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Assembly of azaheterocycles via transition metal-catalyzed annulations involving the activation of C-H bonds

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Assembly of azaheterocycles via transition metal-catalyzed annulations involving the activation of C-H bonds

Borja Cendón Mariño

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Assembly of azaheterocycles via transition metal-catalyzed annulations involving the activation of C-H bonds

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Dedicated to my family and friends.


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“What we Know is a drop, what we don’t know is an ocean.”

Isaac Newton


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Abbreviations and acronyms

Ac	Acetyl
AcOH	Acetic acid
APAO	Acetyl-protected aminomethyl oxazolines
APAQ	Acetyl-protected aminoethyl quinoline
APCI	Atmospheric-pressure chemical ionization
AQ	8-Aminoquinoline
BAr^F	Tetrakis[3,5-bis(trifluoromethyl) phenyl]borate
BINOL	1,1′-Bi-2-naphthol
Boc	*tert*-Butyloxycarbonyl
BQ	*p*-Benzoquinone
CC	Constant current
CMD	Concerted metalation deprotonation
cod	1,5-cyclooctadiene
Cp*	1,2,3,4,5-Pentamethylcyclopentadienyl
d	Doublet
DavePhos	2-Dicyclohexylphosphino-2’-(*N*,*N*-dimethylamino)biphenyl
dba	Dibenzylideneacetone
DBU	1,8-Diazabicyclo(5.4.0)undec-7-ene
DCE	1,2-Dichloroethane
DCM	Dichloromethane
DFT	Density functional theory
DG	Directing group
DIAD	Diisopropyl azodicarboxylate
DMAP	4-Dimethylaminopyridine
DMF	*N*,*N*-Dimethyl formamide
DMSO	Dimethyl sulfoxide
d^{F}ppe	1,2-Bis[bis(pentafluorophenyl) phosphino]ethane
d.r.	Diastereoisomeric ratio
E_a	Activation energy
EDC	1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide
ee	Enantiomeric excess
e.r.	Enantiomeric ratio
ESI	Electrospray ionization
equiv	Equivalent
FG	Functional group
GF	Graphite
HFIP	Hexafluoro-2-propanol
J	Coupling constant
L	Ligand
L-DOPA	L-3,4 dihidroxifenilalanina
[M]	Metal
M	Molarity
m	Multiplet
3-MPA	3-Mercaptopropionic acid
MPAA	Mono-protected amino acids
MPAHA	Mono-protected *α*-amino-O-methylhydroxamic acids
MPAO	Mono-protected aminomethyl oxazolines
M.S.	Molecular sieves
NMO	*N*-Methylmorpholine-*N*-oxide
NMR	Nuclear magnetic resonance
nOe	Nuclear Overhauser effect

Ns	*p*-Nitrobenzenesulfonyl
[O]	Oxidant
PivOH	Pivalic acid
q	Quadruplet
r.r.	Regioisomeric ratio
rt	Room temperature
T	Temperature
t	Time
t	Triplet
t-AmOH	2-methyl-2-butanol
TBS	*tert*-Butyldimethylsilyl
TEABF$_4$	Tetraethylammonium tetrafluoroborate
TEMPO	2,2,6,6,-Tetramethyl-1-piperidinyloxy
Tf	Trifluoromethanesulfonyl
TFA	Trifluoroacetic acid
TFE	2,2,2, Trifluoroethanol
THF	Tetrahydrofuran
TM	Transition metal
TMS	Trimethylsilane
Ts	*p*-Toluenesulfonyl

Introduction


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1. Organic Synthesis: Relevance and perspectives

Organic Synthesis is a branch of science dealing with the construction of organic products, either novel or present in nature. The synthesis of complex organic molecules from simple and available precursors is essential to progress in many other disciplines like medicine or materials science.[1]

The first, and serendipitous, example of an organic synthesis was the obtention of urea reported by F. Wöhler in 1828. Despite the apparently simple achievement, this discovery sparked a field that has had a tremendous impact in human progress. In 1965, R. B. Woodward, the father of modern organic synthesis received Nobel Prize in Chemistry "for his outstanding achievements in the art of organic synthesis". He published the total synthesis of many relevant and complex compounds like strychnine.[2] Following these steps, many other chemists, like E. J. Corey, K. C. Nicolaou or P. Wender, among others, have made impressive contributions to the field.[3]

In more recent decades, the field of organic synthesis has witnessed a great progress, in part associated to the exponential growth of knowledge in areas like organometallic chemistry; and many complex molecules containing cyclic skeletons and stereocenters have been synthesized (figure 1).[4] A particularly attractive type of targets are nitrogen heterocycles, owing to their wide representation in many biologically relevant products and biomolecules, like in the DNA bases.[5]

However, nowadays, the goal is not just making the molecular target, but doing it in a sustainable and practical manner. Modern organic synthesis requires processes that are efficient, economic and green, minimizing the production of wastes and by-products and avoiding the use of toxic or hazardous chemicals, including reagents and solvents.[6] To that end, it is necessary to invent and develop atom, step, redox and pot economy reactions that allow a target-relevant increase in complexity from readily available precursors.[7]

---

[1] Li, J. W.; Vederas, J. C. *Science* **2009**, *325*, 161-165.

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

[3] For selected examples in total synthesis, see: (a) Sheehan, J. C.; Henery-Logan, K. R. *J. Am. Chem. Soc.* **1957**, *79*, 1262-1263. (b) Nicolau, K. C.; Yang, Z.; Liu, J. J.; Ueno, H.; Nantermet, P. G.; Guy, R. K.; Claiborne, C. F.; Renaud, E. A.; Couladouros, E. A.; Paulvannan, K.; Sorensen, E. J. *Nature* **1994**, *367*, 630-634. (c) Nelson, R.; Gulías, M.; Mascareñas. J. L.; López. F. *Angew. Chem. Int. Ed.* **2016**, *55*, 14359-14363.

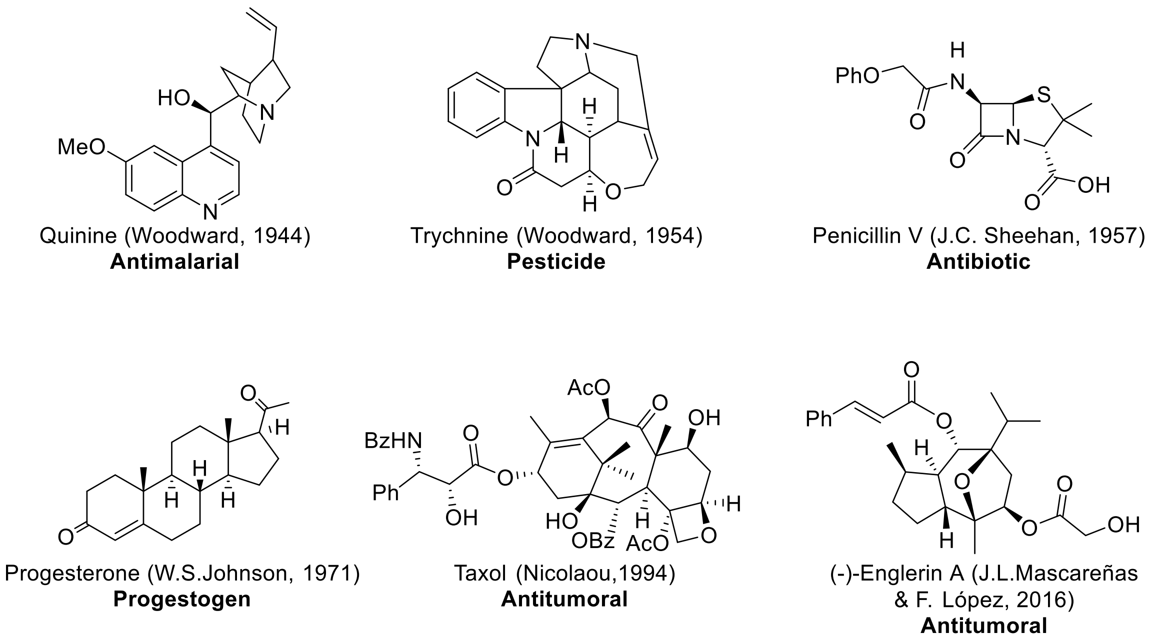
[4] (a) Nicolaou, K. C.; Sorensen, E. J. *Classics in total synthesis: targets, strategies, methods.* Weinheim New York: VCH, **1996**. (b) Nicolaou, K. C.; Snyder, S. A. *Classics in total synthesis II: more targets, strategies, methods*. Wiley-VCH, **2003**. (c) Nicolaou, K. C.; Chen, J. S. *Classics in total synthesis III: further targets, strategies, methods*. Wiley-VCH, **2011**.

[5] Walsh, C. T. *Tetrahedron Lett.* **2015**, *56*, 3075-3081.

[6] (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.

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

Thus, considering these guidelines, organic chemists are more than ever pursuing the ideal synthesis, which is necessarily ligated to the discovery of new, sustainable transformations.[8]



Quinine (Woodward, 1944)
Antimalarial

Trychnine (Woodward, 1954)
Pesticide

Penicillin V (J.C. Sheehan, 1957)
Antibiotic

Progesterone (W.S.Johnson, 1971)
Progestogen

Taxol (Nicolaou,1994)
Antitumoral

(-)-Englerin A (J.L.Mascareñas & F. López, 2016)
Antitumoral

***Figure 1**. Examples of biological active natural products synthesized in the laboratory.*

2. Organometallic Catalysis

2.1 Overview

Undoubtedly, one of the best ways to contribute to modern synthesis consists on the invention of catalytic transformations, as they require sub-stoichiometric amounts of the reagents. In this context, the area of organometallic catalysis is especially attractive owing to the availability of different type of metals, and the possibility of dressing them with a wide variety of ligands.

The field of organometallic catalysis, and specially that involving transition metals, had changed the way in which molecules can be synthesized, and impacted many different research areas.[9,10] Using these technologies, it was possible to reduce dramatically the number of steps required to obtain certain molecules.

Transition metal catalysts introduced unconventional mechanistic paths with low energetic barriers, increasing, in this way, the reaction rates (figure 2) and reduce reaction

---

[8] Gaich, T.; Baran, P. S. *J. Org. Chem.* **2010**, *75*, 4657-4673.

[9] (a) Hegedus, L. S. *Transition metals in the synthesis of complex organic molecules*. University Science of books, **1994**. (b) Crabtree, R. H. *The organometallic chemistry of transition metals*. Wiley-VCH, **2001**.

[10] Busacca, C. A.; Fandrick, D. R.; Song, J. J.; Senanayake, C. H. *Transition metal catalysis in the pharmaceutical industry*. John Wiley and sons, **2012**.

times, temperatures and pressures, thereby providing for practical and safer processes, one of the principles of Green Chemistry.[11]

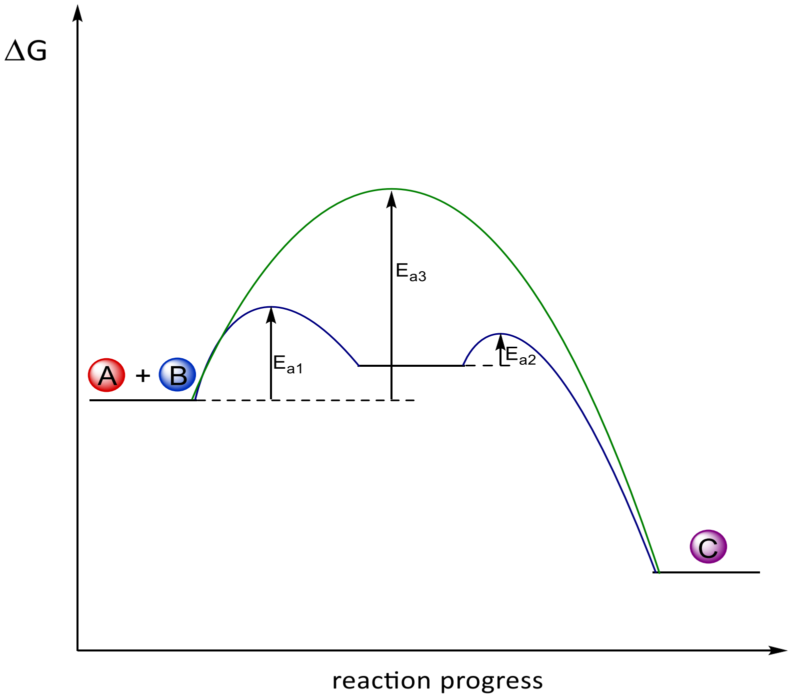
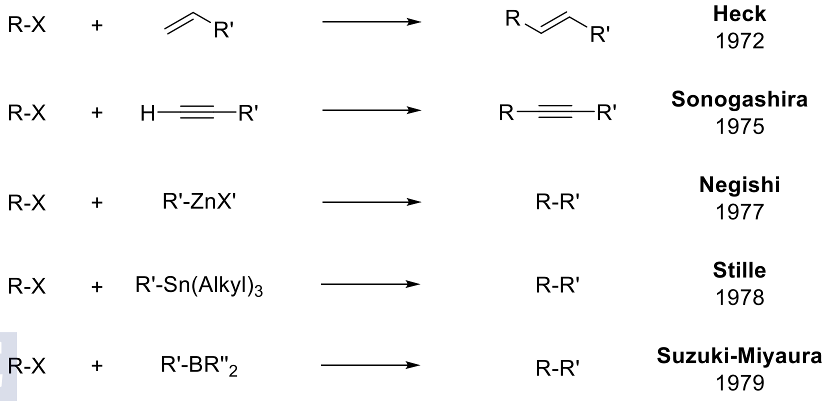


Figure 2. *Energy profiles with (blue) and without (green) catalyst.*

In view of these advantages, organometallic complexes have been widely used to catalyze different type of reactions over the years. For example, the development of palladium-catalyzed cross-coupling reactions (scheme 1) constituted an undoubtable revolution in organic chemistry with broad applications in research and industry.[12] Consequently some of the researchers involved in the discovery, R. F. Heck, E. Negishi and A. Suzuki, were awarded with the Nobel Prize in Chemistry in 2010.[13]



Scheme 1. *General reaction scheme for palladium-catalyzed cross-coupling reactions.*

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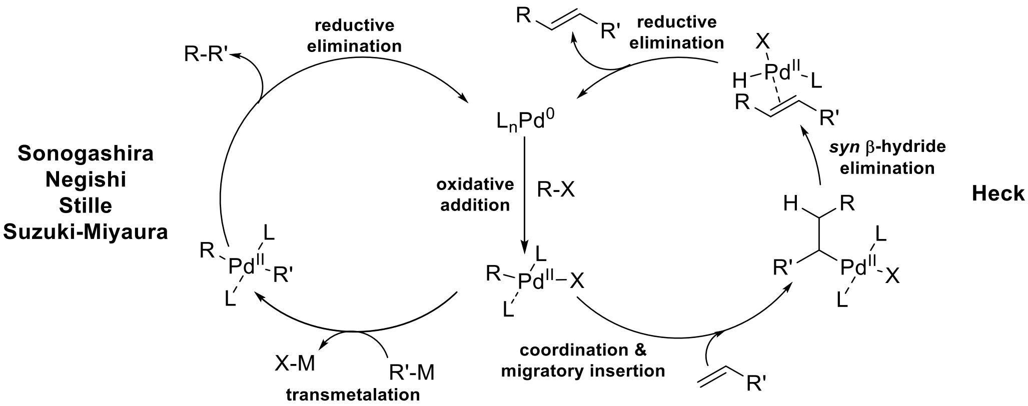
[11] Crabtree, R. H. *Organometallics* **2011**, *30*, 17-19.

[12] Nicolau, K. C.; Bulger, P. G.; Sarlah, D. *Angew. Chem. Int. Ed.* **2005**, *44*, 4442-4489.

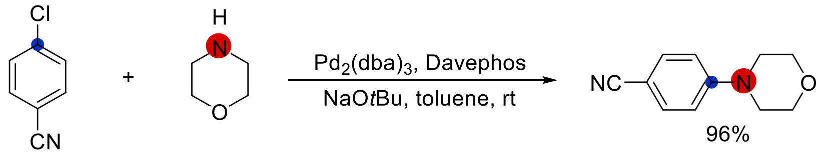
[13] Johansson Seechurn, C. C. C.; Kitching, M. O.; Colacot, T. J.; Snieckus, V. *Angew. Chem. Int. Ed.* **2012**, *51*, 5062–5085.

The mechanism of these transformations follows a general scheme including the following steps: oxidative addition, transmetalation and reductive elimination. In the case of the Heck reaction, the oxidative addition is followed by migratory insertion and syn β-hydride elimination, instead of transmetalation (scheme 2).[14]



Scheme 2. *Mechanism of palladium-catalyzed cross-coupling reactions.*

Despite the exponential growth in the discovery of new reactions experienced in recent years, these transformations continue to be considered among the most powerful tools to form carbon-carbon bonds. More recently, other type of palladium-catalyzed cross-coupling reaction, known as Buchwald-Hartwig amination, have been extensively developed.[15] The reaction generates carbon-nitrogen bonds (scheme 3) and has been used as key step in the large-scale production of pharmaceuticals and agrochemicals in industry.[16]



Scheme 3. *Example of Buchwald-Hartwig amination.*

Organometallic catalysis has not been only used for cross-coupling reactions, but also for other type of reactions such as hydrogenations. For example, the Wilkinson's catalyst $RhCl(PPh_3)_3$ allows for very efficient hydrogenations of double and triple bonds under mild conditions, and can provide chemoselective transformations.[17]

The mechanism of this transformation starts with the dissociation of a phosphine ligand, to form an unsaturated intermediate, followed by oxidative addition of H_2 to form **II**, still with a vacant coordination site. This void is then occupied by the coordination of an alkene, resulting in the octahedral 18-e$^-$ rhodium complex **III**, which evolves through

---

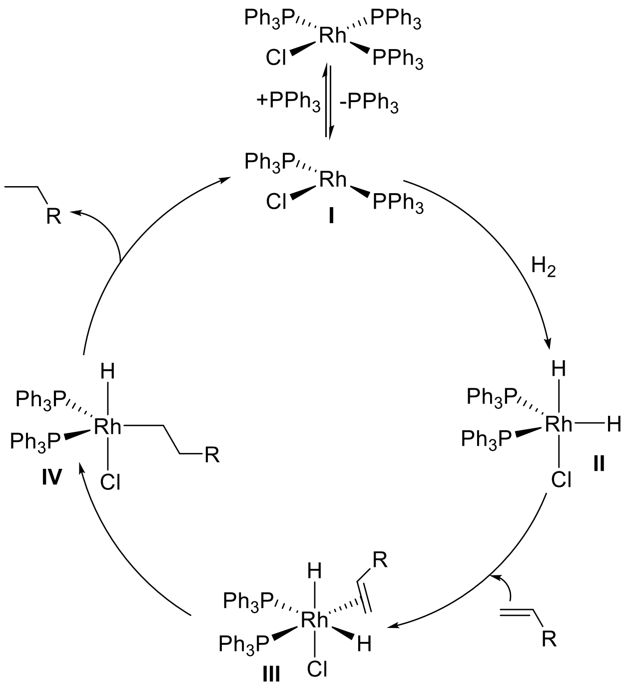
[14] Heck, R. F.; Nolley, J. P. *J. Org. Chem.* **1972**, *37*, 2320-2322.

[15] Yang, B. H.; Buchwald, S. L. *J. Organomet. Chem.* **1999**, *576*, 125-146.

[16] Dorel, R.; Grugel, C. P.; Haydl, A. M. *Angew. Chem. Int. Ed.* **2019**, *58*, 17118-17129.

[17] (a) Osborn, J. A.; Wilkinson, G.; Young, J. F. *Chem. Commun.* **1965**, *2*, 17. (b) Young, J. F.; Osborn, J. A.; Jardine, F. H.; Wilkinson, G. *Chem. Comm.* **1965**, 131-132.

migratory insertion with concomitant intramolecular hydride transfer. The resulting alkyl rhodium complex **IV** undergoes reductive elimination to yield the corresponding alkane derivative (scheme 4). Remarkable, the asymmetric version of this reaction, using chiral bidentate ligands, is being used in the synthesis of many pharmaceuticals, such as L-DOPA.



Scheme 4. *Hydrogenation mechanism with Wilkinson's catalyst.*

2.2 Transition metal-catalyzed cycloadditions

Among the different chemical reactions with high synthetic potential, cycloadditions are especially relevant. The possibility of making at least two bonds and one cycle in a single step, and with atom economy, allows a very rapid increase in molecular complexity from simple and acyclic starting materials, which simplifies synthetic processes.[18] It is important to note that most of the organic molecules with interesting pharmacological applications consist of cyclic compounds, and therefore methods that allow the assembly of cycles in a rapid manner are of prominent interest. This is the case of the Diels-Alder reaction, which has been widely used as key step in many total syntheses.[19]

Diels-Alder reactions, discovered by O. P. H. Diels and K. Alder in 1950 and worth of a Nobel prize, engage a 1,3-diene and a dienophile to give a substituted cyclohexene derivative with high regio- and stereocontrol (scheme 5).[20] Despite the reaction is usually promoted by simple thermal conditions, the electronic requirements of the coupling

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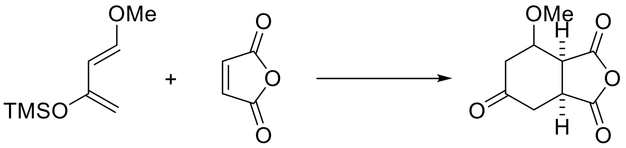
[18] (a) Carruthers, W. *Cycloaddition reactions in organic synthesis*. Pergamon: Oxford, **1990**. (b) Kobayashi, S.; Jørgensen, K. A. *Cycloaddition reactions in organic synthesis*. Wiley-VCH, **2001**.

[19] Nicolaou, K. C.; Snyder, S. A.; Montagnon, T. *Angew. Chem. Int. Ed.* **2002**, *41*, 1668-1698.

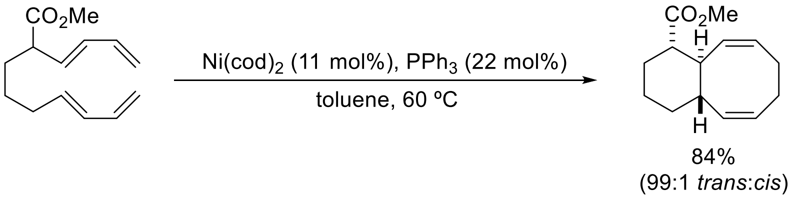
[20] Diels, O.; Alder, K. *Justus Liebigs Ann. Chem.* **1928**, *460*, 98-122.

partners, that must be equipped with additional electron-donor and electron withdrawing substituents, restrict the potential applications of the method. Furthermore, the Diels-Alder reaction is limited to the construction of a very specific type of rings. Therefore, the discovery of methodologies that allow to achieve many other type of annulations is of prominent interest.



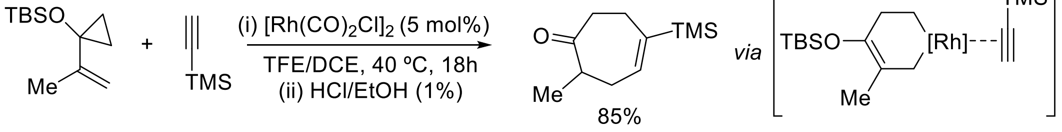
Scheme 5. *Example of Diels-Alder reaction with a Danishefsky's diene.*

It is in this context where transition metal catalysts, by introducing new mechanistic possibilities, can provide alternatives to build up different type of rings from a great variety of precursors.[21] The ability of many transition metals to coordinate and activate pi bonds, has led to the discovery of many formal cycloadditions of alkenes, alkynes, allenes or dienes, reactions that otherwise cannot be promoted under thermal conditions. A pioneering example was introduced by Wender in 1986. Using Ni(0) catalysis, his group demonstrated the viability of performing (4+4) cycloadditions of 1,3-dienes to build a variety of bicyclic systems containing eight-membered rings (scheme 6).[22]



Scheme 6. *Ni(0)-catalyzed intramolecular (4+4) cycloaddition reported by Wender in 1986.*

Many of these metal-catalyzed cycloadditions entail the formation of metalacyclic intermediates, obtained through oxidative cyclometalation steps. This step is followed by a migratory insertion of the partner and then the product is usually released by reductive elimination. A remarkable example published by Wender is the (5+2) process between vinylcyclopropanes (VCPs) and alkynes (scheme 7).[23]



Scheme 7. *Rh(I)-catalyzed (5+2) cycloaddition between VCPs and alkynes.*

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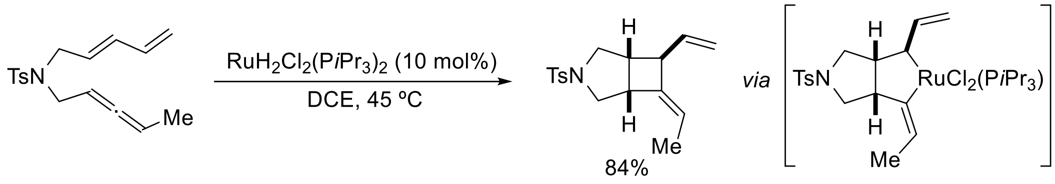
[21] Lautens, M.; Klute, W.; Tam, W. *Chem. Rev.* **1996**, *96*, 49-92.

[22] Wender, P. A.; Ihle, N. C. *J. Am. Chem. Soc.* **1986**, 108, 4678-4679.

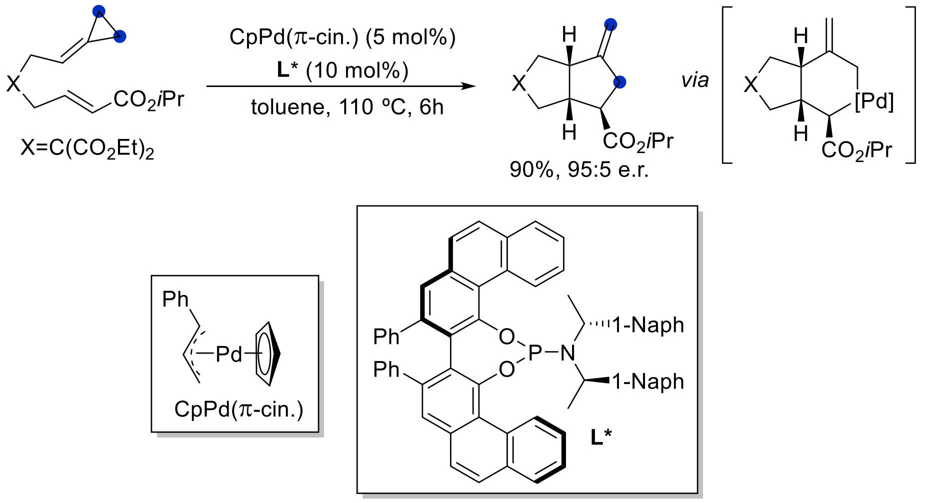
[23] Liu, P.; Sirois, L. E.; Cheong, P. H.-Y.; Yu, Z.-X.; Hartung, I. V.; Rieck, H.; Wender, P. A.; Houk, K. N. *J. Am. Chem. Soc.* **2010**, *132*, 10127-10135.

Another significant example based on an operationally simple protocol, was reported by our group in 2011, and consists of a ruthenium-catalyzed formal (2+2) cycloaddition, which allows for the diastereoselective synthesis of fused bicyclic systems exhibiting a challenging cyclobutane ring (scheme 8).[24]



Scheme 8. *Ru-catalyzed intramolecular (2+2) cycloaddition of allenedienes.*

More recently, a palladium-catalyzed intramolecular (3+2) cycloaddition between alkylidenecyclopropanes (ACPs) and alkenes was also reported by our group. The reaction was developed in a diastereo- and enantioselective manner using phosphoramidites as chiral ligands and produces 5,5-bicyclic systems with enantiomeric excesses up to 94% (scheme 9).[25]



Scheme 9. *Intramolecular (3+2) cycloaddition between ACPs and alkenes.*

Despite the great versatility and helpfulness of these transformations, they depend on the use of highly functionalized substrates with multiple unsaturated bonds. This commonly demands a laborious engineering of the precursors, which limits the synthetic practicability of the processes. Moreover, these transformations usually lead to carbocyclic structures through the formation of new C-C bonds, while the assembly of more appealing heterocyclic skeletons is more difficult.

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[24] Gulías, M.; Collado, A.; Trillo, B.; López, F.; Oñate, E.; Esteruelas, M. A.; Mascareñas, J. L. *J. Am. Chem. Soc.* **2011**, *133*, 7660-7663.

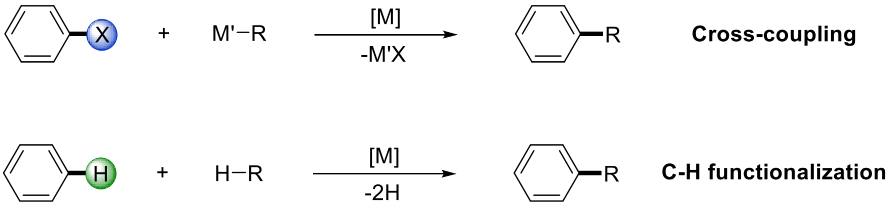
[25] Verdugo, F.; Villarino, L.; Durán, J.; Gulías, M.; Mascareñas, J. L.; López, F. *ACS Catal.* **2018**, *8*, 6100-6105.

3. Transition metal-catalyzed reactions triggered by C-H activations

3.1 Basic considerations

Among the different reactions catalyzed by transition metals, those involving the activation and functionalization of C-H bonds are especially appealing due to the ubiquitous nature of these bonds in organic molecules. Furthermore, these approaches may avoid the need to use pre-functionalized substrates, therefore providing for a much more direct access to the desired products (scheme 10).

Therefore, the development of catalytic methods for the selective and efficient functionalization of "inert" C-H bonds represents a major goal in modern synthetic chemistry. These types of technologies have emerged among the more powerful strategies to build C-C and C-heteroatom bonds, and a greener and step-economic alternative to the cross coupling reactions, enabling a rapid increase in complexity from readily available precursors, which greatly reduce wastes and steps.[26] In addition, these methodologies open up a new world of possibilities for late-stage modification of complex molecules and drugs.[27]



Scheme 10. *Comparison between cross-coupling and oxidative C-H functionalization reactions.*

However, the cleavage of C-H bonds by metal reagents is tricky, especially when compared with that of C-X bonds, required for cross-coupling reactions. This is in part associated to strength and lack of polarization of these bonds (an aromatic C-H bond has a bond strength around 110 Kcal/mol while in an analogous C-I bond is only 65 Kcal/mol).[28] In addition, the large number of C-H bonds in organic molecules frequently brings selectivity issues, usually solved with the preinstallation of directing groups, that direct the metalation process to the desired C-H bond through the formation of metalacyclic intermediates (usually five or six-membered).[29]

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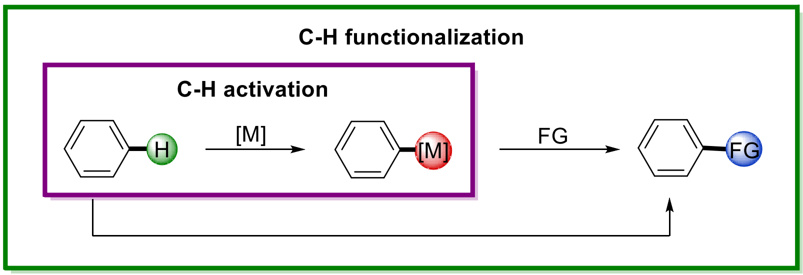
[26] For recent reviews in the field, see: (a) Wang, K.; Hu, F.; Zhang, Y.; Wang, J. *Sci. China Chem.* **2015**, *58*, 1252-1265. (b) He, J.; Wasa, M.; Chan, K. S. L.; Shao, Q.; Yu, J.-Q. *Chem. Rev.* **2017**, *117*, 8754-8786. (c) Park, Y.; Kim, Y.; Chang, S. *Chem. Rev.* **2017**, *117*, 9247-9301. (d) Wozniak, L.; Cramer, N. *Trends Chem.* **2019**, *1*, 471-484.

[27] (a) Wencel-Delord, J.; Glorius, F. *Nature Chem.* **2013**, *5*, 369-375. (b) Karimov, R. R.; Hartwig, J. F. *Angew. Chem. Int. Ed.* **2018**, *57*, 4234-4241. (c) Guillemard, L.; Kaplaneris, N.; Ackermann, L.; Johansson, M. J. *Nature Rev. Chem.* **2021**, *5*, 522-545.

[28] Luo, Y. R. *Comprehensive Handbook of Chemical Bond Energies*. CRC Press, **2007**.

[29] For a comprehensive overview of the use of directing groups in C-H functionalization, see: Sambiagio, C.; Schönbauer, D.; Blieck, R.; Dao-Huy, T.; Pototschnig, G.; Schaaf, P.; Wiesinger, T.; Zia, M. F.; Wencel-Delord, J.; Besset, T.; Maes, B. U. W.; Schnürch, M. *Chem. Soc. Rev.* **2018**, *47*, 6603-6743.

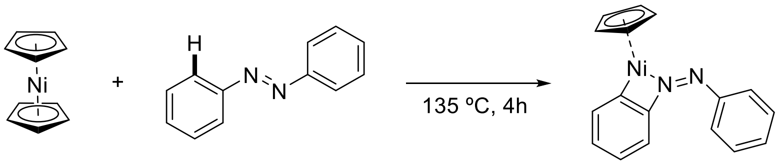
The process of metalation, in which a C-H bond is transformed into a C-metal bond, is known as C-H activation,[30] and should not be confused with C-H functionalization, because not all the C-H functionalization process involve a C-H activation step (scheme 11).



Scheme 11. *Comparison between C-H activation using transition-metal reagents and C-H functionalization.*

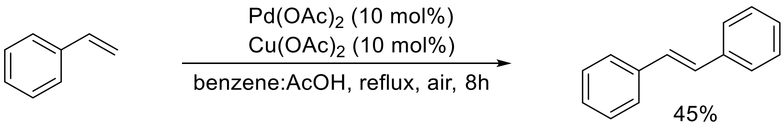
3.2 Pioneering examples

The C-H activation field could be considered to arise in 1963, with the seminal work by Kleiman and Dubeck on the metalation of diazobenzene using bis(cyclopentadienyl)nickel (scheme 12).[31]



Scheme 12. *Metalation of diazobenzene using a Ni complex.*

Despite the tremendous relevance of this publication, the use of stoichiometric amounts of the metal complex, and the absence of protocols to elaborate the nickelacycles restricted its synthetic impact. In 1967, Fujiwara and Moritani reported a C-C bond formation reaction entailing a C-H activation step.[32] They demonstrated the possibility of coupling benzene and styrene using catalytic amounts of palladium and an oxidant (scheme 13).[33,34]



Scheme 13. *Seminal example of catalytic C-H activation (Fujiwara-Moritani reaction).*

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[30] (a) Shilov, A. E.; Shul'pin G. B. *Chem. Rev.* **1997**, 97, 2879-2932. (b) Bergman, R. G. *Nature* **2007**, *446*, 391-393. (c) Hashiguchi, B. G.; Bischof, S. M.; Konnick, M. M.; Periana, R. A. *Acc. Chem. Res.* **2012**, *45*, 885-898. (d) Gensch, T.; Hopkinson, M. N.; Glorius, F.; Wencel-Delord, J. *Chem. Soc. Rev.* **2016**, *45*, 2900-2936. (e) Loup, J.; Dhawa, U.; Pesciaioli, F.; Wencel-Delord, J.; Ackermann, L. *Angew. Chem. Int. Ed.* **2019**, *58*, 12803-12818.

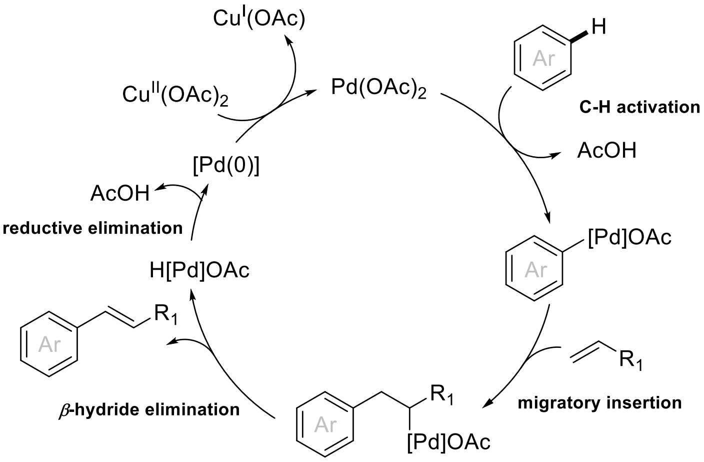
[31] Kleiman, J. P.; Dubeck, M. *J. Am. Chem. Soc.* **1963**, *85*, 1544-1545.

[32] (a) Moritani, I.; Fujiwara, Y. *Tetrahedron Lett.* **1967**, *8*, 1119-1122. (b) Fujiwara, Y.; Moritani, I.; Matsuda, M. *Tetrahedron Lett.* **1968**, *24*, 4819-4824. (c) Fujiwara, Y.; Moritani, I.; Asano, R.; Tanaka, H.; Teranishi, S. *Tetrahedron Lett.* **1969**, *25*, 4815-4818.

[33] Fujiwara, Y.; Moritani, I.; Danno, S.; Asano, R.; Teranishi, S. *J. Am. Chem. Soc.* **1969**, *91*, 7166-7169.

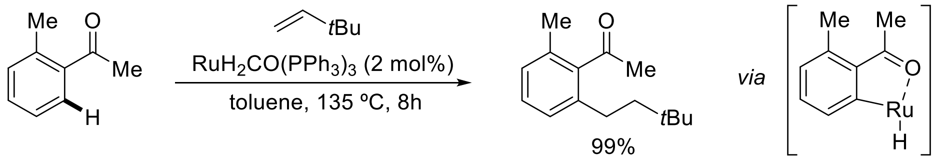
[34] For a related recent work with Rh catalyst, see: Jia, X.; Frye, L. I.; Zhu, W.; Gu, S.; Gunnoe, T. B. *J. Am. Chem. Soc.* **2020**, *142*, 10534-10543.

The mechanistic profile of this reaction is similar to that of a Heck addition. However, in this case, the reaction is initiated by C-H activation instead of oxidative addition to C-X bonds, and, in the final step, the Pd(0) complex, resulting from reductive elimination of the metal hydride species generated after β-hydride elimination, is reoxidized by the copper salt and air (scheme 14).



Scheme 14. *Mechanism of the Fujiwara-Moritani reaction.*

Despite these interesting pioneering reports, it was not until the 90s when the field started to undergo an exponential growth with the publication, by Shinji Murai, of an operationally simple *ortho*-alkylation reaction between aromatic ketones and alkenes, using just a 2 mol% of a ruthenium catalyst (scheme 15).[35] This high-yielding and selective reaction, that proceeds through an oxidative addition mechanism of the C-H bond to the ruthenium, brought a genuine revolution in the field of C-H activation.



Scheme 15. *Ru-catalyzed alkylation reported by Murai in 1993.*

3.3 Main mechanistic profiles proposed for the C-H activation

The metalation of C-H bonds can take place through different type of mechanisms that are strongly influenced by the choice of the metal species and the additives employed in the reaction.[36]

3.3.1 Oxidative addition

Oxidative addition of C-H bonds to metals are typically favored by low-valent, electron-rich and coordinatively unsaturated metal complexes. Like in a classical oxidative addition,

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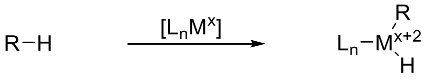
[35] Murai, S.; Kakiuchi, F.; Sekine, S.; Tanaka, Y.; Kamatani, A.; Sonoda, M.; Chatani, N. *Nature* **1993**, *366*, 529-531.

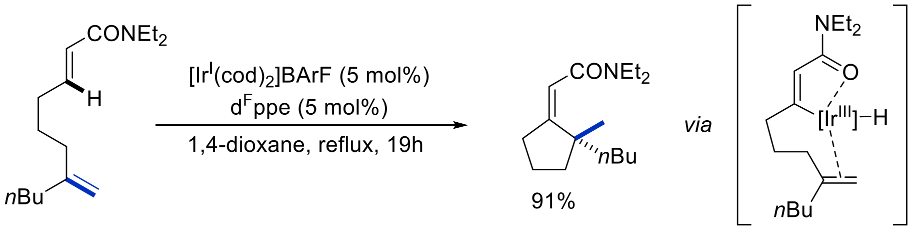
[36] (a) Labinger, J. A.; Bercaw, J. E. *Nature* **2002**, *417*, 507-514. (b) Boutadla, Y.; Davies, D. L.; Macgregor, S. A.; Poblador-Bahamonde, A. I. *Dalton Trans.* **2009**, *30*, 5820-5831. (c) Balcells, D.; Clot, E.; Eisenstein, O. *Chem. Rev.* **2010**, *110*, 749-823.

the metal inserts into the C-H bond, increasing both its oxidation state and coordination number (scheme 16).



Scheme 16. *Oxidative addition mechanism.*

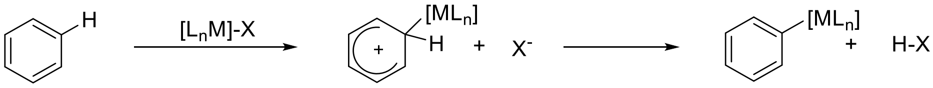
An example of this type of C-H activation, coupled to a cyclization reaction, was recently reported by our group using iridium complexes (scheme 17).[37]



Scheme 17. *Ir(I)-catalyzed intramolecular hydrocarbonation of alkenes.*

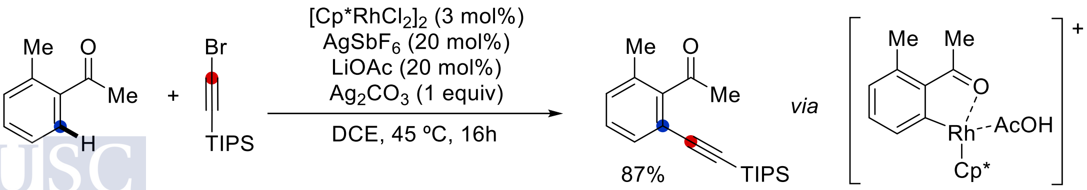
3.3.2 Electrophilic substitution

This type of activation takes place in presence of electrophilic metal complexes, in which the metal is in high oxidation states. Like in a conventional S_EAr reaction, a nucleophilic hydrocarbon of an aromatic compound attacks the transition metal, leading to a delocalized cationic species that finally recovers the aromaticity by deprotonation (scheme 18).



Scheme 18. *Electrophilic substitution mechanism.*

A recent example of this type of reaction was reported by Echavarren and co-workers in 2018. The reaction entails a Rh(III)-catalyzed alkynylation that proceeds, in agreement to mechanistic studies, through a turnover-limiting C-H activation taking place via an electrophilic substitution (scheme 19).[38]



Scheme 19. *Alkynylation reaction that proceeds by an electrophilic substitution mechanism.*

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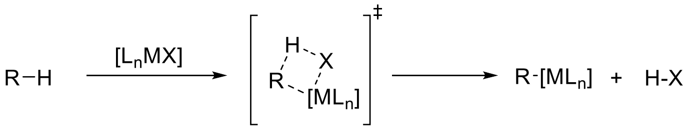
[37] Fernández, F.; Gulías, M.; Mascareñas, J. L.; López, F. *Angew. Chem. Int. Ed.* **2017**, *56*, 9541-9545.

[38] Tan, E.; Quinonero, O.; De Orbe, M. E.; Echavarren, A. M. *ACS Catal.* **2018**, *8*, 2166-2172.

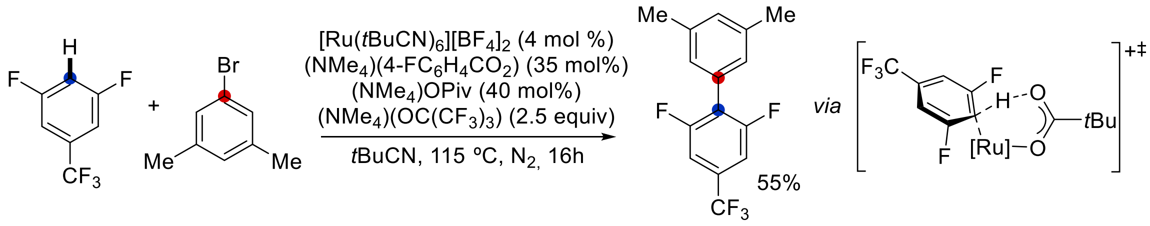
3.3.3 Concerted metalation-deprotonation (CMD)

This type of mechanism, known as CMD, also requires electrophilic metal complexes, and involves the abstraction of a proton in the substrate, usually carried out by a base that is coordinated to the metal centre. The deprotonation and metalation have been proposed to take place simultaneously, via cyclic transition states (scheme 20), generally an acetate-type ligand.[39] This mode of activation is clearly the most frequent in C-H activation reactions catalyzed by transition metals in high oxidation states, such as Pd(II), Ru(II), Rh(III), Ir(III) or Co(III).



Scheme 20. *Mechanism of the CMD.*

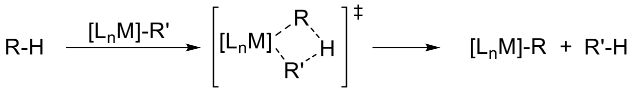
While in many cases the CMD requires a precomplexation of the metal to a directing group of the precursor, the activation can eventually occur directly in compounds that exhibit acidic aromatic protons, like in the Ru-catalyzed arylation of fluoroarenes developed by Larrosa and co-workers, shown in scheme 21.[40]



Scheme 21. *Ru-catalyzed arylation of fluoroarenes with aryl halides.*

3.3.4 σ-Bond metathesis

A slightly different mode of C-H activation implies a formal [2σ + 2σ] transition state entailing a concerted exchange of a metal-ligand sigma bond with a carbon-hydrogen bond (scheme 22).[41]



Scheme 22. *Mechanism of the σ-bond metathesis.*

An example was published by the group of Kuninobu and Takai in 2013 (scheme 23).[42] Mechanistically, the reaction is initiated by the formation of a Lewis base/Lewis acid adduct between the nitrogen of the pyridine and the boron of the 9-BBN. At this point, a

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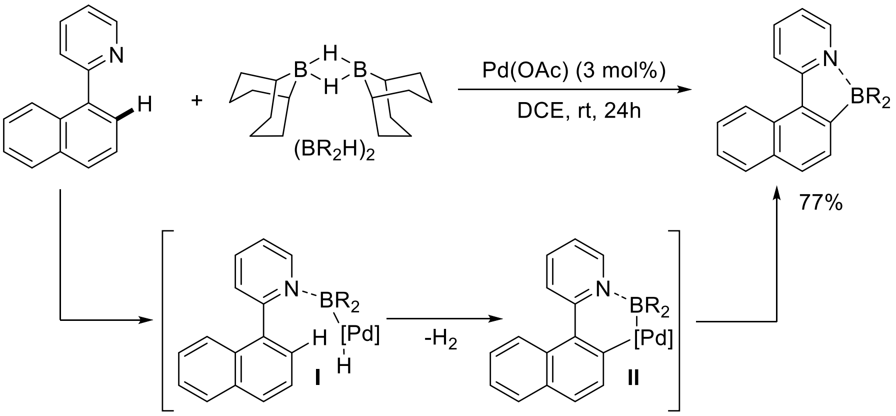
[39] (a) Lapointe, D.; Fagnou, K. *Chem. Lett.* **2010**, *39*, 1118-1126. (b) Ackermann, L. *Chem. Rev.* **2011**, *111*, 1315-1345. (c) Gorelsky, S. I.; Lapointe, D.; Fagnou, K. *J. Am. Chem. Soc.* **2008**, *130*, 10848-10849.

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

[41] Waterman, R. *Organometallics* **2013**, *32*, 7249-7263.

[42] Kuninobu, Y.; Iwanaga, T.; Omura, T.; Takai, K. *Angew. Chem. Int. Ed.* **2013**, *52*, 4431-4434.

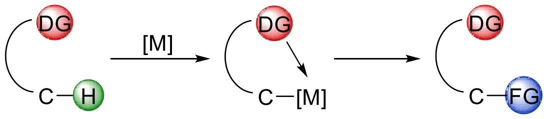
Pd(0) complex evolves through oxidative addition into the B-H bond of the borane, leading to the Pd(II) species **I** that undergoes σ-bond metathesis to form, after loss of H_2, the metalated intermediate **II**. Finally, reductive elimination results in the formation of an *o*-borylated product.



Scheme 23. *Pd-catalyzed o-borylation of 2-phenylpyridines under mild conditions.*

3.4 Directing groups in metal-promoted C-H activations

Despite some C-H functionalization reactions are driven by electronic or steric effects, and do not require the use of directing groups (DG) in the substrates,[43,44] most reactions so far developed involve precursors equipped with a directing group that not only accelerate the process but also allow to control the regioselectivity (scheme 24).[29] In addition to lower the entropic cost of the C-H activation, the DG can also facilitate the reactivity by affecting the electronic properties of the metal center.



Scheme 24. *Directed C-H activation.*

Among these directing groups, a large variety of monodentate[45] and bidentate[46] substituents have been used to accomplish the activation of several C-H bonds, including alcohols, carboxylic acids, ketones, imines, pyridines, amides, sulfonamides, or amines,

---

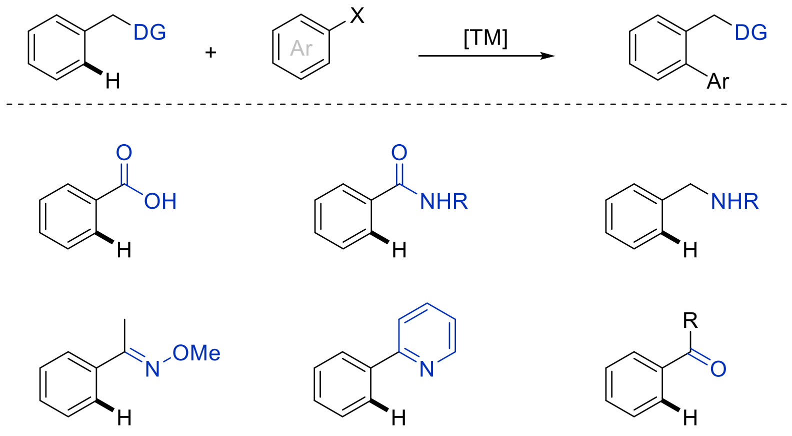
[43] For selected examples of non-directed, allylic C-H activation: (a) Burman, J. S.; Blakey, S. B. *Angew. Chem. Int. Ed.* **2017**, *56*, 13666-13669. (b) Lerchen, A.; Knecht, T.; Koy, M.; Ernst, J. B.; Bergander, K.; Daniliuc, C. G.; Glorius, F. *Angew. Chem. Int. Ed.* **2018**, *57*, 15248-15252. (c) Lei, H.; Rovis, T. *Nature Chem.* **2020**, *12*, 725-731.

[44] For selected examples of non-directed, arene C-H activation: (a) Wang, P.; Verma, P.; Xia, G.; Shi, J.; Qiao, J. X.; Tao, S.; Cheng, P. T. W.; Poss, M. A.; Farmer, M. E.; Yeung, K.-S.; Yu, J. Q. *Nature* **2017**, *551*, 489-494. (b) Chen, H.; Wedi, P.; Meyer, T.; Tavakoli, G.; van Gemmeren, M. *Angew. Chem. Int. Ed.* **2018**, *57*, 2497- 2501. (c) Chen, H.; Farizyan, M.; Ghiringhelli, F.; van Gemmeren, M. *Angew. Chem. Int. Ed.* **2020**, *59*, 12213-12220.

[45] Zhang, M.; Zhang, Y.; Jie, X.; Zhao, H.; Li, G.; Su, W. *Org. Chem. Front.* **2014**, *1*, 843-895.

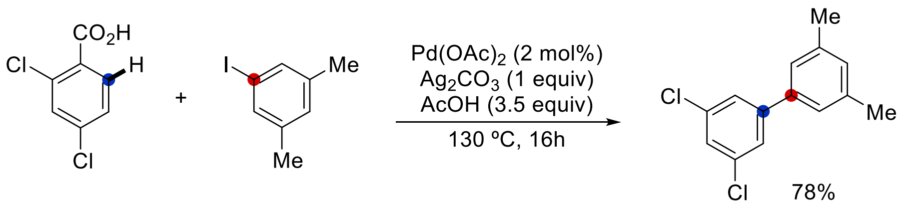
[46] Rej, S.; Ano, Y.; Chatani, N. *Chem. Rev.* **2020**, *120*, 1788-1887.

among others. Some of these are illustrates in the scheme 25 for the general case of an arylation reaction.[47]



Scheme 25. *Examples of directing groups for C-H activation. TM = transition metal (Pd, Rh, Ir, Co or Ru).*

In most cases, the directing groups are used to achieve the desired activation, but are not required in the final products, and therefore they must be removed to recover the native, required functionality. Toward this end, the use of traceless DG is especially indicated.[48] The group of Larrosa applied this approach for the synthesis of biaryl compounds in 2011. In this publication, they performed a carboxylic acid-directed C-H arylation that is followed by decarboxylation of the directing group (scheme 26).[49]



Scheme 26. *Carboxylic acids as traceless directing groups.*

Recently, other strategies for promoting a directed C-H activation have been explored. The use of transient directing groups (tDGs) has emerged as a powerful tool to functionalize substrates lacking such native directing groups.[50,51] In this protocol, the

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[47] (a) Kakiuchi, F.; Kan, S.; Igi, K.; Chatani, N.; Murai, S. *J. Am. Chem. Soc.* **2003**, *125*, 1698-1699. (b) Shi, Z.; Li, B.; Wan, X.; Cheng, J.; Fang, Z.; Cao, B.; Qin, C.; Wang, Y. *Angew. Chem. Int. Ed.* **2007**, *46*, 5554-558. (c) Chiong, H. A.; Pham, Q.-N.; Daugulis, O. *J. Am. Chem. Soc.* **2007**, *129*, 9879-9884. (d) Cho, S. H.; Hwang, S. J.; Chang, S. *J. Am. Chem. Soc.* **2008**, *130*, 9254-9256. (e) Reddy, D. M.; Wang, S.-C.; Du, K.; Lee, C.-F. *J. Org. Chem.* **2017**, *82*, 10070-10076. (f) Kapoor, M.; Chand-Thakuri, P.; Young, M. C. *J. Am. Chem. Soc.* **2019**, *141*, 7980-7989.

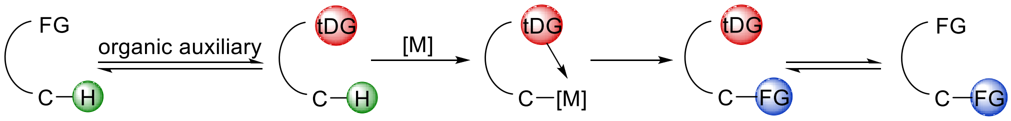
[48] (a) Zhang, F.; Spring, D. R. *Chem. Soc. Rev.* **2014**, *43*, 6906-6919. (b) Font, M.; Quibell, J. M.; Perry, G. J. P.; Larrosa, I. *Chem. Commun.* **2017**, *53*, 5584-5597. (c) Phipps, E. J. T.; Rovis, T. *J. Am. Chem. Soc.* **2019**, *141*, 6807-6811. (d) Chen, S.-Q.; Li, X.-R.; Li, C.-J.; Fan, J.; Liu, Z.-W.; Shi, X.-Y. *Org. Lett.* **2020**, *22*, 1259, 1264. (e) Rani, G.; Luxami, V.; Paul, K. D. *Chem. Commun.* **2020**, *56*, 12479-12521.

[49] Cornella, J.; Righi, M.; Larrosa, I. *Angew. Chem. Int. Ed.* **2011**, *50*, 9429-9432.

[50] For recent reviews in the field, see: (a) Gandeepan, P.; Ackermann, L. *Chem* **2018**, *4*, 199-222. (b) Goswami, N.; Bhattacharya, T.; Maiti, D. *Nature Rev. Chem.* **2021**, *5*, 646-659.

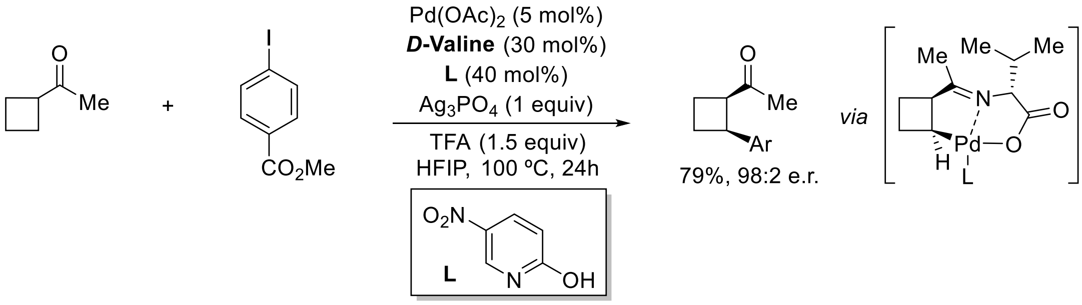
[51] For selected recent examples, see: (a) Park, H.; Verma, P.; Hong, K.; Yu, J.-Q. *Nature Chem.* **2018**, *10*, 755-762. (b) Chen, Y.-Q.; Wang, Z.; Wu, Y.; Wisniewski, S. R.; Qiao, J. X.; Ewing, W. R.; Eastgate, M. D.; Yu, J.-Q. *J. Am. Chem. Soc.* **2018**, *140*, 17884-17894. (c) Xing, D.; Qi, X.; Marchant, D.; Liu, P.; Dong, G. *Angew. Chem. Int. Ed.* **2019**, *58*, 4366-4370. (d) Li, B.; Lawrence, B.; Li, G.; Ge, H. *Angew. Chem. Int. Ed.* **2020**, *59*, 3078-3082.

directing group is transitionally formed in reaction media and released after the C-H functionalization (scheme 27).



Scheme 27. *tDG-assisted C-H functionalization reactions.*

Importantly, this methodology allowed the development of enantioselective protocols by the use of chiral organic auxiliaries as transient directing groups. For example, Yu and coworkers reported in 2020 an efficient entry to chiral cyclobutyl ketones using palladium catalysis and employing *α*-amino acids as TDGs (scheme 28).[52]



Scheme 28. *Asymmetric C-H arylation of cyclobutyl ketones.*

3.5 Activation of different types of C-H bonds

3.5.1 Aromatic C(sp^2)-H bonds

Pioneering examples, and many ensuing reports in the field of transition metal-catalyzed C-H functionalizations entail aromatic substrates. This can be attributed to the fact that the cleavage of aryl C-H bonds is easier, in comparison with that of alkenyl or alkyl C-H bonds. Moreover, the library of aromatic compounds available is very broad, and the resulting products are of high interest.

Even nowadays, most publications reporting C-H activations involve the cleavage of aryl C-H bonds, with arylation reactions being the most common.[53] For instance, in 2007, Yu and coworkers reported an appealing protocol for the *ortho*-arylation of benzoic acids using organoboron reagents as coupling partners and palladium catalysts (scheme 29).[54]

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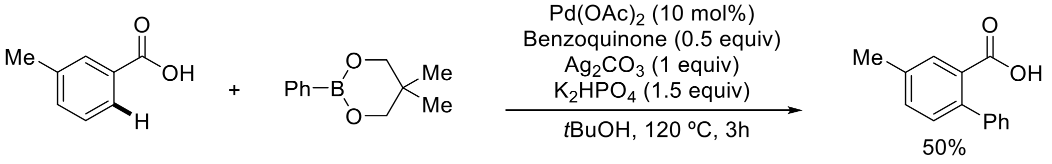
[52] Xiao, L.-J.; Hong, K.; Luo, F.; Hu, L.; Ewing, W. R.; Yeung, K.-S.; Yu, J.-Q. *Angew. Chem. Int. Ed.* **2020**, *59*, 9594-9600.

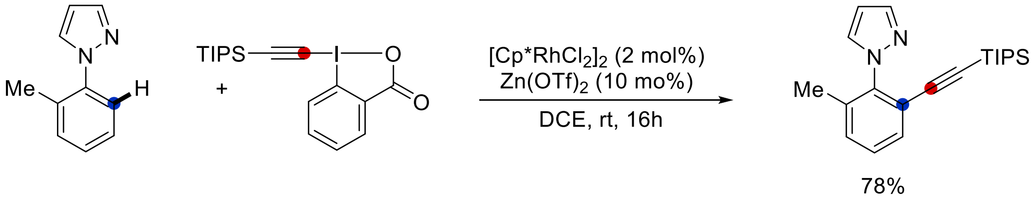
[53] For selected examples, see: (a) Engle, K. M.; Thuy-Boun, P. S.; Dang, M.; Yu, J.-Q. *J. Am. Chem. Soc.* **2011**, *133*, 18183-18193. (b) Xiao, K.-J.; Chu, L.; Chen, G.; Yu, J.-Q. *J. Am. Chem. Soc.* **2016**, *138*, 7796-7800.

[54] Giri, R.; Maugel, N.; Li, J.-J.; Wang, D.-H.; Breazzano, S. P.; Saunders, L. B.; Yu, J.-Q. *J. Am. Chem. Soc.* **2007**, *129*, 3510-3511.



Scheme 29. *Pd-catalyzed arylation at the o-position of benzoic acids.*

Another representative example of a C(sp^2)-H functionalization of aromatic compounds was developed by X. Li in 2014. The reaction consists in an alkynylation process catalyzed by Ir or Rh(III) complexes, and engages substrates with nitrogen-based directing groups and hypervalent iodine-alkyne coupling partners (scheme 30).[55,56]



Scheme 30. *Rh-catalyzed alkynylation reaction published by the group of X. Li.*

Many other relevant functionalizations of aromatic C-H bonds have been reported until the date, including halogenations,[57] aminations,[58] alkenylations,[44, 59] allylations[60] or alkylations.[61]

3.5.2 Alkenyl C(sp^2)-H bonds

The chemo- and regioselective activation of alkenyl C(sp^2)-H bonds is considerably more challenging than that of related aromatic systems. On the one hand, the double bond of olefins can engage in reactions with electrophilic transition metals and/or oxidants, leading to products different than those resulting from the C-H activation. For instance, using palladium catalysts, Heck or Wacker type of transformations could take place. On the other hand, in alkene-containing substrates there are other C-H bonds susceptible of being activated, including those in allylic positions, and therefore the regioselectivity can be an issue (figure 3).

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[55] For selected examples, see: (a) Shang, M.; Wang, H.-L.; Sun, S.-Z.; Dai, H.-X.; Yu, J.-Q. *J. Am. Chem. Soc.* **2014**, *136*, 11590-11593. (b) Mondal, A.; Chen, H.; Flämig, L.; Wedi, P.; van Gemmeren, M. *J. Am. Chem. Soc.* **2019**, *141*, 18662-18667.

[56] Xie, F.; Qi, Z.; Yu, S.; Li, X. *J. Am. Chem. Soc.* **2014**, *136*, 4780-4787.

[57] For selected examples, see: (a) Schröder, N.; Wencel-Delord, J.; Glorius, F. *J. Am. Chem. Soc.* **2012**, *134*, 8298-8301. (b) Wang, X.-C.; Hu, Y.; Bonacorsi, S.; Hong, Y.; Burrell, R.; Yu, J.-Q. *J. Am. Chem. Soc.* **2013**, *135*, 10326-10329. (c) Chu, L.; Xiao, K.-J.; Yu, J.-Q. *Science* **2014**, *346*, 451-455.

[58] For selected examples, see: (a) Ng, K.-H.; Chan, A. S. C.; Yu, W.-Y. *J. Am. Chem. Soc.* **2010**, *132*, 12862-12864. (b) Yoo, E. J.; Ma, S.; Mei, T.-S.; Chan, K. S. L.; Yu, J.-Q. *J. Am. Chem. Soc.* **2011**, *133*, 7652-7655. (c) Park, Y.; Park, K. T.; Kim, J. G.; Chang, S. *J. Am. Chem. Soc.* **2015**, *137*, 4534-4542.

[59] For selected examples, see: (a) Wang, D.-H.; Engle, K. M.; Shi, B.-F.; Yu, J.-Q. *Science* **2010**, *327*, 315-319. (b) Xiao, K.-J.; Chu, L.; Yu, J.-Q. *Angew. Chem. Int. Ed.* **2016**, *55*, 2856-2860. (c) Zhang, Z.; Tanaka, K.; Yu, J.-Q. *Nature* **2017**, *543*, 538-542.

[60] For selected examples, see: (a) Yao, T.; Hirano, K.; Satoh, T.; Miura, M. *Angew. Chem. Int. Ed.* **2011**, *50*, 2990-2994. (b) Lu, Q.; Klauck, F. J. R.; Glorius, F. *Chem. Sci.* **2017**, *8*, 3379-3383. (c) Wang, S.-G.; Cramer, N. *Angew. Chem. Int. Ed.* **2019**, *58*, 2514-2518.

[61] For selected examples, see: (a) Thuy-Boun, P. S.; Villa, G.; Dang, D.; Richardson, P.; Su, S.; Yu, J.-Q. *J. Am. Chem. Soc.* **2013**, *135*, 17508-17513. (b) Gao, K.; Yoshikai, N. *J. Am. Chem. Soc.* **2013**, *135*, 9279-9282. (c) Fruchey, E. R.; Monks, B. M.; Cook, S. P. *J. Am. Chem. Soc.* **2014**, *136*, 13130-13133. (d) Wang, G.-W.; Wheatley, M.; Simonetti, M.; Cannas, D. M.; Larrosa, I. *Chem* **2020**, *6*, 1459-1468.

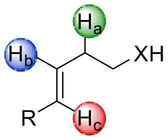
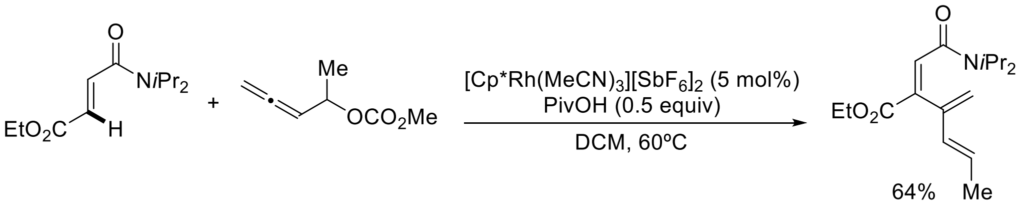


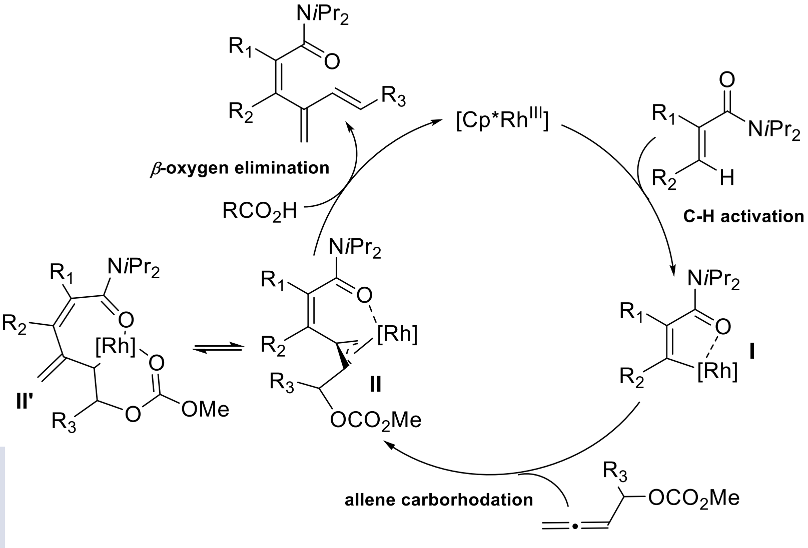
Figure 3. *C-H bonds that are susceptible of activation in alkenyl moieties.*

Despite these challenges, a number of successful methods for the selective functionalization of alkenyl C-H bonds have been recently reported.[62] For example, an attractive coupling protocol that engages acrylamides and allenyl partners and allows the synthesis of dendralene skeletons with high stereoselectivity, was published by the group of Glorius in 2013 (scheme 31).[63]



Scheme 31. *Rh(III)-catalyzed synthesis of dendralenes.*

The proposed mechanism starts with a C-H activation directed by the carbonyl moiety to form the five-membered rhodacycle **I**, that evolves through coordination and regioselective carborhodation of the allene partner, leading to the π-allylic intermediate **II**, which is in equilibrium with the η^1-allyl rhodium complex **II'**, as shown in scheme 32. Finally, β-oxygen elimination delivers the desired product and releases the Rh(III) catalyst that is able to start a new catalytic cycle.



Scheme 32. *Proposed mechanism for the Rh(III)-catalyzed synthesis of dendralenes.*

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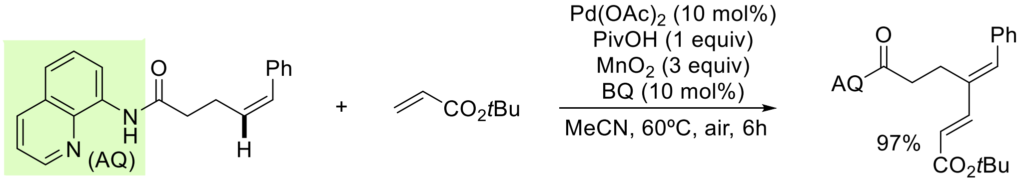
[62] For a recent review, see: Zhang, J.; Lu, X.; Shen, C.; Xu, L.; Ding, L.; Zhong, G. *Chem. Soc. Rev.* **2021**, *50*, 3263-3314.

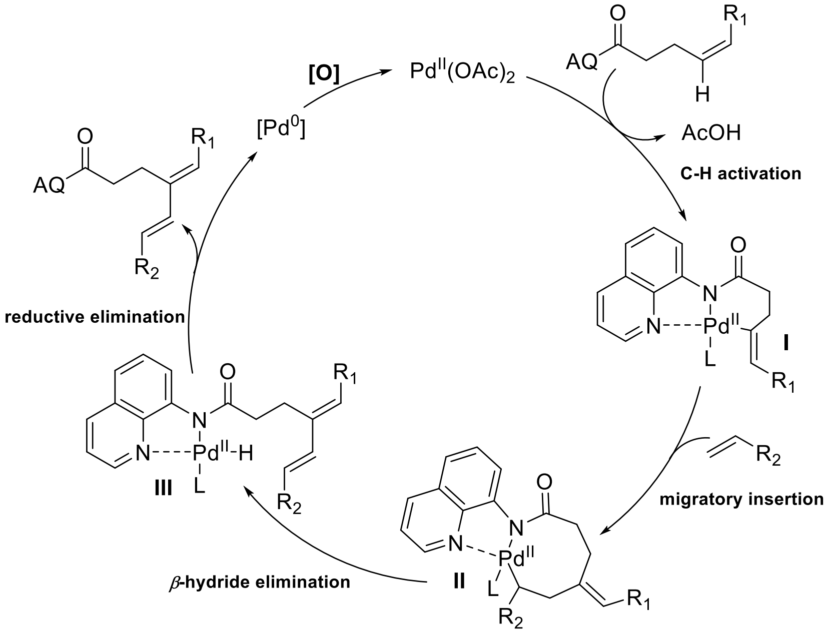
[63] Wang, H.; Beiring, B.; Yu, D.-G.; Collins, K. D.; Glorious, F. *Angew. Chem. Int. Ed.* **2013**, *52*, 12430-12434.

Another efficient and practical protocol for the synthesis of conjugated scaffolds based on alkenyl C-H activations was published by the group of Engle in 2018 (scheme 33).[64] The reaction, that is catalyzed by a Pd(II) complex, requires the employment of a bidentate auxiliary, 8-aminoquinoline, that directs the activation to the proximal C-H bond of the alkene via a 6-*exo*-alkenyl palladacycle.



Scheme 33. *Pd(II)-catalyzed synthesis of 1,3-dienes promoted by a bidentate DG.*

The proposed mechanism starts with a site-selective C-H activation followed by migratory insertion of the electron-poor alkene to give the eight-membered palladacycle intermediate **II**. Subsequent β-hydride elimination generates a palladium hydride complex, which is still coordinated to the product, that undergoes reductive elimination to release the final compound. Finally, the palladium(0) species is reoxidized to re-start the cycle (scheme 34).



Scheme 34. *Mechanistic hypothesis for the Pd(II)-catalyzed synthesis of 1,3-dienes reported by Engle.*

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[64] Liu, M.; Yang, P.; Karunananda, M. K.; Wang, Y.; Liu, P.; Engle, K. M. *J. Am. Chem. Soc.* **2018**, *140*, 5805-5813.

3.5.3 Alkyl C(sp^3)-H bonds

The activation of C(sp^3)-H bonds by transition metals is more challenging than that of C(sp^2)-H bonds. This is associated to the lower acidity of the hydrogens,[26b, 65] the lack of a coordinating double bond that could favour a pre-coordination to the metal complex, and the lower strength of the resulting C(sp^3)-M versus a C(sp^2)-M bond. However, in recent years there have been many advances in the field, especially in reactions catalyzed by palladium complexes, for which the development of metal ligands that favour the C-H activation step has played an important role.[66]

These ligands include mono-*N*-protected amino acids (MPAA),[67] oxazolines,[68] phosphoric acids,[69] thioethers[70] or highly attractive pyridine[71] and quinoline derivatives,[72] that, in addition to previously commented beneficial roles in the C-H activation step, present a relatively strong interaction with the metal, stabilising some intermediates and avoiding the formation of dimeric or trimeric palladium species with less or null activity.

Some interesting examples based on the use of quinoline-type ligands for C(sp^3)-H functionalizations were described by the group of Yu. In 2014, they reported an operationally simple procedure for the palladium-catalyzed alkylation of amides at β-position, in which the use of an acridine ligand was critical for the successful outcome of the reaction (scheme 35, eq 1).[73] One year later, the same group developed the arylation of the same type of substrates using arylsilanes as coupling partners, and employing a different quinoline-based auxiliary, that, again, was essential for the reaction (scheme 35, eq 2).[74]

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[65] For selected reviews of C(sp^3)-H activation, see: (a) Xu, Y.; Dong, G. *Chem. Sci.* **2018**, *9*, 1424-1432. (b) Saint-Denis, T. G.; Zhu, R.-Y.; Cheng, G.; Wu, Q.-F.; Yu, J.-Q. *Science* **2018**, *359*, eaao4798. (c) Chen, Z.; Rong, M.-Y.; Nie, J.; Zhu, X.-F.; Shi, B.-F.; Ma, J.-A. *Chem. Soc. Rev.* **2019**, *48*, 4921-4942. (d) He, C.; Whitehurst, W. G.; Gaunt, M. J. *Chem* **2019**, *5*, 1031-1058. (e) Liu, B.; Romine, A. M.; Rubel, C. Z.; Engle, K. M.; Shi, B.-F. *Chem. Rev.* **2021**, *121*, 14957-15074.

[66] (a) Engle, K. M.; Wang, D.-H.; Yu, J.-Q. *J. Am. Chem. Soc.* **2010**, *132*, 14137-14151. (b) Engle, K. M.; Yu, J.-Q. *J. Org. Chem.* **2013**, *78*, 8927-8955.

[67] For a recent review, see: Shao, Q.; Wu, K.; Zhuang, Z.; Qian, S.; Yu, J.-Q. *Acc. Chem. Res.* **2020**, *53*, 833-851.

[68] For selected examples, see: (a) He, J.; Shao, Q.; Wu, Q.; Yu, J.-Q. *J. Am. Chem. Soc.* **2017**, *139*, 3344-3347. (b) Wu, Q.-F.; Shen, P.-X.; He, J.; Wang, X.-B.; Zhang, F.; Shao, Q.; Zhu, R.-Y.; Mapelli, C.; Qiao, J. X.; Poss, M. A.; Yu, J.-Q. *Science* **2017**, *355*, 499-503. (c) Shao, Q.; Wu, Q.-F.; He, J.; Yu, J.-Q. *J. Am. Chem. Soc.* **2018**, *140*, 5322-5325.

[69] For selected examples, see: (a) Jain, P.; Verma, P.; Xia, G.; Yu, J.-Q. *Nature Chem.* **2017**, *9*, 140-144. (b) Smalley, A. P.; Cuthbertson, J. D.; Gaunt, M. J. *J. Am. Chem. Soc.* **2017**, *139*, 1412-1415.

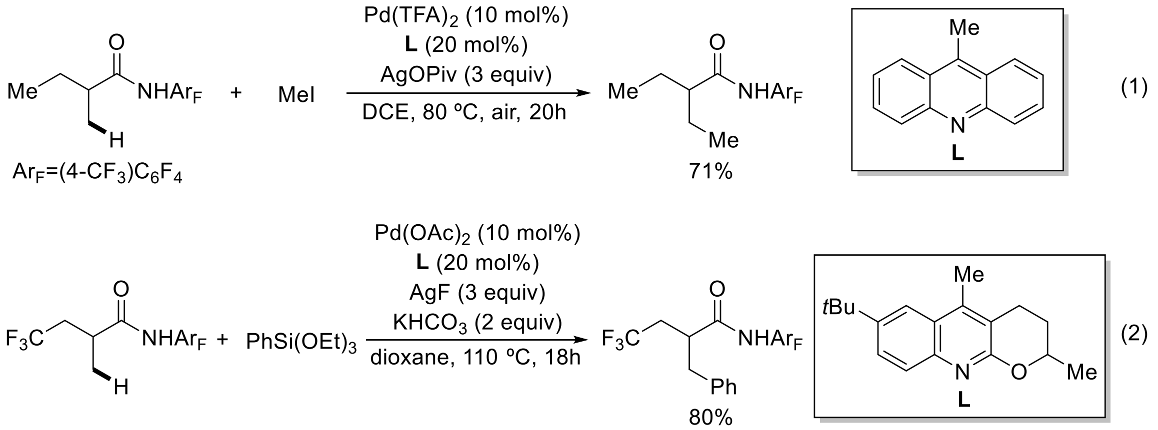
[70] For selected examples, see: (a) Zhuang, Z.; Yu, C.-B.; Chen, G.; Wu, Q.-F.; Hsiao, Y.; Joe, C. L.; Qiao, J. X.; Poss, M. A.; Yu, J.-Q. *J. Am. Chem. Soc.* **2018**, *140*, 10363-10367. (b) Jerhaoui, S.; Djukic, J.-P.; Wencel-Delord, J.; Colobert, F. *ACS Catal.* **2019**, *9*, 2532-2542. (c) Zhuang, Z.; Yu, J.-Q. *J. Am. Chem. Soc.* **2020**, *142*, 12015-12019.

[71] For selected examples, see: (a) Zhu, R.-Y.; Li, Z.-Q.; Park, H. S.; Senanayake, C. H.; Yu, J.-Q. *J. Am. Chem. Soc.* **2018**, *140*, 3564-3568. (b) Park, H.; Li, Y.; Yu, J.-Q. *Angew. Chem. Int. Ed.* **2019**, *58*, 11424-11428. (c) Xia, G.; Weng, J.; Liu, L.; Verma, P.; Li, Z.; Yu, J.-Q. *Nature Chem.* **2019**, *11*, 571-577.

[72] For selected examples, see: (a) Li, S.; Chen, G.; Feng, C.-G.; Gong, W.; Yu, J.-Q. *J. Am. Chem. Soc.* **2014**, *136*, 5267-5270. (b) Cabrera, P. J.; Lee, M.; Sanford, M. S. *J. Am. Chem. Soc.* **2018**, *140*, 5599-5606.

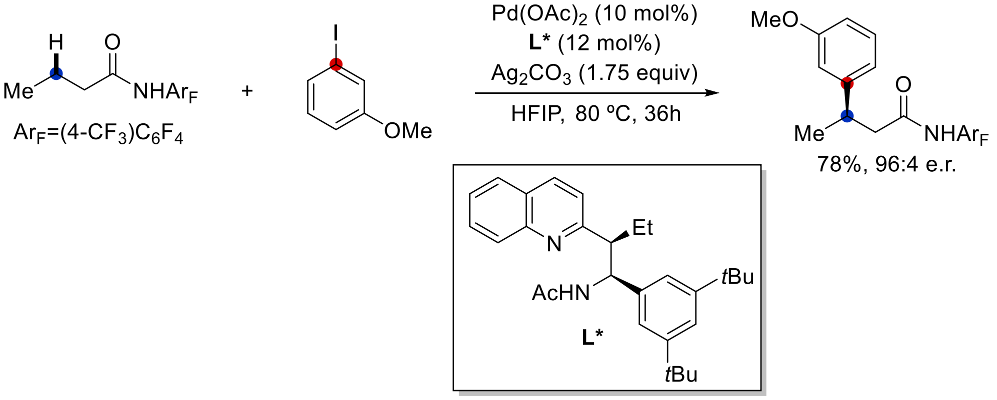
[73] Zhu, R.-Y.; He, J.; Wang, X.-C.; Yu, J.-Q. *J. Am. Chem. Soc.* **2014**, *136*, 13194-13197.

[74] He, J.; Takise, R.; Fu, H.; Yu, J.-Q. *J. Am. Chem. Soc.* **2015**, *137*, 4618-4621.



Scheme 35. *C-H functionalization of amides at β-position using quinoline-based ligands.*

More recently, they developed a new generation of more sophisticated ligands, consisting of chiral bidentate amidoquinolines (APAQ), which not only enabled the activation of challenging methylene C-H bonds, but can also generate the products in an enantioselective manner (scheme 36).[75, 76]



Scheme 36. *Asymmetric functionalization of methylene C-H bonds using an APAQ ligand.*

The mechanistic proposal (scheme 37), based on experimental studies and DFT calculations,[77] starts with the coordination of the APAQ ligand to the palladium complex, leading to species **I**. This intermediate is in equilibrium with an inactive amide-bridged Pd dimer (**I'**), whose formation depends on the size of the ligand; in fact, the presence of a second ring in the quinoline leads to a dramatic decrease in the formation of this off-cycle species, in comparison with a pyridine-based ligand. Coordination of the substrate, from intermediate **I**, allows the formation of **II**, which features a favourable agostic C(sp^3)-H interaction. Then, a CMD-type C-H activation assisted by the acetamide of the APAQ, critical for the acceleration of the process, affords the complex **III**, that evolves through

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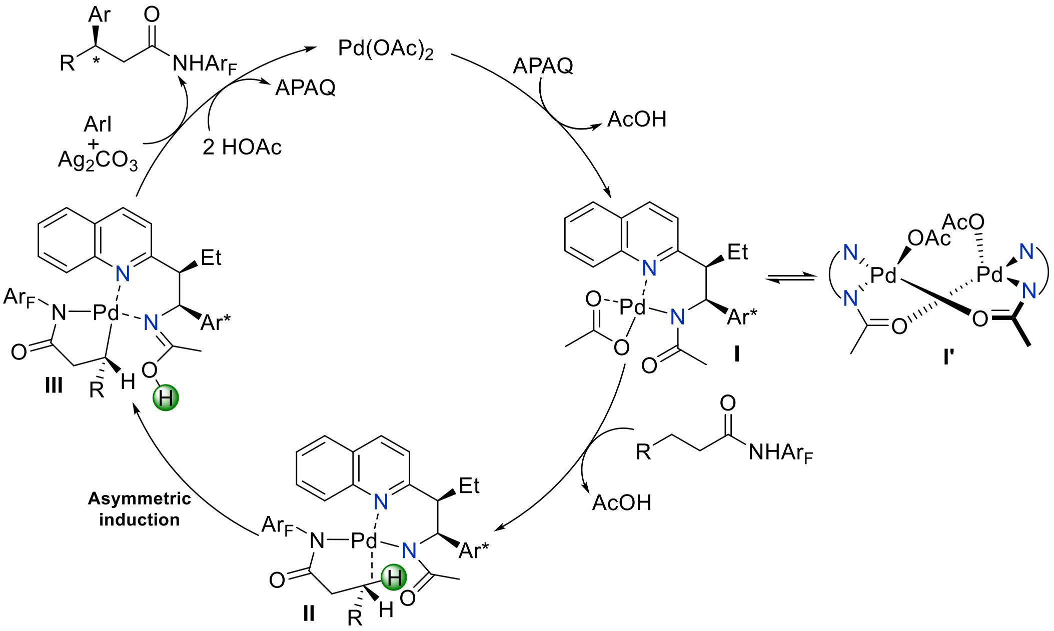
[75] Chen, G.; Gong, W.; Zhuang, Z.; Andrä, M. S.; Chen, Y.-Q.; Hong, X.; Yang, Y.-F.; Liu, T.; Houk, K. N.; Yu, J.-Q. *Science* **2016**, *353*, 1023-1027.

[76] For a racemic version of the reaction, see: Wasa, M.; Chan, K. S. L.; Zhang, X.-G.; He, J.; Miura, M.; Yu, J.-Q. *J. Am. Chem. Soc.* **2012**, *134*, 18570-18572.

[77] For a comprehensive understanding of the role of APAQ ligands, see: (a) Yang, Y.-F.; Chen, G.; Hong, X.; Yu, J.-Q.; Houk, K. N. *J. Am. Chem. Soc.* **2017**, *139*, 8514-8521. (b) Romero, E. A.; Chen, G.; Gembicky, M.; Jazzar, R.; Yu, J.-Q.; Bertrand, G. *J. Am. Chem. Soc.* **2019**, *141*, 16726-16733.

oxidative addition and subsequent reductive elimination to deliver the corresponding product. DFT calculations also demonstrated that non-covalent interactions between the APAQ ligand and the substrate play a key role in the chiral induction.



Scheme 37. *Mechanistic proposal for the asymmetric arylation of methylene C-H bonds.*

4. Formal cycloadditions initiated by the activation of C-H bonds

Among the different type of C-H functionalization reactions, formal cycloadditions are much less common. However, these types of transformations are especially attractive due to their constructive power and atom economy, as commented before for classical cycloaddition reactions.

While in traditional TM-catalyzed formal cycloadditions the metallacycle intermediate is usually generated by oxidative cyclometalation of the metal to unsaturated bonds of the substrate, leading almost exclusively to the formation of carbocycles, in annulations initiated by C-H activations, the metalacyclic intermediates are usually generated through a heteroatom-assisted, metal-promoted C-H activation, which usually furnish heterocyclic products (scheme 38).[78, 79] The incorporation of the heteroatom directing group in the final product is one of the big advantages of these transformations because in other cases it is an auxiliary that needs to be removed after the reaction. Especially relevant is the synthesis of azaheterocycles, since they are present in a large number of natural products and pharmaceuticals.[80]

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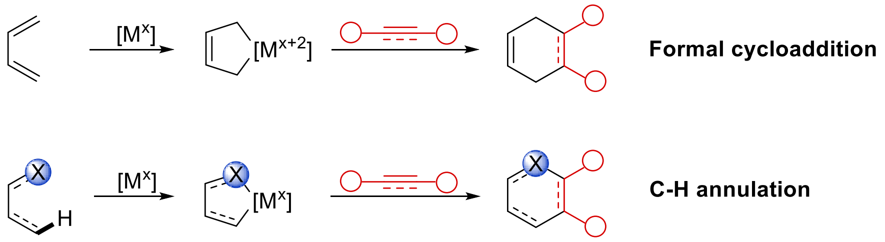
[78] According to the IUPAC Gold Book, an "annulation" is a "transformation involving fusing of a new ring to a molecule via two new bonds".

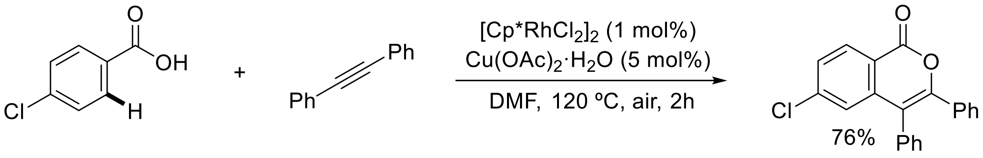
[79] For a recent review, see: Gulías, M.; Mascareñas, J. L. *Angew. Chem. Int. Ed.* **2016**, *55*, 11000-11019.

[80] Vitaku, E.; Smith, D. T.; Njardarson, J. T. *J. Med. Chem.* **2014**, *57*, 10257-10274.



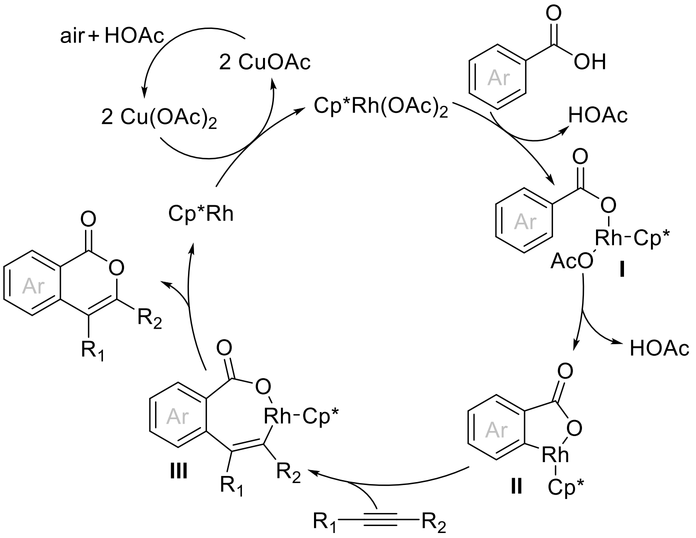
Scheme 38. *Comparison between classical TM-catalyzed cycloadditions and C-H annulations.*

In agreement with previously described C-H functionalization reactions, most of the formal cycloadditions so far described are initiated by the activation of aromatic C(sp^2)-H bonds.[81] A pioneering example, that consists in rhodium-catalyzed (4+2) formal cycloaddition between benzoic acids and alkynes, was introduced by Miura in 2007 (scheme 39).[82]



Scheme 39. *Seminal work based on an oxidative C-H annulation reported by Miura.*

This type of oxidative annulations follows a characteristic mechanism. First, a ligand exchange, associated with the coordination of the substrate, takes place to give an intermediate **I** that evolves by directed C-H activation furnishing the five-membered metallacycle **II**. Then, migratory insertion of the alkyne provides metallacycle **III**, that undergoes a reductive elimination process, leading to the desired product together with a Rh(I) complex that is reoxidized by the copper salt (scheme 40).



Scheme 40. *Mechanistic hypothesis for the (4+2) annulation between benzoic acids and alkynes.*

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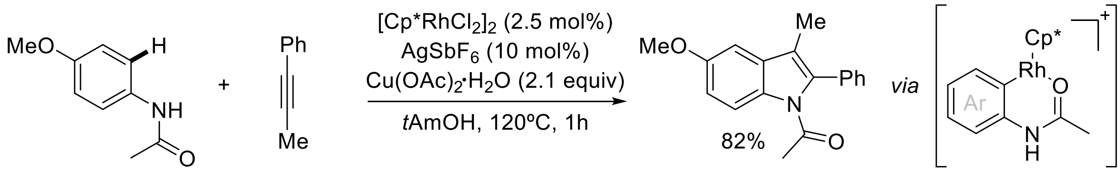
[81] For a recent review, see: Desai, B.; Patel, M.; Dholakiya, B. Z.; Rana, S.; Naveen, T. *Chem. Commun.* **2021**, *57*, 8699-8725.

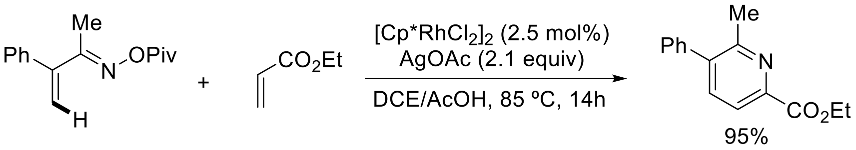
[82] (a) Ueura, K.; Satoh, T.; Miura, M. *Org. Lett.* **2007**, *9*, 1407-1409. (b) Mochida, S.; Hirano, K.; Satoh, T.; Miura, M. *J. Org. Chem.* **2009**, *74*, 6295-6298.

Another early seminal example, based on the activation of aromatic C-H bonds, was published by Fagnou in 2008.[83] His group reported a practical protocol for the synthesis of highly appealing indole structures through a (3+2) annulation that proceeds though a carbonyl-directed six-membered rhodacycle (scheme 41).



Scheme 41. *(3+2) annulation for the synthesis of indoles reported by Fagnou.*

Examples of annulations that involve the activation of alkenyl C-H bonds have been also reported. For instance, Rovis and coworkers published in 2013 an efficient entry to pyridine scaffolds through a formal (4+2) cycloaddition between alkenylimines and acrylates (scheme 42).[84, 85]



Scheme 42. *Rhodium-catalyzed (4+2) annulation between α,β-unsaturated oxime esters and alkenes.*

The mechanistic hypothesis for this transformation starts with reversible C-H activation (scheme 43), leading to the neutral five-membered rhodacycle **I**. At this stage, dissociation of an acetate induces the formation of the cationic complex **II**, which is in equilibrium with the chelated complex **II'**. Then, migratory insertion of the alkene allows the formation of the cationic seven-membered rhodaycle **III** that evolves through deprotonation at the α-position. The resulting neutral complex **IV** undergoes C-N bond formation/N-O bond cleavage followed by tautomerism to give the intermediate **V**. Finally, the product is formed after β-hydride elimination. It is noteworthy that in intermediate **IV**, the complex follows the desired pathway instead of β-hydride elimination due to the chelation of the *O*-pivalate, that prevents this undesired step as a result of the coordinative saturation of the metal.

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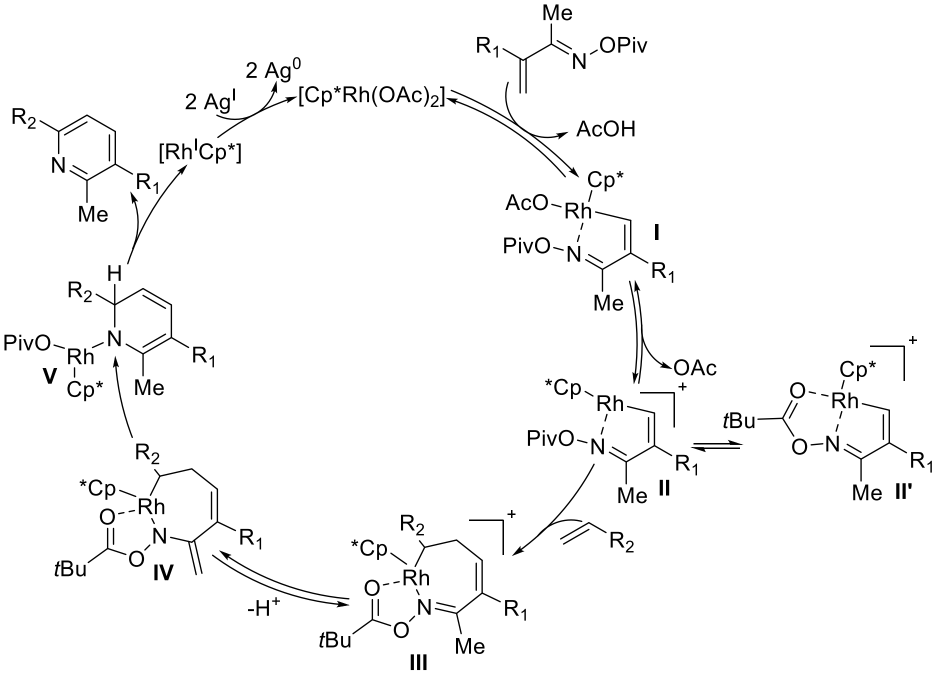
[83] (a) Stuart, D. R.; Bertrand-Laperle, M.; Burgess, K. M. N.; Fagnou, K. *J. Am. Chem. Soc.* **2008**, *130*, 16474-16475. (b) Stuart, D. R.; Alsabeh, P.; Kuhn, M.; Fagnou, K. *J. Am. Chem. Soc.* **2010**, *132*, 18326-18339.

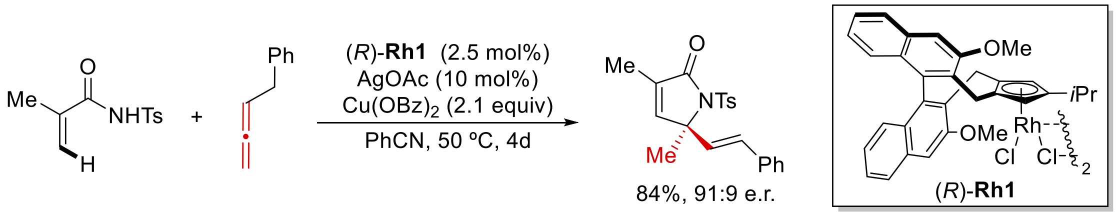
[84] Neely, J. M.; Rovis, T. *J. Am. Chem. Soc.* **2013**, *135*, 66-69.

[85] For related examples by the group of Rovis, see: (a) Neely, J. M.; Rovis, T. *J. Am. Chem. Soc.* **2014**, *136*, 2735-2738. (b) Romanov-Michailidis, F.; Sedillo, K. F.; Nelly, J. M.; Rovis, T.; *J. Am. Chem. Soc.* **2015**, *137*, 8892-8895.



Scheme 43. *Mechanistic proposal for the (4+2) annulation reported by Rovis.*

The development of asymmetric versions for this type of annulations has been also a long-desired goal. However, only recently there has been substantial advances,[86] with the work by the group of Cramer being especially remarkable.[87] Thus, this group developed a formal (4+1) annulation between acrylamides and allenes, that curiously work as one atom units, catalyzed by a chiral rhodium Cp complex (scheme 44).[88,89]



Scheme 44. *Rhodium-catalyzed (4+1) annulation for the synthesis of chiral pyrrol-2-ones.*

Mechanistically, the reaction involves an initial ligand exchange followed by amide-directed CMD-type C-H activation to form rhodacycle **I**. Then, migratory insertion of the allene provides interconverting allyl-rhodium species **IIa**, **IIb** and **IIc**. At this point, instead of a reductive elimination, which would produce a typical (4+2) product, β-hydride elimination is preferred, leading to the triene intermediate **III**. Finally, the product is formed through addition of the rhodium hydride across the terminal double bond, which

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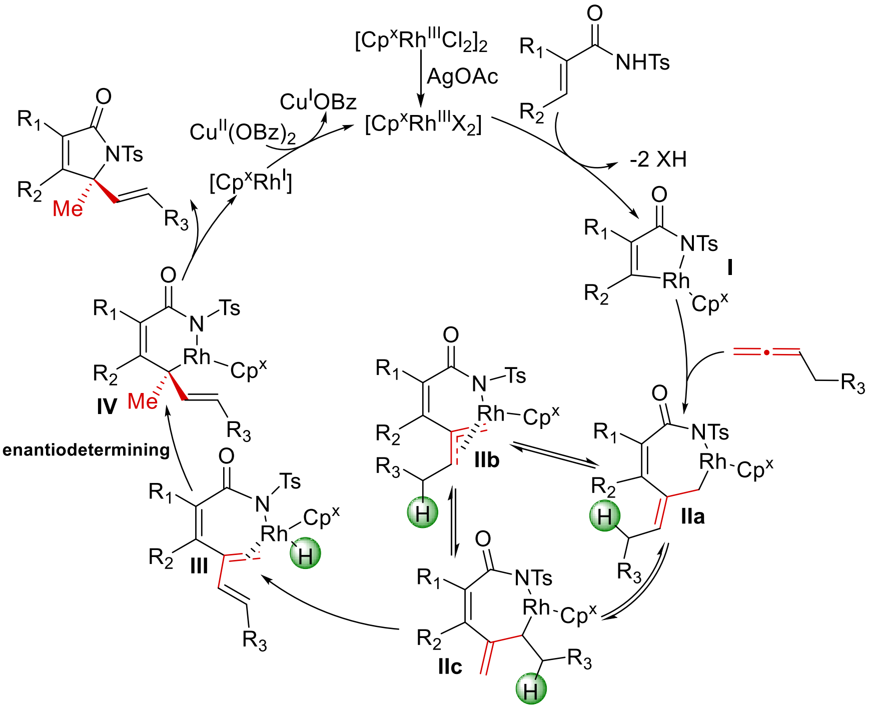
[86] For selected examples, see: (a) Vidal, X.; Mascareñas, J. L.; Gulías, M. *J. Am. Chem. Soc.* **2019**, *141*, 1862-1866. (b) Hassan, I. S.; Ta, A. N.; Danneman, M. W.; Semakul, N.; Burns, M.; Basch, C. H.; Dippon, V. N.; McNaughton, B. R.; Rovis, T. *J. Am. Chem. Soc.* **2019**, *141*, 4815-4819. (c) Cui, W.-J.; Wu, Z.-J.; Gu, Q.; You, S.-L. *J. Am. Chem. Soc.* **2020**, *142*, 7379-7385. (d) González, J. M.; Cendón, B.; Mascareñas, J. L.; Gulías, M. *J. Am. Chem. Soc.* **2021**, *143*, 3747-3752.

[87] Wang, S.-G.; Liu, Y.; Cramer, N. *Angew. Chem. Int. Ed.* **2019**, *58*, 18136-18140.

[88] Ye, B.; Cramer, N. *Science* **2012**, *338*, 504-506.

[89] For a related annulation with acrylic acids, see: Wang, S.-G.; Cramer, N. *ACS Catal.* **2020**, *10*, 8231-8236.

is the enantiodetermining step, and subsequent reductive elimination. The resulting Rh(I) species is reoxidized by the copper salt to recover its catalytic activity (scheme 45).



Scheme 45. *Mechanistic hypothesis for the (4+1) annulation between acryl amides and allenes.*

Cycloadditions relying on metal-promoted C-H activations and leading to larger rings have been also accomplished.[90] For example, our group, reported in 2016 a novel method for the straightforward synthesis of benzoxepines using a palladium(II) catalyst and allenes as coupling partners (scheme 46).[91] Mechanistically, the reaction follows the representative sequence for this type of (n+2) formal cycloadditions with allenes: C-H activation to give the corresponding metallacycle, regioselective migratory insertion, leading to a π-allylic intermediate, and reductive elimination. However, the C-H activation step takes places through a stepwise mechanism, instead of classical CMD, involving a dearomatization and rearomatization process (intermediates **I** and **II**, scheme 46).

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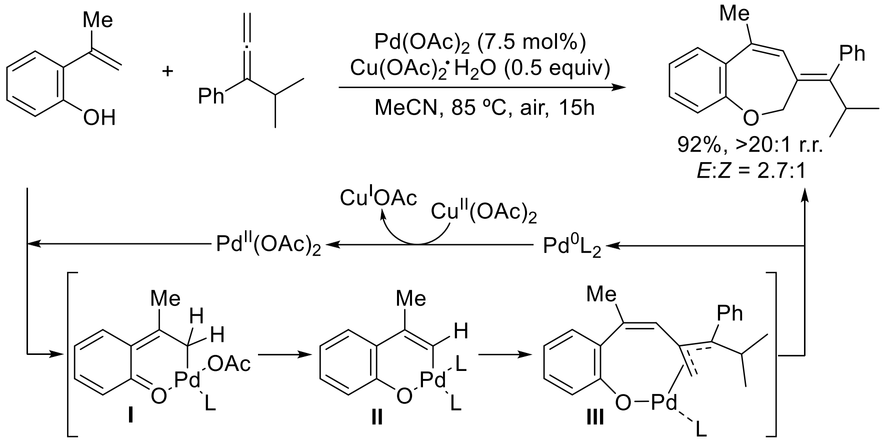
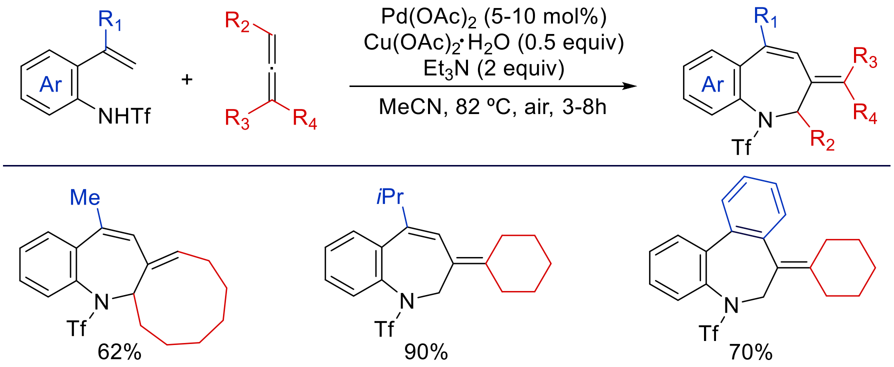
[90] Trost, B. M.; Zuo, Z.; Schultz, J. E. *Chem. Eur. J.* **2020**, *26*, 15354-15377.

[91] Casanova, N.; Del Rio, K. P.; García-Fandiño, R.; Mascareñas, J. L.; Gulías, M. *ACS Catal.* **2016**, *6*, 3349-3353.



Scheme 46. *Pd-catalyzed (5+2) annulations between o-alkenylphenols and allenes.*

During my master thesis, we extended this methodology to *o*-alkenylanilides, accomplishing the synthesis of highly valuable benzazepine scaffolds [92] under operationally simple conditions, through a formal (5+2) cycloaddition with allenes (scheme 47).[93] Remarkable, a screening of bases revealed that the addition of Et_3N improved the yields from moderate to excellent. Moreover, the reaction tolerates a wide range of alkenylanilides, although the internal position of the alkene must be substituted. With regard to the allene partner, the model *o*-alkenylanilide reacted smoothly with 1,1-disubstituted symmetrical and unsymmetrical allenes, leading to cycloadducts with excellent *E:Z* ratios. Additionally, trisubstituted and cyclic allenes were also suitable for the transformation, while other partners failed to react under our standard conditions.[94]



Scheme 47. *Pd-catalyzed (5+2) annulations between o-alkenylanilides and allenes.*

Mechanistically, the reaction follows the same sequence than the previous one, however, in this case, we proposed a classical concerted mechanism for the C-H activation step. This hypothesis was supported by DFT calculations, performed by Dr. Rebeca García-Fandiño, that further investigated the C-H activation step for both substrates, phenols and anilides, providing a comparison of the bond distances for the most stable palladacyclic

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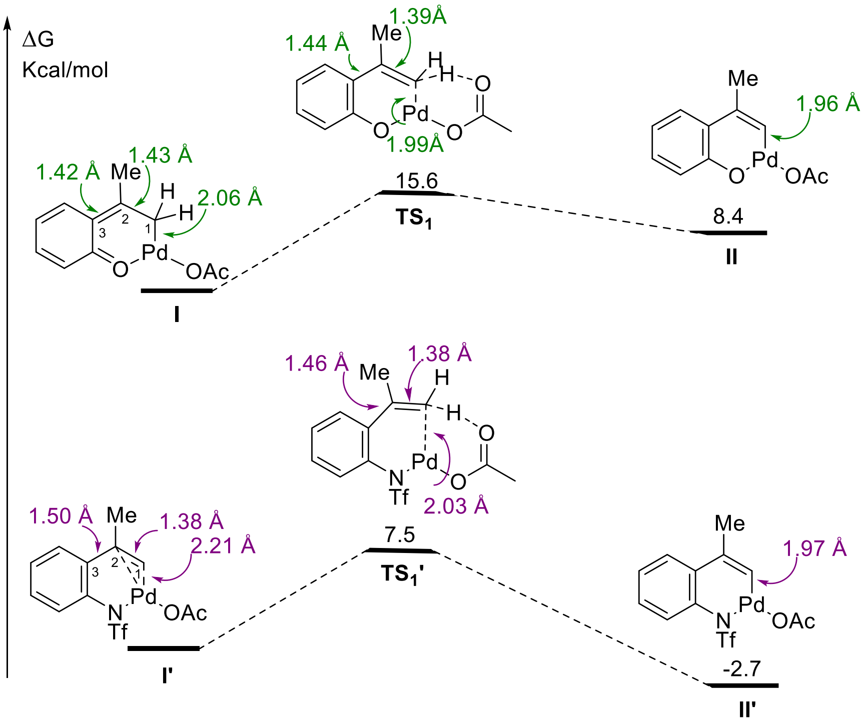
[92] Velasco-Rubio, A.; Varela, J. A.; Saá, C. *Adv. Synth. Catal.* **2020**, *362*, 4861-4875.

