Development of Gold(I)-Catalyzed Reactions Between Alkenes and Acetylene Gas

Tania Medina Gil

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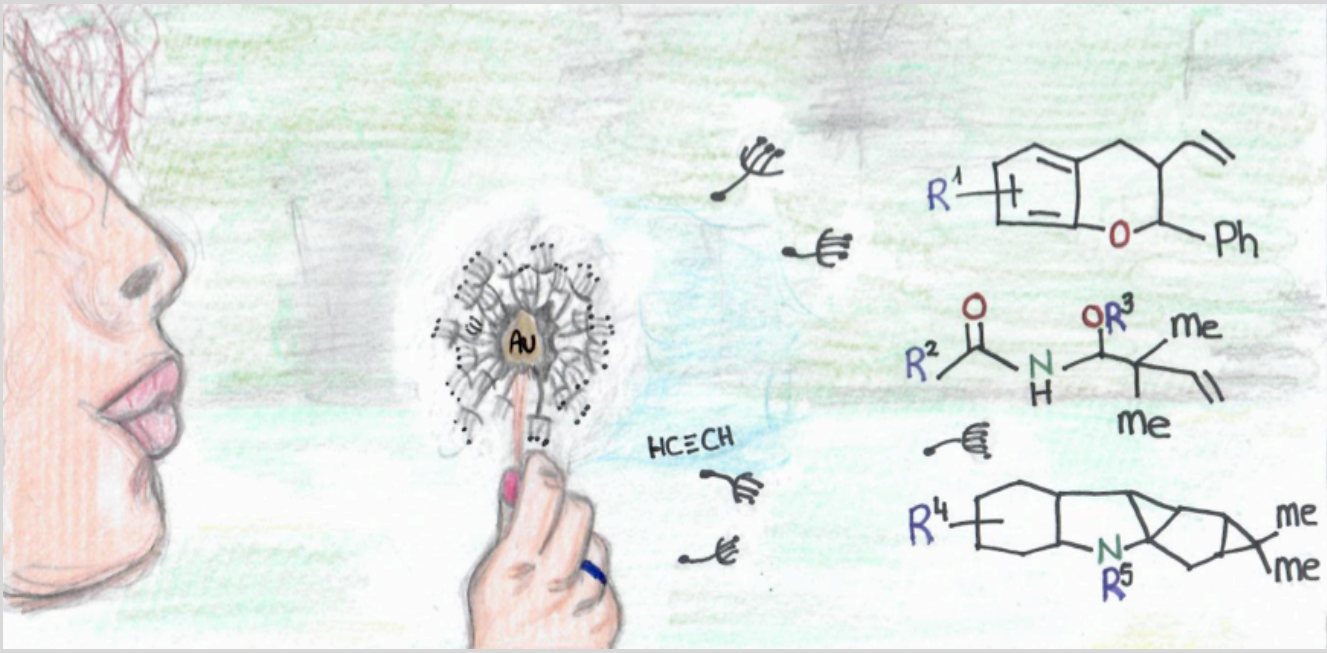

DOCTORAL THESIS
2024

UNIVERSITAT ROVIRA I VIRGILIDevelopment of Gold(I)-Catalyzed Reactions Between Alkenes and Acetylene Gas
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DOCTORAL THESIS

Supervised by Prof. Antonio Echavarren

Institute of Chemical Research of Catalonia (ICIQ)

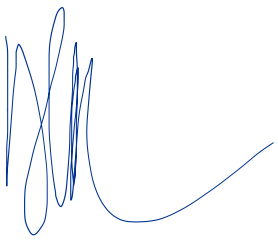
Tarragona 2024

UNIVERSITAT ROVIRA I VIRGILIDevelopment of Gold(I)-Catalyzed Reactions Between Alkenes and Acetylene Gas
Tania Medina Gil

I STATE that the present study, entitled "*Development of Gold(I)-Catalyzed Reactions Between Alkenes and Acetylene Gas"*, presented by Tania Medina Gil for the award of the degree of Doctor, has been carried out under my supervision at the Institut Català d'Investigació Química (ICIQ).

Tarragona, August 30th, 2024

Doctoral Thesis Supervisor



Prof. Antonio M. Echavarren Pablos

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A mis padres y mi hermana

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"Nothing in life is to be feared, it is only to be understood.
Now is the time to understand more, so that we may fear less."
Marie Curie

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At the time of writing this Doctoral Thesis, part of the results was reported in the following publications:

"Gold(I)-Catalyzed Intermolecular Aryloxyvinylation with Acetylene Gas"
Medina-Gil, T.; Sadurní, A.; Hammarback, L. A.; Echavarren, A. M. *ACS Catal.* **2023**, *13*, 10751–10755.

"Three-Component Gold(I)-Catalyzed Alkoxyvinylation"
Hammarback, L. A.; Medina-Gil, T.; Sadurní, A.; Echavarren, A. M. *Org. Lett.* **2024**, *26*, 6375–6379.

In addition, during my stay in the laboratory of Prof. Dirk Trauner (University of Pennsylvania, 2023), I published in Synfacts the following overviews:

"Synthesis of N-Acylsulfonamide Derivates: New Sulfa Drug Analogues by Sulfo-Click Reaction"
T. Medina-Gil, D. Trauner, *Synfacts* **2023**, *19(10),* 0001, DOI: 10.1055/s-0042-1752024.
"Synthesis of p-Extended Coumarins Using d-Acetoxy Allenoate as a 5C-Synthon"
T. Medina-Gil, D. Trauner, *Synfacts* **2023**, *19(11),* 0001, DOI: 10.1055/s-0042-1752292.
"CPA-Catalyzed Synthesis of Chiral a,a–Diaryl Ketones from Unactivated Alkynes"
T. Medina-Gil, D. Trauner, *Synfacts* **2023**, *20(12),* 0001, DOI: 10.1055/s-0043-1763818.

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Prologue

The manuscript of this Doctoral Thesis has been divided into four main parts: a general introduction on gold(I) catalysis and three main research Chapters. These Chapters are preceded by the abstract and general objectives and followed by the overall conclusions. Each Chapter contains five sections including a specific introduction on the topic, the objectives, the discussion of the results, the conclusions and, finally, the experimental section. The numbering of compounds, schemes, figures, tables and references is organized by Chapter.

The **General Introduction** convers the basic principles of homogeneous gold(I) catalysis and gives an overview on the cycloisomerization of 1,*n*-enynes and the gold(I)-catalyzed intermolecular reactions between alkynes and alkenes. Moreover, the characteristic of acetylene and its applications in chemical industry are described.

Chapter I, *"Gold(I)-Catalyzed Intermolecular Heterovinylation Reactions Using Acetylene Gas"* presents the development of a gold(I)-catalyzed aryloxyvinylation reaction to afford chromane-containing products using acetylene gas. The synthetic utility of this transformation is highlighted by the late-stage functionalization of lapachol natural product and several diversifications of the model product. Moreover, preliminary studies on the enantioselective version of this reaction are described. Finally, this chemistry was extended to alkyl amines for the synthesis of pyrrolidine and piperidine containing products. Part of the results described in this Chapter were carried out in collaboration with Dr. Anna Sadurní and Dr. L. Anders Hammarback. Part of this work has been published in *ACS Catal.* **2023**, *13*, 10751–10755 and *Org. Lett.* **2024**, *26*, 6375–6379.

Chapter II, *"Development of a Three Component Gold(I)-Catalyzed Alkoxyvinylation and Studies on the Oligomerization Process"* describes the studies on a fully intermolecular alkoxyvinylation reaction between alkenes, alcohols and acetylene gas. Additionally, in this Chapter, the side oligomerization reactions observed are deeply studied and efforts towards the quantification of the oligomers are presented. This work was performed in collaboration with Dr. Anna Sadurní and Dr. L. Anders Hammarback. Part of this research was published in *Org. Lett.* **2024**, *26*, 6375–6379.

Chapter III, *"Gold(I)-Catalyzed Biscyclopropanation of 2-Substituted Indoles"* presents the development of a gold(I)-catalyzed biscyclopropanation of 2-alkylated indoles to afford a wide variety of polycyclic indole-containing products. Furthermore, DFT studies were performed to elucidate the reaction mechanism. The work presented in this Chapter was performed in collaboration with Dr. Anna Sadurní, Dr. Anders L. Hammarback, Jennifer Tamayo and Mathéo La Torre. These results have not been published yet.

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Abbreviations and Acronyms

In this manuscript, the abbreviations and acronyms most commonly used in organic and organometallic chemistry have been used following the recommendations of *"Guidelines for authors"* published in the *Journal of Organic Chemistry*.

Additional abbreviations and acronyms are listed below:

APCI	Atmospheric Pressure Chemical Ionization
APPI	Atmospheric Pressure Photoionization Ionization
$BAr^{F}{}_{4}^{-}$	Tetrakis[3,5-bis(trifluoromethyl)phenyl]borate
dr	Diastereomeric Ratio
ee	Enantiomeric Excess
er	Enantiomeric Ratio
ESI	Electrospray Ionization
HRMS	High Resolution Mass Spectrometry
Int	Intermediate
IPr	1,3-Bis(2,6-diisopropylphenyl)imidazole-2-ylidene
JohnPhos	(2-Biphenyl)di-*tert*-butylphoshpine
L	Ligand
MALDI	Matrix Assisted Laser Desorption Ionization
Mes	2,4,6-Trimethylphenyl
MW	Microwave Irradiation
NTf_2^-	Bis(trifluoromethyl)imidate
OTf^-	Trifluoromethanesulfonate
*t*BuXPhos	2-(Di-*tert*-butylphosphino)-2',4',6'-triisopropyl-1,1'-biphenyl
TS	Transition State

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Abstract

Gold(I) catalysis has experienced a huge development in the past decades. Our research group has focused on the development of powerful gold(I)-catalyzed methods for the synthesis of complex molecular frameworks. In this context, this Doctoral Thesis covers three topics related on the application of homogenous gold(I) catalysis for the activation of acetylene gas, the smallest existing alkyne.

Firstly, the gold(I)-catalyzed aryloxyvinylation reaction of *o*-allylphenols with acetylene gas was studied in detail. The reaction takes place through the formation of a cyclopropyl gold(I) carbene followed by the intramolecular nucleophilic attack from the phenol group to afford the desired products. A wide variety of 3-vinyl chromanes could be prepared, including the synthesis of 3-vinyl lapachone from the natural product lapachol. The synthetic utility of this methodology was additionally highlighted by many diversifications performed in the vinyl group of the model product. Moreover, preliminary tests on the enantioselective version of this reaction were performed. Despite the moderate enantioselectivities obtained, these are the first examples of gold(I)-catalyzed enantioselective activation of acetylene gas.

Then, a fully intermolecular gold(I)-catalyzed alkoxyvinylation with acetylene gas was studied in detail where neither the alkene, alkyne nor the nucleophile are covalently linked. After a screening of substrates, *N*-vinyl amides were found to be suitable substrates for the gold(I)-catalyzed reaction with acetylene gas in the presence of an external alcohol nucleophile. Side oligomerization reactions were observed in many cases, so the possible quantification of the oligomers obtained was investigated by UHPLC-MS in a model reaction.

Finally, the gold(I)-catalyzed biscyclopropanation of 2-alkylated indoles with acetylene gas was explored. The methodology developed constitutes a powerful strategy for the functionalization of indoles, one of the most ubiquitous heterocyclic scaffold in nature and pharmacologically active compounds. In addition, DFT studies were performed to gain insights into the reaction mechanism.

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General Objectives

The main objective of this Doctoral Thesis was the development of novel gold(I)-catalyzed reactions of alkenes with acetylene gas. In particular, we focused on:

- The combination of gold(I) catalysis and the use of acetylene gas for the aryloxyvinylation of *o*-allylphenols giving rise to chromane-containing products.
- The development of a three component gold(I)-catalyzed alkoxyvinylation of alkenes in the presence of acetylene gas and the study on the side oligomerization processes in these transformations.
- The synthesis of biscyclopropanated products through a gold(I)-catalyzed reaction of substituted indoles and acetylene gas and the study of the mechanism by DFT calculations.

Each Chapter of this manuscript provides a more detailed description of the corresponding objectives.

General Introduction

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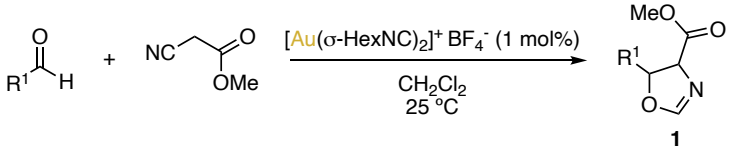
Homogeneus Gold Catalysis

Origin of Gold Chemistry

Gold, with its incorruptible nature and radiant brilliance, has been considered a symbol of power and wealth for the past 3,000 years. The importance of gold was firstly highlighted in the Egyptian era since this precious metal was employed in Tutankhamun's Mask. In ancient Egypt, gold was known as "the flesh of gods" and associated with the sun god Ra. Gold was believed to purify the soul and facilitate the journey of the deceased to the afterlife. Ever since, gold became a symbol and has been broadly applied to the production of coinage, jewelry, and electronics (Figure 1).

Figure 1. (a) Golden necklace. (b) Tutankhamun's mask. (c) Astronaut's helmet.

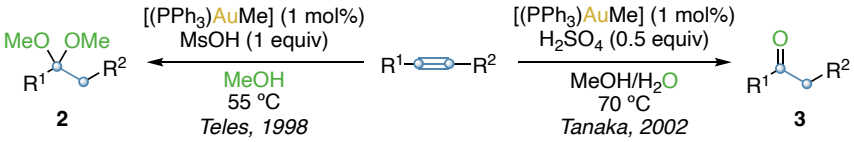
Despite its unique properties, gold has been considered "catalytically dead" for a long time and only its stoichiometric coordination and organic-metallic chemistry was deeply studied.[1] The first example of the use of gold in homogeneous catalysis was reported in 1986 by Ito and Hayashi, for the asymmetric aldol reaction of aldehydes and isocyanides to afford oxazolines **1** (Scheme 1).[2]



Scheme 1. Gold(I)-catalyzed aldol reaction.

More than a decade later, Teles reported the first example of the gold(I) activation of alkynes for the synthesis of acetals **2** (Scheme 2, left).[3] The same phosphine-based gold(I) catalyst was employed later by the group of Tanaka for the hydration of alkenes to afford the Markovnikov ketones **3** (Scheme 2, right).[4]

1. Stephen, A.; Hashmi, K. *Gold Bull.* **2004**, *37*, 51–65.
2. Ito, Y.; Sawamura, M.; Hayashi, T. *J. Am. Chem. Soc.* **1986**, *108*, 6405–6406.
3. Teles, J. H.; Brode, S.; Chabanas, M. *Angew. Chem. Int. Ed.* **1998**, *37*, 1415–1418.
4. (a) Mizushima, E.; Sato, K.; Hayashi, T.; Tanaka, M. *Angew. Chem. Int. Ed.* **2002**, *41*, 4563–4565. (b) Mizushima, E.; Hayashi, T.; Tanaka, M. *Org. Lett.* **2003**, *5*, 3349–3352.



Scheme 2. Gold(I)-catalyzed hydration of alkenes.

These examples set up the starting point for homogenous gold catalysis to become a versatile tool for the formation of carbon–carbon and carbon–heteroatom bonds.[5]

Relativistic Effects of Gold(I) Catalysis and their Consequences

The high ability of gold complexes to selectively activate π-bonds, along with some of its unique properties are attributed to the relativistic effects.[6] These relativistic effects relate to the acceleration of electrons orbiting around a heavy nucleus. They increase with the atomic number since the electrons closer to the nucleus are accelerated.[7] This generates an increase in the mass of the electrons that implies the contraction of the *s* and *p* orbital of these electrons and, at the same time, an expansion of the *d* and *f* orbitals. This contraction/expansion effect is more significant for metals with filled *4f* and *5d* orbitals. In the case of gold, these effects reach a maximum in the periodic table which allows the interaction of the *5d* orbital of gold with the filled π orbitals of unsaturated bonds (Figure 2).

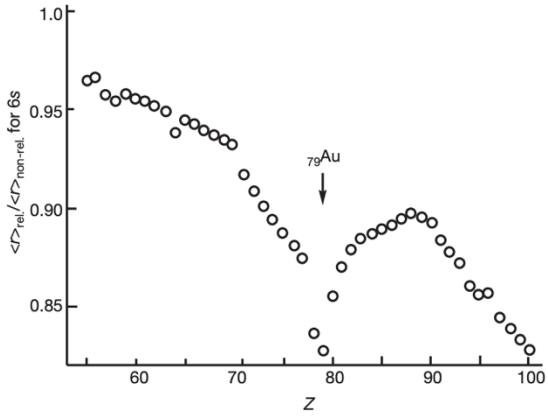


Figure 2. Calculated relativistic contraction of the 6s orbitals.[8]

As mentioned before, relativistic effects are also responsible for some of the most characteristic properties of gold, such as its color, or its high electronegativity and Lewis acidity. Furthermore, the *s*/*p* or *s*/*d* orbital hybridation effectively explains the preference of gold to form linear dicoordinate

5. (a) Jiménez-Núñez, E.; Echavarren, A. M. *Chem. Rev.* **2008**, *108*, 3326–3350. (b) Fürstner, A. *Chem. Soc. Rev.* **2009**, *38*, 3208–3221. (c) Obradors, C.; Echavarren, A. M. *Acc. Chem. Res.* **2014**, *47*, 902–912. (d) Fensterbank, L.; Malacria, M.; *Acc. Chem. Res.* **2014**, *47*, 953–965. (e) Dorel, R.; Echavarren, A. M. *Chem. Rev.* **2015**, *115*, 9028–9072.
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7. Pyykko, P.; Desclaux. J. P. *Acc. Chem. Res.* **1979**, *12*, 276–281.
8. Graphic taken from reference 6b.

complexes.[9] These linear gold(I) complexes do not undergo oxidative addition or *β*-hydride elimination.[10]

Another distinctive characteristic of gold is its *aurophilicity* or tendency to create strong Au–Au interactions to form dimers, trimers or even polymers.[11]

The contraction of the orbital *6s* on gold atom causes a strong Au–L interaction between the gold atom and the ligand. Thus, the outcome of gold(I)-catalyzed reactions can be easily tuned by modulation of the characteristics of the ligand employed, such as its electronics or steric effects.[12] As a general trend, complexes containing more donating *N*-heterocyclic carbenes are less electrophilic that those with phosphine-based ligands. Those with bulky phosphines or biarylphosphines display an intermediate electrophilicity that has proven to be highly convenient. [13] Moreover, gold complexes bearing phosphite ligands are the most electrophilic substrates and exhibit a carbocation-like character (Figure 3).

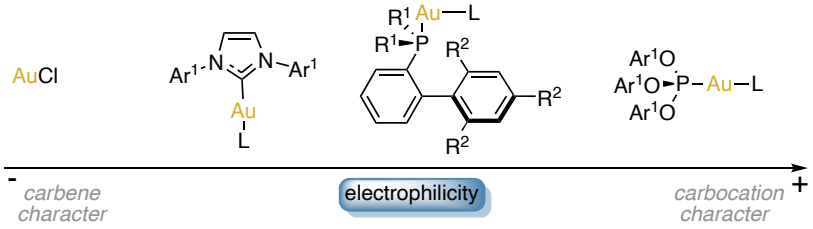
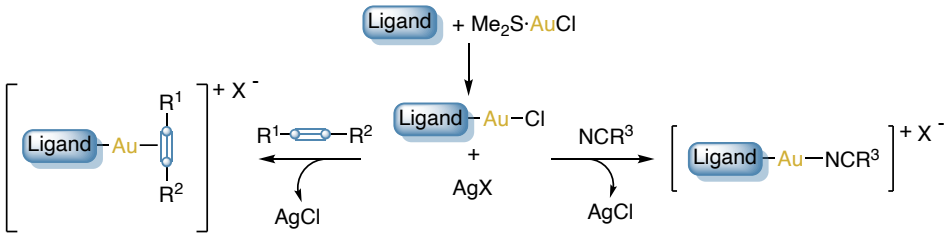


Figure 3. Electrophilicity of gold(I) complexes modulated by ligands.

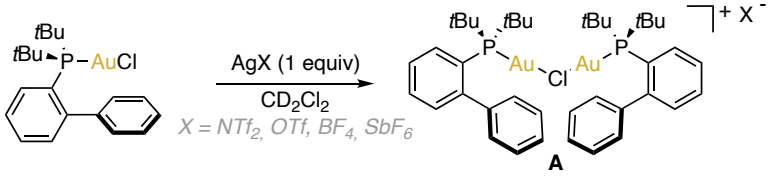
To activate gold(I) complexes and make them catalytically active, the gold center needs to be coordinated to a labile ligand that can be replaced through an associative mechanism by the substrate of the reaction.[14] Chloride is the most used labile ligand for the synthesis of gold(I) precatalysts. To generate the reactive gold complex, chloride scavengers need to be employed to generate the vacant position. The most common scavengers used are either silver or copper salts that give rise to the more reactive cationic gold(I) complexes and insoluble AgCl[15] or CuCl/$CuCl_2$ salts (Scheme 3)[16].

9. Gimeno, M. C.; Laguna, A. *Chem. Rev.* **1997**, *97*, 511–522.
10. Livendahl, M.; Goehry, C.; Maseras, F.; Echavarren, A. M. *Chem. Comm.* **2014**, *50*, 1533–1536.
11. Scherbaum, F.; Grohmann, A.; Huber, B.; Krüger, C.; Schmidbaur, H. *Angew. Chem. Int. Ed.* **1988**, *27*, 1544–1546.
12. Gorin, D. J.; Sherry, B. D.; Toste, F. D. *Chem. Rev.* **2008**, *108*, 3351–3378.
13. Zuccarello, G.; Zanini, M.; Echavarren, A. M. *Isr. J. Chem.* **2020**, *60*, 360–372.
14. (a) Nieto-Oberhuber, C.; López, S.; Muñoz, M. P.; Cárdenas, D. J.; Buñuel, E.; Nevado, C.; Echavarren, A. M. *Angew. Chem. Int. Ed.* **2005**, *44*, 6146–6148. (b) Schmidbaur, H.; Schier, A. *Organometallics* **2010**, *29*, 2–23.
15. (a) Hashmi, A. S. K.; Lothschütz, C.; Böhling, C.; Hengst, T.; Hubbert, C.; Rominger, F. *Adv. Synth. Cat.* **2010**, *352*, 3001–3012. (b) Pérez-Galán, P.; Delpont, N.; Herrero-Gómez, E.; Maseras, F.; Echavarren, A. M. *Chem. Eur. J.* **2010**, *16*, 5324–5332.
16. Guérinot, A.; Fang, W.; Sircoglou, M.; Bour, C.; Bezzenine-Lafollée, S.; Gandon, V. *Angew. Chem. Int. Ed.* **2013**, *52*, 5848–5852.



Scheme 3. Activation of gold(I) chloride complexes.

Despite having been used for decades as chloride scavengers, silver salts can exhibit an unpredictable behavior in catalytic reactions.[17] These effects include the formation of mixed Au–Ag intermediates or dinuclear chloride-bridged gold(I) complexes **A** (Scheme 4).[18]



Scheme 4. Formation of binuclear chloride-bridged gold(I) complexes.

Alternatively, more innovative approaches have been developed based on the use of weakly coordinating counteranions (OTf^- or NTf_2^-)[19] or the formation of cationic complexes with more labile neutral ligands like acetonitrile or benzonitrile. Our group pioneered the design of these complexes that can directly engage in the catalytic cycle and be replaced for the substrate without the formation of secondary species that may interfere with the reaction.[20]

Cycloisomerization of 1,*n*-Enynes

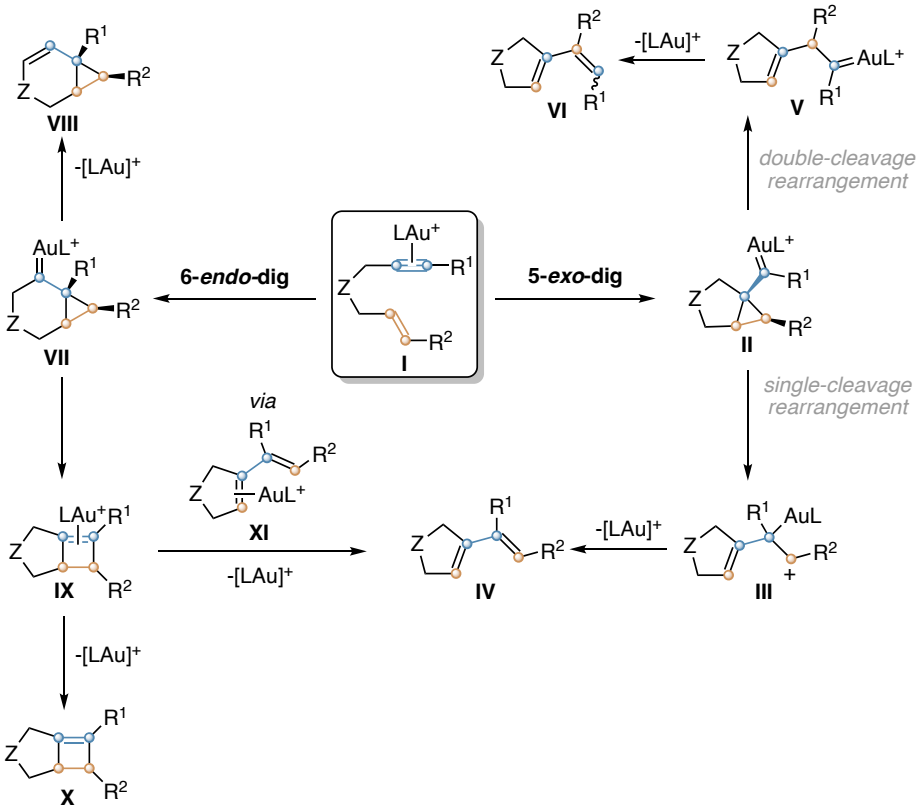
The most extensively studied reaction in gold(I) catalysis is the cycloisomerization of 1,6-enynes. This transformation represents a powerful tool for the construction of complex and polycyclic molecules by the formation of multiple C–C bonds in one step.[5d]

Thanks to its alkynophilic character (due to the relativistic effects), gold can selectively activate alkynes forming (η^2-alkyne)gold(I) species that can be further attacked by a nucleophile. In this context, 1,6-enynes can react with the gold catalyst upon formation of intermediate **I** which can undergo either a 5-*exo*-dig or a 6-*endo*-dig cyclization (Scheme 5).[13a,21] If the reaction takes place via a 5-*exo*-dig

17. Zhu, Y.; Day, C. S.; Zhang, L.; Hauser, K. J.; Jones, A. C. *Chem. Eur. J.* **2013**, *19*, 12264–12271.
18. (a) Wang, D.; Cai, R.; Sharma, S.; Jirak, J.; Thummanapelli, S. K.; Akhmedov, N. G.; Zhang, H.; Liu, X.; Petersen, J. L.; Shi, X. *J. Am. Chem. Soc.* **2012**, *134*, 9012–9019. (b) Homs, A.; Escofet, I.; Echavarren, A. M. *Org. Lett.* **2013**, *15*, 5782–5785.
19. (a) Mézailles, N.; Ricard, L.; Gagosz, F. *Org. Lett.* **2005**, *7*, 4133–4136. (b) Ricard, L.; Gagosz, F. *Organometallics* **2007**, *26*, 4704–4707.
20. Teles, J. H.; Brode, S.; Chabanas, M. *Angew. Chem. Int. Ed.* **1998**, *37*, 1415–1418.
21. (a) Nieto-Oberhuber, C.; Muñoz, M. P.; Buñuel, E.; Nevado, C.; Cárdenas, D. J.; Echavarren, A. M. *Angew. Chem. Int. Ed.* **2004**, *43*, 2402–2406. (b) Ferrer, C.; Raducan, M.; Nevado, C.; Claverie, C. K.; Echavarren, A. M. *Tetrahedron* **2007**, *63*, 6306–6316. (c) Escribano-Cuesta, A.; Pérez-Galán, P.; Herrero-Gómez, E.; Sekine, M.; Braga, A. A. C.; Maseras, F.; Echavarren, A. M. *Org. Biomol. Chem.* **2012**, *10*, 6105–6111.

cyclization, gold(I) carbene **II** is formed and can lead to different intermediates. If intermediate **II** undergoes a single-cleavage rearrangement, a formal 1,3-migration of the terminal carbon of the alkene takes place and gives rise to intermediate **III**.[22] However, if gold(I) carbene **II** undergoes a double cleavage reaction, then rearranged carbene **V** is formed and protodeauration affords dienes **VI** as products.

On the other side, intermediate **I** can go through a 6-*endo*-dig pathway giving rise to carbene **VII** that, upon protodeauration reaction, affords product **VIII**. Additionally, carbene **VII** can rearrange and form intermediate **IX** that leads to highly strained bicyclo[3.2.0]hept-5-enes **X**.[23] Interestingly, the ring opening of **IX** leads to the formation of intermediate **XI**, a precursor of single cleavage products **IV**.

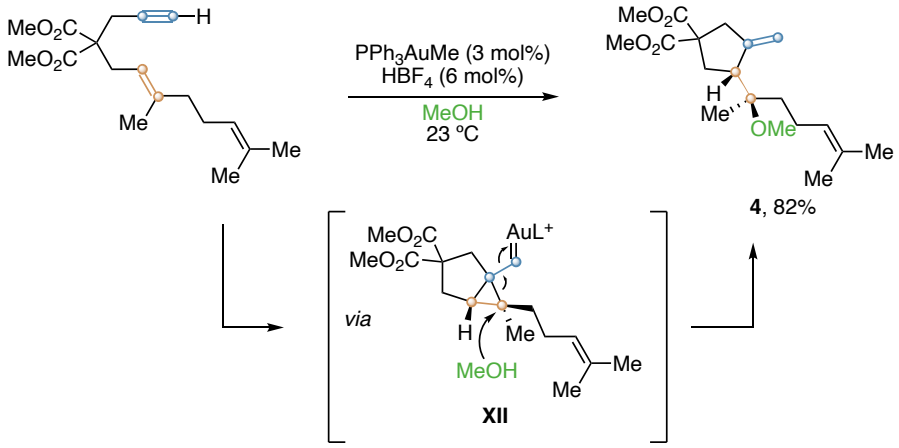


Scheme 5. General pathways for the gold(I)-catalyzed cycloisomerization of 1,6-enynes.

These mechanistic pathways are also followed by 1,5-enynes[24] and 1,7-enynes[25] being the formation of bicyclic derivates more common when higher enynes are employed ($7 \leq n \leq 16$).[26]

22. Cabello, N.; Jiménez-Núñez, E.; Buñuel, E.; Cárdenas, D. J.; Echavarren, A. M. *Eur. J. Org. Chem.* **2007**, *25*, 4217–4223.
23. Lee, S. I.; Kim, S. M.; Choi, M. R.; Kim, S. Y.; Chung, Y. K.; Han, W.-S.; Kang, S. O. *J. Org. Chem.* **2006**, *71*, 9366–9372.
24. (a) Sun, J.; Conley, M. P.; Zhang, L.; Kozmin, S. A. *J. Am. Chem. Soc.* **2006**, *128*, 9705–9710. (b) López-Carrillo, V.; Huguet, N.; Mosquera, Á.; Echavarren, A. M. *Chem. Eur. J.* **2011**, *17*, 10972–10978.
25. Cabello, N.; Rodríguez, C.; Echavarren, A. M. *Synlett* **2007**, 1753–1758.
26. Obradors, C.; Leboeuf, D.; Aydin, J.; Echavarren, A. M. *Org. Lett.* **2013**, *15*, 1576–1579.

In the presence of an external nucleophile, 1,*n*-enynes can undergo alkoxycyclization reactions.[27] The process involves the *anti*-addition of the (η^2-alkyne)gold(I) complex and the nucleophilic alcohol to an alkene following Markovnikov regiochemistry (Scheme 6). This stereospecific process has been shown to require milder conditions when gold is employed compared to the use of other metal catalysts.[26a]



Scheme 6. Gold(I)-catalyzed alkoxycyclization of 1,6 enynes.

Enantioselective Gold(I) Catalysis

Despite the huge achievements made in the field of homogeneous gold(I) catalysis, the enantioselective version of these transformations remains underdeveloped.[28] Typically, enantioselective reactions are based on the use of chiral ligands. However, the linear dicoordination of gold(I) catalysts places the chiral information far away from the reactive center which leads to poor levels of enantioinduction. Moreover, enantioselective gold(I) catalysis faces other challenges such as the free rotation of Au-ligand and Au-substrate bonds and the outer sphere mechanism (Figure 4).

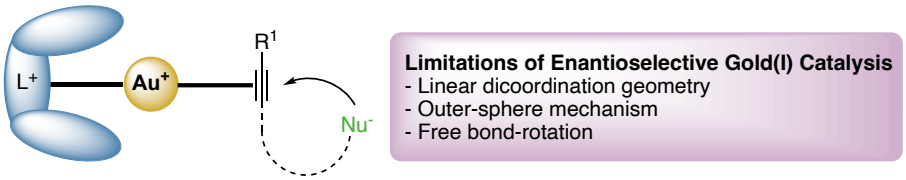


Figure 4. Limitations of enantioselective gold catalysis.

Some conceptual designs have been explored to overcome these limitations in enantioselective gold(I) catalysis.[29] One of the most studied approaches is the use of axially chiral binuclear gold(I) complexes with biphosphines or diaminocarbene ligands (Figure 5a).[30] These novel chiral ligands have been

27. (a) Muñoz, M. P.; Adrio, J.; Carretero, J. C.; Echavarren, A. M. *Organometallics* **2005**, *24*, 1293–1300. (b) Matsumoto, Y.; Selim, K. B.; Nakanishi, H.; Yamada, K.; Yamamoto, Y.; Tomioka, K. *Tetrahedron Lett.* **2010**, *51*, 404–406. (c) Reiersølmoen, A. C.; Csókás, D.; Pápai, I.; Fiksdahl, A.; Erdélyi, M. *J. Am. Chem. Soc.* **2019**, *141*, 18221–18229.
28. Widenhoefer, R. A. *Chem. Eur. J.* **2008**, *14*, 5382–5391.
29. Zuccarello, G.; Escofet, I.; Caniparoli, U.; Echavarren, A. M. *ChemPlusChem* **2021**, *86*, 1283–1296.
30. (a) Wang, Y.-M.; Kuzniewski, C. N.; Rauniyar, V.; Hoong, C.; Toste, F. D. *J. Am. Chem. Soc.* **2011**, *133*, 12972–12975. (b) Niemeyer, Z. L.; Pindi, S.; Khrakovsky, D. A.; Kuzniewski, C. N.; Hong, C. M.; Joyce, L. A.; Sigman, M. S.; Toste, F. D. *J. Am. Chem. Soc.* **2017**, *139*, 12943–12946.

successfully applied to several enantioselective transformations like cyclopropanations, hydrofunctionalizations or cycloisomerization of 1,*n*-enynes.[31]

Additionally, the use of chiral counteranions has emerged as a powerful tool for gold(I)-catalyzed enantioselective transformations (Figure 5b).[32] Their main advantage is the closeness of the chiral information to the reactive center. However, the use of chiral counteranions is restricted to internal alkynes, since the basicity of the phosphates results in the deprotonation of terminal alkenes.[33] Furthermore, highly modular and one-pot binding phosphoramidite ligands have proven to be highly effective for the cyclization of allenes (Figure 5c) [34].

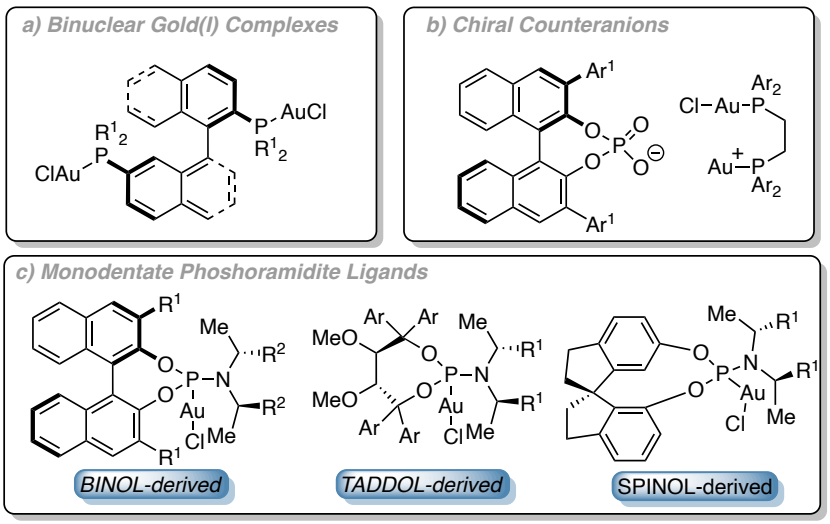
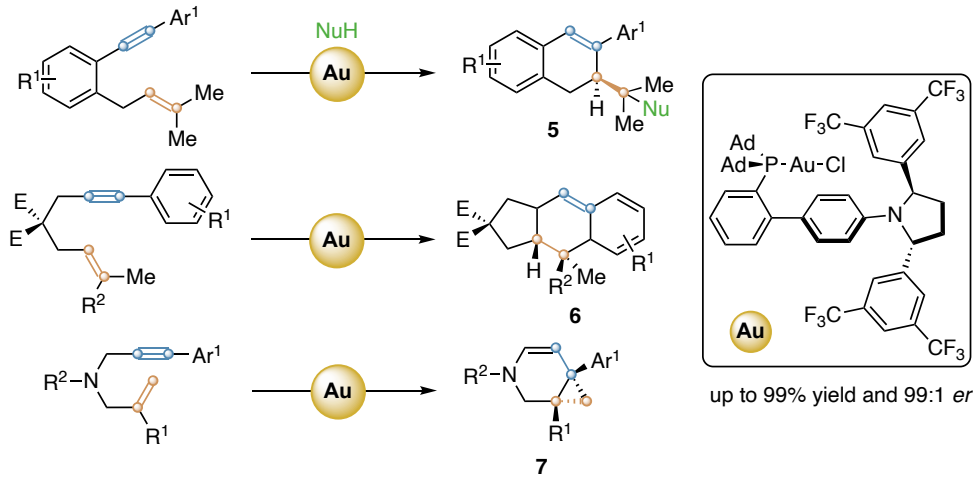


Figure 5. Ligand design approaches for asymmetric gold(I) catalysis.

Our group has been working on the development of new chiral gold(I) catalysts to assemble highly complex structures in an enantioselective manner. In this sense, in 2019, we reported the design and synthesis of a new family of chiral gold(I) catalysts based on a modified JohnPhos ligand including a C_2-2,5-diarylpyrrolidine that creates a chiral binding pocket.[35] These novel chiral catalysts were applied to the cycloisomerization of 1,6-enynes and the total synthesis of several members of the carexane family with excellent levels of enantioinduction (Scheme 7).

31. (a) Johansson, M. J.; Gorin, D. J.; Staben, S. T.; Toste, F. D. *J. Am. Chem. Soc.* **2005**, *127*, 18002–18003. (b) Chao, C.-M.; Beltrami, D.; Toullec, P. Y.; Michelet, V. *Chem. Commun.* **2009**, *45*, 6988–6990. (c) Zhang, Z.; Lee, S. D.; Widenhoefer, R. A. *J. Am. Chem. Soc.* **2009**, *131*, 5372–5373.
32. Inamdar, S. M.; Konala, A.; Patil, N. T. *Chem. Commun.* **2014**, *50*, 15124–15135.
33. (a) Raducan, M.; Moreno, M.; Bour, C.; Echavarren, A. M. *Chem. Comm.* **2012**, *48*, 52–54. (b) Ferrer, S.; Echavarren, A. M. *Organometallics* **2018**, *37*, 781–786.
34. (a) Luzung, M. R.; Mauleón, P.; Toste, F. D. *J. Am. Chem. Soc.* **2007**, *129*, 12402–12403. (b) Alonso, I.; Trillo, B.; López, F.; Montserrat, S.; Ujaque, G.; Castedo, L.; Lledós, A.; Mascareñas, J. L. *J. Am. Chem. Soc.* **2009**, *131*, 13020–13030. (c) Teller, H.; Corbet, M.; Mantilli, L.; Gopakumar, G.; Goddard, R.; Thiel, W.; Fürstner, A. *J. Am. Chem. Soc.* **2012**, *134*, 15331–15342.
35. Zuccarello, G.; Mayans, J. G.; Escofet, I.; Scharnagel, D.; Kirillova, M. S.; Pérez-Jimeno, A. H.; Calleja, P.; Boothe, J. R.; Echavarren, A. M. *J. Am. Chem. Soc.* **2019**, *141*, 11858–11863.



Scheme 7. Enantioselective folding of enynes by gold catalysis.

Later, this family of gold(I) complexes was expanded, and their reactivity was studied computationally with the development of a NEST analysis of the chiral binding pocket.[36]

In 2021, we reported the development of a new family of chiral gold(I)-cavitand complexes that were successfully applied to the alkoxycyclization of 1,6-enynes and the first total synthesis of (+)-mafaicheenamine C (Figure 6a).[37] Moreover, in 2022, we presented the enantioselective 5-*exo*-dig and 6-*endo*-dig cyclization of 1,6-enynes by the combination of an achiral phosphinourea gold(I) chloride complex with a BINOL-derived phosphoramidate silver(I) salt. In this case, the H-bond donor of the ligand allows a precise positioning of the chiral counteranion (Figure 6b).[38]

36. Zuccarello, G.; Nannini, L. J.; Arroyo-Bondía, A.; Fincias, N.; Arranz, I.; Pérez-Jimeno, A. H.; Peeters, M.; Martín-Torres, I.; Sadurní, A.; García-Vázquez, V.; Wang, Y.; Kirillova, M. S.; Montesinos-Magraner, M.; Caniparoli, U.; Núñez, G. D.; Maseras, F.; Besora, M.; Escofet, I.; Echavarren, A. M. *JACS Au* **2023**, *3*, 1742–1754.
37. Martín-Torres, I.; Ogalla, G.; Yang, J.-M.; Rinaldi, A.; Echavarren, A. M. *Angew. Chem. Int. Ed.* **2021**, *60*, 9339–9344.
38. (a) Franchino, A.; Martí, À.; Echavarren, A. M. *J. Am. Chem. Soc.* **2022**, *144*, 3497–3509. (b) Martí, À.; Montesinos-Magraner, M.; Echavarren, A. M.; Franchino, A. *Eur. J. Org. Chem*. **2022**, e202200518.

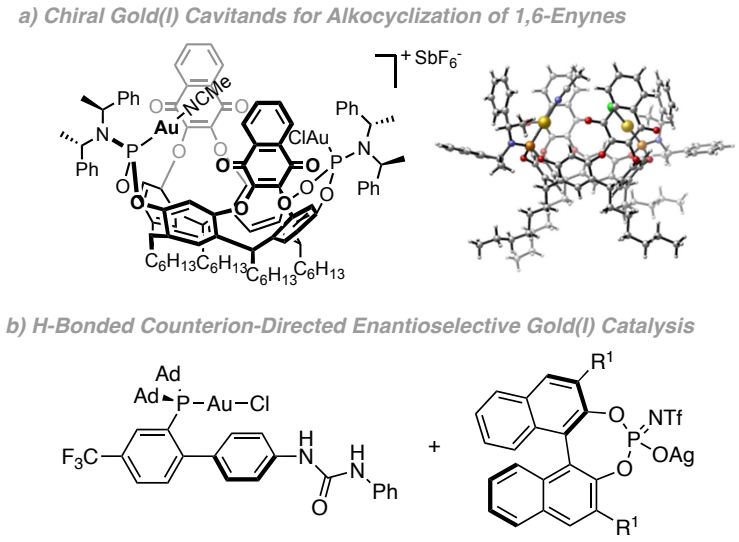
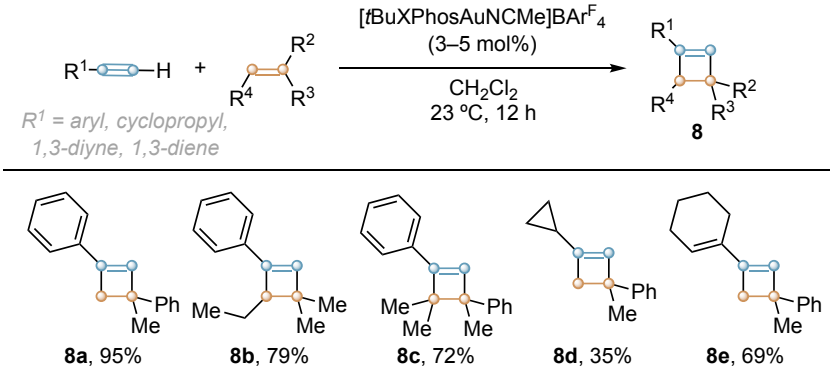


Figure 6. New gold(I) complexes for enantioselective gold catalysis.

Gold(I)-Catalyzed Intermolecular Reactions of Alkynes with Alkenes

Gold(I)-catalyzed intramolecular reactions, as the cycloisomerization of 1,*n*-enynes, have been widely explored in the past decades.[39] However, the development of the intermolecular version of these transformations remains highly challenging.[40] One of the potential problem these transformations face is the competitive binding of the alkene to the gold(I) catalyst forming unreactive (η^2-alkene)gold(I) complexes. Furthermore, possible undesired oligomerization processes could be induced.[41]

Our group reported in 2010 the first example of intermolecular gold(I)-catalyzed cycloaddition of terminal alkynes with alkenes to afford cyclobutenes **8** (Scheme 8).[42] The use of gold(I) catalysts with bulky ligands turned out to be key for the success of the reaction since they selectively activate alkynes, avoiding competitive pathways.

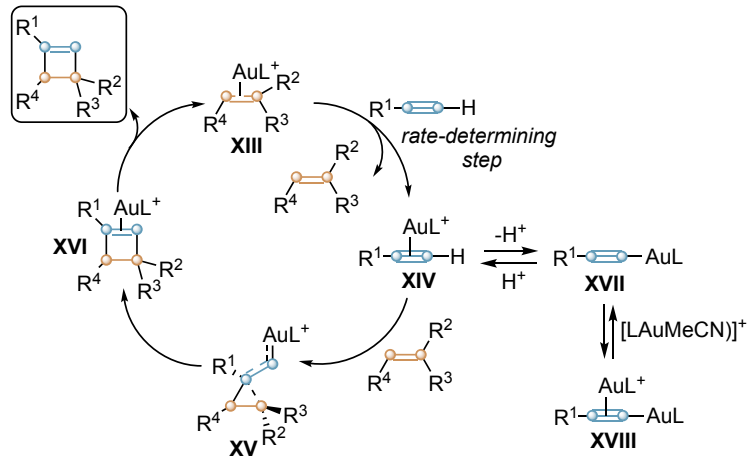


Scheme 8. Selected examples of gold(I)-catalyzed [2+2] cycloaddition of alkynes with alkenes to obtain cyclobutenes.

39. (a) Nieto-Oberhuber, C.; López, S.; Echavarren, A. M. *J. Am. Chem. Soc.* **2005**, *127*, 6178–6179. (b) Hashmi, A. S. K. *Chem. Rev.* **2007**, *107*, 3180–3211.
40. García-Morales, C.; Echavarren, A. M. *Synlett* **2018**, *29*, 2225–2237.
41. Urbano, J.; Hormigo, A. J.; Frémont, P. de; Nolan, S. P.; Díaz-Requejo, M. M.; Pérez, P. J. *Chem. Commun.* **2008**, *6*, 759–761.
42. de Orbe, M. E.; Echavarren, A. M. *Eur. J. Org. Chem.* **2018**, *22*, 2740–2752.

Following studies proved that not only the choice of the ligand is crucial, but also the counterion used for the reaction. Specifically, changing SbF_6^- for a less basic $BAr^F{}_4^-$ increased the yields between 10 and 30%. After studying in deep the influence of the counterion, it could be demonstrated a decrease in the formation of unreactive σ,π-(alkynyl)digold(I) complex when $BAr^F{}_4^-$ was used.[43]

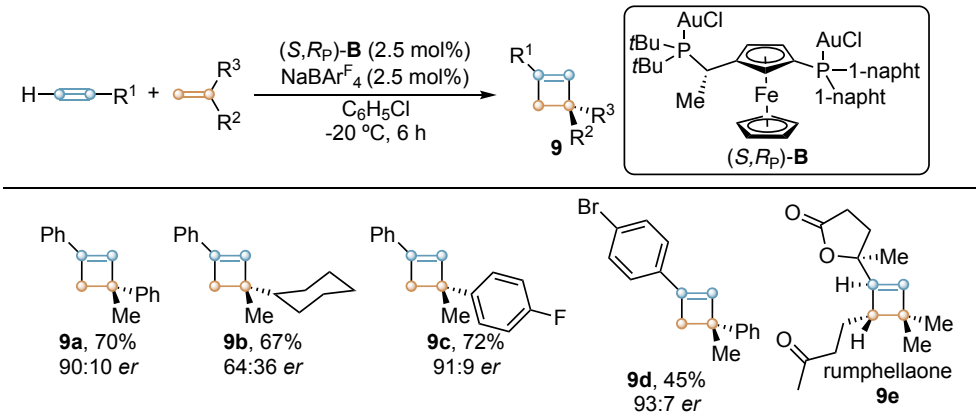
The catalytic cycle starts with the formation of (η^2-alkene) gold(I) complex **XIII** that upon associative ligand exchange with the terminal alkyne gives rise to catalytically active complex **XIV** in what often constitutes the rate determining step (Scheme 9). Complex **XIV** reacts intermolecularly with the alkene giving rise to the cyclopropyl gold(I) carbene **XV**. The final product is obtained via ring expansion to afford complex **XVI** and released through another associative ligand exchange. Additionally, **XIV** can evolve into σ-complex **XVII** and react with another molecule of the catalyst to form σ,π-digold(I) complex **XVIII**.



Scheme 9. Mechanism for the gold(I)-catalyzed [2+2] cycloaddition reaction.

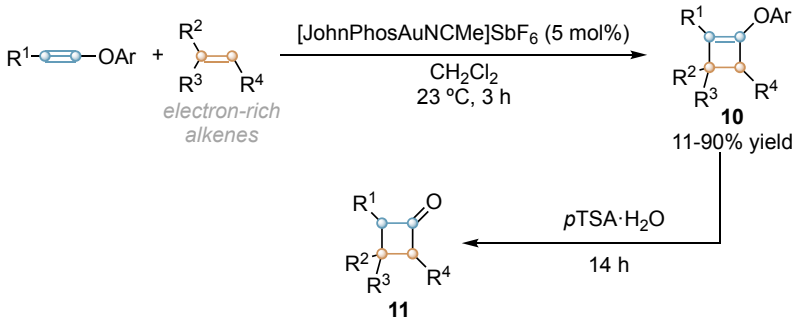
Continuing with this work, in 2017, our group reported the first enantioselective version of the gold(I)-catalyzed [2+2] cycloaddition of terminal alkynes and alkenes using a non-C_2-chiral Josiphos digold(I) complex (*S*, R_P)-**B** (Scheme 10).[44] DFT studies suggest that only one of the gold(I) centers is required to induce enantioselectivity. A wide variety of cyclobutenes (**9**) could be synthetized with moderate to excellent enantioselectivities. Additionally, this methodology was applied in the total synthesis of rumphellaone A (**9e**) in 9 steps.

43. Homs, A.; Obradors, C.; Lebœuf, D.; Echavarren, A. M. *Adv. Synth. Catal.* **2014**, *356*, 221–228.
44. García-Morales, C.; Ranieri, B.; Escofet, I.; López-Suarez, L.; Obradors, C.; Konovalov, A. I.; Echavarren, A. M. *J. Am. Chem. Soc.* **2017**, *139*, 13628–13631.



Scheme 10. Enantioselective gold(I)-catalyzed [2+2] cyclization and application to the total synthesis of rumphellaone A **9e**.

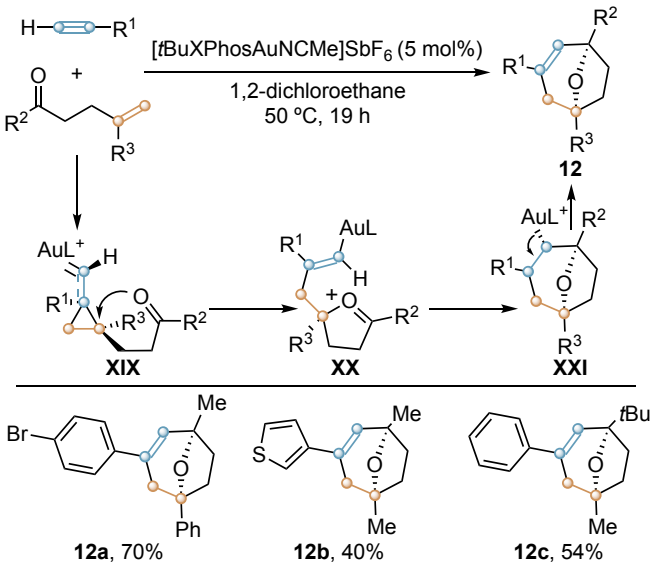
More recently, in 2021, our group reported the synthesis of cyclobutanones **11** by gold(I)-catalyzed cycloaddition of ynol ethers and alkenes.[45] After the [2+2] cycloaddition reaction, enol ethers **10** are obtained and can be easily converted into the desired ketones upon acid treatment (Scheme 11).



Scheme 11. Gold(I)-catalyzed synthesis of cyclobutanones.

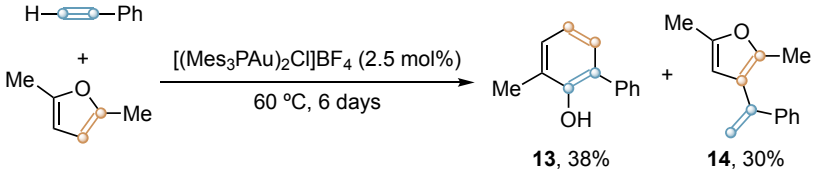
The first reported examples of gold(I)-catalyzed cycloadditions were based on the use of simple alkenes.[42] However, over the years, researchers have been able to increase the molecular complexity of the alkene moiety for these intermolecular transformations. One remarkable example is the [2+2+2] cycloaddition cascade between alkynes and oxoalkenes.[46] This cycloaddition involves the reaction of γ,δ-unsaturated ketones with alkynes to form oxabicyclo[3.2.8]oct-3-enes **12**. Similar to the [2+2] cycloaddition, the mechanism begins with the formation of the cyclopropyl gold(I) carbene intermediate **XIX** followed by a regioselective nucleophilic attack from the carbonyl group. The oxonium cation **XX** formed undergoes a Prins-type cyclization and demetallation to afford intermediate **XXI** that upon metal elimination gives rise to the product **12** (Scheme 12).

45. Zanini, M.; Cataffo, A.; Echavarren, A. M. *Org. Lett.* **2021**, *23*, 8989–8993.
46. Obradors, C.; Echavarren, A. M. *Chem. Eur. J.* **2013**, *19*, 3547–3551.



Scheme 12. [2+2+2] Gold(I)-catalyzed cycloaddition of alkenes with oxoalkenes: selected examples and proposed reaction mechanism.

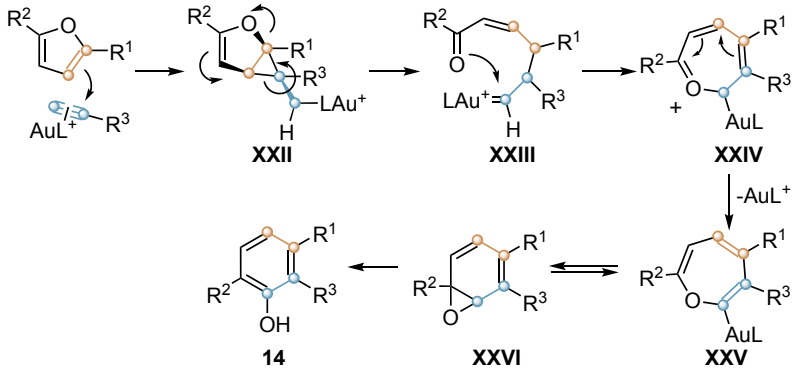
Gold(I)-catalyzed cycloadditions have been also successfully applied to the synthesis of phenols from benzofuranes. Until very recently only one example of this reaction was reported using the Schmidbaur-Bayler binuclear gold(I) complex ($[(Mes_3PAu)_2Cl]BF_4$) as catalyst[47] but with low yields and under extended reaction times and harsh conditions (Scheme 13).[48] Moreover, in addition to the desired phenol **13**, benzofuran **14** was also obtained as a major side product.



Scheme 13. Intermolecular precedent of the formation of phenols.

In 2013, our group discovered that the use of NHC ligands in combination with $BAr^F{}_4^-$ as counterion remarkably improved the yield of the desired phenol.[49] Additionally, they proposed a mechanism based on the formation of the cyclopropyl gold carbene **XXII** followed by ring opening and formation of a new carbene **XXIII** that cyclized to generate the oxonium cation **XXIV**. Upon elimination of gold(I), oxepin **XXV** is generated in equilibrium with the arene-oxide tautomer **XXVI** whose opening leads to the formation of the phenol product **14** (Scheme 14).

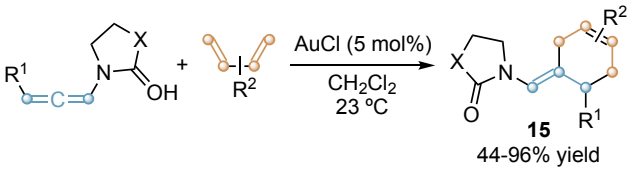
47. Bayler, A.; Bauer, A.; Schmidbaur, H. *Chem. Ber./Recueil* **1997**, *130*, 115–118.
48. Hashmi, A. S. K.; Blanco, M. C.; Kurpejović, E.; Frey, W.; Bats, J. W. *Adv. Synth. Catal.* **2006**, *348*, 709–713.
49. Huguet, N.; Lebœuf, D.; Echavarren, A. M. *Chem. Eur. J.* **2013**, *19*, 6581–6585.



Scheme 14. Mechanism for the gold(I)-catalyzed synthesis of phenols.

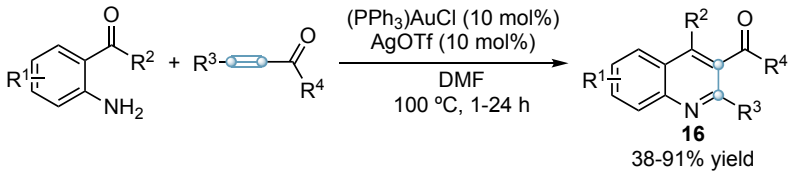
Even though gold(I)-catalyzed cycloadditions between alkenes and alkynes have been widely explore, over the past decades, other cycloadditions reactions have been studied.

It was not until 2011 when the first example of intermolecular cycloadditions of allenes and alkenes was reported.[50] This novel methodology involved the first gold(I)-catalyzed (4+2) cycloaddition of allenamides and acyclic conjugated dienes (Scheme 15).



Scheme 15. Gold(I)-catalyzed cycloaddition of allenes and 1,3-dienes.

Finally, also a wide variety of gold(I)-catalyzed heterocyclization reactions have been reported in the past years. These novel transformations have allowed, for example, the synthesis of polyfunctionalized quinolines (**16**) by combination of 2-aminoaryl carbonyls and ketone-substituted internal alkynes (Scheme 16).[51]

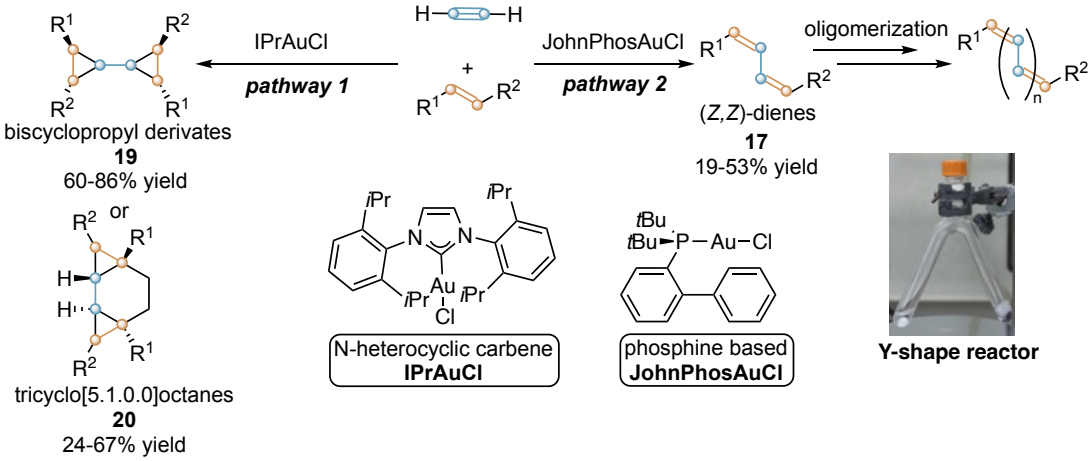


Scheme 16. Gold(I)-catalyzed intermolecular cycloaddition of 2-aminoaryl carbonyls and internal alkynes.

High complex alkene partners have been employed in these intermolecular cycloadditions, however, most of the examples reported are limited to the used arylalkynes.[46]

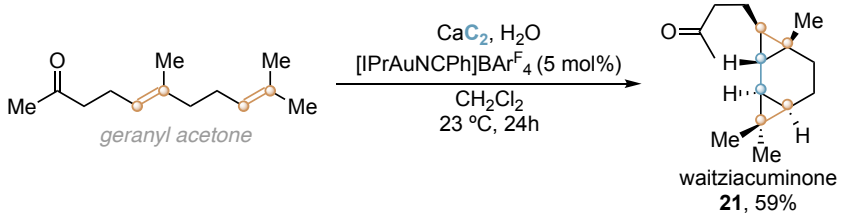
50. Faustino, H.; López, F.; Castedo, L.; Mascareñas, J. L. *Chem. Sci*. **2011**, *2*, 633–637.
51. Cai, S.; Zeng, J.; Bai, Y.; Liu, X.-W. *J. Org. Chem.* **2012**, *77*, 801–807.

Exploring the use of different alkynes, our group recently reported the gold(I)-catalyzed reaction between acetylene gas and *trans*-stilbene by *in situ* formation of acetylene gas from CaC_2 and H_2O.[52] The reaction proceeds through the formation of a cyclopropyl gold(I)-carbene and depending on the nature of the gold catalyst, it can lead either to the formation of (*Z,Z*)-1,3-dienes (**17**) or biscyclopropanes (**19** or **20**) (Scheme 17). The yields obtained were moderate due to oligomerization processes that took place through insertion of C_2 units in the diene products. This process has been observed before for intermolecular reaction of alkenes and alkynes because the products contain double bonds that could keep reacting with the gold catalyst.[53]



Scheme 17. Gold(I)-catalyzed intermolecular reaction of acetylene gas with alkenes.

Moreover, this novel methodology was applied to the first total synthesis in one step of sesquiterpene waitziacuminone[54] (**21**) from commercially available geranyl acetone (Scheme 18).

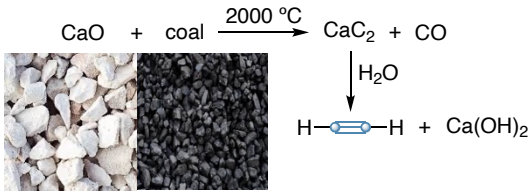


Scheme 18. Total synthesis of waitziacuminone in one step.

52. Scharnagel, D.; Escofet, I.; Armengol-Relats, H.; de Orbe, M. E.; Korber, J. N.; Echavarren, A. M. *Angew. Chem. Int. Ed.* **2020**, *59,* 4888–4891.
53. Brown, T. J.; Dickens, M. G.; Widenhoefer, R. A. *J. Am. Chem. Soc.* **2009**, *131*, 6350–6351.
54. Jakupovic, J.; Schuster, A.; Bohlmann, F.; King, R. M.; Haegit, L. *Phytochem.* **1989**, *28*, 1943–1948.

Acetylene: A Feedstock for Chemical Industry

Ever since 1916, with the beginning of the production of acetaldehyde by acetylene hydration, the use of acetylene in chemical industry has grown exponentially.[55] However, with the introduction of petrochemistry, other small alkene like ethylene or propylene have displaced acetylene due to their cheaper production or easier handling. Despite this, acetylene is more reactive and often provides higher overall selectivity.[56] There are several well-established methods to produce acetylene. The most classical method is known as the "calcium carbide process". In this procedure, CaC_2 is generated from the reaction of quicklime (CaO) and coal at 2000 ºC which then, upon treatment with water, produces acetylene gas (Scheme 19).[57]



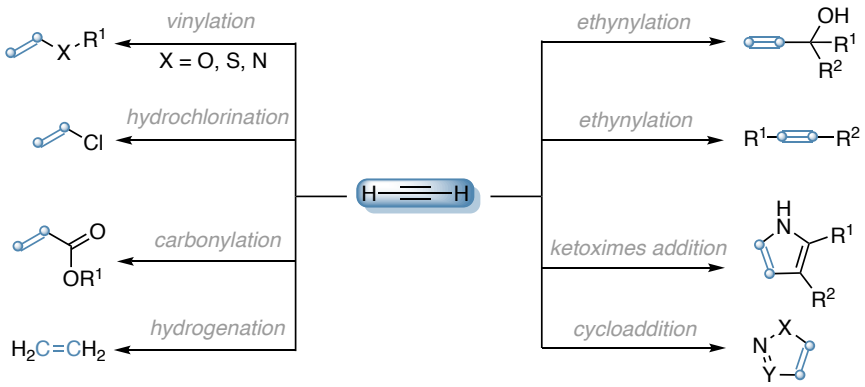
Scheme 19. Acetylene production by the calcium carbide process.

Moreover, acetylene can also be produced by different cracking processes depending on the heat supply. These methods can take place through partial combustion or electrothermal processes.[57]

The relevance of acetylene-based chemistry can be demonstrated by the remarkable growth of its product market that reached 1.9 million tones in 2020 and will continue growing until 2030.[58]

The chemical applications of acetylene are highly diverse, being vinylation reactions the most explored ones (Scheme 20).[59] Furthermore, the hydrochlorination of acetylene is the most widely used route to obtain vinyl chloride.[60] Carbonylation of acetylene represents a powerful tool for the industrial production of acrylic acid (average production 3 tons per year).[61] Worth mentioning also is the ethynylation of acetylene that gives access to different substituted acetylenes.[62]

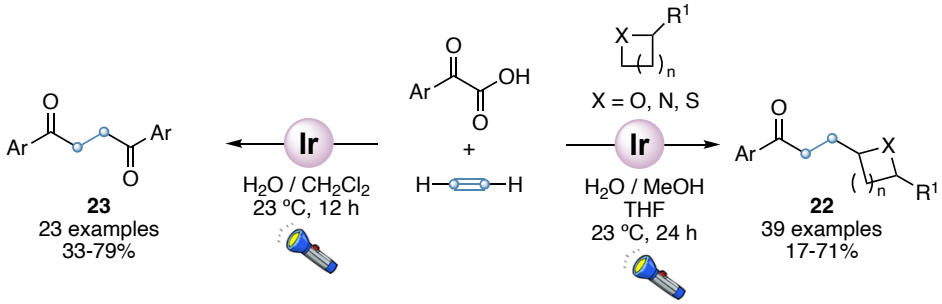
55. Trotuş, I.-T.; Zimmermann, T.; Schüth, F. *Chem. Rev.* **2014**, *114*, 1761–1782.
56. (a) Arpe, H.-J. *Industrial Organic Chemistry*, 5th ed.; Wiley-VCH:Weinheim, Germany, 2010. (b) Steinborn, D. *Fundamentals of Organometallic Catalysis*; Wiley-VCH: Weinheim, Germany, 2012.
57. Schobert, H. *Chem. Rev.* **2014**, *114*, 1743–1760.
58. (a) Rodygin, K.; Ledovskaya, M.; Voronin, V.; Lotsman, K.; Ananikov, V. P. *Eur. J. Org. Chem*. **2021**, *2021*, 43−52. (b) Ledovskaya, M. S.; Voronin, V. V.; Rodygin, K. S.; Ananikov, V. P. *Synthesis* **2022**, *54*, 999−1042.
59. Voronin, V. V.; Ledovskaya, M. S.; Bogachenkov, A. S.; Rodygin, K. S.; Ananikov, V. P. *Molecules* **2018**, *23*, 2442.
60. Pässler, P.; Hefner, W.; Buckl, K.; Meinass, H.; Meiswinkel, A.; Wernicke, H. J.; Ebersberg, G.; Müller, R.; Bässler, J.; Behringer, H.; *Acetylene*; Wiley-VCH Verlag GmbH & Co. KGaA: Weinheim, Germany, 2011; Volume 1.
61. Ohara, T.; Sato, T.; Shimizu, N.; Prescher, G.; Schwind, H.; Weiberg, O.; Marten, K. *Acrylic acid and derivatives. In Ullmann's Encyclopedia of Industrial Chemistry*; Wiley-VCH Verlag GmbH & Co. KGaA: Weinheim, Germany, 2003; Volume 1, pp. 347–364.
62. Kutepow, N.; Viehe, H.G. *Chemistry of Acetylenes*; Marcel Dekker Inc.: New York, NY, USA, 1969.



Scheme 20. Acetylene reactivity.

Despite its unique properties and its high reactivity, the use of acetylene in chemical industry is quite reduced and only a few examples of its employment in catalysis have been report up to date.

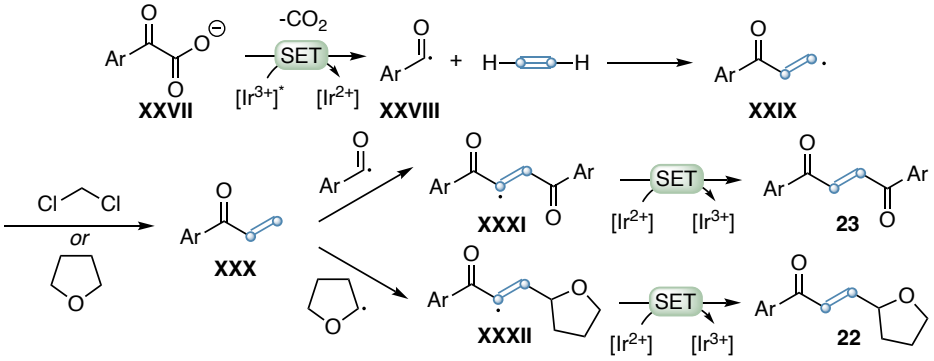
In 2022, Zhu and coworkers reported a remarkable example of the use of acetylene for the photoredox-catalyzed synthesis of C_2-linked functionalized molecules.[63] Taking advantage of the molecular glue strategy, they efficiently prepared a wide range of functionalized molecules with acetylene gas under mild conditions (Scheme 21).



Scheme 21. Synthesis of C_2-linked functional molecules with acetylene gas.

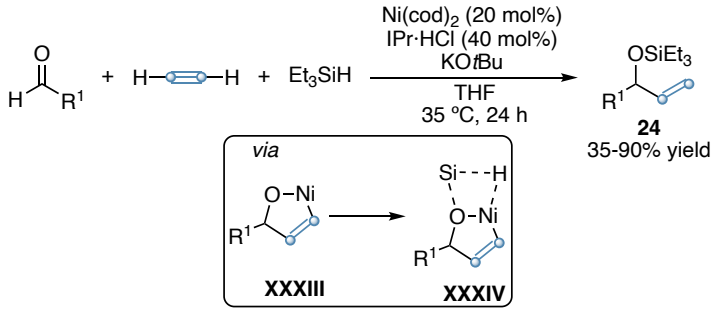
A plausible reaction mechanism starts with an oxidative single electron transfer (SET) to generate an acyl radical **XXVIII** that undergoes addition to acetylene affording a vinyl radical (**XXIX**). This vinyl radical can react further either with CH_2Cl_2 or THF through a hydrogen atom transfer (HAT) that gives rise to intermediates **XXXI** and **XXXII**. Finally, after another single electron transfer (SET), the C_2 products **22** and **23** are formed (Scheme 22).

63. Yang, B.; Lu, S.; Wang, Y.; Zhu, S. *Nat. Commun.* **2022**, *13*, 1858–1870.



Scheme 22. Plausible mechanism for the iridium-catalyzed synthesis of C_2-linked molecules.

More recently, in 2023, the same research group reported the synthesis of vinyl-substituted alcohols through nickel catalysis and using, as in their previous work, acetylene as a C_2 synthon.[64] The reaction takes place via a 5-membered oxa-metallacycle (**XXXIII**) that is formed from the cyclometallation of an aldehyde and acetylene (Scheme 23).



Scheme 23. Synthesis of vinyl alcohols through cyclometallation.

64. Lin, Z.; Liu, B.; Wang, Y.; Li, S.; Zhu, S. *Chem. Sci.* **2023**, *14*, 1912–1918.

UNIVERSITAT ROVIRA I VIRGILIDevelopment of Gold(I)-Catalyzed Reactions Between Alkenes and Acetylene Gas
Tania Medina Gil

UNIVERSITAT ROVIRA I VIRGILIDevelopment of Gold(I)-Catalyzed Reactions Between Alkenes and Acetylene Gas
Tania Medina Gil

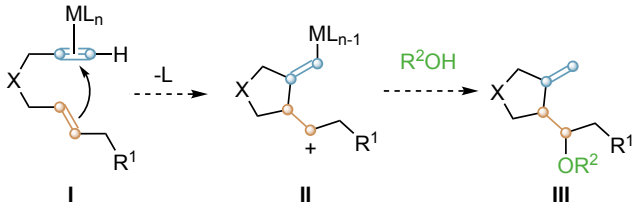
Chapter I
Gold(I)-Catalyzed Intermolecular Heterovinylation Reactions Using Acetylene Gas

UNIVERSITAT ROVIRA I VIRGILIDevelopment of Gold(I)-Catalyzed Reactions Between Alkenes and Acetylene Gas
Tania Medina Gil

Introduction

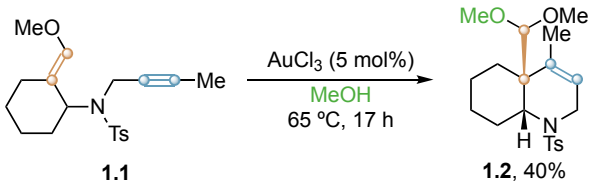
Gold(I)-Catalyzed Heterocyclization Reactions

As has been mentioned in the General Introduction, electrophilic transition metal complexes are known to catalyze the cycloisomerization of 1,n-enynes under mild conditions.[1] Inspired by this reactivity, our group envisioned the possibility of trapping transient carbocation **II** (formed after the cyclization) with a R-OH nucleophile to give alkoxylated product **III** (Scheme 1.1).[2]



Scheme 1.1. Transition metal catalyzed alkoxycyclization reaction.

First examples of these transformations were reported using $PtCl_2$ as catalyst, but these methodologies could later be extended to gold(I) complexes. Specifically, in 2003, our group reported that more reproducible results were obtained when $AuCl_3$ was used instead of $PtCl_2$ for the 6-*endo*-dig cyclization of enyne **1.1** (Scheme 1.2).[3]



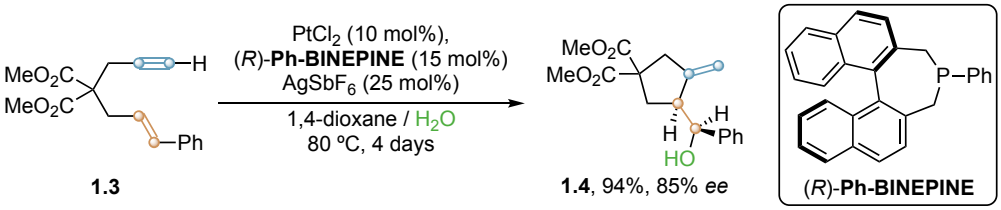
Scheme 1.2. First gold(I)-catalyzed alkoxycyclization reaction.

Ever since, a wide variety of gold(I)-catalyzed alkoxycyclization reactions have been reported.[4] These reactions take place in a regio- and stereospecific manner through the Markovnikov addition of the oxygen nucleophile to the η^2-$(AuL)^+$-activated alkyne complex.[5]

Furthermore, the enantioselective version of these transformations has been broadly explored. In 2004, Genêt's group developed one of the first examples of enantioselective platinum(II)-catalyzed

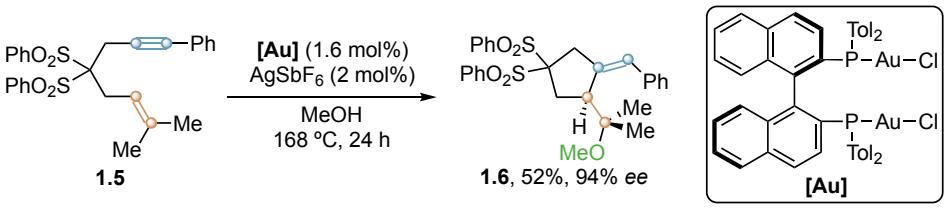
1. (a) Trost, B. M.; Lautens, M.; Chan, C.; Jebaratnam, D. J.; Mueller, T. A, *J. Am. Chem. Soc.* **1991**, *113*, 636–644. (b) Trost, B. M.; Haffner, C. D.; Jebaratnam, D. J.; Krische, M. J.; Thomas, A. P. *J. Am. Chem. Soc.* **1999**, *121*, 6183–6192.
2. Méndez, M.; Muñoz, M. P.; Echavarren, A. M. *J. Am. Chem. Soc.* **2000**, *122*, 11549–11550.
3. Nevado, C.; Cárdenas, D. J.; Echavarren, A. M. *Chem. Eur. J.* **2003**, *9*, 2627–2635.
4. Nieto-Oberhuber, C.; Muñoz, M. P.; López, S.; Jiménez-Núñez, E.; Nevado, C.; Herrero-Gómez, E.; Raducan, M.; Echavarren, A. M. *Chem. Eur. J.* **2006**, *12*, 1677–1693.
5. Zhang, L.; Sun, J.; Kozmin, S. A. *Adv. Synth. Catal.* **2006**, *348*, 2271–2296.

hydroxycyclization of 1,6-enynes (Scheme 1.3).[6] Functionalized enantioenriched five-membered carbo- and heterocycles were obtained in excellent yields using monodentate phosphines (Scheme 1.3).



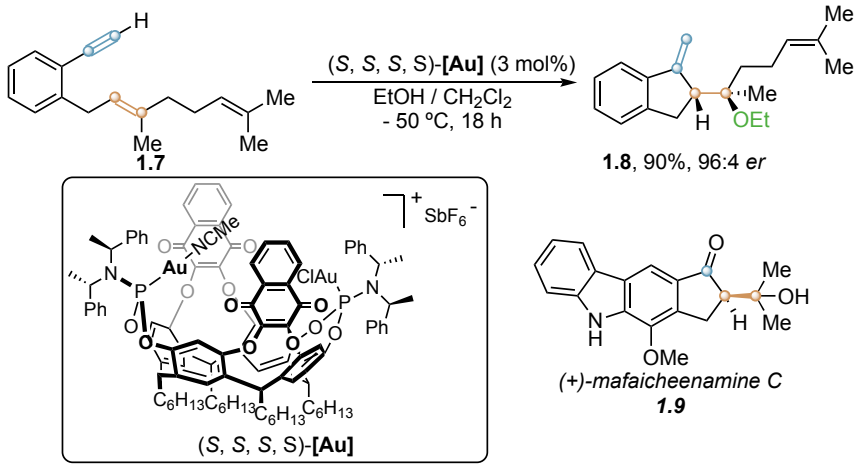
Scheme 1.3. Platinum-catalyzed asymmetric alkoxycyclization of 1,6-enynes.

One year later, our group reported the first example of enantioselective gold(I)-catalyzed alkoxycyclization reaction of 1,6-enynes.[7] The cyclized products were obtained with a good level of enantioinduction and under milder conditions (Scheme 1.4).



Scheme 1.4. First example of enantioselective gold(I)-catalyzed alkoxycyclization.

Over the years many other examples of these enantioselective reactions have been developed. For instance, in 2021 our group synthetized a new family of chiral gold(I)-cavitands for the enantioselective alkoxycyclization of phenyl-linked 1,6-enynes **1.7** (Scheme 1.5).[8] The applicability of this methodology was demonstrated in the first total synthesis of alkaloid (+)-mafaicheenamine C (**1.9**).

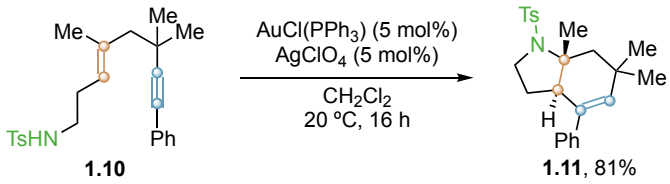


Scheme 1.5. Enantioselective alkoxycyclization of 1,6-enynes with gold(I) cavitands.

6. Charruault, L.; Michelet, V.; Taras, R.; Gladiali, S.; Genêt, J.-P. *Chem. Commun.* **2004**, *7*, 850–851.
7. Muñoz, M. P.; Adrio, J.; Carretero, J. C.; Echavarren, A. M. *Organometallics* **2005**, *24*, 1293–1300.
8. Martín-Torres, I.; Ogalla, G.; Yang, J.-M.; Rinaldi, A.; Echavarren, A. M. *Angew. Chem. Int. Ed.* **2021**, *60*, 9339–9344.

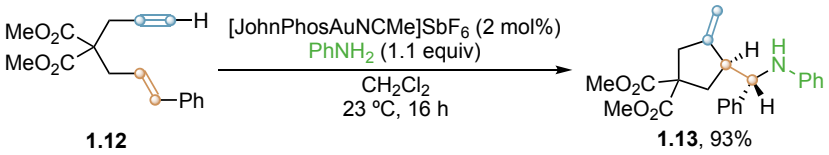
Even though alkoxycyclizations and their versions have been broadly studied in the past decades, the inter- and intramolecular use of amines as nucleophiles for these reactions remains challenging. The main hurdle to overcome for these transformations is the high tendency of amines to coordinate with Lewis acidic gold(I) complexes, thus reducing their availability to activate alkynes.[9]

One of the first examples of the use of amines as nucleophiles was developed by Kozmin and coworkers in 2005, where they reported the gold(I)-catalyzed double cyclization of 1,5-enynes with nitrogen-based nucleophiles. This mild catalytic methodology provided access to azabicyclic alkenes such as **1.11** in excellent yields (Scheme 1.6).[10]



Scheme 1.6. Synthesis of azabicyclic alkenes.

A few years later, our group reported the intermolecular reaction of 1,6-enynes with a wide variety of substituted anilines under mild catalytic conditions (Scheme 1.7).[11]



Scheme 1.7. Intermolecular gold(I)-catalyzed aminocyclization.

Chromanes as Privileged Heterocyclic Scaffolds

Chromanes (3,4-dihydro-2*H*-1-benzopyran) are present in a huge variety of natural products and agrochemicals and pharmaceutical molecules.[12] For example, this skeleton can be found in natural products like (+)-catechin (excellent antioxidant)[13] or α-tocopherol (member of the vitamin E family with radical chain-breaking properties)[14] as well as commercially available drugs such as Deguelin (anti-tumoral properties)[15] or Cromakalim (powerful anti-hypertensive) (Figure 1.1).

9. Young, P. C.; Green, S. L. J.; Rosair, G. M.; Lee, A.-L. *Dalton Trans*. **2013**, *42*, 9645–9653.
10. Zhang, L.; Kozmin, S. A. *J. Am. Chem. Soc*. **2005**, *127*, 6962–6963.
11. Miller, R.; Carreras, J.; Muratore, M. E.; Gaydou, M.; Camponovo, F.; Echavarren, A. M. *J. Org. Chem*. **2016**, *81*, 1839–1849.
12. Li, W.; Shuai, W.; Xu, F.; Sun, H.; Xu, S.; Yao, H.; Liu, J.; Yao, H.; Zhu, Z.; Xu, J. *ACS Med. Chem. Lett*. **2018**, *9*, 974–979.
13. (a) Raab, T.; Barron, D.; Vera, F. A.; Crespy, V.; Oliveira, M.; Williamson, G. *J. Agric. Food Chem*. **2010**, *58*, 2138–2149. (b) Bernatoniene, J.; Kopustinskiene, D. M. *Molecules* **2018**, *23*, 965.
14. Packer, J. E.; Slater, T. F.; Willson, R. L. *Nature* **1979**, *278*, 737–738.
15. Wang, Y.; Ma, W.; Zheng, W. *Mol. Clin. Oncol.* **2013**, *1*, 215–219.

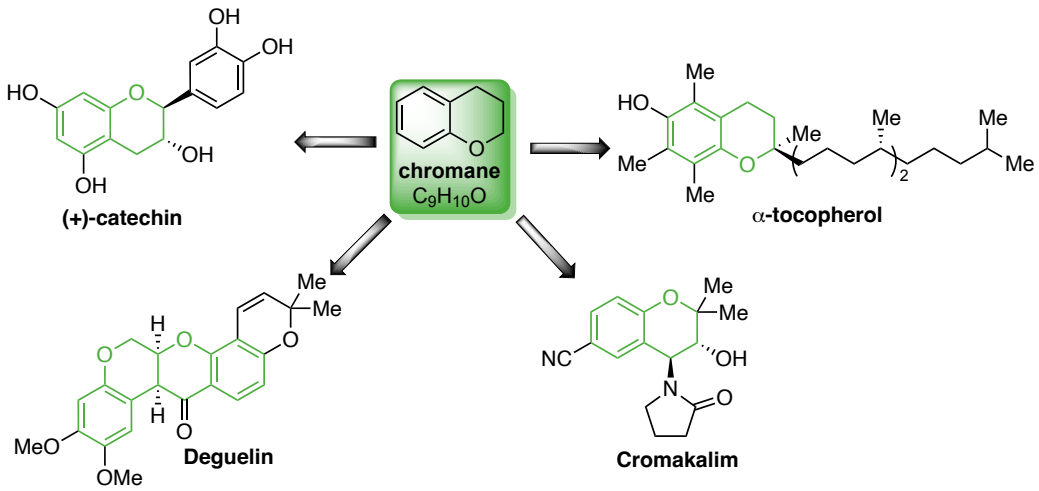
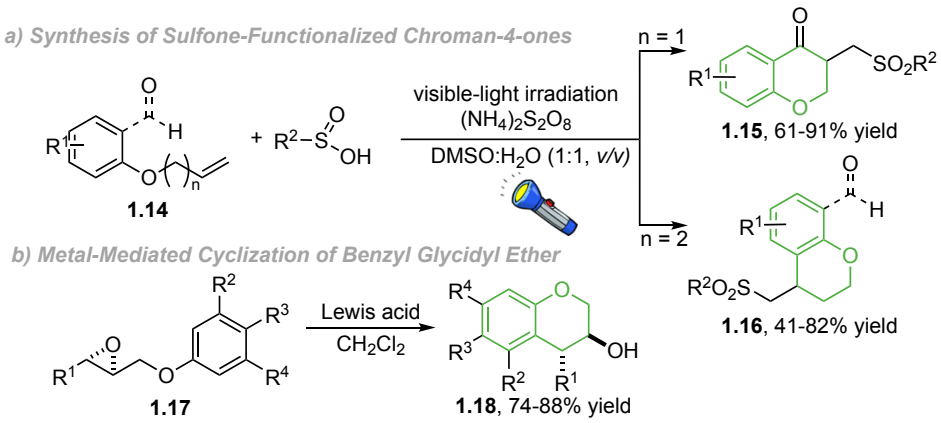


Figure 1.1. Chromane scaffold in nature and biologically active compounds.

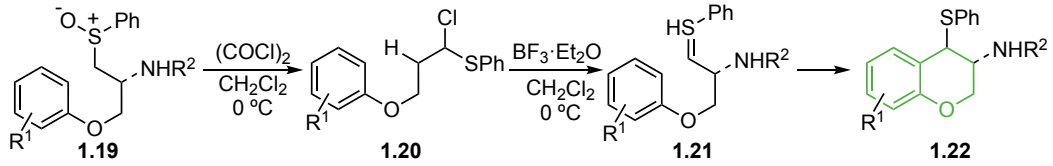
Several methods for the synthesis of chromanes have been developed over the years, most of them based on C–C bond formation processes. Among the wide variety of examples, it is worth highlighting the selective intramolecular radical cyclization of (allyloxy)arylaldehydes (**1.14**) with arylsulfinic acids which afforded the corresponding sulfone-functionalized chroma-4-ones **1.15** and **1.16** in excellent yields (Scheme 1.8a).[16] Moreover, the Lewis acid mediated cyclization of aryl glycidyl ethers (**1.17**) reported in 2008 by the group of Pericàs also constitutes a versatile method for the synthesis of 3-chromanols **1.18** (Scheme 1.8b).[17]



Scheme 1.8. Methodologies for the synthesis of chromanes.

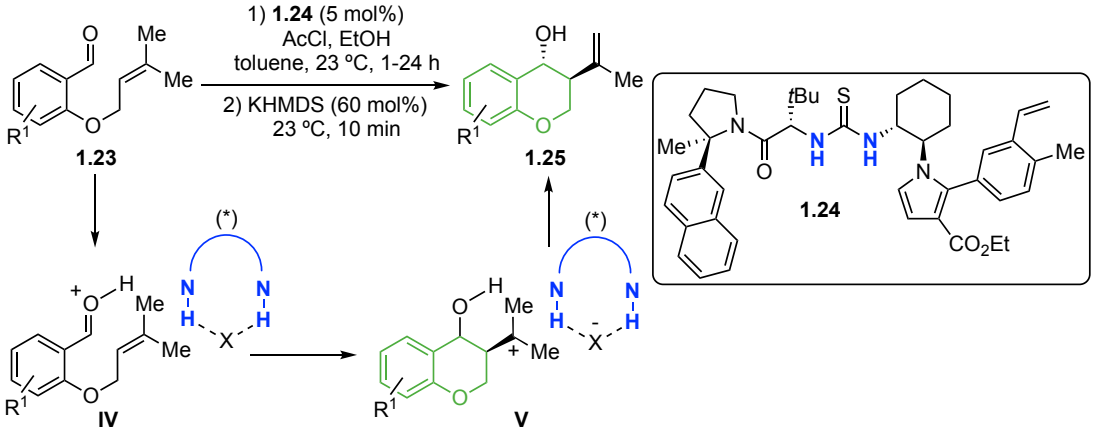
The Pummerer reaction and its variants have also been successfully employed for the synthesis of these heterocyclic scaffolds.[18] However, the scope of nucleophiles is quite limited, presumably due to the competition between nucleophiles and the byproducts obtained (Scheme 1.9).

16. Mei, Y.; Zhao, L.; Liu, Q.; Ruan, S.; Wang, L.; Li, P. *Green Chem.* **2020**, *22*, 2270–2278.
17. Marcos, R.; Rodríguez-Escrich, C.; Herrerías, C. I.; Pericàs, M. A. *J. Am. Chem. Soc.* **2008**, *130*, 16838–16839.
18. Acosta-Guzmán, P.; Rodríguez-López, A.; Gamba-Sánchez, D. *Org. Lett.* **2019**, *21*, 6903–6908.



Scheme 1.9. Synthesis of chromanes by Pummerer reaction.

Moreover, the enantioselective synthesis of chromanes has also been explored. Jacobsen and co-workers reported in 2021 an innovative Prins-type cyclization of alkenyl aldehydes (**1.23**) to afford 4-chromanols **1.25** in good yields and excellent enantioselectivities.[19] This approach is based on the cooperative asymmetric catalysis of chiral dual-hydrogen bond donors (HBDs) with acid media (Scheme 1.10).



Scheme 1.10. Enantioselective synthesis of chromanes by Prins cyclization.

Nitrogen Heterocycles in Drugs and Natural Products

Nitrogen heterocycles are widely used in medicinal chemistry for the treatment of human diseases.[20] In fact, 59% of the number of small-molecule drugs approved by the FDA (Food and Drug Administration) contains a nitrogen heterocycle, specifically, 72 of these compounds contain a piperidine ring and 37 a pyrrolidine one (Figure 1.2).[21]

19. Kutateladze, D. A.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2021**, *143*, 20077–20083.
20. (a) O'Hagan, D. *Nat. Prod. Rep.* **1997**, *14*, 637–651. (b) Li Petri, G.; Raimondi, M. V.; Spanò, V.; Holl, R.; Barraja, P.; Montalbano, A. *Top. Curr. Chem. (Cham)* **2021**, *379*, 34.
21. Gharpure, S. J.; Patel, R. K.; Gupta, K. S. *Org. Lett.* **2023**, *25*, 5850–5855.

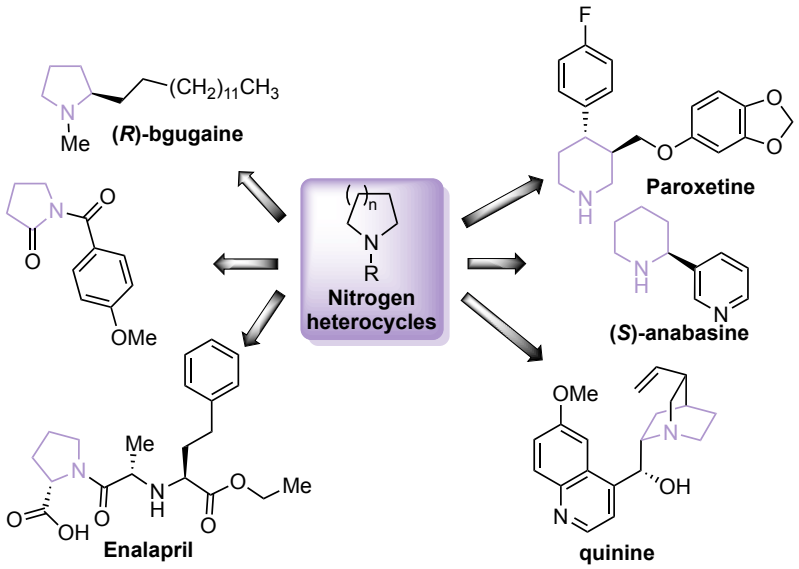
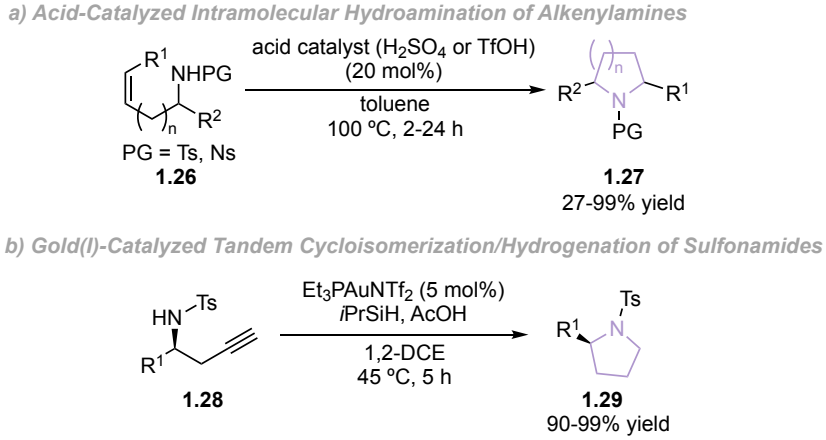


Figure 1.2. Nitrogen heterocycles in drugs and natural products.

The most employed approach for the synthesis of these scaffolds is the hydroamination reaction. In this context, numerous methods for the synthesis of pyrrolidines and piperidines have been described over the past decades. Most recently, in 2022, the group of Hartwig presented a Brønsted acid-catalyzed cyclization of aminoalkenes affording the desired heterocyclic products **1.27** in excellent yields (Scheme 1.11a).[22] Moreover, in 2019, Ye's group published an unprecedented gold(I)-catalyzed tandem cycloisomerization/hydrogenation reaction of homopropargyl sulfonamides (**1.28**) for the synthesis of enantioenriched pyrrolidines **1.29** (Scheme 1.11b).[23]



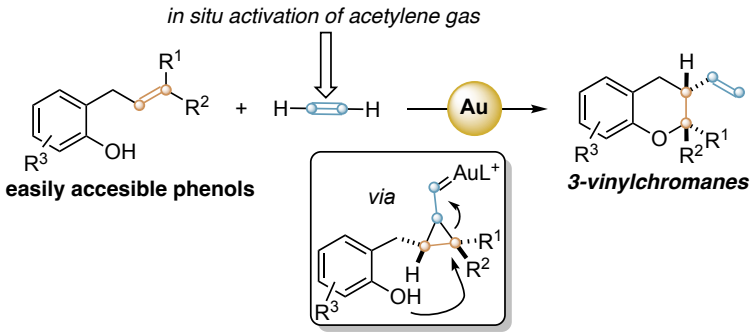
Scheme 1.11. Hydroamination reactions for the synthesis of pyrrolidines and piperidines.

22. Schlummer, B.; Hartwig, J. F. *Org. Lett.* **2002**, *4*, 1471–1474.
23. Yu, Y.-F.; Shu, C.; Tan, T.-D.; Li, L.; Rafique, S.; Ye, L.-W. *Org. Lett.* **2016**, *18*, 5178–5181.

Objectives

Our aim was the development of a novel gold(I)-catalyzed intermolecular aryloxyvinylation reaction using acetylene gas and easily accessible *o*-allyl phenols for the formation of 3-vinyl chromanes. To demonstrate the value of this transformation, we would like to apply this methodology to the late-stage functionalization of natural products such as lapachol. Furthermore, we focus on the application of this reaction to the synthesis of enantioenriched chromanes derivates.

In the second part of this Chapter, we center our attention on the use of amines and anilines as nitrogen based nucleophiles for the gold(I)-catalyzed intermolecular reaction with acetylene gas.[24]



Scheme 1.12. Gold(I)-catalyzed intermolecular aryloxyvinylation reaction using acetylene gas.

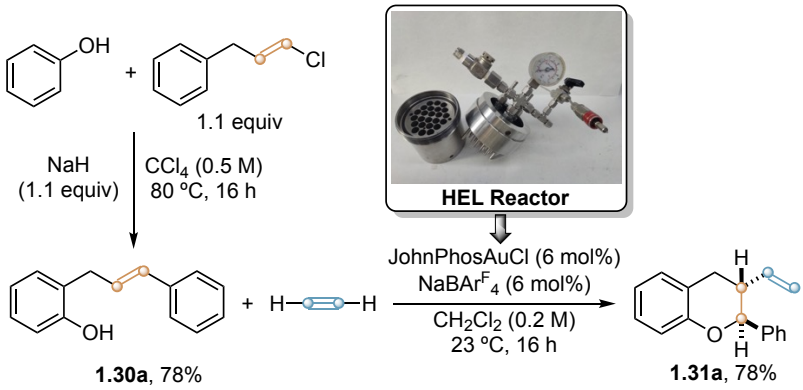
24. Part of the experiments described in this section were performed jointly with Dr. Anna Sadurní and Dr. L. Anders Hammarback.

Results and Discussion

Development of a Gold(I)-Catalyzed Aryloxyvinylation Reaction using Acetylene Gas

As previously mentioned in the introduction of this Chapter, we are highly interested in the development of novel intermolecular reaction between alkynes and alkenes. In this respect, we wanted to explore the combination of acetylene gas (the smallest existing alkyne) and gold(I) catalysis for the intermolecular aryloxyvinylation reaction of alkenes.

Our work started with the synthesis of phenol **1.30a** through a S_EAr reaction (Scheme 1.13).[25] The corresponding product was then submitted to the gold(I)-catalyzed reaction using commercially available JohnPhosAuCl as ligand and $NaBAr^F_4$ as counterion in the presence of an acetylene atmosphere.[26] We were delighted to confirm that the desired 3-vinyl chromane **1.31a** was obtained in good yield.



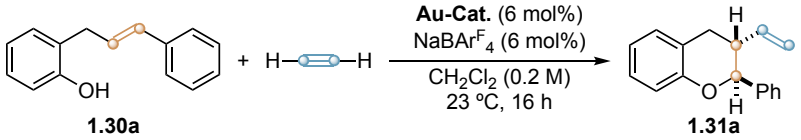
Scheme 1.13. Synthesis of phenol **1.30a** and first attempt of gold(I)-catalyzed reaction with acetylene gas.

Optimization of the Aryloxyvinylation Reaction Conditions

After having tested the feasibility of the reaction, we decided to perform a deeper optimization study whose results are summarized in Table 1. Besides JohnPhosAuCl, other phosphine-based gold complexes afforded the desired product but in lower yields (Table 1.1, entries 2–5). NHC-based gold(I) catalysts such as IPrAuCl led to the formation of vinyl chromane **1.31a** but in a moderate 50% yield, while other like IMesAuCl showed no conversion (Table 1.1, entries 6–7). The use of the cationic gold(I) complexes instead of the gold chloride analogues did not improve the yield of the product (Table 1.1, entries 8–9). Finally, a control test without gold(I) catalyst was performed showing no formation of the desired product (Table 1.1, entry 10).

25. Denmark, S. E.; Kornfilt, D. J. P. *J. Org. Chem.* **2017**, *82*, 3192–3222.
26. Under otherwise stated, the reactions were carried out in a HEL reactor charged with 1 atm of acetylene. Detailed experimental data is described in the experimental section of this Chapter.

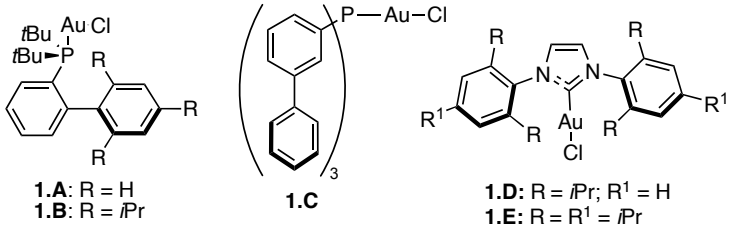
Table 1.1. Screening of gold(I) catalysts.



1.30a **1.31a**

Entry	Au-Cat.	Yield 1.31a (%)[a]
1	**1.A**	78
2	PMe_3AuCl	n.r
3	PPh_3AuCl	n.r
4	**1.B**	71
5	**1.C**	53
6	**1.D**	50
7	**1.E**	n.r
8[b]	**1.F**	75
9[b]	**1.G**	48
10	none	n.r

[a]Yield determined by ^{1}H NMR spectroscopy using 1,1,2,2-tetrachloroethane as internal standard. [b]Cationic gold(I) complex used without scavenger. n.r: no reaction.



1.A: R = H
1.B: R = *i*Pr

1.C

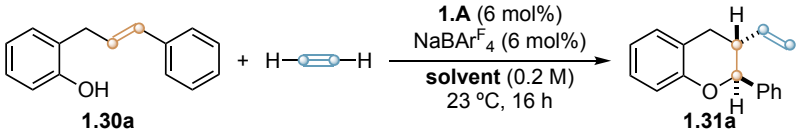
1.D: R = *i*Pr; R^1 = H
1.E: R = R^1 = *i*Pr

1.F: R = *i*Pr; X = BAr$^F_4$

1.G: R = *i*Pr; R^1 = H; X = BAr$^F_4$

After having identified JohnPhosAuCl (**1.A**) as the best catalyst for the reaction, we performed a solvent screening (Table 1.2). In this context, chlorinated solvents were well tolerated affording the product in moderate to excellent yields (Table 1.2, entries 1–4). The use of polar solvents led to a considerable decrease of the yield of the desired chromane **1.31a** (Table 1.2, entries 5–6, 9). Additionally, aromatic solvents were found to be suitable for the reaction, in particular toluene which afforded the product in an excellent 81% yield (Table 1.2, entry 10).

Table 1.2. Screening of solvents.

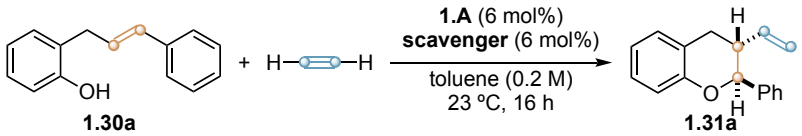


Entry	Solvent	Yield 1.31a (%)[a]
1	CH_2Cl_2	78
2	$CHCl_3$	89
3	CCl_4	57
4	1,2-Dichloroethane	71
5	EtOAc	34
6	Acetone	12
7	THF	8
8	Hexane	68
9	1,4-Dioxane	44
10	Toluene	81
11	Mesitylene	26
12	Chlorobenzene	80
13	α,α,α-Trifluorotoluene	78
14	Anisole	56
15	Xylene	52
16	Nitrobenzene	n.r

[a]Yield determined by ^{1}H NMR spectroscopy using 1,1,2,2-tetrachloroethane as internal standard. n.r: no reaction.

Since both toluene and $CHCl_3$ led to the formation of the vinyl chromane **1.31a** in excellent yields, we decided to perform further optimization studies using both. With toluene as solvent the effect of the chloride scavenger was evaluated and the best results were observed when $NaBAr^F_4$ was used (Table 1.3, entry 1) With $AgSbF_6$ the yield was drastically decreased to 40% while other scavengers such as $AgNTf_2$ or $NaBF_4$ did not show any conversion towards the desired product (Table 1.3, entries 2–4).

Table 1.3. Screening of scavengers using toluene as solvent.



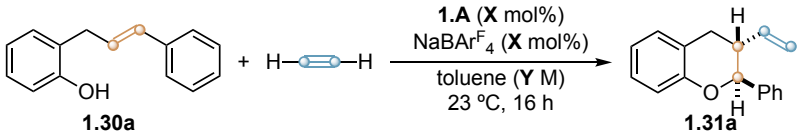
Entry	Scavenger	Yield 1.31a (%)[a]
1	$NaBAr^F_4$	80
2	$AgSbF_6$	40
3	$AgNTf_2$	32
4	$NaBF_4$	n.r
5	none	n.r

[a]Yield determined by ^{1}H NMR spectroscopy using 1,1,2,2-tetrachloroethane as internal standard.

n.r: no reaction.

Additionally, different combinations of catalyst loadings and concentration were tested (Table 1.4). Lowering the catalyst loading led to inferior yields (Table 1.4, entries 2–3) as well as reducing the reaction concentration (Table 1.4, entries 4–5). Resultingly, 6 mol% of catalyst and 0.2 M proved to be the most suitable conditions for the reaction (Table 1.4, entry 1).

Table 1.4. Screening of catalyst loading and concentration using toluene as solvent.

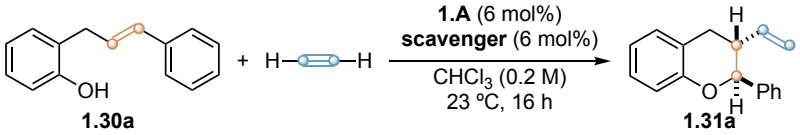


Entry	1.A (mol%)[a]	Concentration (M)	Yield 1.31a (%)[b]
1	6	0.2	80
2	4	0.2	69
3	2	0.2	47
4	6	0.1	60
5	6	0.07	n.r
6	6	0.4	69

[a] All the reactions were made maintaining a 1:1 ratio **1.A**: scavenger. [b]Yield determined by ^{1}H NMR spectroscopy using 1,1,2,2-tetrachloroethane as internal standard. n.r: no reaction.

Finally, the influence of chloride scavenger, catalyst loading, and concentration was studied using $CHCl_3$ as solvent (Tables 1.5 and 1.6). Same as with toluene, $NaBAr^F{}_4$ gave the best results in terms of yield (Table 1.5, entry 1). Furthermore, lowering the catalyst loading or the concentration had a detrimental effect on the yield (Table 1.6, entry 3–4).

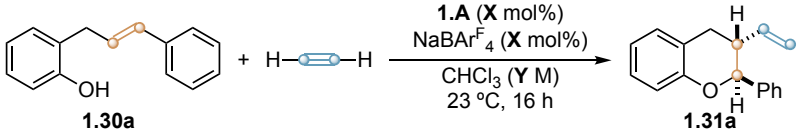
Table 1.5. Screening of scavengers using $CHCl_3$ as solvent.



Entry	Scavenger	Yield 1.31a (%)[a]
1	$NaBAr^F{}_4$	89
2	$AgSbF_6$	49

[a]Yield determined by ^{1}H NMR spectroscopy using 1,1,2,2-tetrachloroethane as internal standard.

Table 1.6. Screening of catalyst loading and concentration using $CHCl_3$ as solvent.

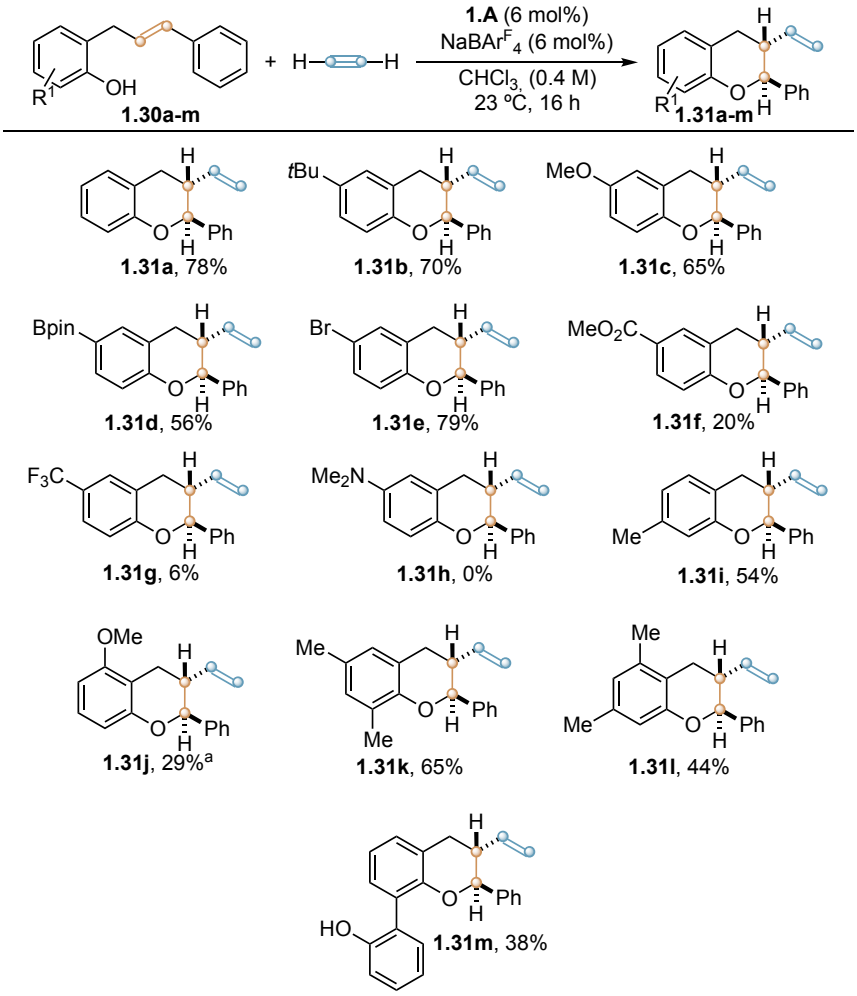


Entry	Catalyst (mol%)	Concentration (M)	Yield 1.31a (%)[a]
1	8	0.2	75
2	6	0.2	89
3	4	0.2	69
4	6	0.1	80
5	6	0.4	91

[a]Yield determined by ^{1}H NMR spectroscopy using 1,1,2,2-tetrachloroethane as internal standard.

Scope of the Gold(I)-Catalyzed Intermolecular Aryloxyvinylation Reaction

After having optimized the reaction conditions, we investigated the reaction scope (Scheme 1.14). First, the influence of substituents on the phenol ring was studied. Substrates bearing electron-donating groups afforded the corresponding vinylated chromanes **1.31a-d**, **1.31i** and **1.31k-m** in moderate yields, whereas product **1.31j** could only be isolated in a 29% yield. The structure of product **1.31b** was confirmed by X-ray diffraction (Figure 1.3). Cinnamyl phenol **1.30e** with a Br substituent in the *para* position led to product **1.31e** in good yield. However, the substitution on the phenol with stronger electron-withdrawing groups was not well tolerated, giving products **1.31f** and **1.31g** in 20% and 6% isolated yield respectively. Presumably, this is due to the less nucleophilicity of the starting phenols. Additionally, an allyl phenol with a NEt_2 group showed no conversion towards the desired product **1.31h**. We hypothesized that this lack of reactivity is caused by the deactivation of the gold(I) catalyst in the presence of an amine group.



[a]Reaction ran at 0 ºC for 3 h.

Scheme 1.14. Scope of phenols for the aryloxyvinylation reaction with acetylene gas.

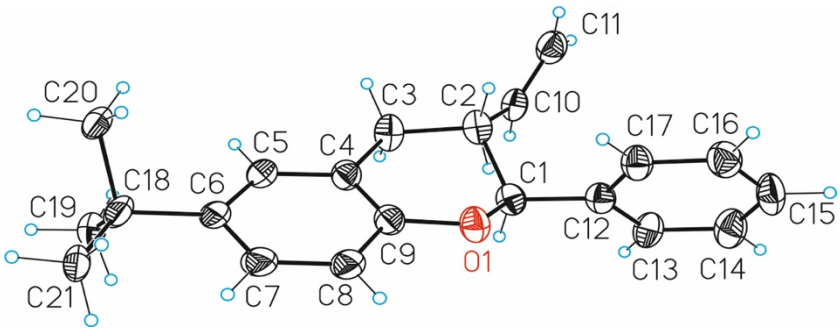
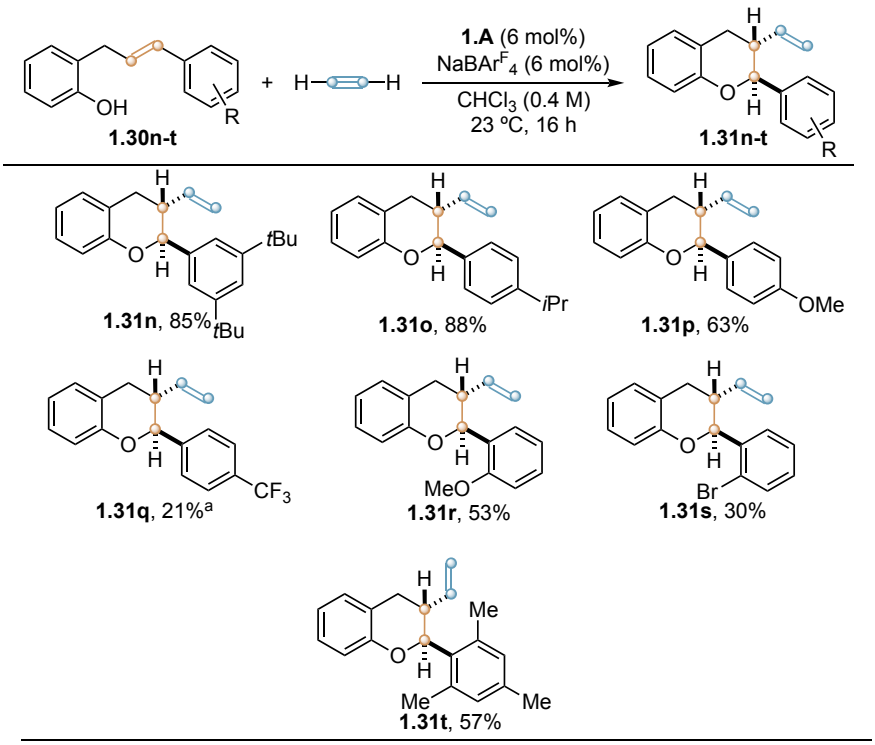


Figure 1.3. X-ray structure of **1.31b**.

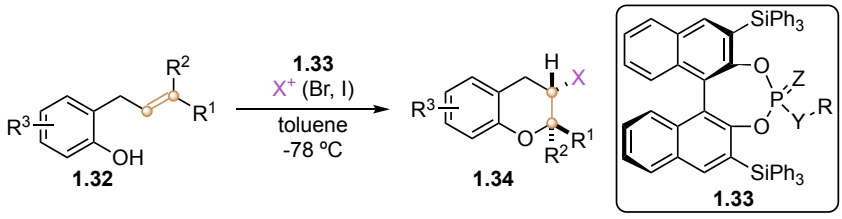
Next, we studied the influence of substituents in the phenyl ring of the cinnamyl group (Scheme 1.15). A variety of substituents were well tolerated and led to the desired product **1.31n** to **1.31t** in good yields, except for compounds **1.31q** and **1.31s** that were isolated in lower yields.



[a]48 h reaction time.

Scheme 1.15. Scope of cinnamyl alkenes for the aryloxyvinylation reaction with acetylene gas.

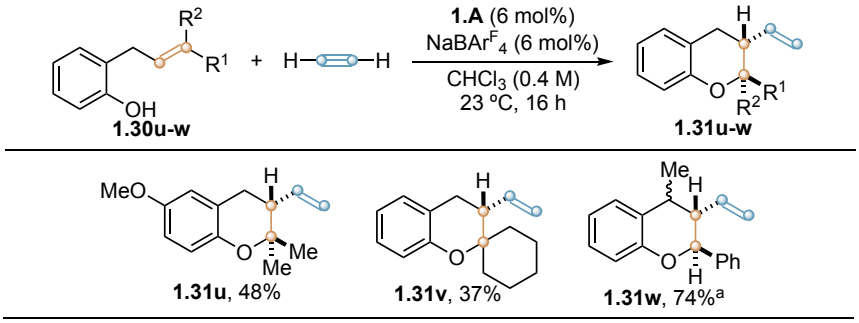
All the products present an *anti*-stereochemistry and 6-*endo*-trig regioselectivity, identical to the one found in similar formation of chromanes by halocyclization of the same substrates (Scheme 1.16).[27] In our case, although, the cyclization reaction is promoted by the addition of acetylene.



Scheme 1.16. Halo-oxycyclization induced by chiral amidophosphonate catalysts and halo-Lewis acids.

Finally, other *o*-allyl phenols with different alkenes were tested (Scheme 1.17). Substrates bearing prenyl and cyclohexyl moieties afforded the corresponding chromanes in moderate yields (products **1.31u** and **1.31v**). Product **1.31w** was obtained in good yields as a 1:1 mixture of stereoisomers.

27. Lu, Y.; Nakatsuji, H.; Okumura, Y.; Yao, L.; Ishihara, K. *J. Am. Chem. Soc.* **2018**, *140*, 6039–6043.



[a]1:1 mixture of stereoisomers.

Scheme 1.17. Test with different alkenes for the aryloxyvinylation reaction with acetylene gas.

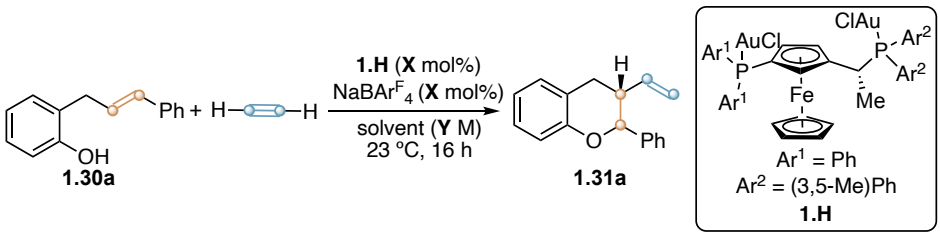
Enantioselective Gold(I)-Catalyzed Aryloxyvinylation with Acetylene Gas

After having applied this novel procedure for the synthesis of a wide variety of 3-vinyl chromanes, we decided to explore the possibility of performing this reaction in an enantioselective manner.

We performed a HTE (High Throughput Experiment) where more than 60 commercially available chiral ligands were tested using **1.30a** as standard substrate. We were delighted to see that monocationic catalyst (generated *in situ* from JosiPhos-type digold(I) complex) (*R*, S_p)-**1.H** turned out to be highly active.

We performed a series of optimization tests and the results obtained were summarized in Table 1.7).

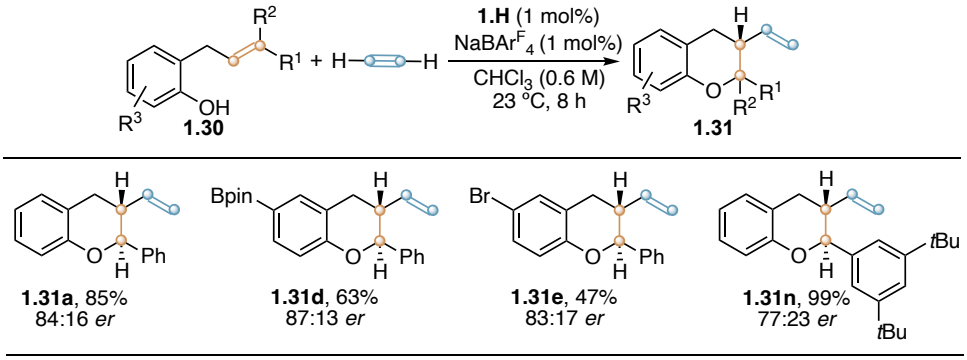
Table 1.7. Optimization of the reaction conditions for the enantioselective aryloxyvinylation.



Entry	Catalyst (mol%)	Concentration (M)	Solvent	Yield 1.31a (%)[a]	*er*
1	3	0.6	CH_2Cl_2	96	81:19
2	1	0.6	CH_2Cl_2	93	80:20
3	0.5	0.6	1,2-DCE	72	83:17
4	0.5	1.0	1,2-DCE	80	83:17
5[b]	1	0.6	1,2-DCE	94	85:15

[a]Yield determined by ^{1}H NMR spectroscopy using 1,1,2,2-tetrachloroethane as internal standard.

Optimized reaction conditions were applied to the synthesis of enantioselective 3-vinyl chromanes **1.31** in good to excellent yields (Scheme 1.18). Even though, the enantioselectivities obtained were moderate, these are the first examples of enantioselective activation of acetylene in gold catalysis. The absolute configuration of the products was confirmed by X-ray diffraction of product **1.31e** (Figure 1.4).



Scheme 1.18. Enantioselective examples of the gold(I)-catalyzed aryloxyvinylation reaction.

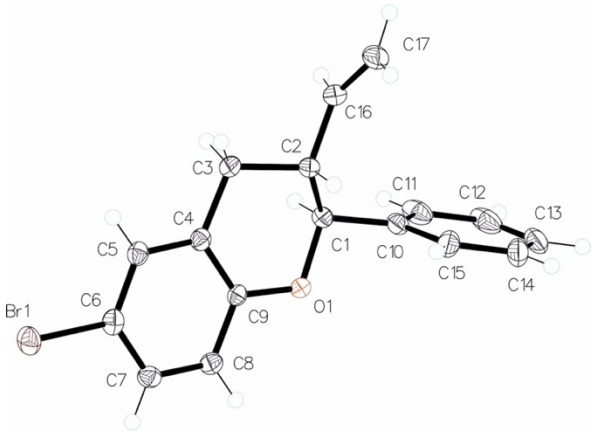
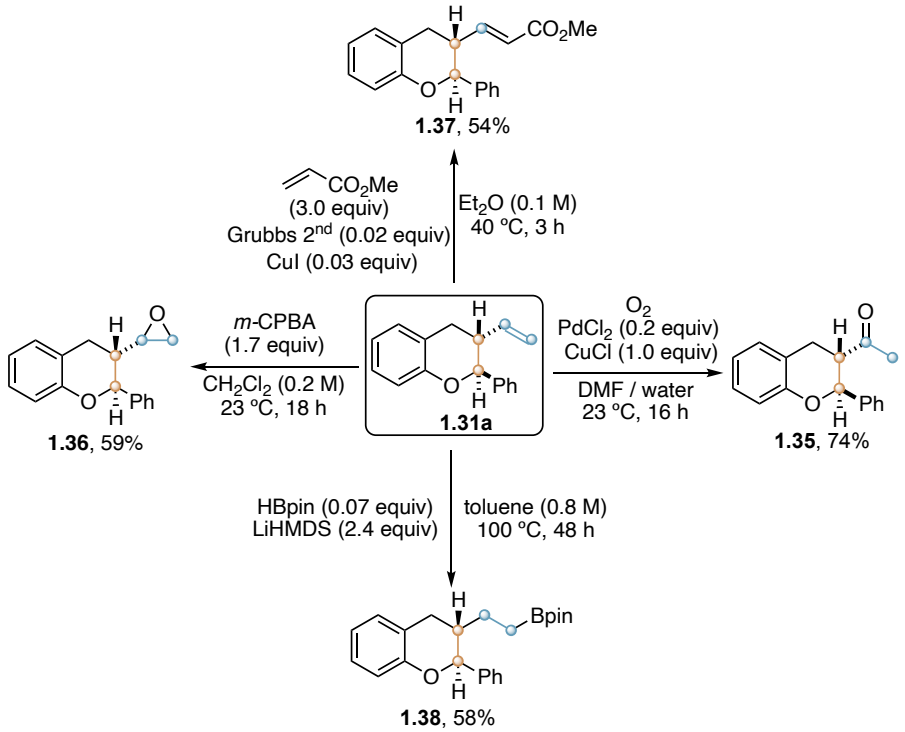


Figure 1.4. X-ray structure of **1.31e**.

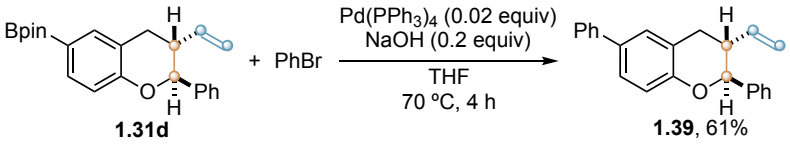
Diversification of the Model Product 1.31a

The vinyl group present in the chromane products provides a highly versatile handle for diversification. In this context, we performed several diversifications of model substrate **1.31a** (Scheme 1.19). Wacker oxidation yielded the corresponding methyl ketone **1.35** in good yield whereas reaction with *m*-CPBA led to the epoxide derivate **1.36** in 59% yield. Additionally, Grubbs metathesis and hydroboration reaction yielded products **1.37** and **1.38** in good yields.



Scheme 1.19. Derivatization of model product **1.31a**.

To further show the applicability of this novel methodology, we also derivatized product **1.31d** through a Suzuki cross coupling reaction with bromobenzene to afford product **1.39** (Scheme 1.20).



Scheme 1.20. Derivatization of **1.31d** by Suzuki cross coupling.

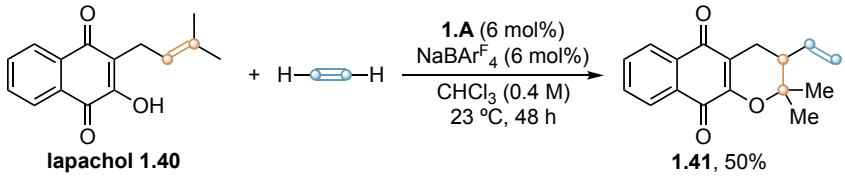
Late-stage Functionalization of Lapachol Natural Product

Thanks to the high abundance of starting *o*-allylphenols in nature we were able to apply this novel aryloxyvinylation reaction to the late-stage functionalization of lapachol natural product. Lapachol is a naturally occurring 1,4-napthoquinone originally isolated from *Tabeuia avellanedae* and with anticancer properties due to its antiproliferative activity and antimetastatic affects, both *in vivo* and *in vitro*. [28]

Figure 1.5. *Tabeuia avellanedae*

28. Epifano, F.; Genovese, S.; Fiorito, S.; Mathieu, V.; Kiss, R. *Phytochem. Rev.* **2014**, *13*, 37–49.

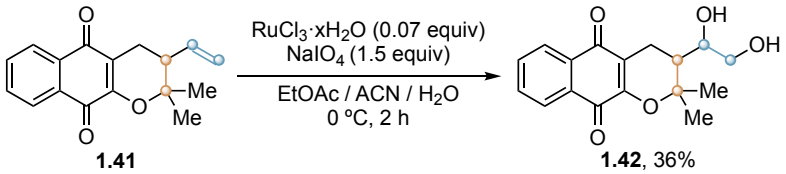
After submitting lapachol (**1.40**) to the optimized reaction conditions in the presence of acetylene gas, 3-vinyl-α-lapachone **1.41** was successfully obtained in 50% yield with extended reaction time (Scheme 1.21).



Scheme 1.21. Late-stage functionalization of lapachol natural product.

The biological properties of **1.41** were studied in the drug discovery program CO-AAD (Community for Open Antimicrobial Drug Discovery) from the University of Queensland (Australia).[29]

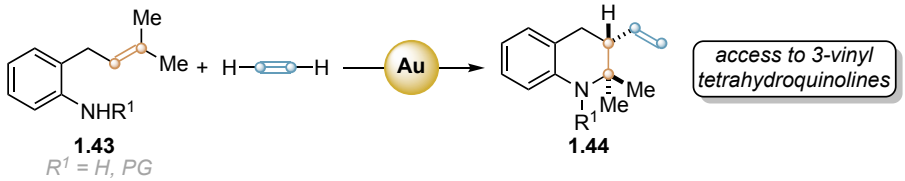
After performing cell growth inhibition assays against different types of bacteria and fungi, lapachol derivate **1.41** was confirmed as a hit for one of the bacteria tested (*Staphylococcus aureus*) and two fungi (*Candida albicans* and *Cryptococcus neoformans*). Further investigations of the antimicrobial properties of **1.41** are currently ongoing. Additionally, a new analogue of the vinyl lapachone was prepared through a *syn*-dihydroxylation reaction to afford compound **1.42** whose biological properties are currently being investigated (Scheme 1.22).



Scheme 1.22. Dihydroxylation of lapachol derivate **1.41**.

Gold(I)-Catalyzed Intermolecular Vinylation with Acetylene Gas: from Alcohols to Amines

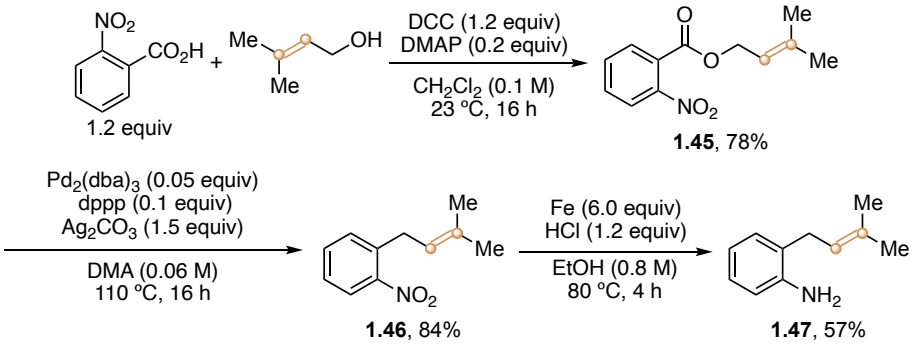
Inspired by the results described in the first part of this Chapter we decided to explore the possibility of expanding this methodology to the use of amines as nucleophiles. In this case, the intramolecular arylaminovinylation reaction would result in the formation of 3-vinylated tetrahydroquinolines **1.44** (Scheme 1.23).



Scheme 1.23. First hypothesis for the vinylation of 3-substituted anilines.

29. Blaskovich, M. A. T.; Zuegg, J.; Elliott, A. G.; Cooper, M. A. *ACS Infect. Dis.* **2015**, *1*, 285–287.

Unlike the synthesis of the starting *o*-allyl phenols (**1.30**), the synthesis of the *o*-allyl anilines resulted to be quite challenging. After exploring different synthetic routes, we were able to prepare the desired prenylated anilines **1.43a** through Pd(0)-catalyzed intramolecular decarboxylative allylation of the nitrobenzoic ester **1.45** followed by nitro reduction (Scheme 1.24).[30] Final monoprotection of the free aniline **1.47** afforded product **1.43a** in good yield.

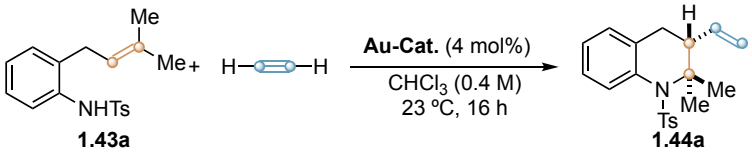


Scheme 1.24. Synthesis of 2-prenylated aniline **1.43a**.

Mono-tosylated aniline **1.43a** was used as standard substrate for the reaction with different commercially available gold(I) catalysts in the presence of acetylene gas (Table 1.8).

Only phosphite **1.J** gave a promising 19% ^{1}H NMR yield (Table 1.8, entry 6) whereas other phosphine-based ligands or NHC ligands gave only traces of the desired tetrahydroquinoline **1.44a** (Table 1.8, entries 1–5).

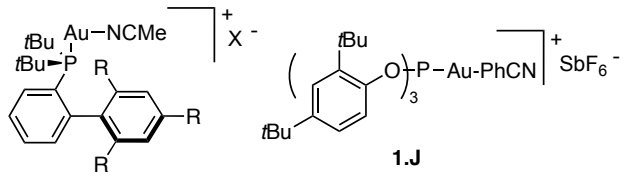
Table 1.8. Screening of gold(I) catalysts.



Entry	Au-Cat.	Yield 1.44a (%)[a]
1	**1.I**	9
2	**1.F**	5
3	**1.D**[b]	2
4	PPh_3AuCl[b]	n.r
5	PEt_3AuCl[b]	n.r
6	**1.J**	19 (15[c])

[a]Yield determined by ^{1}H NMR spectroscopy using 1,4-diacetylbenzene as internal standard. [b]Complex used in combination with $NaBAr^{F}_{4}$ (4 mol%) as chloride scavenger. [c]Isolated yield. n.r: no reaction.

30. Hossian, A.; Singha, S.; Jana, R. *Org. Lett.* **2014**, *16*, 3934–3937.

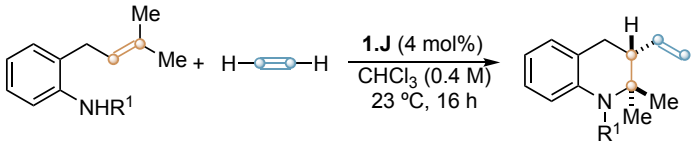


1.I: R = H; X = SbF_6 **1.J**

Additional reactions conditions were tested (higher temperatures, increased reaction time, higher catalyst loading) but none of them led to any improvement of the yield. At this point, the influence of different protecting groups in the nitrogen was evaluated using catalyst **1.J** (Table 1.9).

Only sulfonamides derivates yielded the corresponding products (Table 1.9, entry 1–2), whereas other protecting groups led to either no conversion of the substrate or complex mixtures of products (Table 1.9, entry 1, 3–5).

Table 1.9. Protecting groups screening.



1.43a-e **1.44a-e**

Entry	R^1	Yield 1.44(%)[a]
1	Ts	19(15[b])
2	Ms	47
3	Boc	n.r
4	Ac	n.r
5	Me	n.r

[a]Yield determined by ^{1}H NMR spectroscopy using 1,4-diacetlybenzene as internal standard.

[b]Isolated yield. n.r: no reaction.

The ^{1}H NMR spectra of the crude products **1.44a-e** are shown in Figure 1.6. [31]

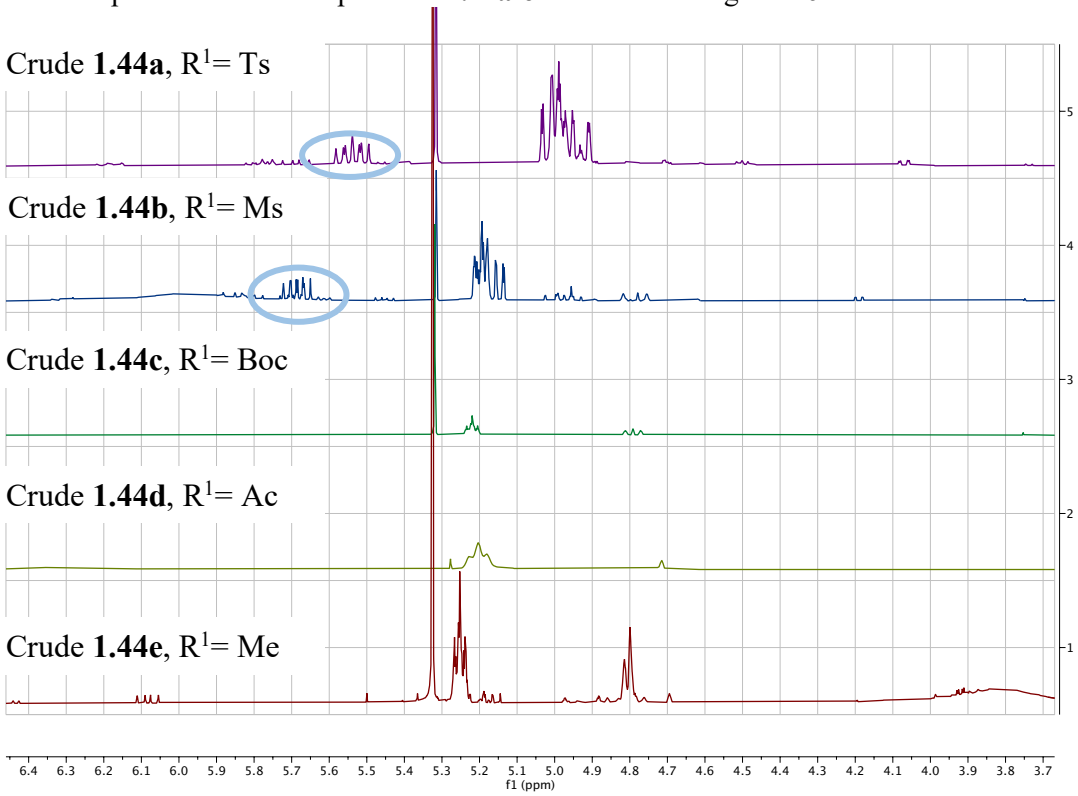


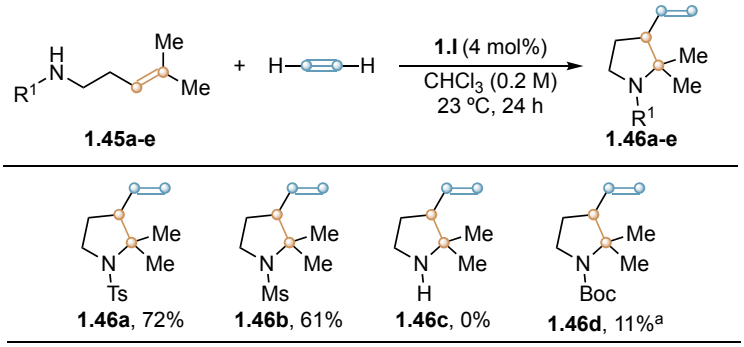
Figure 1.6. ^{1}H NMR spectra of the crude reaction of different protected anilines.

However, we found high reproducibility issues for substrates **1.43a** and **1.43c** since the products could not be synthetized again after repeating the reaction several times.

Giving these results we decided to focus our attention on the use of linear aliphatic amines instead of anilines as model substrates for the aminovinylation of alkenes. In this case, pyrrolidines and piperidines-containing products would be obtained after the gold(I) catalysis.

Using amine **1.45a** as model substrate under previously optimized reaction conditions, we were able to obtain 3-vinyl pyrrolidine **1.46a** in good yield (Scheme 1.25). Additionally, mesyl protecting amine **1.45b** was also found to be a suitable substrate, yielding the desired product **1.46b** in 61% yield. However, the free amine **1.45c** led to no conversion. Boc-protected amine **1.45d** only gave traces of the product, which could not be isolated.

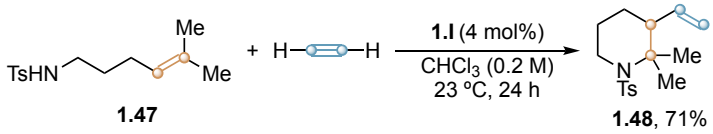
31. In Figure **1.6**, the signals of the protons belonging to the product are marked with a blue circle.



[a]Yield determined by ^{1}H NMR spectroscopy using 1,4-diacetylbenzene as internal standard.

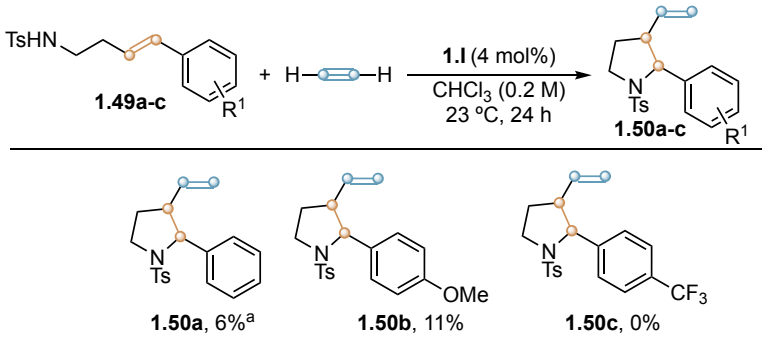
Scheme 1.25. Pyrrolidine derivates formation by aminovinylation reaction with acetylene gas.

We were delighted to see that the reaction could also be applied to longer amines (**1.47**), yielding 3-vinylpiperidine **1.48** in good yield (Scheme 1.26).



Scheme 1.26. Synthesis of 3-vinylated piperidine by gold(I) catalysis.

Finally, we prepare three new substrates bearing a cinammyl alkene and both electron-withdrawing and -donating groups in the aromatic ring (Scheme 1.27). Unfortunately, they proved to be considerably less reactive than the prenylated ones (**1.45**). Only substrate **1.49b** with a *p*-OMe moiety afforded the pyrrolidine product **1.72b** in enough yield to be isolated. We hypothesize that this lack of reactivity could be due to the diminished reactivity of trisubstituted alkenes towards the intramolecular attack of the cyclopropyl gold(I) carbene.



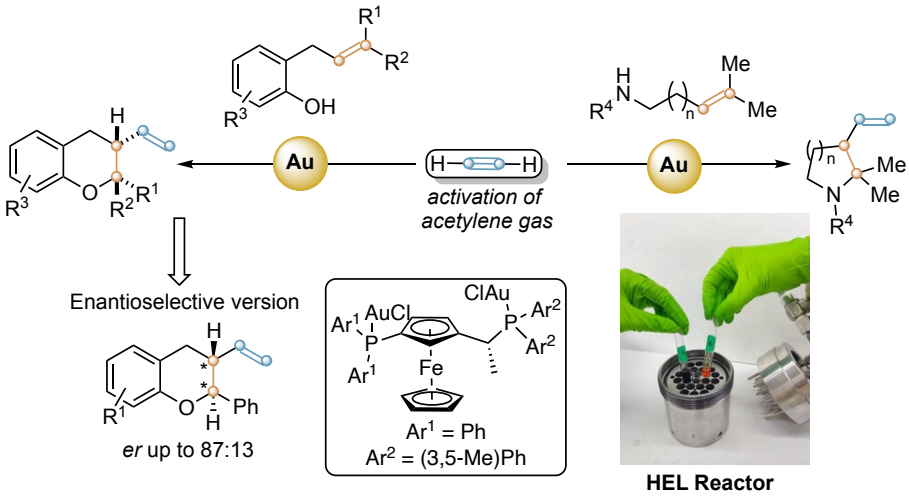
[a]Yield determined by ^{1}H NMR spectroscopy using 1,4-diacetylbenzene as internal standard.

Scheme 1.27. Aminovinylation reaction using cinnamyl alkenes **1.49** as substrates.

Conclusions

In this Chapter we have summarized our study on the gold(I)-catalyzed intermolecular reaction of *o*-allyl phenols with acetylene gas to obtain a wide variety of 3-vinylated chromanes in good to excellent yields. Moreover, the usefulness of this methodology was demonstrated by the late-stage functionalization of natural product lapachol and several diversifications of the standard product. The enantioselective version of this reaction was initially explored, obtaining promising enantioselectivities for the first enantioselective gold(I)-catalyzed activation of acetylene gas.

Additionally, we extended this chemistry to the use of amine as nucleophiles to obtain pyrrolidine and piperidines-containing products, highly abundant in nature and biologically active compounds.



Scheme 1.28. Gold(I)-catalyzed heterovinylation with acetylene gas.

Experimental Section

General Methods

Unless otherwise stated, reactions were performed with magnetic stirring. Compound names were generated using ChemDraw. Chemicals were obtained from commercial suppliers and used as received. Anhydrous solvents were dried by passing through an activated alumina column on a PureSolv^{TM} Solvent Purification System or taken from commercial bottles equipped with septa and molecular sieves. Solutions were evaporated using a Büchi rotary evaporator under reduced pressure at $T \leq 40$ °C. Yields refer to chromatographically and spectroscopically pure homogenous material, unless otherwise stated. Analytical thin-layer chromatography (TLC) was carried out using aluminum sheets coated with 0.2 mm of silica gel (fluorescent-treated Merck Kieselgel 60 F254). Visualization was accomplished under UV light at 254 nm and by staining with an alkaline aqueous potassium permanganate solution, ninhydrin, or vanillin staining dips. Flash column chromatography (FCC) was carried out manually using PanReac Silica Gel 60 (40–63 μm) or employing the automated flash column chromatographer CombiFlash Companion with disposable pre-packed normal phase silica gel columns (Teledyne Isco). Preparative TLC was performed on 20 cm × 20 cm silica gel plates (2.0 mm or 1.0 mm silica thickness, Analtech). Reactions with acetylene were performed in a HEL CAT24 multireactor using an acetylene 2.6 cylinder B50 Messer with regulator BT2000. Enantiomeric excesses were determined by SFC analysis using the chiral stationary phase columns, eluents and conditions specified in the individual procedures and by comparing the sample with the appropriate racemic mixture. SFC analyses were performed on an Agilent Technologies 1260 Infinity II or on a Waters ACQUITY UPC2 instrument.

NMR spectra were recorded at 298 K on Bruker Ultrashield NMR spectrometers operating at ^{1}H resonances of 300, 400 or 500 MHz (in the latter case, with optional cryoprobe for enhanced sensitivity). Proton and carbon chemical shifts (d) are given in parts per million (ppm) downfield from tetramethylsilane, using the solvent resonance as reference. ^{1}H NMR spectra are reported as follows: chemical shift (multiplicity, coupling constant, number of protons). The following abbreviations are used: s = singlet, d = doublet, t = triplet, q = quartet, quint = quintet, m = multiplet, br = broad signal, app = apparent. ^{13}C, ^{31}P and ^{19}F NMR spectra were always acquired with proton decoupling, even when not explicitly written. ^{1}H, $^{13}C\{^{1}H\}$, $^{31}P\{^{1}H\}$ and $^{19}F\{^{1}H\}$ NMR spectra for all novel compounds and for all methodology products (both known and novel ones) are attached. Two-dimensional NMR spectroscopy experiments (COSY, HSQC and HMBC) were used to assist in the assignment of signals in ^{1}H and ^{13}C spectra and data are not reported. High- resolution mass spectra (HRMS) were recorded by ICIQ mass spectrometry staff on MaXis Impact, MicrOTOF II and AutoFlex spectrometers equipped with ESI, APCI or MALDI sources, all by Bruker Daltonics. Melting points were measured using a Mettler Toledo MP70 Melting Point apparatus. Single-crystal X-ray diffraction (XRD) data were collected and refined by ICIQ XRD staff either on a Rigaku MicroMax-007HF diffractometer, equipped

with a Pilatus 200 K area detector, a Rigaku MicroMax-007HF microfocus rotating anode with MoKα radiation, confocal Max Flux optics and an Oxford Cryostream 700 plus, or on a Bruker Apex II DUO diffractometer, equipped with APEX DII 4K CCD area detector, Mo and Cu X-ray sources and an Oxford Cryostream 700 plus.

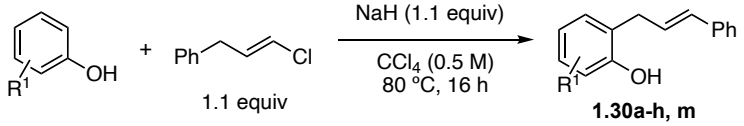
Set Up of the Reactions with Acetylene Gas in a HEL Reactor

Figure below shows the set-up of the reactions using acetylene gas. At lower reaction temperatures, the reactions can also be performed through sparging the reaction solution using a balloon filled with acetylene inside a capped microwave vial.

a) HEL reactor; b) and c) the reactions are placed in the reactor; d) the reactor is closed and connected to the acetylene cylinder; e) the reactor is charged with acetylene (1 atm); f) the cylinder is disconnected, and the reaction is stirred at 600 rpm for 16 h; g) the acetylene gas is released when the valve of the reactor is opened.

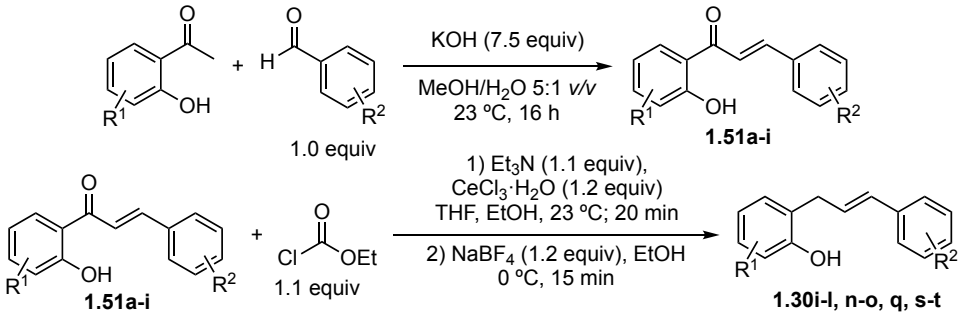
Synthetic Procedures and Analytical Data

General procedure A: Synthesis of o-allylphenols



A microwave vial under argon atmosphere was charged with NaH (1.1 equiv, 60% Wt) in anhydrous CCl_4 (0.5 M). To this mixture, the corresponding phenol (1.0 equiv) was slowly added at 0 ºC and the reaction was stirred for 30 min at 0 ºC. Then, (*E*)-cinnamyl chloride (1.1 equiv) was added in one portion and the mixture was heated to 80 ºC in a metallic heating block and stirred for 16 h. Upon completion of the reaction, the mixture was cooled down to 23 ºC and acidified until pH<1 with an aqueous solution of HCl 1M. Then, it was diluted with H_2O (10 mL) and extracted three times with CH_2Cl_2(3 x 10 mL). The combined organic layers were washed with brine (20 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was purified by flash column chromatography (SiO_2, cyclohexane/EtOAc) to afford the *o*-allylphenols **1.30**.

General procedure B: Synthesis of phenyl substituted o-allylphenols

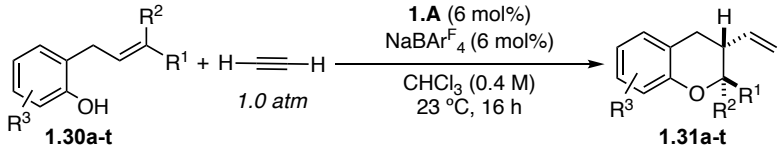


To a round-bottom flask was added the corresponding aldehyde (1.0 equiv) and KOH (7.5 equiv) dissolved in MeOH/H_2O (50%, 5:1, *v/v*). Following stirring for 10 minutes, the corresponding 2-hydroxyacetophenone (1.0 equiv) was added slowly. The reaction mixture was stirred at 23 ºC for 16 h afterwhich the reaction was diluted with H_2O (10 mL) and extracted three times with EtOAc (3 x 15 mL). The organic layer was washed with brine (15 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The crude material was recrystallized from CH_2Cl_2/MeOH and used without further purification.

To a round-bottom flask was added starting chalcone **1.51** (1.0 equiv), Et_3N (1.1 equiv) and THF (1.7 M). Ethyl chloroformate (1.1 equiv) in THF (0.8 M) was added dropwise and the resulting mixture was stirred for 30 min. Thereafter, the insoluble amine salt was removed via filtration and washed with a further portion of THF (0.8 M). The filtrate was added to a solution of $CeCl_3 \cdot 7H_2O$ (1.2 equiv) in EtOH

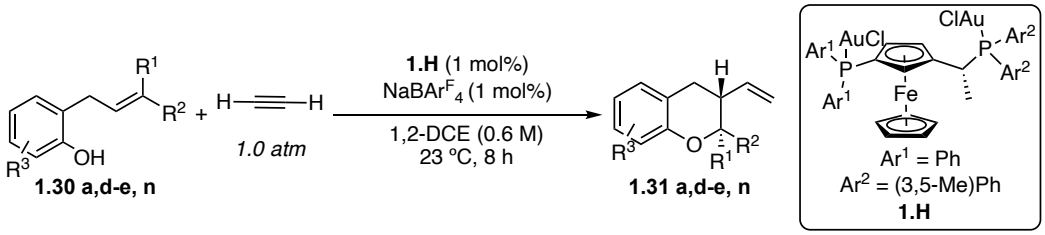
(1.0 M) and stirred for 20 minutes. $NaBF_4$ (1.2 equiv) in EtOH (1.0 M) was added dropwise at 0 °C and the mixture stirred for 15 minutes before being dilluted with H_2O (10 mL). The pH was adjusted to 3–4 using an aqueous solution of HCl (10% in H_2O) and extracted three times with CH_2Cl_2 (3 x 15 mL). The organic layer was washed with H_2O and brine (15 mL) before being dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The crude material was purified by flash column chromatography (SiO_2, cyclohexane/EtOAc) to yield the desired product **1.30**.

General procedure C: Gold(I)-catalyzed aryloxyvinylation using acetylene gas



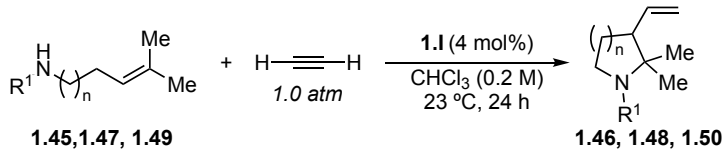
A reaction tube was charged with phenol **1.30** (1.0 equiv), JohnPhosAuCl (**1.A**) (6 mol%) and $NaBAr^F_4$ (6 mol%) in HPLC grade $CHCl_3$ (0.4 M). The tube was introduced in a HEL reactor, which after proper closure, was pressurized with 1.0 atm of acetylene gas. The reaction mixture was stirred at 23 ºC for 16 h and after emptying the remaining gas, the crude was quenched by the addition of 3 drops of Et_3N and concentrated under reduced pressure. The crude product was purified as described in the individual procedures yielding the corresponding products **1.31**.

General procedure D: Enantioselective gold(I)-catalyzed aryloxyvinylation using acetylene gas



A reaction tube was charged with phenol **1.30** (1.0 equiv), chiral catalyst **1.H** (1 mol%) and $NaBAr^F_4$ (1 mol%) in HPLC grade 1,2-dichloroethane (0.6 M). The tube was introduced in a HEL reactor that, after proper closure, was pressurized with 1.0 atm of acetylene gas. The reaction mixture was stirred at 23 ºC for 8 h and after emptying the remaining gas, the crude was quenched by the addition of 3 drops of Et_3N and concentrated under reduced pressure. The crude product was purified as described in the single procedures yielding the corresponding enantioenriched products **1.31**.

General Procedure E: Gold(I)-catalyzed cyclization of amine-tethered alkenes.



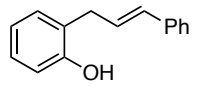
1.45,1.47, 1.49 **1.46, 1.48, 1.50**

A reaction tube was charged with the amine-tethered alkene (1.0 equiv), **1.I** (4 mol%) in HPLC grade $CHCl_3$ (0.2 M). The tube was introduced in a HEL reactor under 1 atm of acetylene gas. The reaction mixture was stirred at 23 ºC for 24 h and after emptying the remaining gas, the reaction was quenched by the addition of 3 drops of Et_3N and concentrated under reduced pressure. The crude product was purified as described in the individual procedures yielding the corresponding products.

Synthesis of *o*-Allylphenols (1.30)

2-Cynnamylphenol (1.30a)

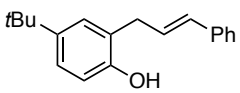
Prepared following the general procedure A using phenol (3.05 g, 20.0 mmol, 1.0 equiv), NaH (840 mg, 21.0 mmol, 1.1 equiv) and (*E)*-cinnamyl chloride (1.8 mL, 22.0 mmol, 1.1 equiv) in CCl_4 (40.0 mL, 0.5 M) at 80 ºC for 16 h. The crude product was purified by flash column chromatography (SiO_2, cyclohexane/EtOAc 100:0 to 85:15, *v/v*) and the product **1.30a** was obtained as a yellow solid (3.30 g, 16.0 mmol, 78% yield).



^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39–7.34 (m, 2H), 7.30 (ddd, *J* = 7.8, 6.8, 1.3 Hz, 2H), 7.24–7.11 (m, 3H), 6.92 (td, *J* = 7.4, 1.2 Hz, 1H), 6.83 (dd, *J* = 8.0, 1.2 Hz, 1H), 6.52 (dt, *J* = 15.9, 1.5 Hz, 1H), 6.40 (dt, *J* = 15.9, 6.4 Hz, 1H), 4.94 (s, 1H), 3.58 (dd, *J* = 6.4, 1.4 Hz, 2H). The characterization data matches those reported in the literature.[32]

4-(*tert*-Butyl)-2-cinnamylphenol (1.30b)

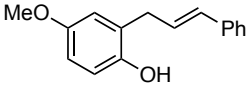
Prepared following the general procedure A using 4-*tert*-butylphenol (751 mg, 5.00 mmol, 1.0 equiv), NaH (210 mg, 5.25 mmol, 1.1 equiv) and (*E)*-cinnamyl chloride (0.8 mL, 5.50 mmol, 1.1 equiv) in CCl_4 (10.0 mL, 0.5 M) at 80 ºC for 16 h. The crude product was purified by flash column chromatography (SiO_2, cyclohexane/EtOAc 100:0 to 80:20, *v/v*) and the product **1.30b** was obtained as a white solid (573 mg, 2.15 mmol, 43% yield).



^{1}H NMR (300 MHz, $CDCl_3$) δ 7.41–7.27 (m, 4H), 7.25–7.12 (m, 3H), 6.76 (d, *J* = 9.1 Hz, 1H), 6.51 (d, *J* = 15.9 Hz, 1H), 6.42 (dt, *J* = 15.8, 6.3 Hz, 1H), 4.80 (s, 1H), 3.63–3.50 (m, 2H), 1.30 (s, 9H). The characterization data matches those reported in the literature.[33]

4-Methoxy-2-cinnamylphenol (1.30c)

Prepared following the general procedure A using 4-methoxyphenol (621 mg, 5.00 mmol, 1.0 equiv), NaH (210 mg, 5.25 mmol, 1.1 equiv) and (*E)*-cinnamyl chloride (0.8 mL, 5.50 mmol, 1.1 equiv) in CCl_4 (10.0 mL, 0.5 M) at 80 ºC for 16 h. The crude product was purified by flash column chromatography (SiO_2, cyclohexane/EtOAc 100:0 to 80:20, *v/v*) and the product **1.30c** was obtained as a white solid (377 mg, 1.57 mmol, 32% yield).

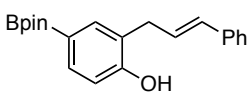


^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39–7.27 (m, 4H), 7.25–7.17 (m, 1H), 6.82–6.73 (m, 2H), 6.73–6.65 (m, 1H), 6.51 (dt, *J* = 15.9, 1.4 Hz, 1H), 6.37 (dt, *J* = 15.9, 6.3 Hz, 1H), 4.63 (s, 1H), 3.77 (s, 3H), 3.54 (dd, *J* = 6.4, 1.3 Hz, 2H). The characterization data matches those reported in the literature.[34]

32. Mino, T.; Kogure, T.; Abe, T.; Koizumi, T.; Fujita, T.; Sakamoto, M. *Eur. J. Org. Chem.* **2013**, *2013*, 1501–1505.
33. Jurd, L.; Stevens, K.; Manners, G. *Tetrahedron* **1973**, *29*, 2347–2353.
34. Zhang, W.; Haight, A. R.; Hsu, M. C. *Tetrahedron Lett.* **2002**, *43*, 6575–6578.

2-Cinnamyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenol (1.30d)

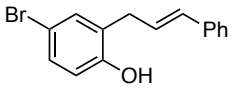
Prepared following the general procedure A using 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenol (1.10 g, 5.00 mmol, 1.0 equiv), NaH (210 mg, 5.25 mmol, 1.1 equiv) and (*E)*-cinnamyl chloride (0.766 mL, 5.50 mmol, 1.1 equiv) in CCl_4 (10.0 mL, 0.5 M) at 80 ºC for 16 h. The crude product was purified by flash column chromatography (SiO_2, cyclohexane/EtOAc 100:0 to 60:40, *v/v*) and the product **1.30d** was obtained as a white sticky solid (655 mg, 1.95 mmol, 39% yield).



^{1}H NMR (500 MHz, $CDCl_3$) δ 7.68–7.59 (m, 2H), 7.38–7.32 (m, 2H), 7.28 (dd, *J* = 8.5, 6.8 Hz, 2H), 7.24–7.18 (m, 1H), 6.81 (d, *J* = 7.8 Hz, 1H), 6.50 (dt, *J* = 15.8, 1.6 Hz, 1H), 6.42–6.34 (m, 1H), 3.58 (dd, *J* = 6.4, 1.5 Hz, 2H), 1.34 (s, 12H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 157.1, 137.6, 137.3, 135.3, 131.5, 128.6, 128.1, 127.4, 126.4, 125.1, 115.5, 83.8, 34.4, 27.1, 25.0. **HRMS** (ESI –) calculated for $[C_{21}H_{24}O_3B]$ $[M–H]^-$ 335.1824 *m/z*; found 335.1826 *m/z.*

4-Bromo-2-cinnamylphenol (1.30e)

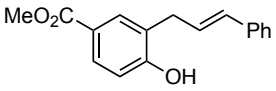
Prepared following the general procedure A using methyl 4-bromophenol (865 mg, 5.00 mmol, 1.0 equiv), NaH (210 mg, 5.25 mmol, 1.1 equiv) and (*E)*-cinnamyl chloride (0.8 mL, 5.50 mmol, 1.1 equiv) in CCl_4 (10.0 mL, 0.5 M) at 80 ºC for 16 h. The crude product was purified by flash column chromatography (SiO_2, cyclohexane/EtOAc 100:0 to 80:20, *v/v*) and the product **1.30e** was obtained as a yellow oil (1.01 g, 3.49 mmol, 70% yield).



^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39–7.21 (m, 7H), 6.70 (d, *J* = 8.5 Hz, 1H), 6.51 (dt, *J* = 15.8, 1.6 Hz, 1H), 6.34 (dt, *J* = 15.9, 6.7 Hz, 1H), 4.95 (s, 1H), 3.53 (dd, *J* = 6.6, 1.5 Hz, 2H). The characterization data matches those reported in the literature.[35]

Methyl 3-Cinnamyl-4-hydroxybenzoate (1.30f)

Prepared following the general procedure A using methyl 4-hydroxybenzoate (122 mg, 0.80 mmol, 1.0 equiv), NaH (34 mg, 0.840 mmol, 1.1 equiv) and (*E)*-cinnamyl chloride (0.1 mL, 0.880 mmol, 1.1 equiv) in CCl_4 (1.6 mL, 0.5 M) at 80 ºC for 16 h. The crude product was purified by flash column chromatography (SiO_2, cyclohexane/EtOAc 100:0 to 50:50, *v/v*) and the product **1.30f** was obtained as a white solid (106 mg, 0.40 mmol, 50% yield).

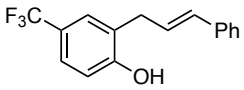


M.p. 122–131 ºC. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.90–7.84 (m, 2H), 7.38–7.33 (m, 2H), 7.32–7.28 (m, 2H), 7.24–7.20 (m, 1H), 6.85 (dd, *J* = 8.6, 7.4 Hz, 1H), 6.55–6.49 (m, 1H), 6.37 (dt, *J* = 15.9, 6.6 Hz, 1H), 3.88 (d, *J* = 1.6 Hz, 3H), 3.60 (dd, *J* = 6.6, 1.6 Hz, 2H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 167.4, 158.6, 137.1, 132.5, 132.1, 130.2, 128.7, 127.5, 127.4, 126.1, 122.8, 115.7, 115.4, 52.1, 34.0. **HRMS** (ESI –) calculated for $[C_{17}H_{15}O_3]$ $[M–H]^-$ 267.1027 *m/z*; found 267.1028 *m/z.*

35. Magolan, J.; Jentsch, N.; Zhang, X.; Piotrowski, M.; Darveau, P.; Fragis, M.; Johnson, J.; Ritchie, N.; Kaul, A. Patent WO2021237371A1, **2021**.

2-Cinnamyl-4-(trifluoromethyl)phenol (1.30g)

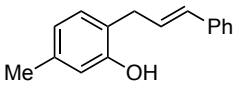
Prepared following the general procedure A using methyl 4-(triflurormethyl)phenol (324 mg, 2.00 mmol, 1.0 equiv), NaH (84 mg, 2.10 mmol, 1.1 equiv) and (*E*)-cinnamyl chloride (0.3 mL, 2.20 mmol, 1.1 equiv) in CCl_4 (4.0 mL, 0.5 M) at 80 ºC for 16 h. The crude product was purified by flash column chromatography (SiO_2, cyclohexane/EtOAc 100:0 to 50:50, *v/v*) and the product **1.30g** was obtained as a orange solid (236 mg, 0.85 mmol, 42% yield).



^{1}H NMR (500 MHz, $CDCl_3$) δ 7.47–7.34 (m, 4H), 7.33–7.28 (m, 2H), 7.26–7.20 (m, 1H), 6.88 (d, J = 8.5 Hz, 1H), 6.54 (dt, J = 15.8, 1.6 Hz, 1H), 6.36 (dt, J = 15.9, 6.6 Hz, 1H), 5.36 (s, 1H), 3.60 (dd, J = 6.6, 1.6 Hz, 2H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 156.9, 136.9, 132.5, 128.7, 128.7, 127.8 (q, $J_{C–F}$ = 3.9 Hz), 127.7, 126.8, 126.4, 125.5 (q, $J_{C–F}$ = 3.9 Hz), 124.5 (q, $J_{C–F}$ = 270.9 Hz), 115.9, 115.6, 34.1. **^{19}F NMR** (471 MHz, $CDCl_3$) δ -61.4. **HRMS** (ESI –) calculated for $[C_{16}H_{12}F_3O]$ $[M–H]^-$ 277.0846 *m/z*; found 277.0838 *m/z.*

2-Cinnamyl-5-methylphenol (1.30i)

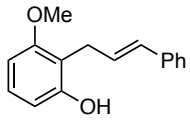
Prepared following the general procedure B using (*E*)-1-(2-hydroxy-4-methylphenyl)-3-phenylpropenone (720 mg, 3.0 mmol, 1.0 equiv), Et_3N (0.5 mL, 0.33 g, 3.3 mmol, 1.1 equiv), ethyl chloroformate (0.3 mL, 0.36 g, 3.3 mmol, 1.1 equiv), $CeCl_3 \cdot 7H_2O$ (1.34 g, 3.6 mmol, 1.2 equiv) and $NaBF_4$ (0.14 g, 3.6 mmol, 1.2 equiv.) in THF (15.0 mL, 0.2 M) and EtOH (30.0 mL, 0.1 M). The crude product was purified by flash column chromatography (SiO_2, cyclohexane/EtOAc 9:1, *v/v*) and the product **1.30i** was obtained as a white solid (311 mg, 1.4 mmol, 46% yield).



^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37–7.33 (m, 2H), 7.31–7.27 (m, 2H), 7.23–7.19 (m, 1H), 7.05 (d, J = 7.6 Hz, 1H), 6.73 (d, J = 7.6 Hz, 1H), 6.65 (s, 1H), 6.50 (dt, J = 15.8, 1.6 Hz, 1H), 6.38 (dt, J = 15.8, 6.5 Hz, 1H), 4.86 (s, 1H), 3.53 (dd, J = 6.6, 1.7 Hz, 2H), 2.30 (s, 3H). The characterization data matches those reported in the literature.[36]

2-Cinammyl-3-methoxyphenol (1.30j)

Prepared following the general procedure B using (*E*)-1-(2-hydroxy-6-methoxyphenyl)-3-phenylpropenone (1.53 g, 6.00 mmol, 1.0 equiv), Et_3N (0.9 mL, 0.67 g, 6.6 mmol, 1.1 equiv), ethyl chloroformate (0.6 mL, 0.72 g, 6.6 mmol, 1.1 equiv), $CeCl_3 \cdot 7H_2O$ (2.68 g, 7.20 mmol, 1.2 equiv) and $NaBF_4$ (0.27 g, 7.2 mmol, 1.2 equiv) in THF (30.0 mL, 0.2 M) and EtOH (60.0 mL, 0.1 M). The crude product was purified by flash column chromatography (SiO_2, cyclohexane/EtOAc 9:1, *v/v*) and the product **1.30j** was obtained as a white solid (812 mg, 3.4 mmol, 56% yield).

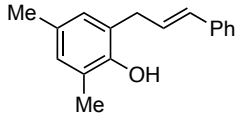


36. Zhang, H.; Lin, S.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2014**, *136*, 16485–16488.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35–7.32 (m, 2H), 7.29–7.25 (m, 2H), 7.21–7.16 (m, 1H), 7.10 (dd, *J* = 8.2, 8.2 Hz, 1H), 6.54–6.45 (m, 3H), 6.35 (dt, *J* = 15.9, 6.3, 1H), 4.99 (s, 1H), 3.84 (s, 3H), 3.62 (dd, *J* = 6.4, 1.6 Hz, 2H). The characterization data matches those reported in the literature.[37]

2-Cinnamyl-4,6-dimethylphenol (1.30k)

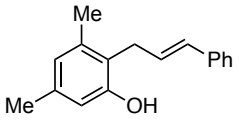
Prepared following the general procedure A using 2,4-dimethylphenol (611 mg, 5.00 mmol, 1.0 equiv), NaH (210 mg, 5.25 mmol, 1.1 equiv) and (*E*)-cinnamyl chloride (0.8 mL, 5.50 mmol, 1.1 equiv) in CCl_4 (10.0 mL, 0.5 M) at 80 ºC for 16 h. The crude product was purified by flash column chromatography (SiO_2, cyclohexane/EtOAc 100:0 to 80:20, *v/v*) and the product **1.30k** was obtained as a yellow solid (615 mg, 2.58 mmol, 52% yield).



^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44–7.38 (m, 2H), 7.38–7.31 (m, 2H), 7.30–7.23 (m, 1H), 6.95–6.84 (m, 2H), 6.62–6.53 (m, 1H), 6.48–6.36 (m, 1H), 4.85 (s, 1H), 3.58 (dd, *J* = 6.6, 1.5 Hz, 2H), 2.30 (d, *J* = 0.7 Hz, 3H), 2.27 (d, *J* = 0.7 Hz, 3H). The spectroscopic data matches those reported in the literature.[37]

2-Cinnamyl-3,5-dimethylphenol (1.30l)

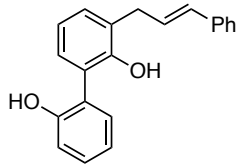
Prepared following the general procedure A using 3,5-dimethylphenol (0.44 g, 3.6 mmol, 1.1 equiv), NaH (0.14 g, 3.4 mmol, 1.1 equiv), (*E*)-cinnamyl chloride (0.5 mL, 3.6 mmol, 1.1 equiv) in CCl_4 (6.0 mL, 0.5 M). The crude product was purified by flash column chromatography (SiO_2, cyclohexane/EtOAc 98:2, *v/v*) and the product **1.30l** was obtained as a white solid (561 mg, 2.40 mmol, 72% yield).



^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33–7.29 (m, 2H), 7.29–7.23 (m, 2H), 7.20–7.15 (m, 1H), 6.63 (s, 1H), 6.52 (s, 1H), 6.41–6.27 (m, 2H), 5.75 (s, 1H), 3.54 (d, *J* = 5.4 Hz, 2H), 2.29 (s, 3H), 2.26 (s, 3H). The characterization data matches those reported in the literature.[38]

3-Cinnamyl-(1,1'-biphenyl)-2,2'-diol (1.30m)

Prepared following the general procedure A using (1,1'-biphenyl)-2,2'-diol (931 mg, 5.00 mmol, 1.0 equiv), NaH (210 mg, 5.25 mmol, 1.1 equiv) and (*E*)-cinnamyl chloride (0.8 mL, 5.50 mmol, 1.1 equiv) in CCl_4 (10.0 mL, 0.5 M) at 80 ºC for 16 h. The crude product was purified by flash column chromatography (SiO_2, cyclohexane/EtOAc 100:0 to 60:40, *v/v*) and the product **1.30m** was obtained as a white sticky solid (1.05 g, 3.47 mmol, 70% yield).



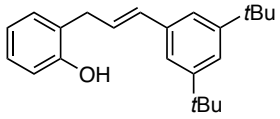
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40–7.25 (m, 8H), 7.23–7.14 (m, 2H), 7.08–6.98 (m, 2H), 6.55 (d, *J* = 15.9 Hz, 1H), 6.44 (dt, *J* = 15.8, 6.7 Hz, 1H), 3.65 (dd, *J* = 6.7, 1.3 Hz, 2H). **^{13}C NMR** (126 MHz,

37. Denmark, S. E.; Kornfilt, D. J. P. *J. Org. Chem.* **2017**, *82*, 3192–3222.
38. Vyvyan, J. R.; Dimmitt, H. E.; Griffith, J. K.; Steffens, L. D.; Swanson, R. A. *Tetrahedron Lett.* **2010**, *51*, 6666–6669.

$CDCl_3$) δ 153.3, 151.4, 137.4, 131.7, 131.4, 130.8, 130.2, 129.4, 128.7, 128.2, 127.7, 127.4, 126.3, 123.4, 123.3, 121.7, 121.5, 116.7, 34.2. **HRMS** (ESI –) calculated for $[C_{21}H_{17}O_2]$ $[M–H]^-$ 301.1234 *m/z*; found 301.1237 *m/z.*

(*E*)-2-(3-(3,5-Di-*tert*-butylphenyl)allyl)phenol (1.30n)

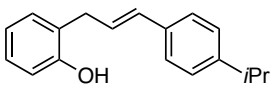
Prepared following the general procedure B using 1-(2-hydroxyphenyl)-3-(3,5-di-*tert*-butylphenyl)propenone (1.01 g, 3.00 mmol, 1.0 equiv), Et_3N (0.5 mL, 0.33 g, 3.3 mmol, 1.1 equiv), ethyl chloroformate (0.3 mL, 3.3 mmol, 1.1 equiv), $CeCl_3 \cdot 7H_2O$ (1.34 g, 3.6 mmol, 1.2 equiv) and $NaBF_4$ (0.25 g, 6.6 mmol, 2.2 equiv) in THF (15.0 mL, 0.2 M) and EtOH (30.0 mL, 0.1 M). The crude product was purified by flash column chromatography (SiO_2, cyclohexane/EtOAc 95:5, *v/v*) and the product **1.30n** was obtained as a white solid (264 mg, 0.800 mmol, 27% yield).



M.p. 103–106 ºC. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.31 (dd, *J* = 7.9, 7.9 Hz, 1H), 7.22–7.14 (m, 4H), 6.92 (ddd, *J* = 7.4, 7.4, 1.2 Hz, 1H), 6.84 (dd, *J* = 8.0, 1.2 Hz, 1H), 6.55 (dt, *J* = 15.9, 1.6 Hz, 1H), 6.38 (dt, *J* = 15.9, 6.6 Hz, 1H), 5.00 (s, 1H), 3.59 (dd, *J* = 6.6, 1.6 Hz, 2H), 1.32 (s, 18H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 154.4, 151.1, 136.3, 132.8, 130.7, 128.1, 127.1, 125.9, 121.9, 121.1, 120.7, 116.1, 35.0, 34.5, 31.6. **HRMS** (ESI –) calculated for $[C_{23}H_{29}O]$ $[M–H]^-$ 321.2224 *m/z*; found 321.2211 *m/z.*

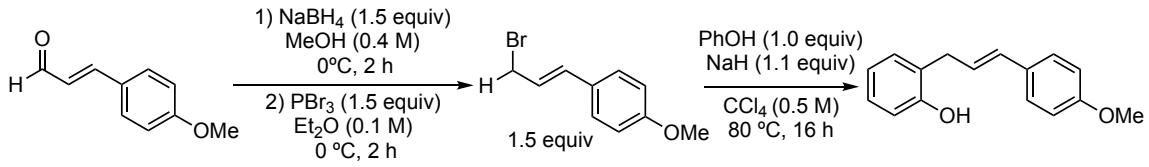
(*E*)-2-(3-(4-*iso*-Propylphenyl)allyl)phenol (1.30o)

Prepared following the general procedure B using 1-(2-hydroxyphenyl)-3-(4-*iso*-propylphenyl)propenone (0.80 g, 3.0 mmol, 1.0 equiv), Et_3N (0.5 mL, 0.33 g, 3.3 mmol, 1.1 equiv), ethyl chloroformate (0.3 mL, 3.3 mmol, 1.1 equiv), $CeCl_3 \cdot 7H_2O$ (1.34 g, 3.6 mmol, 1.2 equiv) and $NaBF_4$ (0.25 g, 6.6 mmol, 2.2 equiv) in THF (15.0 mL, 0.2 M) and EtOH (30.0 mL, 0.1 M). The crude product was purified by flash column chromatography (SiO_2, cyclohexane/EtOAc 95:5, *v/v*) and the product **1.30o** was obtained as a white solid (259 mg, 1.00 mmol, 34% yield).



M.p. 48–50 ºC. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.30 (d, *J* = 8.1 Hz, 2H), 7.20–7.13 (m, 4H), 6.93–6.89 (m, 1H), 6.83 (d, *J* = 7.9 Hz, 1H), 6.52 (d, *J* = 15.8 Hz, 1H), 6.35 (dt, *J* = 15.8, 6.6 Hz, 1H), 5.00–4.98 (m, 1H), 3.58 (d, *J* = 6.6 Hz, 2H), 2.89 (p, *J* = 6.9 Hz, 1H), 1.25 (dd, *J* = 6.9, 1.0 Hz, 6H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 154.3, 148.4, 134.8, 131.6, 130.6, 128.0, 127.0, 126.7, 126.3, 125.9, 121.1, 116.0, 34.3, 34.0, 24.1. **HRMS** (ESI –) calculated for $[C_{18}H_{19}O]$ $[M–H]^-$ 251.1441 *m/z*; found 251.1443 *m/z.*

Synthesis of 2-(3-(4-methoxyphenyl)allyl)phenol (1.30p)

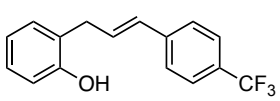


$NaBH_4$ (284 mg, 7.50 mmol, 1.5 equiv) was slowly added to a solution of 3-(4-methoxyphenyl-2-propenal (811 mg, 5.00 mmol, 1.0 equiv) in MeOH (13.0 mL, 0.4 M) at 0 º C and the solution was stirred for 2 h. The crude mixture was quenched by the addition of a saturated NH_4Cl aqueous solution (15 mL) and extracted three times with EtOAc (3 x 15 mL). The combined organic layers were washed with brine (15 mL), dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. Then, the crude alcohol was dissolved in anhydrous Et_2O (50.0 mL, 0.1 M) at 0 ºC and PBr_3 (1.3 mL, 7.50 mmol, 1.50 equiv) was slowly added to the mixture. The reaction was stirred for 2 h at 0 ºC and quenched by the addition of a saturated NH_4Cl aqueous solution (50 mL) and extracted three times with CH_2Cl_2 (3 x 50 mL). The combined organic layers were washed with brine (50 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The crude bromide was directly used without further purification.

In a 250 mL round-bottom flash under argon atmosphere phenol (527 mg, 5.60 mmol, 1.0 equiv) was dissolved in anhydrous CCl_4 (12.3 mL, 0.5 M) and, to this mixture, NaH (259 mg, 60% Wt, 6.47 mmol, 1.1 equiv) was added in one portion at 0 ºC. The reaction was stirred at 0 ºC for 30 min and the previously synthetized crude bromide (1.5 equiv) was added to the mixture, which was further stirred at 80 ºC for 16 h. After completion of the reaction, the mixture was cooled down to room temperature and acidified until pH<1 with an aqueous solution of HCl 1M. Then, it was diluted with H_2O (20 mL) and extracted three times with CH_2Cl_2 (3 x 20 mL). The combined organic layers were washed with brine (20 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was purified by flash column chromatography (SiO_2, cyclohexane/EtOAc 100:0 to 60:40, *v/v*) to afford the product **1.30p** as a yellow oil (361 mg, 1.50 mmol, 24% yield over 3 steps).

M.p. 87–93 ºC. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.41 (dd, *J* = 7.6, 1.7 Hz, 2H), 7.19–7.12 (m, 3H), 6.95–6.81 (m, 4H), 6.38 (dt, *J* = 16.0, 6.9 Hz, 1H), 5.10 (s, 1H), 3.85 (s, 3H), 3.60 (dd, *J* = 6.9, 1.6 Hz, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 159.2, 154.3, 131.2, 130.6, 130.0, 128.0, 127.5, 125.9, 125.7, 121.1, 116.0, 114.1, 55.4, 34.4. **HRMS** (ESI –) calculated for $[C_{16}H_{15}O_2]$ $[M–H]^-$ 239.1078 *m/z*; found 239.1079 *m/z.*

2-(3-(4-(Trifluoromethyl)phenyl)allyl)phenol (1.30q)

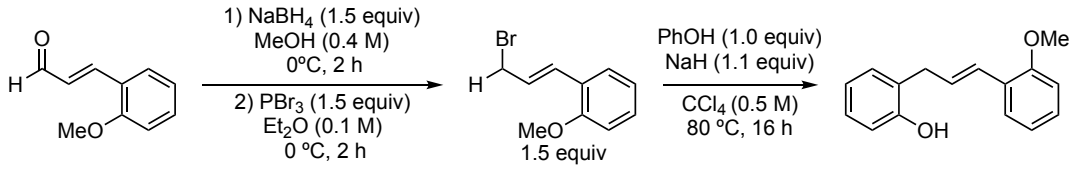


Prepared following the general procedure B using (*E*)-1-(2-hydroxyphenyl)-3-(4-(trifluoromethyl)phenyl)prop-2-en-1-one (0.56 g, 5.0 mmol, 1.0 equiv), Et_3N (0.8 mL, 0.56 g, 5.5 mmol, 1.1 equiv), ethyl chloroformate (0.5 mL, 0.60 g, 5.50 mmol, 1.1 equiv), $CeCl_3 \cdot 7H_2O$ (2.24 g, 6.00 mmol, 1.2 equiv) and $NaBF_4$ (0.23 g,

6.0 mmol, 1.2 equiv) in THF (15.0 mL) and EtOH (30.0 ml). The crude product was purified by flash column chromatography (SiO_2, cyclohexane/EtOAc 9:1, *v/v*) and the product **1.30q** was obtained as a white solid (644 mg, 2.30 mmol, 46% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.54 (d, *J* = 8.2 Hz, 2H), 7.44 (d, *J* = 8.1 Hz, 2H), 7.19–7.13 (m, 2H), 6.92 (ddd, *J* = 7.5, 7.5, 1.3 Hz, 1H), 6.81 (dd, *J* = 8.0, 1.2 Hz, 1H), 6.54–6.46 (m, 2H), 4.83 (s, 1H), 3.59 (d, *J* = 4.8 Hz, 2H). The characterization data matches those reported in the literature.[39]

Synthesis of 2-(3-(2-methoxyphenyl)allyl)phenol (1.30r)



$NaBH_4$ (426 mg, 11.3 mmol, 1.5 equiv) was slowly added to a solution of (*E*)-3-(2-methoxyphenyl)acrylaldehyde (1.10 g, 7.50 mmol, 1.0 equiv) in MeOH (20.0 mL, 0.4 M) at 0 ºC and the solution was stirred for 2 h. The crude mixture was quenched by the addition of a saturated NH_4Cl aqueous solution (20 mL) and extracted three times with EtOAc (3 x 20 mL). The combined organic layers were washed with brine (30 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. Then, the crude alcohol was dissolved in anhydrous Et_2O (75.0 mL, 0.1 M) at 0 ºC and PBr_3 (1.1 mL, 11.3 mmol, 1.50 equiv) was slowly added to the mixture. The reaction was stirred for 2 h at 0 ºC and quenched by the addition of a saturated NH_4Cl aqueous solution (50 mL) and extracted three times with CH_2Cl_2 (3 x 50 mL). The combined organic layers were washed with brine (50 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The crude bromide was directly used without further purification.

In a 250 mL round-bottom flash under argon atmosphere phenol (527 mg, 5.60 mmol, 1.0 equiv) was dissolved in anhydrous CCl_4 (14.0 mL, 0.5 M) and, to this mixture, NaH (298 mg, 60% Wt, 7.46 mmol, 1.1 equiv) was added in one portion at 0 ºC. The reaction was stirred at 0 ºC for 30 min and the previously synthetized crude bromide (1.5 equiv) was added to the mixture, which was further stirred at 80 ºC for 16 h. After completion of the reaction, the mixture was cooled down to room temperature and acidified until pH<1 with an aqueous solution of HCl 1M. Then, it was diluted with H_2O (20 mL) and extracted three times with CH_2Cl_2 (3 x 20 mL). The combined organic layers were washed with brine (20 mL), dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography (SiO_2, cyclohexane/EtOAc 100:0 to 60:40, *v/v*) to afford the product **1.30r** as a yellow oil (335 mg, 1.49 mmol, 21% yield over 3 steps).

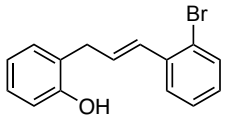
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 (dd, *J* = 7.6, 1.7 Hz, 1H), 7.25–7.12 (m, 3H), 6.95–6.81 (m, 5H), 6.38 (dt, *J* = 16.0, 6.9 Hz, 1H), 5.10 (s, 1H), 3.85 (s, 3H), 3.60 (dd, *J* = 6.9, 1.6 Hz, 2H). **^{13}C NMR** (101

39. Yuan, H.; Chen, H.; Jin, H.; Li, B.; Yue, R.; Ye, J.; Shen, Y.; Shan, L.; Sun, Q.; Zhang, W. *Tetrahedron Lett.* **2013**, *54*, 2776–2780.

MHz, $CDCl_3$) δ 156.6, 154.4, 130.5, 128.8, 128.6, 128.0, 126.9, 126.2, 121.1, 120.8, 116.0, 111.0, 55.6, 35.1. **HRMS** (ESI –) calculated for $[C_{16}H_{15}O_2]$ $[M–H]^-$ 239.1078 *m/z*; found 239.1080 *m/z.*

(*E*)-2-(3-(2-Bromophenyl)allyl)phenol (1.30s)

Prepared following the general procedure B using 1-(2-hydroxyphenyl)-3-(2-bromophenyl)propenone

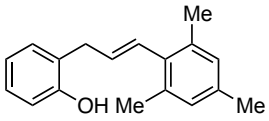


(0.91 g, 3.0 mmol, 1.0 equiv), Et_3N (0.5 mL, 0.33 g, 3.30 mmol, 1.1 equiv), ethyl chloroformate (0.3 mL, 3.3 mmol, 1.1 equiv), $CeCl_3·7H_2O$ (1.34 g, 3.60 mmol, 1.2 equiv) and $NaBF_4$ (0.25 g, 6.6 mmol, 2.2 equiv) in THF (15.0 mL) and EtOH (30.0 ml). The crude product was purified by flash column chromatography (SiO_2, cyclohexane/EtOAc 95:5, *v/v*) and the product **1.30s** was obtained as a white solid (400 mg, 1.40 mmol, 46% yield).

M.p. 77–78 ºC. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.53 (dd, *J* = 8.0, 1.3 Hz, 1H), 7.49 (dd, *J* = 7.8, 1.7 Hz, 1H), 7.25–7.21 (m, 1H), 7.20–7.13 (m, 2H), 7.07 (ddd, *J* = 7.7, 7.7, 1.7 Hz, 1H), 6.91 (ddd, *J* = 7.5, 7.5, 1.2 Hz, 1H), 6.86 (dt, *J* = 15.7, 1.8 Hz, 1H), 6.82 (dd, *J* = 8.0, 1.2 Hz, 1H), 6.31 (dt, *J* = 15.7, 6.8 Hz, 1H), 4.89 (s, 1H), 3.61 (dd, *J* = 6.8, 1.6 Hz, 2H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 154.1, 137.3, 133.0, 131.4, 130.6, 130.6, 128.7, 128.1, 127.6, 127.2, 125.7, 123.5, 121.2, 115.9, 34.4. **HRMS** (ESI –) calculated for $[C_{15}H_{13}BrO]$ $[M–H]^-$ 287.0077 *m/z*; found 287.0067 *m/z.*

(*E*)-2-(3-Mesitylallyl)phenol (1.30t)

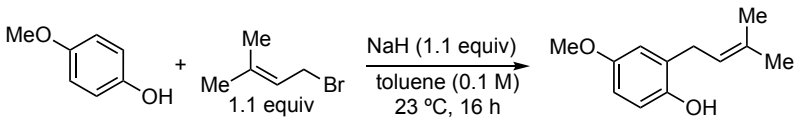
Prepared following the general procedure B using 1-(2-hydroxyphenyl)-3-mesitylpropenone (0.80 g,



3.0 mmol, 1.0 equiv), Et_3N (0.5 mL, 0.33 g, 3.3 mmol, 1.1 equiv), ethyl chloroformate (0.3 mL, 3.3 mmol, 1.1 equiv), $CeCl_3·7H_2O$ (1.34 g, 3.60 mmol, 1.2 equiv) and $NaBF_4$ (0.25 g, 6.6 mmol, 2.2 equiv) in THF (15.0 mL) and EtOH (30.0 ml). The crude product was purified by flash column chromatography (SiO_2, cyclohexane/EtOAc 95:5, *v/v*) and the product **1.30t** was obtained as a white solid (300 mg, 1.20 mmol, 40% yield).

M.p. 65–66 ºC. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.22–7.12 (m, 2H), 6.91 (ddd, *J* = 7.4, 7.4, 1.2 Hz, 1H), 7.87–7.81 (m, 3H), 6.48 (d, *J* = 16.1, Hz, 1H), 5.85 (dt, *J* = 16.2, 6.6 Hz, 1H), 5.02 (s, 1H), 3.60 (dd, *J* = 6.6, 1.7 Hz, 2H), 2.26 (s, 9H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 154.3, 136.2, 136.0, 134.0, 132.5, 130.5, 129.6, 128.7, 128.0, 125.9, 121.1, 115.8, 34.8, 21.0. **HRMS** (ESI –) calculated for $[C_{18}H_{19}O]$ $[M–H]^-$ 251.1441 *m/z*; found 251.1433 *m/z.*

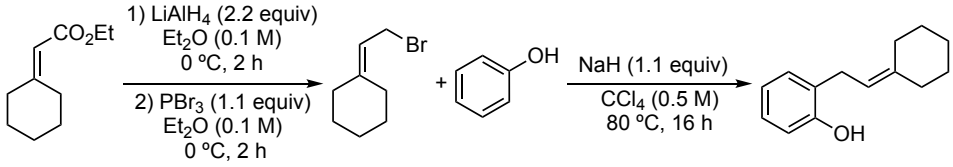
Synthesis of 4-methoxy-2-(3-methylbut-2-en-1-yl)phenol (1.30u)



In a 100 mL round-bottom flash under argon atmosphere 4-methoxyphenol (621 mg, 5.00 mmol, 1.0 equiv) was dissolved in anhydrous toluene (50.0 mL, 0.1 M) and, to this mixture, NaH (220 mg, 60% Wt, 5.50 mmol, 1.10 equiv) was added in one portion at 0 ºC. The reaction was stirred at 0 ºC for 30 min and 1-bromo-3-methylbut-2-ene (0.6 mL, 5.50 mmol, 1.1 equiv) was added to the mixture which was further stirred at 23 ºC for 16 h. After completion of the reaction, it was quenched with H_2O (30 mL) and extracted three times with Et_2O (3 x 30 mL). The combined organic layers were washed with brine (30 mL), dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography (SiO_2, cyclohexane/EtOAc 100:0 to 60:40, *v/v*) to afford the product **1.30u** as a white solid (498 mg, 2.59 mmol, 52% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.77–6.61 (m, 3H), 5.35–5.28 (m, 1H), 4.94 (s, 1H), 3.76 (s, 3H), 3.33 (d, J = 7.2 Hz, 2H), 1.87–1.66 (m, 6H). The spectroscopic data matches those reported in the literature.[40]

Synthesis of 2-(2-cyclohexylideneethyl)phenol (1.30v)



$LiAlH_4$ (32.7 mL, 1.0 M, 32.7 mmol, 2.2 equiv) was slowly added to a solution of 2-cyclohexylidenenacetate (2.50 g, 14.9 mmol, 1.0 equiv) in Et_2O (149.0 mL, 0.1 M) at 0 ºC and the solution was stirred for 2 h. The crude mixture was quenched by the addition of a saturated NH_4Cl aqueous solution (80 mL) and extracted three times with EtOAc (3 x 80 mL). The combined organic layers were washed with brine (100 mL), dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. Then, the crude alcohol (expected 13.5 mmol) was dissolved in anhydrous Et_2O (130.0 mL, 0.1 M) at 0 ºC and PBr_3 (1.5 mL, 14.8 mmol, 1.1 equiv) was slowly added to the mixture. The reaction was stirred for 2 h at 0 ºC and quenched by the addition of a saturated NH_4Cl aqueous solution (50 mL) and extracted three times with CH_2Cl_2 (3 x 50 mL). The combined organic layers were washed with brine (50 mL), dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The crude bromide was directly used without further purification.

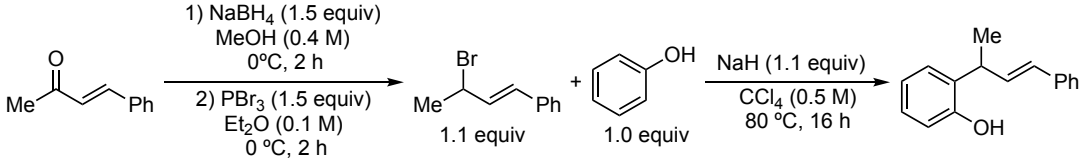
In a 250 mL round-bottom flash under argon atmosphere phenol (1.27 g, 13.5 mmol, 1.0 equiv) was dissolved in anhydrous CCl_4 (25.0 mL, 0.5 M) and, to this mixture, NaH (566 mg, 60% Wt, 14.1 mmol, 1.1 equiv) was added in one portion at 0 ºC. The reaction was stirred at 0 ºC for 30 min and the

40. Trivedi, R.; Tunge, J. A. *Org. Lett.* **2009**, *11*, 5650–5652.

previously synthetized crude bromide (1.1 equiv) was added to the mixture which was further stirred at 80 ºC for 16 h. After completion of the reaction the mixture was cooled down to room temperature and acidified until pH<1 with an aqueous solution of 1M HCl. Then, it was diluted with H_2O (20 mL) and extracted three times with CH_2Cl_2 (3 x 20 mL). The combined organic layers were washed with brine (20 mL), dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography (SiO_2, cyclohexane/EtOAc 100:0 to 60:40, *v/v*) to afford the product **1.30v** as an orange oil (427 mg, 13.5 mmol, 16% yield over 3 steps).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.17–7.10 (m, 2H), 6.89 (td, *J* = 7.4, 1.2 Hz, 1H), 6.82 (dt, *J* = 8.5, 1.1 Hz, 1H), 5.30 (tdd, *J* = 7.3, 2.4, 1.3 Hz, 1H), 3.40 (d, *J* = 7.4 Hz, 2H), 2.17 (t, *J* = 5.3 Hz, 2H), 2.33 (t, *J* = 5.3 Hz, 2H), 1.60 (hept, *J* = 4.9 Hz, 6H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 154.5, 143.0, 130.1, 127.6, 127.0, 120.9, 118.5, 115.9, 37.3, 29.1, 28.8, 28.7, 27.8, 26.9. **HRMS** (ESI –) calculated for $[C_{14}H_{17}O]$ $[M–H]^-$ 201.1285 *m/z*; found 201.1285 *m/z.*

Synthesis of 2-(4-phenylbut-3-en-2-yl)phenol (1.30w)



$NaBH_4$ (426 mg, 11.3 mmol, 1.5 equiv) was slowly added to a solution of 4-phenyl-3-buten-2-one (1.10 g, 7.50 mmol, 1.0 equiv) in MeOH (20.0 mL, 0.4 M) at 0 ºC and the solution was stirred for 2 h. The crude mixture was quenched by the addition of a saturated NH_4Cl aqueous solution (20 mL) and extracted three times with EtOAc (3 x 20 mL). The combined organic layers were washed with brine (30 mL), dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. Then, the crude alcohol was dissolved in anhydrous Et_2O (75.0 mL, 0.1 M) at 0 ºC and PBr_3 (1.1 mL, 11.3 mmol, 1.5 equiv) was slowly added to the mixture. The reaction was stirred for 2 h at 0 ºC and quenched by the addition of a saturated NH_4Cl aqueous solution (50 mL) and extracted three times with CH_2Cl_2 (3 x 50 mL). The combined organic layers were washed with brine (50 mL), dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The crude bromide was directly used without further purification.

In a 250 mL round-bottom flash under argon atmosphere phenol (526 mg, 5.60 mmol, 1.0 equiv) was dissolved in anhydrous CCl_4 (14.0 mL) and, to this mixture, NaH (298 mg, 60% Wt, 7.46 mmol, 1.1 equiv) was added in one portion at 0 ºC. The reaction was stirred at 0 ºC for 30 min and the previously synthetized crude bromide (1.5 equiv) was added to the mixture, which was further stirred at 80 ºC for 16 h. After completion of the reaction the mixture was cooled down to room temperature and acidified until pH<1 with an aqueous solution of HCl 1M. Then, it was diluted with H_2O (20 mL) and extracted three times with CH_2Cl_2 (3 x 20 mL). The combined organic layers were washed with brine (20 mL), dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The

crude product was purified by flash column chromatography (SiO_2, cyclohexane/EtOAc 100:0 to 60:40, *v/v*) to afford the product **1.30w** as a yellow oil (335 mg, 1.49 mmol, 21% yield over 3 steps).

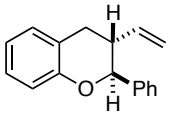
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40–7.34 (m, 2H), 7.34–7.27 (m, 2H), 7.25–7.19 (m, 2H), 7.14 (ddd, *J* = 8.0, 7.4, 1.7 Hz, 1H), 6.94 (td, *J* = 7.5, 1.2 Hz, 1H), 6.81 (dd, *J* = 8.0, 1.3 Hz, 1H), 6.52 (dd, *J* = 16.1, 1.0 Hz, 1H), 6.44 (dd, *J* = 16.0, 5.9 Hz, 1H), 5.00 (s, 1H), 3.91 (p, *J* = 6.5 Hz, 1H), 1.50 (d, *J* = 7.1 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 153.7, 137.3, 134.1, 129.5, 128.7, 128.7, 128.1, 127.8, 127.5, 126.4, 121.2, 116.2, 36.9, 19.6. **HRMS** (ESI –) calculated for $[C_{16}H_{15}O]$ $[M–H]^-$ 223.1128 *m/z*; found 223.1126 *m/z.*

Synthesis of 3-Vinyl Chromanes (1.31)

2-Phenyl-3-vinylchromane

Racemic product (**1.31a**)

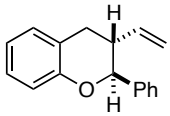
Prepared following the general procedure C using 2-cinnamylphenol **1.30a** (53 mg, 0.25 mmol, 1.0 equiv), JohnPhosAuCl (8 mg, 15 μmol, 6 mol%), $NaBAr^F_4$ (13 mg, 15 μmol, 6 mol%) and 1 atm of acetylene gas in $CHCl_3$ (0.6 mL, 0.4 M) at 23 ºC for 16 h. The crude product was purified by flash column chromatography (SiO_2, cyclohexane/EtOAc 100:0 to 95:5, *v/v*) and the product **1.31a** was obtained as a yellow solid (46 mg, 0.19 mmol, 78% yield).



M.p. 69–72 ºC. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.42–7.32 (m, 5H), 7.17 (ddt, *J* = 8.2, 1.6, 0.7 Hz, 1H), 7.15–7.12 (m, 1H), 6.95–6.89 (m, 2H), 5.61 (ddd, *J* = 17.4, 10.5, 7.1 Hz, 1H), 5.03 (dt, *J* = 10.2, 1.4 Hz, 1H), 5.01–4.99 (m, 1H), 4.81 (d, *J* = 8.9 Hz, 1H), 2.99–2.90 (m, 2H), 2.89–2.79 (m, 1H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 154.8, 140.1, 137.7, 129.5, 128.5, 128.3, 127.6, 127.4, 121.5, 120.6, 116.7, 116.5, 82.2, 42.6, 31.0. **HRMS** (ESI +) calculated for $[C_{17}H_{17}O]$ $[M+H]^+$ 237.1274 *m/z*; found 237.1270 *m/z.*

*Enantioenriched product (***1.31a***)*

Prepared following the general procedure D using 2-cinnamylphenol **1.30a** (53 mg, 0.25 mmol, 1.0 equiv), **1.H** (3 mg, 2.5 μmol, 1 mol%), $NaBAr^F_4$ (2 mg, 2.5 μmol, 1 mol%) and 1 atm of acetylene gas in 1,2-dichloroethane (0.4 mL, 0.6 M) at 23 ºC for 8 h. The crude product was purified by flash column chromatography (SiO_2, cyclohexane/EtOAc 100:0 to 95:5, *v/v*) and the product **1.31a** was obtained as a yellow solid (50 mg, 0.2 mmol, 85% yield).



Characterization data matches the racemic product **1.31a**. **$[\alpha]^{25.0}_D$** +17.9. (c 1.0, CH_2Cl_2, sample with 84:16 er). **SFC** (IG (100 × 3 mm, 3 μm), CO_2:MeOH 80:20, 1.2 mL/min, 25 ºC, BPR 150 bar, 210 nm): en1 (minor, 16%) min 0.90, en2 (major, 84%) min 0.98.

6-(*tert*-Butyl)-2-Phenyl-3-vinylchromane (1.31b)

Prepared following the general procedure C using 4-(*tert*-butyl)-2-cinnamylphenol **1.30b** (67 mg, 0.25 mmol, 1.0 equiv), JohnPhosAuCl (8 mg, 15 μmol, 6 mol%), $NaBAr^F_4$ (13 mg, 15 μmol, 6 mol%) and 1 atm of acetylene gas in $CHCl_3$ (0.6 mL, 0.4 M) at 23 ºC for 16 h. The crude product was purified by flash column chromatography (SiO_2, cyclohexane/EtOAc 100:0 to 95:5, *v/v*) and the product **1.31b** was obtained as a yellow solid (51 mg, 0.17 mmol, 70% yield).

M.p. 127–130 ºC. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.43–7.30 (m, 5H), 7.21–7.16 (m, 1H), 7.14 (dt, *J* = 2.1, 0.9 Hz, 1H), 6.86 (d, *J* = 8.5 Hz, 1H), 5.58 (ddd, *J* = 17.5, 10.5, 7.2 Hz, 1H), 5.01 (dt, *J* = 11.3, 1.4 Hz, 1H), 4.98 (dt, *J* = 4.5, 1.4 Hz, 1H), 4.76 (d, *J* = 9.3 Hz, 1H), 2.98–2.90 (m, 2H), 2.89–2.79 (m, 1H), 1.33 (s, 9H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 152.6, 143.3, 140.2, 137.8, 128.5, 128.3, 127.5, 126.2, 124.6, 120.6, 116.4, 116.2, 82.3, 42.9, 34.2, 31.7, 31.5. **HRMS** (ESI +) calculated for $[C_{21}H_{25}O]$ $[M+H]^+$ 293.1900 *m/z*; found 293.1892 *m/z.*

6-Methoxy-2-phenyl-3-vinylchromane (1.31c)

Prepared following the general procedure C using 2-cinnamyl-4-methoxyphenol **1.30c** (60 mg, 0.25 mmol, 1.0 equiv), JohnPhosAuCl (8 mg, 15 μmol, 6 mol%), $NaBAr^F_4$ (13 mg, 15 μmol, 6 mol%) and 1 atm of acetylene gas in $CHCl_3$ (0.6 mL, 0.4 M) at 23 ºC for 16 h. The crude product was purified by flash column chromatography (SiO_2, cyclohexane/EtOAc 100:0 to 95:5, *v/v*) and the product **1.31c** was obtained as a yellow solid (43 mg, 0.16 mmol, 65% yield).

M.p. 102–104 ºC. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.41–7.30 (m, 5H), 6.85 (d, *J* = 8.9 Hz, 1H), 6.73 (dd, *J* = 8.9, 3.0 Hz, 1H), 6.69–6.65 (m, 1H), 5.59 (ddd, *J* = 17.4, 10.5, 7.1 Hz, 1H), 5.02 (dt, *J* = 11.9, 1.3 Hz, 1H), 4.99 (dt, *J* = 5.2, 1.3 Hz, 1H), 4.75 (d, *J* = 8.9 Hz, 1H), 3.78 (s, 3H), 2.89 (d, *J* = 1.4 Hz, 2H), 2.88–2.79 (m, 1H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 153.6, 148.9, 140.2, 137.8, 128.5, 128.5, 128.2, 127.4, 122.0, 117.3, 116.5, 114.0, 113.6, 55.9, 42.7, 31.3. **HRMS** (ESI +) calculated for $[C_{18}H_{18}NaO_2]$ $[M+Na]^+$ 289.1199 *m/z*; found 289.1202 *m/z.*

4,4,5,5-Tetramethyl-2-(2-phenyl-3-vinylchroman-6-yl)-1,3,2-dioxaborolane

*Racemic product (***1.31d***)*

Prepared following the general procedure C using 2-cinnamyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenol **1.30d** (84 mg, 0.250 mmol, 1.0 equiv), JohnPhosAuCl (8 mg, 15 μmol, 6 mol%), $NaBAr^F_4$ (13 mg, 15 μmol, 6 mol%) and 1 atm of acetylene gas in $CHCl_3$ (0.6 mL, 0.4 M) at 23 ºC for 16 h. The crude product was purified by flash column chromatography (SiO_2, cyclohexane/EtOAc 100:0 to 95:5, *v/v*) and the product **1.31d** was obtained as a sticky yellow solid (51 mg, 0.14 mmol, 56% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.62–7.58 (m, 2H), 7.41–7.30 (m, 5H), 6.90 (dd, *J* = 8.2, 3.1 Hz, 1H), 5.58 (dd, *J* = 10.4, 7.0 Hz, 1H), 5.01 (dt, *J* = 9.7, 1.3 Hz, 1H), 5.00–4.96 (m, 1H), 4.84 (d, *J* = 8.6 Hz, 1H), 2.89 (d, *J* = 7.6 Hz, 2H), 2.84–2.77 (m, 1H), 1.35 (s, 12H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 157.6, 140.0, 137.7, 136.6, 134.5, 128.5, 128.3, 127.3, 120.8, 116.6, 116.2, 83.7, 82.3, 42.5, 30.5, 27.1, 25.0. **HRMS** (ESI +) calculated for $[C_{23}H_{27}NaBO_3]$ $[M+Na]^+$ 385.1945 *m/z*; found 385.1949 *m/z.*

*Enantioenriched product (***1.31d***)*

Prepared following the general procedure D using 2-cinnamyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenol **1.30d** (84 mg, 0.250 mmol, 1.0 equiv), **1.H** (3 mg, 2.5 μmol, 1 mol%), $NaBAr^F{}_4$ (2 mg, 2.5 μmol, 1 mol%) and 1 atm of acetylene gas in 1,2-dichloroethane (0. mL, 0.6 M) at 23 ºC for 8 h. The crude product was purified by flash column chromatography (SiO_2, cyclohexane/EtOAc 100:0 to 95:5, *v/v*) and the product **1.31d** was obtained as a sticky yellow solid (57 mg, 0.16 mmol, 63% yield).

Characterization data matches the racemic product **1.31d**. **$[\alpha]^{25.0}_D$** –6.0. (c 1.1, CH_2Cl_2, sample with 87:13 er). **SFC** (IG (100 × 3 mm, 3 μm), CO_2:MeOH 80:20, 1.2 mL/min, 25 ºC, BPR 150 bar, 210 nm): en1 (minor, 16%) min 0.90, en2 (major, 84%) min 0.98.

2-Phenyl-3-vinyl-6-bromochromane

*Racemic product (***1.31e***)*

Prepared following the general procedure C using 4-bromo-2-cinnamylphenol **1.30e** (72 mg, 0.25 mmol, 1.0 equiv), JohnPhosAuCl (8 mg, 15 μmol, 6 mol%), $NaBAr^F{}_4$ (13 mg, 15 μmol, 6 mol%) and 1 atm of acetylene gas in $CHCl_3$ (0.6 mL, 0.4 M) at 23 ºC for 16 h. The crude product was purified by flash column chromatography (SiO_2, cyclohexane/EtOAc 100:0 to 95:5, *v/v*) and the product **1.31e** was obtained as a yellow solid (62 mg, 0.20 mmol, 79% yield).

M.p. 97–100 ºC. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.40–7.30 (m, 5H), 7.24–7.20 (m, 2H), 6.78 (d, *J* = 8.4 Hz, 1H), 5.61–5.53 (m, 1H), 5.03–5.01 (m, 1H), 5.00–4.98 (m, 1H), 4.78 (d, *J* = 8.7 Hz, 1H), 2.91–2.84 (m, 2H), 2.83–2.75 (m, 1H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 154.0, 139.7, 137.2, 132.0, 130.5, 128.6, 128.5, 127.3, 123.7, 118.5, 116.9, 112.6, 82.2, 42.2, 30.6. **HRMS** (ESI +) calculated for $[C_{17}H_{15}BrNaO]$ $[M+Na]^+$ 337.0198 *m/z*; found 337.0182 *m/z.*

*Enantioenriched product (***1.31e***)*

Prepared following the general procedure D using 4-bromo-2-cinnamylphenol **1.30e** (84 mg, 0.25 mmol, 1.0 equiv), **1.H** (3 mg, 2.5 μmol, 1 mol%), $NaBAr^F{}_4$ (2 mg, 2.5 μmol, 1 mol%) and 1 atm of acetylene gas in 1,2-dichloroethane (0.4 mL, 0.6 M) at 23 ºC for 8 h. The crude product was purified by flash column chromatography (SiO_2,

cyclohexane/EtOAc 100:0 to 95:5, *v/v*) and the product **1.31e** was obtained as a sticky yellow solid (57 mg, 0.16 mmol, 63% yield).

Characterization data matches the racemic product **1.31e**. $[\alpha]_D^{25.0}$ 32.8 (c 0.99, CH_2Cl_2, sample with 87:13 er). **SFC** (IB-N (100 × 3 mm, 3 μm), CO_2:MeOH 95:5, 1.2 mL/min, 25 ºC, BPR 150 bar, 210 nm): en1 (major, 87%) min 2.42, en2 (minor, 13%) min 2.60.

Methyl-2-phenyl-3-vinylchromane-6-carboxylate (1.31f)

Prepared following the general procedure C using methyl 3-cinnamyl-4-hydroxybenzoate **1.30f** (67 mg, 0.250 mmol, 1.0 equiv), JohnPhosAuCl (8 mg, 15 μmol, 6 mol%), $NaBAr^F{}_4$ (13 mg, 15 μmol, 6 mol%) and 1 atm of acetylene gas in $CHCl_3$ (0.6 mL, 0.4 M) at 23 ºC for 16 h. The crude product was purified by flash column chromatography (SiO_2, cyclohexane/EtOAc 100:0 to 95:5, *v/v*) and the product **1.31f** was obtained as a white solid (15 mg, 0.051 mmol, 20% yield).

M.p. 108–112 ºC. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.87–7.80 (m, 2H), 7.42–7.35 (m, 3H), 7.37–7.30 (m, 2H), 6.91 (d, *J* = 8.5 Hz, 1H), 5.63–5.54 (m, 1H), 5.04 (dt, *J* = 7.1, 1.2 Hz, 1H), 5.01 (d, *J* = 1.1 Hz, 1H), 4.86 (d, *J* = 8.8 Hz, 1H), 3.89 (s, 3H), 2.92 (d, *J* = 7.6 Hz, 2H), 2.86–2.77 (m, 1H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 167.1, 158.8, 139.5, 137.1, 131.7, 129.5, 128.6, 128.5, 127.3, 122.5, 121.3, 117.0, 116.7, 82.6, 52.0, 42.2, 30.6. **HRMS** (ESI +) calculated for $[C_{19}H_{18}NaO_3]$ $[M+Na]^+$ 317.1148 *m/z*; found 317.1158 *m/z.*

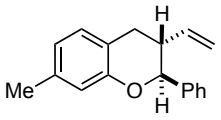
2-Phenyl-6-(trifluoromethyl)-3-vinylchromane-6-carboxylate (1.31g)

Prepared following the general procedure C using methyl 2-cinnamyl-(4-triflurormethyl)phenol **1.30g** (140 mg, 0.503 mmol, 1.0 equiv), JohnPhosAuCl (16 mg, 30 μmol, 6 mol%), $NaBAr^F{}_4$ (27 mg, 30 μmol, 6 mol%) and 1 atm of acetylene gas in $CHCl_3$ (1.26 mL, 0.4 M) at 23 ºC for 16 h. The crude product was purified by flash column chromatography (SiO_2, cyclohexane/EtOAc 100:0 to 95:5, *v/v*) and the product **1.31g** was obtained as a white solid (51 mg, 0.17 mmol, 33% yield).

M.p. 101–106 ºC. **^{1}H NMR (**400 MHz, $CDCl_3$) δ 7.42–7.31 (m, 8H), 6.96 (d, *J* = 9.1 Hz, 1H), 5.58 (ddd, *J* = 17.4, 10.2, 7.1 Hz, 1H), 5.04 (dt, *J* = 4.7, 1.2 Hz, 1H), 5.01 (p, *J* = 1.3 Hz, 1H), 4.85 (d, *J* = 8.8 Hz, 1H), 2.92 (d, *J* = 7.9 Hz, 2H), 2.87–2.78 (m, 1H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 157.4, 139.4, 137.0, 128.6, 128.6, 127.3, 126.9 (q, J_{C-F} = 3.8 Hz), 124.9 (q, J_{C-F} = 3.7 Hz) 124.7 (q, J_{C-F} = 271.5 Hz), 122.9 (q, J_{C-F} = 31.6 Hz), 121.8, 117.1, 117.0, 82.5, 42.1, 30.7. **^{19}F NMR** (376 MHz, $CDCl_3$) δ –61.6. **HRMS** (ESI +) calculated for $[C_{18}H_{16}F_3O]$ $[M+H]^+$ 305.1148 *m/z*; found 305.1146 *m/z.*

2-Phenyl-3-vinyl-7-methylchromane (1.31i)

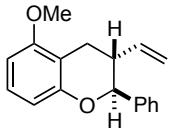
Prepared following the general procedure C using 2-cinnamyl-5-methylphenol **1.30i** (60 mg, 0.25 mmol, 1.0 equiv), JohnPhosAuCl (8 mg, 15 μmol, 6 mol%), $NaBAr^{F}_{4}$ (13 mg, 15 μmol, 6 mol%) and 1 atm of acetylene gas in $CHCl_3$ (0.6 mL, 0.4 M) at 23 ºC for 16 h. The crude product was purified by flash column chromatography (SiO_2, cyclohexane/EtOAc, 100:0 to 95:5, *v/v*) and the product **1.31i** was obtained as a yellow oil (34 mg, 0.14 mmol, 54% yield).



^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41–7.32 (m, 6H), 7.03 (d, *J* = 7.5 Hz, 1H), 6.78–6.72 (m, 2H), 5.61 (ddd, *J* = 17.3, 10.5, 6.9 Hz, 1H), 5.06–4.98 (m, 2H), 4.80 (d, *J* = 8.6 Hz, 1H), 2.92–2.77 (m, 3H), 2.33 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 154.6, 140.2, 137.9, 137.5, 129.3, 128.5, 128.2, 127.4, 121.6, 118.3, 117.1, 116.5, 82.1, 42.8, 30.7, 21.3. **HRMS** (APCI +) calculated for $[C_{18}H_{19}O]$ $[M+H]^+$ 251.1430 *m/z*; found 251.1429 *m/z.*

2-Phenyl-3-vinyl-5-methoxychromane (1.31j)

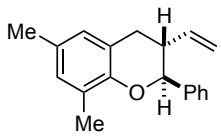
Prepared following the general procedure C using 2-cinammyl-3-methoxyphenol **1.30j** (56 mg, 0.25 mmol, 1.0 equiv), JohnPhosAuCl (8 mg, 15 μmol, 6 mol%), $NaBAr^{F}_{4}$ (13 mg, 15 μmol, 6 mol%) and $CHCl_3$ (0.6 mL, 0.4 M) at 23 ºC for 16 h. The crude product was purified by flash column chromatography (SiO_2, cyclohexane/DCM, 8:2 to 1:1, *v/v*) and the product **1.31j** was obtained as a white solid (20 mg, 0.07 mmol, 29% yield).



M.p. 111–112 ºC. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.40–7.30 (m, 5H), 7.10 (d, *J* = 8.2 Hz, 1H), 6.57 (d, *J* = 8.3 Hz, 1H), 6.47 (d, *J* = 8.2 Hz, 1H), 5.59 (ddd, *J* = 17.5, 10.5, 7.3 Hz, 1H), 5.02 (d, *J* = 17.3 Hz, 1H), 4.98 (d, *J* = 10.5 Hz, 1H), 4.72 (d, *J* = 9.2 Hz, 1H), 3.85 (s, 3H), 2.95 (dd, *J* = 16.8, 5.1 Hz, 1H), 2.80–2.72 (m, 1H), 2.64 (dd, *J* = 16.8, 10.6 Hz, 1H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 158.0, 155.7, 140.1, 137.9, 128.5, 128.3, 127.5, 127.2, 116.5, 110.6, 109.6, 102.2, 81.8, 55.7, 42.3, 25.6. **HRMS** (ESI +) calculated for $[C_{18}H_{18}NaO_2]$ $[M+Na]^+$ 289.1199 *m/z*; found 289.1194 *m/z.*

6,8-Dimethyl-2-phenyl-3-vinylchromane (1.31k)

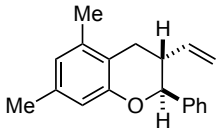
Prepared following the general procedure C using methyl 2-cinnamyl-4,6-dimethylphenol **1.30k** (57 mg, 0.25 mmol, 1.0 equiv), JohnPhosAuCl (8 mg, 15 μmol, 6 mol%), $NaBAr^{F}_{4}$ (13 mg, 15 μmol, 6 mol%) and 1 atm of acetylene gas in $CHCl_3$ (0.6 mL, 0.4 M) at 23 ºC for 16 h. The crude product was purified by flash column chromatography (SiO_2, cyclohexane/EtOAc 100:0 to 95:5, *v/v*) and the product **1.31k** was obtained as a yellow oil (43 mg, 0.16 mmol, 45% yield).



^{1}H NMR (500 MHz, $CDCl_3$) δ 7.42–7.31 (m, 5H), 6.86 (d, *J* = 2.2 Hz, 1H), 6.80–6.78 (m, 1H), 5.68–5.60 (m, 1H), 5.04–5.02 (m, 1H), 5.01–4.99 (m, 1H), 4.82 (d, *J* = 8.8 Hz, 1H), 2.93–2.83 (m, 2H), 2.83–2.72 (m, 1H), 2.29 (s, 3H), 2.20 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 150.7, 140.8, 138.1, 129.5,

129.0, 128.3, 128.0, 127.3, 127.2, 125.6, 120.5, 116.3, 81.9, 43.1, 31.0, 20.6, 16.1. **HRMS** (ESI +) calculated for $[C_{19}H_{21}O]$ $[M+H]^+$ 265.1587 *m/z*; found 265.1581 *m/z.*

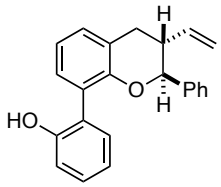
2-Phenyl-3-vinyl-5,7-dimethylchromane (1.31l)



Prepared following the general procedure C using 2-cinnamyl-3,5-dimehtylphenol **1.30l** (60 mg, 0.25 mmol, 1.0 equiv), JohnPhosAuCl (8 mg, 15 μmol, 6 mol%), $NaBAr^F{}_4$ (13 mg, 15 μmol, 0.06 equiv.) and 1 atm of acetylene gas in $CHCl_3$ (0.6 mL, 0.4 M) at 23 ºC for 16 h. The crude product was purified by flash column chromatography (SiO_2, cyclohexane/$CHCl_3$, 100:0 to 8:2, *v/v*) and the product **1.31l** was obtained as a white solid (29 mg, 0.11 mmol, 44% yield).

M.p. 91–93 ºC. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.39–7.29 (m, 5H), 6.62 (s, 1H), 6.61 (s, 1H), 5.60 (ddd, *J* = 17.4, 10.5, 7.4 Hz, 1H), 5.02–4.95 (m, 2H), 4.70 (d, *J* = 8.9 Hz, 1H), 2.84–2.75 (m, 2H), 2.69–2.61 (m, 1H), 2.26 (s, 3H), 2.22 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 154.8, 140.2, 138.1, 137.2, 136.9, 128.5, 128.2, 127.5, 123.2, 117.1, 116.4, 114.9, 81.5, 43.1, 28.8, 21.1, 19.2. **HRMS** (APCI +) calculated for $[C_{19}H_{21}O]$ $[M+H]^+$ 265.1587 *m/z*; found 165.1582 *m/z.*

2-(2-Phenyl-3-vinylchroman-8-yl)phenol (1.31m)



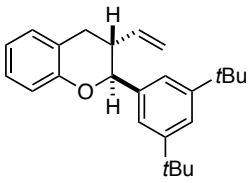
Prepared following the general procedure C using 3-cinnamyl-(1,1'-biphenyl)-2,2'-diol **1.30m** (76 mg, 0.2 mmol, 1.0 equiv), JohnPhosAuCl (8 mg, 15 μmol, 6 mol%), $NaBAr^F{}_4$ (13 mg, 15 μmol, 6 mol%) and 1 atm of acetylene gas in $CHCl_3$ (0. mL, 0.4 M) at 23 ºC for 16 h. The crude product was purified by flash column chromatography (SiO_2, cyclohexane/EtOAc 100:0 to 95:5, *v/v*) and the product **1.31m** was obtained as a yellow sticky solid (34. mg, 0.09 mmol, 38% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.3–7.27 (m, 7H), 7.25 –7.16 (m, 2H), 7.06 (t, *J* = 7.5 Hz, 1H), 6.99 (td, *J* = 7.5, 1.3 Hz, 1H), 6.94 (dd, *J* = 8.1, 1.3 Hz, 1H), 6.44 (s, 1H), 5.65 (ddd, *J* = 17.2, 10.5, 6.7 Hz, 1H), 5.11–5.07 (m, 1H), 5.07–5.04 (m, 1H), 4.98 (d, *J* = 8.0 Hz, 1H), 3.03–2.98 (m, 2H), 2.98–2.93 (m, 1H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 154.0, 150.8, 139.0, 137.2, 131.4, 130.8, 129.5, 129.1, 128.6, 128.4, 127.0, 126.6, 126.5, 122.0, 121.7, 121.0, 117.7, 117.0, 82.9, 42.1, 30.5. **HRMS** (ESI –) calculated for $[C_{23}H_{19}O_2]$ $[M–H]^–$ 327.1391 *m/z*; found 327.1389 *m/z.*

2-(3,5-Di-*tert*-butylphenyl)-3-vinylchromane (1.31n)

*Racemic product (***1.31n***)*

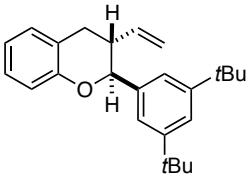
Prepared following the general procedure C using 2-cinnamyl-3,5-dimehtylphenol **1.30n** (81 mg, 0.25 mmol, 1.0 equiv), JohnPhosAuCl (8 mg, 15 μmol, 6 mol%), $NaBAr^F_4$ (13 mg, 15 μmol, 6 mol%) and 1 atm of acetylene gas in $CHCl_3$ (0.6 mL, 0.4 M) at 23 ºC for 16 h. The crude product was purified by flash column chromatography (SiO_2, cyclohexane/EtOAc, 100:0 to 95:5, *v/v*) and the product **1.31n** was obtained as a yellow oil (74 mg, 0.21 mmol, 85% yield).



^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40–7.39 (m, 1H), 7.22–7.20 (m, 2H), 7.18–7.12 (m, 2H), 6.97–6.89 (m, 2H), 5.59 (ddd, *J* = 17.3, 10.5, 6.9 Hz, 1H), 5.05–4.97 (m, 2H), 4.78 (d, *J* = 9.1 Hz, 1H), 3.00–2.83 (m, 3H), 1.35 (s, 18H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 155.1, 150.8, 138.8, 138.0, 129.5, 127.5, 122.2, 121.8, 121.6, 120.5, 116.8, 116.1, 83.0, 42.3, 35.0, 31.6, 31.1. **HRMS** (APCI +) calculated for $[C_{25}H_{33}O]$ $[M+H]^+$ 349.2526 *m/z*; found 349.2523 *m/z.*

*Enantioenriched product (***1.31n***)*

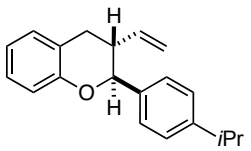
Prepared following the general procedure D using 2-cinnamyl-3,5-dimehtylphenol **1.30n** (81 mg, 0.250 mmol, 1.0 equiv), **1.H** (3 mg, 2.50 μmol, 1 mol%), $NaBAr^F_4$ (2.2 mg, 2.5 μmol, 1 mol%) and 1 atm of acetylene gas in 1,2-dichloroethane (0.4 mL, 0.6 M) at 23 ºC for 8 h. The crude product was purified by flash column chromatography (SiO_2, cyclohexane/EtOAc, 100:0 to 95:5, *v/v*) and the product **1.31n** was obtained as a yellow oil (82 mg, 0.23 mmol, 94% yield).



Characterization data matches the racemic product **1.31n**. **$[\alpha]^{25.0}_D$** +12.1. (c 1.0, CH_2Cl_2, sample with 77:23 er). **SFC** (OD (100 × 3 mm, 3 μm), CO_2:i-PrOH 95:5, 1.2 mL/min, 35 ºC, BPR 150 bar, 210 nm): en1 (minor, 77%) min 0.96, en2 (major, 23%) min 1.12.

2-(4-*iso*-Propylphenyl)-3-Vinylchromane (1.31o)

Prepared following the general procedure C using (*E*)-2-(3-(4-*iso*-propylphenyl)allyl)phenol **1.30o** (63 mg, 0.25 mmol, 1.0 equiv), JohnPhosAuCl (8 mg, 15 μmol, 6 mol%), $NaBAr^F_4$ (13 mg, 15 μmol, 6 mol%) and 1 atm of acetylene gas in $CHCl_3$ (0.6 mL, 0.4 M) at 23 ºC for 16 h. The crude product was purified by flash column chromatography (SiO_2, cyclohexane/EtOAc, 100:0 to 95:5, *v/v*) and the product **1.31o** was obtained as a white solid (61 mg, 0.22 mmol, 88% yield).

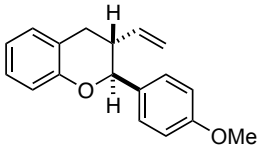


M.p. 85–88 ºC. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.30–7.27 (m, 2H), 7.25–7.21 (m, 2H), 7.15–7.09 (m, 2H), 6.91–6.87 (m, 2H), 5.60 (ddd, *J* = 17.4, 10.5, 6.9 Hz, 1H), 5.06–4.98 (m, 2H), 4.76 (d, *J* = 9.0 Hz, 1H), 2.96–2.79 (m, 4H), 1.26 (d, *J* = 6.9 Hz, 6H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 154.9, 149.0, 137.9,

137.4, 129.5, 127.6, 127.4, 126.6, 121.5, 120.5, 116.7, 116.3, 82.1, 42.3, 34.0, 31.0, 24.1. **HRMS** (APCI +) calculated for $[C_{20}H_{23}O]$ $[M+H]^+$ 279.1743 *m/z*; found 279.1740 *m/z.*

2-(4-Methoxyphenyl)-3-vinylchromane (1.31p)

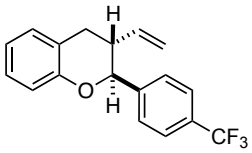
Prepared following the general procedure C using 2-(3-(4-methoxyphenyl)allyl)phenol **1.30p** (60 mg, 0.25 mmol, 1.0 equiv), JohnPhosAuCl (8 mg, 15 μmol, 6 mol%), $NaBAr^F_4$ (13 mg, 15 μmol, 6 mol%) and 1 atm of acetylene gas in $CHCl_3$ (0.6 mL, 0.4 M) at 23 ºC for 16 h. The crude product was purified by flash column chromatography (SiO_2, cyclohexane/EtOAc 100:0 to 95:5, *v/v*) and a second flash column chromatography was needed (SiO_2, cyclohexane/toluene 100:0 to 90:10, *v/v*) to obtain the product **1.31p** as a colorless oil (42 mg, 0.16 mmol, 63% yield).



^{1}H NMR (500 MHz, $CDCl_3$) δ 7.31–7.27 (m, 2H), 7.15–7.09 (m, 2H), 6.93–6.89 (m, 2H), 6.88 (dd, *J* = 7.8, 1.6 Hz, 2H), 5.61–5.50 (m, 1H), 5.05–4.95 (m, 2H), 4.73 (d, *J* = 9.3 Hz, 1H), 3.82 (s, 3H), 2.95–2.87 (m, 2H), 2.85–2.76 (m, 1H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 159.6, 155.0, 137.9, 132.2, 129.5, 128.7, 127.5, 121.5, 120.5, 116.7, 116.4, 114.0, 81.9, 55.4, 42.6, 31.3. **HRMS** (ESI +) calculated for $[C_{18}H_{18}NaO_2]$ $[M+Na]^+$ 289.1199 *m/z*; found 289.1199 *m/z.*

2-(4-Trifluoromethylphenyl)-3-vinylchromane (1.31q)

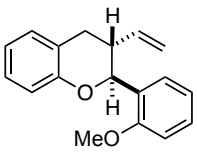
Prepared following the general procedure C using (*E*)-2-(3-(4-(trifluoromethyl)phenyl)allyl)phenol **1.30q** (70 mg, 0.25 mmol, 1.0 equiv), JohnPhosAuCl (8 mg, 15 μmol, 6 mol%), $NaBAr^F_4$ (13 mg, 15 μmol, 6 mol%) and 1 atm of acetylene gas in $CHCl_3$ (0.6 mL, 0.4 M) at 23 ºC for 16 h. The crude product was purified by flash column chromatography (SiO_2, cyclohexane/CH_2Cl_2, 100:0 to 9:1, *v/v*) and the product **1.31q** was obtained as a white solid (46 mg, 0.05 mmol, 21% yield).



M.p. 91–94 ºC. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.63 (d, *J* = 8.1 Hz, 2H), 7.48 (d, *J* = 8.0 Hz, 2H), 7.17–7.10 (m, 2H), 6.94–6.88 (m, 2H), 5.57 (ddd, *J* = 17.1, 10.6, 7.5 Hz, 1H), 5.03–4.97 (m, 2H), 4.81 (d, *J* = 9.0 Hz, 1H), 2.97–2.85 (m, 2H), 2.82–2.74 (m, 1H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 154.3, 144.0, 137.0, 130.3 (q, J_{C-F} = 32.3 Hz), 129.5, 129.1, 127.5, 125.4 (q, J_{C-F} = 3.7 Hz), 124.1 (q, J_{C-F} = 272.1 Hz), 121.1, 120.8, 117.2, 116.6, 81.3, 42.8, 30.8. **^{19}F NMR** (471 MHz, $CDCl_3$) δ –62.6. **HRMS** (APCI +) calculated for $[C_{18}H_{16}F_3O]$ $[M+H]^+$ 305.1148 *m/z*; found 305.1145 *m/z.*

2-(2-Methoxyphenyl)-3-vinylchromane (1.31r)

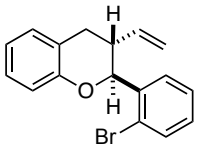
Prepared following the general procedure C using 2-(3-(2-methoxyphenyl)allyl)phenol **1.30r** (60 mg, 0.25 mmol, 1.0 equiv), JohnPhosAuCl (8 mg, 15 μmol, 6 mol%), $NaBAr^{F}_{4}$ (13 mg, 15 μmol, 6 mol%) and 1 atm of acetylene gas in $CHCl_3$ (0.6 mL, 0.4 M) at 23 ºC for 16 h. The crude product was purified by flash column chromatography (SiO_2, cyclohexane/EtOAc 100:0 to 95:5, *v/v*) and the product **1.31r** was obtained as a yellow solid (35 mg, 0.13 mmol, 53% yield).



M.p. 88–95 ºC. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.40 (dd, *J* = 7.6, 1.8 Hz, 1H), 7.29 (ddd, *J* = 8.2, 7.4, 1.8 Hz, 1H), 7.16–7.10 (m, 2H), 6.99 (td, *J* = 7.5, 1.1 Hz, 1H), 6.92–6.86 (m, 3H), 5.72–5.64 (m, 1H), 5.40–5.36 (m, 1H), 4.98 (dt, *J* = 17.3, 1.4 Hz, 1H), 4.94 (ddd, *J* = 10.4, 1.7, 0.8 Hz, 1H), 3.83 (s, 3H), 2.95–2.87 (m, 2H), 2.87–2.82 (m, 1H).**^{13}C NMR** (126 MHz, $CDCl_3$) δ 156.9, 155.3, 138.1, 129.6, 129.0, 128.8, 127.7, 127.5, 121.6, 121.0, 120.4, 116.7, 116.0, 110.8, 75.4, 55.6, 42.5, 31.2. **HRMS** (ESI +) calculated for $[C_{18}H_{18}NaO_2]$ $[M+Na]^+$ 289.1199 *m/z*; found 289.1201 *m/z*.

2-(2-Bromophenyl)-3-vinylchromane (1.31s)

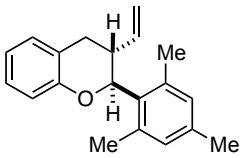
Prepared following the general procedure C using (*E*)-2-(3-(2-bromophenyl)allyl)phenol **1.30s** (72 mg, 0.25 mmol, 1.0 equiv), JohnPhosAuCl (8 mg, 15 μmol, 6 mol%), $NaBAr^{F}_{4}$ (13 mg, 15 μmol, 6 mol%) and 1 atm of acetylene gas in $CHCl_3$ (0.6 mL, 0.4 M) at 23 ºC for 16 h. The crude product was purified by flash column chromatography (SiO_2, cyclohexane/$CHCl_3$, 100:0 to 8:2, *v/v*) and the product **1.31s** was obtained as a white solid (24 mg, 0.08 mmol, 30% yield).



M.p. 58–61 ºC. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.56 (dd, *J* = 8.1, 1.2 Hz, 1H), 7.46 (dd, *J* = 7.8, 1.8 Hz, 1H), 7.34 (ddd, *J* = 7.6, 7.5, 1.2 Hz, 1H), 7.19–7.10 (m, 3H), 6.93–6.87 (m, 2H), 5.72 (ddd, *J* = 16.9, 10.7, 7.4 Hz, 1H), 5.39 (d, *J* = 8.3, 1H), 5.01–4.96 (m, 2H), 2.98–2.82 (m, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 154.8, 139.6, 137.1, 132.8, 129.6, 129.6, 128.7, 127.9, 127.7, 123.5, 121.3, 120.8, 117.0, 116.7, 80.0, 43.1, 30.9. **HRMS** (APCI +) calculated for $[C_{17}H_{16}BrO]$ $[M+H]^+$ 315.0379 *m/z*; found 315.0373 *m/z*.

2-Mesityl-3-vinylchromane (1.31t)

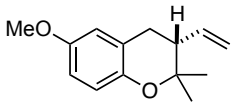
Prepared following the general procedure C using (*E*)-2-(3-mesitylallyl)phenol **1.30t** (63 mg, 0.25 mmol, 1.0 equiv), JohnPhosAuCl (8 mg, 15 μmol, 6 mol%), $NaBAr^{F}_{4}$ (13 mg, 15 μmol, 6 mol%) and 1 atm of acetylene gas in $CHCl_3$ (0.6 mL, 0.4 M) at 23 ºC for 16 h. The crude product was purified by flash column chromatography (SiO_2, cyclohexane/EtOAc 100:0 to 95:5, *v/v*) and the product **1.31t** was obtained as a yellow oil (40. mg, 0.14 mmol, 57% yield).



^{1}H NMR (500 MHz, $CDCl_3$) δ 7.16–7.10 (m, 2H), 7.91–7.84 (m, 4H), 5.58 (ddd, *J* = 17.2, 10.5, 6.7 Hz, 1H), 5.21 (d, *J* = 10.6 Hz, 1H), 5.05 (dd, *J* = 17.3, 1.4 Hz, 1H), 4.97 (dd, *J* = 10.5, 1.3 Hz, 1H), 3.27–3.19 (m, 1H), 3.03–2.89 (m, 2H), 2.37 (s, 6H), 2.27 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 154.9, 137.5, 137.2, 137.1, 132.1, 130.4, 129.7, 127.6, 121.8, 120.4, 116.8, 116.1, 78.9, 39.0, 31.8, 21.2, 21.0. **HRMS** (APCI +) calculated for $[C_{20}H_{23}O]$ $[M+H]^+$ 279.1743 *m/z*; found 279.1743 *m/z*.

6-Methoxy-2,2-dimethyl-3-vinylchromane (1.31u)

Prepared following the general procedure C using 4-methoxy-2-(3-methylbut-2-en-1-yl)phenol **1.30u**

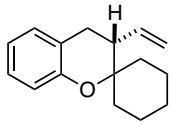


(48 mg, 0.25 mmol, 1.0 equiv), JohnPhosAuCl (8 mg, 15 μmol, 6 mol%), $NaBAr^F{}_4$ (13 mg, 15 μmol, 6 mol%) and 1 atm of acetylene gas in $CHCl_3$ (0.6 mL, 0.4 M) at 23 ºC for 16 h. The crude product was purified by flash column chromatography (SiO_2, cyclohexane/EtOAc 100:0 to 95:5, *v/v*) and the product **1.31u** was obtained as a yellow oil (26 mg, 0.12 mmol, 48% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.71 (s, 1H), 6.71–6.66 (m, 1H), 6.62–6.58 (m, 1H), 5.74 (ddd, *J* = 17.1, 10.3, 8.5 Hz, 1H), 5.18 (ddd, *J* = 17.1, 1.8, 1.0 Hz, 1H), 5.13 (ddd, *J* = 10.3, 1.8, 0.7 Hz, 1H), 3.75 (s, 3H), 2.78 (dd, *J* = 16.8, 5.9 Hz, 1H), 2.68 (ddt, *J* = 16.8, 9.8, 0.9 Hz, 1H), 2.49–2.40 (m, 1H), 1.36 (s, 3H), 1.17 (s, 3H).**^{13}C NMR** (101 MHz, $CDCl_3$) δ 153.2, 147.5, 138.4, 121.4, 117.8, 117.0, 113.9, 113.6, 55.8, 46.1, 29.2, 27.7, 21.4. **HRMS** (ESI –) calculated for $[C_{14}H_{19}O_2]$ $[M+H]^+$ 219.1380 *m/z*; found 219.1377 *m/z*.

3-Vinyl-*spiro*[chromane-2,1'-cyclohexane] (1.31v)

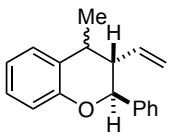
Prepared following the general procedure C using 2-(2-cyclohexylideneethyl)phenol **1.30v** (51 mg,



0.25 mmol, 1.0 equiv), JohnPhosAuCl (8 mg, 15 μmol, 6 mol%), $NaBAr^F{}_4$ (13 mg, 15 μmol, 6 mol%) and 1 atm of acetylene gas in $CHCl_3$ (0.6 mL, 0.4 M) at 23 ºC for 16 h. The crude product was purified by flash column chromatography (SiO_2, cyclohexane/EtOAc 100:0 to 95:5, *v/v*) and the product **1.31v** was obtained as a colorless oil (21 mg, 0.09 mmol, 37% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.13–7.08 (m, 2H), 7.04 (dd, *J* = 7.5, 1.5 Hz, 1H), 6.88–6.81 (m, 1H), 5.76 (ddd, *J* = 17.1, 10.3, 9.0 Hz, 1H), 5.14 (ddd, *J* = 17.1, 1.9, 0.9 Hz, 1H), 5.10 (ddd, *J* = 10.2, 1.9, 0.5 Hz, 1H), 2.85 (dd, *J* = 16.8, 5.9 Hz, 1H), 2.69 (dd, *J* = 16.8, 8.4 Hz, 1H), 2.44 (td, *J* = 8.7, 5.8 Hz, 1H), 1.84–1.41 (m, 6H), 1.34–1.18 (m, 4H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 153.3, 138.5, 129.5, 127.4, 121.1, 120.0, 117.3, 116.8, 45.6, 34.9, 30.2, 29.9, 28.5, 26.0, 21.6, 21.4. **HRMS** (ESI +) calculated for $[C_{16}H_{21}O]$ $[M+H]^+$ 229.1587 *m/z*; found 229.1588 *m/z*.

4-Methyl-2-phenyl-3-vinylchromane (1.31w)

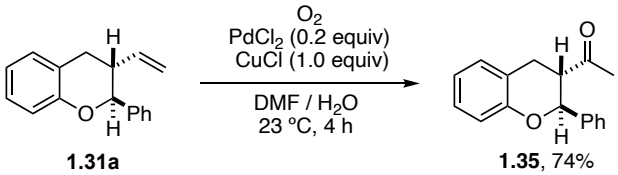


Prepared following the general procedure C using 2-(4-phenylbut-3-en-2-yl)phenol **1.30w** (56 mg, 0.25 mmol, 1.0 equiv), JohnPhosAuCl (8 mg, 15 μmol, 6 mol%), $NaBAr^F{}_4$ (13 mg, 15 μmol, 6 mol%) and 1 atm of acetylene gas in $CHCl_3$ (0.6 mL, 0.4 M) at 23 ºC for 16 h. The crude product was purified by flash column chromatography (SiO_2, cyclohexane/EtOAc 100:0 to 95:5, *v/v*) and the product **1.31w** was obtained as a yellow oil (46 mg, 0.1 mmol, 74% yield) in a 1:1 mixture of isomers.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.42–7.29 (m, 10H), 7.16 (ddddd, *J* = 9.8, 7.2, 5.4, 1.7, 0.7 Hz, 4H), 7.01–6.88 (m, 4H), 5.69 (ddd, *J* = 17.1, 10.3, 9.2 Hz, 1H), 5.44 (ddd, *J* = 17.1, 10.4, 9.1 Hz, 1H), 5.18 (d, *J* = 7.8 Hz, 1H), 5.09–4.97 (m, 3H), 4.83 (ddd, *J* = 17.1, 1.7, 0.7 Hz, 1H), 4.77 (d, *J* = 10.2 Hz, 1H), 3.01–2.91 (m, 2H), 2.90–2.83 (m, 2H), 1.37 (d, *J* = 6.8 Hz, 3H), 1.33 (d, *J* = 7.1 Hz, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 154.7, 153.8, 140.9, 140.2, 137.1, 136.2, 128.5, 128.5, 128.4, 128.3, 128.0, 127.9, 127.7, 127.7, 127.4, 127.3, 126.9, 126.8, 121.0, 120.5, 118.6, 117.9, 117.0, 116.6, 81.8, 78.1, 52.1, 47.9, 34.8, 32.8, 18.7, 18.3. **HRMS** (ESI +) calculated for $[C_{18}H_{19}O]$ $[M+H]^+$ 250.1352 *m/z*; found 250.1349 *m/z*.

Diversification of Standard Product 1.31a

1-(2-Phenylchroman-3-yl)ethan-1-one (1.35)

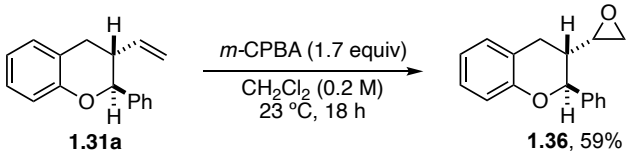


$PdCl_2$ (4 mg, 0.02 mmol, 0.2 equiv) and CuCl (11 mg, 0.11 mmol, 1.0 equiv) were dissolved in a 7:1 mixture of DMF (0.7 mL) and H_2O (0.1 mL) and a balloon of O_2 was placed through one hour (a homogeneous green solution was formed). Then, 2-phenyl-3-vinylchromane **1.31a** (25 mg, 0.11 mmol, 1.0 equiv) was dissolved in DMF (0.4 mL, 0.1 M) and added to the previously prepared mixture under O_2 atmosphere. The reaction mixture was stirred at 23 ºC for 16 h and quenched by the addition of aqueous HCl 1 M solution (5 mL) and extracted three times with Et_2O (3 x 5 mL). The combined organic layers were washed with brine (10 mL), dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography (SiO_2, cyclohexane/EtOAc 100:0 to 60:40, *v/v*) to afford the product **1.35** as a white solid (11 mg, 0.04 mmol, 74% yield).

M.p. 71–76 ºC. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.43–7.31 (m, 5H), 7.19–7.10 (m, 2H), 6.96–6.88 (m, 2H), 4.97 (dd, *J* = 7.8, 1.6 Hz, 1H), 3.24 (dt, *J* = 9.7, 1.4 Hz, 2H), 2.93–2.81 (m, 1H), 1.79 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 209.4, 154.4, 139.1, 129.5, 128.9, 127.8, 127.1, 121.0, 120.7, 116.9, 79.4,

52.3, 31.6, 29.9, 28.7. **HRMS** (ESI +) calculated for $[C_{17}H_{16}NaO_2]$ $[M+Na]^+$ 270.1043 *m/z*; found 270.1048 *m/z*.

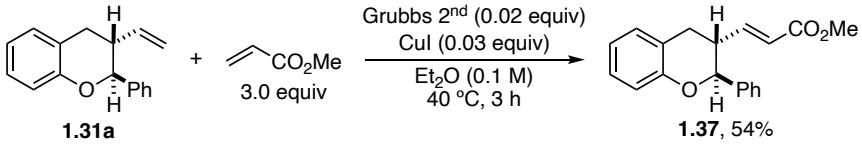
3-(Oxiran-2-yl)-2-phenylchromane (1.36)



m-CPBA (37 mg, 0.22 mmol, 1.7 equiv) was slowly added, under argon atmosphere, to a solution of 2-phenyl-3-vinylchromane **1.31a** (30 mg, 0.13 mmol, 1.0 equiv) in anhydrous CH_2Cl_2 (0.6 mL, 0.2 M) at 0 ºC. The reaction was warmed to 23 ºC and stirred for 18 h. The crude mixture was quenched with a saturated $NaHSO_3$ aqueous solution (5 mL) and extracted three times with CH_2Cl_2 (3 x 5 mL). The combined organic layers were washed with brine (10 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was purified by flash column chromatography (SiO_2, cyclohexane/EtOAc 100:0 to 60:40, *v/v*) to afford the product **1.36** as a colorless oil (19 mg, 0.08 mmol, 59% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.4–7.32 (m, 5H), 7.19–7.10 (m, 2H), 6.94–6.88 (m, 2H), 4.95 (d, *J* = 9.0 Hz, 1H), 2.89 (d, *J* = 7.8 Hz, 2H), 2.74 (ddd, *J* = 6.5, 4.0, 2.7 Hz, 1H), 2.52 (dd, *J* = 4.7, 4.0 Hz, 1H), 2.31 (dd, *J* = 4.7, 2.7 Hz, 1H), 2.06 (dddd, *J* = 9.1, 8.2, 7.4, 6.4 Hz, 1H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 154.6, 139.8, 129.8, 128.8, 128.6, 127.7, 126.9, 120.9, 120.8, 116.8, 79.9, 52.9, 46.4, 41.0, 27.2. **HRMS** (ESI +) calculated for $[C_{17}H_{17}O_2]$ $[M+H]^+$ 253.1223 *m/z*; found 253.1224 *m/z*.

Methyl-(*E*)-3-(2-phenylchroman-3-yl)acrylate (1.37)

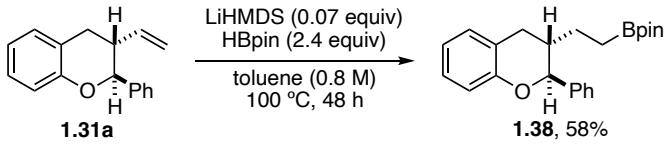


A microwave vial was charged with 2-phenyl-3-vinylchromane **1.31a** (30 mg, 0.13 mmol, 1.0 equiv), methyl acrylate (34 μL, 0.38 mmol, 3.0 equiv), Grubbs 2nd generation catalyst (2 mg, 0.003 mmol, 0.02 equiv) and CuI (0.7 mg, 0.004mmol, 0.03 equiv) under argon atmosphere. Anhydrous Et_2O (1.3 mL, 0.1 M) was added, and the reaction was heated in a metallic heating block at 40 ºC for 3 h. After cooling down to 23 ºC the mixture was concentrated under reduced pressure and the residue was purified by flash column chromatography (SiO_2, cyclohexane/EtOAc 100:0 to 70:30, *v/v*) to afford the product **1.37** as a white solid (20 mg, 0.07 mmol, 54% yield).

M.p. 136–139 ºC. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.41–7.30 (m, 5H), 7.19–7.13 (m, 1H), 7.12–7.09 (m, 1H), 6.95–6.88 (m, 2H), 6.78–6.71 (m, 1H), 5.76 (dd, *J* = 15.7, 1.0 Hz, 1H), 4.89 (d, *J* = 8.4 Hz, 1H), 3.67 (s, 3H), 3.03–2.95 (m, 2H), 2.95–2.88 (m, 1H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 166.5, 154.6, 147.4,

139.4, 129.5, 128.8, 128.6, 127.9, 127.1, 122.7, 120.9, 120.3, 116.9, 81.0, 51.7, 41.9, 30.7. **HRMS** (ESI +) calculated for $[C_{19}H_{18}NaO_3]$ $[M+Na]^+$ 317.1148 *m/z*; found 317.1159 *m/z*.

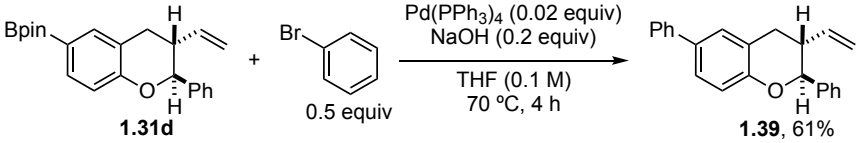
4,4,5,5-Tetramethyl-2-(2-2-phenylchroman-3-yl)ethyl)-1,3,2-dioxaborolane (1.38)



In an argon purged Schlenk tube containing a magnetic stirring bar, anhydrous toluene (0.1 mL), pinacolatoborane (60 μL, 0.41 mmol, 2.4 equiv) and LiHMDS (2 μL, 0.013 mmol, 0.07 equiv) were added sequentially at 23 ºC. The mixture was stirred for 5 min, 2-phenyl-3-vinylchromane **1.31a** (40 mg, 0.17 mmol, 1.0 equiv) was added dropwise in anhydrous toluene (0.1 mL, 0.8 M) and the reaction was stirred at 100 ºC in a metallic heating block for 48 h. After completion of the reaction, the crude was allowed to cool down and quenched by the addition of an aqueous HCl 1 M solution (1 mL) and extracted three times with EtOAc (3 x 1 mL). The combined organic layers were washed with brine (2 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was purified by flash column chromatography (SiO_2, cyclohexane/EtOAc 100:0 to 60:40, *v/v*) to afford the product **1.38** as a white solid (18 mg, 0.05 mmol, 58% yield).

M.p. 66–70 ºC. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.40–7.29 (m, 5H), 7.14–7.05 (m, 2H), 6.87 (d, *J* = 7.7 Hz, 2H), 4.77 (d, *J* = 8.3 Hz, 1H), 2.91 (dd, *J* = 16.3, 5.1 Hz, 1H), 2.57 (dd, *J* = 16.4, 9.6 Hz, 1H), 2.17–2.02 (m, 1H), 1.40 (ddt, *J* = 13.5, 8.2, 3.0 Hz, 1H), 1.31–1.21 (m, 1H), 1.21 (s, 12H), 0.95–0.77 (m, 1H), 0.77–0.66 (m, 1H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 154.9, 140.8, 129.7, 128.6, 128.1, 127.4, 127.3, 122.0, 120.4, 116.5, 83.2, 82.7, 39.3, 30.0, 26.2, 25.0, 24.9. **HRMS** (ESI +) calculated for $[C_{23}H_{29}NaBO_3]$ $[M+Na]^+$ 387.2102 *m/z*; found 387.2108 *m/z*.

Suzuki Coupling of the Product 1.31d: Synthesis of 2,6-Di-phenyl-3-vinylchromane (1.39)



A microwave vial was charged inside the glovebox with $Pd(PPh_3)_4$ (3 mg, 0.002 mmol, 0.02 equiv) in anhydrous THF (1.2 mL, 0.1 M) and then, bromobenzene (6 μL, 0.06 mmol, 0.5 equiv), 4,4,5,5-tetramethyl-2-(2-phenyl-3-vinylchroman-6-yl)-1,3,2-dioxaborolane **1.31d** (42 mg, 0.12 mmol, 1.0 equiv) and 1 M NaOH (0.2 mL, 0.02 mmol, 0.2 equiv) were sequentially added. The mixture was stirred for 4 h at 70 ºC, cooled down, quenched with H_2O (4 mL) and extracted with Et_2O (3 x 6 mL). The combined organic layers were washed with brine (10 mL), dried over anhydrous $MgSO_4$ and concentrated in vacuo. The crude was purified by flash column chromatography (SiO_2,

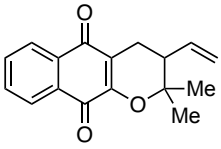
cyclohexane/EtOAc 100:0 to 90:10, *v/v*) to afford the desired product **1.39** as a white solid (22 mg, 0.07 mmol, 61% yield).

M.p. 120–127 ºC. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.59–7.54 (m, 2H), 7.45–7.41 (m, 2H), 7.40–7.29 (m, 8H), 6.98 (d, *J* = 8.4 Hz, 1H), 5.62 (ddd, *J* = 17.5, 10.5, 7.2 Hz, 1H), 5.08–5.03 (m, 1H), 5.02–5.00 (m, 1H), 4.84 (d, *J* = 9.0 Hz, 1H), 3.00–2.94 (m, 2H), 2.91–2.82 (m, 1H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 154.5, 141.1, 140.0, 137.6, 133.8, 128.8, 128.6, 128.4, 128.2, 127.4, 126.9, 126.8, 126.4, 121.7, 117.1, 116.7, 82.4, 42.7, 31.1. **HRMS** (ESI +) calculated for $[C_{23}H_{20}NaO_3]$ $[M+Na]^+$ 335.1406 *m/z*; found 335.1595 *m/z*.

Late-stage Functionalization of lapachol (1.40)

2,2-Dimethyl-3-vinyl-3,4-dihydro-2*H*-benzo[*g*]chromene-5,10-dione-2-hydroxy-3-(3-methylbut-2-en-1-yl) naphthalene-1,4-dione-ethyne (1.41)

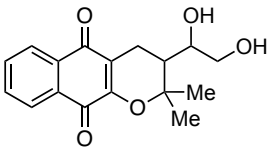
A reaction tube was charged with lapachol **1.40** (61 mg, 0.2 mmol, 1.0 equiv), JohnPhosAuCl (8 mg, 15 mmol, 6 mol%) and $NaBAr^F{}_4$ (13 mg, 15 mmol, 6 mol%) in HPLC grade $CHCl_3$ (0.6 mL, 0.4 M). The tube was introduced in a HEL reactor that, after proper closure, was pressurized with 1.0 atm of acetylene gas. The reaction mixture was stirred at 23 ºC for 48 h and after emptying the remaining gas, the crude was quenched by the addition of 3 drops of Et_3N and concentrated under reduced pressure. The crude product was purified by flash column chromatography (SiO_2, cyclohexane/EtOAc 100:0 to 80:20, *v/v*) and the product **1.41** was obtained as a orange sticky solid (33 mg, 0.12 mmol, 50% yield).



^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 (ddd, *J* = 7.6, 1.4, 0.6 Hz, 1H), 7.80 (ddd, *J* = 7.8, 1.3, 0.5 Hz, 1H), 7.64 (td, *J* = 7.7, 1.4 Hz, 1H), 7.52 (dd, *J* = 7.6, 1.3 Hz, 1H), 5.73 (ddd, *J* = 17.1, 10.3, 7.9 Hz, 1H), 5.25 (ddd, *J* = 17.1, 1.5, 1.0 Hz, 1H), 5.20 (ddd, *J* = 10.3, 1.5, 0.7 Hz, 1H), 2.79–2.69 (m, 1H), 2.49–2.42 (m, 1H), 2.37 (dd, *J* = 16.9, 10.2 Hz, 1H), 1.56–1.50 (m, 3H), 1.29 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 179.9, 178.6, 161.7, 136.4, 135.0, 132.5, 130.9, 130.3, 128.8, 124.3, 118.5, 112.6, 81.8, 45.0, 27.4, 22.3, 21.6. **HRMS** (ESI +) calculated for $[C_{17}H_{17}O_3]$ $[M+H]^+$ 269.1172 *m/z*; found 269.1182 *m/z*.

3-(1,2-Dihydroxyethyl)-2,2-dimethyl-3,4-dihydro-2*H*-benzo[*g*]chromene-5,10-dione (1.42)

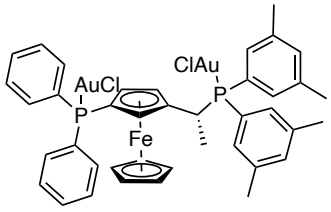
To a vigorously stirred solution of 2,2-dimethyl-3-vinyl-3,4-dihydro-2*H*-benzo[g]chromene-5,10-dione **1.41** (50 mg, 0.19 mmol, 1.0 equiv), in a mixture of EtOAc (1.3 mL, 0.7 M) and acetonitrile (1.3 mL, 0.7 M) was added a solution of $RuCl_3 \cdot xH_2O$ (3 mg, 0.013 mmol, 0.07 equiv) and $NaIO_4$ (60 mg, 0.28 mmol, 1.5 equiv) in H_2O (0.4 mL). The reaction was stirred for 2 h at 0 ºC (ice bath). The crude was quenched with sat. aq. NH_4Cl (1 mL) and extracted with EtOAc (3 x 2 mL). The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$ and concentrated under vacuo. The crude was purified by flash column chromatography (SiO_2, cyclohexane/EtOAc 100:0 to 60:40, *v/v*) and the product **1.42** was obtained as an orange solid (20 mg, 0.07 mmol, 36% yield).



M.p. 131–136 ºC. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.02 (ddd, *J* = 7.6, 2.7, 1.3 Hz, 1H), 7.82–7.74 (m, 1H), 7.67–7.58 (m, 1H), 7.53–7.45 (m, 1H), 3.86 (dd, *J* = 9.1, 4.8 Hz, 1H), 3.77–3.62 (m, 2H), 3.08 (s, 1H), 2.91 (s, 1H), 2.68–2.51 (m, 1H), 2.24–2.12 (m, 1H), 1.82 (dd, *J* = 11.4, 6.0 Hz, 1H), 1.74 (s, 3H), 1.45–1.38 (m, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 180.0, 178.4, 162.4, 135.1, 131.1, 128.8, 124.4, 112.2, 83.3, 72.4, 69.9, 66.2, 64.5, 42.7, 29.5, 21.9, 19.1. **HRMS** (ESI +) calculated for $C_{17}H_{18}NaO_5$ $[M+H]^+$: 325.1046; found: 325.1048

Synthesis of the Chiral Catalyst (1.H)

To a 10 ml round-bottomed flask was added DMSAuCl (124 mg, 0.42 mmol, 2.1 equiv), phosphine ligand (128 mg, 0.20 mmol, 1.0 equiv) and CH_2Cl_2 (2.0 mL, 0.1 M). The resulting solution was stirred at 23 ºC for 1 hour. Following concentration in vacuo, the crude product was purified by flash column chromatography (SiO_2, cyclohexane/EtOAc, 4:1, *v/v*) and gold complex **1.H** was obtained as an organge solid (198 mg, 0.18 mmol, 90% yield).

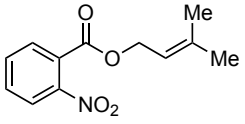


^{1}H NMR (500 MHz, $CDCl_3$) δ 7.79–7.73 (m, 2H), 7.56–7.52 (m, 1H), 7.51–7.46 (m, 3H), 7.45 (s, 1H), 7.38–7.33 (m, 1H), 7.23–7.18 (m, 2H), 7.17–7.13 (m, 3H), 7.11–7.05 (m, 2H), 6.56 (s, 1H), 5.27–5.18 (m, 1H), 5.11–5.07 (m, 1H), 4.73 (dd, *J* = 2.7, 2.7 Hz, 1H), 4.27–4.25 (m, 1H), 3.98 (s, 5H), 2.39 (s, 6H), 2.07 (s, 6H), 1.77 (dd, *J* = 17.8, 7.1 Hz, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 139.6 (d, $J_{C–P}$ = 12.0 Hz), 138.8 (d, $J_{C–P}$ = 12.1 Hz), 135.4 (d, $J_{C–P}$ = 15.0 Hz), 134.2 (d, $J_{C–P}$ = 2.7 Hz), 134.1 (d, $J_{C–P}$ = 2.7 Hz), 132.8 (d, $J_{C–P}$ = 13.4 Hz), 132.5 (d, $J_{C–P}$ = 68.2 Hz), 132.4 (d, $J_{C–P}$ = 2.6 Hz), 132.3 (d, $J_{C–P}$ = 13.3 Hz), 131.9 (d, $J_{C–P}$ = 13.3 Hz), 131.4 (d, $J_{C–P}$ = 63.0 Hz), 131.0 (d, $J_{C–P}$ = 2.7 Hz), 129.23 (d, $J_{C–P}$ = 12.1 Hz), 129.0 (d, $J_{C–P}$ = 11.8 Hz), 128.8 (d, $J_{C–P}$ = 55.2 Hz), 127.9 (d, $J_{C–P}$ = 54.9 Hz), 96.7 (dd, $J_{C–P}$ = 17.5, 7.8 Hz), 73.4 (dd, $J_{C–P}$ = 7.5, 7.5 Hz), 72.9 (d, $J_{C–P}$ = 5.1 Hz), 72.2 (d, $J_{C–P}$ = 7.7 Hz), 71.2, 66.7 (d, $J_{C–P}$ = 68.6 Hz), 31.7 (dd, $J_{C–P}$ = 32.2, 4.3 Hz), 22.8 (d, $J_{C–P}$ = 5.9 Hz), 21.5, 21.4. **^{31}P NMR** (202 MHz, CD_2Cl_2) δ 54.69, 22.80. **HRMS** (ESI +) calculated for $[C_{40}H_{40}Au_2ClP_2Fe]$ $[M+H]^+$ 1067.0969 *m/z*; found 1067.0980 *m/z.*

Synthesis of Alkylated Anilines

3-Methylbut-2-en-1-yl 2-nitrobenzoate (1.45)

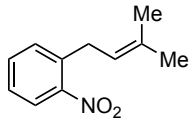
2-Nitrobenzoic acid (2.41 g, 14.4 mmol, 1.2 equiv), dicyclohexylcarbodiimide (2.97 g, 14.4 mmol, 1.2 equiv) and 4-dimethylaminopyridine (293 mg, 2.40 mmol, 0.2 equiv) were added to a solution of 3-methylbut-2-en-1-ol (1.2 mL, 1.03 g, 12.0 mmol, 1.0 equiv) in CH_2Cl_2 (120.0 mL, 0.1 M) and the resulting mixture was stirred at 23 ºC for 16 h. Upon completion, the reaction was filtered and concentrated under vacuo. The crude was purified by flash column chromatography (SiO_2, cyclohexane/EtOAc 100:0 to 90:10, *v/v*) and the product **1.45** was obtained as white solid (951 mg, 3.36 mmol, 84% yield).



^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (dd, *J* = 7.9, 1.4 Hz, 1H), 7.73 (dd, *J* = 7.5, 1.7 Hz, 1H), 7.66 (td, *J* = 7.5, 1.4 Hz, 1H), 7.61 (td, *J* = 7.7, 1.7 Hz, 1H), 5.42 (tdt, *J* = 7.4, 2.9, 1.5 Hz, 1H), 4.83 (d, *J* = 7.4 Hz, 2H), 1.78 (d, *J* = 1.5 Hz, 3H), 1.76 (d, *J* = 1.4 Hz, 3H). The characterization data matches those reported in the literature.[30]

1-(3-Methylbut-2-en-1-yl)-2-nitrobenzene (1.46)

In a 100 mL two-necked round-bottom flask was added 3-methylbut-2-en-yl 2- nitrobenzoate **1.45**

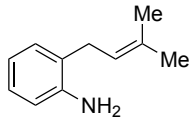


(600 mg, 2.55 mmol, 1.0 equiv), $Pd_2(dba)_3$ (117 mg, 0.13 mmol, 0.05 equiv), Ag_2CO_3 (1.05 g, 3.83 mmol, 1.5 equiv) and 1,3-bis(diphenylphophaneyl)propane (105 mg, 0.26 mmol, 0.1 equiv) in anhydrous dimethylacetamide (43.0 mL, 0.06 M) under argon atmosphere. The reaction was stirred at 110 ºC for 12 h, quenched by the addition of H_2O (30 mL) and extracted with Et_2O (3 x 30 mL). The combined organic layers were washed with brine (40 mL), dried over anhydrous $MgSO_4$ and concentrated under vacuo. The crude was purified by flash column chromatography (SiO_2, cyclohexane/EtOAc 100:0 to 70:30, *v/v*) and the product **1.46** was obtained as a yellow oil (378 mg, 1.98 mmol, 78% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 (dd, *J* = 8.1, 1.4 Hz, 1H), 7.48 (td, *J* = 7.5, 1.4 Hz, 1H), 7.35 (dd, *J* = 7.8, 1.4 Hz, 1H), 7.30 (ddd, *J* = 8.5, 7.5, 1.5 Hz, 1H), 5.23 (tp, *J* = 7.3, 1.5 Hz, 1H), 3.60 (d, *J* = 7.2 Hz, 2H), 1.72 (q, *J* = 1.3 Hz, 3H), 1.71–1.67 (m, 3H). The characterization data matches those reported in the literature.[30]

2-(3-Methylbut-2-en-1-yl)aniline (1.47)

1-(3-Methylbut-2-en-1-yl)-2-nitrobenzene **1.46** (300 mg, 1.57 mmol, 1.0 equiv) was dissolved in EtOH



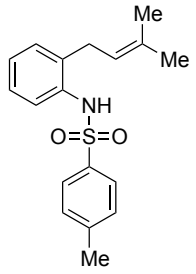
(2.0 mL, 0.8 M) and iron powder (526 mg, 9.41 mmol, 6.0 equiv) and HCl (157 mL, 1.88 mmol, 1.2 equiv, 37%) were added sequentially. The reaction was stirred at reflux (78 ºC) for 4 h and upon completion it was filtered through Celite and the filtrate was concentrated under vacuo and purified by flash column chromatography (SiO_2, cyclohexane/EtOAc 100:0 to 70:30, *v/v*) to afford the desired product **1.47** as a colorless oil (145 mg, 0.90 mmol, 57% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.05 (ddd, *J* = 7.5, 6.5, 1.7 Hz, 2H), 6.74 (td, *J* = 7.4, 1.3 Hz, 1H), 6.68 (dd, *J* = 8.3, 1.3 Hz, 1H), 5.25 (ddq, *J* = 8.4, 5.7, 1.4 Hz, 1H), 3.64 (s, 2H), 3.24 (d, *J* = 7.1 Hz, 2H), 1.77 (q, *J* = 1.4 Hz, 6H). The characterization data matches those reported in the literature.[41]

41. Zhu, B.-H.; Shen, C.-H.; Nie, M.-L.; Zheng, F.; Huang, C.; Chen, F.; Li, L.; Deng, C.; Ye, L.-W.; Qian, P.-C. *Org. Lett.* **2022**, *24*, 7009–7014.

4-Methyl-*N*-(2-(3-methylbut-2-en-1-yl)phenyl)benzenesulfonamide (1.43a)

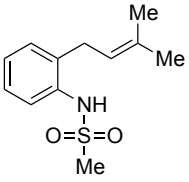
2-(3-Methylbut-2-en-1-yl)aniline **1.47** (100 mg, 0.62 mmol, 1.0 equiv) was dissolved in pyridine (0.5 mL, 1.2 M) and *p*-toluenesulfonyl chloride (130 mg, 0.6 mmol, 1.1 equiv) was added portion-wise into the flask in an ice bath. Then, the reaction was heated in a metallic heating block at 110 ºC for 1 h and washed with 1 M HCl (1 mL), sat. aq. $NaHCO_3$ (1 mL) and extracted with EtOAc (3 x 3 mL). The combined organic layers were washed with brine (4 mL), dried over anhydrous $MgSO_4$ and concentrated under vacuo. The crude was purified by flash column chromatography (SiO_2, cyclohexane/EtOAc 100:0 to 90:10, *v/v*) and the product **1.43a** was obtained as a colorless oil (147 mg, 0.47 mmol, 75% yield).



^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61–7.56 (m, 2H), 7.44 (dd, *J* = 7.8, 1.1 Hz, 1H), 7.24–7.18 (m, 2H), 7.18–7.13 (m, 1H), 7.10–7.04 (m, 2H), 6.59 (s, 1H), 4.97 (dddd, *J* = 8.6, 5.8, 2.9, 1.5 Hz, 1H), 2.96 (d, *J* = 7.0 Hz, 2H), 2.38 (s, 3H), 1.73 (q, *J* = 1.4 Hz, 3H), 1.70 (d, *J* = 1.3 Hz, 3H). The characterization data matches those reported in the literature.[41]

***N*-(2-(3-Methylbut-2-en-1-yl)phenyl)methanesulfonamide (1.43b)**

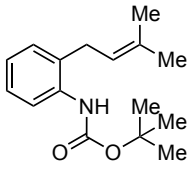
2-(3-Methylbut-2-en-1-yl)aniline **1.47** (200 mg, 1.24 mmol, 1.0 equiv) was dissolved in pyridine (1.0 mL, 1.2 M) and methanesulfonyl chloride (156 mg, 1.36 mmol, 1.1 equiv) was added portion-wise into the flask in an ice bath. Then, the reaction was heated in a metallic heating block at 110 ºC for 1 h and, washed with 1 M HCl (1 mL), sat. aq. $NaHCO_3$ (1 mL) and extracted with EtOAc (3 x 3 mL). The combined organic layers were washed with brine (4 mL), dried over anhydrous $MgSO_4$ and concentrated under vacuo. The crude was purified by flash column chromatography (SiO_2, cyclohexane/EtOAc 100:0 to 90:10, *v/v*) and the product **1.43b** was obtained as a white solid (152 mg, 0.64 mmol, 51% yield).



M.p. 62–67 ºC. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.51–7.46 (m, 1H), 7.26–7.19 (m, 2H), 7.17–7.11 (m, 1H), 5.18 (tdt, *J* = 7.1, 2.9, 1.5 Hz, 1H), 3.37 (d, *J* = 7.1 Hz, 2H), 2.98 (s, 3H), 1.81 (d, *J* = 1.3 Hz, 3H), 1.78 (p, *J* = 1.6 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 135.4, 135.1, 132.9, 130.5, 127.7, 125.9, 122.2, 121.4, 39.8, 31.6, 25.8, 18.0. **HRMS** (ESI +) calculated for $C_{12}H_{17}NNaSO_2$ $[M+Na]^+$: 262.0872; found: 262.0876.

***tert*-Butyl (2-(3-methylbut-2-en-1-yl)phenyl)carbamate (1.43c)**

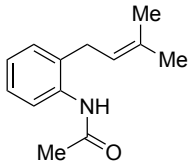
2-(3-Methylbut-2-en-1-yl)aniline **1.47** (200 mg, 1.24 mmol, 1.0 equiv) was dissolved in THF (2.5 mL, 0.5 M) and di-*tert*-butyl decarbonate (325 mg, 1.49 mmol, 1.2 equiv) was added portion-wise into the flask in an ice bath. Then, the reaction was stirred at 23 ºC for 16 h and after evaporation of the solvent, the crude was purified by flash column chromatography (SiO_2, cyclohexane/EtOAc 100:0 to 70:30, *v/v*) and the product **1.43c** was obtained as a colorless oil (237 mg, 0.91 mmol, 73% yield).



^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 (d, *J* = 8.1 Hz, 1H), 7.20 (td, *J* = 7.8, 1.7 Hz, 1H), 7.16–7.10 (m, 1H), 6.99 (td, *J* = 7.5, 1.3 Hz, 1H), 6.56 (s, 1H), 5.20 (dddq, *J* = 7.2, 5.8, 2.9, 1.3 Hz, 1H), 3.29 (d, *J* = 7.2 Hz, 2H), 1.81 (d, *J* = 1.3 Hz, 3H), 1.77 (q, *J* = 1.4 Hz, 3H), 1.51 (s, 9H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 153.2, 146.8, 136.7, 133.9, 129.6, 127.1, 123.7, 122.0, 85.2, 31.7, 28.4, 27.5, 25.8, 17.8. **HRMS** (ESI +) calculated for $C_{16}H_{23}NNaO_2$ $[M+Na]^+$: 284.1621; found: 284.1619.

***N*-(2-(3-Methylbut-2-en-1-yl)phenyl)acetamide (1.43d)**

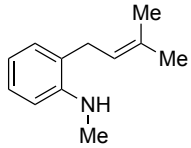
2-(3-methylbut-2-en-1-yl)aniline **1.47** (50 mg, 0.31 mmol, 1.0 equiv) was dissolved in anhydrous CH_2Cl_2 (1.0 mL; 0.3 M) under argon atmosphere. Ac_2O (35 mL, 38.0 mg, 0.37 mmol, 1.2 equiv) was added and the mixture was stirred at 23 ºC for 16 h. The reaction was quenched with sat. aq. Na_2CO_3 (1.0 mL) and extracted with CH_2Cl_2 (3 x 2 mL). The combined organic layers were washed with brine (3 mL), dried over anhydrous $MgSO_4$ and concentrated under vacuo. The crude was purified by flash column chromatography (SiO_2, cyclohexane/EtOAc 100:0 to 70:30, *v/v*) and the product **1.43d** was obtained as a colorless oil (40 mg, 0.20 mmol, 64% yield).



^{1}H NMR (400 MHz, $CDCl_3$) δ 7.9 (d, *J* = 8.1 Hz, 1H), 7.2 (td, *J* = 7.7, 1.7 Hz, 1H), 7.2 (d, *J* = 7.5 Hz, 1H), 7.1 (t, *J* = 7.4 Hz, 1H), 5.2 (t, *J* = 7.2 Hz, 1H), 3.3 (d, *J* = 7.1 Hz, 2H), 2.1 (s, 3H), 1.8 (s, 3H), 1.8 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 168.2, 136.2, 134.1, 129.9, 127.2, 125.1, 123.3, 122.3, 31.8, 31.1, 25.8, 24.6, 18.1. **HRMS** (ESI +) calculated for $C_{13}H_{18}NO$ $[M+H]^+$: 204.1383; found: 204.1380.

***N*-Methyl-2-(3-methylbut-2-en-1-yl)aniline (1.43e)**

2-(3-methylbut-2-en-1-yl)aniline **1.47** (200 mg, 1.24 mmol, 1.0 equiv) and NaOEt (422 mg, 6.20 mmol, 5.0 equiv) were dissolved in anhydrous MeOH (2.2 mL, 0.4 M). Then, formaldehyde (185 µL, 201 mg, 2.48 mmol, 2.0 equiv, 37% Wt) was dissolved in anhydrous MeOH (0.9 mL), added to the free aniline, and stirred at 23 ºC for 16 h and at 68 ºC for 1 h. At this point $NaBH_4$ (103 mg, 2.73 mmol, 2.2 equiv) was added and the mixture was stirred at 68 ºC for 3 extra hours. Then, the reaction was filtered through Celite, evaporated, and extracted with H_2O (3 mL) and EtOAc (3 x 5 mL). The combined organic layers were washed with brine (5 mL), dried over anhydrous $MgSO_4$ and concentrated under vacuo. The crude was purified by flash column



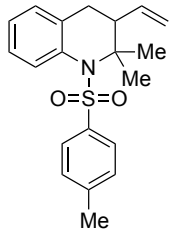
chromatography (SiO_2, cyclohexane/EtOAc 100:0 to 60:40, *v/v*) and the product **1.43e** was obtained as a colorless oil (120 mg, 0.69 mmol, 55% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.24–7.18 (m, 1H), 7.12–7.07 (m, 1H), 6.76–6.71 (m, 1H), 6.67 (dd, *J* = 8.1, 1.2 Hz, 1H), 5.26 (tdq, *J* = 7.2, 2.9, 1.4 Hz, 1H), 3.75 (s, 1H), 3.23 (d, *J* = 7.0 Hz, 2H), 2.90 (s, 3H), 1.80 (q, *J* = 1.4 Hz, 3H), 1.78 (q, *J* = 1.1 Hz, 3H). The characterization data matches those reported in the literature[42]

Gold(I)-Catalyzed Aminovinylation of 2-Alkylated Anilines

2,2-Dimethyl-1-tosyl-3-vinyl-1,2,3,4-tetrahydroquinoline (1.44a)

A reaction tube was charged with **1.43a** (16 mg, 0.05 mmol 1.0 equiv) and **1.H** (2 mg, 0.002 mmol, 0.04 equiv) in HPLC grade $CHCl_3$ (0.1 mL, 0.4 M). The tube was introduced in a HEL reactor, which after proper closure, was pressurized with 1.0 atm of acetylene gas. The reaction mixture was stirred at 23 ºC for 16 h and after emptying the remaining gas, the crude was quenched by the addition of 3 drops of Et_3N and concentrated under reduced pressure. The crude product was purified by flash column chromatography (SiO_2, cyclohexane/EtOAc 100:0 to 90:10, *v/v*) and the product **1.44a** was obtained as a colorless oil (3 mg, 0.007 mmol, 15% yield).

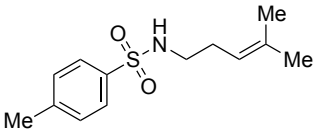


^{1}H NMR (500 MHz, $CDCl_3$) δ 7.57 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.55–7.52 (m, 2H), 7.50–7.45 (m, 1H), 7.26–7.22 (m, 2H), 7.21–7.18 (m, 2H), 5.57–5.47 (m, 1H), 5.00 (dd, *J* = 10.1, 1.8 Hz, 1H), 4.94–4.87 (m, 1H), 2.67 (t, *J* = 10.7 Hz, 1H), 2.53 (t, *J* = 7.0 Hz, 1H), 2.51–2.46 (m, 1H), 1.51 (s, 3H), 1.41 (s, 3H), 1.02 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 138.5, 129.6, 129.5, 128.2, 127.5, 127.4, 126.1, 125.9, 117.2, 61.8, 46.9, 36.2, 31.0, 29.3, 27.6, 24.6, 23.9, 21.7. **HRMS** (ESI +) calculated for $C_{20}H_{23}NNaO_2S$ $[M+Na]^+$: 364.1342; found: 364.1346.

Synthesis of Aliphatic Amines

4-Methyl-*N*-(4-methylpent-3-en-1-yl)benzenesulfonamide (1.45a)

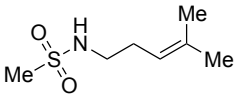
A microwave vial was charged with 5-bromo-2-methylpent-2-ene (482 μL, 587 mg, 3.60 mmol, 1.0 equiv), 4-methylbenzenesulfonamide (616 mg, 3.60 mmol, 1.0 equiv) and K_2CO_3 (498 mg, 3.60 mmol, 1.0 equiv) in acetonitrile (3.6 mL, 1.0 M). The reaction mixture was stirred at 80 ºC for 16 h and then quenched by the addition of H_2O (3 mL) and extracted with CH_2Cl_2 (3 x 5 mL). The combined organic layers were washed with brine (7 mL), dried over anhydrous $MgSO_4$, filtered and concentrated under vacuo. The crude was purified by flash column chromatography (SiO_2, cyclohexane/EtOAc 100:0 to 80:20, *v/v*) to afford the product **1.45a** as a colorless oil (638 mg, 2.52 mmol, 70% yield).



42. Hodjat-Kachani, H.; Perie, J. J.; Lattes, A. *Chem. Lett.* **1976**, *5*, 405–408.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.77–7.70 (m, 2H), 7.30–7.26 (m, 2H), 4.97–4.88 (m, 1H), 2.90 (td, *J* = 6.9, 6.0 Hz, 2H), 2.40 (s, 3H), 2.12 (qt, *J* = 7.1, 1.0 Hz, 2H), 1.63 (q, *J* = 1.2 Hz, 3H), 1.52 (d, *J* = 1.4 Hz, 3H). The characterization data matches those reported in the literature.[41]

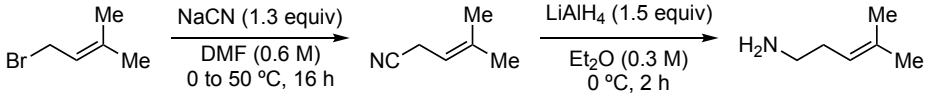
***N*-(4-Methylpent-3-en-1-yl)methanesulfonamide (1.45b)**



A microwave vial was charged with 5-bromo-2-methylpent-2-ene (482 μL, 587 mg, 3.60 mmol, 1.0 equiv), methanesulfonamide (342 mg, 3.60 mmol, 1.0 equiv) and K_2CO_3 (498 mg, 3.60 mmol, 1.0 equiv) in acetonitrile (3.6 mL, 1.0 M). The reaction mixture was stirred at 80 ºC for 16 h and then quenched by the addition of H_2O (3 mL) and extracted with CH_2Cl_2 (3 x 5 mL). The combined organic layers were washed with brine (5 mL), dried over anhydrous $MgSO_4$, filtered and concentrated under vacuo. The crude was purified by flash column chromatography (SiO_2, cyclohexane/EtOAc 100:0 to 80:20, *v/v*) to afford the product **1.45b** as a colorless oil (219 mg, 1.24 mmol, 34% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.03 (tdt, *J* = 7.3, 2.9, 1.4 Hz, 1H), 4.79 (t, *J* = 6.2 Hz, 1H), 3.06 (td, *J* = 7.0, 6.1 Hz, 2H), 2.89 (s, 3H), 2.22 (qt, *J* = 7.0, 1.0 Hz, 2H), 1.67 (q, *J* = 1.3 Hz, 3H), 1.59 (d, *J* = 1.4 Hz, 3H). The characterization data matches those reported in the literature.[41]

4-Methylpent-3-en-1-amine (1.45c)



To a solution of 3,3-dimethylallyl bromide (1.49 g, 1.2 mL, 10.0 mmol, 1.0 equiv) in anhydrous DMF (16.7 mL, 0.6 M) was added NaCN (637 mg, 13.0 mmol, 1.3 equiv) at 0 ºC under argon atmosphere. The reaction mixture was warmed to 23 ºC and then stirred overnight at 50 ºC. Then, it was cooled down, quenched with H_2O (10 mL) and extracted with cyclohexane (3 x 15 mL). The combined organic layers were washed with brine (15 mL), dried over anhydrous $MgSO_4$, filtered and concentrated under vacuo.

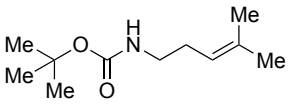
The crude nitrile compound was redissolved in anhydrous Et_2O (30.0 mL, 0.3 M) and $LiAlH_4$ (569 mg, 15.0 mmol, 1.5 equiv) was added in portions at 0 ºC under an argon atmosphere. The reaction was stirred at 0 ºC for 2 h and then quenched by the slow addition of H_2O (15 mL) at 0 ºC. Then, it was extracted with Et_2O (3 x 20 mL), and the combined organic layers were washed with brine (20 mL), dried over anhydrous $MgSO_4$, filtered and concentrated under vacuo to afford the desired free amine **1.45c** as a colorless oil (732 mg, 7.38 mmol, 74% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 4.61 (tdp, *J* = 7.3, 4.3, 1.4 Hz, 1H), 2.16 (t, *J* = 6.9 Hz, 2H), 1.77 (h, *J* = 6.6 Hz, 2H), 1.62 (dddt, *J* = 8.0, 6.9, 5.8, 1.0 Hz, 2H), 1.20 (d, *J* = 1.4 Hz, 3H), 1.13–1.12 (m, 3H). The characterization data matches those reported in the literature.[43]

43. Chiou, W.-H.; Hsu, K.-H.; Huang, W.-W. *ACS Omega* **2020**, *5*, 3717–3724.

***tert*-Butyl (4-methylpent-3-en-1-yl)carbamate (1.45d)**

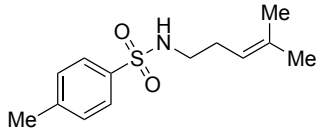
4-methylpent-3-en-1-amine **1.45c** (100 mg, 1.01 mmol, 1.0 equiv) was dissolved in THF (2.0 mL, 0.5 M) and di-*tert*-butyl carbonate (264 mg, 1.21 mmol, 1.2 equiv) was added. The reaction mixture was stirred at 23 ºC for 16 h and then concentrated under vacuo. The crude was purified by flash column chromatography (SiO_2, cyclohexane/EtOAc 100:0 to 80:20, *v/v*) to afford the product **1.45d** as a colorless oil (79 mg, 0.40 mmol, 39% yield).



^{1}H NMR (500 MHz, $CDCl_3$) δ 5.05 (ddq, *J* = 8.7, 5.8, 1.4 Hz, 1H), 4.56 (s, 1H), 3.09 (q, *J* = 6.7 Hz, 2H), 2.15 (q, *J* = 7.0 Hz, 2H), 1.68 (q, *J* = 1.3 Hz, 3H), 1.60 (d, *J* = 1.3 Hz, 3H), 1.42 (s, 9H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 156.1, 134.4, 121.0, 40.6, 28.5, 27.5, 27.0, 25.9, 17.9. **HRMS** (ESI +) calculated for $C_{11}H_{21}NNaO_2$ $[M+Na]^+$: 222.1464; found: 222.1460.

4-Methyl-*N*-(5-methylhex-4-en-1-yl)benzenesulfonamide (1.47)

*n*BuLi (4.66 mL, 707 mg, 2.36 molar, 11.0 mmol, 1.0 equiv) was added dropwise to a solution of acetonitrile (0.6 mL, 10.5 mmol, 1.05 equiv) in anhydrous THF (26.7 mL, 0.4 M) at −70 ºC. After stirring the mixture at −70 ºC for 15 min, 3,3-dimethylallylbromide (1.2 mL, 10.0 mmol, 1.0 equiv) in anhydrous THF (13.3 mL) was added. The mixture was stirred at 50 ºC for 2 additional hours and then quenched by the addition of saturated aqueous NH_4Cl (20 mL) and extracted with Et_2O (3 x 20 mL). The combined organic layers were washed with brine (30 mL), dried over anhydrous $MgSO_4$, filtered and concentrated under vacuo. The crude was purified by flash column chromatography (SiO_2, pentane/Et_2O 100:0 to 80:20, *v/v*) to afford the product as a colorless oil (727 mg, 6.66 mmol, 67% yield).

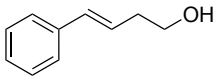


Crude nitrile (727 mg, 6.66 mmol, 1.0 equiv) was dissolved in anhydrous Et_2O (20.0 mL, 0.3 M) and $LiAlH_4$ (379 mg, 10.0 mmol, 1.5 equiv) was added in portions at 0 ºC under argon atmosphere. The reaction was stirred at 0 ºC for 2 h and then quenched by the slow addition of H_2O (15 mL) at 0 ºC. Then, it was extracted with Et_2O (3 x 20 mL) and the combined organic layers were washed with brine (30 mL), dried over anhydrous $MgSO_4$, filtered and concentrated under vacuo to afford the desired free amine as a colorless oil that was used without further purification. *p*-TsCl (797 mg, 4.18 mmol, 1.0 equiv) was added to a mixture of 5-methylhex-4-en-1-amine and Et_3N (874 µL, 6.27 mmol, 1.5 equiv) in anhydrous CH_2Cl_2 (21.0 mL, 0.2 M) under argon atmosphere. The reaction mixture was stirred at 23 ºC for 16 h and then quenched by the addition of HCl 1 M (15 mL) and extracted with CH_2Cl_2 (3 x 15 mL). The combined organic layers were washed with brine (20 mL), dried over anhydrous $MgSO_4$, filtered and concentrated under vacuo. The crude was purified by flash column chromatography (SiO_2, cyclohexane/EtOAc 100:0 to 70:30, *v/v*) to afford the product **1.47** as a colorless oil (242 mg, 0.91 mmol, 22% yield over two steps).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.77–7.70 (m, 2H), 7.30–7.26 (m, 2H), 4.97–4.88 (m, 1H), 2.90 (td, *J* = 6.9, 6.0 Hz, 2H), 2.40 (s, 3H), 2.12 (qt, *J* = 7.1, 1.0 Hz, 2H), 1.63 (q, *J* = 1.2 Hz, 3H), 1.52 (d, *J* = 1.4 Hz, 3H).The characterization data matches those reported in the literature.[44]

(*E*)-4-Phenylbut-3-en-1-ol (1.52)

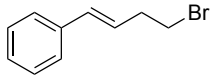
$LiAlH_4$ (395 mg, 10.4 mmol, 2.6 equiv) was added to a solution of *trans*-styrylacetic acid (649 mg, 4.00 mmol, 1.0 equiv) in anhydrous THF (4.0 mL, 1.0 M) at 0 ºC under argon atmosphere. The reaction was stirred at 0 ºC for 20 min and then at 23 ºC for 1 h. The crude was then quenched by the slow addition of H_2O (3 mL) at 0 ºC and aq. 1 M solution of NaOH and extracted with Et_2O (3 x 5 mL). The combined organic layers were washed with brine (5 mL), dried over anhydrous $MgSO_4$ and concentrated under vacuo. The crude was purified by flash column chromatography (SiO_2, cyclohexane/EtOAc 100:0 to 60:0, *v/v*) and the product **1.52** was obtained as a colorless oil (335 mg, 2.26 mmol, 57% yield).



^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40–7.35 (m, 2H), 7.34–7.29 (m, 2H), 7.25–7.21 (m, 1H), 6.51 (dt, *J* = 15.9, 1.5 Hz, 1H), 6.21 (dt, *J* = 15.8, 7.1 Hz, 1H), 3.80–3.73 (m, 2H), 2.49 (dtd, *J* = 7.7, 6.3, 1.4 Hz, 2H). The characterization data matches those reported in the literature.[45]

(*E*)-(4-Bromobut-1-en-1-yl)benzene (1.53)

CBr_4 (2.25 g, 6.78 mmol, 3.0 equiv) and PPh_3 (1.78 g, 6.78 mmol, 3.0 equiv) were added to a solution of (*E*)-4-phenylbut-3-en-1-ol **1.52** (335 mg, 2.26 mmol, 1.0 equiv) in anhydrous Et_2O (15.1 mL, 0.15 M) under argon atmosphere. The mixture was stirred in a metallic heating block at reflux (40 ºC) for 18 h, quenched by the addition of H_2O (10 mL) and extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$ and concentrated under vacuo. The crude was purified by flash column chromatography (SiO_2, cyclohexane/EtOAc 100:0, *v/v*) and the product **1.53** was obtained as a yellow oil (186 mg, 0.88 mmol, 39% yield).

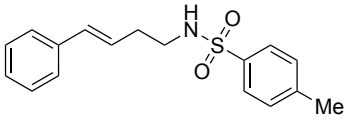


^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37 (dtd, *J* = 8.1, 2.2, 1.1 Hz, 2H), 7.34–7.28 (m, 2H), 7.25–7.21 (m, 1H), 6.50 (dt, *J* = 15.8, 1.5 Hz, 1H), 6.20 (dt, *J* = 15.8, 7.0 Hz, 1H), 3.48 (t, *J* = 7.1 Hz, 2H), 2.79 (qd, *J* = 7.0, 1.4 Hz, 2H). The characterization data matches those reported in the literature.[46]

44. Bondalapati, S.; Indukuri, K.; Ghosh, P.; Saikia, A. K. Eur. *J. Org. Chem.* **2013**, *2013*, 952–956.
45. Tummatorn, J.; Ruchirawat, S.; Ploypradith, P. *Chem. Eur. J.* **2010**, *16*, 1445–1448.
46. He, J.; Jia, Z.; Tan, H.; Luo, X.; Qiu, D.; Shi, J.; Xu, H.; Li, Y. *Angew. Chem. Int. Ed.* **2019**, *58*, 18513–18518.

(*E*)-4-Methyl-*N*-(4-phenylbut-3-en-1-yl)benzenesulfonamide (1.49a)

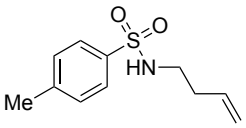
(*E*)-(4-Bromobut-1-en-1-yl)benzene **1.53** (110 mg, 0.52 mmol, 1.0 equiv) was dissolved in MeCN (0.5 mL, 1.0 M) and K_2CO_3 (72 mg, 0.52 mmol, 1.0 equiv) and 4-methylbenzenesulfonamide (89 mg, 0.52 mmol, 1.0 equiv) were added to the mixture. After stirring at 80 ºC for 16 h, the reaction was quenched by the addition of H_2O (5 mL) and extracted with CH_2Cl_2 (3 x 8 mL). The combined organic layers were washed with brine (10 mL), dried over anhydrous $MgSO_4$ and concentrated under vacuo. The crude was purified by flash column chromatography (SiO_2, cyclohexane/EtOAc 100:0 to 90:10, *v/v*) and the product **1.49a** was obtained as a white solid (82 mg, 0.27 mmol, 53% yield).



^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78–7.71 (m, 2H), 7.33–7.25 (m, 6H), 7.25–7.08 (m, 1H), 6.36 (dt, *J* = 15.9, 1.4 Hz, 1H), 5.98 (dt, *J* = 15.9, 7.1 Hz, 1H), 4.57 (t, *J* = 6.1 Hz, 1H), 3.10 (q, *J* = 6.5 Hz, 2H), 2.42 (s, 3H), 2.37 (qd, *J* = 6.8, 1.4 Hz, 2H). The characterization data matches those reported in the literature.[47]

***N*-(But-3-en-1-yl)-4-methylbenzenesulfonamide (1.54)**

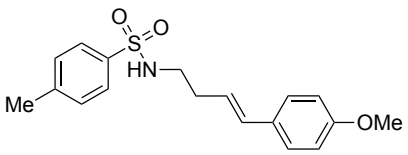
4-bromobut-1-ene (528 µL, 675 mg, 5.00 mmol, 1.0 equiv) was dissolved in acetonitrile (5.0 mL, 1.0 M) and K_2CO_3 (691 mg, 5.00 mmol, 1.0 equiv) and 4-methylbenzenesulfonamide (856 mg, 5.00 mmol, 1.0 equiv) were added to the mixture. After stirring at 80 ºC in a metallic heating block for 16 h, the reaction was quenched by the addition of H_2O (5 mL) and extracted with CH_2Cl_2 (3 x 8 mL). The combined organic layers were washed with brine (10 mL), dried over anhydrous $MgSO_4$ and concentrated under vacuo. The crude was purified by flash column chromatography (SiO_2, cyclohexane/EtOAc 100:0 to 90:10, *v/v*) and the product **1.54** was obtained as a colorless oil (736 mg, 3.27 mmol, 65% yield).



^{1}H NMR (500 MHz, $CDCl_3$) δ 7.76–7.72 (m, 2H), 7.34–7.28 (m, 2H), 5.62 (ddt, *J* = 17.1, 10.3, 6.8 Hz, 1H), 5.10–4.97 (m, 2H), 4.59 (t, *J* = 6.1 Hz, 1H), 3.01 (q, *J* = 6.6 Hz, 2H), 2.42 (s, 3H), 2.19 (qt, *J* = 6.8, 1.3 Hz, 2H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 143.6, 137.1, 134.3, 129.8, 127.2, 118.2, 42.2, 33.7, 21.6. **HRMS** (ESI +) calculated for $C_{11}H_{15}NNaO_2S$ $[M+Na]^+$: 248.0716; found: 248.0721.

(*E*)-*N*-(4-(4-Methoxyphenyl)but-3-en-1-yl)-4-methylbenzenesulfonamide (1.49b)

N-(But-3-en-1-yl)-4-methylbenzenesulfonamide **1.54** (203 mg, 0.90 mmol, 1.0 equiv), tris(*o*-tolyl)phosphine (27 mg, 0.09 mmol, 0.10 equiv), $Pd(OAc)_2$ (10 mg, 0.05 mmol, 0.05 equiv), 4-iodoanisole (211 mg, 0.90 mmol, 1.0 equiv) and Et_3N (251 µL, 182 mg, 1.80 mmol, 2.0 equiv) in anhydrous acetonitrile (2.2 mL, 0.4 M) were added



47. Walker, P. R.; Campbell, C. D.; Suleman, A.; Carr, G.; Anderson, E. *Angew. Chem. Int. Ed.* **2013**, *52*, 9139–9143.

to a microwave vial under argon atmosphere. The mixture was stirred at 80 ºC in a metallic heating block for 3 h and a second batch of $Pd(OAc)_2$ (5 mg, 0.03 mmol, 0.03 equiv), 4-iodoanisole (89 mg, 0.38 mmol, 0.4 equiv) and tris(*o*-tolyl)phosphine (13.7 mg, 0.045 mmol, 0.05 equiv) was added to the reaction. Then, the mixture was stirred at 80 ºC for 16 h, quenched by the addition of H_2O (2 mL) and extracted with EtOAc (3 x 3 mL). The combined organic layers were washed with brine (5 mL), dried over anhydrous $MgSO_4$ and concentrated under vacuo. The crude was purified by flash column chromatography (SiO_2, cyclohexane/EtOAc 100:0 to 80:20, *v/v*) and the product **1.49b** was obtained as a yellow solid (241 mg, 0.73 mmol, 81% yield).

M.p. 131–136 ºC. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.78–7.73 (m, 2H), 7.31–7.26 (m, 2H), 7.24–7.19 (m, 2H), 6.85–6.80 (m, 2H), 6.30 (dt, *J* = 15.9, 1.5 Hz, 1H), 5.84 (dt, *J* = 15.8, 7.1 Hz, 1H), 4.87 (q, *J* = 6.2 Hz, 1H), 3.80 (d, *J* = 2.7 Hz, 3H), 3.08 (q, *J* = 6.6 Hz, 2H), 2.42 (s, 3H), 2.34 (qd, *J* = 6.8, 1.4 Hz, 2H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 159.1, 143.4, 137.0, 132.5, 129.8, 127.3, 127.2, 123.4, 114.0, 55.3, 42.8, 33.0, 27.0, 21.6. **HRMS** (ESI +) calculated for $C_{18}H_{22}NO_3S$ $[M+H]^+$: 332.1315; found: 332.1310.

(*E*)-4-Methyl-*N*-(4-(4-(trifluoromethyl)phenyl)but-3-en-1-yl)benzenesulfonamide (1.49c)

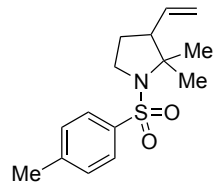
N-(But-3-en-1-yl)-4-methylbenzenesulfonamide **1.54** (203 mg, 0.90 mmol, 1.0 equiv), tris(*o*-tolyl)phosphine (27 mg, 0.09 mmol, 0.10 equiv), $Pd(OAc)_2$ (10 mg, 0.05 mmol, 0.05 equiv), 4-iodobenzotrifluoride (245 mg, 0.90 mmol, 1.0 equiv) and Et_3N (251 µL, 182 mg, 1.80 mmol, 2.0 equiv) in anhydrous acetonitrile (2.2 mL, 0.4 M) were added to a microwave vial under argon atmosphere. The mixture was stirred at 80 ºC in a metallic heating block for 3 h and a second batch of $Pd(OAc)_2$ (5 mg, 0.03 mmol, 0.03 equiv), 4-iodoanisole (103 mg, 0.38 mmol, 0.42 equiv) and tris(*o*-tolyl)phosphine (14 mg, 0.05 mmol, 0.05 equiv) was added to the reaction. Then, the mixture was stirred at 80 ºC for 16 h, quenched by the addition of H_2O (2 mL) and extracted with EtOAc (3 x 3 mL). The combined organic layers were washed with brine (5 mL), dried over anhydrous $MgSO_4$ and concentrated under vacuo. The crude was purified by flash column chromatography (SiO_2, cyclohexane/EtOAc 100:0 to 80:20, *v/v*) and the product **1.49c** was obtained as a yellow solid (111 mg, 0.30 mmol, 33% yield).

M.p. 82–86 ºC. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.85–7.79 (m, 1H), 7.78–7.72 (m, 2H), 7.52 (d, *J* = 8.1 Hz, 2H), 7.35 (d, *J* = 8.1 Hz, 2H), 7.29–7.28 (m, 1H), 6.39 (d, *J* = 15.9 Hz, 1H), 6.11 (dt, *J* = 15.9, 7.1 Hz, 1H), 3.11 (q, *J* = 6.5 Hz, 2H), 2.42 (s, 2H), 2.41 (s, 3H). **^{19}F NMR** (376 MHz, $CDCl_3$) δ -62.6. **^{13}C NMR** (101 MHz, $CDCl_3$) δ 143.7, 140.5, 137.0, 131.9, 129.9, 129.5 (q, *J* = 32.5 Hz), 128.7 (q, *J* = 216.4 Hz), 127.2, 126.4, 125.6 (q, *J* = 3.7 Hz), 42.5, 33.2, 27.0, 21.6. **HRMS** (ESI +) calculated for $C_{18}H_{19}F_3NO_2S$ $[M+Na]^+$: 370.1083; found: 370.1071.

Gold(I)-Catalyzed Formation of Piperidine and Pyrrolidine-Containing Compounds

2,2-Dimethyl-1-tosyl-3-vinylpyrrolidine (1.46a)

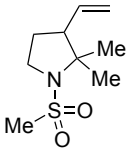
Prepared following general procedure E using 4-methyl-*N*-(4-methylpent-3-en-1-yl)benzenesulfonamide **1.45a** (63 mg, 0.25 mmol, 1.0 equiv), [JohnPhosAuNCMe]SbF_6 (8 mg, 0.01 mmol, 4 mol%) and 1 atm of acetylene gas in $CHCl_3$ (1.3 mL, 0.2 M) at 23 ºC for 16 h. The crude was purified by flash column chromatography (SiO_2, cyclohexane/EtOAc 100:0 to 80:20, *v/v*) to afford the product **1.46a** as colorless oil (50 mg, 0.18 mmol, 72% yield).



^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76–7.71 (m, 2H), 7.29–7.26 (m, 2H), 5.63 (ddd, *J* = 17.0, 10.3, 8.2 Hz, 1H), 5.13–5.01 (m, 2H), 3.58 (ddd, *J* = 9.2, 8.3, 2.0 Hz, 1H), 3.23 (ddd, *J* = 10.2, 9.3, 7.0 Hz, 1H), 2.41 (s, 3H), 2.39–2.32 (m, 1H), 1.95–1.72 (m, 2H), 1.43 (s, 3H), 1.20 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 142.7, 138.9, 135.8, 129.5, 127.3, 117.8, 67.0, 55.8, 47.3, 27.9, 26.8, 23.5, 21.6. **HRMS** (ESI +) calculated for $C_{15}H_{22}NO_2S$ $[M+H]^+$: 280.1366; found: 280.1369.

2,2-Dimethyl-1-(methylsulfonyl)-3-vinylpyrrolidine (1.46b)

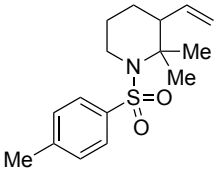
Prepared following general procedure E using *N*-(4-methylpent-3-en-1-yl)methanesulfonamide **1.45b** (44 mg, 0.25 mmol, 1.0 equiv), [JohnPhosAuNCMe]SbF_6 (8 mg, 0.01 mmol, 4 mol%) and 1 atm of acetylene gas in $CHCl_3$ (1.3 mL, 0.2 M) at 23 ºC for 16 h. The crude was purified by flash column chromatography (SiO_2, cyclohexane/EtOAc 100:0 to 80:20, *v/v*) to afford the product **1.46b** as colorless oil (31 mg, 0.15 mmol, 61% yield).



^{1}H NMR (500 MHz, $CDCl_3$) δ 5.67 (ddd, *J* = 16.9, 10.4, 8.1 Hz, 1H), 5.15–5.13 (m, 1H), 5.11 (ddd, *J* = 14.5, 1.7, 0.9 Hz, 1H), 3.55 (ddd, *J* = 9.4, 8.4, 1.8 Hz, 1H), 3.36–3.27 (m, 1H),2.87 (s, 3H) 2.47 (dddt, *J* = 12.0, 8.1, 6.2, 1.0 Hz, 1H), 1.94 (dtd, *J* = 12.9, 6.5, 1.8 Hz, 1H), 1.90–1.81 (m, 1H), 1.47 (s, 3H), 1.19 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 135.6, 117.9, 66.3, 55.8, 47.4, 39.8, 27.8, 26.8, 23.2. **HRMS** (ESI +) calculated for $C_9H_{17}NNaO_2S$ $[M+Na]^+$: 226.0872; found: 226.0872.

2,2-Dimethyl-1-tosyl-3-vinylpiperidine (1.48)

Prepared following general procedure E using 4-methyl-*N*-(5-methylhex-4-en-1-yl)benzenesulfonamide **1.47** (67 mg, 0.25 mmol, 1.0 equiv), [JohnPhosAuNCMe]SbF_6 (8 mg, 0.01 mmol, 4 mol%) and 1 atm of acetylene gas in $CHCl_3$ (1.3 mL, 0.2 M) at 23 ºC for 16 h. The crude was purified by flash column chromatography (SiO_2, cyclohexane/EtOAc 100:0 to 80:20, *v/v*) to afford the product **1.48** as colorless oil (52 mg, 0.18 mmol, 71% yield).

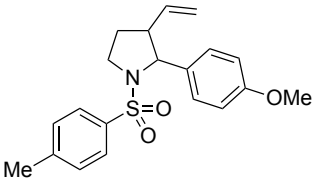


^{1}H NMR (500 MHz, $CDCl_3$) δ 7.69–7.66 (m, 2H), 7.25 (ddd, *J* = 7.5, 1.6, 0.9 Hz, 2H), 5.70–5.58 (m, 1H), 5.05–4.95 (m, 2H), 3.98–3.89 (m, 1H), 3.31 (ddd, *J* = 13.3, 10.1, 3.3 Hz, 1H), 2.40 (s, 3H), 2.12 (td, *J* = 9.6, 3.8 Hz, 1H), 1.76 (ddt, *J* = 12.8, 4.9, 2.3 Hz, 1H), 1.69–1.46 (m, 3H), 1.30 (s, 3H), 1.13 (s,

3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 142.7, 141.0, 138.9, 129.5, 126.9, 117.0, 60.5, 52.2, 43.6, 27.5, 26.6, 25.0, 21.6, 20.6. **HRMS** (ESI +) calculated for $C_{16}H_{23}NNaO_2S$ $[M+Na]^+$: 316.1342; found: 316.1346.

2-(4-Methoxyphenyl)-1-tosyl-3-vinylpyrrolidine (1.50b)

Prepared following general procedure E using (*E*)-*N*-(4-(4-methoxyphenyl)but-3-en-1-yl)-4-methylbenzenesulfonamide **1.49b** (83 mg, 0.25 mmol, 1.0 equiv), [JohnPhosAuNCMe]SbF_6 (8 mg, 0.01 mmol, 4 mol%) and 1 atm of acetylene gas in $CHCl_3$ (1.3 mL, 0.2 M) at 23 ºC for 16 h. The crude was purified by flash column chromatography (SiO_2, cyclohexane/EtOAc 100:0 to 80:20, *v/v*) to afford the product **1.50b** as colorless oil (10 mg, 0.028 mmol, 11% yield).

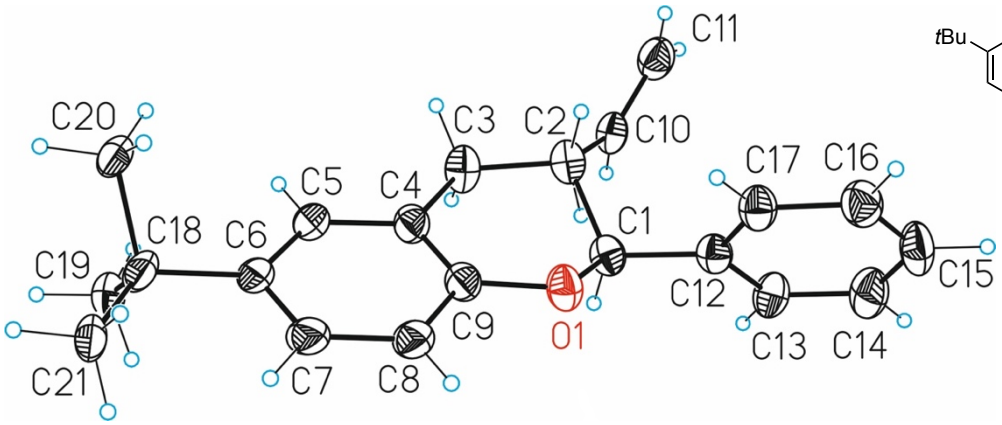


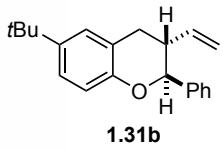
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.62–7.58 (m, 2H), 7.26–7.23 (m, 2H), 7.20–7.15 (m, 2H), 6.83–6.78 (m, 2H), 5.44 (ddd, *J* = 17.1, 10.3, 7.6 Hz, 1H), 4.89 (dt, *J* = 10.2, 1.1 Hz, 1H), 4.84 (dt, *J* = 17.1, 1.3 Hz, 1H), 4.29 (d, *J* = 6.6 Hz, 1H), 3.79 (s, 3H), 3.69 (ddd, *J* = 10.6, 7.7, 4.5 Hz, 1H), 3.58 (ddd, *J* = 10.6, 8.3, 6.4 Hz, 1H), 2.66 (h, *J* = 6.7 Hz, 1H), 2.42 (s, 3H), 2.05–1.94 (m, 1H), 1.55–1.47 (m, 1H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 158.9, 143.3, 137.3, 135.6, 133.8, 129.6, 127.9, 127.6, 116.3, 113.8, 68.5, 55.4, 53.8, 48.8, 30.7, 21.7. **HRMS** (ESI +) calculated for $C_{20}H_{24}NO_3S$ $[M+H]^+$: 358.1471; found: 358.1462.

Crystallographic Data

6-(*tert*-Butyl)-2-phenyl-3-vinylchromane (Product 1.31b)

CCDC 2266134





1.31b

Table 1.10. Crystal data and structure refinement for product **1.31b**.

Identification code	TMG-01-840_P2n_J	
Empirical formula	C21 H24 O	
Formula weight	292.40	
Temperature	100(2)K	
Wavelength	0.71073 Å	
Crystal system	monoclinic	
Space group	P 2/n	
Unit cell dimensions	a = 14.1122(6)Å	a= 90°.
	b = 5.8601(2)Å	b = 97.726(4)°.
	c = 20.4734(9)Å	g = 90°.
Volume	1677.76(12) $Å^3$	
Z	4	
Density (calculated)	1.158 Mg/m^3	
Absorption coefficient	0.069 mm^{-1}	
F(000)	632	
Crystal size	0.600 x 0.050 x 0.050 mm^3	
Theta range for data collection	3.477 to 28.461°.	
Index ranges	-17<=h<=16,-7<=k<=7,-23<=l<=27	
Reflections collected	17284	
Independent reflections	3712[R(int) = 0.0580]	
Completeness to theta =28.461°	87.5%	
Absorption correction	Multi-scan	
Max. and min. transmission	1.00 and 0.42	

Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3712/ 330/ 315
Goodness-of-fit on F^2	1.014
Final R indices [I>2sigma(I)]	R1 = 0.0515, wR2 = 0.1221
R indices (all data)	R1 = 0.0915, wR2 = 0.1359
Largest diff. peak and hole	0.191 and -0.202 e.$Å^{-3}$

(2*S*,3*R*)-4,4,5,5-Tetramethyl-2-(2-phenyl-3-vinylchroman-6-yl)-1,3,2-dioxaborolane (Product 1.31e)

CCDC 2266135

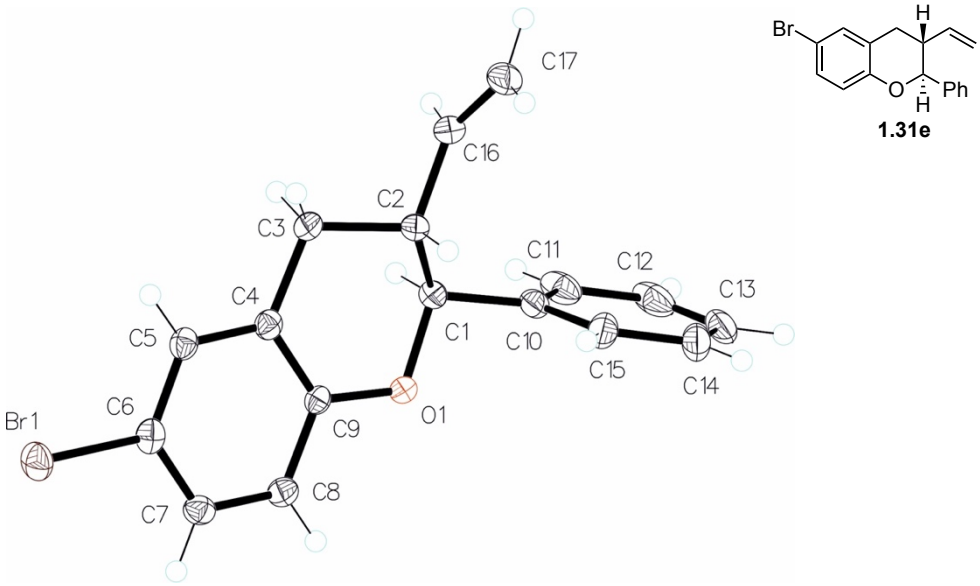


Table 1.11. Crystal data and structure refinement for product **1.31e**.

Identification code	TMG01909F_PB
Empirical formula	$C_{68}H_{60}Br_4O_4$
Formula weight	1260.80
Temperature/K	100
Crystal system	triclinic
Space group	P1
a/Å	9.7946(3)
b/Å	13.0686(3)
c/Å	13.1761(3)
α/°	108.073(2)
β/°	97.027(2)
γ/°	111.729(3)
Volume/Å^3	1434.69(7)
Z	1
ρ_{calc}g/cm^3	1.459
μ/mm^{-1}	2.854
F(000)	640.0
Crystal size/mm^3	0.08 × 0.06 × 0.02
Radiation	MoKα (λ = 0.71073)

2Θ range for data collection/°	3.636 to 64.746
Index ranges	$-14 \leq h \leq 14$, $-19 \leq k \leq 19$, $-19 \leq l \leq 19$
Reflections collected	66225
Independent reflections	18761 [R_{int} = 0.0465, R_{sigma} = 0.0414]
Data/restraints/parameters	18761/3/685
Goodness-of-fit on F^2	1.070
Final R indexes [I>=2σ (I)]	R_1 = 0.0406, wR_2 = 0.0992
Final R indexes [all data]	R_1 = 0.0480, wR_2 = 0.1019
Largest diff. peak/hole / e $Å^{-3}$	0.95/-0.53
Flack parameter	-0.003(3)

Biological results for compound 1.41

The antimicrobial screening was performed by CO-ADD (The Community for Antimicrobial Drug Discovery) and funded by the Welcome Trust (UK) and The University of Queensland (Australia).

Hit Confirmation of active compounds by whole cell growth inhibition assays was conducted as an 8-point dose response to determine the Minimum Inhibitory Concentration (MIC), in duplicate (n=2). The inhibition of growth is measured against those microorganisms that showed susceptibility to the compounds tested in the Primary Screen. Included in the Hit Confirmation were 5 bacteria: *Escherichia coli*, *Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa* and *Staphylococcus aureus*, and 2 fungi *Candida albicans* and *Cryptococcus neoformans*. In addition to determining MIC, active compounds were counter screened for cytotoxicity against a human embryonic kidney cell line, HEK293, by determining their CC_{50} value. The compounds were also screened for haemolysis of human red blood cells.

Assay Parameters	Bacteria	Fungi	HEK293	Haemolysis
Test concentration	32 - 0.25 µg/mL or 20 – 0.15 µM ≤0.5% DMSO	32 - 0.25 µg/mL or 20 – 0.15 µM ≤0.5% DMSO	32 - 0.25 µg/mL or 20 – 0.15 µM ≤0.5% DMSO	32 - 0.25 µg/mL or 20 – 0.15 µM ≤0.5% DMSO
QC	Duplicate (n=2) Control MIC: Pass	Duplicate (n=2) Control MIC: Pass	Duplicate (n=2) Control CC_{50}: Pass	Duplicate (n=2) Control HC_{10}: Pass
Plates	Non-Binding Surface (NBS), 384-well plate	Non-Binding Surface (NBS), 384-well plate	TC, 384-well black wall/clear bottom	Polypropylene 384-well and polystyrene 384-well plates
Media	Cation-adjusted Mueller Hinton broth	Yeast Nitrogen Base	DMEM supplemented with 10% FBS	0.9% NaCl
Read Out	OD_{600}	OD_{630} Resazurin $OD_{600-570}$	Resazurin $F_{560/590}$	OD_{405}

Figure 1.3. Assay parameters for biological studies.

Table 1.12. Cytotoxicity results for product **1.41**.

ID	Project	RunID	Hit	Tox	Sa	Ec	Kp	Pa	Ab	Ca	Cn	Hk	Hm	Unit
C0121693	P0982	HCR00181	2	0	2	>32	>32	>32	>32	16	2	>32	>32	mg/mL

Abbreviation	Code	Name	Description	Strain	Organsim	Type	Media	PlateType
Sa	GP_020	*Staphylococcus aureus*	MRSA	ATCC 43300	Bacteria	G+ve	CAMHB	NBS
Ec	GN_001	*Escherichia coli*	FDA control	ATCC 25922	Bacteria	G-ve	CAMHB	NBS
Kp	GN_003	*Klebsiella pneumoniae*	MDR	ATCC 700603	Bacteria	G-ve	CAMHB	NBS
Ab	GN_034	*Acinetobacter baumannii*	Type strain	ATCC 19606	Bacteria	G-ve	CAMHB	NBS
Pa	GN_042	*Pseudomonas aeruginosa*	Type strain	ATCC 27853	Bacteria	G-ve	CAMHB	NBS
Ca	FG_001	*Candida albicans*	CLSI reference	ATCC 90028	Fungi	Yeast	YNB	NBS
Cn	FG_002	*Cryptococcus neoformans var. grubii*	Type strain	H99; ATCC 208821	Fungi	Yeast	YNB	NBS
Hk	MA_007	Human embryonic kidney cells	HEK-293	ATCC CRL-1573	Human	Eukaryotes	DMEM 10% FBS	TC-PS
Hm	HA_150	Human red blood cells	RBC		Human	Eukaryotes		PS

Summary: Table with Percentile (50%) values of MIC, CC_{50} (cytotoxicity) and HC_{10} (haemolytic activity) for each organism

MIC; Cytox, Haemolyis: individual data points for import in in-house databases. Haemolysis also reports the HC_{50} values, which is used to calculate the HC_{10} values.

Compound Concentration: compounds were plated as a 2-fold dose response from 32 to 0.25 µg/mL (or 20 to 0.156 mM), with a maximum of 0.5% DMSO, final in assay concentration.

UNIVERSITAT ROVIRA I VIRGILIDevelopment of Gold(I)-Catalyzed Reactions Between Alkenes and Acetylene Gas
Tania Medina Gil

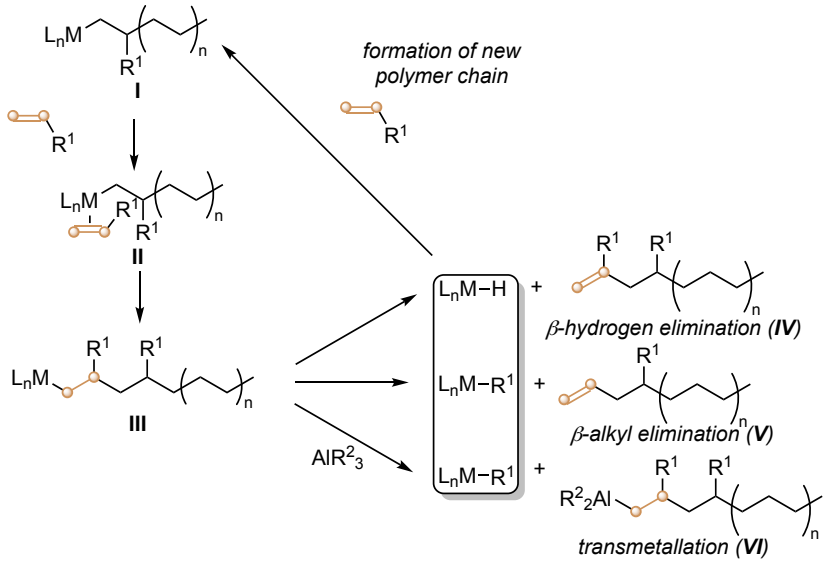
Chapter II
Development of a Three Component Gold(I)-Catalyzed Alkoxyvinylation and Studies on the Oligomerization Process

UNIVERSITAT ROVIRA I VIRGILIDevelopment of Gold(I)-Catalyzed Reactions Between Alkenes and Acetylene Gas
Tania Medina Gil

Introduction

Metal-Catalyzed Polymerization of Alkenes

The synthesis of polymeric materials has grown exponentially over the past decades and can be considered as one of the focus of present chemistry.[1] The primary goal of polymer synthesis nowadays is the development of what is called "living polymerization processes". This concept involves methods that allow the chain-growth polymerization and the addition of monomer units without termination.[2] In the early 1950s, Ziegler and Natta discovered that titanium chloride in the presence of alkylaluminum compounds could effectively catalyze the polymerization of ethylene and propylene.[3] Followed by these studies, many other examples of metal-catalyzed alkene polymerization systems have been reported. The main drawback of these processes is the catalyst tendency to undergo either *β*-elimination reactions (**IV** and **V**) or irreversible chain transfer to metal alkyls (**VI**), which initiates new polymer chains (Scheme 2.1).

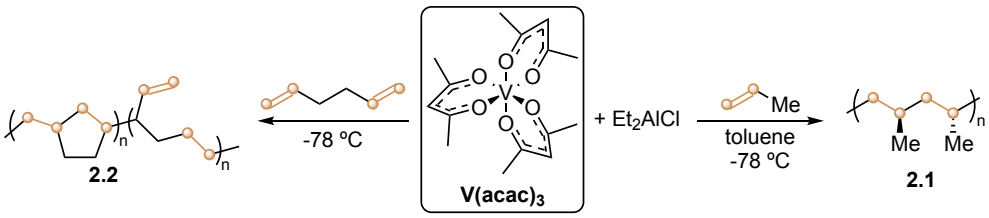


Scheme 2.1. Mechanism of propagation and chain transfer in Ziegler-Natta metal catalyzed alkene polymerization.

To overcome these drawbacks in alkene polymerization, a wide variety of modified ligands and activators have been described in the past decades. In 1979, Doi and coworkers reported the first catalytic alkene polymerization system based on the use of $V(acac)_3$ as catalyst.[4] This was the first example of the use of metal catalysts for these type of transformations. Ever since, a wide variety of vanadium-based systems have been developed for alkene polymerizations processes. Some examples

1. Coates, G. W.; Hustad, P. D.; Reinartz, S. *Angew. Chem. Int. Ed.* **2002**, *41*, 2236–2257.
2. Szwarc, M. *J. Polym. Sci.* **1998**, *36*, IX–XV.
3. (a) Ziegler, K.; Holzkamp, E.; Breil, H.; Martin, H. *Angew. Chem.* **1955**, *67*, 426–426. (b) Natta, G.; Pino, P.; Corradini, P.; Danusso, F.; Mantica, E.; Mazzanti, G. *J. Am. Chem. Soc.* **1955**, *77*, 1708–1710.
4. Doi, Y.; Ueki, S.; Keii, T. *Macromol.* **1979**, *12*, 814–819.

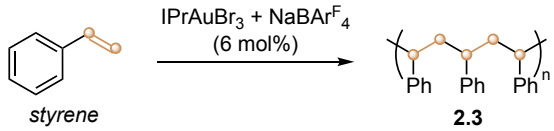
include the polymerization of propylene to obtain syndiotactic polypropylenes **2.1**[5] or the polymerization of 1,5-hexadiene to afford methylene-1,3-cyclopentane structures **2.2** (Scheme 2.2).[6]



Scheme 2.2. Selected examples of vanadium-catalyzed alkene polymerization.

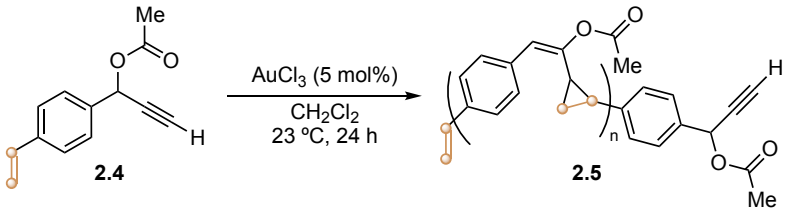
The main limitation of these systems is that the living behavior is restricted to a few monomers. Additionally, the reactions require special conditions since most of them need to be run at –40 ºC or below. These constraints boosted the development of new metal catalysts for living polymerization processes.[7]

Despite vast advances were achieved in this field, it was not until 2008 when the first gold(I)-catalyzed alkene polymerization transformation was described.[8] Pérez and co-workers discovered that styrene can be polymerized at room temperature in the presence of *N*-heterocyclic carbenes gold(I) complexes (Scheme 2.3). Deeper studies into this reaction indicated that the presence of the NHC ligand is crucial for the reaction to take place and determines the properties of the polymer obtained.



Scheme 2.3. Gold(I)-catalyzed polymerization of styrene.

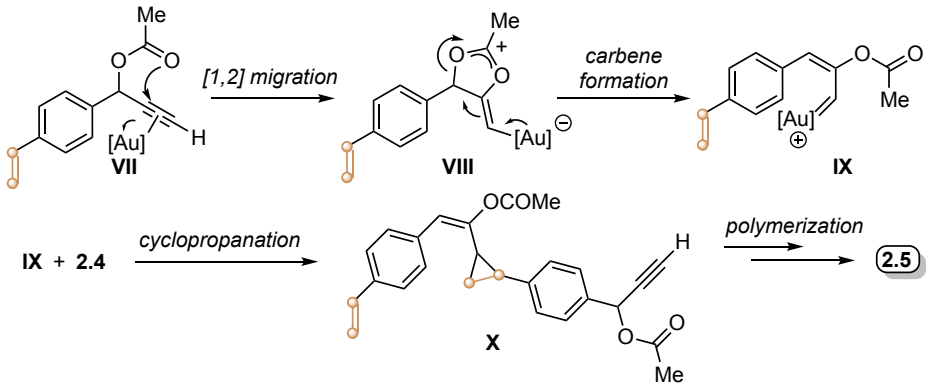
In 2014, the first carbene-to-alkene addition polymerization reaction was reported by the group of Stoffelbach.[9] Monomer **2.4** bearing a propargylic ester and an alkene moiety could easily undergo polymerization through a metallocarbene generation/cyclopropanation sequence to afford macromolecule **2.5** (Scheme 2.4).



Scheme 2.4. Gold-catalyzed polymerization based on carbene polycyclopropanation.

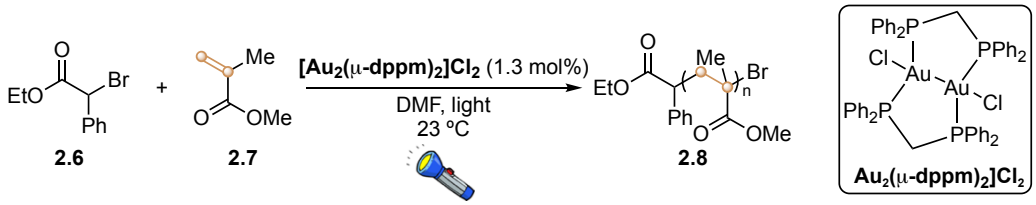
5. Doi, Y.; Ueki, S.; Keii, T. *Macromol. Chem. Phys.* **1979**, *180*, 1359–1361.
6. Doi, Y.; Tokuhiro, N.; Soga, K. *Makromol. Chem.* **1989**, *190*, 643–651.
7. For selected examples: (a) Jeske, G.; Lauke, H.; Mauermann, H.; Swepston, P. N.; Schumann, H.; Marks, T. J. *J. Am. Chem. Soc*. **1985**, *107*, 8091–8103. (b) Sassmannshausen, J.; Bochmann, M.; Rosch, J.; Lilge, D. *J. Organomet. Chem.* **1997**, *548*, 23–28. (c) Boffa, L. S.; Novak, B. M. *Chem. Rev*. **2000**, *100*, 1479–1493.
8. Urbano, J.; Hormigo, A. J.; Frémont, P. de; Nolan, S. P.; Díaz-Requejo, M. M.; Pérez, P. J. *Chem. Commun.* **2008**, *6*, 759–761.
9. Nzulu, F.; Bontemps, A.; Robert, J.; Barbazanges, M.; Fensterbank, L.; Goddard, J.-P.; Malacria, M.; Ollivier, C.; Petit, M.; Rieger, J.; Stoffelbach, F. *Macromol.* **2014**, *47*, 6652–6656.

The mechanism of the reaction starts with the coordination of the gold(I) catalyst to the alkyne moiety, triggering the intramolecular nucleophilic attack of the ester (**VII**) (Scheme 2.5). After 1,2-migration, oxocarbenium **VIII** is formed and upon rearrangement affords gold carbene **IX**. This intermediate undergoes cyclopropanation with the alkene moiety from **2.4** to lead to intermediate **X** that can propagate giving rise to the corresponding oligomers **2.5**.



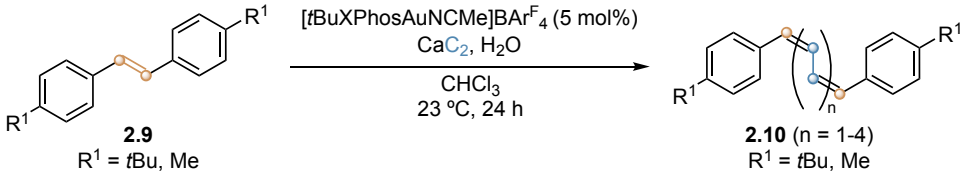
Scheme 2.5. Proposed mechanism for the synthesis of polymer **2.5**.

Gold(I) catalysis has also been successfully applied to the atom transfer radical polymerization (ATRP) of acrylates **2.7**.[10] Using a dinuclear gold(I) complex and ethyl α-bromophenylacetate **2.6** (EBPA) as initiator under UV light, controlled-living ATRP took place affording the desired polymers **2.8** (Scheme 2.6).



Scheme 2.6. Gold(I)-catalyzed light-induced atom transfer radical polymerization.

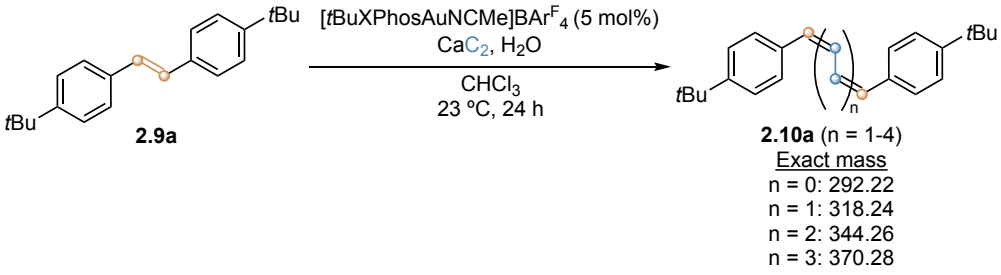
In 2020, our group reported the presence of side oligomerization reactions in the gold(I)-catalyzed synthesis of (*Z,Z*)-1,3-dienes with acetylene gas.[11] When *trans*-stilbene derivates **2.9** were exposed to an acetylene atmosphere and in the presence of [*t*BuXPhosAuNCMe]BAr^F_4 as catalyst, 1,3-dienes **2.10** were obtained. Further studies proved that the low yield of the desired dienes was due to the presence of secondary oligomerization reactions upon insertion of C_2 units from acetylene (Scheme 2.7).[12]



Scheme 2.7. Gold(I)-catalyzed oligomerization of *trans*-stilbene derivates **2.9** with acetylene gas.

10. Nzulu, F.; Telitel, S.; Stoffelbach, F.; Graff, B.; Morlet-Savary, F.; Lalevée, J.; Fensterbank, L.; Goddard, J.-P.; Ollivier, C. A, *Polym. Chem.* **2015**, *6*, 4605–4611.
11. Scharnagel, D.; Escofet, I.; Armengol-Relats, H.; de Orbe, M. E.; Korber, J. N.; Echavarren, A. M. *Angew. Chem. Int. Ed.* **2020**, *59*, 4888–4891.
12. Further studies on the gold(I)-catalyzed oligomerization with acetylene gas will be discussed in this Chapter.

The presence of the oligomers was confirmed by MALDI-TOF MS analysis of the reaction crudes after quenching with Et_3N (Figure 2.1).



Scheme 2.8. Oligomerization experiments.

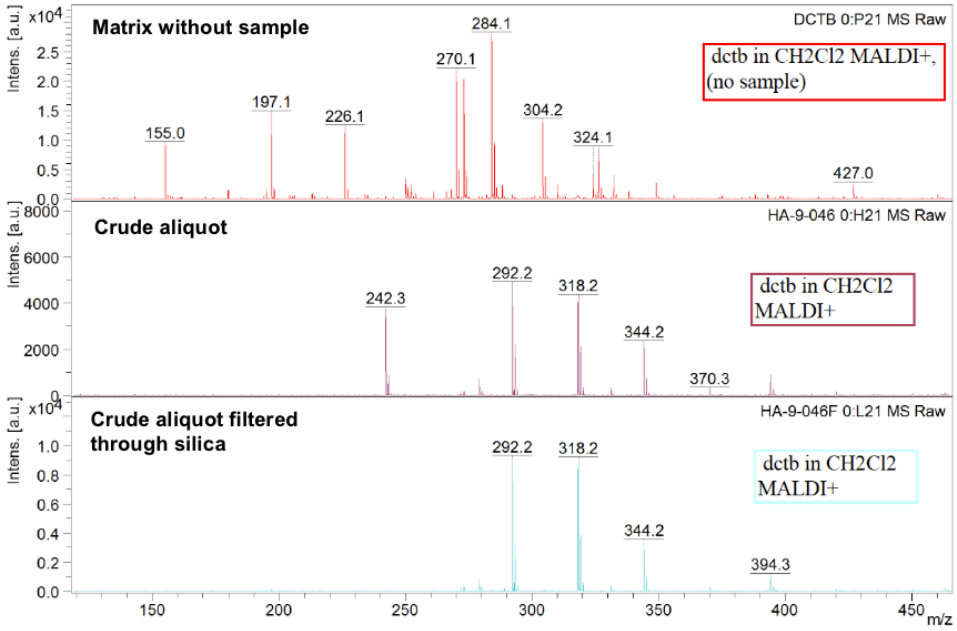


Figure 2.1. MALDI -TOF analysis.

Natural Occurrence and Relevance of Hemiaminals Containing Products

From natural products like (-)-zampanolide or aspidophylline A to biologically active compounds such as Zalcitabine (anti-HIV agent NRTI) or Tegafur (anti-cancer agent), hemiaminal ether skeletons (HESs) play an important role in chemistry (Figure 2.2). Therefore, the development of novel methodologies for the synthesis of this motif results highly appealing for organic chemists.[13]

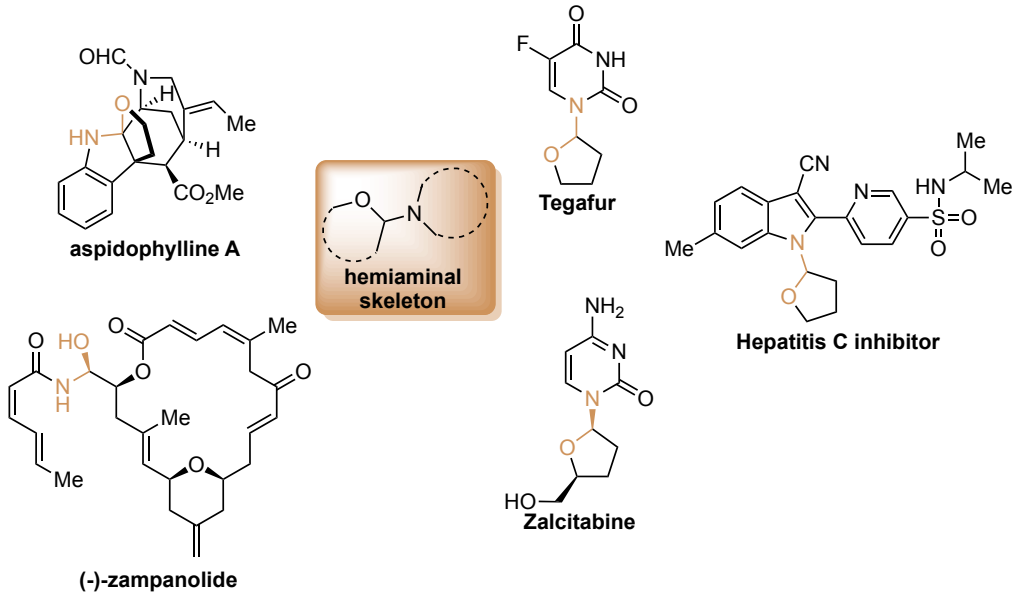
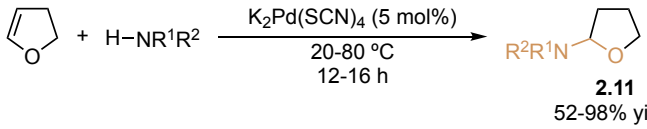


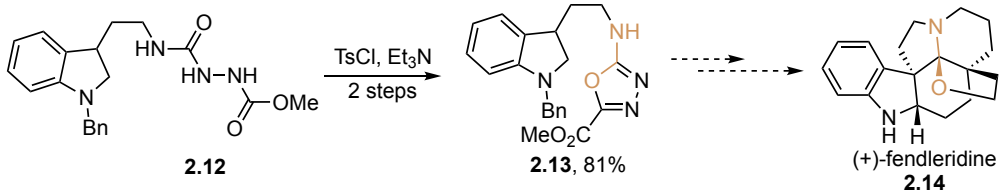
Figure 2.2. Relevant products with hemiaminal ether skeletons (HESs).

Traditional methodologies for the synthesis of HESs rely on transition metal catalysis. Particularly, hydroamination of unsaturated enol ethers has proven to be a powerful strategy and has been successfully applied to the synthesis of α-alkylamine tetrahydrofurans **2.11** using palladium chemistry (Scheme 2.9).[14]



Scheme 2.9. Palladium-catalyzed synthesis of α-amino tetrahydrofurans **2.11**.

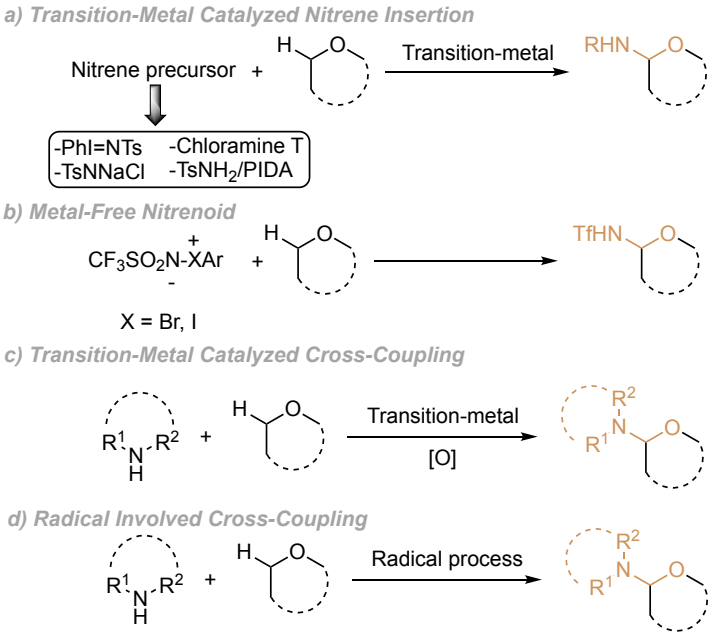
Additionally, cascade reactions have also been applied for the synthesis of HESs. In 2010, Boger's group reported the enantioselective total synthesis of (+)-fendleridine (**2.14**) where the key step is an intramolecular [4+2]/[3+2] cycloaddition cascade of 1,3,4-oxadiazole intermediate **2.13** (Scheme 2.10).[15]



Scheme 2.10. Key steps for the total synthesis of (+)-fendleridine.

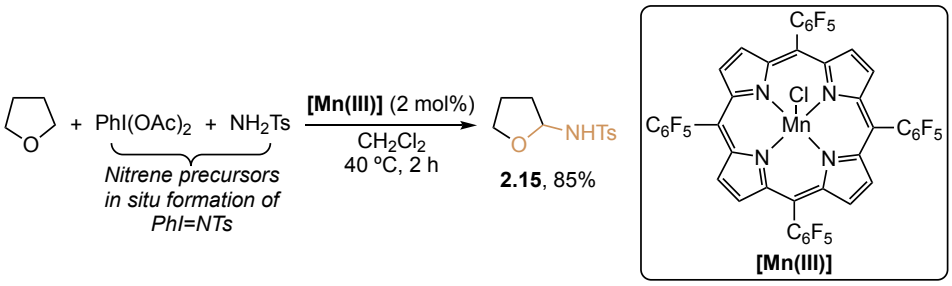
13. Dian, L.; Xing, Q.; Zhang-Negrerie, D.; Du, Y. *Org. Biomol. Chem.* **2018**, *16*, 4384–4398.
14. Cheng, X.; Hii, K. K. *Tetrahedron* **2001**, *57*, 5445–5450.
15. Campbell, E. L.; Zuhl, A. M.; Liu, C. M.; Boger, D. L. *J. Am. Chem. Soc.* **2010**, *132*, 3009–3012.

During the past decades, C–H functionalization has emerged as an effective approach for the synthesis of pharmaceutical active compounds.[16] In this sense, C(sp^3)–H amination of alkyl ethers has been widely applied to the synthesis of hemiaminal skeletons.[17] The synthesis of HESs via C–H activation can be divided in four main groups depending on the mechanism followed (Scheme 2.11).



Scheme 2.11. Mechanistic pathways for the C(sp^3)–H activation of alkyl ethers.

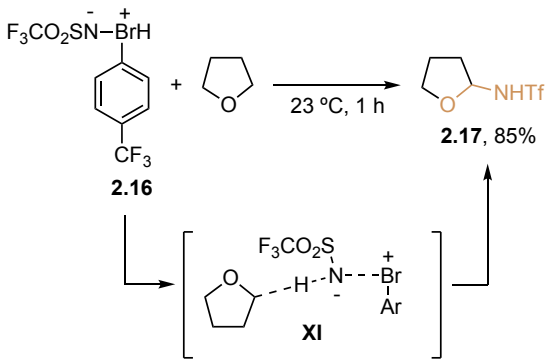
The C(sp^3)–H amination via nitrene insertion into C–H bonds has been one of the first and most studied approaches for the synthesis of HESs. In 2000, the group of Chen reported the amidation of hydrocarbons using *N*-tosyl iodinane (PhI=NTs) as nitrene precursor and ruthenium and manganese porphyrin catalysts. *N*-substituted amides were successfully prepared under mild conditions. In this work, the first example of amination of tetrahydrofuran was reported using manganese catalysis and affording the corresponding hemiaminal skeleton in an excellent 85% yield (Scheme 2.12).[18]



Scheme 2.12. Mn(III)-catalyzed C–H amination of tetrahydrofuran.

16. Hartwig, J. F.; Larsen, M. A. *ACS Cent. Sci.* **2016**, *2*, 281–292.
17. Chang, J. W. W.; Ton, T. M. U.; Chan, P. W. H. *Chem. Rec.* **2011**, *11*, 331–357.
18. Yu, X.-Q.; Huang, J.-S.; Zhou, X.-G.; Che, C.-M. *Org. Lett.* **2000**, *2*, 2233–2236.

Despite their high reactivity, free nitrene C–H insertions turned out to be quite unselective and difficult to control. These limitations promoted the development of transition-metal-free nitrenoid pathways. In this context, imino-λ^3-bromane **2.16** was found to be a highly reactive nitrenoid species by Ochiai and co-workers (Scheme 2.13).[19] Mechanistic studies support a direct C–H insertion pathway where the driving force would be the reduction of hypervalent bromane (III) to bromide (I).



Scheme 2.13. C–H amination via nitrenoid species.

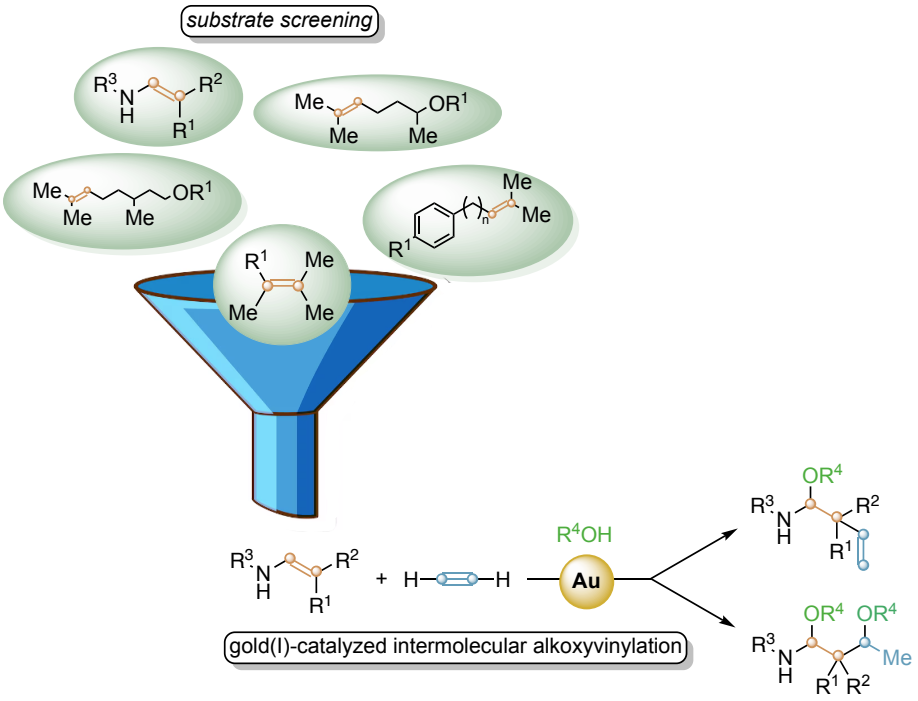
Other strategies developed for the synthesis of HESs through C–H amination are based on transition-metal catalysis (Pd, Co, Cu or Fe)[20] or radical-involving pathways.[21]

Despite the enormous progress made in this field, the scope of amines is still limited to either simple tosylamine or secondary amines with an acidic proton. This limitation makes the development of new methodologies for the synthesis of hemiaminals a high priority in organic chemistry.

19. Ochiai, M.; Yamane, S.; Hoque, M. M.; Saito, M.; Miyamoto, K. *Chem. Commun.* **2012**, *48*, 5280–5282.
20. For selected examples see: (a) May, T. L.; Brown, M. K.; Hoveyda, A. H. *Angew. Chem. Int. Ed*. **2008**, *47*, 7358–7362. (b) Pan, S.; Liu, J.; Li, H.; Wang, Z.; Guo, X.; Li, Z. *Org. Lett*. **2010**, *12*, 1932–1935. (c) Huang, R.; Xie, C.; Huang, L.; Liu, J. *Tetrahedron* **2013**, *69*, 577–582.
21. For selected examples see: (a) Guo, H.-M.; Xia, C.; Niu, H.-Y.; Zhang, X.-T.; Kong, S.-N.; Wang, D.-C.; Qu, G.-R. *Adv. Synth. Catal.* **2011**, *353*, 53–56. (b) Muramatsu, W.; Nakano, K. *Org. Lett.* **2014**, *16*, 2042–2045.

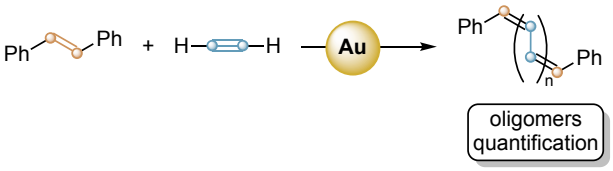
Objectives

In the first Chapter of this Thesis, we described the gold(I)-catalyzed aryloxyvinylation of *o*-allyl phenols with acetylene gas. However, the fully intermolecular version of this reaction, where alkene, alkyne and alcohol are not covalently linked, remained unknown. In Chapter II, we describe our work on the development of this gold(I)-catalyzed three component transformation with acetylene gas.[22]



Scheme 2.14. Gold(I)-catalyzed intermolecular alkoxyvinylation with acetylene gas.

In the second part of this Chapter, we center our attention on the study of gold(I)-catalyzed oligomerization processes. This type of reactivity has been described before but the oligomers quantification was never reported.



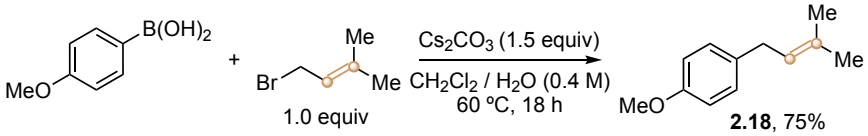
Scheme 2.15. Oligomers quantification.

22. Part of the experiments described in this section were performed jointly with Dr. L. Anders Hammarback and Dr. Anna Sadurní.

Results and Discussion

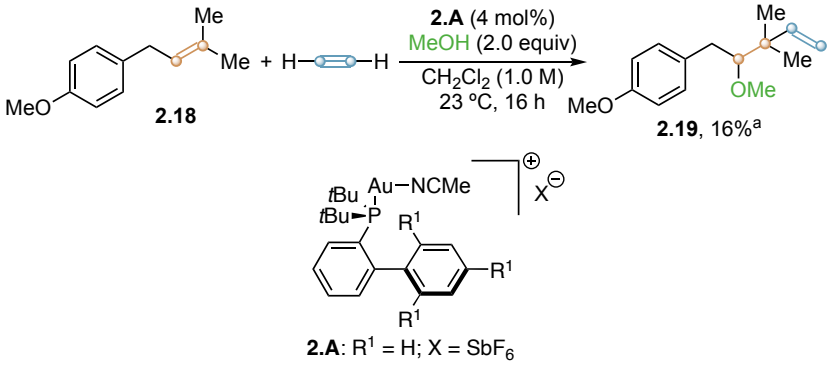
First Attempts of a Fully Intermolecular Gold(I)-Catalyzed Reaction with Acetylene Gas

Given the results summarized in Chapter I, we were intrigued about the possibility of developing a fully intermolecular gold(I)-catalyzed alkoxyvinylation. To start our work we prepared compound **2.18**, an analogue of *o*-allyl phenols **1.30** without the hydroxyl group (Scheme 2.16).



Scheme 2.16. Synthesis of substrate **2.18**.

Alkene **2.18** was submitted to the gold(I) catalysis in the presence of acetylene gas, and we were delighted to confirm the formation of the desired vinyl alkoxylated product **2.19** but in low yield (Scheme 2.17).



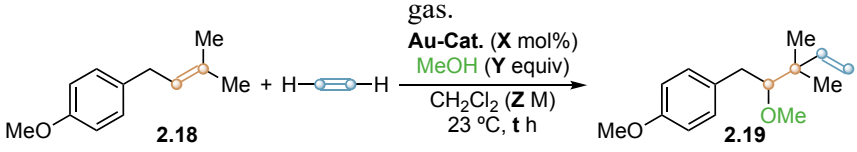
[a]Yield determined by ^{1}H NMR using 1,1,2,2-tetrachloroethane as internal standard.

Scheme 2.17. First attempt of fully intermolecular reaction of alkenes with acetylene gas.

We performed optimization studies on this model reaction and the results obtained were summarized in Table 2.1.

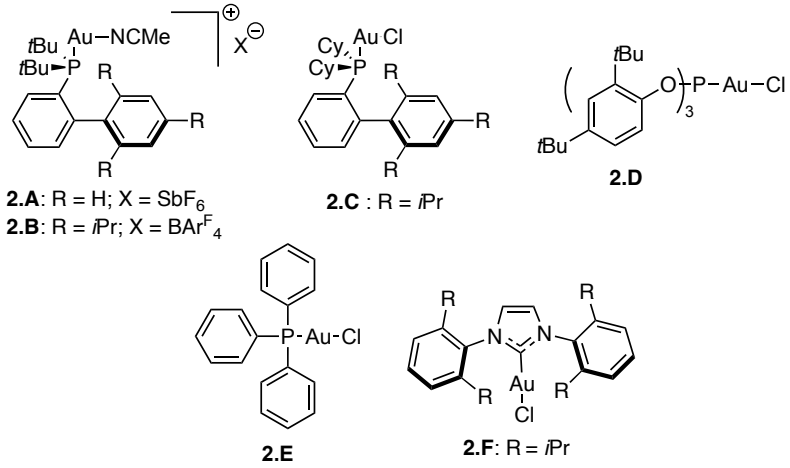
Different gold(I) catalysts were tested but only complexes **2.A**, **2.B** and **2.C** afforded the desired product, although in low yield (Table 2.1, entries 1–5). Decreasing the reaction time to 6 h slightly enhanced the yield of the product (Table 2.1, entry 6) whereas modifying the catalyst loading did not lead to an improvement of the yield (Table 2.1, entries 6–7) We discovered that 2.0 equiv of alcohol was the most suitable amount of external nucleophile, since adding stoichiometric amount (Table 2.1, entry 9), or higher excess (Table 2.1, entries 10–11) led to a drop in the yield.

Table 2.1. Optimization tests for the gold(I)-catalyzed intermolecular reaction of **2.18** with acetylene gas.



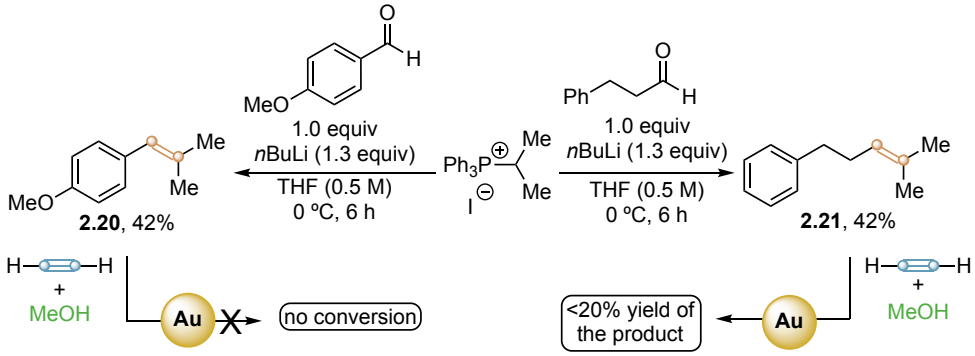
Entry	Au-Cat. (mol%)	Molarity (M)	MeOH (equiv)	Time	Yield 2.19 (%)[a]
1	**2.A** (4)	1.0	2.0	16 h	16
2	**2.B** (4)	1.0	2.0	16 h	10
3	**2.C**[b] (4)	1.0	2.0	16 h	n.r
4	**2.D**[b] (4)	1.0	2.0	16 h	n.r
5	**2.E**[b] (4)	1.0	2.0	16 h	n.r
6	**2.A** (2)	1.0	2.0	6 h	17
7	**2.A** (6)	1.0	2.0	6 h	18
8	**2.A** (4)	0.5	2.0	6 h	15
9	**2.A** (4)	1.0	1.0	6 h	15
10	**2.A** (4)	1.0	5.0	6 h	14
11	**2.A** (4)	1.0	10.0	6 h	12

[a]Yield determined by ^{1}H NMR using 1,1,2,2-tetrachloroethane as internal standard. [b]Complex used with $NaBAr^F_4$ as chloride scavenger. n.r: no reaction.



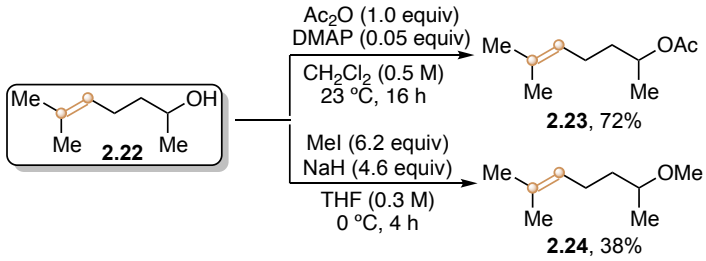
Despite our efforts, we could not obtain the alkoxyvinylated product **2.19** in more than 20% yield. Full conversion of the starting alkene was never reached and, additionally, we encountered a significant amount of undesired oligomerization processes. These side oligomerization reactions have been observed before in gold(I)-catalyzed reactions.[11] To quantify the amount of oligomerization in these type of intermolecular reactions, we performed further studies that will be discussed in the second part of this Chapter.

To avoid undesired alkene oligomerization reactions, we screened different alkenes as substrates. Firstly, we hypothesize that the aryl ring could play an important role and, therefore, placing the alkene closer or further could help enhance its reactivity towards the gold(I) catalysis (Scheme 2.18). Substrates **2.20** and **2.21**, bearing the alkene moiety closer and further from the aryl ring respectively, were successfully prepared by Wittig Reaction. However, none of them proved to be suitable for the gold(I)-catalyzed alkoxyvinylation reaction. Substrate **2.20** did not show any conversion towards the expected product. Additionally, **2.21** only afforded the product in low yield (<20%).



Scheme 2.18. Synthesis and tests of intermolecular gold(I)-catalyzed reaction of **2.20** and **2.21**.

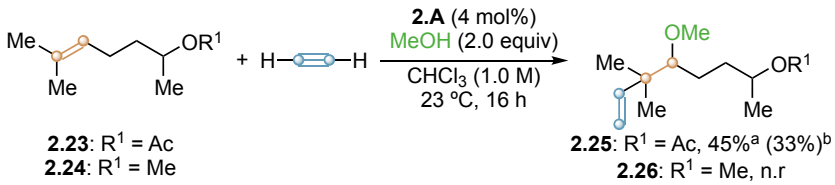
At this point, we moved on to the use of easily accessible prenyl alkenes and turned our attention to sulcatol (**2.22**), a potent insect pheromone.[23] This prenyl alcohol was successfully protected with OAc, and OMe groups, giving rise to compounds **2.23** and **2.24** respectively in moderate to good yields (Scheme 2.19).



Scheme 2.19. Protection reactions of sulcatol **2.22**.

The reactivity of these sulcatol derivates was tested in the gold(I)-catalyzed intermolecular reaction using MeOH as external nucleophile. In the case of substrate **2.23** we were pleased to observe an increased yield of the product (from 20% ^{1}H NMR yield with **2.18** to 45% with **2.23**) whereas alkene **2.24** gave no conversion (Scheme 2.20).

23. Meier, L. R.; Millar, J. G.; Mongold-Diers, J. A.; Hanks, L. M. *J. Chem. Ecol.* **2019**, *45*, 447–454.



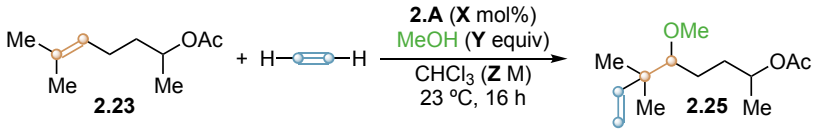
[a]Yield determined by ^{1}H NMR using 1,1,2,2-tetrachloroethane as internal standard. [b]Isolated yield. n.r: no reaction.

Scheme 2.20. Gold(I)-catalyzed intermolecular tests of protecting sulcatol **2.22**.

Giving the moderate yield obtained for substrate **2.25**, we decided to perform further optimization studies. The results obtained are summed in Table **2.2**.

As it happened with substrate **2.18**, we found out that neither changing the catalyst loading or the concentration of the reaction improved the yield of the product (Table 2.2, entries 1–5). Increasing the equivalents of nucleophile or using it as cosolvent (12.5 equiv) afforded the product in lower yields (Table 2.2, entries 6–8). Running the reaction at 50 ºC gave only traces of the alkoxyvinylated product **2.25** (Table 2.3, entry 9).

Table 2.2. Optimization of gold(I)-catalyzed reaction with protected sulcatol **2.23**.

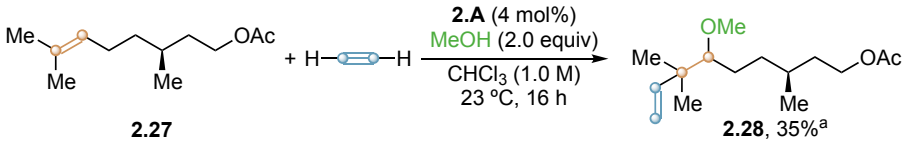


Entry	2.A loading (mol%)	Molarity (M)	MeOH (equiv)	Yield 2.25 (%)[a]
1	2	1.0	2.0	30
2	4	1.0	2.0	45
3	6	1.0	2.0	31
4	4	0.5	2.0	26
5	4	0.5	2.0	26
6	4	1.0	5.0	22
7	4	1.0	10	26
8	4	1.0	12.5	37
9[b]	4	1.0	2.0	2

[a]Yield determined by ^{1}H NMR using 1,1,2,2-tetrachloroethane as internal standard. [b]Reaction ran at 50 ºC.

Even though we were able to improve the yield of the product with sulcatol derivative **2.23**, we could not get past 50% yield. Keeping these type of alkenes as substrates, we decided to test the reactivity of OAc protected citronellol **2.27**.[24] Citronellol is a monoterpene alcohol present in *Cymbopogan citrates* and with potent anti-inflammatory and anti-diabetic properties.

Protected (*S*)-citronellol **2.27** underwent the gold(I)-catalyzed intermolecular alkoxyvinylation but led to the product in lower yield than sulcatol derivate **2.23** (45% ^{1}H NMR yield for **2.25** and 35% ^{1}H NMR for **2.28**) (Scheme 2.21).

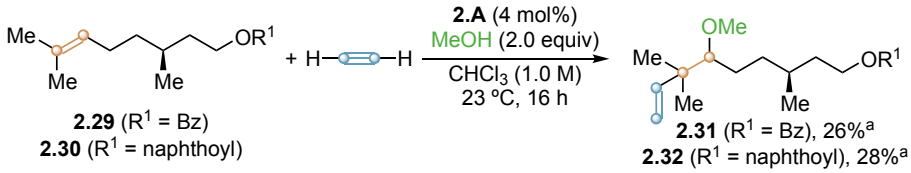


2.27 **2.28**, 35%[a]

[a]Yield determined by ^{1}H NMR using 1,1,2,2-tetrachloroethane as internal standard.

Scheme 2.21. Gold(I) catalysis using protected Citronellol **2.27** as substrate.

Additional protecting groups were used to obtained new citronellol analogues (**2.29** and **2.30**) but none of them improved the yield of the desired products **2.31** and **2.32** (Scheme 2.22).



2.29 (R^1 = Bz)
2.30 (R^1 = naphthoyl)

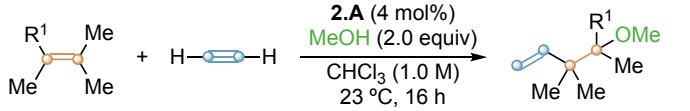
2.31 (R^1 = Bz), 26%[a]
2.32 (R^1 = naphthoyl), 28%[a]

[a]Yield determined by ^{1}H NMR using 1,1,2,2-tetrachloroethane as internal standard.

Scheme 2.22. Tests with protected citronellol derivates **2.29** and **2.30**.

Despite our efforts, employing trisubstituted prenyl alkenes we were not able to obtain yields higher than 50% for the vinyl alkoxylated product. At this point, we decided to explore the use of tetrasubstituted alkenes instead given their high reactivity.

After submitting **2.33** (trisubstituted alkene) and **2.34** (tetrasubstituted alkene) to the reaction conditions, we were pleased to find out that substrate **2.34**, bearing a tetrasubstituted alkene, gave higher yields than the trisubstituted one (Scheme 2.23). This is likely due to the enhanced reactivity of this type of alkenes.



2.33: R^1 = H
2.34: R^1 = Me

2.35: R^1 = H, 34%[a]
2.36: R^1 = Me, 56%[a]

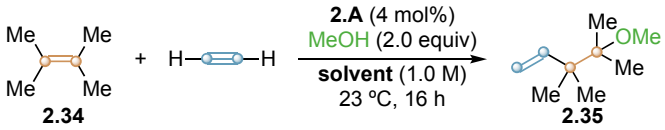
[a]Yield determined by ^{1}H NMR using 1,1,2,2-tetrachloroethane as internal standard.

Scheme 2.23. Comparison between tri- and tetrasubstituted alkene.

24. Brito, R. G.; Guimarães, A. G.; Quintans, J. S. S.; Santos, M. R. V.; De Sousa, D. P.; Badaue-Passos, D.; de Lucca, W.; Brito, F. A.; Barreto, E. O.; Oliveira, A. P.; Quintans, L. J. *J. Nat. Med.* **2012**, *66*, 637–644.

Having obtained a promising 56% ^{1}H NMR yield of the product when tetrasubstituted alkene **2.34** was employed, we decided to explore the use of different solvents to increase the yield (Table 2.3). $CHCl_3$ was confirmed as the most suitable solvent for the reaction (Table 2.3, entry 1), whereas polar solvents such as EtOAc or THF led to the formation of the product in lower yields (Table 2.3, entries 3–4). Aromatic solvents did not work, as well as the use of MeOH as cosolvent (Table 2.3, entries 5–6). Changing the temperature of the reaction also had a detrimental effect on the yield of the product **2.35** (Table 2.3, entries 7–8).

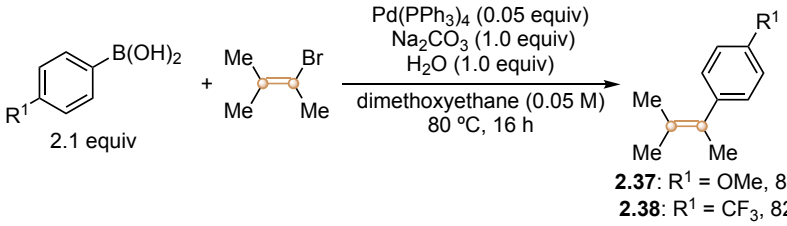
Table 2.3. Solvent screening.



Entry	Solvent	Yield 2.35 (%)[a]
1	$CHCl_3$	56
2	CH_2Cl_2	10
3	AcOEt	20
4	THF	32
5	Toluene	n.r
6	MeOH	n.r
7[b]	$CHCl_3$	31
8[c]	$CHCl_3$	14

[a]Yield determined by ^{1}H NMR using 1,1,2,2-tetrachloroethane as internal standard. [b]Reaction ran at 0 ºC, [c]Reaction ran at 50 ºC. n.r: no reaction.

Due to the low boiling point of product **2.35**, it could not be isolated after column chromatography. To overcome this volatility issue, we prepared two new analogues (**2.37** and **2.38**) by Suzuki cross coupling (Scheme 2.24). However, none of them afforded the alkoxylated product after the gold(I) catalysis.



Scheme 2.24. Synthesis of two new tetrasubstituted alkenes **2.37** and **2.38** by Suzuki coupling.

Despite our efforts to increase the yield of the three component intermolecular reaction with acetylene gas by tunning the substrate, we were not able to obtain the products in high yield. As mentioned before, these results are mainly due to the presence of side alkene oligomerization reactions.

Many other substrates were screened, some of them drawn in Figure 2.3. However, the gold(I)-catalyzed reaction of these substrates with acetylene gas led to either no conversion or low yields of the desired products.

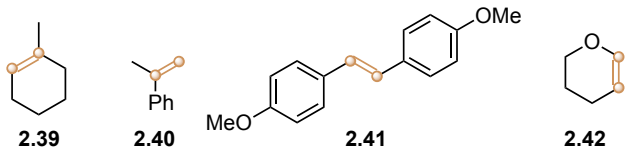
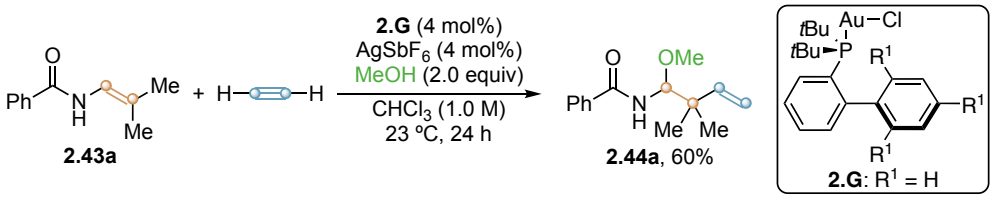


Figure 2.3. Unsuccessful substrates for the intermolecular alkoxyvinylation reaction.

Gold(I)-Catalyzed Three Component Alkoxyvinylation with Benzamides

Pleasingly, we found out that *N*-(2-methylprop-1-en-1-yl)benzamide (**2.43a**) was a suitable substrate for the three component reaction since initial tests afforded the alkoxyvinylated product **2.44a** in 60% yield (Scheme 2.25).

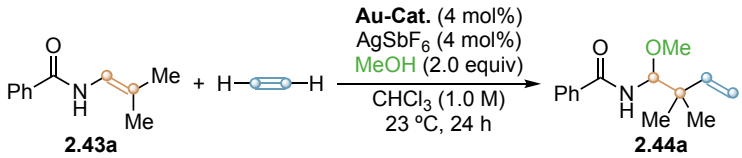


Scheme 2.25. Initial tests with *N*-(2-methylprop-1-en-1-yl)benzamide **2.44a**.

Optimization for Three Component Intermolecular Alkoxyvinylation Reaction

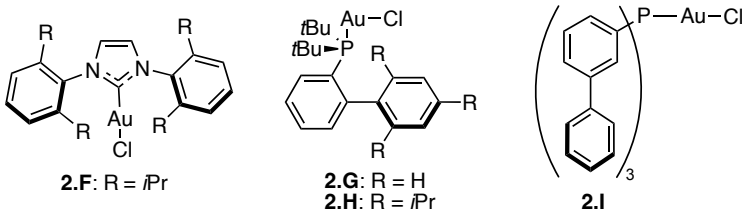
The use of different gold(I) catalysts was investigated in the reaction (Table 2.4). Phosphine-based ligands afforded **2.44a** in moderate yields (Table 2.4, entries 1–3, 6, 8) being cationic complex **2.A** the best one (Table 2.4, entry 8). Phosphite **2.D** completely inhibited the reactivity (Table 2.4, entry 5), as well as NHC complex **2.F** that only afforded traces of the product (Table 2.4, entry 7).

Table 2.4. Catalyst screening.



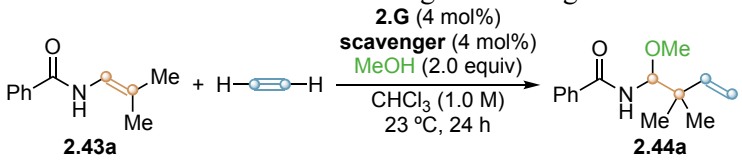
Entry	Au-Cat.	Yield 2.44a (%)[a]
1	**2.G**	55
2	**2.H**	43
3	**2.I**	45
4	**2.C**	36
5	**2.D**	n.r
6	**2.E**	13
7	**2.F**	7
8[b]	**2.A**	60
9	none	n.r

[a]Yield determined by ^{1}H NMR using 1,4-diacetylbenzene as internal standard. [b]Cationic gold(I) complex used without chloride scavenger. n.r: no reaction.



Different chloride scavengers were also tested (Table 2.5). Silver scavengers performed well and led to **2.44a** in moderate to good yields (Table 2.5, entries 1–4) being $AgSbF_6$ the one providing the highest yield (Table 2.5, entry 1). However, the use of $NaBAr^F{}_4$ had a detrimental effect in the yield, giving the product in only 4% yield (Table 2.5, entry 5).[25]

Table 2.5. Halide scavenger screening.



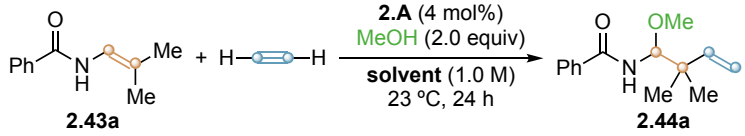
25. Giving these results, for the rest of the optimization and the scope of the reaction cationic complex **2.A** will be used.

Entry	Scavenger	Yield 2.44a (%)[a]
1	$AgSbF_6$	55
2	$AgPF_6$	33
3	$AgNTf_2$	44
4	AgOTf	51
5	$NaBAr^F{}_4$	4

[a]Yield determined by ^{1}H NMR using 1,4-diacetylbenzene as internal standard.

Next, the influence of the solvent of the reaction was evaluated (Table 2.6). Chlorinated solvents performed well and led to **2.44a** in moderate to good yields (Table 2.6, entries 1–4). The use of polar solvents had an unfavorable effect on the yield (Table 2.6, entries 5–7) whilst *n*-heptane gave the product only in 17% yield (Table 2.6, entry 8).

Table 2.6. Solvent screening.



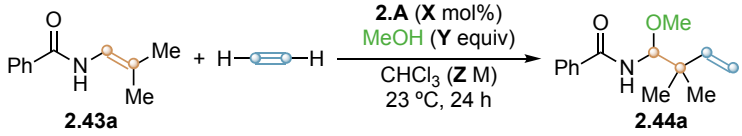
Entry	Solvent	Yield 2.44a (%)[a]
1	CH_2Cl_2	43
2	$CHCl_3$	60
3	1,2-Dichloroethane	44
4	PhCl	53
5	EtOAc	27
6	THF	28
7	MTBE	13
8	*n*-Heptane	17
9	Toluene	37

[a]Yield determined by ^{1}H NMR using 1,4-diacetylbenzene as internal standard.

To finish the optimization of the reaction conditions different combinations of catalyst loading, molarity and equivalents of nucleophile were explored (Table 2.7).

Decreasing the catalyst loading lowered the yield of the product (Table 2.7, entries 2–3). Moreover, as could be expected for an intermolecular reaction, lower concentrations led to lower yields (Table 2.7, entries 6–7) but, surprisingly, doubling the molarity up to 2.0 M did not improve the yield (Table 2.7, entry 5). Moreover, just like it happened with other substrates, reducing the amount of nucleophile worsen the yield (Table 2.7, entry 8).

Table 2.7. Catalyst loading and molarity screening.



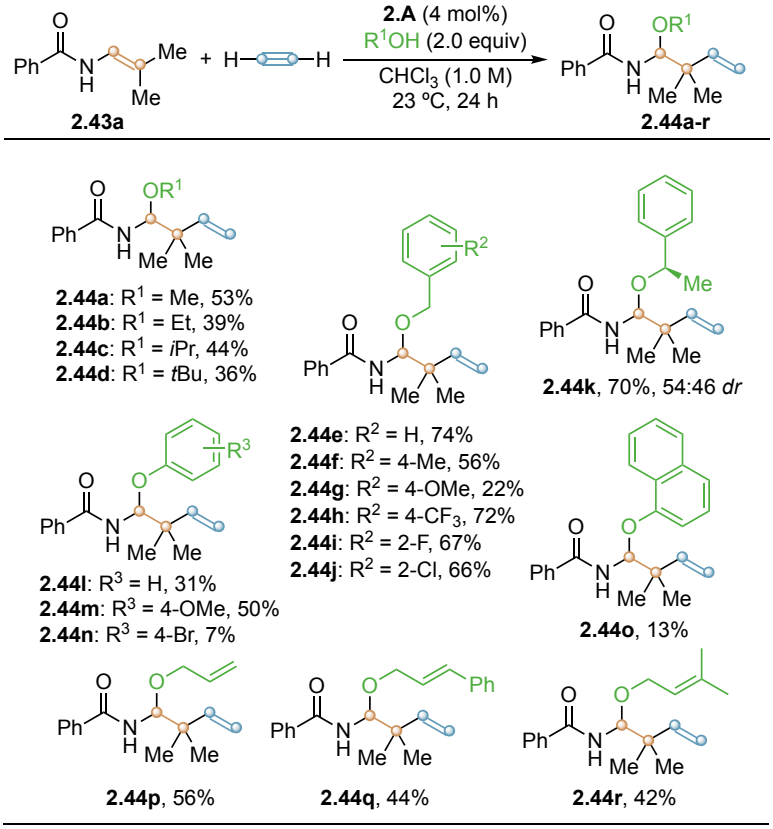
Entry	2.A (mol%)	Molarity (M)	MeOH (equiv)	Yield 2.44a (%)[a]
1	4	1.0	2	60
2	2	1.0	2	51
3	1	1.0	2	46
4	0.1	1.0	2	36
5	4	2.0	2	49
6	4	0.5	2	46
7	4	0.25	2	46
8	4	0.25	1	43

[a]Yield determined by ^{1}H NMR using 1,4-diacetylbenzene as internal standard.

Scope of the Fully Intermolecular Alkoxyvinylation with Acetylene Gas

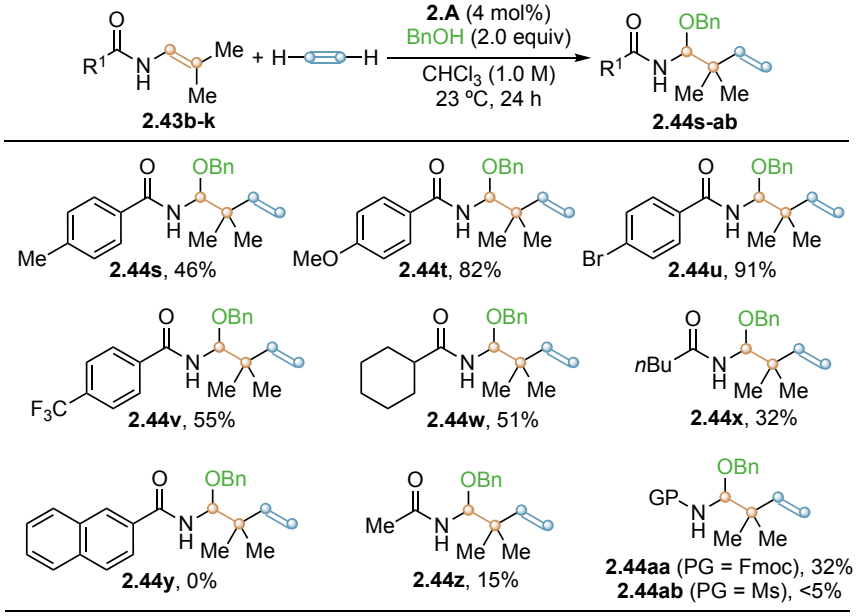
After having optimized the conditions for model substrate *N*-(2-methylprop-1-en-1-yl)benzamide (**2.43a**) we moved on to the evaluation of the scope of the reaction.

At the outset, we screened a variety of alcohols for the formation of the *β*-vinyl hemiaminal products **2.44** (Scheme 2.26). The reaction tolerated primary, secondary, and tertiary alcohols giving the products in moderate to good yields (**2.44a-d**). Moreover, benzylic alcohols bearing electron-withdrawing and neutral substituents performed well (**2.44e-f**, **h-k**) while the presence of a *p*-OMe group in the alcohols had a detrimental effect in the yield (**2.44g**). Phenol nucleophiles were also tested, and, unlike benzyl alcohols, the more electron rich alcohols gave the best yields (**2.44l-o**). Allylic alcohols were successfully employed giving the products **2.44p-r** in good yields despite having alkenes moieties that could keep reacting with acetylene and trigger undesired oligomerization processes.



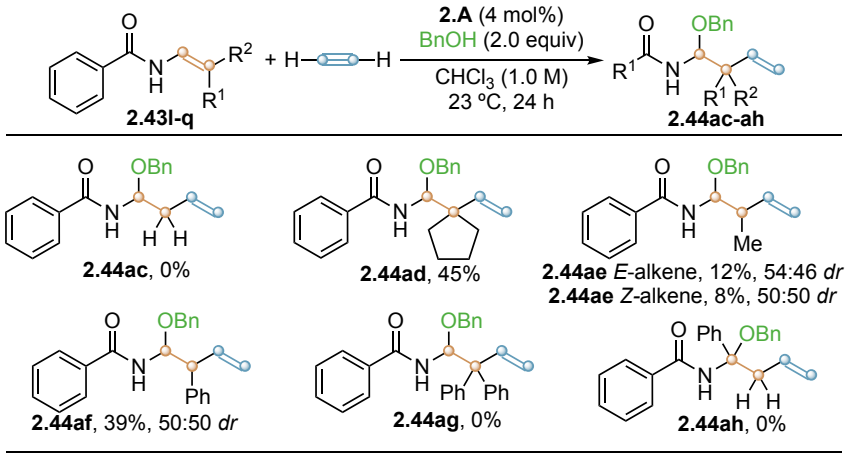
Scheme 2.26. Scope of alcohols for the gold(I)-catalyzed alkoxyvinylation of with acetylene gas.

When evaluating the scope of amides, we were delighted to find out that both electron-withdrawing and electron-donating substituents in the aryl ring were well tolerated (**2.44s-v**) whereas when naphthyl amide was employed, the reaction did not work (**2.44y**). Alkyl amides also worked but gave the *β*-vinyl hemiaminal products in diminished yield (**2.44w-x**, **z**). Different protected amides were tested but only Fmoc group afforded the product in moderate yield (**2.44aa**) while the presence of a methanesulfonyl group gave only traces of the product (**2.44ab**) (Scheme 2.27).



Scheme 2.27. Scope of amides for the gold(I)-catalyzed alkoxyvinylation of with acetylene gas.

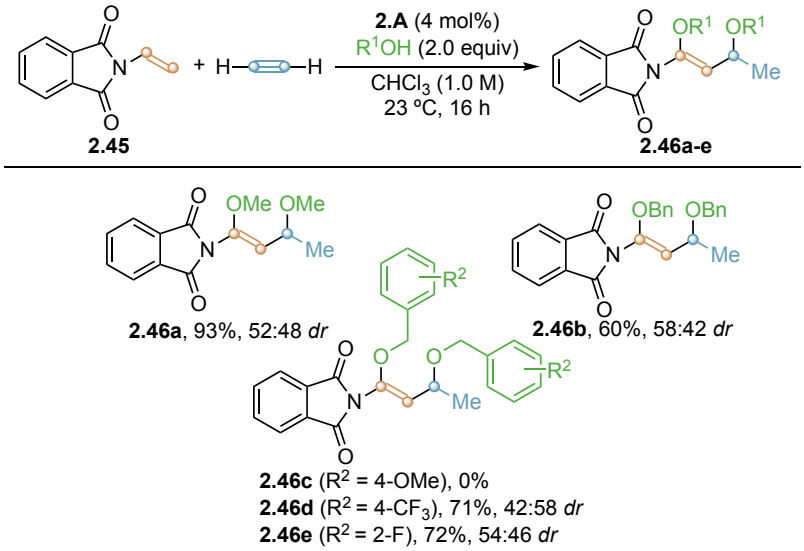
The reaction proved to be highly sensitive to the alkene moiety employed (Scheme 2.28). The modification of the alkene substituent for a cyclopentane ring afforded spirocyclic product **2.44ad** in moderate yield (45%). However, when substrates **2.43l** and **2.43q** with terminal alkenes were employed, only products of oligomerization could be detected (**2.44ac**, **ah**). Removal of one of the methyl groups of the alkene led to the formation of product **2.44ae** in poor yield whilst the use of cinammyl alkene led to the product in moderate yield (**2.44af**). Finally, the substitution of the methyl groups for phenyl ones inhibited completely the reaction (**2.44ag**).



Scheme 2.28. Scope of alkenes for the gold(I)-catalyzed alkoxyvinylation of with acetylene gas.

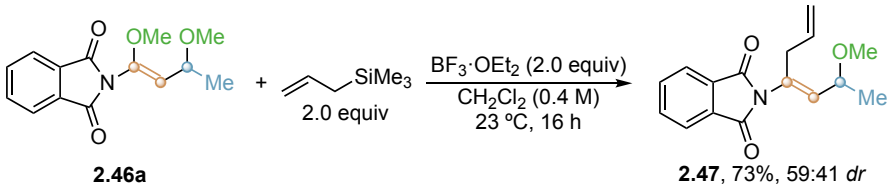
Gold(I)-Catalyzed Double Addition of Alcohols to *N*-Vinyl Phtalimide

Although terminal alkenes did not show any reactivity for the gold(I)-catalyzed reaction, when *N*-vinyl phtalimide **2.45** was employed, we were able to detect the *β*-vinyl hemiaminal **2.46** product but with the addition of two units of the alcohol (Scheme 2.29). In this case, stoichiometric methanol could be used to afford hemiaminals (**2.46a-b**, **d-e**) in good yields as a mixture of isomers. Surprisingly, the use of *p*-OMe benzyl alcohol as nucleophile led to no formation of the product **2.46c**.



Scheme 2.29. Gold(I)-catalyzed double addition of alcohols to *N*-vinyl phtalimide **2.45**.

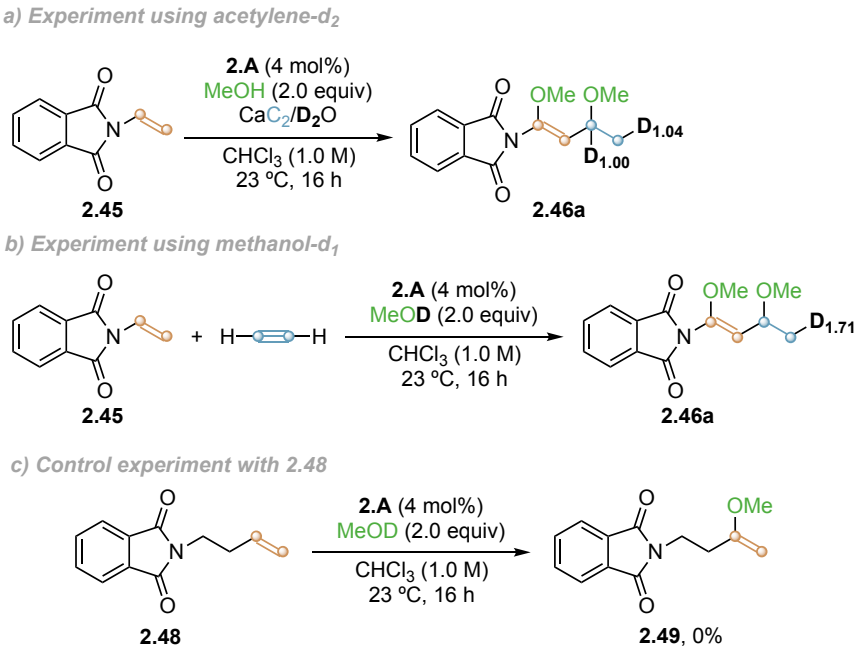
To highlight the applicability of the products, *β*-vinyl hemiaminal **2.46a** was activated by a Lewis acid in the presence of a nucleophile and yielded allylated product **2.47** in good yield (Scheme 2.30).



Scheme 2.30. Derivatization of **2.46a**.

Mechanistic Studies

Since we cannot provide a mechanism for the double addition of nucleophile reaction (Scheme 2.29), we decided to perform some mechanistic studies to gain more insights (Scheme 2.31). When acetylene-d_2 was formed *in situ* from CaC_2 and D_2O, no deuterium scrambling was observed with the expected deuterium incorporation in the two terminal carbons (Scheme 2.31a). Furthermore, when MeOD was employed only deuteration at the terminal carbon was detected (Scheme 2.31b). These experiments support a mechanism where the nucleophile attacks the intermediate cyclopropyl gold(I) carbene before the second addition takes place. However, when **2.48** was submitted to the reaction conditions, no addition of alcohol was observed (Scheme 2.31c).[26]

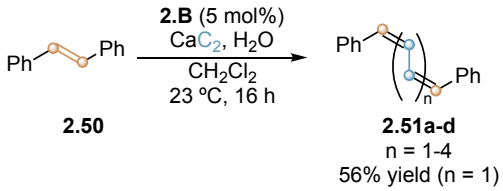


Scheme 2.31. Mechanistic Experiments.

26. Deeper mechanistic studies are currently being done in our lab.

Study on the Oligomerization Process: Quantification of the Oligomers

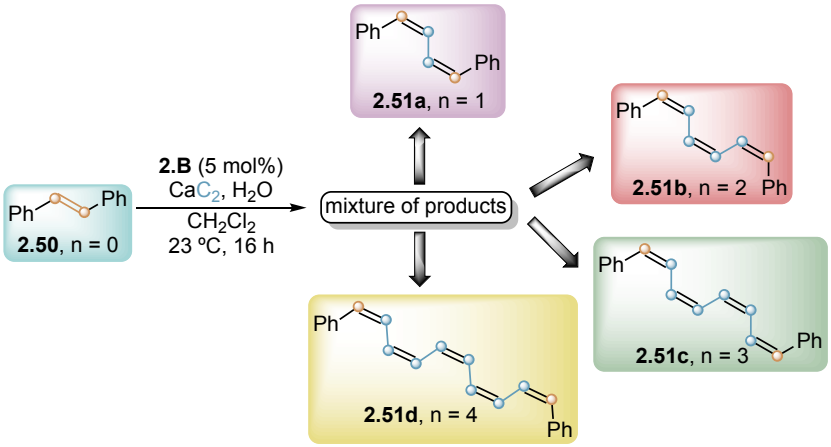
As has been mentioned previously in this Chapter, first attempts for a three component gold(I)-catalyzed alkoxyvinylation reaction faced problems of undesired alkene oligomerization. The presence of this side reaction has been reported in previous works from our group to justify the low yields obtained in some cases. In particular, in 2020 our group developed the gold(I)-catalyzed formation of (*Z,Z*)-1,3-dienes (**2.51a-d**) from the reaction of *trans*-stilbene (**2.50**) with acetylene gas.[11] In this reaction, the formation of oligomers (n = 1–4) through formal insertion of C_2 units was confirmed by MALDI-TOF MS analysis (Scheme 2.32).



Scheme 2.32. Synthesis of **2.51** and its oligomers by gold(I)-catalyzed reaction with acetylene gas.

Intrigued by these results, we focused our attention on the quantification of these oligomers by UHPLC-MS analysis.[27] To do so, our initial idea was to prepare calibration curves for the oligomers and then use these curves to quantify the amount of each oligomer in the reaction crudes.

The calibration curves for both n = 0 and n = 1 products were easily obtained since they are the starting *trans*-stilbene **2.50** and the main product of the gold catalysis **2.51a** respectively (Scheme 2.33). However, the rest of the oligomers were formed in such a small amount in the catalytic reaction that they could not be isolated from the crude. To prepare these calibration curves we had to synthetize independently each one of them.[28]



Scheme 2.33. Gold(I)-catalyzed synthesis of **2.51** and higher oligomers.

27. These analysis were carried out using an UHPLC-MS apparatus with an APPI source (detailed information is given in the experimental part of this Chapter).
28. Detailed experimental data on the synthesis of **2.51b**, **2.51c** and **2.51d** is provided in the experimental data of this Chapter.

Once all the oligomers were prepared and isolated, we were able to obtain their calibration curves by UHPLC-MS (Figure 2.4).

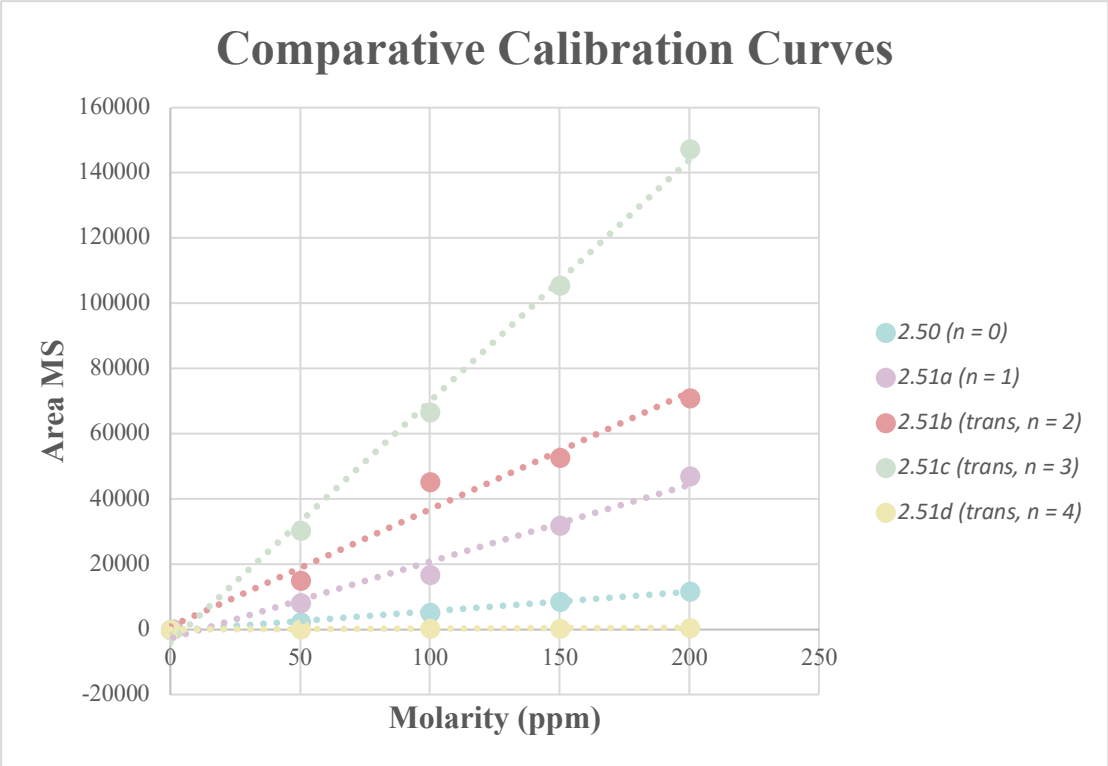
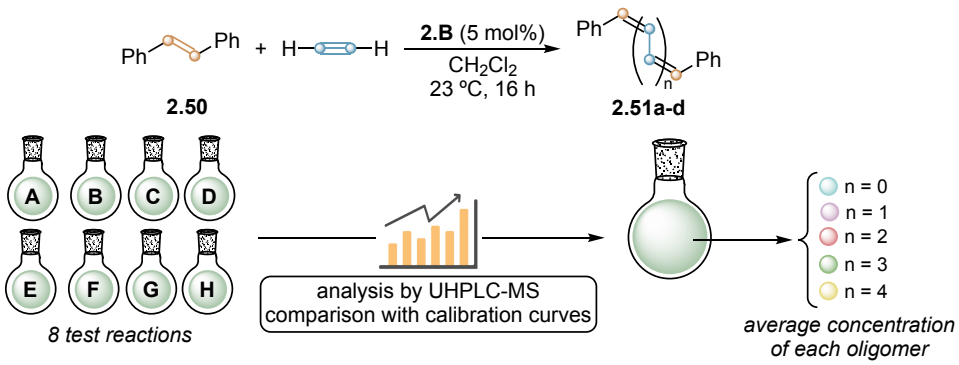


Figure 2.4. Calibration curves for the oligomers **2.51a-d**.

We were delighted to see that from oligomer n = 1 to n = 3 the area of the signals was higher in accordance with the increase of unsaturation. However, for oligomer n = 4 we observed a different pattern since, unexpectedly, the UV absorbance and MS signal for this oligomer was lower than the for the starting material (**2.50**) or the other oligomer (**2.51a-c**).

We use these curves to quantify each oligomers in 8 crudes (Scheme 2.34). However, the amount of each oligomer was considerably different for each one of the crude, even though they were run in the same experimental conditions. Giving these results, we can conclude that the concentration of oligomers is highly dependent on the reaction crude and changes unpredictably. Therefore, it is not possible to quantify the oligomerization or determine the concentration of the different products.

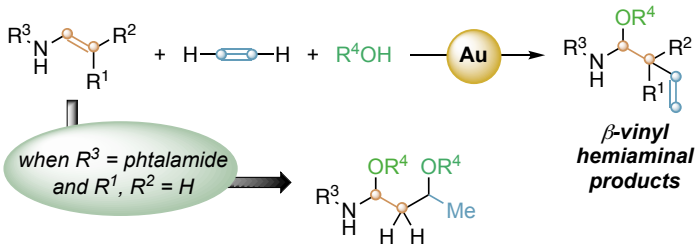


Scheme 2.34. Quantification method for the oligomers.

Conclusions

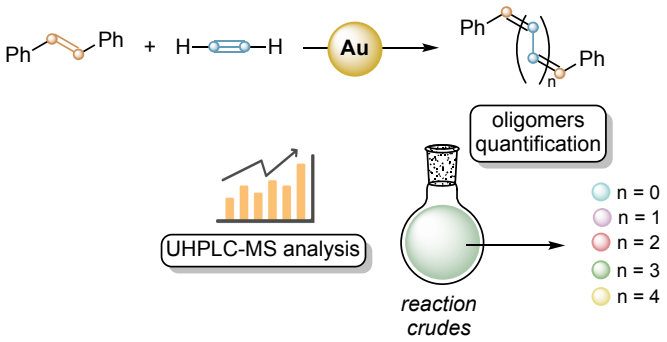
We have developed an unprecedented fully intermolecular gold(I)-catalyzed reaction between alkenes, alcohols and acetylene gas. We found *N*-vinyl amides to be suitable substrates to obtain *β*-vinyl hemiaminal products in good to excellent yield.

Surprisingly, we also found out that, when using *N*-vinyl phtalimide as substrate, two units of nucleophile were added. We carried out some control experiments to gain insights into the mechanism of the second addition, but additional tests are currently ongoing in our laboratory.



Scheme 2.35. Synthesis of *β*-vinyl hemiaminal products through gold(I)-catalyzed reaction with acetylene gas.

We also report the gold(I)-oligomerization reaction of alkenes by the addition of 2–4 units of acetylene.



Scheme 2.36. Quantification of the oligomer by UHPLC-MS analysis.

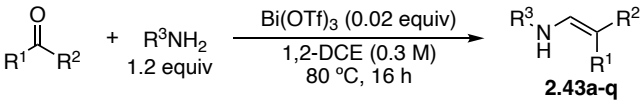
Experimental Section

General Methods

The calibration curves of the oligomers were prepared using UHPLC/MSD Agilent InfitiyLab 1290 series with G6135B MSD XT single quadrupole mass analyzer and G1971C APPI ionization source. The rest of the general information has been provided in the experimental section of Chapter I.

Synthetic Procedures and Analytical Data

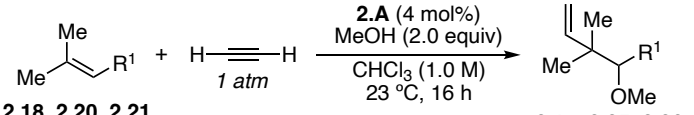
General procedure A: synthesis of N-vinyl amides



2.43a-q

A round-bottom flask was charged with the corresponding aldehyde (1.0 equiv), amine (1.2 equiv) and bismuth(III) trifluoromethanesulfonate (0.02 equiv) in HPLC grade 1,2-dichloroethane (0.25 M). The reaction mixture was stirred at 80 ºC in a metallic heating block for 16 h and filtered through Celite. The crude product was purified by flash column chromatography (SiO_2, cyclohexane/EtOAc) to afford *N*-vinyl amides **2.43a-q**.

General procedure B: Gold(I)-catalyzed intermolecular reactions of alkenes with acetylene gas

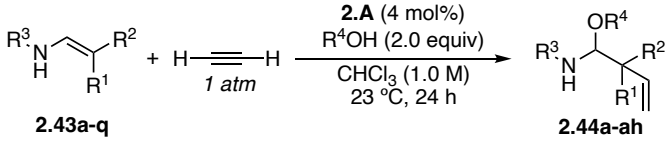


2.18, 2.20, 2.21, 2.23, 2.24, 2.27, 2.29, 2.30

2.19, 2.25, 2.26, 2.28, 2.31,2.32

A reaction tube was charged with the corresponding alkene (1.0 equiv), MeOH (2.0 equiv) and **2.A** (4 mol%) in HPLC grade $CHCl_3$ (1.0 M). The tube was introduced in a HEL reactor under 1 atm of acetylene gas. The reaction mixture was stirred at 23 ºC for 16 h and after emptying the remaining gas, the reaction was quenched by the addition of 3 drops of Et_3N and concentrated under reduced pressure. The crude product was purified as described in the individual procedures affording the corresponding alkoxylated products.

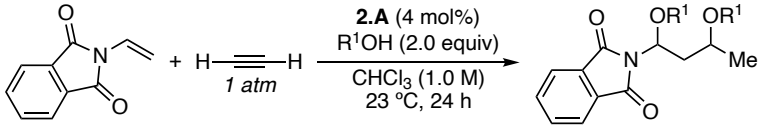
General procedure C: Gold(I)-catalyzed synthesis of β-vinyl hemiaminals



2.43a-q **2.44a-ah**

A reaction tube was charged with *N*-vinyl amides **2.43** (1.0 equiv), the corresponding alcohol (2.0 equiv) and **2.A** (4 mol%) in HPLC grade $CHCl_3$ (1.0 M). The tube was introduced in a HEL reactor under 1 atm of acetylene gas. The reaction mixture was stirred at 23 ºC for 24 h and after emptying the remaining gas, the reaction was quenched by the addition of 3 drops of Et_3N and concentrated under reduced pressure. The crude product was purified as described in the individual procedures affording the *β*-vinyl hemiaminal products **2.44a-ah**.

General procedure D: Gold(I)-catalyzed synthesis of hemiaminals from N-vinyl phtalimide



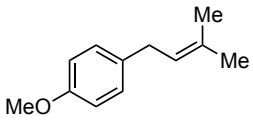
2.45 **2.46a-e**

A reaction tube was charged with *N*-vinyl phtalimide **2.45** (1.0 equiv), the corresponding alcohol (2.0 equiv) and **2.A** (4 mol%) in HPLC grade $CHCl_3$ (1.0 M). The tube was introduced in a HEL reactor under 1 atm of acetylene gas. The reaction mixture was stirred at 23 ºC for 16 h and after emptying the remaining gas, the reaction was quenched by the addition of 3 drops of NEt_3 and concentrated under reduced pressure. The crude product was purified as described in the individual procedures yielding the corresponding hemiaminal products **2.46a-e**.

Synthesis of Substrates for the Intermolecular Alkoxyvinylation of Alkenes

1-Methoxy-4-(3-methylbut-2-en-1-yl)benzene (2.18)

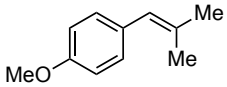
A 25 mL round-bottom flask was charged with 1-bromo-3-methylbut-2-ene (390 μL, 500 mg, 3.36 mmol, 1.0 equiv), Cs_2CO_3 (1.64 g, 5.03 mmol, 1.5 equiv) and (4-methoxyphenyl)boronic acid (663 mg, 4.36 mmol, 1.3 equiv) in a 10:1 mixture of CH_2Cl_2 (7.6 mL, 0.4 M) and H_2O (0.8 mL, 0.4 M). The reaction mixture was stirred at 60 ºC in a metallic heating block for 18 h and, upon completion, it was treated with aq. 1 M HCl (10 mL) and extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were washed with brine (10 mL), dried over anhydrous $MgSO_4$, filtered and concentrated under vacuo. The crude was purified by flash column chromatography (SiO_2, cyclohexane/EtOAc 100:0, *v/v*) to afford the product **2.18** as a colorless oil (443 mg, 2.51 mmol, 75% yield).



^{1}H NMR (400 MHz, $CDCl_3$) δ 7.13–7.08 (m, 2H), 6.87–6.80 (m, 2H), 5.32 (tdt, *J* = 7.4, 2.9, 1.5 Hz, 1H), 3.79 (s, 3H), 3.29 (d, *J* = 7.4 Hz, 2H), 1.75 (q, *J* = 1.3 Hz, 3H), 1.74–1.69 (m, 3H). The characterization data matches those reported in the literature.[29]

1-Methoxy-4-(2-methylprop-1-en-1-yl)benzene (2.20)

To a suspension of isopropyltriphenylphosphonium iodide (572 mg, 1.32 mmol, 1.2 equiv) in anhydrous THF (2.0 mL, 0.5 M) was added dropwise *n*BuLi (573 μL, 2.5 molar, 1.43 mmol, 1.3 equiv) at 0 ºC under argon atmosphere. The mixture was stirred 3 h at 0 ºC followed by the addition of *p*-anisaldehdye (134 μL, 150 mg, 1.10 mmol, 1.0 equiv). The solution was stirred for 3 h at 0 ºC and then slowly warmed to 23 ºC. The reaction was quenched with sat. aq. NH_4Cl (2.0 mL) and extracted with CH_2Cl_2 (3 x 4 mL). The combined organic layers were washed with brine (5 mL), dried over anhydrous $MgSO_4$, filtered and concentrated under vacuo. The crude was purified by flash column chromatography (SiO_2, cyclohexane/EtOAc 100:0, *v/v*) to afford the product **2.20** as a colorless oil (75 mg, 0.46 mmol, 42% yield).

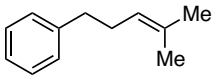


^{1}H NMR (500 MHz, $CDCl_3$) δ 7.22–7.16 (m, 2H), 6.92–6.86 (m, 2H), 6.24 (t, *J* = 1.7 Hz, 1H), 3.82 (s, 3H), 1.91 (d, *J* = 1.5 Hz, 3H), 1.87 (d, *J* = 1.4 Hz, 3H). The characterization data matches those reported in the literature.[30]

29. Gerbino, D. C.; Mandolesi, S. D.; Schmalz, H.-G.; Podestá, J. C. *Eur. J. Org. Chem.* **2009**, *23*, 3964–3972.
30. Albitz, K.; Csókás, D.; Dobi, Z.; Pápai, I.; Soós, T. *Angew. Chem. Int. Ed.* **2023**, *62*, e202216879.

(4-Methylpent-3-en-1-yl)benzene (2.21)

To a suspension of isopropyltriphenylphosphonium iodide (572 mg, 1.32 mmol, 1.2 equiv) in anhydrous

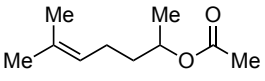


THF (2.0 mL, 0.5 M) was added dropwise *n*BuLi (573 µL, 2.5 M, 1.43 mmol, 1.3 equiv) at 0 ºC under argon atmosphere. The mixture was stirred 3 h at 0 ºC followed by the addition of 3-phenylpropionaldehyde (134 µL, 150 mg, 1.10 mmol, 1.0 equiv). The solution was stirred for 3 h at 0 ºC and then slowly warmed to room temperature. The reaction was quenched with sat. aq. NH_4Cl (2 mL) and extracted with CH_2Cl_2 (3 x 4 mL). The combined organic layers were washed with brine (5 mL), dried over anhydrous $MgSO_4$, filtered and concentrated under vacuo. The crude was purified by flash column chromatography (SiO_2, cyclohexane/EtOAc 100:0, *v/v*) to afford the product **2.21** as a colorless oil (86 mg, 0.52 mmol, 47% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40–7.38 (m, 1H), 7.33 (td, *J* = 7.3, 1.4 Hz, 2H), 7.25–7.22 (m, 2H), 5.25 (tp, *J* = 7.1, 1.4 Hz, 1H), 2.70 (dd, *J* = 9.0, 6.8 Hz, 2H), 2.42–2.33 (m, 2H), 1.76 (q, *J* = 1.3 Hz, 3H), 1.64 (d, *J* = 1.4 Hz, 3H). The characterization data matches those reported in the literature.[31]

6-Methylhept-5-en-2-yl acetate (2.23)

Ac_2O (147 µL, 169 mg, 1.56 mmol, 1.0 equiv) and 4-dimethylaminopyridine (10 mg, 0.08 mmol,

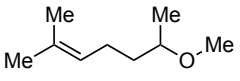


0.05 equiv) were added to a solution of 6-methylhept-5-en-2-ol **2.22** (237 µL, 300 mg, 1.56 mmol, 1.0 equiv) in CH_2Cl_2 (3.1 mL, 0.5 M) and the reaction mixture was stirred at 23 ºC for 16 h. Upon completion, the mixture was poured in ice-cold water (5 mL) and extracted with CH_2Cl_2 (3 x 5 mL). The combined organic layers were washed with brine (5 mL), dried over anhydrous $MgSO_4$, filtered and concentrated under vacuo. The crude was purified by flash column chromatography (SiO_2, pentane/Et_2O 100:0 to 90:10, *v/v*) to afford the product **2.23** as a colorless oil (192 mg, 1.13 mmol, 72% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.07 (ddq, *J* = 8.6, 7.3, 1.4 Hz, 1H), 4.98–4.79 (m, 1H), 2.02 (d, *J* = 1.0 Hz, 3H), 2.01–1.96 (m, 1H), 1.67 (q, *J* = 1.2 Hz, 3H), 1.66–1.59 (m, 2H), 1.58 (d, *J* = 1.4 Hz, 3H), 1.53–1.43 (m, 1H), 1.20 (d, *J* = 6.3 Hz, 3H). The characterization data matches those reported in the literature.[32]

6-Methoxy-2-methylhept-2-ene (2.24)

6-Methylhept-5-en-2-ol **2.22** (456 µL, 385 mg, 3.00 mmol, 1.0 equiv) was added dropwise to a



suspension of NaH (552 mg, 60% Wt, 13.8 mmol, 4.6 equiv) in anhydrous THF (9.4 mL, 0.3 M) at 0 ºC under argon atmosphere. After 90 min, MeI (1.2 mL, 2.64 g, 18.6 mmol, 6.2 equiv) was added dropwise during 30 min at 0 ºC and the mixture was stirred for 4 h at 0 ºC. MeOH (5 mL) and EtOH (5 mL) were added, followed by HCl 0.1 M until pH 6 was

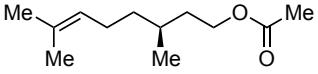
31. Mordini, A.; Peruzzi, D.; Russo, F.; Valacchi, M.; Reginato, G.; Brandi, A. *Tetrahedron* **2005**, *61*, 3349–3360.
32. Steinreiber, A.; Stadler, A.; Mayer, S. F.; Faber, K.; Kappe, C. O. *Tetrahedron Lett.* **2001**, *42*, 6283–6286.

reached and sat. aq. $NaHSO_3$ (10 mL). The crude was extracted with Et_2O (3 x 10 mL) and the combined organic layers were washed with brine (15 mL), dried over anhydrous $MgSO_4$, filtered and concentrated under vacuo. The crude was purified by flash column chromatography (SiO_2, pentane/Et_2O 100:0 to 90:10, *v/v*) to afford the product **2.24** as a colorless oil (164 mg, 1.15 mmol, 38% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.10 (tp, *J* = 7.2, 1.5 Hz, 1H), 3.31 (s, 3H), 3.29–3.23 (m, 1H), 2.03 (q, *J* = 7.6 Hz, 2H), 1.69 (q, *J* = 1.3 Hz, 3H), 1.61 (d, *J* = 1.4 Hz, 3H), 1.58–1.52 (m, 1H), 1.41–1.34 (m, 1H), 1.13 (d, *J* = 6.1 Hz, 3H). The characterization data matches those reported in the literature.[33]

(*S*)-3,7-Dimethyloct-6-en-1-yl acetate (2.27)

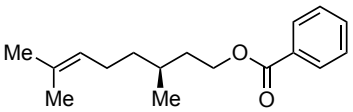
A solution of (*S*)-3,7-dimethyl-6-octen-1-ol (292 µL, 250 mg, 1.60 mmol, 1.0 equiv) in anhydrous CH_2Cl_2 (8.0 mL, 0.2 M) was cooled to 0 ºC followed by the addition of pyridine (518 µL, 506 mg, 6.40 mmol, 4.0 equiv), 4-dimethylaminopyridine (20 mg, 0.16 mmol, 0.1 equiv) and Ac_2O (453 µL, 490 mg, 4.80 mmol, 3.0 equiv). After 45 min stirring at 23 ºC, the reaction mixture was quenched by the addition of H_2O (6.0 mL) and extracted with CH_2Cl_2 (3 x 8 mL). The combined organic layers were washed with brine (10 mL), dried over anhydrous $MgSO_4$, filtered and concentrated under vacuo. The crude was purified by flash column chromatography (SiO_2, cyclohexane/EtOAc 100:0, *v/v*) to afford the product **2.27** as a colorless oil (296 mg, 1.49 mmol, 93% yield).



^{1}H NMR (500 MHz, $CDCl_3$) δ 5.08 (tp, *J* = 7.1, 1.4 Hz, 1H), 4.16–4.03 (m, 2H), 2.03 (s, 3H), 2.011.89 (m, 2H), 1.68 (t, *J* = 1.4 Hz, 3H), 1.66–1.62 (m, 1H), 1.60 (d, *J* = 1.4 Hz, 3H), 1.53 (dtt, *J* = 12.0, 6.6, 1.3 Hz, 1H), 1.47–1.39 (m, 1H), 1.34 (dddd, *J* = 13.3, 9.5, 6.4, 5.5 Hz, 1H), 1.18 (dddd, *J* = 13.5, 9.4, 7.7, 6.0 Hz, 1H), 0.91 (d, *J* = 6.6 Hz, 3H). The characterization data matches those reported in the literature.[34]

(*S*)-3,7-Dimethyloct-6-en-1-yl benzoate (2.29)

To a solution of (*S*)-3,7-dimethyl-6-octen-1-ol (729 µL, 625 mg, 4.00 mmol, 1.0 equiv) and Et_3N (781 µL, 567 mg, 5.60 mmol, 1.4 equiv) in anhydrous Et_2O (6.0 mL, 0.7 M) was slowly added benzoyl chloride (602 µL, 731 mg, 5.20 mmol, 1.3 equiv) at 0 ºC under argon atmosphere and the mixture was stirred at 23 ºC for 16 h. Then, it was quenched by the addition of H_2O (6 mL) and extracted with Et_2O (3 x 8 mL). The combined organic layers were washed with brine (10 mL), dried over anhydrous $MgSO_4$, filtered and concentrated under vacuo. The crude was purified by flash column chromatography



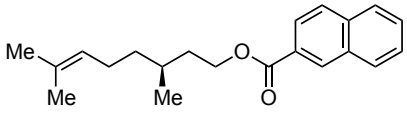
33. Hedenström, E.; Wallin, E. A.; Andersson, J.; Bång, J.; Wang, H.-L.; Löfstedt, C.; Brattström, O.; Baquet, P. *J. Chem. Ecol.* **2015**, *41*, 44–51.
34. Chakraborti, A. K.; Sharma, L.; Gulhane, R. *Tetrahedron* **2003**, *59*, 7661–7668.

(SiO_2, cyclohexane/EtOAc 100:0 to 90:10, *v/v*) to afford the product **2.29** as a colorless oil (746 mg, 2.87 mmol, 72% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.07–8.01 (m, 2H), 7.55 (ddt, *J* = 7.9, 6.9, 1.3 Hz, 1H), 7.44 (ddt, *J* = 7.9, 6.5, 1.1 Hz, 2H), 5.10 (ddq, *J* = 8.5, 5.7, 1.4 Hz, 1H), 4.41–4.31 (m, 2H), 2.09–1.93 (m, 2H), 1.82 (dtd, *J* = 13.5, 7.1, 5.1 Hz, 1H), 1.68 (q, *J* = 1.3 Hz, 3H), 1.66–1.63 (m, 1H), 1.60 (d, *J* = 1.2 Hz, 3H), 1.59–1.54 (m, 1H), 1.41 (dddd, *J* = 13.4, 9.4, 6.5, 5.5 Hz, 1H), 1.24 (dddd, *J* = 13.5, 9.3, 7.6, 6.0 Hz, 1H), 0.98 (d, *J* = 6.6 Hz, 3H). The characterization data matches those reported in the literature.[35]

(*S*)-3,7-Dimethyloct-6-en-1-yl 2-naphthoate (2.30)

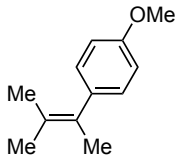
To a solution of (*S*)-3,7-dimethyl-6-octen-1-ol (912 μL, 781 mg, 5.00 mmol, 1.0 equiv) and Et_3N (976 μL, 708 mg, 7.00 mmol, 1.4 equiv) in anhydrous Et_2O (7.5 mL, 0.7 M) was slowly added 2-naphthoyl chloride (1.24 g, 6.50 mmol, 1.3 equiv) at 0 ºC under argon atmosphere and the mixture was stirred at 23 ºC for 16 h. Then, it was quenched by the addition of H_2O (6 mL) and extracted with Et_2O (3 x 8 mL). The combined organic layers were washed with brine (8 mL), dried over anhydrous $MgSO_4$, filtered and concentrated under vacuo. The crude was purified by flash column chromatography (SiO_2, cyclohexane/EtOAc 100:0 to 90:10, *v/v*) to afford the product **2.30** as a colorless oil (1.52 g, 4.90 mmol, 98% yield).



^{1}H NMR (500 MHz, $CDCl_3$) δ 8.64–8.58 (m, 1H), 8.07 (dd, *J* = 8.6, 1.7 Hz, 1H), 7.96 (dd, *J* = 7.9, 1.2 Hz, 1H), 7.88 (dd, *J* = 8.3, 0.9 Hz, 2H), 7.63–7.51 (m, 2H), 5.13 (tp, *J* = 7.1, 1.4 Hz, 1H), 4.50–4.37 (m, 2H), 2.12–1.96 (m, 2H), 1.94–1.83 (m, 1H), 1.69 (t, *J* = 1.4 Hz, 3H), 1.64 (s, 1H), 1.62 (d, *J* = 1.3 Hz, 3H), 1.44 (dddd, *J* = 10.6, 9.5, 5.3, 3.2 Hz, 1H), 1.35–1.22 (m, 2H), 1.01 (d, *J* = 6.5 Hz, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 167.0, 135.6, 132.7, 131.5, 131.1, 129.5, 128.2, 127.9, 126.7, 125.4, 124.7, 63.8, 37.2, 35.7, 29.8, 25.8, 25.6, 22.5, 19.7, 17.8, 14.2.

1-Methoxy-4-(3-methylbut-2-en-2-yl)benzene (2.37)

Bromotrimethylethylene (116 μL, 149 mg, 1.00 mol, 1.0 equiv) and $Pd(PPh_3)_4$ (58 mg, 0.05 mmol, 0.05 equiv) were dissolved in anhydrous 1,2-dimethoxyethane (20.0 mL, 0.05 M) under argon atmosphere and stirred at 23 ºC for 20 min. Then, Na_2CO_3 (106 mg, 1.00 mmol, 1.0 equiv), H_2O (5.0 mL, 1.00 mmol, 1.0 equiv) and 4-methoxybenzene boronic acid (319 mg, 2.10 mmol, 2.1 equiv) were added and the reaction mixture was heated at reflux (85 ºC) in a metallic heating block for 18 h. The reaction was cooled to 23 ºC, quenched with H_2O (15 mL) and extracted with Et_2O (3 x 10 mL). The combined organic layers were washed with brine (20 mL), dried over anhydrous $MgSO_4$, filtered and concentrated under vacuo. The crude was purified



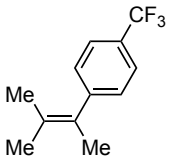
35. Hu, M.-Y.; He, Q.; Fan, S.-J.; Wang, Z.-C.; Liu, L.-Y.; Mu, Y.-J.; Peng, Q.; Zhu, S.-F. *Nat. Commun.* **2018**, *9*, 221.

by flash column chromatography (SiO_2, cyclohexane/EtOAc 100:0 to 80:20, *v/v*) to afford the product **2.37** as a white solid (149 mg, 0.85 mmol, 85% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.09–7.03 (m, 2H), 6.88–6.83 (m, 2H), 3.81 (s, 3H), 1.97–1.93 (m, 3H), 1.80 (d, *J* = 1.2 Hz, 3H), 1.60 (q, *J* = 1.5 Hz, 3H). The characterization data matches those reported in the literature.[36]

1-(3-Methylbut-2-en-2-yl)-4-(trifluoromethyl)benzene (2.38)

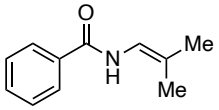
Bromotrimethylethylene (116 μL, 149 mg, 1.00 mol, 1.0 equiv) and $Pd(PPh_3)_4$ (58 mg, 0.05 mmol, 0.05 equiv) were dissolved in anhydrous 1,2-dimethoxyethane (20.0 mL, 0.05 M) under argon atmosphere and stirred at 23 ºC for 20 min. Then, Na_2CO_3 (106 mg, 1.00 mmol, 1.0 equiv), H_2O (5.0 mL, 1.00 mmol, 1.0 equiv) and (4-(trifluoromethyl)phenyl) boronic acid (399 mg, 2.10 mmol, 2.1 equiv) were added and the reaction mixture was heated at reflux (85 ºC) in a metallic heating block for 18 h. The reaction was cooled to 23 ºC, quenched with H_2O (10 mL) and extracted with Et_2O (3 x 10 mL). The combined organic layers were washed with brine (20 mL), dried over anhydrous $MgSO_4$, filtered and concentrated under vacuo. The crude was purified by flash column chromatography (SiO_2, cyclohexane/EtOAc 100:0 to 80:20, *v/v*) to afford the product **2.38** as a white solid (175 mg, 0.82 mmol, 82% yield).



^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61–7.52 (m, 2H), 7.23 (dp, *J* = 7.4, 0.9 Hz, 2H), 2.00–1.93 (m, 3H), 1.83 (d, *J* = 1.2 Hz, 3H), 1.58 (q, *J* = 1.5 Hz, 3H). The characterization data matches those reported in the literature.[37]

***N*-(2-Methylprop-1-en-1-yl)benzamide (2.43a)**

Prepared following the general procedure A using isobutyraldehyde (91 μL, 72 mg, 1.00 mmol, 1.0 equiv), benzamide (145 mg, 1.20 mmol, 1.2 equiv) and bismuth(III) trifluoromethanesulfonate (13.1 mg, 0.02 mmol, 0.02 equiv) in 1,2-dichloroethane (4.0 mL, 0.3 M) at 80 ºC for 16 h. The crude product was purified by flash column chromatography (SiO_2, cyclohexane/EtOAc 100:0 to 70:30, *v/v*) and the product **2.43a** was obtained as a white solid (70 mg, 0.40 mmol, 40% yield).

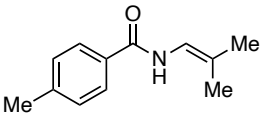


^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82–7.76 (m, 2H), 7.55–7.48 (m, 1H), 7.45 (ddt, *J* = 8.3, 6.5, 1.3 Hz, 2H), 6.74 (dp, *J* = 10.3, 1.5 Hz, 1H), 1.77 (d, *J* = 1.5 Hz, 3H), 1.71 (d, *J* = 1.5 Hz, 3H). The characterization data matches those reported in the literature.[38]

36. Hornillos, V.; Giannerini, M.; Vila, C.; Fañanás-Mastral, M.; Feringa, B. L. *Chem. Sci.* **2015**, *6*, 1394–1398.
37. Wise, D. E.; Gogarnoiu, E. S.; Duke, A. D.; Paolillo, J. M.; Vacala, T. L.; Hussain, W. A.; Parasram, M. *J. Am. Chem. Soc.* **2022**, *144*, 15437–15442.
38. Schneider, A. E.; Manolikakes, G. *J. Org. Chem.* **2015**, *80*, 6193–6212.

4-Methyl-*N*-(2-methylprop-1-en-1-yl)benzamide (2.43b)

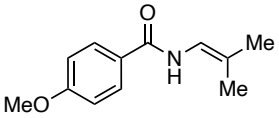
Prepared following the general procedure A using isobutyraldehyde (365 μL, 288 mg, 4.00 mmol, 1.0 equiv), 4-methylbenzamide (649 mg, 1.20 mmol, 1.2 equiv) and bismuth(III) trifluoromethanesulfonate (53 mg, 0.08 mmol, 0.02 equiv) in 1,2-dichloroethane (16.0 mL, 0.3 M) at 80 ºC for 16 h. The crude product was purified by flash column chromatography (SiO_2, cyclohexane/EtOAc 100:0 to 80:20, *v/v*) and the product **2.43b** was obtained as a white solid (249 mg, 1.32 mmol, 33% yield).



^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75–7.66 (m, 2H), 7.28–7.24 (m, 2H), 6.75 (dp, *J* = 10.3, 1.5 Hz, 1H), 2.41 (s, 3H), 1.79–1.76 (m, 3H), 1.71 (dd, *J* = 1.4, 0.6 Hz, 3H). The characterization data matches those reported in the literature.[39]

4-Methoxy-*N*-(2-methylprop-1-en-1-yl)benzamide (2.43c)

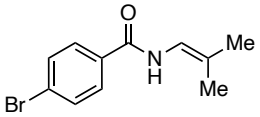
Prepared following the general procedure A using isobutyraldehyde (365 μL, 288 mg, 4.00 mmol, 1.0 equiv), 4-methoxybenzamide (726 mg, 4.80 mmol, 1.2 equiv) and bismuth(III) trifluoromethanesulfonate (53 mg, 0.08 mmol, 0.02 equiv) in 1,2-dichloroethane (16.0 mL, 0.3 M) at 80 ºC for 16 h. The crude product was purified by flash column chromatography (SiO_2, cyclohexane/EtOAc 100:0 to 80:20, *v/v*) and the product **2.43c** was obtained as a white solid (203 mg, 0.99 mmol, 25% yield).



M.p. 83–86 ºC. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.76–7.71 (m, 2H), 7.50 (d, *J* = 10.2 Hz, 1H), 6.91–6.86 (m, 2H), 6.68 (dp, *J* = 10.2, 1.5 Hz, 1H), 3.80 (s, 3H), 1.75–1.71 (m, 3H), 1.68 (dd, *J* = 1.4, 0.7 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 163.7, 162.5, 128.9, 126.6, 117.6, 115.7, 114.0, 55.6, 22.7, 16.7. **HRMS** (ESI +) calculated for $C_{12}H_{15}NNaO_2$ $[M+Na]^+$: 228.0995; found: 228.1002.

4-Bromo-*N*-(2-methylprop-1-en-1-yl)benzamide (2.43d)

Prepared following the general procedure A using isobutyraldehyde (155 μL, 123 mg, 1.70 mmol, 1.0 equiv), 4-bromobenzamide (408 mg, 2.04 mmol, 1.2 equiv) and bismuth(III) trifluoromethanesulfonate (22 mg, 0.03 mmol, 0.02 equiv) in 1,2-dichloroethane (6.8 mL, 0.3 M) at 80 ºC for 16 h. The crude product was purified by flash column chromatography (SiO_2, cyclohexane/EtOAc 100:0 to 80:20, *v/v*) and the product **2.43d** was obtained as a white sticky solid (57 mg, 0.22 mmol, 13% yield).

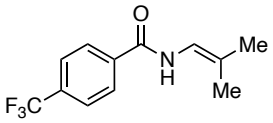


^{1}H NMR (300 MHz, $CDCl_3$) δ 7.70–7.62 (m, 2H), 7.61–7.53 (m, 2H), 7.45 (d, *J* = 9.5 Hz, 1H), 6.69 (dp, *J* = 10.2, 1.5 Hz, 1H), 1.76 (dd, *J* = 1.5, 0.6 Hz, 3H), 1.71 (dd, *J* = 1.5, 0.6 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 163.2, 133.2, 132.1, 128.7, 126.6, 117.3, 117.0, 22.7, 16.8. **HRMS** (ESI +) calculated for $C_{11}H_{13}BrNO$ $[M+H]^+$: 254.0175; found: 254.0178.

39. Wang, L.; Liu, C.; Bai, R.; Pan, Y.; Lei, A. *Chem. Commun.* **2013**, *49*, 7923–7925.

***N*-(2-Methylprop-1-en-1-yl)-4-(trifluoromethyl)benzamide (2.43e)**

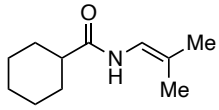
Prepared following the general procedure A using isobutyraldehyde (319 μL, 252 mg, 3.50 mmol, 1.0 equiv), 4-(trifluoromethyl)benzamide (794 mg, 1.20 mmol, 1.2 equiv) and bismuth(III) trifluoromethanesulfonate (46 mg, 0.07 mmol, 0.02 equiv) in 1,2-dichloroethane (14.0 mL, 0.3 M) at 80 ºC for 16 h. The crude product was purified by flash column chromatography (SiO_2, cyclohexane/EtOAc 100:0 to 80:20, *v/v*) and the product **2.43e** was obtained as a white solid (164 mg, 0.67 mmol, 19% yield).



M.p. 125–128 ºC.**^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.90 (d, *J* = 8.1 Hz, 2H), 7.73 (d, *J* = 8.2 Hz, 2H), 7.42 (d, *J* = 10.3 Hz, 1H), 6.78–6.70 (m, 1H), 1.79 (d, *J* = 1.5 Hz, 3H), 1.73 (d, *J* = 3.0 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 163.0, 137.7, 133.7 (q, $J_{C–F}$ = 32.8 Hz), 127.6, 125.9 (q, $J_{C–F}$ = 3.8 Hz), 125.1 (q, $J_{C–F}$ = 272.8 Hz), 117.6, 117.2, 22.7, 16.8. **^{19}F NMR** (376 MHz, $CDCl_3$) δ −63.1. **HRMS** (ESI +) calculated for $C_{12}H_{13}F_3NO$ $[M+H]^+$: 244.0944; found: 244.0951.

***N*-(2-Methylprop-1-en-1-yl)cyclohexanecarboxamide (2.43f)**

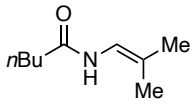
Prepared following the general procedure A using isobutyraldehyde (256 μL, 202 mg, 2.80 mmol, 1.0 equiv), cyclohexanecarboxamide (427 mg, 3.36 mmol, 1.2 equiv) and bismuth(III) trifluoromethanesulfonate (37 mg, 0.06 mmol, 0.02 equiv) in 1,2-dichloroethane (11.2 mL ,0.3 M) at 80 ºC for 16 h. The crude product was purified by flash column chromatography (SiO_2, cyclohexane/EtOAc 100:0 to 60:40, *v/v*) and the product **2.43f** was obtained as a colorless oil (67 mg, 0.37 mmol, 13% yield).



^{1}H NMR (400 MHz, $CDCl_3$) δ 6.87 (s, 1H), 6.50 (ddq, *J* = 10.3, 2.8, 1.5 Hz, 1H), 2.12 (tt, *J* = 11.8, 3.5 Hz, 1H), 1.91–1.75 (m, 5H), 1.67 (s, 3H), 1.64–1.59 (m, 3H), 1.46 (td, *J* = 12.1, 3.3 Hz, 2H), 1.30–1.19 (m, 3H). The characterization data matches those reported in the literature.[40]

***N*-(2-Methylprop-1-en-1-yl)pentanamide (2.43g)**

Prepared following the general procedure A using isobutyraldehyde (913 μL, 721 mg, 10.0 mmol, 1.0 equiv), pentanamide (1.21 g, 12.0 mmol, 1.2 equiv) and bismuth(III) trifluoromethanesulfonate (131 mg, 0.20 mmol, 0.02 equiv) in 1,2-dichloroethane (40.0 mL, 0.3 M) at 80 ºC for 16 h. The crude product was purified by flash column chromatography (SiO_2, cyclohexane/EtOAc 100:0 to 60:40, *v/v*) and the product **2.43g** was obtained as a colorless oil (421 mg, 2.71 mmol, 27% yield).



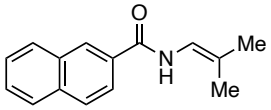
^{1}H NMR (500 MHz, $CDCl_3$) δ 6.83 (s, 1H), 6.52 (dp, *J* = 10.3, 1.4 Hz, 1H), 2.26–2.21 (m, 2H), 1.68 (dd, *J* = 1.4, 0.6 Hz, 3H), 1.62–1.60 (m, 3H), 1.40–1.31 (m, 2H), 1.20–1.13 (m, 1H), 0.93–0.90 (m, 4H).

40. Jiang, L.; Job, G. E.; Klapars, A.; Buchwald, S. L. *Org. Lett.* **2003**, *5*, 3667–3669.

^{13}C NMR (101 MHz, $CDCl_3$) δ 170.2, 117.2, 115.0, 36.7, 27.9, 22.5, 16.6, 13.9. **HRMS** (ESI +) calculated for $C_9H_{17}NNaO$ $[M+Na]^+$: 178.1202; found: 178.1210.

***N*-(2-Methylprop-1-en-1-yl)-2-naphthamide (2.43h)**

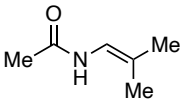
Prepared following the general procedure A using isobutyraldehyde (365 μL, 288 mg, 4.00 mmol, 1.0 equiv), 2-naphthamide (822 mg, 4.80 mmol, 1.2 equiv) and bismuth(III) trifluoromethanesulfonate (53 mg, 0.08 mmol, 0.02 equiv) in 1,2-dichloroethane (16.0 mL, 0.3 M) at 80 ºC for 16 h. The crude product was purified by flash column chromatography (SiO_2, cyclohexane/EtOAc 100:0 to 70:30, *v/v*) and the product **2.43h** was obtained as an orange solid (100 mg, 0.44 mmol, 11% yield).



M.p. 118–114 ºC. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.31 (d, *J* = 1.8 Hz, 1H), 7.97–7.82 (m, 5H), 7.65–7.52 (m, 2H), 6.81 (dp, *J* = 10.3, 1.5 Hz, 1H), 1.80 (d, *J* = 1.5 Hz, 3H), 1.78–1.76 (m, 3H).**^{13}C NMR** (101 MHz, $CDCl_3$) δ 164.3, 135.0, 132.8, 131.6, 129.1, 128.8, 127.9, 127.6, 127.0, 123.6, 117.6, 116.6, 22.7, 19.0, 16.9. **HRMS** (ESI +) calculated for $[C_{15}H_{15}NNaO]$ $[M+Na]^+$ 248.1046 *m/z*; found 248.1046 *m/z.*

***N*-(2-Methylprop-1-en-1-yl)acetamide (2.43i)**

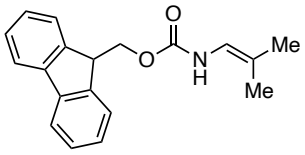
Prepared following the general procedure A using isobutyraldehyde (365 μL, 288 mg, 4.00 mmol, 1.0 equiv), acetamide (284 mg, 4.80 mmol, 1.2 equiv) and bismuth(III) trifluoromethanesulfonate (53 mg, 0.08 mmol, 0.02 equiv) in 1,2-dichloroethane (16.0 mL, 0.3 M) at 80 ºC for 16 h. The crude product was purified by flash column chromatography (SiO_2, cyclohexane/EtOAc 100:0 to 60:40, *v/v*) and the product **2.43i** was obtained as a colorless oil (140 mg, 1.24 mmol, 31% yield).



^{1}H NMR (500 MHz, $CDCl_3$) δ 7.49–7.30 (m, 1H), 6.44 (ddq, *J* = 10.2, 3.0, 1.5 Hz, 1H), 2.01 (s, 3H), 1.64 (d, *J* = 1.5 Hz, 3H), 1.59 (dd, *J* = 1.4, 0.6 Hz, 3H). The characterization data matches those reported in the literature.[41]

(9*H*-Fluoren-9-yl)methyl (2-methylprop-1-en-1-yl)carbamate (2.43j)

Prepared following the general procedure A using isobutyraldehyde (913 μL, 721 mg, 10.0 mmol, 1.0 equiv), (9*H*-fluoren-9-yl)methyl carbamate (2.87 g, 12.0 mmol, 1.2 equiv) and bismuth(III) trifluoromethanesulfonate (131 mg, 0.20 mmol, 0.02 equiv) in 1,2-dichloroethane (40.0 mL, 0.3 M) at 80 ºC for



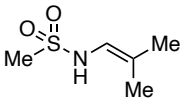
41. Clark, A. J.; Curran, D. P.; Fox, D. J.; Ghelfi, F.; Guy, C. S.; Hay, B.; James, N.; Phillips, J. M.; Roncaglia, F.; Sellars, P. B.; Wilson, P.; Zhang, H. *J. Org. Chem.* **2016**, *81*, 5547–5565.

16 h. The crude product was purified by flash column chromatography (SiO_2, cyclohexane/EtOAc 100:0 to 70:30, *v/v*) and the product **2.43j** was obtained as a colorless oil (278 mg, 0.95 mmol, 9% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (d, *J* = 7.5 Hz, 2H), 7.60 (dd, *J* = 7.5, 1.1 Hz, 2H), 7.45–7.38 (m, 2H), 7.33 (td, *J* = 7.5, 1.2 Hz, 2H), 6.27 (d, *J* = 10.5 Hz, 1H), 6.10 (d, *J* = 10.4 Hz, 1H), 4.47 (d, *J* = 6.9 Hz, 2H), 4.24 (t, *J* = 6.8 Hz, 1H), 1.70 (s, 3H), 1.60 (d, *J* = 1.4 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 153.8, 144.0, 141.5, 127.9, 127.2, 125.1, 120.2, 117.8, 67.0, 47.3, 22.4, 16.5. **HRMS** (ESI +) calculated for $C_{19}H_{19}NNaO_2$ $[M+Na]^+$: 316.1308; found: 316.1320.

***N*-(2-Methylprop-1-en-1-yl)methanesulfonamide (2.43k)**

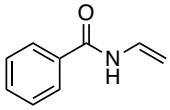
Prepared following the general procedure A using isobutyraldehyde (1.1 mL, 865 mg, 12.0 mmol, 1.0 equiv), 2-methylsulfonamide (1.37 g, 14.4 mmol, 1.2 equiv) and bismuth(III) trifluoromethanesulfonate (158 mg, 0.24 mmol, 0.02 equiv) in 1,2-dichloroethane (48.0 mL, 0.3 M) at 80 ºC for 16 h. The crude product was purified by flash column chromatography (SiO_2, cyclohexane/EtOAc 100:0 to 40:60, *v/v*) and the product **2.43k** was obtained as a colorless oil (87 mg, 0.58 mmol, 5% yield).



^{1}H NMR (400 MHz, $CDCl_3$) δ 6.39 (d, *J* = 9.6 Hz, 1H), 5.83 (dp, *J* = 9.6, 1.5 Hz, 1H), 2.96 (s, 3H), 1.67 (d, *J* = 1.5 Hz, 3H), 1.60 (d, *J* = 1.5 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 120.0, 116.8, 40.2, 22.3, 16.4. **HRMS** (ESI +) calculated for $C_5H_{12}NO_2S$ $[M+H]^+$: 150.0583; found: 150.0583.

***N*-Vinylbenzamide (2.43l)**

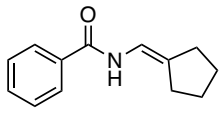
To a 100 mL round botton flask equipped with stirring bar was added benzamide (0.91 g, 7.50 mmol, 1.0 equiv), 4-dimethylaminopyridine (0.92 g, 7.50 mmol, 1.0 equiv), CuF_2 (152 mg, 1.50 mmol, 20 mol%) and 1,2-dichloroethane (50 mL, 0.2 M). Trimethoxyvinylsilane (1.7 mL, 11.3 mmol, 1.5 equiv) was then added and the reaction stirred at 23 ºC for 24 h. The reaction mixture was then filtered through Celite and washed with more 1,2-dichloroethane, before removing the solvent under vacuo. The crude product was purified by flash column chromatography (SiO_2, cyclohexane/EtOAc 90:10 to 80:20, *v/v*) and the product **2.43l** was obtained as a white solid (300 mg, 2.04 mmol, 27% yield).



^{1}H NMR (500 MHz, $CDCl_3$) δ 7.83–7.79 (m, 2H), 7.57–7.52 (m, 1H), 7.50–7.44 (m, 2H), 7.21 (ddd, *J* = 15.8, 10.9, 8.7 Hz, 1H), 4.76 (dd, *J* = 15.8, 0.9 Hz, 1H), 4.55 (d, *J* = 8.7 Hz, 1H). The characterization data matches those reported in the literature.[42]

42. Mondal, K.; Patra, S.; Halder, P.; Mukhopadhyay, N.; Das, P. *Org. Lett.* **2023**, *25*, 1235–1240.

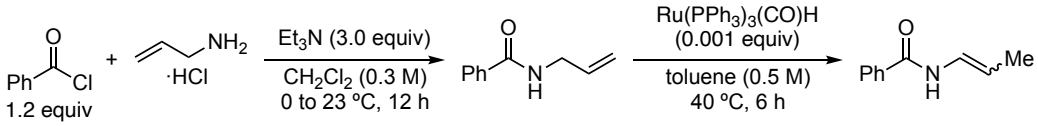
_N_-(Cyclopentylidenemethyl)benzamide (2.43m)



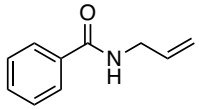
Prepared following the general procedure A using cyclopentanecarbaldehyde (854 μL, 785 mg, 8.00 mmol, 1.0 equiv), benzamide (1.16 g, 9.60 mmol, 1.2 equiv) and bismuth(III) trifluoromethanesulfonate (105 mg, 0.16 mmol, 0.02 equiv) in 1,2-dichloroethane (32.0 mL, 0.03 M) at 80 ºC for 16 h. The crude product was purified by flash column chromatography (SiO_2, cyclohexane/EtOAc 100:0 to 70:30, *v/v*) and the product **2.43m** was obtained as an orange oil (297 mg, 1.48 mmol, 18% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.81–7.76 (m, 2H), 7.57–7.50 (m, 1H), 7.49–7.42 (m, 2H), 7.41 (s, 1H), 6.84 (dp, *J* = 10.3, 2.4 Hz, 1H), 2.36 (ddt, *J* = 7.0, 5.2, 1.7 Hz, 2H), 2.33–2.25 (m, 2H), 1.81–1.73 (m, 2H), 1.69 (qd, *J* = 6.8, 0.9 Hz, 2H).The characterization data matches those reported in the literature.[43]

Alkene Me substrate (2.43n)



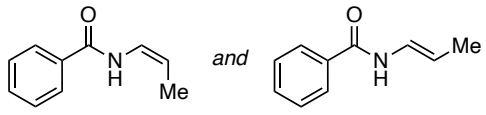
_N_-Allylbenzamide



Benzoyl chloride (695 μL, 843 mg, 6.00 mmol, 1.2 equiv) was added dropwise to a solution of allylamine hydrochloride (498 mg, 5.00 mmol, 1.0 equiv) and Et_3N (2.1 mL, 1.52 g, 15.0 mmol, 3.0 equiv) in dry CH_2Cl_2 (20.0 mL, 0.3 M). The reaction mixture was stirred at 23 ºC for 12 h, quenched with H_2O (20 mL) and extracted with CH_2Cl_2 (3 x 30 mL). The combined organic layers were washed with brine (40 mL) dried over anhydrous $MgSO_4$, filtered and concentrated under vacuo. The crude was purified by flash column chromatography (SiO_2, cyclohexane/EtOAc 100:0 to 70:30, *v/v*) and the product was obtained as white solid (806 mg, 5.00 mmol, quantitative).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85–7.74 (m, 2H), 7.55–7.45 (m, 1H), 7.45–7.36 (m, 2H), 6.37 (s, 1H), 5.93 (ddt, *J* = 17.1, 10.2, 5.7 Hz, 1H), 5.27–5.21 (m, 1H), 5.17 (dq, *J* = 10.2, 1.4 Hz, 1H), 4.08 (tt, *J* = 5.7, 1.6 Hz, 2H). The characterization data matches those reported in the literature.[44]

_N_-(Prop-1-en-1-yl)benzamide (2.43n)



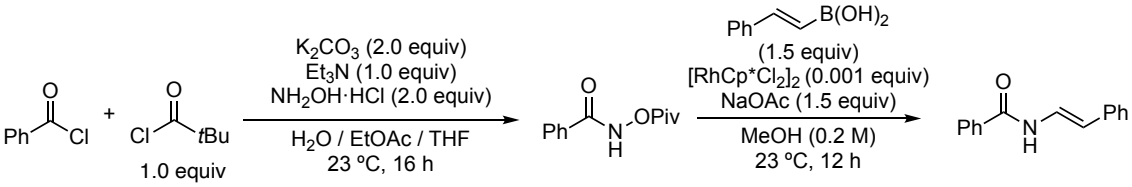
N-allylbenzamide (500 mg, 3.1 mmol, 1.0 equiv) and carbonylchlorohydrotris (triphenylphosphine) ruthenium (30 mg, 0.03 mmol, 0.001 equiv) were dissolved in dry toluene (6.2 mL, 0.5 M) under argon atmosphere and stirred at 40 ºC in a metallic heating block for 6 h. After concentrating under vacuo, the crude product was purified by flash column chromatography (SiO_2, cyclohexane/EtOAc 100:0 to 60:40, *v/v*) to isolate

43. Bai, X.-Y.; Zhao, W.; Sun, X.; Li, B. -J. *J. Am. Chem. Soc.* **2019**, *141*, 19870–19878.
44. Cai, J.; Zeng, G.; Jiang, K.; Luo, H.; Yin, B. *Org. Lett.* **2024**, *26*, 327–331.

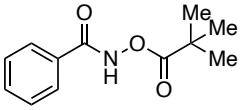
both isomers of the product **2.43n** (*E*-isomer, 263 mg, 1.63 mmol, 53% yield; *Z*-isomer 64 mg, 0.40 mmol, 13% yield).

^{1}H NMR (**2.43n-*Z***) (500 MHz, $CDCl_3$) δ 7.83–7.76 (m, 2H), 7.72–7.64 (m, 1H), 7.54–7.48 (m, 1H), 7.47–7.41 (m, 2H), 6.92 (ddq, *J* = 10.8, 8.9, 1.8 Hz, 1H), 4.93 (dqd, *J* = 8.9, 7.0, 0.7 Hz, 1H), 1.70 (dd, *J* = 7.0, 1.8 Hz, 3H). **^{1}H NMR** (**2.43n-*E***) (500 MHz, $CDCl_3$) δ 8.25 (d, *J* = 9.8 Hz, 1H), 7.84–7.75 (m, 2H), 7.49–7.42 (m, 1H), 7.40–7.33 (m, 2H), 6.92 (ddq, *J* = 13.7, 10.2, 1.7 Hz, 1H), 5.44–5.28 (m, 1H), 1.68 (dd, *J* = 6.7, 1.7 Hz, 3H). The characterization data matches those reported in the literature.[45]

Alkene Ph substrate (2.43o)



***N*-(Pivaloyloxy)benzamide**



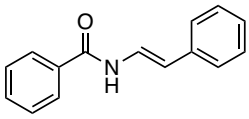
A 250 mL round-bottom flask was charged with K_2CO_3 (2.76 g, 20.0 mmol, 2.0 equiv) and hydroxylammonium chloride (1.39 g, 20.0 mmol, 2.0 equiv) in a mixture of EtOAc (40.0 mL, 0.5 M) and H_2O (20.0 mL, 1.0 M). The reaction was cooled to 0 ºC (ice bath), benzoyl chloride (1.2 mL, 1.41 g, 10.0 mmol, 1.0 equiv) was added, and the solution was stirred at 23 ºC for 6 h. Then, the organic phase was separated, and the aqueous phase was extracted with EtOAc (3 x 30 mL). The combined organic layers were washed with brine (50 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated under vacuo. The crude hydroxamic acid was dissolved in dry THF (40.0 mL) and Et_3N (1.8 mL, 1.32 g, 13.0 mmol, 1.0 equiv) under argon atmosphere followed by dropwise addition of trimethylacetyl chloride (1.2 mL, 1.21 g, 10.0 mmol, 1.0 equiv). After stirring at 23 ºC for 16 h, the reaction mixture was extracted with H_2O (30 mL) and EtOAc (3 x 20 mL). The organic layer was separated, washed with brine (30 mL), dried over anhydrous $MgSO_4$, filtered and concentrated under vacuo. The crude was purified by flash column chromatography (SiO_2, cyclohexane/EtOAc 100:0 to 70:30, *v/v*) and the product was obtained as white solid (555 mg, 2.51 mmol, 25% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.87–7.78 (m, 2H), 7.57 (ddt, *J* = 8.0, 7.0, 1.3 Hz, 1H), 7.52–7.43 (m, 2H), 1.37 (s, 9H). The characterization data matches those reported in the literature.[46]

45. Formentín, P.; Gimeno, N.; Steinke, J. H. G.; Vilar, R. *J. Org. Chem.* **2005**, *70*, 8235–8238.
46. Qi, T.; Fang, N.; Huang, W.; Chen, J.; Luo, Y.; Xia, Y. *Org. Lett.* **2022**, *24*, 5674–5678.

(*E*)-*N*-Styrylbenzamide (2.43o)

A mixture of *N*-(pivaloyloxy)benzamide (160 mg, 0.72 mmol, 1.0 equiv), *trans*-styreneboronic acid

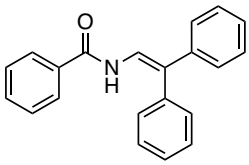


(142 μL, 161 mg, 1.01 mmol, 1.5 equiv), NaOAc (89 mg, 1.1 mmol, 1.5 equiv) and bis(dichloro(pentamethylcyclopentadienyl)rhodium) (5 mg, 0.007 mmol, 0.001 equiv) in anhydrous MeOH (3.6 mL, 0.2 M) was stirred under argon atmosphere at 23 ºC for 16 h and then quenched by the addition of H_2O (4 mL) and extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were washed with brine (15 mL) dried over anhydrous $MgSO_4$, filtered and concentrated under vacuo. The crude was purified by flash column chromatography (SiO_2, cyclohexane/EtOAc 100:0 to 70:30, *v/v*) and the product **2.43o** was obtained as white solid (127 mg, 0.55 mmol, 75% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 (d, *J* = 10.8 Hz, 1H), 7.90–7.82 (m, 2H), 7.74 (dd, *J* = 14.6, 10.8 Hz, 1H), 7.59–7.52 (m, 1H), 7.52–7.43 (m, 2H), 7.39–7.33 (m, 2H), 7.30 (dd, *J* = 8.6, 6.8 Hz, 2H), 7.23–7.16 (m, 1H), 6.28 (d, *J* = 14.6 Hz, 1H). The characterization data matches those reported in the literature.[47]

***N*-(2,2-Diphenylvinyl)benzamide (2.43p)**

Prepared following the general procedure A using 2,2-di(phenyl)acetaldehyde (981 mg, 5.00 mmol,

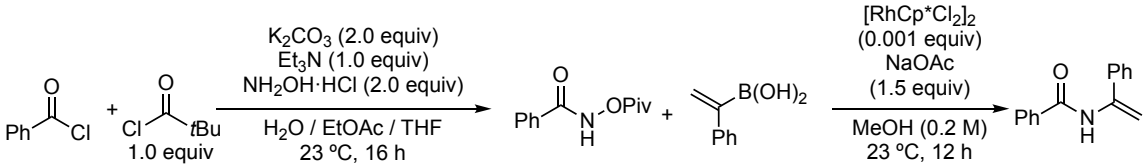


1.0 equiv), benzamide (727 mg, 6.00 mmol, 1.2 equiv) and bismuth(III) trifluoromethanesulfonate (66 mg, 0.10 mmol, 0.02 equiv) in 1,2-dichloroethane (20.0 mL, 0.3 M) at 80 ºC for 16 h. The crude product was purified by flash column chromatography (SiO_2, cyclohexane/EtOAc 100:0 to 70:30, *v/v*) and the product **2.43p** was obtained as a white solid (919 mg, 3.07 mmol, 61% yield).

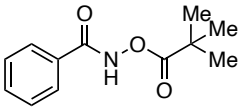
M.p. 123–129 ºC. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.95 (d, *J* = 11.2 Hz, 1H), 7.73 (d, *J* = 11.1 Hz, 1H), 7.66–7.62 (m, 2H), 7.55–7.48 (m, 3H), 7.42 (dtt, *J* = 8.1, 6.2, 1.1 Hz, 3H), 7.36 (d, *J* = 1.5 Hz, 1H), 7.35 (t, *J* = 1.3 Hz, 1H), 7.31–7.29 (m, 4H), 7.26–7.23 (m, 1H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 164.0, 140.1, 137.6, 133.5, 132.2, 130.0, 129.6, 128.9, 128.5, 128.3, 127.1, 127.1, 127.0, 125.5, 120.1.**HRMS** (ESI +) calculated for $[C_{21}H_{17}NNaO]$ $[M+Na]^+$ 322.1202 *m/z*; found 322.1192 *m/z.*

47. Feng, C.; Loh, T.-P. *Org. Lett.* **2014**, *16*, 3444–3447.

Alkene Ph substrate (2.43q)



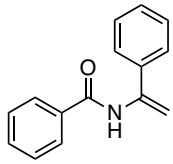
***N*-(Pivaloyloxy)benzamide**



A 250 mL round-bottom flask was charged with K_2CO_3 (2.76 g, 20.0 mmol, 2.0 equiv) and hydroxylammonium chloride (1.39 g, 20.0 mmol, 2.0 equiv) in a mixture of EtOAc (40.0 mL, 0.5 M) and H_2O (20.0 mL, 1.0 M). The reaction was cooled to 0 ºC (ice bath), benzoyl chloride (1.2 mL, 1.41 g, 10.0 mmol, 1.0 equiv) was added, and the solution was stirred at 23 ºC for 6 h. Then, the organic phase was separated, and the aqueous phase was extracted with EtOAc (3 x 30 mL). The combined organic layers were washed with brine (40 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated under vacuo. The crude hydroxamic acid was dissolved in dry THF (40.0 mL, 0.5 M) and Et_3N (1.8 mL, 1.32 g, 13.0 mmol, 1.0 equiv) under argon atmosphere followed by dropwise addition of trimethylacetyl chloride (1.2 mL, 1.2 g, 10.0 mmol, 1.0 equiv). After stirring at 23 ºC for 16 h, the reaction mixture was extracted with H_2O (30 mL) and EtOAc (3 x 20 mL). The organic layer was separated, washed with brine (20 mL) and dried over anhydrous $MgSO_4$, filtered and concentrated under vacuo. The crude was purified by flash column chromatography (SiO_2, cyclohexane/EtOAc 100:0 to 70:30, *v/v*) and the product was obtained as white solid (555 mg, 2.51 mmol, 25% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.87–7.78 (m, 2H), 7.57 (ddt, *J* = 8.0, 7.0, 1.3 Hz, 1H), 7.52–7.43 (m, 2H), 1.37 (s, 9H). The characterization data matches those reported in the literature.[18]

(*N*-(1-Phenylvinyl)benzamide (2.43q)



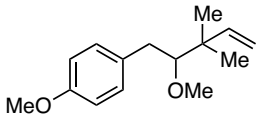
A mixture of *N*-(pivaloyloxy)benzamide (120 mg, 0.54 mmol, 1.0 equiv), 1-phenylvinylboronicacid (120 mg, 0.81 mmol, 1.5 equiv), NaOAc (67 mg, 0.81 mmol, 1.5 equiv) and bis(dichloro(pentamethylcyclopentadienyl)rhodium) (3 mg, 0.005 mmol, 0.01 equiv) in anhydrous MeOH (2.7 mL, 0.2 M) was stirred under argon atmosphere at 23 ºC for 16 h and then quenched by the addition of H_2O (4 mL) and extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were washed with brine (15 mL), dried over anhydrous $MgSO_4$, filtered and concentrated under vacuo. The crude was purified by flash column chromatography (SiO_2, cyclohexane/EtOAc 100:0 to 70:30, *v/v*) and the product **2.43q** was obtained as white solid (12 mg, 0.05 mmol, 10% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.89–7.78 (m, 2H), 7.57–7.52 (m, 1H), 7.51–7.46 (m, 4H), 7.43–7.40 (m, 1H), 7.40–7.36 (m, 2H), 6.06 (s, 1H), 5.22 (d, *J* = 1.0 Hz, 1H). The characterization data matches those reported in the literature.[48]

Products of the Intermolecular Alkoxycyclization of Alkenes

1-Methoxy-4-(2-methoxy-3,3-dimethylpent-4-en-1-yl)benzene (2.19)

Prepared following general procedure B using 1-methoxy-4-(3-methylbut-2-en-1-yl)benzene **2.18**

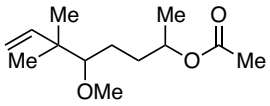


(44 mg, 0.25 mmol, 1.0 equiv), MeOH (20 μL, 16 mg, 0.50 mmol, 2.0 equiv) [JohnPhosAuNCMe]SbF_6 (8 mg, 0.010 mmol, 4 mol%) and 1 atm of acetylene gas in $CHCl_3$ (0.25 mL, 1.0 M) at 23 ºC for 16 h. The crude was purified by flash column chromatography (SiO_2, cyclohexane/EtOAc 100:0 to 80:20, *v/v*) to afford the product **2.19** as a colorless oil (18 mg, 0.08 mmol, 31% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.07–7.02 (m, 2H), 6.86–6.75 (m, 2H), 5.69–5.54 (m, 1H), 4.94 (dd, *J* = 10.2, 2.0 Hz, 1H), 4.77–4.66 (m, 1H), 3.77 (s, 3H), 3.26 (s, 3H), 3.00 (d, *J* = 11.8 Hz, 1H), 2.41–2.28 (m, 2H), 1.18 (d, *J* = 1.8 Hz, 6H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 157.7, 138.4, 133.7, 130.3, 117.6, 113.5, 76.4, 55.3, 54.9, 49.1, 34.3, 23.7, 22.4. **HRMS** (ESI +) calculated for $[C_{15}H_{22}NaO_2]$ $[M+Na]^+$ 257.1512 *m/z*; found 257.1517 *m/z.*

5-Methoxy-6,6-dimethyloct-7-en-2-yl acetate (2.25)

Prepared following general procedure B using 6-methylhept-5-en-2-yl acetate **2.23** (43 mg, 0.25 mmol,



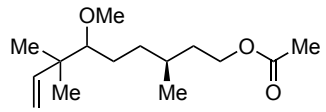
1.0 equiv), MeOH (12 μL, 16 mg 0.50 mmol, 2.0 equiv) [JohnPhosAuNCMe]SbF_6 (8 mg, 0.01 mmol, 4 mol%) and 1 atm of acetylene gas in $CHCl_3$ (0.25 mL, 1.0 M) at 23 ºC for 16 h. The crude was purified by flash column chromatography (SiO_2, cyclohexane/EtOAc 100:0 to 80:20, *v/v*) to afford the product **2.25** as a colorless oil (18 mg, 0.008 mmol, 33 % yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.55 (ddd, *J* = 17.0, 10.2, 9.5 Hz, 1H), 5.08 (dt, *J* = 10.2, 2.2 Hz, 1H), 5.01 (dtd, *J* = 17.1, 2.0, 0.7 Hz, 1H), 4.91–4.84 (m, 1H), 3.35–3.30 (m, 1H), 3.16 (d, *J* = 4.4 Hz, 3H), 2.02 (s, 3H), 1.75–1.60 (m, 2H), 1.52 (dddd, *J* = 13.6, 11.6, 6.0, 4.7 Hz, 1H), 1.44–1.29 (m, 1H), 1.20 (dd, *J* = 6.3, 2.2 Hz, 3H), 1.12–1.09 (m, 3H), 1.07 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 171.0, 139.1, 117.4, 71.5, 71.0, 52.9, 52.5, 49.0, 34.5, 23.6, 22.2, 21.6, 20.3. **HRMS** (ESI +) calculated for $[C_{13}H_{24}NaO_3]$ $[M+Na]^+$ 251.1618 *m/z*; found 251.1625 *m/z.*

48. Kiyohara, H.; Matsubara, R.; Kobayashi, S. *Org. Lett.* **2006**, *8*, 5333–5335.

(*S*)-6-Methoxy-3,7,7-trimethylnon-8-en-1-yl acetate (2.28)

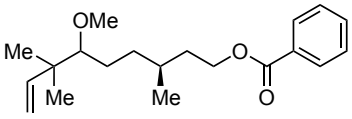
Prepared following general procedure B using 3,7-dimethyloct-6-en-1-yl acetate **2.27** (99 mg, 0.50 mmol, 1.0 equiv), MeOH (41 μL, 32 mg, 1.00 mmol, 2.0 equiv) [JohnPhosAuNCMe]SbF_6 (16 mg, 0.020 mmol, 4 mol%) and 1 atm of acetylene gas in $CHCl_3$ (0.50 mL, 1.0 M) at 23 ºC for 16 h. The crude was purified by flash column chromatography (SiO_2, cyclohexane/EtOAc 100:0 to 80:20, *v/v*) to afford the product **2.28** as a colorless oil (45 mg, 0.18 mmol, 35% yield).



^{1}H NMR (500 MHz, $CDCl_3$) δ 5.54 (dddd, *J* = 17.1, 10.2, 9.5, 2.7 Hz, 1H), 5.05 (dd, *J* = 10.2, 2.2 Hz, 1H), 4.98 (ddt, *J* = 17.1, 2.2, 0.8 Hz, 1H), 4.12–4.03 (m, 2H), 3.16 (d, *J* = 1.4 Hz, 3H), 2.02 (d, *J* = 0.9 Hz, 3H), 1.73–1.57 (m, 3H), 1.56–1.30 (m, 2H), 1.24–1.13 (m, 1H), 1.10 (s, 3H), 1.07 (d, *J* = 1.2 Hz, 3H), 1.05–0.94 (m, 1H), 0.89 (dd, *J* = 8.9, 6.6 Hz, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 171.3, 139.5, 139.5, 117.0, 117.0, 76.4, 63.2, 63.2, 53.1, 52.9, 49.0, 48.9, 35.9, 35.5, 35.3, 35.1, 30.3, 29.9, 25.4, 25.3, 23.6, 22.2, 22.2, 21.2, 19.9, 19.5.[49] **HRMS** (ESI +) calculated for $[C_{15}H_{28}NaO_3]$ $[M+Na]^+$ 279.1931 *m/z*; found 279.1921 *m/z.*

(*S*)-6-Methoxy-3,7,7-trimethylnon-8-en-1-yl benzoate (2.31)

Prepared following general procedure B using 3,7-dimethyloct-6-en-1-yl benzoate **2.29** (52 mg, 0.20 mmol, 1.0 equiv), MeOH (16 μL, 13 mg, 0.40 mmol, 2.0 equiv) [JohnPhosAuNCMe]SbF_6 (6 mg, 0.008 mmol, 4 mol%) and 1 atm of acetylene gas in $CHCl_3$ (0.20 mL, 1.0 M) at 23 ºC for 16 h. The crude was purified by flash column chromatography (SiO_2, cyclohexane/EtOAc 100:0 to 80:20, *v/v*) to afford the product **2.31** as a colorless oil (16 mg, 0.05 mmol, 26% yield).

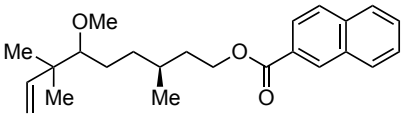


^{1}H NMR (500 MHz, $CDCl_3$) δ 8.06–8.01 (m, 2H), 7.58–7.52 (m, 1H), 7.46–7.41 (m, 2H), 5.55 (dddd, *J* = 17.0, 10.4, 9.5, 1.2 Hz, 1H), 5.05 (ddd, *J* = 10.2, 2.2, 0.9 Hz, 1H), 4.98 (dddd, *J* = 17.1, 2.2, 1.5, 0.7 Hz, 1H), 4.40–4.30 (m, 2H), 3.17 (s, 3H), 2.08–1.99 (m, 1H), 1.88–1.74 (m, 1H), 1.73–1.50 (m, 4H), 1.41 (dddd, *J* = 16.0, 10.2, 4.8, 2.7 Hz, 1H), 1.27–1.18 (m, 1H), 1.11 (s, 3H), 1.08 (d, *J* = 2.2 Hz, 3H), 0.96 (dd, *J* = 9.7, 6.5 Hz, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 166.8, 139.6, 139.5, 132.9, 130.7, 129.7, 128.4, 117.0, 76.4, 63.7, 63.7, 53.2, 53.0, 49.0, 49.0, 36.1, 35.6, 35.5, 35.2, 30.4, 30.1, 25.5, 25.4, 23.6, 22.2, 20.0, 19.6.[49] **HRMS** (ESI +) calculated for $[C_{20}H_{30}NaO_3]$ $[M+Na]^+$ 341.2087 *m/z*; found 341.2095 *m/z.*

49. Compounds **2.28**, **2.31** and **2.32** were isolated as a mixture of diastereoisomers, which explain the extra signals in the ^{13}C NMR spectra.

(*S*)-6-Methoxy-3,7,7-trimethylnon-8-en-1-yl 2-naphthoate (2.32)

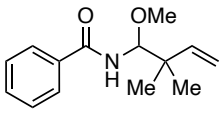
Prepared following general procedure B using 3,7-dimethyloct-6-en-1-yl 2-naphthoate **2.30** (62 mg, 0.20 mmol, 1.0 equiv), MeOH (16 μL, 13 mg, 0.40 mmol, 2.0 equiv) [JohnPhosAuNCMe]SbF_6 (6 mg, 0.008 mmol, 4 mol%) and 1 atm of acetylene gas in $CHCl_3$ (0.20 mL, 1.0 M) at 23 ºC for 16 h. The crude was purified by flash column chromatography (SiO_2, cyclohexane/EtOAc 100:0 to 80:20, *v/v*) to afford the product **2.32** as a colorless oil (21 mg, 0.06 mmol, 28% yield).



^{1}H NMR (500 MHz, $CDCl_3$) δ 8.66–8.56 (m, 1H), 8.06 (dd, *J* = 8.6, 1.7 Hz, 1H), 7.96 (dd, *J* = 8.2, 1.4 Hz, 1H), 7.88 (d, *J* = 8.4 Hz, 2H), 7.65–7.50 (m, 2H), 5.57 (dddd, *J* = 17.1, 10.2, 9.5, 1.5 Hz, 1H), 5.06 (dt, *J* = 10.2, 2.1 Hz, 1H), 5.00 (ddt, *J* = 17.1, 2.2, 0.8 Hz, 1H), 4.48–4.34 (m, 2H), 3.18 (s, 3H), 2.06 (dtd, *J* = 10.8, 8.9, 2.6 Hz, 1H), 1.94–1.80 (m, 1H), 1.76–1.55 (m, 4H), 1.51–1.39 (m, 1H), 1.30–1.20 (m, 1H), 1.12 (s, 3H), 1.09 (d, *J* = 1.8 Hz, 3H), 0.99 (dd, *J* = 9.9, 6.5 Hz, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 167.0, 139.6, 139.5, 135.6, 132.7, 131.1, 129.5, 128.3, 128.2, 127.9, 126.7, 125.4, 117.0, 63.9, 63.9, 53.2, 53.0, 49.0, 49.0, 36.1, 35.6, 35.5, 35.3, 30.5, 30.2, 23.6, 22.2.[49] **HRMS** (ESI +) calculated for $[C_{24}H_{32}NaO_3]$ $[M+Na]^+$ 391.2244 *m/z*; found 391.2247 *m/z*.

***N*-(1-Methoxy-2,2-dimethylbut-3-en-1-yl)benzamide (2.44a)**

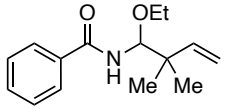
Prepared following the general procedure C using *N*-(2-methylprop-1-en-1-yl) **2.43a** (44 mg, 0.25 mmol, 1.0 equiv), MeOH (20 μL, 0.50 mmol, 2.0 equiv), [JohnPhosAuNCMe]SbF_6 (8 mg, 0.01 mmol, 4 mol%) and 1 atm of acetylene gas in $CHCl_3$ (0.25 mL, 1.0 M) at 23 ºC for 24 h. The crude product was purified by flash column chromatography (SiO_2, cyclohexane/EtOAc 100:0 to 4:1, *v/v*) and the product **2.44a** was obtained as a white solid (31 mg, 0.13 mmol, 53% yield).



M.p. 48–50 ºC. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.79–7.75 (m, 2H), 7.55–7.50 (m, 1H), 7.48–7.43 (m, 2H), 6.28 (d, *J* = 10.1 Hz, 1H), 6.01 (dd, *J* = 17.6, 10.8 Hz, 1H), 5.19 (dd, *J* = 10.8, 1.4 Hz, 1H), 5.14 (dd, *J* = 17.6, 1.4 Hz, 1H), 5.06 (d, *J* = 10.0 Hz, 1H), 3.39 (s, 3H), 1.18 (s, 3H), 1.06 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 167.7, 142.8, 134.2, 132.0, 128.8, 127.0, 114.5, 87.0, 56.7, 42.0, 24.2, 22.2. **HRMS** (ESI +) calculated for $[C_{14}H_{19}NNaO_2]$ $[M+Na]^+$ 256.1308 *m/z*; found 256.1317 *m/z*.

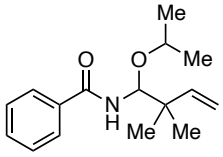
***N*-(1-Ethoxy-2,2-dimethylbut-3-en-1-yl)benzamide (2.44b)**

Prepared following the general procedure C using *N*-(2-methylprop-1-en-1-yl) **2.43a** (44 mg, 0.25 mmol, 1.0 equiv), EtOH (29 μL, 0.50 mmol, 2.0 equiv), [JohnPhosAuNCMe]SbF_6 (8 mg, 0.01 mmol, 4 mol%) and 1 atm of acetylene gas in $CHCl_3$ (0.25 mL, 1.0 M) at 23 ºC for 24 h. The crude product was purified by flash column chromatography (SiO_2, cyclohexane/EtOAc 100:0 to 4:1, *v/v*) and the product **2.44b** was obtained as a white solid (24 mg, 0.10 mmol, 39% yield).



M.p. 49–50 ºC. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.77–7.74 (m, 2H), 7.54–7.50 (m, 1H), 7.47–7.42 (m, 2H), 6.32 (d, *J* = 10.0 Hz, 1H), 6.04 (dd, *J* = 17.6, 10.8 Hz, 1H), 5.18 (dd, *J* = 10.8, 1.5 Hz, 1H), 5.16–5.11 (m, 2H), 3.68 (dq, *J* = 9.8, 7.0 Hz, 1H), 3.55 (dq, *J* = 9.8, 7.0 Hz, 1H), 1.20–1.17 (m, 6H), 1.06 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 167.5, 143.1, 134.3, 131.9, 128.8, 127.0, 114.3, 85.2, 64.5, 42.0, 24.3, 22.2, 15.1. **HRMS** (ESI +) calculated for $[C_{15}H_{21}NNaO_2]$ $[M+Na]^+$ 270.1464 *m/z*; found 270.1475 *m/z*.

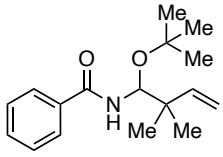
***N*-(1-Isopropoxy-2,2-dimethylbut-3-en-1-yl)benzamide (2.44c)**



Prepared following the general procedure C using *N*-(2-methylprop-1-en-1-yl) **2.43a** (44 mg, 0.25 mmol, 1.0 equiv), *iso*-propanol (38 µL, 0.50 mmol, 2.0 equiv), [JohnPhosAuNCMe]SbF_6 (8 mg, 0.01 mmol, 4 mol%) and 1 atm of acetylene gas in $CHCl_3$ (0.25 mL, 1.0 M) at 23 ºC for 24 h. The crude product was purified by flash column chromatography (SiO_2, cyclohexane/EtOAc 100:0 to 4:1, *v/v*) and the product **2.44c** was obtained as a white solid (29 mg, 0.11 mmol, 44% yield).

M.p. 61–62 ºC. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.78–7.73 (m, 2H), 7.54–7.49 (m, 1H), 7.47–7.42 (m, 2H), 6.31 (d, *J* = 10.0 Hz, 1H), 6.04 (dd, *J* = 17.6, 10.9 Hz, 1H), 5.22 (d, *J* = 9.9 Hz, 1H), 5.16 (dd, *J* = 10.9, 1.5 Hz, 1H), 5.11 (dd, *J* = 17.7, 1.5 Hz, 1H), 3.82 (hept, *J* = 6.1 Hz, 1H), 1.20 (d, *J* = 6.0 Hz, 3H), 1.15 (s, 3H), 1.11 (d, *J* = 6.2 Hz, 3H), 1.05 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 167.3, 143.3, 134.5, 131.9, 128.8, 127.0, 114.2, 83.4, 69.8, 42.1, 24.2, 23.5, 22.2, 21.6. **HRMS** (ESI +) calculated for $[C_{16}H_{23}NNaO_2]$ $[M+Na]^+$ 284.1621 *m/z*; found 284.1624 *m/z*.

***N*-(1-(*tert*-Butoxy)-2,2-dimethylbut-3-en-1-yl)benzamide (2.44d)**

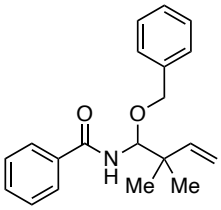


Prepared following the general procedure C using *N*-(2-methylprop-1-en-1-yl) **2.43a** (44 mg, 0.25 mmol, 1.0 equiv), *tert*-butanol (24 µL, 0.50 mmol, 2.0 equiv), [JohnPhosAuNCMe]SbF_6 (8 mg, 0.01 mmol, 4 mol%) and 1 atm of acetylene gas in $CHCl_3$ (0.25 mL, 1.0 M) at 23 ºC for 24 h. The crude product was purified by flash column chromatography (SiO_2, cyclohexane/EtOAc 100:0 to 4:1, *v/v*) and the product **2.44d** was obtained as a white solid (25 mg, 0.09 mmol, 36% yield).

M.p. 63–64 ºC. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.75–7.70 (m, 2H), 7.52–7.47 (m, 1H), 7.4–7.40 (m, 2H), 6.30 (d, *J* = 9.5 Hz, 1H), 6.03 (dd, *J* = 17.6, 10.8 Hz, 1H), 5.32 (d, *J* = 9.6 Hz, 1H), 5.13 (dd, *J* = 10.8, 1.5 Hz, 1H), 5.07 (dd, *J* = 17.6, 1.5 Hz, 1H), 1.23 (s, 9H), 1.11 (s, 3H), 1.03 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 166.2, 143.5, 134.9, 131.7, 128.8, 126.9, 113.9, 79.8, 74.7, 42.8, 28.5, 24.1, 22.1. **HRMS** (ESI +) calculated for $[C_{17}H_{25}NNaO_2]$ $[M+Na]^+$ 298.1777 *m/z*; found 298.1788 *m/z*.

***N*-(1-(Benzyloxy)-2,2-dimethylbut-3-en-1-yl)benzamide (2.44e)**

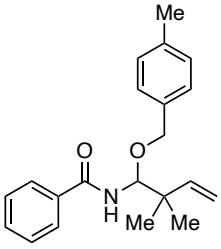
Prepared following the general procedure C using *N*-(2-methylprop-1-en-1-yl)benzamide **2.43a** (44 mg, 0.25 mmol, 1.0 equiv), benzyl alcohol (52 μL, 0.50 mmol, 2.0 equiv), [JohnPhosAuNCMe]SbF_6 (8 mg, 0.01 mmol, 4 mol%) and 1 atm of acetylene gas in $CHCl_3$ (0.25 mL, 1.0 M) at 23 ºC for 24 h. The crude was purified by flash column chromatography (SiO_2, cyclohexane/EtOAc 100:0 to 80:20, *v/v*) to afford the product **2.44e** as a white solid (57 mg, 0.19 mmol, 74% yield).



M.p. 58–62 ºC. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.78–7.72 (m, 2H), 7.57–7.51 (m, 1H), 7.49–7.43 (m, 2H), 7.38–7.35 (m, 2H), 7.34–7.31 (m, 2H), 7.29–7.26 (m, 1H), 6.40 (d, *J* = 10.0 Hz, 1H), 6.10 (dd, *J* = 17.6, 10.8 Hz, 1H), 5.30 (d, *J* = 10.1 Hz, 1H), 5.21 (dd, *J* = 10.8, 1.4 Hz, 1H), 5.16 (dd, *J* = 17.6, 1.4 Hz, 1H), 4.69 (d, *J* = 12.1 Hz, 1H), 4.61 (d, *J* = 12.1 Hz, 1H), 1.21 (s, 3H), 1.08 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 167.6, 142.9, 138.5, 134.2, 132.0, 128.8, 128.4, 127.7, 127.6, 127.0, 114.6, 85.1, 70.6, 42.1, 24.4, 22.2. **HRMS** (ESI +) calculated for $C_{20}H_{23}NNaO_2$ $[M+Na]^+$: 332.1621; found: 332.1620.

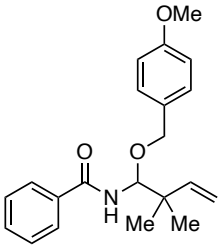
***N*-(2,2-Dimethyl-1-((4-methylbenzyl)oxy)but-3-en-1-yl)benzamide (2.44f)**

Prepared following the general procedure C using *N*-(2-methylprop-1-en-1-yl) **2.43a** (44 mg, 0.25 mmol, 1.0 equiv), 4-methylbenzyl alcohol (61 mg, 0.50 mmol, 2.0 equiv), [JohnPhosAuNCMe]SbF_6 (8 mg, 0.01 mmol, 4 mol%) and 1 atm of acetylene gas in $CHCl_3$ (0.25 mL, 1.0 M) at 23 ºC for 24 h. The crude product was purified by flash column chromatography (SiO_2, cyclohexane/EtOAc 100:0 to 90:10, *v/v*) and the product **2.44f** was obtained as a white solid (45 mg, 0.14 mmol, 56% yield).



M.p. 93–95 ºC. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.76–7.72 (m, 2H), 7.56–7.50 (m, 1H), 7.48–7.42 (m, 2H), 7.27–7.22 (m, 2H), 7.13 (d, *J* = 7.6 Hz, 2H), 6.36 (d, *J* = 10.0 Hz, 1H), 6.08 (dd, *J* = 17.6, 10.9 Hz, 1H), 5.27 (d, *J* = 10.0 Hz, 1H), 5.19 (dd, *J* = 10.8, 1.4 Hz, 1H), 5.14 (dd, *J* = 17.6, 1.4 Hz, 1H), 4.63 (d, *J* = 11.8 Hz, 1H), 4.55 (d, *J* = 11.8 Hz, 1H), 2.33 (s, 3H), 1.19 (s, 3H), 1.07 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 167.6, 143.0, 137.3, 135.4, 134.3, 132.0, 129.1, 128.8, 127.9, 127.1, 114.5, 85.0, 70.6, 42.1, 24.4, 22.3, 21.3. **HRMS** (ESI +) calculated for $[C_{21}H_{25}NNaO_2]$ $[M+Na]^+$ 346.1777 *m/z*; found 346.1777 *m/z.*

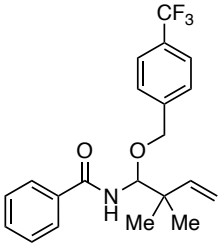
***N*-(1-((4-Methoxybenzyl)oxy)-2,2-dimethylbut-3-en-1-yl)benzamide (2.44g)**



Prepared following the general procedure C using *N*-(2-methylprop-1-en-1-yl) **2.43a** (44 mg, 0.25 mmol, 1.0 equiv), 4-methoxybenzyl alcohol (69 mg, 0.50 mmol, 2.0 equiv), [JohnPhosAuNCMe]SbF_6 (8 mg, 0.01 mmol, 4 mol%) and 1 atm of acetylene gas in $CHCl_3$ (0.25 mL, 1.0 M) at 23 ºC for 24 h. The crude product was purified by flash column chromatography (SiO_2, cyclohexane/EtOAc 100:0 to 9:1, *v/v*) and the product **2.44g** was obtained as a white solid (19 mg, 0.06 mmol, 22% yield).

M.p. 73–74 ºC. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.77–7.73 (m, 2H), 7.55–7.51 (m, 1H), 7.48–7.43 (m, 2H), 7.31–7.27 (m, 2H), 6.87–6.84 (m, 2H), 6.37 (d, *J* = 10.0 Hz, 1H), 6.06 (dd, *J* = 17.6, 10.8 Hz, 1H), 5.25 (d, *J* = 10.0 Hz, 1H), 5.19 (dd, *J* = 10.8, 1.4 Hz, 1H), 5.14 (dd, *J* = 17.7, 1.4 Hz, 1H), 4.61 (d, *J* = 11.7 Hz, 1H), 4.52 (d, *J* = 11.7 Hz, 1H), 3.79 (s, 3H), 1.17 (s, 3H), 1.05 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 167.6, 159.3, 143.0, 134.2, 132.0, 130.5, 129.5, 128.8, 127.1, 114.5, 113.8, 84.8, 70.4, 55.4, 42.1, 24.4, 22.2. **HRMS** (ESI +) calculated for $[C_{21}H_{25}NNaO_3]$ $[M+Na]^+$ 362.1727 *m/z*; found 362.1733 *m/z*.

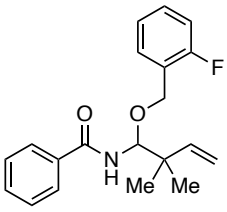
***N*-(2,2-Dimethyl-1-((4-(trifluoromethyl)benzyl)oxy)but-3-en-1-yl)benzamide (2.44h)**



Prepared following the general procedure C using *N*-(2-methylprop-1-en-1-yl) **2.43a** (44 mg, 0.25 mmol, 1.0 equiv), 4-(trifluoromethyl)benzyl alcohol (66 µL, 0.50 mmol, 2.0 equiv), [JohnPhosAuNCMe]SbF_6 (8 mg, 0.01 mmol, 4 mol%) and 1 atm of acetylene gas in $CHCl_3$ (0.25 mL, 1.0 M) at 23 ºC for 24 h. The crude product was purified by flash column chromatography (SiO_2, cyclohexane/EtOAc 100:0 to 90:10, *v/v*) and the product **2.44h** was obtained as a white solid (68 mg, 0.18 mmol, 72% yield).

M.p. 62–64 ºC. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.73–7.70 (m, 2H), 7.60–7.56 (m, 2H), 7.55–7.51 (m, 1H), 7.48–7.43 (m, 4H), 6.40 (d, *J* = 10.1 Hz, 1H), 6.09 (dd, *J* = 17.6, 10.8 Hz, 1H), 5.28 (d, *J* = 10.1 Hz, 1H), 5.23 (dd, *J* = 10.8, 1.3 Hz, 1H), 5.18 (dd, *J* = 17.6, 1.4 Hz, 1H), 4.72 (d, *J* = 12.8 Hz, 1H), 4.66 (d, *J* = 12.8 Hz, 1H), 1.22 (s, 3H), 1.09 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 167.7, 142.7, 134.0, 132.2, 129.8 (q, J_{C-F} = 32.4 Hz), 129.7, 128.9, 127.7, 127.0, 126.4 (q, J_{C-F} = 3.9 Hz), 124.3 (q, J_{C-F} = 272.8 Hz), 114.9, 85.2, 69.9, 42.1, 24.6, 22.3. **^{19}F NMR** (376 MHz, $CDCl_3$) δ 62.59. **HRMS** (ESI +) calculated for $[C_{21}H_{22}F_3NNaO_2]$ $[M+Na]^+$ 400.1495 *m/z*; found 400.1486 *m/z*.

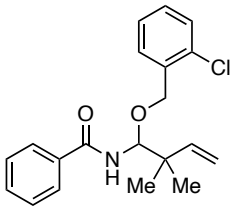
***N*-(1-((2-Fluorobenzyl)oxy)-2,2-dimethylbut-3-en-1-yl)benzamide (2.44i)**



Prepared following the general procedure C using *N*-(2-methylprop-1-en-1-yl) **2.43a** (44 mg, 0.25 mmol, 1.0 equiv), 2-fluorobenzyl alcohol (54 μL, 0.50 mmol, 2.0 equiv), [JohnPhosAuNCMe]SbF_6 (8 mg, 0.01 mmol, 4 mol%) and 1 atm of acetylene gas in $CHCl_3$ (0.25 mL, 1.0 M) at 23 ºC for 24 h. The crude product was purified by flash column chromatography (SiO_2, cyclohexane/EtOAc 100:0 to 90:10, *v/v*) and the product **2.44i** was obtained as a white solid (55 mg, 0.17 mmol, 67% yield).

M.p. 74–75 ºC. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.79–7.75 (m, 2H), 7.56–7.51 (m, 1H), 7.48–7.43 (m, 3H), 7.29–7.23 (m, 1H), 7.14 (ddd, *J* = 7.5, 7.5, 1.2 Hz, 1H), 7.02 (ddd, *J* = 9.6, 8.2, 1.2 Hz, 1H), 6.40 (d, *J* = 10.0 Hz, 1H), 6.07 (dd, *J* = 17.6, 10.8 Hz, 1H), 5.30 (d, *J* = 10.1 Hz, 1H), 5.19 (dd, *J* = 10.8, 1.4 Hz, 1H), 5.15 (dd, *J* = 17.6, 1.4 Hz, 1H), 4.77 (d, *J* = 12.1 Hz, 1H), 4.61 (d, *J* = 12.1 Hz, 1H), 1.18 (s, 3H), 1.07 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 167.7, 161.0 (d, J_{C-F} = 247.7 Hz), 142.8, 134.2, 132.0, 130.3 (d, J_{C-F} = 4.5 Hz), 129.5 (d, J_{C-F} = 8.0 Hz), 128.9, 127.1, 125.5 (d, J_{C-F} = 14.6 Hz), 124.0 (d, J_{C-F} = 3.6 Hz), 115.3 (d, J_{C-F} = 21.2 Hz), 114.6, 85.2, 64.8 (d, J_{C-F} = 3.7 Hz), 42.1, 24.3, 22.3. **^{19}F NMR** (376 MHz, $CDCl_3$) δ −118.20. **HRMS** (ESI +) calculated for [$C_{20}H_{22}FNNaO_2$] $[M+Na]^+$ 350.1527 *m/z*; found 350.1537 *m/z.*

***N*-(1-((2-Chlorobenzyl)oxy)-2,2-dimethylbut-3-en-1-yl)benzamide (2.44j)**



Prepared following the general procedure C using *N*-(2-methylprop-1-en-1-yl) **2.43a** (44 mg, 0.25 mmol, 1.0 equiv), 2-chlorobenzyl alcohol (71 mg, 0.50 mmol, 2.0 equiv), [JohnPhosAuNCMe]SbF_6 (8 mg, 0.01 mmol, 4 mol%) and 1 atm of acetylene gas in $CHCl_3$ (0.25 mL, 1.0 M) at 23 ºC for 24 h. The crude product was purified by flash column chromatography (SiO_2, cyclohexane/EtOAc 100:0 to 90:10, *v/v*) and the product **2.44j** was obtained as a white solid (57 mg, 0.17 mmol, 66% yield).

M.p. 69–70 ºC. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.78–7.75 (m, 2H), 7.55–7.49 (m, 2H), 7.48–7.43 (m, 2H), 7.34 (dd, *J* = 7.7, 1.5 Hz, 1H), 7.28–7.19 (m, 2H), 6.41 (d, *J* = 10.0 Hz, 1H), 6.10 (dd, *J* = 17.6, 10.8 Hz, 1H), 5.33 (d, *J* = 10.1 Hz, 1H), 5.21 (dd, *J* = 10.8, 1.4 Hz, 1H), 5.16 (dd, *J* = 17.6, 1.4 Hz, 1H), 4.79 (d, *J* = 12.6 Hz, 1H), 4.64 (d, *J* = 12.7 Hz, 1H), 1.21 (s, 3H), 1.09 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 167.7, 142.8, 136.0, 134.2, 133.4, 132.0, 129.6, 129.4, 128.9, 128.9, 127.1, 126.8, 114.7, 85.3, 68.0, 42.2, 24.4, 22.3. **HRMS** (ESI +) calculated for [$C_{20}H_{22}ClNNaO_2$] $[M+Na]^+$ 366.1231 *m/z*; found 366.1246 *m/z.*

***N*-(2,2-Dimethyl-1-((*R*)-1-phenylethoxy)but-3-en-1-yl)benzamide (2.44k)**

Prepared following the general procedure C using *N*-(2-methylprop-1-en-1-yl) **2.43a** (44 mg, 0.25 mmol, 1.0 equiv), (*R*)-1-phenylethanol (64 µL, 0.50 mmol, 2.0 equiv), [JohnPhosAuNCMe]SbF_6 (8 mg, 0.01 mmol, 4 mol%) and 1 atm of acetylene gas in $CHCl_3$ (0.25 mL, 1.0 M) at 23 ºC for 24 h. The crude product was purified by flash column chromatography (SiO_2, cyclohexane/EtOAc 100:0 to 90:10, *v/v*) and the product **2.44k** was obtained as a white solid (57 mg, 0.18 mmol, 70% yield, 54:46 *dr*).

M.p. 60–61 ºC. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.82–7.77 (m, 1H), 7.57–7.51 (m, 0.5H), 7.50–7.45 (m, 1H), 7.45–7.20 (m, 7H), 7.17–7.12 (m, 0.5H), 6.38 (d, *J* = 10.0 Hz, 0.5H), 6.17–6.00 (m, 1.5H), 5.42 (d, *J* = 10.0 Hz, 0.5H), 5.21–5.15 (m, 1H), 5.13 (dd, *J* = 6.6, 1.5 Hz, 0.5H), 5.09 (dd, *J* = 6.6, 1.4 Hz, 0.5H), 4.99 (d, *J* = 10.0 Hz, 0.5H), 4.71–4.59 (m, 1H), 1.48 (d, *J* = 6.5 Hz, 1.5H), 1.41 (d, *J* = 6.6 Hz, 1.5H), 1.25 (s, 1.5H), 1.09 (s, 1.5H), 1.05 (s, 1.5H), 0.94 (s, 1.5H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 167.5, 167.3, 145.5, 143.2, 143.1, 143.1, 134.5, 134.3, 131.9, 131.7, 128.9, 128.5, 128.4, 128.3, 127.8, 127.4, 127.1, 127.0, 126.9, 126.4, 125.6, 114.3, 84.5, 82.9, 75.8, 75.0, 42.1, 42.0, 24.5, 24.3, 24.1, 23.3, 22.2, 22.1. **HRMS** (ESI +) calculated for [$C_{21}H_{25}NNaO_2$] $[M+Na]^+$ 346.1777 *m/z*; found 346.1792 *m/z.*

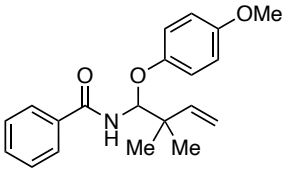
***N*-(2,2-Dimethyl-1-phenoxybut-3-en-1-yl)benzamide (2.44l)**

Prepared following the general procedure C using *N*-(2-methylprop-1-en-1-yl)benzamide **2.43a** (44 mg, 0.25 mmol, 1.0 equiv), phenol (47 mg, 0.50 mmol, 2.0 equiv), [JohnPhosAuNCMe]SbF_6 (8 mg, 0.01 mmol, 4 mol%) and 1 atm of acetylene gas in $CHCl_3$ (0.25 mL, 1.0 M) at 23 ºC for 24 h. The crude was purified by flash column chromatography (SiO_2, cyclohexane/EtOAc 100:0 to 80:20, *v/v*) to afford the product **2.44l** as white solid (23 mg, 0.08 mmol, 31% yield).

M.p. 124–125 ºC. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.73–7.68 (m, 2H), 7.53–7.47 (m, 1H), 7.44–7.39 (m, 2H), 7.30–7.24 (m, 2H), 7.12–7.07 (m, 2H), 6.95 (tt, *J* = 7.3, 1.1 Hz, 1H), 6.45 (d, *J* = 10.1 Hz, 1H), 6.20 (dd, *J* = 17.6, 10.8 Hz, 1H), 5.95 (d, *J* = 10.1 Hz, 1H), 5.26 (dd, *J* = 10.8, 1.3 Hz, 1H), 5.21 (dd, *J* = 17.6, 1.3 Hz, 1H), 1.27 (s, 3H), 1.17 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 167.0, 156.9, 142.3, 133.9, 132.1, 129.8, 128.8, 127.1, 121.8, 115.9, 115.2, 83.3, 42.7, 24.0, 22.0. **HRMS** (ESI +) calculated for $C_{19}H_{21}NNaO_2$ $[M+Na]^+$: 318.1464; found: 318.1474.

***N*-(1-(4-Methoxyphenoxy)-2,2-dimethylbut-3-en-1-yl)benzamide (2.44m)**

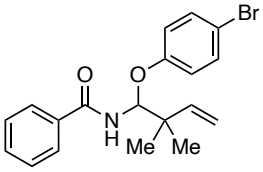
Prepared following the general procedure C using *N*-(2-methylprop-1-en-1-yl) **2.43a** (44 mg, 0.250 mmol, 1.0 equiv), 4-methoxyphenol (62 mg, 0.50 mmol, 2.0 equiv), [JohnPhosAuNCMe]SbF_6 (8 mg, 0.01 mmol, 4 mol%) and 1 atm of acetylene gas in $CHCl_3$ (0.25 mL, 1.0 M) at 23 ºC for 24 h. The crude product was purified by flash column chromatography (SiO_2, cyclohexane/EtOAc 100:0 to 80:20, *v/v*) and the product **2.44m** was obtained as a white solid (41 mg, 0.13 mmol, 50% yield).



M.p. 106–107 ºC. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.73–7.67 (m, 2H), 7.53–7.47 (m, 1H), 7.45–7.37 (m, 2H), 7.05–6.97 (m, 2H), 6.83–6.77 (m, 2H), 6.43 (d, *J* = 10.1 Hz, 1H), 6.18 (dd, *J* = 17.6, 10.8 Hz, 1H), 5.84 (d, *J* = 10.1 Hz, 1H), 5.25 (dd, *J* = 10.9, 1.3 Hz, 1H), 5.20 (dd, *J* = 17.6, 1.4 Hz, 1H), 3.73 (s, 3H), 1.27 (s, 3H), 1.16 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 167.0, 154.6, 151.0, 142.4, 134.0, 132.1, 128.8, 127.1, 117.2, 115.1, 114.8, 84.2, 55.8, 42.6, 24.1, 22.0. **HRMS** (ESI +) calculated for [$C_{20}H_{23}NNaO_3$] $[M+Na]^+$ 348.1570 *m/z*; found 348.1581 *m/z.*

***N*-(1-(4-Bromophenoxy)-2,2-dimethylbut-3-en-1-yl)benzamide (2.44n)**

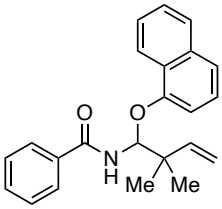
Prepared following the general procedure C using *N*-(2-methylprop-1-en-1-yl) **2.43a** (44 mg, 0.25 mmol, 1.0 equiv), 4-bromophenol (87 mg, 0.50 mmol, 2.0 equiv), [JohnPhosAuNCMe]SbF_6 (8 mg, 0.01 mmol, 4 mol%) and 1 atm of acetylene gas in $CHCl_3$ (0.25 mL, 1.0 M) at 23 ºC for 24 h. The crude product was purified by flash column chromatography (SiO_2, cyclohexane/EtOAc 100:0 to 90:10, *v/v*) and the product **2.44n** was obtained as a white solid (7 mg, 0.02 mmol, 7% yield).



M.p. 135–136 ºC. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.72–7.68 (m, 2H), 7.54–7.49 (m, 1H), 7.46–7.40 (m, 2H), 7.37–7.33 (m, 2H), 7.01–6.95 (m, 2H), 6.44 (d, *J* = 10.2 Hz, 1H), 6.16 (dd, *J* = 17.6, 10.8 Hz, 1H), 5.88 (d, *J* = 10.2 Hz, 1H), 5.27 (dd, *J* = 10.8, 1.2 Hz, 1H), 5.21 (dd, *J* = 17.6, 1.3 Hz, 1H), 1.25 (s, 3H), 1.16 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 167.1, 156.1, 142.0, 133.7, 132.6, 132.3, 128.9, 127.1, 117.8, 115.5, 114.1, 83.5, 42.6, 24.1, 21.9. **HRMS** (ESI +) calculated for [$C_{19}H_{20}BrNNaO_2$] $[M+Na]^+$ 396.0570 *m/z*; found 396.0570 *m/z.*

***N*-(2,2-Dimethyl-1-(naphthalen-1-yloxy)but-3-en-1-yl)benzamide (2.44o)**

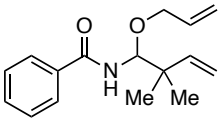
Prepared following the general procedure C using *N*-(2-methylprop-1-en-1-yl) **2.43a** (44 mg, 0.25 mmol, 1.0 equiv), 1-naphthol (72 mg, 0.50 mmol, 2.0 equiv), [JohnPhosAuNCMe]SbF_6 (8 mg, 0.01 mmol, 4 mol%) and 1 atm of acetylene gas in $CHCl_3$ (0.25 mL, 1.0 M) at 23 ºC for 24 h. The crude product was purified by flash column chromatography (SiO_2, cyclohexane/EtOAc 100:0 to 80:20, *v/v*) and the product **2.44o** was obtained as a white solid (11 mg, 0.03 mmol, 13% yield).



M.p. 136–138 ºC. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.77–7.69 (m, 5H), 7.52 (d, *J* = 2.5 Hz, 1H), 7.50–7.42 (m, 1H), 7.43–7.38 (m, 3H), 7.32 (ddd, *J* = 8.1, 6.8, 1.3 Hz, 1H), 7.24 (dd, *J* = 9.0, 2.5 Hz, 1H), 6.49 (d, *J* = 10.1 Hz, 1H), 6.24 (dd, *J* = 17.6, 10.8 Hz, 1H), 6.10 (d, *J* = 10.1 Hz, 1H), 5.29 (dd, *J* = 10.9, 1.3 Hz, 1H), 5.24 (dd, *J* = 17.6, 1.3 Hz, 1H), 1.31 (s, 3H), 1.22 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 167.1, 154.6, 142.3, 134.7, 134.0, 132.1, 129.6, 129.5, 128.8, 127.6, 127.5, 127.1, 126.4, 124.1, 118.7, 115.3, 109.7, 83.4, 42.7, 24.1, 22.0. **HRMS** (ESI +) calculated for [$C_{23}H_{23}NNaO_2$] $[M+Na]^+$ 368.1621 *m/z*; found 368.1628 *m/z.*

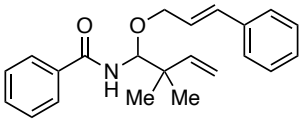
***N*-(1-(Allyloxy)-2,2-dimethylbut-3-en-1-yl)benzamide (2.44p)**

Prepared following the general procedure C using *N*-(2-methylprop-1-en-1-yl) **2.43a** (44 mg, 0.25 mmol, 1.0 equiv), allyl alcohol (34 μL, 0.50 mmol, 2.0 equiv), [JohnPhosAuNCMe]SbF_6 (8 mg, 0.01 mmol, 4 mol%) and 1 atm of acetylene gas in $CHCl_3$ (0.25 mL, 1.0 M) at 23 ºC for 24 h. The crude product was purified by flash column chromatography (SiO_2, cyclohexane/EtOAc 100:0 to 80:20, *v/v*) and the product **2.44p** was obtained as a colourless oil (36 mg, 0.140 mmol, 56% yield).



^{1}H NMR (500 MHz, $CDCl_3$) δ 7.77–7.74 (m, 2H), 7.54–7.50 (m, 1H), 7.47–7.43 (m, 2H), 6.35 (d, *J* = 10.0 Hz, 1H), 6.06 (dd, *J* = 17.7, 10.9 Hz, 1H), 5.90 (dddd, *J* = 17.2, 10.6, 5.7, 5.2 Hz, 1H), 5.30 (dq, *J* = 17.2, 1.7 Hz, 1H), 5.21–5.18 (m, 2H), 5.17–5.12 (m, 2H), 4.14 (ddt, *J* = 13.2, 5.2, 1.5 Hz, 1H), 4.04 (ddt, *J* = 13.2, 5.7, 1.5 Hz, 1H), 1.20 (s, 3H), 1.07 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 167.5, 142.9, 134.6, 134.2, 132.0, 128.8, 127.0, 116.9, 114.5, 84.9, 69.7, 42.1, 24.4, 22.3. **HRMS** (ESI +) calculated for [$C_{16}H_{21}NNaO_2$] $[M+Na]^+$ 282.1464 *m/z*; found 282.1460 *m/z.*

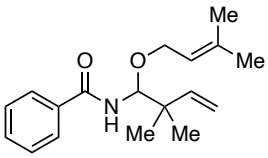
***N*-(1-(Cinnamyloxy)-2,2-dimethylbut-3-en-1-yl)benzamide (2.44q)**



Prepared following the general procedure C using *N*-(2-methylprop-1-en-1-yl) **2.43a** (44 mg, 0.25 mmol, 1.0 equiv), cinnamyl alcohol (64 μL, 0.50 mmol, 2.0 equiv), [JohnPhosAuNCMe]SbF_6 (8 mg, 0.01 mmol, 4 mol%) and 1 atm of acetylene gas in $CHCl_3$ (0.25 mL, 1.0 M) at 23 ºC for 24 h. The crude product was purified by flash column chromatography (SiO_2, cyclohexane/EtOAc 100:0 to 80:20, *v/v*) and the product **2.44q** was obtained as a colourless oil (37 mg, 0.11 mmol, 44% yield).

^{1}H NMR (400 MHz, CD_2Cl_2) δ 7.79–7.74 (m, 2H), 7.57–7.51 (m, 1H), 7.49–7.43 (m, 2H), 7.41–7.35 (m, 2H), 7.34–7.28 (m, 2H), 7.26–7.21 (m, 1H), 6.64 (d, *J* = 15.9 Hz, 1H), 6.41 (d, *J* = 10.0 Hz, 1H), 6.35–6.27 (m, 1H), 6.09 (dd, *J* = 17.6, 10.9 Hz, 1H), 5.27–5.23 (m, 1H), 5.23–5.12 (m, 2H), 4.30 (ddd, *J* = 13.0, 5.7, 1.5 Hz, 1H), 4.20 (ddd, *J* = 13.0, 6.1, 1.4 Hz, 1H), 1.22 (s, 3H), 1.10 (s, 3H). **^{13}C NMR** (101 MHz, CD_2Cl_2) δ 167.6, 143.4, 137.3, 134.7, 132.3, 132.1, 129.0, 128.9, 128.0, 127.3, 126.8, 126.5, 114.4, 85.3, 69.5, 42.4, 24.3, 22.4. **HRMS** (ESI +) calculated for [$C_{22}H_{25}NNaO_2$] $[M+Na]^+$ 358.1777 *m/z*; found 358.1781 *m/z.*

***N*-(2,2-Dimethyl-1-((3-methylbut-2-en-1-yl)oxy)but-3-en-1-yl)benzamide (2.44r)**

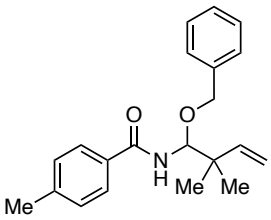


Prepared following the general procedure C using *N*-(2-methylprop-1-en-1-yl)benzamide **2.43a** (44 mg, 0.25 mmol, 1.0 equiv), prenyl alcohol (51 μL, 0.50 mmol, 2.0 equiv), [JohnPhosAuNCMe]SbF_6 (8 mg, 0.01 mmol, 4 mol%) and 1 atm of acetylene gas in $CHCl_3$ (0.25 mL, 1.0 M) at 23 ºC for 24 h. The crude was purified by flash column chromatography (SiO_2, cyclohexane/EtOAc 100:0 to 80:20, *v/v*) to afford the product **2.44r** as colorless oil (31 mg, 0.106 mmol, 42% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.80–7.73 (m, 2H), 7.54–7.50 (m, 1H), 7.47–7.42 (m, 2H), 6.35–6.28 (m, 1H), 6.04 (dd, *J* = 17.6, 10.8 Hz, 1H), 5.32 (tdp, *J* = 7.4, 2.9, 1.4 Hz, 1H), 5.18–5.15 (m, 1H), 5.12 (dd, *J* = 17.6, 1.5 Hz, 1H), 4.14–4.03 (m, 2H), 1.72 (dd, *J* = 2.9, 1.8 Hz, 3H), 1.66–1.62 (m, 3H), 1.17 (s, 3H), 1.06 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 167.5, 143.0, 137.1, 134.4, 131.9, 128.8, 127.0, 121.0, 114.3, 85.1, 65.7, 42.1, 25.9, 24.2, 22.2, 18.3. **HRMS** (ESI +) calculated for $C_{18}H_{25}NNaO_2$ $[M+Na]^+$: 310.1780; found: 310.1780.

***N*-(1-(Benzyloxy)-2,2-dimethylbut-3-en-1-yl)-4-methylbenzamide (2.44s)**

Prepared following the general procedure C using 4-methyl-*N*-(2-methylprop-1-en-1-yl)benzamide

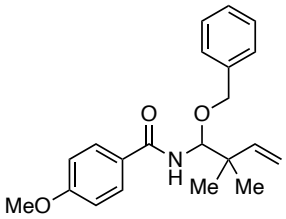


2.43b (47 mg, 0.25 mmol, 1.0 equiv), benzyl alcohol (52 μL, 0.50 mmol, 2.0 equiv), [JohnPhosAuNCMe]SbF_6 (8 mg, 0.01 mmol, 4 mol%) and 1 atm of acetylene gas in $CHCl_3$ (0.25 mL, 1.0 M) at 23 ºC for 24 h. The crude was purified by flash column chromatography (SiO_2, cyclohexane/EtOAc 100:0 to 80:20, *v/v*) to afford the product **2.44s** as a white solid (37 mg, 0.11 mmol, 46% yield).

M.p. 88–91 ºC. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.67–7.63 (m, 2H), 7.37–7.34 (m, 4H), 7.33–7.31 (m, 1H), 7.27–7.23 (m, 2H), 6.36 (d, *J* = 10.0 Hz, 1H), 6.09 (dd, *J* = 17.6, 10.8 Hz, 1H), 5.28 (d, *J* = 10.1 Hz, 1H), 5.20 (dd, *J* = 10.9, 1.4 Hz, 1H), 5.15 (dd, *J* = 17.6, 1.4 Hz, 1H), 4.70–4.65 (m, 1H), 4.58 (dd, *J* = 11.9, 10.2 Hz, 1H), 2.41 (s, 3H), 1.20 (s, 3H), 1.07 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 167.6, 143.0, 142.5, 138.5, 131.3, 129.5, 128.4, 127.7, 127.6, 127.1, 114.5, 85.0, 70.6, 42.1, 24.5, 22.2, 21.6. **HRMS** (ESI +) calculated for $C_{21}H_{25}NNaO_2$ $[M+Na]^+$: 346.1777; found: 346.1783.

***N*-(1-(Benzyloxy)-2,2-dimethylbut-3-en-1-yl)-4-methoxybenzamide (2.44t)**

Prepared following the general procedure C using 4-methoxy-*N*-(2-methylprop-1-en-1-yl)benzamide

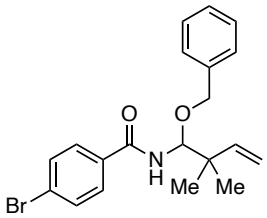


2.43c (37 mg, 0.18 mmol, 1.0 equiv), benzyl alcohol (38 μL, 0.36 mmol, 2.0 equiv), [JohnPhosAuNCMe]SbF_6 (6 mg, 0.007 mmol, 4 mol%) and 1 atm of acetylene gas in $CHCl_3$ (0.18 mL, 1.0 M) at 23 ºC for 24 h. The crude was purified by flash column chromatography (SiO_2, cyclohexane/EtOAc 100:0 to 80:20, *v/v*) to afford the product **2.44t** as a white solid (50 mg, 0.15 mmol, 82% yield).

M.p. 120–122 ºC. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.75–7.68 (m, 2H), 7.39–7.29 (m, 4H), 7.29–7.24 (m, 1H), 6.97–6.91 (m, 2H), 6.31 (d, *J* = 10.0 Hz, 1H), 6.10 (dd, *J* = 17.6, 10.8 Hz, 1H), 5.28 (d, *J* = 10.1 Hz, 1H), 5.20 (dd, *J* = 10.9, 1.4 Hz, 1H), 5.15 (dd, *J* = 17.6, 1.4 Hz, 1H), 4.67 (d, *J* = 12.1 Hz, 1H), 4.59 (d, *J* = 12.1 Hz, 1H), 3.86 (s, 3H), 1.20 (s, 3H), 1.07 (s, 3H).**^{13}C NMR** (126 MHz, $CDCl_3$) δ 167.1, 162.6, 143.0, 138.6, 128.9, 128.4, 127.7, 127.5, 126.3, 114.0, 85.1, 70.6, 55.6, 42.1, 29.8, 24.5, 22.2. **HRMS** (ESI +) calculated for $C_{21}H_{25}NNaO_3$ $[M+Na]^+$: 362.1727; found: 362.1730.

***N*-(1-(Benzyloxy)-2,2-dimethylbut-3-en-1-yl)-4-bromobenzamide (2.44u)**

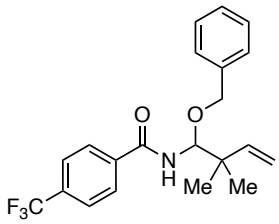
Prepared following the general procedure C using 4-bromo-*N*-(2-methylprop-1-en-1-yl)benzamide



2.43d (64 mg, 0.25 mmol, 1.0 equiv),benzyl alcohol (52 μL, 0.50 mmol, 2.0 equiv), [JohnPhosAuNCMe]SbF_6 (8 mg, 0.01 mmol, 4 mol%) and 1 atm of acetylene gas in $CHCl_3$ (0.25 mL, 1.0 M) at 23 ºC for 24 h. The crude was purified by flash column chromatography (SiO_2, cyclohexane/EtOAc 100:0 to 90:10, *v/v*) to afford the product **2.44u** as a white sticky solid (88 mg, 0.23 mmol, 91% yield). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.58 (s, 4H), 7.37–7.30 (m, 4H), 7.27 (dd, *J* = 7.4, 1.5 Hz, 1H), 6.32 (d, *J* = 10.0 Hz, 1H), 6.08 (dd, *J* = 17.6, 10.8 Hz, 1H), 5.26 (d, *J* = 10.0 Hz, 1H), 5.20 (dd, *J* = 10.8, 1.4 Hz, 1H), 5.14 (dd, *J* = 17.7, 1.4 Hz, 1H), 4.66 (d, *J* = 12.1 Hz, 1H), 4.60 (d, *J* = 12.1 Hz, 1H), 1.20 (s, 3H), 1.06 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 166.6, 142.7, 138.3, 132.0, 128.5, 127.8, 127.6, 114.6, 98.9, 85.1, 70.7, 67.0, 42.0, 24.3, 22.1, 19.8. **HRMS** (ESI +) calculated for $C_{20}H_{22}BrNNaO_2$ $[M+Na]^+$: 410.0726; found: 410.0731.

***N*-(1-(Benzyloxy)-2,2-dimethylbut-3-en-1-yl)-4-(trifluoromethyl)benzamide (2.44v)**

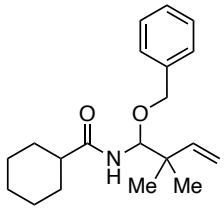
Prepared following the general procedure C using *N*-(2-methylprop-1-en-1-yl)-4-(trifluoromethyl)benzamide **2.43e** (55 mg, 0.23 mmol, 1.0 equiv), benzyl alcohol (47 μL, 0.45 mmol, 2.0 equiv), [JohnPhosAuNCMe]SbF_6 (7.0 mg, 0.009 mmol, 4 mol%) and 1 atm of acetylene gas in $CHCl_3$ (0.23 mL, 1.0 M) at 23 ºC for 24 h. The crude was purified by flash column chromatography (SiO_2, cyclohexane/EtOAc 100:0 to 90:10, *v/v*) to afford the product **2.44v** as a colorless sticky solid (46 mg, 0.12 mmol, 55% yield).



^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 (d, *J* = 8.1 Hz, 2H), 7.71 (d, *J* = 8.2 Hz, 2H), 7.38–7.32 (m, 3H), 7.31–7.27 (m, 2H), 6.36 (d, *J* = 9.9 Hz, 1H), 6.08 (dd, *J* = 17.6, 10.8 Hz, 1H), 5.28 (d, *J* = 10.0 Hz, 1H), 5.21 (dd, *J* = 10.8, 1.3 Hz, 1H), 5.15 (dd, *J* = 17.6, 1.4 Hz, 1H), 4.67 (d, *J* = 12.1 Hz, 1H), 4.61 (d, *J* = 12.1 Hz, 1H), 1.20 (s, 3H), 1.07 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 166.4, 142.8, 138.3, 137.5, 133.9, 133.6 (q, J_{C-F} = 32.8 Hz), 128.5, 127.7, 127.5, 125.9 (q, J_{C-F} = 3.8 Hz), 122.4 (q, J_{C-F} = 273.9 Hz), 114.8, 85.3, 71.0, 42.2, 24.3, 22.3. **^{19}F NMR** (376 MHz, $CDCl_3$) δ −63.1. **HRMS** (ESI +) calculated for $C_{21}H_{22}F_3NNaO_2$ $[M+Na]^+$: 400.1495; found: 400.1497.

***N*-(1-(Benzyloxy)-2,2-dimethylbut-3-en-1-yl)cyclohexanecarboxamide (2.44w)**

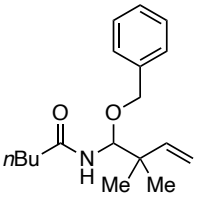
Prepared following the general procedure C using *N*-(2-methylprop-1-en-1-yl)cyclohexanecarboxamide **2.43f** (28 mg, 0.15 mmol, 1.0 equiv),benzyl alcohol (32 μL, 0.31 mmol, 2.0 equiv), [JohnPhosAuNCMe]SbF_6 (5 mg, 0.006 mmol, 4 mol%) and 1 atm of acetylene gas in $CHCl_3$ (0.15 mL, 1.0 M) at 23 ºC for 24 h. The crude was purified by flash column chromatography (SiO_2, cyclohexane/EtOAc 100:0 to 70:30, *v/v*) to afford the product **2.44w** as white crystals (27 mg, 0.08 mmol, 51% yield).



M.p. 77–81 ºC. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.33 (d, *J* = 4.4 Hz, 4H), 7.29–7.23 (m, 1H), 5.99 (dd, *J* = 17.6, 10.8 Hz, 1H), 5.67 (d, *J* = 10.1 Hz, 1H), 5.17–5.10 (m, 2H), 5.09–5.04 (m, 2H), 4.57 (d, *J* = 12.1 Hz, 1H), 4.49 (d, *J* = 12.1 Hz, 1H), 2.08 (tt, *J* = 11.7, 3.5 Hz, 1H), 1.90–1.75 (m, 3H), 1.72–1.64 (m, 1H), 1.42 (tdd, *J* = 11.5, 9.4, 5.4 Hz, 2H), 1.34–1.19 (m, 3H), 1.12 (s, 3H), 0.99 (s, 3H).**^{13}C NMR** (101 MHz, $CDCl_3$) δ 176.5, 143.0, 138.6, 128.3, 127.7, 127.5, 114.3, 84.3, 70.4, 45.9, 41.8, 30.0, 29.8, 25.9, 25.8, 25.8, 24.3, 22.3. **HRMS** (ESI +) calculated for $C_{20}H_{29}NNaO_2$ $[M+Na]^+$: 338.2090; found: 338.2101.

***N*-(1-(Benzyloxy)-2,2-dimethylbut-3-en-1-yl)pentanamide (2.44x)**

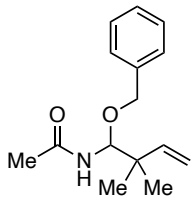
Prepared following the general procedure C using *N*-(2-methylprop-1-en-1-yl)pentanamide **2.43g** (39 mg, 0.25 mmol, 1.0 equiv), benzyl alcohol (52 μL, 0.50 mmol, 2.0 equiv), [JohnPhosAuNCMe]SbF_6 (8 mg, 0.01 mmol, 4 mol%) and 1 atm of acetylene gas in $CHCl_3$ (0.25 mL, 1.0 M) at 23 ºC for 24 h. The crude was purified by flash column chromatography (SiO_2, cyclohexane/EtOAc 100:0 to 50:50, *v/v*) to afford the product **2.44x** as a colorless oil (22 mg, 0.08 mmol, 32% yield).



^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35–7.31 (m, 4H), 7.30–7.25 (m, 1H), 5.99 (dd, *J* = 17.6, 10.8 Hz, 1H), 5.63 (d, *J* = 10.2 Hz, 1H), 5.13 (dd, *J* = 10.8, 1.4 Hz, 1H), 5.11–5.05 (m, 2H), 4.59 (d, *J* = 12.1 Hz, 1H), 4.51 (d, *J* = 12.1 Hz, 1H), 2.18 (ddd, *J* = 9.0, 6.5, 1.4 Hz, 2H), 1.68–1.54 (m, 2H), 1.42–1.31 (m, 2H), 1.12 (s, 3H), 1.00 (s, 3H), 0.92 (t, *J* = 7.4 Hz, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 173.7, 142.9, 138.6, 128.4, 127.7, 127.6, 114.3, 84.5, 70.5, 41.7, 36.8, 27.8, 24.2, 22.5, 22.3, 13.9. **HRMS** (ESI +) calculated for $C_{18}H_{27}NNaO_2$ $[M+Na]^+$: 312.1934; found: 312.1941.

_N_-(1-(Benzyloxy)-2,2-dimethylbut-3-en-1-yl)acetamide (2.44z)

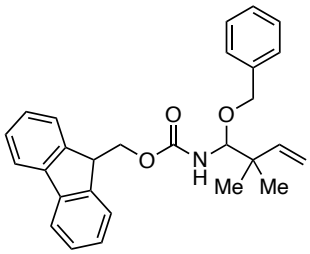
Prepared following the general procedure C using _N_-(2-methylprop-1-en-1-yl)acetamide **2.43i** (28 mg, 0.25 mmol, 1.0 equiv), benzyl alcohol (52 μL, 0.50 mmol, 2.0 equiv), [JohnPhosAuNCMe]SbF_6 (8 mg, 0.01 mmol, 4 mol%) and 1 atm of acetylene gas in $CHCl_3$ (0.25 mL, 1.0 M) at 23 ºC for 24 h. The crude was purified by flash column chromatography (SiO_2, cyclohexane/EtOAc 100:0 to 40:60, *v/v*) to afford the product **2.44z** as a colorless oil (9 mg, 0.04 mmol, 15% yield).



^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33 (d, *J* = 4.4 Hz, 4H), 7.29–7.26 (m, 1H), 5.98 (dd, *J* = 17.6, 10.8 Hz, 1H), 5.64 (d, *J* = 10.2 Hz, 1H), 5.17–5.09 (m, 1H), 5.09–5.03 (m, 1H), 4.60 (d, *J* = 12.1 Hz, 1H), 4.52 (d, *J* = 12.1 Hz, 1H), 1.99 (s, 3H), 1.12 (s, 3H), 1.01 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 170.7, 142.8, 138.5, 128.4, 127.6, 127.6, 114.3, 84.7, 70.6, 41.7, 24.2, 23.6, 22.2. **HRMS** (ESI +) calculated for $C_{15}H_{21}NNaO_2$ $[M+Na]^+$: 270.1464; found: 270.1469.

(9*H*-Fluoren-9-yl)methyl 2-((1-(benzyloxy)-2,2-dimethylbut-3-en-1-yl)amino)-2-oxoacetate (2.44aa)

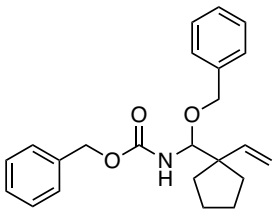
Prepared following the general procedure C using (9*H*-fluoren-9-yl)methyl (2-methylprop-1-en-1-yl)carbamate **2.43j** (73 mg, 0.25 mmol, 1.0 equiv), benzyl alcohol (52 μL, 0.50 mmol, 2.0 equiv), [JohnPhosAuNCMe]SbF_6 (8 mg, 0.01 mmol, 4 mol%) and 1 atm of acetylene gas in $CHCl_3$ (0.25 mL, 1.0 M) at 23 ºC for 24 h. The crude was purified by flash column chromatography (SiO_2, cyclohexane/EtOAc 100:0 to 80:20, *v/v*) to afford the product **2.44aa** as a white sticky solid (35 mg, 0.08 mmol, 32% yield).



^{1}H NMR (500 MHz, $CDCl_3$) δ 7.77 (dd, *J* = 7.6, 4.6 Hz, 2H), 7.62–7.56 (m, 2H), 7.43–7.38 (m, 2H), 7.34–7.29 (m, 7H), 5.96 (dd, *J* = 17.6, 10.9 Hz, 1H), 5.14 (dd, *J* = 10.8, 1.4 Hz, 1H), 5.11–5.05 (m, 1H), 5.05 (d, *J* 10.5 Hz, 1H), 4.79 (d, *J* = 10.5 Hz, 1H), 4.58 (d, *J* = 12.0 Hz, 1H), 4.52–4.46 (m, 1H), 4.46 (s, 1H), 4.23 (t, *J* = 6.9 Hz, 1H), 1.11 (s, 3H), 1.01 (s, 3H).**^{13}C NMR** (126 MHz, $CDCl_3$) δ 156.4, 144.0, 142.7, 141.5, 138.4, 128.4, 127.9, 127.8, 127.6, 127.2, 125.2, 120.2, 120.2, 114.4, 87.4, 70.2, 66.7, 47.5, 42.0, 24.1, 22.3. **HRMS** (ESI +) calculated for $C_{28}H_{29}NNaO_3$ $[M+Na]^+$: 450.2040; found: 450.2049.

***N*-((Benzyloxy)(1-vinylcyclopentyl)methyl)benzamide (2.44ad)**

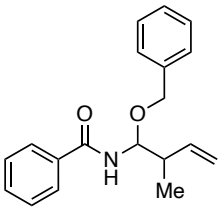
Prepared following the general procedure C using *N*-(cyclopentylidenemethyl)benzamide **2.43m** (50 mg, 0.25 mmol, 1.0 equiv), benzyl alcohol (52 μL, 0.50 mmol, 2.0 equiv), [JohnPhosAuNCMe]SbF_6 (8 mg, 0.01 mmol, 4 mol%) and 1 atm of acetylene gas in $CHCl_3$ (0.25 mL, 1.0 M) at 23 ºC for 24 h. The crude was purified by flash column chromatography (SiO_2, cyclohexane/EtOAc 100:0 to 80:20, *v/v*) to afford the product **2.44ad** as colorless oil (38 mg, 0.11 mmol, 45% yield).



^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76–7.72 (m, 2H), 7.53 (ddt, *J* = 8.3, 6.5, 1.4 Hz, 1H), 7.45 (ddt, *J* = 8.1, 6.5, 1.3 Hz, 2H), 7.39–7.34 (m, 3H), 7.33–7.31 (m, 1H), 7.28 (d, *J* = 1.7 Hz, 1H), 6.52 (d, *J* = 10.0 Hz, 1H), 6.13 (dd, *J* = 17.7, 10.8 Hz, 1H), 5.35 (d, *J* = 10.0 Hz, 1H), 5.28 (dd, *J* = 10.8, 1.4 Hz, 1H), 5.20 (dd, *J* = 17.7, 1.4 Hz, 1H), 4.68 (d, *J* = 12.2 Hz, 1H), 4.60 (d, *J* = 12.2 Hz, 1H), 1.84 (dt, *J* = 13.1, 7.9 Hz, 1H), 1.78–1.68 (m, 2H), 1.67–1.60 (m, 3H), 1.53 (ddd, *J* = 15.8, 8.0, 4.1 Hz, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 167.5, 141.3, 138.6, 134.2, 132.0, 128.8, 128.4, 127.8, 127.6, 127.1, 115.3, 84.4, 70.5, 54.6, 36.0, 31.6, 24.1, 24.0. **HRMS** (ESI +) calculated for $C_{22}H_{25}NNaO_2$ $[M+Na]^+$: 358.1798; found: 358.1781.

***N*-(1-(Benzyloxy)-2-methylbut-3-en-1-yl)benzamide (2.44ae)**

Prepared following the general procedure C using (*E*)-*N*-(prop-1-en-1-yl)benzamide **2.43n** (40 mg, 0.250 mmol, 1.0 equiv), benzyl alcohol (52 μL, 0.50 mmol, 2.0 equiv), [JohnPhosAuNCMe]SbF_6 (8 mg, 0.01 mmol, 4 mol%) and 1 atm of acetylene gas in $CHCl_3$ (0.25 mL, 1.0 M) at 23 ºC for 24 h. The crude was purified by flash column chromatography (SiO_2, cyclohexane/EtOAc 100:0 to 80:20, *v/v*) to afford the product **2.44ae** as a colorless oil (9 mg, 0.03 mmol, 12% yield, 54:46 *dr*).

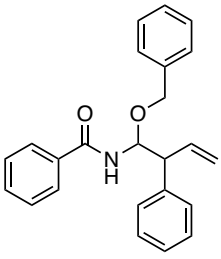


^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77–7.71 (m, 2H), 7.53 (tq, *J* = 6.6, 1.2 Hz, 1H), 7.45 (ddd, *J* = 8.6, 6.6, 1.6 Hz, 2H), 7.39–7.30 (m, 4H), 7.30–7.25 (m, 1H), 6.54 (d, *J* = 9.8 Hz, 0.5H), 6.37 (d, *J* = 9.9 Hz, 0.5H), 6.07–5.88 (m, 1H), 5.47 (ddd, *J* = 10.0, 8.2, 4.7 Hz, 1H), 5.24–5.14 (m, 2H), 4.79–4.56 (m, 2H), 2.70 (td, *J* = 7.0, 5.6 Hz, 0.5H), 2.46 (dq, *J* = 10.9, 7.0 Hz, 0.5 H), 1.17 (d, *J* = 6.9 Hz, 1.5H), 1.12 (d, *J* = 6.9 Hz, 1.5H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 167.7, 167.3, 138.7, 138.5, 138.4, 138.3, 134.2, 134.2, 132.0, 132.0, 128.8, 128.8, 128.5, 128.4, 127.8, 127.8, 127.7, 127.7, 127.1, 127.1, 117.2, 116.7, 82.5, 81.9, 70.7, 70.6, 44.1, 42.4, 16.5, 15.0. **HRMS** (ESI +) calculated for $C_{19}H_{21}NNaO_2$ $[M+Na]^+$: 318.1464; found: 318.1476.

The experimental procedure described above was also performed using (*Z*)-*N*-(prop-1-en-1-yl)benzamide **2.43n** to afford the product **2.44ae** as a colorless oil (6 mg, 0.021 mmol, 8% yield, 50:50 *dr*).

***N*-(1-(Benzyloxy)-2-phenylbut-3-en-1-yl)benzamide (2.44af)**

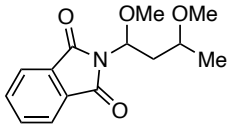
Prepared following the general procedure C using (*E*)-*N*-styrylbenzamide **2.43o** (56 mg, 0.25 mmol, 1.0 equiv), benzyl alcohol (52 μL, 0.50 mmol, 2.0 equiv), [JohnPhosAuNCMe]SbF_6 (8 mg, 0.01 mmol, 4 mol%) and 1 atm of acetylene gas in $CHCl_3$ (0.25 mL, 1.0 M) at 23 ºC for 24 h. The crude was purified by flash column chromatography (SiO_2, cyclohexane/EtOAc 100:0 to 80:20, *v/v*) to afford the product **2.44af** as a white solid (35 mg, 0.10 mmol, 39% yield, 50:50 *dr*).



M.p. 93–97 ºC. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.71–7.67 (m, 1H), 7.67–7.63 (m, 1H), 7.55–7.49 (m, 1H), 7.46–7.40 (m, 2H), 7.37–7.33 (m, 4H), 7.33–7.29 (m, 1H), 7.29–7.24 (m, 4H), 7.22–7.18 (m, 1H), 6.51 (d, *J* = 9.9 Hz, 0.5H), 6.36–6.27 (m, 1H), 6.26–6.16 (m, 0.5H), 5.85 (ddd, *J* = 9.7, 6.1, 5.2 Hz, 1H), 5.33 (ddd, *J* = 10.3, 1.6, 0.8 Hz, 0.5H), 5.26 (ddd, *J* = 17.2, 1.7, 1.1 Hz, 0.5H), 5.22–5.14 (m, 1H), 4.69 (dd, *J* = 12.0, 3.7 Hz, 1H), 4.59 (dd, *J* = 12.0, 9.7 Hz, 1H), 3.69 (dd, *J* = 8.6, 4.4 Hz, 0.5H), 3.65 (ddt, *J* = 8.1, 5.9, 1.1 Hz, 0.5H).**^{13}C NMR** (126 MHz, $CDCl_3$) δ 167.3, 167.3, 139.6, 139.2, 138.2, 138.1, 137.5, 136.3, 134.1, 134.0, 132.0, 132.0, 129.2, 128.8, 128.8, 128.7, 128.7, 128.6, 128.4, 128.4, 127.7, 127.7, 127.6, 127.6, 127.3, 127.2, 127.1, 127.0, 118.7, 117.5, 81.9, 81.5, 70.9, 70.8, 55.7, 55.2. **HRMS** (ESI +) calculated for $C_{24}H_{23}NNaO_2$ $[M+Na]^+$: 380.1621; found: 380.1633.

2-(1,3-Dimethoxybutyl)isoindoline-1,3-dione (2.46a)

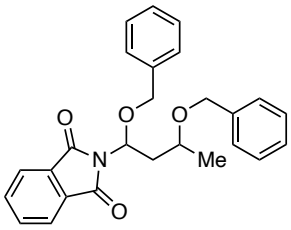
Prepared following the general procedure D using *N*-vinyl phthalimide **2.45** (43 mg, 0.25 mmol, 1.0 equiv), MeOH (20 μL, 0.50 mmol, 2.0 equiv), [JohnPhosAuNCMe]SbF_6 (8 mg, 0.01 mmol, 4 mol%) and 1 atm of acetylene gas in $CHCl_3$ (0.25 mL, 1.0 M) at 23 ºC for 24 h. The crude product was purified by flash column chromatography (SiO_2, cyclohexane/EtOAc 100:0 to 90:10, *v/v*) and the product **2.46a** was obtained as a colourless oil (61 mg, 0.23 mmol, 93% yield, 52:48 *dr*).



^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91–7.84 (m, 2H), 7.78–7.71 (m, 2H), 5.49 (ddd, *J* = 8.5, 5.0, 2.5 Hz, 1H), 3.52 (dqd, *J* = 9.5, 6.1, 3.3 Hz, 0.5 H), 3.35 (s, 1.5H), 3.33 (s, 1.5H), 3.29–3.19 (m, 3.5H), 2.57–2.45 (m, 1H), 2.27 (ddd, *J* = 14.1, 8.6, 5.4 Hz, 0.5H), 2.03 (ddd, *J* = 14.3, 9.6, 4.7 Hz, 0.5H), 1.16 (d, *J* = 6.2 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 168.2, 168.2, 134.4, 134.3, 131.9, 131.8, 123.7, 123.6, 81.1, 81.0, 73.7, 73.6, 56.7, 56.6, 56.3, 56.3, 40.1, 38.9, 19.2, 18.9. **HRMS** (ESI +) calculated for $[C_{14}H_{17}NNaO_4]$ $[M+Na]^+$ 286.1050 *m/z*; found 286.1059 *m/z*.

2-(1,3-Bis(benzyloxy)butyl)isoindoline-1,3-dione (2.46b)

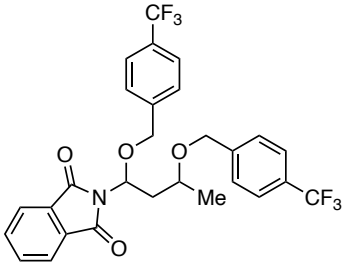
Prepared following the general procedure D using *N*-vinyl phthalimide **2.45** (43 mg, 0.25 mmol, 1.0 equiv), benzyl alcohol (52 μL, 0.50 mmol, 2.0 equiv), [JohnPhosAuNCMe]SbF_6 (8 mg, 0.01 mmol, 4 mol%) and 1 atm of acetylene gas in $CHCl_3$ (0.25 mL, 1.0 M) at 23 ºC for 24 h. The crude product was purified by flash column chromatography (SiO_2, cyclohexane/EtOAc 100:0 to 95:5, *v/v*) and the product **2.46b** was obtained as a colouless oil (62 mg, 0.15 mmol, 60% yield, 58:42 *dr*).



^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83–7.74 (m, 2H), 7.73–7.65 (m, 2H), 7.35–7.16 (m, 9H), 7.15–7.08 (m, 1H), 5.80–5.71 (m, 1H), 4.62–4.41 (m, 3H), 4.29 (d, *J* = 11.2 Hz, 0.4H), 4.18 (d, *J* = 11.5 Hz, 0.6H), 3.74 (dqd, *J* = 9.3, 6.2, 3.0 Hz, 0.6H), 3.55–3.45 (m, 0.4H), 2.72–2.61 (m, 1H), 2.41 (ddd, *J* = 14.0, 8.4, 5.3 Hz, 0.4H), 2.09 (ddd, *J* = 14.1, 9.8, 4.0 Hz, 0.6H), 1.25–1.18 (m, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 168.2, 168.1, 138.8, 138.4, 137.5, 137.5, 134.2, 134.2, 131.8, 131.8, 128.4, 128.4, 128.2, 128.1, 127.9, 127.9, 127.8, 127.7, 127.6, 127.5, 123.5, 123.5, 79.4, 78.9, 71.7, 71.5, 71.4, 71.3, 70.7, 70.6, 40.8, 39.3, 19.8, 19.4. **HRMS** (ESI +) calculated for [$C_{26}H_{25}NNaO_4$] $[M+Na]^+$ 438.1676 *m/z*; found 438.1670 *m/z*.

2-(1,3-Bis((4-(trifluoromethyl)benzyl)oxy)butyl)isoindoline-1,3-dione (2.46d)

Prepared following the general procedure D using *N*-vinyl phthalimide **2.45** (43 mg, 0.25 mmol, 1.0 equiv), 4-(trifluoromethyl)benzyl alcohol (66 μL, 0.50 mmol, 2.0 equiv), [JohnPhosAuNCMe]SbF_6 (8 mg, 0.01 mmol, 4 mol%) and 1 atm of acetylene gas in $CHCl_3$ (0.25 mL, 1.0 M) at 23 ºC for 24 h. The crude product was purified by flash column chromatography (SiO_2, cyclohexane/EtOAc 100:0 to 95:5, *v/v*) and the product **2.46d** was obtained as a colouless oil (106 mg, 0.18 mmol, 71% yield, 42:58 *dr*), co-eluted with **2.52** (13%).

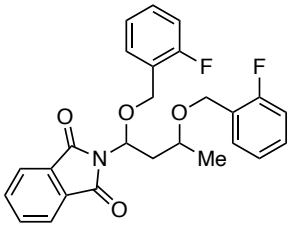


^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78–7.72 (m, 2H), 7.72–7.64 (m, 2H), 7.56–7.27 (m, 8H), 5.80–5.70 (m, 1H), 4.70–4.64 (m, 0.6H), 4.60–4.47 (m, 2.4H), 4.32 (d, *J* = 11.5 Hz, 0.6H), 4.22 (d, *J* = 12.0 Hz, 0.4H), 3.77 (dqd, *J* = 9.3, 6.1, 3.0 Hz, 0.4H), 3.53 (dqd, *J* = 8.5, 6.2, 3.8 Hz, 0.6H), 2.78–2.65 (m, 1H), 2.41 (ddd, *J* = 14.4, 8.4, 5.2 Hz, 0.6H), 2.17 (ddd, *J* = 14.4, 9.9, 4.4 Hz, 0.4H), 1.29–1.22 (m, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 168.1, 168.0, 139.8, 139.4, 138.6, 138.5, 134.4, 134.3, 131.6, 131.5, 131.3, 131.2, 131.2, 131.0, 131.0, 30.8, 130.7, 130.7 (q, J_{C-F} = 32.6 Hz), 130.7 (q, J_{C-F} = 32.1 Hz), 128.9, 128.9, 124.6, 124.6, 124.6, 124.5, 124.5, 124.5, 124.5, 124.4, 124.4, 124.4, 124.3, 124.3, 124.3, 124.1 (q, J_{C-F} = 3.8 Hz), 123.6, 123.5, 124.3 (q, J_{C-F} = 272.2 Hz), 124.2 (q, J_{C-F} = 272.3 Hz), 124.1 (q, J_{C-F} = 272.4 Hz), 124.0 (q, J_{C-F} = 272.3 Hz), 79.6, 79.1, 72.3, 72.2, 70.8, 70.5, 70.1, 69.7, 40.4, 39.1, 19.7,

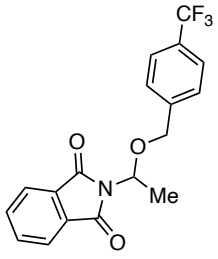
19.4. **^{19}F NMR** (376 MHz, $CDCl_3$) δ −62.66, −62.67, −62.83, −62.84. **HRMS** (ESI +) calculated for $[C_{28}H_{23}F_6NNaO_4]$ $[M+Na]^+$ 574.1423 *m/z*; found 574.1427 *m/z*.[50]

2-(1,3-Bis((2-fluorobenzyl)oxy)butyl)isoindoline-1,3-dione (2.46e)

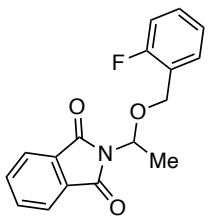
Prepared following the general procedure D using *N*-vinyl phthalimide **2.45** (43 mg, 0.25 mmol, 1.0 equiv), 2-fluorobenzyl alcohol (54 μL, 0.50 mmol, 2.0 equiv), $[JohnPhosAuNCMe]SbF_6$ (8 mg, 0.01 mmol, 4 mol%) and 1 atm of acetylene gas in $CHCl_3$ (0.25 mL, 1.0 M) at 23 ºC for 24 h. The crude product was purified by flash column chromatography (SiO_2, cyclohexane/EtOAc 100:0 to 95:5, *v/v*) and the product **2.46e** was obtained as a colouless oil (90 mg, 0.18 mmol, 72% yield, 54:46 *dr*), co-eluted with **2.53** (16%).



^{1}H NMR (500 MHz, $CDCl_3$) δ 7.87–7.80 (m, 2H), 7.76–7.68 (m, 2H), 7.43–7.30 (m, 2H), 7.24–6.89 (m, 6H), 5.81–5.74 (m, 1H), 4.64–4.53 (m, 2.5H), 4.47 (d, *J* = 12.2 Hz, 0.5H), 4.36–4.28 (m, 1H), 3.85–3.75 (m, 0.5H), 3.58–3.49 (m, 0.5H), 2.77–2.62 (m, 1H), 2.41 (ddd, *J* = 14.1, 8.5, 5.4 Hz, 0.5H), 2.05 (ddd, *J* = 14.1, 10.1, 3.8 Hz, 0.5H), 1.27–1.21 (m, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 168.1, 168.1, 160.8 (d, J_{C-F} = 247.8 Hz), 160.7 (d, J_{C-F} = 247.2 Hz), 160.6 (d, J_{C-F} = 246.4), 160.6 (d, J_{C-F} = 246.2), 134.3, 134.3, 131.8, 131.8, 130.5, 130.5, 130.4, 130.4, 130.3, 130.2, 130.1, 130.0, 129.7, 129.6, 129.6, 129.5, 129.2, 129.2, 129.2, 129.1, 125.9 (d, J_{C-F} = 14.6 Hz), 125.6 (d, J_{C-F} = 14.6 Hz), 124.6 (d, J_{C-F} = 14.4 Hz), 124.5 (d, J_{C-F} = 14.5 Hz), 124.2, 124.2, 124.1, 124.1, 124.1, 124.1, 124.0, 124.0, 123.6, 123.5, 115.4, 115.4, 115.2, 115.2, 115.2, 115.2, 115.0, 115.0, 79.2, 79.0, 72.1, 71.9, 64.9 (d, J_{C-F} = 3.7 Hz), 64.8 (d, J_{C-F} = 3.9 Hz), 64.0 (d, J_{C-F} = 4.0 Hz), 63.8 (d, J_{C-F} = 4.0 Hz), 40.7, 39.2, 19.7, 19.3. **^{19}F NMR** (376 MHz, $CDCl_3$) δ −118.38, −118.55, −118.65, −119.23, −119.31. **HRMS** (ESI +) calculated for $[C_{26}H_{23}F_2NNaO_4]$ $[M+Na]^+$ 474.1487 *m/z*; found 474.1499 *m/z*.[21]



2.52



2.53

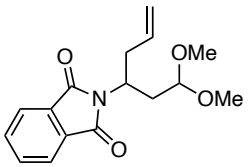
Note on impurity **2.46d** and **2.46e**: As stated above, products **2.46d** and **2.46e** could not be separated from side-products **2.52** and **2.53** The identification of these compounds was determined through comparison to the literature for related phthalimide-containing hemiaminal compounds.[51]

50. The multiplicity and coupling constants for the ^{13}C NMR are given where possible, while the rest of the signals are listed due to the presence of diastereomers and fluorine-coupling.

51. (a) Adamek, J.; Mazurkiewicz, R.; Węgrzyk, A.; Erfurt, K. *Beilstein J. Org. Chem.* **2017**, *13*, 1446–1455. (b) Gasonoo, M.; Thom, Z. W.; Laulhé, S. *J. Org. Chem.* **2019**, *84*, 8710–8716.

2-(6-Methoxyhept-1-en-4-yl)isoindoline-1,3-dione (2.47)

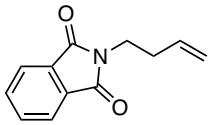
Adapted from literature procedure.[52] To a solution of **2.46a** (26 mg, 0.10 mmol, 1.0 equiv), $BF_3{\cdot}OEt_2$ (25 µL, 0.20 mmol, 2.0 equiv) in CH_2Cl_2 (0.25 mL, 0.4 M) under argon was added allyltrimethylsilane (32 µL, 0.20 mmol, 2.0 equiv). The reaction was stirred for 16 h, after which it was quenched by addition of by addition of sat. aq. $NaHCO_3$ (0.2 mL) at 0 °C. The mixture was extracted with CH_2Cl_2 (3 x 0.5 mL) and the orgnic phase washed with brine (1 mL), dried over anhydrous $MgSO_4$ and filtered. Following concentration under vacuo, the crude product was purified by preparative TLC (SiO_2, cyclohexane/EtOAc 80:20, *v/v*) and the product **2.47** was obtained as a colourless oil (20 mg, 0.07 mmol, 73% yield, 59:41 *dr*).



^{1}H NMR (300 MHz, $CDCl_3$) δ 7.85–7.77 (m, 2H), 7.73–7.65 (m, 2H), 5.70 (dddd, *J* = 16.9, 10.1, 8.3, 6.0 Hz, 1H), 5.09–4.88 (m, 2H), 4.65–4.53 (m, 0.4H), 4.49–4.37 (m, 0.6H), 3.37–3.25 (m, 0.6H), 3.22 (s, 1.2H), 3.17–3.06 (m, 2.2 H), 2.89–2.72 (m, 1H), 2.58–2.28 (m, 2H), 1.83–1.68 (m, 1H), 1.15–1.08 (m, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 168.8, 168.8, 134.8, 134.7, 134.0, 133.9, 132.1, 132.0, 123.2, 123.2, 118.0, 117.9, 75.4, 74.0, 56.5, 56.1, 49.5, 48.4, 39.2, 38.5, 37.4, 37.3, 19.2, 19.0. **HRMS** (ESI +) calculated for $[C_{16}H_{19}NNaO_3]$ $[M+Na]^+$ 296.1257 *m/z*; found 296.1256 *m/z.*

2-(But-3-en-1-yl)isoindoline-1,3-dione (2.48)

To a mixture of phthalimide (1.41 g, 9.60 mmol, 1.0 equiv), K_2CO_3 (3.32 g, 24.0 mmol, 3.0 equiv) in acetonitrile (20.0 mL, 0.5 M), in a 50 mL round-bottom flask, was added 4-bromobut-1-ene (0.8 ml, 8.00 mmol, 1.0 equiv). The reaction mixture was then stirred at 90 °C in a metallic heating block for 16 h afterwich the reaction mixture was filtered through Celite and concentrated under vacuo. The crude product was purified by flash column chromatography (SiO_2, cyclohexane/EtOAc 95:5, *v/v*) and the product **2.48** was obtained as a white solid (1.45 g, 7.21 mmol, 90% yield).

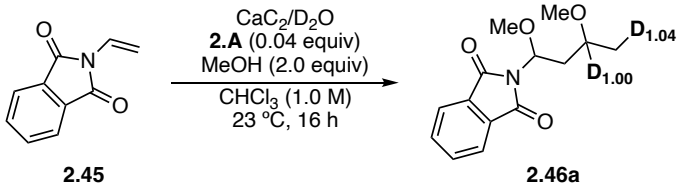


^{1}H NMR (500 MHz, $CDCl_3$) δ 7.86–7.82 (m, 2H), 7.73–7.69 (m, 2H), 5.79 (ddt, *J* = 17.1, 10.2, 6.9, 1H), 5.09–5.04 (m, 1H), 5.04–5.00 (m, 1H), 3.77 (t, *J* = 7.1 Hz, 2H), 2.48–2.42 (m, 2H). The characterization data matches those reported in the literature.[53]

52. Kende, A. S.; Martin Hernando, J. I.; Milbank, J. B. J. *Tetrahedron* **2002**, *58*, 61–74.
53. Chen, X.-M.; Ning, X.-S.; Kang, Y.-B. *Org. Lett.* **2016**, *18*, 5368–5371.

Deuterium Labelling Experiments

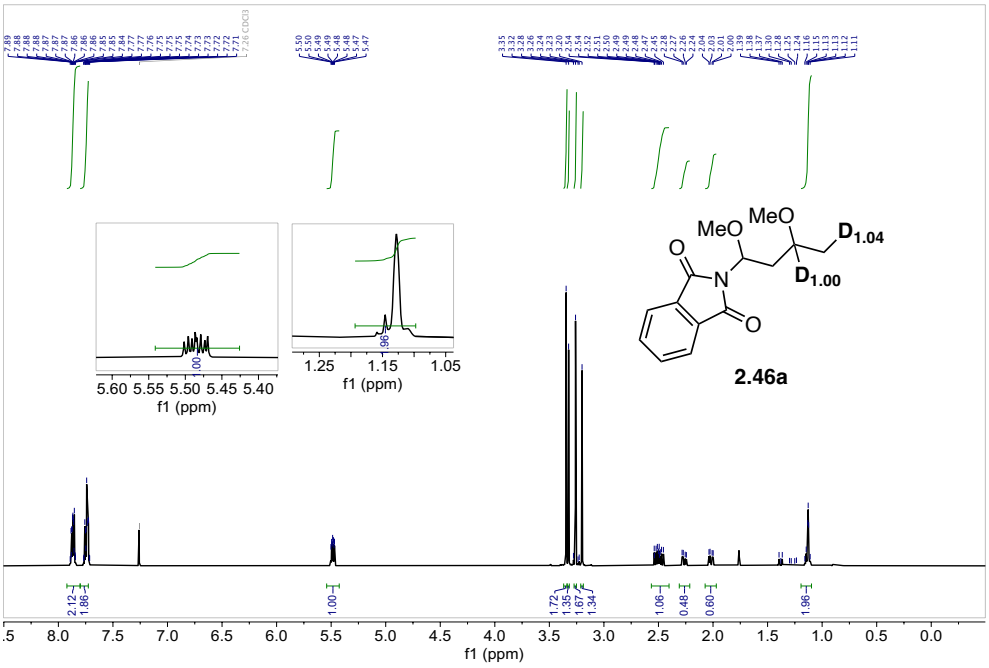
Gold(I)-Catalyzed Double Addition of Methanol to *N*-Vinyl Phtalimide 2.45 using Deuterated Acetylene



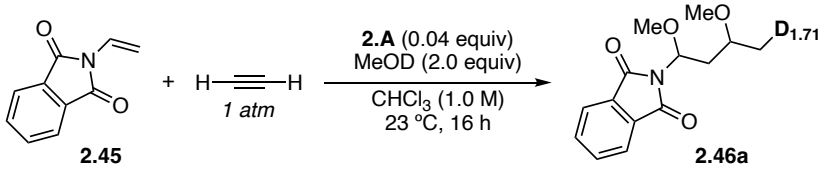
2.45 **2.46a**

This experiment was performed using a previously reported procedure with a two-chamber Y-shape reactor.[11] A stirring bar was placed in each vessel and the first vessel was loaded with CaC_2 (100 mg, 1.56 mmol, 3.1 equiv) and HPLC grade $CHCl_3$ (0.50 mL, 1.0 M). A solution of 2-vinylisoindoline-1,3-dione **2.45** (87 mg, 0.50 mmol, 1.0 equiv) and [JohnPhosAuNCMe]SbF_6 (15 mg, 0.02 mmol, 4 mol%) in HPLC grade $CHCl_3$ (0.50 mL, 1.0 M) was added to the second vessel. Then, D_2O (0.1 mL) was cautiously added to the first vessel. The reactor was immediately sealed, and the mixture was stirred at 23 ºC for 16 h. After emptying the remaining gas, the reaction was quenched by the addition of 3 drops of Et_3N and concentrated under reduced pressure. The crude product was purified by flash column chromatography (SiO_2, cyclohexane/EtOAc 100:0 to 90:10, *v/v*) and the deuterium incorporation was determined using ^{1}H NMR spectroscopic analysis.

Compound 2.46a-*d*$_2$ ^{1}H NMR (500 MHz, $CDCl_3$, 298K)

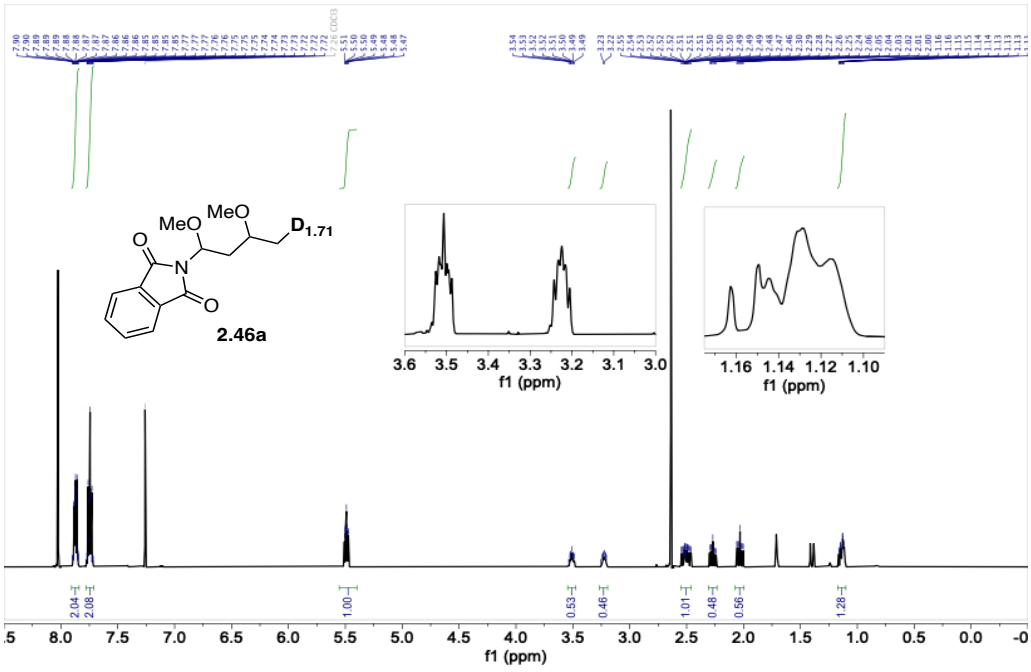


Gold(I)-Catalyzed Double Addition of Methanol to *N*-Vinyl Phtalimide 2.45 using MeOD



Prepared following general procedure D using *N*-vinyl phthalimide **2.45** (22 mg, 0.13 mmol, 1.0 equiv), methanol-d_4 (10 µL, 0.25 mmol, 2.0 equiv), [JohnPhosAuNCMe]SbF_6 (4 mg, 0.005 mmol, 4 mol%) and 1 atm of acetylene gas in $CHCl_3$ (0.25 mL, 1.0 M) at 23 ºC for 16 h. The crude product was purified by flash column chromatography (SiO_2, cyclohexane/EtOAc 100:0 to 90:10, *v/v*) and the deuterium incorporation was determined using ^{1}H NMR spectroscopic analysis.

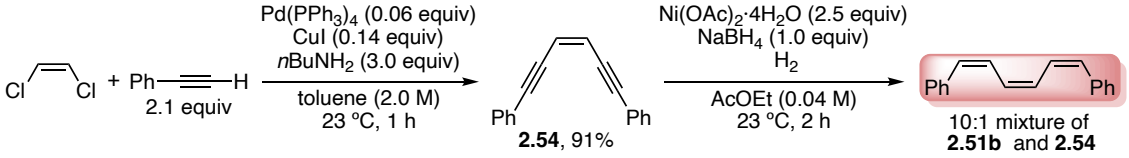
Compound 2.46a-*d*$_2$ ^{1}H NMR (500 MHz, $CDCl_3$, 298K)



Quantification of Oligomers

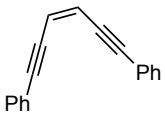
Synthesis of the oligomers[54]

Oligomer **2.51b** (n = 2)



(*Z*)-1,6-Diphenylhexa-3-en-1,5-diyne (2.54)

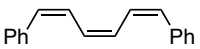
A solution of ethynylbenzene (0.7 mL, 664 mg, 6.50 mmol, 2.1 equiv) in anhydrous toluene (2.0 mL, 2.0 M) was added to a mixture of (*Z*)-1,2-dichloroethene (234 µL, 300 mg, 3.09 mmol, 1.0 equiv), $Pd(PPh_3)_4$ (215 mg, 0.186 mmol, 0.06 equiv), butan-1-amine (0.92 mL, 9.28 mmol, 3.0 equiv) and CuI (82.5 mg, 0.433 mmol, 0.14 equiv) under argon atmosphere. The reaction mixture was stirred at 23 ºC for 1 h and then filtered through a pad of Celite and washed with CH_2Cl_2 (3 x 2 mL). The residue was concentrated under vacuo and purified by flash column chromatography (SiO_2, cyclohexane/EtOAc 100:0 *v/v*) and the product **2.54** was obtained as an orange solid (644 mg, 2.82 mmol, 91% yield).



^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56–7.49 (m, 4H), 7.35 (ddt, *J* = 4.2, 2.7, 1.6 Hz, 6H), 6.11 (s, 2H). The characterization data matches those reported in the literature.[55]

(1*Z*,3*Z*,5*Z*)-1,6-Diphenylhexa-1,3,5-triene (2.51b)

Procedure for the formation of the Nickel-Boride Catalyst: $Ni(OAc)_2·4H_2O$ (622 mg, 2.50 mmol, 2.5 equiv) was dissolved in H_2O (25.0 mL). To the mixture was added a 1 M solution of $NaBH_4$ (3 mg, 0.09 mmol, 1.0 equiv) in H_2O (7.5 mL) and the black solid formed was washed with EtOH (20 mL) and dried under high vacuum.

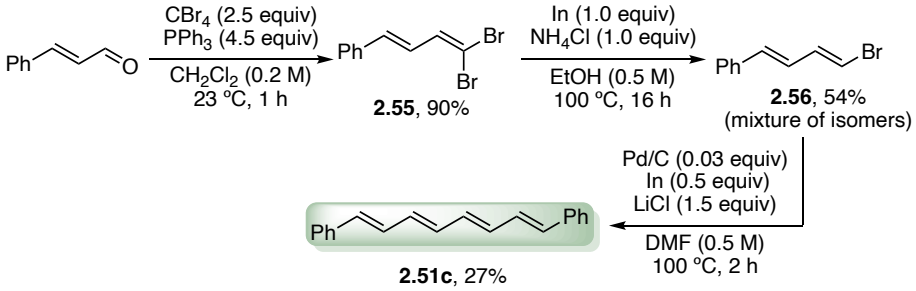


Procedure for the hydrogenation reaction: Ni-Boride catalyst (5 mg) was added to a solution of (*Z*)-1,6-diphenylhexa-3-en-1,5-diyne **2.54** (20 mg, 0.09 mmol, 1.0 equiv) in AcOEt (2.0 mL, 0.04 M) and a balloon of H_2 was placed in the reaction. After stirring at 23 ºC for 16 h the reaction was filtered through Celite and concentrated under vacuo to yield the product as a 10:1 mixture of **2.51b** and the starting material **2.54**.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47–7.42 (m, 4H), 7.39–7.32 (m, 4H), 7.28–7.23 (m, 2H), 6.96–6.86 (m, 2H), 6.63 (d, *J* = 15.5 Hz, 2H), 6.55 (d, *J* = 10.0 Hz, 2H). The characterization data matches those reported in the literature.[56]

54. Oligomer n= 0 is *trans*-stilbene and oligomer with n= 1 is the main product of the catalysis reaction hence their calibration curves were directly obtained.
55. Kosinski, C.; Hirsch, A.; Heinemann, F. W.; Hampel, F. *Eur. J. Org. Chem.* **2001**, *20*, 3879–3890.
56. Mesganaw, T.; Im, G.-Y. J.; Garg, N. K. *J. Org. Chem.* **2013**, *78*, 3391–3393.

Oligomer **2.51c** (trans, n = 3)[57]



(*E*)-(4,4-Dibromobuta-1,3-dien-1-yl)benzene (2.55)

To a solution of PPh_3 (4.47 g, 17.0 mmol, 4.5 equiv) in anhydrous CH_2Cl_2 (15.0 mL, 0.2 M) was slowly added at 0 ºC under argon atmosphere CBr_4 (3.14 g, 9.46 mmol, 2.5 equiv). After stirring for 30 min, cinnamaldehyde (476 µL, 500 mg, 3.78 mmol) in anhydrous CH_2Cl_2 (8.0 mL) was added. The reaction was stirred for 1 h at 23 ºC, filtered through Celite and extracted with H_2O (15 mL) and CH_2Cl_2 (3 x 20mL). The organic layer was washed with brine (20 mL), dried over anhydrous $MgSO_4$, filtered and concentrated under vacuo. The crude was purified by flash column chromatography (SiO_2, cyclohexane/EtOAc 100:0 to 90:10 *v/v*) and the product **2.55** was obtained as a white solid (983 mg, 3.41 mmol, 90% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03–7.96 (m, 2H), 7.93–7.85 (m, 3H), 7.60 (dd, *J* = 10.2, 0.7 Hz, 1H), 7.37 (dd, *J* = 15.7, 10.2 Hz, 1H), 7.24–7.14 (m, 1H). The characterization data matches those reported in the literature.[58]

(4-Bromobuta-1,3-dien-1-yl)benzene (2.56)

A mixture of (*E*)-(4,4-dibromobuta-1,3-dien-1-yl)benzene **2.55** (600 mg, 2.08 mmol, 1.0 equiv) and Indium (239 mg, 2.08 mmol, 1.0 equiv) in EtOH (4.0 mL, 0.5 M) and sat. aq. NH_4Cl (4 mL, 2.08 mmol, 1.0 equiv) was stirred at 90 ºC for 16 h in a metallic heating block. After cooling down to 23 ºC, the mixture was extracted with Et_2O (3 x 3 mL). The combined organic layers were washed with brine (4 mL), dried over anhydrous $MgSO_4$, filtered and concentrated under vacuo. The crude was purified by flash column chromatography (SiO_2, cyclohexane/EtOAc 100:0 to 90:10 *v/v*) and the product (mixture of isomers) **2.56** was obtained as a colorless oil (233 mg, 1.11 mmol, 54% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.54–7.46 (m, 2H), 7.45–7.30 (m, 3H), 7.18–7.10 (m, 1H), 6.90 (dd, *J* = 13.4, 10.6 Hz, 0.5H), 6.85–6.82 (m, 0.5H), 6.82–6.79 (m, 0.5H), 6.76 (d, *J* = 4.1 Hz, 0.5H), 6.69 (dd, *J* = 10.6, 0.7 Hz, 0.5H), 6.60 (d, *J* = 15.6 Hz, 0.5H), 6.46 (dt, *J* = 13.4, 0.7 Hz, 0.5H), 6.27 (dt, *J* = 7.1, 1.0 Hz, 0.5H). The characterization data matches those reported in the literature.[59]

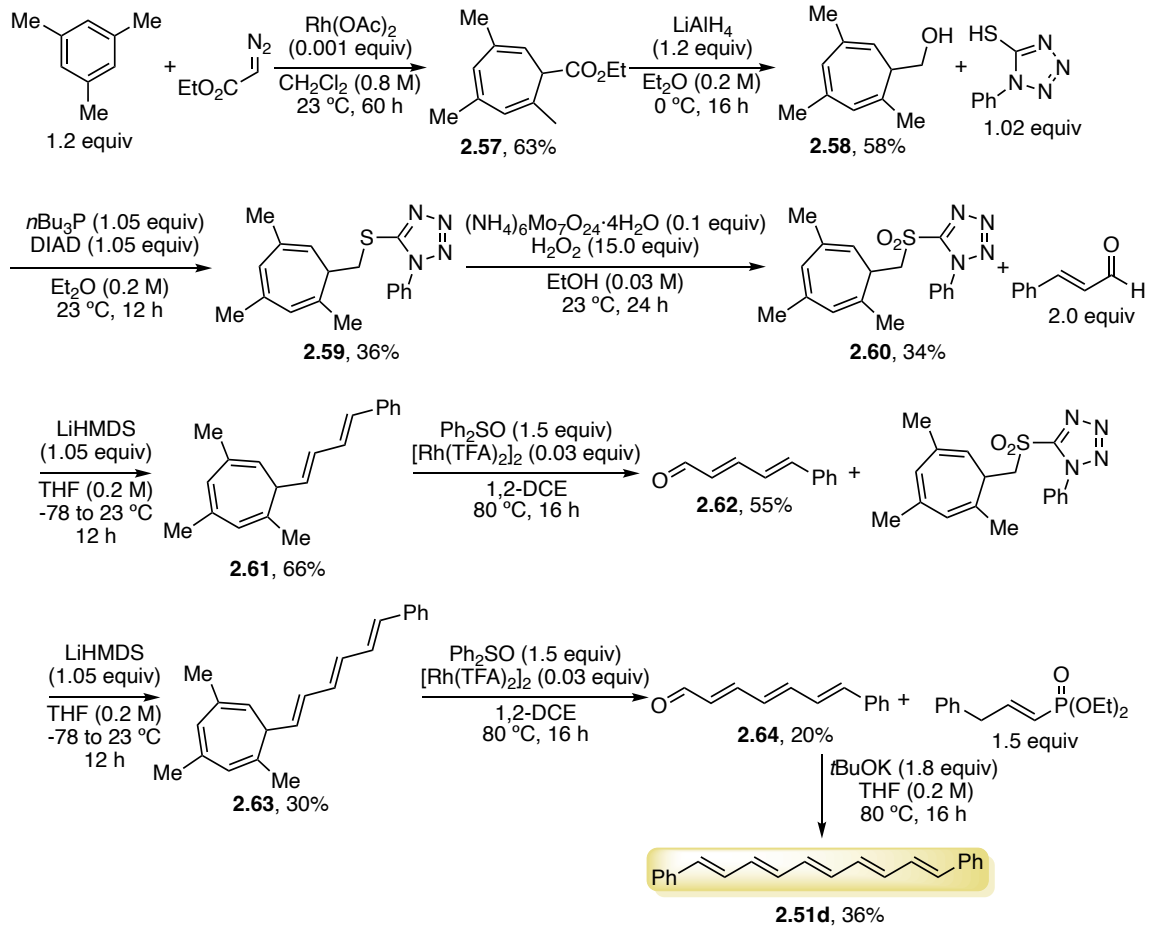
57. The synthesis of the *Z*-isomer of **2.51c** failed, so we report the synthesis of the *E*-isomer of **2.51c** instead.
58. Yamamoto, K.; Bruun, T.; Kim, J. Y.; Zhang, L.; Lautens, M. *Org. Lett.* **2016**, *18*, 2644–2647.
59. Naskar, D.; Roy, S. *Tetrahedron* **2000**, *56*, 1369–1377.

(1*E*,3*E*,5*E*,7*E*)-1,8-Diphenylocta-1,3,5,7-tetraene (2.51c)

A mixture of (4-bromobuta-1,3-dien-1-yl)benzene **2.56** (40 mg, 0.19 mmol, 1.0 equiv), Pd/C (5 mg, 10% Wt, 0.005 mmol, 0.03 equiv), Indium (11 mg, 0.10 mmol, 0.5 equiv) and LiCl (12 mg, 0.29 mmol, 1.5 equiv) in anhydrous DMF (0.4 mL, 0.5 M) was stirred at 100 ºC for 2 h under argon atmosphere. The reaction was then quenched with sat. aq. NH_4Cl (0.3 mL) and extracted with Et_2O (3 x 0.5 mL). The combined organic layers were washed with brine (1 mL), dried over anhydrous $MgSO_4$, filtered and concentrated under vacuo. The crude was purified by flash column chromatography (SiO_2, cyclohexane/EtOAc 100:0 to 90:10 *v/v*) and the product **2.51c** was obtained as a colorless oil (13 mg, 0.05 mmol, 27% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.44–7.38 (m, 4H), 7.35–7.28 (m, 4H), 7.25–7.18 (m, 2H), 6.93–6.84 (m, 2H), 6.60 (s, 1H), 6.57 (s, 1H), 6.46 (dt, *J* = 3.2, 2.1 Hz, 4H). The characterization data matches those reported in the literature.[60]

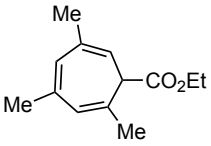
Oligomer **2.51d** (*trans*, n = 4)



60. Cao, X.-P. *Tetrahedron* **2002**, *58*, 1301–1307.

Ethyl 2,4,6-Trimethylcyclohepta-2,4,6-triene-1-carboxylate (2.57)

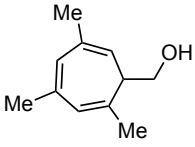
To a two-neck 1 L round-bottom flask charged with $Rh_2(OAc)_4$ (72 mg, 0.16 mmol, 0.001 equiv) was added mesitylene (27.0 mL, 24.0 g, 0.20 mol, 1.2 equiv) dissolved in CH_2Cl_2 (211 mL, 0.8 M) and the mixture was stirred 1 h at 23 ºC. Then, ethyl diazoacetate (18.0 mL, 19.0 g, 0.16 mol, 1.0 equiv) was then added using a syringe pump over 60 hours at 23 ºC. Upon completion, the crude was filtered through a big plug of silica gel, which was eluted with cyclohexane/EtOAc (9:1 *v/v*) until no more product came out. The solvent was removed under vacuo and the product was dried in high vacuum overnight (to remove the excess of mesitylene) affording the product **2.57** as a yellow oil (21.3 g, 0.10 mol, 63% yield).



^{1}H NMR (500 MHz, $CDCl_3$) d 6.25 (s, 1H), 5.84 (s, 1H), 5.38 (d, J = 6.5 Hz, 1H), 4.29- 4.19 (m, 2H), 2.86 (d, J = 6.5 Hz, 1H), 2.01 (s, 3H), 1.93 (d, J = 1.2 Hz, 3H), 1.90 (t, J = 1.1 Hz, 3H), 1.30 (t, J = 7.1 Hz, 3H) ppm. The characterization data matches those reported in the literature.[61]

(2,4,6-Trimethylcyclohepta-2,4,6-trien-1-yl)methanol (2.58)

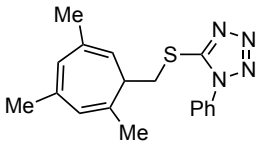
$LiAlH_4$ (4.00 g, 0.10 mol, 1.2 equiv) were slowly added at 0 ºC to a solution of ethyl 2,4,6-trimethylcyclohepta-2,4,6-triene-1-carboxylate **2.57** (18.0 g, 0.087 mol, 1.0 equiv) in anhydrous Et_2O (440 mL, 0.2 M) and the mixture was stirred at 23 ºC for 16 h. Upon completion, the reaction was quenched by the slow addition of H_2O (200 mL) at 0 ºC and extracted with Et_2O (3 x 200 mL). The combined organic layers were washed with brine (200 mL), dried over anhydrous $MgSO_4$, filtered and concentrated under vacuo. The product **2.58** was obtained as a colorless oil (8.3 g, 0.9 mmol, 58% yield) without further purification.



^{1}H NMR (500 MHz, $CDCl_3$) δ 6.12 (s, 1H), 5.80 (p, *J* = 1.4 Hz, 1H), 4.96 (d, *J* = 7.4 Hz, 1H), 3.71–3.60 (m, 2H), 2.45 (p, *J* = 7.3 Hz, 1H), 1.95 (dt, *J* = 3.1, 1.5 Hz, 6H), 1.86–1.83 (m, 3H). The characterization data matches those reported in the literature.[61]

1-Phenyl-5-(((2,4,6-trimethylcyclohepta-2,4,6-trien-1-yl)methyl)thio)-1*H*-tetrazole (2.59)

Anhydrous Et_2O (225 mL, 0,2 M) was added to a mixture of (2,4,6-trimethylcyclohepta-2,4,6-trien-1-yl)methanol **2.58** (6.60 g, 40.2 mmol, 1.0 equiv) and 1-phenyltetrazoline-5-thione (7.30 g, 41.0 mmol, 1.02 equiv). *n*Bu_3P (10.5 mL, 8.54 g, 42.2 mmol, 1.05 equiv) was added in one portion to this mixture at 0 ºC under argon atmosphere. To the resulting solution was added diisopropyl azodicarboxylate (9.1 mL, 8.53 g, 42.2 mmol, 1.05 equiv) via syringe in one portion (less than 1 min). The mixture was stirred at 23 ºC for 12 h, quenched with H_2O (100 mL) and extracted with Et_2O (3 x 200 mL). The combined organic layers were washed with brine (200 mL), dried over anhydrous $MgSO_4$, filtered and concentrated under



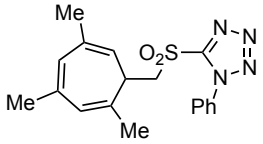
61. Mato, M.; Echavarren, A. M. *Angew. Chem. Int. Ed.* **2019**, *58*, 2088–2092.

vacuo. The crude was purified by flash column chromatography (SiO_2, cyclohexane/EtOAc 100:0 to 80:20 *v/v*) and the product **2.59** was obtained as a pale yellow oil (4.7 g, 14.0 mmol, 36% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63–7.49 (m, 5H), 6.15 (d, *J* = 1.8 Hz, 1H), 5.86 (t, *J* = 1.5 Hz, 1H), 5.13 (d, *J* = 7.9 Hz, 1H), 3.42 (qd, *J* = 12.7, 8.1 Hz, 2H), 2.93 (q, *J* = 8.0 Hz, 1H), 1.98 (dd, *J* = 4.1, 1.4 Hz, 6H), 1.86 (d, *J* = 1.3 Hz, 3H). The characterization data matches those reported in the literature.[61]

1-Phenyl-5-(((2,4,6-trimethylcyclohepta-2,4,6-trien-1-yl)methyl)sulfonyl)-1*H*-tetrazole (2.60)

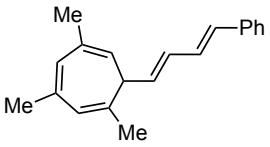
1-Phenyl-5-(((2,4,6-trimethylcyclohepta-2,4,6-trien-1-yl)methyl)thio)-1*H*-tetrazole **2.59** (1.0 g, 3.08 mmol, 1.0 equiv) was dissolved in EtOH (95.0 mL, 0.03 M) under air and the solution was cooled to 0 ºC in an ice bath. A solution of hexaammonium heptamolybdate tetrahydrate (362 mg, 0.311 mmol, 0.1 equiv) in H_2O_2 (4.8 mL, 5.24 g, 46.2 mmol, 15.0 equiv) was added dropwise using a syringe pump over 1 h, and the resulting mixture was further stirred for 20 h at 23 ºC: The reaction was quenched by the addition of H_2O (70 mL) and extracted with CH_2Cl_2 (3 x 80 mL). The combined organic layers were washed with brine (100 mL), dried over anhydrous $MgSO_4$, filtered and concentrated under vacuo. The crude was purified by flash column chromatography (SiO_2, cyclohexane/EtOAc 100:0 to 80:20 *v/v*) and the product **2.60** was obtained as a white solid (370 mg, 1.00 mmol, 34% yield).



^{1}H NMR (300 MHz, $CDCl_3$) δ 7.69–7.56 (m, 5H), 6.19 (s, 1H), 5.86 (s, 1H), 5.14 (d, *J* = 8.5 Hz, 1H), 3.71 (dd, *J* = 7.0, 4.8 Hz, 2H), 3.36 (d, *J* = 7.5 Hz, 1H), 1.99 (d, *J* = 1.6 Hz, 6H), 1.81 (d, *J* = 1.3 Hz, 3H). The characterization data matches those reported in the literature.[61]

1,3,5-Trimethyl-7-((1*E*,3*E*)-4-phenylbuta-1,3-dien-1-yl)cyclohepta-1,3,5-triene (2.61)

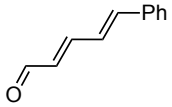
1-Phenyl-5-(((2,4,6-trimethylcyclohepta-2,4,6-trien-1-yl)methyl)sulfonyl)-1*H*-tetrazole **2.60** (700 mg, 1.96 mmol, 1.0 equiv) was dissolved in anhydrous THF (8.0 mL, 0.2 M) under argon atmosphere. The mixture was cooled down to -78 ºC and a freshly prepared solution of bis(trimethylsilyl)amide (410 μL, 345 mg, 2.06 mmol, 1.05 equiv) in anhydrous THF (4.0 mL) was added dropwise. After stirring for 30 minutes at –78 ºC, *trans*-cinnamyl aldehyde (494 μL, 519 mg, 3.93 mmol, 2.0 equiv) was added in one portion and the reaction was stirred at 23 ºC for 12 h. Then, the crude was quenched by the addition of H_2O (5 mL) and extracted with Et_2O (3 x 8 mL). The combined organic layers were washed with brine (10 mL), dried over anhydrous $MgSO_4$, filtered and concentrated under vacuo. The crude was purified by flash column chromatography (SiO_2, cyclohexane/EtOAc 100:0 to 80:20 *v/v*) and the product **2.61** was obtained as a white solid (307 mg, 1.17 mmol, 60% yield).



^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51–7.45 (m, 2H), 7.43–7.36 (m, 2H), 7.33–7.26 (m, 1H), 6.98–6.87 (m, 1H), 6.57 (d, *J* = 15.7 Hz, 1H), 6.38–6.30 (m, 2H), 6.17–6.09 (m, 1H), 5.90 (t, *J* = 1.4 Hz, 1H), 5.13

(dt, *J* = 6.8, 1.4 Hz, 1H), 2.88 (t, *J* = 7.6 Hz, 1H), 2.12 (d, *J* = 1.3 Hz, 3H), 2.04 (dd, *J* = 8.3, 1.4 Hz, 3H), 1.99 (t, *J* = 1.1 Hz, 3H). The characterization data matches those reported in the literature.[61]

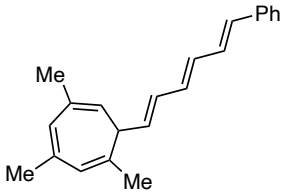
(2*E*,4*E*)-5-Phenylpenta-2,4-dienal (2.62)



1,3,5-Trimethyl-7-((1*E*,3*E*)-4-phenylbuta-1,3-dien-1-yl)cyclohepta-1,3,5-triene **2.61** (100 mg, 0.381 mmol, 1.0 equiv) and diphenyl sulfoxide (116 mg, 0.572 mmol, 1.5 equiv) were dissolved in anhydrous 1,2-dichloroethane (2.0 mL, 0.2 M) under argon atmosphere before $Rh_2(TFA)_4$ (8 mg, 0.01 mmol, 0.03 equiv) was added. The mixture was stirred at 80 ºC for 16 h. Upon completion, the crude was concentrated under vacuo and purified by flash column chromatography (SiO_2, cyclohexane/EtOAc 100:0 to 60:40 *v/v*) and the product **2.62** was obtained as a colorless oil (18 mg, 0.11 mmol, 30% yield).

^{1}H NMR (300 MHz, $CDCl_3$) δ 9.63 (d, *J* = 8.0 Hz, 1H), 7.54–7.47 (m, 2H), 7.42–7.34 (m, 3H), 7.32–7.23 (m, 1H), 7.01 (d, *J* = 6.8 Hz, 2H), 6.28 (dd, *J* = 15.1, 7.9 Hz, 1H). The characterization data matches those reported in the literature.[62]

1,3,5-Trimethyl-7-((1*E*,3*E*,5*E*)-6-phenylhexa-1,3,5-trien-1-yl)cyclohepta-1,3,5-triene (2.63)



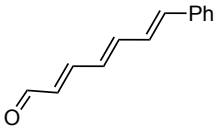
1-Phenyl-5-(((2,4,6-trimethylcyclohepta-2,4,6-trien-1-yl)methyl)sulfonyl)-1*H*-tetrazole **2.60** (41 mg, 0.12 mmol, 1.0 equiv) was dissolved in anhydrous THF (0.6 mL, 0.2 M) under argon atmosphere. The mixture was cooled down to -78 ºC and a freshly prepared solution of bis(trimethylsilyl)amide (24 μL, 20 mg, 0.12 mmol, 1.05 equiv) in anhydrous THF (0.3 mL) was added dropwise. After stirring for 30 minutes at -78 ºC, (2*E*,4*E*)-5-phenylpenta-2,4-dienal **2.62** (18 mg, 0.11 mmol, 1.0 equiv) was added in one portion and the reaction was stirred at 23 ºC for 12 h. Then, the crude was quenched by the addition of H_2O (0.5 mL) and extracted with Et_2O (3 x 0.8 mL). The combined organic layers were washed with brine (1 mL), dried over anhydrous $MgSO_4$, filtered and concentrated under vacuo. The crude was purified by flash column chromatography (SiO_2, cyclohexane/EtOAc 100:0 to 80:20 *v/v*) and the product **2.63** was obtained as a white solid (16 mg, 0.06 mmol, 48% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43–7.35 (m, 2H), 7.31 (dd, *J* = 8.6, 6.7 Hz, 2H), 7.24–7.17 (m, 1H), 6.86–6.72 (m, 1H), 6.54 (dd, *J* = 15.6, 7.8 Hz, 1H), 6.42–6.27 (m, 2H), 6.22–6.12 (m, 2H), 5.95 (dd, *J* = 15.0, 8.5 Hz, 1H), 5.82–5.75 (m, 1H), 5.05–4.94 (m, 1H), 2.72 (t, *J* = 7.7 Hz, 1H), 2.07–1.99 (m, 3H), 1.91 (dd, *J* = 10.4, 1.2 Hz, 3H), 1.87 (t, *J* = 1.0 Hz, 3H). The characterization data matches those reported in the literature.[61]

62. Mutule, I.; Borovika, D.; Rozenberga, E.; Romanchikova, N.; Zalubovskis, R.; Shestakova, I.; Trapencieris, P. *J. Enz. Inhib. Med. Chem.* **2015**, *30*, 216–223.

(2*E*,4*E*,6*E*)-7-Phenylhepta-2,4,6-trienal (2.64)

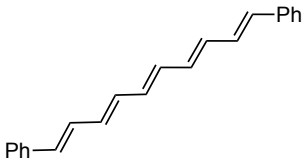
1,3,5-Trimethyl-7-((1*E*,3*E*,5*E*)-6-phenylhexa-1,3,5-trien-1-yl)cyclohepta-1,3,5-triene **2.63** (24 mg, 0.08 mmol, 1.0 equiv) and diphenyl sulfoxide (25 mg, 0.12 mmol, 1.5 equiv) were dissolved in anhydrous 1,2-dichloroethane (0.5 mL, 0.2 M) under argon atmosphere before $Rh_2(TFA)_4$ (2 mg, 0.003 mmol, 0.03 equiv) was added. The mixture was stirred at 80 ºC for 16 h. Upon completion, the crude was concentrated under vacuo and purified by flash column chromatography (SiO_2, cyclohexane/EtOAc 100:0 to 60:40 *v/v*) and the product **2.64** was obtained as a colorless oil (3 mg, 0.02 mmol, 20% yield).



^{1}H NMR (300 MHz, $CDCl_3$) δ 9.60 (d, *J* = 8.0 Hz, 1H), 7.50–7.43 (m, 2H), 7.39–7.28 (m, 3H), 7.22–7.13 (m, 1H), 6.86 (dd, *J* = 13.9, 1.3 Hz, 2H), 6.79 (d, *J* = 6.0 Hz, 1H), 6.57 (dd, *J* = 13.9, 11.2 Hz, 1H), 6.21 (dd, *J* = 15.2, 8.0 Hz, 1H). The characterization data matches those reported in the literature.[62]

(1*E*,3*E*,5*E*,7*E*,9*E*)-1,10-Diphenyldeca-1,3,5,7,9-pentaene (2.51d)

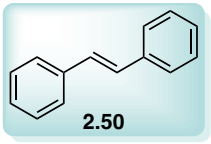
*t*BuOK (3 mg, 0.03 mmol, 1.8 equiv) was added to a solution of diethyl cinammylphosphonate (6 mg, 0.02 mmol, 1.5 equiv) in anhydrous THF (0.1 mL, 0.2 M) at 0 ºC. The reaction mixture was stirred at 0 ºC for 30 min and (2*E*,4*E*,6*E*)-7-phenylhepta-2,4,6-trienal **2.64** (3 mg, 0.02 mmol, 1.0 equiv) was slowly added. Then, the mixture was stirred at 80 ºC for 16 h, quenched by the addition of H_2O (0.1 mL) and extracted with Et_2O (3 x 0.2 mL). The combined organic layers were washed with brine (0.3 mL), dried over anhydrous $MgSO_4$, filtered and concentrated under vacuo. The crude was purified by flash column chromatography (SiO_2, cyclohexane/EtOAc 100:0 *v/v*) and the product **2.51d** was obtained as a colorless oil (1.5 mg, 0.005 mmol, 30% yield).[63]



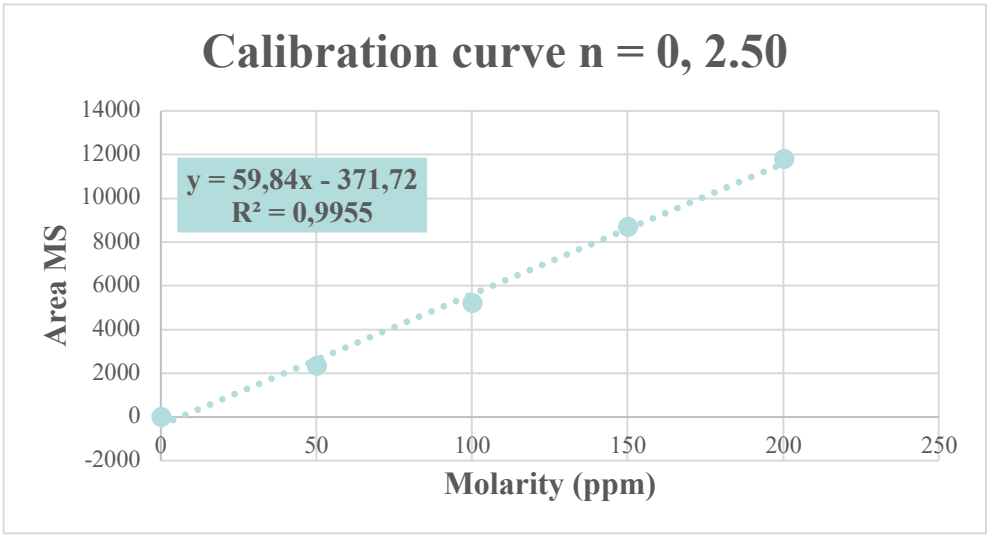
63. Due to the small amount recovered of **2.51d**, the product could not be characterized by ^{1}H NMR spectroscopy. The formation of the desired product was confirmed by UHPLC-MS.

Calibration Curves

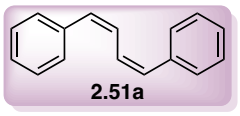
Calibration Curve for 2.50 (n = 0)



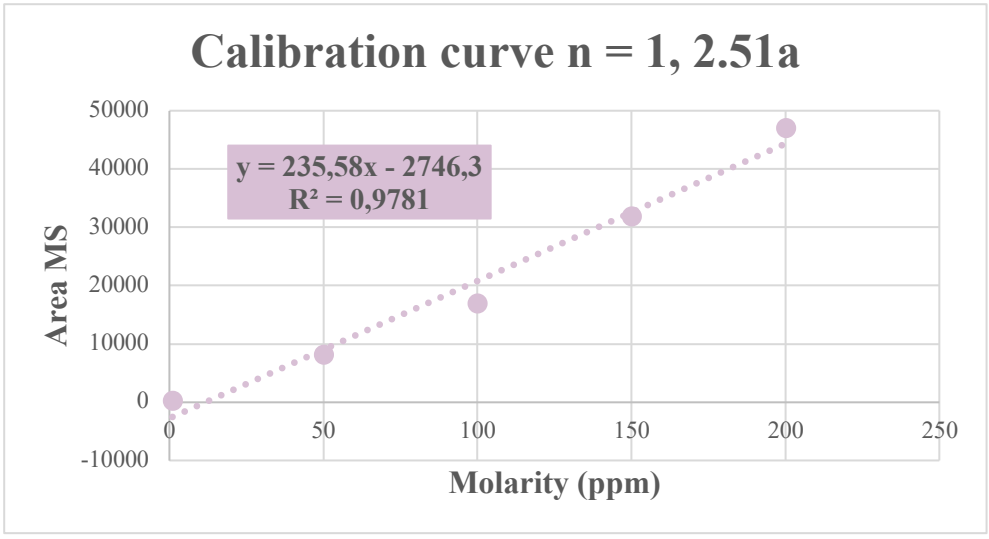
Entry	M (ppm)	Area MS
1	0	0
2	50	2357,6
3	100	5219,2
4	150	8691,4
5	200	11793,0



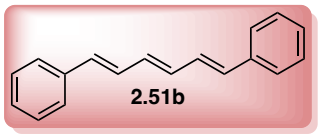
Calibration Curve for 2.51a (n = 1)



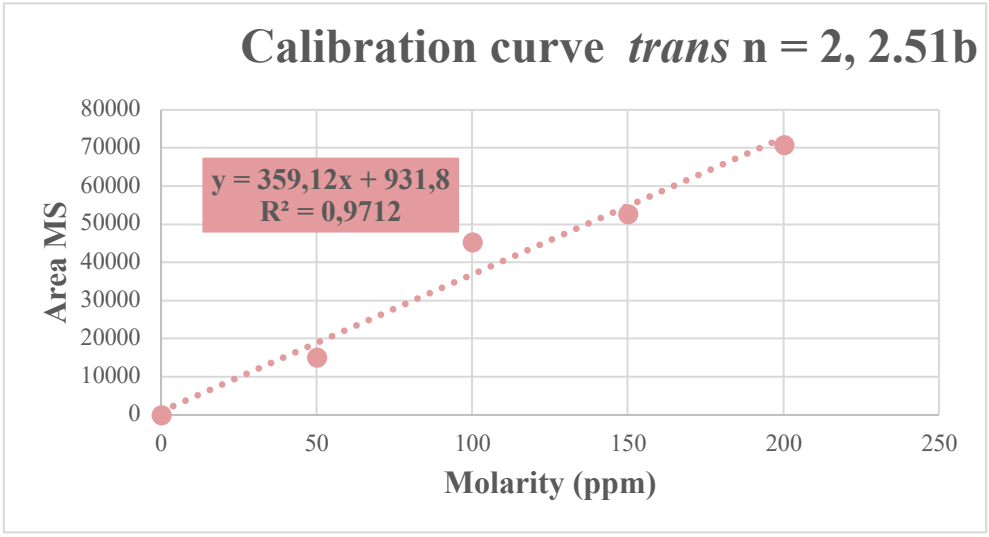
Entry	M (ppm)	Area MS
1	1	232,1
2	50	8213,5
3	100	16928,0
4	150	31898,0
5	200	47021,0



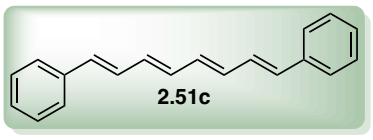
Calibration Curve for 2.51b (*trans*, n = 2)



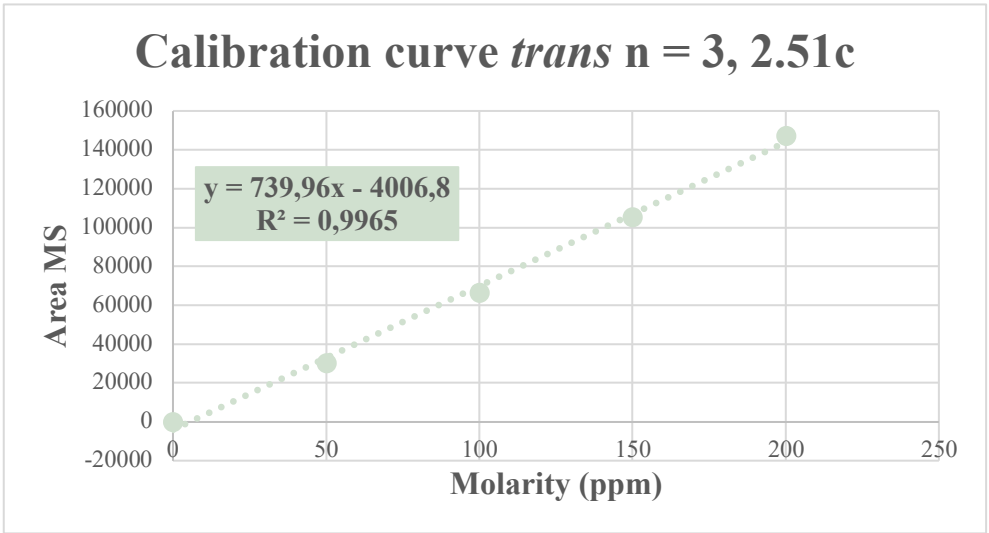
Entry	M (ppm)	Area MS
1	0	0
2	50	15125,0
3	100	45390,0
4	150	31898,0
5	200	47021,0



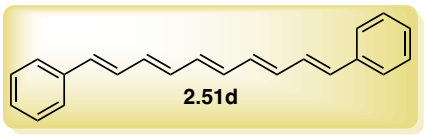
Calibration Curve for 2.51c (*trans*, n = 3)



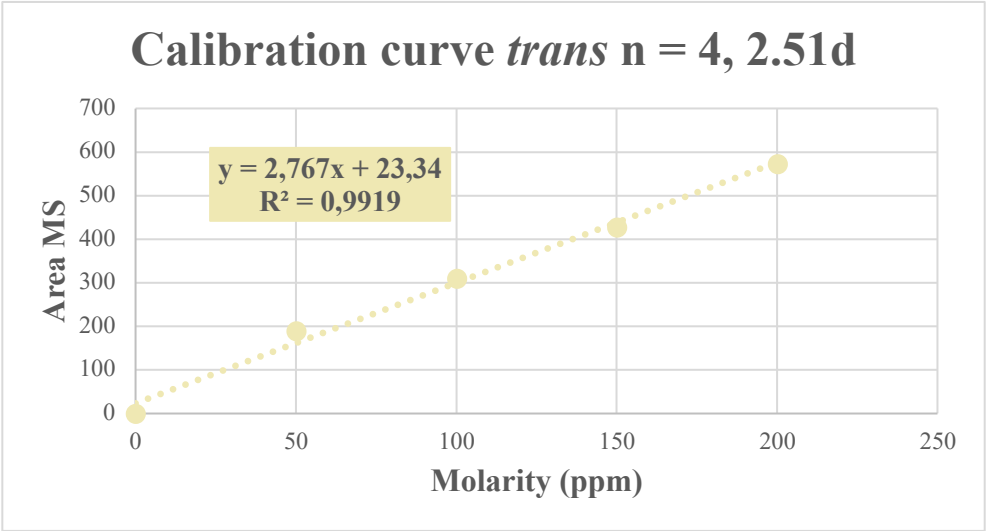
Entry	M (ppm)	Area MS
1	0	0
2	50	30339,0
3	100	66718,0
4	150	105460,0
5	200	147430,0



Calibration Curve for 2.51d (*trans*, n = 4)

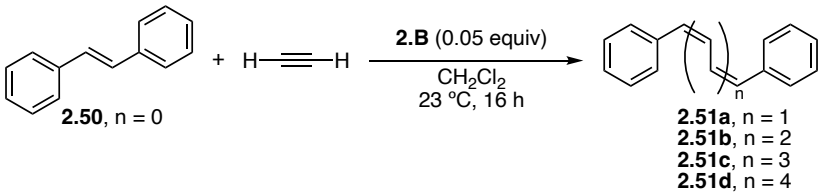


Entry	M (ppm)	Area MS
1	0	0
2	50	189,5
3	100	310,6
4	150	427,2
5	200	572,9



Analysis of the Reaction Crudes

Once the calibration curves for each oligomer were prepared, we analyzed 8 different crudes of the model reaction (Scheme **2.37**).



Scheme 2.37. Gold(I)-catalyzed oligomerization of *trans*-stilbene with acetylene gas.

For every crude, using the different calibration curves, the concentration of the different oligomers was calculated. The results can be summarized in Table 2.8.

Table 2.8. Quantification of the oligomers.

		Crude A		**Crude B**		**Crude C**	
RT (min)	n	Area MS	M (ppm)	Area MS	M (ppm)	Area MS	M ppm)
2.427	0	14950	256	16670,3	285	24083,3	409
3.117	1	39270,2	178	44998,5	203	77852	342
3.445	2	20651,1	60	24211,6	70	40516,5	115
3.822	3	9406,7	7	11162,1	10	19405,2	21
4.132	4	-		-	-	-	-
		Crude D		**Crude E**		**Crude F**	
RT (min)	n	Area MS	M (ppm)	Area MS	M (ppm)	Area MS	M ppm)
2.427	0	22106,9	376	11361,1	196	8974,5	156
3.117	1	65469	290	33459,1	154	26434,7	124
3.445	2	34002,9	97	21105,1	61	18849,5	55
3.822	3	14942,6	15	11431,8	10	8877,45	7
4.132	4	-	-	-	-	-	-
		Crude G		**Crude H**			
RT (min)	n	Area MS	M (ppm)	Area MS	M (ppm)		
2.427	0	7214,1	127	8700,6	152		
3.117	1	17460,3	86	18988,3	92		
3.445	2	10448,8	32	9264,8	28		
3.822	3	3839,5	-	2985,4	-		
4.132	4	-	-	-	-		

Even though all the reaction crudes were run under the same conditions, the amount of each oligomer is not reproducible and changes unpredictably.

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Chapter III
Gold(I)-Catalyzed Biscyclopropanation of 2-Substituted Indoles

UNIVERSITAT ROVIRA I VIRGILIDevelopment of Gold(I)-Catalyzed Reactions Between Alkenes and Acetylene Gas
Tania Medina Gil

Introduction

Natural Occurrence and Synthesis of Indole-Containing Products

Indoles are one of the most studied heterocycles in organic chemistry. This bicyclic structure consists of a five-membered pyrrole ring fused to a benzene six-membered ring. They remain as one of the most ubiquitous scaffolds not only in nature, but also, in an extremely wide variety of pharmacologically active compounds.[1] More than a thousand indole alkaloids have been described up to date, most of which share their synthetic origin in tryptophan aminoacid.[2] Other examples of high relevant naturally occurring indoles are serotonin[3], mitomycin C[4] or reserpine (Figure 3.1, left).[5] Biologically, these indole alkaloids can induce apoptosis or inhibit cancer cell proliferation.[6]

Furthermore, indole skeleton is present in a huge number of therapeutically active compounds (Figure 3.1, right). Noteworthy, in 2010, the sales of indoles containing drugs accounted for more than 3 billions of dollars.[7]

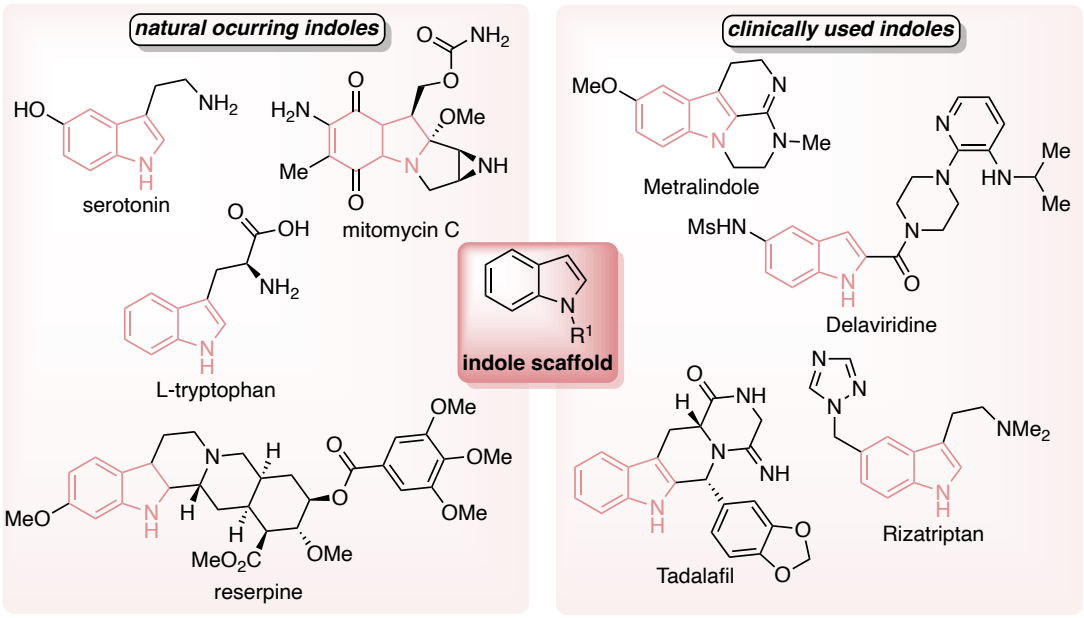
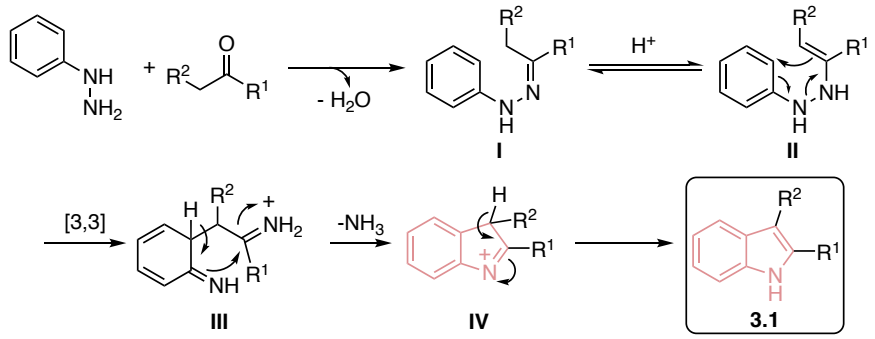


Figure 3.1. Selected examples of indole-containing natural products and drugs.

1. (a) de Sá Alves, F. R.; Barreiro, E. J.; Manssour Fraga, C. A. *Mini Rev. Med. Chem.* **2009**, *9*, 782–793. (b) Humphrey, G. R.; Kuethe, J. T. *Chem. Rev.* **2006**, *106*, 2875–2911.
2. (a) Umer, S. M.; Solangi, M.; Khan, K. M.; Saleem, R. S. Z. *Molecules* **2022**, *27*, 7586–7631. (b) Brown, E. G. Ed. Springer Netherlands: Dordrecht, 1998; pp 192–207.
3. Mohammad-Zadeh, L. F.; Moses, L.; Gwaltney-Brant, S. M. *J. Vet. Pharmacol. Ther.* **2008**, *31*, 187–199.
4. Crooke, S. T.; Bradner, W. T. *Cancer Treat. Rev.* **1976**, *3*, 121–139.
5. Chen, F.-E.; Huang, J. *Chem. Rev.* **2005**, *105*, 4671–4706.
6. Song, J.; Zhang, B.; Li, M.; Zhang, J. *Fitoterapia* **2023**, *165*, 105430.
7. Inman, M.; Moody, C. J. *Chem. Sci.* **2013**, *4*, 29–41.

Despite have been reported more than one century ago, the Fischer synthesis remains as the preeminent approach for the preparation of indoles.[8] This transformation involves the reaction of enolizable *N*-arylhydrazones and aldehydes or ketones under acidic conditions to form the indole skeleton (Scheme 3.1). The reaction mechanism begins with the tautomerization of arylhydrazone **I** to the enehydrazine **II** followed by a [3,3]-sigmatropic rearrangement to functionalize one of the aromatic positions (**III**). Further tautomerization and imine exchange (**IV**) afford the desired indoles **3.1**.



Scheme 3.1. Fischer synthesis of indoles.

The main drawback of this classical approach is the use of toxic and expensive arylhydrazones as indole precursors. Numerous modern versions of the Fischer synthesis have been developed in the past decades, including the use of new catalysts or different approaches for the synthesis of these starting arylhydrazines.[9]

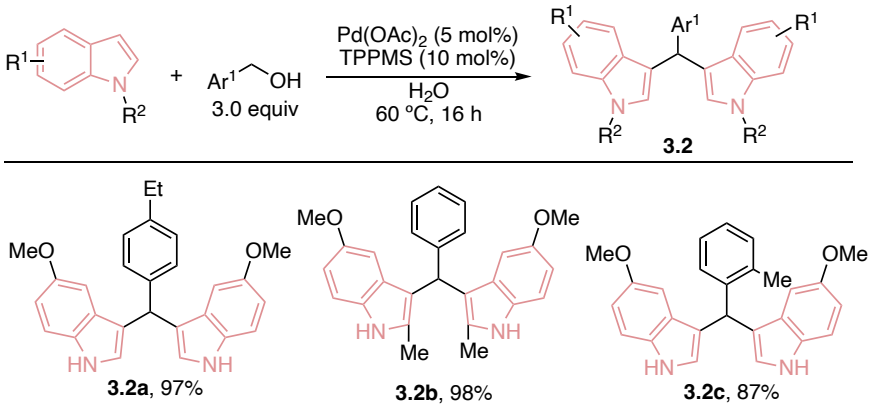
Functionalization of Indoles

Not only the synthesis of indoles has attracted great attention in the past decades, but also their functionalization to obtain products of high relevance in pharmacology due to their biological properties.[10]

Some of the most powerful strategies for the functionalization of indoles are based on alkylation reactions. In this sense, in 2013, Yokoyama's group reported the palladium-catalyzed reaction of

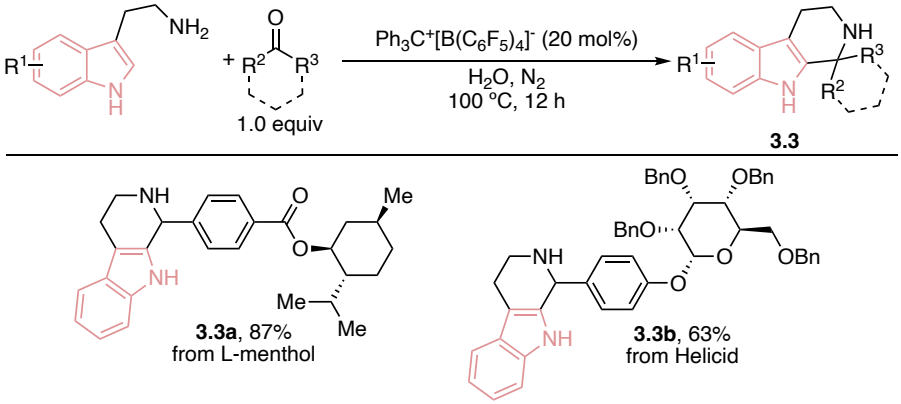
8. (a) Robinson, *The Fischer Indole Synthesis,* John Wiley & Sons Inc., New York, 1982. (b) Fischer, E.; Jourdan, F.; *Ber. Dtsch. Chem. Ges*. **1883**, *16*, 2241–2245.
9. Bugaenko, D.; Karchava, A.; Yurovskaya, M. *Russ. Chem. Rev.* **2018**, *87*.
10. Pang, Q.; Zuo, W.-F.; Zhang, Y.; Li, X.; Han, B. *Chem. Rec.* **2023**, *23*, e202200289.

indoles with benzyl alcohols (Scheme 3.2). This transformation involves the C3-benzylation of indoles and benzylic C–H functionalization in water.[11]



Scheme 3.2. Pd-catalyzed synthesis of bis(indole) methane (BIM) derivates.

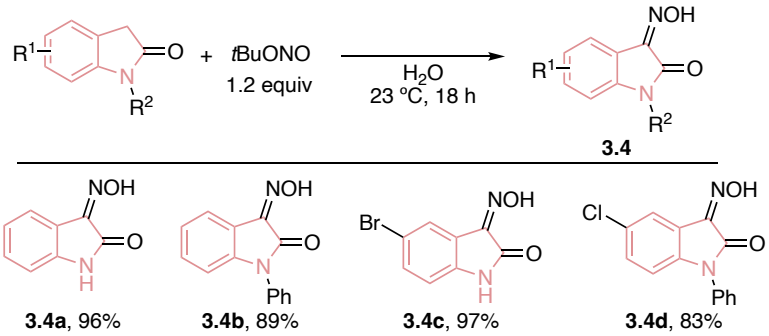
Moreover, methods for the synthesis of annulated indoles have been widely explored, due to their natural occurrence. One of the most recent examples of these reactions was reported by Loh and coworkers in 2022.[12] They presented a metal-free triarylcarbonium ion-pair-catalyzed Pictet-Spengler reaction of tryptamines to obtain tetrahydro-*β*-carbolines **3.3**. Overcoming previous issues, this method allowed the formation of annulated indoles in acid and metal-free conditions and could be applied to the late-stage functionalization of natural products (Scheme 3.3).



Scheme 3.3. Pictet-Spengler reaction for the late-stage functionalization of tryptamines-containing natural products.

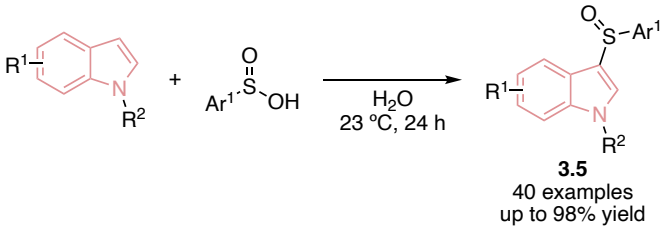
The formation of C–C bonds is the most explored method for the functionalization of indoles. However, reactions involving C–N bond formation have also attracted great attention lately. In this context, Liang and co-workers reported in 2017 a metal-free synthesis of isatin oximes **3.4** via radical coupling reactions (Scheme 3.4).[13] The reaction involves the use of *tert*-butyl nitrite (*t*BuONO) as nitrogen source and H_2O as solvent, which makes it a highly sustainable approach.

11. Hikawa, H.; Yokoyama, Y. *RSC Adv*. **2012**, *3*, 1061–1064.
12. Zhang, Z.; Liu, X.; Ji, L.; Zhang, T.; Jia, Z.; Loh, T. -P. *ACS Catal*. **2022**, *12*, 2052–2057.
13. Wei, W.-T.; Zhu, W.-M.; Ying, W.-W.; Wu, Y.; Huang, Y.-L.; Liang, H. *Org. Biomol. Chem*. **2017**, *15*, 5254–5257.



Scheme 3.4. Metal-free synthesis of isatin oximes.

Methods for functionalization reactions of indoles based on the formation of C–S bonds have also been described recently. As an example, in 2015, the group of Wang reported the direct synthesis of 3-arylsulfinylindoles **3.5** from arylsulfinic acids and indoles (Scheme 3.5).[14]

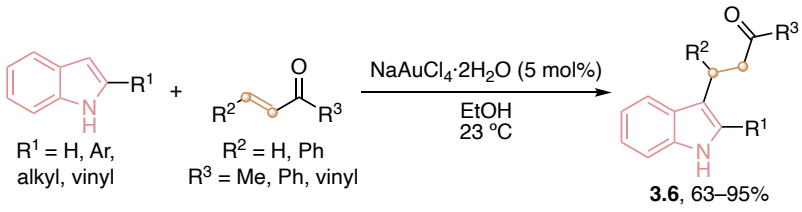


Scheme 3.5. Synthesis of 3-arylsulfinylindoles.

Gold(I)-Catalyzed Functionalization Reactions of Indoles

Considering the nucleophilic positions of indoles, it is easy to understand that they can easily undergo reactions with the electrophilic species generated after gold activation. Over the past years, the combination of gold catalysis and indoles chemistry has been profoundly explored.[15]

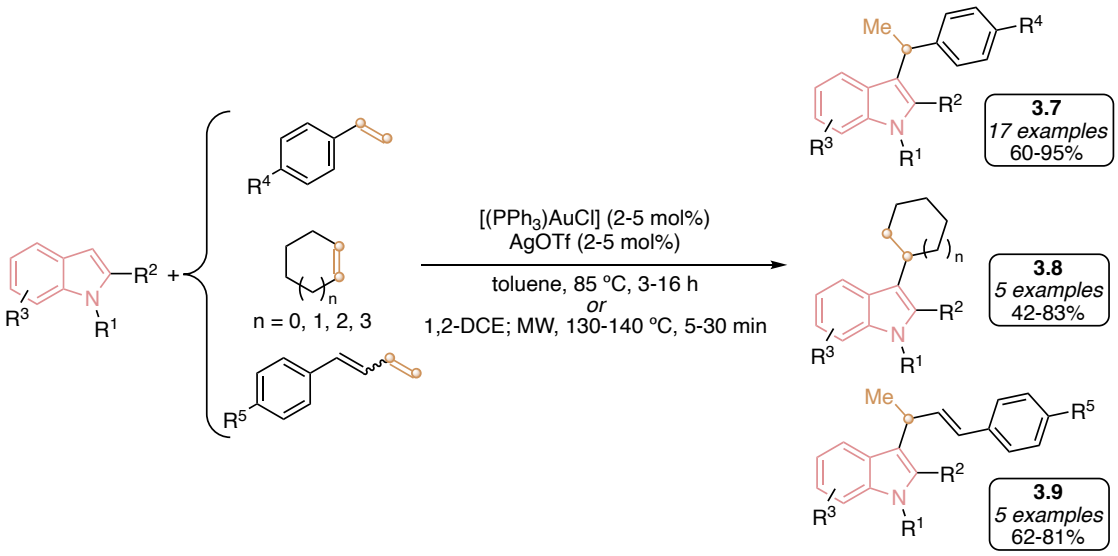
One of the first examples was reported in 2004 by Arcadi and co-workers. They described the use of $NaAuCl_4 \cdot 2H_2O$ as catalyst for the alkylation of indoles at the C3 position (Scheme 3.6).[16] This transformation takes place through conjugate addition with α,β-unsaturated ketones.



Scheme 3.6. Gold(I)-catalyzed 3-alkylation of indoles.

14. Miao, T.; Li, P.; Zhang, Y.; Wang, L. *Org. Lett*. **2015**, *17*, 832–835.
15. Pirovano, V. *Eur. J. Org. Chem*. **2018**, *17*, 1925–1945.
16. Arcadi, A.; Bianchi, G.; Chiarini, M.; D'Anniballe, G.; Marinelli, F. *Synlett* **2004**, 944–950.

Additionally, in the past decades, numerous gold(I)-catalyzed hydroarylation reactions with indoles as nucleophiles have been investigated. In 2008 Wong and Che presented the first gold(I)-catalyzed intermolecular hydroarylation of alkenes, cycloalkanes and conjugated dienes with indoles under microwave irradiation (Scheme 3.7).[17]

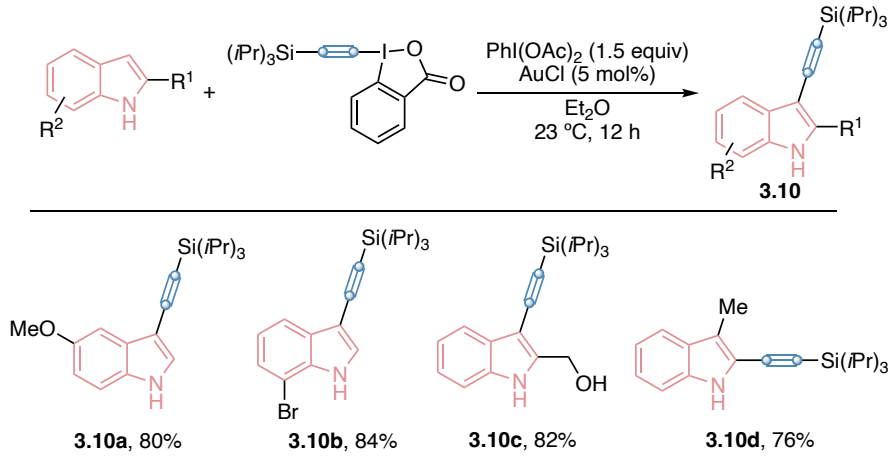


Scheme 3.7. Gold(I)-catalyzed intermolecular hydroarylation of alkenes.

Since then, many other examples of gold(I)-catalyzed inter- and intramolecular hydroarylation reactions with alkynes and allenes have been reported.[18]

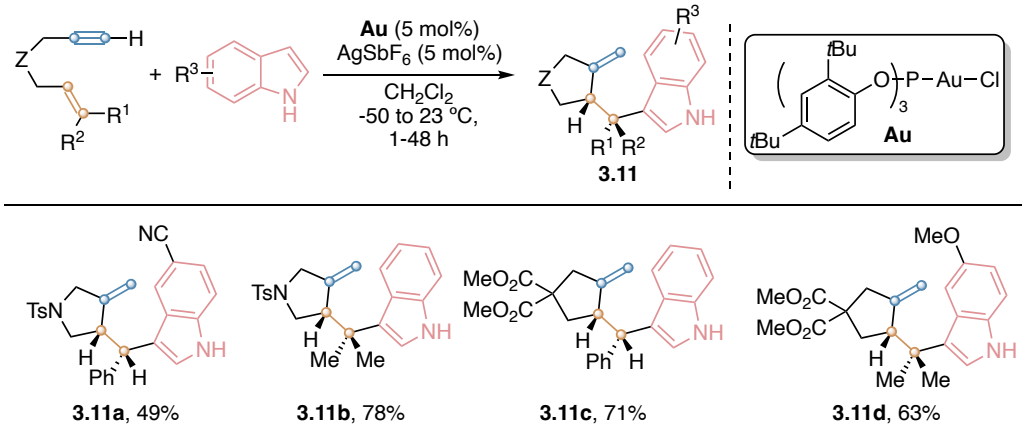
Pioneering work by Waser in 2009 set the starting point for the use of gold catalysis in the direct alkynylation of indoles. His research group reported the alkynylation of indole heterocycles using a benziodoxolone-based hypervalent iodine reagent. This innovative approach improved the functional group tolerance and afforded products with an unprecedented substitution pattern. (Scheme 3.8).[19] Later on, the group of Nevado extended the use of hypervalent iodine reagents for the ethynylation of arenes with electron-deficient alkynes.[20]

17. Wang, M.-Z.; Wong, M.-K.; Che, C.-M. *Chem. Eur. J.* **2008**, *14*, 8353–8364.
18. (a) Li, Z.; Shi, Z.; He, C. *J. Organomet. Chem.* **2005**, *690*, 5049–5054. (b) Ferrer, C.; Amijs, C. H. M.; