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da Concepción Vicente

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Transition metal promoted cycloadditions of strained three-membered carbocycles

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Transition metal promoted cycloadditions of strained three-membered carbocycles

Eduardo da Concepción Vicente

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Transition metal promoted cycloadditions of 3C strain carbocycles

D. José Luis Mascareñas Cid

D. Fernando José López García

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A mis padres

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Abbreviations and acronyms

Ac	Acetyl/CH3CO-
ACP	Alkylidenecyclopropane
AcOH	Acetic acid
BArF	Tetrakis[3,5-bis(trifluoromethyl)phenyl] borate
BINAP	2,2'-Bis(diphenylphosphino)-1,1'-binaphthalene
BINOL	1,1'-Bi(2-naphthol)
Bn	Benzyl/C6H5CH2
Boc	*tert*-Butyloxycarbonyl
br	Broad
BrettPhos	2-(Dicyclohexylphosphino) 3,6-dimethoxy-2',4',6'-triisopropyl-1,1'-biphenyl
BzO	Benzoyl/C6H5CO-
BzOH	Benzoic acid
COD	1,5-cyclooctadiene
Cy	Cyclohexyl
d	Doublet
dd	Double doublet
ddd	Doublet of doublet of doublets
dq	Doublet of quartet
dt	Doublet of triplets
dba	dibenzylideneacetone
DAD	Diode array detector
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCE	1,2-dichloroethane
DFT	Density functional theory
DMAP	4-dimethylaminopyridine
DME	Dimethoxy ethane
DMEDA	N,N'-Dimethylethylene diamine
DMF	*N,N*-dimethyl formamide
DMSO	Dimethyl sulfoxide
dr	Diastereomeric ratio
ee	Enantiomeric excess
eq/equiv	Equivalents
er	Enantiomeric ratio
ESI	Electrospray
EWG	Electron-withdrawing group
GC-MS	Gas chromatography mass spectrometry
HOMO	Highest occupied molecular orbital
HPLC	High performance liquid chromatography
HRMS	High resolution mass spectra
IPr	1,3-Bis(2,6-diisopropylphenyl)imidazol-2-ylidene
JohnPhos	(2-Biphenyl)di-tert-butylphosphine
LRMS	Low resolution mass spectra
LUMO	Lowest unoccupied molecular orbital
m	Multiplet
MCP	Methylenecyclopropane
min	Minute/s
Ms	Methanesulfonyl/Mesyl
MS	Molecular sieves
MTBE	Methyl-*tert*-butyl ether
n.a.	Not available
NMR	Nuclear magnetic resonance
p	Pentet
PDC	Pyridinium dichromate
PG	Protecting group
phen	1,10-phenanthroline
PivO	Pivaloyl/(CH3)3CCO-
P(O-*o*-biPh)3	tris(2-phenylphenyl)phosphite
Pyr	Pyridine
q	Quartet

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qd	Quartet of doublets
rt	Room temperature
RuPhos	2-Dicyclohexylphosphino-2',6'-diisopropoxybiphenyl
s	Singlet
SOMO	Singly occupied molecular orbital
SPhos	2-Dicyclohexylphosphino-2',6'-dimethoxybiphenyl
SPINOL	2,2',3,3'-tetrahydro-1,1'-spirobi[indene]-7,7'-diol
t	Triplet
t	time
T	Temperature
ta	"Temperatura ambiente"
TBDPS	*tert*-butyldiphenylsilyl
TBS	*tert*-butyldimethylsilyl
tBuBrett Phos	2-(Di-tert-butylphosphino)-2',4',6'- triisopropyl-3,6-dimethoxy-1,1'-biphenyl
tBuXPhos	2-Di-tert-butylphosphino-2',4',6'-triisopropylbiphenyl
td	Triple doublet
TFA	Trifluoroacetic acid
Tf	Trifluoromethanesulfonyl
THF	Tetrahydrofuran
THP	Tetrahydropyran
TIPS	Triisopropylsilyl
TLC	Thin layer chromatography
TMS	Trimethylsilyl
TMM	Trimethylenemethane
Tol	Tolyl
Ts	*para*-toluenesulfonyl/Tosyl
VAPOL	2,2'-Diphenyl-(4-biphenanthrol)
VANOL	3,3'-Diphenyl-2,2'-bi-1-naphthalol
VCP	Vinylcyclopropane
VDCP	Vinylidenecyclopropane
Xantphos	4,5-Bis(diphenylphosphino)-9,9-dimethylxanthene
XPhos	2-Dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl

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Disclaimer

Throughout this thesis, when referring to cycloadditions we use the Huisgen notation, using parenthesis, where the numbers refer to the atoms involved in the forming ring (for instance in (4+3), (4+2), (2+2) cycloadditions) to distinguish from the Woodward-Hoffman notation, using brackets, where the numbers refer to the electrons involved in bonding changes.[1] However, in some specific examples we use the brackets notation that is also acceptable.

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[1] (a) Huisgen, R.; *Angew. Chem. Int. Ed.* **1968**, *7*, 321. (b) Limanto, J.; Khuong, K. S.; Houk, K. N.; Snapper, M. L.; *J. Am. Chem. Soc.* **2003**, *125*, 16310.

Introduction

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1. Modern synthetic organic chemistry

Chemistry can in some way be considered as a scientific bridge that connects the macrocosm with the microcosm, our perceived visible world with the invisible world of atoms and molecules. Its power is primarily derived from the ability to understand the structure and properties of molecules, as well as from the possibility of building them using synthetic chemistry.[2]

One of the most vital and valued subdisciplines of chemistry is organic synthesis, a branch of science aimed to construct organic molecules, natural or designed. The field of synthesis emerged in the late 18^{ths} and early 19^{ths}, with the discovery of practical methods to synthetize a variety of natural occurring substances like urea, quinine, morphine or strychnine. In more recent decades, the field or organic synthesis has witnessed a great progress, tackling more and more difficult synthetic challenges, like the antitumoral products *Taxol*[3] or *Englerin A,*[4] complex polycyclic products containing numerous stereocenters (**Figure 1**).

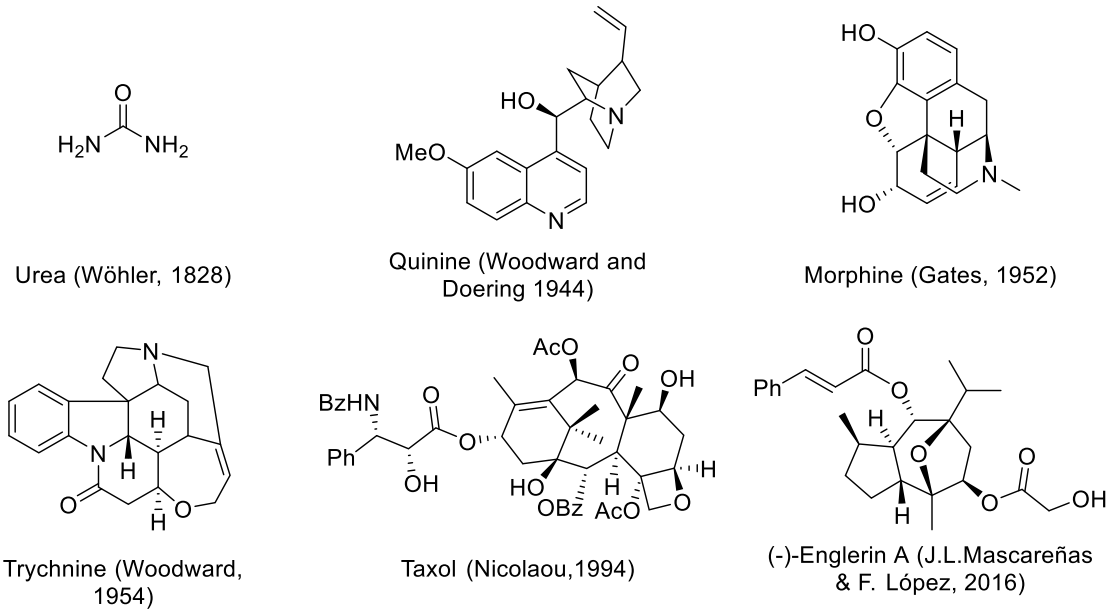


***Figure 1**. Examples of natural products whose total synthesis were performed in a laboratory.*

Along the last decades, the goal of synthesis has changed from just making the target molecule at any cost, to the development of sustainable and practical synthetic processes. To comply with this goal, modern organic synthesis requires processes that are efficient, economic and green, minimizing the production of waste and by-products

[2] Nicolaou, K. C. *Angew. Chem. Int. Ed*, **2013**, *52*, 131–146.
[3] Nicolaou, K. C., Yang, Z., Liu, J. J., Ueno, H., Nantermet, P. G., Guy, R. K., Claiborne, C. F., Renaud, J., Couladouros, E. A., Paulvannan, K.; Sorensen, E. J. *Nature* **1994***, 367,* 630–634.
[4] Nelson, R.; Gulías, M.; Mascareñas. J. L.; López. F. *Angew. Chem. Int. Ed.* **2016**, *55*, 14359-14363.

as well as avoiding the use of toxic or hazardous chemicals.[5] Towards this end, it is necessary to invent and develop atom-, step-, redox- and pot- economical reactions that allow a target-relevant increase in complexity from readily available precursors.[6]

2. Catalysis

Catalysis appears as one of the 12 key factors of green chemistry.[5] By definition, a catalyst is *"a substance that changes the rate of a reaction without being consumed in the process"* (**Figure 2**). A catalyst does not affect the rate of the reaction varying the ΔH or ΔS of the process, but instead, it diminishes its activation energy barrier.

According to this definition, a catalytic process presents two main advantages over the classical reactions. On one hand, the capacity of the catalyst to be regenerated allows to reduce the waste and cost of the process. On another hand, the change in the reaction rate by diminishing the energetic barrier of the process, not only accelerates the reaction but it might also make feasible chemical transformations that otherwise would not be possible.

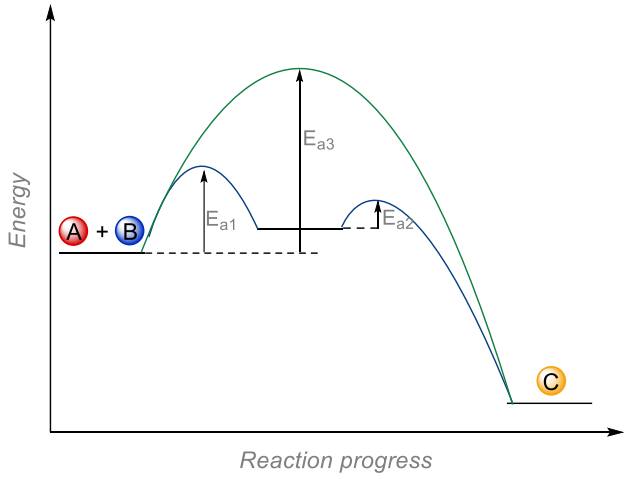


***Figure 2**. Example of a rection energy profile without catalyst (green) and in the presence of a catalyst (blue).*

From a general point of view, catalysts can be classified as heterogeneous, if they are not in the same phase as the substrates, or homogeneous, if both the catalyst and the substrate are in the same phase. Moreover, catalysis can also be divided in subcategories depending on the nature of the catalyst: biocatalysis,[7] when the catalytic

[5] (a) Anastas, P. T.; Warner, J. C. *Green chemistry: Theory and practice.* Ed. Oxford university press, **1998**. (b) Erythropel, H. C.; Zimmerman, J. B.; De Winter, T. M.; Petitjean, L.; Melnikov, F.; Lam, C. H.; Lounsbury, A. W.; Mellor, K. E.; Janković, N. Z.; Tu, Q.; Pincus, L. N.; Falinski, M. M.; Shi, W.; Coish, P.; Plata, D. L.; Anastasas, P. T. *Green Chem.* **2018**, *20*, 1929-1961.

[6] Wender, A.; Miller B. L. *Nature* **2009**, *460*, 197-201.

[7] Drauz, K.; Waldmann. H. *Enzyme Catalysis in Organic Synthesis*. Wiley-VCH, Weinheim, **2002**.

activity is driven by enzymes; organocatalysis,[8] when an organic molecule is responsible for the rate acceleration; and, organometallic catalysis, when the catalyst consists of a metal complex, usually a transition metal, with coordinated organic ligands.[9]

3. Organometallic catalysis

3.1. Transition metals and main catalytic transformations

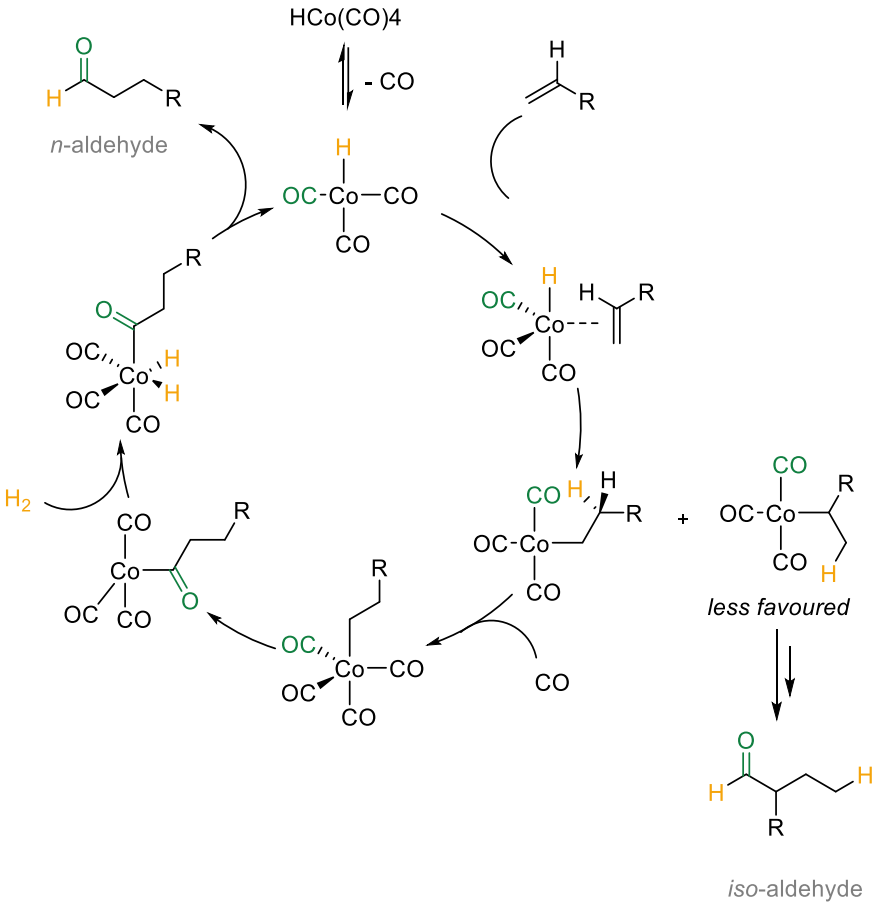
Organometallic catalysis has mainly relied on the use of transition metals. The particular reactivity of these species derives from the availability of *d* orbitals at the metal that can interact and activate a wide variety of functional groups of organic compounds. In addition, this kind of orbitals allows the metals to easily cycle among different oxidation states.

It is worth to mention that the reactivity of transition metal complexes as organometallic catalysts is not exclusively based on the properties of the metal. The presence of ancillary ligands coordinated to the metal has a definitive influence on the chemical behaviour of the complex. Therefore, by tuning the ligand sterics, electronics and coordination ability, the performance of the metal catalyst can be modulated.

An illustrative example of the potential of the organometallic chemistry is the "oxo synthesis", today named hydroformylation reaction, discovered in 1938 by Otto Roelen at Ruhrchemie (now Oxea). This reaction allows the synthesis of aldehydes from easily available CO and H_2 in conjunction with terminal olefins. The wide use of aldehydes as synthetic intermediates, as well as their relevance in the fragrance and drug industry, made this process one of the premier achievements of the industrial synthetic chemistry in the 20th century. Even more, this reaction is still the most general procedure in industry for the synthesis of aldehydes.

Mechanistically, the reaction starts from the hydridic species $HCo(CO)_4$ which, after the dissociation of a CO ligand, can undergo a reversible olefin coordination. A subsequent migratory insertion determines the formation of either linear or branched aldehydes (*n*- or *iso*-aldehyde), depending on the regioselectivity of the carbonyl insertion. The catalytic cycle continues with a CO insertion that leads to acylcobalt species. A subsequent oxidative addition of molecular hydrogen and a final reductive C-H elimination, delivers the aldehyde (**Scheme 1**).[10]

[8] Reetz, M.T.; List, B.; Jaroch, S.; Weinmann. H. *Organocatalysis*. Springer-Verlag, Berlin, **2008**.
[9] Crabtree, R. H. *The Organometallic Chemistry of Transition Metals*. Wiley-Interscience, New Jersey, **2005**.
[10] Hartwig, J.F. (2010). Organotransition Metal Chemistry – From Bonding to Catalysis, 752ff. Sausalito: University Science Press.

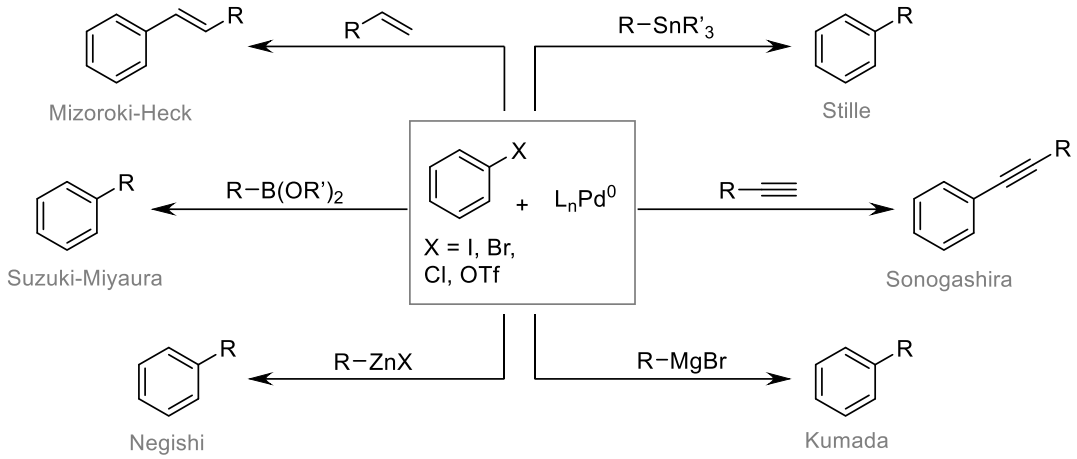


Scheme 1. *Mechanism of the classical cobalt-catalysed hydroformylation reaction of terminal olefins.*

Among the many types of reactions promoted by organometallic catalysts, those that forge new C-C bonds are particularly relevant in synthetic chemistry. The relevance and impact of this area has been widely recognized by the scientific community. For instance, only in the last two decades, the topic of metal-catalysed C-C bond forming reactions was awarded twice with the Nobel prize.[11]

In this sense, the palladium catalysed cross-couplings initially developed by Richard Heck, Ei-ichi Negishi and Akira Suzuki in the early 1970s, revolutionized modern synthetic chemistry. These methodologies enable the formation of new C-C bonds in a very efficient manner, from easily available precursors and with excellent chemoselectivities. The different types of cross-couplings depend on the nature of the nucleophile that is used. Thus, a Suzuki-Miyaura cross-coupling employs a boronic acid or analogue boron reagent, the Stille reaction relies on stannanes and Negishi cross-couplings employ organozinc reagents. Moreover, several other types of cross-couplings have been also developed along these last decades (**Scheme 2**).

[11] (a) https://www.nobelprize.org/prizes/chemistry/2005/summary/,
(b) https://www.nobelprize.org/nobel_prizes/chemistry/laureates/2010/.



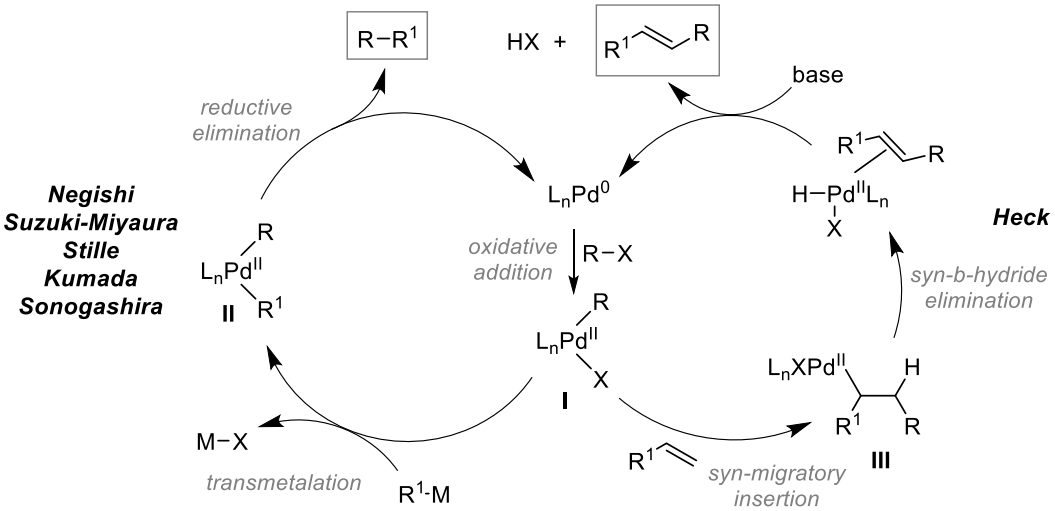
***Scheme 2**. Principal Pd-catalysed cross couplings C-C bond formation reactions (exemplified for aryl halides or pseudohalides).*

Mechanistically, palladium-catalysed cross-couplings generally begin with an oxidative addition of an organic halide or pseudohalide to a Pd^0 species. In most of these processes, this step is followed by a transmetalation with an organometallic reagent (zinc, boron, tin…etc.), to generate a new intermediate **II**. Finally, a reductive elimination leads to the new C-C bond, delivering the corresponding product and regenerating the L_nPd^0 species. On the other hand, in the Heck coupling, after the oxidative addition, a *syn*-migratory insertion of an alkene takes place, generating the organopalladium species **III**. The catalytic cycle is then completed with a β-hydride elimination process and a subsequent reductive elimination (**Scheme 3**).[12]

Cross-coupling reactions are not limited to Pd catalysts. In particular, non-precious and cheaper metal catalysts based on Fe, Co, Cu, or Ni have been progressively developed over the last three decades. These 3d metal catalysts tend to exhibit complementary reactivity to Pd complexes, and, in some cases, they allow the use of more challenging partners. For instance, while alkyl halides often suffer from β-elimination side reactions when using Pd catalysts, they are very well tolerated by cobalt or nickel counterparts, so that numerous examples of cross couplings between alkyl halides and different organometallic reagents have been developed employing this earth abundant metals.[13]

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[12] Johansson Seechurn, C.C.C.; Kitching, M. O.; Colacot, T. J.; Snieckus, V. *Angew. Chem. Int. Ed.* **2012**, *51*, 5062-5085.
[13] Guérinot, A; Cossy, J. *Acc. Chem. Res.* **2020**, *53*, *7*, 1351–1363.

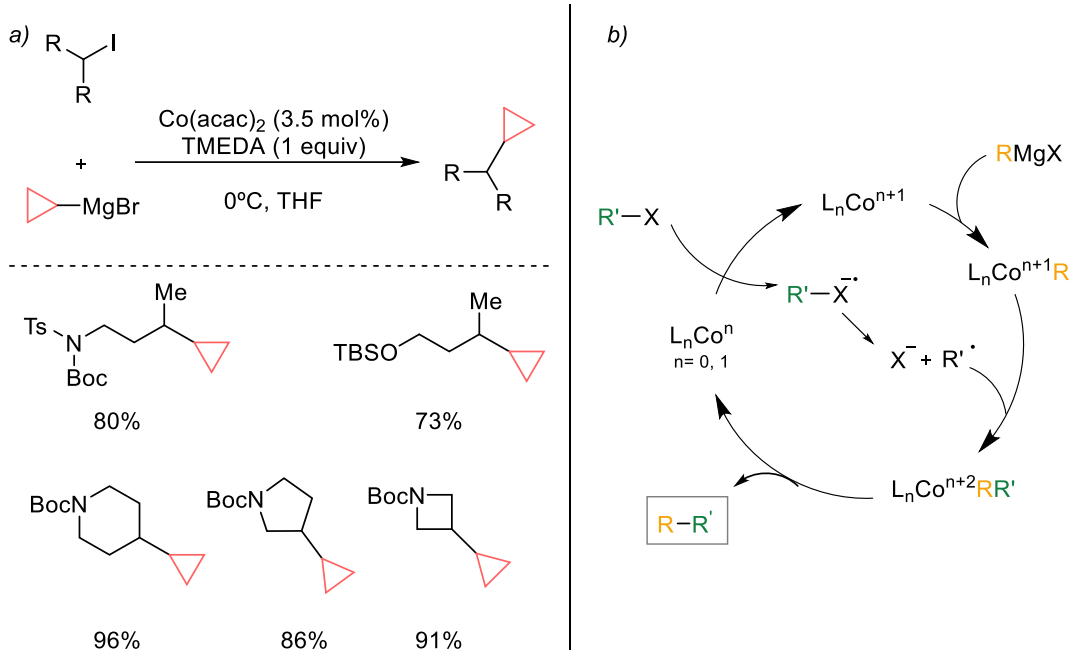


***Scheme 3**. General mechanism for Pd-catalysed cross couplings.*

For example, cobalt can mediate a cross-coupling reaction of alkyl iodides with cyclopropyl Grignard reagents allowing the synthesis of a variety of monosubstituted cyclopropanes (**Scheme 4a**).[14] The key success of cobalt catalysts with respect to Pd counterparts in this cross-coupling reactions arises from a different reaction mechanism (**Scheme 4b**). While palladium catalysts initiate the cycle through an oxidative addition, cobalt complexes can undergo one electron oxidation via single electron transfer to the alkyl halide (**Scheme 4b**, LnCo(n+1)). Then, a transmetalation of the Grignard reagent followed by an alkyl radical recombination affords the heteroleptic complex [LnCo(n+2)RR'], which, upon a reductive elimination delivers the coupling product and regenerates the catalyst.

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[14] Andersen, C.; Ferey, V.; Daumas, M.; Bernardelli, P.; Guérinot, A.; Cossy. J. *Org. Lett.* **2019**, *21,* 2285-2289.



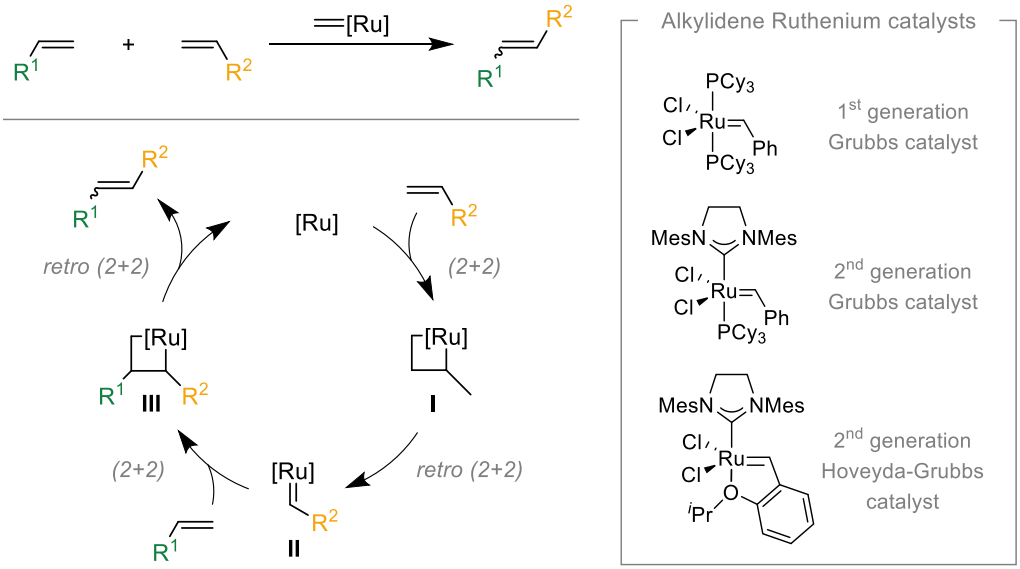
***Scheme 4**. a) Cobalt-catalysed cross-coupling reaction of cyclopropyl magnesium bromide and alkyl iodides. b) General mechanism for these cobalt-catalysed cross-couplings.*

Another highly valuable strategy for the construction of C-C bonds is based on olefin metathesis. While Pd-catalysed cross-couplings constitute a well-known method for the construction of simple C-C bonds, the olefin metathesis reaction allows the straightforward formation of multiple C-C bonds. The metathesis reaction can be understood as the redistribution of a pair of alkenes (or, to a lesser extent, alkynes and enynes) into a new isomeric pair (**Scheme 5**). Among the different types, ring-closing and ring-opening metathesis, as well as alkene cross-metathesis, experienced an exponential growth during the last decades. The evolution of this reaction until becoming one of the most important synthetic methods to date, is directly related with the development of new catalysts (especially alkylidene Ruthenium complexes), with enhanced selectivity and functional group tolerance.[15] Based on the impact of these catalysts and the generality of this method in organic synthesis, the pioneers of this field, Grubbs, Schrock and Chovin received the Nobel Prize in Chemistry in 2005.[11a]

Regarding the mechanism of olefin cross-metathesis, the reaction is initiated by a formal (2+2) cycloaddition between one of the olefins and the ruthenium-carbene to afford a metalacyclobutane **I**, which undergoes a retro (2+2) cycloaddition to yield a new alkylidene intermediate of type **II**. Finally, a new (2+2)/retro (2+2) sequence between

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

this intermediate **II** and the second olefin yields the final product through the key metalacyclobutane species of type **III (Scheme 5)**.



***Scheme 5**. General reaction scheme, mechanism, and principal catalysts of the olefin metathesis.*

3.2. Transition metal-catalysed cycloadditions

Many biologically and pharmaceutically relevant compounds feature complex carbon and/or heterocyclic scaffolds as main core of their structures. Therefore, the development of efficient catalytic methodologies that allow the assembly of these (poly)cyclic scaffolds in a selective manner from easily available feedstocks is a major goal in organic synthesis.

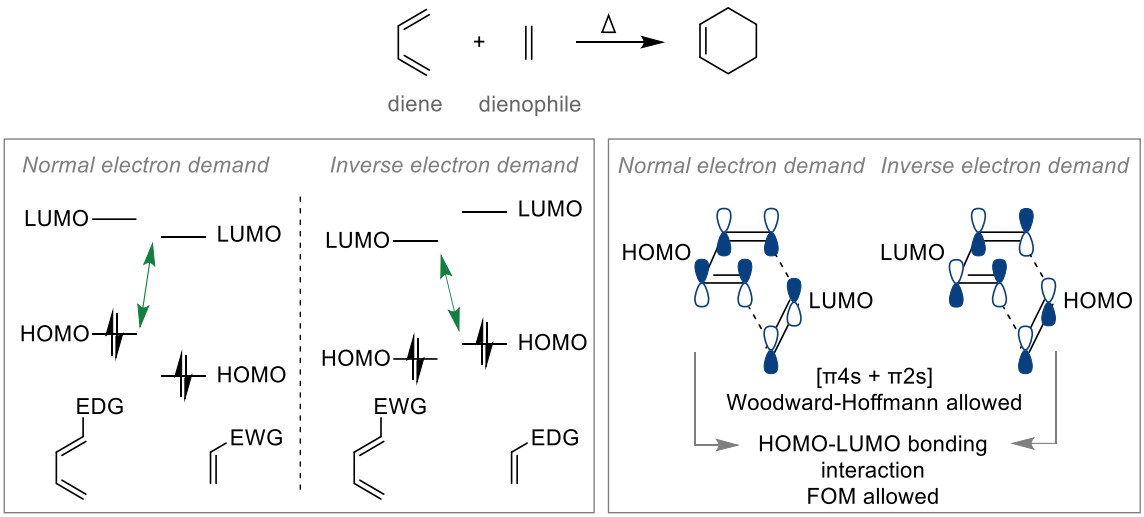
In this context, cycloaddition reactions constitute an excellent strategy to build such (hetero)cyclic systems, as they enable the formation of two new bonds and at least one new cycle from two or more simple acyclic precursors in just one step.

One of the most illustrative examples of a cycloaddition reaction is the Diels-Alder reaction. This (4+2) annulation involves the coupling of a diene (4π component) and a dienophile (2π component) in a concerted manner with the consequent generation of a six-membered ring, with up to four new stereogenic centres (**Scheme 5**). Like many other classical cycloadditions, the Diels-Alder reaction can be explained using the Woodward-Hoffmann rules[16] or the frontier molecular orbital theory of Fukui.[17] In this specific case, the HOMO-LUMO interaction is highly influenced by the substituents of the reaction partners. Thus, we can differentiate between de *normal electron demand*

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[16] Woodward, R. B.; Hoffmann, R. *Angew. Chem. Int. Ed.* **1969**, *8*, 781-853.
[17] Inagaki, S.; Fujimoto, H.; Fukui, K. *J. Am. Chem. Soc.* **1976**, *98*, 4693-4701.

Diels-Alder, when the HOMO of the diene and the LUMO of the dienophile are involved, and *inverse electron demand variants,* when the HOMO of the dienophile and the LUMO of the diene are implicated (**Scheme 6**).[18]



Scheme 6. *The Diels-Alder reaction and the rules that govern the annulation.*

While cycloadditions permitted by the Woodward-Hoffmann rules, like the Diels-Alder reaction, take place spontaneously or by heating the reaction media, those that are forbidden, usually called "formal cycloadditions", need photochemical conditions, radical initiators, or the action of other reagents to happen.

In this context, transition metals appear as key reagents to develop new formal cycloadditions. The use of metal catalysts not only can promote cycloadditions allowed by the Woodward-Hoffmann rules, but also open the possibility of discovering new reaction pathways that otherwise were not viable. The ability of the metal catalysts to drive new type of annulations is usually a consequence of the coordination of the metal to an unsaturated partner (usually an alkene or alkyne), which polarizes the π cloud and activates the rearrangement of these electrons.[19]

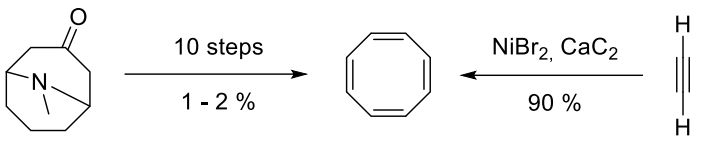
A representative example of the extraordinary power of transition metal catalysts is the synthesis of cyclooctatetraene (COT). Reppe reported a nickel catalysed transformation that delivers COT from acetylene in just one step in 90% yield through a tetramerization (2+2+2+2) cycloaddition (**Scheme 7**).[20] Comparatively, classical methods for the

[18] Fringuelli, F.; Taticchi. A. *The Diels-Alder Reaction: Selected Practical Methods*. John Wiley and Sons, Chichester, **2002**. b) Nikolau, K. C.; Snyder, S. A.; Montagnon, T.; Vassilikogiannakis, G. *Angew. Chem. Int. Ed.* **2002**, *41*, 1668-1698. c) Takao, K.-I.; Munakata, R.; Tadano, K. *Chem. Rev.* **2005**, *105*, 4779-4807.

[19] Lautens, M.; Klute, W.; Tam, W. *Chem. Rev.* **1996**, *96*, 49-92.

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

synthesis of COT, like the one developed by Arthur C. Cope in 1947, required 10 steps and gave very low overall yields.[21]

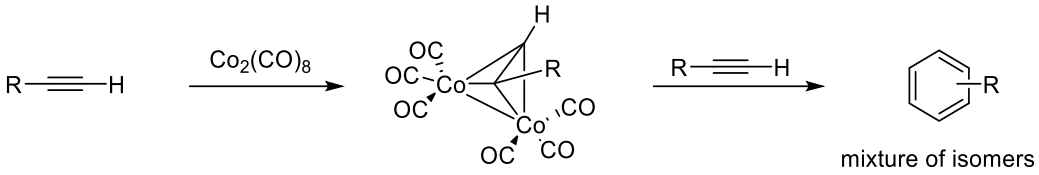


Scheme 7. *Classic and Ni-catalysed synthesis of cyclooctatetraene (COT).*

Another example of the utility of an organometallic catalyst for promoting annulation reactions can be inferred from (2+2+2) cycloadditions. As illustrated by the seminal report by Berthelot 150 years ago regarding the cyclotrimerization of acetylene,[22] in principle, thermal (2+2+2) cycloadditions are symmetry allowed by the Woodward-Hoffmann rule.[16] However, the entropic barriers associated with bringing three reaction partners together with enthalpic costs make the process rather difficult[23] and, therefore, literature examples of purely thermal (2+2+2) cycloadditions are rare and required harsh conditions.[24] However, the use of a transition metal catalyst enables the entropic constraints to be circumvented by coordination of the reaction partners to the metal complex, which also activates the π electrons.

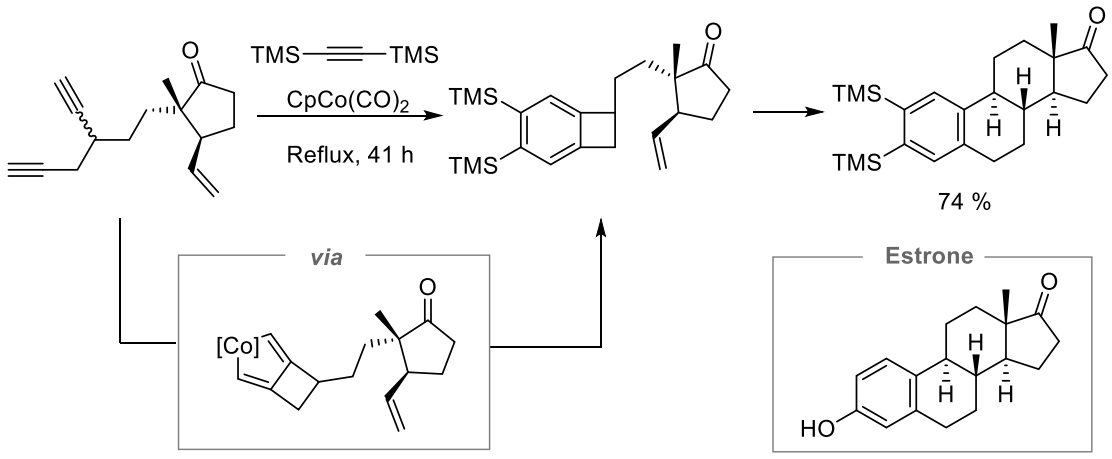
In this regard, the metal-catalysed cyclotrimerization of acetylenes to benzene derivatives, a formal (2+2+2) cycloaddition, is a well-known process that can be promoted by many transition metal complexes.[25] For example, in 1960 Hübel *et al* reported the trimerization of acetylene derivatives mediated by $Co_2(CO)_8$.[26] Although this stoichiometric reaction needed long reaction times and high temperatures, and the products were frequently obtained as mixture of isomers, this pioneering work opened the landscape of the (2+2+2) alkyne cycloadditions catalysed by cobalt (**Scheme 8**).

[21] Cope, A. C., Overberger, C. G. *Journal of the American Chemical Society*, **1947**, *69*, 976.
[22] Berthelot, M. *Liebigs Ann. Chem.* **1866**, *139*, 272-282.
[23] Houk, K. N.; Gandour, R. W.; Strozier, R. W.; Rondan, N. G.; Paquette, L. A *J. Am. Chem. Soc*. **1979**, *101*, 6797–6802.
[24] Barkovich, A. J.; Vollhardt, K. P. C*. J. Am. Chem. Soc.* **1976**, *98*, 2667-2668.
[25] For Co: (a) Vollhardt, K. P. C. *Angew Chem. Int. Ed. Engl.* **1984**, *23*, 53. For Ni: (b) Jolly, P. W. In Comprehensive Organometallic Chemistry; Wilkinson, G., Stone, F. G. A., Abel, E. W., Eds.; Pergamon: New York, 1982; Vol. 8, p 649. For Rh: (c) Grigg, R.; Scott, R.; Stevenson, P. *Tetrahedron Lett*. **1982**, *23*, 2691. For Ta: (d) R.; Bruck, M. A.; Wigley, D. E. *J. Am. Chem. Soc.* **1990**, *112*, 2814. For Pd: (e) Maitlis, P. M. *Acc. Chem. Res*. **1976**, *9*, 93. For a mechanistic review: (f) Roglans, A.; Pla-Quintana, A.; Solà. M. *Chem. Rev.* **2021**, *121*, 3, 1894–1979.
[26] Hübel, W.; Hoogzand, C. *Chem. Ber*. **1960**, *93*, 103–115.



***Scheme 8**. Cyclotrimerization of acetylene derivates by cobalt catalysis.*

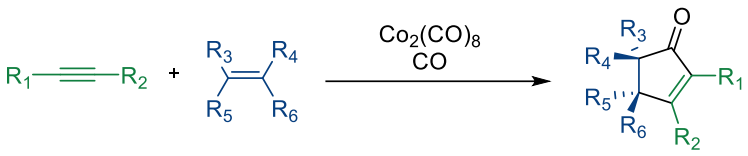
In the 1970's, the discovery of new catalysts like the $CpCo(CO)_2$ by Vollhardt *et al.* improved the efficiency and selectivity of this type of transformations.[27] The importance and utility of the alkyne (2+2+2) cycloadditions can be illustrated in the synthesis of estrone by Vollhardt.[28] Here, a one pot diyne-alkyne (2+2+2) cycloaddition followed by a cyclobutene ring opening and a Diels-Alder cycloaddition, affords the core scaffold of estrone in only one step (**Scheme 9**).



***Scheme 9.** (2+2+2) cycloaddition of a diyne and alkyne catalysed by $CpCo(CO)_2$ in the total synthesis of estrone.*

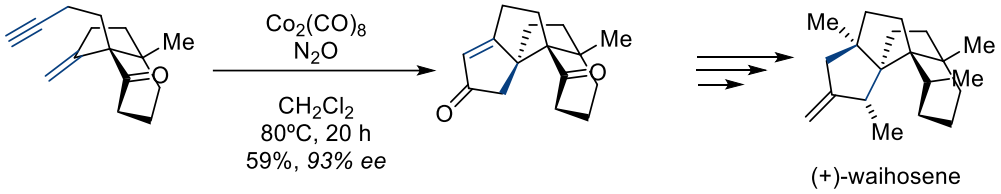
Another transformation that illustrates the impact of organometallic catalysis in organic synthesis is the Pauson-Khand reaction (PKR). This transformation can be described as a cobalt mediated (2+2+1) cycloaddition between an alkyne, an alkene and carbon monoxide to afford α,β-cyclopentanones (**Scheme 10**). Although initially reported in the late 70*s* by P.L. Pauson and I.U. Khand as a stoichiometric cobalt reaction,[29] Livinghouse and Kraft demonstrated that it can be carried out in a catalytic manner under mild pressure and temperature.[30]

[27] Vollhardt, K. P. C. *Acc. Chem. Res*. **1977**, 10, 1–8.
[28] Funk, R. L.; Vollhardt, K. P. C *J. Am. Chem. Soc.* **1980**, *102*, 5253–5261.
[29] Pauson, P.L.; I. U. Khand, I. U. *Ann. N.Y. Acad. Sci.* **1977**, *295*, 2-14.
[30] a) Pagenkopf, B. L.; Livinghouse, T. J. *Am. Chem. Soc.,* **1996**, *118*, 2285-2286.; b) Belanger, D. B.; Livinghouse, T. *Tetrahedron Lett*., **1998**, *39*, 7641-7644.



***Scheme 10**. Cobalt-promoted Pauson-Khand reaction.*

Despite the high importance of the PKR, the intermolecular version of this transformation presents some limitations. For example, when using non-symmetric alkenes, the corresponding cyclopentanones are usually obtained as mixtures of regio- and/or stereoisomers. However, the intramolecular PKR has proven very efficient, especially for the construction of 5,5-fused bicyclic systems. Accordingly, this cycloaddition has been used as the key step of many total synthesis along the last 40 years.[31] For example, a PKR reaction was the critical step in the total synthesis (+)-waihosene, for the construction of its bicyclic core (**Scheme 11**).[32]



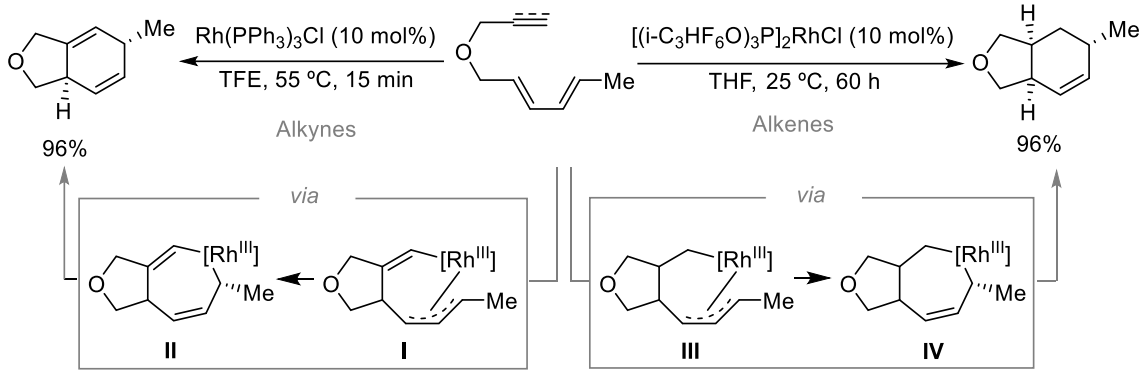
***Scheme 11.** PKR in the total synthesis of (+)-waihosene.*

As illustrated before, the initial reports of organometallic catalytic cycloadditions during the beginning of the 20th century were focused on the use of earth abundant metals like Ni or Co. However, 3d metals are known to undergo facile one electron redox changes, often with changes in their spin state,[33] uncontrolled reactions with dioxygen[34] or facile ligand redistribution. These issues induced the chemistry community to progressively focus more on precious metal homogeneous catalysts, particularly on those based on Rh, Pd or Ir, which seemed to have more predictable mechanistic pathways.

A good example of the behaviour of precious transition metals in cycloadditions is described in the **Scheme 12.**[35] Although the (4+2) annulation of a 1,6-diene-alkyne is allowed by the Woodward-Hoffmann rules, these reactions required high temperatures and afford the cycloadducts in low yields and selectivities. However, the use of a Rh(I) catalyst opens a new reaction pathway that delivers the cycloadducts under milder conditions, with shorter reaction times and higher yields. Mechanistically, the reaction

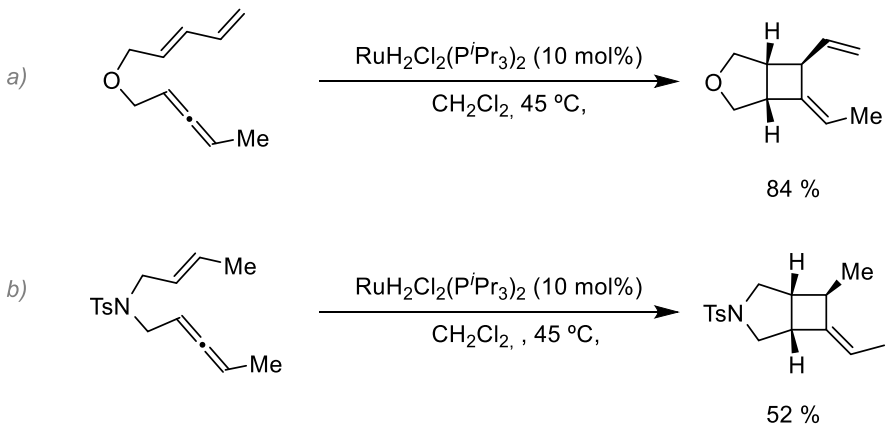
[31] Yang, Z. *Acc. Chem. Res*. **2021**, *54*, 556−568.
[32] Qu, Y.-Z.; Wang, Z.-Y.; Zhang, Z. C.; Zhang, W.-D.; Huang, J.; Yang, Z. *J. Am. Chem. Soc. 2020*, **142**, 6511−6515.
[33] a) Bedford, R.B. *Acc. Chem. Res*. **2015**, *48*, 5, 1485-1493. b) Holland, P.L. *Acc. Chem. Res.* **2015**, *48*, 6, 1696-1702
[34] McCann, S. D.; Stahl, S.S. *Acc. Chem. Res.* **2015**, *48*, 6, 1756-1766
[35] R. S. Jolly, G. Luedtke, D. Sheehan, T. Livinghouse, *J. Am. Chem. Soc.* **1990**, *112*, 4965-4966.

is initiated through an oxidative cyclization between the diene and the alkene or alkyne leading to intermediates **I** or **III**. These intermediates evolve to species **II** or **IV** and, finally, after a reductive elimination, to the corresponding cyclic products.



***Scheme 12**. Rh-catalysed intramolecular (4+2) cycloadditions between alkynes or alkenes and 1,3-dienes.*

In the same context, precious transitions metals can unlock cycloaddition pathways that are forbidden according to the Woodward-Hoffmann rules. For example, our group reported the intramolecular (2+2) cycloaddition between allenes, and dienes or alkenes promoted by a Ru catalyst (**Scheme 13**).[36] Thus, the catalyst provides a new diastereoselective way of making fused-cyclobutanes from non-activated systems, expanding the scope of classical cycloaddition processes.



***Scheme 13**. a) Ruthenium catalysed intramolecular (2+2) cycloaddition between a diene and allene. b) Ruthenium catalysed Intramolecular (2+2) cycloaddition between an alkene and allene*

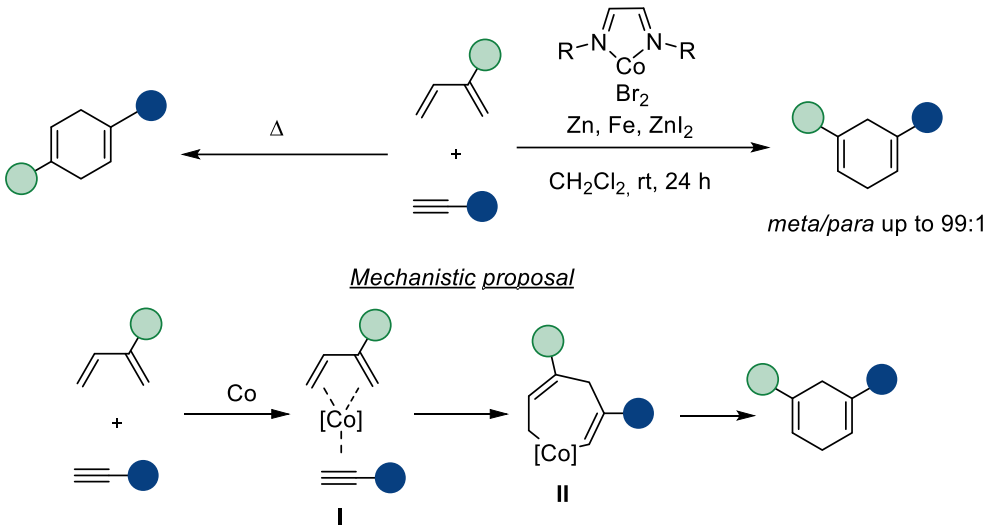
Despite organometallic cycloadditions have been mostly developed during the last 50 years using precious transition metal catalysts, in recent years there has been a renewed interest for the use of 3d transition metals, mainly because their abundancy in the earth crust and their lower cost compared to elements like Pd, Rh or Pt. Moreover, their

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[36] Gulias, M.; Collado, A.; Trillo, B.; López, F.; Oñate, E.; Esteruelas, M.A.; Mascareñas, J.L. *J. Am. Chem. Soc*. **2011**, *133*, 20, 7660–7663.

implementation in large scale industrial processes seems more economically accessible. [e.g. $(Pd(OAc)_2$ is approximately \$75/gram, while $Ni(OAc)_2$ is approximately \$10/g)]. In addition, 3d row transition metals often have less health and environmental impact than 4d and 5d metals. Nevertheless, the most exciting issue that has fuelled the use of this type of metals in organometallic transformations is the opportunity for discovering previously unknown mechanistic patterns or reactivity principles.[37]

An illustrative example of the alternatives offered by first row transitions metals is the cobalt catalysed Diels-Alder of isoprene derivatives and alkynes.[38] While the thermally driven Diels-Alder reaction between these partners mainly delivers *ortho*- or *para*-substituted cycloadducts, the use of an *in situ* generated low valent diimine cobalt catalysts provides *meta*- substituted adducts with high regioselectivity (**Scheme 14**). Although in the initial work no comments were made about the reaction mechanism, subsequent DFT calculations contributed to its elucidation.[39] Accordingly, the reaction was proposed to be initiated with the formation of complex **I,** followed by a stepwise oxidative cyclization and alkyne migratory insertion towards intermediate **II**. Later on, an eventual reductive elimination delivers the 1,3-substituted cyclohexadiene.

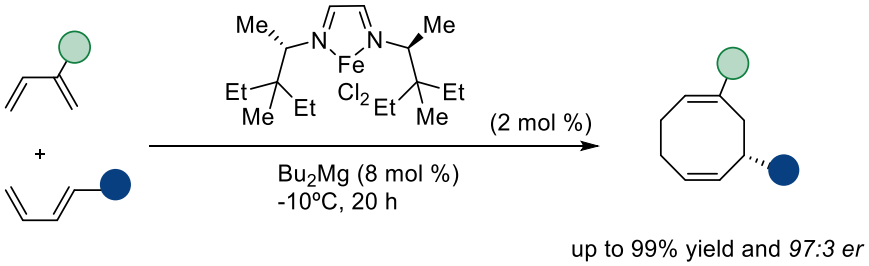


***Scheme 14**. Diimine cobalt complexes catalysed meta-directing Diels-Alder reaction.*

Another example of the potential of non-precious transition metals in cycloaddition reactions is depicted in **Scheme 15**.[40] Here, under iron catalysis (one of the most abundant metals in the earth crust) an otherwise forbidden (4+4) intermolecular

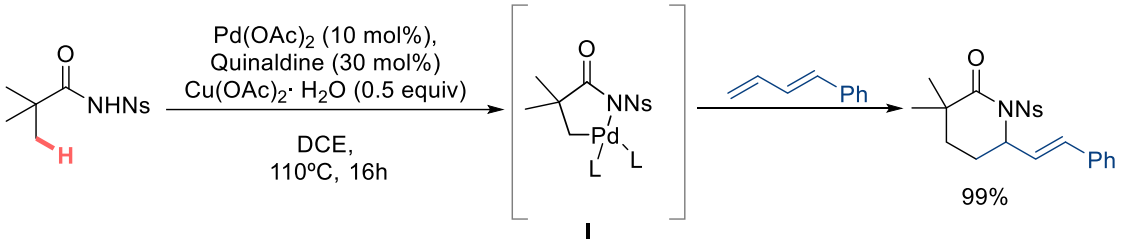
[37] Chirik, P.; Morris, R. *Acc. Chem. Res.* **2015**, *48*, 2495.
[38] Hilt, G.; Janikowski, J.; Hess, W.; *Angew. Chem. Int. Ed*. **2006**, *45*, 5204–5206.
[39] Mörschel, P.; Janikowski, J.; Hilt, G.; Frenking, G J. *Am. Chem. Soc.* **2008**, *130*, 8952–8966.
[40] Braconi, E.; Götzinger, A. C.; Cramer, N. J. *Am. Chem. Soc.* **2020**, *142*, 19819–19824.

cycloaddition between 1,3-dienes occurs, even in an enantioselective manner, delivering chiral cyclooctadiene scaffolds with up to 97:3 enantiomeric ratio (er).



Scheme 15. *Fe(II)-catalysed enantioselective (4+4) cycloaddition of 1,3-dienes.*

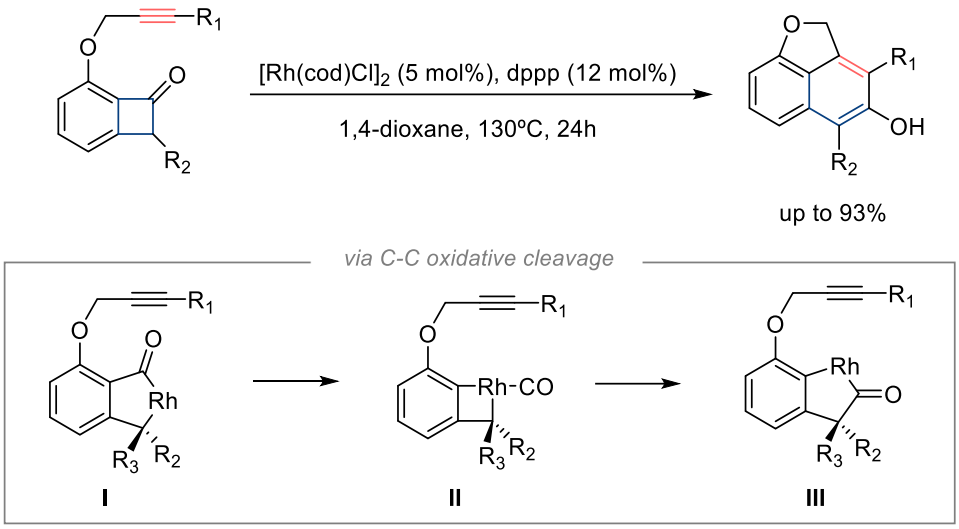
Most of the formal cycloadditions mediated by transition metal catalysts, both precious and non-precious, are based on the ability of these metals to coordinate unsaturated molecules, particularly alkynes, allenes, and alkenes, triggering oxidative cyclizations and /or oxidative additions that deliver key metallacyclic intermediates. However, the state of the art in this field has gone beyond this paradigm. For example, cycloadditions can be triggered by the initial activation of an "*inert*" C-H bond which also delivers analogous metallacyclic species. As illustrated in **Scheme 16**, an intermediate like **I** is proposed to be initially formed by a C-H activation step and then to evolve to the desired cycloadduct through a migratory insertion of the diene and a final reductive elimination.[41]



Scheme 16. *Palladium-catalysed formal (4+2) cycloaddition between alkyl amides and dienes initiated by the activation of C(sp3)–H bonds.*

On the other hand, cycloadditions can be also started by the activation of even more challenging C-C bonds. For example, the Dong group has focused their attention in recent years on the activation of C-C bonds of cyclic ketones, like cyclobutanones, particularly under Rh catalysis.[42] In this context, benzocyclobutanones bearing a pendant alkyne can be transformed into polycyclic naphtols under the presence of a Rh(I) catalyst (**Scheme 17**).[43]

[41] Cendón, B.; Font, M.; Mascareñas, J.L; Gulías, M. *ACS Catal.* **2020**, *5*, 3425-3430.
[42] Chen, P.; Billett, B. A.; Tsukamoto, T.; Dong, G. *ACS Catalysis*, **2017,** *7*, 1340-1360.
[43] Chen, P.-H.; Xu, T.; Dong, G. *Angew. Chem. Int. Ed.* **2014**, *53*, 1674–1678.

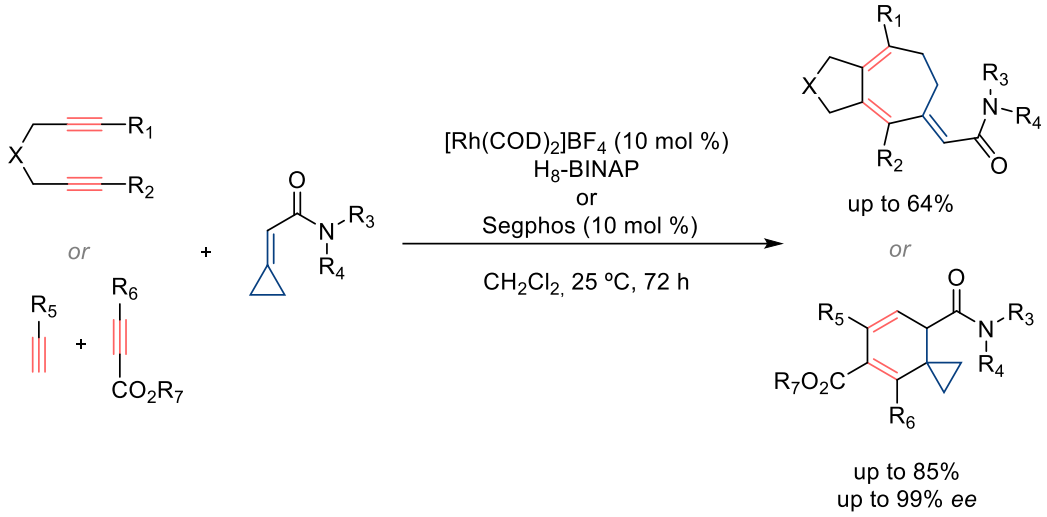


Scheme 17. *Rh (I) catalysed intramolecular cycloaddition of alkyne-tethered benzocyclobutanones.*

Besides cyclobutanones, several other cyclic strained systems have been employed to unveil new TMC cycloaddition processes. Among them, particularly relevant to this PhD thesis are methylene- and alkylidenecyclopropanes, as well as cyclopropenes. Due to its reactivity characteristics, this kind of structures have been widely employed in an array of non-asymmetric cycloadditions with a bunch of carbonade π-unsaturated partners like alkenes, allenes or dienes. Thus, the construction of interesting carbon based-polycyclic scaffolds has been demonstrated using a variety of precious transition metal catalysts based on Rh, Pd or Ru. Although important advances have been also described with nickel catalysts, overall, there is still a clear need of further exploring the potential of 3d metal series in this type of annulations.

Even though the participation in TMC cycloadditions of alkylidenecyclopropanes and cyclopropenes will be covered in the following chapters of this manuscript, an illustrative example of the potential synthetic utility of these scaffolds is depicted in **Scheme 18,** where an alkylidenecyclopropane can work as a two- or three-carbon *synthon* depending on the reaction conditions and rhodium catalyst used.

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***Scheme 18**. Rh(I) catalysed (3+2+2) or (2+2+2) cycloaddition of cyclopropylideneacetamides.*

4. Asymmetric reactions

4.1. Introduction

Molecular chirality plays a key role in science and technology; indeed, life depends on molecular chirality, since many biological functions are inherently dissymmetric. For example, biomolecules like DNA, enzymes, antibodies, or hormones appear in nature as one exclusive enantiomorphic form. Because of this asymmetry of natural biomolecules, multitude of drugs and biomedically relevant molecules that operate by interacting with biological receptors are more efficient when presented as single enantiomers.

In this context, it is obvious that the development of efficient synthetic methods to assemble these relevant products with high enantiopurity is highly relevant. However, the discovery of truly efficient enantioselective methods has been a big challenge for decades, both in academia and industry.

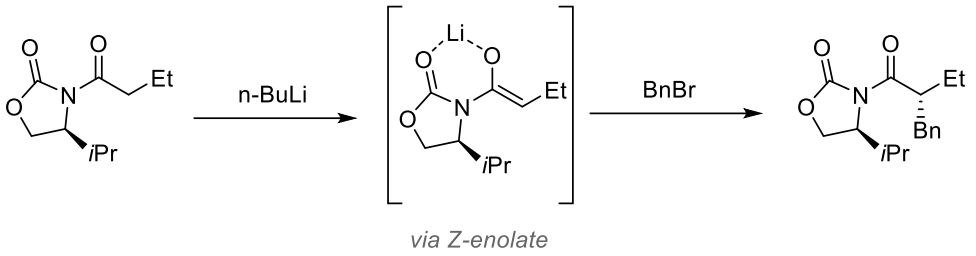
Classically, enantiomerically pure compounds were obtained by the resolution of racemates or by transforming readily accessible naturally occurring chiral enantiopure compounds, such as amino acids, tartaric and lactic acids, carbohydrates, terpenes, or alkaloids (chiral pool strategy). Although effective, this approach is very limited in terms of scope.[44]

The stereoselective conversion of prochiral precursors into chiral products is one of the most attractive approaches for the synthesis of chiral compounds as single isomers. In this regard, one of the more common strategies consisted of the use of chiral auxiliaries

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[44] Doraiswamy, L. K. Asymmetric Synthesis; Organic Synthesis Engineering, **2001**.

which can control de stereochemical outcome of a particular stoichiometric reaction. For example, David A. Evans popularized the use of chiral oxazolidinone auxiliaries in several stereoselective transformations like aldol,[45] alkylation,[46] or Diel-Alder reactions.[47]



***Scheme 19**. Stereoselective alkylation of carbonyl compounds mediated by oxazolidinones.*

Although this methodology proved to be highly effective for a variety of transformations,[48] it has important drawbacks. Chiral auxiliaries tend to be expensive and/or difficult to be made and recycled. Moreover, they need to be incorporated and removed, making this strategy poor from an atom-economical perspective.

4.2. Asymmetric catalysis

The use of asymmetric catalytic processes allows to overcome most of the limitations of the strategies based on chiral auxiliaries. Chiral catalysts, can transfer asymmetry to the reaction products without being consumed, delivering a high atom-economic transformation. However, the development of these methods has been traditionally hampered by the difficulties for designing effective chiral catalysts.

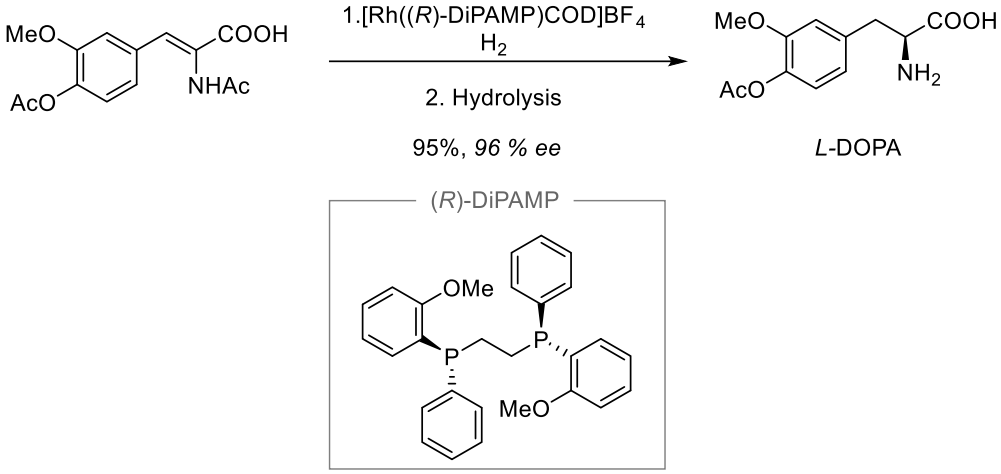
Along the years, three general branches of asymmetric catalysis have been fundamentally studied and developed. Depending on the nature of the catalyst, they can be classified as biocatalysis (i.e enzymes and chiral metalloproteins), organocatalysis (based on chiral organic molecules) and organometallic catalysts (usually metals bearing organic chiral ligands). The three areas are exciting and complement each other, and their importance is easily reflected by the recognition with the Nobel prize to several of their pioneers, in particular to W. S. Knowles, R, Noyori and K.B. Sharpless, for chiral organometallic catalysis,[49] and to B. List and D.W.C. MacMillan, for asymmetric organocatalysis.[50]

[45] Evans, D. A., Bartroli, J., Shih, T. L. *J. Am. Chem. Soc.* **1981**, *103*, 2127–2129.
[46] Evans, D. A., Ennis, M. D., Mathre, D. J. *J. Am. Chem. Soc.* **1982**, *104*, 1737–1739.
[47] Evans, D. A., Chapman, K. T., Bisaha, J. *J. Am. Chem. Soc.* **1984**, *106*, 4261–4263.
[48] Bull, S. D., Davies, S. G., Fox, D. J., Garner, A. C., & Sellers, T. G. R. *Current Trends in Organic Synthesis*, **1999**, 1–6.
[49] https://www.nobelprize.org/prizes/chemistry/2001/summary/
[50] https://www.nobelprize.org/prizes/chemistry/2021/summary/

4.3 Asymmetric organometallic catalysis

In an organometallic enantiocatalytic process, the chiral character of the catalyst is usually derived from the ancillary ligands, thus, opening a lot of different alternatives for the design of new enantioselective strategies.

An illustrative example of the magnitude and importance of an enantioselective organometallic catalytic process is the synthesis of *L*-DOPA, developed by William S. Knowles through a Rh-catalysed asymmetric hydrogenation (**Scheme 20**). While working in the Monsanto Company, Knowles developed an enantioselective hydrogenation of enamines that allows the obtention of a wide range of aminoacids on an enantioselective manner. The synthesis of *L*-DOPA stands out since it was used as one of the first treatments for Parkinson's disease.[51]



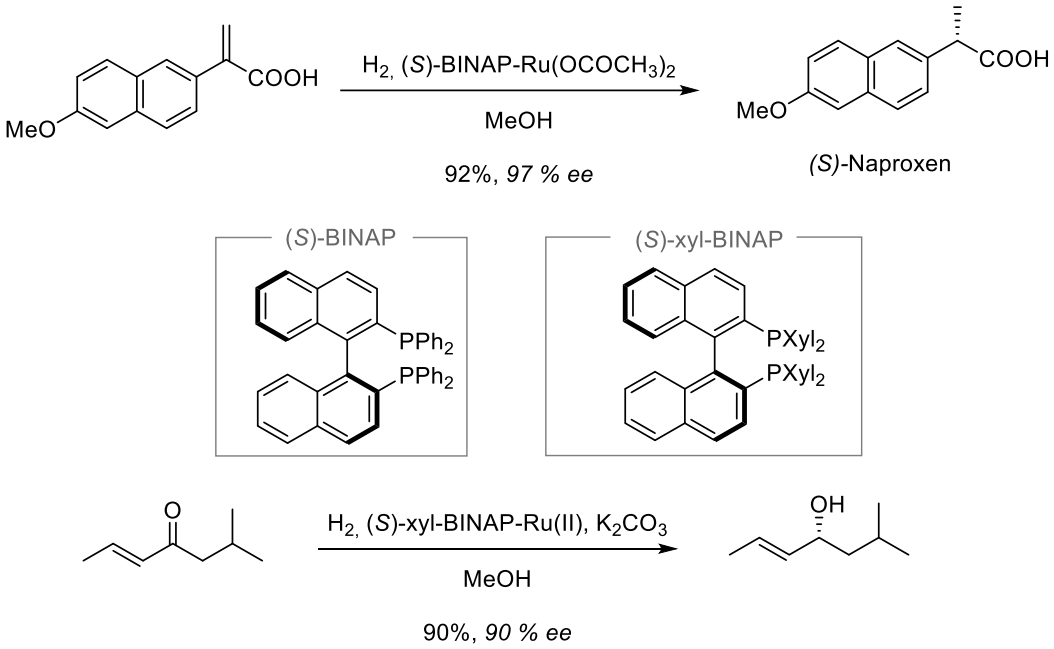
***Scheme 20**. Asymmetric synthesis of L-DOPA through a catalytic Rh hydrogenation.*

In the context of asymmetric hydrogenation processes, the contribution of R. Noyori to the field also deserves to be highlighted. This Nobel awardee,[49] pioneered the use of axial chiral ligands on asymmetric synthesis. Thus, Noyori reported the use of BINAP-ruthenium complexes for the asymmetric hydrogenation of C-C bonds and C-O double bonds.[52] The importance of this methodology and its robustness can be easily deduced from the synthesis of important pharmacology motives like the anti-inflammatory drug Naproxen, or a key intermediate in the preparation of vitamin E (**Scheme 21)**.

BINAP type of ligands have not only been used in hydrogenations reactions with ruthenium complexes, but in many other types of reactions and with many other metals. For example, BINAP-containing metal complexes can catalyse asymmetric Diels-Alder

[51] Knowles, W.S. *Acc. Chem. Res*. **1983**, 16, 106-112.
[52] a) Ohta, T.; Takaya, H.; and Noyori, R. *Inorg. Chem*. **1988**, *27*, 566. b) Ohkuma, T.; Ooka, H; Hashiguchi, S.; Ikariya, T.; Noyori, R. *J. Am. Chem. Soc.* **1995**, *117*, 2675.

reactions, nucleophilic additions, Michael-type reactions, cycloadditions or isomerizations, among many other transformations.[53] This broad applicability illustrates one of the main advantages of organometallic asymmetric catalysis with C2-symmetric chiral ligands: its generality. Unlike natural enzymes, which are usually substrate specific, man-made chiral organometallic complexes proved to be quite general for a range of mechanistically dissimilar organometallic transformations.



***Scheme 21**. Enantioselective hydrogenation catalysed by BINAP-Ru complexes.*

The common chiral ligands that enable organometallic catalysts to be general are known as *privileged chiral ligands*.[54] These ligands were initially limited to phosphines and diols but, with the years, other chiral ligands based on oxazolines, pyridines, *N*-heterocyclic carbenes or other phosphorous-bases ligands like phosphoramidites or phosphites were progressively included (**Figure 3**). Among all of them, ligands with C_2 symmetry like BINAP are especially efficient because of their symmetry and rotation restrictions, which limits the number of possible transition states, and also makes easier the study of their mechanism by computational tools.

[53] (a) Ohkuma, T. Kurono, N. BINAP. *Privileged Chiral Ligands and Catalysts*, **2011**, 1–53. (b) Teichert, J. F.; Feringa, B. L. *Angew. Chem. Int. Ed.* **2010**, *49*, 2486-2528. (c) Zhou, Q. *L Privileged Chiral Ligands and Catalysts*. WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim, **2011**.

[54] Yoon, T.P.; Jacobsen, E.N. *Science* **2003**, *299*, 1691-1693.

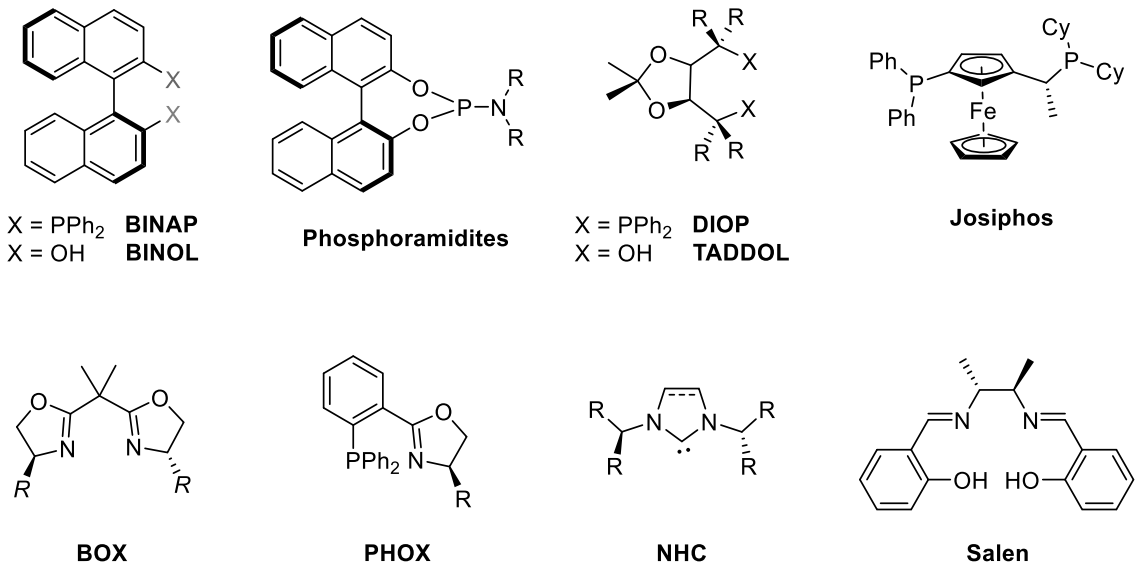
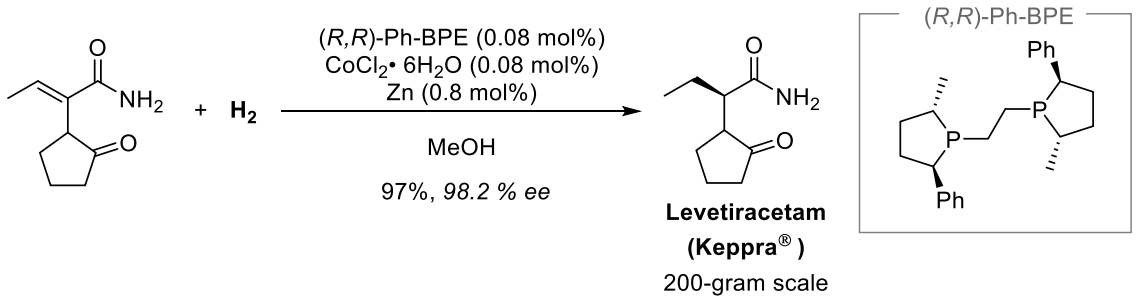


Figure 3. *Selected examples of privileged chiral ligands used in asymmetric transition-metal catalysis.*

From its early years, the use of chiral privileged ligands in asymmetric organometallic catalysis relied on precious transition metals like Rh, Pd, Ir and Ru, among others. However, more recently, a growing number of examples with alternative, non-precious metals have also been reported.

For instance, Chirik and co-workers disclosed an enantioselective hydrogenation of enamides using a chiral cobalt catalyst made from $CoCl_2$ and a commercially available bidentate chiral ligand, Ph-BPE (**Scheme 22**).[55] Here, the ability of Co to undergo single electron processes allows to overcome deactivation pathways usually associated with the use of precious transition metals. Moreover, using this transformation, a 200 g scale synthesis of Levetiracetam, a drug used for the treatment of epilepsy, was accomplished.



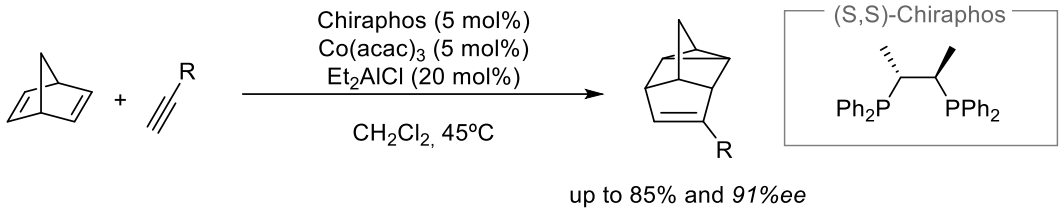
Scheme 22. *Enantioselective hydrogenation of enamides catalysed by a low valent cobalt catalyst.*

The merge of abundant metals and privilege chiral ligands is not limited to hydrogenation reactions, but also apply to synthetically relevant C–C bond forming

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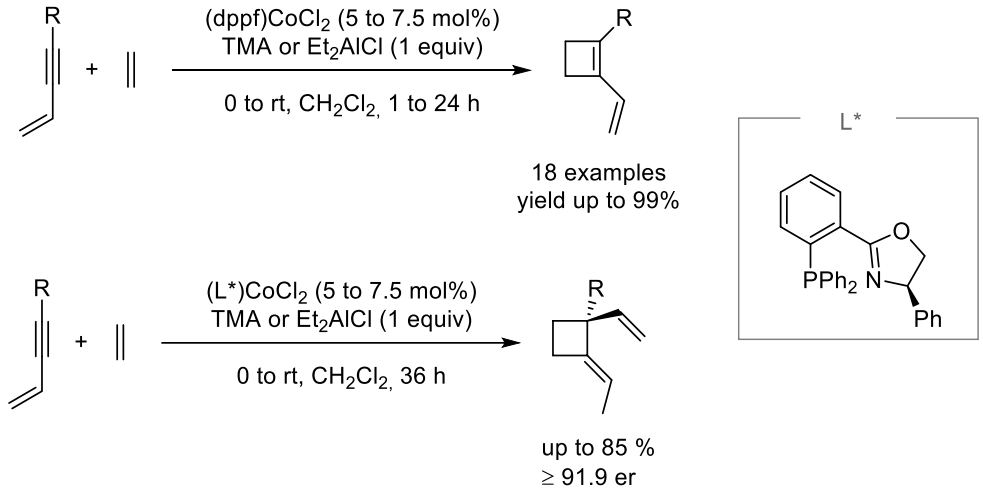
[55] Friedfeld, M. R.; Zhong, H.; Ruck, R. T.; Shevlin, M.; Chirik, P. J. *Science,* **2018**, *360*, 888–893.

reactions, including cycloadditions. For example, Lautens and co-workers developed in 1990 the first highly enantioselective cobalt-catalysed (2+2+2) cycloaddition. By the *in situ* reduction of $Co(acac)_3$ with Et_2AlCl in presence of chiral bidentate phosphine (*S,S*)-Chiraphos, monosubstituted deltacycles were synthetized with enantioselectivities up to 91% (**Scheme 23**).[56]



***Scheme 23**. Enantioselective Diels-Alder catalysed by cobalt.*

Rajanbabu and co-workers developed an asymmetric annulation between enynes and ethylene to construct chiral functionalized cyclobutanes (**Scheme 22**).[57]Although the cyclobutene derived from the (2+2) cycloaddition can be easily isolated at short reaction times, leaving the transformation for longer times led to the tandem event and the asymmetric formation of cyclobutane scaffolds.

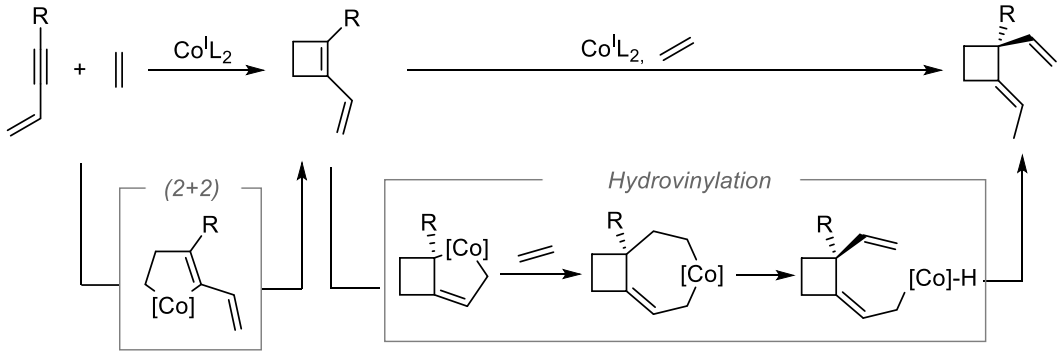


***Scheme 22.** Asymmetric annulation of ethylene and enynes to give functionalized cyclobutanes.*

Mechanistically, this transformation involves a first (2+2) cycloaddition of inexpensive feedstocks, enyne and ethylene, through an oxidative cyclization followed by a reductive elimination to afford the corresponding cyclobutene. Over this cycloadduct, an in situ asymmetric hydrovinylation with another equivalent of ethylene lead to the formation of chiral polisubstituted cyclobutanes (**Scheme 23**).

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[56] Lautens, M.; Lautens, J. C.; Smith, A. C. *J. Am. Chem. Soc*. **1990**, *112*, 5627-5628.
[57] Pagar V.V.; RajanBabu T. V. *Science*. **2018**, *361*, 68-72.



***Scheme 23**. Mechanistic proposal for the cobalt catalysed tandem for asymmetric coupling of ethylene and enynes to functionalized cyclobutanes.*

These last examples illustrate the high efficiency of cobalt in the development of asymmetric transformations, especially in cycloaddition reactions. However, despite all these recent advances, this field can be considered still in its infancy. Therefore, the developing of new and efficient formal asymmetric cycloadditions promoted by earth abundant metals is a highly interesting challenge with lots of unexplored opportunities.

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General objectives

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Considering the abovementioned precedents and current challenges in the field of transition metal catalysed cycloadditions, we proposed the following general objectives for this PhD thesis:

- The discovery of new formal cycloadditions of strained carbocycles using earth abundant metal catalysts. Among the many types of transition metal promoted cycloadditions reported in the literature, those promoted by 3d earth abundant metal catalysts, especially by cobalt, remains very scarce. The availability and distinctive properties of this transition metal might unveil interesting mechanistic novelties and allow to discover new cycloadditions based on the activation of C-C bonds of strained ring systems such as alkylidenecyclopropanes (ACPs) and cyclopropenes.

- The development of asymmetric versions. Due to the importance of molecular chirality in science and particularly in medicinal chemistry, the development of efficient enantioselective transformations is of great interest. Therefore, expanding the scope of the above cycloaddition methods to include efficient enantioselective variants should significantly increase their utility and will further impact this area of synthetic chemistry.

- The discovery of metal-catalysed formal cycloadditions to ensemble heterocycles. Heterocycles are among the most abundant scaffolds in nature and are highly interesting in the context of medicinal chemistry. Thus, the development of a simple and straightforward methodology towards the synthesis of these structures is of major interest. Among then, the discovery of new transition metal catalysed cycloadditions with strained systems seems particularly attractive.

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CHAPTER I

Cobalt catalysed intramolecular cycloadditions of ACPs with C-C unsaturated partners

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1. Introduction

1.1. Alkylidenecyclopropanes: general properties and reactivity

Alkylidenecyclopropanes (ACPs) are organic scaffolds that bear a cyclopropane moiety and an exocyclic double bond. The simplest ACP, bearing a terminally unsubstituted exocyclic double bond, is called methylenecyclopropane (MCP). These kinds of structures are characterized by their high strain energy compared to other small carbocyclic systems, even higher than cyclopropanes, but below than cyclopropenes (**Figure 4**).[58]

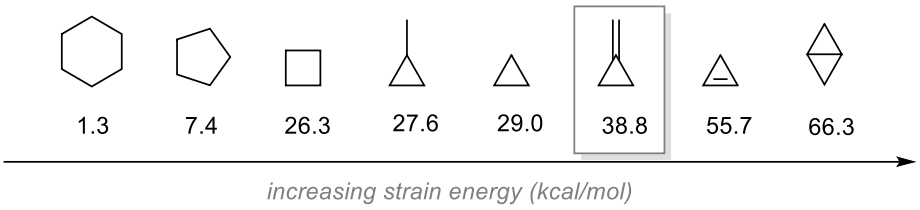


***Figure 4**. Strain energy of small ring systems.*

Their high strain energy is due to the presence of the cyclopropane-fused double bond, which induces a wider angle at the cyclopropyl sp^2 carbon (63.5°vs 60°) and an increased length of distal C-C bond (1.54 vs 1.51 Å) compared to the cyclopropane **(Figure 5a**).[59] Despite their high strain energy, ACPs and MCPs are generally stable molecules that can be handled without any special precaution. Indeed, this structural motif can be found in nature in natural amino acids like hypoglycin[60] and methylenecyclopropylglycine[61] (**Figure 5b**) and many synthetic methods towards these structures have been developed over the years.[62]

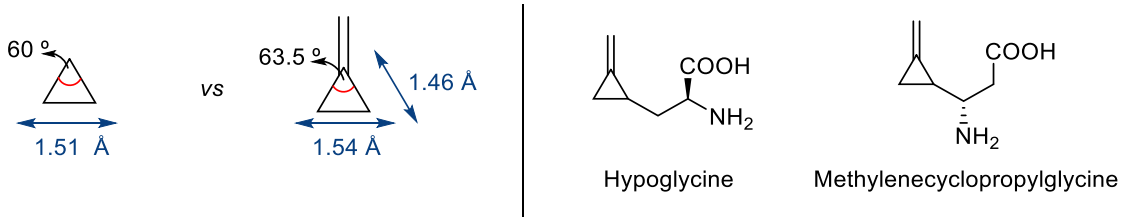
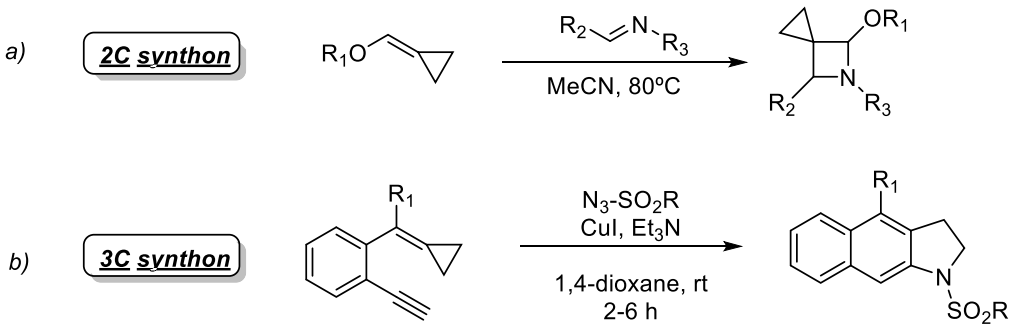


***Figure 5**. a) Structural features of ACPs and cyclopropanes. b) Natural aminoacids containing the ACP scaffold in their structure.*

[58] Souillart, L.; Cramer, N. *Chem. Rev*. **2015**, 115, 9410−9464.
[59] Laurie, V. W.; Stigliani, W. M. *J. Am. Chem. Soc.* **1970**, *92*, 1485.
[60] Hassall, C. H.; Reyle, K. *Biochem. J.***1955**, *60*, 334−338.
[61] Grey, D. O.; Fowden, L. *Biochem. J.***1962**, *82*, 385−389.
[62] Brandi, A.; Goti, A. *Chem. Rev.* **1998**, *98*, 2, 589–636.

Besides their presence in nature, the interest of the chemical community in these structures derives mainly from their versatile reactivity. For example, ACPs and MCPs can use their exocyclic alkene to react as a *2C synthon* in a variety of transformations like hydrofunctionalizations[63] and cycloadditions[64,65] (**Scheme 24a**). However, and more importantly, due to the structural features of these motifs, ACPs and MCPs can also participate as *3C synthons* in several reactions that involve the opening of the cyclopropyl ring (**Scheme 24b**). Among them, formal cycloaddition reactions are particularly relevant for their potential to build complex polycarbocyclic and heterocyclic systems in a rapid, efficient, and atom-economical manner.



Scheme 24. *(a) (2+2) cycloaddition of imines and ACPs. (b) Cycloaddition of sulfonylazides and ACPs catalysed by Cu(I).*

1.2 Transition metal catalysed cycloadditions of ACPs

The cleavage of C-C σ-bonds promoted by transition metal reagents is not easy for multiple reasons. On one hand, a non-strained carbon-carbon single bond is thermodynamically very stable; the dissociation energy is around 356 kJ/mol (85 kcal/mol). Through the oxidative addition of a C–C bond to a transition metal, less stable M–C bonds [around 293 kJ/mol (70 kcal/mol)] are formed. Moreover, the breaking of a C–C single bond is also hampered by the linear directionality of its σ-orbital, which makes difficult its interaction with a metal orbital. In addition, there are several substituents on both ends that can provide steric hinderance. On the contrary, (**Figure 6A**) the π-orbital of a C–C double bond, which is oriented sideways, can coordinate a metal complex much easier.

This situation contrasts with C-H bonds. Although the σ-orbital connecting a hydrogen and a carbon atom lies along the bond axis, the constituent 1s orbital of the hydrogen

[63] a) J. C. Timmerman, B. D. Robertson, R. A. Widenhoefer, J. C. Timmerman, B. D. Robertson, *Angew. Chem. Int. Ed.* **2015**, *54*, 2251–2254. (b) J. C. Timmerman, R. A. Widenhoefer, *Adv. Synth. Catal.* **2015**, *357*, 3703–3706.
[64] K. Estieu, J. Ollivier, J. Salau, F. M. Cordero, A. Goti, A. Brandi, *Communications* **1997**, *3263*, 8276–8277.
[65] I. Nakamura, T. Nemoto, Y. Yamamoto, M. De Armin, *Angew. Chem. Int. Ed.* **2006**, *45*, 5176–5179.

atom is spherical. It has no other substituents except the bonded carbon, making an end-on approach to the metal sterically viable (**Figure 6A**).[66]

A special case is the C-C bond activation of a cyclopropane unit. In this situation, the C-C bond cleavage is more favourable from the thermodynamic and kinetic point of view. The formation of an adduct with the metal complex is thermodynamically driven by the relief of the structural strain. In addition, the orbitals connecting the carbon atoms are bent outwards from the internuclear axis, which favours the interaction with metal orbitals and the kinetics of the cleavage (**Figure 6B**).

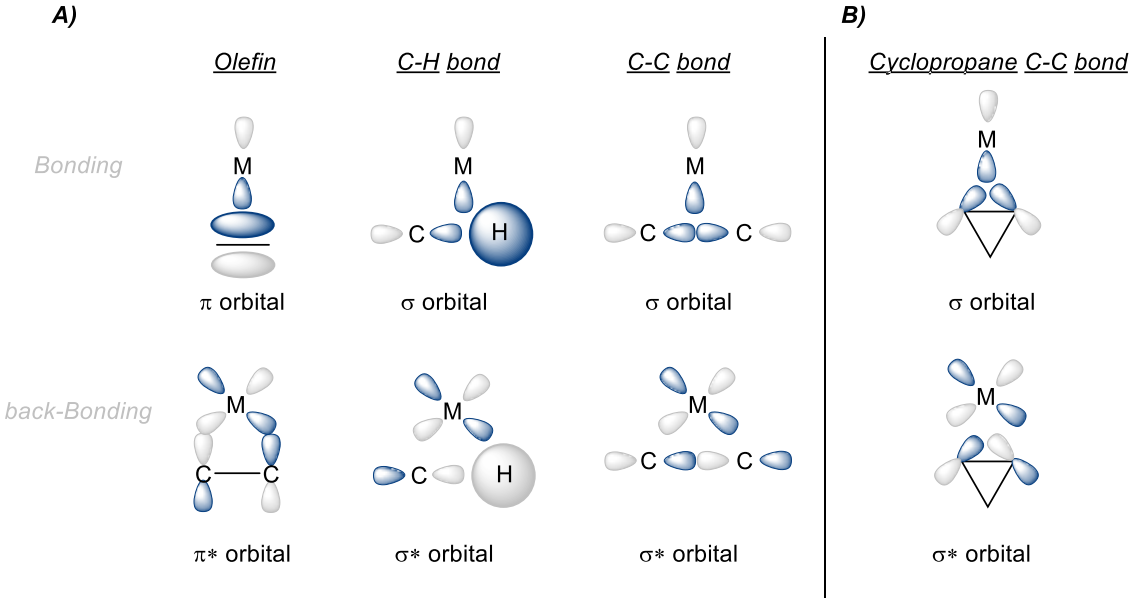


Figure 6. *A) Orbital interaction in the oxidative addition of a double C-C bond, C-H bond, and single C-C bond to metal centre. B) Orbital interaction in the oxidative addition of the C-C bond of a cyclopropane to a metal center.*[66]

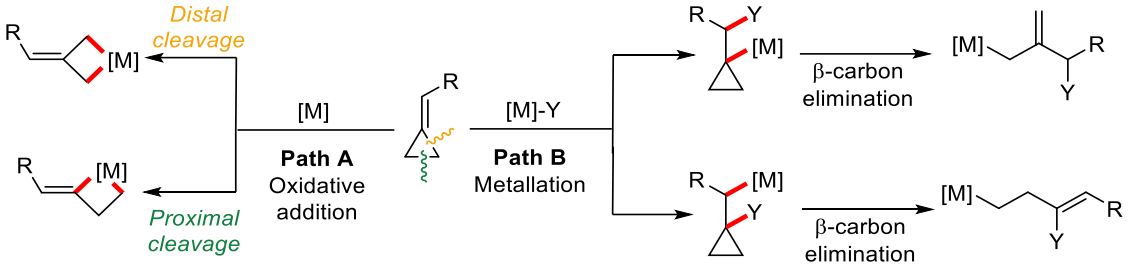
These properties of cyclopropanes can also be extended to ACPs. However, due to the presence of the exocyclic double bond, the insertion of the metal can occur into the distal C-C bond or in one of their two proximal counterparts (**Scheme 25, path A**). Thus, two different metallacyclobutanes can be formed that, in the presence of appropriate unsaturated partners, can undergo migratory insertions and subsequent reductive elimination steps to give different types of cyclopentane products.

On other hand, if instead of the oxidative addition a metallation of the exomethylene part of the ACP occurs, two different regioisomers could be formed (**Scheme 25, path B**). The *Markonikov* adduct gives allyl metal species after a β-carboelimination, while the *anti-Markonikov* adduct forms homoallyl intermediates.

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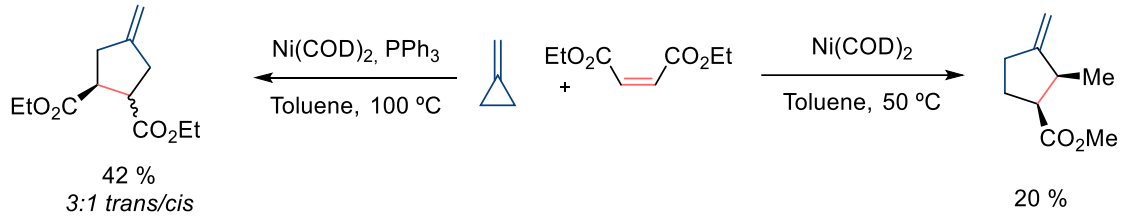
[66] Murakami, M.; Ito, Y. (ed.) *Topics in Organometallic Chemistry*, Vol 3; Springer, Berlin 1999.

Due to the synthetic versatility of ACPs as a 3-carbon *synthon*, the reactivity of these scaffolds with metal reagents has been widely studied, especially in cycloaddition reactions.



Scheme 25. *Possible reaction pathways between a transition metal and an alkylidencyclopropane.*

For example, the following pioneering examples reported by Noyori[67] and Binger[68] demonstrate how the presence of an ancillary ligand in the metal catalyst influences the outcome of the reaction. While the reaction between MCPs and diethyl maleate in the presence of $Ni(COD)_2$ produces the cycloadduct resulting from the proximal cleavage of the cyclopropyl ring (**Scheme 26,** right), the addition of triphenyl phosphine to this metal dramatically changes the chemoselectivity of the reaction towards the product of the distal opening of the cyclopropyl ring (**Scheme 26,** left). These examples illustrate how Ni(0)-catalysed reactions of ACPs or MCPs are extremely sensitive to changes in the electronic properties of the catalyst.



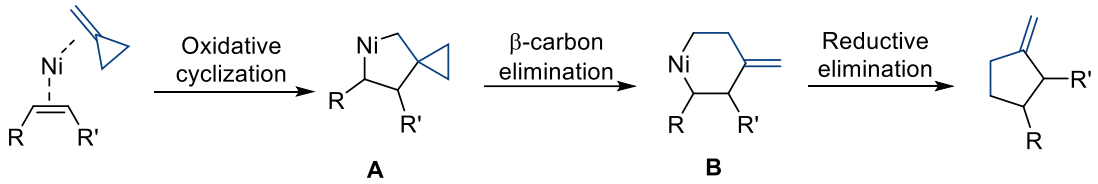
Scheme 26. *Formal cycloadditions of MCPs using different Ni(0) catalysts..*

While studying the mechanism of these transformations, Binger was able to detect metallacycles **A** and **B** by NMR (**Scheme 27**). Accordingly, instead of the initially suggested direct oxidative addition of the proximal C-C bond of the MCP to the Ni(0) catalyst, the authors proposed an alternative oxidative cyclization towards the observed spirometallacyclic species **A**, followed by a β-carboelimination to the metallacycle **B**. Finally, a reductive elimination would afford the corresponding cycloadduct resulting

[67] Noyori, R.; Yamakawa, M.; Takaya, H. *Tetrahedron Lett*. **1978**, *19*, 4823

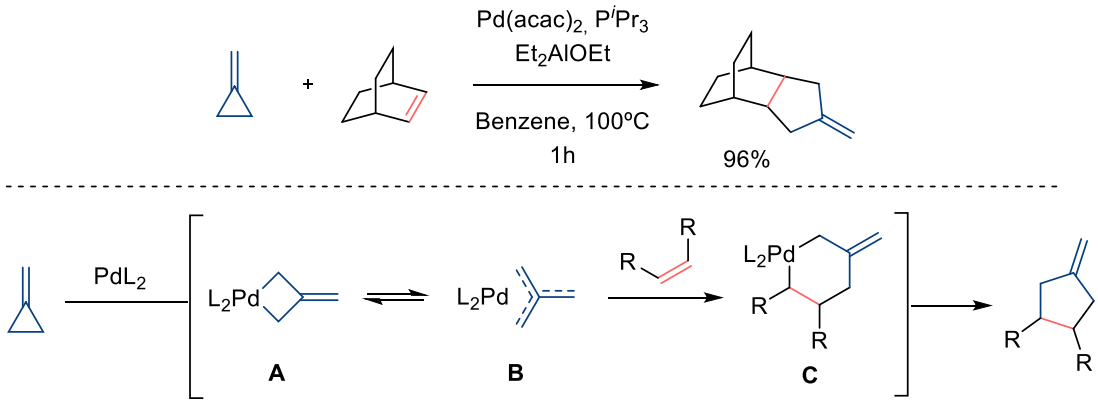
[68] (a) Binger, P.; Doyle, M. J.; Benn, R. *Chem. Ber.* **1983**, *116*, 1. (b) Binger, P.; Brinkmann, A.; Wedemann, P. *Chem. Ber.* **1983**, *116*, 2920.

from the formal proximal cleavage. The adduct of the distal cleavage would proceed via the originally proposed oxidative addition pathway.



***Scheme 27**. Proposed mechanism for the formation of the (3+2) cycloadducts.*

Palladium can also promote different types of transformations of ACPs and MCPs. This metal usually promotes the cleavage of the distal C-C bond of the cyclopropyl ring, as exemplified in the pioneer example described by Binger (**Scheme 28**).[69] Mechanistically, the reaction has been proposed to proceed through a metallacycle **A,** resulting from the insertion of Pd into the distal bond, which might evolve to a trimethylmethane (TMM) species like **B**. This intermediate can react with the alkene partners leading to a palladacyclohexane intermediate **C** that evolves through a reductive elimination to form the corresponding cycloadduct.

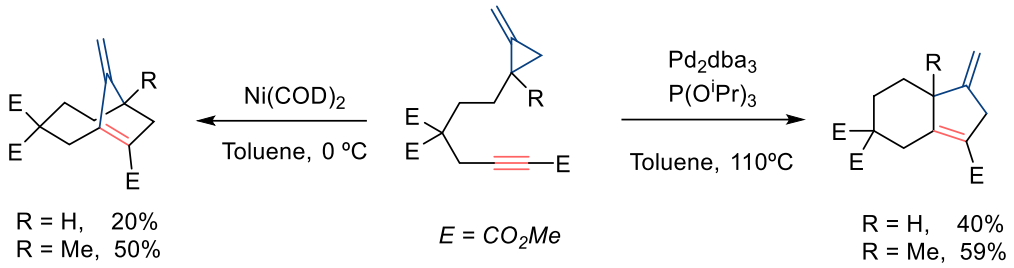


***Scheme 28.** Palladium catalysed (3+2) annulation between MCP and strained alkenes.*

This type of reactivity promoted by Pd and Ni catalysts is not limited to intermolecular annulation processes. In a pioneering example, Motherwell carried out a comparison of the reactivity of alkynyl-tethered MCPs under Pd and Ni catalysis (**Scheme 29**). Thus, whereas the use of $Ni(COD)_2$ led to the formation of byciclo[4.2.1]nonane scaffolds, resulting from a proximal C-C bond cleavage, the use of a palladium-phosphite catalyst afforded bicyclo[4.3.0]nonane derivatives.

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[69] Binger, P.; Schuchardt, U. *Chem. Ber.* **1980**, *113*, 3334.



***Scheme 29**. Divergent behaviour of alkynyl-tethered MCPs under the presence of Ni or Pd catalyst.*

These examples illustrate the synthetic versatility of ACPs as 3-carbon partners in presence of transition metal reagents, since, depending on the substrate, the metal, or even the type of ancillary ligands, different outcomes with respect to the chemo-, regio- and/or stereoselectivity of the reaction are observed. This versatility confirms the rich chemistry of ACPs in presence of transition metal catalysts, but also highlights the enormous challenge of predicting and controlling the reactivity and the selectivity of the processes.

1.3 Intramolecular cycloadditions of ACPs with C-C unsaturated partners

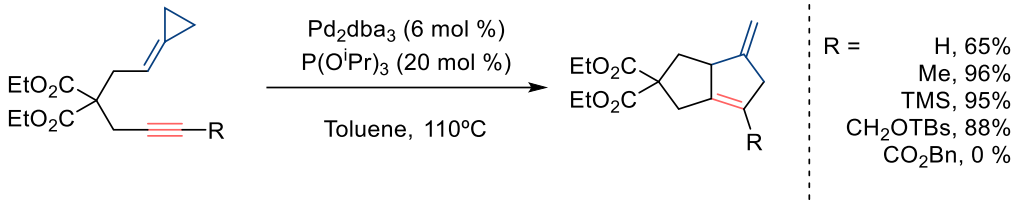
Although the early reports of cycloadditions of MCPs and ACPs were mainly focused on intermolecular processes, in recent years the attention has been shifted to intramolecular reactions, as they can provide more complex polycyclic structures.[70] The reaction manifold depends on which bond, either proximal or distal, is cleaved, as well as on the potential incorporation of one or more unsaturated C-C partners. Thus, these powerful synthetic precursors serve for the construction of several small-to-medium sized carbocyclic systems.

1.3.1. Assembly of 5-membered fused bicyclic systems

ACPs with tethered unsaturated units can undergo formal (3+2) cycloadditions in presence of metal catalysts to give bicyclic products featuring five-membered rings. Our group reported the first intramolecular cycloaddition of an ACP that bears a pendant alkyne, mediated by a palladium-phosphite catalyst (**Scheme 30**).[71] In general, the reaction provides the corresponding cycloadducts in high yields, with the exception of alkynes bearing electron withdrawing groups (EWG, e.g. CO_2Bn), which failed to participate in the reaction.

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[70] Gulías, M.; López, F.; Mascareñas, J.L. *Pure Appl. Chem.* **2011**, *83*, 495–506. (b) Fumagalli, G.; Stanton, S.; Bower, J. F. *Chem. Rev.* **2017**, *117*, 9404–9432. (c) Shi, M.; Lu, J. M.; Wei, Y.; Shao, L. X. *Acc. Chem. Res.* **2012**, *45*, 641–652.
[71] Delgado, A.; Rodríguez J. R.; Castedo, L.; Mascareñas, J. L. *J. Am. Chem. Soc.* **2003**, *125*, 9282–9283.



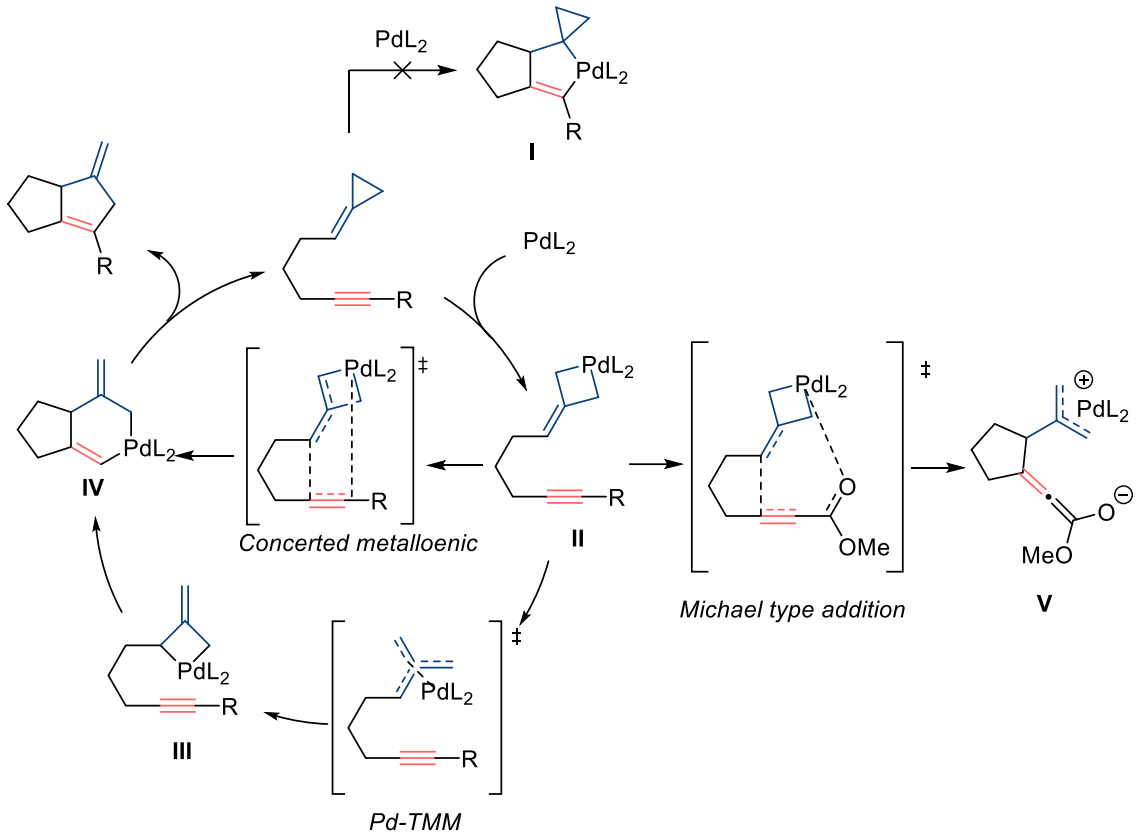
***Scheme 30**. Pd catalysed intramolecular (3+2) cycloaddition between ACPs and alkynes.*

In order to shed some light into the reaction mechanism, DFT calculations were carried out in collaboration with Prof. Cárdenas. Initially, the reaction was thought to involve an oxidative cyclization to give intermediate **I**; however, this was rapidly discarded because of its high energetic barrier (40 kcal/mol). Based on this result, other pathways were evaluated and, eventually, two main pathways were found viable and proved to be energetically very similar.[72] Both of them begin with an oxidative addition of the distal C-C bond of the cyclopropane to the Pd^0 complex. Then, the resulting intermediate **II** can evolve through two different paths. The first one involved the evolution of **II** via a TMM species to the palladacyclobutane **III** and the subsequent alkyne migratory insertion to afford intermediate **IV**. The other option would involve the direct formation of this intermediate **IV** from **II**, through a concerted metalloenic rearrangement. Eventually, a reductive elimination would lead to the final cycloadduct. Although the path through the Pd-TMM intermediate was energetically more favourable, the small energy difference between both pathways does not allow to rule out the direct metalloenic rearrangement (**Scheme 31**).

Moreover, DFT calculations helped to understand why alkynes bearing a terminal EWG like CO_2Me failed to participate in the process. In this situation, calculations indicate that a Michael type of addition to the activated alkyne, leading to an intermediate like **V**, would hamper the progress towards the desired cycloadduct.

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[72] García-Fandiño, R.; Gulías, M.; Castedo, L.; Granja, J. R.; Mascareñas, J. L.; Cárdenas, D. J. *Chem. Eur. J.* **2008**, 14, 272.

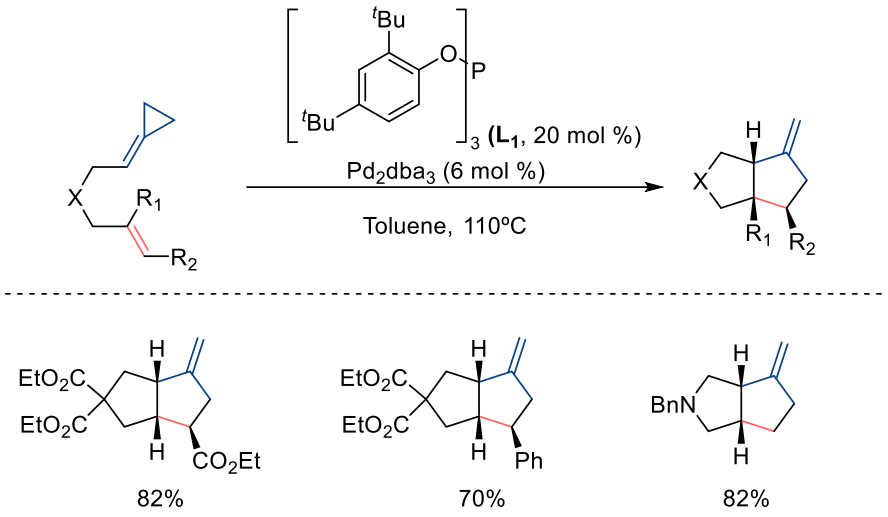


Scheme 31. *Mechanistic proposal based on DFT calculations for the Pd catalysed intramolecular (3+2) cycloaddition between ACPs and alkynes.*

During the following years, our group demonstrated that alkenes were also viable partners for this type of intramolecular processes, so that the corresponding cycloadducts can be obtained with total diastereoselectivity when a Pd catalyst comprising a phosphite ligand is employed (**Scheme 32**).[73] Mechanistically, the reaction proved to be similar to what had been previously reported with alkynes.[74]

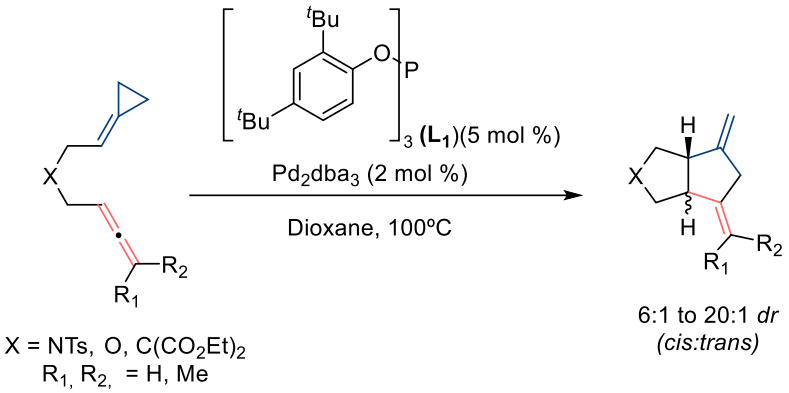
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[73] Gulías, M.; García, R.; Delgado, A.; Castedo, L.; Mascareñas, J.L *J. Am. Chem. Soc.* **2006**, *128*, 384–385.
[74] Garcia-Fandiño, R.; Gulías, M.; Mascareñas, J. L.; Cárdenas, D. J. *Dalton Trans.* **2012**, *41*, 9468–9481.



Scheme 32. *Pd catalysed intramolecular (3+2) cycloaddition between ACPs and alkenes.*

Palladium catalysts also promote (3+2) intramolecular cycloadditions of ACPs with allenes (**Scheme 33**). In this case, the bulky phosphite **L_1** was selected as the optimal ligand. Depending on the substrate, the corresponding cycloadduct was obtained as a variable mixture of *trans*- and *cis*-fused diastereoisomers, prevailing in all cases the formation of the *cis* adduct.[75]

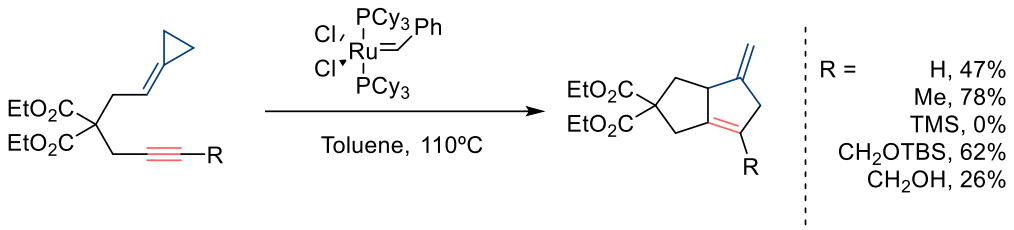


Scheme 33. *Pd catalysed intramolecular (3+2) cycloaddition between ACPs and allenes.*

The (3+2) cycloadditions between ACPs and alkynes are not limited to the use of palladium catalysts. For example, our group reported that the first-generation Grubbs ruthenium catalyst, widely employed in the alkene metathesis reaction, is also able to promote this process quite efficiently (**Scheme 34**).[76]

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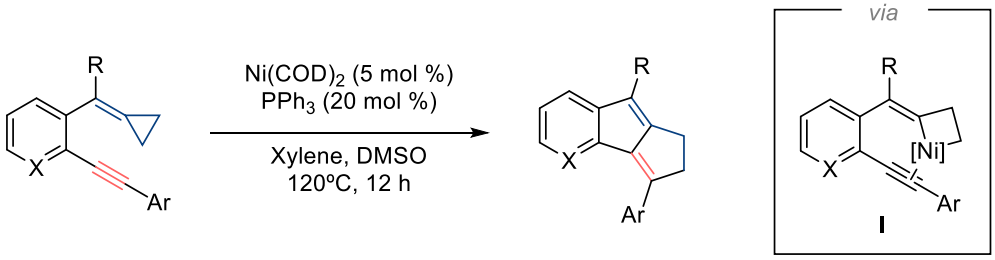
[75] Trillo, B.; Gulías, M.; López, F.; Castedo, L.; Mascareñas, J. L. *Adv. Synth. Catal.* **2006**, *348*, 2381–2384.
[76] López, F.; Delgado, A.; Rodríguez, J. R.; Castedo, L.; Mascareñas, J.L. *J. Am. Chem. Soc.*, **2004**, *126*, 10262–10263.



***Scheme 34**. Ru-catalysed intramolecular (3+2) cycloaddition between ACPs and alkynes.*

Although the scope of the reaction is similar to the one reported previously with Pd, this reaction proved to be very interesting from a mechanistic point of view, since the Grubbs ruthenium complex was proposed to be just a precatalyst that evolves *in situ* to a ruthenium non-carbene active species.

Contrary to what was reported previously with Pd and Ru, the use of nickel catalysts affords the five membered cycloadducts resulting from the cleavage of the proximal C-C bond of the ACP. For example, Zhang and co-workers reported a Ni(0) catalysed intramolecular cycloaddition of ACPs bearing aryl-substituted alkynes that deliver (3+2) cycloadducts bearing endocyclic alkenes (**Scheme 35**).[77] The authors proposed the participation of an intermediate like **I** that, after the alkyne insertion and a subsequent reductive elimination, leads to the observed carbocycles.



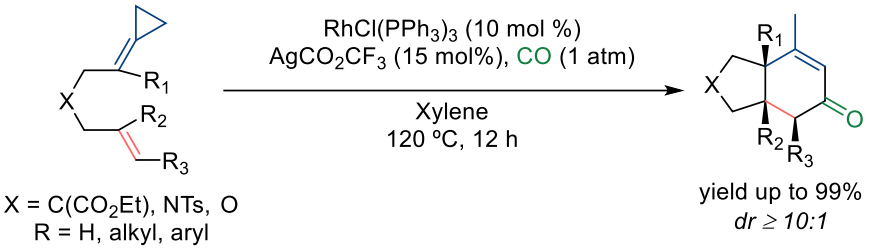
***Scheme 35.** Ni(0) catalysed intramolecular cycloaddition of ACPs and alkynes through a proximal C-C bond oxidative addition.*

1.3.2. Assembly of 6-membered carbocycles

The synthesis of six-membered carbocycles through intramolecular cycloadditions of ACPs has been monopolized by Rh catalysts. Evans and co-workers reported a (3+2+1) cycloaddition between alkene-tethered alkylidencyclopropanes and carbon monoxide, to afford *cis*-fused bicyclohexenenones (**Scheme 36**).[78] Remarkable, both the ACP and the alkene tolerate substituents at their internal positions, leading to the corresponding cyclohexenones in high yields and diastereoselectivities.

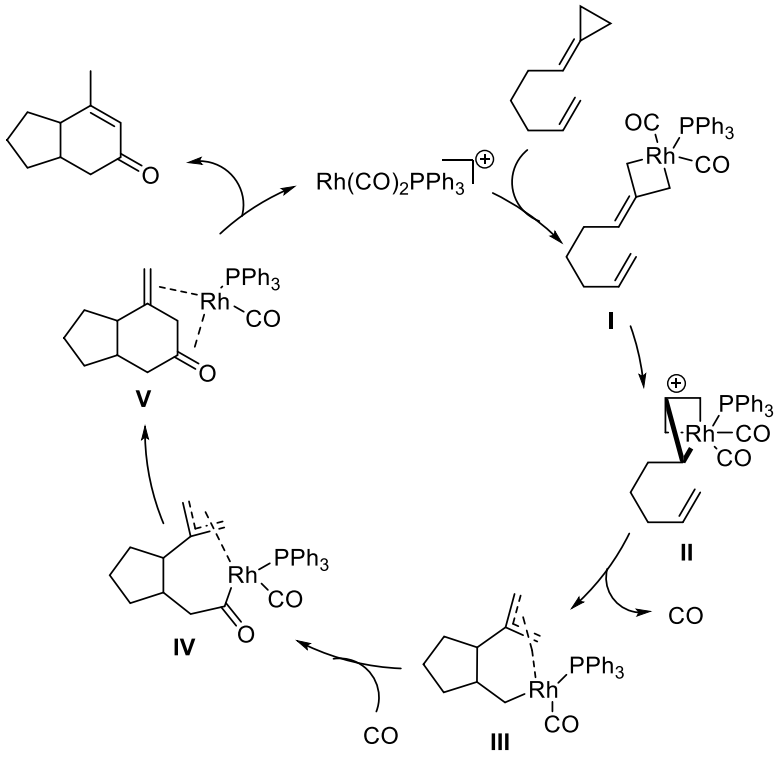
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[77] Yao, B.; Li, Y.; Liang, Z.; Zhang, Y. *Org. Lett.* **2011**, *13*, 640–643.
[78] Mazumder, S.; Shang, D.; Negru, D.; Baik, Evans P. A. *J. Am. Chem. Soc.* **2012**, *134*, 20569-20572.



Scheme 36. *Rh catalysed (3+2+1) cycloaddition of alkene-tethered ACPs and CO.*

A computational analysis of (**Scheme 37**) allowed the authors to propose an oxidative addition of the distal C-C of the cyclopropane to the Rh(I) catalyst (**I**) to evolve towards a Rh(III)-TMM intermediate like **II**. Interestingly, after dissociation of a CO ligand**,** a stereoselective insertion of the pendant alkene provides a Rh π-allyl intermediate **III**. Then, a migratory insertion of CO and a reductive elimination affords intermediate **V** that, prior to decoordination, catalyses a 1,3-H shift leading to the isomerization of the exocyclic double bond.



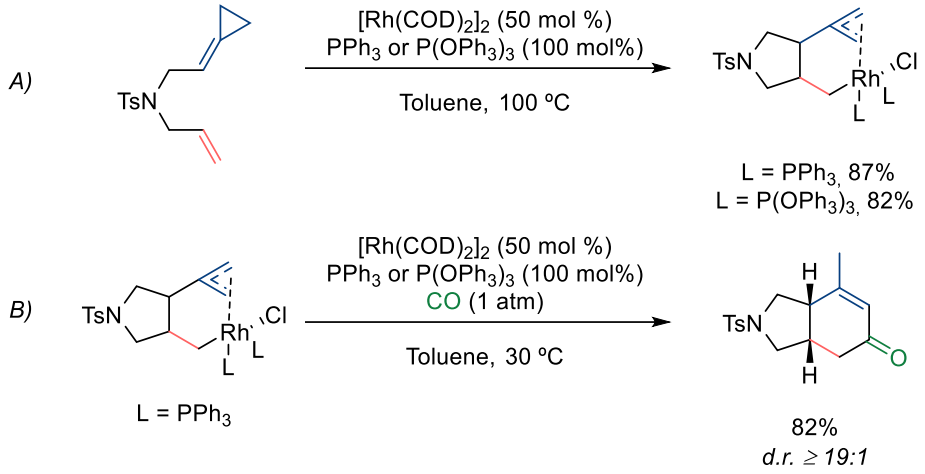
Scheme 37. *Mechanistic proposal for the Rh catalysed (3+2+1) cycloaddition of alkene-tethered ACPs and CO.*

Supporting this mechanistic hypothesis, Evans and co-workers were able to isolate and fully characterized a π-allyl rhodacycle intermediate like **III** (**Scheme 38A**).[79] Moreover, they proved that these species are competent intermediates, so that when they

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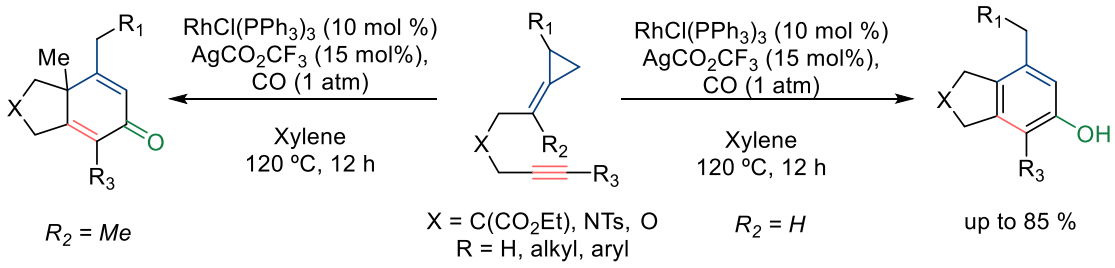
[79] Inglesby, P.A.; Bacsa, J.; Negru, D. E.; Evans, P. A *Angew. Chem. Int. Ed.* **2014**, *53*, 3952–3956.

submitted each rhodacycle to a CO atmosphere, the corresponding cyclohexanone was obtained (**Scheme 38B**).



Scheme 38. *A) Isolation of π-allyl rhodacycle intermediate. B) π-allyl rhodacycle as an intermediate in the Rh catalysed (3+2+1) cycloaddition.*

This type of (3+2+1) cycloaddition with CO was also developed using alkynes instead of alkenes as cycloaddition partners. Thus, when alkyne-tethered ACPs are used, two kinds of products can be obtained, depending on the substitution of the double bond at the ACP. If the internal position of this alkene is substituted (e.g with a methyl group), bicyclohexa-2,5-dienone are obtained.[80] However, when this position is not substituted (R_2 = H), polysubstituted phenols are obtained, through an aromatization of the initially formed cyclohexa-2,5-dienones (**Scheme 39**).[81]



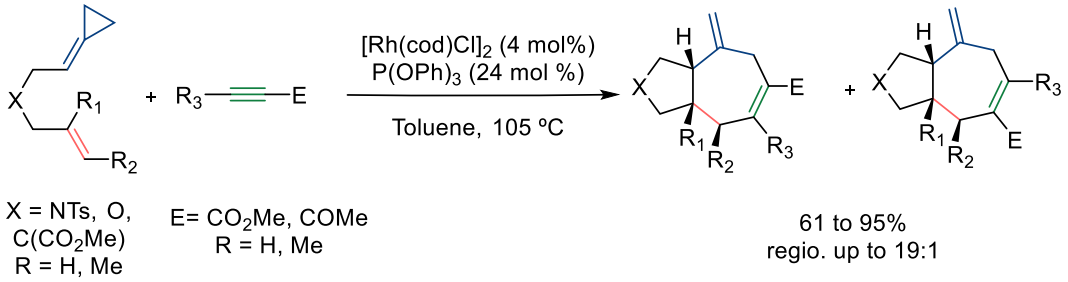
Scheme 39. *Rh catalysed (3+2+1) cycloaddition of alkyne-tethered ACPs and CO.*

1.3.3. Assembly of 7-membered carbocycles

Following their studies with Rh catalysts, Evans and co-workers also developed several (3+2+2) cycloadditions of ACPs with different π-unsaturated partners as third reaction components, instead of CO. For example, activated alkynes successfully engaged in this

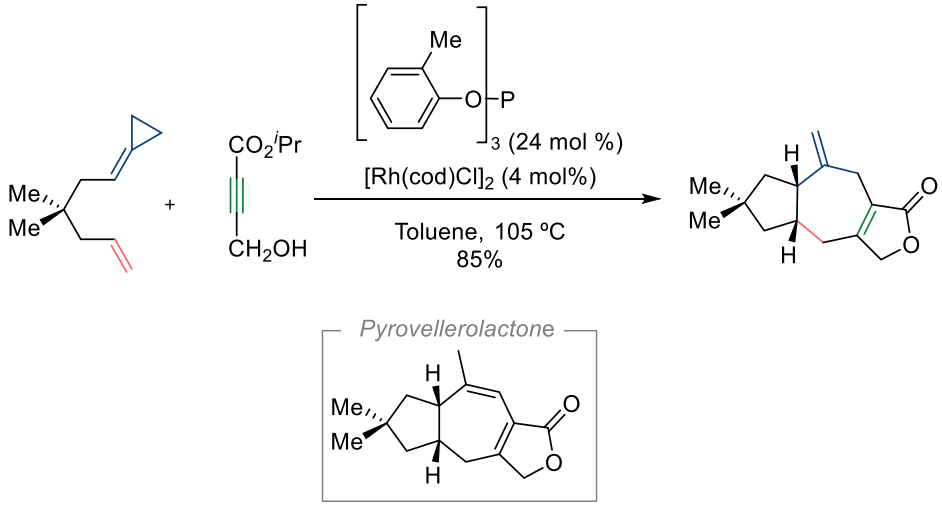
[80] Burnie, A. J; Evans, P.A *Chem. Commun.* **2018**, 54, 7621-7624.
[81] (a) Evans, P.A.; Burnie, A. J.; Negru, D. E. *Org. Lett.* **2014,** *16*, 4356-4359. (b) Kim, S.; Chung, Y. K. *Org. Lett.* **2014,** *16*, 4352-4355.

type of cycloadditions with alkenyl-tethered ACPs, generating *cis*-fused bicycloheptadienes in a regioselective and diastereoselective manner (**Scheme 40**).



Scheme 40. *Rh catalysed (3+2+2) cycloaddition of alkene-tethered ACPs and activated alkynes.*

The utility of this methodology is illustrated by the same group in the total synthesis of Pyrovellerolactone for which the core of this sesquiterpene was constructed through a (3+2+2) cycloaddition, as shown in **Scheme 41**.[82]

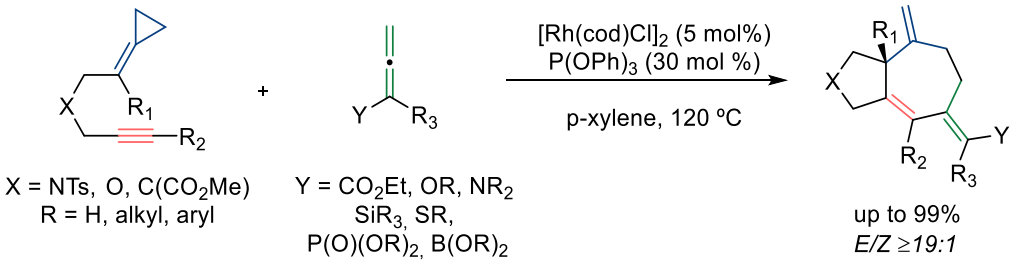


Scheme 41. *Total synthesis of pyrovellerolactone through a Rh catalysed (3+2+2) cycloaddition.*

In 2015, Evans and co-workers demonstrated that rhodium (I) complexes can catalyse the (3+2+2) cycloaddition of alkyne-tethered ACPs with 1,1-disubstituted allenes, to deliver bicycloheptadiene scaffolds bearing a tri- or tetrasubstituted exocyclic olefins (**Scheme 42**).[83] Remarkably, the insertion of the allene is totally regioselective, entailing the less substituted C-C bond.

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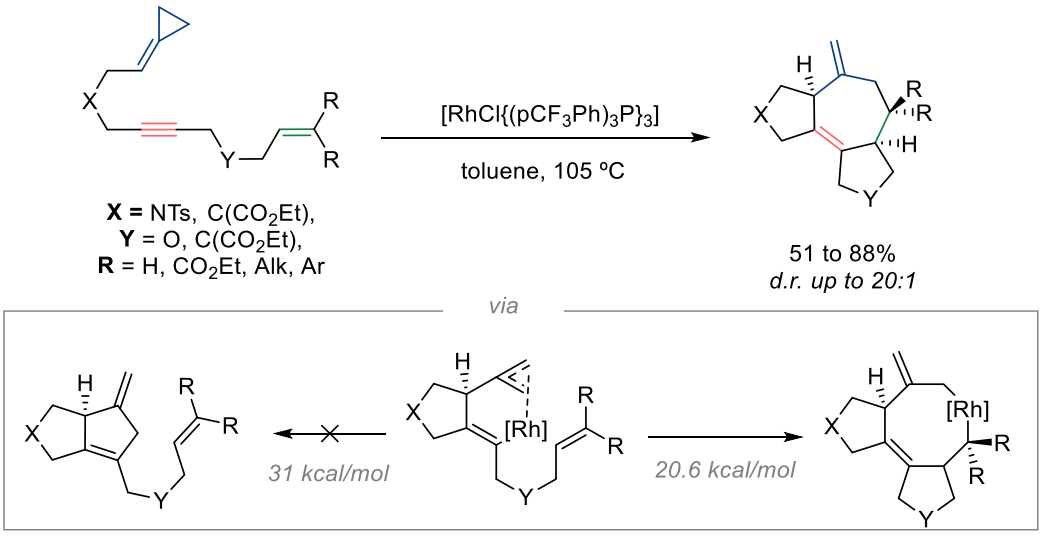
[82] Evans, P. A.; Inglesby, P. A.; Kilbride, K. *Org. Lett.* **2013**, *15*, 1798–1801.
[83] Evans, P. A.; Negru, D. E.; Shang, D. *Angew. Chem. Int. Ed.* **2015**, *54*, 4768–4772.



Scheme 42. *Rh catalysed (3+2+2) cycloaddition of alkyne-tethered ACPs and allenes.*

The development of multicomponent Rh-catalysed (3+2+2) cycloadditions of ACPs is not only limited to intermolecular approaches. Thus, our group has already developed in 2014 a fully intramolecular version to provide 5,7,5-fused tricyclic systems in good yields and moderate to high diastereoselectivities (**Scheme 43**).[84] Importantly, although the method allows substituents at the terminal position of the alkene, substituents at the internal position are not tolerated, so that complex mixtures of products are obtained in these cases.

DTF calculations allowed to propose that the reductive elimination towards the (3+2) cycloadduct from the putative π-allyl rhodacycle has a relatively high energy barrier, hence the intermediate evolves through a less demanding intramolecular migratory insertion of the pendant alkene to eventually afford the (3+2+2) adduct after a reductive elimination.

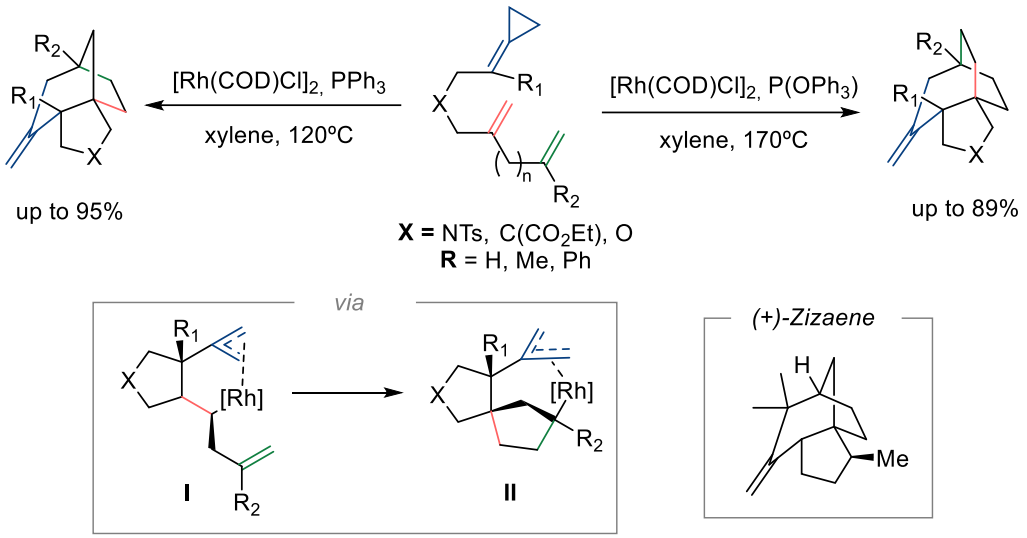


Scheme 43*. Rh catalysed intramolecular (3+2+2) cycloaddition of enynylidenecyclopropanes.*

Very recently, Evans and co-workers developed a novel intramolecular (3+2+2) cycloaddition of skipped diene-tethered ACPs catalysed by Rh(I) that affords complex

[84]Araya, M.; Gulías, M.; Fernández, I.; Bhargava, G.; Castedo, L.; Mascareñas, J. L.; López, F.; *Chem. Eur. J.* **2014**, *20*, 10255–10259.

tricyclic scaffolds (**Scheme 44**).[85] Indeed, the authors show the utility synthetic of this structures accomplishing the asymmetric total synthesis of (+)-Zizazene. Mechanistically, the reaction is similar to the ones reported before since operates through a π-allyl rhodacycle **I** that suffers a migratory insertion of the pendant alkene to afford intermediate **II.**



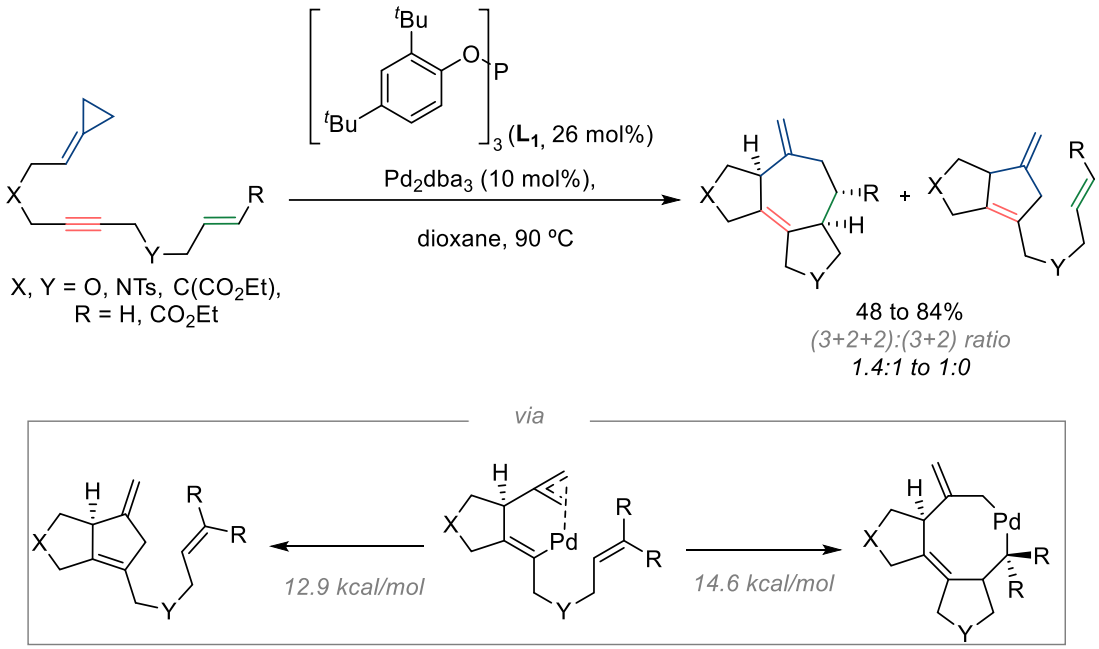
***Scheme 44**. Rh(I) catalysed (3+2+2) cycloaddition of dienylidenecyclopropanes.*

Besides Rh, other metal catalysts have been shown to promote similar intramolecular multicomponent cycloadditions of ACPs. Indeed, our group showed in 2010 that Pd(0) catalysts bearing a bulky phosphite ligand (**L_1**), can promote the (3+2+2) cycloaddition of enynylidenecyclopropanes to deliver the corresponding tricyclic adducts in moderate to good yields.[86] The reaction could only be carried out when terminal or acrylate type pendant alkenes are used; however, depending on the substrate employed in the transformation, appreciable amounts of the (3+2) adducts were formed. Moreover, other internal or terminal substituted alkenes only provide the (3+2) cycloadduct.

To explain this problem of chemoselectivity in the transformation, DFT calculations were performed. The mechanism was similar to the one illustrated above for Rh (**Scheme 43**). However, in this case, it was observed that the reductive elimination (12. 9 kcal/ mol) to give the cyclopentene adducts is a competitive step with the carbometallation of the pendant alkene (14.6 kcal/mol) that evolves towards the (3+2+2) cycloadduct **(Scheme 45**).

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[85] Zhu, Y.; Zheng, J.; Evans, P. A. J. *Am. Chem. Soc.* **2023**, *145*, 7, 3833–3838.
[86] Bhargava, G.; Trillo, B.; Araya, M.; López, F.; Castedo, L.; Mascareñas, J. L. *Chem. Commun*. **2010**, *46*, 270-27.

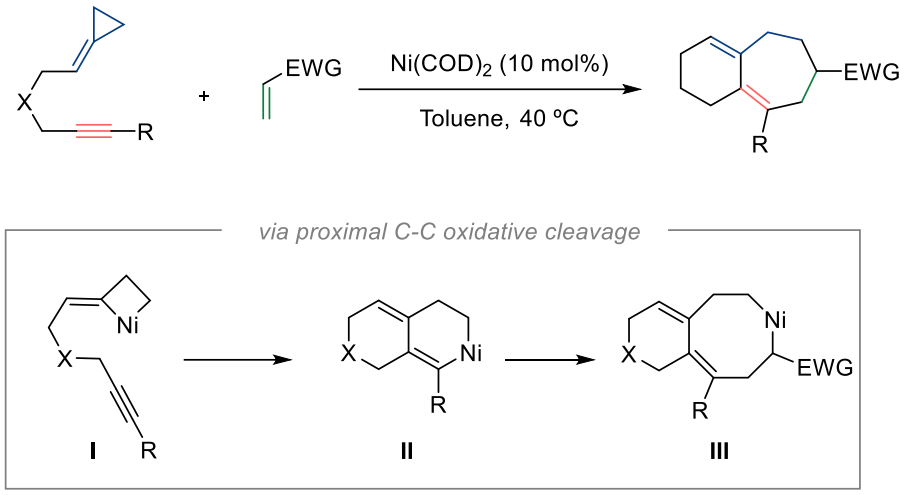


Scheme 45. Pd catalysed intramolecular (3+2+2) cycloaddition of enynylidenecyclopropanes.

Nickel catalysts have also been shown effective in related (3+2+2) cycloadditions that deliver seven-membered fused carbocycles. Thus, under very mild conditions, in the presence of $Ni(COD)_2$, alkyne-tethered ACPs react with an external alkene featuring an electron withdrawing group to provide the corresponding (3+2+2) cycloadduct. Mechanistically, the reaction has been suggested to be initiated by proximal oxidative addition of the ACP to the Ni(0) complex, followed by the intramolecular insertion of the alkyne. Then, the metallacycle **II** can be trapped with external alkenes that, after reductive elimination, affords the corresponding 6,7- fused bicycles **(Scheme 46)**.[87]

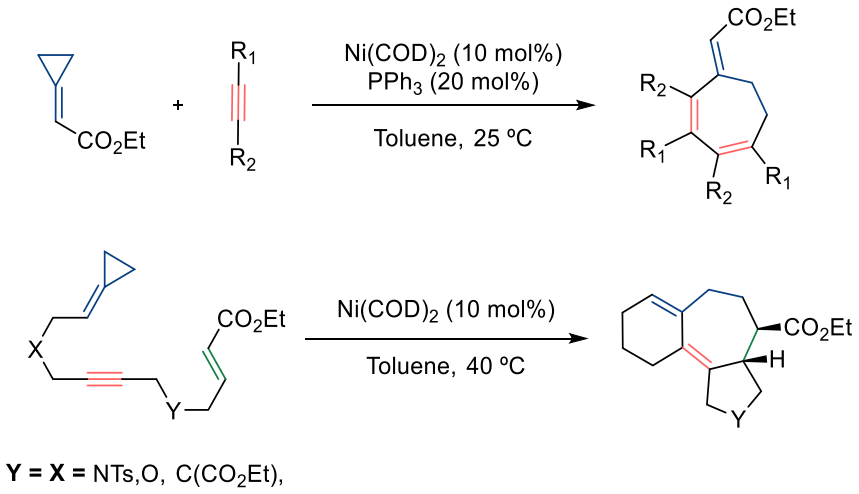
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[87] Saya, L.; Bhargava, G.; Navarro, M. A.; Gulías, M.; López, F.; Fernández, I.; Castedo, L.; Mascareñas, J. L. *Angew. Chem. Int. Ed.* **2010**, 9886–9890.



***Scheme 46**. Ni(0) catalysed (3+2+2) cycloaddition of alkyne-tethered ACPs and an external activated alkene.*

Saito and co-workers have also developed a fully intermolecular Ni-catalysed (3+2+2) cycloaddition of ACPs.[88] Alternatively, the annulation can be also performed in a fully intramolecular manner to construct 6,7,5-tricyclic frameworks in a single-pot reaction (**Scheme 47**), as shown by our group in 2014.[89]

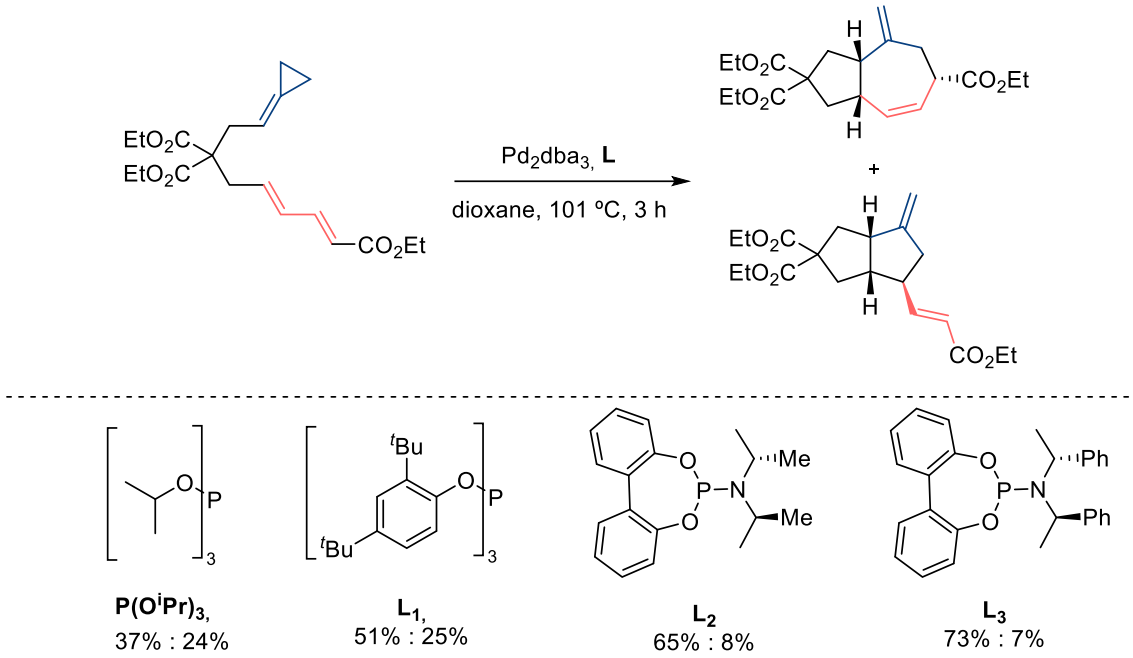


***Scheme 47.** Ni catalysed intramolecular (3+2+2) cycloaddition of enynylidenecyclopropanes.*

We have also shown that the synthesis of seven-membered carbocycles can be achieved by means of intramolecular Pd-catalysed (4+3) cycloaddition between ACPs and conjugated dienes, a reaction that delivers bicyclo[5.3.0]octane systems with good yields and moderate to good selectivities (**Scheme 48**).[90] The use of a Pd catalyst

[88] Saito, S.; Masuda, M.; Komagawa, S. *J. Am. Chem. Soc.* **2004**, *126*, 34, 10540–10541.
[89] Saya, L.; Fernandez, I.; López, F.; Mascareñas, J. L. *Org. Lett*. **2014**, *16*, 19, 5008–5011.
[90] Gulías, M.; Durán, J.; López, F.; Fernández, I.; Castedo, L.; Mascareñas, J. L *J. Am. Chem. Soc.* **2007**, *129*, 36, 11026-11027.

containing a phosphoramidite ligand proved to be essential to afford good chemoselectivity between the competitive (3+2) adduct and the (4+3) counterpart, as other typical ligands employed in cycloadditions of ACPs, like **L_1**, failed to give the seven-membered cycloadduct in a selective manner.

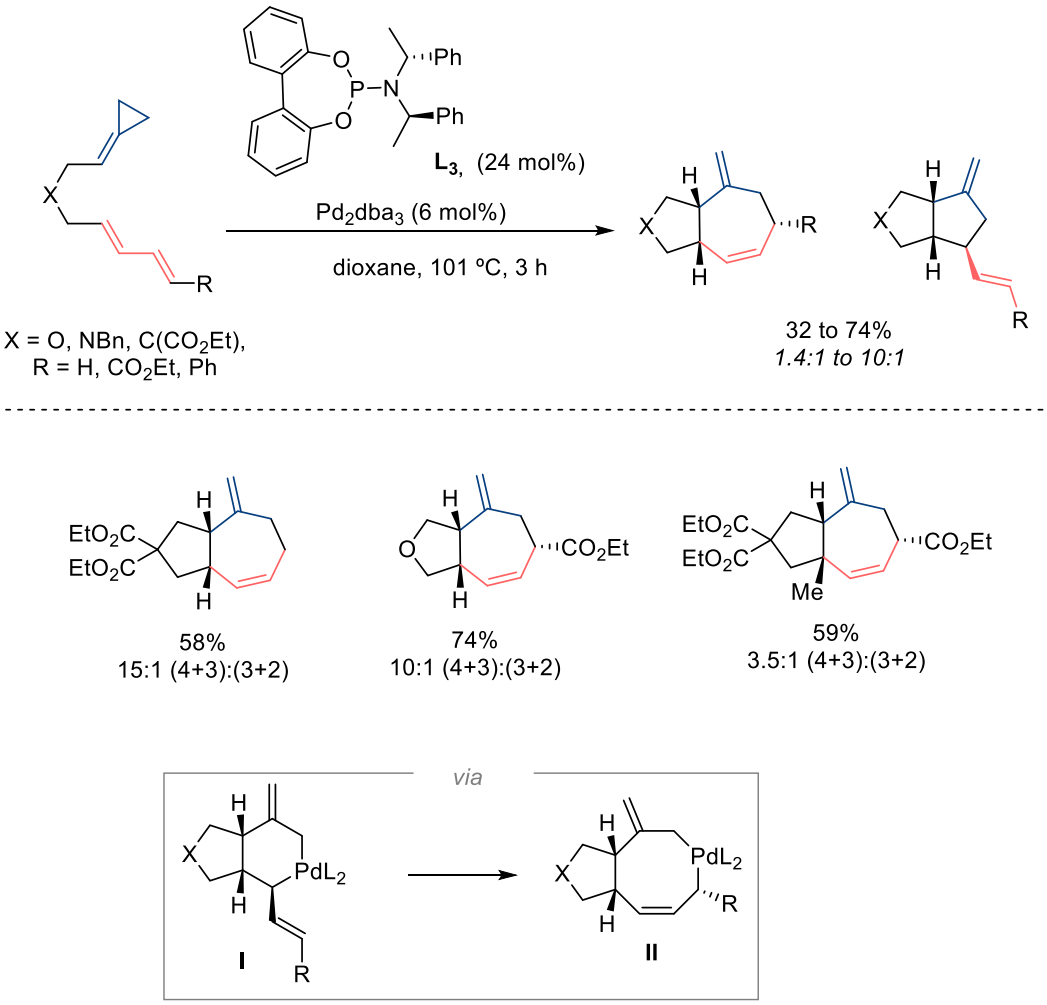


***Scheme 48**. Ligands screening for the intramolecular Pd-catalysed (4+3) cycloaddition of dienes and ACPs. Yield ratio of (4+3) vs (3+2) cycloadditions.*

Nevertheless, as illustrate in **Scheme 49**, depending on the ACP employed in the cycloaddition, different ratios of the (3+2) and (4+3) cycloaddition are obtained, albeit with a good overall yield in every case.

The proposed mechanism is based on a distal oxidative addition followed by the migratory insertion of the internal alkene of the diene to afford palladacycle **I**. From here, a reductive elimination would afford the (3+2) cycloadduct whereas an allylic isomerization gives intermediate **II** which, after a reductive elimination, delivers the observed (4+3) cycloadduct.

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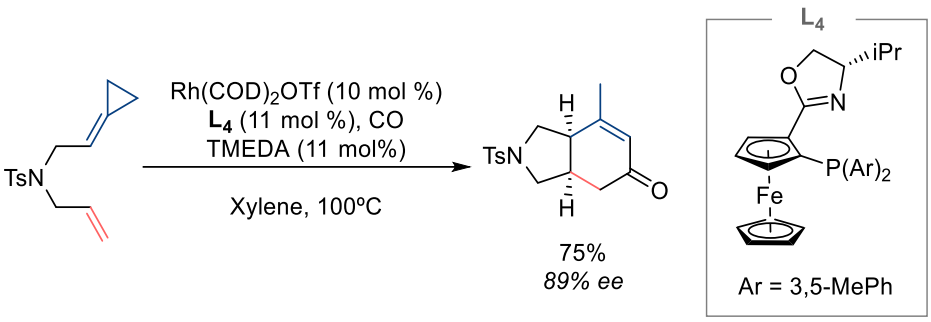


Scheme 49. *Pd catalysed intramolecular (4+3) cycloaddition of ACPs and dienes.*

1.4 Enantioselective transition metal cycloadditions of ACPs

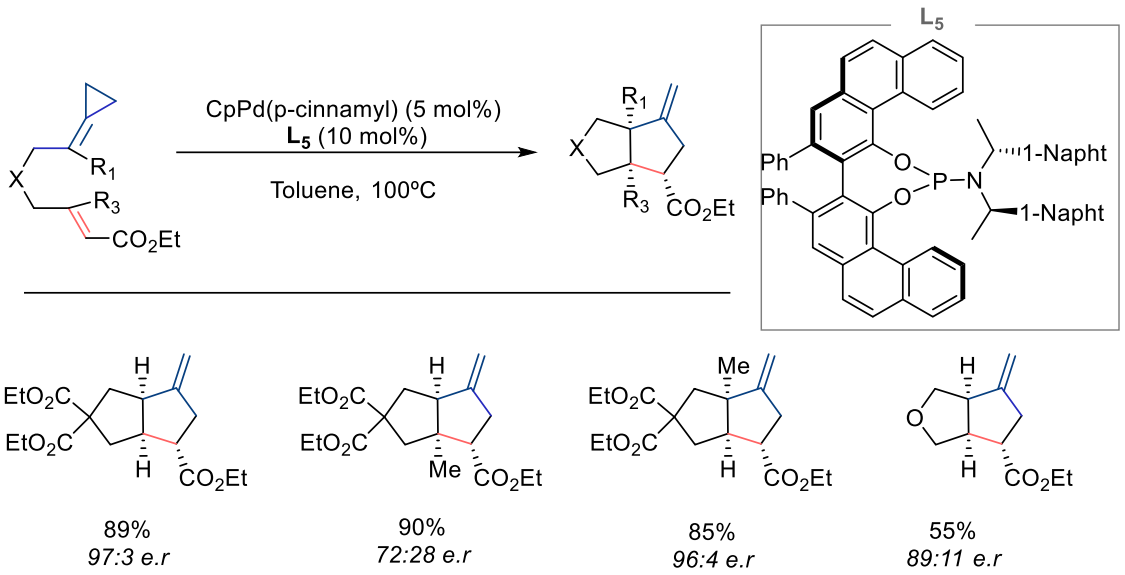
Despite the number of different types of TMC cycloadditions of ACPs, the development of enantioselective versions is an unsolved challenge. For example, under Rh catalysis, only one isolated example can be found in the literature. In particular, in the context of the development of the (3+2+1) cycloadditions of alkene-tethered ACPs with CO, Evans reported an enantioselective example using a chiral ferrocene-phosphine ligand (**Scheme 50**).[78]

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Scheme 50. *Enantioselective example of the Rh catalysed (3+2+1) cycloaddition of alkene-tethered ACPs and CO.*

The other only enantioselective method was reported by our group in 2018.[91] Under the presence of a Pd(0) catalyst bearing a very bulky phosphoramidite ligand like **L5**, (3+2) and (4+3) cycloadditions between ACPs and alkenes or dienes were successfully achieved.



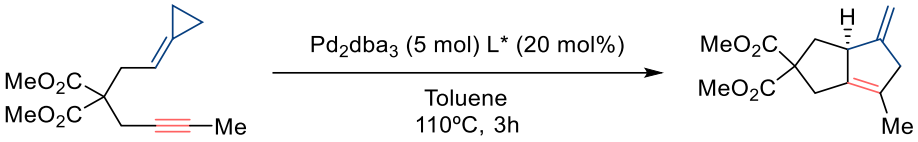
Scheme 51. *Pd catalysed enantioselective (3+2) cycloaddition of alkene-tethered ACPs.*

However, these methodologies hold several limitations. For example, the (3+2) cycloaddition was limited to the presence of electron withdrawing groups at the alkene. Moreover, slight structural changes like the introduction of a Me group in the internal position of the alkene or a simple change of the connecting tethered, from a malonate to an ether, produces a significant erosion of the enantioselectivity of the process (**Scheme 51).**

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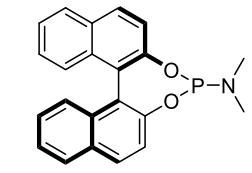
[91] Verdugo, F.; Villarino, L.; Durán, J.; Gulías, M.; Mascareñas, J. L.; López, F. *ACS Catal.* **2018**, *8*, 7, 6100–6105.

Our group also evaluated the viability of an enantioselective (3+2) cycloaddition of alkyne-tethered alkylidenecyclopropanes.[92] Despite the extensive evaluation of chiral phosphoramidites, successful catalysts could not be found. Thus, the simplest chiral phosphoramidite, (*R*)-Monophos, did not induce asymmetry. Using a phosphoramidite derived from Binol and (*R*)-1-Phenylmethylamine **(*R,R,R*)-L$_6$**), allowed to achieve certain enantiocontrol (**Entry 2, Table 1**). Moreover, when **(*R,S,S*)-L$_6$** was used as chiral ligand, an increase to 67:33 er was achieved illustrating a match/mismatch effect in the phosphoramidite. Unfortunately, further modifications at the ligand (**Entry 4-6**) did not bring substantial improvements in the selectivity of the process, confirming that the development of enantioselective variants of TMC reactions between ACPs and alkynes is a daunting goal.

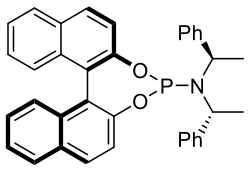


Entry	L*	Conversion	*er*
1	(R)-Monophos	81	*0*
2	(*R,R,R*)-L$_6$	100	*58:42*
3	(*R,S,S*)-L$_6$	100	*67:33*
4	(R,R,R)-L$_7$	66	*62:48*
5	(S,R,R)-L$_8$	100	*60:40*
6	(*R,R,R*)-L$_5$	12	-

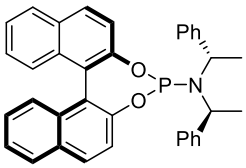
Table 1. *Exploration of an enantioselective Pd-catalysed (3+2) cycloaddition of alkyne-tethered ACPs.*



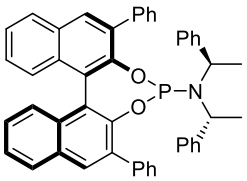
(*R*)-Monophos



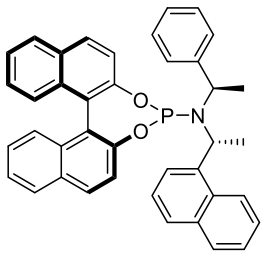
(*R,R,R*)-L$_6$



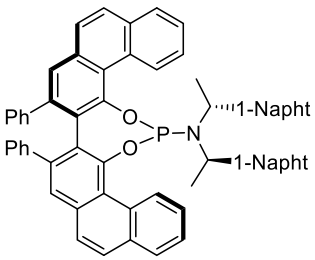
(*R,S,S*)-L$_6$



(*R,R,R*)-L$_7$



***(S,R,R)*-L$_8$**

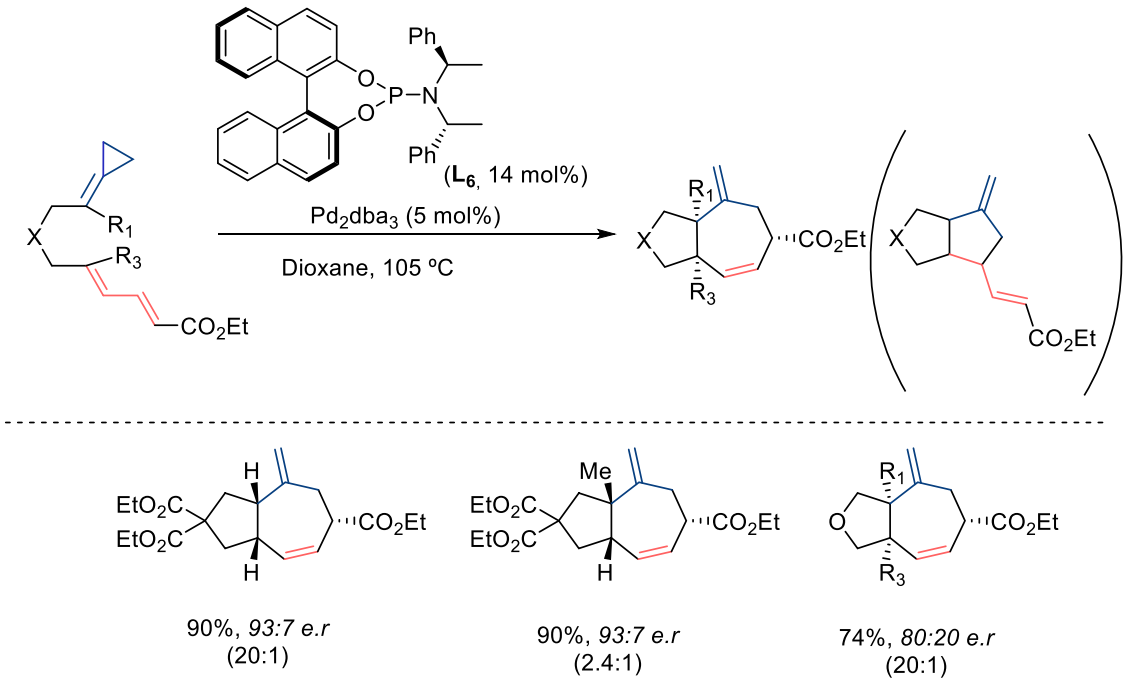


(*R,R,R*)-L$_5$

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[92] Durán Verdasco, Juan **2011** "*Cicloadiciones catalíticas y asimétricas de alquilidenciclopropanos mediante complejos de paladio",* PhD thesis, University of Santiago de Compostela, Santiago de Compostela.

Based on the same type of Pd-phosphoramidite catalyst, our group has also developed an asymmetric variant of the (4+3) cycloaddition between ACPs and diene. After a rigorous investigation it was found that phosphoramidite **L_6** was the best ligand in combination with Pd_2dba_3 as Pd(0) source. Thus, the cycloaddition of diene-tethered ACPs delivered the desired cycloadducts with er's up to 93:7. However, the enantioselective reaction only works well with terminally unsubstituted dienes or with an EWG at the *trans*-terminal position. Moreover, as in the case of the (3+2) cycloaddition of alkene-tethered ACPs, slightly modifications on the tether led to significant changes in the *er* of the reaction. It is worth to mention that the chemoselectivity of the reaction was not always controlled, since in several cases the (3+2) cycloadduct was also detected in considerable proportions (**Scheme 52**).

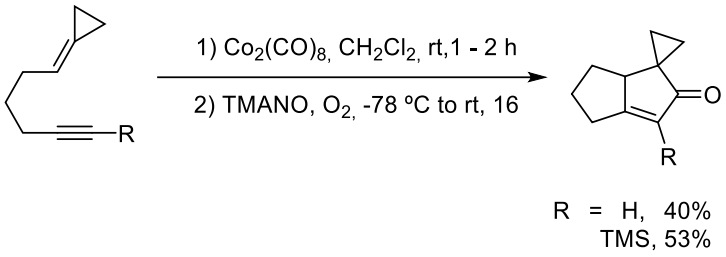


***Scheme 52**. Pd catalysed enantioselective (4+3) cycloaddition of diene-tethered ACPs. In parenthesis (4+3): (3+2) ratio.*

1.5 Cobalt promoted formal cycloadditions of ACPs and related strained systems

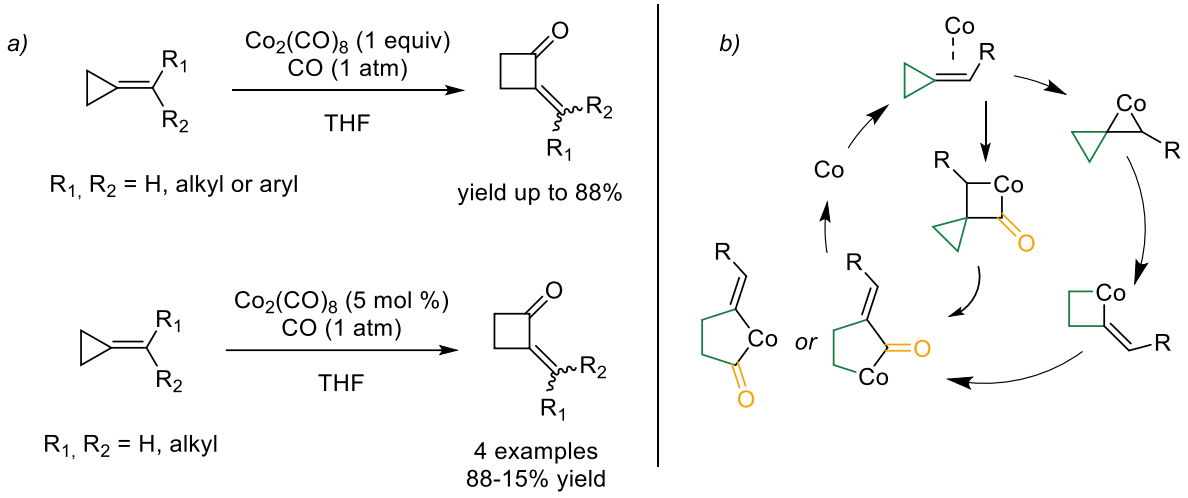
As commented before, there is an increasing interest in using earth abundant metals like cobalt in catalytic reactions, not only because of environmental issues but also in terms of obtaining new reactivity profiles. Cobalt catalysts have been used in formal cycloaddition reactions of unsaturated precursors (**Introduction, page 29 and 37**), but very scarcely with substrates exhibiting strained rings, like ACPs. Most reports in this topic have been focused on Pauson-Khand reactions, where the high reactivity of the exocyclic alkene of the ACP allows the reaction to work more efficiently compared to

other types of alkenes. In the example shown in **Scheme 53,** the alkyne- tethered ACP reacts with an stoichiometric amount of $Co_2(CO)_8$ to afford the σ,β-unsaturated cyclopentanone in moderate yield.



Scheme 53. *Pauson-Khand reaction of alkyne-tethered ACPs by cobalt catalyst.*

De Meijere also developed a (3+1) formal cycloaddition of methylencyclopropanes and carbon monoxide to render 2-alkylidenecyclobutanes (**Scheme 54a**).[93] Although some catalytic examples were included in the manuscript, stoichiometric amounts of the metal were typically required to achieve good yields. Mechanistically, the reaction is proposed to be initiated with the opening of the cyclopropane through a β-carbon elimination followed by CO insertion and reductive elimination (**Scheme 54b**). However, the authors did not rule out the possibility of a first cyclization between CO and the exocyclic alkene to afford a cobaltacyclobutanone that evolves by β-carbon elimination to open the spirocyclopropane. Finally, a reductive elimination would regenerate the catalyst and afford the corresponding cyclobutanone.

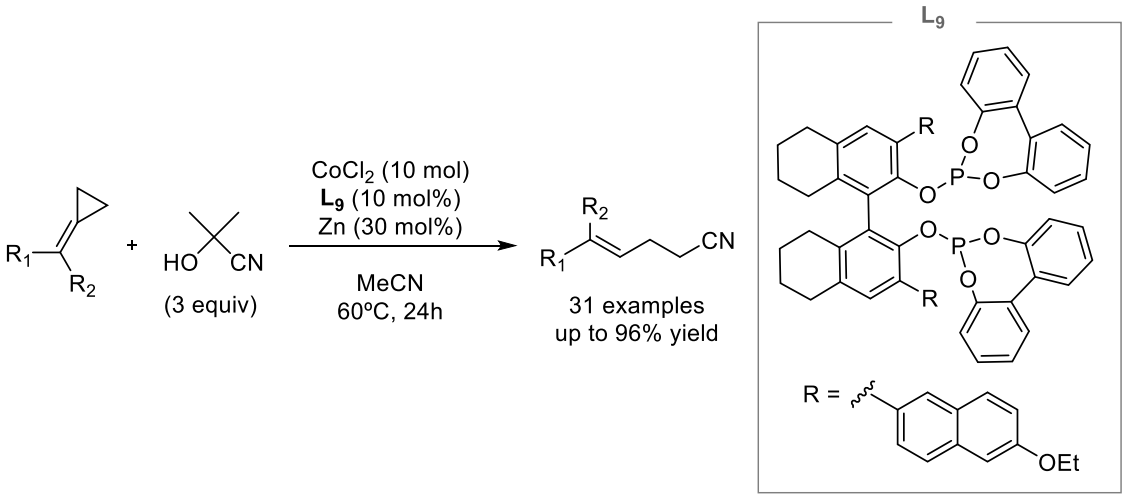


Scheme 54*. a) Carbonylation of ACPs mediated by cobalt. b) Mechanistic proposal.*

At the time we started the research associated to this PhD thesis, there were not additional examples of Co-catalysed annulations with ACPs. Other cobalt-catalysed processes involving ACPs beyond annulation reactions were also uncommon. One of the

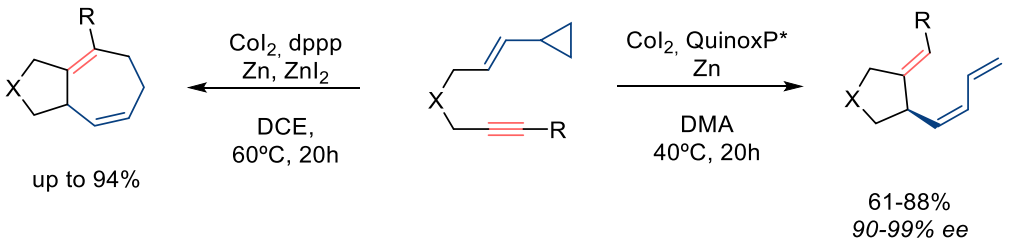
[93] Kurahashi, T.; de Meijere, A. *Angew. Chem. Int. Ed*. **2005**, *44*, 7881 –7884.

few reported cases, recently disclosed, consists of a cobalt-catalysed hydrocyanation of ACPs with acetone cyanohydrin, a reaction that provides homoallylic nitriles in good yields. The reaction is efficiently catalysed by a low valent cobalt catalyst in situ generated from $CoCl_2$ and Zn and a very bulky bisphosphite ligand (**L9**, **Scheme 55**).[94]



Scheme 55. *Co-catalysed hydrocyanation of ACPs.*

While the use of cobalt catalysts to promote reactions of ACPs was almost unprecedented, there was only one example of formal cycloadditions with alkenylcyclopropanes. Yoshikai and co-workers reported in 2018 a low-valent cobalt-catalysed intramolecular (5+2) cycloaddition between vinylcyclopropanes and alkynes (**Scheme 56**).[95] Interestingly, depending on the ligand and solvent employed, the reactivity of this system can be tuned towards a cycloisomerization product. Curiously, although the authors reported a successful enantioselective variant of this cycloisomerization with a chiral cobalt catalyst, the asymmetric version of the (5+2) cycloaddition was not achieved.

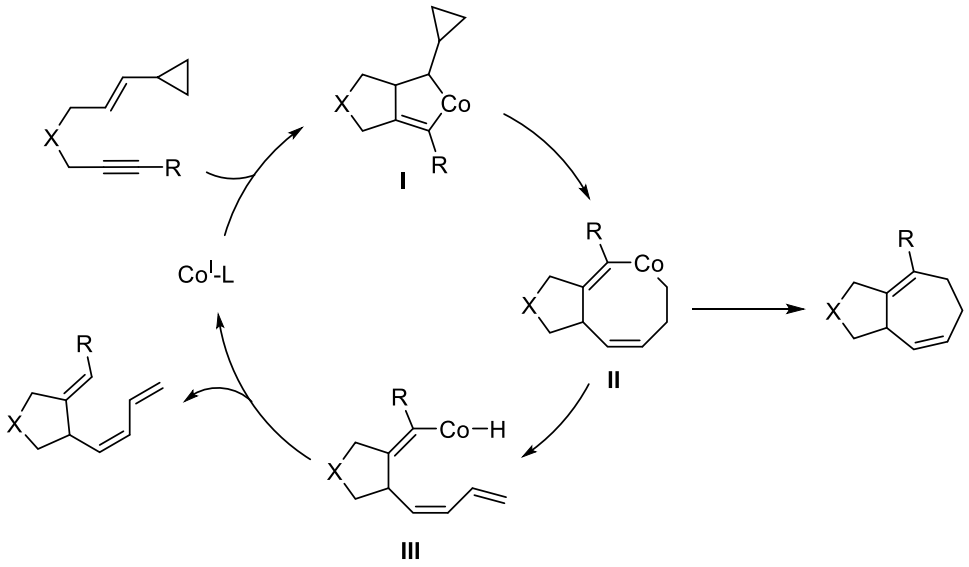


Scheme 56. *Intramolecular Co-catalysed cycloaddition of VCPs and alkynes.*

Based on DFT calculations the authors proposed that the reaction is initiated by an oxidative cyclization between the vinylcyclopropane and the alkyne. The resulting

[94] Jiao, M.; Fang, X. *Org. Lett*, **2022**, *24*, 8890-8894.
[95] Wu, C.; Yoshikai, N. *Angew. Chem. Int. Ed.* **2018**, *57*, 6558 –6562.

cobaltacycle **I** evolves then through a β-carbon elimination with the opening of the cyclopropyl ring to give the cobaltacyclooctadiene intermediate **II.** Here, two possibilities arise: through a reductive elimination, the (5+2) product might be obtained or, an alternative a β-hydride elimination can deliver the homo-ene product after an eventual C-H reductive elimination (**Scheme 57**).



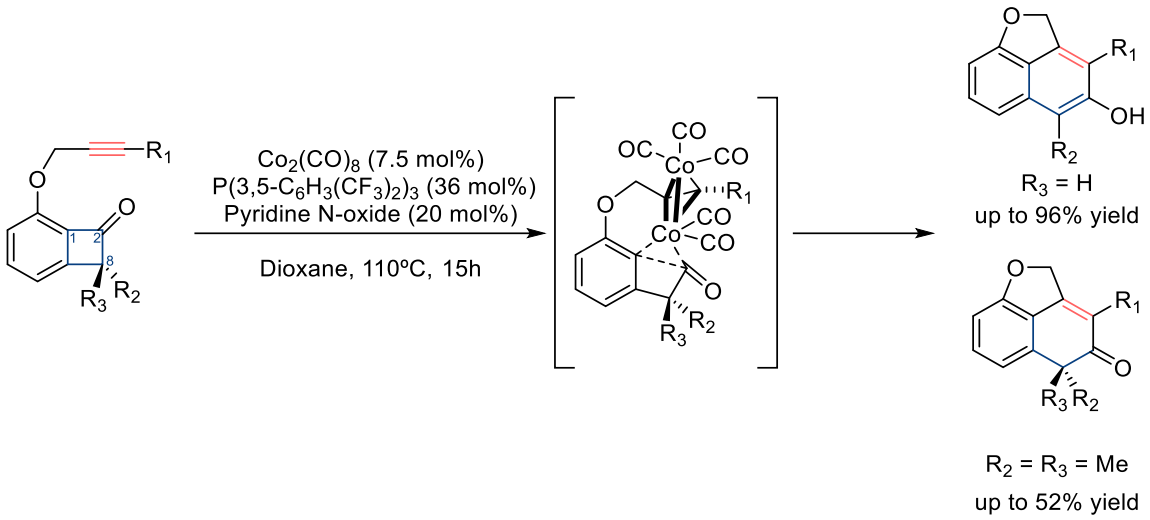
Scheme 57. *Mechanistic proposal based on DFT calculations for the intramolecular Co-catalysed cycloaddition of VCPs and alkynes.*

As mentioned in the introduction of this manuscript (**page 29, Scheme 17**), the Dong group reported a Rh intramolecular cycloaddition of benzocyclobutanones and alkynes towards the synthesis of polysubstiuted naphthols. However, substituents in C_8 ($R_2 \neq H$) were not tolerated or afforded the corresponding products in low yields. The authors of this work proposed that due to steric clash, the initial oxidative addition is difficult, thus hampering the reaction.

In this context, the same group found later that using a Co(0) complex is possible to promote the cycloaddition of benzocyclobutanones and alkynes and solve this drawback (**Scheme 58**). [96]

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[96] Zhu, Z.; Li, X.; Chen, S.; Chen, P.; Billet, B. A.; Huang, Z.; Dong. G. *ACS Catal*. **2018**, *8*, 845–849.



***Scheme 58**. Cobalt catalysed cycloaddition of benzocyclobutanones and alkynes.*

Mechanistically, contrary to what was proposed with Rh, the reaction under cobalt catalysis is initiated by the coordination to the alkyne and direct cleavage of the C_1-C_2 bond of the benzocyclobutanone. Because of this different coordination ability, no steric clashed occurred during the C-C bond activation step and substitutions at the C_8 are well tolerated. This work exemplifies the mechanistic particularities that 3d row metals could bring with respect to more frequently studied 4d or 5d transition metals, and how their reactivity can be complementary.

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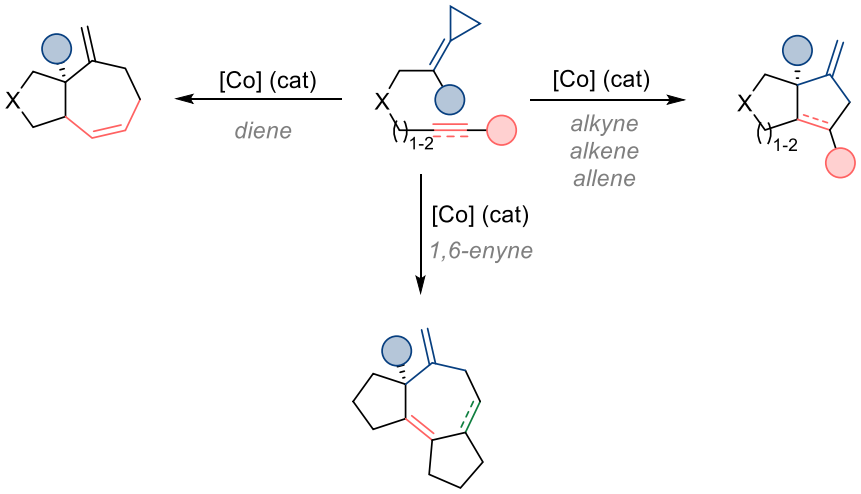
2. Objectives

As mentioned in the introduction of this chapter, the intramolecular cycloadditions of ACPs to construct medium-sized carbocycles have been widely explored by our group and others. However, despite these efforts, there are still important challenges to be addressed. In particular, very few examples of highly enantioselective methodologies have been reported. Moreover, the reactivity of 3d transition metals like cobalt with ACPs has not really been explored.

Considering the mechanistic singularities of low valent cobalt catalysts with other cyclic strained systems, we envisioned that this metal could open new reaction alternatives in the chemistry of ACPs.

On these bases, we decided to evaluate the reactivity of ACPs with earth abundant cobalt catalysts. Specifically, we questioned whether alkyne-, alkene-, diene- and allene-tethered alkylidenecyclopropanes would react with low valent cobalt catalyst in a formal cycloaddition manner. Moreover, substrates that lead to multicomponent cycloadditions could also be explored.

On the other hand, considering the outstanding potential of low valent chiral cobalt catalysts in other enantioselective transformations, the exploration of enantioselective variants of the different cycloadditions with ACPs will also be addressed.



***Scheme 59**. Proposed intramolecular cycloadditions mediated by a low valent cobalt catalyst.*

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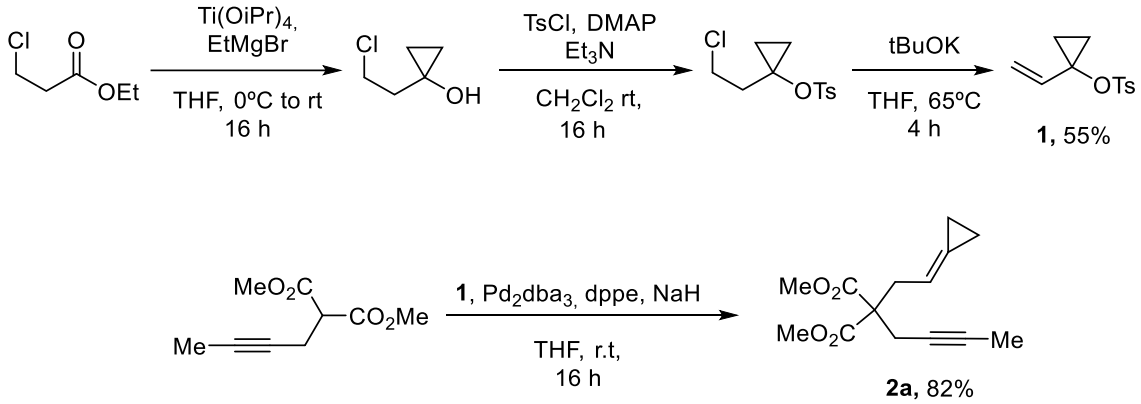
3. Results and Discussion

3.1. (3+2) cycloadditions of alkyne-tethered ACPs: enantioselective versions

The (3+2) intramolecular cycloaddition of ACPs and alkynes has been studied with Pd, Ni, Ru or Rh metal complexes, but never with cobalt catalysts. Therefore, our initial efforts were focused to explore the viability of using cobalt catalysts, and eventually develop an enantioselective version with chiral phosphine ligands.

3.1.1 Development of the methodology

To test the viability of a cobalt-catalysed (3+2) cycloaddition between alkynes and ACPs, we initially prepared the model enyne **2a**. As shown in **Scheme 60,** this precursor was easily synthesized through a Pd catalysed allylic nucleophilic substitution between propargyl malonate and the vinyl tosylate **1**. This key intermediate, can be prepared in a multigram scale with an overall 55% yield following a well-established procedure which involves a Kulinkovich cyclopropanation, a tosylation and a base-promoted elimination (**Scheme 60**).[97]



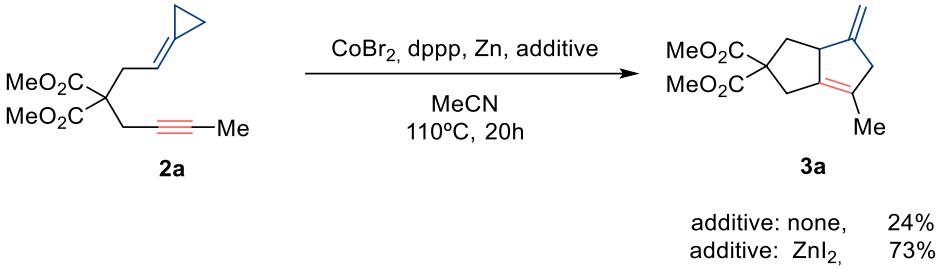
Scheme 60. *Synthesis of vinyl tosylate **1** and model ACP **2a.***

With the model substrate in our hands, our first goal was to analyse the reactivity of a low valent Co catalyst in the reaction, species that could be generated *in situ* by mixing a Co(II) salt with a reductant and the corresponding ligand, typically a bisphosphine. We initially selected a combination of $CoBr_2$ as cobalt(II) source, Zn as reductant, and dppp as ligand, since these conditions had been found successful by Yoshikai for Co-catalysed (5+2) cycloadditions of VCPs. Gratifyingly, treatment of **2a** with these catalyst precursors in MeCN at 110°C for 20 h, led to the formation of the cycloadduct **3a**, which could be

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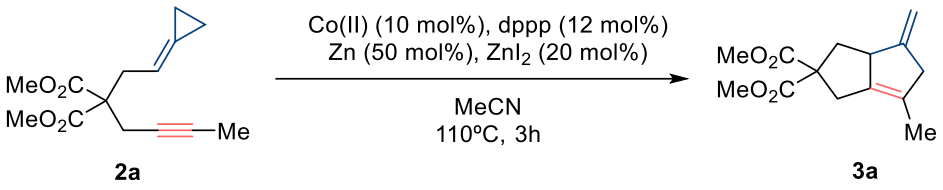
[97] Ojo, O. S.; Inglesby, P. A.; Negru, D. E.; Evans, P. A. *Org. Chem. Front.*, **2014**, *1*, 821-824.

isolated in 24% yield. Noticeably, the yield could be significantly improved when ZnI_2 was added to the reaction mixture (**Scheme 61**). This additive has been previously postulated to act as a halide abstractor, thus favouring the formation of cationic cobalt species.[38]



Scheme 61. *First reaction conditions analysed for the (3+2) cycloaddition of alkyne-tethered ACPs.*

Encouraged by this result, a further analysis of the reaction conditions was performed, aiming to improve the efficiency of the transformation. First of all, several commercially available Co(II) salts were tested using Zn (50 mol%) and ZnI_2 (20 mol%) as additives for promoting the formation of the low-valent Co active species, in CH_3CN at 110°C. (**Table 2**). From the different Co-halide sources, no one improved the result previously obtained with $CoBr_2$. $Co(acac)_2$ only provided the cycloadduct in a modest 34% yield. Curiously, the cationic $Co(BF_4)_2{\cdot}6H_2O$ did not give the cycloadduct. When the preformed $Co(dppp)Br_2$ complex, which already features the bisphosphine dppp coordinated to the cobalt centre, was used instead of $CoBr_2$ and dppp, the adduct **3a** was obtained with the same yield (72%).

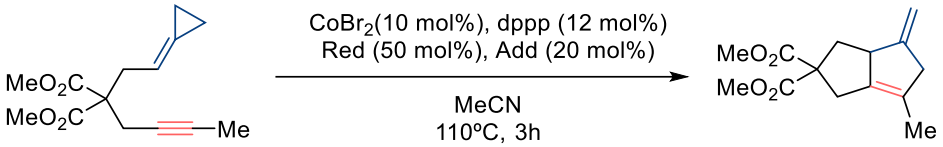


Entry	[Co(II)]	% yield
1	$CoBr_2$	73
2	$CoCl_2$	61
3	CoI_2	71
4	$Co(acac)_2$	34
5	$Co(BF_4)_2{\cdot}6H_2O$	-
6	$Co(dppp)Br_2$	72

Table 2*. Evaluation of different Co(II) sources for the (3+2) cycloaddition of* ***1a****.*

In addition to other cobalt sources, different reductants and additives were also screened (**Table 3**). Reductants commonly employed to reduce Co(II) salts *in situ*, like

Zn, Mg, or Mn,[101] were tested under otherwise identical reaction conditions, but only Zn was effective. This result could be slightly improved when an anionic scavenger, such as $NaBAR^F$, was used instead of ZnI_2. Finally, during the screening of reductants, it was found that the use of indium provides a slightly better result than Zn/ZnI_2. Curiously, in this case the addition of InI_3 as additive did not make any significant improvement in the reaction outcome.



2a **3a**

Entry	Reductant (50 mol%)	Additive (20 mol%)	Yield (%)
1	Zn	ZnI_2	73
2	Zn	-	24
3	Zn	$NaBAr^F$	30
4	Mn	-	-
5	Mg	-	-
6	Et_2Zn	-	traces
7	In	-	82
8	In	InI_3	86

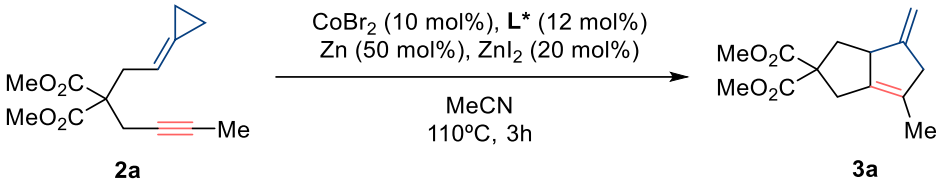
Table 3. *Evaluation of different reductants and additives for the (3+2) cycloaddition of* ***1a****,*

Once we found promising results in the racemic cobalt (3+2) cycloaddition, and considering that the reaction requires bis-phosphine ligands, we explored the viability of a more challenging enantioselective (3+2) variant, something that, as we mentioned in the introduction, had never been accomplished, even with any other transition metal catalysts using chiral ligands. Therefore, a range of phosphines were tested instead of dppp, keeping all other reaction parameters identical ($CoBr_2$ as cobalt source, Zn as reductant and ZnI_2 as additive and MeCN as solvent at 100°C) (**Table 4**).

A variety of bidentate chiral phosphines were evaluated, including several with C_2-symmetrical ligands with axial chirality (e.g. SEGPHOS, BINAP, GARPHOS), with carbon-based chirality (BPE, Chiraphos, BDPP) or phosphorous-central quirality (QuinoxP*, BenzP*), as well as others with non C2-symmetrical ligands such as Josiphos SL-J001-1. Morever, a P-N ligand such as QUINAP was also tested.

From all of them, BINAP and Ph-Garphos stood out above the rest, affording the cycloadduct **3a** with an excellent *95:5* er. Despite their equal enantioselectivity, the efficiency of both ligands in terms of reaction yield was very different. Thus, while when

using (*R*)-Ph-Garphos the reaction only gave a 16% yield (32% conversion) after 3 h at 110 °C, with (*S*)-BINAP the yield was much better (72%). Therefore, BINAP was selected as the ligand of choice, which is also highly attractive since it is one of the most affordable chiral ligands in the market.



Entry	**Ligand (L*, 12 mol%)**	**Yield (%)**	**er**
1	(*S*)-SDP	33	0
2	(*R,R,S,S*)-DUANPHOS	71	70:30
3	(*R,R*)-Me-DUPHOS	54	71:29
4	(*S,S*)- CHIRAPHOS	25	57:43
5	(*S,S*)-Ph-BPE	-	-
6	(*R,R*)-QUINOX-P*	65	84:16
7	(*S*)- DTBM-SEGPHOS	31	91:9
8	(*S*)- Ph-BIBOP	69	91:9
9	(*R,R,R*)-Ph-SKP	22	53:47
10	(*R*)-Ph-GARPHOS	16	95:5
11	(*S*)-BINAP	72	95:5
12	(*S*)-Xyl-BINAP	77	90:10
13	(*S*)-Tol-BINAP	80	91:9
14	(*S*)-C_3-TUNEPHOS	80	91:9
15	(*S*)-QUINAP	56	80:20
16	(*S*)-SYNPHOS	81	89:11
17	(*S*)-DIFLUOROPHOS	80	84:16
18	(*S*)-SEGPHOS	68	92:8
19	(*S*)-MeO-BIPHEP	-	-
20	(*R,R*)-BenzP*	-	-
21	(*R*)-JOSHIPHOS-SL-J001-1	-	-

Table 4. *Evaluation of different asymmetric ligands for the (3+2) cycloaddition of* ***1a****.*

To conclude the optimization, we also checked the influence of the solvent and temperature (**Table 5**). Curiously, the yield and the *er* slightly decreases at lower temperatures. The maximum value was obtained at 110°C, while heating at 120°C did not bring any further improvement. Moreover, from all the solvents evaluated, 1,2-dichloroethane (DCE) provided the best yield, while keeping the excellent

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enantioselectivity, so that the cycloadduct **3a** was obtained in a good 83% yield and a 95:5 *er*, at 110°C.

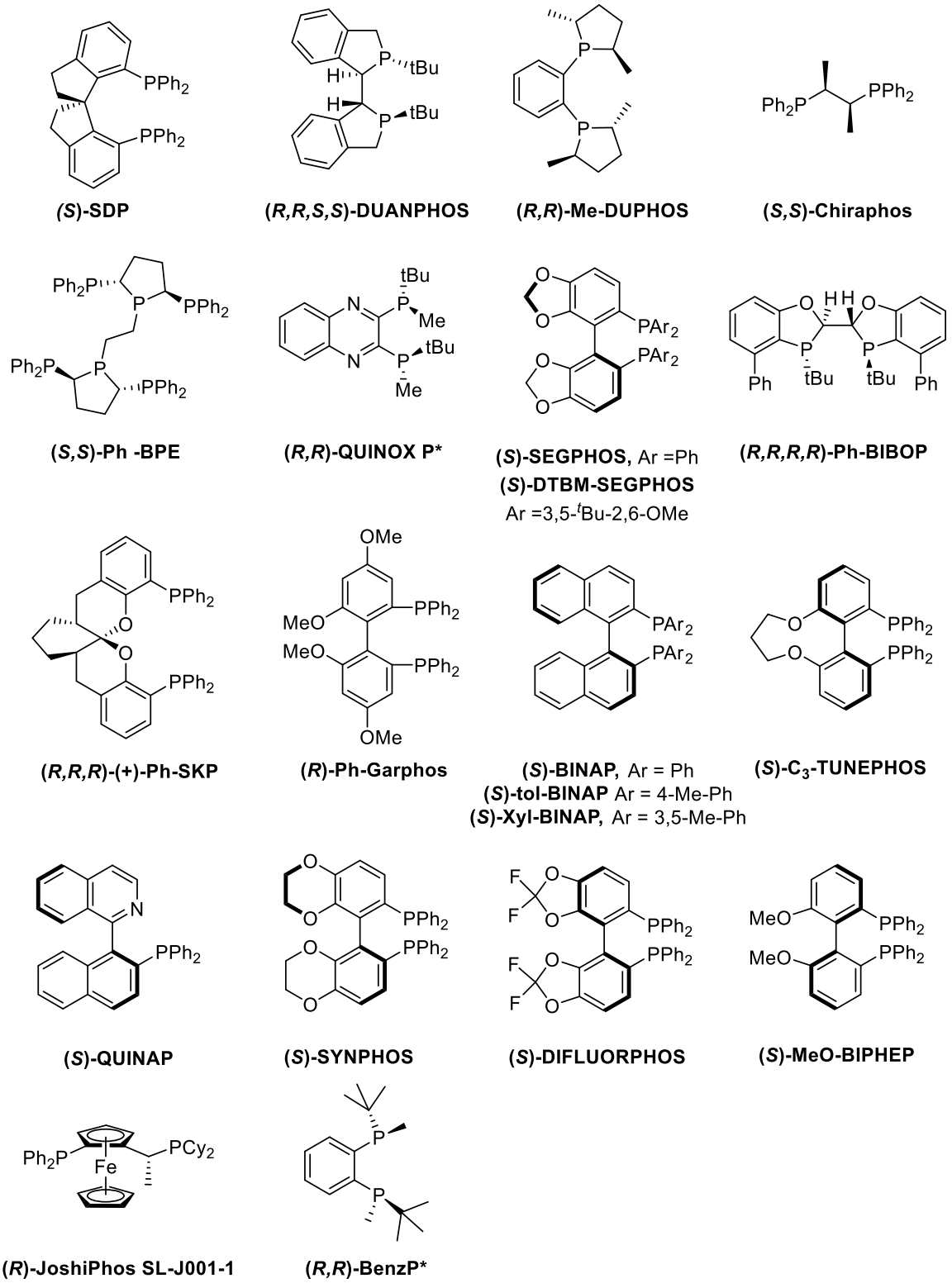
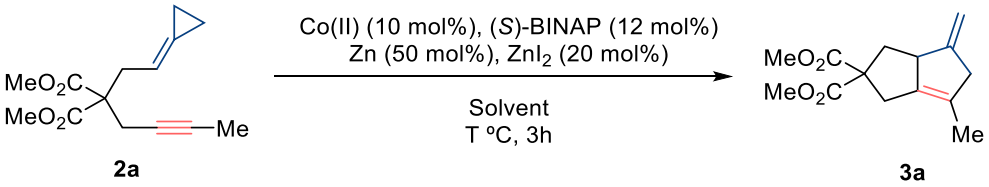


***Figure 7**. Structure of the chiral ligands tested for the development of a (3+2) cycloaddition of **2a**.*

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2a **3a**

Entry	Solvent	Temperature (T)	Yield (%)	er
1	CH_3CN	120	72	95:5
2	CH_3CN	110	72	95:5
3	CH_3CN	100	58	91:9
4	CH_3CN	90	44	89:11
5	Toluene	110	-	-
6	1,2-DCE	110	83	95:5
7	DMF	110	-	-

Table 5. *Effect of the solvent and temperature on the enantioselective (3+2) cycloaddition of* ***1a***

To sum up, the best conditions consisted of the use of $CoBr_2$ as cobalt source (10 mol%), (S)-BINAP as chiral ligand (12 mol%), Zn (50 mol%) as reductant, ZnI_2 (20 mol%) as halogen abstractor, in 1,2-DCE at 110°C.

At this point, we evaluated the scope of the asymmetric transformation. First, the alkyne substitution pattern was assessed using different ACP precursors that hold a germinal diester in the connecting-tether. Thus, the methyl group at the alkyne terminus can be substituted by other alkyl groups like butyl (**2b**) to give the expected adduct **3b** (85% yield, 96:4 er) and by a bulkier methyl tertbutylsilyl ether, which provided the cycloadduct **3c** in 84% yield, and with a 92:8 er. Interestingly, the reaction is compatible with free hydroxyl groups as it can be seen in the reaction of **2d** that gave the corresponding cycloadduct **3d** in 84% yield and 92:8 er. The allyl derivative **3e** was also efficiently formed in a good 73% yield and with enantiomeric ratio of 96:4.

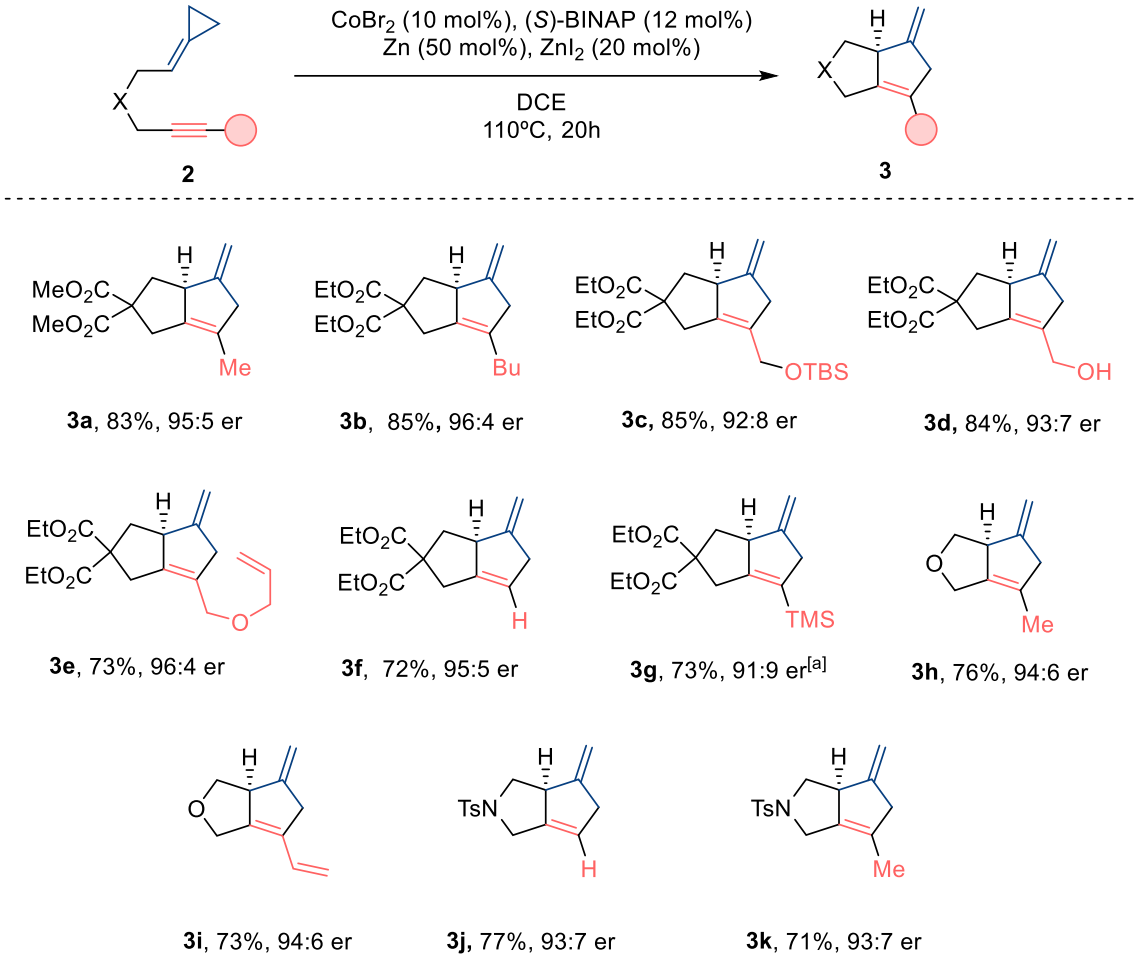
Remarkably, an unsubstituted alkyne, that could a priori yield cobalt acetylides and therefore fail in the desired annulation,[98] gave the desired (3+2) adduct **3f** in good 72% yield and with a 95:5 er.

Besides alkyl chains, the alkyne can also be substituted with other groups such as a bulky TMS to provide its corresponding adduct **3g** in good yield and with high enantioselectivity. Curiously, in this case the combination of Zn/ZnI_2 as reductant cocktail led to low conversion (20%), while the mixture of In/InI_3 turned out to be more effective instead (73% yield, 91:9 er).

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[98] Ruhl, K. E.; Rovis, T. *J. Am. Chem. Soc.* **2016**, *138*, 48, 15527–15530.

ACPs with heteroatoms in the connecting tethers also participate in the cycloaddition and, therefore, the (3+2) adduct **3h**, with an ether connector, was obtained in 76% yield and an excellent 94:6 er. A very interesting example is illustrated in the cycloaddition delivering the adduct **3i**. Here, an 1,3-enyne functional group, which usually presents a particular reactivity in presence of a low valent cobalt catalyst,[99] undergoes the desired cycloaddition without the detection of any side product. Besides ether, malonates and sulfonamides can also be present in the connecting tether, so that the cycloadducts **3j** and **3k** can be obtained in good yields and good asymmetric control.



***Scheme 62**. Scope of the enantioselective intramolecular (3+2) cycloaddition of alkyne-tethered ACPs. [a] Used of In/InI₃ instead of Zn/ZnI₂*

Interestingly, product **3k** could be crystallized and further characterized by X-ray analysis. Thus, it could be confirmed that the absolute configuration of the chiral centre of the cycloadduct corresponds to the (*S*)-enantiomer (**Figure 8**).

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[99] Nishimura, A.; Tamai, E.; Ohashi, M.; Ogoshi, S. *Chem. Eur. J.* **2014**, *20*, 6613 – 6617.

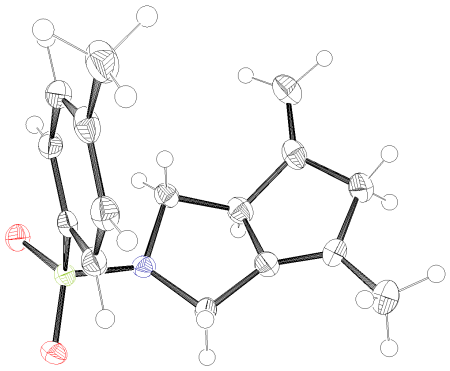
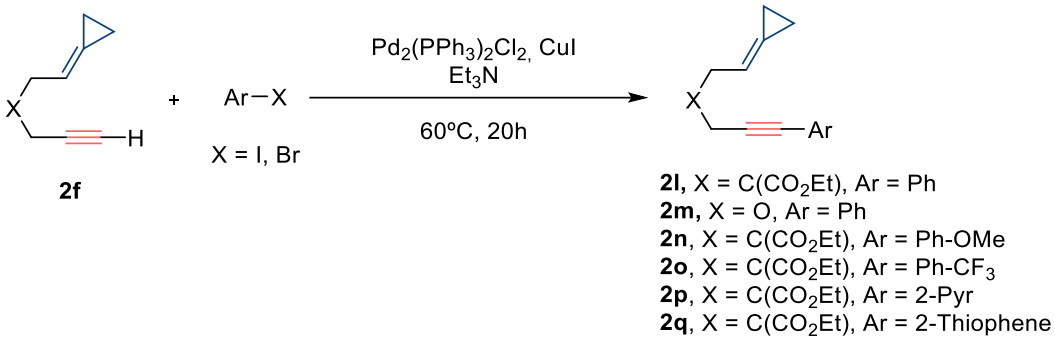


Figure 8. *Crystal structure of cycloadduct* ***3k****.*

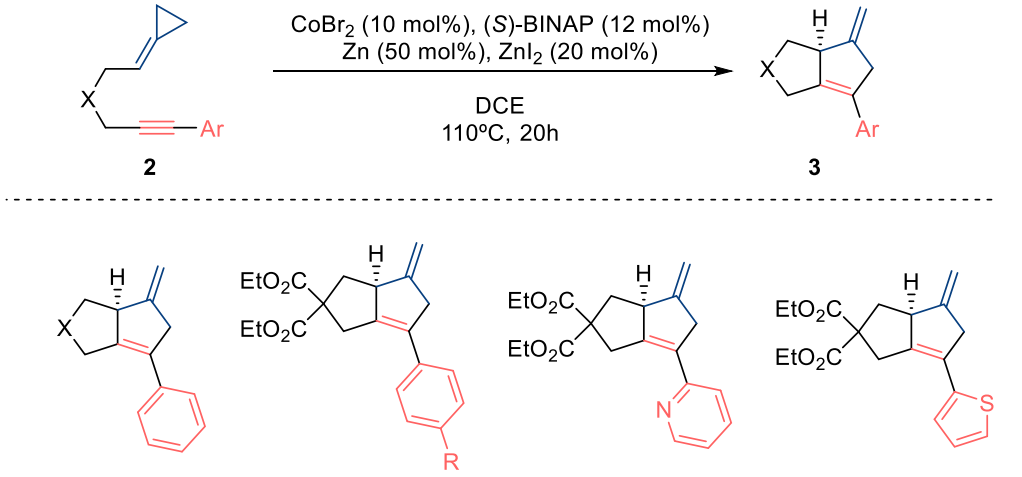
We next checked whether the reaction could also be performed with alkynes bearing aromatic and heteroaromatic substituents. Theses substrates were easily synthesized through a Sonogashira cross-coupling from the precursor **2f** as illustrated in **Scheme 63.**



Scheme 63. *Sonogashira cross coupling for the synthesis of ACPs containing aromatic alkynes.*

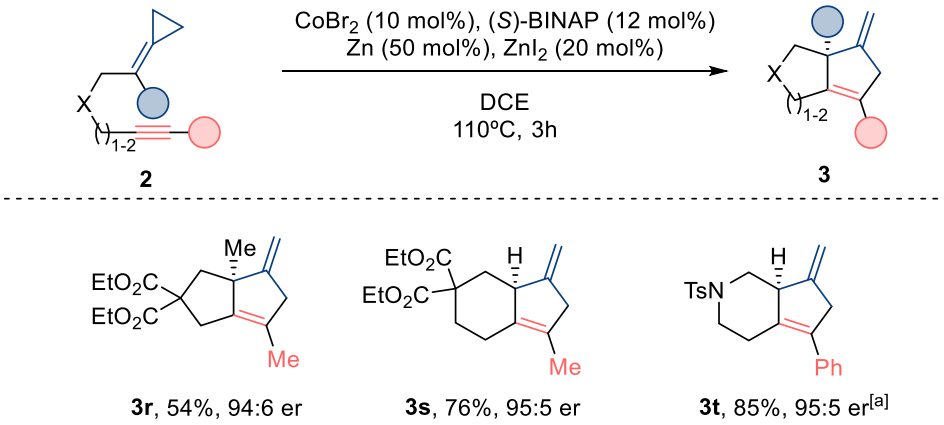
ACP precursors **2l** and **2m** with alkynes bearing a simple phenyl group afforded the corresponding cycloadducts in moderate or good yields and with good enantiomeric ratios. However, the cycloaddition of precursor **2m**, equipped with an oxygenated tether, required the use of In/InI_3 as reductant couple, since the use of Zn/ZnI_2, under otherwise identical reaction conditions, led to recovery of the starting material. Phenyl groups substituted at their *para* position with electron rich (-OMe, **2n**) and electron withdrawing (-CF_3, **2o**) functional groups were also tolerated at the alkyne moiety. Nevertheless, with the less reactive substrate **2o**, which holds a CF_3 group at the *para* position, the use of In/In_3 was again required. The use of In/InI_3 was also key for the cycloaddition of the derivative **2p**, which bears a pyridine moiety attached to the alkyne. Thus, cycloadduct **3p** was obtained in a moderate 56% yield, but with an excellent 94:6 er. Moreover, other heteroaromatic rings like a thiophene were equally tolerated, so that **3q** could be obtained in 63% yield and good 91:9 er.

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Scheme 64. *Scope of the enantioselective intramolecular (3+2) cycloaddition of aromatic alkyne-tethered ACPs. [a] In/InI₃ was used instead of Zn/ZnI₂*

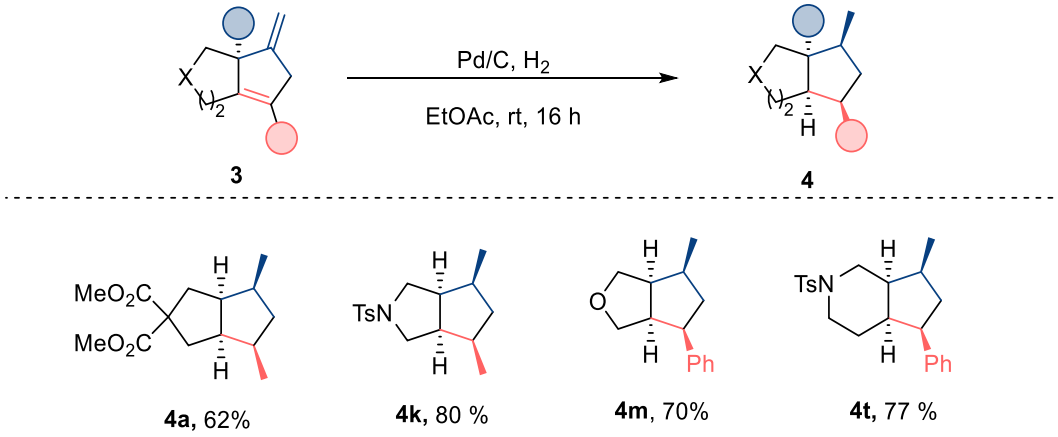
The robustness of the transformation was further analysed by testing a precursor that holds a substituent at the internal position of the ACP alkene or bearing longer connecting tethers between the alkyne and the ACP. Thus, the cycloaddition of **2r**, which bears a methyl at the ACP internal position provided the adduct **3r**, bearing a fully substituted quaternary carbon centre at the ring fusion, in 54% yield and an excellent 94:6 er. On the other hand, the preparation of 6,5-bicyclic systems was also possible, just by elongating the connecting tethered in one methylene unit. Thus, the reaction of an alkyl substituted alkyne **2s** afforded the corresponding cycloadduct **3s** in 76% yield and 95:5 er, whereas the reaction of the NTs derivative bearing a phenyl group at the alkyne was also possible using In/InI$_3$ as reductant, providing **3t** in 85% yield and 95:5 er.



Scheme 65*. Scope of the enantioselective intramolecular (3+2) cycloaddition of alkyne-tethered ACPs. [a] Carried out with In/InI₃ instead of Zn/ZnI₂*

To further prove the synthetic potential of our methodology, a brief synthetic manipulation of the cycloadducts was performed. Thus, when cycloadducts **3a**, **3k, 3m**

and **3t** were submitted to classical hydrogenation conditions with Pd/C and H_2 (1 atm), their respective, totally reduced carbocycles, were obtained. in good yields. As shown in **Scheme 66,** different functional groups in the connecting tether were tolerated (malonate, ether or tosylamides), as well as alkyl or aromatic substituents at the alkynes. Moreover, the 6,5-byciclyc adduct **3t**, containing an azaheterocyle scaffold, was also diastereoselectively hydrogenated, leading to the saturated carbocycle **4d** in 77% yield, as a single diastereoisomer.



***Scheme 66**. Diastereoselective hydrogenation of the (3+2) cycloadduct.*

Interestingly, the crystal structure of **4k** could be elucidated, allowing us to corroborate the *cis*-fused stereochemistry of the fully saturated bicyclic systems.

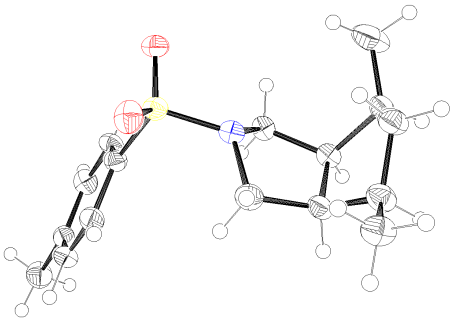


Figure 9.** Crystal structure of cycloadduct **4k.

3.1.2 Mechanistic studies

With the scope of the reaction and synthetic utility well stablished, it was timely to study the mechanistic scenery. Initially, we focused on determining the oxidation state of the low valent active cobalt species that is formed in situ from the Co(II) source and the reducing additive. A priori, according to related precedents,[100] two possible redox cycles could be considered, a Co(0)/Co(II) catalytic cycle or a Co(I)/Co (III) counterpart. To shed

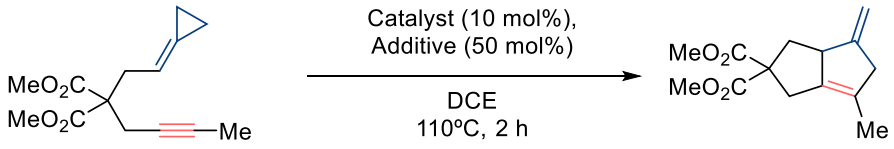
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[100] Hapke, M.; Hilt, G.; *Cobalt Catalysis in Organic Synthesis: Methods and Reactions.* Wiley-VCH, Weinheim, **2020**.

some light on this issue, a series of control experiments were performed using cobalt complexes in different oxidation states (**Table 6**).

First, to see whether a Co(0) complex could be the active catalyst, we tested a mixture of $CoBr_2$/dppp in the presence of Et_2Zn, which is a strong reductant and has been shown to generate Co(0) species *in situ in* related low valent cobalt-catalysed hydroacylation processes.[101] Interestingly, no reaction was observed at 110 °C after 3 h, suggesting that the participation of Co(0) species is unlikely (**Table 6, entry 1**). Moreover, treatment of **2a** with other Co(0) complexes such a as $Co(PMe_3)_4$ (**Table 6, entry 2**) or $Co(PMe_3)_4$/BINAP (**Table 6, entry 3**) neither provided **3a** nor other identifiable product after heating **2a** at 110°C in 1,2-DCE for 2h.

To check whether the active catalyst could be a Co(I) species, the well-known Co(I) catalyst $Co(PPh_3)Cl$ was synthetized.[102] When the model substrate **2a** was treated with this complex in 1,2-DCE at 110°C, no reaction whatsoever was observed (**Table 6, entry 4**). Moreover, the addition of a bidentante ligand BINAP in order to favour a ligand exchange with the complex $Co(PPh_3)_3Cl$ did not provide any detectable product (**Table 6, entry 5**). However, we were glad to observe that the reaction takes place when ZnI_2, is added to this mixture of $Co(PPh_3)_3Cl$ and BINAP (**Table 6, entry 6**). This reagent has been proposed to act as a halogen (i.e chloride) scavenger and generates the corresponding cationic Co(I) species. Hence, based on these experiments, we propose that our active cobalt species is a Co(I) cationic complex, in situ prepared from the Co(II) precursor, after reduction to Co(I) and halide abstraction.



2a **3a**

Entry	Catalyst	Additive	Yield (%)
1	$CoBr_2$/dppp	Et_2Zn	0
2	$Co(PMe_3)_4$	-	0
3	$Co(PMe_3)_4$/BINAP	-	0
4	$Co(PPh_3)_3Cl$	-	0
5	$Co(PPh_3)_3Cl$/BINAP	-	0
6	$Co(PPh_3)_3Cl$/BINAP	ZnI_2	52[a]

Table 6. *Reactivity evaluation of different cobalt complexes. [a] 92:8 er.*

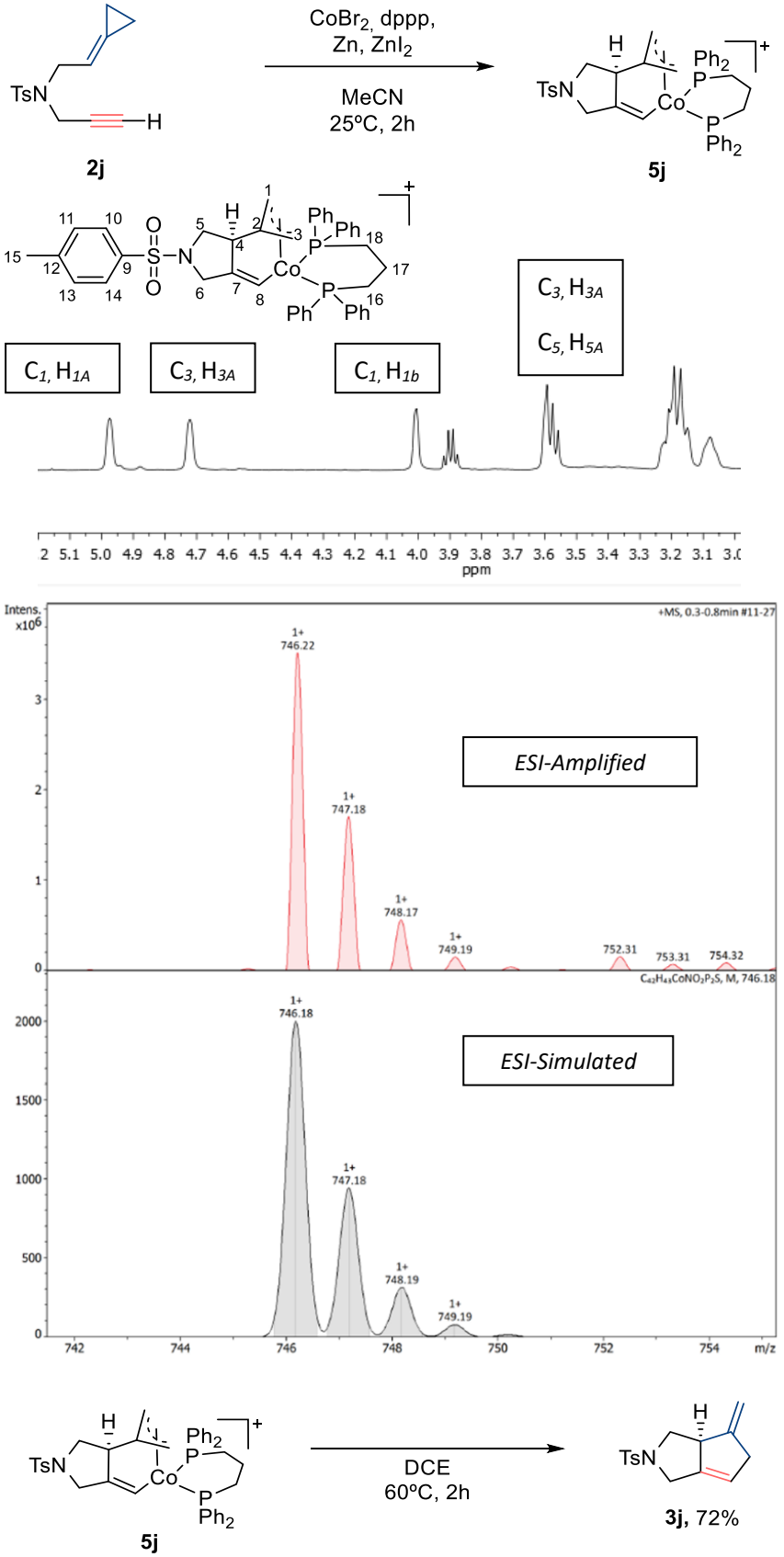
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[101] Kim, D.K.; Riedel, J.; Kim, R. S.; Dong, V. M. *J. Am. Chem. Soc.* **2017**, *139*, 10208–10211.
[102] Brennan, M.R.; Kim, D.; Fout A.R. *Chem. Sci.*, **2014**, *5*, 4831-4839.

To obtain more clues about the elementary steps of our reaction, we carried out stoichiometric experiments, aiming to detect and isolate any catalytically competent, or resting state intermediate. Gladly, after several attempts with different precursors and reaction conditions, we found that mixing the enyne precursor **2j** with stoichiometric amounts of $CoBr_2$, dppp, Zn and ZnI_2 in MeCN at rt for 2h, led to its complete conversion (by TLC) towards a new product, which could be isolated after column chromatography. In order to fully characterize this compound, extensive efforts were made to crystalize the solid and thus confirm its structure through X-ray analysis, but with unsuccessful results. However, NMR analysis was sufficient to suggest its structure. In particular, we observed 3 characteristic signals in the ^1H NMR at 4.97, 4.70, 4.00 *ppm* that, analogously to those previously reported by Evans for the Rh intermediate (see **Scheme 38, page 54**), suggest a π-allyl cobalt complex like **5j.** Moreover, by mass spectroscopy (ESI-MS *m/z* 746.18) we could also confirm the validity of this proposal and corroborate the cationic character of this cobalt complex.

Gratifyingly, heating this pi-allyl complex **5j** at 60 °C for 2h, led to full conversion towards the corresponding cycloadduct **3j** in 72% yield (**Scheme 67**), confirming that it is an intermediate in the catalytic cycle.

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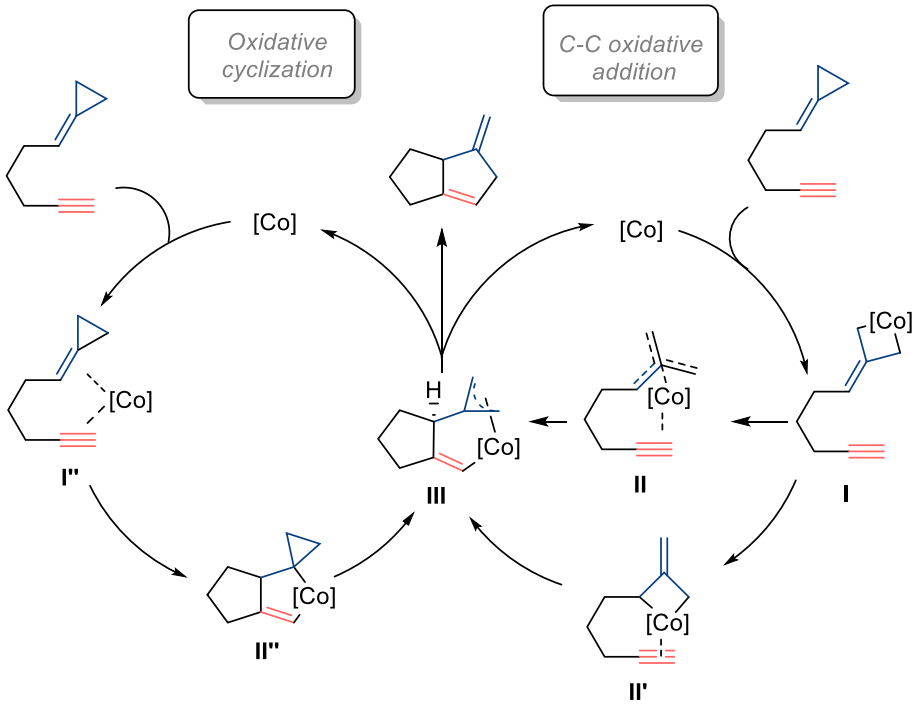
Scheme 67. *Stoichiometric studies of the cobalt catalysed intramolecular (3+2) cycloaddition of alkyne-tethered ACPs. Amplification of the 1H-NMR and ESI-MS spectrums of* ***5j****.*

Considering that the cobalt complex **5j** proved to be an intermediate in the reaction, and taking into account all previously reported precedents on cycloadditions of ACPs with different transition metals,[72,78] as well as precedents of low valent cobalt- catalysed cycloadditions of strained ring systems,[95] we proposed several mechanistic pathways as viable alternatives (**Scheme 68**).

Thus, we initially considered a mechanistic pathway based on what was previously suggested by Evans for the rhodium-catalysed (3+2+n) cycloadditions (see **Scheme 37, page 53**). The cobalt catalysed reaction could be initiated through a distal C-C oxidative addition to afford metallacyclobutane **I**, which could then evolve through a Co-TMM species **II** towards a π-allyl intermediate **III**, like the one we isolated. Finally, reductive elimination would yield the corresponding cycloadduct. Alternatively, considering the previously reported mechanistic Pd catalysed (3+2) cycloadditions of ACPs and alkynes, we did not rule out the possibility of an isomerization of intermediate **I** to the cobaltacyclobutane **II'**, that would then evolve through the migratory insertion of the alkyne to the intermediate **III**.

The reaction could also follow a pathway that would be initiated through an oxidative cyclization to afford a cobaltacyclopentene intermediate **II**' that, after a β-carbon elimination, could afford the previously proposed intermediate **III**, analogous to the one experimentally isolated. Again, reductive elimination from this intermediate would afford the corresponding 5,5-bicyclic adduct.

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Scheme 68. *Mechanistical proposal for the cobalt catalysed intramolecular (3+2) cycloaddition of alkyne-tethered ACPs.*

In order to find out which of these alternatives could be operative, Prof. Israel Fernández (UCM) carried out computational mechanistic studies using precursor **1a'** as model reactant, and cationic complex $[Co(dppp)]^+$ as model Co(I) catalyst.[103]

We first explored a pathway involving a distal coordination and subsequent insertion of $[Co(dppp)]^+$, followed by alkyne-coordination leading to the five-coordinate 18-electron Co(III) trimethylenemethane (TMM) complex **INT1** (via **TS1**). This intermediate could be transformed into the π-allyl complex **INT2** through a migratory insertion of the alkyne, which requires a very low energetic barrier (2.9 kcal/mol). From **INT2** a C-C reductive elimination occurs with a very accessible barrier (12.7 kcal/mol, **TS3**) to deliver the observed 5,5-bicyclic adduct coordinated to the Co(I) catalyst. Finally, metal decoordination releases the observed cycloadduct and regenerates the active Co(I) catalyst (**Figure 10**, pathway in black).

It is worth to mention that the oxidative addition step of the pathway described above, which directly yields the Co(III)-TMM **INT1**, is different from that proposed for related processes involving Rh (I) or Pd (0) catalysts, which were suggested to generate metallacyclobutane intermediates.

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[103] Density Functional Theory (DFT) calculations were carried out at the dispersion-corrected PCM(DCE)-B3LYP-D3/def2-SVPlevel.

On the other hand, a very stable I**NT0'** was located computationally in which both the alkene and alkyne units are coordinated to the metal centre. Interestingly, this species can be transformed into the *exo*-methylene cobaltacyclobutane **INT1'** with an energy barrier of 31 kcal/mol in a highly endergonic process (ΔG = 17.2 kcal/mol). In particular, **INT1'** can be directly transformed into the Co-TMM intermediate **INT1** through a barrierless ligand slippage process.

More importantly, besides this pathway, we additionally found that **INT0'** can alternatively evolve through oxidative cyclization to **INT1''**, with a very accessible barrier (14.1 kcal/mol). Interestingly, this spiro-metallacycle can be transformed into the experimentally isolated intermediate like **INT2** through a cyclopropyl to π-allyl rearrangement. This step is not a canonical β-carbon elimination, but instead consists of a distal opening of the cyclopropyl ring (C-C bond distance of 2.10 Å TS2''), a process reminiscent to that previously proposed for cyclopropyl Rh (III) complexes and other transition metal derivatives.[104] Finally, as in the mechanism described before, a reductive elimination from **INT2** leads to the corresponding cycloadduct.

The high stability of **INT0'**, together with the low activation barriers associated with the subsequent steps, clearly favor the mechanism involving the cobaltacyclopentene **INT1''**. Therefore, this computational analysis revealed that the cobalt catalysed (3+2) cycloaddition of alkyne-tethered ACPs proceeds through a different mechanism than that reported with precious transition metals such as Pd or Rh.

[104] (a) Periana, R. A.; Bergman, R. G. *J. Am. Chem. Soc.* **1986**, *108*, 7346–7355. (b) Omrcen, T.; Conti, N. J.; Jones, W. M. *Organometallics,* **1991**, *10*, 913 –917. (c) Conti, N. J.; Crowther, D. J.; Tivakornpannarai, S.; Jones, W. M. *Organometallics* **1990**, *9*, 175 –184. (d) Parker, K. D. J.; Labat, S.; Sotiropoulos, J. M.; Miqueu, K.; Pimienta, V.; Vendier, L.; Etienne, M. *Eur. J. Inorg. Chem*. **2019**, 4555–4563.

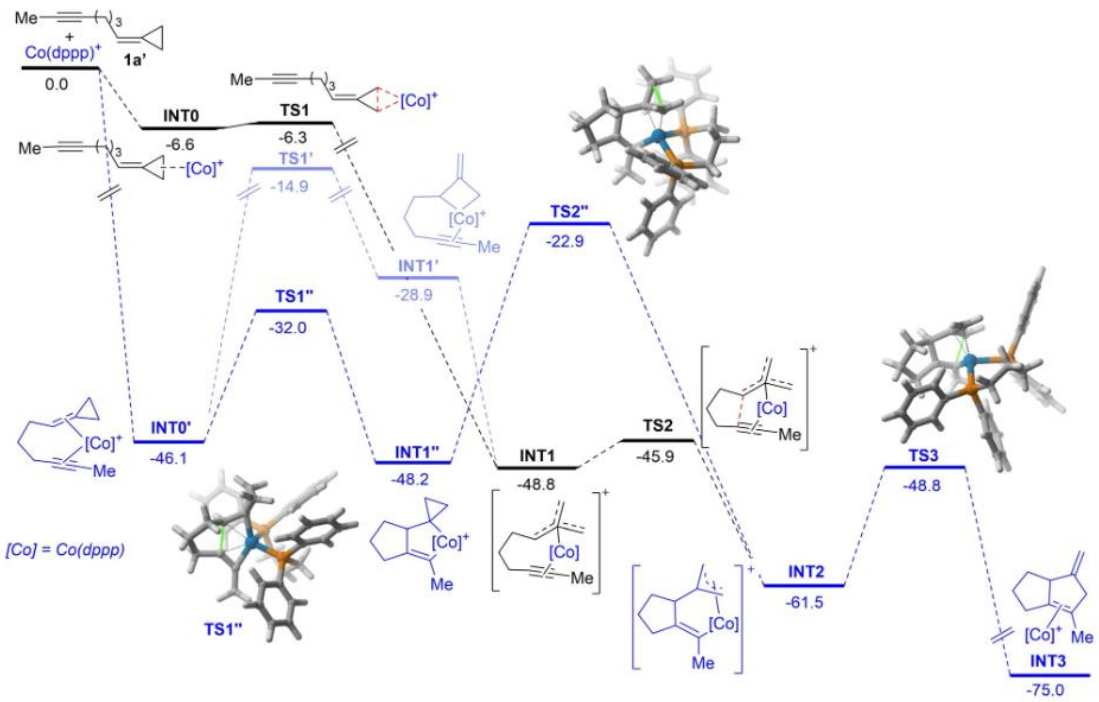


Figure 10. *Computed reaction profile for the reaction model ACP* ***1a'*** *and [Co(dppp)]⁺. Relative free energies (ΔG, at 298 K) and bond distances are given in kcal/mol and Angstroms, respectively. All data have been computed at the PCM(DCE)-B3LYP-D3/def2-SVP level.*

To gain more information on the origin of the enantioinduction, the cyclometallation step that conduces to **INT1''** through **TS1''** was computationally analysed. Using a chiral [(S)-BINAP-Co]⁺ catalyst it was found that the formation towards the (*S*)-enantiomer, whose the one obtain experimentally, it is favoured by 1.6 kcal/mol. This energy in difference can be attributed to stabilizing π- C-H interactions established between one of the phenyl groups of BINAP and a C-H bond adjacent to the reactive carbon atom (**Figure 11,** green surfaces). It Is worth to mention that this kind of interactions are not observed in the TS that conduces to the formation of the (*R*)-enantiomer.

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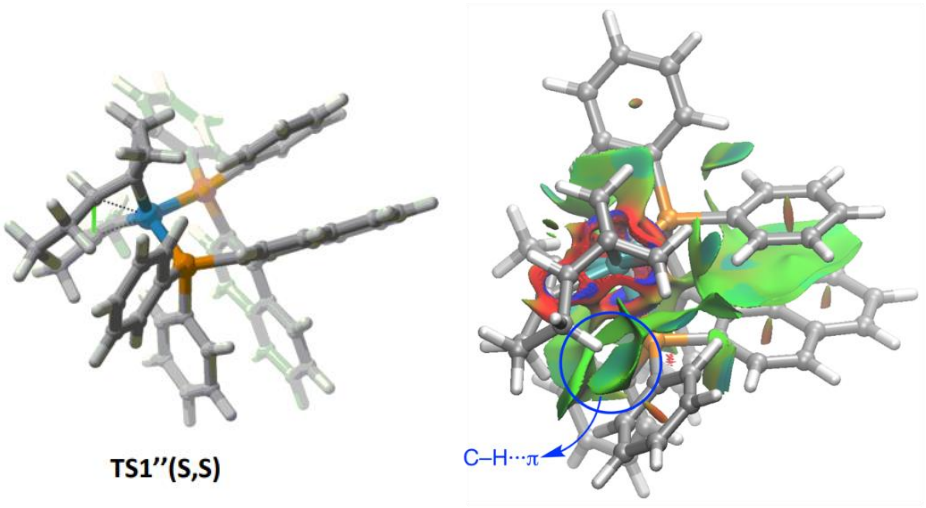


***Figure 11**. Computed diasteriomeric transition states associated with the migratory insertion step (**TS1''**) mediated by (S)-BINAP-Co+ catalyst and corresponding NCI plots. All data have been computed at the PCM(dichloroethane)-B3LYP-D3/def2-SVP level.*

A common characteristic for the 3d row metals complexes, including Co complexes, is their capacity to be presented as low or high spin complexes. This characteristic has proven to be highly influential in the reaction pathway of similar systems as the reaction studied in this section.[105] In this sense, Prof. Israel Fernández computed both spin states for every intermediate belonging to the most plausible profile, using single-point frequency calculations using the M06L functional, since it well-known that calculations perform using B3LYP atypically overestimates the stability of triplets.[106]

As it can be seen in **Figure 12**, the reaction pathway involving cobalt triplet states (S=1) revealed a reaction pathway with a higher energetic demand in comparison to the analogous path involving cobalt singlet states (S=1/2). Therefore, the pathway involving cobalt complexes with low spin is kinetically more favourable. In addition, the stationary points along the singlet hyper surface are more stable than their corresponding triplet analogues, and very much in particular in the case of **INT2**.

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[105] Wang, C.-S.; Di Monaco, S.; Thai, A. N.; Rahman, Md. S.; Pang, B. P.; Wang, C.; Yoshikai, N. *J. Am. Chem. Soc.* **2020**, *142*, 12878-12889.
[106] Esselman, B. J.; McMahon, R. J. *J. Phys. Chem. A* **2012**, *116*, 483-490.

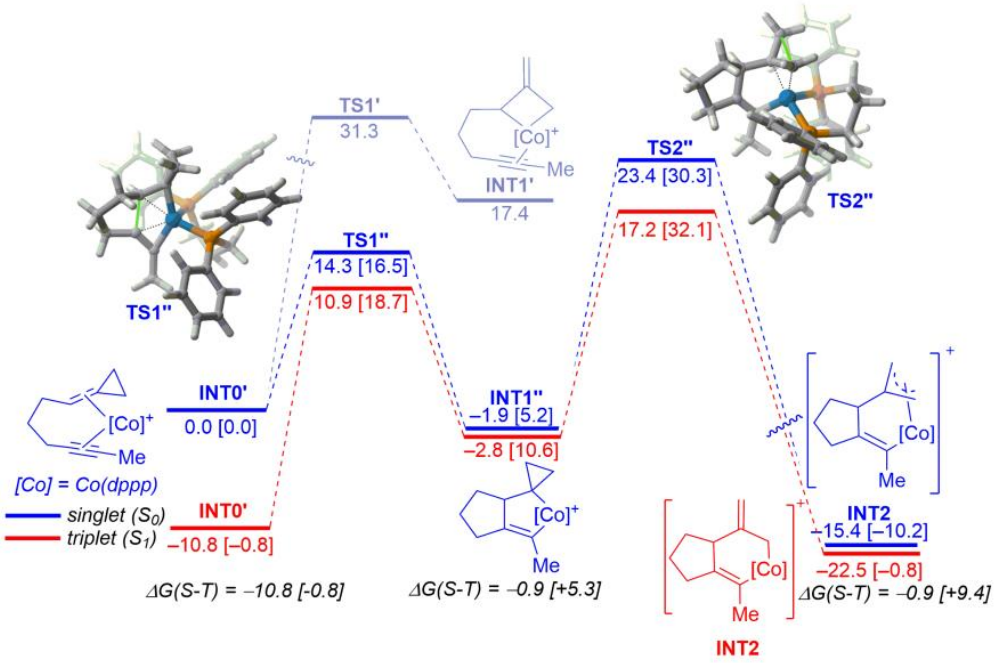
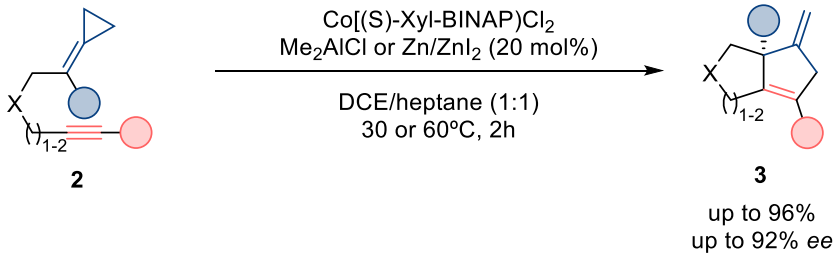


Figure 12. *Computed reaction profile for the evolution of* ***INT0'*** *in the singlet (blue) and triplet (red) hypersurfaces. Relative free energies (ΔG, at 298 K) are given in kcal/mol. Plain values were computed at the PCM(DCE)-B3LYP-D3/def2-SVP level whereas values in brackets were computed at the PCM(DCE)-M60LD3/def2-SVP//PCM(DCE)-B3LYP-D3/def2-SVP level.*

Curiously, just after the publication of our work, the group of Zhi-Xiang Yu reported the same transformation under almost identical conditions.[107] As illustrated in **Scheme 69**, the reaction conditions reported in this work are similar to our best conditions, with small changes in the ligand ((*S*)-Xyl-BINAP vs (*S*)-BINAP), the reductant cocktail (Me_2AlCl or Zn/ZnI_2 vs Zn/ZnI_2 In/InI_3), and the temperature of the reaction (60°C vs 110°C). Despite the fact that this contribution explores a limited scope of the transformation, the study shows very similar results to ours. To our delight, DFT calculations performed by Zhi-Xiang Yu agree with our mechanistical hypothesis described above.



Scheme 69. *Related (3+2) cycloaddition of yne-alkylidenecyclopropanes.*

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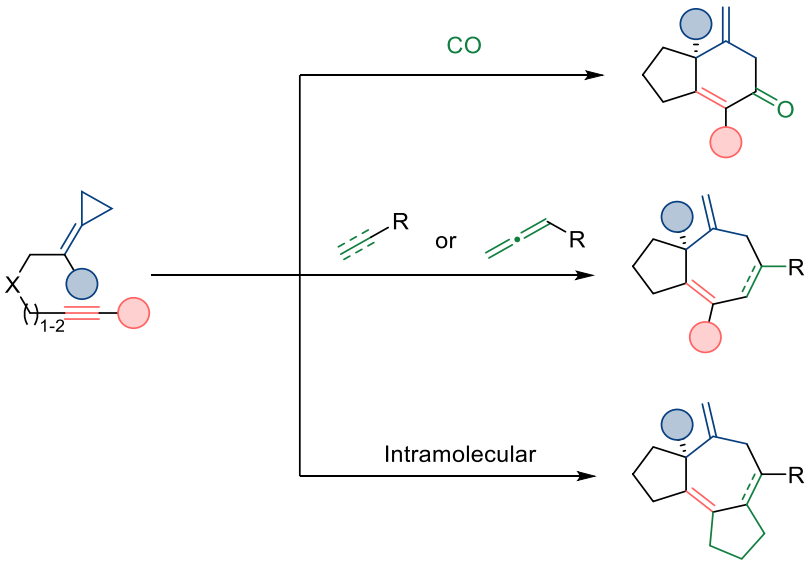
[107] Xiao, X.; Yu, Z. *Chem. Eur. J.* **2021**, *27*, 7176 –7182.

3.2. (3+2+n) Multicomponent Cycloadditions of Alkyne-tethered ACPs

3.2.1 Introduction

As mentioned in the introduction of this chapter, ACPs can participate in a wide variety of (3+n) transition metal catalysed cycloadditions. Moreover, our group and others have also demonstrated the viability of adding an additional unsaturated 2C component to the reaction, and therefore carry out formal (3+2+2) cycloadditions. These methods are fundamentally based on the use of noble metal catalysts such as Rh (**Page 53, Scheme 45**) or Pd (**Page 55, Scheme 47**), and entail a mechanism initiated by metal insertion in the distal C-C bond of the ACP. Examples with more abundant first row metals are limited to the use of selected Ni (0) complexes, that promotes the reaction through a proximal C-C bond cleavage of the cyclopropane ring (**Page 55, Scheme 48** and **Page 56, Scheme 49**). These technologies allowed to build a variety of polycyclic structures containing seven-membered carbocycles, which constitute the core of many types of bioactive natural products.[108]

Encouraged by the good results described in the Chapter 3.1 of this manuscript, and the requirements of modern organic synthesis for developing more sustainable methods using inexpensive and earth abundant materials, we envisioned the possibility of implementing cobalt-catalysed multicomponent cycloadditions, including (3+2+2) processes (**Scheme 70**).

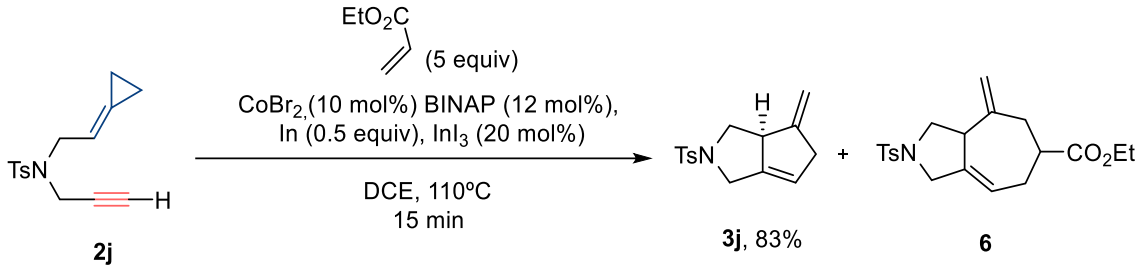


Scheme 70. *Possible intra- or intermolecular (3+2+2) cycloadditions among alkyne-tethered ACPs and unsaturated additional partners.*

[108] (a) Heathcock, C. H.; Graham, S. L.; Pirrung, M. C.; Pavoac, F.; White, C. T. *The Total Synthesis of Natural Products*, Vol. 5 (Ed.: J. ApSimon), Wiley, New York, 1983, 333 – 393; (b) Rigby, J. H. *Studies in Natural Products Chemistry*, Vol. 12 (Ed.: A. Rahman), Elsevier, Amsterdam, 1988, 233 – 274; (c) Fraga, M. B. *Nat. Prod. Rep*. **2005**, *22*, 465 – 486.

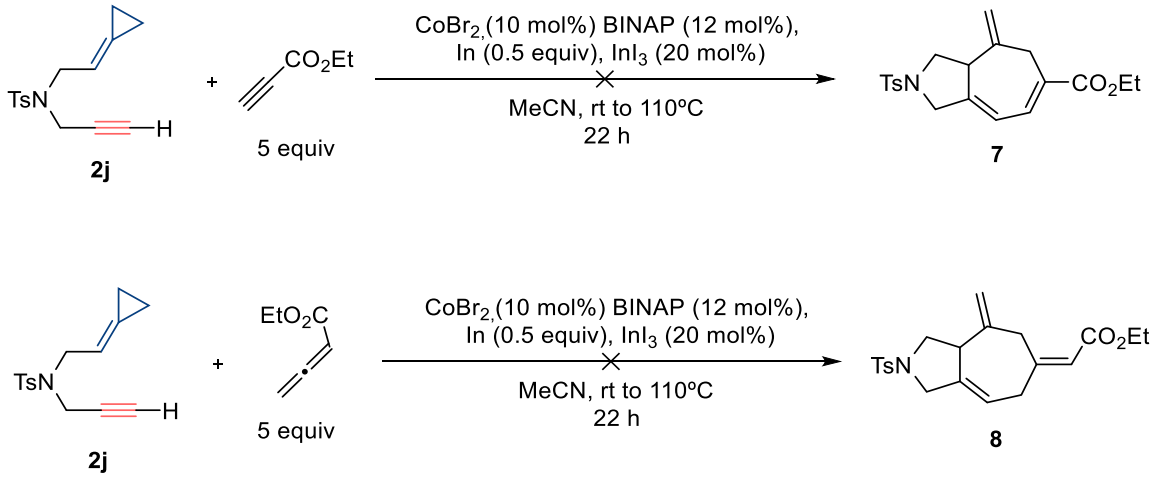
3.2.2 Attempts to promote intermolecular (3+2+2) cycloadditions of alkyne-tethered ACPs with external unsaturated partners

We initially wondered whether alkyne-tethered ACPs could react with external 2π C-C unsaturated partners and give formal (3+2+2) cycloadducts. To test this hypothesis, enyne **2j** was heated in the presence of ethyl acrylate (5 equiv) under the best conditions found for the (3+2) cycloaddition. Unfortunately, the reaction only delivered the previously known (3+2) cycloadduct **3j**, without traces of a (3+2+2) adduct like **6 (Scheme 71)**. Curiously, the reaction rate seemed to be higher than in the absence of acrylate, as it was finished in just 15 minutes.



***Scheme 71**. Attempts to develop a (3+2+2) cycloaddition with external alkenes.*

On other hand, when **2j** was reacted with ethyl propiolate or ethyl -2,3-butadienoate, the reactivity was completed shut down and full recovery of the starting material was observed (**Scheme 72**).

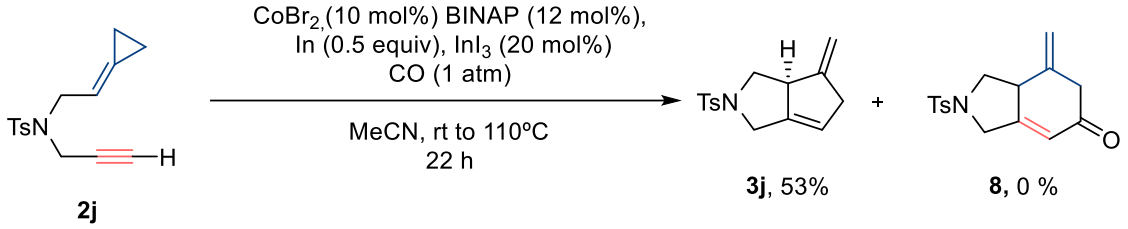


***Scheme 72.** Attempts to develop a (3+2+2) cycloaddition with external alkynes or allenes.*

Other attempts to improve these results by changing the ligand (dppp, dppe, Xantphos or dppf), reductant (Zn, Mn), additive (ZnI_2, $NaBAR^F$) or solvent (DCE, 1,4- Dioxane) failed.

We also wondered about the viability of develop a novel (3+2+1) cycloaddition of alkyne-tethered ACPs using CO instead of two-carbon partners. To do that, we submitted

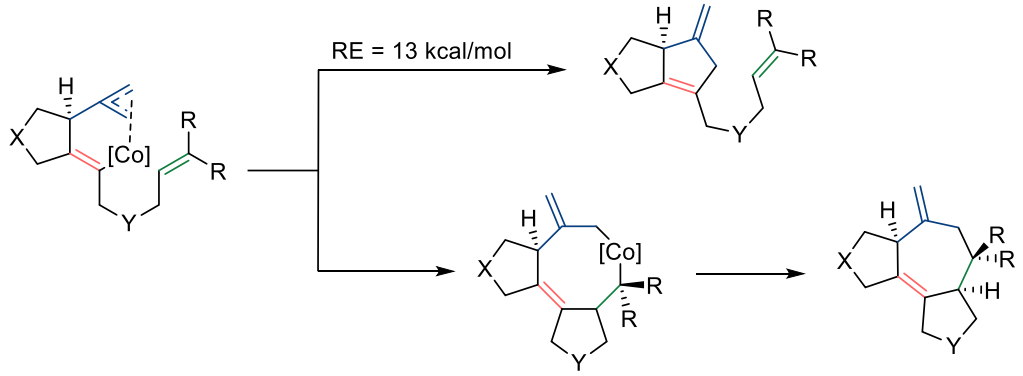
substrate **2j** under an atmosphere of CO to the most general conditions observed in the (3+2) cycloaddition of alkyne-tethered ACPs. However, only the (3+2) cycloadduct **3j** was detected after 22 h of reaction (**Scheme 73**).



Scheme 73. *Attempts to develop a (3+2+2) cycloaddition with CO.*

3.2.3. Fully intramolecular (3+2+2) cycloaddition of alkyne-tethered ACPs

The failure of a multicomponent intermolecular (3+2+2) cycloaddition with external alkene, allene or alkynes led us to check whether a fully intramolecular version would be more feasible, by decreasing the entropic cost of the second annulation. Nonetheless, the low barrier of the reductive elimination that delivers the competitive (3+2) cycloadduct [lower than with other metals like Rh (DDG of about 9 kcal)][84] still makes this hypothesis quite uncertain (**Scheme 74**).

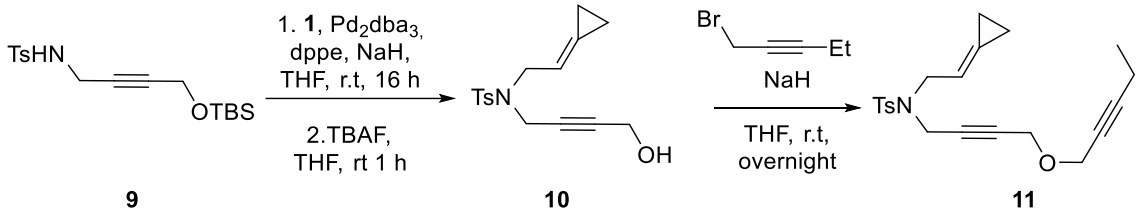


Scheme 74*. Possible competition between the (3+2) or the intramolecular (3+2+2) cycloaddition.*

Inspired by other cobalt mediated cycloadditions involving 1,5-diynes,[109] we initially tested the viability of an intramolecular (3+2+2) cycloaddition of a diyne precursor like **11**, that bears the ACPs tethered to a 1,5-diyne. Model substrate **11** could be easily synthetize in 3 steps with high efficiency, according to a previously described procedure (**Scheme 75**).[87]

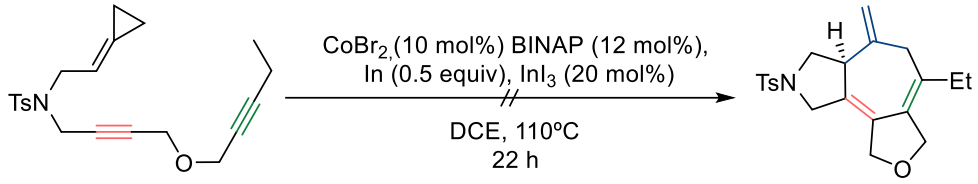
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[109] Gläsel, T.; Baumann, B., N.; Hapke, M. *Chem. Rec.* **2021**, *21*, 3727– 3745.



Scheme 75. *Synthetic route of diyne ACP.*

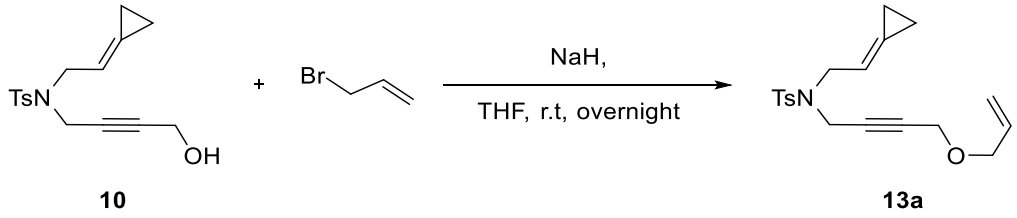
Unfortunately, when we submitted ACP **11** to the conditions previously optimized for the (3+2) cycloadditions of alkyne-tethered ACPs, we observed no reactivity. Moreover, other attempts to promote this reaction by changing the ligand, reductant, additive or solvent (**Table 7**) were completely unsuccessful, recovering in all cases the starting precursors.



Entry	Variations	Yield (%)
1	dppp instead of BINAP	0
2	$Zn/ZnBr_2$ instead of In/InI_3	0
3	NaBARF instead of InI_3	0
4	MeCN instead of DCE	0
5	dppp instead of BINAP	0
6	dppp instead of BINAP	0

Table 7*. Screening conditions for the intramolecular (3+2+2) cycloaddition of diynes and ACPs.*

The lack of reactivity of ACP **11** is likely associated to the well-known ability of cobalt complexes to strongly coordinate 1,*n*-diynes.[100] Therefore, we prepared the derivative **13a,** which bears a terminal alkene as third cycloaddition partner (**Scheme 77)**.



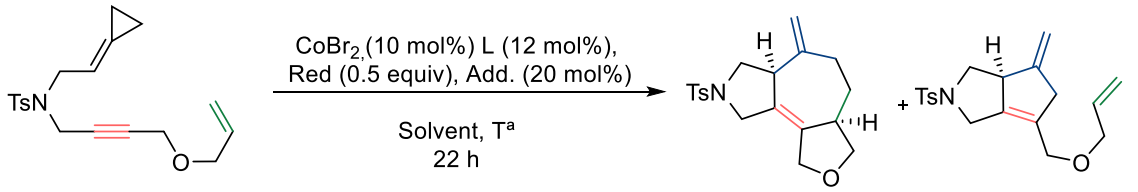
Scheme 76. *Synthesis of the model substrate for the development of the intramolecular (3+2+2) cycloaddition of ACPs, alkynes and alkenes.*

With precursor **13a** in our hands, we started a brief evaluation of reaction conditions that could provide the desired (3+2+2) cycloadduct. When this precursor was treated

with the catalyst generated *in situ* from $CoBr_2$, BINAP and a reducing agent (Zn / $ZnBr_2$), at 110°C in 1,2-dichloroethane, we observed its clean transformation into a product that, unfortunately, turned out to be the (3+2) cycloadduct **3u**, which was isolated in a good 83% yield (**Table 8, entry 1**). Modifying the reaction temperature or the solvent did not bring any change in the chemoselectivity of the process (**entries 2 and 3**). However, we were glad to observe that changing the bisphosphine ligand from Binap to the simpler dppp, the desired (3+2+2) cycloadduct **14a** could be isolated in 51% yield (**entry 4**). Gladly, the reaction was totally diastereoselective, and led to the formation of a product that holds the hydrogen atoms at the ring fusion in *cis* disposition (determined by comparison with previously reported adducts, under Rh catalysis).[84]

The same reactivity was observed when MeCN was used as solvent (**entry 5)** and, more importantly, we observed that the reaction efficiency with this model substrate was maintained even when the temperature was decreased to even 40°C (**entries 6-8**).

Aiming to improve the yield of the reaction, other parameters besides the solvent and temperature were screened. Thus, when a mixture of Zn/$ZnBr_2$ was used as reductant, an increase in the reaction yield up to 63% yield was observed (**entry 9**).



13a **14a** **3u**

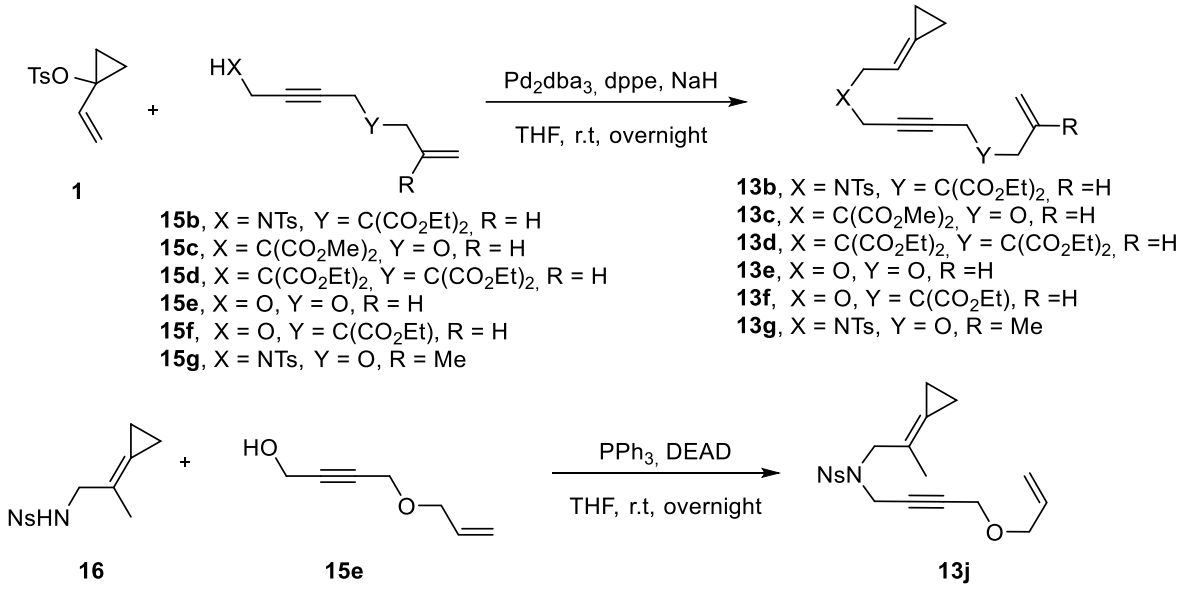
Entry	Ligand	Solvent	Red/Add.	Temperature (T)	Yield 14a (%)	Yield 3u (%)
1	BINAP	DCE	In/$InBr_3$	110	-	83
2	BINAP	MeCN	In/$InBr_3$	110	-	77
3	BINAP	DCE	In/$InBr_3$	80	-	53
4	dppp	DCE	In/$InBr_3$	110	51	-
5	dppp	MeCN	In/$InBr_3$	110	47	-
6	dppp	DCE	In/$InBr_3$	80	50	-
7	dppp	DCE	In/$InBr_3$	60	52	-
8	dppp	DCE	In/$InBr_3$	40	53	
9	dppp	DCE	Zn/$ZnBr_2$	110	63	-

Table 8. *Screening conditions for the intramolecular (3+2+2) cycloaddition of ACPs, alkynes and alkenes.*

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We then analysed the generality of the cobalt catalysed (3+2+2) cycloaddition using these latter conditions, namely using $CoBr_2$ (10%) as cobalt source, dppp (12%) as ligand, Zn (50%) as reductant, $ZnBr_2$ (20%) as additive and DCE as solvent.

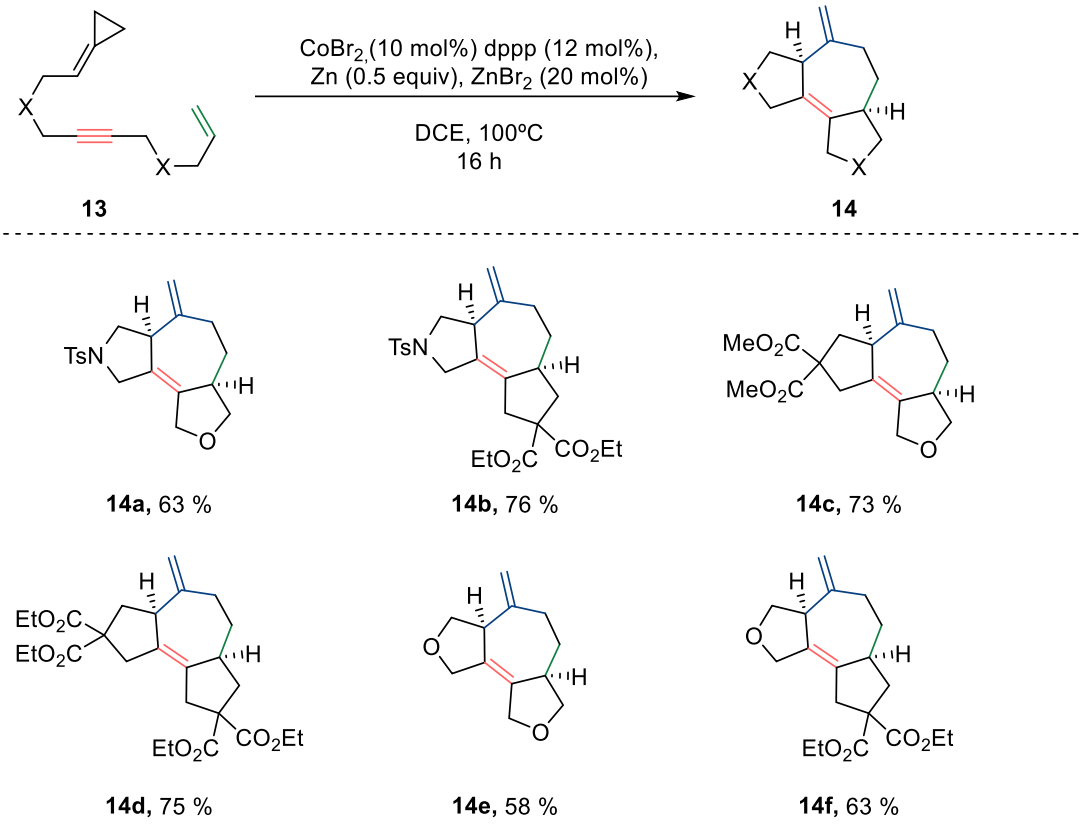
Firstly, a series of precursors bearing different connecting tethers between the ACP, alkyne and alkene and several substitution patterns in the alkene were synthesized following the previously commented Tsuji-Trost Pd-catalysed allylic substitution between the vinyl tosylate **1** and a series of 1,6-enynes. In addition, a precursor with a methyl group at the internal position of the ACP was also synthetized through a simple Mitsunobu reaction from ACP **16** and propargyl alcohol **15e.**



***Scheme 77**. General synthesis of 1,6-enyne-tethered ACPs.*

Firstly, a variety of ACPs containing different connecting tethers between the ACP, alkyne and alkene moieties were evaluated. We first confirmed that tricyclic adducts with partial carbocyclic skeletons like **14b** or **14c** were obtained with good yields. In addition, the strategy also provides fully carbonade cycloadducts such as **14d**. Furthermore, cycloadducts with oxygen atoms in the five-membered rings, like **14e** and **14f,** were also formed with good yield and with total diastereoselectivity towards the *cis* adducts (**Scheme 78**).

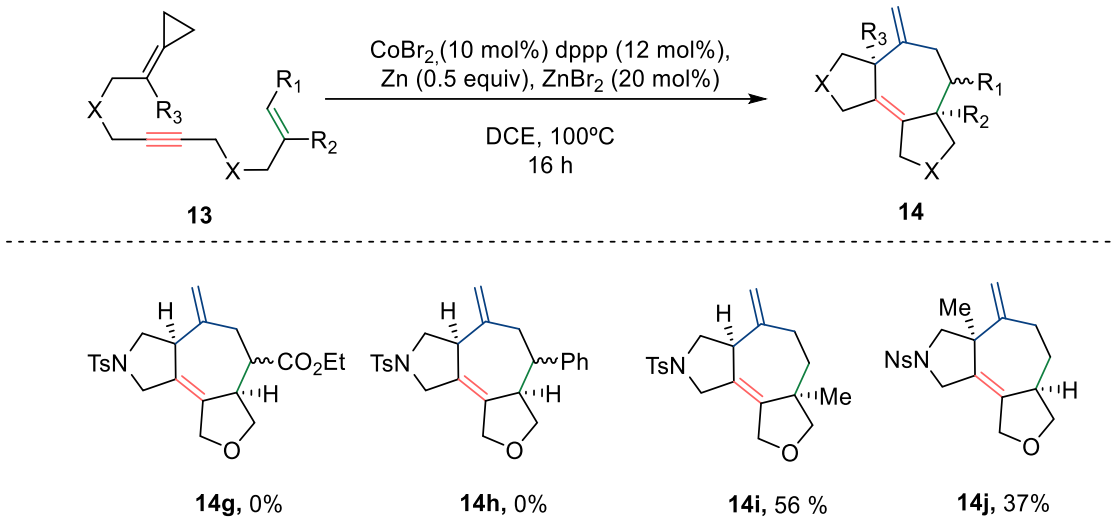
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***Scheme 78**. Scope of different connecting tethered of the intramolecular (3+2+2) cycloaddition of ACPs, alkynes and terminal alkenes.*

Then, we checked the influence of the alkene substitution in the multicomponent cycloaddition reaction (**Scheme 79**). Curiously, and contrary to previously developed Pd and Rh-catalysed methods,[84,87] which are tolerant to the presence of certain substituents at the terminal position of the alkene partner, such a carboxy ester (i.e. CO_2Et, **13g**) or an aryl group (**13h**), the Co catalysed cycloaddition of these precursors failed to give the tricyclic products, and led only to the (3+2) adducts. However, the use of a precursor that holds a methyl substituent at the alkene internal position was well tolerated, affording the desired tricyclic product, **14i**, which bears a carbon quaternary centre at the ring fusion in a good 56% yield. Likewise, another 5,7,5-tricyclic system bearing a quaternary stereocenter was prepared (**14k**, 41%) by using an internally substituted ACP.

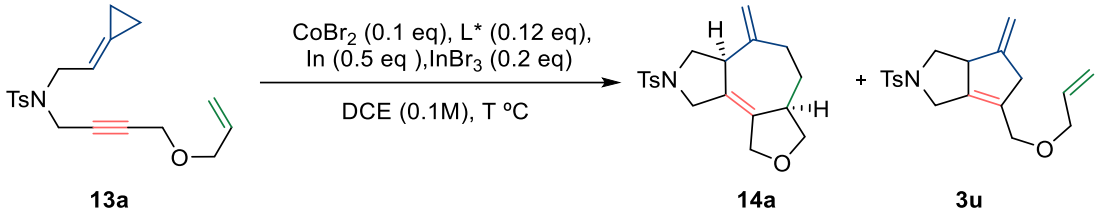
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***Scheme 79**. Evaluation of the substitution pattern of the alkenes in the intramolecular (3+2+2) cycloaddition of ACPs, alkynes and alkenes.*

Having developed an optimal protocol for a racemic cycloaddition, we preliminary addressed the development of an asymmetric variant of this multicomponent (3+2+2) cycloaddition. Towards this end, some of the most successful ligands previously found for the (3+2) ACP-alkyne cycloadditions were tested in the reaction employing model substrate **13a**. With BINAP or Ph-Garphos (**Table 9, Entries 1-2**) which provide high er's in the (3+2) cycloaddition, we only observed the (3+2) cycloadduct **3u**. However, using (S)-Bdpp, which is structurally very similar to dppp, we could exclusively observe the desired tricyclic cycloadduct **14a,** which was isolated in a good 73% yield and with moderate 81:19% *er* (**Table 9, entry 2**). Encouraged by these results, we decreased the reaction temperature to see if we could improve the asymmetric induction. Carrying out the reaction at 80°C the enantioselectivity of the reaction increased up to excellent 95:5% er, however, a mixture of the (3+2) and (3+2+2) cycloadducts were observed (**Table 9, Entry 4**).

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13a 14a 3u

Entry	Ligand (L*)	Temperature (T)	Yield 13a (%)	Yield 3u (%)	er 14a (%)
1	(*S*)-BINAP	100	-	81	-
2	(*S*)-Ph-Garphos	100	-	57	-
3	(*S*)-Bdpp	100	73	-	81:19
4	(*S*)-Bdpp	80	40	50	95:5
5	(*S*)-BINAP	80	-	68	-
6	(*S*)-Bdpp	60	-	-	-

Table 9. *Screening conditions in the attempts of an enantioselective intramolecular (3+2+2) cycloaddition of ACPs, alkynes and alkenes.*

Thus, enantioselective (3+2+2) cycloadditions are feasible, but further study of the reaction conditions would be necessary to optimize conditions and expand the scope.

To gain some mechanistic insights into the polycyclizations, Prof. Israel Fernandez performed DFT calculations.[110]

Using precursor **1n** as model substrate and the cationic Co(I) complex $[Co(dppp)]^+$ as reference catalyst (**Figure 12)**, the calculations identified an initial, very stable intermediate in which the alkyne and the C-C double bond of the ACP are coordinated to $[Co(dppp)]^+$ (**INT0**). From this Co(I) complex, we confirmed that the oxidative cyclometallation to provide the spiro-cobaltacyclopentene intermediate **INT1** is highly accessible (energy barrier of 14.1 kcal/mol). This intermediate **INT1** would then evolve via a cyclopropyl to π-allyl rearrangement towards the intermediate **INT2**, which is more than 20 kcal/mol more stable than **INT1**. At this point, a C-C reductive elimination through **TS3** would deliver the (3+2) cycloadduct, a process that involves an energy barrier of 20.1 kcal/mol.

Gratifyingly, the computational analysis found that the coordination of the alkene to provide **INT4**, followed by an almost barrierless migratory insertion to the Co(III) centre occurs through **TS4** with a lower energy barrier, of only 17.8 kcal/mol. Therefore, the pathway eventually leading to the (3+2+2) adduct is favoured by almost 3 kcal/mol respect to the competitive (3+2). From **INT5**, a C-C reductive elimination (ΔG = 21.5 kcal/mol) delivers the 5,7,5-tricyclic adduct (**Figure 13**).

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[110] Density Functional Theory (DFT) calculations at the dispersion-corrected PCM(DCE)-B3LYP-D3/def2-SVP level.

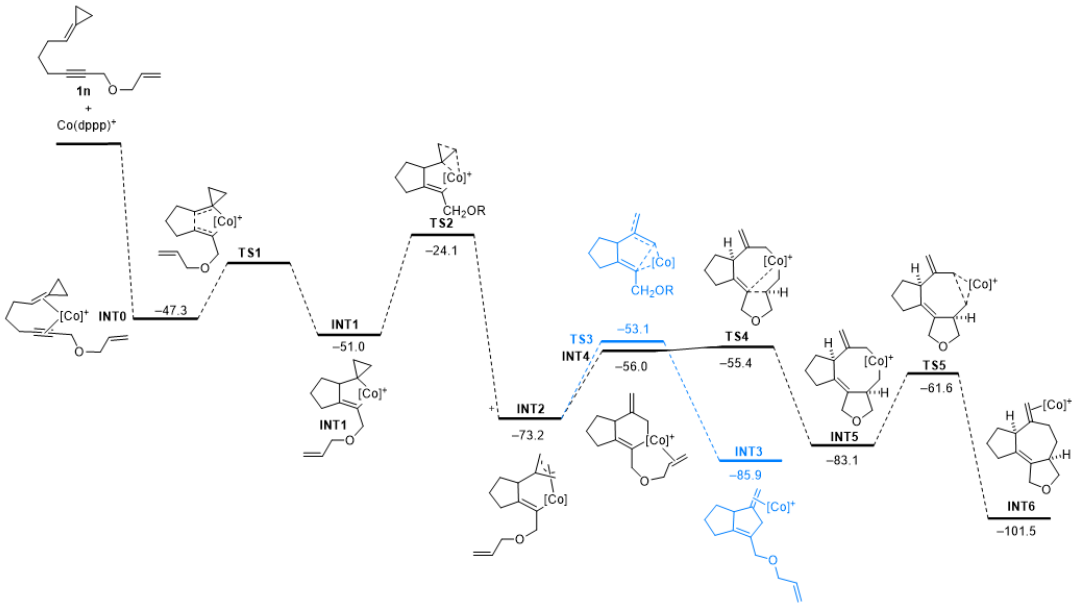


Figure 13. *DFT calculations for the (3+2+2) cycloadditions of ACPs, alkynes and alkenes initiated through an oxidative cyclization between ACP and alkyne.*

Moreover, Prof. Fernández also evaluated a reaction profile initiated through an oxidative cyclization between the alkene and the alkyne. Accordingly, **INT0'** which holds the $[Co(dppp)]^+$ coordinated to the alkene and the alkyne was found to be energetically comparable to **INT0** (-48.4 *vs* -47.3 kcal/mol). The next step involving the oxidative cyclization process leading to **INT1'** again proved to be comparable from an energetic point of view to the reaction pathway illustrated in Figure 12 (ΔG = 14.1 and 15.0 kcal/mol). However, all attempts to find a transition state that links **INT1'** with **INT2'** were unfruitful, suggesting that the presence of the fused-cyclopropyl ring hinders the migratory insertion step. In any case, a cyclopropyl to π -allyl rearrangement from a hypothetical intermediate **INT2'**, which was independently located, to yield the corresponding π -allyl intermediate of type **INT-3'** was found to involve an energy barrier of more than 40 kcal/mol (**TS3'**), which makes this alternative pathway very unlikely (**Figure 14**).

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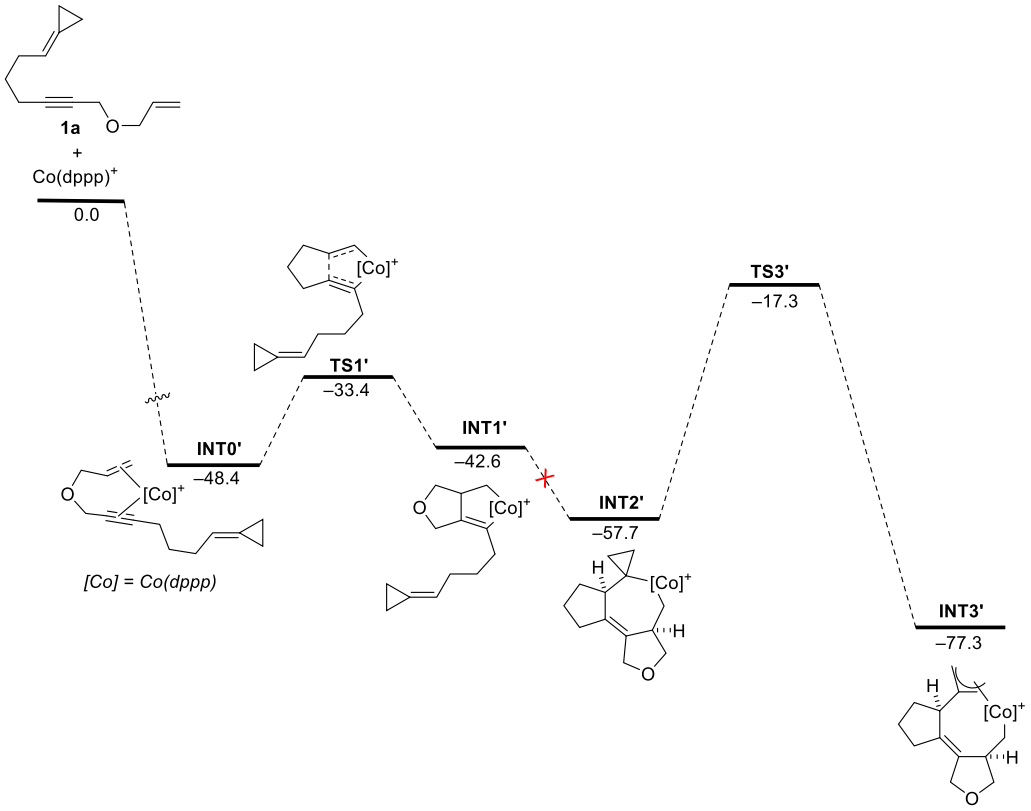


Figure 14. *DFT calculations for the (3+2+2) cycloadditions of ACPs, alkynes and alkenes initiated through an oxidative cyclization between alkene and alkyne.*

In conclusion, considering the computational data, we established that the most probable reaction mechanism would be the one depicted in **Figure 13.**

3.3. (3+2) Cycloaddition of ACPs tethered to alkenes, allenes or conjugated dienes

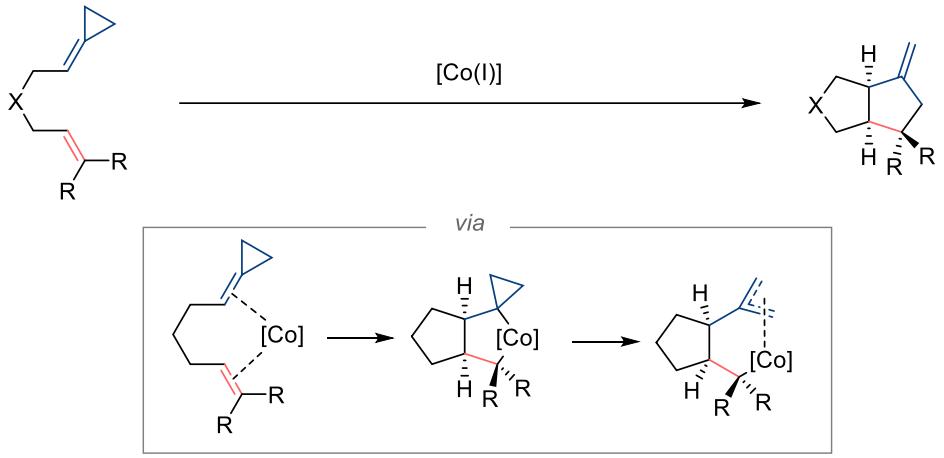
3.3.1. Cycloadditions with alkenes and allenes

At this point, after confirming the successful behaviour of alkyne-tethered ACPs in an enantioselective (3+2) cycloaddition and a multicomponent (3+2+2) intramolecular cycloaddition, we wondered about the behaviour of alkene-tethered ACPs in the presence of a low valent cobalt catalyst. A (3+2) cycloaddition of these systems would lead to bicyclic 5,5 scaffolds, bearing up to 4 stereocenters, which is quite attractive from a synthetic perspective.

From a mechanistic point of view, we hypothesize that this new (3+2) cycloaddition would follow a similar pathway that the one previously stablished for the reaction with alkynes. However, we expect that initial coordination of the cobalt complex with the alkene-tethered ACP would be more difficult than the previously studied alkynyl partners. This could hamper a hypothetic oxidative cyclization. Moreover, another challenging facet of this transformation is the eventual C-C reductive elimination, which,

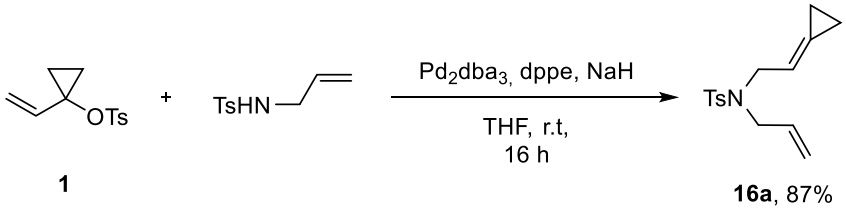
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compared to the (3+2) cycloaddition with alkynes, should be more difficult as it involves a sp^3 carbon **(Scheme 80).**



***Scheme 80**. Proposal for the Co(I) catalysed (3+2) cycloaddition of alkene-tethered ACPs.*

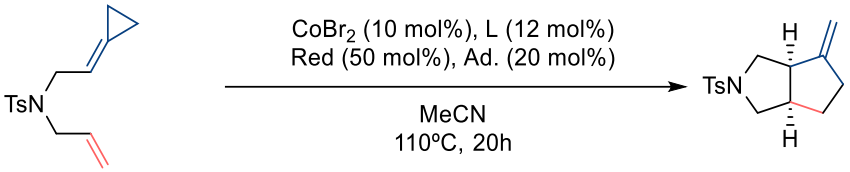
To tackle these challenges, we prepare a model substrate, **16a** following the abovementioned protocol based on a Tsuji-Trost Pd catalysed allylic substitution, using the tosylate **1** (**Scheme 81**).