[93] Cendón, B.; Casanova, N.; Comanescu, C.; García-Fandiño, R.; Seoane, A.; Gulias, M.; Mascareñas, J. L. *Org. Lett.* **2017**, *19*, 1674-1677.

[94] For a later work with alkynes, see: Li, D.; Zeng, F. *Org. Lett.* **2017**, *19*, 6498-6501.

intermediates (scheme 48). In the case of the phenols, the bond distances between C(1) and C(2) and C(2) and C(3), with a clear double bond character (1.42 Å), suggested a partial desaromatization of the molecule and the Pd-C(1) bond also exhibits a typical distance of Pd-C σ-bonds, intermediate **I**. Then, the aromaticity, as suggested by the change in the bond distances in **TS$_1$**, is recovered by an intramolecular hydrogen abstraction assisted by an acetate. On the other hand, in the case of the *o*-alkenylanilides, the C-C bond distances in intermediate **I'** are not consistent with a desaromatization mechanism, 1.50 Å between C(2) and C(3), and the Pd-C distance is also not compatible with a σ-bond. In addition, the transition state (**TS$_2$**) fully agrees with a CMD-type mechanism.



Scheme 48. *Comparison, by DFT calculations, of the C-H activation step in o-alkenylphenols and anilides.*

All these annulation examples involve the activation of C(sp^2)-H bonds. Cycloadditions initiated by C(sp^3)-H activation are much scarcer, and essentially restricted to carbonylation reactions of bulky amines or to some rare allylic activations.[95]

For instance, between 2014 and 2016 Gaunt published several examples of carbonylation reactions for the synthesis of strained *β*-lactams. Firstly, he reported the reaction in quite hindered aliphatic amines, that are crucial to avoid inactive diamine palladium complexes (scheme 49, eq 1).[96] Later on, the group explored the reactivity of less hindered amines, obtaining good results when using a quinoline ligand for the palladium catalyst, and more

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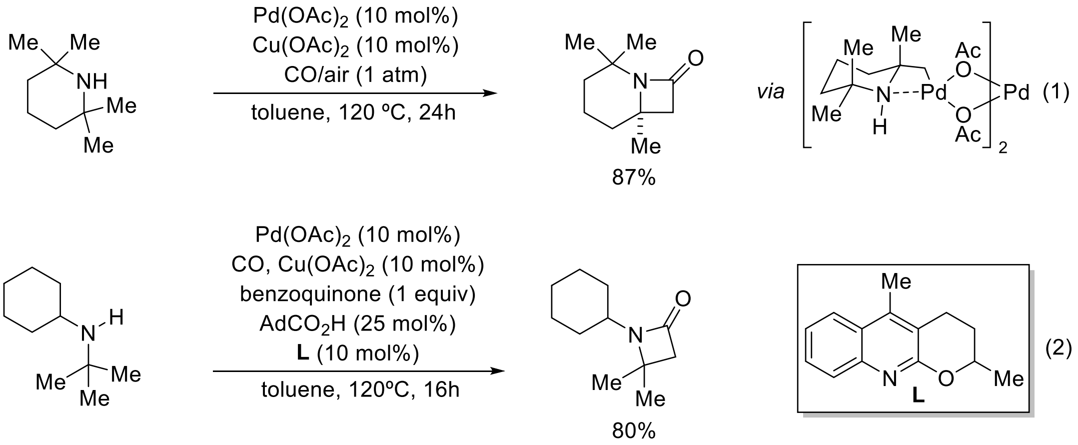
[95] (a) Kazerouni, A. M.; McKoy, Q. A.; Blakey, S. B. *Chem. Commun.* **2020**, *56*, 13287-13300. (b) Font, M.; Gulías, M.; Mascareñas, J. L. *Angew. Chem. Int. Ed.* **2022**, *61*, e202112848.

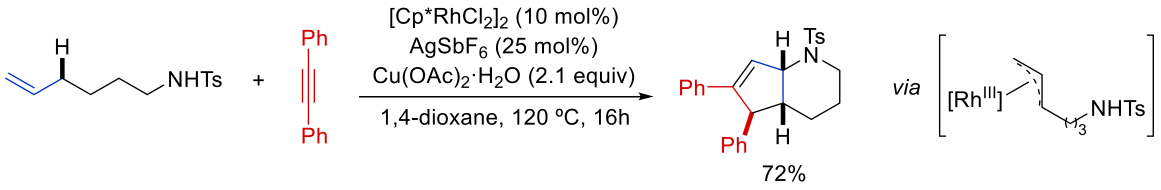
[96] McNally, A.; Haffemayer, B.; Collins, B. S. L.; Gaunt, M. J. *Nature* **2014**, *510*, 129-133.

elaborated conditions (scheme 49, eq 2).[97] It is noteworthy that both reactions proceed through an unusual and highly appealing four-membered palladacycle intermediate.



Scheme 49. *Carbonylation reactions of aliphatic amines reported by Gaunt.*

As already commented, annulations entailing the activation of C(sp^3)-H bonds can be also performed by allylic activations. A quite interesting example based on this activation was reported by Rovis in 2015, consisting of a diastereoselective synthesis of azabicyclic structures by reaction between long-chain unsaturated sulfonamides and alkynes in presence of a cationic rhodium catalyst (scheme 50).[98]



Scheme 49. *Rh(III)-catalyzed allylic C(sp^3)-H activation for the synthesis of azabicycles.*

As shown, metal-promoted annulations initiated by C-H activation offer a great number of possibilities for the rapid assembly of cyclic structural motifs, however, they continue to be less developed than other, more standard C-H functionalization reactions. To expand the scope of these reactions it is important to device robust mechanistic manifolds that avoid side processes and favor the organometallic steps required to complete the catalytic cycle of these transformations.

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[97] Willcox, D.; Chappell, B. G. N.; Hogg, K. F.; Calleja, J.; Smalley, A. P.; Gaunt, M. J. *Science* **2016**, *354*, 851-857.

[98] Archambeau, A.; Rovis, T. *Angew. Chem. Int. Ed.* **2015**, *54*, 13337-13340.

Overall objectives

Considering the existing precedents in the activation and functionalization of C-H bonds and the current challenges, previously indicated in the introduction, the work of this PhD thesis aimed at the following general objectives:

- Discovery and development of **new transition metal-catalyzed formal cycloadditions initiated by the activation of alkenyl and alkyl C-H bonds**, which would provide a straightforward access to a variety of valuable scaffolds. We will specially focus on palladium and rhodium-catalyzed annulations for the synthesis of azaheterocycles.

- Develop mild reaction conditions, seeking to comply with the principles of Green Chemistry, especially considering some alternatives, such as electrochemistry, to traditional metal oxidants.

- Unveil mechanistic details, so that these possible findings can be useful and relevant for discovering new transformations.

Chapter I – Rhodium(III)-catalyzed annulation of 2-alkenyl anilides with alkynes through C-H activation: direct access to 2-substituted indolines

Chapter adapted from:
Font, M.[a]; Cendón, B.[a]; Seoane, A.[a]; Mascareñas, J. L.[a]*; Gulías, M.[a]* *Angew. Chem. Int. Ed.* **2018**, *57*, 8255-8259.

[a] 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)


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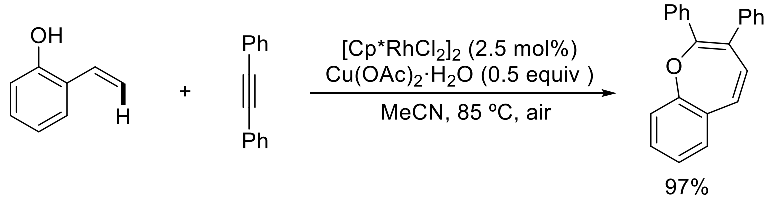
1. Introduction

1.1 Antecedents

As already commented, our group has made several contributions to the field of C-H activation over the years, being especially significant the results published in 2014 about the reactivity of 2-alkenylphenols with alkynes catalyzed by a Rh(III)-complex.

The first article described a straightforward and operationally simple protocol for the synthesis of highly appealing benzoxepine skeletons through a formal (5+2) cycloaddition (scheme 51).[99]



Scheme 51. *Rh-catalyzed synthesis of benzoxepine skeletons.*

The mechanism proposed for this transformation starts with a ligand exchange between the substrate and an acetate of the catalyst followed by phenol-directed C-H activation to form the six-membered rhodacycle **II**. Interestingly, instead of a classical CMD process (**path A**), the C-H activation probably occurs though a non-concerted pathway, involving an intramolecular attack of the conjugated alkene to the electrophilic rhodium(III) species followed by base-assisted deprotonation, triggering the rearomatization of the corresponding compound (**path B**). The intermediate **II** evolves through migratory insertion of the alkyne to give the eight-membered rhodacycle **III** and, finally, reductive elimination produces the expected benzoxepine together with a Rh(I) species that is reoxidized by copper and air to re-start the catalytic cycle (scheme 52).

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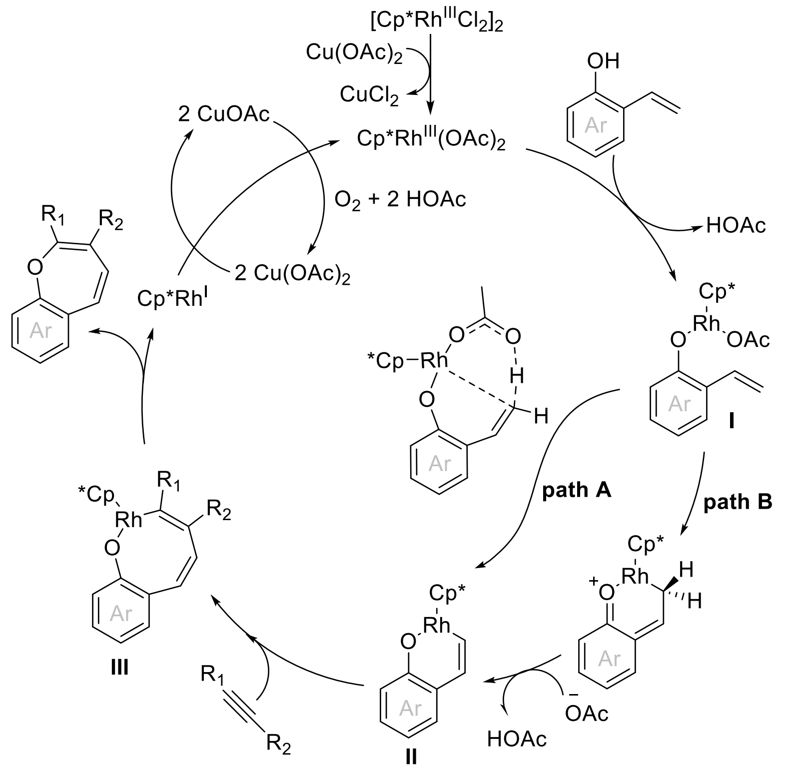
[99] Seoane, A.; Casanova, N.; Quiñones, N.; Mascareñas, J. L.; Gulías, M. *J. Am. Chem. Soc.* **2014**, *136*, 834-837.



Scheme 52. *Plausible mechanism for the formation of the (5+2) adduct.*

During the analysis of this reaction, it was observed that using alkenylphenols in which the internal position of the alkene was substituted, the reaction preferred to give spirocyclic (3+2) adducts.[100] As depicted in scheme 53, their formation was explained through an equilibrium between the eight-membered rhodacycle, obtained after migratory insertion, and a keto form that, in this case, is favored due to the steric clash between the substituent of the alkene and the hydrogen of the aromatic ring. Finally, reductive elimination from this intermediate furnishes the spirocyclic compound. Alternatively, a direct 1,3-reductive elimination from the eight-membered rhodacycle has been also proposed in similar systems.[101]

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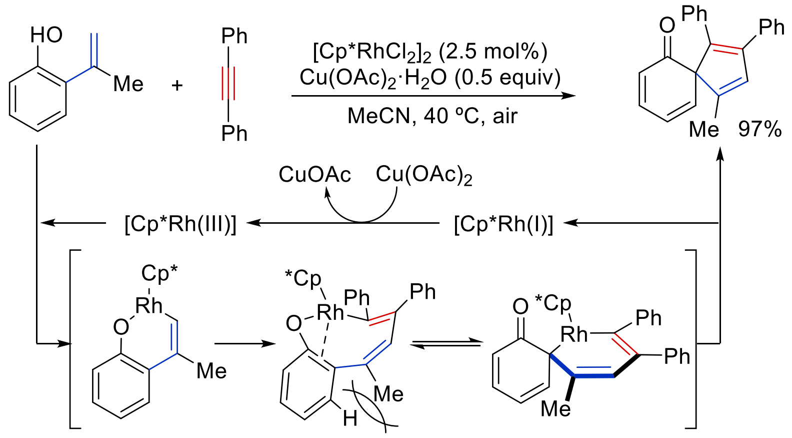
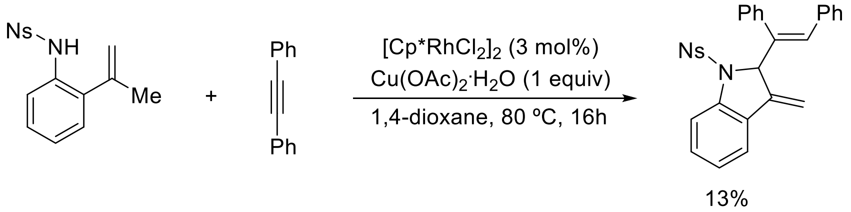
[100] Seoane, A.; Casanova, N.; Quiñones, N.; Mascareñas, J. L.; Gulías, M. *J. Am. Chem. Soc.* **2014**, *136*, 7607-7610.
[101] Zheng, C.; Zheng, J.; You, S.-L. *ACS Catal.* **2016**, *6*, 262-271.



Scheme 53. Rhodium-catalyzed synthesis of spirocyclic compounds.

We also wanted to explore the reactivity of analogous nitrogenated substrates, and we discovered that using palladium catalysts it was possible to perform formal (5+2) cycloadditions between o-alkenylanilides and allenes as reaction partners (scheme 47, page 30). Considering the reactivity of alkenylphenols in presence of the rhodium catalysts, we expected that alkenylanilides would also react in a similar way to give benzazepine skeletons. However, initial attempts to develop the desired annulation in presence of [Cp*RhCl$_2$]$_2$ led to a complex mixture of products, but we were able to identify a small proportion (over 15% yield) of an interesting, unexpected indoline adduct (scheme 54).



***Scheme 54.** Initial observations in the reactivity of o-alkenylanilides in presence of a rhodium catalyst.*

Surprised by this finding, we initially envisioned that this annulation could proceed through an unconventional mechanism, probably involving a π-allylrhodium intermediate, that might be further favoured by tuning the electronic and/or steric properties of the Cp ligand of the rhodium catalyst.

Indeed, several studies had demonstrated that the electronic and steric features of the Cp ligand can have a deep effect in the reaction efficiency or even in the regioselectivity or chemoselectivity of certain transformations based on C-H activations.[102] The groups of Rovis, Cramer or Tanaka, among others, have develop practical methodologies to build a number of substituted cyclopentadienyl ligands with different properties such Cp*^{tBu},[103]

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[102] (a) Piou, T.; Romanov-Michailidis, F.; Romanova-Michaelides, M.; Jackson, K. E.; Semakul, N.; Taggart, T. D.; Newell, B. S; Rithner, C. D.; Paton, R. S.; Rovis, T. *J. Am. Chem. Soc.* **2017**, *139*, 1296-1310. (b) Piou, T.; Rovis, T. *Acc. Chem. Res.* **2018**, *51*, 170-180.

[103] Piou, T.; Rovis, T. *Nature* **2015**, *527*, 86-90.

Cp*^{Cy}, Cp*^{CF3},[48c,85b] Cp^{t},[104] Cp^{iPr},[105] Cp^{E} [106] or chiral Cp^{x} [86c,87,88,107], and demonstrated that rhodium complexes with these ligands can raise different type of reactivities (figure 4).

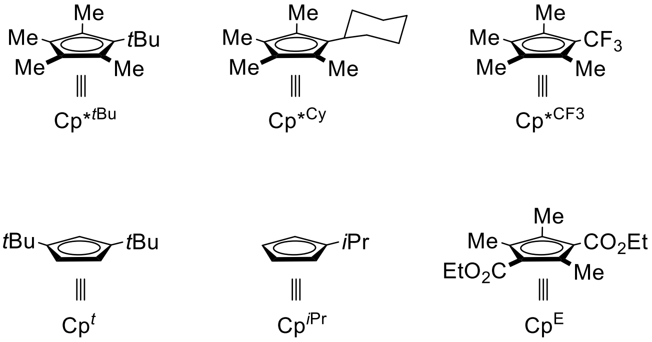
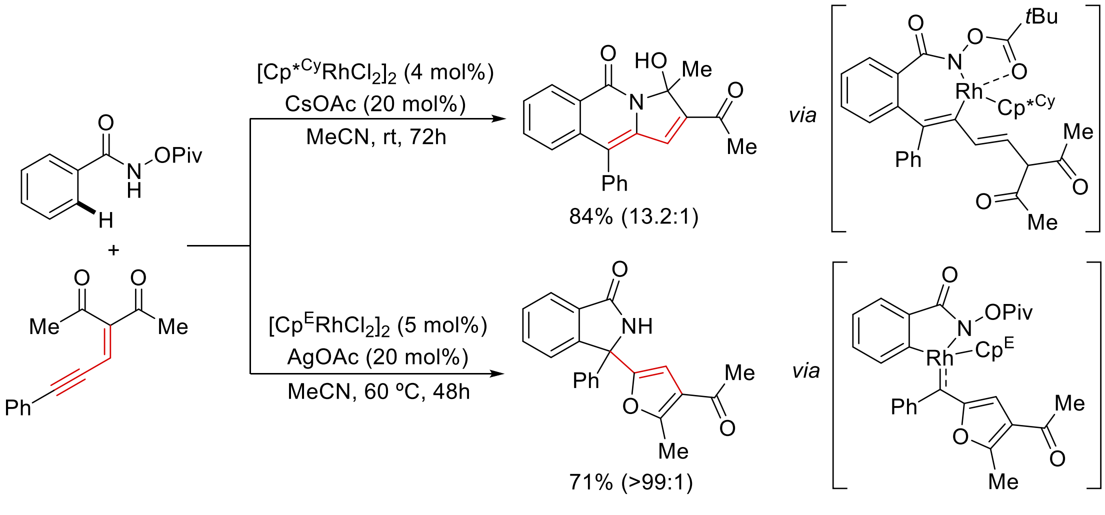


***Figure 4**. Structure of different Cp ligands.*

A representative example of the influence of the Cp ligand in the reactivity has been recently reported by Sukbok Chang.[108] His group demonstrated that benzamides could engage either in (4+2) or (4+1) rhodium-promoted annulations with conjugated enynones depending on the characteristics of the Cp ligand. Using an electron-donating Cp ligand (Cp*^{Cy}), the Rh catalyst is more basic and the alkyne insertion is favored after the C-H activation step; thus the reaction furnishes tricyclic isoquinolinones. However, when a rhodium catalyst bearing an electron-withdrawing Cp (Cp^{E}) is employed, the metal presents a high Lewis acidity which favors a 5-*exo*-dig cyclization of the enyne to give a key carbene intermediate that evolve to give isoindolinones (scheme 55).



***Scheme 55.** Divergent synthesis of (4+2) or (4+1) adducts depending on the Cp ligand.*

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[104] For selected examples, see: (a) Hyster, T. K.; Rovis, T. *Chem. Sci.* **2011**, *2*, 1606-1610. (b) Hyster, T. K.; Dalton, D. M.; Rovis, T. *Chem. Sci.* **2015**, *6*, 254-258. (c) Lee, S.; Semakul, N.; Rovis, T. *Angew. Chem. Int. Ed.* **2020**, *59*, 4965-4969.

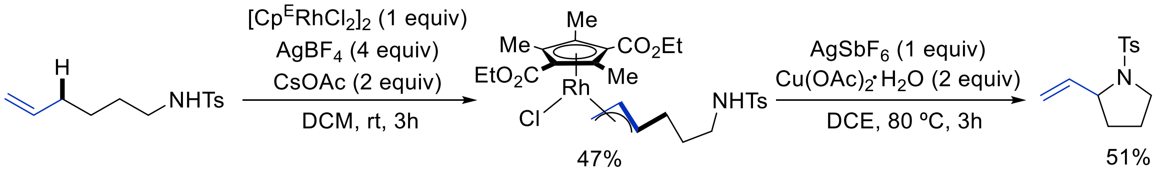
[105] Piou, T.; Rovis, T. *J. Am. Chem. Soc.* **2014**, *136*, 11292-11295.

[106] For selected examples, see: (a) Hoshino, Y.; Shibata, Y.; Tanaka, K. *Adv. Synth. Catal.* **2014**, *356*, 1577-1585. (b) Fukui, M.; Hoshino, Y.; Satoh, T.; Miura, M.; Tanaka, K. *Adv. Synth. Catal.* **2014**, *356*, 1638-1644.

[107] (a) Duchemin, C.; Cramer, N. *Chem. Sci.* **2019**, *10*, 2773-2777. (b) Duchemin, C.; Cramer, N. *Angew. Chem. Int. Ed.* **2020**, *59*, 14129-14133. (c) Mas-Roselló, J.; Herraiz, A. G.; Audic, B.; Laverny, A.; Cramer, N. *Angew. Chem. Int. Ed.* **2021**, *60*, 13198-13224.

[108] Hong, S. Y.; Jeong, J.; Chang, S. *Angew. Chem. Int. Ed.* **2017**, *56*, 2408-2412.

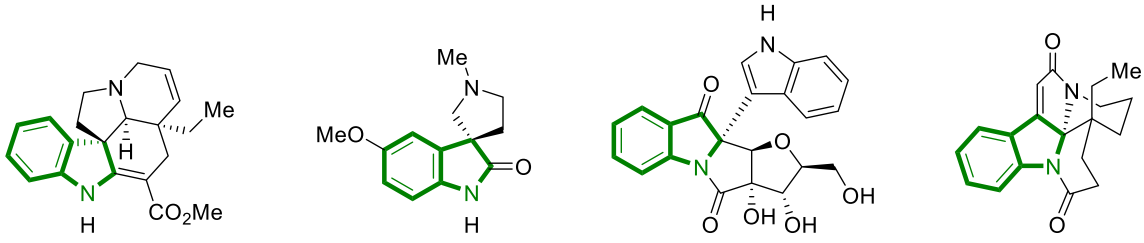
Interestingly, the electron-deficient Cp^E ligand, firstly reported by Tanaka,[109] has also demonstrated to favor the activation of allylic C(sp^3)-H bonds by rhodium catalysts.[98] The research group of Tanaka reported the facile generation and isolation of several π-allyl complexes from terminal aliphatic alkenes using this Cp ligand.[110] Remarkable, when an alkenyltosylamide is used as substrate, the resulting π-allyl complex is able to evolve through an azacyclization process (scheme 56).



***Scheme 56.** Intramolecular oxidative allylic amination using an electron-withdrawing Cp ligand.*

1.2 Indoline cores: Relevance and synthesis by organometallic processes

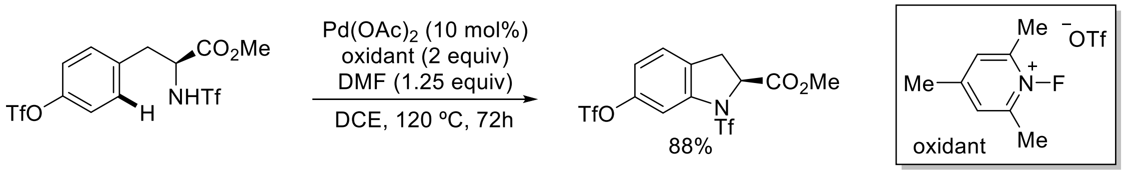
Indolines are privileged structural motifs present in a large variety of natural products with interesting biological activities (figure 5).[111] Therefore, the assembly of their skeleton has been pursued over the years by a quite number of research groups.[112] A number of strategies based on organometallic catalysis, mostly with palladium reagents, have been developed.[113]



Tabersonine Horsfiline (+)-Isatisine A (+)-Melodinine E

***Figure 5.** Representative alkaloids containing the indoline core.*

Among these palladium-catalyzed processes, Yu and co-workers reported an interesting dehydrogenative cyclization that involves a Pd^{II}/Pd^{IV} mechanistic pathway, employing a pyridinium salt (F$^+$ source) as two-electrons oxidant (scheme 57).[114]



***Scheme 57.** C-H amination for the synthesis of indolines.*

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[109] Shibata, Y.; Tanaka, K. *Angew. Chem. Int. Ed.* **2011**, *50*, 10917-10921.

[110] Shibata, Y.; Kudo, E.; Sugiyama, H.; Uekusa, H.; Tanaka, K. *Organometallics* **2016**, *35*, 1547-1552.

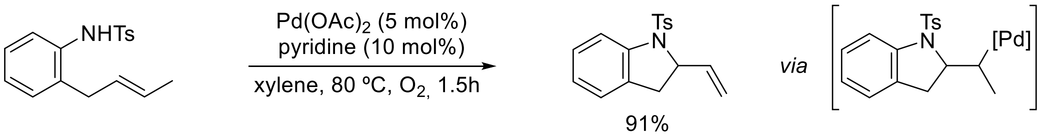
[111] Fattorusso, E.; Taglialatela-Scafati, O. *Modern Alkaloids: Structure, Isolation, Synthesis and Biology*. Wiley-VCH, **2008.**

[112] Silva, T. S.; Rodrigues Jr, M. T.; Santos, H.; Zeoly, L. A.; Almeida, W. P.; Barcelos, R. C.; Gomes, R. C.; Fernandes, F. S.; Coelho, F. *Tetrahedron* **2019**, *75*, 2063-2097.

[113] Li, J.-J.; Mei, T.-S.; Yu, J.-Q. *Angew. Chem. Int. Ed.* **2008**, *47*, 6452-6455.

[114] Mei, T.-S.; Wang, X.; Yu, J.-Q. *J. Am. Chem. Soc.* **2009**, *131*, 10806-10807.

Another classical approach for the synthesis of these skeletons consists of aza-Wacker-type cyclizations.[115] An appealing example based on this strategy was published by Stahl in 2002 (scheme 58).[116]



Scheme 58. *Aza-Wacker cyclization of tosylamides using O_2 as single oxidant.*

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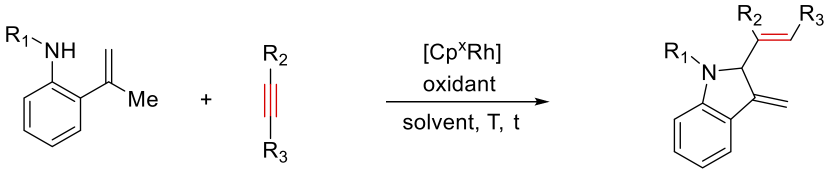
[115] Kotov, V.; Scarborough, C. C.; Stahl, S. S. *Inorg. Chem.* **2007**, *46*, 1910-1923.

[116] Fix, S. R.; Brice, J. L.; Stahl, S. S. *Angew. Chem. Int. Ed.* **2002**, *41*, 164-166.

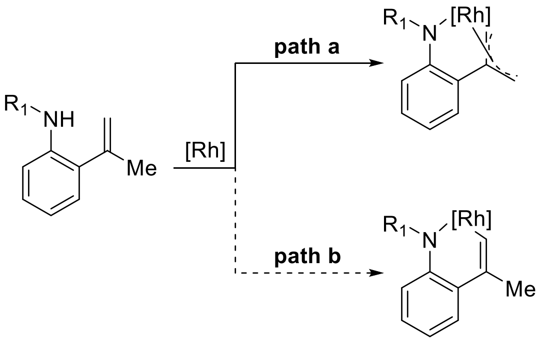
2. Objectives

Considering the relevance of the indoline skeleton and taking into account the preliminary results shown before on the reaction between *o*-alkenylanilides and alkynes under rhodium catalysis, we proposed the development of this annulation in a practical and efficient manner (scheme 59).



Scheme 59. *General objective.*

For that goal, we hypothesized that the use of unconventional Cp ligands could favor the desired reactivity. Specifically, we hypothesized that a rhodium complex bearing the electron deficient Cp^E ligand could favor an allylic C-H activation process (scheme 60, **path a**). However, at the outset, other mechanistic pathways involving the activation of the olefinic $C(sp^2)$-H bond could not be ruled out (scheme 60, **path b**). Therefore, we also planned to synthesize several types of precursors that could allow to explore and understand the transformation.

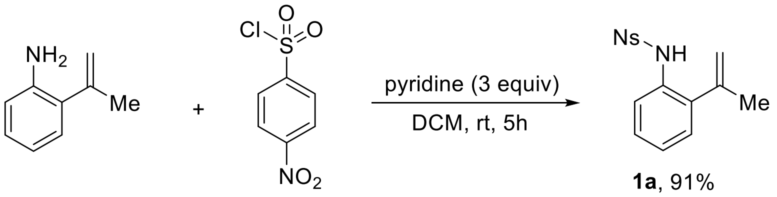


Scheme 60. *Possible C-H activation options.*

3. Results and discussion

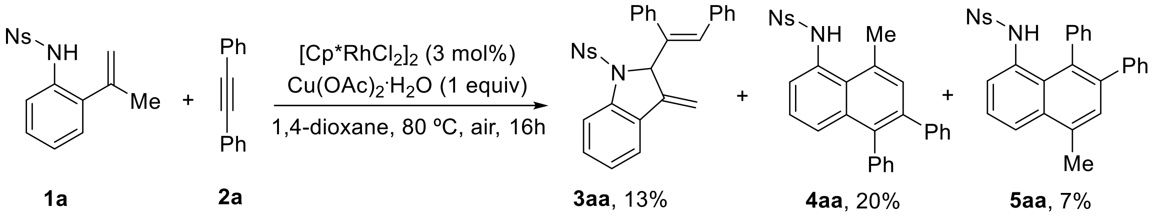
3.1 Exploration of reaction conditions

To evaluate the reactivity of the 2-alkenylanilides, we first synthesized the model substrate **1a** with a nosyl substituent in the amine moiety.[117] This precursor was easily obtained from commercially available 2-isopropenylaniline and 4-nitrobenzenesulfonyl chloride (scheme 61).



Scheme 61. *Synthesis of model substrate **1a**.*

We then performed some initial experiments between this substrate (1 equiv) and diphenylacetylene (1 equiv) as coupling partner. Running the reaction in presence of $[Cp^*RhCl_2]_2$ as catalyst and $Cu(OAc)_2{\cdot}H_2O$ as oxidant in dioxane at 80 °C for 16h, we obtained a complex crude mixture in which we were able to isolate a small amount of the indoline **3aa** (13%), together with a mixture of naphthylamides **4aa** and **5aa** in a combined yield of 27% (scheme 62). Importantly, while the rest of the alkyne was recovered, we observed some decomposition of the *o*-alkenylanilide.



Scheme 62. *Initial discovery of the formation of an indoline.*

As previously commented, we reasoned that the introduction of electron-deficient Cp ligands at the rhodium catalyst, such as in the complex $[Cp^ERhCl_2]_2$ equipped with two ester groups (page 42), could further favor the desired transformation. Luckily, when we tested this rhodium catalyst bearing a Cp^E ligand, we obtained an interesting increase in the yield of the indoline to a 52% (table 1, entry 2) and, more importantly, this product was obtained with total selectivity with only some decomposition of the starting material. Increasing the reaction temperature to 100 °C the yield was lower, observing a higher decomposition of the anilide (table 1, entry 3). At this point, we reduced the amount of the copper salt to 0.25 equivalents (table 1, entry 4), trying to minimize the decomposition

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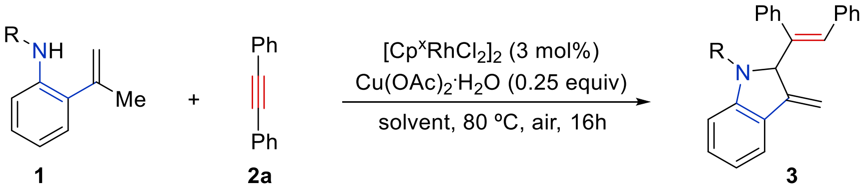
[117] For selected examples of the use of *N*-nosyl amides as directing groups, see: (a) Shao, Q.; He, J.; Wu, Q.-F.; Yu, J.-Q. *ACS Catal.* **2017**, *7*, 7777-7782. (b) Ding, Q.; Ye, S.; Cheng, G.; Wang, P.; Farmer, M. E.; Yu, H.-Q. *J. Am. Chem. Soc.* **2017**, *139*, 417-425. (c) Reference 50b. (d) Jiang, H.; He, J.; Liu, T.; Yu, J.-Q. *J. Am. Chem. Soc.* **2016**, *138*, 2055-2059. (e) Laforteza, B. N.; Chan, K. S. L.; Yu, J.-Q. *Angew. Chem. Int. Ed.* **2015**, *54*, 11143-11146.

of the substrate. However, the same result was obtained. Gratifyingly, increasing the amount of the *o*-alkenylanilide to 1.5 equivalents, the product was obtained in better yields (table 1, entry 5).

Table 1. *Screening of reaction conditions.*[a]



	R	Equiv. anilide	Solvent	Cp^x	**3** (%)
1	Ns	1	Dioxane[b]	Cp*	13
2	Ns	1	Dioxane[b]	Cp^E	52
3	Ns	1	Dioxane[b,c]	Cp^E	45
4	Ns	1	Dioxane	Cp^E	51
5	Ns	1.5	Dioxane	Cp^E	65
6	Ns	1.5	Toluene	Cp^E	0
7	Ns	1.5	Toluene[d]	Cp^E	84
8	Ns	1.5	Toluene[d]	Cp*	29
9	Ns	1.5	Toluene[d]	Cp^{*CF3}	0
10	Ns	1.5	Toluene[d]	Cp^t	63
11	Ns	1.5	Toluene[d]	Cp^{iPr}	83
12	Ns	1.5	Toluene[d]	Cp	84
13	H	1.5	Toluene[d]	Cp^E	0
14	Ac	1.5	Toluene[d]	Cp^E	0
15	Tf	1.5	Toluene[d]	Cp^E	40
16	Ts	1.5	Toluene[d]	Cp^E	25
17	Ns	1.5	Toluene[d,e]	Cp^E	0
18	Ns	1.5	Toluene[d]	-	0

[a] Reaction conditions: Anilide (0.2 or 0.3 mmol), alkyne (0.2 mmol), solvent (2 mL). [b] 1 equiv of $Cu(OAc)_2·H_2O$. [c] 100 °C. [d] H_2O (5 equiv) as additive. [e] Without $Cu(OAc)_2·H_2O$.

Curiously, changing the solvent from dioxane to toluene, the reaction failed, recovering most of the starting material. However, after adding 5 equivalents of water, we obtained an excellent 84% yield (table 1, entry 7), probably due to a better solubilization of the copper salt, which favors the formation of an active rhodium monomer and the reoxidation step.

At this point, we further evaluated a variety of rhodium catalysts with different electronic and steric properties (table 1, entries 8-12) and, again, in presence of $[Cp^*RhCl_2]_2$, yields dropped and the naphthylamide adducts were observed. Remarkable, using a rhodium complex with a Cp ligand bearing a CF_3 group led to the recovery of the anilide precursor, while a bulkier Cp with two *tert*-butyls, Cp^t, provided good results of the indoline with only traces of the naphthylamide as byproduct. Curiously, using a complex with an unsubstituted Cp ligand or with an isopropyl, Cp^{iPr}, we observed the selective formation of the indoline scaffold in comparable yields to those obtained with Cp^E.

We also synthesized other anilide precursors with substituents different from Ns in the amine moiety (see experimental section for more information). However, all of them showed a poorer performance in the desired annulation (table 1, entries 13-16), suggesting a deep influence of the nosyl group in the reaction efficiency. While the parent aniline decomposed in reaction media and the acetylated one failed to react, other groups widely used in this type of functionalizations, like *N*-tosyl or *N*-triflyl amides led to much lower yields and conversions.

Finally, we also carried out some control experiments which confirmed that the reaction doesn't take place in the absence of copper acetate or the rhodium catalyst (table 1, entries 17-18), with full recovery of the anilide and the alkyne.[118]

3.2 Reaction scope

Once the optimal conditions were established, we evaluated the scope of the reaction with regard to the alkyne component (scheme 63). Symmetrical alkynes with aromatic substituents worked nicely, leading to the expected products (**3aa**-**3ac**) in excellent yields, up to 89%, independently of their electronic properties. In addition, a symmetrical alkyne with a simple alkyl chain was also well tolerated (**3ad**). Non-symmetrical alkynes equipped with an aromatic ring and different alkyl substituents, including one bearing a TBS protected alcohol, were also suitable for the annulation, obtaining the desired products in good yields, and excellent regioisomeric ratios, in favor of products in which the aryl substituent is in the terminal position of the alkene (**3ae**-**3ag**). Remarkably, enynes are also efficient reaction partners, as exemplified for the synthesis of **3ah**.[118]

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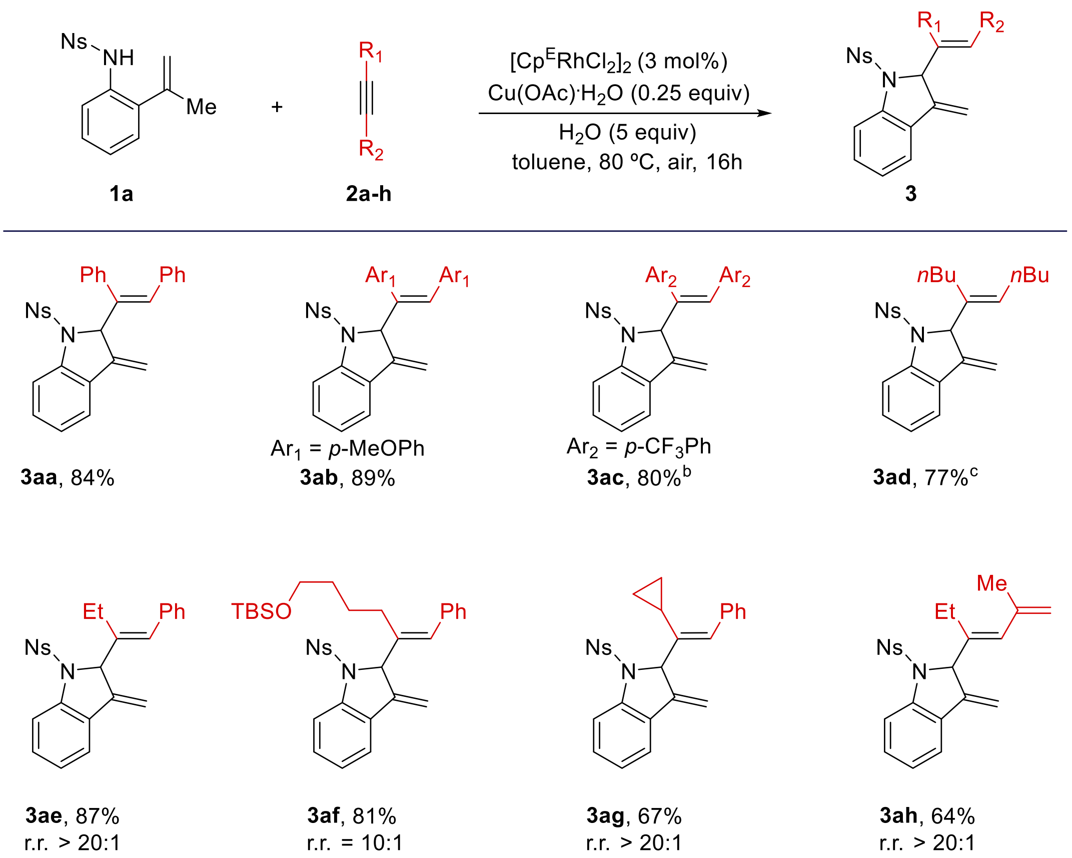
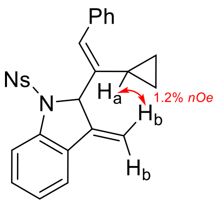
[118] Experiments carried out in collaboration with Dr. Marc Font.



[a] Reaction conditions: Anilide (0.3 mmol), alkyne (0.2 mmol), toluene (2 mL). [b] 90 ºC. [c] 24h.

Scheme 63. *Scope of the reaction with regard to the alkyne.*

The regiochemistry of the adducts obtained from the use of unsymmetrical alkynes was deduced from nOe experiments considering the hydrogens of the exomethylene group and the aliphatic substituents coming from the alkyne counterpart, as exemplified below for **3ag**.



3ag

Figure 6. *nOe experiment to determine the regiochemistry of **3ag**.*

We next explored the scope with regard to the 2-alkenylanilide. The precursors were synthesized by addition of the corresponding Grignard reagents to the required 2-aminobenzonitriles, followed by Wittig reaction and protection with 4-NsCl (scheme 64).[119]

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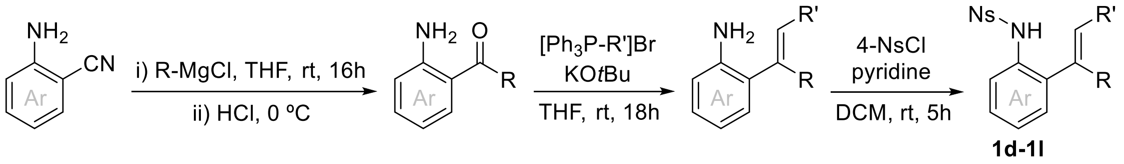
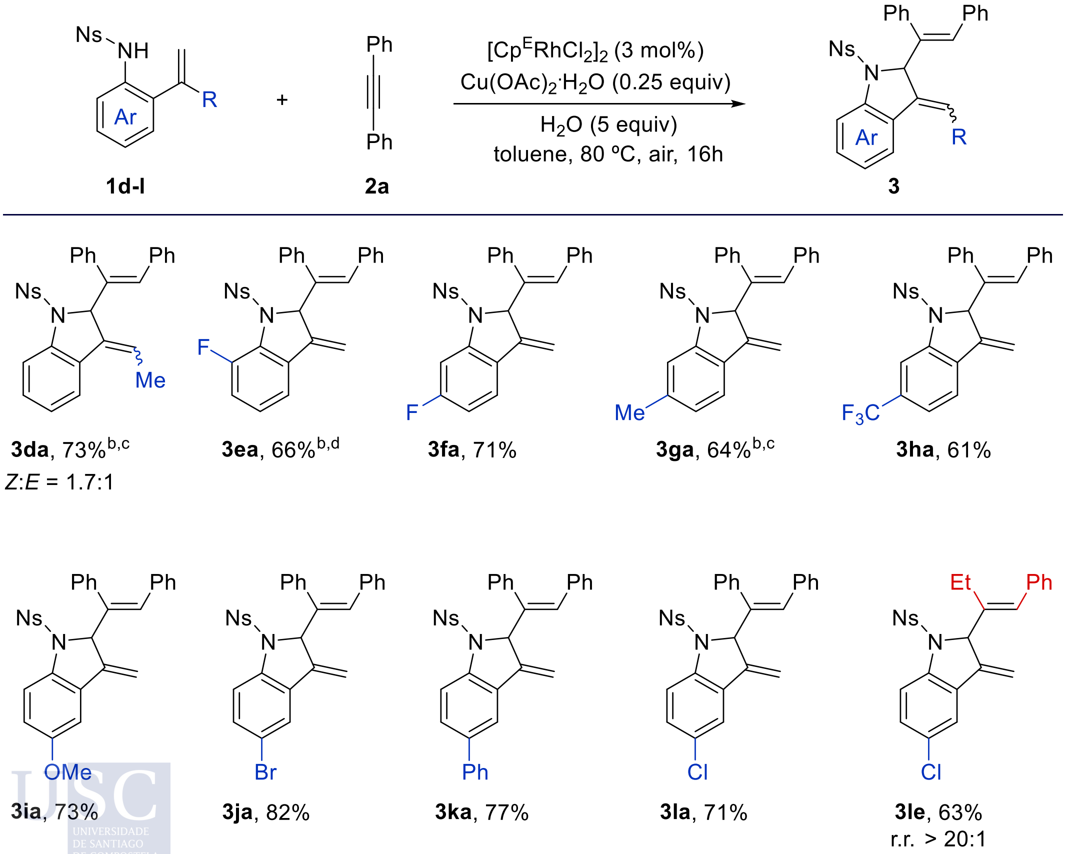
[119] For more information see experimental section.



***Scheme 64**. Synthesis of nosyl-protected o-alkenylanilides.*

As disclosed above, a substrate bearing an ethyl (instead of a methyl) group in the internal position of the alkene also participates in the process, leading to the expected indoline as a *Z:E* mixture of isomers in an almost 2:1 ratio (**3da**). Additionally, the reaction tolerates a wide range of substituents in different positions of the aryl ring. With regard to the *ortho* substitution, a fluorine is well tolerated (**3ea**, 66% yield) and, in the case of the meta substitution, either a fluorine, a CF_3 or a methyl group are compatible with the reaction conditions (**3fa**-**3ha**), albeit higher catalyst loading and more time are needed in the last case. Finally, the reaction also proceeds efficiently with electronically diverse substituents in para position (**3ia**-**3la**, 71-82% yield), and can be extended to other alkynes than **2a**, as exemplified in **3le**.



[a] Reaction conditions: Anilide (0.3 mmol), alkyne (0.2 mmol), toluene (2 mL). [b] 5 mol% of the Rh catalyst. [c] 35h. [d] 6 mL of toluene.

***Scheme 65.** Scope of the reaction regarding the anilide component.*

The structure of the products was further and unambiguously confirmed by X-Ray diffraction of indoline **3ha** as seen below.

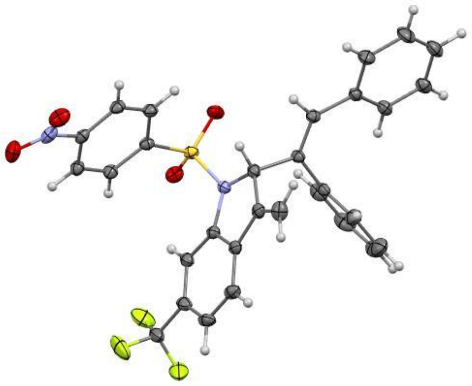
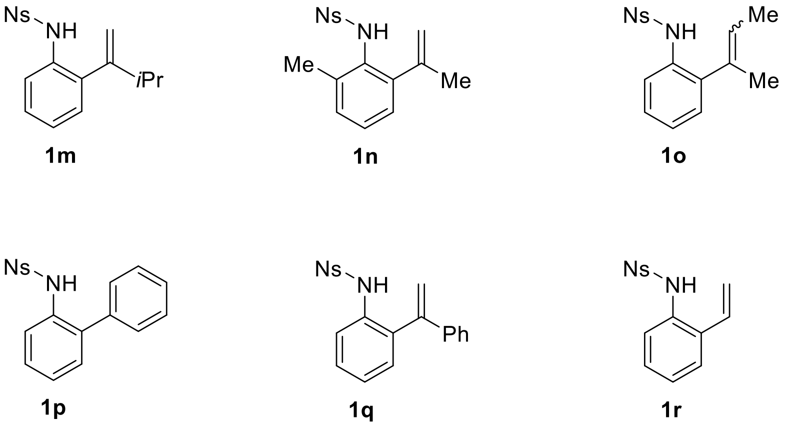


Figure 7. *Structure of* ***3ha*** *obtained by X-Ray diffractometry.*

Despite these excellent results, some anilide substrates failed to give the expected adducts (figure 8). When the internal position of the alkene was substituted with a bulky group, like isopropyl (**1m**), the starting material was mostly recovered with some formation of an indole derivative, formally resulting from the cyclization of the anilide (probably by reductive elimination after C-H activation). Curiously, when a methyl group was introduced in the *ortho* position of the aryl ring of the nosylamide (**1n**), the annulation didn't take place. The reason behind this lack of reactivity, could be the steric clash between the nosyl substituent and the methyl group, which hampers a suitable coordination to the rhodium catalyst. Moreover, a substrate with a substituent in the external position of the alkene (**1o**), also failed to undergo the desired annulation, with almost complete recovery of the precursors. As expected, with anilides **1p**-**1r**, which do not bear allylic hydrogens, we observed no conversion under the standard reaction conditions.



1m **1n** **1o**

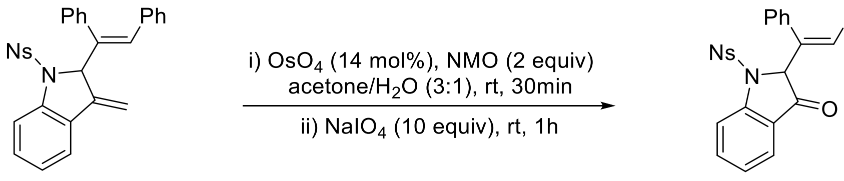
1p **1q** **1r**

Figure 8. *Unsuccessful substrates.*

Overall, we have developed a novel and attractive strategy to synthesize a wide range of indoline skeletons in an efficient manner from trivial starting materials.

3.3 Manipulation of the products

Considering that many indoline containing natural products feature a 3-oxoindoline skeleton (page 43), we decided to explore the selective oxidation of the exomethylene group.[120] Gratifyingly, we were able to successfully perform this transformation, for instance in adduct **3aa**, using osmium tetroxide as oxidizing reagent (scheme 66).[118]

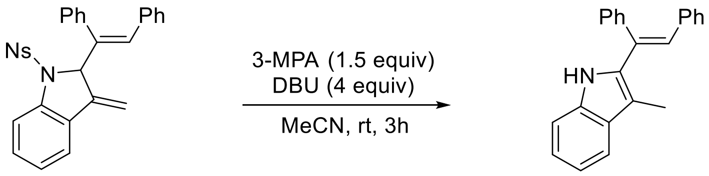


3aa

6aa, 83%

Scheme 66. *Oxidation of the exomethylene group.*

Importantly, the nosyl group can be easily removed from the model product, although the reaction conditions also led to an isomerization of the exocyclic alkene to the corresponding functionalized indole (scheme 67). Nonetheless, this isomerization is relevant, as this type of disubstituted indoles are present in numerous biologically active compounds.[121,122]



3aa

7aa, 72%

Scheme 67. *Removal of the nosyl group.*

3.4 Mechanistic studies

In order to shed light into the intriguing mechanism of the annulation, we decided to synthesize the deuterated substrates **1a**-d_2, with deuterium in the olefinic positions, and **1a**-d_3, which bears a deuterated methyl group in the internal position of the alkene.

Compound **1a**-d_2 was synthesized in three steps, following reported procedures, from 2'-nitroacetophenone.[119] A Wittig reaction, employing the required deuterated triphenylphosphonium salt, gave the expected alkene, and the nitro group was then

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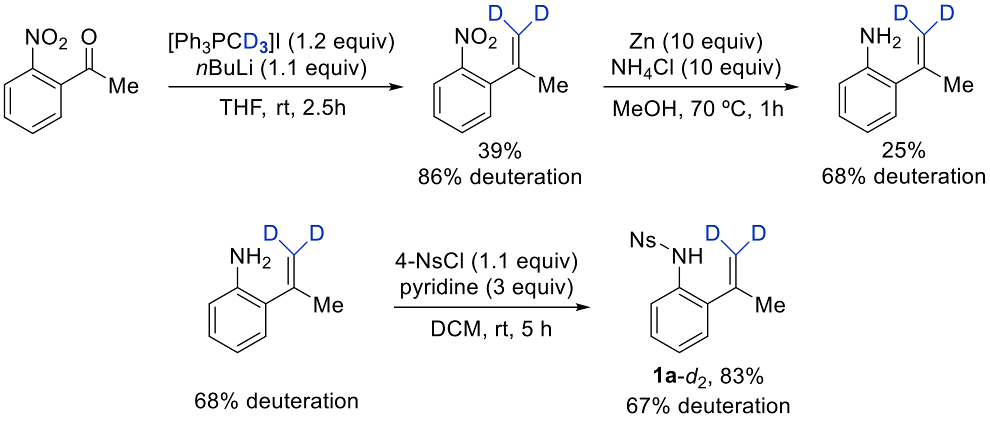
[120] For examples of total synthesis of compounds with a 3-oxoindoline skeleton, see: (a) Karedeolian, A.; Kerr, M. A. *Angew. Chem. Int. Ed.* **2010**, *49*, 1133-1135. (b) Lee, J.; Panek, J. S.; *J. Org. Chem.* **2015**, *80*, 2959-2971. (c) Nakajima, M.; Arai, S.; Nishida, A. *Angew. Chem. Int. Ed.* **2016**, *55*, 3473-3476.

[121] (a) Yap, W.-S.; Gan, C.-Y.; Low, Y.-Y.; Choo, Y.-M.; Etoh, T.; Hayashi, M.; Komiyama, K.; Kam, T.-S. *J. Nat. Prod.* **2011**, *74*, 1309-1312. (b) Sharma, V.; Kumar, P.; Pathak, D. *J. Heterocyclic Chem.* **2010**, *47*, 491-502. (c) Lim, K.-H.; Hiraku, O.; Komiyama, K.; Koyano, T.; Hayashi, M.; Kam, T.-S. *J. Nat. Prod.* **2007**, *70*, 1302-1307.

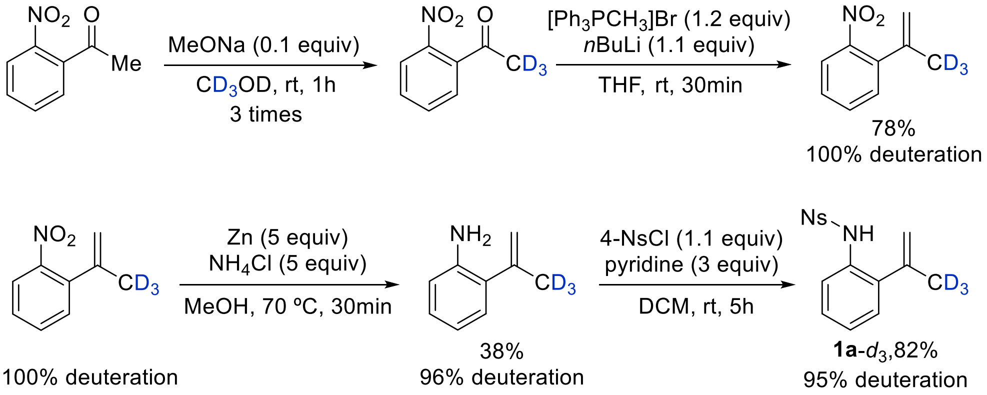
[122] For selected reviews on transition-metal catalyzed synthesis of indoles, see: (a) Youn, S. W.; Ko, T. Y. *Asian J. Org. Chem.* **2018**, *7*, 1467-1487. (b) Guo, T.; Huang, F.; Yu, L.; Yu, Z. *Tetrahedron Lett.* **2015**, *56*, 296-302. (c) Zeni, G.; Larock, R. C. *Chem. Rev.* **2006**, *106*, 4644-4680.

reduced with Zn to the parent aniline. As in the model substrate, it was finally protected with 4-nitrobenzenesulfonyl chloride (scheme 68).



Scheme 68. *Synthesis of deuterated substrate* ***1a****-d₂.*

On the other hand, substrate **1a**-*d*$_3$ was synthesized in four steps from the same starting material and following a similar synthetic route, introducing an initial deuteration step of the methyl group in the presence of methanol-*d*$_4$ and sodium methoxide (scheme 69).



Scheme 69. *Synthesis of deuterated substrate* ***1a****-d₃.*

Once that we had these deuterated substrates in hand, they were tested under the standard reaction conditions in presence of diphenylacetylene. In the case of **1a**-*d*$_2$, the annulation product was obtained with only one deuterium remaining in the molecule in *alpha* to the amine moiety (scheme 70, eq 1), suggesting an olefinic C-H activation. The lack of deuterium scrambling seemed to rule out the possibility of an initial allylic intermediate.

Importantly, the reaction of **1a**-*d*$_3$ also provided some relevant information, as the product was formed with deuterium in both positions of the exomethylene group and the olefinic position resulting from the alkyne insertion (scheme 70, eq 2). This deuteration pattern suggest the existence of an unusual 1,5-hydrogen shift.[123]

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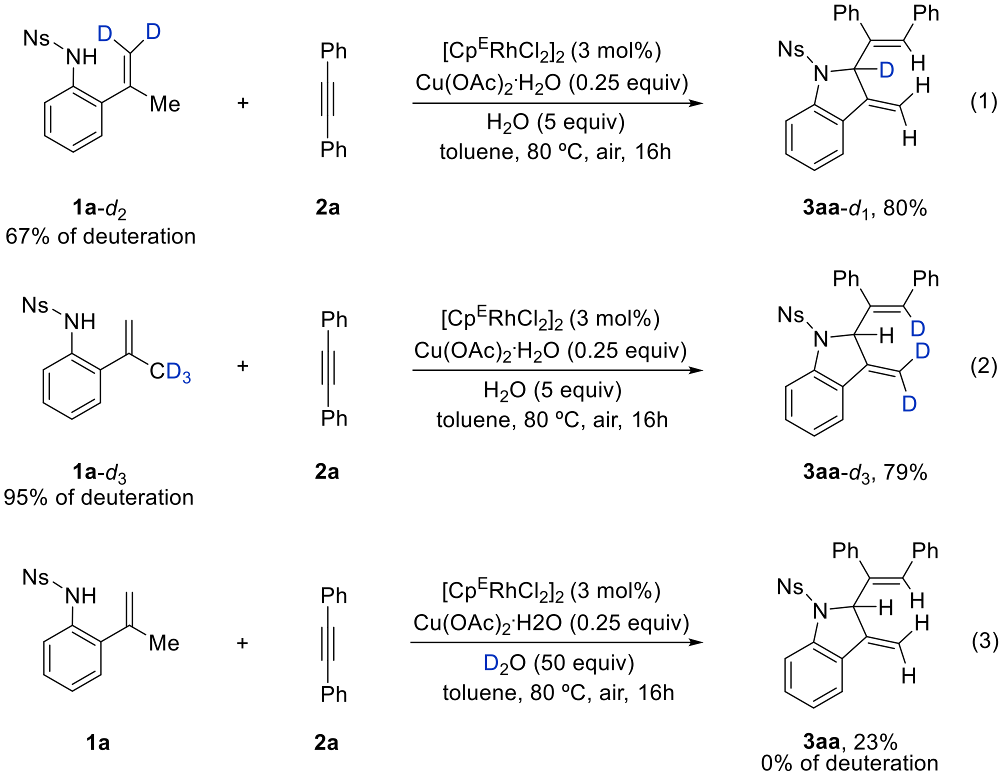
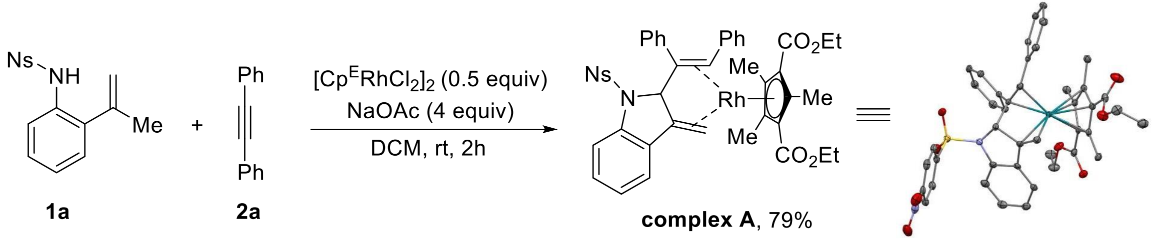
[123] For a recent review on transition-metal migrations, see: Dong, X.; Wang, H.; Liu, H.; Wang, F. *Org. Chem. Front.* **2020**, *7*, 3530-3556.

Finally, we also performed a standard experiment with **1a** in the presence of deuterated water (scheme 70, eq 3). The lack of deuterium in the final compound is consistent with an internal rhodium/hydrogen exchange and an irreversible C-H activation.[124]



Scheme 70. *Mechanistic experiments based on the use of deuterated probes.*

In addition to these deuterium-labelling experiments, we also performed some stoichiometric experiments aimed at isolating reaction intermediates. After some attempts with and without alkyne we were able to obtain a rhodium complex that we identified, after X-Ray diffraction, as a Rh(I) complex in which the metal center is coordinated to both alkenes of the product (scheme 71, hydrogens of X-Ray structure omitted for clarity).



Scheme 71. *Isolation of a Rh(I) intermediate.*

We also performed this stoichiometric experiment in toluene and water at 80 °C, employing different additives. In presence of sodium or silver acetate, the **complex A** was the main product while the indoline adduct was only obtained in small amounts. However,

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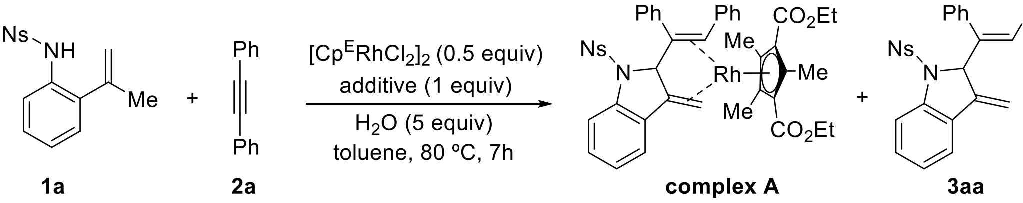
[124] Deuteration experiments were carried out by Dr. Marc Font.

the rhodium complex was not detected when $Cu(OAc)_2$ was added, proving the oxidizing potential of the copper salt (table 2).

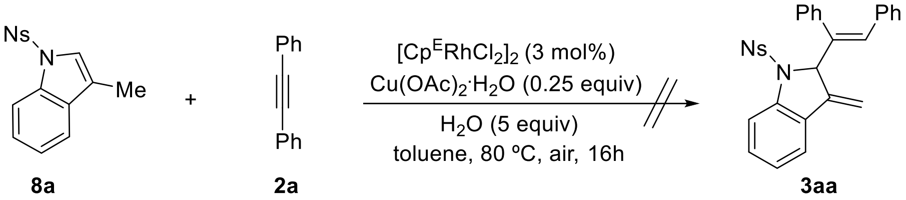
Table 2. *Stoichiometric experiments with different additives.*[a]



	Additive	Conversion (%)[b]	**A** (%)[b]	**3aa** (%)[b]
1	NaOAc	78	50	9
2	AgOAc	79	21	55
3	$Cu(OAc)_2 \cdot H_2O$	85	-	78

[a] Reaction conditions: Anilide (0.1 mmol), alkyne (0.1 mmol), toluene (4 mL). [b] Results by internal standard.

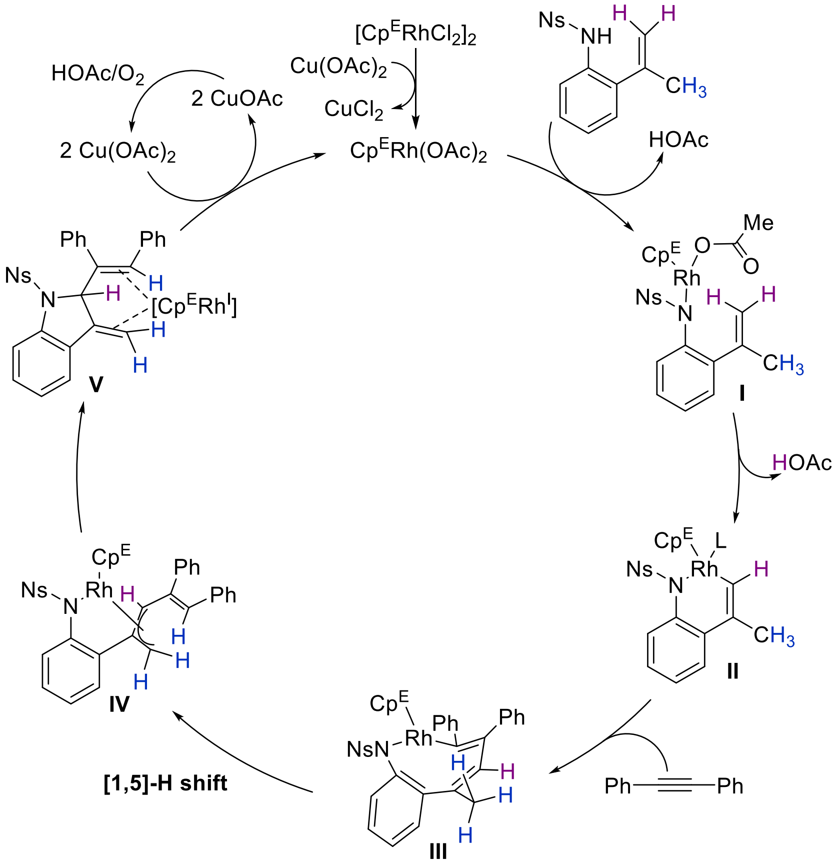
To discard the possibility of a mechanism involving an indole intermediate, we treated **8a** under the reaction conditions. As expected, we observed no reactivity, mostly recovering the starting materials (scheme 72).



Scheme 72. *Control experiment to discard an indole intermediate.*

With all this information at hand, we proposed a plausible mechanistic hypothesis for the transformation (scheme 73). It likely starts with the formation of an active monomeric rhodium species that is able to coordinate the 2-alkenylanilide to form intermediate **I**, responsible for the C-H activation step. Then, the resulting six-membered rhodacycle **II** evolves though migratory insertion of the alkyne, leading to the eight-membered rhodacycle **III**, followed by an unusual 1,5-hydrogen shift with concomitant rhodium migration.[123] At this point, the key π-allylic intermediate **IV** affords, after reductive elimination, compound **V** (**complex A**). Finally, the product is released by oxidation of the rh(I) species by copper and air.

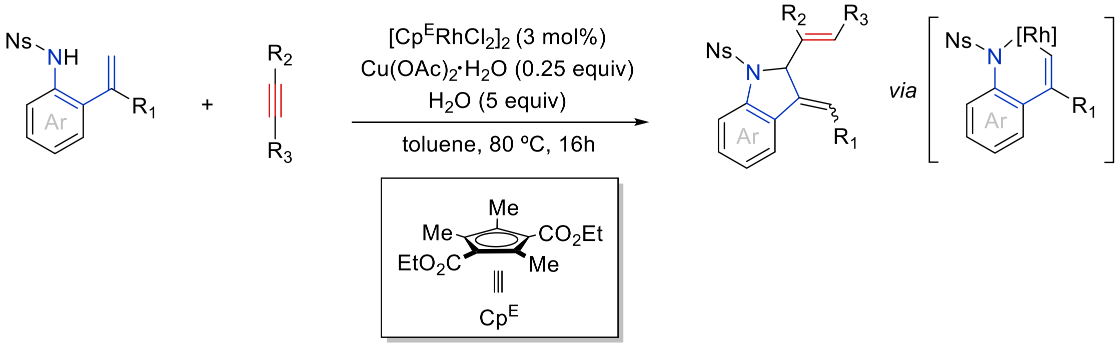
This mechanistic proposal is consistent not only with the deuterium-labelling experiments, but also with the unsuccessful substrates **1p**-**1r** that are not compatible with the mechanistic sequence showed below. However, it does not fully discard other alternatives.



Scheme 73. *Mechanistic hypothesis.*

4. Conclusions

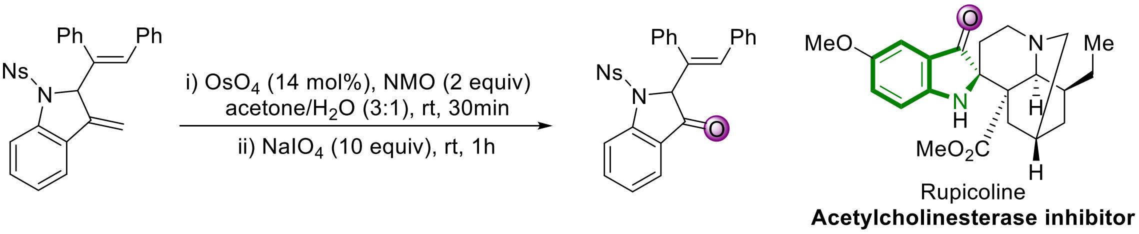
In summary, we have discovered a new type of rhodium-catalyzed annulation between 2-alkenylanilides and alkynes, which leads to interesting indoline skeletons in a simple and efficient way. Remarkable, we found that the use of a rhodium catalyst bearing an electron-deficient Cp^E ligand is crucial for the successful outcome of the reaction, very likely because it favors key steps in the mechanistic pathway and minimizes secondary pathways.



Scheme 74. *Rh(III)-catalyzed synthesis of 2-substituted indolines.*

Moreover, key deuterium labelling experiments allow us to discard the first hypothesis based on an initial allylic C-H activation, and led us to propose an alternative pathway, initiated by alkenyl C-H activation, that involves a rare rhodium migration together with a concomitant [1,5]-H shift.

Finally, we also demonstrated that the adducts can be manipulated in a synthetically useful manner. Specifically, we were able to perform the selective oxidation of the exocyclic alkene, leading to highly appealing 3-oxoindolines, core present in a large number of natural products.[125]



Scheme 75. *Synthesis of 3-oxoindolines by selective oxidation of the exomethylene group.*

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[125] Highlighted in: Snieckus, V.; Jalil Miah, M. A. *Synfacts* **2018**, *14*, 0915.

5. Addendum

5.1 Subsequent mechanistic studies by the Lu, Zhang and Liu group

After reporting our results, the group of Tao Liu, Jing Zhang and Gang Lu performed several DFT calculations to shed light into the intriguing mechanisms of our reactions between 2-alkenyl phenols[99, 100] and anilides[126] with alkynes.[127] In both cases, they employed the eight-membered rhodacycle, obtained after migratory insertion of the alkyne, as starting point for the study.

For the case of the indoline assembly, computational studies suggested (scheme 76, **path B**) an alternative pathway than that of our initial hypothesis (scheme 76, **path A**): an intramolecular migratory insertion of the alkene into the Rh-N bond of the eight-membered rhodacycle **III** to give an interesting tricyclic intermediate (**IVb**). Then, the indoline adduct is obtained after β-hydride elimination and final reductive elimination from the resulting rhodium hydride **Vb**. The authors indicated that the initially postulated 1,5-Rh migration is disfavored due to the steric environment caused by the required three anionic ligands of the Rh(III) species.

This hypothesis is also in agreement with our experimental results. Specifically, they are consistent with our findings during the deuterium-labelling experiments that showed the appearance of one hydrogen of the methyl group in the olefinic position resulting from the alkyne insertion, and also agreed with the β-hydride elimination and C-H reductive elimination sequence.

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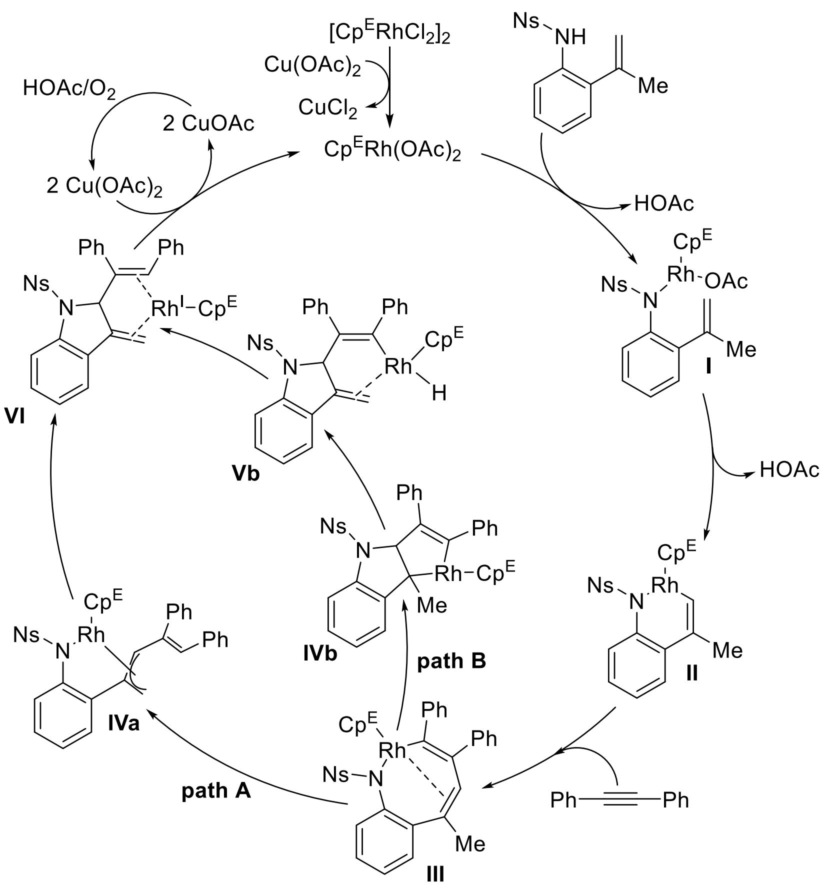
[126] Font, M.; Cendón, B.; Seoane, A.; Mascareñas, J. L.; Gulías, M. *Angew. Chem. Int. Ed.* **2018**, *57*, 8255-8259.

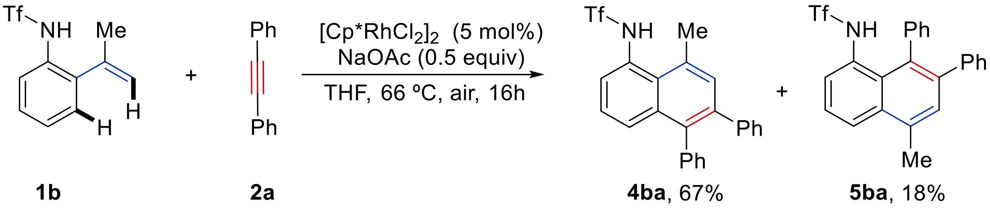
[127] Liu, T.; Han, L.; Zhang, J.; Lu, G. *J. Org. Chem.* **2021**, *86*, 10484-10491.



Scheme 76. *Alternative pathways for the assembly of the indoline scaffolds*.

5.2 Subsequent related works

As indicated in scheme 62, using a Cp* ligand in the Rh catalyst, allowed the formation of surprising naphthalene adducts. Subsequent research by our group demonstrated that using [Cp*RhCl$_2$]$_2$ as catalyst, and *N*-triflyl anilides, these products become majoritarian (scheme 77).[128]



Scheme 77. *Rh-catalyzed (4+2) annulation between o-alkenylanilides and alkynes.*

Significantly, the screening of conditions of this transformation revealed that the best yields were achieved in THF at 66 °C, employing NaOAc as additive and air as the only oxidant. As shown in scheme 77, the reaction gives a formal (4C + 2C) cycloadduct arising from a canonical cycloaddition (**4ba**), but also a rearranged product (**5ba**). We later found

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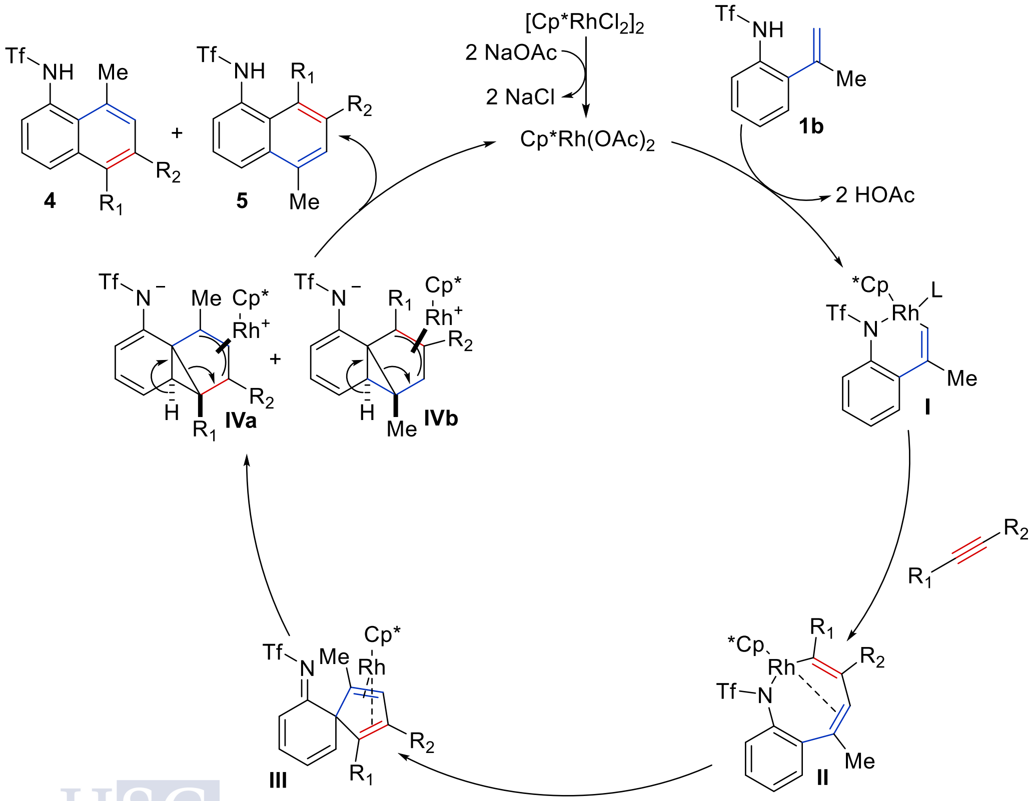
[128] Seoane, A.; Comanescu, C.; Casanova, N.; García-Fandiño, R.; Diz, X.; Mascareñas, J. L.; Gulías, M. *Angew. Chem. Int. Ed.* **2019**, *58*, 1700-1704.

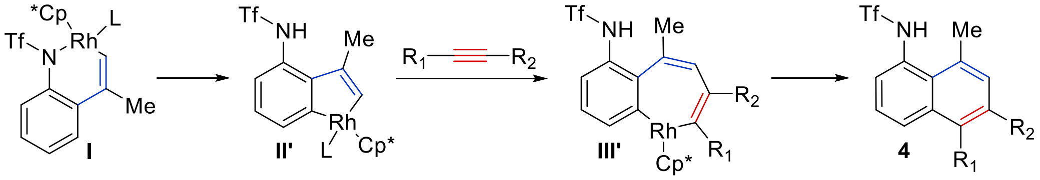
that while employing alkynes with an aromatic substituent, the reaction mainly gives the (4+2) adduct, the employment of alkynes bearing alkyl groups as substituents, switched the selectivity in favour of the rearranged product. Mechanistically, while product **4ba** could be considered as result of a dehydrogenative (4+2) annulation, the formation of **5ba** was totally unexpected and necessarily implies the cleavage and formation of new C-C bonds.

Therefore, to further understand the mechanistic sequence, we performed DFT calculations, and they supported a mechanism initiated by olefinic C-H activation and subsequent migratory insertion of the alkyne to give the eight-membered rhodacycle **II**. At this point, the mechanism diverges from that proposed in the case of the indoline adducts, due to the different electronic properties of the Cp ligands. A formal [1,3'] reductive elimination takes places to give a key spirocyclic intermediate **III**, that readily progress to the cyclopropyl tricyclic intermediates **IVa** or **IVb**. Then, aromatization through ring expansion generates the corresponding naphthylamides featuring a rhodium hydride complex that readily evolve to produce the final naphthalene adducts (scheme 78).



Scheme 78. Mechanistic hypothesis for the synthesis of naphthylamides.

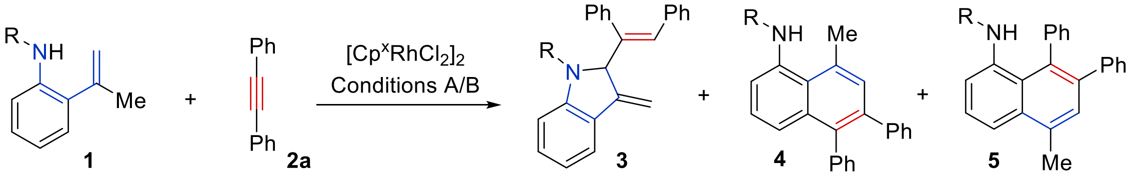
Alternatively, the formation of the non-rearranged product could proceed through a different mechanism. After the olefinic C-H activation, a rollover process can take places to achieve a second C-H activation, leading to the five-membered rhodacycle **II'**. From this complex, the corresponding naphthylamide would be formed after migratory insertion and reductive elimination (scheme 79).



Scheme 79. *Mechanistic alternative for the formation of the non-rearranged naphthylamide.*

Given these results and considering the initial findings showed at the beginning of the chapter (page 46), we were interested in a deeper evaluation of the influence of the different parameters in the selective formation of the indoline or the naphthalene adducts. For that purpose, we submitted *N*-triflyl or *N*-nosyl *o*-alkenylanilides to the best conditions of both reactions in presence of $[Cp^*RhCl_2]_2$ or $[Cp^ERhCl_2]_2$ (table 3).

Table 3. *Influence of diverse factors in the formation of each adduct.*



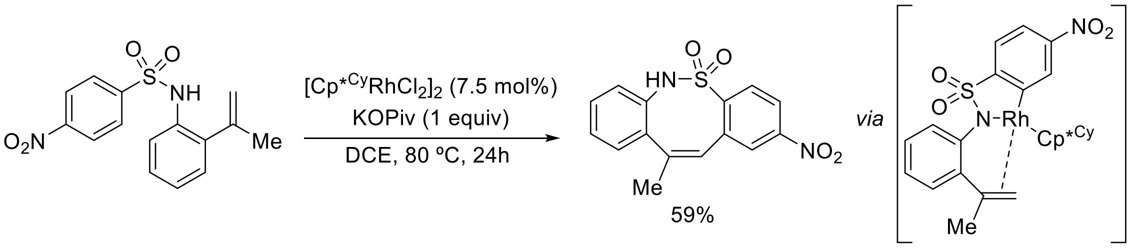
	R	Conditions*	Cp^X	**3** (%)	**4+5** (%)
1	Tf	A	Cp*	19	13
2	Tf	A	Cp^E	40	-
3	Ns	A	Cp*	29	25
4	Ns	A	Cp^E	84	-
5	Tf	B	Cp*	<5	85
6	Tf	B	Cp^E	-	-
7	Ns	B	Cp*	14	23
8	Ns	B	Cp^E	-	-

*Conditions **A**: Anilide (1.5 equiv), alkyne (1 equiv), Rh (3 mol%), $Cu(OAc)_2{\cdot}H_2O$ (0.25 equiv), toluene, 80 ºC, air, 16h.
*Conditions **B**: Anilide (1 equiv), alkyne (1 equiv), Rh (5 mol%), NaOAc (0.5 equiv), THF, 66 ºC, air, 16h.

As can be deduced from the results indicated in the table, using the Rh catalyst with a Cp^E ligand, the naphthylamide adduct was never formed, independently of the reaction conditions or the substituent at the nitrogen. However, when $[Cp^*RhCl_2]_2$ was used as catalyst, this product was always formed in reaction media in the cases in which some reactivity was observed. In these examples, variable amounts of the indoline scaffold were obtained, in lower amounts when *N*-triflyl anilides are employed. Using the optimal conditions for the synthesis of the naphthylamides, the indoline product is almost suppressed.

These results remark the enormous influence of the characteristics of the Cp ligand in the selective formation of each product. On the other hand, the substituent at the nitrogen proved to be crucial to achieve great results in terms of yields for both transformations.

Aside from these results, during the mechanistic investigation of the synthesis of the indoline adduct we also observed the formation of unusual eight-membered products when we carried out stoichiometric experiments in absence of alkyne. Even though we conducted some experiments to investigate and optimize this transformation, the annulation was recently published by the research group of Zhou and Yi, employing an electron-rich Cp*^{Cy} ligand, that was critical to achieve high conversions (scheme 80).[129]



Scheme 80. *Rh(III)-catalyzed dehydrogenative annulation for the synthesis of sultams.*

After carrying out several experimental and computational studies for this dehydrogenative annulation, these authors were able to propose the following mechanistic sequence: aromatic C-H activation, alkene insertion, β-hydride elimination and, finally, a hydrogen-transfer process assisted by HOPiv, which allows a redox-neutral catalytic cycle with concomitant release of H_2 as byproduct.

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[129] Li, L.; Gao, H.; Sun, M.; Zhou, Z.; Yi, W. *Org. Lett.* **2020**, *22*, 5473-5478.

Chapter II – Divergent synthesis of azepines and pyrrolidines through a Rh(III)-catalyzed annulation between homoallylamides and alkynes, triggered by C-H activation

1. Introduction

1.1 Allyl and Homoallylamines as substrates for transformations involving C-H activation processes

Allylic and homoallylic amines are considered particularly challenging substrates for transition metal catalyzed C-H functionalization reactions due to multiple reasons. First, because in presence of oxidants it can be difficult to avoid competitive oxidations to the corresponding imines. Moreover, the alkene functionality is sensitive to oxidation, and to reactions with electrophiles and nucleophiles promoted by the metal catalyst (see introduction, page 20). An additional issue can be the competition of Aza-Wacker type of processes.[115]

Despite these drawbacks, there are a few reports that demonstrate the viability of activating and functionalizing alkenyl C-H bonds in allylamines.[130] For example, the group of X. Li reported in 2012 an attractive work that revealed the diverse reactivity of N-allyl sulfonamides with alkynes in presence of a rhodium catalyst (scheme 81).[131] Using allylamines with non-substituted alkenes, they only observed the formation of pyridines; however, introducing a substituent in the internal position of the alkene, and adding water as reagent, cyclopentenone and a 1,2-dihydropyridine skeletons were obtained. The selectivity was controlled by modifying the amount of the added silver salt, which favors the formation of the cyclopentenone.

Mechanistically, the assembly of both products starts with the C-H activation step followed my migratory insertion of the alkyne to give intermediate **I** (scheme 81). Then, pyridines are obtained upon reductive elimination (intermediate **II**) and subsequent tosyl migration, that occurs through an S_N1-type mechanism, with a final oxidative aromatization. On the other hand, when a substituent is placed in the internal position of the alkene, the 1,3-shift of the tosyl moiety is blocked, making this pathway less favored. Therefore, in presence of higher amounts of the silver salt, rhodacycle **I** evolve through β-hydride elimination, providing imine **II'**. Then, migratory insertion of the alkenyl rhodium moiety into the imine generates intermediate **III'**. At this point, a new β-hydride elimination followed by water addition and final tautomerization furnishes the product.

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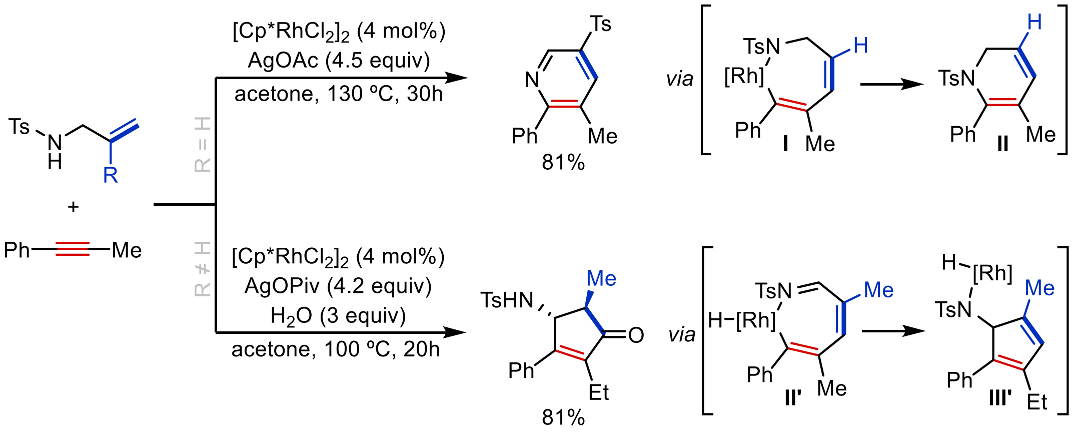
[130] For selected examples, see: (a) Hu, S.; Wang, D.; Liu, J.; Li, X. *Org. Biomol. Chem.* **2013**, *11*, 2761-2765. (b) Han, Y. R.; Shim, S.-H.; Kim, D.-S.; Jun, C.-H. *Org. Lett.* **2017**, *19*, 2941-2944. (c) Parella, R.; Babu, S. A. *J. Org. Chem.* **2017**, *82*, 6550-6567.

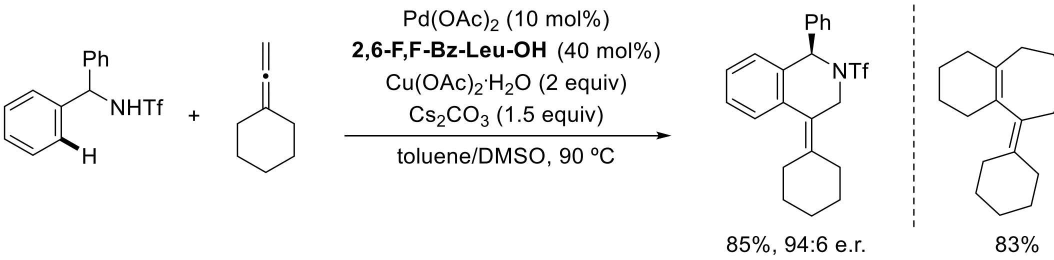
[131] Wang, D.; Wang, F.; Song, G.; Li, X. *Angew. Chem. Int. Ed.* **2012**, *51*, 12348-12352.



Scheme 81. *Reactivity of N-allyl sulfonamides with alkynes under Rh(III) catalysis.*

The use of homoallylamines in C-H functionalization reactions has been even more limited than that of allylamines. This may be due to the requirement of assembling larger metalacyclic intermediates. However, some palladium-catalyzed reactions, including annulations, have been reported (vide infra).

In 2019 our group demonstrated the viability of performing formal cycloadditions between allyl and benzyltriflamides and allenes using palladium catalysis, even in an enantioselective manner, employing MPAA as ligands (scheme 82).[86a] This article also included some preliminary examples with homoallylamides instead of benzylamides as coupling partners, to give azepine type of products.



Scheme 82. *Pd-catalyzed formal (4+2) cycloaddition for the synthesis of chiral tetrahydroisoquinolines, and an example of a cycloaddition product resulting from homoallylamides.*

Another more recent contribution by our group published in 2021 consisted on a kinetic resolution of α-branched allylamides via C-H annulation with allenes, project in which I contributed with the synthesis and evaluation of some precursors, together with the derivatization of the chiral products.[86d] The reactions took place with impressive values of enantioselectivity (up to 99% *ee*) and selectivity, using mono-*N*-protected α-amino-*O*-methylhydroxamic acids (MPAHA) or mono-*N*-protected amino acids (MPAA) as palladium ligands.[132]

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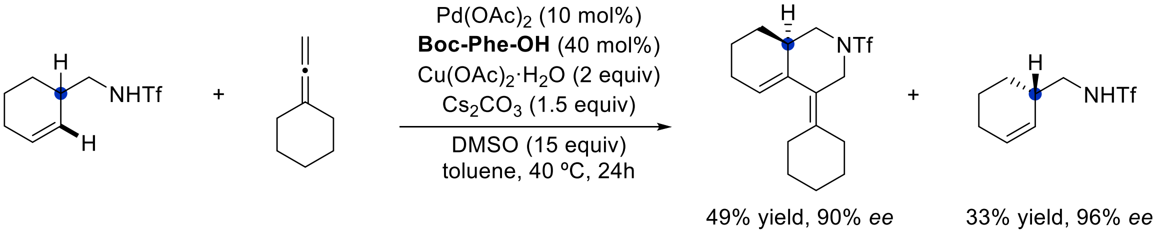
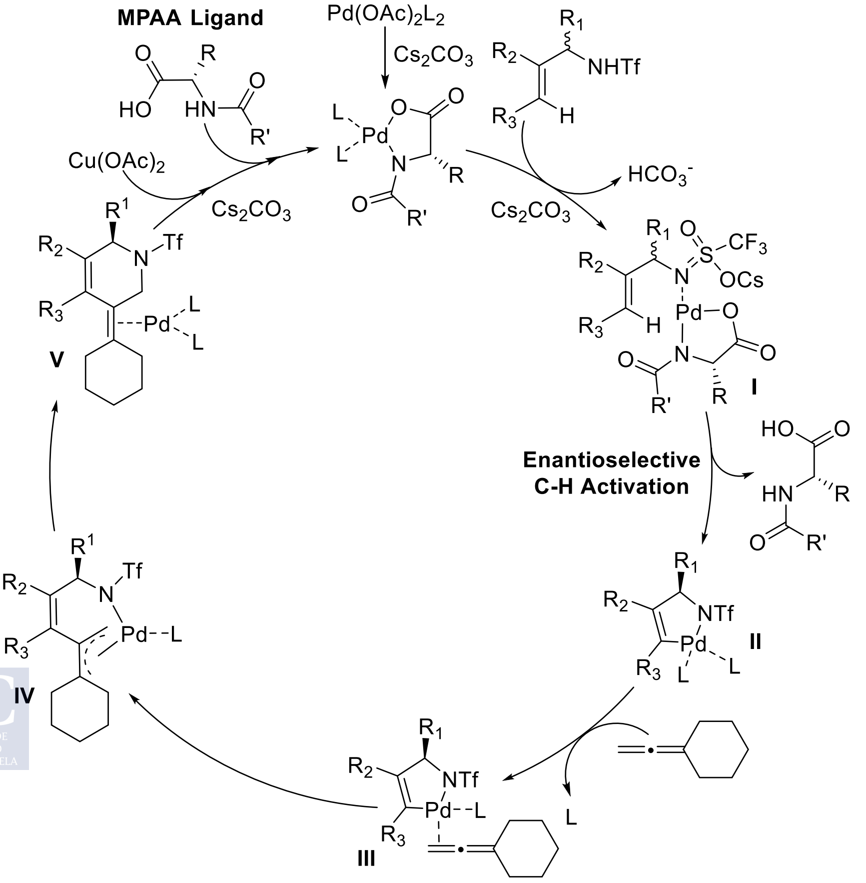
[132] For selected examples of the use of MPAHA ligands, see: (a) Xiao, K.-J.; Lin, D. W.; Miura, M.; Zhu, R.-Y.; Gong, W.; Wasa, M.; Yu, J.-Q. *J. Am. Chem. Soc.* **2014**, *136*, 8138-8142. (b) Reference 53b. (c) Cheng, X.-F.; Fei, F.; Li, Y.; Hou, Y.-M.; Zhou, X.; Wang, X.-S. *Org. Lett.* **2020**, *22*, 6394-6398. (d) Li, Y.; Cheng, X.-F.; Fei, F.; Wu, T.-R.; Bian, K.-J.; Zhou, X.; Wang, X.-S. *Chem. Commun.* **2020**, *56*, 11605-11508.

This publication also includes a couple of examples of homoallylic amide precursors with β-substitution, such as that shown in scheme 83. However, the success with homoallylamide substrates was limited to this type of precursors.



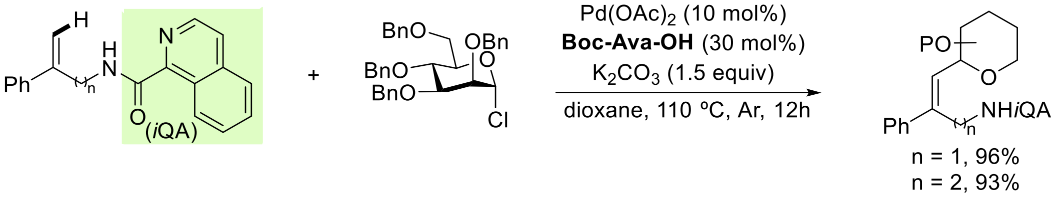
Scheme 83. *Kinetic resolution of (homo)allylic substrates through C-H functionalization with allenes.*

A general mechanism for this transformation is outlined in scheme 84. First, the metal-ligand complex formed initially coordinates the allyltriflamide, that acts as L ligand in presence of Cs$_2$CO$_3$, to give species **I**. At this point, the mono-protected amino acid plays a key role promoting the C-H activation in a stereoselective fashion, resulting in the formation of the chiral palladacycle **II** with concomitant release of the MPAA ligand. Then, coordination of the allene and subsequent migratory insertion provides π-allylic intermediate **IV**, which evolves through reductive elimination to afford the desired cycloadduct coordinated to a Pd(0) species. Finally, the catalyst is reoxidized in presence of the copper salt, enabling a new catalytic cycle.



Scheme 84. *Mechanistic hypothesis for the Pd(II)-catalyzed kinetic resolution of allylamines.*

Aside from cycloaddition reactions, the group of G. He and G. Chen reported in 2021 a C-H glycosylation reaction for the synthesis of *C*-vinyl glycosides, based on the C-H activation of allyl and homoallylamides equipped with a bidentate auxiliary, as depicted in scheme 85.[133] This approach, which involves a Pd^{II}/Pd^{IV} catalytic cycle, requires the use of a bidentate auxiliary as directing group.



Scheme 85. *Pd-catalyzed C(sp^2)-H glycosylation of (homo)allylamine moieties.*

Overall, formal cycloadditions between homoallylamides and unsaturated moieties, which would provide a direct access to highly appealing azepine skeletons, have not been truly developed. All isolated advances have been limited to specifically engineered substrates, and in all cases based on the use of palladium reagents.

Given that one of the problems in the C-H activation reactivity of allyl and homoallylamides is associated to their lability to oxidants, we reasoned that the use more benign oxidizing sources, such as electrochemistry, could be beneficial.

1.2 Electrochemistry: A greener alternative to traditional oxidizing reagents

As already mentioned, one of the current main goals of organometallic catalysis is the development of greener processes. While C-H functionalization reactions tend to fulfil these conditions, the usual requirement of oxidising agents to close catalytic cycles, increases the amount of residues of the reactions, and therefore strategies to avoid such waste are highly welcome.

It is in this context that some researchers, with a special relevant contribution by the group of P. Baran,[134] started to explore the use of electricity as a redox agent, looking for a cheaper, more efficient, and greener synthetic organic chemistry.[135] Basically, electrochemistry consists of the use of a power source, which is connected to two (or even three) electrodes in solution. The power pulls electrons from the anode to the cathode triggering a potential difference, that also causes a determined movement of charged

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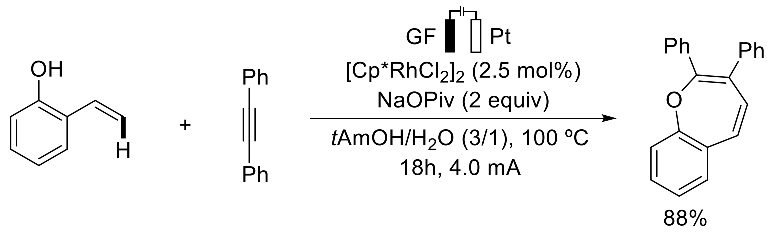
[133] Sun, Q.; Zhang, H.; Wang, Q.; Qiao, T.; He, G.; Chen, G. *Angew. Chem. Int. Ed.* **2021**, *60*, 19620-19625.

[134] For selected examples of the use of electrochemistry by the Baran's group, see: (a) Rosen, B. R.; Werner, E. W.; O'Brien, A. G.; Baran, P. S. *J. Am. Chem. Soc.* **2014**, *136*, 5571-5574. (b) Horn, E. J.; Rosen, B. R.; Chen, Y.; Tang, J.; Chen, K.; Eastgate, M. D.; Baran, P. S. *Nature* **2016**, *533*, 77-81. (c) Kawamata, Y.; Yan, M.; Liu, Z.; Bao, D.-H.; Chen, J.; Starr, J. T.; Baran, P. S. *J. Am. Chem. Soc.* **2017**, *139*, 7448-7451. (d) Gnaim, S.; Takahira, Y.; Wilke, H. R.; Yao, Z.; Li, J.; Delbrayelle, D.; Echeverria, P.-G.; Vantourout, J. C.; Baran, P. S. *Nature Chem.* **2021**, *13*, 367-372.

[135] Horn, E. J.; Rosen, B. R.; Baran, P. S. *ACS Cent. Sci.* **2016**, *2*, 302-308.

species in solution, thereby generating a reductive environment in the cathode and an oxidative environment in the anode.[136]

Electrochemical oxidations have been increasingly used in the field of C-H activation,[137] specially by the Ackermann's group, and of course in the development of formal cycloadditions. For instance, this group applied this methodology in one of our reactions (scheme 86),[99] eliminating the need for a copper salt in the Rh(III)-catalyzed synthesis of benzoxepines, with almost no erosion in yield employing graphite (GF) and platinum (PT) electrodes (88% versus 97%).[138] Moreover, the reaction conditions are different that those used in the classical reaction, as the electrochemical reactions require an electrolyte, sodium pivalate in this specific case, that serves as source of ions, improving conductivity and reducing resistance. Moreover, the solvent, that must be stable under electrochemical conditions, is also crucial to stabilise intermediates and dissolve the electrolyte completely. Therefore, polar and protic solvents are often used as in this illustrative example, in which they employ a mixture of *tert*-amyl alcohol and water.



Scheme 86. *Electrochemistry-enabled Rh-catalyzed formal (5+2) cycloaddition.*

Another leading researcher merging electrochemistry with C-H functionalization is T.-S. Mei. His recent publications have been notable for the quality and the in-depth mechanistic studies, such as in the divergent synthesis of α-pyridones and cyclic imidates.[139] This remarkable method consist on a Rh(III)-catalyzed vinylic C-H activation and formal (4+2) cycloaddition between acrylamides and alkynes, in which there are two different mechanistic pathways in function of the substituent in the amide moiety. As shown in scheme 87, when *N*-phenyl acrylamides are used, a classical mechanistic sequence takes places to give the corresponding α-pyridones, however, when *N*-tosyl amides are employed, an ionic stepwise pathway is preferred, resulting in the formation of the cyclic imidates.

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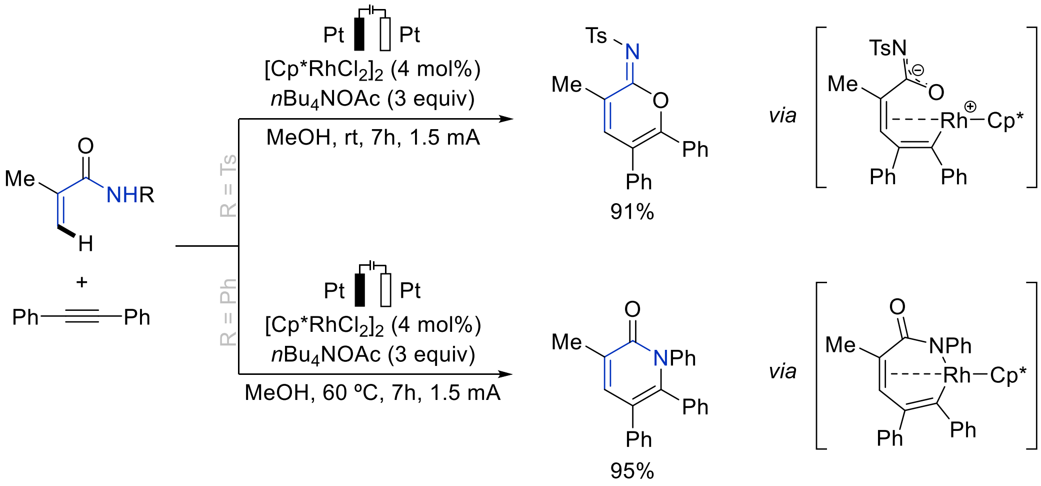
[136] For a comprehensive overview of the basic concepts and applications of electrochemistry, see: (a) Kingston, C.; Palkowitz, M. D.; Takahira, Y.; Vantourout, J. C.; Peters, B. K.; Kawamata, Y.; Baran, P. S. *Acc. Chem. Res.* **2020**, *53*, 72-83. (b) Schotten, C.; Nicholls, T. P.; Bourne, R. A.; Kapur, N.; Nguyen, B. N.; Willans, C. E. *Green Chem.* **2020**, *22*, 3358-3375.

[137] For selected reviews of the use of electrochemistry in C-H functionalization, see: (a) Meyer, T. H.; Finger, L. H.; Gandeepan, P.; Ackermann, L. *Trends Chem.* **2019**, *1*, 63-76. (b) Jiao, K.-J.; Xing, Y.-K.; Yang, Q.-L.; Qiu, H.; Mei, T.-S. *Acc. Chem. Res.* **2020**, *53*, 300-310.

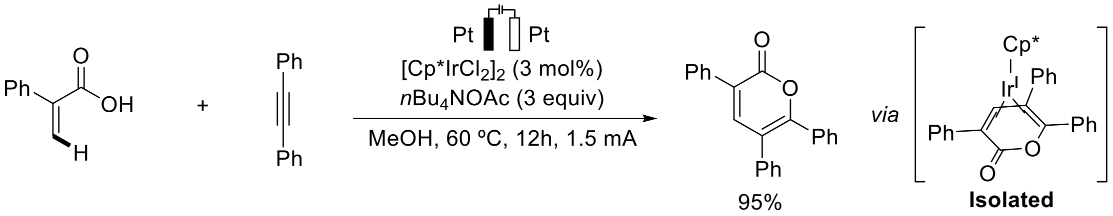
[138] Wang, Y.; Oliveira, J. C. A.; Lin, Z.; Ackermann, L. *Angew. Chem. Int. Ed.* **2021**, *60*, 6419-6424.

[139] Xing, Y.-K.; Chen, X.-R.; Yang, Q.-L.; Zhang, S.-Q.; Guo, H.-M.; Hong, X.; Mei, T.-S. *Nature Commun.* **2021**, *12*, 930.



Scheme 87. *Electrooxidative assembly of α-pyridones and cyclic imidates.*

Another appealing work by the same group employing acrylic acids with iridium catalyst is depicted below in scheme 88.[140] This example is especially interesting because it illustrates perfectly the potential of electrochemistry, as they obtained clearly superior results employing electricity than using traditional oxidants. They rationalize this observation in terms of the formation of a stable 18e$^-$ diene-Ir(I) complex after reductive elimination, which is difficult to oxidize. Remarkable, they were able to isolate this intermediate and demonstrate that only in presence of electric current it evolved to an Ir(III) intermediate, with concomitant release of the product, through anodic oxidation.



Scheme 88. *Ir(III)-catalyzed formal (4+2) cycloaddition between acrylic acids and alkynes.*

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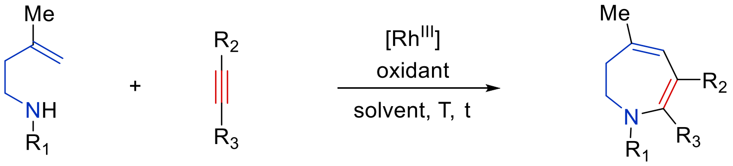
[140] Yang, Q.-L.; Xing, Y.-K.; Wang, X.-Y.; Ma, H.-X.; Weng, X.-J.; Yang, X.; Guo, H.-M.; Mei, T.-S. *J. Am. Chem. Soc.* **2019**, *141*, 18970-18976.

