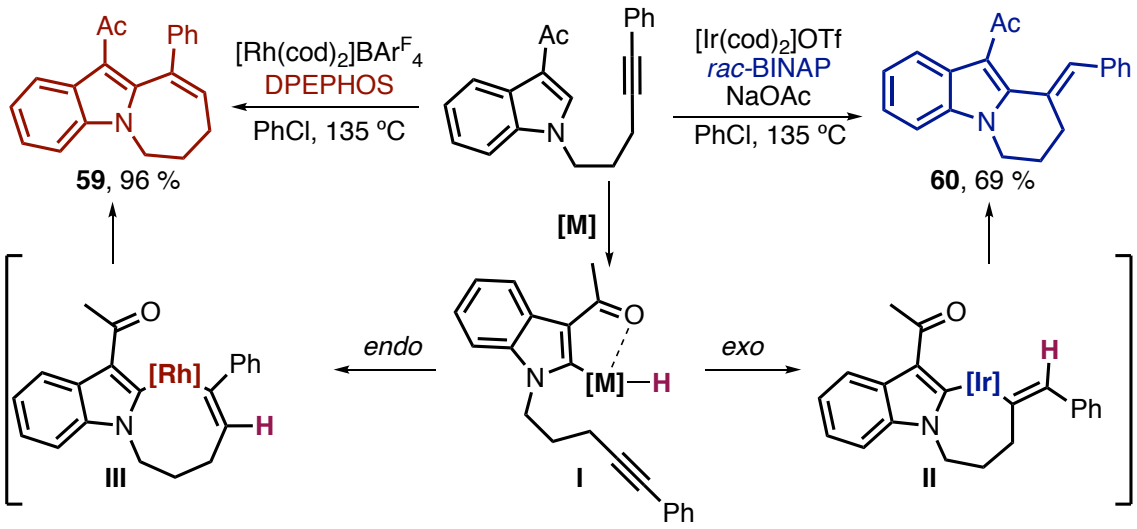
On the other hand, Ellman also showed that when the alkyne is tethered to the α,β-unsaturated imine through the β-carbon, a cyclohexenyl product **58** bearing a *Z*-exocyclic enal is obtained, using the same catalytic system composed by $[Rh(coe)_2Cl]_2$ and the electron rich phosphine 4-$Me_2NPhPEt_2$ (scheme 62).[115]

58, 45 %, 20:1 *Z/E*

Scheme 62. Rh-catalyzed intramolecular hydroalkynylation developed by Ellman.

With respect to iridium catalysts, at the outset of our work, we were not aware of any report on the topic. Nonetheless, while our work was in progress, in 2017, Shibata and coworkers described an iridium-catalyzed intramolecular hydroarylation of *N*-tethered alkynyl indoles.[116] Remarkably, the selectivity of the cyclization could be tuned by the choice of metal catalyst. Thus, while an iridium catalyst such as $[Ir(cod)_2]OTf$ / BINAP promotes a 6-*exo*-dig cyclization to yield the tricyclic product **60**, an homologous Rh catalyst induces an alternative 7-*endo*-dig cyclization that delivers **59** (Scheme 63).[117] From a mechanistic perspective, the authors suggested that, after an initial chelation-assisted C–H oxidative addition (**I**), a *trans* hydrometalation[118] would occur in the case of the rhodium catalyst, to yield an eight-membered rhodacyclic intermediate **III**. Then, a reductive elimination would yield the observed seven-membered derivative. On the other hand, with the iridium catalyst, an *exo*-selective hydrometalation would take place, to afford **II.** After a C–C reductive elimination, the six-membered product would be generated.[119] Reasons on the metal-dependent regioselectivity were not discussed.

[115] J. Ellman, Y. Matsushima, E. Phillips, R. Bergman, *Synlett*, **2015**, *26*, 1533–1536.
[116] T. Shibata, T. Baba, H. Takano, K. S. Kanyiva, *Adv. Synth. Catal.*, **2017**, *359*, 1849–1853.
[117] The use of a base such as NaOAc is essential with the Iridium (I) conditions to avoid partial isomerization of the double bond of **60**, to the internal position.
[118] K. Tanaka, G. C. Fu, *J. Am. Chem. Soc.*, **2003**, *125*, 8078–8079.
[119] The authors indicate that an alternative mechanistic scenario based on a carbometalation and C-H reductive elimination cannot be fully excluded.



Scheme 63. Metal-dependent intramolecular hydroarylation with alkynes developed by Shibata.

As a summary of section 5, great efforts have been devoted to the development of highly versatile and powerful intermolecular metal-promoted hydroarylation reactions using unsaturated partners such as alkynes, alkenes or allenes. Very recently, the first examples of intramolecular reactions have also been disclosed (section 6), although the processes are still very limited in terms of substrate scope, asymmetric reactions or the building of products with chiral carbon quaternary centers. Hydroalkenylations instead of hydroarylations have also been much scarcely explored.

Importantly, mechanistic studies based on DFT calculations and deuterium labeling experiments have also been performed. While most initial studies suggested that the reactions involve hydrometallation pathways, recent data, especially with iridium catalysts, suggest that carbometalation/C–H reductive eliminations could be operative.

Chapter I - Iridium(I)-Catalyzed Intramolecular Hydrocarbonation of Alkenes: Efficient Access to Cyclic Systems Bearing Quaternary Stereocenters

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1. Introduction

As can be deduced from the discussion of section 5.1 and 6.1, the hydrocarbonation of alkenes by activation of a Csp^2-H bond in aromatic or alkenyl precursors is a very powerful transformation from the synthetic and sustainable point of view. Research in this field has been mostly focused on intermolecular couplings (section 5.1), using low-valent transition metal catalysts (including Ni^0, Ru^0, Co^0 and Rh^I complexes), and aromatic or heteroaromatic precursors. Several examples with iridium catalysts have also been described. These transformations allow to access linear and branched products, with the former being the most common in the literature. Mechanistically there are yet many aspects which are not clear, especially if the reactions proceed by hydro or carbometallation.

Although being even more relevant in terms of synthetic opportunities, the intramolecular scenario has been far less studied. As described in the section 6.1, Murai, as well as Ellman and Bergman, have pioneered such intramolecular processes using pyridines and imines as directing groups (DGs), and Rh^I or Ru^0 catalysts, with iridium being much less explored. Curiously, most examples are limited to heteroaromatic or aromatic precursors and usually proceed via *endo*-selective cyclizations.

Another key feature of these described processes is the limitation to build secondary or tertiary carbon centers, remaining elusive the assembly of highly appealing quaternary carbon centers. Finally, the development of enantioselective approaches in the intramolecular hydrocarbonation of alkenes is still in its infancy.

1.2. Building of quaternary stereocenters using cyclization reactions

Despite the magnificent development of synthetic methodologies over the last decades, the stereoselective construction of chiral carbon quaternary centers through catalytic methods remains a significant challenge in organic synthesis.[120]

[120] Quaternary center is a term that causes controversy in literature because it is used as synonym of "quaternary-substituted carbon", which includes tri-carbon substituted sp^3 carbon. In this memory we use the expression "carbon quaternary center" to describe tetra-carbon substituted carbon centers.

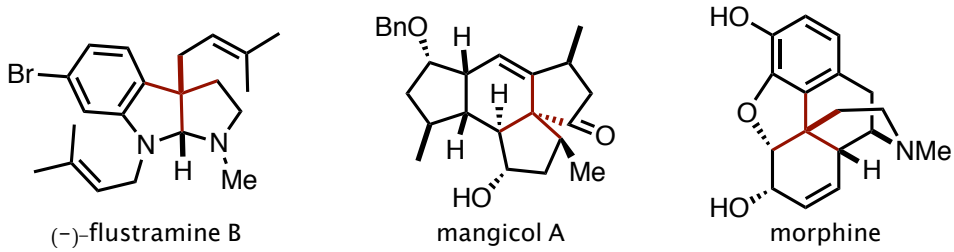


Figure 4. Quaternary stereocenters in relevant biologically-active molecules

Carbon quaternary stereocenters are found in numerous biologically active natural molecules (Fig. 4) and also in the bestseller pharmaceutical agents.[121] The inherent steric hindrance is the main issue in building quaternary carbon centers. Moreover, the stereoselective assembly of these centers relies on the mandatory use of C–C bond-forming reactions that provide a specific three-dimensional orientation of the substituents.

While the stereoselective preparation of chiral "fully-substituted carbons" can be successfully accomplished by the face-selective addition of nucleophiles to carbon-heteroatom double bonds such as asymmetrical ketones or imines,[122] the stereoselective assembly of all-carbon quaternary centers is much more challenging, and there are very limited methodologies that allow their formation.[123]

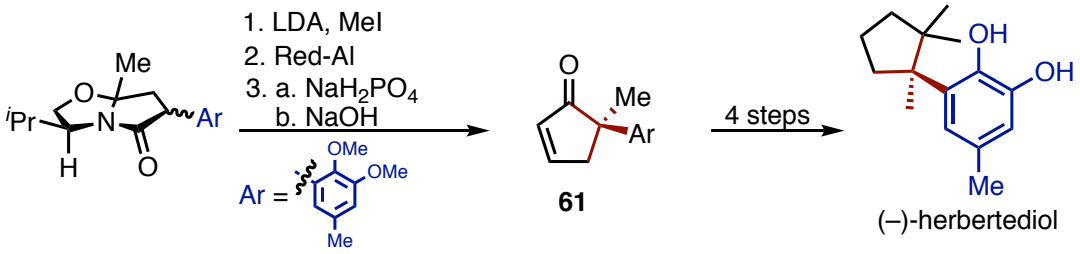
Regarding intermolecular processes, many of the strategies rely on the alkylation of enolates. For example, in the synthesis of (-)-herbertenediol,[124] the authors developed an *endo*-face selective methylation of a chiral bicyclic lactam which delivers a quiral quaternary stereogenic center. Reduction with Red-Al, hydrolysis and subsequent intramolecular aldol condensation affords the cyclopentanone **61**, which was converted to (-)-herbertenediol in 4 simple steps.

[121] A. Fuentes, M. Pineda, K. Venkata, *Pharmacy*, **2018**, *6*, 43.

[122] a) L. Pu, H.-B. Yu, *Chem. Rev.*, **2001**, *101*, 757–824; b) S. E. Denmark, N. Nakajima, O. J.-C. Nicaise, *J. Am. Chem. Soc.*, **1994**, *116*, 8797–8798.

[123] a) Sharpless asymmetric epoxidation; R. A. Johnson, K. B. Sharpless, in *Catalytic Asymmetric Synthesis*, ed. I. Ojima, 2nd ed., Wiley-VCH, New York, **2000**, Chapter 6A; b) Sharpless asymmetric dihydroxylation; K. B. Sharpless et al., *J. Org. Chem.* **1992**, *57*, 2768–2771; c) Chiral dioxirane epoxidation; M. Frohn, Y. Shi, *Synthesis,* **2000**, 1979–2000; d) Jacobsen asymmetric epoxide ring opening reaction; E. N. Jacobsen, *Acc. Chem. Res.,* **2000**, *33*, 421–431.

[124] A. P. Degnan, A. I. Meyers, *J. Am. Chem. Soc.,* **1999**, *121*, 2762–2769.



Scheme 64. Total synthesis of (-)-herbertenediol described by Meyers

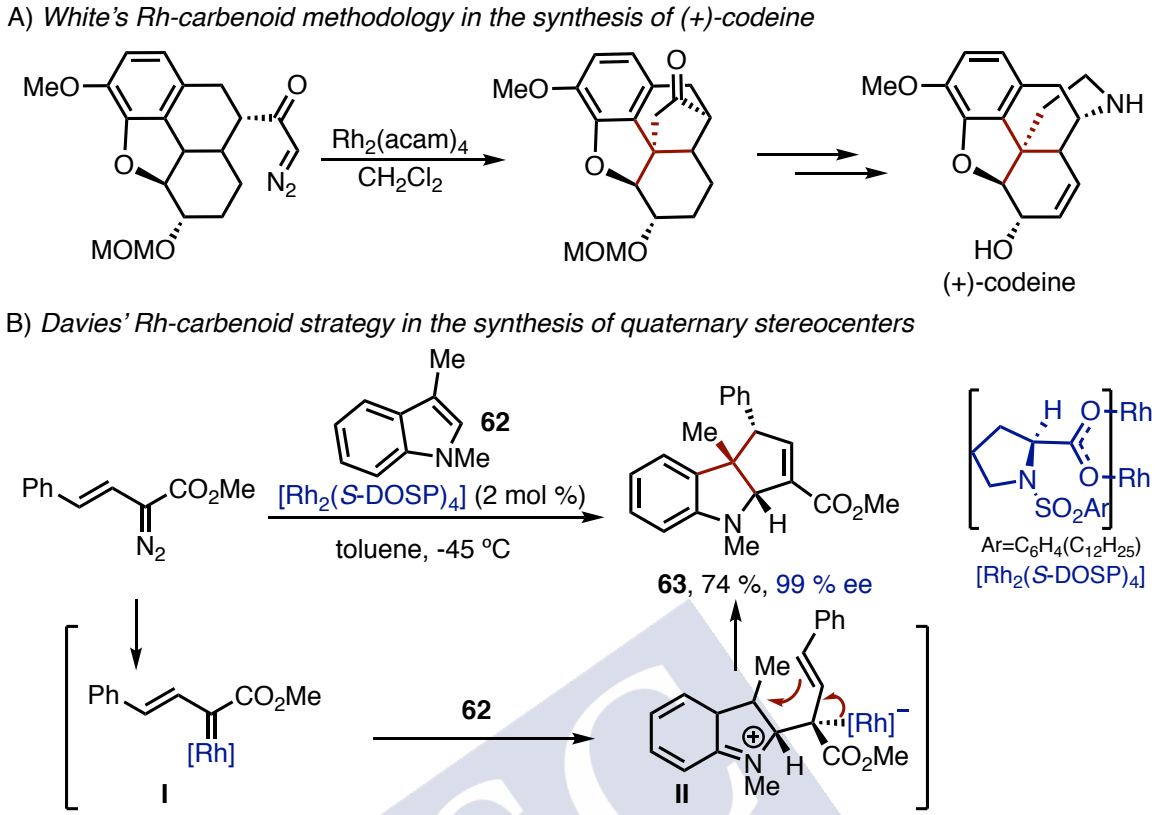
In these technologies, the requirement of chiral auxiliaries represents a severe limitation in terms of efficiency and atom-economy, and thus there is a great interest on the development of catalytic methods. In recent years, a number of catalytic reactions that allow to build fully quaternary stereocenters, even in an enantioselective manner, have been reported.[125,126] Some of these methods rely on C–H activation processes. For instance, White and collaborators described in 1998 an inspiring work towards (+)-codeine core by an elegant Rh-carbenoid methodology (Scheme 65, A).[127] Related enantioselective C–H functionalizations with chiral Rh complexes were also reported during the last decade, albeit they are still limited. In the example shown in Scheme 65 (B) described by Davies and coworkers, the intermolecular C–H functionalization of indole **62**, with the rhodium carbenoid **I** generated from methyl phenyldiazoacetate delivers cyclopentene fused indolines **63**, bearing a chiral quaternary stereocenter.[128] The reaction is believed to proceed through the dipolar intermediate **II** and occurs with excellent yields and enantioselectivities.

[125] a) Y. Hamashima, D. Hotta, M. Sodeoka, *J. Am. Chem. Soc.*, **2002**, *124*, 11240–11241; b) J. F. Austin, S.-G. Kim, C. J. Sinz, W.-J. Xiao, D. W. C. MacMillan, *PNAS*, **2004**, *101*, 5482–5487; c) M. Bruncko, D. Crich, R. Samy, *J. Org. Chem.*, **1994**, *59*, 5543–5549; d) M. Ishizaki, Y. Niimi, O. Hoshino, *Tetrahedron Lett.* **2003**, *44*, 6029–6031; e) F. W. Ng, H. Lin, P. Chiu, S. J. Danishefsky, *J. Am. Chem. Soc.*, **2003**, *125*, 13303–13303; f) B. M. Trost, O. R. Thiel, H.-C. Tsui, *J. Am. Chem. Soc.*, 2003, 125, 13155–13164. For relevant reviews on this topic see: g) R. Long, J. Huang, J. Gong and Z. Yang, *Nat. Prod. Rep.*, **2015**, *32*, 1584–1601; h) J. Christoffers and A. Baro, *Adv. Synth. Catal.*, **2005**, *347*, 1473–1482; i) I. D. G. Watson and F. D. Toste, *Chem. Sci.*, **2012**, *3*, 2899; j) K. W. Quasdorf and L. E. Overman, *Nature*, **2014**, *516*, 181–191.

[126] R. E. Giudici, A. H. Hoveyda, *J. Am. Chem. Soc.*, **2007**, *129*, 3824–3825.

[127] J. D. White, P. Hrnciar, F. Stappenbeck, *J. Org. Chem.*, **1997**, *62*, 5250–5251.

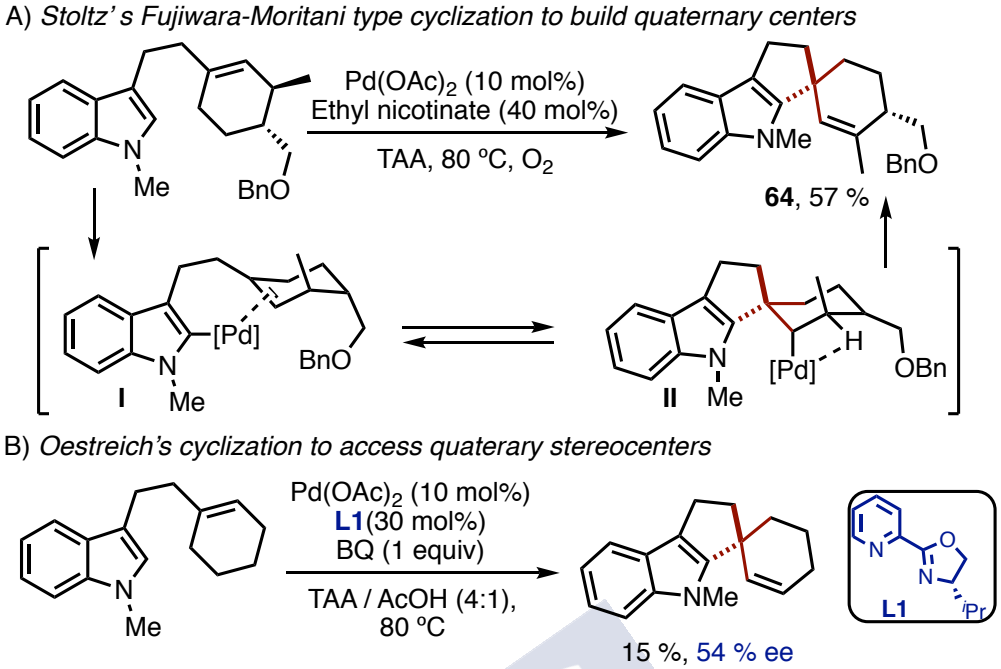
[128] Y. Lian, H. M. L. Davies, *J. Am. Chem. Soc.*, **2010**, *132*, 440–441.



Scheme 65. Rh-carbenoids in the synthesis of quaternary centers.

Focusing on intramolecular processes based on C–H activation reactions, it is remarkable the Fujiwara–Moritani cyclization reported by Stoltz 2003. In particular, these authors used a palladium-mediated C–H activation to create five-membered cyclic structures with a quaternary center adjacent to the C_2 position of the indole (Scheme 66, A).[129] The cyclization optimal conditions involved the use of $Pd(OAc)_2$ and ethyl nicotinate in *tert*-amyl alcohol, under oxygen. From a mechanistic perspective, the cyclization starts with a palladation to yield intermediate **I**, that after a reversible olefin insertion generates **II**. Subsequent β-hydrogen elimination closes the catalytic cycle yielding the indole derivative **64**. In 2008, Oestreich and coworkers described an asymmetric variant of this Fujiwara-Moritani cyclization, using palladium acetate and a chiral PyBOX ligand as catalyst precursors.[130] In this intramolecular enantioselective work, moderate yields and modest enantiomeric ratios of indole polycyclic scaffolds bearing carbon quaternary centers are obtained (Scheme 66, B).

[129] E. M. Ferreira, B. M. Stoltz, *J. Am. Chem. Soc.*, **2003**, *125*, 9578–9579.
[130] a) M. Oestreich, J. Schiffner, A. Machotta, *Synlett*, **2008**, *15*, 2271–2274; b) J. A. Schiffner, T. H. Wöste, M. Oestreich, *Eur. J. Org. Chem.*, **2010**, 174–182.



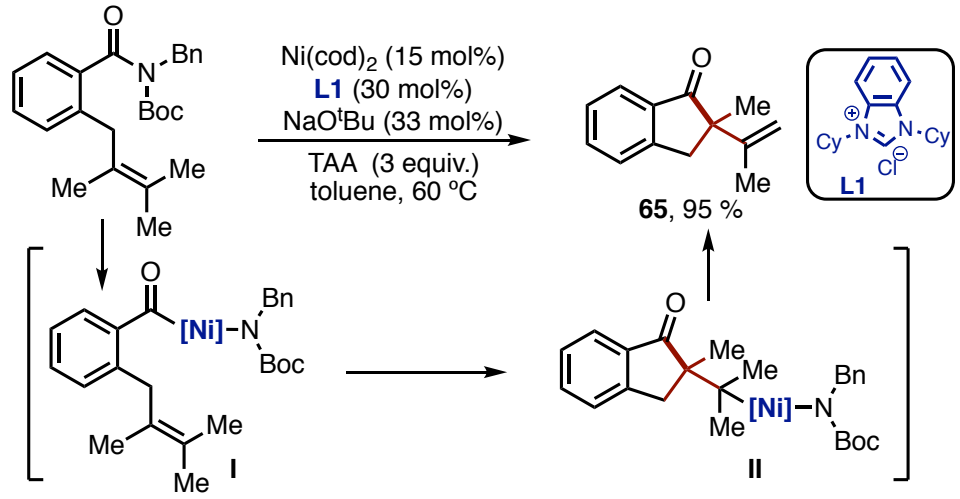
Scheme 66. Pd-catalyzed Fujiwara–Moritani cyclizations in the synthesis of quaternary centers.

Recently, a Mizoroki-Heck cyclization of amide derivatives was reported by Garg and coworkers to provide cyclic systems with carbon quaternary centers.[131] The best catalytic conditions for the transformation consisted of the use of low valent nickel complex [Ni(cod)$_2$] and a *N*-heterocyclic carbene ligand (**L1**, Scheme 67, A). The reaction proceeds smoothly with a variety of alkenes, leading to the formation of relevant cyclopentanone derivatives with a quaternary center adjacent to the oxo group. From a mechanistic point of view, the cyclization reaction is initiated by the oxidative addition into the C-N group to give **I**, followed by the olefin insertion to generate the intermediate **II** that upon β-hydride elimination leads to the ketone **65**.

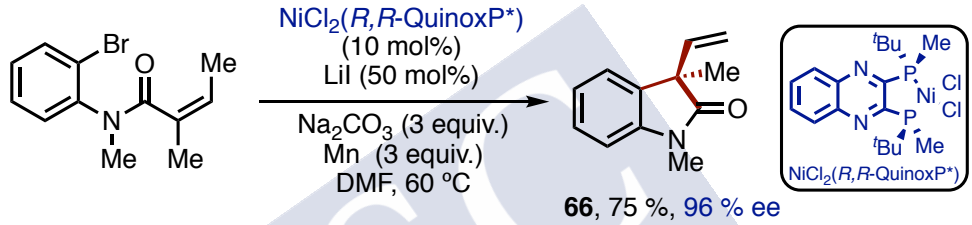
A related quaternary carbon forming strategy based on enantioselective Mizoroki-Heck cyclization of 2-bromo anilides was reported in 2017.[132] The optimal catalytic system involves the use of $NiCl_2$(*R*,*R*-QuinoxP*), lithium iodide, sodium carbonate and manganese as reductant. This methodology allows the formation of the oxindole derivatives **66** (Scheme 67, B) in high yields and enantiomeric excesses.

[131] J. M. Medina, J. Moreno, S. Racine, S. Du, N. K. Garg, *Angew. Chem. Int. Ed.* **2017**, *56*, 6567–6571.
[132] J.-N. Desrosiers, J. Wen, S. Tcyrulnikov, S. Biswas, B. Qu, L. Hie, D. Kurouski, L. Wu, N. Grinberg, N. Haddad, et al., *Org. Lett.* **2017**, *19*, 3338–3341.

A) *Garg's Mizoroki-Heck cyclization of benzamide derivatives*

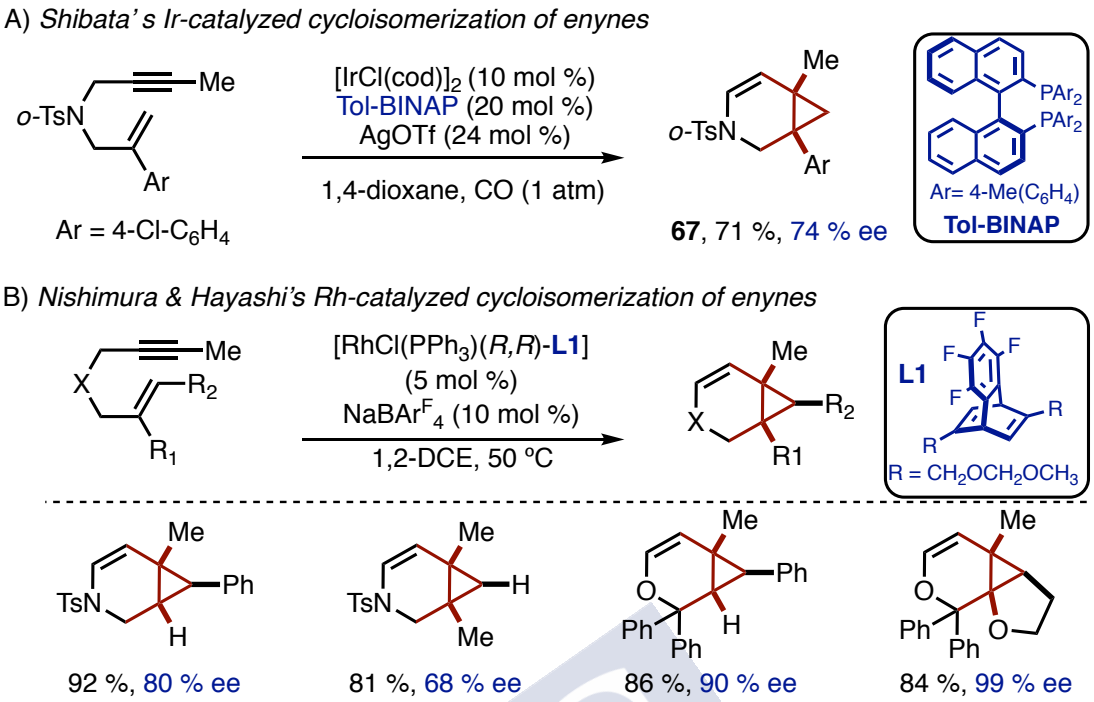


B) *Garg's & CW Mizoroki-Heck cyclization of anilide derivatives*



Scheme 67. Pd-catalyzed Mizoroki-Heck cyclizations in the synthesis of quaternary centers.

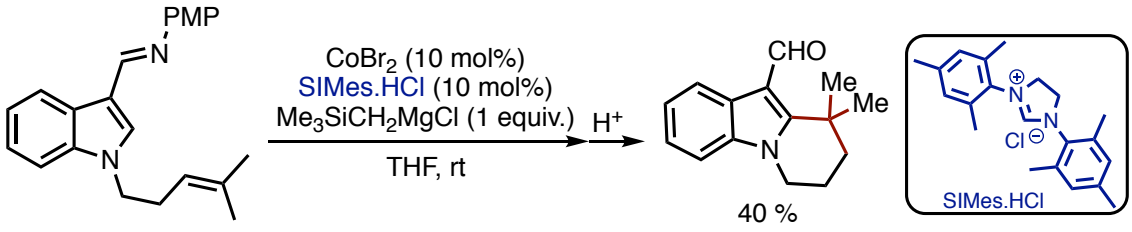
In 2005, Shibata and coworkers reported a metal-mediated method that delivers cyclopropyl containing cyclic systems bearing quaternary carbon centers. Specifically, these authors developed an iridium-catalyzed enantioselective cycloisomerization of nitrogen-bridged 1,6-enynes to yield azabicyclo[4.1.0]heptenes (**67**, Scheme 68, A). $[IrCl(cod)]_2$, TolBINAP and AgOTf were the optimal conditions found for the transformation. The bicyclic structures are obtained with moderate to good yields and enantioselectivities. Later on, in 2010 Nishimura and Hayashi reported a scope-expanded asymmetric cycloisomerization approach using rhodium complexes bearing chiral diene ligands. The best catalytic system, shown in scheme 68 (B) allows the formation of 3-oxa and 3-aza-bicyclo[4.1.0] heptenes in high yields and remarkable enantiomeric excesses.



Scheme 68. Ir and Rh-catalyzed enantioselective cycloisomerizations in the synthesis of quaternary centers.

With regard to cycloisomerizations based on TMC hydrocarbonation processes, most of the examples so far described do not generate chiral carbon stereocenters and very few have been developed in an enantioselective fashion.

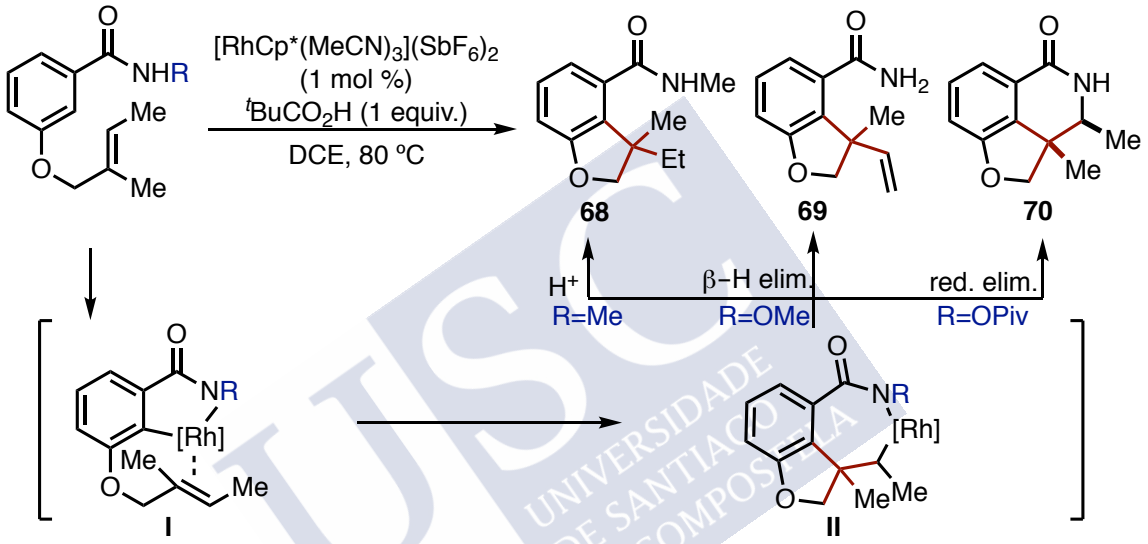
In 2013, Yoshikai reported a cobalt-NHC-catalyzed intramolecular hydroarylation to afford dihydropyrroloindole and tetrahydropyridoindole derivatives under mild conditions (Scheme 69).[133] This aldimine-directed C–H activation was found optimal using $CoBr_2$ and the SIMes carbene in THF at room temperature. Despite the novelty of this transformation, the methodology was not used to build chiral carbon quaternary centers.



Scheme 69. Co-catalyzed cycloisomerization in the synthesis of quaternary centers.

[133] Z. Ding, N. Yoshikai, *Angew. Chem. Int. Ed.*, **2013**, *125*, 8736–8740.

In 2013, Rovis and collaborators reported a rhodium-catalyzed intramolecular cyclization of benzamides bearing tethered alkenes, albeit it does not really consist of a hydrocarbonation, but relies on CMD C–H activation followed by a carbometallation and protodemetalation (Scheme 70).[134] With the methodology, they could generate quaternary carbon centers in a racemic fashion. The optimal conditions involved the cationic Rh(III) complex $[RhCp^*(MeCN)_3](SbF_6)_2$, together with pivalic acid in dichloroethane. From the intermediate **II**, resulting from the carbometalation, and depending on the R substituent at the nitrogen, a protonation to yield **68**, a β-hydride elimination to give **69** or a reductive elimination to afford **70** can occur.



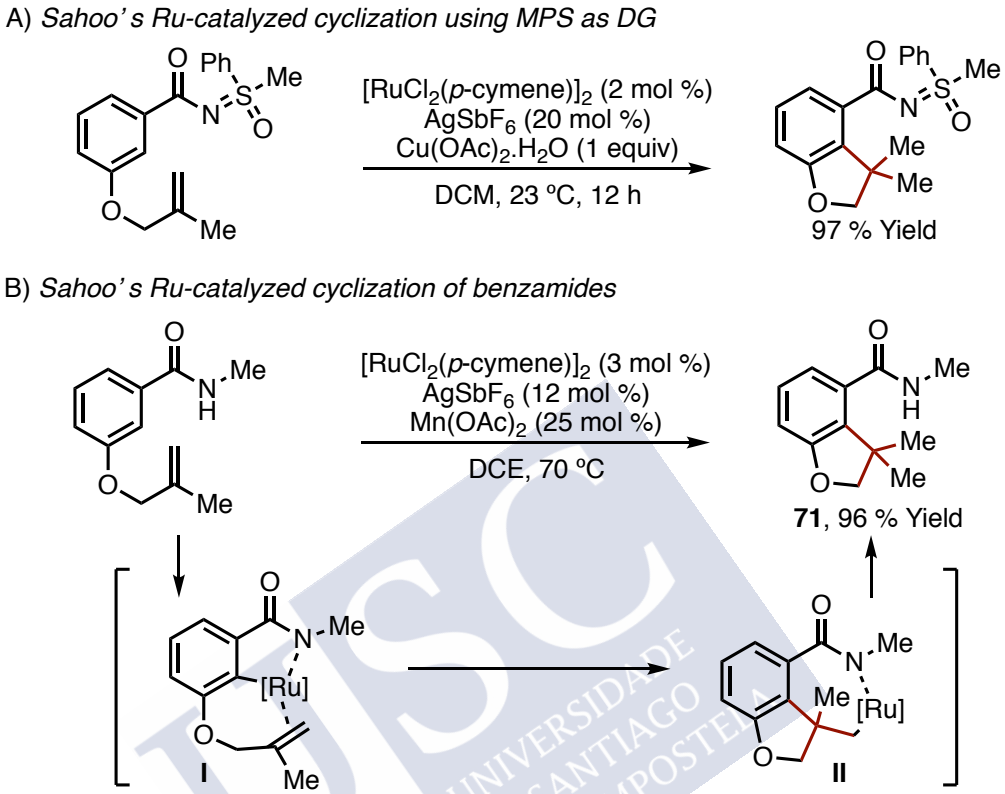
Scheme 70. Rh-catalyzed intramolecular cyclization in the synthesis of quaternary centers.

In 2016, Sahoo and coworkers disclosed a mechanistically-related ruthenium-catalyzed alternative using methyl phenyl sulfoximine as directing group and the cationic ruthenium complex *in situ* formed from $[RuCl_2(p\text{-cymene})]_2$, $AgSbF_6$ and $Cu(OAc)_2$.[135] The silver salt presumable acts as a chloride scavenger, while a copper salt is also used to regenerate the catalyst. Despite the remarkable scope of the process, enantioselective versions were not reported.

The same group published an analogous methodology using simple and readily available amides as directing group.[136] In this case the best conditions involved the use of $[RuCl_2(p\text{-cymene})]_2$, $AgSbF_6$, and $Mn(OAc)_2$ in dichloroethane at 70 ºC. From a mechanistic point of view the authors suggested that the initial step is the C–H activation via a CMD pathway

[134] T. A. Davis, T. K. Hyster, T. Rovis, *Angew. Chem. Int. Ed.*, **2013**, *52*, 14181–14185.
[135] K. Ghosh, R. K. Rit, E. Ramesh, A. K. Sahoo, *Angew. Chem. Int. Ed.*, **2016**, *55*, 7821–7825.
[136] R. K. Rit, K. Ghosh, R. Mandal, A. K. Sahoo, *J. Org. Chem.*, **2016**, *81*, 8552–8560.

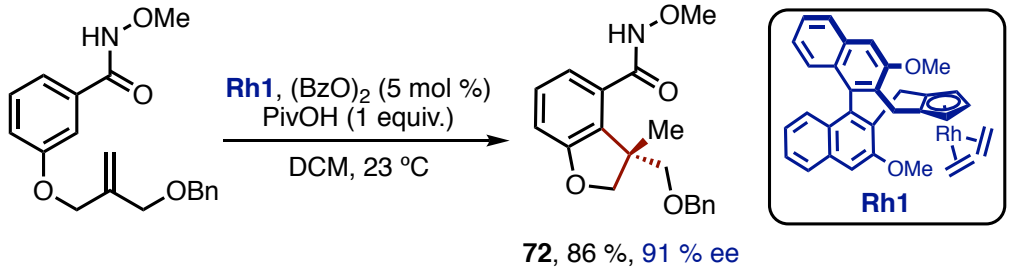
to generate the intermediate **I**. Subsequent alkene migratory insertion yields the intermediate **II** that evolves through protodemetalation to the cyclic product **71** (Scheme 71, B).



Scheme 71. Ru-catalyzed intramolecular cyclizations in the synthesis of quaternary centers.

One of the main limitations of high-valent transition metals consist of the difficulties for the development of asymmetric processes, since the conditions used with these catalysts are not compatible with chiral ligands such as phosphines, phosphites, phosphoramidites, bipyridines or N-heterocycliccarbenes. In 2014, Cramer reported a beautiful example toovercome this limitation, which relies on newly developed chiral cyclopentadienyl ligands for Rh(III). The chiral catalyst generated from **Rh1** upon oxidation with $(BzO)_2$ was able to catalyze the hydroarylation of alkenyl tethered benzamides of type **72** to yield the corresponding bicyclic systems bearing a quaternary carbon stereocenter with good enantioselectivities.[137]. The process is limited to the cyclization of aromatic precursors, and as commented, it is not a cycloisomerization, but an addition/protonation reaction.

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



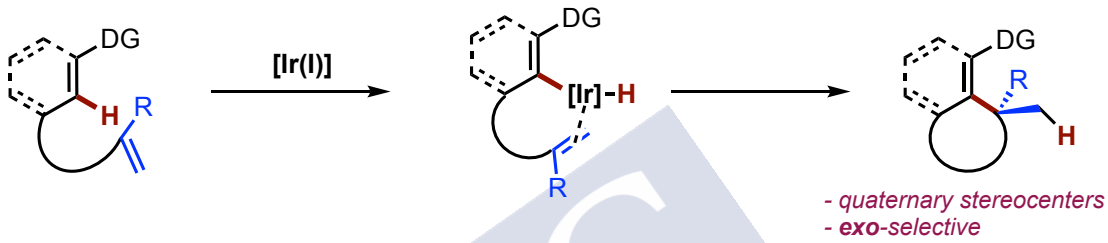
72, 86 %, 91 % ee

Scheme 72. Rh-catalyzed intramolecular cyclization of benzamides described by Cramer.

In summary, the development of intramolecular transition metal catalyzed hydrocarbonation reactions leading to cyclic systems with chiral carbon quaternary stereocenters is essentially unknown. Most examples are based on the use of Rh(III) and Ru(II) catalysts that proceed through a CMD process and an eventual protodemetallation. Moreover, the development of enantioselective variants of these cyclizations processes is almost unprecedented and the only example reported so far makes use of a Rh(III) complex with a chiral Cp ligand.

2. Objectives

On the basis of the above precedents, and the lack of methods to build carbon quaternary sterocenters using cycloisomerization reactions, we set as one of our goals the development of an intramolecular hydrocarbonation reaction that could generate quaternary carbon centers, by activation of C(sp^2)–H bonds of aromatic, heteroaromatic and olefin precursors. Moreover, we planned to carry out mechanistic studies and develop enantioselective versions of the developed method.



Scheme 73. Hydrocarbonation of alkenes. Design and proposal

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3. Article 1: Iridium(I)-Catalyzed Intramolecular Hydrocarbonation of Alkenes: Efficient Access to Cyclic Systems Bearing Quaternary Stereocenters.

Doi : https://doi.org/10.1002/anie.201705105

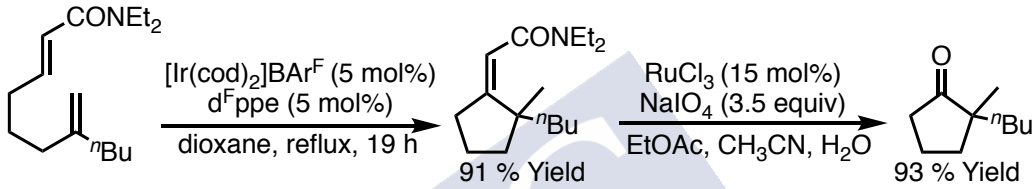
David F. Fernández, Moisés Gulías, José Luís Mascareñas and Fernando López, *Angew. Chem. Int. Ed.*, **2017**, *56*, 9541–9545.

Author contributions

J.L.M, M.G. and F.L. supervised the research. D.F. performed all the experiments as well as the amide precursors synthesis. F. L. and JLM wrote the manuscript with inputs from all authors. All authors discussed the results and revised the manuscript.

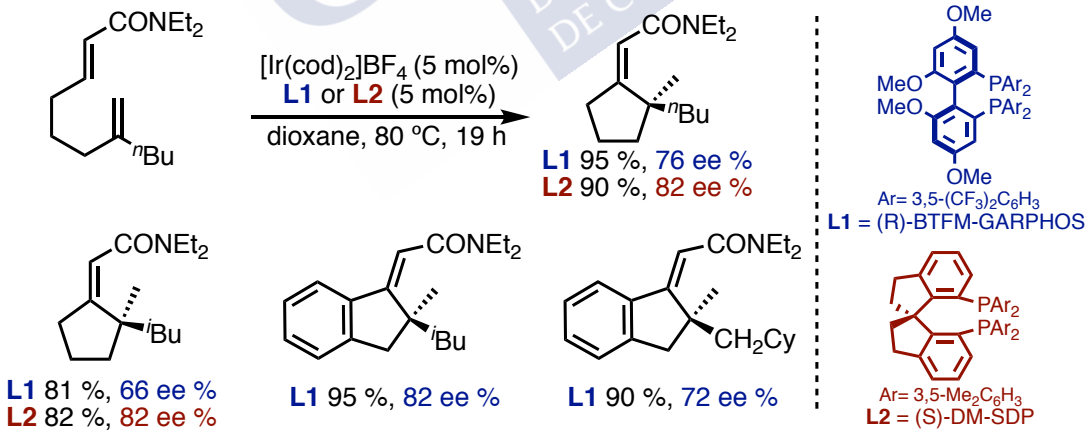
4. Conclusion

In summary, we have developed a new type of iridium-catalyzed intramolecular hydroalkenylation reaction that generates cyclic products bearing quaternary carbon stereocenters. A carboxamide-directed C(sp^2)–H activation followed by an *exo*-cyclization pathway is involved. The methodology tolerates alkenyl precursors and aromatic and heteroaromatic systems, allowing the synthesis of a variety of cyclic scaffolds featuring quaternary stereocenters. Moreover, these products can be easily manipulated to obtain synthetically challenging cyclic ketones.



Scheme 74. Ir-catalyzed cyclization and relevant transformation of the unsaturated system

We also demonstrated the viability of asymmetric variants, using iridium catalysts in situ generated from commercially available iridium complexes and chiral bisphosphines.

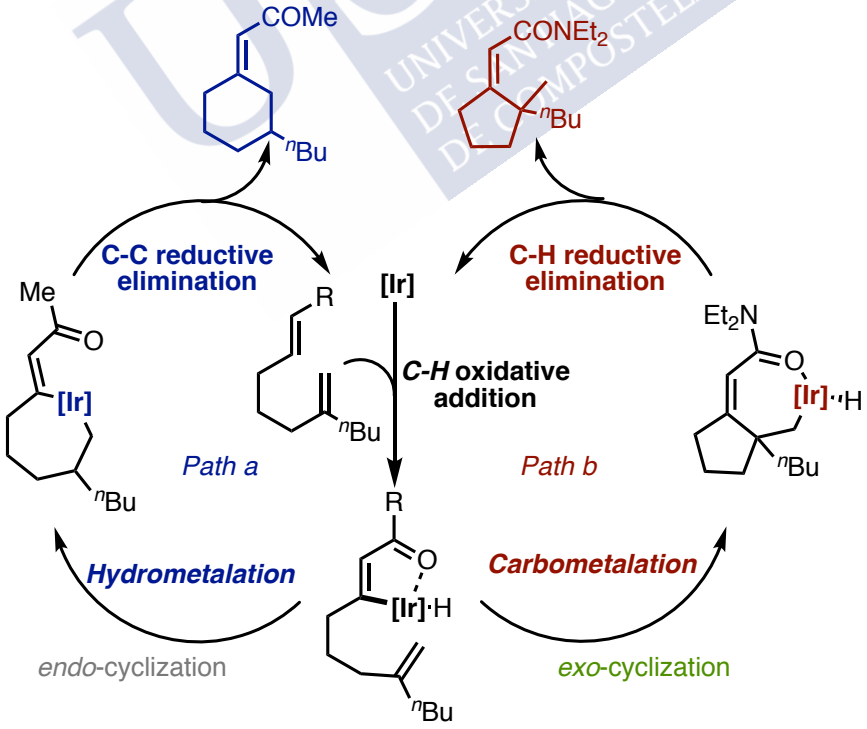


Scheme 75. Asymmetric Ir-catalyzed cyclization development

5. Appendice: Mechanistic studies by Huang's group

After reporting our results, the group of Huang described a computational mechanistic study of our reaction.[138] The first step of the catalytic cycle is well stablished, an oxidative addition into the C(sp^2)–H bond. After that, the reaction can take place through a migratory insertion into the Ir–H bond followed by a C–C reductive elimination (Scheme 75, path a) or through a migratory insertion into the Ir–C bond followed by a C–H reductive elimination (Scheme 75, path b).

Remarkably, the computational study concludes that a hypothetical *endo*-cyclization product should be the result of a migratory insertion into the Ir–H bond followed by a C–C reductive elimination (Scheme 75, path a). On the other hand, the *exo*-cyclization that is experimentally observed, should arise from the migratory insertion into the Ir–C bond, and a final C–H reductive elimination (Scheme 75, path b). The calculated difference of 4.0 kcal·mol^{-1} between both pathways (*endo* versus *exo*) matches our experimental results in which the *exo* product was exclusively detected with dialkyl carboxamides as directing groups.



Scheme 75. Mechanistic scenario for the cyclization of amides

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

Moreover, Huang's calculations indicate that, the step of higher energy barrier in the experimentally observed *exo* pathway corresponds to the carbometalation (TS2, Fig. 5), whereas the final C–H reductive elimination involves a significantly lower energy barrier (TS3, Fig. 5).

Therefore, considering Huang's theoretical calculation and our own mechanistic studies, we can conclude that that after the C–H oxidative addition, the *exo*-cyclization product is generated by the migratory insertion into the Ir–C bond and C–H reductive elimination.

Finally, Huang also analyzed the influence of the directing group to check whether the calculations could also reproduce the preferential formation of the *endo*-cyclization product when a methyl ketone is used as directing group (result described in the manuscript, Table 1, entry 9, page 9542).

In this case, the calculations indicate that the weaker coordination of the keto group to the iridium center causes a decrease in the barrier of the C–C reductive elimination (*endo* pathway) and, as a result, the *endo* pathway becomes favored by 1.3 kcal·mol^{-1}. (Described in Huang' manuscript[138]; Fig. 3, page 2680).

Therefore, these studies are consistent with our proposal that the directing group is crucial for determining the *exo*/*endo* selectivity: when the diethyl amide was used as DG, an *exo*-cyclization occurs exclusively; however, when the ketone is used, we observed the *endo* cyclization product together with a mixture of other unidentified products.

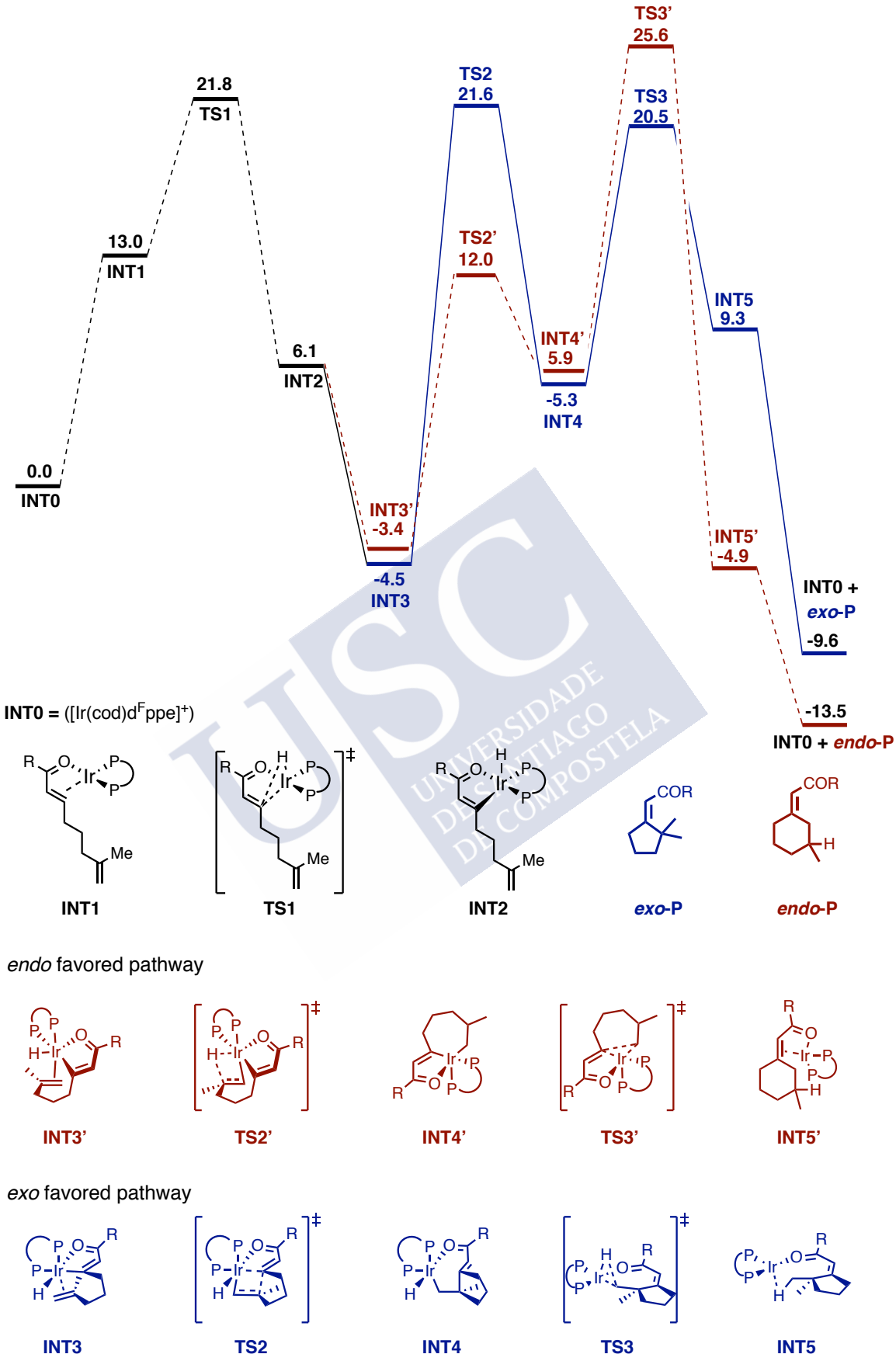


Figure 5. Transition states of C−C RE in endo and exo pathways described by Huang.

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Chapter II - Iridium(I)-Catalyzed Intramolecular Cycloisomerization of Enynes: Scope and Mechanistic Course

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1. Introduction

1.1. Intramolecular hydrocarbonation of alkynes by activation of C(sp^2-H) bonds

As mentioned in sections 5.2 and 6.2, the hydrocarbonation of alkynes is a powerful and atom economical synthetic tool. Most studies in this area have been focused on intermolecular processes using Pd, Ru, or Rh catalysts, as described in the section 5.2 (Schemes 47-54). In contrast, reports on iridium-promoted additions of C(sp^2)– H bonds across alkynes are very scarce, and essentially limited to precursors with (hetero)aromatic moieties (Schemes 61-63).

Intramolecular versions of these transformations are especially attractive, because in addition to the building of a ring and making a C–C bond, they generate a new double bond that can be used for further manipulations. There are very few precedents on these processes, and, importantly, iridium-promoted additions of alkenyl C– H bonds to alkynes had not been described before our work.

Regarding the mechanistic aspects, these hydrocarbonation processes catalyzed by low-valent transition-metal complexes, have been generally proposed to involve a C–H oxidative addition step, followed by hydrometalation of the unsaturated bond. Finally, a C-C reductive elimination delivers the cyclic products. However, as was explained at the appendix of the previous chapter, recent mechanistic work suggested that a path based on a carbometalation / C–H reductive elimination sequence could operate in the Ir-catalyzed hydrocarbonation of alkenes, and therefore, it should also be considered in the analog reaction of alkynes.

The hydroalkenylation of alkynes could generate exocyclic dienes that are of high interest from a synthetic perspective. The proposed cyclization methodology based on the C–H activation of alkenes would provide a very competitive strategy with respect to other current methods to make these diene systems, some of which are indicated in the next section.

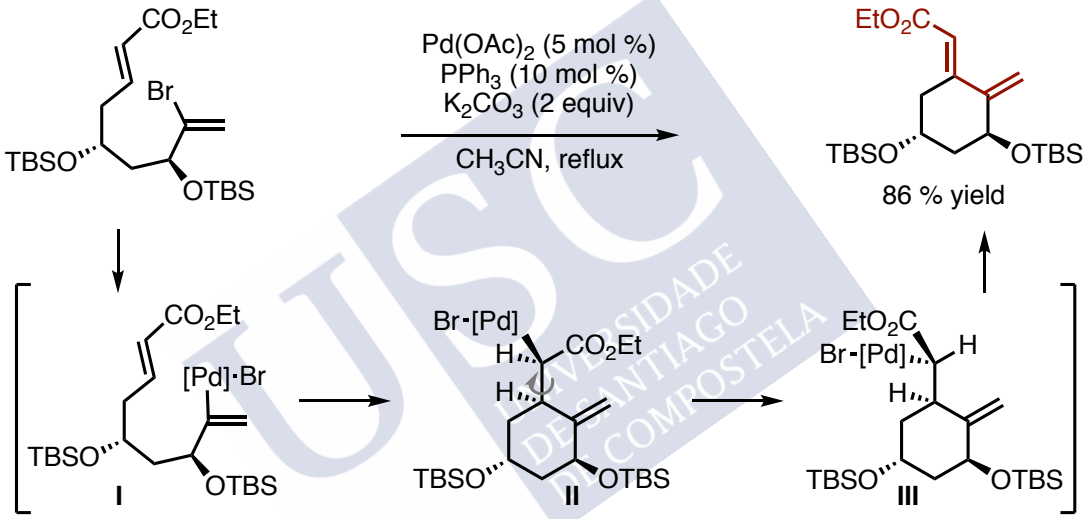
1.2. Precedents on metal-catalyzed cyclizations of unsaturated precursors to build exocyclic dienes

Conjugated dienes and polyene scaffolds are very interesting motifs due to its synthetic value, as they can participate in conjugate additions, cycloadditions, cross couplings, etc.

Although dienic structures can be easily found in nature, regioselective and stereoselective approaches to synthesize exocyclic dienes from acyclic precursors using metal catalysis are quite limited.[139]

In addition to the hydroalkenylation reactions indicated in the section 5.1, several metal catalyzed approaches to build exocyclic dienes from unsaturated systems had been described.

One of the most appealing transition-metal based methodologies to build exocyclic dienes in a regioselective manner is the intramolecular Heck reaction.[140] Early in the 90's several groups described total synthesis of the vitamin D_3 derivatives using an intramolecular Heck 6-*exo* cyclization as the key step (scheme 76). [141]



Scheme 76. Pd-catalyzed intramolecular Heck reaction to access exocyclic dienes described by Shimizu.

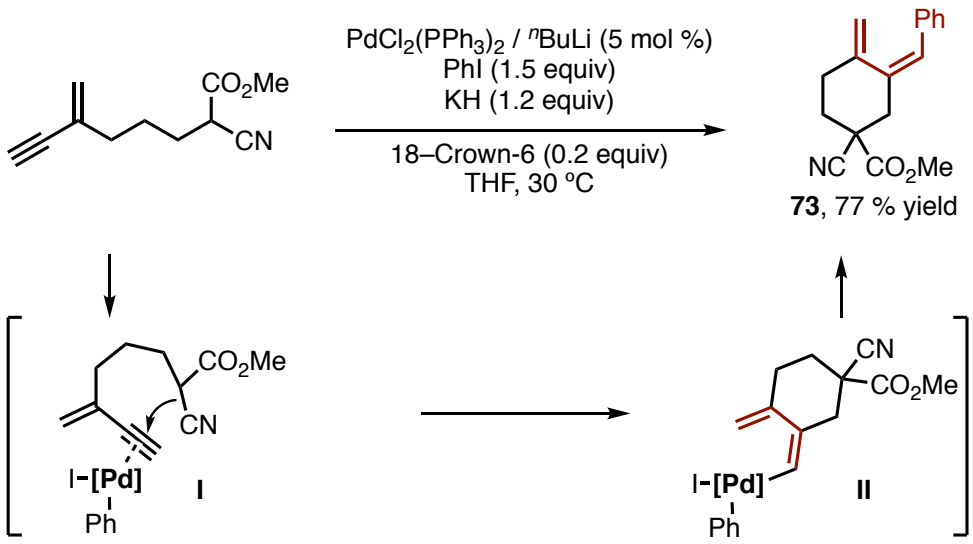
Also cascade palladium-catalyzed cyclizations are competitive approaches for the straightforward synthesis of highly appealing exocyclic dienes, such as the ones obtained in scheme 77 described by Balme and coworkers.[142] This transformation works efficiently for a variety of aryl iodides, obtaining cyclohexane derivatives of type **73** containing exocyclic dienes from moderate to good yield.

[139] a) X. Zeng, M. Qian, Q. Hu, E. Negishi, *Angew. Chem. Int. Ed.*, **2004**, *43*, 2259–2263; b) G. A. Molander, Y. Yokoyama, *J. Org. Chem.*, **2006**, *71*, 2493–2498.

[140] S. E. Gibson (née Thomas), R. J. Middleton, *Contemp. Org. Synth.* **1996**, *3*, 447–471.

[141] a) C. Chen, D. Crich, *Tetrahedron* **1993**, *49*, 7943–7954; b) K. Nagasawa, H. Ishihara, Y. Zako, I. Shimizu, *J. Org. Chem.* **1993**, *58*, 2523–2529.

[142] a) G. Balme, T. Lomberget, D. Bouyssi, *Synthesis* **2005**, *2*, 311–329; b) M. Ghosh, S. Dhara, Y. Nuree, J. K. Ray, *RSC Adv.* **2014**, *4,* 41561–41564.

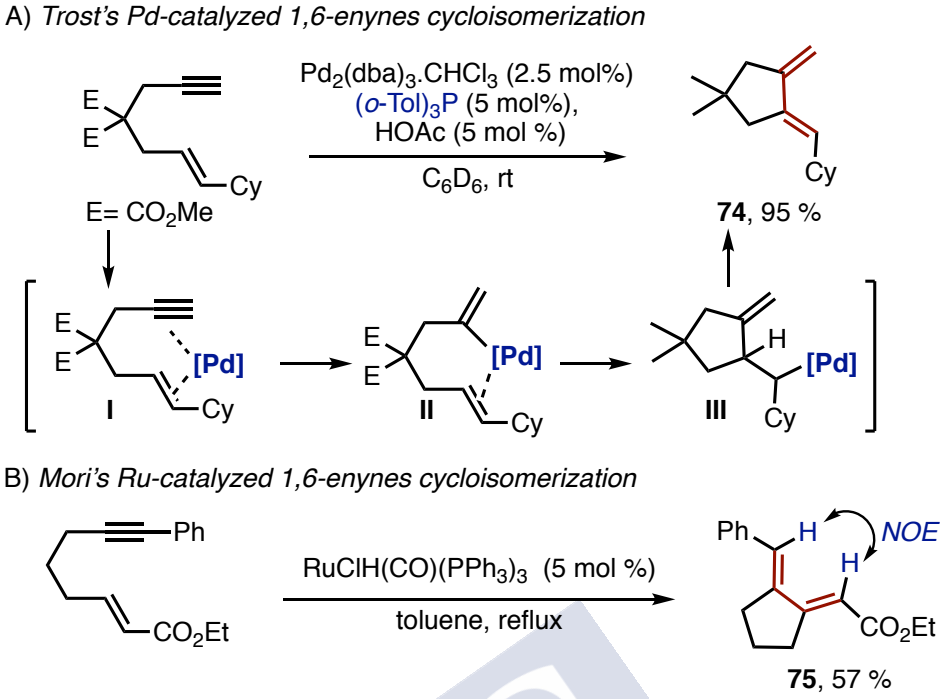


Scheme 77. Pd-catalyzed cascade cyclization to access exocyclic dienes by Balme.

A quite pioneering approach consists of the cycloisomerization of 1,6-enynes. In 1994, Trost and coworkers demonstrated that treatment of 1,6-enynes with a palladium catalyst consisting of $Pd_2(dba)_3.CHCl_3$, tri-*ortho*-tolylphosphine and acetic acid affords 1,2-dialkylidenecycloalkanes of type **74** with precise selectivity.[143] The proposed mechanism starts with the generation of the Pd (II)-hydride catalyst that is able to coordinate the enyne (**I**). Insertion into the alkyne forms the complex **II**, which evolves through insertion into the alkene to give **III**. A final β-hydride elimination step regenerates the catalyst and yields the 1,2-dialkylidenecycloalkanes **74** (Scheme 78, A).

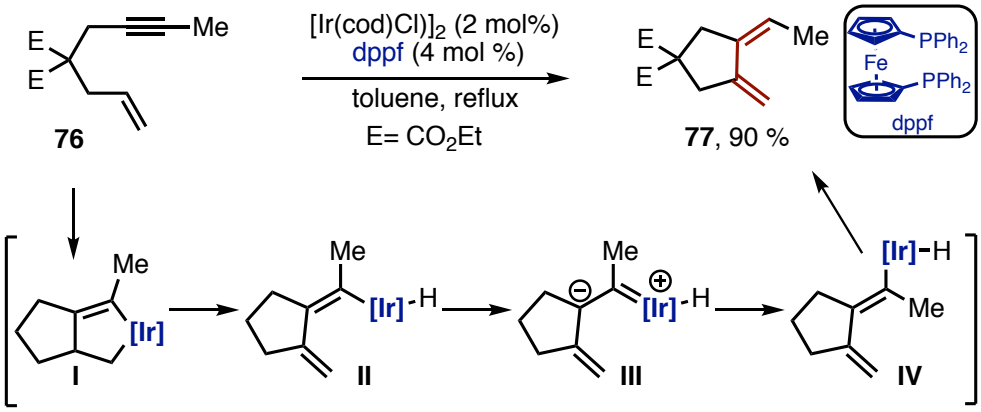
In 1998, Mori and coworkers described a related cycloisomerization process catalysed by the ruthenium catalyst $RuClH(CO)(PPh_3)_3$.[144] Similarly to the previous process with palladium, the authors proposed the coordination and hydroruthenation of the alkyne. Subsequent intramolecular olefin insertion and β-hydride elimination steps produce the cyclized product **75** (Scheme 78, B).

[143] B. M. Trost, D. L. Romero, F. Rise, *J. Am. Chem. Soc.*, **1994**, *116*, 4268–4278.
[144] M. Nishida, N. Adachi, K. Onozuka, H. Matsumura, M. Mori, *J. Org. Chem.*, **1998**, *63*, 9158–9159



Scheme 78. TM-catalyzed cycloisomerizations of 1,6-enynes to access exocyclic dienes.

On the other hand, iridium complexes have also been shown effective for promoting cycloisomerization reactions of 1,6-enynes leading to exocyclic dienes. In particular Takeuchi demonstrated in 2005 that the iridium complex prepared *in situ* from $[Ir(cod)Cl]_2$ and dppf was able to catalyse the cycloisomerization of **76** to yield **77** with good yield and almost complete selectivity.[145] In this case, an oxidative cyclization to yield the iridacyclic intermediate **I** was proposed. Subsequent β-H elimination generates **II**, that evolves through a zwitterionic carbene intermediate (**III**) to afford **IV**. Finally, a C–H reductive elimination would deliver the observed product **77** with Z configuration (Scheme 79).



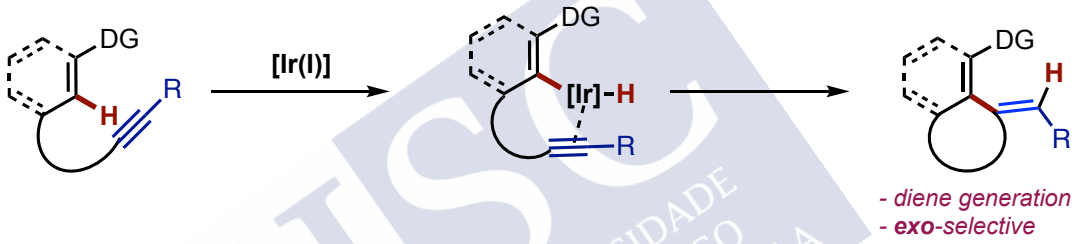
Scheme 79. Ir-catalyzed cycloisomerization of 1,6-enynes to access exocyclic dienes by Takeuchi.

[145] S. Kezuka, T. Okado, E. Niou, R. Takeuchi, *Org. Lett.* **2005**, *7*, 1711–1714.

2. Objectives

Considering the lack of intramolecular hydroalkenylation reactions based on metal-catalyzed C–H activations, and the relevance of discovering new methods to build exocyclic dienes from acyclic precursors in an effective way, and given our studies on hydroalkenylations of alkenes (Chapter 1) we designed as objective the development of a iridium-catalyzed cycloisomerization of enynes involving a C(sp^2)-H functionalization strategy.

Likewise, we also intended to elucidate the associated mechanistic pathways. As mentioned in sections 5 and 6 of the introduction, there is controversy associated to the olefin insertion step in Iridium hydrocarbonation reactions.



Scheme 80. Hydrocarbonation of alkynes. Design and proposal

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3. Article 2: Iridium(I)-Catalyzed Intramolecular Cycloisomerization of Enynes: Scope and Mechanistic Course.

Doi: https://doi.org/10.1021/acscatal.8b02139

David F. Fernández, Catarina A. B. Rodrigues, Martín Calvelo, Moisés Gulías, José Luís Mascareñas and Fernando López, *ACS Catal*., **2018**, *8*, 7397–7402.

Author contributions

J.L.M., M.G. and F.L. directed the research. D.F. and C.A.B.R. performed all the experiments as well as the amide precursors synthesis. M.C. performed the DFT theoretical analysis. F. L. and JLM wrote the manuscript with inputs from all authors. All authors discussed the results and revised the manuscript,

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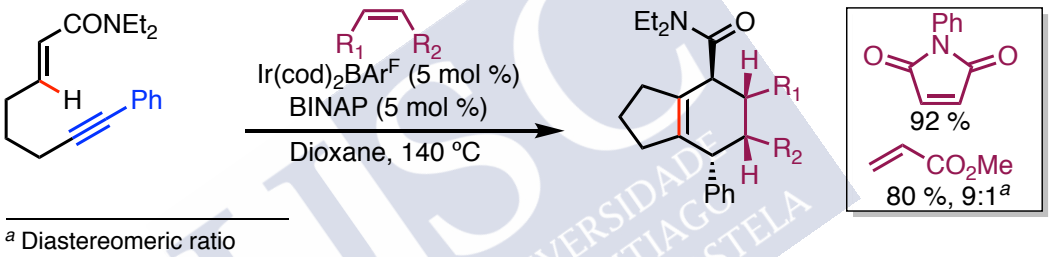
4. Conclusion

In summary, we have developed a new type of cycloisomerization of enynes involving a C– H activation process catalyzed by iridium complexes. The reaction, which relies on a carboxamide-assisted C–H activation, generates cyclic products bearing an *exo*-dienyl moiety with defined stereochemistry. Aromatic and heteroaromatic substrates are viable candidates for the transformation and, remarkably, the reaction allows the construction of five- to eight-membered rings.

To further unveil the synthetic power of the methodology, we demonstrate that it is possible to couple the cycloisomerization with a [4+2] cycloaddition in situ, as a domino process, which provides a fully atom-economical entry to stereochemically enriched polycarbocyclic products.



Scheme 81. ***One-pot*** **Ir-catalyzed cycloisomerization plus cycloaddition transformation**

Finally, DFT calculations established the initial oxidative addition as the rate-determining step. Regarding the migratory insertion of the alkyne, both the carbometalation and hydrometalation paths are energetically feasible, albeit the C–H reductive elimination is easier than the alternative C–C bond formation.

5. Addendum: Preliminary study on Iridium-mediated hydrocarbonations involving the activation of C(sp^3)–H bonds

5.1 Introduction

All the previous studies on cycloisomerization reactions involve the metal activation of C(sp^2) –H bonds. Extending this chemistry to C(sp^3)–H bonds is extremely attractive, as it could open impressive opportunities for novel synthetic disconnections and for the construction of sterocenters. However, achieving selective functionalization C(sp^3)–H bonds is extremely difficult, not only owing to the lowest reactivity but also because they are ubiquitous, and offer serious regioselectivity issues. Indeed, the field of metal-catalyzed C(sp^3)–H activation is yet in its infancy.

Usually the activation requires a heteroatom directing group, which could favor the formation of a thermodynamically stable five or six-membered metalacycle. The more frequently used transition metals for this purpose are Pd, Ru, Rh, Co and Ir.

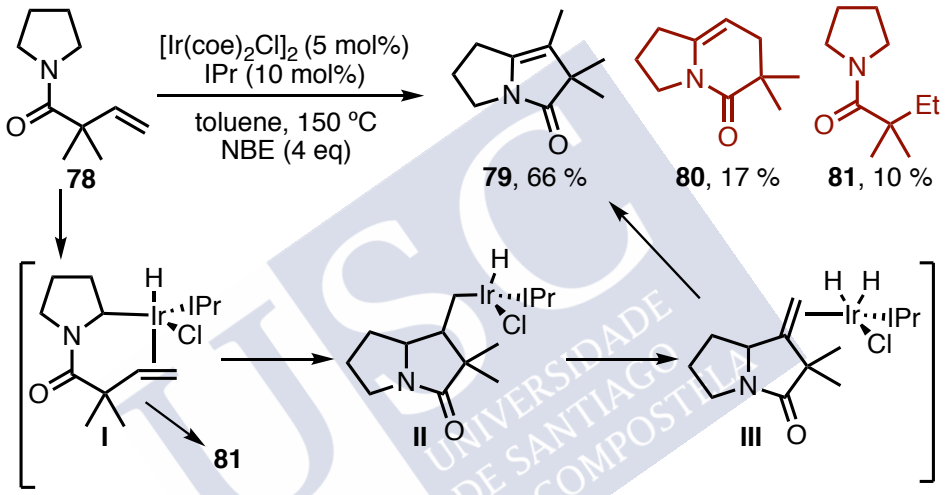
Despite important achievements have been already accomplished in the direct C(sp^3)–H arylation,[146] amination and oxygenation reactions, the development of direct C(sp^3)–H alkenylation and alkylation processes, respectively using alkynes or alkenes as partners, remains as a great synthetic challenge. Most of the advances in this field have been achieved using palladium, [147] while iridium catalysts have received attention only recently. Nonetheless, several examples described in the last few years suggest that the hydrocarbonation strategy can provide impressive solutions for the atom-economical construction of C(sp^3)- C(sp^2) and C(sp^3)- C(sp^3) bonds. We present next a brief summary with the more relevant contributions.

5.2 Precedents on the hydroalkylation of unsaturated partners via iridium-mediated C(sp^3)–H activations

A pioneer hydrocarbonation reaction with iridium catalysts was reported by Sames in 2004 and consists of an intramolecular cyclization of amide-tethered alkenes of type **78**, promoted by $[Ir(coe)_2Cl]_2$ / IPr.[148] Despite the limited scope of the process, the high temperatures required, high catalyst loadings and the moderate yields of the product **79**,

[146] a) O. Baudoin, *Chem. Soc. Rev.,* **2011**, *40*, 4902–4911.
[147] a) Y. Ano, M. Tobisu, N. Chatani, *J. Am. Chem. Soc.* **2011**, *133*, 12984–12986; b) J. He, M. Wasa, KSL Chan, J-Q Yu, *J. Am. Chem. Soc.,* **2013**, *135*, 3387–3390.
[148] B. DeBoef, S. J. Pastine, D. Sames, *J. Am. Chem. Soc.*, **2004**, *126*, 6556–6557.

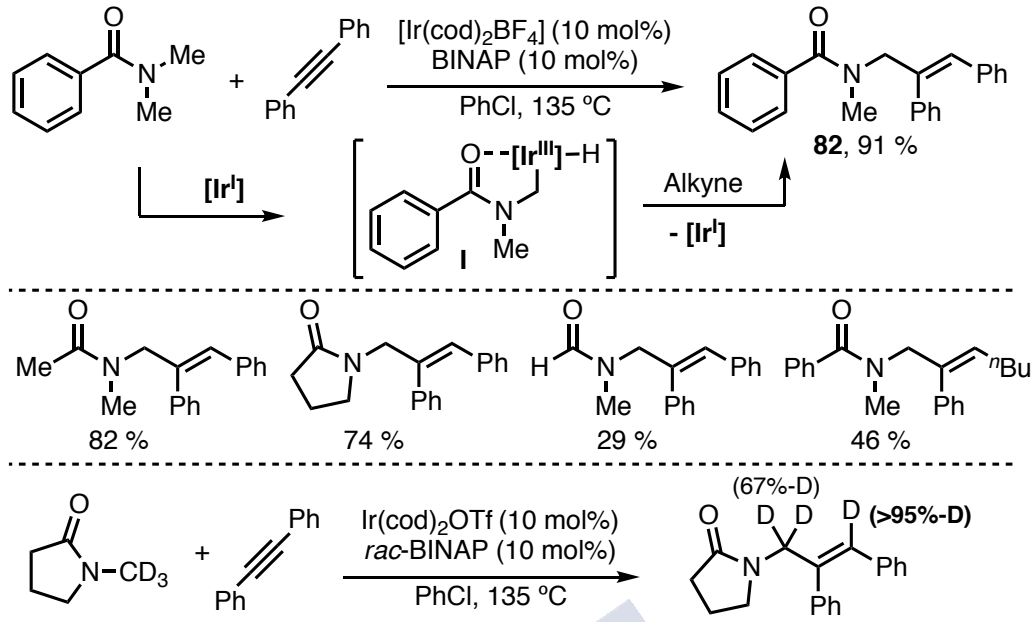
due to competing formation products **80** and **81**, this seminal publication paved the way for further contributions in this field. From a mechanistic point of view, this transformation involves an initial coordination of the substrate to the carbonyl moiety followed by an insertion into a C(sp^3)–H bond that is adjacent to the amide nitrogen, to deliver iridium hydride intermediate species of type **I**. A 5-*exo* alkene migratory insertion and a final β-hydride elimination generates the bicyclic amide coordinated to an iridium bishydride complex **III**. Isomerization of **III** eventually provides the observed adduct of type **79**. The formation of **80** and **81** can be explained through a hydrogenation of **78** or by an *endo* cyclization on **I**.



Scheme 82. Ir-catalyzed sp^3 cyclization of amides developed by Sames.

Reports on iridium-promoted C(sp^3)–H functionalization with alkynes as coupling partners are also scarce. In 2009, Shibata described an iridium-catalyzed intermolecular C(sp^3)–H alkenylation of dimethyl benzamides with alkynes.[149] The combination of $[Ir(cod)_2]OTf$ and BINAP in refluxing chlorobenzene allows to obtain the monoalkenylated amide **82** from moderate to good yields. Deuterium labeling experiments showed a complete deuterium transfer from the methyl group of the amide to the vinylic position as well as fractional protonation at the methylene group. Accordingly, the authors proposed the participation of an iridium hydride intermediate of type **I**, followed by the alkyne insertion and a reductive elimination step (Scheme 83).

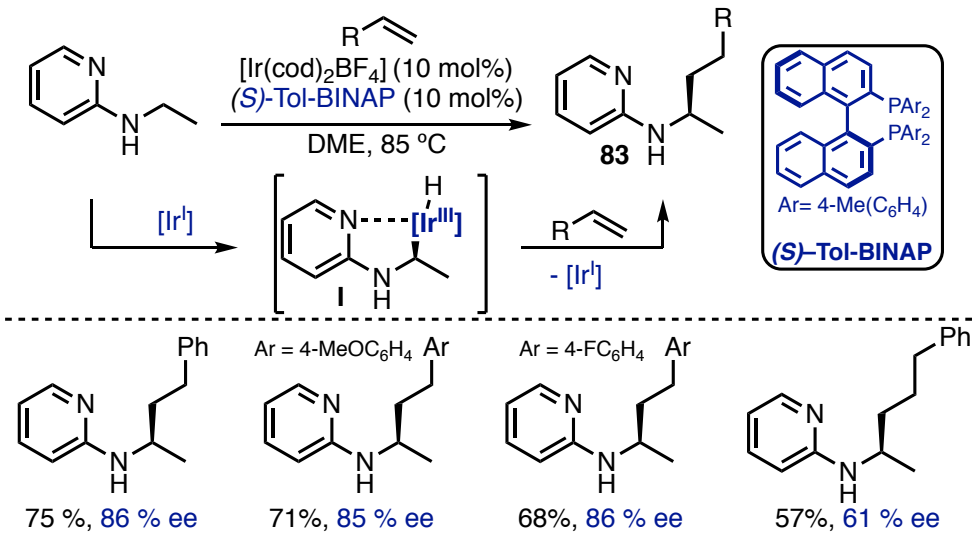
[149] K. Tsuchikama, M. Kasagawa, K. Endo, T. Shibata, *Org. Lett.*, **2009**, *11*, 1821–1823.