***Scheme 81.** Synthesis of model substrate **16a** through a Tsuji-Trost reaction.*

The annulation was first tested by heating ACP **16a** for 20 h in MeCN at 110°C in the presence of $CoBr_2$ (10 mol%), dppp (12 mol%), In (50 mol%), and InI_3 (20 mol%). To our delight, total consumption of ACP **16a** was observed, and the cycloadduct **17a**, with a *cis* ring fusion, was exclusively observed and eventually isolated in a 52% yield (**Table 10, entry 1**). Aiming to increase the efficiency of the transformation, we tested different bidentate phosphines such as BINAP, dppf or dppe. However, none of them afforded better results than dppp (**entries 2-5**). In addition, monodentate phosphines are also suitable ligands for this transformation (**entries 6-7**) giving an especially good result the use of electron deficient phosphite **L1**.

In this sense, other reductants and additives were evaluated using dppp as ligand. Curiously, a reductant cocktail of Zn/ZnI_2 did not afford any conversion of ACP **16a** (**entry 7**), but when NaBARF was used as additive the yield was improved up to a moderate 61% yield **(entry 9**). Moreover, by raising up the temperature until 140°C the corresponding cycloadduct was isolated in a good 71% yield (**entry 11**).



16a **17a**

Entry	Ligand	Reductant	Additive	Temperature	Yield (%)
1	dppp	In	$InBr_3$	110	51
2	BINAP	In	$InBr_3$	110	50
3	dppf	In	$InBr_3$	110	47
4	dppe	In	$InBr_3$	110	0
5	PPh_3	In	$InBr_3$	110	10
6	L_1	In	$InBr_3$	110	61
7	dppp	Zn	ZnI_2	110	0
8	dppp	In	InI_3	110	52
9	dppp	In	$NaBAR^F$	110	61
10	dppp	In	-	110	0
11	dppp	In	$NaBAR^F$	140	71

***Table 10**. Reductant and additive evaluation for the intramolecular (3+2) cycloaddition of alkene-tethered ACPs.*

We then explored an enantioselective version of this reaction. Thus, a variety of C_2 symmetric bidentate chiral phosphine that proved to work nicely with alkynes were evaluated as ligands. Curiously, while (*S*)-BINAP and (*R*)-Ph-Garphos allowed the (3+2) cycloaddition of alkyne-tethered ACPs with enantiomeric ratios up to 95:5, they provided a null enantioselectivity in the cycloaddition of the model precursor **16a** (**Figure 15**). Moreover, the same lack of asymmetric induction was observed when other chiral bidentate phosphines such as (S)-BPE, (S)-BINAPINE, (S)-Segphos or (S)-Bdpp were used.

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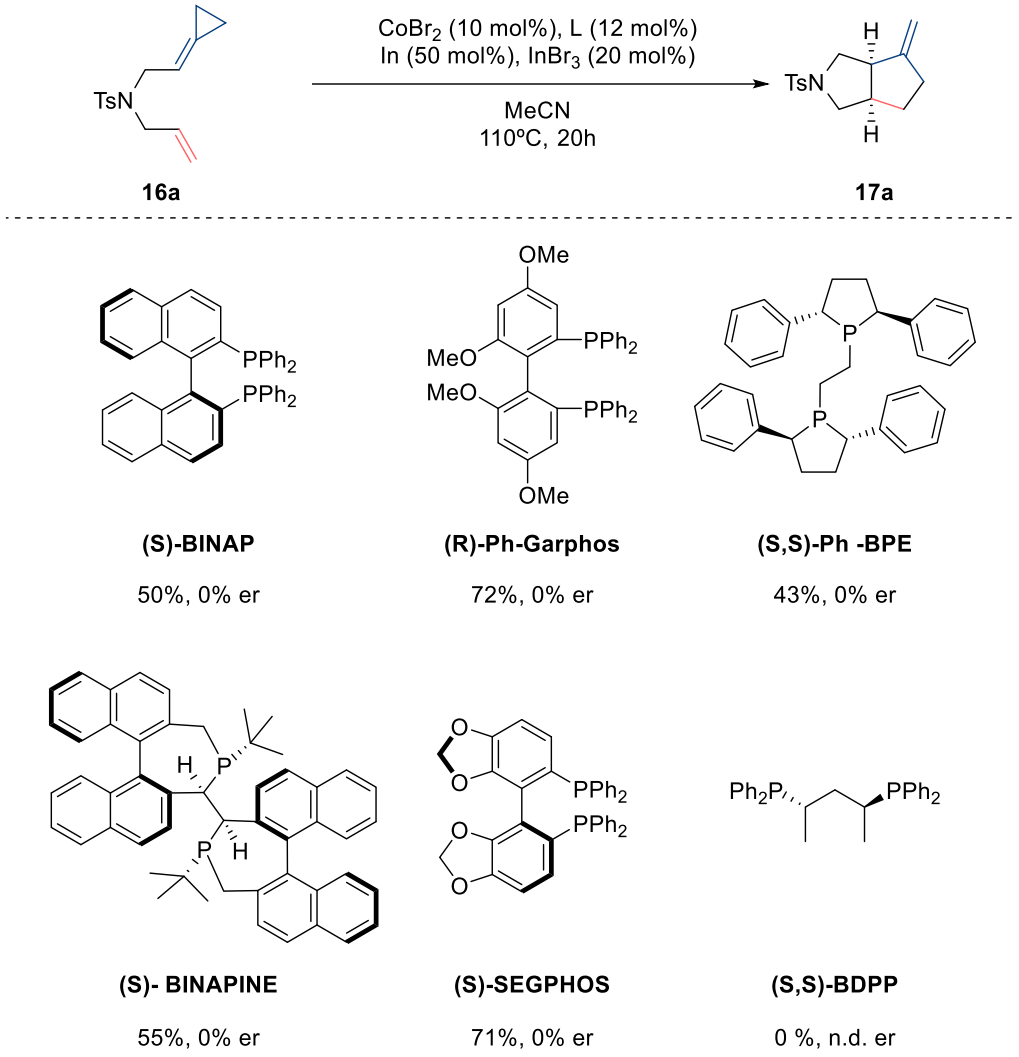
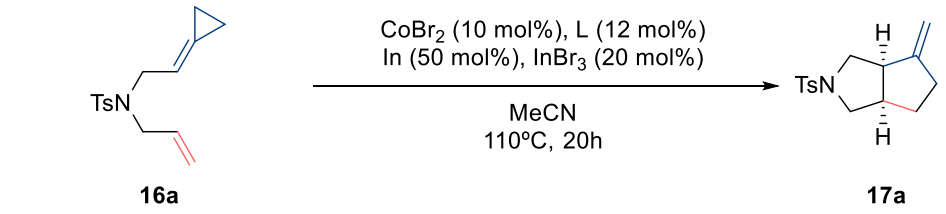


Figure 15. *Bidentate chiral phosphines used in the optimization of the (3+2) cycloaddition of alkene-tethered ACP* ***12a****.*

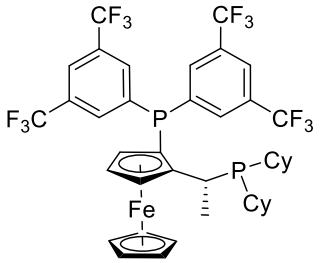
We then explored alternative chiral ligands that had been successfully applied in other low valent cobalt-catalysed formal cycloadditions, like chiral ferrocenyl bisphosphines. [111] Thus, analysis of different commercially available Josiphos ligands led to low yields but moderate enantioinduction. Other type of ferrocenyl bisphosphine ligands of the Walphos and Mandyphos series were also explored but proved to be ineffective. Besides, other ferrocenyl bisphosphines like (*R,R*)-Me-Ferrocelane and (*S,S*)-f-BINAPHANE were also tested but provided low yields; and chiral ligands bearing other chiral motives like oxazolines or axial naphtyl groups neither increase the asymmetric control of the reaction (**Figure 16**).

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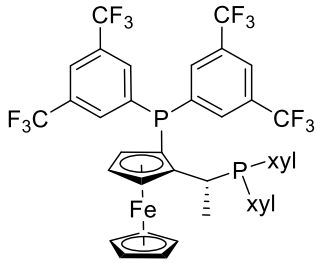
[111] Jing, S. M.; Balasanthiran, V.; Pagar, V.; Gallucci, J. C.; RajanBabu, T. V. *J.Am. Chem. Soc.* **2017**, *139*, 18034−18043.



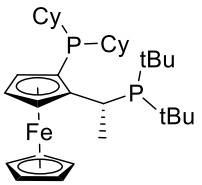
16a **17a**



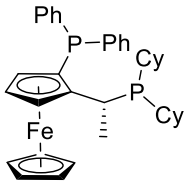
Josiphos SL-0006-2
20%, 56:44 er



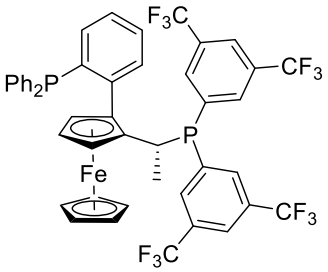
Josiphos SL-J008-1
22%, 50:40 % er



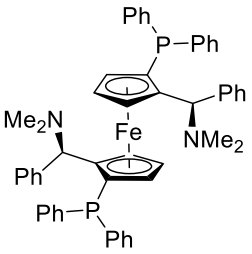
Josiphos SL-0009-1
15%, 72:28 er



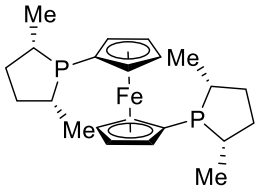
Josiphos SL-0001-1
20%, 65:35 er



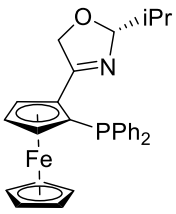
Walphos SL-W001-2
10%, 50:40 er



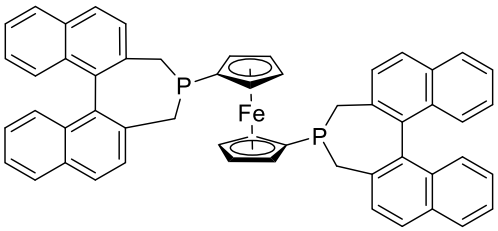
Mandyphos SL-M001-1
0%



***(R,R)*-Me-Ferrocelane**
32%, 65:35 er



L2,
30%, 60:40 er



***(S,S)*-f-BINAPHANE**
26%, 60:40 er

Figure 16. *Chiral ferrocenes used in the optimization of the (3+2) cycloaddition of alkene-tethered ACPs.*

At this point, in view of the poor performance of bidentante chiral ligands, we decided to explore the behaviour of π-acceptor monodentate chiral ligands (**Figure 17**). The use of phosphoramidite $\mathbf{L_6}$ (24 mol %) led to full recovery of the starting material. However, with the more electrodeficient phosphite ligand $\mathbf{L_{10}}$, the (3+2) cycloadduct **16a** was obtained, although with a low 10% yield. Inspired by the performance of $\mathbf{L_{10}}$, other phosphites were also evaluated. Gladly, we found that a type of chiral triskelion P ligand,

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namely helical C3-symmetric monophosphites **L_{11}**,[112] led to the (3+2) cycloadduct in excellent 80% yield and with a good 85:15 er. Aiming to improve this result structural variants of **L_{11}** were evaluated. Substitution in the 3,3' position of the BINOL scaffolds, like in ligand **L_{12}**, led to a poor 56:44 er. Moreover, changing the BINOL scaffolds for its hydrogenated isomer **L_{13}**, or for other axial chiral diol like VAPOL (**L_{14}**) again led to low enantiomeric ratios. Therefore, **L_{11}** is the ligand that afforded the highest enantioselectivity in the cobalt mediated (3+2) cycloaddition of alkene-tethered ACPs like **16a**.

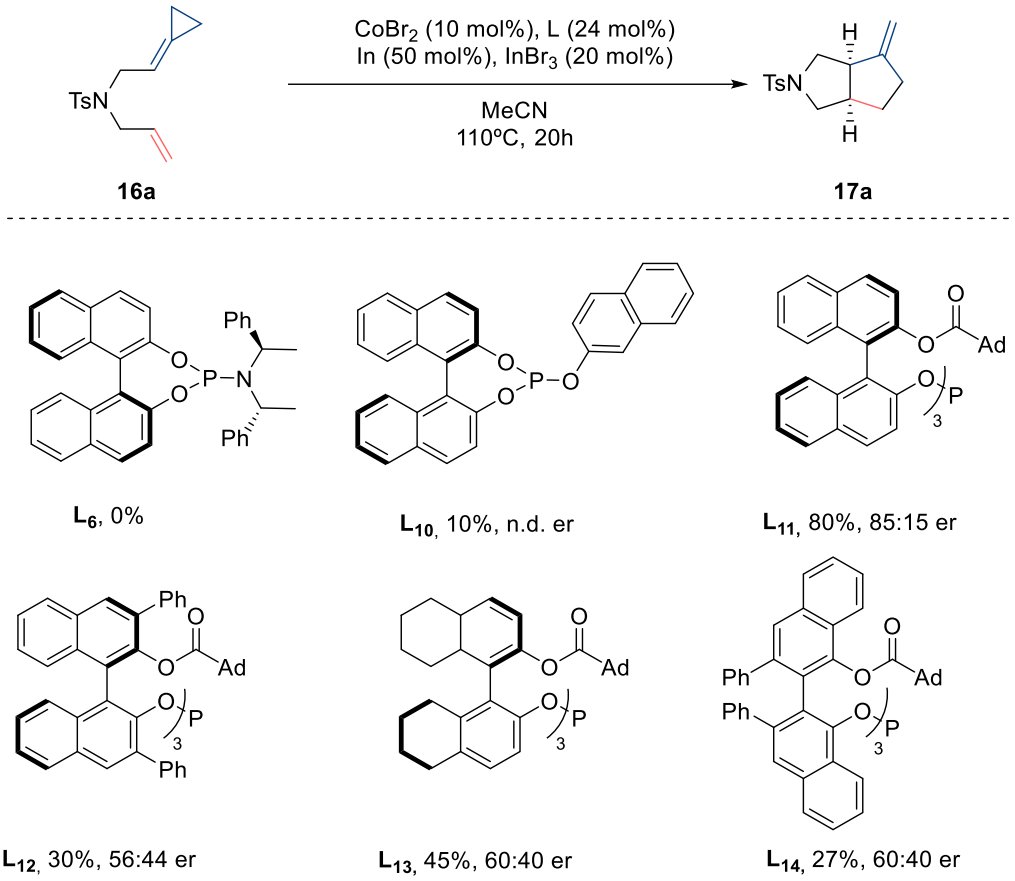


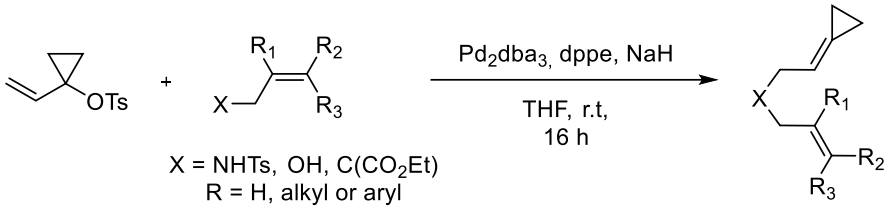
Figure 17. *Chiral monodentate ligands used in the optimization of the (3+2) cycloaddition of alkene-tethered ACPs.*

These results highlight the difficulties associated to the development of enantioselective cycloadditions with ACPs which, in this particular case, might be in part associated to the existence of certain background reactivity promoted by low valent cobalt complexes that lack any phosphorous-based ligand. Indeed, carrying out the reaction of **16a** without ligand, under otherwise identical reaction conditions, led to the (3+2) adduct **17a** in 31% yield.

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[112] Reetz, M. T.; Guo, H.; Ma, J.; Goddard, R.; Mynott, R. J. *J. Am. Chem. Soc.* **2009**, *131*, 11, 4136–4142.

Considering the difficulties for obtaining a highly enantioselective methodology, we analysed the scope of the non-asymmetric method using the best conditions which consisted of the use of $CoBr_2$ (10 mol%), dppp (12 mol%), In (50 mol%) and $NaBAr^F$ (20 mol%) (**entry 11, Table 10).** Therefore, we prepared a variety of ACPs with different functional groups in the connecting tethered, and with different substitution patterns in the alkene (**Scheme 82**).



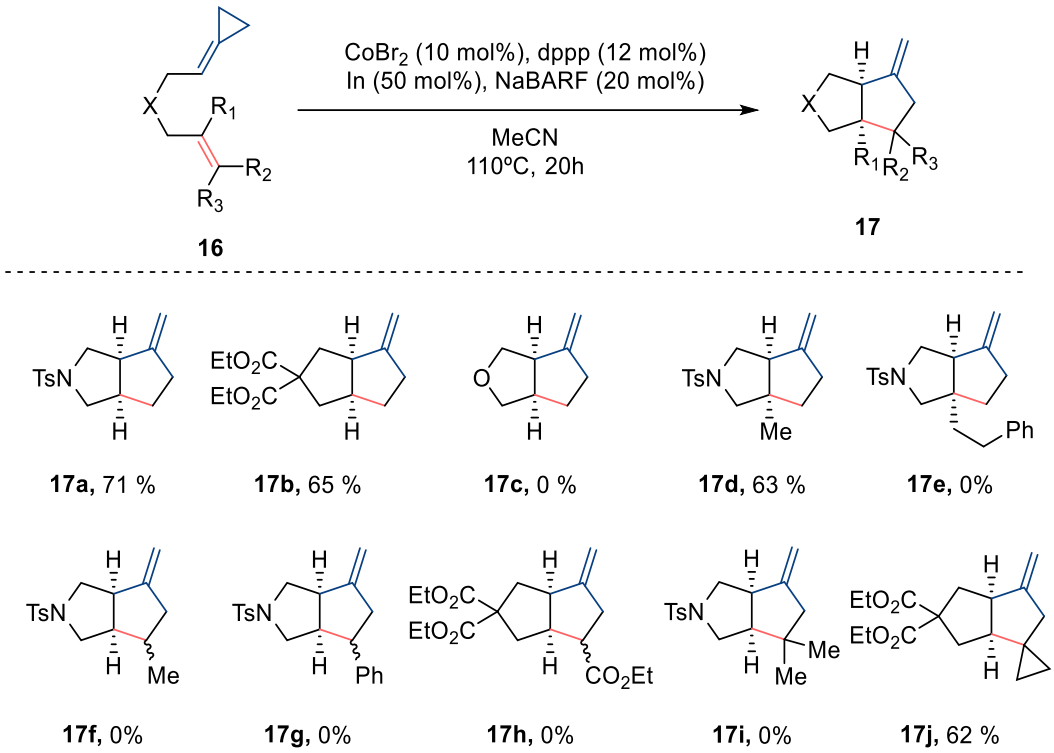
***Scheme 82**. General synthetic route towards alkene-tethered ACPs.*

Initial experiments demonstrated that besides the model substrate **16a** bearing an NTs-group in the tether, substrates with fully carbonade (malonate connection) tether do also work, to give the cycloadduct **17b** in 65% yield (**Scheme 83**). Curiously, the precursor with an ether connection failed to give the expected adduct **17c**, decomposing under the reaction conditions. Internally substituted alkenes were suitable partners for the annulation. Thus, cycloadduct **17d** bearing a quaternary stereocenter in the fusion of the bicyclic systems was obtained in 63% yield and with total diastereoselectivity. However, when the substituent is large, the reaction fails, and cycloadduct **17e** was not obtained, recovering the starting material.

A crotyl tethered ACP also failed to give the expected cycloadduct **17f**, observing a complex mixture of products, probably due to competitive β-hydride pathways prior to the reductive elimination. To avoid this side reactivity, a cinnamyl tethered ACP was also tested. However, no traces of cycloadduct **17g** were observed, and the starting material was recovered. The same result was observed when ACP **16h**, which bears an electronically activated alkene was evaluated.

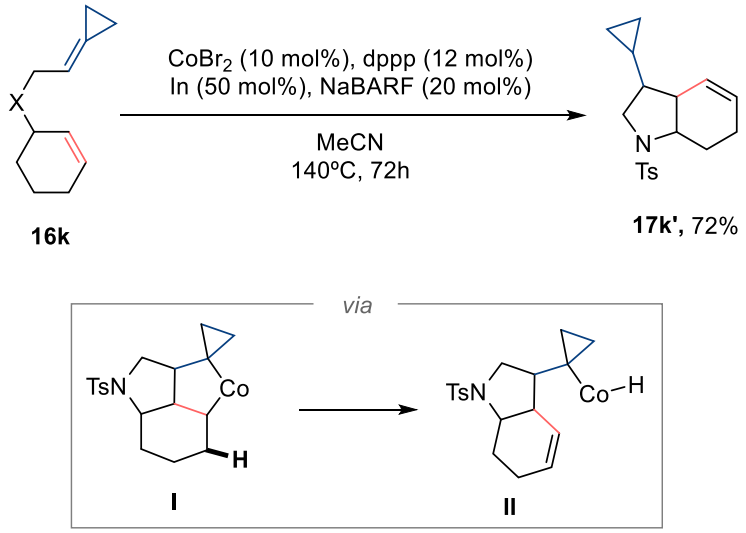
Regarding disubstituted alkenes, when a dimethyl-alkene was tested, a complex mixture of products was observed, with no traces of cycloadduct **17i**. However, a more reactive bis-ACP proved suitable for this transformation, and cycloadduct **17j** was isolated in an acceptable 62% yield.

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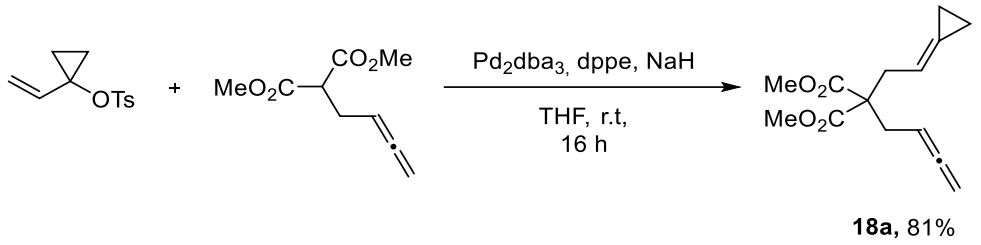
***Scheme 83**. Scope of intramolecular cobalt catalysed (3+2) cycloaddition of alkene-tethered ACPs.*

A mechanistically interesting result was obtained when the cyclohexene containing ACP **16k** was submitted to the optimal reaction conditions developed for the (3+2) cycloaddition of alkene-tethered ACPs (**Scheme 85**). Instead of the expected (3+2) cycloadduct, a new 5,6-bicyclic systems **17k'** was obtained in 75% yield. This could be explained by the initial formation of metallacycle **I** that, instead of undergoing the expected cyclopropyl to π-allyl rearrangement, might suffer a β-hydride elimination to deliver intermediate **II**, and eventually the product **17k'** after a final reductive elimination.



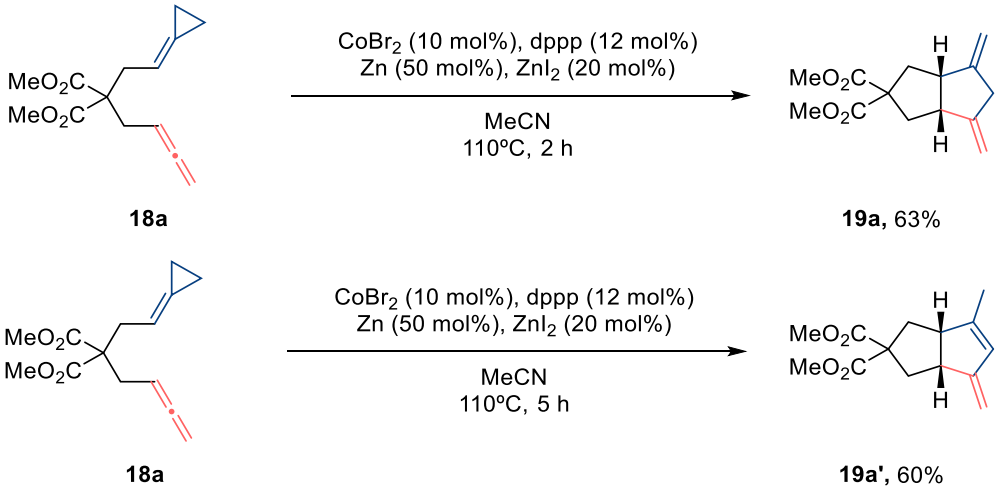
***Scheme 84**. Low valent cobalt catalysed cycloisomerization of ACP **12k**.*

We next decided to test if the cycloaddition could also be performed using an allene as 2C-unsaturated partner. Thus, we selected substrate **18a** as model **(Scheme 85**).[75]



***Scheme 85**. Synthesis of model substrate **16a** through a Tsuji-Trost reaction.*

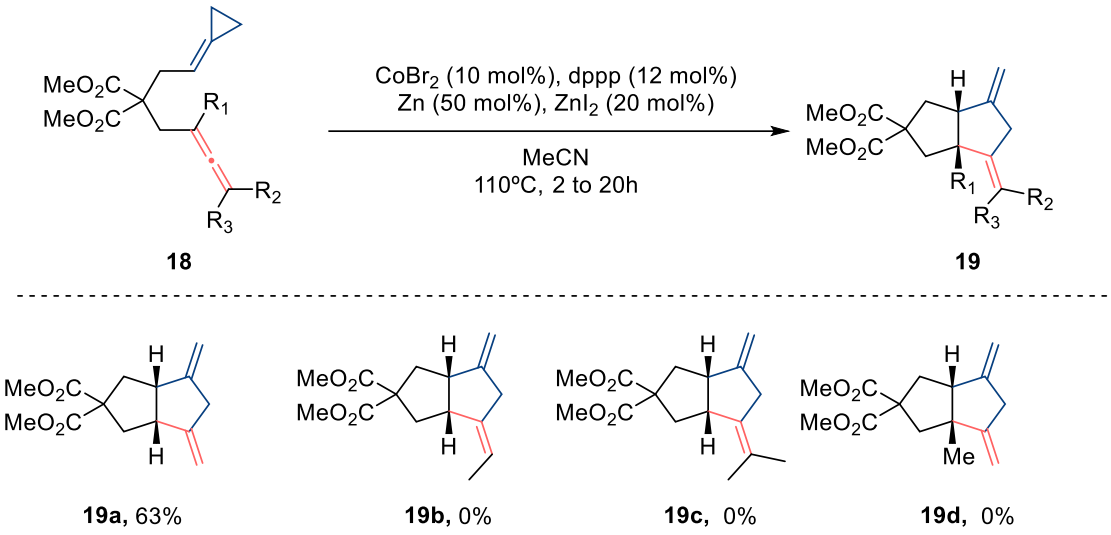
To our delight, when ACP **18a** was submitted to the reaction conditions illustrated in **Scheme 86a**, the corresponding (3+2) cycloadduct was obtained in 63% yield as only one diastereoisomer. Comparation with previously reported products with similar structures led us to establish that the product **19a** bears a *cis*-fused bicyclic system. Interestingly, if the substrate **18a** was reacted for a longer time, product **19a'** was isolated, due to an isomerization of initially formed **19a (Scheme 86b).**



***Scheme 86**. Cobalt catalysed (3+2) cycloaddition of allene-tethered ACPs.*

With these conditions in our hands, we explored the scope of (3+2) cycloaddition with allenes. Thus, a variety of internal and terminal substituted allenes were synthetized, following the procedures previously used for the synthesis of **18a.** We observed that the cycloaddition reaction is only feasible when monosubstituted allenes are used. For example, when a disubstituted allene like **18b** was used, the reaction was completely inhibited, so that **19b** was not detected. The same lack of reactivity was observed when a trisubstituted (**18c**) or internally substituted allene (**19c**) were tested, fully recovering the starting material (**Scheme 87**).

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***Scheme 87**. Scope of the (3+2) cycloaddition of ACPs and allenes mediated by a low valent cobalt catalyst.*

Moreover, any attempt to expand the scope of the reaction by changing the reaction conditions: other ligands (dppf or BINAP), reductant cocktail (In/$InIn_3$, Zn/$NaBAR^F$, Mn or Mg) or solvents (DCE, Dioxane), were ineffective, so that we only observed reactivity with the precursor **18a.**

During the evaluation of the scope of the (3+2) cycloaddition of ACPs with alkenes or allenes we observed an intriguing sensitivity of this methodology to the degree of substitution in each unsaturated moiety of the substrate. To shed light on this issue, Prof. Fernández made a computational assessment of a potential mechanistic profile (**Figure 18**). According to his calculations, the mechanism should be similar to the one previously calculated for the (3+2) cycloaddition of alkyne-tethered ACPs. First, an oxidative cyclometallation of the precoordinated **INT0** takes place. Although our initial assumption was that this step could be problematic, DFT calculations revealed that is indeed quite feasible, and with a similar activation energy (14.3 kcal/mol) than previously calculated with an alkyne (14 kcal/mol). Then, a cyclopropyl to π-allyl rearrangement followed by a reductive elimination would lead to the corresponding cycloadduct. As in the case of the (3+2) cycloaddition of alkyne-tethered ACPs, the reductive elimination was the rate limiting step. However, while in the reaction with alkynes the reductive elimination had a barrier of about 12 kcal/mol, in this case the barrier was calculated to be ≈28 kcal/mol. This huge change could be behind the poor reactivity of alkene-tethered ACPs under low valent cobalt catalysis.

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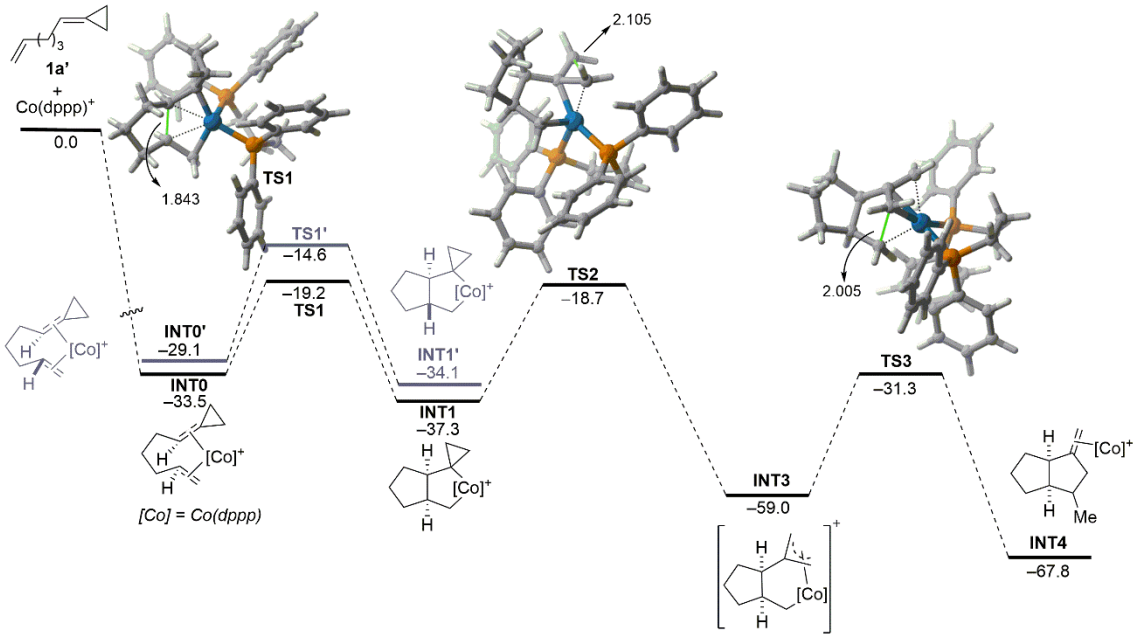


***Figure 18**. Mechanism profile calculated for the cobalt mediated intramolecular (3+2) cycloaddition of alkene-tethered ACPs.*

Moreover, due to the extreme sensitivity of the (3+2) cycloaddition towards the substitution at the alkene moiety, we compared the reductive elimination of two different model precursors, one with a non-substituted alkene, which experimentally provides the corresponding cycloadduct, and a second one with a methyl substituent at the terminal position of the alkene, which is known to deliver a complex mixture of products under our reaction conditions. As we expected, the energy barrier of the precursor bearing a methyl-substituted alkene (33.6 kcal/mol) turned out to be significantly higher than that of the unsubstituted one (27.7 kcal/mol) by approximately 6 kcal/mol. This huge energy variation could explain the limited scope of the reaction when substituted alkenes are used, as side processes from **INT3**, like β-hydride eliminations could more easily be competitive (**Figure 19**).

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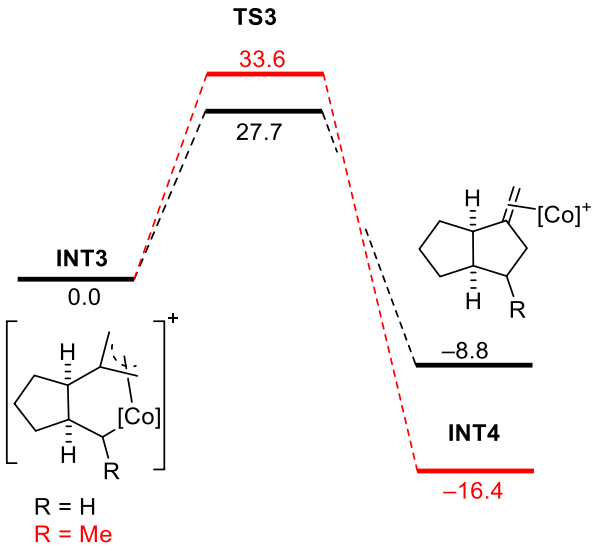
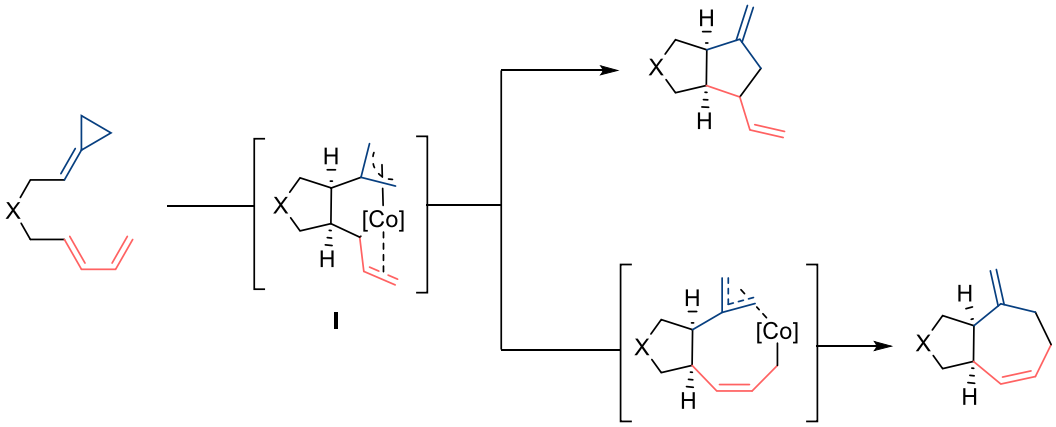


***Figure 19**. Energy profile for the reductive elimination of terminal and methyl-substituted alkene-tethered ACPs*

3.3.2. Cycloadditions with 1,3-dienes

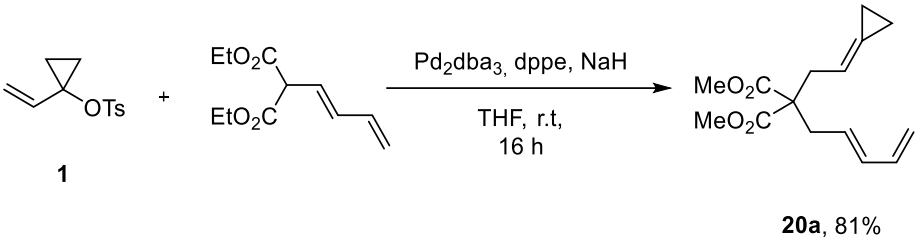
At this point, we envisioned that dienes could be interesting cycloaddition partners. On one hand, these unsaturated partners could facilitate the (3+2) cycloadditions by stabilizing a π-allyl cobaltacycle **I** or by decreasing the energy barrier of its subsequent reductive elimination to afford vinyl 5,5-bicycloadducts. However, if this intermediate evolves via π-allyl rearrangement, instead of a reductive elimination, 5,7-bicyclic scaffolds, resulting from a formal (4+3) cycloaddition could be obtained **(Scheme 88**).



***Scheme 88**. Possible outcomes for the cobalt mediated cycloaddition for diene-tethered ACPs.*

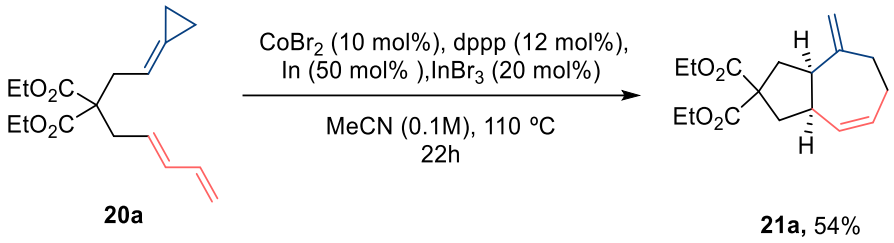
The reactivity was explored in substrate **20a**, which was synthesized according to previous methods described in the literature (**Scheme 89**).[90]

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Scheme 89. *Synthesis of model substrate* ***14a*** *through a Tsuji-Trost reaction.*

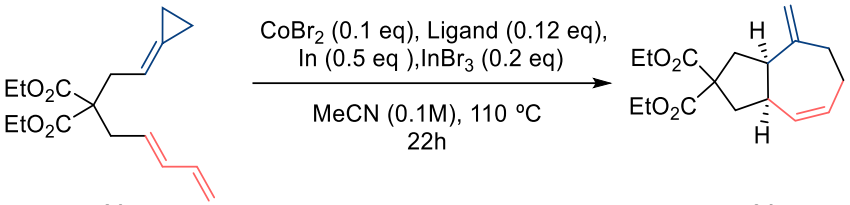
Remarkably, using **20a** and typical conditions tested for other systems consisted of $CoBr_2$ (10 mol%), dppp (12 mol%), In (50 mol%) and $InBr_3$ (20 mol%) (**Scheme 90**), we did observe the formation of the (4+3) cycloadduct **21a**, which was isolated in an acceptable 54% yield.



Scheme 90*. Cobalt catalysed intramolecular (4+3) cycloaddition of ACPs and dienes.*

Encouraged by this result and considering the absence of a general intramolecular (4+3) cycloaddition of diene-tethered ACPs, we decided to evaluate different chiral ligands (**Table 12**). The results obtained were very similar to the ones observed with alkenes. While bidentate chiral phosphines like BINAP or Garphos delivered cycloadduct **21a** as a racemate, the used of a ferrocene phosphine type chiral ligand induces a slight asymmetry (**Entry 6, Table 12**). Moreover, as in the case of alkenes, the best result was obtained when employing phosphite $\mathbf{L_{11}}$ which affords bicycle **21a** in a good 65% yield and 85:15 er.

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20a **21a**

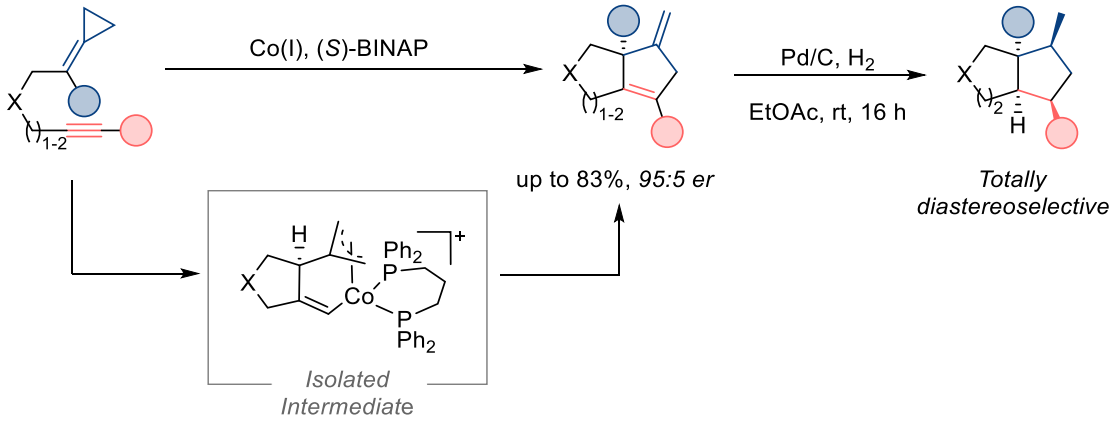
Entry	Ligand	Yield (%)	er (%)
1	*(S)*-BINAP	52	0
2	*(S)*-Ph-Garphos	68	0
3	*(S)*-BPE	53	0
4	*(S)*-IPr-PHOX	21	0
5	*(S)*-QUINAP	27	0
6	JOSIPHOS-SL-009-01	32	65:35
7	**L_{11}**	65	85:15

***Table 11**. Evaluation of chiral ligands in the intramolecular (4+3) cycloaddition of ACPs and dienes*

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4. Conclusions

In conclusion, we have developed the first enantioselective (3+2) intramolecular cycloaddition of alkyne-tethered ACPs. An *in-situ* Co(I) cationic complex bearing (S)-BINAP as ancillary chiral ligand promotes the reaction, allowing the assembly of several 5,5 or 5,6-fused carbocycles in good yield and with high enantiomeric control. The transformation is tolerant to a variety of alkyl-, aromatic- or terminal-substituted alkynes containing several functional groups like alcohols or silyl-ethers rings. Moreover, different groups in the connecting tether as well as internally substituted ACPs are allowed. In addition, the methodology also allowed the total diastereoselective construction of 5,5- or 5,6-carbocycles bearing up to 4 stereocenters after a simple hydrogenation protocol.

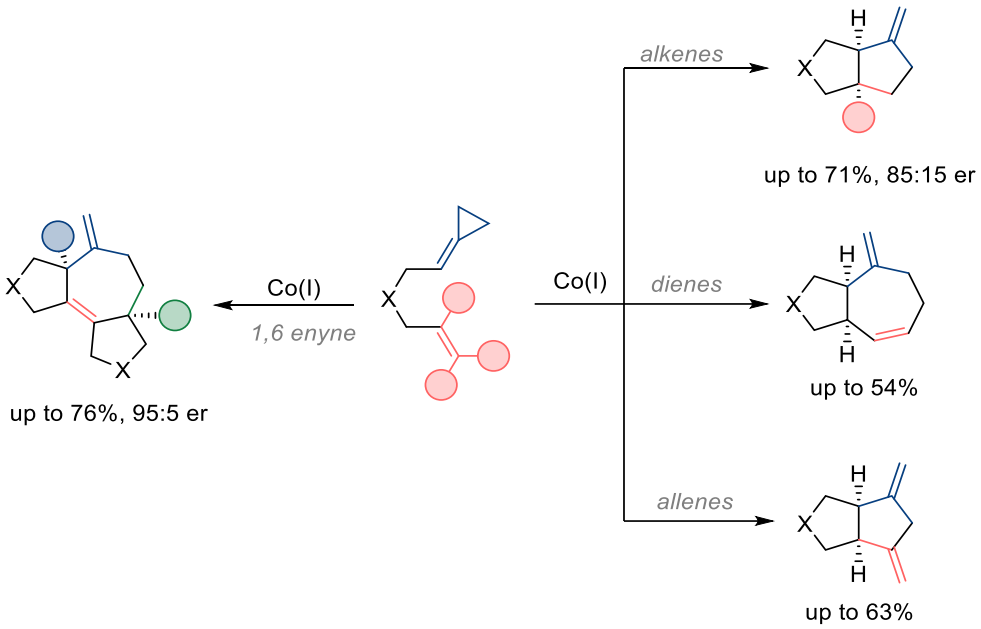


Stoichiometric experiments allowed to trap a π-allyl cobalt species that was confirmed to be a key intermediate. Finally, DFT calculations performed by Prof. Israel Fernandez shed further light into the reaction mechanism. Contrary to what was reported with Pd or Rh, the reaction involves an initial oxidative cyclometallation follow by a cyclopropyl to π-allyl rearrangement and a final reductive elimination to afford the corresponding cycloadduct.

The stability of the π-allyl cobalt species intermediate suggested that it would be possible to add a third component to the cycloaddition. Accordingly, we developed a Co-catalysed intramolecular (3+2+2) cycloaddition between ACPs, alkynes and alkenes that provides a variety of 5,7,6-tricyclic systems with different functional groups in the connecting tether, with high chemo and stereoselectivities. Contrary to the previously developed Pd and Rh-catalysed versions of this method, internally substituted alkenes and ACPs are tolerated by the cobalt catalyst, which allowed to synthetize 5,7,6-tricyclic systems bearing all carbon quaternary stereocenters at the ring fusion positions.

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Finally, we also studied the intramolecular cycloadditions with alkenes, allenes and 1,3-dienes. While alkene and allenes conduce to the formation of *cis*-(3+2) cycloadducts in good yields although with a relatively narrow scope, dienes engage in a formal (4+3) cycloaddition when terminal substituted dienes are employed. Preliminary enantioselective variants of these methods were explored although further efforts to reach a high enantioselective will be necessary.



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CHAPTER II

Palladium catalysed intermolecular (3+2) hetereocycloadditions of ACPs and carbonyls

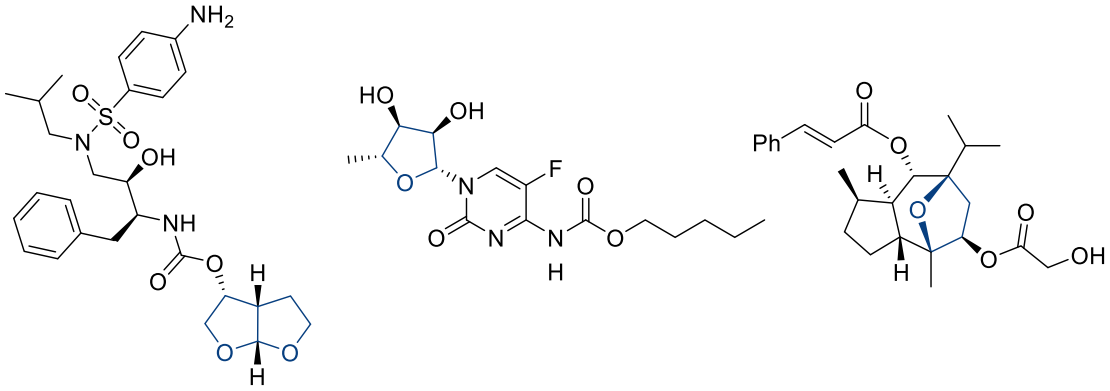
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1. Introduction

1.1 Relevance of 5-membered oxacycles

Many natural products with relevant applications in the pharmaceutical or agrochemical fields, among others, feature heterocyclic structural cores.[113] The rigidity of the cyclic structure plus the polarization of the molecule by the presence of heteroatom, and the eventual ability to engage in intermolecular interactions, raise interesting physicochemical properties responsible for the observed properties. Due to these unique properties such as solubility, lipophilicity, or hydrogen bonding capacity, there is a continuous demand of novel efficient synthetic methods towards the construction of structurally relevant heterocyclic systems.

Saturated oxygen heterocycles are highly abundant in nature, and present in a wide array of systems such a as macrolides,[114] polyether ionophores,[115] acetogenins[116] or oxidized lipids.[117] Among this kind of oxygen heterocycles, five membered oxacycles, commonly known as tetrahydofurans (THFs) are particularly abundant and relevant. These cyclic ethers have been frequently found as key structural units in therapeutic compounds (**Figure 20**) as well as important intermediates in the synthesis of complex molecules.[118] Thus, considerable efforts have been devoted to the development of simple and efficient methods for their assembly.



Darunavir
HIV protease inhibitor

Capecitabine
Antineoplastic

(-)-Englerin A
Renal cancer drug

Figure 20. *Natural products containing a 5-membered oxacycle with interesting therapeutic activity.*

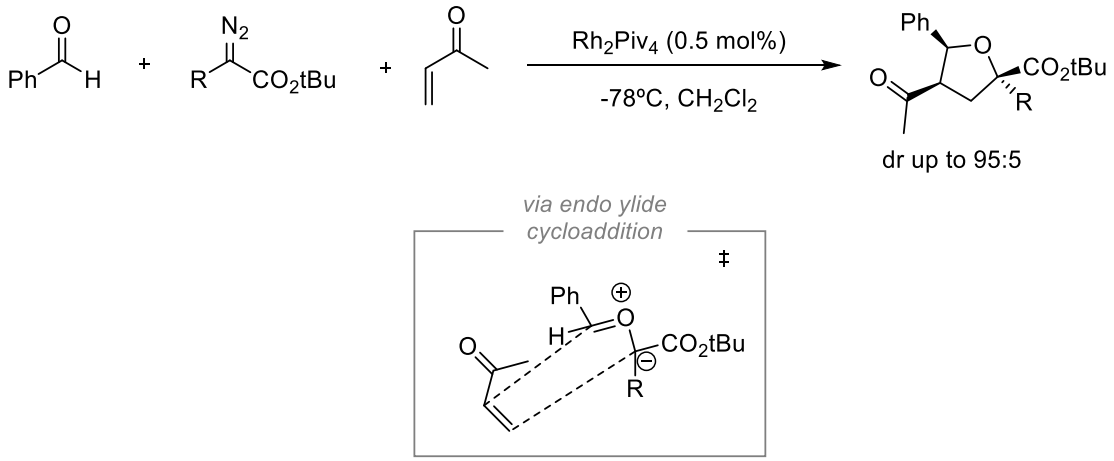
[113] Blakemore, D. C.; Castro, L.; Churcher, I.; Rees, D. C.; Thomas, A. W.; Wilson, D. M.; Wood, A. *Nat. Chem.* **2018**, *10*, 383–394.
[114] Lorente, A.; Lamariano-Merketegi, J.; Albericio, F.; Alvarez, M. *Chem. Rev.* **2013**, *113*, 4567e4610.
[115] Faul, M. M.; Huff, B. E. *Chem. Rev*. **2000**, *100*, 2407e2474.
[116] Li, N.; Shi, Z.; Tang, Y.; Chen, J.; Li, X. *Beilstein J. Org. Chem.* **2008**, 4.
[117] Jahn, U.; Galano, J.-M.; Durand, T. *Angew. Chem., Int. Ed.* **2008**, *47*, 5894e5955.
[118] Blutn, J. W.; Copp, B. R.; Keyzers, R. A; Munro, M. H. G.; Prinsep, M. R., *Nat. Prod. Rep.*, **2016**, *33*, 382-431.

1.2. Transition metal-catalysed cycloadditions and cyclizations towards tetrahydrofuran skeletons

As mentioned before, the assembly of 5-membered oxacycles represents a major goal in synthetic organic chemistry. Most methodologies for their synthesis are based in cyclization processes, including Prins cyclizations or ring-closing metathesis, among many others.[119] The assembly of tetrahydrofurans using formal cycloadditions is more attractive in terms of step economy, but methods based on this type of annulations, especially catalytic reactions, are less abundant. Needless to say, one of the most relevant methodologies to assemble oxacycles from simpler acyclic precursors involve the use of metal catalysts.

1.2.1 Methods involving metal carbene species

One of the most widely used cycloaddition strategies for the synthesis of these scaffolds relies on metal carbenes. For example, M. J. Fox and co-workers developed a formal (2+1+1) cycloaddition to highly substituted THFs, using a diazo compound, a carbonyl partner and activated alkenes, under the presence of a Rh(II) catalyst. The annulation involves the initial formation of a carbonyl ylide, by the reaction between the carbonyl and the metal carbene generated from the diazo species, and its subsequent dipolar cycloaddition with the alkene. The cycloadducts are obtained with high diastereomeric ratios bearing a configuration that corresponds to *endo* approach between the carbonyl ylide and the alkene (**Scheme 91**).[120]



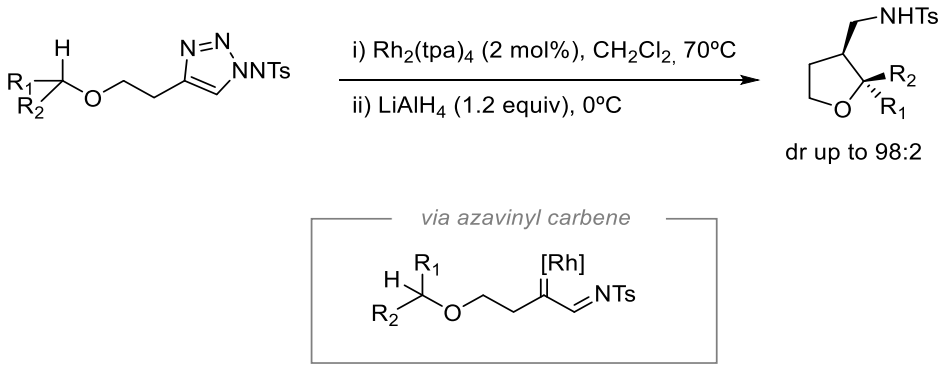
Scheme 91. *(2+2+1) cycloaddition of aldehydes, diazoesters and alkenes catalysed by Rh(II).*

Sarpong and co-workers developed a strategy where Rh(II)-azavinyl carbenes, generated in situ from a N-sulfonyltriazole, engage in intramolecular C(sp_3)-H functionalizations to

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[119] (a) Wolfe, J. P.; Hay, M. B. *Tetrahedron* **2007**, *63*, 261−290. (b) Jalce, G.; Franck, X.; Figadere, B. *Tetrahedron: Asymmetry* **2009**, *20*, 2537−2581.
[120] DeAngelis, A.; Taylor, M.T.; Fox, J. M. J. *Am. Chem. Soc.* **2009**, *131*, 3, 1101–1105.

deliver *cis*-2,3-disubstituted tetrahydrofurans in good yield and excellent diastereoselectivity (**Scheme 92**).[121]



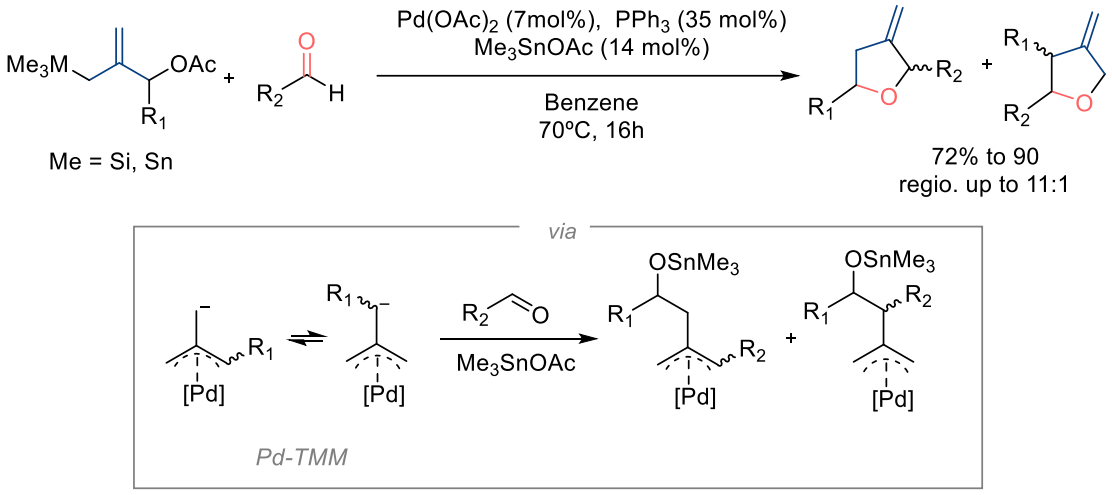
Scheme 92. *Intramolecular C(sp3)–H functionalization of azavinyl carbenes.*

1.2.2 Pd-TMM cycloadditions

Another common approach towards the synthesis of 5-membered oxacycles is based on formal transition metal-catalysed (3+2) cycloadditions between carbonyl compound and a 3C *synthon*. In this context, one of the pioneer examples of this strategy was reported by Trost and co-workers in 1990. This group demonstrated that a variety of silicon- or tin-based allylic reagents could participate as 3C partners in a formal (3+2) cycloaddition with different aldehydes, using a combination of $Pd(OAc)_2/PPh_3$ and trialkyl tin acetate (R_3SnOAc) as catalyst (**Scheme 93**).[122] Mechanistically, the authors proposed the formation of a Pd-trimethylenmethane (TMM) species which undergoes a 1,2-addition to the aldehyde to generate the corresponding tin alkoxide intermediate. An eventual intramolecular trapping of the π-allyl-Pd moiety by the tin alkoxide delivers the final furan. The possible formation of 2 isomeric Pd-TMM species explains why a mixture of regioisomers is obtained.

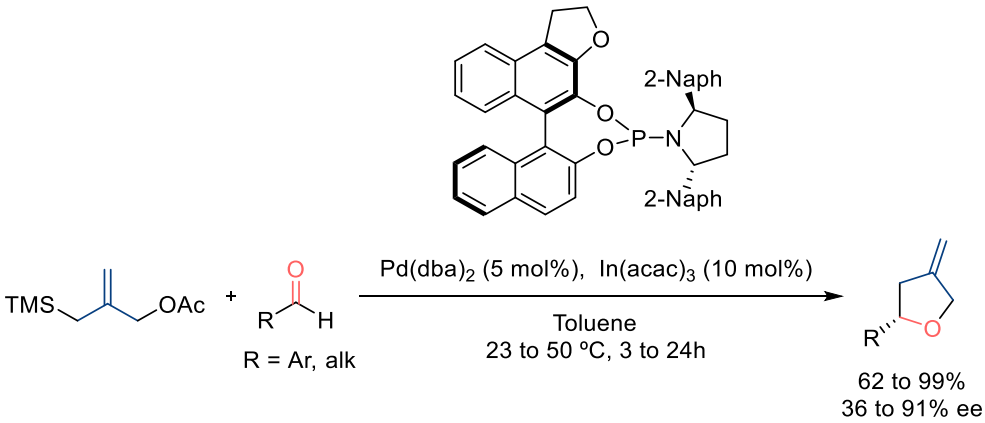
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[121] Lindsay, V.G.; Viart, H. M.F.; Saprong, R. *J. Am. Chem. Soc.* **2015**, *137*, 26, 8368–8371.
[122] Trost, B.M; King, S.A *J. Am. Chem. Soc.* **1990**, *112*, 1, 408–422.



***Scheme 93**. Pd-catalysed (3+2) cycloaddition between TMM precursors and aldehydes, and mechanism exemplified for the case of a stannane.*

Two decades later the same authors developed the enantioselective variant of this transformation. The successful control of the asymmetric outcome in the reaction arises from the use of a conformationally constrained phosphoramidite and 3-acetoxy-2-trimethylsilylmethyl-1-propene as TMM precursor (**Scheme 94**). Although several types of aldehydes are tolerated (aromatic, hetereoaromatic or allylic) affording the corresponding products in good yields, only two examples show high enantioselectivities, above 90% *ee*.[123]

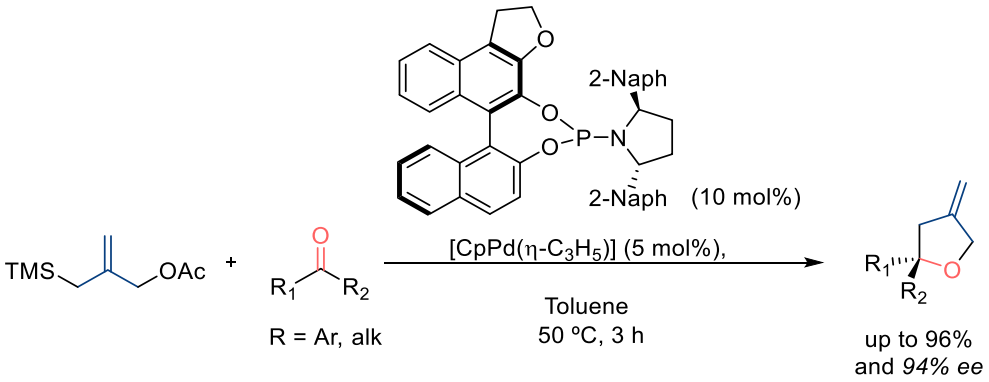


***Scheme 94**. Pd-catalysed enantioselective (3+2) cycloaddition between TMM precursors and aldehydes.*

Interestingly, the same chiral ligand was also found to be key for the development of enantioselective (3+2) cycloadditions of these TMM-precursors with a variety of aromatic ketones, instead of aldehydes (**Scheme 95**).[124]

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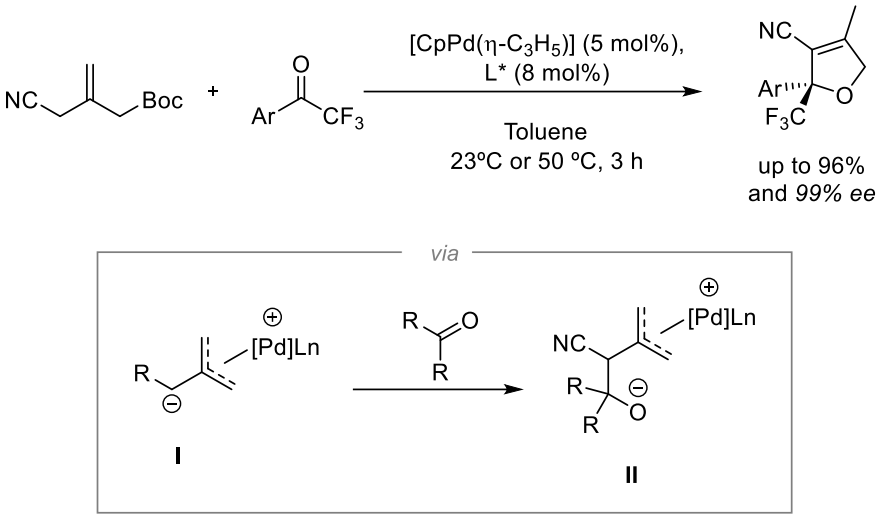
[123] Trost, B. M.; Bringley, D. A.; Silverman, S.M., J. *Am. Chem. Soc.* **2011**, 7664–7667.
[124] Trost, B. M.; Bringley, D. A, *Angew. Chem. Int. Ed.* **2013**, *52*, 4466–4469.



Scheme 95. *Pd-catalysed enantioselective (3+2) cycloaddition between TMM precursors and ketones*

Trying to expand this methodology towards the construction of more complex products, Trost and co-workers proposed the use of nitrile substituted-TMM precursors. Although these substrates were not reactive with simple ketones, fluorinated ketones did participate in the process. Thus, the asymmetric construction of trifluoromethylated dihydrofurans was successfully achieved (**Scheme 96**).[125] These results are relevant because fluorinated compounds are extremely important in medicinal chemistry, given that the presence of an electronegative group such as F, CF_3 or a similar variant in a molecule can improve important aspects such as the acidity, lipophilicity or its metabolic stability.[126] In addition, despite the importance of fluorinated furans in medicinal chemistry, only a handful of methods can be found in the literature towards the construction of these scaffolds though a simple and straightforward cycloaddition reaction.[127]

[125] Trost, B.M.; Mata, G., *Angew. Chem. Int. Ed.* **2018**, *57*, 12333–12337.
[126] Purser, S.; Moore, P. R.; Swallow, S.; Gouverneur, V. *Chem. Soc. Rev.*, **2008**, *37*, 320–330.
[127] a) Uno, H.; Kawai, K.; Araki, T.; Shiri, M.; Shibata, N. *Angew. Chem.Int. Ed*. **2022**, *61*, e2021176. b) Malhotra, D.; Liu, L.; Wang, W.; Durham, M.; Hammond, G. B. Xu, B. *Journal of Fluorine Chemistry* **2014**, *167*, 179–183.



***Scheme 96**. Pd-catalysed enantioselective (3+2) cycloaddition between TMM precursors and ketones and trifluoromethyl ketones.*

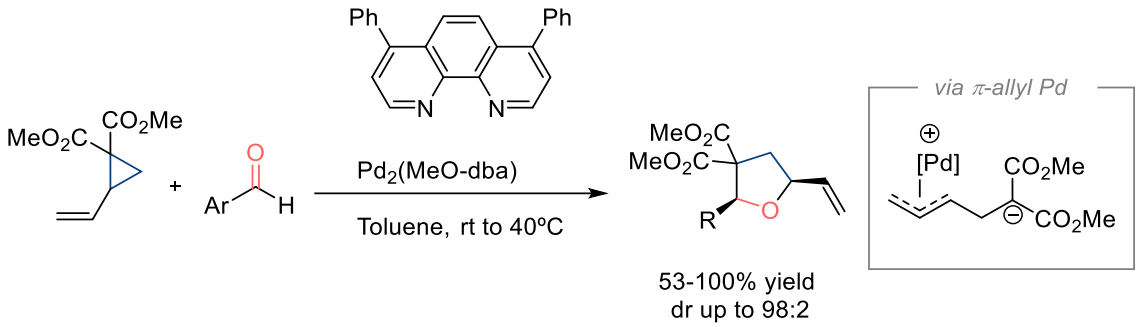
Mechanistically, all the cycloadditions illustrated above operate in the same manner. The Pd-TMM **I** adds on a regioselective fashion in the corresponding carbonyl compound to afford intermediate **II** (**Scheme 96**) Finally, intramolecular interception of the Pd π-allyl moiety affords the corresponding tetrahydrofuran.

1.2.3 Cycloadditions of Donor-Acceptor cyclopropanes

The generation of 3C dipoles for the synthesis of tetrahydrofurans is not limited to Pd-TMM species or metal carbene intermediates. For example, Tsuji proved that vinyl donor-acceptor (D-A) cyclopropanes can also generate 1,3-carbon dipoles in the presence of Pd^0 catalysts, and these dipolar species can be subsequentially trapped with an adequate electrophile.[128] In this context, Johnson and co-workers proved that this strategy was valid towards the synthesis of tetrahydrofurans. The merge of donor-acceptor vinycyclopropane and an aromatic aldehyde under a Pd^0 catalysis conduces to the diastereoselective synthesis of vinyl tetrahydrofurans (**Scheme 97**). [129]

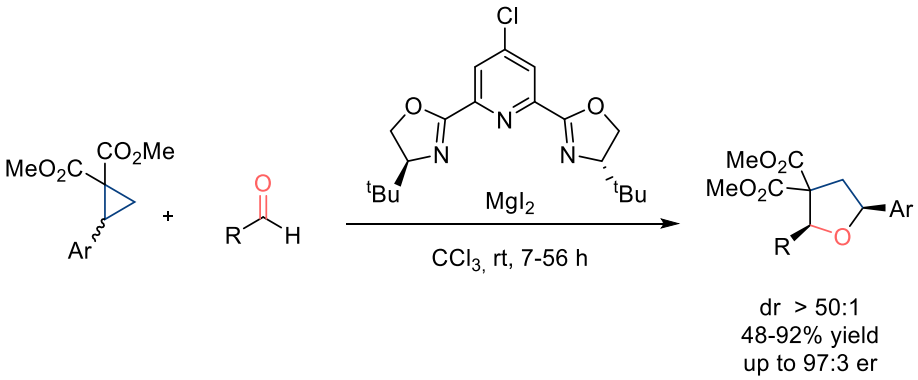
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[128] (a) Yamamoto, K.; Ishida, T.; Tsuji, J. *Chem. Lett*. **1987**, 1157. (b) Shimizu, I.; Ohashi, Y.; Tsuji, J. *Tetrahedron Lett.* **1985**, *26*, 3825.
[129] Parsons, A. T.; Campbell, M. J.; Johnson, J. S. *Org. Lett.* **2008**, *10*, 12, 2541–2544.



Scheme 97. *Pd-catalysed (3+2) cycloaddition of D-A cyclopropanes and aldehydes.*

The same authors also developed an interesting, (^{t}Bu-pybox)MgI_2 mediated dynamic kinetic (3+2) cycloaddition of racemic donor-acceptor cyclopropanes and aldehydes to afford THFs in good to excellent yields, with complete diastereoselectivities and er's up to 97:3 (**Scheme 98**).[130]



Scheme 98*. Enantioselective (3+2) cycloaddition of D-A cyclopropanes and aldehydes.*

1.2.4 Cycloadditions of ACPs and carbonyl compounds

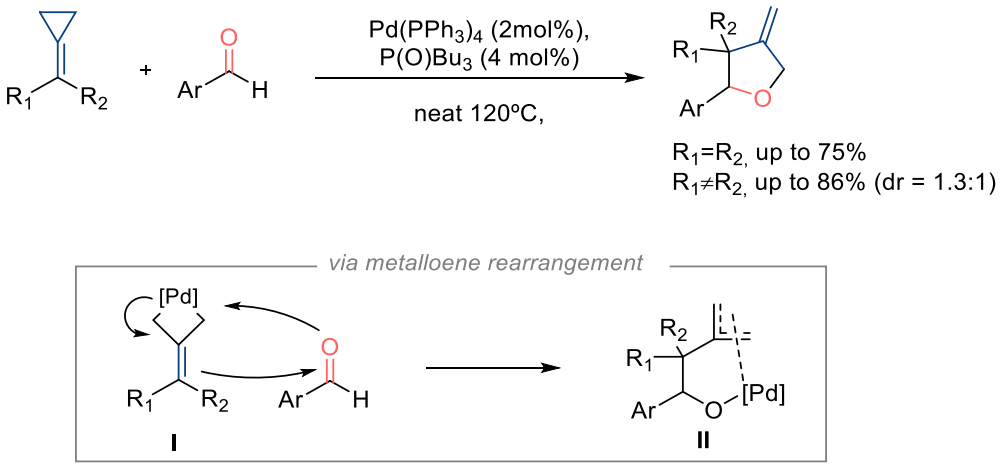
As mentioned in Chapter 1 of this manuscript, ACPs can participate in numerous transition metal-mediated cycloadditions as 3C *synthons*. However, only one cycloaddition with carbonyl compounds was reported before the beginning of this thesis. In particular, Yamamoto described in 2001 the first example of a TMC (3+2) cycloaddition between ACPs and aromatic aldehydes (**Scheme 99**).[131] Although the method allows the assembly of functionalized tetrahydrofurans with good efficiency, it required the use of neat conditions and proved to be limited to aldehydes, (ketones do not participate in the process) and to ACPs with two substituents at their alkene moiety. Thus, when monosubstituted ACPs are used, the yields were low.

Mechanistically, the authors proposed that the reaction is initiated by the characteristic Pd-mediated distal cleavage of the C-C of the ACP. Then the palladacyclobutane would

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[130] Parsons, A.T.; Johson, J. S., J. *Am. Chem. Soc.* **2009**, *131*, 9, 3122–3123.
[131] Nakamura, I.; Oh, B. H.; Saito, S.; Yamamoto, Y. *Angew. Chem. Int. Ed.* **2001**, *40*, 1298–1300.

experiment a metalloene rearrangement with the aromatic aldehyde leading to π-allyl palladium complex **II** (**Scheme 99**). Finally, a reductive elimination affords the corresponding tetrahydrofuran.



Scheme 99. *Pd-catalysed (3+2) cycloaddition of ACPs and aldehydes.*

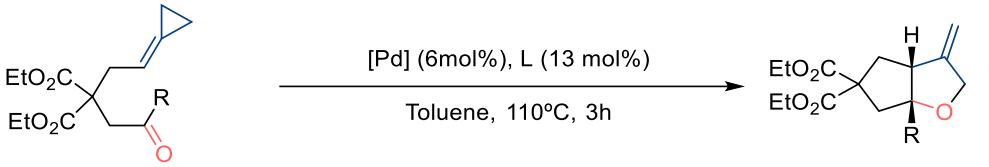
Considering these scarce precedents and the lack of intramolecular variants of the cycloaddition between ACPs and carbonyl partners, our group decided to explore these processes.[132]

During the optimization of a model substrate (**Table 12**), Dr. Verdugo found that the use of bulky phosphites, phosphoramidites or phosphine oxides as ligands, previously successful for the intermolecular (3+2) cycloaddition of ACPs and aldehydes developed by Yamamoto failed to give the cycloadducts in good yields.

In this context, Dr. Verdugo found that the use of Buchwald's bulky biaryl monophosphines, which are excellent ligands for the formation of C-N or C-O bonds through Pd- mediated cross-couplings,[133] was also relevant in the (3+2) cycloaddition of ACPs with carbonyl compounds, to give tetrahydrofuran skeletons. In particular, after an optimization of the reaction conditions, Brettphos was chosen as the optimum ligands for the cycloadditions of ACP-tethered to aldehydes, while Ruphos performed better when ketones were involved in the cycloaddition. In both cases, the reaction provides an efficient and stereoselective assembly of fused-THF skeletons.

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[132] Verdugo, F.; Da Concepción, E.; Rodiño, R.; Calvelo, M.; Mascareñas, J.L.; López, F. *ACS Catal.* **2020**, 10, 7710–7718.
[133] Ingoglia, B. T.; Wagen, C.C.; Buchwald, S. L. *Tetrahedron*, **2019**, *75*, 4199-4211.

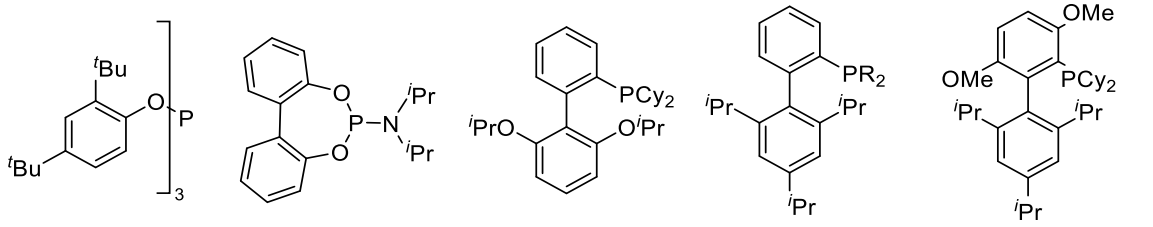


22a, R = H
24a, R = Me

23a, R = H
25a, R = Me

Entry	R	[Pd]	L	Yield(%)
1	H	$Pd_2(dba)_3$	L1	0
2	H	$Pd_2(dba)_3$	L2	20
3	H	$Pd_2(dba)_3$	Ruphos	45
4	H	$Pd_2(dba)_3$	Brettphos	75
5	H	$Pd_2(dba)_3$	Xphos	71
6	H	$Pd(PPh_3)_4$	$P(O)Bu_3$	20
7	Me	$Pd_2(dba)_3$	Brettphos	65
8	Me	$Pd_2(dba)_3$	tBuXPhos	80
9	Me	$Pd_2(dba)_3$	Ruphos	90

Table 12. *Screening conditions for the intramolecular Pd-catalysed (3+2) cycloaddition of ACPs and aldehydes or ketones.*



L1 **L2** **RuPhos**

R = Cy, **XPhos**
R = tBu, **^{t}BuXPhos**

R = Cy,**Brettphos**

DFT calculations confirmed that the success of these ligands is based on their ability to undergo secondary hemilabile interactions with the Pd centre which stabilizes intermediates and transition states (**Figure 20**).

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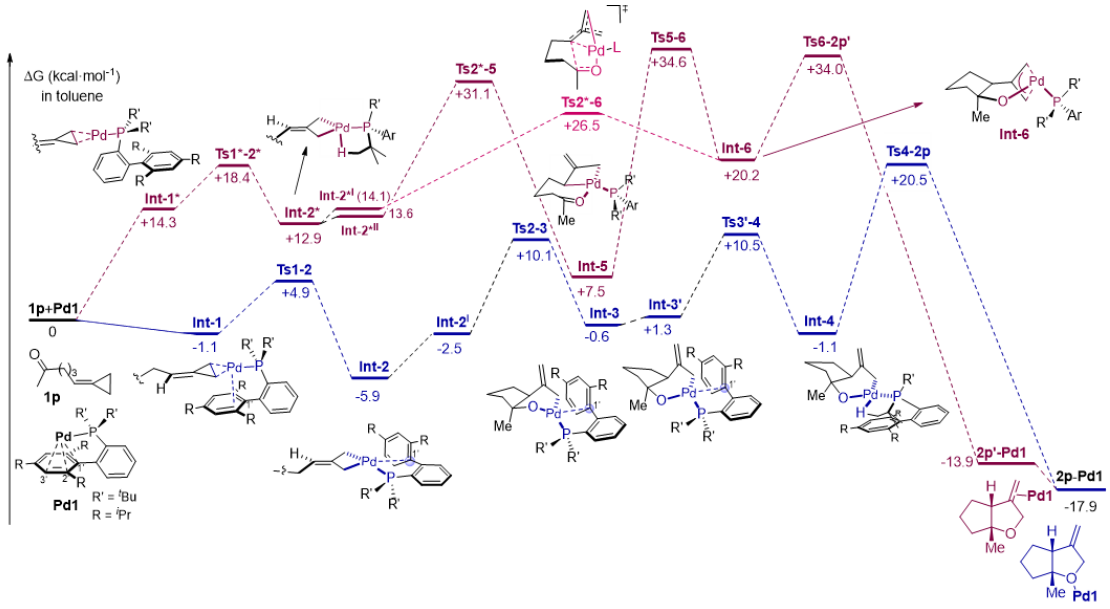
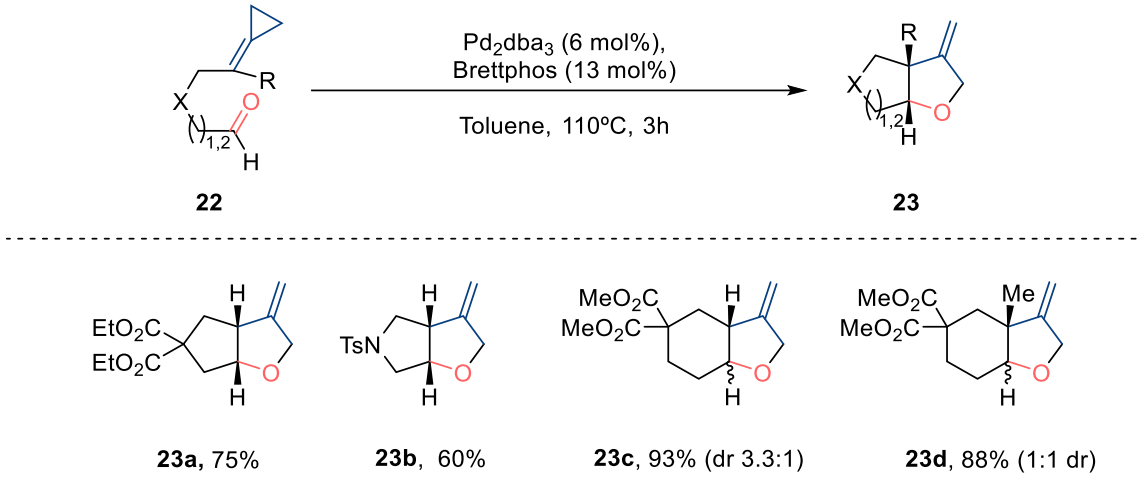


Figure 21. *Gibbs Energy Profile for the intramolecular (3+2) cycloaddition of ACPs and carbonyls catalysed by the Pd-t BuXPhos Complex Pd1, in Toluene.*

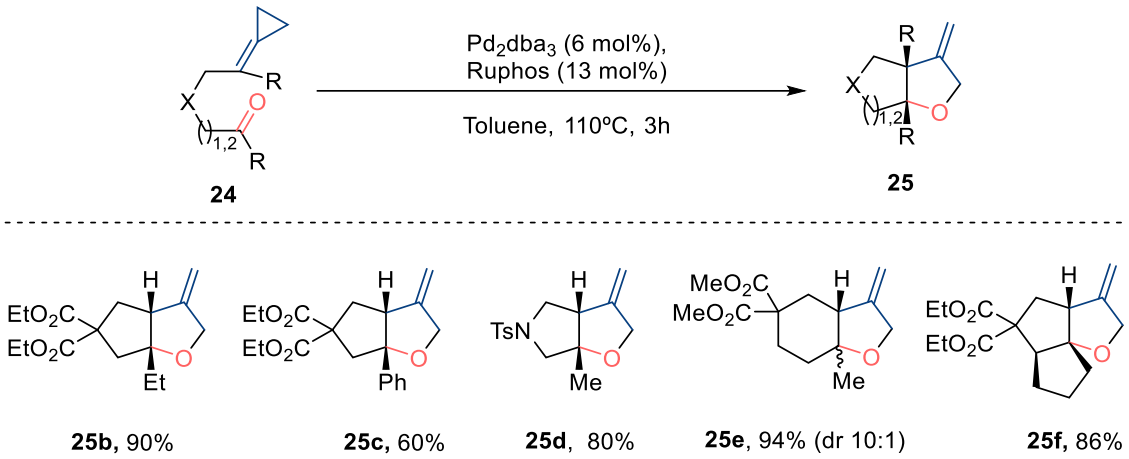
The methodology was also valid for other precursors. So, in the (3+2) cycloaddition of aldehydes, different connecting tethers featuring malonate (**23a**) or NTs (**23b**) groups are tolerated. Moreover, cyclohexane-fused methylene-THFs can also be made, although with erosion in the diastereoselectivity of the reaction (**23c**). Notably, the annulation could also be carried out with a precursor that bears a methyl group at the internal alkene position of the ACP to afford the corresponding bicyclic product **23d**, featuring a quaternary carbon stereocenter at the ring fusion (**Scheme 100**).



Scheme 100*. Scope of the intramolecular Pd-catalysed (3+2) cycloaddition of ACPs and aldehydes.*

When using ketones as cycloaddition partners, the reaction tolerates different substituents at the carbonyl moiety such as ethyl (**25b**) or phenyl (**25c**). Moreover, as in the case of the aldehydes, different connecting tethers are tolerated (**25c**) and the reaction could be extended to build cyclohexane-fused methylene-THFs (**25e**). Notably,

the cycloaddition of a substrate bearing the ACP tethered to a cyclopentanone moiety through its α-carbonyl position was also accomplished. Despite this precursor already holds a stereocenter, the cycloaddition proceeded smoothly, delivering the tricyclic adduct **25f**, which exhibits three consecutive stereocenters, in excellent yield and complete diastereoselectivity (**Scheme 101**).

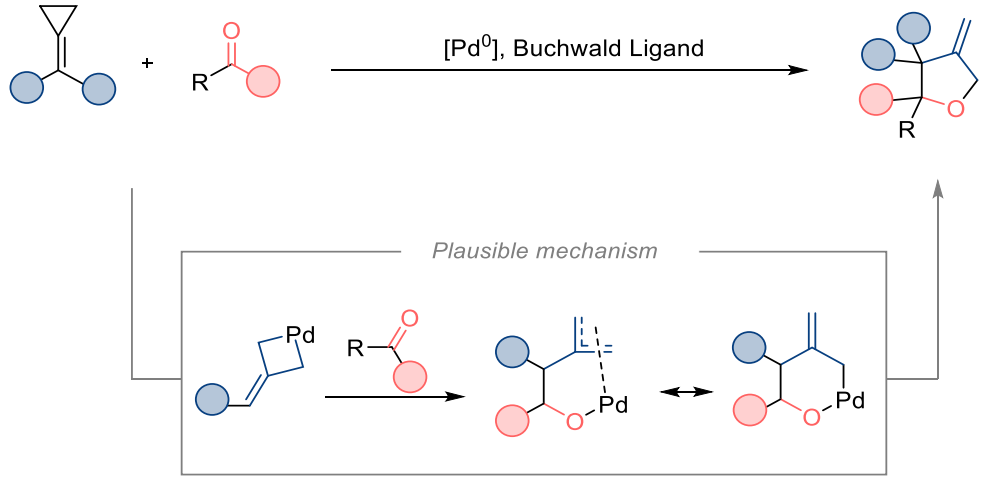


***Scheme 101**. Illustrative examples for the scope of the intramolecular Pd-catalysed (3+2) cycloaddition of ACPs and ketones.*

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2. Objectives

Based on the previous results of the group in the Pd-catalysed intramolecular cycloadditions of ACPs and carbonyls, and considering the scarcity of related metal catalysed intermolecular cycloadditions, in particular with ketones, which are unprecedented, our main goal in this chapter consisted of the development of highly selective intermolecular (3+2) cycloadditions between ketones and ACPs. Based on the previous results by the group, the use of Buchwald ligands might be key to enable these reactions.

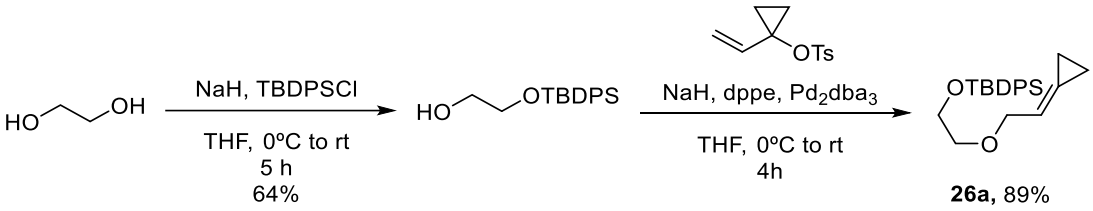


***Scheme 102**. Palladium catalysed (3+2) heterocycloaddition reaction and mechanistic hypothesis.*

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3. Results and discussion

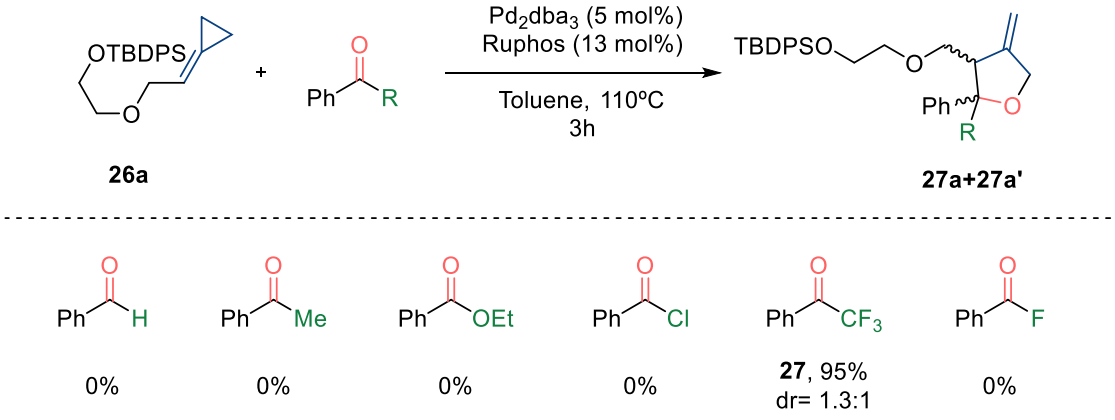
To study the viability of the reaction we prepared the alkylidenecyclopropane **26a** as model cycloaddition precursor. This compound was synthesized in two steps consisting of TBDPS monoprotection of ethyleneglycol and a subsequent Pd-catalysed allylic etherification with the vinyltosylate **1 (Scheme 103)**. The desired product **26a** was obtained with an overall 72% yield (two steps).



***Scheme 103**. General synthesis of model substrate **22a**.*

We then assayed the reaction with ketones using the optimal conditions developed for the intramolecular (3+2) process. When the reaction was carried out using 2 equivalents of benzaldehyde, acetophenone, ethyl benzoate or benzoyl chloride, in toluene at 110 °C full conversion of **26a** was observed, but unfortunately, only a complex mixture of undesired by-products was observed.

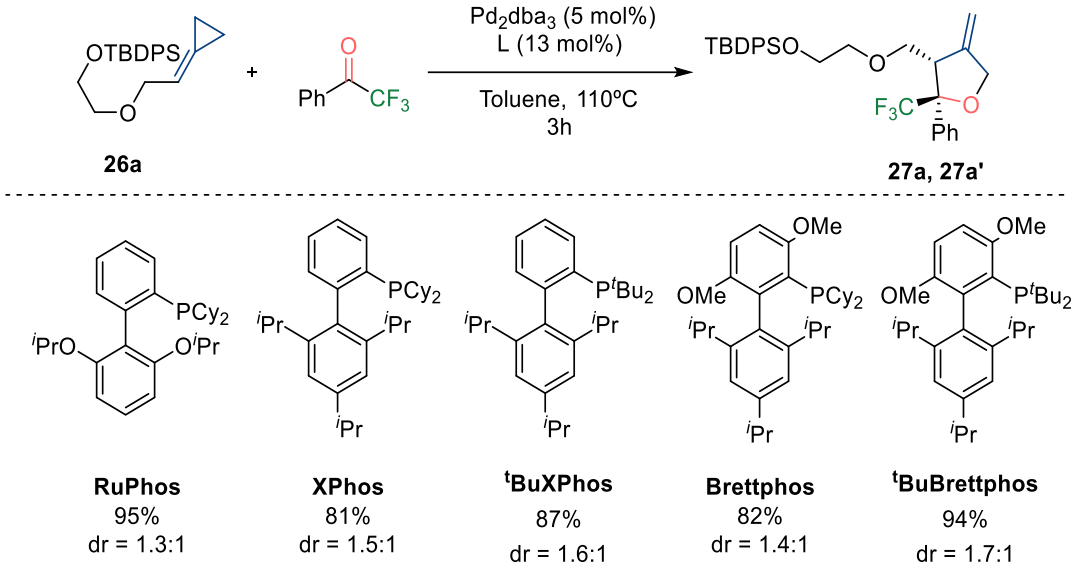
However, 2,2,2-trifluoroacetophenone reacted smoothly with complete regioselectivity, affording the corresponding (3+2) cycloadducts **27a** and **27a'** in excellent overall yield as a mixture of diastereoisomers (dr = 1.3: 1). The major diastereoisomer was assigned by analogy with other cases (*vide infra*) and holds the CF_3 group and the α-hydrogen in *cis* disposition (**Scheme 104**).



***Scheme 104.** Reactivity evaluation of different carbonyl compounds with model ACP **22a**.*

Trying to improve the diastereoselectivity, we evaluated different biaryl Buchwald phosphines. Unfortunately, despite the excellent overall yields observed in most cases,

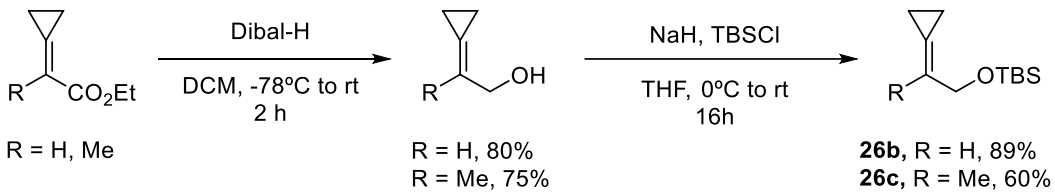
the diastereomeric ratio remained low, being ^{t}BuBrettphos the best ligand (dr = 1.7: 1, **Scheme 105**). Nonetheless, subsequent optimization studies were carried out with RuPhos**,** due to its lower cost but similar performance.



Scheme 105*. Ligand screening in the endeavours of the Pd-catalysed (3+2) cycloaddition of ACPs and trifluoromethyl ketones. Major diastereoisomer determine by NMR.*

In conclusion, we established as optimal conditions for the intermolecular (3+2) cycloaddition of ACPs and trifluoromethyl ketones the use of Pd_2dba_3 (5 mol%) as catalyst, Ruphos as ligand (13 mol%) in toluene at 110°C for 3 hours.

At this point we wonder about the viability of the reaction employing other ACPs than **26a.** The silyl ether analogue **26b** was easily made by reduction of α,β-unsaturated ester ACP[134] with DIBAL-H followed by silylation of the alcohol. The same strategy can be also applied to the synthesis of internally substituted ACP **26c** (**Scheme 106**).

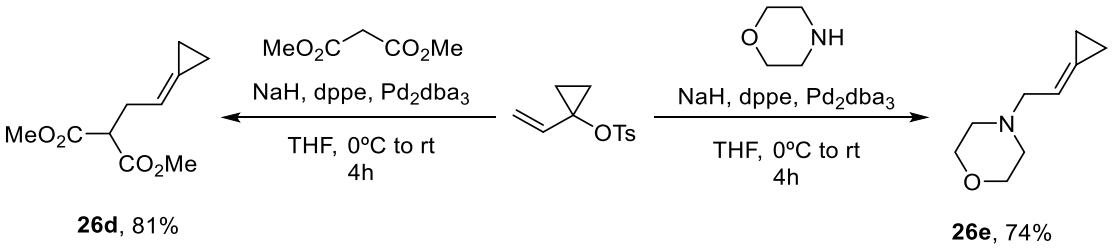


Scheme 106. *Synthesis of simple OTBS-ACPs*

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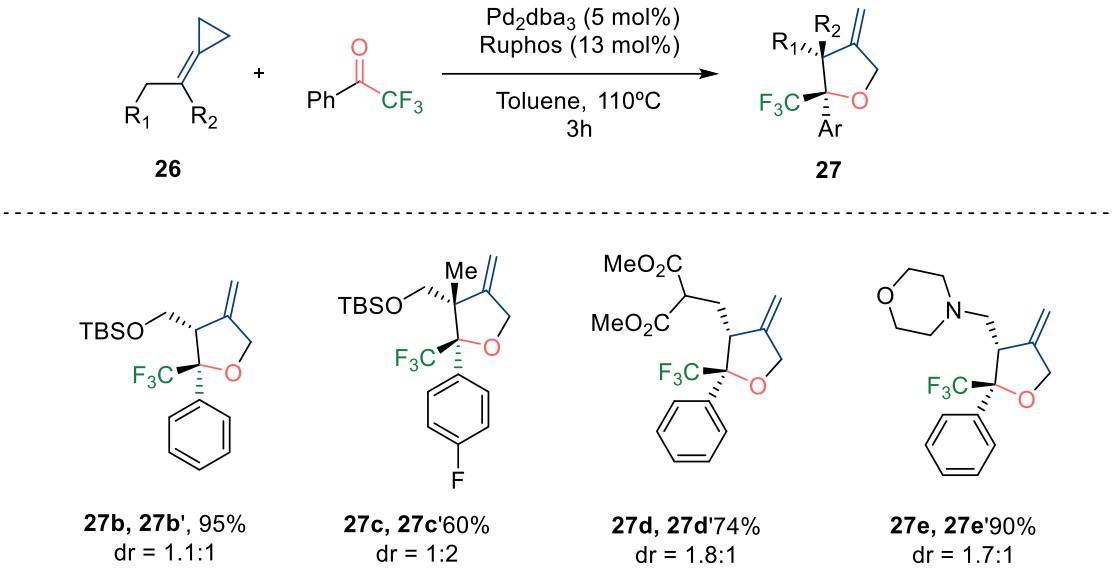
[134] Hori, H.; Arai, S.; Nishida, A. *Adv. Synth. Catal.* **2017**, *359*, 1170–1176.

Moreover, we were curious to analyse the behaviour of ACPs lacking an oxygenated tether. So, ACPs **26d** with a fully carbonated skeleton or **26e** with a morpholine group were synthetized through a Pd-catalysed allylic substitution (**Scheme 107).**



Scheme 107. *Synthesis of non-oxygenated tethered ACPs.*

The reactivity of substrates **26b-26e** was evaluated in presence of 2,2,2-trifluoroacetophenone. Gratifyingly, the corresponding *exo*-methylene THF products were formed in very good yields albeit in general with low diastereoselectivies. In the case of the tetrasubstituted analogue **26c** it was needed to heat up 130 °C to provide the corresponding adduct bearing two adjacent chiral quaternary centres (60% yield **27c:27c'** = 1:2) (**Scheme 108**).



Scheme 108. *Scope of ACPs in its Pd-catalysed (3+2) cycloaddition with trifluoromethyl ketones. Major diastereoisomer determine by NMR.*

The relative configuration for the malonate- containing product, both *cis* (**27d**) and *trans* (**27d'**) was confirmed by 1D-nOe experiments (**Figure 22**). Thus, isomer *syn* is obtained preferentially, similarly to the intramolecular reaction. By analogy, the relative configuration could also be determined for other examples.

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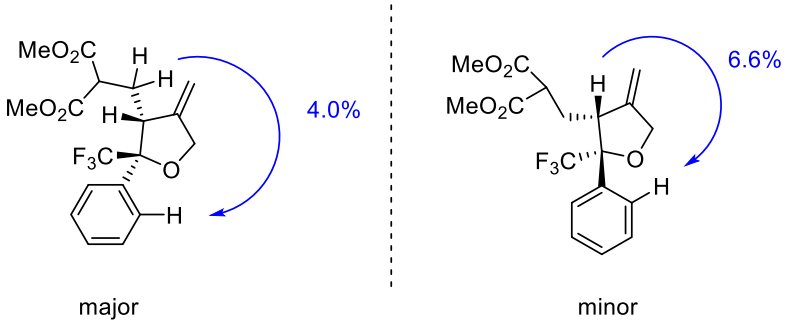
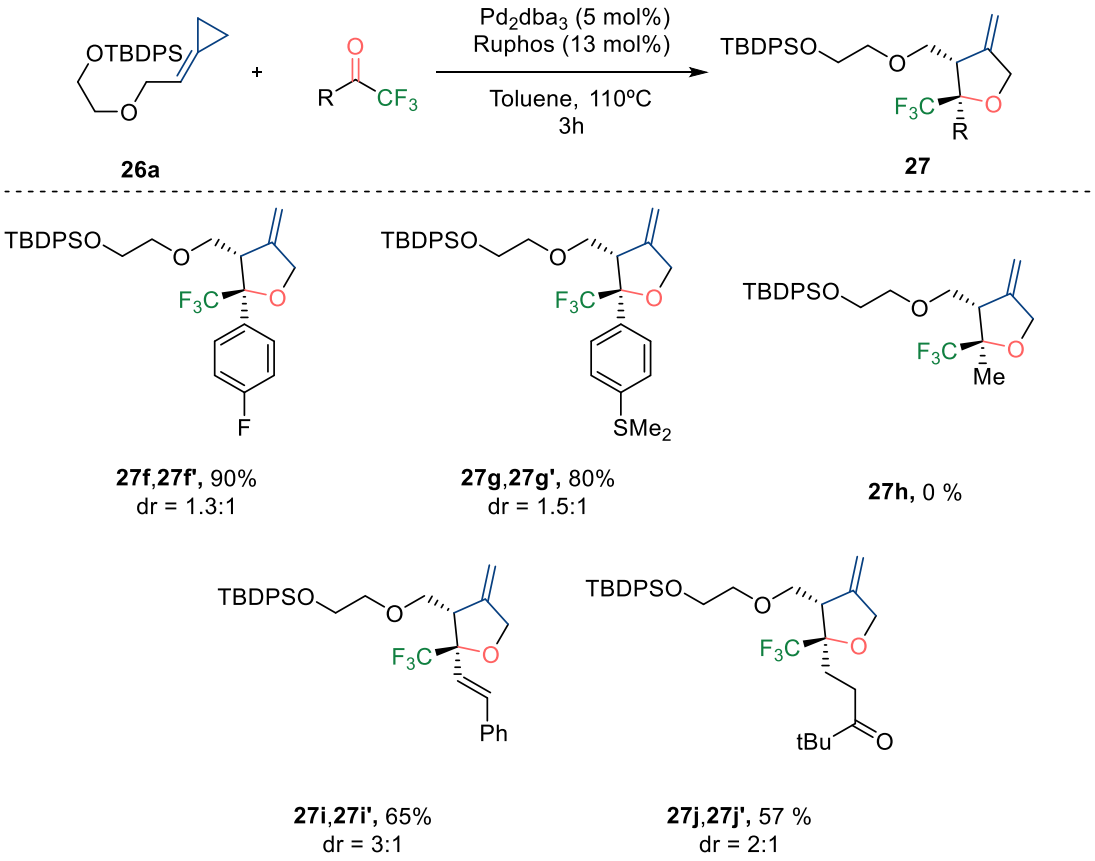


Figure 22. *nOe experiments to assign diastereoisomers of the Pd-catalysed (3+2) cycloaddition of ACPs and trifluoromethyl ketones.*

At this point, other trifluoromethyl ketones beyond the model 2,2,2-trifluoroacetophenone were also evaluated. Thus, aromatic trifluoromethyl ketones bearing electron-withdrawing and electron-rich groups deliver the corresponding tetrahydrofurans in excellent yields (90% and 80% respectively) albeit with low diastereomeric control (dr = 1.3:1 for **27g** and dr = 1.5:1 for **27h**).

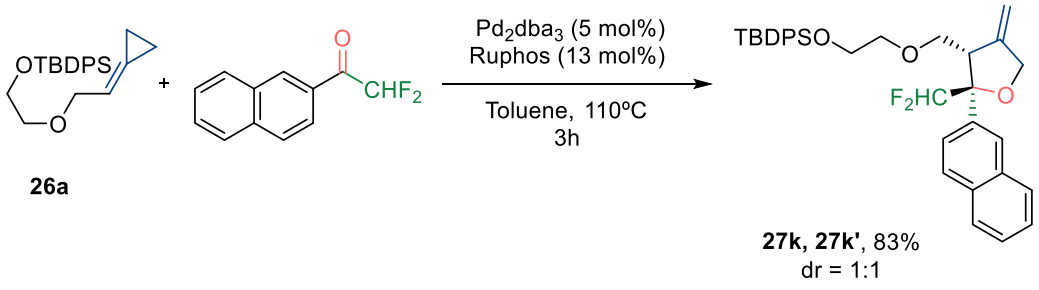
The cycloaddition did not proceed with aliphatic ketones such as trifluoromethyl acetone (decomposition of starting material). However, we were pleased to observe that an α,β-unsaturated ketone such as the cinnamyl derivative reacts with **26a** to give the desired cycloadduct **27j** as a 3:1 mixture of isomers (65% yield). Moreover, the reaction works with 3-oxo-alkyltrifluoromethyl ketones, and thus, *exo*-methylene THFs like **27k** could be obtained in 57% yield (dr 2:1).

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Scheme 109. *Scope of trifluoromethyl ketones in its Pd-catalysed (3+2) cycloaddition with ACPs.*

Interestingly, the scope of the reaction could be extended to other fluorinated ketones like difluoromethyl ketones. Thus, the expected THF **27l** was formed in good 83% yield but as in the case trifluoromethyl ketones, with non-diastereomeric control (dr = 1:1) (**Scheme 110**).



Scheme 110*. Pd catalysed (3+2) cycloaddition of ACP 22a and difluromethyl ketone.*

Finally, we were intrigued by the special behaviour observed with trifluoromethyl ketone, with respect to other carbonyl compounds. Hence, Ricardo Rodiño, PhD student of our research group, performed a set of preliminary calculations in order to shed light in this topic. As it is illustrated in **Figure 23**, a comparative energetic profile of the reaction with trifluoromethyl acetophenone (black path) and its analogue acetophenone (blue pathway) was performed. According to the DFT calculations, the

main difference into these two situations relies on the migratory insertion step. From the palladacyclobutane formed after a distal oxidative addition, the migratory insertion of acetophenone needs to overcome a barrier of 25.1 kcal/mol. However, the trifluoromethyl analogue requires only 7.2 kcal/mol in the same step. This enormous energetic difference could be the reason of the reactivity observed experimentally.

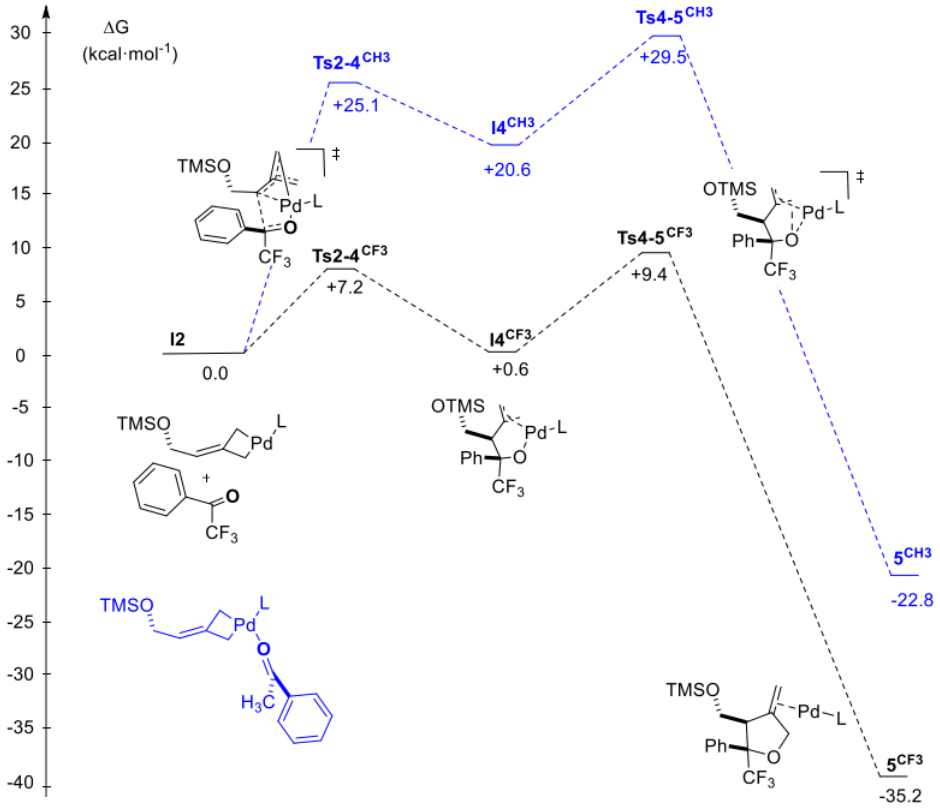
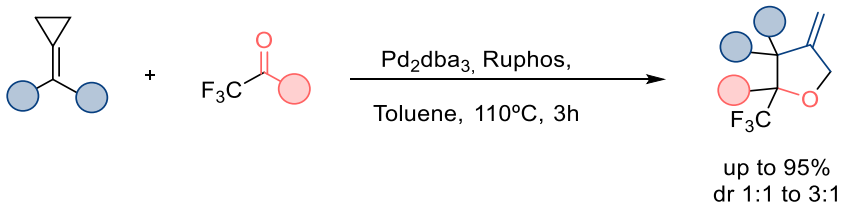


***Figure 23**. Energetic profile for the (3+2) cycloaddition of trifluoromethyl acetophenone (black) and acetophenone (blue).*

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4. Conclusions

In conclusion, we developed a new intermolecular Pd-catalysed (3+2) cycloaddition between ACPs and trifluoromethyl ketones for the construction of *exo*-methylene trifluoro-THFs. The used of bulky biaryl monophosphines is key for the success of the reaction, as it might favour the challenging *Csp*^{3}*-O* reductive elimination.



Thus, a variety of different mono or di-substituted ACPs bearing carbonated, oxygenated or nitrogenated chains were converted into their corresponding THFs with great efficiency but moderate diastereoselectivity. Moreover, this methodology tolerates the use of aromatic, allyl or alkyl trifluoromethyl ketones. Interestingly, the reactivity could be extended to other fluorinated carbonyl compounds like difluoromethyl ketones. Finally, preliminary calculations revealed an essential role of the CF_3 group that facilitates the migratory insertion step.

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CHAPTER III:

Cobalt catalysed intramolecular (3+2) cycloaddition of cyclopropenes and alkynes

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1. Introduction

1.1. Cyclopropenes: general features and reactivity

Cyclopropenes are among the higher strained three-membered rings, as is illustrated in **Figure 24,** therefore these motifs have attracted the attention of theoretical and experimental chemists for years.

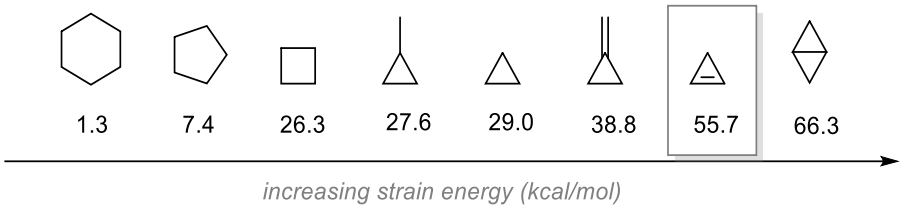


***Figure 24**. Strain energy of small ring systems.*

Although cyclopropenes were postulated already in the 19th century, the first synthesis was reported in 1922 by Dem'yanov and Doyarenko.[135] Nevertheless, studies on the chemistry of cyclopropenes were not tackled until mid-1950s, when the cyclopropene motif was identified in some natural products, like Malvalic acid.[136]

Structurally, a cyclopropene bears a double bond with an inferior length (1.27 Å) respect to a classical C_{sp2}-C_{sp2} bond of a straight-chain alkene (1.34 Å). This characteristic gives the π-bond in the cyclopropene ring more electron density compared to a classical π - bond, making it more reactive than straight-chain alkenes. Moreover, due to the presence of the double bond, the angle of this structure narrows down to 51°C respect to the 60°C observed in the case cyclopropane, illustrating the high strain of these structures (**Figure 25**).[137]

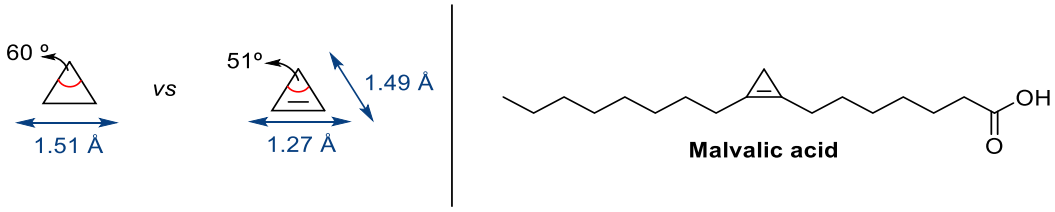


***Figure 25**. (a) Structural features of a cyclopropanes vs a cyclopropene. (b) Natural product containing a cyclopropene in its structure.*

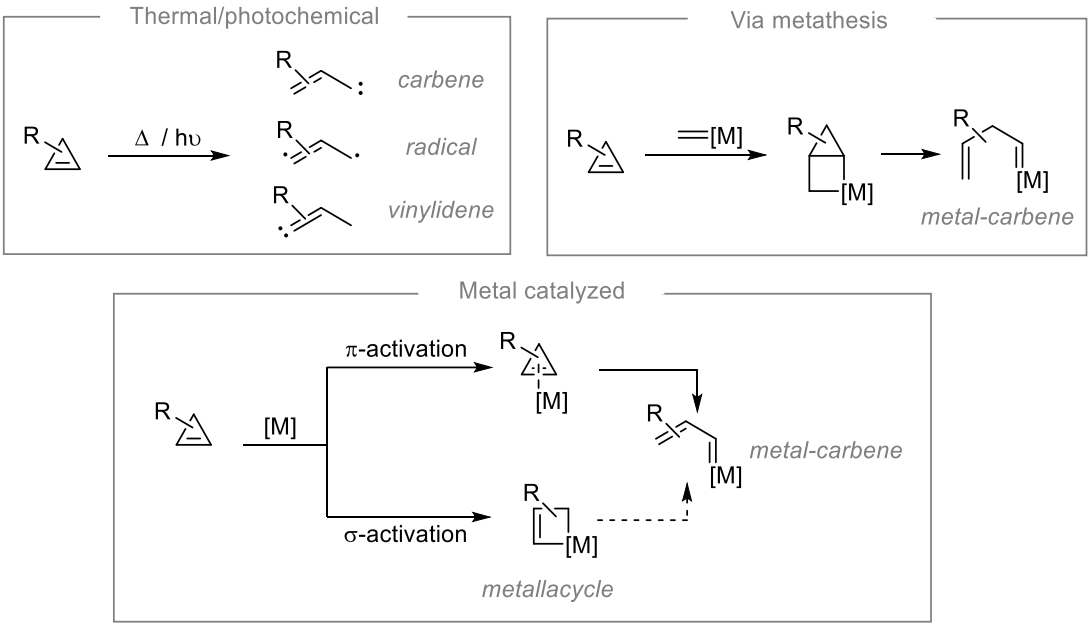
Due to their characteristic structural features, cyclopropenes have shown a fascinating and sometimes unique reactivity. This kind of motifs haven been involved in numerous

[135] Dem'janov, N. Y.; Doyarenko, M. N. *Bull. Acad. Sci. Russ. (Eng. Trans.)* **1922**, *16*, 297-320.
[136] Shenstone, F. S.; Vickery, J. R. *Nature* **1956**, *177*, 94.
[137] Rubin, M.; Rubina, M.; Gevorgyan, V. *Chem. Rev.* **2007**, *107*, 3117-3175.

transformations as 2C *synthons*, like in carbo- or hydrometallations, annulations or cross-coupling reactions.[137] Although less common, they can also be induced to undergo ring-cleavage reactions.

In general, some reactivity patterns can be established when cyclopropenes undergo a ring-cleavage reaction. For example, under thermal or photochemical conditions, cyclopropenes may suffer a σ C-C bond cleavage, whose regioselectivity is controlled by the substitution pattern. In this sense, three possible types of intermediates can be formed: carbenes, diradicals or vinylidenes.

Another interesting situation arises from metal-catalysed cyclopropene ring opening reactions, either under stoichiometric or catalytic conditions. On one hand, metals can act as π-acids and the coordination to the double bond of the cyclopropene triggers the ring opening by a rearrangement with σ-C−C bond cleavage to afford a metal vinyl carbene intermediate. On the other hand, the metal complexes can undergo oxidative additions and insert into the σ-C−C bond to generate a metallacyclobutene. Eventually, these species might evolve to the same carbene intermediates or react in different manners. Alternatively, metathesis reactions could lead to the formation of other type of metal-carbene intermediates (**Scheme 112**).



Scheme 111. *General trends in C-C bond cleavage reactions of cyclopropenes.*

Therefore, cyclopropenes can exhibit a rich chemistry in presence of transition metal reagents. They can be used as synthetic platforms for the obtention of highly reactive

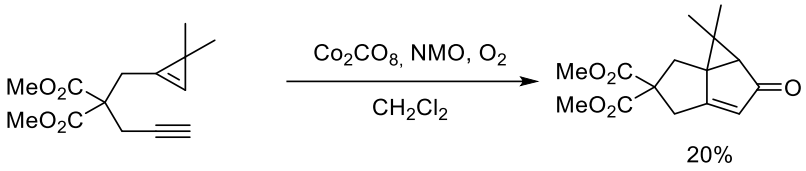
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intermediates that can potentially engage in a wide variety of transformations such as cycloisomerizations, insertions, or annulations, among many others. [138]

1.2. TM catalysed annulations of cyclopropenes

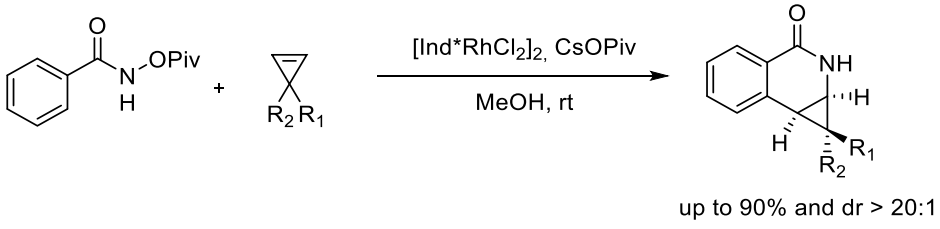
As illustrated in **Scheme 112**, cyclopropenes are highly versatile reactive molecules, even just under thermal conditions, and can participate in multitude transformations, including cycloadditions reactions. For example, as early as in 1960, a cyclopropene was already described to participate as dienophiles in Diels-Alder reactions.[139]

Cycloaddition reactions involving cyclopropenes have been also reported in the presence of transition metals. As illustrated in **Scheme 112**, alkyne-tethered cyclopropenes can participate in an intramolecular PKR using a stoichiometric amount of $Co_2(CO)_8$ to produce the expected tricyclic enone, albeit in low yield. [140]



Scheme 112. *Intramolecular Pauson-Khand reaction of alkyne-tethered cyclopropenes.*

Moreover, cyclopropenes also participate in catalytic cycloadditions promoted by transition metal complexes. For example, a (4+2) cycloaddition of *O*-substituted arylhydroxamates and cyclopropenes mediated by Rh(III) catalysis furnish cyclopropa[*c*]dihydroisoquinolones in good yields and with high diastereocontrol (**Scheme 113**).[141]

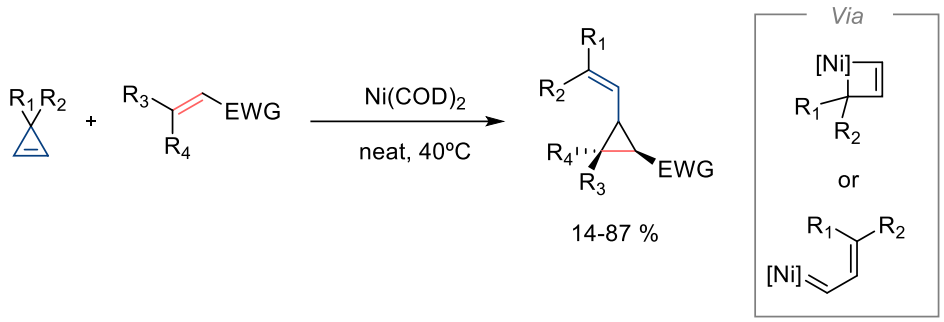


Scheme 113*. Rh(III) catalysed (4+2) cycloaddition of benzamides and cyclopropenes.*

In these annulations, cyclopropenes participate as effective 2C *synthon*. However, they might also be used as 3C partners when a ring cleavage occurs during the process.

[138] Vicente, R. *Chem. Rev.* **2021**, *121*, 1, 162–226.
[139] Wiberg, K. B.; Bartley, W. J. *J. Am. Chem. Soc.* **1960**, *82*, 6375−6380.
[140] Stolle, A.; Becker, H.; Salaün, J.; de Meijere, A. *Tetrahedron Lett*. **1994**, *35*, 3517-3520.
[141] Semakul, N.; Jackson, K. E.; Paton, R. S.; Rovis, T.; *Chem. Sci.* **2017**, *8*, 1015-1020.

One of the pioneer contributions in this topic was reported by Binger and co-workers in 1974. They were able to develop an intermolecular cyclopropanation of electron-deficient alkenes, a formal (2+1) cycloaddition, using 3,3-disubstituted cyclopropenes and catalytic amounts of $Ni(COD)_2$ (**Scheme 114**). The authors proposed a Ni(0) vinyl carbene or a nickellacyclobutene as intermediates of the reaction.[142]

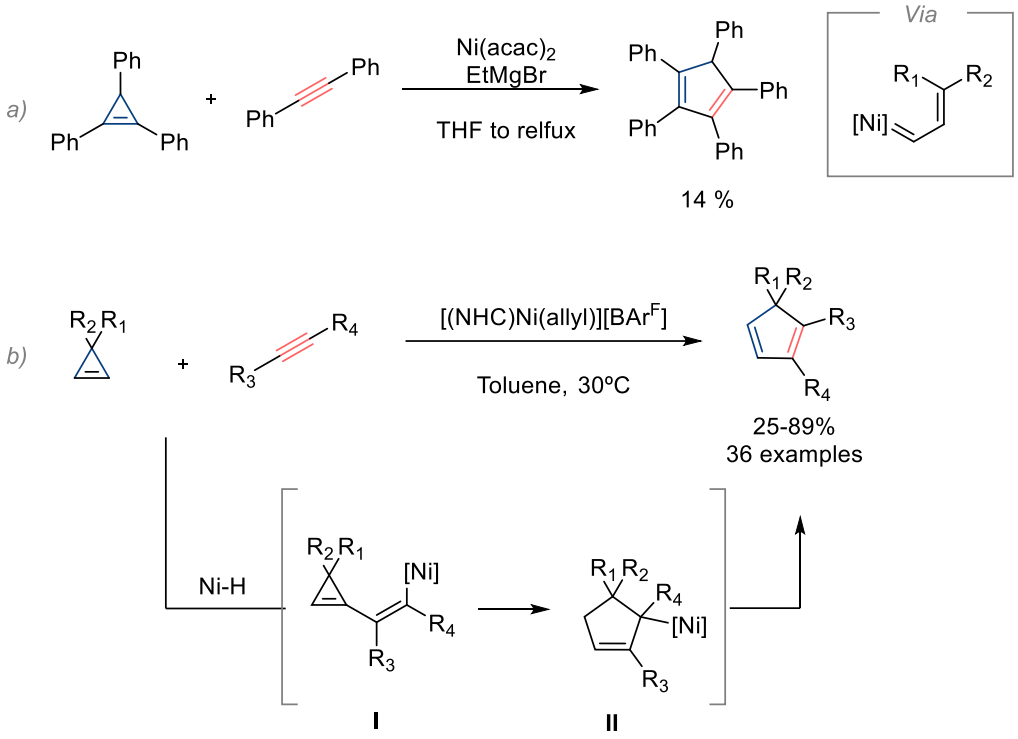


Scheme 114. *Nickel catalysed (2+1) cycloaddition of cyclopropenes and electron-deficient alkenes.*

Curiously, in the presence of alkynes and a Ni(0) catalyst, instead of a formal (2+1) cycloaddition, a (3+2) process was observed (**Scheme 115a**). In particular, Eich's and co-workers showed that a Ni(0) catalyst generated in situ from $Ni(acac)_2$ and a reductant, can promote the cycloaddition between 1,2,3-triphenylcyclopropene and diphenylacetylene to deliver 1,2,3,4,5-pentaphenylcyclopentadiene, albeit in a poor yield. The reaction was proposed to take place via a vinyl nickel(0) carbene intermediate, although no mechanistic evidences were provided.[143]

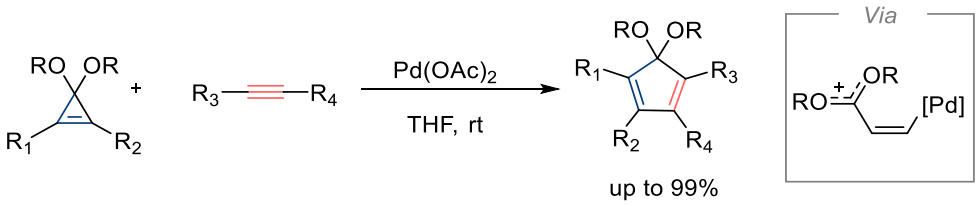
Recently, Ho and co-workers developed a similar strategy using a NHC-Ni catalyst, to make a wide variety of polisubstituted cyclopropenes (**Scheme 115b**).[144] However, in this case, a different mechanism from previously commented Ni-promoted reactions was proposed. Specifically, the authors suggested a hydroalkenylation of the cyclopropene promoted by a Ni-H species, followed by a rearrangement to afford a cyclopentene intermediate like **II**. Then, a 1,3-metal shift and a β-hydride elimination produces the cyclopentadiene.

[142] Binger, P.; McMeeking, J. *Angew. Chem., Int. Ed. Engl.* **1974**, *13,* 466−467.
[143] (a) Eisch, J. J.; Qian, Y.; Singh, M. *J. Organomet. Chem*. **1996**, *512*, 207−217. (b) Eisch, J. J.; Aradi, A. A.; Lucarelli, M. A.; Qian, Y. *Tetrahedron* **1998**, *54*, 1169−1184.
[144] Huang, J.-Q.; Ho, C.-Y. *Angew. Chem., Int. Ed.* **2019**, *58*, 5702−5706.



***Scheme 115**. (3+2) cycloaddition of cyclopropenes and alkynes catalysed by Ni(0).*

Precious transition metals have also been studied in the cycloaddition chemistry of cyclopropenes. For example, Nakamura reported a Pd-catalysed (3+2) cycloaddition of cyclopropenone ketals and alkynes to prepare a series of cyclopentadienone ketals. Although the reaction occurs under thermal conditions, the use of a Pd catalyst enables the transformation to take place at room temperature and with better results (**Scheme 116**). [145]

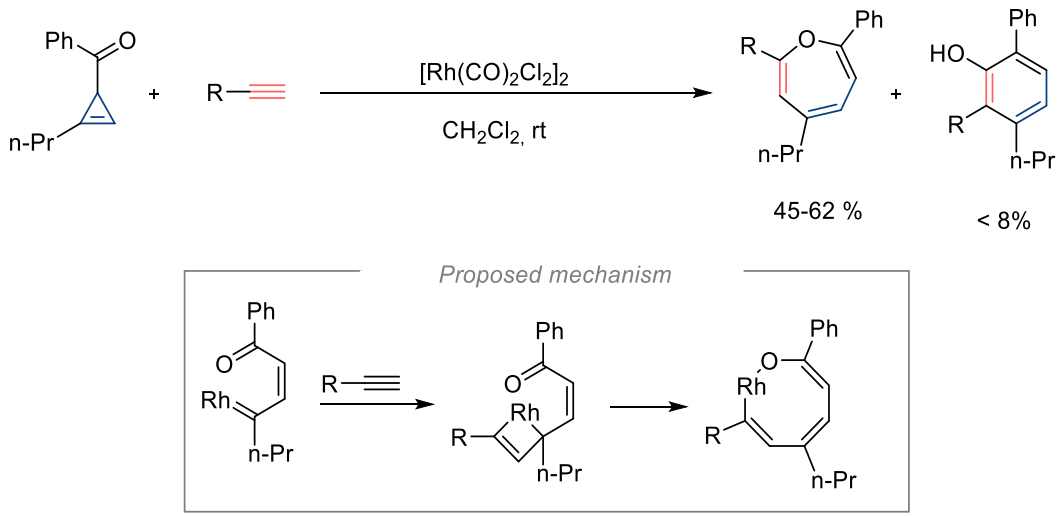


***Scheme 116.** Pd-catalysed (3+2) cycloaddition of cyclopropenone ketals and alkynes.*

Moreover, the merge of Rh catalysts and cyclopropenes has provided interesting transformations over the years. For example, one of the first reports in this issue allowed the construction of oxepines, which are highly interesting molecules from a bioactive point of view.[146] Mechanistically, the reaction was proposed to occur with the regioselective formation of a rhodium-vinyl carbene at the most substituted carbon of the original cyclopropene. Then, regioselective (2+2) cycloaddition with the alkyne and

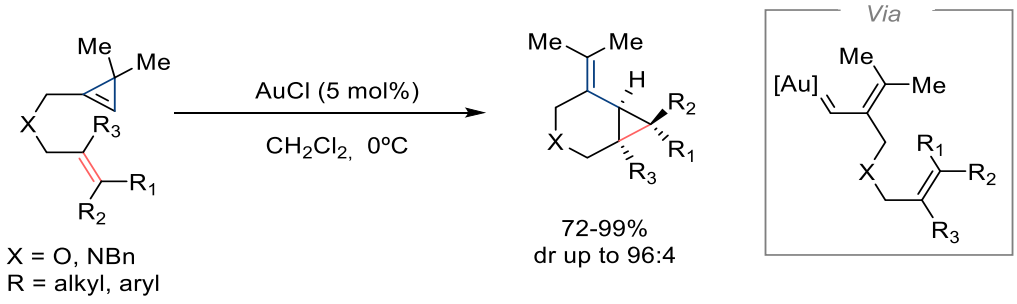
[145] Isobe, H.; Sato, S.; Tanaka, T.; Tokuyama, H.; Nakamura, E. *Org. Lett.* **2004**, *6*, 3569−3571.
[146] Padwa, A.; Xu, S. L. *J. Am. Chem. Soc.* **1992**, *114*, 5881−5882.

subsequent cyclization via a 1,5-sigmatropic shift or by retro (2+2) and 8π-electrocyclization leads to an eight-membered cyclic intermediate, which by reductive elimination provides the corresponding oxepines. It is worth to mention that the reaction usually affords small amounts of phenol, which may arise from the opposite regioselectivity in the (2+2) cycloaddition of the rhodium vinyl carbene and the alkyne (**Scheme 117**).



***Scheme 117**. Rh(I) catalysed intermolecular cycloaddition of cyclopropenes and alkynes.*

All these precedents refer to intermolecular processes, but some intramolecular transformations of cyclopropenes have also been accomplished. For example, under homogeneous gold catalysis it is known that the ring opening of the cyclopropene occurs generating a terminal gold carbene. This gold carbene can engage in several transformations like the one illustrated in **Scheme 118** where an intramolecular cyclopropanation of a pendant alkene takes place towards the construction of a variety of 3-oxa and -3azabicycles.[147]

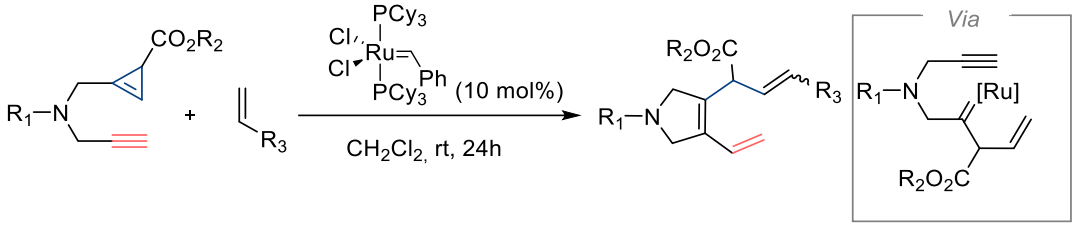


***Scheme 118.** Au(I) catalysed cyclosiomerization of alkene-tethered cyclopropenes*

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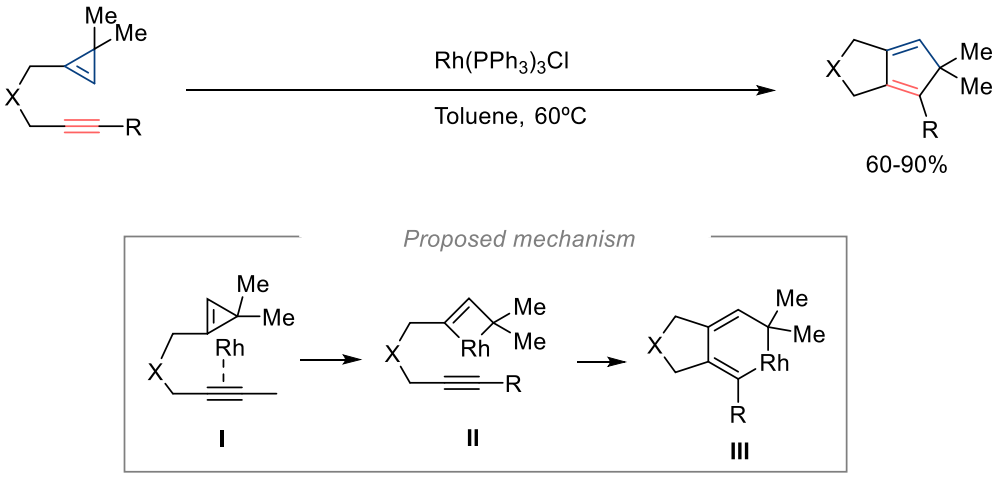
[147] Miege, F.; Meyer, C.; Cossy, J. *Org. Lett.* **2010**, *12*, 18, 4144–4147.

Ruthenium carbene complexes are also able to catalyse the ring opening of cyclopropenes. However, opposite to what was previously mentioned for gold catalysis which leads to the terminal carbene, the internal carbene is formed, which can participate in several transformations like the one illustrated in **Scheme 119**.[148]



***Scheme 119**. Ru(II) catalysed tandem ring-opening/ring-closing/cross-metathesis of cyclopropenes.*

Rhodium catalysts can also trigger intramolecular reactions of cyclopropenes entailing their ring-opening. Thus, as indicated in **Scheme 120**, Shibata and co-workers developed a (3+2) cycloaddition of alkyne-tethered cyclopropenes catalysed by the Wilkinson catalyst. Although the scope of the reaction proved to be limited to dimethyl substituted cyclopropenes, it reveals the possibility to use aryl or alkyl substituted alkynes in order to synthesize polysubstituted fused cyclopentadienes. Mechanistically, the authors proposed that the transformation starts with coordination of the alkyne to a Rh(I) species, in which the metal-fragment resided in the proximity of the σ-bond of the cyclopropene enabling an oxidative addition. Then, alkyne insertion into the rhodacyclobutene intermediate **II** would generate a metallacycle **III** that, after reductive elimination, led to fused-cyclopentadienes.[149]

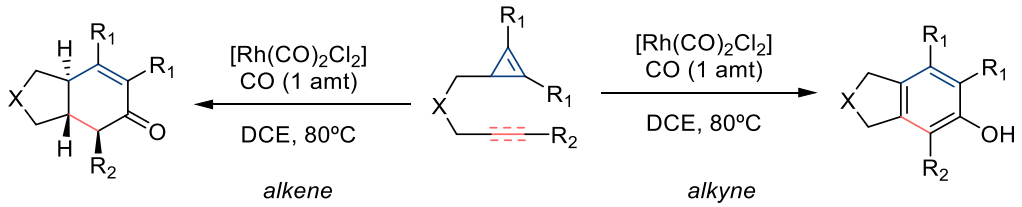


***Scheme 120.** Rh(I) catalysed intramolecular (3+2) cycloaddition of cyclopropenes and alkynes.*

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[148] Zhu, Z. B.; Shi, M. *Org. Lett.* **2010**, *12*, 20, 4462–4465.
[149] Shibata, T.; Shibata, T.; Maekawa, S.; Tamura, K. *Heterocycles* **2008**, *76*, 1261− 1270.

In a similar manner, alkyne connected to cyclopropenes through the sp^3 carbon of the ring, under an atmosphere of CO can generate bicyclic phenols in presence of a Rh(I) catalyst. Moreover, in the same contribution, Wang and co-workers proved that the transformation could be extended to alkene-tethered cyclopropenes to construct a variety of cyclic fused enones (**Scheme 121**).[150]

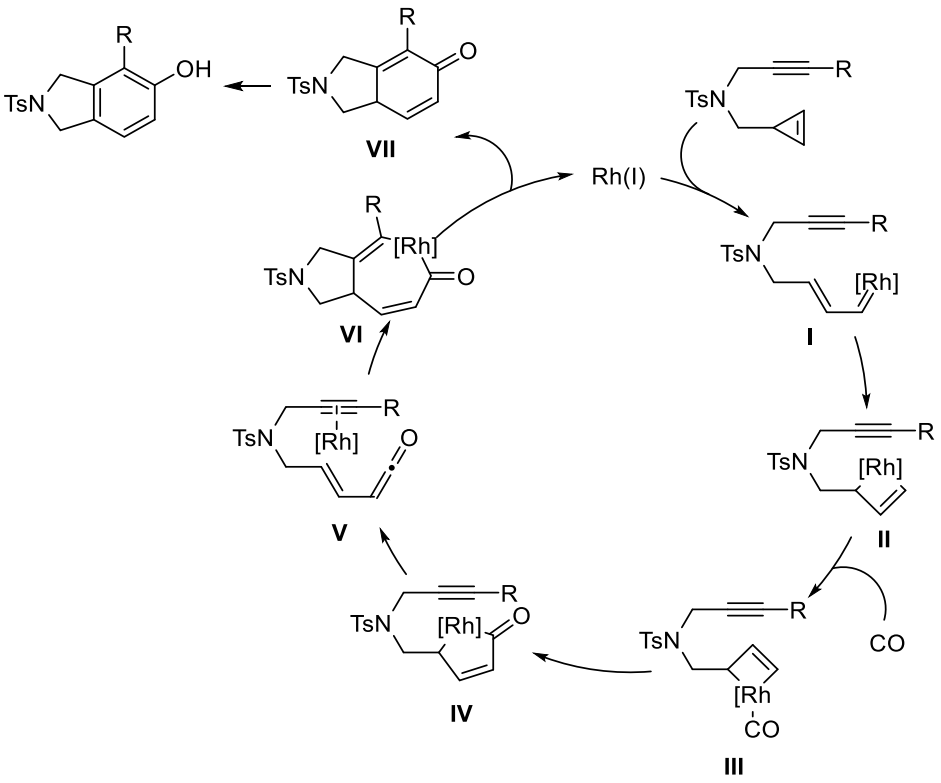


Scheme 121. *Carbonylative (3+2+1) cycloaddition of alkene or alkyne-tethered cyclopropenes.*

Though in the original publication no mechanistic information was provided, a subsequent computational study indicated that the most possible reaction pathway is the one draw below (**Scheme 122**).[151] Contrary what was proposed by Shibata, the reaction would be initiated with the formation of the Rh vinyl carbene **I** that rearranges to metallacyclobutene **II.** Then, CO insertion into the metallacyclobutene would yield intermediate **IV.** Finally, alkyne insertion through a ketene intermediate and reductive elimination generates the bicyclic phenol.

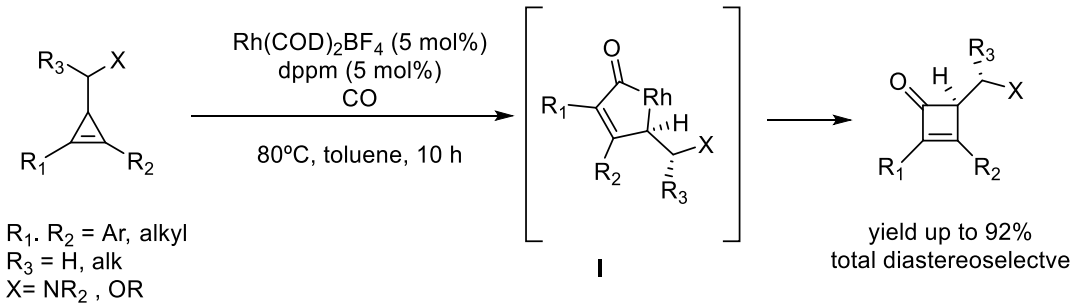
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[150] Li, C.; Zhang, H.; Feng, J.; Zhang, Y.; Wang, J. *Org. Lett*. **2010**, *12*, 3082−3085.
[151] Dai, P.; Ogunlana, A. A.; Bao, X. *J. Org. Chem.* **2018**, *83*, 12734−12743.



***Scheme 122**. Mechanism proposed for the intramolecular Rh catalysed (3+2+1) cycloaddition of alkyne-tethered cyclopropenes and CO.*

Likewise, Wang and co-workers have recently reported an interesting methodology for the synthesis of cyclobutenones by insertion of CO.[152] Apparently, the reaction required the presence of heteroatom pendants, that work as coordinative directing groups (**Scheme 123**).



***Scheme 123.** Rh(I) catalysed carbonylative (3+1) of cyclopropenes and CO.*

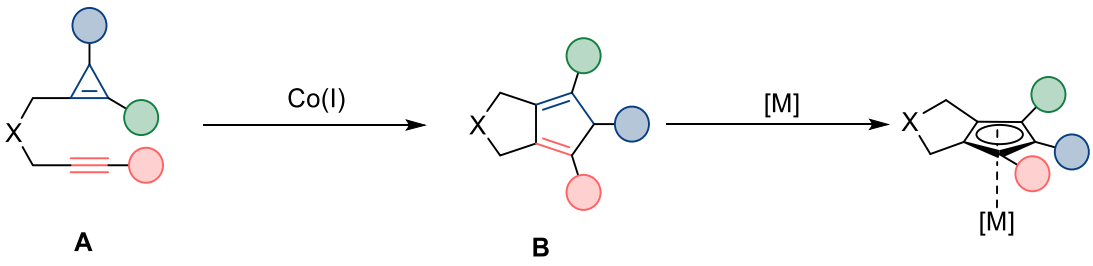
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[152] Xu, W.; Li, C.; Wang, J. *Chem.Eur.* **2018**, *24*, 15786–15790.