2. Objectives

Homoallylamines are very attractive substrates for metal-promoted alkenyl C-H functionalizations and annulations, however there are very few precedents on exploiting this potential reactivity, and they are mainly limited to the use of palladium reagents. We questioned whether it would be possible to extend the Rh-catalyzed chemistry of *o*-alkenylanilides to homoallylamides.[126, 128] Particularly intriguing was the possibility of developing a formal (5+2) cycloaddition with alkynes and therefore assemble valuable azepine scaffolds (scheme 89). We would explore rhodium catalysts equipped with different type of Cp ligands and, additionally, we aimed to explore the use of electricity as a potential source of oxidative power.

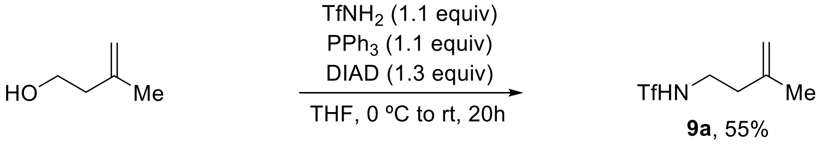


***Scheme 89**. Main goal.*

3. Results and discussion

3.1 Exploration of reaction conditions

To evaluate the feasibility of the desired annulation, we made the model substrate **9a** with a *N*-triflyl moiety. Its synthesis was accomplished in one step, via Mitsunobu reaction,[141] from the corresponding commercially available alcohol (scheme 90).



Scheme 90. *Synthesis of model homoallylamine* ***9a****.*

We evaluated the reactivity of this substrate (1 equiv) with diphenylacetylene (1 equiv), in presence of $[Cp^*RhCl_2]_2$ (5 mol%) as catalyst and $Cu(OAc)_2 \cdot H_2O$ (0.5 equiv) as oxidant in THF at 70 °C (table 4, entry 1). In this initial experiment we detected traces of the adduct by GC-MS, but not enough to be isolated, however conversions of the starting homoallylamide were relatively high, up to 40%, indicating some decomposition of the substrate in reaction media. We then proceed to test other solvents, without any improvement in yield (table 4, entries 2-3). At this point, we increased the amount of copper and, also, we thought in the possibility of employing Cs_2CO_3 as additive, considering its beneficial role in related C-H functionalizations.[86a,86d] However, again, only traces of the product were obtained (table 4, entry 4), with even higher decomposition of the starting material, with conversions around 60%.

We then moved to other alkynes. Remarkably, with 3-hexyne we obtained a 20% yield of the desired (5+2) cycloadduct with a 56% conversion (table 4, entry 5). However, despite these high conversions, the TLC of the reaction was clean, and we only isolated the desired product. Increasing the temperature to 100 °C, we observed full conversion, but a worst yield (table 4, entry 6). Using Rh reagents with other Cp ligands, as well as iridium or cobalt catalysis, we couldn't detect the desired cycloadduct, despite we observed comparable values of conversion (table 4, entry 7-11).

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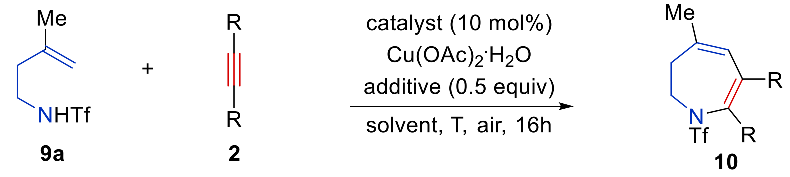
[141] For a comprehensive overview of the Mitsunobu reaction, see: But, T. Y. S.; Toy, P. H. *Chem. Asian J.* **2007**, *2*, 1340-1355.

Table 4. *Initial screening of reaction conditions.*[a]



	R	Catalyst	Equiv [Cu^{II}]	Additive	Solvent (T)	10 (%)
1	Ph	[Cp*RhCl$_2$]$_2$	0.5	-	THF (70 °C)	<5
2	Ph	[Cp*RhCl$_2$]$_2$	0.5	-	Dioxane (100 °C)	<5
3	Ph	[Cp*RhCl$_2$]$_2$	0.5	-	*t*AmOH (100 °C)	0
4	Ph	[Cp*RhCl$_2$]$_2$	2	Cs_2CO_3	THF (70 °C)	<5
5	Et	[Cp*RhCl$_2$]$_2$	2	Cs_2CO_3	THF (70 °C)	20
6	Et	[Cp*RhCl$_2$]$_2$	2	Cs_2CO_3	THF (100 °C)	10
7	Et	[Cp*Rh(MeCN)$_3$] (SbF$_6$)$_2$	2	Cs_2CO_3	THF (70 °C)	12
8	Et	[Cp^{E}RhCl$_2$]$_2$	2	Cs_2CO_3	THF (70 °C)	<5
9	Et	[Cp^{ipr}RhCl$_2$]$_2$	2	Cs_2CO_3	THF (70 °C)	<5
10	Et	[Cp*IrCl$_2$]$_2$	2	Cs_2CO_3	THF (70 °C)	0
11	Et	[Cp*CoI$_2$]$_2$	2	Cs_2CO_3	THF (70 °C)	0

[a] Reaction conditions: Homoallyltriflamide (0.1 mmol), alkyne (0.1 mmol), solvent (1.1 mL).

We then checked other parameters starting from the conditions that gave the best results (table 5). Increasing the amount of the rhodium catalyst didn't lead to better yields (table 5, entry 2) and the presence of additives like amino acids or quinolines, usually beneficial in palladium-catalyzed reactions, didn't give good results (table 5, entries 3-4).[142,143] We also tried to saturate the reaction media with CO, but again, we didn't observe relevant results (table 5, entries 5). The use of other bases than Cs_2CO_3 didn't bring any improvement (table 5, entries 6-8 and 11). However, the employment of silver carbonate as additive afforded a slightly better yield, perhaps by favoring the oxidative processes, but, unfortunately, higher amounts of this silver salt were not effective (table 5, entries 8-10). In all cases, conversions were reasonably high (between 50-70%), suggesting the sensitivity of the substrate to decomposition pathways under reaction conditions.

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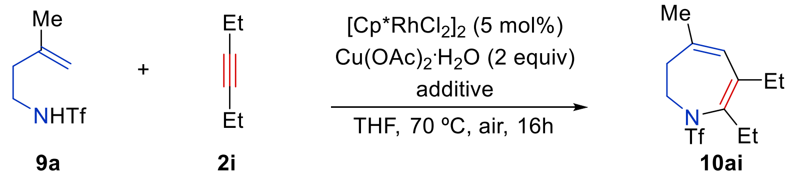
[142] For selected examples of the use of amino acids with rhodium catalyst, see: (a) Kang, Y.-S.; Zhang, P.; Li, M.-Y.; Chen, Y.-K.; Xu, H.-J.; Zhao, J.; Sun, W.-Y.; Yu, J.-Q.; Lu, Y. *Angew. Chem. Int. Ed.* **2019**, *58*, 9099-9103. (b) Wang, H.-W.; Qiao, Y.-H.; Wu, J.-X.; Wang, Q.-P.; Tian, M.-X.; Li, Y.-F.; Yao, Q.-X.; Li, D.-C.; Dou, J.-M.; Lu, Y. *Org. Lett.* **2021**, *23*, 656-662.

[143] For selected examples of the use of quinolines with rhodium catalyst, see: (a) Wang, H.-W.; Lu, Y.; Zhang, B.; He, J.; Xu, H.-J.; Kang, Y.-S.; Sun, W.-Y.; Yu, J.-Q, *Angew. Chem. Int. Ed.* **2017**, *56*, 7449-7453. (b) Zhang, P.; Chang, W.; Kang, Y.-S.; Zhao, W.; Cui, P.-P.; Liang, Y.; Sun, W.-Y.; Lu, Y. *Org. Lett.* **2020**, *22*, 9462-9467.

***Table 5.** Screening of additives.*[a]

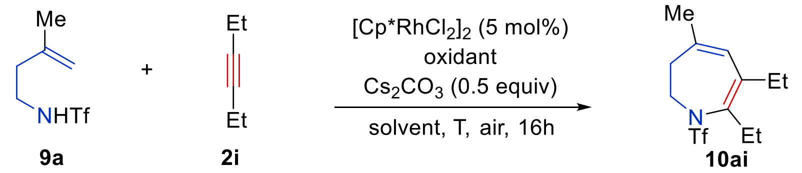


	Additive	Derivation from above conditions	**10ai** (%)
1	Cs_2CO_3 (0.5 equiv)	-	20
2	Cs_2CO_3 (0.5 equiv)	15 mol% $[Cp^*RhCl_2]_2$	20
3	Cs_2CO_3 (0.5 equiv)	Boc-Phe-OH (10 mol%) added	10
4	Cs_2CO_3 (0.5 equiv)	Li-Yu Quinoline (10 mol%) added	12
5	Cs_2CO_3 (0.5 equiv)	CO balloon	0
6	CsOPiv (1 equiv)	-	23
7	CsOAc (1 equiv)	-	18
8	Na_2CO_3 (1 equiv)	-	12
9	Ag_2CO_3 (1 equiv)	-	25
10	Ag_2CO_3 (2 equiv)	-	22
11	Et_3N (1 equiv)	-	10

[a] Reaction conditions: Homoallyltriflamide (0.1 mmol), alkyne (0.1 mmol), solvent (1.1 mL). Yields by internal standard.

After these unsuccessful attempts to improve the reaction efficiency, we proceed to further evaluate additional parameters such as the oxidant or the solvent (table 6). Regarding the oxidants, we tried different copper salts, as well as manganese and silver acetates or even organic oxidants, but the yields were worse than 20% in all cases (table 6, entries 2-6). This screening of oxidants revealed that the decomposition of the homoallylamide partner was clearly influenced by the type of oxidant. In fact, using $Mn(OAc)_3$ instead of $Cu(OAc)_2$, conversions dropped to values close to 15%. Regarding the solvents, only acetonitrile was effective, leading to a quite similar reaction efficiency than THF, although with similar values of conversion (table 6, entries 7-11).

Table 6. *Screening of oxidants and solvents.*[a]



	Oxidant	**Solvent** (T)	**10ai** (%)
1	$Cu(OAc)_2 \cdot H_2O$ (2 equiv)	THF (70 °C)	20
2	$Cu(OAc)_2 \cdot H_2O$ (4 equiv)	THF (70 °C)	13
3	$Cu(acac)_2 \cdot H_2O$ (2 equiv)	THF (70 °C)	8
4	$Mn(OAc)_3 \cdot 2H_2O$ (2 equiv)	THF (70 °C)	13
5	AgOAc (2 equiv)	THF (70 °C)	16
6	$PhI(OAc)_2$ (2 equiv)	THF (70 °C)	0
7	$Cu(OAc)_2 \cdot H_2O$ (2 equiv)	Toluene (100 °C)	10
8	$Cu(OAc)_2 \cdot H_2O$ (2 equiv)	HFIP (60 °C)	0
9	$Cu(OAc)_2 \cdot H_2O$ (2 equiv)	MeCN (80 °C)	17
10	$Cu(OAc)_2 \cdot H_2O$ (2 equiv)	$CHCl_3$ (70 °C)	<5
11	$Cu(OAc)_2 \cdot H_2O$ (2 equiv)	DMSO (120 °C)	<5

[a] Reaction conditions: Homoallyltriflamide (0.1 mmol), alkyne (0.1 mmol), solvent (1.1 mL). Yields by internal standard.

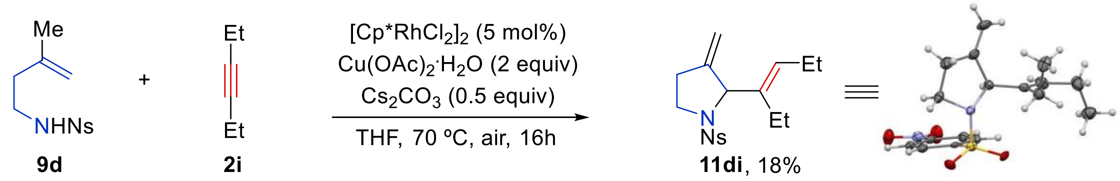
In addition to all these failed efforts, other experiments using more equivalents of amine and alkyne, or with slow addition of any of the substrates, were also unsuccessful.

At this point, we thought that, probably, our initial model substrate could not be the best choice, and we decided to explore the viability of performing the annulation reaction with other related precursors (figure 9). However, when substrate **9b** was submitted to the optimal reaction conditions we observed decomposition, and only traces of product by GC-MS. When we employed a substrate without substitution in the internal position of the alkene, **9c**, we observed a relatively rapid decomposition.

9b **9c**

Figure 9. *Failed substrates.*

Our last attempts to improve the reaction efficiency consisted of the substitution of the *N*-triflyl moiety by a nosyl group. Curiously, when we submitted this new substrate to standard conditions, the NMR spectra did not match with the azepine scaffold and, after X-Ray diffraction, we could determine that the major product was a pyrrolidine, analog to the indoline scaffold of the aromatic precursos,[126] although, in this case, with a Rh catalyst featuring a Cp* instead of a Cp^E ligand (scheme 91).



Scheme 91. *Assembly of pyrrolidines through a Rh-catalyzed C-H annulation.*

This initial experiment afforded a 18% yield of the adduct. We made some additional experiments to improve this yield, specially focusing our attention on the rhodium catalyst, but, unfortunately, we didn't get better results. Nonetheless, the reaction is interesting, and deserves a deeper investigation.

3.2 Reactivity attempts using an electrochemical undivided cell

Owing to the inability to increase yields beyond 20% and considering the precedent of Mei with acrylic acids and alkynes, in which they were not able to increase yields with traditional oxidants due to the stability of the complex between the low valent iridium and the product,[140] we decided to examine the reaction using electrochemical oxidation conditions. Toward this end we build a homemade undivided electrochemical cell (pictures indicated in figure 10).

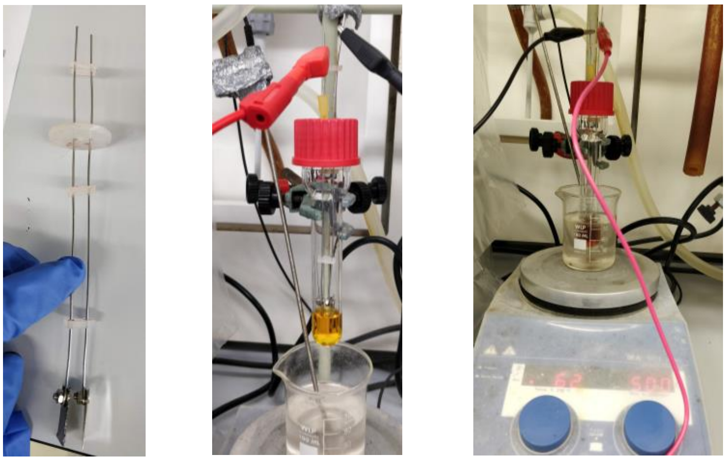
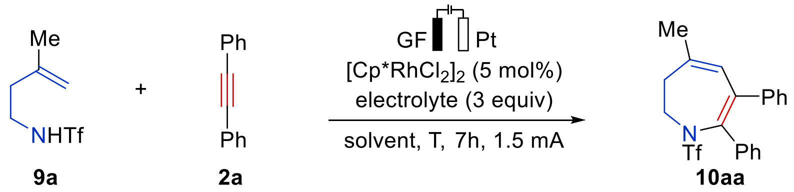


Figure 10. *Homemade electrochemical undivided cell.*

To confirm that the equipment worked correctly, we reproduced one of the Mei reactions and,[139] after obtaining comparable results, we tested this set-up in our transformation. Initially, we evaluated Mei conditions, employing $[Cp^*RhCl_2]_2$ as catalyst, $n$$Bu_4NOAc$ as electrolyte and MeOH as solvent, in presence of graphite and platinum electrodes with a CC (constant current) of 1.5 mA (table 7, entry 1). Unfortunately, only degradation of the amide was observed, also switching from rhodium to an iridium catalyst, $[Cp^*IrCl_2]_2$ (table 7, entry 2). We moved to other solvents and, importantly, employing a tAmOH/H_2O mixture, commonly used by Ackermann's group, we detected a small amount of the desired azepine scaffold (table 7, entry 4). Then, we tested other electrolytes, such as pivalates, obtaining comparable results (table 7, entries 5-6). Other attempts to obtain higher yields modifying some parameters like temperature, current or electrode materials were unsuccessful (table 7, entries 7-8).

Table 7. *Screening of conditions using electricity as oxidant.*[a]

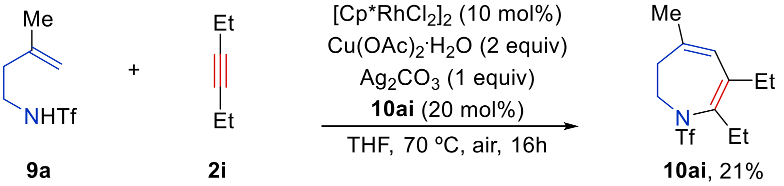


	Electrolyte	**Solvent** (T)	**10aa** (%)
1	*n*Bu$_4$NOAc	MeOH (60 °C)	0
2	*n*Bu$_4$NOAc	MeOH (60 °C)	0[b]
3	*n*Bu$_4$NOAc	MeCN (70 °C)	0
4	*n*Bu$_4$NOAc	*t*AmOH/H$_2$O 3:1 (80 °C)	8
5	CsOPiv	*t*AmOH/H$_2$O 3:1 (80 °C)	10
6	NaOPiv	*t*AmOH/H$_2$O 3:1 (80 °C)	5
7	CsOPiv	*t*AmOH/H$_2$O 3:1 (100 °C)	10
8	CsOPiv[b]	*t*AmOH/H$_2$O 3:1 (80 °C)	8[c]
9	CsOPiv	TFE (70 °C)	0
10	CsOPiv	DMF (120 °C)	0

[a] Reaction conditions: Homoallyltriflamide (0.25 mmol), alkyne (0.17 mmol), solvent (2.4 mL). Yields by internal standard. [b] [Cp*IrCl$_2$]$_2$ as catalyst. [c] 4mA.

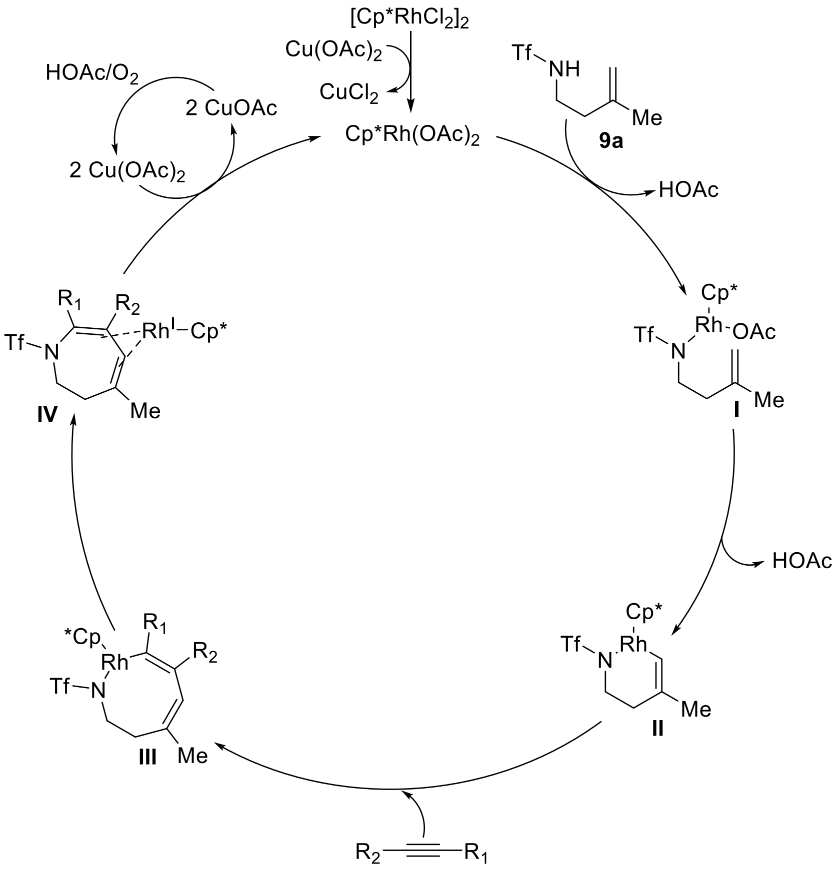
3.3 Mechanistic studies

In order to gain insights into the reaction mechanism, that could help in devising better reaction conditions, we made several experiments. For example, we carried out the reaction introducing a 20 mol% of the product in reaction media, to check whether it could inhibit the process (scheme 92). After 16h, only a 21% yield of the cycloadduct was isolated, the same amount that we had added, which is consistent with the inhibition pathway. However, inexplicably, when the cycloaddition experiment was carried out employing large quantities of the rhodium catalyst, and even in stoichiometric experiments, the yields were also similar to the ones obtained under catalytic conditions, suggesting that the reoxidation (regeneration of the Rh(III) catalyst) is not the problem. It seems that the product is somewhat inactivating the annulation process, but it is still no clear how.



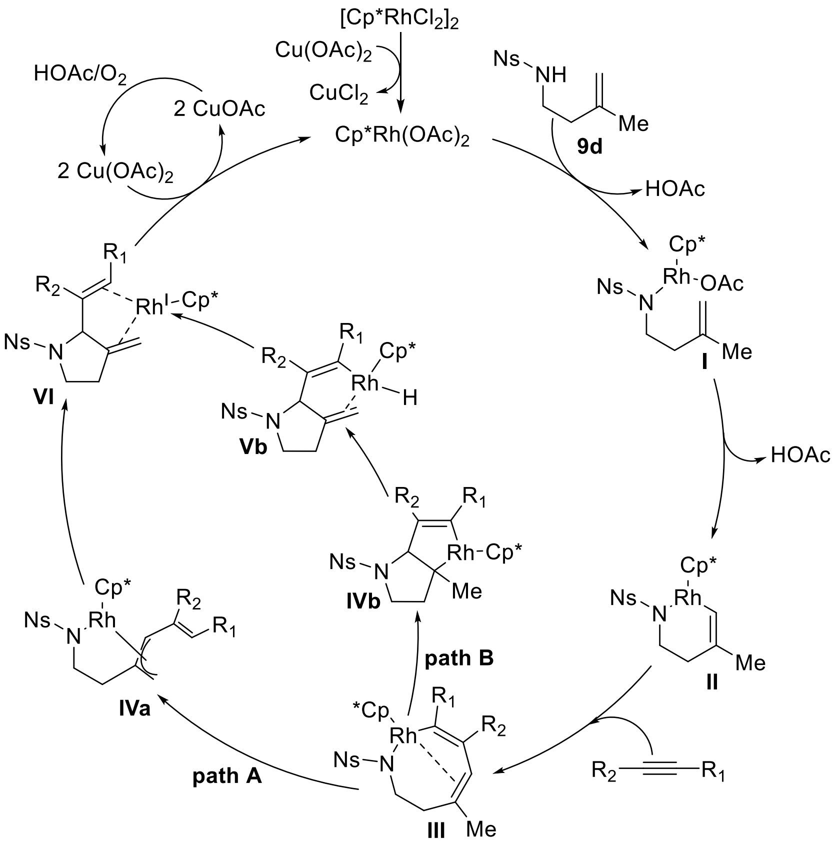
Scheme 94. *Experiment of product inhibition.*

Despite the annulation is low yielding, we can propose a mechanistic hypothesis (scheme 95). The reaction may start with a ligand exchange between the homoallylic *N*-triflyl amide and an acetate of the rhodium catalyst. Then, the C-H activation step takes place, leading to the six-membered rhodacycle **II**, which evolves through migratory insertion to the eight-membered rhodacycle **III**. Finally, reductive elimination from this intermediate affords the azepine scaffold coordinated to the resulting Rh(I), that should be oxidized to start a new catalytic cycle.



Scheme 95. Mechanistic hypothesis for the synthesis of azepines.

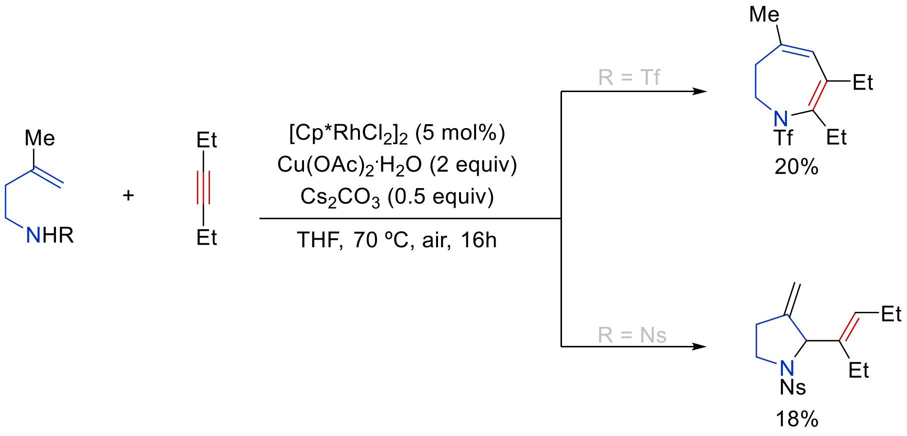
With regard to the mechanism for the assembly of pyrrolidines (scheme 96), it likely starts in an analogous way until the formation of the eight-membered rhodacycle **III**. Then, this reaction could proceed through two different pathways. The first alternative (**path A**) consists, in agreement with the indoline proposal,[126] in a 1,5-hydrogen shift with concomitant rhodium migration to give the π-allyl intermediate **IVa**, that affords the corresponding adduct after reductive elimination. The other alternative (**path B**), consistent with the DFT calculations by the Liu, Zhang and Lu group,[127] is based on an additional migratory insertion that leads to the bicyclic structure **IVb**. This intermediate undergoes a β-hydride elimination process to yield the Rh-hydride species **Vb,** which evolves to the product after final C-H reductive elimination. As can be observed in the scheme, both pathways conclude with the formation of a stable Rh(I) complex, **VI**, that should be able to start a new catalytic cycle after oxidation and release of the functionalized pyrrolidine. However, our results seem to indicate that this step does not occur efficiently.



Scheme 96. *Mechanistic hypothesis for the synthesis of pyrrolidines.*

4. Conclusions

In summary, we have discovered two novel annulations involving the reaction between homoallylic amines and alkynes, catalyzed by rhodium(III) species (scheme 97). Unfortunately, despite our methodological efforts, the best results led to the formation of the cycloadducts in only 20% yield. We have also examined the use of an undivided electrochemical cell in order to improve the reaction efficiency, however, no successful results have been achieved until now.



Scheme 97. *Rh(III)-catalyzed divergent synthesis of azepines and pyrrolidines.*

While some experiment suggested that the product could be inhibiting the catalysts, it is not clear that this is reason behind the observed low yields. My work has confirmed that the cycloaddition is feasible, but very challenging, and requires further investigation.

Chapter III – Palladium-catalyzed formal (4+2) cycloaddition between alkyl amides and dienes initiated by the activation of C(sp^3)-H bonds

Chapter adapted from:
Cendón, B.[a]; Font, M.[a]; Mascareñas, J. L.[a]*; Gulías, M.[a]* *ACS Catal.* **2020**, *10*, 3425-3430.

[a] 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)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1. Introduction

1.1 Pd-catalyzed activation of $C(sp^3)$-H bonds in alkyl amides

The selective functionalization of $C(sp^3)$-H bonds using metal catalysis represents a challenging but highly prominent objective in modern organic synthesis.[65] This functionalization depends on the presence of appropriate directing groups in the molecule that can accelerate the activation and control the selectivity.[144] Amides can work as directing groups in these processes, despite their weak metal-coordination ability.[145] These amides are usually synthesized from the corresponding carboxylic acids in an easy way and can be equipped with different protecting/directing groups. In most of the cases reported, amide-directed $C(sp^3)$-H activation reactions allow the functionalization of the β-position in the alkyl chain, as they involve the formation of highly favored five-membered metallacycles. Indeed, only a few examples of γ $C(sp^3)$-H activation have been reported until the date.[71a,146]

The research group of Jin-Quan Yu has widely explored the reactivity of alkylamides to construct $C(sp^3)$-$C(sp^2)$, $C(sp^3)$-$C(sp)$, $C(sp^3)$-$C(sp^3)$ or $C(sp^3)$-X bonds. Regarding the formation of $C(sp^3)$-$C(sp^2)$ bonds, the greatest number of examples consist in arylation reactions, already shown in the introduction (page 24).[70b,74-76,132a,147] Olefination reactions have also been eventually performed. For example, the enantioselective vinylation of cyclobutylamides using alkenyl iodides as coupling partners was successfully achieved in 2018 employing palladium catalysts and chiral mono-*N*-protected aminomethyl oxazoline (MPAO) ligands (scheme 98, eq 1).[147b]

Additionally, an alkynylation reaction for the construction of $C(sp^3)$-$C(sp)$ bonds was also introduced recently. The reaction, that involves a Pd^{II}/Pd^{IV} catalytic cycle, and requires the use of pyridine or quinoline-type of ligands to obtain some reactivity (scheme 98, eq 2).[148,149] Importantly, this reaction is not limited to the activation of methyl C-H bonds, it can be also applied to functionalize selected methylene C-H bonds.

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[144] (a) Zhang, Q.; Shi, B.-F. *Chem. Sci.* **2021**, *12*, 841-852. (b) Talukdar, K.; Shah, T. A.; Sarkar, T.; Roy, S.; Maharana, P. K.; Punniyamurthy, T. *Chem. Commun.* **2021**, *57*, 13221-13233.

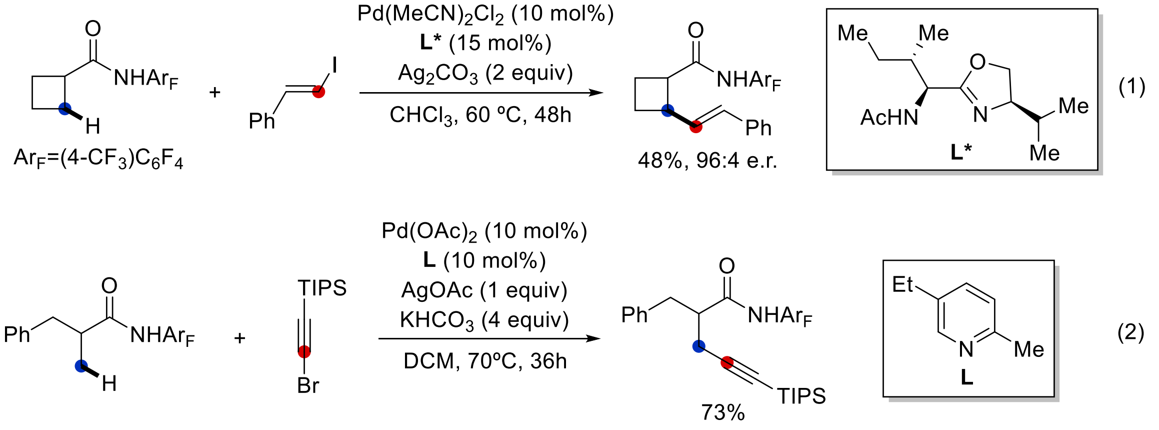
[145] (a) Zhu, R.-Y.; Farmer, M. E.; Chen, Y.-Q.; Yu, J.-Q. *Angew. Chem. Int. Ed.* **2016**, *55*, 10578-10599. (b) Zheng, Q.; Liu, C.-F.; Chen, J.; Rao, G.-W. *Adv. Synth. Catal.* **2020**, *362*, 1406-1446.

[146] (a) Li, S.; Zhu, R.-Y.; Xiao, K.-J.; Yu, J.-Q. *Angew. Chem. Int. Ed.* **2016**, *55*, 4317-4321. (c) Thirimurtulu, N.; Khan, S.; Maity, S.; Volla, C. M. R.; Maiti, D. *Chem. Commun.* **2017**, *53*, 12457-12460.

[147] For additional examples, see: (a) Wu, Q.-F.; Wang, X.-B.; Shen, P.-X.; Yu, J.-Q. *ACS Catal.* **2018**, *8*, 2577-2581. (b) Andrä, M. S.; Schifferer, L.; Pollok, C. H.; Merten, C.; Goossen, L. J.; Yu, J.-Q. *Chem. Eur. J.* **2019**, *25*, 8503-8507.

[148] Fu, H.; Shen, P.-X.; He, J.; Zhang, F.; Li, S.; Wang, P.; Liu, T.; Yu, J.-Q. *Angew. Chem. Int. Ed.* **2017**, *56*, 1873-1876.

[149] For previous examples, see: (a) Ano, Y.; Tobisu, M.; Chatani, N. *J. Am. Chem. Soc.* **2011**, *133*, 12984-12986. (b) He, J.; Wasa, M.; Chan, K. S. L.; Yu, J.-Q. *J. Am. Chem. Soc.* **2013**, *135*, 3387-3390.



Scheme 98. *Amide-directed formation of C(sp^3)-C(sp^2) and C(sp^3)-C(sp) bonds.*

Additionally, the formation of C(sp^3)-C(sp^3) bonds is limited to an alkylation reaction that was previously commented in page 24.[73]

With regard to the formation of C(sp^3)-X bonds we can distinguish between three different types of transformations: borylations, halogenations and aminations. In 2016, Yu described a palladium-promoted borylation initiated by the activation of C(sp^3)-H bonds in substrates containing α-quaternary and tertiary centers (scheme 99, eq 1).[150,151] Later, he also developed an enantioselective borylation, using cyclobutyl ketones, changing the electron-rich quinoline ligand for a chiral bidentate oxazoline-type APAO ligand.[68a] In 2017 it was reported a protocol for selective bromination and iodation of similar substrates, however, in this case, the reaction was only applied to the activation of methyl C-H bonds (scheme 99, eq 2).[152,153,154]

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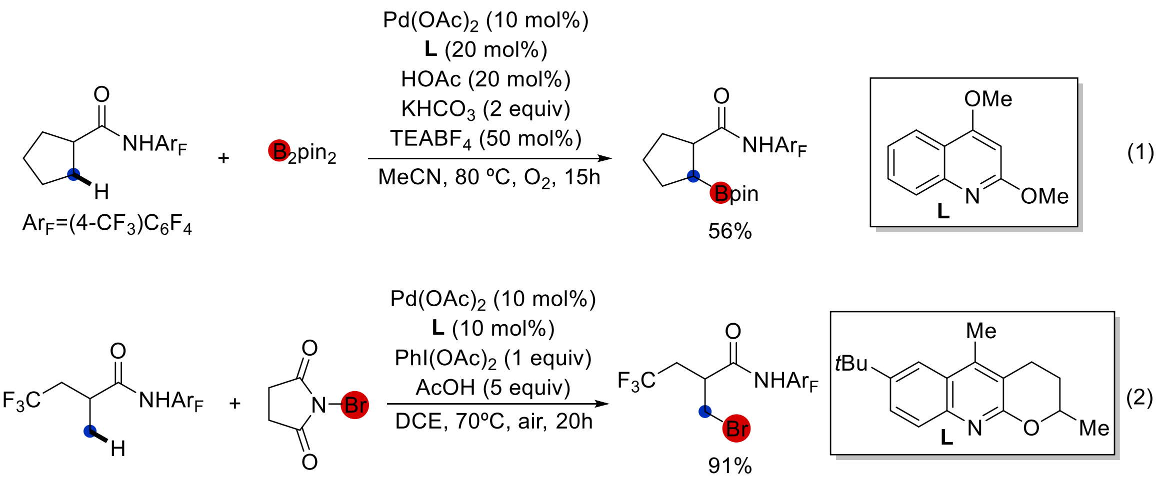
[150] He, Jian; Jiang, H.; Takise, R.; Zhu, R.-Y.; Chen, G.; Dai, H.-X.; Dhar, T. G. M.; Shi, J.; Zhang, H.; Cheng, P. T. W.; Yu, J.-Q. *Angew. Chem. Int. Ed.* **2016**, *55*, 785-789.

[151] For a previous C(sp^3)-H borylation using a bidentate directing group, see: Zhang, L.-S.; Chen, G.; Wang, X.; Guo, Q.-Y.; Zhang, X.-S.; Pan, F.; Chen, K.; Shi, Z.-J. *Angew. Chem. Int. Ed.* **2014**, *53*, 3899-3903.

[152] Zhu, R.-Y.; Saint-Denis, T. G.; Shao, Y.; He, J.; Sieber, J. D.; Senanayake, C. H.; Yu, J.-Q. *J. Am. Chem. Soc.* **2017**, *139*, 5724-5727.

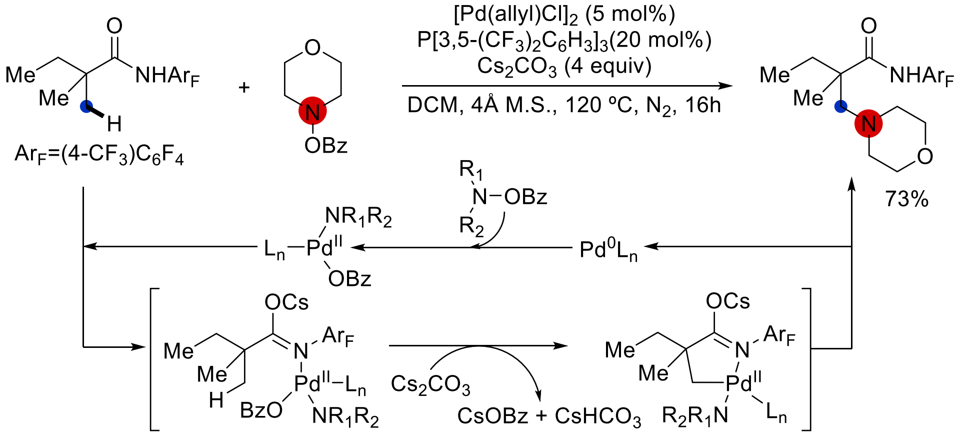
[153] For a previous stereoselective fluorination, see: Zhu, R.-Y.; Tanaka, K.; Li, G.-C.; He, J.; Fu, H.-Y.; Li, S.-H.; Yu, J.-Q. *J. Am. Chem. Soc.* **2015**, *137*, 7067-7070.

[154] For a previous C(sp3)-H halogenation using a bidentate directing group, see: Yang, X.; Sun, Y.; Sun, T.-Y.; Rao, Y. *Chem. Commun.* **2016**, *52*, 6423-6426.



***Scheme 99**. Borylation and halogenation reactions initiated by the activation of C(sp^3)-H bonds.*

Finally, as last example of the formation of appealing C(sp^3)-X bonds, an amination protocol using electron-deficient phosphine ligands was also developed by Yu (scheme 100).[155] Nevertheless, in this case, the reaction is clearly more restricted with regard to the amide substrate. It only works with substrates containing α-quaternary centers and it is exclusively applied to the activation of methyl C-H bonds. With regard to the mechanistic proposal, the transformation involves a Pd^0/Pd^{II} catalytic cycle and, interestingly, the authors suggest a cesium induced, imidate-directed C-H activation process, as can be visualized in scheme 100.



***Scheme 100.** Pd-catalyzed amination of C(sp^3)-H bonds.*

Other type of intriguing amide-directed reactions initiated by the activation of C(sp^3)-H bonds has been associated to the assembly of nitrogen heterocycles. These transformations are especially relevant due to the prevalence of these structures in FDA-approved drugs.[80] For instance, an efficient entry to succinimides is described in scheme 101. This palladium-catalyzed carbonylation protocol can be used for the activation of methyl and cyclopropyl methylene C-H bonds.[156]

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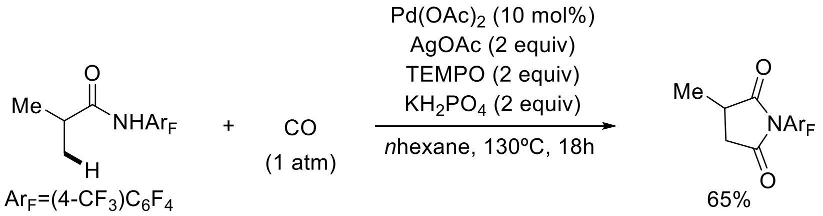
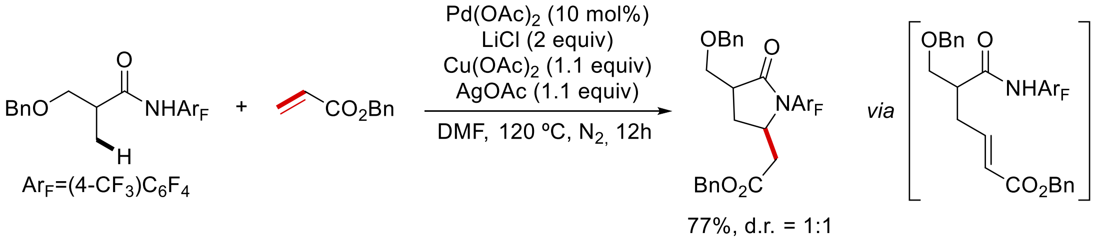
[155] He, J.; Shigenari, T.; Yu, J.-Q. *Angew. Chem. Int. Ed.* **2015**, *54*, 6545-6549.
[156] Yoo, E. J.; Wasa, M.; Yu, J.-Q. *J. Am. Chem. Soc.* **2010**, *132*, 17378-17380.



Scheme 101. *Pd(II)-catalyzed carbonylation of C(sp^3)-H bonds.*

Another formal (4+1) annulation consists in the reaction of alkyl amides and acrylates, and involves an olefination followed by an intramolecular Michael-type of addition (scheme 102).[157] Remarkable, this protocol is also useful for the activation of methylene C-H bonds using cyclopropyl amides as substrates.



Scheme 102. *Pd(II)-catalyzed olefination of C(sp^3)-H bonds and subsequent cyclization.*

It should be noted that all these reactions are directed by an amide bearing an electron withdrawing perfluorinated aromatic ring, that is crucial for their success. This substituent increases the acidity of the amide, and generates a weakly coordinating directing group, that is highly relevant for the catalytic cycle. Moreover, the *ortho* positions of the aromatic ring in Ar$_F$, are blocked with the introduction of the fluorine atoms, which avoids possible secondary C-H activations.

Moreover, the groups of Liu and He and Chen have recently described a smart approach to β-lactams using amides with bidentate chelating groups (scheme 103).[158,159] The reaction, that involves a Pd^{II}/Pd^{IV} catalytic cycle, consists on an intramolecular amidation with a chiral BINOL derivative as additive.[160] The oxidant chosen for this reaction, an unconventional aryl iodide, is key to control the possible reductive elimination pathways and, consequently, achieve the desired C-N reductive elimination. However, the reaction requires an aromatic substituent at β-position to proceed.

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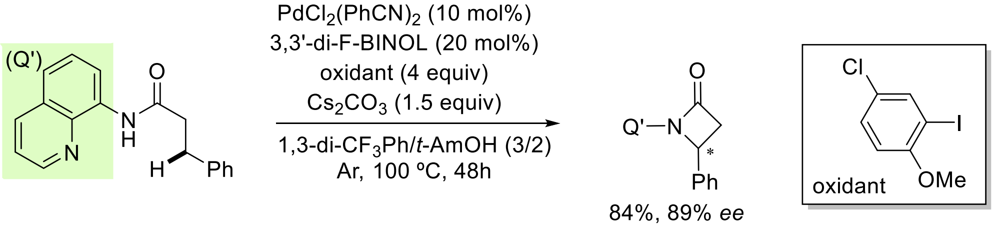
[157] Wasa, M.; Engle, K. M.; Yu, J.-Q. *J. Am. Chem. Soc.* **2010**, *132*, 3680-3681.

[158] Tong, H.-R.; Zheng, W.; Lv, X.; He, G.; Liu, P.; Chen, G. *ACS Catal.* **2020**, *10*, 114-120.

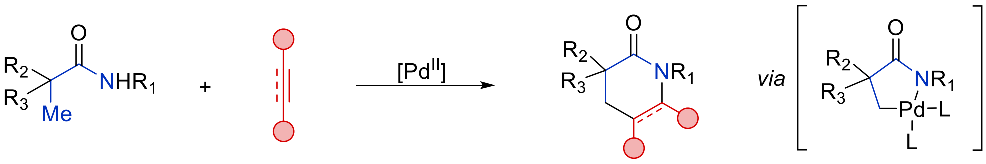
[159] For a previous racemic version of the reaction, see: Sun, W.-W.; Cao, P.; Mei, R.-Q.; Li, Y.; Ma, Y.-L.; Wu, B. *Org. Lett.* **2014**, *16*, 480-483.

[160] For selected examples of C-H activation using a 3,3'-di-F-BINOL ligand, see: (a) Han, Y.-Q.; Ding, Y.; Zhou, T.; Yan, S.-Y.; Song, H.; Shi, B.-F. *J. Am. Chem. Soc.* **2019**, *141*, 4558-4563. (b) Ding, Y.; Han, Y.-Q.; Wu, L.-S.; Zhou, T.; Yao, Q.-J.; Feng, Y.-L.; Li, Y.; Kong, K.-X.; Shi, B.-F. *Angew. Chem. Int. Ed.* **2020**, *59*, 14060-14064.



Scheme 103. *Pd-catalyzed enantioselective intramolecular amidation.*

Despite these precedents on C-H functionalizations involving the activation of C(sp^3)-H bonds, formal (n+2) cycloadditions initiated by the activation of these bonds were unknown.[95] Therefore, we considered relevant to explore the viability of performing annulation reactions employing alkyl amides as substrates, and palladium catalysts (scheme 104). While at the outset the reaction would be explored with different type of unsaturated partners, including allenes, we were specially attracted by the possibility of using dienes, trying to take advantage of the "diene effect" (vide infra).



Scheme 104. *Initial hypothesis.*

1.2 Dienes as partners in oxidative annulations initiated by the activation of C-H bonds

1,3-Dienes are common 2-carbon partners in transition metal-catalyzed cycloaddition reactions. They possess a unique reactivity associated to the presence of the conjugated extra alkene, which offers an additional binding site for the metal center. It usually stabilizes the species formed after migratory insertion, lowering the energy of this intermediate and favoring the final reductive elimination. These advantages are known as the "diene effect".[161]

Moreover, in contrast with other partners with similar reactivity, like allenes, a considerable number of dienes are inexpensive and commercially available (figure 11) or can be easily synthesized from the corresponding aldehyde. All these characteristics, together with the inherent stability (it is less prone to polymerization than other unsaturated systems), make dienes especially attractive partners to develop new annulations processes.

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[161] Croatt, M. P.; Wender, P. A. *Eur. J. Org. Chem.* **2010**, 19-32.

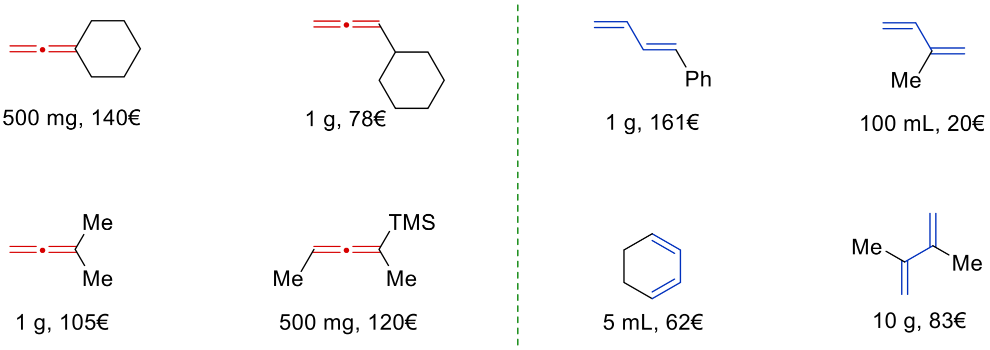
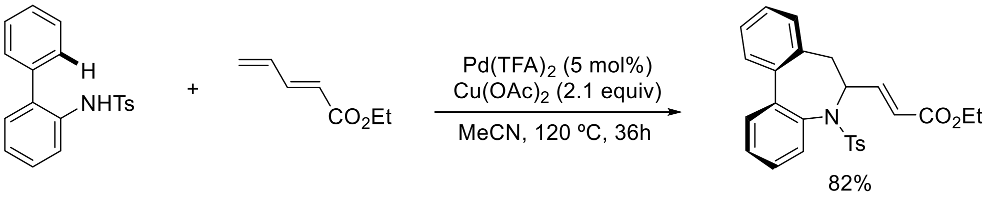


Figure 11. *Price comparison between allenes and dienes in Sigma-Aldrich (03/22).*

Dienes have been sporadically used in oxidative annulations initiated by the activation of C(sp^2)-H bonds. In most of the cases the reactions require an electron withdrawing group or an aromatic substituent attached to the diene, to increase its coordination ability and reactivity. For example, the group of Luan published in 2017 an efficient entry to highly interesting dibenzoazepine skeletons[162] by reaction between *o*-arylanilines and dienes (scheme 105).[163,164]



Scheme 105. *Synthesis of dibenzoazepine skeletons reported by the group of Luan.*

The mechanism for this palladium-catalyzed diastereoselective (5+2) annulation likely starts with the complexation of the palladium(II) species and subsequent sulfonamide-directed C-H activation to form the six-membered palladacycle **I**. Then, coordination of the diene followed by regiospecific migratory insertion leads to the formation of the key π-allylic eight-membered palladacycle **III**. Finally, C-N reductive elimination delivers the expected product together with a Pd(0) species that is reoxidized by the copper salt (scheme 106). Remarkable, the additional binding site provided by the conjugated C-C double bond in intermediate **III** may avoid possible β-hydride elimination processes, which would lead to undesired Heck-type alkenylated byproducts, in agreement with previous reactions with alkenes instead of 1,3-dienes.[165]

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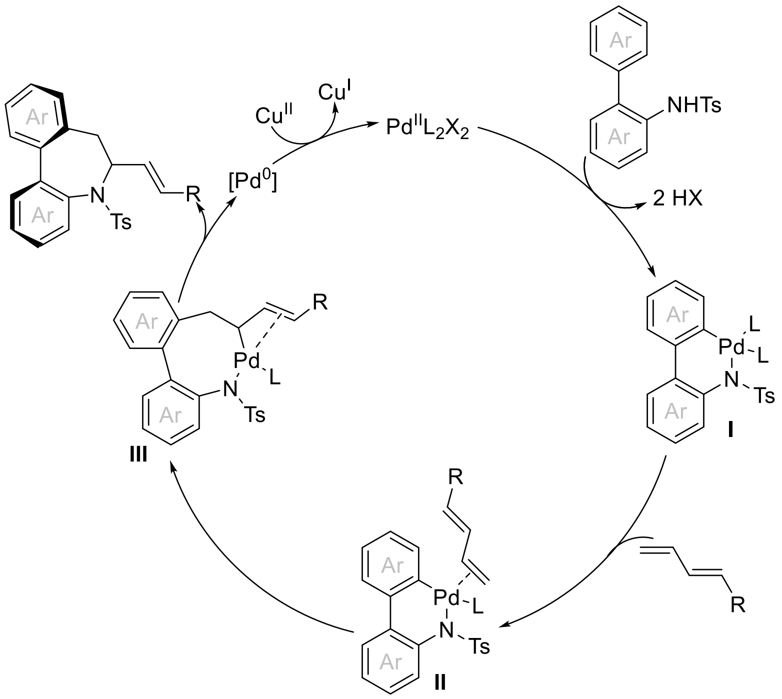
[162] (a) Pegoraro, S.; Lang, M.; Dreker, T.; Kraus, J.; Hamm, S.; Meere, C.; Feurle, J.; Tasler, S.; Prütting, S.; Kuras, Z.; Visan, V.; Grissmer, S. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 2299-2304. (b) Nair, J. S.; Sheikh, T.; Ho, A. L.; Schwartz, G. K. *Anticancer Res*. **2013**, *33*, 1307-1316.

[163] Bai, L.; Wang, Y.; Ge, Y.; Liu, J., Luan, X. *Org. Lett.* **2017**, *19*, 1734-1737.

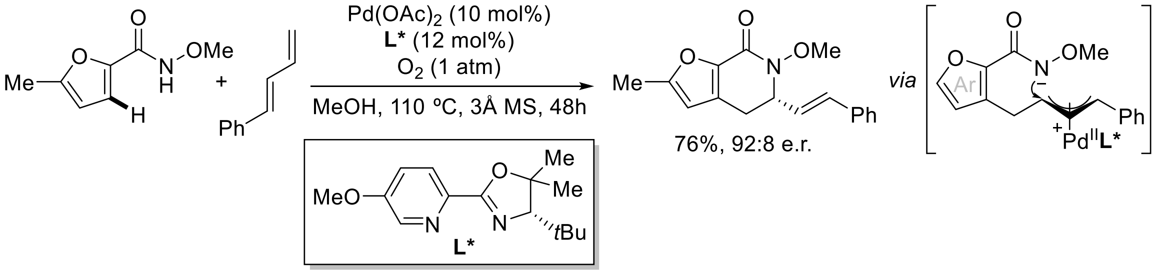
[164] For additional selected examples of the use of dienes in C-H annulations, see: (a) Houlden, C. E.; Baily, C. D.; Ford, J. G.; Gagné, M. R.; Lloyd-Jones, G. C.; Booker-Milburn, K. I. *J. Am. Chem. Soc.* **2008**, *130*, 10066-10067. (b) Zhao, D.; Lied, F.; Glorius, F. *Chem. Sci.* **2014**, *5*, 2869-2873. (c) Khan, I.; Chidipudi, S. R.; Lam, H. W. *Chem. Commun.* **2015**, *51*, 2613-2616. (d) Velasco-Rubio, A.; Varela, J. A.; Saa, C. *Org. Lett.* **2020**, *22*, 3591-3595.

[165] (a) Liu, Y.-Y.; Song, R.-J.; Wu, C.-Y.; Gong, L.-B.; Hu, M.; Wang, Z.-Q.; Xie, Y.-X.; Li, J.-H. *Adv. Synth. Catal.* **2012**, *354*, 347-353. (b) Liang, Z.; Ju, L.; Xie, Y.; Huang, L.; Zhang, Y. *Chem. Eur. J.* **2012**, *18*, 15816-15821.



Scheme 106. *Mechanistic hypothesis for the assembly of dibenzoazepines.*

Another example of the use of dienes in oxidative annulations was recently developed by Han and Gong (scheme 107).[166] This palladium-catalyzed reaction, that is directed by an amide moiety, allows access to a wide range of six-membered chiral lactams under mild conditions. Interestingly, this protocol employs a green oxidant, O_2, and a pyridine-oxazoline bidentate ligand, whose structure is essential to promote reactivity and enantioselectivity.[167] In this reaction, the final cyclization involves the nucleophilic attack of the nitrogen to a pi-allyl intermediate, via an outer-sphere mechanism.



Scheme 107. *Asymmetric oxidative annulation between aromatic amides and 1,3-dienes.*

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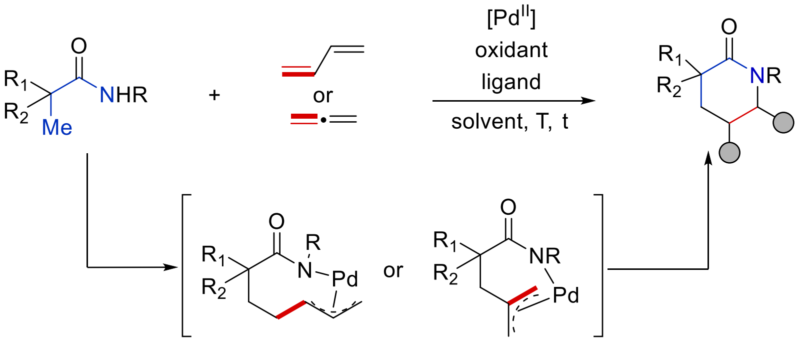
[166] Zhang, T.; Shen, H.-C.; Xu, J.-C.; Fan, T.; Han, Z.-Y.; Gong, L.-Z. *Org. Lett.* **2019**, *21*, 2048-2051.

[167] For a racemic version of the reaction, see: (a) Wrigglesworht, J. W.; Cox, B.; Lloyd-Jones, G. C.; Booker-Milburn, K. I. *Org. Lett.* **2011**, *13*, 5326-5329. (b) Sun, M.; Li, J.; Chen, W.; Wu, H.; Yang, J.; Wang, Z. *Synthesis* **2020**, *52*, 1253-1265.

2. Objectives

As indicated before, the objective of this work is the development of a formal (n+2) oxidative annulation between alkyl amides and unsaturated partners, a type of transformation that had never been investigated.

Considering the palladium-catalyzed olefination reaction between amides and acrylates reported by Yu,[157] we hypothesized that using allenes or dienes as unsaturated partners, it could be possible to avoid the final β-hydride elimination through the formation of a key π-allylic intermediate that could favor the desired reductive elimination (scheme 108).

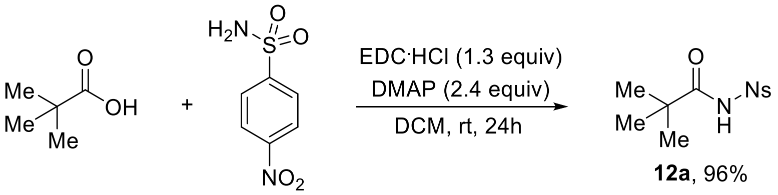


Scheme 108. *Proposed Pd-catalyzed formal (n+2) cycloaddition.*

3. Results and discussion

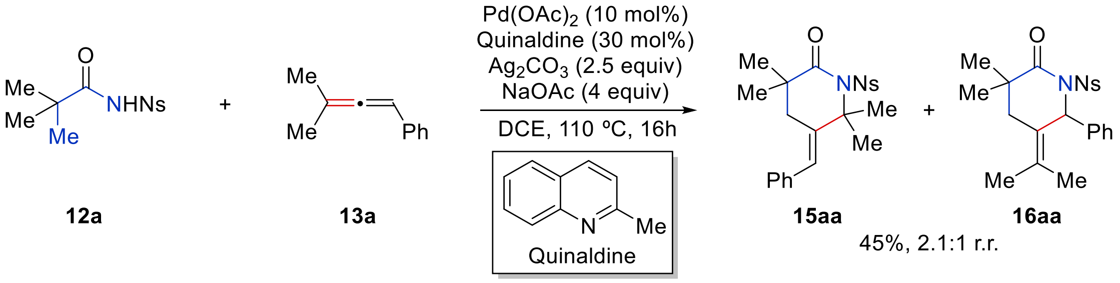
3.1 Exploration of reaction conditions

To examine the possibilities of performing the desired cycloaddition, we first made the nosylated substrate **12a** from commercially available pivalic acid (scheme 109), owing to our previous successful results with this protecting/directing group in the reactions discussed in previous chapters.[168]



Scheme 109. *Synthesis of model substrate* ***12a****.*

Taking into account previous works from the group,[86a, 91, 93] we considered that allenes could be optimal partners for the cycloaddition, by facilitating the formation of π-allyl intermediates, which might be instrumental in favoring reductive elimination instead of undesired *β*-hydride elimination processes. After the initial screening, starting from previously used conditions in related C(sp^3)-H functionalizations,[117d] and testing a wide range of ligands, we found that the desired reaction worked modestly employing trisubstituted allene **13a**, in presence of quinaldine as ligand and silver carbonate as oxidant, in DCE at 110 °C for 16h (scheme 110). However, yields were not as desired, and we were not able to increase these values.



Scheme 110. *Best result obtained with allenes.*

Moreover, using other allenes, yields were clearly worst, observing in all the cases a high decomposition of the allene partner (figure 12).

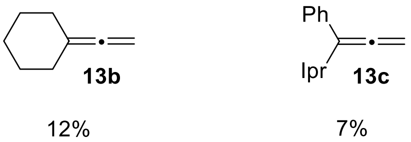


Figure 12. *Results for some representative allenes.*

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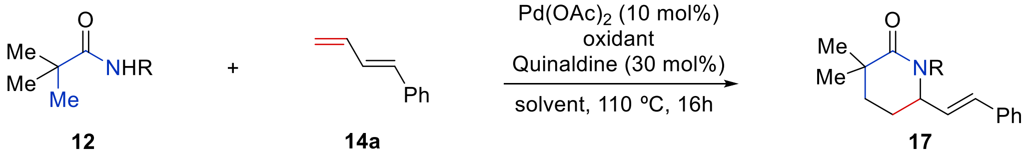
[168] For an additional example of the use of *N*-nosyl amides as directing group, see: Sun, M.; Chen, W.; Xia, X.; Shen, G.; Ma, Y.; Yang, J.; Ding, H.; Wang, Z. *Org Lett.* **2020**, *22*, 3229-3233.

We then decided to change the reaction partner, and test dienes instead of allenes, as they would also provide for the formation of π-allyl intermediates, but should be much more stable under the reaction conditions.

We selected commercially available *trans*-1-phenyl-1,3-butadiene (**14a**) as model diene, and we proceeded to screen several reaction conditions in order to maximize conversion and yield. We tested different substituents in the amide moiety, oxidants, solvents or ligands and, after an intense screening, we were pleased to find that the desired cycloadduct could be obtained in a 99% yield using *N*-nosyl pivalamide (1 equiv), 2 equivalents of diene, 10 mol% of $Pd(OAc)_2$, 0.5 equivalents of $Cu(OAc)_2{\cdot}H_2O$ and 30 mol% of quinaldine (table 8, entry 1). Its use as ligand came after the screening of many other alternatives as can be viewed later.

Table 8. *Screening of reaction conditions.*[a]



	R	Solvent	Oxidant	Additive	**17** (%)
1	Ns	DCE	$Cu(OAc)_2{\cdot}H_2O^b$	-	99
2	Ts	DCE	$Cu(OAc)_2{\cdot}H_2O^b$	-	73
3	Tf	DCE	$Cu(OAc)_2{\cdot}H_2O^b$	-	0
4	Ar_F	DCE	$Cu(OAc)_2{\cdot}H_2O^b$	-	16
5	AQ	DCE	$Cu(OAc)_2{\cdot}H_2O^b$	-	0
6	Ns	DCE	$Ag_2CO_3^c$	NaOAc (4 equiv)	46
7	Ns	DCE	$Ag_2CO_3^c$	NaOAc (4 equiv) + TFA (2 equiv)	80
8	Ns	HFIP	$Cu(OAc)_2{\cdot}H_2O^b$	-	0
9	Ns	Toluene	$Cu(OAc)_2{\cdot}H_2O^b$	-	28
10	Ns	TFT	$Cu(OAc)_2{\cdot}H_2O^b$	-	39
11	Ns	Dioxane	$Cu(OAc)_2{\cdot}H_2O^b$	-	39

[a] Reaction conditions: Alkyl amide (0.2 mmol), diene (0.4 mmol), solvent (2 mL). [b] 0.5 equiv. [c] 2.5 equiv. Ar_F = $(4\text{-}CF_3)C_6F_4$. AQ = aminoquinoline. TFT = Trifluotoluene.

As can be deduced from the table, changing the substituent at the nitrogen from nosyl to tosyl leads to a lower reaction yield (table 8, entry 2), associated with a lower conversion. Most surprisingly, substrates with a perfluorinated aromatic ring at the nitrogen, widely used by Jin-Quan Yu, or with the bidentate aminoquinoline developed by Daugulis, led to poor results in terms of yield and conversion (table 8, entries 4-5).[169] Also remarkably, when a triflyl moiety was placed at the nitrogen, the reaction failed to produce the expected cycloadduct, but we could isolate the olefination/dehydration product indicated

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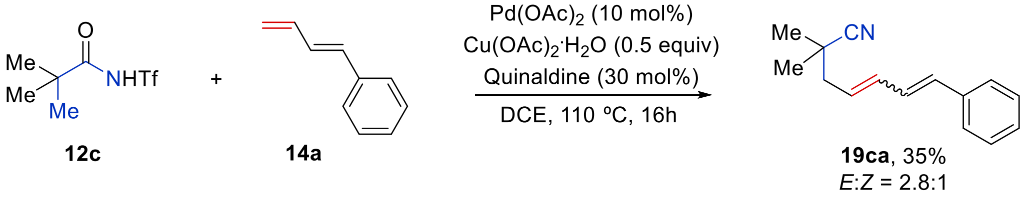
[169] Corbet, M.; De Campo, F. *Angew. Chem. Int. Ed.* **2013**, *52*, 9896-9898.

in scheme 111. Despite the yield was moderate (35%), the reaction crude was clean, recovering the rest of the starting material.



Scheme 111. *Reaction of the N-triflyl amide **12c** with diene **14a**.*

The structure of the adduct was confirmed by crystallizing the product resulting from the reaction with a diene bearing a nitro group (figure 13).

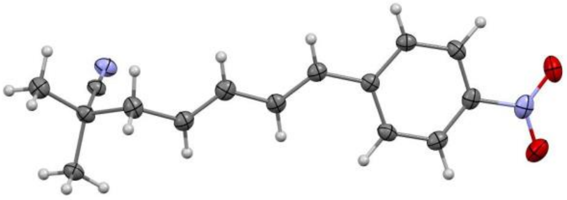


Figure 13. *X-Ray structure of the obtained nitrile.*

We also analyzed the influence of the oxidant in the reaction. With silver carbonate, we observed comparable yields than when using copper acetate, although we needed to use stoichiometric amounts and harsher conditions (table 8, 6-7). Regarding solvents, changing from DCE to others that have been previously used in C-H activation reactions, the reaction efficiency dropped dramatically (table 8, entries 8-11). It should be noted that the rest of the substrate was totally recovered in all cases, while the diene partner decomposed in some of the reaction conditions, like in presence of silver carbonate or in HFIP as solvent.

As commented before, the use of quinaldine as the optimal palladium ligand came after screening a great variety of alternatives (figure 14). The ligand plays a crucial role, as without ligand or with a simple pyridine, only traces of the cycloadduct were detected. Introducing a methyl group in *ortho* resulted in a much better result (61% yield), while adding another methyl group in the other *ortho* position to the pyridine did not increase the efficiency of the transformation. Moreover, replacing these methyl groups by methoxy, in order to modify the electronic characteristics of the ligand, yields dropped.

Changing pyridine by quinoline was beneficial for the reaction, and it was here when we discovered that introducing an *o*-methyl group in the quinoline leads to the best ligand choice. Apparently, this ligand offers the best combination of steric and electronic effects to favor the desired annulation. In fact, other substituents, or additional rings at the quinoline skeleton led to worse results. In addition, yields were also low when the reaction was carried out with other ligands extensively used in C-H activation reactions, like amino acids,[67] APAO [68] or APAQ.[75-77]

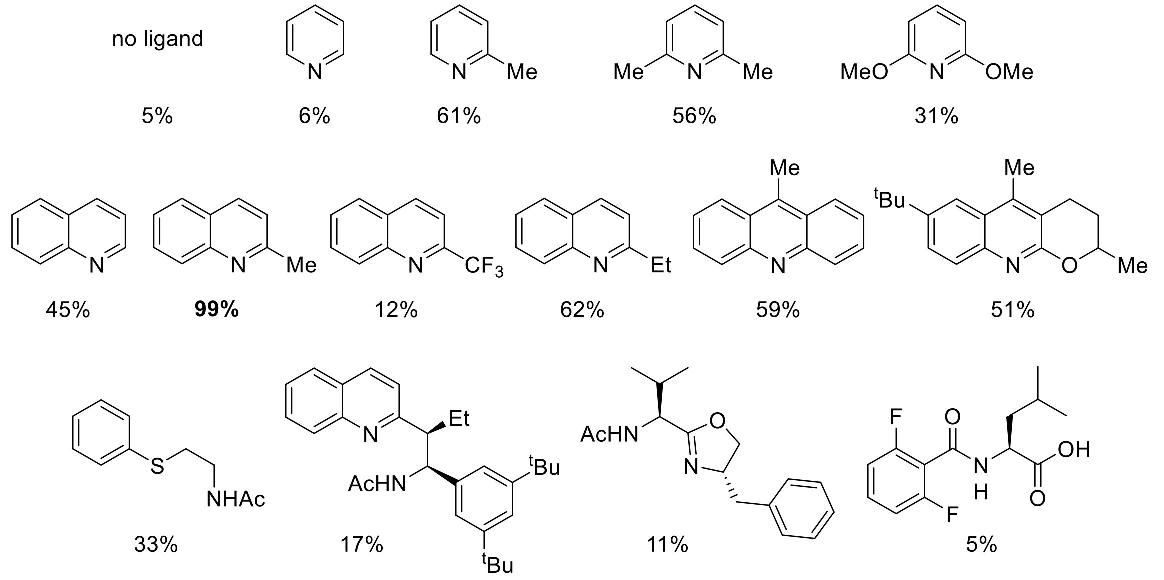


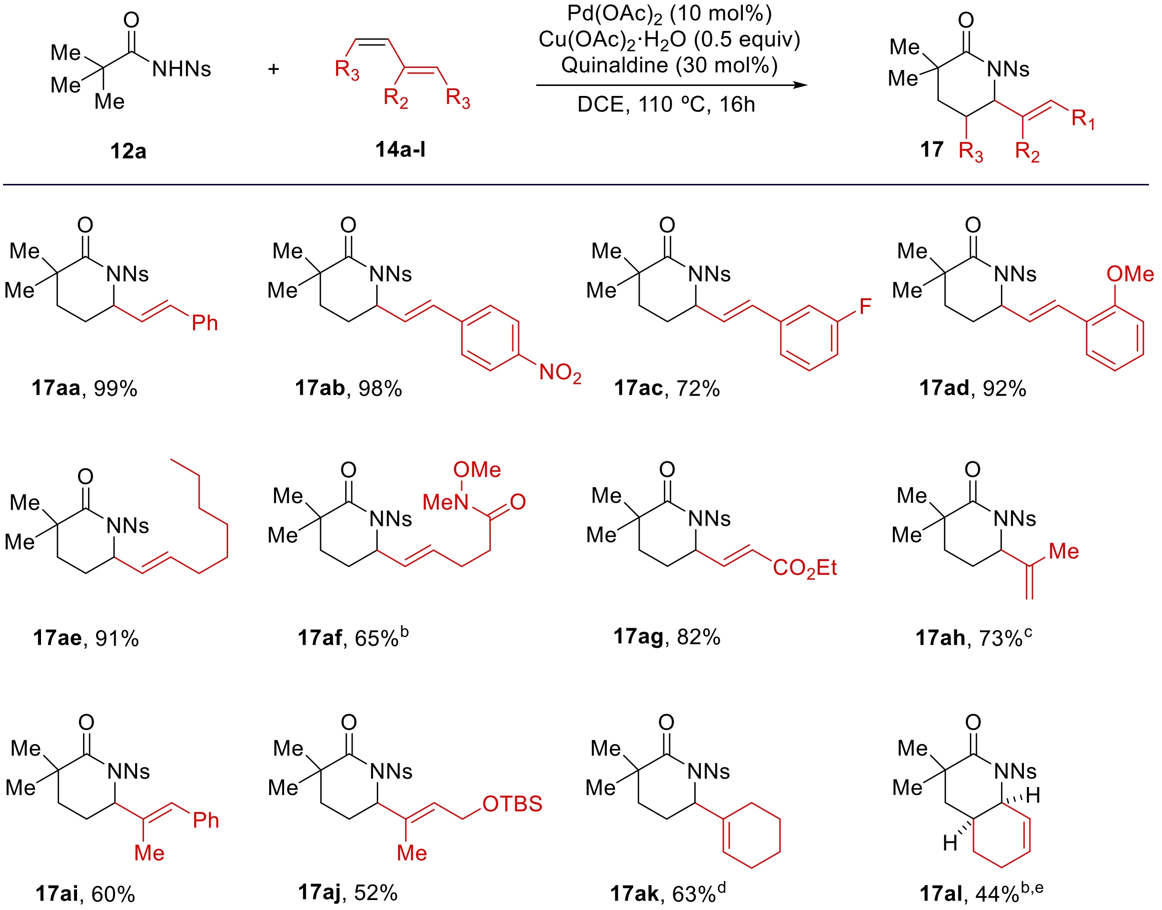
Figure 14. *Results with other ligands under standard conditions.*

Our results also demonstrated the relevance of using dienes as reaction partners. Performing an additional experiment with a simple olefin, 1-octene, a mixture of olefination products was obtained in a yield lower than 15%, while the starting material was completely recovered when the reaction was attempted with diphenylacetylene.

3.2 Reaction scope

With the optimized conditions in hand, we focused our attention on analyzing the reaction scope. Interestingly, we found that the reaction is quite robust and tolerate a wide range of substituents in the diene partner (scheme 112). Dienes bearing aromatic groups led to excellent results independently of the electronic characteristics of the substituents (**17aa**-**17ad**, 72-99%). In addition, dienes featuring a simple alkyl group or equipped with an amide moiety along the aliphatic chain worked well, leading to the expected (4+2) adducts in good yields (**17ae**-**17af**, 65-91%). Remarkable, when a strongly electron-withdrawing group was placed at the terminal position of the diene, only the expected product was obtained in an excellent yield (**17ag**).

Dienes bearing other patterns of substitution were also suitable for the transformation, indeed, isoprene is also an excellent reaction partner (product **17ah**, 73%). Moreover, we found that the reaction was not limited to monosubstituted dienes, as challenging 1,2-disubstituted partners were also well tolerated (**17ai**-**17ak**) and, importantly, the transformation also proceeds reasonably well with highly challenging and commercially available 1,3-cyclohexadiene, leading to an interesting bicyclic adduct (**17al**).[170]



^{a} Reaction conditions: Alkyl amide (0.2 mmol), diene (0.4 mmol), DCE (2 mL). ^{b} 1 equiv Cu(OAc)$_2$·H$_2$O. ^{c} 10 equiv diene. ^{d} 3 equiv diene. ^{e} 60 mol% quinaldine.

Scheme 112. *Scope of the diene partner.*

The structure of these compounds, as well as the configuration of the remaining double bond, was fully corroborated by X-Ray diffraction of 2-piperidones **17aa** and **17af** (figure 15).

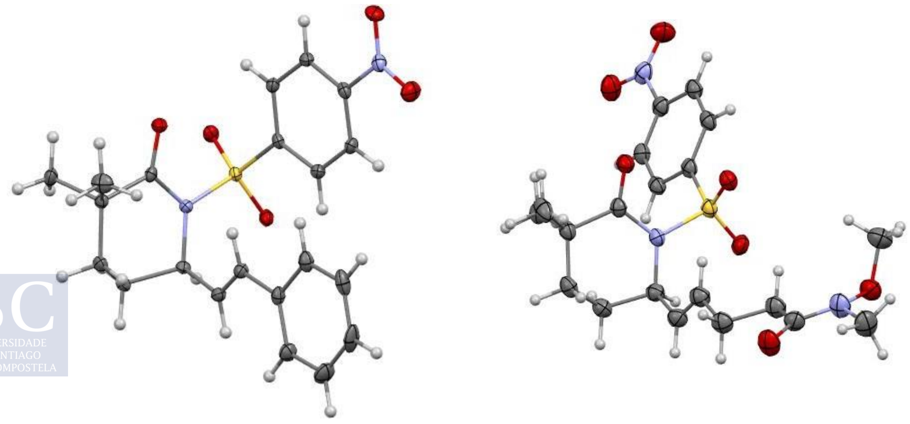


Figure 15. *X-Ray structure of compounds **17aa** and **17af**.*

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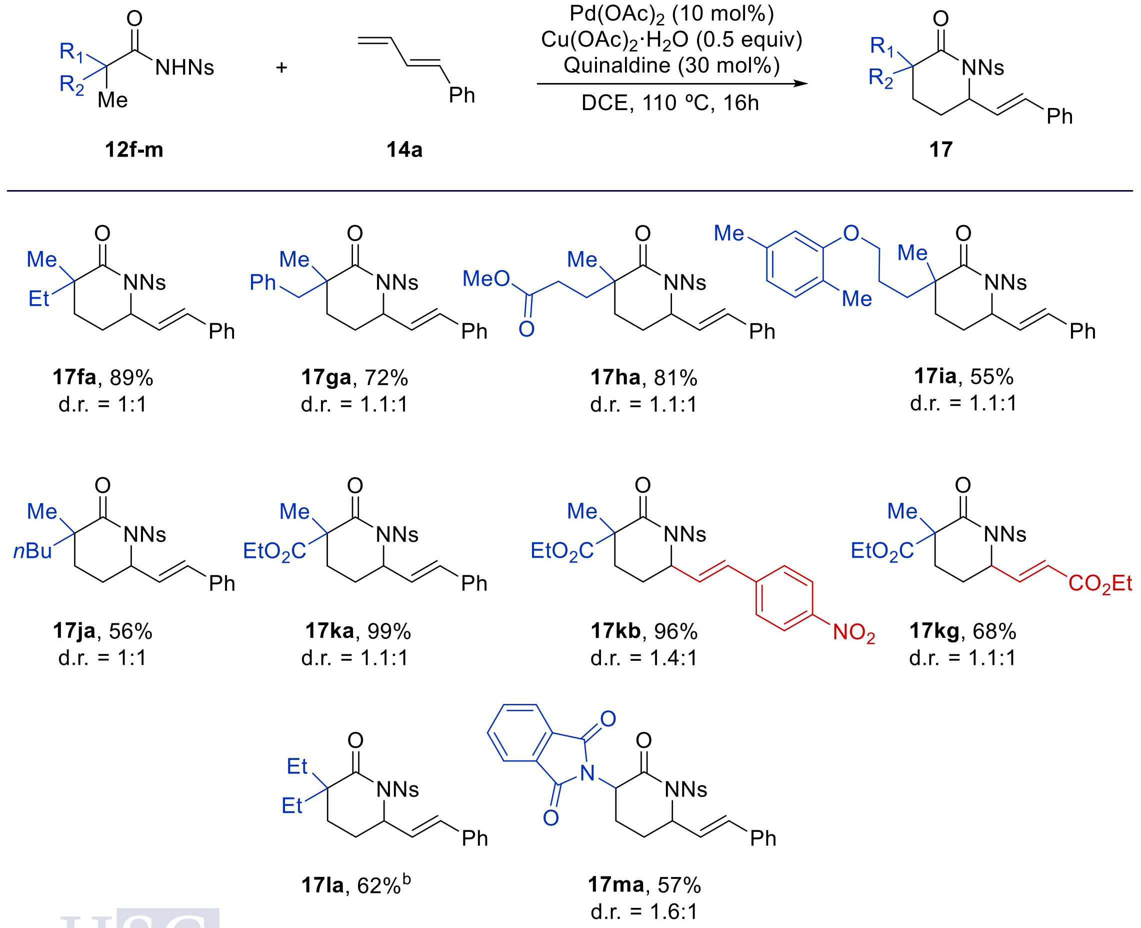
[170] Experiments carried out in collaboration with Dr. Marc Font.

Encouraged by these appealing results, we evaluated the scope for the alkyl amides (scheme 113), easily synthesized from commercially available carboxylic acids as exemplified in scheme 109.[171] The reaction efficiency was almost unaffected replacing one of the methyl groups by other substituents, providing cycloadducts with diastereomeric ratios close to 1:1 (**17fa**-**17ka**). However, large substituents led to lower yields (**17ia**-**17ja**, 55-56%), with recovery of the resting starting material, while an alkyl amide containing an *alpha*-ester group worked specially well (**17ka**, 99%), even with other dienes as coupling partners (**17kb** and **17kg**). Substrates containing only one methyl group were less reactive but also suitable for the transformation (**17la**-**17ma**, 57-62%).

In addition, especially attractive precursors with an α-hydrogen were also capable of promoting the cycloaddition, although providing inseparable mixtures of saturated and *α,β*-unsaturated lactams, except in the case of the alanine-derived amide **12m**, in which only the desired product was obtained.



[a] Reaction conditions: Alkyl amide (0.2 mmol), diene (0.4 mmol), DCE (2 mL). [b] 10 mol% of Pd(OAc)$_2$ added after 7h.

Scheme 113. *Scope of the reaction with regard to the alkyl amide.*

Encouraged by these results, we speculated that other alanine derivatives could be also optimal for the process. However, changing the phthalimide by a Boc-protected

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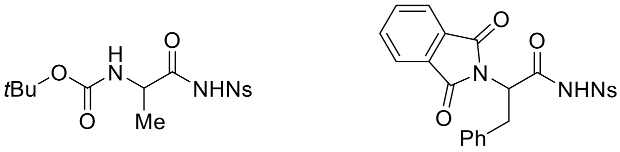
[171] For additional information see experimental section.

compound resulted in the total recovery of the starting substrate (**12o**, figure 16). Moreover, we also wanted to evaluate if a phthalimide-protected phenylalanine could be suitable for our transformation through the activation of more challenging methylene C(sp^3)-H bonds (**12p**, figure 16). However, unfortunately, no reactivity was observed.



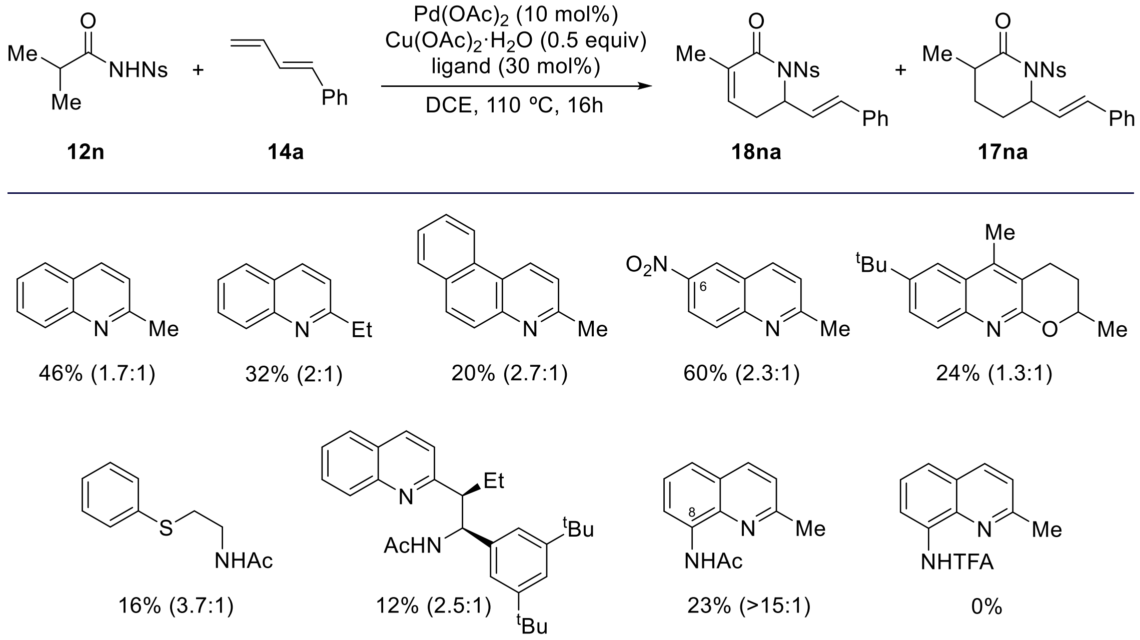
12o **12p**

Figure 16. *Unsuccessful substrates.*

Regarding the simple *N*-nosyl isobutyramide, the yields obtained under standard conditions were moderate (46%), observing a chromatographically inseparable 1.7:1 mixture between the α,β-unsaturated lactam **18na**, probably obtained by β-hydride elimination in the starting amide and subsequent cycloaddition, and the saturated piperidone **17na**. At this point, we envisioned that an appropriate ligand could allow to control the selectivity.

Therefore, we tested several quinoline and not quinoline-type ligands to verify that hypothesis (scheme 114). Introducing a larger substituent in *alpha* (ethyl instead of methyl) led to a decrease in yields with a similar ratio between products. Introducing additional rings or substituents in the quinoline skeleton did not produce any significant change in terms of selectivity, but a nitro moiety in C(6) gave the highest yield (60%).

As in the general screening, typical bidentate ligands afforded worst yields, thought highest selectivities in favor of the α,β-unsaturated product were obtained. Importantly, a new type of bidentate quinoline with a -NHAc in C(8) afforded almost exclusively the unsaturated piperidone, albeit in poor yields. However, in this case, some activation in the nosyl ring of the starting amide was also detected. Attempts to increase yields by modifying the electronic properties of the -NH with the introduction of other groups like TFA failed.



[a] Reaction conditions: Alkyl amide (0.1 mmol), diene (0.2 mmol), DCE (1 mL).

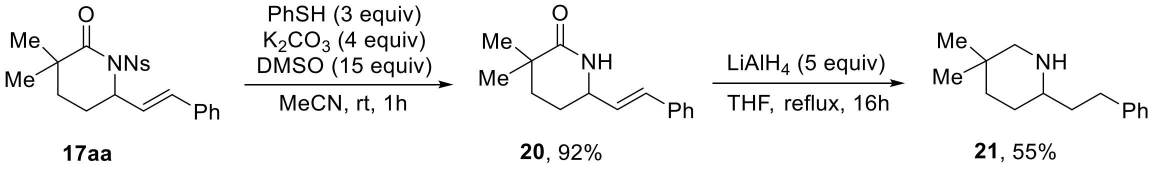
Scheme 114. *Attempts with different ligands to avoid β-hydride elimination.*

Additional experiments modifying the substituent in the amide moiety of the alkyl amide, the solvent or the additives failed to afford better results. Moreover, the saturated lactam was never obtained as major product.

Despite these limitations with substrates like **12n**, our methodology is novel and powerful allowing a straightforward assembly of saturated lactams in good yields.

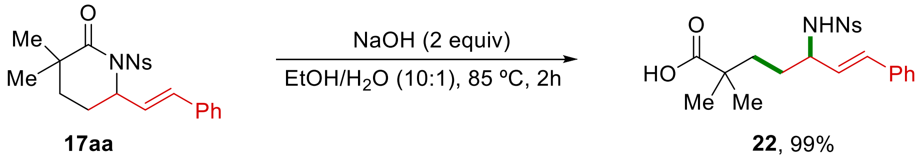
3.3 Manipulation of the products

As a demonstration of the synthetic utility of our method, we performed some manipulations of the cycloadducts. For instance, the nosyl group can be easily removed in presence of thiophenol to produce lactam **20** in an excellent yield. Then, this product can be reduced with LiAlH$_4$, leading to the piperidine **21** (scheme 115).



Scheme 115. *Formation of piperidines from model lactam **17aa**.*

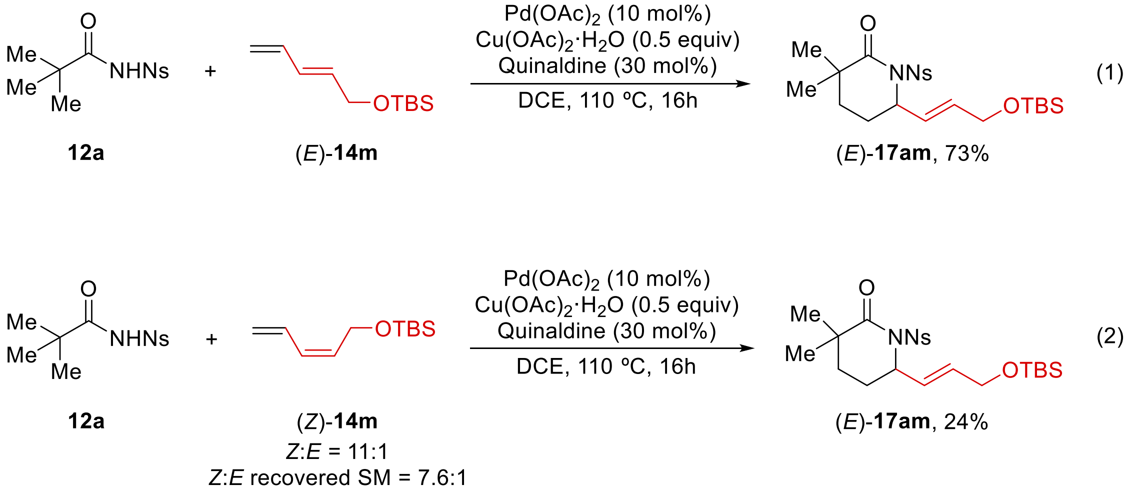
Moreover, a δ-amino acid can be formed in a quantitative yield by treatment of the model lactam with NaOH (scheme 116). This compound can be formally perceived as the consequence of a regio- and chemoselective 1,2-carboamination of the starting 1,3-diene.[172]



Scheme 116. *Hydrolysis of the (4+2) cycloadduct to a δ-amino acid.*

3.4 Mechanistic studies

We initially conducted parallel experiments for the reaction between alkyl amide **12a** and diastereoisomeric dienes (*E*) and (*Z*)-**14m**, to extract information on the stereospecificity of the reaction. In both cases, we observed the formation of the same cycloadduct, with *trans* configuration in the remaining alkene, which suggests, as expected, the formation of a π-allyl intermediate (scheme 117). Despite the formation of the same product, the yields were clearly different, 73% for (*E*)-**14m** vs 24% for (*Z*)-**14m**, probably due to a higher activation barrier of the migratory insertion in the case of the (*Z*)-diene.



Scheme 117. *Reaction of diastereoisomeric dienes (E) and (Z)-**14m**.*

Then, we turned our attention to the C-H activation step. Carrying out a standard experiment in presence of deuterated water (50 equiv) resulted in a diminished yield (42% vs 99%) with no deuteration in the final product, which suggests that the C-H activation step is irreversible (scheme 118).

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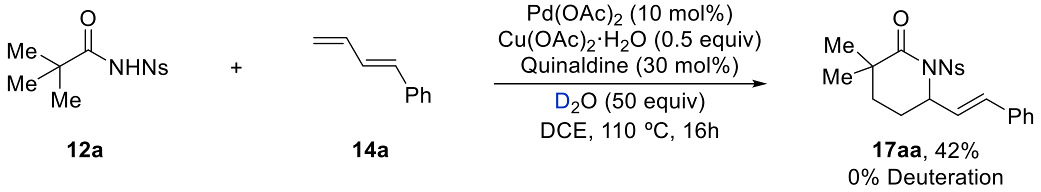
[172] For selected reviews on difunctionalization of 1,3-dienes, see: (a) Perry, G. J. P.; Jia, T.; Procter, D. J. *ACS Catal.* **2020**, *10*, 1485-1499. (b) Xiong, Y.; Sun, Y.; Zhang, G. *Tetrahedron Lett.* **2018**, *59*, 347-355. (c) Wu, X.; Gong, L.-Z. *Synthesis* **2019**, *51*, 122-134.



Scheme 118. *Standard reaction in presence of D₂O.*

In addition, in an effort to obtain mechanistic information about the role of the ligand, we focused our attention on the possibility of isolating palladacyclic intermediates after the C-H activation.[173] We initially carried out an stoichiometric experiment with the alkyl amide **12a** in presence of 1 equivalent of Pd(OAc)$_2$ and 2 equivalents of quinaldine and, gratifyingly, we were able to isolate a five-membered palladacycle with a distorted square planar geometry (**complex B**, scheme 119), in which only one molecule of quinaldine was coordinated to the palladium centre in *trans* to the amide moiety, being the last coordination vacancy occupied by an aquo ligand. The X-Ray structure of the complex reflects the lability of this ligand, owing to the observed length of the Pd-O bond (2.21 Å).

Additionally, when we performed an identical experiment in presence of pyridine instead of quinaldine, we isolated a similar five-membered palladacycle. However, in this case, two molecules of the nitrogenated ligand were coordinated to the palladium centre (**complex C**, scheme 119), probably due to the smaller size of the pyridine. Analysis of the X-Ray structure showed that the most labile position was the equivalent to the one occupied by the aquo ligand in **complex B**, *trans* to the alkyl group, with a Pd-N length of 2.17 Å.[174]

With these isolated complexes at hand, we performed parallel experiments submitting both compounds to reaction conditions in presence of diene **14a**. Curiously, while **complex B** afforded the desired cycloadduct in excellent yield after 3h, **complex C** only reacted in a poor 15% yield (scheme 119). These results indicate that the isolated five-membered palladacycles are part of the catalytic cycle, while the differences in yield can be attributed to the easily realising of the aquo ligand in **complex B** in comparison to the extra pyridine of **complex C**.

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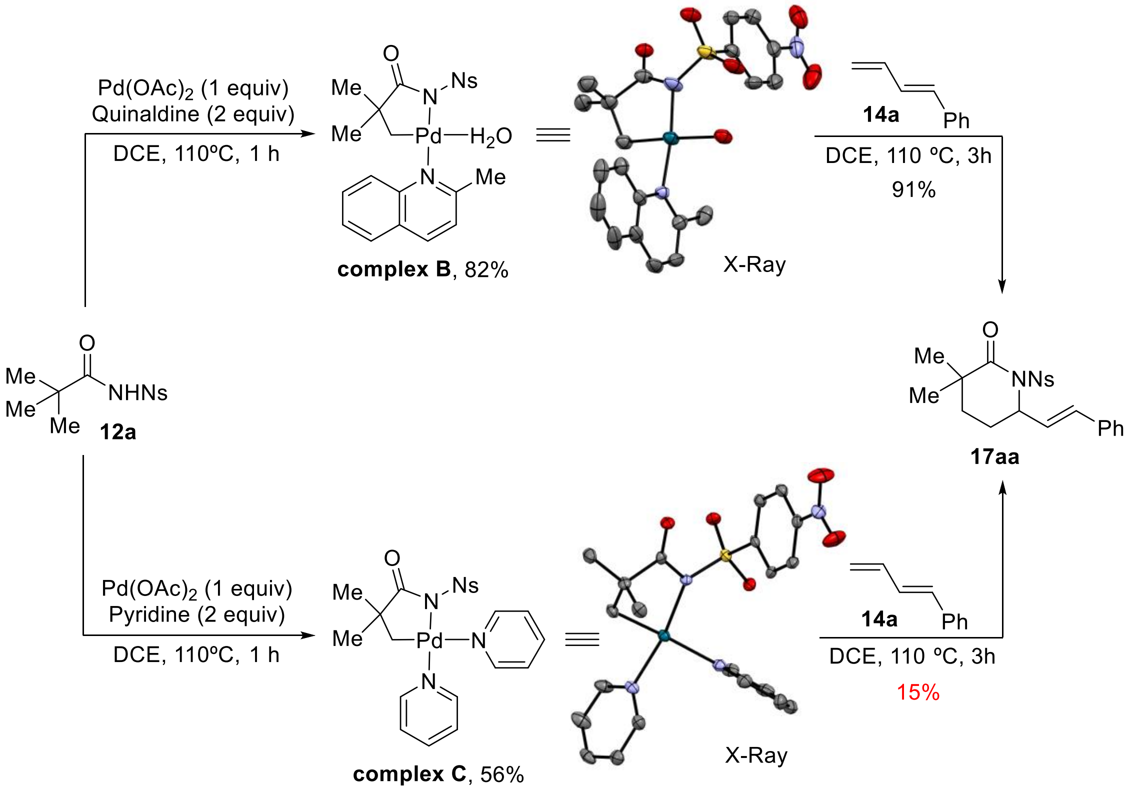
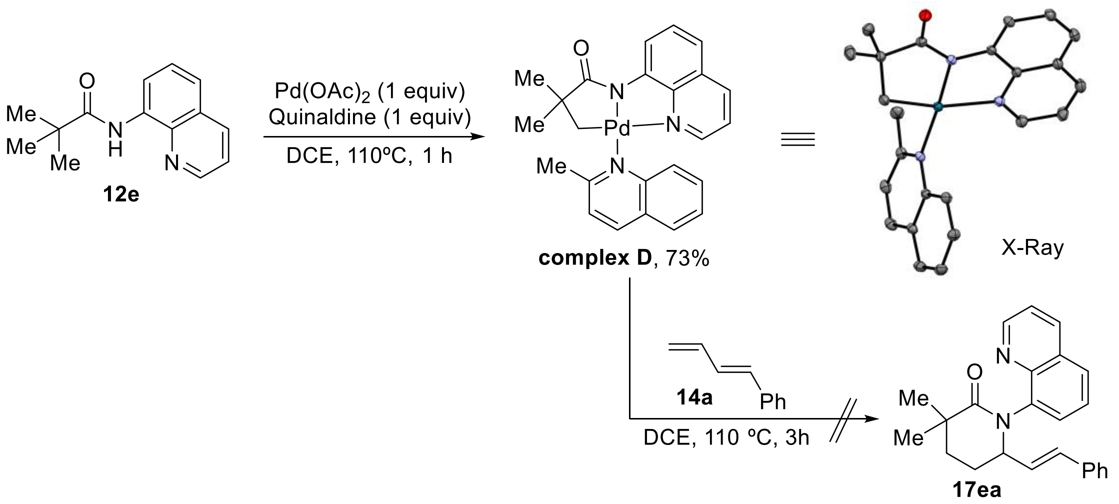
[173] Stoichiometric experiments carried out by Dr. Marc Font.

[174] For a recent review on organometallic intermediates in C(sp^3)-H functionalization, see: Suseelan, A. S.; Dutta, A.; Lahiri, G. K.; Maiti, D. *Trends Chem.* **2021**, *3*, 188-203.



Scheme 119. *Stoichiometric experiments with different ligands.*

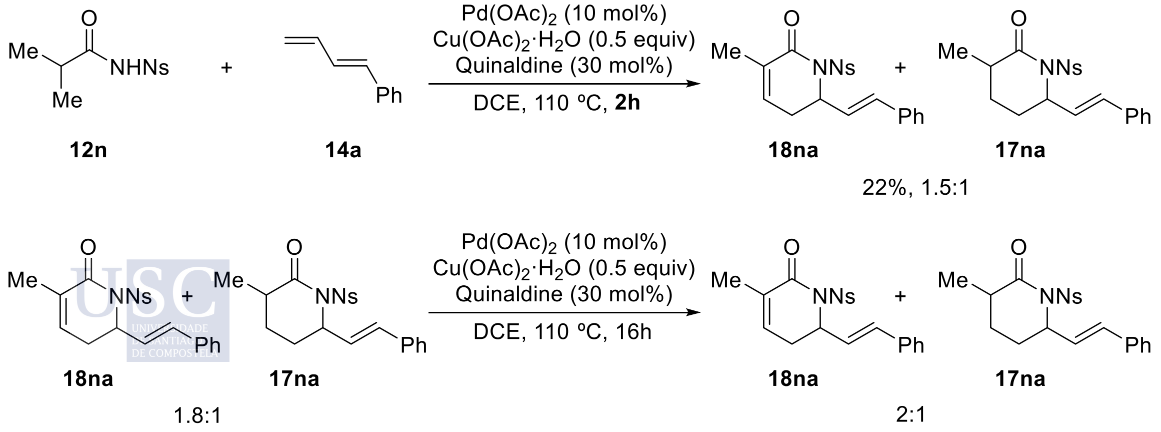
Surprised by our observation during the optimization process, in which the bidentate aminoquinoline failed to give any product, we conducted an analogous stoichiometric experiment employing the alkyl amide bearing an aminoquinoline as directing group, which has been proven to be very useful in C-H other kinds of C-H functionalization reactions (scheme 120).[169] Again, a five-membered palladacycle resulting from the C-H activation step was isolated in an excellent yield, **complex D**. However, this complex did not evolve to the (4+2) cycloadduct in presence of the diene partner, suggesting that the bidentate directing group is capable of promoting the C-H activation, but it is not suitable for further steps of the mechanism, probably by hindering an appropriate coordination of the diene, required for migratory insertion.



Scheme 120. *Stoichiometric experiment with bidentate alkyl amide* ***12e****.*

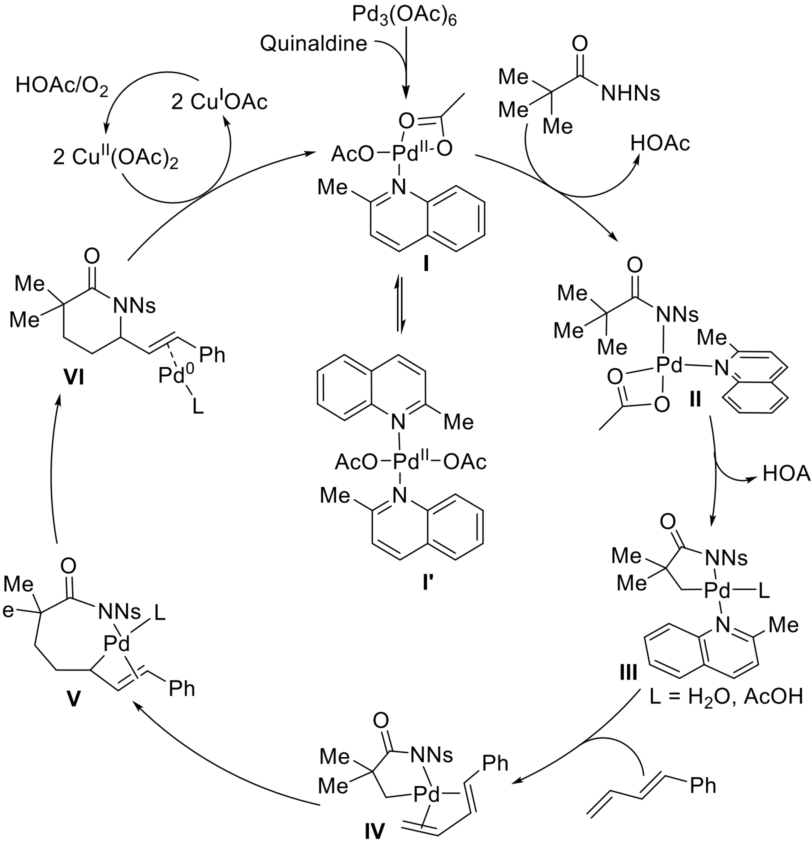
Additional stoichiometric experiments to isolate any intermediate resulting from some of the α-tertiary amides failed. In the case of the phthalic alanine derivative, a very polar white precipitate was formed. However, it was insoluble in all solvents, hampering the characterization or crystallization of the compound. On the other hand, with regard to the isobutyramide, the reaction turned black after some time, maybe suggesting the formation of Pd(0), and no signals different from the starting material were detected by NMR.

In this last case we performed some experiments to rule-out, at least, the possibility of oxidation of the saturated lactam to the *α,β*-unsaturated one (scheme 121). Quenching the reaction at 2h instead of 16h, a 22% yield was obtained in a 1.5:1 mixture, a comparable result in terms of ratio between products with the one achieved at 16h. Moreover, introducing a mixture of the products in reaction conditions gave, after 16h, almost the same mixture with a slight difference that can be associated with the error of the NMR software.



Scheme 121. *Attempts to rule out the oxidation of the saturated lactam.*

All this data allowed us to propose the catalytic cycle indicated below (scheme 122). The reaction likely stars with the formation of the active monomeric species **I**, which is in equilibrium with its dimeric form **I’**. However, this intermediate is destabilized by the steric environment of the quinaldine. Then, a ligand exchange between an acetate and the alkyl amide facilitates the formation of compound **II**, which evolves to the five-membered palladacycle **III** (**complex B**) through a concerted metalation deprotonation (CMD) C-H activation process, step that could be also favoured in presence of the ligand. At this point, coordination of the diene, presumably favoured by its bidentate properties, followed by migratory insertion, allows the formation of the π-allyl intermediate **V**, being the extra-coordination site provided by the diene partner crucial to avoid undesired *β*-hydride elimination. Instead, reductive elimination takes place, leading, probably, to the desired product coordinated to the resulting Pd(0) species. Finally, a new catalytic cycle is able to start by reoxidation of the palladium by cooper and air. An alternative pathway where the dienes is coordinated to the substrate as monodentate ligand and the other position around the palladium is occupied by the quinaldine should be also considered.

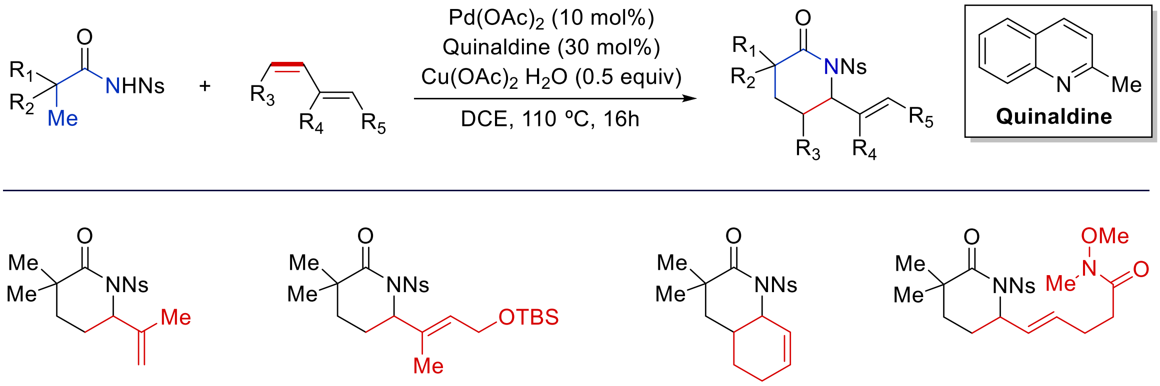


__Scheme 122.__ Mechanistic hypothesis.

With regard to the formation of the *α,β*-unsaturated lactam, it is presumably formed after *β*-hydride elimination and subsequent cycloaddition from the corresponding acrylic amide. However, additional experiments and DFT calculations are being performed by our group in collaboration with Dr. Manuel Ortuño in order to propose an entire mechanism that could explain its formation.

4. Conclusions

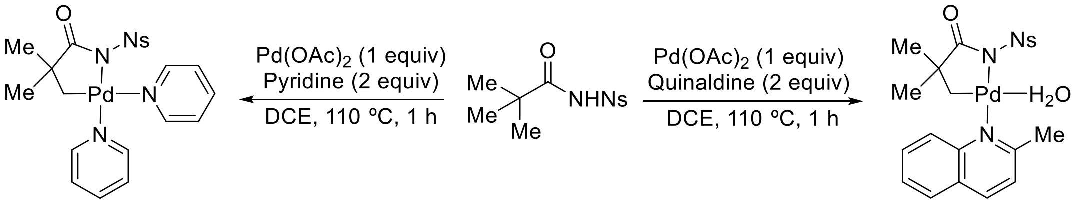
In summary, we have developed, for the first time, a palladium-catalyzed (n+2) formal cycloaddition, which engages alkyl amides and dienes, initiated by the activation of C(sp^3)-H bonds. The reaction tolerates a wide range of including disubstituted, cyclic or simple alkyl dienes (scheme 123).



Scheme 123. Pd-catalyzed formal (4+2) cycloaddition between alkyl amides and dienes.

The presence of a conjugated alkene in the 1,3-diene partner has proven to be essential for the successful outcome of the reaction, probably aiding in the release of the quinoline ligand and, also, favouring the evolution to the desired cycloadduct through the formation of a key π-allylic intermediate after migratory insertion.

Moreover, the use of a nitrogenated quinoline-type ligand presenting the right electronic and steric characteristics proven to be crucial. We were able to isolate palladacyclic intermediates after the C-H activation using different ligands, which allowed us to better understand the role of these types of ligands and the influence of different parameters, like size or denticity, in the reaction efficiency (scheme 124).[175]



Scheme 124. Isolation of C-H activation palladacycles with different ligands.