Scheme 83. Ir-catalyzed sp³ hydrocarbonation with alkynes developed by Shibata.

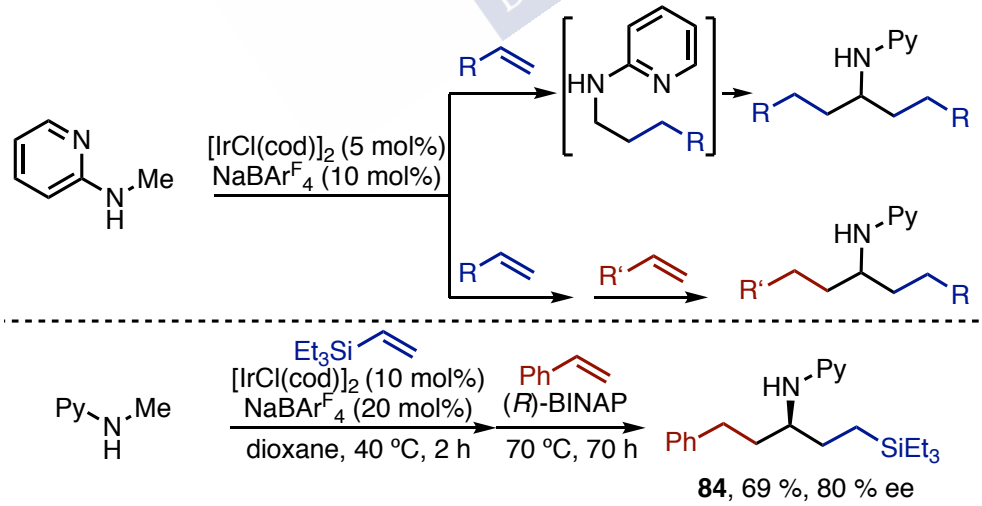
In 2011, the same group reported an enantioselective alkylation of 2-(alkylamino)pyridines with styrenes, catalyzed by the chiral iridium catalyst generated from $Ir(cod)_2BF_4$ and (*S*)-*tol*-BINAP in refluxing DME. Linear alkylation products of type **83** were selectively obtained in moderate to good yields and with enantioselectivities typically above 80% (Scheme 84).[150,151] Deuterium labeling studies confirmed an initial cleavage of the C(sp^3)–H bond adjacent to the nitrogen through an oxidative addition to the iridium(I) catalyst to generate a chiral Ir-hydride intermediate (**I**) that was tentatively identified by ^{31}P-NMR (-16.04 ppm). An improvement of this method was published in 2012 by the same group, demonstrating that not only styrenes but also β-unsubstituted acrylates, vinyl silanes, aliphatic alkenes and even alkynes were suitable partners for this hydrocarbonation, keeping the complete selectivity for the linear regioisomer and enantioselectivities that varied from 55 to 99 % ee, depending on the C–C unsaturated partner employed.[152]

[150] S. Pan, K. Endo, T. Shibata, *Org. Lett.*, **2011**, *13*, 4692–4695.
[151] For a report on this type of transformation based on ruthenium catalysts, see: a) C.-H. Jun, *Chem. Commun.*, **1998**, *0*, 1405–1406; b) Y. Ishii, N. Chatani, F. Kakiuchi, S. Murai, *Organometallics*, **1997**, *16*, 3615–3622.
[152] S. Pan, Y. Matsuo, K. Endo, T. Shibata, *Tetrahedron*, **2012**, *68*, 9009–9015.



Scheme 84. Ir-catalyzed sp³ enantioselective alkylation of 2-(alkylamino)pyridines developed by Shibata.

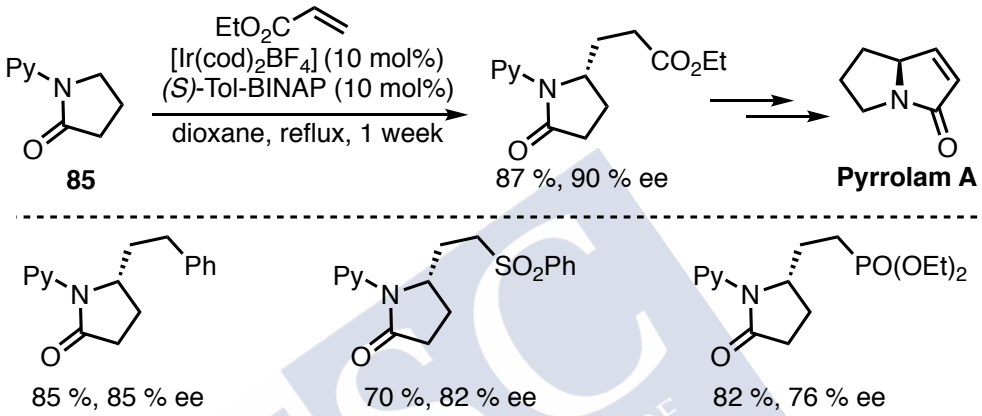
On the other hand, Nishimura has recently extended this methodology, demonstrating that the cationic iridium complex $[IrCl(cod)]_2$ / $NaBAr^F_4$ is able to perform a double C–H alkylation of 2-(methylamino)pyridines to yield α-substituted amines.[153] The reaction process can be carried out with the same alkene to give an achiral product or, alternatively, two different alkenes can be introduced in a sequential manner, provided that a vinyl silane such as triethylvinylsilane is used as the first alkene partner. Interestingly, if BINAP is added just before the addition of the second alkene, the resulting α-substituted chiral amine (**84**) is obtained with good enantioselectivities, varying from 80 to 89%.



Scheme 85. Ir-catalyzed double alkylation of 2-(methylamino)pyridines developed by Nishimura.

[153] H. Hattori, T. Nishimura, *Adv. Synth. Catal.* **2018**, *360*, 4827–4831

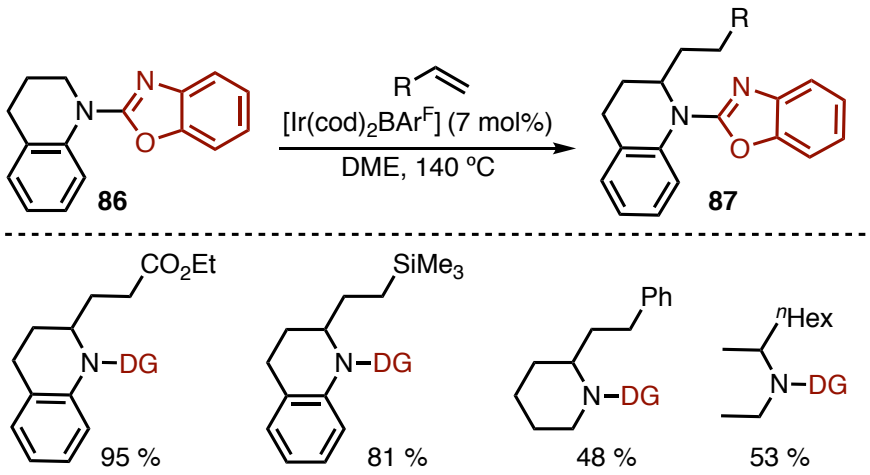
The use of a nitrogen-tethered pyridine to assist the activation of C(sp^3)–H bonds adjacent to the nitrogen atom was further explored by Shibata in a related strategy, demonstrating that γ-lactams of type **85** can undergo enantioselective alkylations with styrenes and acrylates, promoted by $[Ir(cod)_2]BF_4$ / (*S*)-tolBINAP, in refluxing dioxane.[154] Remarkably, the obtained products could be easily converted into substituted γ-aminoacids by removal of the pyridine directing group and a hydrolysis step. Moreover, the methodology was also applied to the formal asymmetric synthesis of pyrrolam A (Scheme 86).



Scheme 86. Ir-catalyzed enantioselective alkylation of lactams developed by Shibata.

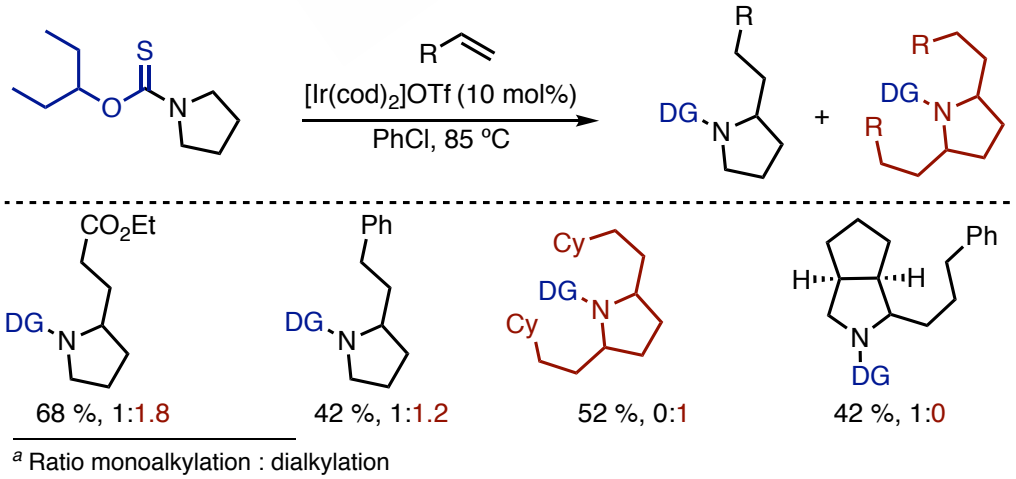
In 2014, Opatz and coworkers described a related strategy using benzoxazole scaffolds as directing groups (Scheme 87). Thus, using the simple cationic catalysts $[Ir(cod)_2]BF_4$ or $[Ir(cod)_2]BAr^F{}_4$, without any additional ligand, these authors demonstrate that tetrahydroquinolines like **86**, as well as other cyclic and acyclic amines, can be catalytically monoalkylated at the nitrogen-adjacent position, yielding linear alkylation products of type **87**. Albeit using harsh reductive or basic conditions, the authors demonstrated that the directing group can be removed without affecting the functionalized amine.

[154] Y. Tahara, M. Michino, M. Ito, K. S. Kanyiva, T. Shibata, *Chem. Commun.,* **2015**, *51*, 16660-16663.



Scheme 87. Ir-catalyzed benzoxazole-directed alkylation developed by Opatz.

In 2017, Yu demonstrated that, instead of a sp^2-nitrogen atom (i.e pyridine or benzooxazole directing groups) an alkoxythiocarbonyl moiety could also be successfully used as directing group for the activation of related C(sp^3)–H bonds adjacent to the nitrogen atom of an azacycle.[155] Thus, using [Ir(cod)$_2$]OTf as catalyst, the α-functionalization of several pyrrolidines, prolines and piperidines could be performed using different types of terminal alkenes as alkylating partner. In many cases, mixtures of monoalkylated and dialkylated products were obtained. Although the authors did not comment about the mechanistic aspects of the transformation, presumably, a C–H oxidative addition is involved followed by a subsequent alkene migratory insertion and reductive elimination, albeit it is not clear if the process involves a carbo- or a hydro-metalation.

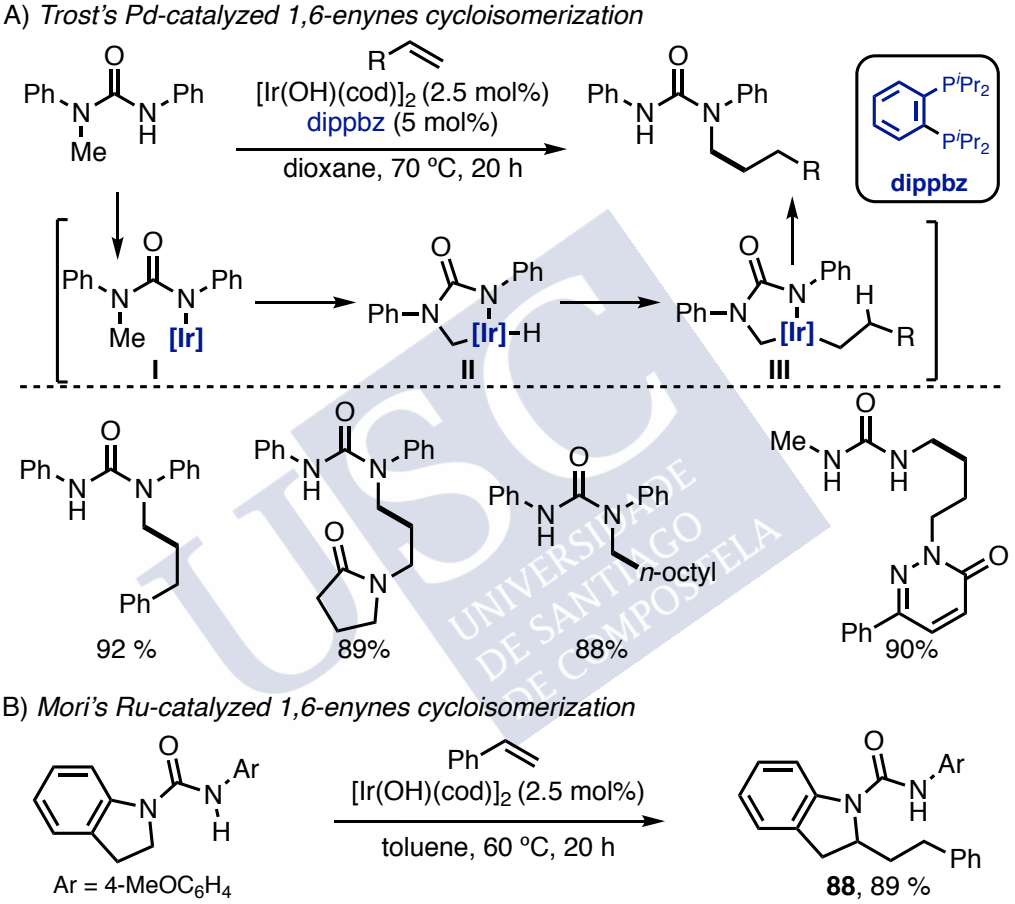


[a] Ratio monoalkylation : dialkylation

Scheme 88. Ir-catalyzed alkoxythiocarbonyl directed alkylation of pyrrolidines developed by Yu.

[155] A. T. Tran, J.-Q. Yu, *Angew. Chem. Int. Ed.*, **2017**, *56*, 10530–10534.

In 2017, Nishimura and coworkers reported that bisphosphine hydroxoiridium complexes, previously introduced by this group for the hydroalkenylation of alkenes (see schemes 34, 35), was also able to catalyze a hydroalkylation reaction of terminal alkenes by a catalytic activation of one of the C(sp3)–H bonds of 1-methyl-1,3-diphenylurea.[156] The optimal conditions involved the iridium catalyst *in situ* generated from $[Ir(OH)(cod)]_2$ and the bisphosphine dippbz, at an unusually low reaction temperature of 70 ºC (Scheme 89, A).



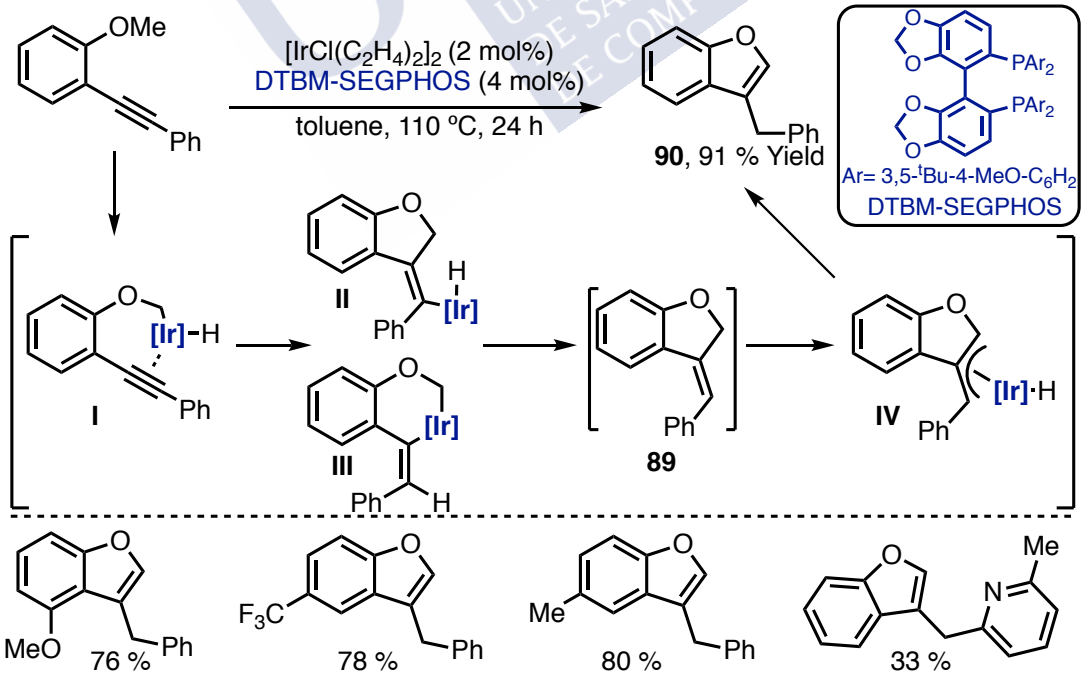
Scheme 89. Ir-catalyzed alkylation of ureas developed by Nishimura.

Despite the methodology is restricted to terminal alkenes, the scope was broad, and it was further extended to the use of secondary $C(sp^3)$–H bonds of indoline urea derivatives (Scheme 89, B).[157] In this latter case, the best conditions consisted of using $[Ir(OH)(cod)]_2$ without any additional ligand. The methodology tolerates a variety of terminal alkenes; however, it is limited to very few indoline derivatives. From a mechanistic point of view, these processes are proposed to proceed through an amidoiridium intermediate **I** that

[156] D. Yamauchi, T. Nishimura, H. Yorimitsu, *Angew. Chem. Int. Ed.*, **2017**, *56*, 7200–7204.
[157] I. Nakamura, D. Yamauchi, T. Nishimura, *Asian J. Org. Chem.*, **2018**, *7*, 1347–1350.

evolves through an oxidative C–H insertion and a linear-selective carbometalation, both reversible steps as confirmed by deuterium labeling studies. Eventually an irreversible reductive elimination and protonation affords de alkylated urea product **88.**

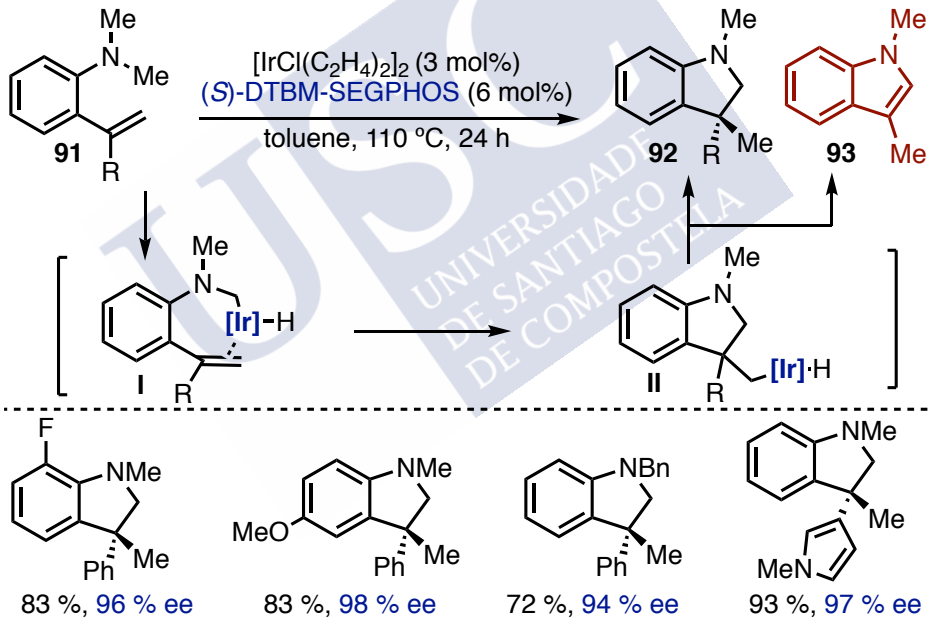
In 2016, Suginome and Ohmura reported a cycloisomerization reaction of *ortho*-alkynyl phenol methyl ethers, based on an iridium-catalyzed C(sp^3)–H bond activation of the methoxy group, a process wherein the *ortho*-alkyne acts as directing group.[158] Optimal conditions involved the use of the iridium catalyst generated from $[IrCl(C_2H_4)_2]_2$ and (*S*)-DTBM-SEGPHOS. Labeling experiments indicated that the initial oxidative addition is the rate-determining step. Subsequent intramolecular *syn*-selective insertion of the C–C triple bond into the Ir–C or Ir–H afford intermediates **II** or **III**. Both intermediates could evolve through a reductive elimination to yield a dihydrobenzofuran derivative **89**, which was experimentally isolated as a side product under specific reaction conditions. An isomerization reaction of **89** through a 1,3-H shift via π-allyl iridium species **IV** would eventually deliver the benzofuran product **90**. Although the reaction does not involve the generation of any stereocenter, the authors demonstrate that the use of DTBM-SEGPHOS is important to obtain not only excellent overall yields but also complete isomerization of intermediates **89** into the benzofurans **90**.



Scheme 90. Ir-catalyzed cycloisomerization of o-alkynyl phenols developed by Suginome.

[158] T. Torigoe, T. Ohmura, M. Suginome, *Chem. Eur. J.*, **2016**, *22*, 10415–10419.

In 2017, the same group further extended this strategy to an iridium catalyzed asymmetric cycloisomerization of *ortho* alkenyl-*N*-methylanilines.[159] The catalyst generated from $[IrCl(C_2H_4)_2]_2$ and (*S*)-DTBM-SEGPHOS delivers indolines of type **92** bearing a chiral carbon quaternary stereocenter, with high efficiency and excellent enantiomeric ratios. The authors proposed a mechanism involving the alkenyl-assisted insertion of the iridium complex into a C(sp^3)–H bond of the dimethyl amine to generate the intermediate **I**. Subsequent carboiridation step, in a *5-exo* fashion, would deliver the intermediate **II** which undergoes a C–H reductive elimination to yield the indoline product. According to the authors, the formation of **93** as side product in the cyclization of **91** (R = H) can only be explained assuming a β-H elimination from the iridium-hydride intermediate **II** (R = H) and a subsequent isomerization. This allowed them to conclude that an alternative hydrometallation/C–C reductive elimination pathway is very unlikely.



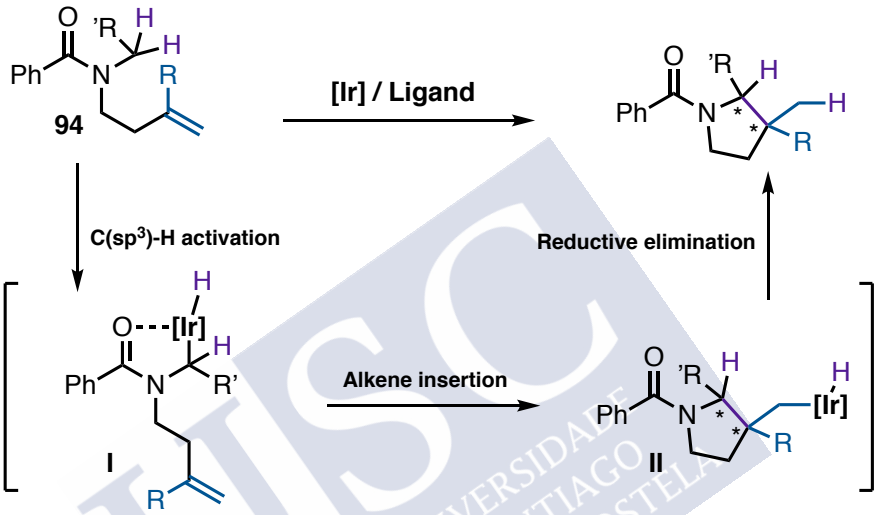
Scheme 91. Ir-catalyzed cycloisomerization of o-alkenyl-N-methylaninlines developed by Suginome.

Overall, this field is yet undeveloped, there are many unknowns not only with regard to the C–H activation, but also in terms of the requirements of the substrates, and the influence of the different mechanistic steps in the reaction rate.

[159] T. Torigoe, T. Ohmura, M. Suginome, Angew. Chem. Int. Ed, **2017**, *56*, 14272–14276.

5.3 Proposal development

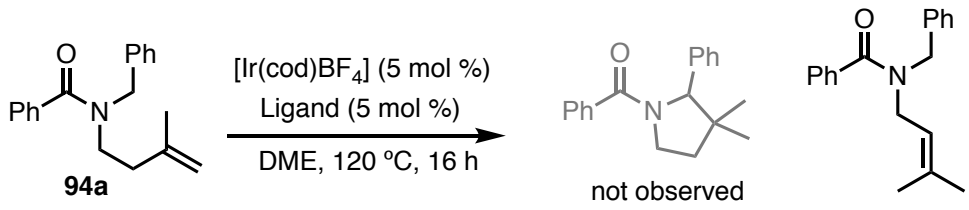
Taking into account the above precedents, and considering the paucity of intramolecular hydrocarbonation reactions based on iridium catalyzed activations of C(sp^3)–H bonds, we initiated a research project aimed at developing an intramolecular hydroalkylation of alkenyl amides of type **94**, a process that could provide a direct entry to pyrrolidines and related aza-heterocycles (Scheme 92). Depending on the nature of the R' group, up to two stereocenters could be generated.



Scheme 92. Csp^3–H Hydrocarbonation of alkenes. Initial design and proposal

At the outset, we selected the amide **94a** as a model substrate, to evaluate the possibility of activating the hydrogen at its benzylic position. Several catalytic conditions tested are summarized in table **1**. Monodentate phosphines such as PPh_3, in combination with $[Ir(cod)_2]BF_4$, led to the exclusive recovery of the starting material (table **1**, entry 1). On the other hand, bisphosphines such as BINAP, d^Fppe and Xantphos showed some reactivity and the conversions of the starting amide are summarized in table **1**, entries 2-4. The use of bulkier and electron rich bisphosphines such as DTBM-SEGPHOS did not bring any improvement in the reactivity.

At this point, based on the NMR and GC-MS analysis, we hypothesized that the small conversion observed is consistent with an isomerization of the double bond of the starting amide to the more substituted-alkene derivative, but not to the formation of the cyclic desired product.



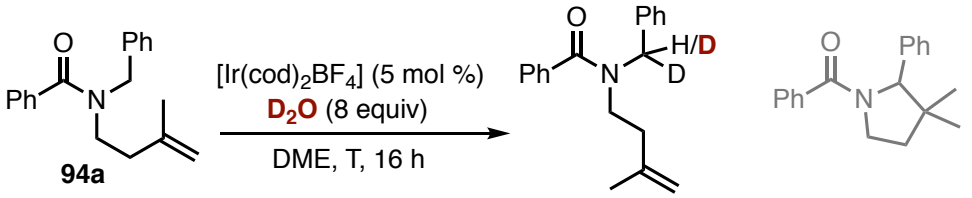
Entry	**Ligand**	**SM Conv %**
1[a]	PPh_3	0
2	BINAP	< 10 %
3	d^Fppe	< 10 %
4	Xantphos	< 10 %
5	DTBM-SEGPHOS	< 5 %

[a] 10 % of PPh_3 was used

Table 1. Initial results in the Ir-catalyzed Csp³–H Hydrocarbonation of alkenes

To elucidate whether the C–H activation was occurring, we carried out the reaction with $[Ir(cod)_2]BF_4$ and BINAP in the presence of an excess of D_2O (table 2). After 16h at 120 ºC (entry 1), we recovered 90% of the starting material which showed deuterium incorporation at the adjacent position of the nitrogen moiety by ^{2}H-NMR analysis. Accordingly, a reversible C(sp^3)–H activation and a deuterium-hydrogen exchange on the iridium hydride intermediate might be occurring.

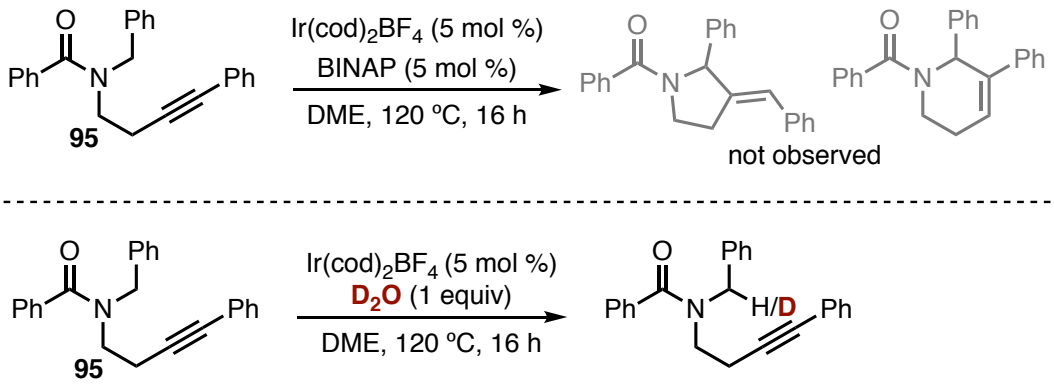
Therefore, it seems that the reactivity problem is associated to the intramolecular migratory insertion. We carried out this deuterium incorporation experiment at lower temperatures, confirming that the C–H activation needed at least heating up to 80 ºC (entries 2-3). We further examined the reactivity by increasing the temperature up to 140 ºC and using BINAP as ligand but, unfortunately, we could not detect any traces of the desired cyclic compound (Table 2, entry 4).



Entry	Ligand	T (ºC)	SM Recovery %	Deuteration
1	-	120	> 90	Yes
2	-	80	> 90	Yes
3	-	60	> 90	No
4	BINAP	140	80 %	Yes

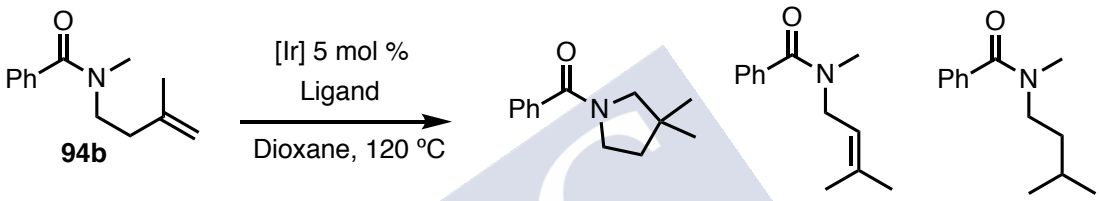
Table 2. Ir-catalyzed Csp³–H deuteration with D_2O

At this point, we realized that alkynes could avoid the isomerization and perhaps react faster. We synthesize the amide **95** and we tested the iridium catalytic conditions described before, $[Ir(cod)_2]BF_4$ and BINAP in dimethoxyethane at 120ºC (scheme 93, top). Unfortunately, we observed poor conversions and weren't able to identify the products. We next examined the reaction of amide **95** in presence of deuterated water (scheme 93, bottom) and we observed deuteration in the position α to the nitrogen of the amide. We also carried out similar D_2O experiments with rhodium and ruthenium complexes observing 0 % of deuteration. We could conclude that iridium species are indeed activating the C(sp³)–H in these systems but the hydrocarbonation process does not occur.



Scheme 93. Initial experiments in the Csp³–H hydrocarbonation of alkynes

We next examined the reaction with substrates that bear a methyl group adjacent to the nitrogen (**94b**), instead of the benzyl (table 3). The reaction mixtures were analyzed by GC-MS. Interestingly, three new peaks that may correspond to the cyclic structure, the internal isomerized alkene and the saturated amide were found (table 3, entries 1-3). We also perform deuterium incorporation studies and we observed small amounts of deuteration in the methyl group by NMR analysis. Attempts to isolate the products were unsuccessful due to both starting material and products had the same retention factor. We also tried to derivatize the mixture of products by treatment of the crude with $LiAlH_4$. Unfortunately, identification of the possible product was not possible until now. This work is ongoing.



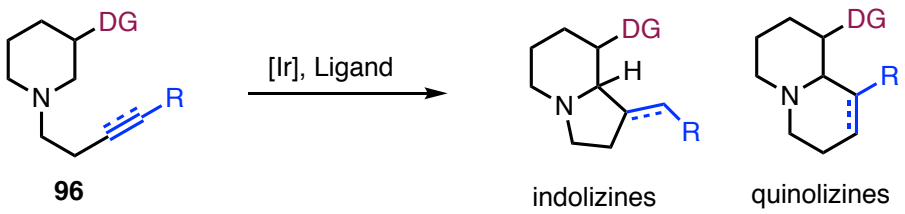
Entry	[Ir]	Ligand	Additive	Conv %[a]
1	$Ir(cod)_2OTf$	BINAP	-	36[b]
2	$Ir(cod)_2BF_4$	BINAP	-	34[b]
3	$Ir(cod)_2BF_4$	d^Fppe	-	46[b]
4	$Ir(cod)_2BF_4$	-	D_2O	52[b,c]

[a] Analyzed by GC-MS; [b] 3 peaks in GC-MS: two $[M]^+$, one $[M+2]^+$; [c] Treatment with $LiAlH_4$

Table 3. Initial results in the Ir-catalyzed Csp^3–H Hydrocarbonation of alkene 94b

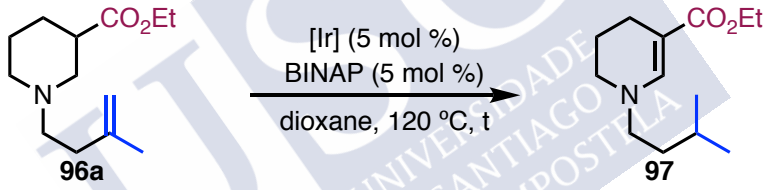
At the same time, we also explored a different intramolecular alkylation approach with substrate **96**, in which the methylene adjacent to the nitrogen atom of a piperidine ring would be activated prior to the migratory insertion of the tethered alkyne. This particular methodology would be extremely interesting due to the possibility to generate chiral indolizines or quinolizines, both of them wide-present in bioactive molecules (Scheme 94).[160]

[160] a) J. P. Michael, *Nat. Prod. Rep.* **2008**, *25*, 139–165; b) T. Lutz, T. Wein, G. Höfner, K. T. Wanner, *ChemMedChem* **2017**, *12*, 362–371.



Scheme 94. Csp³–H piperidine functionalization. Initial design and proposal

We first selected an alkene tethered ethyl nipecotate **96a** derivative as model substrate. We submitted this substrate to various iridium complexes in combination with BINAP in dioxane. Despite we observed conversions, with the cationic complexes being more active, in none of the cases the bicyclic product was formed (table 4, entries 1-4). Instead, what we found is a formal double bond migration. The optimal conditions for this transformation were achieved by using $Ir(cod)_2BF_4$ with BINAP in dioxane at 120 ºC for three days (table 4, entry 5). Isolation and characterization of the product confirms the proposed structure **97**.



Entry	[Ir]	time (h)	Conv %[a]
1	$Ir(cod)_2OTf$	16	20
2	$Ir(cod)_2BF_4$	16	26
3	$Ir(cod)_2BAr^F$	16	22
4	$[Ir(cod)Cl]_2$	16	< 5
5	$Ir(cod)_2BF_4$	72	> 99 (92)[b]

[a] Conversions based on NMR analysis; [b] Isolated yield.

Table 4. Initial results in the Ir-catalyzed Csp³–H functionalization of piperidines

The formation of this product could be explained assuming a first C(sp^3)–H activation followed by a β-hydride elimination to produce a dihydride iridium species, which could be responsible for the alkene hydrogenation. Currently, we are performing experiments to determine the origin of this reactivity as well as studies on the nature of the directing group and coupling partner, in order to facilitate the migratory insertion and avoid the generation of the bishydride intermediate via β-H elimination.

Chapter III – Rhodium(III)-Catalyzed Intramolecular Annulations of Acrylic and Benzoic Acids to Alkynes

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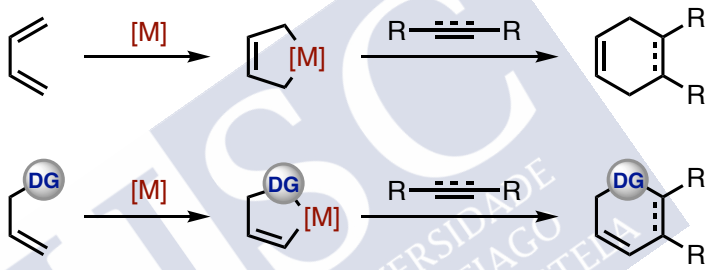
1. Introduction

1.1. Formal metal-catalyzed cycloadditions of benzoic and acrylic acids with unsaturated partners involving a C(sp²)-H activation

As commented in the introduction of the thesis, the metal catalyzed formal cycloaddition of unsaturated partners usually occurs via metalacyclic structures resulting from oxidative cyclometallations. An alternative way of generating related metalacycles could involve TMC C–H activation protocols (Scheme 95, bottom).[161] These transformations involve the creation of two new σ-bonds while the directing group can be incorporated into the final cyclic structure, allowing for a rapid increased in molecular complexity. Moreover, these methods represent a very interesting and atom economical alternative for the preparation of heterocyclic skeletons that constitute the cores of countless natural products and molecules employed in pharmaceutical companies and materials sciences.[162]



Scheme 95. Different strategies in the generation of metalacyles

From a mechanistic point of view, these transformations proceed through the formation of a metalacyclic species, followed by a migratory insertion of an unsaturated partner, typically an alkyne, allene or alkene, to generate a second metallacyclic intermediate. This can subsequently evolve through a reductive elimination to yield the cyclic product. Metal complexes engaged in these processes are often derived from transition metals in high oxidation states (Pd^{II}, Co^{III}, Ru^{II}, Rh^{III}, Ir^{III}), which usually provide the C–H activation through a directed CMD pathway and require an additional reoxidation step after the reductive elimination step (Scheme 96).[163]

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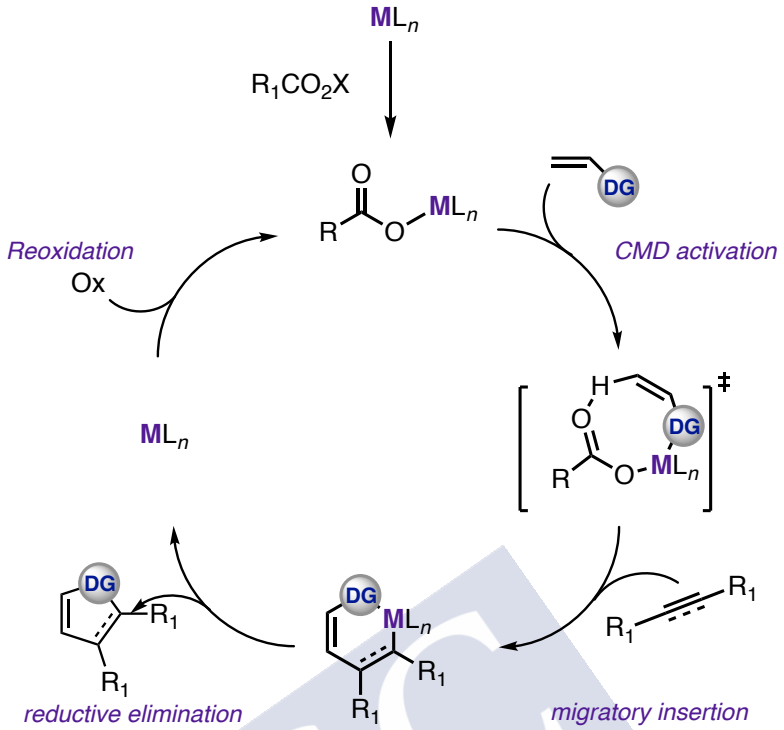
[161] M. Gulías, J. L. Mascareñas, *Angew. Chem. Int. Ed.* **2016**, *55*, 11000–11019.

[162] A) C. Wei, J. Zhuang, D. Zhang, W. Guo, D. Yang, Z. Xie, J. Tang, W. Su, H. Zeng, Z. Cui, *ACS Appl. Mater. Interfaces* **2017**, *9*, 38716–38727. B) S.-Y. Lu, S. Mukhopadhyay, R. Froese, P. M. Zimmerman, *J. Chem. Info. Modeling* **2018**, DOI 10.1021/acs.jcim.8b00044.

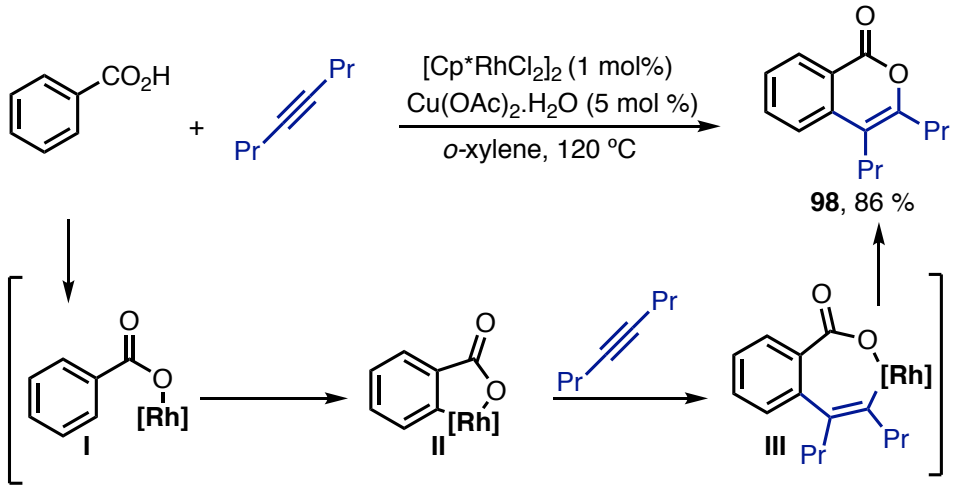
[163] a) K. Ueura, T. Satoh, M. Miura, *J. Org. Chem.* **2007**, *72*, 5362–5367; b) S. Würtz, S. Rakshit, J. J. Neumann, T. Dröge, F. Glorius, *Angew. Chem. Int. Ed.* **2008**, *47*, 7230–7233. c) N. Guimond, K. Fagnou, *J. Am. Chem. Soc.* **2009**, *131*, 12050–12051; d) N. Guimond, C. Gouliaras, K. Fagnou, *J. Am. Chem. Soc.* **2010**, *132*, 6908–6909; e) L. Ackermann, L. Wang, A. V. Lygin, *Chem. Sci.* **2012**, *3*, 177–180; f) M. Deponti, S. I. Kozhushkov, D. S. Yufit, L. Ackermann, *Org. Biomol. Chem.* **2013**, 142–148.



Scheme 96. General C−H activation mechanism involving a CMD pathway

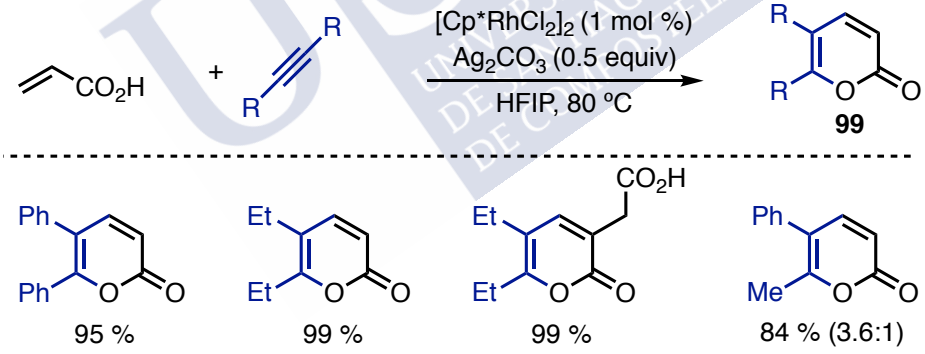
One of the pioneering examples on this type of oxidative annulations was developed by Miura and coworkers in 2007, who reported the reaction of benzoic acids with alkynes described in scheme 97.[164] The optimal conditions involved the use of $[Cp^*RhCl_2]_2$ and $Cu(OAc)_2$ in *ortho*-xylene at 120 ºC. The authors propose a mechanism that starts with the coordination of the carboxylate oxygen to the metal catalyst providing the intermediate **I**. Subsequent C–H activation generates the rhodacycle **II** that can evolve through alkyne insertion (intermediate **III**). Finally, a reductive elimination yields the isocumarin **98** and the Rh (I) is reoxidized to Rh (III) by the action of the copper salt.

[164] K. Ueura, T. Satoh, *M. Miura, J. Org. Chem.*, **2007**, *72*, 5362–5367.



Scheme 97. Rhodium oxidative annulation of benzoic acids developed by Miura

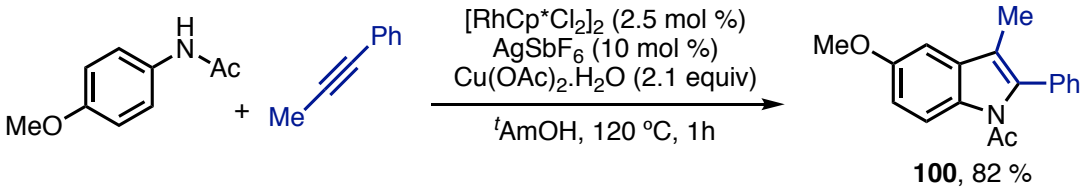
The same group reported the annulations of acrylic acids with alkynes (and alkenes), a methodology designed for the synthesis of pyran-2-ones **99**, an important motif in natural or therapeutic-relevant products.[165] More recently, Zhao and coworkers reported the same transformations under milder conditions (Scheme 98).[166] Namely using $[RhCp^*Cl_2]_2$ and Ag_2CO_3 in HFIP at 80 ºC under air. The mechanistic proposal is analogous to the previous described.



Scheme 98. Rh-catalyzed oxidative annulation of acrylic acids developed by Zhao

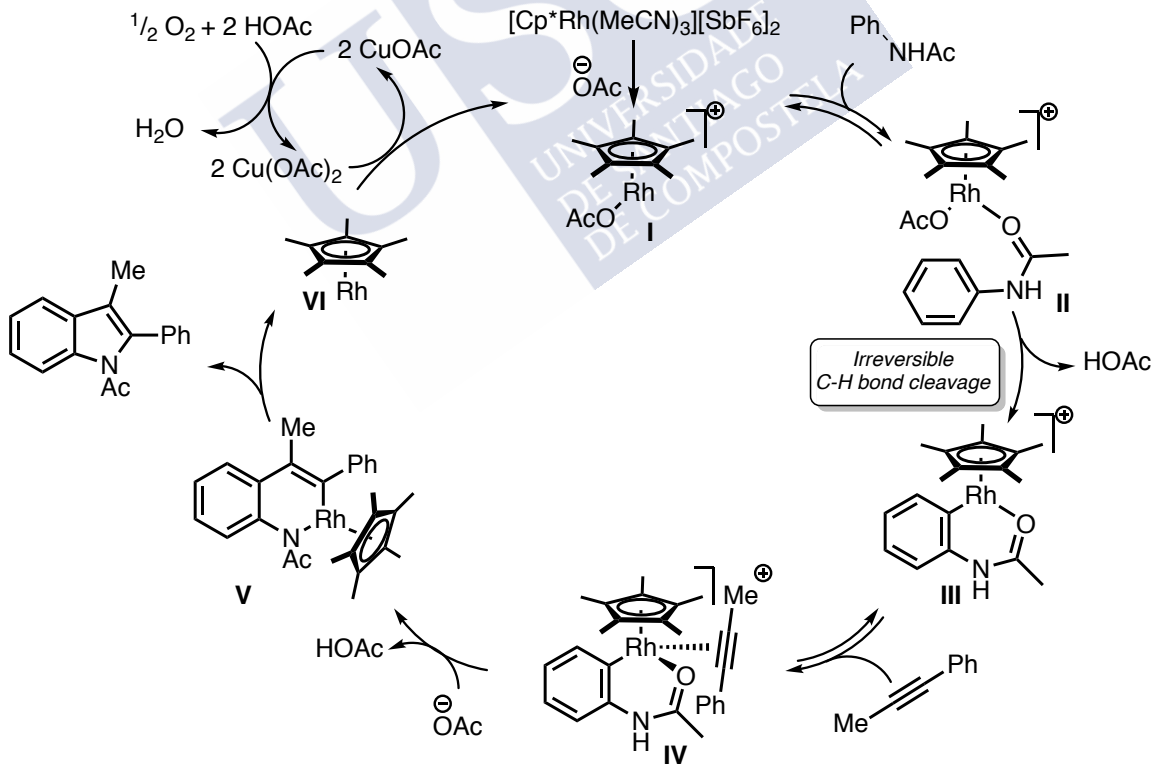
Related to these pioneering strategies, Fagnou and collaborators reported an inspiring work in oxidative annulations of anilides with internal alkynes to yield relevant indole scaffolds of type **100** under rhodium (III) catalysis.[167] Optimal conditions involved the rhodium dimer complex $[Cp^*RhCl_2]_2$ in combination with $AgSbF_6$ and $Cu(OAc)_2$ as oxidant in *tert*-amyl alcohol (Scheme 99).

[165] A. Goel, V. J. Ram, *Tetrahedron,* **2009**, *65*, 7865–7913.
[166] Y.-T. Li, Y. Zhu, G.-L. Tu, J.-Y. Zhang, Y.-S. Zhao, *Chem. Asian J.* **2018**, *13*, 3281–3284.
[167] D. R. Stuart, M. Bertrand-Laperle, K. M. N. Burgess, K. Fagnou, *J. Am. Chem. Soc.* **2008**, *130*, 16474–16475.



Scheme 99. Oxidative annulation of anilides with alkynes developed by Fagnou

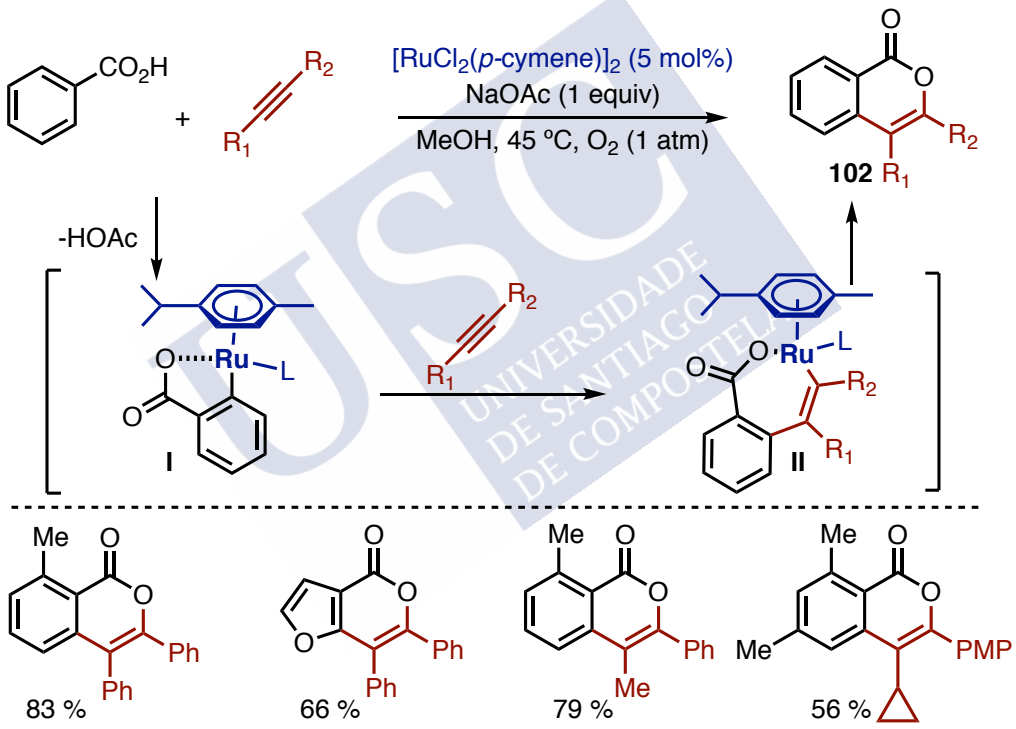
The mechanistic aspects of these transformations were disclosed by the same group in 2010[168], and involve an initial coordination of the Lewis basic amide oxygen to the rhodium complex **I** to afford species **II**, which undergoes irreversible and rate-determining C–H bond cleavage by a CMD pathway, yielding species **III**. Alkyne coordination and carbometalation leads to **V**, which undergoes C-N reductive elimination to extrude the indole product along with a rhodium (I) species of type **VI**, which is oxidized back by the combination of $Cu(OAc)_2$, molecular oxygen and the acetic acid generated in the reaction media (Scheme 100).



Scheme 100. Mechanism on oxidative annulation of anilides with alkynes

[168] D. R. Stuart, P. Alsabeh, M. Kuhn, K. Fagnou, *J. Am. Chem. Soc.* **2010**, *132*, 18326–18339.

Since these oxidative couplings of benzoic and acrylic acids and anilines were reported, many other groups have contributed to the field using different metal complexes (Rh, Ru, Co).[169] For instance, Ackermann and coworkers described in 2015 a very mild oxidative annulation strategy using a ruthenium catalyst.[170] The optimal conditions were achieved with the wide known $[RuCl_2(p\text{-cymene})]_2$ complex, sodium acetate in methanol at 45 ºC. Remarkably, the methodology is highly regioselective when unsymmetrical alkynes are used. From a mechanistic perspective, after the analysis of the kinetic isotope effect (KIE = 4.5), the authors proposed the initial C–H ruthenation (**I**) to be the rate-determining step. Thereafter, the alkyne coordination and insertion steps yield the intermediate **II**, that after reductive elimination leads to the isocumarine **101** (Scheme 102).



Scheme 102. Ruthenium catalyzed oxidative coupling of benzoic acids developed by Ackermann

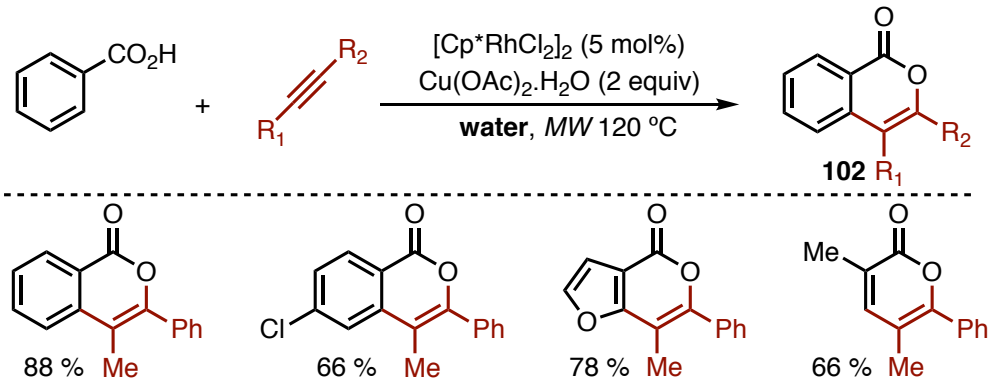
Yi and Xu reported an analogous rhodium-catalyzed oxidative coupling of benzoic acids in water (Scheme 103).[171] The optimal catalytic system consist on the rhodium dimer

[169] a) K. Ueura, T. Satoh, M. Miura, *Org. Lett.*, **2007**, *9*, 1407–1409; b) M. Shimizu, K. Hirano, T. Satoh, M. Miura, *J. Org. Chem.*, **2009**, *74*, 3478–3483; c) L. Ackermann, J. Pospech, K. Graczyk, K. Rauch, *Org. Lett.*, **2012**, *14*, 930–933; d) T. T. Nguyen, L. Grigorjeva, O. Daugulis, *Angew. Chem. Int. Ed.*, **2018**, *57*, 1688–1691.

[170] S. Warratz, C. Kornhaaß, A. Cajaraville, B. Niepötter, D. Stalke, L. Ackermann, *Angew. Chem. Int. Ed.*, **2015**, *54*, 5513–5517.

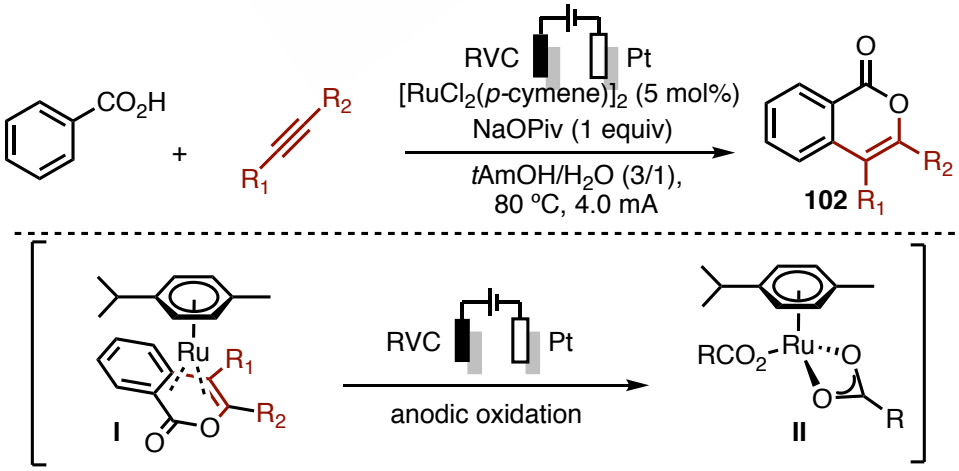
[171] Q. Li, Y. Yan, X. Wang, B. Gong, X. Tang, J. Shi, H. E. Xu, W. Yi, *RSC Adv.* **2013**, *3*, 23402–23408.

$[RhCp^*Cl_2]_2$ in combination with $Cu(OAc)_2$ in water under microwave heating. The methodology tolerates heteroaromatic carboxylic acids and acrylic acid as well.



Scheme 103. Rh-catalyzed oxidative coupling of benzoic acids in water developed by Yi & Xu.

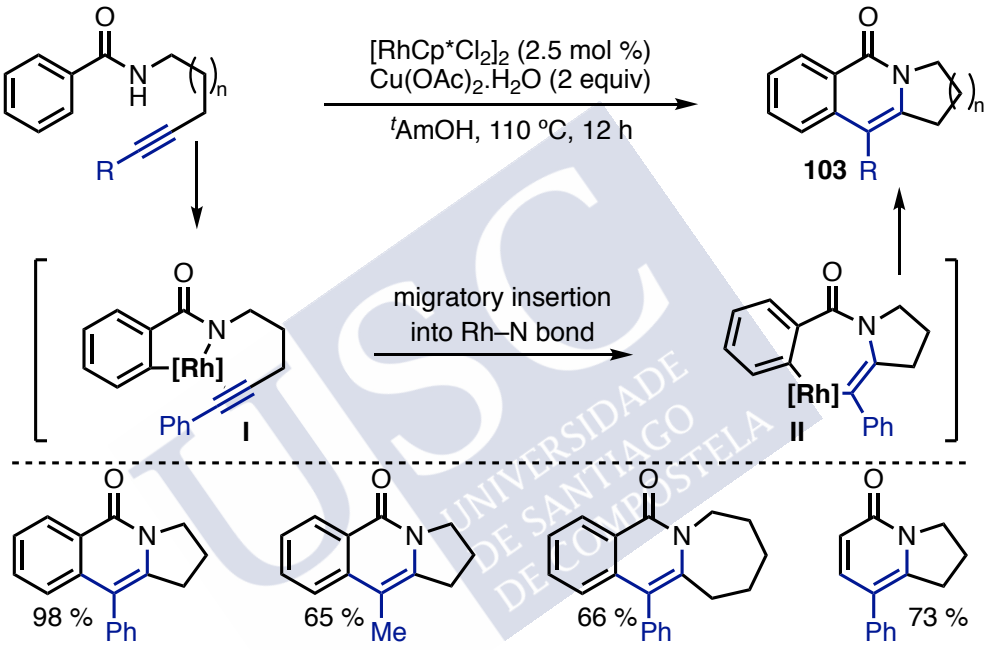
Very recently, Ackermann and coworkers reported a related transformation avoiding the use of metal oxidants.[172] They achieved the first example of electrocatalytic C–H activation by weak O-coordination using a ruthenium (II) carboxylate catalyst *in situ* generated by the mixture of $[RuCl_2(p\text{-cymene})]_2$ and sodium pivalate. The scope is wide for symmetrical alkynes and even with unsymmetrical alkynes high levels of regioselectivity and yield are obtained. From a mechanistic perspective, the authors propose a catalytic cycle related with the previous described, but in this case after the reductive elimination and generation of sandwich complex **I**, an anodic oxidation promotes formation of the isocoumarin and regenerates the initial Ru catalytic species **II** (Scheme 104).



Scheme 104. Ru-catalyzed electrocatalytic C–H activation developed by Ackermann

[172] Y. Qiu, C. Tian, L. Massignan, T. Rogge, L. Ackermann, *Angew. Chem. Int. Ed.* **2018**, *57*, 5818–5822.

In 2013, as part our effort to develop new methodologies to build heterocycles through C–H activation,[173] our group reported an intramolecular oxidative annulation of benzamides and acrylamides tethered to alkynes under rhodium (III) catalysis (Scheme 105). The methodology avoids the regioselectivity problems associate to the intermolecular processes and allows the access to a great variety of tricyclic structures of type **103** which form the core of many bioactive heterocyles. From a mechanistic perspective based on DFT calculations, after the C–H activation by a CMD path, the insertion of the alkyne into the Rh-N bond is more favourable than into the Rh-C. Subsequent reductive elimination yields the product and a Rh (I) species that is re-oxidized by the copper salt.



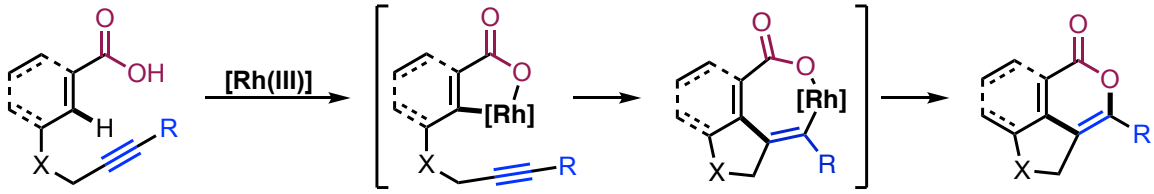
Scheme 105. Rh-catalyzed intramolecular oxidative annulation of benzamides developed by our group.

Remarkably, despite the efforts in this area, intramolecular approaches involving C–H activation/formal cycloaddition sequences remain scarce.[174] Indeed, we are not conscious of intramolecular variants for the annulations of acrylic acids, which would be relevant because in addition to control the regioselectivity, it could allow to build relevant bicyclic pyran-2-ones and tricyclic isocoumarins.

[173] N. Quiñones, A. Seoane, R. García-Fandiño, J. L. Mascareñas and M. Gulías, *Chem. Sci.*, **2013**, *4*, 2874–2879.
[174] a) Y. Wang, C. Wang, Y. Wang, L. Dong, J. Sun, *RSC Adv.* **2015**, *5*, 12354–12357; b) S. W. Youn, H. J. Yoo, *Adv. Synth. Catal.* **2017**, *359*, 2176–2183.

2. Objectives

As indicated, intramolecular formal cycloadditions initiated by a metal catalyzed C–H activation are scarce. Specifically, we proposed to develop a regioselective intramolecular annulation of acrylic and benzoic acids equipped with tethered alkynes to access 2-pyrone scaffolds.



Scheme 106. Intramolecular oxidative annulation of aromatic and acrylic acids. Design and proposal

Moreover, we intended to explore their reactivity because 2-pyrone motifs are interesting intermediates in total synthesis and are present in relevant natural products.

3. Article 3: Rhodium(III)-Catalyzed Intramolecular Annulations of Acrylic and Benzoic Acids to Alkynes

Doi: https://doi.org/10.1021/acsomega.9b00022

David F. Fernández, Noelia Casanova, José Luís Mascareñas and Moisés Gulías, *ACS Omega*, **2019**, *4*, 6257–6263.

Author contributions

J.L.M and M.G. directed the research. D.F. performed all the experiments as well as the acid precursors synthesis. M. G. wrote the manuscript, discussed the results and revised the manuscript with inputs from J.L.M, and D.F.

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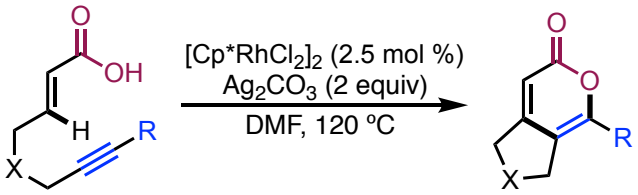
4. Conclusion

In summary, we have developed the first examples of intramolecular (4+2) annulations between acrylic acids and alkynes. The oxidative annulation permits the direct assembly of pyrone-containing adducts from readily available precursors using a Rh(III) catalyst.



Scheme 107. Rh-catalyzed oxidative annulation of acrylic acids tethered to alkynes

Moreover, the transformation also works with benzoic acids as well as other heteroaromatic precursors. Remarkably, interesting seven and eight membered tricyclic structures can be assembled from simple pyrrole carboxylic acids tethered to an alkyne moiety.

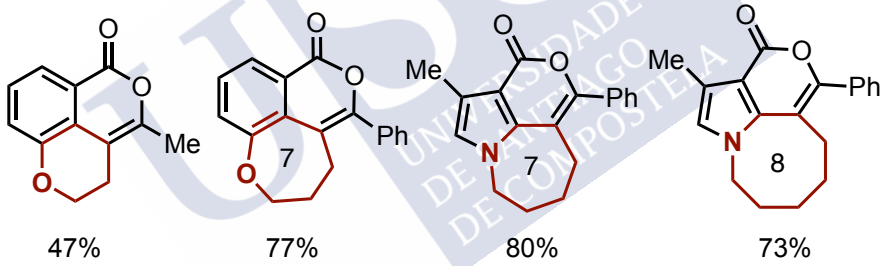
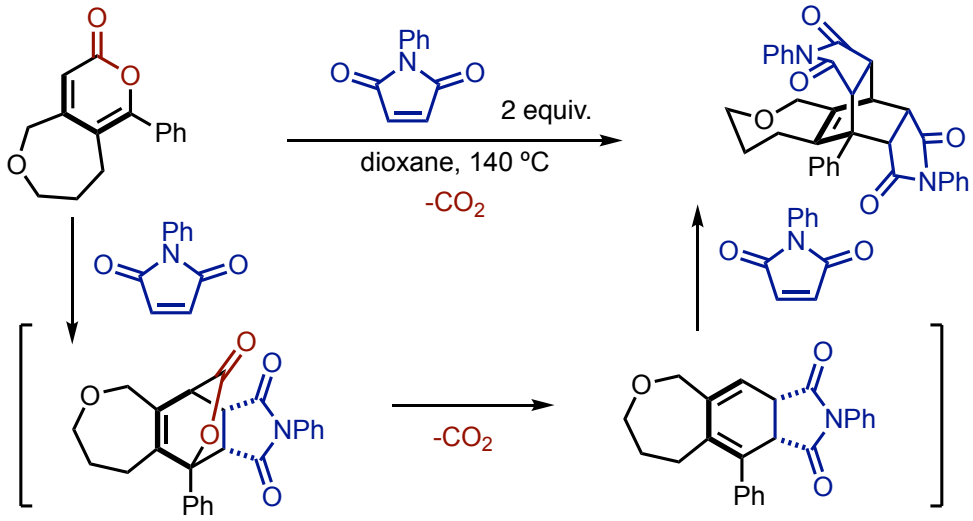


Figure 7. Relevant heterocyclic compounds assembled with the Rh-catalyzed oxidative annulation

To further unveil the synthetic power of the methodology, we demonstrated different manipulations of the α-pyrone derivatives, including a unique thermal cycloaddition cascade in presence of an electron poor dienophile.



Scheme 108. [4+2] Cascade process of *cis*-diene compounds generated with the catalytic strategy

Summary

TRANSITION METAL-CATALYZED ANNULATIONS BASED ON THE ACTIVATION OF C–H BONDS

Transition metal catalysis is an impressive tool to promote relevant synthetic transformations. A particularly appealing chase are metal C–H activation protocols which are at the vanguard of organic synthesis due to the advantages in terms of atomic waste prevention, one of the principles of the *Green Chemistry*,[10] step economy and selectivity. On the other hand, annulations processes are among the most appealing transformations in terms of atom economy, efficiency and increase in molecular complexity.

Merging these processes result in a powerful strategy in the synthesis of challenging bioactive molecules.[175] During this PhD work we have discovered several cyclization and cycloaddition transition-metal promoted reactions that allow to access to relevant cyclic scaffolds.

Iridium(I)-Catalyzed Intramolecular Hydrocarbonation of Alkenes: Efficient Access to Cyclic Systems Bearing Quaternary Stereocenters

At the outset of this PhD thesis, we were aware of reports on intermolecular Csp^2-H hydrocarbonation reactions mainly using rhodium and cobalt catalysts. Notwithstanding these reports did not allow to access quaternary stereocenters.

We also realize that Iridium hydrocarbonation chemistry was not hardly explored and could offer great opportunities. Thus, we wanted to develop a cyclization strategy that allow us to build quaternary stereocenters in a straightforward manner using iridium complexes as catalysts.

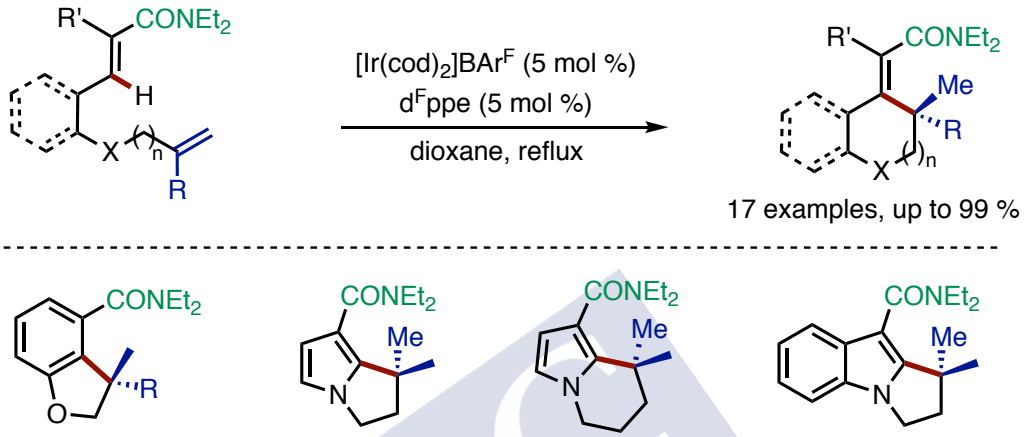
Initially, we focus our attention in acrylamides tethered to alkenes. We tested commercially available Iridium (I) complexes in combination with phosphines. After an initial screening of conditions, we gratifyingly realised that the reaction led to an *exo*-cyclization product which generates a quaternary center. The new transformation afforded the best results using bidentate phosphines in combination with $[Ir(cod)_2]BAr^F_4$ in refluxing dioxane. From this

[10] 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, et al., *Green Chemistry* **2018**, *20*, 1929–1961.

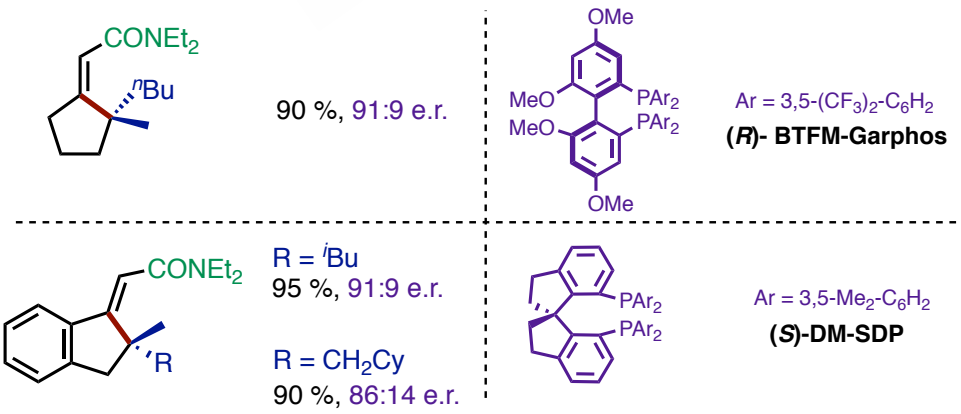
[175] J.-R. Chen, X.-Q. Hu, L.-Q. Lu, W.-J. Xiao, *Chem. Rev.* **2015**, *115*, 5301–5365.

initial screening we demonstrated that BINAP and d^{F}ppe are the best ligands for the Ir(I)-catalyzed intermolecular hydrocarbonation of alkenes.

Moving forward to the scope of the process, we stablished that the new methodology is compatible not only with acrylamides but also with functionalized benzamides and heteroaromatic amides tethered to alkenes.



Importantly, taking into account the scarcity in enantioselective cyclizations to build quaternary stereocenters, we wondered about the possibility of developing an enantioselective variant of the method. We first examined readily available structure-related BINAP ligands and we gratifyingly observed an induction in chirality. A preliminary development of an asymmetric variant was successfully achieved with (*R*)-BTFM-Garphos and (*S*)-DM-SDP as ligands, achieving up to 91:9 enantiomeric ratios.



We also demonstrated the utility of the products developing a very efficient transformation of the cyclic amides into ketones bearing α-quaternary stereocenters, that cannot be trivially assembled using other catalytic methods.

Regarding the key step of the mechanism of the reaction, we synthesized a deuterated probe to get insight into the alkene insertion, concluding at that time that hydrometallation or carbometallation pathway were both feasible for this transformation.

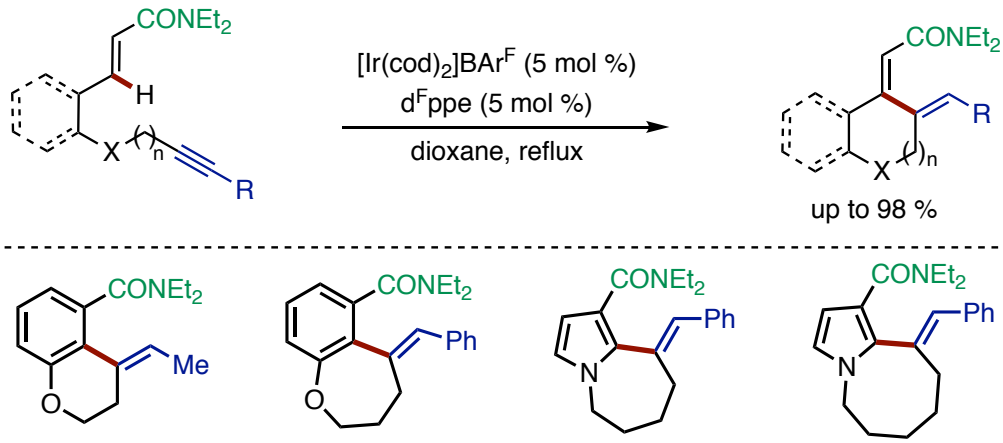
After the publication of the manuscript, several groups have focused their attention into related Ir-catalyzed C-H hydrocarbonations. In 2016, Huang and coworkers disclosed a detailed mechanistic proposal based on DFT calculations for our reaction. Their studies conclude that the pathway involving carbometallation and subsequent C-H reductive elimination is the most probable scenario for this Ir-catalyzed hydrocarbonation of alkenes.

Iridium(I)-Catalyzed Intramolecular Cycloisomerization of Enynes: Scope and Mechanistic Course.

Taking into account that reports on hydrocarbonation of alkynes based on TMC activation of Csp^2–H bonds are very scarce and limited to precursors with aromatic and heteroaromatic moieties and, particularly in the intramolecular scenario. We proposed the development of a cycloisomerization of enynes, a powerful strategy to access carbocycles and heterocycles. Moreover, we intended to build these molecules bearing synthetic-relevant *exo*-cyclic dienic functionalities using the abovementioned iridium catalysts.

With this envision in mind, we designed an N,N-diethylacrylamide tethered to an phenylalkyne as our model substrate (manuscript; compound **1a**, Table 1, page 7398). We initially tested several metal complexes in combination with different phosphine ligands. As in the case of the hydrocarbonation of alkenes, monodentate phosphines were proved unsuccessful and the optimal conditions for the Ir-catalyzed cycloisomerization of enynes were achieved by merging $[Ir(cod)_2]BAr^F{}_4$ and BINAP in refluxing dioxane.

We next moved to explore the reaction scope, satisfyingly stablishing that the reaction is compatible with electron-donating and electron-withdrawing substituents at the aryl group of the alkyne, obtaining the *exo*-dienyl cyclopentanes and cyclohexanes in good yields. To further unveil the versatility of the methodology we analyze the behaviour of related aromatic and heteroaromatic Csp^2–H activations. Chromane and tetrahydroindolizine derivatives were obtained from good to excellent yields.



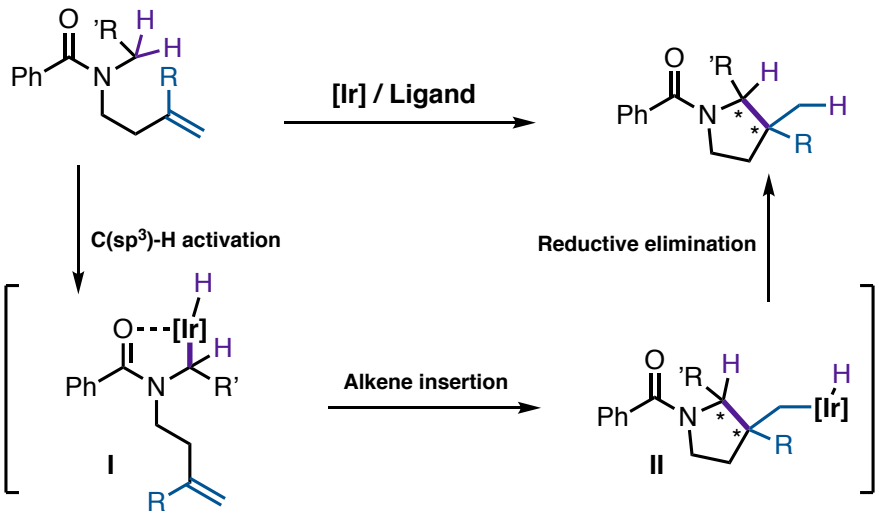
In order to shed light into the mechanism several experiments were developed, including the preparation of a deuterated probe, that demonstrated the initial C-H activation step. Importantly, DFT theoretical analysis was performed, concluding that in the case of the Iridium-catalyzed cycloisomerization of enynes, the initial oxidative addition is the rate-determining step. Regarding the olefin insertion, both the carbometalation and hydrometalation paths are energetically feasible, being easier the carbon-hydrogen reductive elimination resulting from the carbometallation step.