2. Objectives

The intrinsically rich reactivity of cyclopropenes, especially in presence of transition metal catalysts, suggests that they could be further exploited as 3C partners in annulation reactions. This could be even more relevant if the reactions are mediated by earth abundant metal catalysts, such as cobalt derivatives. Therefore, we proposed as main objective of this chapter the development of new annulation reactions of alkyne-tethered cyclopropenes based on this type of metal catalyst. Importantly, we focused on precursors in which the cyclopropene and the alkyne are connected through the double bond of the cyclopropene, as the substrates would be relatively simple from a synthetic and stereochemical perspective.

Considering the precedent of Shibata with Rhodium (**Scheme 120**),[149] precursors of type **A** might provide cyclopentadienes **B**, in which all carbons of the new cycle are completely substituted. These products are very interesting from a synthetic perspective, not only because of the possibility of manipulating the double bonds to obtain highly functionalized bicyclic cyclopentane adducts, but also as potential precursors of new highly substituted cyclopentadienyl ligands for piano stool transition metal complexes of several transition metals like Rh.



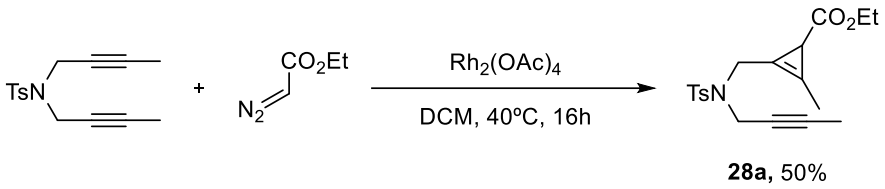
***Scheme 124**. Proposed (3+2) cycloaddition of alkyne-tethered cyclopropenes and the potential utility as Cp ligands.*

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3. Results and discussion

3.1 Development of the methodology

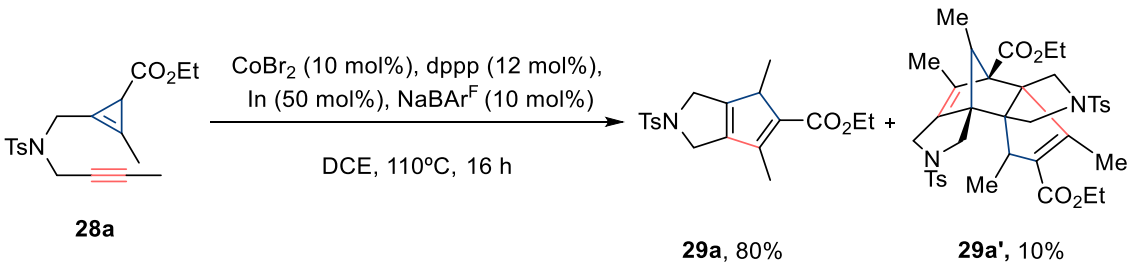
For testing the viability of the approach, we selected compound **28a**, because it can be easily made from a symmetric diyne using a Rh(II)-catalysed reaction with ethyldiazoacetate (**Scheme 125**).[150]



***Scheme 125**. Synthesis of model alkyne-tethered cyclopropene **28a**.*

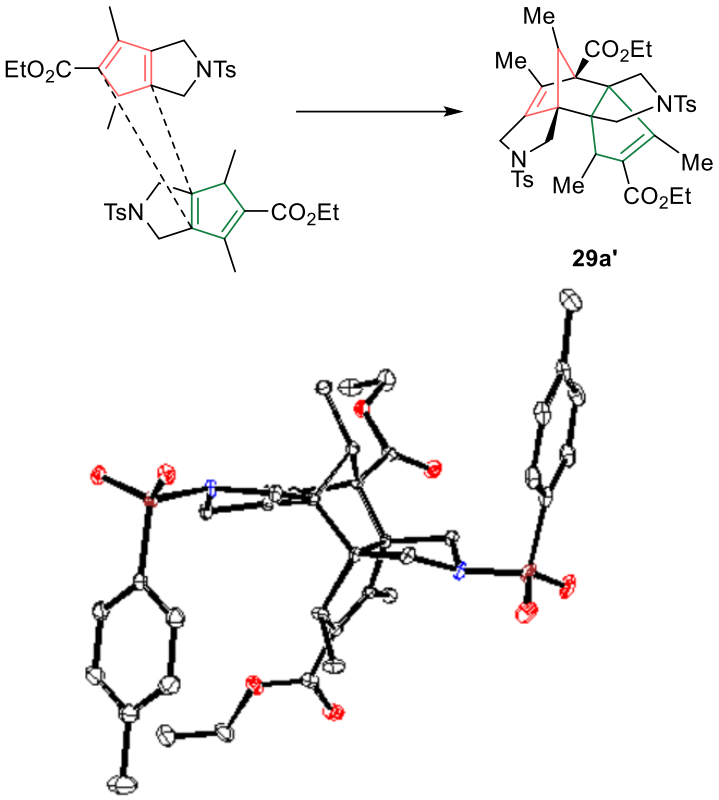
With substrate **28a** in our hands, we selected as initial conditions $CoBr_2$ as cobalt source, dppp as ligand, In as reductant, $NaBAr^F$ as halide scavenger, in 1,2-dichloroethane, at 110 °C. To our delight, under these conditions we were able to isolate a cyclopentadiene adduct, which was identified as **29a** (80% yield). We also obtained a 10% of an additional compound, that could be later unequivocally determined by X-ray analysis as **29a'** (**Scheme 126**). Curiously, this product is a consequence of a spontaneous electronically inverse Diels-Alder homodimerization of **29a**, where the electron deficient diene of one unit reacts with the more electron rich internal alkene of other.

It is important to note that the double bonds of the diene product **29a** are not in the position expected considering the proposal formal (3+2) cycloaddition with opening of the cyclopropene ring.



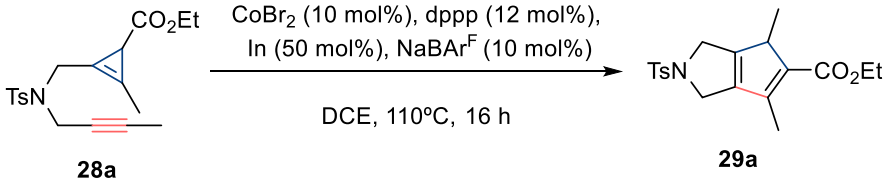
***Scheme 126.** Co catalysed (3+2) cycloaddition of alkyne-tethered cyclopropenes.*

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Scheme 127**. Spontaneous Diels Alder of **29a** and the X-ray structure of **29a'.

After these good results, it was essential to perform a series of control experiments to learn more about the reaction (**Table 13**). To our delight, no reactivity was observed in absence of cobalt, ligand, reductant, or halide scavenger. Moreover, no thermal reactivity was observed when substrate **28a** was heated alone at 110 °C.

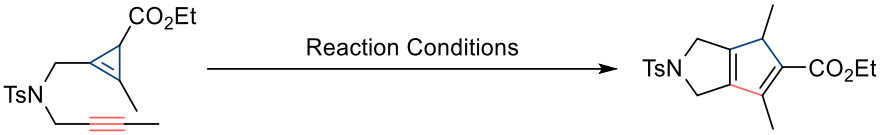


Entry	Deviation from standard conditions	Yield(%)
1	None	80
2	No $CoBr_2$	n.d
3	No dppp	n.d
4	No In	n.d
5	No BAr^F	n.d
6	None of the reagents	n.d

***Table 13.** Control experiments of the (3+2) cycloaddition of alkyne-tethered cyclopropenes*

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At this point, we were curious to know the behaviour of **28a** using metal catalysts that have been commonly employed in other reactions of strained ring systems. Curiously, none of them gave the adduct cyclopentadiene **29a**. Even the Rh catalyst previously developed by Shibata and co-workers for the cycloaddition of alkyne-tethered cyclopropenes (**Scheme 120**) provided a complex mixture of adducts, but **29a** could not be detected. Therefore, the cobalt reagent was the only one giving the desired reactivity.



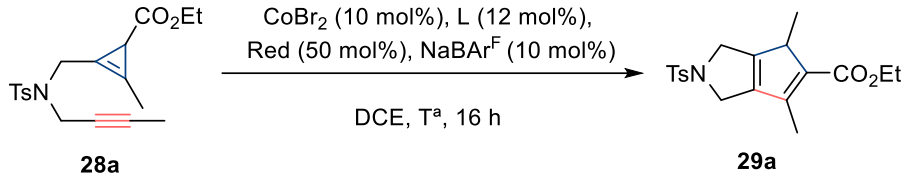
28a **29a**

Entry	Reaction conditions	Conversion (%)	Yield(%)
1	$RhCl(PPh_3)_3$, toluene, 60 °C	100	n.d
2	Au-Dalphos, $AgSbF_6$, DCM, rt	0	n.d
3	$[Ir(Cod)Cl]_2$, Binap, toluene 100°C	100	n.d
4	Pd_2dba_3, $\mathbf{L_1}$, 100°C	100	n.d

***Table 14**. Analisis of reactivity of **28a** under the presence of several transition metals.*

Once it was established that the reaction illustrated in **Scheme 126** was a cobalt-catalysed process, we sought to improve its efficiency (**Table 15**). We first found that the optimal temperature for this reaction is 80°C, as in this case the cyclopentadiene was isolated with an excellent 90% yield without any trace of the dimer **29a'**. Other bidentate phosphine ligands with similar bite angle than dppp, such as BINAP, dppf and dppe, were tested. However, none of them provided **29a** in better yield than dppp. Finally, zinc also proved to be a competent reductant, but the yield was lower than with Indium. In this context, we can conclude that the best reaction conditions for the (3+2) cycloaddition of **28a** involves the use of $CoBr_2$ (10 mol%) as cobalt source, dppp (12 mol%) as ligand, In (50 mol%) as reductant, $NaBAr^F$ (10 mol%) as halide scavenger in 1,2-dichloroethane (0.1 M) at 80 °C.

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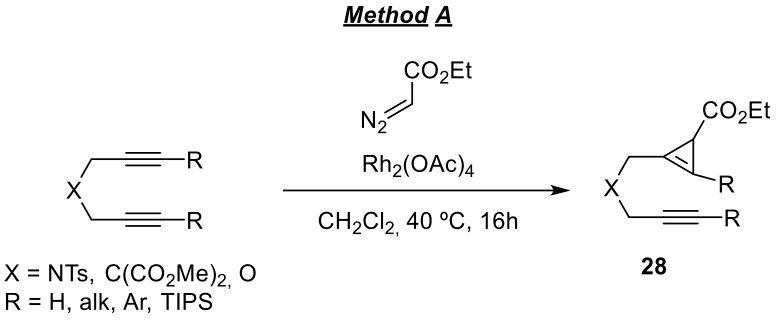


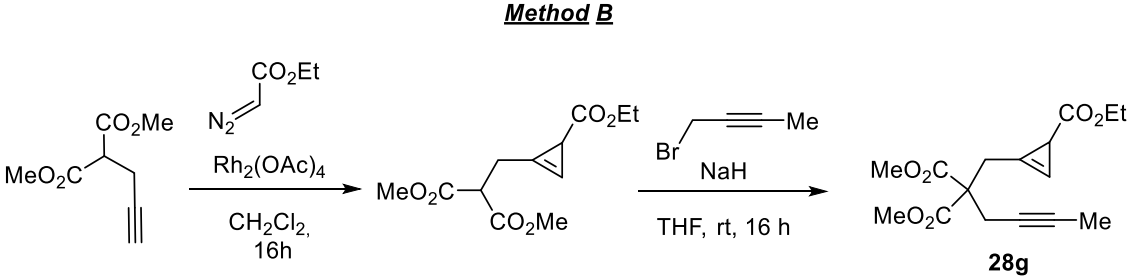
28a **29a**

Entry	Ligand	Temperature	Reductant	Yield (%)
1	dppp	110	In	80
2	dppp	80	In	90
3	BINAP	80	In	43
4	dppf	80	In	61
5	dppe	80	In	30
6	dppp	80	Zn	71

***Table 15**. Optimization of the reaction conditions for the Co catalysed (3+2) cycloaddition of alkyne-tethered cyclopropenes.*

Once the reaction conditions were optimized for the model substrate **28a**, we investigated the scope of the method. Therefore, a variety of alkyne-tethered cyclopropenes were synthetized following two general strategies. The alkyne-tethered cyclopropene can be made as the model substrate, through a Rh(II) catalysed cyclopropenation of the selected diyne (**Scheme 128a**). But in the case in which the substituents of the alkyne and cyclopropene are different, we followed the route illustrated in **Scheme 128b** which consists on the cyclopropenation of the propargyl malonate followed by its propargylation.

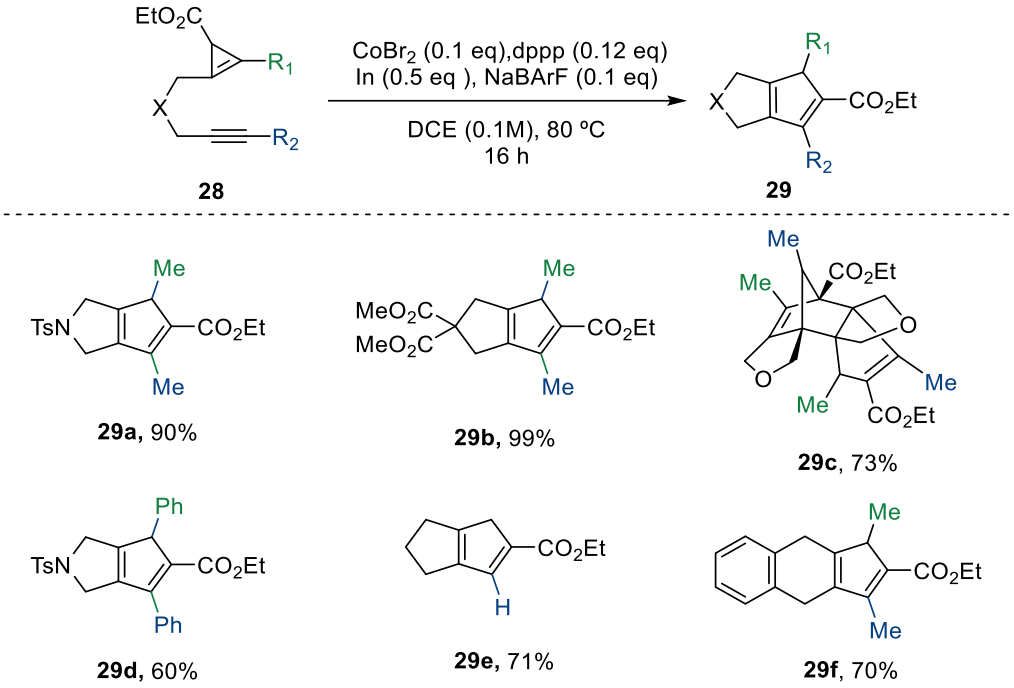




***Scheme 128**. General synthetic methods employed in the construction of alkyne-tethered cyclopropenes.*

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With the alkynyl cyclopropenes in hand, and in collaboration with Dr. Carlos Lázaro, we tested the cobalt-catalysed (3+2) cycloaddition. As can be deduced from **Scheme 129**, the precursor exhibiting a carbon tether (with the diester pendant) gave the expected cyclopentadiene **29b** in a quantitative manner. A precursor with an oxygen in the tether was also efficiently converted into the cycloadduct. However, the product experiments a spontaneous Diels Alder under the reaction conditions and only the dimer **29c'** could be isolated. Pleasingly, the annulation methodology also allowed to construct polysubstituted cyclopentadienes holding two aromatic rings in good yields (77%, **29d**). Gratifyingly, a full carbonade cyclopentane fused cyclopentadiene can also be constructed using this Co catalysed cycloaddition (**29e**, 71%). Moreover, this example also illustrates the possibility to use terminal alkynes without any erosion of the efficiency of the reaction. In addition, it is also possible to make fully carbonade cyclopentadienes fused to six-membered rings, like **29f**.



Scheme 129. *Scope of the Co catalysed intramolecular (3+2) cycloaddition of alkyne-tethered cyclopropenes.*

Gratifyingly, the structure of **29f** could be unequivocally assigned through X- analysis (**Figure 26**).

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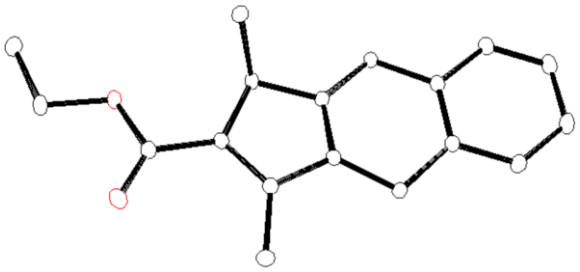
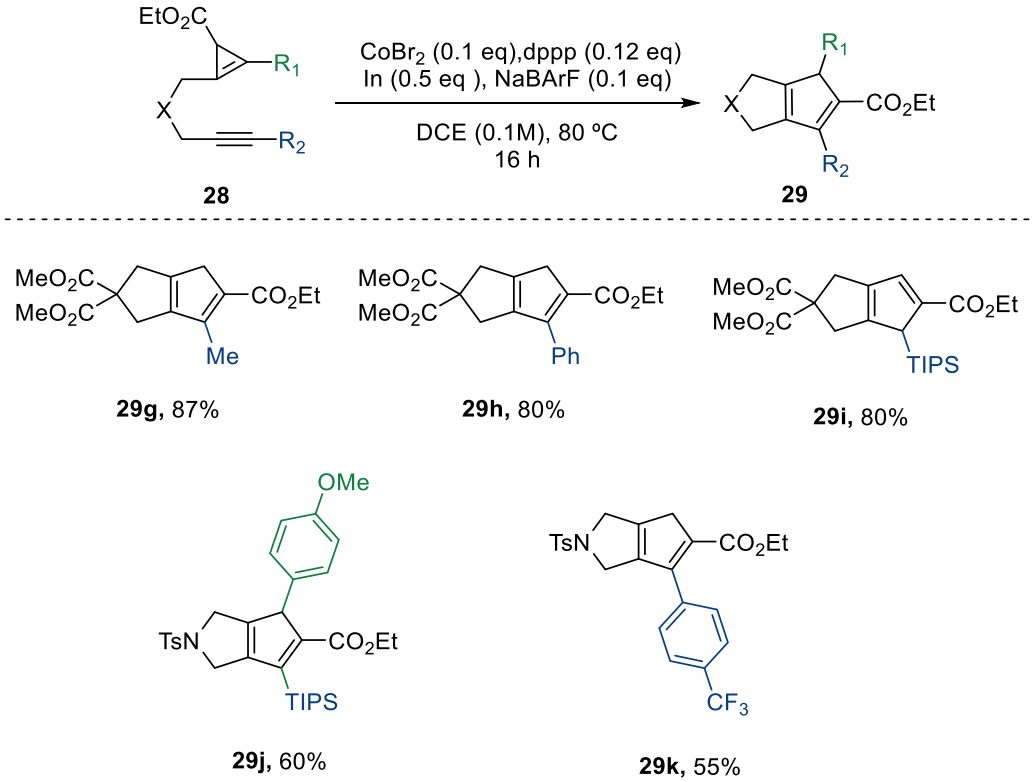


Figure 26**. X-ray structure of cyclopentadiene **29f.

To our delight, non-substituted cyclopropenes with R_1=H reacted smoothly towards the corresponding cyclopentadiene with an array of different substituted alkynes. Thus, with methyl or phenyl-substituted alkynes the expected cyclopentadienes **29g** or **29h** in were obtained in excellent yields (**Scheme 130**).

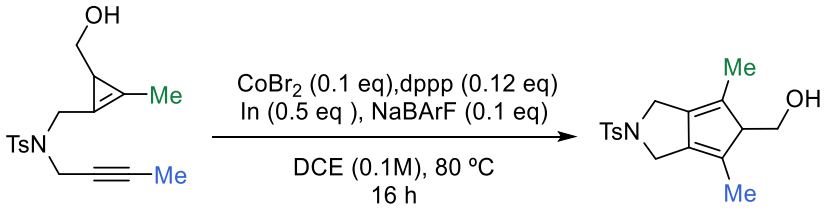
Curiously, a precursor with an alkyne bearing a bulky silyl group like **28i** also participated in the process, but provided the cyclopentadiene product **29i**, which presents an alternative distribution of double bonds, suggesting that the rearrangement of the π-cloud of the cyclopentadiene occurs after the cycloaddition reaction. In addition, under this methodology cyclopentadienes containing electron rich (**29j**) or electron deficient (**29k**) aromatic substituents can be efficiently synthetized (**Scheme 130**).



***Scheme 130.** Scope of the Co catalysed intramolecular (3+2) cycloaddition of alkyne-tethered cyclopropenes.*

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At this point, we were curious about the requirement of an ester at the sp^3 carbon of the cyclopropene. Thus, the alkyne-tethered cyclopropene **28a** was transformed into the alcohol **28l**, in 71% yield, through a simple reduction with DIBAL-H. When we submitted **28l** to the reaction conditions, cyclopentadiene **29l** was isolated in a good 51% yield. As can be deduced from **Scheme 131**, **29l** contains a different arrangement of the double bonds with respect to the examples showed before, which is mechanistically very interesting.



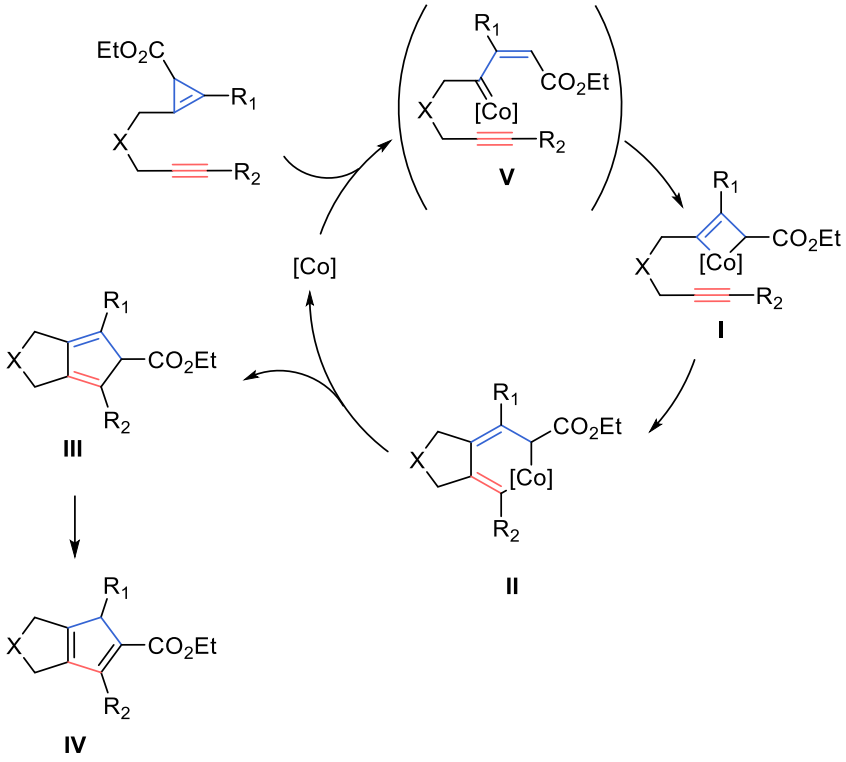
28l **29l**, 51%

Scheme 131. *(3+2) cycloaddition of cyclopropene* ***29j.***

3.2 Preliminary mechanistic studies

Considering the mechanistic proposal of Shibata for the rhodium promoted process depicted in **Scheme 120**, [149,151] a plausible mechanism for the reaction could consist of an initial oxidative insertion of a low valent cobalt complex (Co(0) or Co(I)) into the cyclopropene to give a cobaltacyclobutene **I**, followed by migratory insertion of the alkyne towards **II**, and, a final reductive elimination. The resulting diene would somewhat undergo a rearrangement to the more stable conjugated diene (this is under investigation). Alternatively, the reaction might involve the formation of vinyl carbene **V** that could be in equilibrium with the cobaltacyclobutene (**Scheme 132)**.[151]

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Scheme 132. *Proposed mechanism for the (3+2) cycloaddition of alkyne-tethered cyclopropenes*

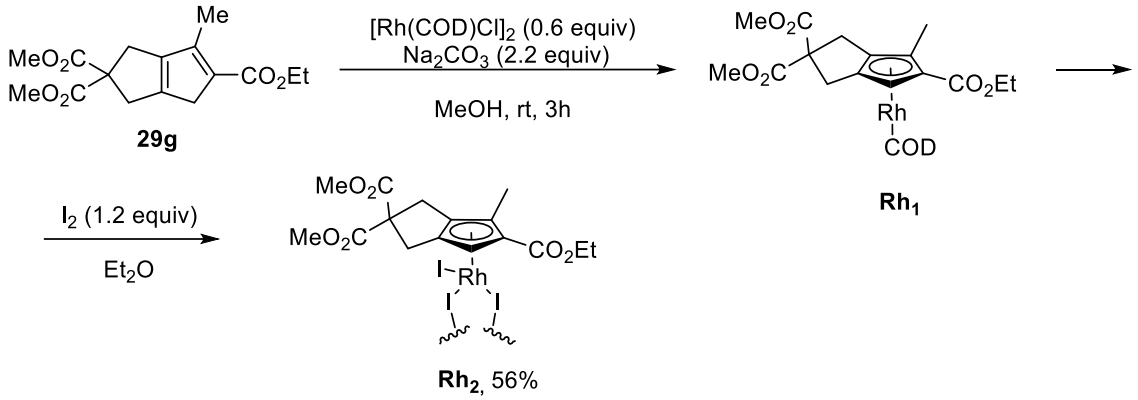
While we are in the process of delineating the mechanistic details of the reaction, it is very important to mention that the conditions developed by Shibata based on Rh(I) catalysts did not work with our substrates, which highlights the relevance of using cobalt complexes, and suggest that the mechanism could be distinct in the case of cobalt or rhodium.

3.3 Preliminary elaborations of the cyclopentadiene products

Given that the methodology proposes a very rapid and practical access to highly substituted cyclopentadienes, we envisioned that this strategy could be used as a synthetic platform towards the construction of novel type of Cp metal complexes.

To preliminary tackle this goal, we treated cyclopentadiene **29g** with a substoichiometric amount of $[Rh(COD)Cl]_2$ in presence of a base, and observed that the expected Rh(I) cyclopentadienyl complex was efficiently formed and easily isolated through column chromatography. In addition, the corresponding Rh(III) dimer could be easily obtained in an overall yield of 56% by a I_2 mediated oxidation (**Scheme 133**).

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Scheme 133. *Synthesis of Rh(I) and Rh(III) cyclopentadienyl complexes.*

It is worth to mention that the structure of the Rh (I) complex Rh1 could undoubtly attributed by X-ray analysis (**Figure 27**).

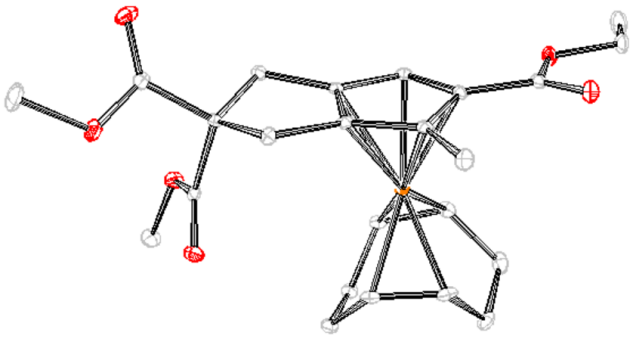
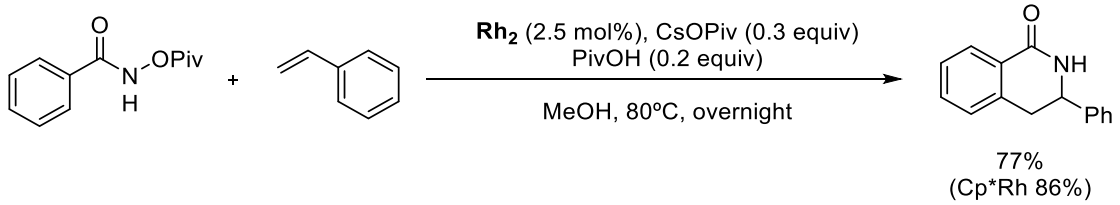


Figure 27*. X-ray structure of Rh1.*

With this preliminary result in our hands, we also made a preliminary test of the activity if this new Rh(III) complex **Rh_2**, using as model reaction the (4+2) cycloaddition of N-Pivaloxybenzamides and alkenes developed by Glorious in 2011.[153] Pleasingly, when we performed this reaction under the optimal conditions reported in the literature but changing the $[Cp^*RhCl_2]_2$ for our catalyst **Rh_2** the expected tetrahydroisoquinolinone product was obtained in a good 77% yield, which is comparable with the one reported using $[Cp^*RhCl_2]_2$ (**Scheme 134**).



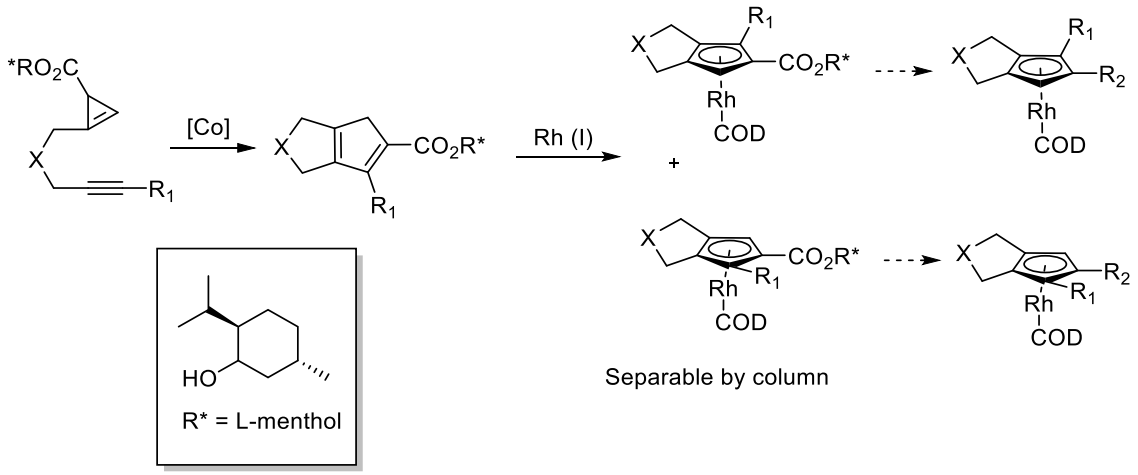
Scheme 134*. Rh(III) catalysed (3+2) cycloaddition of N-pivaloxybenzamides and alkenes.*

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[153] Rakshit, S.; Grohmann, C.; Besset, T.; Glorius, F. *J. Am. Chem. Soc.* **2011**, *133*, 2350–2353.

A major current goal in the use of this type of cyclopentadienyl metal complexes is related with the field of asymmetric catalysis.[154] Different approaches have been made to introduce chirality in the complexes, including strategies that create point or axial chirality. However, the Cp-metal complexes exhibiting planar chirality is much less common.

Given that our cyclopentadiene products can be tailored to introduce different type of substituents, we envisioned that the strategy could be especially useful for this purpose of creating chiral Cp-metal complexes exhibiting planar chirality. In this sense, we decided to take an approach similar to what was previously reported by Wang,[155] consisting of building diasteroisomeric chiral ester derivative, like the one derived from menthol. After chromatographic separation and removal of the auxiliary, we could obtain the desired optically active CpM complexes, exhibiting planar chirality (**Scheme 135**).

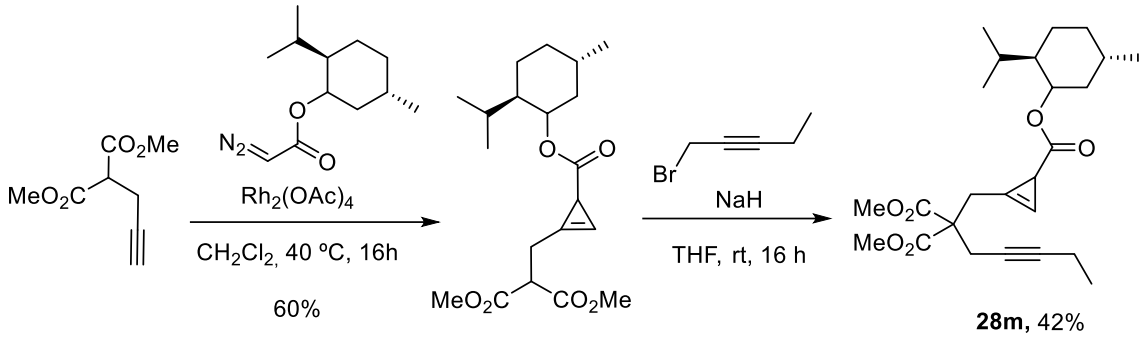


Scheme 135. *Potential strategy towards the synthesis of chiral Cp Rh complexes*

Towards this goal, we prepared substrate **28m**, bearing a chiral ester derived from the menthol in the cyclopropene moiety. Thus, its synthesis was carried out by Rh (II) cyclopropenation of propargyl malonate with the *L*-menthol diazo derivative followed by the propargylation of the malonic cyclopropene derivative (**Scheme 136**).

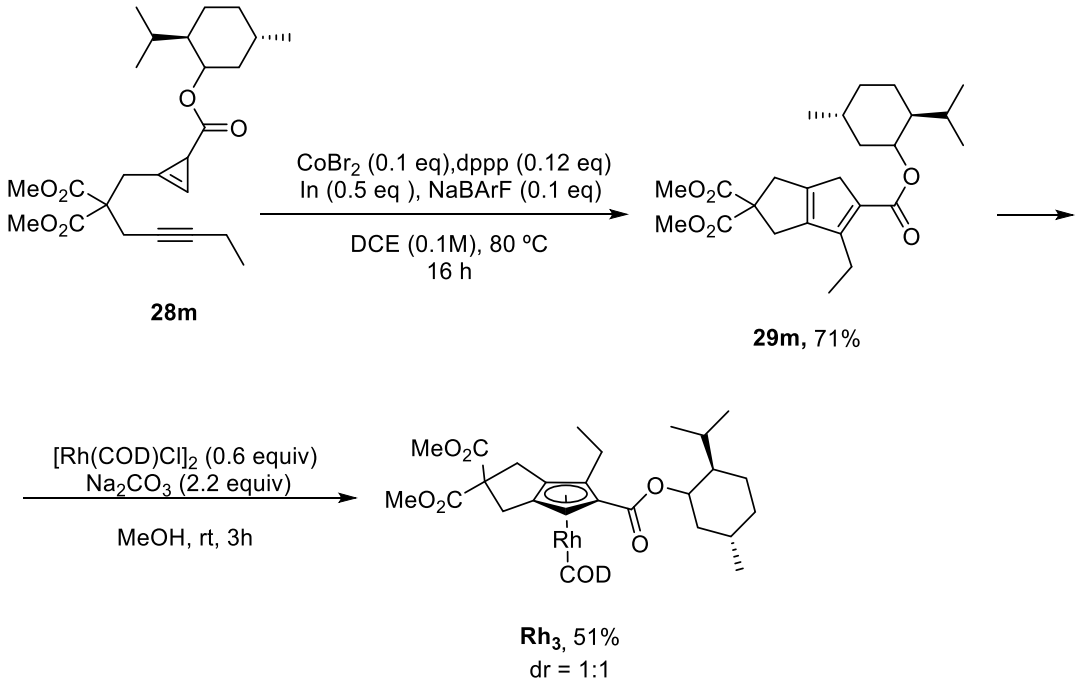
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[154] Mas-Roselló, J.; Herraiz, A. G.; Audic. B.; LAverny, A.; Cramer, N. Angew. Chem.Int. Ed. **2021**, *60*, 13198–13224.
[155] Yan, Z.; Jiang, J.; Wang, J. *Angew. Chem.Int. Ed*. **2022**, *61*, e202201522.



***Scheme 136**. Synthetic strategy towards substrate **28m**.*

With substrate **28m** at hand, we performed the cycloaddition under standard conditions, and were pleased to observe the formation of the desired cyclopentadiene **29m** in a good 71% yield. The Rh(I) cyclopentadienyl complex could also be readily made in an analogous manner as describe before in this chapter, with a good 51% yield and as an expected as 1:1 diastereomeric mixture. Unfortunately, up to now we have not been able to separate these complexes by column chromatography. Work to solve this problem is currently ongoing in the group (**Scheme 137**).



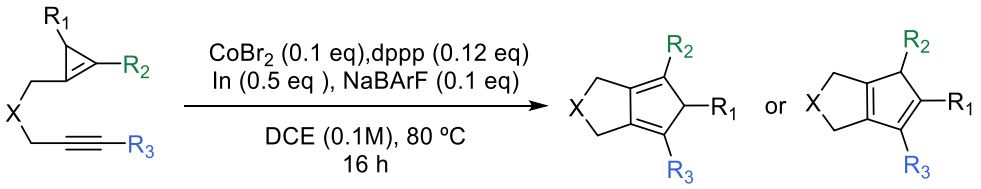
***Scheme 137.** Synthetic strategy towards the obtention of chiral Rh complexes.*

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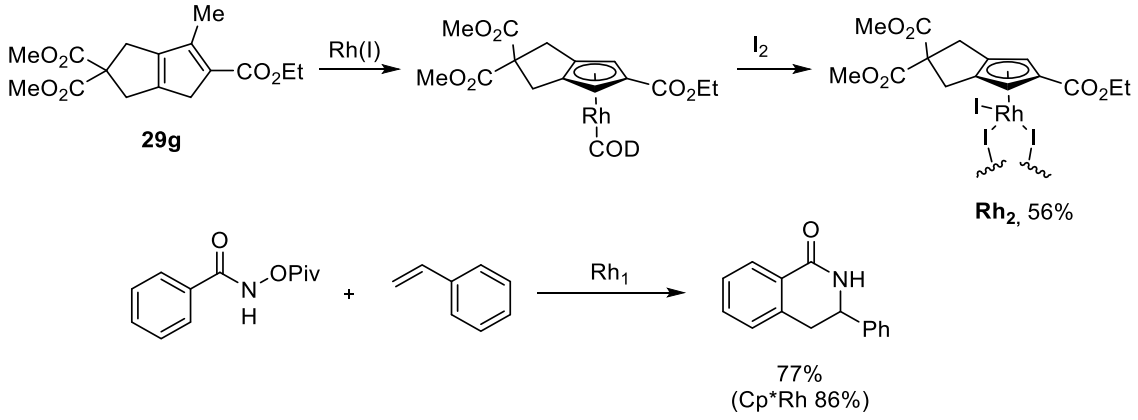
4. Conclusions

In conclusion, we have discovered a novel cycloaddition reaction promoted by a cobalt catalyst. The reaction provides a very rapid entry to a variety of highly substituted, fused cyclopentadienes from readily available cyclopropenylalkyne precursors, and tolerates multiple substituents in the cyclopropene and alkyne moieties, as well as different functional groups in the connecting tethers, delivering the cyclopentadienes with good yields in almost all the cases. The arrangement of the conjugated double bonds in the products depend on the cyclopropenyl substituents.

Very importantly, using related rhodium (I) catalysts the reaction didn't work, highlighting the essential role of cobalt.



A preliminary demonstration of the synthetic utility of this methodology was also validated with the synthesis of a novel type of cyclopendatienyl Rh (I) and Rh(III) complexes. Moreover, the catalytic activity of these Cp-Rh(III) complexes proved to be comparable to the commonly employed $[Cp^*RhCl_2]_2$ in the (4+2) cycloaddition of N-pivaloxybenzamides and alkenes.



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Overall conclusions

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As general conclusions of this thesis wok we can establish the following:

- We have discovered a novel low valent cobalt-catalysed enantioselective intramolecular (3+2) cycloaddition of alkyne-tethered ACPs. In addition of a wide scope, the synthetic utility of the products was proved using a simple hydrogenation protocol. Moreover, a mechanistically relevant, competent intermediate was experimentally isolated and fully characterized. Finally, along with all the experimental data, DFT calculations allowed us to propose a robust mechanistic proposal that confirms a different profile for cobalt (I) catalysts than for other counterparts based on rhodium or palladium.
- Low valent cobalt catalysts can also be used for multicomponent cycloadditions of ACPs, such as intramolecular (3+2+2) cycloaddition of ACPs, alkynes and alkenes, a reaction which shows a scope different than that previously observed with rhodium and palladium catalysts.
- The intramolecular cycloadditions of alkene-, allene- and diene-tethered ACPs was also demonstrated, although the scopes are quite limited. All these methodological studies were accompanied with mechanistic experiments and DFT calculations carried out by Prof. I. Fernández.
- We have developed a Pd(0)-catalysed intermolecular (3+2) cycloaddition of ACPs and trifluoromethylketones. Although the diastereoselectivity of the transformation was low, the scope is broad. DFT calculations indicate that the success of these ketones relies on their excellent behaviour in the migratory insertion step.
- Using a low valent cobalt complex, we have discovered a novel type of (3+2) intramolecular cycloaddition between cyclopropenes and alkynes, to give a wide variety of highly substituted bicyclic cyclopentadienes, interesting scaffolds that have been proven to be precursors of new types of cyclopentadienyl Rh(III) catalysts.

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Summary

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Introduction

One of the most vital and valued subdisciplines of chemistry is organic synthesis, the art and science of constructing carbon-containing products, either natural or designed. Although the primary goal of this discipline is the synthesis of a specific target product, along the decades this objective has evolved from achieving this synthesis at any cost to a new scenario wherein becomes essential to reach the goal in the most sustainable and practical manner.

Towards this end, it is essential to discover and develop new synthetic methodologies that are rapid, practical, and sustainable. In this context, catalytic reactions occupy a privileged position. By definition, a catalyst is *"a substance that changes the rate of a reaction without being consumed in the process"* and therefore, it has the capacity to be regenerated in the process leading to more sustainable processes. On another hand, the change in the reaction rate by diminishing the energetic barrier of the process, not only accelerates the chemical transformation but also allows reactions that otherwise could not be achieved.

From a general point of view, catalysts can be classified in heterogeneous, if they are not in the same phase as the substrates, or homogeneous, if both the catalyst and the substrate are in the same phase. Moreover, homogeneous catalysis can be divided in subcategories depending on its nature: biocatalysis, when the catalytic activity is accomplished by enzymes; organocatalysis, when an organic molecule is responsible for the acceleration; and organometallic catalysis, when the structure of the catalyst combines a metal and ancillary ligands, at least one of them being an organic molecule.

Among the subcategories of homogeneous catalysis, organometallic catalysis has been prominent and demonstrated a tremendous power. This area has been specially focused on the use of transition metal complexes due to their interesting redox properties as well as their versatility and easy *tuneability* by modifying their ancillary ligands. Thus, numerous interesting and valuable transformations have been developed over the years, such as the cross-coupling or metathesis reactions, which allow the formation of highly valuable C-C bonds in a specific and practical manner.

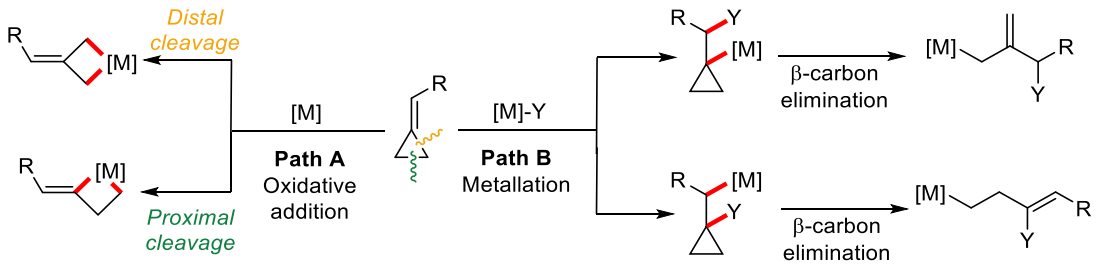
Within the toolbox of catalytic organometallic transformations, formal cycloaddition reactions are particularly valuable because they enable the formation of two new bonds and at least one new cycle from two or more simple precursors, in just one step, which is usually associated to a shortening of the synthetic processes.

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Over the years, the field of organometallic catalysis has not been limited to the development and discovery of new transformations or the improvement of the ones already reported, but it has also provided new tools for the construction of enantiopure molecules, usually relying on chiral ancillary ligands (enantioselective catalysis). In this context, the development of metal-catalysed asymmetric cycloadditions is particularly relevant in synthetic chemistry.

Along the years, our group has contributed to the invention and development of new organometallic catalytic cycloadditions. Among these contributions, one of the main research topics explored has been related with the use of alkylidenecyclopropanes (ACPs) as 3C *synthon*s in numerous transition metal-catalysed cycloadditions.

Alkylidenecyclopropanes are organic scaffolds that bear a cyclopropane moiety and an exocyclic double bond. These structural features make ACPs one of the most strained carbocycles, even more than a simple cyclopropane. The double bond can also be used as a handle for triggering metal-catalysed transformations. For example, ACPs can suffer an oxidative addition of certain metal complexes to give metallacyclobutane species, that further evolve in the presence of appropriate reaction partners. Interestingly, depending on whether a distal or a proximal cleavage, two different metallacyclobutanes can be formed.



This kind of reactivity has been evaluated over the years, and it has been shown that depending on the metal complex employed the selectivity of the oxidative addition can be tuned. Thus, when a Pd or a Rh catalyst are used, a distal cleavage of the cyclopropyl ring tends to be the preferred reaction pathway. On another hand, with a Ni catalyst the alternative proximal oxidative addition takes place.

Over the years, a wide variety of cycloadditions involving the ring opening of ACPs have been successfully developed. For example, in presence of a Pd catalyst, our group has successfully developed Pd-catalysed intramolecular cycloadditions of ACPs with alkenes,[73] alkynes[71] or allenes, [75] to give a variety of 5,5-bicyclic carbocycles. Moreover, multicomponent cycloadditions have been also developed, allowing the construction of larger polycyclic scaffolds.[83,84]

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CHAPTER I: Co(I)-catalysed intramolecular cycloadditions of ACPs with C-C unsaturated partners

(3+2) cycloaddition of alkyne-tethered ACPs: enantioselective versions

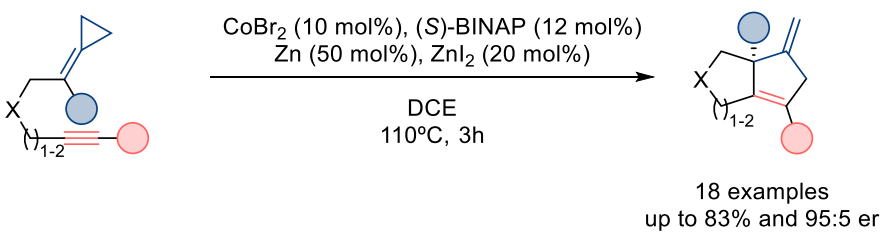
Even though a broad range of cycloadditions involving ACPs had been successfully developed, most of these transformations relied on precious transition metal complexes, such as Pd or Rh. Moreover, enantioselective cycloadditions of ACPs are very scarce, and only a handful of examples can be found in the literature.

In this context, the use of earth-abundant 3d transition metals, such as cobalt, are highly attractive, not only because of the more sustainable character, but also because they can open new reactivity pathways. Indeed, low valent cobalt catalysts had demonstrated interesting reactivities with alternative strained systems such as benzcyclobutanones [42] or vinylcyclopropanes.[95]

On these bases, we decided to evaluate the viability of promoting cobalt catalysed formal cycloadditions of ACPs with different type of partners. To our delight, we found out that using $CoBr_2$ as cobalt source, dppp as ligand, Zn as reductant and ZnI_2 as additive in MeCN at 110°C, ACPs undergo very efficient, formal intramolecular (3+2) cycloadditions with alkynes. We have also explored enantioselective versions of this transformation. Pleasingly, using the conditions mentioned before, but enantiopure BINAP as ligand, and 1,2-dichloroethane as solvent, the desired cycloadducts could be obtained with very good enantiomeric ratios.

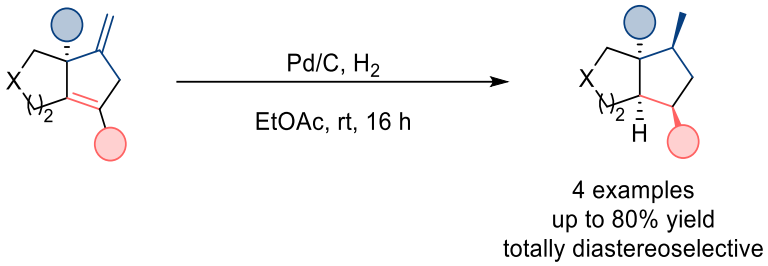
This asymmetric cycloaddition presents an excellent scope; thus, a variety of alkynes with different substituents, including alkyl or alkenyl groups, aromatic and heteroaromatic rings or silane, and even unsubstituted alkynes, gave the products with good yields and high enantioselectivities. In addition, different functional groups are tolerated in the connecting tethers like sulfonamides or ethers.

Moreover, the reaction also allowed the enantioselective construction of 5,5-bicyclic structures bearing quaternary carbon centres in the ring fusion. Finally, we also have proven that using this low valent cobalt catalysed cycloaddition of alkyne-tethered ACPs, the construction of larger 6,5-bicyclic scaffolds is possible.

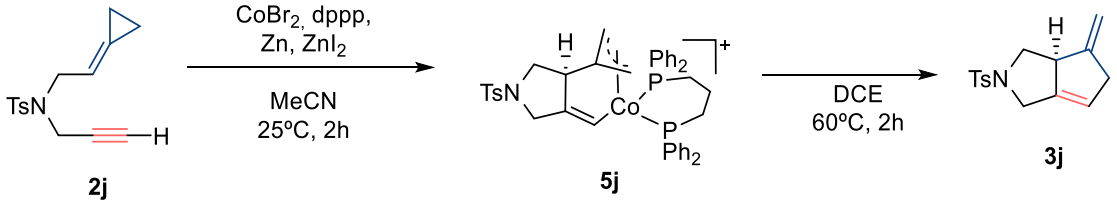


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We preliminary proved the synthetic potential of our method by running a classical hydrogenation using Pd/C as catalyst, which provided for the stereoselective construction of 5,5 and 5,6-bicyclic systems bearing up to 4 stereocenters.

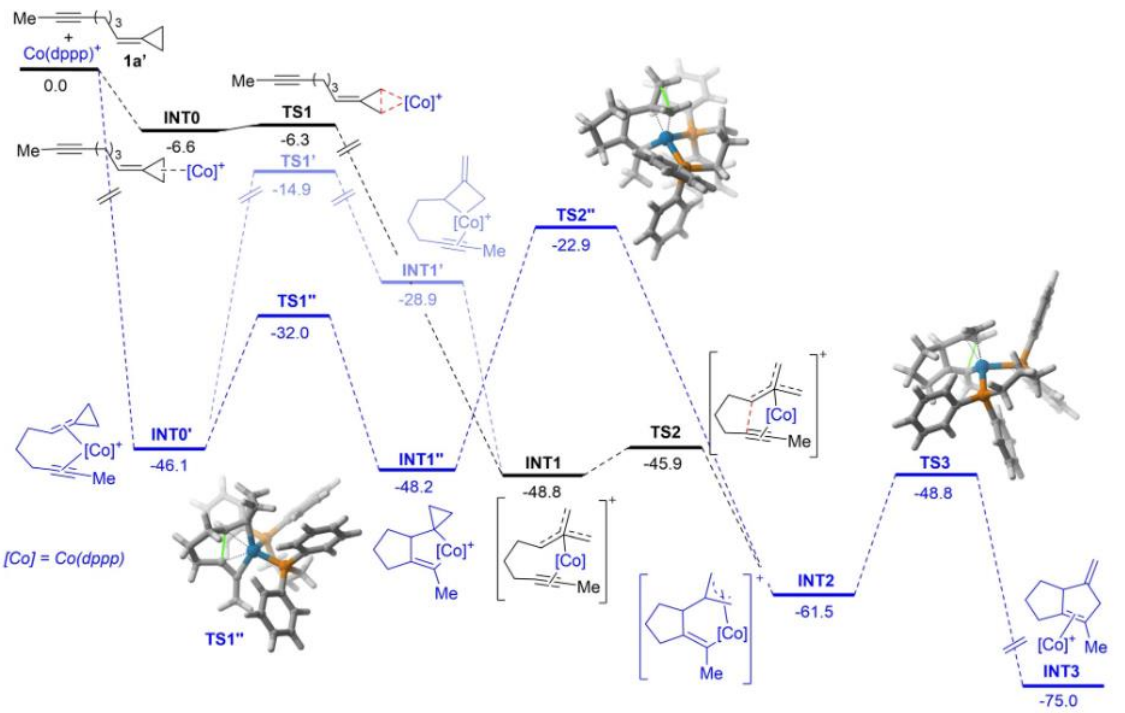


Once the technology was established and demonstrated to have a wide scope, we studied the mechanism of this transformation. Initially, we investigated the oxidation state of the catalytically active cobalt species. Thus, several experiments employing a Co(0) and/or a Co(I) complexes were evaluated, concluding that our active cobalt species should be a Co(I) cationic complex. In addition to these experimental mechanistic studies, we were pleased to isolate and fully characterize by NMR and mass spectroscopy the π-allyl cobaltacycle **5j**. Moreover, this species proved to be a competent intermediate of the reaction.



This information was complemented with DFT calculations performed by Prof. Israel Fernandez. To our delight, these computational data revealed that the more plausible mechanism is different from that previously reported with Pd or Rh catalysts. Indeed, the reaction likely starts by an initial oxidative cyclometallation to give intermediate INT0'', followed by a cyclopropyl to π-allyl rearrangement towards a π-allyl species similar to the isolated complex **5j**. From this intermediate, a reductive elimination affords the corresponding cycloadduct.

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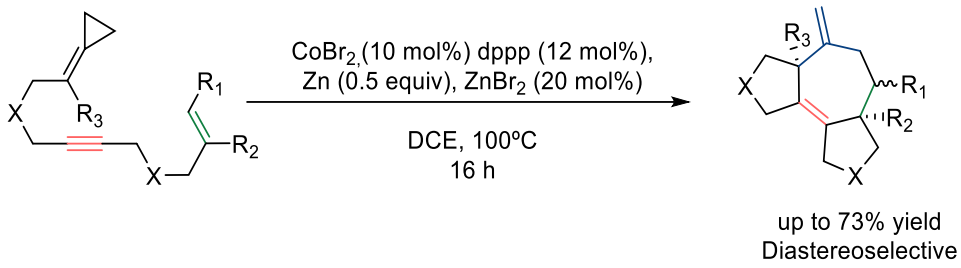
Multicomponent cycloaddition of alkyne-tethered ACPs

Based on the excellent results obtained in the development of the asymmetric Co(I) catalysed (3+2) cycloaddition of alkyne-tethered ACPs, we envisioned the possibility of developing multicomponent processes towards the construction of larger polycyclic carbocycles.

Initially, external cycloaddition partners such as CO, alkenes, allenes or alkynes were added in presence of the alkyne-tethered ACPs. However, under the optimal conditions for the (3+2) cycloaddition, the desired multicomponent cycloadducts were not formed. Based on these results, we envisioned that a fully intramolecular approach would be easier. Thus, we were glad to find out that 1,6-enyne-tethered ACPs afforded the desired 5,7,6-tricyclic adducts in a totally diastereoselective manner (only *cis* isomer formed).

This (3+2+2) methodology enabled the construction of several tricyclic scaffolds bearing a variety of functional groups in the connecting tethers between the ACP, the alkyne, and the alkene, when terminal substituted alkenes are employed. The scope was not very broad, but substrates with internal substituted alkenes bearing a methyl group were tolerated. We also demonstrated the viability of using precursors in which the alkene of the ACP exhibits a substituent.

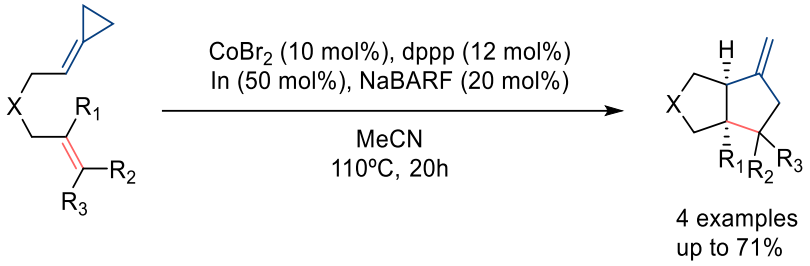
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(3+2) Cycloaddition of alkene-, allene- and diene-tethered ACPs

Considering the excellent behaviour of alkyne tethered ACPs, we were curious to know if other 2C partners could also participate in the cobalt-catalysed cycloaddition.

The (3+2) cycloaddition between ACPs and-tethered alkenes proceed efficiently to give the *cis-fused* isomer of the expected cycloadduct. The substitution of the alkene is key, since terminally substituted alkenes do not participate in the process whereas the internal position of the alkene can be substituted, providing access to, 5,5-bicyclic systems with a quaternary carbon centre at the ring fusion. We also explored enantioselective versions of this (3+2) cycloaddition; however, after screening many different types of chiral ligands such as bisphosphines, ferrocenes and phosphoramidites, the best result was a moderate 85:15 er, with the very bulky phosphite **L_{11}**.



The mechanism of the reaction was also explored using DFT calculations. Although the profile is similar to that previously calculated for alkynes, in the case of alkenyl partners we observed a more demanding reductive elimination step, which could be the origin of the relatively poor scope of the transformation.

On other hand, the (3+2) cycloaddition of allene-tethered ACPs was also evaluated and again we proved that, although feasible, its scope is extremely sensitive towards the substitution pattern, so that only a monosubstituted allene successfully participated in the (3+2) cycloaddition process.

Finally, we demonstrated the viability of performing cobalt-catalysed (4+3) cycloadditions using 1,3-dienes. Although the scope was again limited, a preliminary exploration of chiral ligands for an enantioselective version, allowed us to find out that

the use of **L11** affords in a model (4+3) cycloaddition reaction an enantiomeric ratio of 85:15.

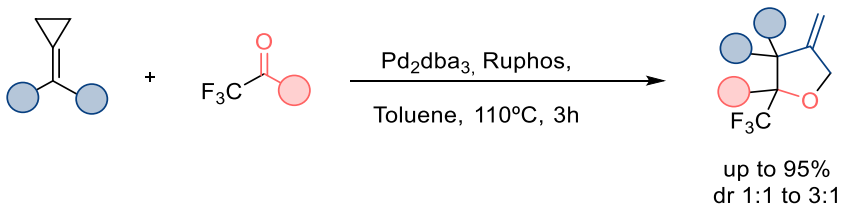
CHAPTER II: Pd catalysed Intermolecular (3+2) Hetereocycloadditions of ACPs and carbonyls

Heterocyclic structures are abundant natural products with plenty of applications in the pharmaceutical and agrochemical field. From all the heterocyclic scaffolds, saturated oxygen heterocycles are among the most abundant in nature and since they are known to appear in a wide array of systems. Among this kind of oxygen heterocycles, five membered oxacycles, commonly known as tetrahydofurans (THFs) are particular abundant.

The synthesis of 5-membered oxacycles has been mainly explored using cyclization methodologies, with cycloaddition methods, especially those based on transition metal catalysis, being scarcer.

Due to our expertise in Pd-catalysed cycloadditions of ACPs, we envisioned the possibility of developing heterocycloadditions using carbonyl functional groups as π unsaturated partners. In this context, our group successfully developed a Pd-catalysed intramolecular (3+2) cycloaddition of ACPs and aldehydes or ketones, a reaction that is favoured by the use of Buchwald biaryl phopshine ligands.

Inspired by these results, at the beginning of my PhD we decided to explore the advantages of the Buchwald ligands in the development of intermolecular cycloadditions between ACPs and carbonyl compounds. Although normal ketones do not participate in the reaction, we found that using trifluoromethylketones as cycloaddition partners and RuPhos as optimal ligands the reaction takes place very efficiently, albeit with low diasteromeric ratio.



The reaction presents a very good scope, and the methodology tolerates a wide array of aromatic substituted trifluoromethylketones as well alkenyl trifluoromethylketones. Moreover 3-oxo-alkyltrifluoromethyl ketone was also a suitable cycloaddition partner. Interestingly, the scope of the reaction could also be extended to other fluorinated ketones like difluoromethylketones.

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Moreover, several ACPs with nitrogenated, oxygenated or carbon-based chains could be used for the construction of the corresponding fluorinated *exo*-methylene THFs. Despite the fact that all the examples mentioned before afforded the corresponding cycloadducts with high efficiency, the diastereoselectivity of the transformation was usually modest.

Finally, intrigued by the special behaviour of trifluoromethylketones, compared to other carbonyl compounds, we performed DFT calculations that could shed light on the origin of these differences. Preliminary DFT calculations indicated that the main difference relies on the migratory insertion step. While acetophenone needs to overcome a barrier of 25.1 kcal/mol, its trifluoromethyl analogue requires only 7.2 kcal/mol. This enormous energetic difference could be the reason of the reactivity observed experimentally.

CHAPTER III Cobalt-catalysed intramolecular (3+2) cycloaddition of cyclopropenes and alkynes

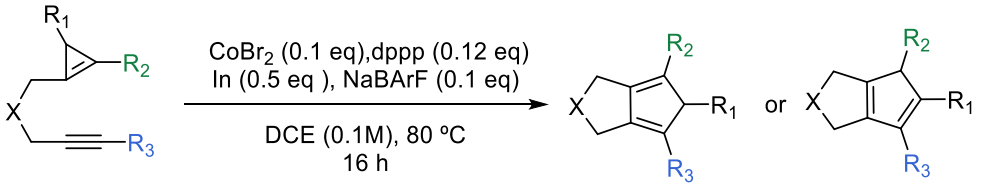
Cyclopropenes present a very high strain and therefore are very attractive in terms of reactivity. Structurally, a cyclopropene bears a double bond with a shorter length (1.27 Å) than a typical C_{sp2}-C_{sp2} double bond (1.34 Å). This fact gives the π-bond of the cyclopropene ring more electron density compared to a classical π -bond.

Due to their characteristic structural features, cyclopropenes have shown a fascinating and unique reactivity. They have been extensively used as 2C synthons in different types of reactions like carbo-, hydro-metalations and annulations.[137] However, due to their high strain energy, cyclopropenes can also undergo ring-cleavage reactions, and eventually work as 3C synthons.

Inspired by our successful results in the Co(I)-catalysed (3+2) cycloadditions of alkyne-tethered ACPs and the lack of cycloadditions of cyclopropenes mediated by cobalt catalysts, we explored the feasibility of cobalt catalysed (3+2) cycloadditions of alkyne-tethered cyclopropenes, which could yield synthetically relevant cyclopentadienyl-fused bicyclic scaffolds..

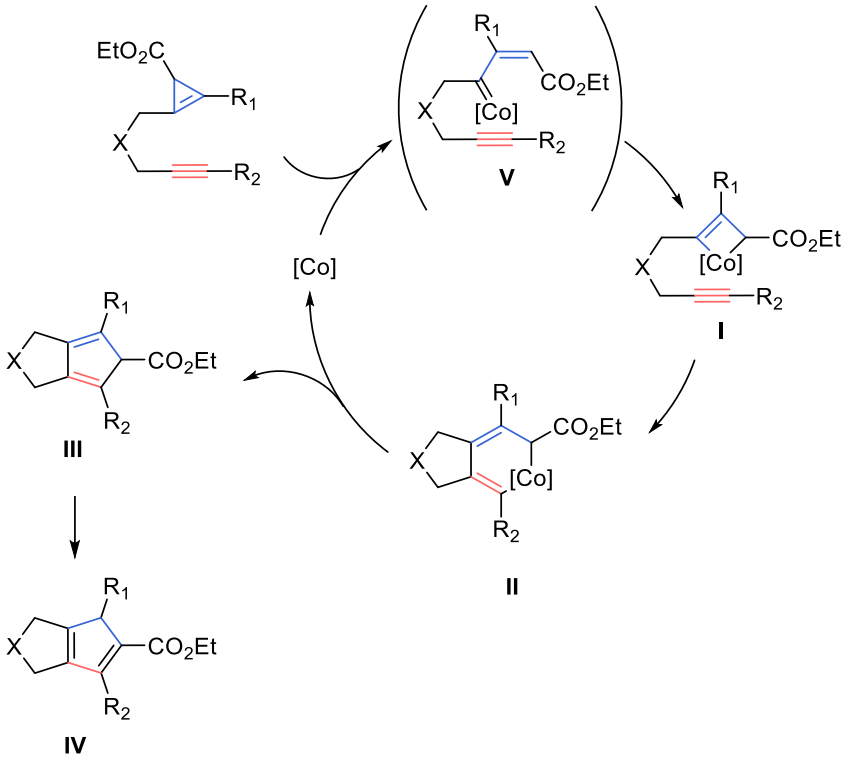
Gratifyingly, we found out that the reaction is feasible using the catalyst derived from $CoBr_2$ as cobalt source, dppp as ligand, In as reductant and $NaBAr^F$ as halide scavenger, in 1,2-dichloroethane at 80 °C. Moreover, control experiments demonstrated that all these reaction components are needed for the cycloaddition to occur.

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Regarding the scope of the reaction, a wide variety of substituted alkynes were tolerated. Thus, alkyl, aryl, terminal or hetereosubstituted alkynes worked very well, affording the corresponding cyclopentadiene in good yields. Moreover, different functional groups in the connecting tether between the ACP and the alkyne were also well-tolerated.

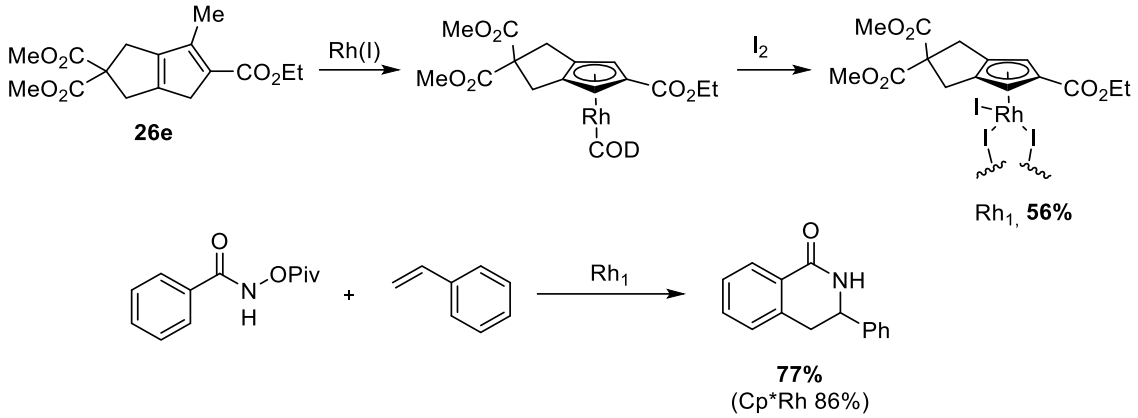
From a mechanistic perspective, the reaction might involve the insertion of the Cobalt(I) complex into the cyclopropene to form cobaltacyclobutene species **I**. Then, a migratory insertion and reductive elimination would afford a cyclopentadienyl intermediate **III**, which could further isomerize to cyclopentadiene I**V** depending on the functional group placed in the vinylic position of the cyclopropene. In addition, we could not rule out the participation of a vinyl cobalt carbene V that could further evolve to cobaltacyclobutene **I.**



To illustrate the synthetic utility of this cycloaddition, we envisioned that this strategy could be used as a synthetic platform towards the construction of novel Cp-metal complexes. Thus, when the substrate **26e** was reacted with a substoichiometric amount of $[Rh(COD)Cl]_2$ in the presence of a base, the corresponding Rh(I) cyclopentadienyl

ligand was obtained. Moreover, the corresponding Rh(III) dimer could be easily obtain in an overall 56% yield by a simple I_2 mediated oxidation.

To further prove the utility of this novel Rh complexes, we explored Rh(III) complex **Rh1** as catalyst for a model (4+2) cycloaddition of N-pivaloxybenzamides and alkenes, obtaining the expected tetrahydroisoquinolinones in a good 77% yield, which is comparable with the one reported using $[Cp^*RhCl_2]_2$.



Overall conclusion

As general conclusion, we have uncovered a variety of cobalt-catalysed intramolecular cycloadditions of strained cyclopropyl derivatives, both alkylidencyclopropanes and cyclopropenes. Particularly successful were the cycloadditions involving alkynes as cycloaddition partners.

We have also found that trifluoromethyl ketones are excellent reaction partners for intermolecular palladium-catalysed (3+2) heterocycloadditions with ACPs, to give five-membered oxacycles.

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Resumen

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Introducción

Una de las subdisciplinas más vitales y valoradas de la química es la síntesis orgánica, el arte y la ciencia de construir productos que contienen carbono, ya sean naturales o diseñados. Aunque el objetivo principal de esta disciplina es la síntesis de un producto objetivo específico, a lo largo de las décadas este objetivo ha evolucionado desde lograr esta síntesis a cualquier costo a un nuevo escenario en el que se vuelve esencial alcanzar la meta de una manera más sostenible y práctica.

Para ello, es esencial descubrir y desarrollar nuevas metodologías sintéticas que sean rápidas, prácticas y sostenibles. En este contexto, las reacciones catalíticas ocupan una posición privilegiada. Por definición, un catalizador es "una sustancia que cambia la velocidad de una reacción sin ser consumida en el proceso" y, por lo tanto, tiene la capacidad de regenerarse en el proceso, conduciendo a procesos más sostenibles. Por otro lado, el cambio en la velocidad de reacción al disminuir la barrera energética del proceso, no solo acelera la transformación química, sino que también permite reacciones que de otra manera no podrían lograrse.

Desde un punto de vista general, los catalizadores se pueden clasificar en heterogéneos, si no están en la misma fase que los sustratos, u homogéneos, si tanto el catalizador como el sustrato están en la misma fase. Además, la catálisis homogénea se puede dividir en subcategorías según su naturaleza: biocatálisis, cuando la actividad catalítica se realiza mediante enzimas; organocatálisis, cuando una molécula orgánica es responsable de la aceleración; y catálisis organometálica, cuando la estructura del catalizador combina un metal y ligandos auxiliares, siendo al menos uno de ellos una molécula orgánica.

Entre las subcategorías de catálisis homogénea, la catálisis organometálica ha sido prominente y ha demostrado un tremendo poder. Esta área se ha centrado especialmente en el uso de complejos de metales de transición debido a sus interesantes propiedades redox, así como a su versatilidad y fácil puesta a punto mediante la modificación de sus ligandos auxiliares. Así, a lo largo de los años se han desarrollado numerosas transformaciones interesantes y valiosas, como el acoplamiento cruzado o las reacciones de metátesis, que permiten la formación de enlaces C-C de gran valor de una manera específica y práctica.

Dentro de la caja de herramientas de las transformaciones organometálicas catalíticas, las reacciones formales de cicloadición son particularmente valiosas porque permiten la formación de dos nuevos enlaces y al menos un nuevo ciclo a partir de dos o más

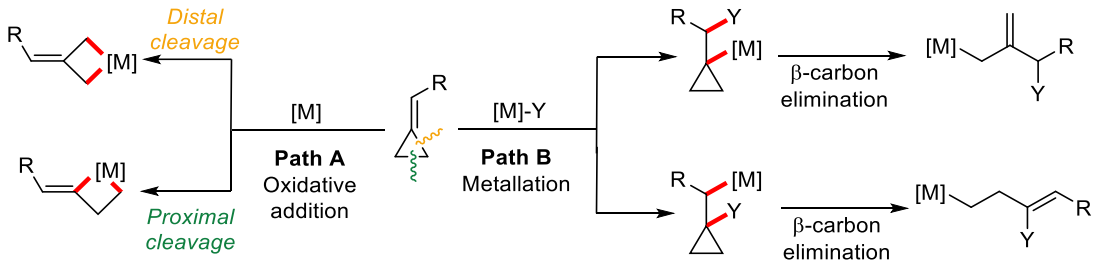
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precursores simples, en un solo paso, que generalmente se asocia a un acortamiento de los procesos sintéticos.

A lo largo de los años, el campo de la catálisis organometálica no se ha limitado al desarrollo y descubrimiento de nuevas transformaciones o a la mejora de las ya reportadas, sino que también ha proporcionado nuevas herramientas para la construcción de moléculas enantiopuras, generalmente basadas en ligandos auxiliares quirales (catálisis enantioselectiva). En este contexto, el desarrollo de cicloadiciones asimétricas catalizadas por metales es particularmente relevante en química sintética.

A lo largo de los años, nuestro grupo ha contribuido a la invención y desarrollo de nuevas cicloadiciones catalíticas organometálicas. Entre estas contribuciones, uno de los principales temas de investigación explorados ha estado relacionado con el uso de alquilidenciclopropanos (ACP) como sintones 3C en numerosas cicloadiciones catalizadas por metales de transición.

Los alquilidenciclopropanos son andamios orgánicos que tienen una fracción de ciclopropano y un doble enlace exocíclico. Estas características estructurales hacen de los ACP uno de los carbociclos más tensos, incluso más que un simple ciclopropano. El doble enlace también se puede utilizar como mango para desencadenar transformaciones catalizadas por metales. Por ejemplo, los ACP pueden sufrir una adición oxidativa de ciertos complejos metálicos para dar especies de metalaciclobutano, que evolucionan aún más en presencia de socios de reacción apropiados. Curiosamente, dependiendo de si es una escisión distal o proximal, se pueden formar dos metalaciclobutanos diferentes.



Este tipo de reactividad se ha evaluado a lo largo de los años, y se ha demostrado que dependiendo del complejo metálico empleado se puede ajustar la selectividad de la adición oxidativa. Por lo tanto, cuando se utiliza un catalizador de Pd o Rh, una escisión distal del anillo de ciclopropilo tiende a ser la vía de reacción preferida. Por otro lado, con un catalizador de Ni tiene lugar la adición oxidativa proximal alternativa.

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A lo largo de los años, se ha desarrollado con éxito una amplia variedad de cicloadiciones que implican la apertura del anillo de los ACP. Por ejemplo, en presencia de un catalizador de Pd, nuestro grupo ha desarrollado con éxito cicloadiciones intramoleculares catalizadas por Pd de ACPs con alquenos[73], alquinos[71] o alenos,[75] para dar una variedad de carbociclos 5,5-bicíclicos. Además, también se han desarrollado cicloadiciones multicomponente, lo que permite la construcción de andamios policíclicos más grandes.[83,84]

CAPÍTULO I: Cicloadiciones intramoleculares catalizadas por Co(I) de ACPs con componentes insaturados C-C.

Cicloadición (3+2) de ACPs unidos a alquinos: versiones enantioselectivas.

A pesar de que se había desarrollado con éxito una amplia gama de cicloadiciones que involucraban ACP, la mayoría de estas transformaciones se basaron en complejos de metales de transición preciosos, como Pd o Rh. Además, las cicloadiciones enantioselectivas de los ACP son muy escasas, y sólo se pueden encontrar un puñado de ejemplos en la literatura.

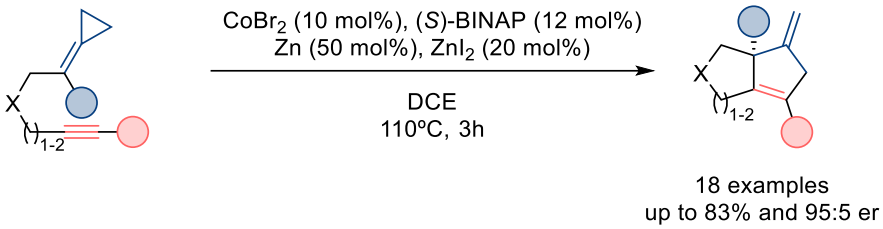
En este contexto, el uso de metales de transición 3D abundantes en la tierra, como el cobalto, son muy atractivos, no solo por el carácter más sostenible, sino también porque pueden abrir nuevas vías de reactividad. De hecho, los catalizadores de cobalto de baja valencia habían demostrado reactividades interesantes con sistemas tensados como benzociclobutanonas [42] o vinilciclopropanos.[95]

Sobre estas bases, decidimos evaluar la viabilidad de promover cicloadiciones formales catalizadas por cobalto de los ACP con diferentes tipos de socios. Para nuestro deleite, descubrimos que usando CoBr2 como fuente de cobalto, dppp como ligando, Zn como reductor y ZnI2 como aditivo en MeCN a 110 ° C, los ACP experimentan cicloadiciones intramoleculares formales (3 + 2) muy eficientes con alquinos. También hemos explorado versiones enantioselectivas de esta transformación. Agradablemente, utilizando las condiciones mencionadas anteriormente, pero enantiopure BINAP como ligando, y 1,2-dicloroetano como disolvente, se podrían obtener los cicloaductos deseados con muy buenas proporciones enantioméricas.

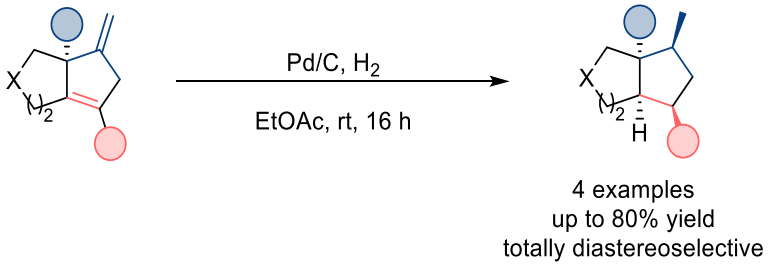
Esta cicloadición asimétrica presenta un excelente alcance; Así, una variedad de alquinos con diferentes sustituyentes, incluyendo grupos alquilo o alqueno, anillos aromáticos y heteroaromáticos o silano, e incluso alquinos no sustituidos, dieron a los productos buenos rendimientos y altas enantiosselectividades. Además, se toleran diferentes grupos funcionales en las correas de conexión como sulfonamidas o éteres.

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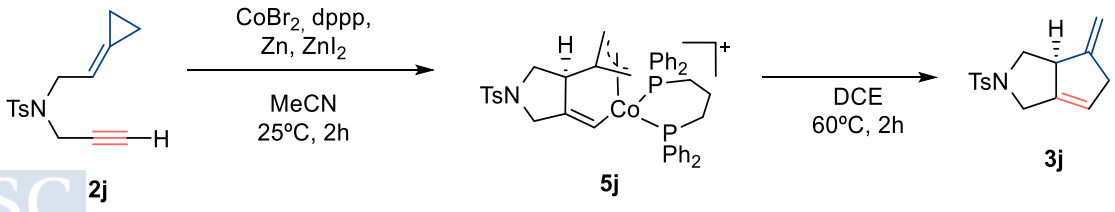
Además, la reacción también permitió la construcción enantioselectiva de estructuras 5,5-bicíclicas que llevan centros de carbono cuaternario en la fusión de anillos. Finalmente, también hemos demostrado que usando esta cicloadición catalizada por cobalto de baja valencia de ACP atados a alquinos, es posible la construcción de andamios 6,5-bicíclicos más grandes.



Para probar aún más el potencial sintético de nuestro método, hicimos una breve exploración sobre las posibilidades de derivatización de los cicloaductos. Así, en condiciones clásicas de hidrogenación utilizando Pd/C se realizó con éxito una construcción diastereoselectiva total de sistemas 5,5 y 5,6-bicíclicos con hasta 4 estereocentros.

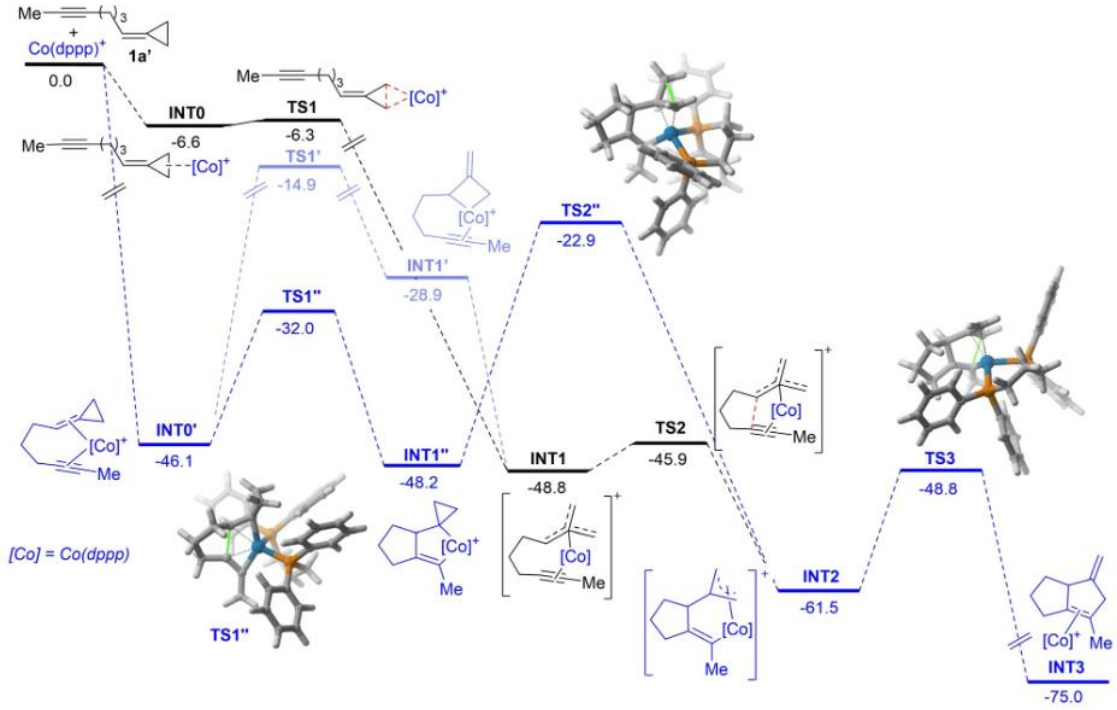


Una vez que se estableció la tecnología y se demostró que tenía un amplio alcance, estudiamos el mecanismo de esta transformación. Inicialmente, investigamos el estado de oxidación de las especies de cobalto catalíticamente activas. Así, se evaluaron varios experimentos que emplearon un complejo Co(0) y/o Co(I), concluyendo que nuestras especies activas de cobalto deberían ser un complejo catiónico Co(I). Además de estos estudios mecanicistas experimentales, tuvimos el placer de aislar y caracterizar completamente por RMN y espectroscopia de masas el cobaltaciclo **5j** de π-alilo. Además, esta especie demostró ser un intermediario competente de la reacción.



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Esta información se complementó con cálculos DFT realizados por el Prof. Israel Fernández. Para nuestro deleite, estos datos computacionales revelaron que el mecanismo más plausible es diferente del reportado previamente con catalizadores de Pd o Rh. De hecho, la reacción probablemente comienza con una ciclometalación oxidativa inicial para dar **INT0''** intermedio, seguido de un reordenamiento de ciclopropilo a π-alilo hacia una especie de π-alilo similar al complejo aislado **5j**. A partir de este intermedio, una eliminación reductiva proporciona el cicloaducto correspondiente.



Cicloadición multicomponente de ACPs unidos a alquinos.

Basándonos en los excelentes resultados obtenidos en el desarrollo de la cicloadición asimétrica catalizada por Co(I) (3+2) de ACPs atados a alquinos, vislumbramos la posibilidad de desarrollar procesos multicomponentes hacia la construcción de carbociclos policíclicos más grandes.

Inicialmente, se agregaron socios externos de cicloadición como CO, alquenos, alenos o alquinos en presencia de los ACP atados a alquinos. Sin embargo, en las condiciones óptimas para la cicloadición (3 + 2), no se formaron los cicloaductos multicomponentes deseados. Sobre la base de estos resultados, previmos que un enfoque totalmente intramolecular sería más fácil. Por lo tanto, nos alegramos de descubrir que los ACP atados a 1,6-eninos proporcionaron los aductos 5,7,6-tricíclicos deseados de una manera totalmente diastereoselectiva (solo se formó el isómero *cis*).

Esta metodología (3 + 2 + 2) permitió la construcción de varios andamios tricíclicos que llevan una variedad de grupos funcionales en las ataduras de conexión entre el ACP, el alquino y el alqueno, cuando se emplean alquenos terminales sustituidos. El alcance no fue muy amplio, pero se toleraron sustratos con alquenos sustituidos internos que llevaban un grupo metilo. También demostramos la viabilidad de utilizar precursores en los que el alqueno del ACP exhibe un sustituyente.



Además de todos los datos experimentales, los cálculos de DFT revelan la vía del mecanismo de esta transformación y las diferencias energéticas respecto las publicaciones anteriores utilizando Pd y Rh.

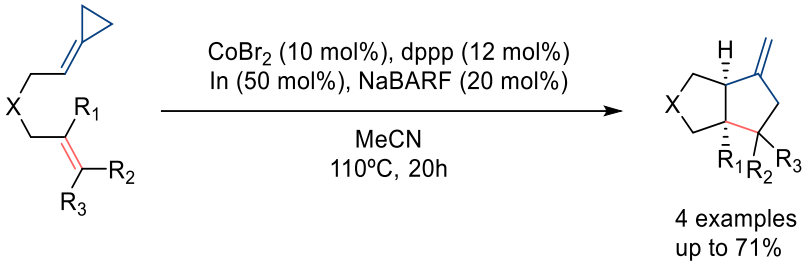
(3+2) Cicloadición de ACP unidos a alqueno, aleno y dieno

Teniendo en cuenta el excelente comportamiento de los ACP atados con alquino, teníamos curiosidad por saber si otros socios de 2C también podrían participar en la cicloadición catalizada por cobalto.

La cicloadición (3+2) entre ACPs y alquenos atados procede eficientemente a dar el isómero cis-fusionado del cicloaducto esperado. La sustitución del alqueno es clave, ya que los alquenos sustituidos terminalmente no participan en el proceso, mientras que la posición interna del alqueno puede ser sustituida, proporcionando acceso a sistemas 5,5-bicíclicos con un centro de carbono cuaternario en la fusión del anillo. También exploramos versiones enantioselectivas de esta cicloadición (3+2); sin embargo, después de examinar muchos tipos diferentes de ligandos quirales como bisfosfinas, ferrocenos y fosforamidas, el mejor resultado fue un 85:15 ER moderado, con el fosfito muy voluminoso **L11**.

El mecanismo de la reacción también se exploró utilizando cálculos DFT. Aunque el perfil es similar al calculado previamente para los alquinos, en el caso de los socios alquenilos observamos un paso de eliminación reductiva más exigente, que podría ser el origen del alcance relativamente pobre de la transformación.

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Por otro lado, también se evaluó la cicloadición (3+2) de ACPs atados a aleno y nuevamente se demostró que, aunque factible, su alcance es extremadamente sensible al patrón de sustitución, de modo que solo un aleno monosustituido participó con éxito en el proceso de cicloadición (3+2).

Finalmente, demostramos la viabilidad de realizar cicloadiciones catalizadas por cobalto (4+3) utilizando 1,3-dienos. Aunque el alcance fue nuevamente limitado, una exploración preliminar de ligandos quirales para una versión enantioselectiva, nos permitió descubrir que el uso de **L11** proporciona en un modelo (4+3) una reacción de cicloadición una relación enantiomérica de 85:15.

CAPÍTULO II: Hetereocicloadiciones intermoleculares (3+2) catalizadas por Pd entre ACP y carbonilos.

Las estructuras heterocíclicas son abundantes productos naturales con muchas aplicaciones en el campo farmacéutico y agroquímico. De todos los andamios heterocíclicos, los heterociclos de oxígeno saturado se encuentran entre los más abundantes en la naturaleza y ya que se sabe que aparecen en una amplia gama de sistemas. Entre este tipo de heterociclos de oxígeno, los oxaciclos de cinco miembros, comúnmente conocidos como tetrahidofuranos (THF) son particularmente abundantes.

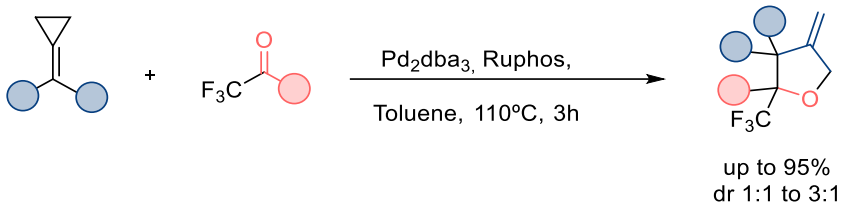
La síntesis de oxaciclos de 5 miembros se ha explorado principalmente utilizando metodologías de ciclación, siendo más escasos los métodos de cicloadición, especialmente los basados en catálisis de metales de transición.

Debido a nuestra experiencia en cicloadiciones catalizadas por PD de ACP, imaginamos la posibilidad de desarrollar heterocicloadiciones utilizando grupos funcionales carbonilo como socios π insaturados. En este contexto, nuestro grupo desarrolló con éxito una cicloadición intramolecular (3+2) catalizada por Pd de ACP y aldehídos o cetonas, una reacción que se ve favorecida por el uso de ligandos Buchwald biaryl phopshine.

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Inspirados por estos resultados, al comienzo de mi doctorado decidimos explorar las ventajas de los ligandos de Buchwald en el desarrollo de cicloadiciones intermoleculares

entre ACP y compuestos carbonílicos. Aunque las cetonas normales no participan en la reacción, encontramos que usando trifluorometilcetonas como socios de cicloadición y RuPhos como ligandos óptimos, la reacción tiene lugar de manera muy eficiente, aunque con una baja relación diastereomérica.



up to 95%
dr 1:1 to 3:1

La reacción presenta un alcance muy bueno, y la metodología tolera una amplia gama de trifluorometilcetonas aromáticas sustituidas, así como trifluorometilcetonas de alqueno. Además, la cetona 3-oxo-alquiltrifluorometilcetona también fue un socio de cicloadición adecuado. Curiosamente, el alcance de la reacción también podría extenderse a otras cetonas fluoradas como las difluorometilcetonas.

Además, varios ACP con cadenas nitrogenadas, oxigenadas o basadas en carbono podrían utilizarse para la construcción de los correspondientes THF de exometileno fluorado. A pesar de que todos los ejemplos mencionados anteriormente ofrecían los cicloaductos correspondientes con alta eficiencia, la diastereoselectividad de la transformación era generalmente modesta.

Finalmente, intrigados por el comportamiento especial de las trifluorometilcetonas, en comparación con otros compuestos carbonílicos, realizamos cálculos DFT que podrían arrojar luz sobre el origen de estas diferencias. Los cálculos preliminares de DFT indicaron que la principal diferencia depende de la etapa de inserción migratoria. Mientras que la acetofenona necesita superar una barrera de 25.1 kcal / mol, su análogo trifluorometilo requiere solo 7.2 kcal / mol. Esta enorme diferencia energética podría ser la razón de la reactividad observada experimentalmente.

CAPÍTULO III Cicloadición intramolecular (3+2) catalizada por Co entre ciclopropenos y alquinos.

Los ciclopropenos presentan una tensión muy alta y, por lo tanto, son muy atractivos en términos de reactividad. Estructuralmente, un ciclopropeno tiene un doble enlace con una longitud más corta (1,27 Å) que un doble enlace típico Csp2-Csp2 (1,34 Å). Este hecho le da al enlace π del anillo de ciclopropeno más densidad de electrones en comparación con un enlace π clásico.

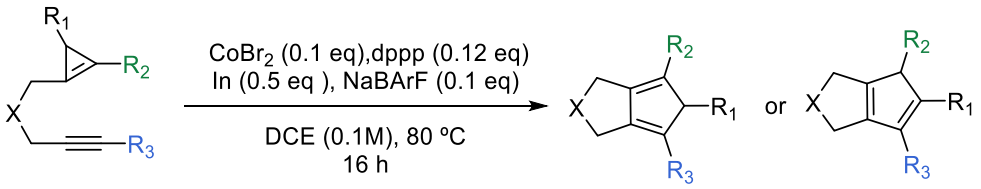
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Debido a sus características estructurales, los ciclopropenos han mostrado una reactividad fascinante y única. Se han utilizado ampliamente como sintones 2C en diferentes tipos de reacciones como carbo-, hidrometalaciones y anulaciones.[137] Sin embargo, debido a su alta energía de deformación, los ciclopropenos también pueden sufrir reacciones de escisión de anillo, y eventualmente funcionar como sintones 3C.

Los ciclopropenos han sido excelentes compuestos para el desarrollo de diferentes tipos de reacciones de cicloadiciones, especialmente cicloadiciones catalizadas por metales de transición. Por lo tanto, bajo la presencia de varios metales de transición como Pd, Rh o Ni, se desarrollaron con éxito una serie de cicloadiciones intermoleculares e intramoleculares a lo largo de los años.

Inspirados por nuestros resultados exitosos en las cicloadiciones catalizadas por Co(I) (3+2) de ACP atados a alquinos y la falta de cicloadiciones de ciclopropenos mediados por catalizadores de cobalto, exploramos la viabilidad de cicloadiciones catalizadas por cobalto (3+2) de ciclopropenos atados a alquinos, que podrían producir andamios bicíclicos fusionados con ciclopentadienilo sintéticamente relevantes.

Gratificantemente, descubrimos que la reacción es factible utilizando el catalizador derivado de CoBr2 como fuente de cobalto, dppp como ligando, In como reductor y NaBArF como eliminador de haluros, en 1,2-dicloroetano a 80 °C. Además, los experimentos de control demostraron que todos estos componentes de reacción son necesarios para que ocurra la cicloadición.

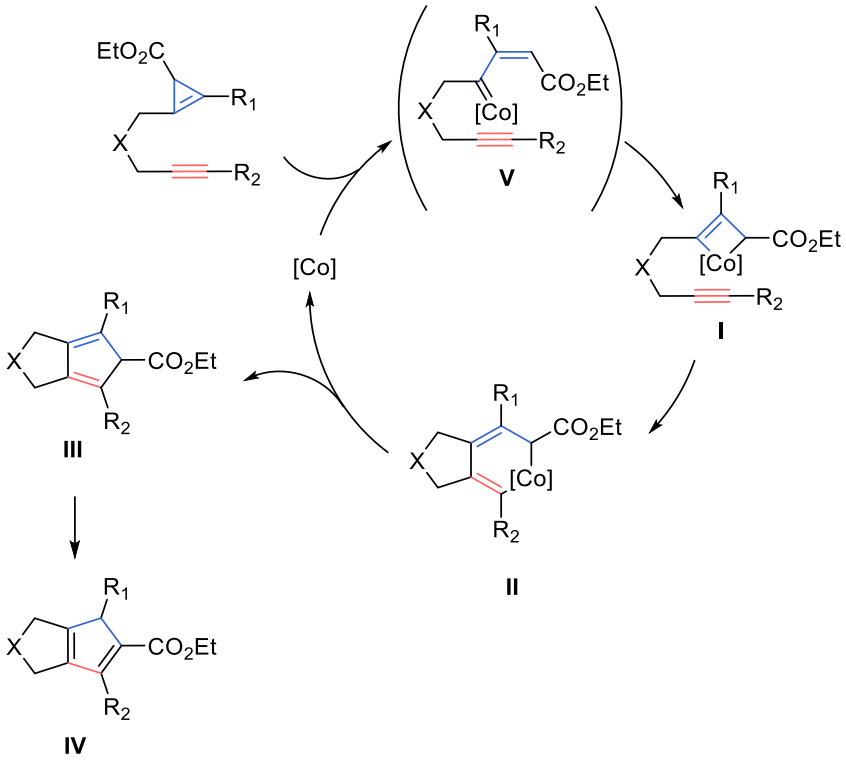


En cuanto al alcance de la reacción, se toleró una amplia variedad de alquinos sustituidos. Por lo tanto, los alquilos, arilos, terminales o hetereosustituidos funcionaron muy bien, proporcionando el ciclopentadieno correspondiente en buenos rendimientos. Además, diferentes grupos funcionales en la correa de conexión entre el ACP y el alquino también fueron bien tolerados.

Desde una perspectiva mecanicista, la reacción podría implicar la inserción del complejo de cobalto (I) en el ciclopropeno para formar la especie I de cobaltaciclobuteno. Luego, una inserción migratoria y eliminación reductora proporcionaría un intermediario III de ciclopentadienilo, que podría isomerizarse aún más al ciclopentadieno IV dependiendo del grupo funcional colocado en la posición vinílica del ciclopropeno. Además, no

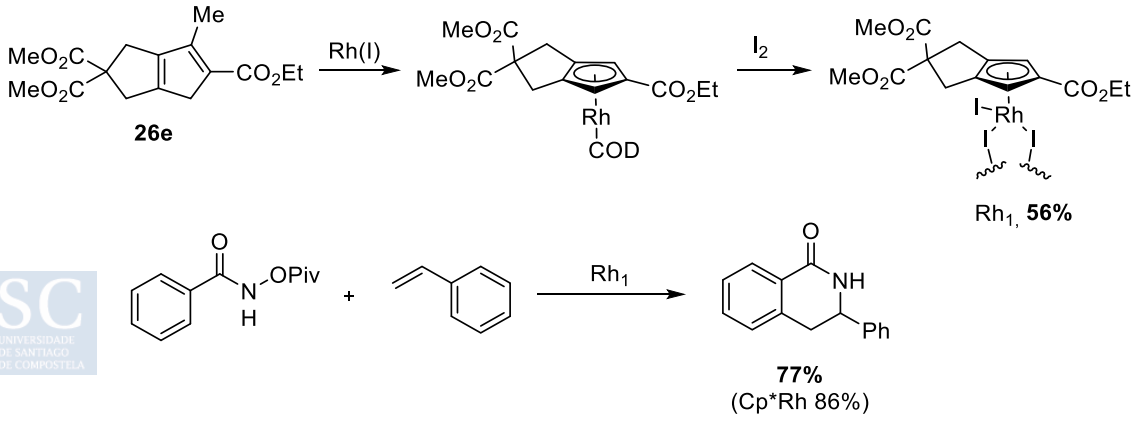
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podíamos descartar la participación de un vinilo cobalto carbeno V que podría evolucionar aún más a cobaltaciclobuteno I.



Para ilustrar la utilidad sintética de esta cicloadición, imaginamos que esta estrategia podría usarse como una plataforma sintética hacia la construcción de nuevos complejos de metal Cp. Así, cuando el sustrato 26e reaccionó con una cantidad subestequiométrica de [Rh(COD)Cl]2 en presencia de una base, se obtuvo el correspondiente ligando Rh(I) ciclopentadienilo. Además, el dímero Rh (III) correspondiente podría obtenerse fácilmente en un rendimiento general del 56% mediante una oxidación mediada por I2 simple.

Para probar aún más la utilidad de estos nuevos complejos Rh, exploramos el complejo Rh(III) Rh1 como catalizador para un modelo (4+2) de cicloadición de N-pivaloxibenzamidas y alquenos, obteniendo las tetrahidroisoquinolinonas esperadas con un buen rendimiento del 77%, comparable con el reportado usando [Cp*RhCl2]2.



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Conclusión general.

Como conclusión general, hemos descubierto una variedad de cicloadiciones intramoleculares catalizadas por cobalto de derivados de ciclopropil tensados, tanto alquilidenciclopropanos como ciclopropenos. Particularmente exitosas fueron las cicloadiciones que involucran alquinos como socios de cicloadición. También hemos encontrado que las cetonas trifluorometilmetil son excelentes socios de reacción para heterocicloadiciones intermoleculares catalizadas por paladio (3 + 2) con ACP, para dar oxaciclos de cinco miembros.

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Resumo

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Introdución

Unha das subdisciplinas máis vitais e valoradas da química é a ciencia da síntese orgánica, a arte e a ciencia de construír substancias, naturais ou deseñadas, cuxo elemento principal é o carbono. Aínda que o obxectivo primordial desta disciplina é a síntese da molécula diana, ao longo das décadas este obxectivo foi evolucionando, pasando de acadalo a calquera prezo, a requirir facelo de maneira sostible e práctica.

Para satisfacer estas demandas da sociedade, o químico orgánico sintético centrou a súa atención no desenvolvemento de métodos catalíticos. Por definición, un catalizador é "unha *substancia que cambia a velocidade dunha reacción sen ser consumida* no proceso" e polo tanto, ten a capacidade de rexenerarse no proceso o que conduce a procesos máis sostibles. Por outro lado, o cambio na velocidade de reacción ó diminuí-la barreira enerxética do proceso non só acelera a transformación química, senón que permite que ocorran procesos que doutro modo serían completamente inaccesibles.

Desde un punto de vista xeral, os catalizadores pódense clasificar en heteroxéneos, se non están na mesma fase que os substratos, ou homoxéneos, se tanto o catalizador como o substrato están na mesma fase. Ademais, a catálise homoxénea pódese dividir en subcategorías dependendo da natureza do catalizador: biocatálise, cando a actividade catalítica é realizada por encimas; organocatálise, cando unha molécula orgánica é responsable da aceleración na velocidade do proceso; e, catálise organometálica, cando a estrutura do catalizador combina un metal cos seus ligandos auxiliares, que son na súa maioría moléculas orgánicas.

Entre as subcategorías de catálise homoxénea, a catálise organometálica foi a máis investigada ao longo dos anos. Esta área centrouse especialmente no uso de complexos de metais de transición debido as súas interesantes propiedades redox, así como aos numerosos ligandos auxiliares tolerados por eles. Así, ao longo dos anos desenvolvéronse numerosas transformacións interesantes e valiosas, como as reaccións de acoplamiento cruzado ou a reacción de metátese, que permiten a formación de novos enlaces C-C de gran valor dunha maneira específica e sinxela.

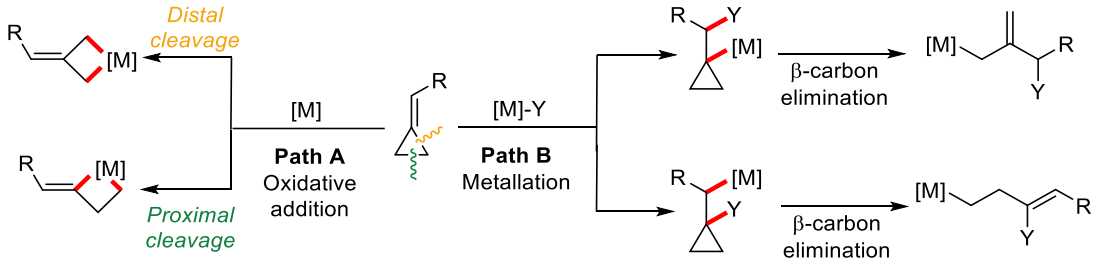
Dentro das transformacións organometálicas catalíticas, as reaccións de cicloadición tamén foron moi exploradas. Este tipo de reaccións constitúen unha excelente estratexia para construír sistemas (hetero)cíclicos interesantes, xa que permiten a formación de dous novos enlaces e polo menos un novo ciclo a partir de dous ou máis precursores simples nun só paso.

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Ao longo dos anos, o campo da catálise organometálica non se limitou ao desenvolvemento e descubrimento de novas transformacións ou á mellora das xa reportadas, senón que tamén proporcionaron novas ferramentas para a construción de moléculas enantiopuras. Utilizando principalmente ligandos auxiliares quirais, as transformacións organometálicas, como as cicloadicións, lograron a conversión de materiais de partida non quirais cara ao produto enatiopuro correspondente.

Neste contexto, o noso grupo contribuíu ao desenvolvemento de novas cicloadicións catalíticas organometálicas. Entre estas achegas, un dos principais temas de investigación explorados polo noso grupo foi o estudo de alquilidenciclopropanos (ACPs) como sintón de tres carbonos en numerosas reaccións de cicloadición catalizadas por metais de transición.

Os alquilidenciclopropanos son estruturas orgánicas que constan dunha unidade de ciclopropano e un dobre enlace exocíclico. Estas características estruturais fan dos ACP un dos carbociclos máis tensos, mesmo máis que un simple ciclopropano. É debido á súa enerxía de tensión, que os ACP mostran unha reactividade única e interesante. Por exemplo, os ACP poden sufrir unha adición oxidativa de certos complexos metálicos no anel de ciclopropilo, o que conduce a unha especie de metalociclobutano que pode evolucionar aínda máis en presenza do socio de reacción apropiado. Curiosamente, dependendo de se se trata dunha inserción distal ou proximal, pódense formar dous tipos de metallaciclobutanos diferentes.



Este tipo de reactividade evaluose ao longo dos anos e estableceuse que, dependendo do metal empregado, se pode predicir a selectividade da adición oxidativa. Polo tanto, cando se utiliza un catalizador de Pd ou Rh, unha inserción distal do anel de ciclopropilo é a preferente vía de reacción. Por outro lado, cando se emprega un catalizador de Ni prodúcese principalmente unha adición oxidativa proximal.

Ao longo dos anos, desenvolveuse con éxito unha ampla variedade de cicloadicións que implican a apertura do anel dos ACP. Por exemplo, baixo a presenza dun catalizador de Pd, o noso grupo desenvolveu con éxito as cicloadicións intramoleculares destes sistemas con alquenos, alquinos ou alenos que conducen á construción de varios

carbociclos 5,5-bicíclicos. Ademais, tamén se desenvolveron cicloadicións multicomponente, o que permite a construción de estruturas policíclicas máis grandes.

CAPÍTULO I: Cicloadicións intramoleculares catalizadas por Co(I) de ACPs con compoñentes insaturados C-C.

Cicloadición (3+2) de ACPs unidos a alquinos: versións enantioselectivas.

A pesares de que se desenvolveron con éxito multitude de cicloadicións que involucran aos ACP, estas transformacións centráronse no uso de complexos de metais de transición preciosos, como Pd ou Rh. Ademais, as cicloadicións enantioselectivas dos ACP apenas exploráronse, e só se poden atopar un puñado de exemplos na literatura.

Neste contexto, os metais de transición abundantes 3d, como o cobalto, comezaron a chamar a atención debido ás súas vías de reacción alternativas con respecto aos seus prezosos e non abundantes análogos metais das filas 4d e 5d.

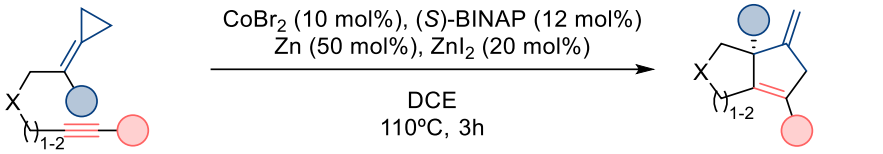
Neste sentido, ao principio desta teses non tiñamos coñecemento de ningunha exploración do potencial dos metais de transición 3d como o cobalto para promover transformacións dos ACPs. Neste sentido, as singularidades mecanísticas que recentemente foron observadas por catalizadores de cobalto de baixa valencia con sistemas alternativos de tensión cíclica fan que esta investigación sexa particularmente atractiva.

Sobre estas bases, decidimos avaliar a reactividade de catalizadores de cobalto para o desenvolvemento de cicloadicións intramoleculares de ACPs. Inspirados polas exitosas cicloadicións catalizadas por cobalto de baixa valencia que involucran alquinos e sistemas tensos como benzciclobutanonas ou vinilciclopropanos, decidimos analizar o comportamento dos ACPs unidos con alquinos en presenza dun catalizador de cobalto de baixa valencia. Para o noso deleite, descubrimos que en presenza de $CoBr_2$ como fonte de cobalto, dppp como ligando, Zn como redutor e ZnI_2 como aditivo en MeCN a 110 ° C, o cicloaduto correspondente (3 + 2) podería formarse en bos rendementos. Inspirados por este resultado inicial, decidimos ir un paso máis alá e avaliar a posibilidade de desenvolver unha versión enantioselectiva desta transformación. Agradablemente, utilizando as condicións mencionadas anteriormente co cambio do ligando a (*S*)-BINAP e o disolvente a 1,2-dicloroetano, o modelo ACP proporcionou o cicloaduto desexado cun gran rendemento do 83% e 95:5 er.

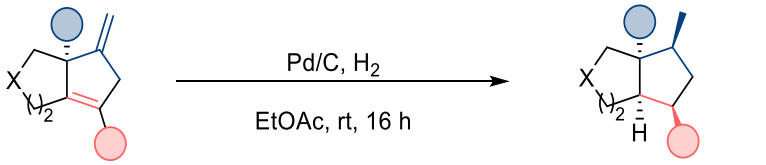
Neste punto avaliamos o alcance desta cicloadición asimétrica. Con moito gusto, unha variedade de alquinos con diferentes substituíntes como cadeas alquílicas, alquinos terminais, 1,3-eninos, aneis aromáticos e heteroaromáticos ou aqluinos substituídos por

silano son ben tolerados e conducen a formación dos cicloadutos correspondentes en bos rendementos e altas enantioselectividades. Ademais, toléranse diferentes grupos funcionais en unión entre o ACP e ao alquino como malonatos, sulfonamidas ou ésteres.

Por outra banda, a construción do centro de carbono cuaternario na fusión das estruturas 5,5-bicíclicas pode ser enantioselectivamente construída cando se empregou unha ACP interno substituído. Finalmente, tamén demostramos que utilizando esta cicloadición catalizada por cobalto de baixa valencia de ACP unidos a alquinos, podería ser posible a construción de compostos 6,5-bicíclicos máis grandes.

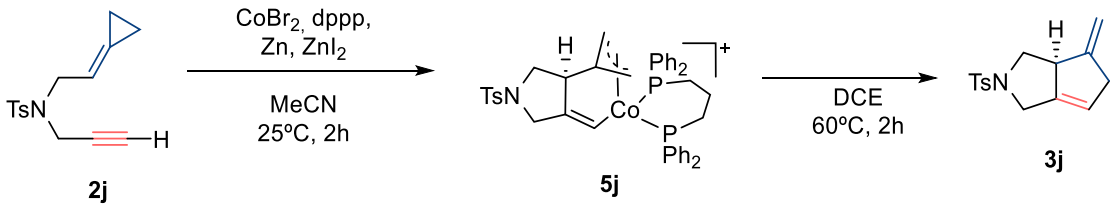


Para probar aínda máis o potencial sintético do noso método, fixemos unha breve exploración sobre as posibilidades de derivatización dos cicloadutos. Así, en condicións clásicas de hidroxenación utilizando Pd/C realizouse con éxito unha construción diastereoselectiva total de sistemas 5,5 e 5,6-bicíclicos con ata 4 estereocentros.

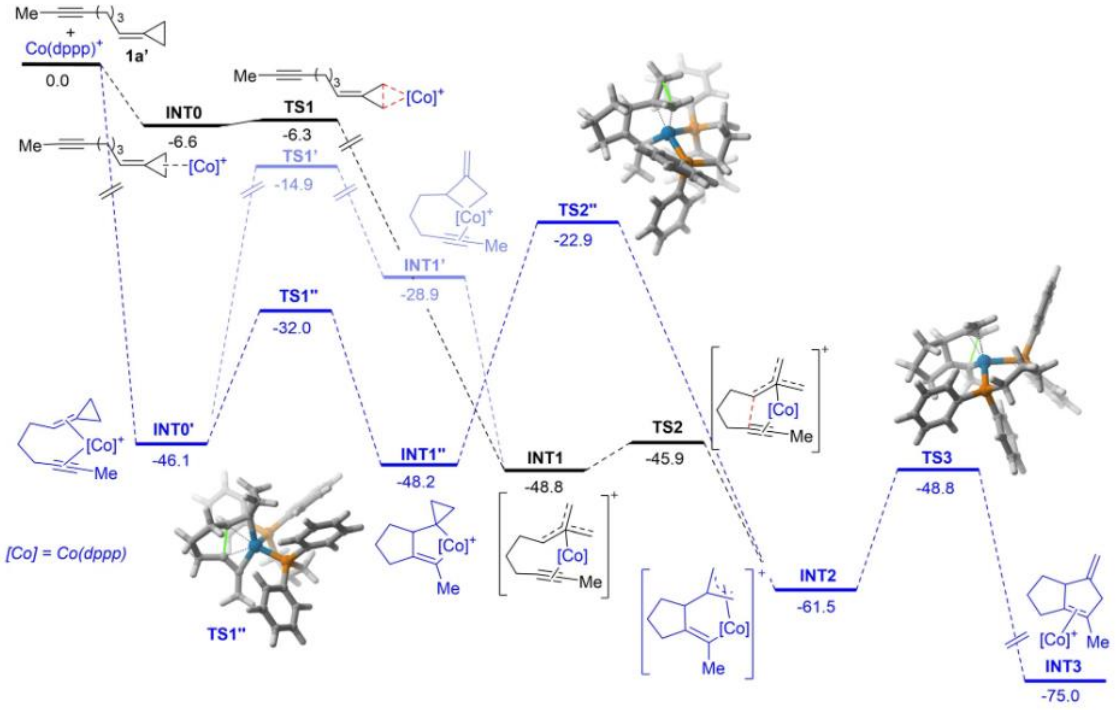


Unha vez que se estableceu o alcance e a utilidade sintética da cicloadición asimétrica catalizada por cobalto (3 + 2) de ACP atados a alquinos, preguntámonos sobre as cuestións mecanicistas desta transformación. Inicialmente, decidimos establecer o estado de oxidación da nosa especie activa de cobalto. Polo tanto, avaliáronse varios experimentos que empregaron un complexo de Co(0) e/ou Co(I), concluíndo que a nosa especie activa de cobalto debería ser un complexo catiónico de Co(I). Ademais destes estudos mecanisticos experimentais, tivemos o pracer de illar e caracterizar completamente por RMN e espectroscopia de masas un cobaltaciclo **5j** de π-alilo. Ademais, esta especie demostrou ser un intermediario competente da reacción.

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Basándonos nestes resultados experimentais, contactamos co profesor Israel Fernández para arroxar algo de luz sobre o mecanismo de reacción a través de cálculos DFT. Para o noso deleite, os datos computacionais revelaron un mecanismo novidoso con respecto ao que se informou previamente con Pd ou Rh que implica unha ciclación oxidativa inicial seguida dun reordenamento de ciclopropilo a π-alilo cara a unha especie como o illado **5j**. A partir deste intermedio, unha eliminación redutora formaría o cicloaduto correspondente.



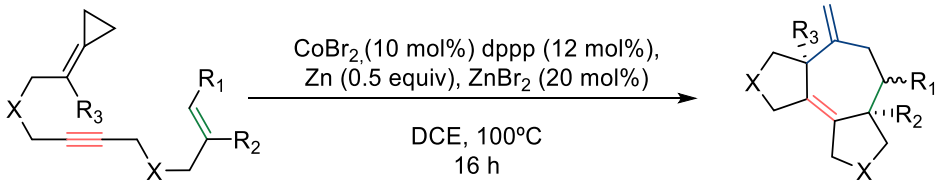
<u>Cicloadición multicomponente de ACPs unidos a alugueiros.</u>

Basándonos nos excelentes resultados obtidos no desenvolvemento da cicloadición (3+2) asimétrica catalizada por Co(I) de ACPs atados a alquinos, visualizamos a posibilidade de desenvolver unha cicloadición multicomponente cara á construción de carbociclos policíclicos máis grandes.

Inicialmente, engadíronse compoñentes externos de cicloadición como monoxido de carbono, alquenos, alenos ou alquinos en presenza do ACP atado ao alquino. Porén, nas condicións óptimas para a cicloadición (3+2), non se formaron os cicloadutos desexados. Con base destes resultados, pensamos que un enfoque totalmente intramolecular sería

máis doado. Polo tanto, nos alegramos de atopar que os ACP atados a 1,6-enino proporcionaban o aduto 5,7,6-tricíclico desexado de maneira totalmente diastereoselectiva cara ao isómero *cis*, sendo as condicións óptimas as que utilizan $CoBr_2$ como fonte de cobalto, dppp como ligando, Zn como redutor e ZnI_2 como aditivo en 1,2-DCE a 100°C.

Para o noso deleite, esta metodoloxía permite a construción de varios estruturas tricíclicas que levan unha variedade de grupos funcionais na conexión atada entre o ACP, o alquino e o alqueno, cando se empregan alquenos terminais non substituídos. Porén, só un alqueno substituído interno que leva un grupo metilo foi tolerado nesta cicloadición catalizada por cobalto. Ademais, outro exemplo que conduce a un estereocentro cuaternario totalmente substituído construíuse con éxito cando se empregou un ACP substituído interno.



Ademais de todos os datos experimentais, os cálculos de DFT revelan a vía do mecanismo desta transformación e as diferenzas enerxéticas respecto as publicacións anteriores utilizando Pd e Rh.

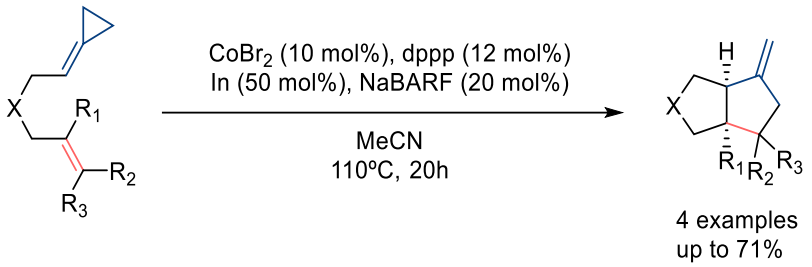
(3+2) Cicloadición de ACP unidos a alqueno, aleno e dieno

Neste momento, evidenciamos con éxito o gran comportamento dos complexos de Co(I) nas cicloadicións de ACPs atados a alquinos. Polo tanto, tiñamos curiosidade sobre o comportamento deste tipo de complexos con outros compoñentes de cicloadición insaturados como alquenos, alenos ou dienos.

Para o noso deleite, compraceunos descubrir que despois dunha breve optimización das condicións de reacción, o cicloaduto modelo podería construírse cun bo rendemento do 71% e con diastereoselectividade total cara ao isómero *cis*. Animados por estes resultados, decidimos probar a versión enantioselectiva desta cicloadición (3 + 2). Porén, despois da avaliación de moitos ligandos quirais diferentes, como bisfosfinas, ferrocenos ou fosforamidas, o mellor resultado foi un 70% *ee* moderado cun fosfito moi voluminoso.

Malia os resultados moderados nos esforzos da versión asimétrica, decidiuse avaliar o alcance da reacción racémica. Así, avaliáronse unha serie de ACPs atados a alqueno, mostrando esta metodoloxía unha sensibilidade extrema no patrón de sustitución do

alqueno. Para arroxar algo de luz e obter coñecemento sobre estas limitacións, leváronse a cabo cálculos DFT. Polo tanto, aínda que o mecanismo de reacción é análogo ao calculado previamente para os alquinos, neste caso observamos unha eliminación redutora de enerxía moi alta que podería ser a orixe do escaso alcance desta transformación.



Por outra banda, tamén se avaliou a cicloadición (3+2) de ACPs atados a alenos. Ao igual que no caso dos alquenos, o alcance da reacción foi extremadamente sensible ao seu patrón de substitución e só un aleno terminal transformouse con éxito no seu cicloaduto correspondente.

Por último, tamén se levou a cabo a avaliación dos ACP atados con dieno. Así, observouse unha cicloadición (4 + 3) análoga ao que se reportou previamente con Pd. Porén, de maneira similar ao comentado anteriormente con respecto aos alquenos e alenos, só se reaccionou un dieno terminal nas nosas mellores condicións de reacción.

CAPÍTULO II: Hetereocicloadiciones intermoleculares (3+2) catalizadas por Pd entre ACP e carbonilos.

As estructuras heterocíclicas son abundantes productos naturais con moitas aplicacións no campo farmacéutico e agroquímico. De todos os motivos estruturais heterocíclicos, os heterociclos de oxíxeno saturado atópanse entre os máis abundantes na natureza, xa que se sabe que aparecen nunha ampla gama de sistemas. Entre este tipo de heterociclos de oxíxeno, os oxaciclos de cinco membros, comunmente coñecidos como tetrahidrofuranos (THF) son particularmente abundantes.

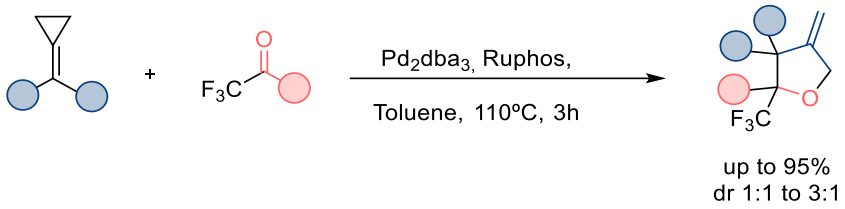
A síntese de oxaciclos de 5 membros abordouse abundantemente nas últimas décadas. Multitude de transformacións sintéticas empregáronse con éxito para a construción destes compostos, incluídas as cicloadicións catalizadas por metais de transición.

Debido á nosa experiencia en cicloaddiciones catalizadas por paladio dos ACP, imaxinamos a posibilidade de desenvolver unha nova hetereocicloadición utilizando grupos funcionais carbonilo como compoñentes π insaturados. Neste contexto, o noso grupo desenvolveu con éxito unha cicloadición intramolecular catalizada por Pd (3+2)

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de ACPs e aldehídos ou cetonas. No desenvolvemento desta transformación, observouse que a selección de fosfinas biarilicas voluminosas desenvolvida por Buchwald como ligandos, que se sabe que facilitan a formación de enlaces C-O, foi clave.

Inspirados por estes resultados, ao comezo do meu doutorado decidimos explorar as vantaxes dos ligandos de Buchwald no desenvolvemento de cicloadicións intermoleculares entre ACP e compostos carbonílicos. Agradablemente, atopamos que usando trifluorometilcetonas como socios de cicloadición e RuPhos como ligandos óptimos, conseguiuse sintetizar o THF modelo en excelente rendementos aínda que en baixa proporción diastereomérica.



En canto ao alcance da reacción, esta metodoloxía tolera unha ampla gama de trifluorometilcetonas aromáticas substituídas, así como unha trifluorometilcetona derivada de cinamilo. Ademais, a cetona 3-oxo-alquil-trifluororometilcetona tamén foi un socio de cicloadición adecuado. Curiosamente, o alcance da reacción tamén se podería estender a outras cetonas fluoradas como as difluorometil cetonas.

Por outro lado, pódense utilizar varios ACP con cadeas nitroxenadas, oxixenadas ou carbonadas para a construción do correspondente THFs. Porén, a pesar de que todos os exemplos mencionados anteriormente permiten formar o cicloaduto correspondente con alta eficiencia, a diastereoselectividade da transformación non se controlou completamente en ningún dos casos.

Finalmente, intrigounos o comportamento especial observado das trifluorometilcetonas con respecto a outros compostos carbonílicos. Polo tanto, realizouse un conxunto de cálculos preliminares para arroxar luz sobre este tema. Así, de acordo cos cálculos de DFT, a principal diferenza entre un estudo comparativo dun modelo de trifluorometilcetonas e unha cetona baséase no paso de inserción migratoria. Mentres que a acetofenona necesita superar unha barreira de 25.1 kcal / mol, a súa análogo trifluorometilico require superar unha barreira de só 7.2 kcal / mol no mesmo paso. Esta enorme diferenza enerxética podería ser a razón da reactividade observada experimentalmente.

CAPÍTULO III Cicloadición intramolecular (3+2) catalizada por Co entre ciclopropenos e alquinos.

Os ciclopropenos son os cicloalquenos máis simples de todos os compostos orgánicos. Debido á súa alta tensión**,** este tipo de estruturas atraeron a atención dos químicos teóricos e experimentais durante anos.

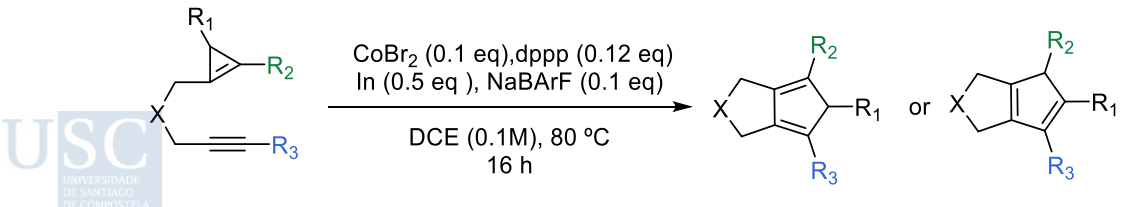
Estruturalmente, un ciclopropeno ten un dobre enlace cunha lonxitude inferior (1.27 A) con respecto a un enlace C_{sp2}-C_{sp2} clásico dun alqueno de cadea lineal (1.34 A). Esta característica dá ao enlace π no animal de ciclopropeno máis densidade de electróns en comparación cun enlace π clásico, facéndoos máis reactivos que os alquenos de cadea lineal.

Debido ás súas características estruturais, os ciclopropenos mostraron unha reactividade fascinante e, a veces, única. Este tipo de motivos estiveron involucrados en numerosas transformacións actúando como sintón de 2 carbonos como hidrometalacións, anulacións ou reaccións de acoplamento cruzado. [137] Porén, debido á súa alta enerxía de deformación, os ciclopropenos poden sufrir reaccións de escisión de animais, actuando neste caso como un sintón de 3 carbonos.

Os ciclopropenos foron excelentes compostos para o desenvolvemento de diferentes tipos de reaccións de cicloadicións, especialmente cicloadicións catalizadas por metais de transición. Polo tanto, baixo a presenza de varios metais de transición como Pd, Rh ou Ni, desenvolvéronse con éxito unha serie de cicloadicións intermoleculares e intramoleculares ao longo dos anos.

Inspirados polos nosos resultados exitosos no desenvolvemento da cicloaddicion (3+2) asimetrica catalizada por cobalto entre ACPs e alquinos, e, a ausencia de cicloadicións de ciclopropenos mediados por un catalizador de cobalto de baixa valencia, imaxinamos a posibilidade de desenvolver unha nova cicloadición (3 + 2) de ciclopropenos atados con alquinos.

Afortunadamente, descubrimos que a cicloadición (3 + 2) de ciclopropenos atados a alquinos era factible sendo as condicións óptimas as que utilizan $CoBr_2$ como fonte de cobalto, dppp como ligando, In como reductor, $NaBAr^F$ como eliminador de haluros en 1,2-dicloroetano a 80 °C. Ademais, os experimentos de control aseguran a necesidade de cada compoñente de reacción para o resultado exitoso.

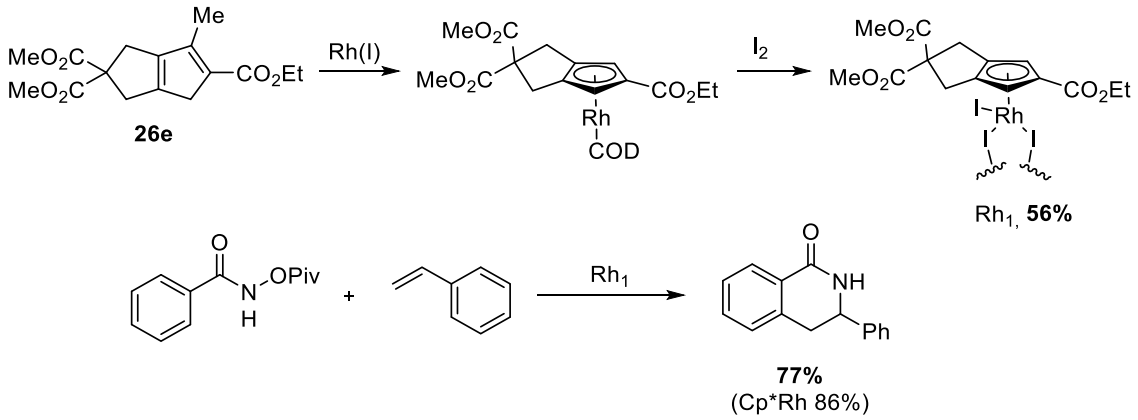


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En canto ao alcance da reacción, tolérase unha ampla variedade de alquinos substituídos. Así, os alquinos substituídos con grupos alquilo, arilo, terminais ou hetereosustituídos son tolerados nesta metodoloxía, proporcionando o ciclopentadieno correspondente en bos rendementos. Ademais, diferentes grupos funcionais na conexión atada entre o ACP e o alquino como o malonato, a sulfonamida ou un éter, son altamente tolerados. Mecanisticamente interesante, o ciclopropeno non necesita manter un grupo de extracción de electróns como un ester na súa posición vinílica. Sen embargo, neste caso observouse unha reorganización diferente do dobre enlace no produto.

Para ilustrar a utilidade sintética desta cicloadición, imaxinamos que esta estratexia se podería usar como unha plataforma sintética cara á construción de novos complexos metálicos de ciclopentadienilo. Así, cando reaccionamos o ciclopentadieno **26e** cunha cantidade subestequiométrica de $[Rh(COD)Cl]_2$ baixo a presenza dunha base, o correspondente complexo Rh(I) ciclopentadienilo obtivose en tan só 3h. Ademais, o dímero de Rh (III) correspondente podería obterse facilmente nun rendemento total do 56% mediante unha simple oxidación mediada por I_2.

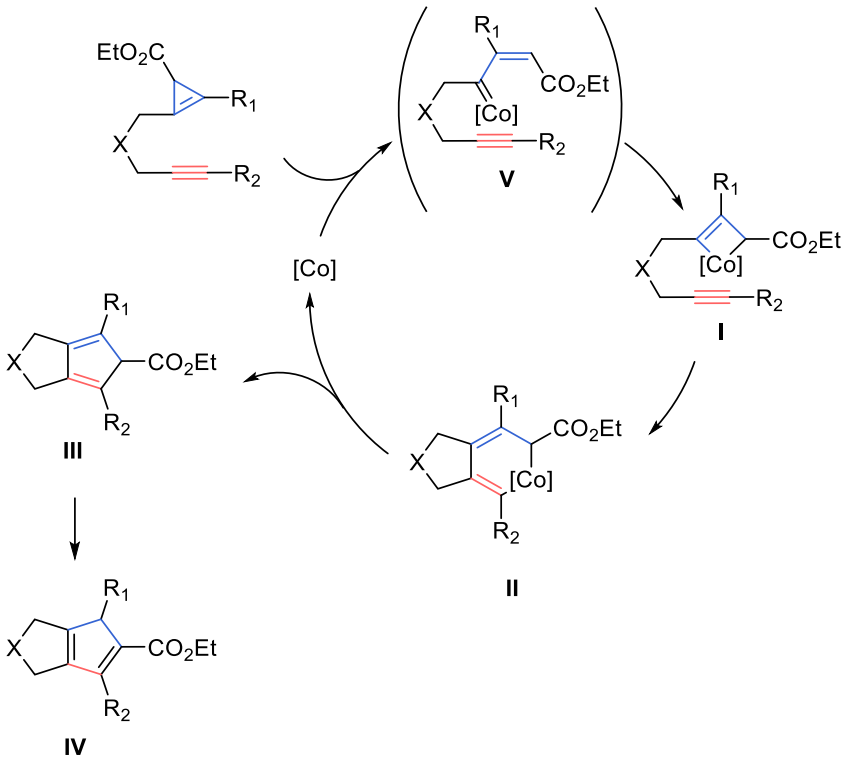
Para demostrar aínda máis a utilidade destes novos complexos Rh, decidimos estudar a actividade deste novo complexo Rh (III) **Rh1** nunha reacción modelo. Así, seleccionando como modelo a cicloadicion (4+2) de N-Pivaloxibenzamidas e alquenos, o noso novo catalizador **Rh1**, proprocionou o producto esperado cun bo rendemento do 77%, comparable co reportado usando $[Cp^*RhCl_2]_2$.



En base aos resultados experimentais e os precedentes previos atopados na literatura, propuxemos un mecanismo iniciado por unha apertura do anel do ciclopropeno cara ó cobaltaciclobuteno **I**. Logo, tras a inserción migratoria e a eliminación redutora formaríase o ciclopentadenno **III** que se podería isomerizar aínda máis ao ciclopentadieno **IV** dependendo do grupo funcional colocado na posición vinílico do

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ciclopropeno. Ademais, tendón en conta os precedentes bibliográficos, non podemos descartar a existencia dun vinil carbeno tipo **V** no mecanismo de reacción.



<u>Conclusión xeral.</u>

Como conclusión xeral, neste manuscrito ilustrouse o desenevolvemento dunha serie de cicloadicións intramoleculares catalizadas por cobalto cuxa forza motriz foi a liberación de tensión de aneles de ciclopropanos ou ciclopropenos. Especificamente exitosas foron as cicloadicións onde os alquinos se usaron como compoñentes de cicloadición.

Por outra banda, a construción de tetrahidrofuranos altamente interesante logrouse con éxito baixo unha cicloadición intermolecular (3 + 2) catalizada por paladio entre ACPs e trifluorometilcetonas.

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Experimental section

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General Information

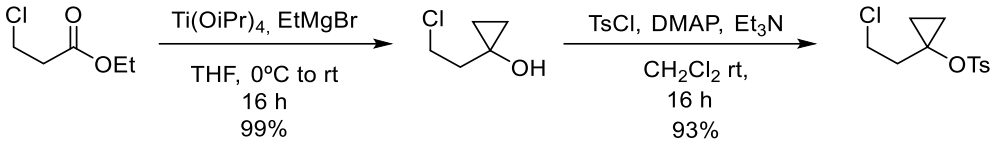
All reactions were conducted in dry solvents under Ar atmosphere unless otherwise stated. The abbreviation "rt" refers to reactions carried out at 20-25 °C. Reaction mixtures were stirred using Teflon-coated magnetic stir bars. Reaction temperatures were maintained using Thermowatch-controlled silicone oil baths. Dry solvents were obtained from a solvent purification system (Mbraun, SPS-5) or freshly distilled under Ar from an appropriate drying agent before use (toluene from Na / benzophenone, CH_2Cl_2 and Et_3N were distilled form CaH_2). Pd_2dba_3 and all other reagents for the synthesis of precursors were purchased from Aldrich. All the reagents used for the cycloaddition's reaction were purchased from Aldrich with the exception of $CoBr_2$, that was purchased from Alfa Aesar. Previous to use, Zn powder was purified according to the literature. Thin-layer chromatography (TLC) was performed on silica gel plates and components were visualized by observation under UV light, or by treating the plates with either *p*-anisaldehyde, ninhydrin, potassium permanganate or cerium nitrate solutions, followed by heating. Flash chromatography was carried out on silica gel unless otherwise stated. Dryings were performed with anhydrous Na_2SO_4. Concentration refers to the removal of volatile solvents via distillation using a Buchi rotary evaporator, followed by residual solvent removal under high vacuum. In reactions carried out in sealed tubes, the mixture must be at rt before sealing, to avoid overpressure at high temperatures.

^1H and ^{13}C-NMR spectra were recorded in $CDCl_3$ at 300 MHz (Varian) for cycloaddition precursors and cycloadducts or Bruker 500 MHz for some cycloadducts. Carbon types were determined from DEPT-NMR experiments. NMR spectra were analysed using MestreNova© processing software (www.mestrelab.com). 1,3,5-Trimethoxybenzene was used as internal standard for analyzing the reaction crudes by NMR.

^1H-NMR spectral data are reported as follows: chemical shift (δ ppm), integration, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, dd = double doublet, td = triple doublet, m = multiplet, br = broad). Data for ^{13}C are reported in terms of chemical shift relative to the residual solvent peak. Mass spectra were acquired using chemical ionization (CI) or electron impact techniques (EI) and were recorded at the CACTUS facility of the USC. The structure of the cycloadducts was determined by 2D-NMR experiments (COSY, NOESY, HMBC and HMQC), in addition to standard 1D-NMR experiments.

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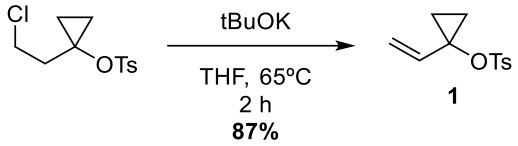
Synthesis of 1-Vinylcyclopropyl 4-methylbenzenesulfonate (1)



On a three-necked round bottom flask equipped with a pressure equalizing dropping funnel was added ethyl 3-chloropropionate (30 g, 220 mmol), anhydrous THF (700 ml) and titanium isopropoxide (13 mL, 43.9 mmol). The reaction mixture was cooled to 0°C using an ice bath. Then, the addition funnel was charged with ethyl magnesium bromide (146 ml, 439 mmol; 3 M in Et_2O) which was added dropwise to the stirred reaction mixture (*ca.* 30 minutes). After the addition was complete, the salt-ice bath was removed, and the reaction mixture was warmed to room temperature and stirred for ca. 2 hours. The reaction was quenched by addition of a 1 M aqueous hydrochloric chloride solution (300 mL) over 20 minutes using an ice bath to maintain the reaction temperature between 20–25 °C. The mixture was then poured into a 1 L separatory funnel, diluted with deionized water (500 mL) and partitioned with diethyl ether (2 × 500 mL). The organic phases were combined, washed with saturated aqueous sodium bicarbonate solution (500 mL), saturated aqueous NaCl solution (200 mL), dried (anhyd. $MgSO_4$), filtered and concentrated in vacuo to provide 1-(2-chloroethyl)cyclopropanol as a colorless oil (26.45 g, 219 mmol, 99%), which was used without further purification. **^{1}H NMR (300 MHz, $CDCl_3$)** δ (ppm): 7.75 (2H, m), 7.33 (2H, m), 3.67 (2H, t, *J* = 7.0 Hz), 2.42 (3H, s), 2.22 (2H, t, *J* = 7.5 Hz), 1.10 (2H, t, J = 7.0 Hz), 0.70 (2H, t, *J* = 7.0 Hz).

To a flame-dried 2 L two-necked round-bottomed flask, equipped with a magnetic stirrer bar, was added 1-(2-chloroethyl)cyclopropanol 11 (26.45 g, 219 mmol) and anhydrous dichloromethane (700 mL) under an atmosphere of argon. Triethylamine (36.6 mL, 263 mmol) was slowly added to the stirred reaction mixture followed by 4-dimethylaminopyridine (2.67 g, 21.9 mmol) in one portion. The reaction mixture was stirred at room temperature for ca. 30 minutes before p-toluenesulfonyl chloride (55.4 g, 285 mmol) was added and the resulting mixture stirred for ca. 16 hours at room temperature. The reaction mixture was concentrated in vacuo to a volume of approximately 100 mL, quenched with deionized water (500 mL) and transferred to a 3L separatory funnel. The aqueous phase was partitioned with diethyl ether (500 mL), diluted with saturated aqueous ammonium chloride (350 mL) and further partitioned with diethyl ether (2 × 350 mL). The combined organic phases were washed with deionized water (250 mL), dried (anhyd. $MgSO_4$), filtered and concentrated in) to afford the crude product. The crude material was dry-packed onto silica gel and purified via

flash chromatography (SiO_2, eluting with 5–15% Et_2O/Hexane) to afford 1-(2-chloroethyl)cyclopropyl 4-methylbenzenesulfonate 12 (56.50 g, 206 mmol, 93%) as a yellow oil. **^{1}H NMR (300 MHz, $CDCl_3$)** δ (ppm): 7.75 (d, *J* = 8.3 Hz, 2H), 7.33 (d, *J* = 8.0 Hz, 2H), 3.68 (t, *J* = 7.1 Hz, 2H), 2.43 (s, 2H), 2.23 (t, *J* = 7.1 Hz, 1H), 1.11 (t, *J* = 7.1 Hz, 2H), 0.81 –0.63 (m, 2H).



To a flame-dried 1 L one-necked round-bottom flask, equipped with a magnetic stirrer bar was added 1-(2-chloroethyl)cyclopropyl 4-methylbenzenesulfonate 12 (56.5 g, 206 mmol) and anhydrous THF (700 mL) under an atmosphere of argon. Potassium tert-butoxide (35.7 g, 308 mmol) was added at room temperature in one portion to the stirred solution, and the resulting suspension was stirred for an additional ca. 2 hours (monitored by NMR). The reaction mixture was concentrated in vacuo to a volume of approximately 500 mL, diluted with deionized water (300 mL), transferred into a 1 L separatory funnel and partitioned with diethyl ether (350 mL). The aqueous layer was diluted with saturated aqueous ammonium chloride solution (200 mL) and further partitioned with diethyl ether (2 × 300 mL). The combined organic phases were washed with deionized water (300 mL), saturated aqueous NaCl solution (200 mL), dried (anhyd. $MgSO_4$), filtered and concentrated in vacuo to afford the crude product. The crude material was dry-packed onto silica gel and purified via flash chromatography (SiO_2, eluting with 5–10% diethyl ether– petroleum ethers) to afford **1** (42.40 g, 178 mmol, 87%) as a pale yellow solid. **^{1}H NMR (300 MHz, $CDCl_3$)** δ (ppm): 7.78 (d, J = 8.3 Hz, 2H), 7.32 (d, J = 8.2 Hz, 2H), 5.89 (dd, J = 17.2, 10.8 Hz, 1H), 5.10 (d, J = 17.2 Hz, 1H), 5.01 (d, J = 11.1 Hz, 1H), 2.45 (s, 3H), 1.36 (d, J= 6.3 Hz, 1H), 1.35 (d, J = 6.1 Hz, 1H), 0.92 (dd, J = 5.6, 1.0 Hz, 1H), 0.91 (dd, J = 6.0, 0.8 Hz, 1H). **^{13}C-NMR (75 MHz, $CDCl_3$)** δ (ppm): 145.1 (C), 136.8 (CH), 135.3 (C), 129.9 (CH), 128.1 (CH), 113.6 (CH_2), 65.2 (C), 21.2 (CH_3), 13.5 (CH_2); EMBR: 239 ([M+ +1], 20); **HRMS** (APCI-TOF): *m/z* calculated for $C_{12}H_{15}O_3S$ 239.0742, found 239.0738.