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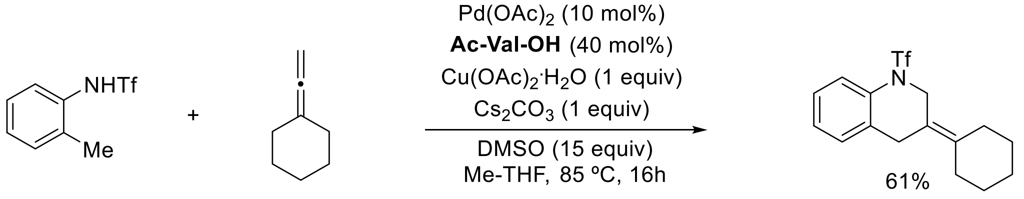
[175] Highlighted in: Vidal, X.; Font, C.; Cendón, B.; Mascareñas, J. L.; Gulías, M. *Trends Chem.* **2021**, *3*, 1102-1103.

5. Addendum

5.1 Preliminary results on other Pd-catalyzed C(sp^3)-H formal cycloadditions

After the publication of this work, our group continued to explore the viability of performing other Pd-catalyzed formal cycloadditions initiated by the activation of C(sp^3)-H bonds.

As a result of this intense work, a fascinating example, that engages *o*-methylanilides and allenes, was recently published by the group, work carried out by my colleague X. Vidal (scheme 125).[176] This novel protocol not only allowed the access to tetrahydroquinoline scaffolds, but it was also extended to the assemble of 2-benzazepines in an unconventional fashion through a (5+2) annulation, using *o*-methylbenzylamides as substrates. Remarkable, in this case, we found that allenes reacted efficiently, in contrast with the results with alkyl amides. Moreover, its use also enabled to develop a preliminary asymmetric version, in the case of the formal (5+2) cycloaddition, consisting of a kinetic resolution with α-substituted compounds.



Scheme 125. *Assembly of tetrahydroquinolines through Pd-catalyzed C(sp^3)-H annulation with allenes.*

Considering our results with dienes, we wondered whether they could also work as partners in this reaction. Such transformation would be attractive in terms of the structure of the resulting tetrahydroquinoline, which would feature a stereocenter in α to the amine moiety, opening the possibility of an asymmetric version.

Again, as previously established, the combination of dienes with quinolines as ligands demonstrated their effectiveness and we could isolate a promising 16% yield in the first attempt, using *N*-triflylanilides as substrates (initial essays with *N*-nosyl compounds afforded mixtures of products due to the activation of the aromatic ring of the nosyl group), in quite similar conditions to that previously used in the project with alkyl amides (table 9, entry 1).[177] We tested other solvents different from DCE, and we obtained better yields in toluene and dioxane (table 9, entries 2-3). Employing 2-MeTHF as solvent, at 85 ºC, inspired by the work with allenes, only traces of the cycloadduct were detected, however, increasing the temperature to 110 ºC, the same used for the other solvents, a

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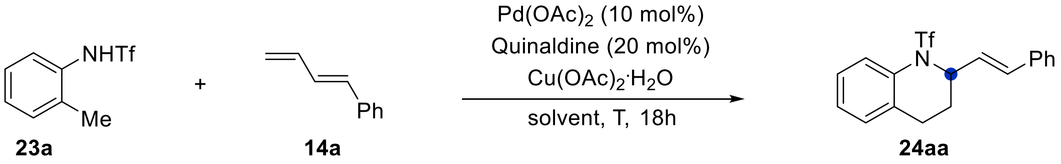
[176] Vidal, X.; Mascareñas, J. L.; Gulías, M. *Org. Lett.* **2021**, *23*, 5323-5328.

[177] Cendón, B.; Font, M.; Mascareñas, J. L.; Gulías, M. *ACS Catal.* **2020**, *10*, 3425-3430.

23% was obtained (table 9, entry 5) and also increasing the temperature for dioxane to 140 °C, the yield raised to a promising 57% (table 9, entry 6).

The efficiency of the reaction was clearly improved with higher amounts of the copper salt (table 9, entry 7), suggesting that the oxidation of the Pd(0) to Pd(II) could be challenging. Following this line, increasing the dilution of the reaction from 0.1 M to 0.05 M, which enhanced the solubility of the copper salt, the yield was further improved to a great 70% (table 9, entry 8), and, in this case, higher temperatures had not a significant impact (table 9, entry 9). Therefore, considering this little difference, we selected 110 °C as the optimal condition to avoid the use of sealed tubes.

Table 9. *Preliminary results.*[a]



	Solvent (T)	**[M]**	**Equiv [Cu^{II}]**	**24aa** (%)
1	DCE (110 °C)	0.1	1	16
2	Toluene (110 °C)	0.1	1	26
3	Dioxane (110 °C)	0.1	1	37
4	2-MeTHF (85 °C)	0.1	1	<5
5	2-MeTHF (110 °C)	0.1	1	23
6	Dioxane (140 °C)	0.1	1	57
7	Dioxane (110 °C)	0.1	2	53
8	Dioxane (110 °C)	0.05	2	70
9	Dioxane (140 °C)	0.05	2	77

[a] Reaction conditions: *o*-methylanilide (0.1 mmol), diene (0.2 mmol).

Currently, further experiments are ongoing in our lab with the goal of achieving the activation of methylene C(sp^3)-H bonds or developing an asymmetric version of the reaction.

Overall conclusions

- We have developed an unconventional annulation between o-alkenylanilides and alkynes for the synthesis of functionalized indoline scaffolds. The reaction is promoted by a rhodium catalyst bearing an electron deficient Cp ligand (Cp^E) under mild conditions. Importantly, we performed a detailed investigation that provided crucial information about the mechanism of this novel transformation.

- We have demonstrated that homoallylamides can engage in different rhodium-catalyzed annulations with alkynes, with the substituent of the amine moiety playing a key role. Despite these findings provided a straightforward method for the assembly of azepines and pyrrolidines, no better yields than 20% were obtained.

- We have discovered a novel palladium-catalyzed formal (4+2) cycloaddition between alkyl amides and dienes initiated by the activation of a $C(sp^3)$-H bond. Key mechanistic experiments shed light into the crucial role of the conjugated doble bond of the diene and the nitrogenated ligand, which proved to be essential for the successful outcome of the reaction.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Summary

Assembly of azaheterocycles via transition metal-catalyzed annulations involving the activation of C-H bonds

During the past decades, transition metal-catalyzed reactions have provided an amazing toolbox of methods for the synthesis of highly appealing structures that otherwise would not be accessible using classical chemistry. For example, the development of palladium-catalyzed cross-coupling reactions constituted an undoubted revolution in organic chemistry with broad applications in research and industry, especially for the formation of C-C bonds. However, the requirement of pre-functionalized substrates usually introduces additional synthetic steps in order to install these functional groups, which clearly compromises the efficiency and practicality of the methods.

In this context, transition metal-catalyzed reactions initiated by the activation of C-H bonds have emerged as an especially attractive approach to modify and assemble a large number of compounds due to the ubiquity of C-H bonds in organic molecules, avoiding the pre-functionalization of substrates, and hence favoring the step and atom economy of these processes, which is key from the perspective of Green Chemistry. These technologies proved to be really useful for the formation of C-X bonds, in contrast to cross-coupling reactions, which were mostly restricted to the formation of C-C bonds. Moreover, several chiral ligands and catalysts have been developed, which has made it possible to perform asymmetric transformations, one of the main goals of organic synthesis for many years. However, this attractive approach presents numerous challenges. For example, the cleavage of C-H bonds is tricky, due to the strength and lack of polarization of these bonds. In addition, the large number of C-H bonds in organic molecules frequently brings selectivity issues, usually solved with the preinstallation of a directing group.

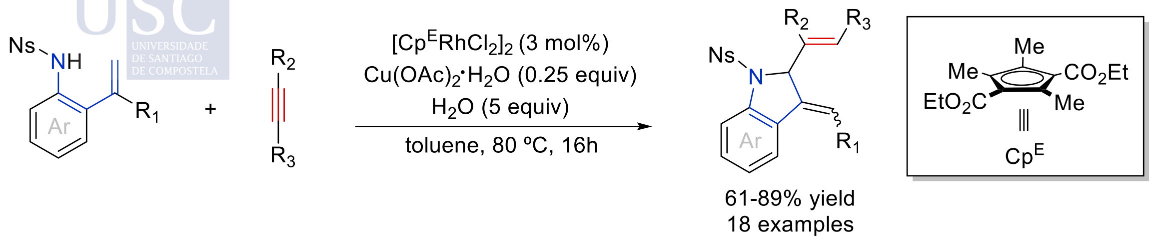
Our group has been particularly interested in the development of transition metal-catalyzed annulations, in which the directing group is part of the final adduct, as this would provide a straightforward approach to heterocyclic structures in a simple, efficient and practical way from readily available precursors. Considering that most of the existing precedents were based on aromatic C(sp^2)-H activation, our group decided to face new challenges, like the activation of alkenyl C(sp^2)-H bonds, that is considerably more challenging, owing to the intrinsic reactivity of olefins, prone to additions or oxidations. Moreover, the presence of different positions that are susceptible of activation also bring selectivity issues in this type of C-H activations. However, despite these challenges, successful results have been recently published. Thus, our group has reported several intermolecular cycloadditions of 2-alkenylphenols in presence of rhodium and palladium catalysis, providing a direct access to benzoxepines, spirocarbocycles or chromenes.

In this context, during my master thesis, we expanded this reactivity to 2-alkenylanilides, and we developed a straightforward method to assemble relevant benzazepine scaffolds through a formal (5+2) cycloaddition in presence of palladium catalysis and allenes as coupling partners and, in this PhD thesis, we described our efforts towards the synthesis of other highly interesting azaheterocycles through the metal-triggered activation of alkenyl and alkyl C-H bonds.

Rhodium(III)-catalyzed annulation of 2-alkenyl anilides with alkynes through C-H activation: direct access to 2-substituted indolines

Previously to my PhD work, our group discovered that *o*-alkenylphenols reacted with alkynes in presence of $[Cp^{*}RhCl_2]_2$ to give benzoxepines or spirocyclic compounds in function of the substituent in the internal position of the alkene. Moreover, when palladium was used as catalyst, benzoxepines were obtained in presence of allenes as reaction partners. Due to the appealing reactivity of these substrates, we wondered whether it could be possible to extend this reactivity to more attractive o-alkenylanilines. With this goal in mind, during my master thesis, we explored its reactivity in presence of palladium catalysis and allenes, obtaining a practical protocol for the assemble of meaningful benzazepine scaffolds in high yields. After this successful project, we wanted to explore, as part of my PhD studies, if it could be possible to extend this methodology to the assemble of benzazepines in presence of a rhodium catalyst and employing alkynes as coupling partners. However, initial experiments in presence of $[Cp^{*}RhCl_2]_2$ afforded a complex mixture, in which we were able to detect traces amounts of an unexpected indoline derivative together with different type of naphthylamides.

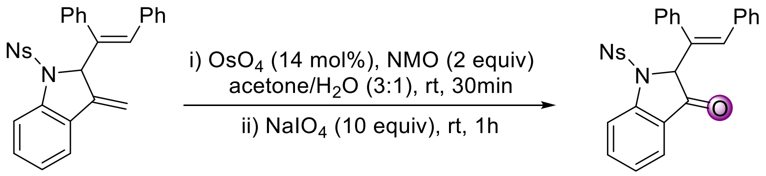
Considering the relevance of the indoline skeleton, present in some biologically active compounds, and the lack of suitable methods to assemble functionalized ones, we proceed to optimize the process and we envisioned that other Cp ligands could favor the reaction, in terms of yield and chemoselectivity. We initially hypothesized an allylic C-H activation for this unconventional annulation, and we envisioned that an electron-deficient Cp^E ligand could favor the process. Gratifyingly, this Cp ligand containing two ester groups afforded, in combination with a *N*-nosyl substituent in the *o*-alkenylaniline, excellent yields of the indoline adduct in a totally selective manner. After screening additives, oxidants and solvents, we found that the best yields were obtained in toluene at 80 ºC in presence of water and $Cu(OAc)_2$, that demonstrated to be the best oxidant.



Regarding the scope, the reaction tolerated a wide range of symmetrical and unsymmetrical alkynes bearing aromatic substituents or simple alkyl chains, providing products with high yields, up to 89%, and regioselectivities, not worse than 10:1. Remarkable, enynes were also suitable reaction partners for the transformation.

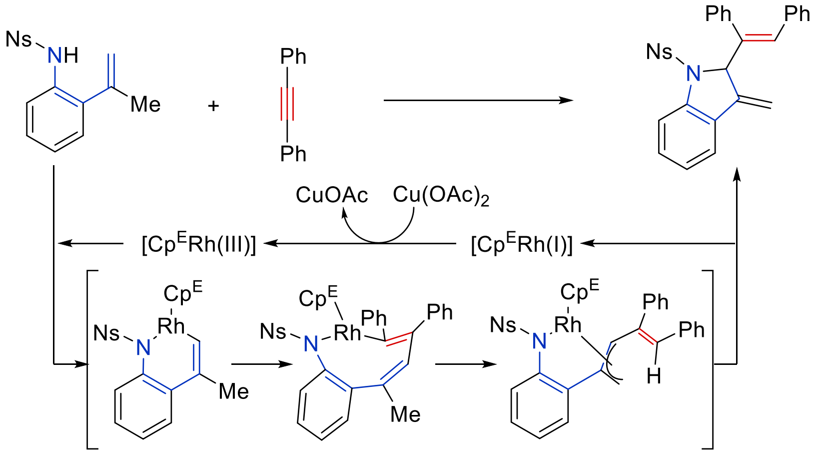
A large number of *o*-alkenylanilides were also effective in reaction conditions. For example, multiple substituents were tolerated in the aromatic ring, independently of their electronic characteristics, and only sterically demanding substituents in *ortho* to the amine hampered the reactivity. However, the substitution of the alkene moiety was more problematic. For example, alkenylanilides bearing linear substituents in the internal position of the alkene reacted well, while introducing an isopropyl or a phenyl group was detrimental. In addition, substrates with non-substitution in this position or with substitution in the external position, were also ineffective.

Furthermore, we also demonstrated the synthetic utility of the method by selective oxidation of the exomethylene moiety with OsO_4, which provided an efficient entry to 3-oxoindolines, basic scaffold of some biologically active compounds.



Moreover, we also proved that the nosyl group can be easily removed from the standard product, although with concomitant isomerization of the exocyclic double bond to the formation of the corresponding indole, equally interesting from a synthetic point of view.

In agreement with the results obtained during the study of the scope and with some experiments with deuterated substrates, we postulated an unconventional mechanistic pathway for this intriguing annulation. In contrast with our initial thoughts, in which we proposed allylic C-H activation, we postulated that the reaction was initiated by alkenyl C-H activation, followed by migratory insertion of the alkyne. At this point, the obtained eight-membered rhodacycle evolves, presumably, trough a 1,5-hydrogen shift with concomitant rhodium migration and, finally, reductive elimination from the resulting π-allylic intermediate produces a Rh(I)-complex in which the metal center is coordinated to the diene of the final product, complex that we were able to isolate after some stoichiometric experiments. Finally, reoxidation of the Rh(I) species by the copper salt delivers the desired adduct.



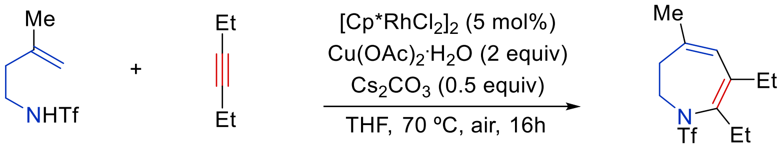
However, recent DFT calculations suggest that the reaction could proceed in a different way from the eight-membered rhodacycle. Instead of the Rh-migration, which could be disfavored due to the steric ambiance caused by the required three anionic ligands on the Rh(III) species, an intramolecular migratory insertion of the alkene of the anilide into the Rh-N bond could take place, providing an interesting tricyclic intermediate. Then, the indoline adduct would be formed after β-hydride elimination and final reductive elimination from the resulting rhodium hydride.

Remarkable, the reaction for the synthesis of naphthylamides was also optimized and published by our group a little bit latter. In this case, we found that $[Cp^*RhCl_2]_2$ was the optimal catalyst for this intriguing transformation in combination with a *o*-alkenyl *N*-triflylanilide. Interested by this divergence, we evaluated the influence of different parameters in the formation of both adducts. As concluding remarks, we found that using the Cp^E ligand or other less electron-rich ligands than Cp*, like Cp^{iPr} or Cp, the naphthylamide adduct was never formed. However, when $[Cp^*RhCl_2]_2$ was used, this product was always formed in reaction media, independently of the conditions used or the substituent at the nitrogen, indicating a high dependence of the chosen Cp ligand in the formation of the naphthylamide. With regard to the indoline scaffold, its formation was observed in a wider range of conditions, and both the nosyl protecting group and the Cp^E ligand were required to achieve a selective and efficient process.

Divergent synthesis of azepines and pyrrolidines through a Rh(III)-catalyzed annulation between homoallylamides and alkynes, triggered by C-H activation

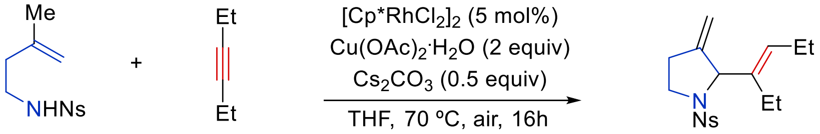
Considering the above results, we wondered if could be possible to achieve similar annulations employing analogous non-aromatic substrates, as this would expand the synthetic potential of the strategy. However, homoallylamides are even more challenging starting materials because they are more sensitive to side reactions, like the oxidation to imines. In fact, the use of these substrates in TM-catalyzed reactions involving the activation of C-H bonds was limited to a couple of examples in Pd-catalyzed transformations.

Initial experiments employing *N*-triflyl homoallylamides and diphenylacetylene in presence of [Cp*RhCl$_2$]$_2$ afforded traces amounts of the desired azepine products. We then found that using an alkyne with aliphatic substituents, yields increased to values close to 20% in presence of Cs$_2$CO$_3$ as base and Cu(OAc)$_2$ as oxidant, and employing THF (70 °C) as solvent. Unfortunately, further efforts to increase these yields using other solvents, additives, oxidants or catalysts were ineffective, with higher decomposition of the starting homoallylamide. Other attempts to increase the reaction efficiency by modifying the structure of the substrate with substituents in different positions, *alpha* to the amine for example, also failed.



We reasoned that one of the problems of the reaction could be the coordination of the rhodium catalyst to the diene of the product, which stops the catalytic cycle and hampers the desired reactivity. Inspired by a recent publication between acrylic acids and alkynes, in which they proposed a similar problem that was only solved carrying out the reaction in an electrochemical undivided cell, we decided to assemble our own electrochemical cell with platinum and graphite electrodes using an external power source. However, the best yields obtained employing electrochemistry for the oxidation step independently of the electrode materials, solvents or additives were over 10%. Nevertheless, further efforts employing electricity as oxidant are being carried by our group, looking for cheaper, more efficient, and greener transformations.

Importantly, using a *N*-nosyl homoallylamide, we detected the formation of a different adduct in a 18% yield, that after a deep NMR study and X-Ray diffraction was characterized as a pyrrolidine.



This divergence in reactivity by modifying the substituent at the nitrogen was surprising, and even more considering that in the case of the *o*-alkenylanilides this type of adducts were only obtained as major product in presence of an electron deficient Cp, and not with the classical Cp*. Unfortunately, all attempts up to now to improve yields were ineffective, even by modifying the electronic properties of the Cp ligand.

Mechanistically, the formation of both products starts with the activation of the alkenyl C-H bond, followed by migratory insertion of the alkyne to give an eight-membered rhodacycle that can evolve through different mechanistic pathways, by reductive elimination to give the azepine or by [1,5]-H shift with concomitant rhodium migration and final reductive elimination for the formation of the pyrrolidine. However, in this case, according to the DFT calculation for the formation of the indolines, an alternative pathway that leads to a bicyclic structure by migratory insertion of the alkene of the homoallylanilide from the eight-membered rhodacycle could take place. This intermediate would undergo a β-hydride elimination process to yield a Rh-hydride species**,** which gives the final product after C-H reductive elimination. Remarkable, both pathways conclude with the formation of a stable Rh(I) complex that should be able to start a new catalytic cycle after oxidation and release of the desired product. However, our results seem to indicate that this step does not occur efficiently.

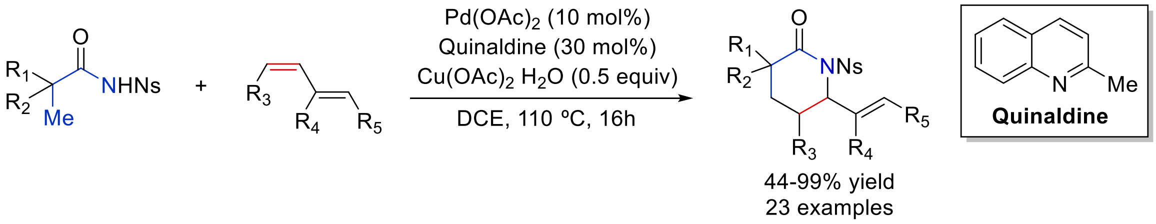
Palladium-catalyzed formal (4+2) cycloaddition between alkyl amides and dienes initiated by the activation of C(sp^3)-H bonds

Considering our success on transition metal-catalyzed annulations involving the activation of alkenyl C-H bonds, we decided to focus our attention on cycloaddition reactions initiated by the activation of alkyl C-H bonds. These bonds are even more challenging owing to the lower acidity of the hydrogens, the lower polarization of C-H bond, the lack of a coordinating double bond that could favour a pre-coordination to the metal complex, and the lower strength of a C(sp^3)-M versus a C(sp^2)-M bond. Therefore, promoting this type of activations usually requires the employment of designed ligands that favour the process.

Despite all the difficulties, in the past few years there have been multiple reports on palladium-catalyzed C-H functionalization reactions initiated by the activation of C(sp^3)-H bonds. In contrast, formal cycloadditions have been extremely scarce, and essentially restricted to some carbonylation reactions. Therefore, the development of (n+2) cycloadditions would be novel and could provide access to saturated heterocyclic compounds from simple acyclic starting materials.

Analyzing possible substrates that could engage in these annulations, we considered alkyl amides as the best choice, relying in the great capabilities of this weak coordinating directing group for directed C(sp^3)-H activation, as already demonstrated in a great examples for the formation of different C(sp^3)-C(sp^3, sp^2 or sp) or C(sp^3)-X bonds. Taking into account the existing precedents on the reaction of this type of compounds with acrylates, in which β-hydride elimination takes places after migratory insertion, we reasoned that using allenes as partners would produce π-allyl intermediates that could favor reductive elimination instead of the non-desired β-hydride elimination.

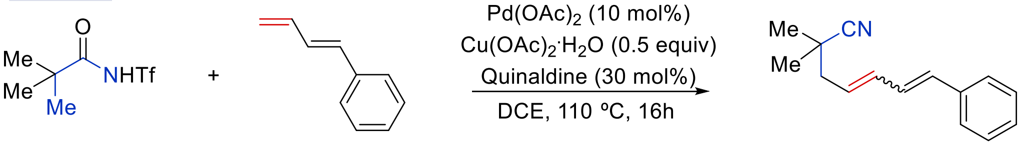
Initial experiments revealed that our hypothesis was right. However, after a deep optimization with allenes, yields of the resulting saturated lactams were not as high as desired with strong decomposition of the allene in reaction media. At this point, we confirmed that alkynes or simple alkenes were not suitable for the reaction, however, dienes, which would also provide an analogous π-allyl intermediate, afforded quite good yields of the desired (4+2) cycloadduct. A broad optimization with parallel testing of different parameters demonstrated that a monodentate nitrogenated ligand, quinaldine, and the substituent at the nitrogen played a crucial role in the reaction efficiency. Moreover, other parameters, like the oxidant or the solvent were also important to obtain high yields.



Regarding the scope, monosubstituted aromatic dienes worked nicely independently of the electronic characteristic of the substituents. Dienes bearing aliphatic substituents were also suitable and a diene containing an ester moiety also reacted well. Moreover, dienes with other patterns of substitution, like isoprene, or disubstituted were also good partners, although the reaction provided lower yields. Importantly, a cyclic diene, 1,3-cyclohexadiene, led to an appealing bicyclic structure. With regard to the alkyl amide, substrates containing quaternary centers with two methyl groups and a variety of other substituents provided excellent yields. Moreover, quaternary alkyl amides with only one methyl group were also optimal for the process, although they exhibited lower reactivity. Precursors with tertiary instead of quaternary carbons in *alpha* to the amide also participated in the reaction, but provided chromatographically inseparable mixtures of other products, including cycloadducts featuring an additional double bond. Attempts to control the formation of these product, specially focused on the modification of the structure of the nitrogenated ligand, were ineffective. However, importantly, some substrates containing α-hydrogens, such as an alanine-derived amide, also gave excellent yields of the desired product with total selectivity in favor of the saturated lactam.

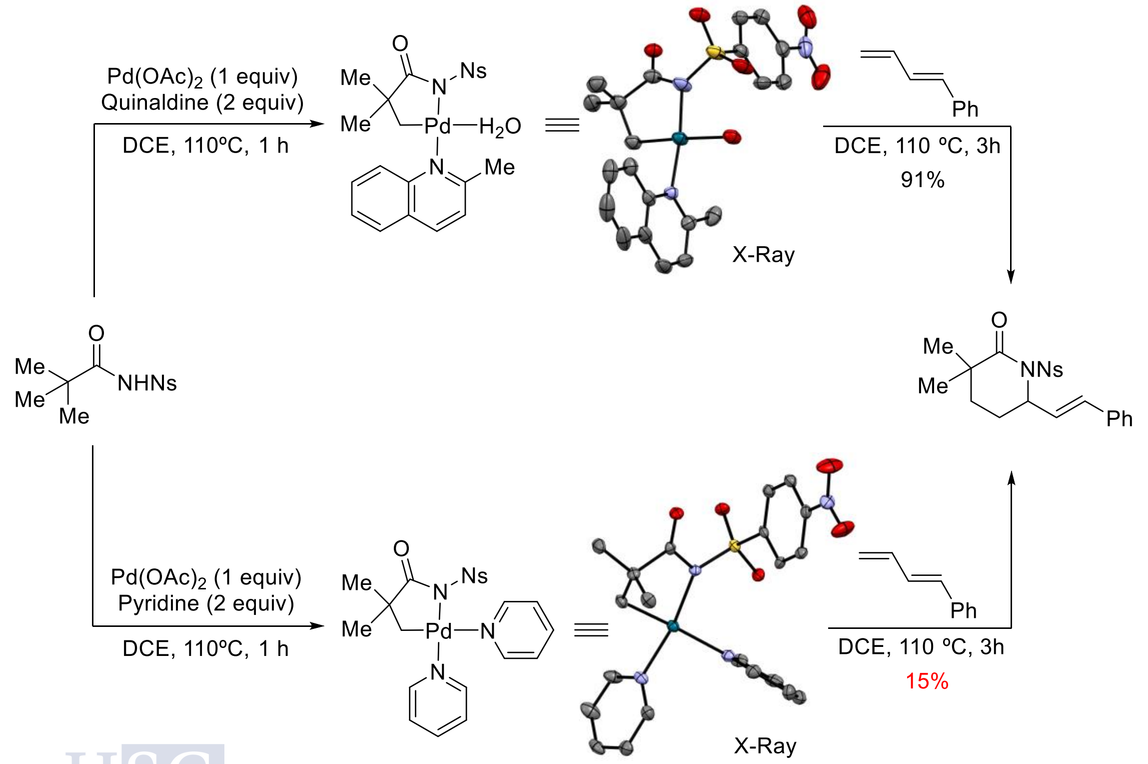
Remarkable, cycloadducts can be manipulated into divergent appealing ways, for instance, the nosyl group can be easily removed, and the resulting amide can be also reduced to the corresponding piperidine. Furthermore, ring-opening of the (4+2) adduct led to interesting δ-amino acids.

Curiously, when the reaction was performed under standard conditions with an *N*-triflyl amide, an acyclic product containing a nitrile with a diene in γ-position was obtained.



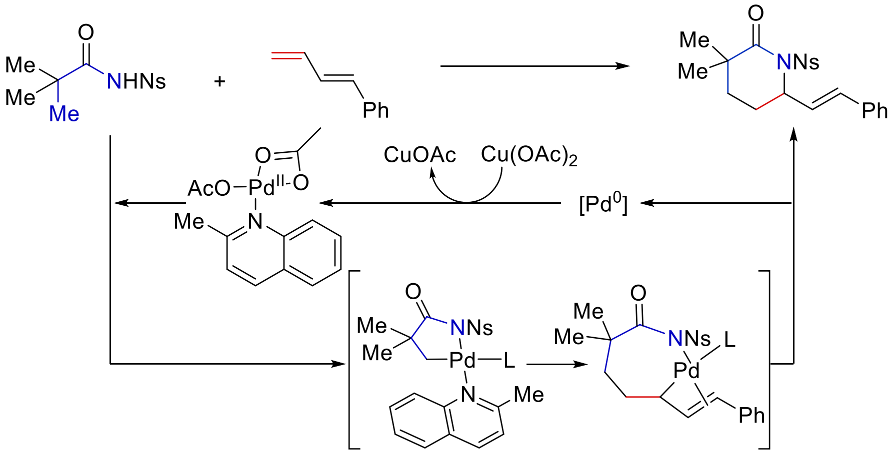
To shed light into the intriguing role of the ligand in the canonical cycloaddition, we performed several stoichiometric experiments in presence of different ligands. Using quinaldine, we isolated the five-membered palladacycle resulting from the C-H activation step, complex that contained only one quinaldine coordinated to the palladium, which presented a distorted square-planar geometry. Moreover, we demonstrated that this palladacycle was part of the catalytic cycle by submitting the complex to standard conditions in presence of the diene, which afforded an excellent yield of the (4+2) cycloadduct.

However, when we performed another stoichiometric experiment in presence of pyridine instead of quinaldine, we isolated a five-membered palladacycle containing two pyridines attached to the palladium, which indicated the relevance of the steric environment of the ligand for avoiding the formation of this type of inactive dimeric species. In addition, treatment of this complex with 2 equivalents of the diene only provided a 15% yield of the product, which indicates the problems associated with the release of the extra ligand. Similarly, we associated the low yields obtained with bidentate ligands with the lack of binding sites necessary for the coordination and subsequent migratory insertion of the diene.



Additionally, we were also able to isolate the palladacycle resulting from the C-H activation step in the case of a bidentate directing group, discovering that it is suitable for the activation but hampers a suitable coordination of the diene, compromising by this way the catalytic cycle.

All this data allowed us to propose a plausible catalytic cycle in which quinaldine plays several crucial roles. In addition to hinder the coordination of two units of ligand due to its steric environment, it probably breaks the initial less-active palladium trimer to give a monomer with high catalytic activity. Moreover, it likely avoids the coordination of two amide moieties previously to the C-H activation step. Therefore, the mechanistic sequence starts with the formation of the palladium monomer that evolves through the C-H activation step to give the isolated palladacycle intermediate. Then, coordination and migratory insertion of the diene provides a π-allylic intermediate that delivers the product after final reductive elimination.



Remarkable, we also found that this methodology of combination of quinoline-type ligands with dienes can be applied to the activation of C(sp^3)-H bonds in other type of substrates with slight modifications. For example, we achieved some preliminary successful results on the activation of benzylic C(sp^3)-H bonds in *o*-methyl *N*-triflylanilides, reaction that would provide access to attractive tetrahydroquinoline scaffolds in an efficient and practical way. Currently, yields up to 70% were obtained by modifying the solvent to dioxane and increasing the amount of the copper salt to 2 equivalents.

Resumen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Síntesis de azaheterociclos mediante anulaciones catalizadas por metales de transición que implican la activación de enlaces C-H.

A lo largo de las últimas décadas, las reacciones catalizadas por metales de transición se han convertido en una gran herramienta para la síntesis de nuevas estructuras que no podrían ser sintetizadas en ausencia de metal. Ello es posible gracias a que estos catalizadores dan lugar a nuevos mecanismos con barreras energéticas más bajas, haciendo posible la reducción de los tiempos de reacción, las temperaturas y las presiones necesarias, dando lugar a procesos más prácticos y seguros. Por ejemplo, el desarrollo de las reacciones de acoplamiento cruzado catalizadas por paladio constituyó una auténtica revolución en síntesis orgánica, con grandes aplicaciones en investigación e industria. Sin embargo, la necesidad de substratos pre-funcionalizados implica un aumento desmesurado de las etapas necesarias para llegar a la molécula objetivo, lo que restringe claramente las posibles aplicaciones de estas reacciones.

En este contexto, las reacciones catalizadas por metales de transición iniciadas por la activación de enlaces C-H han emergido como una nueva metodología alternativa para la modificación y síntesis de un gran número de compuestos debido a la ubicuidad de los enlaces C-H en las moléculas orgánicas, evitando de este modo la prefuncionalización de los precursores, aumentando así la economía atómica del proceso y minimizando los residuos generados, principios de la *Química Sostenible*. Además, estas metodologías tienen la ventaja de que pueden realizarse generalmente sin necesidad de una atmósfera inerte y en presencia de humedad, lo que facilita el trabajo experimental y sus posibles aplicaciones en la química industrial. Otra ventaja de la activación C-H incluye el gran número de ligandos y catalizadores quirales disponibles que son adecuados para estos procesos y que habitualmente son comerciales o pueden ser sintetizados de manera sencilla, siendo la síntesis asimétrica uno de los grandes objetivos de la síntesis orgánica. No obstante, esta metodología también presenta algunas desventajas. Por ejemplo, la escisión de un enlace C-H es más difícil que la de un enlace C-X, debido a la falta de polarización y fuerza de estos enlaces. Además, el gran número de enlaces C-H presentes en las moléculas orgánicas puede dar lugar a problemas de selectividad, solventados habitualmente con la introducción de un grupo director.

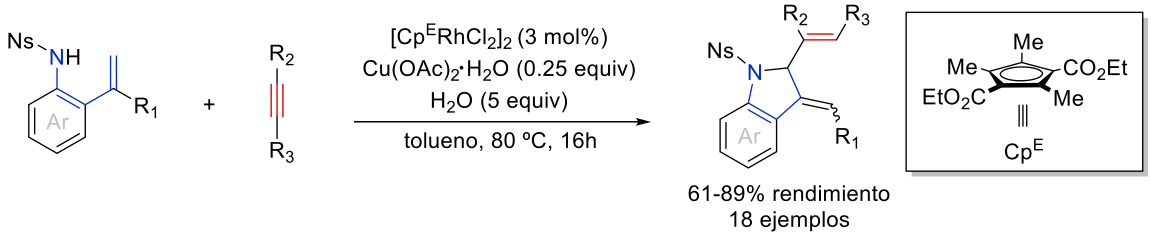
Debido a esto, nuestro grupo de investigación ha estado especialmente interesado a lo largo de los últimos años en el desarrollo de cicloadiciones, en las cuales el grupo director es parte del compuesto final, catalizadas por metales de transición que conllevan la activación de enlaces C-H, con el objetivo final de sintetizar heterociclos de manera simple, eficiente y práctica a partir de precursores sencillos. Teniendo en cuenta que la mayoría de los precedentes existentes consistían en la activación de enlaces C-H aromáticos, nuestro grupo decidió afrontar nuevos desafíos como la activación de enlaces C-H de alquenos, la cual es considerablemente más difícil en términos de selectividad debido a la reactividad intrínseca de los alquenos, los cuales son susceptibles de sufrir procesos de adición y oxidación, además de presentar varios enlaces C-H susceptibles de ser activados. Sin embargo, a pesar de estos impedimentos, en los últimos años se han reportado algunos ejemplos exitosos de este tipo de activación. De hecho, nuestro grupo de investigación ha publicado recientemente varias cicloadiciones intermoleculares de *o*-alquenilfenoles en presencia de catalizadores de rodio y de paladio.

En este contexto, durante mi trabajo de fin de máster, expandimos esta metodología a las o-alquenilanilidas a través de una cicloadición formal (5+2) con alenos catalizada por paladio. Como resultado de ello, en esta tesis doctoral se describen los esfuerzos realizados para la síntesis de otros azaheterociclos, presentes en un gran número de moléculas con actividad biológica, mediante la activación de enlaces C-H de alquenos y cadenas alquílicas, menos explorada hasta el momento.

Síntesis de indolinas funcionalizadas a través de una anulación oxidativa entre 2-alquenil anilidas y alquinos en presencia de un catalizador de rodio

Con anterioridad a este trabajo de doctorado, nuestro grupo descubrió que los *o*-alquenilfenoles reaccionaban con alquinos en presencia de $[Cp^*RhCl_2]_2$, dando lugar a benzoxepinas o compuestos espirocíclicos en función del sustituyente en la posición interna del alqueno. Por otra parte, empleando un catalizador de paladio y alenos en lugar de alquinos también se obtuvieron benzoxepinas. Teniendo en cuanta estos resultados tan interesantes, quisimos saber si esta reactividad se podía extender a o-alquenilanilinas. Con este objetivo en mente, durante mi trabajo de fin de máster, exploramos la reactividad de estos substratos en presencia de alenos y $Pd(OAc)_2$, dando lugar a un método práctico y sencillo para la síntesis de benzazepinas en grandes rendimientos. Después de la conclusión de este proyecto, ya dentro de mis estudios de doctorado, quisimos explorar la posibilidad de obtener el mismo tipo de productos con catálisis de rodio y alquinos. Sin embargo, los primeros experimentos en presencia de $[Cp^*RhCl_2]_2$ dieron lugar a una mezcla de reacción compleja en la que fuimos capaces de aislar una pequeña cantidad de un aducto derivado de la indolina.

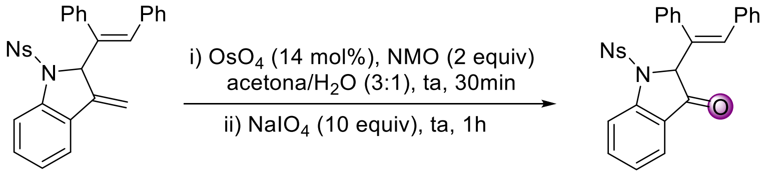
Debido a la importancia de esta estructura y la falta de métodos adecuados para su síntesis, decidimos optimizar esta reacción y vislumbramos que otros Cp, distintos del Cp* clásico, podrían favorecer esta transformación ya que muchos estudios previos habían demostrado que las propiedades electrónicas y estéricas del Cp podían tener una gran influencia en la eficiencia y la regio- y quimioselectividad de muchas reacciones. Atendiendo a la estructura del producto, especulamos inicialmente con la posibilidad de una activación alílica y, por lo tanto, pensamos que un Cp deficiente en electrones, Cp^E, que ya había mostrado su utilidad en otras activaciones alílicas, podría ser el adecuado para nuestra anulación.



Afortunadamente, este Cp con dos ésteres junto con un nosilo como sustituyente en el nitrógeno, proporcionaron rendimientos excelentes de la indolina de forma totalmente selectiva. Además de estos parámetros, también probamos una gran variedad de aditivos, oxidantes y disolventes, alcanzándose los mejores resultados en tolueno a 80 °C en presencia de agua como aditivo y $Cu(OAc)_2$, el cual demostró ser la mejor opción como oxidante.

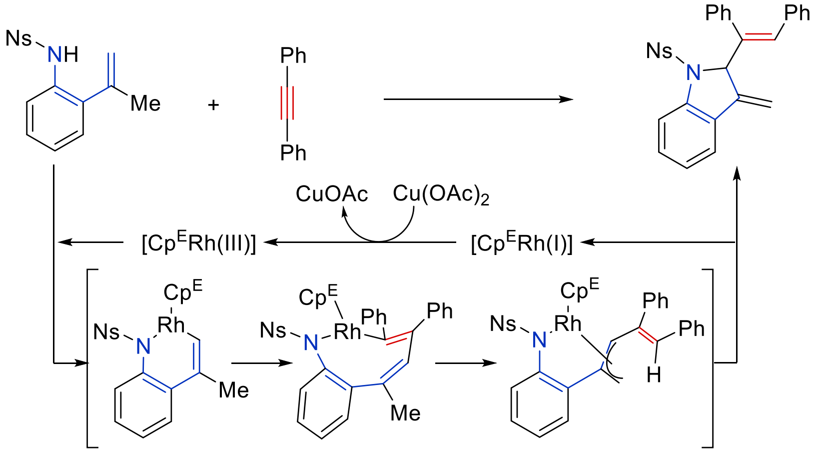
Con respecto al alcance de la reacción, esta funciona con alquinos simétricos y no-simétricos con sustituyentes aromáticos y alquílicos, obteniéndose rendimientos de hasta el 89% con regioselectividades, en el caso de los no-simétricos, superiores a 10:1. Cabe destacar que la reacción también tiene lugar cuando se emplean eninos. Por otra parte, con respecto a las anilinas, la anulación también funciona cuando se introducen diversos sustituyentes en el anillo aromático, independientemente de la electrónica de estos, a excepción de los sustituyentes de mayor tamaño que un flúor en *orto* a la amina. No obstante, la reacción es mucho más sensible a los sustituyentes introducidos en el alqueno ya que sólo funciona cuando hay cadenas lineales alquílicas en la posición interna de este. Sin embargo, cualquier sustituyente en la posición externa imposibilita que la reacción tenga lugar.

Por otra parte, también demostramos la utilidad sintética de nuestra transformación oxidando selectivamente el doble enlace proveniente de la *o*-alquenilanilida con OsO_4, generando 3-oxoindolinas, esqueleto básico de muchos compuestos con interés farmacológico.



Igualmente, también demostramos que el grupo nosilo puede eliminarse del producto modelo de manera sencilla, aunque al quitarlo el doble enlace exocíclico isomeriza generando el indol correspondiente.

La propuesta mecanística, en consonancia con los resultados obtenidos y con algunos experimentos con substratos deuterados, comienza, en contraposición con nuestra idea inicial, con la activación del enlace C-H del alqueno seguido de la inserción migratoria del alquino, dando lugar a un rodaciclo de 8 miembros. Este intermedio se propone que evoluciona a través de una trasposición [1,5] de hidrógeno con la consiguiente migración de rodio. Finalmente, eliminación reductora desde el π-alilo resultante de este desplazamiento genera un complejo de Rh(I), aislado en condiciones estequiométricas, coordinado el producto. Este complejo de Rh(I) libera el producto después de ser oxidado a Rh(III) por el cobre.



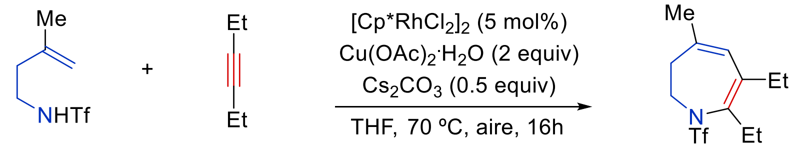
No obstante, cálculos DFT recientes sugieren que la reacción podría transcurrir por otro camino a partir del rodaciclo de 8 miembros. En lugar de la migración de rodio, la cual estaría bastante desfavorecida por el entorno estérico del Rh(III) con sus tres ligandos aniónicos, tendría lugar la inserción intramolecular del alqueno de la anilida en el enlace Rh-N, generando un intermedio tricíclico de bastante interés. Desde este intermedio, β-eliminación de hidruro y posterior eliminación reductora darían lugar al aducto final.

Nuestro grupo también descubrió que este tipo de substratos, con un triflato en el nitrógeno, pueden reaccionar con alquinos en presencia de $[Cp^*RhCl_2]_2$ para dar naftilamidas. Intrigados por estos resultados, procedimos a evaluar la influencia de distintos parámetros en la formación de uno u otro producto. Como conclusiones generales, observamos que usando el ligando Cp^E u otros menos ricos electrónicamente que el Cp*, como Cp^{iPr} o Cp, la naftilamida nunca se formaba. Sin embargo, usando $[Cp^*RhCl_2]_2$ siempre se detectaba este producto en medio de reacción, independientemente de las condiciones o el sustituyente empleando en el nitrógeno. Con respecto a la indolina, esta se forma en un rango de condiciones más amplio, aunque tanto el nosilo como el Cp^E son necesarios para conseguir un proceso selectivo y eficiente.

Síntesis divergente de azepinas y pirrolidinas a través de una anulación catalizada por rodio(III) entre homoalilamidas y alquinos iniciada por la activación de enlaces C-H

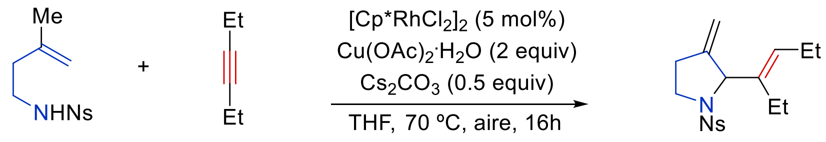
Después de la conclusión del proyecto previo, nos preguntamos si sería posible conseguir una reactividad parecida empleando precursores análogos no aromáticos. Sin embargo, las homoalilaminas son una sustancia de partida aún más compleja ya que son susceptibles de oxidarse a las correspondientes iminas en presencia de reactivos oxidantes. Además, su uso como precursores en reacciones catalizadas por metales de transición que son iniciadas por la activación de enlaces C-H está limitado a un par de ejemplos en algunas transformaciones catalizadas por paladio, en parte porque estas moléculas son muy sensibles a reaccionar con nucleófilos y electrófilos después de la coordinación del metal al alqueno. No obstante, sería realmente interesante profundizar en nuevos estudios con estos sustratos ya que desarrollar anulaciones con ellos puede dar lugar a múltiples esqueletos de productos naturales u otras sustancias bioactivas.

Tras realizar algunos experimentos iniciales empleando *N*-triflil homoalilamidas y difenilacetileno en presencia de $[Cp^*RhCl_2]_2$, detectamos trazas de azepina, esqueleto de siete miembros con un gran interés sintético. Esta observación atrajo aún más nuestra atención sobre estos sustratos ya que habíamos sido incapaces de obtener este tipo de compuesto con los precursores aromáticos en presencia de catalizadores de rodio. Centrando nuestra atención en la optimización de la reacción, descubrimos que cambiando a un alquino alquílico, 3-hexino, los rendimientos aumentaron hasta el 20% en presencia de Cs_2CO_3 como base y $Cu(OAc)_2$ como oxidante en THF como disolvente. Desafortunadamente, por mucho que intentamos mejorar estos rendimientos modificando diversos parámetros como el disolvente, los aditivos, el oxidante o el catalizador, no tuvimos éxito. También quisimos ver como influía en la eficacia de la reacción la introducción de algunos sustituyentes en la estructura de la homoalilamida, sin embargo, cualquier modificación, dio lugar a peores resultados.



Ante la incapacidad de incrementar los rendimientos, independientemente de la modificación que se hiciese, pensamos que podía estar teniendo lugar algún tipo de inhibición por parte del producto, probablemente a través de la coordinación de Rh(I) al dieno generado en el producto final. Inspirados por una publicación reciente entre ácidos acrílicos y alquinos en la cual tenían un problema similar, el cual solo fueron capaces de solventar empleando electroquímica, decidimos ensamblar nuestra propia celda electroquímica con electrodos de platino y grafito y una fuente de potencial externa. Sin embargo, todos nuestros intentos de mejorar el rendimiento fracasaron.

Cabe destacar, que cuando cambiamos el triflato por un nosilo en la homoalilamina, detectamos por RMN la formación de un producto mayoritario distinto que después de difracción de Rayos X identificamos cómo una pirrolidina en un 18% de rendimiento.



Este resultado sorprendente incrementó aún más nuestro interés en esta transformación ya que esa divergencia entre productos simplemente modificando el sustituyente en el nitrógeno es poco habitual y más considerando que en el caso de las *o*-alquenilanilidas este aducto sólo se formaba mayoritariamente en presencia de $[Cp^{E}RhCl_2]_2$ y no con el Cp* clásico. Sin embargo, todos los intentos por mejorar el rendimiento de la reacción fracasaron de nuevo.

Con respecto al mecanismo, ambos productos se forman a partir de la activación del enlace C-H del alqueno y posterior inserción migratoria del alquino. El rodaciclo de 8 miembros que se obtiene tras esta etapa es a partir del que tiene lugar la divergencia que explica la formación de un u otro producto. Mientras que la azepina se forma mediante eliminación reductora, la pirrolidina puede obtenerse a partir de la migración de rodio propuesta para las indolinas o, de acuerdo con los cálculos DFT, mediante la inserción del alqueno en el enlace Rh-N y posterior β-eliminación de hidruro seguida de eliminación reductora. Ambas propuestas mecanísticas concluirían con la formación de un complejo de Rh(I)-producto, teniendo que oxidarse el rodio para poder empezar un nuevo ciclo catalítico, sin embargo, todo parece indicar que esta etapa no ocurre de manera eficiente.

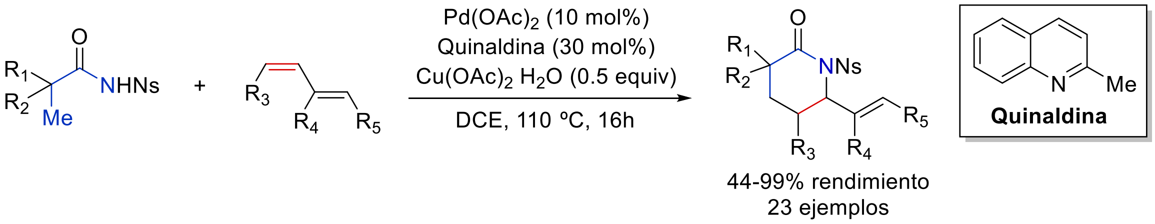
Cicloadición formal (4+2) catalizada por paladio entre amidas alquílicas y dienos iniciada por la activación de enlaces C(sp^3)-H.

Después del éxito cosechado por nuestro grupo de investigación en el descubrimiento y optimización de cicloadiciones iniciadas por la activación de enlaces C-H de alquenos, decidimos centrar nuestra atención en el siguiente desafío, desarrollar anulaciones iniciadas por la activación de enlaces C(sp^3)-H. Esta activación, no obstante, se considera más complicada debido a la menor acidez de estos hidrógenos, la falta de un doble enlace que coordine el metal y lo acerque al enlace que se desea activar y la menor fuerza del enlace C(sp^3)-M en comparación al C(sp^2)-M. Esto explica porque esta activación ha sido menos explorada y porque requiere en muchas ocasiones el uso de ligandos que bajan la barrera energética de la activación.

Sin embargo, en los últimos años, este campo ha sufrido un gran avance, publicándose múltiples ejemplos de funcionalizaciones C(sp^3)-H catalizadas por paladio. No obstante, con respecto a las cicloadiciones, estas están principalmente restringidas a carbonilaciones y algunos ejemplos peculiares de activación C-H alílica. Por lo tanto, el desarrollo de cicloadiciones (n+2) sería muy útil y daría lugar a esqueletos heterocíclicos saturados a partir de precursores acíclicos muy sencillos.

Después de analizar posibles sustratos para llevar a cabo la cicloadición deseada, pensamos que las amidas alquílicas serían una buena opción debido a las grandes características de la amida como grupo director débil, habiéndose utilizado ya previamente para múltiples funcionalizaciones C(sp^3)-H. Considerando especialmente el precedente de este tipo de precursores con acrilatos, en el cual no tenía lugar una cicloadición debido a que después de la inserción, la β-eliminación de hidruro está más favorecida. Entonces pensamos que los alenos podrían evitar esta etapa debido a la formación de un intermedio π-alílico estabilizado.

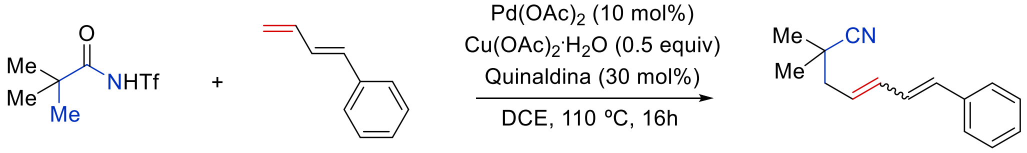
Algunos experimentos iniciales revelaron que nuestra hipótesis era correcta. Sin embargo, después de un largo proceso de optimización los rendimientos no eran lo suficientemente buenos. Llegado este punto, procedimos a evaluar otros compuestos típicos y mientras alquinos o alquenos fracasaron, dienos, los cuales también proporcionan un intermedio π-alílico, reaccionaron exitosamente hacia la formación del producto 4+2. Después de un amplio proceso de optimización, descubrimos que tanto el uso de un ligando monodentado nitrogenado, quinaldina, como la introducción de un grupo nosilo en la amida eran fundamentales para obtener buenos rendimientos. Además, otros parámetros como el oxidante o el disolvente demostraron no ser triviales.



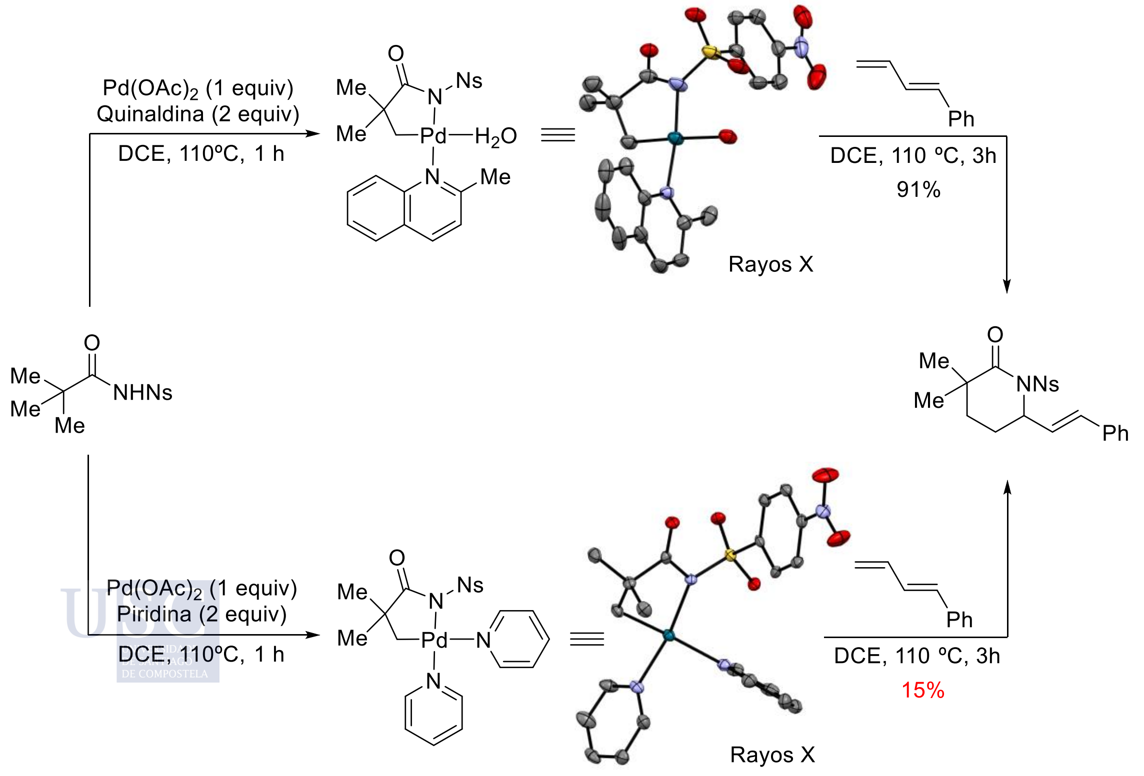
Con respecto al alcance de la reacción, se obtuvieron muy buenos rendimientos con diversos dienos aromáticos, independientemente de la electrónica de los sustituyentes. Dienos con sustituyentes alquílicos o con un éster también reaccionaron bien. Además, dienos con otro tipo de substitución, como el isopreno, o disustituidos también dieron lugar al producto deseado, aunque en rendimientos más bajos. Inesperadamente, también tuvimos reacción cuando usamos un dieno cíclico, 1,3-ciclohexadieno, obteniéndose una estructura bicíclica bastante interesante. Con respecto a la amida, los sustratos cuaternarios con dos metilos y diversos sustituyentes en la otra posición funcionaron muy bien mientras que aquellos con un solo metilo dieron lugar a peores resultados. Por otra parte, los sustratos con hidrógenos en α, generaron mezclas de lactamas saturadas y α,β-insaturadas, excepto en el caso de una amida con un sustituyente derivado de la alanina, en el cual se obtuvo únicamente la saturada.

Para demostrar la utilidad sintética del método, nos encargamos de eliminar el grupo nosilo y de reducir la lactama a la correspondiente piperidina. Además, la apertura del ciclo proporcionó un interesante δ-aminoácido.

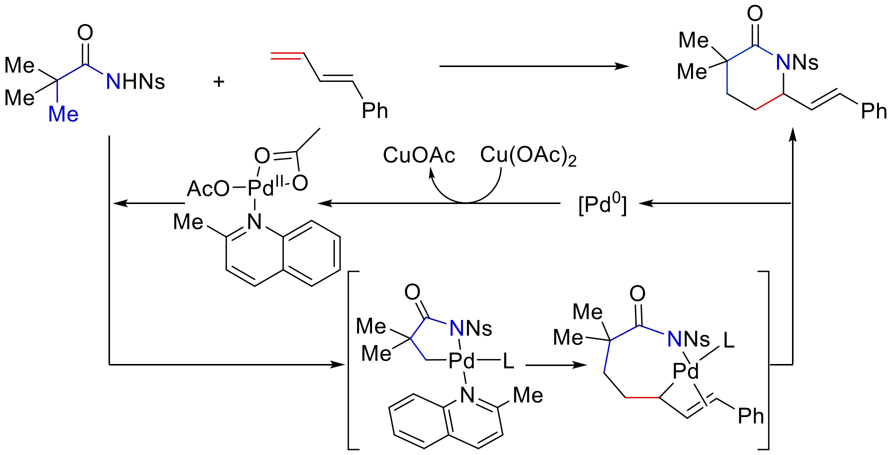
Sorprendentemente, cuando realizamos la reacción modelo en presencia de una homoalilamina triflada, se obtuvo un producto acíclico de olefinación con un nitrilo en vez de la amida esperable.



Con el objetivo de descubrir el rol fundamental de la quinaldina, realizamos varios experimentos estequiométricos en presencia de diferentes ligandos. Usando quinaldina, fuimos capaces de aislar el paladaciclo de 5 miembros resultante de la activación C-H, cuya estructura de Rayos X mostró una disposición plano-cuadrada distorsionada con una única molécula de ligando coordinada al paladio. Cuando sometimos este complejo a las condiciones de reacción en presencia de dieno, vimos que se obtenía un gran rendimiento del producto deseado, demostrándose así que el complejo aislado es un intermedio de reacción. Por otra parte, llevando a cabo un experimento idéntico en presencia de piridina en vez de quinaldina, esta vez aislamos un complejo con dos moléculas de ligando coordinadas, atribuible al menor tamaño de la piridina. Cuando hicimos reaccionar este complejo con el dieno, en este caso sólo se obtuvo un 15% de rendimiento, lo que indica la dificultad asociada a desplazar uno de estos ligandos por el dieno, por lo que entorno estérico del ligando parece crucial para evitar que la formación de este tipo de dímeros tenga lugar.



Toda esta información nos ayudó a proponer un ciclo catalítico en el que la quinaldina juega varios papeles clave. Además de evitar la coordinación de dos unidades de ligando por sus propiedades estéricas, también evita la coordinación de dos amidas antes de la activación C-H y rompe el trímero de paladio inicial, el cual presenta poca o nula actividad catalítica. Más allá de estas funciones especiales de la quinaldina, la reacción sigue una secuencia mecanística clásica en este tipo de cicloadiciones (n+2): activación C-H, coordinación e inserción migratoria del alquino y eliminación reductora desde el π-alilo resultante.



Después de la conclusión de este proyecto tratamos de desarrollar otras cicloadiciones iniciadas por la activación de este tipo de enlaces C(sp^3)-H. Afortunadamente, descubrimos que esta combinación de ligandos tipo quinolina con dienos podía ser aplicable a otros substratos sin apenas modificaciones. Por ejemplo, fuimos capaces de obtener un 70% de rendimiento en unos pocos experimentos empleando *o*-metilanilidas como precursores.

Resumo

Síntese de azaheterociclos mediante anelacións catalizadas por metais de transición que implican a activación de enlaces C-H.

Ao longo das últimas décadas, as reaccións catalizadas por metais de transición convertéronse nunha gran ferramenta para a síntese de novas estruturas que no poderían ser obtidas en ausencia de metal. Isto é posible grazas a que estes catalizadores dan lugar a novos mecanismos con barreiras enerxéticas máis baixas, facendo posible a redución dos tempos de reacción, das temperaturas e das presións necesarias, xerando procesos máis prácticos e seguros. Por exemplo, o desenvolvemento das reaccións de acoplamento cruzado catalizadas por paladio deu lugar a unha auténtica revolución en síntese orgánica, con grandes aplicacións en investigación e industria. Non obstante, a necesidade de substratos pre-funcionalizados implica un aumento desmesurado das etapas necesarias para alcanzar a síntese da molécula obxectivo, o que restrinxe claramente as posibles aplicacións destas reaccións.

Neste contexto, as reacciones catalizadas por metais de transición iniciadas pola activación de enlaces C-H emerxeu como unha nova metodoloxía alternativa para a modificación e síntese dun gran número de compostos debido á ubicuidade dos enlaces C-H nas moléculas orgánicas, evitando deste modo a prefuncionalización dos precursores e incrementando así a economía atómica do proceso, ao mesmo tempo que se minimizan os residuos xerados, principios da *Química Sostible*. Ademais, estas metodoloxías teñen a vantaxe de que se poden realizar, xeralmente, sen necesidade de unha atmosfera inerte ou en presencia de humidade, o que facilita o traballo experimental e as súas posibles aplicacións na química industrial. Outra vantaxe da activación C-H inclúe a dispoñibilidade dun gran número de ligandos e catalizadores quirais adecuados para estes procesos e que xeralmente son comerciais ou poden sintetizarse de maneira sinxela, sendo a síntese asimétrica un dos grandes obxectivos da síntese orgánica dende fai moito tempo. Non obstante, esta metodoloxía tamén presenta algunhas desvantaxes. Por exemplo, a escisión dun enlace C-H é mais difícil que a dun enlace C-X, debido á falta de polarización e a forza destes enlaces. Ademais, o gran número de enlaces C-H presentes nas moléculas orgánicas pode dar lugar a problemas de selectividade, solucionados a miúdo coa introdución dun grupo director que dirixe a activación.

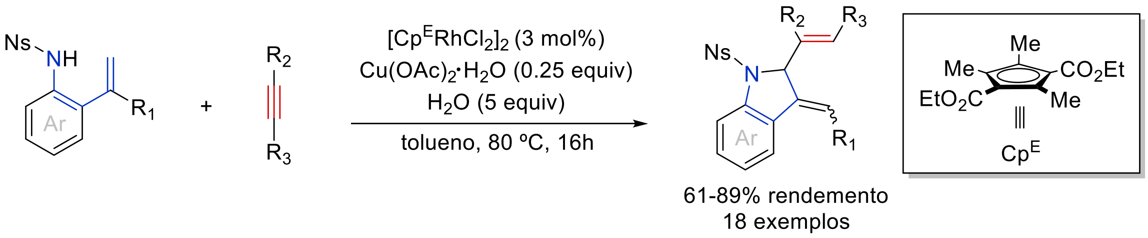
Debido a isto, o noso grupo de investigación estivo especialmente interesado ao longo dos últimos anos no desenrolo de cicloadicións, nas cales o grupo director é parte do composto final, iniciadas pola activación de enlaces C-H e catalizadas por metais de transición, co obxectivo final de sintetizar heterociclos de xeito simple, eficiente e práctico a partir de precursores sinxelos. Tendo en conta que a maioría dos precedentes existentes consistían na activación de enlaces C-H aromáticos, o noso grupo decidiu afrontar novos retos como a activación de enlaces C-H de alquenos, a cal é considerablemente mais complexa en termos de quimio- e rexioselectividade debido á reactividade intrínseca dos alquenos, os cales son susceptibles de sufrir procesos de adición e oxidación, ademais de presentar varios enlaces C-H susceptibles de ser activados. Con todo, a pesar destes impedimentos, nos últimos anos reportáronse algúns exemplos frutíferos deste tipo de activación. De feito, o noso grupo de investigación publicou recentemente varias cicloadicións intermoleculares de *o*-alquenilfenois en presencia de catalizadores de rodio e paladio.

Neste contexto, durante o meu traballo de fin de mestrado, estendemos esta metodoloxía a precursores nitroxenados a través dunha cicloadición formal (5+2) con alenos en presenza de paladio e nesta tese doutoral descríbense os esforzos realizados para acadar a síntese de outros azaheterociclos, presentes nun gran número de moléculas con actividade biolóxica, mediante a activación catalítica de enlaces C-H de alquenos e cadeas alquílicas, cuxa activación se encontra menos explorada.

Síntese de indolinas funcionalizadas a través dunha anelación oxidativa entre 2-alquenil anilidas e alquinos en presencia dun catalizador de rodio

Con anterioridade a este traballo de doutoramento, o noso grupo descubriu que os *o*-alquenilfenois reaccionaban con alquinos en presencia de $[Cp^*RhCl_2]_2$, dando lugar a benzoxepinas ou compostos espirocíclicos en función do substituínte na posición interna do alqueno. Por outra banda, empregando un catalizador de paladio e alenos en lugar de alquinos tamén se obtiveron benzoxepinas. Por mor destes resultados tan interesantes, quixemos saber se esta reactividade se podía estender a *o*-alquenilanilinas. Con este obxectivo en mente, durante o meu traballo de fin de mestrado, exploramos a reactividade destes substratos en presencia de alenos e $Pd(OAc)_2$, dando lugar a un método práctico e sinxelo para a síntese de benzazepinas en grandes rendementos. Despois da conclusión deste proxecto, xa dentro dos meus estudos de doutoramento, quixemos explorar a posibilidade de obter o mesmo tipo de produtos con catálise de rodio e alquinos. Non obstante, os primeiros experimentos en presencia de $[Cp^*RhCl_2]_2$ deron lugar a una mestura de reacción complexa na que fomos capaces de illar unha pequena cantidade dun composto cíclico derivado da indolina.

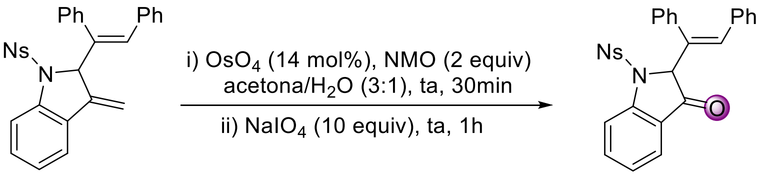
Debido á importancia desta estrutura e á falta de métodos adecuados para a súa síntese, decidimos optimizar esta reacción e conxecturamos que outros Cp, distintos do Cp* clásico, poderían favorecer esta transformación, xa que moitos estudios previos demostraran que as propiedades electrónicas e estéricas do Cp podían ter unha gran influencia na eficiencia e na rexio- e quimioselectividade de certas transformacións. Atendendo á estrutura do produto, especulamos inicialmente que a reacción estivese iniciada por unha activación alílica e, polo tanto, pensamos que un Cp deficiente en electróns, Cp^E, que xa demostrara a súa utilidade noutras activacións alílicas, podería ser o adecuado para a nosa anelación.



Afortunadamente, este Cp con dous ésteres xunto con un nosilo como substituínte no nitróxeno, proporcionaron rendementos excelentes da indolina de forma totalmente selectiva. Ademais destes parámetros, tamén probamos unha gran variedade de aditivos, oxidantes e solventes, acadándose os mellores resultados en tolueno a 80 ºC en presencia de auga como aditivo e Cu(OAc)$_2$, o cal demostrou ser a mellor opción como oxidante.

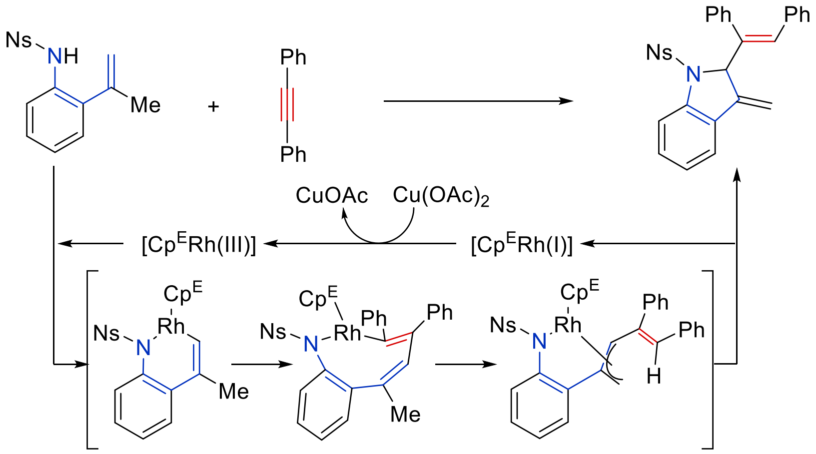
Con respecto ao alcance da reacción, esta tivo lugar en presenza de alquinos simétricos e non-simétricos con substituíntes aromáticos e alquílicos, obténdose rendementos de ata o 89% con rexioselectividades, no caso dos non simétricos, superiores a 10:1. Cabe destacar que a reacción tamén ten lugar cando se empregan eninos. Por outra banda, con respecto ás anilinas, a anelación tamén funciona cando se introducen diversos substituíntes no anel aromático, independentemente da electrónica destes, a excepción dos substituíntes de maior tamaño que o flúor en *orto* á amina. Non obstante, a reacción é moito máis sensible aos substituíntes introducidos no alqueno xa que só funciona cando hai cadeas lineais alquílicas na posición interna deste. Ademais, calquera substituínte na posición externa imposibilita que a reacción teña lugar.

Por outra banda, tamén demostramos a utilidade sintética da nosa transformación oxidando selectivamente o dobre enlace derivado da *o*-alquenilanilida con OsO$_4$, xerando 3-oxoindolinas, esqueleto básico de moitos compostos con interese farmacolóxico.



Igualmente, tamén demostramos que o grupo nosilo pode eliminarse do produto modelo de maneira sinxela, aínda que ao quitalo o dobre enlace exocíclico isomeriza xerando o indol correspondente.

A nosa proposta mecanística para esta transformación, en consonancia cos resultados obtidos e con algúns experimentos con substratos deuterados, comeza, en contraposición coa nosa idea inicial, coa activación do enlace C-H externo do alqueno seguido da inserción migratoria do alquino, dando lugar a un rodaciclo de 8 membros. Este intermedio proponse que evoluciona a través dunha transposición [1,5] de hidróxeno coa conseguinte migración do rodio(III). A continuación, eliminación redutora dende o complexo π-alílico resultante deste desprazamento xera un complexo de Rh(I), illado en condicións estequiométricas, coordinado ao produto. Finalmente, este complexo de Rh(I) libera o produto despois de ser oxidado a Rh(III) pola acción do cobre.



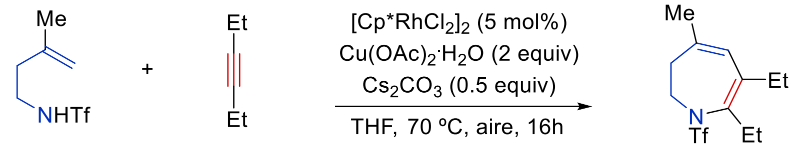
Non obstante, cálculos DFT recentes suxiren que a reacción podería transcorrer por outro camiño a partir do rodaciclo de 8 membros. En lugar da migración de rodio, a cal estaría bastante desfavorecida polo entorno estérico do Rh(III) cos seus tres respectivos ligandos aniónicos, tería lugar a inserción intramolecular do alqueno da anilida no enlace Rh-N, xerando un intermedio tricíclico de bastante interese. Dende este intermedio, β-eliminación de hidruro e posterior eliminación redutora daría lugar ao composto final.

O noso grupo de investigación tamén descubriu que este tipo de substratos, cun triflato no nitróxeno, poden reaccionar con alquinos en presenza de $[Cp^*RhCl_2]_2$ para dar lugar a naftilamidas. Intrigados por este descubrimento, procedemos a avaliar a influencia de distintos parámetros na formación de un ou outro produto. Como conclusións xerais, observamos que empregando o ligando Cp^E ou outros menos ricos electrónicamente que o Cp*, como Cp^{iPr} ou Cp, a naftilamida nunca se formaba. Non obstante, empregando $[Cp^*RhCl_2]_2$ sempre se detectaba este produto en medio de reacción, independentemente das condicións escollidas ou do substituínte presente no nitróxeno. Con respecto á indolina, esta fórmase nun rango maior de condicións, aínda que tanto o nosilo como o Cp^E son necesarios para acadar un proceso selectivo e eficiente.

Síntese diverxente de azepinas e pirrolidinas a través dunha anelación catalizada por rodio(III) entre homoalilamidas e alquinos iniciada pola activación de enlaces C-H

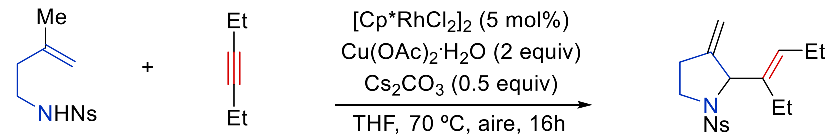
Despois da conclusión do proxecto previo, preguntámonos se sería posible acadar unha reactividade parecida empregando precursores análogos non aromáticos. Non obstante, as homoalilaminas son unha sustancia de partida aínda máis complexa xa que son susceptibles de oxidarse ás correspondentes iminas en presenza de reactivos oxidantes. Ademais, o seu uso como precursores en reaccións catalizadas por metais de transición que son iniciadas pola activación de enlaces C-H está limitado a un par de exemplos en algunhas transformacións catalizadas por paladio, en parte debido a que estas moléculas son moi sensibles a reaccionar con nucleófilos e electrófilos despois da coordinación do metal ao alqueno. Non obstante, sería realmente interesante afondar en novos estudios con estes substratos xa que desenrolar anulacións con eles pode dar lugar a múltiples esqueletos de produtos naturais e outras sustancias bioactivas.

Tras realizar algúns experimentos iniciais empregando *N*-triflil homoalilamidas e difenilacetileno en presenza de $[Cp^*RhCl_2]_2$, detectamos trazas de azepina, composto de sete membros con un gran interese sintético. Esta observación atraeu aínda máis a nosa atención sobre estes substratos xa que non foramos capaces de obter este tipo de esqueleto cos precursores aromáticos en presencia de catalizadores de rodio. Centrando a nosa atención na optimización da reacción, descubrimos que cambiando a un alquino alquílico, 3-hexino, os rendementos aumentaron ata o 20% en presenza de Cs_2CO_3 como base e $Cu(OAc)_2$ como oxidante en THF como solvente. Desafortunadamente, por moito que intentamos mellorar estes rendementos modificando diversos parámetros como o solvente, os aditivos, o oxidante ou o catalizador, non tivemos éxito. Tamén quixemos estudar como influía na eficacia da reacción a introdución de algúns substituíntes na estrutura da homoalilamida, así e todo, calquera modificación deu lugar a peores resultados.



Ante a incapacidade de incrementar os rendementos, independentemente da modificación que fixeramos, pensamos que podíamos ter algún tupo de problema asociado coa inhibición da reacción por parte do produto desta, probablemente mediante a coordinación de Rh(I) ao dieno xerado no produto final. Inspirados por unha publicación recente entre ácidos acrílicos e alquinos na cal tiñan un problema similar, o cal só foron capaces de solucionar empregando electroquímica, decidimos ensamblar a nosa propia cela electroquímica con eléctrodos de platino e grafito e unha fonte de potencial externa. Non obstante, todos os nosos intentos de mellorar o rendemento empregando electroquímica para a oxidación do Rh(I) fracasaron independentemente dos materias empregados nos eléctrodos, do solvente ou dos aditivos empregados. Non obstante, novos estudios nesta liña están sendo levados a cabo no noso laboratorio na actualidade co obxectivo de acadar procesos máis baratos, eficientes e verdes.

Curiosamente, cando cambiamos o triflato por un nosilo como substituínte na homoalilamina, detectamos por RMN a formación dun produto maioritario distinto que despois de difracción de Raios X identificamos como unha pirrolidina nun 18% de rendemento.



Este resultado sorprendeunos e incrementou aínda máis o noso interese nesta transformación, xa que esa diverxencia entre produtos simplemente modificando o substituínte no nitróxeno é pouco habitual e máis considerando que no caso das *o*-alquenilanilidas este produto só se formaba de xeito maioritario en presenza de [Cp^{E}RhCl$_2$]$_2$ e non co Cp* clásico. Non obstante, todos os intentos por mellorar o rendemento da reacción, incluído o emprego de distintos Cp, fracasaron de novo.

Con respecto ao mecanismo, ambos produtos fórmanse a partir da activación do enlace C-H do alqueno e posterior inserción migratoria do alquino. O rodaciclo de 8 membros que se obtén tras esta etapa é a partir do cal ten lugar a diverxencia que explica a formación dun ou outro produto. Mentres que a azepina se forma mediante eliminación redutora, a pirrolidina pode obterse a partir da migración de rodio proposta para as indolinas ou, de acordo cos cálculos DFT, mediante a inserción do alqueno no enlace Rh-N e posterior β-eliminación de hidruro seguida de eliminación redutora. Ambas propostas mecanísticas concluirían coa formación dun complexo de Rh(I)-produto, tendo que oxidarse o rodio para poder comezar un novo ciclo catalítico, non obstante, todo parece indicar que esta etapa non ocorre de xeito eficiente.

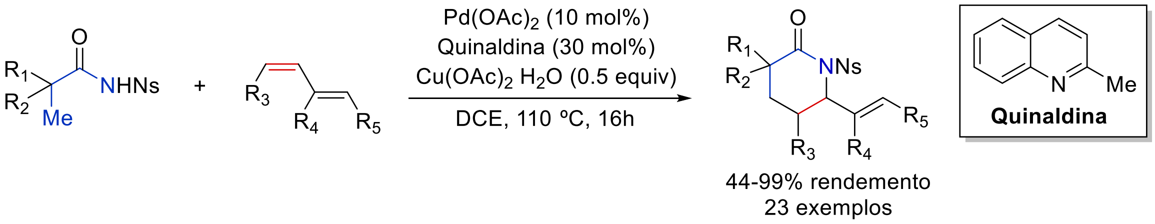
Cicloadición formal (4+2) catalizada por paladio entre amidas alquílicas e dienos iniciada pola activación de enlaces C(sp^3)-H.

Despois do éxito colleitado polo noso grupo de investigación no descubrimento e optimización de cicloadicións iniciadas pola activación de enlaces C-H de alquenos, decidimos centrar a nosa atención no seguinte desafío, desenvolver anelacións iniciadas pola activación de enlaces C(sp^3)-H. Esta activación, non obstante, considérase máis complicada debido á menor acidez destes hidróxenos, á falta dun dobre enlace que coordine ó metal e o aproxime ao enlace que se desexa activar e á menor forza do enlace C(sp^3)-M en comparación ao C(sp^2)-M. Isto explica porque esta activación foi menos explorada ao longo dos anos e porque require en moitas ocasións do emprego de ligandos que baixan a barreira enerxética da activación.

Non obstante, nos últimos anos, este campo experimentou un gran avance, publicándose múltiples exemplos de funcionalizacións C(sp^3)-H catalizadas por paladio. Así e todo, con respecto ás cicloadicións, estas están principalmente restrinxidas a reaccións de carbonilación e algúns exemplos peculiares de activación C-H alílica. Polo tanto, o desenvolvemento de cicloadicións (n+2) sería moi útil e daría lugar a esqueletos heterocíclicos saturados a partir de precursores acíclicos realmente sinxelos.

Polo tanto, despois de analizar posibles substratos para levar a cabo a cicloadición desexada, consideramos que as amidas alquílicas serían unha boa opción debido ás grandes características da amida como grupo director débil, utilizándose estas xa previamente en múltiples funcionalizacións C(sp^3)-H. Tendo en conta o precedente deste tipo de precursores con acrilatos, no cal non tiña lugar unha cicloadición xa que despois da inserción migratoria estaba máis favorecido un proceso de β-eliminación de hidruro en lugar da desexada eliminación redutora. Entón pensamos que empregando alenos poderíamos evitar esta etapa debido á formación dun intermedio π-alílico estabilizado.

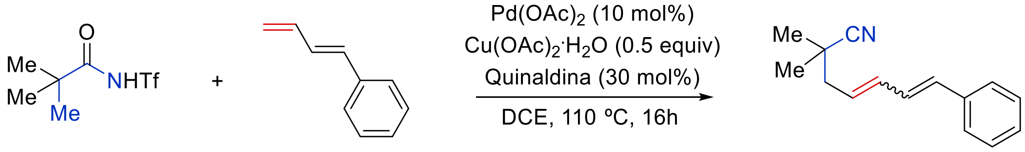
Algúns experimentos iniciais revelaron que a nosa hipótese era correcta. Non obstante, despois dun largo proceso de optimización os rendementos non eran o suficientemente bos. Chegados a este punto, procedemos a avaliar outros compostos típicos e mentres alquinos ou alquenos fracasaron, dienos, os cales tamén proporcionan un intermedio π-alílico, reaccionaron eficientemente cara á formación do produto 4+2 desexado. Despois dun amplo proceso de optimización, descubrimos que tanto o uso dun ligando monodentado nitroxenado, quinaldina, como a introdución dun grupo nosilo na amida eran fundamentais para obter rendementos altos. Ademais, outros parámetros como o oxidante ou o solvente demostraron non ser triviais.



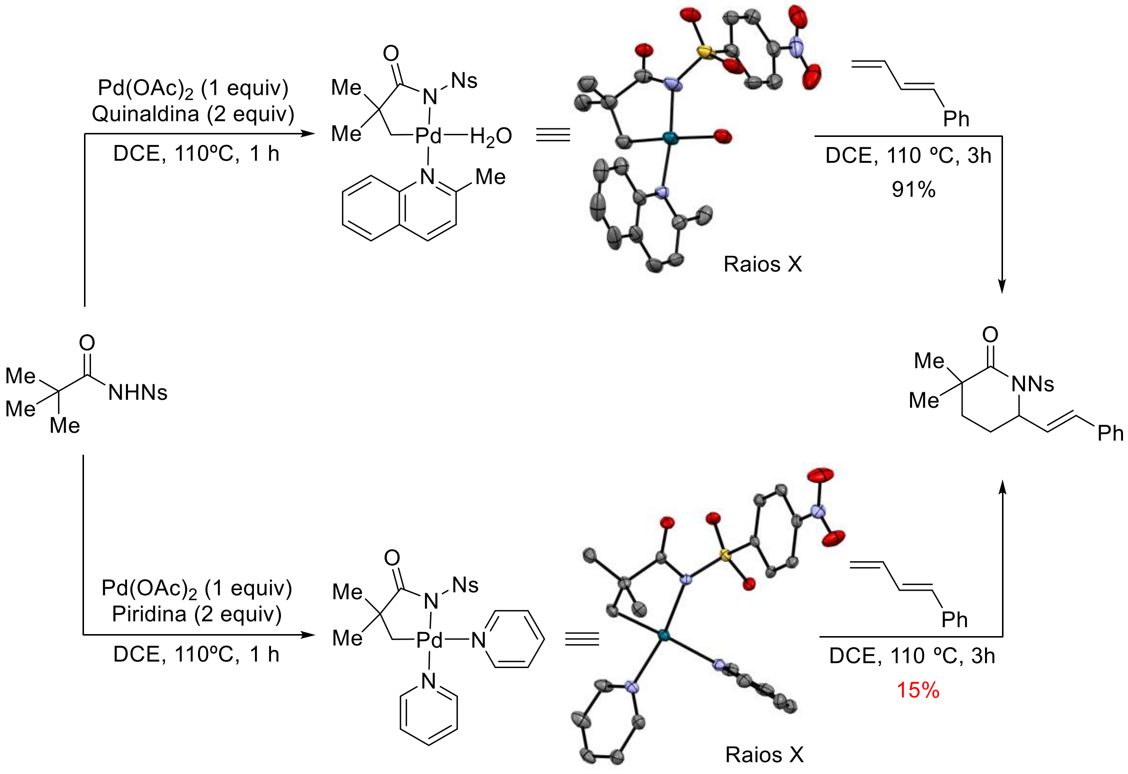
Con respecto ao alcance da reacción, obtivemos moi bos rendementos con diversos dienos aromáticos, independentemente da electrónica dos substituíntes. Dienos con substituíntes alquílicos ou cun éster tamén reaccionaron eficientemente. Ademais, dienos con outro tipo de substitución, como o isopreno, ou disubstituídos tamén deron lugar ao produto desexado, aínda que en rendementos máis baixos. Inesperadamente, tamén tivemos reacción cando empregamos un dieno cíclico, 1,3-ciclohexadieno, obténdose unha estrutura bicíclica bastante interesante. Con respecto á amida, os substratos cuaternarios con dous metilos e diversos substituíntes na posición restante funcionaron moi ben mentres que aqueles cun só metilo deron lugar a peores resultados. Por outra banda, os substratos con hidróxenos en α, xeraron mesturas inseparables de lactamas saturadas e α,β-insaturadas, excepto no caso dunha amida cun substituínte derivado da alanina, co cal se obtivo unicamente o composto saturado. No caso dos substratos que daban lugar a mesturas realizamos un profundo estudo para tratar de controlar a selectividade entre ambos produtos, non obstante, nunca fomos capaces de obter a lactama saturada de xeito maioritario.

Para demostrar a utilidade sintética deste método, encargámonos de eliminar o grupo nosilo e de reducir a lactama á correspondente piperidina. Ademais, a apertura do ciclo proporcionou un interesante δ-aminoácido.

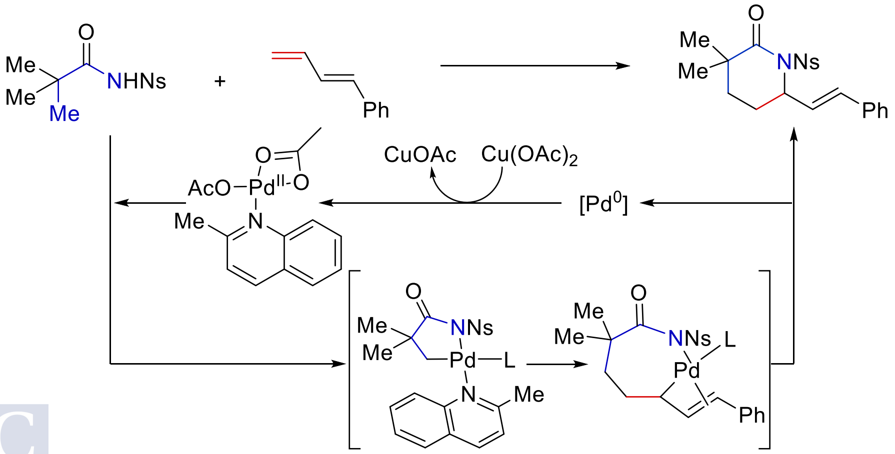
Sorprendentemente, cando levamos a cabo a reacción modelo en presencia dunha homoalilamina triflada, obtivemos un produto acíclico de olefinación cun nitrilo en vez da amida esperada.



Co obxectivo de descubrir o rol fundamental da quinaldina, realizamos varios experimentos estequiométricos en presencia de diferentes ligandos. Empregando quinaldina, fomos capaces de illar o paladaciclo de 5 membros resultante da activación C-H, cuxa estrutura de Raios X mostrou una disposición plano-cadrada distorsionada cunha única molécula de ligando coordinada ao paladio. Ademais, cando sometemos este complexo ás condicións de reacción en presencia de dieno, vimos que se obtiña un gran rendemento do produto desexado, demostrándose así que este complexo é un intermedio de reacción. Por outra banda, levando a cabo un experimento idéntico en presenza de piridina en vez de quinaldina, obtivemos un complexo con dúas moléculas de ligando coordinadas, atribuíble ao menor tamaño da piridina. Neste caso, cando fixemos reaccionar este complexo co dieno, só obtivemos un 15% de rendemento, o que indica a dificultade asociada ao desprazamento dun destes ligandos polo dieno, polo que o entorno estérico do ligando parece crucial para evitar a formación deste tipo de dímeros.



Toda esta información axudounos a propoñer un ciclo catalítico no que a quinaldina xoga varios papeis clave. Ademais de evitar a coordinación de dúas unidades de ligando polas súas propiedades estéricas, tamén evita a coordinación de dúas amidas antes da activación C-H e rompe o trímero de paladio inicial, o cal presenta pouca ou nula actividade catalítica. Máis aló destas funcións especiais da quinaldina, a reacción segue unha secuencia mecanística clásica neste tipo de cicloadicións (n+2): activación C-H, coordinación e inserción migratoria do dieno e eliminación redutora dende o π-alilo resultante.



Finalmente, despois da conclusión deste proxecto, tratamos de desenvolver outras cicloadicións iniciadas pola activación deste tipo de enlaces C(sp^3)-H. Afortunadamente, descubrimos que esta combinación de ligandos tipo quinolina con dienos podía aplicarse a outros substratos sen apenas modificacións. Por exemplo, fomos capaces de obter un

70% de rendemento nuns poucos experimentos empregando *o*-metilanilidas como precursores.

Experimental section

General procedures

Reactions were conducted in dry solvents under inert atmosphere unless otherwise stated. Dry solvents were obtained from Acros Organics, Extra Dry over Molecular Sieves, or Sigma-Aldrich, and used without further purification. $[Cp^*RhCl_2]_2$ (97%) [12354-85-7] was obtained from Sigma-Aldrich and $Pd(OAc)_2$ (98%) [3375-31-1] was obtained from Strem while $[Cp^ERhCl_2]_2$ was synthesized following reported procedures.[109] All other chemicals were purchased from Sigma-Aldrich, Acros Organics, TCI Chemicals, Alfa Aesar or Fluorochem and they were used as received. All rhodium- or palladium-catalyzed reactions were carried out without precautions to elude moisture or oxygen.

With regard to the electrochemical reactions, they were performed in an undivided cell equipped with platinum electrodes (20 x 10 x 0.25 mm, 99.9 %; obtained from ChemPur,® Germany) and graphite electrodes (20 x 10 x 0.5 mm, 99.8%; obtained from Alfa Aesar) and they were connected using stainless steel adapters with a gap of 6 mm. Electrocatalysis was performed using an AXIOMET AX-3003P potentiostat.

The abbreviation "rt" refers to reactions carried out at a temperature between 21-25 ºC. Reaction mixtures were stirred using Teflon-coated magnetic stir bars. Thin layer chromatography (TLC) was carried out on pre-coated silica gel F_{254} plates with visualization under UV light and/or by dipping the plate into solutions of *p*-anisaldehyde, ninhydrin or cerium nitrate followed by heating. Column chromatography was performed on silica gel (40-63 µm) unless otherwise stated.

NMR data was collected on Varian Mercury 300 MHz, Varian Innova 500 MHz or Bruker AVIII 500 MHz spectrometers. Chemical shifts are given in ppm (δ) and are referenced to the residual $CDCl_3$ solvent peak at 7.26 ppm (^1H NMR) and 77.16 ppm (^{13}C NMR). Conventional one-dimensional (1D) ^1H NMR, ^{19}F NMR, ^{13}C NMR, Distortionless Enhancement by Polarization Transfer Spectra (DEPT) and two-dimensional (2D) ^1H-^1H Correlation Spectroscopy (COSY), ^1H-^1H Nuclear Overhauser Effect Spectroscopy (NOESY), ^1H-^{13}C heteronuclear single quantum coherence (HSQC), ^1H-^{13}C Heteronuclear Multiple-Bond Correlation Spectroscopy (HMBC) experiments were recorded at room temperature under routine conditions. NMR data was analyzed using MestReNova NMR data processing software (http://mestrelab.com/). High Resolution Mass Spectra (HRMS) were performed at the CACTUS facility of the University of Santiago de Compostela on a Bruker micrOTOF spectrometer.

X-ray crystallographic analysis was performed at the CACTUS facility of the University of Santiago de Compostela or the CACTI facility of the University of Vigo.

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Chapter I – Rhodium(III)-catalyzed annulation of 2-alkenyl anilides with alkynes through C-H activation: direct access to 2-substituted indolines

Chapter adapted from:
Font, M.[a]; Cendón, B.[a]; Seoane, A.[a]; Mascareñas, J. L.[a]*; Gulías, M.[a]* *Angew. Chem. Int. Ed.* **2018**, *57*, 8255-8259.

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1. Synthesis of starting materials

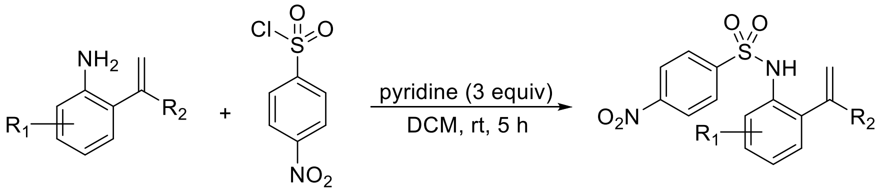
1.1 Preparation of alkynes

Alkynes **2a** (diphenylacetylene), **2d** (5-decyne), **2e** (1-phenyl-1-butyne) and enyne **2h** (2-methyl-1-hexen-3-yne) were purchased from Sigma-Aldrich. Alkynes **2b** (1,2-bis-(4-methoxyphenyl)ethyne) and **2c** (1,2-bis(4-(trifluoromethyl)phenyl)ethyne,[178] **2f** (*tert*-butyldimethyl((6-phenylhex-5-yn-1-yl)oxy)silane) [179] and **2g** ((cyclopropylethynyl)benzene)[180] were synthesized according to the literature and the recorded spectral data was in agreement with the previously described.

1.2 Preparation of 2-alkenylanilides

Non-commercially available alkenylanilines were synthesized from the addition of the corresponding Grignard reagent to the corresponding substituted 2-aminobenzonitrile followed by Wittig reaction of the corresponding ketone, except for **1o**, whose synthesis was accomplished, as previously described, from 2-nitrobenzaldehyde by Wittig reaction followed by reduction of the nitro group.[181] Moreover, **1k** required an additional initial step from the corresponding aryl iodide via cross-coupling reaction. Tosyl,[182] acetyl[183] and triflyl[93] protected *o*-alkenylanilines were synthesized as previously described in the literature. Spectral data recorded was in agreement with the previously reported.

General procedure for the synthesis of nosyl-protected 2-alkenylanilides (1a-1r):



To a solution of 2-alkenylaniline (1.5 mmol) and 4-nitrobenzenesulfonyl chloride (360 mg, 1.65 mmol) in dichloromethane (5 mL) under Argon atmosphere was added pyridine (0.360 ml, 4.5 mmol) and the reaction mixture was stirred at room temperature. Upon completion (3-5h), as monitored by TLC, the reaction was quenched with H_2O. Then, the resulting mixture was extracted with dichloromethane three times and the combined organic layers were washed with HCl 1M and dried over anhydrous Na_2SO_4. Evaporation of the solvent followed by purification by flash column chromatography on silica gel (20% Et_2O/hexanes) afforded the pure *N*-nosylated 2-alkenylanilines.

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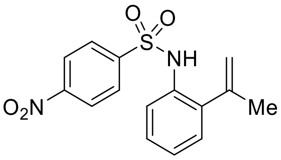
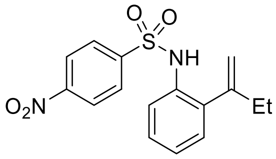
4-nitro-*N*-(2-(prop-1-en-2-yl)phenyl)benzenesulfonamide (1a)



1a

1a obtained as a pale yellow solid (435 mg, 91% yield). **^{1}H NMR** (300 MHz $CDCl_3$) δ, ppm: 8.28 (d, *J* = 8.6 Hz, 2H), 7.92 (d, *J* = 8.6 Hz, 2H), 7.65 (d, *J* = 8.1 Hz, 1H), 7.26 (t, *J* = 8.0 Hz 1H), 7.14–7.10 (m, 2H), 7.05 (d, *J* = 7.5 Hz, 1H), 5.28 (s, 1H), 4.68 (s, 1H), 1.70 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ, ppm: 150.5 (C), 145.1 (C), 142.0 (C), 135.4 (C), 132.0 (C), 128.7 (CH), 128.6 (CH) 128.6 (CH), 125.6 (CH), 124.4 (CH), 121.1 (CH), 117.7 (CH_2), 24.5 (CH_3). **HRMS** (APCI, **$[M\text{-}H]^-$**) *m/z* calculated for $C_{15}H_{13}N_2O_4S$: 317.0602, found 317.0599.

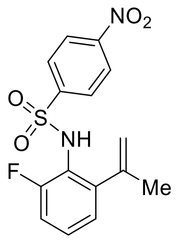
***N*-(2-(but-1-en-2-yl)phenyl)-4-nitrobenzenesulfonamide (1d)**



1d

1d obtained as a white solid (429 mg, 86% yield). **^{1}H NMR** (300 MHz, $CDCl_3$) δ, ppm: 8.25 (d, *J* = 8.9 Hz, 2H), 7.94 (d, *J* = 8.9 Hz, 2H), 7.64 (d, *J* = 8.2 Hz, 1H), 7.25 (t, *J* = 7.7 Hz, 1H), 7.13–7.06 (m, 2H), 7.01 (d, *J* = 7.5 Hz, 1H), 5.25 (s, 1H), 4.66 (s, 1H), 1.98 (q, *J* = 7.3 Hz, 2H), 0.87 (t, J = 7.4 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ, ppm: 150.4 (C), 147.6 (C), 145.0 (C), 134.5 (C), 132.4 (C), 128.8 (CH), 128.6 (CH), 128.4 (CH), 125.2 (CH), 124.3 (CH), 120.2 (CH), 115.5 (CH_2), 30.8 (CH_3), 12.0 (CH_2). **HRMS** (APCI, **$[M\text{-}H]^-$**) *m/z* calculated for $C_{16}H_{15}N_2O_4S$: 331.0758, found: 331.0758.

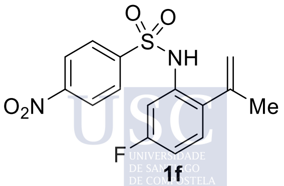
***N*-(2-fluoro-6-(prop-1-en-2-yl)phenyl)-4-nitrobenzenesulfonamide (1e)**



1e

1e obtained as a yellow solid (262 mg, 52% yield). **^{1}H NMR** (300 MHz, DMF-d_7) δ, ppm: 10.02 (s, 1H), 8.50 (d, *J* = 7.4 Hz, 2H), 8.12 (d, *J* = 7.4 Hz, 2H), 7.38 (q, *J* = 7.6 Hz, 1H), 7.20–7.11 (m, 2H), 5.13 (s, 1H), 5.00 (s, 1H), 2.03 (s, 3H). **^{13}C NMR** (75 MHz, DMF-d_7) δ, ppm: 160.5 (d, $J_{C\text{-}F}$ = 248.1 Hz, C), 151.1 (C), 149.1 (C), 147.0 (C), 143.2 (C), 130.4 (d, $J_{C\text{-}F}$ = 8.6 Hz, CH), 129.5 (CH), 125.9 (CH), 125.4 (CH), 121.8 (d, $J_{C\text{-}F}$ = 14.1 Hz, C), 118.2 (CH_2), 115.8 (d, $J_{C\text{-}F}$ = 21.1 Hz, CH), 24.2 (CH_3). **HRMS** (APCI, **$[M\text{-}H]^-$**) *m/z* calculated for $C_{15}H_{12}FN_2O_4S$: 335.0507, found: 335.0506.

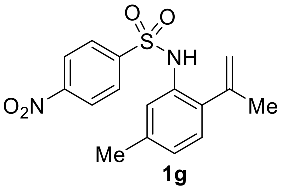
***N*-(5-fluoro-2-(prop-1-en-2-yl)phenyl)-4-nitrobenzenesulfonamide (1f)**



1f

1f obtained as a yellow solid (434 mg, 86% yield). **^{1}H NMR** (300 MHz, $CDCl_3$) δ, ppm: 8.31 (d, *J* = 8.8 Hz, 2H), 7.97 (d, *J* = 8.8 Hz, 2H), 7.40 (dd, *J* = 10.3 Hz, *J* = 2.5 Hz, 1H), 7.21 (s, 1H), 7.02 (dd, *J* = 8.5 Hz, *J* = 6.2 Hz, 1H), 6.80 (td, *J* = 8.3, *J* = 2.5 Hz, 1H), 5.31 (s, 1H), 4.68 (s, 1H), 1.72 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ, ppm: 162.0 (d, $J_{C\text{-}F}$ = 246.9 Hz, C), 150.5 (C), 144.6 (C), 141.1 (C), 133.4 (d, $J_{C\text{-}F}$ = 10.7 Hz, C), 130.6 (C), 129.8 (d, $J_{C\text{-}F}$ = 9.0 Hz, CH), 128.6 (CH), 124.5 (CH), 118.2 (CH_2), 112.2 (d, $J_{C\text{-}F}$ = 21.5 Hz, CH), 107.7 (d, $J_{C\text{-}F}$ = 26.6 Hz, CH), 24.7 (CH_3). **HRMS** (APCI, **$[M\text{-}H]^-$**) *m/z* calculated for $C_{15}H_{12}FN_2O_4S$: 335.0507, found: 335.0505.

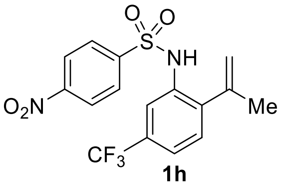
N-(5-methyl-2-(prop-1-en-2-yl)phenyl)-4-nitrobenzenesulfonamide (1g)



1g

1g obtained as a pale yellow solid (388 mg, 78% yield). **^{1}H NMR** (300 MHz, $CDCl_3$) δ, ppm: 8.28 (d, *J* = 8.9 Hz, 2H), 7.91 (d, *J* = 8.9 Hz, 2H), 7.47 (s, 1H), 7.12 (s, 1H), 6.94-6.91 (m, 2H), 5.24 (s, 1H), 4.62 (s, 1H), 2.35 (s, 3H), 1.65 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ, ppm: 150.2 (C), 144.9 (C), 141.8 (C), 138.4 (C), 132.5 (C), 131.6 (C), 128.5 (CH), 128.1 (CH), 126.3 (CH), 124.2 (CH), 121.7 (CH), 117.2 (CH_2), 24.6 (CH_3), 21.4 (CH_3). **HRMS** (APCI, **[M-H]$^-$**) *m/z* calculated for $C_{16}H_{15}N_2O_4S$: 331.0758, found: 331.0756.

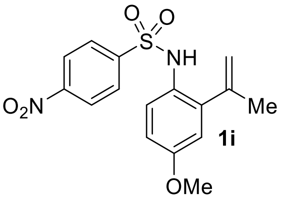
4-nitro-*N*-(2-(prop-1-en-2-yl)-5-(trifluoromethyl)phenyl)benzenesulfonamide (1h)



1h

1h obtained as a pale yellow solid (504 mg, 87% yield). **^{1}H NMR** (300 MHz, $CDCl_3$) δ, ppm: 8.31 (d, *J* = 8.7 Hz, 2H), 7.96 (d, *J* = 8.6 Hz, 2H), 7.91 (s, 1H), 7.36 (d, *J* = 8.0 Hz, 1H), 7.25 (s, 1H), 7.18 (d, *J* = 8.0 Hz, 1H), 5.37 (s, 1H), 4.75 (s, 1H), 1.76 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ, ppm: 150.6 (C), 144.5 (C), 140.8 (C), 138.4 (C), 132.7 (C), 130.8 (q, J_{C-F} = 32.7 Hz, C), 129.2 (CH), 128.7 (CH), 124.6 (CH), 123.6 (q, J_{C-F} = 270.6 Hz, C), 122.0 (q, J_{C-F} = 3.3 Hz, CH), 118.7 (CH_2), 117.4 (CH), 24.3 (CH_3). **HRMS** (APCI, **[M-H]$^-$**) *m/z* calculated for $C_{16}H_{12}F_3N_2O_4S$: 385.0475, found: 385.0473.

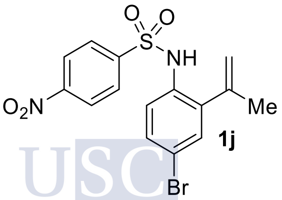
N-(4-methoxy-2-(prop-1-en-2-yl)phenyl)-4-nitrobenzenesulfonamide (1i)



1i

1i obtained as a yellow solid (387 mg, 74% yield). **^{1}H NMR** (300 MHz, $CDCl_3$) δ, ppm: 8.26 (d, *J* = 8.8 Hz, 2H), 7.85 (d, *J* = 8.8 Hz, 2H), 7.55 (d, *J* = 8.9 Hz, 1H), 6.88 (s, 1H), 6.81 (dd, *J* = 8.9 Hz, *J* = 2.8 Hz, 1H), 6.56 (d, *J* = 2.8 Hz, 1H), 5.19 (s, 1H), 4.58 (s, 1H), 3.77 (s, 3H), 1.59 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ, ppm: 157.6 (C), 150.3 (C), 145.1 (C), 145.1 (C), 141.9 (C), 138.1 (C), 128.7 (CH), 124.5 (CH), 124.3 (CH), 117.3 (CH_2), 113.9 (CH), 113.7 (CH), 55.6 (CH_3), 24.4 (CH_3). **HRMS** (APCI, **[M-H]$^-$**) *m/z* calculated for $C_{16}H_{15}N_2O_5S$: 347.0707, found: 347.0705.

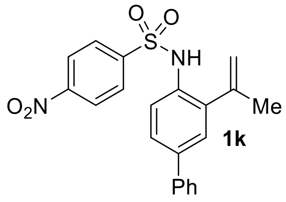
N-(4-bromo-2-(prop-1-en-2-yl)phenyl)-4-nitrobenzenesulfonamide (1j)



1j

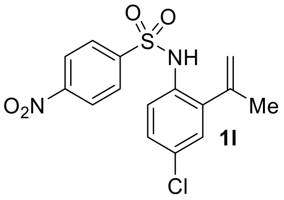
1j obtained as a yellow solid (501 mg, 84% yield). **^{1}H NMR** (300 MHz, $CDCl_3$) δ, ppm: 8.30 (d, *J* = 8.9 Hz, 2H), 7.92 (d, *J* = 8.9 Hz, 2H), 7.52 (d, *J* = 8.7 Hz, 1H), 7.36 (dd, *J* = 8.7 Hz, *J* = 2.2 Hz, 1H), 7.18 (d, *J* = 2.3 Hz, 1H), 7.08 (s, 1H), 5.29 (s, 1H), 4.67 (s, 1H), 1.68 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ, ppm: 150.5 (C), 144.7 (C), 140.7 (C), 137.2 (C), 131.5 (CH), 131.4 (CH), 131.1 (C), 128.6 (CH), 124.5 (CH), 122.6 (CH), 118.8 (C), 118.5 (CH_2), 24.4 (CH_3). **HRMS** (APCI, **[M-H]$^-$**) *m/z* calculated for $C_{15}H_{12}BrN_2O_4S$: 394.9707, found: 394.9709.