Summary of the addendum to Chapter II

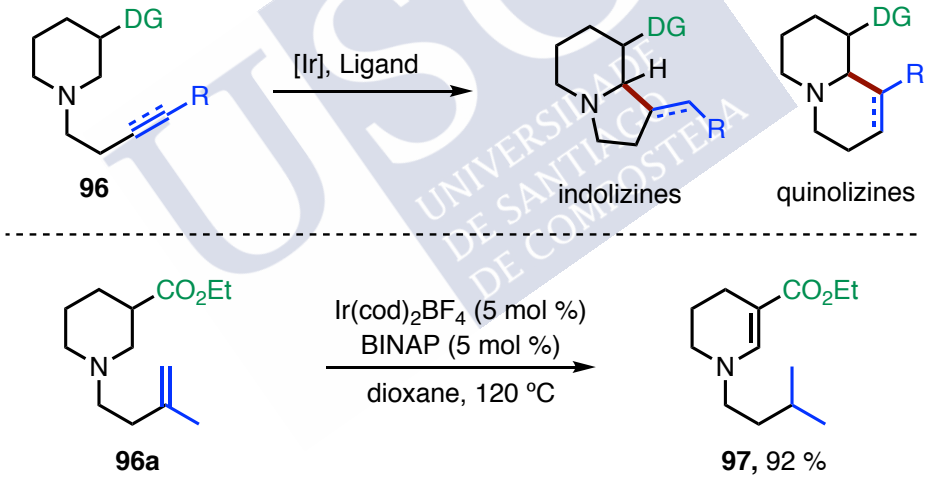
Csp^3–H functionalization is a highly attractive strategy to increase molecular complexity from simple starting materials. Nevertheless, achieving selective functionalization C(sp^3)–H bonds is extremely difficult, particularly due to poor reactivity of Csp^3–H.

Despite several groups had disclosed elegant intermolecular alkylation protocols based on Pd, Co, Rh, Ru and Ir-catalyzed processes, intramolecular variants that are still scarce and limited to highy activated systems, would straightforward the access to all types of cyclic molecules.

We proposed an intramolecular Ir-mediated Csp^3–H activation alkylation of alkenes and alkynes. Initially, we synthesized benzamides of type **94** and **95**, and we screened different TM-catalysts. Although we were not able to identify the products generated in the catalytic reaction, we discovered a protocol to deuterate Csp^3–H of N-alkyl amides, proving that the initial Csp^3–H activation is feasible.



Moreover, we also hypothesize a Csp^3–H cyclization strategy using piperidines tethered to alkenes, **96**. The initial results shown that instead of the envisioned indolizine or quinolizine structure, what we found is a formal double bond migration, resulting in the formation of **97**.

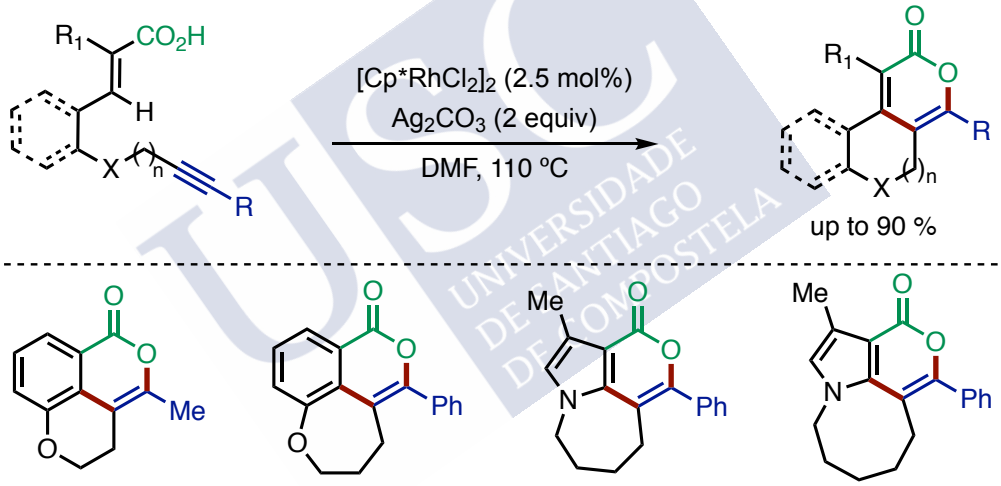


Rhodium(III)-Catalyzed Intramolecular Annulations of Acrylic and Benzoic Acids to Alkynes

Oxidative annulations are extremely appealing transformations since they allow to construct complex cyclic structures minimizing the atom waste. One of the key features of this strategy is the formation of metalacyclic intermediates through C–H activation promoted by transition metals in high oxidation states, that can further react with unsaturated partners such us alkenes, alkynes, allenes, etc. Most of the research in this area is based on intermolecular reactions, however, reports on related intramolecular

transformations are scarce which prompted us to develop an intramolecular oxidative annulation of benzamides and acrylamides to access relevant bicyclic and tricyclic structures. Being aware of the utility and versatility of this approach, our desire was to expand this strategy to related systems to build interesting bicyclic and tricyclic scaffolds. Taking all these considerations, we envisioned a new oxidative annulation of acrylic acids tethered to alkynes. Initial results shown that rhodium (III) complexes worked much better than ruthenium or iridium catalysts. The optimal conditions were achieved using the commercially available $[Cp^*RhCl_2]_2$ and Ag_2CO_3 in DMF.

The scope of the process was broad, tolerating different alkyl and aryl substitution patterns in the alkyne moiety. We also demonstrated that activating aryl and heteroaryl Csp^2–H bonds is also possible, obtaining bicyclic and tricyclic compounds containing even medium-size rings (7, 8 and 9 members).



We designed relevant manipulations for the pyrone derivatives obtaining by the catalytic process. On one hand, keto carboxylic acids are obtained by basic treatment of the pyrone derivative with KOH in ethanol. Moreover, cascade Diels-Alder processes have been developed to access complex polycyclic structures.

Overall Conclusion

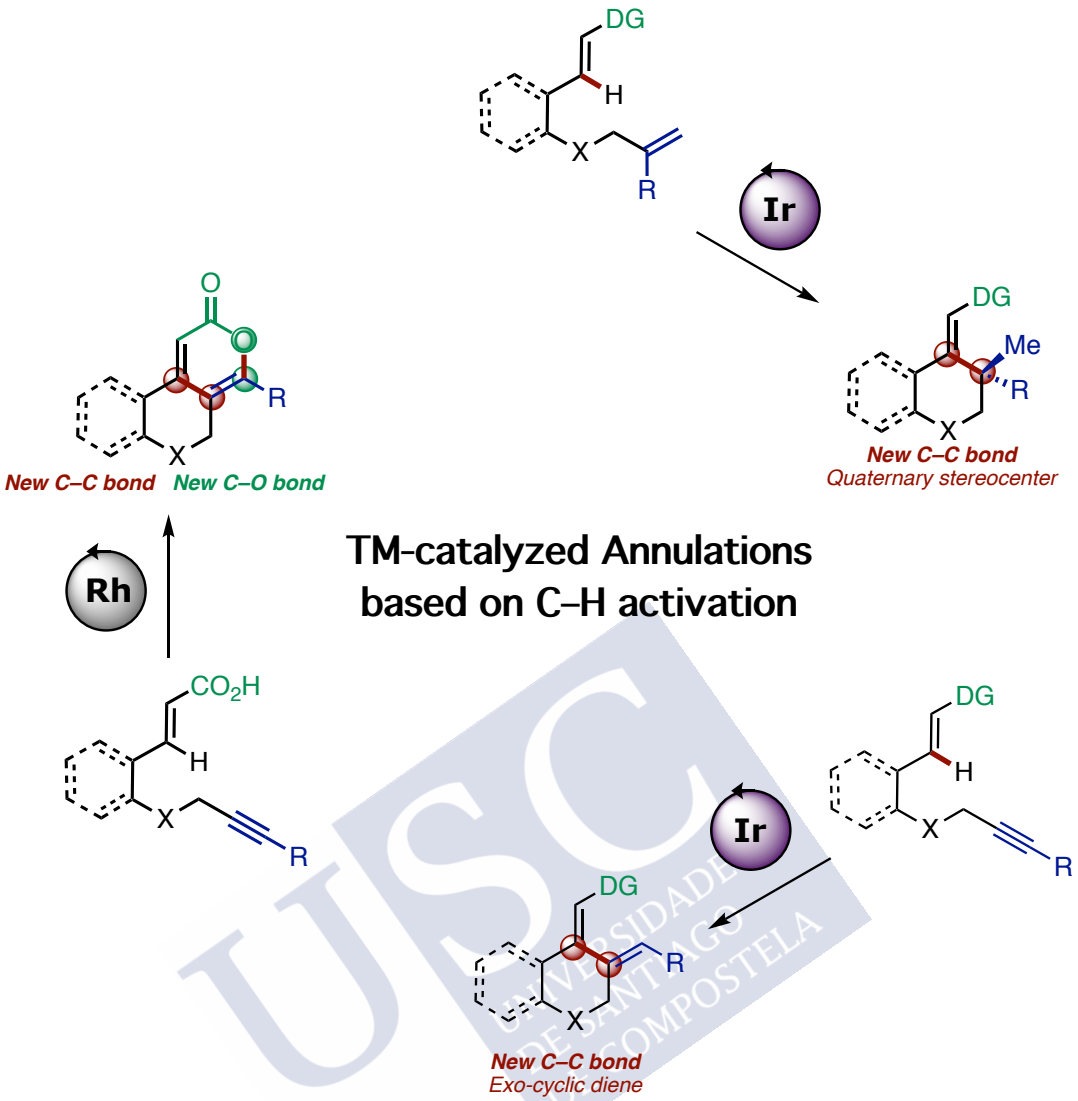
During the course of this PhD thesis we have disclosed several TM-mediated transformations for the synthesis of cyclic derivatives.

First, we evaluated the behavior of cationic iridium complexes for the Csp^2–H activation of alkenyl derivatives. We gratifyingly observed that a N,N-dialkyl amide derivative bearing an alkene moiety undergoes a cyclization event with the concomitant generation of a quaternary center. Stablishing the optimal catalytic conditions, $[Ir(cod)_2]BAr^F_4$ and d^Fppe in dioxane, we moved to the reaction scope. Alkenyl derivatives, as well as aromatic and heteroaromatic Csp^2–H were activating, yielding the corresponding cyclic structure bearing quaternary centers. We also explored the asymmetric version of this transformation, stablishing a versatile protocol to assemble ketones bearing α-quaternary stereocenters.

Secondly, we have demonstrated the viability of intramolecular Csp^2–H alkenyl hydrocarbonation of alkynes to access *exo*-cyclic dienes using iridium catalysts. Moreover, we have taken advantage of these functionalities to obtain well defined complex polycyclic structures using cascade cyclization and cycloaddition protocols. Regarding the mechanistic aspects of the transformation, we performed DFT theoretical analysis as well as several experiments involving deuterated probes, concluding that the C–H oxidative addition step is the rate-determining step and both alkyne insertion pathways (carbometalation and hydrometalation) are feasible.

We also set preliminary results in the Csp^3–H activation of N-alkyl amides, developing a deuteration procedure involving cationic iridium species and D_2O. Likewise, we discovered a formal double bond migration in piperidines tethered to alkenes using iridium catalysts.

Finally, we developed an intramolecular approach involving C–H activation and formal cycloaddition sequence. Key to this success was the catalyst choice, a high valent Rh(III) complex in combination with Ag_2CO_3 promoted the oxidative annulation of acrylic acids tethered to alkynes. The bicyclic structures generated in the transformation are prone to suffer relevant derivatizations, such us Diels-Alder cycloadditions, leading to complex polycyclic scaffolds.


DG
H
X
R
Ir
DG
Me
R
X
New C–C bond
Quaternary stereocenter
O
R
X
New C–C bond
New C–O bond
TM-catalyzed Annulations
based on C–H activation
Rh
CO2H
H
X
R
DG
H
X
R
Ir
DG
R
X
New C–C bond
Exo-cyclic diene

Resumo

A catálise con metais de transición é unha ferramenta extremadamente útil á hora de promover transformacións sintéticas. Particularmente, a C–H activación atópase na vangarda da síntese orgánica, presentando vantaxes tales como minimizar a xeración de residuos ou a economía atómica, ambos principios da denominada Green Chemistry, ademais de erixirse como unha estratexia altamente selectiva. Por outra banda, os procesos de anelación áchanse entre as transformacións máis atractivas en canto a economía atómica, eficiencia e incremento en complexidade molecular.

A fusión destes procesos resulta nunha potente estratexia na síntese de moléculas bioactivas que presentan un desafío por outros métodos. No transcurso desta tese, descubrimos diferentes reaccións de ciclación e cicloadición promovidas por metais de transición que nos permitiron a síntese de estruturas cíclicas relevantes.

Hidrocarbonacións intramoleculares de alquenos catalizadas mediante complexos de iridio (I).

No primeiro capítulo descríbese unha metodoloxía catalítica, versátil e de grande economía atómica baseada en procesos de C–H activación que permite sintetizar unha grande variedade de sistemas cíclicos á vez que se xeran centros cuaternarios.

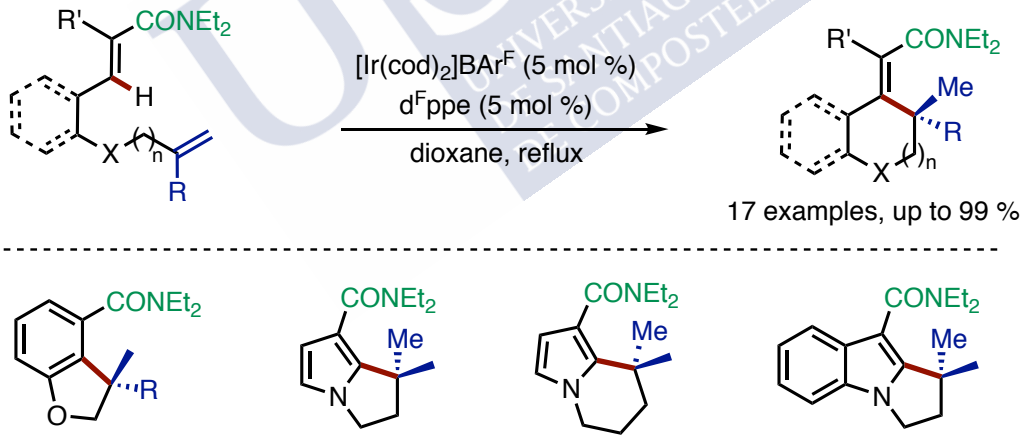
A pesares de existir traballos de investigación no eido das hidroarilacións intermoleculares con diversos metais de transición, incluíndo ao iridio, ata a data de publicación do primeiro dos artigos que se presenta, non se reportara ningunha contribución intramolecular xeral na activación de $C(sp^2)$–H de alquenos e aneis aromáticos e heteroaromáticos para a síntese das devanditas estruturas cíclicas. Curiosamente tamén a selectividade da reacción que se describe é novidosa, existindo só dous exemplos limitados a precursores de tipo indol.

Inicialmente, sintetizamos amidas acrílicas conectadas a funcionalidades de alqueno, probáronse condicións catalíticas nas que se avaliaron diferentes complexos neutros de iridio e tamén complexos catiónicos, variando o contraión asociado aos mesmos. Tamén se estudou unha grande variedade de fosfinas como ligandos dos devanditos complexos metálicos , chegando á conclusión de que as condicións óptimas para a ciclación resultaban daa combinación de $[Ir(cod)_2]BAr^F{}_4$ e a bisfosfina BINAP en dioxano a refluxo.

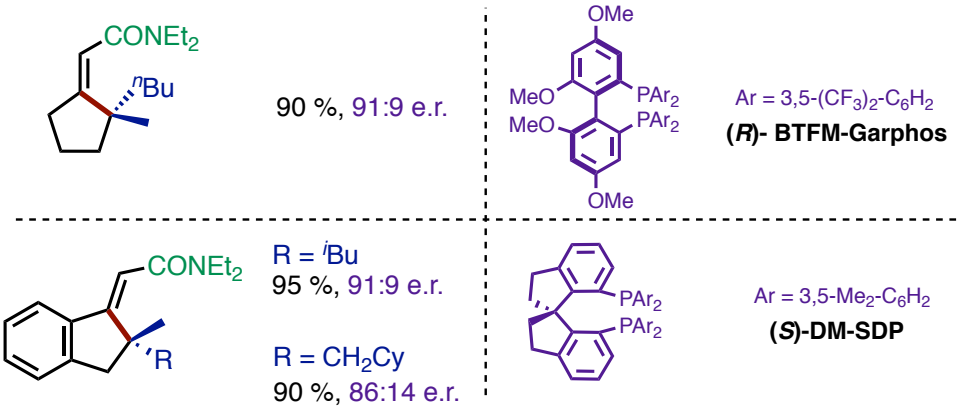
No devir do proxecto, tamén se estudaron diferentes grupos directores. No caso das cetonas observouse reactividade, mais a reacción contaba cunha menor selectividade e eficiencia. Pola contra, os ésteres non resultaron grupos directores efectivos para a transformación. As amidas erixíronse como a mellores opción para a ciclación con selectividade *exo*, e entre elas destacou en canto a eficacia a amida disubstituída por grupos etilo.

Unha vez optimizadas as condicións catalíticas e a natureza do grupo director, procedeuse a avaliar o alcance da transformación. Compostos totalmente acíclicos, onde se activa o carbono que presenta hibridación sp^2, son substratos perfectamente válidos para a reacción de ciclación. Tamén, a posición alfa da amida pode tamén sufrir substitucións alquílicas sen afectar ao rendemento da reacción catalítica. Outros compostos carbonados como os indenos, son substratos viables, permitindo a xeración de ciclos de cinco e seis membros de maneira *exo* selectiva.

Para aínda darlle máis valor á metodoloxía, decidiuse probar a activación de $C(sp^2)$–H de compostos heteroaromáticos baixo as mesmas condicións catalíticas. Os resultados foron fabulosos, permitindo utilizar derivados de fenol, pirrol e indol na ciclación, para así obter biciclos e triciclos fusionados, combinando carbociclos con heterociclos.



Ademais de desenvolver a variante racémica, tamén se estudou a ciclación enantioselectiva empregando fosfinas enriquecidas na súa forma *R* ou *S*. A síntese quiral de centros cuaternarios é unha das grandes problemáticas á hora de afrontar a síntese total dunha molécula específica debido á escaseza de metodoloxías dispoñibles para tal fin. Neste ámbito, tras a proba de numerosos ligandos comerciais e outros sintetizados no laboratorio, atopáronse dúas fosfinas que permitían acceder aos cicloadutos con elevada enantioselectividade: o (*S*)-DM-SDP e o (*R*)-BTFM-Garphos, acadando ratios de 91:9.



Outro dos elementos interesantes neste capítulo é a derivatización dos produtos obtidos. Mediante unha simple e rápida rutenólise, o alqueno α,β-insaturado da amida pode escindir, xerando unha cetona que presenta múltiples posibilidades sintéticas. Como xa se comentou, a importancia desta transformación radica na dificultade de formar centros cuaternarios de maneira enantioselectiva en alfa ao carbonilo dunha cetona.

Alén do aspecto sintético puro, tamén se traballou para elucidar o mecanismo da reacción. Probas de deuteración xunto aos nosos cálculos DFT e aos do grupo de Huang, permitiron establecer unha proposta mecanística na que o primeiro paso é a activación do enlace Csp^2–H, seguida da carbometalación do alqueno non conxugado con selectividade *exo*. Este intermedio experimenta unha eliminación redutora C–H para xerar o produto cíclico e rexenerar o catalizador.

Cicloisomerizacións intramoleculares de eninos catalizadas mediante iridio (I): Alcance e estudo mecanístico.

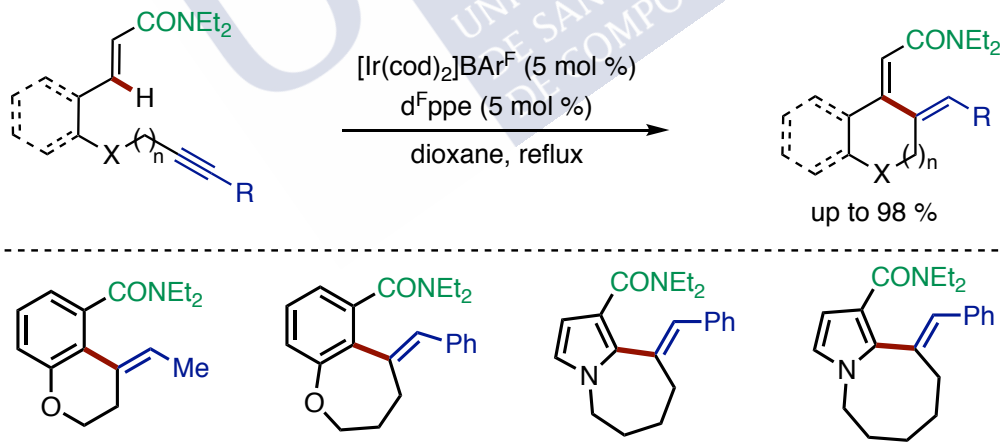
Continuando no eido do iridio (I), no capítulo segundo descríbese unha nova metodoloxía que permite o acceso a sistemas cíclicos que contan na súa estrutura cun dieno con xeometría definida. Este tipo de esqueletos son de grande relevancia dende un punto de vista sintético, debido as múltiples posibilidades de derivatización que presentan, entre elas as amplamente empregadas e recoñecidas Diels-Alder.

A maioría de estudos ata a data céntranse en procesos de hidroarilación intermoleculares, independentemente do metal empregado. Empregando iridio (I) como catalizador, a nosa aportación é a primeira que permite a adición de enlaces C–H con hibridación sp^2 de alquenos mediante C–H activación a alquinos substituídos. Asemade, existe unha grande

controversia na comunidade científica acerca dos mecanismos que gobernan as inserciónsmigratorias empregando catalizadores de iridio (I).

Para comezar o estudo da reactividade sintetizouse unha acrilamida conectada cun alquino substituído. A continuación, someteuse a condicións catalíticas de iridio (I) en combinación con fosfinas. No devir da investigación, observouse que os ligandos monodentados non eran aptos para a transformación. Tamén se viu que dependendo da bisfosfina empregada ou mesmo do contraión do complexo de iridio, a reactividade mudaba, sendo posible a identificación de produtos secundarios procedentes de isomerizacións. Finalmente, cas condicións óptimas, $[Ir(cod)_2]BAr^F$ xunto á bisfosfina BINAP en dioxano a 100 ºC, obtívose o cicloaduto nun noventa e dous por cento de rendemento.

Avaliouse o alcance da metodoloxía, comprobando satisfactoriamente que se obtiñan cicloadutos de cinco e seis membros en moi bos rendementos independentemente das substitucións no alquino. De novo, para coñecer o potencial do método, testáronse as condicións óptimas para activar $C(sp^2)$–H de compostos aromáticos e heteroaromáticos. En ambos casos obtivéronse excelentes resultados para a síntese de biciclos que contiñan aneis de 6, 7 e 8 membros. Así, esta metodoloxía permite o acceso simple e eficiente a sistemas heteroaromáticos dificilmente sintetizables por outros procedementos.

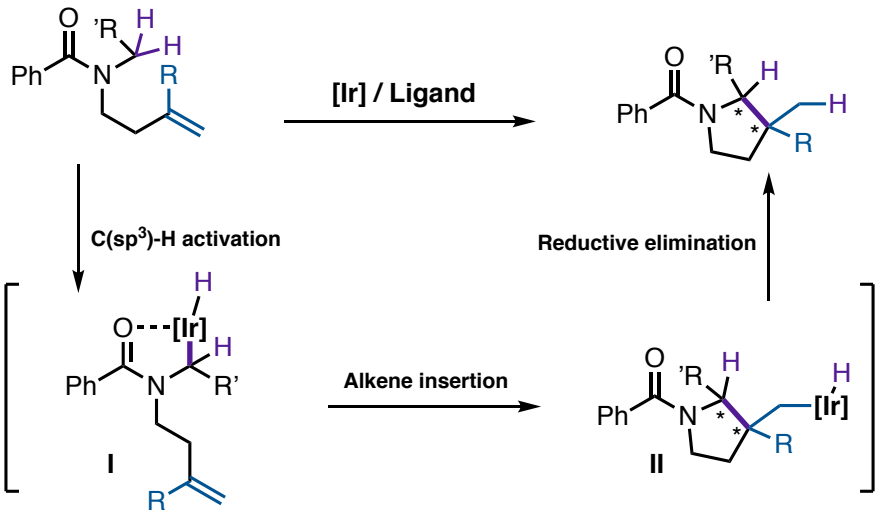


Como xa se mencionou, os dienos obtidos coa configuración definida trala ciclación brindan unhas oportunidades excelentes para a manipulación, sendo posible o desenvolvemento dunha técnica *one-pot* que combina a hidrocarbonación mediada por iridio cun proceso (4+2) tipo Diels-Alder cunha especie dienófila. A partires dunha simple molécula acíclica, xéranse moléculas policarbocíclicas enriquecidas esteroquímicamente, con total economía atómica.

No que respecta ao mecanismo da reacción, leváronse a cabo estudos experimentais, coma a análise da migración exclusiva de deuterio dunha das amidas precursoras deuterada, suxerindo unha etapa de activación do enlace Csp^2–H do alqueno. Estudos mecanísticos teóricos amosan que non é posible acadar unha conclusión do camiño que percorre a reacción tras a etapa de C–H activación, as barreiras enerxéticas resultantes da análise dos cálculos DFT son similares, sendo, *a priori*, viables a carbometalación e eliminación redutora C–H ou ben a hidrometalación e posterior eliminación redutora C–C. Aínda que no primeiro caso a barreira da eliminación redutora C–H é lixeiramente máis sinxela.

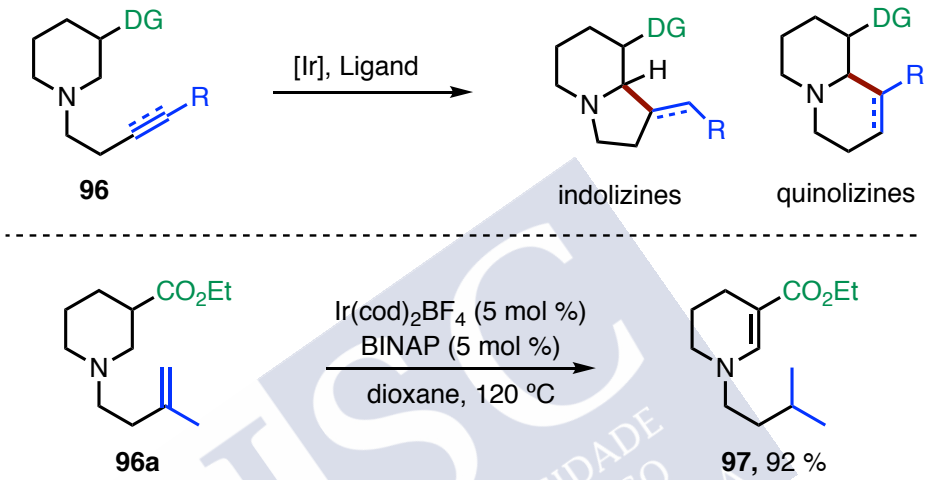
Ademais dos artigos publicados, estanse a investigar procesos de activación de enlaces carbono-hidróxeno con hibridación sp^3, moito menos reactivos e difíciles de controlar debido á enerxía intrínseca que posúen. Nas moléculas cotiás, xeralmente existe un número moito maior deste tipo de enlaces fronte aos $C(sp^2)$–H de alquenos, o que dificulta os procesos selectivos.

Nunha primeira aproximación, propúxose como obxectivo a síntese de heterociclos mediante a activación dun $C(sp^3)$–H en posición alfa a un nitróxeno, o que permite aumentar a selectividade dese carbono-hidróxeno en particular. Seguindo a liña de investigación dos complexos de iridio (I) empregados nos dous proxectos previos, ideouse unha amida como grupo director. Despois de tentar diferentes condicións catalíticas, observouse que existe un intercambio protón-deuterio mediado por complexos catiónicos de iridio. Este feito observado permítenos elaborar unha hipótese mediante a cal existe unha coordinación da amida ao iridio, de xeito análogo aos traballos previos, e este realiza unha activación do devandito $C(sp^3)$–H reversible. A continuación, a auga deuterada presente no medio pode intercambiar o deuterio polo hidruro.



Non obstante, neste sistema non puido detectar a presencia do produto cíclico, lamentablemente, a coexistencia de rotámeros de longa vida na escala de tempos do NMR dificultou a análise das reaccións catalíticas.

Por outra banda, no sistema do derivado do éster de etilo do nipecotato, no canto de observar a ciclación agardada, observouse unha transposición formal de hidróxeno mediada por complexos catiónicos de iridio.



Actualmente estase a continuar a investigación nos dous últimos eidos citados, que agardamos que permitan xerar unha nova metodoloxía xeral útil en síntese orgánica.

Anelacións intramoleculares de ácidos acrílicos e benzílicos con alquinos catalizadas por complexos de rodio (III).

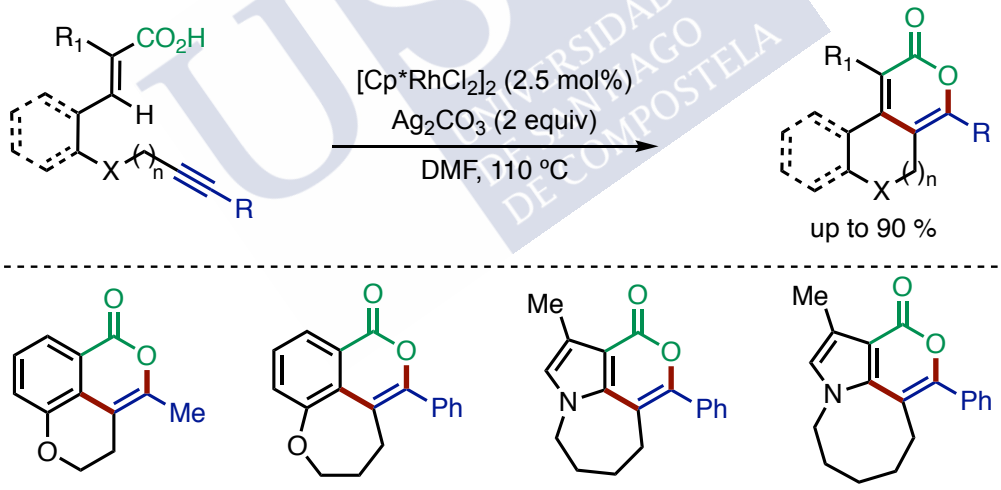
No terceiro capítulo descríbese o pioneiro traballo intramolecular con ácidos acrílicos e benzoicos que conteñen un alquino na súa estrutura para obter biciclos ou triciclos mediante unha metodoloxía de C–H funcionalización con catálise de rodio (III). Este método permite a obtención de carbociclos ou heterociclos fusionados con lactonas, motivo característico de moléculas con relevantes propiedades farmacolóxicas ou bioactivas coma a *Nagilactone F* ou a *Clavulactone*.

Leváronse a cabo diferentes reaccións catalíticas ata atopar as condicións óptimas: o complexo de rodio $[Cp^*RhCl_2]_2$ xunto á sal de prata Ag_2CO_3, que actúa como oxidante na reacción, en DMF a 120 ºC. O complexo análogo de iridio non amosou reactividade para a

anelación. Observouse tamén que catalizadores catiónicos de rodio ou o complexo de rutenio [(*p*-cymene)$RuCl_2]_2$ amosan eficiencias moi inferiores ao dímero de rodio previamente citado.

Ademais de participar na reacción, o grupo carboxílico tamén ten o rol de grupo director, permitindo a especificidade da activación do C(sp^2)–H. A metodoloxía é válida para unha morea de ácidos acrílicos, permitindo obter con bo rendemento biciclos de tamaño variable, dende fusións 5-6 ata fusións 7-6. Así, a metodoloxía permite obter tamén aneis de oito membros fusionados co anel de seis lactónico, aínda que con menor rendemento. Comprobouse que a reacción é compatible con diferentes substitucións electrónicas no anel aromático do alquino. Tamén é posible a substitución da posición alfa ao grupo carboxilo por grupos alquilo sen observar detrimento na reactividade.

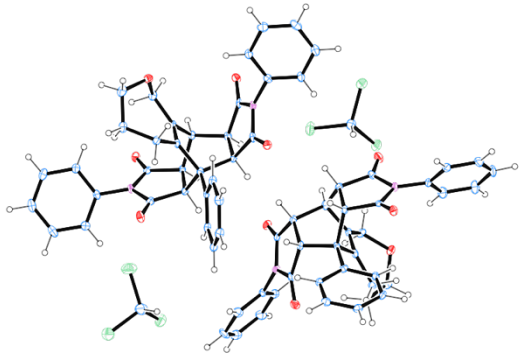
No referente a substratos aromáticos e heteroaromáticos, a metodoloxía tamén se erixiu como válida e eficiente, sendo posible sintetizar triciclos 6-6-6 ou 6-6-7 no caso de derivados de fenois e triciclos 5-6-7 e 5-6-8 a partir de derivados pirrólicos en bo rendemento.



Neste último capítulo tamén se recollen manipulacións clave dos produtos obtidos, sendo posible levar a cabo hidrólise da lactona para producir moléculas cas funcionalidades de grupo carboxílico e carbonílico, que poden ser empregadas nunha grande variedade de transformacións.

Outra das modificacións clave destes esqueletos moleculares é a dobre cicloadición en tándem, eliminando unha molécula de CO_2 no devir da reacción. Nesta transformación,

xéranse moléculas de grande complexidade estrutural, formándose cinco enlaces carbono-carbono e contando con cinco ciclos na súa estrutura, con grande economía atómica.



Supporting Material[176]

[176] The complete list of NMR Spectra of the products can be found in the digital folder "Supporting Information"

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Angewandte Chemie
Eine Zeitschrift der Gesellschaft Deutscher Chemiker

Supporting Information

Iridium(I)-Catalyzed Intramolecular Hydrocarbonation of Alkenes: Efficient Access to Cyclic Systems Bearing Quaternary Stereocenters

David F. Fernández, Moisés Gulías, José L. Mascareñas,* and Fernando López**

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Supporting Information

69451 Weinheim, Germany

Table of Contents

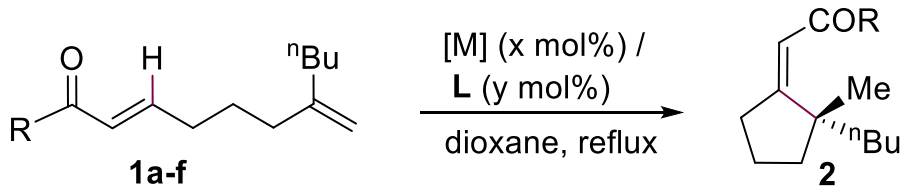
General Procedures

Dry solvents were freshly distilled under argon from an appropriate drying agent before use. Bis(cyclooctadiene)iridium(I) tetrakis(3,5-bis(trifluoromethyl) phenyl) borate (abbreviated as $Ir(cod)_2BArF$), Bis(1,5-cyclooctadiene)iridium(I) tetrafluoroborate (abbreviated as $Ir(cod)_2BF_4$, 1,2-Bis[bis(pentafluoro-phenyl)phosphino]ethane (abbreviated as dpp^Fe) were purchased from Aldrich. 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.

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 approximately at 23 °C. Reaction mixtures were stirred using Teflon-coated magnetic stirring bars. Reaction temperatures were maintained using Thermowatch-controlled silicone oil baths. Thin-layer chromatography (TLC) was performed on silica gel plates and components were visualized by observation under UV light, and / or 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 or $MgSO_4$. Concentration refers to the removal of volatile solvents via distillation using a Büchi rotary evaporator followed by residual solvent removal under high vacuum. NMR spectra were recorded in $CDCl_3$, at 300 MHz (Varian), 400 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). 1,3,5-Trimethoxybenzene was used as internal standard. 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. Mass spectra (ESI-MS) were acquired using IT-MS Bruker AmaZon SL at CIQUS and also using chemical ionization (CI) electron impact (EI), or electrospray ionization (ESI) at the CACTUS facility of the University of Santiago de Compostela. The reactions were monitored by TLC. Enantioselectivities were determined in an Agilent HPLC 1100 Series with Chiralpak IA, IB, IC, IA3 or OZ-H analytical columns.

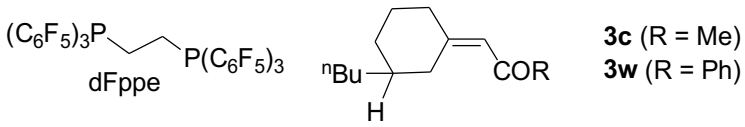
Optimization of the reaction conditions

Table S1. Optimization of the reaction conditions[a]



entry	**1**	R	[M] (X mol%)	**L** (y mol%)	Yield (%)[b]
1	**1a**	NEt_2	$Ir(cod)_2BArF$ (5)	d^Fppe (5)	**2a**, 91
2	**1a**	NEt_2	$Ir(cod)_2BArF$ (5)	$P(C_6F_5)_3$ (10)	**2a**, <5
3	**1a**	NEt_2	$Ir(cod)_2BArF$ (5)	dppe (5)	**2a**, 32
4	**1a**	NEt_2	$Ir(cod)_2BArF$ (5)	dppb (5)	**2a**, 62
5	**1a**	NEt_2	$Ir(cod)_2BArF$ (5)	*rac*-Binap (5)	**2a**, 80
6[c]	**1a**	NEt_2	$Ir(cod)_2BF_4$ (5)	d^Fppe (5)	**2a**, 75
7	**1a**	NEt_2	$[Ir(cod)Cl]_2$ (2.5)	d^Fppe (5)	**2a,** –
8[d]	**1a**	NEt_2	$Rh(cod)_2BArF$ (5)	dppe (5)	**2a**, <2
9[d]	**1a**	NEt_2	$Rh(cod)_2BArF$ (5)	d^Fppe (5)	**2a**, <2
10	**1a**	NEt_2	$Rh(cod)_2BArF$ (5)	*rac*-Binap (5)	**2a**, <2
11	**1b**	Pyr	$Ir(cod)_2BArF$ (5)	d^Fppe (5)	**2b**, 44
12	**1u**	OEt	$Ir(cod)_2BArF$ (5)	d^Fppe (5)	**2u**, –
13	**1v**	OH	$Ir(cod)_2BArF$ (5)	d^Fppe (5)	**2v**, –
14	**1c**	Me	$Ir(cod)_2BArF$ (5)	d^Fppe (5)	**3c**, 32
15	**1w**	Ph	$Ir(cod)_2BArF$ (5)	d^Fppe (5)	**3w**, 33

[a] Conditions: **1** was added to a solution of complex [M] (x mol%) and **L** (y mol%) in dioxane and the mixture was heated at the indicated temperature. [b] Isolated yield. [c] The same result was obtained when the catalyst was generated from $[Ir(cod)Cl]_2$ (2.5 %), d^Fppe (5 %) and $AgBF_4$ (5 %). [d] The same result was obtained at 140 ºC.

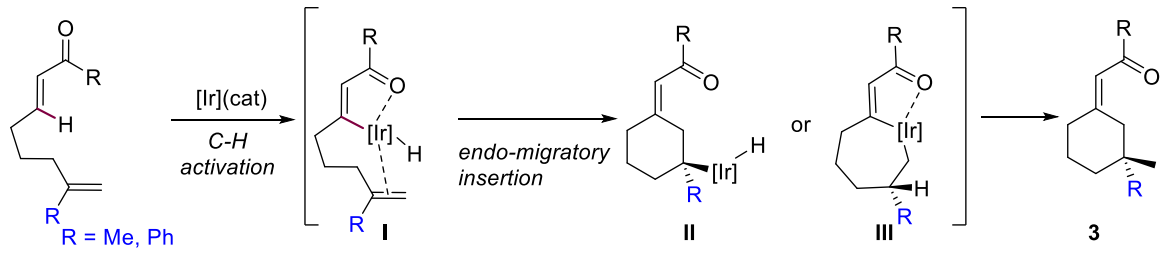


3c (R = Me)
3w (R = Ph)

Hypothesis for the formation of products of type 3

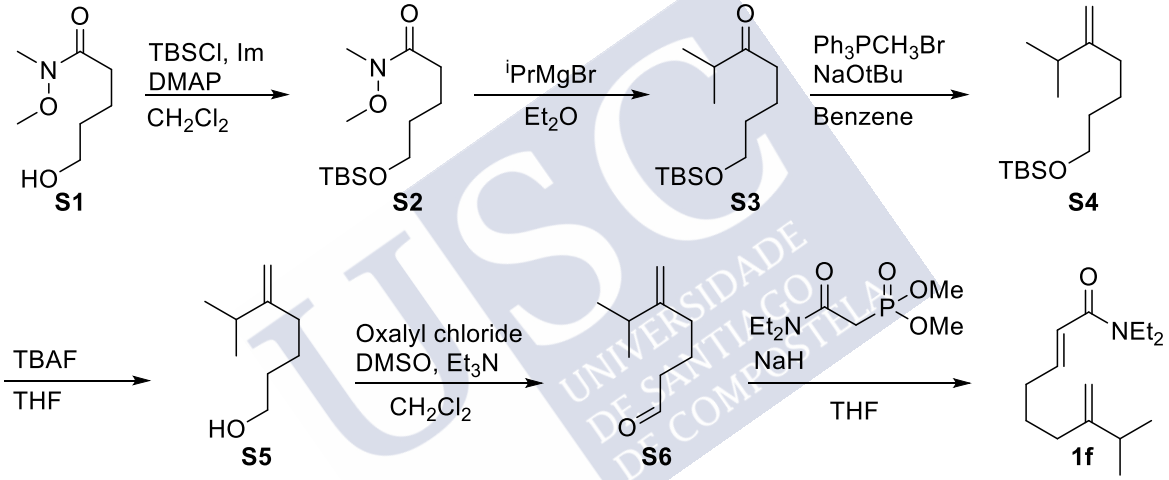
The results obtained with the methyl and phenyl ketone derivatives **1c** and **1w** (Table S1, entries 14 and 15) would suggest that, for these substrates, an *endo*-cyclization to afford intermediates like **II** and **III** would be preferred, eventually leading to products of type **3** after a reductive elimination. The

reason for the formation of *endo* product **3** is not clear, but might be related to the weaker coordinating ability of the keto with respect to the amide group

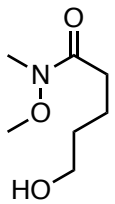


Synthesis of the substrates for catalysis

General procedure A for preparation of 1,6-diene precursors 1a, 1b, 1d, 1e, 1f, 1g, 1j, 1h and 1i (exemplified for the synthesis of **1f**).



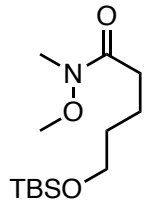
5-Hydroxy-*N*-methoxy-*N*-methylpentanamide (S1)



Prepared following a procedure described by Flick and coworkers.[1]

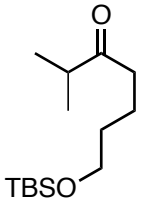
$AlMe_3$, (60 mL, 120 mmol, 2.0 M in hexane) was added dropwise to a stirred solution of N,O-dimethylhydroxyl-amine hydrochloride[1] (11.7 g, 120 mmol) in dry CH_2Cl_2 (26 mL) at 0 °C. (CAUTION: The reaction is very exotermic). The mixture was stirred for 20 min at 0 °C and D-valerolactone (8.0 g, 80 mmol) of was added dropwise. After stirring at 0 °C for 20 min, the mixture was diluted with $CHCl_3$ (125 mL) and then HCl (aq) (15 mL, 0.1 N) was added dropwise at 0 °C. The mixture was stirred for 1 h, the organic phases were separated, dried, filtered, and concentrated under reduced pressure to give 5-hydroxy-*N*-methoxy-*N*-methylpentanamide (12.9 g, 99% yield) as a white solid. The NMR data was consistent with previous characterization.

5-((*tert*-Butyldimethylsilyl)oxy)-*N*-methoxy-*N*-methylpentanamide (S2)



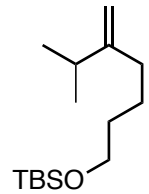
Prepared following a modified procedure described by Stork and coworkers.[2] imidazole (13.2 g, 194 mmol), *tert*-butyldimethylsilyl choride (17.3 g, 115 mmol) and 4-dimethyl aminopyridine (117 mg, 0.96 mmol) were sequentially added to a solution of 5-hydroxy-*N*-methoxy-*N*-methylpentanamide (12.9 g, 80 mmol) in CH_2Cl_2 (275 mL, 0.29 M). The solution was stirred for 15 minutes, water (10 ml) was added and the reaction mixture was extracted with Et_2O (3 x 10 mL). The combined organic extracts were washed with water and brine, dried and evaporated. The crude was purified by column chromatography on silica gel (1:1 Et_2O – hexane) to obtain the desired product as colorless oil (21.0 g, 95% yield). The characterization analysis was consistent with the previous data.[2]

7-((*tert*-Butyldimethylsilyl)oxy)-2-methylheptan-3-one (S3) [3]



*i*PrMgBr (98 mL, 98 mmol), 1.0 M) was added dropwise to a solution of 5-((*tert*-butyldimethylsilyl)oxy)-*N*-methoxy-*N*-methylpentanamide (**S2**, 9.0 g, 32.6 mmol) in Et_2O (220 mL, 0.15 M) at -78 ºC. The reaction was allowed to warm to rt and stirred overnight. Then Rochelle's Salt (sat) (50 mL) was added at 0 ºC, the organic phse was separated and subsequently washed with NH_4Cl (sat) (250 mL), water (200 mL) and brine (200 mL). After extraction with Et_2O (3 x 280 mL), the combined organic extracts were dried and evaporated to yield a crude residue that was purified by column chromatography on silica gel (1:8 Et_2O – hexanes) to obtain the desired product (**S3**) as colorless oil (8.4 g, 57% yield) The NMR data is consistent with that previously described in literature.[3] **^{1}H NMR** (300 MHz, $CDCl_3$): δ 3.56 (t, *J* = 6.2 Hz, 2H), 2.54 (p, *J* = 6.9 Hz, 1H), 2.42 (t, *J* = 7.2 Hz, 2H), 1.63 – 1.52 (m, 2H), 1.50 – 1.41 (m, 2H), 1.03 (d, *J* = 6.9 Hz, 6H), 0.84 (s, 9H), -0.01 (s, 6H).**^{13}C NMR** (75 MHz, $CDCl_3$): δ 214.64 (C), 62.95 (CH_2), 40.78 (CH), 40.12 (CH_2), 32.39 (CH_2), 26.01 (CH_3), 20.33 (CH_2), 18.32 (CH_3), -5.26 (CH_3). **MS** (ESI): ($[M+H]^+$) 259.2.

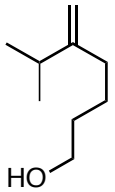
***tert*-Butyldimethyl((6-methyl-5-methyleneheptyl)oxy)silane (S4)**



Sodium *tert*-butoxide (3.84 g, 40 mmol) was added to a suspension of methyltriphenylphosphonium bromide (16.2 g, 45.4 mmol) in benzene (90 mL, 0.2 M). The mixture was refluxed for 4 hours, allowed to cooled down to rt and a solution of 7-((*tert*-butyldimethylsilyl)oxy)-2-methylheptan-3-one, (**S3**, 4.7 g, 18.18 mmol) in benzene (10 mL) was added. The mixture was stirred for 12 hours, concentrated and most of the phosphine oxide was precipitated by adding cold hexane. After filtration of this oxide and evaporation of the solvent, the resulting crude was purified by column chromatography (1:40 Et_2O – hexane) to obtain desired product as colorless oil (3.9 g, 84 % yield). **^{1}H NMR** (300 MHz, $CDCl_3$): δ 4.77 – 4.66 (m, 2H), 3.63 (t, *J* = 6.2 Hz, 2H), 2.31 – 2.16 (m, 1H), 2.04 (t, *J* = 6.9 Hz, 2H), 1.61 – 1.43 (m, 2H), 1.03 (d, *J* = 6.8 Hz, 6H), 0.90 (s, 9H), 0.05 (s, 6H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 156.06 (C), 106.41 (CH_2),

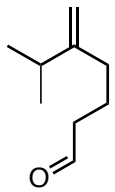
63.29, (CH_2) 34.34 (CH_2), 33.86 (CH), 32.87 (CH_2), 26.15 (CH_3), 24.51(CH_2), 22.05 (CH_3), -5.10 (CH_3). **MS (ESI):** ($[M+H]^+$) 257.2

6-Methyl-5-methyleneheptan-1-ol (S5)



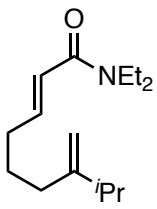
TBAF (38 mL, 1 M, 38 mmol) was added to a solution of *tert*-butyldimethyl((6-methyl-5-methyleneheptyl)oxy)silane (**S4**, 3.90 g, 15.2 mmol) in THF (152 mL, 0.1M) at 0 ºC. The reaction mixture was allowed to warm to rt and stirred for 30 min. NH_4Cl (sat) (20 mL) was then added and the layers were separated. The aqueous phase was extracted with Et_2O (3 x 70 mL) and the combined organic extracts were dried, evaporated and purified by column chromatography (1:5 Ethyl acetate – hexane) to yield the desired alcohol as a colorless oil (1.90 g, 88% yield). **^{1}H NMR** (300 MHz, $CDCl_3$): δ 4.76 – 4.62 (m, 2H), 3.60 (t, *J* = 6.4 Hz, 2H), 2.32 – 2.14 (m, 2H), 2.02 (t, *J* = 7.2 Hz, 2H), 1.62 – 1.43 (m, 4H), 0.99 (d, *J* = 6.8 Hz, 6H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 155.80 (C), 106.43 (CH_2), 62.78 (CH_2), 34.20 (CH_2), 33.75 (CH), 32.64 (CH_2), 24.34 (CH_2), 21.92 (CH_3). **MS (ESI):** ($[M+H]^+$) 143.1

6-Methyl-5-methyleneheptanal (S6)



DMSO (2.7 mL, 38.0 mmol) in CH_2Cl_2 (4.1 mL, 2.5 M) was added dropwise to a solution of oxalyl chloride (1.6 mL, 19.0 mmol) in CH_2Cl_2 (60 mL, 0.18 M) at –78 °C. The reaction was stirred for 10 min and then a solution of 6-methyl-5-methyleneheptan-1-ol (**S5**) (1.5 g, 10.6 mmol) in CH_2Cl_2 (7.5 mL, 1.4 M) was added slowly. After 45 min Et_3N (7.3 mL) was added at –78 °C. After stirring at that temperature for 30 min, the mixture was warmed to rt and stirred for 30 min. H_2O (10 mL) was then added, the organic phase was separated and washed with HCl (1.0 M solution), $NaHCO_3$ (sat) and brine. The organic phases was dried and carefully concentrated under vacuum at 0 °C. The crude aldehyde was submitted to the next step without purification. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 9.78 (t, *J* = 1.7 Hz, 1H), 4.80 – 4.68 (m, 2H), 2.48 – 2.41 (m, 2H), 2.27 – 2.17 (m, 1H), 2.06 (t, *J* = 7.6 Hz, 2H), 1.86 – 1.72 (m, 2H), 1.02 (d, *J* = 6.9 Hz, 6H). **^{13}C NMR (**75 MHz, $CDCl_3$): δ 202.47 (COH), 154.74 (C), 107.22 (CH_2), 43.53 (CH_2), 33.64 (CH_2), 21.90 (CH), 21.83 (CH_3), 20.48 (CH_2).

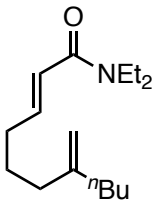
(*E*)-*N*,*N*-Diethyl-8-methyl-7-methylenenon-2-enamide (1f)



Dimethyl (2-(diethylamino)-2-oxoethyl) phosphonate (1.52 g, 6.85 mmol) was added dropwise to a suspension of NaH (60 %) (251 mg, 6.28 mmol) in THF (36 mL) at rt. The mixture was stirred for 15 minutes before 6-methyl-5-methyleneheptanal (800 mg, 5.71 mmol) was added dropwise to the mixture. After one hour, water and Et_2O were successively added and the layers were separated. The organic phase was washed with water (2 x 10 mL). The aqueous combined phases were extracted with CH_2Cl_2 (2 x 10

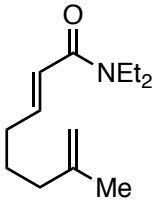
mL) and the combined organic phases were dried and concentrated. Purification of the crude residue by flash chromatography on silica gel (1:10 to 1:3 EtOAc: Hexanes) afforded the desired product as a colorless oil (907 mg, 67 % yield). **^{1}H NMR** (300 MHz, $CDCl_3$): δ 6.92 – 6.75 (m, 1H), 6.19 – 6.02 (m, 1H), 4.75 – 4.56 (m, 2H), 3.39 – 3.26 (m, 4H), 2.21 – 2.11 (m, 3H), 2.03 – 1.95 (m, 2H), 1.60 – 1.50 (m, 2H), 1.18 – 1.04 (m, 6H), 1.00 – 0.89 (m, 6H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 165.79 (C), 155.27 (C), 145.72 (CH), 120.65 (CH), 106.59 (CH_2), 42.08 (CH_2), 40.73 (CH_2), 33.80 (CH_2), 33.64 (CH), 32.16 (CH_2), 26.79 (CH_2), 21.83 (CH_3), 14.84 (CH_3), 13.15 (CH_3). **HRMS** (ESI-TOF): m/z calculated for $C_{15}H_{28}NO$ ($[M+H]^+$) 238.2164, found 238.2165.

(*E*)-*N*,*N*-Diethyl-7-methyleneundec-2-enamide (1a)



This compound was prepared according to the general procedure **A** using ^{n}BuMgBr instead of *i*PrMgBr.**^{1}H NMR** (300 MHz, $CDCl_3$): δ 6.85 (dt, *J* = 14.5, 7.0 Hz, 1H), 6.15 (dd, *J* = 15.0, 1.6 Hz, 1H), 4.69 – 4.63 (m, 2H), 3.40 – 3.30 (m, 4H), 2.20 – 2.11 (m, 2H), 2.02 – 1.91 (m, 4H), 1.60 – 1.48 (m, 2H), 1.39 – 1.20 (m, 4H), 1.17 – 1.06 (m, 6H), 0.85 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 165.86 (C), 149.40 (C), 145.78 (CH), 120.71 (CH), 109.04 (CH_2), 42.13 (CH_2), 40.80 (CH_2), 35.68 (CH_2), 35.49 (CH_2), 32.10 (CH_2), 30.02 (CH_2), 26.50 (CH_2), 22.49 (CH_2), 14.89(CH_3), 14.00 (CH_3), 13.20 (CH_3). **HRMS (ESI-TOF):** m/z calculated for $C_{16}H_{30}NO$ ($[M+H]^+$) 252.2321, found 252.2322.

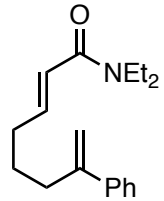
(*E*)-*N*,*N*-Diethyl-7-methylocta-2,7-dienamide (1d)



This compound was prepared according the general procedure **A** using MeMgBr instead of *i*PrMgBr. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 6.79 (dt, *J* = 14.5, 7.0 Hz, 1H), 6.13 – 6.05 (m, 1H), 4.61 – 4.55 (m, 2H), 3.33 – 3.23 (m, 4H), 2.14 – 2.05 (m, 2H), 1.96 – 1.90 (m, 2H), 1.59 (s, 3H), 1.55 – 1.43 (m, 2H), 1.12 – 0.99 (m, 6H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 165.66 (C), 145.53 (CH), 145.07 (C), 120.62 (CH), 110.12 (CH_2), 41.98 (CH_2), 40.64 (CH_2), 37.03 (CH_2), 31.81 (CH_2), 26.16 (CH_2), 22.12 (CH_3), 14.74 (CH_3), 13.05 (CH_3). **HRMS** (ESI-TOF): m/z calculated for $C_{13}H_{24}NO$ ($[M+H]^+$) 210.1851, found 210.1852.

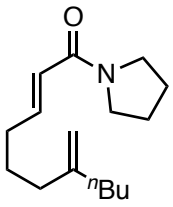
(*E*)-*N*,*N*-Diethyl-7-phenylocta-2,7-dienamide (1h)

This compound was prepared according to the general procedure **A** using PhMgBr instead of



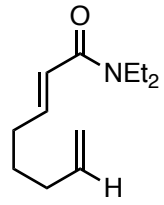
*i*PrMgBr. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.41 – 7.22 (m, 5H), 6.94 – 6.82 (m, 1H), 6.16 (dt, *J* = 15.0, 1.5 Hz, 1H), 5.29 – 5.01 (m, 2H), 3.44 – 3.29 (m, 4H), 2.53 (td, *J* = 7.5, 1.2 Hz, 2H), 2.28 – 2.17 (m, 2H), 1.67 – 1.55 (m, 2H), 1.21 – 1.06 (m, 6H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 165.83 (C), 148.08 (C), 145.55 (CH), 141.16 (C), 128.33 (CH), 127.41 (CH), 126.16 (CH), 120.90 (CH), 112.68 (CH_2), 42.14 (CH_2), 40.81 (CH_2), 34.76, (CH_2) 31.92 (CH_2), 26.93 (CH_2), 14.92 (CH_3), 13.24 (CH_3). **HRMS** (ESI-TOF): m/z calculated for $C_{18}H_{26}NO$ ($[M+H]^+$) 272.2009, found 272.2009.

(*E*)-7-Methylene-1-(pyrrolidin-1-yl)undec-2-en-1-one (1b)



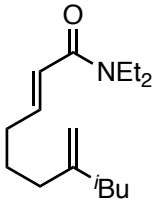
This compound was prepared according to the general procedure **A** using dimethyl (2-oxo-2-(pyrrolidin-1-yl)ethyl)phosphonate in the last step.**^{1}H NMR** (300 MHz, $CDCl_3$): δ 6.89 (dt, *J* = 15.1, 7.0 Hz, 1H), 6.08 (dt, *J* = 15.1, 1.6 Hz, 1H), 4.72 – 4.64 (m, 2H), 3.48 (dd, *J* = 6.7, 3.6 Hz, 4H), 2.23 – 2.13 (m, 2H), 2.05 – 1.90 (m, 6H), 1.88 – 1.80 (m, 2H), 1.61 – 1.53 (m, 2H), 1.43 – 1.22 (m, 4H), 0.88 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 164.63 (C), 149.14 (C), 145.11 (CH), 121.77 (CH), 108.89 (CH_2), 46.31 (CH_2), 45.59 (CH_2), 35.51 (CH_2), 35.28 (CH_2), 31.81 (CH_2), 29.84 (CH_2), 26.31 (CH_2), 25.99 (CH_2), 24.18 (CH_2), 22.31 (CH_2), 13.83 (CH_3). **HRMS** (ESI-TOF): m/z calculated for $C_{16}H_{28}NO$ ($[M+H]^+$) 250.2167, found found 250.2165.

(*E*)-*N*,*N*-Diethylocta-2,7-dienamide (1i)



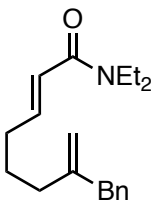
This compound was prepared according to the last two steps of the general procedure **A** using the commercial available hex-5-enal as the aldehyde. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 6.84 (dt, *J* = 14.4, 7.0 Hz, 1H), 6.14 (d, *J* = 15.1 Hz, 1H), 5.82 – 5.65 (m, 1H), 4.99 – 4.88 (m, 2H), 3.34 (dd, *J* = 16.2, 7.6 Hz, 4H), 2.21 – 2.1 (m, 2H), 2.08 – 1.98 (m, 2H), 1.56 – 1.44 (m, 2H), 1.18 – 1.05 (m, 6H). **^{13}C NMR (75 MHz, $CDCl_3$):** δ 165.81 (C), 145.60 (CH), 138.24 (CH), 120.76 (CH), 114.90 (CH_2), 42.11 (CH_2), 40.78 (CH_2), 33.17 (CH_2), 31.82 (CH_2), 27.61 (CH_2), 14.88 (CH_3), 13.18 (CH_3). **HRMS** (ESI-TOF): m/z calculated for $C_{12}H_{22}NO$ ($[M+H]^+$) 196.1697, found 196.1697.

(*E*)-*N*,*N*-Diethyl-8-methyl-7-methylenenon-2-enamide (1e)



This compound was prepared according to the general procedure **A** using iBuMgBr instead of *i*PrMgBr. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 6.94 – 6.80 (m, 1H), 6.16 (dd, *J* = 15.0, 1.7 Hz, 1H), 4.73 – 4.62 (m, 2H), 3.37 (dq, *J* = 14.7, 7.2 Hz, 4H), 2.22 – 2.12 (m, 2H), 1.98 (t, *J* = 7.7 Hz, 2H), 1.88 – 1.80 (m, 2H), 1.78 – 1.63 (m, 1H), 1.62 – 1.50 (m, 2H), 1.22 – 1.07 (m, 6H), 0.89 – 0.79 (m, 6H).**^{13}C NMR** (75 MHz, $CDCl_3$): δ 165.93 (C), 148.15 (C), 145.85 (CH), 120.76 (CH), 110.57 (CH_2), 45.92 (CH_2), 42.18 (CH_2), 40.85 (CH_2), 35.21 (CH_2), 32.18 (CH_2), 26.49 (CH_2), 26.06 (CH), 22.57 (CH_3), 14.95 (CH_3), 13.26 (CH_3).**HRMS** (ESI-TOF): m/z calculated for $C_{16}H_{30}NO$ ($[M+H]^+$) 252.2320, found 252.2322.

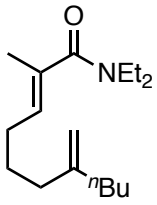
(*E*)-7-Benzyl-*N*,*N*-diethylocta-2,7-dienamide (1g)



This compound was prepared according to the general procedure **A** using BnMgBr instead of *i*PrMgBr. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.30 – 7.23 (m, 2H), 7.21 – 7.14 (m, 3H), 6.93 – 6.81 (m, 1H), 6.15 (dd, *J* = 15.0, 1.3 Hz, 1H), 4.79 (d, *J* = 19.5 Hz, 2H), 3.46 – 3.24 (m, 6H), 2.24 – 2.10 (m, 2H), 2.06 – 1.94 (m, 2H), 1.66 – 1.53 (m, 2H),

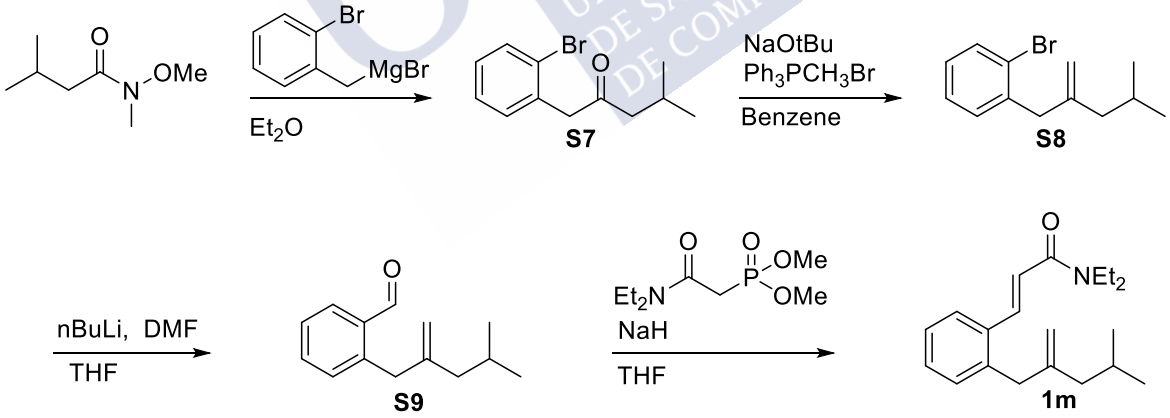
1.21 – 1.09 (m, 6H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 165.86 (C), 148.39 (C), 145.64 (CH), 139.69 (C), 129.00 (CH), 128.33 (CH), 126.13 (CH), 120.81 (CH), 111.62 (CH_2), 43.03 (CH_2), 42.15 (CH_2), 40.82 (CH_2), 34.91 (CH_2), 32.05 (CH_2), 26.37 (CH_2), 14.93 (CH_3), 13.24 (CH_3). **HRMS (ESI-TOF):** m/z calculated for $C_{19}H_{28}NO$ ([M+H]$^+$) 286.2165, found 286.2165.

(*E*)-*N*,*N*-Diethyl-2-methyl-7-methyleneundec-2-enamide (1j)

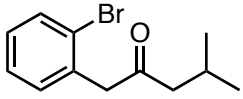


This compound was prepared according the general procedure **A** using **S6** and the appropriate dimethyl (1-(diethylamino)-1-oxopropan-2-yl)phosphonate instead of dimethyl (2-(diethylamino)-2-oxoethyl)phosphonate. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 5.45 (t, *J* = 7.2 Hz, 1H), 4.67 (d, *J* = 7.0 Hz, 2H), 3.33 (q, *J* = 7.1 Hz, 3H), 2.10 – 1.93 (m, 6H), 1.79 (s, 3H) , 1.56 – 1.44 (m, 2H), 1.42 – 1.22 (m, 4H), 1.14 – 1.05 (m, 6H), 0.87 (t, *J* = 7.0 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 173.51 (C), 149.62 (C), 132.28 (C), 129.34 (CH), 108.95 (CH_2), 42.61 (CH_2), 38.77 (CH_2), 35.74 (CH_2), 30.05 (CH_2), 27.25 (CH_2), 27.21 (CH_2), 22.53 (CH_2), 14.56 (CH_3), 14.06 (CH_3), 13.47 (CH_3) {NOTE: This latter signal at 13.47 ppm corresponds to the methyl group of the amide moiety which, due to the existence of rotamers, can only be clearly observed carrying out the NMR at 60 ºC}. **HRMS** (ESI-TOF): m/z calculated for $C_{17}H_{32}NO$ ([M+H]$^+$) 266.2479, found 266.2478.

General procedure B for preparation of indene precursors 1l, 1m, 1n and 1t (exemplified for the synthesis of **1m**)



1-(2-Bromophenyl)-4-methylpentan-2-one (S7)



(2-Bromobenzyl)magnesium bromide was prepared following a modified procedure described by Whitesides et. al.[5] Under an inert atmosphere, magnesium turnings (1.1 equiv) were covered with Et_2O (0.35 M) and activated with iodine and 1,2-dibromoethane. A solution of bromobenzyl-bromide (1 equiv) in Et_2O (0.35 M) was added dropwise to the activated magnesium. The solution was refluxed for 20 min before being allowed to cool down to rt. The resulting solution containing the Grignard reagent (17.2 mmol) was

added dropwise to a solution of *N*-methoxy-*N*,3-dimethylbutanamide[4] (6.88 mmol) at -78 ºC in Et_2O (46 mL). The reaction was allowed to warm to rt and was stirred overnight. The mixture was cooled in an ice-water bath and a solution of Rochelle salt was added. NH_4Cl (sat) was added and the layers were separated. The aqueous phase was extracted with Et_2O and the combined organic phases were dried and concentrated to yield a crude residue that was purified by flash chromatography (from 1 : 40 to 1 : 10, Et_2O: Hexanes) to afford the desired product (**S7**) as colorless oil (1.35 g, 77 % yield). **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.56 (dd, *J* = 8.0, 1.3 Hz, 1H), 7.27 (td, *J* = 7.4, 1.3 Hz, 1H), 7.20 (dd, *J* = 7.6, 2.0 Hz, 1H), 7.13 (ddd, *J* = 7.9, 7.1, 1.9 Hz, 1H), 3.83 (s, 2H), 2.38 (d, *J* = 6.9 Hz, 2H), 2.25 – 2.12 (m, 1H), 0.93 (d, *J* = 6.6, 0.6 Hz, 6H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 206.61 (C), 134.87 (C), 132.90 (CH), 131.82 (CH), 128.80 (CH), 127.65 (CH), 125.11 (C), 51.53 (CH_2), 50.55 (CH_2), 24.55 (CH), 22.66 (CH_3). **MS** (ESI): ($[M+H]^+$) 255.0 and 257.0

1-Bromo-2-(4-methyl-2-methylenepentyl)benzene (S8)

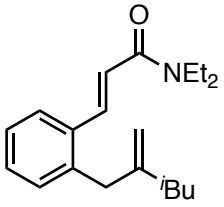
Methyltriphenylphosphonium bromide (3.35 g, 9.40 mmol) was dissolved in benzene (20 mL) under argon. Sodium *tert*-butoxide (0.83 g, 8.62 mmol) was added portion wise to this solution and the mixture was refluxed for 2 hours. The yellow solution was allowed to reach rt, the ketone (**S7**, 3.92 mmol) in benzene (0.2 M) was added dropwise and the reaction was stirred overnight. Water (40 mL) and Et_2O (40 mL) were sequentially added. The layers were separated and the aqueous phase was extracted with Et_2O (2 x 40 mL). The combined organic layers were dried and concentrated. The crude residue was dissolved in Et_2O, cooled to -78 ºC, and carefully decanted into another flask to separate the phosphine oxide (this operation was repeated three times). Combined organic phases were concentrated and the resulting crude residue was chromatographed (1:40 to 1:20, Et_2O : Hexane) to afford the desired **S8** as colorless oil (678 mg, 67% yield) **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.60 – 7.55 (m, 1H), 7.30 – 7.22 (m, 2H), 7.16 – 7.04 (m, 1H), 4.97 – 4.52 (m, 2H), 3.47 (s, 2H), 2.02 – 1.83 (m, 3H), 0.96 (d, *J* = 6.2 Hz, 6H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 146.47 (C), 139.44 (C), 132.90 (CH), 131.29 (CH), 127.88 (CH), 127.38 (CH), 125.33 (C), 112.92 (CH_2), 46.23 (CH_2), 42.31 (CH_2), 26.28 (CH_3), 22.68 (CH_3). **MS** (ESI): ($[M+H]^+$) 253.1 and 255.1

2-(4-Methyl-2-methylenepentyl) benzaldehyde (S9)

^{n}BuLi (6.52 mmol, 2.6 mL, 2.5 M) was added dropwise to a solution of **S8** (550 mg, 2.1 mmol) in THF (2 mL) at -78 ºC. After stirring for 30 min, DMF (0.83 mL, 10.8 mmol) in THF (0.67 mL) was added dropwise and the reaction was allowed to slowly warm to rt. After TLC indicates full conversion, NH_4Cl (sat) (5 mL) was added. After extraction with Et_2O (3 x 10 mL), the combined organic phases were dried and concentrated. Purification of the crude residue by flash chromatography on silica gel (Et_2O: Pentane 1 : 20) afforded the titled aldehyde as colorless oil (222 mg, 51% yield). **^{1}H NMR** (300 MHz, $CDCl_3$): δ 10.22 (s, 1H), 7.86 (dd, *J* = 7.7,

1.5 Hz, 1H), 7.55 – 7.47 (m, 1H), 7.37 (t, *J* = 7.6 Hz, 1H), 7.25 (d, *J* = 7.3 Hz, 1H), 4.86 – 4.35 (m, 2H), 3.69 (s, 2H), 1.96 (d, *J* = 7.1 Hz, 2H), 1.91 – 1.79 (m, 1H), 0.90 (d, *J* = 6.5 Hz, 6H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ **^{13}C NMR** (75 MHz, cdcl$_3$) δ 192.07 (C), 148.32 (C), 142.29 (C), 134.43 (C), 133.87 (CH), 131.89 (CH), 130.39 (CH), 127.02 (CH), 113.20 (CH_2), 46.58 (CH_2), 38.52 (CH_2), 26.19 (CH), 22.58 (CH_3). **MS (ESI):** ([M+H]$^+$) 203.1

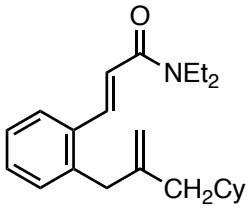
(*E*)-*N*,*N*-Diethyl-3-(2-(4-methyl-2-methylenepentyl)phenyl) acrylamide (1m)



Following the procedure for the Horner–Wadsworth–Emmons reaction (previously exemplified for the synthesis of compound **1f,** (see page S7), the product was obtained as a white solid. (206 mg, 63%yield). **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.93 (d, *J* = 15.2 Hz, 1H), 7.53 (dd, *J* = 7.3, 1.7 Hz, 1H), 7.29 – 7.14 (m, 3H), 6.70 (d, *J* = 15.2 Hz, 1H), 4.65 (d, *J* = 90.7 Hz, 2H), 3.50 – 3.38 (m, 6H), 1.94 – 1.77 (m, 3H), 1.24 – 1.16 (m, 6H), 0.88 (d, *J* = 6.3 Hz, 6H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 165.72 (C), 147.33 (C), 140.27 (CH), 139.02 (C), 135.27 (C), 130.91 (CH), 129.17 (CH), 126.62 (CH), 126.53 (CH), 119.59 (CH), 113.13 (CH_2), 46.24 (CH_2), 42.33 (CH_2), 41.07 (CH_2), 39.71 (CH_2), 26.15 (CH), 22.58 (CH_3), 15.16 (CH_3), 13.33 (CH_3). **HRMS** (ESI-TOF): m/z calculated for $C_{20}H_{30}NO$ ([M+H]$^+$) 300.2322, found 300.2322.

(*E*)-3-(2-(2-(Cyclohexylmethyl)allyl)phenyl)-*N*,*N*-diethylacrylamide (1n)

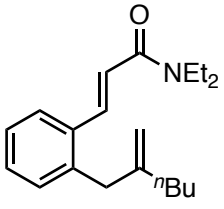
This compound was prepared according the general procedure **B** starting from 2-cyclohexyl-*N*-methoxy-*N*-methylacetamide instead of *N*-methoxy-*N*,3-dimethylbutanamide.



^{1}H NMR (300 MHz, $CDCl_3$): δ 7.93 (d, *J* = 15.2 Hz, 1H), 7.53 – 7.48 (m, 1H), 7.28 – 7.11 (m, 3H), 6.68 (d, *J* = 15.2 Hz, 1H), 4.64 (d, *J* = 79.4 Hz, 2H), 3.48 – 3.37 (m, 6H), 1.90 (d, *J* = 7.1 Hz, 2H), 1.74 – 1.58 (m, 6H), 1.53 – 1.38 (m, 1H), 1.27 – 1.12 (m, 8H), 0.89 – 0.77 (m, 2H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 165.57 (C), 146.63 (C), 140.16 (CH), 138.92 (C), 135.16 (C), 130.75 (CH), 129.02 (CH), 126.50 (CH), 126.44 (CH), 119.49 (CH), 113.01 (CH_2), 44.52 (CH_2), 42.21 (CH_2), 40.96 (CH_2), 39.74 (CH_2), 35.50 (CH), 33.28 (CH_2), 26.59 (CH_2), 26.28 (CH_2), 15.05 (CH_3), 13.22 (CH_3). **HRMS** (ESI-TOF): m/z calculated for $C_{23}H_{34}NO$ ([M+H]$^+$) 340.2635, found 340.2635.

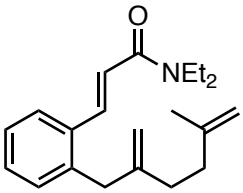
(*E*)-*N*,*N*-Diethyl-3-(2-(2-methylenehexyl)phenyl)acrylamide (1l)



This compound was prepared according the general procedure **B** starting from *N*-methoxy-*N*-methylpentanamide instead of *N*-methoxy-*N*,3-dimethylbutanamide. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.94 (d, *J* = 15.2 Hz, 1H), 7.56 – 7.47 (m, 1H), 7.31 – 7.13 (m, 3H), 6.69 (d, *J* = 15.3 Hz, 1H), 4.82 (s, 1H), 4.48 (s, 1H), 3.49 – 3.38 (m, 6H), 2.02 (t, *J* = 7.6 Hz, 2H), 1.50 – 1.38 (m, 2H), 1.36 – 1.12 (m, 8H), 0.88 (t, *J* = 7.2 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 165.68 (C), 148.55 (C), 140.22 (CH),

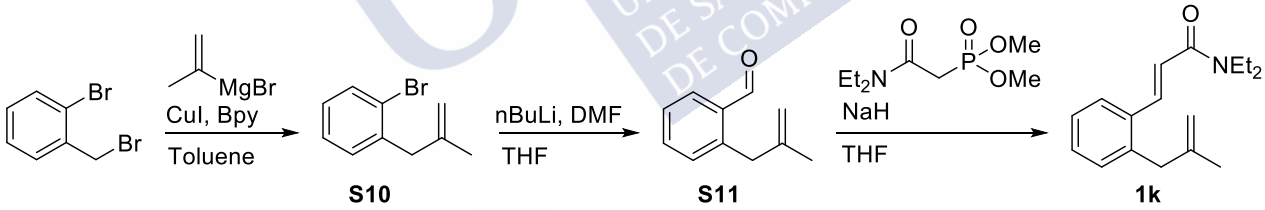
138.95 (C), 135.17 (C), 130.82 (CH), 129.11 (CH), 126.56 (CH), 126.50 (CH), 119.49 (CH), 111.42 (CH_2), 42.28 (CH_2), 41.02 (CH_2), 39.95 (CH_2), 35.99 (CH_2), 29.90 (CH_2), 22.46 (CH_2), 15.10 (CH_3), 14.00 (CH_3), 13.27 (CH_3). **HRMS** (ESI-TOF): m/z calculated for $C_{20}H_{30}NO$ ($[M+H]^+$) 300.2321, found 300.2322.