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CHAPTER I

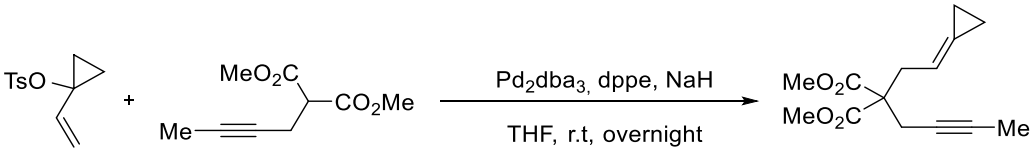
Co(I) catalysed intramolecular cycloadditions of ACPs

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1. (3+2) cycloaddition of alkyne tethered ACPs: enantioselective versions.

1.1. Synthesis of alkyne-tethered ACPs

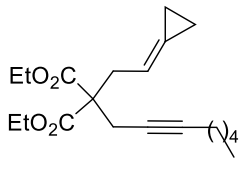
General procedure A: synthesis of of alkyl substituted cycloaddition precursors



1 **2a**

A solution of dimethyl 2-(but-2-yn-1-yl)malonate (500 mg, 2.715 mmol) in THF (2.2 mL) was added to an ice-cooled suspension of NaH (114 mg, 2.852 mmol) in THF (1 ml). After stirring at rt for 15 min, a mixture of tosylate **1** (712 mg, 2.986 mmol), Pd_2dba_3 (25 mg, 0.027 mmol) and 1,2- bis(diphenylphosphino)ethane (0.022 mg, 0.054 mol) in THF (6 mL), previously stirred for 15 min at room temperature, was transferred via cannula to the solution. The reaction mixture was then allowed to stir for 30 min at rt, poured into water and extracted with Et_2O. The combined organic layers were dried, filtered and concentrated and the crude product was purified by flash chromatography (1 to 5 % Et_2O / hexanes) to obtain 565 mg of **2a** (82% yield) as a colourless oil. **^{1}H NMR (300 MHz, $CDCl_3$)** δ (ppm): 5.55 (m, 1H), 3.69 (s, 6H), 2.90 (dt, *J* = 7.4, 1.1 Hz, 2H), 2.70 (q, *J* = 2.6 Hz, 2H), 1.73 (t, *J* = 2.6 Hz, 3H), 1.06-0.97 (m, 4H). **^{13}C-NMR (75 MHz, $CDCl_3$)** δ (ppm): 170.7 (CO), 127.0 (C), 111.4 (CH), 78.5 (C), 73.5 (C), 57.4 (C), 52.5 (CH_3), 34.5 (CH_2), 23.0 (CH_2), 3.55 (CH_3), 2.9 (CH_2), 1.8 (CH_2). **HRMS** (APCI-TOF): *m/z* calculated for $C_{14}H_{19}O_4$ $[M+H]^+$: *m/z* 250.1205, found 250.1207.

Diethyl 2-(2-cyclopropylideneethyl)-2-(oct-2-ynyl)malonate (2b)[71]

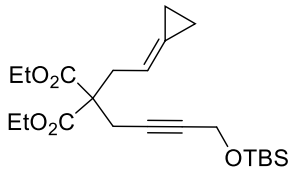


2b

67% yield, colourless oil. **^{1}H NMR (300 MHz, $CDCl_3$)** δ (ppm): 5.61 – 5.47 (m, 1H), 4.14 (qt, *J* = 7.1, 2.3 Hz, 4H), 2.89 (d, *J* = 7.4 Hz, 2H), 2.69 (q, *J* = 2.3 Hz, 2H), 2.07 (tq, *J* = 7.0, 2.2 Hz, 2H), 1.50 – 1.35 (m, 2H), 1.35 – 1.25 (m, 4H), 1.21 (t, *J* = 7.1 Hz, 6H), 1.07 – 0.91 (m, 4H), 0.86 (t, *J* = 6.9 Hz, 3H). **^{13}C-NMR (75 MHz, $CDCl_3$)** δ (ppm): 170.2 (C), 126.7 (C), 111.6 (CH), 83.1 (C), 74.5 (C), 61.2 (CH_2), 57.3 (C), 34.4 (CH_2), 30.9 (CH_2), 28.5 (CH_2), 22.8 (CH_2), 22.1 (CH_2), 18.5 (CH_2), 14.0 (CH_3), 13.9 (CH_3), 2.85 (CH_2), 1.82 (CH_2). **HRMS** (APCI-TOF): *m/z* calculated for $C_{20}H_{31}O_4$ $[M + H]^+$: *m/z* 335.2144, found 335.2141.

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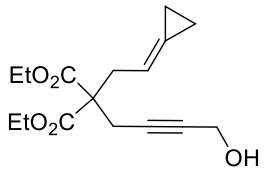
Diethyl-2-(4-((*tert*-butyldimethylsilyl)oxy)but-2-yn-1-yl)-2-(2-cyclopropylideneethyl) malonate (2c)[71]



2c

81% yield, colourless oil. **^{1}H NMR (300 MHz, $CDCl_3$)** δ (ppm): 5.60-5.52 (m, 1H), 4.24 (t, *J* = 2.2 Hz, 2H), 4.16 (*q*, *J* = 6.9 Hz, 4H), 2.89 (*d*, *J* = 7.2 Hz, 2H), 2.79 (*t*, *J* = 2.2 Hz, 2H), 1.22 (*t*, *J* = 7.1 Hz, 6H), 1.05-0.98 (bs, 4H), 0.87 (s, 9H), 0.07 (s, 6H). **^{13}C-NMR (75 MHz, $CDCl_3$)** δ (ppm): 170.1 (CO), 127.0 (C), 111.5 (CH), 81.5 (C), 79.8 (C), 61.4 (CH_2), 57.09, 51.78, 34.61, 25.8 (CH_3), 22.93, 18.27, 14.0 (CH_3), 2.9 (CH_2), 1.9 (CH_2), -5.2 (CH_3). **HRMS** (APCI-TOF): *m/z* calculated for $C_{22}H_{37}O_5Si$ $[M + H]^+$: *m/z* calculated 409.2410, found 409.2422.

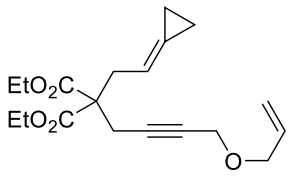
Diethyl 2-(2-cyclopropylideneethyl)-2-(4-hydroxybut-2-yn-1-yl)malonate (2d)[71]



2d

Obtained by treatment of a solution of **2c** in THF at rt with TBAF (1.0 M in THF, 1.10 equiv) followed by conventional work up and silica gel chromatography (20% Et_2O/hexanes), 97% yield, colourless oil. **^{1}H NMR (300 MHz, $CDCl_3$)** δ (ppm): 5.59-5.52 (m, 1H), 4.21-4.12 (m, 6H), 2.89 (d, *J* = 7.2 Hz, 2H), 2.78 (s, 2H), 1.22 (t, *J* = 7.1 Hz, 6H), 1.02 (s, 4H). **^{13}C-NMR (75 MHz, $CDCl_3$)** δ (ppm): 170.1 (CO), 127.2 (C), 111.3 (CH), 82.2 (C), 81.3 (C), 61.6 (CH_2), 57.1 (C), 51.1 (CH_2), 34.6 (CH_2), 22.9 (CH_2), 13.9 (CH_3), 2.99 (CH_2), 1.95 (CH_2). **HRMS** (APCI-TOF): *m/z* calculated for $C_{16}H_{23}O_5$ $[M + H]^+$: *m/z* 295.1545, found 295.1554

Diethyl 2-(4-(allyloxy)but-2-yn-1-yl)-2-(2-cyclopropylideneethyl)malonate (2e)[84]

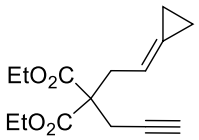


2e

66% yield, colourless oil. **^{1}H NMR (300 MHz, $CDCl_3$)** δ (ppm): 5.91-5.75 (m, 1H), 5.52 (ddd, *J* = 7.31, 4.63, 1.87 Hz, 1H), 5.20 (d, *J* = 17.2 Hz, 1H), 5.09 (d, *J* = 10.4 Hz, 1H), 4.26-4.12 (m, 4H), 4.11 (t, *J* =2.2 Hz, 2H), 3.97 (dd, *J* = 5.68, 1.20 Hz, 2H), 2.87 (d, *J* = 7.43 Hz, 2H), 2.77 (t, *J* = 1.85 Hz, 2H), 1.24-1.14 (m, 6H), 0.99 (bs, 4H). **^{13}C-NMR (75 MHz, $CDCl_3$)** δ (ppm): 170.1 (CO), 134.2 (CH), 127.9 (C), 117.8 (CH_2), 111.5 (CH), 81.7 (C), 78.9 (C), 70.3 (CH_2), 61.6 (CH_2), 57.5 (CH_2), 57.2 (C), 34.8 (CH_2), 23.0 (CH_2), 14.2 (CH_3), 3.09 (CH_2), 2.0 (CH_2). **HRMS** (APCI-TOF): *m/z* calculated for $C_{19}H_{27}O_5$ 335.1858, found 335.1856.

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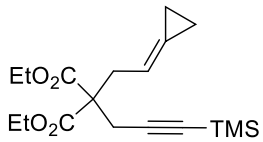
Diethyl 2-(2-cyclopropylideneethyl)-2-(prop-2-yn-1-yl)malonate (2f)[71]



2f

87% yield, colourless oil. **^{1}H NMR (300 MHz, $CDCl_3$)** δ (ppm): 5.59-5.52 (m, 1H), 4.22-4.13 (q, *J* = 7.01 Hz, 4H), 2.92 (d, *J* = 7.2 Hz, 2H), 2.77-2.75 (m, 2H), 1.98 (t, *J* = 2.3 Hz, 1H), 1.26-1.19 (t, *J* = 7.22 Hz, 6H), 1.13-0.98 (br s, 4H). **^{13}C-NMR (75 MHz, $CDCl_3$)** δ (ppm): 169.98 (CO), 127.3 (C), 111.3 (CH), 79.2 (C), 71.1 (CH), 61.5 (CH_2), 56.94, 34.5 (CH_2), 22.5 (CH_2), 14.0 (CH_3), 2.9 (CH_2), 1.9 (CH_2). **HRMS** (APCI-TOF): *m/z* calculated for $C_{15}H_{21}O_4$ $[M + H]^+$: *m/z* 265.1362, found 265.1366.

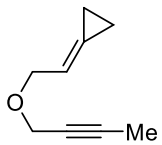
Diethyl-2-(2-cyclopropylidenethyl)-2-(3-(trimethylsilyl)prop-2-yn-1-yl)malonate (2g)[71]



2g

87% yield, colourless oil. Colourless oil**^{1}H NMR (300 MHz, $CDCl_3$)** δ (ppm): 5.60-5.45 (m, 1H), 4.30-4.00 (m, 4H), 2.93 (d, *J*= 8.8 Hz, 2H), 2.79 (s, 2H), 1.23 (t, *J* = 7.06 Hz, 6H), 1.05 (s, 4H), 0.12 (s, 9H). **^{13}C-NMR (75 MHz, $CDCl_3$)** δ (ppm): 170.0 (CO), 127.2 (C), 111.9 (CH), 101.9 (CH), 87.7 (C), 61.5 (CH_3), 57.2 (C), 34.6 (CH_3), 23.9 (CH_3), 14.1 (CH_3), 3.0 (CH_2), 2.0 (CH_2), 0.03 (CH_3). **HRMS** (APCI-TOF): *m/z* calculated for $C_{18}H_{29}O_4Si$ $[M + H]^+$: *m/z* 337.1835, found 337.1820.

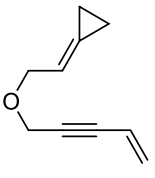
(2-(Prop-2-yn-1-yloxy)ethylidene)cyclopropane (2h)[81b]



2h

57% yield, yellow oil. **^{1}H NMR (300 MHz, $CDCl_3$)** δ (ppm): 5.87 (m, 1H), 4.11 (d, *J* = 6.8 Hz, 2H), 4.03 (d, *J* = 2.3 Hz, 2H), 1.79 (s, 3H), 1.05 (bs, 4H). **^{13}C-NMR (75 MHz, $CDCl_3$)** δ (ppm): 127.2 (C), 114.2 (CH), 81.9 (C), 75.2 (C), 69.5 (CH_2), 57.3 (CH_2), 3.15 (CH_3), 2.19 (CH_2), 1.64 (CH_2). **HRMS** (APCI-TOF): *m/z* calculated for $C_9H_{13}O$ $[M + H]^+$: *m/z* 137.0888, found 137.0890.

(2-(Pent-4-en-2-yn-1-yloxy)ethylidene)cyclopropane (2i)

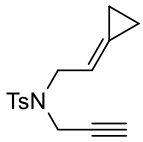


2i

66% yield, yellow oil. **^{1}H NMR (300 MHz, $CDCl_3$)** δ (ppm): 5.99 – 5.89 (m, 1H), 5.82 (ddt, *J* = 17.5, 10.9, 1.9 Hz, 1H), 5.64 (dd, *J* = 17.6, 2.4 Hz, 1H), 5.48 (dd, *J* = 10.9, 2.4 Hz, 1H), 4.25 (d, *J* = 1.9 Hz, 2H), 4.20 (d, *J* = 6.8 Hz, 2H), 1.16 – 1.01 (m, 4H). **^{13}C-NMR (75 MHz, $CDCl_3$)** δ (ppm): 127.8 (C), 127.4 (CH_2), 116.8 (CH), 114.2 (CH), 86.1 (C), 84.8 (C), 69.9 (CH_2), 57.5 (CH_2), 2.5 (CH_2), 1.9 (CH_2). **HRMS** (APCI-TOF): *m/z* calculated for $C_{10}H_{13}O$ $[M + H]^+$: *m/z* 148.0888, found 148.0890.

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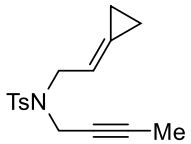
N-(2-Cyclopropylideneethyl)-4-methyl-N-(prop-2-yn-1-yl)benzenesulfonamide (2j) [81b]



2j

77% yield, white solid. **^{1}H NMR (300 MHz, $CDCl_3$)** δ (ppm): 7.74 (d, *J* = 8.1 Hz, 2H), 7.29 (d, *J* = 8.0 Hz, 2H), 5.75-5.65 (m, 1H), 4.07 (d, *J* = 2.5 Hz, 2H), 3.98 (d, *J* = 6.9 Hz, 2H), 2.42 (s, 3H), 1.97 (t, *J* = 2.5 Hz, 1H), 1.12-1.05 (m, 4H). **^{13}C-NMR (75 MHz, $CDCl_3$)** δ (ppm): 143.5 (C), 136.3 (C), 129.6 (CH), 128.9 (C), 127.9 (CH), 112.0 (CH), 76.9 (C), 73.4 (C), 47.92 (CH_2), 35.80 (CH_2), 21.69 (CH_3), 2.76 (CH_2), 2.09 (CH_2). **HRMS** (APCI-TOF): *m/z* calculated for $C_{15}H_{18}NO_2S$ [M + H]$^+$: *m/z* 276.0980, found 276.0982.

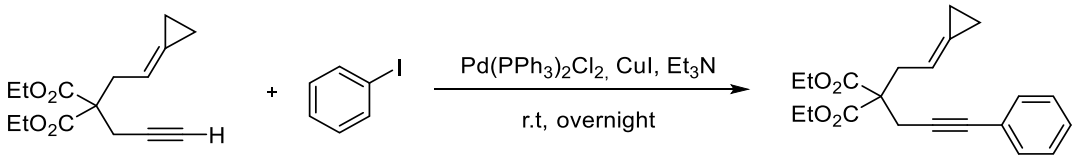
N-(But-2-yn-1-yl)-N-(2-cyclopropylideneethyl)-4-methylbenzenesulfonamide (2k) [81b]



2k

72% yield, white solid. **^{1}H NMR (300 MHz, $CDCl_3$)** δ (ppm): 7.74 (d, *J* = 8.3 Hz, 2H), 7.29 (d, *J* = 8.1 Hz, 2H), 5.70 (m, 1H), 3.99 (d, *J* = 2.2 Hz, 2H), 3.93 (d, *J* = 6.8 Hz, 2H), 2.42 (s, 3H), 1.53 (t, *J* = 2.3 Hz, 3H), 1.09-1.05 (m, 4H). **^{13}C-NMR (75 MHz, $CDCl_3$)** δ (ppm): 143.2 (C), 136.4 (C), 129.3 (CH), 128.4 (C), 128.0 (CH), 112.2 (CH), 81.2 (C), 72.0 (C), 47.9 (CH_2), 36.4 (CH_2), 21.6 (CH_3), 3.3 (CH_3), 2.7 (CH_2), 1.9 (CH_2). **HRMS** (APCI-TOF): *m/z* calculated for $C_{16}H_{20}NO_2S$ [M + H]$^+$: *m/z* 290.1136, found 290.1139.

General procedure B: synthesis (hetero)aromatic-substituted alkyne
(exemplified for **2l**)



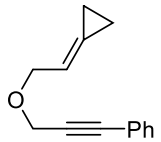
2f **2l**

A mixture of iodobenzene (231.5 mg, 1.135 mmol), Et_3N (4.7 mL), $PdCl_2(PPh_3)_2$ (19.9 mg, 0.03 mmol), and CuI (5.4 mg, 0.03 mmol) was stirred for 15 min. Then, **2f** (250.0 mg, 0.95 mmol) was added to the reaction mixture and stirred for 12 h at rt. After completion of reaction (TLC), the mixture was poured into water, then NH_4Cl(sat) and was extracted with EtOAc. The organic layer was dried over $MgSO_4$, filtered, and concentrated under vacuum. The crude products were purified by flash column chromatography using silica gel (5% hexane/Et_2O) to afford the desired precursor **2l** as colourless oil (260.2 mg, 80%).[81b] **^{1}H NMR (300 MHz, $CDCl_3$)** δ (ppm): 7.38-7.36 (m, 2H), 7.28-7.27 (m, 3H), 5.63 (m, 1H), 4.32-4.12 (m, 4H), 3.06-2.98 (m, 4H), 1.27 (q, *J* = 6.7 Hz, 6H) 1.15-0.95 (m, 4H). **^{13}C-NMR (75 MHz, $CDCl_3$)** δ (ppm): 170.1 (CO), z131.7 (CH), 128.2 (CH), 127.8 (CH), 127.2 (C), 123.4 (C), 111.5 (CH), 84.8 (C), 83.2 (C), 61.5 (CH_2), 57.3 (C), 34.7 (CH_2),23.5 (CH_2),

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14.1 (CH_3), 3.0 (CH_2), 1.9 (CH_2). **HRMS** (APCI-TOF): *m/z* calculated for $C_{21}H_{25}O_4$ $[M + H]^+$: *m/z* 341.1674, found 341.1676.

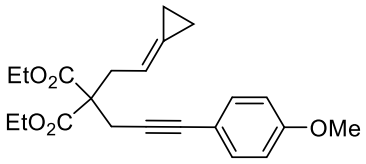
(3-(2-Cyclopropylideneethoxy)prop-1-yn-1-yl)benzene (2m)[81b]



2m

77 % yield, yellow oil. **^{1}H NMR (300 MHz, $CDCl_3$)** δ (ppm): 7.48 – 7.42 (m, 2H), 7.35–7.28 (m, 3H), 6.02 – 5.92 (m, 1H), 4.37 (s, 2H), 4.28 (d, *J* = 6.8 Hz, 2H), 1.13 (s, 4H). **^{13}C-NMR (75 MHz, $CDCl_3$)** δ (ppm): 131.8 (CH), 128.4 (CH), 128.3 (CH), 122.8 (C), 114.1 (CH), 86.1 (C), 85.3 (C), 69.8 (CH_2), 57.5 (CH_2), 2.48 (CH_2), 1.88 (CH_2). **HRMS** (APCI-TOF): *m/z* calculated for $C_{14}H_{14}O$ $[M + H]^+$: *m/z* 198.1049, found 149.1050.

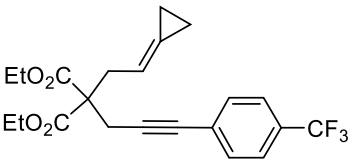
Diethyl 2-(2-cyclopropylideneethyl)-2-(3-(4-methoxyphenyl)prop-2-yn-1-yl)malonate (2n)



2n

75 % yield, colourless oil. **^{1}H NMR (300 MHz, $CDCl_3$)** δ (ppm): 7.31 (d, *J* = 8.8 Hz, 2H), 6.81 (d, *J* = 8.8 Hz, 2H), 5.65 (tdd, *J* = 7.3, 3.4, 1.6 Hz, 1H), 4.23 (qt, *J* = 7.1, 3.4 Hz, 4H), 3.80 (s, 3H), 3.09 – 2.91 (m, 4H), 1.31 – 1.24 (m, 6H), 1.11 – 1.06 (m, 4H). **^{13}C-NMR (75 MHz, $CDCl_3$)** δ (ppm): 170.2 (CO), 159.2 (C), 132.9 (CH), 127.1 (C), 115.5 (C), 113.8 (CH), 111.6 (CH), 83.16 (C), 83.0 (C), 61.5 (CH_2), 57.4 (C), 55.2 (CH_3), 34.7 (CH_2), 23.5 (CH_2), 14.1 (CH_3), 3.01 (CH_2), 1.98 (CH_2). **HRMS** (APCI-TOF): *m/z* calculated for $C_{22}H_{27}O_5$ $[M + H]^+$: *m/z* 370.1780, found 370.1781.

Diethyl 2-(2-cyclopropylideneethyl)-2-(3-(4-(trifluoromethyl)phenyl)prop-2-yn-1-yl)malonate (2o)

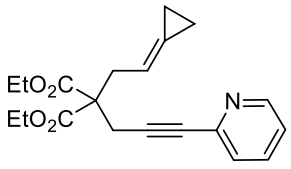


2o

55 % yield, colourless oil. **^{1}H NMR (300 MHz, $CDCl_3$)** δ (ppm): 7.52 (d, *J* = 8.1 Hz, 2H), 7.46 (dd, *J* = 8.4, 3.7 Hz, 2H), 5.73 – 5.55 (m, 1H), 4.33 – 4.11 (m, 4H), 3.00 (d, *z*= 7.7 Hz, 4H), 1.25 (t, *J* = 7.0 Hz, 6H), 1.11 – 0.99 (m, 4H). **^{13}C-NMR (75 MHz, $CDCl_3$)** δ (ppm): 169.5 (CO), 131.4 (CH), 126.9 (C), 124.7 (CH), 110.9 (CH), 87.3 (C), 81.6 (C), 61.2 (CH_2), 56.8 (C), 34.4 (CH_2), 23.1 (CH_2), 13.6 (CH_3), 2.5 (CH_2), 1.5 (CH_2). **^{19}F NMR (282 MHz, $CDCl_3$)** δ -63.77. **HRMS** (APCI-TOF): *m/z* calculated for $C_{22}H_{24}F_3O_5$ $[M + H]^+$: *m/z* 408.1548, found 408.1552.

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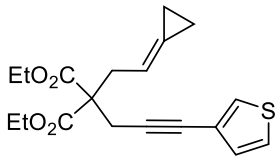
Diethyl 2-(2-cyclopropylideneethyl)-2-(3-(pyridin-2-yl)prop-2-yn-1-yl)malonate (2p)



2p

78% yield, colourless oil. **^{1}H NMR (300 MHz, $CDCl_3$)** δ (ppm): 8.47 (ddd, *J* = 4.9, 1.8, 1.0 Hz, 1H), 7.55 (td, *J* = 7.7, 1.8 Hz, 1H), 7.29 (dt, *J* = 7.8, 1.1 Hz, 1H), 7.13 (ddd, *J* = 7.7, 4.9, 1.2 Hz, 1H), 5.59 (tt, *J* = 7.3, 2.0 Hz, 1H), 4.16 (qd, *J* = 7.1, 1.4 Hz, 4H), 3.11 – 2.88 (m, 4H), 1.20 (td, *J* = 7.1, 0.8 Hz, 6H), 1.02 – 0.97 (br s, 4H). **^{13}C-NMR (75 MHz, $CDCl_3$)** δ (ppm): 169.9 (CO), 149.8 (CH), 143.2 (C), 135.9 (CH), 127.3 (CH), 127.0 (C), 122.5 (CH), 111.3 (CH), 85.3 (C), 82.8 (C), 61.5 (CH_2), 57.0 (C), 34.7 (CH_2), 23.4 (CH_2), 14.0 (CH_3), 2.9 (CH_2), 1.9 (CH_2). **HRMS** (APCI-TOF): *m/z* calculated for $C_{20}H_{23}NO_4$ $[M + H]^+$: *m/z* 342.1627, found 342, 1628.

Diethyl 2-(2-cyclopropylideneethyl)-2-(3-(thiophen-3-yl)prop-2-yn-1-yl)malonate (2q)

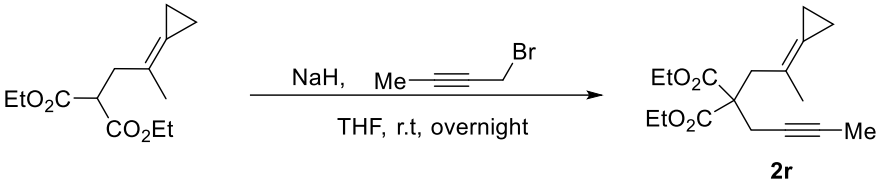


2q

2-thiophenebromide was used in this case and the reaction was carried out at 80 °C for 16 h. 63 % yield, colourless oil**^{1}H NMR (300 MHz, $CDCl_3$)** δ (ppm): 7.19 (d, *J* = 5.1 Hz, 1H), 7.11 (dd, *J* = 3.6, 1.3 Hz, 1H), 6.93 (dd, *J* = 5.1, 3.6 Hz, 1H), 5.68 – 5.57 (m, 1H), 4.29 – 4.13 (m, 4H), 3.03 (s, 2H), 3.00 (d, *J* = 8.2 Hz, 2H), 1.27 (t, *J* = 7.1 Hz, 6H), 1.08 (s, 4H). **^{13}C-NMR (75 MHz, $CDCl_3$)** δ (ppm): 170.0 (CO), 131.4 (CH), 127.3 (C), 126.7 (CH), 126.3 (CH), 111.4 (CH), 88.9 (C), 76.3 (C), 61.6 (CH_2), 57.2 (C), 34.8 (CH_2), 23.84 (CH_2), 14.11 (CH_3), 3.0 (CH_2), 2.0 (CH_2). **HRMS** (APCI-TOF): *m/z* calculated for $C_{19}H_{23}O_4S$ $[M + H]^+$: *m/z* 346.1238, found 346.1239.

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General procedure C: Synthesis of internal substituted ACP (exemplified for 2r)



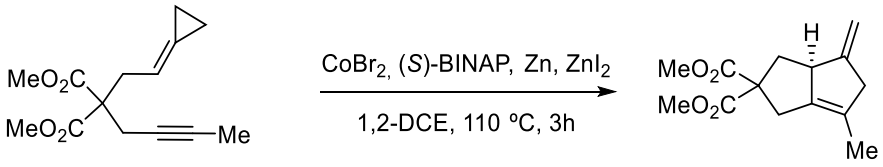
2r

A solution of diethyl 2-(2-cyclopropylidenepropyl)malonate[156] (225 mg, 0.936 mmol) in THF (0.375 ml) was slowly added to a suspension of NaH (41.2 mg, 1.03 mmol) in THF (1.9 mL) at 0 °C. After stirring for 15 min, propargyl bromide (0.09 mL, 1.03 mmol) was added and the resulting mixture was stirred overnight. The reaction was quenched with water and extracted with Et_2O. The organic layers were dried, filtered, concentrated and the resulting rude product was purified by flash chromatography (1 - 5 % Et_2O / hexanes) to obtain dimethyl 2-(2-cyclopropylidenepropyl)-2-(prop-2-yn-1-yl)malonate (**2r**, 232 mg, 0.74 mmol) in 85% yield as a colourless oil. **^{1}H NMR (300 MHz, $CDCl_3$)** δ (ppm): 4.15 (qq, *J* = 10.8, 7.1 Hz, 4H), 2.94 (s, 2H), 2.68 (q, *J* = 2.5 Hz, 2H), 1.75 – 1.68 (m, 6H) 1.23 (t, *J* = 7.1 Hz, 6H), 1.07 – 0.92 (m, 4H). **^{13}C-NMR (75 MHz, $CDCl_3$)** δ (ppm): 170.7 (CO), 121.8 (C), 119.0 (C), 78.4 (C), 74.1 (C), 61.3 (CH_2), 56.9 (C), 38.6 (CH_2), 22.9 (CH_2), 21.4 (CH_3), 13.9 (CH_3), 3.6 (CH_2), 3.4 (CH_3), 2.5 (CH_2). **HRMS** (APCI-TOF): *m/z* calculated for $C_{17}H_{25}O_4$ $[M + H]^+$: *m/z* 293.1675 , found 293.1677.

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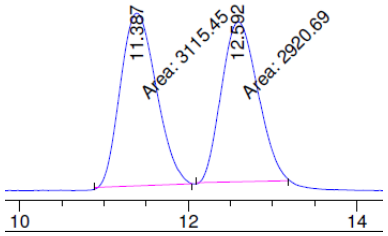
[156] Bernard, Angela M.; Piras, Pier P. *Synth. Comm.* **1997**, *27*, 709-723.

1.2. General procedure for the enantioselective (3+2) cycloaddition between ACPs and alkynes (exemplified for 3a).



2a **3a**

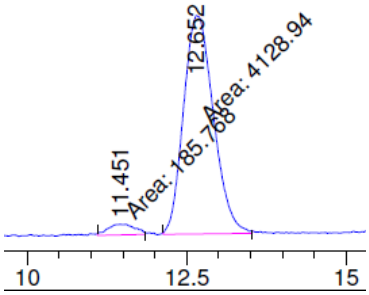
$CoBr_2$ (8.75 mg, 0.04 mmol), (*S*)-BINAP (29.9 mg, 0.048 mmol), Zn (13.1, 0.20 mmol) and ZnI_2 (25.5 mg, 0.08 mmol) were successively added to a dried Schlenk tube under Argon. Then, **2a** (100 mg, 0.40 mmol) in 1,2-dichloroethane (4 mL) was added under Ar atmosphere and the resulting mixture was stirred for 3 h at 110 °C before it was filtered through a short pad of Florisil® and concentrated under vacuum. The residue was purified by flash column chromatography (5 % Et_2O / hexanes) to give 83 mg of **3a** (83% yield, 96:4 *e.r*) as a colourless oil.[71] **^{1}H NMR (300 MHz, $CDCl_3$)** δ (ppm): 4.84 (s, 1H), 4.79 (s, 1H), 3.73 (dd, *J* = 11.2, 1.3 Hz, 6H), 3.61 – 3.49 (m, 1H), 3.39 (d, *J* = 19.5 Hz, 1H), 3.03 – 2.83 (m, 2H), 2.83 – 2.66 (m, 1H), 2.66 – 2.52 (m, 1H), 1.87 – 1.70 (m, 1H), 1.63 (s, 3H). **^{13}C-NMR (75 MHz, $CDCl_3$)** δ (ppm): 172.8 (CO), 172.3 (CO), 152.5 (C), 139.9 (C), 127.9 (C), 106.2 (CH_2), 63.0 (C), 53.9 (CH), 52.8 (CH_3), 52.7 (CH_3), 48.0 (CH_2), 38.0 (CH_2), 31.9 (CH_2), 14.21 (CH_3). **HRMS** (APCI-TOF): *m/z* calculated for $C_{14}H_{19}O_4$ $[M + H]^+$: *m/z* 250.1205, found 250.1207. Enantioselectivity (96:4 er) was determined by chiral HPLC analysis on Chiralpak® OZ-H at rt, (Hexane :^{i}PrOH = 98:2, 0.5 mL/min).



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	11.387	MM	0.4933	3115.45020	105.26733	51.6133
2	12.592	MM	0.4982	2920.68726	97.70597	48.3867

Figure S1. *HPLC trace report of a racemic sample of* ***2a.***

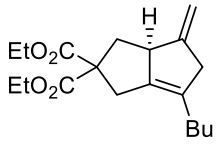
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Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	11.451	MM	0.4907	185.76828	6.31028	4.3055
2	12.652	MM	0.5436	4128.94238	126.58966	95.6945

Figure S2. *HPLC trace report of an enantioenriched sample of* ***3a.***

Diethyl 4-methylene-6-pentyl-3,3a,4,5-tetrahydropentalene-2,2(1H)-dicarboxylate (3b) [71]



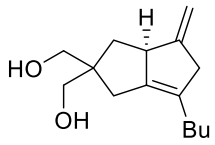
3b

85% yield, colourless oil. **^{1}H NMR (300 MHz, $CDCl_3$)** δ (ppm): 4.84 (s, 1H), 4.80 (s, 1H), 4.18 (dqd, *J* = 12.3, 7.1, 1.4 Hz, 4H), 3.55 (q, *J* = 6.7, 3.8 Hz, 1H), 3.37 (d, *J* = 19.4 Hz, 1H), 3.05 – 2.84 (m, 2H), 2.72 (d, *J* = 19.4 Hz, 1H), 2.57 (dd, *J* = 12.4, 7.5 Hz, 1H), 2.02 (q, *J* = 7.4 Hz, 2H), 1.79 (d, *J* = 11.1 Hz, 1H), 1.73 (s, 1H), 1.49 – 1.16 (m, 11H), 0.88 (t, *J* = 7.0 Hz, 3H). **^{13}C-NMR (75 MHz, $CDCl_3$)** δ (ppm): 172.4 (C), 171.8 (C), 152.7 (C), 139.8 (C), 132.1 (C), 106.1 (CH_2), 63.0 (C), 61.5 (CH_2), 61.4 (CH_2), 53.9 (CH), 45.8 (CH_2), 37.7 (CH_2), 31.9 (CH_2), 31.6 (CH_2), 30.8 (CH_2), 29.1 (CH_2), 27.4 (CH_2), 22.4 (CH_2), 14.0 (CH_3). **HRMS** (APCI-TOF): *m/z* calculated for $C_{20}H_{31}O_4$ $[M + H]^+$: *m/z* 334.2144, found 334.2148.

The enantioselectivity of the reaction was measured in the corresponding diol **3b'**, which was obtained as following: To a suspension of $LiAlH_4$ (13.6 mg, 0.359 mmol) in THF (0.6 mL), a solution of **3b** (30 mg, 0.09 mmol) in THF (0.3 mL) was added. The reaction was stirred at 65 °C for 1 h, carefully quenched with HCl (10% aq)., extracted with EtOAc (x3), dried and concentrated. The residue was purified by column chromatography (Hex/EtOAc 30%) to obtain 15 mg of **3b'** (66% yield), as a colourless oil.

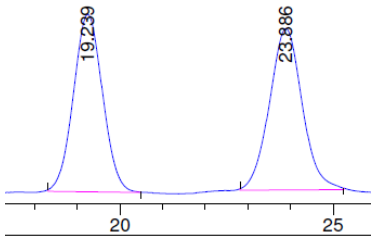
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(S)-(4-Methylene-6-pentyl-1,2,3,3a,4,5-hexahydropentalene-2,2-diyl)dimethanol (3b')



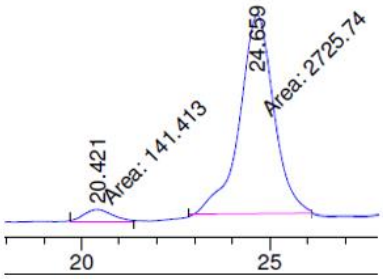
3b'

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 4.83 (s, 1H), 4.76 (s, 1H), 3.72 (d, *J* = 4.5 Hz, 2H), 3.58 (s, 2H), 3.54 – 3.47 (m, 1H), 3.36 (d, *J* = 20.1 Hz, 1H), 2.95 (d, *J* = 19.3 Hz, 1H), 2.17 (d, *J* = 15.9 Hz, 1H), 2.08 – 1.99 (m, 4H), 1.98 – 1.86 (m, 9H), 0.88 (3H). **^{13}C-NMR (75 MHz, $CDCl_3$)** δ (ppm): 154.2 (C), 141.3 (C), 131.5 (C), 105.5 (CH_2), 71.0 (CH_2), 70.0 (CH_2), 52.9 (CH), 52.2 (C), 45.4 (CH_2), 35.2 (CH_2), 31.6 (CH_2), 30.0 (CH_2), 28.9 (CH_2), 27.5 (CH_2), 22.4 (CH_2), 14.0 (CH_3). **HRMS** (APCI-TOF): *m/z* calculated for $C_{16}H_{27}O_2$ $[M + H]^+$: *m/z* 251.1938, found 251.1942. Enantioselectivity (96:4 er) was determined by chiral HPLC analysis on Chiralpak® IE3 at rt, (Hexane :^{i}PrOH = 95:5, 0.5 mL/min).



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	19.239	BB	0.7220	1938.64954	40.68145	49.4725
2	23.886	BB	0.7789	1979.98743	36.96620	50.5275

Figure S3**. HPLC trace report of a racemic sample of **3b'.

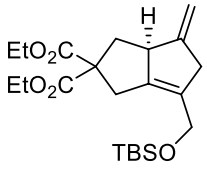


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	20.421	MM	0.8953	141.41338	2.63250	4.9322
2	24.659	MM	1.0586	2725.74365	42.91631	95.0678

Figure S4**. HPLC trace report of an enantioenriched sample of **3b'.

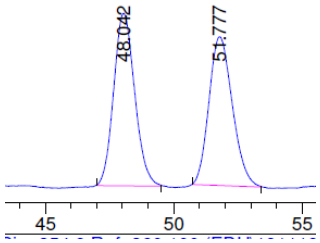
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Diethyl-6-(tertbutylsilyloxymethyl)-4-methylene-1,2,3,3a,4,5-hexahydro-2,2-pentalene dicarboxylate (3c) [71]



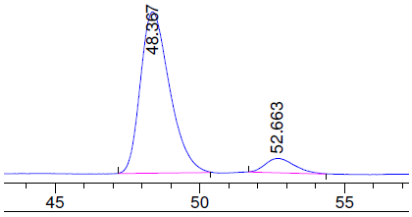
3c

85% yield, colourless oil. **^{1}H NMR (300 MHz, $CDCl_3$)** δ (ppm): 4.89 (s, 1H), 4.82 (s, 1H), 4.23-4.0 (m, 6H), 3.6-3.3 (m, 2H), 3.10-3.00 (m, 2H), 2.87-2.75 (m, 1H), 2.61-2.53 (dd, *J* = 7.5, 5.0 Hz,1H), 1.82-1.71 (m, 1H), 1.24 (q, *J* = 6.6 Hz, 6H), 0.88 (s, 9H), 0.04 (s, 6H). **^{13}C-NMR (75 MHz, $CDCl_3$)** δ (ppm): 172.3 (CO), 171.6 (CO), 151.8 (C), 141.5 (C), 130.6 (C), 106.6 (CH_2), 63.1 (C), 61.5 (CH_2), 61.4 (CH_2), 60.7 (CH_2), 54.4 (CH), 44.0 (CH_2), 37.3 (CH_2), 32.0 (CH_2), 25.9 (CH_3), 18.3 (C), 14.0 (CH_3), -5.3 (CH_3), -5.4 (CH_3). **HRMS** (APCI-TOF): *m/z* calculated for $C_{22}H_{37}O_5Si$ $[M + H]^+$: *m/z* 409.2410, found 409.2418. The enantioselectivity could only be determined after TBS deprotection, which was carried out by treatment of a solution of **3c** in THF at rt with TBAF (1.0 M in THF, 1.1 equiv), followed by conventional work up and silica gel chromatography (20% Et_2O/hexanes). Thus, **3d** was obtained in 92 % yield and its enantioselectivity (92:8 er) was determined by chiral HPLC analysis on Chiralpak® IE3 at rt, (Hexane :^{i}PrOH = 95:5, 0.5 mL/min).



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	48.042	BB	0.7820	1432.71960	25.17316	50.9694
2	51.777	BB	0.7942	1378.21851	21.72177	49.0306

***Figure S5**. HPLC trace report of a racemic sample of **3d**.*

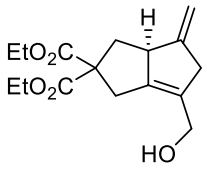


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	48.367	BB	0.9861	8353.05762	119.11977	91.9054
2	52.663	BB	0.8291	735.70331	10.53057	8.0946

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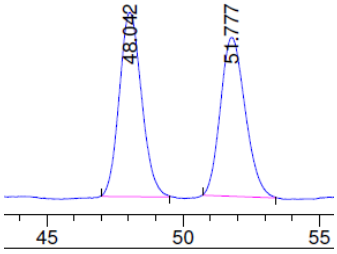
*Figure S6. HPLC trace report of an enantioenriched sample of **3d** (prepared from **3c**).*

Diethyl 6-(hydroxymethyl)-4-methylene-3,3a,4,5-tetrahydropentalene-2,2(1H)-dicarboxylate (3d) [71]



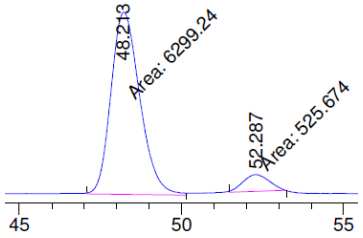
3d

84% yield, colourless oil. **^{1}H NMR (300 MHz, $CDCl_3$)** δ (ppm): 4.88 (s, 1H), 4.81 (s, 1H), 4.20-4.00 (m, 6H), 3.64 – 3.54 (m, 1H), 3.36 (t, *J* = 16.9 Hz, 1H), 3.17-2.97 (m, 2H), 2.74 (s, 1H), 2.64 (dd, *J* = 8.0, 4.75 Hz, 1H), 1.75 (dd, *J* = 10.8, 1.9 Hz, 1H), 1.21 (q, *J* = 6.91 Hz, 6H). **^{13}C-NMR (75 MHz, $CDCl_3$)** δ (ppm): 172.0 (CO), 171.8 (CO), 151.7 (C), 143.1(C), 130.9 (C), 106.9 (CH_2), 62.7 (C), 61.6 (CH_2), 61.5 (CH_2), 59.8 (CH_2), 53.9 (CH), 43.7 (CH_2), 37.2 (CH_2), 32.0 (CH_2), 14.0 (CH_3). **HRMS** (APCI-TOF): *m/z* calculated for $C_{16}H_{23}O_5$ $[M + H]^+$: *m/z* 295.1545, found 295.1554. Enantioselectivity (93:7 er) was determined by chiral HPLC analysis on Chiralpak® IE3 at rt, (Hexane :^{i}PrOH = 95:5, 0.5 mL/min).



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	48.042	BB	0.7820	1432.71960	25.17316	50.9694
2	51.777	BB	0.7942	1378.21851	21.72177	49.0306

Figure S7. HPLC trace report of a racemic sample of **3d.**

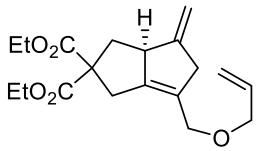


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	48.211	MM	1.0299	8920.05859	144.34613	92.9462
2	52.284	MM	0.9065	676.95618	12.44660	7.0538

Figure S8. *HPLC trace report of an enantioenriched sample of* ***3d.***

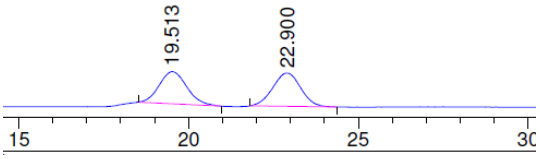
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Diethyl 6-((allyloxy)methyl)-4-methylene-3,3a,4,5-tetrahydropentalene-2,2(1H)-dicarboxylate (3e)[86]



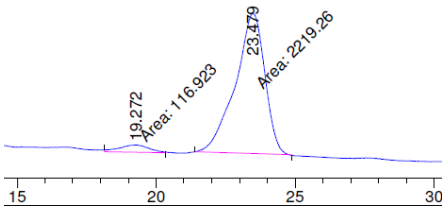
3e

73% yield. **^{1}H NMR (300 MHz, $CDCl_3$)** δ (ppm): 5.87-5.81 (m, 1H), 5.21 (dd, *J* = 17.2, 1.6 Hz, 1H), 5.11 (dd, *J* = 10.5, 1.6 Hz, 1H), 4.82 (s, 1H), 4.76 (s, 1H), 4.16-4.08 (m, 4H), 3.94 (s, 2H), 3.87-3.85 (m, 2H), 3.56 (t, *J* = 8.23 Hz, 1H), 3.36 (d, *J* = 20.4 Hz, 1H), 3.05 (d, *J* = 19.4 Hz, 1H), 2.92 (d, *J* = 17.3 Hz, 1H), 2.73 (d, *J* = 16.9 Hz, 1H), 2.56 (dd, *J* = 12.6, 7.87 Hz, 1H), 1.73 (dd, *J* = 12.5, 11.2 Hz, 1H), 1.26-1.15 (m, 6H). **^{13}C-NMR (75 MHz, $CDCl_3$)** δ (ppm): 172.2 (CO), 171.5 (CO), 151.6 (C), 144.5 (C), 134.8 (CH), 128.3 (C), 116.9 (CH_2), 106.8 (CH_2), 71.0 (CH_2), 66.7 (CH_2), 61.8 (C), 61.6 (CH_2), 61.5 (CH_2), 54.3 (CH), 37.4 (CH_2), 31.9 (CH_2), 29.7 (CH_2), 14.0 (CH_3). **HRMS** (APCI-TOF): *m/z* calculated for $C_{19}H_{27}O_5$ $[M + H]^+$: *m/z* 335.1780, found 335.1853. Enantioselectivity (96:4 er) was determined by chiral HPLC analysis on Chiralpak® OZ-H at rt, (Hexane :^{i}PrOH = 99:1, 0.5 mL/min).



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	19.515	MM	0.9864	1063.86792	17.97620	50.6478
2	22.900	BB	0.7691	1036.65283	18.12971	49.3522

Figure S9**. HPLC trace report of a racemic sample of **3e.

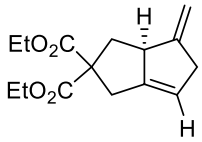


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	19.274	MM	1.1437	99.27438	1.44671	4.1962
2	23.479	MM	1.2483	2266.52710	30.26151	95.8038

Figure S10. HPLC trace report of an enantioenriched sample of **3e.**

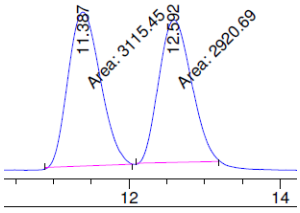
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Diethyl 4-methylene-3,3a,4,5-tetrahydropentalene-2,2(1H)-dicarboxylate (3f) [71]



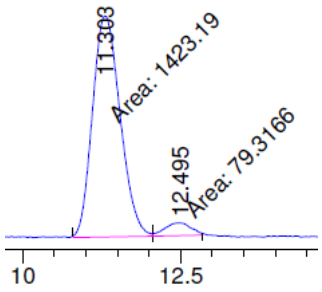
3f

72% yield. Colourless oil. **^{1}H NMR (300 MHz, $CDCl_3$)** δ (ppm): 5.37 (s, 1H), 4.89 (s, 1H), 4.83 (s, 1H), 4.24-4.13 (m, 4H), 3.61-3.51 (m, 1H), 3.43-3.31 (m, 1H), 3.18-3.04 (m, 1H), 2.99-2.78 (m, 2H), 2.62 (dd, *J* = 8.1, 4.6 Hz, 1H), 1.79 (dd, *J* = 10.9, 1.8 Hz, 1H), 1.28- 1.20 (m, 6H). **^{13}C-NMR (75 MHz, $CDCl_3$)** δ (ppm): 172.3 (CO), 171.7 (CO), 152.9 (C), 148.3 (C), 118.7 (CH), 106.7 (CH_2), 63.0 (C), 61.5 (CH_2), 61.4 (CH_2), 53.5 (CH), 43.6 (CH_2), 37.6 (CH_2), 32.3 (CH_2), 14.0 (CH_3). **HRMS** (APCI-TOF): *m/z* calculated for $C_{15}H_{21}O_4$ $[M + H]^+$: *m/z* 265.1362, found 265.1366. Enantioselectivity (95:5 er) was determined by chiral HPLC analysis on Chiralpak® OZ-H at rt, (Hexane :^{i}PrOH = 99:1, 0.5 mL/min).



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	11.387	MM	0.4933	3115.45020	105.26733	51.6133
2	12.592	MM	0.4982	2920.68726	97.70597	48.3867

Figure S11. *HPLC trace report of a racemic sample of* ***3f.***

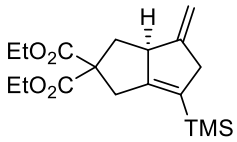


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	11.303	MM	0.5070	1423.18774	46.78818	94.7210
2	12.495	MM	0.4899	79.31655	2.69851	5.2790

Figure S12. *HPLC trace report of an enantioenriched sample of* ***3f.***

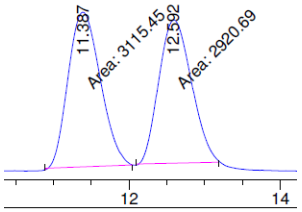
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Diethyl 4-methylene-6-(trimethylsilyl)-3,3a,4,5-tetrahydropentalene-2,2(1H)-dicarboxylate (3g) [71]



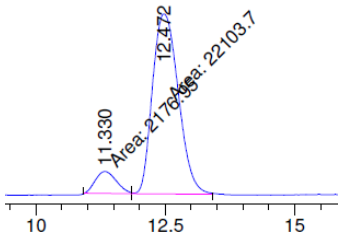
3g

This reaction was carried out using a combination of (*R*)-BINAP, In (0.5 equiv) and InI_3 (0.2 equiv), instead of Zn/ZnI_2; at 130 °C for 5h. 73% yield, colourless oil. Colourless oil. **^{1}H NMR (300 MHz, $CDCl_3$)** δ (ppm): 4.84 (s, 1H), 4.77 (s, 1H), 4.24-4.11 (m, 4H), 3.65-3.56 (m, 1H), 3.46- 3.34 (m, 1H,), 3.16-3.08 (m, 1H,), 2.97-2.79 (m, 2H), 2.64-2.55 (dd, *J*= 8.01, 4.71 Hz, 1H,), 1.78 (dd, *J*= 11.30, 1.26 Hz, 1H), 1.23 (m, 6H), 0.08 (s, 9H). **^{13}C-NMR (75 MHz, $CDCl_3$)** δ (ppm): 172.25 (CO), 171.6 (CO), 157.8 (C), 153.7 (C), 130.8 (C), 105.4 (CH_2), 63.4 (C), 61.6 (CH_2), 61.4 (CH_2), 55.9 (CH), 47.8 (CH_2), 36.6 (CH_2), 34.1 (CH_2), 14.0 (CH_3), -1.3 (CH_3). **HRMS** (APCI-TOF): *m/z* calculated for $C_{18}H_{29}O_4Si$ [M + H]$^+$: *m/z* 337.1835, found 337.1820. The enantioselectivity could only be determined after the treatment of a solution of **3g** in THF at rt with TBAF (1.0 M in THF, 1.10 equiv) followed by conventional work up and silica gel chromatography (5% Et_2O/hexanes) Thus, **3f** was obtained in 42 % yield. Enantioselectivity (91:9) was determined by chiral HPLC analysis on Chiralpak® OZ-H at rt, (Hexane :^{i}PrOH = 99:1, 0.5 mL/min).



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	11.387	MM	0.4933	3115.45020	105.26733	51.6133
2	12.592	MM	0.4982	2920.68726	97.70597	48.3867

***Figure S13**. HPLC trace report of a racemic sample of **3f** (prepared from **3g**).*

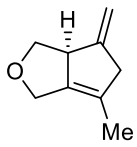


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	11.330	MF	0.4696	2176.94824	77.25555	8.9658
2	12.472	FM	0.5797	2.21037e4	635.50995	91.0342

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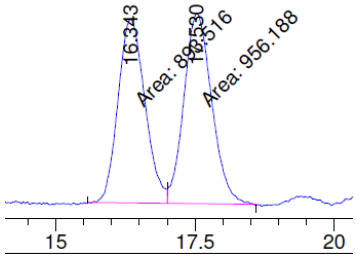
***Figure S14**. HPLC trace report of an enantioenriched sample of **3f** (prepared from **3g**).*

6-Methyl-4-methylene-3,3a,4,5-tetrahydro-1H-cyclopenta[c]furan (3h)



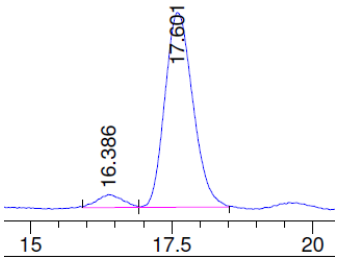
3h

76% yield, yellow oil. **^{1}H NMR (300 MHz, $CDCl_3$)** δ (ppm): 4.90 (s, 1H), 4.75 (s, 1H), 4.25 (d, *J* = 11.4 Hz, 1H), 4.17 – 4.03 (m, 2H), 3.81 (td, *J* = 11.7, 9.2, 3.1 Hz, 1H), 3.54 (d, *J* = 19.7 Hz, 1H), 3.24 (dd, *J* = 9.7, 7.3 Hz, 1H), 3.07 (d, *J* = 20.3 Hz, 1H), 1.69 (s, 3H). **^{13}C-NMR (75 MHz, $CDCl_3$)** δ (ppm): 149.4 (C), 139.9 (C), 129.3 (C), 107.5 (CH_2), 69.9 (CH_2), 63.0 (CH_2), 55.1 (CH), 49.2 (CH_2), 14.7 (CH_3). **HRMS** (APCI-TOF): *m/z* calculated for $C_9H_{13}O$ $[M + H]^+$: *m/z* 137.0888, found 137.0890. Enantioselectivity (94:6 er) was determined by chiral HPLC analysis on Chiralpak® IE3 at rt, (Hexane :^{i}PrOH = 99:1, 0.5 mL/min).



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	16.343	MF	0.5640	898.38312	26.54687	48.8458
2	17.530	FM	0.5745	940.84119	27.29375	51.1542

Figure S15**. HPLC trace report of a racemic sample of **3h.

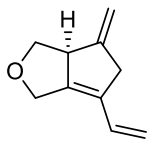


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	16.386	VV	0.3847	108.35532	3.40978	5.7850
2	17.601	VB	0.5006	1764.67468	51.13774	94.2150

Figure S16.** HPLC trace report of a racemic sample of **3h.

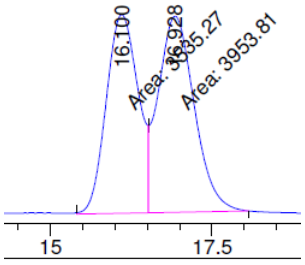
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4-Methylene-6-vinyl-3,3a,4,5-tetrahydro-1H-cyclopenta[c]furan (3i)



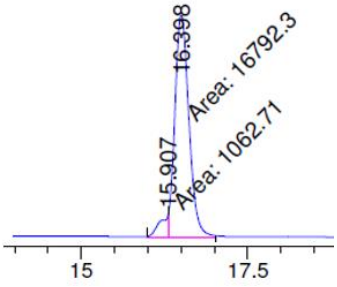
3i

73% yield, yellow oil. **^{1}H NMR (300 MHz, $CDCl_3$)** δ (ppm): 6.38 (dd, *J* = 17.3, 10.6 Hz, 1H), 5.15 (d, *J* = 10.5 Hz, 1H), 5.09 (d, *J* = 17.4 Hz, 1H), 4.98 – 4.95 (m, 1H), 4.78 (t, *J* = 2.4 Hz, 1H), 4.38 (d, *J* = 12.8 Hz, 1H), 4.25 (dd, *J* = 11.9, 3.2 Hz, 1H), 4.12 (t, *J* = 7.8 Hz, 1H), 4.00 – 3.87 (m, 1H), 3.61 (dt, *J* = 19.1, 3.7 Hz, 1H), 3.38 (d, *J* = 18.8 Hz, 1H), 3.28 (ddd, *J* = 9.8, 7.3, 1.0 Hz, 1H). **^{13}C-NMR (75 MHz, $CDCl_3$)** δ (ppm): 148.2 (C), 145.5 (C), 131.3 (C), 130.7 (CH), 115.8 (CH_2), 108.3 (CH_2), 69.7 (CH_2), 63.9 (CH_2), 55.8 (CH), 44.0 (CH_2). **HRMS** (APCI-TOF): *m/z* calculated for $C_{10}H_{13}O$ $[M + H]^+$: *m/z* 149.0885, found 149.0889. Enantioselectivity (94:6 er) was determined by chiral HPLC analysis on Chiralpak® IE3 at rt, (Hexane :^{i}PrOH = 99:1, 0.5 mL/min).



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	16.100	BV	0.5309	3501.61108	102.41618	46.8823
2	16.928	VB	0.5947	3967.32471	101.35813	53.1177

Figure S17. HPLC trace report of a racemic sample of **3i.**

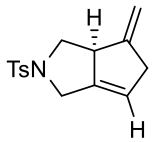


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	15.907	MF	0.3811	1062.70618	46.48098	5.9519
2	16.398	FM	0.6135	1.67923e4	456.17923	94.0481

Figure S18*. HPLC trace report of an enantioenriched sample of* ***3i.***

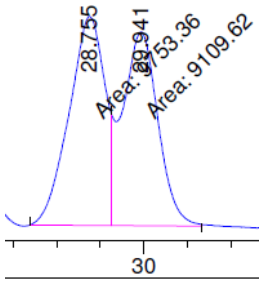
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4-Methylene-2-tosyl-1,2,3,3a,4,5-hexahydrocyclopenta[c]pyrrole (3j)



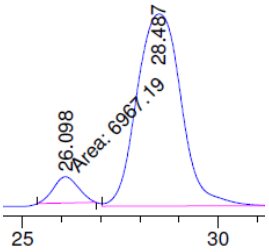
3j

77% yield, white solid. **^{1}H NMR (300 MHz, $CDCl_3$)** δ (ppm): 7.71 (d, *J* = 8.0 Hz, 2H), 7.31 (d, *J* = 7.9 Hz, 2H), 5.47 (s, 1H), 4.91 (q, *J* = 2.2 Hz, 1H), 4.80 (t, *J* = 2.4 Hz, 1H), 3.97 – 3.69 (m, 3H), 3.61 (t, *J* = 8.5 Hz, 1H), 3.34 (d, *J* = 20.1 Hz, 1H), 3.07 (d, *J* = 19.9 Hz, 1H), 2.67 (t, *J* = 9.3 Hz, 1H), 2.42 (s, 3H). **^{13}C-NMR (75 MHz, $CDCl_3$)** δ (ppm): 149.2 (C), 143.4 (C), 129.7 (CH), 127.4 (CH), 121.1 (CH), 108.5 (CH_2), 59.7 (C), 52.5 (CH), 51.1 (CH_2), 46.6 (CH_2), 43.3 (CH_2), 21.5 (CH_3). **HRMS** (APCI-TOF): *m/z* calculated for $C_{15}H_{18}NO_2S$ $[M + H]^+$: *m/z* 276.0980, found 276.0982. Enantioselectivity (93:7 er) was determined by chiral HPLC analysis on Chiralpak® IA3 at rt, (Hexane :^{i}PrOH = 95:5, 0.5 mL/min).



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	28.755	MF	0.9455	9753.36328	171.93106	51.7064
2	29.941	FM	0.9520	9109.61719	159.48720	48.2936

***Figure S19**. HPLC trace report of a racemic sample of **3j**.*

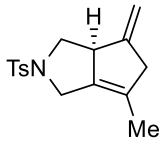


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	26.098	MM	0.7414	6967.19238	156.63297	7.1328
2	28.487	VB	0.9318	9.07114e4	1150.60437	92.8672

***Figure S 20**. HPLC trace report of an enantioenriched sample of **3j**.*

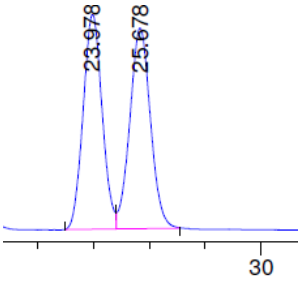
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6-Methyl-4-methylene-2-tosyl-1,2,3,3a,4,5-hexahydrocyclopenta[c]pyrrole (3k)



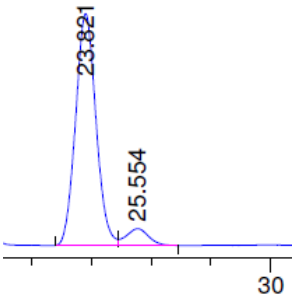
3k

71% yield, white solid. **^{1}H NMR (300 MHz, $CDCl_3$)** δ (ppm): 7.73 (d, *J* = 8.1 Hz, 2H), 7.33 (d, *J* = 7.8 Hz, 2H), 4.89 (s, 1H), 4.77 (s, 1H), 3.85 – 3.72 (m, 3H), 3.61 (t, *J* = 9.6 Hz, 1H), 3.38 (d, *J* = 19.9 Hz, 1H), 2.91 (d, *J* = 19.7 Hz, 1H), 2.70 (t, *J* = 9.1 Hz, 1H), 2.44 (s, 3H), 1.61 (s, 3H). **^{13}C-NMR (75 MHz, $CDCl_3$)** δ (ppm): 149.2 (C), 143.3 (C), 135.5 (C), 134.5 (C), 130.7 (C), 129.7 (CH), 127.4 (CH), 107.9 (CH_2), 52.9 (CH), 51.2 (CH_2), 47.7 (CH_2), 45.4 (CH_2), 21.5 (CH_3), 14.5 (CH_3). **HRMS** (APCI-TOF): *m/z* calculated for $C_{16}H_{20}NO_2S$ $[M + H]^+$: *m/z* 290.1136, found 290.1139. Enantioselectivity (93:7) was determined by chiral HPLC analysis on Chiralpak® IA3 at rt, (Hexane :^{i}PrOH = 95:5, 0.5 mL/min).



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	23.978	BV	0.7219	1.00451e4	213.11668	49.6008
2	25.678	VB	0.7781	1.02068e4	199.09477	50.3992

Figure S21**. HPLC trace report of a racemic sample of **3k.

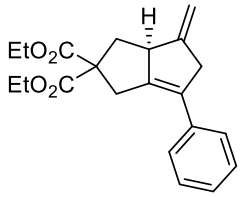


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	23.821	BV	0.7236	1.24777e4	263.93018	92.7009
2	25.554	VB	0.7214	982.46356	19.12282	7.2991

Figure S22**. HPLC trace report of an enantioenriched sample of **3k.

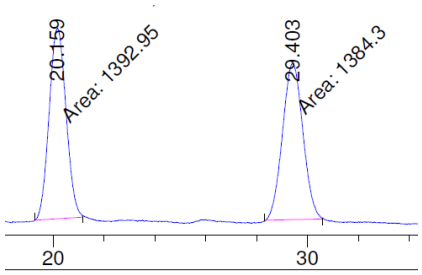
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Diethyl 4-methylene-6-phenyl-3,3a,4,5-tetrahydropentalene-2,2(1H)-dicarboxylate (3l)



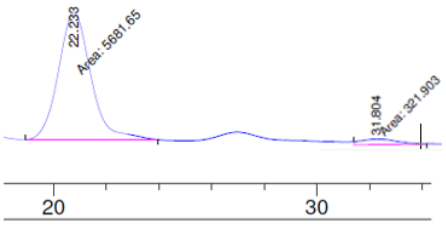
3l

64% yield, colourless oil. **^{1}H NMR (300 MHz, $CDCl_3$)** δ (ppm): 7.37 (d, J = 4.4 Hz, 4H), 7.26 (h, J = 4.1 Hz, 1H), 5.01 (s, 1H), 4.93 (s, 1H), 4.47-4.08 (m, 4H), 3.87 (ddt, J = 12.1, 7.5, 2.5 Hz, 1H), 3.73 (s, 2H), 3.39-3.09 (m, 2H), 2.69 (dd, J = 12.5, 7.4 Hz, 1H), 1.87 (t, J = 12.0 Hz, 1H), 1.35 – 1.16 (m, 6H). **^{13}C-NMR (75 MHz, $CDCl_3$)** δ (ppm): 172.2 (CO), 171.4 (CO), 150.6 (C), 143.5 (C), 135.7 (C), 129.8 (C), 128.3 (CH), 126.9 (CH), 126.8 (CH), 106.8 (CH_2), 63.9 (C), 61.7 (CH_2), 61.5 (CH_2), 56.0 (CH), 44.7 (CH_2), 36.9 (CH_2), 34.3 (CH_2), 14.1 (CH_3), 14.0 (CH_3). **HRMS** (APCI-TOF): m/z calculated for $C_{21}H_{25}O_4$ $[M + H]^+$: m/z 341.1674, found 341.1676. Enantioselectivity (95:5 er) was determined by chiral HPLC analysis on Chiralpak® IA3 at rt, (Hexane :^{i}PrOH = 99:1, 0.5 mL/min).



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	20.159	BB	0.6231	1424.50085	30.37809	49.9259
2	29.403	BB	0.6889	1428.72729	25.06906	50.0741

***Figure S23**. HPLC trace report of a racemic sample of **3l**.*

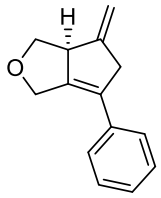


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	22.233	MM	0.8133	5681.64795	116.43898	94.6381
2	31.804	MM	0.9944	321.90286	5.39537	5.3619

***Figure S24.** HPLC trace report of an enantioenriched sample of **3l**.*

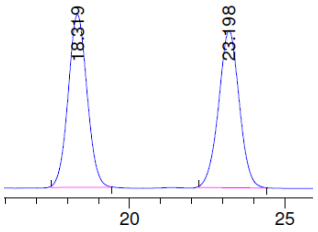
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4-Methylene-6-phenyl-3,3a,4,5-tetrahydro-1H-cyclopenta[c]furan (3m)



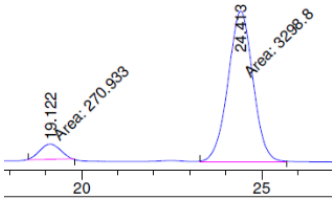
3m

This reaction was carried out using a combination of (*R*)-BINAP, In (0.5 equiv) and InI_3 (0.2 equiv), instead of Zn/ZnI_2 .75% yield, yellow oil. **^{1}H NMR (300 MHz, $CDCl_3$)** δ (ppm): 7.37 (t, *J* = 7.6 Hz, 2H), 7.27 (d, *J* = 8.7 Hz, 1H), 7.19 (d, *J* = 7.1 Hz, 2H), 5.05 (s, 1H), 4.86 (s, 1H), 4.63 – 4.42 (m, 2H), 4.21 – 4.14 (m, 2H), 3.85 (s, 2H), 3.32 (dd, *J* = 9.1, 6.4 Hz, 1H). **^{13}C-NMR (75 MHz, $CDCl_3$)** δ (ppm): 128.7 (CH), 127.4 (C), 126.9 (CH), 108.4 (CH_2), 69.2 (CH_2), 65.6 (CH_2), 57.1 (CH), 45.8 (CH_2). **HRMS** (APCI-TOF): *m/z* calculated for $C_{14}H_{15}O$ [M + H]$^+$: *m/z* 199.1047, found 199.1050. Enantioselectivity (93:7 er) was determined by chiral HPLC analysis on Chiralpak® IA3 at rt, (Hexane :^{i}PrOH = 99:1, 0.5 mL/min).



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	18.319	BB	0.6526	2232.56519	52.87336	50.1847
2	23.198	BB	0.6959	2216.13525	48.06569	49.8153

Figure S25**.HPLC trace report of a racemic sample of **3m.

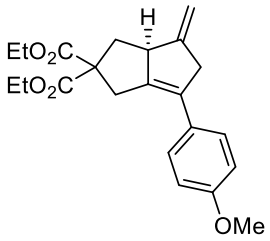


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	19.122	MM	0.6579	270.93259	6.86330	7.5897
2	24.413	MM	0.8076	3298.80200	68.08120	92.4103

Figure S26**. HPLC trace report of an enantioenriched sample of **3m.

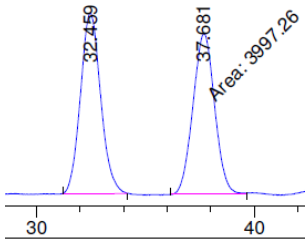
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Diethyl 6-(4-methoxyphenyl)-4-methylene-3,3a,4,5-tetrahydropentalene-2,2(1H)-dicarboxylate (3n)



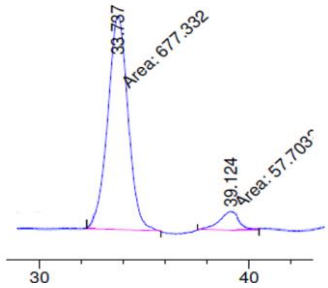
3n

73% yield, colourless oil. **^{1}H NMR (300 MHz, $CDCl_3$)** δ (ppm): 7.29 (d, J = 8.8 Hz, 2H), 6.89 (d, J = 8.8 Hz, 2H), 4.97 (d, J = 2.2 Hz, 1H), 4.89 (d, J = 2.4 Hz, 1H), 4.31 – 4.11 (m, 4H), 3.82 (s, 3H), 3.66 (dd, J = 3.3, 2.0 Hz, 2H), 3.33 – 2.95 (m, 3H), 2.66 (dd, J = 12.4, 7.4 Hz, 1H), 1.84 (dd, J = 12.5, 11.5 Hz, 1H), 1.33 – 1.17 (m, 6H). **^{13}C-NMR (75 MHz, $CDCl_3$)** δ (ppm): 172.2 (CO), 171.4 (CO), 158.4 (C), 150.8 (C), 141.0 (C), 128.0 (CH), 113.7 (CH), 106.6 (CH_2), 64.0 (C), 61.7 (CH_2), 61.5 (CH_2), 55.8 (CH), 55.2 (CH_3), 44.9 (CH_2), 37.0 (CH_2), 34.3 (CH_2), 14.02 (CH_3). **HRMS** (APCI-TOF): *m/z* calculated for $C_{22}H_{27}O_5$ $[M + H]^+$: *m/z* 371.1780, found 371.1782. Enantioselectivity (92:8 er) was determined by chiral HPLC analysis on Chiralpak® IA3 at rt, (Hexane :^{i}PrOH = 99:1, 0.5 mL/min).



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	32.459	BB	0.9040	4275.21680	66.14946	51.4577
2	37.681	BP	0.8750	4032.99194	58.59539	48.5423

Figure S27**.HPLC trace report of a racemic sample of **3n.

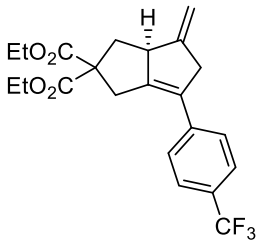


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	33.737	MM	1.1312	677.33179	9.97949	92.1496
2	39.124	MM	1.0861	57.70319	8.85467e-1	7.8504

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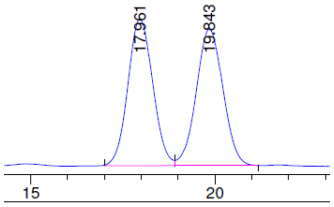
Figure S28**. HPLC trace report of an enantioenriched sample of **3n.

Diethyl 4-methylene-6-(4-(trifluoromethyl)phenyl)-3,3a,4,5-tetrahydropentalene-2,2(1H)-dicarboxylate (3o)



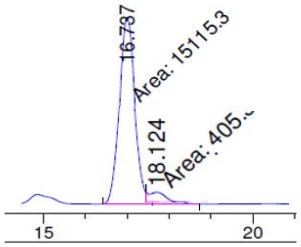
3o

This reaction was carried out using a combination of In (0.5 equiv) and InI_3 (0.2 equiv), instead of Zn/ZnI_2. 51% yield, colourless oil. **^{1}H NMR (300 MHz, $CDCl_3$)** δ (ppm): 7.59 (d, *J* = 7.7 Hz, 2H), 7.44 (d, *J* = 8.1 Hz, 2H), 5.01 (d, *J* = 2.0 Hz, 1H), 4.93 (d, *J* = 2.3 Hz, 1H), 4.26 (q, *J* = 7.1 Hz, 2H), 4.16 (qd, *J* = 7.1, 1.9 Hz, 2H), 3.91 – 3.84 (m, 1H), 3.71 (s, 2H), 3.27 (dq, *J* = 17.9, 3.1 Hz, 1H), 3.13 (dd, *J* = 17.8, 2.1 Hz, 1H), 2.70 (dd, *J* = 12.6, 7.6 Hz, 1H), 1.87 (dd, *J* = 12.5, 11.6 Hz, 1H), 1.30 (t, *J* = 7.1 Hz, 3H), 1.22 (t, *J* = 7.1 Hz, 3H). **^{13}C-NMR (75 MHz, $CDCl_3$)** δ (ppm): 172.1 (CO), 171.3 (CO), 150.0 (C), 146.8 (C), 139.3 (C), 129.0 (C), 127.0 (CH), 125.4 (C), 107.5 (CH_2), 64.0 (C), 62.0 (CH_2), 61.8 (CH_2), 56.3 (CH), 44.8 (CH_2), 36.9 (CH_2), 34.5 (CH_2), 14.2 (CH_3), 14.1 (CH_3). **^{19}F NMR (282 MHz $CDCl_3$)** δ -62.92. **HRMS** (APCI-TOF): *m/z* calculated for $C_{22}H_{24}F_3O_4$ $[M + H]^+$: *m/z* 408.1584, found 408.1589. Enantioselectivity (97:3 er) was determined by chiral HPLC analysis on Chiralpak® IA3 at rt, (Hexane :^{i}PrOH = 99:1, 0.5 mL/min).



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	17.961	BV	0.7351	4002.46240	85.34682	50.0172
2	19.843	VP	0.7886	3999.70459	79.27663	49.9828

Figure S2923*. HPLC trace report of a racemic sample of* ***3o.***

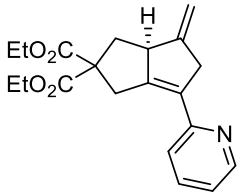


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	16.737	MF	0.8574	1.51153e4	293.83313	97.3886
2	18.124	FM	0.7049	405.30002	9.58352	2.6114

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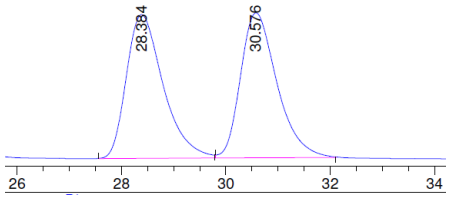
Figure S30*.* HPLC trace report of an enantioenriched sample of **3o.**

Diethyl (S)-4-methylene-6-(pyridin-2-yl)-3,3a,4,5-tetrahydropentalene-2,2(1H)-dicarboxylate (3p)



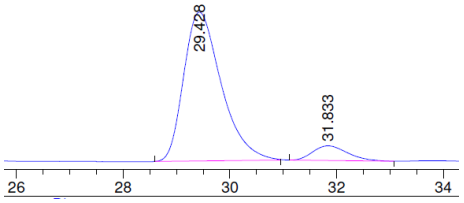
3p

This reaction was carried out using a combination of In (0.5 equiv) and InI_3 (0.2 equiv), instead of Zn/ZnI_2.54% yield, colourless oil. **^{1}H NMR (300 MHz, $CDCl_3$)** δ (ppm): 8.62 (d, *J* = 4.3 Hz, 1H), 7.75 – 7.62 (m, 1H), 7.31 (d, *J* = 8.0 Hz, 1H), 7.13 (dd, *J* = 7.1, 5.2 Hz, 1H), 5.00 (d, *J* = 2.3 Hz, 1H), 4.91 (d, *J* = 2.4 Hz, 1H), 4.25 (q, *J* = 7.1 Hz, 2H), 4.17 (q, *J* = 7.1 Hz, 2H), 3.97 – 3.87 (m, 1H), 3.86 – 3.70 (m, 2H), 3.34 (dt, *J* = 8.2, 2.9 Hz, 2H), 2.73 (dd, *J* = 12.5, 7.6 Hz, 1H), 1.87 (dd, *J* = 12.5, 11.7 Hz, 1H), 1.29 (t, *J* = 7.2 Hz, 3H), 1.23 (t, *J* = 7.1 Hz, 3H). **^{13}C-NMR (75 MHz, $CDCl_3$)** δ (ppm): 172.2 (C), 171.5 (C), 154.13 (C), 150.4 (C), 148.9 (CH), 136.6 (CH), 130.0 (C), 121.9 (CH), 121.4 (CH), 107.3 (CH_2), 64.0 (C), 61.9 (CH_2), 61.7 (CH_2), 56.5 (CH), 44.4 (CH_2), 37.0 (CH_2), 35.0 (CH_2), 14.2 (CH_3), 14.1 (CH_3). **HRMS** (APCI-TOF): *m/z* calculated for $C_{20}H_{24}NO_4$ $[M + H]^+$: *m/z* 342.1627 found 342.1630. Enantioselectivity (94:6 er) was determined by chiral HPLC analysis on Chiralpak® IE3 at rt, (Hexane :^{i}PrOH = 95:5, 0.5 mL/min).



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	28.384	MF	0.8190	6245.13184	127.08325	49.9649
2	30.576	FM	0.8115	6253.91553	128.44341	50.0351

Figure S24. *HPLC trace report of a racemic sample of* ***3p.***

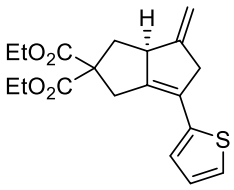


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	29.428	MM	0.8170	5181.09766	105.68882	93.7969
2	31.833	MM	0.6337	342.64047	9.01179	6.2031

Figure S32. HPLC trace report of an enantioenriched sample of **3p.**

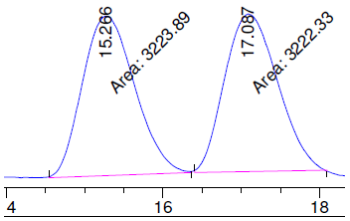
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diethyl 4-methylene-6-(thiophen-2-yl)-3,3a,4,5-tetrahydropentalene-2,2(1H)-dicarboxylate (3q)



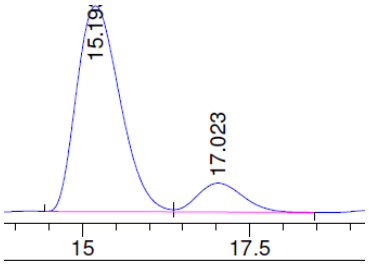
3q

63% yield, colourless oil. **^{1}H NMR (300 MHz, C_6D_6)** δ (ppm): 6.95 (d, *J* = 5.2 Hz, 1H), 6.85 (t, *J* = 4.5 Hz, 1H), 6.79 (s, 1H), 4.96 (s, 1H), 4.93 (s, 1H), 4.20-3.92 (m, 4H), 3.78 – 3.23 (m, 5H), 3.02 (dd, *J* = 12.3, 7.7 Hz, 1H), 2.16 (t, *J* = 11.9 Hz, 1H), 0.98 (dtd, *J* = 18.0, 7.2, 1.9 Hz, 6H). **^{13}C-NMR (75 MHz, C_6D_6)** δ (ppm): 172.0 (CO), 171.1 (CO), 150.8 (C), 142.7 (C), 140.0 (C), 127.4 (CH), 124.9 (CH), 124.4 (CH), 107.1 (CH_2), 64.54, 61.6 (CH_2), 61.4 (CH_2), 55.9 (CH), 46.1 (CH_2), 37.7 (CH_2), 34.5 (CH_2), 14.0 (CH_3), 13.9 (CH_3). **HRMS** (APCI-TOF): *m/z* calculated for $C_{19}H_{23}O_4S$ 347.1239, found 347.1241. Enantioselectivity (91:9 er) was determined by chiral HPLC analysis on Chiralpak® IB at rt, (Hexane :^{i}PrOH = 99:1, 0.5 mL/min).



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	15.266	MM	0.7755	3223.88525	69.28945	50.0120
2	17.087	MM	0.7837	3222.33472	68.52834	49.9880

Figure S33. HPLC trace report of a racemic sample of **3q.**

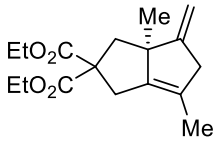


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	15.193	MM	0.7556	2.01553e4	444.56992	90.5261
2	17.023	MM	0.6613	2109.33057	53.16376	9.4739

Figure S34.**. HPLC trace report of an enantioenriched sample of **3q.

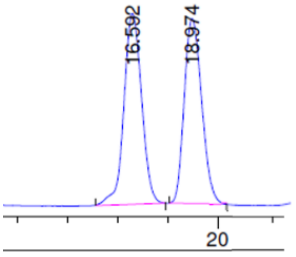
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Diethyl 3a-methyl-4-methylene-3,3a,4,5-tetrahydropentalene-2,2(1H)-dicarboxylate (3r)



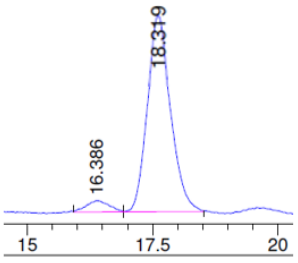
3r

54% yield, colourless oil. **^{1}H NMR (300 MHz, $CDCl_3$)** δ (ppm): 4.79 (d, *J* = 6.1, 2H), 4.17 (dq, *J* = 22.5, 7.1 Hz, 4H), 3.40 (d, *J* = 22.1 Hz, 1H), 3.01 – 2.66 (m, 3H), 2.33 (d, *J* = 13.4 Hz, 1H), 2.22 (d, *J* = 13.4 Hz, 1H), 1.64 (d, *J* = 1.8 Hz, 3H), 1.30 – 1.17 (m, 6H), 1.10 (s, 3H). **^{13}C-NMR (75 MHz, $CDCl_3$)** δ (ppm): 172.5 (CO), 172.2 (CO), 159.0 (C), 143.6 (C), 126.7 (C), 104.6 (CH_2), 61.5 (C), 61.4 (CH_2), 57.7 (C), 45.9 (CH_2), 44.1 (CH_2), 31.2 (CH_2), 25.8 (CH_3), 14.1 (CH_3), 14.0 (CH_3). **HRMS** (APCI-TOF): *m/z* calculated for $C_{17}H_{25}O_4$ $[M + H]^+$: *m/z* 293.1675, found 293.1678. Enantioselectivity (94:6 er) was determined by chiral HPLC analysis on Chiralpak® IE3 at rt, (Hexane :^{i}PrOH = 99:1, 0.5 mL/min).



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	16.592	BB	0.7664	8854.29199	179.85103	51.2753
2	18.974	BB	0.7614	8413.86035	174.22781	48.7247

Figure S35. *HPLC trace report of a racemic sample of* ***3r.***

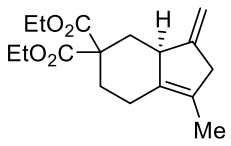


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	16.386	VV	0.3847	108.35532	3.40978	5.7850
2	18.319	VB	0.5006	1764.67468	51.13774	94.2150

Figure S36. *HPLC trace report of an enantioenriched sample of* ***3r.***

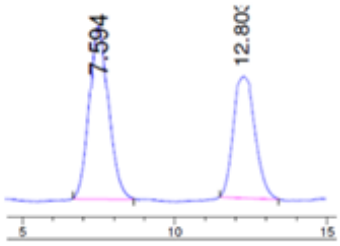
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Diethyl 1-methyl-3-methylene-2,3,3a,4,6,7-hexahydro-5H-indene-5,5-dicarboxylate (3s)



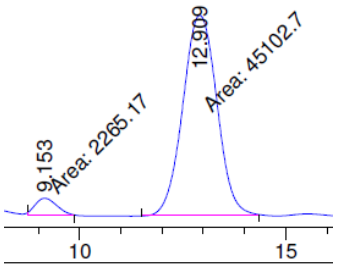
3s

76% yield, colourless oil. **^{1}H NMR (300 MHz, $CDCl_3$)** δ (ppm): 4.84 (s, 1H), 4.80 (s, 1H), 4.18 (dq, *J* = 19.0, 7.1 Hz, 4H), 3.63 – 3.49 (m, 1H), 3.39 (d, *J* = 19.3 Hz, 1H), 2.94 (d, *J* = 18.6 Hz, 1H), 2.87 (d, *J* = 16.6 Hz, 1H), 2.74 – 2.67 (m, 1H), 2.58 (dd, *J* = 12.6, 7.7 Hz, 1H), 1.83 – 1.70 (m, 1H), 1.64 (s, 3H), 1.61 – 1.57 (m, 2H) 1.28 – 1.19 (m, 6H). **^{13}C-NMR (75 MHz, $CDCl_3$)** δ (ppm): 171.4 (CO), 170.8 (CO), 151.7 (C), 139.1 (C), 126.7 (C), 105.1 (CH_2), 62.1 (C), 60.51 (CH_2), 52.9 (CH), 47.0 (CH_2), 36.8 (CH_2), 30.7 (CH_2), 13.2 (CH_3), 13.0 (CH_3). **HRMS** (APCI-TOF): *m/z* calculated for $C_{17}H_{25}O_4$ $[M + H]^+$: *m/z* 293.1673, found 293.1676. Enantioselectivity (95:5) was determined by chiral HPLC analysis on Chiralpak® OZ-H at rt, (Hexane :^{i}PrOH = 99:1, 0.5 mL/min).



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	7.594	MM	0.6539	3660.34229	93.29112	49.1342
2	12.807	MM	1.0752	3789.34082	58.73591	50.8658

Figure S37.**. HPLC trace report of a racemic sample of **3s.

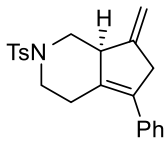


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	9.153	MM	0.5849	2265.17480	64.54350	4.7821
2	12.909	MM	0.9492	4.51027e4	791.93646	95.2179

Figure S3825.** HPLC trace report of an enantioenriched sample of **3s.

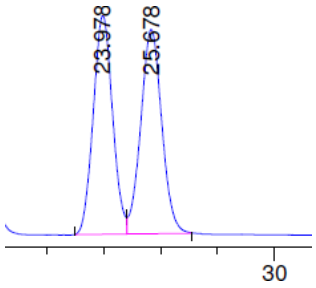
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7-Methylene-5-phenyl-2-tosyl-2,3,4,6,7,7a-hexahydro-1H-cyclopenta[c]pyridine (3t)



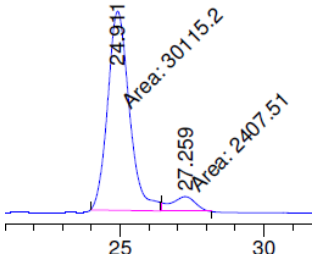
3t

This reaction was carried out using a combination of In (0.5 equiv) and InI_3 (0.2 equiv), instead of Zn/ZnI_2. 85% yield, white solid. **^{1}H NMR (300 MHz, $CDCl_3$)** δ (ppm): 7.67 (d, *J* = 8.1 Hz, 2H), 7.41 – 7.29 (m, 5H), 7.21 (d, *J* = 7.9 Hz, 2H), 5.12 (d, *J* = 2.4 Hz, 1H), 5.05 (d, *J* = 2.5 Hz, 1H), 4.16 (ddd, *J* = 10.9, 6.0, 1.9 Hz, 1H), 4.05 (d, *J* = 6.9 Hz, 1H), 3.90 (ddd, *J* = 13.4, 5.0, 1.8 Hz, 1H), 3.63 – 3.52 (m, 1H), 3.51 – 3.44 (m, 1H), 2.79 (d, *J* = 13.7, 1H), 2.43 (s, 3H), 2.10 (td, *J* = 11.0, 0.8 Hz, 3H). **^{13}C-NMR (75 MHz, $CDCl_3$)** δ (ppm): 147.9 (C), 129.8 (CH), 128.4(CH), 127.8 (CH), 127.7 (CH), 127.3 (CH), 108.3 (CH_2), 52.2 (CH_2), 49.8 (CH), 46.7 (CH_2), 42.7 (CH_2), 26.8 (CH_2), 21.6 (CH_3). **HRMS** (APCI-TOF): *m/z* calculated for $C_{22}H_{24}NO_2S$ $[M + H]^+$: *m/z* 366.1449, found 366.1450. Enantioselectivity (95:5 er) was determined by chiral HPLC analysis on Chiralpak® IA3 at rt, (Hexane :^{i}PrOH = 95:5, 0.5 mL/min).



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	24.419	VV	0.7658	2.07898e4	412.66843	50.5602
2	26.759	VB	0.7844	2.03291e4	389.83511	49.4398

Figure S39. HPLC trace report of a racemic sample of **3t.**

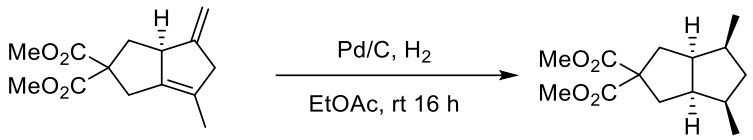


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	24.711	MM	0.8339	4944.29932	98.81570	95.0776
2	27.145	MM	0.7058	255.97925	6.04496	4.9224

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Figure S40. *HPLC trace report of an enantioenriched sample of* ***3t.***

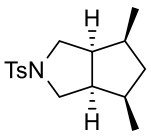
1.3. General procedure for the hydrogenation of the cycloadducts (exemplified for 4a).



3a **4a**

Pd/C (14.7 mg, 0.014 mmol) was added to a Schlenk tube previously purged with N_2 and a solution of **3a** (40 mg, 0.138 mmol) in EtOAc (not dry, 3.5 mL) was added. Hydrogen was bubbled for 15 min with a H_2 balloon and the resulting reaction mixture was stirred for 16 h at rt under a H_2 atmosphere (balloon). The reaction was quenched with water and extracted with EtOAc (3x). The organic layers were dried, concentrated, and purified by flash column chromatography (10 % Et_2O/ Hexanes) to afford **4a** (25 mg, 0.082mmol) as a colourless oil (62% yield). **^{1}H NMR (500 MHz, $CDCl_3$)** δ (ppm): 3.72 (s, 3H), 3.71 (s, 3H), 2.51 (q, *J* = 7.5 Hz, 2H), 2.26 – 2.18 (m, 2H), 1.93 (dddd, *J* = 13.6, 8.1, 6.9, 5.3 Hz, 2H), 1.74 – 1.66 (m, 2H), 1.51 (dt, *J* = 11.2, 5.3 Hz, 1H), 1.35 – 1.23 (m, 1H), 0.93 (s, 3H), 0.92 (s, 3H). **^{13}C-NMR (126 MHz, $CDCl_3$)** δ (ppm): 172.7 (CO), 172.4 (CO), 61.5 (C), 52.6 (CH), 45.8 (CH), 39.5 (CH_2), 36.3 (CH_3), 35.7 (CH_2), 14.7 (CH_3). **HRMS** (APCI-TOF): *m/z* calculated for $C_{14}H_{23}O_4$ $[M + H]^+$: *m/z* 254.1581 found 254.1583

(3aR,4R,6S,6aS)-4,6-dimethyl-2-tosyloctahydrocyclopenta[c]pyrrole (4k)



4k

80% yield. white solid. **^{1}H NMR (300 MHz, $CDCl_3$)** δ (ppm): δ 7.69 (d, *J* = 8.3 Hz, 2H), 7.32 (d, *J* = 8.1 Hz, 2H), 3.05 (dd, *J* = 10.0, 4.0 Hz, 2H), 2.93 – 2.84 (m, 2H), 2.56 (dt, *J* = 8.2, 4.4 Hz, 2H), 2.44 (s, 3H), 1.99 (dq, *J* = 13.4, 6.8 Hz, 2H), 1.61 (d, *J* = 3.9 Hz, 1H), 0.93 (s, 3H), 0.91 (s, 3H). **^{13}C-NMR (75 MHz, $CDCl_3$)** δ (ppm): 143.5 (C), 132.1 (C), 129.6 (CH), 128.2 (CH), 49.1 (CH_2), 46.6 (CH), 41.1 (CH_2), 36.2 (CH_3), 21.6 (CH), 15.2 (CH_3). **HRMS** (APCI-TOF): *m/z* calculated for $C_{16}H_{24}NO_2S$ $[M + H]^+$: *m/z* 294.1450, found 366.1454.

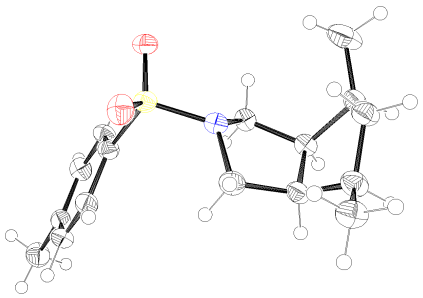
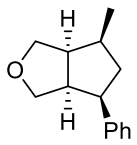


Figure S41. *X-ray crystallographic structure of* ***4k*** *(CCDC 2042080)*

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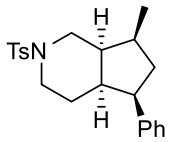
(3aS,4S,6R,6aR)-4-Methyl-6-phenylhexahydro-1H-cyclopenta[c]furan (4m)



4m

70% yield, colourless oil. **^{1}H NMR (300 MHz, $CDCl_3$)** δ (ppm): 7.31 – 7.26 (m, 3H), 7.22 – 7.16 (m, 2H), 4.28 – 4.17 (m, 1H), 3.81 (dd, *J* = 9.4, 4.7 Hz, 1H), 3.64 (dd, *J* = 9.4, 7.4 Hz, 1H), 3.43 (dd, *J* = 9.5, 7.9 Hz, 1H), 3.38 – 3.29 (m, 1H), 3.21 (dd, *J* = 9.6, 5.1 Hz, 1H), 3.06 (qd, *J* = 8.1, 5.0 Hz, 1H), 2.82 – 2.70 (m, 1H), 2.22 (dddd, *J* = 12.5, 8.4, 7.0, 5.6 Hz, 1H), 1.91 (dt, *J* = 11.4, 5.6 Hz, 1H), 1.66 (q, *J* = 12.4 Hz, 1H), 1.10 (d, *J* = 6.9 Hz, 3H). **^{113}C-NMR (75 MHz, $CDCl_3$)** δ (ppm): 142.0 (C), 128.1 (CH), 127.8 (CH), 125.9 (CH), 70.8 (CH_2), 69.6 (CH_2), 48.5 (CH), 47.4 (CH), 47.2 (CH), 36.6 (CH_2), 36.0 (CH), 15.21 (CH_3). **HRMS** (APCI-TOF): *m/z* calculated for $C_{14}H_{19}O$ $[M + H]^+$: *m/z* 203.1357 found 203.1366.

(4aR,5R,7S,7aS)-7-Methyl-5-phenyl-2-tosyloctahydro-1H-cyclopenta[c]pyridine (4t)



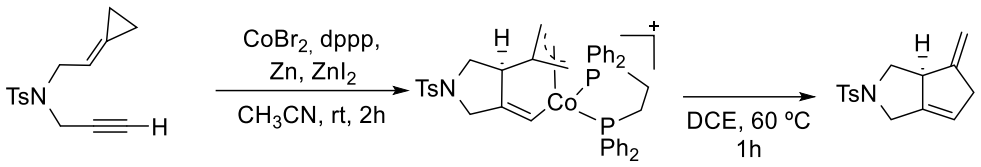
4t

77% yield, colorless oil. **^{1}H NMR (300 MHz, $CDCl_3$)** δ (ppm): 7.62 (d, *J* = 7.9 Hz, 2H), 7.31 (d, *J* = 8.2 Hz, 2H), 7.25 – 6.96 (m, 5H), 3.86 – 3.38 (m, 2H), 3.22 (dt, *J* = 12.7, 6.7 Hz, 1H), 2.62 (dd, *J* = 12.1, 4.6 Hz, 1H), 2.43 (s, 3H), 2.37 – 2.01 (m, 3H), 1.92 – 1.71 (m, 1H), 1.36 – 1.22 (m, 4H), 1.19 – 1.09 (m, 1H), 1.10 – 1.05 (m, 1H), 0.87 (d, *J* = 7.1 Hz, 1H) . **^{13}C-NMR (75 MHz, $CDCl_3$)** δ (ppm): 143.3 (C), 141.1 (C), 133.2 (C), 129.6 (CH), 128.2 (CH), 128.0 (CH), 127.8 (CH), 126.17 (CH), 47.3 (CH_2), 45.2 (CH_3), 42.3 (CH), 40.0 (CH_2), 36.6 (CH), 34.1 (CH), 23.9 (CH), 21.6 (CH_2), 18.9 (CH_3). **HRMS** (APCI-TOF): *m/z* calculated for $C_{22}H_{27}NO_2S$ $[M + H]^+$: *m/z* 369.1767 found 369.1772.

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1.4.Mechanistic experiments

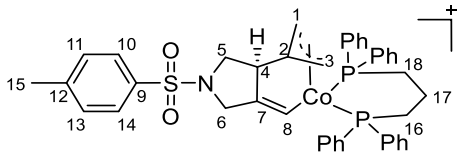
Synthesis of π-allyl cobalt complex 5j



2j **5j** **3j**

$CoBr_2$ (23.8 mg, 0.109 mmol), dppp (44.9 mg, 0.109 mmol), Zn (7.1 mg, 0.109 mmol) and ZnI_2 (34.8 mg, 0.109 mmol) and **2j** (30.0 mg, 0.109 mmol) were added to a previously dried sealed tube under argon atmosphere. After 3 vacuum/argon cycles, CH_3CN 1.1 mL) was added under argon. The reaction was stirred for 2 h at rt, concentrated and the crude residue submitted to flash column chromatography (25 % EtOAc / Hexane) to give **5** jas an air stable orange solid.

In an NMR tube, a solution of **5** (30 mg, 0.04 mmol) in DCE under argon atmosphere was heated at 60°C. Progress of the reaction was followed by 1H-NMR. After 1h, full conversion was observed, and the reaction mixture was concentrated and purified by flash column chromatography /10% Et_2O to obtain **3j** (6.60 mg, 0.024 mmol, 60% yield).



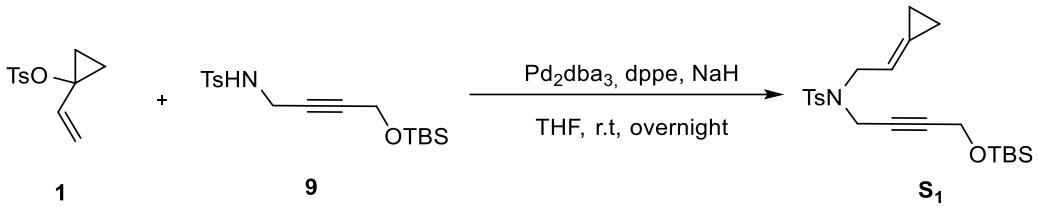
5

^{1}H NMR (300 MHz, C_6D_6) δ (ppm): 8.05 (t, J = 8.4 Hz, 4H_{Ar}), 7.69 (d, J = 7.9 Hz, 2H_{Ar}), 7.06 (qd, J = 9.7, 8.6, 3.8 Hz, 10H_{Ar}), 6.83 (q, J = 8.5, 7.6 Hz, 8H_{Ar}), 4.97 (s, H_{1A}), 4.72 (s, H_{2A}), 4.01 (s, H_{1B}), 3.62 – 3.58 (m, H_{2B}), 3.57 (d, J = 8.8 Hz, H_{5A}), 3.19 (p, J = 11.0 Hz, 4H, $H_{5B,}$ $H_{6B,}$ H_{17A}, H_{17B}), 3.09 (d, J = 9.1 Hz, H_4), 2.87 (d, J = 11.2 Hz, H_{6A}), 2.65 (dd, J = 15.7, 8.7 Hz, H_8), 2.35 (td, J = 15.0, 14.0, 6.7 Hz, $H_{16A,}$ H_{16B}), 2.22 – 2.02 (m, H_{18A}), 1.96 (d, J = 12.7 Hz, H_{18B}), 1.90 (s, $H_{15A,}H_{15B,}H_{15C}$). **^{13}C-NMR (126 MHz, C_6D_6)** δ (ppm): 143.1 (C_{Ar}), 142.6 (C_{12}), 138.2(C_{Ar}), 137.9(C_{Ar}), 137.5(C_8), 136.5 (C_{Ar}), 134.4 (CH_{Ar}), 134.3 (CH_{Ar}), 134.1 (CH_{Ar}), 134.0 (CH_{Ar}), 133.5 (C_{Ar}), 133.2 (C_{Ar}), 133.1 (CH_{Ar}), 133.1 (CH_{Ar}), 132.9 (C_{Ar}), 132.9 (C_{Ar}) 132.8 (CH_{Ar}), 132.6 (C_{Ar}), 129.5 (CH_{Ar}), 129.4 (CH_{Ar}), 129.3 (CH_{Ar}), 129.2 (CH_{Ar}), 128.6 (CH_{Ar}), 127.9 (CH_{Ar}), 127.6 (CH_{Ar}), 127.5 (CH_{Ar}), 71.6 (C_1), 71.4 (C_3), 60.4 (C_2), 51.7 (C_5), 51.1 (C_4), 49.4 (C_6), 26.2 (C_{16}), 25.9 (C_{18}), 21.1 (C_{15}), 20.9 (C_{17}). **^{31}P NMR (202 MHz, C_6D_6)** δ 29.42, 27.07.

2. (3+2+n) Multicomponent Cycloadditions of Alkyne-tethered ACPs.

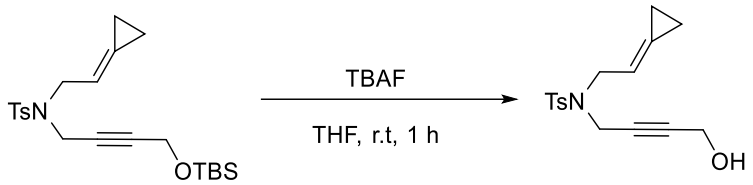
2.1. Synthesis of alkyne-alkene-ACP cycloaddition precursors

General procedure A: alkylation approach (illustrated for 11)



1 **9** **S_1**

Alkyne **9** (g, 4.75 mmol mmol) was added slowly to a suspension of NaH (200 mg, 5.00 mmol) in THF (23.7 mL), cooled at 0°C. After stirring for 15 min, a solution of allylcylopropyltosilate **1** (1.13 g, 4.75 mmol), $Pd_2(dba)_3$ (87.0 mg, 0.095 mmol) and dppe (76.0 mg, 0.19 mmol) in THF (24 mL) previously stirred for 20 min, was added "via cannula". The reaction mixture was stirred overnight at rt, poured into water, and extracted with Et_2O (3 x 20 mL). The organic phases were dried, filtered and concentrated to give a crude oily residue that was purified by flash chromatography (10 % Et_2O/hexanes) to yield 1.68 g of **S_1** as pale-yellow oil (84 % yield).[87] **^{1}H NMR (300 MHz, $CDCl_3$)** δ (ppm): 7.74 (d, *J* = 8.4 Hz, 2H), 7.28 (d, *J* = 8.5 Hz, 2H), 5.70 (t, *J* = 1.9 Hz, 1H), 4.09 (s, 2H), 4.03 (s, 2H), 3.95 (d, J = 6.9 Hz, 2H), 2.42 (s, 3H), 0.86 (s, 9H), 0.03 (s, 6H).

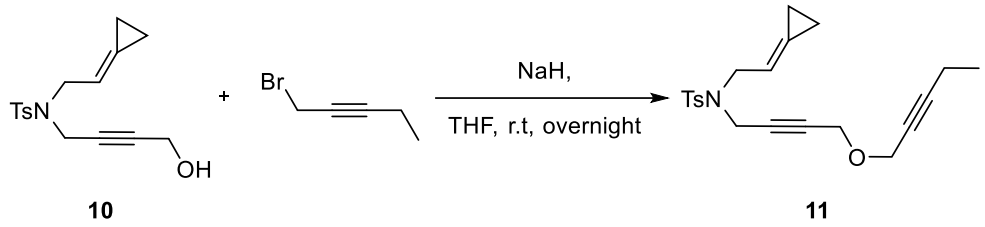


S_1 **10**

To a solution of **S_1** (2.8 g, 6.7 mmol) in THF (33.4 ml) was slowly added a 1M solution of TBAF in THF (7.3 ml). The reaction mixture was stirred at room temperature until full consumption of **S_1** (1 h) The reaction was quenched with water, extracted with Et_2O (x3) and concentrate under vacuum. Finally, flash column chromatography (Hex/EtOAc 10%) afford 2 g of ACP **10** as a yellowish oil (75% yield). [84] **^{1}H NMR (300 MHz, $CDCl_3$)** δ (ppm): 7.68 (d, *J* = 8.3 Hz, 2H), 7.26 (d, *J* = 8.0 Hz, 2H), 5.62 (ddt, *J* = 6.9, 4.3, 2.2 Hz, 1H), 4.16 – 3.93 (m, 3H), 3.94 – 3.81 (m, 5H), 2.36 (s, 4H), 1.98 (s, 1H), 1.20 (t, *J* = 7.1 Hz, 1H), 1.06 – 0.92 (m, 4H). **^{13}C-NMR (75 MHz, $CDCl_3$)** δ (ppm):143.5 (C), 136.0 (C), 129.3 (CH), 128.7 (C), 127.7 (CH), 111.8 (CH), 83.7 (C), 78.2 (C), 50.4 (CH_2), 47.9 (CH_2), 36.0 (CH_2), 21.4 (CH_3), 2.5 (CH_2), 1.8 (CH_2).

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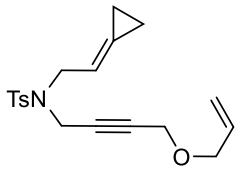
N-(2-Cyclopropylideneethyl)-4-methyl-N-(4-(pent-2-yn-1-yloxy)but-2-yn-1-yl)benzenesulfonamide



10 **11**

To a suspention of NaH (39.5 mg, 0.987 mmol) in THF (10 ml), previously stirred for 10 min, a solution of N-(2-cyclopropylideneethyl)-N-(4-hydroxybut-2-yn-1-yl)-4-methylbenzenesulfonamide **10** (250 mg, 0.858 mmol) in THF (2 ml) was added at 0 °C. After stirring the reaction mixture for 15 min, 1-bromopent-2-yne (519 mg, 4.29 mmol) was added and the reaction mixture was stirred overnight. Then, the reaction was quenched with water and extracted with Et_2O (x3). The combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by flash column cromatography (10% Et_2O/Hexane) to obtain 200 mg of **11** as a colourless oil (65 % yield). **^{11}H-NMR (300 MHz, $CDCl_3$)** δ (ppm): 7.72 (d, *J* = 8.2 Hz, 2H), 7.28 (d, *J* = 8.2 Hz, 2H), 5.68 (tq, *J* = 6.8, 2.0 Hz, 1H), 4.08 (s, 2H), 4.00 – 3.87 (m, 5H), 2.40 (s, 3H), 2.21 (qt, *J* = 7.5, 2.2 Hz, 2H), 2.13 (s, 1H), 1.12 (t, *J* = 7.5 Hz, 3H), 1.07 (s, 3H). **^{13}C-NMR (75 MHz, CDCl3)** δ (ppm): 143.3 (C), 136.2 (C), 129.4 (C), 128.6 (C), 127.7 (C), 111.9 (CH), 88.8 (C), 80.6 (C), 79.5 (C), 74.3 (C), 56.9 (CH_2), 56.1 (CH_2), 47.9 (CH_2), 36.0 (CH_2), 21.4 (CH_3), 13.7 (CH_3), 12.3 (CH_2), 2.5 (CH_2), 1.8 (CH_2). **HRMS** (APCI-TOF): calculated for $C_{21}H_{25}NO_3S$ $[M + H]^+$: *m/z* 372.1576 found 372.1641.

N-(4-(Allyloxy)but-2-yn-1-yl)-N-(2-cyclopropylideneethyl)-4-methylbenzenesulfonamide (**13a**)[84]

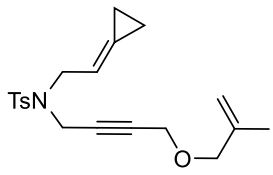


13a

Following same procedure for **11** using allyl bromide. 62% yield, white solid. **^{1}H-NMR (300 MHz, $CDCl_3$)** δ (ppm): δ 7.70 (d, *J* = 8.3 Hz, 2H), 7.25 (d, *J* = 7.9 Hz, 2H), 5.86 – 5.70 (m, 1H), 5.66 (tt, *J* = 6.8, 2.0 Hz, 1H), 5.23 – 5.05 (m, 2H), 4.07 (d, *J* = 1.9 Hz, 2H), 3.92 (d, *J* = 7.0 Hz, 2H), 3.84 (s, 2H), 3.79 (dd, *J* = 5.6, 1.4 Hz, 2H), 2.37 (s, 3H), 1.04 (t, *J* = 1.9 Hz, 4H). **^{13}C-NMR (75 MHz, CDCl3)** δ (ppm): 143.3 (C), 136.1 (C), 133.8 (C), 129.3 (CH), 128.6 (C), 127.7 (CH), 117.5 (CH_2), 111.9 (CH), 81.2 (C), 79.1 (C), 70.2 (CH_2), 57.0 (CH_2), 47.9 (CH_2), 36.0 (CH_2), 21.4 (CH_3), 2.5 (CH_2), 1.8 (CH_2). **HRMS** (APCI-TOF): calculated for $C_{19}H_{23}NO_3S$ $[M + H]^+$: *m/z* 346.1457 found 346.1470

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N-(2-cyclopropylideneethyl)-4-methyl-N-(4-((2-methylallyl)oxy)but-2-yn-1 yl)benzenesulfonamide (13g)

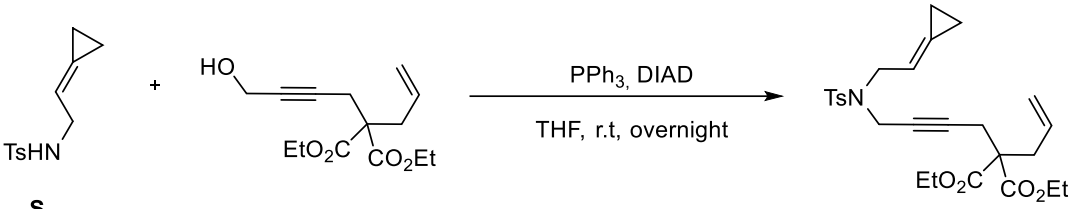


13g

Following same procedure for **11** using 3-Bromo-2-methylpropene. 43% yield, colourless oil.**^{1}H-NMR (300 MHz, $CDCl_3$)** δ (ppm): 7.73 (d, *J* = 8.3 Hz, 2H), 7.28 (d, *J* = 8.0 Hz, 2H), 5.70 (ddt, *J* = 6.8, 4.3, 2.1 Hz, 1H), 4.89 (s, 2H), 4.11 (s, 2H), 3.96 (d, *J* = 7.1 Hz, 2H), 3.86 (d, *J* = 2.0 Hz, 2H), 3.74 (s, 2H), 2.40 (s, 3H), 1.69 (s, 3H), 1.16 – 0.97 (m, 4H). **^{13}C-NMR (75 MHz, CDCl3)** δ (ppm): 143.3 (C), 141.3 (C), 136.3 (C), 129.4 (CH_2), 128.7 (C), 127.8 (CH), 112.8 (CH), 112.0 (CH), 81.3 (C), 79.2 (C), 73.4 (CH_2), 56.9 (CH_2), 48.0 (CH_2), 36.1 (CH_2), 21.5 (CH_3), 19.4 (CH_3), 2.6 (CH_2), 1.9 (CH_2). **HRMS** (APCI-TOF): calculated for $C_{20}H_{25}NO_3S$ $[M + H]^+$: *m/z* 360.1622 found 360.1630.

General procedure B: Mitsunobu reaction

Diethyl 2-allyl-2-(4-((N-(2-cyclopropylideneethyl)-4-methylphenyl)sulfonamido)but-2-yn-1-yl)malonate (13b)



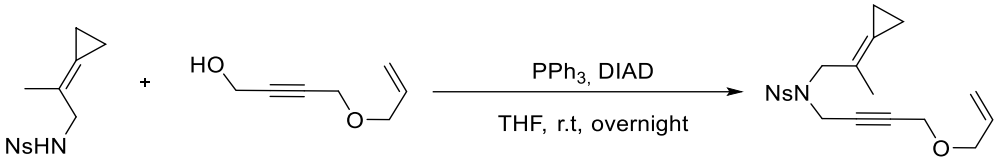
S_2 **15b** **13b**

To a solution of *tert*-butyl tosylcarbamate **S_2** (200 mg, 0.843 mmol) and triphenylphosphine (265.8 mg, 1.01 mmol) in THF (2.3 mL) was added diethyl 2-allyl-2-(4-hydroxybut-2-yn-1-yl)malonate **15b** (249 mg, 0.928 mmol) and the resulting mixture was stirred for 5 min. Then, the reaction was cooled down to 0 °C and diisopropyl azodicarboxylate (0.2 mL, 1.01 mmol) was added dropwise. After stirring at room temperature for 18 h, the reaction was quenched with water. The mixture was extracted with EtOAc and the combined organic phases were dried over anhydrous Na_2SO_4 and concentrated in vacuo. The residue was purified by flash column chromatography (10 % EtOAc / Hexane) to afford 300 mg of **10c** as a colourless oil (73 % yield). **^{1}H-NMR (300 MHz, $CDCl_3$)** δ (ppm): 7.68 (d, *J* = 8.3 Hz, 2H), 7.26 (d, *J* = 8.7 Hz, 2H), 5.65 (tt, *J* = 6.8, 1.9 Hz, 1H), 5.46 (ddt, *J* = 16.4, 10.2, 7.5 Hz, 1H), 5.08 – 4.89 (m, 2H), 4.11 (qd, *J* = 7.1, 1.5 Hz, 4H), 4.00 (d, *J* = 2.1 Hz, 2H), 3.89 (d, *J* = 6.8 Hz, 2H), 2.60 – 2.46 (m, 4H), 2.38 (s, 3H), 1.18 (t, *J* = 7.2 Hz, 6H), 1.04 (s, 4H). **^{13}C-NMR (75 MHz, CDCl3)** δ (ppm): 169.4 (CO), 143.2 (C), 136.5 (C), 131.7 (CH), 129.4 (CH), 127.5 (CH), 119.4 (CH_2), 112.1 (CH), 79.9 (C), 76.2 (C), 61.5 (CH_2), 56.4 (C), 47.5 (CH_2), 36.3 (CH_2), 35.9 (CH_2), 22.6 (CH_2), 21.4 (CH_3), 13.9

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(CH), 2.5 (CH_2), 1.8 (CH_2). **HRMS** (APCI-TOF): calculated for $C_{19}H_{23}NO_3S$ [M+H]: *m/z* 487.6109, found 487.6111.

N-(4-(Allyloxy)but-2-yn-1-yl)-N-(2-cyclopropylidenepropyl)-4-nitrobenzenesulfonamide (13j)

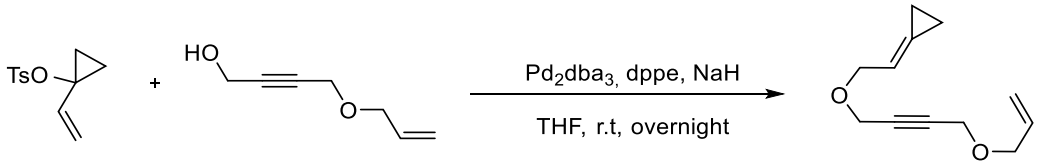


16 **15e** **13j**

To a solution of nosylcarbamate **16** (141 mg, 0.50 mmol) and triphenylphosphine (328 mg, 0.75 mmol) in THF (2.5 mL) was added 4-(allyloxy)but-2-yn-1-ol **15e** (97.5 mg, 0.75 mmol) and stirred for 5 min. Then, the reaction was cooled to 0 °C and diisopropyl azodicarboxylate (0.15 mL, 0.75 mmol) was added dropwise. After stirring at room temperature for 3 h, the reaction was quenched with water. The mixture was extracted with EtOAc (x3) and the combined organic phases were dried over anhydrous Na_2SO_4 and concentrated in vacuo. The residue was purified by flash column chromatography (10 % EtOAc in Hexane) to afford 150 mg of **13j** (77 % yield) as a colourless oil. **^{1}H-NMR (300 MHz, $CDCl_3$)** δ (ppm): 8.35 (d, *J* = 8.9 Hz, 2H), 8.06 (d, *J* = 8.8 Hz, 2H), 5.79 (ddt, *J* = 16.6, 11.1, 5.7 Hz, 1H), 5.22 (dd, *J* = 6.9, 1.6 Hz, 1H), 5.18 (s, 1H), 4.08 (s, 2H), 3.93 (s, 2H), 3.87 – 3.71 (m, 4H), 1.85 (d, *J* = 1.8 Hz, 3H), 1.07 (s, 4H). **^{13}C-NMR (75 MHz, CDCl3)** δ (ppm): 150.0 (C), 144.9 (C), 133.5 (CH), 128.9 (CH), 124.0 (CH), 123.7 (C), 117.7 (C), 117.5 (CH_2), 81.8 (C), 78.3 (C), 70.5 (CH_2), 56.8 (CH_2), 51.9 (CH_2), 35.7 (CH_2), 17.9 (CH_3), 2.7 (CH_2), 2.3 (CH_2). **HRMS** (APCI-TOF): calculated for $C_{19}H_{23}N_2O_5S$ $[M+H]^+$ *m/z* 390.1246 found 390,1249.

General procedure C: Tsuji-Trost reaction

(2-((4-(Allyloxy)but-2-yn-1-yl)oxy)ethylidene)cyclopropane (13e) [86]



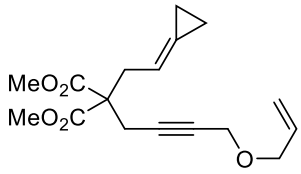
1 **15e** **13e**

4-(allyloxy)but-2-yn-1-ol 134 (300 mg, 2.38 mmol) was added slowly to a suspension of NaH (96 mg, 4.00 mmol) in THF (15 mL), cooled at 0°C. After stirring for 15 min, a solution of allylcylopropyltosilate **1** (566 mg, 2.38 mmol), $Pd_2(dba)_3$ (22 mg, 0.024 mmol) and dppe (19 mg, 0.048 mmol) in THF (5 mL), (previously stirred for 20 min), was added "via cannula". The reaction mixture was stirred overnight at rt, poured into water and

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extracted with Et_2O (3 x 20 mL). The organic phases were dried, filtered and concentrated to give a crude oily residue that was purified by flash chromatography (10 % Et2O/hexanes) to yield 232 mg of **10b** as pale yellow oil (51 % yield). **^{1}H-NMR (300 MHz, $CDCl_3$)** δ (ppm): δ 6.01-5.68 (m, 2H), 5.21 (d, J = 17.1 Hz, 2H), 5.12 (d, *J* = 10.4 Hz, 2H), 4.22-4.04 (m, 6H), 4.03- 3.89 (m, 2H), 1.02 (s, 4H); **^{13}C-NMR (75 MHz, CDCl3)** δ (ppm): 133.6 (CH), 127.3 (C), 117.2 (CH_2), 113.7 (CH), 82.2 (C), 81.6 (C), 70.0 (CH_2), 69.3 (CH_2), 56.9 (CH_2), 56.6 (CH_2), 1.9 (CH_2), 1.4 (CH_2). **HRMS** (APCI-TOF): calculated for $C_{12}H_{16}O_2$ $[M + H]^+$: *m/z* 193.1221, found 193.1224.

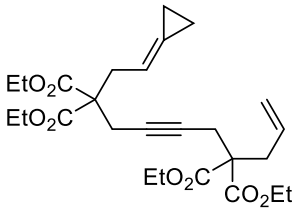
Dimethyl 2-(4-(allyloxy)but-2-yn-1-yl)-2-(2-cyclopropylideneethyl)malonate (13c)



13c

Prepared following the same procedure as used for **13e** using dimethyl 2-(4-(allyloxy)but-2-yn-1-yl)malonate **15c**. 77% yield, colourless oil. **^{1}H-NMR (300 MHz, $CDCl_3$)** δ (ppm): 5.86 (ddt, *J* = 16.5, 11.3, 5.9 Hz, 1H), 5.54 (t, *J* = 7.7 Hz, 1H), 5.27 (d, *J* = 17.1 Hz, 1H), 5.17 (d, *J* = 10.3 Hz, 1H), 4.09 – 4.05 (m, 2H), 3.99 (d, *J* = 5.9 Hz, 2H), 3.69 (s, 6H), 2.90 (d, *J* = 7.5 Hz, 2H), 2.80 (d, *J* = 2.5 Hz, 2H), 1.11 – 0.92 (m, 4H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 170.4 (CO), 134.0 (CH), 127.3 (C), 117.6 (CH_2), 111.2 (CH), 81.4 (C), 78.8 (C), 70.1 (CH_2), 57.3 (C), 57.2 (CH_2), 52.6 (CH_3), 34.7 (CH_2), 23.0 (CH_2), 2.9 (CH_2), 1.8 (CH_2). **HRMS** (APCI-TOF): calculated for $C_{17}H_{22}O_5$ $[M + H]^+$: *m/z* 307.1544 found 307.1545.

Tetraethyl 1-cyclopropylideneundec-10-en-5-yne-3,3,8,8-tetracarboxylate (13d) [84]

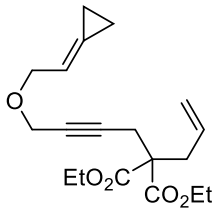


13d

Prepared following the same procedure as used for **13e** using tetraethyl non-8-en-3-yne-1,1,6,6-tetracarboxylate **15d**. 71% yield. Colourless oil. **^{1}H-NMR (300 MHz, $CDCl_3$)** δ (ppm): 5.62 (dd, *J* = 16.2, 8.3 Hz, 2zH), 5.18 (d, *J* = 17.1 Hz, 1H), 5.11 (d, *J* = 10.1 Hz, 1H), 4.19 (q, *J* = 7.3 Hz, 8H), 2.89 (d, *J* = 7.5 Hz, 2H), 2.75 (s, 6H), 1.24 (t, *J* = 7.1 Hz, 12H), 1.04 (s, 4H). **^{13}C-NMR (75 MHz, CDCl3)** δ (ppm): 170.1 (CO), 169.8 (CO), 132.0 (CH), 126.9 (C), 119.6 (CH_2), 111.7 (CH), 78.1 (C), 77.5 (C), 61.5 (CH_2), 61.4 (CH_2), 57.2 (C), 56.8 (C), 36.3 (CH_2), 34.5 (CH_2), 22.8 (CH_2), 14.1 (CH_3), 2.9 (CH_2), 2.0 (CH_2). **HRMS** (APCI-TOF): calculated for $C_{26}H_{37}O_8$ $[M + H]^+$: *m/z* 477.2410 , found 477.2486.

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Diethyl 2-allyl-2-(4-(2-cyclopropylideneethoxy)but-2-yn-1-yl)malonate (13f)

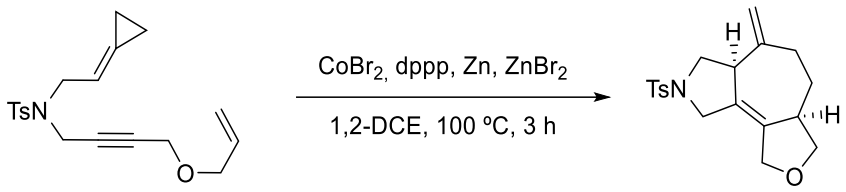


13f

Prepared following the same procedure as used for **13e** using diethyl 2-allyl-2-(4-hydroxybut-2-yn-1-yl)malonate **15f**. 82% yield. Colourless oil. **^{1}H-NMR (300 MHz, $CDCl_3$)** δ (ppm): 5.97 – 5.86 (m, 1H), 5.65 (tt, *J* = 17.1, 7.9 Hz, 1H), 5.25 – 5.07 (m, 2H), 4.30 – 4.13 (m, 6H), 4.10 (s, 1H), 2.84 (d, *J* = 1.9 Hz, 1H), 2.81 (s, 2H), 2.79 (s, 1H), 1.31 – 1.19 (m, 5H), 1.11 (s, 4H). **^{13}C-NMR (75 MHz, $CDCl_3$)** δ (ppm): 169.8 (CO), 131.9 (CH), 127.8 (C), 119.7 (CH_2), 114.2 (CH), 81.0 (C), 79.4 (C), 69.5 (CH_2), 61.6 (CH_2), 57.2 (CH_2), 56.89, 36.6 (CH_2), 23.0 (CH_2), 14.1 (CH_3), 2.4 (CH_2), 1.8 (CH_2). **HRMS** (APCI-TOF): calculated for $C_{19}H_{27}O_5$ $[M+H]^+$ *m/z* 334.1782 found 334.1784.

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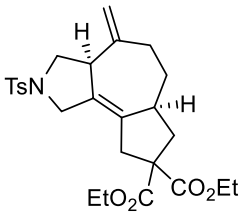
2.2. General procedure for the intramolecular (3+2+2) cycloaddition between ACPs alkynes and alkenes (exemplified for 13a).



13a **14a**

$CoBr_2$ (2.2 mg, 0.01 mmol), dppp (4.9 mg, 0.012 mmol), Zn (3.3, 0.05 mmol) and $ZnBr_2$ (4.5 mg, 0.02 mmol) were successively added to a dried Schlenk tube under Argon. Then, **1a** (34.5 mg, 0.100 mmol) in 1,2-dichloroethane (1 mL) was added under Ar atmosphere and the resulting mixture was stirred for 3 h at 100 °C before it was filtered through a short pad of Florisil® and concentrated under vacuum. The residue was purified by flash column chromatography (25 % Et_2O / hexanes) to give 22 mg of **2a** (63% yield) as a white solid.[84] **^{1}H-NMR (300 MHz, $CDCl_3$)** δ (ppm): 7.72 (2H, d, J = 8.2 Hz), 7.35 (2H, d, J = 8.3 Hz), 4.77 (1H, s), 4.66 (1H, s), 4.26 – 4.02 (3H, m), 3.73 (1H, d, J = 13.4 Hz), 3.60 – 3.31 (4H, m), 3.15 (1H, t, J = 8.5 Hz), 2.89 – 2.72 (1H, m), 2.58 – 2.44 (1H, m), 2.42 (3H, s), 2.26 – 2.01 (2H, m), 1.92 – 1.78 (1H, m). **^{13}C-NMR (75 MHz, $CDCl_3$)** δ (ppm): 145.6 (C), 143.9 (C), 135.5 (C), 131.8 (C), 129.7 (CH), 128.0 (CH), 126.8 (C), 109.2 (CH_2), 75.0 (CH_2), 70.8 (CH_2), 51.6 (CH_2), 51.0 (CH_2), 48.0 (CH), 43.9 (CH), 37.8 (CH_2), 30.9 (CH2), 21.5 (CH_3). **HRMS** (APCI-TOF): calculated for $C_{19}H_{23}NO_3S$ [M+H]: *m/z* 346.1399, found 346.1412.

Diethyl (3aS,6aS)-4-methylene-2-tosyl-1,2,3,3a,4,5,6,6a,7,9-decahydro-8H-azuleno[4,5-c]pyrrole-8,8-dicarboxylate (14b)

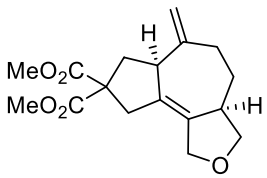


14b

76% yield. Colourless oil. **^{1}H-NMR (500 MHz, $CDCl_3$)** δ (ppm): 7.72 (d, *J* = 8.3 Hz, 2H), 7.35 (d, *J* = 7.9 Hz, 2H), 4.72 (s, 1H), 4.62 (s, 1H), 4.24 – 4.11 (m, 4H), 3.81 (d, *J* = 13.5 Hz, 1H), 3.59 – 3.50 (m, 1H), 3.48 (dd, *J* = 9.3, 7.5 Hz, 1H), 3.30 (s, 1H), 3.20 (dd, *J* = 9.3, 8.0 Hz, 1H), 2.85 – 2.72 (m, 2H), 2.71 – 2.65 (m, 1H), 2.60 – 2.48 (m, 2H), 2.44 (s, 3H), 2.08 (td, *J* = 12.6, 3.0 Hz, 1H), 1.89 (ddt, *J* = 12.7, 6.2, 3.2 Hz, 1H), 1.76 (dd, *J* = 12.9, 10.6 Hz, 1H), 1.55 (s, 3H), 1.24 (td, *J* = 7.1, 4.7 Hz, 6H). **^{13}C-NMR (126 MHz, $CDCl_3$)** δ (ppm): 171.5 (CO), 171.4 (CO), 146.3 (C), 143.9 (C), 135.6 (C), 131.95 (C) 129.8 (CH), 128.3 (CH), 108.3 (CH_2), 61.7 (CH_2), 59.0 (C), 52.1 (CH_2), 52.0 (CH_2), 47.7 (CH), 43.3 (CH), 41.8 (CH_2), 39.8 (CH_2), 39.3 (CH_2), 34.3 (CH_2), 21.7 (CH_3), 14.1 (CH_3). **HRMS** (APCI-TOF): calculated for $C_{19}H_{23}NO_3S$ [M+H]: *m/z* 487.6110, found 487.6112.

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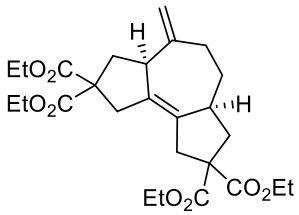
Dimethyl (3aR,6aS)-6-methylene-1,3a,4,5,6,6a,7,9-octahydroazuleno[4,5-c]furan-8,8(3H)-dicarboxylate (14c)



14c

74% yield. Colourless oil. **^{1}H-NMR (300 MHz, $CDCl_3$)** δ (ppm): 4.78 (s, 1H), 4.74 (s, 1H), 4.34 (d, *J* = 13.3 Hz, 1H), 4.20 – 4.07 (m, 2H), 3.74 (d, *J* = 2.6 Hz, 6H), 3.37 (t, *J* = 8.6 Hz, 1H), 3.30 – 3.21 (m, 1H), 2.90-2.70 (m, 4H), 2.63 (ddd, *J* = 13.2, 6.2, 2.5 Hz, 1H), 2.52 (ddd, *J* = 12.8, 7.0, 1.6 Hz, 1H), 2.32 (t, *J* = 12.4 Hz, 1H), 2.19 – 2.06 (m, 1H), 1.87 (ddd, *J* = 13.3, 6.4, 3.2 Hz, 1H), 1.62 (s, 2H), 1.32 – 1.09 (m, 2H) . **^{13}C-NMR (75 MHz, $CDCl_3$)** δ (ppm): 171.8 (C), 147.9 (C), 135.2 (C), 129.7 (C), 108.2 (CH_2), 75.4 (CH_2), 71.6 (CH_2), 58.6 (C), 52.8 (CH_3), 48.0 (CH), 44.1 (CH), 39.1 (CH_2), 38.6 (CH_2), 38.0 (CH_2), 30.8 (CH_2). **HRMS** (APCI-TOF): calculated for $C_{19}H_{27}O_5$ [M+H]: *m/z* 306,1467 found 306,1468.

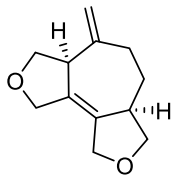
Tetraethyl (3aS,6aS)-4-methylene-1,3a,4,5,6,6a,7,9-octahydro-2H-cyclopenta[e]azulene-2,2,8,8(3H)-tetracarboxylate (14d) [86]



14d

75% yield. Colourless oil. **^{1}H NMR (300 MHz, $CDCl_3$)** δ (ppm): 4.72 (s, 1H), 4.70 (s, 1H), 4.23- 4.14 (m, 8H), 3.18 (m, 1H), 2.94-2.90 (m, 2H), 2.81-2.77 (m, 2H), 2.67 (m, 1H), 2.62-2.53 (m, 2H), 2.52-2.38 (m, 1H), 2.33-2.28 (m, 1H), 2.08 (dt, J = 12.69, 2.57 Hz, 1H), 1.95- 1.86 (m, 1H), 1.80 (dd, J = 12.68, 10.77 Hz, 1H), 1.38-1.14 (m, 12H), 1.13 (d, J = 9.89 Hz, 1H). **^{13}C-NMR (75 MHz, $CDCl_3$)** δ (ppm): 171.6 (CO), 148.6 (C), 135.0 (C), 132.7 (C), 107.3 (CH_2), 61.4 (CH_2), 61.39 (CH_2), 61.36 (CH_2), 61.33 (CH_2), 58.8 (C), 58.4 (C), 47.5 (CH), 43.1 (CH), 42.0 (CH_2), 40.5 (CH_2), 39.8 (CH_2), 39.6 (CH_2), 37.9 (CH_2), 34.3 (CH_2), 14.0 (CH_3). **HRMS** (APCI-TOF): calculated for $C_{26}H_{37}O_8$ [M+H]: *m/z* 477.2488, found 477.2489.

(3aR,6aS)-4-Methylene-1,3a,4,5,6,6a,7,9-octahydro-3H-2,8-dioxacyclopenta[e]azulene (14e) [86]

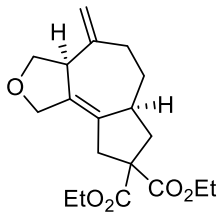


14e

58 % yield. Colourless oil. **^{1}H-NMR (300 MHz, $CDCl_3$)** δ (ppm): 4.79 (s, 1H), 4.67 (s, 1H), 4.25-4.06 (m, 6H), 3.93 (t, J = 8.65 Hz, 1H), 3.39 (t, J = 8.52 Hz, 2H), 2.89-2-86 (m, 1H), 2.62 (ddd, J = 13.15, 6.04, 2.79 Hz, 1H), 2.26-2.14 (m, 1H), 1.96-1.86 (m, 1H), 1.45-1.30 (m, 1H); **^{13}C-NMR (75 MHz, $CDCl_3$)** δ (ppm): δ 146.2 (C), 132.3 (C), 130.6 (C), 108.3 (CH_2), 75.0 (CH_2), 71.8 (CH_2), 70.6 (CH_2), 70.4 (CH_2), 49.4 (CH), 44.2 (CH), 38.5 (CH_2), 31.2 (CH_2). **HRMS** (APCI-TOF): calculated for $C_{12}H_{16}O_2$ $[M + H]^+$: *m/z* 193.1225 , found 193.1227.

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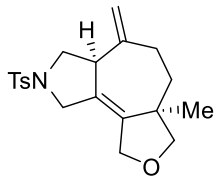
Diethyl (3aS,6aS)-4-methylene-1,3a,4,5,6,6a,7,9-octahydroazuleno[4,5-c]furan-8,8(3H)-dicarboxylate (14f)



14f

63% yield. Colorless oil. **^{1}H-NMR (300 MHz, $CDCl_3$)** δ (ppm): 4.74 (s, 1H), 4.64 (s, 1H), 4.32 (d, *J* = 13.1 Hz, 1H), 4.19 (qt, *J* = 7.1, 3.7 Hz, 5H), 4.08 (dd, *J* = 8.8, 7.4 Hz, 1H), 3.95 (t, *J* = 8.5 Hz, 1H), 3.31 (s, 1H), 2.77 (t, *J* = 2.8 Hz, 3H), 2.69 – 2.51 (m, 2H), 2.16 (td, *J* = 12.6, 2.8 Hz, 1H), 2.01 – 1.90 (m, 1H), 1.90 – 1.72 (m, 1H), 1.24 (td, *J* = 7.1, 2.1 Hz, 7H). **^{13}C-NMR (75 MHz, $CDCl_3$)** δ (ppm): 171.5 (CO), 171.4 (CO), 146.7 (C), 133.5 (C), 132.2 (C), 107.4 (CH_2), 72.1 (CH_2), 71.2 (CH_2), 61.5 (CH_2), 48.9 (CH), 43.3 (CH), 41.6 (CH_2), 39.7 (CH_2), 39.4 (CH_2), 34.4 (CH_2), 14.0 (CH_3). **HRMS** (APCI-TOF): calculated for $C_{19}H_{27}O_5$ $[M+H]^+$ *m/z* 334,1780 found 334,1782.

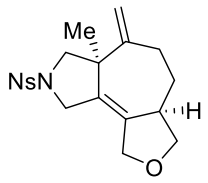
(3aR,6aS)-3a-Methyl-6-methylene-8-tosyl-1,3,3a,4,5,6,6a,7,8,9-decahydrofuro[3',4':3,4]cyclohepta[1,2-c]pyrrole (14i)



14i

^{1}H-NMR (300 MHz, $CDCl_3$) δ δ 7.72 (d, J = 8.2 Hz, 2H), 7.35 (d, J = 8.4 Hz, 2H), 4.79 (s, 1H), 4.67 (s, 1H), 4.35 – 4.17 (m, 1H), 4.11 (d, J = 19.4 Hz, 2H), 4.06 – 3.98 (m, 2H), 3.90 (d, J = 13.5 Hz, 1H), 3.44 – 3.29 (m, 3H), 3.05 (d, J = 8.9 Hz, 1H), 2.85 (s, 3.), 2.44 (s, 1H), 2.32 – 2.21 (m, 1H), 1.96 – 1.81 (m, 1H), 1.57 (s, 3H). **^{13}C-NMR (75 MHz, $CDCl_3$)** δ (ppm): 145.6 (C), 143.9 (C), 135.5 (C), 131.8 (C), 129.7 (CH), 128.0 (CH), 126.8 (C), 109.2 (CH_2), 75.0 (CH_2), 70.8 (CH_2), 51.6 (CH_2), 51.0 (CH_2), 48.0 (CH), 43.9 (CH), 37.8 (CH_2), 30.9 (CH_2), 21.5 (CH_3). **HRMS** (APCI-TOF): calculated for $C_{20}H_{26}NO_3S$ [M+H]: *m/z* 359.4899, found 359.4850.

(3aR,6aS)-6a-Methyl-6-methylene-8-((4-nitrophenyl)sulfonyl)-1,3,3a,4,5,6,6a,7,8,9-decahydrofuro[3',4':3,4]cyclohepta[1,2-c]pyrrole (14j)



14j

37% yield. Yellowish soild.**^{1}H-NMR (500 MHz, $CDCl_3$)** δ (ppm): 8.41 (d, *J* = 8.8 Hz, 2H), 8.03 (d, *J* = 8.8 Hz, 2H), 4.83 (s, 1H), 4.69 (s, 1H), 4.18 – 4.06 (m, 2H), 4.06 – 3.95 (m, 2H), 3.46 (dd, *J* = 13.2, 2.3 Hz, 1H), 3.39 (t, *J* = 8.8 Hz, 2H), 3.12 (d, *J* = 9.0 Hz, 1H), 2.85 (d, *J* = 9.5 Hz, 1H), 2.46 – 2.34 (m, 1H), 2.29 (ddd, *J* = 13.4, 7.6, 4.1 Hz, 1H), 1.90 (ddt, *J* = 12.7, 7.7, 4.6 Hz, 1H), 1.34 (s, 3H), 1.27 (d, *J* = 6.3 Hz, 1H). **^{13}C-NMR (126 MHz, $CDCl_3$)** δ (ppm): 149.3 (C), 148.9 (C), 140.7 (C), 133.9 (C), 127.9 (C), 127.8 (CH), 123.4 (CH), 109.6 (CH_2), 73.9 (CH_2), 69.8 (CH_2), 58.2 (CH_2), 50.0 (CH_2), 49.3 (C), 40.6 (CH), 32.6 (CH_2), 30.0 (CH_2),

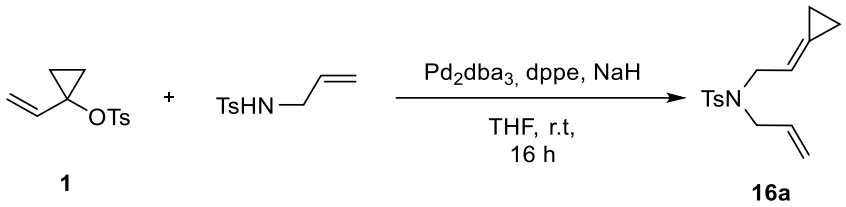
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23.4 (CH_3). **HRMS** (APCI-TOF): calculated for $C_{19}H_{23}N_2O_5S$ $[M+H]^+$ *m/z* 390,1249 found 390,1250.