4-nitro-*N*-(3-(prop-1-en-2-yl)-[1,1'-biphenyl]-4-yl)benzenesulfonamide (1k)


1k

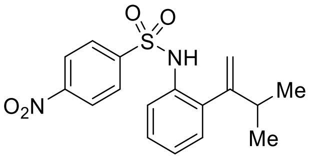
1k obtained as a yellow solid (556 mg, 94% yield). **^{1}H NMR** (300 MHz, $CDCl_3$) δ, ppm: 8.29 (d, *J* = 8.6 Hz, 2H), 7.98 (d, *J* = 8.5 Hz, 2H), 7.72 (d, *J* = 8.4 Hz, 1H), 7.56-7.48 (m, 3H), 7.42 (t, *J* = 7.4 Hz, 2H), 7.35 (d, *J* = 7.1 Hz, 2H), 7.29 (d, *J* = 1.8 Hz, 1H), 7.22 (s, 1H), 5.33 (s, 1H), 4.74 (s, 1H), 1.76 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ, ppm: 150.3 (C), 144.9 (C), 141.8 (C), 139.7 (C), 138.3 (C), 135.7 (C), 131.0 (C), 129.0 (CH), 128.6 (CH), 127.7 (CH), 127.0 (CH), 127.0 (CH), 126.9 (CH), 124.4 (CH), 121.3 (CH), 117.8 (CH_2), 24.6 (CH_3). **HRMS** (APCI, **$[M-H]^-$**) *m/z* calculated for $C_{21}H_{17}N_2O_4S$: 393.0915, found: 393.0915.

N-(4-chloro-2-(prop-1-en-2-yl)phenyl)-4-nitrobenzenesulfonamide (1l)


1l

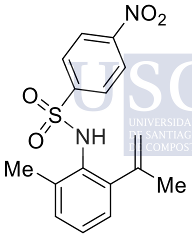
1l obtained as a pale orange solid (376 mg, 71% yield). **^{1}H NMR** (300 MHz, $CDCl_3$) δ, ppm: 8.29 (d, *J* = 7.3 Hz, 2H), 7.92 (d, *J* = 7.3 Hz, 2H), 7.57 (d, *J* = 8.0 Hz, 1H), 7.21 (d, *J* = 8.7 Hz, 1H), 7.12 (s, 1H), 7.02 (s, 1H), 5.28 (s, 1H), 4.66 (s, 1H), 1.67 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ, ppm: 150.4 (C), 144.6 (C), 140.6 (C), 137.0 (C), 131.0 (C), 130.5 (C), 128.6 (CH), 128.4 (CH), 124.5 (CH), 122.6 (CH), 122.5 (CH), 118.4 (CH_2), 24.3 (CH_3). **HRMS** (APCI, **$[M-H]^-$**) *m/z* calculated for $C_{15}H_{12}ClN_2O_4S$: 351.0212, found 351.0211.

N-(2-(3-methylbut-1-en-2-yl)phenyl)-4-nitrobenzenesulfonamide (1m)


1m

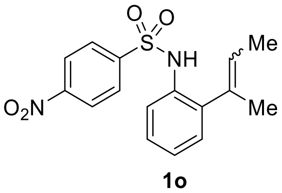
1m obtained as a yellowish solid (317 mg, 61% yield). **^{1}H NMR** (300 MHz, $CDCl_3$) δ, ppm: 8.28 (d, *J* = 8.9 Hz, 2H), 7.99 (d, *J* = 8.9 Hz, 2H), 7.64 (d, *J* = 8.2 Hz, 1H), 7.28 – 7.21 (m, 1H), 7.11 – 7.04 (m, 1H), 7.03 – 6.97 (m, 2H), 5.25 (s, 1H), 4.60 (s, 1H), 2.36 – 2.19 (m, 1H), 0.92 (d, *J* = 6.8 Hz, 6H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ, ppm; 152.1 (C), 150.4 (C), 145.1 (C), 133.9 (C), 132.9 (C), 129.1 (CH), 128.6 (CH), 128.4 (CH), 124.7 (CH), 124.4 (CH), 118.9 (CH), 114.6 (CH_2), 35.1 (CH), 21.2 (CH_3). **HRMS** (APCI, **$[M-H]^-$**) *m/z* calculated for $C_{17}H_{17}N_2O_4S$: 345.0915, found 345.0914.

N-(2-methyl-6-(prop-1-en-2-yl)phenyl)-4-nitrobenzenesulfonamide (1n)


1n

1n obtained as a white solid (429 mg, 86% yield). **^{1}H NMR** (300 MHz, $CDCl_3$) δ, ppm: 8.28 (d, *J* = 8.9 Hz, 2H), 7.92 (d, *J* = 8.9 Hz, 2H), 7.20 – 7.14 (m, 2H), 7.03 – 6.91 (m, 1H), 6.85 (s, 1H), 4.91 (s, 1H), 4.67 (s, 1H), 2.32 (s, 3H), 1.65 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ, ppm: 150.1 (C), 146.5 (C), 143.2 (C), 142.7 (C), 138.3 (C), 130.5 (CH), 129.8 (C), 128.9 (CH), 128.2 (CH), 126.8 (CH), 124.1 (CH), 116.8 (CH_2), 23.7 (CH_3), 19.7 (CH_3). **HRMS** (APCI, **$[M-H]^-$**) *m/z* calculated for $C_{16}H_{15}N_2O_4S$: 331.0758, found 331.0758.

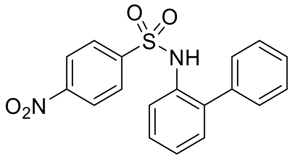
N-(2-(but-2-en-2-yl)phenyl)-4-nitrobenzenesulfonamide (1o)



1o
E:*Z* = 2.5:1

1o obtained as an inseparable mixture 2.5:1 of *E*:*Z* isomers as a yellow solid (399 mg, 80% yield). **^{1}H NMR** (300 MHz, $CDCl_3$) δ, ppm: 8.32 – 8.22 (m, 2H), 7.98 (d, *J* = 8.9 Hz, 1.5H), 7.90 (d, *J* = 8.9 Hz, 0.5H), 7.62 (t, *J* = 9.1 Hz, 1H), 7.30 – 7.17 (m, 1.1H), 7.15 – 7.05 (m, 1H), 7.02 – 6.93 (m, 1.3H), 6.82 (s, 0.6H), 5.71 (q, *J* = 6.8 Hz, 0.7H), 5.12 (q, *J* = 6.7 Hz, 0.3H), 1.70 (d, *J* = 6.7 Hz, 0.8H), 1.60 – 1.54 (m, 3H), 1.31 – 1.25 (m, 2.2H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ, ppm: 150.4 (2 x C), 145.2 (C), 145.1 (C), 137.5 (2 x C), 132.7 (C), 132.6 (C), 132.4 (C), 132.2 (C), 129.1 (2 x CH), 128.6 (2 x CH), 128.3 (CH), 128.0 (CH), 127.1 (CH), 126.4 (CH), 125.5 (CH), 125.4 (CH), 124.4 (2 x CH), 121.0 (CH), 119.1 (CH), 25.0 (CH_3), 17.9 (CH_3), 14.6 (CH_3), 14.1 (CH_3). **HRMS** (APCI, **$[M-H]^-$**) *m/z* calculated for $C_{16}H_{15}N_2O_4S$: 331.0758, found 331.0761.

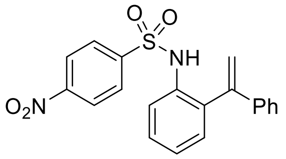
N-([1,1'-biphenyl]-2-yl)-4-nitrobenzenesulfonamide (1p)



1p

1p obtained as a yellowish solid (462 mg, 87% yield). **^{1}H NMR** (300 MHz, $CDCl_3$) δ, ppm: 8.16 (d, *J* = 8.9 Hz, 2H), 7.70 (d, *J* = 8.1 Hz, 1H), 7.65 (d, *J* = 8.9 Hz, 2H), 7.43 – 7.29 (m, 4H), 7.24 (td, *J* = 7.6, 1.2 Hz, 1H), 7.14 (dd, *J* = 7.6, 1.5 Hz, 1H), 6.89 – 6.80 (m, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ, ppm: 150.3 (C), 144.8 (C), 137.1 (C), 135.2 (C), 132.5 (C), 130.6 (CH), 129.3 (CH), 129.0 (CH), 128.7 (CH), 128.4 (CH), 128.4 (CH), 126.4 (CH), 124.2 (CH), 123.3 (CH). **HRMS** (APCI, **$[M-H]^-$**) *m/z* calculated for $C_{18}H_{13}N_2O_4S$: 353.0602, found 353.0606.

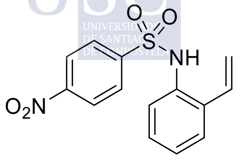
4-nitro-*N*-(2-(1-phenylvinyl)phenyl)benzenesulfonamide (1q)



1q

1q obtained as a white solid (479 mg, 84% yield). **^{1}H NMR** (300 MHz, $CDCl_3$) δ, ppm: 8.07 (d, *J* = 8.9 Hz, 2H), 7.74 (d, *J* = 8.1 Hz, 1H), 7.64 (d, *J* = 8.9 Hz, 2H), 7.38 (t, *J* = 7.7 Hz, 1H), 7.31 – 7.23 (m, 1H), 7.21 – 7.10 (m, 4H), 6.98 (d, *J* = 7.2 Hz, 2H), 6.62 (s, 1H), 5.70 (s, 1H), 4.93 (s, 1H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ, ppm: 150.2 (C), 144.9 (C), 144.6 (C), 138.4 (C), 133.8 (C), 133.1 (C), 130.9 (CH), 129.3 (CH), 129.0 (CH), 128.9 (CH), 128.4 (CH), 126.1 (CH), 126.0 (CH), 124.1 (CH), 122.2 (CH), 117.5 (CH_2). **HRMS** (APCI, **$[M-H]^-$**) *m/z* calculated for $C_{20}H_{15}N_2O_4S$: 379.0758, found 379.0759.

4-nitro-*N*-(2-vinylphenyl)benzenesulfonamide (1r)



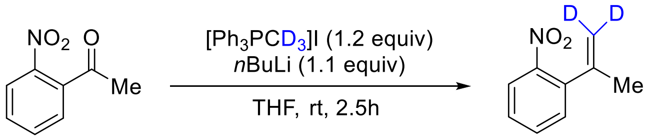
1r

1r obtained as a white solid (406 mg, 89% yield). **^{1}H NMR** (300 MHz, $CDCl_3$) δ, ppm: 8.27 (d, *J* = 8.9 Hz, 2H), 7.89 (d, *J* = 8.9 Hz, 2H), 7.43 – 7.37 (m, 1H), 7.36 – 7.28 (m, 1H), 7.28 – 7.20 (m, 2H), 6.74 (s, 1H), 6.51 (dd, *J* = 17.4, 11.0 Hz, 1H), 5.51 (dd, *J* = 17.4, 0.9 Hz, 1H), 5.24 (dd, *J* = 11.0, 0.9 Hz, 1H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ, ppm: 150.4 (C), 145.1 (C), 133.5 (C), 132.1 (C), 131.1 (CH), 129.1 (CH), 128.7 (CH), 127.7 (CH), 127.3 (CH), 126.0

(CH), 124.4 (CH), 118.8 (CH_2). **HRMS** (APCI, **$[M-H]^-$**) *m/z* calculated for $C_{14}H_{11}N_2O_4S$: 303.0445, found 303.0455.

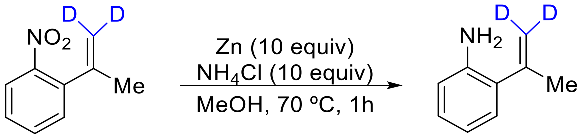
1.3 Preparation of deuterated 2-alkenylanilides

Procedure for the synthesis of 1-nitro-2-(prop-1-en-2-yl-1,1-*d₂*)benzene:



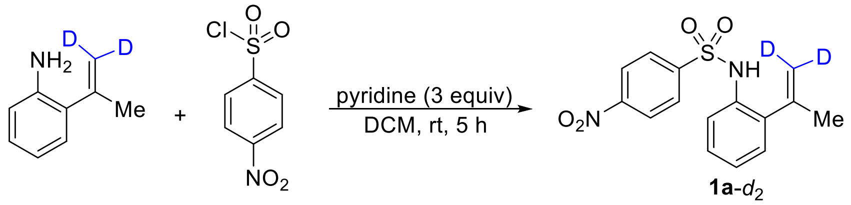
A flame dried round bottom flask was loaded with methyl-*d_3*-triphenylphosphonium iodide (1.5 g, 3.63 mmol), capped with a rubber septum and evacuated and filled with argon three times. Then, dry THF (6 mL) was added via syringe and the solution was cooled to 0 ºC. A freshly titrated solution of *n*-butyl lithium in hexanes (2.41 M, 1.4 mL) was added dropwise. After reacting for 30 min, a solution of 2'-nitroacetophenone (500 mg, 3.03 mmol) in THF (2.7 mL) was added via syringe, and the reaction was warmed up to room temperature and monitored by TLC. After 2h, the reaction was quenched by addition of 30 mL of an aqueous solution of saturated NH_4Cl and the aqueous phase was extracted with CH_2Cl_2 (3 x 30 mL). The combined organic layers were dried over Na_2SO_4 and evaporated under reduced pressure. The crude residue was purified by column chromatography on silica gel (5 to 10% EtOAc/hexanes) to afford 1-nitro-2-(prop-1-en-2-yl-1,1-*d_2*)benzene as a yellow oil with 86% deuteration (200 mg, 39%). **^{1}H NMR** (300 MHz, $CDCl_3$) δ, ppm: 7.85 (d, *J* = 8.1 Hz, 1H), 7.53 (t, *J* = 7.5 Hz, 1H), 7.39 (t, *J* = 7.8 Hz, 1H), 7.33 (d, *J* = 7.6 Hz, 1H), 5.16 (s, 0.1H), 4.93 (s, 0.1H), 2.09 (s, 3H).

Procedure for the synthesis of 2-(prop-1-en-2-yl-1,1-*d₂*)aniline:



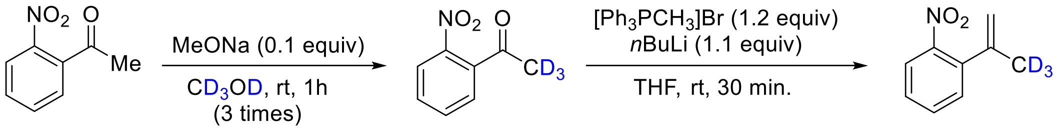
A suspension of 1-nitro-2-(prop-1-en-2-yl-1,1-*d_2*)benzene (200 mg, 1.18 mmol), activated Zn powder (100 mesh, 773 mg, 11.82 mmol) and NH_4Cl (632 mg, 11.82 mmol) was stirred under reflux for 1 hour. After filtration through a pad of Celite, the filtrate was concentrated in vacuo. Then, a solution of saturated $NaHCO_3$ (10 mL) was added to the residue and the mixture was extracted with CH_2Cl_2 (3 x 15 mL). The crude residue was purified by column chromatography on silica gel (5 to 15% EtOAc/hexanes) to afford 2-(prop-1-en-2-yl-1,1-*d_2*)aniline as a yellow oil with 68% deuteration (40.2 mg, 25%). **^{1}H NMR** (300 MHz, $CDCl_3$) δ, ppm: 7.08 (d, *J* = 7.4 Hz, 2H), 6.82-6.69 (m, 2H), 5.32 (s, 0.3H), 5.08 (s, 0.3H), 3.81 (brs, 2H), 2.11 (s, 3H).

Procedure for the synthesis of the nosyl-protected 2-alkenylaniline 1a-*d*$_2$:



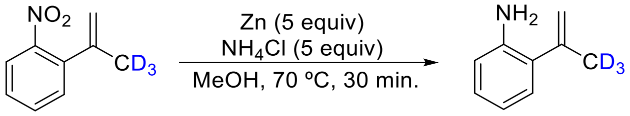
To a solution of 2-(prop-1-en-2-yl-1,1-*d*$_2$)aniline (40.2 mg, 0.29 mmol) and 4-nitrobenzenesulfonyl chloride (70.4 mg, 0.32 mmol) in dichloromethane (0.2 mL) under Ar atmosphere was added pyridine (0.09 ml, 0.87 mmol). The reaction was stirred at room temperature until consumption of the starting material as monitored by TLC. Once completion, the reaction was quenched with H_2O and the resulting mixture was extracted with dichloromethane three times. The combined organic layers were washed with HCl 1M and dried over anhydrous Na_2SO_4. Evaporation of the solvent followed by purification by flash column chromatography on silica gel (20% Et_2O/hexanes) afforded the pure 4-nitro-*N*-(2-(prop-1-en-2-yl-*d*$_2$)phenyl)benzenesulfonamide (**1a**-*d*$_2$) as a white solid with 68% deuteration (77.4 mg, 83%). ^{1}**H NMR** (300 MHz $CDCl_3$) δ, ppm: 8.28 (d, *J* = 8.8 Hz, 2H), 7.93 (d, *J* = 8.7 Hz, 2H), 7.64 (d, *J* = 8.2 Hz, 1H), 7.26 (t, *J* = 7.6 Hz 1H), 7.19 (bs, 1H), 7.12 (d, *J* = 7.4 Hz, 1H), 5.27 (s, 0.3H), 4.66 (s, 0.3H), 1.70 (s, 3H).

Procedure for the synthesis of 1-nitro-2-(prop-1-en-2-yl-3,3,3-*d*$_3$)benzene:



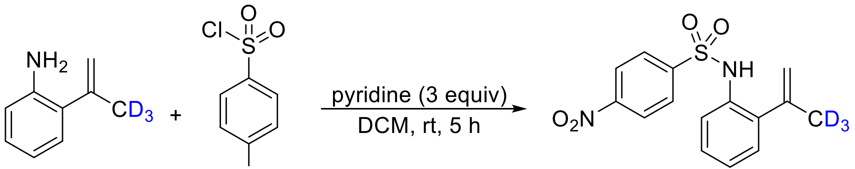
A flame dried round bottom flask was loaded with 2'-nitroacetophenone (600 mg, 3.50 mmol), sodium methoxide (18.4 mg, 0.35 mmol) and dry CD_3OD (2 mL) and the mixture was stirred under N_2 for 1 h. The solvent was then removed in vacuo and the process was repeated two more times until complete deuteration of the methyl group as monitored by ^{1}H NMR. Other flame dried round bottom flask was loaded with methyltriphenylphosphonium bromide (1.5 g, 4.2 mmol), the flask was capped with a rubber septum and evacuated and filled with argon three times. Dry THF (6.8 mL) was then added via syringe, the solution was cooled to 0 ºC and a freshly titrated solution of *n*butyl lithium in hexanes (2.5 M, 1,5 mL) was added dropwise. After reacting for 30 min, the crude mixture of 1-(2-nitrophenyl)ethan-1-one-2,2,2-*d*$_3$ was added in THF (3.2 mL) via syringe and the reaction was warmed to room temperature and monitored by TLC. After 30 min, the reaction was quenched by addition of 30 mL of an aqueous solution of saturated NH_4Cl. The aqueous phase was extracted with CH_2Cl_2 (3 x 30 mL) and the combined organic layers were dried over Na_2SO_4 and evaporated under reduced pressure. The crude residue was purified by column chromatography on silica gel (5 to 10% EtOAc/hexanes) to afford 1-nitro-2-(prop-1-en-2-yl-3,3,3-*d*$_3$)benzene as a yellow oil with 100% deuteration (471 mg, 78%). ^{1}**H NMR** (300 MHz, $CDCl_3$) δ, ppm: 7.85 (d, *J* = 8.1 Hz, 1H), 7.54 (td, *J* = 7.5 Hz, *J* = 0.9 Hz, 1H), 7.40 (td, *J* = 7.8 Hz, *J* = 1.0 Hz, 1H), 7.33 (dd, *J* = 7.6 Hz, *J* = 1.1 Hz, 1H), 5.17 (s, 1H), 4.94 (s, 1H).

Procedure for the synthesis of 2-(prop-1-en-2-yl-1,1-d_2)aniline:



A suspension of 1-(2-nitrophenyl)ethan-1-one-2,2,2-d_3 (250 mg, 1.45 mmol), activated Zn powder (100 mesh, 475 mg, 7.25 mmol) and NH_4Cl (338 mg, 7.25 mmol) was stirred under reflux for 30 min. After filtration through a pad of Celite, the filtrate was concentrated in vacuo. A solution of saturated $NaHCO_3$ (10 ml) was added to the obtained residue and the mixture was extracted with CH_2Cl_2 (3 x 15 mL). The crude residue was purified by column chromatography on silica gel (3 to 8% EtOAc/hexanes) to afford 2-(prop-1-en-2-yl-1,1-d_2)aniline as a yellow oil with 96% deuteration (78.2 mg, 38%). **^{1}H NMR** (300 MHz, $CDCl_3$) δ, ppm: 7.11–7.01 (m, 2H), 6.78–6.69 (m, 2H), 5.30 (d, *J* = 2.0 Hz, 1H), 5.08 (d, *J* = 2.1 Hz, 1H), 3.75 (bs, 2H).

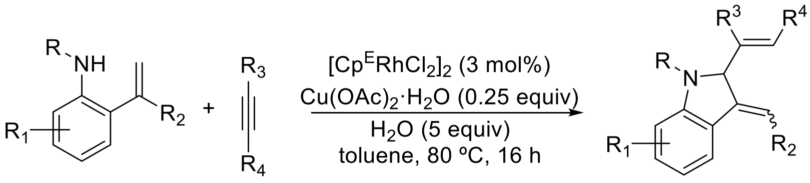
Procedure for the synthesis of the nosyl-protected 2-alkenylaniline 1a-d_3:



1a-d_3

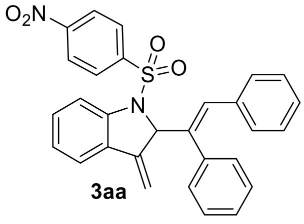
To a solution of 2-(prop-1-en-2-yl-1,1-d_2)aniline (78.2 mg, 0.57 mmol) and 4-nitrobenzenesulfonyl chloride (124.5 mg, 0.57 mmol) in dichloromethane (0.4 mL) under Ar atmosphere was added pyridine (0.120 ml, 1.49 mmol). The reaction was stirred at room temperature until consumption of the starting material as monitored by TLC. Once completion, the reaction was quenched with H_2O and the resulting mixture was extracted three times with dichloromethane. The combined organic layers were washed with HCl 1M and dried over anhydrous Na_2SO_4. Evaporation of the solvent followed by purification by flash column chromatography on silica gel (20% Et_2O/hexanes) afforded the pure 4-nitro-*N*-(2-(prop-1-en-2-yl-3,3,3-d_3)phenyl)benzenesulfonamide (**1a**-d_3) as a white solid with 95% deuteration (150.9 mg, 82%). **^{1}H NMR** (300 MHz $CDCl_3$) δ, ppm: 8.27 (d, *J* = 8.7 Hz, 2H), 7.92 (d, *J* = 8.7 Hz, 2H), 7.64 (d, *J* = 8.1 Hz, 1H), 7.26 (t, *J* = 7.7 Hz 1H), 7.18–7.08 (m, 2H), 7.05 (dd, *J* = 7.6 Hz, *J* = 1.3 Hz, 1H), 5.27 (s, 1H), 4.67 (s, 1H).

2. Procedure for the Rh-catalyzed synthesis of functionalized indolines



A Schlenk tube was loaded with the corresponding 2-alkenylanilide (0.3 mmol), $[Cp^ERhCl_2]_2$ (5.1 mg, 3 mol%), $Cu(OAc)_2{\cdot}H_2O$ (10 mg, 0.05 mmol), alkyne (0.2 mmol), H_2O (18 µl, 1 mmol) and toluene (2 mL). The tube was capped with a rubber septum and stirred in a vortex mixer. Then, the resulting mixture was heated at 80 ºC with a balloon of air for 16h. The reaction was cooled to room temperature, filtered through a short pad of silica gel using CH_2Cl_2 (20 mL) as eluent, and concentrated *in vacuo*. Purification of the residue by column chromatography, by loading the crude product absorbed on silica gel, and using the indicated eluents, afforded 2-substituted indoline products **3**.

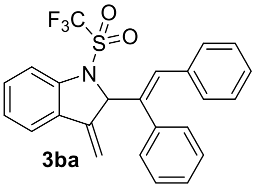
(*E*)-2-(1,2-diphenylvinyl)-3-methylene-1-((4-nitrophenyl)sulfonyl)indoline (3aa)



3aa

According to the general procedure, **3aa** was isolated by column chromatography (5 to 20% EtOAc/hexane) as a yellow solid (82.7 mg, 84% yield). **^{1}H NMR** (500 MHz, $CDCl_3$) δ, ppm: 8.23 (d, *J* = 8.8 Hz, 2H), 7.94 (d, *J* = 8.8 Hz, 2H), 7.62 (d, *J* = 8.2 Hz, 1H), 7.28 (d, *J* = 7.6 Hz, 1H), 7.25-7.22 (m, 1H), 7.20-7.19 (m, 5H), 7.11-7.08 (m, 3H), 7.02 (td, *J* = 7.5 Hz, *J* = 0.7 Hz, 1H), 6.97-6.93 (m, 2H), 6.72 (s, 1H), 5.46 (d, *J* = 2.5 Hz, 1H), 5.42 (d, *J* = 2.2 Hz, 1H), 4.99 (d, *J* = 2.1 Hz, 1H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ, ppm: 150.4 (C), 143.4 (C), 143.1 (C), 143.1 (C) 139.8 (C), 136.6 (C), 136.0 (C), 130.4 (CH), 130.1 (C), 130.0 (CH), 129.8 (C), 129.6 (CH), 128.5 (CH), 128.1 (CH), 127.8 (CH), 127.4 (CH), 125.0 (CH), 124.4 (CH), 121.4 (CH), 115.8 (CH), 105.4 (CH_2), 73.9 (CH). **HRMS** (APCI, **$[M+H]^+$**) *m/z* calculated for $C_{29}H_{23}N_2O_4S$: 495.1373, found: 495.1373.

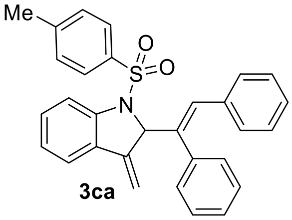
(*E*)-2-(1,2-diphenylvinyl)-3-methylene-1-((trifluoromethyl)sulfonyl)indoline (3ba)



3ba

According to the general procedure, **3ba** was isolated by column chromatography (5% Et_2O/hexane) as a yellow oil (35.3 mg, 40% yield). **^{1}H NMR** (300 MHz, $CDCl_3$) δ, ppm: 7.41 (d, *J* = 8.3 Hz, 2H), 7.23-7.15 (m, 6H), 7.12-7.06 (m, 4H), 6.98-6.94 (m, 2H), 6.74 (s, 1H), 5.74 (s, 1H), 5.67 (d, *J* = 1.5 Hz, 1H), 5.17 (s, 1H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ, ppm: 142.6 (C), 141.6 (C), 139.5 (C), 135.9 (C), 135.9 (C), 130.4 (CH), 130.4 (CH), 129.9 (CH), 129.6 (CH), 129.5 (C), 128.5 (CH), 128.1 (CH), 127.9 (CH), 127.5 (CH), 125.5 (CH), 121.4 (CH), 120.4 (C, $J_{C\text{-}F}$ = 324.8 Hz), 115.2 (CH), 106.0 (CH_2), 75.1 (CH). **^{19}F NMR** (282 MHz, $CDCl_3$) δ, ppm: 73.0 (s). **HRMS** (APCI, **$[M+H]^+$**) *m/z* calculated for $C_{24}H_{19}F_3NO_2S$: 442.1083, found: 442.1083.

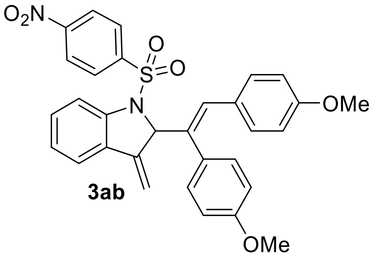
(*E*)-2-(1,2-diphenylvinyl)-3-methylene-1-tosylindoline (3ca)



3ca

According to the general procedure, **3ca** was isolated by column chromatography (5% Et_2O/hexane) as a white solid (23.2 mg, 25% yield). **^{1}H NMR** (300 MHz, $CDCl_3$) δ, ppm: 7.65 (t, *J* = 7.7 Hz, 3H), 7.24-7.14 (m, 9H), 7.10-7.08 (m, 3H), 6.99-6.93 (m, 3H), 6.72 (s, 1H), 5.42-5.38 (m, 2H), 4.94 (s, 1H), 2.34 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ, ppm: 144.2 (C), 144.2 (C), 143.9 (C), 140.4 (C), 137.0 (C), 136.4 (C), 134.9 (C), 130.2 (CH), 130.2 (CH), 129.8 (CH), 129.8 (CH), 129.6 (CH), 128.3 (CH), 128.0 (CH), 127.5 (CH), 127.4 (CH), 127.1 (CH), 124.2 (CH), 121.1 (CH), 116.1 (CH), 104.4 (CH_2), 73.6 (CH), 21.7 (CH_3). **HRMS** (APCI, **$[M+H]^+$**) *m/z* calculated for $C_{30}H_{26}NO_2S$: 464.1682, found: 464.1679.

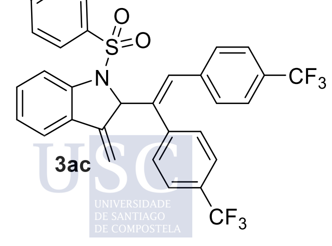
(*E*)-2-(1,2-bis(4-methoxyphenyl)vinyl)-3-methylene-1-((4-nitrophenyl)sulfonyl)indoline (3ab)



3ab

According to the general procedure, **3ab** was isolated by column chromatography (5 to 15% EtOAc/hexane) as a yellow solid (98.1 mg, 89% yield). **^{1}H NMR** (500 MHz, $CDCl_3$) δ, ppm: 8.21 (d, *J* = 8.7 Hz, 2H), 7.94 (d, *J* = 8.8 Hz, 2H), 7.62 (d, *J* = 8.2 Hz, 1H), 7.29-7.20 (m, 2H), 7.09 (d, *J* = 8.6 Hz, 2H), 7.01 (t, *J* = 7.5 Hz, 1H), 6.89 (d, *J* = 8.7 Hz, 2H), 6.72 (d, *J* = 8.6 Hz, 2H), 6.64 (d, *J* = 8.7 Hz, 2H), 6.60 (s, 1H), 5.45 (d, *J* = 2.2 Hz, 1H), 5.37 (s, 1H), 4.99 (d, *J* = 1.3 Hz, 1H), 3.74 (s, 3H), 3.73 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ, ppm: 159.0 (C), 158.8 (C), 150.4 (C), 143.5 (C), 143.4 (C), 143.2 (C), 137.3 (C), 131.2 (CH), 130.8 (CH), 130.4 (CH), 129.8 (C), 129.7 (CH), 128.9 (C), 128.8 (C), 128.5 (CH), 124.9 (CH), 124.4 (CH), 121.4 (CH), 115.8 (CH), 114.0 (CH), 113.5 (CH), 105.1 (CH_2), 74.3 (CH), 55.3 (CH_3), 55.2 (CH_3). **HRMS** (APCI, **$[M+H]^+$**) *m/z* calculated for $C_{31}H_{27}N_2O_6S$: 555.1584, found: 555.1585.

(*E*)-2-(1,2-bis(4-(trifluoromethyl)phenyl)vinyl)-3-methylene-1-((4-nitrophenyl)sulfonyl)indoline (3ac)

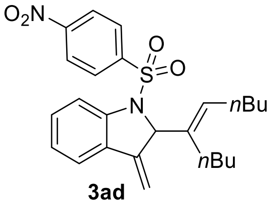


3ac

According to the general procedure at 90 °C as modification, **3ac** was isolated by column chromatography (10 to 30% Et_2O/hexane) as a yellow solid (99.6 mg, 80% yield). **^{1}H NMR** (300 MHz, $CDCl_3$) δ, ppm: 8.23 (d, *J* = 8.6 Hz, 2H), 7.92 (d, *J* = 8.6 Hz, 2H), 7.60 (d, *J* = 8.1 Hz, 1H), 7.44 (d, *J* = 8.0 Hz, 2H), 7.37-7.20 (m, 6H), 7.04-6.99 (m, 3H), 6.84 (s, 1H), 5.49 (s, 1H), 5.37 (s, 1H), 5.00 (s, 1H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ, ppm: 150.6 (C), 142.9 (C), 142.8 (C), 142.6 (C), 141.2 (C), 139.8 (C), 139.0 (C), 130.9 (CH), 130.4 (CH), 130.0 (C, q, J_{CF} = 9.2 Hz), 129.8 (CH), 129.7 (CH), 128.5 (CH), 125.5 (CH, q, J_{CF} = 3.5 Hz), 125.4 (CH), 125.2 (CH, q, J_{CF} = 3.6 Hz), 124.5 (CH), 124.1 (C, q, J_{CF} =

270.5 Hz), 121.6 (CH), 115.9 (CH), 105.8 (CH_2), 73.4 (CH). **^{19}F NMR** (282 MHz, $CDCl_3$) δ, ppm: -62.7 (s), -62.8 (s). **HRMS** (APCI, **$[M+H]^+$**) *m/z* calculated for $C_{31}H_{21}F_6N_2O_4S$: 631.1121, found: 631.1121.

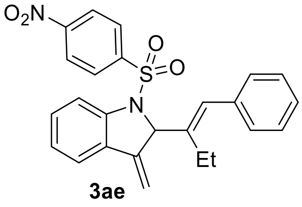
(*E*)-2-(dec-5-en-5-yl)-3-methylene-1-((4-nitrophenyl)sulfonyl)indoline (3ad)



3ad

According to the general procedure for 24h as modification, **3ad** was isolated by column chromatography (100% hexane to 4% EtOAc/hexane) as a yellow oil (69.6 mg, 77% yield). **^{1}H NMR** (300 MHz, $CDCl_3$) δ, ppm: 8.24 (d, *J* = 8.8 Hz, 2H), 7.90 (d, *J* = 8.9 Hz, 2H), 7.77 (d, *J* = 8.2 Hz, 1H), 7.36-7.28 (m, 2H), 7.08 (td, *J* = 7.5 Hz, *J* = 0.6 Hz, 1H), 5.52 (t, *J* = 7.2 Hz, 1H), 5.41 (d, *J* = 1.9 Hz, 1H), 4.93-4.91 (m, 2H), 2.14-2.04 (m, 2H), 1.99-1.89 (m, 1H), 1.80-1.70 (m, 1H), 1.46-1.29 (m, 6H), 1.17 (sext, *J* = 7.3 Hz, 2H), 0.93 (t, *J* = 7.0 Hz, 3H), 0.75 (t, *J* = 7.2 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ, ppm: 150.4 (C), 143.8 (C), 143.4 (C), 143.2 (C), 138.0 (C), 131.7 (CH), 130.4 (CH), 130.2 (C), 128.6 (CH), 125.0 (CH), 124.3 (CH), 121.4 (CH), 116.2 (CH), 104.9 (CH_2), 74.5 (CH), 32.1 (CH_2), 31.9 (CH_2), 27.7 (CH_2), 26.7 (CH_2), 23.2 (CH_2), 22.6 (CH_2), 14.2 (CH_3), 13.8 (CH_3). **HRMS** (APCI, **$[M+H]^+$**) *m/z* calculated for $C_{25}H_{31}N_2O_4S$: 455.1999, found: 455.2001.

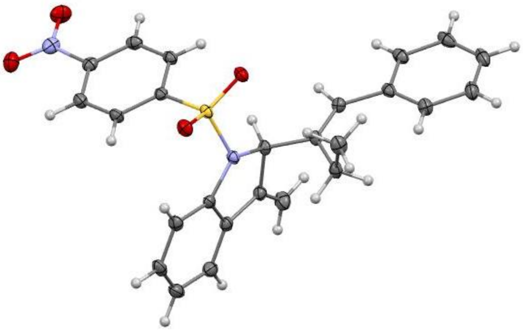
(*E*)-2-(2-cyclopropyl-1-phenylvinyl)-3-methylene-1-((4-nitrophenyl)sulfonyl)indoline (3ae)



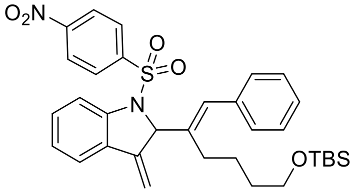
3ae

According to the general procedure, **3ae** was isolated by precipitation of the product from the reaction crude mixture, using 5 mL of hexanes, as a yellow solid (77.5 mg, 87% yield). **^{1}H NMR** (500 MHz, $CDCl_3$) δ, ppm: 8.24 (d, *J* = 8.9 Hz, 2H), 7.97 (d, *J* = 8.9 Hz, 2H), 7.82 (d, *J* = 8.2 Hz, 1H), 7.41 (d, *J* = 7.6 Hz, 1H), 7.38-7.34 (m, 5H), 7.29-7.25 (m, 1H), 7.12 (td, *J* = 7.6 Hz, *J* = 0.7 Hz, 1H), 6.58 (s, 1H), 5.51 (d, *J* = 2.6 Hz, 1H), 5.15 (t, *J* = 2.4 Hz, 1H), 5.08 (d, *J* = 2.2 Hz, 1H), 2.30-2.17 (m, 1H), 2.17-2.05 (m, 1H), 1.04 (t, *J* = 7.5 Hz, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ, ppm: 150.4 (C), 143.5 (C), 143.4 (C), 143.1 (C), 141.9 (C), 136.9 (C), 130.6 (CH), 130.0 (CH), 129.9 (C), 128.9 (CH), 128.6 (CH), 128.4 (CH), 127.3 (CH), 125.1 (CH), 124.3 (CH), 121.6 (CH), 116.0 (CH), 105.3 (CH_2), 74.5 (CH), 20.8 (CH_2), 14.4 (CH_3). **HRMS** (APCI, **$[M+H]^+$**) *m/z* calculated for $C_{25}H_{23}N_2O_4S$: 447.1373, found: 447.1373.

To confirm the structure, suitable crystals of **3ae** for X-ray diffraction analysis were grown by slow evaporation from a concentrated solution of the compound in $CHCl_3$. The crystallographic data was deposited in the Cambridge Structural Database (1824646).



(*E*)-2-(6-((*tert*-butyldimethylsilyl)oxy)-1-phenylhex-1-en-1-yl)-3-methylene-1-((4-nitrophenyl)sulfonyl)indoline (3af)

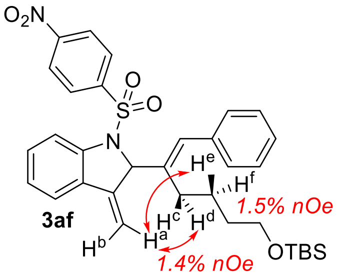


3af, 10:1 *r.r.*

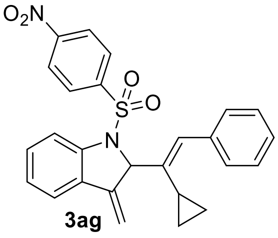
According to the general procedure, **3af** was isolated by column chromatography (10 to 20% EtOAc/hexane) to afford a mixture of regioisomers (10:1 ratio) as a dark yellow oil (97.9 mg, 81% yield). **^{1}H NMR** *of the major regioisomer* (500 MHz, CDCl$_3$) δ, ppm: 8.24 (d, *J* = 8.8 Hz, 2H), 7.95 (d, *J* = 8.8 Hz, 2H), 7.82 (d, *J* = 8.2 Hz, 1H), 7.40-7.34 (m, 4H), 7.33-7.30 (m, 2H), 7.26 (t, *J* = 7.2 Hz, 1H), 7.12 (t, *J* = 7.5 Hz, 1H), 6.59 (s, 1H), 5.49 (d, *J* = 2.6 Hz, 1H), 5.13 (s, 1H), 5.08 (d, *J* = 2.1 Hz, 1H), 3.47-3.42 (m, 2H), 2.28-2.22 (m, 1H), 2.15-2.09 (m, 1H), 1.59-1.44 (m, 2H), 1.41-1.36 (m, 2H), 0.86 (s, 9H), 0.00- -0.01 (m, 6H). **^{13}C NMR** *of the major regioisomer* (126 MHz, CDCl$_3$) δ, ppm: 150.5 (C), 143.5 (C), 143.4 (C), 143.1 (C), 140.7 (C), 137.0 (C), 130.6 (CH), 130.3 (CH), 130.0 (C), 128.9 (CH), 128.6 (CH), 128.5 (CH), 127.2 (CH), 125.2 (CH), 124.3 (CH), 121.6 (CH), 116.2 (CH), 105.3 (CH$_2$), 74.4 (CH), 62.9 (CH$_2$), 33.4 (CH$_2$), 27.7 (CH$_2$), 26.1 (CH$_3$), 25.8 (CH$_2$), 18.4 (C), -5.2 (CH$_3$). **HRMS** (APCI, **[M+H]$^+$**) *m/z* calculated for $C_{33}H_{41}N_2O_5SSi$: 605.2500, found: 605.2494.

Assignment of the regiochemistry

The major regioisomer was assigned based on HSQC, HMBC and COSY experiments and by the observation of a nOe between H^a and H^c and H^d and between H^a and H^e and H^f.



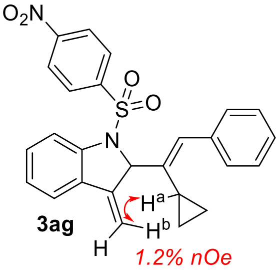
(*E*)-2-(2-cyclopropyl-1-phenylvinyl)-3-methylene-1-((4-nitrophenyl)sulfonyl)indoline (3ag)



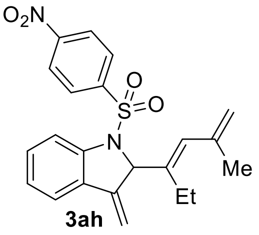
According to the general procedure, **3ag** was isolated by column chromatography (100% hexane to 6% EtOAc/hexane) as a yellow solid (63.9 mg, 67% yield). **^{1}H NMR** (500 MHz, $CDCl_3$) δ, ppm: 8.24 (d, *J* = 8.9 Hz, 2H), 7.94 (d, *J* = 8.6 Hz, 2H), 7.80 (d, *J* = 8.1 Hz, 1H), 7.46 (d, *J* = 7.6 Hz, 1H), 7.39 (d, *J* = 7.8 Hz, 1H), 7.36-7.31 (m, 3H), 7.26-7.23 (m, 1H), 7.11 (t, *J* = 7.6 Hz, 1H), 6.65 (s, 1H), 5.46 (d, *J* = 2.5 Hz, 1H), 5.14 (s, 1H), 5.10 (d, *J* = 2.0 Hz, 1H), 1.55-1.48 (m, 1H), 0.61-0.53 (m, 2H), 0.48-0.33 (m, 2H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ, ppm: 150.5 (C), 144.3 (C), 143.4 (C), 143.3 (C), 139.5 (C), 136.5 (C), 131.2 (CH), 130.6 (CH), 129.9 (C), 129.8 (CH), 128.6 (CH), 127.9 (CH), 127.2 (CH), 125.1 (CH), 124.4 (CH), 121.6 (CH), 116.1 (CH), 104.7(CH_2), 73.6 (CH), 10.7 (CH), 8.5 (CH_2), 7.3 (CH_2). **HRMS** (APCI, **$[M+H]^+$**) *m/z* calculated for $C_{26}H_{23}N_2O_4S$: 459.1373, found: 459.1372.

Assignment of the regiochemistry

The major regioisomer was assigned based on HSQC, HMBC and COSY experiments and by the observation of a nOe between H^a and H^b.



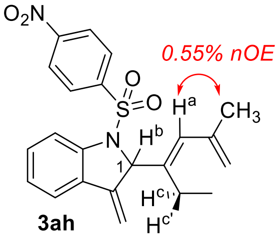
(*E*)-3-methylene-2-(5-methylhexa-3,5-dien-3-yl)-1-((4-nitrophenyl)sulfonyl)indoline (3ah)



According to the general procedure, **3ah** was isolated by column chromatography (100% hexane to 6% EtOAc/hexane) as a yellow solid (52.1 mg, 64% yield). **^{1}H NMR** (500 MHz, $CDCl_3$) δ, ppm: 8.25 (d, *J* = 9.0 Hz, 2H), 7.93 (d, *J* = 9.0 Hz, 2H), 7.78 (d, *J* = 8.2 Hz, 1H), 7.37 (d, *J* = 7.6 Hz, 1H), 7.33 (td, *J* = 7.8 Hz, *J* = 1.0 Hz, 1H), 7.10 (td, *J* = 7.6 Hz, *J* = 0.7 Hz, 1H), 5.98 (s, 1H), 5.45 (d, *J* = 2.6 Hz, 1H), 5.04 (s, 1H), 5.00 (d, *J* = 2.1 Hz, 1H), 4.97-4.96 (m, 2H), 2.18 (dq, *J* = 15.1 Hz, *J* = 7.6 Hz, 1H), 2.04 (qd, *J* = 14.9 Hz, *J* = 7.6 Hz, 1H), 1.92 (s, 3H), 0.99 (t, *J* = 7.6 Hz, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ, ppm: 150.5 (C), 143.7 (C), 143.5 (C), 143.3 (C), 141.2 (C), 140.9 (C), 131.9 (CH), 130.6 (CH), 130.0 (C), 128.6 (CH), 125.1 (CH), 124.3 (CH), 121.5 (CH), 116.1 (CH), 116.0 (CH_2), 105.1 (CH_2), 74.6 (CH), 23.3 (CH_3), 20.7 (CH_2), 15.2 (CH_3). **HRMS** (APCI, **$[M+H]^+$**) *m/z* calculated for $C_{22}H_{23}N_2O_4S$: 441.1373, found: 447.1371.

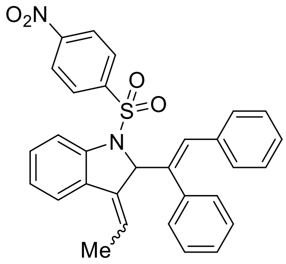
Assignment of the regiochemistry

The major regioisomer was assigned based on HSQC, HMBC and COSY experiments. HMBC between C^1 in the indoline ring and H^c and $H^{c'}$ is diagnostic. Observation of a nOe between H^a and the methyl group of the allyl moiety further confirms the regiochemistry of product **3ah**.



3ah

2-((*E*)-1,2-diphenylvinyl)-2-ethylidene-1-((4-nitrophenyl)sulfonyl)indoline (3da)



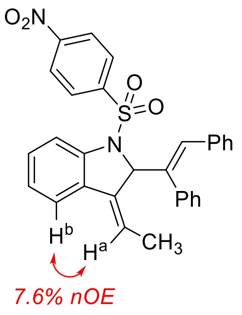
3da

Z:*E* = 1.7:1

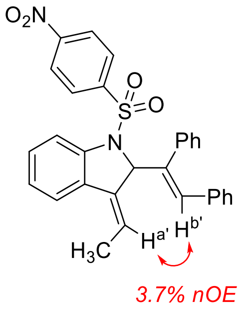
According to the general procedure for 35h and employing 5 mol% of the Rh catalyst as modification, **3da** was isolated by column chromatography (5% Et_2O/hexane) to afford an inseparable mixture 1.7:1 of *Z*:*E* isomers as a yellow solid (74.2 mg, 73% yield). **^{1}H NMR** *of the mixture of stereoisomers* (500 MHz, $CDCl_3$) δ, ppm: 8.24–8.20 (m, 3.3H), 7.95–7.92 (m, 3.3H), 7.61 (d, *J* = 8.2 Hz, 0.6H), 7.53 (d, *J* = 8.1 Hz, 1H), 7.39 (d, *J* = 7.6 Hz, 0.6H), 7.19–7.14 (m, 3.6H), 7.13–7.08 (m, 9.8H), 7.06 (d, *J* = 7.6 Hz, 1.8H), 7.00 (td, *J* = 7.6 Hz, *J* = 0.9 Hz, 0.6H), 6.96 – 6.89 (m, 4.5H), 6.81 (s, 1H), 6.67 (s, 0.6H), 5.93 (qd, *J* = 7.3 Hz, *J* = 2.2 Hz, 1H), 5.66–5.60 (m, 1.6H), 5.37 (t, *J* = 1.9 Hz, 0.6 Hz), 1.91 (dd, *J* = 7.5, *J* = 1.9 Hz, 1.8H), 1.79 (dd, *J* = 7.3, *J* = 1.2 Hz, 1.8H). **^{13}C NMR** *of the mixture of stereoisomers* (126 MHz, $CDCl_3$) δ, ppm: 150.4 (C), 150.3 (C), 143.8 (C), 143.6 (C), 143.5 (C), 142.0 (C), 140.7 (C), 137.7 (C), 136.7 (C), 136.3 (C), 136.1 (C), 135.9 (C), 135.2 (C), 134.8 (C), 131.6 (C), 131.6 (CH), 130.4 (C), 129.9 (CH), 129.7 (CH), 129.7 (CH), 129.5 (CH), 129.1 (CH), 128.9 (CH), 128.5 (CH), 128.4 (CH), 128.4 (CH), 128.2 (CH), 128.1 (CH), 128.1 (CH), 127.6 (CH), 127.6 (CH), 127.5 (CH), 127.3 (CH), 125.0 (CH), 125.0 (CH), 124.8 (CH), 124.3 (CH), 124.3 (CH), 120.8 (CH), 120.0 (CH), 118.2 (CH), 116.2 (CH), 115.8 (CH), 74.6 (CH), 73.0 (CH), 14.7 (CH3), 14.3 (CH_3). **HRMS** (APCI, **$[M+H]^+$**) *m/z* calculated for $C_{30}H_{25}N_2O_4S$: 509.1529, found: 509.1543.

Assignment of the stereochemistry

The two stereoisomers were assigned based on HSQC, HMBC and COSY experiments and by the observation of a nOe between H^a and H^b in the *Z* isomer and $H^{a'}$ and $H^{b'}$ in the *E* isomer.

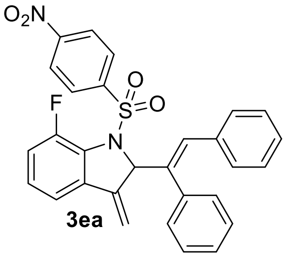


(*Z*)-3da



(*E*)-3da

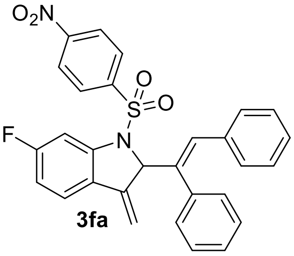
(*E*)-2-(1,2-diphenylvinyl)-7-fluoro-3-methylene-1-((4-nitrophenyl)sulfonyl)indoline (3ea)



3ea

According to the general procedure employing 5 mol% of the Rh catalyst and 6 mL of Toluene as modification, **3ea** was isolated by column chromatography (5% Et_2O/hexane) as a yellow solid (67.6 mg, 66% yield). **^{1}H NMR** (300 MHz, $CDCl_3$) δ, ppm: 8.20 (d, *J* = 7.8 Hz, 2H), 8.00 (d, *J* = 8.4 Hz, 2H), 7.21–7.08 (m, 7H), 7.03-6.89 (m, 6H), 6.77 (s, 1H), 6.11 (s, 1H), 5.56 (s, 1H), 5.08 (s, 1H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ, ppm: 151.6 (d, $J_{C\text{-}F}$ = 248.9 Hz, C), 149.9 (C), 145.3 (C), 143.1 (d, $J_{C\text{-}F}$ = 2.6 Hz, C), 139.0 (C), 136.3 (C), 135.7 (C), 134.4 (d, $J_{C\text{-}F}$ = 2.0 Hz, C), 130.6 (CH), 130.5 (d, $J_{C\text{-}F}$ = 15.7 Hz, C), 129.7 (CH), 129.6 (CH), 129.1 (d, $J_{C\text{-}F}$ = 2.0 Hz, CH), 128.6 (CH), 128.3 (CH), 128.0 (CH), 127.7 (CH), 126.4 (d, $J_{C\text{-}F}$ = 6.6 Hz, CH), 124.0 (CH), 117.6 (d, $J_{C\text{-}F}$ = 20.3 Hz, CH), 117.1 (d, $J_{C\text{-}F}$ = 3.1 Hz, CH), 106.9 (CH_2), 74.6 (CH). **^{19}F NMR** (282 MHz, $CDCl_3$) δ, ppm: -119.5 (d, *J* = 7.2 Hz). **HRMS** (APCI, **$[M+H]^+$**) *m/z* calculated for $C_{29}H_{22}FN_2O_4S$: 513.1279, found: 513.1282.

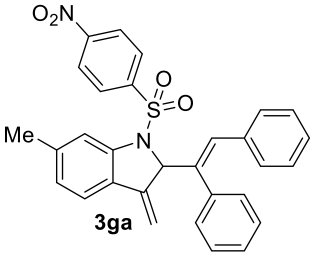
(*E*)-2-(1,2-diphenylvinyl)-6-fluoro-3-methylene-1-((4-nitrophenyl)sulfonyl)indoline (3fa)



3fa

According to the general procedure, **3fa** was isolated by column chromatography (5% Et_2O/hexane) as a pale yellow solid (72.6 mg, 71% yield). **^{1}H NMR** (300 MHz, $CDCl_3$) δ, ppm: 8.27 (d, *J* = 8.9 Hz, 2H), 7.98 (d, *J* = 8.9 Hz, 2H), 7.35 (dd, *J* = 9.6, 2.2 Hz, 1H), 7.25–7.16 (m, 6H), 7.14–7.06 (m, 3H), 6.99–6.92 (m, 2H), 6.75–6.68 (m, 2H), 5.45–5.42 (m, 1H), 5.42–5.40 (m, 1H), 4.99 (s, 1H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ, ppm: 164.1 (d, $J_{C\text{-}F}$ = 247.5 Hz, C), 150.6 (C), 144.3 (d, $J_{C\text{-}F}$ = 12.2 Hz, C) 143.3 (C), 142.1 (C), 139.5 (C), 136.3 (C), 135.9 (C), 130.5 (CH), 130.0 (CH), 129.6 (CH), 128.6 (CH), 128.5 (CH), 128.2 (CH), 127.9 (CH), 127.6 (CH), 125.8 (d, $J_{C\text{-}F}$ = 2.6 Hz, C), 124.6 (CH), 122.5 (d, $J_{C\text{-}F}$ = 10.1 Hz, CH), 112.2 (d, $J_{C\text{-}F}$ = 23.3 Hz, CH), 104.9 (d, $J_{C\text{-}F}$ = 2.2 Hz, CH_2), 103.7 (d, *J* = 28.1 Hz, CH), 74.8 (CH). **^{19}F NMR** (282 MHz, $CDCl_3$) δ, ppm: -108.4 (m). **HRMS** (APCI, **$[M+H]^+$**) *m/z* calculated for $C_{29}H_{22}FN_2O_4S$: 513.1279, found: 513.1277.

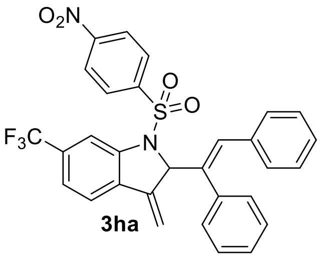
(*E*)-2-(1,2-diphenylvinyl)-6-methyl-3-methylene-1-((4-nitrophenyl)sulfonyl)indoline (**3ga**)



3ga

According to the general procedure for 35h and employing 5 mol% of the Rh catalyst as modification, **3ga** was isolated by column chromatography (5% Et_2O/hexane) as a yellow solid (65 mg, 64% yield). **^{1}H NMR** (300 MHz, $CDCl_3$) δ, ppm: 8.24 (d, *J* = 8.8 Hz, 2H), 7.94 (d, *J* = 8.8 Hz, 2H), 7.45 (s, 1H), 7.22–7.15 (m, 6H), 7.12–7.06 (m, 3H), 6.97–6.90 (m, 2H), 6.84 (d, *J* = 7.8 Hz, 1H), 6.69 (s, 1H), 5.40 – 5.36 (m, 2H), 4.90 (s, 1H), 2.36 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ, ppm: 150.4 (C), 143.5 (C), 143.3 (C), 143.0 (C), 141.1 (C), 139.9 (C), 136.7 (C), 136.1 (C), 130.1 (CH), 130.0 (CH), 129.6 (CH), 128.5 (CH), 128.5 (CH), 128.1 (CH), 127.7 (CH), 127.4 (CH), 127.2 (C), 126.1 (CH), 124.4 (CH), 121.2 (CH), 116.3 (CH), 104.2 (CH_2), 74.2 (CH), 22.2 (CH_3). **HRMS** (APCI, **$[M+H]^+$**) *m/z* calculated for $C_{30}H_{25}N_2O_4S$: 509.1530, found: 509.1526.

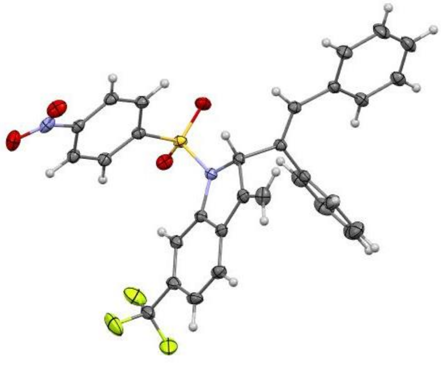
(*E*)-2-(1,2-diphenylvinyl)-3-methylene-1-((4-nitrophenyl)sulfonyl)-6-(trifluoromethyl)indoline (3ha)



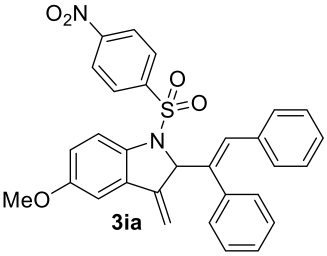
3ha

According to the general procedure, **3ha** was isolated by column chromatography (5% Et_2O/hexane) as a yellow solid (68.4 mg, 61% yield). **^{1}H NMR** (300 MHz, $CDCl_3$) δ, ppm: 8.27 (d, *J* = 8.9 Hz, 2H), 7.97 (d, *J* = 8.9 Hz, 2H), 7.86 (s, 1H), 7.36 (d, *J* = 8.0 Hz, 1H), 7.30–7.24 (m, 1H), 7.23–7.14 (m, 5H), 7.14–7.08 (m, 3H), 6.99–6.92 (m, 2H), 6.71 (s, 1H), 5.60 (d, *J* = 1.9 Hz, 1H), 5.49 (s, 1H), 5.14 (d, *J* = 1.1 Hz, 1H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ, ppm: 150.7 (C), 143.4 (C), 143.1 (C), 142.0 (C), 139.2 (C), 136.2 (C), 135.7 (C), 132.9 (C), 132.3 (q, $J_{C\text{-}F}$ = 32.4 Hz, C), 130.7 (CH), 130.0 (CH), 129.6 (CH), 128.6 (CH), 128.5 (CH), 128.2 (CH), 128.0 (CH), 127.7 (CH), 127.4 (q, $J_{C\text{-}F}$ = 271.0 Hz, C), 124.6 (CH), 121.9 (q, $J_{C\text{-}F}$ = 3.9 Hz, CH), 121.8 (CH), 112.6 (q, $J_{C\text{-}F}$ = 4.0 Hz, CH), 108.2 (CH_2), 74.3 (CH). **^{19}F NMR** (282 MHz, $CDCl_3$) δ, ppm: -62.5 (s). **HRMS** (APCI, **$[M+H]^+$**) *m/z* calculated for $C_{30}H_{22}F_3N_2O_4S$: 563.1247, found: 563.1248.

To confirm the structure, suitable crystals of **3ha** for X-Ray diffraction analysis were grown by slow evaporation from a concentrated solution of the compound in $CHCl_3$. The crystallographic data was deposited in the Cambridge Structural Database (1824645).



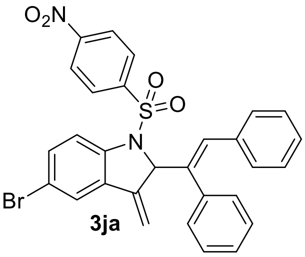
(*E*)-2-(1,2-diphenylvinyl)-5-methoxy-3-methylene-1-((4-nitrophenyl)sulfonyl)indoline (3ia)



3ia

According to the general procedure, **3ia** was isolated by column chromatography (5% Et_2O/hexane) as a yellow solid (76.6 mg, 73% yield). **^{1}H NMR** (300 MHz, $CDCl_3$) δ, ppm: 8.24 (d, *J* = 8.7 Hz, 2H), 7.90 (d, *J* = 8.7 Hz, 2H), 7.55 (d, *J* = 8.8 Hz, 1H), 7.23–7.16 (m, 5H), 7.13–7.07 (m, 3H), 6.98–6.91 (m, 2H), 6.80 (dd, *J* = 8.9 Hz, 2.2 Hz, 1H), 6.75–6.70 (m, 2H), 5.39 (s, 1H), 5.33 (s, 1H), 4.93 (s, 1H), 3.75 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ, ppm: 157.6 (C), 150.4 (C), 143.2 (C), 143.0 (C), 139.8 (C), 136.7 (C), 136.6 (C), 136.0 (C), 131.3 (C), 130.1 (CH), 129.6 (CH), 128.6 (CH), 128.5 (CH), 128.1 (CH), 127.8 (CH), 127.4 (CH), 124.4 (CH), 117.4 (CH), 117.0 (CH), 105.6 (CH_2), 105.6 (CH), 74.2 (CH), 55.7 (CH_3). **HRMS** (APCI, **$[M+H]^+$**) *m/z* calculated for $C_{30}H_{25}N_2O_5S$: 525.1479, found: 525.1478.

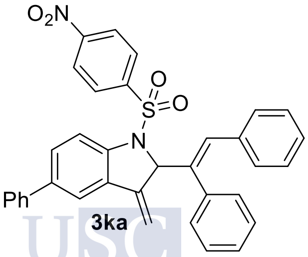
(*E*)-5-bromo-2-(1,2-diphenylvinyl)-3-methylene-1-((4-nitrophenyl)sulfonyl)indoline (3ja)



3ja

According to the general procedure, **3ja** was isolated by column chromatography (5% Et_2O/hexane) as a yellow solid (94 mg, 82% yield). **^{1}H NMR** (300 MHz, $CDCl_3$) δ, ppm: 8.26 (d, *J* = 8.9 Hz, 2H), 7.94 (d, *J* = 8.9 Hz, 2H), 7.50 (d, *J* = 8.6 Hz, 1H), 7.38 (d, *J* = 1.8 Hz, 1H), 7.32 (dd, *J* = 8.7 Hz, *J* = 1.9 Hz, 1H), 7.24–7.15 (m, 5H), 7.14–7.06 (m, 3H), 6.98-6.91 (m, 2H), 6.71 (s, 1H), 5.47 (d, *J* = 1.9 Hz, 1H), 5.41 (s, 1H), 5.05 (d, *J* = 1.1 Hz, 1H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ, ppm: 150.6 (C), 143.0 (C), 142.2 (C), 141.9 (C), 139.4 (C), 136.3 (C), 135.8 (C), 133.2 (CH), 131.8 (C), 130.5 (CH), 130.0 (CH), 129.6 (CH), 128.6 (CH), 128.5 (CH), 128.1 (CH), 127.9 (CH), 127.6 (CH), 124.6 (CH), 124.5 (CH), 118.1 (C), 117.2 (CH), 107.0 (CH_2), 74.2 (CH). **HRMS** (APCI, **$[M+H]^+$**) *m/z* calculated for $C_{29}H_{22}BrN_2O_4S$: 573.0478, found: 573.0475.

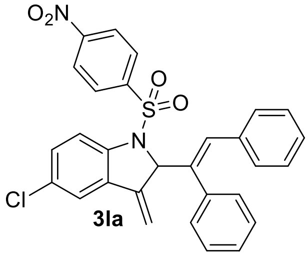
(*E*)-2-(1,2-diphenylvinyl)-3-methylene-1-((4-nitrophenyl)sulfonyl)-5-phenylindoline (3ka)



3ka

According to the general procedure, **3ka** was isolated by column chromatography (5% Et_2O/hexane) as a yellow solid (88 mg, 77% yield). **^{1}H NMR** (300 MHz, $CDCl_3$) δ, ppm: 8.25 (d, *J* = 8.6 Hz, 2H), 8.00 (d, *J* = 8.4 Hz, 2H), 7.71 (d, *J* = 8.2 Hz, 1H), 7.57–7.46 (m, 4H), 7.43 (t, *J* = 7.4 Hz, 2H), 7.35 (d, *J* = 7.2 Hz, 1H), 7.29-7.19 (m, 5H), 7.18–7.08 (m, 3H), 7.05–6.93 (m, 2H), 6.76 (s, 1H), 5.57 (s, 1H), 5.48 (s, 1H), 5.05 (s, 1H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ, ppm: 150.4 (C), 143.3 (C), 143.0 (C), 142.4 (C), 140.0 (C), 139.7 (C), 138.2 (C), 136.6 (C), 136.0 (C), 130.2 (CH), 130.1 (CH), 129.6 (CH), 129.5 (CH), 129.0 (CH), 128.6 (CH), 128.5 (CH), 128.1 (CH), 127.8 (CH), 127.6 (CH), 127.4 (CH), 126.9 (CH), 124.5 (CH), 119.9 (CH), 116.0 (CH), 105.6 (CH_2), 74.2 (CH). **HRMS** (APCI, **$[M+H]^+$**) *m/z* calculated for $C_{35}H_{27}N_2O_4S$: 571.1686, found: 571.1682.

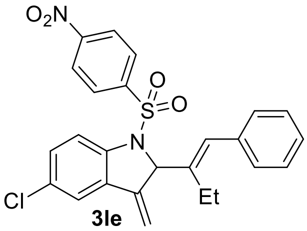
(*E*)-5-chloro-2-(1,2-diphenylvinyl)-3-methylene-1-((4-nitrophenyl)sulfonyl)indoline (3la)



3la

According to the general procedure, **3la** was isolated by column chromatography (5% Et_2O/hexane) as a yellow solid (75.2 mg, 71% yield). **^{1}H NMR** (300 MHz, $CDCl_3$) δ, ppm: 8.27 (d, *J* = 7.9 Hz, 2H), 7.94 (d, *J* = 7.9 Hz, 2H), 7.55 (d, *J* = 8.4 Hz, 1H), 7.27–7.14 (m, 7H), 7.13–7.06 (m, 3H), 6.97–6.90 (m, 2H), 6.70 (s, 1H), 5.47 (s, 1H), 5.40 (s, 1H), 5.04 (s, 1H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ, ppm: 150.6 (C), 143.1 (C), 142.1 (C), 141.7 (C), 139.4 (C), 136.3 (C), 135.8 (C), 131.5 (C), 130.7 (C), 130.5 (CH), 130.4 (CH), 130.0 (CH), 129.6 (CH), 128.6 (CH), 128.5 (CH), 128.1 (CH), 127.9 (CH), 127.6 (CH), 124.6 (CH), 121.5 (CH), 116.9 (CH), 107.0 (CH_2), 74.3 (CH). **HRMS** (APCI, **$[M+H]^+$**) *m/z* calculated for $C_{29}H_{22}ClN_2O_4S$: 529.0983, found: 529.0986.

(*E*)-5-chloro-3-methylene-1-((4-nitrophenyl)sulfonyl)-2-(1-phenylbut-1-en-2-yl)indoline (3le)

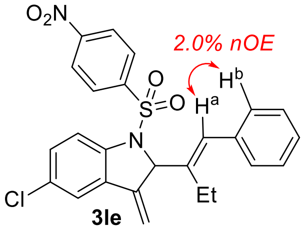


3le

According to the general procedure, **3le** was isolated by column chromatography (5% Et_2O/hexane) as a yellow solid (61.8 mg, 63% yield). **^{1}H NMR** (300 MHz, $CDCl_3$) δ, ppm: 8.27 (d, *J* = 8.3 Hz, 2H), 7.95 (d, *J* = 8.4 Hz, 2H), 7.75 (d, *J* = 8.6 Hz, 1H), 7.44–7.20 (m, 7H), 6.56 (s, 1H), 5.50 (s, 1H), 5.13 (s, 2H), 2.22 (dt, *J* = 15.6 Hz, *J* = 7.3 Hz, 1H), 2.12 (dt, *J* = 15.5 Hz, *J* = 7.3 Hz, 1H), 1.03 (t, *J* = 7.5 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ, ppm: 150.6 (C), 142.8 (C), 142.4 (C), 142.0 (C), 141.5 (C), 136.7 (C), 131.6 (C), 130.7 (C), 130.5 (CH), 130.4 (CH), 128.9 (CH), 128.6 (CH), 128.5 (CH), 127.4 (CH), 124.5 (CH), 121.7 (CH), 117.0 (CH), 106.8 (CH_2), 74.9 (CH), 20.8 (CH_2), 14.4 (CH_3). **HRMS** (APCI, **$[M+H]^+$**) *m/z* calculated for $C_{25}H_{22}ClN_2O_4S$: 481.0983, found: 481.0991.

Assignment of the regiochemistry

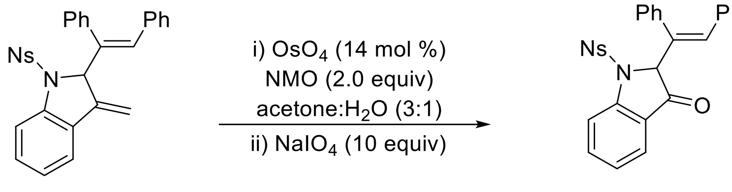
The major regioisomer was assigned based on HSQC, HMBC and COSY experiments and by the observation of a nOe between H^a and H^b.



3le

3. Manipulation of the products

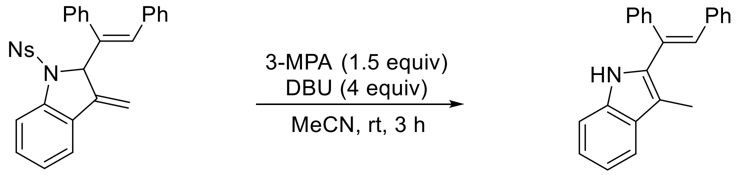
Procedure for the oxidation of the exomethylene group:



3aa **6aa**

To a solution of the functionalized indoline **3aa** (49.5 mg, 0.1 mmol) in acetone (1 mL) at room temperature was added NMO (23.4 mg, 0.2 mmol) and H_2O (0.35 mL). After all the solids were dissolved, OsO_4 (0.1 M in H_2O, 3.6 mg, 0.014 mmol, 14 mol%) was added. The reaction was then stirred at room temperature for 30 min, at which point solid $NaIO_4$ (213.9 mg, 1 mmol) was added in three portions. After stirring the resulting mixture at room temperature for 1h the solution was filtered through a pad of Celite to remove the solids. The filtrate was then diluted with H_2O (15 mL) and extracted with EtOAc (3 x 15 mL). The combined organic layers were washed with brine (50 mL), dried over $MgSO_4$ and concentrated *in vacuo*. Purification of the residue by column chromatography (10 to 20% EtOAc/hexane) afforded (*E*)-2-(1,2-diphenylvinyl)-1-((4-nitrophenyl)sulfonyl)indolin-3-one (**6aa**) as an orange solid (41.2 mg, 83% yield). **^{1}H NMR** (300 MHz, $CDCl_3$) δ, ppm: 8.27 (d, *J* = 8.7 Hz, 2H), 8.01 (d, *J* = 8.7 Hz, 1H), 7.93 (d, *J* = 8.4 Hz, 2H), 7.69-7.59 (m, 2H), 7.23-7.06 (m, 9H), 6.72 (s, 1H), 4.82 (s, 1H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ, ppm: 195.9 (C), 152.4 (C), 150.7 (C),143.0 (C), 137.7 (CH), 135.4 (CH), 133.3 (C), 128.6 (CH), 125.3 (CH), 125.2 (CH), 124.7 (C), 124.6 (CH), 116.2 (CH), 73.4 (CH), 21.3 (CH_2), 20.6 (CH_2), 14.0 (CH_3), 13.9 (CH_3). **HRMS** (ESI, **[M+H]$^+$**) *m/z* calculated for $C_{28}H_{21}N_2O_5S$: 497.1166, found: 497.1167.

Procedure for the removal of the nosyl group:

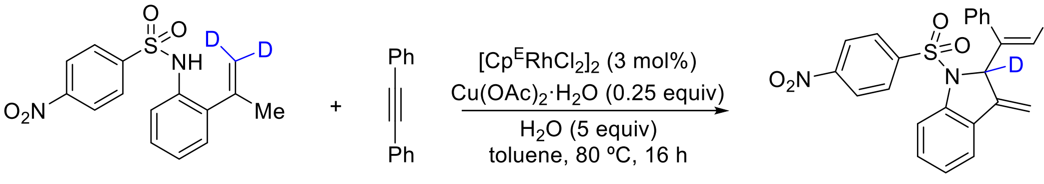


3aa **7aa**

To a solution of the functionalized indoline **3aa** (98.9 mg, 0.2 mmol) in acetonitrile (2 mL) at room temperature was added DBU (0.12 mL, 0.8 mmol) and 3-mercaptopropionic acid (26 µL, 0.3 mmol) and the mixture was stirred for 3h. Once completion, the crude mixture was concentrated *in vacuo* and purified by column chromatography (5 to 20% Et_2O/hexane), which afforded (*E*)-2-(1,2-diphenylvinyl)-3-methyl-1H-indole (**7aa**) as a yellow solid (44.6 mg, 72% yield). **^{1}H NMR** (300 MHz, $CDCl_3$) δ, ppm: 7.67 (d, *J* = 7.2 Hz, 2H), 7.46 – 7.35 (m, 5H), 7.22 (m, 8H), 7.03 – 6.99 (m, 1H), 2.36 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ, ppm: 138.9 (C), 136.9 (C), 135.7 (C), 135.4 (C), 134.4 (C), 130.4 (CH), 129.9 (C), 129.6 (CH), 129.0 (CH), 128.2 (CH), 128.1 (CH), 127.0 (CH), 122.6 (CH), 119.5 (CH), 119.0 (CH), 110.9 (C), 110.7 (CH), 10.3 (CH_3). **HRMS** (APCI, **[M+H]$^+$**) calculated for $C_{23}H_{20}N$: 310.1590, found 310.1593.

4. Mechanistic experiments

Procedure for the reaction with deuterated substrate 1a-*d₂*:



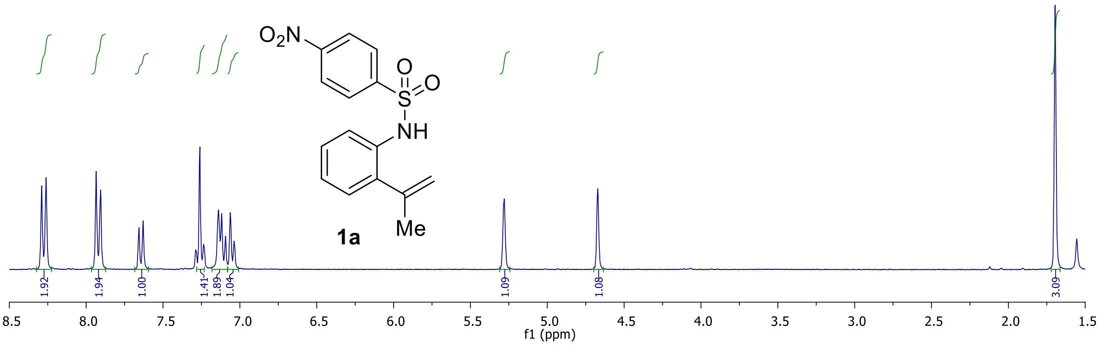
1a-*d*$_2$
67% deuteration

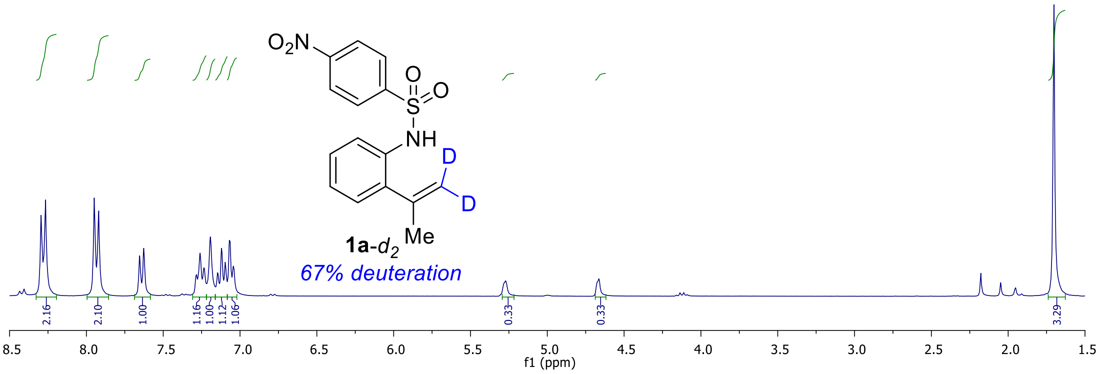
2a

3aa-*d*$_1$
67% deuteration

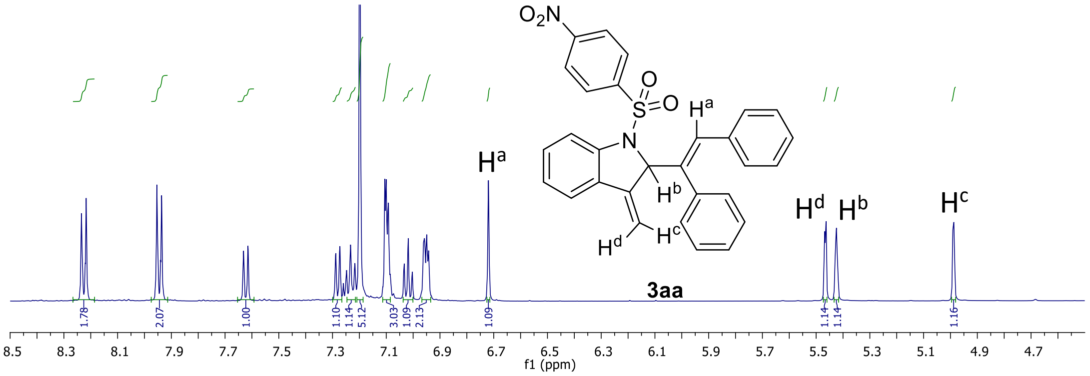
A Schlenk tube was loaded with **1a**-*d*$_2$ (48.0 mg, 0.15 mmol) and diphenylacetylene (**2a**) (17.8 mg, 0.1 mmol) in the presence of [Cp^{E}RhCl$_2$]$_2$ (2.6 mg, 0.006 mmol, 3 mol%), $Cu(OAc)_2$ (5 mg, 0.025 mmol) and H_2O (9 µl, 0.5 mmol) in toluene (1 mL). The tube was capped with a rubber septum and stirred in a vortex mixer. The resulting solution was heated at 80 ºC under a balloon of air for 16 h. The reaction was then cooled to room temperature, filtered through a short pad of silica gel using CH_2Cl_2 (20 mL) as eluent and concentrated *in vacuo*. Purification of the residue by column chromatography (5 to 20% EtOAc/hexane) afforded ((*E*)-2-(1,2-diphenylvinyl)-3-methylene-1-((4-nitrophenyl)sulfonyl)indoline-2-*d*$_1$ (**3aa**-*d*$_1$) as a yellow solid (39.6 mg, 80% yield, 67% deuteration).

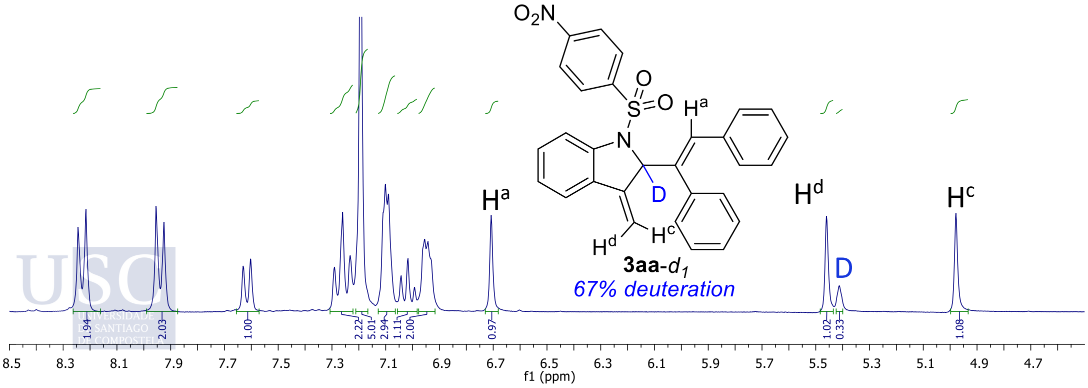
*Deuterated analog of nosyl-protected 2-alkenylanilide substrate (**1a**-d$_2$)*



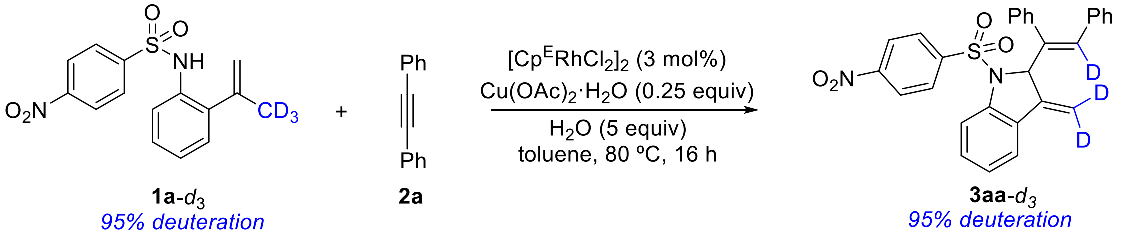


*Deuterated indoline (**3aa**-d$_1$)*



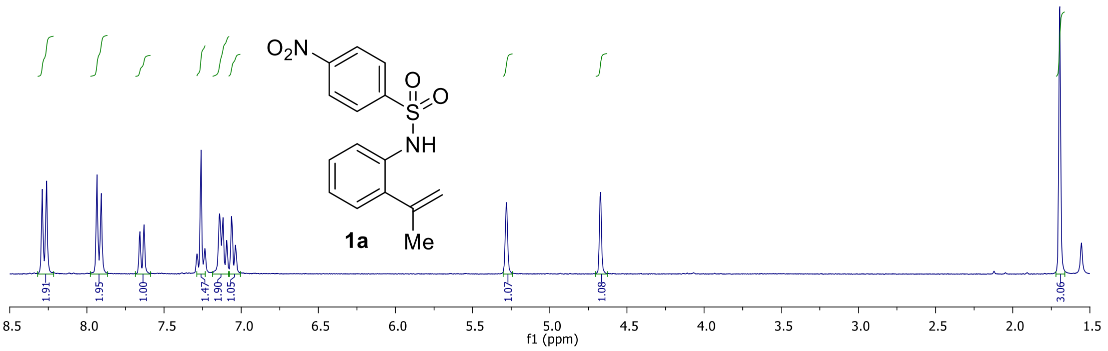


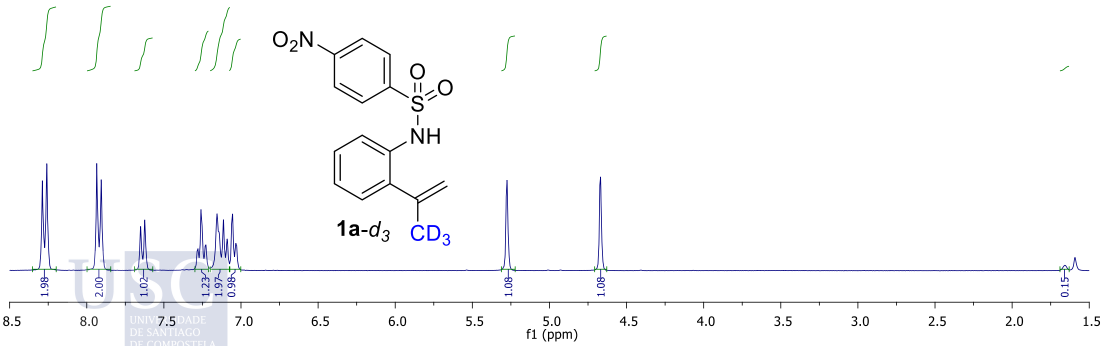
Procedure for the reaction with deuterated substrate 1a-*d*₃:



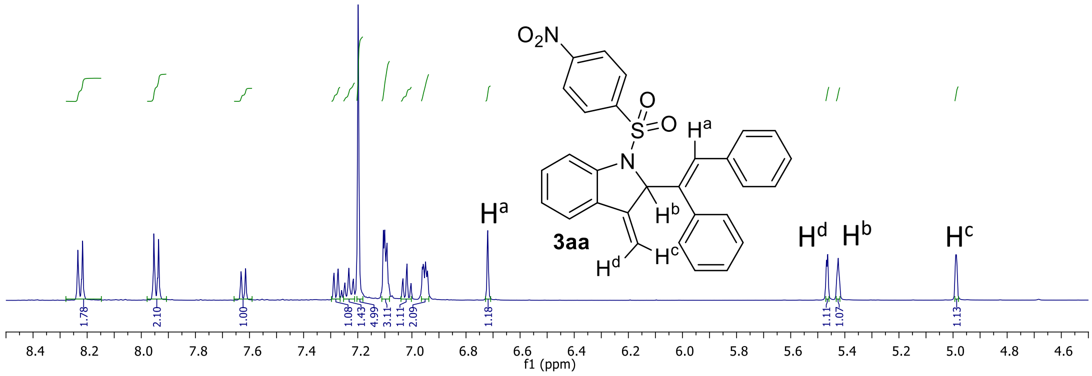
A Schlenk tube was loaded with **1a**-*d*₃ (48.2 mg, 0.15 mmol) and diphenylacetylene (**2a**) (17.8 mg, 0.1 mmol) in the presence of $[Cp^ERhCl_2]_2$ (2.6 mg, 0.006 mmol, 3 mol%), $Cu(OAc)_2$ (5 mg, 0.025 mmol) and H_2O (9 µl, 0.5 mmol) in toluene (1 mL). The tube was capped with a rubber septum and stirred in a vortex mixer. The resulting solution was heated at 80 ºC under a balloon of air for 16 h. The reaction was then cooled to room temperature, filtered through a short pad of silica gel using CH_2Cl_2 (20 mL) as eluent and concentrated *in vacuo*. Purification of the residue by column chromatography (5 to 20% EtOAc/hexane) afforded (*E*)-2-(1,2-diphenylvinyl-2-*d*₁)-3-(methylene-*d*₂)-1-((4-nitrophenyl)sulfonyl)indoline (**3aa**-*d*₃) as a yellow solid (39.3 mg, 79% yield, 95% deuteration).

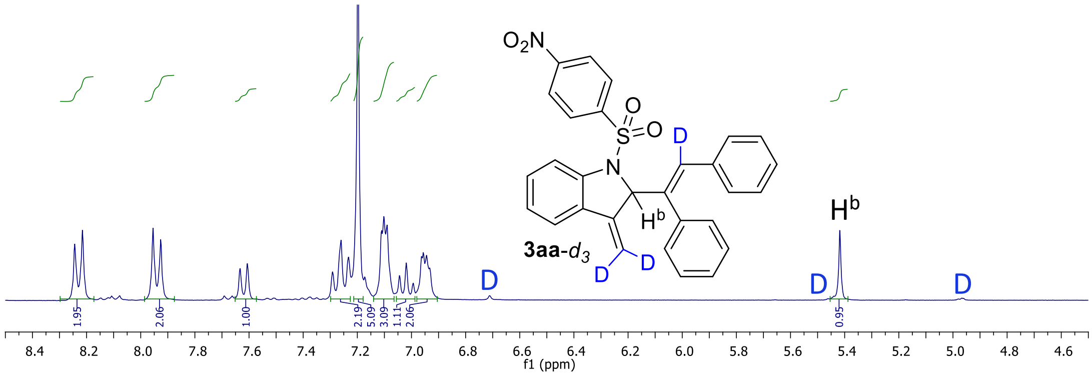
*Deuterated analog of nosyl-protected 2-alkenylanilide (**1a**-d₃)*



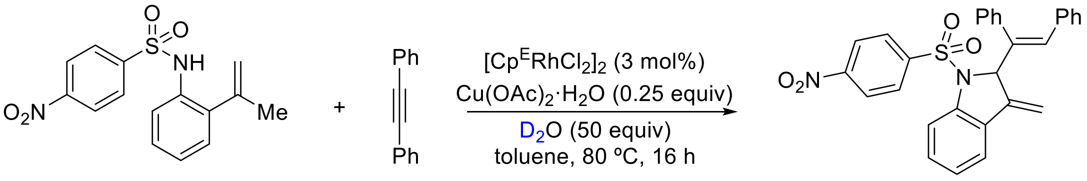


Deuterated indoline ***3aa****-d*$_3$





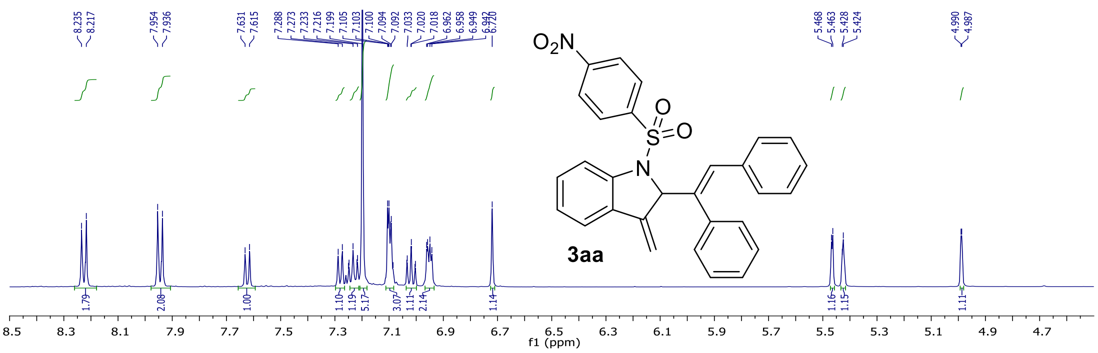
Procedure for the model reaction in presence of deuterated water:



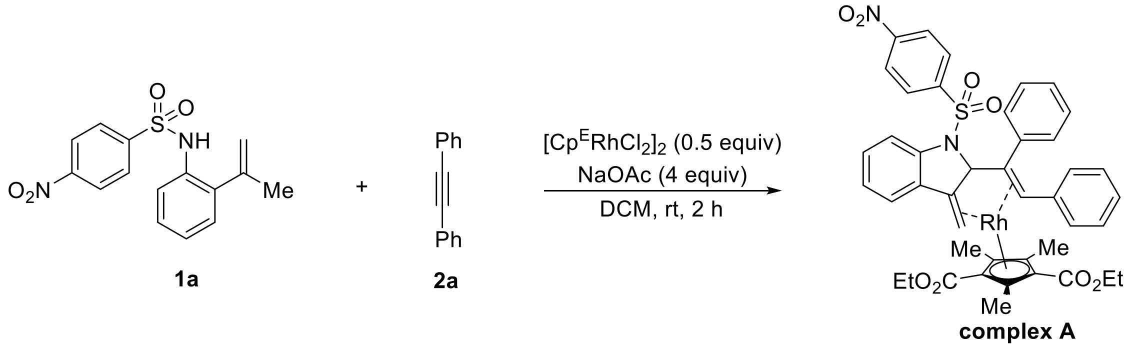
1a **2a** **3aa**

0% deuteration

A Schlenk tube was loaded with **1a** (95.5 mg, 0.3 mmol) and diphenylacetylene (**2a**) (35.6 mg, 0.2 mmol) in the presence of [Cp^{E}RhCl$_2$]$_2$ (5.1 mg, 0.006 mmol, 3 mol%), Cu(OAc)$_2$ (10 mg, 0.05 mmol) and D_2O (180 µl, 10 mmol) in toluene (2 mL). The tube was capped with a rubber septum and stirred in a vortex mixer. The resulting solution was heated at 80 ºC under a balloon of air for 16 h. The reaction was then cooled to room temperature, filtered through a short pad of silica gel using CH_2Cl_2 (20 mL) as eluent and concentrated *in vacuo*. Purification of the residue by column chromatography (5 to 20% EtOAc/hexane) to afford (*E*)-2-(1,2-diphenylvinyl)-3-methylene-1-((4-nitrophenyl)sulfonyl)indoline (**3aa**) as a yellow solid (22.2 mg, 23% yield, 0% deuteration).

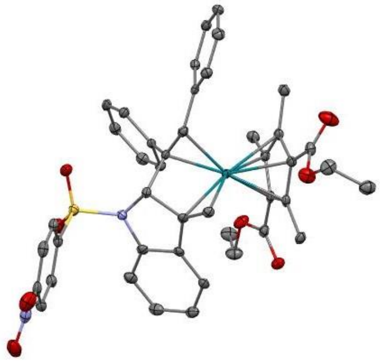


Procedure for the isolation of the rhodium complex A:

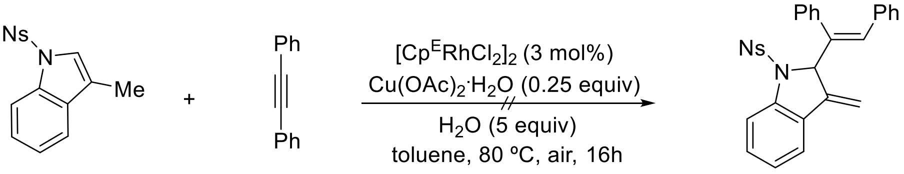


A Schlenk tube was loaded with nosyl-protected 2-alkenylaniline (**1a**) (16.0 mg, 0.05 mmol), [Cp^{E}RhCl$_2$]$_2$ (21.0 mg, 0.025 mmol), NaOAc (16.4 mg, 0.2 mmol), diphenylacetylene (**2a**) (9.0 mg, 0.05 mmol), and CH_2Cl_2 (2 ml). The tube was capped with a rubber septum, stirred in a vortex mixer and the resulting mixture was stirred at room temperature with a balloon of air for 2 h. The reaction was then cooled to room temperature and concentrated *in vacuo*. The obtained residue was finally purified by column chromatography (20% EtOAc/hexanes) affording **complex A** (33.7 mg, 79%). **^{1}H NMR** (300 MHz, $CDCl_3$) δ, ppm: 8.12 (d, *J* = 8.3 Hz, 2H), 7.58 (d, *J* = 8.2 Hz, 4H), 7.40–7.32 (m, 3H), 7.28 (t, *J* = 8.3 Hz, 1H), 7.17 (t, *J* = 7.4 Hz, 1H), 7.12–7.01 (m, 3H), 6.98 (d, *J* = 7.4 Hz, 1H), 6.91 (d, *J* = 7.6 Hz, 1H), 5.18 (s, 1H), 4.31–4.10 (m, 2H), 3.88 (q, *J* = 7.1 Hz, 2H), 3.43 (s, 1H), 2.64 (s, 1H), 2.53 (s, 1H), 2.00 (s, 3H), 1.48 (s, 3H), 1.30 (t, *J* = 7.1 Hz, 3H), 1.23 (t, *J* = 7.1 Hz, 3H), 0.60 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ, ppm: 166.0 (C), 164.4 (C), 150.3 (C), 143.6 (C), 142.8 (C), 139.3 (d, $J_{C\text{-}Rh}$ = 1.1 Hz, C), 136.6 (C), 133.8 (d, $J_{C\text{-}Rh}$ = 1.5 Hz, C), 133.3 (CH), 129.3 (CH), 128.6 (CH), 128.1 (CH), 128.1 (CH), 127.6 (CH), 127.5 (CH), 125.8 (CH), 125.0 (CH), 124.2 (CH), 121.5 (CH), 115.1 (CH), 112.3 (d, $J_{C\text{-}Rh}$ = 3.9 Hz, C), 105.1 (d, $J_{C\text{-}Rh}$ = 3.9 Hz, C), 102.2 (d, $J_{C\text{-}Rh}$ = 4.3 Hz, C), 94.6 (d, $J_{C\text{-}Rh}$ = 4.7 Hz, C), 91.8 (d, $J_{C\text{-}Rh}$ = 3.9 Hz, C), 73.6 (d, $J_{C\text{-}Rh}$ = 3.4 Hz, CH), 64.8 (d, $J_{C\text{-}Rh}$ = 12.8 Hz, CH), 60.2 (CH_2), 60.2 (CH_2), 53.7 (d, $J_{C\text{-}Rh}$ = 8.6 Hz, C), 47.7 (d, $J_{C\text{-}Rh}$ = 9.8 Hz, C), 43.7 (d, $J_{C\text{-}Rh}$ = 14.3 Hz, CH_2), 14.5 (CH_3), 14.3 (CH_3), 11.8 (CH_3), 11.1 (CH_3), 7.9 (CH_3).

To confirm the structure, suitable crystals of **complex A** for X-Ray diffraction analysis were grown by slow diffusion of heptane in a CH_2Cl_2 solution of the complex. The crystallographic data was deposited in the Cambridge Structural Database (1827835).



Procedure for the evaluation of the indole as possible reaction intermediate:



8a **2a** **3aa**

A Schlenk tube was loaded with **8a** (63.3 mg, 0.2 mmol), synthesized according to the literature,[184] and diphenylacetylene (**2a**) (35.6 mg, 0.2 mmol) in the presence of $[Cp^ERhCl_2]_2$ (5.1 mg, 0.006 mmol, 3 mol%), $Cu(OAc)_2$ (10 mg, 0.05 mmol) and H_2O (18 µl, 1 mmol) in toluene (2 mL). The tube was capped with a rubber septum and stirred in a vortex mixer. The resulting solution was heated at 80 ºC under a balloon of air for 16 h. The reaction was then cooled to room temperature, filtered through a short pad of silica gel using CH_2Cl_2 (20 mL) as eluent and concentrated *in vacuo*. The obtained TLC, together with NMR of the crude, reveled the recovery of the starting material with no detection of the product **3aa**.

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[184] Liwosz, T. W.; Chemler, S. R. *Synlett* **2015**, *26*, 335-339.


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Chapter II – Divergent synthesis of azepines and pyrrolidines through a Rh(III)-catalyzed annulation between homoallylamides and alkynes, triggered by C-H activation

1. Synthesis of starting materials

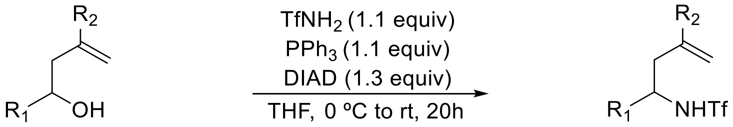
1.1 Preparation of alkynes

Alkyne **2a** (diphenylacetylene) was purchased from Sigma-Aldrich and alkyne **2i** (3-hexyne) was purchased from Alfa Aesar.

1.2 Preparation of homoallylamides

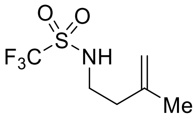
Homoallylamides were synthesized via Mitsunobu reaction from the corresponding alcohols. **9a**, **9c**, and **9d** were obtained from commercially available starting materials while **9b** required the synthesis of the corresponding precursor, 4-methylpent-4-en-2-ol, according to the literature.[185]

General procedure for the synthesis of the homoallyltriflamides (9a-9c):



The corresponding homoallylic alcohol (11 mmol) was dissolved in dry THF (110 mL, 0.1M) and the mixture was cooled at 0^{o}C. Then, PPh_3 (3.2 g, 12.1 mmol) and trifluoromethanesulfonamide (1.8 g, 12.1 mmol) were added followed by dropwise addition of DIAD (98%, 2.9 mL, 14.3 mmol). After stirring overnight at room temperature, the solvent was removed *in vacuo* and the crude reaction mixture was purified by flash column chromatography on silica gel (5 to 20% Et_2O/hexanes) to afford the pure homoallyltriflamides **9a**-**9c**.

1,1,1-trifluoro-*N*-(3-methylbut-3-en-1-yl)methanesulfonamide (9a)



9a

9a obtained as a colourless oil (1.3 g, 55% yield). **^{1}H NMR** (300 MHz, $CDCl_3$) δ, ppm: 5.01 – 4.90 (m, 2H), 4.82 (s, 1H), 3.44 (q, *J* = 6.2 Hz, 2H), 2.33 (t, *J* = 6.6 Hz, 2H), 1.76 (s, 3H). **^{19}F NMR** (282 MHz, $CDCl_3$) δ, ppm: -77.93 (s). **^{13}C NMR** (75 MHz, $CDCl_3$) δ, ppm: 140.7 (C), 118.7 (q, *J* = 321.0 Hz, C), 114.2 (CH_2), 41.9 (CH_2), 38.0 (CH_2), 21.8 (CH_3). **HRMS** (APCI, **[M+H]$^+$**) *m/z* calculated for $C_6H_{11}F_3NO_2S$: 218.0457, found 218.0457.

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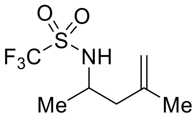
[185] Chanh, H.; Fadilla, D.-B.; Gerard, L. *Tetrahedron Lett.* **1979**, *17*, 1503-1506.

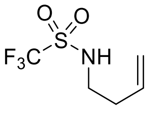
1,1,1-trifluoro-*N*-(4-methylpent-4-en-2-yl)methanesulfonamide (9b)



9b

9b obtained as a yellowish oil (0.84 g, 33% yield). **^{1}H NMR** (300 MHz, $CDCl_3$) δ, ppm: 5.01 (d, *J* = 7.4 Hz, 1H), 4.91 – 4.88 (m, 1H), 4.79 – 4.76 (m, 1H), 3.80 (hept, *J* = 6.9 Hz, 1H), 2.25 (h, *J* = 7.1 Hz, 2H), 1.74 (s, 3H), 1.28 (d, *J* = 6.6 Hz, 3H). **^{19}F NMR** (282 MHz, $CDCl_3$) δ, ppm: -77.90 (s). **^{13}C NMR** (75 MHz, $CDCl_3$) δ, ppm: 140.9 (C), 119.7 (q, *J* = 320.7 Hz, C), 115.0 (CH_2), 50.5 (CH), 46.5 (CH_2), 22.0 (CH_3), 22.0 (CH_3). **HRMS** (APCI, **[M-H]$^-$**) *m/z* calculated for $C_7H_{11}F_3NO_2S$: 230.0468, found 230.0467.

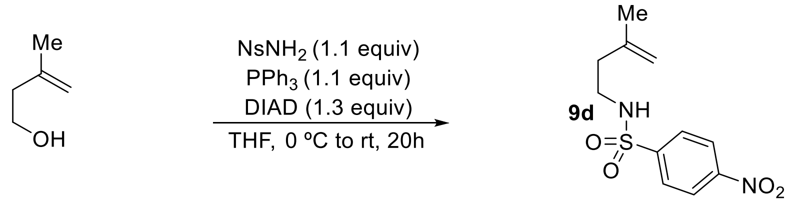
N-(but-3-en-1-yl)-1,1,1-trifluoromethanesulfonamide (9c)



9c

9c obtained as a colourless oil (0.76 g, 34% yield). **^{1}H NMR** (300 MHz, $CDCl_3$) δ, ppm: 5.73 (ddt, *J* = 18.1, 9.5, 6.9 Hz, 1H), 5.23 – 5.07 (m, 3H), 3.36 (q, *J* = 6.3 Hz, 2H), 2.35 (q, *J* = 6.7 Hz, 2H). **^{19}F NMR** (282 MHz, $CDCl_3$) δ, ppm: -77.51 (s). **^{13}C NMR** (75 MHz, $CDCl_3$) δ, ppm: 133.3 (CH), 119.8 (q, *J* = 320.8 Hz, C), 119.2 (CH_2), 43.5 (CH_2), 34.4 (CH_2). **HRMS** (APCI, **[M-H]$^-$**) *m/z* calculated for $C_5H_7F_3NO_2S$: 202.0155, found 202.0161.

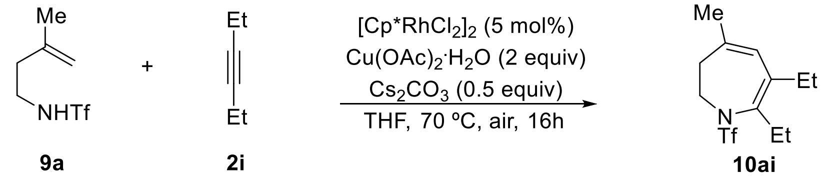
Procedure for the synthesis of the homoallylnosylamide 9d:



3-methyl-3-buten-1-ol (0.95 g, 11 mmol) was dissolved in dry THF (110 mL, 0.1M) and the mixture was cooled at 0^{0}C. Then, PPh_3 (3.2 g, 12.1 mmol) and 4-nitrobenzenesulfonamide (2.4 g, 12.1 mmol) were added followed by dropwise addition of DIAD (98%, 2.9 mL, 14.3 mmol). After stirring overnight at room temperature, the solvent was removed *in vacuo* and the crude reaction mixture was purified by flash column chromatography on silica gel (10 to 20% EtOAc/hexanes), affording *N*-(3-methylbut-3-en-1-yl)-4-nitrobenzenesulfonamide (**9d**) as a pale orange solid (1.3 g, 32% yield). **^{1}H NMR** (300 MHz, $CDCl_3$) δ, ppm: 8.36 (d, *J* = 8.9 Hz, 2H), 8.05 (d, *J* = 8.8 Hz, 2H), 4.87 (t, *J* = 5.5 Hz, 1H), 4.80 (s, 1H), 4.65 (s, 1H), 3.12 (q, *J* = 6.6 Hz, 2H), 2.18 (t, *J* = 6.7 Hz, 2H), 1.61 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ, ppm: 150.1 (C), 146.0 (C), 141.2 (C), 128.4 (CH), 124.5 (CH), 113.6 (CH_2), 40.8 (CH_2), 37.4 (CH_2), 21.8 (CH_3). **HRMS** (APCI, **[M-H]$^-$**) *m/z* calculated for $C_{11}H_{13}N_2O_4S$: 269.0628, found 269.0627.

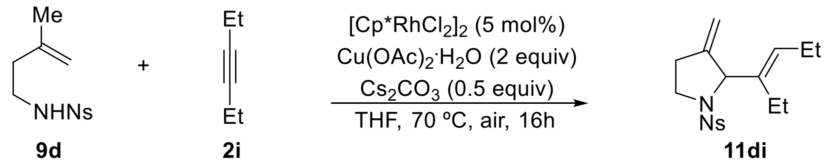
2. Procedure for the Rh-catalyzed synthesis of azepines and pyrrolidines

Procedure for the synthesis of azepine 10ai:



$[Cp^*RhCl_2]_2$ (3.1 mg, 5 mol%), $Cu(OAc)_2 \cdot H_2O$ (40 mg, 0.2 mmol) and Cs_2CO_3 (16.3 mg, 0.05 mmol) were weighed in air and placed in a Schlenk tube with a magnetic stir bar. Then, tetrahydrofuran (1.1 mL), homoallyltriflamide **9a** (18 µl, 0.1 mmol) and 3-hexyne (11 µl, 0.1 mmol) were added. The tube was sealed with a rubber septum and the reaction mixture was stirred 16 hours at 70^{o}C. Then, the resulting mixture was cooled to room temperature and concentrated *in vacuo*. The resulting residue was purified by flash column chromatography on silica gel (5 to 20% DCM/hexanes) affording 6,7-diethyl-4-methyl-1-((trifluoromethyl)sulfonyl)-2,3-dihydro-1*H*-azepine (**10ai**) as a yellowish oil (5.9 mg, 20% yield). **^{1}H NMR** (500 MHz, $CDCl_3$) δ, ppm: 5.58 (s, 1H), 4.35 – 3.52 (m, 2H), 2.53 – 2.38 (m, 4H), 2.18 – 2.05 (m, 2H), 1.88 (s,3H), 1.09 (t, *J* = 7.5 Hz, 3H), 1.01 (t, *J* = 7.6 Hz, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ, ppm: 140.8 (C), 137.7 (C), 135.8 (C), 125.5 (CH), 120.2 (q, *J* = 324.4 Hz, C), 56.2 (CH_2), 34.9 (CH_2), 26.9 (CH_2), 25.8 (CH_3), 25.5 (CH_2), 13.7 (CH_3), 13.3 (CH_3). **HRMS** (APCI, **$[M+H]^+$**) *m/z* calculated for $C_{12}H_{19}F_3NO_2S$: 298.1084, found 298.1089.