(*E*)-*N*,*N*-Diethyl-3-(2-(5-methyl-2-methylenehex-5-en-1-yl)phenyl)acrylamide (1t)

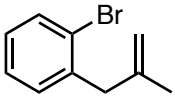


This compound was prepared according the general procedure **B** starting from N-methoxy-N,4-dimethylpent-4-enamide instead of *N*-methoxy-*N*,3-dimethylbutanamide. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.94 (d, *J* = 15.2 Hz, 1H), 7.53 (dd, *J* = 7.5, 1.8 Hz, 1H), 7.32 – 7.12 (m, 3H), 6.70 (d, *J* = 15.4 Hz, 1H), 4.85 (s, 1H), 4.70 – 4.65 (m, 2H), 4.52 (s, 1H), 3.53 – 3.38 (m, 6H), 2.20 – 2.14 (m, 4H), 1.70 (s, 3H), 1.28 – 1.16 (m, 6H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 165.71 (C), 148.09 (C), 145.52 (C), 140.23 (CH), 138.80 (C), 135.21 (C), 130.88 (CH), 129.20 (CH), 126.67 (CH), 126.56 (CH), 119.57 (CH), 111.77 (CH_2), 110.10 (CH_2), 42.33 (CH_2), 41.08 (CH_2), 40.06 (CH_2), 36.08 (CH_2), 34.42 (CH_2), 22.53 (CH_3), 15.15 (CH_3), 13.31 (CH_3). **HRMS** (ESI-TOF): m/z calculated for $C_{21}H_{30}NO$ ($[M+H]^+$) 312.2321, found 312.2322; m/z calculated for $C_{21}H_{29}NNaO$ ($[M+Na]^+$) 334.2142, found 334.2141.

General procedure C for preparation of precursors 1k and 1o (exemplified for the synthesis of **1k**)



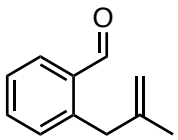
1-Bromo-2-(2-methylallyl)benzene (S10)



This compound was synthetized according of a previous slightly modified procedure by Toste and coworkers.[6]

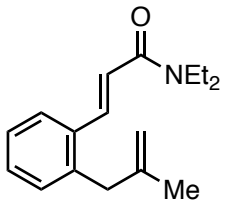
Prop-1-en-2-ylmagnesium bromide solution (0.5 M, 1 equiv) was slowly added to solution of 2-bromobenzyl bromide (2.50 g, 10.0 mmol), CuI (190.5 mg, 1.0 mmol,) and 2,2'-bipyridyne (156.2 mg, 1.0 mmol) in toluene (15.1 mL) at 0 °C. The reaction was allowed to warm to rt and stirred for 4 h, when TLC indicates that the reaction is complete. NH_4Cl (sat) (25 mL) was added. After extraction (3 × 25 mL, Et_2O), the combined organic layers were dried and concentrated and chromatographed to yield the product[8] as a colorless oil (87% yield).

2-(2-Methylallyl)benzaldehyde (S11)



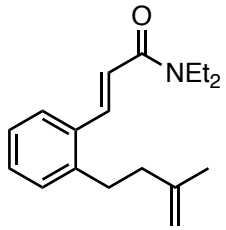
This compound was prepared according to the procedure described for the synthesis of **S9** (see page S11). The product was isolated as clear oil (89% yield). The NMR and MS analysis were consistent with those previously reported in the literature.[6]

(*E*)-*N*,*N*-Diethyl-3-(2-(2-methylallyl)phenyl)acrylamide (1k)



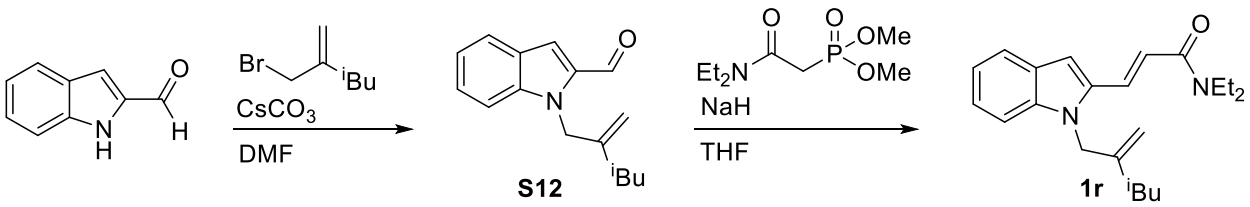
Prepared following the previously shown Horner–Wadsworth–Emmons procedure from **S11** (see experimental procedure at page S7), the product was obtained in 76% yield as clear oil. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.96 (d, *J* = 15.2 Hz, 1H), 7.55 – 7.50 (m, 1H), 7.30 – 7.14 (m, 3H), 6.70 (d, *J* = 15.2 Hz, 1H), 4.85 – 4.48 (m, 2H), 3.51 – 3.39 (m, 6H), 1.73 (s, 3H), 1.28 – 1.14 (m, 6H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 165.78 (C), 144.46 (C), 140.23 (CH), 138.90 (C), 135.16 (C), 130.84 (CH), 129.22 (CH), 126.68 (CH), 126.59 (CH), 119.53 (CH), 112.54 (CH_2), 42.36 (CH_2), 41.51 (CH_2), 41.11 (CH_2), 22.87 (CH_3), 15.17 (CH_3), 13.33 (CH_3). **HRMS** (ESI-TOF): m/z calculated for $C_{17}H_{24}NO$ ($[M+H]^+$) 258.1851, found 258.1852.

(*E*)-*N*,*N*-Diethyl-3-(2-(3-methylbut-3-en-1-yl)phenyl)acrylamide (1o)



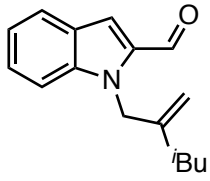
This compound was prepared according the general procedure **C** using (2-methylallyl)magnesium bromide instead of prop-1-en-2-ylmagnesium bromide. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 8.01 (d, *J* = 15.2 Hz, 1H), 7.55 – 7.49 (m, 1H), 7.27 – 7.15 (m, 3H), 6.73 (d, *J* = 15.2 Hz, 1H), 4.75 – 4.68 (m, 2H), 3.51 – 3.43 (m, 4H), 2.92 – 2.86 (m, 2H), 2.30 – 2.23 (m, 2H), 1.77 (s, 3H), 1.29 – 1.16 (m, 6H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 165.71 (C), 145.03 (C), 141.55 (C), 139.89 (CH), 134.27 (C), 129.81 (CH), 129.30 (CH), 126.51 (CH), 126.35 (CH), 119.59 (CH), 110.55 (CH_2), 42.33 (CH_2), 41.10 (CH_2), 39.40 (CH_2), 31.75 (CH_2), 22.68 (CH_3), 15.15 (CH_3), 13.31 (CH_3). **HRMS** (ESI-TOF): m/z calculated for $C_{18}H_{26}NO$ ($[M+H]^+$) 272.2009, found 272.2009.

General procedure D for preparation of precursors 1p, 1q, 1r and 1s, (exemplified for the synthesis of **1r**)



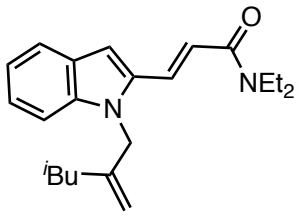
1-(4-Methyl-2-methylenepentyl)-1*H*-indole-2-carbaldehyde (S12)

Following a modified procedure reported by L. M. Stanley.[7] DMF (7.65 mL, 0.27 M) was added to



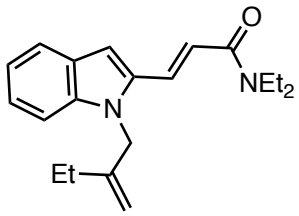
1*H*-indole-2-carbaldehyde (300 mg, 2.06 mmol,) and Cs_2CO_3 (875 mg, 2.68 mmol) and the resulting mixture was stirred at rt for 0.5 h. 2-(Bromomethyl)-4-methylpent-1-ene[8,9] (2.7 mmol) was added dropwise. The mixture was stirred at rt until the TLC indicates full conversion of the limiting reagent. Water (30 mL) was added to the mixture, and the resulting solution was extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with water (100 mL), brine (100 mL), dried and concentrated to yield a crude residue that was purified by flash column chromatography on silica gel (hexane : EtOAc) to give the product as orange oil (404 mg, 81% yield). **^{1}H NMR** (300 MHz, $CDCl_3$): δ 9.88 (s, 1H), 7.78 – 7.73 (m, 1H), 7.44 – 7.32 (m, 2H), 7.29 (s, 1H), 7.22 – 7.15 (m, 1H), 5.19 – 5.11 (m, 2H), 4.78 – 4.72 (m, 1H), 4.27 – 4.19 (m, 1H), 1.97 (d, *J* = 7.0 Hz, 2H), 1.93 – 1.83 (m, 1H), 0.95 (d, *J* = 6.3 Hz, 6H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 182.49 (CHO), 144.08, (C) 140.79 (C), 135.55 (C), 127.04 (CH), 126.45 (C), 123.43 (CH), 121.13 (CH), 117.96 (CH), 111.14 (CH), 110.84 (CH_2), 49.05 (CH_2), 43.93 (CH_2), 26.31 (CH), 22.62 (CH_3).

(*E*)-*N*,*N*-Diethyl-3-(1-(4-methyl-2-methylenepentyl)-1*H*-indol-2-yl)acrylamide (1r)



Prepared following the previously shown Horner–Wadsworth–Emmons procedure from **S12** (see experimental procedure at page S7) (471 mg, 84% yield). **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.79 (d, *J* = 15.1 Hz, 1H), 7.65 (d, *J* = 7.9 Hz, 1H), 7.28 – 7.23 (m, 2H), 7.20 – 7.11 (m, 1H), 7.00 – 6.89 (m, 2H), 4.86 (s, 1H), 4.73 (s, 2H), 4.43 (s, 1H), 3.57 – 3.45 (m, 4H), 2.00 (d, *J* = 7.1 Hz, 2H), 1.96 – 1.85 (m, 1H), 1.32 – 1.20 (m, 6H), 1.00 (d, *J* = 6.3 Hz, 6H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 165.26 (C), 143.33 (C), 138.42 (C), 136.15 (C), 130.58 (CH), 127.52 (C), 122.99 (CH), 120.93 (CH), 120.27 (CH), 118.32 (CH), 111.82 (CH_2), 109.77 (CH), 102.20 (CH), 47.82 (CH_2), 43.59 (CH_2), 42.20 (CH_2), 41.08 (CH_2), 26.34 (CH), 22.51 (CH_3), 15.11 (CH_3), 13.22 (CH_3). **HRMS** (ESI-TOF): m/z calculated for $C_{22}H_{31}N_2O$ ($[M+H]^+$) 339.2432, found 339.2431.

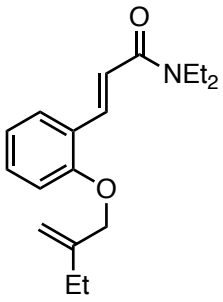
(*E*)-*N*,*N*-Diethyl-3-(1-(2-methylenebutyl)-1*H*-indol-2-yl)acrylamide (1s)



This compound was prepared according the general procedure **D** using 2-(bromomethyl)but-1-ene instead of 2-(bromomethyl)-4-methylpent-1-ene (see the synthesis of **S12** at page S14). **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.80 – 7.74 (m, 1H), 7.63 – 7.58 (m, 1H), 7.27 – 7.20 (m, 2H), 7.14 – 7.07 (m, 1H), 6.96 – 6.84 (m, 2H), 4.86 (d, *J* = 1.2 Hz, 1H), 4.75 (s, 2H), 4.44 (d, *J* = 1.0 Hz, 1H), 3.52 – 3.42 (m, 4H), 2.11 – 2.02 (m, 2H), 1.22 (dt, *J* = 16.7, 7.1 Hz, 6H), 1.12 (t, *J* = 7.4 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 165.39 (C), 146.21 (C), 138.56 (C), 136.23 (C), 130.73 (CH), 127.58 (C), 123.07 (CH), 120.99 (CH), 120.34 (CH), 118.29 (CH), 109.92 (CH), 109.39 (CH_2), 102.40

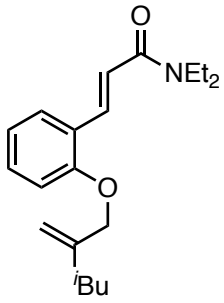
(CH), 48.19 (CH_2), 42.29 (CH_2), 41.19 (CH_2), 26.39 (CH_2), 15.18 (CH_3), 13.28 (CH_3), 11.97 (CH_3). **HRMS** (ESI-TOF): m/z calculated for $C_{20}H_{27}N_2O$ ($[M+H]^+$) 311.2119, found 311.2118.

(*E*)-*N*,*N*-Diethyl-3-(2-(2-methylenebutoxy)phenyl)acrylamide (1p)



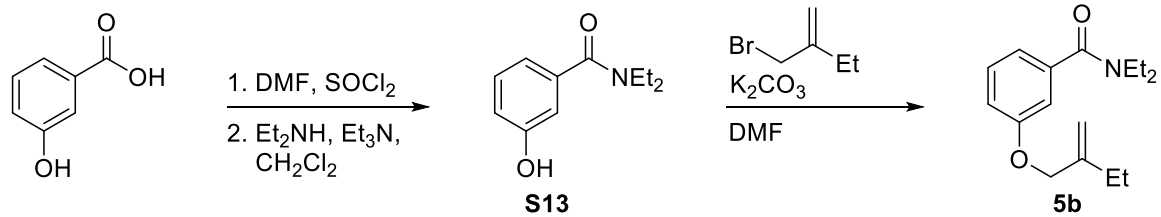
This compound was prepared according the general procedure **D** using 2-hydroxybenzaldehyde and 2-(bromomethyl)but-1-ene as starting materials. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.94 (d, *J* = 15.5 Hz, 1H), 7.48 (dd, *J* = 7.6, 1.8 Hz, 1H), 7.31 – 7.23 (m, 1H), 7.05 – 6.87 (m, 3H), 5.16 – 4.97 (m, 2H), 4.53 (s, 2H), 3.51 – 3.41 (m, 4H), 2.19 (q, *J* = 7.5 Hz, 2H), 1.25 – 1.15 (m, 6H), 1.10 (t, *J* = 7.5 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 166.46 (C), 157.57 (C), 146.22 (C), 138.18 (CH), 130.42 (CH), 129.79 (CH), 124.81 (C), 120.80 (CH), 119.12 (CH), 112.41 (CH), 111.61 (CH_2), 71.42 (CH_2), 42.34 (CH_2), 41.12 (CH_2), 26.11 (CH_2), 15.16 (CH_3), 13.38 (CH_3), 12.10 (CH_3). **HRMS** (ESI-TOF): m/z calculated for $C_{18}H_{26}NO_2$ ($[M+H]^+$) 288.1958, found 288.1958.

(*E*)-*N*,*N*-Diethyl-3-(2-((4-methyl-2-methylenepentyl)oxy)phenyl) acrylamide (1q)

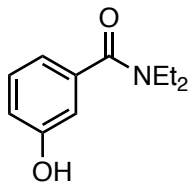


This compound was prepared according the general procedure **D** using 2-hydroxybenzaldehyde and 2-(bromomethyl)-4-methylpent-1-ene as starting materials. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.91 (d, *J* = 15.5 Hz, 1H), 7.44 (dd, *J* = 7.6, 1.7 Hz, 1H), 7.27 – 7.17 (m, 1H), 7.05 – 6.80 (m, 3H), 5.06 (dd, *J* = 64.4, 1.5 Hz, 2H), 4.46 (s, 2H), 3.48 – 3.38 (m, 4H), 2.03 – 2.00 (m, 2H), 1.83 – 1.71 (m, 1H), 1.25 – 1.11 (m, 6H), 0.88 (d, *J* = 6.5 Hz, 6H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 166.32 (C), 157.45 (C), 143.34 (C), 138.02 (CH), 130.30 (CH), 129.63 (CH), 124.78 (C), 120.72 (CH), 119.13 (CH), 113.71 (CH_2), 112.38 (CH), 70.90 (CH_2), 43.05 (CH_2), 42.23 (CH_2), 40.97 (CH_2), 26.23 (CH_3), 22.50 (CH_3), 15.06 (CH_3), 13.26 (CH_3). **HRMS** (ESI-TOF): m/z calculated for $C_{20}H_{30}NO_2$ ($[M+H]^+$) 316.2272, found 316.2271.

Procedure E for preparation of precursors 5a and 5b (exemplified for the synthesis of **5b**)



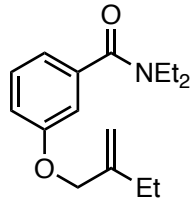
***N*,*N*-Diethyl-3-hydroxybenzamide (S13)**



3-Hydroxybenzoic acid (5.0 g, 36.2 mmol) was placed in a flask equipped with a reflux condenser. Thionyl chloride (20 mL, 270 mmol) and a few drops of DMF were added and the mixture was refluxed for 4 hours. The reaction was allowed to cool to

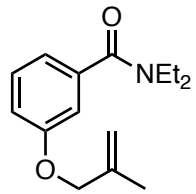
rt and the excess of $SOCl_2$ was carefully removed with a rotary evaporator equipped with a intermediate cooled trap (Et_2O – N_2 bath). The crude acid chloride was dissolved in CH_2Cl_2 (72 mL) and Et_3N (15.26 mL, 108.6 mmol) was added. The mixture was cooled in a ice-water bath and Et_2NH (13.9 mL, 133.9 mmol) was added dropwise. The reaction was stirred for 19 hours at rt, concentrated and the resulting crude mixture was purified via flash column chromatography (1:2 to 3:1 EtOAc: Hex) to provide the amide product as yellow solid (6.50 g, 95% yield). The NMR and MS analysis were consistent with those previously published.[10]

_N,N_-Diethyl-3-(2-methylenebutoxy)benzamide (5b)



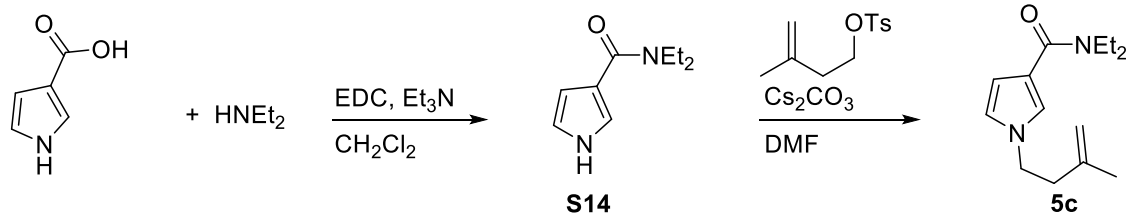
2-(Bromomethyl)but-1-ene (463 mg, 3.1 mmol) was added dropwise to a solution of *N*,*N*-diethyl-3-hydroxybenzamide (**S13**, 500 mg, 2.59 mmol) and K_2CO_3 (430 mg, 3.1 mmol) in DMF (3 mL). The mixture was stirred 20 hours at rt, diluted with Et_2O (10 mL) and washed with water (3 x 15 mL). The organic phase was dried, concentrated and chromatographed to yield **5b** as colorless oil (278 mg, 41 %). **^{1}H NMR** (300 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** (75 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** (ESI-TOF): m/z calculated for $C_{16}H_{24}NO_2$ ($[M+H]^+$) 262.1801, found 262.1802.

_N,N_-Diethyl-3-((2-methylallyl)oxy)benzamide (5a)

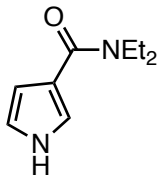


This compound was prepared according the general procedure **E** using 3-bromo-2-methylprop-1-ene as alkylating agent. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.29 – 7.22 (m, 1H), 6.94 – 6.87 (m, 3H), 5.08 – 4.94 (m, 2H), 4.41 (s, 2H), 3.58 – 3.14 (m, 4H), 1.80 (s, 3H), 1.27 – 1.00 (m, 6H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 170.99 (C), 158.77 (C), 140.65 (C), 138.58 (C), 129.55 (CH), 118.60 (CH), 115.78 (CH), 112.86 (CH_2), 112.66 (CH), 71.83 (CH_2), 43.29 (CH_2), 39.26 (CH_2), 19.43 (CH_3), 14.30 (CH_3), 12.98 (CH_3). **HRMS** (ESI-TOF): m/z calculated for $C_{15}H_{22}NO_2$ ($[M+H]^+$) 248.1645, found 248.1645.

Synthesis of _N,N_-Diethyl-1-(3-methylbut-3-en-1-yl)-1*H*-pyrrole-3-carboxamide (5c).

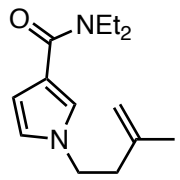


_N_,_N_-Diethyl-1_H_-pyrrole-3-carboxamide (S14)



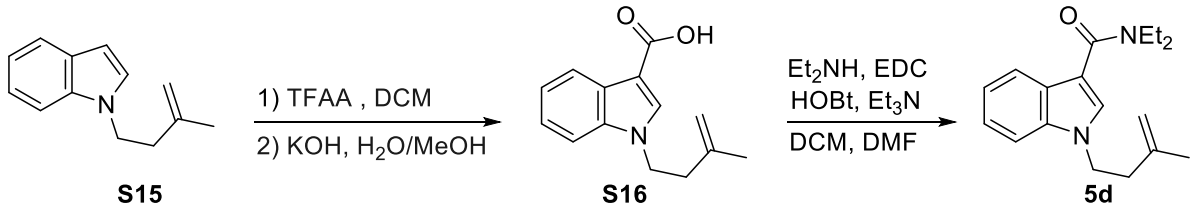
Et_2NH (2.14 mL, 20.7 mmol) was added to a solution of 1*H*-pyrrole-3-carboxylic acid (2.0 g, 18.0 mmol), EDC.HCl (5.17 g, 27.0 mmol) and Et_3N (7.5 mL, 53.9 mmol) in CH_2Cl_2 (72 mL, 0.25 M). The resulting mixture was stirred for 16 h and then water (50 mL) was added. The layers were separated and the aqueous phase was extracted with CH_2Cl_2 (2 x 50 mL). The combined organic layers were dried and concentrated to yield a crude residue that was purified by column chromatography (1:1 to 9:1, EtOAc : Hexane) to yield **S14** as a pale yellow solid (1.88 g, 63% yield). **^{1}H NMR** (300 MHz, $CDCl_3$): δ 10.40 (s, 1H), 6.97 – 6.92 (m, 1H), 6.61 – 6.57 (m, 1H), 6.34 – 6.30 (m, 1H), 3.52 (q, *J* = 7.1 Hz, 4H), 1.20 (t, *J* = 7.1 Hz, 6H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 167.87 (C), 121.01 (CH), 118.98 (C), 118.22 (CH), 108.31 (CH), 41.75 (CH_2), 13.82 (CH_3). **HRMS** (ESI): m/z calculated for $C_9H_{15}N_2O$ ($[M+H]^+$) 167.1178, found 167.1179.

_N_,_N_-Diethyl-1-(3-methylbut-3-en-1-yl)-1_H_-pyrrole-3-carboxamide (5c)

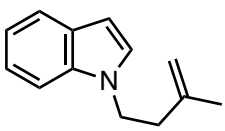


Prepared following a modified procedure from Schreiber and coworkers.[11] 3-methylbut-3-en-1-yl 4-methylbenzenesulfonate (694 mg, 2.9 mmol) was slowly added to a solution of *N*,*N*-diethyl-1*H*-pyrrole-3-carboxamide (300 mg, 1.80 mmol) and cesium carbonate (1.35 g, 4.14 mmol) in anhydrous DMF (4.5 mL, 0.4 M). The reaction mixture was stirred at 85 ºC for 16 hours, allowed to cool to rt and water (30 mL) was added. The mixture was extracted with Et_2O (5 x 10 mL). The organic phase was dried, concentrated and the crude residue was purified by flash chromatography (1:3 to 2:1 AcOEt : Hexane) to yield **5c** as clear oil (402 mg, 96% yield). **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.04 – 7.01 (m, 1H), 6.56 – 6.52 (m, 1H), 6.29 – 6.26 (m, 1H), 4.78 – 4.76 (m, 1H), 4.66 (s, 1H), 3.94 (t, *J* = 7.4 Hz, 2H), 3.49 (q, *J* = 7.1 Hz, 4H), 2.44 (t, *J* = 7.4 Hz, 2H), 1.71 (s, 3H), 1.18 (td, *J* = 7.1, 1.5 Hz, 6H). **^{13}C NMR** (126 MHz, $CDCl_3$): δ 166.58 (C), 141.77 (C), 123.59 (CH), 120.36 (CH), 119.32 (C), 112.66 (CH_2), 108.78 (CH), 48.41 (CH_2), 41.43 (CH_2), 39.45 (CH_2), 22.41 (CH_3), 13.79 (CH_3). **HRMS** (ESI-TOF): m/z calculated for $C_{14}H_{23}N_2O$ ($[M+H]^+$) 235.1806, found 235.1805.

Synthesis of _N_,_N_-Diethyl-1-(3-methylbut-3-en-1-yl)-1_H_-indole-3-carboxamide (5d).



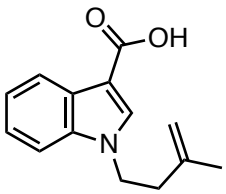
1-(3-Methylbut-3-en-1-yl)-1_H_-indole (S15)



Following a modified reported procedure.[12] Indole (1.17 g, 10.0 mmol, 1.0 equiv) was added in portions to a NaH (560 mg, 14.0 mmol, 1.4 equiv) suspension in DMF (25 mL, 0.4 M), at 0ºC. The reaction mixture was then warmed to 50 °C to

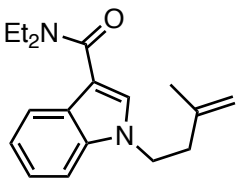
ensure complete deprotonation. Subsequently, it was cooled to 0 °C and 3-methyl-3-butenyl methanesulfonate[13] was added dropwise. (CAUTION, the reaction is very exothermic!) The ice bath was removed and the reaction mixture was allowed to slowly warm up and stirred overnight at rt. After quenching with water, the aqueous phase was extracted with hexane (4 x 20 mL), the combined organic layers were washed with brine, dried, filtered and the organic phases were concentrated to yield a crude residue that was purified by flash chromatography (hexane–EtOAc = 99:1) to afford the product as a colorless oil (690 mg, 37% yield). The data was consistent with that previously described.[12]

1-(3-Methylbut-3-en-1-yl)-1*H*-indole-3-carboxylic acid (S16)



To a solution of 1-(3-Methylbut-3-en-1-yl)-1*H*-indole (**S15**, 690 mg, 3.72 mmol, 1 equiv) in CH_2Cl_2 (5.0 mL, 0.75 M) at 0 ºC was added dropwise trifluoroacetic anhydride (0.79 mL, 5.59 mmol). The solution was stirred at rt for 1h, and the volatile components were removed in a rotary evaporator under vacuum: The crude product was carried to the next step without further purification. To a solution of 2,2,2-Trifluoro-1-(1-(3-methylbut-3-en-1-yl)-1*H*-indol-3-yl)ethan-1-one (1.04 g, 3.72 mmol) in MeOH (3.7 mL, 1 M), was added an aqueous solution of KOH (3.7 mL, 5M). The mixture was stirred overnight at 80 ºC. The reaction was cooled to rt and HCl (10 %) was added until the solution reach pH 1-2. At this point, the mixture was extracted with EtOAc (3 x 10 mL). The organic layer was dried with Na_2SO_4 and the solvent was removed. The pure product (825 mg, 97% yield) was obtained as white solid after column chromatography (1:3 to 2:1, EtOAc:Hexane). The data was consistent with the previous described.[14]

***N*,*N*-Diethyl-1-(3-methylbut-3-en-1-yl)-1*H*-indole-3-carboxamide (5d)**

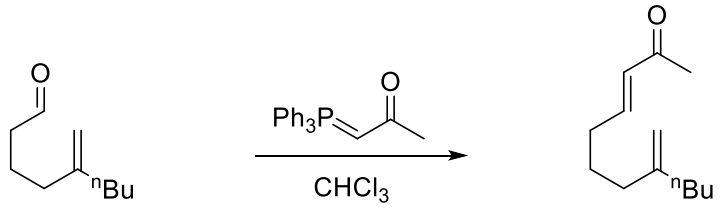


To a solution of 1-(3-Methylbut-3-en-1-yl)-1*H*-indole-3-carboxylic acid (**S16**, 825 mg, 3.60 mmol, 1.0 equiv), in CH_2Cl_2 (58 mL, 0.06 M) and DMF (2.9 mL, 1.25M), EDC.HCl (897 mg, 4.68 mmol, 1.3 equiv), HOBt (606 mg, 3.96 mmol, 1.1 equiv) and triethylamine (1.6 mL, 11.52 mmol, 3.2 equiv) were added. The mixture was stirred 20 minutes and diethylamine (0.43 mL, 4.14 mmol, 1.15 equiv) was added. The resulting mixture was stirred at 40 ºC for 4 h and at rt for 16 hours. The reaction was poured into water and the organic layer was separated. The aqueous phase was extracted with EtOAc (3 x 20 mL) The combined organic layers were washed and dried with Na_2SO_4 and the solvent was evaporated. The crude product was purified by column chromatography (1:2 to 3:1, AcOEt:Hexane). The indole derivative was obtained as beige solid (645 mg, 63 %). **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.74 (d, *J* = 7.8 Hz, 1H), 7.32 – 7.27 (m, 2H), 7.23 – 7.10 (m, 2H), 4.77 – 4.61 (m, 2H), 4.17 (t, *J* = 7.3 Hz, 2H), 3.55 – 3.47 (m, 4H), 2.48 (t, *J* = 7.4 Hz, 2H), 1.72 (s, 3H), 1.20 – 1.13 (m, 6H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 166.81 (C), 141.84 (C), 135.56 (C), 128.26 (CH), 126.98 (C), 122.29 (CH), 121.08 (CH),

120.60 (CH), 112.91 (CH_2), 111.14 (C), 109.52 (CH), 45.08 (CH_2), 41.34 (CH_2), 37.98 (CH_2), 22.47 (CH_3), 13.96 (CH_3). **HRMS** (ESI-TOF): m/z calculated for $C_{18}H_{25}N_2O$ ($[M+H]^+$) 285.1961, found 285.1961.

Synthesis of ketones, ester and acid 1c, 1u, 1v, and 1w.

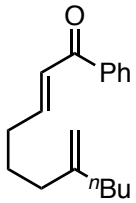
(*E*)-8-Methylenedodec-3-en-2-one (1c)



1c

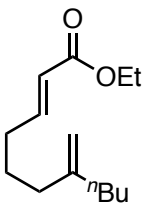
5-Methylenenonanal (700 mg, 4.54 mmol) was added to a solution of 1-(triphenyl-λ5-phosphaneylidene)propan-2-one (1.7 g, 5.45 mmol, 1.2 equiv) in $CHCl_3$ (18 mL, 0.25 M) The mixture was stirred for 20 hours at rt, the solvent was removed, and the crude residue was purified by column chromatography (1:10, Et_2O:Hexane) to afford (*E*)-8-methylenedodec-3-en-2-one as clear oil (514 mg, 58% yield). **^{1}H NMR** (300 MHz, $CDCl_3$): δ 6.79 (dt, *J* = 16.0, 6.9 Hz, 1H), 6.06 (dt, *J* = 15.9, 1.5 Hz, 1H), 4.73 – 4.67 (m, 2H), 2.26 – 2.16 (m, 5H), 2.00 (dt, *J* = 13.9, 7.8 Hz, 4H), 1.65 – 1.53 (m, 2H), 1.44 – 1.23 (m, 4H), 0.88 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 198.69 (C), 149.16 (C), 148.25 (CH), 131.53 (CH), 109.32 (CH_2), 35.73 (CH_2), 35.50 (CH_2), 32.13 (CH_2), 30.06 (CH_2), 26.93 (CH_3), 26.19 (CH_2), 22.55 (CH_2), 14.07 (CH_3). **MS** (ESI): ($[M+H]^+$) 195.2

(*E*)-7-Methylene-1-phenylundec-2-en-1-one (1w)



Prepared following the procedure for the synthesis of **1c**, using 1-phenyl-2-(triphenyl-λ5-phosphaneylidene)ethan-1-one as Wittig reagent**. ^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.90 (d, *J* = 7.4 Hz, 2H), 7.53 – 7.45 (m, 1H), 7.40 (t, *J* = 7.4 Hz, 2H), 7.10 – 6.98 (m, 1H), 6.86 (d, *J* = 15.4 Hz, 1H), 4.71 (d, *J* = 6.6 Hz, 2H), 2.33 – 2.22 (m, 2H), 2.07 – 1.94 (m, 4H), 1.70 – 1.56 (m, 2H), 1.44 – 1.23 (m, 4H), 0.88 (t, *J* = 7.0 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 190.47 (C), 149.44 (CH), 148.95 (C), 137.90 (C), 132.48 (CH), 128.41 (CH), 125.95 (CH), 109.21 (CH_2), 35.58 (CH_2), 35.41 (CH_2), 32.32 (CH_2), 29.91 (CH_2), 26.15 (CH_2), 22.41 (CH_2), 13.94 (CH_3). **MS (ESI):** ($[M+H]^+$) 257.2

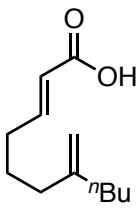
Ethyl (*E*)-7-methyleneundec-2-enoate (1u)



Prepared following the procedure for the synthesis of **1c**, using ethyl 2-(triphenyl-λ5-phosphaneylidene)acetate as Wittig reagent.**^{1}H NMR (300 MHz, $CDCl_3$):** δ 6.95 (dt, *J* = 15.5, 6.9 Hz, 1H), 5.81 (d, *J* = 15.7 Hz, 1H), 4.70 (d, *J* = 8.2 Hz, 2H), 4.17 (q, *J* = 7.1 Hz, 2H), 2.23 – 2.14 (m, 2H), 2.05 – 1.94 (m, 4H), 1.64 – 1.52 (m, 2H), 1.44 – 1.21 (m,

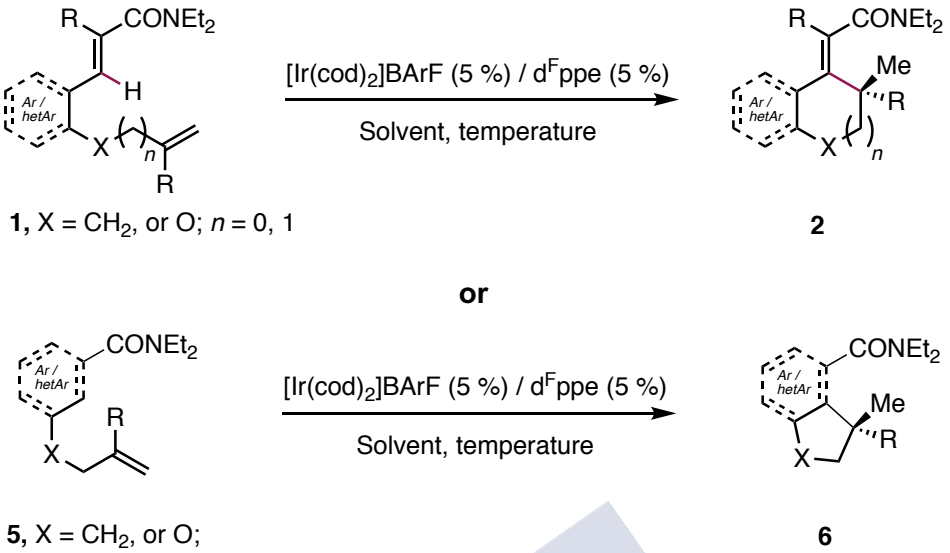
7H), 0.89 (t, *J* = 7.0 Hz, 3H). **^{13}C NMR (75 MHz, $CDCl_3$):** δ 166.81 (C), 149.27 (C), 149.15 (CH), 121.59 (CH), 109.27 (CH), 60.24 (CH_2), 35.76 (CH_2), 35.50 (CH_2), 31.88 (CH_2), 30.09 (CH_2), 26.16 (CH_2), 22.58 (CH_2), 14.38 (CH_3), 14.09 (CH_3). **HRMS (ESI-TOF):** m/z calculated for $C_{14}H_{24}NaO_2$ ($[M+Na]^+$) 247.1662, found 247.1669.

(*E*)-7-Methyleneundec-2-enoic acid (1v).



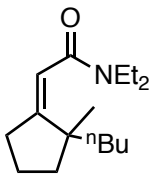
LiOH (42 mg, 0.178 mmol, 2 equiv) in water (3.3 mL) was added to a solution of ethyl (*E*)-7-methyleneundec-2-enoate (**1u**, 200 mg, 0.89 mmol, 1 equiv) in MeOH (1.6 mL) and THF (4 mL), and the reaction mixture was stirred at 45 ºC for 20 hours. Then, HCl (10 %) was added until a pH of 1-2 was reached. After extraction with EtOAc (3 x 10 mL), the organic layer was dried and the solvent removed. The pure product (156 mg, 89% yield) was obtained as white solid after column chromatography (1:3 to 1:1, AcOEt:Hexane). **^{1}H NMR** (300 MHz, $CDCl_3$): δ 11.60 (s, 1H), 7.09 (dt, *J* = 15.6, 7.0 Hz, 1H), 5.84 (dt, *J* = 15.6, 1.6 Hz, 1H), 4.76 – 4.68 (m, 2H), 2.29 – 2.18 (m, 2H), 2.08 – 1.96 (m, 4H), 1.68 – 1.55 (m, 2H), 1.45 – 1.25 (m, 4H), 0.90 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 172.41 (C), 152.25 (CH), 149.18 (C), 121.02 (CH), 109.41 (CH_2), 35.77 (CH_2), 35.51 (CH_2), 32.01 (CH_2), 30.11 (CH_2), 26.02 (CH_2), 22.61 (CH_2), 14.12 (CH_3). **MS** (ESI): ($[M+H]^+$) 197.1

Procedure for the Iridium-catalyzed intramolecular hydrocarbonation reaction



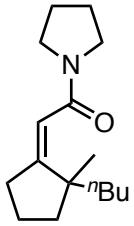
$Ir(cod)_2BArF$ (0.05 equiv), d^Fppe (0.05 equiv), the carboxamide precursor (typically 50 -200 mg, 1.0 equiv) and the appropriate solvent [dioxane or 1,2-DCE (0.124 M)] were sequentially added to a Schlenk tube under Argon. The reaction mixture was then stirred at the appropriate temperature [100 °C for dioxane or 140 ºC for 1,2-DCE (in a sealed tube)]. After 19 h, the reaction mixture was concentrated and the crude residue was purified by flash chromatography on silica gel (typically 1:20 to 1:10 EtOAc : Hexanes) to afford the cyclic product.

(*Z*)-2-(2-Butyl-2-methylcyclopentylidene)-*N*,*N*-diethylacetamide (2a)



Carried out in refluxing dioxane. The product was isolated by flash chromatography (5 to 10 % EtOAc/Hexanes) as a pale yellow oil (91% yield). **^{1}H NMR** (300 MHz, $CDCl_3$): δ 5.82 (t, *J* = 2.1 Hz, 1H), 3.51 – 3.20 (m, 4H), 2.48 – 2.38 (m, 2H), 1.77 – 1.38 (m, 8H), 1.28 – 1.22 (m, 2H), 1.20 (s, 3H), 1.15 – 1.08 (m, 6H), 0.85 (t, *J* = 7.0 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 167.81 (C), 161.80 (C), 114.45 (CH), 46.18 (C), 42.57 (CH_2), 40.70 (CH_2), 39.15 (CH_2), 38.51 (CH_2), 36.88 (CH_2), 27.37 (CH_2), 25.44 (CH_3), 23.60 (CH_2), 22.68 (CH_2), 14.34 (CH_3), 13.99 (CH_3), 12.90 (CH_3). **HRMS** (ESI-TOF): m/z calculated for $C_{16}H_{30}NO$ ($[M+H]^+$) 252.2322, found 252.2322.

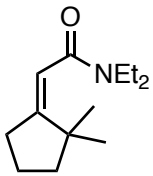
(*Z*)-2-(2-Butyl-2-methylcyclopentylidene)-1-(pyrrolidin-1-yl)ethan-1-one (2b)



Carried out in refluxing dioxane. The product was isolated by flash chromatography (5 to 15 % EtOAc/Hexanes) as a yellow pale oil (44 %). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 5.84 (s, 1H), 3.50 – 3.34 (m, 4H), 2.51 – 2.36 (m, 2H), 1.95 – 1.81 (m, 4H), 1.78 – 1.71 (m, 2H), 1.71 – 1.57 (m, 4H), 1.49 – 1.42 (m, 1H), 1.27 – 1.24 (m, 5H), 1.14 – 1.04 (m, 1H), 0.86

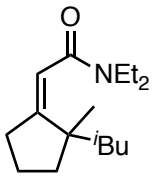
(t, *J* = 6.9 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 166.55 (C), 163.63 (C), 114.80 (CH), 46.20 (C), 40.93 (CH_2), 38.19 (CH_2), 37.74 (CH_2), 27.39 (CH_2), 25.59 (CH_3), 23.61 (CH_2), 22.86 (CH_2), 14.36 (CH_3). **HRMS** (ESI-TOF): m/z calculated for $C_{16}H_{28}NO$ ($[M+H]^+$) 250.2167, found 250.2165.

(*Z*)-2-(2,2-Dimethylcyclopentylidene)-*N*,*N*-diethylacetamide (2d)



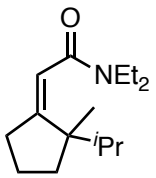
Carried out in refluxing dioxane. The product was isolated by flash chromatography (5 to 10 % EtOAc/Hexanes) as a pale yellow oil (80% yield). **^{1}H NMR** (500 MHz, $CDCl_3$): δ 5.81 (t, *J* = 2.1 Hz, 1H), 3.38 (q, *J* = 7.1 Hz, 2H), 3.32 (q, *J* = 7.1 Hz, 2H), 2.47 (td, *J* = 7.3, 2.1 Hz, 2H), 1.67 – 1.59 (m, 2H), 1.56 (t, *J* = 6.4 Hz, 2H), 1.22 (s, 5H), 1.14 – 1.10 (m, 7H). **^{13}C NMR** (126 MHz, $CDCl_3$): δ 167.99 (C), 161.21 (C), 114.67 (CH), 44.76 (CH_2), 42.86 (C), 42.69 (CH_2), 39.18 (CH_2), 36.05 (CH_2), 26.88 (CH_3), 22.44 (CH_2), 14.06 (CH_3), 12.90 (CH_3). **HRMS** (ESI-TOF): m/z calculated for $C_{13}H_{24}NO$ ($[M+H]^+$) 210.1851, found 210.1852.

(*Z*)-*N*,*N*-Diethyl-2-(2-isobutyl-2-methylcyclopentylidene)acetamide (2e)



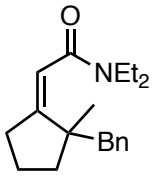
Carried out in refluxing dioxane. The product was isolated by flash chromatography (5 to 10 % EtOAc/Hexanes) as a pale yellow oil (93% yield). **^{1}H NMR** (300 MHz, $CDCl_3$): δ 5.81 – 5.78 (m, 1H), 3.52 – 3.38 (m, 1H), 3.37 – 3.21 (m, 3H), 2.48 – 2.41 (m, 2H), 1.80 – 1.72 (m, 1H), 1.70 – 1.57 (m, 4H), 1.54 – 1.40 (m, 2H), 1.23 (s, 3H), 1.15 – 1.08 (m, 6H), 0.93 – 0.83 (m, 6H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 167.99 (C), 162.65 (C), 114.37 (CH), 47.05 (CH_2), 46.52 (C), 42.54 (CH_2), 41.06 (CH_2), 39.10 (CH_2), 36.51 (CH_2), 25.51 (CH), 25.34 (CH_3), 25.24 (CH_3), 24.85 (CH_3), 22.52 (CH_2), 13.87 (CH_3), 12.77 (CH_3). **HRMS** (ESI-TOF): m/z calculated for $C_{16}H_{30}NO$ ($[M+H]^+$) 252.2322, found 252.2322.

(*Z*)-*N*,*N*-Diethyl-2-(2-isopropyl-2-methylcyclopentylidene)acetamide (2f)



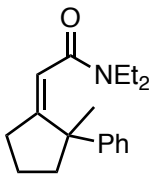
Carried out in refluxing dioxane**.** The product was isolated by flash chromatography (5 to 10 % EtOAc/Hexanes) as a yellow oil (96% yield). **^{1}H NMR** (300 MHz, $CDCl_3$): δ 5.88 – 5.85 (m, 1H), 3.47 – 3.23 (m, 4H), 2.53 – 2.25 (m, 3H), 1.82 – 1.70 (m, 1H), 1.67 – 1.50 (m, 2H), 1.36 – 1.27 (m, 1H), 1.24 (s, 3H), 1.17 – 1.07 (m, 6H), 0.86 – 0.75 (m, 6H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 167.72 (C), 162.70 (C), 114.01 (CH), 49.76 (C), 42.38 (CH_2), 39.04 (CH_2), 38.70 (CH_2), 35.01 (CH_2), 33.13 (CH), 25.43 (CH_3), 22.90 (CH_2), 18.54 (CH_3), 17.89 (CH_3), 13.92 (CH_3), 12.74 (CH_3). **HRMS** (ESI-TOF): m/z calculated for $C_{15}H_{28}NO$ ($[M+H]^+$) 238.2161, found 238.2165.

(*Z*)-2-(2-Benzyl-2-methylcyclopentylidene)-*N*,*N*-diethylacetamide (2g)



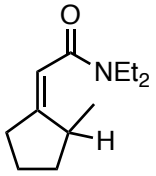
Carried out in refluxing Dioxane. The product was isolated by flash chromatography (5 to 10 % EtOAc/Hexanes) as yellow oil (94% yield). **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.20 – 7.10 (m, 5H), 5.87 (t, *J* = 1.6 Hz, 1H), 3.40 – 3.28 (m, 3H), 3.02 – 2.88 (m, 2H), 2.43 – 2.25 (m, 2H), 1.82 – 1.68 (m, 1H), 1.53 – 1.42 (m, 2H), 1.28 – 1.19 (m, 2H), 1.15 (s, 3H), 1.14 - 1.06 (m, 6H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 167.92 (C), 162.01 (C), 139.98 (C), 130.92 (CH), 127.84 (CH), 125.94 (CH), 115.07 (CH), 47.06 (C), 44.31 (CH_2), 42.64 (CH_2), 40.08 (CH_2), 39.35 (CH_2), 36.76 (CH_2), 24.79 (CH_3), 22.28 (CH_2), 14.01 (CH_3), 12.88 (CH_3). **HRMS** (ESI-TOF): m/z calculated for $C_{19}H_{28}NO$ ($[M+H]^+$) 286.2164, found 286.2165.

(*Z*)-*N*,*N*-Diethyl-2-(2-methyl-2-phenylcyclopentylidene)acetamide (2h)



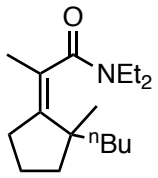
Carried out in 1,2-DCE at 140 ºC (in a sealed tube). The product was isolated by flash chromatography (5 to 15 % EtOAc/Hexanes) as white solid (83% yield). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.33 – 7.28 (m, 2H), 7.22 (t, *J* = 7.7 Hz, 2H), 7.11 – 7.06 (m, 1H), 5.92 (t, *J* = 2.1 Hz, 1H), 3.22 – 3.13 (m, 2H), 2.86 – 2.74 (m, 2H), 2.72 – 2.65 (m, 2H), 2.09 – 2.01 (m, 1H), 1.89 – 1.73 (m, 3H), 1.71 (s, 3H), 1.02 (t, *J* = 7.2 Hz, 3H), 0.63 (t, *J* = 7.2 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 166.66 (C), 161.78 (C), 148.08 (C), 127.65 (CH), 126.93 (CH), 125.44 (CH), 116.16 (CH), 50.86 (C), 47.71 (CH_2), 42.10 (CH_2), 38.83 (CH_2), 36.08 (CH_2), 24.73 (CH_3), 23.08 (CH_2), 13.89 (CH_3), 12.59 (CH_3). **HRMS** (ESI-TOF): m/z calculated for $C_{18}H_{26}NO$ ($[M+H]^+$) 272.2005, found 272.2009.

(*Z*)-*N*,*N*-Diethyl-2-(2-methylcyclopentylidene)acetamide (2i)



Carried out in 1,2-DCE at 140 ºC (in a sealed tube). The product was isolated by flash chromatography (2 to 10 % EtOAc/Hexanes) as a yellow pale oil (38% yield). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 5.96 – 5.94 (m, 1H), 3.51 – 3.28 (m, 5H), 2.56 – 2.43 (m, 1H), 2.41 – 2.29 (m, 1H), 1.92 – 1.82 (m, 1H), 1.77 – 1.65 (m, 1H), 1.64 – 1.53 (m, 1H), 1.47 – 1.38 (m, 1H), 1.18 – 1.11 (m, 6H), 1.06 (d, *J* = 7.0 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 167.18 (C), 165.21 (C), 112.54 (CH), 42.41 (CH_2), 39.93 (CH_2), 36.53 (CH), 35.17 (CH_2), 34.98 (CH_2), 23.29 (CH_2), 19.98 (CH_3), 14.59 (CH_3), 13.28 (CH_3). **HRMS** (ESI-TOF): m/z calculated for $C_{12}H_{22}NO$ ($[M+H]^+$) 196.1697, found 196.1696.

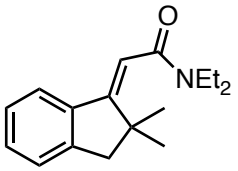
(*Z*)-2-(2-Butyl-2-methylcyclopentylidene)-*N*,*N*-diethylpropanamide (2j)



98% yield. {NOTE: The presence of two rotamers is clearly observed in the ^{1}H and ^{13}C NMR spectra. This was further confirmed by performing the spectra at different temperatures} **^{1}H NMR** (300 MHz, $CDCl_3$, *rt*): δ 3.71 – 3.53 (m, 1H), 3.49 – 3.36 (m, 1H), 3.23 – 3.05 (m, 2H), 2.38 – 2.17 (m, 2H), 1.71 (s, 3H), 1.66 – 1.44 (m, 5H), 1.32 – 1.07 (m, 14H), 0.84 (t, *J* = 7.0 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 172.80 (C), 172.68 (C), 149.69

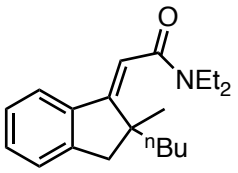
(C), 148.77 (C), 121.98 (C), 121.91 (C), 46.11 (C), 46.07 (C), 42.61 (CH_2), 42.40 (CH_2), 40.73 (CH_2), 39.80 (CH_2), 38.90 (CH_2), 38.71 (CH_2), 37.44 (CH_2), 37.28 (CH_2), 32.30 (CH_2), 32.12 (CH_2), 27.48 (CH_2), 27.08 (CH_2), 24.64 (CH_3), 23.78 (CH_2), 23.59 (CH_3), 23.48 (CH_2), 21.93 (CH_2), 21.73 (CH_2)*, 19.04 (CH_3), 19.01 (CH_3), 14.36 (CH_3), 14.33 (CH_3), 13.91 (CH_3), 13.81 (CH_3), 12.29 (CH_3). **HRMS** (ESI-TOF): m/z calculated for $C_{17}H_{32}NO$ ($[M+H]^+$) 266.2479, found 266.2478.

(*E*)-2-(2,2-Dimethyl-2,3-dihydro-1*H*-inden-1-ylidene)-*N*,*N*-diethylacetamide (2k)



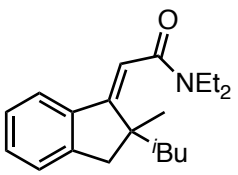
Carried out in refluxing dioxane. The product was isolated by flash chromatography (5 to 10 % EtOAc/Hexanes) as a yellow solid (99% yield). **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.38 (d, *J* = 7.3 Hz, 1H), 7.23 – 7.09 (m, 3H), 6.32 (s, 1H), 3.46 – 3.27 (m, 5H), 2.79 (s, 2H), 1.34 (s, 6H), 1.16 – 1.04 (m, 6H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 167.72 (C), 158.03 (C), 144.54 (C), 140.50 (C), 129.39 (CH), 126.69 (CH), 125.43 (CH), 121.15 (CH), 112.14 (CH), 49.06 (C), 44.28 (CH_2), 42.80 (CH_2), 39.35 (CH_2), 27.31 (CH_3), 14.09 (CH_3), 12.87 (CH_3). **HRMS** (ESI-TOF): m/z calculated for $C_{17}H_{24}NO$ ($[M+H]^+$) 258.1852, found 258.1852.

(*E*)-2-(2-Butyl-2-methyl-2,3-dihydro-1*H*-inden-1-ylidene)-*N*,*N*-diethylacetamide (2l)



Carried out in refluxing dioxane. The product was isolated by flash chromatography (5 to 10 % EtOAc/Hexanes) as a pale yellow oil (99% yield). **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.47 (d, *J* = 7.6 Hz, 1H), 7.31 – 7.19 (m, 3H), 6.46 (s, 1H), 3.53 – 3.36 (m, 4H), 3.05 (d, *J* = 16.5 Hz, 1H), 2.74 (d, *J* = 16.5 Hz, 1H), 1.89 (ddd, *J* = 13.0, 11.9, 4.5 Hz, 1H), 1.75 (ddd, *J* = 13.1, 12.1, 4.4 Hz, 1H), 1.40 (s, 3H), 1.31 – 1.23 (m, 3H), 1.20 (t, *J* = 7.1 Hz, 6H), 1.17 – 1.10 (m, 1H), 0.85 (t, *J* = 7.2 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 167.60 (C), 158.12 (C), 145.12 (C), 141.02 (C), 129.43 (CH), 126.65 (CH), 125.33 (CH), 120.85 (CH), 112.07 (CH), 47.61 (C), 45.71 (CH_2), 41.5 (br, CH_2) 39.37 (CH_2), 27.56 (CH_3), 26.46 (CH_2), 23.51 (CH_2), 14.25 (CH_3), 13.52 (CH_3). **HRMS** (ESI-TOF): m/z calculated for $C_{20}H_{30}NO$ ($[M+H]^+$) 300.2322, found 300.2322.

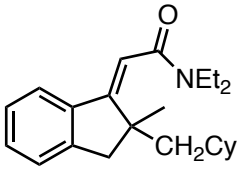
(*E*)-*N*,*N*-Diethyl-2-(2-isobutyl-2-methyl-2,3-dihydro-1*H*-inden-1-ylidene)acetamide (2m)



Carried out in refluxing dioxane. The product was isolated by flash chromatography (5 to 10 % EtOAc/Hexanes) as a colorless oil (99% yield)
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.48 – 7.42 (m, 1H), 7.31 – 7.17 (m, 3H), 6.42 (s, 1H), 3.51 – 3.34 (m, 4H), 3.10 (d, *J* = 16.6 Hz, 1H), 2.79 (d, *J* = 16.6 Hz, 1H), 1.90 – 1.70 (m, 2H), 1.70 – 1.55 (m, 1H), 1.40 (s, 3H), 1.18 (t, *J* = 7.2 Hz, 6H), 0.86 (t, *J* = 6.5 Hz, 6H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 167.59 (C), 158.80 (C), 145.22 (C), 140.97 (C), 129.48 (CH), 126.68 (CH), 125.32 (CH), 120.89 (CH), 111.98 (CH), 48.35 (CH_2), 47.75 (C), 46.49 (CH_2), 41.0 (br, CH_2) 26.87 (CH_3), 25.70 (CH), 25.04 (CH_3), 24.69 (CH_3), 13.48 (CH_3). **HRMS** (ESI-TOF): m/z calculated

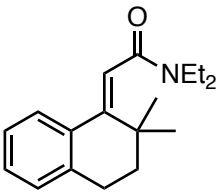
for $C_{20}H_{30}NO$ ([M+H]$^+$) 300.2322, found 300.2322; m/z calculated for $C_{20}H_{29}NONa$ ([M+Na]$^+$) 322.2143, found 322.2141.

(*E*)-2-(2-(Cyclohexylmethyl)-2-methyl-2,3-dihydro-1*H*-inden-1-ylidene)-*N*,*N*-diethylacetamide (2n)



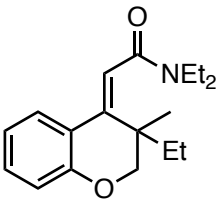
Carried out in refluxing dioxane. The product was isolated by flash chromatography (5 to 10 % EtOAc/Hexanes) as a colorless oil (98% yield). **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.47 – 7.44 (m, 1H), 7.29 – 7.25 (m, 1H), 7.24 – 7.19 (m, 2H), 6.41 (s, 1H), 3.51 – 3.33 (m, 4H), 3.09 (d, *J* = 16.5 Hz, 1H), 2.78 (d, *J* = 16.5 Hz, 1H), 1.80 – 1.71 (m, 2H), 1.69 – 1.51 (m, 5H), 1.40 (s, 3H), 1.33 – 1.25 (m, 1H), 1.19 (t, *J* = 7.1 Hz, 6H), 1.16 – 1.05 (m, 3H), 1.02 – 0.89 (m, 2H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 167.57 (C), 158.90 (C), 145.14 (C), 140.88 (C), 129.43 (CH), 126.61 (CH), 125.33 (CH), 120.90 (CH), 111.81 (CH), 47.73 (C), 46.53 (CH_2), 42.02 (br, N-CH_2), 40.25 (br, N-CH_2), 35.44 (CH_2), 35.29 (CH), 35.16 (CH_2), 26.86 (CH_3), 26.62 (CH_2), 26.43 (CH_2), 13.47 (CH_3). **HRMS** (ESI-TOF): m/z calculated for $C_{23}H_{34}NO$ ([M+H]$^+$) 340.2634, found 340.2635.

(*E*)-2-(2,2-Dimethyl-3,4-dihydronaphthalen-1(2*H*)-ylidene)-*N*,*N*-diethylacetamide (2o)



Carried out in refluxing dioxane. The product was isolated by flash chromatography (10 to 20 % EtOAc/ Hexanes) as an orange pale oil (92% yield) **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.53 – 7.47 (m, 1H), 7.22 – 7.14 (m, 2H), 7.14 – 7.08 (m, 1H), 6.23 (s, 1H), 3.43 (dq, *J* = 18.7, 7.1 Hz, 4H), 2.82 (t, *J* = 6.5 Hz, 2H), 1.69 (t, *J* = 6.5 Hz, 2H), 1.26 (s, 6H), 1.20 – 1.11 (m, 6H). **^{13}C NMR (**75 MHz, $CDCl_3$): δ 169.44 (C), 148.62 (C), 137.87 (C), 136.47 (C), 128.46 (CH), 127.85 (CH), 126.27 (CH), 126.20 (CH), 118.73 (CH), 42.78 (CH_2), 39.20 (CH_2), 38.77 (CH_2), 36.35 (CH_2), 29.81 (C), 27.14 (CH_3), 26.83 (CH_2), 13.78 (CH_3), 12.34 (CH_3). **HRMS** (ESI-TOF): m/z calculated for $C_{18}H_{26}NO$ ([M+H]$^+$) 272.2010, found 272.2009.

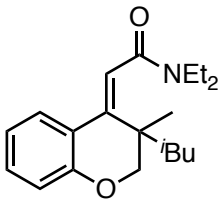
(*E*)-*N*,*N*-Diethyl-2-(3-ethyl-3-methylchroman-4-ylidene)acetamide (2p)



Carried out in refluxing dioxane. The product was isolated by flash chromatography (5 to 10 % EtOAc/Hexanes) as yellow oil (82 % yield). **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.48 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.19 (ddd, *J* = 8.4, 7.2, 1.6 Hz, 1H), 6.90 (ddd, *J* = 8.2, 7.2, 1.3 Hz, 1H), 6.83 (dd, *J* = 8.2, 1.3 Hz, 1H), 6.37 (s, 1H), 3.94 (d, *J* = 11.1 Hz, 1H), 3.79 (d, *J* = 11.1 Hz, 1H), 3.62 – 3.41 (m, 2H), 3.40 – 3.26 (m, 2H), 1.83 – 1.70 (m, 1H), 1.61 – 1.47 (m, 1H), 1.20 – 1.12 (m, 9H), 0.91 (t, *J* = 7.5 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 168.75 (C), 154.58 (C), 143.34 (C), 129.91 (CH), 125.72 (CH), 121.46 (C), 121.03 (CH), 117.12 (CH), 116.35 (CH), 73.83 (CH_2), 42.83 (CH_2), 38.99 (CH_2), 38.52

(C), 28.17 (CH_2), 19.02 (CH_3), 13.85 (CH_3), 12.41 (CH_3), 8.66 (CH_3). **HRMS** (ESI-TOF): m/z calculated for $C_{18}H_{26}NO_2$ ($[M+H]^+$) 288.1959, found 288.1958.

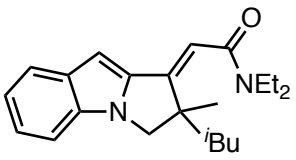
(*E*)-*N*,*N*-Diethyl-2-(3-isobutyl-3-methylchroman-4-ylidene) acetamide (2q)



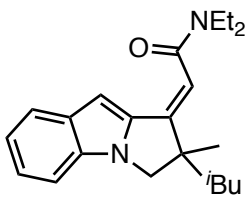
Carried out in refluxingdDioxane. The product was isolated by flash chromatography (5 to 10 % EtOAc/Hexanes) as yellow pale oil (90 %). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.43 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.22 – 7.17 (m, 1H), 6.93 – 6.87 (m, 1H), 6.82 (dd, *J* = 8.1, 1.3 Hz, 1H), 6.29 (s, 1H), 3.90 (d, *J* = 11.0 Hz, 1H), 3.79 (d, *J* = 11.0 Hz, 1H), 3.63 – 3.53 (m, 1H), 3.52 – 3.41 (m, 1H), 3.37 – 3.25 (m, 2H), 1.98 – 1.87 (m, 1H), 1.67 (dd, *J* = 14.3, 6.6 Hz, 1H), 1.34 (dd, *J* = 14.2, 4.5 Hz, 1H), 1.21 (s, 3H), 1.19 – 1.13 (m, 6H), 0.90 (d, *J* = 6.7 Hz, 3H), 0.82 (d, *J* = 6.6 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 168.67 (C), 154.37 (C), 144.18 (C), 129.93 (CH), 126.08 (CH), 121.92 (C), 121.04 (CH), 116.85 (CH), 116.59 (CH), 75.42 (CH_2), 44.62 (CH_2), 42.81 (CH_2), 39.05 (CH_2), 38.61 (C), 25.52 (CH), 24.51 (CH_3), 24.14 (CH_3), 19.96 (CH_3), 13.87 (CH_3), 12.47 (CH_3). **HRMS** (ESI-TOF): m/z calculated for $C_{20}H_{30}NO_2$ ($[M+H]^+$) 316.2275, found 316.2271.

(*E*)-*N*,*N*-Diethyl-2-(2-isobutyl-2-methyl-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indol-1-ylidene)acetamide (*E*-2r) and **(*Z*)-*N*,*N*-Diethyl-2-(2-isobutyl-2-methyl-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indol-1-ylidene)acetamide (*Z*-2r)**

Carried out in refluxing dioxane**,** the products were isolated by flash chromatography (5 to 20 % EtOAc/Hexanes) as dark brown oil [90% combined yield, E / Z = 1:1)]



***E*-2r** : NMR data of *E*-**2r** was deduced from a 3.9 : 1 E / Z sample of **2r**, obtained after careful column chromatography. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.53 (d, *J* = 7.9 Hz, 1H), 7.21 – 7.17 (m, 1H), 7.10 (ddd, *J* = 8.2, 6.9, 1.2 Hz, 1H), 7.02 (ddd, *J* = 8.1, 6.9, 1.2 Hz, 1H), 6.47 (s, 2H), 4.12 (d, *J* = 10.1 Hz, 1H), 3.82 (d, *J* = 10.1 Hz, 1H), 3.44 – 3.30 (m, 4H), 2.07 (dd, *J* = 13.9, 6.3 Hz, 1H), 1.75 (dd, *J* = 14.0, 6.0 Hz, 1H), 1.62 – 1.57 (m, 1H), 1.51 (s, 3H), 1.16 – 1.10 (m, 6H), 0.83 – 0.77 (m, 6H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 166.29 (C), 148.97 (C), 143.83 (C), 133.64 (C), 132.77 (C), 121.95 (CH), 121.51 (CH), 120.23 (CH), 113.33 (CH), 109.96 (CH), 92.08 (CH), 56.64 (CH_2), 51.80 (C), 47.54 (CH_2), 42.88 (CH_2) 39.90 (CH_2), 26.39 (CH), 25.77 (CH_3), 24.69 (CH_3), 24.38 (CH_3), 14.33 (CH_3), 13.08 (CH_3). **HRMS** (ESI-TOF): m/z calculated for $C_{22}H_{31}N_2O$ ($[M+H]^+$) 339.2434, found 339.2431.

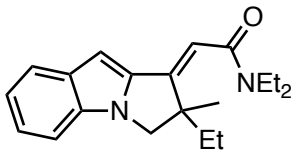


Z-2r: NMR data of *Z*-2r was deduced from a 1 : 3.5 E / Z sample of **2r**, obtained after careful column chromatography. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.55 (d, *J* = 8.1 Hz, 1H), 7.17 (d, *J* = 8.5 Hz, 1H), 7.10 (ddd, *J* = 8.2, 6.7, 1.1 Hz, 1H), 7.04 (s, 1H), 6.99 (ddd, *J* = 8.0, 6.8, 1.2 Hz, 1H), 5.86 (s, 1H), 4.06 (d, *J* = 10.1 Hz,

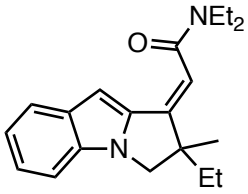
1H), 3.80 (d, *J* = 10.1 Hz, 1H), 3.50 – 3.31 (m, 4H), 1.68 – 1.61 (m, 1H), 1.58 (t, *J* = 5.7 Hz, 2H), 1.34 (s, 3H), 1.21 – 1.07 (m, 6H), 0.86 – 0.80 (m, 6H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 166.75 (C), 148.74 (C), 139.17 (C), 133.56 (C), 133.00 (C), 122.43 (CH), 122.33 (CH), 119.90 (CH), 112.01 (CH), 109.71 (CH), 100.50 (CH), 54.13 (CH_2), 51.78 (C), 50.42 (CH_2), 42.91 (CH_2), 40.24 (CH_2), 28.11 (CH), 25.44 (CH_3), 25.01 (CH_3), 24.76 (CH_3), 14.80 (CH_3), 13.45 (CH_3). **HRMS** (ESI-TOF): m/z calculated for $C_{22}H_{31}N_2O$ ($[M+H]^+$) 339.2433, found 339.2431.

(*E*)-*N*,*N*-Diethyl-2-(2-ethyl-2-methyl-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indol-1-ylidene)acetamide (*E*-2s) and **(*Z*)-*N*,*N*-Diethyl-2-(2-ethyl-2-methyl-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indol-1-ylidene)acetamide (*Z*-2s)**

Carried out in refluxing Dioxane. The products were separately isolated by flash chromatography (5 to 20 % EtOAc/Hexanes) [***E*-2s:** 43 % yield and ***Z*-2s**: 43% yield)].



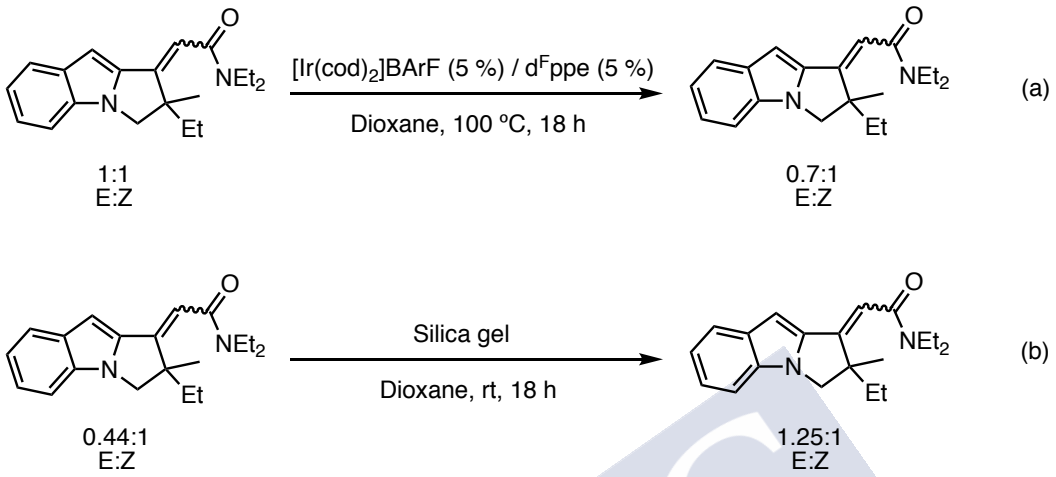
***E*-2s: ^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.59 (d, *J* = 8.0 Hz, 1H), 7.25 (d, *J* = 7.7 Hz, 1H), 7.19 – 7.13 (m, 1H), 7.08 (ddd, *J* = 8.1, 7.0, 1.1 Hz, 1H), 6.55 (s, 1H), 6.52 (s, 1H), 4.09 (d, *J* = 10.1 Hz, 1H), 3.83 (d, *J* = 10.1 Hz, 1H), 3.49 – 3.38 (m, 4H), 2.22 – 2.11 (m, 1H), 1.95 – 1.84 (m, 1H), 1.55 (s, 3H), 1.22 – 1.15 (m, 6H), 0.83 (t, *J* = 7.4 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 166.34 (C), 148.12 (C), 143.90 (C), 133.64 (C), 132.71 (C), 121.95 (CH), 121.50 (CH), 120.21 (CH), 113.57 (CH), 109.94 (CH), 91.98 (CH), 55.35 (CH_2), 52.15 (C), 42.91 (CH_2), 39.85 (CH_2), 31.57 (CH_2), 25.11 (CH_3), 14.34 (CH_3), 13.04 (CH_3), 9.43 (CH_3). **HRMS** (ESI-TOF): m/z calculated for $C_{20}H_{27}N_2O$ ($[M+H]^+$) 311.2118, found 311.2118; m/z calculated for $C_{20}H_{27}N_2ONa$ ($[M+Na]^+$) 333.1941, found 333.1937.



***Z*-2s: ^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.61 (d, *J* = 8.0 Hz, 1H), 7.22 (d, *J* = 9.1 Hz, 1H), 7.16 (ddd, *J* = 8.1, 6.8, 1.1 Hz, 1H), 7.11 (s, 1H), 7.05 (ddd, *J* = 8.1, 6.8, 1.2 Hz, 1H), 5.90 (s, 1H), 4.04 (d, *J* = 10.1 Hz, 1H), 3.83 (d, *J* = 10.1 Hz, 1H), 3.55 – 3.50 (m, 2H), 3.43 – 3.36 (m, 2H), 1.72 (q, *J* = 7.4, 6.9 Hz, 2H), 1.39 (s, 3H), 1.26 – 1.14 (m, 6H), 0.88 (t, *J* = 7.4 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 166.74 (C), 148.13 (C), 139.35 (C), 133.59 (C), 132.96 (C), 122.44 (CH), 122.35 (CH), 119.88 (CH), 111.88 (CH), 109.70 (CH), 100.47 (CH), 53.22 (CH_2), 51.87 (C), 42.97 (CH_2), 40.33 (CH_2), 34.40 (CH_2), 26.82 (CH_3), 14.81 (CH_3), 13.47 (CH_3), 9.15 (CH_3). **HRMS** (ESI-TOF): m/z calculated for $C_{20}H_{27}N_2O$ ($[M+H]^+$) 311.2116, found 311.2118.

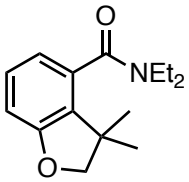
Control experiments related to the formation of E / Z isomers of 2r and 2s

Control experiments carried out for the cyclizations of **1r** and **1s** suggest that these mixtures are the result of an isomerization of the initially formed *e*-isomer (*E*- **2r** , *E*-**2s)**, presumably mediated by the Ir(I) catalyst (Scheme S1, eq. a). The isomerization is also observed during the isolation process in the contact to silica-gel (Scheme S1, eq. b).



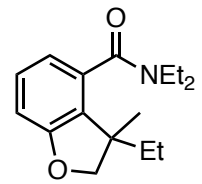
Scheme S1. Isomerization experiments of **2s**.

***N*,*N*-Diethyl-3,3-dimethyl-2,3-dihydrobenzofuran-4-carboxamide (6a)**



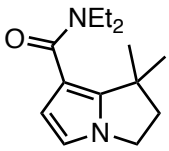
Carried out in refluxing dioxane. The product was isolated by flash chromatography (5 to 10 % EtOAc/Hexanes) as yellow oil (82 % yield). **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.12 (td, *J* = 7.8, 2.6 Hz, 1H), 6.79 (dd, *J* = 8.0, 2.6 Hz, 1H), 6.69 (dd, *J* = 7.5, 2.6 Hz, 1H), 4.25 – 4.21 (m, 1H), 4.17 – 4.13 (m, 1H), 4.03 – 3.96 (m, 1H), 3.21 – 3.03 (m, 3H), 1.40 (s, 3H), 1.28 (s, 3H), 1.24 – 1.19 (m, 3H), 1.09 – 1.04 (m, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$): δ 169.31 (C), 159.56 (C), 133.01 (C), 131.05 (C), 128.52 (CH), 117.57 (CH), 110.30 (CH), 84.44 (CH_2), 42.70 (CH_2), 42.64 (C), 38.01 (CH_2), 27.54 (CH_3), 24.31 (CH_3), 13.76 (CH_3), 12.34 (CH_3). **HRMS** (ESI-TOF): m/z calculated for $C_{15}H_{21}NO_2$ ($[M+H]^+$) 248.1644, found 248.1645.

***N*,*N*,3-Triethyl-3-methyl-2,3-dihydrobenzofuran-4-carboxamide (6b)**



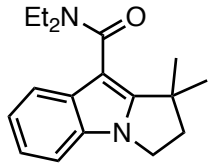
Carried out in refluxing dioxane. The product was isolated by flash chromatography (5 to 10 % EtOAc/Hexanes) as yellow oil (92 % yield). **^{1}H NMR** (400 MHz, $CDCl_3$): **^{1}H NMR** (300 MHz, $CDCl_3$, at 60 ºC): δ 7.09 (td, *J* = 7.8, 1.6 Hz, 1H), 6.75 (dd, *J* = 8.1, 0.7 Hz, 1H), 6.65 (dd, *J* = 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, $CDCl_3$, at 60 ºC): 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.

***N*,*N*-Diethyl-1,1-dimethyl-2,3-dihydro-1*H*-pyrrolizine-7-carboxamide (6c)**



Carried out in refluxing dioxane. The product was isolated by flash chromatography (10 to 30 % EtOAc/Hexanes) as light brown solid (95% yield) **^{1}H NMR (300 MHz, $CDCl_3$):** δ 6.38 (d, *J* = 2.8 Hz, 1H), 6.16 (d, *J* = 2.8 Hz, 1H), 3.92 (t, *J* = 6.9 Hz, 2H), 3.49 (q, *J* = 7.1 Hz, 4H), 2.28 (t, *J* = 6.9 Hz, 2H), 1.40 (s, 6H), 1.17 (t, *J* = 7.1 Hz, 6H). **^{13}C NMR (75 MHz, $CDCl_3$):** δ 167.85 (C), 146.94 (C), 112.15 (CH), 111.39 (CH), 109.94 (C), 45.16 (CH_2), 44.78 (CH_2), 41.42 (CH_2), 39.68 (C), 26.92 (CH_3), 13.86 (CH_3). **HRMS (ESI-TOF):** m/z calculated for $C_{14}H_{23}N_2O$ ($[M+H]^+$) 235.1805, found 235.1805.

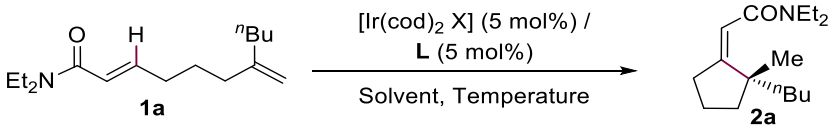
***N*,*N*-Diethyl-1,1-dimethyl-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indole-9-carboxamide (6d)**



Carried out in 1,2-DCE at 140 ºC. The product was isolated by flash chromatography (10 to 20 % EtOAc/ Hexanes) as a pale yellow oil (99% yield). **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.40 (dt, *J* = 7.8, 1.1 Hz, 1H), 7.22 (dt, *J* = 8.0, 1.1 Hz, 1H), 7.16 – 7.12 (m, 1H), 7.12 – 7.07 (m, 1H), 4.10 (t, *J* = 6.8 Hz, 2H), 3.62 – 3.45 (m, 4H), 2.44 – 2.41 (m, 2H), 1.50 (s, 6H), 1.22 – 1.11 (m, 6H). **^{13}C NMR** (126 MHz, $CDCl_3$): δ 167.42 (C), 152.91 (C), 131.29 (C), 129.99 (C), 121.03 (CH), 120.07 (CH), 119.73 (CH), 109.76 (CH), 102.67 (C), 44.31 (CH_2), 42.69 (CH_2), 39.58 (C), 27.02 (CH_3), 14.00 (CH_3). **HRMS** (ESI-TOF): m/z calculated for $C_{18}H_{25}N_2O$ ($[M+H]^+$) 285.1961, found 285.1961. {NOTE: This compound was also characterized at 60 ºC in $CDCl_3$, in order to more clearly show the amide carbons, which sometimes are not fully visible at rt due to the existence of rotamers. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.41 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.23 – 7.19 (m, 1H), 7.17 – 7.06 (m, 2H), 4.09 (t, *J* = 6.9 Hz, 2H), 3.55 (q, *J* = 7.1 Hz, 4H), 2.43 (t, *J* = 7.0 Hz, 2H), 1.51 (s, 6H), 1.18 (t, *J* = 7.1 Hz, 6H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 167.51 (C), 152.87 (C), 131.57 (C), 130.32 (C), 121.13 (CH), 120.18 (CH), 119.86 (CH), 109.78 (CH), 103.10 (C), 44.52 (CH_2), 42.71 (CH_2), 41.30 (CH_2), 39.67 (C), 27.15 (CH_3), 13.99 (CH_3).