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3. (3+2) Cycloaddition of ACPs tethered to alkenes, allenes or dienes

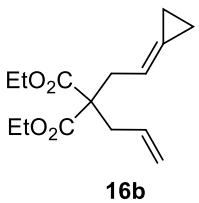
3.1. General procedure for the synthesis of alkene-, allene- and diene-tethered ACPs (exemplified for 16a)



1 **16a**

A solution of the N-Tosyl allyl amine (761 mg, 3.195 mmol) in THF (6 mL) was added to an ice-cooled suspension of NaH (153.3 mg, 3.195 mmol) in THF (10 ml). After stirring at rt for 15 min, a mixture of tosylate **1** (675 mg, 3.195 mmol), Pd_2dba_3 (58.5 mg, 0.064 mmol) and 1,2- bis(diphenylphosphino)ethane (50.9 mg, 0.128 mol) in THF (10 mL), previously stirred for 15 min at room temperature, was transferred via cannula to the solution. The reaction mixture was then allowed to stir for 30 min at rt, poured into water and extracted with Et_2O. The combined organic layers were dried, filtered, and concentrated and the crude product was purified by flash chromatography (5 % Et_2O / hexanes) to obtain 775 mg of **16a** (87% yield) as a yellowish oil.[78] **^{1}H NMR (300 MHz, $CDCl_3$)** δ (ppm): 7.70 (d, J = 8.3 Hz, 2H), 7.29 (d, *J* = 8.3 Hz, 2H), 5.77-5.47 (m, 2H), 5.12 (s, 1H), 5.07 (d, *J* = 7.5 Hz, 1H), 3.94 (d, *J* = 6.8 Hz, 2H), 3.78 (d, J = 6.3 Hz, 2H), 2.43 (s, 3H), 1.07-1.02 (m, 2H), 1.00-0.95 (m, 2H). **^{13}C-NMR (75 MHz, $CDCl_3$)** δ (ppm): 143.2 (e), 137.6 (CH), 133.1 (CH), 129.75 (CH), 127.39 (C), 127.27 (CH), 118.50 (CH_2), 112.76 (CH), 49.51 (CH_2), 48.30 (CH_2), 21.67 (CH_3), 2.59 (CH_2), 2.04 (CH_2). **HRMS** (APCI-TOF): calculated for $C_{15}H_{20}NO_2S$ $[M+H]^+$ *m/z* 278.1207, found 278.1206.

Diethyl 2-allyl-2-(2-cyclopropylideneethyl)malonate (16b) [78]

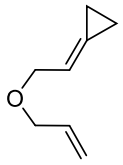


16b

85% yield. Colourless oil. **^{1}H NMR (300 MHz, $CDCl_3$)** δ (ppm): 5.73-5.61 (2H, m), 5.09 (1H, s), 5.06 (1H, s), 4.31 (4H, q, *J* = 7.2 Hz), 2.77 (2H, d, *J* = 7.4 Hz), 2.63 (2H, d, *J* = 7.4 Hz), 1.25 (6H, t, *J* = 7.2 Hz), 1.09-0.97 (4H, m); **^{13}C-NMR (75 MHz, $CDCl_3$)** δ (ppm): 170.8 (C), 132.5 (C), 126.0 (CH), 118.6 (CH_2), 111.8 (CH), 61.0 (CH_2), 57.5 (C), 36.6 (CH_2), 34.7 (CH_2), 13.9 (CH_3), 2.7 (CH_2), 1.8 (CH_2); **HRMS** (APCI-TOF): calculated for $C_{15}H_{23}O_4$ $[M+H]^+$ *m/z* 267.1596, found 267.1584.

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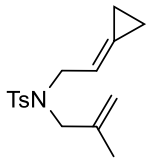
(2-(Allyloxy)ethylidene)cyclopropane (16c) [78]



16c

60% yield. Yellowish liquid. **^{1}H-NMR (300 MHz, $CDCl_3$)** δ (ppm): 5.98-5.90 (m, 2H), 5.28 (dq, *J* = 17.2, 1.5 Hz, 1H), 5.18 (dd, *J* = 10.4, 1.3 Hz, 1H), 4.12 (d, *J* = 6.7 Hz, 2H), 3.99 (dt, *J* = 5.6, 1.2 Hz, 2H) 1.14-1.05 (m, 4H). **^{13}C-NMR (75 MHz, $CDCl_3$)** δ (ppm): 135.12 (CH), 126.94 (C), 117.03 (CH_2), 114.95 (CH), 71.09 (CH_2), 70.44 (CH_2), 2.41 (CH_2), 1.90 (CH_2). **HRMS** (APCI-TOF): calculated for $C_8H_{13}O$ 125.0966, found 125.0967. **HRMS** (APCI-TOF): calculated for $C_8H_{13}O$ $[M+H]^+$ *m/z* 125.0966, found 125.0967.

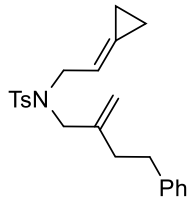
N-(2-Cyclopropylideneethyl)-4-methyl-N-(2-methylallyl)benzenesulfonamide (16d) [78]



16d

80% yield. Yellowish oil.**^{1}H NMR (300 MHz, $CDCl_3$)** δ (ppm): 7.66 (d, *J* = 8.1 Hz, 2H), 7.25 (d, *J* = 8.1 Hz, 2H), 5.46 (tt, *J* = 6.9, 2.1 Hz, 1H), 4.83 (s, 1H), 4.76 (s, 1H), 3.87 (d, *J* = 6.9 Hz, 2H), 3.66 (s, 2H), 2.37 (s, 3H), 1.66 (s, 3H), 1.01 – 0.85 (m, 4H). **^{13}C-NMR (75 MHz, $CDCl_3$)** δ (ppm): 143.0 (C), 140.4 (C), 137.5 (C), 129.5 (CH), 127.0 (CH), 113.9 (CH_2), 112.3 (CH), 52.9 (CH_2), 48.1 (CH_2), 21.4 (CH_3), 19.7 (CH_3), 2.40 (CH_2), 1.8 (CH_2). **HRMS** (APCI-TOF): calculated for $C_{16}H_{22}NO_2S$ $[M+H]^+$ *m/z* 292.1371, found 292.1371.

N-(2-Cyclopropylideneethyl)-4-methyl-N-(2-methylene-4-phenylbutyl)benzenesulfonamide (16e)

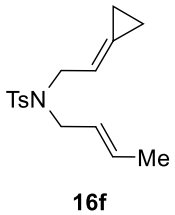


16e

81% yield. Yellowish oil.**^{1}H NMR (300 MHz, $CDCl_3$)** δ 7.71 (d, *J* = 7.8 Hz, 2H), 7.33 – 7.25 (m, 4H), 7.18 (d, *J* = 8.2 Hz, 3H), 5.51 (td, *J* = 6.9, 3.4 Hz, 1H), 4.93 (s, 1H), 4.87 (s, 1H), 3.91 (d, *J* = 6.8 Hz, 2H), 3.76 (s, 2H), 2.76 (t, *J* = 8.1 Hz, 2H), 2.42 (s, 3H), 2.32 (t, *J* = 8.1 Hz, 2H), 1.07 – 0.89 (m, 4H). **^{13}C NMR (75 MHz, $CDCl_3$)** δ 143.7 (C), 143.0 (C), 141.7 (C), 137.5 (C), 129.5 (CH), 128.4 (CH), 128. (CH), 127.1 (CH), 125.8 (CH), 113.7 (CH_2), 112.4 (CH), 51.9 (CH_2), 48.2 (CH_2), 34.7 (CH_2), 33.9 (CH_2), 21.5 (CH_3), 2.43 (CH_2), 1.8 (CH_2). **HRMS** (APCI-TOF): calculated for $C_{23}H_{28}NO_2S$ $[M+H]^+$ *m/z* 381.1762, found 381.1763.

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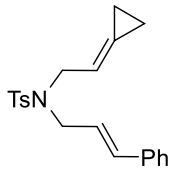
(E)-N-(But-2-en-1-yl)-N-(2-cyclopropylideneethyl)-4-methylbenzenesulfonamide (16f)[157]



16f

90% yield. Colourless oil. **^{1}H NMR (300 MHz, $CDCl_3$)** δ (ppm): 7.69 (d, *J* = 8.2 Hz, 2H), 7.28 (d, *J* = 8.2 Hz, 2H), 5.60-5.57 (m, 1H), 5.50 (dq, *J* = 15.1, 6.5 Hz, 1H), 5.26 (dtq, *J* = 15.1, 6.7, 1.6 Hz, 1H), 3.92 (d, *J* = 6.7 Hz, 2H), 3.72 (d, *J* = 6.6 Hz, 2H), 2.42 (s, 3H), 1.62 (d, *J* = 6.5 Hz, 3H), 1.08-1.02 (m, 2H), 1.00-0.95 (m, 2H). **^{13}C-NMR (75 MHz, $CDCl_3$)** δ (ppm): 143.0 (CO), 137.9 (C), 130.1 (CH), 129.6 (CH), 127.3 (CH), 127.0 (C), 125.7 (CH), 113.0 (CH), 48.8 (CH_2), 48.0 (CH_2), 21.6 (CH_3), 17.8 (CH_3), 2.5 (CH_2), 1.9 (CH_2). **HRMS** (APCI-TOF): calculated for $C_{16}H_{22}NO_2S$ $[M+H]^+$ *m/z* 292.1371, found 292.1376.

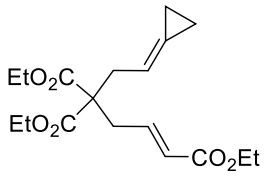
N-Cinnamyl-N-(2-cyclopropylideneethyl)-4-methylbenzenesulfonamide (16g)[158]



16g

72% yield. White solid.**^{1}H NMR (300 MHz, $CDCl_3$)** δ (ppm): 7.79 (dd, *J* = 16.2, 8.1 Hz, 2H), 7.43 – 7.18 (m, 6H), 6.40 (d, *J* = 15.6, 1.4 Hz, 1H), 6.00 (ddd, *J* = 15.7, 7.0, 6.0 Hz, 1H), 5.72 – 5.61 (m, 1H), 4.00 (dd, *J* = 9.8, 6.6 Hz, 4H), 2.44 (s, 3H), 1.28 (d, *J* = 6.3 Hz, 1H), 1.11 – 1.02 (m, 2H), 1.01 – 0.97 (m, 2H). **^{13}C-NMR (75 MHz, $CDCl_3$)** δ (ppm): 143.2 (C), 137.6 (C), 136.3 (C), 133.4 (CH), 129.7 (CH), 128.6, 127.8 (CH), 127.2 (CH), 126.3 (CH), 124.2 (CH), 112.9 (CH), 49.1 (CH_2), 48.4 (CH_2), 22.7 (CH_3), 2.5 (CH_2), 1.9 (CH_2). **HRMS** (APCI-TOF): calculated for $C_{21}H_{23}NO_2SNa$: $[M+Na]^+$ *m/z* 376.1342, found 376.1347.

Triethyl (E)-6-cyclopropylidenehex-1-ene-1,4,4-tricarboxylate (16h)[73]



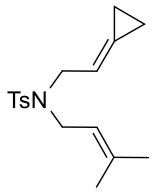
16h

61% yield. Colourless oil.**^{1}H NMR (300 MHz, $CDCl_3$)** δ (ppm): 6.80 (1H, m), 5.80 (1H, d, *J* = 15.7 Hz), 5.59 (1H, m), 4.17-4.10 (6H, m), 2.78-2.73 (4H, m), 1.27-1.21 (9H, m), 1.08-0.97 (4H, m); **^{13}C-NMR (75 MHz, $CDCl_3$)** δ (ppm): 170.4 (C), 165.8 (C), 142.9 (CH), 126.9 (C), 124.8 (CH), 111.5 (CH), 61.4 (CH_2), 60.3 (CH2), 57.3 (C), 35.3 (CH_2), 35.3 (CH_2), 14.2 (CH_3), 14.0 (CH_3), 2.9 (CH_2), 1.9 (CH_2). **HRMS** (APCI-TOF): calculated for $C_{18}H_{27}O_6$ $[M+H]^+$ *m/z* 339.1808, found 339.1799.

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[157] Evans, P. A.; Inglesby, P. *J. Am. Chem. Soc.* **2012**, *134*, 3635-3638.
[158] Qi, J.; Zhang, F.; Huang, Y.; Xu, A.; Ren, S. *Org. Lett.* **2018**, *20*, 2360-2364.

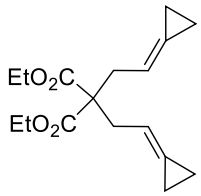
N-(2-Cyclopropylideneethyl)-4-methyl-N-(3-methylbut-2-en-1-yl)benzenesulfonamide (16i)



16i

77% yield. White solid.**^{1}H NMR (300 MHz, $CDCl_3$)** δ 7.69 (d, *J* = 8.1 Hz, 1H), 7.28 (d, *J* = 8.1 Hz, 1H), 5.61 (tt, *J* = 6.9, 2.3 Hz, 1H), 5.08 – 4.97 (m, 1H), 3.92 (d, *J* = 6.8 Hz, 1H), 3.78 (d, *J* = 7.0 Hz, 1H), 2.42 (s, 1H), 1.64 (s, 2H), 1.54 (s, 1H), 1.05 – 0.94 (m, 2H). **^{13}C-NMR (75 MHz, $CDCl_3$)** δ (ppm): 142.87, 137.74, 136.22, 129.47, 127.17, 126.59, 119.19, 113.21, 48.17, 44.54, 25.72, 21.46, 17.62, 2.39, 1.72. **HRMS** (APCI-TOF): calculated for $C_{17}H_{24}NO_2S$ $[M+H]^+$ *m/z* 305,1499 found 305,1451.

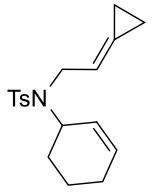
Diethyl 2,2-bis(2-cyclopropylideneethyl)malonate (16j) [73]



16j

61% yield. Colourless oil.**^{1}H NMR (300 MHz, $CDCl_3$)** δ (ppm): 6 5.64 (2H, m), 4.13 (4H, q, *J* = 7.1 Hz), 2.77 (4H, d, *J* = 7.4 Hz), 1.22 (6H, t, *J* = 7.1 Hz), 0.97 (4H, m). **^{13}C-NMR (75 MHz, $CDCl_3$)** δ (ppm): 171.2 (C), 125.9 (CH), 112.2 (CH), 61.0 (CH_2), 57.8 (C), 34.9 (CH_2), 14.0 (CH_3), 2.82 (CH_2), 1.8 (CH_2). **HRMS** (APCI-TOF): calculated for $C_{17}H_{25}O_4$ $[M+H]^+$ *m/z* 293.1753, found 293.1759.

N-(Cyclohex-2-en-1-yl)-N-(2-cyclopropylideneethyl)-4-methylbenzenesulfonamide (16k)

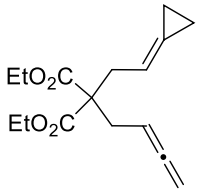


16k

46% yield. White solid. **^{1}H NMR (300 MHz, $CDCl_3$)** δ (ppm): 7.69 (d, *J* = 8.0 Hz, 2H), 7.25 (d, *J* = 7.9 Hz, 2H), 5.94 – 5.63 (m, 2H), 5.13 (d, *J* = 10.3 Hz, 1H), 4.65 – 4.37 (m, 1H), 4.05 – 3.65 (m, 2H), 2.39 (s, 3H), 1.97 – 1.45 (m, 6H), 1.02 (s, 3H). **^{13}C-NMR (75 MHz, $CDCl_3$)** δ (ppm): 143.1 (C), 138.9 (C), 132.1 (CH), 129.8 (CH), 128.2 (CH), 127.3 (CH), 124.8 (C), 116.8 (CH), 55.5 (CH), 45.7(CH_2), 29.0 (CH_2), 24.7 (CH_2), 22.0 (CH_2), 21.7 (CH_3), 2.5 (CH_2), 2.2 (CH_2). **HRMS** (APCI-TOF): calculated for $C_{18}H_{24}NO_2S$ $[M+H]^+$ *m/z* 317,1499 found 317,1450.

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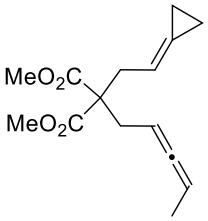
Diethyl 2-(buta-2,3-dien-1-yl)-2-(2-cyclopropylideneethyl)malonate (18a)[75]



18a

77% yield, colourless oil. **^{1}H NMR (300 MHz, $CDCl_3$)** δ (ppm): 5.60 (1H, m), 4.97 (1H, m), 4.63 (2H, dt, J = 6.5 y 2.5 Hz), 4.20-4.09 (4H, m), 2.81 (2H, dd, J = 8.8, 1.1 Hz), 2.60 (2H, dt, J = 8.0 y 2.6 Hz), 1.24 (6H, t, J = 7.1 Hz), 1.08-1.00 (4H, m); **^{13}C-NMR (75 MHz, $CDCl_3$)** δ (ppm): 209.7 (C), 170.7 (CO), 126.3 (C), 111.8 (CH), 84.4 (CH), 74.4 (CH_2), 61.2(CH_2), 57.8 (C), 34.8 (CH_2), 31.9 (CH_2), 14.2 (CH_3), 3.0 (CH_2), 2.0 (CH_2); **HRMS** (APCI-TOF): calculated for $C_{16}H_{23}O_4$ $[M+H]^+$ *m/z* 279.1596, found 279.1600.

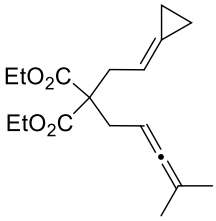
Dimethyl 2-(2-cyclopropylideneethyl)-2-(penta-2,3-dien-1-yl)malonate (18b) [75]



18b

61% yield, colourless oil. **^{1}H NMR (300 MHz, $CDCl_3$)** δ (ppm): 5.60 (t, *J* = 7.6 Hz, 1H), 5.11 – 4.99 (m, 1H), 4.97 – 4.87 (m, 1H), 3.71 (s, 6H), 2.82 (d, *J* = 7.6 Hz, 2H), 2.57 (d, *J* = 6.5 Hz, 2H), 1.62 (dd, *J* = 6.9, 3.2 Hz, 3H), 1.12 – 0.95 (m, 4H). **^{13}C-NMR (75 MHz, $CDCl_3$)** δ (ppm): 206.5 (C), 171.3 (CO), 126.5 (C), 111.8 (CH), 85.5 (CH), 84.3 (CH), 58.0 (C), 52.4 (CH_3), 52.3 (CH_3), 34.7 (CH_2), 32.4 (CH_2), 14.3(CH_3), 2.9 (CH_2), 1.8 (CH_2). **HRMS** (APCI-TOF): calculated for $C_{15}H_{21}O_4$ $[M+H]^+$ *m/z* 264.1332, found 264.1333.

Diethyl 2-(2-cyclopropylideneethyl)-2-(4-methylpenta-2,3-dien-1-yl)malonate (18c) [75]

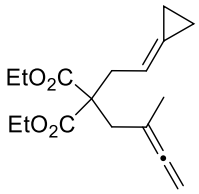


18c

55% yield, colourless oil.**^{1}H NMR (300 MHz, $CDCl_3$)** δ (ppm): 5.61 (1H, m), 4.79 (1H, m), 4.14 (4H, c, *J* = 7.1 Hz), 2.80 (2H, d, *J* = 7.4 Hz), 2.53 (2H, d, *J* = 7.6 Hz), 1.64 (3H, s), 1.63 (3H, s), 1.22 (6H, t, *J* = 7.1 Hz), 1.04-0.96 (4H, m); **^{13}C-NMR (75 MHz, $CDCl_3$)** δ (ppm): 204.1 (C), 171.4 (CO), 126.5 (C), 112.5 (CH), 95.3 (C), 83.3 (CH), 61.4 (CH_2), 58.3 (C), 34.9 (CH_2), 32.9 (CH_2), 20.9 (CH_3) 14.5 (CH_3), 3.2 (CH_2), 2.2 (CH_2); **HRMS** (APCI-TOF): calculated for $C_{18}H_{27}O_4$ $[M+H]^+$ *m/z* 307.1909, found 307.1905.

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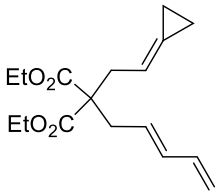
Diethyl 2-(2-cyclopropylideneethyl)-2-(2-methylbuta-2,3-dien-1-yl)malonate (18d)



18d

48% yield, colourless oil.**^{1}H NMR (300 MHz, $CDCl_3$)** δ (ppm): 5.73 – 5.56 (m, 1H), 4.52 (d, *J* = 3.0 Hz, 1H), 4.09 (qd, *J* = 7.1, 1.4 Hz, 3H), 2.83 (dt, *J* = 7.4, 1.4 Hz, 1H), 2.73 (dt, *J* = 7.4, 1.4 Hz, 1H), 2.56 (s, 1H), 1.60 (s, 1H), 1.18 (t, *J* = 7.1 Hz, 4H), 1.07 – 0.87 (m, 2H). **^{13}C-NMR (75 MHz, $CDCl_3$)** δ (ppm): 207.3 (C), 171.1 (CO), 170.9 (CO), 125.7 (C), 112.3 (CH), 93.5 (C), 74.4 (CH_2), 61.0 (CH_2), 57.3 (C), 35.4 (CH_2), 34.6 (CH_2), 20.0 (CH_3), 13.9 (CH_3), 2.7 (CH_2)z (CH_2), 1.7 (CH_2). **HRMS** (APCI-TOF): calculated for $C_{17}H_{25}O_4$ $[M+H]^+$ *m/z* 292.1675, found 292.1677.

Diethyl (E)-2-(2-cyclopropylideneethyl)-2-(penta-2,4-dien-1-yl)malonate (20a)[90]

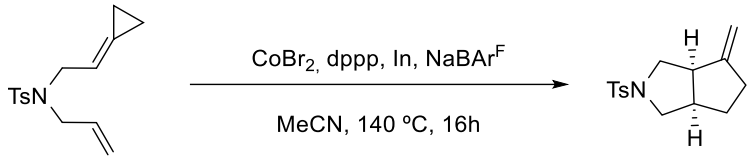


20a

81% yield. Colourless oil.**^{1}H NMR (300 MHz, $CDCl_3$)** δ (ppm): 6.23 (1H, dt, *J* = 16.7 y 10.2 Hz), 6.01 (1H, dd, *J* = 15.0 y 10.5 Hz), 5.61-5.46 (2H, m), 5.05 (1H, d, *J* = 16.8 Hz), 4.95 (1H, d, *J* = 10.5 Hz), 4.20-4.08 (4H, m), 2.73 (2H, d, *J* = 7.4 Hz), 2.62 (1H, d, *J* = 7.60 Hz), 1.19 (6H, t, *J* = 7.1 Hz), 1.06-0.91 (4H, m); **^{13}C-NMR (75 MHz, $CDCl_3$)** δ (ppm): 170.8 (CO), 136.6 (CO), 134.7 (CH), 128.1 (CH), 126.0 (CH), 116.0 (CH_2), 111.8 (CH), 61.0 (CH_2), 57.7 (C), 35.7 (CH_2), 35.0 (CH_2), 14.0 (CH_3), 2.7 (CH_2), 1.8 (CH_2); **HRMS** (APCI-TOF): calculated for $C_{17}H_{25}O_4$ $[M+H]^+$ *m/z* 293.1753, found 293.1753.

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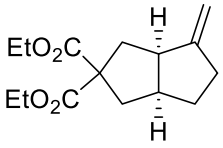
3.2. General procedure for the (3+2) cycloaddition between ACPs and alkenes (exemplified for 17a).



16a **17a**

$CoBr_2$ (2.2 mg, 0.01 mmol), dppp (4.7 mg, 0.012 mmol), In (5.9, 0.05 mmol) and $NaBAr^F$ (8.9 mg, 0.02 mmol) were successively added to a dried Schlenk tube under Argon. Then, **16a** (27.7 mg, 0.1 mmol) in MeCN (1 mL) was added under Ar atmosphere and the resulting mixture was stirred for 16 h at 140 °C before it was filtered through a short pad of Florisil® and concentrated under vacuum. The residue was purified by flash column chromatography (10 % Et_2O / hexanes) to give 17 mg of **17a** (62% yield) as a colourless oil. **^{1}H NMR (300 MHz, $CDCl_3$)** δ (ppm): 7.69 (d, *J* = 8.2 Hz, 2H), 7.31 (d, *J* = 7.9 Hz, 2H), 4.89 (d, *J* = 2.1 Hz, 1H), 4.78 (d, *J* = 2.1 Hz, 1H), 3.32 (dd, *J* = 9.7, 8.4 Hz, 1H), 3.23 (dd, *J* = 9.8, 7.7 Hz, 1H), 3.16 – 3.07 (m, 1H), 3.00 (d, *J* = 4.5 Hz, 1H), 2.97 (d, *J* = 4.4 Hz, 1H), 2.74 – 2.61 (m, 1H), 2.43 (s, 3H), 2.37 – 2.11 (m, 2H), 1.80 (dq, *J* = 12.8, 7.6 Hz, 1H), 1.52 – 1.37 (m, 1H). **^{13}C-NMR (75 MHz, $CDCl_3$)** δ (ppm): 154.0 (C), 143.5 (C), 129.6 (CH), 128.0 (CH), 107.3 (CH_2), 54.3 (CH_2), 53.7 (CH_2), 47.5 (CH), 43.2 (CH), 33.1 (CH_2), 30.4 (CH_2), 21.6 (CH_3). **HRMS** (APCI-TOF): calculated for $C_{15}H_{20}NO_2S$ $[M+H]^+$ *m/z* 278.1207, found 278.1206.

Diethyl (3aR,6aS)-4-methylenehexahydropentalene-2,2(1H)-dicarboxylate (17b) [73]

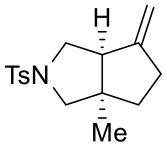


17b

65% yield. Colourless oil. **^{1}H NMR (300 MHz, $CDCl_3$)** δ 4.84 (1H, s), 4.76 (1H, s), 4.21-4.12 (4H, m), 2.96 (1H, m), 2.68-2.61 (2H, m), 2.49-2.42 (2H, m), 2.26 (1H, m), 1.95-1.73 (4H, m), 1.48 (1H, m), 1.27-1.20 (6H, m). **^{13}C NMR (75 MHz, $CDCl_3$)** δ 172.1, (CO), 171.7 (CO), 156.3 (C), 105.6 (CH2), 62.7 (C), 61,3 (CH2), 47.6 (CH), 43.1 (CH), 40.8 (CH_2), 40.2 (CH_2), 32.6 (CH_2), 30.6 (CH_2), 14.0 (CH_3). **HRMS** (APCI-TOF): calculated for $C_{15}H_{23}O_4$ $[M+H]^+$ *m/z* 267.1596, found 267.1594.

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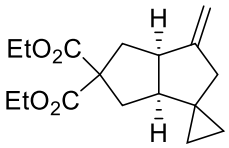
(3aR,6aS)-3a-Methyl-6-methylene-2-tosyloctahydrocyclopenta[c]pyrrole (17d)



17d

63% yield. Colourless oil. **^{1}H NMR (300 MHz, $CDCl_3$)** δ 7.69 (d, *J* = 8.3 Hz, 2H), 7.31 (d, *J* = 7.9 Hz, 2H), 4.85 (d, *J* = 2.1 Hz, 1H), 4.75 (d, *J* = 2.2 Hz, 1H), 3.44 – 3.36 (m, 1H), 3.16 (dd, *J* = 10.0, 4.6 Hz, 1H), 3.10 (d, *J* = 9.6 Hz, 1H), 2.91 (d, *J* = 9.6 Hz, 1H), 2.50 (d, *J* = 6.4 Hz, 1H), 2.44 (s, 3H), 2.40 – 2.29 (m, 1H), 1.82 – 1.60 (m, 1H), 1.53 – 1.38 (m, 1H), 1.20 (dd, *J* = 7.0, 1.5 Hz, 1H), 1.05 (s, 3H). **^{13}C NMR (75 MHz, $CDCl_3$)** δ 153.6 (C), 143.3 (C), 133.1 (C), 129.5 (CH), 127.7 (CH), 107.7 (CH_2), 59.1 (CH_2), 54.4 (CH), 53.8 (CH2), 50.2 (C), 36.5 (CH_2), 31.8 (CH_2), 24.6 (CH_3), 21.5 (CH_3). **HRMS** (APCI-TOF): calculated for $C_{16}H_{22}NO_2S$ $[M+H]^+$ *m/z* 292.1371, found 292.1371.

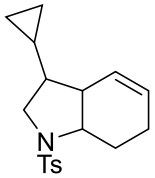
Diethyl (3a'R,6a'S)-3'-methylenehexahydro-5'H-spiro[cyclopropane-1,1'-pentalene]-5',5'-dicarboxylate (17j) [73]



17j

62% yield. Colourless oil. **^{1}H NMR (300 MHz, $CDCl_3$)** δ (ppm): 4.79 (2H, t, *J* = 0.8 Hz), 4.20-4.11 (4H, m), 3.15 (1H, m), 2.76 (1H, dd, *J* = 15.8 y 1.9 Hz), 2.66 (1H, ddd, *J* = 13.4, 8.8 y 1.8 Hz), 2.31 (1H, ddd, *J* = 12.9, 7.9 y 1.4 Hz), 2.13 (1H, q, *J* = 9.2 Hz), 1.98 (2H, m), 1.83 (1H, d, *J* = 15.8 Hz), 1.26-1.20 (6H, m), 0.52-0.38 (4H, m); **^{13}C-NMR (75 MHz, $CDCl_3$)** δ (ppm): 172.1 (CO), 171.5 (CO), 155.2 (C), 106.4 (CH_2), 62.6 (C), 61.70 (CH_2), 61.68 (CH_2), 51.3 (CH), 48.9 (CH), 41.5 (CH_2), 41.3 (CH_2), 38.9 (CH_2), 25.5 (CH_2), 15.8 (CH_2), 14.4 (CH_3), 7.5 (CH_2);). **HRMS** (APCI-TOF): calculated for $C_{17}H_{25}O_4$ $[M + H]^+$: *m/z* 293.1753 found 293.1744.

3-cyclopropyl-1-tosyl-2,3,3a,6,7,7a-hexahydro-1H-indole (17k')

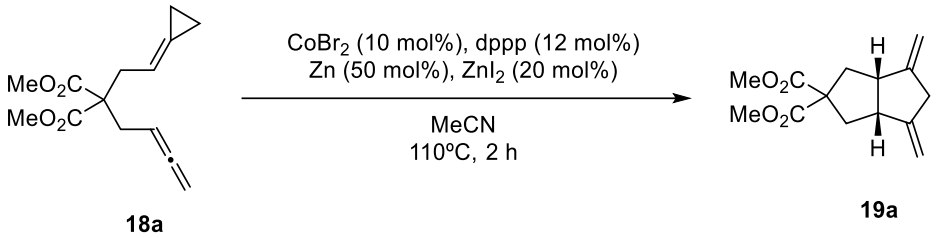


17k'

Reaction was carried out for 72hours. 71% yield. White solid. **^{1}H NMR (300 MHz, $CDCl_3$)** δ (ppm): 7.71 (d, *J* = 8.2 Hz, 2H), 7.29 (d, *J* = 8.2 Hz, 2H), 6.00 – 5.87 (m, 1H), 5.67 – 5.57 (m, 1H), 3.75 (t, *J* = 4.3 Hz, 1H), 3.44 (dd, *J* = 11.0, 7.1 Hz, 1H), 3.29 – 3.03 (m, 1H), 2.61 (dt, *J* = 6.5, 3.6 Hz, 1H), 2.42 (s, 3H), 2.22 (ddt, *J* = 11.3, 9.0, 3.9 Hz, 2H), 1.93 (dd, *J* = 14.1, 6.8 Hz, 2H), 1.78 – 1.55 (m, 3H), 0.84 (tt, *J* = 9.8, 6.8 Hz, 2H), 0.58 – 0.47 (m, 2H), 0.02 – -0.15 (m, 2H). **^{13}C-NMR (75 MHz, $CDCl_3$)** δ (ppm): 143.1 (C), 135.1 (C), 130.4 (CH), 129.5 (CH), 127.4 (CH), 124.3 (CH), 59.4 (CH), 52.6 (CH_2), 47.4 (CH), 42.1 (CH), 26.8 (CH_2), 21.4 (CH), 20.3 (CH_2), 9.1 (CH), 4.4 (CH_2), 3.2 (CH_2). **HRMS** (APCI-TOF): calculated for $C_{18}H_{24}NO_2S$ $[M+H]^+$ *m/z* 317,1499 found 317,1450.

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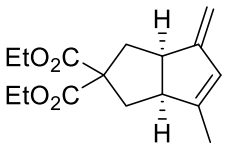
3.3. General procedure for the (3+2) cycloaddition between ACPs and allenes (exemplified for 19a).



18a **19a**

$CoBr_2$ (2.2 mg, 0.01 mmol), dppp (4.7 mg, 0.012 mmol), Zn (2.3 mg, 0.05 mmol) and $ZnBr_2$ (7.1 mg, 0.02 mmol) were successively added to a dried Schlenk tube under Argon. Then, **18a** (27.7 mg, 0.1 mmol) in MeCN (1 mL) was added under Ar atmosphere and the resulting mixture was stirred for 2 h at 110 °C before it was filtered through a short pad of Florisil® and concentrated under vacuum. The residue was purified by flash column chromatography (10 % Et_2O / hexanes) to give 17 mg of **2a** (62% yield) as a colourless oil. [75] **^{1}H NMR (300 MHz, $CDCl_3$)** δ (ppm): 4.87 (2H, s), 4.84 (2H, s), 4.19 (2H, q, J = 7.1 Hz), 4.13 (2H, q, J = 7.1 Hz), 3.26-3.03 (4H, m), 2.57 (2H, m), 2.09 (2H, dd, J = 13.8 and 7.1 Hz), 1.25 (3H, t, J = 7.1 Hz), 1.22 (3H, t, J = 7.1 Hz); **^{13}C-NMR (75 MHz, $CDCl_3$)** δ (ppm): 172.0 (CO), 171.4 (CO), 152.8 (C), 106.6 (CH2), 62.6 (C), 61.4 (CH2), 61.3 (CH2), 48.9 (CH), 40.2 (CH2), 39.9 (CH2), 14.0 (CH3). **HRMS** (APCI-TOF): calculated for $C_{16}H_{23}O_4$ 279.1596, found 279.1588.

Diethyl (3aR,6aS)-6-methyl-4-methylene-3,3a,4,6a-tetrahydropentalene-2,2(1H)-dicarboxylate (19a') [75]

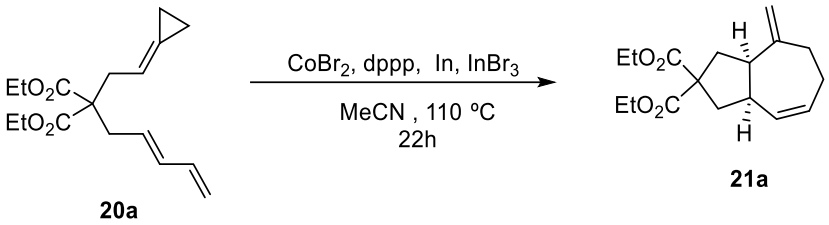


19a'

60% yield when the reaction was left for 5 h. Colourless oil. **^{1}H NMR (300 MHz, $CDCl_3$)** δ (ppm): 5.69 (1H, s), 4.73 (1H, s), 4.62 (1H, s), 4.18 (2H, q, *J* = 7.0 Hz), 4.10 (2H, q, *J* = 7.1 Hz), 3.27-3.12 (2H, m), 2.63- 2.54 (1H, m), 2.43-2.34 (1H, m), 2.12-2.02 (2H, m), 1.79 (3H, s), 1.24 (3H, t, *J* = 7.1 Hz), 1.21 (3H, t, *J* = 7.2 Hz).**^{13}C-NMR (75 MHz, $CDCl_3$)** δ (ppm): 172.1 (C), 171.3 (C), 158.21, 151.32, 128.9 (CH), 101.5 (CH_2), 62.16, 61.5 (CH_2), 61.3 (CH_2), 52.9 (CH), 46.5 (CH), 41.0 (CH_2), 37.2 (CH_2), 15.6 (CH_3), 14.1 (CH_3), 14.0 (CH_3). **HRMS** (APCI-TOF): calculated for $C_{16}H_{23}O_4$ 279.1596, found 279.1588.

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3.4. General procedure for the (3+2) cycloaddition between ACPs and allenes (exemplified for 21a).



20a **21a**

$CoBr_2$ (2.2 mg, 0.01 mmol), dppp (4.7 mg, 0.012 mmol), In (5.9, 0.05 mmol) and $InBr_3$ (7.1 mg, 0.02 mmol) were successively added to a dried Schlenk tube under Argon. Then, **20a** (27.7 mg, 0.1 mmol) in MeCN (1 mL) was added under Ar atmosphere and the resulting mixture was stirred for 22 h at 120 °C before it was filtered through a short pad of Florisil® and concentrated under vacuum. The residue was purified by flash column chromatography (10 % Et_2O / hexanes) to give 17 mg of **2a** (62% yield) as a colourless oil.[90] **^{1}H NMR (300 MHz, $CDCl_3$)** δ (ppm): 5.51 (1H, m), 5.35 (1H, dd, *J* = 11.4, 2.4 Hz), 4.79 (1H, s), 4.74 (1H, s), 4.19-4.13 (4H, m), 3.03 (1H, m), 2.93 (1H, m), 2.47 (1H, dd, *J* = 7.3, 6.5 Hz), 2.41 (1H, dd, *J* = 7.1, 6.7 Hz), 2.38-2.10 (8H, m), 1.24-1.20 (6H, m); **^{13}C-NMR (75 MHz, $CDCl_3$)** δ (ppm): 172.6 (CO), 172.1 (CO), 150.4 (C), 132.3 (CH), 128.8 (CH), 110.9 (CH_2), 61.4 (CH_2), 61.4 (CH_2), 59.0 (C), 49.7 (CH), 41.2 (CH_2) 41.0 (CH), 37.8 (CH_2), 33.8 (CH_2), 29.5 (CH_2), 14.1 (CH_3), 14.0 (CH_3); **HRMS** (APCI-TOF): calculated for $C_{17}H_{25}O_4$ $[M+H]^+$ *m/z* 293.1753, found 293.1754.

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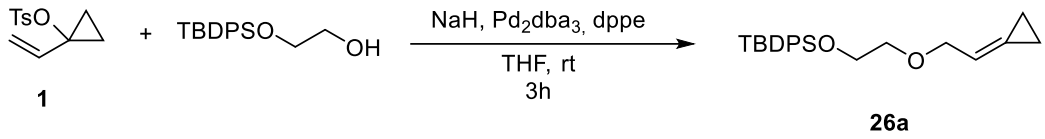
CHAPTER II

Pd catalysed Intermolecular (3+2) Hetereocycloadditions of ACPs and carbonyls

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1. Synthesis of Precursors for the Intermolecular (3 + 2) Heterocycloaddition

Tert-butyl(2-(2-cyclopropylideneethoxy)ethoxy)diphenylsilane (26a)

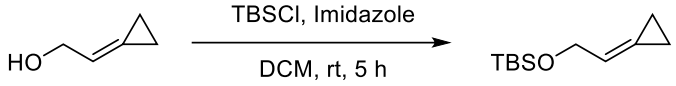


1 **26a**

2-((tert-butyldiphenylsilyl)oxy)ethan-1-ol was added dropwise over a suspension of NaH (0.127 g, 3.16 mmol) in THF (3.8 mL) at 0°C. After stirring for 10 min at rt, a solution of Pd_2dba_3 (50.3 mg, 0.06 mmol), dppe (46.0 mg, 0.12 mmol) and tosylate 1 (685 mg, 2.34 mmol) in THF (11 mL)-previously stirred for 10 minutes was added via cannula. The resulting mixture was further stirred for 3h and then the reaction was quenched with $NH_4Cl_{(sat)}$, extracted with Et_2O (3x30 mL). The organic layers were dried, evaporated and the resulting crude was purified by flash chromatography (5% Et_2O/ Hexanes) to yield *tert*-butyl(2-(2-cyclopropylideneethoxy)ethoxy)diphenylsilane **26a** (0.750 mg, 2.05 mol, 89% yield) as a colourless oil. **^{1}H NMR (300 MHz, $CDCl_3$)** δ (ppm): 7.79 – 7.74 (m, 4H), 7.52 – 7.36 (m, 6H), 6.25 – 5.48 (m, 1H), 4.33 – 4.09 (m, 2H), 3.89 (t, *J* = 5.5 Hz, 2H), 3.63 (t, *J* = 5.4 Hz, 2H), 1.13 (s, 13H). **^{13}C-NMR (75 MHz, $CDCl_3$)** δ (ppm): 135.74 (CH), 133.84 (C), 129.70 (CH), 127.73 (CH), 126.60 (C), 115.13 (CH), 71.50 (CH_2), 71.21 (CH_2), 63.64 (CH_2), 26.94 (CH_3), 19.32 (C), 2.37 (CH_2), 1.85 (CH_2). **HRMS** (ESI-TOF): m/z calculated for $C_{23}H_{30}O_2Si$ $[M+H]^+$: *m/z* 367.2087, found 367.2088.

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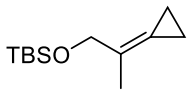
Tert-butyl(2-cyclopropylideneethoxy)dimethylsilane (26b)



26b

Imidazole (1.09 g, 12.96 mmol) and TBSCl (2.92 mL, 19.43 mmol) were successively added over a solution of 2-cyclopropylideneethan-1-ol [81b] (1.5 g, 10.69 mmol) in CH_2Cl_2 (11 mL) at 0°C. The mixture was stirred for 5 h, quenched with $NH_4Cl_{(sat)}$, extracted with Et_2O (3x60 mL). The organic layers were dried and concentrated to give a residue that was purified by flash column chromatography (5 % EtOAc/Hexane) to yield tert-butyl(2-cyclopropylideneethoxy)dimethylsilane **26b** (2.54 g, 10.76 mmol, 99%) as a colourless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 5.95 – 5.85 (m, 1H), 4.30 (d, J = 6.3 Hz, 2H), 1. 05 (s, 4H), 0.91 (s, 9H), 0.07 (s, 6H). **^{13}C-NMR (75 MHz, $CDCl_3$)** δ (ppm): 123.6 (C), 117.8 (CH), 63.9 (CH_2), 26.0 (CH_3), 18.5 (C), 1.99 (CH_2), 1.72 (CH_2) -5.08 (CH_3). **HRMS** (APCI-TOF): m/z calculated for $C_{11}H_{22}OSi$ $[M+H]^+$: *m/z* 199.1513, found 199.1513.

***tert*-Butyl(2-cyclopropylidenepropoxy)dimethylsilane (26c)**



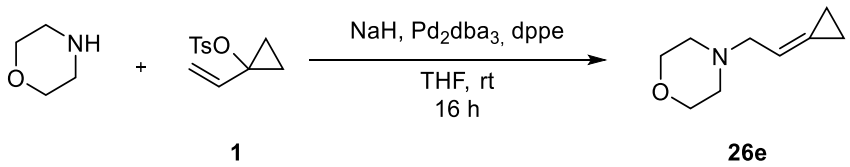
26c

Compound **26c** was synthesized following the abovementioned procedure for **26b**, from 2-cyclopropylidenepropan-1-ol.[159] 60% yield, colourless oil. **^{1}H NMR (300 MHz, $CDCl_3$)** δ (ppm): 4.27 (s, 2H), 1.87 (s, 3H), 1.1-0.95 (m, 4H), 0.94 (s, 9H), 0.09 (s, 6H). **^{13}C-NMR (75 MHz, $CDCl_3$)** δ (ppm): 123.9 (C), 117.4 (C), 67.1 (CH_2), 25.9(CH_3), 18.4 (C), 17.7 (CH_3), 2.43 (CH_2), 1.21 (CH_2) -5.3 (CH_3) . **HRMS** (APCI-TOF): m/z calculated for $C_{11}H_{22}OSi$ $[M+H]^+$: *m/z* 213.1669, found 213.1669.

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[159] Nemoto, H.; Ishibashi, H.; Nagamochi, M.; Fukumoto, K. *J. Org. Chem*. **1992**, *57*, 1707-1712.

4-(2-Cyclopropylideneethyl)morpholine (26e)

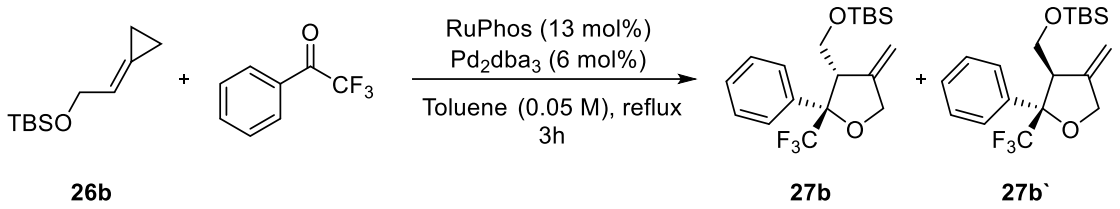


1 **26e**

Morpholine (165 µL, 1.89 mmol) was added over a suspension of NaH (70 mg, 1.76 mmol) in THF (5mL) at 0°C. After stirring for 10 min at rt, a solution of Pd_2dba_3 (23.3 mg, 0.03 mmol, 2 mol%), dppe (20.0 mg, 0.05 mmol, 4 mol%) and tosylate 13 (300 mg, 1.26 mmol) in THF (4 mL), previously stirred for 10 minutes, was added via cannula. The resulting mixture was further stirred for 16 h and then the reaction was quenched with $NH_4Cl_{(sat)}$, extracted with Et_2O (3x30 mL) and the organic layers were dried and evaporated under reduced pressure. The crude was purified by flash chromatography (60% Et_2O/Pentane) to yield 4-(2-cyclopropylideneethyl)morpholine **26e** (144 mg, 0.93 mmol, 74 % yield) as a yellow liquid. **^{1}H NMR (300 MHz, $CDCl_3$)** δ (ppm): 5.83 (td, *J* = 7.0, 3.9 Hz, 1H), 3.70 (t, *J* = 4.2 Hz, 4H), 3.10 (d, *J* = 6.9 Hz, 2H), 2.53 – 2.34 (m, 4H), 1.05 (q, *J* = 5.8 Hz, 4H). **^{13}C-NMR (75 MHz, $CDCl_3$)** δ (ppm): 126.2 (C), 114.0 (CH), 67.0 (CH_2), 60.3 (CH_2), 53.5 (CH_2), 2.4 (CH_2), 1.8(CH_2). **HRMS** (ESI-TOF): m/z calculated for $C_9H_{15}NO$ $[M+H]^+$: 154.1226, found 154.227.

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2. General Procedure for the Intermolecular Reaction Between Trifluoromethylketones and ACPs (exemplified for 27b)

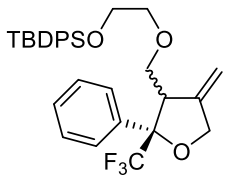


26b **27b** **27b`**

In a dried Schlenck tube, Pd_2dba_3 (7.8 mg, 0.01 mmol), RuPhos (9.1 mg, 0.02 mmol), tert-butyl(2-cyclopropylideneethoxy)dimethylsilane **26b** (28 mg, 0.14 mmol) and 2,2,2-trifluroacetophenone (43 µL , 0.29 mmol) were dissolved in freshly distilled toluene (3 mL, 0.05 M), and the mixture was refluxed while stirring for 3 h. Then the reaction was cooled down to rt, diluted with Et_2O and filtered through a short pad of Fluorisil®. The resulting organic phase was evaporated and purified by flash chromatography (1% EtOAc/Hexane) to afford the corresponding cycloadduct as a mixture of isomers **27b** + **27b'** as a colourless oil (50 mg, 0.13 mmol, 95 % yield, dr = 1.1 : 1.[**NOTE:** in all cases the diastereomeric ratio was determined in the crude residue comparing the integration of the diastereoisomers in the ^{19}F-NMR] **^{1}H NMR (300 MHz, C_6D_6)** δ (ppm): 7.77 (d, *J* = 7.7 Hz, 0.9H), 7.60 (d, *J* = 7.2 Hz, 1.1H), 7.14-7.02 (m, 3H), 5.07 (d, *J* = 2.3 Hz, 0.45H), 4.98 (d, *J* = 2.3 Hz, 0.55H), 4.76 (d, *J* = 2.3 Hz, 0.55H), 4.62 (d, *J* = 2.3 Hz, 0.45H), 4.56 (s, 1.1 H), 4.46 (dd, *J* = 12.8, 2.1 Hz, 0.45H), 4.37 – 4.29 (m, 0.45H), 4.24 (d, *J* = 12.6 Hz, 0.45H), 4.00 (ddd, *J* = 10.5, 7.9, 1.3 Hz, 0.45H), 3.39 – 3.23 (m, 1.55H), 3.19 – 3.13 (m, 0.55H), 0.96 (s, 4.05H), 0.81 (s, 4.95H), 0.04 (s, 2.7H), -0.23 (s, 1.65H), -0.33 (s, 1.65H). **^{13}C-NMR (75 MHz, C_6D_6)** δ (ppm): 148.8 ($C_{(27b)}$), 147.2 ($C_{(27b')}$), 138.4 (C), 135.1 (C), 128.8 (CH), 128.4 (CH), 127.5 ($CH_{(27b)}$), 127.2 ($CH_{(27b')}$), 124.9 (C), 124.0 (C), 106.6 ($CH_{2(27b')}$), 105.9 ($CH_{2(27b)}$), 87.9 ($C_{(27b)}$), 87.6 ($C_{(27b')}$), 72.9 ($CH_{2(27b)}$), 71.3 ($CH_{2(27b')}$), 63.7 ($CH_{2(27b)}$) , 62.3 ($CH_{2(27b')}$), 55.5 ($CH_{(27b)'}$), 50.2 ($CH_{(27b)}$), 26.03 (CH_3), 25.96 ($CH_{3(27b)}$), 18.4 ($C_{(27b')}$), 18.2 ($C_{(27b)}$), -5.48 ($CH_{3(27b')}$), -5.50 ($CH_{3(27b)}$), -5.90 ($CH_{3(27b)}$). **^{19}F-NMR (282 MHz, $CDCl_3$)** δ (ppm): -73.09, -77.28. **HRMS** (APCI-TOF): *m/z* calculated for $C_{19}H_{27}F_3O_2Si$ $[M+H]^+$: 373.1805, found 373.1809.

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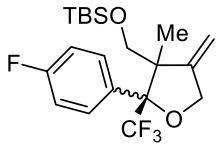
tert-Butyl(2-((4-methylene-2-phenyl-2-(trifluoromethyl)tetrahydrofuran-3-yl)methoxy) ethoxy)diphenylsilane (27a+27a')



27a + 27a'

93% yield, **27a** : **27a'** ratio = 1.4 : 1; colourless oil. **^{1}H NMR (300 MHz, $CDCl_3$)** δ (ppm): 7.75-7.63 (m, 5H), 7.56-7.50 (m, 1H), 7.48-7.29 (m, 9H), 5.31 (d, *J* = 2.5 Hz, 0.45H), 5.20 (d, *J* = 2.2 Hz, 0.55H), 5.08 (d, *J* = 2.2 Hz, 0.55H), 4.99 (d, *J* = 2.5 Hz, 0.45H), 4.80-4.56 (m, 2H), 4.15 (dd, *J* = 9.7, 5.0 Hz, 0.45H), 3.88 (q, *J* = 5.1 Hz, 1.55H), 3.70 (dd, *J* = 5.9, 4.4 Hz, 0.9H) 3.63 (t, *J* = 5.2 Hz, 1.1H), 3.43 (d, *J* = 5.9 Hz, 1.1H), 3.32 (dd, *J* = 9.5, 4.9 Hz, 0.45H), 3.25-3.07 (m, 1.45H), 1.10 (s, 4.05H), 1.05 (s, 4.95H). **^{13}C-NMR (75 MHz, $CDCl_3$)** δ (ppm): 147.3 (C), 147.2 (C), 135.6 (CH), 135.6 (CH), 129.6 (CH), 128.6 (CH), 128.3 (CH), 128.2 (CH), 127.8 (CH), 127.7 (CH), 127.6 (CH), 126.8 (CH), 126.8 (CH), 126.6 (CH), 106.8 (CH_2), 106.2 (CH_2), 87.9 (C), 86.6 (C), 72.7 (CH_2), 72.5 (CH_2), 72.2 (CH_2), 71.5 (CH_2), 71.1 (CH_2), 70.2 (CH_2), 63.5 (CH_2), 63.2 (CH_2), 52.4 (CH), 47.9 (CH), 26.8 (CH_3), 26.7 (CH_3), 19.2 (C), 19.1 (C). **^{19}F-NMR (282 MHz, $CDCl_3$)** δ (ppm): -73.37, -76.86 **HRMS** (APCI-TOF): *m/z* calculated for $C_{31}H_{35}F_3O_3Si$ $[M+H]^+$: 540.2308, found for 540.2311.

((2S,3R)-2-(4-Fluorophenyl)-3-methyl-4-methylene-2-(trifluoromethyl)tetrahydrofuran-3-yl) methanol (27c + 27c')

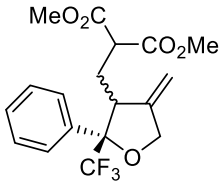


27c + 27c'

60% yield, as an inseparable mixture of **27c** and **27c'** (1:2) as a colourless oil. **^{1}H NMR (300 MHz, $CDCl_3$)** δ (ppm): 7.83 (dd, *J* = 8.8, 5.5 Hz, 1.66H), 7.03 (dt, *J* = 13.1, 8.8 Hz, 2.34H), 5.05 – 4.85 (m, 2H), 4.83 – 4.60 (m, 2H), 4.08 (d, *J* = 10.7 Hz, 0.66H), 3.86 (d, *J* = 10.2 Hz, 0.66H), 3.04 (d, *J* = 9.6 Hz, 0.34H), 2.90 (d, *J* = 9.6 Hz, 0.34H), 1.43 (d, *J* = 2.2 Hz, 1H), 0.96 (s, 6.0 H), 0.82 (s, 2H), 0.76 (s, 3H) 0.13 (d, *J* = 2.9 Hz, 4H), -0.23 (d, *J* = 12.3 Hz, 2H). **^{13}C-NMR (75 MHz, $CDCl_3$)** δ (ppm): 153.2 (C), 129.9 (CH), 129.8 (CH), 114.5 (CH), 114.2 (CH), 104.4 (CH_2), 103.1 (CH_2), 71.8 (CH_2), 71.0 (CH_2), 68.0 (CH_2), 65.6 (CH_2), 52.03, 51.65, 25.9 (CH_3), 25.8 (CH_3), 25.7 (CH_3), 23.9 (CH_3), 18.4 (C), 18.1 (C), 16.3 (CH), -5.37 (CH_3), -5.69 (CH_3), -5.92 (CH_3), -6.01 (CH_3). **^{19}F-NMR (282 MHz, $CDCl_3$)** δ (ppm): -72.59, -72.83, -114.94, -114.99; **HRMS** (APCI-TOF): *m/z* calculated for $C_{20}H_{28}F_4O_2Si$ $[M+H]^+$: 405.1797 found, 405.1803.

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Dimethyl 2-((4-methylene-2-phenyl-2-(trifluoromethyl)tetrahydrofuran-3-yl)methyl) malonate (27d + 27d')



27d + 27d'

74% yield as an inseparable mixture of **27d** and **27d'** (1.8 : 1) as a colourless oil. **^{1}H NMR (300 MHz, $CDCl_3$)** δ (ppm): 7.56 - 7.47 (m, 2H), 7.47 – 7.32 (m, 3H), 5.10 (s, 0.65H), 5.06 (s, 0.65H), 4.94 (s, 0.7H), 4.78 – 4.60 (m, 1.65H), 4.47 (d, *J* = 12.7 Hz, 0.35H), 3.79 (s, 1.95H), 3.75 (s, 1.05H), 3.72 (s, 1.05H), 3.62 (s, 1.95H), 3.57 – 3.44 (m, 0.65H), 3.21 – 3.03 (m, 1H), 2.63 (t, *J* = 12.4 Hz, 0.35H), 2.24 (t, *J* = 11.4 Hz, 0.35H), 1.90 (t, *J* = 11.9 Hz, 0,65H), 1.29 – 1.15 (m, 1H). **^{13}C-NMR (75 MHz, $CDCl_3$)** δ (ppm): 169.7 (C), 169.6(C), 147.7 (C), 146.6 (C), 137.8 (C), 134.4 (C), 129.0 (CH), 128.9, 128.6 (CH), 128.4 (CH), 127.3 (CH), 126.4 (CH), 108.4 (CH_2), 108.0 (CH_2), 71.9 (CH_2), 70.9 (CH_2), 53.0 (CH_3), 52.9 (CH_3), 51.5 (CH), 50.0 (CH), 49.0 (CH), 46.1 (CH), 29.0 (CH_2), 27.7 (CH_2). **^{19}F-NMR (282 MHz, $CDCl_3$)** δ (ppm): -71.85, -76.41. **HRMS** (APCI-TOF): m/z calculated for $C_{18}H_{19}F_3O_5$ $[M+H]^+$: 373.1254, found 373.1257. Stereochemistry of **27d** and **27d'** was determined by noe experiments:

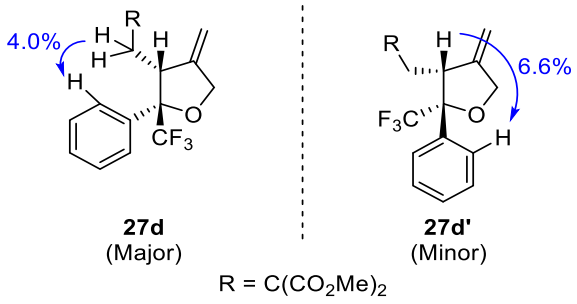
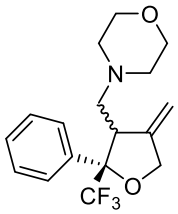


***Figure S26**. Noe experiments to determine the major diastereosiomer.*

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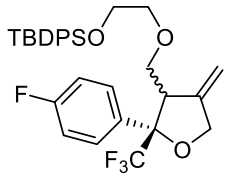
4-((4-Methylene-2-phenyl-2-(trifluoromethyl)tetrahydrofuran-3-yl)methyl)morpho-line (27e + 27e')



27e + 27e'

90% yield, as an inseparable mixture of **27e** and **27e'** (1.7 : 1) as a yellowish oil . **^{1}H NMR (300 MHz, $CDCl_3$)** δ (ppm): 7.76 (d, *J* = 7.0 Hz, 0.7H), 7.56 (d, *J* = 6.8 Hz, 1.3H), 7.45 – 7.30 (m, 3H), 5.35 (s, 0.35H), 5.20 (s, 0.65H), 5.10 (s, 0.65H), 5.00 (s, 0.35H), 4.72 (s, 1.3H), 4.66 (d, *J* = 8.5Hz, 0.7H), 3.72 (d, *J* = 4.0 Hz, 1.4H), 3.63 (s, 2.6H), 3.38 (t, *J* = 7.1Hz, 0.65H), 3.20 (t, *J* = 8.3Hz, 0.35H), 3.01 (dd, *J* = 13.3, 5.4 Hz, 0.35H), 2.78 (dd, *J* = 13.0, 8.7 Hz, 0.35H), 2.6-2.4 (m, 1.4H), 2.3-2.15 (m, 2.6H), 2.13-1.95 (m, 1.4). **^{13}C-NMR (75 MHz, $CDCl_3$)** δ (ppm): 148.4 (C), 147.7 (C), 134.7 (C), 128.5 (CH), 128.3 (CH), 128.1 (CH), 127.7 (CH), 127.2 (CH), 126.5 (CH), 106.6 (CH_2), 105.5 (CH_2), 72.4 (CH_2), 71.7 (CH_2), 66.98 (CH_2), 66.94 (CH_2), 59.1 (CH_2), 58.1 (CH_2), 53.8 (CH_2), 53.7 (CH_2), 48.8 (CH), 44.5 (CH). **^{19}F-NMR (282 MHz, $CDCl_3$)** δ (ppm): -72.55, -76.35; **HRMS** (APCI-TOF): m/z calculated for $C_{17}H_{20}F_3NO_2$ $[M+H]^+$: 328.1517, found 328.1512.

***tert*-Butyl(2-((2-(4-fluorophenyl)-4-methylene-2-(trifluoromethyl)tetrahydrofuran-3-yl)oxy)etho-xy)diphenylsilane (27f + 27f')**

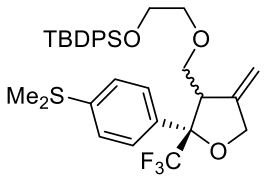


27f + 27f'

90% yield, **27f : 27f'** ratio = 1.3 : 1; colourless oil. **^{1}H NMR (300 MHz, $CDCl_3$)** δ (ppm): 7.68 (ddt, *J* = 15.8, 7.9, 1.7 Hz, 5H), 7.55 – 7.33 (m, 7.45H), 7.01 (dt, *J* = 10.6, 8.7 Hz, 1.55H), 5.26 (q, *J* = 2.4 Hz, 0.45H), 5.18 (q, *J* = 2.2 Hz, 0.55H), 5.07 (q, *J* = 2.0 Hz, 0.55H), 4.99 (q, *J* = 2.3 Hz, 0.45H), 4.80 – 4.52 (m, 1.55H), 4.07 (t, *J* = 6.8 Hz, 0.45H), 3.91 – 3.78 (m, 1.55H), 3.73 – 3.49 (m, 2.55H), 3.44 – 3.02 (m, 2.9H), 1.07 (s, 4.95H), 1.03 (s, 4.05H). **^{13}C-NMR (75 MHz, $CDCl_3$)** δ (ppm): 164.4 (C), 164.2 (C), 161.1 (C), 160.9 (C), 147.1 (C), 147.0 (C), 135.5 (CH), 133.5(CH), 133.5(CH), 130.2 (C), 129.6 (CH), 128.7 (CH), 127.6 (CH), 123.92 (C), 115.2 (CH), 114.9 (CH), 114.5 (CH), 106.8 (CH_2), 106.1 (CH_2), 87.7 (C), 87.4 (C), 72.7 (CH_2), 72.5 (CH_2), 72.2 (CH_2), 71.5 (CH_2), 71.1 (CH_2), 70.13 (C), 63.5 (CH_2), 63.22 (CH_2), 52.3 (CH), 48.0 (CH), 26.7 (CH_3), 19.2 (C), 19.1 (C). **^{19}F-NMR (282 MHz, $CDCl_3$)** δ (ppm): -73.28, -76.73, -113.70, -113.89. **HRMS** (APCI-TOF): *m/z* calculated for $C_{31}H_{34}F_4O_3Si$ $[M+H]^+$: 559.2398, found *m/z* 559.2396.

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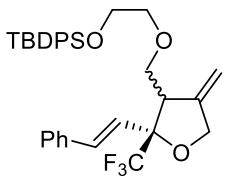
tert-Butyl(2-((4-methylene-2-(4-(methylthio)phenyl)-2-(trifluoromethyl)tetrahydro furan-3-yl)methoxy)ethoxy)diphenylsilane (27g + 27g')



27g + 27g'

80% yield, **27g : 27g'** ratio = 1.5 : 1; colourless oil. **^{1}H NMR (300 MHz, $CDCl_3$)** δ (ppm): 8.00 (d, J = 8.3 Hz, 0.8H), 7.73 (d, J = 6.3 Hz, 1.4H), 7.68 (d, J = 7.8 Hz, 2H), 7.60 (d, J = 8.2 Hz, 0.8H), 7.53 – 7.32 (m, 7H), 7.27 (d, J = 7.1 Hz, 0.6H) 7.21 (d, J = 8.5 Hz, 1.4H), 5.29 (s, 0.4H), 5.21 (s, 0.6H), 5.08 (s, 0.6H), 5.00 (s, 0.4H), 4.79-4.56 (m, 2H), 4.10 (dd, J = 9.5, 5.5 Hz, 0.6H), 3.92 – 3.85 (m, 1.2H), 3.71 – 3.62 (m, 2H), 3.45 – 3.09 (m, 3.2H), 2.57 (s, 1.2H), 2.50 – 2.46 (m, 1.8H), 1.09 (s, 3.6H), 1.05 (s, 5.4H). **^{13}C-NMR (75 MHz, $CDCl_3$)** δ (ppm): 147.1 (C), 147.0 (C), 139.3 (C), 138.9 (C), 135.6 (CH), 133.4 (CF3), 129.7 (CH), 127.9 (CH), 127.8 (CH), 127.7 (CH), 127.3 (CH), 127.2 (CH), 125.8 (CH), 125.5 (CH), 125.2 (CH), 124.9 (C), 120.5 (CH), 106.9 (CH_2), 106.2 (CH_2), 96.3 (CH), 72.7 (CH_2), 72.5 (CH_2), 72.3 (CH_2), 71.5 (CH_2), 71.0 (CH_2), 70.1 (CH_2), 69.3 (CH_2), 63.5 (CH_2), 63.3 (CH_2), 63.1 (CH_2), 52.3 (CH), 47.8 (CH), 31.2 (CH_2), 26.8 (CH_3), 26.7 (CH_3), 23.1 (CH), 19.2 (C), 19.1 (C), 15.4 (CH_3), 15.2 (CH_3). **^{19}F-NMR (282 MHz, $CDCl_3$)** δ (ppm **HRMS** (APCI-TOF): *m/z* calculated for $C_{32}H_{37}F_3O_3SSi$ $[M+H]^+$: 587.2519, found *m/z* 587.2523.

(E)-_tert_-butyl(2-((4-methylene-2-styryl-2-(trifluoromethyl)tetrahydrofuran-3-yl)oxy) ethoxy) diphenylsilane (27i + 27i')

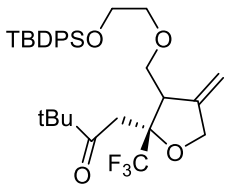


27i + 27i'

65% yield, **27i** : **27i'** ratio = 3 : 1; colourless oil. **^{1}H NMR (300 MHz, $CDCl_3$)** δ (ppm): 7.68 (d, *J* = 6.4 Hz, 4H), 7.46-7.33 (m, 7H), 7.32-7.17 (m, 4H), 6.98 (d, *J* = 16.0 Hz, 0.25 H), 6.91 (d, *J* = 15.9 Hz, 0.75 H), 6.43 (d, *J* = 16.0 Hz, 0.25 H), 6.29 (d, *J* = 15.9 Hz, 0.75 H), 5.20-5.10 (m, 1H), 5.08-5.04 (m, 0.75H), 5.01-4.95 (m, 0.25H), 4.72-4.54 (m, 2H), 3.85 (t, *J* = 5.1Hz, 1H), 3.77 (t, *J* = 5.0 Hz, 1.25H), 3.52 – 3.44 (m, 2.25H), 3.38-3.28 (m, 1H), 3.28-3.23 (m, 0.75H), 3.16 (dd, *J* = 9.1, 5.4 Hz, 0.75H), 1.05 (s, 9H) **^{13}C-NMR (75 MHz, $CDCl_3$)** δ (ppm): 146.54 (C), 135.98 (C), 135.63 (CH), 135.61 (CH), 133.63 (C), 132.7 (CH), 129.67 (CH), 128.6 (CH) , 128.0 (CH) , 127.6 (CH), 126.9 (CH) , 126.8 (CH), 121.2 (CH), 107.0 (CH_2), 72.7 (CH_2), 72.3 (CH_2), 72.2 (CH_2), 71.3 (CH_2), 63.5 (CH_2), 47.85 (CH) , 26.7 (CH_3) , 19.18 (C). **^{19}F-NMR (282 MHz, $CDCl_3$)** δ (ppm): -74.63, -79.51. **HRMS** (APCI-TOF): *m/z* calculated for $C_{33}H_{39}F_3O_3Si$ $[M+H]^+$: 567.2538, found 567.2534

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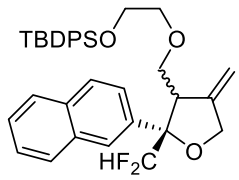
1-(3-(2-((tert-Butyldiphenylsilyl)oxy)ethoxy)-4-methylene-2-(trifluoromethyl)tetra hydrofuran -2-yl)-2,2-dimethylpropan-1-one (27j + 27j')



27j + 27j'

57% yield, **27**j : **27j'** ratio = 2 : 1; colourless oil. **^{1}H NMR (300 MHz, $CDCl_3$)** δ (ppm):7.70 (m, 4H), 7.40 (m, 6H), 4.95 (s, 0.33 H), 4.87 (s, 0.66H), 4.80 (s, 0.66H), 4.77 (d, *J* = 4.7 Hz, 0.33H), 4.74 (dd, *J* = 8.8, 0.33H), 3.80 (t, *J* = 5.2 Hz, 2H), 3.65-3.53 (m, 4.33H), 2.76 (dd, *J* = 15.2, 8.9 Hz, 1H), 2.52 (dd, *J* = 15.1, 4.7 Hz, 1H), 2.28 (t, *J* = 6.6 Hz, 2.33H), 1.30-1.15 (m, 9H), 1.06 (s, 9H). **^{13}C-NMR (75 MHz, $CDCl_3$)** δ (ppm): 206.7 (C), 142.3 (C), 135.6 (CH), 133.6 (CF3), 129.6 (CH), 127.6 (CH), 113.5 (CH_2), 72.2 (CH_2), 69.8 (CH_2), 68.1 (C), 63.4 (CH_2), 52.7 (CH), 45.4 (C), 36.1 (CH_2), 35.4 (CH_2), 29.7 (C), 26.8 (CH_3), 26.4 (CH_3), 19.2 (C), 15.3 (CH). **^{19}F-NMR (282 MHz, $CDCl_3$)** δ (ppm): -77.88, -83.61 **HRMS** (APCI-TOF): *m/z* calculated for $C_{31}H_{41}F_3O_4Si$ $[M+H]^+$: 563.2726, found 563.2721.

***tert*-Butyl(2-((2-(difluoromethyl)-4-methylene-2-(naphthalen-2-yl)tetrahydrofuran-3-yl)methoxy) ethoxy)diphenylsilane (27k + 27k')**



27k + 27k'

83% yield, **27k** : **27k'** ratio 1 : 1; colourless oil. **^{1}H NMR (300 MHz, $CDCl_3$)** δ (ppm): 8.08 (s, 0.48H), 7.98 (s, 0.52H), 7.90-7.81 (m, 2.48H), 7.80-7.66 (m, 4.52H), 7.59 – 7.35 (m, 9H), 6.28 (td, *J* = 55.6, 55.1, 53.6 Hz, 1H), 5.07 (d, *J* = 2.1 Hz, 0.52H), 5.06 – 5.01 (m, 1H), 4.97 (d, J = 2.2 Hz, 0.48H), 4.80 (m, 1.52H), 4.61 (d, J = 13.1 Hz, 0.48H), 4.01 (t, J = 8.9 Hz, 0.48H), 3.95 – 3.83 (m, 1.52H), 3.71 (tdd, J = 6.4, 4.8, 1.9 Hz, 2H), 3.55-3.45 (m, 1H), 3.35 (td, J = 10.2, 9.7, 5.7 Hz, 1.48H), 3.21 (dd, J = 9.5, 7.1 Hz, 0.52H), 1.10 (s, 4.32H), 1.06 (s, 4.68H) **^{13}C-NMR (75 MHz, $CDCl_3$)** δ (ppm): 147.4 (C), 146.6 (C), 135.6 (CH), 135.6 (CH), 133.5 (C), 133.5 (C), 133.0 (C), 132.9 (C), 132.8 (C), 129.7 (CH), 129.6 (CH), 128.4 (CH), 128.4 (CH), 128.0 (CH), 127.7 (CH), 127.7 (CH), 127.5 (CH), 127.5 (CH), 126.3 (CH), 126.2 (CH), 126.14, 125.9 (CH), 124.4 (CH), 124.3 (CH), 106.4 (CH2), 106.1 (CH2), 87.69 (d, JC-F = 19.6 Hz) 72.7 (CH2), 72.3 (CH2), 72.07 (CH2), 71.2 (CH2), 71.1 (CH2), 69.9 (CH2), 63.4 (CH2), 63.3 (CH2), 53.0 (CH), 47.4 (CH), 31.6 (C), 26.8 (CH3), 26.7 (CH3), 19.1 (C). **^{19}F-NMR (282 MHz, $CDCl_3$)** δ (ppm): -125.87 (dd, J = 285.4, 54.7 Hz), -128.07 (dd, J = 217.1, 55.4 Hz), -129.07 (dd, J = 208.2, 55.0 Hz), -131.46 (dd, J = 276.9, 55.5 Hz). **HRMS** (APCI-TOF): m/z calculated for $C_{34}H_{38}F_2O_3Si$ $[M+H]^+$: 572.2902, found 572.2906.

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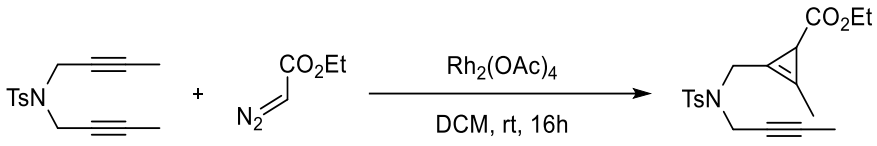
CHAPTER III:

Co catalysed intramolecular (3+2) cycloaddition of cyclopropenes and alkynes

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1. General synthesis alkyne-tethered cyclopropenes

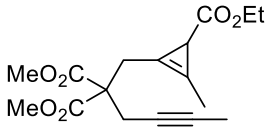
General procedure A: cyclopropenation of diynes (illustrated for **28a**)



27a **28a**

$[Rh_2(OAc)_4]$ (44.0 mg, 0.1 mmol, 1.0 mol %) was added to a flame dried Schlenk tube and freshly distilled CH_2Cl_2 (5.0 mL) was then added. The homogeneous green solution was stirred for 5 min before a solution of **27a** (2.5 g, 10 mmol) in anhydrous CH_2Cl_2 (5.0 mL) was added. Ethyl 2-diazoacetate (1.4 g, 12 mmol) in anhydrous CH_2Cl_2 (20 mL) was added to this solution through a syringe pump at a rate of 4.0 mL/h. Upon completion of addition the solvent was removed under reduced pressure. The resulting solid material was purified by flash chromatography on silica gel (8:1 Hexane:EtOAc) to provide 1.60 g of **28a** as a colourless oil (49% yield). **^{1}H NMR (300 MHz, $CDCl_3$)** δ (ppm): 7.73 (d, *J* = 8.3 Hz, 1H), 7.29 (d, *J* = 8.1 Hz, 1H), 4.33 (s, 1H), 4.17 – 4.02 (m, 1H), 2.42 (s, 1H), 2.03 (s, 1H), 1.93 (s, 1H), 1.60 (t, *J* = 2.4 Hz, 1H), 1.24 (t, *J* = 7.1 Hz, 1H). **^{13}C-NMR (75 MHz, $CDCl_3$)** δ (ppm): 175.4 (CO), 143.5 (C), 136.1 (C), 129.5 (CH), 127.9 (CH), 107.6 (C), 101.4 (C), 81.9 (C), 71.7 (C), 65.9 (C), 60.2 (CH_2), 41.7 (CH_2), 37.4 (CH_2), 23.3 (CH_3), 21.6 (CH), 14.4 (CH_3), 9.7 (CH_3), 3.4 (CH_3). **HRMS** (APCI-TOF): m/z calculated for $C_{19}H_{24}NO_4S$ $[M+H]^+$: 361.1448, found 361.1449.

Dimethyl 2-(but-2-yn-1-yl)-2-((3-(ethoxycarbonyl)-2-methylcycloprop-1-en-1-yl)methyl)malonate (28b)

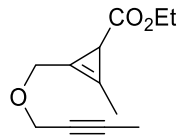


28b

40% yield, colourless oil. **^{1}H NMR (300 MHz, $CDCl_3$)** δ (ppm): 4.07 (dd, *J* = 7.2, 3.7 Hz, 2H), 3.72 (s, 6H), 3.19 (d, *J* = 1.7 Hz, 2H), 2.85 – 2.77 (m, 2H), 2.01 (d, *J* = 1.6 Hz, 2H), 1.98 (s, 1H), 1.72 (d, *J* = 2.4 Hz, 2H), 1.22 (t, *J* = 7.1 Hz, 2H). **^{13}C-NMR (75 MHz, $CDCl_3$)** δ (ppm): 175.8 (CO), 169.9 (CO), 169.8 (CO), 105.6 (C), 101.6 (C), 79.0 (C), 72.9 (C), 59.8 (CH_2), 56.1 (C), 52.8 (CH_3), 28.3 (CH_2), 23.5 (CH_2), 22.5 (CH), 14.3 (CH_3), 9.9 (CH_3), 3.3 (CH_3). **HRMS** (APCI-TOF): m/z calculated for $C_{17}H_{23}O_6$ $[M+H]^+$: 322.1466, found 322.1468.

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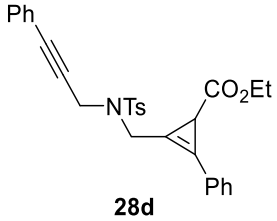
Ethyl 2-((but-2-yn-1-yloxy)methyl)-3-methylcycloprop-2-ene-1-carboxylate (28c)



28c

42% yield, colourless oil.**^{1}H NMR (300 MHz, $CDCl_3$)** δ (ppm): 4.42 (s, 2H), 4.16 – 3.92 (m, 4H), 2.12 (s, 1H), 2.06 (s, 3H), 1.79 (s, 3H), 1.18 (t, *J* = 7.1 Hz, 3H). **^{13}C-NMR (75 MHz, $CDCl_3$)** δ (ppm): 175.5 (CO), 106.5 (C), 102.8 (C), 82.8 (C), 74.5 (C), 62.2 (CH_2), 59.9 (CH_2), 57.9 (CH_2), 22.9 (CH), 14.2 (CH_3), 9.7 (CH_3), 3.4 (CH_3). **HRMS** (APCI-TOF): m/z calculated for $C_{12}H_{27}O_3$ $[M+H]^+$: 208.1099, found 208.1010.

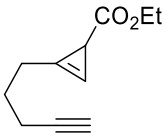
Ethyl 2-(((4-methyl-N-(3-phenylprop-2-yn-1-yl)phenyl)sulfonamido)methyl)-3-phenylcycloprop-2-ene-1-carboxylate (28d)



28d

25% yield, colourless oil.**^{1}H NMR (300 MHz, $CDCl_3$)** δ (ppm): 7.84 (d, *J* = 8.2 Hz, 2H), 7.50 (dd, *J* = 5.6, 2.2 Hz, 2H), 7.42 – 7.34 (m, 3H), 7.35 – 7.23 (m, 5H), 7.11 (d, *J* = 8.2 Hz, 2H), 4.65 (d, *J* = 3.1 Hz, 2H), 4.48 (q, *J* = 18.4 Hz, 2H), 4.13 (dt, *J* = 7.0, 3.5 Hz, 2H), 2.55 (s, 1H), 2.36 (s, 3H), 1.24 (td, *J* = 7.0, 1.6 Hz, 3H). **^{13}C-NMR (75 MHz, $CDCl_3$)** δ (ppm): 174.5 (CO), 143.9 (C), 135.9 (C), 131.6 (CH), 130.0 (CH), 129.8 (CH), 129.7 (CH), 128.9 (CH), 128.6 (CH), 128.2 (CH), 127.9 (CH), 125.9 (C), 122.2 (C), 110.5 (C), 104.4 (C), 86.2 (C), 81.5 (C), 68.3 (C), 60.5 (CH_2), 42.5 (CH_2), 37.9 (CH_2), 23.0 (CH), 21.5 (CH_3), 14.4 (CH_3). **HRMS** (APCI-TOF): m/z calculated for $C_{29}H_{28}NO_4S$ $[M+H]^+$: 485.1661, found 485.1661.

Ethyl 2-(pent-4-yn-1-yl)cycloprop-2-ene-1-carboxylate (28e)

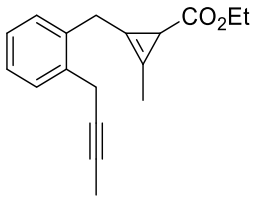


28e

42% yield. Colourless oil. **^{1}H NMR (300 MHz, $CDCl_3$)** δ (ppm): 6.38 (d, *J* = 1.5 Hz, 1H), 4.11 (qd, *J* = 7.2, 2.9 Hz, 2H), 2.63 (td, *J* = 7.3, 1.3 Hz, 2H), 2.27 (td, *J* = 7.0, 2.6 Hz, 2H), 2.13 (d, *J* = 1.5 Hz, 1H), 2.00 – 1.92 (m, 1H), 1.81 (t, *J* = 7.1 Hz, 2H), 1.30 – 1.14 (m, 5H). **^{13}C-NMR (75 MHz, $CDCl_3$)** δ (ppm): 176.4 (CO), 129.9 (C), 114.82, 95.15, 83.5 (C), 69.09, 60.3 (CH_2), 25.7 (CH_2), 24.0 (CH_2), 19.8 (CH), 17.9 (CH_2), 14.4 (CH_3). **HRMS** (APCI-TOF): m/z calculated for $C_{11}H_{15}O_2$ $[M+H]^+$: 178.0992, found 178.0994.

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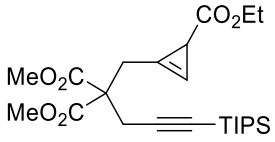
Ethyl 2-(2-(but-2-yn-1-yl)benzyl)-3-methylcycloprop-2-ene-1-carboxylate (28f)



28f

42% yield. Colourless oil.**^{1}H NMR (300 MHz, $CDCl_3$)** δ (ppm): δ 7.50 – 7.39 (m, 1H), 7.23 (d, *J* = 6.4 Hz, 3H), 4.18 – 4.01 (m, 2H), 3.90 – 3.67 (m, 2H), 3.53 (q, *J* = 2.6 Hz, 2H), 2.01 (s, 3H), 1.84 (s, 3H), 1.21 (t, *J* = 7.1 Hz, 3H). **^{13}C-NMR (75 MHz, $CDCl_3$)** δ (ppm): 176.2 (CO), 135.76, 134.86, 129.4 (CH), 128.8 (CH), 127.1 (CH), 126.9 (CH), 104.87, 103.83, 78.1 (C), 76.2 (C), 59.8 (CH_2), 28.3 (CH_2), 23.1 (CH), 22.7 (CH_2), 14.3 (CH_3), 9.5 (CH_3), 3.5 (CH_3). **HRMS** (APCI-TOF): m/z calculated for $C_{18}H_{20}O_2$ $[M+H]^+$: 268.1463, found 268.1466.

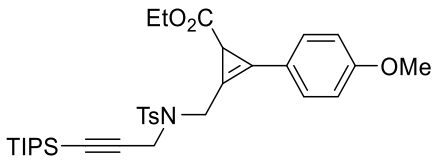
Dimethyl 2-((3-(ethoxycarbonyl)cycloprop-1-en-1-yl)methyl)-2-(3-(triisopropylsilyl)prop-2-yn-1-yl)malonate (28i)



28i

45% yield. Colourless oil.**^{1}H NMR (300 MHz, $CDCl_3$)** δ (ppm): 6.52 (d, J = 1.4 Hz, 1H), 4.12 (q, J = 7.1 Hz, 23H), 3.76 (s, 6H), 3.36 (d, J = 1.4 Hz, 2H), 3.16 – 2.78 (m, 2H), 2.12 (d, J = 1.5 Hz, 1H), 1.26 (t, J = 7.1 Hz, 3H), 1.05 (s, 21H). **^{13}C-NMR (75 MHz, $CDCl_3$)** δ (ppm): 175.4 (CO), 169.4 (CO), 169.3 (CO), 111.0 (C), 102.1 (C), 98.1 (CH), 84.5 (C), 60.2 (CH_2), 55.9 (C), 53.0 (CH_3), 52.9 (CH_3), 28.2 (CH_2), 24.5 (CH_2), 19.6 (CH), 18.5 (CH_3), 14.2 (CH_3), 11.14 (CH). **HRMS** (APCI-TOF): m/z calculated for $C_{24}H_{39}O_6Si$ $[M+H]^+$: 450.6470, found 450.6471.

Ethyl 2-(4-methoxyphenyl)-3-(((4-methyl-N-(3-(triisopropylsilyl)prop-2-yn-1-yl)phenyl)sulfonamido)methyl)cycloprop-2-ene-1-carboxylate (28j)

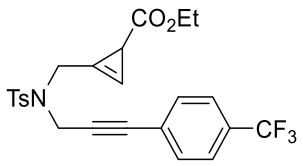


28j

25% yield. Colourless oil.**^{1}H NMR (300 MHz, $CDCl_3$)** δ (ppm): δ 7.78 (d, J = 8.5 Hz, 2H), 7.43 (d, J = 8.7 Hz, 2H), 7.28 (d, J = 8.0 Hz, 2H), 6.93 (d, J = 8.8 Hz, 2H), 4.59 (s, 2H), 4.33 (d, J = 9.6 Hz, 2H), 4.14 (q, J = 7.1 Hz,2H), 3.84 (s, 3H), 2.49 (s, 1H), 2.41 (s, 3H), 1.25 (t, J = 7.2 Hz, 3H), 1.05 – 0.88 (m, 21H). **^{13}C-NMR (75 MHz, $CDCl_3$)** δ (ppm): 174.6 (CO), 160.7 (C), 143.5 (C), 136.4 (C), 132.9 (C), 131.5 (CH), 129.7 (CH), 127.5 (CH), 118.5 (C), 114.3 (CH), 113.7 (C), 109.9 (C), 101.2 (C), 99.5 (C), 87.5 (C), 60.3 (CH_2), 55.3 (CH_3), 41.7 (CH_2), 37.6 (CH_2), 22.8 (CH_3), 21.4 (CH), 18.4 (CH_3), 14.3 (CH_3), 11.0 (CH). **HRMS** (APCI-TOF): m/z calculated for $C_{33}H_{46}NO_5SSi$ $[M+H]^+$: 592.8704, found 592.8706.

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Ethyl 2-(((4-methyl-N-(3-(4-(trifluoromethyl)phenyl)prop-2-yn-1-yl)phenyl)sulfonamido)methyl)cycloprop-2-ene-1-carboxylate (28k)

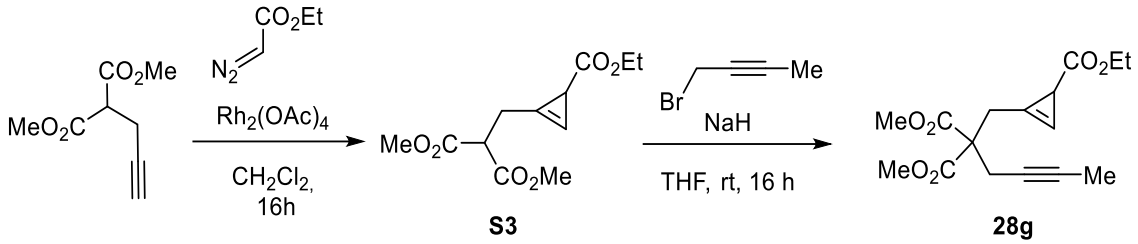


28k

55% yield. Colourless oil.**^{1}H NMR (300 MHz, $CDCl_3$)** δ (ppm): δ 7.80 (d, J = 8.0 Hz, 2H), 7.54 (d, J = 8.1 Hz, 2H), 7.29 (s, 4H), 6.58 (s, 1H), 4.52 (s, 2H), 4.45 (s, 2H), 4.13 (dt, J = 6.6, 3.3 Hz, 2H), 2.39 (d, J = 3.8 Hz, 3H), 2.25 (d, J = 3.5 Hz, 1H), 1.38 – 1.13 (m, 3H). **^{13}C-NMR (75 MHz, $CDCl_3$)** δ (ppm): 174.9 (CO), 143.9 (C), 135.8 (C), 131.8 (CH), 129.6 (CH), 127.8 (CH), 127.6 (C), 125.1 (C), 110.5 (C), 99.8 (CH), 84.5 (C), 84.3 (C), 60.4 (CH_2), 42.5 (CH_2), 37.6 (CH_2), 21.3 (CH_3), 20.5 (CH), 14.2 (CH_3). **^{19}F NMR (282 MHz, $CDCl_3$)** δ (ppm) -62.93. **HRMS** (APCI-TOF): m/z calculated for $C_{24}H_{23}F_3NO_4S$ $[M+H]^+$: 417.4985, found 417.4988.

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General procedure B: cyclopropenation of propargyl malonates followed by propargylation (illustrated for 28g)

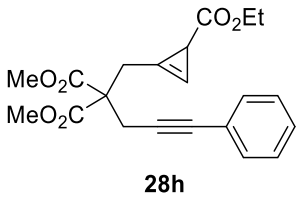


S3 **28g**

$[Rh_2(OAc)_4]$ (44.0 mg, 0.1 mmol, 1.0 mol %) and freshly distilled CH_2Cl_2 (5.0 mL) were sequentially added to a flame dried Schlenk tube. The homogeneous green solution was stirred for 5 min and a solution of propargyl dimethyl malonate (2.5 g, 10 mmol) in anhydrous CH_2Cl_2 (5.0 mL) was added. A solution of ethyl 2-diazoacetate (1.4 g, 12 mmol) in anhydrous CH_2Cl_2 (20 mL) was added through a syringe pump at a rate of 4.0 mL/h. Upon completion, the solvent was removed under reduced pressure and the resulting residue was purified by flash chromatography on silica gel (8:1 hexane:ethyl acetate) to provide **S3 (**1.3 g)as a colourless oil (52% yield).

NaH (103 mg, 2.576 mmol) was added in portions to a stirred solution of **S3** in THF anh. (9.4 mL), at 0 °C. Once the addition was completed, 1-bromo-butyne (0.30ml, 3.5 mmol) was added slowly and the mixture was allowed to warm up to room temperature and stirred overnight. The reaction was then quenched with H_2O, extracted with Et_2O (x3) and the combined organic phases were washed with brine. The organic phase was then dried over $MgSO_4$, filtered, and concentrated under vacuum. The resulting material was purified by flash chromatography on silica gel (8:1 hexane:EtOAC) to provide pure 0.33 mg of **28g** as a colourless oil (45% yield). **HRMS** (APCI-TOF): m/z calculated for $C_{16}H_{21}O_6S[M+H]^+$: 308.3312, found 308.3314.

Dimethyl 2-((3-(ethoxycarbonyl)cycloprop-1-en-1-yl)methyl)-2-(3-phenylprop-2-yn-1-yl)malonate (28h)



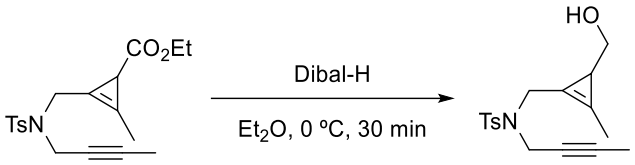
28h

Following the same procedure for **28g** using (3-bromoprop-1-yn-1-yl)benzene. 33% yield. Colourless oil. **^{1}H NMR (300 MHz, $CDCl_3$)** δ (ppm): 7.35 (dd, *J* = 6.6, 3.0 Hz, 2H), 7.26 (dd, *J* = 4.9, 2.1 Hz, 3H), 6.54 (s, 1H), 4.10 (q, *J* = 7.2 Hz, 2H), 3.77 (s, 6H), 3.37 (s, 2H), 3.13 (d, *J* = 7.6 Hz, 2H), 2.14 (s, 1H), 1.23 (t, *J* = 7.2 Hz, 3H). **^{13}C-NMR (75 MHz, $CDCl_3$)** δ (ppm): 175.4 (CO), 169.5 (CO), 169.4 (CO), 131.6 (CH), 128.2 (CH), 122.9 (C), 111.0 (C), 98.2 (CH), 83.9 (C), 83.6 (C), 60.3 (CH_2), 56.1 (C),

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53.0 (CH_3), 28.3 (CH_2), 24.0 (CH_2), 19.6 (CH), 14.2 (CH_3). **HRMS** (APCI-TOF): m/z calculated for $C_{21}H_{23}O_6$ $[M+H]^+$: 370.4010, found 370.4011.

N-(but-2-yn-1-yl)-N-((3-(hydroxymethyl)-2-methylcycloprop-1-en-1-yl)methyl)-4-methylbenzenesulfonamide

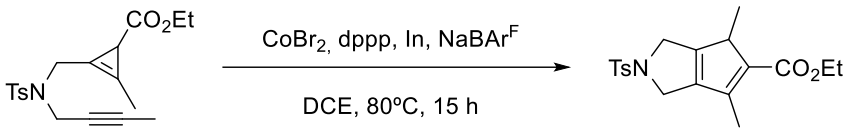


28a **28l**

Cyclopropenyl ester **28a** (230 mg, 0.636 mmol**)** was dissolved in Et_2O (0.64 ml) in a flame dried three necked flask and cooled to -30 °C. DIBAL-H (1.4 ml, 1.4 mmol, 1 M in hexane) was added dropwise and the reaction mixture was stirred at -30 ºC until full consumption of cyclopropenyl ester (30 min). The reaction was diluted with Et_2O and quenched with water and the mixture was stirred until the two phases were separated. The aqueous layer was extracted three times with Et_2O, and the combined organic phases were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude reaction mixture was then purified by flash chromatography using Et_2O / Hexane as eluent (40%) to obtained 103 mg of alcohol **28l** (52% yield) as a colourless oil. **^{1}H NMR (300 MHz, $CDCl_3$)** δ (ppm): 7.74 (d, *J* = 8.3 Hz, 2H), 7.30 (d, *J* = 8.6 Hz, 2H), 4.30 (d, *J* = 1.7 Hz, 2H), 4.12 – 4.03 (m, 2H), 3.60 (ddd, *J* = 10.9, 3.8, 0.7 Hz, 1H), 3.40 (ddd, *J* = 11.0, 4.8, 0.7 Hz, 1H), 2.42 (s, 3H), 1.98 (dt, *J* = 2.2, 1.1 Hz, 3H), 1.62 (td, *J* = 2.4, 0.7 Hz, 3H). **^{13}C-NMR (75 MHz, $CDCl_3$)** δ (ppm): 143.6 (C), 136.1 (C), 129.5(CH), 127.9 (CH), 115.3 (C), 109.7 (C), 82.0 (C), 71.9 (C), 67.7 (CH_2), 42.7 (CH_2), 37.5 (CH_2), 23.7 (CH_3), 21.6 (CH_3), 10.8 (CH_3), 3.4 (CH). **HRMS** (APCI-TOF): m/z calculated for $C_{17}H_{22}NO_3S$ $[M+H]^+$: 319.4187, found 319.4190.

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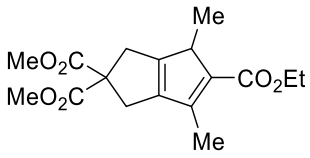
2. General procedure for the intramolecular (3+2) cycloaddition between cyclopropenes and alkynes (exemplified for 29a).



28a **29a**

$CoBr_2$ (2.2 mg, 0.01 mmol), dppp (4.7 mg, 0.012 mmol), In (5.9, 0.05 mmol) and $NaBAr^F$ (8.9 mg, 0.02 mmol) were successively added to a dried Schlenk tube under Argon. Then, **28a** (36 mg, 0.1 mmol) in DCE (1 mL) was added under Ar atmosphere and the resulting mixture was stirred for 16 h at 80 °C before it was filtered through a short pad of Florisil® and concentrated under vacuum. The residue was purified by flash column chromatography (10 % Et_2O / hexanes) to give 33 mg of **2a** (90% yield) as white solid. **^{1}H NMR (300 MHz, $CDCl_3$)** δ (ppm): 7.74 (d, *J* = 8.3 Hz, 2H), 7.32 (d, *J* = 7.9 Hz, 2H), 4.38 – 4.10 (m, 6H), 3.34 – 3.19 (m, ºH), 2.42 (s, 3H), 2.21 (d, *J* = 2.1 Hz, 3H), 1.30 (t, *J* = 7.1 Hz, 3H), 1.19 (d, *J* = 7.6 Hz, 3H). **^{13}C-NMR (75 MHz, $CDCl_3$)** δ (ppm): 164.5 (CO), 153.0 (C), 148.4 (C), 144.1 (C), 143.7 (C), 138.5 (C), 134.8 (C), 130.0 (CH), 127.4 (CH), 59.7 (CH_2), 51.9 (CH_2), 50.2 (CH_2), 43.9 (CH), 21.66 (CH_3), 14.5 (CH_3), 14.4 (CH_3), 14.3 (CH_3). **HRMS** (APCI-TOF): m/z calculated for $C_{19}H_{24}NO_4S$ $[M+H]^+$: 361.1448, found 361.1450.

5-Ethyl 2,2-dimethyl 4,6-dimethyl-3,4-dihydropentalene-2,2,5(1H)-tricarboxylate (29b)

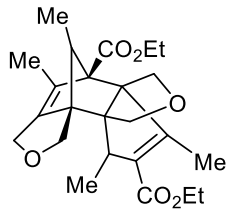


29b

99% yield. Colourless oil.**^{1}H NMR (300 MHz, $CDCl_3$)** δ (ppm): 4.30 – 4.16 (m, 2H), 3.77 (d, *J* = 1.9 Hz, 6H), 3.17 (qq, *J* = 4.3, 3.0, 2.2 Hz, 5H), 2.26 (d, *J* = 2.0 Hz, 3H), 1.32 (t, *J* = 7.1 Hz, 3H), 1.22 (d, *J* = 7.6 Hz, 3H). **^{13}C-NMR (75 MHz, $CDCl_3$)** δ (ppm): 172.2 (CO), 172.1 (CO), 164.7 (CO), 157.0 (C), 150.6 (C), 146.2 (C), 137.5 (C), 63.8 (C), 59.2 (CH_2), 52.9 (CH_3), 43.8 (CH), 37.2 (CH_2), 35.5 (CH_2), 14.4 (CH_3), 14.3 (CH_3), 14.2 (CH_3). **HRMS** (APCI-TOF): m/z calculated for $C_{17}H_{23}O_6$ $[M+H]^+$: 322.1466, found 322.1469.

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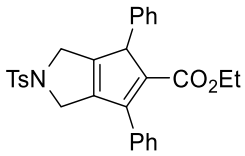
Diethyl (5R,5aR,8aR,8bR)-4,6,8,9-tetramethyl-1H,8H-5,8b-methano-5a,8a-(methanooxymethano)indeno[4,5-c]furan-5,7(3H)-dicarboxylate (29c')



29c'

71% yield. Colourless oil.**^{1}H NMR (300 MHz, $CDCl_3$)** δ (ppm): 4.29 (d, J = 14.2 Hz, 2H), 4.25 – 4.17 (m, 4H), 4.17 – 4.12 (m, 2H), 4.10 (s, 1H), 3.97 (d, J = 10.3 Hz, 1H), 3.77 (d, J = 9.8 Hz, 1H), 3.69 (d, J = 9.8 Hz, 1H), 3.49 (d, J = 10.0 Hz, 1H), 3.07 (q, J = 6.3 Hz, 1H), 2.85 – 2.67 (m, 1H), 1.99 (s, 3H), 1.65 (s, 3H), 1.38 – 1.22 (m, 6H), 1.12 (d, J = 7.1 Hz, 3H), 0.96 (d, J = 6.4 Hz, 3H). **^{13}C-NMR (75 MHz, $CDCl_3$)** δ (ppm): 170.9 (CO), 165.5 (CO), 150.4 (C), 146.0 (C), 137.0 (C), 127.7 (C), 82.3 (C), 74.2 (C), 73.9 (CH_2), 73.2 (CH_2), 69.5 (C), 67.8 (C), 66.4 (CH_2), 65.6 (CH_2), 60.73 (CH_2) 59.9 (CH_2), 57.6 (CH), 44.0 (CH_3), 17.38 (CH_3), 14.5 (CH_3), 14.5 (CH_3), 14.4 (CH_3), 9.6 (CH_3). **HRMS** (APCI-TOF): m/z calculated for $C_{24}H_{33}O_6$ $[M+H]^+$: 416.2196, found 416.2199.

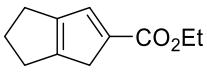
Ethyl 4,6-diphenyl-2-tosyl-1,2,3,4-tetrahydrocyclopenta[c]pyrrole-5-carboxylate (29d)



29d

54% yield. White solid.**^{1}H NMR (500 MHz, $CDCl_3$)** δ (ppm): 7.75 (d, *J* = 8.0 Hz, 2H), 7.34 – 7.23 (m, 10H), 7.17 (t, *J* = 7.7 Hz, 2H), 5.14 (s, 1H), 4.43 (dd, *J* = 15.0, 2.2 Hz, 2H), 4.31 (dd, *J* = 14.9, 2.3 Hz, 2H), 3.94 (q, *J* = 7.1 Hz, 2H), 2.36 (s, 3H), 1.48 (s, 3H), 0.91 (t, *J* = 7.1 Hz, 3H). **^{13}C-NMR (126 MHz, $CDCl_3$)** δ (ppm): 168.8 (CO), 143.3 (C), 142.9 (C), 132.8 (C), 132.4 (C), 132.2 (C), 129.0 (CH), 127.9 (CH), 126.5 (CH), 126.3 (CH), 125.2 (CH), 62.73 (CH) 60.3 (CH_2), 46.8 (CH_2), 20.5 (CH_3), 12.9 (CH_3). **HRMS** (APCI-TOF): m/z calculated for $C_{29}H_{28}NO_4S$ $[M+H]^+$: 485.1661, found 485.1663.

Ethyl 1,4,5,6-tetrahydropentalene-2-carboxylate (29e)

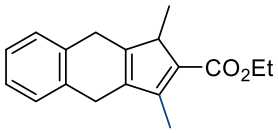


29e

71% yield. Colourless oil. **^{1}H NMR (500 MHz, $CDCl_3$)** δ (ppm): 7.32 (s, 1H), 4.22 (qd, J = 7.1, 1.0 Hz, 2H), 3.14 (d, J = 2.1 Hz, 2H), 2.54 (dd, J = 8.5, 6.0 Hz, 2H), 2.48 – 2.44 (m, 2H), 2.33 (q, J = 7.3 Hz, 2H), 1.30 (td, J = 7.1, 1.0 Hz, 3H). **^{13}C-NMR (126 MHz, $CDCl_3$)** δ (ppm): 163.4 (CO), 156.4 (C), 148.3 (C), 139.0 (CH), 138.2 (C), 58.7 (CH_2), 36.3 (CH_2), 28.6 (CH_2), 27.4 (CH_2), 26.5 (CH_2), 13.4 (CH_3). **HRMS** (APCI-TOF): m/z calculated for $C_{11}H_{15}O_2$ $[M+H]^+$: 178.0992, found 178.0994.

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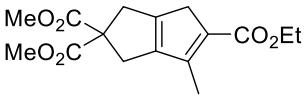
Ethyl 1,3-dimethyl-4,9-dihydro-1H-cyclopenta[b]naphthalene-2-carboxylate (29f)



29f

61% yield. Colourless solid.**^{1}H NMR (300 MHz, $CDCl_3$)** δ (ppm): 7.49 – 7.10 (m, 4H), 4.50 – 4.15 (m, 2H), 3.97 – 3.57 (m, 4H), 3.29 (dq, *J* = 6.2, 2.0 Hz, 1H), 2.38 (s, 3H), 1.54 – 1.08 (m, 6H). **^{13}C-NMR (75 MHz, $CDCl_3$)** δ (ppm): 165.2 (CO), 154.0 (C), 148.5 (C), 136.0 (C), 133.6 (C), 133.5 (C), 133.3 (C), 129.3 (CH), 129.1 (CH), 126.2 (CH), 126.1 (CH), 59.3 (CH_2), 48.1 (CH), 29.1 (CH_2), 27.8 (CH_2), 14.6 (CH_3), 14.5 (CH_3), 13.3 (CH_3). **HRMS** (APCI-TOF): m/z calculated for $C_{18}H_{20}O_2$ $[M+H]^+$: 268.1463, found 268.1467.

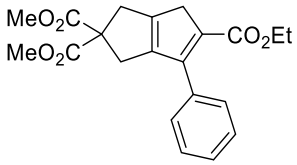
5-Ethyl 2,2-dimethyl 6-methyl-3,4-dihydropentalene-2,2,5(1H)-tricarboxylate (29g)



29g

87% yield. Colourless oil.**^{1}H NMR (300 MHz, $CDCl_3$)** δ (ppm): 4.17 (q, *J* = 7.1 Hz, 2H), 3.73 (s, 6H), 3.22 (t, *J* = 1.9 Hz, 2H), 3.12 (dt, *J* = 6.8, 2.3 Hz, 4H), 2.25 (t, *J* = 2.2 Hz, 3H), 1.27 (t, *J* = 7.1 Hz, 3H). **^{13}C-NMR (75 MHz, $CDCl_3$)** δ (ppm): 172.2 (CO), 165.0 (CO), 151.5 (C), 150.2 (C), 149.4 (C), 131.9 (C), 64.2 (C), 59.4 (CH_2), 53.0 (CH_3), 38.7 (CH_2), 37.8 (CH_2), 35.6 (CH_2), 14.5 (CH_3), 14.3 (CH_3). **HRMS** (APCI-TOF): m/z calculated for $C_{16}H_{21}O_6S$ $[M+H]^+$: 308.3312, found 308.3313.

5-Ethyl 2,2-dimethyl 4-methyl-6-phenyl-3,4-dihydropentalene-2,2,5(1H)-tricarboxylate (29h)

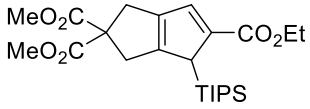


29h

80% yield. Colourless oil.**^{1}H NMR (300 MHz, $CDCl_3$)** δ (ppm): 7.72 – 7.32 (m, 5H), 4.12 (q, J = 7.2 Hz, 2H), 3.76 (s, 6H), 3.37 (s, 2H), 3.33 (s, 2H), 3.18 (s, 2H), 1.16 (t, J = 7.1 Hz, 3H). **^{13}C-NMR (75 MHz, $CDCl_3$)** δ (ppm): 172.0 (C), 164.1 (C), 152.0 (C), 150.6 (C), 148.4 (C), 134.7 (C), 132.4 (C), 131.6 (C), 128.6 (CH), 128.1 (CH), 127.6 (CH), 64.0 (C), 59.6 (CH_2), 52.9 (CH_2), 38.7 (CH_2), 38.5 (CH_2), 36.6 (CH_2), 14.0 (CH_3). **HRMS** (APCI-TOF): m/z calculated for $C_{21}H_{23}O_6$ $[M+H]^+$: 370.4010, found 370.4013.

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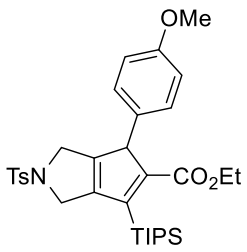
5-Ethyl 2,2-dimethyl 4-(triisopropylsilyl)-3,4-dihydropentalene-2,2,5(1H)-tricarboxylate (29i)



29i

80% yield. Colourless oil.**^{1}H NMR (300 MHz, $CDCl_3$)** δ (ppm): 7.22 (s, 1H), 4.33 – 4.22 (m, 1H), 4.21 – 4.07 (m, 1H), 3.83 (d, *J* = 2.1 Hz, 1H), 3.75 (s, 3H), 3.74 (s, 3H), 3.39 (d, *J* = 2.0 Hz, 2H), 3.26 – 3.17 (m, 2H), 1.37 – 1.16 (m, 6H), 1.05 (t, *J* = 8.4 Hz, 18H). **^{13}C-NMR (75 MHz, $CDCl_3$)** δ (ppm): 172.1 (CO), 172.0 (CO), 164.6 (C), 155.2 (C), 144.4 (C), 143.4 (C), 135.8 (CH), 64.61, 59.7 (CH_2), 52.9 (CH_3), 52.9 (CH_3), 43.7 (CH), 39.9 (CH_2), 35.9 (CH_2), 18.8 (CH_3), 18.6 (CH_3), 17.6 (CH), 14.4 (CH_3), 12.5 (CH_3). **HRMS** (APCI-TOF): m/z calculated for $C_{24}H_{39}O_6Si$ $[M+H]^+$: 450.6470, found 450.6472.

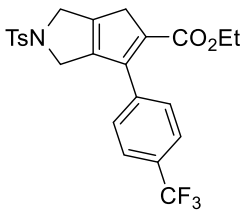
Ethyl 4-(4-methoxyphenyl)-2-tosyl-6-(triisopropylsilyl)-1,2,3,4-tetrahydrocyclopenta[c]pyrrole-5-carboxylate (29j)



29j

60% yield. Colourless oil.**^{1}H NMR (300 MHz, $CDCl_3$)** δ (ppm): 7.80 (d, *J* = 8.3 Hz, 2H), 7.50 (d, *J* = 8.9 Hz, 2H), 7.30 (d, *J* = 8.6 Hz, 2H), 6.91 (d, *J* = 8.8 Hz, 2H), 5.40 (s, 1H), 4.43 (s, 2H), 4.21 (s, 2H), 4.11 (q, *J* = 7.1 Hz, 2H), 3.83 (s, 3H), 2.43 (s, 3H), 1.44 (t, *J* = 7.0 Hz, 3H), 0.95 – 0.70 (m, 21H). **^{13}C-NMR (75 MHz, $CDCl_3$)** δ (ppm): 159.6 (C), 158.7 (C), 143.3 (C), 141.6 (C), 136.3 (C), 129.7 (CH), 127.2 (CH), 127.2 (CH), 123.2 (C), 114.5 (C), 114.0 (CH), 99.7 (C), 83.6 (CH), 66.8 (CH_2), 55.2 (CH_3), 42.0 (CH_2), 36.6 (CH_2), 21.4 (CH), 18.4 (CH_3), 14.5 (CH_3), 10.9 (CH_3). **HRMS** (APCI-TOF): m/z calculated for $C_{33}H_{46}NO_5SSi$ $[M+H]^+$: 592.8704, found 592.8705.

Ethyl 2-tosyl-6-(4-(trifluoromethyl)phenyl)-1,2,3,4-tetrahydrocyclopenta[c]pyrrole-5-carboxylate (29k)



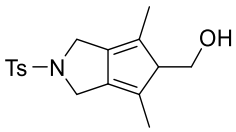
29k

55% yield. Colourless oil.**^{1}H NMR (500 MHz, $CDCl_3$)** δ (ppm): 7.73 (d, J = 8.7 Hz, 1H), 7.63 (d, J = 6.4 Hz, 1H), 7.44 (d, J = 6.9 Hz, 1H), 7.32 (d, J = 6.8 Hz, 1H), 4.41 (d, J = 4.3 Hz, 1H), 4.21 (d, J = 5.5 Hz, 1H), 4.10 (dt, J = 10.3, 4.9 Hz, 1H), 3.43 (t, J = 2.4 Hz, 1H), 2.42 (s, 1H), 1.14 (td, J = 6.6, 3.5 Hz, 2H). **^{13}C-NMR (126 MHz, $CDCl_3$)** δ (ppm): 162.4 (CO), 147.5 (C), 146.1 (C), 144.5 (C), 142.7 (C), 133.4 (C), 133.3 (C), 129.7 (CH), 128.9 (CH), 127.7 (CH), 126.3 (CH), 124.9 (C), 59.2 (CH_2), 51.6 (CH_2), 49.4 (CH_2), 37.4

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(CH_2), 20.5 (CH_3), 13.0 (CH_3). **^{19}F NMR (282 MHz, $CDCl_3$)** δ (ppm) -62.78. **HRMS** (APCI-TOF): m/z calculated for $C_{24}H_{23}F_3NO_4S$ $[M+H]^+$: 417.4985, found 417.4988.

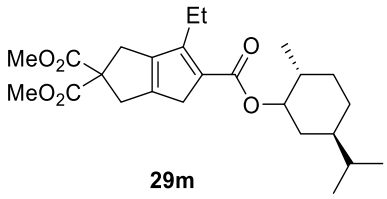
(4,6-Dimethyl-2-tosyl-1,2,3,5-tetrahydrocyclopenta[c]pyrrol-5-yl)methanol (29l)



29l

51% yield. Colourless oil.**^{1}H NMR (300 MHz, $CDCl_3$)** δ (ppm): δ 7.74 (d, *J* = 8.3 Hz, 2H), 7.32 (d, *J* = 8.0 Hz, 2H), 3.99 (s, 4H), 3.89 (dd, *J* = 5.4, 3.9 Hz, 2H), 3.15 – 3.04 (m, 1H), 2.42 (s, 3H), 1.84 (s, 6H). **^{13}C-NMR (75 MHz, $CDCl_3$)** δ (ppm): 143.5 (C), 140.4 (C), 133.8 (C), 129.8 (C), 129.7 (CH), 127.6 (CH), 66.1 (CH), 60.5 (CH_2), 46.4 (CH_2), 21.5 (CH_3), 12.7 (CH_3). **HRMS** (APCI-TOF): m/z calculated for $C_{17}H_{22}NO_3S$ $[M+H]^+$: 319.4187, found 319.4190.

5-((*2R,5R*)-5-Isopropyl-2-methylcyclohexyl) 2,2-dimethyl 4-ethyl-3,4-dihydropentalene-2,2,5(1H)-tricarboxylate (29m)

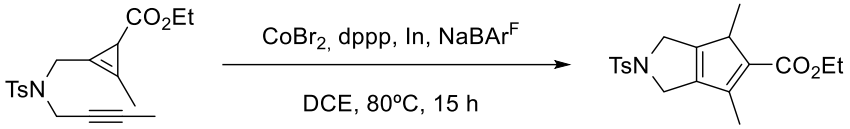


29m

71% yield. Colourless oil.**^{1}H NMR (300 MHz, $CDCl_3$)** δ (ppm): 4.77 (td, *J* = 10.8, 4.3 Hz, 1H), 3.78 (s, 6H), 3.33 – 3.03 (m, 6H), 2.89 – 2.69 (m, 2H), 2.08 (d, *J* = 11.9 Hz, 1H), 1.93 (pd, *J* = 6.9, 2.5 Hz, 1H), 1.76 – 1.65 (m, 2H), 1.57 (s, 1H), 1.53 – 1.37 (m, 2H), 1.14 (t, *J* = 7.6 Hz, 3H), 1.08 – 0.96 (m, 2H), 0.92 (dd, *J* = 6.7, 3.4 Hz, 6H), 0.79 (d, *J* = 6.9 Hz, 3H). **^{13}C-NMR (75 MHz, $CDCl_3$)** δ (ppm): 172.3 (CO), 164.5 (C), 157.1 (C), 150.7 (C), 148.8 (C), 131.6 (C), 73.2 (CH), 64.5 (C), 53.1 (CH_3), 47.5 (CH), 41.4 (CH_2), 38.6 (CH_2), 38.0 (CH_2), 36.2 (CH_2), 34.5 (CH_2), 31.5 (CH), 26.5 (CH), 23.7 (CH_2), 22.2 (CH_3), 21.7 (CH_2), 20.9 (CH_3), 16.6 (CH_3), 13.2 (CH_3). **HRMS** (APCI-TOF): m/z calculated for $C_{25}H_{36}O_6S$ $[M+H]^+$: 432.2570, found 432.2571.

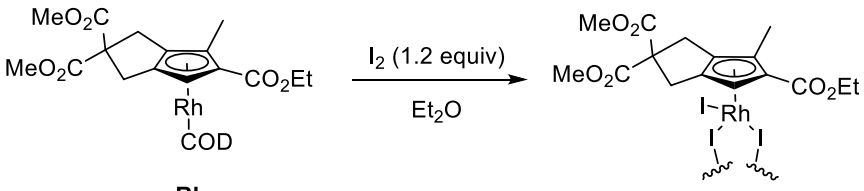
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3. Synthesis of cyclopentadienyl metal complexes



28a **29a**

To a solution of cyclopentadiene **29g** (35 mg, 0.114 mmol) in MeOH (1.7 mL) were added $[Rh(COD)Cl]_2$ (33.6 mg, 0.07 mmol) and Na_2CO_3 (26.5 mg, 0.25 mmol). The mixture was stirred at room temperature for 3 h under inert atmosphere. The solvent was removed under reduced pressure and the residue was purified by flash chromatography on silica gel (Hexane/EtOAc = 8/2 as eluent) to afford 45 mg (88 % yield) of the rhodium cyclopentadienyl complex **Rh1** as a yellow solid. **^{1}H NMR (500 MHz, $CDCl_3$)** δ (ppm): 4.92 (s, 1H), 4.23 (dq, J = 10.8, 7.1 Hz, 1H), 4.19 – 4.13 (m, 1H), 3.78 (s, 3H), 3.69 (s, 3H), 3.68 – 3.62 (m, 2H), 3.40 (q, J = 4.6, 4.2 Hz, 4H), 3.37 (d, J = 2.9 Hz, 2H), 2.06 (dddd, J = 18.6, 15.3, 8.3, 4.8 Hz, 4H), 1.87 (ddd, J = 10.6, 6.4, 2.2 Hz, 2H), 1.81 (s, 3H), 1.79 – 1.75 (m, 2H), 1.26 (t, J = 7.1 Hz, 3H). **^{13}C-NMR (126 MHz, $CDCl_3$)** δ (ppm): 171.1 (CO), 170.6 (CO), 164.9 (C), 113.5 (d, *J* = 3.5 Hz, C), 109.4 (d, *J* = 3.6 Hz, C), 94.0 (d, *J* = 3.5 Hz, C), 91.3 (d, *J* = 4.5 Hz, C), 77.2 (d, *J* = 4.0 Hz, CH), 71.5 (d, *J* = 14.0 Hz, CH), 69.0 (d, *J* = 13.7 Hz, CH), 63.8 (C), 58.2 (CH_2), 52.1 (CH_3), 52.0 (CH_3), 33.3 (CH_2), 32.3 (CH_2), 31.4 (CH_2), 30.5 (CH_2), 13.6 (CH_3), 9.8 (CH_3 **HRMS** (APCI-TOF): m/z calculated for $C_{24}H_{32}O_6Rh^+$ $[M]^+$ 533.1438; found 533.1437.

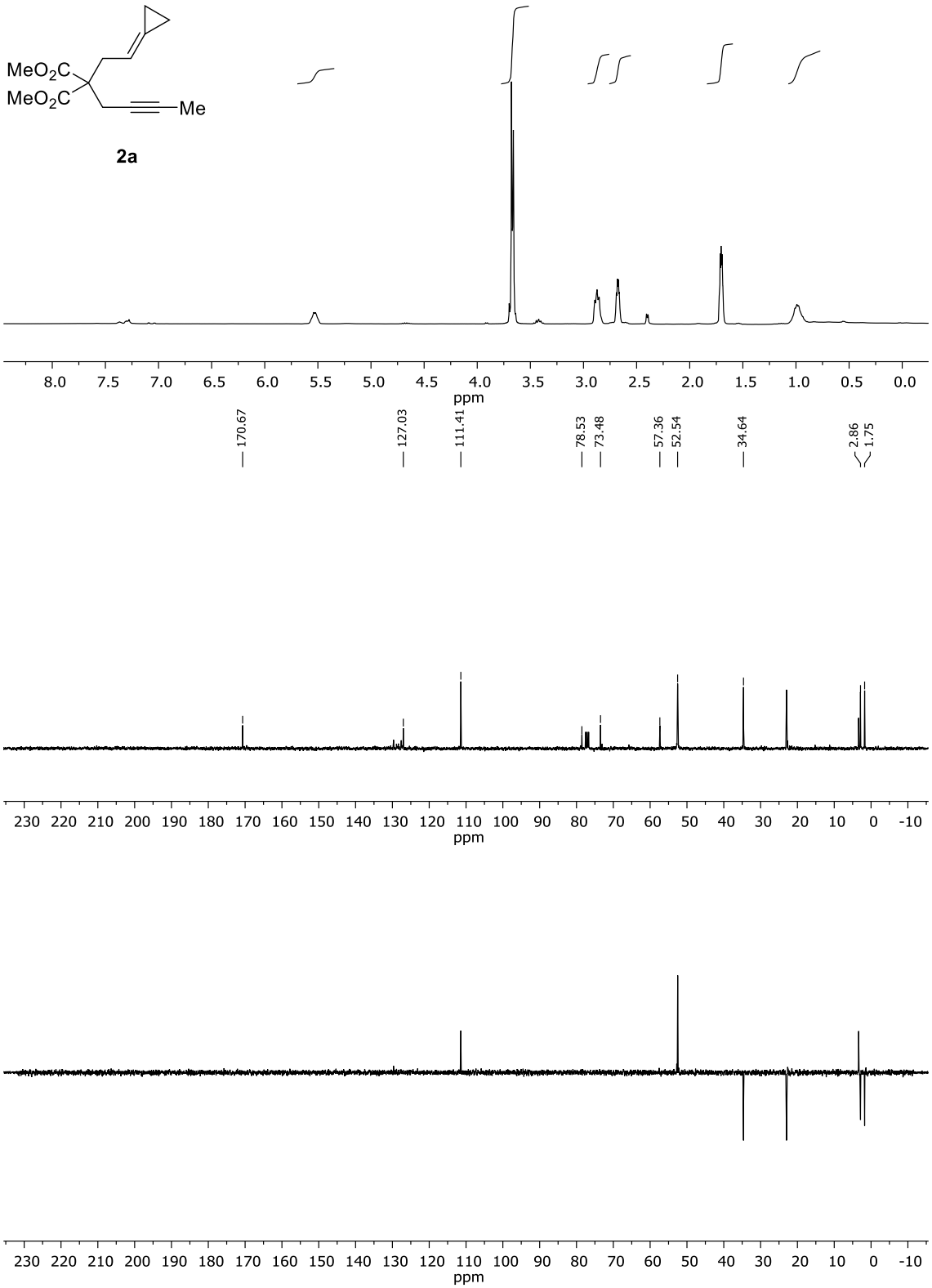


Rh_1 **Rh_2**

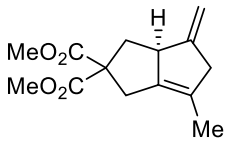
A solution of I_2 (15.2 mg, 0.06 mmol, 1.2 equiv) in Et_2O (1 mL) was added to a stirred solution of **Rh_1** (22 mg, 0.05 mmol,) in Et2O (1 mL) under air. After stirring for 30 min, the solid was filtered, washed with ether (5 mL×3) to remove the unreacted iodine, and dried in vacuo to give 30 mg (55% yield) of a dark solid identified as complex **Rh_3**. **^{1}H NMR (500 MHz, DMSO)** δ (ppm): 5.35 (s, 1H), 3.34 (q, J = 7.1 Hz, 2H), 2.80 (d, J = 3.3 Hz, 6H), 2.76 (s, 1H), 2.68 (d, J = 18.2 Hz, 1H), 2.59 (d, J = 18.2 Hz, 2H), 1.37 (s, 3H), 0.38 (t, J = 7.1 Hz, 3H). **^{13}C-NMR (126 MHz, DMSO)** δ (ppm): 175.0 (CO), 173.0 (CO), 167.4 (CO), 123.7 (d, *J* = 4.9 Hz, C). 117.2 (d, *J* = 5.9 Hz, C) 104.5 (d, *J* = 4.4 Hz, C), 92.8 (d, *J* = 9.7 Hz, C), 86.3 (d, *J* = 6.8 Hz, CH), 68.9 (C), 65.8 (CH_2), 57.8 (CH_3), 57.1 (CH_3), 36.9 (CH_2), 36.7 (CH_2), 18.2 (CH_3), 16.8 (CH_3).

Selected Spectra

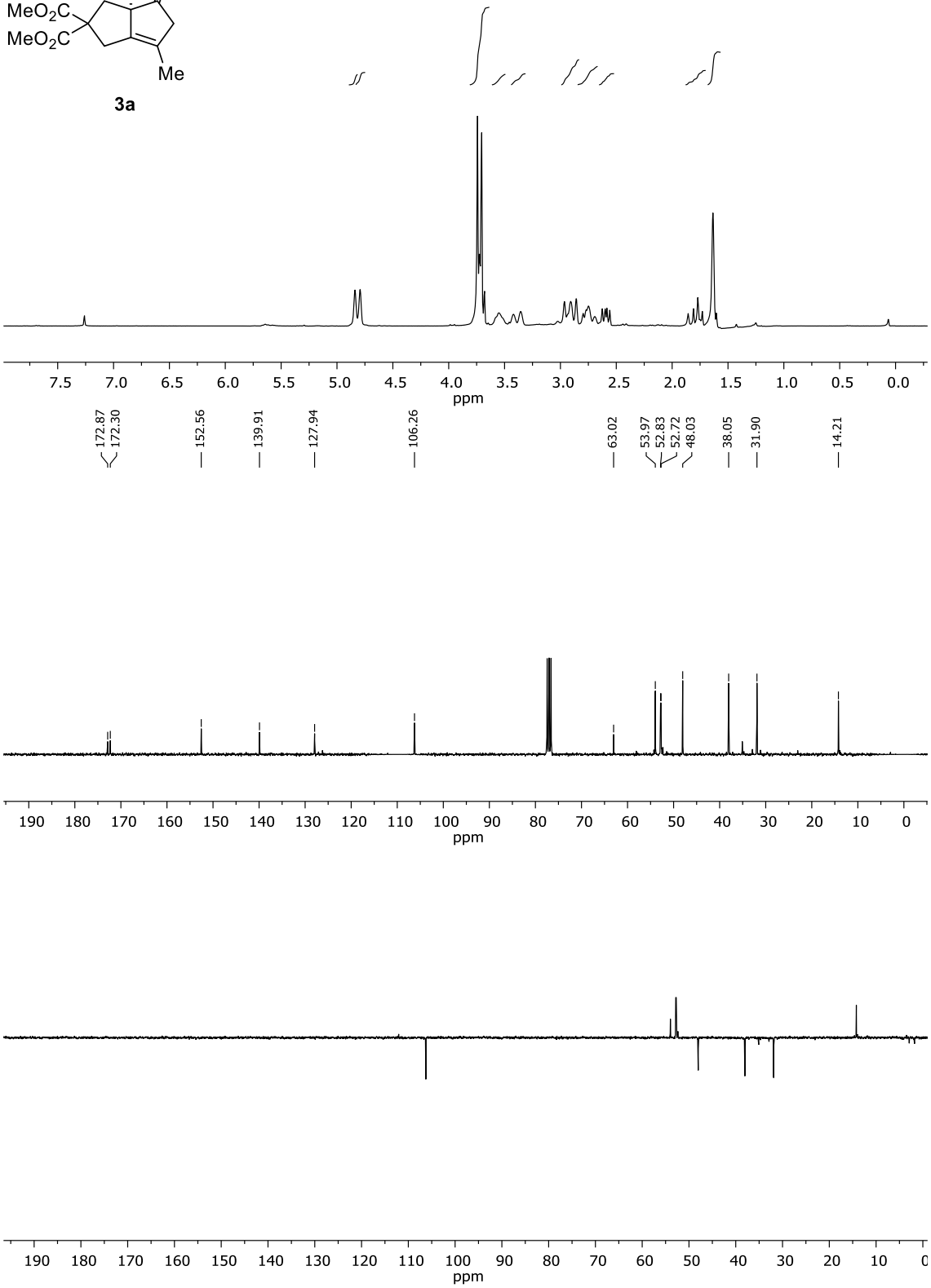
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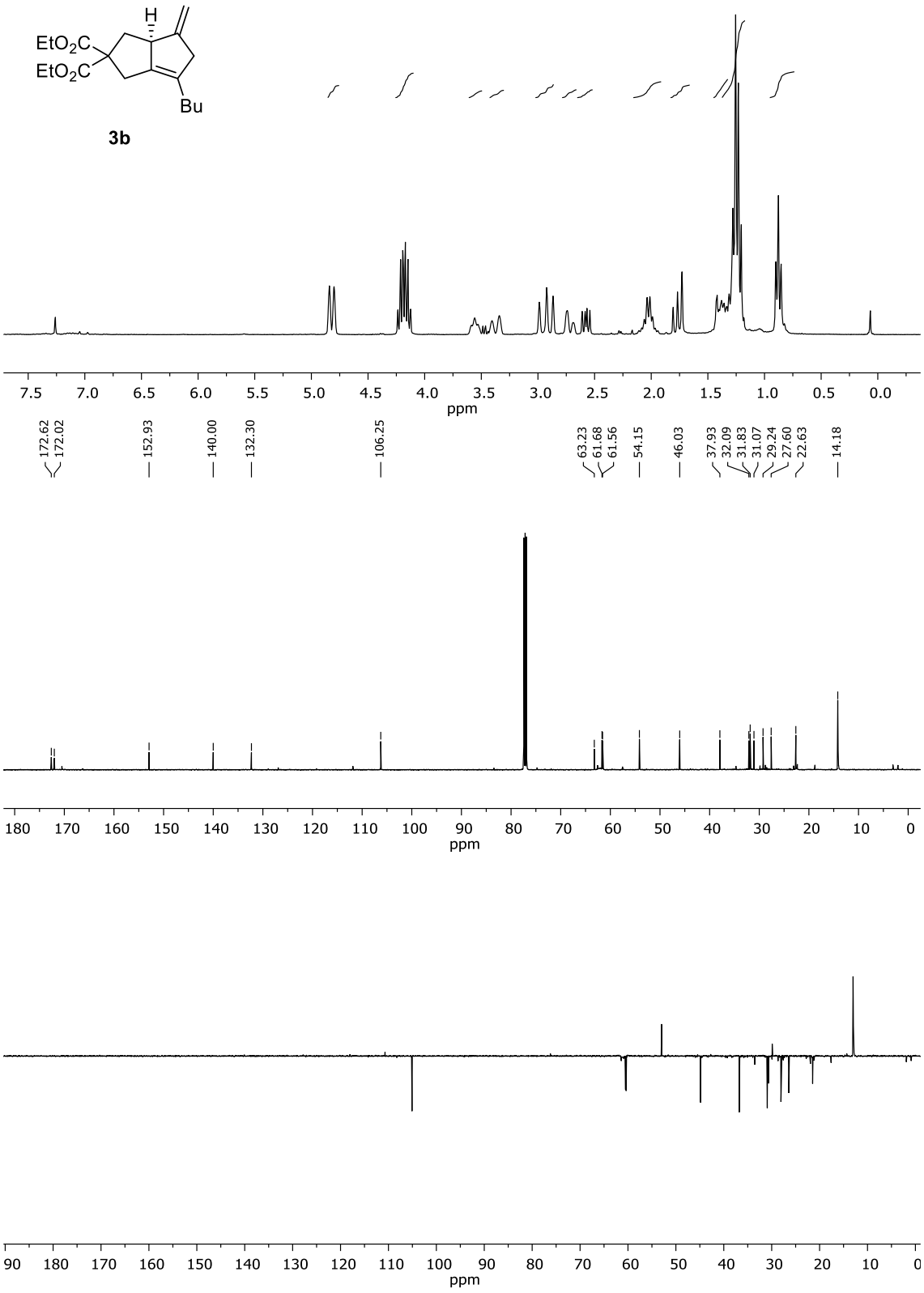
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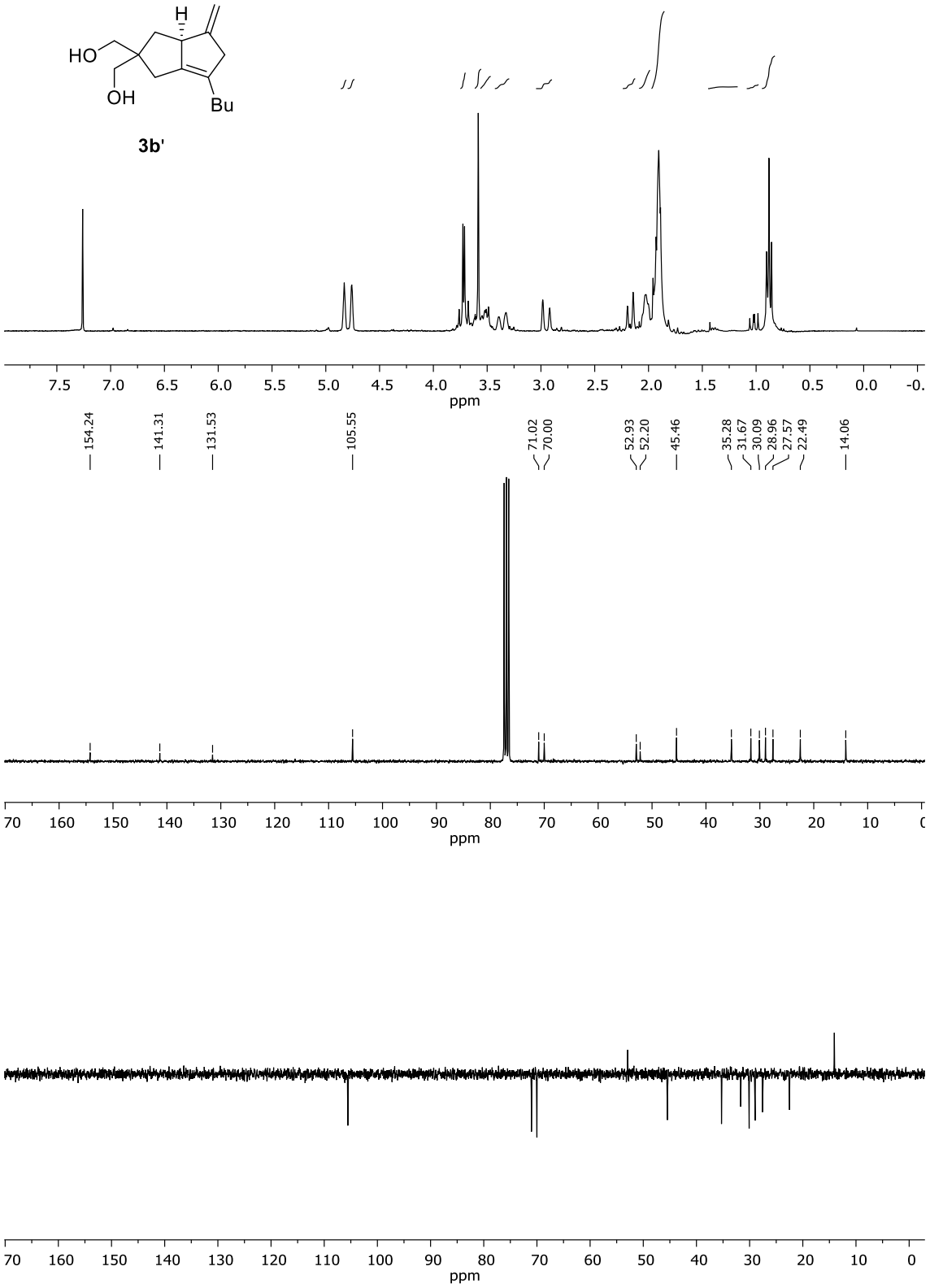
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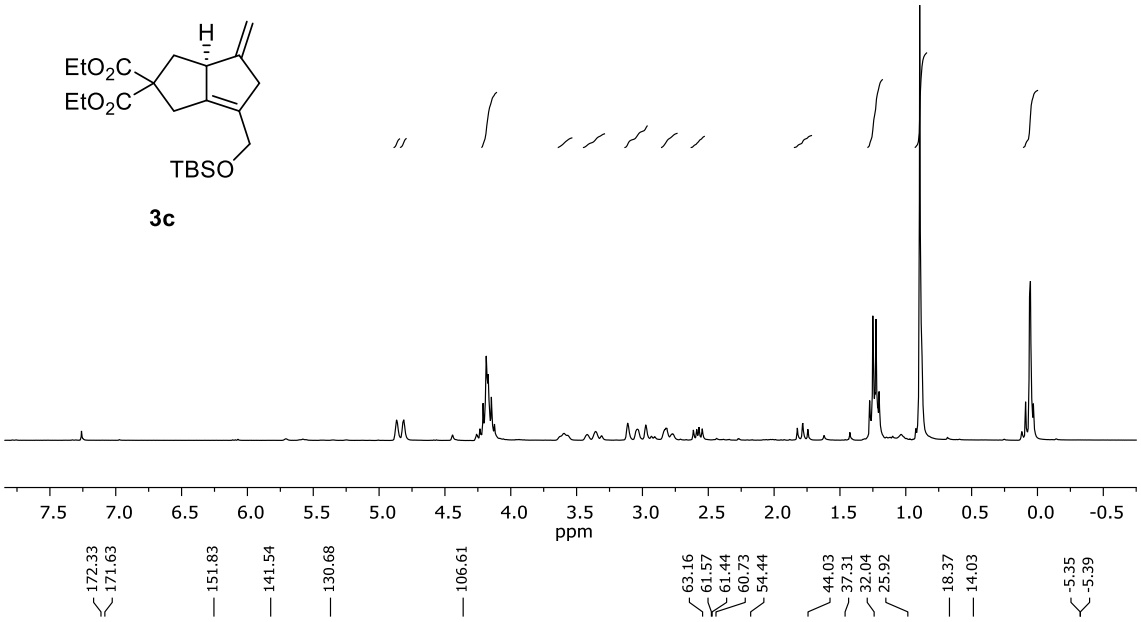


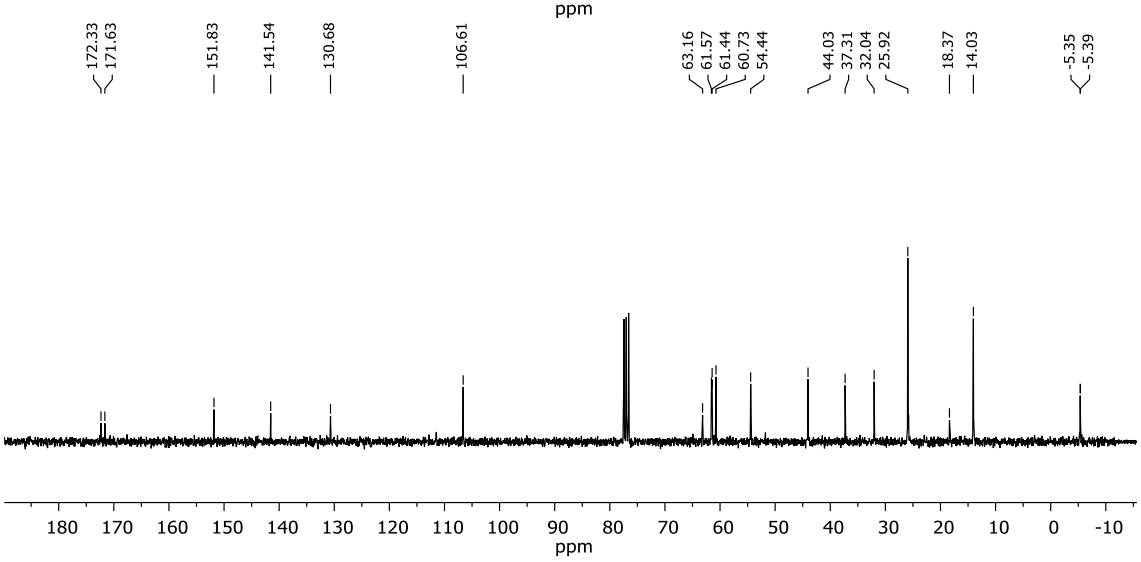
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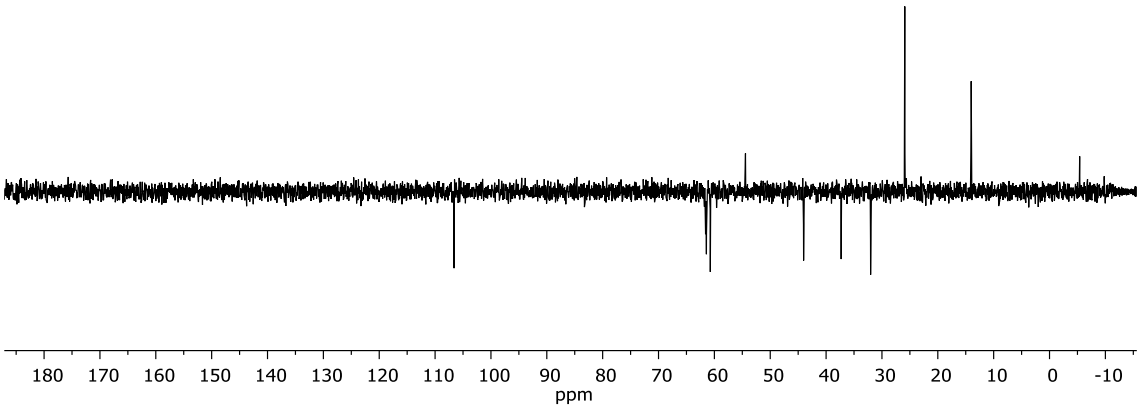


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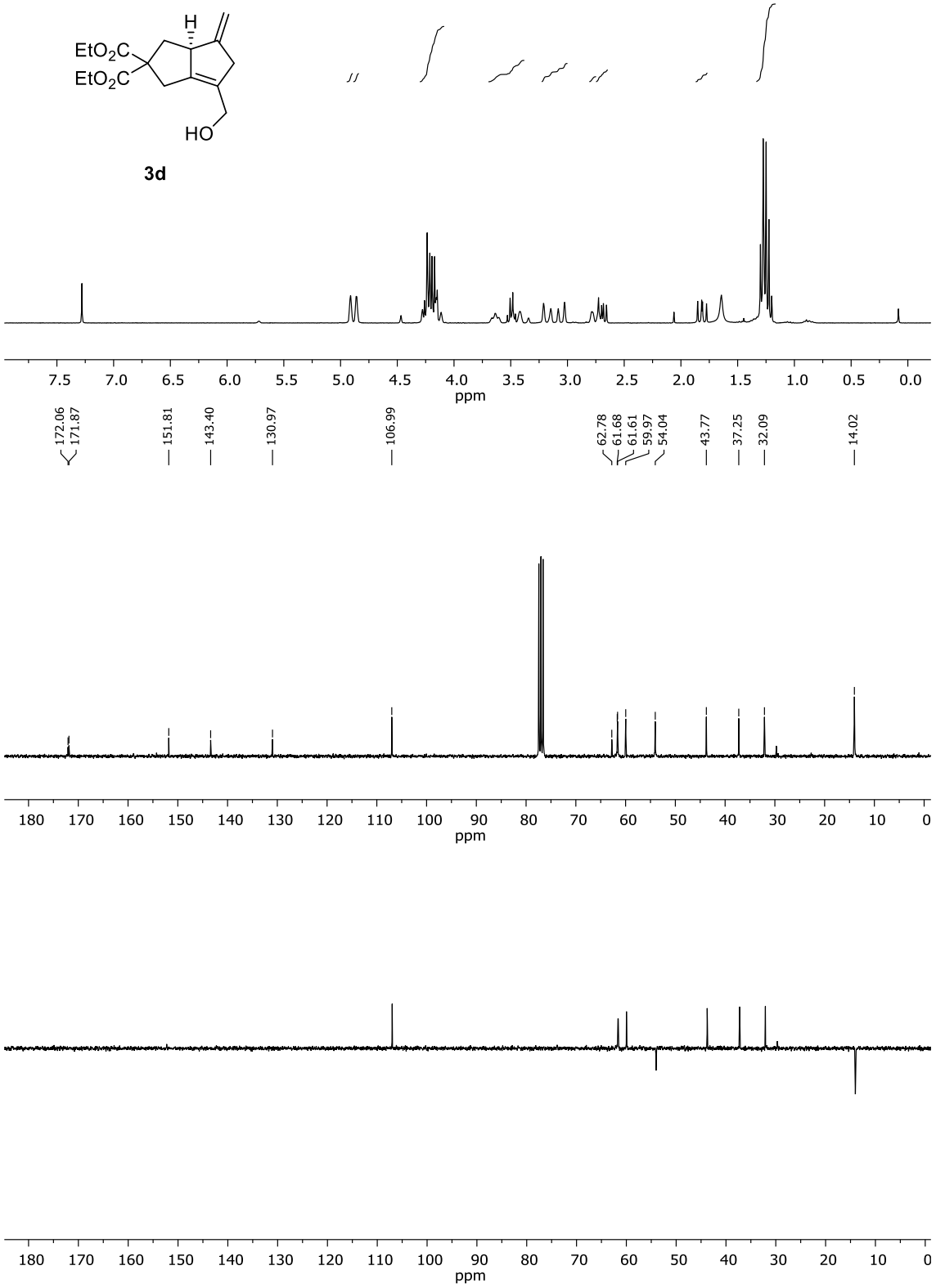
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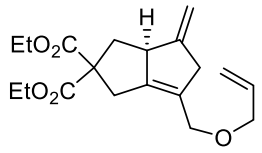




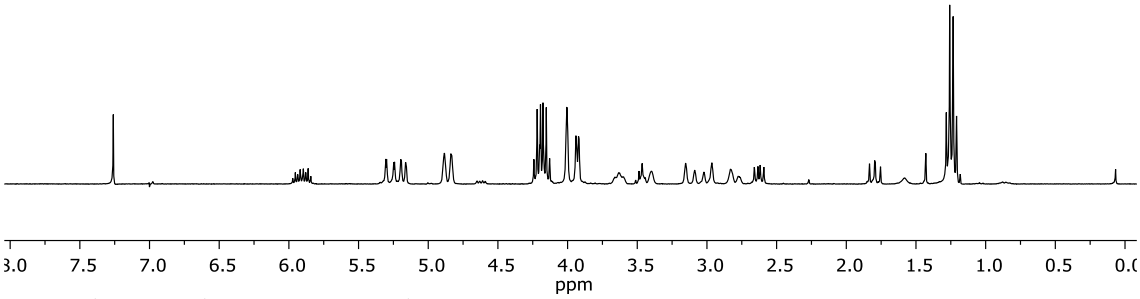
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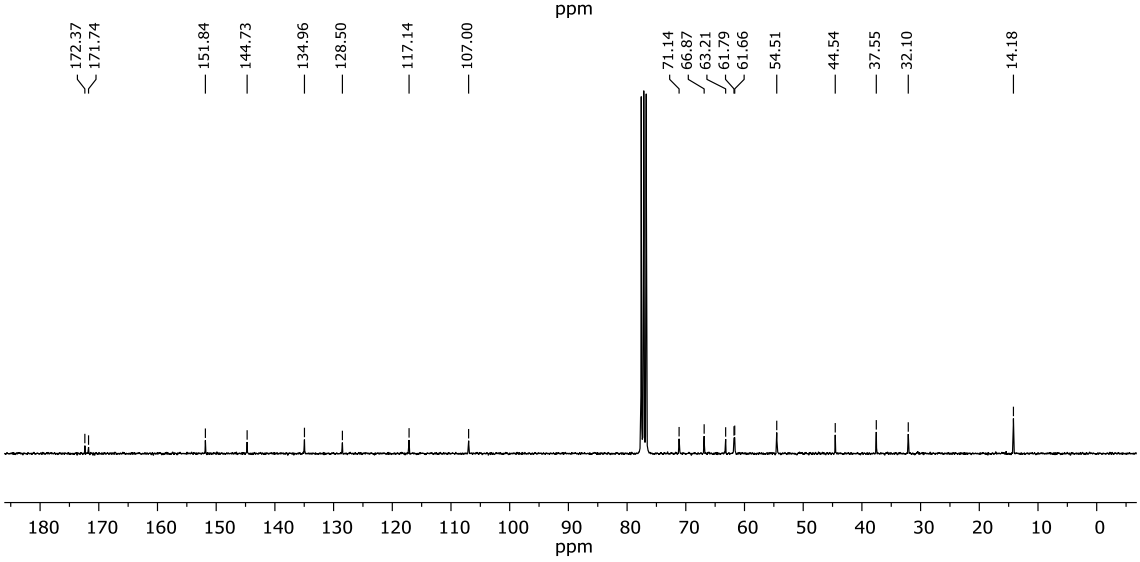


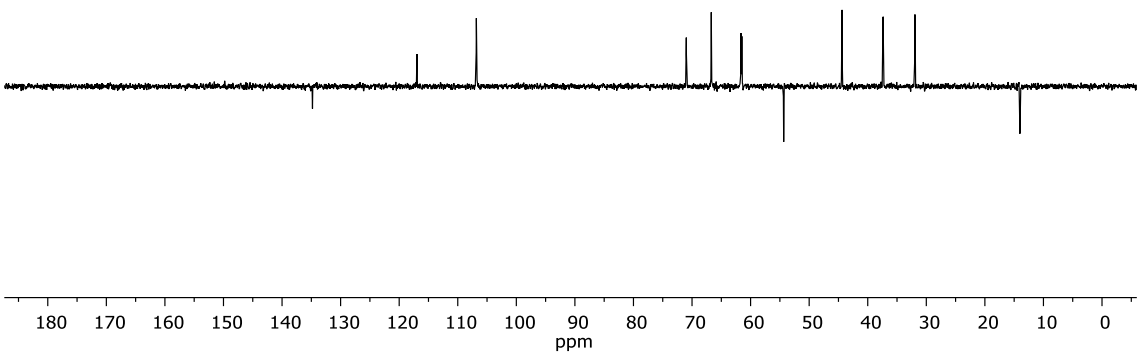
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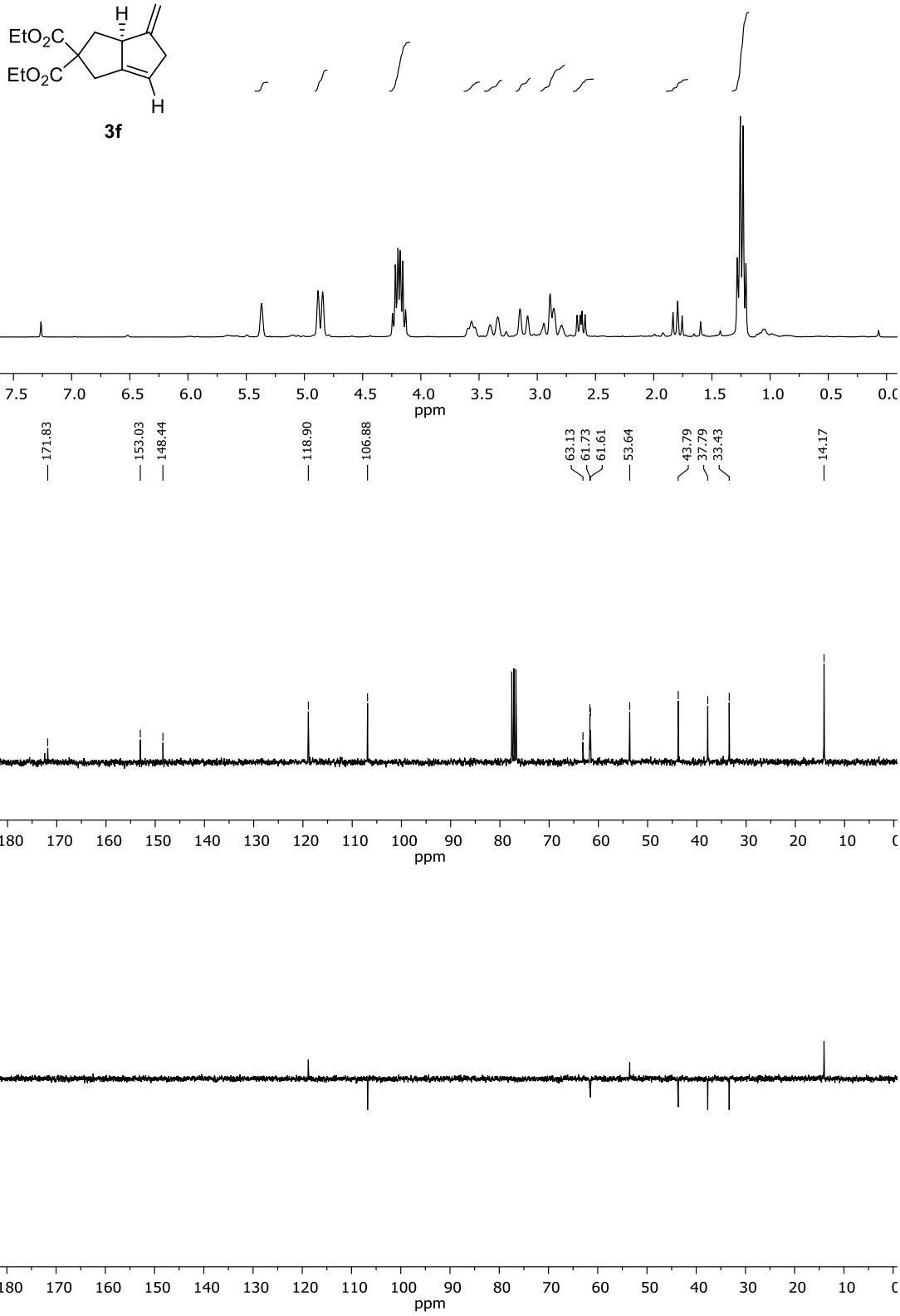
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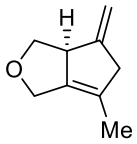




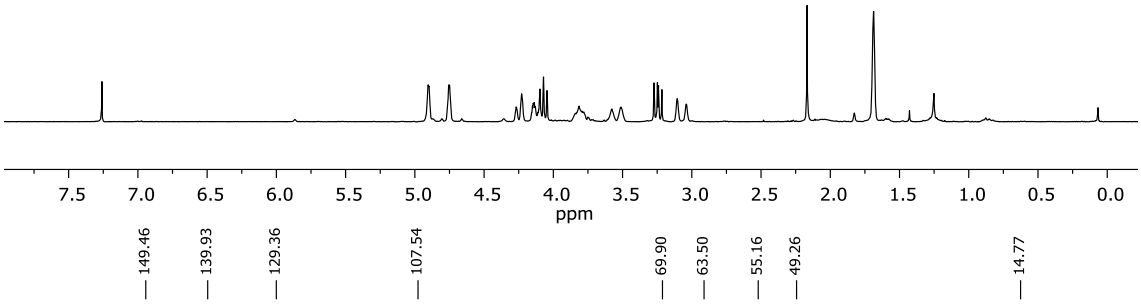
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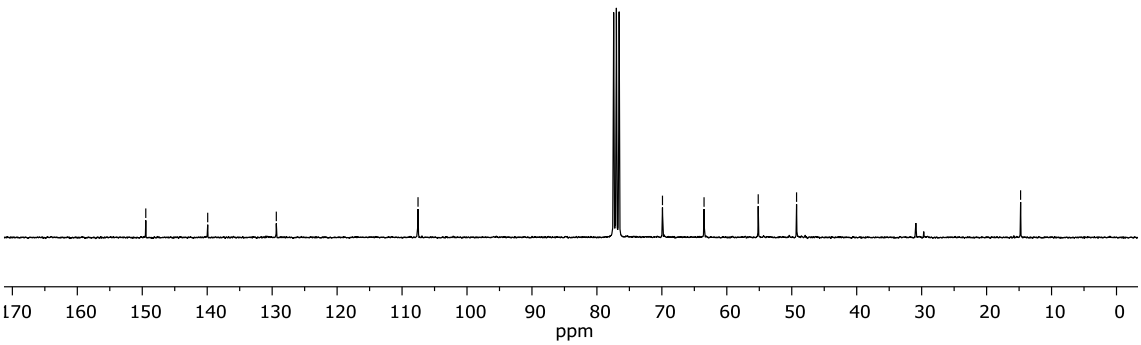


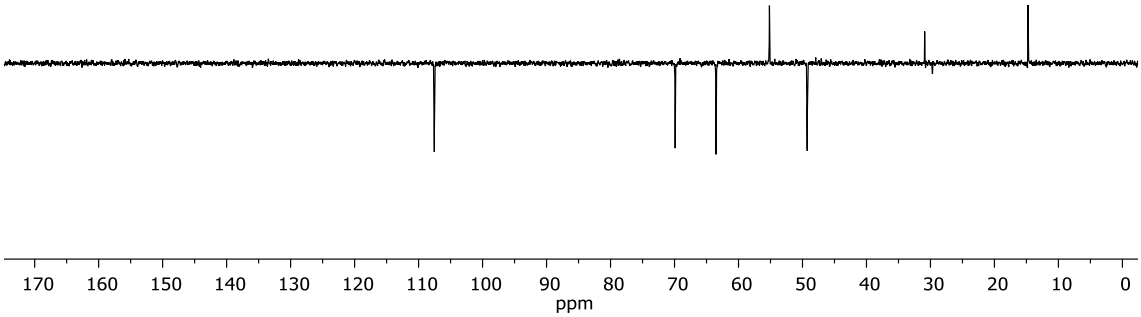
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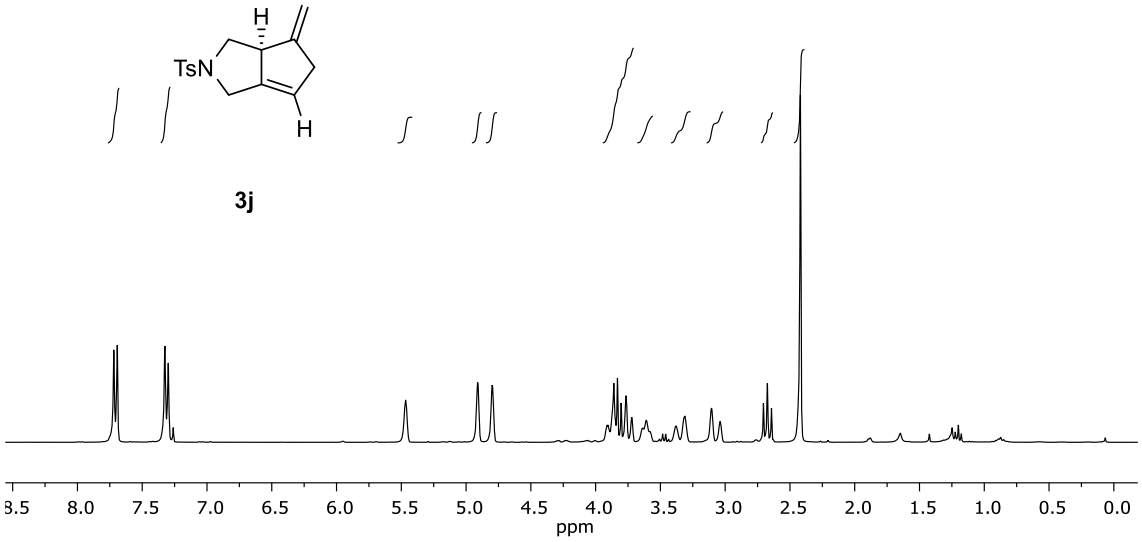
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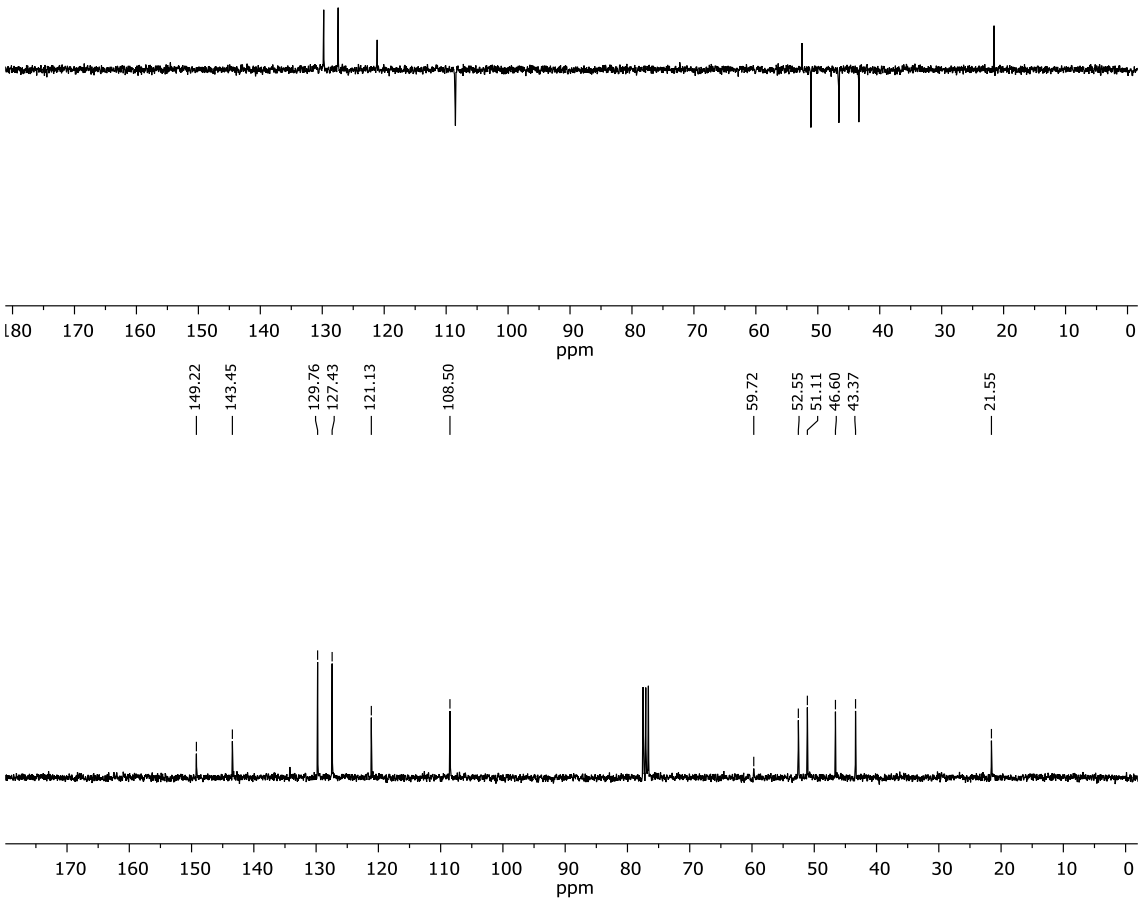




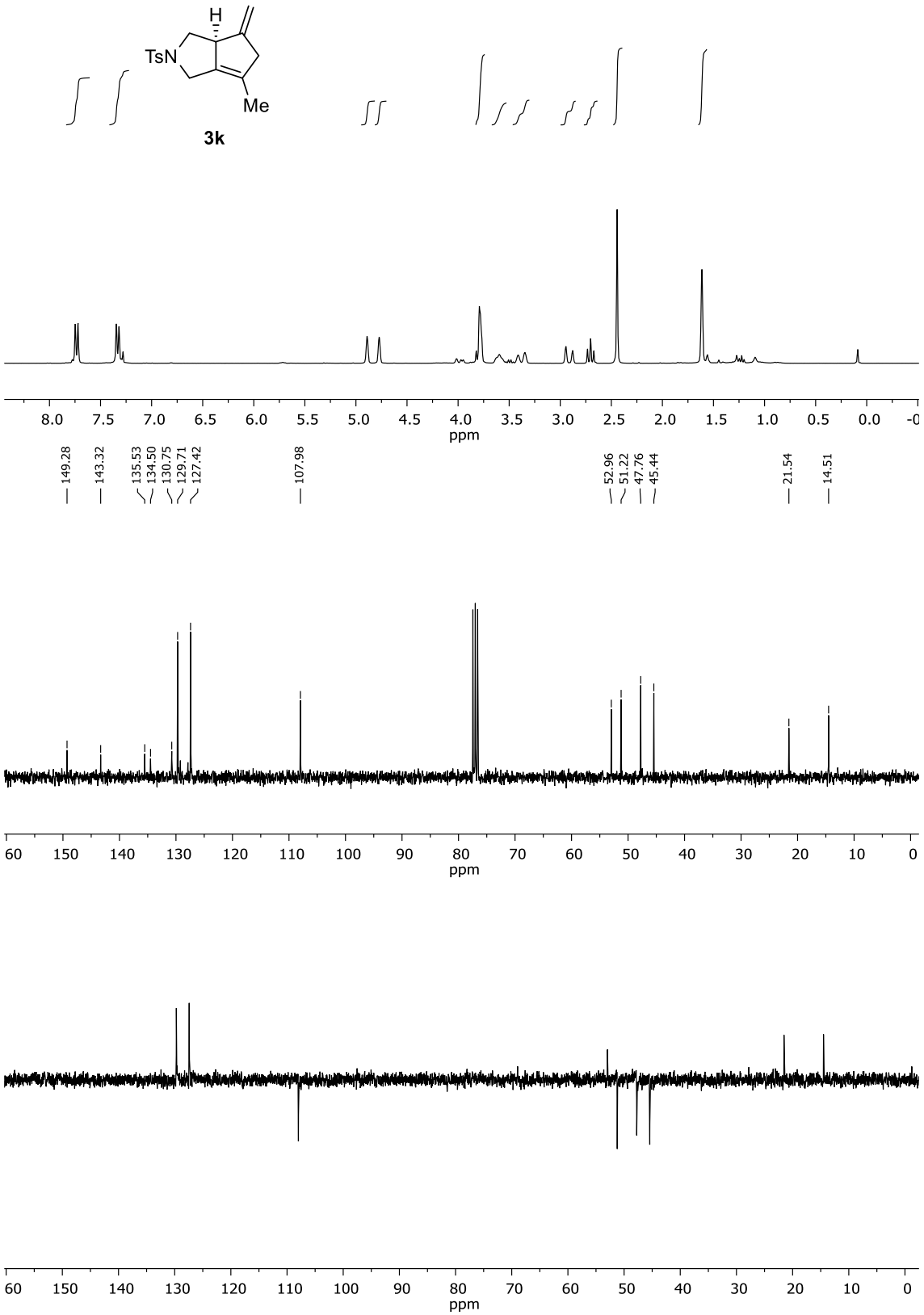
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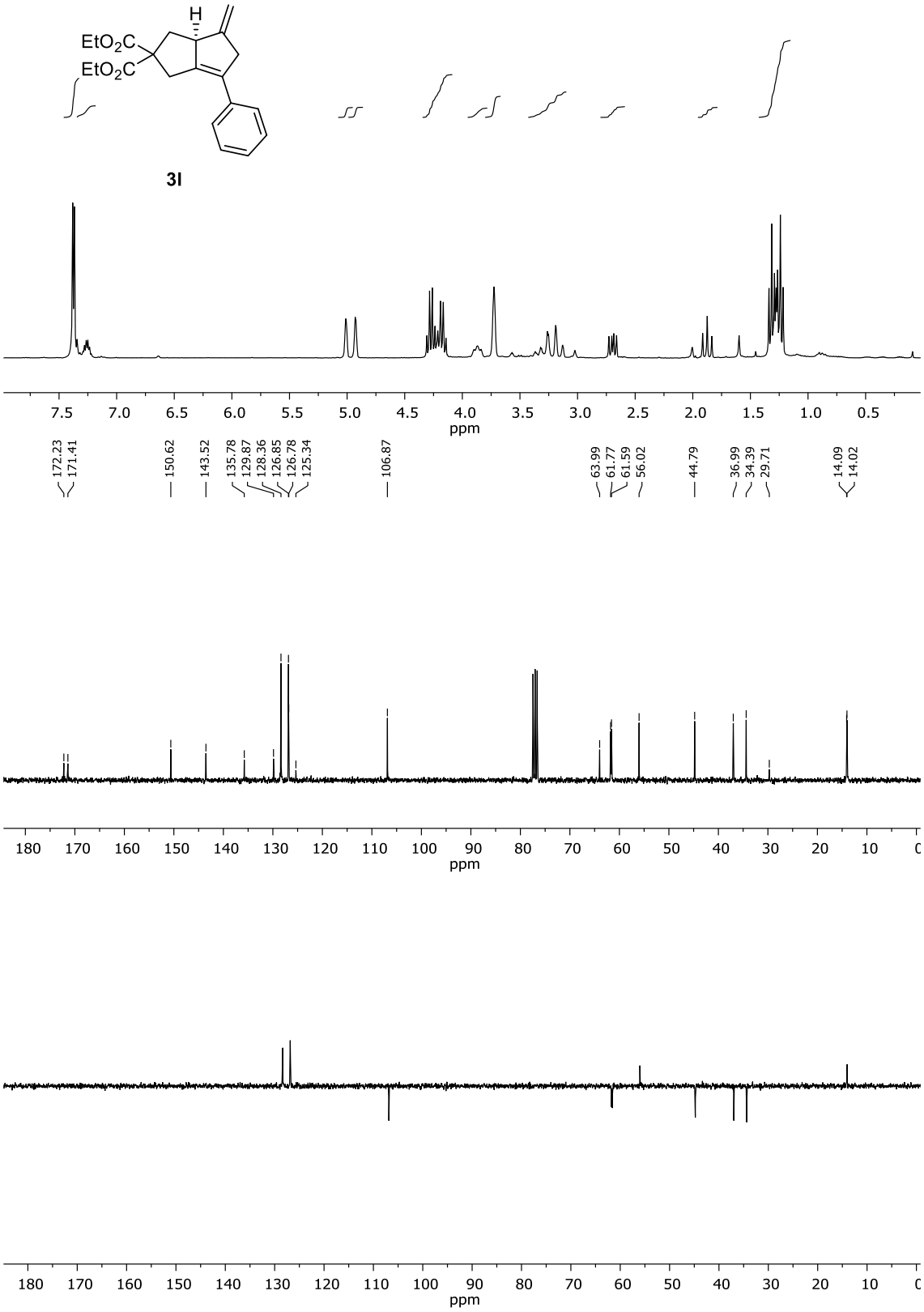
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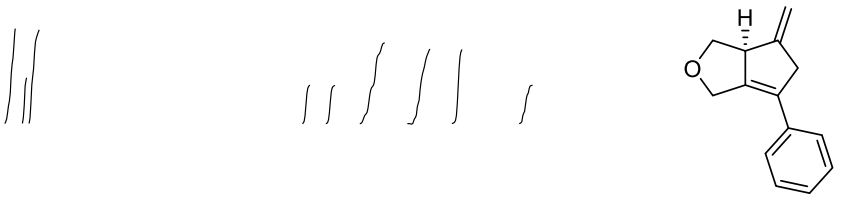
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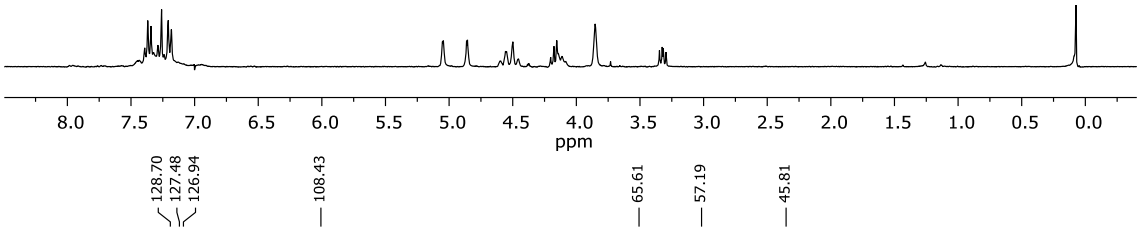
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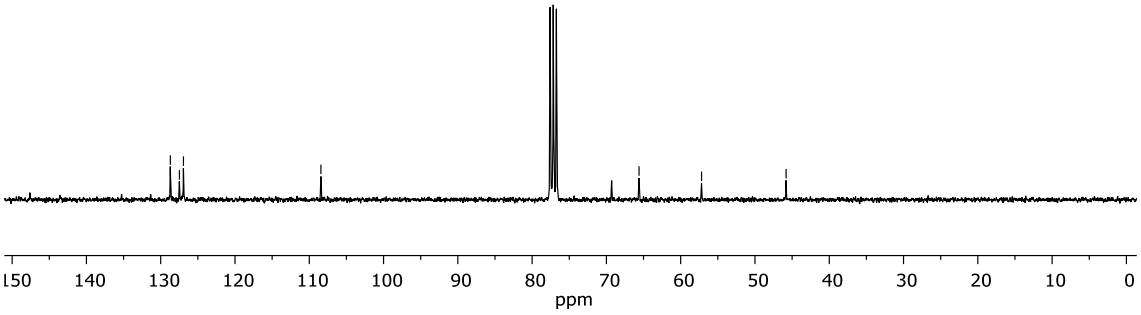


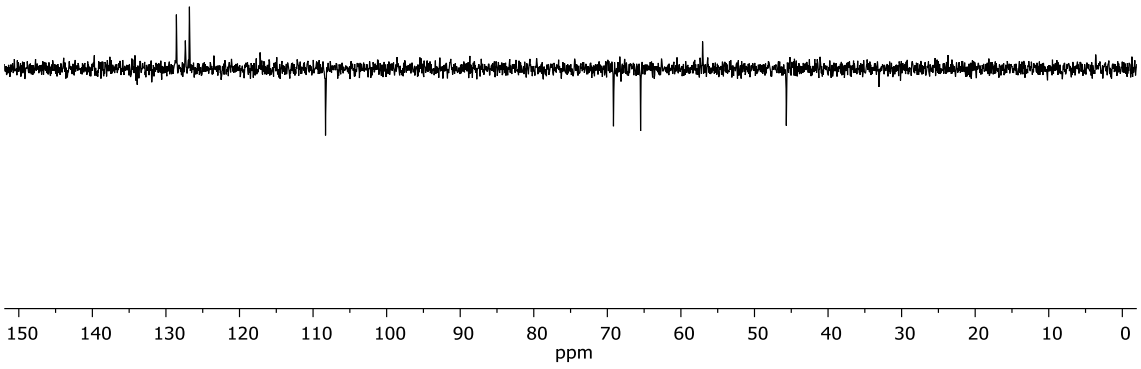
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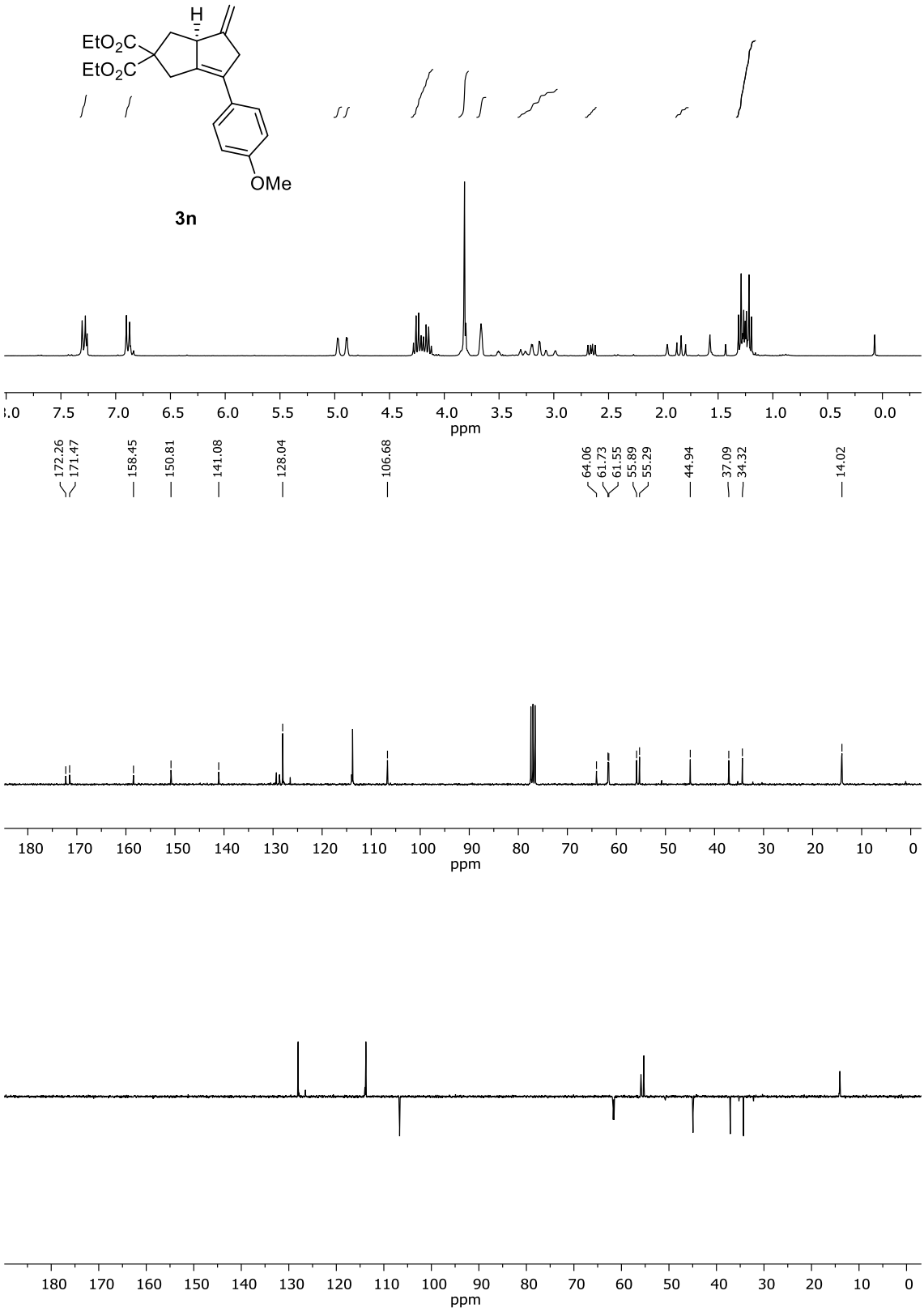
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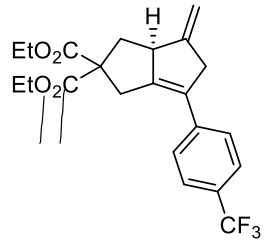




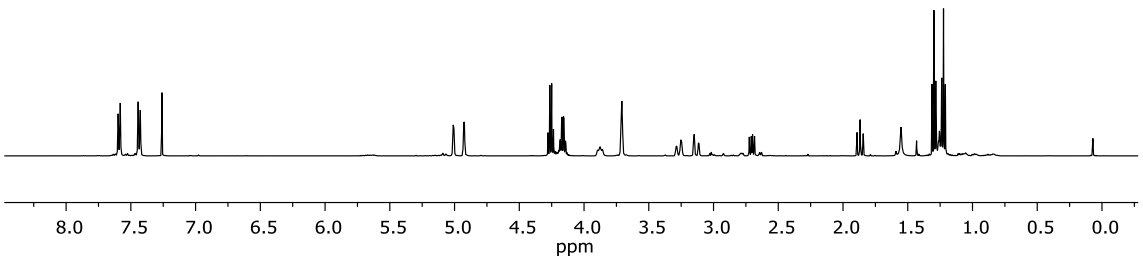
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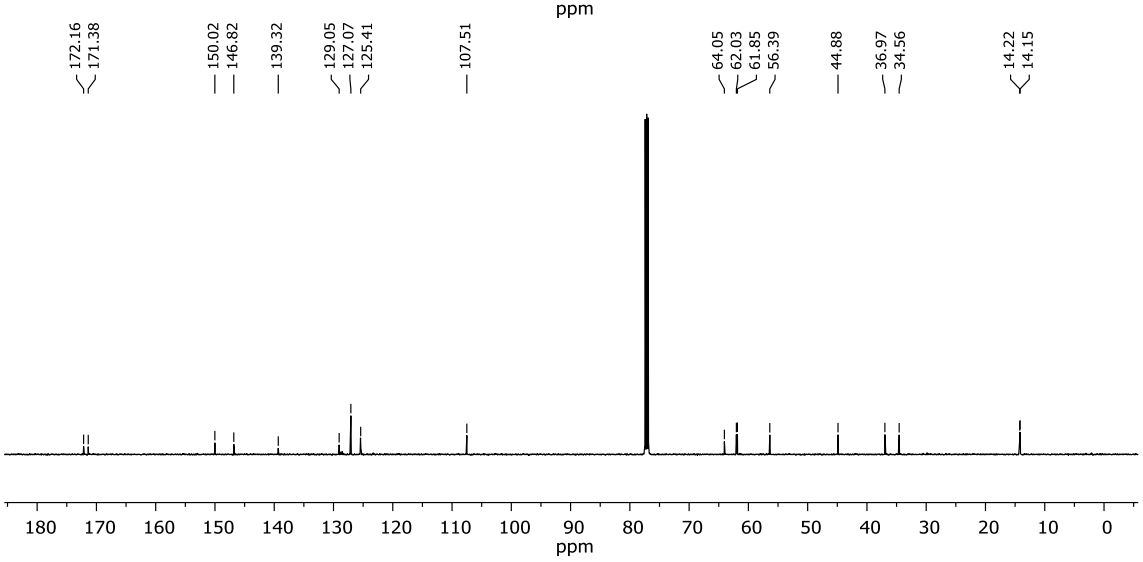


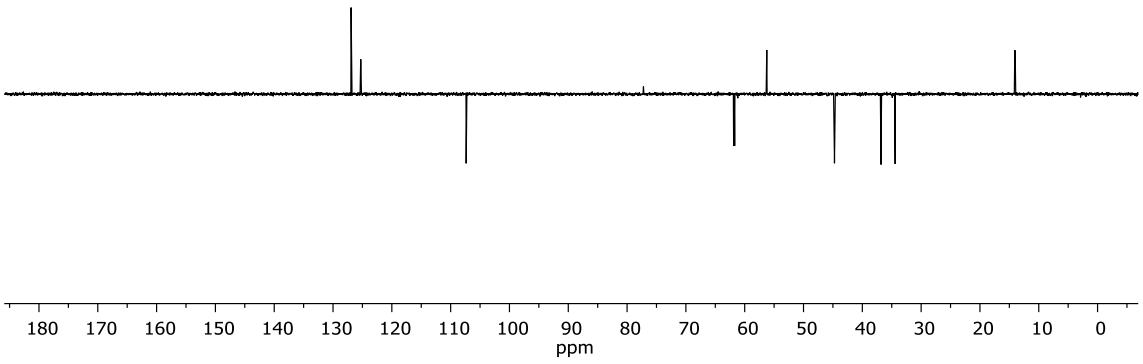
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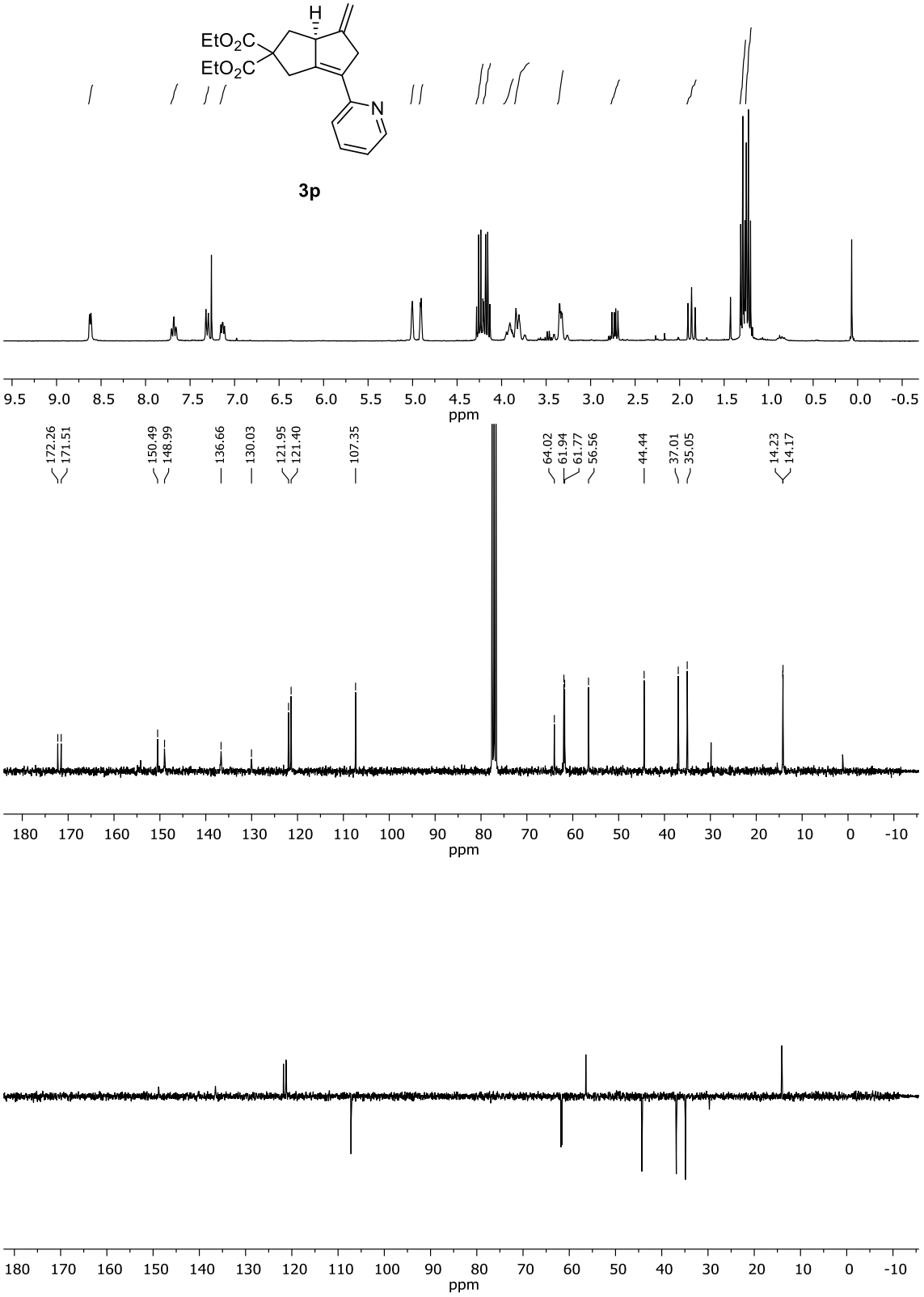
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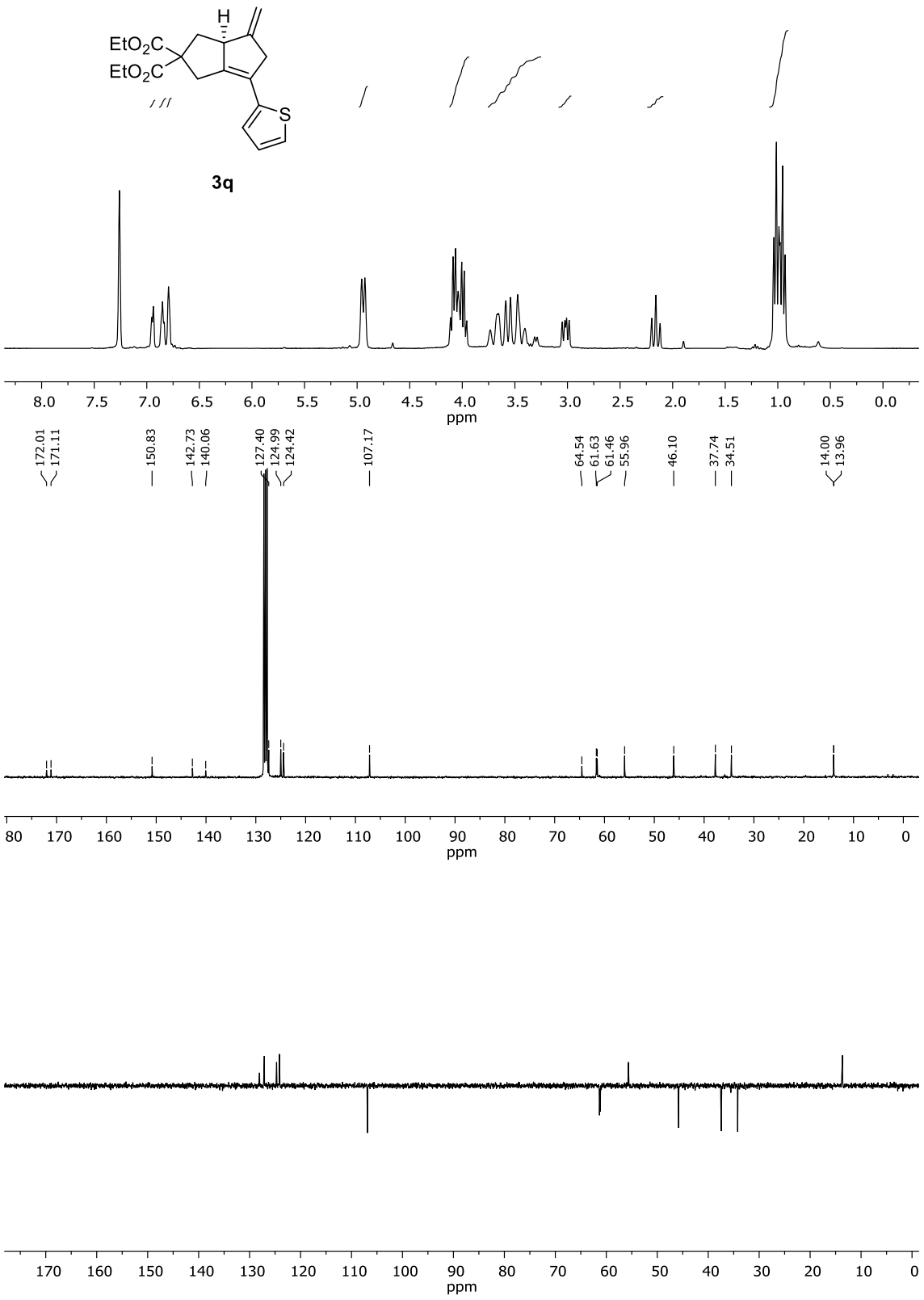




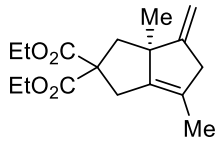
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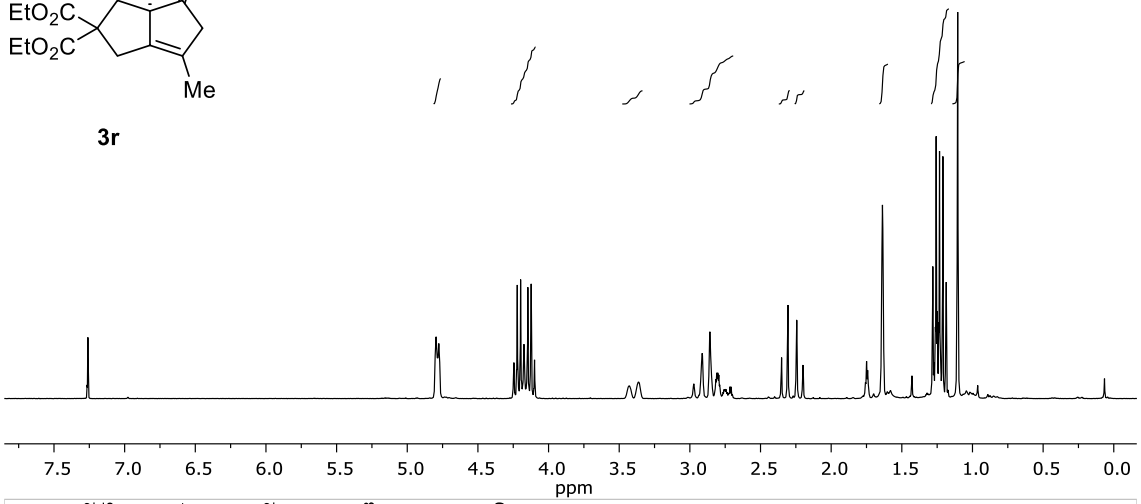
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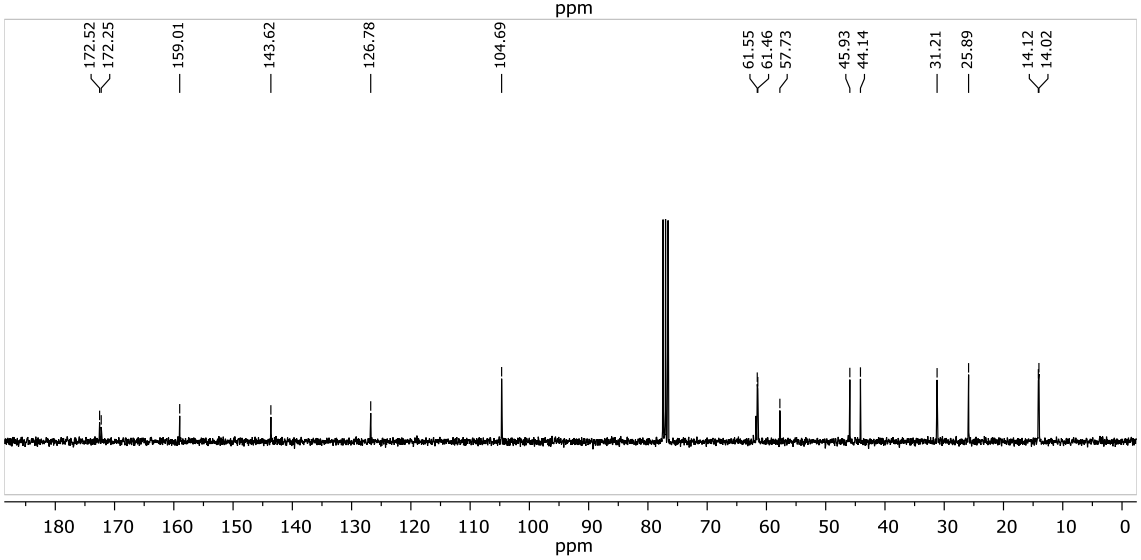


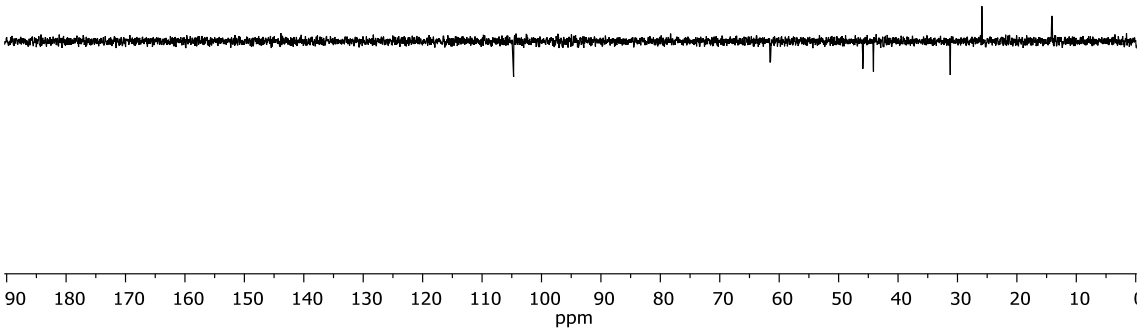
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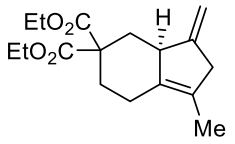
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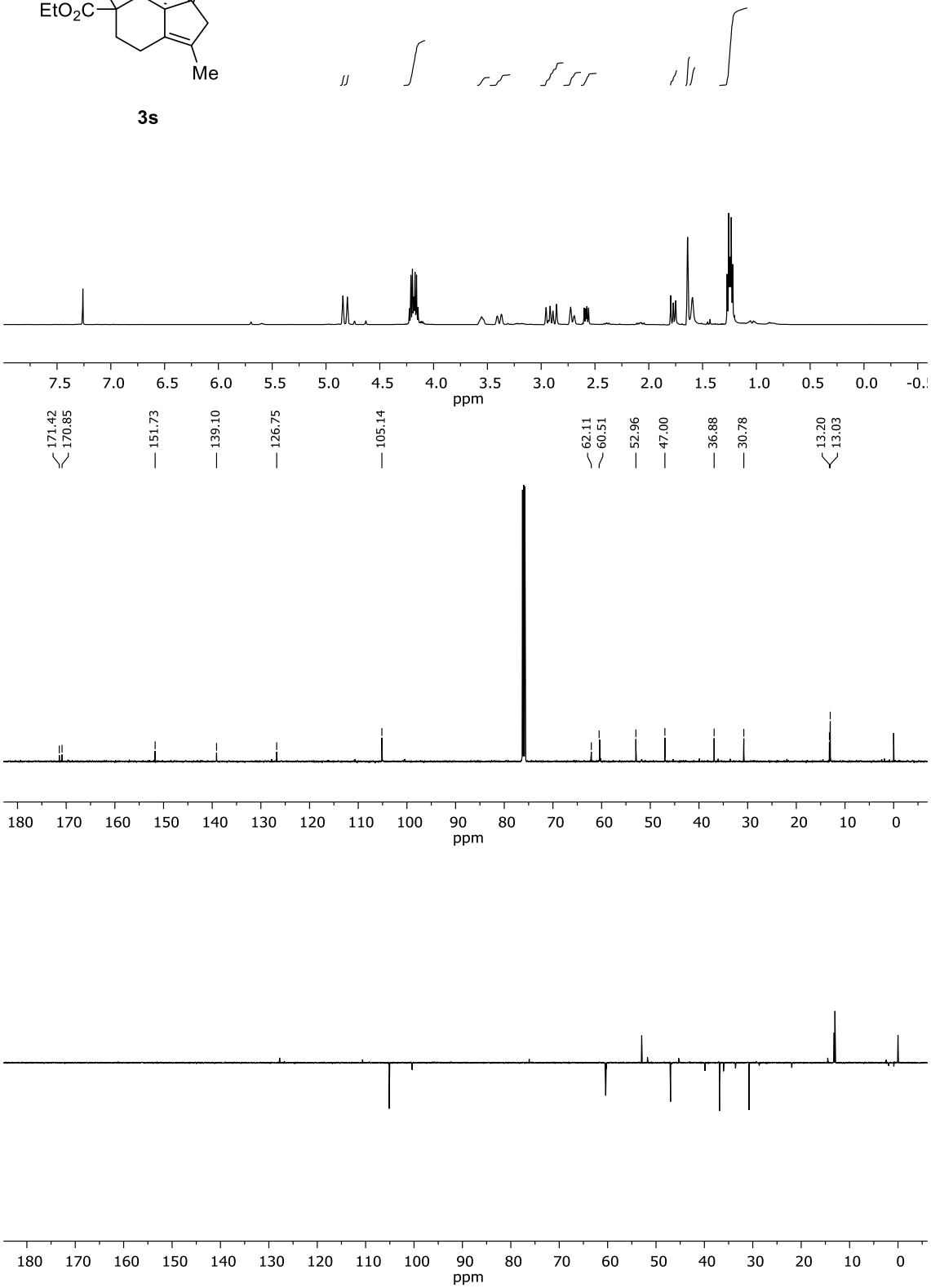




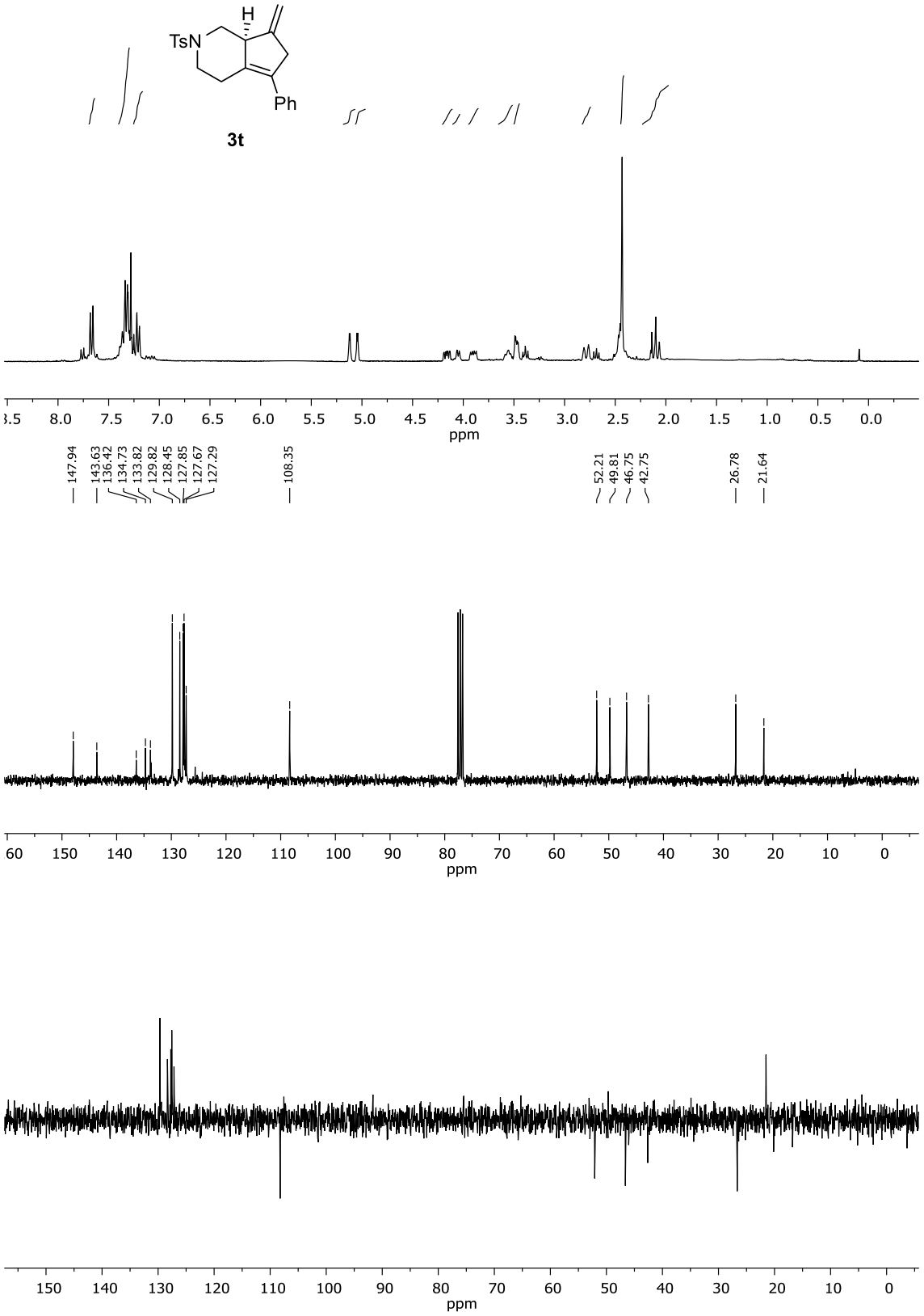
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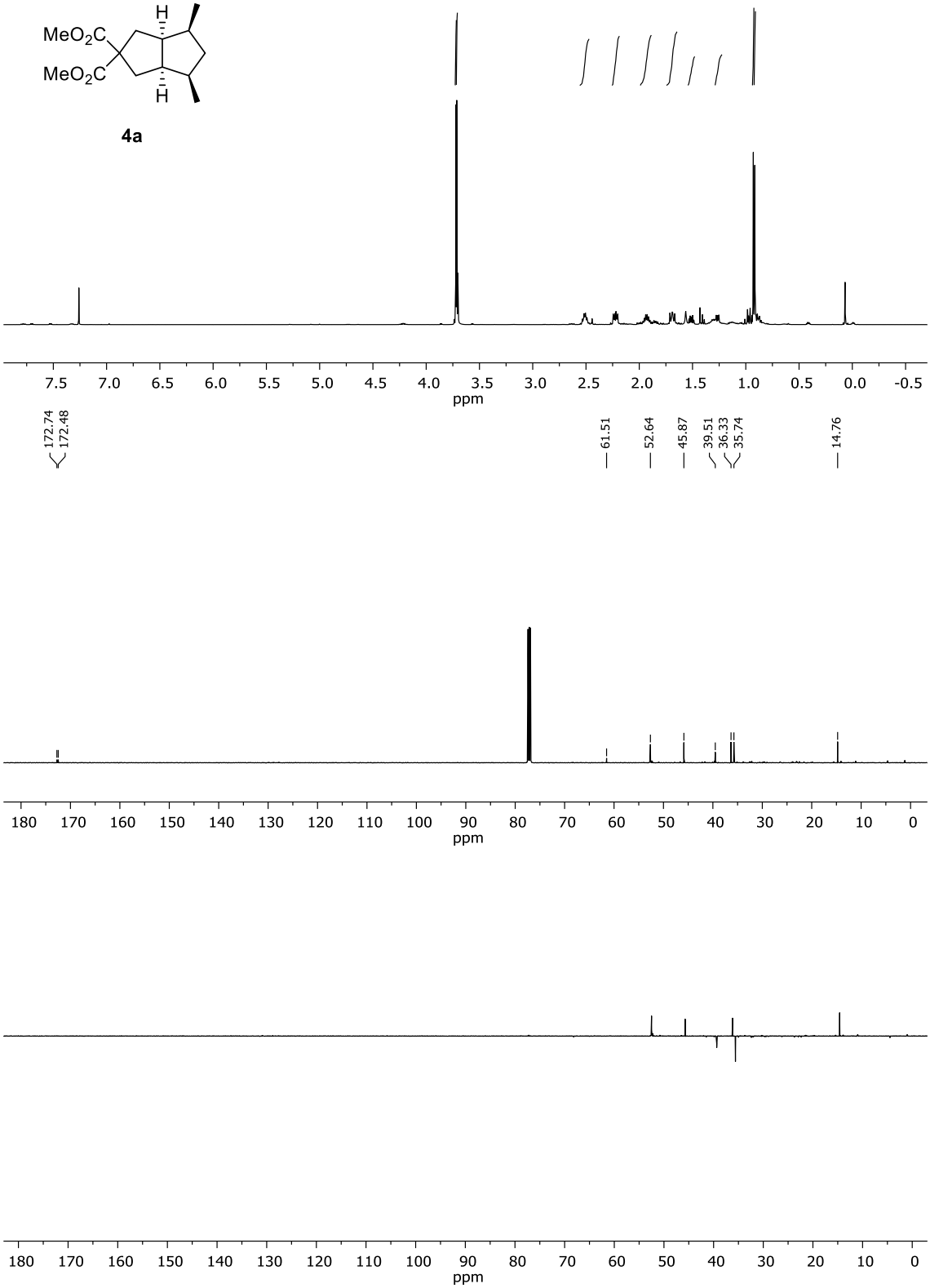


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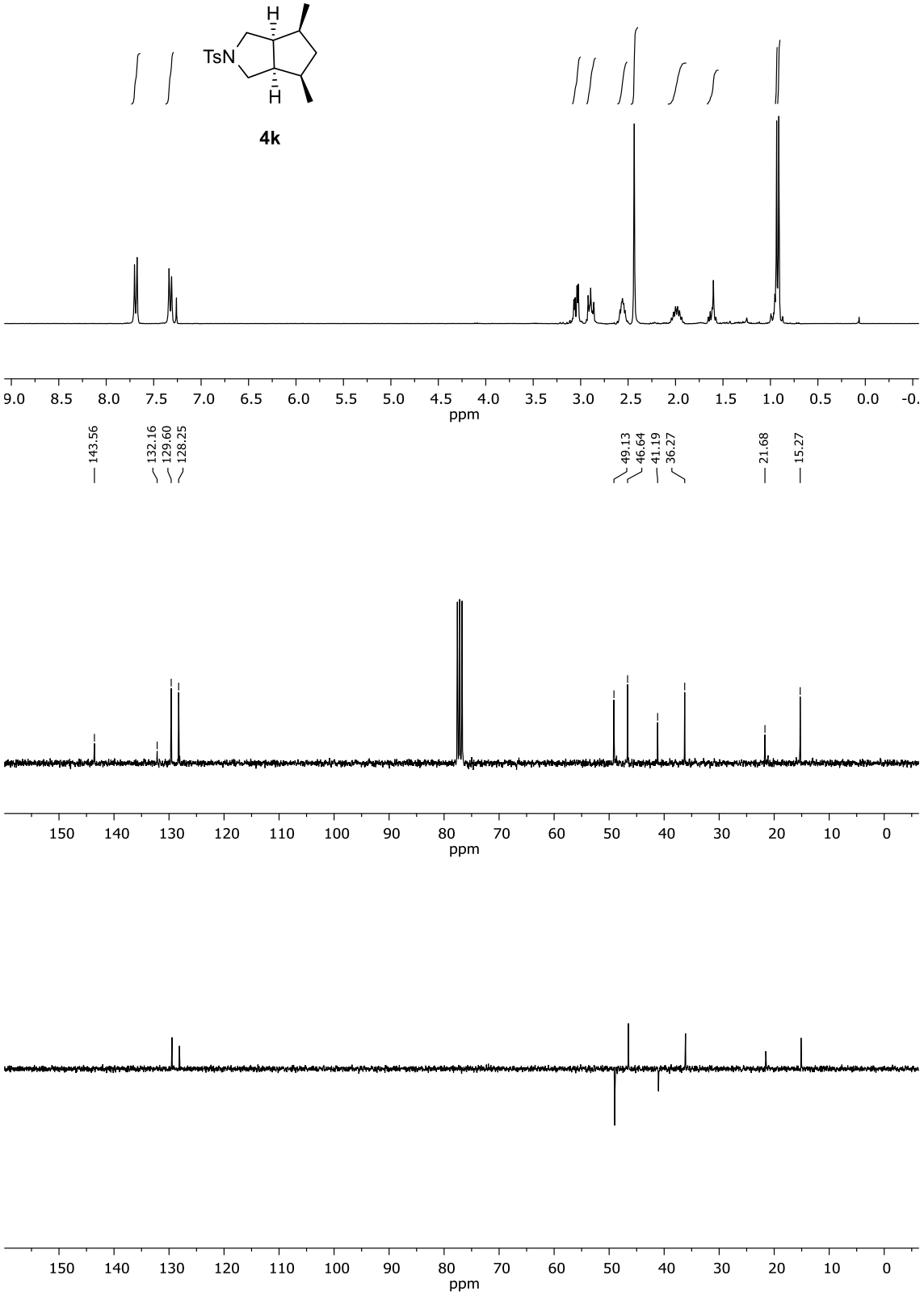


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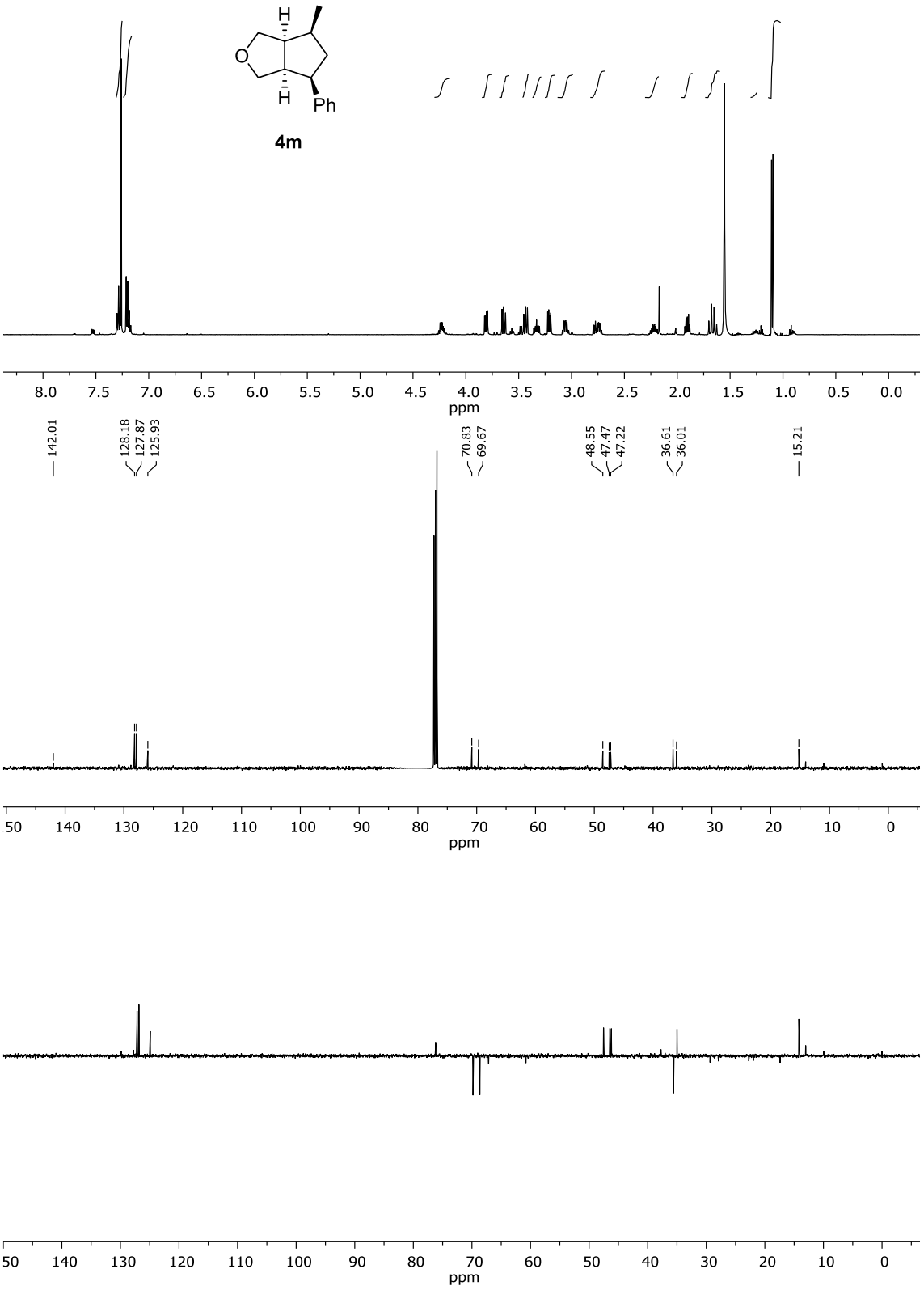
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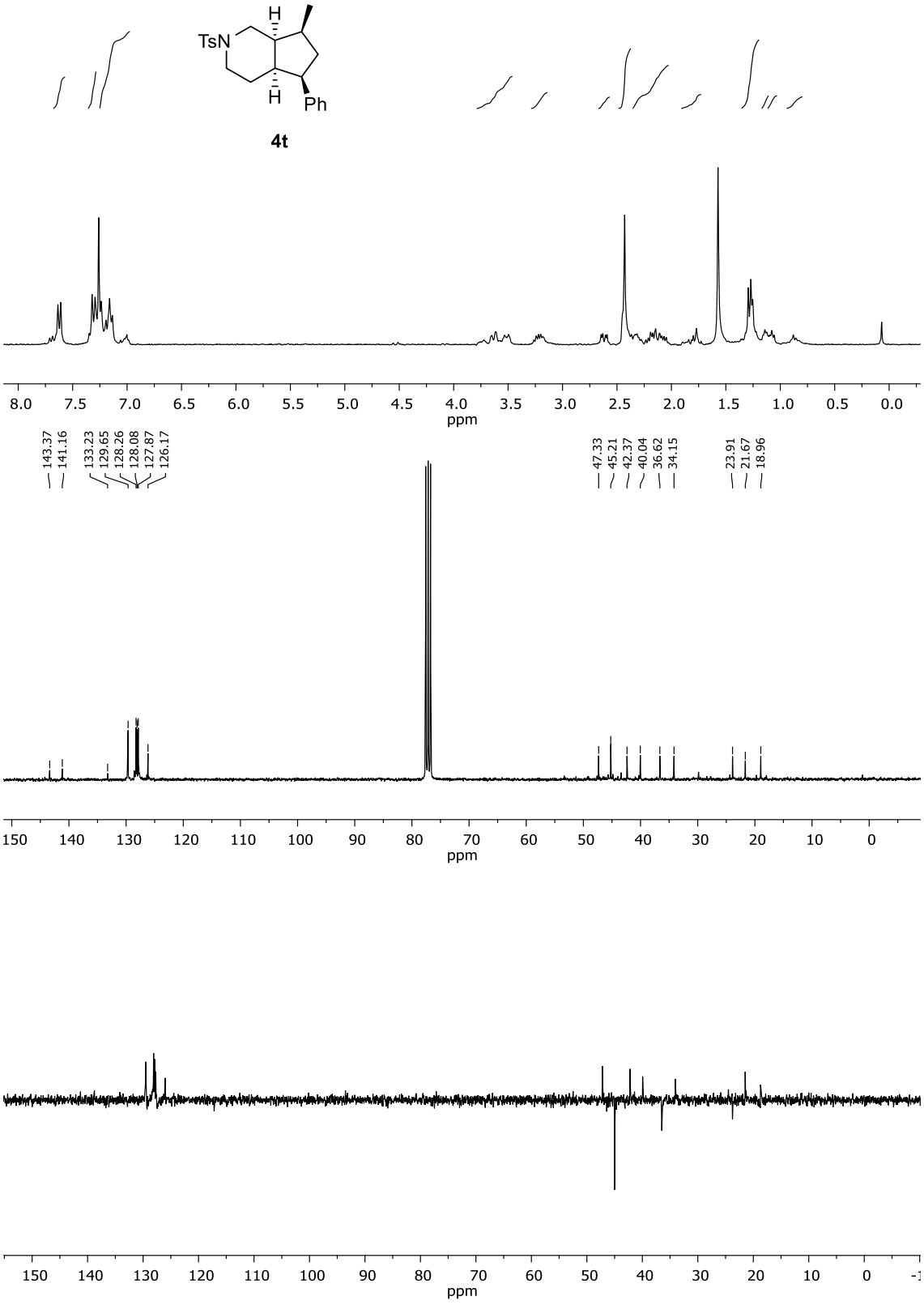
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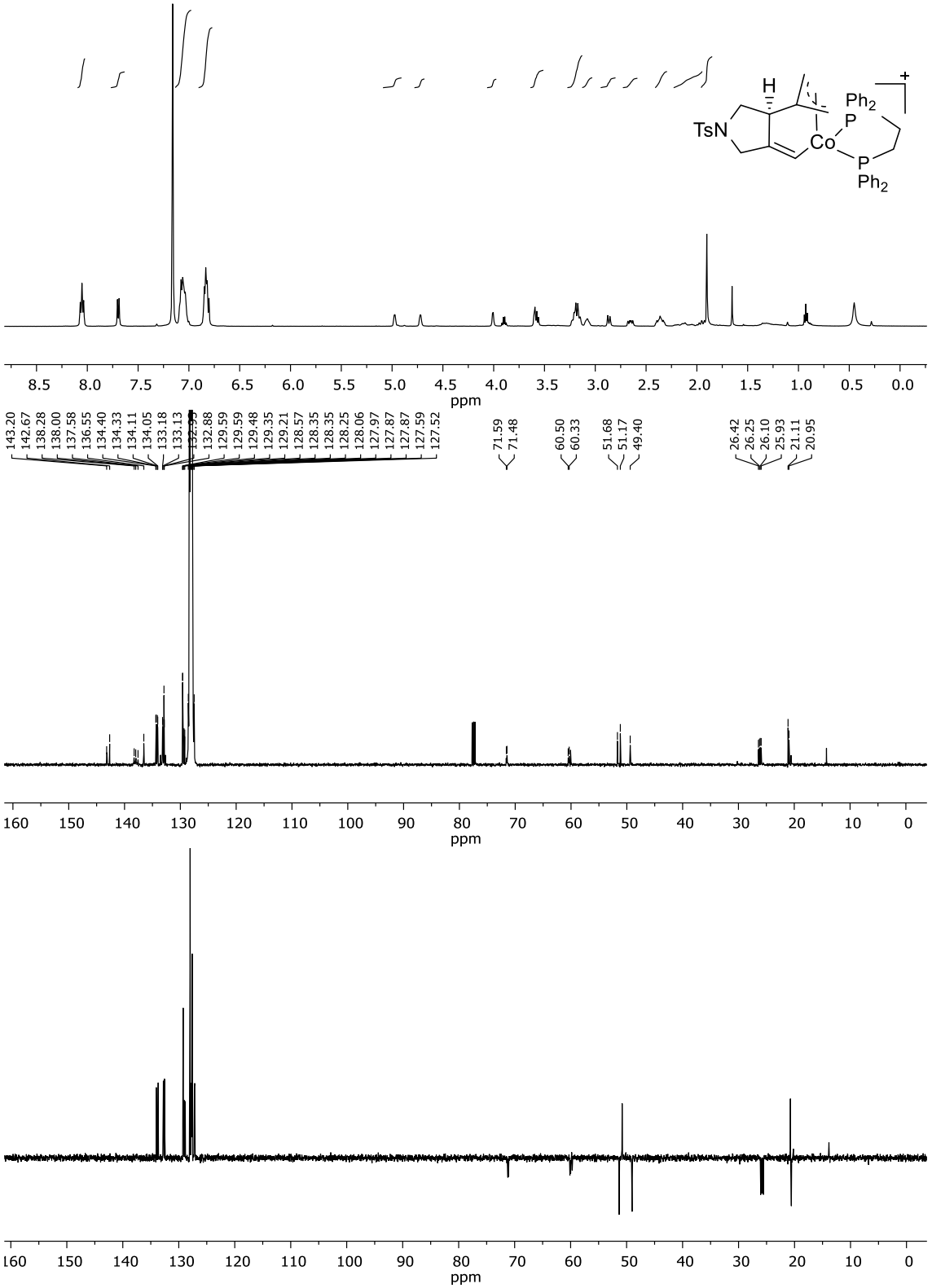
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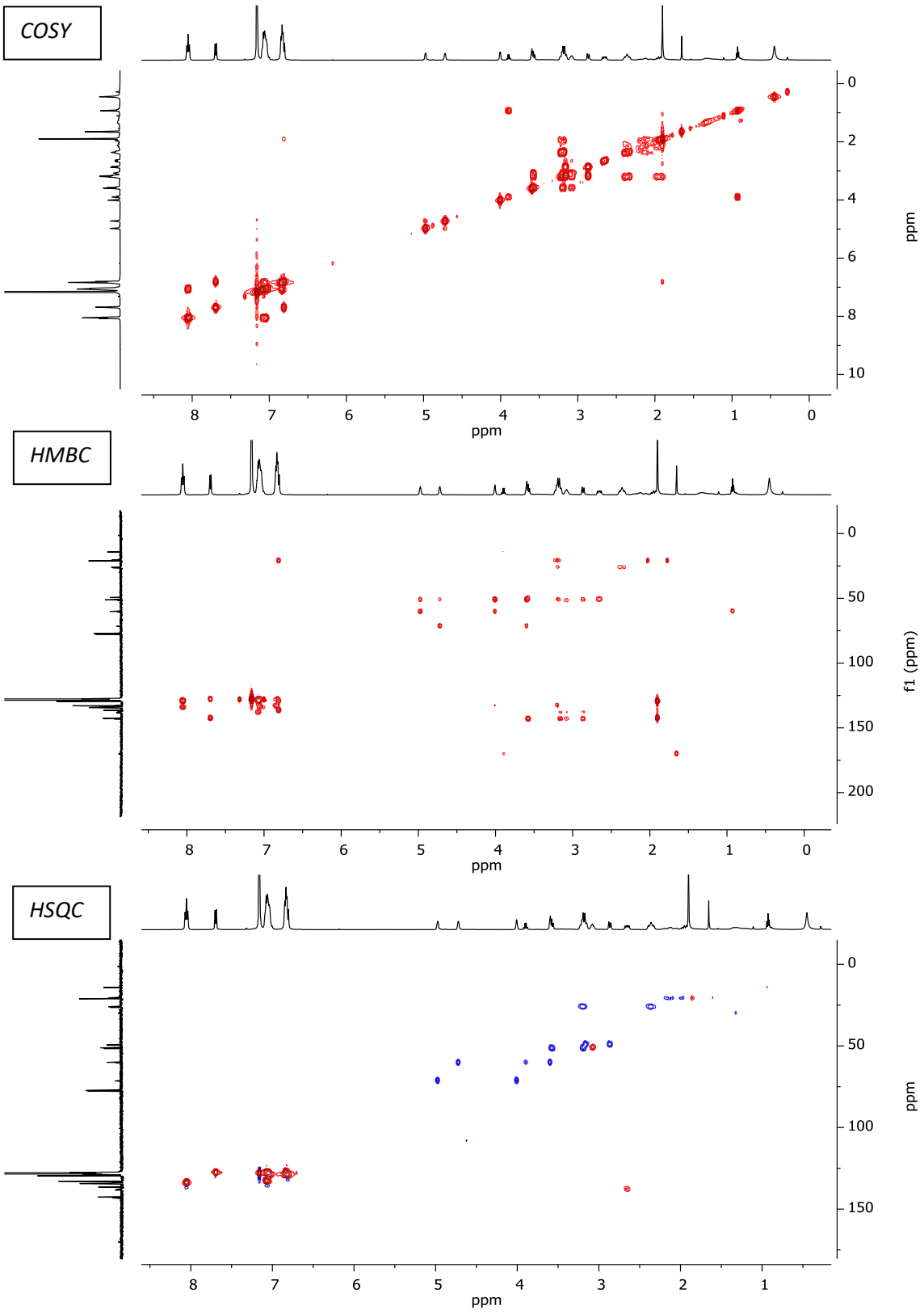
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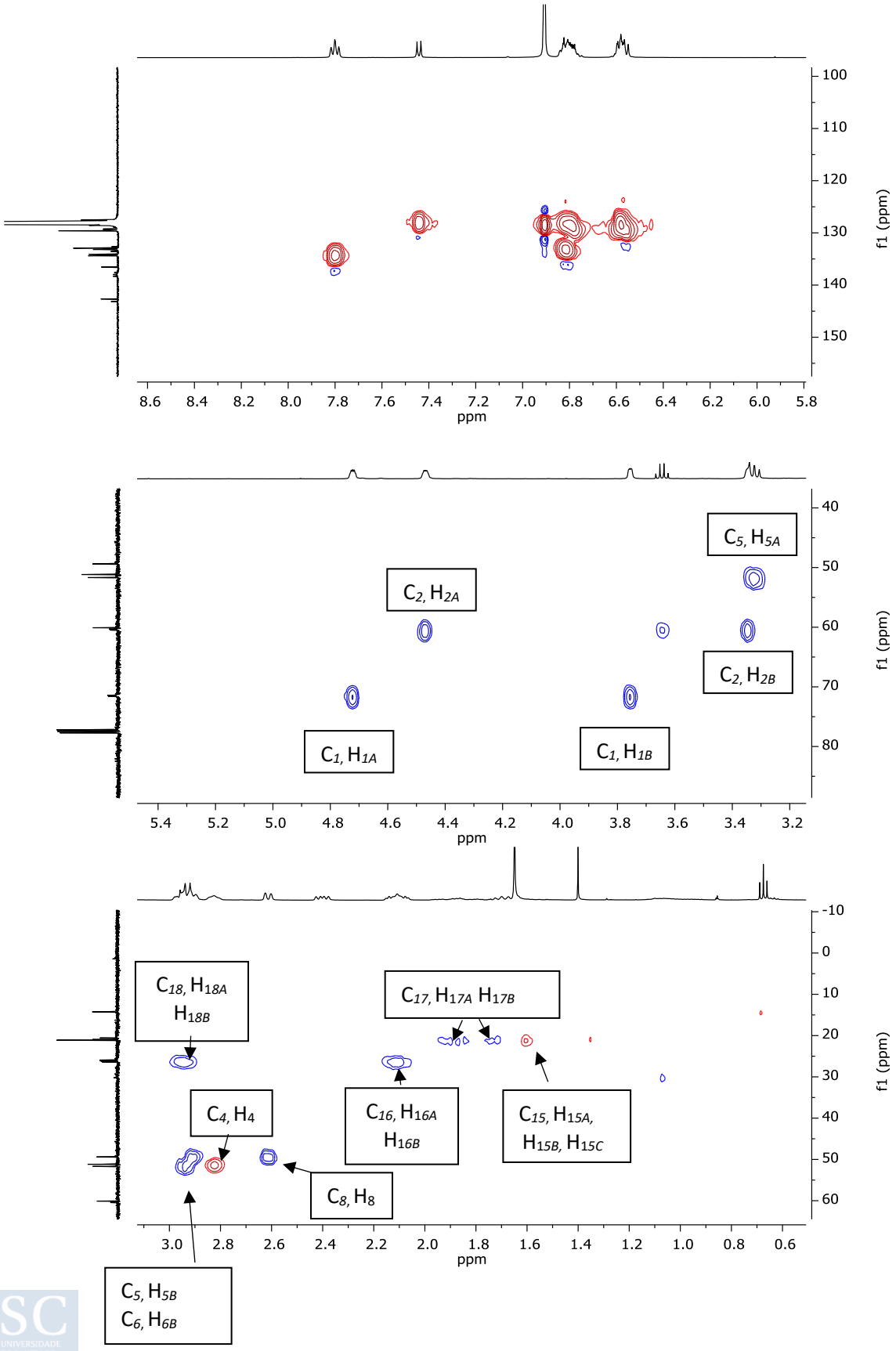


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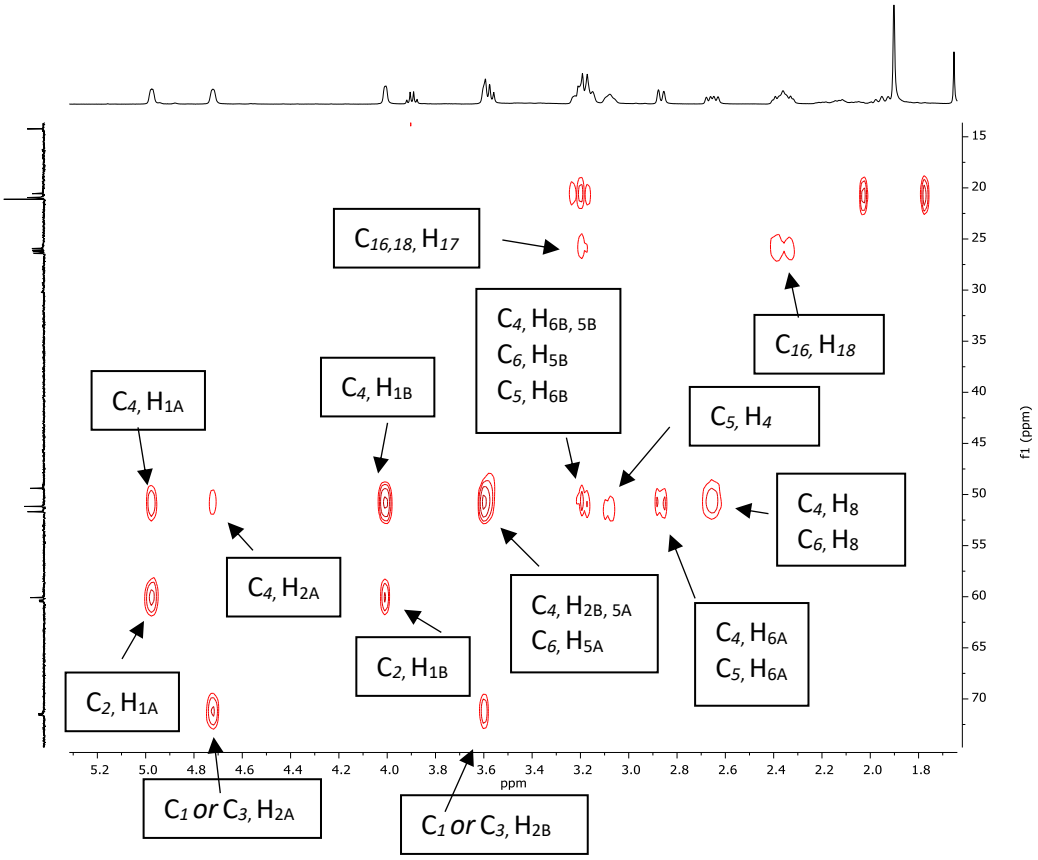
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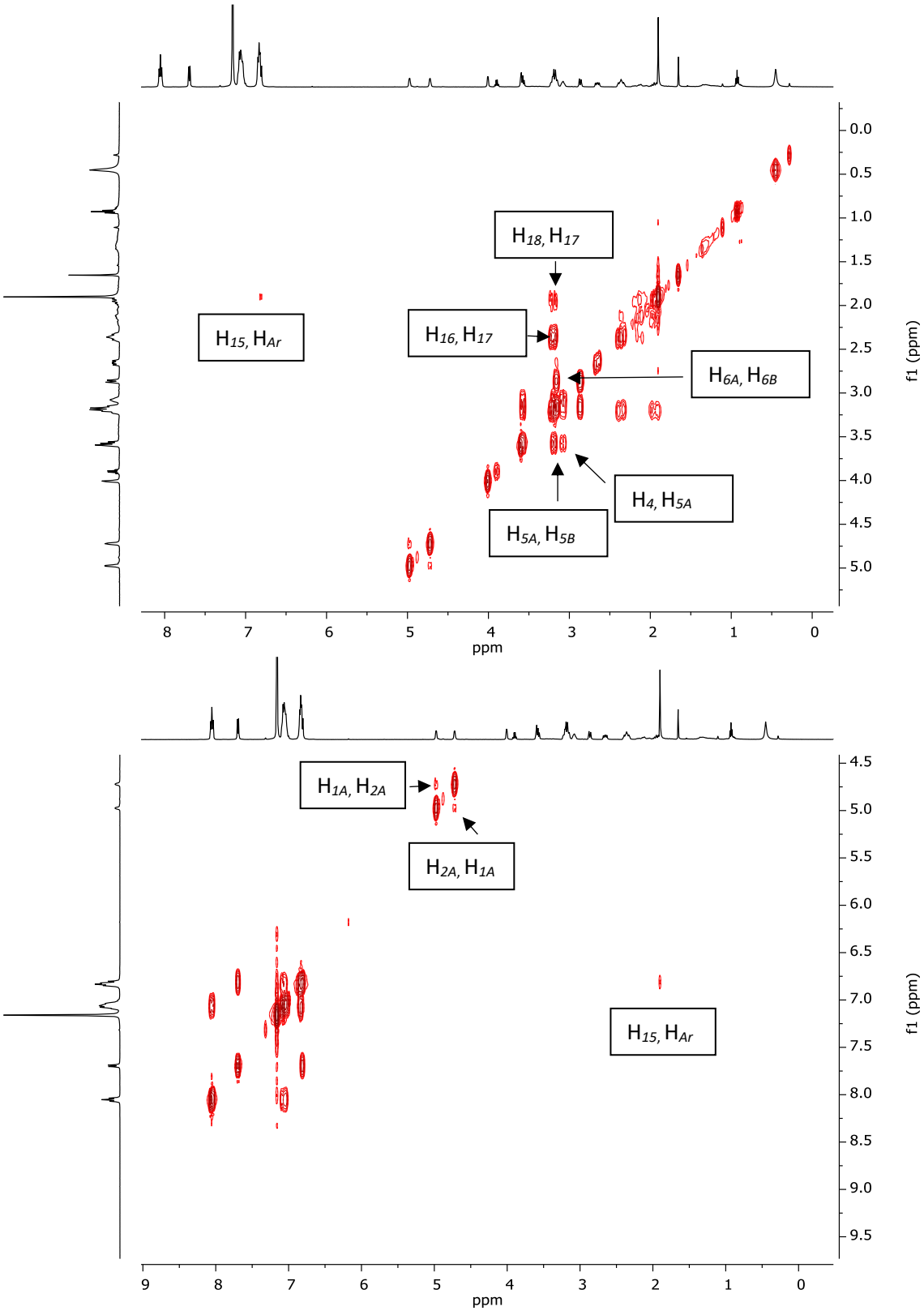


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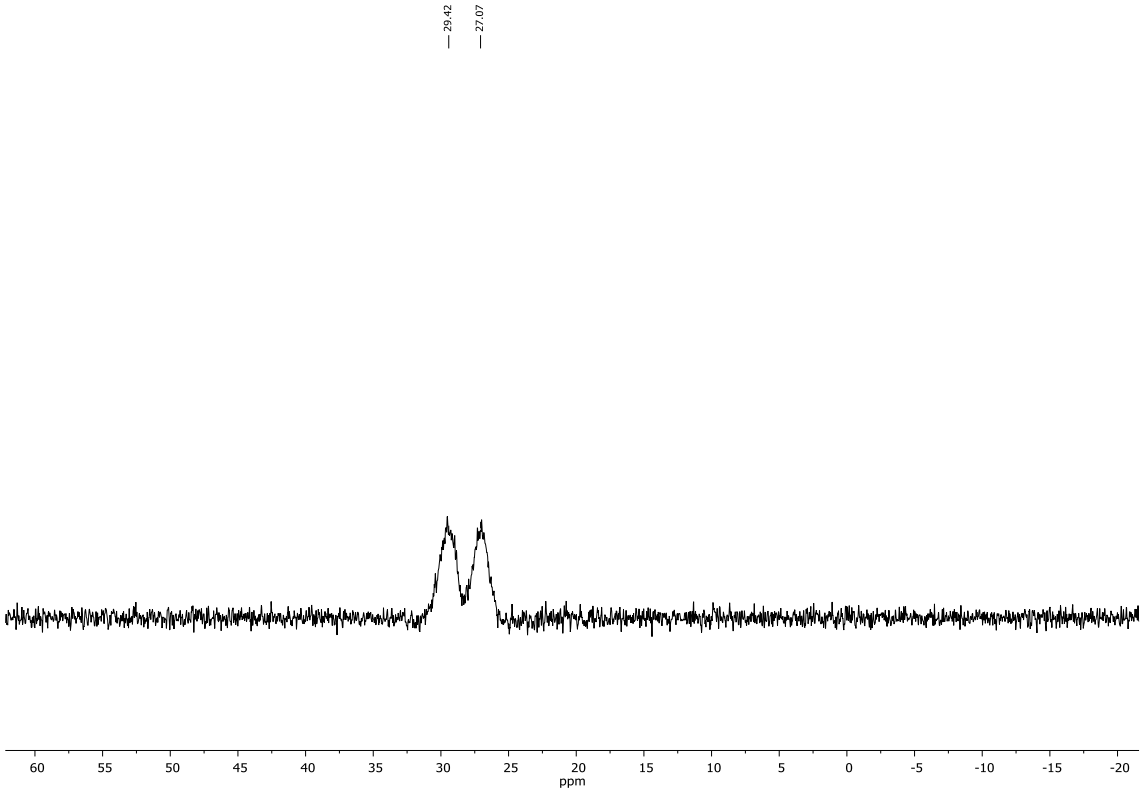


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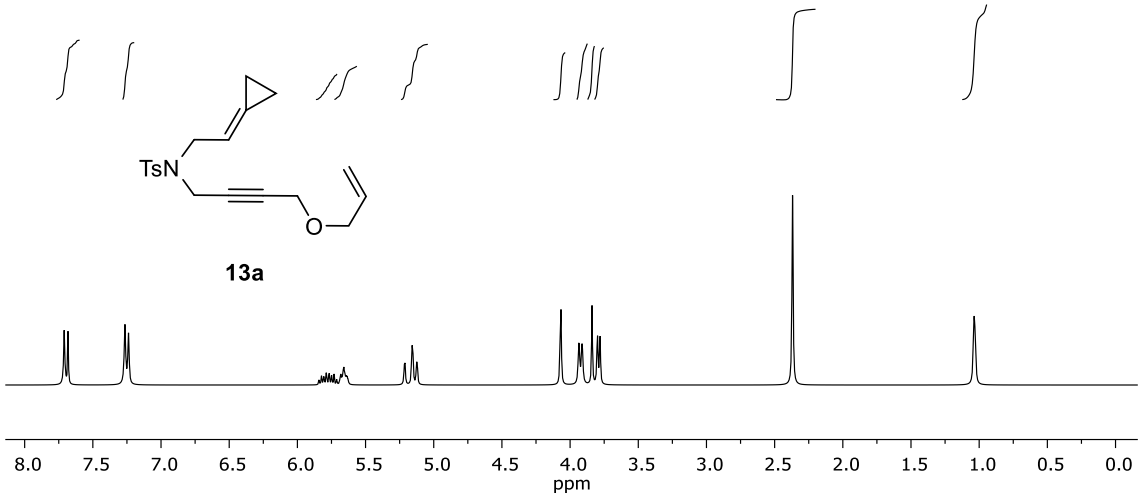


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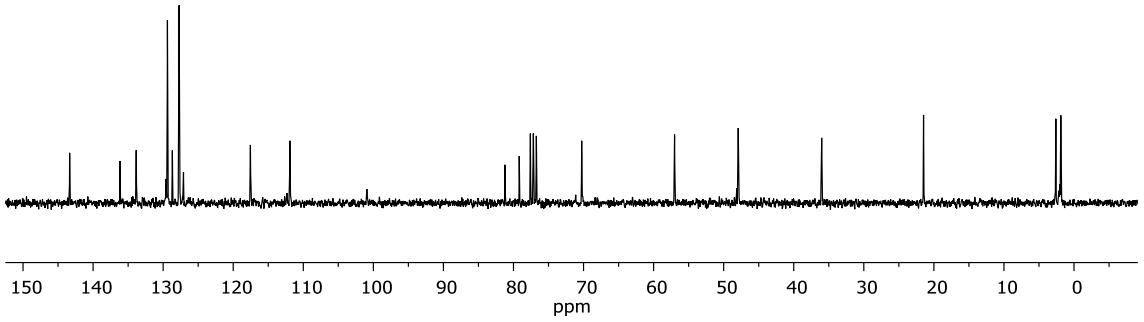
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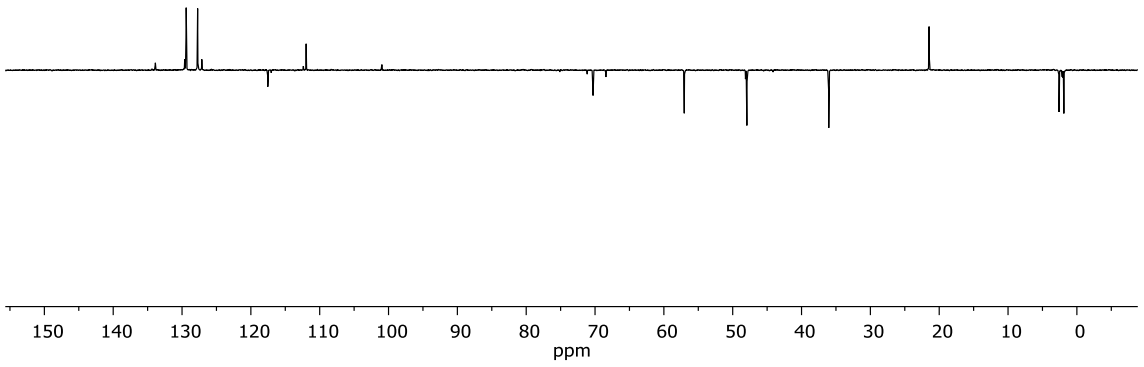


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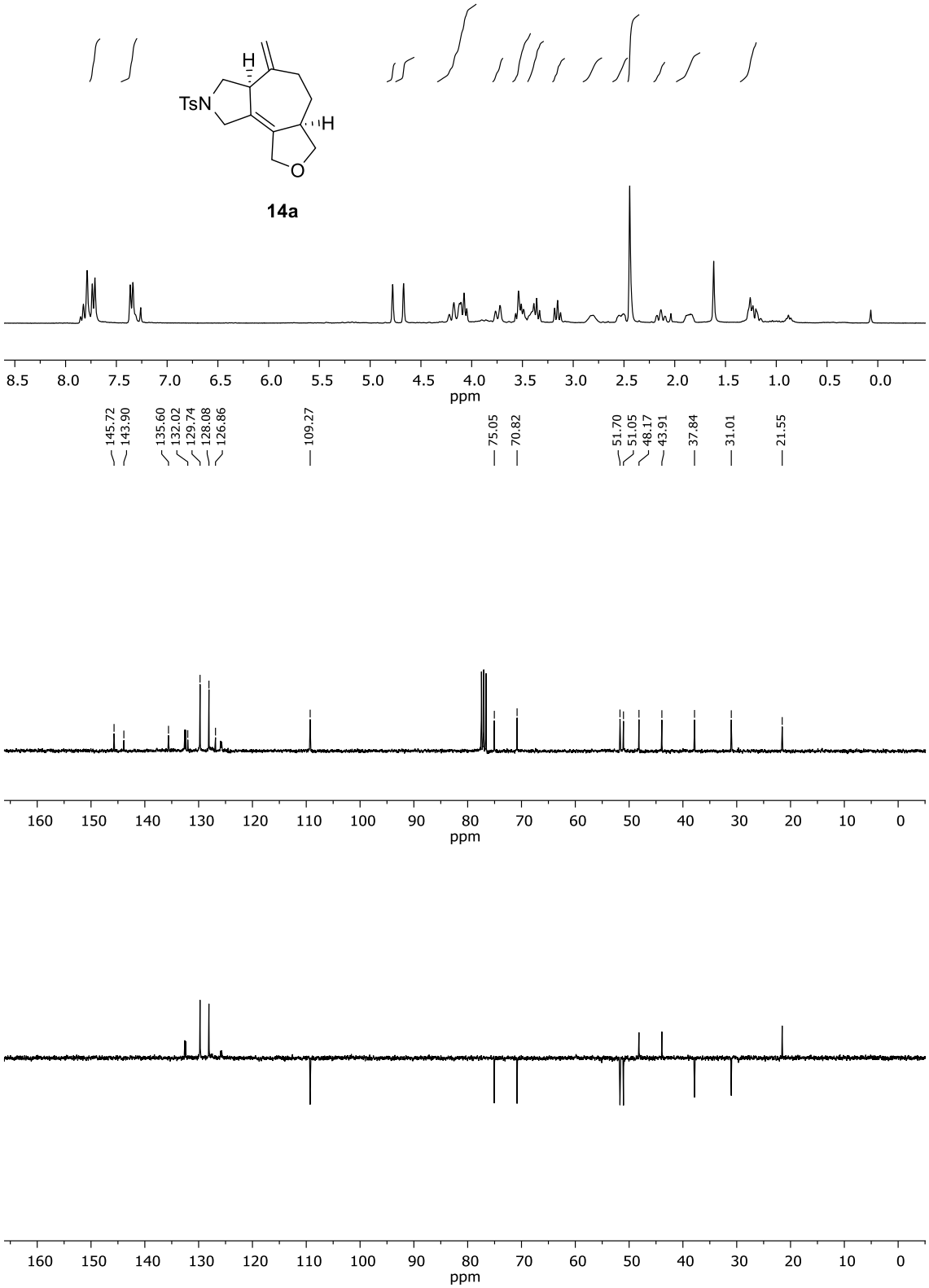


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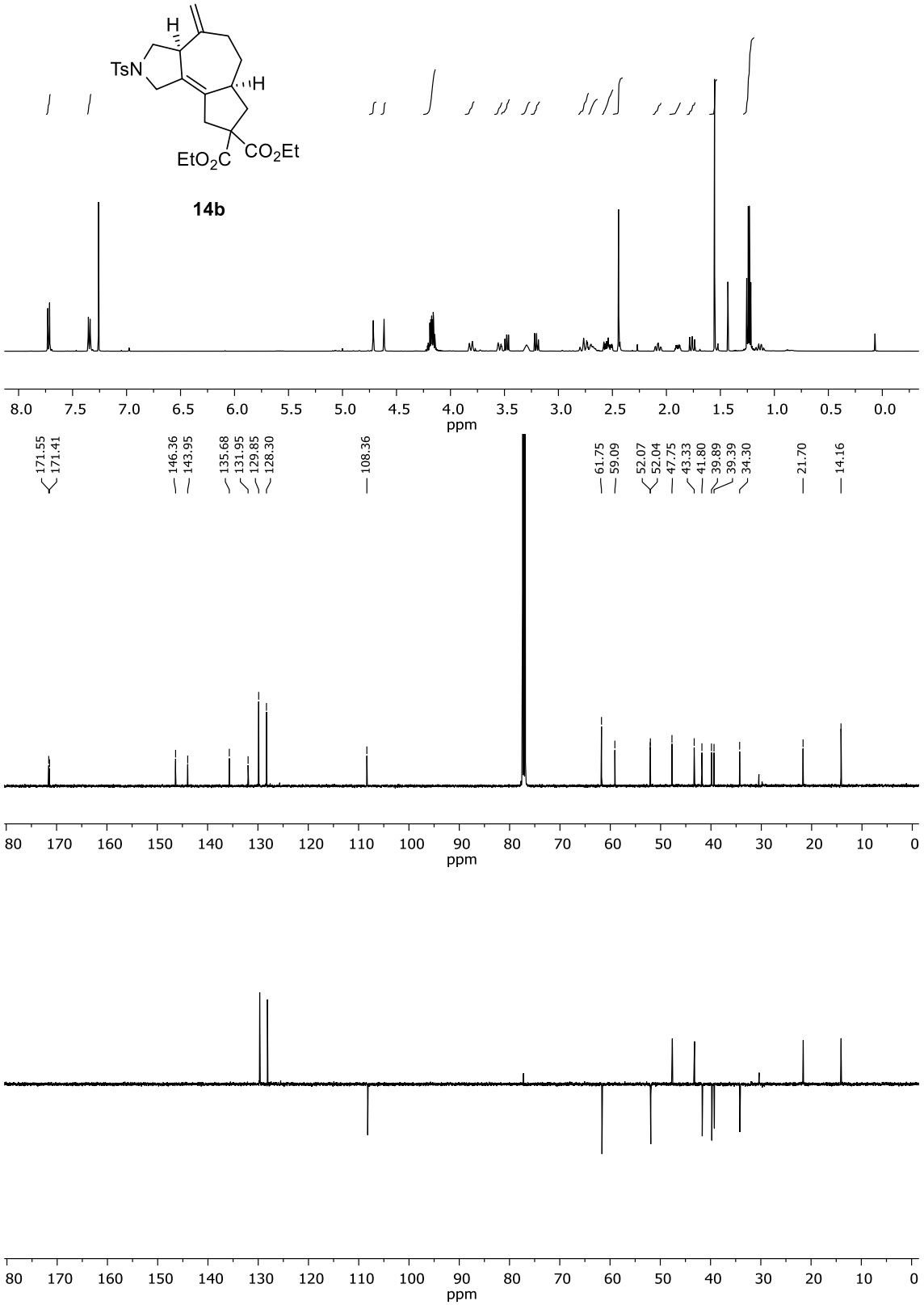




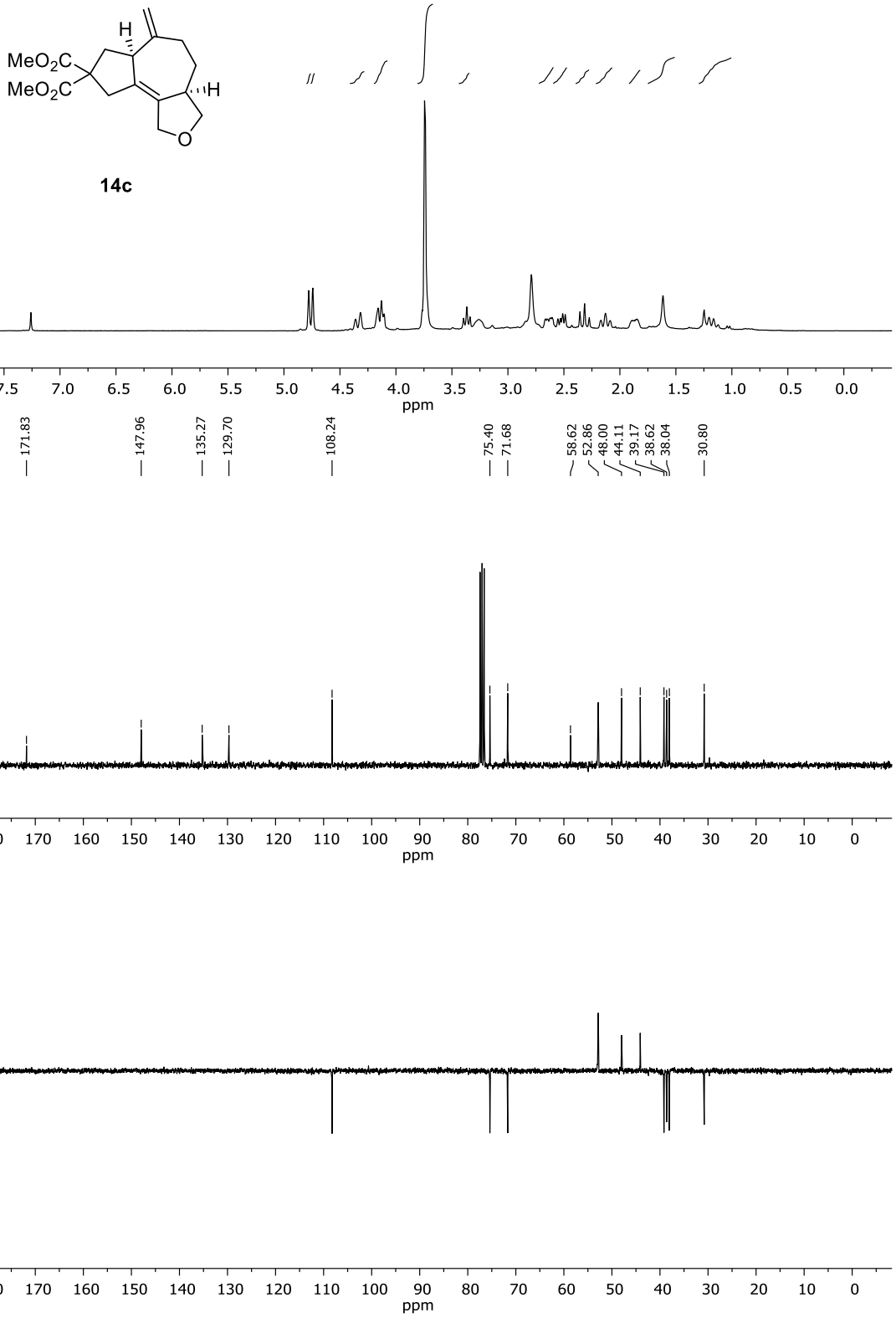
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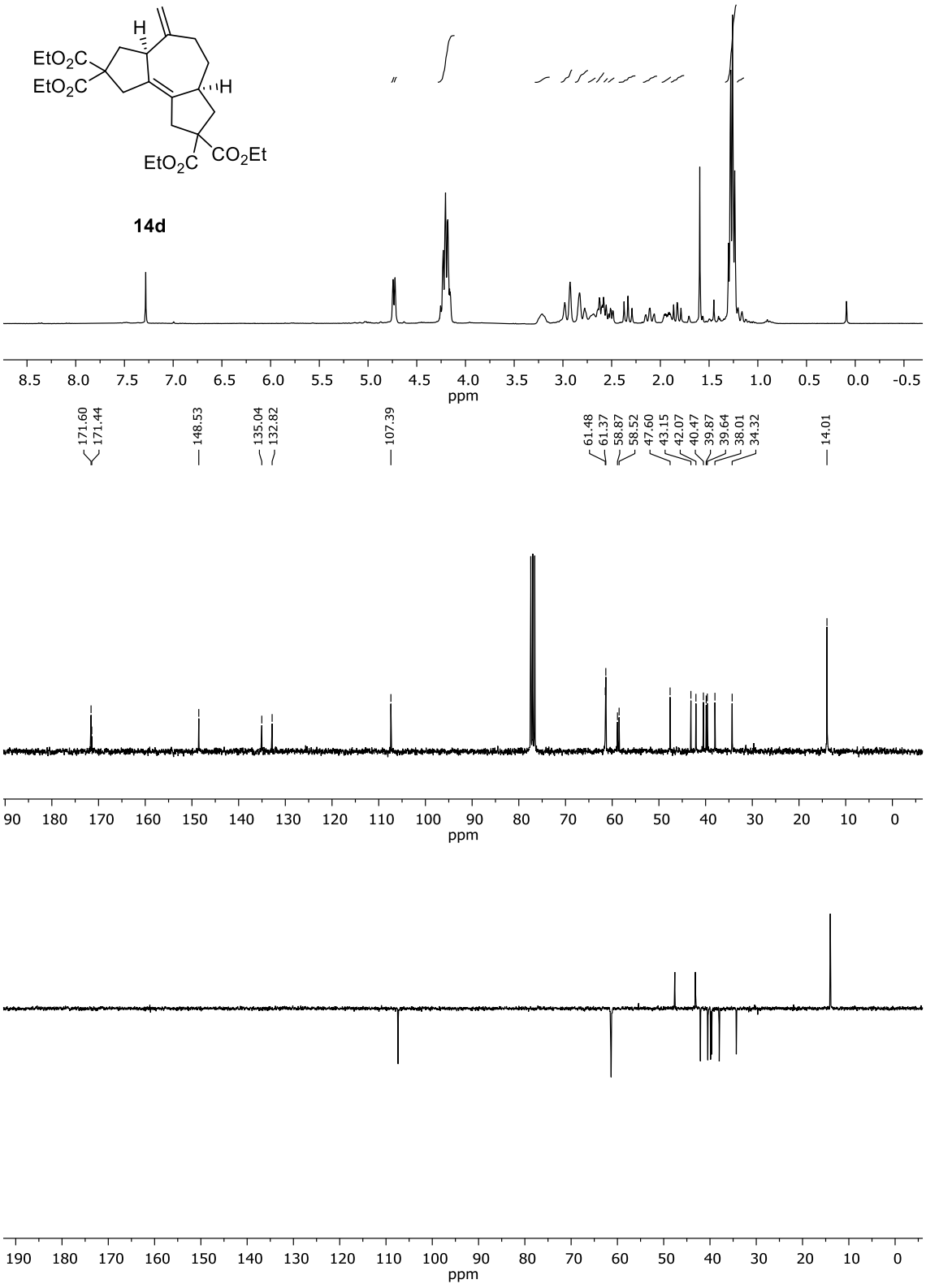
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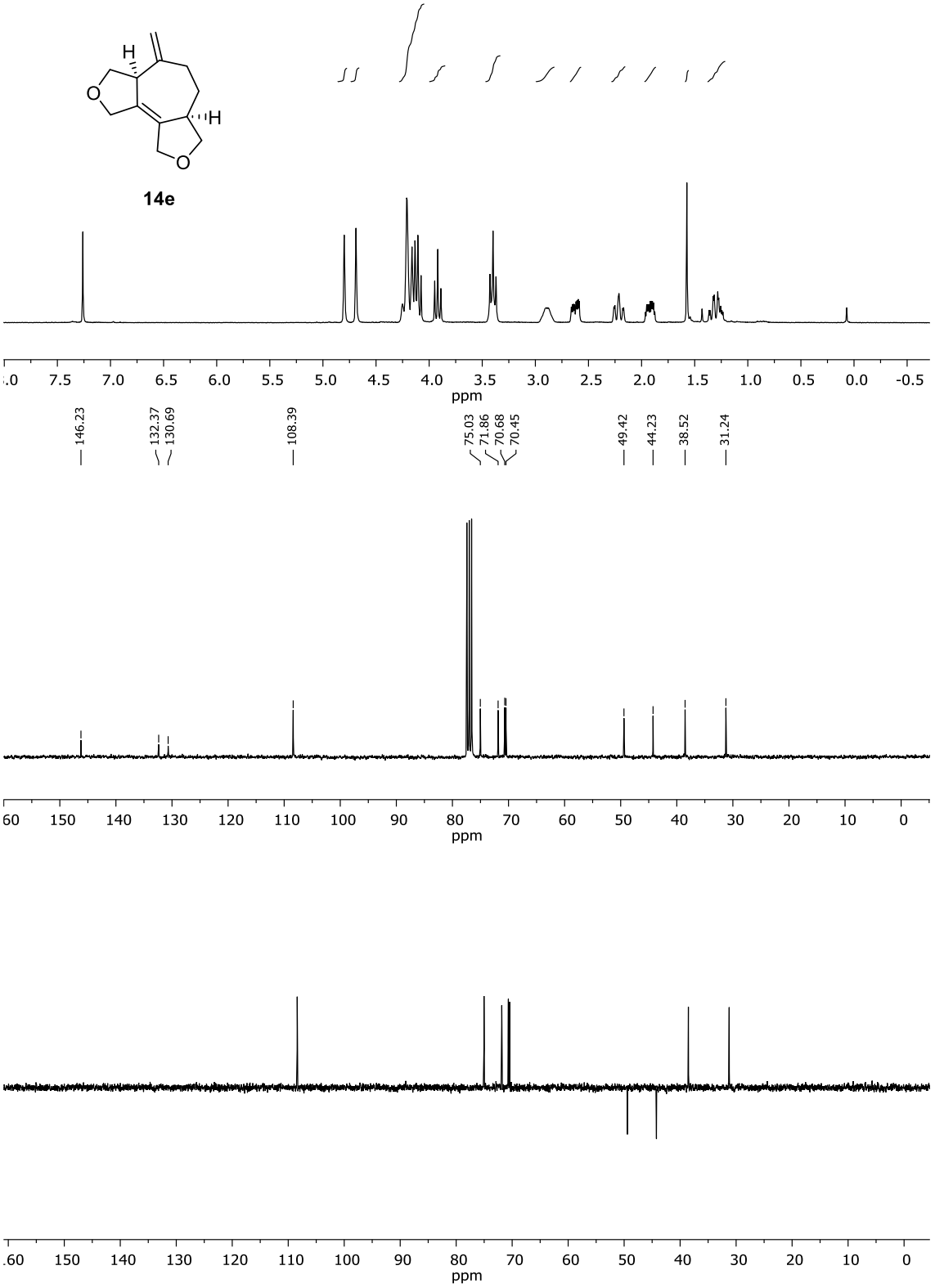
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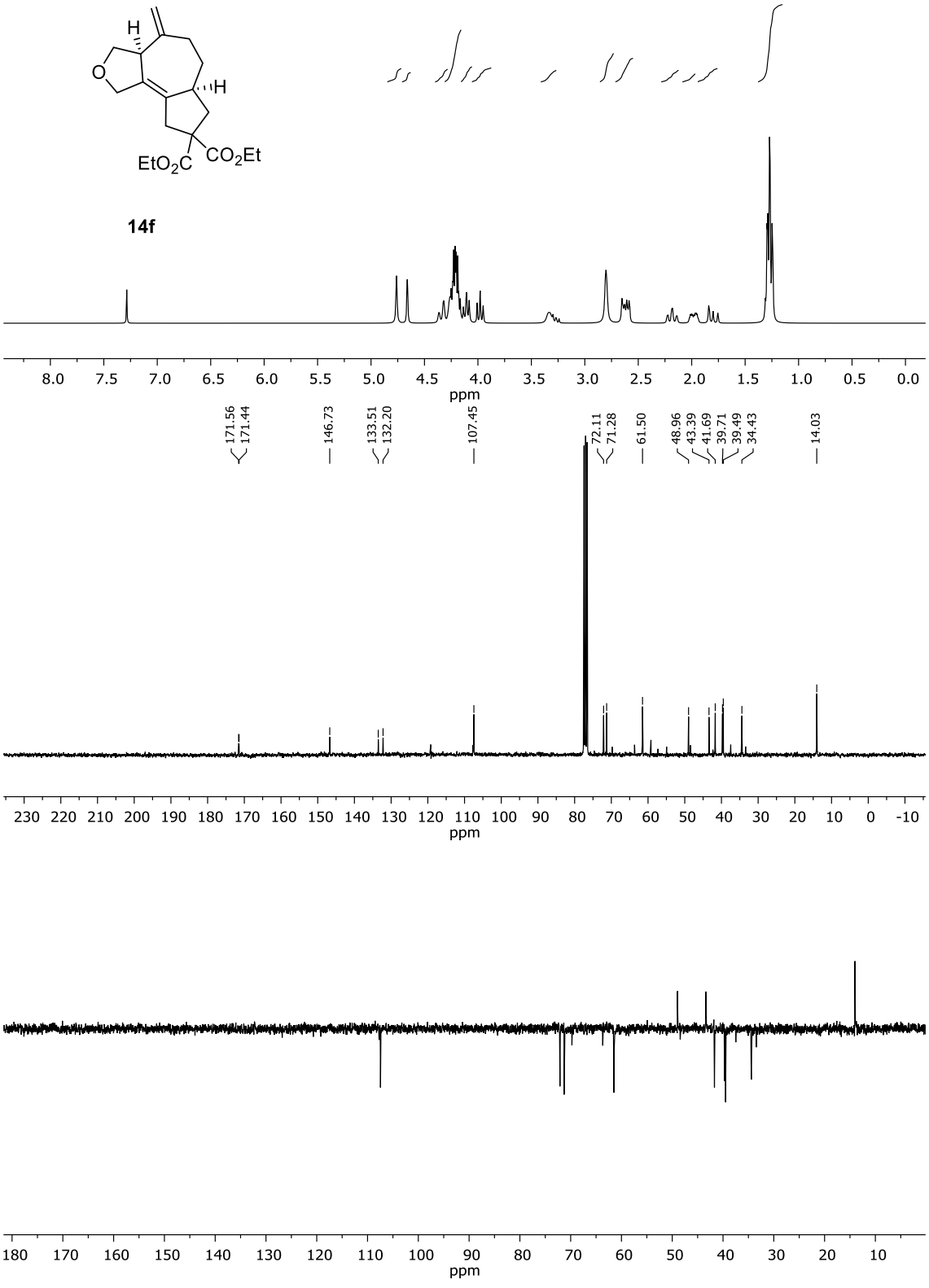


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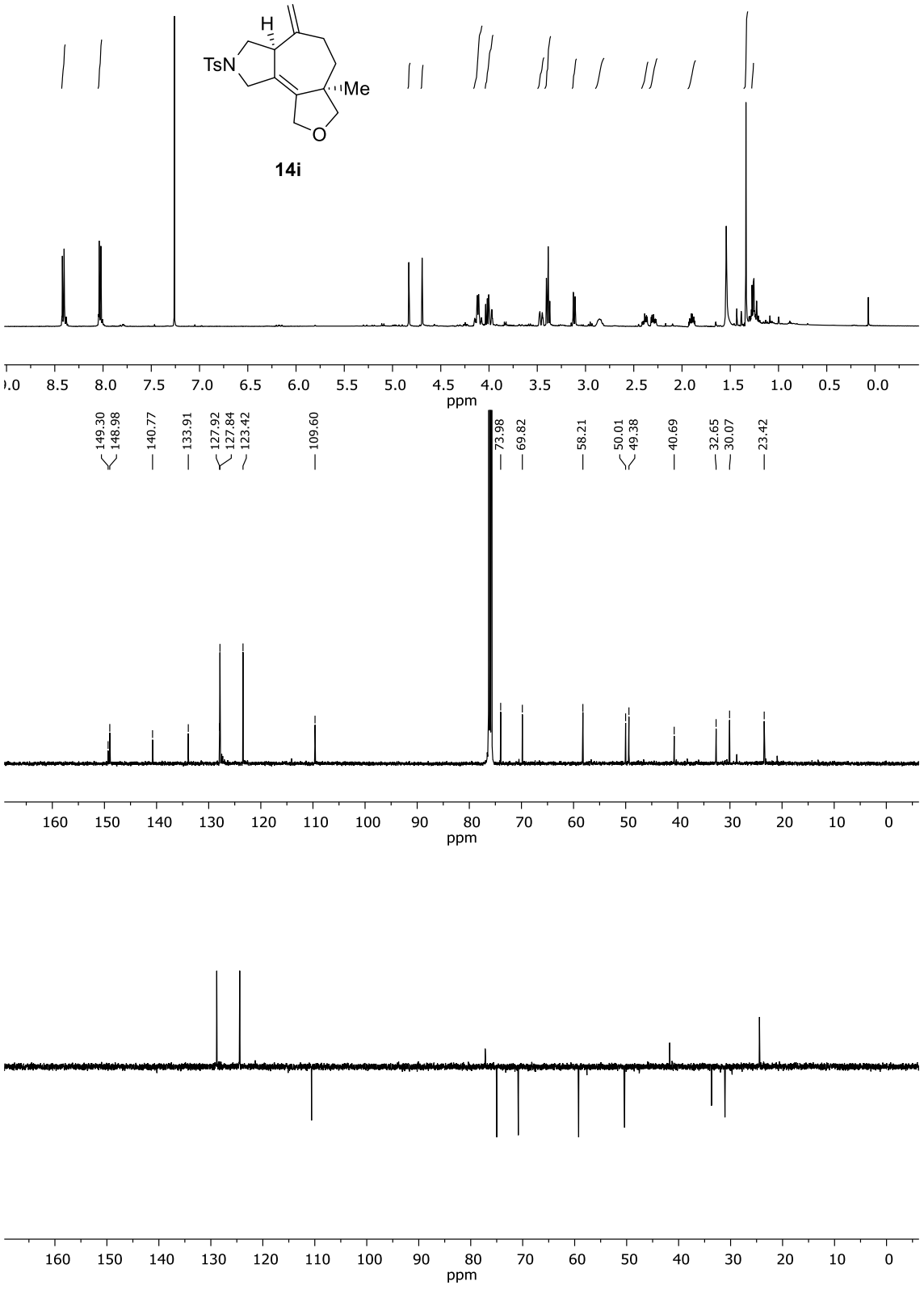


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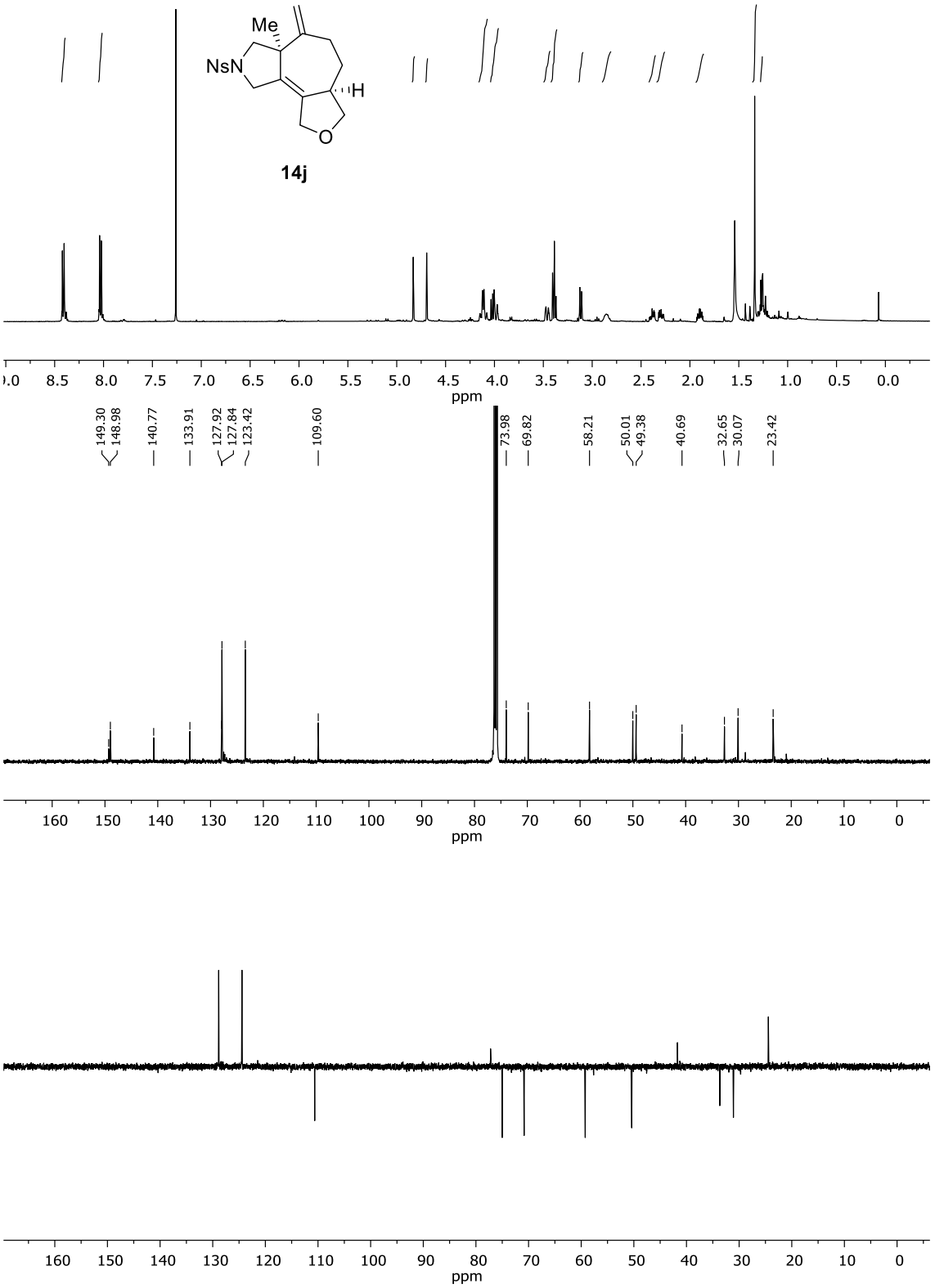
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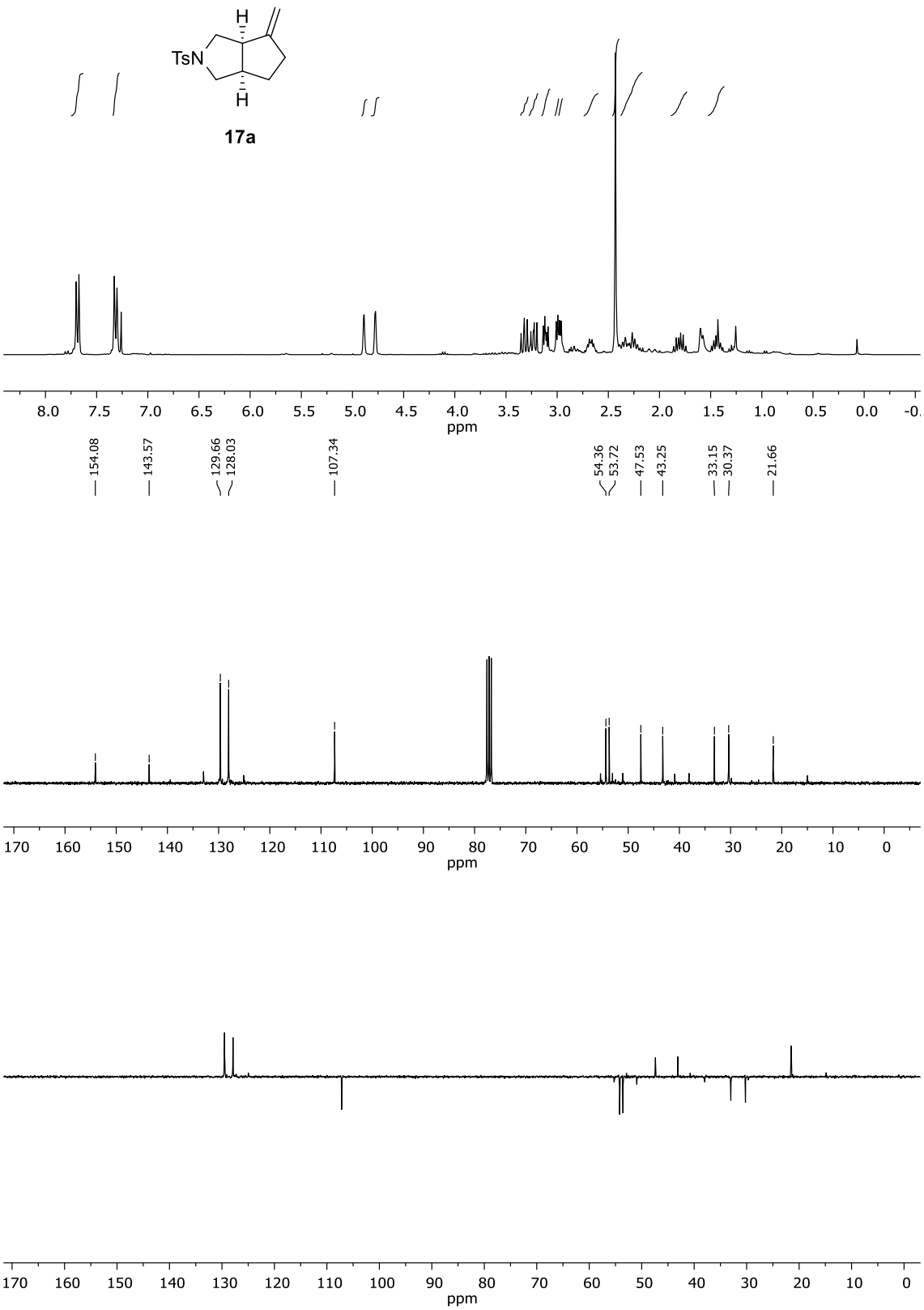
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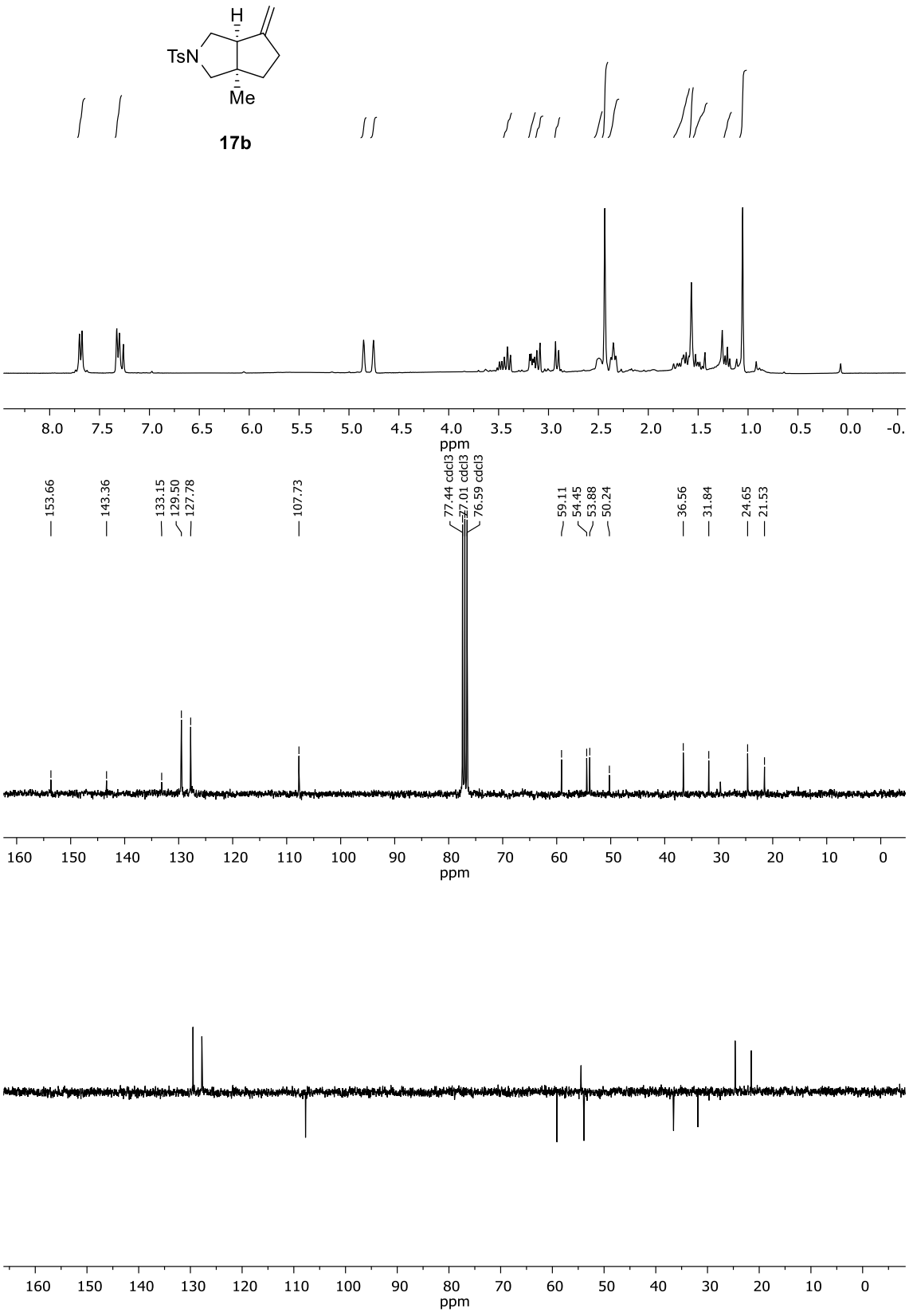
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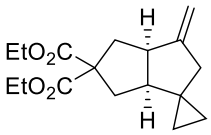
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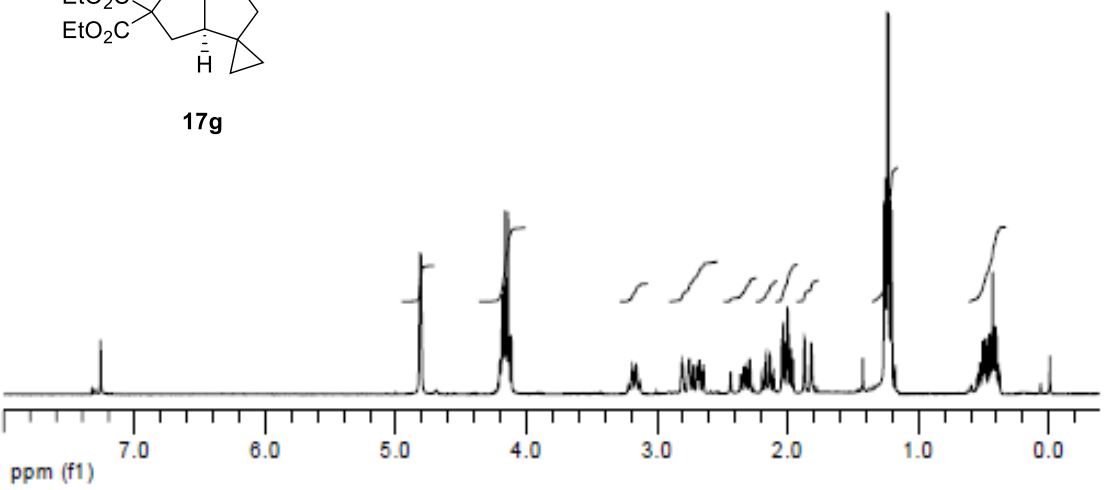
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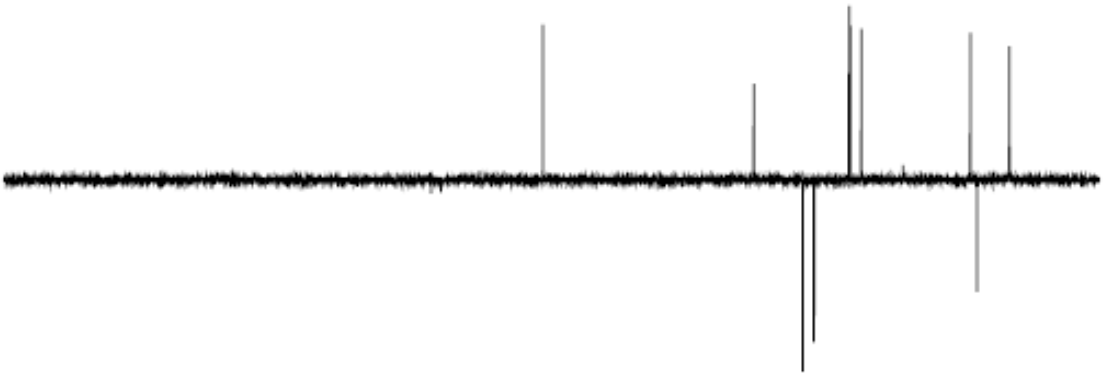


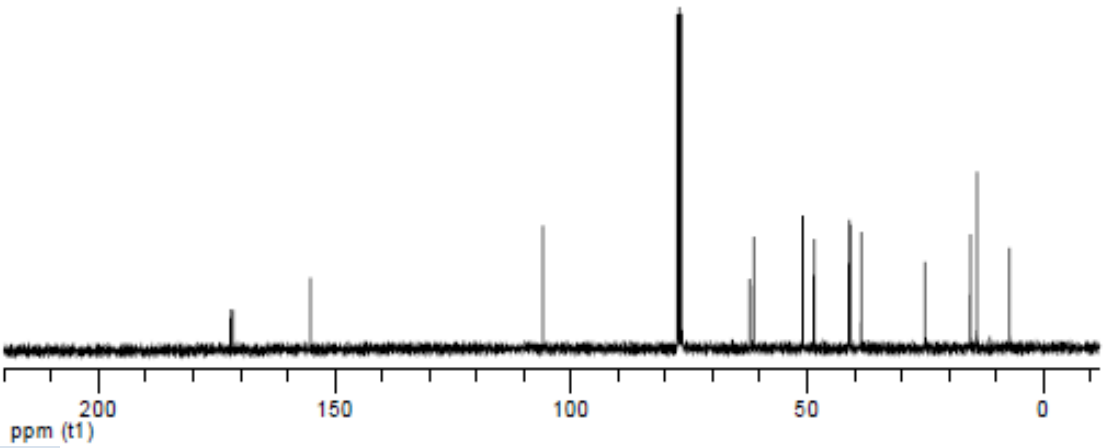
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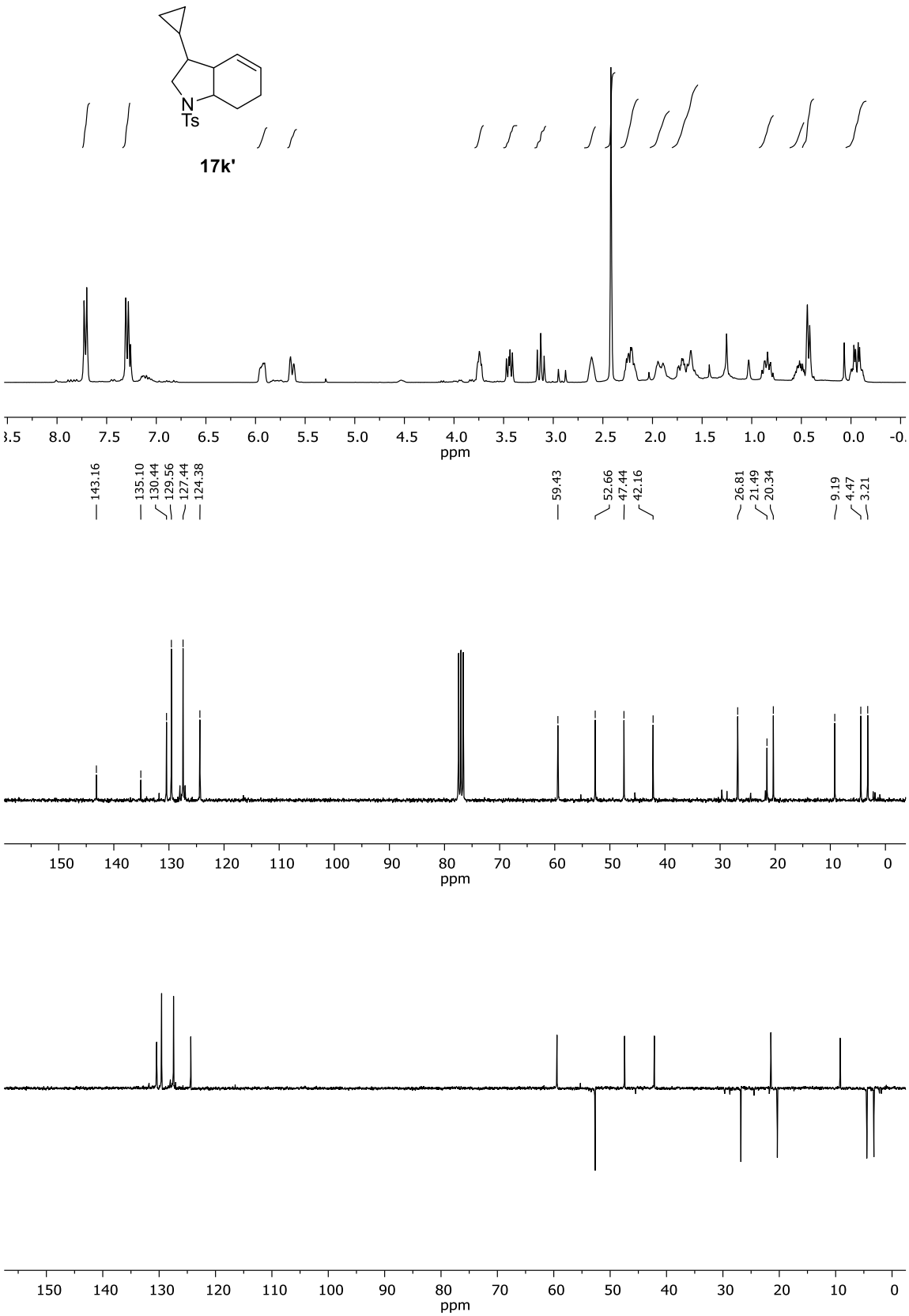
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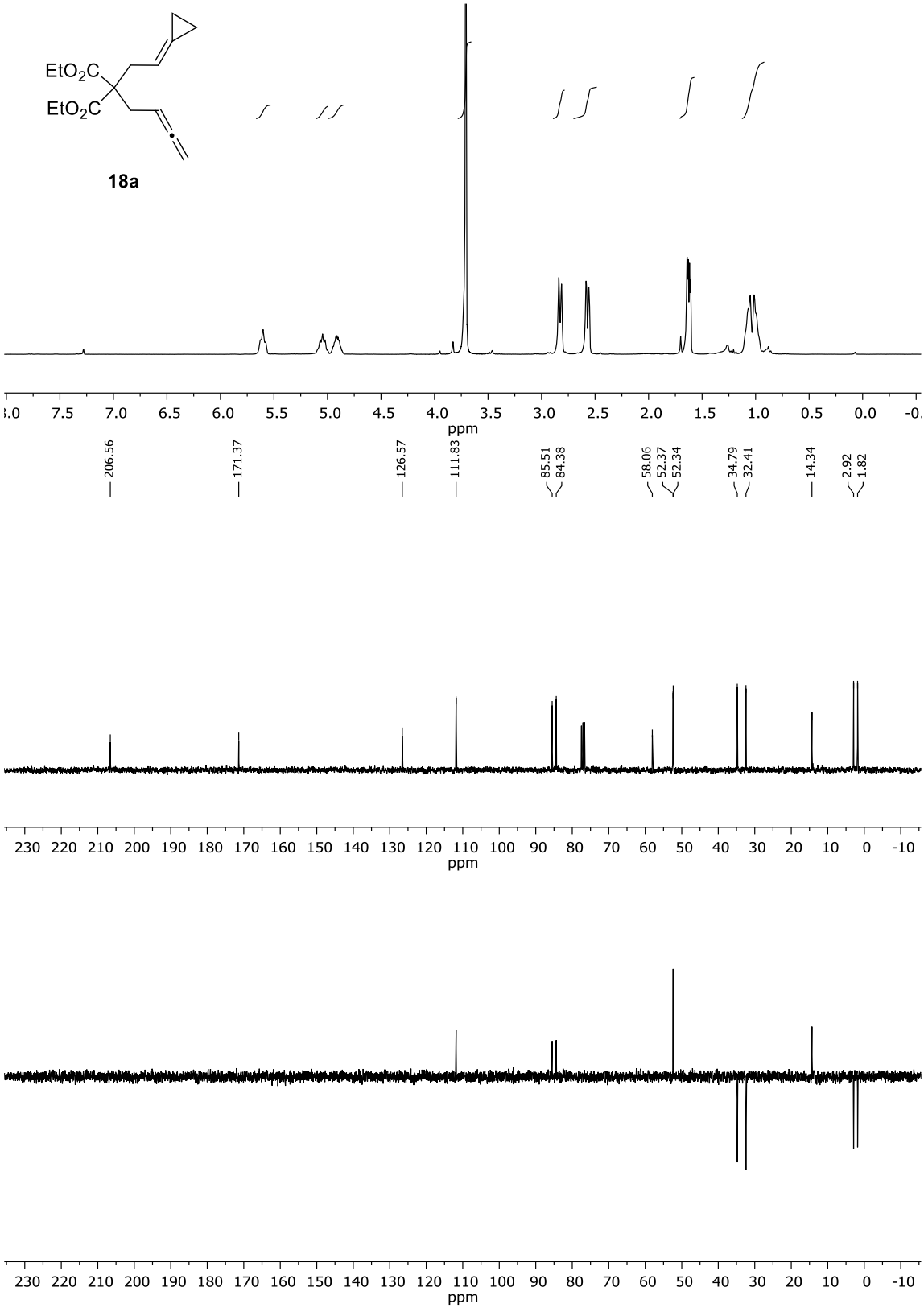




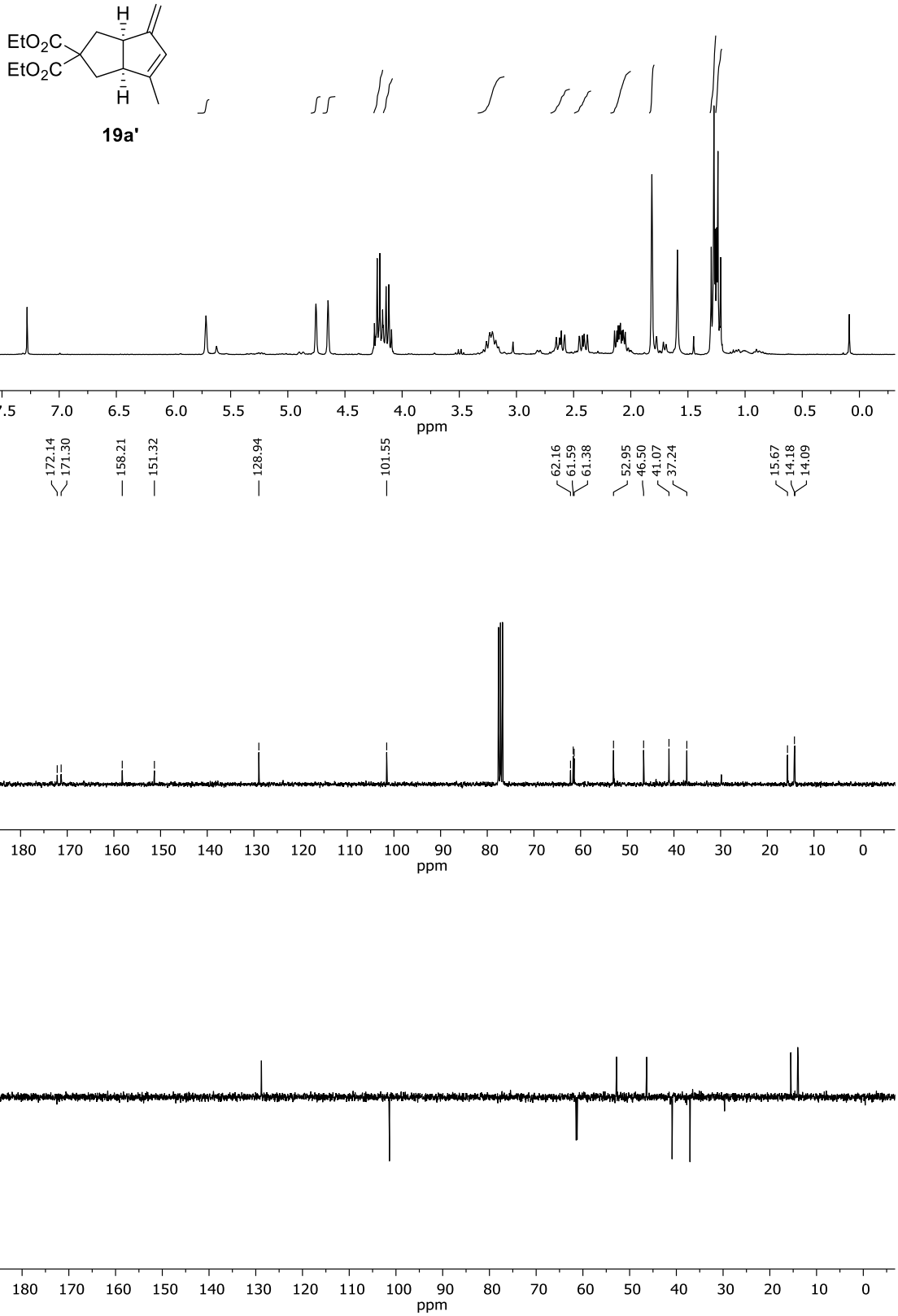
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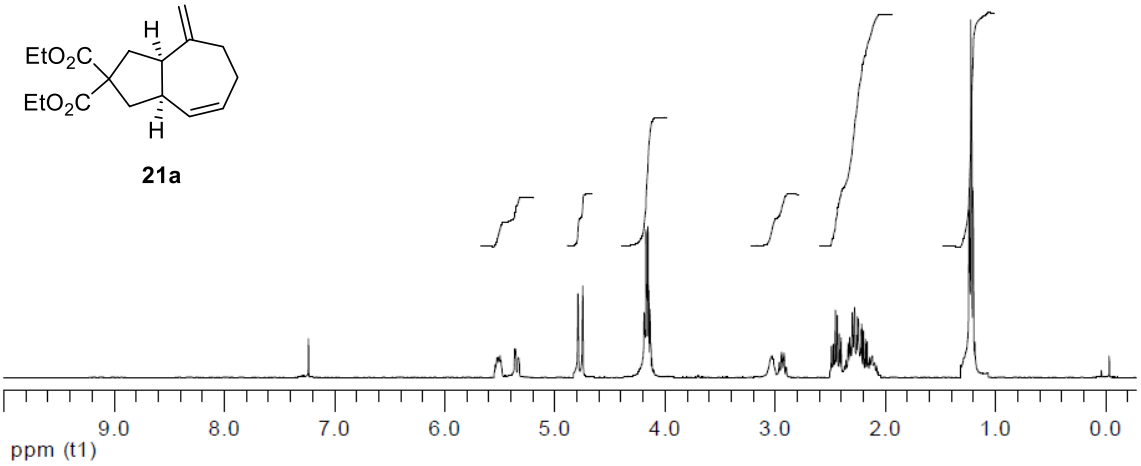


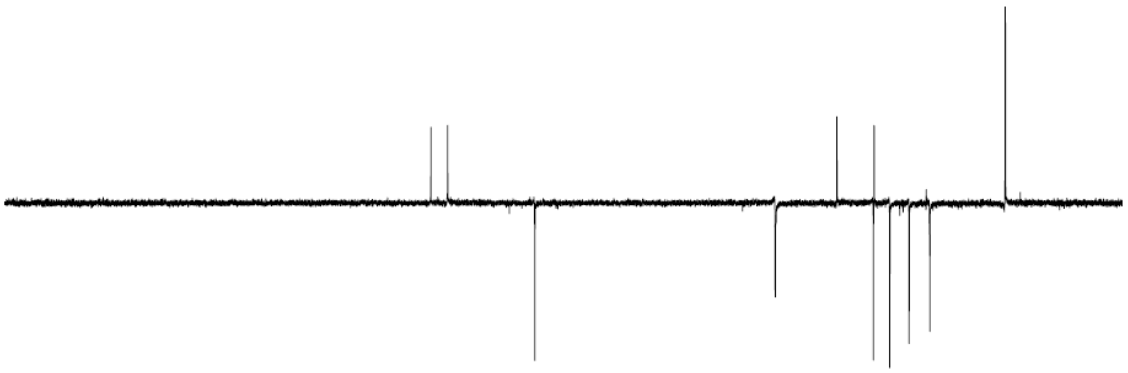
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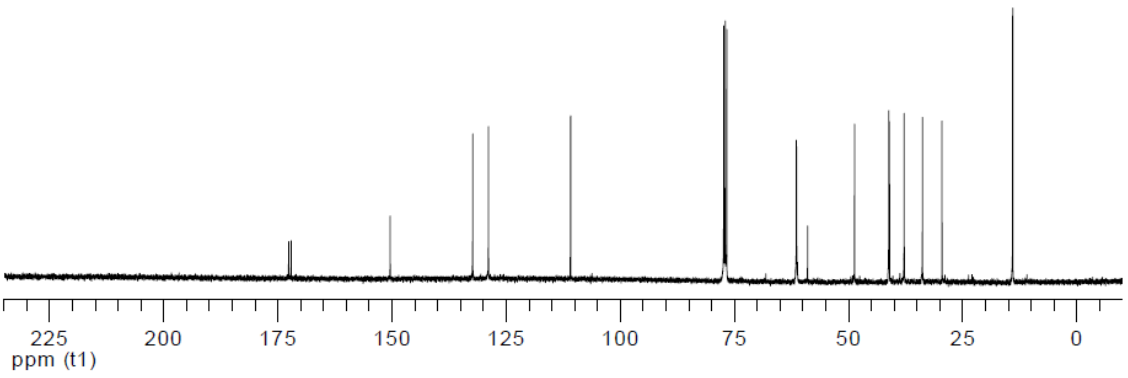


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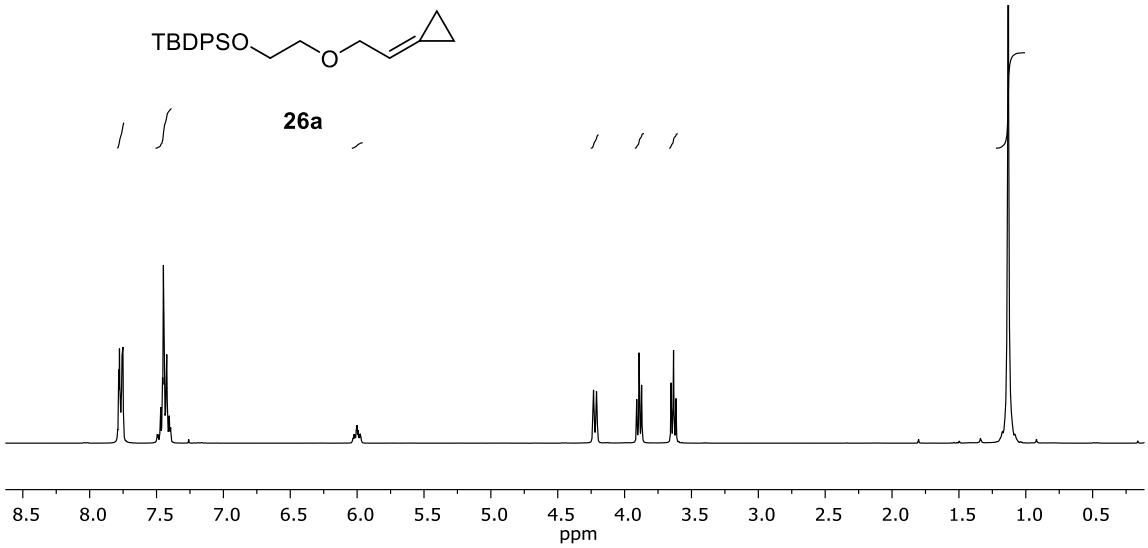
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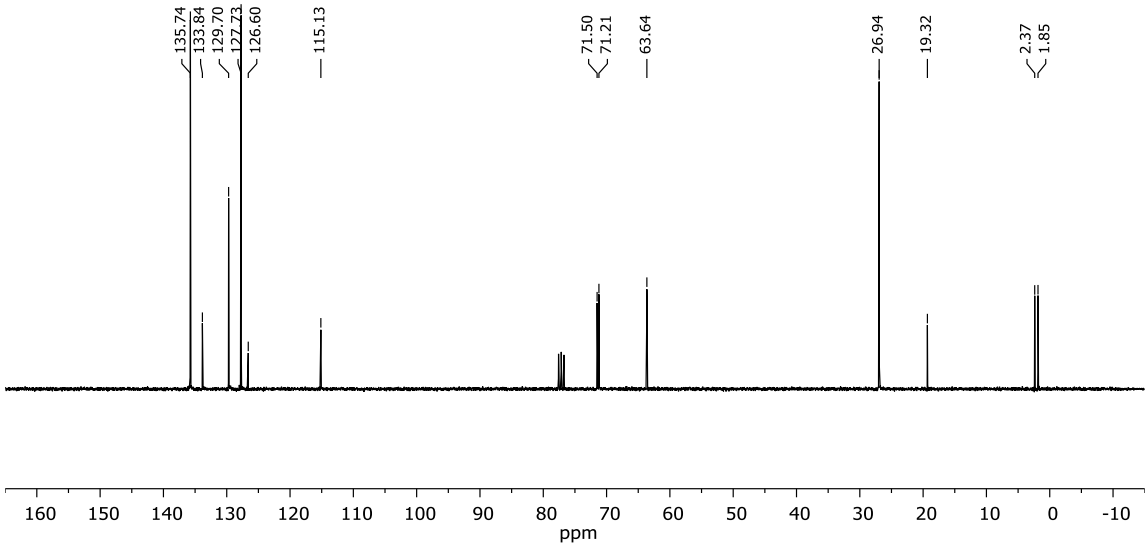


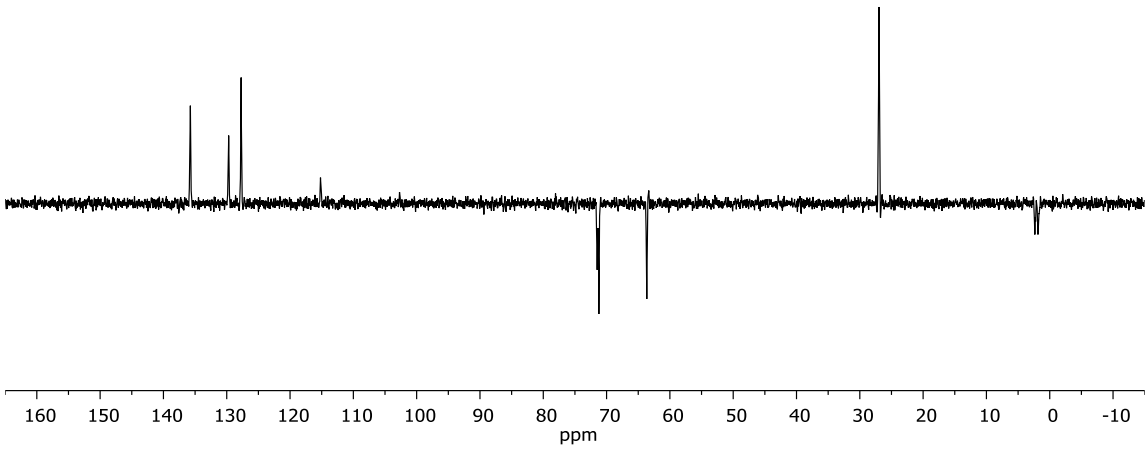


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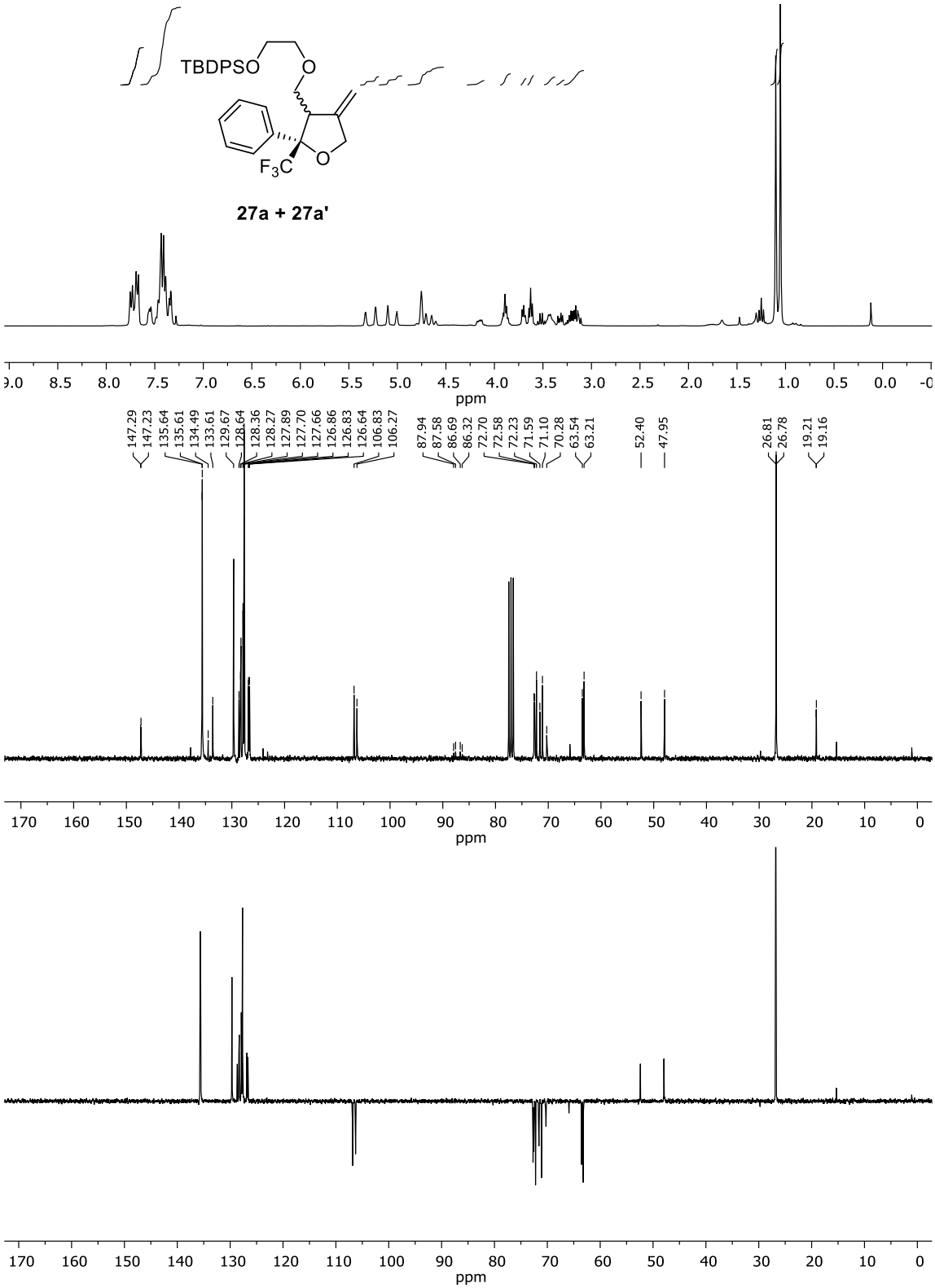


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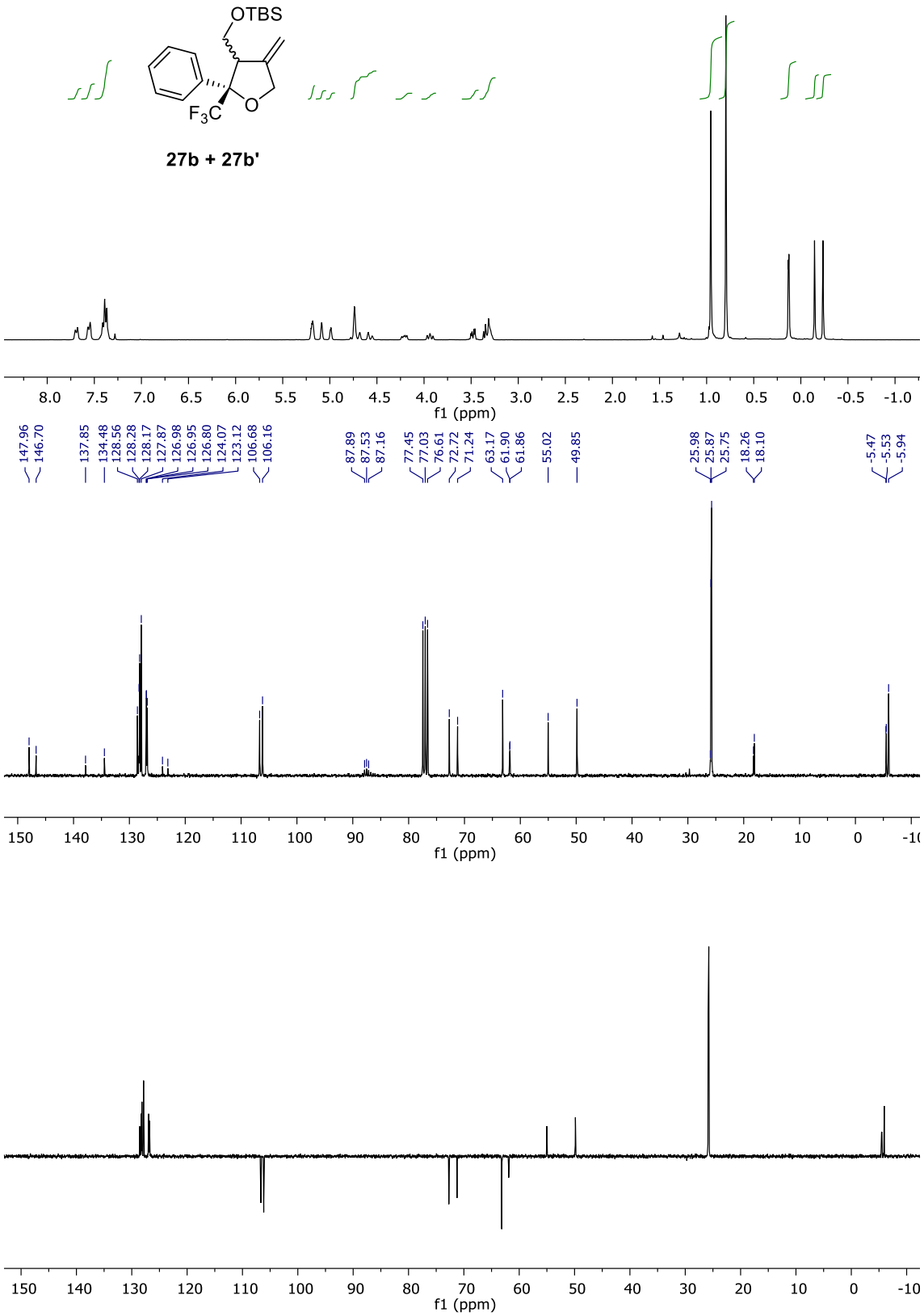




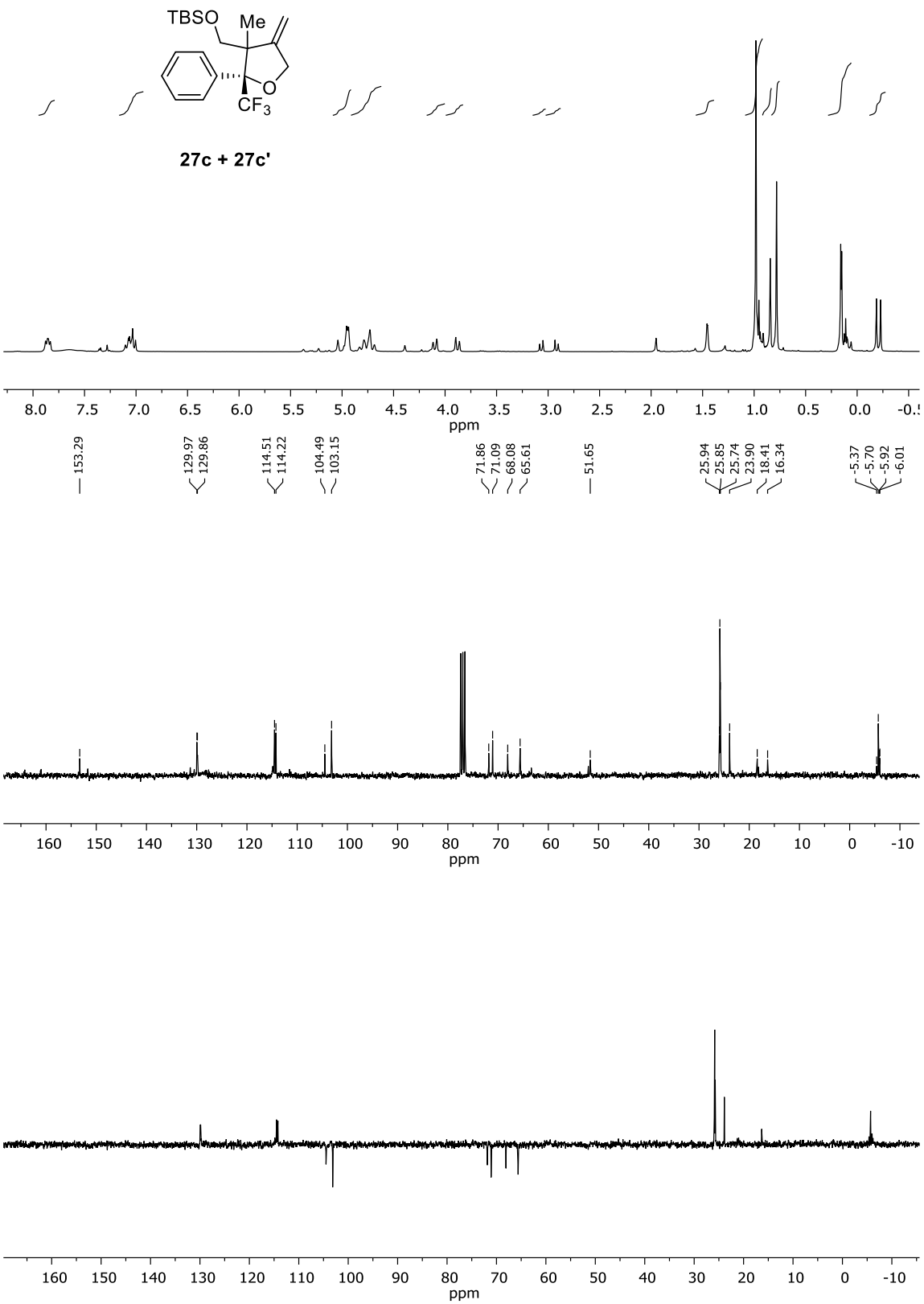
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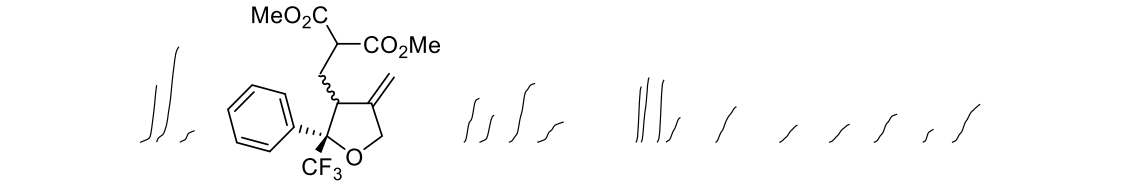
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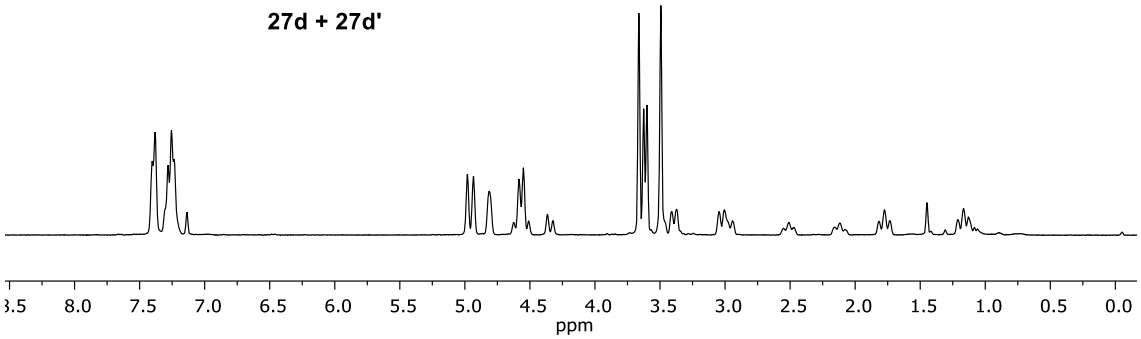
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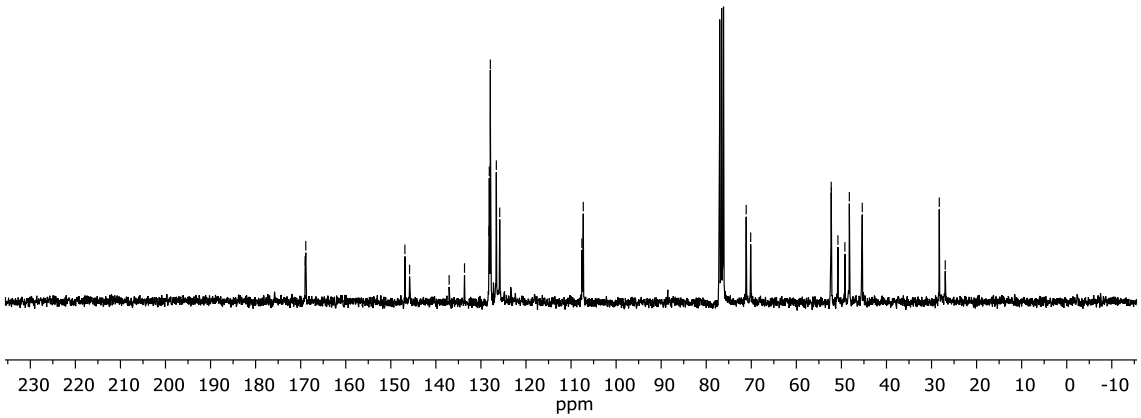
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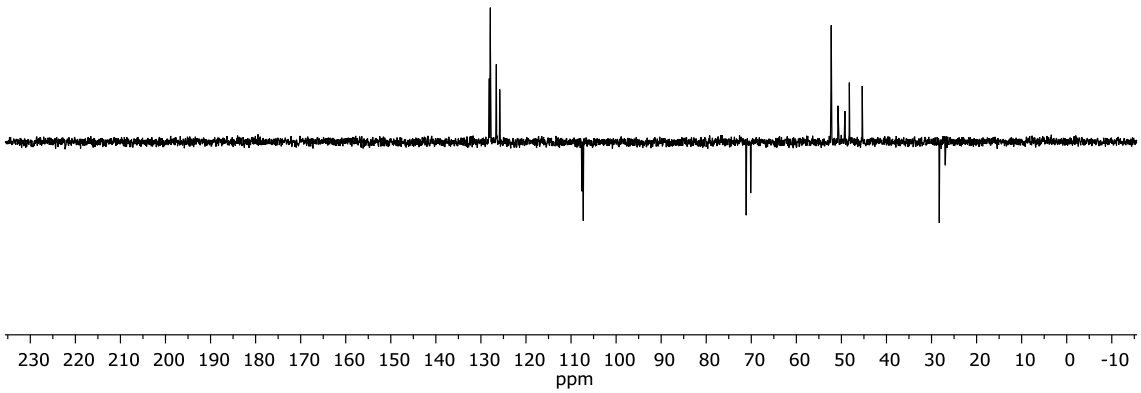


27d + 27d'

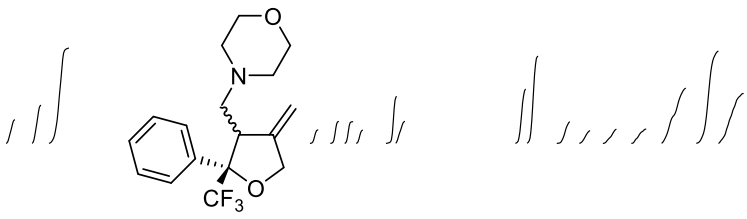


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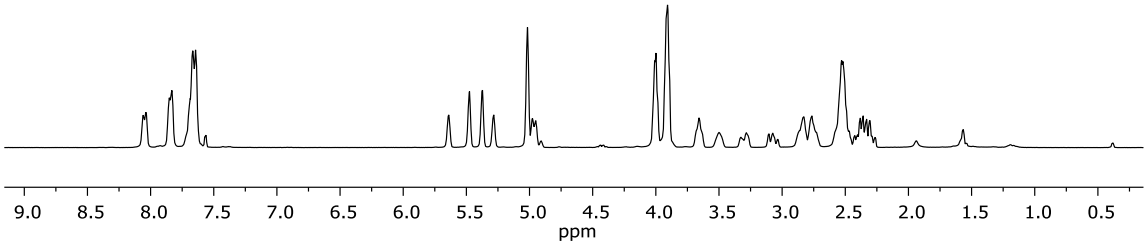


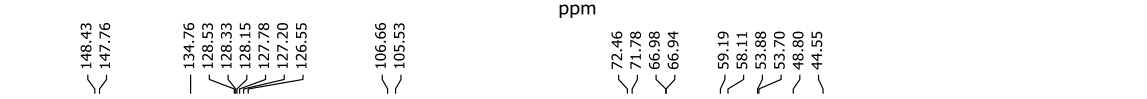


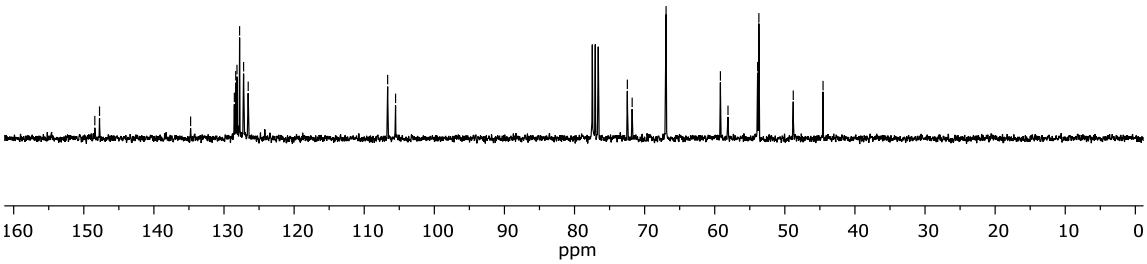
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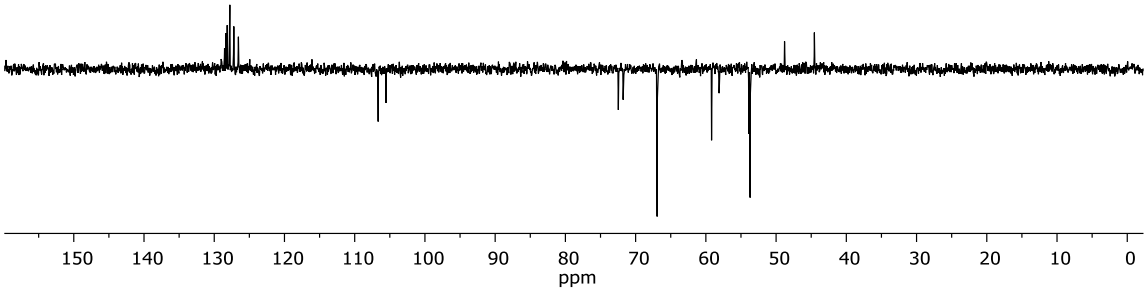


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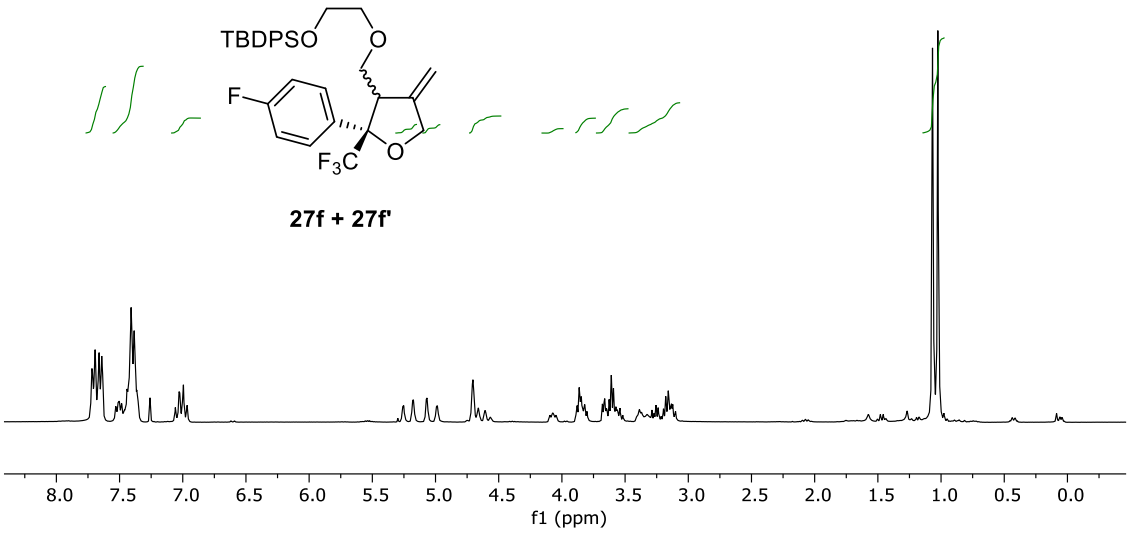




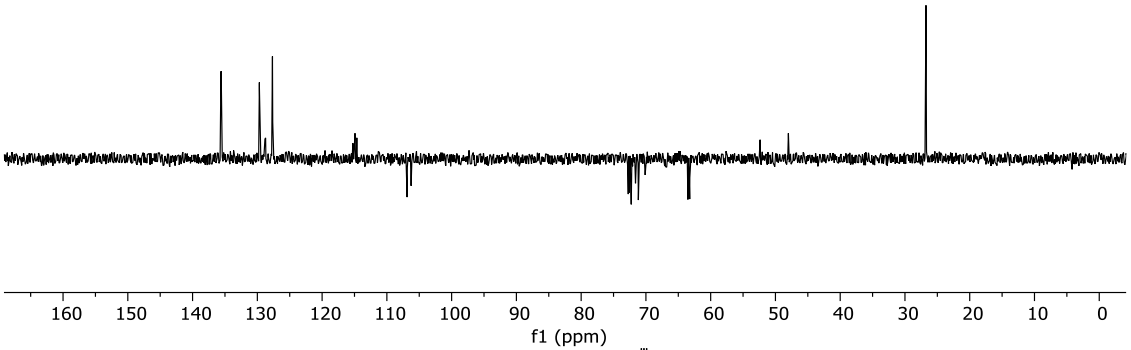


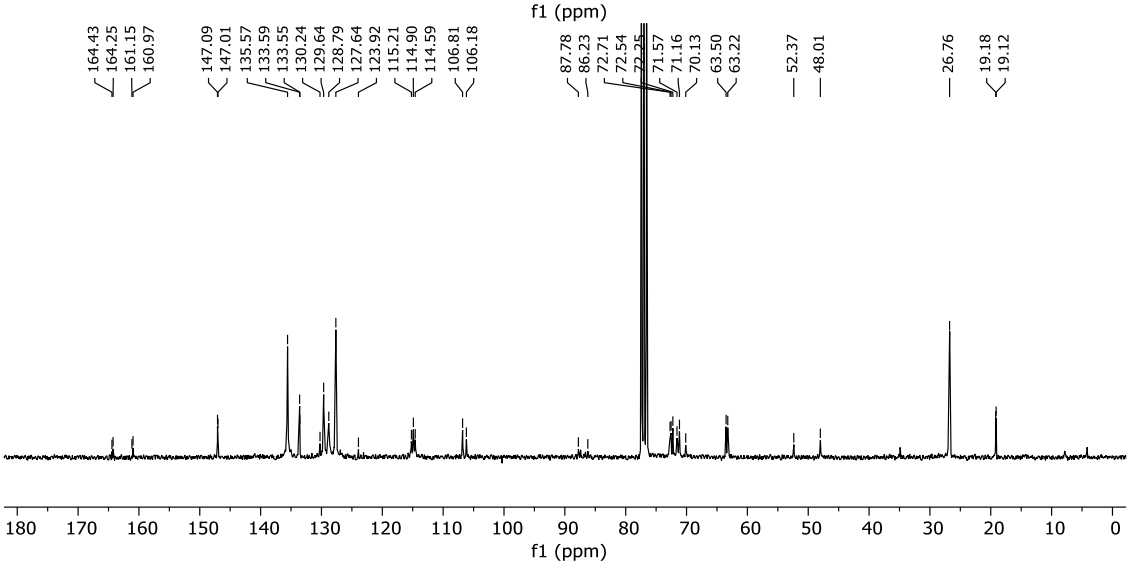


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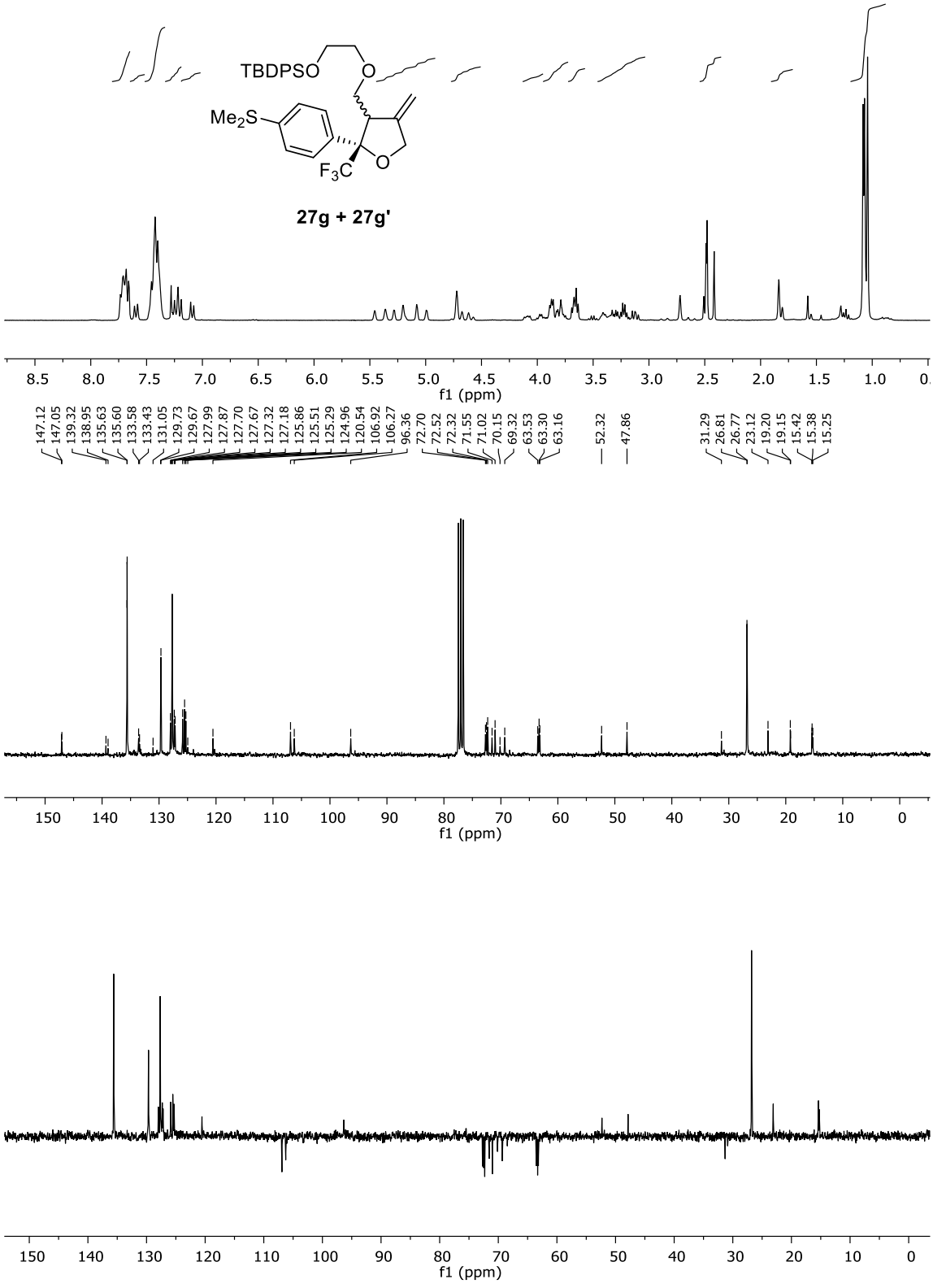


27f + 27f'

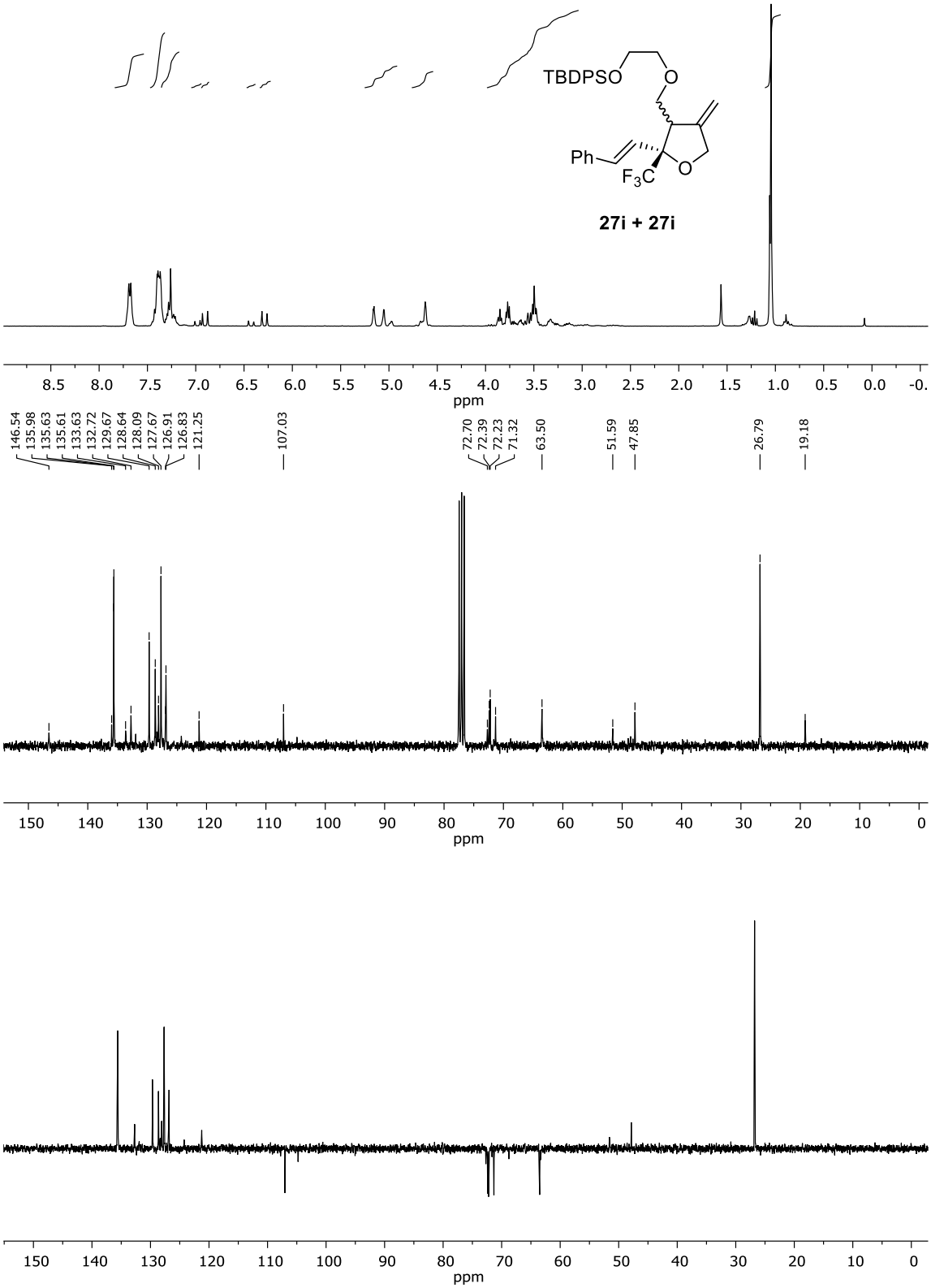




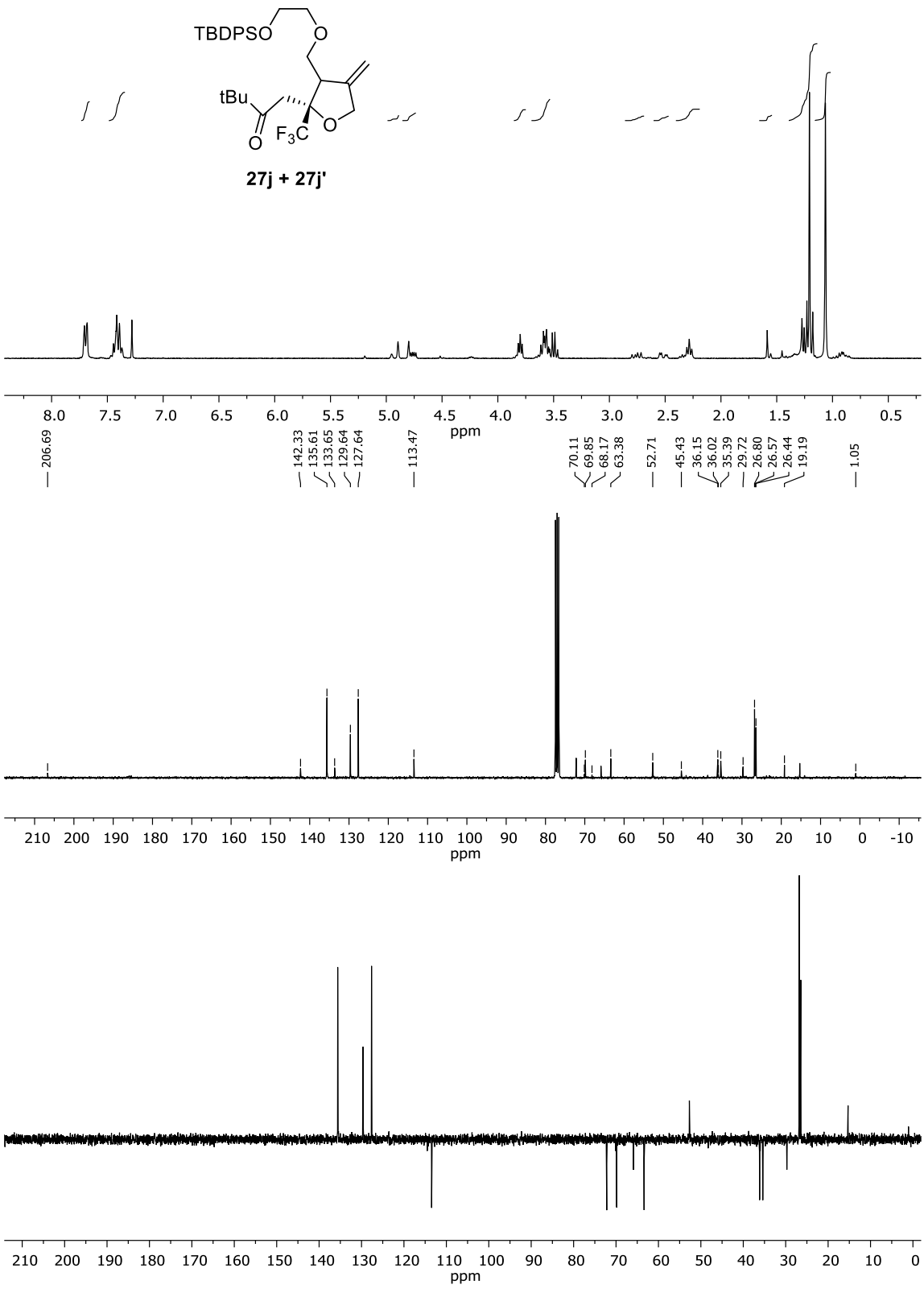
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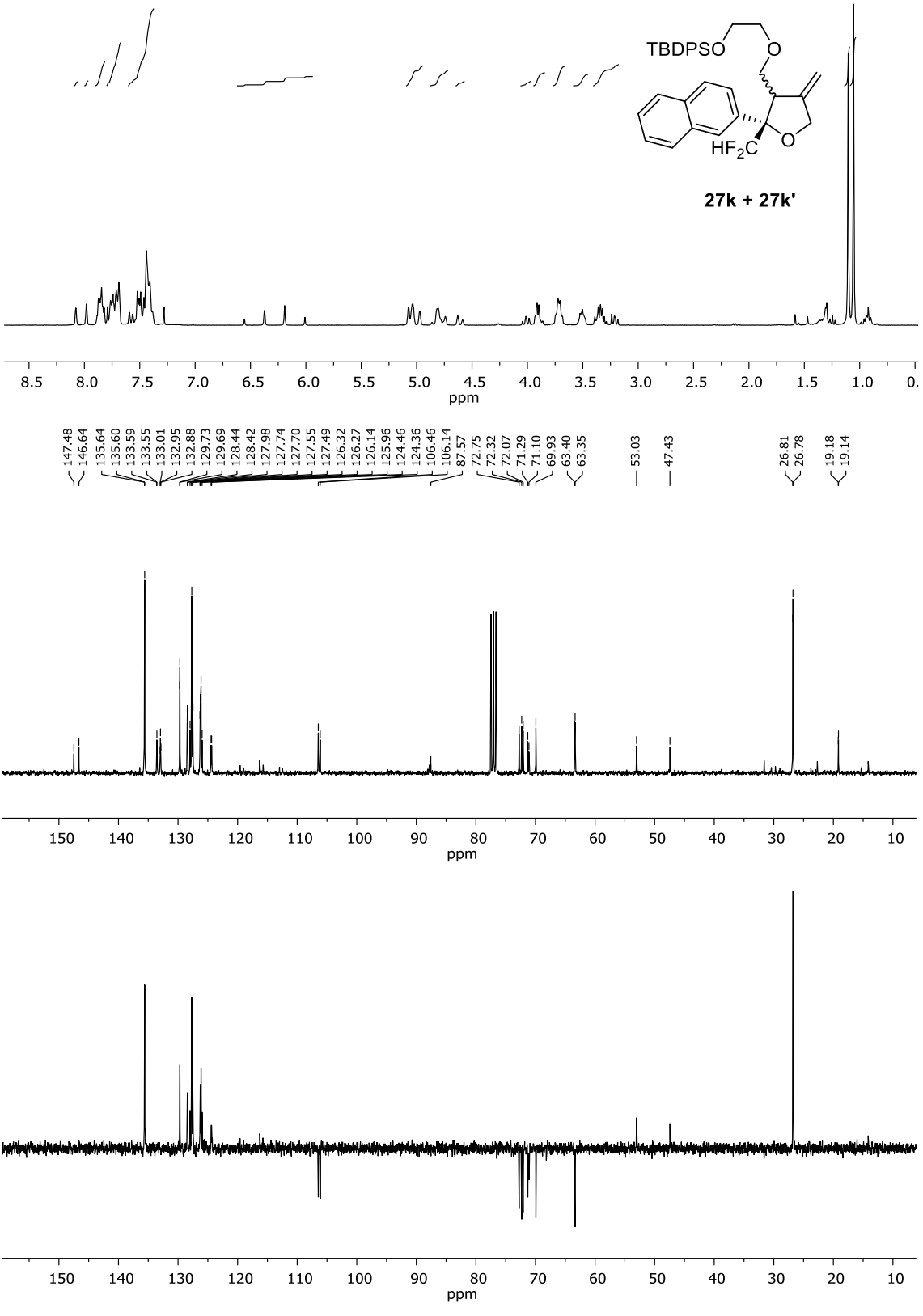
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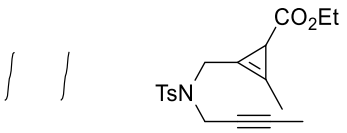
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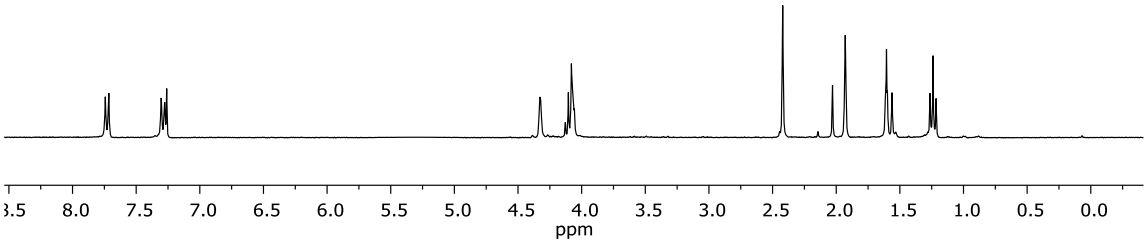
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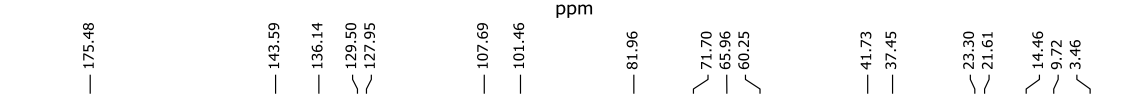


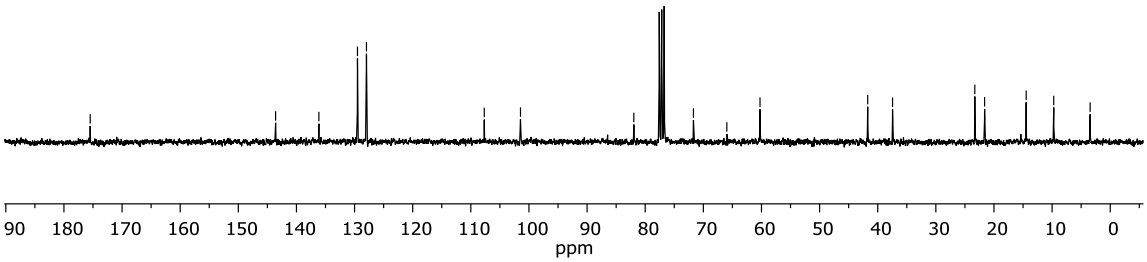
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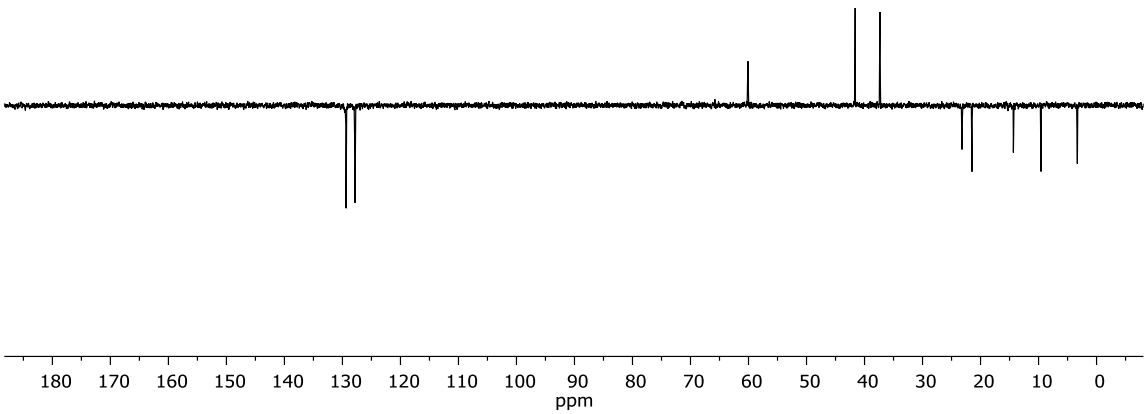


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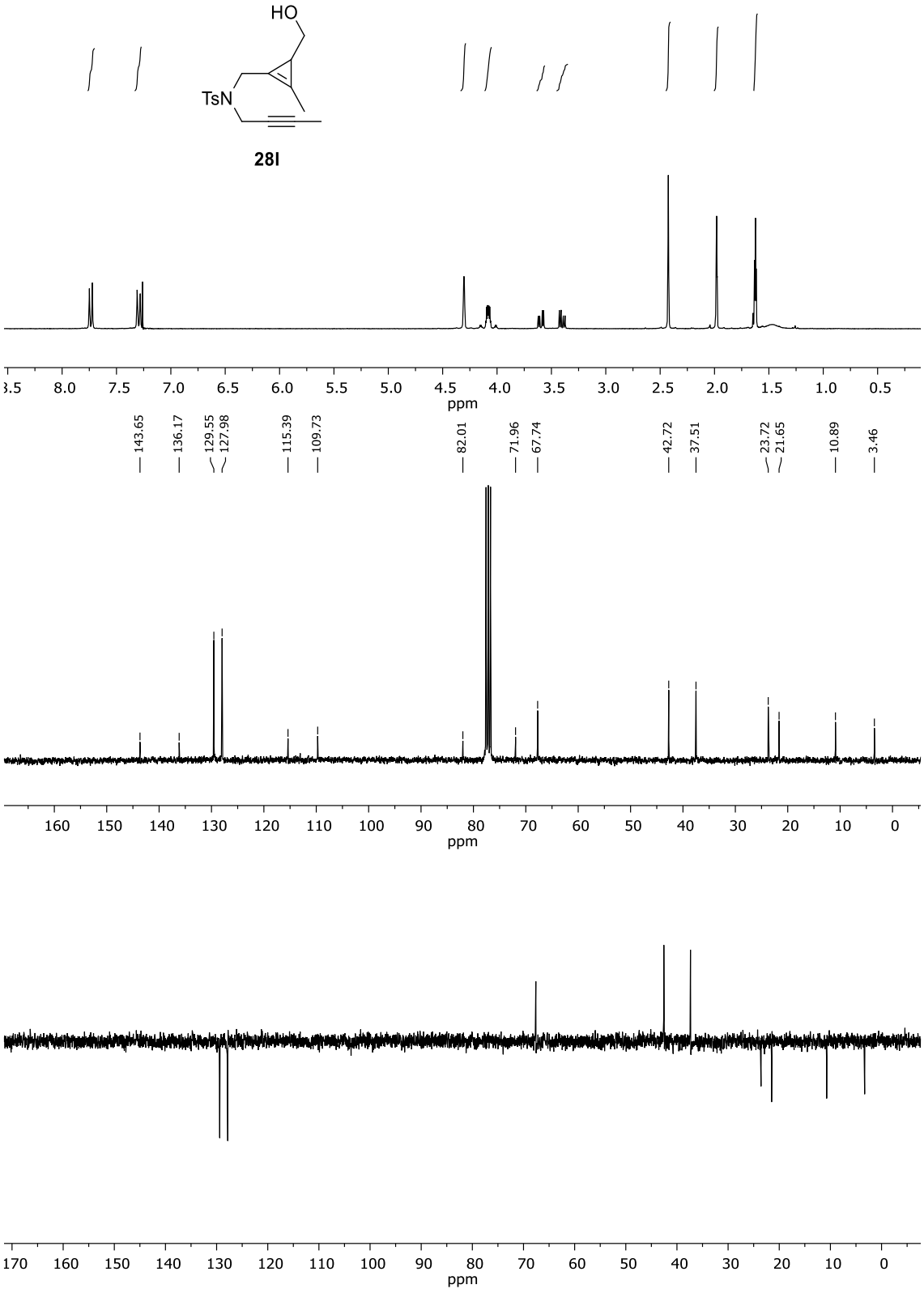




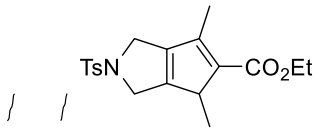




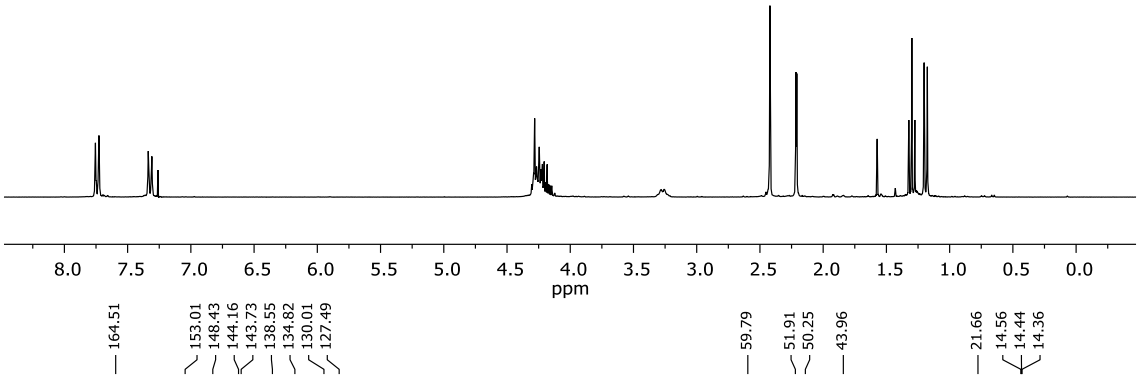
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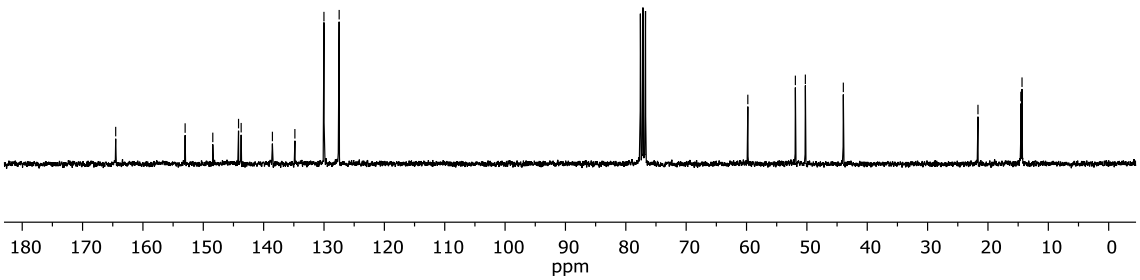


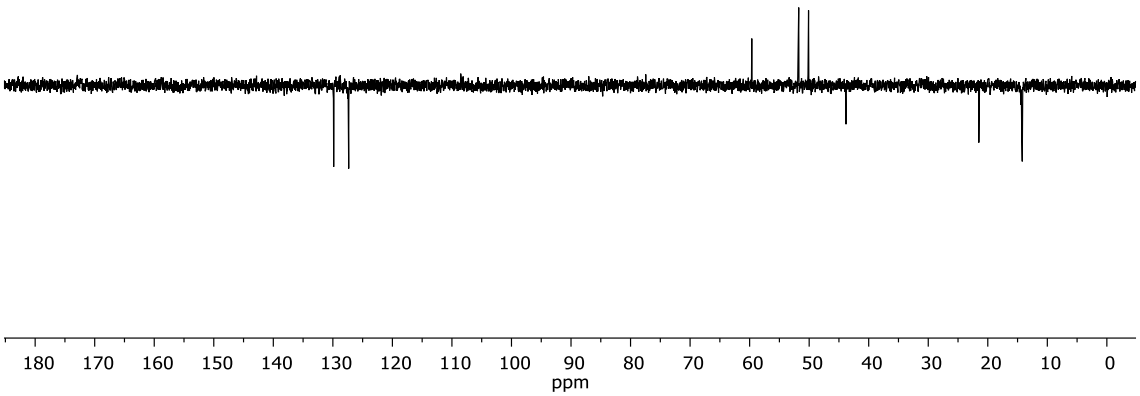
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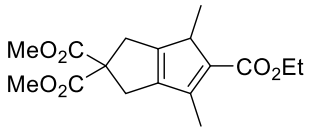
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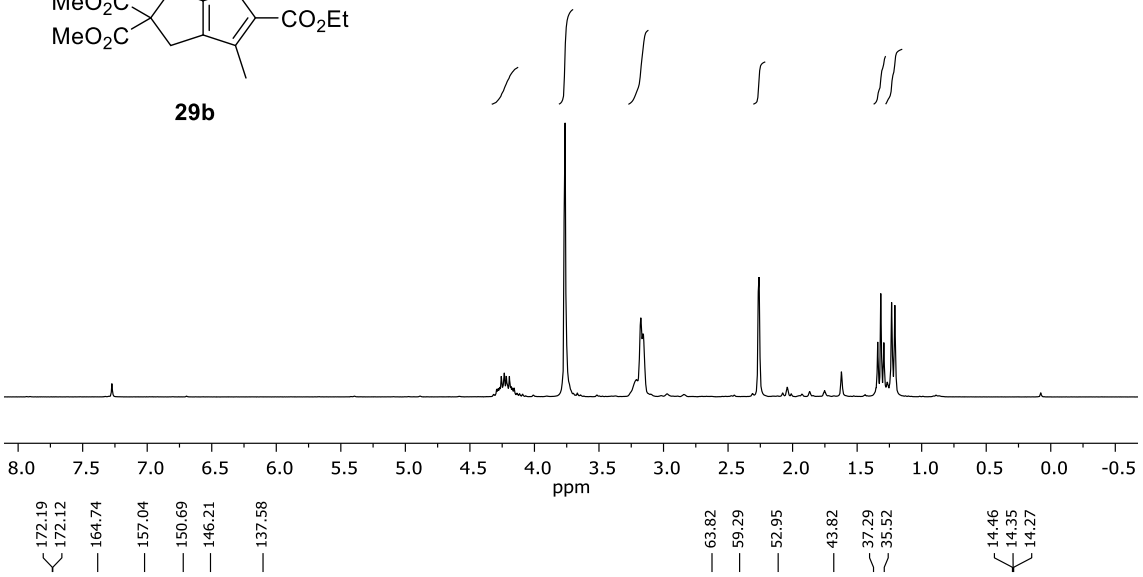


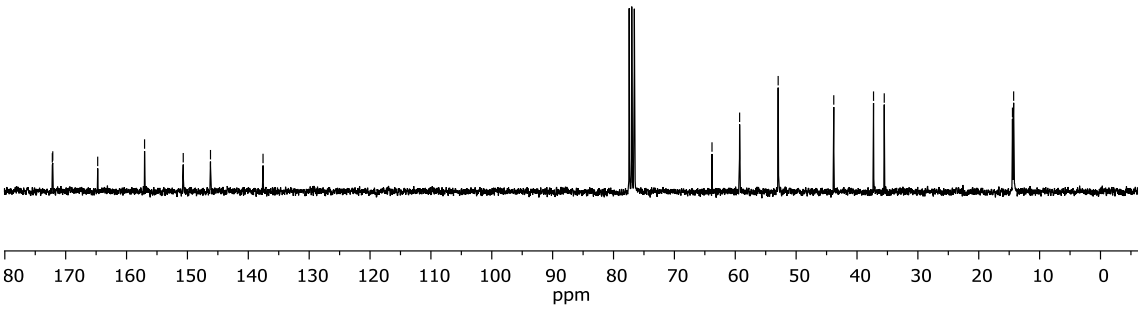


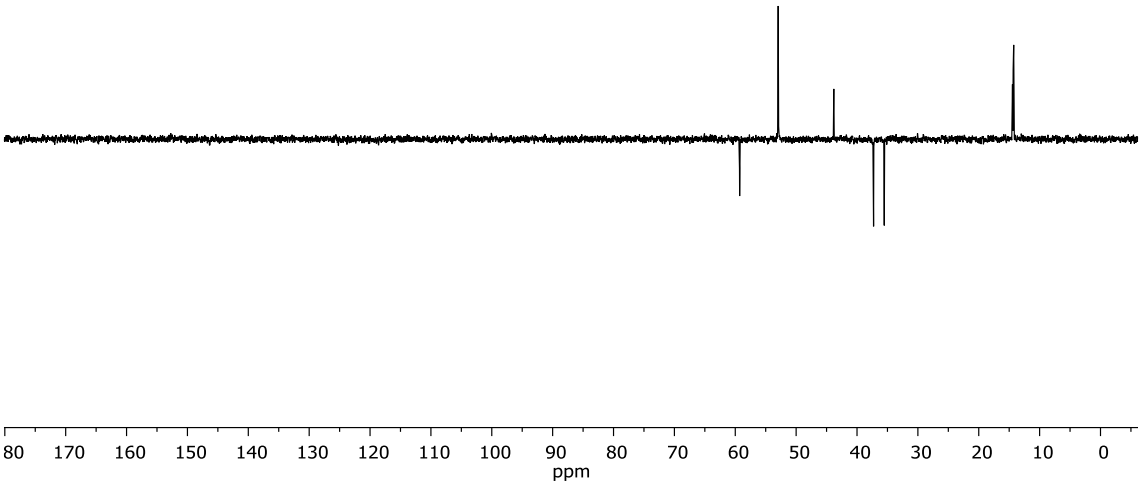
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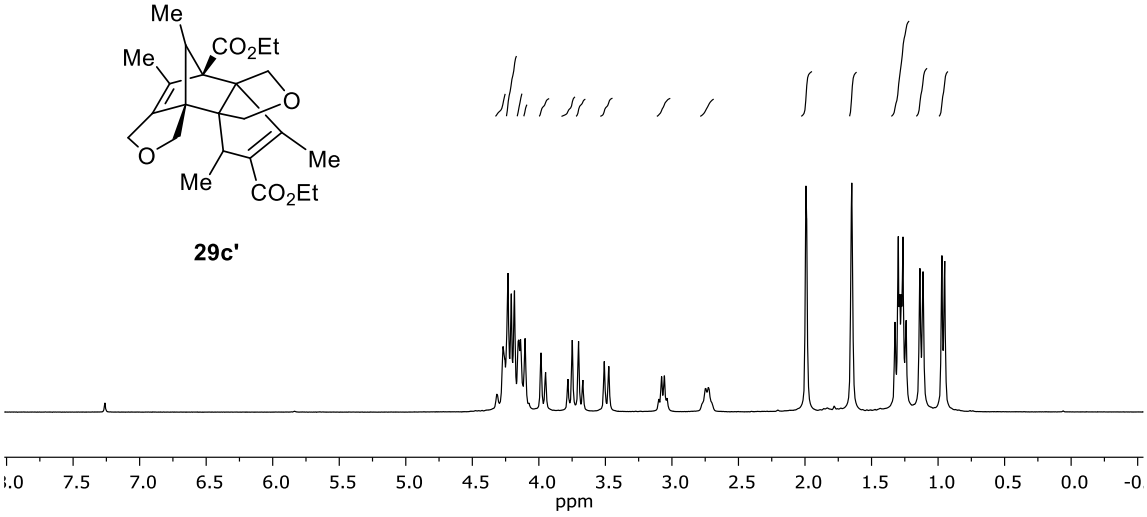


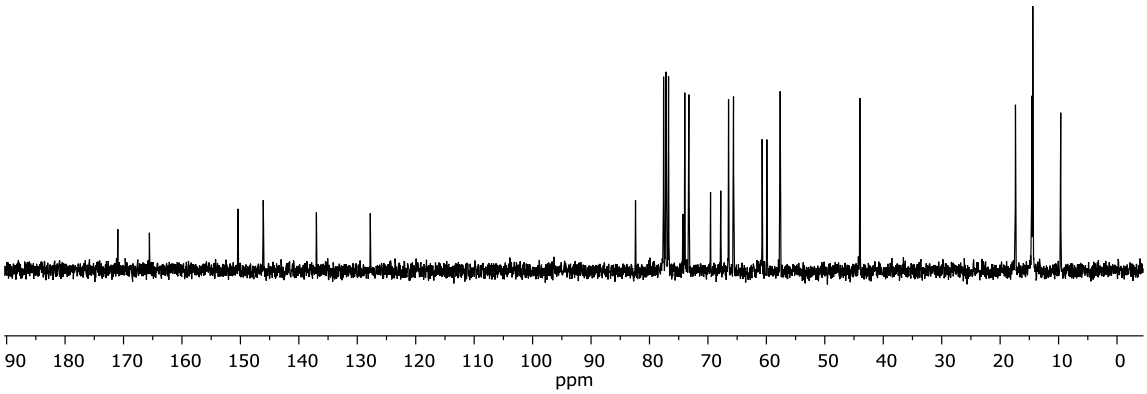


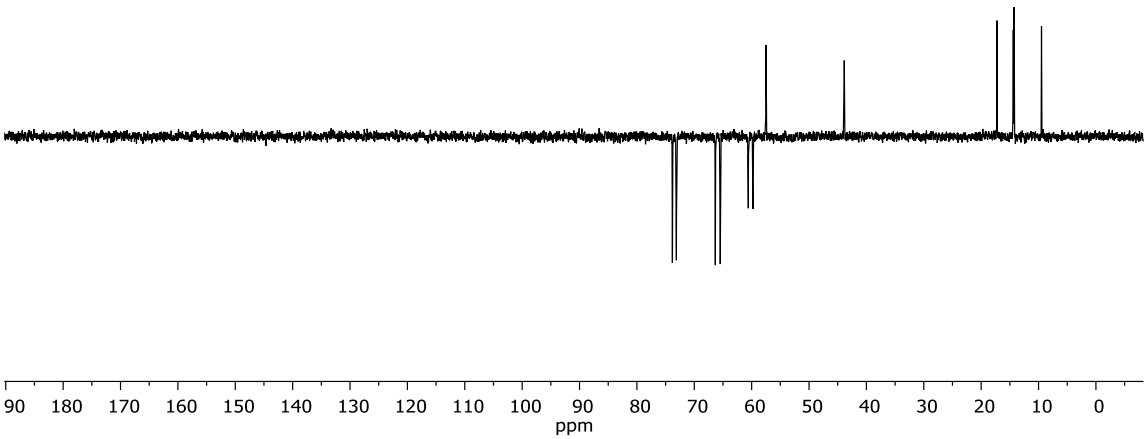


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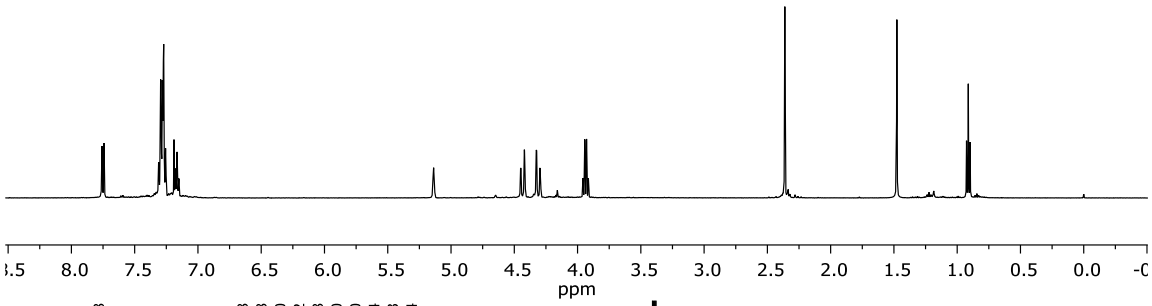


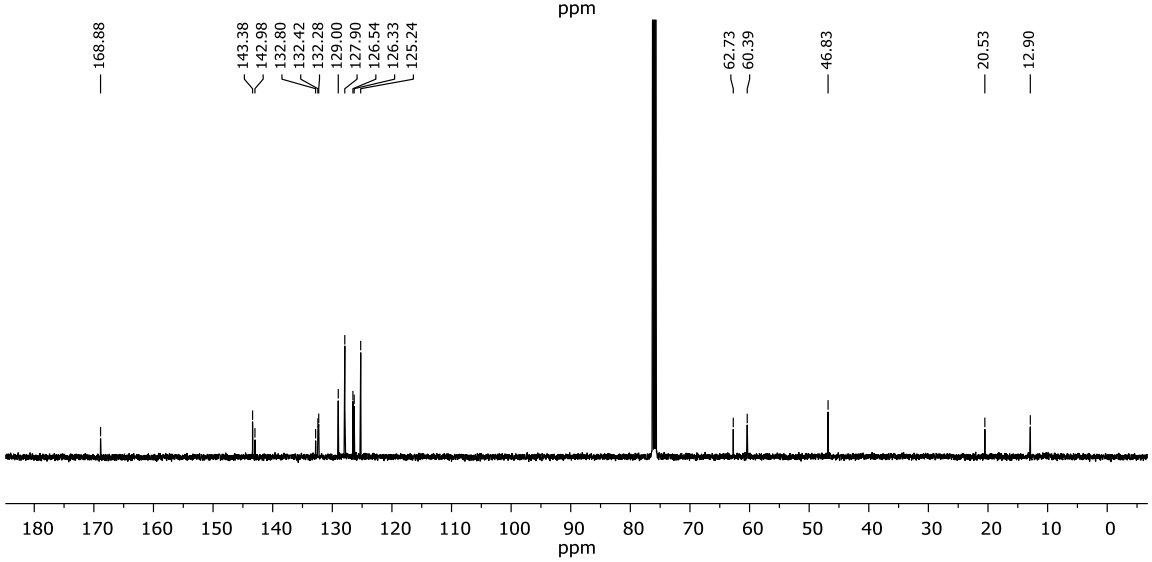


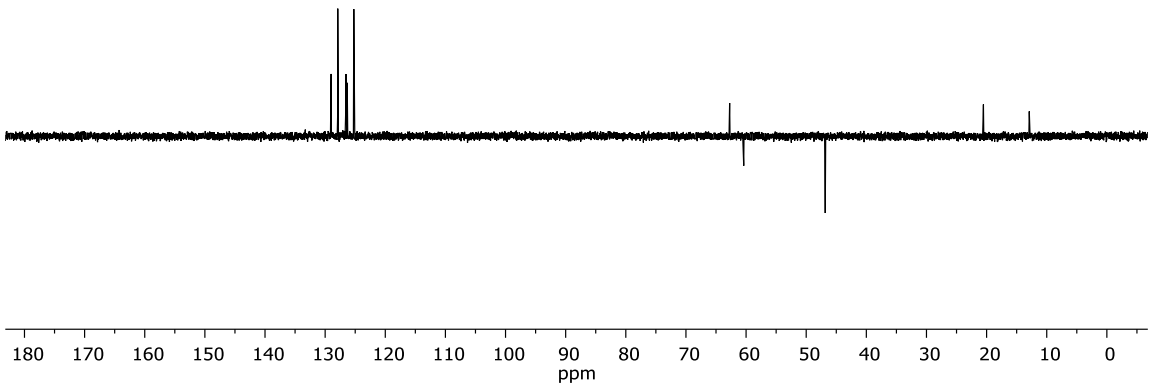
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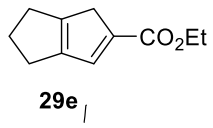
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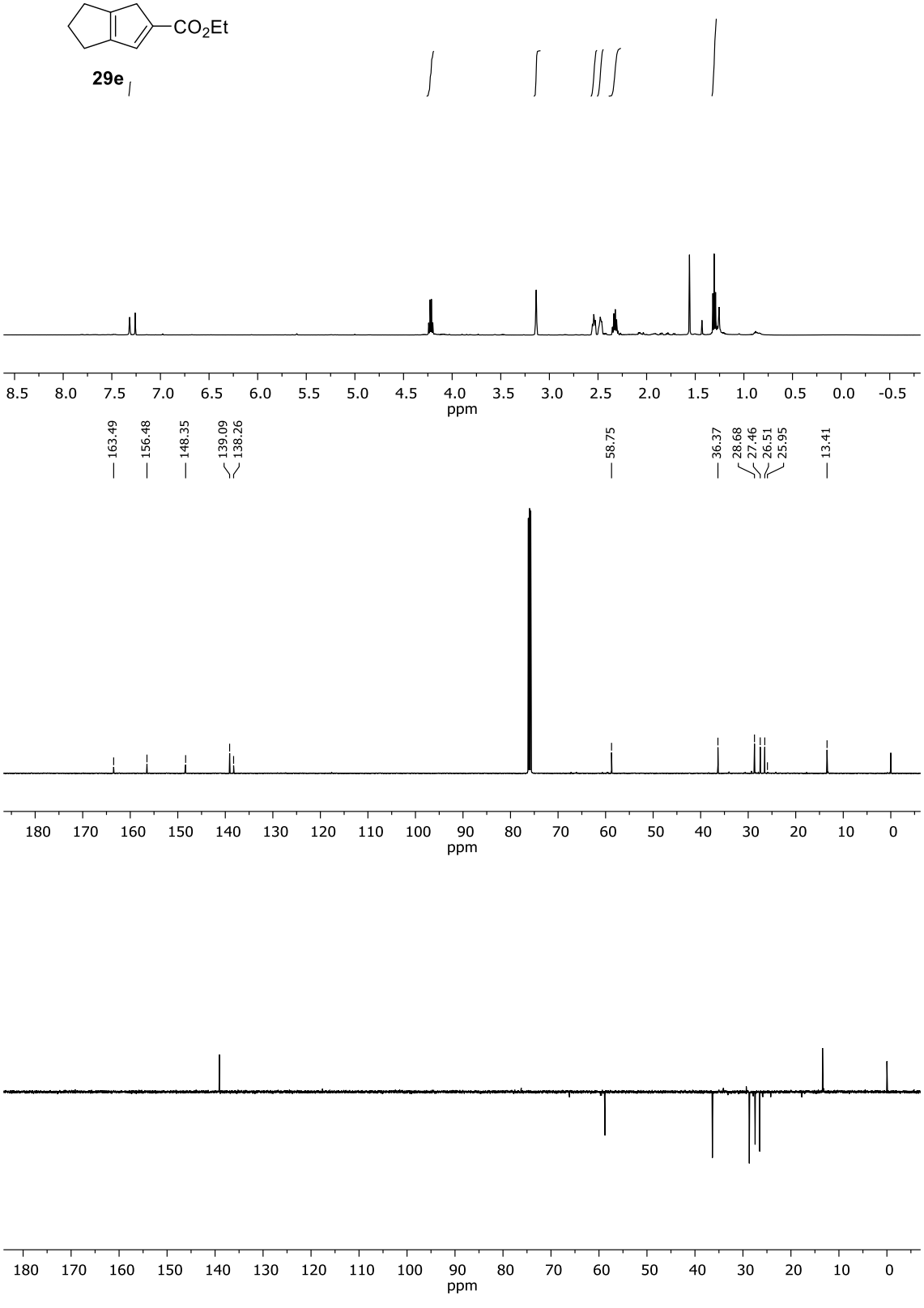




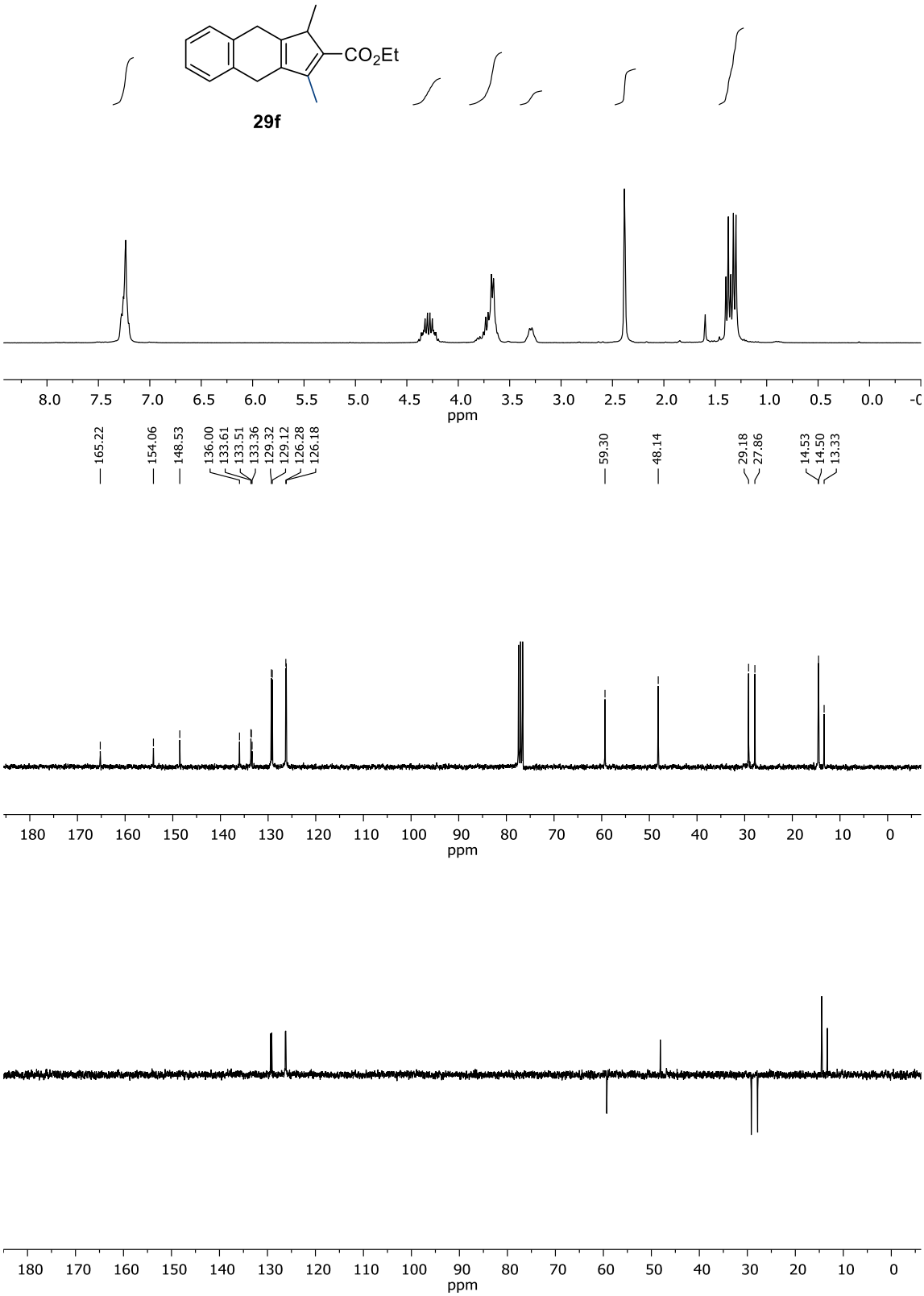
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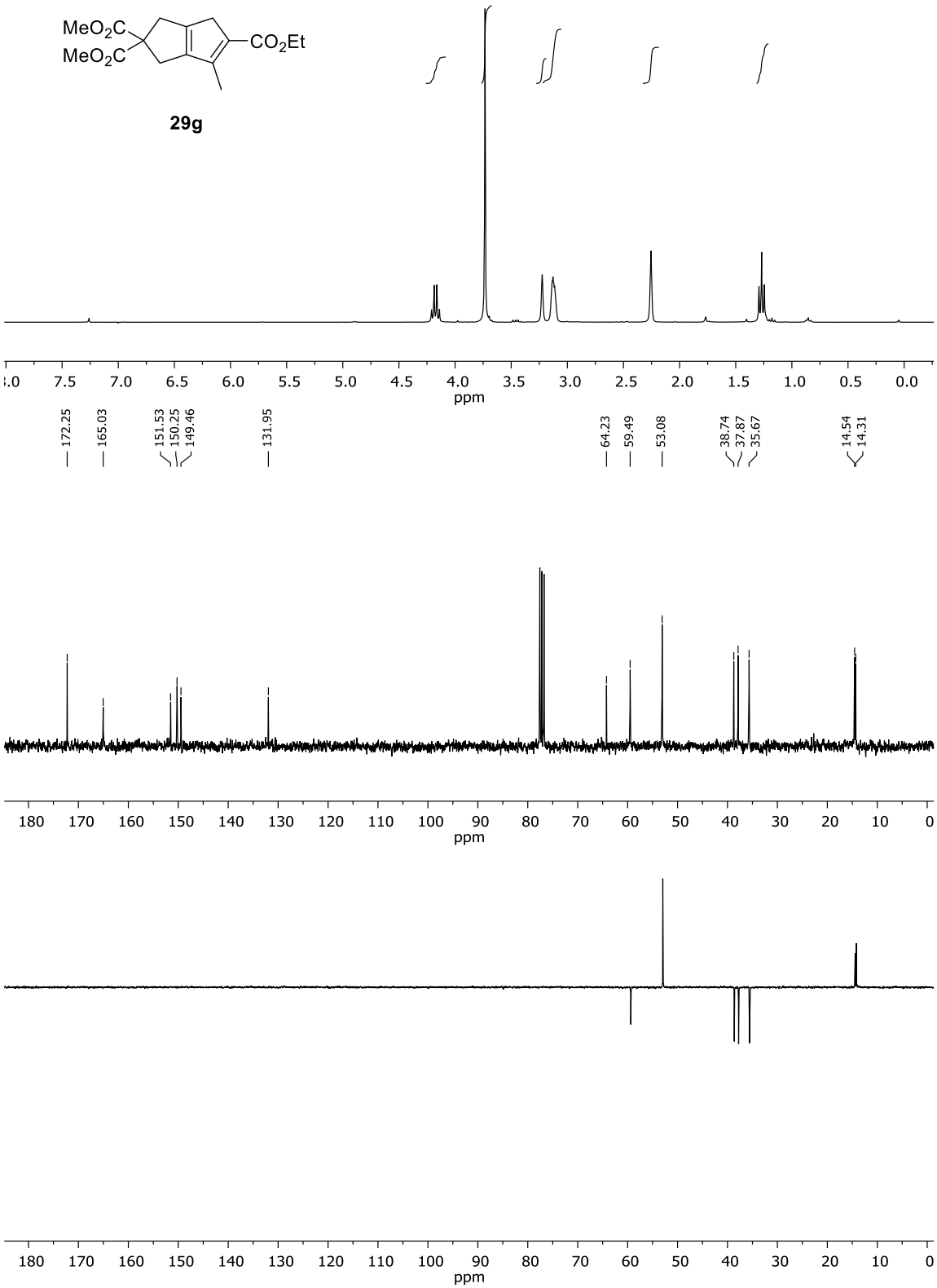
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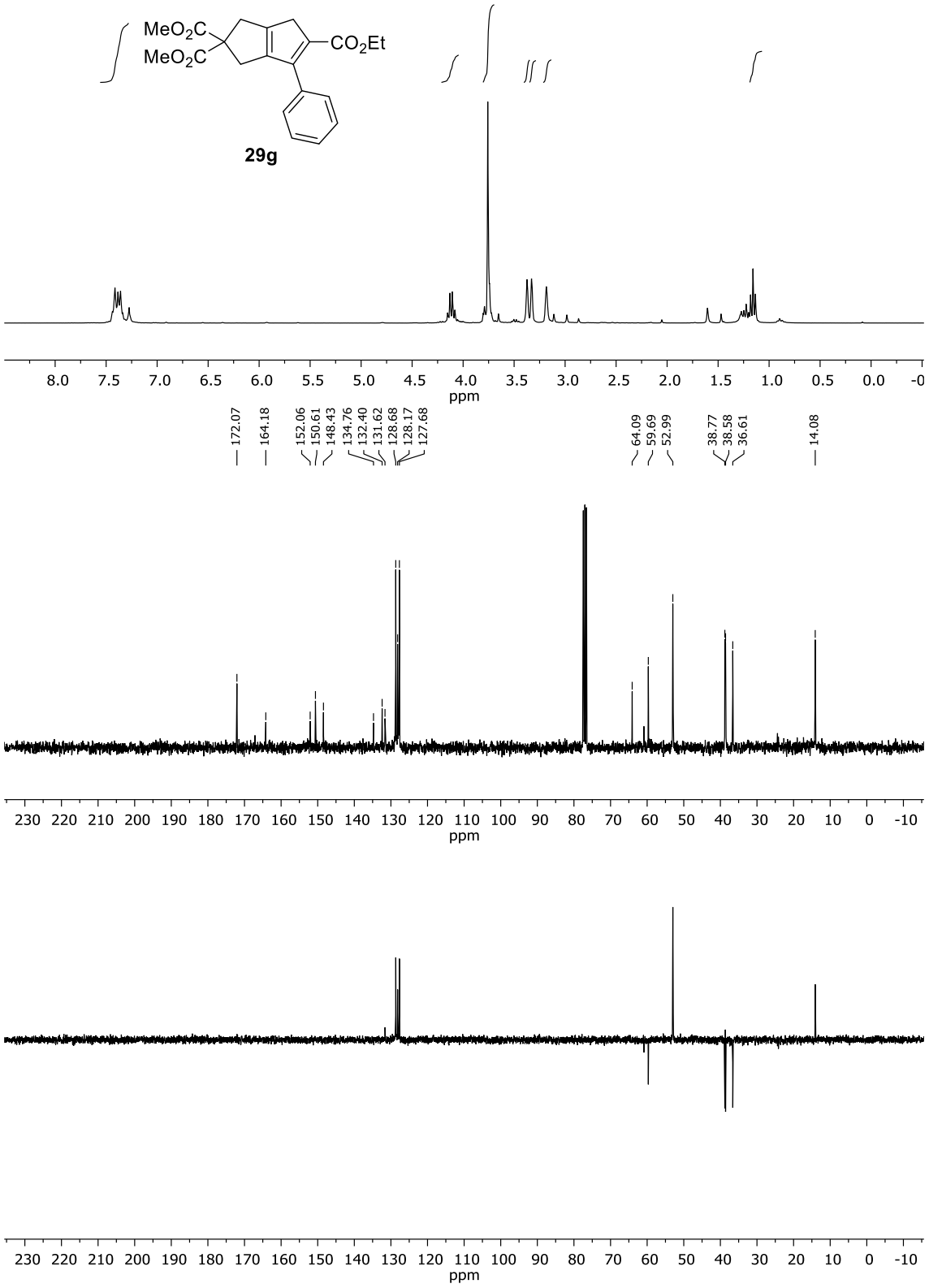
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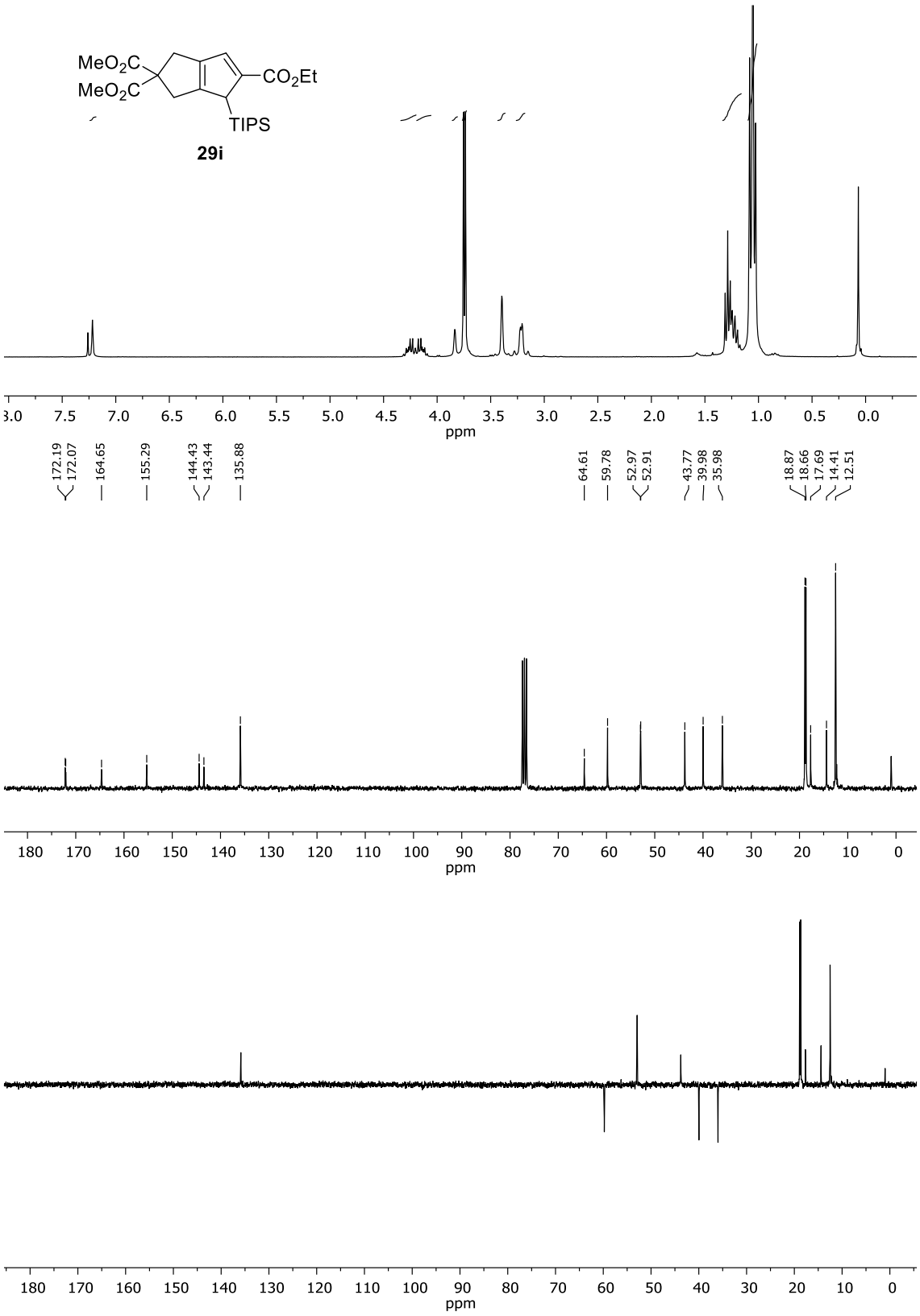
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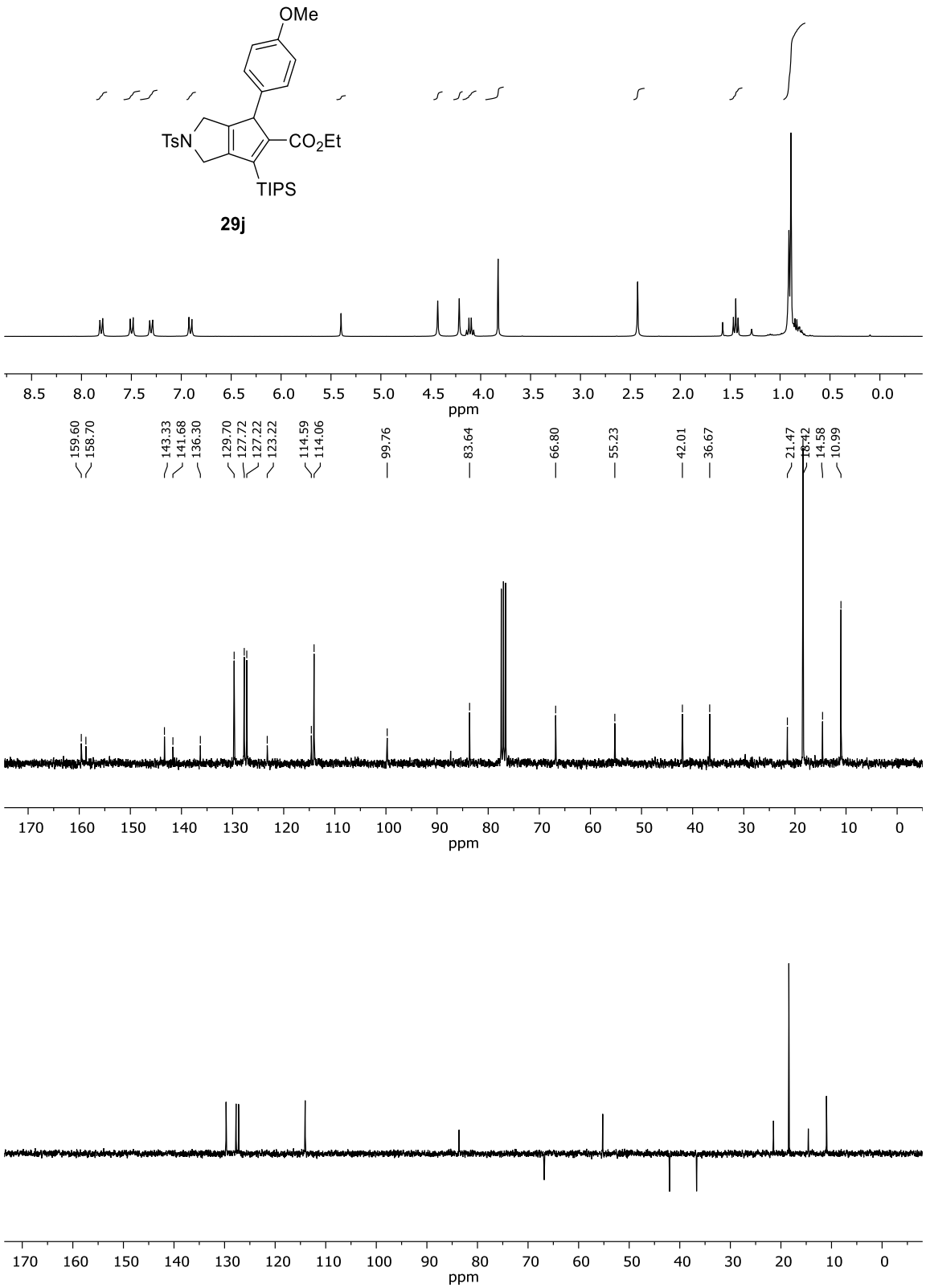
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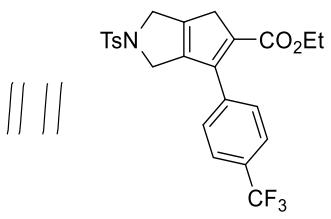
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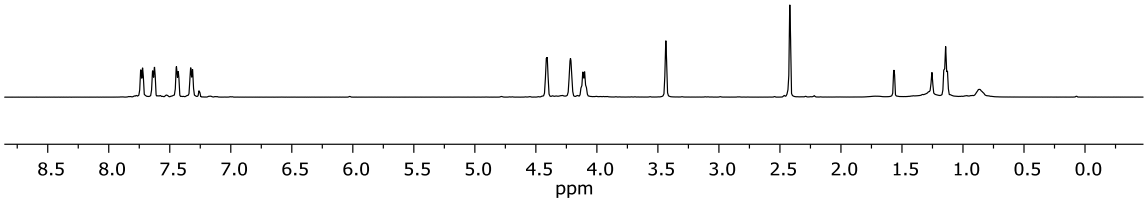
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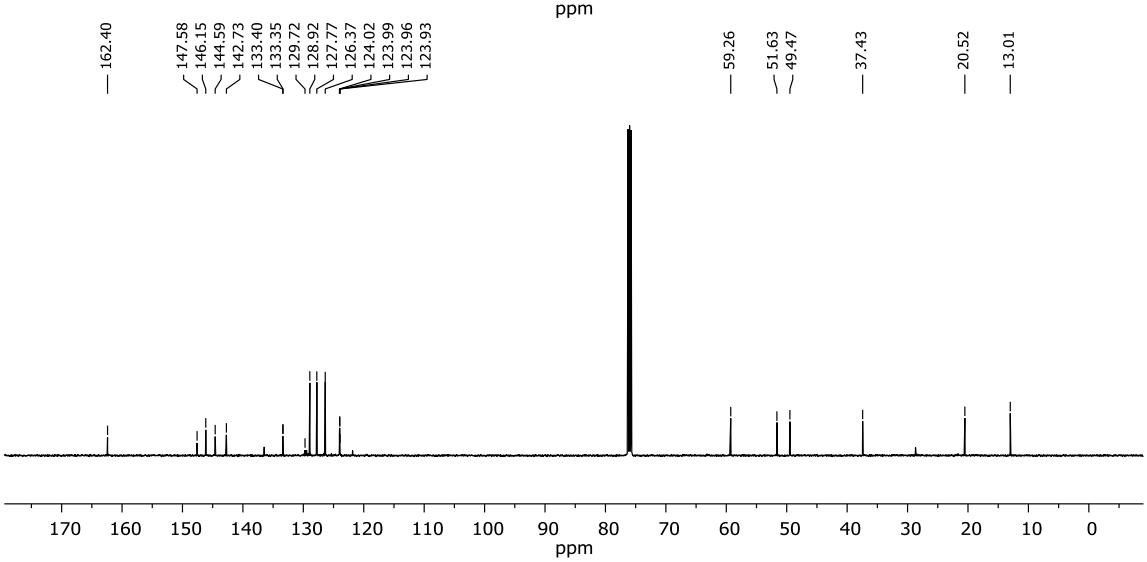


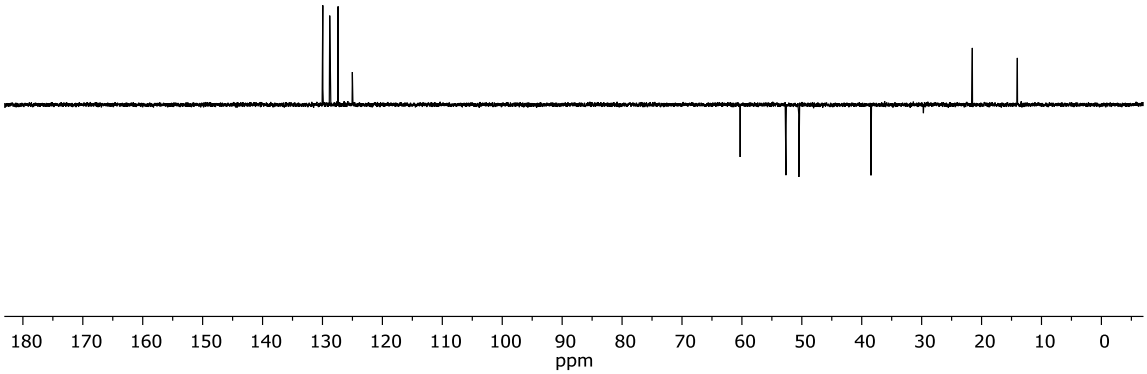
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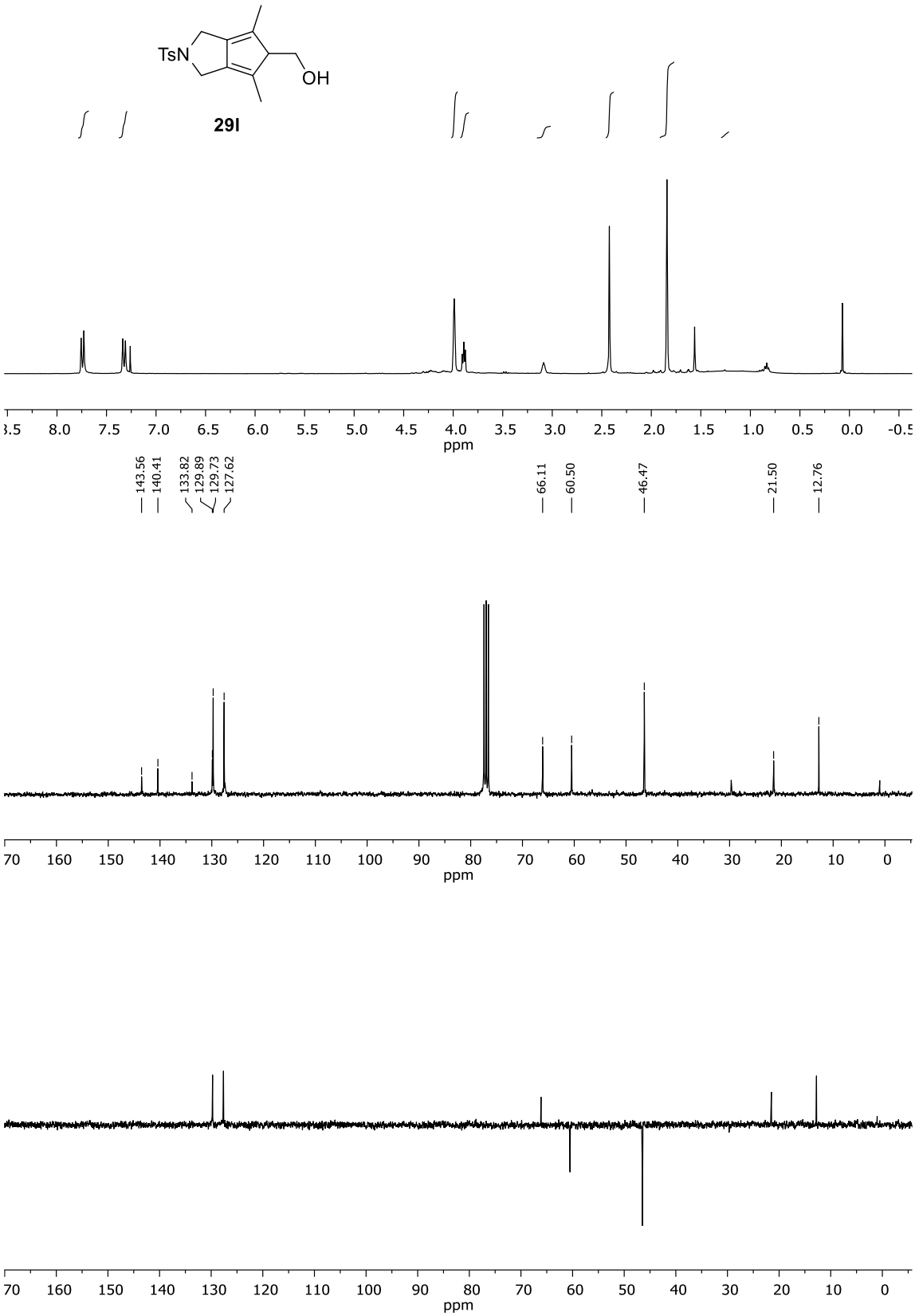
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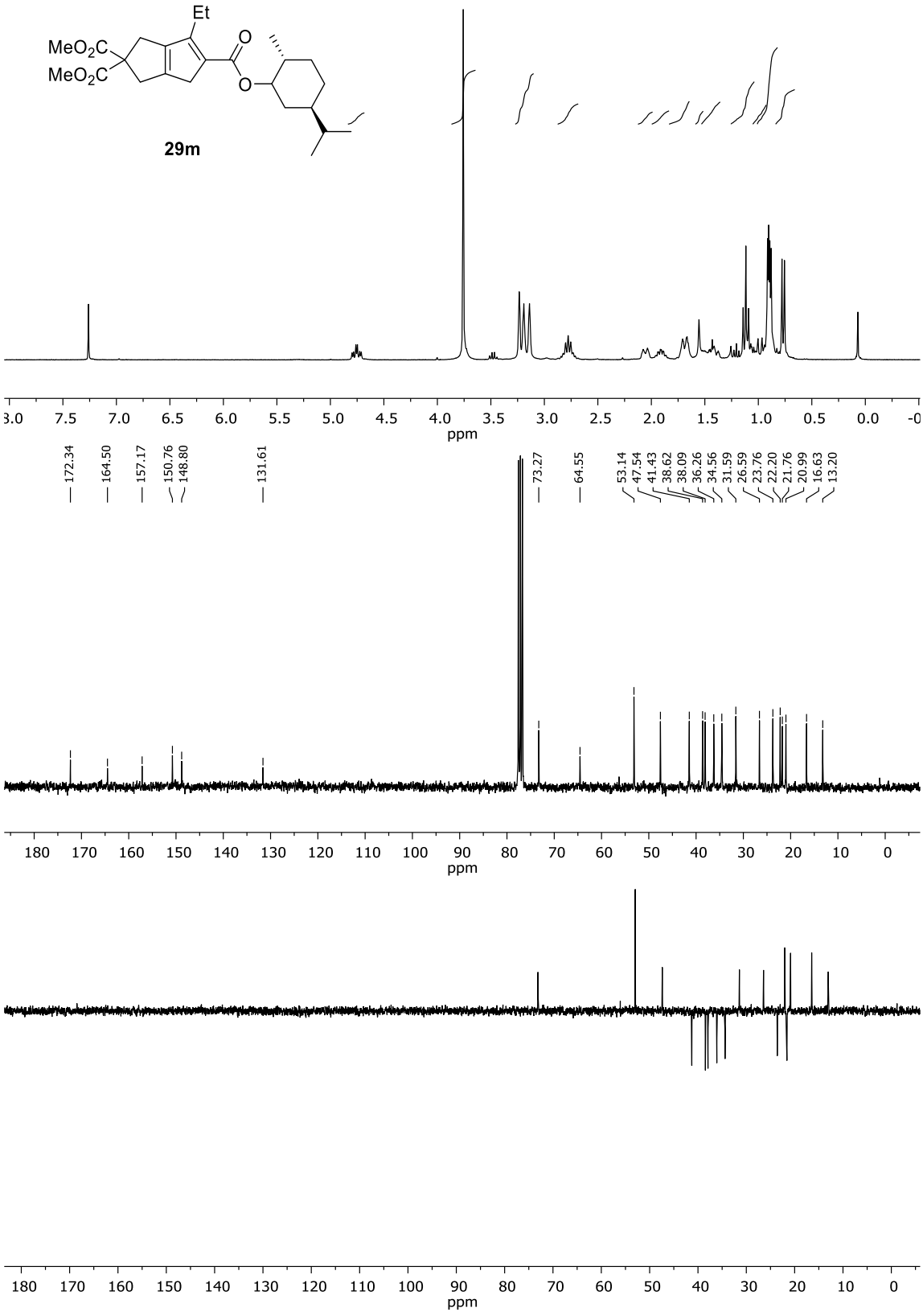




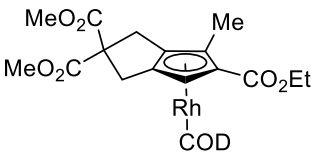
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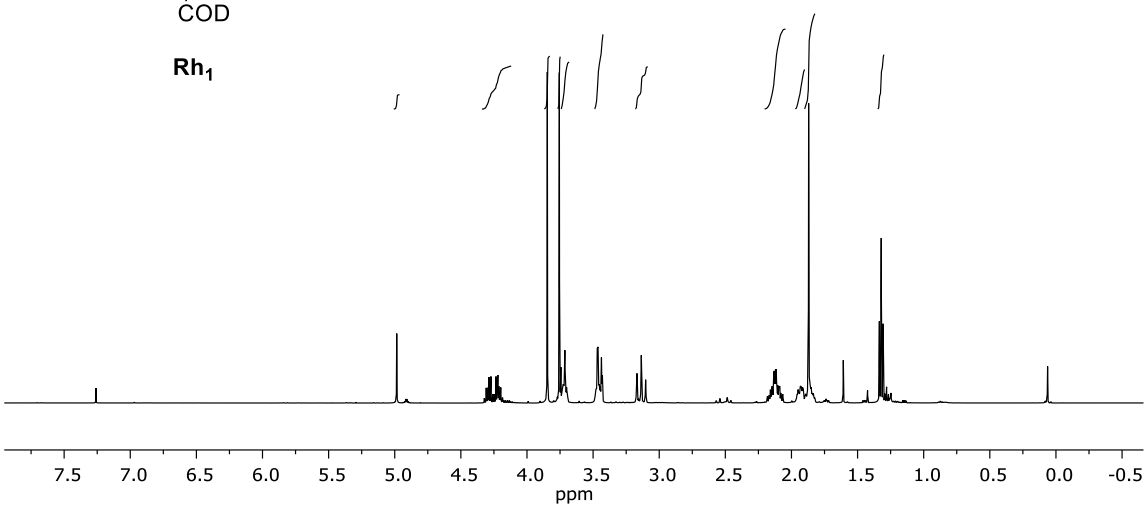
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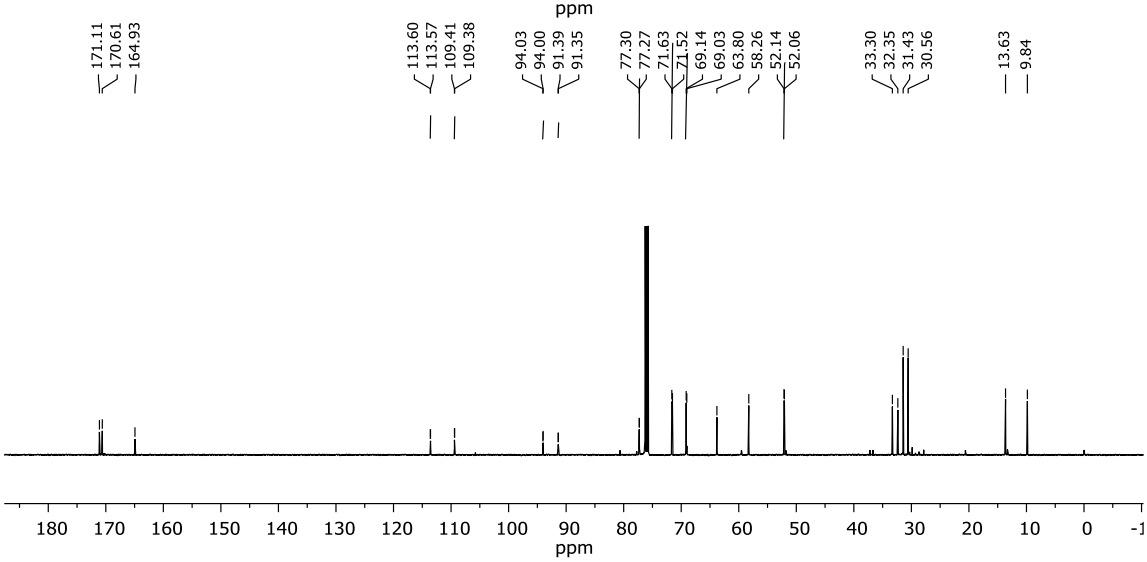


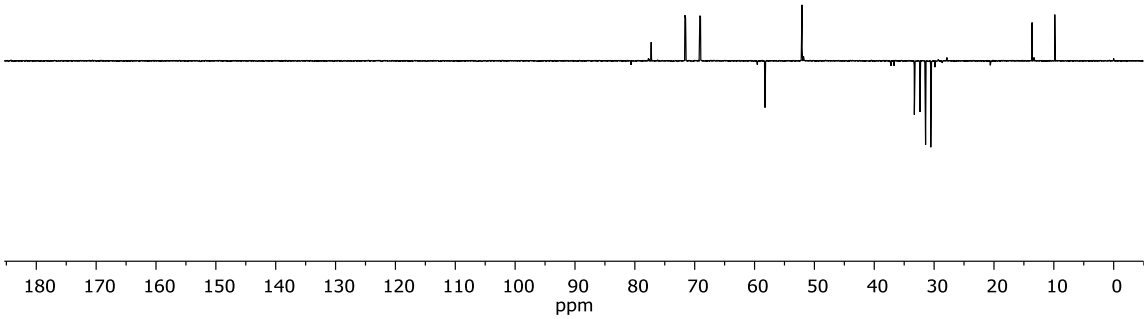
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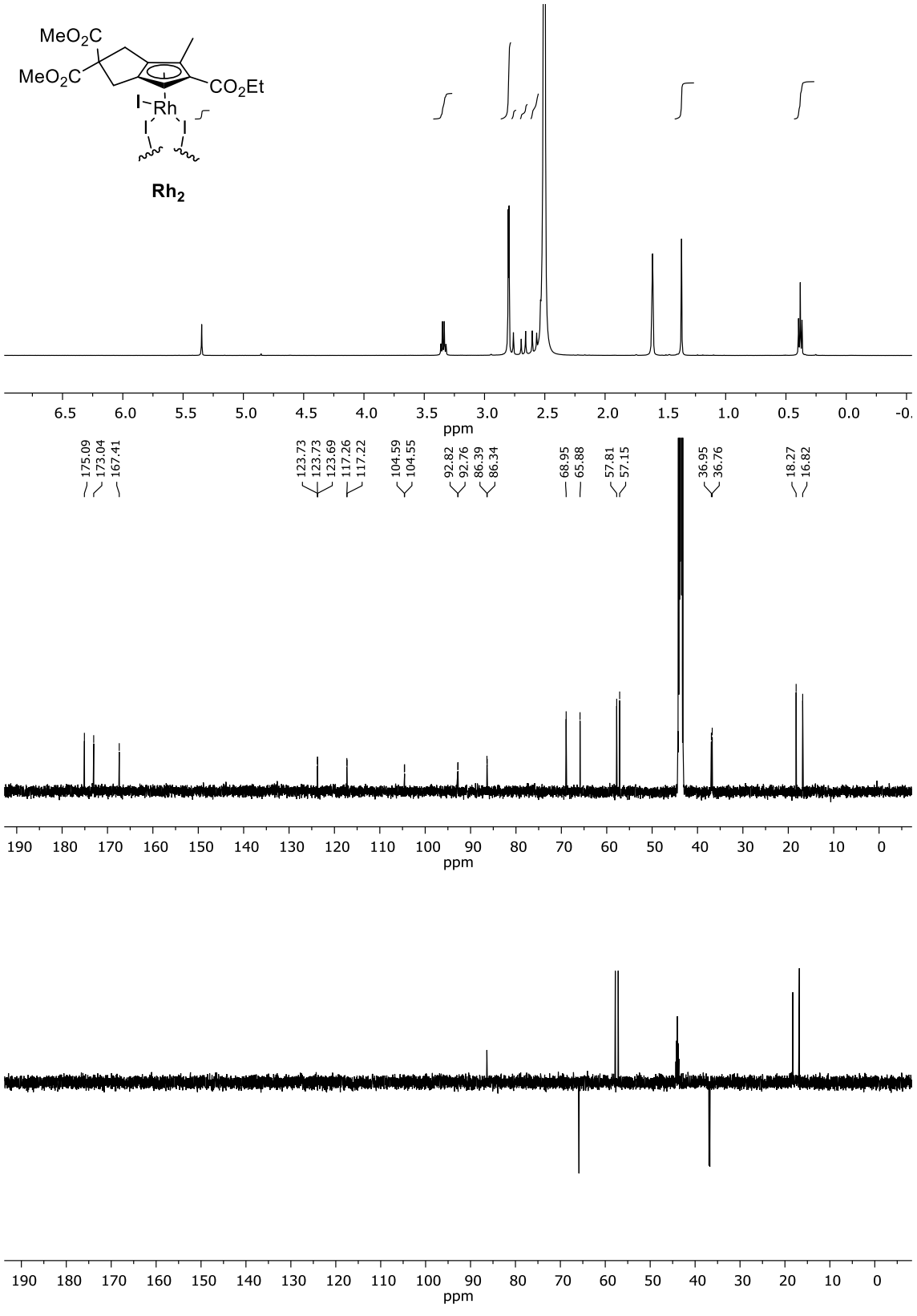
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CHAPTER 1

Title:	Highly enantioselective cobalt-catalysed (3+2) cycloaddition of alkynylidenecyclopropanes
Authors:	Eduardo da Concepción, Israel Fernandez, Jose Luis Mascareñas, Fernando López
Affiliation:	Centro Singular de Investigación en Química Biolóxica e Materiais Moleculares (CIQUS) and Departamento de Química Orgánica, Universidade de Santiago de Compostela, 15782 Santiago de Compostela (Spain)
Journal:	Angewandte Chemie International Edition
Year:	2021
Volume, pages:	60, 8182-8188
Impact factor:	15.336 (2020)
PhD student contribution:	Discovery of the reaction; Synthesis of starting materials; Screening of conditions; Synthesis and characterization of all compounds; Manipulation of the products; Discussion of the results and revision of the manuscript



Highly Enantioselective Cobalt-Catalyzed (3 2) Cycloadditions of Alkynylidenecyclopropanes

Author: Fernando López, José L. Mascareñas, Israel Fernández, et al

Publication: Angewandte Chemie International Edition

Publisher: John Wiley and Sons

Date: Mar 5, 2021

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Licensed Content Author	Fernando López, José L. Mascareñas, Israel Fernández, et al
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CHAPTER 2

Title:	Pd-Catalysed (3 2) Heterocycloadditions between Alkylidenecyclopropanes and Carbonyls: Straightforward Assembly of Highly Substituted Tetrahydrofurans
Authors:	Felipe Verdugo, Eduardo da Concepción, Ricardo Rodiño, Martín Calvelo, Jose Luis Mascareñas, Fernando López
Affiliation:	Centro Singular de Investigación en Química Biolóxica e Materiais Moleculares (CIQUS) and Departamento de Química Orgánica, Universidade de Santiago de Compostela, 15782 Santiago de Compostela (Spain)
Journal:	ACS Catalysis
Year:	2020
Volume, pages:	10, 7710-7718
Impact factor:	13.084 (2020)
PhD student contribution:	Discovery of the reaction; Synthesis of starting materials; Screening of conditions; Synthesis and characterization of ACPs and tetrahydrofurans; Manipulation of the products; Discussion of the results and revision of the manuscript

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Pd-Catalyzed (3 2) Heterocycloadditions between Alkylidenecyclopropanes and Carbonyls: Straightforward Assembly of Highly Substituted Tetrahydrofurans

Author: Felipe Verdugo, Eduardo da Concepción, Ricardo Rodiño, et al
Publication: ACS Catalysis
Publisher: American Chemical Society
Date: Jul 1, 2020

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