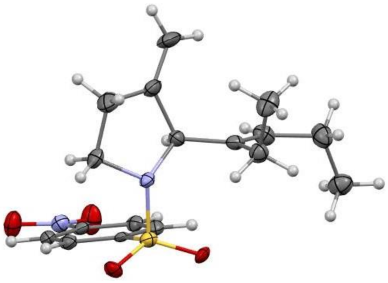
Procedure for the synthesis of pyrrolidine 11di:



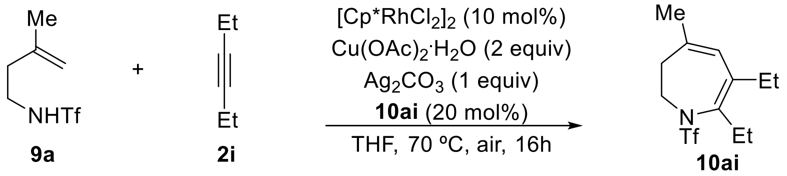
Homoallylnosylamide **9d** (27 mg, 0.1 mmol), $[Cp^*RhCl_2]_2$ (3.1 mg, 5 mol%), $Cu(OAc)_2 \cdot H_2O$ (40 mg, 0.2 mmol) and Cs_2CO_3 (16.3 mg, 0.05 mmol) were weighed in air and placed in a Schlenk tube with a magnetic stir bar. Then, tetrahydrofuran (1.1 mL) and 3-hexyne (11 µl, 0.1 mmol) were added. The tube was sealed with a rubber septum and the reaction mixture was stirred 16 hours at 70^{o}C. Then, the resulting mixture was cooled to room temperature and concentrated *in vacuo*. The resulting residue was purified by flash column chromatography on silica gel (10% DCM/hexanes to 40% Et_2O/hexanes) affording (*E*)-2-(hex-3-en-3-yl)-3-methylene-1-((4-nitrophenyl)sulfonyl)pyrrolidine (**11di**) as a yellowish solid (6.3 mg, 18% yield). **^{1}H NMR** (500 MHz, $CDCl_3$) δ, ppm: 8.34 (d, *J* = 9.0 Hz, 2H), 7.98 (d, *J* = 9.0 Hz, 2H), 5.33 (t, *J* = 7.2 Hz, 1H), 4.96 (q, *J* = 2.0 Hz, 1H), 4.87 (q, *J* = 2.0 Hz, 1H), 4.41 (s, 1H), 3.62 – 3.56 (m, 1H), 3.50 – 3.43 (m, 1H), 2.63 – 2.54 (m, 1H), 2.42 – 2.34 (m, 1H), 2.04 (p, *J* = 7.4 Hz, 2H), 1.92 – 1.82 (m, 2H), 1.02 – 0.93 (m, 6H). **^{13}C NMR**

(126 MHz, $CDCl_3$) δ, ppm: 150.1 (C), 147.0 (C), 144.2 (C), 138.5 (C), 131.9 (CH), 128.9 (CH), 124.2 (CH), 109.4 (CH_2), 70.3 (CH), 48.2 (CH_2), 31.3 (CH_2), 21.2 (CH_2), 20.7 (CH_2), 14.6 (CH_3), 14.3 (CH_3). **HRMS** (APCI, **$[M+H]^+$**) *m/z* calculated for $C_{17}H_{23}N_2O_4S$: 351.1374, found 351.1380.

To confirm the structure, suitable crystals of **11di** for X-Ray diffraction analysis were grown by slow diffusion of heptane in a CH_2Cl_2 solution of the compound.



3. Mechanistic experiments



$[Cp^*RhCl_2]_2$ (6.2 mg, 10 mol%), $Cu(OAc)_2 \cdot H_2O$ (40 mg, 0.2 mmol) and Ag_2CO_3 (27.6 mg, 0.1 mmol) were weighed in air and placed in a Schlenk tube with a magnetic stir bar. Then, tetrahydrofuran (1.1 mL), homoallyltriflamide **9a** (18 µl, 0.1 mmol), 3-hexyne (11 µl, 0.1 mmol) and azepine **10ai** (5.9 mg, 0.02 mmol) were added. The tube was sealed with a rubber septum and the reaction mixture was stirred 16 hours at 70^{o}C. Then, the resulting mixture was cooled to room temperature and concentrated *in vacuo*. The resulting residue was purified by flash column chromatography on silica gel (5 to 20% DCM/hexanes) affording 6,7-diethyl-4-methyl-1-((trifluoromethyl)sulfonyl)-2,3-dihydro-1*H*-azepine (**10ai**) as a yellowish oil (6.2 mg, 21% yield).

Chapter III – Palladium-catalyzed formal (4+2) cycloaddition between alkyl amides and dienes initiated by the activation of C(sp^3)-H bonds

Chapter adapted from:
Cendón, B.[a]; Font, M.[a]; Mascareñas, J. L.[a]*; Gulías, M.[a]* *ACS Catal.* **2020**, *10*, 3425-3430.

[a] 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)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1. Synthesis of starting materials

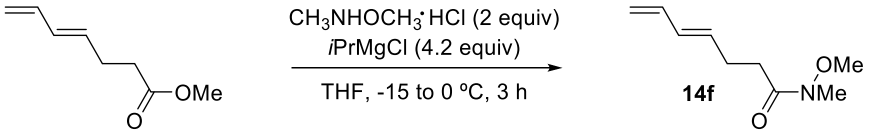
1.1 Preparation of allenes

Allene **13b** (vinylidenecyclohexane) was purchased from Sigma-Aldrich. Allenes **13a** ((3-methylbuta-1,2-dien-1-yl)benzene)[186] and **13c** ((4-methylpenta-1,2-dien-3-yl)benzene)[187] were prepared according to the literature and the spectral data was in agreement with the previously reported.

1.2 Preparation of dienes

Dienes **14a** ((*E*)-buta-1,3-dien-1-ylbenzene), **14h** (isoprene) and **14l** (1,3-cyclohexadiene) were commercially available. **14a** and **14h** were purchased from Aldrich and **14l** from Acros Organics. Dienes **14b** ((*E*)-1-(1,3-butadienyl)-4-nitrobenzene), **14c** ((*E*)-1-(1,3-buta dienyl)-3-fluorobenzene), **14d** ((*E*)-1-(1,3-butadienyl)-2-methoxybenzene), **14e** ((*E*)-deca-1,3-diene), **14i** ((*E*)-(2-methylbuta-1,3-dien-1-yl)benzene), **14k** (1-vinylcyclohex-1-ene) and (*E*) and (*Z*)-**14m** (*tert*-butyldimethyl(penta-2,4-dien-1-yloxy)silane) were synthesized from the corresponding aldehyde *via* Wittig reaction according to the literature.[188] Diene **14g** (ethyl (*E*)-penta-2,4-dienoate) was also synthesized with a method previously reported in literature.[164b] Spectral data was in agreement with the previously reported.

Diene **14f** ((*E*)-N-methoxy-N-methylhepta-4,6-dienamide) was prepared from the corresponding ester, already prepared in the literature,[189] following the procedure shown below.



*i*PrMgCl (2.0 M in THF, 15 mL, 30 mmol) was added to a suspension of CH$_3$NH(OCH$_3$)·HCl (1.46 g, 14.63 mmol) in THF (71 mL), under Ar atmosphere, at -15 ºC. The resulting mixture was stirred for 20 minutes. Then, the ester (1 g, 7.13 mmol) was added, and the solution was warmed to 0 °C. The mixture was stirred for 3 h before NH$_4$Cl (sat.) (25 mL) was added to quench the reaction. The layers were separated, and the aqueous layer was extracted with EtOAc (3 × 50 mL). The combined organic layers were washed with brine (50 mL), dried over Na$_2$SO$_4$ and concentrated in vacuo. The crude product was purified by flash column chromatography on silica gel (20 to 60% EtOAc/hexanes) to give diene **14f** as a pale-yellow oil (1.19 g, 99%).**^{1}H NMR** (300 MHz, CDCl$_3$) δ, ppm: 6.24 (dt, *J* = 16.9, 10.2 Hz, 1H), 6.04 (dd, *J* = 14.8, 10.6 Hz, 1H), 5.74 – 5.62 (m, 1H), 5.05 (d, *J* = 16.8 Hz, 1H), 4.92 (d, *J* = 10.0 Hz, 1H), 3.62 (s, 3H), 3.12 (s, 3H), 2.47 (t, *J* = 7.4 Hz, 2H), 2.41 – 2.31 (m, 2H). **^{13}C**

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[186] Boreux, A.; Indukuri, K.; Gagosz, F.; Riant, O. *ACS Catal.* **2017**, *7*, 8200-8204.

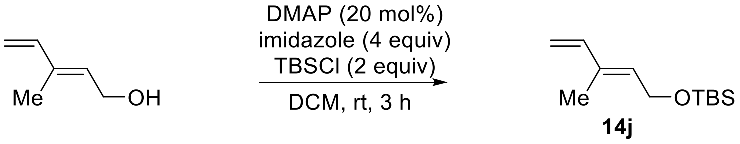
[187] Zhao, Z.; Racicot, L.; Murphy, G. K. *Angew. Chem. Int. Ed.* **2017**, *56*, 11620-11623.

[188] Fernandez, E.; Davenport, E. *Chem. Commun*. **2018**, *54*, 10104-10107.

[189] Cossy, J.; Tsuchiya, T.; Ferrié, L.; Reymond, S.; Kreuzer, T; Colobert, F.; Jourdain, P.; Markó I. E. *Synlett* **2007**, *14*, 2286-2288.

NMR (75 MHz, $CDCl_3$) δ, ppm: 173.7 (C), 137.0 (CH), 133.5 (CH), 131.6 (CH), 115.4 (CH_2), 61.2 (CH_3), 32.1 (CH_3), 31.4 (CH_2), 27.4 (CH_2). **HRMS** (APCI, **$[M+H]^+$**) *m/z* calculated for $C_9H_{16}NO_2$: 170.1176, found 170.1174.

Diene **14j** ((*E*)-*tert*-butyldimethyl((3-methylpenta-2,4-dien-1-yl)oxy)silane) was synthesized by protection, with TBSCl, of the corresponding alcohol, prepared according with the previously described.[190]



A solution of the alcohol (1 g, 10.19 mmol) in dichloromethane (17 mL) was added to a solution of imidazole (2.77 g, 40.76 mmol), DMAP (249 mg, 2.04 mmol) and TBSCl (3.07 g, 20.38 mmol) in dichloromethane (52 mL) under Ar atmosphere. The resulting reaction mixture was stirred for 3 h at rt. Then, water (10 mL) was added, and the resulting mixture was extracted with dichloromethane. The combined extracts were washed with brine (30 mL), dried over Na_2SO_4, filtered and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (0.5 to 1% Et_2O/hexanes) to give diene **14j** as a colorless oil (1.95 g, 92% yield). **^{1}H NMR** (300 MHz, $CDCl_3$) δ, ppm: 6.37 (dd, *J* = 17.4, 10.7 Hz, 1H), 5.59 (t, *J* = 6.3 Hz, 1H), 5.16 (d, *J* = 17.4 Hz, 1H), 5.01 (d, *J* = 10.7 Hz, 1H), 4.33 (d, *J* = 6.3 Hz, 2H), 1.74 (s, 3H), 0.91 (s, 9H), 0.08 (s, 6H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ, ppm: 141.1 (CH), 134.4 (C), 132.1 (CH), 112.3 (CH_2), 60.4 (CH_2), 26.1 (CH_3), 18.5 (C), 12.0 (CH_3), -5.0 (CH_3). **HRMS** (APCI, **$[M+H]^+$**) *m/z* calculated for $C_{12}H_{25}OSi$: 213.1669, found 213.1668.

1.3 Preparation of alkyl amides

N-nosyl, *N*-tosyl and *N*-triflyl amides were prepared following the same procedure using the corresponding carboxylic acid as starting material. All non-commercially available carboxylic acids, 2-ethyl-2-methylbutanoic acid[191] and 5-methoxy-2,2-dimethyl-5-oxopentanoic acid,[192] were prepared according to the literature. Alkyl amides **12d** (*N*-(2,3,5,6-tetrafluoro-4-(trifluoromethyl)phenyl)pivalamide)[148] and **14e** (*N*-(quinolin-8-yl)pivalamide)[193] were also prepared according with the previously described. All the recorded spectral data for known compounds was in agreement with those in the corresponding literature.

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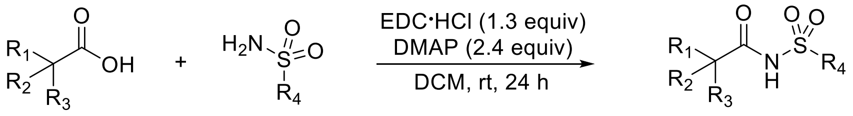
[190] Yildizhan, S.; Schulz, S. *Synlett* **2011**, *19*, 2831-2833.

[191] Yang, Q.-L.; Li, Y.-Q.; Ma, C.; Fang, P.; Zhang, X.; Mei, T.-S. *J. Am. Chem. Soc.* **2017**, *139*, 3293-3298.

[192] Kiyokawa, K.; Watanabe, T.; Fra, L.; Kojima, T.; Minakata, S. *J. Org. Chem.* **2017**, *82*, 11711-11720.

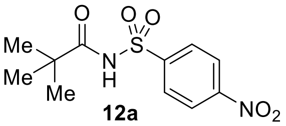
[193] Xiao, H.-Z.; Wang, W.-S.; Sun, Y.-S.; Li, B.-W.; Wang, X.-D.; Lin, W.-L.; Luo, F.-X. *Org. Lett.* **2019**, *21*, 1668-1671.

General procedure for the synthesis of *N*-nosyl, *N*-tosyl and *N*-trflyl amides (12a-12p):



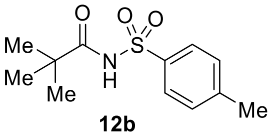
To a suspension of EDC·HCl (1.22 g, 6.36 mmol) in CH_2Cl_2 (10 mL) was added DMAP (1.44 g, 11.75 mmol). The mixture was stirred at rt until all the solids were dissolved. The corresponding carboxylic acid (4.9 mmol) and sulfonamide (4.9 mmol) were then added at 0 °C and the resulting solution was stirred at room temperature for 24 hours. The mixture was quenched with aqueous HCl (10% aq.) until pH = 1 and the aqueous layer was extracted three times with CH_2Cl_2. The combined organic layers were washed with NH_4Cl (sat.), then with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo to afford, without further purification,[194] the pure alkyl amides.

N-((4-nitrophenyl)sulfonyl)pivalamide (12a)


12a

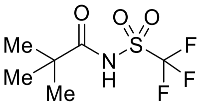
12a obtained as a pale yellow solid (1.35 g, 96% yield). **^{1}H NMR** (300 MHz, $CDCl_3$) δ, ppm: 8.70 (s, 1H), 8.40 (d, *J* = 8.8 Hz, 2H), 8.28 (d, *J* = 8.9 Hz, 2H), 1.17 (s, 9H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ, ppm: 176.4 (C), 150.9 (C), 143.9 (C), 130.1 (CH), 124.3 (CH), 40.3 (C), 26.7 (CH_3). **HRMS** (APCI, **$[M+H]^+$**) *m/z* calculated for $C_{11}H_{15}N_2O_5S$: 287.0696, found 287.0695.

N-tosylpivalamide (12b)


12b

12b obtained as a white solid (0.99 g, 79% yield). **^{1}H NMR** (300 MHz, $CDCl_3$) δ, ppm: 8.80 (s, 1H), 7.94 (d, *J* = 7.9 Hz, 2H), 7.33 (d, *J* = 7.9 Hz, 2H), 2.43 (s, 3H), 1.13 (s, 9H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ, ppm: 176.3 (C), 145.1 (C), 135.6 (C), 129.7 (CH), 128.5 (CH), 40.1 (C), 26.7 (CH_3), 21.8 (CH_3). **HRMS** (APCI, **$[M+H]^+$**) *m/z* calculated for $C_{12}H_{18}NO_3S$: 256.1002, found 256.1000.

N-((trifluoromethyl)sulfonyl)pivalamide (12c)


12c

12c obtained as a white solid (0.82 g, 72% yield). **^{1}H NMR** (300 MHz, $CDCl_3$) δ, ppm: 8.43 (s, 1H), 1.28 (s, 9H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ, ppm: 175.3 (C), 119.3 (q, J_{C-F} = 322.0 Hz, C), 41.1 (C), 26.5 (CH_3). **^{19}F NMR** (282 MHz, $CDCl_3$) δ, ppm: -75.7 (s). **HRMS** (APCI, **$[M+H]^+$**) *m/z* calculated for $C_6H_{11}F_3NO_3S$: 234.0406, found 234.0407.

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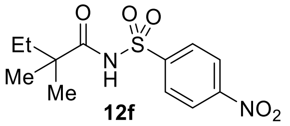
[194] In the case of alkyl amides **12c**, **12k**, **12m**, **12o** and **12p** purification by flash column chromatography on silica gel (20 to 80% EtOAc/hexanes) was needed to afford pure compounds.

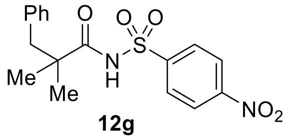
2,2-dimethyl-*N*-((4-nitrophenyl)sulfonyl)butanamide (12f)



12f

12f obtained as a pale yellow solid (1.10 g, 85% yield). **^{1}H NMR** (300 MHz, CDCl$_3$) δ, ppm: 8.60 (s, 1H), 8.39 (d, *J* = 8.5 Hz, 2H), 8.27 (d, *J* = 8.5 Hz, 2H), 1.51 (q, *J* = 7.5 Hz, 2H), 1.12 (s, 6H), 0.72 (t, *J* = 7.4 Hz, 3H). **^{13}C NMR** (75 MHz, CDCl$_3$) δ, ppm: 175.9 (C), 150.9 (C), 144.1 (C), 130.1 (CH), 124.3 (CH), 44.1 (C), 33.5 (CH$_2$), 24.2 (CH$_3$), 9.0 (CH$_3$). **HRMS** (APCI, **[M+H]$^+$**) *m/z* calculated for $C_{12}H_{17}N_2O_5S$: 301.0853, found 301.0850.

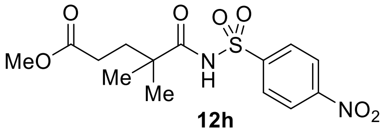
2,2-dimethyl-*N*-((4-nitrophenyl)sulfonyl)-3-phenylpropanamide (12g)



12g

12g obtained as a pale yellow solid (0.89 g, 88% yield). **^{1}H NMR** (300 MHz, CDCl$_3$) δ, ppm: 8.52 (s, 1H), 8.38 (d, *J* = 8.7 Hz, 2H), 8.23 (d, *J* = 8.7 Hz, 2H), 7.17 (d, J = 7.2 Hz, 1H), 7.10 (t, *J* = 7.4 Hz, 2H), 6.87 (d, *J* = 7.4 Hz, 2H), 2.76 (s, 2H), 1.18 (s, 6H). **^{13}C NMR** (75 MHz, CDCl$_3$) δ, ppm: 175.5 (C), 150.9 (C), 143.9 (C), 136.3 (C), 130.3 (CH), 130.0 (CH), 128.3 (CH), 127.1 (CH), 124.2 (CH), 46.2 (CH$_2$), 44.9 (C), 24.7 (CH$_3$). **HRMS** (APCI, **[M+H]$^+$**) *m/z* calculated for $C_{17}H_{19}N_2O_5S$: 363.1009, found 363.1008

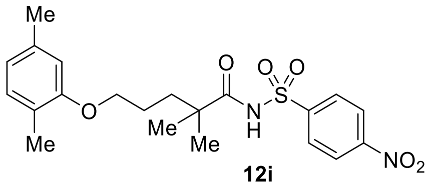
methyl 4,4-dimethyl-5-((4-nitrophenyl)sulfonamido)-5-oxopentanoate (12h)



12h

12h obtained as a pale yellow solid (0.83 g, 81% yield). **^{1}H NMR** (300 MHz, CDCl$_3$) δ, ppm: 8.96 (s, 1H), 8.38 (d, *J* = 8.5 Hz, 2H), 8.27 (d, *J* = 8.4 Hz, 2H), 3.64 (s, 3H), 2.14 (t, *J* = 8.0 Hz, 2H), 1.85 (t, *J* = 8.1 Hz, 2H), 1.16 (s, 6H). **^{13}C NMR** (75 MHz, CDCl$_3$) δ, ppm: 175.2 (C), 173.8 (C), 150.9 (C), 144.0 (C), 130.1 (CH), 124.3 (CH), 52.2 (CH$_3$), 43.3 (C), 34.8 (CH$_2$), 29.5 (CH$_2$), 24.6 (CH$_3$). **HRMS** (APCI, **[M+H]$^+$**) *m/z* calculated for $C_{14}H_{19}N_2O_7S$: 359.0907, found 359.0906.

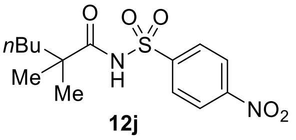
5-(2,5-dimethylphenoxy)-2,2-dimethyl-*N*-((4-nitrophenyl)sulfonyl)pentanamide (12i)



12i

12i obtained as a pale yellow solid (0.87 g, 99% yield). **^{1}H NMR** (300 MHz, CDCl$_3$) δ, ppm: 8.49 (s, 1H), 8.34 (d, *J* = 8.8 Hz, 2H), 8.24 (d, *J* = 8.9 Hz, 2H), 7.01 (d, *J* = 7.4 Hz, 1H), 6.68 (d, *J* = 7.4 Hz, 1H), 6.56 (s, 1H), 3.85 (t, *J* = 5.6 Hz, 2H), 2.30 (s, 3H), 2.16 (s, 3H), 1.75 – 1.66 (m, 2H), 1.65 – 1.53 (m, 2H), 1.20 (s, 6H). **^{13}C NMR** (75 MHz, CDCl$_3$) δ, ppm: 175.8 (C), 156.7 (C), 150.8 (C), 144.0 (C), 136.8 (C), 130.6 (CH), 130.0 (CH), 124.2 (CH), 123.5 (C), 121.2 (CH), 112.2 (CH), 67.5 (CH$_2$), 43.6 (C), 37.0 (CH$_2$), 24.9 (CH$_2$), 24.7 (CH$_3$), 21.5 (CH$_3$), 15.9 (CH$_3$). **HRMS** (APCI, **[M+H]$^+$**) *m/z* calculated for $C_{21}H_{27}N_2O_6S$: 435.1584, found 435.1583.

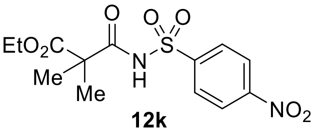
2,2-dimethyl-*N*-((4-nitrophenyl)sulfonyl)hexanamide (12j)



12j

12j obtained as a pale yellow solid (1.04 g, 91% yield). **^{1}H NMR** (300 MHz, CDCl$_3$) δ, ppm: 8.63 (s, 1H), 8.39 (d, *J* = 8.6 Hz, 2H), 8.27 (d, *J* = 8.6 Hz, 2H), 1.49 – 1.40 (m, 2H), 1.23 – 1.14 (m, 2H), 1.12 (s, 6H), 1.06 – 0.95 (m, 2H), 0.79 (t, *J* = 7.2 Hz, 3H). **^{13}C NMR** (75 MHz, CDCl$_3$) δ, ppm: 175.9 (C), 150.9 (C), 144.0 (C), 130.1 (CH), 124.3 (CH), 43.7 (C), 40.5 (CH$_2$), 26.7 (CH$_2$), 24.6 (CH$_3$), 23.0 (CH$_2$), 14.0 (CH$_3$). **HRMS** (APCI, **[M+H]$^+$**) *m/z* calculated for $C_{14}H_{21}N_2O_5S$: 329.1166, found 329.1165.

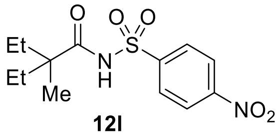
ethyl 2,2-dimethyl-3-((4-nitrophenyl)sulfonamido)-3-oxopropanoate (12k)



12k

12k obtained as a pale yellow solid (0.87g, 82% yield). **^{1}H NMR** (300 MHz, CDCl$_3$) δ, ppm: 9.94 (s, 1H), 8.37 (d, *J* = 8.1 Hz, 2H), 8.27 (d, *J* = 8.0 Hz, 2H), 4.20 (q, *J* = 7.1 Hz, 2H), 1.41 (s, 6H), 1.25 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR** (75 MHz, CDCl$_3$) δ, ppm: 174.5 (C), 170.3 (C), 150.9 (C), 144.0 (C), 130.1 (CH), 124.2 (CH), 62.9 (CH$_2$), 50.8 (C), 23.5 (CH$_3$), 14.0 (CH$_3$). **HRMS** (APCI, **[M+H]$^+$**) *m/z* calculated for $C_{13}H_{17}N_2O_7S$: 345.0751, found 345.0750.

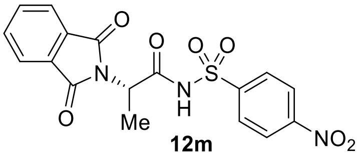
2-ethyl-2-methyl-*N*-((4-nitrophenyl)sulfonyl)butanamide (12l)



12l

12l obtained as a pale yellow solid (1.1 g, 91% yield). **^{1}H NMR** (300 MHz, CDCl$_3$) δ, ppm: 8.39 (d, *J* = 8.8 Hz, 2H), 8.27 (d, *J* = 8.7 Hz, 2H), 1.64 – 1.50 (m, 2H), 1.50 – 1.37 (m, 2H), 1.06 (s, 3H), 0.73 (t, *J* = 7.5 Hz, 3H). **^{13}C NMR** (75 MHz, CDCl$_3$) δ, ppm: 175.2 (C), 150.9 (C), 144.1 (C), 130.2 (CH), 124.3 (CH), 48.1 (C), 32.0 (CH$_2$), 19.4 (CH$_3$), 8.7 (CH$_3$). **HRMS** (APCI, **[M+H]$^+$**) *m/z* calculated for $C_{13}H_{19}N_2O_5S$: 315.1009, found 315.1007.

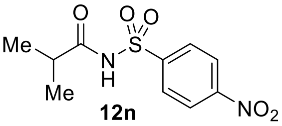
(*S*)-2-(1,3-dioxoisoindolin-2-yl)-*N*-((4-nitrophenyl)sulfonyl)propenamide (12m)



12m

12m obtained as a pale yellow solid (0.92 g, 99% yield). **^{1}H NMR** (300 MHz, CDCl$_3$) δ, ppm: 9.50 (s, 1H), 8.35 (d, *J* = 8.6 Hz, 2H), 8.12 (d, *J* = 8.6 Hz, 2H), 7.79 – 7.61 (m, 4H), 4.88 (q, *J* = 7.1 Hz, 1H), 1.50 (d, *J* = 6.9 Hz, 3H). **^{13}C NMR** (75 MHz, CDCl$_3$) δ, ppm: 167.7 (C), 167.4 (C), 151.0 (C), 143.2 (C), 134.7 (CH), 131.7 (C), 130.1 (CH), 124.3 (CH), 123.9 (CH), 49.4 (CH), 14.7 (CH$_3$). **HRMS** (APCI, **[M+H]$^+$**) *m/z* calculated for $C_{17}H_{14}N_3O_7S$: 404.0547, found 404.0546.

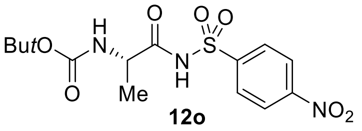
N-((4-nitrophenyl)sulfonyl)isobutyramide (12n)



12n

12n obtained as a pale yellow solid (1.18g, 76% yield). **^{1}H NMR** (300 MHz, CDCl$_3$) δ, ppm: 8.39 (d, *J* = 8.9 Hz, 2H), 8.28 (d, *J* = 8.7 Hz, 2H), 8.02 (s, 1H), 2.48 – 2.36 (m, 1H), 1.14 (d, *J* = 6.9 Hz, 6H). **^{13}C NMR** (75 MHz, CDCl$_3$) δ, ppm: 174.8 (C), 151.1 (C), 144.3 (C), 130.2 (CH), 124.4 (CH), 35.9 (CH), 18.6 (CH3). **HRMS** (APCI, **[M+H]$^+$**) *m/z* calculated for $C_{10}H_{13}N_2O_5S$: 273.0540, found 273.0539.

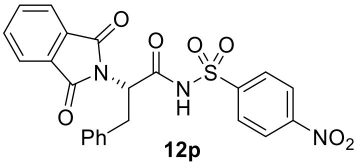
***tert*-butyl (*S*)-(1-((4-nitrophenyl)sulfonamido)-1-oxopropan-2-yl)carbamate** (**12o**)



12o

12o obtained as a white solid (0.94 g, 64% yield). **^{1}H NMR** (300 MHz, $CDCl_3$) δ, ppm: 8.36 (d, *J* = 8.8 Hz, 2H), 8.25 (d, *J* = 8.7 Hz, 2H), 5.06 (brs, 1H), 4.19 – 4.05 (m, 1H), 1.42 (s, 9H), 1.30 (d, *J* = 7.1 Hz, 3H. **^{13}C NMR** (75 MHz, $CDCl_3$) δ, ppm: 171.0 (C), 156.6 (C), 150.9 (C), 144.1 (C), 130.0 (CH), 124.3 (CH), 81.9 (C), 50.6 (CH), 28.3 (CH_3), 28.3 (CH_3), 16.5 (CH_3). **HRMS** (ESI, **[M+Na]$^+$**) *m/z* calculated for $C_{14}H_{19}N_3NaO_7S$: 396.0836, found 396.0832.

(*S*)-2-(1,3-dioxoisoindolin-2-yl)-*N*-((4-nitrophenyl)sulfonyl)-3-phenylpropanamide (**12p**)

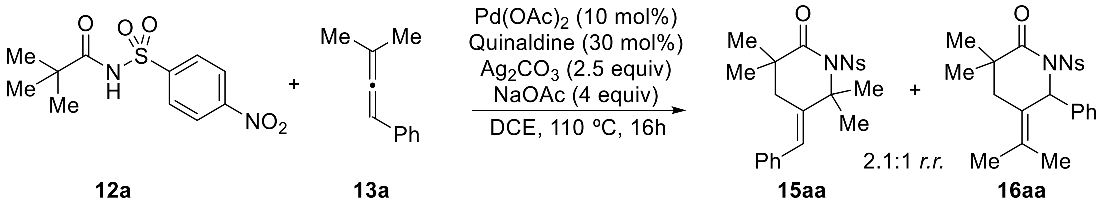


12p

12p obtained as a white solid (1.36 g, 58% yield). **^{1}H NMR** (300 MHz, DMSO-d$_6$) δ, ppm: 8.47 (d, *J* = 8.9 Hz, 2H), 8.17 (d, *J* = 8.9 Hz, 2H), 7.81 (s, 4H), 7.12 – 7.02 (m, 5H), 5.13 (dd, *J* = 11.2 Hz, *J* = 4.6 Hz, 1H), 3.39 (dd, *J* = 13.8 Hz, *J* = 4.6 Hz, 1H), 3.05 (dd, *J* = 13.5 Hz, *J* = 11.6 Hz, 1H). **^{13}C NMR** (75 MHz, DMSO-d$_6$) δ, ppm: 168.2 (C), 166.9 (C), 150.3 (C), 144.6 (C), 136.6 (C),134.6 (CH), 131.3 (C), 129.4 (CH), 129.0 (CH), 128.2 (CH), 126.6 (CH), 124.4 (CH), 123.2 (CH), 54.0 (CH), 33.7 (CH_2). **HRMS** (ESI, **[M+H]$^+$**) *m/z* calculated for $C_{23}H_{18}N_3O_7S$: 480.0860, found 480.0862.

2. Procedure for the Pd-catalyzed synthesis of 2-piperidones

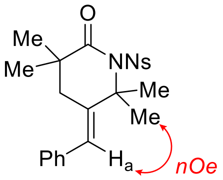
Procedure for the reaction between alkyl amide 12a and allene 13a:

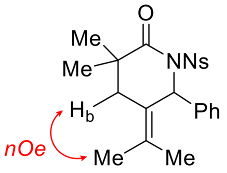


N-((4-nitrophenyl)sulfonyl)pivalamide **12a** (57.3 mg, 0.2 mmol), Pd(OAc)$_2$ (4.5 mg, 0.02 mmol), Ag_2CO_3 (137.9 mg, 0.5 mmol) and NaOAc (65.6 mg, 0.8 mmol) were weighed in air and placed in a reaction tube (10 mL) with a magnetic stir bar. Then, dichloroethane (2 mL), quinaldine (9 µL, 0.06 mmol) and allene ((3-methylbuta-1,2-dien-1-yl)benzene) **13a** (34.6 mg, 0.24 mmol) were added. The tube was sealed, and the mixture was stirred 16 hours at 110 ºC. After cooling to room temperature, the mixture was concentrated in vacuo. Purification of the crude by flash column chromatography on silica gel (5 to 50% Et_2O/hexanes) afforded an inseparable 2.1:1 mixture of (*E*)-5-benzylidene-3,3,6,6-tetramethyl-1-((4-nitrophenyl)sulfonyl)piperidin-2-one (**15aa**) and 3,3-dimethyl-1-((4-nitrophenyl)sulfonyl)-6-phenyl-5-(propan-2-ylidene)piperidin-2-one (**16aa**) as a yellow solid (38.6 mg, 45% yield). **^{1}H NMR** (500 MHz, $CDCl_3$) δ, ppm: 8.27 (d, *J* = 8.8 Hz, 1.4H), 8.14 – 8.06 (m, 2H), 7.77 (d, *J* = 8.8 Hz, 0.6H), 7.28 (t, *J* = 7.6 Hz, 1.4H), 7.23 – 7.18 (m, 1.8H), 7.08 (d, *J* = 7.5 Hz, 1.3H), 7.00 – 6.96 (m, 0.7H), 6.76 (s, 0.7H), 6.59 (s, 0.3H), 2.50 (s, 1.4H), 2.25 (d, *J* = 14.2 Hz, 0.3H), 2.14 – 2.09 (m, 1.6H), 2.07 (s, 4.7H), 1.17 (s, 1.3H), 0.84 (s, 4.7H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ, ppm: 178.8 (C), 177.8 (C), 150.4 (C), 150.1 (C), 147.2 (C), 144.7 (C), 141.2 (C), 140.6 (C), 136.7 (C), 130.8 (CH), 130.6 (C), 129.4 (CH), 129.0 (CH), 128.9 (CH), 128.6 (CH), 128.0 (CH), 127.3 (CH), 126.0 (CH), 125.6 (CH), 124.1 (C), 123.8 (CH), 123.4 (CH), 70.2 (C), 62.7 (CH), 42.7 (C), 42.0 (C), 35.4 (CH_2), 34.8 (CH_2), 28.6 (CH_3), 27.3 (CH_3), 26.2 (CH_3), 26.1 (CH_3), 21.2 (CH_3), 20.8 (CH_3). **HRMS** (APCI, **$[M+H]^+$**) *m/z* calculated for $C_{22}H_{25}N_2O_5S$: 429.1479, found 429.1491.

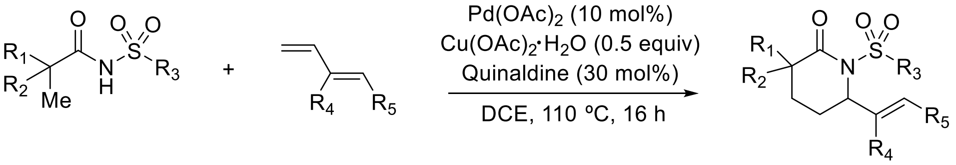
Assignment of the regio- and stereochemistry

Both regioisomers were assigned based on the shifts of the ^{1}H NMR and ^{13}C NMR signals. Moreover, bidimensional experiments HSQC, HMBC, COSY and, specially, NOESY confirmed both structures together with the stereochemistry of isomer **15aa**.





General procedure for the reaction between alkyl amides (12a-12p) and dienes (14a-14l):



The corresponding alkyl amide (0.2 mmol), $Pd(OAc)_2$ (4.5 mg, 0.02 mmol) and $Cu(OAc)_2 \cdot H_2O$ (20 mg, 0.1 mmol) were weighed in air and placed in a reaction tube (10 mL) with a magnetic stir bar. Then, dichloroethane (2 mL), quinaldine (9 µL, 0.06 mmol) and the pertinent diene (0.4 mmol) were added. The tube was sealed, and the mixture was stirred 16 hours at 110 ºC. After cooling to room temperature, the mixture was concentrated in vacuo. Purification of the reaction crude by flash column chromatography on silica gel afforded the corresponding 2-piperidones.[195]

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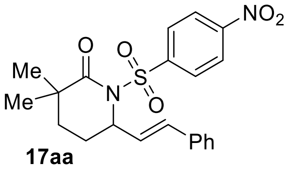
[195] If there were problems to separate completely quinaldine and the corresponding product, an extraction with aqueous HCl (10%) can be made after column chromatography.

(*E*)-3,3-dimethyl-1-((4-nitrophenyl)sulfonyl)-6-styrylpiperidin-2-one (17aa)

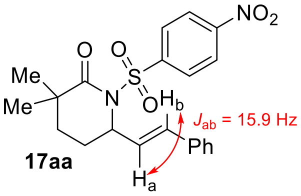


17aa

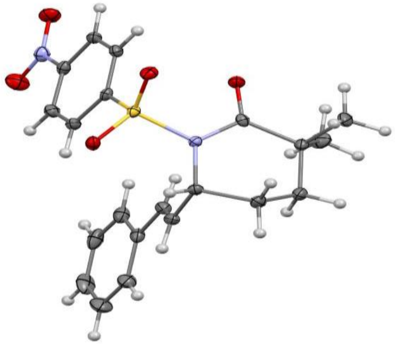
According to the general procedure, **17aa** was isolated by column chromatography (5 to 30% Et_2O/hexanes) as a yellow solid (81.8 mg, 99% yield). **^{1}H NMR** (300 MHz, $CDCl_3$) δ, ppm: 8.25–8.16 (m, 4H), 7.38–7.24 (m, 5H), 6.45 (d, *J* = 15.9 Hz, 1H), 6.10 (dd, *J* = 15.9 Hz, *J* = 6.7 Hz, 1H), 5.38 (s, 1H), 2.42–2.28 (m, 1H), 2.00–1.87 (m, 2H), 1.62–1.53 (m, 1H), 1.25 (s, 3H), 1.19 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ, ppm: 177.6 (C), 150.4 (C), 145.1 (C), 135.4 (C), 133.5 (CH), 130.9 (CH), 129.0 (CH), 128.6 (CH), 127.6 (CH), 126.6 (CH), 123.6 (CH), 59.9 (CH), 41.2 (C), 31.6 (CH_2), 27.8 (CH_3), 26.7 (CH_3), 26.3 (CH_2). **HRMS** (APCI, **$[M+H]^+$**) *m/z* calculated for $C_{21}H_{23}N_2O_5S$: 415.1322, found: 415.1322.

Assignment of the stereochemistry

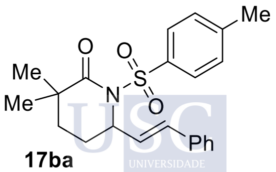
Geometric isomerism of the double bond was assigned based on the ***J*** value between **H_a** and **H_b**.



To confirm the structure, suitable crystals of **17aa** for X-Ray diffraction analysis were grown by slow diffusion of heptane in a CH_2Cl_2 solution of the complex. The crystallographic data was deposited in the Cambridge Structural Database (1970311).



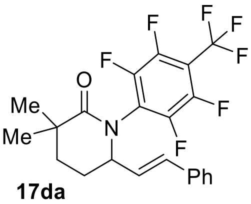
(*E*)-3,3-dimethyl-6-styryl-1-tosylpiperidin-2-one (17ba)



17ba

According to the general procedure, **17ba** was isolated by column chromatography (20% Et_2O/hexanes) as a white solid (55.6 mg, 73% yield). **^{1}H NMR** (300 MHz, $CDCl_3$) δ, ppm: 7.91 (d, *J* = 8.0 Hz, 2H), 7.38 – 7.27 (m, 5H), 7.23 (d, *J* = 8.0 Hz, 2H), 6.44 (d, *J* = 15.9 Hz, 1H), 6.14 (dd, *J* = 16.0, 5.8 Hz, 1H), 5.45 – 5.38 (m, 1H), 2.41 (s, 3H), 2.36 – 2.27 (m, 1H), 2.00 – 1.87 (m, 2H), 1.60 – 1.50 (m, 1H), 1.22 (s, 3H), 1.19 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ, ppm: 177.2 (C), 144.5 (C), 136.6 (C), 136.0 (C), 132.9 (CH), 129.5 (CH), 129.2 (CH), 128.8 (CH), 128.6 (CH), 128.2 (CH), 126.7 (CH), 59.1 (CH), 41.0 (C), 31.8 (CH_2), 27.9 (CH_3), 26.9 (CH_3), 26.4 (CH_2), 21.8 (CH_3). **HRMS** (APCI, **$[M+H]^+$**) *m/z* calculated for $C_{22}H_{26}NO_3S$: 384.1628, found 384.1629.

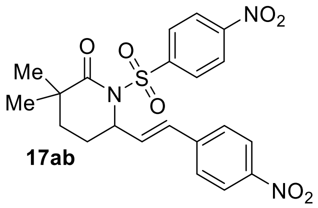
(*E*)-3,3-dimethyl-6-styryl-1-(2,3,5,6-tetrafluoro-4-(trifluoromethyl)phenyl)piperidin-2-one (**17da**)



17da

According to the general procedure, **17da** was isolated by column chromatography (20% Et_2O/hexanes) as a yellow solid (13.8 mg, 16% yield). **^{1}H NMR** (300 MHz, $CDCl_3$) δ, ppm: 7.37 – 7.25 (m, 5H), 6.43 (d, *J* = 15.7 Hz, 1H), 6.07 (dd, *J* = 15.7, 8.8 Hz, 1H), 4.51 – 4.43 (m, 1H), 2.31 – 2.19 (m, 1H), 2.14 – 1.89 (m, 3H), 1.42 (s, 3H), 1.35 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ, ppm: 176.4 (C), 135.5 (C), 133.8 (CH), 128.9 (CH), 128.6 (CH), 127.4 (CH), 126.7 (CH), 63.8 (CH), 39.1 (C), 33.7 (CH_2), 27.6 (CH_3), 27.6 (CH_3), 27.1 (CH_2). **HRMS** (APCI, **$[M+H]^+$**) *m/z* calculated for $C_{22}H_{19}F_7NO$: 446.1349, found 446.1349.

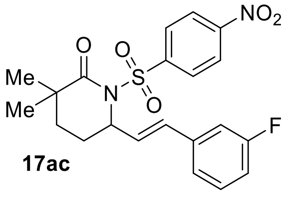
(*E*)-3,3-dimethyl-1-((4-nitrophenyl)sulfonyl)-6-(4-nitrostyryl)piperidin-2-one (**17ab**)



17ab

According to the general procedure, **17ab** was isolated by column chromatography (20 to 70% EtOAc/hexanes) as a yellow solid (90.0 mg, 98% yield). **^{1}H NMR** (300 MHz, $CDCl_3$) δ, ppm: 8.28 (d, *J* = 8.9 Hz, 2H), 8.22–8.14 (m, 4H), 6.62 (d, *J* = 15.9 Hz, 1H), 6.38 (dd, *J* = 15.9 Hz, *J* = 6.0 Hz, 1H), 5.41 (s, 1H), 2.41–2.27 (m, 1H), 2.03–1.85 (m, 2H), 1.60 (d, *J* = 13.9 Hz, 1H), 1.20 (s, 3H), 1.16 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ, ppm: 177.1 (C), 150.6 (C), 147.6 (C), 144.9 (C), 141.9 (C), 133.0 (CH), 131.3 (CH), 130.6 (CH), 127.3 (CH), 124.3 (CH), 123.8 (CH), 59.4 (CH), 41.1 (C), 31.6 (CH_2), 27.6 (CH_3), 26.8 (CH_3), 25.9 (CH_2). **HRMS** (APCI, **$[M+H]^+$**) *m/z* calculated for $C_{21}H_{22}N_3O_7S$: 460.1173, found: 460.1171

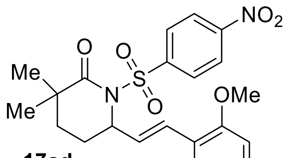
(*E*)-6-(3-fluorostyryl)-3,3-dimethyl-1-((4-nitrophenyl)sulfonyl)piperidin-2-one (**17ac**)



17ac

According to the general procedure, **17ac** was isolated by column chromatography (10 to 20% Et_2O/hexanes) as a yellow solid (62.2 mg, 72% yield). **^{1}H NMR** (300 MHz, $CDCl_3$) δ, ppm: 8.27–8.24 (m, 2H), 8.19–8.16 (m, 2H), 7.34–7.27 (m, 1H), 7.04–6.97 (m, 3H), 6.46 (d, *J* = 15.9 Hz, 1H), 6.13 (dd, *J* = 15.8 Hz, *J* = 6.5 Hz, 1H), 5.39–5.36 (m, 1H), 2.40–2.28 (m, 1H), 1.97–1.87 (m, 2H), 1.62–1.53 (m, 1H), 1.22 (s, 3H), 1.19 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ, ppm: 177.5 (C), 163.2 (d, *J* = 245.1 Hz, C), 150.5 (C), 145.1 (C), 137.8 (d, *J* = 7.6 Hz, C), 132.4 (d, *J* = 2.4 Hz, CH), 130.8 (CH), 130.5 (d, *J* = 8.3 Hz, CH), 129.2 (CH), 123.7 (CH), 122.7 (d, *J* = 2.6 Hz, CH), 115.5 (d, *J* = 21.2 Hz, CH), 113.0 (d, *J* = 21.8 Hz, CH), 59.6 (CH), 41.2 (C), 31.6 (CH_2), 27.8 (CH_3), 26.8 (CH_3), 26.2 (CH_2). **^{19}F NMR** (282 MHz, $CDCl_3$) δ, ppm: -112.8 (m). **HRMS** (APCI, **$[M+H]^+$**) *m/z* calculated for $C_{21}H_{22}FN_2O_5S$: 433.1225, found: 433.1228.

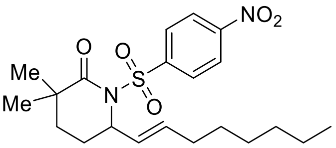
(*E*)-6-(2-methoxystyryl)-3,3-dimethyl-1-((4-nitrophenyl)sulfonyl)piperidin-2-one (17ad)



17ad

According to the general procedure, **17ad** was isolated by column chromatography (10 to 40% Et_2O/hexanes) as a yellow solid (81.8 mg, 92% yield). **^{1}H NMR** (300 MHz, $CDCl_3$) δ, ppm: 8.24–8.16 (m, 4H), 7.31–7.23(m, 2H), 6.95–6.84 (m, 2H), 6.72 (d, J = 16.0 Hz, 1H), 6.11 (dd, J = 16.0 Hz, J = 7.0 Hz, 1H), 5.39 (s, 1H), 3.77 (s, 3H), 2.43–2.29 (m, 1H), 2.02–1.85 (m, 2H), 1.61–1.51 (m, 1H), 1.29 (s, 3H), 1.19 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ, ppm: 177.8 (C), 157.0 (C), 150.4 (C), 145.2 (C), 131.2 (CH), 129.7 (CH), 128.7 (CH), 127.9 (CH), 127.1 (CH), 124.4 (C), 123.5 (CH), 120.9 (CH), 111.1 (CH), 60.2 (CH), 55.5 (CH_3), 41.3 (C), 31.6 (CH_2), 28.0 (CH_3), 26.7 (CH_3), 26.5 (CH_2). **HRMS** (APCI, **$[M+H]^+$**) *m/z* calculated for $C_{22}H_{25}N_2O_6S$: 445.1428, found: 445.1426.

(*E*)-3,3-dimethyl-1-((4-nitrophenyl)sulfonyl)-6-(oct-1-en-1-yl)piperidin-2-one (17ae)

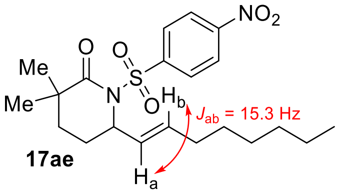


17ae

According to the general procedure, **17ae** was isolated by column chromatography (10 to 20% Et_2O/hexanes) as a yellow oil (77.0 mg, 91% yield). **^{1}H NMR** (300 MHz, $CDCl_3$) δ, ppm: 8.31 (d, J = 8.9 Hz, 2H), 8.19 (d, J = 8.9 Hz, 2H), 5.63–5.51 (m, 1H), 5.41 (dd, J = 15.3 Hz, J = 6.3 Hz, 1H), 5.17 (s, 1H), 2.30–2.16 (m, 1H), 2.04 (q, J = 6.6 Hz, 2H), 1.90 (td, J = 13.7 Hz, J = 3.2 Hz, 1H), 1.79 (dq, J = 13.7 Hz, J = 3.1 Hz, 1H), 1.51 (td, J = 13.8 Hz, J = 3.3 Hz, 1H), 1.39-1.22 (m, 8H), 1.18 (s, 3H), 1.15 (s, 3H), 0.88 (t, J = 6.5 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ, ppm: 177.7 (C), 150.4 (C), 145.4 (C), 135.0 (CH), 130.7 (CH), 128.4 (CH), 123.6 (CH), 59.5 (CH), 41.1 (C), 32.3 (CH_2), 31.8 (CH_2), 31.7 (CH_2), 29.1 (CH_2), 29.0 (CH_2), 27.8 (CH_3), 26.7 (CH_3), 26.4 (CH_2), 22.7 (CH_2), 14.2 (CH_3). **HRMS** (APCI, **$[M+H]^+$**) *m/z* calculated for $C_{21}H_{31}N_2O_5S$: 423.1948, found: 423.1948.

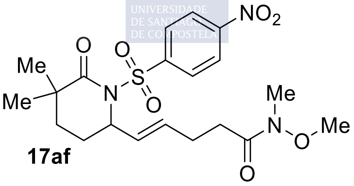
Assignment of the stereochemistry

Geometric isomerism of the double bond was assigned based on the ***J*** value between **H_a** and **H_b**.



17ae

(*E*)-5-(5,5-dimethyl-1-((4-nitrophenyl)sulfonyl)-6-oxopiperidin-2-yl)-*N*-methoxy-*N*-methylpent-4-enamide (17af)

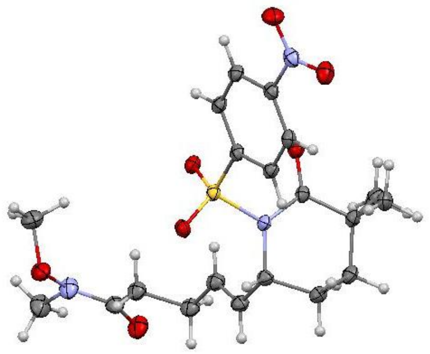


17af

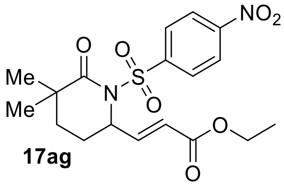
According to the general procedure, using 1 equivalent of $Cu(OAc)_2 \cdot H_2O$ as modification, **17af** was isolated by column chromatography (30 to 60% EtOAc/hexanes) as a pale yellow solid (58.9 mg, 65% yield). **^{1}H NMR** (300 MHz, $CDCl_3$) δ, ppm: 8.32 (d, J = 8.9 Hz, 2H), 8.17 (d, J = 8.9 Hz, 2H), 5.66 – 5.46 (m, 2H), 5.14 (dt, J = 5.8, 3.5 Hz, 1H), 3.66 (s, 3H), 3.15 (s, 3H), 2.53 – 2.45 (m, 2H), 2.44 – 2.34 (m, 2H), 2.23 – 2.14 (m, 1H), 1.90 (dd, *J* = 13.9, 3.3 Hz, 1H), 1.83 – 1.75 (m, 1H), 1.53 – 1.45 (m, 1H), 1.18 – 1.09 (m, 6H). **^{13}C NMR 55 ºC** (126 MHz, $CDCl_3$) δ, ppm: 177.5 (C), 173.3 (C), 150.7 (C), 145.6 (C), 133.5 (CH), 130.7 (CH), 129.8 (CH), 123.7 (CH), 61.4 (CH), 59.4 (CH_3), 41.2 (C), 32,5 (CH_3), 31.6 (CH_2), 31.1 (CH_2), 27.8 (CH_3), 27.1 (CH_2), 26.8 (CH_3), 26.5 (CH_2). **HRMS** (APCI, **$[M+H]^+$**) *m/z* calculated for $C_{20}H_{28}N_3O_7S$: 454.1642, found 454.1643.

Assignment of the stereochemistry

To confirm the structure and its geometric isomerism, suitable crystals of **17af** for X-Ray diffraction analysis were grown by slow diffusion of heptane in a CH_2Cl_2 solution of the complex. The crystallographic data was deposited in the Cambridge Structural Database (1970274).



Ethyl (*E*)-3-(5,5-dimethyl-1-((4-nitrophenyl)sulfonyl)-6-oxopiperidin-2-yl)acrylate (17ag)

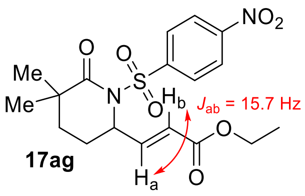


17ag

According to the general procedure, **17ag** was isolated by column chromatography (20 to 60% Et_2O/hexanes) as a white solid (67.3 mg, 82% yield). **^{1}H NMR** (300 MHz, $CDCl_3$) δ, ppm: 8.33 (d, *J* = 8.6 Hz, 2H), 8.17 (d, *J* = 8.6 Hz, 2H), 6.87 (dd, *J* = 15.7, 5.3 Hz, 1H), 5.85 (d, *J* = 15.7 Hz, 1H), 5.39 – 5.32 (m, 1H), 4.25 – 4.14 (m, 2H), 2.28 (tdd, *J* = 14.3, 6.1, 3.4 Hz, 1H), 1.93 (dq, *J* = 14.5, 3.4 Hz, 1H), 1.79 (td, *J* = 14.1, 3.3 Hz, 1H), 1.55 (dt, *J* = 14.2, 3.7 Hz, 1H), 1.28 (t, *J* = 7.1 Hz, 3H), 1.16 (s, 6H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ, ppm: 177.0 (C), 165.4 (C), 150.6 (C), 145.7 (CH), 144.6 (C), 130.8 (CH), 124.3 (CH), 123.8 (CH), 61.1 (CH_2), 58.3 (CH), 41.1 (C), 31.5 (CH_2), 27.6 (CH_3), 26.8 (CH_3), 25.1 (CH_2), 14.3 (CH_3). **HRMS** (APCI, **$[M+H]^+$**) *m/z* calculated for $C_{18}H_{23}N_2O_7S$: 411.1220, found 411.1221.

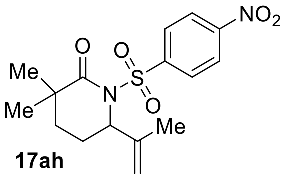
Assignment of the stereochemistry

Geometric isomerism of the double bond was assigned based on the ***J*** value between **H_a** and **H_b.**



17ag

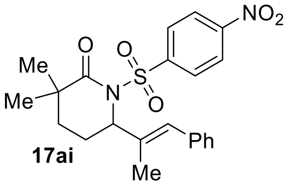
3,3-dimethyl-1-((4-nitrophenyl)sulfonyl)-6-(prop-1-en-2-yl)piperidin-2-one (**17ah**)



17ah

According to the general procedure, using 10 equivalents of diene as modification, **17ah** was isolated by column chromatography (20% Et_2O/hexanes) as a pale yellow solid (51.4 mg, 73% yield). **^{1}H NMR** (300 MHz, $CDCl_3$) δ, ppm: 8.31 (d, *J* = 9.0 Hz, 2H), 8.19 (d, *J* = 9.0 Hz, 2H), 5.09 – 5.01 (m, 2H), 4.54 (s, 1H), 2.11 (tdd, *J* = 14.1, 5.6, 3.0 Hz, 1H), 1.94 (dd, *J* = 5.7, 3.1 Hz, 1H), 1.91 – 1.86 (m, 1H), 1.82 (s, 3H), 1.45 (dt, *J* = 13.8, 2.8 Hz, 1H), 1.17 – 1.14 (m, 6H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ, ppm: 177.7 (C), 150.5 (C), 145.0 (C), 143.6 (C), 130.9 (CH), 123.6 (CH), 114.0 (CH_2), 62.3 (CH), 40.9 (C), 30.9 (CH_2), 27.8 (CH_3), 27.0 (CH_3), 23.1 (CH_2), 20.7 (CH_3). **HRMS** (APCI, **$[M+H]^+$**) *m/z* calculated for $C_{16}H_{21}N_2O_5S$: 353.1166, found 353.1167.

(*E*)-3,3-dimethyl-1-((4-nitrophenyl)sulfonyl)-6-(1-phenylprop-1-en-2-yl)piperidin-2-one (**17ai**)

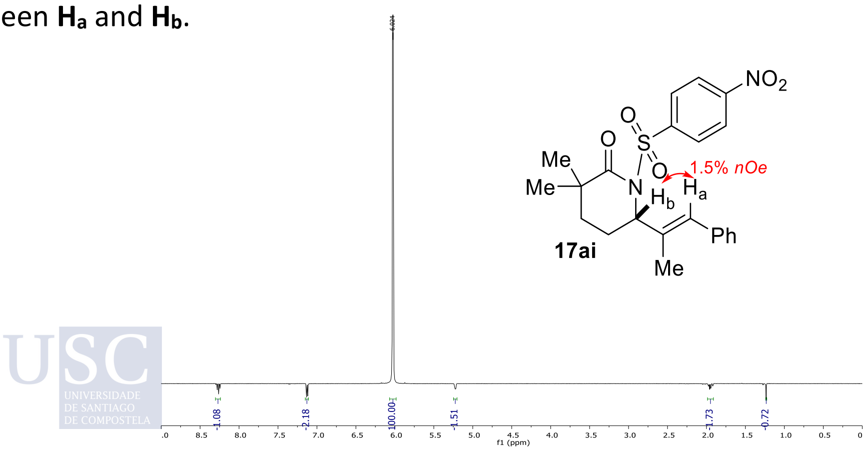


17ai

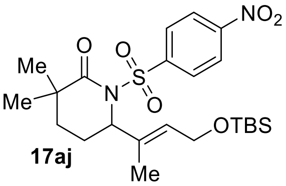
According to the general procedure, **17ai** was isolated by column chromatography (20% Et_2O/hexanes) as a pale yellow solid (51.4 mg, 60% yield). **^{1}H NMR** (300 MHz, $CDCl_3$) δ, ppm: 8.34 – 8.21 (m, 4H), 7.40 – 7.33 (m, 2H), 7.32 – 7.27 (m, 1H), 7.16 – 7.10 (m, 2H), 6.02 (s, 1H), 5.26 – 5.20 (m, 1H), 2.27 (tdd, *J* = 13.8, 5.8, 3.0 Hz, 1H), 2.11 – 1.92 (m, 5H), 1.56 (dt, *J* = 13.9, 3.7 Hz, 1H), 1.29 – 1.23 (m, 6H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ, ppm: 178.0 (C), 150.4 (C), 145.0 (C), 136.2 (C), 136.2 (C), 131.0 (CH), 128.9 (CH), 128.5 (CH), 127.7 (CH), 127.3 (CH), 123.6 (CH), 63.8 (CH), 41.1 (C), 31.1 (CH_2), 27.9 (CH_3), 26.9 (CH_3), 23.7 (CH_2), 17.0 (CH_3). **HRMS** (APCI, **$[M+H]^+$**) *m/z* calculated for $C_{22}H_{25}N_2O_5S$: 429.1479, found 429.1478.

Assignment of the stereochemistry

Geometric isomerism of the double bond was assigned based on the observation of a **nOe** between **H_a** and **H_b**.



(*E*)-6-(4-((tert-butyldimethylsilyl)oxy)but-2-en-2-yl)-3,3-dimethyl-1-((4-nitrophenyl) sulfonyl)piperidin-2-one (17aj)

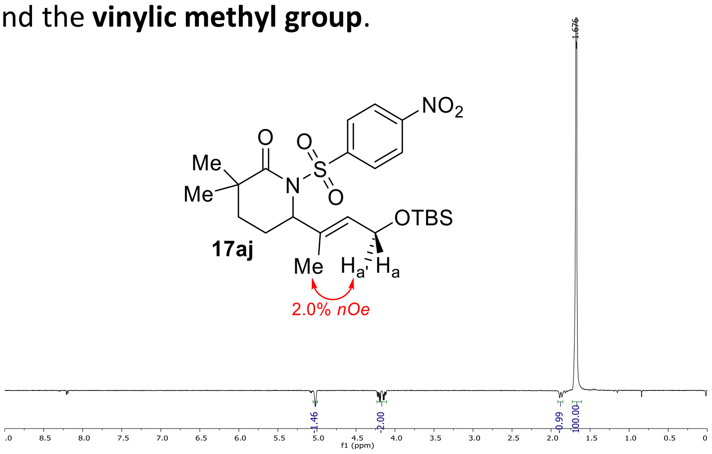


17aj

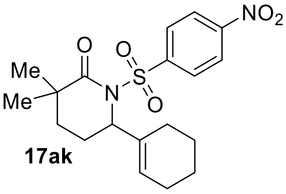
According to the general procedure, **17aj** was isolated by column chromatography (20% Et_2O/hexanes) as a white solid (51.6 mg, 52% yield). **^{1}H NMR** (300 MHz, $CDCl_3$) δ, ppm: 8.30 (d, *J* = 8.8 Hz, 2H), 8.20 (d, *J* = 8.7 Hz, 2H), 5.12 – 4.98 (m, 2H), 4.17 (qd, *J* = 13.1, 6.0 Hz, 2H), 2.19 – 2.02 (m, 1H), 1.92 – 1.80 (m, 2H), 1.68 (s, 3H), 1.44 (dt, *J* = 14.0, 3.8 Hz, 1H), 1.22 – 1.13 (m, 6H), 0.84 (s, 9H), 0.02 (s, 6H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ, ppm: 177.8 (C), 150.4 (C), 145.0 (C), 134.5 (C), 131.1 (CH), 128.0 (CH), 123.6 (CH), 62.8 (CH), 59.8 (CH_2), 41.0 (C), 30.9 (CH_2), 27.9 (CH_3), 26.9 (CH_3), 26.0 (CH_3), 23.4 (CH_2), 18.4 (C), 15.4 (CH_3), -5.1 (CH_3), -5.2 (CH_3). **HRMS** (APCI, **$[M+H]^+$**) *m/z* calculated for $C_{23}H_{37}N_2O_6SSi$: 497.2136, found 497.2134.

Assignment of the stereochemistry

Geometric isomerism of the double bond was assigned based on the observation of a **nOe** between **H_a**, **$H_{a'}$** and the **vinylic methyl group**.



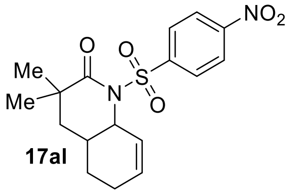
6-(cyclohex-1-en-1-yl)-3,3-dimethyl-1-((4-nitrophenyl)sulfonyl)piperidin-2-one (17ak)



17ak

According to the general procedure, using 3 equivalents of diene as modification, **17ak** was isolated by column chromatography (20% Et_2O/hexanes) as a white solid (49.7 mg, 63% yield). **^{1}H NMR** (300 MHz, $CDCl_3$) δ, ppm: 8.33 (d, *J* = 8.9 Hz, 2H), 8.20 (d, *J* = 9.0 Hz, 2H), 5.10 (td, *J* = 3.7, 1.7 Hz, 1H), 5.02 – 4.94 (m, 1H), 2.13 (tdd, *J* = 14.4, 5.5, 3.2 Hz, 1H), 2.03 – 1.81 (m, 6H), 1.75 – 1.53 (m, 4H), 1.45 (dt, *J* = 13.5, 3.6 Hz, 1H), 1.21 (s, 3H), 1.16 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ, ppm: 178.1 (C), 150.4 (C), 145.1 (C), 136.2 (C), 131.1 (CH), 124.9 (CH), 123.4 (CH), 62.6 (CH), 41.0 (C), 31.2 (CH_2), 27.9 (CH_3), 27.0 (CH_2), 26.9 (CH_3), 24.9 (CH_2), 23.5 (CH_2), 22.5 (CH_2), 22.3 (CH_2). **HRMS** (APCI, **$[M+H]^+$**) *m/z* calculated for $C_{19}H_{25}N_2O_5S$: 393.1479, found 393.1476.

3,3-dimethyl-1-((4-nitrophenyl)sulfonyl)-3,4,4a,5,6,8a-hexahydroquinolin-2(1*H*)-one (17al)



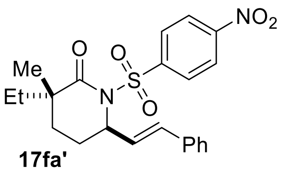
17al

According to the general procedure, using 60 mol% of quinaldine and 1 equivalent of $Cu(OAc)_2{\cdot}H_2O$ as modification, **17al** was isolated by column chromatography (20% Et_2O/hexanes) as a white solid (32.1 mg, 44% yield). **^{1}H NMR** (300 MHz, $CDCl_3$) δ, ppm: 8.35 (d, *J* = 8.9 Hz, 2H), 8.20 (d, *J* = 8.9 Hz, 2H), 5.80 (dd, *J* = 10.3, 2.4 Hz, 1H), 5.71 (dt, *J* = 10.2, 1.8 Hz, 1H), 5.15 (s, 1H), 2.49 (d, *J* = 13.5 Hz, 1H), 2.10 – 1.93 (m, 4H), 1.82 – 1.73 (m, 1H), 1.35 (dd, *J* = 13.5, 2.1 Hz, 1H), 1.13 (s, 6H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ, ppm: 177.1 (C), 150.5 (C), 145.7 (C), 130.1 (CH), 129.1 (CH), 126.7 (CH), 124.0 (CH), 58.3 (CH), 40.6 (C), 35.5 (CH_2), 28.4 (CH), 27.8 (CH_3), 27.1 (CH_3), 26.5 (CH_2), 20.4 (CH_2). **HRMS** (APCI, **$[M+H]^+$**) *m/z* calculated for $C_{17}H_{21}N_2O_5S$: 365.1166, found 365.1166.

3-ethyl-3-methyl-1-((4-nitrophenyl)sulfonyl)-6-((*E*)-styryl)piperidin-2-one (17fa)

According to the general procedure, **17fa** was isolated by column chromatography (15% Et_2O/5% CH_2Cl_2/hexanes) as a 1:1 diastereomeric mixture as a pale yellow solid (76.3 mg, 89% yield). A small amount of each diastereoisomer was separated to be identified.

(±)(3*R*,6*S*)-3-ethyl-3-methyl-1-((4-nitrophenyl)sulfonyl)-6-((*E*)-styryl)piperidin-2-one (17fa')

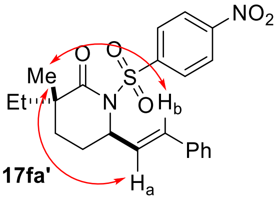


17fa'

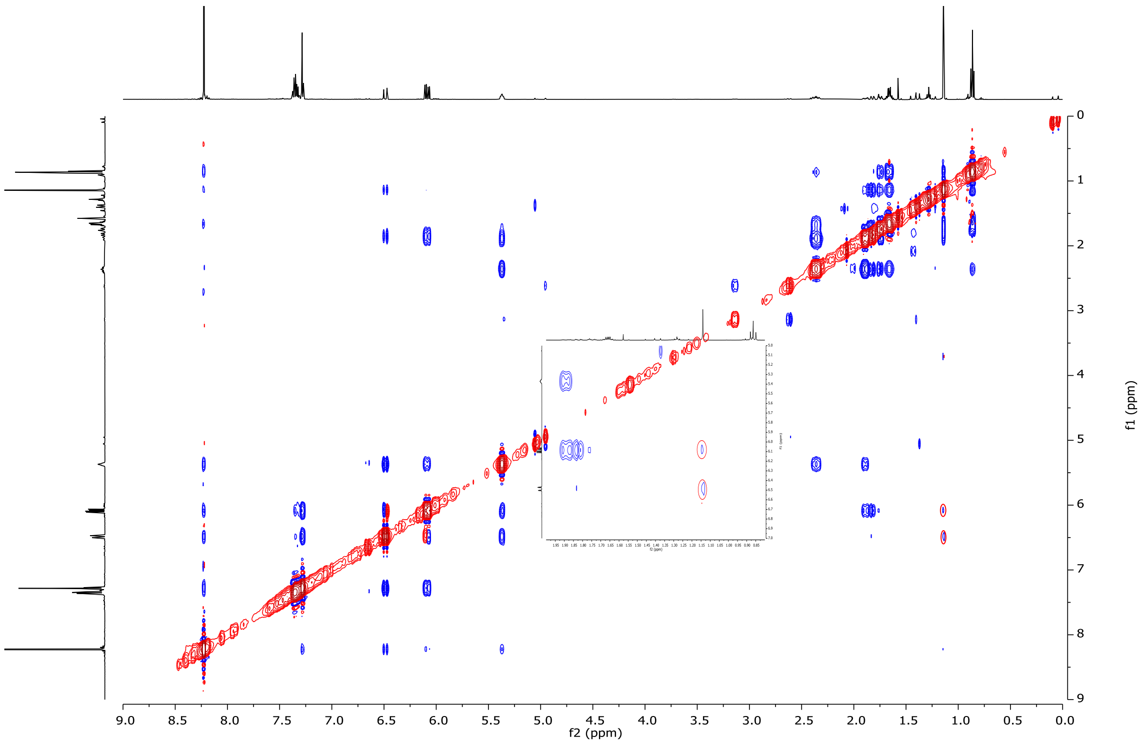
^{1}H NMR (300 MHz, $CDCl_3$) δ, ppm: 8.28 – 8.16 (m, 4H), 7.40 – 7.31 (m, 3H), 7.30 – 7.25 (m, 2H), 6.48 (d, *J* = 15.9 Hz, 1H), 6.08 (dd, *J* = 15.9, 7.0 Hz, 1H), 5.40 – 5.33 (m, 1H), 2.43 – 2.29 (m, 1H), 1.94 – 1.82 (m, 2H), 1.77 (dd, *J* = 9.8, 4.3 Hz, 1H), 1.66 (q, *J* = 7.5 Hz, 2H), 1.13 (s, 3H), 0.86 (t, *J* = 7.5 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ, ppm: 177.6 (C), 150.4 (C), 145.3 (C), 135.4 (C), 133.6 (CH), 131.1 (CH), 129.0 (CH), 128.7 (CH), 127.7 (CH), 126.6 (CH), 123.6 (CH), 60.2 (CH), 44.5 (C), 32.5 (CH_2), 28.9 (CH_2), 26.4 (CH_2), 23.7 (CH_3), 8.4 (CH_3). **HRMS** (APCI, **$[M+H]^+$**) *m/z* calculated for $C_{22}H_{25}N_2O_5S$: 429.1479, found 429.1480.

Assignment of the stereochemistry

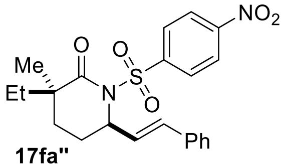
The corresponding diastereoisomer was assigned based on the observation of a **nOe** between the hydrogens of the double bond, **H_a** and **H_b**, and the **methyl** group.



17fa'



(±)(3*S*,6*S*)-3-ethyl-3-methyl-1-((4-nitrophenyl)sulfonyl)-6-((*E*)-styryl)piperidin-2-one (17fa'')



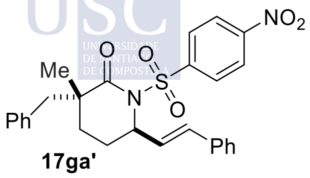
17fa''

^{1}H NMR (300 MHz, CDCl$_3$) δ, ppm: 8.32 – 8.16 (m, 4H), 7.40 – 7.27 (m, 5H), 6.52 (d, *J* = 15.9 Hz, 1H), 6.16 (dd, *J* = 15.8, 6.3 Hz, 1H), 5.43 – 5.36 (m, 1H), 2.42 – 2.28 (m, 1H), 2.15 – 1.95 (m, 2H), 1.80 (dq, *J* = 14.4, 7.3 Hz, 1H), 1.49 – 1.36 (m, 2H), 1.22 (s, 3H), 0.77 (t, *J* = 7.3 Hz, 3H). **^{13}C NMR** (75 MHz, CDCl$_3$) δ, ppm: 177.0 (C), 150.4 (C), 145.2 (C), 135.5 (C), 133.7 (CH), 130.8 (CH), 129.0 (CH), 128.6 (CH), 127.7 (CH), 126.6 (CH), 123.7 (CH), 59.4 (CH), 45.1 (C), 32.4 (CH$_2$), 27.3 (CH$_2$), 26.9 (CH$_3$), 26.2 (CH$_2$), 8.9 (CH$_3$). **HRMS** (APCI, **[M+H]$^+$**) *m/z* calculated for $C_{22}H_{25}N_2O_5S$: 429.1479, found 429.1478.

3-benzyl-3-methyl-1-((4-nitrophenyl)sulfonyl)-6-((*E*)-styryl)piperidin-2-one (17ga)

According to the general procedure, **17ga** was isolated by column chromatography (10 to 40% Et$_2$O/hexanes) as a 1.1:1 (**17ga'**:**17ga''**) diastereomeric mixture as a pale yellow solid (70.7 mg, 72% yield). A small amount of each diastereoisomer was separated to be identified.

(±)(3*S*,6*S*)-3-benzyl-3-methyl-1-((4-nitrophenyl)sulfonyl)-6-((*E*)-styryl)piperidin-2-one (17ga')



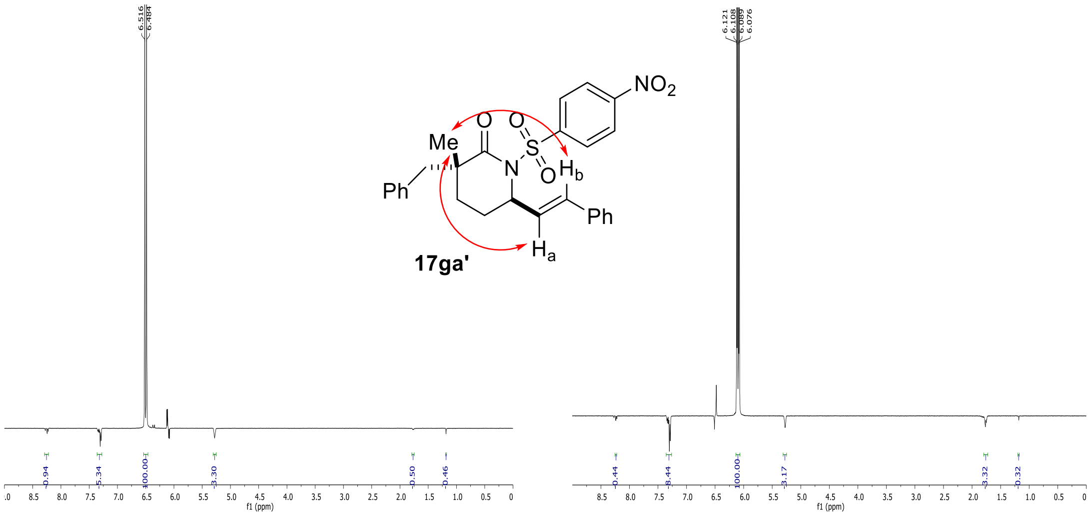
17ga'

^{1}H NMR (300 MHz, CDCl$_3$) δ, ppm: 8.34 – 8.20 (m, 4H), 7.40 – 7.20 (m, 8H), 7.03 – 6.97 (m, 2H), 6.51 (d, *J* = 15.9 Hz, 1H), 6.11 (dd, *J* = 15.9, 6.4 Hz, 1H), 5.32 – 5.26 (m, 1H), 3.13 (d, *J* = 13.3 Hz, 1H), 2.65 (d, *J* = 13.3 Hz, 1H), 1.87 – 1.74 (m, 4H), 1.19 (s, 3H). **^{13}C NMR** (75 MHz, CDCl$_3$) δ, ppm: 177.0 (C), 150.5 (C), 145.2 (C), 136.5 (C), 135.5 (C), 133.4 (CH), 131.2 (CH), 130.3 (CH), 129.0 (CH), 128.6 (CH), 128.5

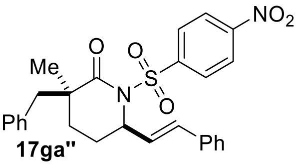
(CH), 127.8 (CH), 127.2 (CH), 126.6 (CH), 123.6 (CH), 59.8 (CH), 46.2 (CH_2), 45.4 (C), 28.3 (CH_2), 26.6 (CH_2), 26.4 (CH_3). **HRMS** (APCI, **[M+H]$^+$**) *m/z* calculated for $C_{27}H_{27}N_2O_5S$: 491.1635, found 491.1635.

Assignment of the stereochemistry

The corresponding diastereoisomer was assigned based on the observation of a **nOe** between the hydrogens of the double bond, **H$_a$** and **H$_b$**, and the **methyl** group.

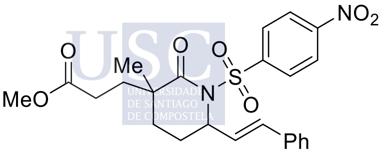


(±)(3*R*,6*S*)-3-benzyl-3-methyl-1-((4-nitrophenyl)sulfonyl)-6-((*E*)-styryl)piperidin-2-one (17ga'')


17ga''

^{1}H NMR (300 MHz, $CDCl_3$) δ, ppm: 8.25 (d, *J* = 8.8 Hz, 2H), 8.11 (d, *J* = 8.8 Hz, 2H), 7.33 – 7.28 (m, 3H), 7.19 (t, *J* = 7.5 Hz, 1H), 7.02 – 6.94 (m, 4H), 6.77 (d, *J* = 7.5 Hz, 2H), 6.35 (d, *J* = 14.3 Hz, 1H), 5.18 – 5.06 (m, 2H), 3.37 (d, *J* = 13.2 Hz, 1H), 2.36 (d, *J* = 13.2 Hz, 1H), 2.31 – 2.11 (m, 2H), 1.91 – 1.83 (m, 1H), 1.41 (s, 3H), 1.24 (d, *J* = 11.3 Hz, 1H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ, ppm: 175.7 (C), 150.5 (C), 145.0 (C), 137.5 (C), 135.3 (C), 133.7 (CH), 131.2 (CH), 130.7 (CH), 128.7 (CH), 128.6 (CH), 128.4 (CH), 126.9 (CH), 126.9 (CH), 126.7 (CH), 123.5 (CH), 59.5 (CH), 46.5 (C), 45.5 (CH_2), 28.8 (CH_3), 27.1 (CH_2), 26.7 (CH_2). **HRMS** (APCI, **[M+H]$^+$**) *m/z* calculated for $C_{27}H_{27}N_2O_5S$: 491.1635, found 491.1634.

Methyl (*E*)-3-(3-methyl-1-((4-nitrophenyl)sulfonyl)-2-oxo-6-styrylpiperidin-3-yl)propanoate (17ha)


17ha, d.r. : 1.1:1

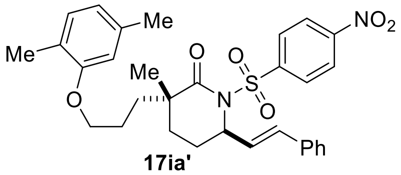
According to the general procedure, **17ha** was isolated by column chromatography (40% Et_2O/hexanes) as an inseparable mixture 1.1:1 of diastereoisomers as a yellow solid (78.4 mg, 81% yield). **^{1}H NMR** (300 MHz, $CDCl_3$) δ, ppm: 8.26 – 8.15 (m, 8H), 7.41 – 7.20 (m, 10H), 6.52 – 6.43 (m, 2H), 6.14 (dd, *J* = 15.9, 6.4 Hz, 1H), 6.06 (dd, *J* = 15.9, 6.8 Hz, 1H), 5.40 – 5.32 (m, 2H), 3.64 (s, 3H), 3.55 (s, 3H), 2.47 – 1.72 (m, 14H), 1.67 (dt, *J* = 13.7, 3.7 Hz, 1H), 1.50 – 1.41

(m, 1H), 1.23 (s, 3H), 1.13 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ, ppm: 176.4 (C), 176.3 (C), 173.4 (C), 150.5 (C), 150.4 (C), 145.0 (C), 135.4 (C), 133.7 (CH), 131.1 (CH), 130.9 (CH), 129.0 (CH), 129.0 (CH), 128.7 (CH), 128.7 (CH), 127.6 (CH), 127.6 (CH), 126.6 (CH), 126.6 (CH), 123.7 (CH), 123.6 (CH), 60.1 (CH), 59.4 (CH), 51.9 (CH_3), 51.8 (CH_3), 44.0 (C), 43.7 (C), 34.3 (CH_2), 34.2 (CH_2), 30.3 (CH_2), 29.5 (CH_2), 29.0 (CH_2), 28.1 (CH_2), 26.6 (CH_3), 26.1 (CH_2), 26.0 (CH_2), 23.8 (CH_3). **HRMS** (APCI, **[M+H]$^+$**) *m/z* calculated for $C_{24}H_{27}N_2O_7S$: 487.1533, found 487.1538.

3-(3-(2,5-dimethylphenoxy)propyl)-3-methyl-1-((4-nitrophenyl)sulfonyl)-6-((*E*)-styryl)piperidin-2-one (**17ia**)

According to the general procedure, **17ia'** (31.9 mg, 28% yield) and **17ia''** (30.0 mg, 27% yield) were completely separate by column chromatography (15 to 40% Et_2O/hexanes) in a 1.1:1 diastereomeric ratio as pale yellow solids.

(±)(3*R*,6*R*)-3-(3-(2,5-dimethylphenoxy)propyl)-3-methyl-1-((4-nitrophenyl)sulfonyl)-6-((*E*)-styryl)piperidin-2-one (**17ia'**)

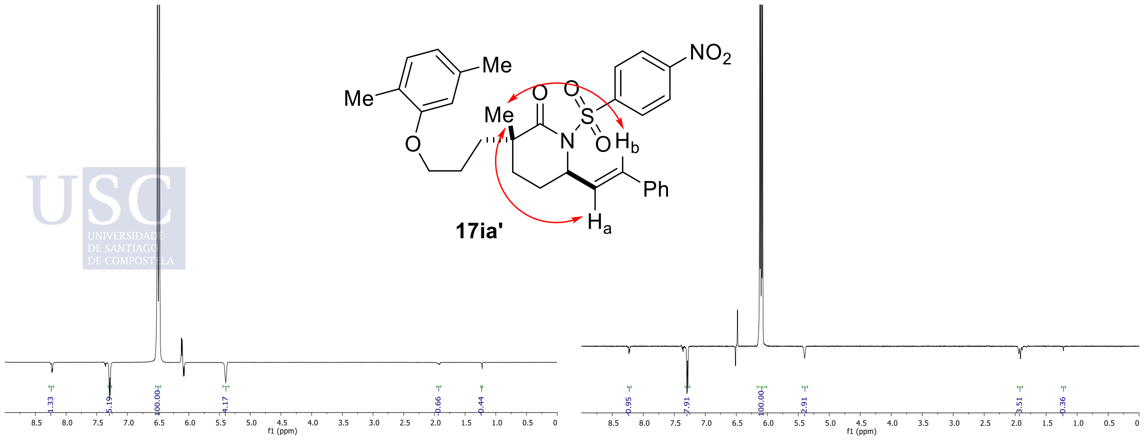


17ia'

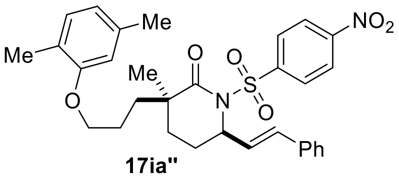
^{1}H NMR (300 MHz, $CDCl_3$) δ, ppm: 8.25 – 8.17 (m, 4H), 7.40 – 7.31 (m, 3H), 7.30 – 7.24 (m, 2H), 7.02 (d, *J* = 7.5 Hz, 1H), 6.69 (d, *J* = 7.5 Hz, 1H), 6.61 (s, 1H), 6.48 (d, *J* = 15.9 Hz, 1H), 6.08 (dd, *J* = 15.9, 7.0 Hz, 1H), 5.42 – 5.35 (m, 1H), 3.97 – 3.83 (m, 2H), 2.46 – 2.36 (m, 1H), 2.33 (s, 3H), 2.18 (s, 3H), 1.96 – 1.67 (m, 7H), 1.20 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ, ppm: 177.3 (C), 156.9 (C), 150.4 (C), 145.2 (C), 136.7 (C), 135.4 (C), 133.7 (CH), 131.1 (CH), 130.5 (CH), 129.0 (CH), 128.7 (CH), 127.6 (CH), 126.6 (CH), 123.6 (CH), 123.5 (C), 121.0 (CH), 112.1 (CH), 67.6 (CH_2), 60.2 (CH), 44.2 (C), 36.3 (CH_2), 29.6 (CH_2), 26.4 (CH_2), 24.2 (CH_2), 24.1 (CH_3), 21.5 (CH_3), 15.9 (CH_3). **HRMS** (APCI, **[M+H]$^+$**) *m/z* calculated for $C_{31}H_{35}N_2O_6S$: 563.2210, found 563.2209.

Assignment of the stereochemistry

The corresponding diastereoisomer was assigned based on the observation of a **nOe** between the hydrogens of the double bond, **H$_a$** and **H$_b$**, and the **methyl** group.



(±)(3*S*,6*R*)-3-(3-(2,5-dimethylphenoxy)propyl)-3-methyl-1-((4-nitrophenyl)sulfonyl)-6-((*E*)-styryl)piperidin-2-one (17ia'')



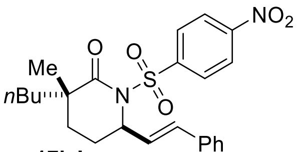
17ia''

^{1}H NMR (300 MHz, CDCl$_3$) δ, ppm: 8.28 – 8.16 (m, 4H), 7.37 – 7.24 (m, 5H), 6.97 (d, *J* = 7.5 Hz, 1H), 6.64 (d, *J* = 7.5 Hz, 1H), 6.53 (s, 1H), 6.48 (d, *J* = 15.9 Hz, 1H), 6.15 (dd, *J* = 15.9, 6.1 Hz, 1H), 5.45 – 5.36 (m, 1H), 3.91 – 3.77 (m, 2H), 2.43 – 2.29 (m, 1H), 2.27 (s, 3H), 2.19 – 2.06 (m, 4H), 2.05 – 1.96 (m, 1H), 1.92 – 1.70 (m, 2H), 1.68 – 1.46 (m, 3H), 1.25 (s, 3H). **^{13}C NMR** (75 MHz, CDCl$_3$) δ, ppm: 176.9 (C), 156.8 (C), 150.4 (C), 145.1 (C), 136.6 (C), 135.4 (C), 133.6 (CH), 130.8 (CH), 130.4 (CH), 129.0 (CH), 128.7 (CH), 127.7 (CH), 126.6 (CH), 123.7 (CH), 123.5 (C), 120.9 (CH), 111.9 (CH), 67.7 (CH$_2$), 59.3 (CH), 44.5 (C), 36.1 (CH$_2$), 28.1 (CH$_2$), 27.0 (CH$_3$), 26.1 (CH$_2$), 24.6 (CH$_2$), 21.5 (CH$_3$), 15.8 (CH$_3$). **HRMS** (APCI, **[M+H]$^+$**) *m/z* calculated for $C_{31}H_{35}N_2O_6S$: 563.2210, found 563.2209.

3-butyl-3-methyl-1-((4-nitrophenyl)sulfonyl)-6-((*E*)-styryl)piperidin-2-one (17ja)

According to the general procedure, **17ja'** (25.6 mg, 28% yield) and **17ja''** (25.5 mg, 28% yield) were completely separate by column chromatography (10 to 40% Et$_2$O/hexanes) in a 1:1 diastereomeric ratio as pale yellow solids.

(±) (3*R*,6*S*)-3-butyl-3-methyl-1-((4-nitrophenyl)sulfonyl)-6-((*E*)-styryl)piperidin-2-one (17ja')

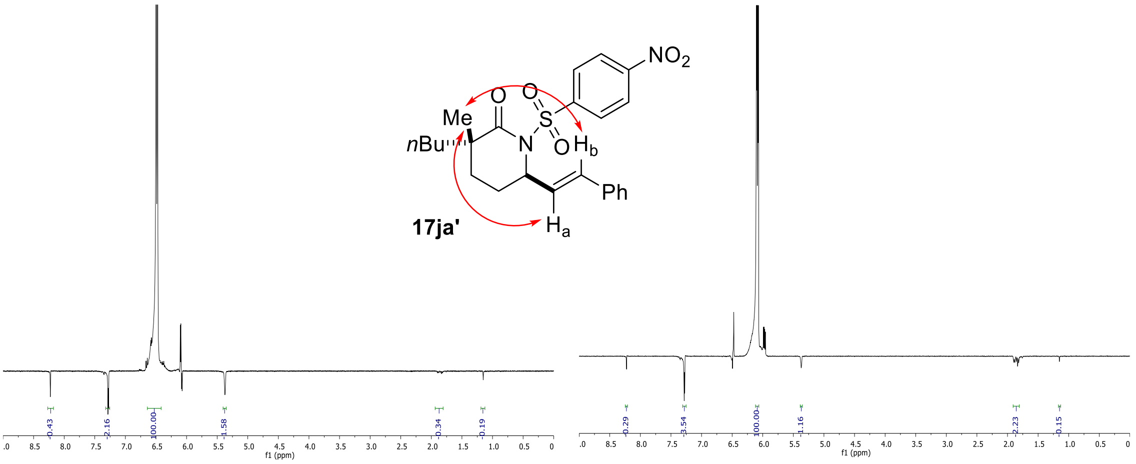


17ja'

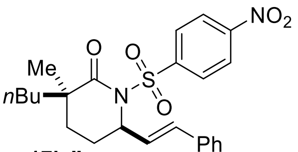
^{1}H NMR (750 MHz, CDCl$_3$) δ, ppm: 8.25 – 8.22 (m, 4H), 7.37 – 7.35 (m, 2H), 7.34 – 7.31 (m, 1H), 7.28 (d, *J* = 6.5 Hz, 2H), 6.48 (d, *J* = 15.8 Hz, 1H), 6.09 (dd, *J* = 15.8, 6.9 Hz, 1H), 5.40 – 5.35 (m, 1H), 2.37 (tdd, *J* = 13.6, 5.6, 3.4 Hz, 1H), 1.89 (dq, *J* = 13.8, 3.1 Hz, 1H), 1.84 (td, *J* = 13.8, 3.5 Hz, 1H), 1.75 (dt, *J* = 14.4, 4.1 Hz, 1H), 1.59 (t, *J* = 8.5 Hz, 2H), 1.28 – 1.25 (m, 2H), 1.22 – 1.17 (m, 2H), 1.15 (s, 3H), 0.89 (t, *J* = 7.3 Hz, 3H). **^{13}C NMR** (75 MHz, CDCl$_3$) δ, ppm: 177.6 (C), 150.4 (C), 145.3 (C), 135.4 (C), 133.6 (CH), 131.1 (CH), 129.0 (CH), 128.7 (CH), 127.7 (CH), 126.6 (CH), 123.6 (CH), 60.1 (CH), 44.4 (C), 39.6 (CH$_2$), 29.3 (CH$_2$), 26.5 (CH$_2$), 26.0 (CH$_2$), 24.3 (CH$_3$), 23.2 (CH$_2$), 14.1 (CH$_3$). **HRMS** (APCI, **[M+H]$^+$**) *m/z* calculated for $C_{24}H_{29}N_2O_5S$: 457.1792, found 457.1794.

Assignment of the stereochemistry

The corresponding diastereoisomer was assigned based on the observation of a **nOe** between the hydrogens of the double bond, **H$_a$** and **H$_b$**, and the **methyl** group.



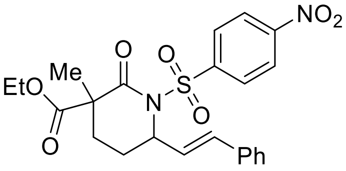
(±)(3*R*,6*R*)-3-butyl-3-methyl-1-((4-nitrophenyl)sulfonyl)-6-((*E*)-styryl)piperidin-2-one (**17ja''**)



17ja''

^{1}H NMR (300 MHz, CDCl$_3$) δ, ppm: 8.26 (d, *J* = 9.0 Hz, 2H), 8.18 (d, *J* = 9.0 Hz, 2H), 7.39 – 7.27 (m, 5H) 6.50 (d, *J* = 15.9 Hz, 1H), 6.14 (dd, *J* = 15.9, 6.2 Hz, 1H), 5.41 – 5.33 (m, 1H), 2.37 – 2.24 (m, 1H), 2.13 – 2.04 (m, 1H), 2.02 – 1.93 (m, 1H), 1.76 – 1.63 (m, 1H), 1.47 – 1.35 (m, 2H), 1.28 – 1.20 (m, 4H), 1.18 (s, 3H), 0.80 (t, *J* = 7.0 Hz, 3H). **^{13}C NMR** (75 MHz, CDCl$_3$) δ, ppm: 177.1 (C), 150.4 (C), 145.2 (C), 135.6 (C), 133.6 (CH), 130.7 (CH), 129.0 (CH), 128.6 (CH), 127.8 (CH), 126.6 (CH), 123.7 (CH), 59.4 (CH), 44.7 (C), 39.5 (CH$_2$), 27.9 (CH$_2$), 27.1 (CH$_3$), 26.7 (CH$_2$), 26.2 (CH$_2$), 23.2 (CH$_2$), 14.1 (CH$_3$). **HRMS** (APCI, **[M+H]$^+$**) *m/z* calculated for $C_{24}H_{29}N_2O_5S$: 457.1792, found 457.1792.

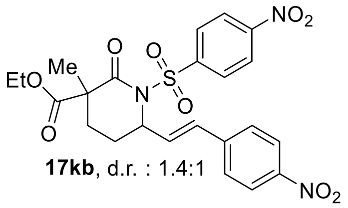
Ethyl (*E*)-3-methyl-1-((4-nitrophenyl)sulfonyl)-2-oxo-6-styrylpiperidine-3-carboxylate (**17ka**)



17ka, d.r. : 1.1:1

According to the general procedure, **17ka** was isolated by column chromatography (20 to 40% Et$_2$O/hexanes) as an inseparable mixture 1.1:1 of diastereoisomers as a yellow solid (93.6 mg, 99% yield). **^{1}H NMR** (300 MHz, CDCl$_3$) δ, ppm: 8.30 – 8.15 (m, 8H), 7.40 – 7.26 (m, 10H), 6.62 (d, *J* = 16.1 Hz, 1H), 6.54 (d, *J* = 15.9 Hz, 1H), 6.24 – 6.11 (m, 2H), 5.46 – 5.35 (m, 2H), 4.18 – 4.03 (m, 4H), 2.51 – 2.39 (m, 1H), 2.36 – 2.23 (m, 2H), 2.19 – 2.10 (m, 1H), 2.06 – 1.94 (m, 3H), 1.80 – 1.70 (m, 1H), 1.51 (s, 3H), 1.43 (s, 3H), 1.18 (t, *J* = 7.1 Hz, 3H), 1.08 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR** (75 MHz, CDCl$_3$) δ, ppm: 172.0 (C), 171.9 (C), 171.5 (C), 171.0 (C), 150.6 (C), 150.5 (C), 144.8 (C), 144.5 (C), 135.4 (C), 135.4 (C), 134.3 (CH), 133.6 (CH), 131.0 (CH), 131.0 (CH), 129.0 (CH), 129.0 (CH), 128.8 (CH), 128.7 (CH), 127.4 (CH), 126.7 (CH), 126.6 (CH), 123.6 (CH), 62.3 (CH$_2$), 61.9 (CH$_2$), 59.6 (CH), 59.3 (CH), 53.2 (C), 52.6 (C), 29.3 (CH$_2$), 28.9 (CH$_2$), 26.8 (CH_2), 26.5 (CH_2), 22.8 (CH_3), 22.4 (CH_3), 14.1 (CH_3), 14.0 (CH_3). **HRMS** (APCI, **$[M+H]^+$**) *m/z* calculated for $C_{23}H_{25}N_2O_7S$: 473.1377, found 473.1376.

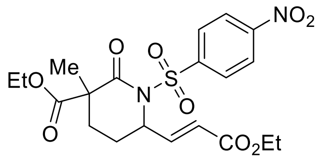
ethyl (*E*)-3-methyl-1-((4-nitrophenyl)sulfonyl)-6-(4-nitrostyryl)-2-oxopiperidine-3-carboxylate (**17kb**)



17kb, d.r. : 1.4:1

According to the general procedure, **17kb** was isolated by column chromatography (20 to 60% EtOAc/hexanes) as a mixture 1.4:1 of diastereoisomers as an orange solid (99.4 mg, 96% yield). **^{1}H NMR** (300 MHz, $CDCl_3$) δ, ppm: 8.36 – 8.23 (m, 4H), 8.23 – 8.14 (m, 8H), 7.49 (t, *J* = 7.9 Hz, 4H), 6.79 – 6.67 (m, 2H), 6.48 – 6.37 (m, 2H), 5.48 – 5.39 (m, 2H), 4.15 – 3.98 (m, 4H), 2.49 – 2.21 (m, 3H), 2.19 – 1.88 (m, 4H), 1.75 (d, *J* = 13.3 Hz, 1H), 1.43 (s, 6H), 1.15 – 1.06 (m, 6H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ, ppm: 171.8 (C), 171.7 (C), 171.2 (C), 170.5 (C), 150.7 (C), 150.6 (C), 147.6 (C), 147.6 (C), 144.4 (C), 144.3 (C), 141.9 (C), 141.9 (C), 132.8 (CH), 131.9 (CH), 131.9 (CH), 131.3 (CH), 130.7 (CH), 127.4 (CH), 127.3 (CH), 124.3 (CH), 124.2 (CH), 123.8 (CH), 123.7 (CH), 62.2 (CH_2), 62.1 (CH_2), 59.2 (CH), 58.8 (CH), 53.1 (C), 52.6 (C), 29.3 (CH_2), 28.9 (CH_2), 26.2 (CH_2), 26.0 (CH_2), 22.6 (CH_3), 22.3 (CH_3), 14.1 (CH_3). **HRMS** (APCI, **$[M+H]^+$**) *m/z* calculated for $C_{23}H_{24}N_3O_9S$: 518.1228, found 518.1232.

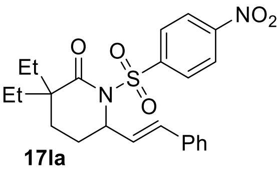
ethyl (*E*)-6-(3-ethoxy-3-oxoprop-1-en-1-yl)-3-methyl-1-((4-nitrophenyl)sulfonyl)-2-oxopiperidine-3-carboxylate (**17kg**)



17ka, d.r. : 1.1:1

According to the general procedure, **17kg** was isolated by column chromatography (20 to 40% EtOAc/hexanes) as an inseparable mixture 1.1:1 of diastereoisomers as a yellow oil (63.8 mg, 68% yield). **^{1}H NMR** (300 MHz, $CDCl_3$) δ, ppm: 8.36 – 8.30 (m, 4H), 8.23 – 8.16 (m, 4H), 6.96 – 6.86 (m, 2H), 6.07 – 5.96 (m, 2H), 5.41 – 5.33 (m, 2H), 4.27 – 4.16 (m, 4H), 4.12 – 3.98 (m, 4H), 2.34 – 2.18 (m, 3H), 2.14 – 1.92 (m, 3H), 1.83 (dd, *J* = 14.4, 2.9 Hz, 1H), 1.77 – 1.67 (m, 1H), 1.43 – 1.38 (m, 6H), 1.29 (t, *J* = 7.1 Hz, 6H), 1.14 – 1.07 (m, 6H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ, ppm: 171.7 (C), 171.4 (C), 171.0 (C), 170.3 (C), 165.4 (C), 165.4 (C), 150.8 (C), 150.7 (C), 145.5 (CH), 144.5 (CH), 144.2 (C), 144.0 (C), 130.9 (CH), 130.8 (CH), 125.1 (CH), 124.5 (CH), 123.8 (CH), 123.7 (CH), 62.2 (CH_2), 62.1 (CH_2), 61.1 (CH_2), 61.0 (CH_2), 58.2 (CH), 57.7 (CH), 52.8 (C), 52.5 (C), 29.3 (CH_2), 28.8 (CH_2), 25.4 (CH_2), 25.3 (CH_2), 22.6 (CH_3), 22.3 (CH_3), 14.3 (CH_3), 14.0 (CH_3), 13.7 (CH_3). **HRMS** (APCI, **$[M+H]^+$**) *m/z* calculated for $C_{20}H_{25}N_2O_9S$: 469.1275, found 469.1272.

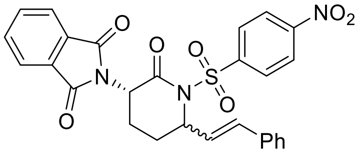
(*E*)-3,3-diethyl-1-((4-nitrophenyl)sulfonyl)-6-styrylpiperidin-2-one (**17la**)



17la

According to the general procedure, adding a new portion of Pd(OAc)$_2$ (10 mol%) after 7 hours of reaction as modification, **17la** was isolated by column chromatography (20 to 40% Et$_2$O/hexanes) as a pale yellow solid (54 mg, 61% yield). **^{1}H NMR** (300 MHz, CDCl$_3$) δ, ppm: 8.27 – 8.16 (m, 4H), 7.38 – 7.24 (m, 5H), 6.50 (d, *J* = 15.9 Hz, 1H), 6.11 (dd, *J* = 15.9, 6.5 Hz, 1H), 5.40 – 5.33 (m, 1H), 2.40 – 2.27 (m, 1H), 2.05 – 1.89 (m, 2H), 1.78 – 1.51 (m, 4H), 1.47 – 1.34 (m, 1H), 0.84 – 0.71 (m, 6H). **^{13}C NMR** (75 MHz, CDCl$_3$) δ, ppm: 176.6 (C), 150.4 (C), 145.4 (C), 135.5 (C), 133.7 (CH), 130.9 (CH), 129.0 (CH), 128.6 (CH), 127.8 (CH), 126.6 (CH), 123.6 (CH), 59.6 (CH), 48.3 (C), 31.9 (CH$_2$), 29.3 (CH$_2$), 26.3 (CH$_2$), 24.9 (CH$_2$), 8.9 (CH$_3$), 8.6 (CH$_3$). **HRMS** (APCI, **[M+H]$^+$**) *m/z* calculated for $C_{23}H_{27}N_2O_5S$: 443.1635, found 443.1633.

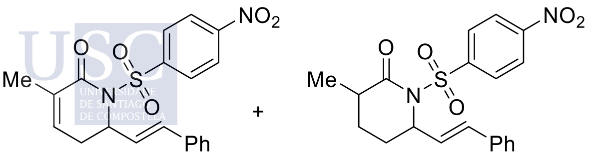
2-(3*S*)-(1-((4-nitrophenyl)sulfonyl)-2-oxo-6-(*E*)-styrylpiperidin-3-yl)isoindoline-1,3-dione (**17ma**)



17ma, d.r. : 1.6:1

According to the general procedure, **17ma** was isolated by column chromatography (40% Et$_2$O/hexanes to 40% EtOAc/hexanes) as an inseparable mixture 1.6:1 of diastereoisomers as a yellow solid (60.6 mg, 57% yield). **^{1}H NMR** (300 MHz, CDCl$_3$) δ, ppm: 8.30 (d, *J* = 8.8 Hz, 0.7H), 8.19 (d, *J* = 8.8 Hz, 0.7H), 8.15 (s, 2.6H), 7.85 – 7.76 (m, 2H), 7.75 – 7.69 (m, 2H), 7.45 – 7.31 (m, 5H), 6.82 – 6.71 (m, 1H), 6.49 (dd, *J* = 15.9, 7.9 Hz, 0.7H), 6.27 (dd, *J* = 15.9, 5.8 Hz, 0.3H), 5.53 – 5.41 (m, 1H), 4.97 – 4.88 (m, 1H), 2.70 – 2.54 (m, 1H), 2.50 – 2.37 (m, 1H), 2.28 – 2.16 (m, 1H), 2.10 – 1.99 (m, 1H). **^{13}C NMR** (75 MHz, CDCl$_3$) δ, ppm: 167.4 (C), 167.2 (C), 150.8 (C), 150.6 (C), 144.5 (C), 144.4 (C), 135.5 (C), 135.5 (C), 135.0 (CH), 134.5 (CH), 133.5 (CH), 131.9 (C), 131.8 (C), 131.1 (CH), 130.5 (CH), 129.1 (CH), 129.0 (CH), 128.8 (CH), 128.7 (CH), 126.9 (CH), 126.9 (CH), 126.8 (CH), 125.9 (CH), 124.0 (CH), 123.9 (CH), 123.8 (CH), 123.7 (CH), 60.0 (CH), 59.4 (CH), 50.8 (CH), 48.7 (CH), 29.2 (CH$_2$), 28.1 (CH$_2$), 23.8 (CH$_2$), 22.3 (CH$_2$). **HRMS** (APCI, **[M+H]$^+$**) *m/z* calculated for $C_{27}H_{22}N_3O_7S$: 532.1173, found 532.1172.

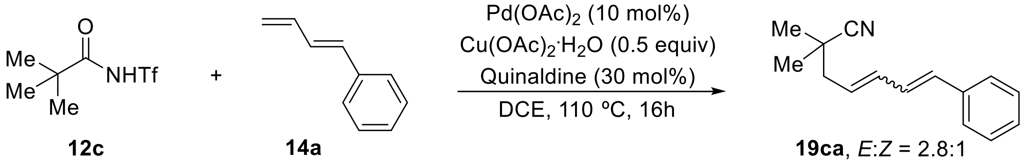
(*E*)-3-methyl-1-((4-nitrophenyl)sulfonyl)-6-styryl-5,6-dihydropyridin-2(1*H*)-one (**18na**) and (*E*)-3-methyl-1-((4-nitrophenyl)sulfonyl)-6-styrylpiperidin-2-one (**17na**)



18na **17na**

According to the general procedure, **18na** and **17na** were isolated as an inseparable 1.7:1 mixture by column chromatography (20 to 40% Et$_2$O/hexanes) as a yellow solid (36.7 mg, 46% yield). **^{1}H NMR** (300 MHz, CDCl$_3$) δ, ppm: 8.25 – 8.19 (m, 5.7H), 7.38 – 7.28 (m, 7.3H), 6.64 (d, *J* = 15.9 Hz, 1H), 6.56 – 6.44 (m, 1.5H), 6.24 – 6.07 (m, 1.6H), 5.49 (t, *J* = 7.4 Hz, 1H), 5.42 – 5.35 (m, 0.6H), 3.17 – 3.03 (m, 1H), 2.63 (q, *J* = 6.9 Hz, 0.3H), 2.58 – 2.47 (m, 1.3H), 2.34 – 1.96 (m, 1.7H), 1.84 (s, 3H), 1.61 – 1.52 (m, 0.8H), 1.24 – 1.17 (m, 1.6H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ, ppm: 174.8 (C), 174.2 (C), 163.8 (C), 150.6 (C), 150.5 (C), 150.5 (C), 145.1 (C), 145.1 (C), 144.9 (C), 137.4 (CH), 135.5 (C), 135.4 (C), 135.3 (C), 134.3 (CH), 133.7 (CH), 133.2 (CH), 131.1 (CH), 131.0 (CH), 130.8 (CH), 129.0 (CH), 128.8 (CH), 128.7 (CH), 127.6 (CH), 127.6 (CH), 126.7 (CH), 126.7 (CH), 125.7 (CH), 123.7 (CH), 123.7 (CH), 59.9 (CH), 59.1 (CH), 57.8 (CH), 39.6 (CH), 37.5 (CH), 31.2 (CH_2), 29.6 (CH_2), 26.7 (CH_2), 25.4 (CH_2), 24.8 (CH_2), 17.8 (CH_3), 16.5 (CH_3), 16.4 (CH_3). **HRMS** (APCI, **$[M+1]^+$**) *m/z* calculated for $C_{20}H_{19}N_2O_5S$: 399.1009, found 399.1023. **HRMS** (APCI, **$[M+1]^+$**) *m/z* calculated for $C_{20}H_{21}N_2O_5S$: 401.1166, found 401.1151.

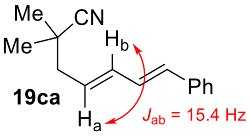
3. Procedure for the Pd-catalyzed synthesis of functionalized nitriles



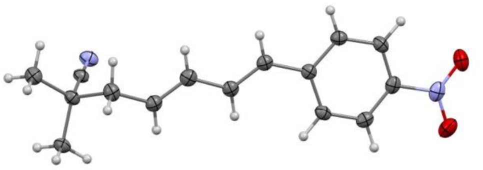
The corresponding alkyl amide (0.2 mmol), $Pd(OAc)_2$ (4.5 mg, 0.02 mmol) and $Cu(OAc)_2 \cdot H_2O$ (20 mg, 0.1 mmol) were weighed in air and placed in a reaction tube (10 mL) with a magnetic stir bar. Then, dichloroethane (2 mL), quinaldine (9 µL, 0.06 mmol) and (*E*)-buta-1,3-dien-1-ylbenzene **14a** (59 µL, 0.4 mmol) were added. The tube was sealed, and the mixture was stirred 16 hours at 110 ºC. After cooling to room temperature, the mixture was concentrated in vacuo. Purification of the reaction crude by flash column chromatography on silica gel afforded 2,2-dimethyl-7-phenylhepta-4,6-dienenitrile (**19ca**) as an inseparable mixture 2.8:1 of *E*:*Z* isomers as a yellowish oil (14.8 mg, 35% yield). **^{1}H NMR** (300 MHz, $CDCl_3$) δ, ppm: 7.47 – 7.29 (m, 4H), 7.25 – 7.17 (m, 1H), 6.97 (dd, *J* = 14.9, 10.7 Hz, 0.3H), 6.79 (dd, *J* = 15.8, 10.3 Hz, 0.7H), 6.63 (d, *J* = 15.7 Hz, 0.3H), 6.53 (d, *J* = 15.4 Hz, 0.7H), 6.44 – 6.26 (m, 1H), 5.85 (dt, *J* = 15.4, 7.7 Hz, 0.7H), 5.68 – 5.56 (m, 0.3H), 2.54 (d, *J* = 7.8 Hz, 0.5H), 2.38 (d, *J* = 7.6 Hz, 1.5H), 1.40 (s, 1.5H), 1.37 (s, 4.5H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ, ppm: 137.4 (C), 135.5 (CH), 134.6 (CH), 133.1 (CH), 132.6 (CH), 128.9 (2 x CH), 128.5 (CH), 128.1 (CH), 127.9 (CH), 127.9 (CH), 126.8 (CH), 126.6 (CH), 125.3 (CH), 125.0 (C), 123.5 (CH), 111.3 (C), 44.3 (CH_2), 44.1 (CH_2), 38.9 (C), 32.7 (C), 26.7 (CH_3), 26.4 (CH_3). **HRMS** (APCI, **$[M+H]^+$**) *m/z* calculated for $C_{15}H_{18}N$: 212.1434, found 212.1442.

Assignment of the stereochemistry

Geometric isomerism of the double bond of the major isomer was assigned based on the ***J* value** between **H_a** (5.85 ppm) and **H_b** (6.44 – 6.26 ppm).

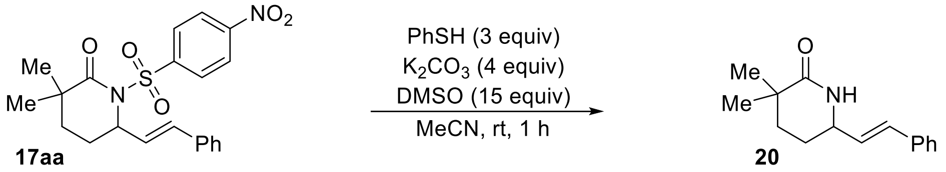


To confirm the structure, suitable crystals of the product, resulting from the reaction with a diene bearing a nitro group, for X-Ray diffraction analysis were grown by slow diffusion of heptane in a CH_2Cl_2 solution of the complex.



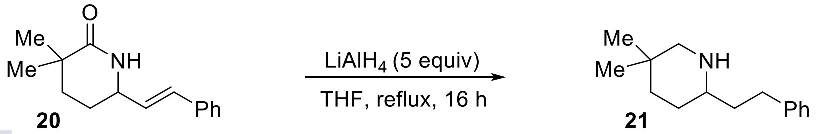
4. Manipulation of the products

Procedure for the removal of the nosyl group:



To a suspension, under Ar atmosphere, of PhSH (66 µL, 0.65 mmol) and K_2CO_3 (120 mg, 0.87 mmol) in MeCN (0.9 mL) was added a solution of the 2-piperidinone **17aa** (90 mg, 0.22 mmol) in MeCN (5.4 mL). DMSO was then added (230 µL, 3.3 mmol) and the mixture was stirred at room temperature for 1 hour. The mixture was concentrated in vacuo, diluted with EtOAc and filtered through a pad of Celite. The resulting solution was concentrated in vacuo and the crude product was purified by column chromatography on silica gel (5% Et_2O/hexanes to 80% EtOAc/hexanes) affording (*E*)-3,3-dimethyl-6-styrylpiperidin-2-one (**20**) as a white solid (47.4 mg, 92% yield). **^{1}H NMR** (300 MHz, $CDCl_3$) δ, ppm: 7.40 – 7.23 (m, 5H), 6.54 (d, *J* = 15.8 Hz, 1H), 6.13 (dd, *J* = 15.8, 6.8 Hz, 1H), 5.81 (s, 1H), 4.17 – 4.08 (m, 1H), 2.06 – 1.95 (m, 1H), 1.81 – 1.66 (m, 3H), 1.26 (s, 6H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ, ppm: 178.4 (C), 136.2 (C), 131.1 (CH), 130.4 (CH), 128.7 (CH), 128.0 (CH), 126.6 (CH), 55.9 (CH), 37.7 (C), 34.3 (CH_2), 27.3 (CH_3), 27.2 (CH_3), 26.2 (CH_2). **HRMS** (APCI, **$[M+H]^+$**) *m/z* calculated for $C_{15}H_{20}NO$: 230.1539, found 230.1537.

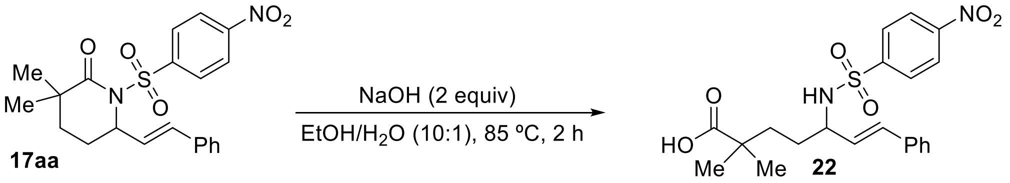
Procedure for the formation of piperidines:



To a suspension, under Ar atmosphere, of $LiAlH_4$ (33 mg, 0.87 mmol) in THF (1.2 mL) was slowly added a solution of the 2-piperidinone **20** (40 mg, 0.17 mmol) in THF (0.4 mL). The mixture was refluxed for 16 hours. After cooling to 0 °C, the reaction was quenched by slow addition of H_2O and NaOH (10%) and the resulting suspension was filtered through a pad of Celite, washing with small portions of EtOAc. The obtained solution was concentrated in vacuo to remove the THF and the mixture was extracted three times with

EtOAc. The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. Finally, the crude product was purified by column chromatography on silica gel (60% EtOAc/hexanes to 20% CH_2Cl_2/EtOH) affording 5,5-dimethyl-2-phenethylpiperidine (**21**) as a beige solid (20.8 mg, 55% yield). **^{1}H NMR** (300 MHz, $CDCl_3$) δ, ppm: 7.47 – 7.32 (m, 5H), 3.12 (d, *J* = 13.0 Hz, 1H), 3.07 – 2.98 (m, 1H), 2.90 (dt, *J* = 9.1, 5.8 Hz, 2H), 2.76 (d, *J* = 12.9 Hz, 1H), 2.70 – 2.56 (m, 1H), 2.36 – 2.21 (m, 1H), 2.06 – 1.86 (m, 2H), 1.79 – 1.69 (m, 1H), 1.54 – 1.42 (m, 2H), 1.34 (s, 3H), 1.09 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ, ppm: 140.4 (C), 128.7 (CH), 128.6 (CH), 126.3 (CH), 56.7 (CH), 54.4 (CH_2), 35.9 (CH_2), 34.3 (CH_2), 31.7 (CH_2), 29.5 (C), 29.0 (CH_3), 25.1 (CH_2), 24.3 (CH_3). **HRMS** (APCI, **$[M+H]^+$**) *m/z* calculated for $C_{15}H_{24}N$: 218.1903, found: 218.1900.

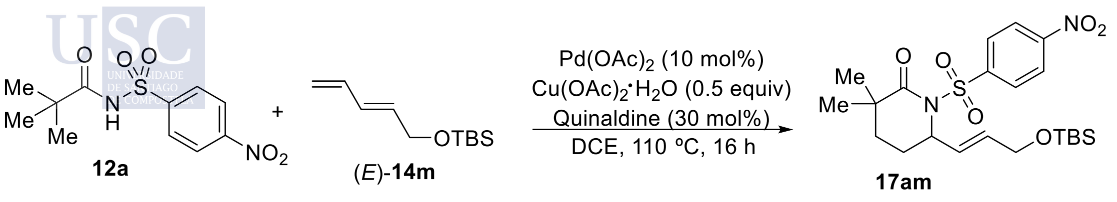
Procedure for the formation of *δ*-amino acids:



To a solution of the 2-piperidinone **17aa** (124.3 mg, 0.3 mmol) in absolute EtOH (3 mL) was added a solution of NaOH (2.0 M in H_2O, 0.3 mL, 0.6 mmol). The mixture was refluxed (85 ºC) 2 hours. After cooling to 0 °C, the mixture was diluted with H_2O, acidified to pH = 1 with aqueous HCl (10%) and the aqueous layer was extracted three times with EtOAc. The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo to afford, without further purification (*E*)-2,2-dimethyl-5-((4-nitrophenyl)sulfonamido)-7-phenylhept-6-enoic acid (**22**) as a yellow solid (129.6 mg, 99% yield). **^{1}H NMR** (300 MHz, $CDCl_3$) δ, ppm: 8.16 (d, *J* = 8.3 Hz, 2H), 7.98 (d, *J* = 8.4 Hz, 2H), 7.25 – 7.20 (m, 3H), 7.10 – 7.04 (m, 2H), 6.26 (d, *J* = 15.8 Hz, 1H), 5.62 (dd, *J* = 15.9, 7.9 Hz, 1H), 5.28 (d, *J* = 7.5 Hz, 1H), 4.05 – 3.96 (m, 1H), 1.67 – 1.45 (m, 4H), 1.23 – 1.18 (m, 6H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ, ppm: 182.1 (C), 149.9 (C), 147.2 (C), 135.6 (C), 132.8 (CH), 128.8 (CH), 128.7 (CH), 128.5 (CH), 127.7 (CH), 126.4 (CH), 124.2 (CH), 57.4 (CH), 42.0 (C), 36.2 (CH_2), 31.5 (CH_2), 25.6 (CH_3), 24.9 (CH_3). **HRMS** (APCI, **$[M]^+$**) *m/z* calculated for $C_{21}H_{24}N_2O_6S$: 432.1350, found 432.1347.

5. Mechanistic experiments

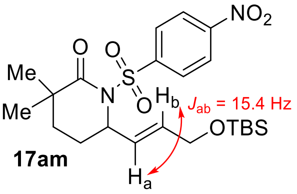
Procedure for the reaction with diene (*E*)-14m:



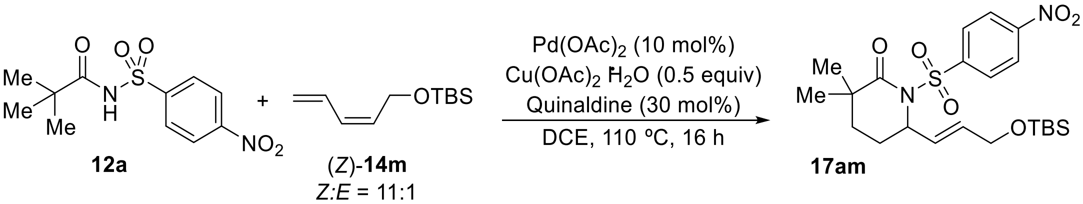
N-((4-nitrophenyl)sulfonyl)pivalamide **12a** (57.3 mg, 0.2 mmol), $Pd(OAc)_2$ (4.5 mg, 0.02 mmol) and $Cu(OAc)_2 \cdot H_2O$ (20 mg, 0.1 mmol) were weighed in air and placed in a reaction tube (10 mL) with a magnetic stir bar. Then, dichloroethane (2 mL), quinaldine (9 µL, 0.06 mmol) and diene (*E*)-**14m** (79.4 mg, 0.4 mmol) were added. The tube was sealed, and the mixture was stirred 16 hours at 110 ºC. After cooling to room temperature, the mixture was concentrated in vacuo. Purification of the crude product by column chromatography on silica gel (5 to 20% EtOAc/hexanes) afforded (*E*)-6-(3-((tert-butyldimethylsilyl)oxy)prop-1-en-1-yl)-3,3-dimethyl-1-((4-nitrophenyl)sulfonyl)piperidin-2-one (**17am**) as a yellow solid (70.3 mg, 73% yield). **^{1}H NMR** (500 MHz, CD_3CN) δ, ppm: 8.35–8.32 (m, 2H), 8.19–8.16 (m, 2H), 5.79 (ddt, *J* = 15.4 Hz, *J* = 5.7 Hz, *J* = 1.8 Hz, 1H), 5.68 (dtd, *J* = 15.4 Hz, *J* = 4.3 Hz, *J* = 1.3 Hz, 1H), 5.24–5.21 (m, 1H), 4.24–4.16 (m, 2H), 2.33–2.26 (m, 1H), 1.89–1.80 (m, 2H), 1.56–1.51 (m, 1H), 1.11 (s, 3H), 1.09 (s, 3H), 0.90 (s, 9H), 0.08 (s, 3H), 0.07 (s, 3H). **^{13}C NMR** (126 MHz, CD_3CN) δ, ppm: 178.3 (C), 151.6 (C), 146.0 (C), 133.7 (CH), 131.2 (CH), 129.5 (CH), 124.7 (CH), 63.2 (CH_2), 41.6 (C), 31.7 (CH_2), 27.6 (CH_3), 26.9 (CH_3), 26.4 (CH_2), 26.2 (CH_3), 18.9 (C), -5.2 (CH_3), -5.1 (CH_3). **HRMS** (APCI, **[M+H]$^+$**) *m/z* calculated for $C_{22}H_{34}N_2O_6SSi$: 483.1980, found: 483.1980.

Assignment of the stereochemistry

Geometric isomerism of the double bond was assigned based on the ***J*** value between **H$_a$** and **H$_b$**.

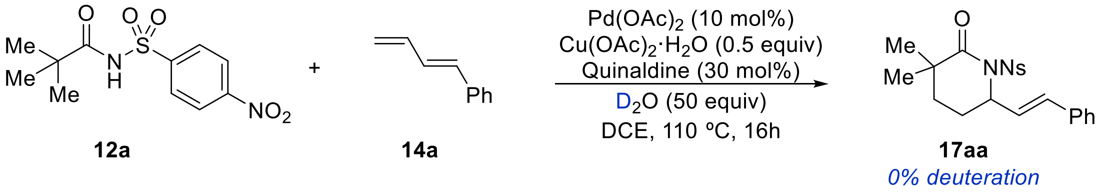


Procedure for the reaction with diene (*Z*)-14m:



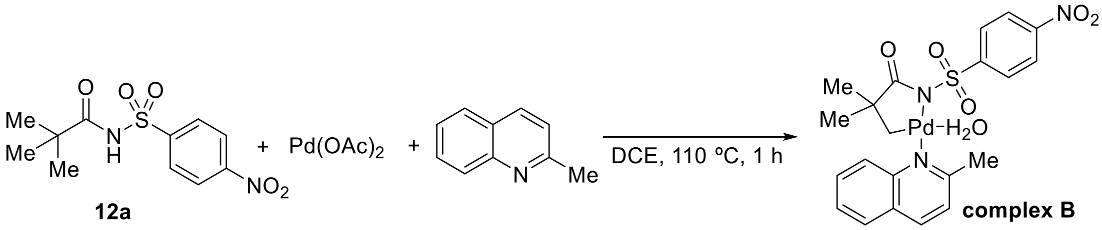
N-((4-nitrophenyl)sulfonyl)pivalamide **12a** (57.3 mg, 0.2 mmol), $Pd(OAc)_2$ (4.5 mg, 0.02 mmol) and $Cu(OAc)_2 \cdot H_2O$ (20 mg, 0.1 mmol) were weighed in air and placed in a reaction tube (10 mL) with a magnetic stir bar. Then, dichloroethane (2 mL), quinaldine (9 µL, 0.06 mmol) and diene (*Z*)-**14m** (79.4 mg, 0.4 mmol, *Z:E* = 11:1) were added. The tube was sealed, and the mixture was stirred 16 hours at 110 ºC. After cooling to room temperature, the mixture was concentrated in vacuo. Purification of the crude product by column chromatography on silica gel (5 to 20% EtOAc/hexanes) afforded (*E*)-6-(3-((tert-butyldimethylsilyl)oxy)prop-1-en-1-yl)-3,3-dimethyl-1-((4-nitrophenyl)sulfonyl)piperidin-2-one (**17am**) as a yellow solid (23.1 mg, 24% yield), recovering the remaining diene as a 7.6:1 ratio of *Z:E* isomers. Spectral data is in agreement with the product obtained with diene (*E*)-**14m**.

Procedure for the model reaction in presence of deuterated water:



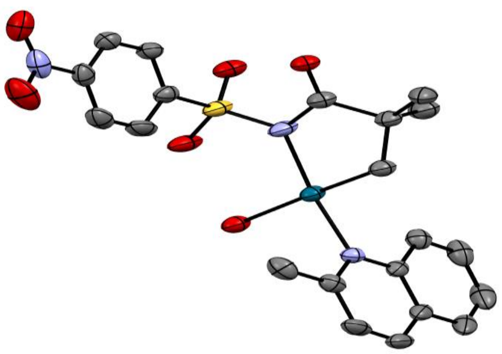
N-((4-nitrophenyl)sulfonyl)pivalamide **12a** (57.3 mg, 0.2 mmol), $Pd(OAc)_2$ (4.5 mg, 0.02 mmol) and $Cu(OAc)_2{\cdot}H_2O$ (20 mg, 0.1 mmol) were weighed in air and placed in a reaction tube (10 mL) with a magnetic stir bar. Then, dichloroethane (2 mL), quinaldine (9 µL, 0.06 mmol), (*E*)-buta-1,3-dien-1-ylbenzene **14a** (59 µL, 0.4 mmol) and D_2O (180 µL, 10 mmol) were added. The tube was sealed, and the mixture was stirred 16 hours at 110 ºC. After cooling to room temperature, the mixture was concentrated in vacuo. Purification of the crude product by column chromatography on silica gel (5 to 30% Et_2O/hexanes) afforded (*E*)-3,3-dimethyl-1-((4-nitrophenyl)sulfonyl)-6-styrylpiperidin-2-one (**17aa**) as a yellow solid (34.8 mg, 42%, 0% deuteration).

Procedure for the isolation of complex B:

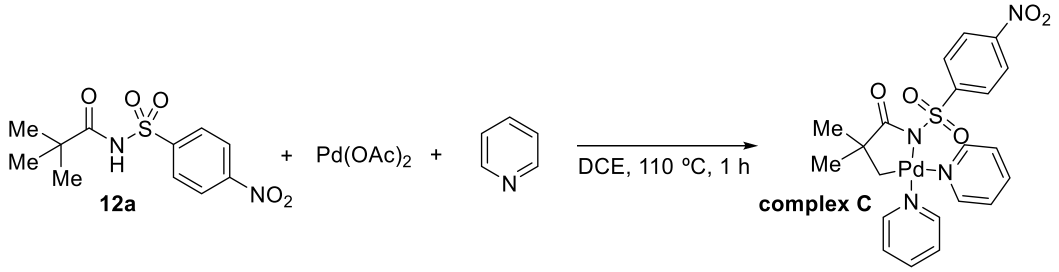


A pressure tube, equipped with a magnetic stir bar, was loaded with nosyl-protected alkylamide **12a** (100 mg, 0.35 mmol), $Pd(OAc)_2$ (78.4 mg, 0.35 mmol), quinaldine (100 µl, 0.7 mmol) and DCE (3.5 mL). The tube was sealed and heated at 110 ºC for 1 h. The yellow mixture was cooled to room temperature and filtered through an Acrodisk filter. Slow *n*-pentane diffusion over the resulting solution afforded yellow crystals of the desired complex (158.3 mg, 82% yield). **^{1}H NMR** (500 MHz, $CDCl_3$) δ, ppm: 9.80 (d, *J* = 8.6 Hz, 1H), 8.21–8.17 (m, 3H), 8.08 (d, *J* = 8.8 Hz, 2H), 7.91–7.87 (m, 1H), 7.82 (d, *J* = 8.1 Hz, *J* = 1.2 Hz, 1H), 7.63–7.59 (m, 1H), 7.48 (d, *J* = 8.4 Hz, 1H), 3.57 (s, 3H), 2.23 (bb, 2H), 1.60 (s, 2H), 1.06 (s, 6H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ, ppm: 187.9 (C), 163.0 (C), 149.5 (C), 148.1 (C), 147.3 (C), 138.9 (CH), 131.1 (CH), 129.8 (CH), 128.8 (CH), 128.3 (CH), 127.6 (C), 127.5 (CH), 123.6 (CH), 123.3 (CH), 46.3 (C), 29.1 (CH_3), 27.8 (CH_3), 25.9 (CH_2).

To confirm the structure, crystals of **complex B** were submitted to X-Ray diffraction. The crystallographic data was deposited in the Cambridge Structural Database (1970275).

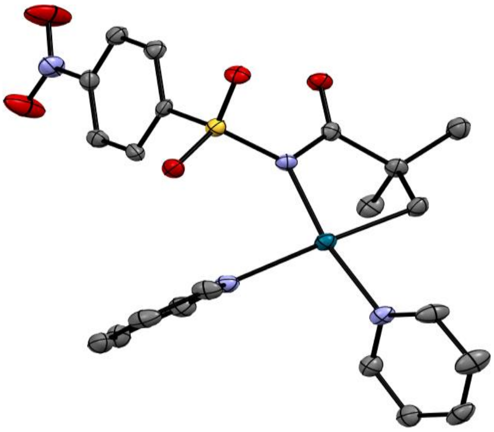


Procedure for the isolation of complex C:

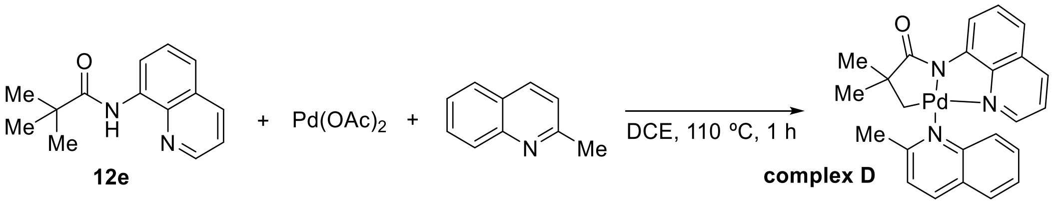


A pressure tube, equipped with a magnetic stir bar, was loaded with nosyl-protected alkylamide **12a** (28.6 mg, 0.1 mmol), Pd(OAc)$_2$ (22.5 mg, 0.1 mmol), pyridine (17 µl, 0.2 mmol) and DCE (1 ml). The tube was sealed and heated at 110 ºC for 1 h. The yellow mixture was cooled down to room temperature and filtered through an Acrodisk filter. Slow pentane diffusion over the resulting solution afforded yellow crystals of the desired complex (30.8 mg, 56% yield). **^{1}H NMR** (300 MHz, CDCl$_3$) δ, ppm: 8.73 (d, *J* = 4.7 Hz, 2H), 8.55 (d, *J* = 5.0 Hz, 2H), 8.18 (d, *J* = 8.8 Hz, 2H), 7.99 (d, *J* = 8.8 Hz, 2H), 7.79 (t, *J* = 7.7 Hz, 1H), 7.72 (t, *J* = 7.7 Hz, 1H) 7.37–7.30 (m, 4H), 1.59 (s, 2H), 1.19 (s, 6H). **^{13}C NMR** (75 MHz, CDCl$_3$) δ, ppm: 188.8 (C), 152.2 (CH), 150.7 (CH), 149.6 (C), 149.2 (C), 138.1 (CH), 137.5 (CH), 128.8 (CH), 125.8 (CH), 124.8 (CH), 123.4 (CH), 46.5 (C), 30.1 (CH$_2$), 29.0 (CH$_3$).

To confirm the structure, crystals of **complex c** were submitted to X-Ray diffraction. The crystallographic data was deposited in the Cambridge Structural Database (1970278).

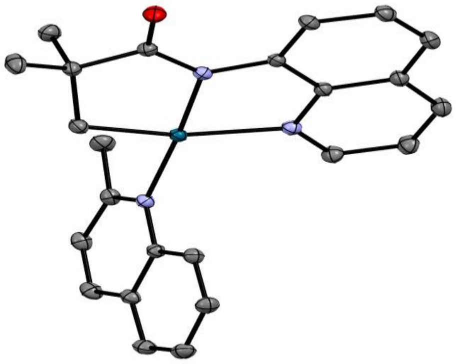


Procedure for the isolation of complex D:

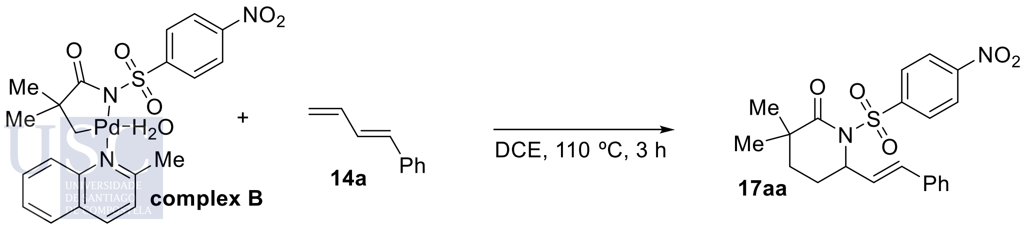


A pressure tube, equipped with a magnetic stir bar, was loaded with 8-aminoquinoline-protected pivalic acid **12e** (68.5 mg, 0.3 mmol), $Pd(OAc)_2$ (67.4 mg, 0.3 mmol), quinaldine (43 µl, 0.3 mmol) and DCE (3 ml). The tube was sealed and heated at 110 ºC for 1 h. The deep yellow mixture was cooled down to room temperature and filtered through an Acrodisk filter. Slow *n*-pentane diffusion over the resulting solution afforded yellow crystals of the desired complex (103.9 mg, 73% yield). **^{1}H NMR** (300 MHz, $CDCl_3$) δ, ppm: 9.86 (d, *J* = 8.6 Hz, 1H), 9.24 (dd, *J* = 8.0 Hz, *J* = 1.3 Hz, 1H), 8.25 (d, *J* = 8.4 Hz, 1H), 8.10 (dd, *J* = 8.3 Hz, *J* = 1.6 Hz, 1H), 7.86 (dd, *J* = 8.1 Hz, *J* = 1.5 Hz, 1H), 7.76 (dd, *J* = 8.6 Hz, *J* = 7.0 Hz, 1H), 7.58 (ddd, *J* = 8.1 Hz, *J* = 6.9 Hz, *J* = 1.2 Hz, 1H), 7.55–7.45 (m, 3H), 7.24 (dd, *J* = 8.1 Hz, *J* = 1.3 Hz, 1H), 7.08 (dd, *J* = 8.3 Hz, *J* = 4.6 Hz, 1H), 3.39 (s, 3H), 1.60 (d, *J* = 9.0 Hz, 1H), 1.54 (d, *J* = 9.0 Hz, 1H), 1.33 (s, 3H), 1.32 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ, ppm: 189.8 (C), 162.1 (C), 148.2 (C), 147.9 (C), 145.7 (C), 145.3 (CH), 138.0 (CH), 137.7 (CH), 130.6 (CH), 130.3 (CH), 130.1 (C), 129.4 (CH), 127.9 (CH), 127.5 (C), 127.3 (CH), 123.1 (CH), 121.0 (CH), 120.5 (CH), 118.0 (CH), 50.2 (C), 30.6 (CH_3), 30.2 (CH_3), 28.8 (CH_3), 24.7 (CH_2).

To confirm the structure, crystals of **complex D** were submitted to X-Ray diffraction. The crystallographic data was deposited in the Cambridge Structural Database (1970251).

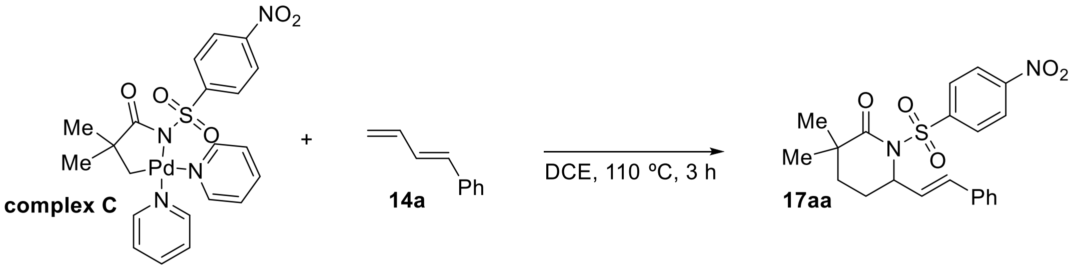


Procedure for the reaction of complex B with diene 14a:



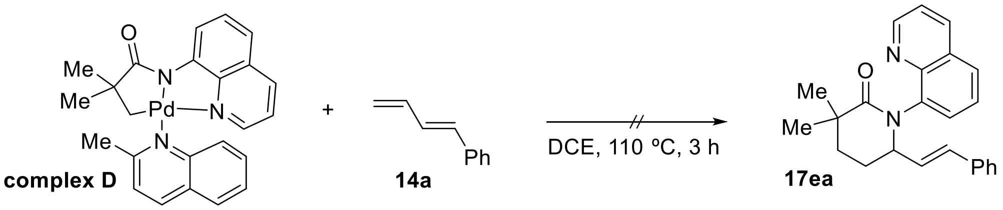
A pressure tube, equipped with a magnetic stir bar, was loaded with **complex B** (55.1 mg, 0.1 mmol), (*E*)-buta-1,3-dien-1-ylbenzene (**14a**) (30 µL, 0.2 mmol) and dichloroethane (1 mL), the tube was sealed and the mixture was stirred for 3 h at 110 ºC. After cooling the mixture to room temperature, it was transferred to a round bottom flask and concentrated in vacuo. Purification of the crude product by flash column chromatography on silica gel (5 to 30% Et_2O/hexanes) afforded the desired product **17aa** as a yellow solid (37.7 mg, 91% yield).

Procedure for the reaction of complex B with diene 14a:



A pressure tube, equipped with a magnetic stir bar, was loaded with **complex C** (54.8 mg, 0.1 mmol), (*E*)-buta-1,3-dien-1-ylbenzene (**14a**) (30 µL, 0.2 mmol) and dichloroethane (1 mL), the tube was sealed and the mixture was stirred for 3 h at 110 ºC. After cooling the mixture to room temperature, it was transferred to a round bottom flask and concentrated in vacuo. Purification of the crude product by flash column chromatography on silica gel (5 to 30% Et_2O/hexanes) afforded the desired product **17aa** as a yellow solid (6.3 mg, 15% yield).

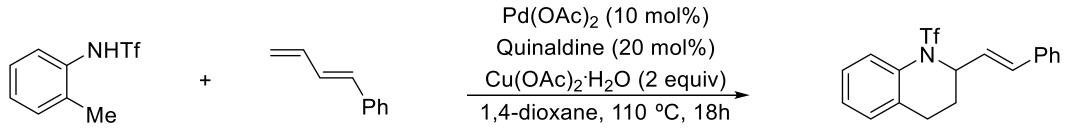
Procedure for the reaction of complex D with diene 14a:



A pressure tube, equipped with a magnetic stir bar, was loaded with **complex D** (47.6 mg, 0.1 mmol), (*E*)-buta-1,3-dien-1-ylbenzene (**14a**) (30 µL, 0.2 mmol) and dichloroethane (1 mL), the tube was sealed and the mixture was stirred for 3 h at 110 ºC. After cooling the mixture to room temperature, it was transferred to a round bottom flask and concentrated in vacuo. The mixture was analyzed by TLC and ^{1}H NMR. Any formation of the product was observed.

6. Procedures of the addendum

Procedure for the Pd-catalyzed formal (4+2) cycloaddition between *o*-methylanilide 23a and diene 14a:



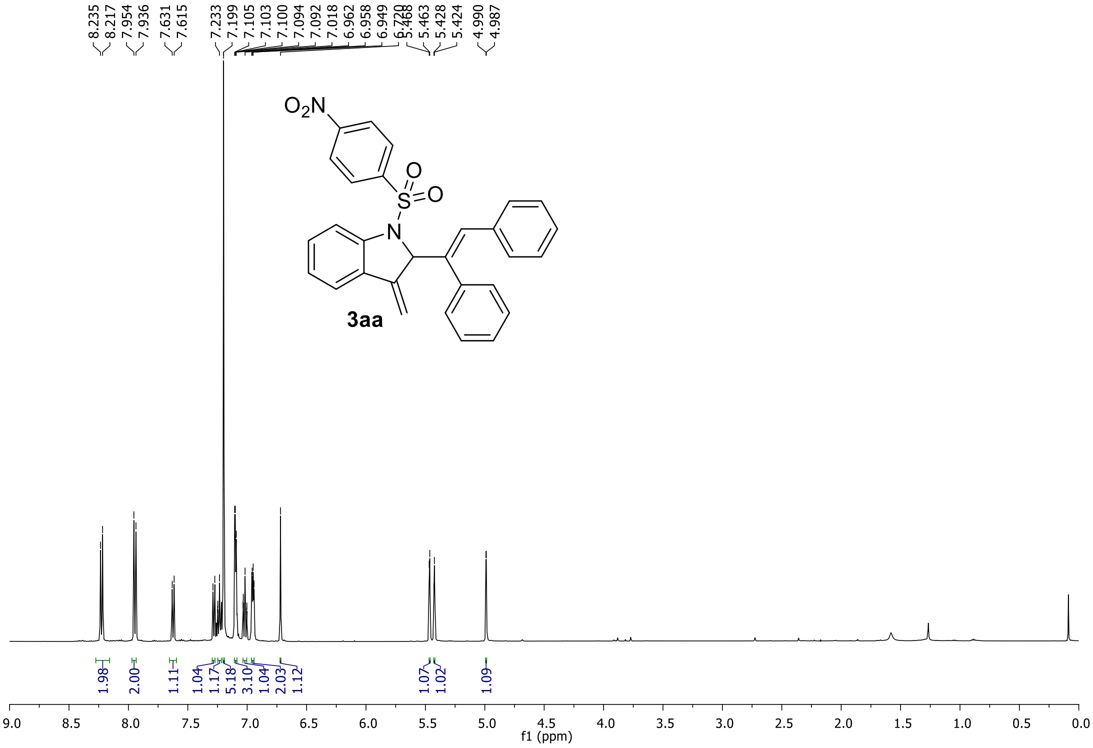
23a **14a** **24aa**

1,1,1-trifluoro-*N*-(*o*-tolyl)methanesulfonamide **23a** (47.8 mg, 0.2 mmol), synthesized according to the literature,[176] $Pd(OAc)_2$ (4.5 mg, 0.02 mmol) and $Cu(OAc)_2 \cdot H_2O$ (80 mg, 0.4 mmol) were weighed in air and placed in a Schlenk tube with a magnetic stir bar. Then, 1,4-dioxane (4 mL), quinaldine (6 µL, 0.04 mmol) and (*E*)-buta-1,3-dien-1-ylbenzene (59 µL, 0.4 mmol) were added and the mixture was stirred 18 hours at 110 ºC. After cooling to room temperature, the mixture was concentrated in vacuo. Purification of the crude product by column chromatography on silica gel (3% Et_2O/hexanes) afforded (*E*)-2-styryl-1-((trifluoromethyl)sulfonyl)-1,2,3,4-tetrahydroquinoline (**24aa**) as a yellowish solid (51.4 mg, 70% yield). **^{1}H NMR** (300 MHz, $CDCl_3$) δ, ppm: 7.62 (d, *J* = 7.8 Hz, 1H), 7.36 – 7.17 (m, 8H), 6.60 (dd, *J* = 15.9, 1.1 Hz, 1H), 6.08 (dd, *J* = 15.9, 6.4 Hz, 1H), 5.20 (q, *J* = 6.0 Hz, 1H), 2.86 (t, *J* = 6.7 Hz, 2H), 2.52 (dq, *J* = 13.6, 6.8 Hz, 1H), 1.98 (dq, *J* = 12.7, 6.3 Hz, 1H). **^{19}F NMR** (282 MHz, $CDCl_3$) δ, ppm: -74.89 (s). **^{13}C NMR** (75 MHz, $CDCl_3$) δ, ppm: 136.1 (C), 133.9 (C), 133.7 (CH), 132.8 (C), 132.6 (CH), 128.9 (CH), 128.7 (CH), 128.2 (CH), 127.3 (CH), 126.8 (CH), 126.7 (CH), 125.1 (CH), 120.3 (q, *J* = 324.5 Hz, C) 59.8 (CH), 30.1 (CH_2), 24.6 (CH_2). **HRMS** (APCI, **$[M+H]^+$**) *m/z* calculated for $C_{18}H_{17}F_3NO_2S$: 368.0927, found 368.0935.

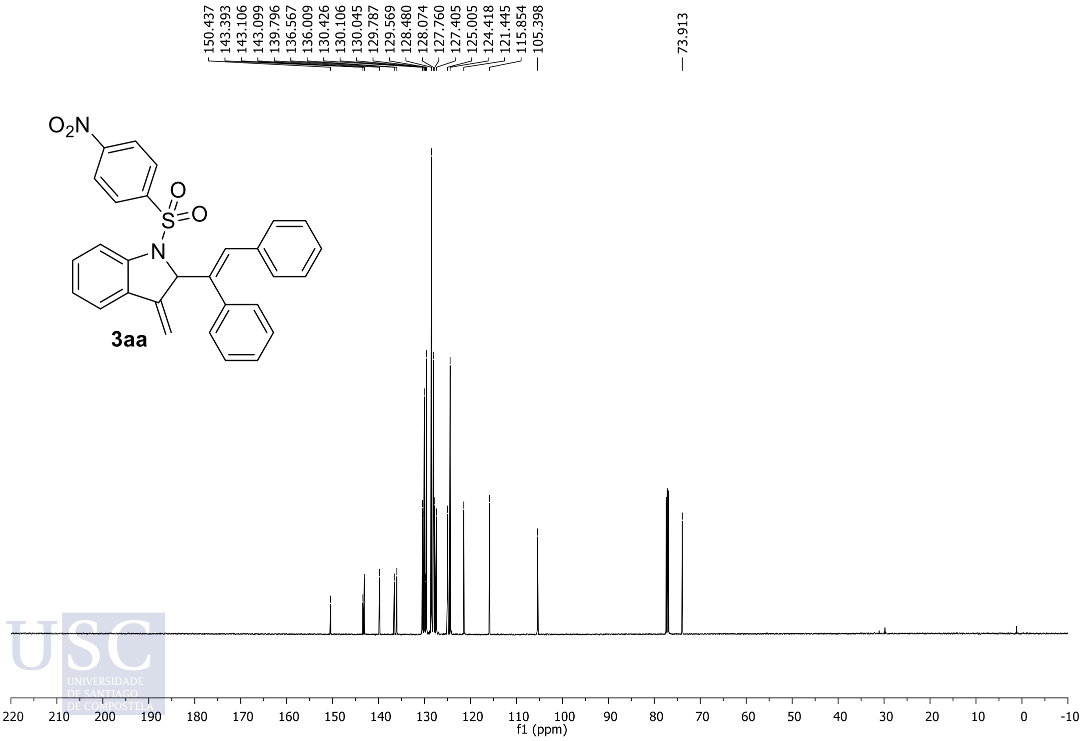
Selected NMR spectra


USC
UNIVERSIDADE
DE SANTIAGO
DE COMPOSTELA

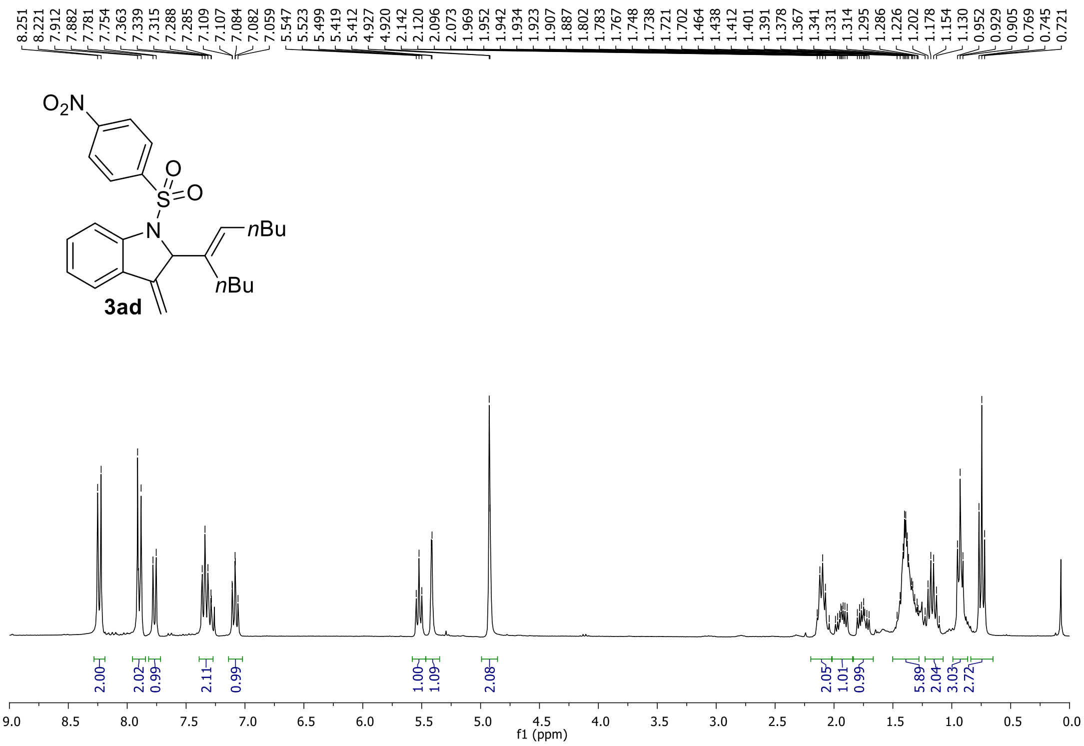
^{1}H NMR



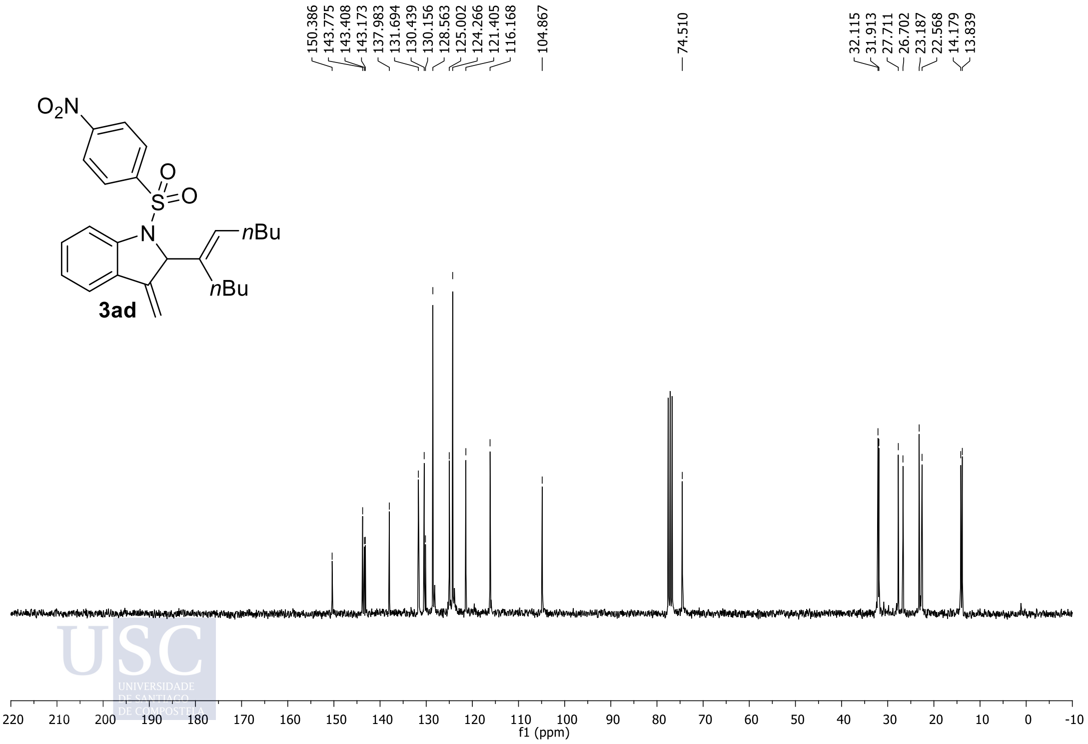
^{13}C NMR



^{1}H NMR



^{13}C NMR



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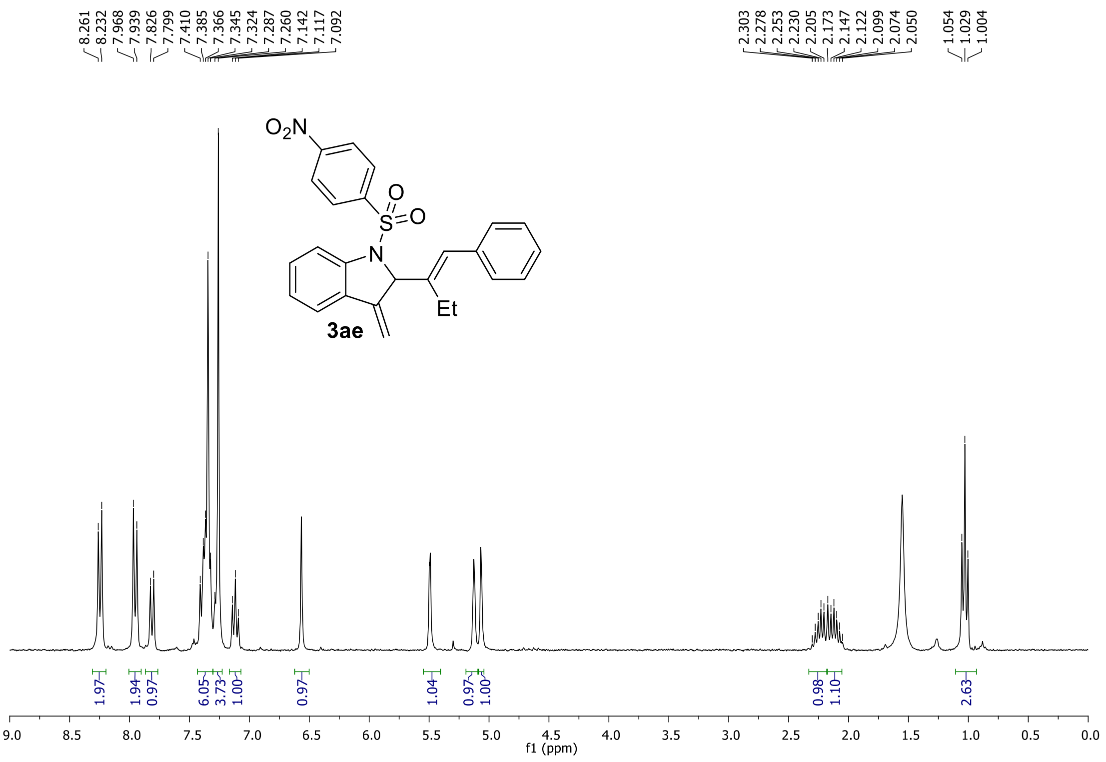

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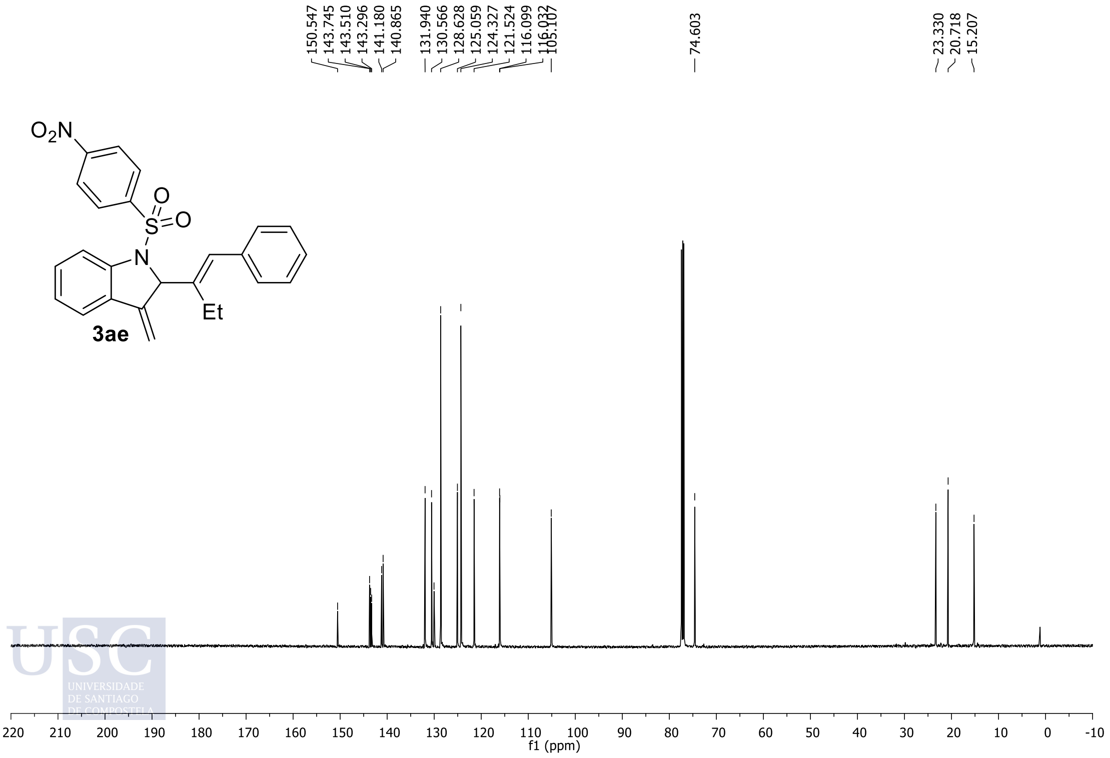

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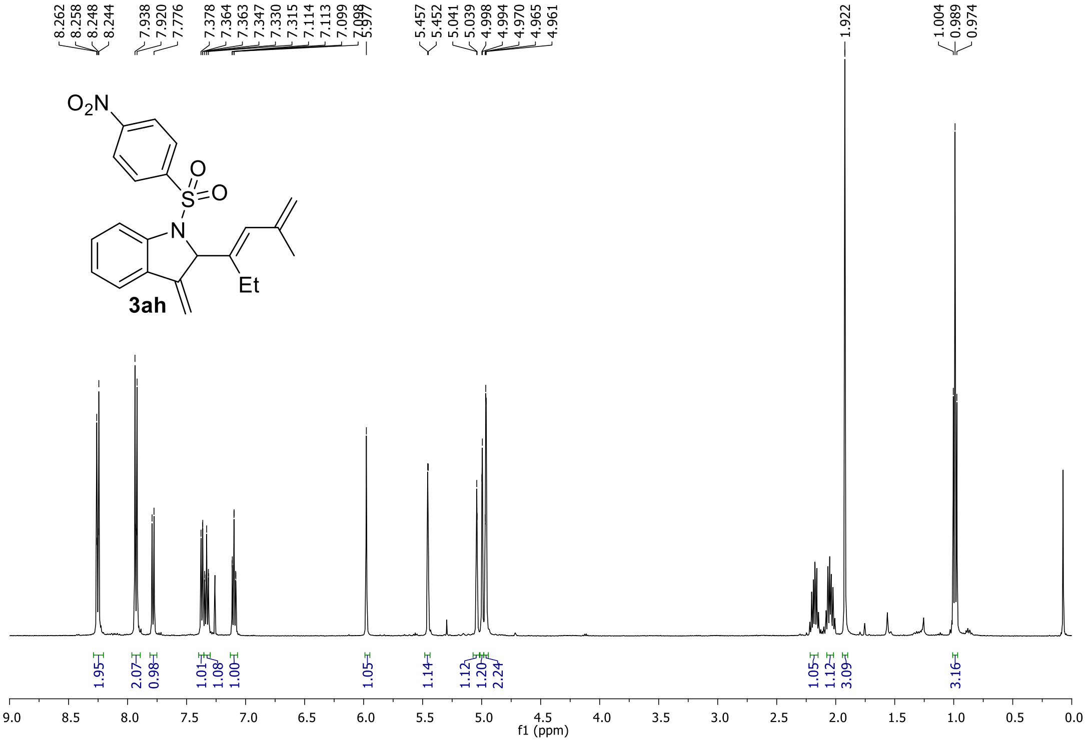

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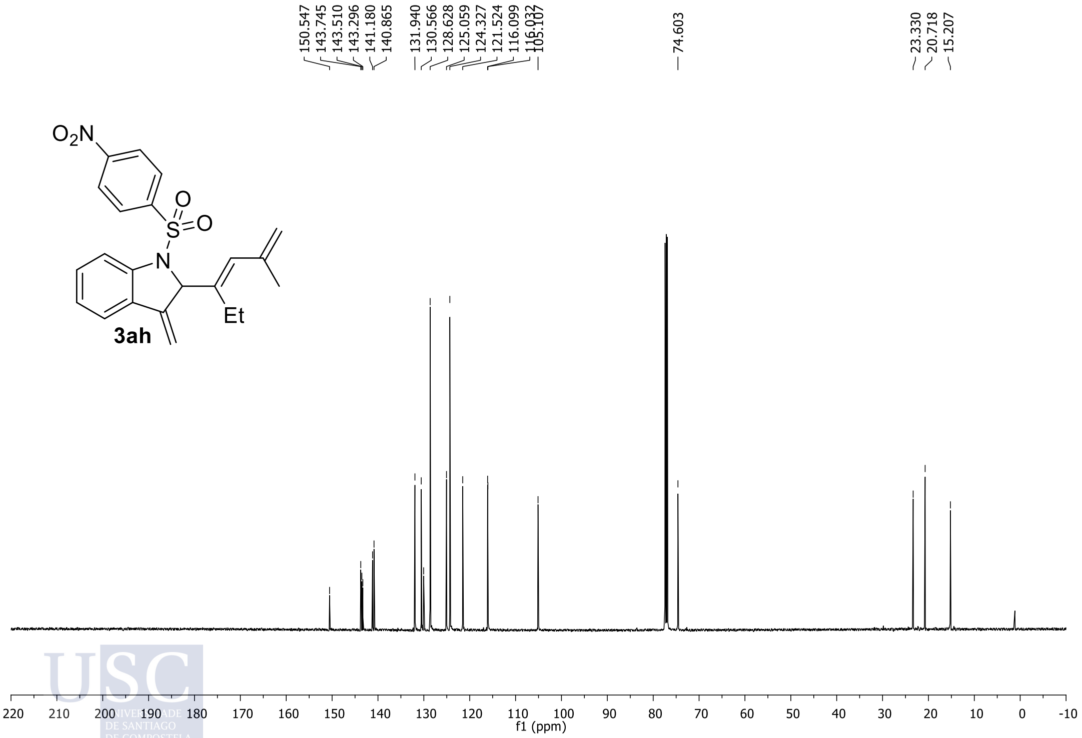

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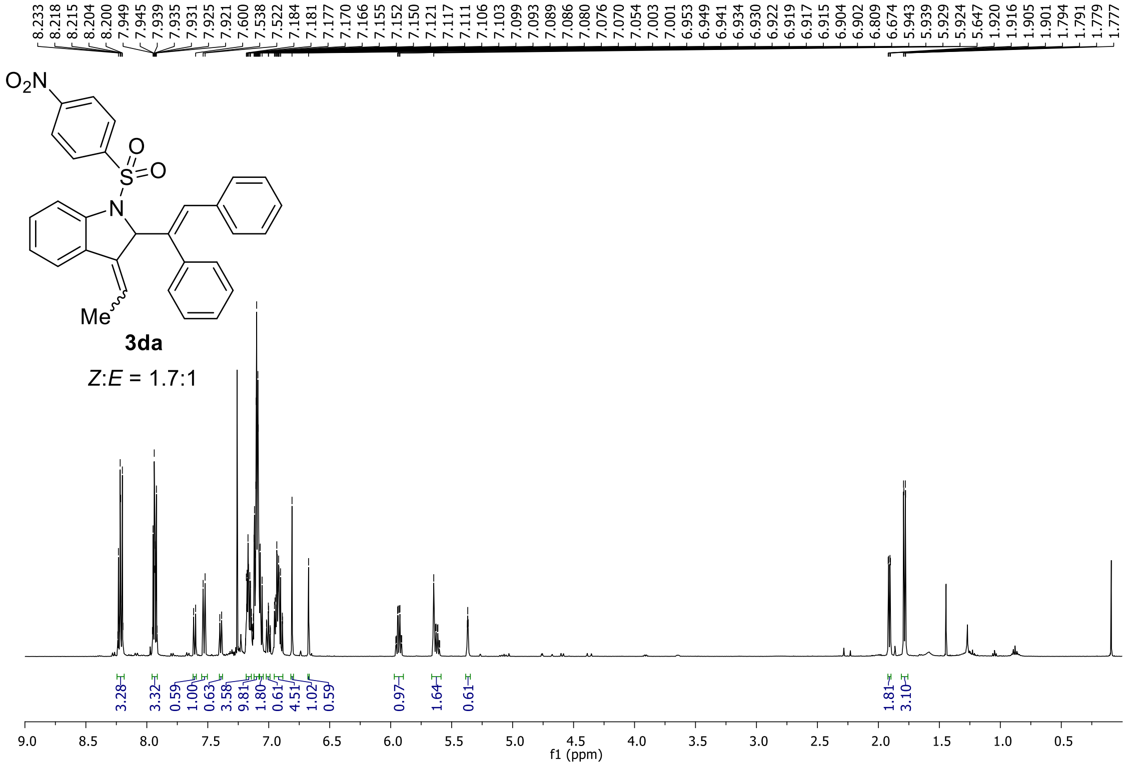

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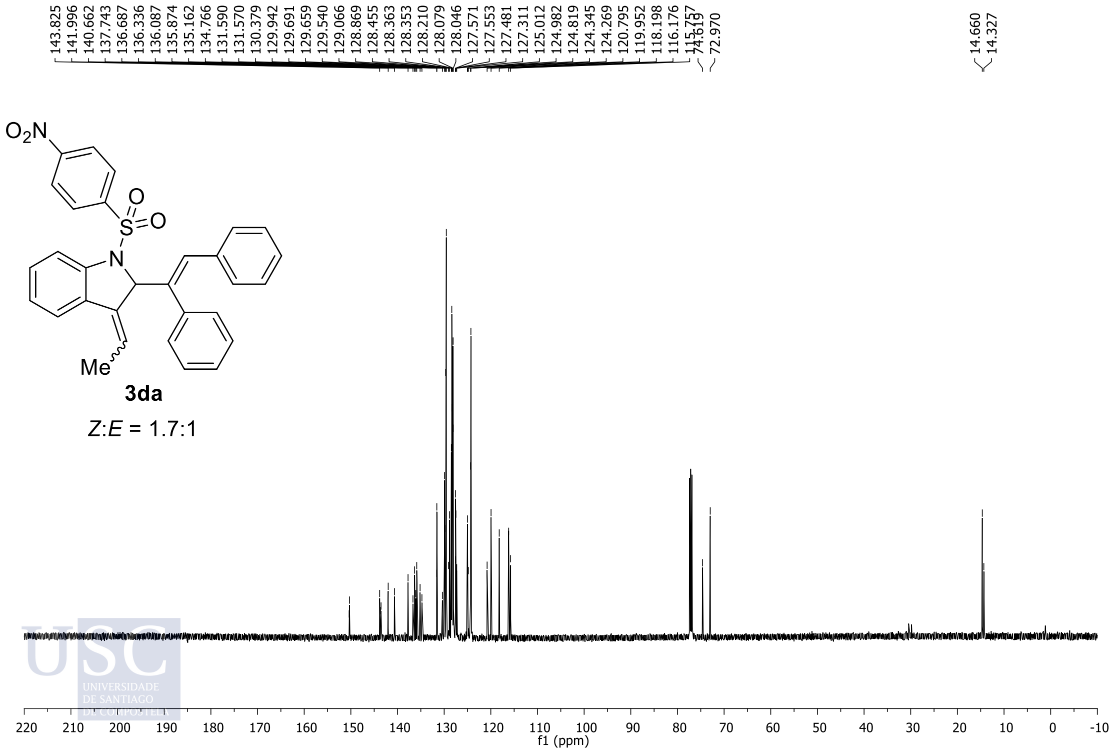

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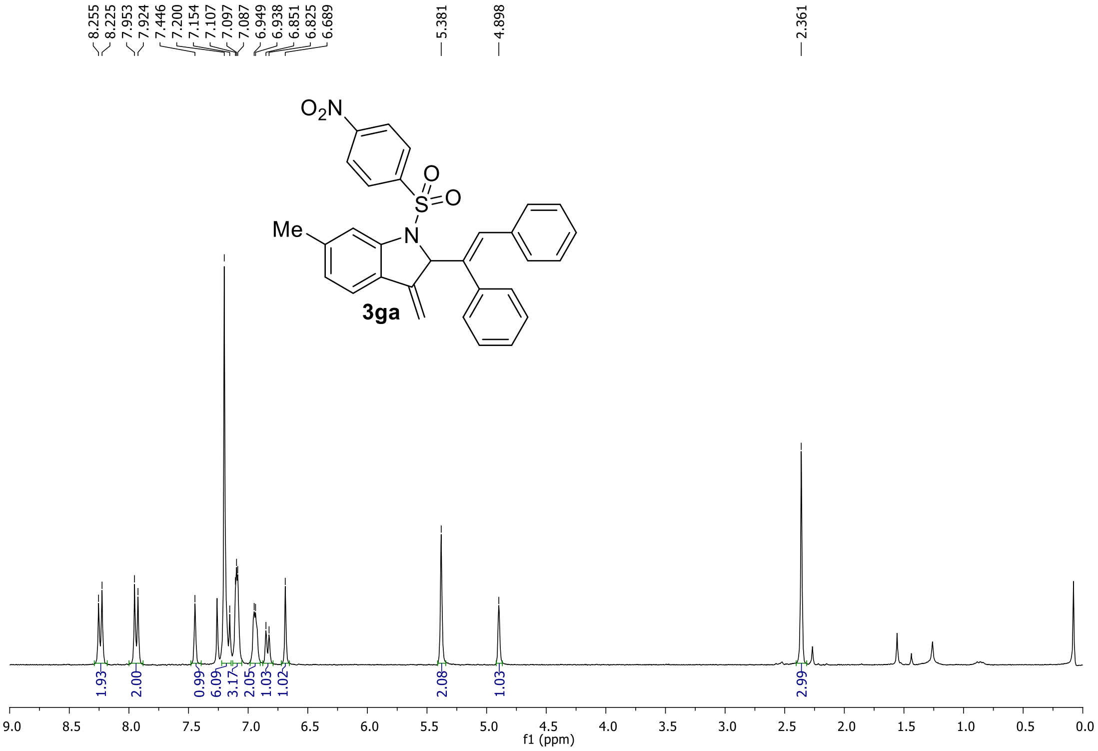

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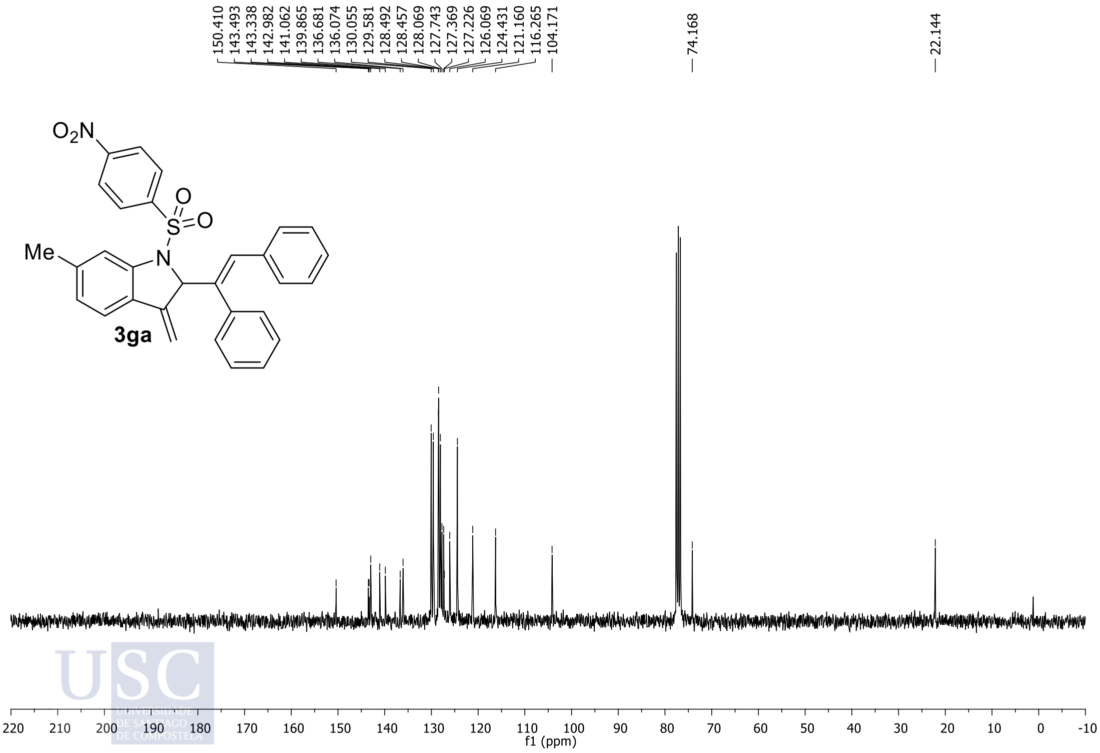

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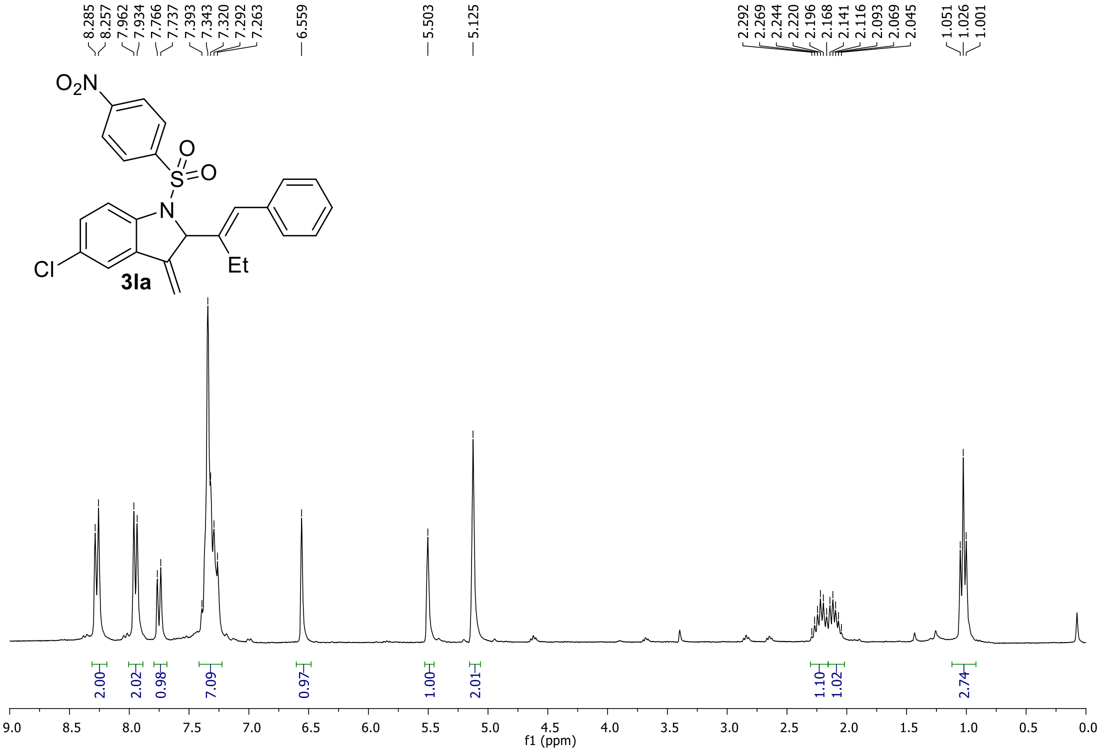

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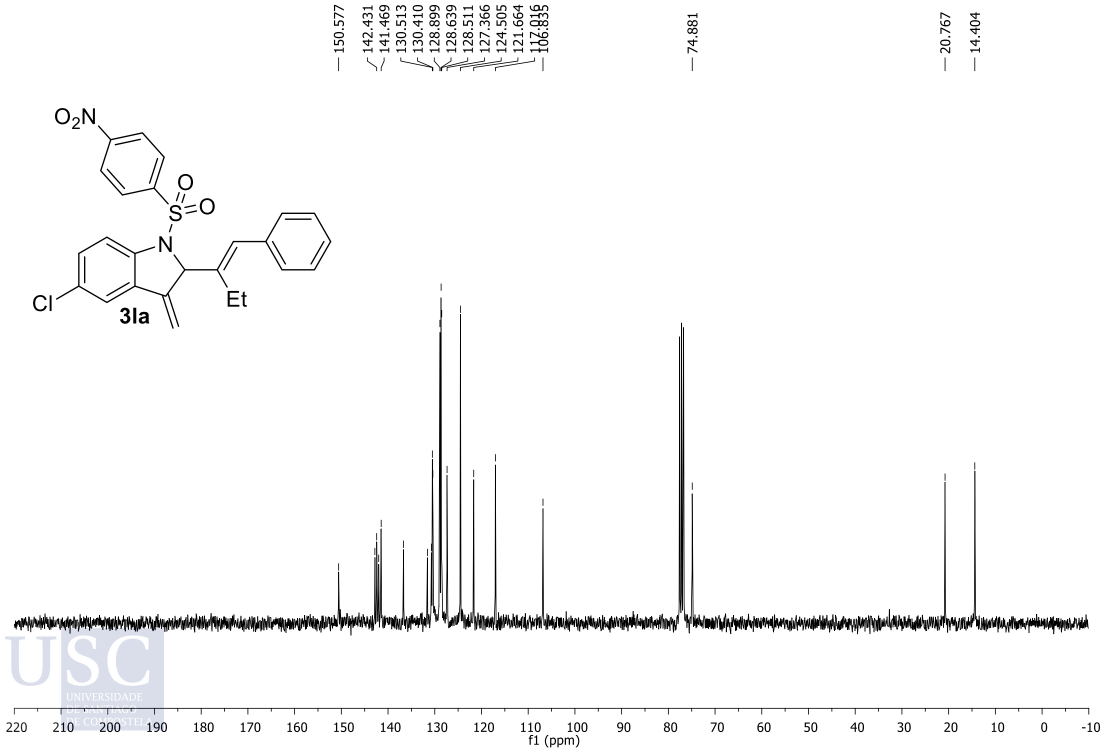

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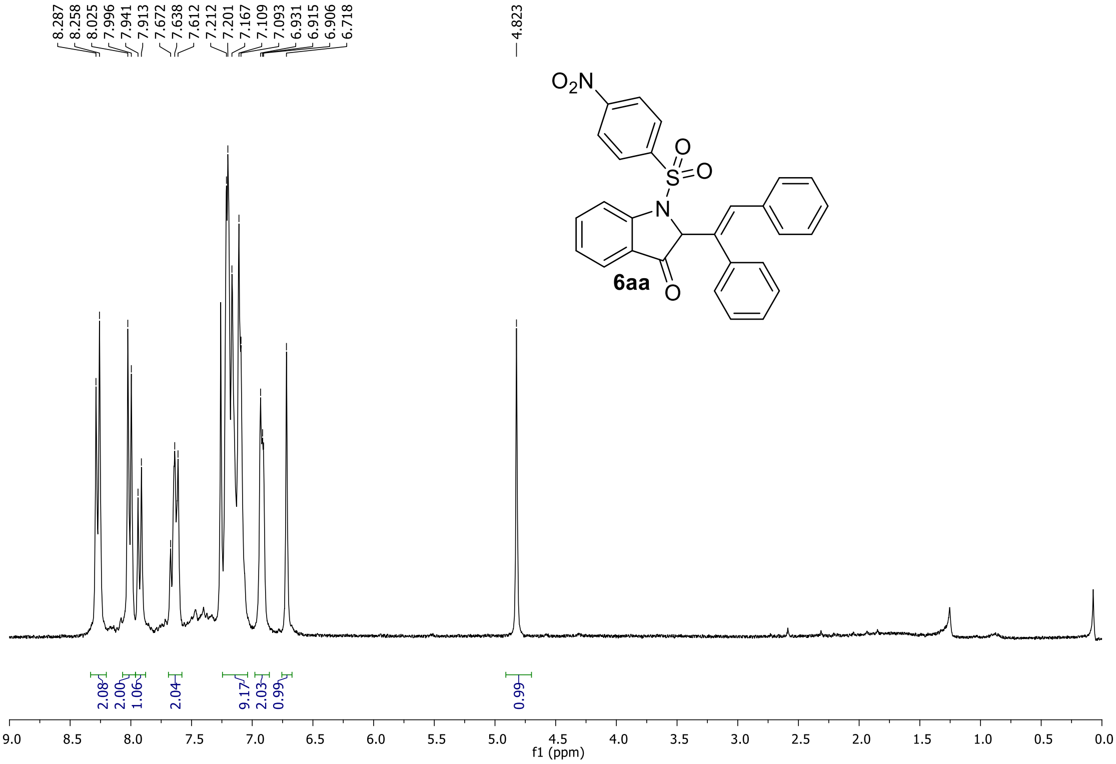

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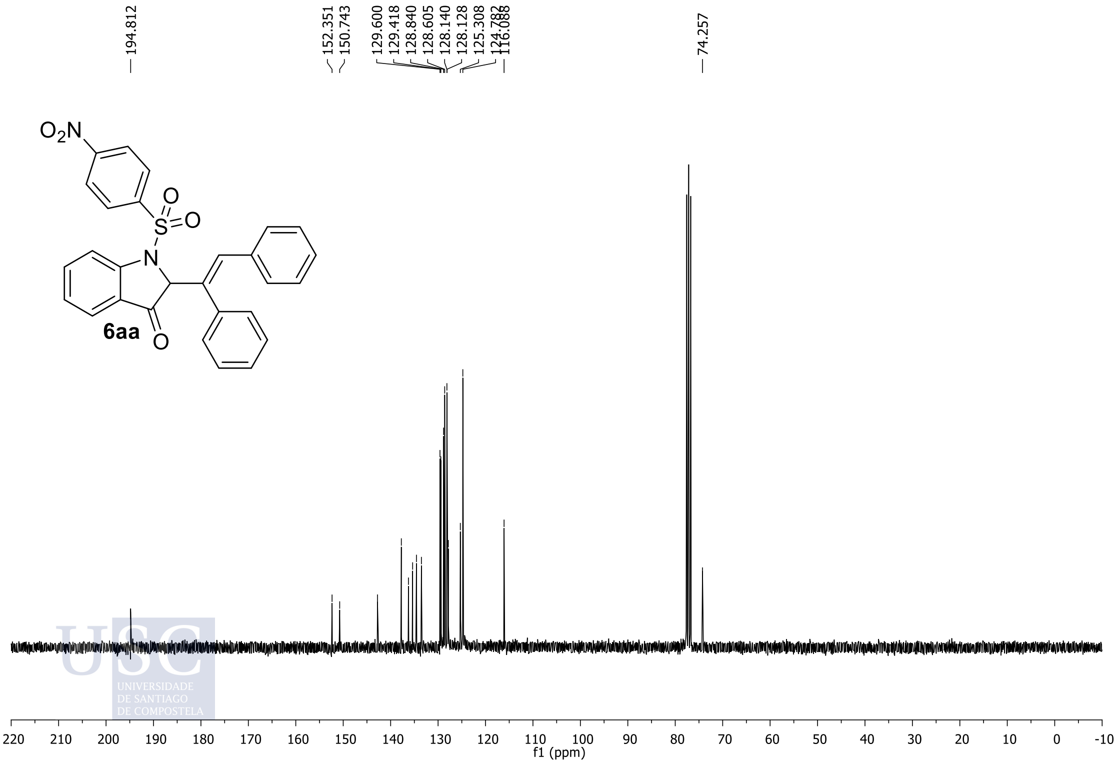

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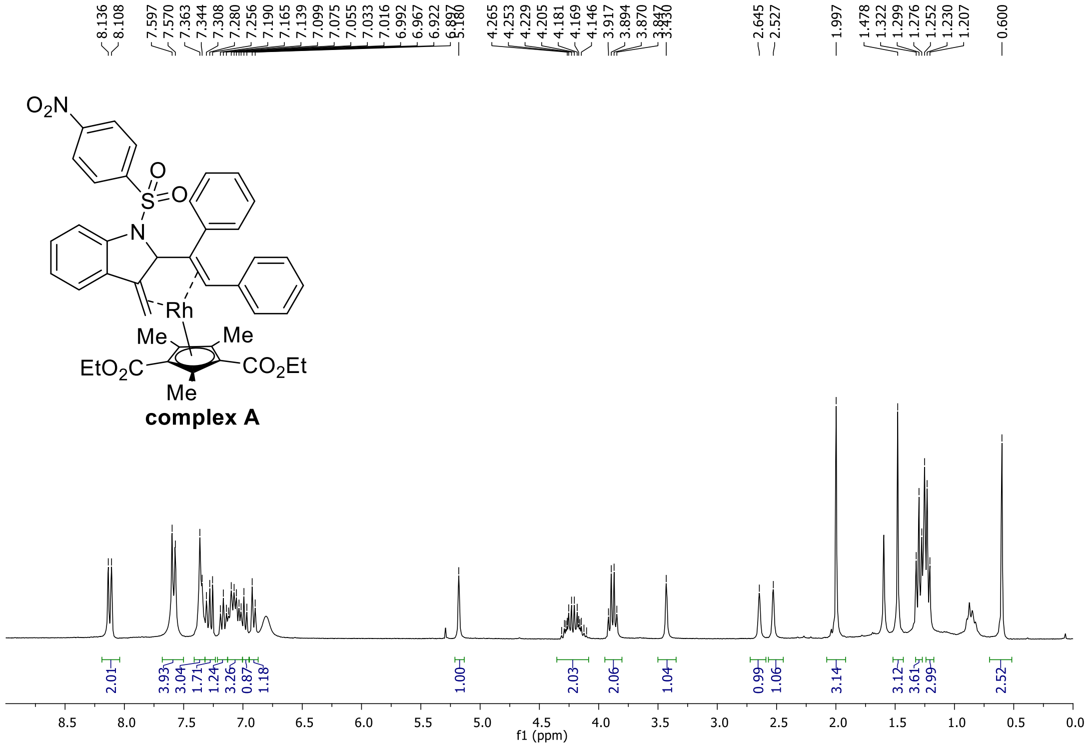

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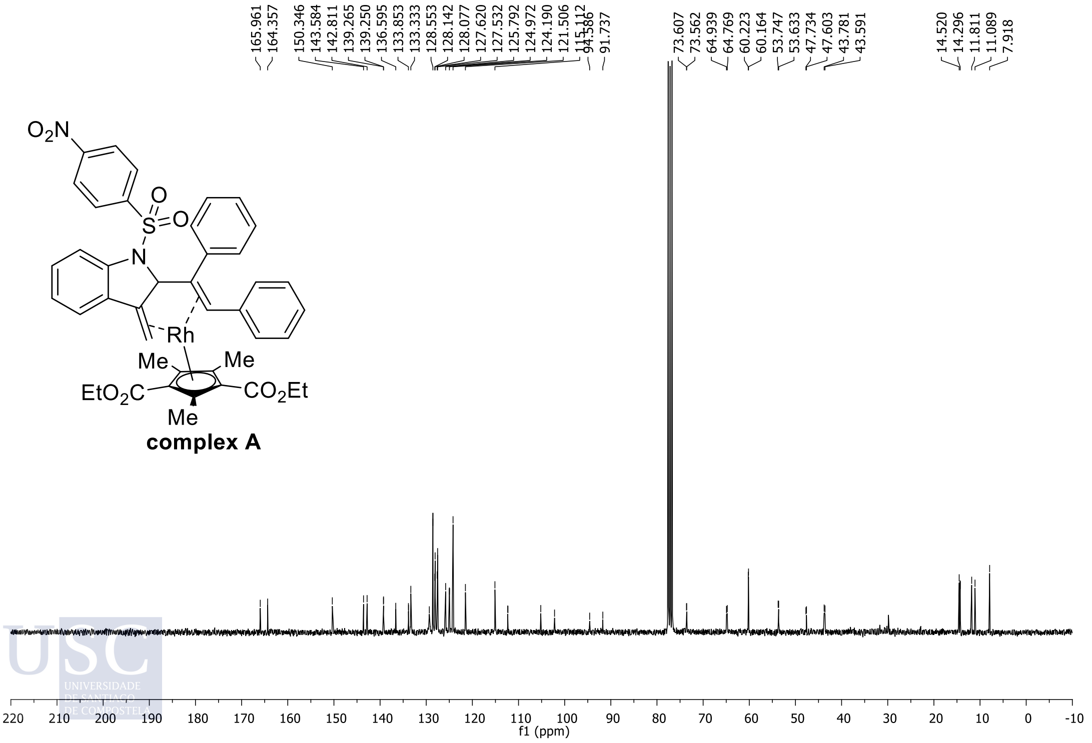

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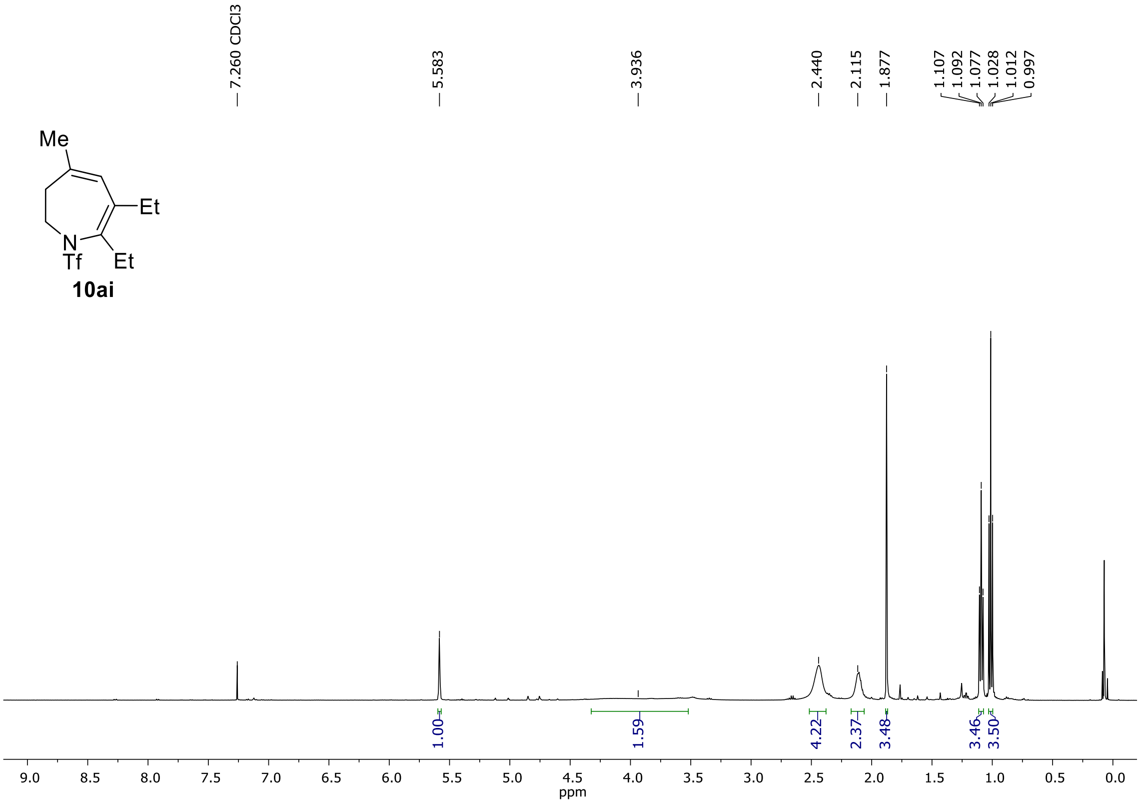

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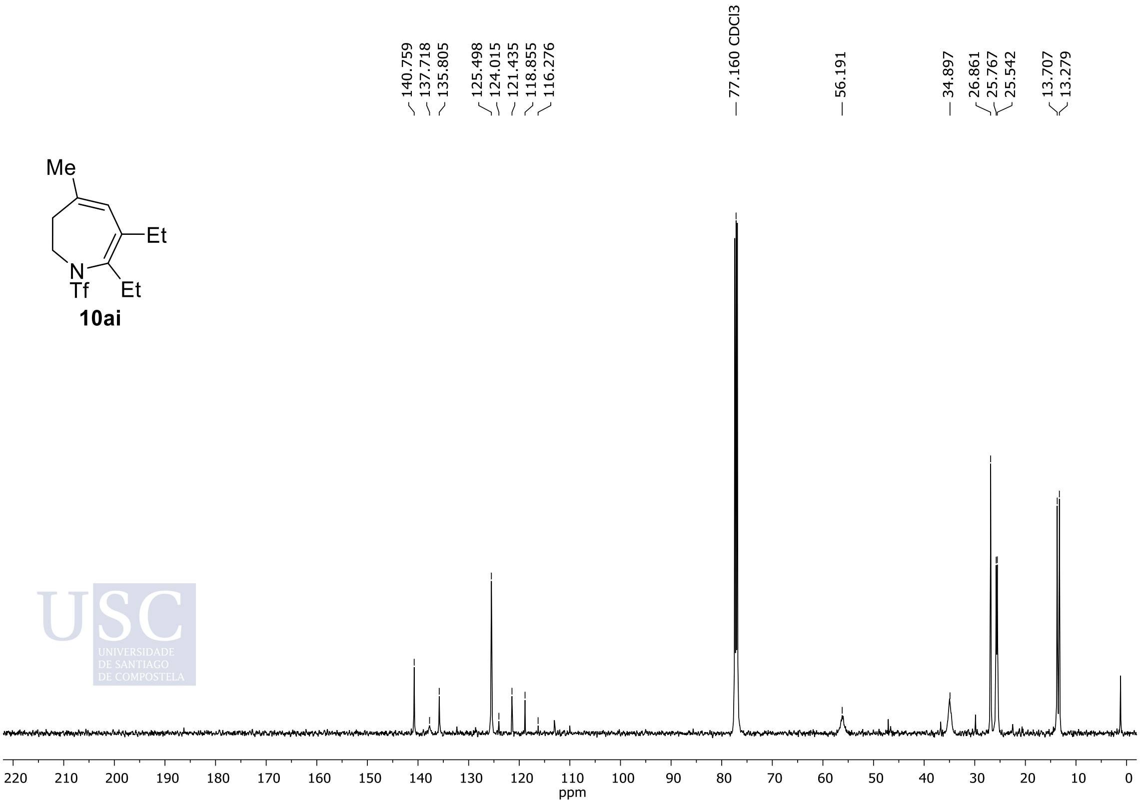

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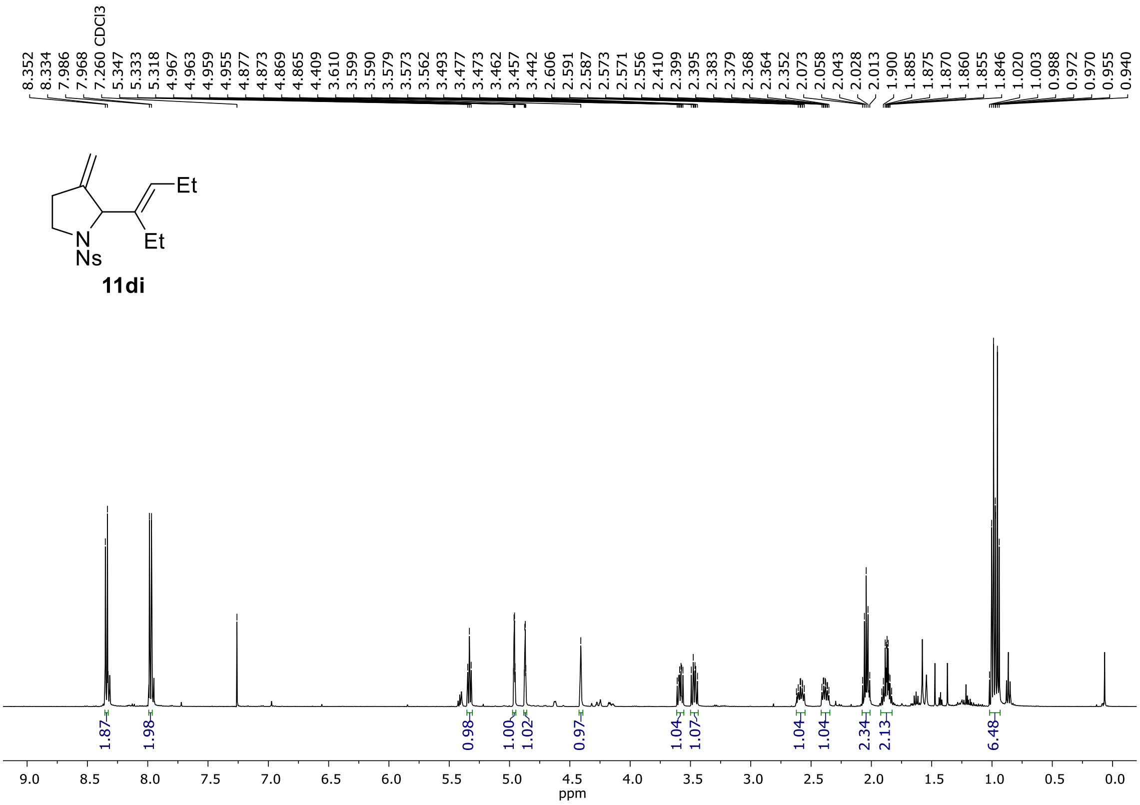

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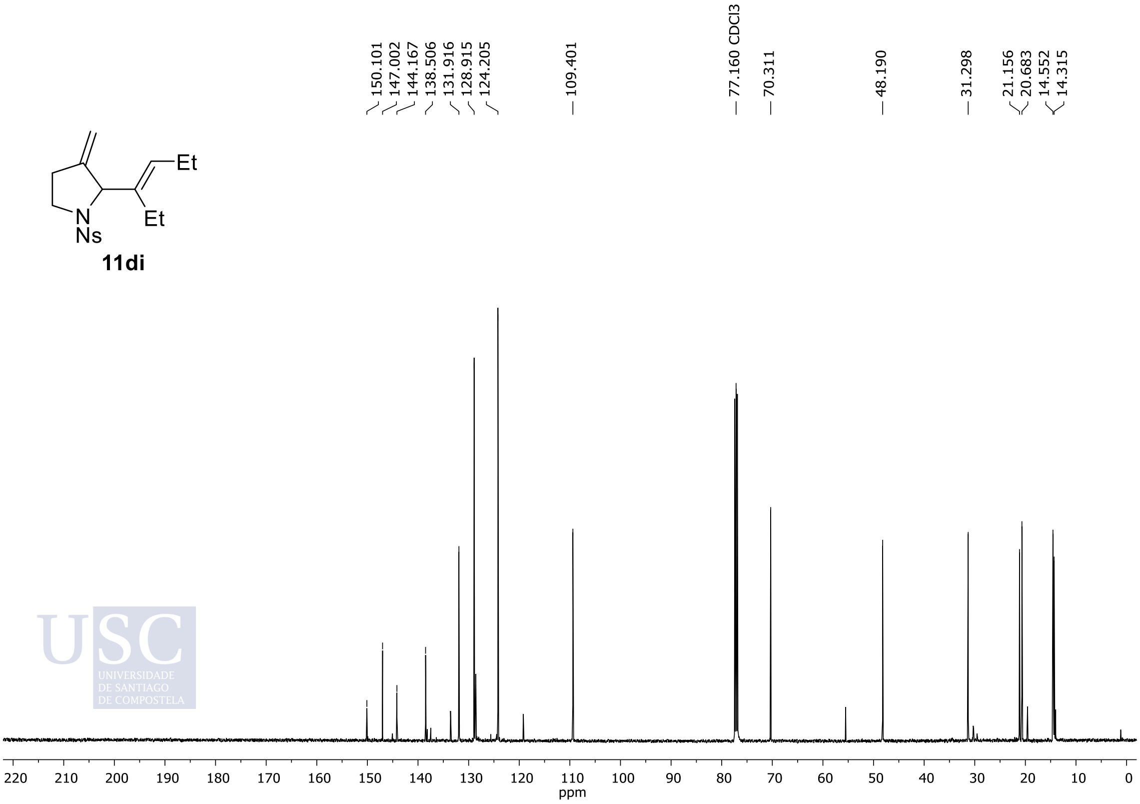

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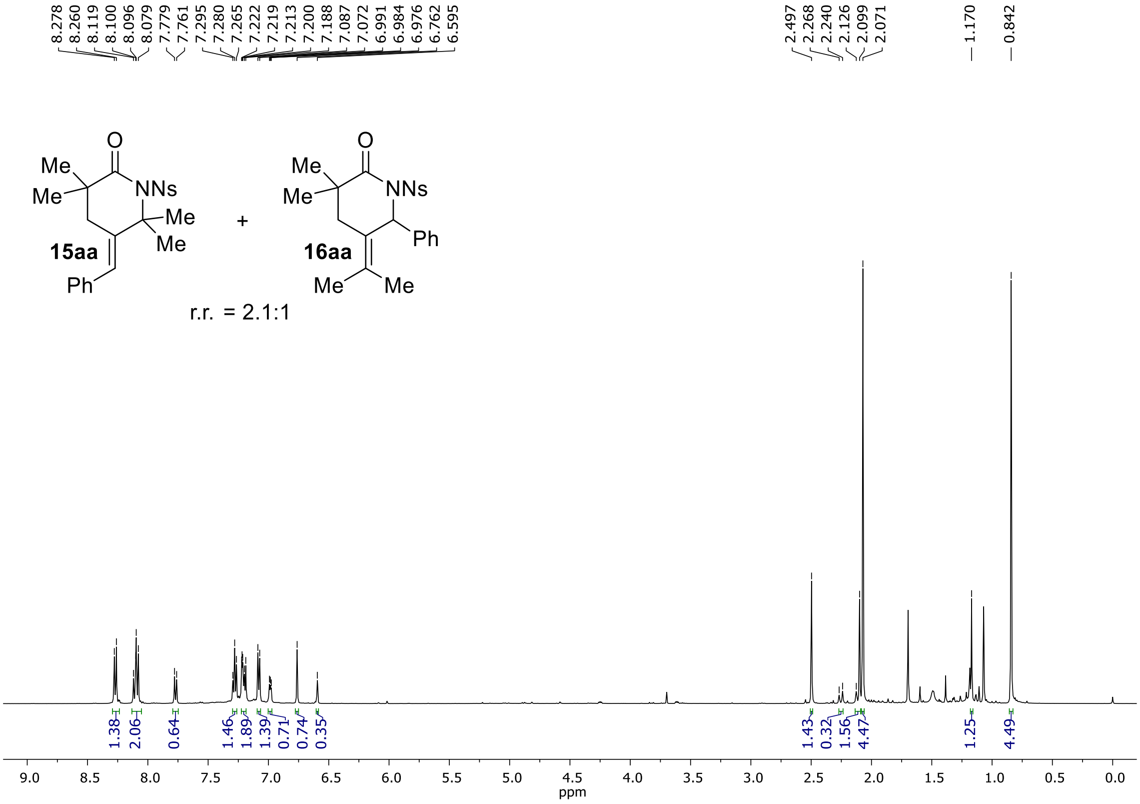

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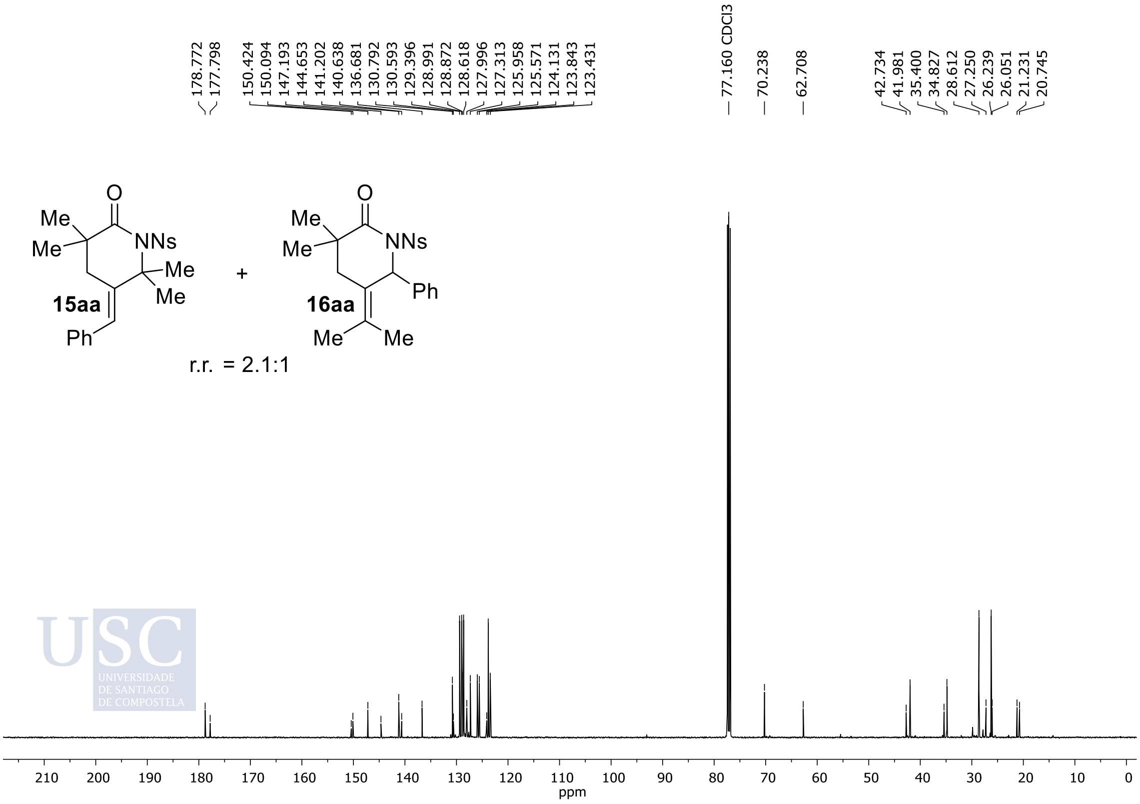

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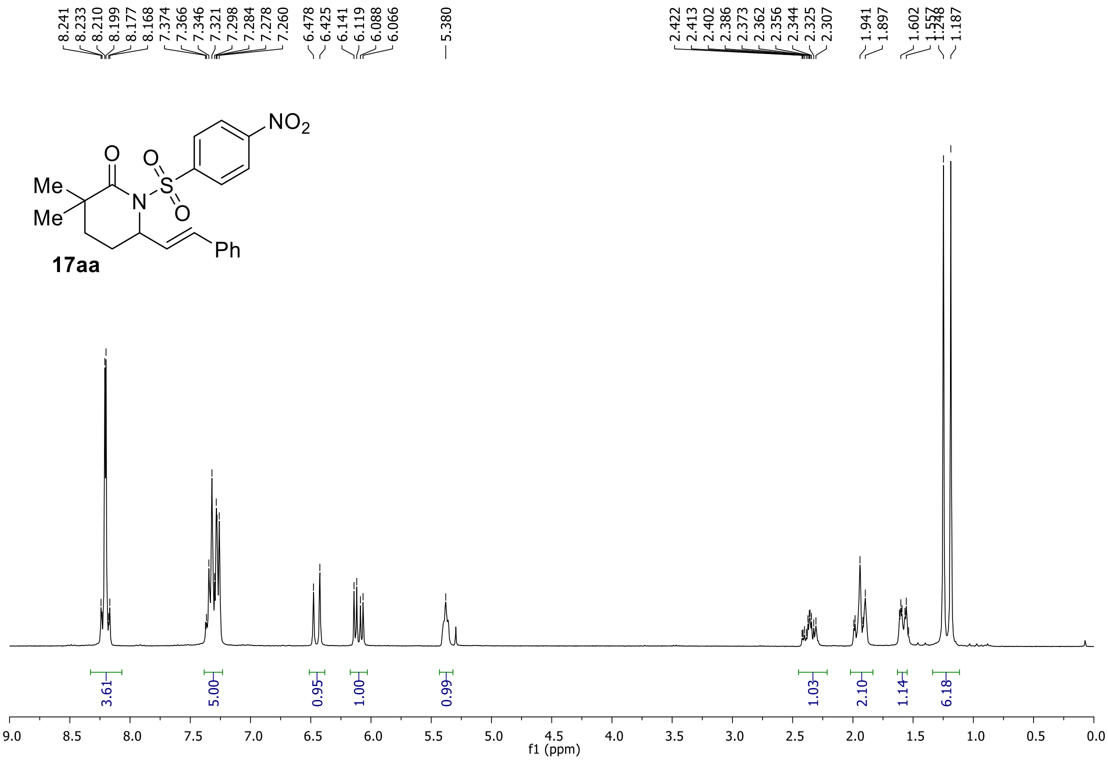

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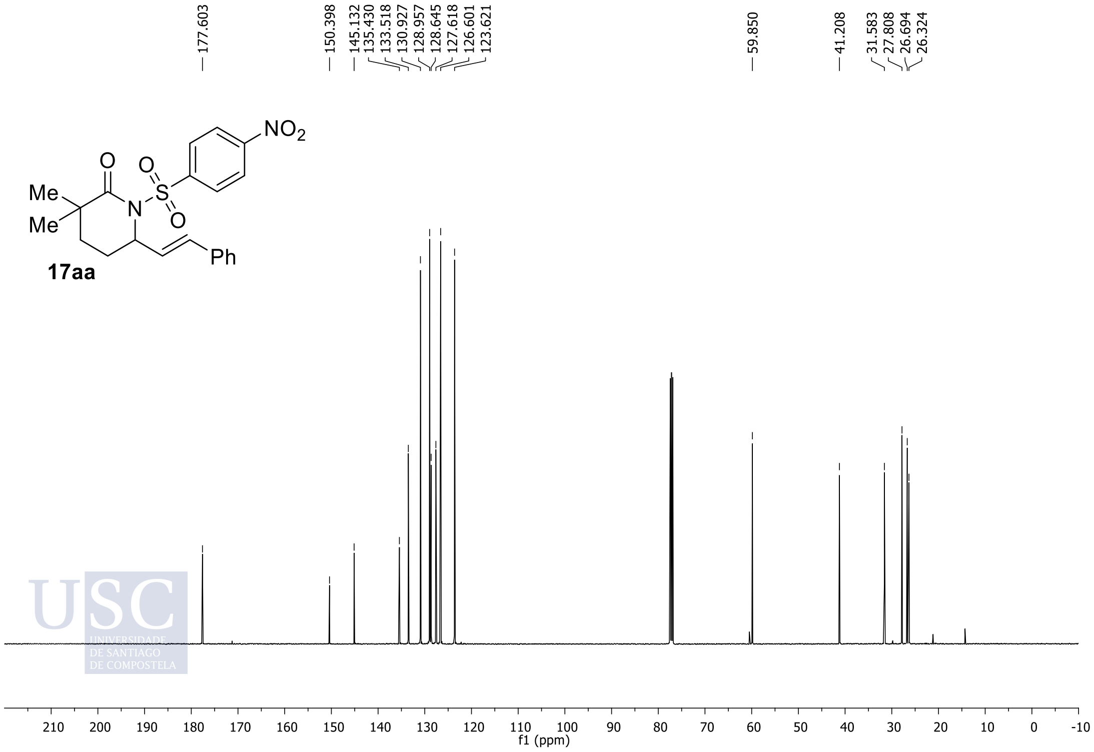

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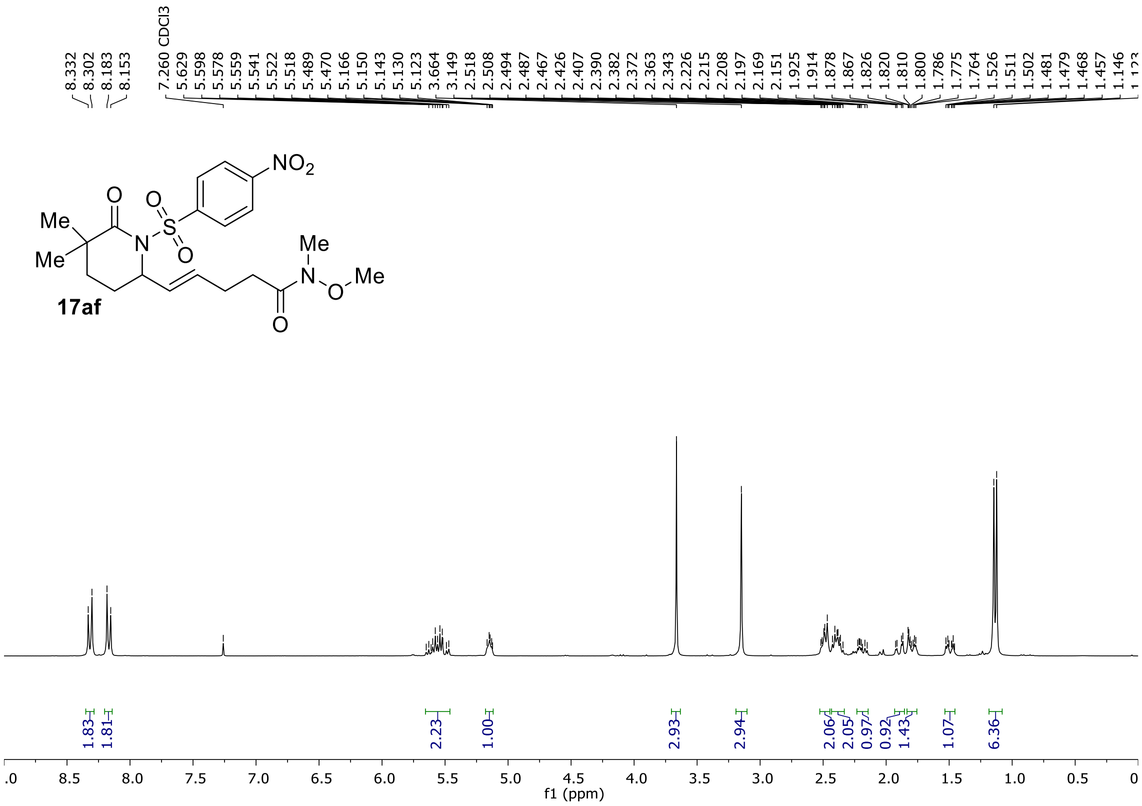

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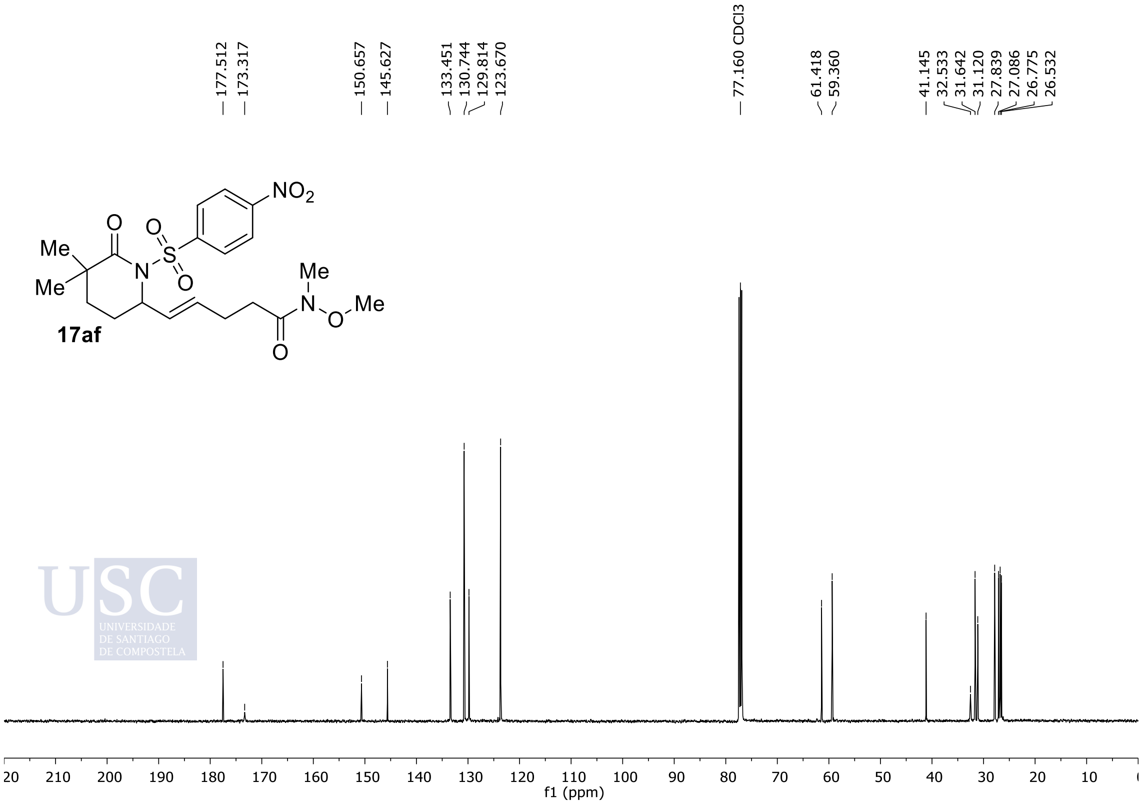

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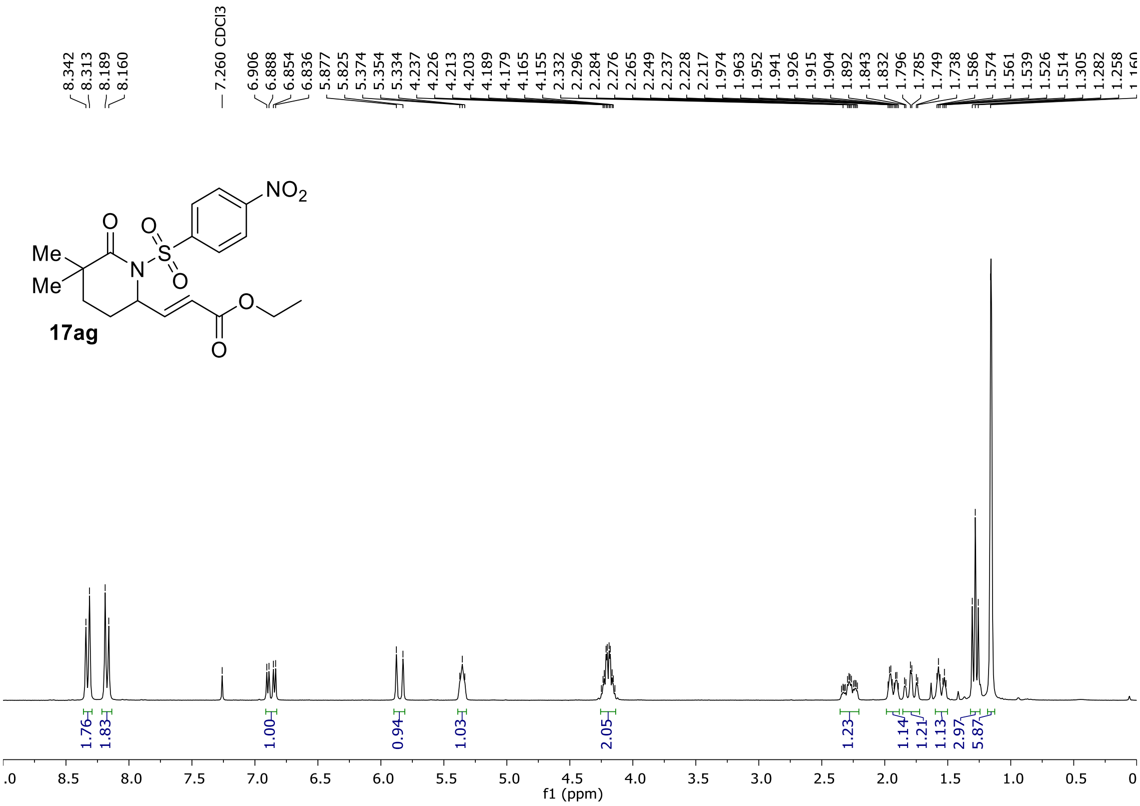

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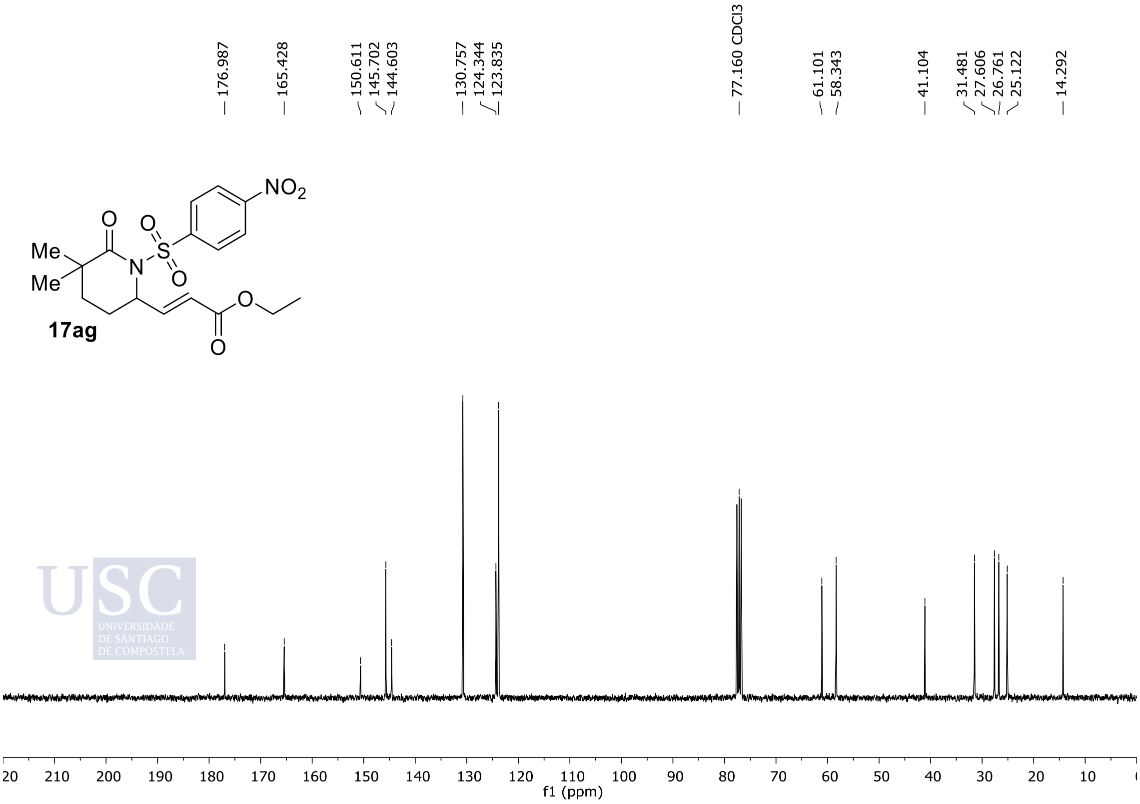

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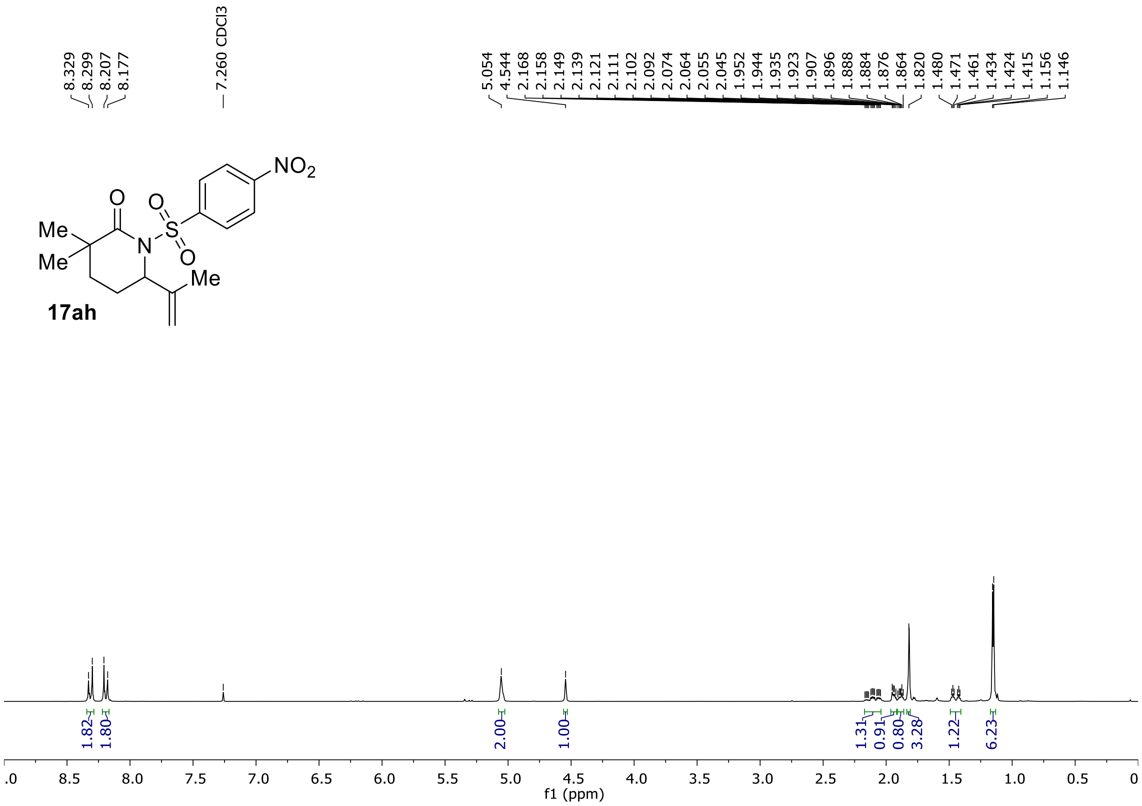

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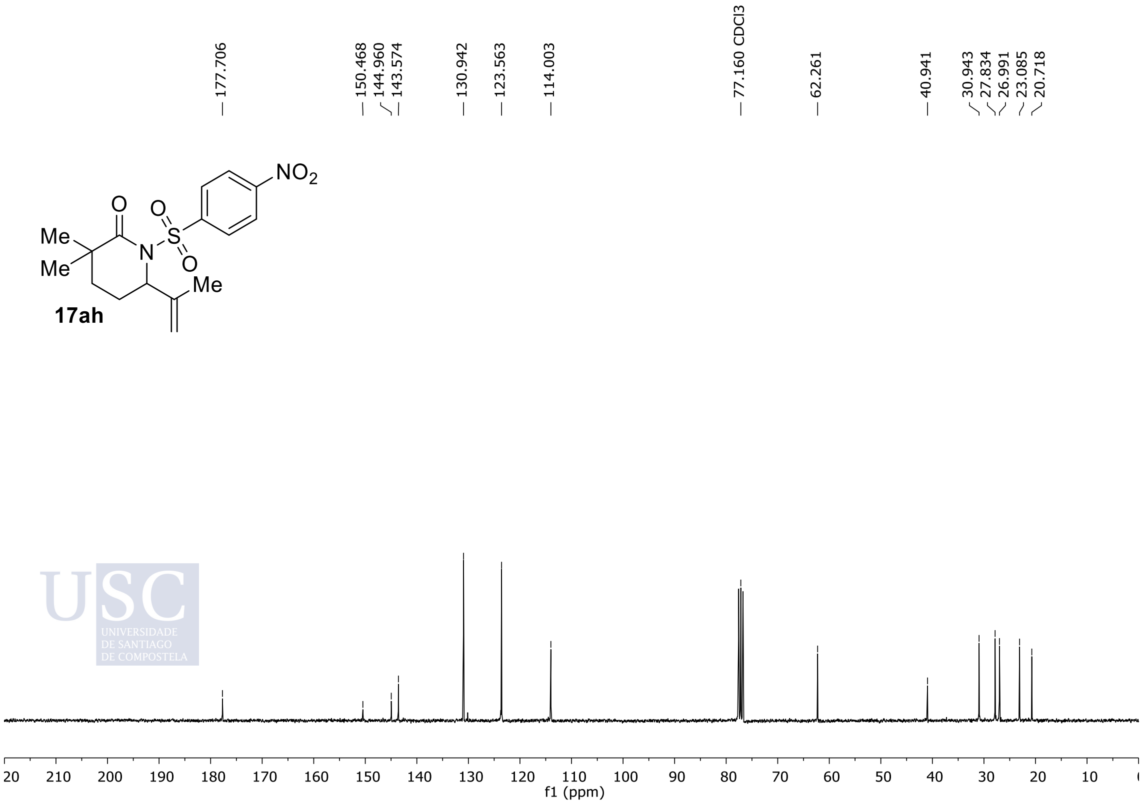

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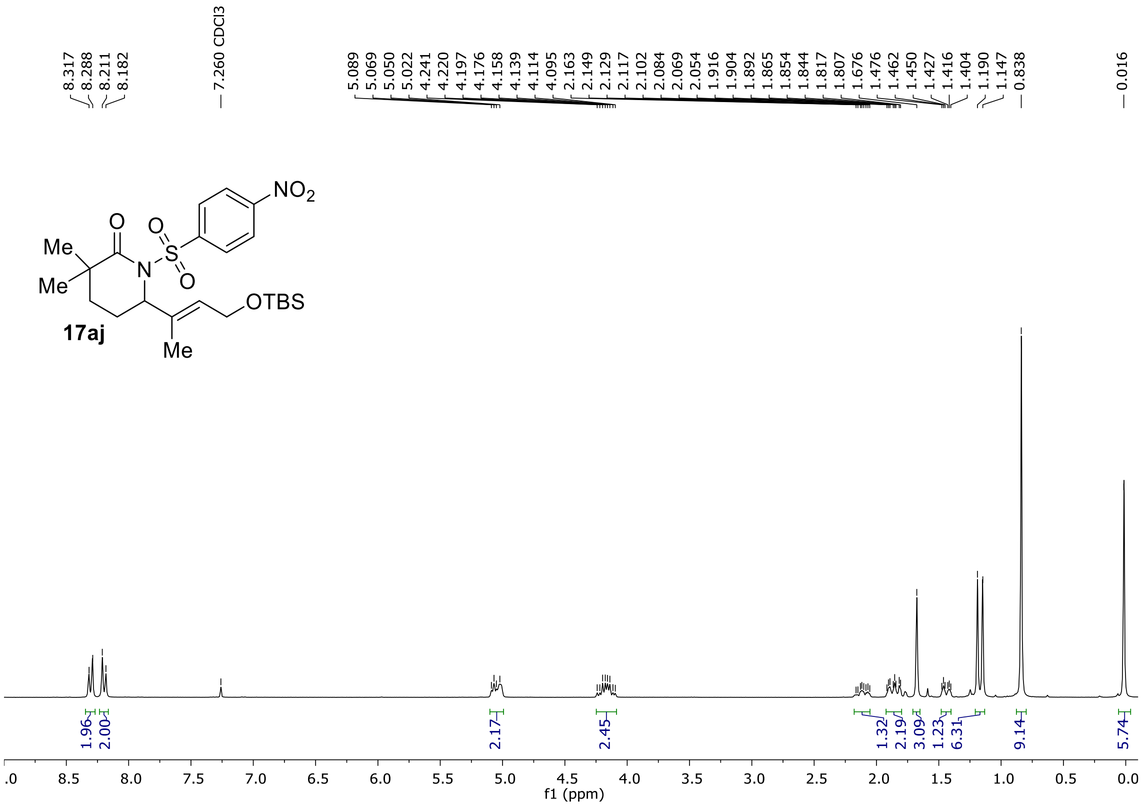

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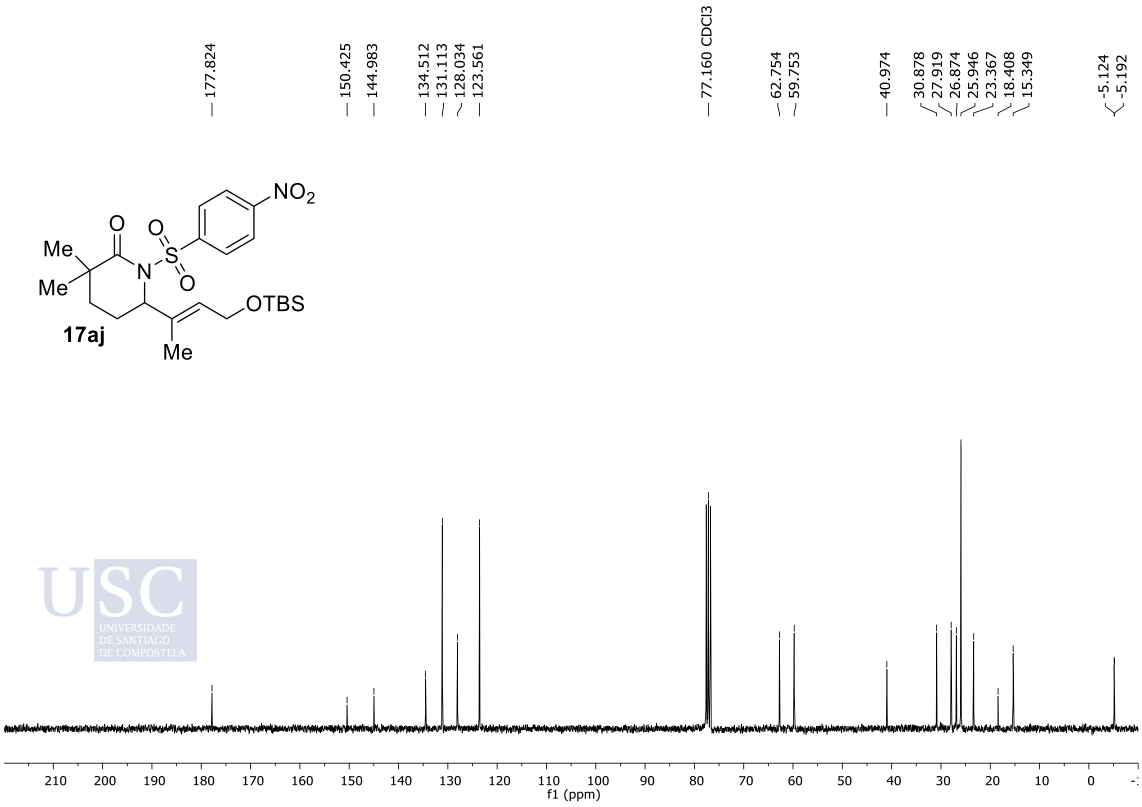

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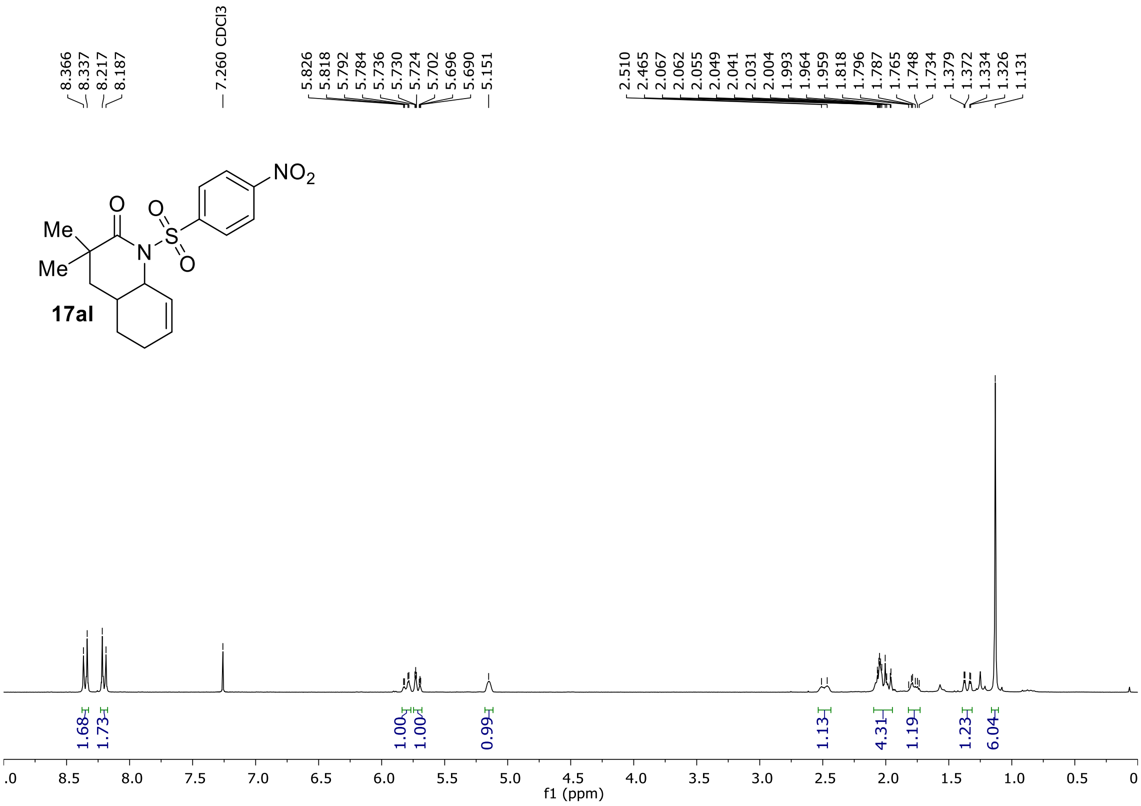

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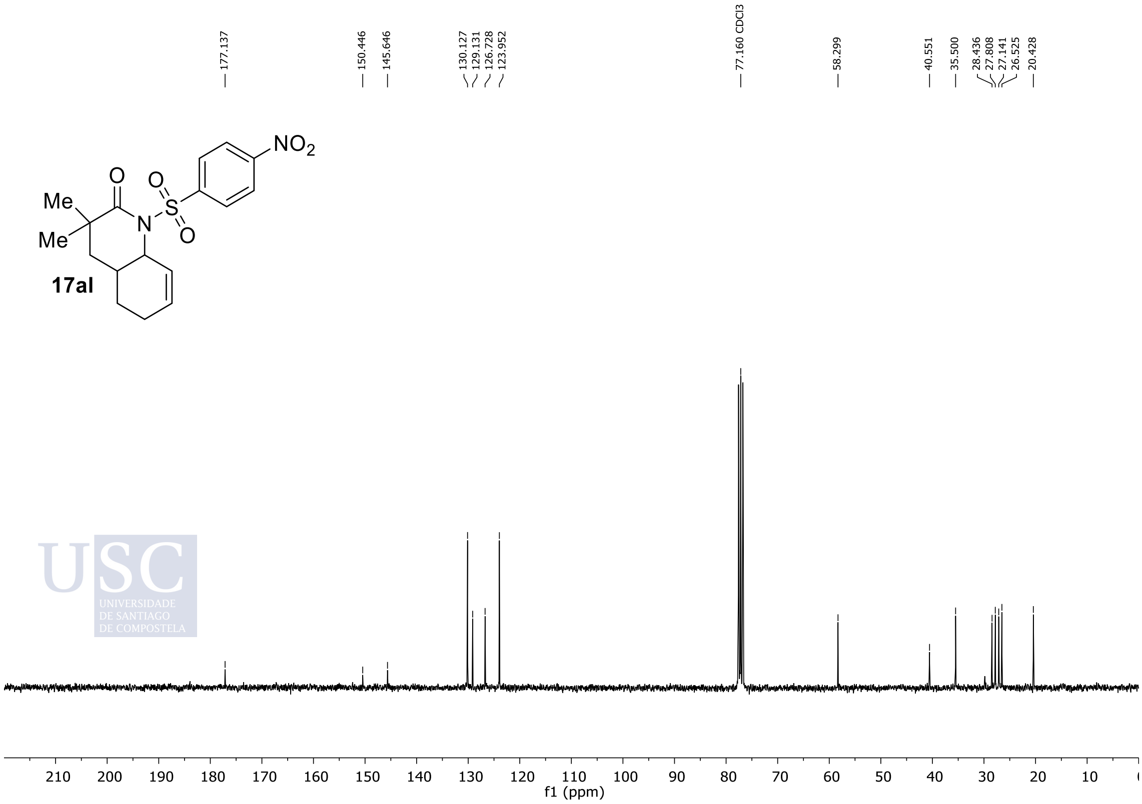

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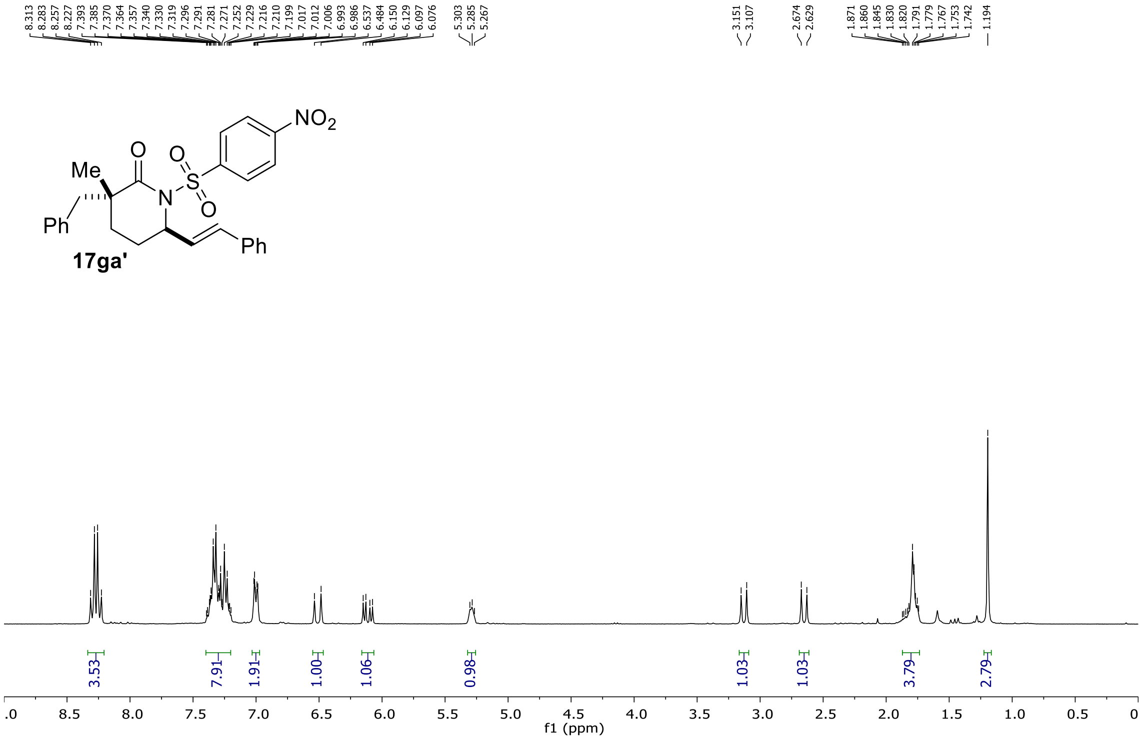

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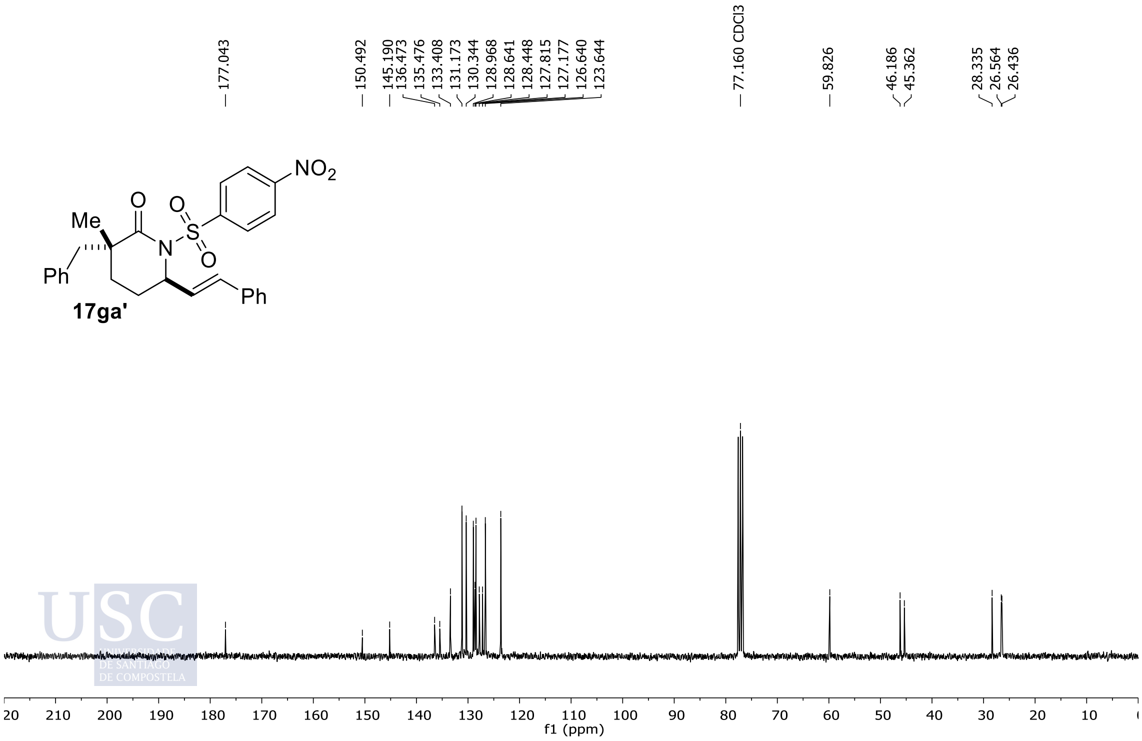

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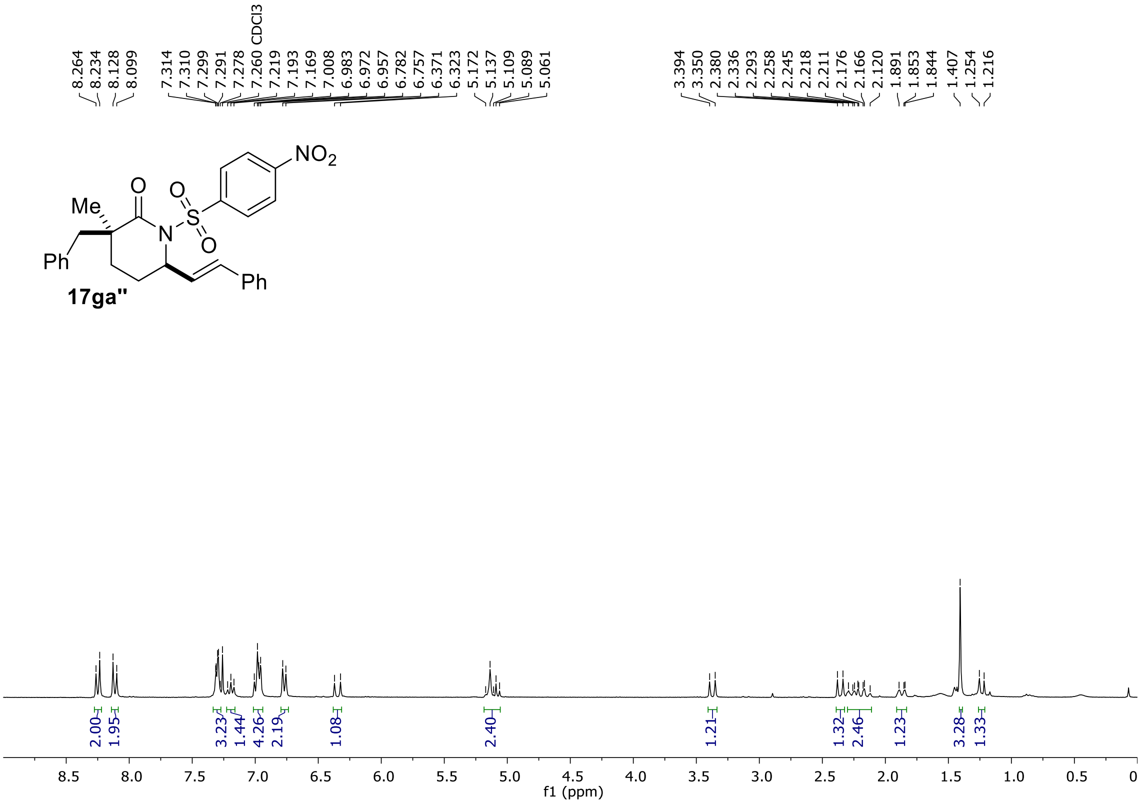

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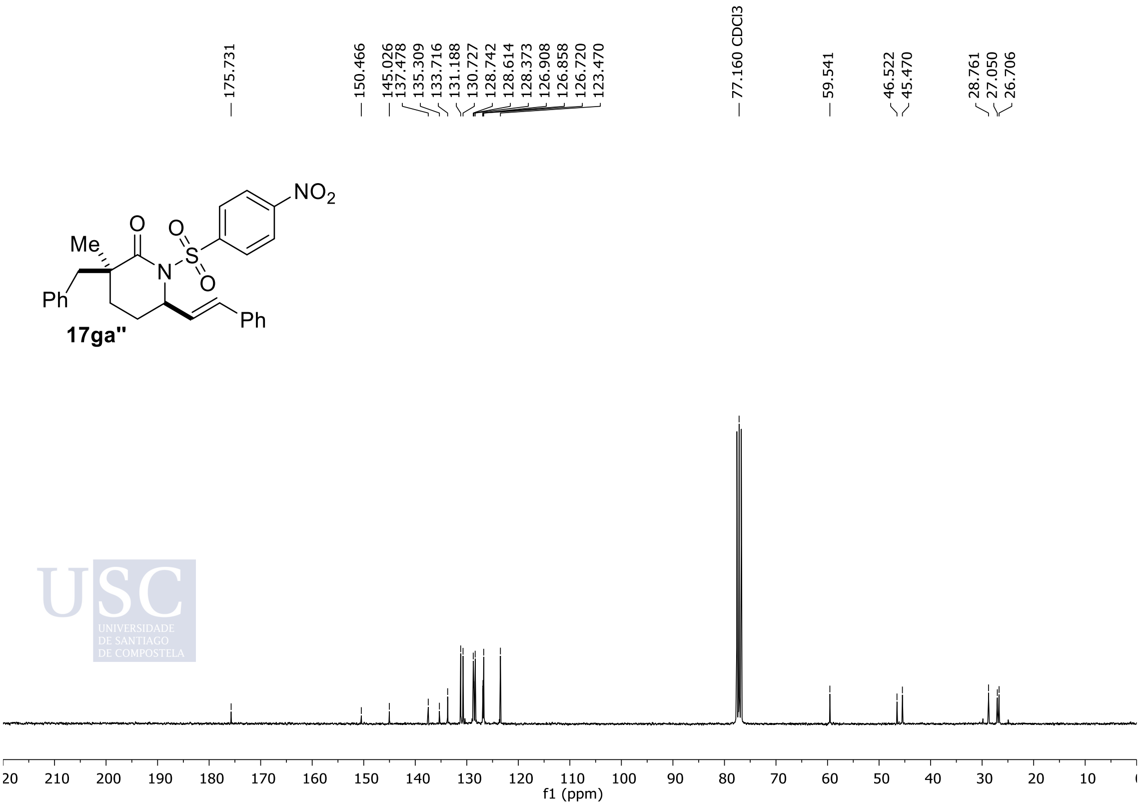

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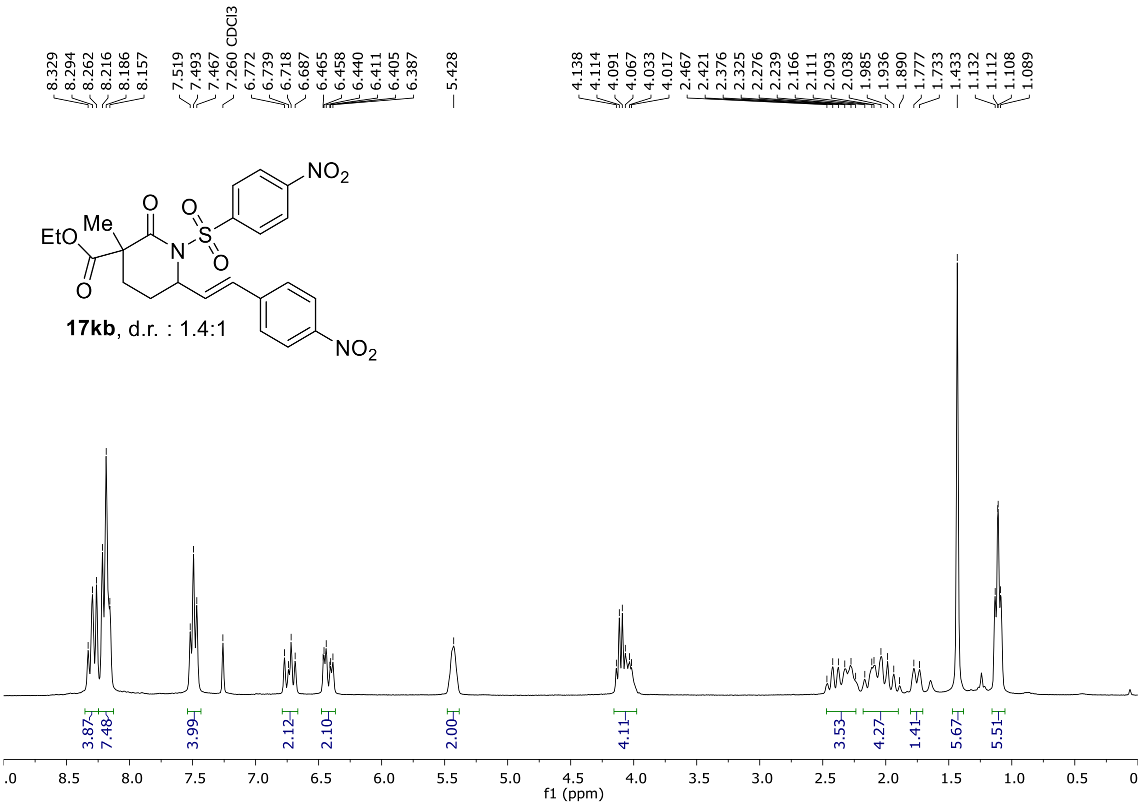
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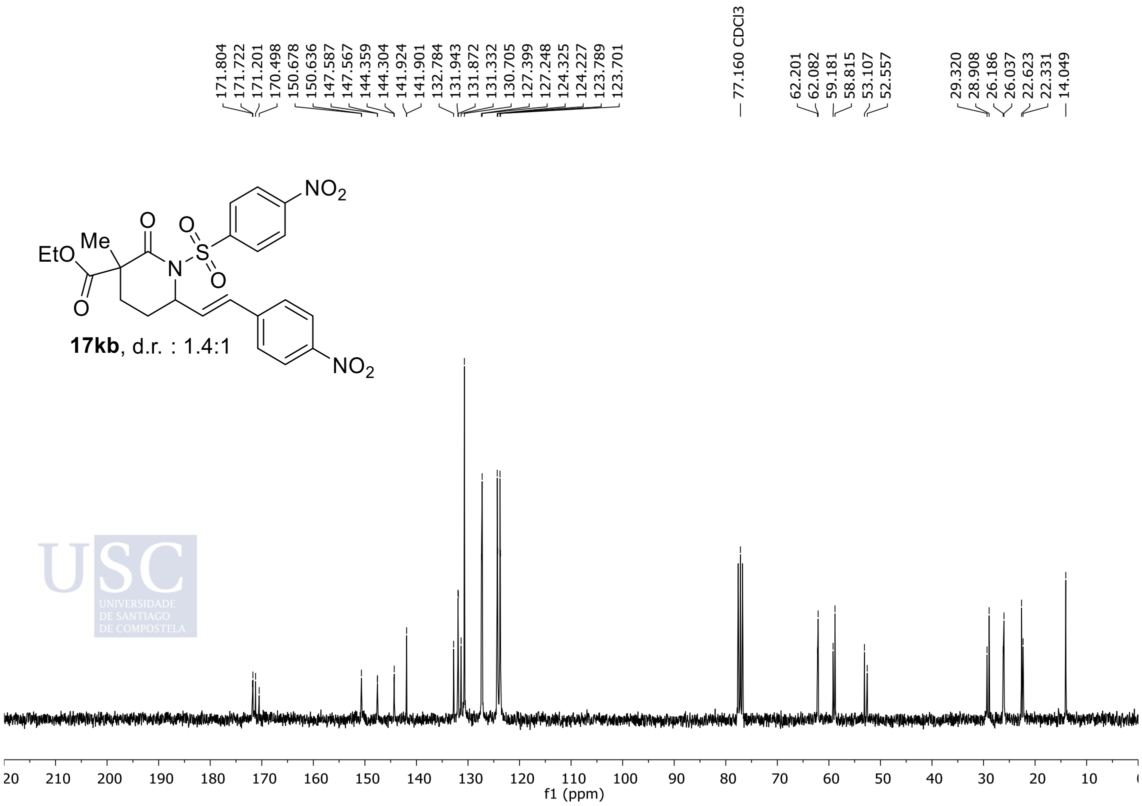
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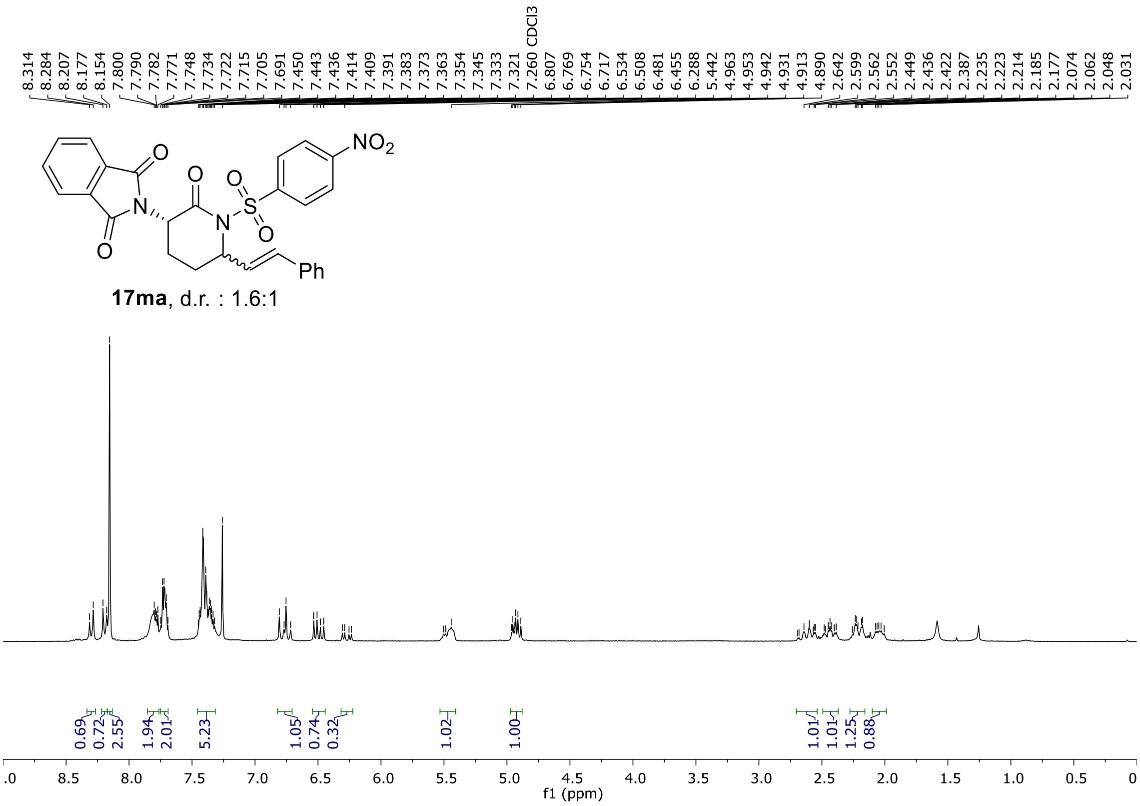

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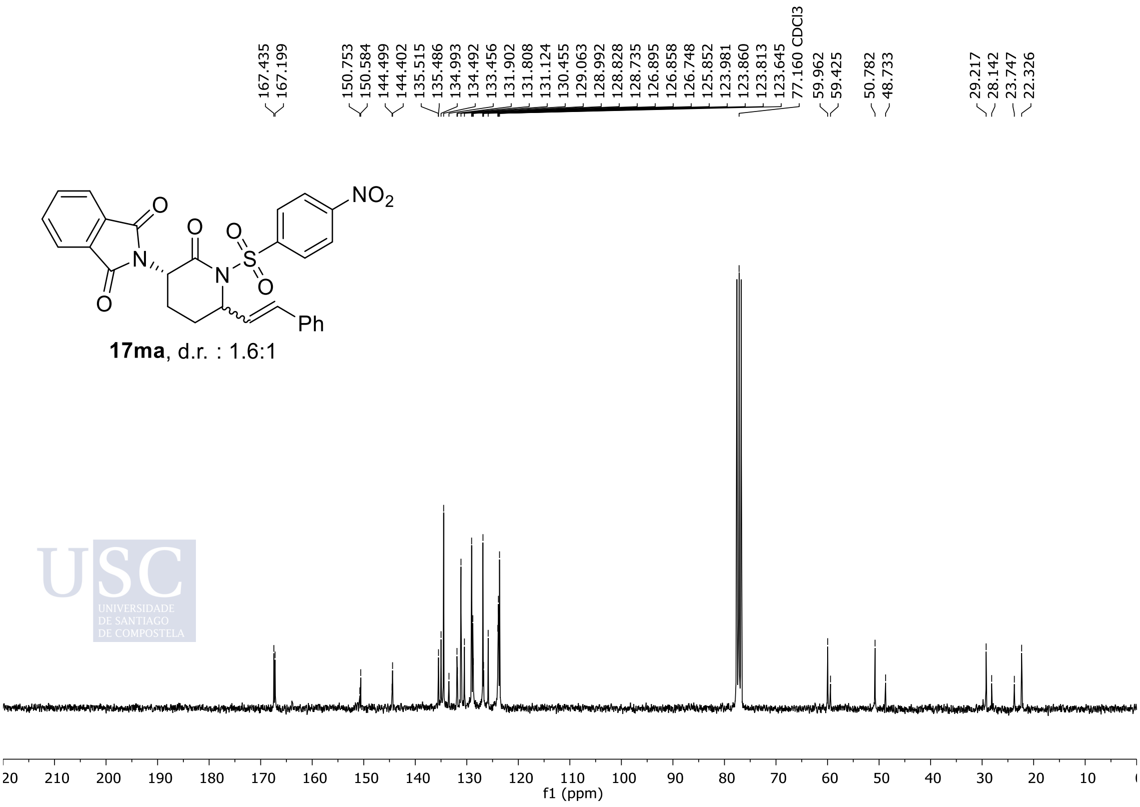

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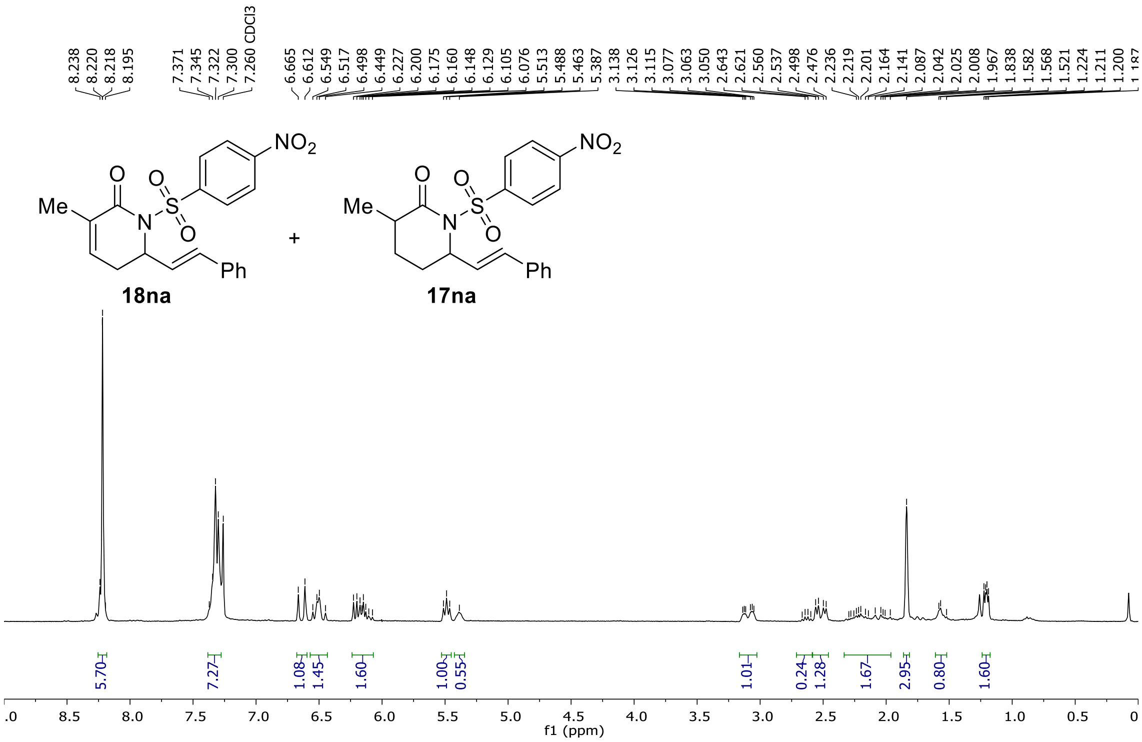

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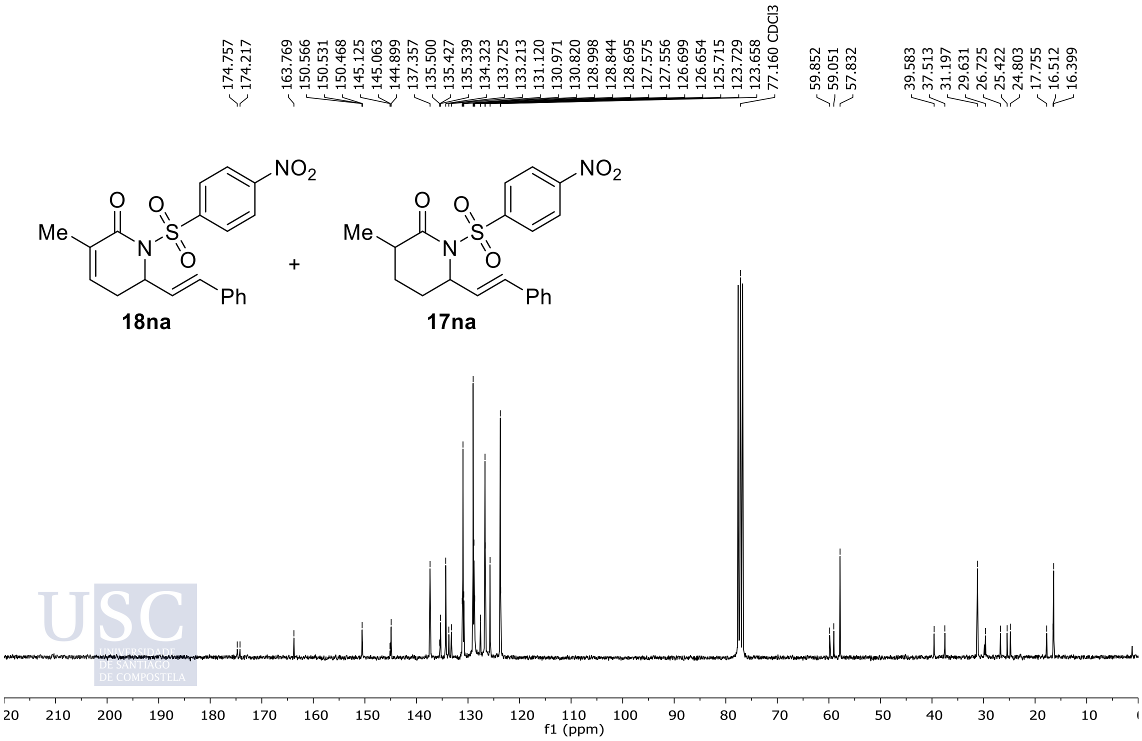

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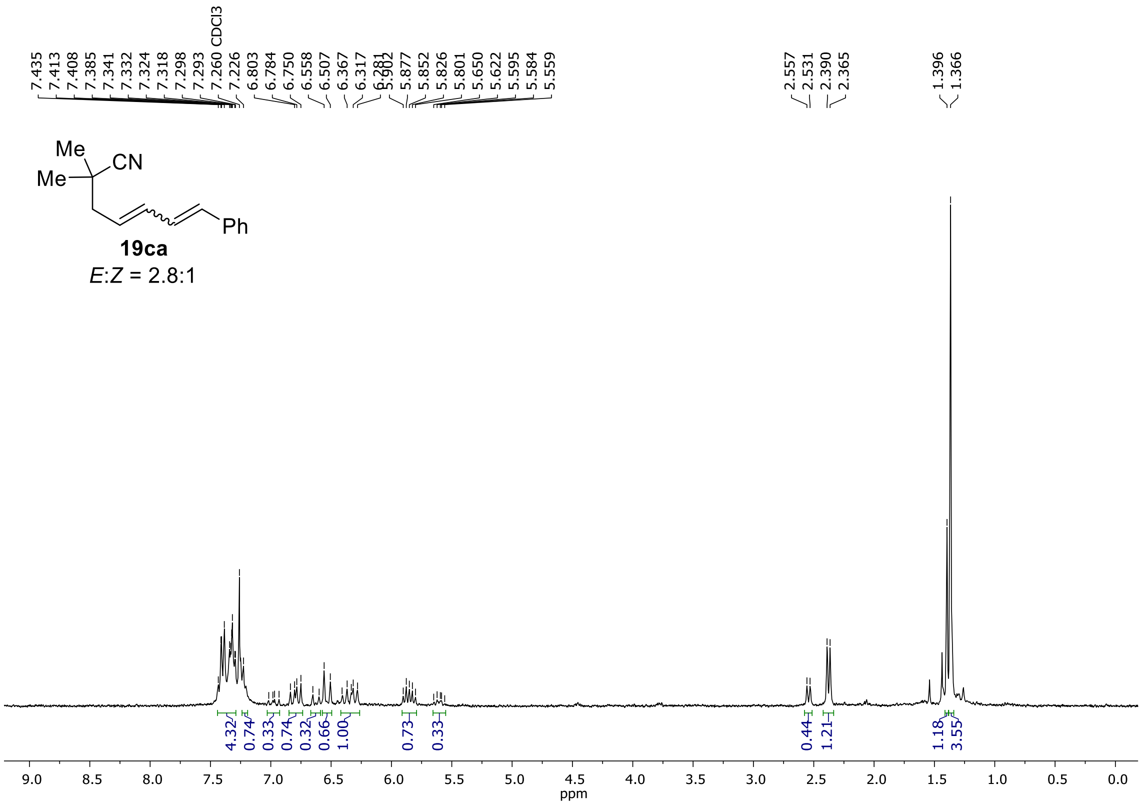

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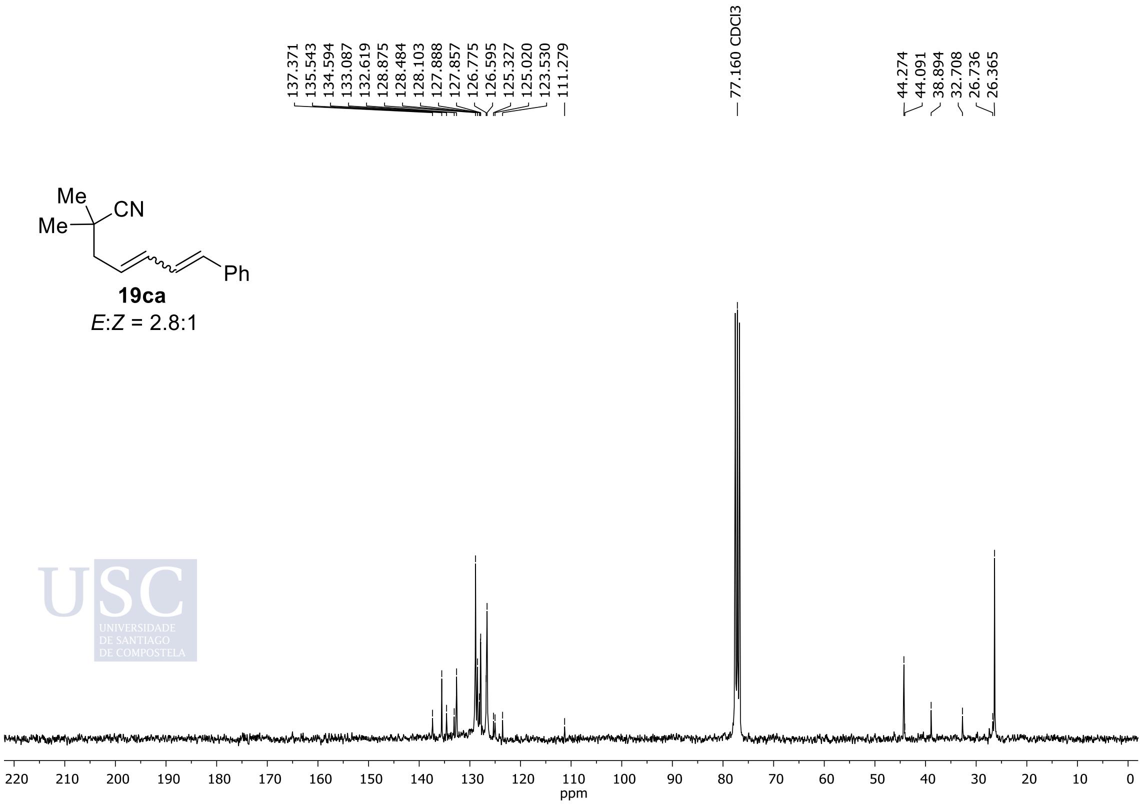

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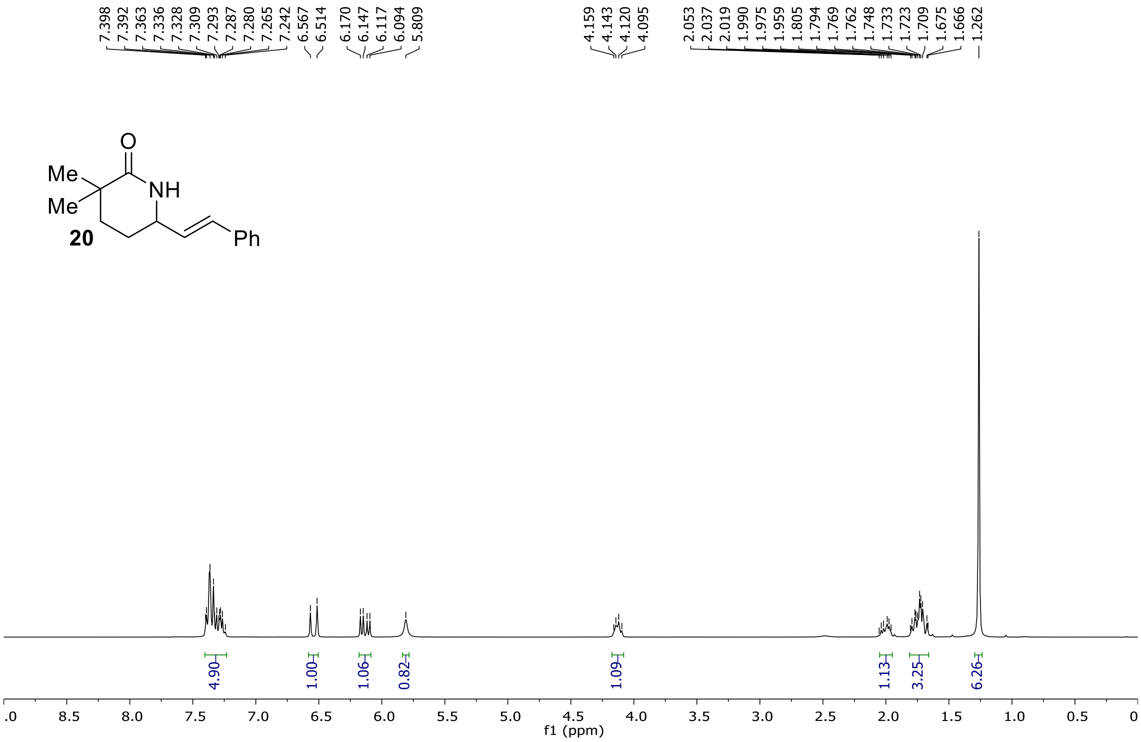

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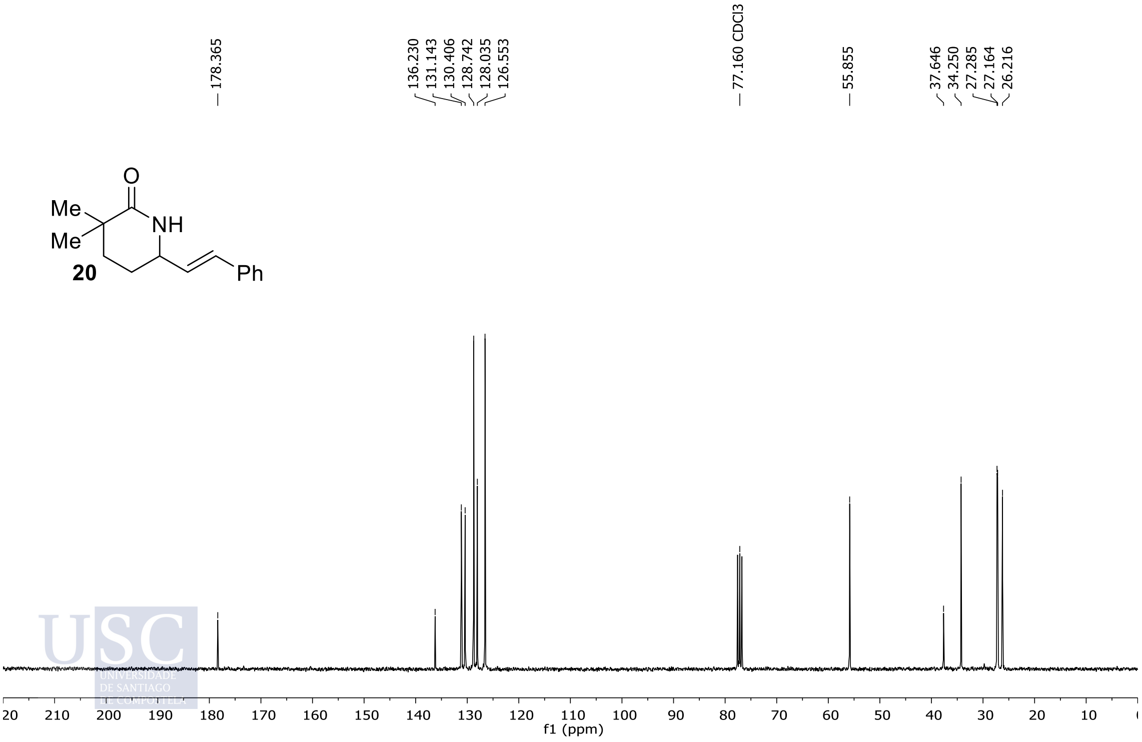

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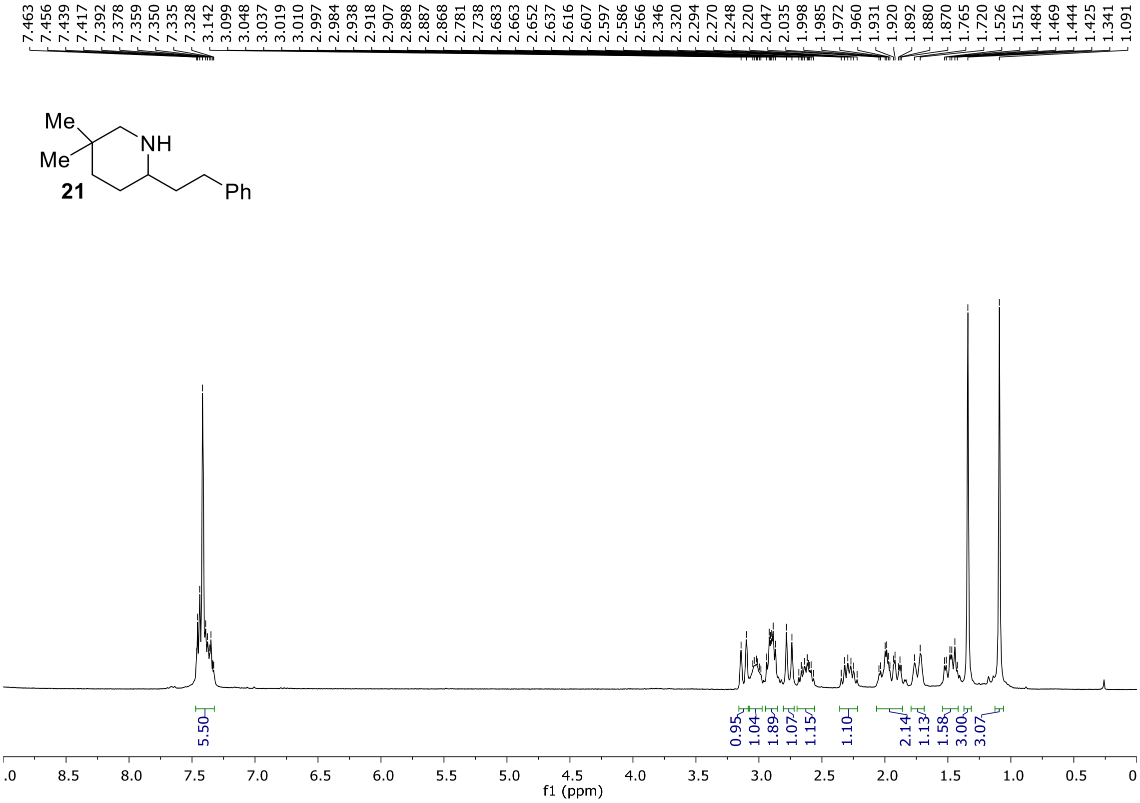

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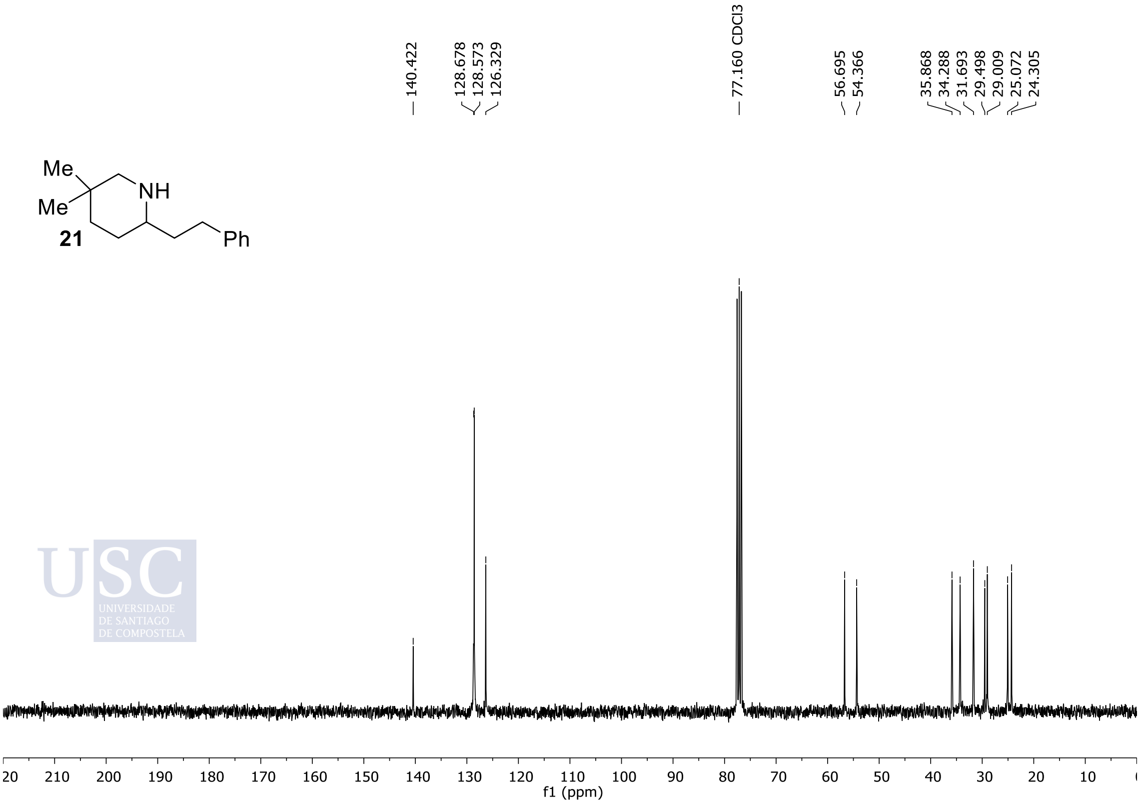

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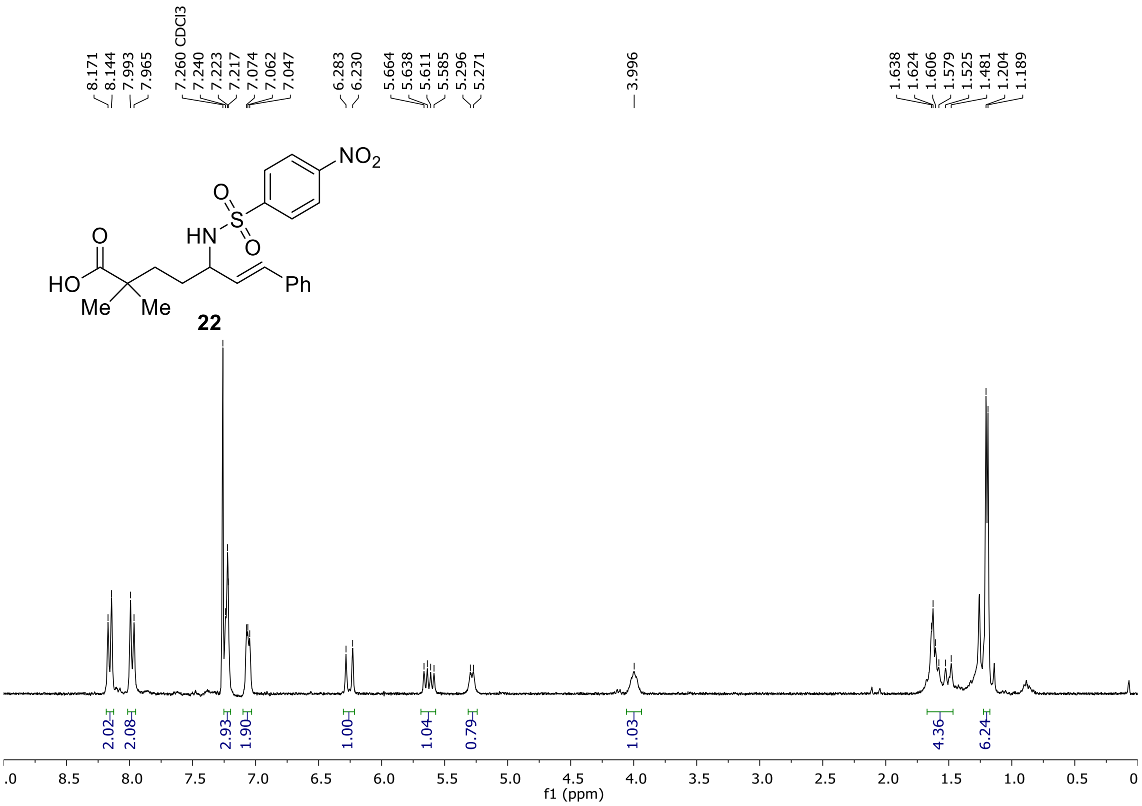

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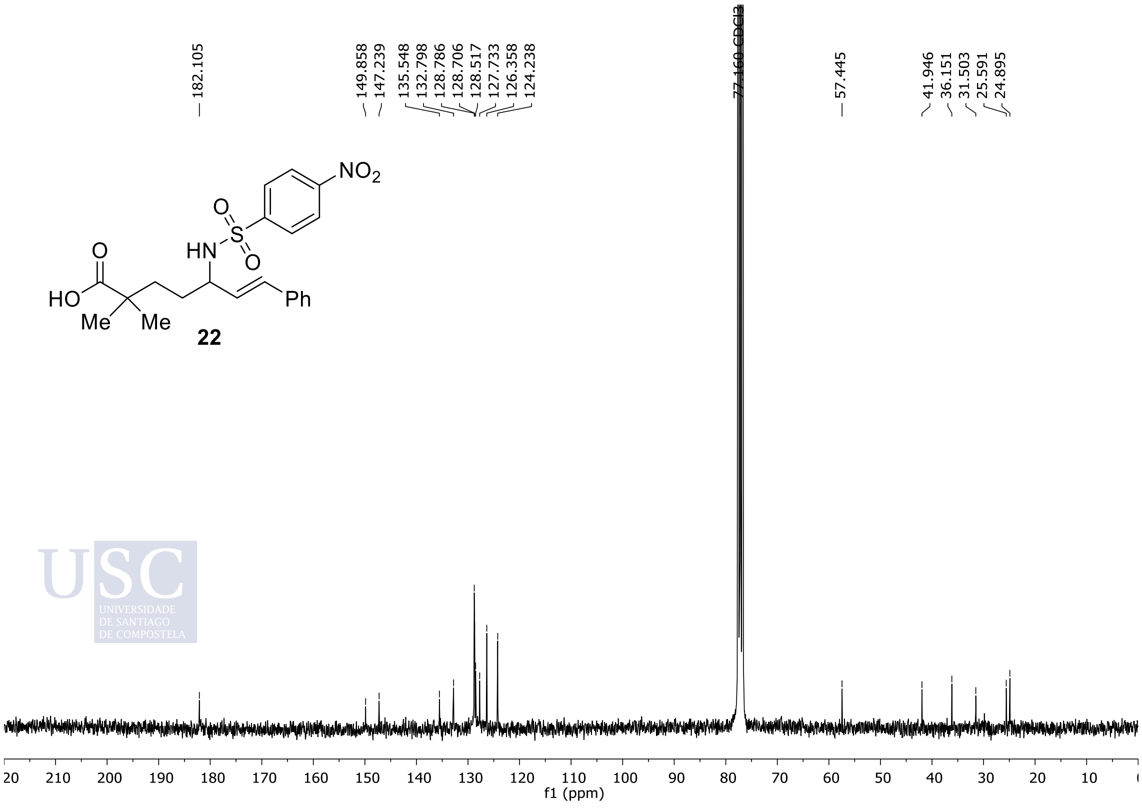

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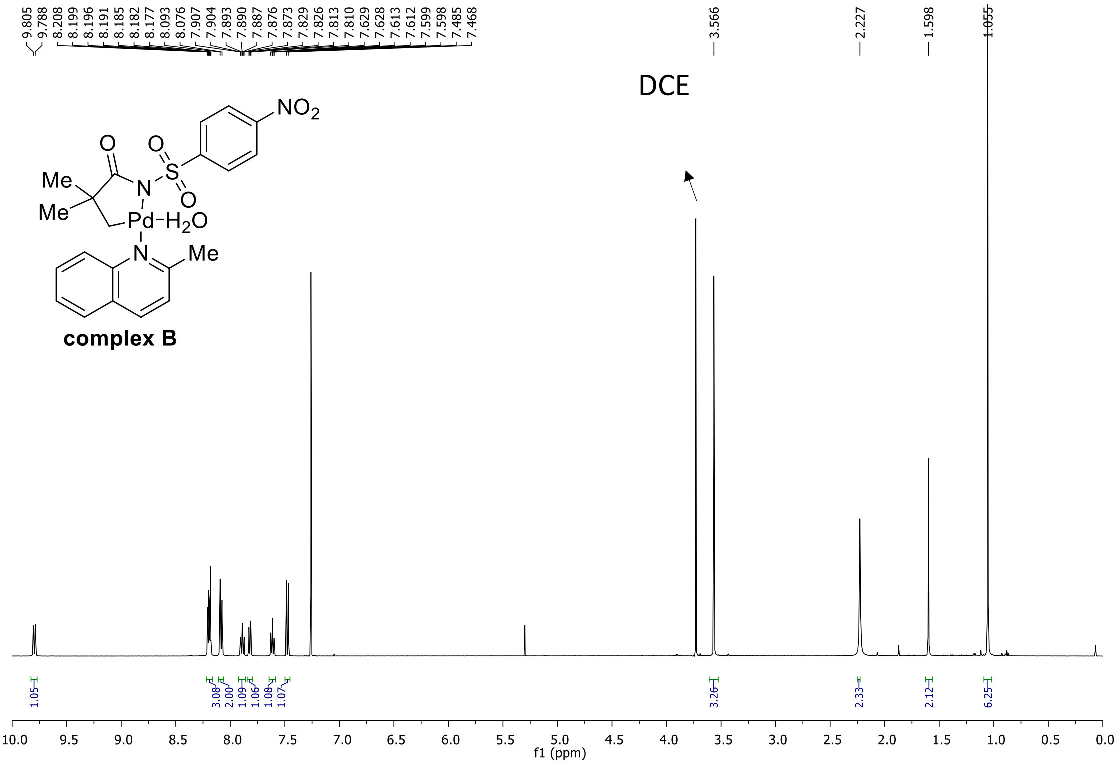

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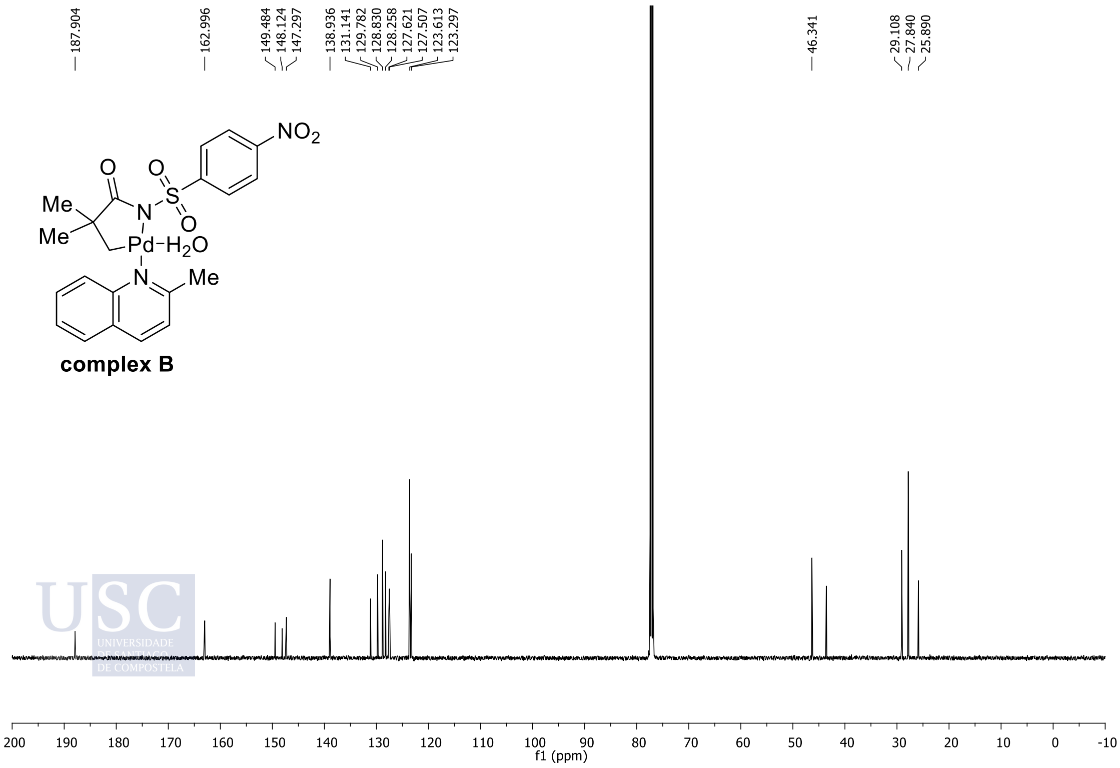

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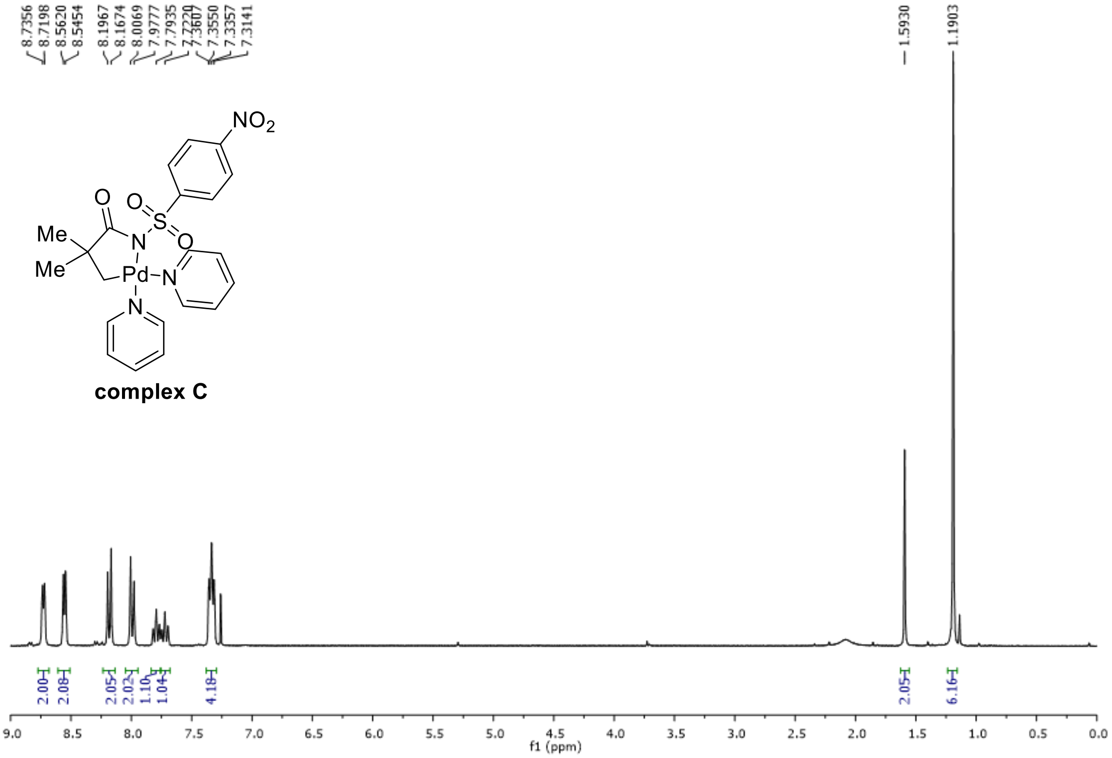

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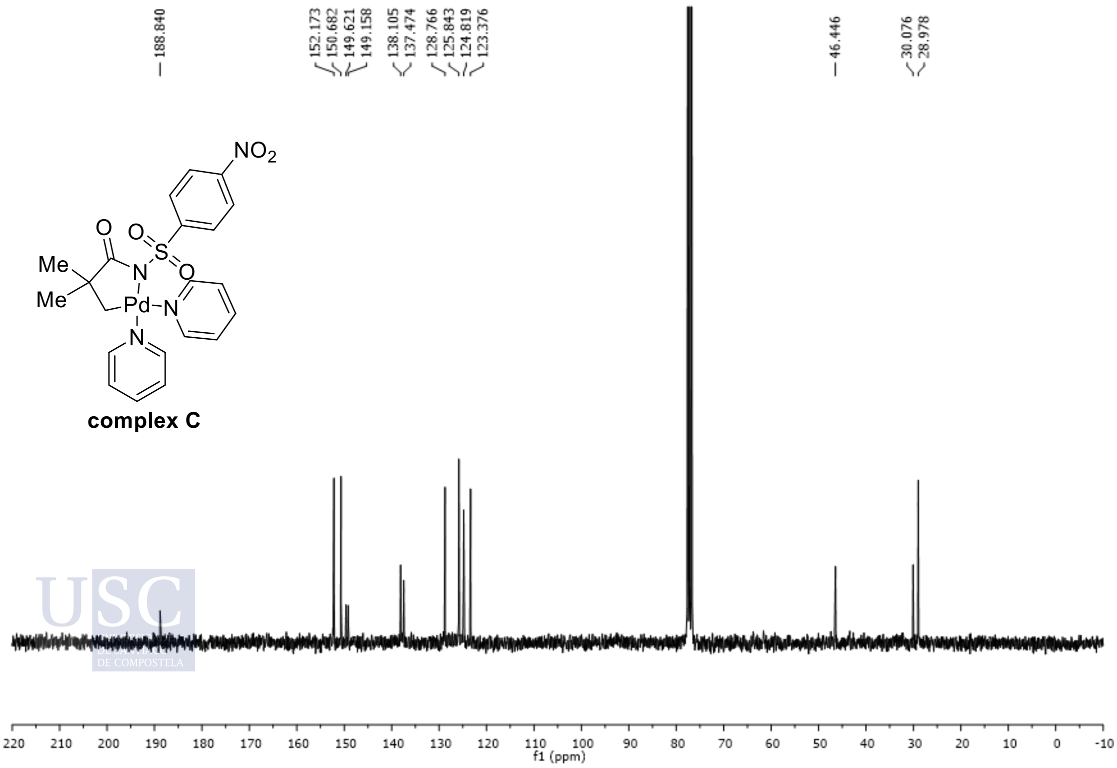

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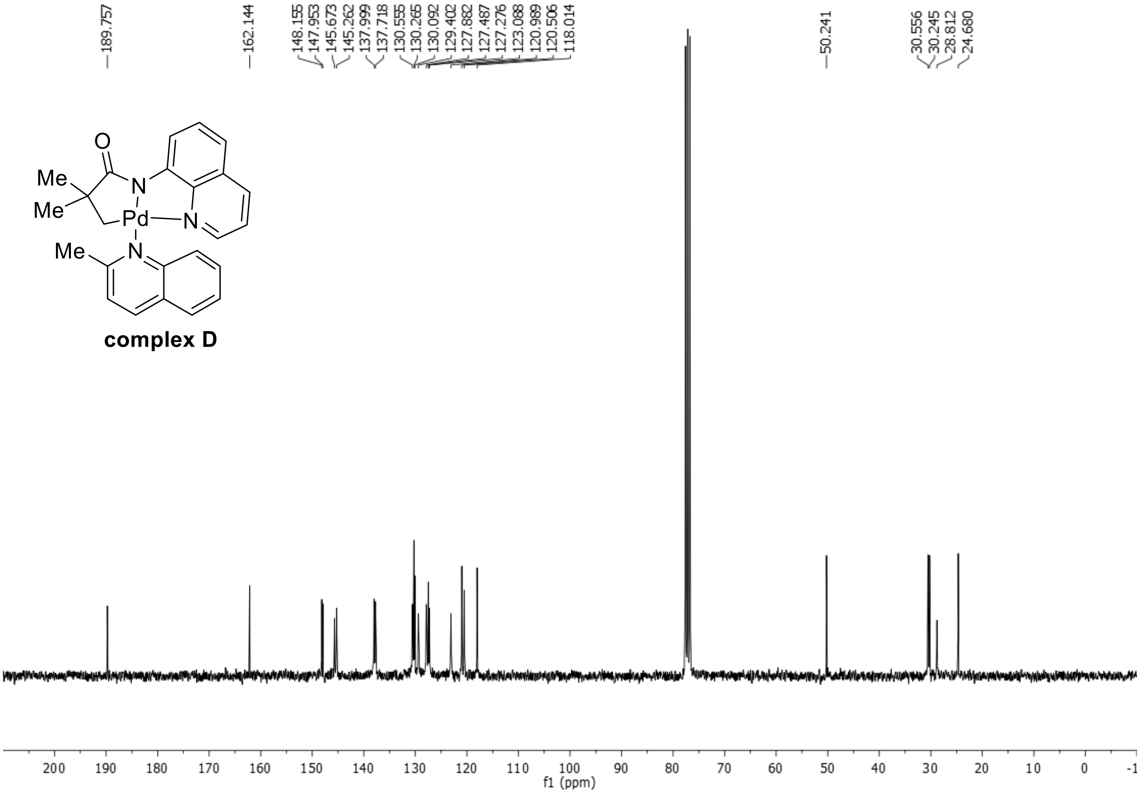

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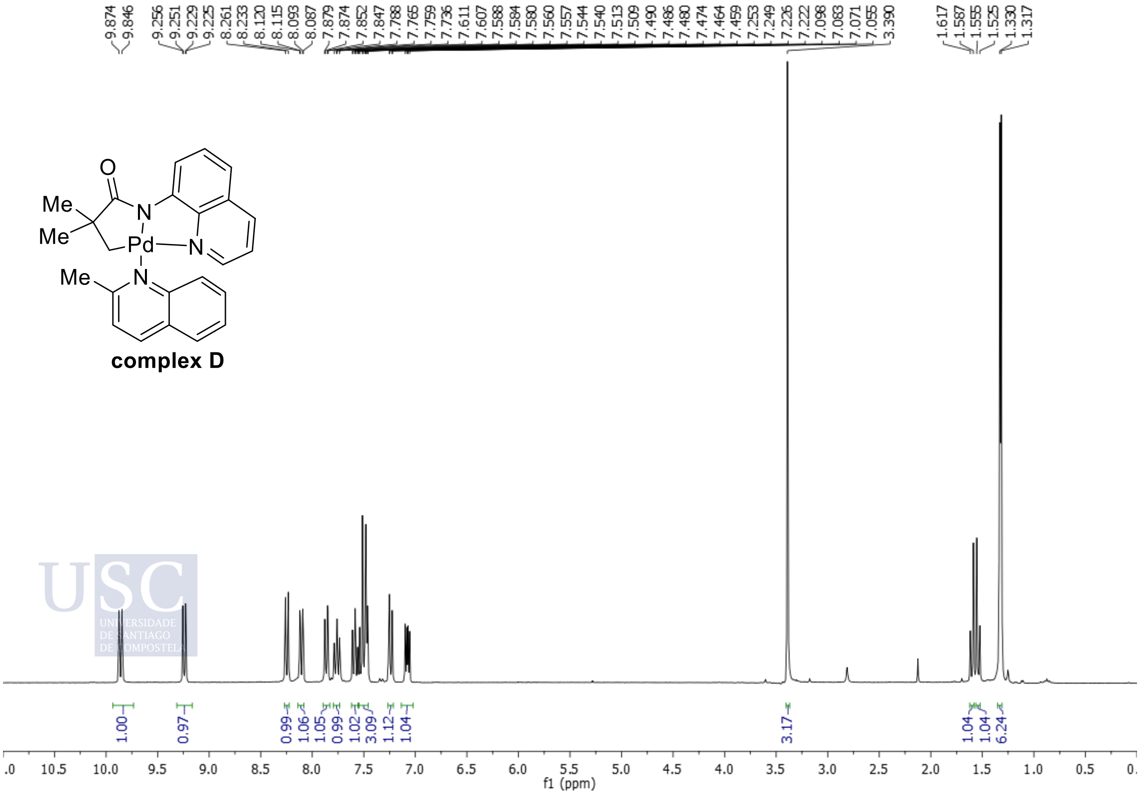

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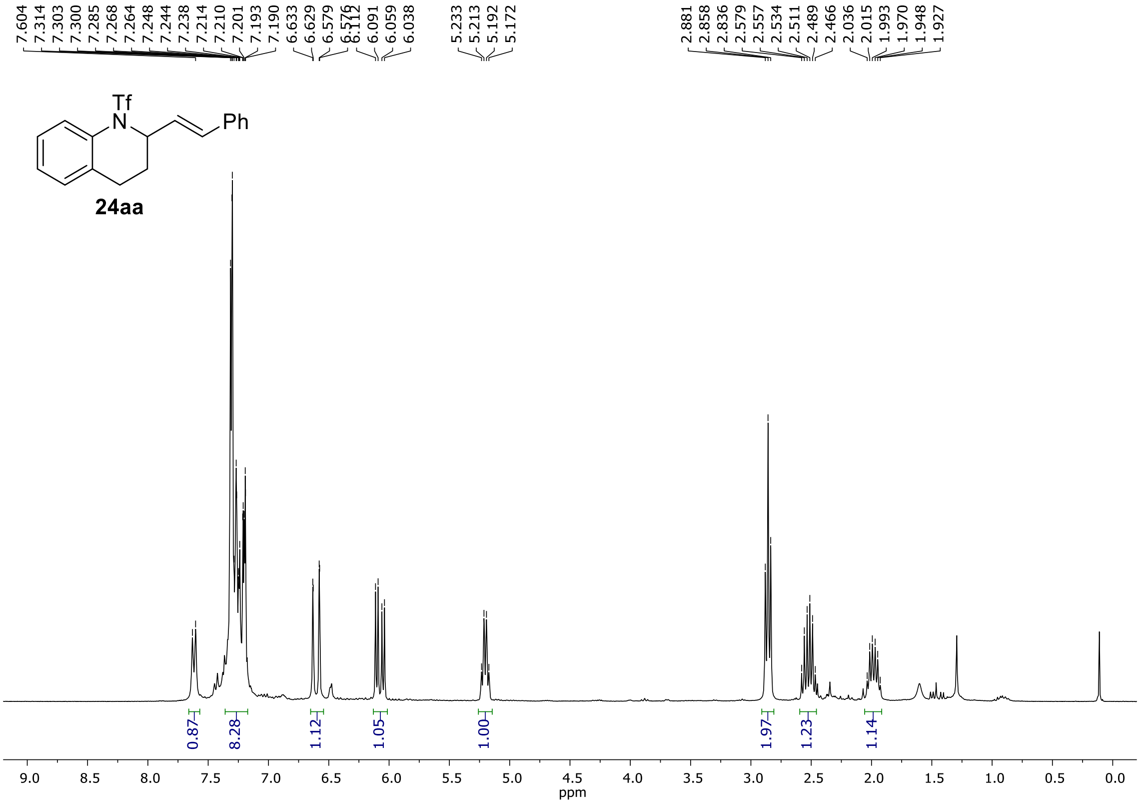

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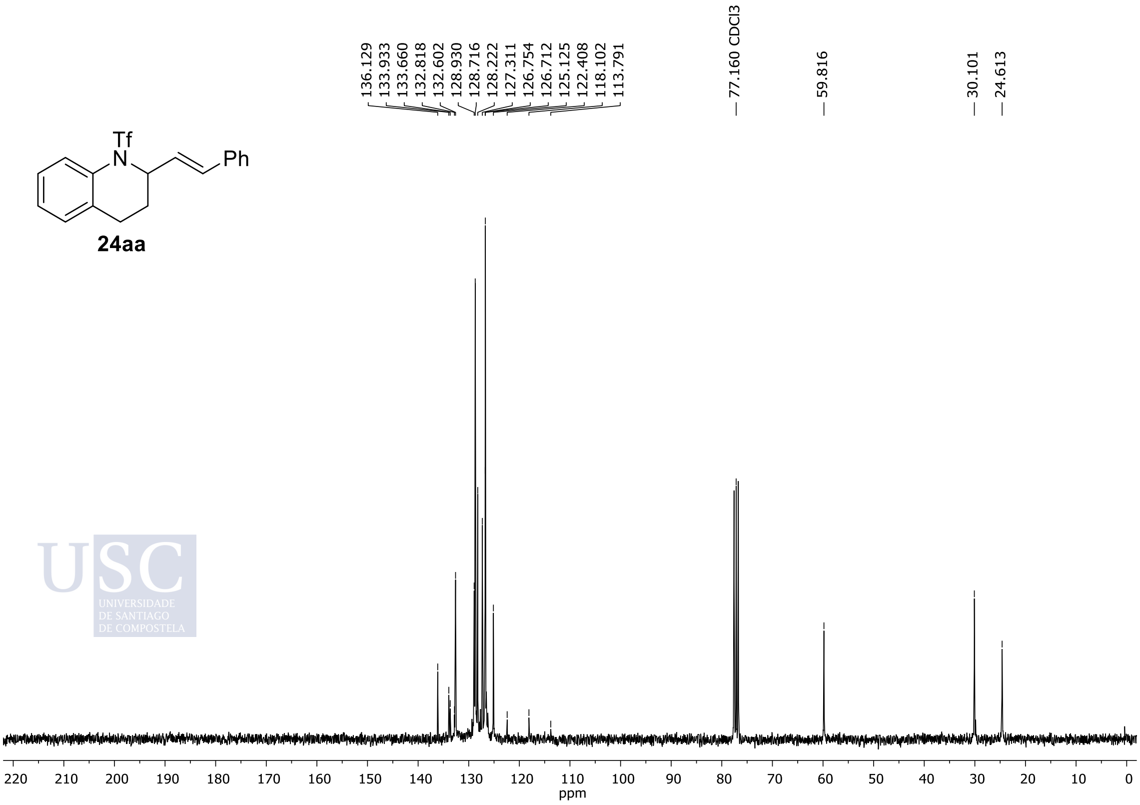

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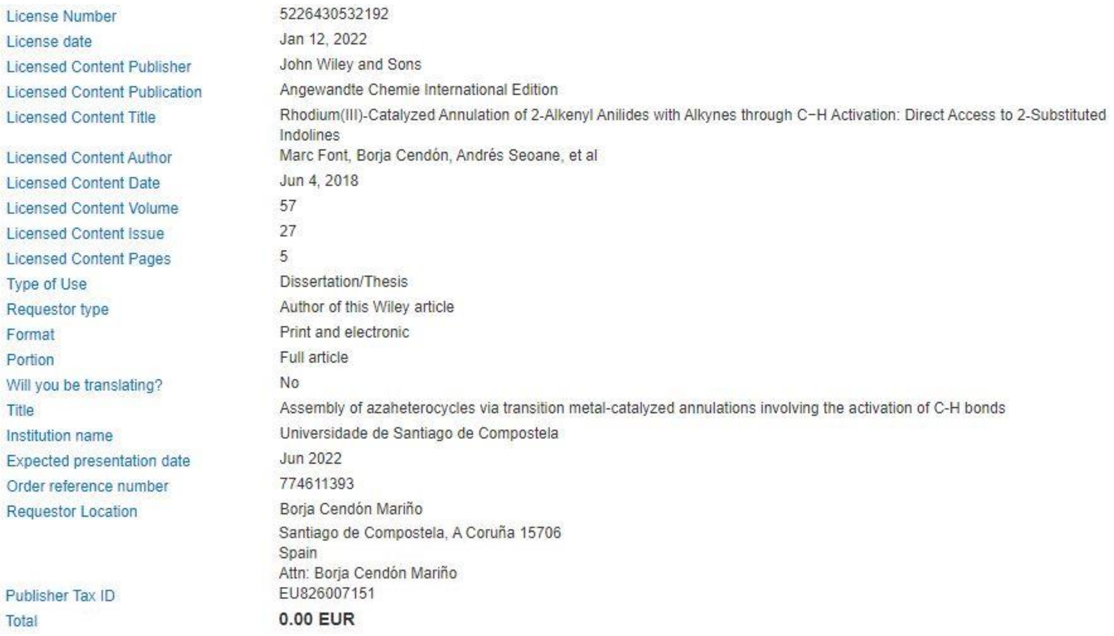
Chapter I

Title:	Rhodium(III)-Catalyzed Annulation of 2-Alkenyl Anilides with Alkynes through C-H Activation: Direct Access to 2-Substituted Indolines
Authors:	Marc Font, Borja Cendón, Andrés Seoane, José Luis Mascareñas, and Moisés Gulías
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:	2018
Volume, pages:	57, 8255-8259
Impact factor:	15.336 (2020)
PhD student contribution:	Synthesis of starting materials; Screening of conditions; Synthesis and characterization of about half of the 2-substituted indolines; Deprotection of the product; Isolation of the Rh(I) complex; Discussion of the results and revision of the manuscript



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Licensed Content Title	Rhodium(III)-Catalyzed Annulation of 2-Alkenyl Anilides with Alkynes through C−H Activation: Direct Access to 2-Substituted Indolines
Licensed Content Author	Marc Font, Borja Cendón, Andrés Seoane, et al
Licensed Content Date	Jun 4, 2018
Licensed Content Volume	57
Licensed Content Issue	27
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Type of Use	Dissertation/Thesis
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Format	Print and electronic
Portion	Full article
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Title	Assembly of azaheterocycles via transition metal-catalyzed annulations involving the activation of C-H bonds
Institution name	Universidade de Santiago de Compostela
Expected presentation date	Jun 2022
Order reference number	774611393
Requestor Location	Borja Cendón Mariño Santiago de Compostela, A Coruña 15706 Spain Attn: Borja Cendón Mariño
Publisher Tax ID	EU826007151
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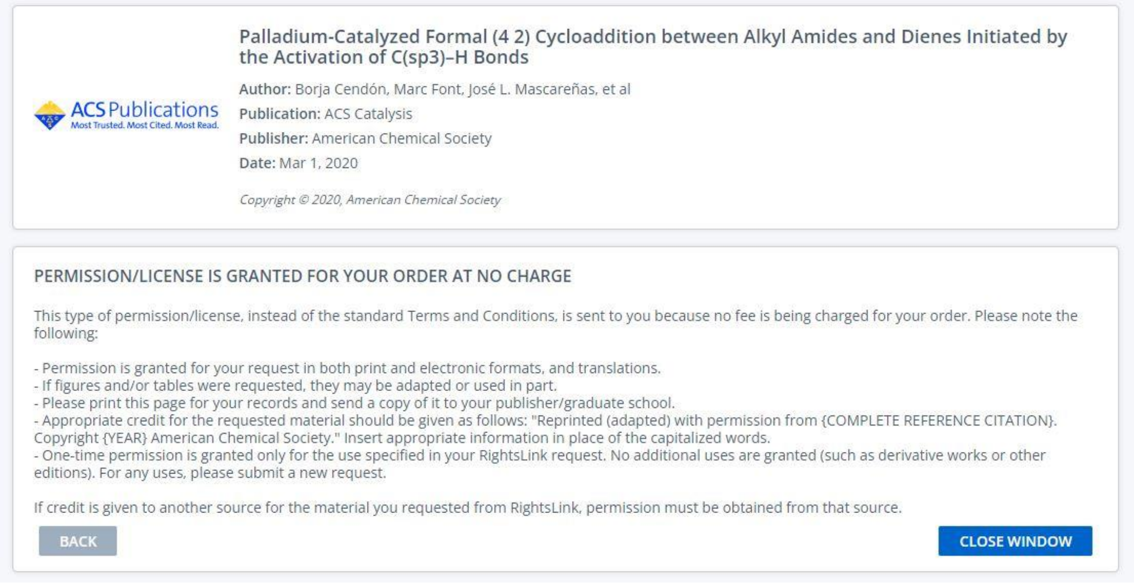
Chapter III

Title:	Palladium-Catalyzed Formal (4+2) Cycloaddition between Alkyl Amides and Dienes Initiated by the Activation of C(sp^3)-H bonds
Authors:	Borja Cendón, Marc Font, José Luis Mascareñas, and Moisés Gulías
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, 3425-3430
Impact factor:	13.084 (2020)
PhD student contribution:	Discovery of the reaction; Synthesis of starting materials; Screening of conditions; Synthesis and characterization of several 2-piperidones; Manipulation of the products; Discussion of the results and revision of the manuscript



Palladium-Catalyzed Formal (4 2) Cycloaddition between Alkyl Amides and Dienes Initiated by the Activation of C(sp3)–H Bonds

Author: Borja Cendón, Marc Font, José L. Mascareñas, et al
Publication: ACS Catalysis
Publisher: American Chemical Society
Date: Mar 1, 2020

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Transition metal-catalyzed reactions initiated by the activation of C-H bonds have emerged as an especially attractive approach to assemble and modify a large number of compounds due to the ubiquity of C-H bonds in organic molecules. In this context, annulations are particularly interesting since they provide a straightforward approach to heterocyclic structures from readily available precursors. In this PhD thesis, we described our efforts towards the synthesis of several highly appealing azaheterocycles, like indolines or piperidones, through the metal-triggered activation of alkenyl and alkyl C-H bonds and annulation with unsaturated partners. Our efforts have notably demonstrated that the employment of suitable ligands is crucial to achieve selective and efficient transformations.