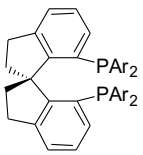
Assays for the development of an enantioselective version

Table S2. Preliminary screening of an asymmetric catalyst for the hydrocarbonation of **1a**.[a]

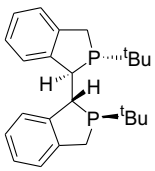


entry	L	X	Solvent	Temp (ºC)	time (h)	Yield (%)	er
1	**L1**	BArF	dioxane	reflux	19	40	88 : 12
2	**L2**	BArF	dioxane	reflux	19	72	84 : 16
3	**L3**	BArF	dioxane	reflux	19	74	79 : 21
4	**L4**	BArF	dioxane	reflux	19	65	68 : 32
5	**L5**	BArF	dioxane	reflux	19	70	51 : 49
6	**L6**	BArF	dioxane	reflux	19	40	59: 41
7	**L7**	BArF	dioxane	reflux	19	99	56 : 44
8	**L8**	BArF	dioxane	reflux	19	68	65 : 35
9	**L9**	BArF	dioxane	reflux	19	61	52 : 48
10	**L1**	BArF	dioxane	80	19	34	90 : 10
11[c]	**L2**	BArF	dioxane	80	19	30	85 :1 5
12	**L3**	BArF	dioxane	80	19	80	82 : 18
13[b]	**L1**	BF_4	dioxane	80	48	95	80 : 20
14[b]	**L3**	BF_4	dioxane	80	19	90	91 : 9
15[b]	**L3**	BF_4	1,2-DCE	60	7	70	87 : 13
16[d]	**L3**	BF_4	CH_2Cl_2	50	19	95	89 : 11

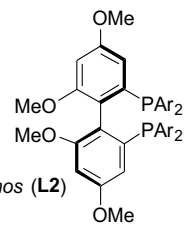
[a] **1a** was added to a solution of $[Ir(cod)_2X]$ (5 %) and **L** (5 %) in the solvent (125 mM) and the mixture was heated at the indicated temperature. Isolated yields. [b] Carried out at 250 mM (**1a**). [c] 67% conversion. [d] In a sealed tube.



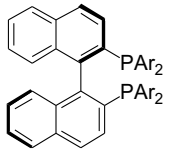
Ar = 3,5-Me_2-Ph, (*S*)-DM-SDP (**L1**)
Ar = Ph, (*S*)-SDP (**L4**)



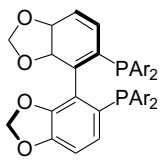
(R,R,S,S)-*Duanphos* (**L2**)



Ar = 3,5-$(CF_3)_2$-Ph, (*R*)-BTFM-*Garphos* (**L3**)
Ar = Ph, (*R*)-*Garphos* (**L5**),
Ar = 3,5-Me_2Ph, (*R*)-DM-*Garphos* (**L6**)

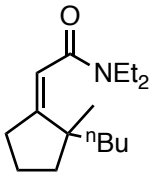


Ar = Ph, (**L7**): (*R*)-Binap
Ar = 3,5-Me_2Ph, (**L8**): (*R*)-DM-Binap

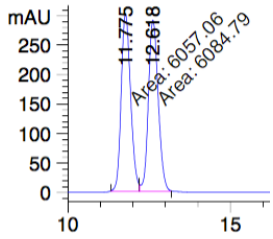


Ar = 3,5-Me_2Ph
(*R*)-*DM-Segphos* (**L9**)

Conditions for the determination of the er of 2a and HPLC traces of all entries of Table S2

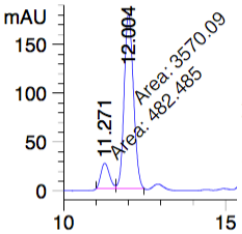


(*Z*)-2-(2-Butyl-2-methylcyclopentylidene)-*N*,*N*-diethylacetamide (2a). Enantiomeric ratios determined by chiral HPLC on Chiralpak IF3 at rt, (Hexane : iPrOH = 98:2, 1 ml/min).



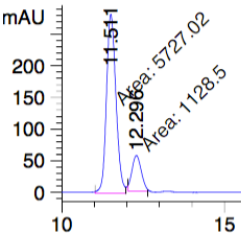
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	11.775	MF	0.3359	6057.06250	300.50378	49.8858
2	12.618	FM	0.3491	6084.78711	290.52817	50.1142

Figure S1. HPLC trace and report of a racemic sample of **2a** [Chiralpak IF3 at rt, (Hexane : iPrOH = 98:2, 1 ml/min)]



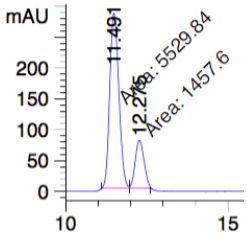
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	11.271	MF	0.3069	482.48453	26.20628	11.9056
2	12.004	FM	0.3327	3570.09497	178.86932	88.0944

Figure S2. HPLC trace and report of a sample of **2a** obtained from the reaction catalyzed by [Ir(cod)$_2$]BArF / **L1** at reflux (Chiralpak IF3 at rt, Hexane : iPrOH = 98:2, 1 ml/min). Table S2, entry 1.



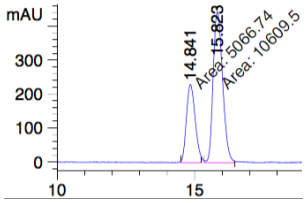
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	11.511	MM	0.3370	5727.01953	283.22543	83.5388
2	12.296	MM	0.3322	1128.50061	56.62397	16.4612

Figure S3. HPLC trace and report of a sample of **2a** obtained from the reaction catalyzed by [Ir(cod)$_2$]BArF / **L2** at reflux (Chiralpak IF3 at rt, Hexane : iPrOH = 98:2, 1 ml/min). Table S2, entry 2.



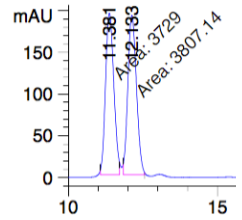
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	11.491	MF	0.3246	5529.83691	283.90775	79.1397
2	12.275	FM	0.3156	1457.60315	76.97363	20.8603

Figure S4. HPLC trace and report of a sample of **2a** obtained from the reaction catalyzed by [Ir(cod)$_2$]BArF / **L3** at reflux (Chiralpak IF3 at rt, Hexane : iPrOH = 98:2, 1 ml/min). Table S2, entry 3.



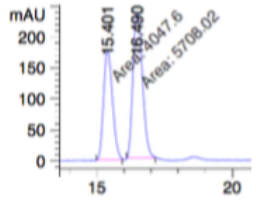
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	14.841	MF	0.3671	5066.73828	230.05960	32.3212
2	15.823	FM	0.3977	1.06095e4	444.60541	67.6788

Figure S5. HPLC trace and report of a sample of **2a** obtained from the reaction catalyzed by [Ir(cod)$_2$]BArF / **L4** at reflux (Chiralpak IF3 at rt, Hexane : iPrOH = 98:2, 1 ml/min). Table S2, entry 4.



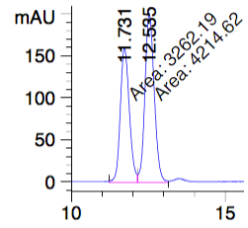
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	11.381	FM	0.3210	3729.00269	193.62558	49.4816
2	12.133	FM	0.3322	3807.14355	190.97899	50.5184

Figure S6. HPLC trace and report of a sample of **2a** obtained from the reaction catalyzed by [Ir(cod)$_2$]BArF / **L5** at reflux (Chiralpak IF3 at rt, Hexane : iPrOH = 98:2, 1 ml/min). Table S2, entry 5.



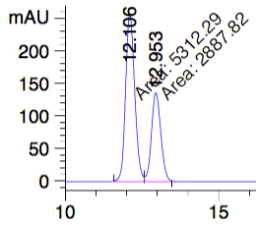
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	15.401	MM	0.3819	4047.59619	176.63699	41.4899
2	16.490	MM	0.4037	5708.02100	235.64784	58.5101

Figure S7. HPLC trace and report of a sample of **2a** obtained from the reaction catalyzed by [Ir(cod)$_2$]BArF / **L6** at reflux (Chiralpak IF3 at rt, Hexane : iPrOH = 98:2, 1 ml/min). Table S2, entry 6.



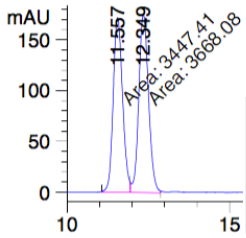
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	11.731	MF	0.3398	3262.18921	159.99806	43.6308
2	12.535	FM	0.3511	4214.61768	200.08028	56.3692

Figure S8. HPLC trace and report of a sample of **2a** obtained from the reaction catalyzed by [Ir(cod)$_2$]BArF / **L7** at reflux (Chiralpak IF3 at rt, Hexane : iPrOH = 98:2, 1 ml/min). Table S2, entry 7.



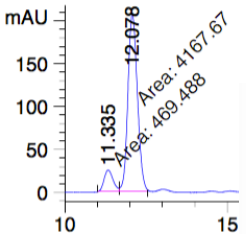
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	12.106	MF	0.3441	5312.29004	257.30539	64.7831
2	12.953	FM	0.3531	2887.82495	136.30952	35.2169

Figure S9. HPLC trace and report of a sample of **2a** obtained from the reaction catalyzed by [Ir(cod)$_2$]BArF / **L8** at reflux (Chiralpak IF3 at rt, Hexane : iPrOH = 98:2, 1 ml/min). Table S2, entry 8.



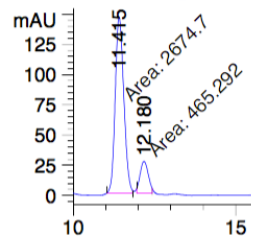
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	11.557	MF	0.3342	3447.41260	171.91162	48.4494
2	12.349	FM	0.3479	3668.07959	175.71895	51.5506

Figure S10. HPLC trace and report of a sample of **2a** obtained from the reaction catalyzed by [Ir(cod)$_2$]BArF / **L9** at reflux (Chiralpak IF3 at rt, Hexane : iPrOH = 98:2, 1 ml/min). Table S2, entry 9.



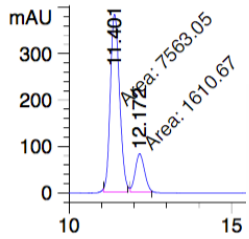
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	11.335	MF	0.3157	469.48810	24.78300	10.1245
2	12.078	FM	0.3370	4167.66797	206.09866	89.8755

Figure S11. HPLC trace and report of a sample of **2a** obtained from the reaction catalyzed by [Ir(cod)$_2$]BArF / **L1** at 80 ºC (Chiralpak IF3 at rt, Hexane : iPrOH = 98:2, 1 ml/min). Table S2, entry 10.



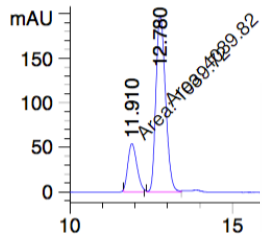
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	11.415	MM	0.3058	2674.69702	145.77469	85.1817
2	12.180	MM	0.2917	465.29156	26.58092	14.8183

Figure S12. HPLC trace and report of a sample of **2a** obtained from the reaction catalyzed by [Ir(cod)$_2$]BArF / **L2** at 80 ºC (Chiralpak IF3 at rt, Hexane : iPrOH = 98:2, 1 ml/min). Table S2, entry 11.



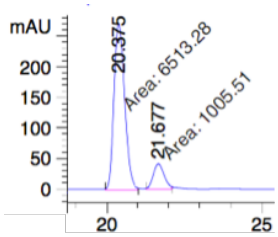
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	11.401	MF	0.3294	7563.05078	382.68466	82.4426
2	12.172	FM	0.3291	1610.67041	81.55900	17.5574

Figure S13. HPLC trace and report of a sample of **2a** obtained from the reaction catalyzed by [Ir(cod)$_2$]BArF / **L3** at 80 ºC (Chiralpak IF3 at rt, Hexane : iPrOH = 98:2, 1 ml/min). Table S2, entry 12.



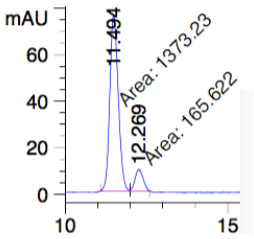
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	11.910	MF	0.3214	1039.71643	53.91303	20.4687
2	12.780	FM	0.3397	4039.82031	198.21083	79.5313

Figure S14. HPLC trace and report of a sample of **2a** obtained from the reaction catalyzed by $[Ir(cod)_2]BF_4$ / **L1** at 80 ºC (Chiralpak IF3 at rt, Hexane : iPrOH = 98:2, 1 ml/min). Table S2, entry 13.



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	20.375	MM	0.3995	6513.27783	271.72876	86.6267
2	21.677	MM	0.4062	1005.51215	41.25425	13.3733

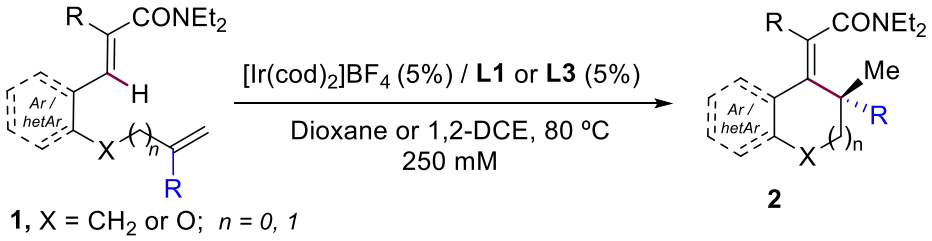
Figure S15 HPLC trace and report of a sample of **2a** obtained from the reaction catalyzed by $[Ir(cod)_2]BF_4$ / **L3** at 60 ºC in 1,2-DCE (Chiralpak IF3 at rt, Hexane : iPrOH = 98:2, 1 ml/min). Table S2, entry 15, Supporting information.



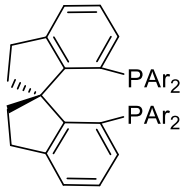
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	11.494	MF	0.3022	1373.22583	75.73701	89.2373
2	12.269	FM	0.2938	165.62189	9.39498	10.7627

Figure S16. HPLC trace and report of a sample of **2a** obtained from the reaction catalyzed by $[Ir(cod)_2]BF_4$ / **L3** at 50 ºC in CH_2Cl_2 (Chiralpak IF3 at rt, Hexane : iPrOH = 98:2, 1 ml/min). Table S2, entry 16, Supporting information.

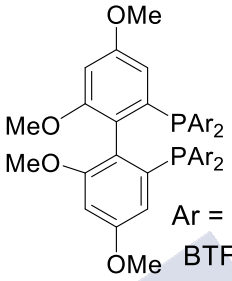
Procedure for the enantioselective Ir-catalyzed intramolecular hydrocarbonation process



1, X = CH_2 or O; *n = 0, 1*



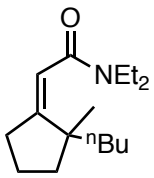
Ar = 3,5-Me_2-C_6H_2
Xylyl-SDP (**L1**)



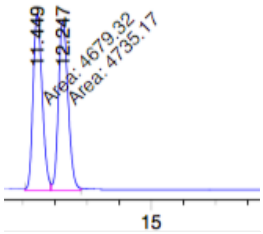
Ar = 3,5-$(CF_3)_2$-C_6H_2
BTFM-*Garphos* (**L3**)

An oven dried schlenk tube equipped with a Teflon septum and magnetic stir bar was charged with **L1** or **L3** (5 mol%), Bis(1,5-cyclooctadiene)iridium(I) tetrafluoroborate (5 mol%), the amide substrate (1.0 equiv) and the solvent (dioxane or 1,2-DCE, 0.250 M). The reaction mixture was then stirred at 80 °C. After TLC indicated full conversion of the starting material, the reaction mixture was concentrated in vacuo. Purification of the crude product by flash chromatography on silica gel (typically 1:20 to 1:10 EtOAc : hexanes) afforded the desired product.

(*Z*)-2-(2-Butyl-2-methylcyclopentylidene)-*N*,*N*-diethylacetamide (2a)

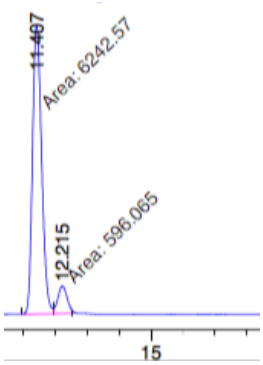


Using the general procedure, dioxane and **L3**, (*Z*)-2-(2-butyl-2-methylcyclopentylidene)-*N*,*N*-diethylacetamide (**2a**) was obtained in 90 % yield and 91:9 er. Enantioselectivity was determined by chiral HPLC analysis on Chiralpak IF3 at rt, (Hexane : iPrOH = 98:2, 1 ml/min).



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	11.449	MF	0.3305	4679.32031	235.95372	49.7034
2	12.247	FM	0.3449	4735.16895	228.80946	50.2966

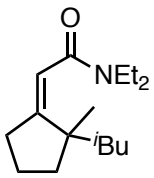
Figure S17. HPLC trace and report of a racemic sample of **2a** [Chiralpak IF3 at rt, (Hexane : iPrOH = 98:2, 1 ml/min)]



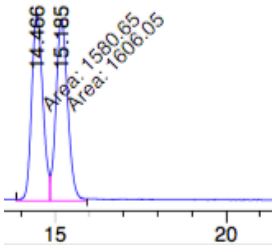
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	11.407	MF	0.3315	6242.56934	313.85229	91.2839
2	12.215	FM	0.3332	596.06464	29.81482	8.7161

Figure S18. HPLC trace and report of a sample of **2a** obtained from the reaction catalyzed by $[Ir(cod)_2]BF_4$ / **L3** (Chiralpak IF3 at rt, Hexane : iPrOH = 98:2, 1 ml/min). Table 4, entry 5, main manuscript or Table S2, entry 14.

(*Z*)-*N*,*N*-Diethyl-2-(2-isobutyl-2-methylcyclopentylidene)acetamide (2e)

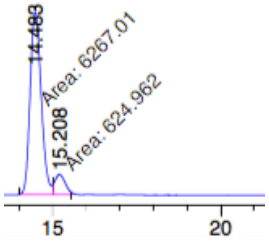


Using the general procedure, 1,2-DCE and **L3**, (*Z*)-*N*,*N*-diethyl-2-(2-isobutyl-2-methylcyclopentylidene)acetamide (**2e**) was obtained in 82 % yield and 91:9 er. Enantioselectivity was determined by chiral HPLC analysis on Chiralpak IF3 at rt, (Hexane : iPrOH = 99:1, 1 ml/min).



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	14.466	MF	0.3769	1580.64807	69.90287	49.6015
2	15.185	FM	0.3957	1606.04871	67.64574	50.3985

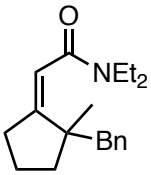
Figure S19. HPLC trace and report of a racemic sample of **2e** [Chiralpak IF3 at rt, (Hexane : iPrOH = 99:1, 1 ml/min)]



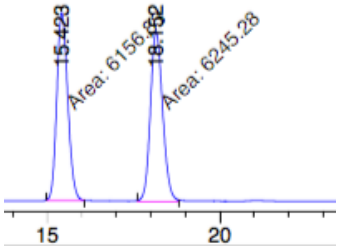
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	14.483	MF	0.3807	6267.01074	274.34186	90.9320
2	15.208	FM	0.3457	624.96240	30.12778	9.0680

Figure S20. HPLC trace and report of a sample of **2e** obtained from the reaction catalyzed by $[Ir(cod)_2]BF_4$ / **L3** (Chiralpak IF3 at rt, Hexane : iPrOH = 99:1, 1 ml/min). Table 4, entry 8, main manuscript.

(*Z*)-2-(2-Benzyl-2-methylcyclopentylidene)-*N*,*N*-diethylacetamide (2g)

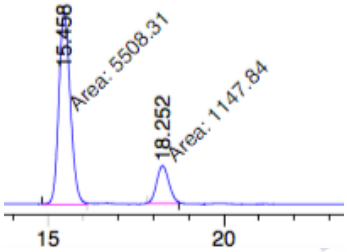


Using the general procedure, dioxane and **L1** (10 mol%), (*Z*)-2-(2-benzyl-2-methylcyclopentylidene)-*N*,*N*-diethylacetamide (**2g**) was obtained after 48 hours in 81 % yield and 83:17 er. Enantioselectivity was determined by chiral HPLC analysis on Chiralpak IF3 at rt, (Hexane : iPrOH = 98:2, 1 ml/min).



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	15.423	MM	0.3656	6156.83203	280.66541	49.6434
2	18.152	MM	0.4099	6245.27832	253.94766	50.3566

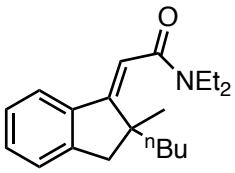
Figure S21. HPLC trace and report of a racemic sample of **2g** [Chiralpak IF3 at rt, (Hexane : iPrOH = 98:2, 1 ml/min)]



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	15.458	MM	0.3776	5508.30713	243.11473	82.7551
2	18.252	MM	0.4017	1147.84314	47.62255	17.2449

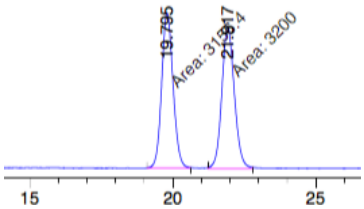
Figure S22. HPLC trace and report of a sample of **2g** obtained from the reaction catalyzed by $[Ir(cod)_2]BF_4$ / **L1** (Chiralpak IF3 at rt, Hexane : iPrOH = 98:2, 1 ml/min). Table 4, entry 9, main manuscript.

(*E*)-2-(2-Butyl-2-methyl-2,3-dihydro-1*H*-inden-1-ylidene)-*N*,*N*-diethylacetamide (2l)



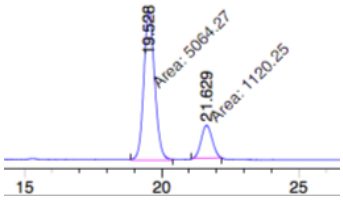
Using the general procedure, dioxane and DM-SDP (**L1,** 10 %), (*E*)-2-(2-butyl-2-methyl-2,3-dihydro-1*H*-inden-1-ylidene)-*N*,*N*-diethylacetamide (**2l**) was obtained after 48 hours in 98 % yield and 82:18 er. Enantioselectivity was determined by chiral HPLC analysis on Chiralpak IF3 at rt, (Hexane : iPrOH = 99:1, 1 ml/min).

Note: In this reaction, DM-SDP (**L1**) proved to be superior to BTFM-Garphos, which provided the product **2l** in 95% yield and 61:39 er (5% catalyst, dioxane, 80 ºC for 19 h)}.



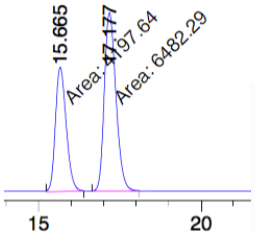
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	19.795	MM	0.4599	3156.39917	114.37659	49.6570
2	21.917	MM	0.5085	3200.00488	104.89346	50.3430

Figure S23. HPLC trace and report of a racemic sample of **2l** [Chiralpak IF3 at rt, (Hexane : iPrOH = 99:1, 1 ml/min)]



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	19.528	MM	0.4617	5064.27246	182.83029	81.8862
2	21.629	MM	0.4619	1120.25403	40.42273	18.1138

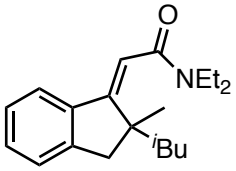
Figure S24. HPLC trace and report of a sample of **2l** obtained from the reaction catalyzed by $[Ir(cod)_2]BF_4$ / **L1** (Chiralpak IF3 at rt, Hexane : iPrOH = 99:1, 1 ml/min). Table 4, entry 10, main manuscript.



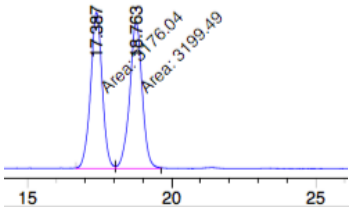
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	15.665	MM	0.3834	4197.64307	182.45636	39.3040
2	17.177	MM	0.4134	6482.28809	261.31970	60.6960

Figure S25. HPLC trace and report of a sample of **2l** obtained from the reaction catalyzed by $[Ir(cod)_2]BF_4$ / BTFM-Garphos (Chiralpak IF3 at rt, Hexane : iPrOH = 99:1, 1 ml/min).

(*E*)-*N*,*N*-Diethyl-2-(2-isobutyl-2-methyl-2,3-dihydro-1*H*-inden-1-ylidene)acetamide (2m)

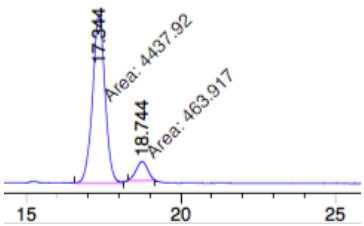


Using the general procedure, dioxane and DM-SDP (**L1**, 10 %), (*E*)-*N*,*N*-diethyl-2-(2-isobutyl-2-methyl-2,3-dihydro-1*H*-inden-1-ylidene)acetamide (**2m**) was obtained after 48 hours in 95 % yield and 91:9 er. Enantioselectivity was determined by chiral HPLC analysis on Chiralpak IF3 at rt, (Hexane : iPrOH = 99:1, 1 ml/min). {**Note**: In this reaction, DM-SDP (**L1**) proved to be superior to BTFM-Garphos, which provided the product **2m** in 90% yield and 71:29 er (5% catalyst, dioxane, 80 ºC for 19 h)}.



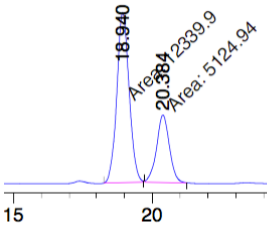
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	17.387	MF	0.4678	3176.03662	113.16500	49.8160
2	18.763	FM	0.5043	3199.49341	105.74580	50.1840

Figure S26. HPLC trace and report of a racemic sample of **2m** [Chiralpak IF3 at rt, (Hexane : iPrOH = 99:1, 1 ml/min)]



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	17.344	MM	0.4697	4437.91992	157.46263	90.5358
2	18.744	MM	0.4331	463.91736	17.85435	9.4642

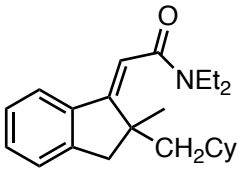
Figure S27. HPLC trace and report of a sample of **2m** obtained from the reaction catalyzed by $[Ir(cod)_2]BF_4$ / **L1** (Chiralpak IF3, rt, Hex.: iPrOH = 99:1, 1 ml/min). Table 4, entry 11, main manuscript.



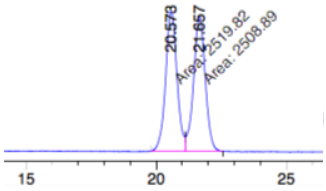
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	18.940	MM	0.5086	1.23399e4	404.40640	70.6557
2	20.384	MM	0.5334	5124.94287	160.14006	29.3443

Figure S28. HPLC trace and report of a sample of **2m** obtained from the reaction catalyzed by $[Ir(cod)_2]BF_4$ / BTFM-Garphos (**L3**) (Chiralpak IF3 at rt, Hexane : iPrOH = 99:1, 1 ml/min).

(*E*)-2-(2-(Cyclohexylmethyl)-2-methyl-2,3-dihydro-1*H*-inden-1-ylidene)-*N*,*N*-diethylacetamide (2n)

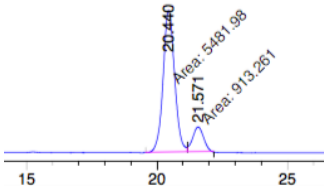


Using the general procedure, dioxane and DM-SDP (**L1,** 10 %), (*E*)-2-(2-(cyclohexylmethyl)-2-methyl-2,3-dihydro-1*H*-inden-1-ylidene)-*N*,*N*-diethylacetamide (**2n**) was obtained after 48 hours in 90 % yield and 86:14 er. Enantioselectivity was determined by chiral HPLC analysis on Chiralpak IF3 at rt, (Hexane : iPrOH = 99:1, 1 ml/min). {**Note**: In this reaction, DM-SDP (**L1**) proved to be superior to BTFM-Garphos, which provided the product **2n** in 85% yield and a 66:34 er (5 mol% catalyst, Dioxane, 80 ºC for 19 h)}.



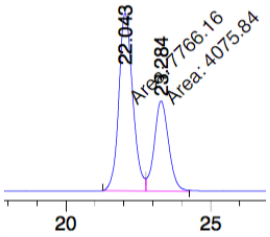
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	20.573	MF	0.5038	2519.82080	83.35898	50.1087
2	21.657	FM	0.5196	2508.88721	80.47191	49.8913

Figure S29. HPLC trace and report of a racemic sample of **2n** [Chiralpak IF3 at rt, (Hexane : iPrOH = 99:1, 1 ml/min)]



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	20.440	MF	0.5087	5481.98291	179.59882	85.7197
2	21.571	FM	0.4845	913.26099	31.41613	14.2803

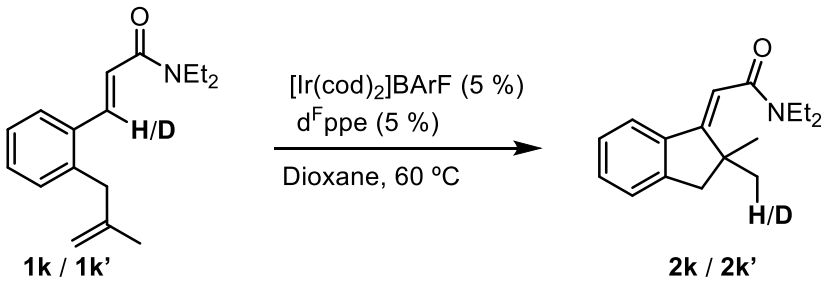
Figure S30. HPLC trace and report of a sample of **2n** obtained from the reaction catalyzed by $[Ir(cod)_2]BF_4$ / **L1** (Chiralpak IF3 at rt, Hexane : iPrOH = 99:1, 1 ml/min). Table 4, entry 12, main manuscript.



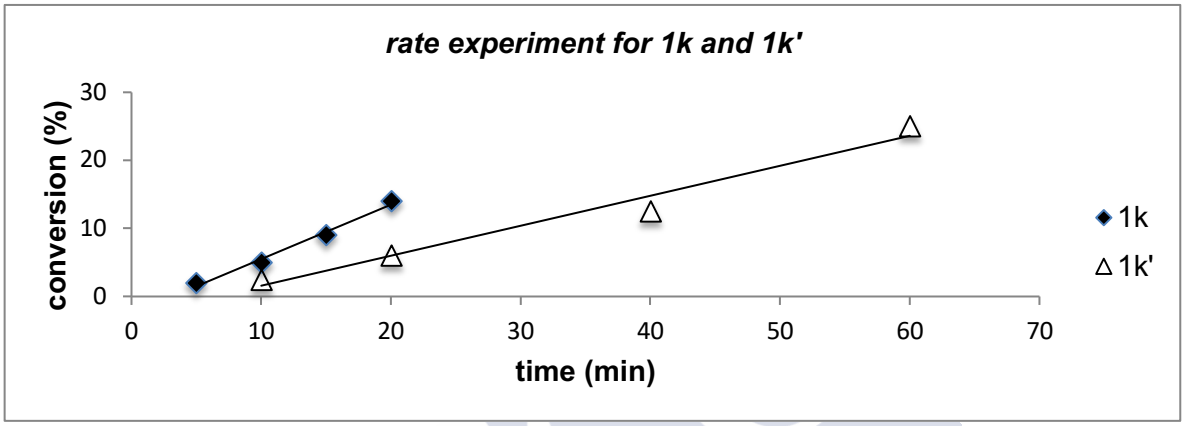
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	22.043	MF	0.5560	7766.16162	232.81895	65.5815
2	23.284	FM	0.5755	4075.84155	118.03354	34.4185

Figure S31. HPLC trace and report of a sample of **2n** obtained from the reaction catalyzed by $[Ir(cod)_2]BF_4$ / BTFM-Garphos (**L3**).

Determination of the Kinetic Isotope effect



1k / 1k' **2k / 2k'**



In two different Schlenk flasks equipped with their respective stirring bars, Ir(cod)$_2$BArF (24.7 mg, 0.019 mmol), dpp^{F}e (14.7 mg, 0.019 mmol) and **1k** (100 mg, 0.389 mmol, Schlenk 1) or **1k'** (101 mg, 0.389 mmol, Schlenk 2), were successively added under Argon. Dioxane (1.6 mL, each one) was then added and the flasks were sealed with rubber septa and placed in a pre-heated (70 °C) oil bath. Aliquots (300 μL) were taken at the times indicated in the Table S3 (for **1k**) and Table S4 (for **1k'**). The aliquots were filtered through a florisil pad and the volatiles were removed so that the the crude residues were taken and analyzed by ^{1}H NMR.

Table S3. Conversions observed from the reaction of **1k** (determined by ^{1}H-NMR analysis).

t (min)	2k (%)
5	2
10	5
15	9
20	14

y = 0,8x - 2,5
R² = 0,98765

Table S4. Conversions observed from the reaction of **1k'** (determined by ^{1}H-NMR analysis)..

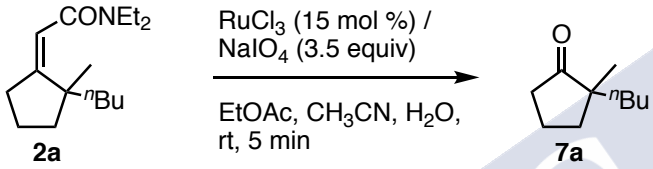
t (min)	2k' (%)
10	2.5
20	6
40	12.5
60	25

y' = 0,4407x' - 2,822
R^2 = 0,97263

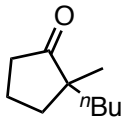
KIE= (0.8)/(0.4407)=1.8

Transformation of the products into the corresponding ketone derivatives.

Synthesis of ketones 7a, 7g, 7m and 7q (exemplified for **7a**).

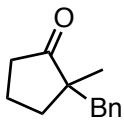


2-Butyl-2-methylcyclopentan-1-one (7a)



A solution of $NaIO_4$ (89.3 mg, 0.42 mmol) in water (0.7 mL, 0.17 M) was added to a solution of $RuCl_3$ (3.7 mg, 0.018 mmol) in MeCN (0.9 mL, 0.13 M). This mixture was stirred 2 minutes and then a solution of the **2a** (30 mg, 0.12 mmol) in EtOAc (0.9 mL, 0.13 M) was added. The mixture was stirred for 5-10 minutes until TLC indicates complete consumption of the starting material. $MgSO_4$ was added and the resulting heterogeneous mixture was washed with EtOAc. The combined organic phases were carefully evaporated and the crude residue was purified by column chromatography (1:10 Et_2O : Pentane) to yield **7a** as a colorless oil (17 mg, 93% yield). **^{1}H NMR** (500 MHz, $CDCl_3$): δ 2.32 – 2.13 (m, 2H), 1.93 – 1.82 (m, 3H), 1.73 – 1.63 (m, 1H), 1.42 – 1.23 (m, 5H), 1.17 – 1.07 (m, 1H), 0.98 (s, 3H), 0.88 (t, *J* = 7.0 Hz, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$): δ 223.95 (C), 48.43 (C), 37.85 (CH_2), 36.57 (CH_2), 35.81 (CH_2), 26.63 (CH_2), 23.43 (CH_2), 21.99 (CH_3), 18.85 (CH_2), 14.12 (CH_3). **HRMS** (APCI-FIA-TOF): m/z calculated for $C_{10}H_{19}O$ ($[M+H]^+$) 155.1431, found 155.1430.

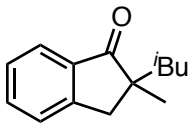
2-Benzyl-2-methylcyclopentan-1-one (7g)



Colorless oil, 85% yield. **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.21 – 7.17 (m, 2H), 7.16 – 7.11 (m, 1H), 7.05 – 7.02 (m, 2H), 2.79 (d, *J* = 13.3 Hz, 1H), 2.52 (d, *J* = 13.3 Hz, 1H), 2.22 (ddd, *J* = 18.9, 8.4, 5.3 Hz, 1H), 1.98 (dt, *J* = 19.0, 8.6 Hz, 1H), 1.89 (dt, *J* = 13.0, 7.6 Hz, 1H), 1.76 – 1.62 (m, 2H), 1.59 – 1.53 (m, 1H), 0.95 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$): δ 223.39 (C), 138.12 (C), 130.38 (CH), 128.26 (CH), 126.50 (CH), 49.89 (C), 42.81 (CH_2), 38.13 (CH_2), 34.79 (CH_2),

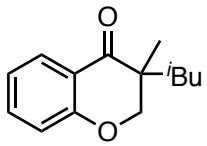
22.84 (CH_3), 18.75 (CH_2). **HRMS** (ESI-TOF): m/z calculated for $C_{13}H_{16}NaO$ ($[M+Na]^+$) 211.1091, found 211.1093.

2-Isobutyl-2-methyl-2,3-dihydro-1*H*-inden-1-one (7m)



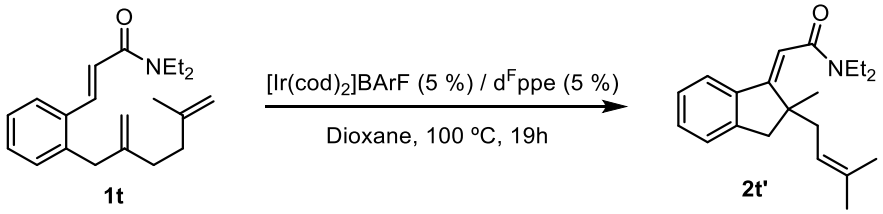
Colorless oil, 66% yield. **^{1}H NMR** (400 MHz, $CDCl_3$):δ 7.76 (d, *J* = 7.6 Hz, 1H), 7.58 (td, *J* = 7.5, 1.2 Hz, 1H), 7.43 (dt, *J* = 7.7, 1.0 Hz, 1H), 7.39 – 7.34 (m, 1H), 3.21 (d, *J* = 17.2 Hz, 1H), 2.88 (d, *J* = 17.2 Hz, 1H), 1.69 – 1.61 (m, 2H), 1.59 – 1.50 (m, 1H), 1.19 (s, 3H), 0.90 (d, *J* = 6.4 Hz, 3H), 0.78 (d, *J* = 6.5 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 211.70 (C), 152.82 (C), 136.06 (C), 134.85 (CH), 127.50 (CH), 126.70 (CH), 124.46 (CH), 49.25 (C), 46.57 (CH_2), 40.61 (CH_2), 25.48 (C), 25.33 (CH_3), 24.94 (CH_3), 23.75 (CH_3). **HRMS** (ESI-TOF): m/z calculated for $C_{14}H_{19}O$ ($[M+H]^+$) 203.1430, found 203.1430.

3-Isobutyl-3-methylchroman-4-one (7q)



Colorless oil, 87% yield. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.89 (dd, *J* = 7.9, 1.8 Hz, 1H), 7.46 (ddd, *J* = 8.4, 7.2, 1.8 Hz, 1H), 7.02 (ddd, *J* = 8.1, 7.1, 1.1 Hz, 1H), 6.95 (dd, *J* = 8.4, 1.1 Hz, 1H), 4.27 (d, *J* = 11.5 Hz, 1H), 4.13 (d, *J* = 11.5 Hz, 1H), 1.77 – 1.67 (m, 1H), 1.61 (dd, *J* = 6.0, 2.1 Hz, 2H), 1.18 (s, 3H), 0.93 (d, *J* = 6.6 Hz, 3H), 0.83 (d, *J* = 6.5 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$): 197.41 (C), 161.12 (C), 135.56 (CH), 127.92 (CH), 121.56 (CH), 120.15 (C), 117.66 (CH), 75.62 (CH_2), 45.19 (CH), 42.86 (CH_2), 24.82 (CH_3), 24.69 (CH_3), 24.34 (CH), 18.70 (CH_3). **HRMS** (ESI-TOF): m/z calculated for $C_{14}H_{19}O_2$ ($[M+H]^+$) 219.1378, found 219.1380.

Cycloisomerization of 1t to afford the isomerized indene product 2t'



Carried out following the general procedure, in Dioxane at reflux for 19 h. The product (**2t'**) was isolated by flash chromatography (5 to 10 % EtOAc/Hexanes) as a pale yellow oil (99 % yield). **(*E*)-*N*,*N*-Diethyl-2-(2-methyl-2-(3-methylbut-2-en-1-yl)-2,3-dihydro-1*H*-inden-1-ylidene) acetamide (2t') ^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.46 (dd, *J* = 8.1, 1.6 Hz, 1H), 7.29 – 7.17 (m, 3H), 6.44 (s, 1H), 5.09 – 5.02 (m, 1H), 3.51 – 3.32 (m, 4H), 3.04 (d, *J* = 16.4 Hz, 1H), 2.65 (d, *J* = 16.4 Hz, 1H), 2.61 – 2.43 (m, 2H), 1.63 (s, 3H), 1.59 (s, 3H), 1.40 (s, 3H), 1.21 – 1.13 (m, 6H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 167.61 (C), 157.90 (C), 145.09 (C), 140.87 (C), 133.33 (C), 129.41 (CH), 126.60 (CH), 125.43 (CH), 121.54 (CH), 120.98 (CH), 112.22 (CH), 48.21 (C), 45.15 (CH_2), 42.83 (CH_2), 39.46 (CH_2), 36.95 (CH_2), 26.02 (CH_3), 18.24 (CH_3), 14.09 (CH_3), 12.92 (CH_3). **HRMS** (ESI-TOF): m/z calculated for $C_{21}H_{30}NO$ ([M+H]$^+$) 312.2322, found 312.2322. Assignment of structure of **2t'** was based on the HMBC, HSQC, COSY and nOe experiments.

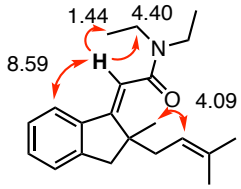
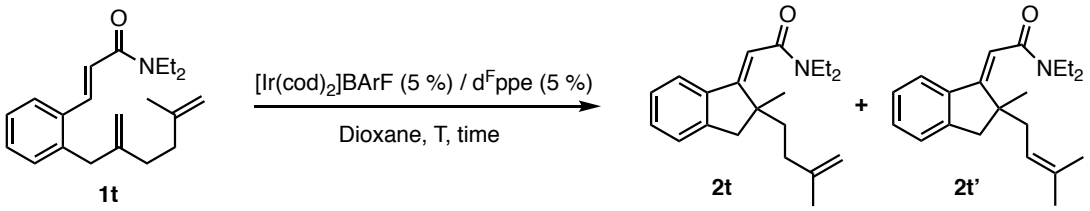


Figure S1. Significant nOe signals observed for **2t'**

The following control experiments, carrying out the cyclization of **1t** at lower temperatures indicate that the observed isomerization of the pendant double bond occurs in the reaction media, after the initial formation of the expected, non-isomerized, product **2t.**

Table S3. Control experiments related to the cycloisomerization of **1t** (ref. 21, main manuscript)

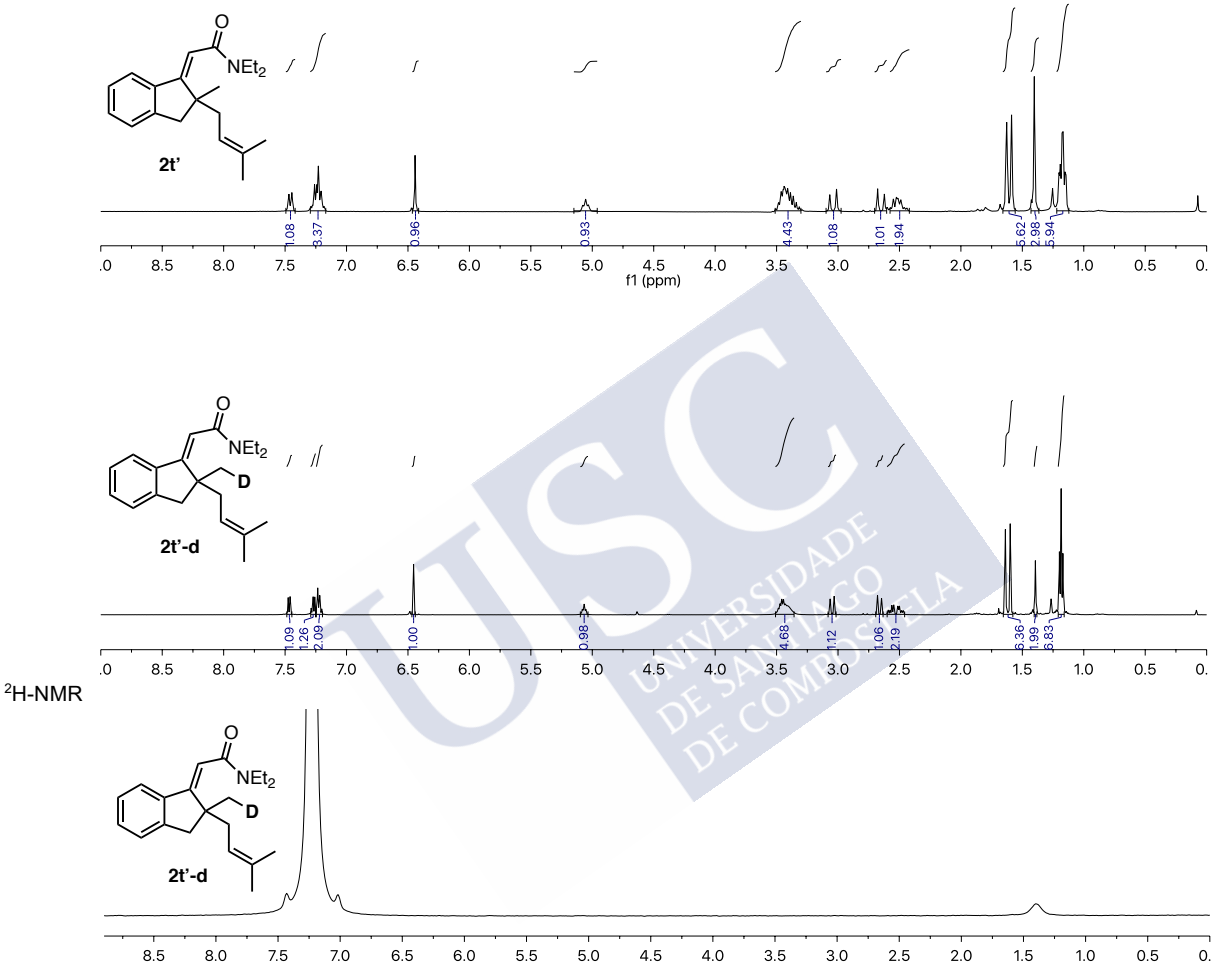


entry	Temperature	time (h)	Conversion	**2t** (%)	**2t'** (%)
1	60 ºC	1	55%	55	-
2	100 ºC	1	70%	20	50
3	100 ºC	18	100%	-	99

Mechanistic probe: NMR spectra of D-2t', resulting from the cycloaddition of D-1t (related to Scheme 3, eq. 2, main manuscript)

As can be seen in the following Figures, deuteration of D-**2t'** is only observed at the methyl group of the quaternary stereocenter (signal at 1.40 ppm). While in **2t'** the signal for this methyl group integrates for 3H, that of D-**2t'** corresponds to 2H. Accordingly, ^{2}H-NMR spectra of D-**2t'** shows that deuterium is only located at this particular methyl group (1.40 ppm).

^{1}H-NMR



^{2}H-NMR

Figure S14. ^{1}H-NMR and ^{2}H-NMR of **2t'** and D-**2t'.**

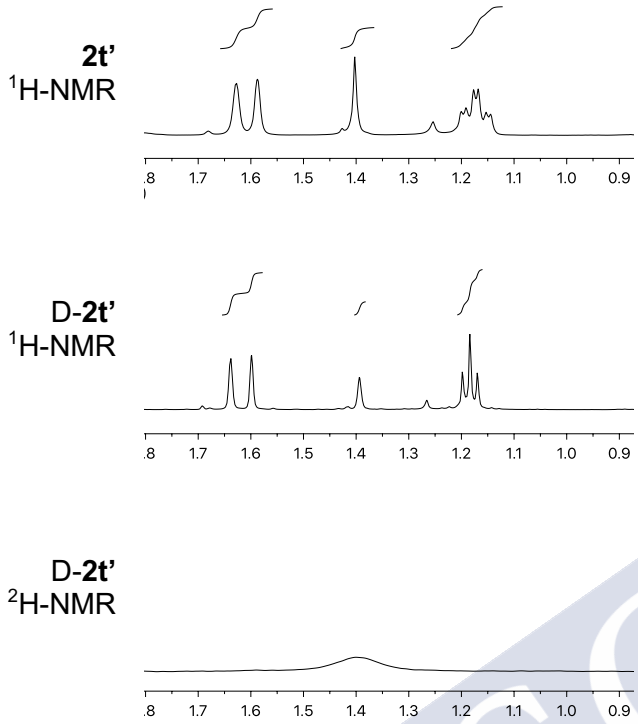


Figure S15. Amplified NMR window between 1.8 and 0.9 ppm (**2t'** and D-**2t'**)

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SUPPORTING INFORMATION

Iridium(I)-Catalyzed Intramolecular Cycloisomerization of Enynes: Scope and Mechanistic Course

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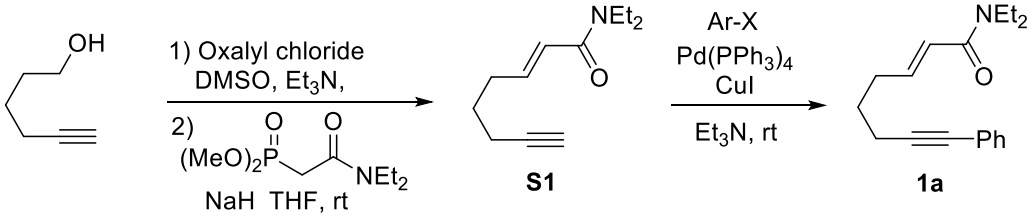
General Procedures

Dry solvents were freshly distilled under argon from an appropriate drying agent before use. Bis(cyclooctadiene)iridium(I) tetrakis(3,5-bis(trifluoromethyl) phenyl) borate, Bis(1,5-cyclooctadiene)iridium(I) tetrafluoroborate, (±)-BINAP, 1,2-Bis[bis(pentafluoro-phenyl)phosphino]ethane (abbreviated as d^Fppe) were purchased from Aldrich. 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.

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 approximately at 23 °C. Reaction mixtures were stirred using Teflon-coated magnetic stirring bars. Reaction temperatures were maintained using Thermowatch-controlled silicone oil baths. Thin-layer chromatography (TLC) was performed on silica gel plates and components were visualized by observation under UV light, and / or 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 or $MgSO_4$. Concentration refers to the removal of volatile solvents via distillation using a Büchi rotary evaporator followed by residual solvent removal under high vacuum. Melting points (m.p.) were determined with an M-560 BÜCHI apparatus. NMR spectra were recorded in $CDCl_3$, at 300 MHz (Varian), 400 MHz (Varian) or 500 MHz (Varian), unless other solvent is specified. Carbon types and structure assignments were determined from DEPT-NMR. NMR spectra were analyzed using MestreNova© NMR data processing software (www.mestrelab.com). 1,3,5-Trimethoxybenzene was used as internal standard. 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. Mass spectra (ESI-MS) were acquired using IT-MS Bruker AmaZon SL at CIQUS and also using chemical ionization (CI) electron impact (EI), or electrospray ionization (ESI) at the CACTUS facility of the University of Santiago de Compostela. The reactions were monitored by TLC.

Synthesis of the substrates for catalysis

General procedure (A) for preparation of precursors 1a-1h (exemplified for the synthesis of (*E*)-*N*,*N*-Diethyl-8-phenyloct-2-en-7-ynamide, **1a**).



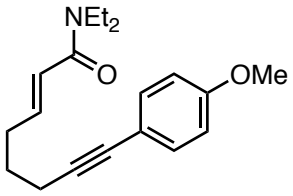
DMSO (10.4 mL, 146.7 mmol) in CH_2Cl_2 (16.0 mL) was added dropwise to a solution of oxalyl chloride (6.3 mL, 73.4 mmol) in CH_2Cl_2 (230.0 mL) at –78 °C. The reaction was stirred for 10 min and then a solution of hex-5-yn-1-ol (4.0 g, 40.8 mmol) in CH_2Cl_2 (29 mL,) was added slowly. After 45 min Et_3N (28.3 mL, 203.7 mmol) was added at –78 °C. After stirring at that temperature for 30 min, the mixture was warmed to rt and stirred for 30 min. H_2O (150 mL) was then added, the organic phase was separated and washed with HCl (1.0 M solution), $NaHCO_3$ (sat) and brine. The organic phases was dried and carefully concentrated under vacuum at 0 °C. The crude Hex-5-ynal was obtained in quantitative yield as yellow oil and submitted to the next step without purification. The NMR and MS data were consistent with those previously published.[1]

Dimethyl (2-(diethylamino)-2-oxoethyl) phosphonate[2] (10.2 g, 40.6 mmol) was added dropwise to a suspension of NaH (60 %) (1.5 g, 37.5 mmol) in THF (195.0 mL) at rt. The mixture was stirred for 15 minutes before the crude Hex-5-ynal (3.0 g, 31.2 mmol) was added dropwise to the mixture. After one hour, water and Et_2O were successively added and the layers were separated. The organic phase was washed with water (2 x 30 mL). The aqueous combined phases were extracted with CH_2Cl_2 (2 x 30 mL) and the combined organic phases were dried and concentrated. Purification of the crude residue by flash chromatography on silica gel (1:10 to 1:3 EtOAc: Hexanes) afforded (*E*)-*N*,*N*-Diethyloct-2-en-7-ynamide (**S1**) as colorless oil (4.3 g, 71 % yield). **^{1}H NMR** (300 MHz, $CDCl_3$): δ 6.82 (dt, *J* = 14.6, 7.1 Hz, 1H), 6.20 (d, *J* = 15.0 Hz, 1H), 3.44 – 3.28 (m, 4H), 2.30 (q, *J* = 7.3 Hz, 2H), 2.18 (td, *J* = 7.0, 2.5 Hz, 2H), 1.93 (t, *J* = 2.7 Hz, 1H), 1.65 (p, *J* = 7.2 Hz, 2H), 1.19 – 1.06 (m, 6H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 165.70 (C), 144.54 (CH), 121.47 (CH), 83.78 (C), 68.87 (CH), 42.17 (CH_2), 40.84 (CH_2), 31.26 (CH_2), 27.10 (CH_2), 17.88 (CH_2), 14.92 (CH_3), 13.21 (CH_3). **HRMS** (ESI-TOF): m/z calculated for $C_{12}H_{20}NO$ ($[M+H]^+$) 194.1533, found 194.1539.

A Schlenk tube under argon equipped with a Teflon septum and magnetic stir bar was charged with CuI (39.6 mg, 0.20 mmol) and $Pd(PPh_3)_4$ (120.2 mg, 0.10 mmol). Et_3N (23.1 mL), iodobenzene (0.78 mL, 6.9 mmol) and (*E*)-*N*,*N*-diethyloct-2-en-7-ynamide (**S1**, 670 mg, 3.47 mmol) were sequentially added. The reaction mixture was stirred at rt. After 20 h, the reaction mixture was concentrated in vacuo. Purification of the crude product by flash chromatography on silica gel (1:10

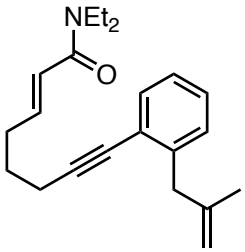
to 1:3 EtOAc: Hexane) afforded (*E*)-*N*,*N*-Diethyl-8-phenyloct-2-en-7-ynamide (**1a**) as a pale yellow oil (793 mg, 85% yield). **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.38 – 7.30 (m, 2H), 7.25 – 7.17 (m, 3H), 6.86 (dt, *J* = 14.5, 7.0 Hz, 1H), 6.26 – 6.16 (m, 1H), 3.43 – 3.23 (m, 4H), 2.45 – 2.28 (m, 4H), 1.78 – 1.64 (m, 2H), 1.20 – 1.03 (m, 6H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 165.58 (C), 144.55 (CH), 131.42 (CH), 128.12 (CH), 127.52 (CH), 123.77 (C), 121.34 (CH), 89.29 (C), 81.18 (C), 42.04 (CH_2), 40.70 (CH_2), 31.33 (CH_2), 27.23 (CH_2), 18.75 (CH_2), 14.79 (CH_3), 13.10 (CH_3). **HRMS** (ESI-TOF): m/z calculated for $C_{18}H_{24}NO$ ($[M+H]^+$) 270.1850, found 270.1852.

(*E*)-*N*,*N*-Diethyl-8-(4-methoxyphenyl)oct-2-en-7-ynamide (1b)



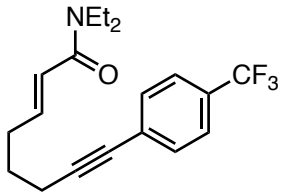
This compound was prepared according to the previously described general procedure **A**, using p-methoxyiodobencene as coupling partner. 66 % yield, yellowish oil. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.27 (d, *J* = 8.6 Hz, 2H), 6.86 (dt, *J* = 14.6, 7.1 Hz, 1H), 6.75 (d, *J* = 8.7 Hz, 2H), 6.20 (d, *J* = 15.4 Hz, 1H), 3.72 (s, 3H), 3.41 – 3.25 (m, 4H), 2.42 – 2.28 (m, 4H), 1.70 (p, *J* = 7.2 Hz, 2H), 1.17 – 1.04 (m, 6H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 165.62 (C), 159.01 (C), 144.71 (CH), 132.77 (CH), 121.26 (CH), 115.91 (C), 113.75 (CH), 87.66 (C), 80.89 (C), 55.15 (CH_3), 42.06 (CH_2), 40.72 (CH_2), 31.39 (CH_2), 27.34 (CH_2), 18.79 (CH_2), 14.82 (CH_3), 13.12 (CH_3). **HRMS** (ESI-TOF): m/z calculated for $C_{19}H_{26}NO_2$ ($[M+H]^+$) 300.1958, found 300.1958.

(*E*)-*N*,*N*-Diethyl-8-(2-(2-methylallyl)phenyl)oct-2-en-7-ynamide (1c)



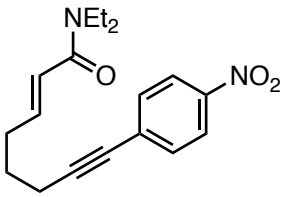
This compound was prepared according to the previously described general procedure **A**, using the corresponding iodophenyl derivative for the coupling reaction. 80 % yield, yellowish oil. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.36 (d, *J* = 7.4 Hz, 1H), 7.20 – 7.07 (m, 3H), 6.95 – 6.83 (m, 1H), 6.23 (d, *J* = 15.0 Hz, 1H), 4.78 (s, 1H), 4.63 (s, 1H), 3.48 (s, 2H), 3.41 – 3.30 (m, 4H), 2.46 (t, *J* = 6.9 Hz, 2H), 2.42 – 2.34 (m, 2H), 1.76 (q, *J* = 7.2 Hz, 2H), 1.70 (s, 3H), 1.19 – 1.09 (m, 6H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 165.70 (C), 144.80 (CH), 144.62 (C), 141.38 (C), 132.17 (CH), 129.09 (CH), 127.69 (CH), 125.99 (CH), 123.81 (C), 121.36 (CH), 111.90 (CH_2), 93.01 (C), 80.00 (C), 42.50 (CH_2), 42.16 (CH_2), 40.84 (CH_2), 31.50 (CH_2), 27.51 (CH_2), 22.44 (CH_3), 19.04 (CH_2), 14.91 (CH_3), 13.21 (CH_3). **HRMS** (ESI-TOF): m/z calculated for $C_{22}H_{30}NO$ ($[M+H]^+$) 324.2321, found 324.2322.

(*E*)-*N,N*-Diethyl-8-(4-(trifluoromethyl)phenyl)oct-2-en-7-ynamide (1d)



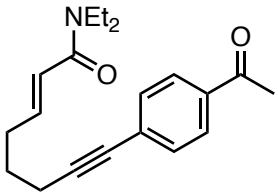
This compound was prepared according to the previously described general procedure **A**, using the corresponding bromo aryl derivative for the coupling reaction. 81 % yield, colorless oil. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.42 – 7.24 (m, 4H), 6.85 – 6.67 (m, 1H), 6.11 (d, *J* = 15.0 Hz, 1H), 3.32 – 3.08 (m, 4H), 2.38 – 2.15 (m, 4H), 1.69 – 1.52 (m, 2H), 1.07 – 0.89 (m, 6H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 165.37 (C), 144.22 (CH), 131.60 (CH), 129.05 (C, q, *J* = 32.5 Hz), 127.67 (C), 124.85 (CH, q, *J* = 3.6 Hz), 123.86 (CF_3, q, *J* = 272.0 Hz), 121.37 (CH), 92.19 (C), 79.92 (C), 41.93 (CH_2), 40.61 (CH_2), 31.23 (CH_2), 26.99 (CH_2), 18.64 (CH_2), 14.60 (CH_3), 12.92 (CH_3). **HRMS** (ESI-TOF): m/z calculated for $C_{19}H_{23}F_3NO$ ($[M+H]^+$) 338.1726, found 338.1724.

(*E*)-*N,N*-Diethyl-8-(4-nitrophenyl)oct-2-en-7-ynamide (1e)



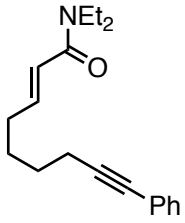
This compound was prepared according to the previously described general procedure **A**, using the corresponding p-nitro iododerivative. 76 % yield, yellowish oil. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.13 (d, *J* = 8.8 Hz, 2H), 7.50 (d, *J* = 8.8 Hz, 2H), 7.03 – 6.79 (m, 1H), 6.25 (d, *J* = 15.0 Hz, 1H), 3.38 (h, *J* = 7.0 Hz, 4H), 2.48 (t, *J* = 7.0 Hz, 2H), 2.38 (q, *J* = 7.3 Hz, 2H), 1.79 (p, *J* = 7.3 Hz, 2H), 1.29 – 1.03 (m, 6H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 165.58 (C), 146.65 (C), 144.37 (CH), 132.24 (CH), 130.89 (C), 123.47 (CH), 121.50 (CH), 95.62 (C), 79.86 (C), 42.12 (CH_2), 40.82 (CH_2), 31.46 (CH_2), 27.04 (CH_2), 19.01 (CH_2), 14.86 (CH_2), 13.14 (CH_2). **HRMS** (ESI-TOF): m/z calculated for $C_{18}H_{23}N_2O_3$ ($[M+H]^+$) 315.1703, found 315.1700.

(*E*)-8-(4-Acetylphenyl)-*N,N*-diethyloct-2-en-7-ynamide (1f)



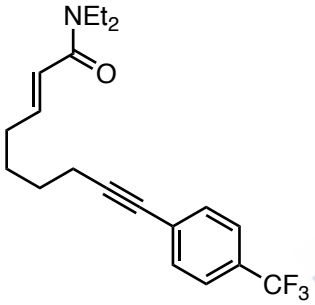
This compound was prepared according to the previously described general procedure **A**, using the corresponding iodophenyl derivative for the coupling. 75 % yield, yellow oil. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.70 (d, *J* = 8.4 Hz, 2H), 7.29 (d, *J* = 8.4 Hz, 2H), 6.83 – 6.66 (m, 1H), 6.12 (d, *J* = 15.0 Hz, 1H), 3.34 – 3.14 (m, 4H), 2.40 (s, 3H), 2.36 – 2.16 (m, 4H), 1.63 (q, *J* = 7.1 Hz, 2H), 1.07 – 0.92 (m, 6H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 196.99 (C), 165.41 (C), 144.27 (CH), 135.59 (C), 131.47 (CH), 128.69 (C), 128.01 (CH), 121.39 (CH), 93.18 (C), 80.61 (C), 42.00 (CH_2), 40.65 (CH_2), 31.28 (CH_2), 27.03 (CH_2), 26.40 (CH_3), 18.82 (CH_2), 14.77 (CH_3), 13.05 (CH_3). **HRMS** (ESI-TOF): m/z calculated for $C_{20}H_{26}NO_2$ ($[M+H]^+$) 312.1958, found 312.1957.

(*E*)-*N,N*-Diethyl-9-phenylnon-2-en-8-ynamide (1g)



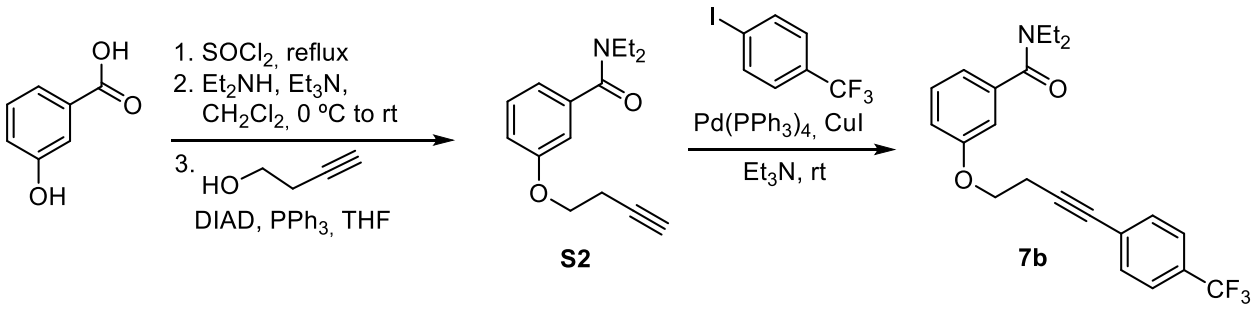
This compound was prepared according the general procedure **A** for the synthesis of **1a**, using hep-6-yn-1-ol instead of hex-5-yn-1-ol. 70 % yield, yellow oil. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.37 – 7.31 (m, 2H), 7.25 – 7.19 (m, 3H), 6.87 (dt, *J* = 14.4, 7.0 Hz, 1H), 6.17 (dd, *J* = 15.0, 1.5 Hz, 1H), 3.43 – 3.26 (m, 4H), 2.42 – 2.34 (m, 2H), 2.27 – 2.18 (m, 2H), 1.65 – 1.56 (m, 4H), 1.19 – 1.06 (m, 6H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 165.82 (C), 145.55 (CH), 131.54 (CH), 128.21 (CH), 127.57 (CH), 123.97 (C), 120.84 (CH), 89.86 (C), 80.91 (C), 42.14 (CH_2), 40.80 (CH_2), 31.98 (CH_2), 28.17 (CH_2), 27.65 (CH_2), 19.22 (CH_2), 14.89 (CH_3), 13.21 (CH_3). **HRMS** (ESI-TOF): m/z calculated for $C_{19}H_{26}NO$ ($[M+H]^+$) 284.2009, found 284.2009.

(*E*)-*N,N*-Diethyl-9-(4-(trifluoromethyl)phenyl)non-2-en-8-ynamide (1h)



This compound was prepared according the general procedure **A** for the synthesis of **1g**, using the corresponding iododerivative. 92 % yield, yellow oil. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.55 – 7.44 (m, 4H), 6.92 (dt, *J* = 14.5, 7.0 Hz, 1H), 6.22 (d, *J* = 15.0 Hz, 1H), 3.46 – 3.31 (m, 4H), 2.49 – 2.38 (m, 2H), 2.33 – 2.22 (m, 2H), 1.70 – 1.59 (m, 4H), 1.25 – 1.07 (m, 6H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 165.84 (C), 145.49 (CH), 134.32 (C) 131.83 (CH), 129.35 (C, q, *J* = 32.5 Hz), 125.16 (CH, q, *J* = 4.2 Hz), 122.28 (CF_3, q, *J* = 271.6 Hz), 120.95 (CH), 92.80 (C), 79.86 (C), 42.19 (CH_2), 40.88 (CH_2), 32.00 (CH_2), 28.01 (CH_2), 27.74 (CH_2), 19.29 (CH_2), 14.92 (CH_3), 13.23 (CH_3). **HRMS** (ESI-TOF): m/z calculated for $C_{20}H_{25}F_3NO$ ($[M+H]^+$) 352.1885, found 352.1883.

General procedure (B) for preparation of precursors 7a -7e (exemplified for the synthesis of *N*,*N*-diethyl-3-((4-(4-(trifluoromethyl)phenyl)but-3-yn-1-yl)oxy)benzamide, **7b**).



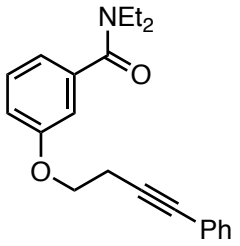
3-Hydroxybenzoic acid (5.0 g, 36.2 mmol) was placed in a flask equipped with a reflux condenser. Thionyl chloride (20 mL, 270 mmol) and five drops of DMF were added and the mixture was refluxed for 4 hours. The reaction was allowed to cool to rt and the excess of $SOCl_2$ was carefully removed

with a rotary evaporator equipped with an intermediate cooled trap (Et_2O – N_2 bath). The crude acid chloride was dissolved in CH_2Cl_2 (72 mL) and Et_3N (15.3 mL, 108.6 mmol) was added. The mixture was cooled in an ice-water bath and Et_2NH (13.9 mL, 133.9 mmol) was added dropwise. The reaction was stirred for 19 hours at rt, concentrated and purified via flash column chromatography (1:2 to 3:1 EtOAc: Hexane) to provide *N*,*N*-Diethyl-3-hydroxybenzamide as a yellowish solid (6.50 g, 95% yield). The NMR and MS data were consistent with those previously published.[3]

Following a procedure described by Urabe and co-workers[4], *N*,*N*-diethyl-3-hydroxybenzamide (400 mg, 2.1 mmol), PPh_3 (651 mg, 2.48 mmol), and 3-butyn-1-ol (218 mg, 3.1 mmol) were dissolved in THF (10 mL) and DIAD (0.5 mL, 2.48 mmol) was added dropwise to this mixture at 0ºC. After stirring at reflux for 6 h, the mixture was concentrated in vacuo to give a crude oil, which was purified on silica gel (1:10 to 1:2 EtOAc: Hex) to provide the 3-(but-3-yn-1-yloxy)-*N*,*N*-diethylbenzamide (264 mg, 52% yield). **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.25 – 7.18 (m, 1H), 6.89 – 6.82 (m, 3H), 4.03 (t, *J* = 7.0 Hz, 2H), 3.54 – 3.07 (m, 4H), 2.65 – 2.55 (m, 2H), 2.01 – 1.94 (m, 1H), 1.23 – 0.98 (m, 6H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 170.82 (C), 158.42 (C), 138.67 (C), 129.63 (CH), 118.85 (CH), 115.66 (CH), 112.50 (CH), 80.28 (C), 70.04 (CH), 66.11 (CH_2), 43.23 (CH_2), 39.20 (CH_2), 19.53 (CH_2), 14.22 (CH_3), 12.91 (CH_3). **HRMS** (ESI-TOF): m/z calculated for $C_{15}H_{20}NO_2$ ($[M+H]^+$) 246.1488, found 246.1489.

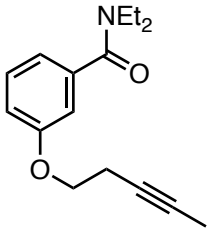
An oven dried Schlenk tube under argon equipped with a Teflon septum and magnetic stir bar was charged with CuI (15.2 mg, 0.08 mmol) and $Pd(Ph_3P)_4$ (46.2 mg, 0.04 mmol). Et_3N (5.8 mL, 0.15 M), 4-Iodo benzotrifluoride (0.26 mL, 1.76 mmol) and 3-(but-3-yn-1-yloxy)-*N*,*N*-diethyl benzamide (216.6 mg, 0.88 mmol) were sequentially added. The reaction mixture was stirred at rt. After 20 h, the reaction mixture was concentrated in vacuo. Purification of the crude product by flash chromatography on silica gel (1:10 to 1:3 EtOAc: Hexane) afforded the **7b** (31 mg, 50% yield). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.59 – 7.49 (m, 4H), 7.32 (t, *J* = 8.0 Hz, 1H), 7.00 – 6.94 (m, 3H), 4.20 (t, *J* = 7.0 Hz, 2H), 3.60 – 3.49 (m, 2H), 3.34 – 3.20 (m, 2H), 2.93 (t, *J* = 7.0 Hz, 2H), 1.39 – 0.99 (m, 6H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 170.84 (C), 158.45 (C), 138.65 (C), 131.90 (CH), 129.65 (C, q, *J* = 32.6 Hz), 129.63 (CH),127.21 (C), 125.15 (CH, q, *J* = 3.7 Hz), 123.94 (CF_3, q, *J* = 272.7 Hz), 118.85 (CH), 115.71 (CH), 112.52 (CH), 88.54 (C), 80.93 (C), 66.05 (CH_2), 43.25 (CH_2), 39.22 (CH_2), 20.47 (CH_2), 14.26 (CH_3), 12.89 (CH_3). **HRMS** (ESI-TOF): m/z calculated for $C_{22}H_{23}F_3NO_2^+$ ([M+H]+) 390.1675, found 390.1703.

***N,N*-Diethyl-3-((4-phenylbut-3-yn-1-yl)oxy)benzamide (7a)**



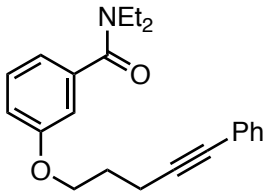
This compound was prepared according to the previously described general procedure **B**, using iodobencene for the coupling reaction. 94% yield, colorless oil. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.36 – 7.28 (m, 2H), 7.23 – 7.16 (m, 4H), 6.91 – 6.83 (m, 3H), 4.09 (t, *J* = 7.1 Hz, 2H), 3.52 – 3.36 (m, 2H), 3.24 – 3.09 (m, 2H), 2.80 (t, *J* = 7.1 Hz, 2H), 1.21 – 0.97 (m, 6H).**^{13}C NMR** (75 MHz, $CDCl_3$): δ 170.92 (C), 158.54 (C), 138.63 (C), 131.67 (CH), 129.65 (CH), 128.25 (CH), 127.94 (CH), 123.39 (C), 118.80 (CH), 115.72 (CH), 112.55 (CH), 85.68 (C), 82.13 (C), 66.34 (CH_2), 43.29 (CH_2), 39.19 (CH_2), 20.48 (CH_2), 14.21 (CH_3), 12.91 (CH_3). **HRMS** (ESI-TOF): m/z calculated for $C_{21}H_{24}NO_2$ ($[M+H]^+$) 322.1802, found 322.1802.

***N,N*-Diethyl-3-(pent-3-yn-1-yloxy)benzamide (7c)**



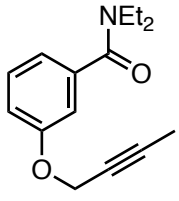
This compound was prepared according to the previously described general procedure **B**, using pent-3-yn-1-ol instead of 3-butyn-1-ol. 93% yield, colorless oil. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.32 – 7.28 (m, 1H), 6.98 – 6.85 (m, 3H), 4.05 (t, *J* = 7.1 Hz, 2H), 3.53 (br, 2H), 3.25 (br, 2H), 2.68 – 2.55 (m, 2H), 1.86 – 1.73 (m, 3H), 1.33 – 1.02 (m, 6H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 170.88 (C), 158.57 (C), 138.63 (C), 129.59 (CH), 118.67 (CH), 115.63 (CH), 112.47 (CH), 77.41 (C), 74.91 (C), 66.73 (CH_2), 43.22 (CH_2), 39.16 (CH_2), 19.79 (CH_2), 14.22 (CH_3), 12.92 (CH_3), 3.52 (CH_3). **HRMS** (ESI-TOF): m/z calculated for $C_{16}H_{22}NO_2$ ($[M+H]^+$) 260.1644, found 260.1645.

***N,N*-Diethyl-3-((5-phenylpent-4-yn-1-yl)oxy)benzamide (7d)**



This compound was prepared according to the general procedure **B** using pent-4-yn-1-ol instead of 3-butyn-1-ol. 95% yield, yellowish oil. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.36 – 7.30 (m, 2H), 7.27 – 7.18 (m, 4H), 6.92 – 6.85 (m, 3H), 4.08 (t, *J* = 6.1 Hz, 2H), 3.47 (br, 2H), 3.19 (br, 2H), 2.57 (t, *J* = 6.9 Hz, 2H), 2.08 – 1.96 (m, 2H), 1.26 – 0.97 (m, 6H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 170.98 (C), 158.95 (C), 138.63 (C), 131.59 (CH), 129.59 (CH), 128.24 (CH), 127.71 (CH), 123.75 (C), 118.47 (CH), 115.57 (CH), 112.39 (CH), 88.98 (C), 81.26 (C), 66.54 (CH_2), 43.25 (CH_2), 39.21 (CH_2), 28.48 (CH_2), 16.20 (CH_2), 14.26 (CH_3), 12.94 (CH_3). **HRMS** (ESI-TOF): m/z calculated for $C_{22}H_{26}NO_2$ ($[M+H]^+$) 336.1957, found 336.1958.

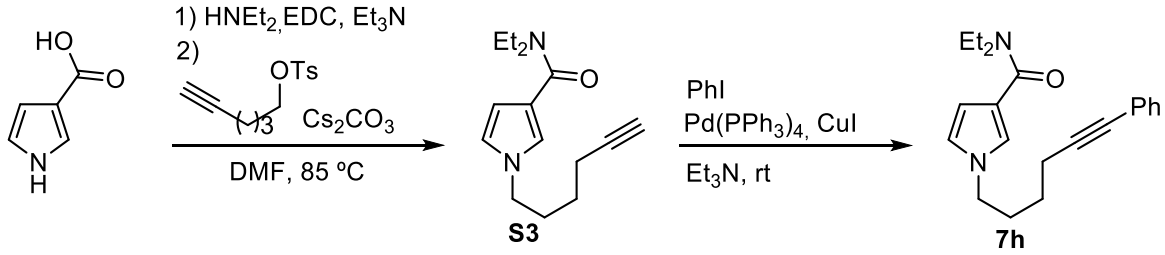
3-(But-2-yn-1-yloxy)-*N,N*-diethylbenzamide (7e)



This compound was prepared according to the general procedure **B** using but-2-yn-1-ol instead of 3-butyn-1-ol. 97 % yield, colorless oil. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.29 – 7.15 (m, 1H), 6.94 – 6.83 (m, 3H), 4.58 (s, 2H), 3.54 – 3.10 (m, 4H), 1.77 (s, 3H), 1.23 – 0.98 (m, 7H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 170.86 (C), 157.75 (C), 138.53

(C), 129.60 (CH), 119.07 (CH), 115.92 (CH), 112.58 (CH), 83.97 (C), 73.83 (C), 56.50 (CH_2), 43.25 (CH_2), 39.25 (CH_2), 14.23 (CH_3), 12.95 (CH_3), 3.70 (CH_3). **HRMS** (ESI-TOF): m/z calculated for $C_{15}H_{20}NO_2$ ([M+H]$^+$) 246.1488, found 246.1489.

General procedure C for preparation of precursors 7f -7i (exemplified for the synthesis of **7h**).



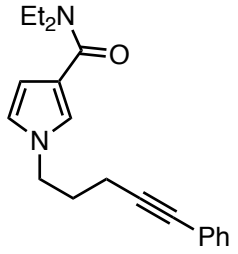
Et_2NH (2.14 mL, 20.7 mmol) was added to a solution of 1*H*-pyrrole-3-carboxylic acid (2.0 g, 18 mmol), EDC·HCl (5.17 g, 27 mmol) and Et_3N (7.5 mL, 54 mmol) in CH_2Cl_2 (72 mL, 0.25 M). The resulting mixture was stirred for 16 h and then was quenched with water (50 mL). The layers were separated and the aqueous phase was extracted twice with CH_2Cl_2 (2 x 50 mL). The combined organic layers were dried and the solvent was evaporated. The crude product was purified by column chromatography (1:1 to 9:1, EtOAc:Hexane). *N,N*-diethyl-1H-pyrrole-3-carboxamide was obtained as pale yellow solid (1.88 g, 63% yield). **^{1}H NMR** (300 MHz, $CDCl_3$): δ 10.40 (s, 1H), 6.97 – 6.92 (m, 1H), 6.61 – 6.57 (m, 1H), 6.34 – 6.30 (m, 1H), 3.52 (q, *J* = 7.1 Hz, 4H), 1.20 (t, *J* = 7.1 Hz, 6H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 167.87 (C), 121.01 (CH), 118.98 (C), 118.22 (CH), 108.31 (CH), 41.75 (CH_2), 13.82 (CH_3). **HRMS** (ESI-TOF): m/z calculated for $C_9H_{15}N_2O$ ([M+H]$^+$) 167.1178, found 167.1179.

Following a modified procedure from Schreiber and coworkers,[5] hex-5-yn-1-yl 4-methylbenzenesulfonate (972 mg, 3.85 mmol) was slowly added to a solution of *N,N*-diethyl-1*H*-pyrrole-3-carboxamide (400 mg, 2.41 mmol) and Cs_2CO_3 (1.80 g, 5.54 mmol) in anhydrous DMF (6 mL, 0.4 M). The reaction mixture was stirred at 85 ºC for 16 h, allowed to cool to rt and water (45 mL) was added. The mixture was extracted with Et_2O (5 x 15 mL). The organic phase was dried, concentrated and the crude residue was purified by flash chromatography (1:3 to 2:1 EtOAc : Hexane) to yield *N*,*N*-Diethyl-1-(hex-5-yn-1-yl)-1*H*-pyrrole-3-carboxamide (**S3**) as a clear oil (592 mg, 92% yield). **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.03 – 6.99 (m, 1H), 6.54 – 6.49 (m, 1H), 6.29 – 6.24 (m, 1H), 3.83 (t, *J* = 7.1 Hz, 2H), 3.51 – 3.41 (m, 4H), 2.20 – 2.10 (m, 2H), 1.93 – 1.77 (m, 3H), 1.51 – 1.38 (m, 2H), 1.20 – 1.12 (m, 6H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 166.48 (C), 123.56 (CH), 123.54 (C) 120.34 (CH), 108.79 (CH), 83.52 (C), 68.95 (CH), 49.29 (CH_2), 41.47 (CH_2), 30.13 (CH_2), 25.35 (CH_2), 17.95 (CH_2), 13.74 (CH_3). **HRMS (ESI-TOF):** m/z calculated for $C_{15}H_{22}N_2NaO$ ([M+H]$^+$) 269.1617, found 269.1624.

Following the general procedure **A** but using N,N-Diethyl-1-(6-phenylhex-5-yn-1-yl)-1H-pyrrole-3-carboxamide instead of (*E*)-*N*,*N*-Diethyloct-2-en-7-ynamide*, N,N*-Diethyl-1-(6-phenylhex-5-yn-1-yl)-1H-pyrrole-3-carboxamide (**7h**) was obtained as a yellow oil (241mg, 92 %). **^{1}H NMR** (300

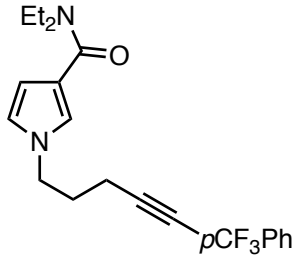
MHz, $CDCl_3$): δ 7.33 – 7.26 (m, 2H), 7.22 – 7.15 (m, 3H), 7.02 – 6.97 (m, 1H), 6.53 – 6.47 (m, 1H), 6.27 – 6.23 (m, 1H), 3.82 (d, *J* = 7.1 Hz, 2H), 3.48 – 3.38 (m, 4H), 2.33 (d, *J* = 7.0 Hz, 2H), 1.92 – 1.80 (m, 2H), 1.56 – 1.43 (m, 2H), 1.16 – 1.09 (m, 6H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 166.58 (C), 131.57 (CH), 128.21 (CH), 127.65 (CH), 123.92 (C), 123.54 (CH), 120.37 (CH), 119.69 (C), 108.92 (CH), 89.18 (C), 81.43 (C), 49.40 (CH_2), 41.55 (CH_2), 30.38 (CH_2), 25.76 (CH_2), 19.01 (CH_2), 13.78 (CH_3). **HRMS** (ESI-TOF): m/z calculated for $C_{21}H_{27}N_2O$ ($[M+H]^+$) 323.2118, found 323.2118.

***N,N*-Diethyl-1-(5-phenylpent-4-yn-1-yl)-1*H*-pyrrole-3-carboxamide (7f)**



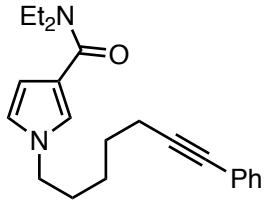
This compound was prepared according the general procedure **C** using *N,N*-diethyl-1-(pent-4-yn-1-yl)-1*H*-pyrrole-3-carboxamide instead of *N*,*N*-Diethyl-1-(hex-5-yn-1-yl)-1*H*-pyrrole-3-carboxamide and iodobenzene, 82% yield, yellowish oil. **^{1}H NMR** (300 MHz, $CDCl_3$, 60ºC) δ 7.42 – 7.31 (m, 2H), 7.28 – 7.18 (m, 3H), 7.09 – 7.00 (m, 1H), 6.62 – 6.51 (m, 1H), 6.35 – 6.27 (m, 1H), 4.00 (t, *J* = 6.8 Hz, 2H), 3.49 (q, *J* = 7.2 Hz, 4H), 2.35 (t, *J* = 6.8 Hz, 2H), 2.05 – 1.92 (m, 2H), 1.17 (t, *J* = 7.1 Hz, 6H). **^{13}C NMR** (75 MHz, $CDCl_3$, 60ºC) δ 166.44 (C), 131.47 (CH), 128.15 (CH), 127.71 (CH), 123.61 (C), 123.46 (CH), 120.49 (CH), 119.72 (C), 108.99 (CH), 88.02 (C), 81.99 (C), 48.25 (CH_2), 41.47 (CH_2), 30.05 (CH_2), 16.50 (CH_2), 13.68 (CH_3). **HRMS (ESI-TOF):** m/z calculated for $C_{20}H_{25}N_2O$ ($[M+H]^+$) 309.1961, found 309.1961.

***N,N*-Diethyl-1-(5-(4-(trifluoromethyl)phenyl)pent-4-yn-1-yl)-1*H*-pyrrole-3-carboxamide (7g)**



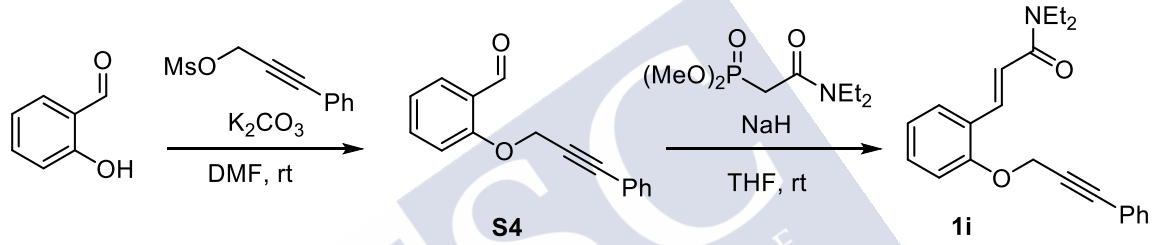
This compound was prepared according the general procedure **C** using *N,N*-diethyl-1-(pent-4-yn-1-yl)-1H-pyrrole-3-carboxamide instead of *N*,*N*-Diethyl-1-(hex-5-yn-1-yl)-1*H*-pyrrole-3-carboxamide, and a bromophenyl derivative as coupling partners. 60% yield, red oil. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.48 – 7.34 (m, 4H), 7.04 – 6.94 (m, 1H), 6.56 – 6.46 (m, 1H), 6.30 – 6.20 (m, 1H), 3.94 (t, *J* = 6.7 Hz, 2H), 3.50 – 3.34 (m, 4H), 2.31 (t, *J* = 6.8 Hz, 2H), 2.02 – 1.89 (m, 2H), 1.11 (t, *J* = 7.0 Hz, 6H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 166.27 (C), 131.69 (CH), 129.49 (C, q, *J* = 33.1 Hz), 127.46 (C), 124.96 (CH, q, *J* = 4.0 Hz), 123.87 (CF_3, q, *J* = 271.4 Hz), 123.37 (CH), 120.38 (CH), 119.80 (C), 108.98 (CH), 90.98 (C), 80.58 (C), 48.18 (CH_2), 41.38 (CH_2), 29.78 (CH_2), 16.43 (CH_2), 13.55 (CH_3). **HRMS (ESI-TOF):** m/z calculated for $C_{21}H_{24}F_3N_2O$ ($[M+H]^+$) 377.1835, found 377.1837.

***N*,*N*-Diethyl-1-(7-phenylhept-6-yn-1-yl)-1*H*-pyrrole-3-carboxamide (7i)**



^{1}H NMR (300 MHz, $CDCl_3$): δ 7.39 – 7.32 (m, 2H), 7.27 – 7.21 (m, 3H), 7.07 – 7.02 (m, 1H), 6.57 – 6.53 (m, 1H), 6.32 – 6.28 (m, 1H), 3.85 (t, *J* = 7.1 Hz, 2H), 3.51 (q, *J* = 7.2 Hz, 4H), 2.39 (t, *J* = 6.8 Hz, 2H), 1.81 (p, *J* = 7.2 Hz, 2H), 1.61 (p, *J* = 7.0 Hz, 2H), 1.54 – 1.41 (m, 2H), 1.19 (t, *J* = 7.1 Hz, 6H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 166.68 (C), 131.64 (CH), 128.25 (CH), 127.60 (CH), 124.18 (C), 123.65 (CH), 120.44 (CH), 119.71 (C), 108.92 (CH), 89.73 (C), 81.20 (C), 49.81 (CH_2), 41.64 (CH_2), 30.87 (CH_2), 28.34 (CH_2), 26.05 (CH_2), 19.35 (CH_2), 13.85 (CH_3). **HRMS (ESI-TOF):** m/z calculated for $C_{22}H_{29}N_2O$ ($[M+H]^+$) 337.2274, found 337.2274.

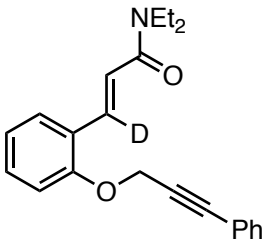
Synthesis of precursors 1i and *d*-1i.



3-Phenylprop-2-yn-1-yl methanesulfonate[6] was added dropwise to a vigorously stirred solution of salicylaldehyde (610,6 mg, 5.0 mmol) and K_2CO_3 (1.36 g, 6.5 mmol) in DMF (5 mL, 1M) at rt. The resulting mixture was stirred for 20 hours and then was quenched with water (30 mL). The aqueous layer was extracted with Et_2O (5 x 10mL). The combined organic portions were washed with brine, dried with Na_2SO_4 and concentrated under reduce pressure. The aldehyde **S4** was obtained pure after silica gel column chromatography (1:10 to 1:3 Diethyl ether: hexane). **^{1}H NMR** (300 MHz, $CDCl_3$): δ 10.42 (s, 1H), 7.79 – 7.73 (m, 1H), 7.49 – 7.41 (m, 1H), 7.35 – 7.28 (m, 2H), 7.23 – 7.17 (m, 3H), 7.08 (d, *J* = 8.5 Hz, 1H), 6.96 (t, *J* = 7.6 Hz, 1H), 4.92 (s, 2H). **^{13}C NMR (**75 MHz, $CDCl_3$): δ 189.68 (CH), 160.09 (C), 135.80 (CH), 131.82 (CH), 128.98 (CH), 128.52 (CH), 128.41 (CH), 125.53 (C), 121.91 (C), 121.56 (CH), 113.47 (C), 88.12 (C), 83.04 (C), 57.30 (CH_2). **HRMS** (ESI-TOF): m/z calculated for $C_{16}H_{13}O_2$ ($[M+H]^+$) 237.0900, found 237.0910.

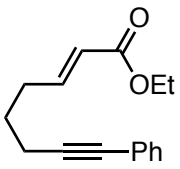
(*E*)-*N*,*N*-Diethyl-3-(2-((3-phenylprop-2-yn-1-yl)oxy)phenyl)acrylamide (1i) was obtained from this aldehyde following the general procedure **A** described for the aliphatic aldehydes. White solid, m.p. 71-72 ºC. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.93 (d, *J* = 15.5 Hz, 1H), 7.52 – 7.46 (m, 1H), 7.44 – 7.39 (m, 2H), 7.34 – 7.24 (m, 4H), 7.11 – 6.95 (m, 3H), 4.95 (s, 2H), 3.52 – 3.36 (m, 4H), 1.24 – 1.12 (m, 6H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 166.32 (C), 156.55 (C), 137.80 (CH), 131.87 (CH), 130.32 (CH), 129.84 (CH), 128.81 (CH), 128.37 (CH), 125.18 (C), 122.25 (C), 121.52 (CH), 119.62 (CH), 112.83 (CH), 87.32 (C), 83.73 (C), 57.12 (CH_2), 42.35 (CH_2), 41.07 (CH_2), 15.07 (CH_3), 13.32 (CH_3). **HRMS (ESI-TOF):** m/z calculated for $C_{22}H_{24}NO_2$ ($[M+H]^+$) 334.1805, found 334.1802.

(*E*)-*N*,*N*-Diethyl-3-(2-((3-phenylprop-2-yn-1-yl)oxy)phenyl)acrylamide-3-*d* (*d*-1i)



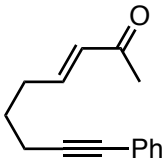
The deuterated analog ***d*-1i** was synthesized according to the procedure described before; using the deuterated aldehyde.[7] White solid, m.p. 72-73 ºC. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.53 – 7.47 (m, 1H), 7.45 – 7.39 (m, 2H), 7.35 – 7.25 (m, 4H), 7.11 – 7.03 (m, 2H), 6.99 (t, *J* = 7.5 Hz, 1H), 4.95 (s, 2H), 3.53 – 3.36 (m, 4H), 1.23 – 1.12 (m, 6H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 166.26 (C), 156.50 (C), [137.43, 137.09] (CD), 131.81 (CH), 130.29 (CH), 129.75 (CH), 128.76 (CH), 128.32 (CH), 125.02 (C), 122.19 (C), 121.47 (CH), 119.44 (CH), 112.76 (CH), 87.26 (C), 83.68 (C), 57.04 (CH_2), 42.29 (CH_2), 41.01 (CH_2), 15.01 (CH_3), 13.27 (CH_3).
^{2}H NMR (46 MHz, $CDCl_3$): δ 7.94 (D). **HRMS (ESI-TOF):** m/z calculated for $C_{22}H_{23}DNO_2$ ($[M+H]^+$) 335.1863, found 335.1864.

Synthesis of ester and ketone analogs 1b and 1c.



Triethyl phosphonoacetate (1.3 g, 6.0 mmol) was added dropwise to a suspension of NaH (60 %) (244 m, 6.0 mmol) in THF (36 mL) at rt. The mixture was stirred for 15 minutes before phenylhex-5-ynal[8] (1.0 g, 6.0 mmol) was added dropwise to the mixture and the mixture was stirred for 17 h. NH_4Cl (sat.) (50 ml) was added, the resulting mixture was extracted with EtOAc (2 x 30 mL) and the combined organic phases were dried over Na_2SO_4 and concentrated. Purification of the crude residue by flash chromatography on silica gel (1:10 to 1:2 EtOAc: Hexane) afforded the desired product as colorless oil (1.0 g, 71% yield). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.44 – 7.30 (m, 2H), 7.27 (dq, *J* = 3.9, 2.3, 1.4 Hz, 3H), 6.99 (dtd, *J* = 15.6, 7.0, 1.5 Hz, 1H), 5.88 (dq, *J* = 15.7, 1.5 Hz, 1H), 4.19 (qd, *J* = 7.1, 1.5 Hz, 2H), 2.51 – 2.32 (m, 4H), 1.86 – 1.71 (m, 2H), 1.29 (td, *J* = 7.2, 1.5 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 166.55 (C), 148.02 (CH), 131.52 (CH), 128.19 (CH), 127.64 (CH), 123.74 (C), 122.03 (CH), 89.09 (C), 81.36 (C), 60.18 (CH_2), 31.16 (CH_2), 27.02 (CH_2), 18.87 (CH_2), 14.26 (CH_3). **HRMS** (ESI-TOF): m/z calculated for $C_{16}H_{19}O_2$ ($[M+H]^+$) 243.1380, found 243.1378.

(E)-9-Phenylnon-3-en-8-yn-2-one (1c)

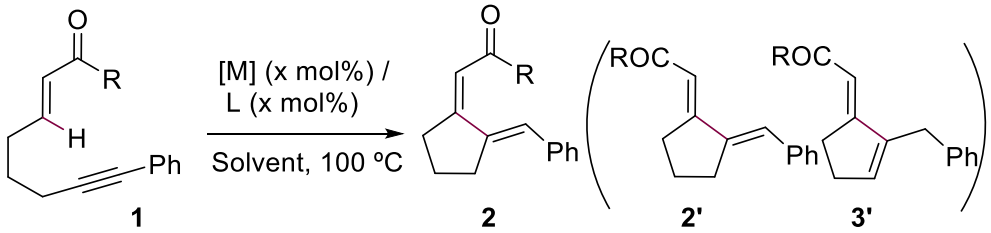


Diethyl (2-oxopropyl)phosphonate (1.13 g, 6.0 mmol) was added dropwise to a suspension of NaH (60 %) (244 mg, 6.0 mmol) in THF (36 mL) at rt. The mixture was stirred for 15 minutes before phenylhex-5-ynal (1.0 g, 6.0 mmol) was added dropwise to the mixture and the resulting mixture was stirred for 17 hrs.. NH_4Cl (sat.) (50 ml) was added, the resulting mixture was extracted with EtOAc (2 x 30 mL) and the combined organic phases were dried over Na_2SO_4 and concentrated. Purification of the crude residue by flash chromatography on silica gel (1:10 to 1:2; EtOAc: Hexane) afforded the desired product as colorless oil (0.83 g, 67 % yield). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.45 – 7.32 (m, 2H), 7.28 (ddd, *J* = 5.1, 2.8, 1.8 Hz, 3H), 6.83 (dt, *J* = 16.0, 6.9 Hz, 1H), 6.13 (dt, *J* = 16.0, 1.5 Hz, 1H), 2.52 – 2.35 (m, 4H), 2.24 (s,

3H), 1.87 – 1.71 (m, 2H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 198.50 (C), 147.13 (CH), 131.81 (CH), 131.51 (CH), 128.21 (CH), 127.69 (CH), 123.68 (C), 89.00 (C), 81.47 (C), 31.46 (CH_2), 27.08 (CH_2), 26.92 (CH_3), 18.93 (CH_2). **HRMS** (ESI-TOF): m/z calculated for $C_{15}H_{17}O$ ($[M+H]^+$) 213.1274, found 213.1274.

Iridium-catalyzed intramolecular hydrocarbonation

Table S1. Optimization of the reaction conditions.[a]

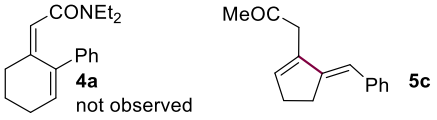


1 **2** **2'** **3'**

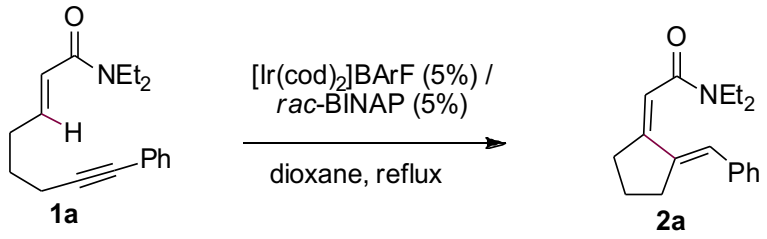
a, R = NEt_2; **b**, R = OEt; **c**, R = Me

entry	**1**	[M] (x mol%)	Conv.	**L**	Products, % yield[b]
1[c]	**1a**	$[Ir(cod)_2]BArF$ (5)	77%	d^Fppe	**2a**, 61 / **2a'**, 6
2[c]	**1a**	$[Ir(cod)_2]BArF$ (5)	80%	*rac*-BINAP	**2a**, 70 /**2a'**, 2
3	**1a**	$[Ir(cod)_2]BArF$ (5)	99%	*rac*-BINAP	**2a**, 92 / **2a'**, 4 /
4	**1a**	$[Ir(cod)_2]BArF$ (5)	0%	PPh_3 (10%)	-
5	**1a**	$[Ir(cod)_2]BF_4$ (5)	99%	*rac*-BINAP	**2a**, 60 / **2a'**, 3 / **3a'**, 12
6	**1a**	$[Ir(cod)_2]OTf$ (5)	99%	*rac*-BINAP	**2a**, 85 / **2a'**, 3 / **3a'**, 8
7	**1a**	$[Ir(cod)_2]BArF$(5)/NaOAc (20%)	74%	*rac*-BINAP	**2a**, 71
8[d]	**1b**	$[Ir(cod)_2]BArF$ (5)	99%	*rac*-BINAP	-[e]
9[d,f]	**1c**	$[Ir(cod)_2]BArF$ (5)	99%	*rac*-BINAP	**5c**, 42
10[g]	**1a**	$RuH_2CO(PPh_3)_3$ (5)	99%	-	**2a**, 7 / **3a'**, 61
11[h]	**1a**	$[Ir(cod)_2]BArF$ (5)	65%	*rac*-BINAP	**2a,** 52
12[i]	**1a**	$[Ir(cod)_2]BArF$ (5)	76%	*rac*-BINAP	**2a,** 60
13	**1a**	$[Ir(cod)_2]BArF$ (5)	34%	dppb	**2a,** 7 **/ 2a',** 3
14[j]	**1a**	$[Ir(cod)_2]BArF$ (5)	99%	dppe	**2a,** 63 **/ 2a',** 13 **/ 3a',** 17
15	**1a**	$[Ir(cod)_2]BArF$ (5)	21%	d^Fppe	**2a,** 3
16[k]	**1a**	$[Ir(cod)_2]OTf$ (10)	99%	*rac*-BINAP	**2a,** 55 **/ 2a',** 6 **/ 3a',**30
17[k]	**1a**	$[Ir(cod)_2]OTf$ (10) /NaOAc 20 %	99%	*rac*-BINAP	**2a,** 51 **/ 2a',** 8 **/ 3a',**36
18	**1a**	$[Ir(cod)Cl]_2$ (2.5) / $AgBF_4$ (5)	69%	*rac*-BINAP	**2a,** 8 **/ 2a',** 2 **/ 3a',**17
19	**1a**	$[Rh(cod)_2]BArF$ (5)	5%	*rac*-BINAP	-
20[l]	**1a**	$[Rh(cod)_2]BF_4$ (5)	0%	*rac*-BIPHEP	-
21[m]	**1a**	$RhCl(PPh_3)_3$	30%		**2a,** 1 **/ 2a',** 1 **/ 3a',**20

[a] Conditions: **1a** was added to a solution of [M] (x mol%) and **L** (x mol%) in dioxane, unless otherwise noted, and the mixture was heated at 100 ºC for 24 h. [b] Isolated yields. [c] Carried out in 1,2-DCE (100 ºC, sealed tube). [d] Carried out at 120 ºC. [e] A complex mixture of products obtained. [f] Reaction time: 6 days. [g] Carried out in refluxing toluene. [h] Carried out at 80 ºC. [i] Carried out under air. [j] Carried out at 140 ºC (sealed tube). [k] Carried out in PhCl at 135 ºC. [l] Carried out in DCE at 80 ºC.[m] Carried out in toluene at 140 º C (sealed tube).d^Fppe : $(C_6F_5)_3P(CH_2)_2P(C_6F_5)_3$



General procedure for the Iridium-catalyzed intramolecular hydrocarbonation (exemplified for the reaction of **1a**)



1a **2a**

An oven dried Schlenk tube equipped with a septum and magnetic stirring bar was charged with (+/)-BINAP (28.9 mg, 0.05 equiv), bis(cyclooctadiene)iridium(I) tetrakis(3,5-bis(trifluoromethyl)phenyl) borate (59.0 mg, 0.05 equiv), **1a** (250 mg, 1.0 equiv) and dioxane (3.7 mL, 0.25 M). The reaction mixture was then stirred at 100 °C. After 19 h, the reaction mixture was concentrated in vacuum. Purification of the crude product by flash chromatography on silica gel (1:15 to 1:2 EtOAc: Hexane) afforded the desired product (**2a**) as yellow pale oil (230 mg, 92 %). **(*Z*)-2-(2-((*E*)-benzylidene)cyclopentylidene)-*N*,*N*-diethylacetamide.** **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.26 – 7.22 (m, 4H), 7.17 – 7.09 (m, 1H), 6.90 (t, *J* = 2.5 Hz, 1H), 5.80 (s, 1H), 3.46 – 3.26 (m, 4H), 2.65 (t, *J* = 7.2 Hz, 2H), 2.44 (t, *J* = 7.4 Hz, 2H), 1.75 – 1.63 (m, 2H), 1.16 – 1.01 (m, 6H). **^{13}C NMR** (126 MHz, $CDCl_3$): δ 168.66 (C), 146.33 (C), 139.79 (C), 138.05 (C), 129.14 (CH), 128.24 (CH), 126.94 (CH), 126.47 (CH), 114.84 (CH), 42.79 (CH_2), 39.13 (CH_2), 35.02 (CH_2), 33.20 (CH_2), 24.19 (CH_2), 14.37 (CH_3), 12.92 (CH_3). **HRMS** (ESI-TOF): m/z calculated for $C_{18}H_{24}NO$ ($[M+H]^+$) 270.1852, found 270.1852. Assignment of structure of **2a** was based on the HMBC, HSQC, COSY and NOESY experiments.

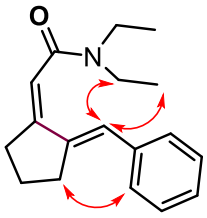
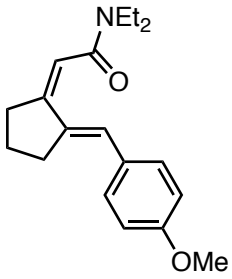


Figure S1. Significant NOESY signals observed for **2a**.

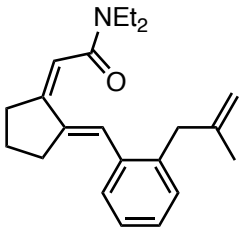
(*Z*)-*N*,*N*-Diethyl-2-(2-((*E*)-4-methoxybenzylidene)cyclopentylidene)acetamide (2b)



According to the general procedure, the product was isolated by flash chromatography (5 to 30% EtOAc/Hexanes) as yellow oil in 98 % yield. **^{1}H NMR** (300 MHz, CD_2Cl_2): δ 7.29 – 7.24 (m, 2H), 6.90 – 6.84 (m, 3H), 5.81 (s, 1H), 3.78 (s, 3H), 3.47 – 3.32 (m, 4H), 2.70 (td, *J* = 7.2, 2.5 Hz, 2H), 2.48 (td, *J* = 7.4, 2.1 Hz, 2H), 1.75 (p, *J* = 7.3 Hz, 2H), 1.19 – 1.07 (m, 6H). **^{13}C NMR** (75 MHz, CD_2Cl_2): δ 168.81 (C), 159.23 (C), 146.80 (C), 138.35 (C), 131.31 (C), 130.88 (CH), 126.18 (CH), 114.86 (CH), 114.21 (CH), 55.76 (CH_3), 43.20 (CH_2), 39.54 (CH_2), 35.64 (CH_2), 33.63 (CH_2),

24.74 (CH_2), 14.65 (CH_3), 13.23 (CH_3). **HRMS** (ESI-TOF): m/z calculated for $C_{19}H_{26}NO_2$ ($[M+H]^+$) 300.1956, found 300.1958.

(*Z*)-*N*,*N*-Diethyl-2-(2-((*E*)-2-(2-methylallyl)benzylidene)cyclopentylidene)acetamide (2c)



According to the general procedure, the product was isolated by flash chromatography (5 to 30% EtOAc/Hexanes) as light yellow oil in 86 % yield. **^{1}H NMR** (300 MHz, CD_2Cl_2): δ 7.31 – 7.24 (m, 1H), 7.21 – 7.14 (m, 3H), 7.09 – 7.05 (m, 1H), 5.88 (s, 1H), 4.76 (s, 1H), 4.50 (s, 1H), 3.44 – 3.34 (m, 4H), 3.28 (s, 2H), 2.53 (t, *J* = 7.1 Hz, 4H), 1.78 – 1.62 (m, 5H), 1.16 – 1.06 (m, 6H). **^{13}C NMR** (75 MHz, CD_2Cl_2): δ 168.60 (C), 146.08 (C), 145.41 (C), 141.05 (C), 138.92 (C), 138.10 (C), 130.11 (CH), 129.45 (CH), 127.54 (CH), 126.28 (CH), 125.42 (CH), 115.88 (CH), 112.04 (CH_2), 43.17 (CH_2), 41.77 (CH_2), 39.51 (CH_2), 35.64 (CH_2), 33.49 (CH_2), 24.65 (CH_2), 22.95 (CH_3), 14.77 (CH_3), 13.23 (CH_3). **HRMS** (ESI-TOF): m/z calculated for $C_{22}H_{29}NNaO$ ($[M+Na]^+$) 346.2138, found 346.2141. Assignment of structure of **2c** was based on the HMBC, HSQC, COSY and nOe experiments.

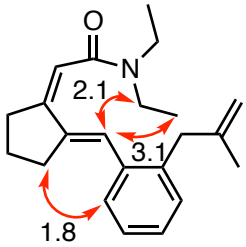
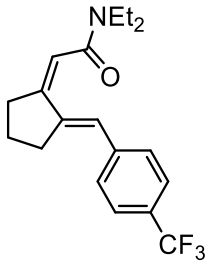


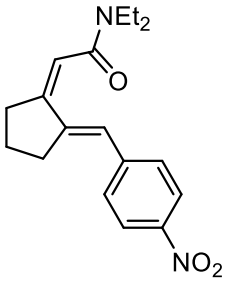
Figure S2. Significant nOe signals observed for **2c**.

(*Z*)-*N*,*N*-diethyl-2-(2-((*E*)-4-(trifluoromethyl)benzylidene)cyclopentylidene)acetamide (2d)



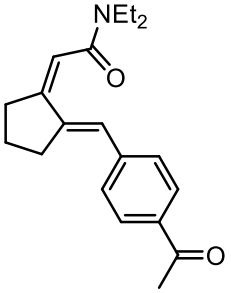
Carried out at 120ºC for 46 hours. The product was isolated by flash chromatography (10 to 40 % EtOAc/Hexanes) as a yellow oil in 73% yield. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.57 (d, *J* = 8.5 Hz, 2H), 7.41 (d, *J* = 8.1 Hz, 2H), 7.03 (s, 1H), 5.95 (s, 1H), 3.49 (q, *J* = 7.1 Hz, 2H), 3.41 (q, *J* = 7.2 Hz, 2H), 2.73 (td, *J* = 7.2, 2.5 Hz, 2H), 2.54 (td, *J* = 7.4, 2.1 Hz, 2H), 1.79 (p, *J* = 7.3 Hz, 2H), 1.19 (t, *J* = 7.1 Hz, 3H), 1.14 (t, *J* = 7.2 Hz, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 168.31 (C), 146.07 (C), 142.15 (C), 141.41 (C), 129.06 (CH), 128.51 (C, q, *J* = 32.4 Hz), 125.08 (CH, q, *J* = 3.9 Hz), 124.99 (CH), 115.88 (CH), 42.77 (CH_2), 39.14 (CH_2), 34.83 (CH_2), 33.17 (CH_2), 24.02 (CH_2), 14.24 (CH_3), 12.81 (CH_3). **^{19}F NMR** (282 MHz, $CDCl_3$) δ -62.60. **HRMS** (ESI-TOF): m/z calculated for $C_{19}H_{23}F_3NO^+$ ([M+H]+) 338.1726, found 338.1733

(*Z*)-*N,N*-diethyl-2-(2-((*E*)-4-nitrobenzylidene)cyclopentylidene)acetamide (2e)



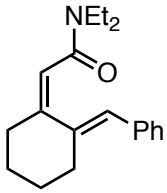
Carried out at 120ºC for 48 hours. The product was isolated by flash chromatography (10 to 40 % EtOAc/Hexanes) as a yellow oil (54% yield). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.16 (d, *J* = 8.7 Hz, 2H), 7.42 (d, *J* = 8.6 Hz, 2H), 7.08 (s, 1H), 5.99 (s, 1H), 3.64 – 3.30 (m, 4H), 2.73 (t, *J* = 7.2 Hz, 2H), 2.54 (t, *J* = 7.4 Hz, 2H), 1.81 (p, *J* = 7.2 Hz, 2H), 1.27 – 1.02 (m, 6H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 167.92 (C), 145.99 (C), 144.50 (C), 144.17 (C), 129.39 (CH), 124.42 (CH), 123.77 (C), 123.55 (CH), 116.94 (CH), 42.76 (CH_2), 39.15 (CH_2), 34.82 (CH_2), 33.41 (CH_2), 23.98 (CH_2), 14.25 (CH_3), 12.87 (CH_3). **HRMS** (ESI-TOF): m/z calculated for $C_{18}H_{23}N_2O_3$+ ([M+H]+) 315.1703, found 315.1703.

(*Z*)-2-(2-((*E*)-4-acetylbenzylidene)cyclopentylidene)-N,N-diethylacetamide (2f)



Carried out at 100ºC for 52 hours. The product was isolated by flash chromatography (10 to 40 % EtOAc/Hexanes) as a yellow oil, 80% yield. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.89 (d, *J* = 8.4 Hz, 2H), 7.38 (d, *J* = 8.2 Hz, 2H), 7.02 (s, 1H), 5.93 (s, 1H), 3.54 – 3.29 (m, 4H), 2.73 (t, *J* = 7.3 Hz, 2H), 2.57 (s, 3H), 2.52 (t, *J* = 7.4 Hz, 2H), 1.78 (p, *J* = 7.3 Hz, 2H), 1.23 – 1.07 (m, 6H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 197.50 (C), 168.24 (C), 146.10 (C), 142.67 (C), 142.45 (C), 135.12 (C), 129.02 (CH), 128.29 (CH), 125.38 (CH), 115.99 (CH), 42.73 (CH_2), 39.09 (CH_2), 34.85 (CH_2), 33.33 (CH_2), 26.54 (CH_3), 24.03 (CH_2), 14.25 (CH_3), 12.82 (CH_3). **HRMS** (ESI-TOF): m/z calculated for $C_{20}H_{26}NO_2^+$ ([M+H]+) 312,1958, found 312.1959.

(*Z*)-2-(2-((*E*)-Benzylidene)cyclohexylidene)-*N,N*-diethylacetamide (2g)



According to the general procedure**,** the product was isolated by flash chromatography (5 to 30% EtOAc/Hexanes) as colorless oil in 92 % yield**. ^{1}H NMR** (500 MHz, CD_2Cl_2): δ 7.33 – 7.28 (m, 2H), 7.22 – 7.17 (m, 3H), 6.45 (s, 1H), 5.67 (t, *J* = 1.5 Hz, 1H), 3.41 (q, *J* = 7.1 Hz, 2H), 3.31 (q, *J* = 7.1 Hz, 2H), 2.55 – 2.50 (m, 2H), 2.37 – 2.33 (m, 2H), 1.80 – 1.73 (m, 2H), 1.66 – 1.60 (m, 2H), 1.14 (t, *J* = 7.1 Hz, 3H), 0.92 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR** (126 MHz, CD_2Cl_2): δ 168.40 (C), 147.42 (C), 139.95 (C), 137.91 (C), 129.65 (CH), 128.56 (CH), 127.03 (CH), 126.74 (CH), 118.62 (CH), 42.99 (CH_2), 38.95 (CH_2), 37.47 (CH_2), 30.45 (CH_2), 27.81 (CH_2), 27.24 (CH_2), 14.57 (CH_3), 12.98 (CH_3). **HRMS** (ESI-TOF): m/z calculated for $C_{19}H_{26}NO$ ([M+H]$^+$) 284.2008, found 284.2009. Assignment of structure of **2g** was based on the HMBC, HSQC, COSY and nOe experiments.

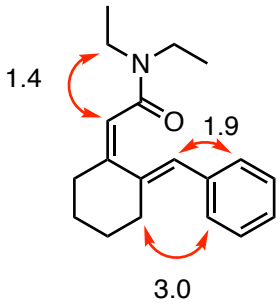
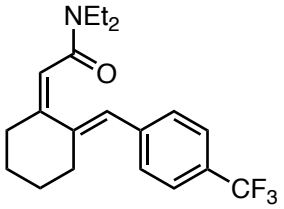


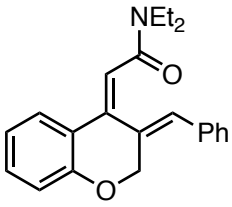
Figure S3. Significant nOe signals observed for **2g**.

(*Z*)-*N*,*N*-Diethyl-2-(2-((*E*)-4-(trifluoromethyl)benzylidene)cyclohexylidene)acetamide (2h)



According to the general procedure**,** the product was isolated by flash chromatography (5 to 30% EtOAc/Hexanes) as a white solid in 89 % yield, m.p. 69-70 ºC . **^{1}H NMR** (300 MHz, CD_2Cl_2): δ 7.57 (d, *J* = 8.1 Hz, 2H), 7.31 (d, *J* = 8.0 Hz, 2H), 6.47 (s, 1H), 5.73 – 5.71 (m, 1H), 3.46 – 3.26 (m, 4H), 2.51 (t, *J* = 6.1 Hz, 2H), 2.36 (t, *J* = 6.2 Hz, 2H),,1.84 – 1.75 (m, 2H), 1.68 – 1.60 (m, 2H), 1.14 (t, *J* = 7.1 Hz, 3H), 0.91 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR** (75 MHz, CD_2Cl_2): δ 168.19 (C), 147.24 (C), 142.27 (C), 141.72 (C), 129.92 (CH), 128.64 (C, q, *J* = 32.0 Hz), 126.75 (C), 125.47 (CH, q, *J* = 3.9 Hz) ,125.42 (CF_3, q, *J* = 271.3 Hz), 125.22 (CH), 123.15 (C), 119.07 (CH), 43.05 (CH_2), 39.05 (CH_2), 37.43 (CH_2), 30.55 (CH_2), 27.71 (CH_2), 27.23 (CH_2), 14.57 (CH_3), 13.00 (CH_3). **^{19}F NMR** (282 MHz, $CDCl_3$): DCl MHz, **HRMS** (ESI-TOF): m/z calculated for $C_{20}H_{25}F_3NO$ ($[M+H]^+$) 352.1882, found 352.1883.

2-((*E*)-3-((*Z*)-Benzylidene)chroman-4-ylidene)-*N*,*N*-diethylacetamide (2i)



According to the general procedure**,** the product was isolated by flash chromatography (7 to 40% EtOAc/Hexanes) as a white solid in 85 % yield, m.p. 86-87 ºC. **^{1}H NMR** (300 MHz, Methanol-d_4) δ 7.70 (d, *J* = 8.2 Hz, 1H), 7.43 – 7.28 (m, 3H), 7.25 – 7.17 (m, 3H), 7.04 (s, 1H), 6.96 (t, *J* = 7.6 Hz, 1H), 6.81 (d, *J* = 7.4 Hz, 1H), 6.65 (s, 1H), 4.91 (s, 2H), 3.54 – 3.38 (m, 4H), 1.22 (t, *J* = 7.1 Hz, 3H), 0.98 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 168.34 (C), 154.93 (C), 135.82 (C), 135.19 (C), 131.92 (CH), 130.24 (CH), 129.39 (C), 129.23 (CH), 128.52 (CH), 127.92 (CH), 123.85 (CH), 121.40 (CH), 121.22 (C), 117.72 (CH), 115.32 (CH), 65.50 (CH_2), 42.68 (CH_2), 39.04 (CH_2), 14.44 (CH_3), 12.69 (CH_3). **HRMS** (ESI-TOF): m/z calculated for $C_{22}H_{24}NO_2$ ($[M+H]^+$) 334.1800, found 334.1802 .

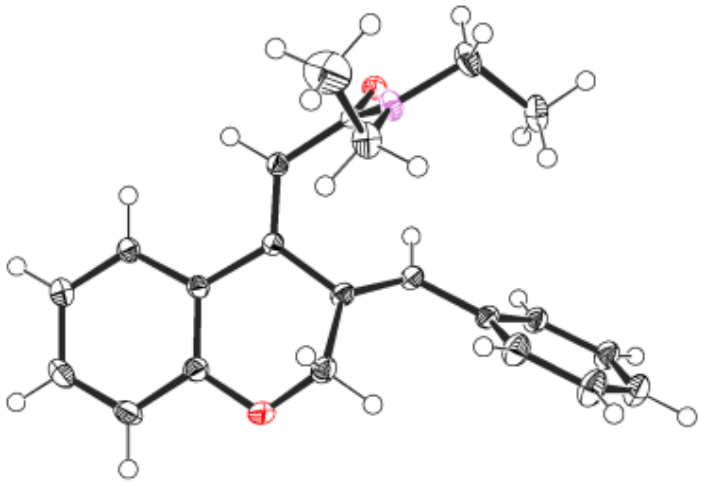


Figure S4. X-ray structure of **2i** [CCDC 1841782 (see page S45)]

***N*,*N*-Diethyl-2-((3*Z*,4*E*)-3-(phenylmethylene-*d*)chroman-4-ylidene)acetamide (*d*-2i)**

According to the general procedure**,** the product was isolated by flash chromatography (7 to 40% EtOAc/Hexanes) as a white solid in 83 % yield, m.p. 87-89 ºC. **^{1}H NMR** (500 MHz, Methanol-d_4) δ 7.66 (d, *J* = 8.1 Hz, 1H), 7.35 (t, *J* = 7.6 Hz, 2H), 7.28 (t, *J* = 7.4 Hz, 1H), 7.19 – 7.15 (m, 3H), 6.92 (t, *J* = 7.2 Hz, 1H), 6.77 (d, *J* = 8.3 Hz, 1H), 6.60 (s, 1H), 4.87 (s, 2H), 3.44 (q, *J* = 7.1 Hz, 2H), 3.38 (q, *J* = 7.1 Hz, 2H), 1.17 (t, *J* = 7.7, Hz, 3H), 0.94 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 168.38 (C), 154.95 (C), 135.77 (C), 135.16 (C), 130.26 (CH), 129.31 (C), 129.27 (CH), 128.54 (CH), 127.95 (CH), 123.88 (CH), 121.43 (CH), 121.25 (C), 117.74 (CH), 115.35 (CH), 65.51 (CH_2), 42.71 (CH_2), 39.06 (CH_2), 14.46 (CH_3), 12.72 (CH_3). **HRMS** (ESI-TOF): m/z calculated for $C_{22}H_{23}DNO_2$ ($[M+H]^+$) 335.1874, found 335.1864.

(*E*)-4-Benzylidene-*N*,*N*-diethylchromane-5-carboxamide (8a)

According to the general procedure**,** the product was isolated by flash chromatography (5 to 30% EtOAc/Hexanes) as yellow oil (44 mg, 88 %).

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.32 (t, *J* = 7.4 Hz, 2H), 7.24 – 7.20 (m, 3H), 7.18 (t, *J* = 7.9 Hz, 1H), 7.06 (s, 1H), 6.85 – 6.79 (m, 2H), 4.33 – 4.27 (m, 1H), 4.11 – 4.05 (m, 1H), 3.81 – 3.73 (m, 1H), 3.21 – 2.99 (m, 4H), 2.74 – 2.66 (m, 1H), 1.01 – 0.96 (m, 6H). **^{13}C NMR** (126 MHz, $CDCl_3$): δ 171.19 (C), 154.68 (C), 136.93 (C), 135.89 (C), 129.74 (C), 129.33 (CH), 129.11 (CH), 128.31 (CH), 127.61 (CH), 126.96 (CH), 119.93 (CH), 119.87 (C), 117.44 (CH), 66.82 (CH_2), 42.56 (CH_2), 38.84 (CH_2), 26.50 (CH_2), 13.56 (CH_3), 12.32 (CH_3). **HRMS** (ESI-TOF): m/z calculated for $C_{21}H_{24}NO_2$ ($[M+H]^+$) 322.1801, found 322.1802. Assignment of structure of **8a** was based on the NOE experiments.

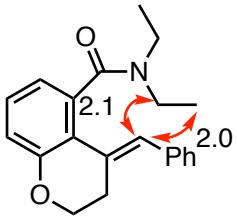
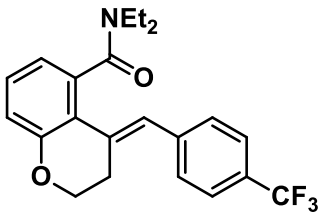


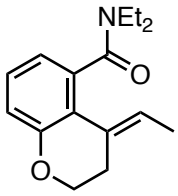
Figure S5. Significant nOe signals observed for **8a**.

(*E*)-*N*,*N*-Diethyl-4-(4-(trifluoromethyl)benzylidene)chromane-5-carboxamide (8b)



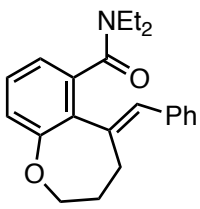
Carried out at 80ºC. The product was isolated by flash chromatography (10 to 40 % EtOAc/Hexanes) as a yellow oil in 48% yield for 7 days (66% yield based on recovered **7b**). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.60 (d, *J* = 8.3 Hz, 2H), 7.34 (d, *J* = 8.0 Hz, 2H), 7.27 – 7.20 (m, 1H), 7.10 (s, 1H), 6.87 (dd, *J* = 8.3, 1.2 Hz, 1H), 6.83 (dd, *J* = 7.5, 1.2 Hz, 1H), 4.34 (dt, *J* = 10.9, 4.4 Hz, 1H), 4.11 (td, *J* = 11.0, 3.2 Hz, 1H), 3.85 – 3.74 (m, 1H), 3.24 – 3.01 (m, 3H), 2.98 (dt, *J* = 14.0, 3.7 Hz, 1H), 2.79 – 2.69 (m, 1H), 1.01 (q, *J* = 7.2 Hz, 6H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 170.94 (C), 154.81 (C), 140.46 (C), 135.88 (C), 131.81 (C), 129.58 (CH), 129.39 (CH), 128.80 (C, q, *J* = 32.6 Hz), 125.89 (CH), 125.22 (CH, q, *J* = 3.7 Hz), 124.13 (CF_3, q, *J* = 272.16Hz), 119.87 (CH), 119.12 (C), 117.55 (CH), 66.53 (CH_2), 42.55 (CH_2), 38.79 (CH_2), 26.46 (CH_2), 13.48 (CH_3), 12.26 (CH_3). **HRMS (ESI-TOF):** m/z calculated for $C_{22}H_{23}F_3NO_2$+ ([M+H]+) 390.1673, found 390.1675.

(*E*)-*N*,*N*-Diethyl-4-ethylidenechromane-5-carboxamide (8c)



According to the general procedure**,** the product was isolated by flash chromatography (5 to 30% EtOAc/Hexanes) as colorless oil in 78 % yield. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.08 (t, *J* = 7.8 Hz, 1H), 6.80 – 6.68 (m, 2H), 6.01 (q, *J* = 7.0 Hz, 1H), 4.33 – 4.23 (m, 1H), 4.20 – 4.07 (m, 1H), 3.90 – 3.77 (m, 1H), 3.24 – 3.11 (m, 1H), 3.07 – 2.91 (m, 2H), 2.79 – 2.69 (m, 1H), 2.51 – 2.39 (m, 1H), 1.69 (d, *J* = 6.9 Hz, 3H), 1.16 (t, *J* = 7.1 Hz, 3H), 0.93 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 171.41 (C), 154.29 (C), 135.14 (C), 128.08 (CH), 128.06 (C), 122.39 (CH), 120.65 (C), 119.76 (CH), 117.32 (CH), 66.93 (CH_2), 42.50 (CH_2), 38.68 (CH_2), 25.55 (CH_2), 13.48 (CH_3), 13.42 (CH_3), 12.25 (CH_3). **HRMS** (ESI-TOF): m/z calculated for $C_{16}H_{22}NO_2$ ($[M+H]^+$) 260.1643, found 260.1645.

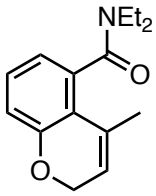
(*E*)-5-Benzylidene-*N*,*N*-diethyl-2,3,4,5-tetrahydrobenzo[*b*]oxepine-6-carboxamide (8d)



According to the general procedure**,** the product was isolated by flash chromatography (5 to 30% EtOAc/Hexanes) as a white solid in 68 % yield, m.p. 96-97 ºC. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.29 – 7.14 (m, 5H), 7.14 – 7.09 (m, 1H), 6.94 – 6.88 (m, 2H), 6.56 (s, 1H), 4.17 – 4.07 (m, 2H), 3.72 – 3.58 (m, 1H), 3.28 – 3.12 (m, 2H), 3.11 – 2.94 (m, 1H), 2.84 – 2.69 (m, 1H), 2.60 – 2.47 (m, 1H), 2.04 – 1.85

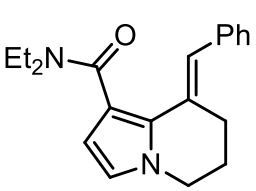
(m, 2H), 1.05 – 0.95 (m, 6H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 170.43 (C), 157.51 (C), 137.79 (C), 137.67 (C), 137.34 (C), 132.71 (C), 131.13 (CH), 128.86 (CH), 128.42 (CH), 128.31 (CH), 126.88 (CH), 121.43 (CH), 121.27 (CH), 71.89 (CH_2), 42.94, (CH_2) 38.59 (CH_2), 29.75 (CH_2), 29.14 (CH_2), 13.94 (CH_3), 12.92 (CH_3). **HRMS (ESI-TOF):** m/z calculated for $C_{22}H_{26}NO_2$ ([M+H]$^+$) 336.1957, found 336.1958.

***N,N*-Diethyl-4-methyl-2*H*-chromene-5-carboxamide (8e)**



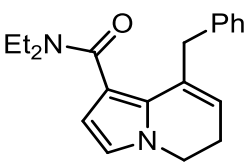
According to the general procedure**,** the product was isolated by flash chromatography (5 to 30% EtOAc/Hexanes) as light yellow oil in 35 % yield. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.12 (t, *J* = 7.8 Hz, 1H), 6.81 (d, *J* = 8.1 Hz, 1H), 6.69 (d, *J* = 7.5 Hz, 1H), 5.84 – 5.74 (m, 1H), 5.11 – 5.06 (m, 2H), 3.79 – 3.63 (m, 1H), 3.52 – 3.40 (m, 1H), 3.21 – 3.12 (m, 2H), 1.71 – 1.65 (m, 3H), 1.27 (t, *J* = 7.1 Hz, 3H), 1.02 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 169.73 (C), 163.96 (C), 135.17 (C), 131.80 (C), 129.46 (CH), 121.80 (C), 118.56 (CH), 115.27 (CH), 110.59 (CH), 73.86 (CH_2), 42.78 (CH_2), 38.88 (CH_2), 15.26 (CH_3), 13.92 (CH_3), 12.70 (CH_3). **HRMS** (ESI-TOF): m/z calculated for $C_{15}H_{20}NO_2$ ([M+H]$^+$) 246.1488, found 246.1489.

(*E*)-8-Benzylidene-*N,N*-diethyl-5,6,7,8-tetrahydroindolizine-1-carboxamide (8f)



Carried out at 80ºC for 23 hours. The product was isolated by flash chromatography (10 to 40 % EtOAc/Hexanes) as a yellow oil in 79% yield. Additionally, a 14% yield of its isomer **8f'** (see bellow) was also obtained. **^{1}H NMR** (300 MHz, DMSO-d_6) δ 7.46 – 7.28 (m, 2H), 7.28 – 7.06 (m, 3H), 6.79 (d, *J* = 2.6 Hz, 1H), 6.58 (s, 1H), 6.02 (d, *J* = 2.7 Hz, 1H), 4.00 (t, *J* = 5.9 Hz, 2H), 3.49 – 3.15 (m, 4H), 2.73 (t, *J* = 5.3 Hz, 2H), 1.95 – 1.77 (m, 2H), 1.07 (t, *J* = 7.1 Hz, 3H), 0.96 (t, *J* = 6.9 Hz, 3H). **^{13}C NMR** (75 MHz, DMSO-d_6) δ 173.51 (C), 142.31 (C), 134.32 (C), 133.89 (CH), 133.52 (CH), 131.37 (CH), 130.78 (C), 126.24 (CH), 126.11 (CH), 121.38 (C), 112.87 (CH), 50.18 (CH_2), 47.49 (CH_2), 43.48 (CH_2), 30.82 (CH_2), 28.48 (CH_2), 19.24 (CH_3), 17.72 (CH_3). **HRMS** (ESI-TOF): m/z calculated for $C_{20}H_{24}N_2NaO$+ ([M+Na]+) 331.1781, found 331.1782.

8-Benzyl-N,N-diethyl-5,6-dihydroindolizine-1-carboxamide (8f')



Carried out at 80ºC for 23 hours. The product was isolated by flash chromatography (10 to 40 % EtOAc/Hexanes) as a yellow oil (14% yield). **^{1}H NMR** (500 MHz, DMSO-d_6) δ 7.23 (t, *J* = 7.4 Hz, 2H), 7.14 (t, *J* = 7.4 Hz, 1H), 7.09 (d, *J* = 7.5 Hz, 2H), 6.73 (d, *J* = 2.7 Hz, 1H), 5.92 (d, *J* = 2.7 Hz, 1H), 5.46 (t, *J* = 4.7 Hz, 1H), 3.90 (t, *J* = 7.3 Hz, 2H), 3.65 (s, 2H), 3.31 – 3.24 (m, 2H), 2.88 (q, *J* = 6.4 Hz, 2H), 2.40 (q, *J* = 6.8 Hz, 2H), 1.03 (t, *J* = 7.1 Hz, 3H), 0.88 (t, *J* = 7.0 Hz, 3H). **^{13}C NMR** (126 MHz, DMSO-d_6) δ 168.04 (C), 139.84 (C), 131.48 (C), 128.98 (CH), 128.49 (CH), 127.17 (C), 126.30 (CH), 120.98

(CH), 120.42 (CH), 116.64 (C), 106.77 (CH), 43.61 (CH_2), 43.18 (CH_2), 39.01 (CH_2), 37.58 (CH_2), 24.25 (CH_2), 14.35 (CH_3), 13.16 (CH_3). **HRMS** (ESI-TOF): m/z calculated for $C_{20}H_{24}N_2NaO^+$ ([M+H]+) 331.1781, found 331.1782.

Products **8f** and **8f'** can isomerize even in $CDCl_3$, probably due to the presence of traces of acid, to reach an equilibrium (**8f : 8f'** = 1 : 1.5, after 4 days).

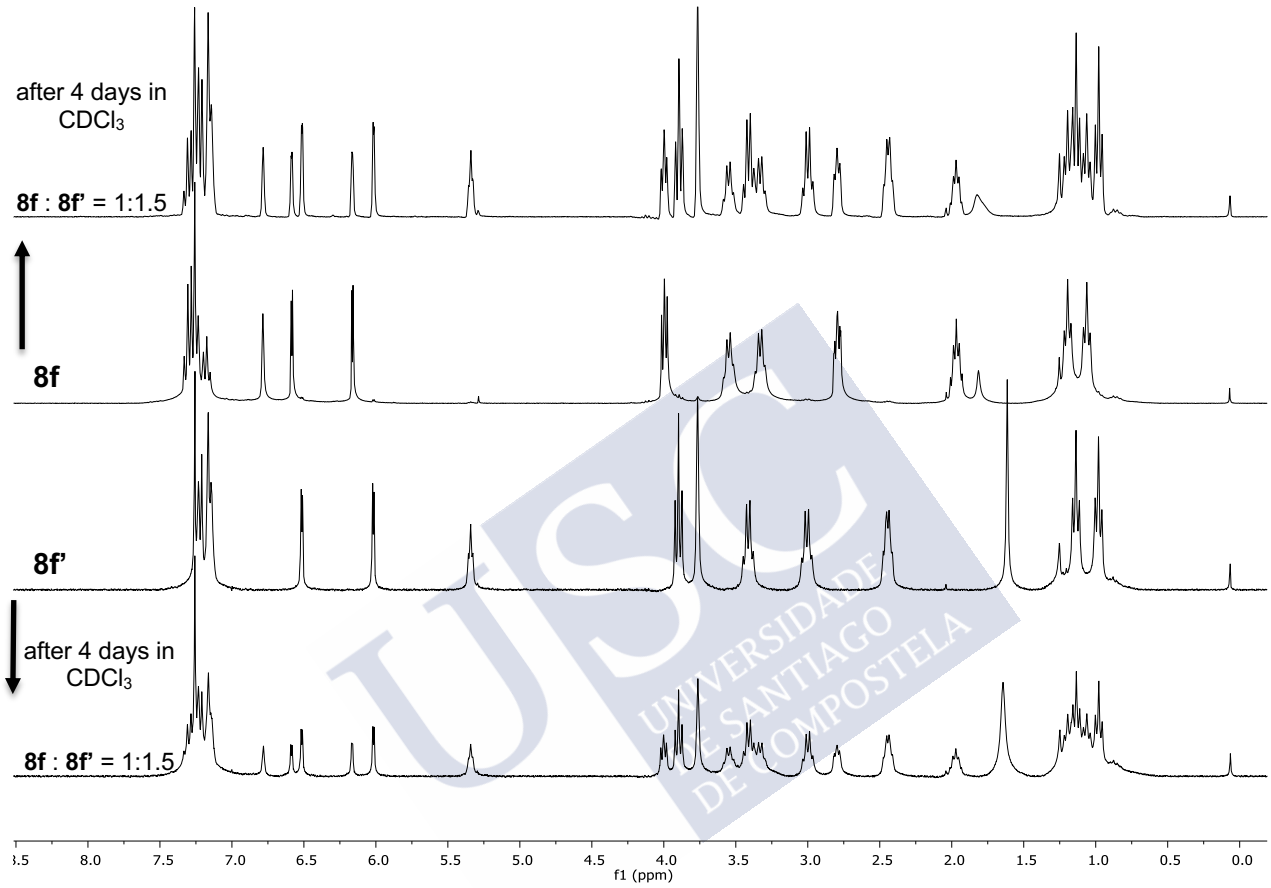
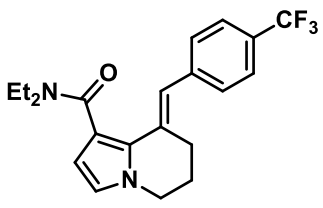


Figure S6. ^{1}H NMR spectra of **8f** and **8f'** and after after 4 days in $CDCl_3$.

(*E*)-*N,N*-Diethyl-8-(4-(trifluoromethyl)benzylidene)-5,6,7,8-tetrahydroindolizine-1-carboxamide (8g)



Carried out at 80ºC for 23 hours. The product was isolated by flash chromatography (10 to 40 % EtOAc/Hexanes) as a yellow oil in 69% yield. Additionally, a 10% yield of the isomer **8g'** was obtained.**^{1}H NMR** (500 MHz, DMSO-d_6) δ 7.68 (d, J = 8.1 Hz, 2H), 7.43 (d, J = 8.0 Hz, 2H), 6.86 (d, J = 2.7 Hz, 1H), 6.64 (s, 1H), 6.07 (d, J = 2.6 Hz, 1H), 4.06 – 3.99 (m, 2H), 3.47 – 3.37 (m, 2H), 3.27 – 3.16 (m, 2H), 2.77 (t, J = 5.3 Hz, 2H), 1.90 (p, J = 6.1 Hz, 2H), 1.08 (t, J = 7.0 Hz, 3H), 0.98 (t, J = 7.1 Hz, 3H). **^{13}C NMR** (126 MHz, DMSO-d_6) δ 168.63 (C), 141.75 (C), 132.17 (C), 129.65 (CH), 126.63 (C, q, J = 31.8 Hz), 125.65 (CH, q, J = 3.7 Hz), 125.59 (C), 124.81 (CF_3, q, J = 271.8 Hz), 122.02 (CH), 119.75 (CH), 117.49 (C), 108.32 (CH), 45.43 (CH_2), 42.80 (CH_2),

38.80 (CH_2), 26.11 (CH_2), 23.68 (CH_2), 14.49 (CH_3), 12.98 (CH_3). **^{19}F NMR** (282 MHz, DMSO-d_6) δ -60.83. **HRMS** (ESI-TOF): m/z calculated for $C_{21}H_{23}F_3N_2NaO$+ ([M+Na]+) 399.1655, found 399.1656. Products **8g** and **8g'** do isomerize in soft acidic media such as $CDCl_3$ to reach an equilibrium between then (**8g : 8g'** = 1 : 2, after 7 days.

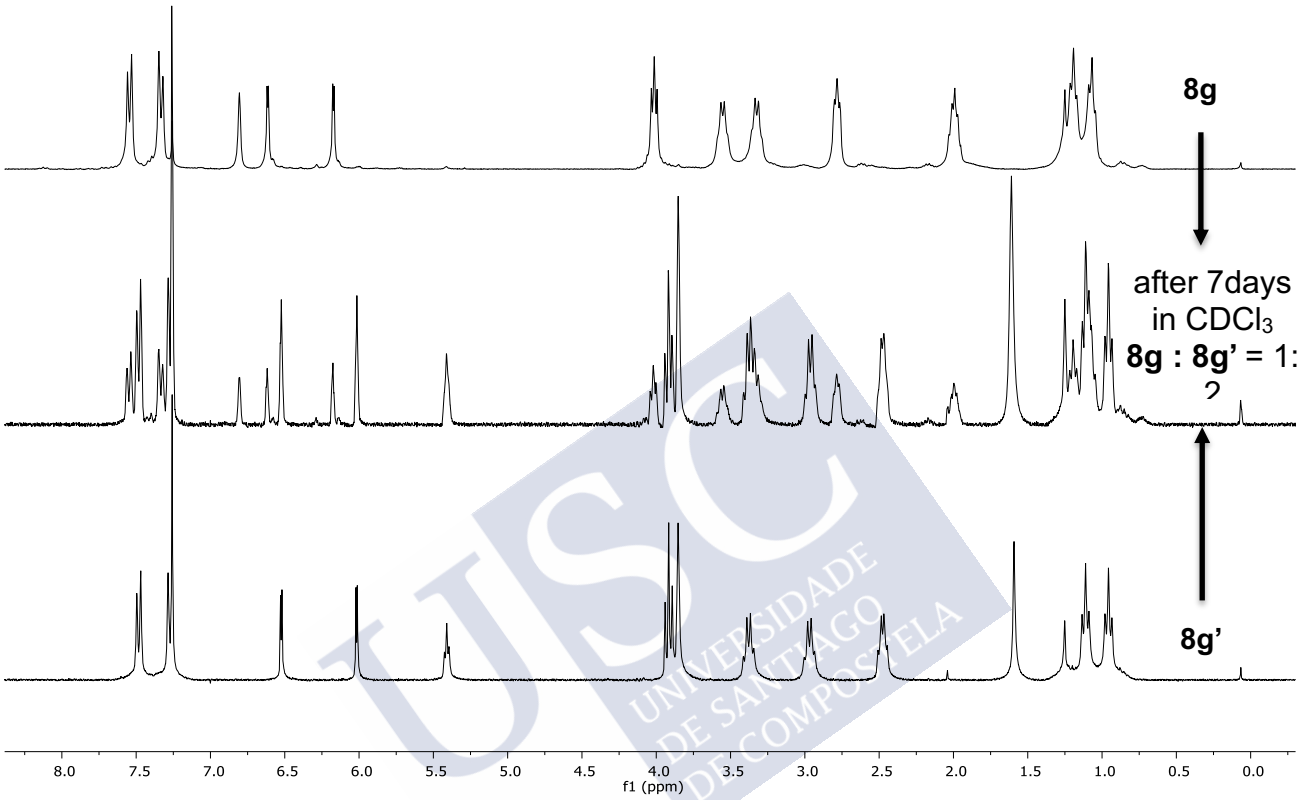
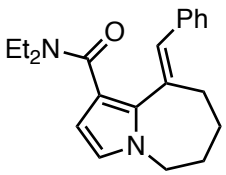


Figure S7. ^{1}H NMR spectra of **8g** and **8g'** after purification and after 7 days in $CDCl_3$.

(*E*)-9-Benzylidene-*N*,*N*-diethyl-6,7,8,9-tetrahydro-5*H*-pyrrolo[1,2-*a*]azepine-1-carboxamide (8h)



According to the general procedure**,** the product was isolated by flash chromatography (5 to 30% EtOAc/Hexanes) as a light brown solid in 96 % yield, m.p. 92-93 ºC. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.33 – 7.11 (m, 5H), 6.59 (s, 1H), 6.46 (d, *J* = 2.8 Hz, 1H), 6.03 (d, *J* = 2.7 Hz, 1H), 3.92 – 3.80 (m, 2H), 3.50 – 3.17 (m, 4H), 2.58 – 2.46 (m, 2H), 1.93 – 1.75 (m, 4H), 1.15 – 0.90 (m, 6H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 168.85 (C), 137.58 (C), 134.96 (C), 133.04 (C), 131.64 (CH), 128.91 (CH), 128.27 (CH), 126.80 (CH), 122.17 (CH), 118.27 (C), 106.75 (CH), 50.10 (CH_2), 43.18 (CH_2), 38.96 (CH_2), 30.34 (CH_2), 29.24 (CH_2), 28.60 (CH_2), 14.23 (CH_3), 13.26 (CH_3). **HRMS** (ESI-TOF): m/z calculated for $C_{21}H_{27}N_2O$ ($[M+H]^+$) 323.2117, found 323.2118.

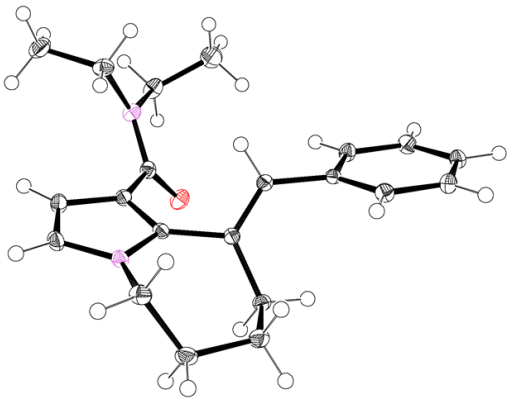
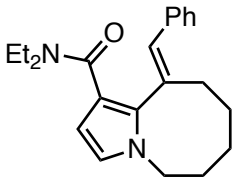


Figure S8. X-ray structure of **8h** [CCDC 1841781 (see page S45)]

(*E*)-10-Benzylidene-*N*,*N*-diethyl-5,6,7,8,9,10-hexahydropyrrolo[1,2-*a*]azocine-1-carboxamide (8i)



According to the general procedure**,** the product was isolated by flash chromatography (5 to 30% EtOAc/Hexanes) as a light brown solid in 81 % yield, m.p. 95-97 ºC. **^{1}H NMR** (300 MHz, $CDCl_3$, 60ºC): δ 7.34 – 7.29 (m, 4H), 7.27 – 7.20 (m, 1H), 6.55 (s, 1H), 6.53 – 6.49 (m, 1H), 6.19 – 6.14 (m, 1H), 4.01 – 3.93 (m, 2H), 3.53 – 3.41 (m, 4H), 2.78 – 2.70 (m, 2H), 1.79 – 1.69 (m, 2H), 1.57 – 1.39 (m, 4H), 1.19 – 1.09 (m, 6H). **^{13}C NMR** (75 MHz, $CDCl_3$, 60ºC): δ 168.28 (C), 137.68 (C), 135.95 (C), 135.35 (C), 133.21 (CH), 129.15 (CH), 128.23 (CH), 126.85 (CH), 118.90 (CH), 117.30 (C), 107.13 (CH), 46.80 (CH_2), 41.24 (CH_2), 34.95 (CH_2), 31.98 (CH_2), 26.13 (CH_2), 25.94 (CH_2), 13.87 (CH_3). **HRMS** (ESI-TOF): m/z calculated for $C_{22}H_{29}N_2O$ ($[M+H]^+$) 337.2274, found 337.2274. Assignment of structure of **8i** was based on the nOe experiments.

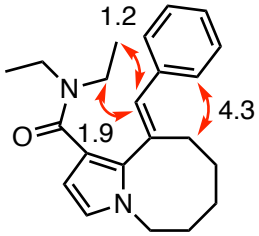
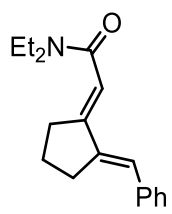


Figure S9. Significant nOe signals observed for **8i**.

(*E*)-2-((*E*)-2-Benzylidenecyclopentylidene)-N,N-diethylacetamide (2a')



^{1}H NMR (750 MHz, $CDCl_3$) δ 7.41 (d, *J* = 7.7 Hz, 2H), 7.36 (t, *J* = 7.2 Hz, 2H), 7.28 – 7.22 (m, 1H), 6.96 (s, 1H), 6.51 (s, 1H), 3.49 – 3.40 (m, 4H), 2.91 (t, *J* = 7.4 Hz, 2H), 2.71 (t, *J* = 7.3 Hz, 2H), 1.79 (p, *J* = 7.9, 7.4 Hz, 2H), 1.23 (t, *J* = 7.1 Hz, 3H), 1.17 (t, *J* = 7.1 Hz, 3H).**^{13}C NMR (75 MHz, $CDCl_3$) δ** 167.09 (C), 156.75 (C), 143.35 (C), 137.45 (C), 129.15 (CH), 128.32 (CH), 127.12 (CH), 121.72 (CH), 108.44 (CH), 42.46

(CH_2), 40.17 (CH_2), 32.03 (CH_2), 32.00 (CH_2), 24.56 (CH2), 14.77 (CH_3), 13.32 (CH_3). **HRMS** (ESI-TOF): m/z calculated for $C_{18}H_{24}NO$ ($[M+H]^+$) 270.1852, found 270.1849. Assignment of structure of **2'** was based on the HMBC, HSQC, COSY and nOe experiments

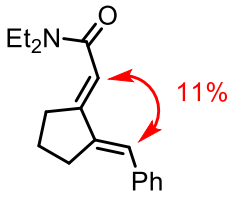
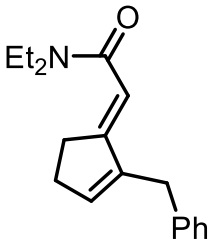


Figure S10. Significant nOe signals observed for **2'**

(*E*)-2-(2-Benzylcyclopent-2-en-1-ylidene)-*N,N*-diethylacetamide (3a')



^{1}H NMR (500 MHz, $CDCl_3$) δ 7.31 (d, *J* = 8.1 Hz, 2H), 7.25 (t, *J* = 7.8 Hz, 2H), 7.09 (t, *J* = 7.3 Hz, 1H), 6.13 (d, *J* = 2.6 Hz, 1H), 5.95 (s, 1H), 3.35 (q, *J* = 7.1 Hz, 2H), 3.28 – 3.13 (m, 4H), 2.94 – 2.82 (m, 2H), 2.55 – 2.42 (m, 2H), 1.15 – 1.05 (m, 6H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 170.10 (C), 148.24 (C), 140.03 (C), 138.32 (C), 135.74 (CH), 128.31 (CH), 128.13 (CH), 125.86 (CH), 116.97 (CH), 42.55 (CH_2), 39.97 (CH_2), 33.49 (CH_2), 31.10 (CH_2), 30.09 (CH_2), 14.44 (CH_3), 12.96 (CH_3). **HRMS** (ESI-TOF): m/z calculated for $C_{18}H_{24}NO$ ($[M+H]^+$) 270.1852, found 270.1854. Assignment of structure of **3a'** was based on the HMBC, HSQC, COSY and nOe experiments.

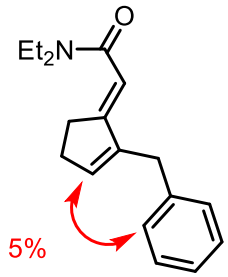
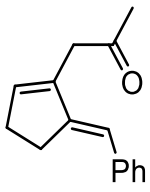


Figure S11. Significant nOe signals observed for **3'**

(*E*)-1-(5-Benzylidenecyclopent-1-en-1-yl)propan-2-one (5c)



Carried out at 120ºC for 45 hours. The product was isolated by flash chromatography (10 to 40 % EtOAc/Hexanes) as a yellow oil (42% yield). **^{1}H NMR** (500 MHz, $CDCl_3$) **δ** 7.33 – 7.29 (m, 2H), 7.29 – 7.22 (m, 2H), 6.10 (s, 1H), 6.07 (s, 1H), 3.31 (s, 2H), 2.94 – 2.84 (m, 2H), 2.57 – 2.50 (m, 2H), 2.12 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 207.12 (C), 148.30 (C), 139.84 (C), 138.61 (C), 138.46 (CH), 128.73 (CH), 128.57 (CH), 126.40 (CH), 118.24 (CH), 43.65 (CH_2), 31.60 (CH_2), 30.40 (CH_2), 29.38 (CH_3). **HRMS (**ESI-TOF): m/z calculated for $C_{15}H_{17}O$ ($[M+H]^+$) 213.1274, found 213.1277.

Mechanistic probe: NMR spectra of *D*-2i', resulting from the cycloaddition of *D*-1i (90% deuterium content)

As can be seen in the following Figure, deuteration of *d*-**2i'** is only observed at the olefinic (signal at 7.93 ppm). While in **2i'** this signal integrates for 1H, that of *d*-**2i'** corresponds to 0.1H. Accordingly, ^{2}H-NMR spectra of *d*-**2i'** shows that deuterium is only located at this particular position.

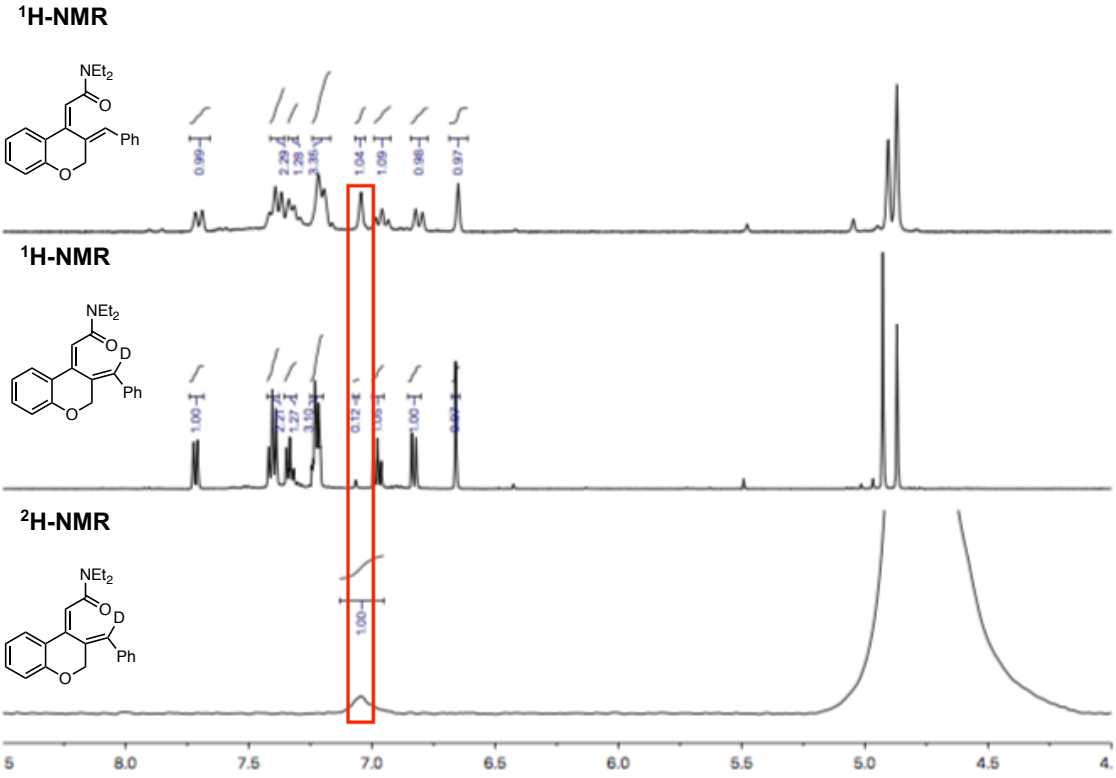
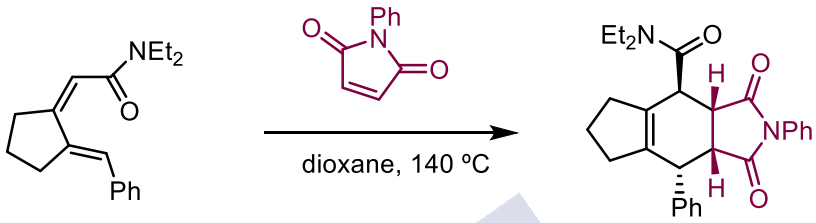


Figure S12. Spectral evidence of exclusive deuterium incorporation into the distal position of the alkene

Tandem, one pot Ir-catalyzed hydrocarbonation/ [4 + 2] cycloaddition.

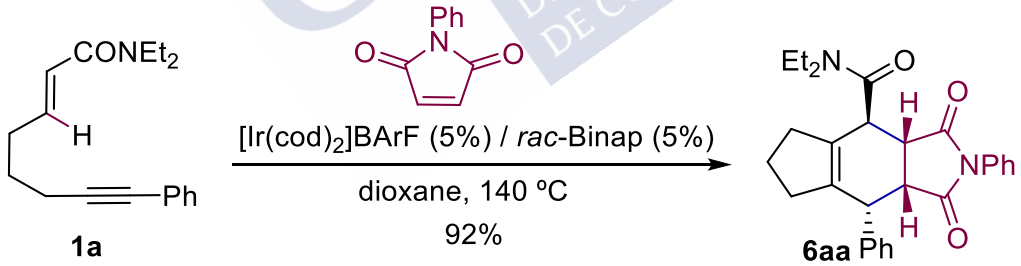
Independent preparation of the Diels-Alder adduct 6aa from 2a

An oven dried sealed tube equipped with a magnetic stir bar was charged with N-phenylmaleimide (4.5 equiv), (*Z*)-2-(2-((*E*)-benzylidene)cyclopentylidene)-*N*,*N*-diethylacetamide (**2a**, 1.0 equiv) and dioxane (0.124 M). The reaction mixture was then stirred at 140 °C. After 24 h, the reaction mixture was concentrated in vacuo. Purification of the crude product by flash chromatography on silica gel (1:10 to 1:2 EtOAc: Hexane) afforded the desired product in 90 % yield.

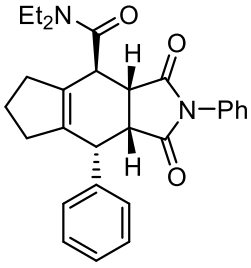


One-pot general procedure for the synthesis of tandem products (exemplified for **6aa**).

An oven dried sealed tube equipped with a magnetic stir bar was charged with (+/-)-BINAP (5.8 mg, 0.05 equiv), [Ir(cod)$_2$]BArF (11.8 mg, 0.05 equiv), N-Phenylmaleimide (112.5 mg, 3.5 equiv), the alkyne-tethered amide substrate **1a** (50 mg, 1.0 equiv) and dioxane (1.5 mL, 0.124 M). The reaction mixture was then stirred at 140 °C. After 24 h, the mixture was concentrated in vacuo. Purification of the crude product by flash chromatography on silica gel (typically 1:10 to 1:2 EtOAc: Hexane) afforded the desired product as yellowish oil (76 mg, 92 %).



(*3aR,4S,8R,8aR*)-*N,N*-Diethyl-1,3-dioxo-2,8-diphenyl-1,2,3,3a,4,5,6,7,8,8a-decahydrocyclopenta[*f*]isoindole-4-carboxamide (6aa)



.^{1}**H NMR** (750 MHz, C_6D_6): δ 7.12 (d, *J* = 6.9 Hz, 2H), 7.04 – 6.96 (m, 4H), 6.95 (t, *J* = 6.8 Hz, 1H), 6.90 (t, *J* = 7.5 Hz, 1H), 6.62 (d, *J* = 7.2 Hz, 2H), 4.32 (s, 1H), 3.87 (d, *J* = 8.0 Hz, 1H), 3.66 – 3.57 (m, 2H), 3.54 (t, *J* = 8.5 Hz, 1H), 3.34 – 3.26 (m, 1H), 3.16 – 3.09 (m, 1H), 2.97 – 2.89 (m, 1H), 2.48 – 2.41 (m, 1H), 2.24 – 2.17 (m, 1H), 2.09 – 2.01 (m, 2H), 1.74 – 1.65 (m, 1H), 1.65 – 1.57 (m, 1H), 1.11 (t, *J* = 7.1 Hz, 3H), 1.02 (t, *J* = 7.0 Hz, 3H). ^{13}**C NMR** (189 MHz, C_6D_6): δ 178.53 (C), 175.91 (C), 172.36 (C), 139.09 (C), 138.74 (C), 133.94 (C), 132.97 (C), 130.01 (CH),

129.14 (CH), 128.92 (CH), 128.71 (CH), 128.01 (CH), 127.02 (CH), 45.72 (CH), 43.55 (CH), 43.28(CH_2), 42.94 (CH), 41.70 (CH_2), 37.05 (CH), 35.41 (CH_2), 34.55 (CH_2), 22.38 (CH_2), 15.24 (CH_3), 13.67 (CH_3). **HRMS** (ESI-TOF):m/z calculated for $C_{28}H_{31}N_2O_3$ ($[M+H]^+$) 443.2329, found 443.2330. Assignment of structure of **6aa** was based on the HMBC, HSQC, COSY and nOe experiments

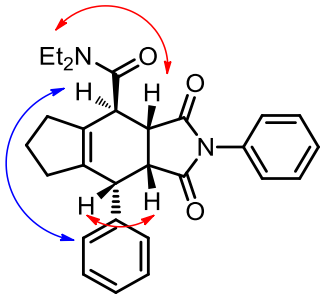
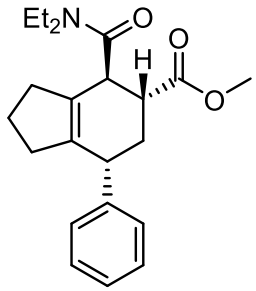


Figure S13. Significant nOe signals observed for **6aa**

(*4S,5R,7R*)-Methyl 4-(diethylcarbamoyl)-7-phenyl-2,3,4,5,6,7-hexahydro-1*H*-indene-5-carboxy late (6ab)



This synthesis was carried out with 9 equivalents of methyl acrylate. Using the one-pot procedure the product was isolated by flash chromatography (10 to 40 % EtOAc/Hexanes) as yellow oil (80% yield). **^{1}H NMR** (500 MHz, C_6D_6) δ 7.33 – 7.26 (m, 4H), 7.23 (m, 1H), 4.35 – 4.25 (m, 1H), 4.13 – 4.06 (m, 1H), 3.44 – 3.36 (m, 1H), 3.31 (m, 5H), 2.95 (q, J = 7.2 Hz, 1H), 2.65 – 2.55 (m, 1H), 2.45 – 2.32 (m, 1H), 2.32 – 2.22 (m, 3H), 2.22 – 2.13 (m, 2H), 2.00 – 1.87 (m, 1H), 1.81 (m, 1H), 1.05 (t, J = 7.0 Hz, 3H), 0.90 (t, J = 7.1 Hz, 3H). **^{13}C NMR** (126 MHz, C_6D_6) δ 173.86 (C), 172.34 (C), 140.10 (C), 138.81 (C), 134.89 (C), 129.57 (CH), 128.39 (CH), 127.23 (CH), 50.62 (CH_3), 44.21 (CH), 42.85 (CH), 42.12 (CH2), 40.67 (CH2), 37.25 (CH), 34.93 (CH2), 34.79 (CH2), 24.69 (CH2), 22.42 (CH_2), 15.11 (CH_3), 13.44 (CH_3). **HRMS** (ESI-TOF): m/z calculated for $C_{22}H_{29}NNaO_3^+$ ([M+Na]+) 378.2040, found 378.2045. Assignment of structure of **6ab** was based on the HMBC, HSQC, COSY and nOe experiments

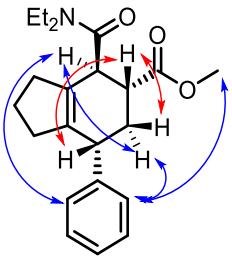
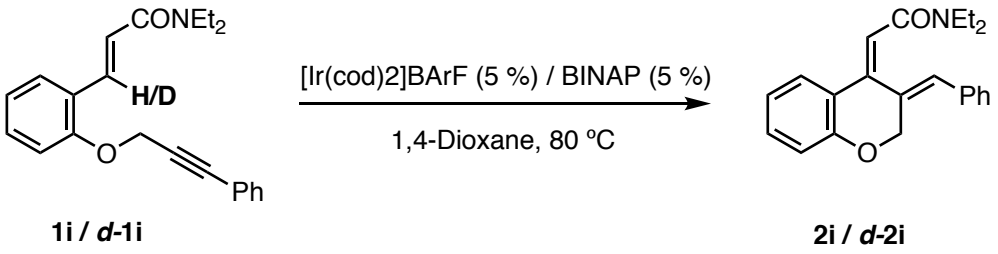
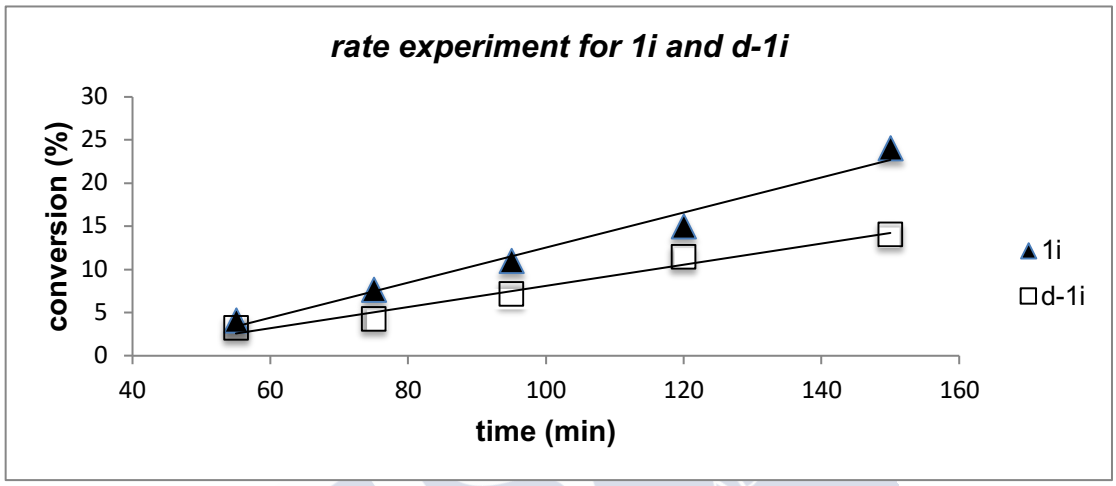


Figure S14. Significant nOe signals observed for **6ab.**

Determination of the Kinetic Isotope effect



1i / *d*-1i **2i / *d*-2i**



In two different Schlenk flasks equipped with the corresponding stirring bars, *rac*-BINAP (7.5 mg, 0.012 mmol), $Ir(cod)_2BArF$ (15.3 mg, 0.012 mmol) and **1i** (80 mg, 0.24 mmol, Schlenk 1) or ***d*-1i** (80.3 mg, 0.24 mmol, Schlenk 2), were sequentially added under Argon. Dioxane (1.9 mL, each reaction) was then added and the flasks were sealed with rubber septa and placed in a preheated (80 °C) oil bath. Aliquots (200 μL) were taken at the times indicated in the Table S2 (for **1i**) and Table S3 (for *d*-**1i**). The aliquots were filtered through a florisil pad and the volatiles were removed so that the crude residues were taken and analyzed by ^{1}H NMR.

Table S2. Conversions observed from the reaction of **1i** (determined by ^{1}H-NMR).

t (min)	2i (%)
55	4.1
75	7.6
95	11
120	15
150	24

y = 0,2033x - 7,7835
R^2 = 0,97852

Table S3. Conversions observed from the reaction of ***d*-1i** (determined by ^{1}H-NMR).

t (min)	***d*-2i (%)**
55	3.2
75	4.2
95	7.1
120	11.4
150	14

y = 0,1227x - 4,1666
R^2 = 0,97671

KIE=(0.2033)/(0.1227)=1.7

Considering that D-**1i** has 90% deuterium content, the resulting KIE is of 1.90

COMPUTATIONAL DETAILS

Computational analysis was performed with Gaussian 09.[9] The geometries of all complexes here reported were optimized using the M06 hybrid functional. Optimizations were carried out using the 6-31G(d,p) basis set for C, H, O, N, and P. The SDD (with an additional f orbital) [(a) Andrae, D.; Haeussermann, U.; Dolg, M.; Stoll, H.; Preuss, H. *Theor. Chim. Acta* **1990**, *77*, 123-141; (b) Ehlers, A. W.; Böhme, M.; Dapprich, S.; Gobbi, A.; Höllwarth, A.; Jonas, V.; Köhler, K. F.; Stegmann, R.; Veldkamp, A.; Frenking, G. *Chem. Phys. Lett.* **1993**, *208*, 111-114] basis set was used for Ir. Harmonic frequencies were calculated at the same level to characterize the stationary points and to determine the zero-point energies (ZPE). The starting approximate geometries for the transition states (TS) were located graphically. Intrinsic reaction coordinate (IRC) studies were performed in ambiguous cases to confirm the relation of the transition states with the corresponding minima. Single-point calculations were performed using the 6-311++G(d,p) basis set for C, H, O, N and P, and SDD (with an additional f orbital) for Ir. Electronic energy values calculated with the smaller basis set have been corrected using the residual energy at the zero point vibrational energy (ZPE). The evaluation of enthalpy (H) and Gibbs free energy (G) implies the use of the harmonic-oscillator/rigid rotor approximation, which introduces some uncertainty in the calculation of the vibrational entropy. Unless otherwise stated, the energy values included in the main text refer to the single point calculations performed with the higher quality base on previously optimized structures. To obtain solvation-corrected relative free-energies, we employed a self-consistent reaction field (SCRF) method using the SMD model [Marenich, A. V.; Cramer, C. J.; Truhlar, D. G. *J. Phys. Chem. B* **2009**, *113*, 6378.] to do single-point calculations for all the species studied. 1,4-Dioxane (ε=2.2099) was employed as the solvent, corresponding to the experimental conditions.

NOTES:

Several isomers of **Int-1** have been analysed resulting in significantly higher energetic profiles, compared to those from I**nt-1a** and **Int-1b**.

As can be seen in Figure 15, the C-H activation can equally occur from **Int-0'**, wherein the alkyne is coordinated to the Ir, with a similar barrier than that from **Int-0** ($\Delta\Delta G$ (**TS1'**-**TS1**)= 0.1 kcal mol^{-1}).

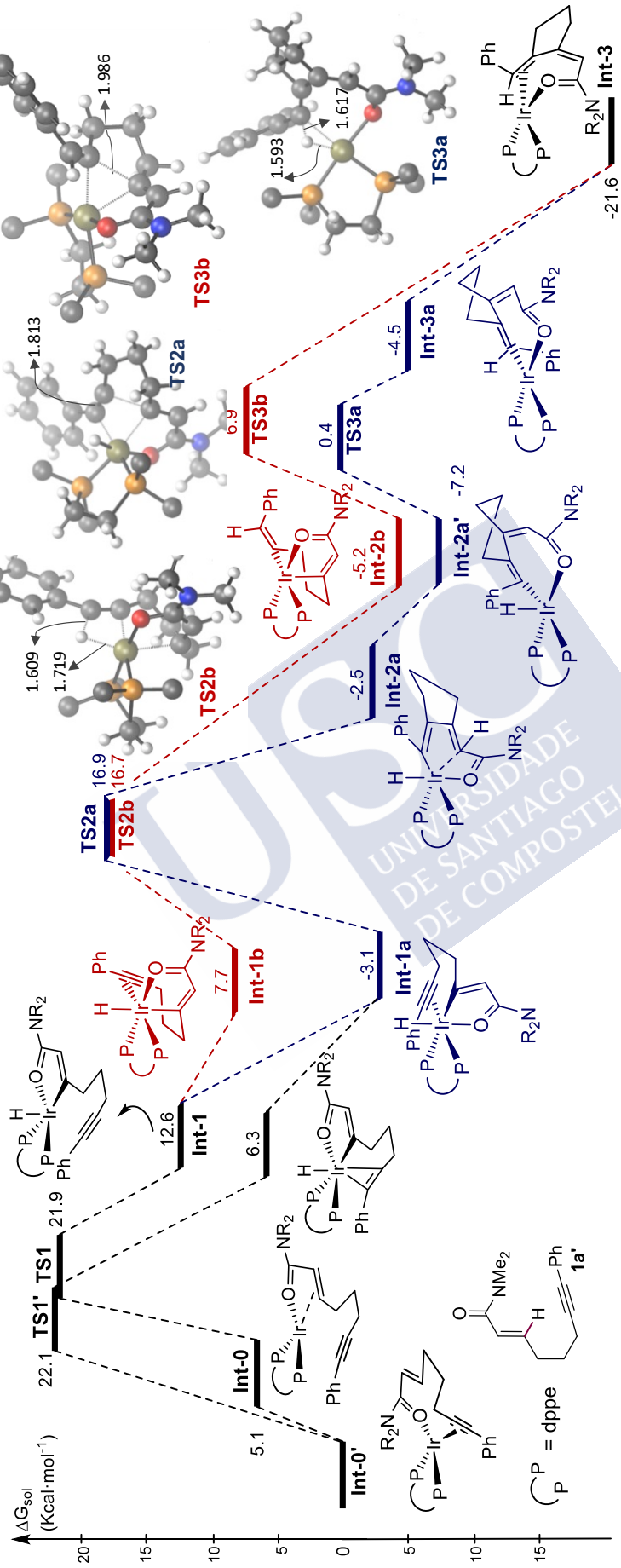


Figure S15. Calculated energy profile ΔG_{solv} (kcal·mol^{-1}) for the hydrocarbonation of 1a' (R = Me) [M06/6-31G(d,p); SDD for Ir // M06/6-311++G(d,p); SDD for Ir]. . Key bond distances in Å.

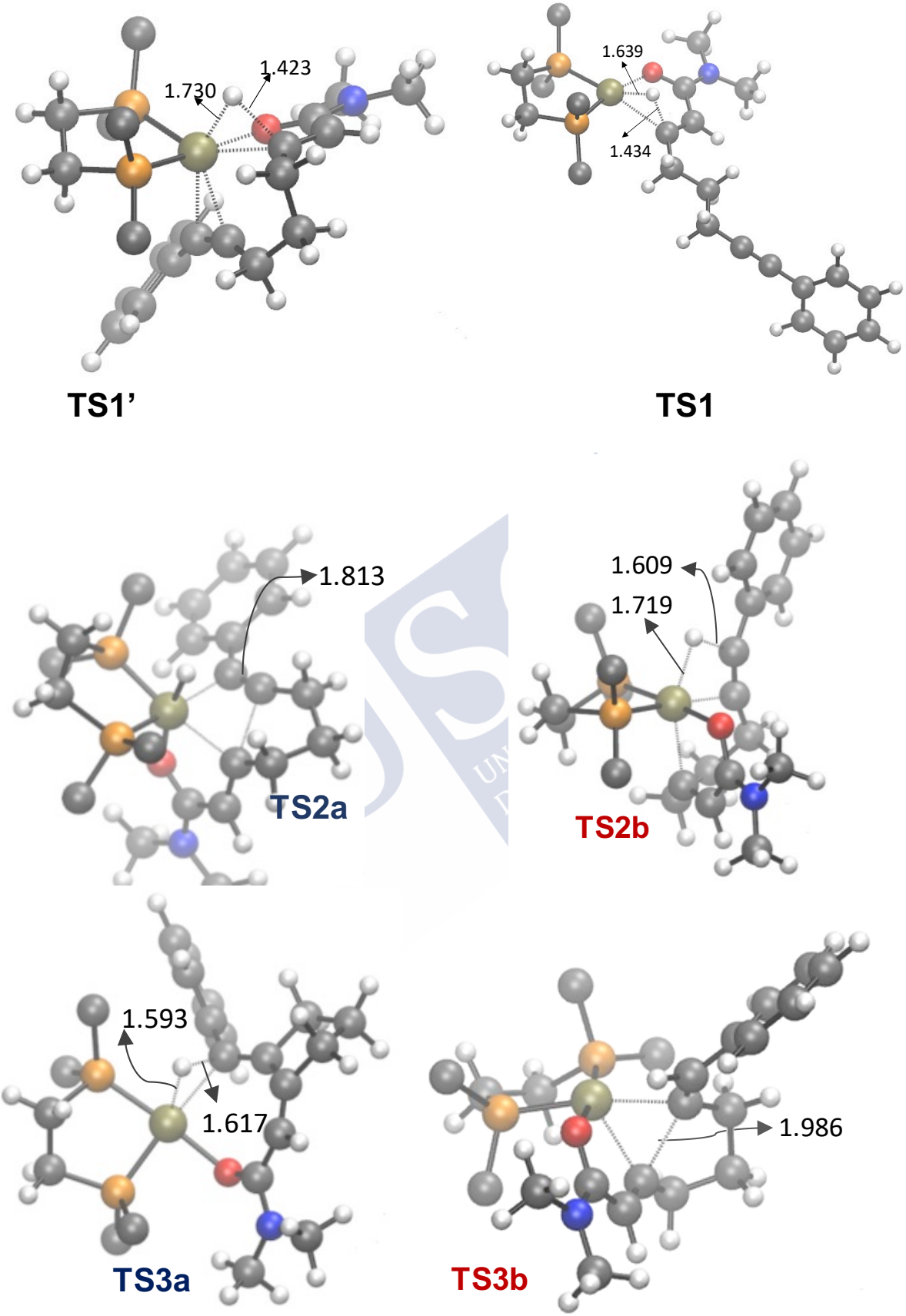


Figure S16. Key transition states (**TS1**, **TS1'**, **Ts2a**, **TS3a, TS2b**, and **TS3b**) Phenyl rings of dppe ligand are omitted for clarity.

CARTESSIAN COORDINATES and ENERGIES

Int-0'

Zero-point correction= 0.737700 (Hartree/Particle)
Thermal correction to Energy= 0.783463
Thermal correction to Enthalpy= 0.784408
Thermal correction to Gibbs Free Energy= 0.655660
Sum of electronic and zero-point Energies= -2541.213357
Sum of electronic and thermal Energies= -2541.167594
Sum of electronic and thermal Enthalpies= -2541.166650
Sum of electronic and thermal Free Energies= -2541.295398
HF (M06/6-311+G(d,p) and SDD, SMD[1-4 dioxane])= -2542.4016149000

C	2.074105	-1.116916	2.503861
O	1.751670	-0.884566	1.311025
N	2.978917	-2.077693	2.767974
C	3.439042	-2.961624	1.712527
H	2.703487	-2.994961	0.906293
H	4.404422	-2.627828	1.307768
H	3.565807	-3.968465	2.125193
C	3.600746	-2.263454	4.067730
H	4.660208	-2.499663	3.919914
H	3.550264	-1.350464	4.663757
H	3.137163	-3.089150	4.622970
C	1.442728	-0.420124	3.631502
C	0.804927	0.740507	3.445844
H	1.387977	-0.934171	4.591520
H	0.890433	1.221233	2.465293
C	-0.163562	1.327745	4.412083
H	0.200075	1.226077	5.442741
H	-0.306004	2.399210	4.218466
C	-1.510060	0.597402	4.291374
H	-2.228352	1.073898	4.970100
H	-1.386155	-0.439402	4.633237
C	-2.118670	0.592627	2.884887
H	-2.169295	1.625383	2.505398
H	-3.159403	0.245143	2.962675
C	-1.455262	-0.275121	1.885677
C	-1.269426	-1.302387	1.183042
Ir	0.037326	0.157580	0.309158
P	1.467543	0.783964	-1.404382
P	-1.550345	1.073108	-0.946059
C	2.983604	1.750408	-1.121536
C	3.146351	2.425309	0.090228
C	3.960170	1.865411	-2.116123
C	4.275236	3.209901	0.306974
H	2.384326	2.328151	0.864992
C	5.086681	2.647772	-1.895757
H	3.842948	1.334061	-3.060612
C	5.244007	3.318613	-0.684889
H	4.400722	3.731722	1.252741
H	5.846661	2.732977	-2.668856
H	6.129009	3.926869	-0.513776
C	2.016132	-0.739722	-2.246361
C	1.421859	-1.202841	-3.422983
C	2.987424	-1.526339	-1.614987
C	1.785439	-2.437423	-3.953952
H	0.671912	-0.606232	-3.938931
C	3.351059	-2.755158	-2.150925
H	3.445081	-1.176339	-0.690763
C	2.746177	-3.216216	-3.318146
H	1.319493	-2.786843	-4.872265
H	4.110532	-3.356934	-1.655575
H	3.029978	-4.179430	-3.735288
C	-2.089884	2.761034	-0.485095
C	-1.413373	3.453438	0.522908
C	-3.123730	3.401611	-1.178488
C	-1.767434	4.762277	0.839727
H	-0.600997	2.953936	1.054354
C	-3.478581	4.706150	-0.858480
H	-3.661482	2.875058	-1.966925
C	-2.801173	5.386727	0.150810
H	-1.234199	5.293847	1.624565
H	-4.285885	5.195226	-1.398321
H	-3.080093	6.408307	0.397872
C	-3.073627	0.082875	-1.124141
C	-3.027727	-1.082795	-1.897028
C	-4.224031	0.364817	-0.382365
C	-4.124435	-1.934109	-1.952685
H	-2.122411	-1.348233	-2.443586
C	-5.317540	-0.494585	-0.432707
H	-4.271477	1.261721	0.234284
C	-5.270823	-1.640679	-1.220117
H	-4.074654	-2.838523	-2.554688
H	-6.211007	-0.263567	0.142765
H	-6.127154	-2.309902	-1.258498
C	-0.936739	1.325788	-2.683355
C	0.517454	1.775807	-2.647063
H	0.587756	2.815327	-2.294746
H	0.996478	1.737953	-3.634170
H	-1.045894	0.372466	-3.214202
H	-1.575857	2.056978	-3.193336
C	-1.485112	-2.622049	0.645133
C	-0.600173	-3.191236	-0.281382
C	-2.642787	-3.325171	1.010073
C	-0.874761	-4.434999	-0.835578
H	0.292815	-2.636533	-0.571972
C	-2.908841	-4.568149	0.452971
H	-3.337460	-2.873997	1.716926
C	-2.028639	-5.124880	-0.472947
H	-0.183033	-4.864890	-1.556941
H	-3.812265	-5.103620	0.736031
H	-2.242832	-6.097200	-0.910546

Int-0

Zero-point correction= 0.738063 (Hartree/Particle)
Thermal correction to Energy= 0.784077
Thermal correction to Enthalpy= 0.785021
Thermal correction to Gibbs Free Energy= 0.653570
Sum of electronic and zero-point Energies= -2541.201348
Sum of electronic and thermal Energies= -2541.155335
Sum of electronic and thermal Enthalpies= -2541.154390
Sum of electronic and thermal Free Energies= -2541.285841
HF (M06/6-311+G(d,p) and SDD, SMD[1-4 dioxane])= - -2542.3914746400

C	0.290996	-0.154284	-2.287460
C	0.330259	-1.417224	-1.676004
H	1.226790	-1.777908	-1.174477
Ir	-1.146181	-0.231667	-0.566229
H	-0.464014	0.008115	-3.062714
C	-0.775190	-2.362906	-1.944121
O	-1.933507	-1.853400	-1.832153
N	-0.575638	-3.651632	-2.203167
C	0.741085	-4.208797	-2.465144
H	1.113002	-4.764489	-1.595861
H	0.671932	-4.896855	-3.314455
C	-1.693235	-4.578786	-2.275113
H	-1.897365	-4.854634	-3.316275
H	-2.584728	-4.118418	-1.847039
P	-2.994733	0.102128	0.804116
P	-0.188840	1.275542	0.792495
C	-3.338827	-1.442276	1.711246
C	-3.742654	-2.553847	0.960491
C	-3.993163	-3.765650	1.589638
C	-3.835578	-3.882165	2.969395
C	-3.432959	-2.782621	3.718184
C	-3.185067	-1.562922	3.093156
C	-4.575998	0.578617	0.048664
C	-5.751605	0.581444	0.806923
C	-6.946790	0.986079	0.227298
C	-6.974577	1.383385	-1.108141
C	-5.809279	1.376056	-1.866835

C	-4.608175	0.973439	-1.290422
C	-2.623058	1.398079	2.065270
C	-1.137908	1.344532	2.389922
C	-0.275398	3.015389	0.226485
C	0.119381	4.077625	1.049883
C	-0.018091	5.390711	0.616497
C	-0.561325	5.659018	-0.637609
C	-0.969505	4.612979	-1.457350
C	-0.827962	3.296770	-1.027095
C	1.523737	0.959362	1.339207
C	2.568056	1.877073	1.200207
C	3.854189	1.539734	1.612005
C	4.106723	0.289121	2.165521
C	3.071563	-0.632283	2.304632
C	1.786925	-0.301925	1.889530
H	-0.814976	2.202736	2.991531
H	-0.883431	0.433809	2.949682
H	-2.882123	2.357388	1.594525
H	-3.260992	1.292899	2.951518
H	1.454649	-3.424024	-2.725650
H	-1.444302	-5.484565	-1.711382
C	1.494443	0.747690	-2.387789
H	1.637395	0.982926	-3.454239
H	1.279206	1.719852	-1.915859
C	2.790490	0.179797	-1.832787
H	2.679625	-0.080486	-0.771241
H	3.050991	-0.749184	-2.361344
C	3.948016	1.169647	-1.969804
H	4.114959	1.409688	-3.030585
H	3.672914	2.120330	-1.484442
C	5.170502	0.658353	-1.369790
C	6.151279	0.192981	-0.829492
H	-1.154711	2.469765	-1.659427
H	-1.403120	4.819952	-2.432795
H	-0.670595	6.687672	-0.972658
H	0.295740	6.208214	1.261048
H	0.543191	3.882016	2.034595
H	2.384062	2.856930	0.762738
H	4.664770	2.254672	1.491062
H	5.115787	0.029704	2.478974
H	3.266158	-1.611825	2.735641
H	0.981431	-1.033190	1.978086
H	-3.315475	-2.868935	4.795714
H	-4.030617	-4.831997	3.461315
H	-4.313321	-4.623662	1.002698
H	-3.859592	-2.462158	-0.119804
H	-2.877786	-0.709788	3.695370
H	-5.733413	0.256664	1.847463
H	-3.689211	0.954691	-1.877611
H	-5.834802	1.679441	-2.910574
H	-7.913146	1.696053	-1.559575
H	-7.861326	0.988313	0.815365
C	7.296616	-0.352230	-0.175586
C	8.558005	0.242142	-0.324550
C	7.169435	-1.489007	0.637542
C	9.662819	-0.290063	0.326010
H	8.657592	1.123029	-0.954714
C	8.279414	-2.014978	1.284752
H	6.190323	-1.952377	0.748137
C	9.527739	-1.417639	1.131504
H	10.636698	0.178281	0.203745
H	8.171219	-2.897623	1.911004
H	10.395690	-1.831633	1.639173

TS1'

Zero-point correction= 0.733930 (Hartree/Particle)
Thermal correction to Energy= 0.778409
Thermal correction to Enthalpy= 0.779353
Thermal correction to Gibbs Free Energy= 0.655889
Sum of electronic and zero-point Energies= -2541.183316
Sum of electronic and thermal Energies= -2541.138836
Sum of electronic and thermal Enthalpies= -2541.137892
Sum of electronic and thermal Free Energies= -2541.261356
HF (M06/6-311+G(d,p) and SDD, SMD[1-4 dioxane])= - -2542.3665788000

C	1.322572	0.589321	3.088460
O	1.561170	0.251199	1.876130
N	2.352011	0.765688	3.939763
C	3.703763	0.386166	3.575516
H	3.717689	-0.018550	2.563292
H	4.370957	1.255784	3.620230
H	4.080497	-0.375366	4.270296
C	2.149843	1.177460	5.315739
H	3.068613	1.648980	5.677535
H	1.348189	1.916957	5.390284
H	1.919277	0.326099	5.971026
C	-0.045821	0.727370	3.487104
C	-0.985998	0.581061	2.491564
H	-0.343409	0.773683	4.532798
H	-0.753911	1.495655	1.425735
C	-2.392452	0.238534	2.858336
H	-2.740494	0.836432	3.712814
H	-3.085858	0.413811	2.025235
C	-2.398599	-1.243140	3.278078
H	-3.410720	-1.524427	3.595196
H	-1.755072	-1.342836	4.161882
C	-1.949430	-2.238165	2.200983
H	-2.782533	-2.396387	1.501092
H	-1.768943	-3.214474	2.671418
C	-0.772333	-1.892438	1.376396
C	0.199150	-2.131641	0.598253
Ir	-0.193256	0.056391	0.647066
P	1.101255	0.871917	-1.230585
P	-1.898142	0.053756	-0.870180
C	1.679430	2.602392	-1.099510
C	1.497662	3.333713	0.074848
C	2.301118	3.209060	-2.198009
C	1.924241	4.657338	0.150068
H	1.021322	2.861628	0.934073
C	2.719708	4.530815	-2.122396
H	2.465961	2.642245	-3.114288
C	2.531696	5.255656	-0.947333
H	1.782073	5.219377	1.070147
H	3.197570	4.997238	-2.980562
H	2.863732	6.289543	-0.889321
C	2.599228	-0.018918	-1.774331
C	2.528203	-1.043043	-2.722489
C	3.833627	0.298082	-1.197303
C	3.678744	-1.722219	-3.107053
H	1.574310	-1.320341	-3.170306
C	4.981103	-0.385731	-1.582595
H	3.900737	1.098116	-0.460359
C	4.906312	-1.391541	-2.542102
H	3.613843	-2.514916	-3.848985
H	5.939312	-0.123614	-1.139899
H	5.806020	-1.920387	-2.848194
C	-2.882928	1.586477	-1.078893
C	-2.633909	2.747009	-0.344963
C	-3.882758	1.605259	-2.061989
C	-3.374461	3.902962	-0.579187
H	-1.851066	2.754521	0.411206
C	-4.617646	2.759501	-2.295873
H	-4.100277	0.709140	-2.642356
C	-4.364953	3.910548	-1.553132
H	-3.169681	4.799586	0.000663
H	-5.391734	2.760659	-3.059474
H	-4.941076	4.814024	-1.737634
C	-3.153599	-1.266697	-0.791246
C	-2.855971	-2.542116	-1.280953
C	-4.379803	-1.047104	-0.153145
C	-3.766560	-3.581949	-1.130696
H	-1.905707	-2.734191	-1.776169
C	-5.289446	-2.088726	-0.006961
H	-4.632270	-0.055717	0.220909
C	-4.982068	-3.357242	-0.490725
H	-3.526405	-4.569745	-1.517259
H	-6.242210	-1.907681	0.484693
H	-5.694197	-4.170609	-0.374927
C	-1.126058	-0.139638	-2.542834

C	-0.028375	0.899542	-2.705676
H	-0.458912	1.909692	-2.745053
H	0.538000	0.751944	-3.632914
H	-0.710319	-1.155375	-2.598053
H	-1.897063	-0.050636	-3.319126
C	1.163504	-2.999340	-0.036757
C	2.533850	-2.817609	0.193867
C	0.742337	-4.049628	-0.864615
C	3.458263	-3.684743	-0.371237
H	2.852840	-1.991632	0.827865
C	1.675925	-4.901094	-1.444345
H	-0.323696	-4.207051	-1.026908
C	3.033791	-4.725189	-1.194752
H	4.518803	-3.542936	-0.174898
H	1.339725	-5.716774	-2.080705
H	3.761278	-5.400201	-1.639699

TS1

Zero-point correction= 0.733382 (Hartree/Particle)
Thermal correction to Energy= 0.779452
Thermal correction to Enthalpy= 0.780397
Thermal correction to Gibbs Free Energy= 0.648114
Sum of electronic and zero-point Energies= -2541.172333
Sum of electronic and thermal Energies= -2541.126262
Sum of electronic and thermal Enthalpies= -2541.125318
Sum of electronic and thermal Free Energies= -2541.257601
HF (M06/6-311+G(d,p) and SDD, SMD[1-4 dioxane])= - -2542.359105

C	0.976550	-0.665101	-0.602235
C	1.181126	-1.990725	-0.841193
H	2.171042	-2.434886	-0.780255
Ir	-1.058906	-0.218143	-0.347162
H	0.075346	-0.023640	-1.514516
C	0.008065	-2.815521	-1.067311
O	-1.143272	-2.288667	-0.930636
N	0.115854	-4.110212	-1.390684
C	1.397047	-4.756788	-1.631535
H	1.884570	-5.055641	-0.694923
H	1.220529	-5.656049	-2.227608
C	-1.060955	-4.957400	-1.480195
H	-1.237398	-5.259659	-2.519441
H	-1.936392	-4.420326	-1.115634
P	-3.297155	-0.151800	0.432374
P	-1.048345	1.970233	0.240026
C	-3.441655	-0.942033	2.065750
C	-2.910187	-2.231057	2.201609
C	-3.003100	-2.898929	3.415811
C	-3.616507	-2.283836	4.504408
C	-4.143460	-1.003276	4.376071
C	-4.060104	-0.332021	3.159576
C	-4.586660	-0.886238	-0.613292
C	-5.775181	-1.379881	-0.068887
C	-6.763261	-1.880477	-0.908711
C	-6.568821	-1.889756	-2.287270
C	-5.386092	-1.398861	-2.832482
C	-4.392696	-0.899885	-1.997945
C	-3.756507	1.619790	0.643935
C	-2.568017	2.353516	1.244286
C	-1.173663	3.163551	-1.139567
C	-1.305086	4.535522	-0.887968
C	-1.441796	5.431327	-1.940153
C	-1.455318	4.967560	-3.253844
C	-1.333703	3.607493	-3.513465
C	-1.194576	2.707215	-2.460328
C	0.314209	2.557038	1.304981
C	1.275016	3.470375	0.866578
C	2.361168	3.786118	1.677934
C	2.495159	3.193141	2.929119
C	1.541495	2.278712	3.372059
C	0.459074	1.957612	2.562648
H	-2.727209	3.437798	1.277621
H	-2.378412	2.017714	2.272955
H	-3.977420	1.992328	-0.367131
H	-4.676411	1.733976	1.231006
H	2.068166	-4.110052	-2.201576
H	-0.907360	-5.857833	-0.874561
C	2.096811	0.276303	-0.292824
H	2.005759	1.156508	-0.951983
H	1.921801	0.675620	0.718796
C	3.511576	-0.273053	-0.363794
H	3.631180	-1.117899	0.328446
H	3.732704	-0.653183	-1.370964
C	4.523588	0.814363	0.005860
H	4.410484	1.668232	-0.680321
H	4.284813	1.204559	1.007866
C	5.898504	0.340458	-0.019810
C	7.035987	-0.078540	-0.043072
H	-1.112267	1.637849	-2.655903
H	-1.349548	3.243032	-4.537717
H	-1.563289	5.671092	-4.075860
H	-1.538606	6.494809	-1.735603
H	-1.287604	4.909955	0.135294
H	1.186338	3.931026	-0.115921
H	3.105993	4.497001	1.328080
H	3.345079	3.441002	3.560413
H	1.645416	1.810280	4.347778
H	-0.265213	1.215271	2.902075
H	-4.626172	-0.523562	5.223992
H	-3.684696	-2.805703	5.455788
H	-2.592745	-3.900895	3.515003
H	-2.429091	-2.708530	1.347105
H	-4.485449	0.666248	3.073601
H	-5.927346	-1.376700	1.010024
H	-3.456319	-0.525891	-2.414756
H	-5.233198	-1.411918	-3.908809
H	-7.342951	-2.285459	-2.940434
H	-7.687464	-2.266450	-0.485619
C	8.379031	-0.562685	-0.061888
C	9.038620	-0.785625	-1.279274
C	9.056110	-0.822294	1.138642
C	10.344604	-1.255716	-1.291671
H	8.513847	-0.583298	-2.210370
C	10.362077	-1.291896	1.118084
H	8.544463	-0.648958	2.082821
C	11.009473	-1.509807	-0.095130
H	10.848340	-1.423647	-2.240873
H	10.879327	-1.488378	2.054445
H	12.033148	-1.876561	-0.108021

Int-1'

Zero-point correction= 0.737697 (Hartree/Particle)
Thermal correction to Energy= 0.782337
Thermal correction to Enthalpy= 0.783281
Thermal correction to Gibbs Free Energy= 0.660397
Sum of electronic and zero-point Energies= -2541.208422
Sum of electronic and thermal Energies= -2541.163782
Sum of electronic and thermal Enthalpies= -2541.162838
Sum of electronic and thermal Free Energies= -2541.285723
HF (M06/6-311+G(d,p) and SDD, SMD[1-4 dioxane])= - -2542.3963385000

C	0.630789	2.339213	2.429646
O	1.163644	1.540582	1.587588
N	1.422462	3.149520	3.148778
C	2.867810	3.037362	3.070852
H	3.150916	2.057172	2.682980
H	3.289018	3.818129	2.423917
H	3.291110	3.151900	4.074434
C	0.900824	4.158400	4.054353
H	1.613726	4.986999	4.102000
H	-0.046345	4.562636	3.691208
H	0.763115	3.761763	5.068823
C	-0.799320	2.285845	2.614453
C	-1.471345	1.385917	1.846191
H	-1.282417	2.817241	3.435071
H	-0.481561	1.790029	-0.439979
C	-2.856338	1.001748	2.252936
H	-3.380317	1.848176	2.721215
H	-3.467838	0.668252	1.403538

C	-2.734013	-0.124143	3.287493
H	-3.732953	-0.429231	3.623599
H	-2.203963	0.268132	4.165767
C	-2.014021	-1.367381	2.767481
H	-2.666519	-1.889617	2.055915
H	-1.856057	-2.067674	3.599456
C	-0.703326	-1.174889	2.131609
C	0.481253	-1.316276	1.790594
Ir	-0.305202	0.464275	0.423039
P	1.184175	0.109933	-1.485787
P	-1.919000	-0.360149	-0.970178
C	2.213363	1.557878	-1.908640
C	2.979783	2.168978	-0.910227
C	2.316495	2.019635	-3.225287
C	3.833439	3.219963	-1.226770
H	2.889747	1.832562	0.120799
C	3.164199	3.078134	-3.535085
H	1.747468	1.550326	-4.024944
C	3.925662	3.677313	-2.537450
H	4.429715	3.686601	-0.445965
H	3.233435	3.429870	-4.561645
H	4.591604	4.501355	-2.782189
C	2.319537	-1.307741	-1.746356
C	1.893655	-2.590353	-1.385446
C	3.587464	-1.147399	-2.312788
C	2.710820	-3.693323	-1.599546
H	0.924586	-2.724668	-0.904516
C	4.406735	-2.252818	-2.520096
H	3.944107	-0.157914	-2.592747
C	3.971020	-3.524821	-2.165844
H	2.370325	-4.683851	-1.305782
H	5.391887	-2.116293	-2.960075
H	4.615165	-4.386147	-2.326002
C	-3.146240	0.850890	-1.593774
C	-3.163482	2.179170	-1.162989
C	-4.075738	0.437002	-2.558327
C	-4.090524	3.076751	-1.686007
H	-2.445182	2.516152	-0.418260
C	-4.998235	1.334436	-3.079213
H	-4.091159	-0.598049	-2.898336
C	-5.006094	2.657194	-2.643287
H	-4.091886	4.108462	-1.342976
H	-5.713212	1.000140	-3.826897
H	-5.727926	3.360209	-3.052037
C	-2.920568	-1.794602	-0.437709
C	-2.306326	-3.048029	-0.327420
C	-4.257886	-1.656258	-0.052117
C	-3.017654	-4.140897	0.152672
H	-1.259464	-3.176571	-0.601723
C	-4.967037	-2.752267	0.430190
H	-4.755177	-0.691282	-0.134966
C	-4.348735	-3.993947	0.534029
H	-2.531256	-5.110293	0.229612
H	-6.007605	-2.633749	0.722311
H	-4.904452	-4.849685	0.909547
C	-1.125622	-0.963514	-2.532490
C	0.012510	-0.036874	-2.915730
H	-0.369446	0.971962	-3.130585
H	0.538333	-0.403167	-3.805789
H	-0.756714	-1.982387	-2.357908
H	-1.883273	-1.025707	-3.322909
C	1.794120	-1.910743	1.768685
C	2.957268	-1.179214	1.505459
C	1.891158	-3.286902	2.023816
C	4.191665	-1.815323	1.490515
H	2.875205	-0.110561	1.317024
C	3.128209	-3.915817	2.007037
H	0.983692	-3.853474	2.227438
C	4.280684	-3.182752	1.735764
H	5.090585	-1.241139	1.277610
H	3.193179	-4.983453	2.204191
H	5.248647	-3.677710	1.716069

Int-1

Zero-point correction= 0.734790 (Hartree/Particle)
Thermal correction to Energy= 0.781113
Thermal correction to Enthalpy= 0.782057
Thermal correction to Gibbs Free Energy= 0.649147
Sum of electronic and zero-point Energies= -2541.187592
Sum of electronic and thermal Energies= -2541.141270
Sum of electronic and thermal Enthalpies= -2541.140325
Sum of electronic and thermal Free Energies= -2541.273235
HF (M06/6-311+G(d,p) and SDD, SMD[1-4 dioxane])= - -2542.37495

C	0.943508	-0.837463	0.023878
C	1.152337	-2.182507	0.068799
H	2.138711	-2.636153	0.151364
Ir	-1.073722	-0.344284	-0.076490
H	-1.083879	-0.352258	-1.612645
C	-0.027245	-3.025787	0.014058
O	-1.183169	-2.478451	-0.053853
N	0.064126	-4.360741	0.036438
C	1.349358	-5.040771	0.133957
H	1.877186	-4.775665	1.056646
H	1.168723	-6.117492	0.147426
C	-1.123780	-5.197531	-0.004109
H	-1.039875	-5.920710	-0.822998
H	-2.007378	-4.579952	-0.162459
P	-3.419189	0.030185	-0.089281
P	-0.934507	1.924267	-0.224754
C	-4.066715	-0.005949	1.617452
C	-3.655694	-1.073934	2.426269
C	-4.085468	-1.161454	3.745436
C	-4.920740	-0.179610	4.271230
C	-5.332790	0.884248	3.474968
C	-4.909858	0.972293	2.152261
C	-4.539585	-1.008150	-1.073580
C	-5.918328	-1.014871	-0.839006
C	-6.752283	-1.794618	-1.630217
C	-6.215790	-2.570227	-2.655398
C	-4.844967	-2.569090	-2.890705
C	-4.005101	-1.792149	-2.099319
C	-3.667011	1.759411	-0.684730
C	-2.632172	2.655148	-0.017062
C	-0.351881	2.597765	-1.821020
C	-0.510170	3.960406	-2.106172
C	-0.075068	4.480791	-3.318526
C	0.523292	3.648171	-4.260498
C	0.694279	2.296821	-3.983796
C	0.261417	1.773358	-2.769306
C	0.070068	2.719027	1.072065
C	1.174430	3.525019	0.790162
C	1.970005	4.003552	1.827093
C	1.671937	3.676920	3.145506
C	0.571056	2.873179	3.433650
C	-0.225177	2.392563	2.401947
H	-2.658979	3.675699	-0.415308
H	-2.814931	2.730067	1.063899
H	-3.511608	1.725847	-1.773333
H	-4.692670	2.113737	-0.523171
H	1.989623	-4.814516	-0.725488
H	-1.232719	-5.748186	0.938217
C	2.079973	0.129650	0.106537
H	1.980724	0.849974	-0.724483
H	1.922635	0.746963	1.009271
C	3.499591	-0.413792	0.120522
H	3.646763	-1.094440	0.970330
H	3.697474	-0.998387	-0.789037
C	4.511929	0.730391	0.217464
H	4.339966	1.439644	-0.607495
H	4.328619	1.298839	1.142619
C	5.892521	0.273109	0.188042
C	7.034144	-0.134137	0.156615
H	0.403873	0.715114	-2.557067
H	1.164843	1.643700	-4.714554
H	0.858834	4.055925	-5.210897
H	-0.204415	5.539510	-3.529023
H	-0.960035	4.629055	-1.373227
H	1.426658	3.770306	-0.240170

H	2.829953	4.629253	1.600471
H	2.298677	4.048365	3.952537
H	0.335720	2.617991	4.463959
H	-1.078063	1.751165	2.635351
H	-5.988885	1.649067	3.883590
H	-5.252854	-0.244182	5.304483
H	-3.767251	-1.996644	4.364678
H	-3.008186	-1.847501	2.010176
H	-5.245157	1.809007	1.541117
H	-6.339931	-0.418746	-0.029903
H	-2.928678	-1.799882	-2.266805
H	-4.426765	-3.180329	-3.686809
H	-6.871110	-3.182729	-3.270133
H	-7.823591	-1.801151	-1.444542
C	8.382000	-0.603768	0.122424
C	9.022502	-0.839273	-1.102901
C	9.083218	-0.837088	1.314381
C	10.333151	-1.295454	-1.131381
H	8.478987	-0.658102	-2.027590
C	10.393822	-1.292798	1.277794
H	8.586475	-0.654174	2.264693
C	11.022056	-1.523157	0.056858
H	10.821601	-1.473480	-2.086764
H	10.929521	-1.468829	2.207822
H	12.049252	-1.879295	0.031384

Int-1a

Zero-point correction= 0.736888 (Hartree/Particle)
Thermal correction to Energy= 0.781780
Thermal correction to Enthalpy= 0.782725
Thermal correction to Gibbs Free Energy= 0.658205
Sum of electronic and zero-point Energies= -2541.222254
Sum of electronic and thermal Energies= -2541.177362
Sum of electronic and thermal Enthalpies= -2541.176418
Sum of electronic and thermal Free Energies= -2541.300937
HF (M06/6-311+G(d,p) and SDD, SMD[1-4 dioxane])= - -2542.4090521000

C	1.262739	1.249340	2.450331
O	0.307059	1.280486	1.610564
N	1.554746	2.360420	3.154225
C	0.695768	3.528033	3.069103
H	0.124711	3.507928	2.138228
H	-0.009371	3.564860	3.910831
H	1.309745	4.434629	3.088484
C	2.573003	2.368319	4.192261
H	2.798607	3.406205	4.449642
H	2.236997	1.855196	5.102675
H	3.499013	1.906362	3.839404
C	2.004931	0.017528	2.617951
C	1.653658	-1.016722	1.809130
H	2.741872	-0.094286	3.413771
H	0.242428	-2.010590	-0.312612
C	2.166453	-2.393597	2.075905
H	2.346020	-2.938421	1.136950
H	3.116776	-2.366613	2.630749
C	1.128903	-3.146073	2.918213
H	1.011094	-2.630364	3.881278
H	1.495343	-4.156172	3.136907
C	-0.237716	-3.267026	2.244364
H	-0.932653	-3.791202	2.913831
H	-0.147688	-3.881826	1.335559
C	-0.859836	-1.989646	1.873458
C	-1.642239	-1.030185	1.747264
Ir	0.192829	-0.610277	0.411715
P	1.815392	-0.121910	-1.178094
P	-1.332606	-0.123884	-1.389375
C	0.998928	0.010211	-2.846508
C	-0.373169	-0.645884	-2.888434
H	0.902220	1.088683	-3.034950
H	1.679373	-0.384671	-3.612008
H	-0.911624	-0.376737	-3.805431
H	-0.302410	-1.740839	-2.858082
C	-2.884789	-1.076281	-1.495047
C	-4.138845	-0.463607	-1.524958
C	-2.805240	-2.474550	-1.467247
C	-5.295087	-1.237626	-1.555764
H	-4.218436	0.622026	-1.514205
C	-3.961790	-3.243510	-1.501911
H	-1.833799	-2.967554	-1.408091
C	-5.209313	-2.624980	-1.549289
H	-6.266683	-0.749312	-1.577608
H	-3.890247	-4.328595	-1.488956
H	-6.114369	-3.227290	-1.575491
C	-1.756538	1.610280	-1.777257
C	-2.389625	1.956874	-2.977902
C	-1.385392	2.619305	-0.884214
C	-2.651930	3.288790	-3.272446
H	-2.691580	1.182104	-3.682341
C	-1.645793	3.953534	-1.184864
H	-0.886071	2.355283	0.047230
C	-2.279045	4.288222	-2.376101
H	-3.147641	3.549064	-4.204606
H	-1.349718	4.733073	-0.485702
H	-2.482844	5.330278	-2.611041
C	2.820571	1.401770	-1.124876
C	3.987312	1.498771	-1.892962
C	2.368447	2.519858	-0.418811
C	4.699240	2.691335	-1.932458
H	4.346453	0.639399	-2.457501
C	3.087732	3.710299	-0.459118
H	1.452327	2.455341	0.163154
C	4.253752	3.796199	-1.211360
H	5.606339	2.758030	-2.528213
H	2.731453	4.572792	0.100614
H	4.816235	4.726344	-1.241200
C	3.024697	-1.481531	-1.300020
C	2.732044	-2.611781	-2.068467
C	4.189597	-1.460770	-0.527015
C	3.593405	-3.703480	-2.066903
H	1.824101	-2.650183	-2.669796
C	5.050189	-2.553420	-0.530370
H	4.428647	-0.588394	0.079851
C	4.752535	-3.675701	-1.296913
H	3.359656	-4.576440	-2.671577
H	5.957153	-2.526663	0.068819
H	5.426620	-4.528820	-1.297549
C	-2.858004	-0.261219	1.833490
C	-4.078987	-0.951649	1.827382
C	-2.857704	1.136748	1.919103
C	-5.275265	-0.251765	1.900273
H	-4.077210	-2.037056	1.748252
C	-4.060414	1.828481	1.981950
H	-1.905639	1.662050	1.943920
C	-5.269839	1.138785	1.971287
H	-6.216937	-0.795941	1.888125
H	-4.052777	2.914672	2.041940
H	-6.208860	1.685000	2.021155

TS2a

Zero-point correction= 0.735445 (Hartree/Particle)
Thermal correction to Energy= 0.779703
Thermal correction to Enthalpy= 0.780647
Thermal correction to Gibbs Free Energy= 0.657899
Sum of electronic and zero-point Energies= -2541.194001
Sum of electronic and thermal Energies= -2541.149744
Sum of electronic and thermal Enthalpies= -2541.148800
Sum of electronic and thermal Free Energies= -2541.271547
HF (M06/6-311+G(d,p) and SDD, SMD[1-4 dioxane])= - -2542.3769335000

C	1.099697	0.432266	2.796009
O	0.251360	0.857178	1.952748
N	1.399003	1.174398	3.879630
C	0.884843	2.524061	4.016883
H	0.510277	2.884522	3.056356
H	0.065697	2.563291	4.746299
H	1.689238	3.184584	4.360751
C	2.235748	0.690786	4.964950
H	1.947156	1.205896	5.886075

H	2.088874	-0.379137	5.130289
H	3.299782	0.888667	4.779224
C	1.733715	-0.843337	2.565264
C	1.218637	-1.675159	1.601266
H	2.593721	-1.157477	3.155173
H	-0.034300	-1.654944	-0.951757
C	1.858458	-3.021960	1.386467
H	1.922783	-3.237850	0.308488
H	2.877304	-3.044398	1.791817
C	0.939574	-4.022702	2.076007
H	1.053565	-3.925412	3.164508
H	1.160454	-5.061048	1.808629
C	-0.461053	-3.603719	1.662866
H	-1.244182	-3.964081	2.341454
H	-0.699733	-3.987553	0.658491
C	-0.543718	-2.101849	1.606850
C	-1.471183	-1.212967	1.374117
Ir	0.078290	-0.531305	0.143678
P	1.899952	0.139940	-1.200368
P	-1.189276	0.601367	-1.447155
C	1.217889	0.896879	-2.759833
C	-0.222090	0.478792	-3.022678
H	1.264980	1.982345	-2.593755
H	1.878891	0.674893	-3.607321
H	-0.680498	1.098472	-3.803373
H	-0.283450	-0.565229	-3.356226
C	-2.796953	-0.176502	-1.813986
C	-4.005380	0.471142	-1.551293
C	-2.812834	-1.502903	-2.262294
C	-5.211812	-0.194827	-1.746553
H	-4.009462	1.496525	-1.185874
C	-4.019157	-2.158843	-2.470194
H	-1.877151	-2.034327	-2.437587
C	-5.221133	-1.505413	-2.209044
H	-6.147301	0.316105	-1.530346
H	-4.021419	-3.185557	-2.828555
H	-6.165521	-2.022313	-2.362428
C	-1.496150	2.389164	-1.264273
C	-2.067849	3.133611	-2.303755
C	-1.115591	3.032916	-0.083526
C	-2.252637	4.502760	-2.161796
H	-2.385706	2.639524	-3.221791
C	-1.300937	4.406358	0.052447
H	-0.674364	2.454144	0.728241
C	-1.866183	5.139824	-0.984405
H	-2.699439	5.075491	-2.970806
H	-1.002510	4.904173	0.972609
H	-2.009795	6.212402	-0.877218
C	3.071275	1.424889	-0.640853
C	4.275785	1.643317	-1.319681
C	2.708449	2.276483	0.406174
C	5.110429	2.687567	-0.940696
H	4.566085	0.994103	-2.144886
C	3.548012	3.321298	0.781679
H	1.762492	2.119788	0.921010
C	4.749599	3.524443	0.112526
H	6.045590	2.850593	-1.471135
H	3.259951	3.980197	1.598238
H	5.406186	4.339897	0.406559
C	2.948917	-1.262271	-1.710044
C	2.575334	-2.070034	-2.788210
C	4.048433	-1.631228	-0.928314
C	3.296104	-3.221894	-3.085324
H	1.715014	-1.806105	-3.403643
C	4.768048	-2.782627	-1.229361
H	4.346747	-1.015353	-0.080122
C	4.392492	-3.579891	-2.306088
H	3.002755	-3.839275	-3.931098
H	5.625992	-3.057043	-0.619957
H	4.955710	-4.479937	-2.540371
C	-2.879894	-0.940288	1.555179
C	-3.815131	-1.984918	1.528649
C	-3.329700	0.373227	1.745339
C	-5.168094	-1.716581	1.690939
H	-3.472327	-3.005130	1.361546
C	-4.680905	0.632433	1.933208
H	-2.598809	1.180553	1.761284
C	-5.602843	-0.410301	1.901577
H	-5.887614	-2.531548	1.656724
H	-5.017289	1.653816	2.097178
H	-6.661987	-0.205636	2.040346

Int-2a

Zero-point correction= 0.737657 (Hartree/Particle)
Thermal correction to Energy= 0.782034
Thermal correction to Enthalpy= 0.782978
Thermal correction to Gibbs Free Energy= 0.660136
Sum of electronic and zero-point Energies= -2541.226280
Sum of electronic and thermal Energies= -2541.181903
Sum of electronic and thermal Enthalpies= -2541.180959
Sum of electronic and thermal Free Energies= -2541.303801
HF (M06/6-311+G(d,p) and SDD, SMD[1-4 dioxane])= - -2542.4101250000

C	1.261267	-0.948819	2.345054
O	0.429494	-0.011460	2.283953
N	1.973324	-1.206258	3.446584
C	1.876423	-0.330587	4.602655
H	1.481713	0.641260	4.300852
H	1.215303	-0.759885	5.365008
H	2.875169	-0.200674	5.033397
C	2.838021	-2.363747	3.593166
H	2.630649	-2.847107	4.554438
H	2.652400	-3.093720	2.801859
H	3.894596	-2.068971	3.573327
C	1.542230	-1.718162	1.097357
C	0.734244	-2.712606	0.545806
H	2.594554	-1.732262	0.800642
H	-0.206525	-1.046149	-1.413225
C	1.233086	-3.881102	-0.246549
H	0.917586	-3.792817	-1.296655
H	2.321253	-4.006932	-0.223713
C	0.447841	-5.009701	0.454805
H	0.952461	-5.263607	1.396909
H	0.406446	-5.921976	-0.147440
C	-0.945679	-4.418181	0.744847
H	-1.399046	-4.828643	1.655522
H	-1.630575	-4.654189	-0.081828
C	-0.683622	-2.926602	0.807388
C	-1.402248	-1.770084	0.748327
Ir	0.028840	-0.412455	0.000482
P	1.811738	0.701257	-1.099029
P	-1.214307	1.302880	-0.879641
C	1.099777	1.957796	-2.274656
C	-0.389205	1.722770	-2.485361
H	1.263788	2.935111	-1.800835
H	1.657414	1.959335	-3.219436
H	-0.878259	2.586564	-2.952110
H	-0.579707	0.863787	-3.143516
C	-2.952911	1.055128	-1.363377
C	-3.933756	2.017357	-1.113347
C	-3.302008	-0.138165	-2.003219
C	-5.247673	1.790246	-1.509489
H	-3.680335	2.941903	-0.598475
C	-4.615466	-0.360737	-2.395279
H	-2.547564	-0.907917	-2.169234
C	-5.589610	0.603044	-2.146931
H	-6.007248	2.542500	-1.310794
H	-4.882809	-1.295361	-2.882654
H	-6.619252	0.423699	-2.447119
C	-1.157086	2.851523	0.083742
C	-1.298575	4.099291	-0.536243
C	-0.975789	2.791554	1.468740
C	-1.258758	5.265297	0.218811
H	-1.454391	4.168355	-1.611969
C	-0.938842	3.961927	2.220647
H	-0.846104	1.828007	1.958129
C	-1.078664	5.197131	1.597680
H	-1.369627	6.229599	-0.271081
H	-0.797931	3.906193	3.297474

H	-1.047011	6.111084	2.185996
C	3.093066	1.633481	-0.195172
C	4.232902	2.116143	-0.849306
C	2.898228	1.924579	1.158048
C	5.169472	2.868298	-0.151910
H	4.391519	1.895572	-1.904800
C	3.841369	2.677603	1.852968
H	2.000202	1.569487	1.663039
C	4.975890	3.145659	1.200070
H	6.054093	3.240286	-0.663174
H	3.684944	2.900865	2.906161
H	5.712927	3.732788	1.742852
C	2.733168	-0.495772	-2.126957
C	2.201296	-0.902236	-3.355033
C	3.885737	-1.124162	-1.643346
C	2.813268	-1.912080	-4.088913
H	1.300486	-0.428774	-3.745760
C	4.494328	-2.136804	-2.378693
H	4.324778	-0.808353	-0.697325
C	3.958648	-2.533532	-3.599956
H	2.395615	-2.212795	-5.046828
H	5.395736	-2.611750	-1.998236
H	4.437302	-3.323160	-4.173868
C	-2.849263	-1.644377	0.931994
C	-3.745857	-2.685390	0.641725
C	-3.380095	-0.440583	1.417845
C	-5.114317	-2.518877	0.813082
H	-3.371617	-3.631299	0.258682
C	-4.745345	-0.278172	1.607239
H	-2.693936	0.373947	1.652680
C	-5.620074	-1.315892	1.296800
H	-5.790887	-3.335284	0.569203
H	-5.130472	0.666356	1.986074
H	-6.691510	-1.187391	1.432690

Int-2a'

Zero-point correction= 0.737879 (Hartree/Particle)
Thermal correction to Energy= 0.782065
Thermal correction to Enthalpy= 0.783009
Thermal correction to Gibbs Free Energy= 0.660218
Sum of electronic and zero-point Energies= -2541.233404
Sum of electronic and thermal Energies= -2541.189219
Sum of electronic and thermal Enthalpies= -2541.188274
Sum of electronic and thermal Free Energies= -2541.311065
HF (M06/6-311+G(d,p) and SDD, SMD[1-4 dioxane])= - -2542.4176472000

C	2.129121	2.392762	-0.882148
O	1.635232	1.280444	-1.242935
N	3.426221	2.606774	-1.180465
C	4.240995	1.516967	-1.692888
H	3.863167	0.558103	-1.330030
H	4.243610	1.502932	-2.790597
H	5.268453	1.652295	-1.339752
C	4.084649	3.900504	-1.099829
H	4.835170	3.958794	-1.894100
H	3.378250	4.717718	-1.255687
H	4.593726	4.034954	-0.135648
C	1.406824	3.454669	-0.193410
C	0.074056	3.718808	-0.257402
H	2.025687	4.197683	0.305728
H	0.321684	1.183001	1.057840
C	-0.488538	5.041915	0.187865
H	-1.066981	4.896098	1.115295
H	0.273784	5.803720	0.381450
C	-1.443040	5.376399	-0.961991
H	-0.861908	5.762141	-1.810024
H	-2.182589	6.138025	-0.695926
C	-2.066648	4.023459	-1.323284
H	-2.332202	3.943758	-2.384305
H	-2.996328	3.865682	-0.756490
C	-1.023242	2.996100	-0.899374
C	-1.171292	1.652728	-0.954481
Ir	0.109737	0.254083	-0.148950
P	1.687785	-1.287853	0.752309
P	-1.335159	-0.833248	1.215881
C	0.922517	-2.087469	2.254676
C	-0.320367	-1.316047	2.692181
H	0.643836	-3.109738	1.965096
H	1.654977	-2.160725	3.067271
H	-0.919135	-1.890041	3.410084
H	-0.051241	-0.374223	3.190597
C	-2.733279	0.112879	1.902474
C	-4.043210	-0.370377	1.879527
C	-2.480151	1.392842	2.409858
C	-5.085360	0.416848	2.360693
H	-4.257306	-1.354850	1.467361
C	-3.522543	2.175398	2.889850
H	-1.464004	1.788354	2.409498
C	-4.827500	1.687768	2.862924
H	-6.103507	0.036058	2.336156
H	-3.318198	3.169269	3.281256
H	-5.644604	2.302679	3.232508
C	-2.016799	-2.402658	0.590880
C	-2.487040	-3.398600	1.455798
C	-2.081029	-2.608682	-0.789256
C	-3.007907	-4.579753	0.941748
H	-2.465652	-3.248690	2.534699
C	-2.607543	-3.789845	-1.301309
H	-1.739502	-1.830533	-1.472373
C	-3.067214	-4.776264	-0.436124
H	-3.372634	-5.348541	1.618571
H	-2.661012	-3.932771	-2.378168
H	-3.477623	-5.701175	-0.834065
C	2.181337	-2.663710	-0.333093
C	2.707156	-3.864844	0.154578
C	2.020375	-2.493370	-1.712029
C	3.059724	-4.880239	-0.726757
H	2.851294	-4.006469	1.225537
C	2.376471	-3.510369	-2.592103
H	1.614633	-1.555016	-2.097687
C	2.893345	-4.703481	-2.098230
H	3.466170	-5.812852	-0.343075
H	2.246112	-3.371969	-3.662638
H	3.168039	-5.501257	-2.784000
C	3.250984	-0.510103	1.298130
C	3.176357	0.707167	1.987115
C	4.505956	-1.045583	0.996247
C	4.334842	1.374194	2.367175
H	2.204744	1.147828	2.213568
C	5.664458	-0.375066	1.378394
H	4.584179	-1.984288	0.450336
C	5.581645	0.834615	2.059854
H	4.263699	2.319674	2.900602
H	6.635823	-0.800954	1.138127
H	6.488615	1.358098	2.353063
C	-2.271072	1.017019	-1.702523
C	-3.592449	0.973710	-1.237896
C	-1.956841	0.337893	-2.892913
C	-4.560431	0.254041	-1.929058
H	-3.853928	1.497350	-0.319390
C	-2.933179	-0.368264	-3.589737
H	-0.935895	0.391172	-3.276869
C	-4.236205	-0.422071	-3.103404
H	-5.579389	0.224716	-1.547236
H	-2.674633	-0.877572	-4.515991
H	-4.999564	-0.978645	-3.641882

TS3a

Zero-point correction= 0.735091 (Hartree/Particle)
Thermal correction to Energy= 0.779667
Thermal correction to Enthalpy= 0.780612
Thermal correction to Gibbs Free Energy= 0.655623
Sum of electronic and zero-point Energies= -2541.218807
Sum of electronic and thermal Energies= -2541.174231
Sum of electronic and thermal Enthalpies= -2541.173287
Sum of electronic and thermal Free Energies= -2541.298275
HF (M06/6-311+G(d,p) and SDD, SMD[1-4 dioxane])= - -2542.4010175000

C	2.284885	2.288027	-0.781749
O	1.691974	1.232825	-1.152866
N	3.629362	2.338682	-0.874422
C	4.401446	1.173713	-1.274302
H	3.744195	0.320257	-1.438235
H	4.945219	1.384242	-2.203213
H	5.127608	0.924807	-0.489550
C	4.410550	3.527887	-0.563666
H	5.436485	3.362551	-0.900267
H	4.028211	4.410135	-1.084866
H	4.436830	3.725550	0.515710
C	1.594293	3.485980	-0.323351
C	0.299632	3.805903	-0.568865
H	2.206529	4.270930	0.112606
H	-0.632802	1.525011	0.592514
C	-0.203944	5.215859	-0.398903
H	-0.851911	5.269230	0.489979
H	0.597729	5.950977	-0.275159
C	-1.047206	5.402418	-1.662052
H	-0.384617	5.610869	-2.512079
H	-1.755298	6.232750	-1.585243
C	-1.731849	4.043552	-1.846103
H	-1.899303	3.788501	-2.899493
H	-2.721908	4.028658	-1.367498
C	-0.811984	3.050239	-1.151652
C	-1.137475	1.751127	-0.927310
Ir	0.075559	0.271320	-0.088716
P	1.639734	-1.388505	0.597683
P	-1.353317	-0.967040	1.138438
C	0.831500	-2.518313	1.830517
C	-0.347165	-1.793745	2.464712
H	0.480506	-3.399718	1.276227
H	1.557625	-2.855845	2.579682
H	-0.977481	-2.474256	3.051422
H	-0.008038	-1.000090	3.144819
C	-2.663892	-0.135174	2.098755
C	-4.009915	-0.494574	2.011829
C	-2.289791	0.933849	2.922121
C	-4.968614	0.208131	2.736066
H	-4.318353	-1.309586	1.359948
C	-3.249200	1.632120	3.644797
H	-1.242336	1.232378	2.988423
C	-4.591211	1.271019	3.549334
H	-6.015894	-0.074474	2.657874
H	-2.950468	2.461247	4.281734
H	-5.343203	1.820742	4.110327
C	-2.123178	-2.380289	0.278515
C	-2.755069	-3.410409	0.986941
C	-2.032027	-2.462587	-1.112814
C	-3.298082	-4.493918	0.308313
H	-2.834043	-3.361895	2.072697
C	-2.579593	-3.547797	-1.790659
H	-1.537616	-1.663177	-1.664542
C	-3.211982	-4.561808	-1.080843
H	-3.790145	-5.288767	0.863644
H	-2.510799	-3.597240	-2.874833
H	-3.639712	-5.410784	-1.608787
C	2.290542	-2.481113	-0.705774
C	2.778025	-3.763351	-0.429609
C	2.274477	-2.019303	-2.027011
C	3.252182	-4.566307	-1.460608
H	2.787819	-4.140493	0.592476
C	2.751221	-2.826522	-3.054743
H	1.890932	-1.021888	-2.247062
C	3.239708	-4.097978	-2.771531
H	3.629552	-5.561896	-1.240387
H	2.734813	-2.463522	-4.079484
H	3.608332	-4.729758	-3.576065
C	3.086525	-0.658057	1.445770
C	2.917343	0.567924	2.099507
C	4.340055	-1.275468	1.456960
C	3.987981	1.166741	2.755636
H	1.941776	1.057943	2.074101
C	5.408540	-0.673450	2.113552
H	4.490403	-2.221590	0.938485
C	5.234856	0.547715	2.760039
H	3.848263	2.119821	3.261362
H	6.381764	-1.158506	2.116830
H	6.073454	1.016864	3.269198
C	-2.408836	1.222903	-1.468058
C	-3.604330	1.281967	-0.743880
C	-2.421367	0.654265	-2.749293
C	-4.776012	0.752908	-1.275819
H	-3.612584	1.747588	0.241978
C	-3.596037	0.134973	-3.280742
H	-1.493717	0.625458	-3.321943
C	-4.775436	0.173393	-2.541063
H	-5.696388	0.800227	-0.696460
H	-3.591153	-0.301746	-4.277304
H	-5.693320	-0.238002	-2.954146

Int-3a

Zero-point correction= 0.739989 (Hartree/Particle)
Thermal correction to Energy= 0.784632
Thermal correction to Enthalpy= 0.785576
Thermal correction to Gibbs Free Energy= 0.659934
Sum of electronic and zero-point Energies= -2541.226404
Sum of electronic and thermal Energies= -2541.181762
Sum of electronic and thermal Enthalpies= -2541.180818
Sum of electronic and thermal Free Energies= -2541.306459
HF (M06/6-311+G(d,p) and SDD, SMD[1-4 dioxane])= - -2542.4130630000

C	2.164764	2.391705	-0.544413
O	1.617031	1.414678	-1.130165
N	3.495298	2.381477	-0.329928
C	4.338189	1.343832	-0.901616
H	3.734930	0.633880	-1.467263
H	5.071624	1.806522	-1.574317
H	4.875656	0.811857	-0.107370
C	4.214139	3.431154	0.377670
H	5.166011	3.016937	0.721553
H	4.428420	4.291583	-0.269212
H	3.665982	3.765380	1.262426
C	1.443512	3.624872	-0.217721
C	0.197666	3.938339	-0.634682
H	2.030400	4.450437	0.176289
H	-1.108056	1.782116	0.351693
C	-0.297125	5.357078	-0.735873
H	-1.084099	5.532922	0.012330
H	0.490808	6.100047	-0.579093
C	-0.899736	5.370718	-2.146934
H	-0.102293	5.542485	-2.879513
H	-1.641709	6.162711	-2.280338
C	-1.496808	3.962390	-2.333443
H	-1.292486	3.562099	-3.333652
H	-2.588794	3.945911	-2.215913
C	-0.855942	3.126248	-1.249016
C	-1.388701	1.996123	-0.721689
Ir	0.121916	0.237608	-0.026977
P	1.613374	-1.397159	0.342545
P	-1.244212	-1.062887	1.168650
C	0.889964	-2.728543	1.419788
C	-0.189354	-2.101206	2.286044
H	0.453284	-3.490509	0.759169
H	1.678426	-3.204143	2.015323
H	-0.786762	-2.854534	2.813603
H	0.243708	-1.429711	3.040113
C	-2.423384	-0.257284	2.311145
C	-3.789516	-0.546534	2.339914
C	-1.917015	0.737785	3.156608
C	-4.634753	0.149862	3.198906
H	-4.203067	-1.300959	1.673506
C	-2.762915	1.430413	4.014514
H	-0.853454	0.981023	3.130265
C	-4.124771	1.138900	4.033294
H	-5.698031	-0.078737	3.210214
H	-2.360156	2.200746	4.667991
H	-4.788430	1.684454	4.699933

C	-2.181102	-2.337008	0.247152
C	-2.857764	-3.372930	0.903878
C	-2.159259	-2.314553	-1.149434
C	-3.515505	-4.354382	0.172509
H	-2.880399	-3.413194	1.992863
C	-2.822061	-3.296614	-1.879988
H	-1.617434	-1.516579	-1.658489
C	-3.500114	-4.314951	-1.220087
H	-4.040104	-5.154276	0.689805
H	-2.805083	-3.263378	-2.967153
H	-4.015675	-5.084855	-1.789520
C	2.238477	-2.280163	-1.128231
C	2.681447	-3.605972	-1.059749
C	2.254064	-1.613919	-2.358699
C	3.142785	-4.249949	-2.202804
H	2.666478	-4.146238	-0.114088
C	2.719400	-2.261767	-3.498224
H	1.895458	-0.586363	-2.417126
C	3.163628	-3.578129	-3.421133
H	3.483234	-5.280857	-2.141773
H	2.727047	-1.738329	-4.451414
H	3.521767	-4.085095	-4.314000
C	3.099214	-0.861393	1.281577
C	2.999678	0.250453	2.124266
C	4.306060	-1.564793	1.217333
C	4.087941	0.648018	2.895944
H	2.060887	0.807407	2.159576
C	5.393117	-1.163436	1.986490
H	4.406629	-2.421388	0.552234
C	5.285904	-0.057005	2.825706
H	4.000264	1.512097	3.551301
H	6.328627	-1.714778	1.928007
H	6.137462	0.253724	3.426600
C	-2.603713	1.362321	-1.261182
C	-3.741812	1.210542	-0.461188
C	-2.641761	0.913272	-2.587407
C	-4.889596	0.618007	-0.975058
H	-3.726355	1.572167	0.566827
C	-3.789628	0.319471	-3.097860
H	-1.749347	1.011778	-3.205443
C	-4.915554	0.167830	-2.292088
H	-5.768787	0.510761	-0.342551
H	-3.804634	-0.031365	-4.127405
H	-5.812610	-0.299469	-2.691206

Int-3

ero-point correction= 0.741444 (Hartree/Particle)
Thermal correction to Energy= 0.785531
Thermal correction to Enthalpy= 0.786475
Thermal correction to Gibbs Free Energy= 0.664117
Sum of electronic and zero-point Energies= -2541.256887
Sum of electronic and thermal Energies= -2541.212800
Sum of electronic and thermal Enthalpies= -2541.211855
Sum of electronic and thermal Free Energies= -2541.334214
HF (M06/6-311+G(d,p) and SDD, SMD[1-4 dioxane])= - -2542.4444339000

C	-0.688692	3.996292	0.312347
C	1.476468	3.098174	-0.149090
C	-0.885830	2.831120	-0.618933
C	-2.126950	2.526558	-1.073094
H	-2.931864	3.208585	-0.806253
Ir	-0.119657	0.098203	-0.258297
C	-2.506443	1.288830	-1.739777
O	-1.816185	0.234638	-1.627061
N	-3.651539	1.246811	-2.442657
C	-4.458174	2.419148	-2.733558
H	-4.938763	2.280754	-3.707248
H	-5.243312	2.561122	-1.977423
C	-4.155261	-0.010014	-2.966189
H	-4.018668	-0.059031	-4.053779
H	-5.226631	-0.089211	-2.746546
P	-1.527530	-1.050188	1.145589
P	1.494839	-0.553513	1.171095
C	-2.034854	-2.725861	0.643690
C	-1.526045	-3.269099	-0.539209
C	-1.878478	-4.560187	-0.922936
C	-2.738918	-5.309406	-0.128440
C	-3.253048	-4.771944	1.050325
C	-2.903958	-3.484589	1.436583
C	-3.071831	-0.114194	1.401363
C	-3.063848	1.028262	2.209686
C	-4.179930	1.852588	2.273847
C	-5.311103	1.554802	1.517109
C	-5.326394	0.422339	0.709079
C	-4.213918	-0.412558	0.652662
C	-0.710890	-1.282222	2.785678
C	0.741035	-1.637668	2.505293
C	2.426127	0.703688	2.127111
C	3.773837	0.990200	1.894980
C	4.394996	2.041476	2.564908
C	3.680741	2.812149	3.475266
C	2.338855	2.529762	3.720146
C	1.716062	1.486445	3.046597
C	2.757984	-1.687292	0.490504
C	3.757304	-2.224709	1.311326
C	4.673018	-3.133063	0.794729
C	4.594311	-3.519855	-0.541328
C	3.595887	-3.002498	-1.358513
C	2.678992	-2.089936	-0.844553
H	1.357537	-1.602214	3.411819
H	0.801006	-2.661781	2.109589
H	-0.795783	-0.349050	3.355940
H	-1.217428	-2.066635	3.361159
H	-3.843995	3.319630	-2.792838
H	-3.626407	-0.846750	-2.508385
C	0.757750	1.343581	-1.916980
C	0.752472	4.423243	0.090686
C	0.452600	2.213656	-0.849855
H	-1.436601	4.783751	0.172582
H	-0.809108	3.614441	1.341343
H	0.820162	5.060352	-0.800686
H	1.173025	4.982994	0.932356
H	2.373826	3.229309	-0.761978
H	1.796194	2.671174	0.807149
H	4.344959	0.392391	1.185664
H	5.443671	2.256271	2.373329
H	4.168762	3.632380	3.996018
H	1.776150	3.127001	4.433989
H	0.655573	1.299706	3.218533
H	-2.175790	1.289290	2.784759
H	-4.166931	2.731888	2.913789
H	-6.183411	2.202484	1.564576
H	-6.213088	0.179284	0.126964
H	-4.235450	-1.300702	0.022346
H	-3.318155	-3.062124	2.352486
H	-3.927939	-5.359284	1.668257
H	-3.012850	-6.318516	-0.427173
H	-1.478588	-4.979852	-1.842805
H	-0.854763	-2.672345	-1.158887
H	3.828175	-1.926758	2.357214
H	5.449968	-3.541677	1.436575
H	5.314212	-4.228830	-0.943571
H	3.533223	-3.297691	-2.403423
H	1.901874	-1.672210	-1.485067
H	-0.024962	1.184330	-2.660744
C	2.080495	0.957945	-2.425661
C	2.133525	0.419276	-3.721818
C	3.279834	1.025481	-1.698522
C	3.329563	-0.019058	-4.274285
H	1.211844	0.347643	-4.298735
C	4.476552	0.592043	-2.252834
H	3.278844	1.388758	-0.674908
C	4.510432	0.069133	-3.542427
H	3.340368	-0.427560	-5.282270
H	5.390544	0.648543	-1.664134
H	5.449131	-0.273012	-3.971374

Int1b

Zero-point correction= 0.736414 (Hartree/Particle)
Thermal correction to Energy= 0.781263
Thermal correction to Enthalpy= 0.782207
Thermal correction to Gibbs Free Energy= 0.657032
Sum of electronic and zero-point Energies= -2541.205455
Sum of electronic and thermal Energies= -2541.160606
Sum of electronic and thermal Enthalpies= -2541.159662
Sum of electronic and thermal Free Energies= -2541.284837
HF (M06/6-311+G(d,p) and SDD, SMD[1-4 dioxane])= -2542.3907553

C	-2.446871	-1.217080	1.774536
O	-1.650949	-0.224054	1.855713
N	-3.597218	-1.202135	2.468559
C	-3.941428	-0.089468	3.333759
H	-3.148781	0.658538	3.311170
H	-4.880266	0.369527	2.996524
H	-4.076434	-0.436158	4.365581
C	-4.550948	-2.296770	2.409296
H	-5.524826	-1.925549	2.741782
H	-4.668758	-2.664437	1.385469
H	-4.261715	-3.128900	3.063937
C	-2.071816	-2.346276	0.946454
C	-0.966420	-2.202265	0.175100
H	-2.618622	-3.288203	1.011345
H	0.303247	1.287824	0.676271
C	-0.374712	-3.414265	-0.464922
H	-0.172041	-3.243343	-1.533419
H	-1.080016	-4.257925	-0.408176
C	0.952287	-3.797067	0.239288
H	1.805763	-3.515258	-0.384379
H	1.000609	-4.885314	0.355998
C	1.130376	-3.158127	1.617480
H	2.080228	-3.497808	2.054891
H	0.334294	-3.494644	2.297869
C	1.150542	-1.685494	1.604765
C	1.456828	-0.509771	1.934277
Ir	-0.049687	-0.274479	0.369509
P	-1.550096	0.709485	-1.131930
P	1.435562	-0.124978	-1.339370
C	-3.100991	-0.201779	-1.421497
C	-4.212212	0.062570	-0.616445
C	-3.157903	-1.241075	-2.354271
C	-5.363842	-0.708141	-0.741287
C	-4.311927	-2.004752	-2.480650
C	-5.414110	-1.742612	-1.670839
C	-2.117759	2.394592	-0.735391
C	-2.738252	3.154758	-1.733182
C	-1.994267	2.914924	0.554923
C	-3.205255	4.431598	-1.447651
C	-2.473803	4.190690	0.837950
C	-3.071870	4.949776	-0.162029
C	2.717488	-1.405133	-1.497973
C	3.724439	-1.431813	-0.524795
C	2.721061	-2.356087	-2.520738
C	4.702447	-2.416336	-0.559350
C	3.710242	-3.336397	-2.555871
C	4.692682	-3.373165	-1.572440
C	2.400049	1.423390	-1.571100
C	3.403302	1.423922	-2.551135
C	2.132847	2.603528	-0.875440
C	4.120708	2.580535	-2.823739
C	2.857015	3.761086	-1.148937
C	3.849814	3.751629	-2.120431
C	0.423242	-0.181630	-2.886500
C	-0.691803	0.851226	-2.771008
H	-2.297619	-1.465917	-2.984397
H	-4.352871	-2.805367	-3.215324
H	-6.316960	-2.340074	-1.772107
H	-6.226193	-0.493031	-0.113145
H	-4.180896	0.876290	0.108473
H	-1.527739	2.315486	1.335020
H	-2.377544	4.592017	1.843978
H	-3.439547	5.948553	0.060640
H	-3.677712	5.022017	-2.228785
H	-2.862724	2.748044	-2.736619
H	1.957926	-2.344261	-3.296745
H	3.710754	-4.072868	-3.355841
H	5.459829	-4.143282	-1.600135
H	5.480052	-2.432368	0.200916
H	3.746681	-0.674084	0.258805
H	1.359635	2.618471	-0.110006
H	2.642439	4.671447	-0.594420
H	4.416297	4.655732	-2.330518
H	4.898184	2.566254	-3.583836
H	3.634261	0.512078	-3.101363
C	2.285625	0.419114	2.669756
C	3.495025	-0.064674	3.195206
C	1.932032	1.752985	2.898281
C	4.328426	0.770681	3.925376
H	3.769762	-1.104829	3.020959
C	2.767373	2.582625	3.635195
H	0.990914	2.126233	2.497669
C	3.967199	2.097034	4.146752
H	5.264368	0.385368	4.323027
H	2.479876	3.616472	3.811789
H	4.620744	2.751462	4.718445
H	0.011691	-1.196427	-2.977956
H	1.053699	0.014310	-3.763472
H	-1.413766	0.763103	-3.591438
H	-0.273380	1.866606	-2.811392

TS2b

Zero-point correction= 0.733412 (Hartree/Particle)
Thermal correction to Energy= 0.778129
Thermal correction to Enthalpy= 0.779074
Thermal correction to Gibbs Free Energy= 0.653535
Sum of electronic and zero-point Energies= -2541.190562
Sum of electronic and thermal Energies= -2541.145845
Sum of electronic and thermal Enthalpies= -2541.144901
Sum of electronic and thermal Free Energies= -2541.270440
HF (M06/6-311+G(d,p) and SDD, SMD[1-4 dioxane])= -2542.3728323000

C	-2.486252	-1.385792	1.693792
O	-1.709019	-0.382523	1.833828
N	-3.637625	-1.433092	2.382699
C	-3.972541	-0.412695	3.356925
H	-3.104746	0.218629	3.547613
H	-4.798660	0.213313	2.992408
H	-4.285251	-0.886622	4.294777
C	-4.622859	-2.480417	2.178354
H	-5.613479	-2.077853	2.413255
H	-4.638169	-2.806527	1.134846
H	-4.441425	-3.345570	2.829770
C	-2.058094	-2.477433	0.843266
C	-0.939718	-2.268269	0.099619
H	-2.518124	-3.462650	0.935127
H	0.679923	0.878951	1.228347
C	-0.187768	-3.455850	-0.405422
H	0.124434	-3.323651	-1.451859
H	-0.830842	-4.348149	-0.376844
C	1.088652	-3.717969	0.452050
H	1.978876	-3.504804	-0.147975
H	1.133690	-4.786383	0.691575
C	1.211463	-2.948530	1.776398
H	2.138202	-3.259844	2.278652
H	0.387081	-3.229668	2.449721
C	1.180246	-1.478432	1.635391
C	1.529909	-0.286067	1.942389
Ir	-0.094298	-0.386428	0.358501
P	-1.567914	0.781018	-1.049257
P	1.304236	-0.257542	-1.421155
C	-3.216483	0.019063	-1.225597
C	-4.261253	0.414342	-0.385377
C	-3.422030	-1.026379	-2.129933
C	-5.497115	-0.220254	-0.460341
C	-4.659021	-1.655948	-2.205837
C	-5.698273	-1.253053	-1.371278
C	-1.949615	2.522055	-0.659438

C	-2.601210	3.329996	-1.597560
C	-1.622777	3.043836	0.593126
C	-2.899099	4.651682	-1.290557
C	-1.931712	4.365841	0.901142
C	-2.563502	5.169579	-0.041598
C	2.591642	-1.519966	-1.652608
C	3.670861	-1.508394	-0.758630
C	2.531680	-2.494234	-2.650711
C	4.665579	-2.471613	-0.853680
C	3.533100	-3.458624	-2.741331
C	4.594027	-3.451101	-1.842488
C	2.242849	1.303927	-1.643532
C	3.224476	1.361296	-2.641900
C	1.956000	2.452389	-0.904097
C	3.906052	2.545816	-2.887222
C	2.645448	3.637030	-1.148187
C	3.619598	3.684560	-2.137994
C	0.221936	-0.276300	-2.918546
C	-0.832883	0.814695	-2.758751
H	-2.611579	-1.360017	-2.778446
H	-4.812968	-2.461072	-2.920355
H	-6.667130	-1.742814	-1.434776
H	-6.308545	0.100549	0.189877
H	-4.112221	1.227970	0.324516
H	-1.127461	2.404683	1.324713
H	-1.678168	4.767430	1.879495
H	-2.799990	6.203826	0.197095
H	-3.397548	5.279262	-2.025388
H	-2.882818	2.925045	-2.569430
H	1.709874	-2.510312	-3.364771
H	3.484533	-4.214521	-3.521453
H	5.372834	-4.206330	-1.916262
H	5.500816	-2.457168	-0.157557
H	3.733540	-0.739497	0.012225
H	1.189204	2.419136	-0.132301
H	2.416495	4.523221	-0.560851
H	4.159145	4.609398	-2.327709
H	4.668771	2.578679	-3.661544
H	3.466269	0.473382	-3.225545
C	2.477059	0.563482	2.639879
C	3.599617	-0.058440	3.210276
C	2.325022	1.946373	2.774849
C	4.535621	0.690851	3.907235
H	3.727108	-1.134420	3.096865
C	3.267149	2.691668	3.472268
H	1.457821	2.435227	2.330847
C	4.373139	2.067996	4.040594
H	5.400665	0.198525	4.345143
H	3.136007	3.766452	3.572175
H	5.110728	2.653831	4.583436
H	-0.243755	-1.268884	-2.987477
H	0.823583	-0.114996	-3.822806
H	-1.617298	0.730192	-3.520367
H	-0.371333	1.804383	-2.876334

Int2b

Zero-point correction= 0.740111 (Hartree/Particle)
Thermal correction to Energy= 0.784530
Thermal correction to Enthalpy= 0.785474
Thermal correction to Gibbs Free Energy= 0.660955
Sum of electronic and zero-point Energies= -2541.224385
Sum of electronic and thermal Energies= -2541.179966
Sum of electronic and thermal Enthalpies= -2541.179022
Sum of electronic and thermal Free Energies= -2541.303541
HF (M06/6-311+G(d,p) and SDD, SMD[1-4 dioxane])= -2542.4151946

C	1.590591	2.628162	-0.287473
O	1.121644	1.932425	0.676994
N	2.488795	3.594451	-0.045470
C	2.921088	3.903313	1.303852
H	2.487646	3.189796	2.005408
H	4.015402	3.846282	1.364283
H	2.610261	4.916678	1.586689
C	3.039887	4.403305	-1.119281
H	3.918386	4.931228	-0.738914
H	3.362025	3.777120	-1.958310
H	2.321946	5.151261	-1.478513
C	1.102223	2.348971	-1.613900
C	0.261474	1.283015	-1.720181
H	1.288302	3.009935	-2.458515
H	-1.389968	1.764918	1.928581
C	-0.645027	1.120053	-2.885125
H	-0.197814	1.586856	-3.775008
H	-0.840839	0.067631	-3.127054
C	-1.959420	1.845203	-2.551386
H	-2.639689	1.755218	-3.408521
H	-1.728308	2.914028	-2.438100
C	-2.684341	1.351431	-1.293602
H	-3.136954	0.374539	-1.521546
H	-3.525485	2.035391	-1.114199
C	-1.823563	1.247042	-0.061851
C	-2.156346	1.765137	1.142160
Ir	-0.007403	0.238182	-0.075151
P	2.086863	-0.974422	-0.038490
P	-0.829266	-1.773973	-0.783338
C	1.799546	-2.657454	-0.775594
C	0.537689	-2.680799	-1.634893
H	2.675721	-2.988815	-1.345721
H	1.686303	-3.343807	0.074222
H	0.223561	-3.708484	-1.860051
H	0.706059	-2.176642	-2.596980
C	3.384925	-0.190345	-1.049664
C	4.249950	0.736671	-0.461627
C	3.437892	-0.397605	-2.431193
C	5.161614	1.437585	-1.244735
H	4.216844	0.906401	0.614745
C	4.352594	0.301584	-3.210377
H	2.760513	-1.105551	-2.909419
C	5.214657	1.220986	-2.618662
H	5.836702	2.152166	-0.777573
H	4.394811	0.125322	-4.282610
H	5.931945	1.764333	-3.229117
C	2.880710	-1.277252	1.571712
C	3.935025	-2.187319	1.706085
C	2.437277	-0.562586	2.687974
C	4.524404	-2.390077	2.947337
H	4.301962	-2.733570	0.837105
C	3.034655	-0.764437	3.928977
H	1.632008	0.165031	2.579249
C	4.073525	-1.679606	4.057953
H	5.340804	-3.100940	3.049483
H	2.687810	-0.205620	4.794879
H	4.539229	-1.838834	5.027627
C	-2.320892	-2.059698	-1.779657
C	-3.560678	-2.112525	-1.131705
C	-2.265880	-2.133923	-3.174543
C	-4.729534	-2.225480	-1.873733
H	-3.612439	-2.050814	-0.044533
C	-3.439881	-2.245307	-3.912358
H	-1.309452	-2.105839	-3.695455
C	-4.669785	-2.285915	-3.263669
H	-5.689663	-2.265418	-1.365424
H	-3.392399	-2.305131	-4.996811
H	-5.586010	-2.371102	-3.842687
C	-1.109850	-2.706496	0.756633
C	-1.199793	-4.101118	0.783742
C	-1.203799	-1.984326	1.950047
C	-1.369745	-4.760729	1.994813
H	-1.146791	-4.673108	-0.142511
C	-1.370295	-2.647131	3.162431
H	-1.178544	-0.889872	1.931606
C	-1.450440	-4.035256	3.182020
H	-1.442406	-5.845320	2.014577
H	-1.445475	-2.079544	4.086453
H	-1.583155	-4.556773	4.126731
C	-3.428417	2.373910	1.568199
C	-4.678933	1.896916	1.150262
C	-3.400154	3.450906	2.465246
C	-5.853431	2.501739	1.583341

H	-4.729374	1.024015	0.500419
C	-4.572383	4.057560	2.895648
H	-2.435862	3.818501	2.815691
C	-5.805792	3.588601	2.450822
H	-6.813684	2.114493	1.249008
H	-4.525143	4.898923	3.583848
H	-6.725469	4.060270	2.789065

TS3b

Zero-point correction= 0.738697 (Hartree/Particle)
Thermal correction to Energy= 0.782774
Thermal correction to Enthalpy= 0.783718
Thermal correction to Gibbs Free Energy= 0.659846
Sum of electronic and zero-point Energies= -2541.210100
Sum of electronic and thermal Energies= -2541.166023
Sum of electronic and thermal Enthalpies= -2541.165079
Sum of electronic and thermal Free Energies= -2541.288951
HF (M06/6-311+G(d,p) and SDD, SMD[1-4 dioxane])= -2542.3947697

C	1.603114	2.642816	0.024341
O	1.289880	1.712841	0.852279
N	2.510866	3.567090	0.386409
C	3.256331	3.448926	1.624752
H	2.977537	2.530153	2.142355
H	4.334106	3.432586	1.414515
H	3.047745	4.301766	2.282594
C	2.888106	4.648971	-0.503470
H	3.376362	5.431688	0.083507
H	3.587789	4.310304	-1.281330
H	2.009767	5.093576	-0.979743
C	0.956136	2.640493	-1.247579
C	-0.009064	1.670716	-1.436276
H	1.215870	3.329821	-2.047327
H	-0.801515	2.225050	1.624387
C	-0.709413	1.573275	-2.755051
H	-0.147644	2.125257	-3.519959
H	-0.752581	0.523394	-3.077535
C	-2.113934	2.136166	-2.577103
H	-2.763447	1.890440	-3.425549
H	-2.043966	3.231395	-2.519117
C	-2.675304	1.599282	-1.261136
H	-3.085558	0.593423	-1.419948
H	-3.508065	2.228501	-0.924710
C	-1.583242	1.586567	-0.227892
C	-1.704351	2.105913	1.021055
Ir	0.086889	0.180003	-0.067016
P	1.991477	-1.133959	-0.174741
P	-0.937585	-1.694817	-0.852830
C	1.619057	-2.735705	-1.039851
C	0.315439	-2.647991	-1.825824
H	2.461381	-3.033839	-1.675859
H	1.532365	-3.487874	-0.244199
H	-0.067926	-3.640703	-2.093004
H	0.461221	-2.097917	-2.765370
C	3.217412	-0.238861	-1.185252
C	4.128900	0.620753	-0.565327
C	3.133100	-0.258160	-2.581245
C	4.92690	1.447910	-1.333243
H	4.04588	0.643374	0.521424
C	3951927	0.565027	-3.345072
H	.420773	-0.914011	-3.082004
C	4.853090	1.424282	-2.721850
H	5.656162	2.108268	-0.844017
H	3.887189	0.535711	-4.430178
H	5.492228	2.069221	-3.320300
C	2.883213	-1.616663	1.335732
C	4.029751	-2.416232	1.265780
C	2.409936	-1.189852	2.578088
C	4.686137	-2.791919	2.430243
H	4.414767	-2.736957	0.297575
C	3.072493	-1.566670	3.743218
H	1.525115	-0.554922	2.628206
C	4.206298	-2.367829	3.668128
H	5.576188	-3.413948	2.374489
H	2.702080	-1.232905	4.709432
H	4.723677	-2.662495	4.578088
C	-2.465245	-1.770934	-1.843189
C	-3.697508	-1.900944	-1.192329
C	-2.438043	-1.591408	-3.229880
C	-4.881719	-1.837952	-1.917508
H	-3.731776	-2.045416	-0.112955
C	-3.625349	-1.530107	-3.951485
H	-1.491869	-1.492382	-3.759638
C	-4.847072	-1.646368	-3.295653
H	-5.834653	-1.940663	-1.404238
H	-3.595298	-1.391725	-5.029524
H	-5.774322	-1.594248	-3.860899
C	-1.303443	-2.736502	0.602728
C	-1.437495	-4.124835	0.504945
C	-1.465374	-2.114619	1.845955
C	-1.709929	-4.879809	1.639525
H	-1.340687	-4.621203	-0.460397
C	-1.740593	-2.873213	2.979663
H	-1.390937	-1.026392	1.918407
C	-1.857266	-4.255328	2.875893
H	-1.811778	-5.959305	1.558860
H	-1.868504	-2.383015	3.941564
H	-2.071030	-4.849770	3.760861
C	-2.934698	2.518641	1.707305
C	-4.161772	1.863233	1.525307
C	-2.869608	3.561598	2.642726
C	-5.290652	2.265099	2.228431
H	-4.221041	1.009787	0.850634
C	-4.000698	3.970015	3.335578
H	-1.915643	4.059745	2.812642
C	-5.217139	3.325000	3.127539
H	-6.232383	1.741135	2.080878
H	-3.933291	4.789669	4.047352
H	-6.102240	3.637803	3.676435

X-RAY CRYSTALLOGRAPHIC DETAILS

CCDC 1841781 and CCDC 1841782 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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SUPPORTING INFORMATION

Rhodium (III)-catalyzed intramolecular annulations of acrylic and benzoic acids to alkynes

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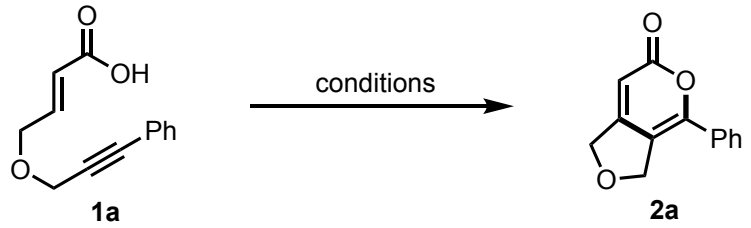
General Procedures

Dry solvents were freshly distilled under argon from an appropriate drying agent before use. Dried *N,N*-dimethylformamide were purchased from Aldrich and used without further purification. $[RhCp^*Cl_2]_2$ (99%) [12354-85-7] and Ag_2CO_3 (99%) [534-16-7] were purchased from Sigma-Aldrich. All other chemicals were purchased from Sigma-Aldrich, TCI, Alfa Aesar and Strem-Chemicals and used without further purification. 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 approximately at 23 °C. Reaction mixtures were stirred using Teflon-coated magnetic stirring bars. Reaction temperatures were maintained using Thermowatch-controlled silicone oil baths. Thin-layer chromatography (TLC) was performed on silica gel plates and components were visualized by observation under UV light, and / or 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 or $MgSO_4$. Concentration refers to the removal of volatile solvents via distillation using a Büchi rotary evaporator followed by residual solvent removal under high vacuum. Melting points (m.p.) were determined with an M-560 BÜCHI apparatus. NMR spectra were recorded in $CDCl_3$, at 300 MHz (Varian), 400 MHz (Varian) or 500 MHz (Varian), unless other solvent is specified. Carbon types and structure assignments were determined from DEPT-NMR. NMR spectra were analyzed using MestreNova© NMR data processing software (www.mestrelab.com). 1,3,5-Trimethoxybenzene was used as internal standard. 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; brs, broad singlet. Mass spectra (ESI-MS) were acquired using IT-MS Bruker AmaZon SL at CIQUS and also using chemical ionization (CI) electron impact (EI), electrospray ionization (ESI) or (APCI) atmospheric-pressure chemical ionization at the CACTUS facility of the University of Santiago de Compostela. The reactions were monitored by TLC.

Table S1. Optimization of the reaction conditions.[a]



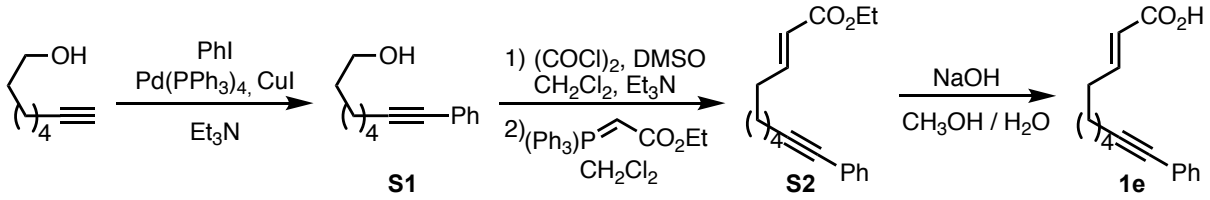
1a **2a**

Entry	Catalyst	Oxidant	Solvent	T (ºC)	Yield (%)
1	$[Cp^*RhCl_2]_2$	$Cu(OAc)_2.H_2O$	*t*AmOH	100	50
2	$[Cp^*RhCl_2]_2$	$Cu(OAc)_2.H_2O$	DMF	120	25
3	**$[Cp^*RhCl_2]_2$**	**Ag_2CO_3**	**DMF**	**120**	**82**[b]
4	$[Cp^*RhCl_2]_2$	Ag_2CO_3	DCE	80	20
5	$[Cp^*RhCl_2]_2$	Ag_2CO_3	toluene	110	36
6	$[(p\text{-cymene})\ RuCl_2]_2$	Ag_2CO_3	DMF	120	28
7	$[Cp^*IrCl_2]_2$	Ag_2CO_3	DMF	120	-
8	$[Cp^*Rh(CH_3CN)_3](SbF_6)_2$	Ag_2CO_3	DMF	120	21[b,c]
9	$[Cp^*RhCl_2]_2$	Ag_2CO_3	DMF	120	21[d]
10	$[Cp^*RhCl_2]_2$	Ag_2CO_3	MeOH	80	71
11	$[Cp^*RhCl_2]_2$	Ag_2CO_3	HFIP	80	26[e]
12	$[Cp^*RhCl_2]_2$	Ag_2CO_3	HFIP	80	48[b]
13	$[Cp^*RhCl_2]_2$	1,3-DNB	DMF	120	28
14	$[Cp^*RhCl_2]_2$	BQ/AgOAc	DMF	120	<5[f]
15	$[Cp^*RhCl_2]_2$	Air	DMF	120	<5[g]
16	$[Cp^*RhCl_2]_2$	Ag_2CO_3	DMF	120	31[h]

[a] Reaction conditions: 0.20 mmol of **1a**, catalyst (2.5 mol%), 2 equiv. of oxidant, solvent (0.8 mL), 12 h. Yields determined by internal standard. [b] Isolated yield. [c] 5 mol% of catalyst. [d] $AgSbF_6$ (1 equiv.) was used as additive. [e] 1 mol% of catalyst, 0.5 equiv. oxidant. [f] 2 equiv. AgOAc, 1 equiv. 1,4-benzoquinone. [g] 1 equiv. NaOAc. [h] 1 equiv. Ag_2CO_3

Synthesis of precursors

General procedure (A) for preparation of acid precursors 1c, 1e, 1h, 1i, 1j, 1k and 1l (exemplified for the synthesis of (*E*)-10-phenyldec-2-en-9-ynoic acid, **1e**).



Scheme S12. General procedure A for preparation of acid precursors

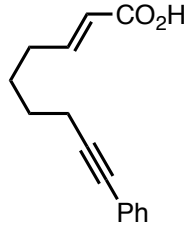
A flame-dried Schlenk flask under argon equipped with a Teflon septum and magnetic stir bar was charged with CuI (135.8 mg, 0.71 mmol) and $Pd(PPh_3)_4$ (412.5 mg, 0.36 mmol). Et_3N (47.5 mL), iodobenzene (4.0 mL, 35.66 mmol) and oct-7-yn-1-ol (3.0 g, 23.77 mmol) were sequentially added. The reaction mixture was stirred at rt. After 20 h, the reaction mixture was concentrated in vacuo. Purification of the crude product by flash chromatography on silica gel (1:10 to 1:4 EtOAc: Hexane) afforded 8-phenyloct-7-yn-1-ol (**S1**) as a yellow oil (4.6 g, 96 % yield). **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.44 – 7.39 (m, 2H), 7.32 – 7.26 (m, 3H), 3.66 (td, *J* = 6.6, 2.4 Hz, 2H), 2.43 (t, *J* = 6.9 Hz, 2H), 2.08 – 1.93 (m, 1H), 1.69 – 1.55 (m, 4H), 1.54 – 1.37 (m, 4H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 131.60 (CH), 128.27 (CH), 127.58 (CH), 124.07 (C), 90.34 (C), 80.75 (C), 62.90 (CH_2), 32.68 (CH_2), 28.75 (CH_2), 25.38 (CH_2), 19.41 (CH_2). **HRMS** (APCI-FIA-TOF): m/z calculated for $C_{14}H_{19}O$ ($[M+H]^+$) 203.1429, found 203.1430.

DMSO (1.3 mL, 17.79 mmol) in CH_2Cl_2 (1.9 mL) was added dropwise to a solution of oxalyl chloride (0.76 mL, 8.90 mmol) in CH_2Cl_2 (16.5 mL) at –78 °C. The reaction was stirred for 10 min and then a solution of 8-phenyloct-7-yn-1-ol (1.0 g, 4.94 mmol) in CH_2Cl_2 (3.5 mL,) was added slowly. After 45 min Et_3N (3.4 mL, 24.71 mmol) was added at –78 °C. After stirring at that temperature for 30 min, the mixture was warmed to rt and stirred for 45 min. H_2O (30 mL) was then added, the organic phase was separated and washed with HCl (1.0 M solution), $NaHCO_3$ (sat) and brine. The organic phases were dried and carefully concentrated under vacuum at 0 °C. The crude 8-phenyloct-7-ynal was obtained in quantitative yield as yellow oil and submitted to the next step without purification. To a solution of ethyl 2-(triphenyl-l^5-phosphaneylidene)acetate (4.30 g, 12.35 mmol) in CH_2Cl_2 (10 mL) at 0 ºC was added dropwise the crude 8-phenyloct-7-ynal (990 mg, 4.94 mmol). The reaction mixture was stirring at. After

18h, the solvent was evaporated *in vacuo* and the crude was purified by flash chromatography (pentane:diethylether 8:1) to obtain ethyl (*E*)-10-phenyldec-2-en-9-ynoate (**S2**) (940 mg, 70.5%). Colorless oil. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.56 – 7.49 (m, 2H), 7.43 – 7.36 (m, 3H), 7.10 (dt, *J* = 15.6, 6.9 Hz, 1H), 5.96 (dt, *J* = 15.6, 1.6 Hz, 1H), 4.31 (q, *J* = 7.1 Hz, 2H), 2.53 (t, *J* = 6.9 Hz, 2H), 2.42 – 2.29 (m, 2H), 1.79 – 1.69 (m, 2H), 1.69 – 1.56 (m, 4H), 1.40 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 166.7 (C), 149.1 (CH), 131.6 (CH), 128.2 (CH), 127.5 (CH), 124.0 (C), 121.5 (CH), 90.0 (C), 80.8 (C), 60.1 (CH_2), 32.1 (CH_2), 28.5 (CH_2), 28.4 (CH_2), 27.6 (CH_2), 19.3 (CH_2), 14.3 (CH_3). **HRMS** (APCI-FIA-TOF): m/z calculated for $C_{18}H_{23}O_2$ ($[M+H]^+$) 271.1693, found 271.1693.

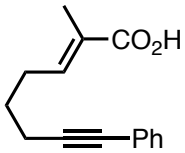
A NaOH aqueous solution (8.8 mL, 1M mmol) was added to solution that contains ethyl (*E*)-10-phenyldec-2-en-9-ynoate (**S2**, 600 mg, 2.21 mmol) in MeOH (4.1 mL). The reaction mixture was stirring at 45 ºC. After 20 h, a solution of HCl (10 %) was added to adjust the pH to 1. The mixture was extracted with EtOAc (3 x 10 mL). The combined organic layers were dried, and the solvent removed *in vacuo.* Purification of the crude product by flash chromatography on silica gel (1:5 to 2:1 EtOAc: Hexane) afforded (*E*)-10-phenyldec-2-en-9-ynoic acid (**1e**) as a colorless oil. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 11.03 (s, 1H), 7.47 – 7.37 (m, 2H), 7.34 – 7.26 (m, 3H), 7.13 (dt, *J* = 15.6, 6.9 Hz, 1H), 5.87 (d, *J* = 15.6 Hz, 1H), 2.44 (t, *J* = 6.8 Hz, 2H), 2.35 – 2.25 (m, 2H), 1.71 – 1.47 (m, 6H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 172.3, 152.3, 131.7, 128.3, 127.7, 124.1, 120.9, 90.1, 80.9, 32.3, 28.6, 28.5, 27.5, 19.4. **HRMS** (APCI-FIA-TOF): m/z calculated for $C_{16}H_{19}O_2$ ($[M+H]^+$) 243.1373, found 243.1380.

(*E*)-9-Phenylnon-2-en-8-ynoic acid (1c)



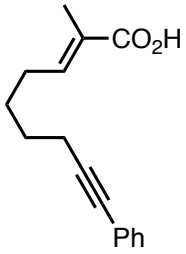
This compound was prepared according to the previously described general procedure **A**, using 7-phenylhept-6-yn-1-ol instead of 8-phenyloct-7-yn-1-ol. White solid, **m.p.** 71 -72 ºC. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.45 – 7.35 (m, 2H), 7.33 – 7.23 (m, 3H), 7.10 (dt, *J* = 15.6, 6.9 Hz, 1H), 5.87 (dt, *J* = 15.6, 1.6 Hz, 1H), 2.47 – 2.39 (m, 2H), 2.36 – 2.25 (m, 2H), 1.74 – 1.59 (m, 4H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 171.9 (C), 151.9 (CH), 131.7 (CH), 128.3 (CH), 127.7 (CH), 124.0 (C), 121.04 (CH), 89.7 (C), 81.2 (C), 32.0 (CH_2), 28.3 (CH_2), 27.2 (CH_2), 19.3 (CH_2). **HRMS** (APCI-FIA-TOF): m/z calculated for $C_{15}H_{17}O_2$ ($[M+H]^+$) 229.1221, found 229.1223.

(*E*)-2-Methyl-8-phenyloct-2-en-7-ynoic acid (1h)



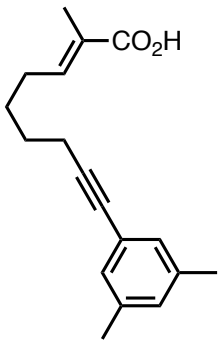
This compound was prepared according to the previously described general procedure **A**, using 6-phenylhex-5-yn-1-ol and ethyl ethyl 2-(triphenyl-λ^5-phosphaneylidene)propanoate instead of 8-phenyloct-7-yn-1-ol and ethyl 2-(triphenyl-l^5-phosphaneylidene)acetate. Light yellow solid, **m.p.** 77 -79 ºC. ^{1}H NMR (300 MHz, $CDCl_3$): δ 11.94 (brs, 1H), 7.34 – 7.26 (m, 2H), 7.22 – 7.12 (m, 3H), 6.85 (t, *J* = 7.1 Hz, 1H), 2.38 – 2.24 (m, 4H), 1.79 (s, 3H), 1.66 (p, *J* = 7.1 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 173.9 (C), 144.1 (CH), 131.6 (CH), 128.3 (CH), 128.1 (C), 127.7 (CH), 123.9 (C), 89.3 (C), 81.4 (C), 28.0 (CH_2), 27.5 (CH_2), 19.1 (CH_2), 12.1 (CH_3). **HRMS** (APCI-FIA-TOF): m/z calculated for $C_{15}H_{16}O_2$ ([M+H]$^+$) 229.1225, found 229.1223.

(*E*)-2-Methyl-9-phenylnon-2-en-8-ynoic acid (1i)



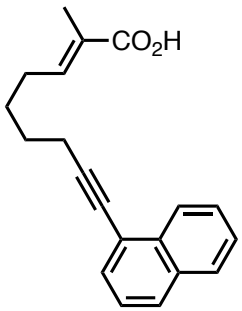
This compound was prepared according to the previously described general procedure **A**, using 7-phenylhept-6-yn-1-ol and ethyl 2-(triphenyl-λ^5-phosphaneylidene)propanoate instead of 8-phenyloct-7-yn-1-ol and ethyl 2-(triphenyl-l^5-phosphaneylidene)acetate. Viscous oil. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 11.55 (brs, 1H), 7.45 – 7.40 (m, 2H), 7.33 – 7.27 (m, 3H), 7.01 – 6.94 (m, 1H), 2.49 – 2.42 (m, 2H), 2.31 – 2.23 (m, 2H), 1.88 (s, 3H), 1.70 – 1.61 (m, 4H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 174.0 (C), 144.9 (CH), 131.6 (CH), 128.2 (CH), 127.6 (CH), 127.4 (CH), 124.0 (C), 89.8 (C), 81.1 (C), 28.5 (CH_2), 28.4 (CH_2), 27.7 (CH_2), 19.3 (CH_2), 12.0 (CH_3). **HRMS** (APCI-FIA-TOF): m/z calculated for $C_{16}H_{19}O_2$ ([M+H]$^+$) 243.1378, found 243.1380.

(*E*)-9-(3,5-Dimethylphenyl)-2-methylnon-2-en-8-ynoic acid (1j)



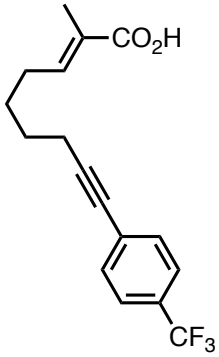
This compound was prepared according to the previously described general procedure **A**, using 7-phenylhept-6-yn-1-ol and ethyl ethyl 2-(triphenyl-λ^5-phosphaneylidene) propanoate instead of 8-phenyloct-7-yn-1-ol and ethyl 2-(triphenyl-l^5-phosphaneylidene)acetate. 1-bromo-3,5-dimethylbenzene was used for the Sonogashira coupling. Amorphous yellow solid. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 11.54 (brs, 1H), 6.93 (s, 2H), 6.85 (t, *J* = 7.5 Hz, 1H), 6.79 (s, 1H), 2.37 – 2.26 (m, 2H), 2.17 (s, 6H), 1.79 – 1.72 (m, 3H), 1.59 – 1.49 (m, 4H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 174.0 (C), 145.0 (CH), 137.8 (C), 129.6 (CH), 129.3 (CH), 127.4 (C), 123.6 (C), 89.0 (C), 81.3 (C), 28.5 (CH_2), 28.5 (CH_2), 27.7 (CH_2), 21.2 (CH_3), 19.3 (CH_2), 12.1 (CH_3). **HRMS** (APCI-FIA-TOF): m/z calculated for $C_{15}H_{16}O_2$ ([M+H]$^+$) 271.1695, found 271.1698.

(*E*)-2-Methyl-9-(naphthalen-1-yl)non-2-en-8-ynoic acid (1k)



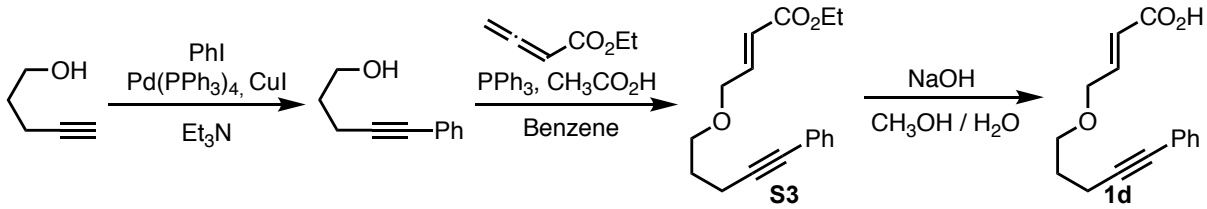
This compound was prepared according to the previously described general procedure **A**, using 7-phenylhept-6-yn-1-ol and ethyl 2-(triphenyl-λ^5-phosphaneylidene) propanoate instead of 8-phenyloct-7-yn-1-ol and ethyl 2-(triphenyl-l^5-phosphaneylidene)acetate. 1-bromonaphthalene was used for the Sonogashira coupling. Light yellow solid, **m.p.** 72-74 ºC. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 12.10 (brs, 1H), 8.43 (d, *J* = 8.3 Hz, 1H), 7.92 – 7.79 (m, 2H), 7.71 (d, *J* = 7.1 Hz, 1H), 7.67 – 7.52 (m, 2H), 7.50 – 7.41 (m, 1H), 7.04 (t, *J* = 7.3 Hz, 1H), 2.63 (t, *J* = 6.4 Hz, 2H), 2.38 – 2.27 (m, 2H), 1.93 (s, 3H), 1.84 – 1.70 (m, 4H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 174.0 (C), 144.9 (CH), 133.5 (C), 133.3 (C), 130.1 (CH), 128.3 (CH), 128.1 (CH), 127.5 (C), 126.6 (CH), 126.3 (CH), 126.3 (CH), 125.3 (CH), 121.7 (C), 94.9 (C), 79.1 (C), 28.6 (CH_2), 28.5 (CH_2), 27.8 (CH_2), 19.6 (CH_2), 12.1 (CH_3). **HRMS** (APCI-FIA-TOF): m/z calculated for $C_{20}H_{21}O_2$ ($[M+H]^+$) 293.1537, found 293.1536.

(*E*)-2-Methyl-9-(4-(trifluoromethyl)phenyl)non-2-en-8-ynoic acid (1l)



This compound was prepared according to the previously described general procedure **A**, using 7-phenylhept-6-yn-1-ol and ethyl 2-(triphenyl-λ^5-phosphaneylidene) propanoate instead of 8-phenyloct-7-yn-1-ol and ethyl 2-(triphenyl-l^5-phosphaneylidene)acetate. 1-bromo-4-(trifluoromethyl) Benzene was used for the Sonogashira coupling. Amorphous yellowish solid. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 11.51 (brs, 1H), 7.46 – 7.35 (m, 4H), 6.88 – 6.81 (m, 1H), 2.39 – 2.29 (m, 2H), 2.21 – 2.10 (m, 2H), 1.75 (s, 3H), 1.58 – 1.50 (m, 4H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 174.0 (C), 144.8 (CH), 131.9 (CH), 129.4 (C, q, *J* = 32.8 Hz), 127.6 (C), 126.8 (C), 125.2 (CH, q, *J* = 4.0 Hz), 120.5 (CF_3, q, *J* = 272.6 Hz), 92.7 (C), 80.0 (C), 28.5 (CH_2), 28.2 (CH_2), 27.7 (CH_2), 19.3 (CH_2), 12.0 (CH_3). **HRMS** (APCI-FIA-TOF): m/z calculated for $C_{17}H_{18}F_3O_2$ ($[M+H]^+$) 311.1257, found 311.1259.

General procedure (B) for preparation of acid precursors 1a, 1b, 1d, 1f, 1g, 1m and 1n (exemplified for the synthesis of (*E*)-4-((5-Phenylpent-4-yn-1-yl)oxy)but-2-enoic acid, **1d**).



Scheme S13. General procedure B for preparation of acid precursors

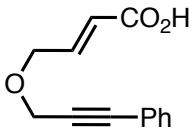
A flame-dried Schlenk flask under argon equipped with a Teflon septum and magnetic stir bar was charged with CuI (271.7 mg, 1.43 mmol) and $Pd(PPh_3)_4$ (824.3 mg, 0.71 mmol). Et_3N (95.0 mL), iodobenzene (8.0 mL, 71.33 mmol) and 4-pentyn-1-ol (4.0 g, 47.55 mmol) were sequentially added. The reaction mixture was stirred at rt, and after 20 h concentrated in vacuo. Purification of the crude product by flash chromatography on silica gel (1:10 to 1:2 EtOAc: Hexane) afforded 5-phenylpent-4-yn-1-ol as an orange oil (7.4 g, 97% yield). The NMR and MS data were consistent with those previously published. [1]

PPh_3 (163.7 mg, 0.62 mmol) was added to a solution of 5-phenylpent-4-yn-1-ol (2.0 g, 12.48 mmol) and ethyl buta-2,3-dienoate (2.9 mL, 24.97 mmol) in benzene (27.7 mL). To this orange solution, acetic acid (0.14 mL, 2.49 mmol) was added and the reaction was heated up to 60 ºC. After 16 h, the solvent was removed in vacuo. Purification of the crude product by flash chromatography on silica gel (1:20 to 1:4 EtOAc: Hexane) afforded ethyl (*E*)-4-((5-Phenylpent-4-yn-1-yl)oxy)but-2-enoate as a pale yellow oil (1.9 g, 58 % yield). **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.45 – 7.37 (m, 2H), 7.33 – 7.26 (m, 3H), 6.99 (dt, *J* = 15.7, 4.2 Hz, 1H), 6.11 (dt, *J* = 15.7, 2.1 Hz, 1H), 4.26 – 4.16 (m, 4H), 3.65 (t, *J* = 6.0 Hz, 2H), 2.56 (t, *J* = 7.0 Hz, 2H), 1.91 (p, *J* = 6.9, 6.5 Hz, 2H), 1.30 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 166.5 (C), 144.6 (CH), 131.7 (CH), 128.3 (CH), 127.7 (CH), 123.9 (C), 121.3 (CH), 89.4 (C), 81.1 (C), 69.6 (CH_2), 60.5 (CH_2), 29.0 (CH_2), 16.3 (CH_2), 14.4 (CH_3). **HRMS** (APCI-FIA-TOF): m/z calculated for $C_{17}H_{21}O_3$ ($[M+H]^+$) 273.1483, found 273.1485.

A NaOH aqueous solution (22.4 mL, 1M) was added to a solution that contains ethyl (*E*)-4-((5-Phenylpent-4-yn-1-yl)oxy)but-2-enoate (1500 mg, 5.51 mmol) in MeOH (10.2 mL). The reaction mixture was stirred at 45 ºC. After 20 h, a solution of HCl (10 %) was added to adjust the pH to 1. The mixture was extracted with EtOAc (3 x 20 mL). The combined organic layers were dried and the solvent removed *in vacuo.* Purification of the crude product by flash chromatography on silica gel (1:5 to 2:1 EtOAc: Hexane) afforded (*E*)-4-((5-Phenylpent-4-yn-

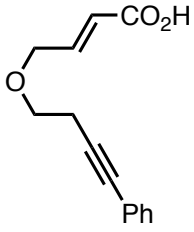
1-yl)oxy)but-2-enoic acid (**1d**) as a white solid, **m.p.** 62-64 ºC, (1.23 g, 92 % yield). **^{1}H NMR** (300 MHz, $CDCl_3$): δ 11.64 (brs, 1H), 7.47 – 7.39 (m, 2H), 7.35 – 7.27 (m, 3H), 7.11 (dt, *J* = 15.7, 4.0 Hz, 1H), 6.15 (dt, *J* = 15.7, 2.1 Hz, 1H), 4.24 – 4.18 (m, 2H), 3.66 (t, *J* = 6.1 Hz, 2H), 2.57 (t, *J* = 7.0 Hz, 2H), 1.93 (p, *J* = 6.5 Hz, 2H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 171.9 (C), 147.5 (CH), 131.6 (CH), 128.3 (CH), 127.7 (CH), 123.9 (C), 120.4 (CH), 89.3 (C), 81.1 (C), 69.6 (CH_2), 69.4 (CH_2), 28.8 (CH_2), 16.2 (CH_2). **HRMS** (APCI-FIA-TOF): m/z calculated for $C_{15}H_{17}O_3$ ($[M+H]^+$) 245.1172, found 245.1172.

(*E*)-4-((3-Phenylprop-2-yn-1-yl)oxy)but-2-enoic acid (1a)



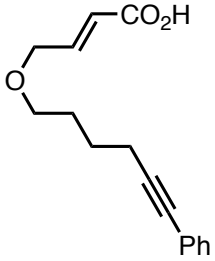
This compound was prepared according to the previously described general procedure **B**, using prop-2-yn-1-ol instead of 4-pentyn-1-ol. White solid, **m.p.** 66 -67 ºC. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.51 – 7.39 (m, 2H), 7.36 – 7.28 (m, 3H), 7.19 – 7.04 (m, 1H), 6.22 – 6.08 (m, 1H), 4.45 (s, 2H), 4.34 (s, 2H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 171.3 (C), 146.6 (CH), 131.9 (CH), 128.8 (CH), 128.5 (CH), 122.5 (C), 120.9 (CH), 87.1 (C), 84.4 (C), 68.2 (CH_2), 59.0 (CH_2). **HRMS** (APCI-FIA-TOF): m/z calculated for $C_{13}H_{13}O_3$ ($[M+H]^+$) 217.0855, found 217.0859.

(*E*)-4-((4-Phenylbut-3-yn-1-yl)oxy)but-2-enoic acid (1b)



This compound was prepared according to the previously described general procedure **B**, using but-3-yn-1-ol instead of 4-pentyn-1-ol. White solid, **m.p.** 80 -81 ºC.^{1}H NMR (300 MHz, $CDCl_3$): δ 11.51 (brs, 1H), 7.48 – 7.40 (m, 2H), 7.35 – 7.27 (m, 3H), 7.11 (dt, *J* = 15.7, 4.0 Hz, 1H), 6.19 (dt, *J* = 15.7, 2.1 Hz, 1H), 4.27 (dd, *J* = 4.1, 2.1 Hz, 2H), 3.72 (t, *J* = 6.9 Hz, 2H), 2.75 (t, *J* = 6.9 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.9 (C), 147.1 (CH), 131.7 (CH), 128.3 (CH), 127.9 (CH), 123.6 (C), 120.6 (CH), 86.5 (C), 81.8 (C), 69.5 (CH_2), 69.4 (CH_2), 20.9 (CH_2). **HRMS** (APCI-FIA-TOF): m/z calculated for $C_{14}H_{15}O_3$ ($[M+H]^+$) 231.1016, found 231.1016.

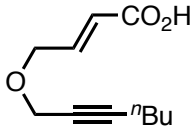
(*E*)-4-((6-Phenylhex-5-yn-1-yl)oxy)but-2-enoic acid (1f)



This compound was prepared according to the previously described general procedure **B**, using hex-5-yn-1-ol instead of 4-pentyn-1-ol. White solid, **m.p.** 78 -79 ºC.^{1}H NMR (300 MHz, $CDCl_3$): δ 11.31 (brs, 1H), 7.33 – 7.26 (m, 2H), 7.22 – 7.12 (m, 3H), 6.97 (dt, *J* = 15.7, 4.1 Hz, 1H), 6.00 (dt, *J* = 15.7, 2.0 Hz, 1H), 4.06 – 4.00 (m, 2H), 3.42 (t, *J* = 6.2 Hz, 2H), 2.35 (t, *J* = 6.7 Hz, 2H), 1.75 – 1.52 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.8 (C), 147.5 (CH), 131.6 (CH), 128.2 (CH), 127.6 (CH), 124.0 (C), 120.3 (CH), 89.9 (C), 81.0 (C), 70.7

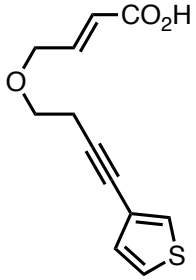
(CH_2), 69.2 (CH_2), 28.8 (CH_2), 25.4 (CH_2), 19.2 (CH_2). **HRMS** (IE-FIA-TOF): m/z calculated for $C_{16}H_{18}O_3$ ($[M]^+$) 258.1256, found 258.1258.

(*E*)-4-(Hept-2-yn-1-yloxy)but-2-enoic acid (1g)



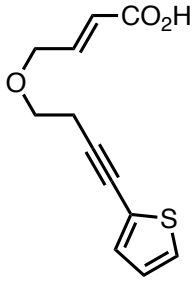
This compound was prepared according to the previously described general procedure **B**, using hept-2-yn-1-ol instead of 4-pentyn-1-ol. Viscous yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 11.49 (brs, 1H), 7.11 – 6.99 (m, 1H), 6.12 – 6.02 (m, 1H), 4.24 – 4.19 (m, 2H), 4.16 (s, 2H), 2.25 – 2.14 (m, 2H), 1.56 – 1.28 (m, 4H), 0.88 (t, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 173.8 (C), 148.7 (CH), 122.7 (CH), 89.9 (C), 77.2 (C), 69.8 (CH_2), 60.7 (CH_2), 32.6 (CH_2), 24.0 (CH_2), 20.4 (CH_2), 15.6 (CH_3). **HRMS** (APCI-FIA-TOF): m/z calculated for $C_{11}H_{17}O_3$ ($[M+H]^+$) 197.1172, found 197.1172.

(*E*)-4-((4-(Thiophen-3-yl)but-3-yn-1-yl)oxy)but-2-enoic acid (1m)



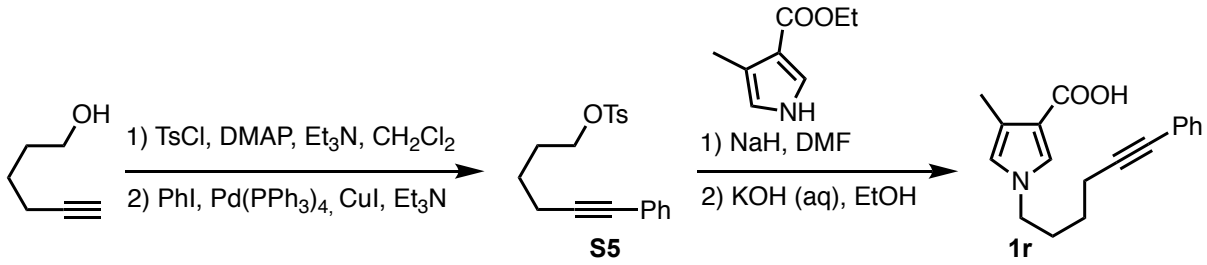
This compound was prepared according to the previously described general procedure **B**, using 3-bromothiophene (90%) instead of iodobenzene. Amorphous white solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 10.99 (brs, 1H), 7.41 (dd, *J* = 3.0, 1.2 Hz, 1H), 7.25 (dd, *J* = 5.0, 3.0 Hz, 1H), 7.17 – 7.03 (m, 2H), 6.18 (dt, *J* = 15.7, 2.1 Hz, 1H), 4.26 (dd, *J* = 4.1, 2.1 Hz, 2H), 3.70 (t, *J* = 6.9 Hz, 2H), 2.73 (t, *J* = 6.9 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.8 (C), 147.1 (CH), 130.1 (CH), 128.3 (CH), 125.2 (CH), 122.5 (C), 120.6 (CH), 86.0 (C), 76.9 (C), 69.5 (CH_2), 69.3 (CH_2), 20.9 (CH_2). **HRMS** (APCI-FIA-TOF): m/z calculated for $C_{12}H_{13}O_3S$ ($[M+H]^+$) 237.0577, found 237.0580.

(*E*)-4-((4-(Thiophen-2-yl)but-3-yn-1-yl)oxy)but-2-enoic acid (1n)



This compound was prepared according to the previously described general procedure **B**, using 2-bromothiophene instead of iodobenzene. Amorphous yellow solid.^{1}H NMR (300 MHz, $CDCl_3$): δ 11.64 (brs, 1H), 7.22 – 7.12 (m, 2H), 7.07 (dt, *J* = 15.7, 4.1 Hz, 1H), 6.93 (dd, *J* = 5.2, 3.6 Hz, 1H), 6.14 (dd, *J* = 15.7, 2.2 Hz, 1H), 4.23 (dd, *J* = 4.2, 2.1 Hz, 2H), 3.68 (t, *J* = 6.9 Hz, 2H), 2.74 (t, *J* = 6.9 Hz, 2H).^{13}C NMR (75 MHz, $CDCl_3$): δ 171.8 (C), 147.0 (CH), 131.6 (CH), 126.9 (CH), 126.4 (CH), 123.6 (C), 120.6 (CH), 90.5 (C), 75.0 (C), 69.5 (CH_2), 69.1 (CH_2), 21.1 (CH_2). **HRMS** (APCI-FIA-TOF): m/z calculated for $C_{12}H_{13}O_3S$ ($[M+H]^+$) 237.0577, found 237.0580.

General procedure (C) for preparation of acid precursors 1p, 1q, 1r, 1s, 1t and 1u (exemplified for the synthesis of 4-Methyl-1-(6-phenylhex-5-yn-1-yl)-1*H*-pyrrole-3-carboxylic acid, **1r**).



Scheme S14. General procedure C for preparation of acid precursors

5-Hexyn-1-ol (4.0 g, 40.8 mmol) was added to a solution of Et_3N (11.3 mL, 81.5 mmol), Tosyl chloride (8.2 g, 42.8 mmol) and 4-Dimethylaminopyridine (747 mg, 6.1 mmol) in CH_2Cl_2 (60.8 mL) at 0°C. The mixture was warmed to rt and stirred for 3 h. NH_4Cl (sat) (80 mL) was then added, the organic phase separated, and the aqueous phase extracted twice with CH_2Cl_2 (30 mL). The organic phases were dried and concentrated under vacuum. Purification of the crude residue by flash chromatography on silica gel (1:20 to 1:3 EtOAc: Hexanes) afforded hex-5-yn-1-yl 4-methylbenzenesulfonate (**S4**) as colorless oil (10.1 g, 98 % yield). **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.74 (d, *J* = 8.4 Hz, 2H), 7.31 (d, *J* = 8.0 Hz, 2H), 4.01 (t, *J* = 6.3 Hz, 2H), 2.41 (s, 3H), 2.12 (td, *J* = 6.9, 2.7 Hz, 2H), 1.90 (t, *J* = 2.7 Hz, 1H), 1.80 – 1.67 (m, 2H), 1.51 (p, *J* = 6.9 Hz, 2H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 144.8 (C), 133.0 (C), 129.9 (CH), 127.8 (CH), 83.4 (C), 70.0 (CH_2), 69.0 (CH), 27.7 (CH_2), 24.2 (CH_2), 21.6 (CH_3), 17.7 (CH_2). **HRMS** (ESI-TOF): m/z calculated for $C_{13}H_{17}O_3S$ ($[M+H]^+$) 253.0893, found 253.0893.

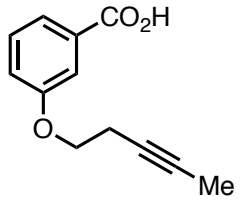
A Schlenk tube under argon equipped with a Teflon septum and magnetic stir bar was charged with CuI (22.6 mg, 0.12 mmol) and $Pd(PPh_3)_4$ (68.7 mg, 0.06 mmol). Et_3N (7.9 mL), iodobenzene (0.53 mL, 4.7 mmol) and hex-5-yn-1-yl 4-methylbenzenesulfonate (**S4**, 600 mg, 2.38 mmol) were sequentially added. The reaction mixture was stirred at rt. After 20 h, the reaction mixture was concentrated in vacuo. Purification of the crude product by flash chromatography on silica gel (1:20 to 1:4 EtOAc: Hexane) afforded 6-phenylhex-5-yn-1-yl-4-methylbenzenesulfonate (**S5**) as a colorless oil (723 mg, 93% yield). **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.79 – 7.74 (m, 2H), 7.37 – 7.33 (m, 2H), 7.30 – 7.28 (m, 1H), 7.28 – 7.22 (m, 4H), 4.06 (t, *J* = 6.3 Hz, 2H), 2.38 – 2.30 (m, 5H), 1.85 – 1.73 (m, 2H), 1.65 – 1.53 (m, 2H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 144.7 (C), 132.9 (C), 131.3 (CH), 129.8 (CH), 128.1 (CH), 127.6 (CH), 127.5 (CH), 123.6 (C), 89.0 (C), 81.2 (C), 70.0 (CH_2), 27.8 (CH_2), 24.4 (CH_2), 21.4 (CH_3),

18.6 (CH_2). **HRMS** (ESI-TOF): m/z calculated for $C_{19}H_{21}O_3S$ ($[M+H]^+$) 329.1208, found 329.1206.

Following a modified procedure described by Schreiber and co-workers[2], to a solution of ethyl 4-methyl-1*H*-pyrrole-3-carboxylate (250 mg, 1.63 mmol) in anhydrous DMF (4 mL) at 0 ºC was added sodium hydride (60 % mineral oil) (97.9 mg, 2.45 mmol). After 20 minutes, 6-phenylhex-5-yn-1-yl-4-methylbenzenesulfonate (540 mg, 1.64 mmol) was added. The reaction mixture was stirred at 85 °C for 16 hours. The reaction mixture was allowed to cool to room temperature, water (30 mL) and Et_2O (10 mL) were successively added, and the layers were separated. The aqueous phase was extracted with Et_2O (4 x 10 mL) and the combined organic phases were dried and concentrated. Purification of the crude residue by flash chromatography on silica gel (1:10 to 1:2 EtOAc: Hexanes) afforded ethyl 4-methyl-1-(6-phenylhex-5-yn-1-yl)-1*H*-pyrrole-3-carboxylate (**S6**) as yellow pale oil (396 mg, 78 % yield). **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.45 – 7.39 (m, 2H), 7.33 – 7.25 (m, 4H), 6.42 – 6.38 (m, 1H), 4.28 (q, *J* = 7.1 Hz, 2H), 3.82 (t, *J* = 7.0 Hz, 2H), 2.43 (t, *J* = 6.9 Hz, 2H), 2.31 (s, 3H), 1.97 – 1.84 (m, 2H), 1.63 – 1.50 (m, 2H), 1.35 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 165.3 (C), 131.4 (CH), 128.2 (CH), 127.6 (CH), 126.4 (CH), 123.7 (C), 121.4 (C), 120.2 (C), 120.1 (CH), 114.0 (C), 89.2 (C), 81.2 (C), 59.1 (CH_2), 49.3 (CH_2), 30.2 (CH_2), 25.5 (CH_2), 18.9 (CH_2), 14.5 (CH_3), 11.7 (CH_3). **HRMS** (APCI-FIA-TOF): m/z calculated for $C_{20}H_{24}NO_2$ ($[M+H]^+$) 310.1798, found 310.1802.

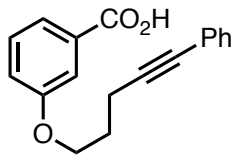
Following a modified procedure described by Sieber and co-workers[3], to a solution of ethyl 4-methyl-1-(6-phenylhex-5-yn-1-yl)-1*H*-pyrrole-3-carboxylate (**S6**, 390 mg, 1.26 mmol) in EtOH (6.3 mL) was added an aqueous solution of KOH (0.5 mL, 10 M) and the reaction mixture was stirred for 24 h at room temperature. The solution was acidified by adding aqueous 1 M HCl, the reaction mixture extracted with EtOAc (4 x 10 mL), and the combined organic extracts were washed with brine (40 mL), dried and concentrated under reduced. Purification of the crude residue by flash chromatography on silica gel (1:5 to 2:1 EtOAc: Hexanes) afforded 4-methyl-1-(6-phenylhex-5-yn-1-yl)-1*H*-pyrrole-3-carboxylic acid (**1r**) as a light-yellow solid, **m.p.** 77 -88 ºC, (323 mg, 91 % yield). **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.45 – 7.40 (m, 2H), 7.38 – 7.35 (m, 1H), 7.35 – 7.27 (m, 3H), 6.46 – 6.42 (m, 1H), 3.89 (t, *J* = 6.9 Hz, 2H), 2.47 (t, *J* = 6.9 Hz, 2H), 2.31 (s, 3H), 1.97 (p, *J* = 7.1 Hz, 2H), 1.61 (p, *J* = 7.1 Hz, 2H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 171.2 (C), 131.7 (CH), 128.4 (CH), 128.0 (CH), 127.8 (CH), 123.8 (C), 122.4 (C), 120.6 (CH), 113.4 (C), 89.2 (C), 81.5 (C), 49.6 (CH_2), 30.3 (CH_2), 25.7 (CH_2), 19.1 (CH_2), 11.8 (CH_3). **HRMS** (APCI-FIA-TOF): m/z calculated for $C_{18}H_{20}NO_2$ ($[M+H]^+$) 282.1491, found 282.1489.

3-(Pent-3-yn-1-yloxy)benzoic acid (1p)



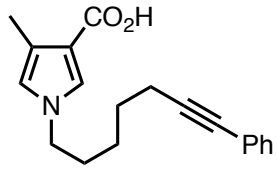
This compound was prepared according to the previously described general procedure **C**, using pent-3-yn-1-ol and methyl 3-hydroxybenzoate instead of 5-Hexyn-1-ol and ethyl 4-methyl-1H-pyrrole-3-carboxylate. White solid, **m.p.** 146 -147 ºC. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 10.37 (brs, 1H), 7.73 (d, *J* = 7.7 Hz, 1H), 7.64 (s, 1H), 7.38 (t, *J* = 8.0 Hz, 1H), 7.17 (dd, *J* = 8.3, 2.7 Hz, 1H), 4.11 (t, *J* = 7.1 Hz, 2H), 2.72 – 2.60 (m, 2H), 1.81 (t, *J* = 2.5 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 172.2 (C), 158.8 (C), 130.7 (C), 129.7 (CH), 123.1 (CH), 121.2 (CH), 115.4 (CH), 77.7 (C), 75.0 (C), 67.0 (CH_2), 19.9 (CH_2), 3.7 (CH_3). **HRMS** (APCI-FIA-TOF): m/z calculated for $C_{12}H_{12}O_3$ ($[M+H]^+$) 205.0859, found 205.0859.

3-((5-Phenylpent-4-yn-1-yl)oxy)benzoic acid (1q)



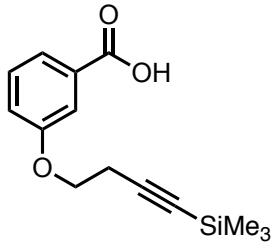
This compound was prepared according to the previously described general procedure **C**, using pent-4-yn-1-ol and methyl 3-hydroxybenzoate instead of 5-Hexyn-1-ol and ethyl 4-methyl-1H-pyrrole-3-carboxylate. White solid, **m.p.** 116 -117 ºC. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 11.44 (brs, 1H), 7.75 (d, *J* = 7.7 Hz, 1H), 7.68 (s, 1H), 7.47 – 7.38 (m, 3H), 7.33 – 7.26 (m, 3H), 7.20 (dd, *J* = 8.3, 2.6 Hz, 1H), 4.20 (t, *J* = 6.1 Hz, 2H), 2.67 (t, *J* = 6.9 Hz, 2H), 2.13 (p, *J* = 6.5 Hz, 2H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 172.4 (C), 159.1 (C), 131.7 (CH), 130.7 (C), 129.7 (CH), 128.3 (CH), 127.8 (CH), 123.8 (C), 122.8 (CH), 121.1 (CH), 115.3 (CH), 89.0 (C), 81.4 (C), 66.8 (CH_2), 28.5 (CH_2), 16.3 (CH_2). **HRMS** (APCI-FIA-TOF): m/z calculated for $C_{18}H_{17}O_3$ ($[M+H]^+$) 281.1171, found 281.1172.

4-Methyl-1-(7-phenylhept-6-yn-1-yl)-1*H*-pyrrole-3-carboxylic acid (1s)



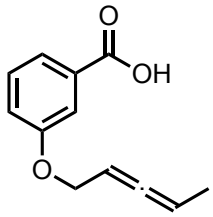
This compound was prepared according to the previously described general procedure **C**, using hept-6-yn-1-ol instead of 5-Hexyn-1-ol. Viscous orange oil. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 12.00 (brs, 1H), 7.45 – 7.39 (m, 2H), 7.38 – 7.34 (m, 1H), 7.34 – 7.27 (m, 3H), 6.43 (s, 1H), 3.84 (t, *J* = 6.9 Hz, 2H), 2.44 (t, *J* = 6.9 Hz, 2H), 2.31 (s, 3H), 1.83 (p, *J* = 7.1 Hz, 2H), 1.65 (p, *J* = 7.0 Hz, 2H), 1.55 – 1.43 (m, 2H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 171.3 (C), 131.6 (CH), 128.3 (CH), 128.0 (CH), 127.7 (CH), 123.9 (C), 122.3 (C), 120.6 (CH), 113.3 (C), 89.7 (C), 81.1 (C), 49.9 (CH_2), 30.7 (CH_2), 28.2 (CH_2), 25.9 (CH_2), 19.3 (CH_2), 11.8 (CH_3). **HRMS** (APCI-FIA-TOF): m/z calculated for $C_{19}H_{22}NO_2F_3$ ($[M+H]^+$) 296.1650, found 296.1645.

3-((4-(Trimethylsilyl)but-3-yn-1-yl)oxy)benzoic acid (1t)



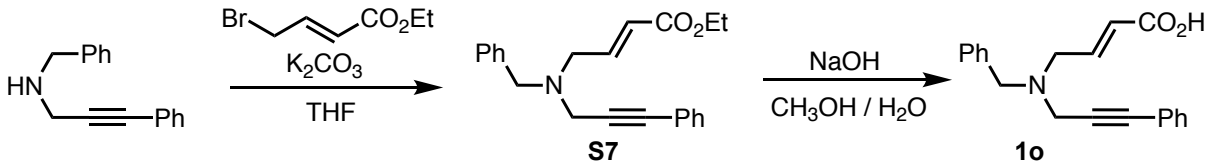
This compound was prepared according to the previously described general procedure **C**, using but-3-yn-1-ol and methyl 3-hydroxybenzoate instead of 5-Hexyn-1-ol and ethyl 4-methyl-1H-pyrrole-3-carboxylate[4]. White solid (5:1, $SiMe_3$: H). **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.74 (dt, J = 7.7, 1.3 Hz, 1H), 7.64 (dd, J = 2.7, 1.5 Hz, 1H), 7.39 (t, J = 7.9 Hz, 1H), 7.22 – 7.12 (m, 1H), 4.14 (t, J = 7.2 Hz, 2H), 2.75 (t, J = 7.3 Hz, 2H), 0.17 (s, 9H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 172.3 (C), 151.8 (C), 130.7 (C), 129.7 (CH), 123.1 (CH), 121.2 (CH), 115.3 (CH), 102.4 (C), 86.8 (C), 66.5 (CH_2), 21.0 (CH_2), 0.2 (CH_3). **HRMS** (APCI-FIA-TOF): m/z calculated for $C_{14}H_{19}O_3Si$ ([M+H]$^+$) 263.1097, found 263.1098.

3-(Penta-2,3-dien-1-yloxy)benzoic acid (1u)



This compound was prepared according to the previously described general procedure **C**, using penta-2,3-dien-1-ol and methyl 3-hydroxybenzoate instead of 5-Hexyn-1-ol and ethyl 4-methyl-1H-pyrrole-3-carboxylate. White solid. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 9.20 (s, 1H), 7.71 (dt, *J* = 7.7, 1.3 Hz, 1H), 7.65 (dd, *J* = 2.7, 1.4 Hz, 1H), 7.36 (t, *J* = 7.9 Hz, 1H), 7.16 (ddd, *J* = 8.3, 2.6, 1.0 Hz, 1H), 5.37 – 5.20 (m, 2H), 4.60 (dd, *J* = 6.4, 2.6 Hz, 2H), 1.68 (dd, *J* = 6.8, 3.4 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 206.3 (C), 172.2 (C), 158.5 (C), 130.9 (C), 129.6 (CH), 122.9 (CH), 121.40 (CH), 115.7 (CH), 87.9 (CH), 86.8 (CH), 66.7 (CH_2), 14.0 (CH_3). **HRMS** (APCI-FIA-TOF): m/z calculated for $C_{12}H_{13}O_3$ ([M+H]$^+$) 205.0858, found 205.0859.

Procedure for preparation of (E)-4-(Benzyl(3-phenylprop-2-yn-1-yl)amino)but-2-enoic acid 1o.



Scheme S15. Synthesis of (E)-4-(Benzyl(3-phenylprop-2-yn-1-yl)amino)but-2-enoic acid 1o.

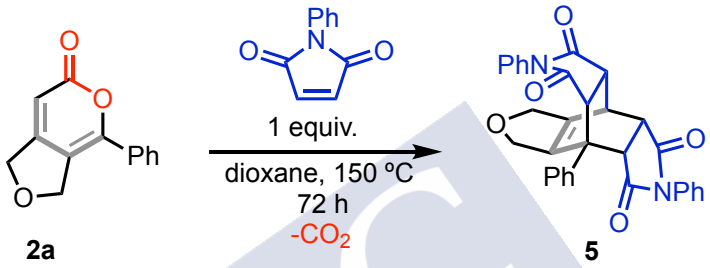
Following a modified procedure described by ourselves[5], N-Benzyl-3-phenylprop-2-yn-1-amine (2.5 g, 11.3 mmol) was added to a suspension of K_2CO_3 (2.6 g, 19.2 mmol) in THF (39 mL) at -10 ºC. After stirring for 15 min, ethyl (E)-4-bromobut-2-enoate (2.7 mL, 14.7 mmol) was added dropwise and the mixture was stirred overnight at rt. Then, the mixture was poured into

water and extracted with Et_2O (3x40 mL). The organic phases were dried, filtered and concentrated. Purification of the crude residue by flash chromatography on silica gel gave (1:20 to 1:1 EtOAc: Hexanes) ethyl (E)-4-(benzyl(3-phenylprop-2-yn-1-yl)amino)but-2-enoate (**S7**) as a light-yellow oil, (3.1 g, 84 % yield). **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.54 – 7.48 (m, 2H), 7.46 – 7.39 (m, 2H), 7.39 – 7.30 (m, 6H), 7.05 (dtd, *J* = 15.7, 6.0, 1.1 Hz, 1H), 6.15 (dt, *J* = 15.7, 1.3 Hz, 1H), 4.24 (q, *J* = 7.2 Hz, 2H), 3.78 (s, 2H), 3.58 (s, 2H), 3.43 (dd, *J* = 6.0, 1.7 Hz, 2H), 1.33 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 166.4 (C), 145.8 (CH), 138.4 (C), 131.9 (CH), 129.1 (CH), 128.5 (CH), 128.4 (CH), 128.3 (CH), 127.4 (CH), 123.4 (CH), 123.2 (C), 86.1 (C), 84.0 (C), 60.5 (CH_2), 58.0 (CH_2), 54.4 (CH_2), 42.8 (CH_2), 14.4 (CH_3). **HRMS** (APCI-FIA-TOF): m/z calculated for $C_{22}H_{23}NO_2$ ($[M+H]^+$) 333.1729, found 333.1727.

A NaOH aqueous solution (3 mL, 1M) was added to a solution that contains ethyl (E)-4-(benzyl(3-phenylprop-2-yn-1-yl)amino)but-2-enoate (1.0 g, 3.0 mmol) in MeOH (4.5 mL). The reaction mixture was stirred at rt. After 8 h, a solution of HCl (5 %) was added to adjust the pH to 2. The mixture was extracted with EtOAc (3 x 20 mL). The combined organic layers were dried and the solvent removed *in vacuo.* Purification of the crude product by flash chromatography on silica gel (1:5 to 2:1 EtOAc: Hexane) afforded (E)-4-(benzyl(3-phenylprop-2-yn-1-yl)amino)but-2-enoic acid (**1o**) as a colorless oil, (450 mg, 49 % yield). **^{1}H NMR** (300 MHz, $CDCl_3$): δ 11.05 (s, 1H), 7.51 – 7.46 (m, 1H), 7.40 (ddd, *J* = 8.3, 6.8, 1.7 Hz, 2H), 7.36 – 7.27 (m, 4H), 7.14 (dt, *J* = 15.7, 6.0 Hz, 1H), 6.14 (dd, *J* = 15.7, 1.6 Hz, 1H), 3.78 (s, 2H), 3.58 (s, 2H), 3.46 (dd, *J* = 6.1, 1.7 Hz, 2H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 171.4 (C), 148.0 (CH), 137.9 (C), 131.9 (CH), 129.3 (CH), 128.6 (CH), 128.47 (CH), 128.46 (C), 128.4 (CH), 127.6 (CH), 123.1 (CH), 86.4 (C), 83.6 (C), 58.0 (CH_2), 54.4 (CH_2), 42.7 (CH_2). **HRMS** (APCI-FIA-TOF): m/z calculated for $C_{20}H_{20}NO_2$ ($[M+H]^+$) 306.1489, found 306.1489.

Further insights into the cascade DA transformation

Preliminary tests on the amount of dienophile used were performed with **2a**, as in this way we would also confirm the viability of the tandem process on other substrates than **2d**. Heating 2a in presence of 1 equiv of the maleimide led exclusively to the cascade DA adduct **5** (47 %), and recovery of the remaining starting material **2a** (52 %). This result suggests that the intermediate resulting from the initial cycloadditions reacts faster than the initial pyrone.



Scheme S16. Cascade DA reaction

An oven dried sealed tube equipped with a magnetic stir bar was charged with *N*-phenylmaleimide (28.3 mg, 0.16 mmol), 4-phenyl-3*H*-furo[3,4-*c*]pyran-6(1*H*)-one (**2a**) (35 mg, 0.16 mmol) and dioxane (1.3 mL). The reaction mixture was then stirred at 150 °C. After 72 h, the reaction mixture was concentrated in vacuo. Purification of the crude product by flash chromatography on silica gel (1:10 to 2:1 EtOH: Hexane) afforded the cascade product **5** as a white solid (39.6 mg, 47 % yield). Light yellow solid. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.49 – 7.31 (m, 10H), 7.11 – 7.04 (m, 5H), 5.08 (t, J = 5.2 Hz, 2H), 4.72 (t, J = 5.2 Hz, 2H), 4.18 (t, J = 3.0 Hz, 1H), 3.62 (d, J = 8.0 Hz, 2H), 3.34 (dd, J = 8.0, 3.0 Hz, 2H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 175.0 (C), 173.5 (C), 138.9 (C), 137.5 (C), 137.1 (C), 131.3 (C), 129.5 (CH), 129.2 (CH), 128.0 (CH), 126.5 (CH), 76.4 (CH_2), 75.2 (CH_2), 51.2 (C), 49.8 (CH), 44.4 (CH), 34.2 (CH).

X-Ray Crystallographic Details

CCDC 1885153 (**2c**) and CCDC 1885154 (**4**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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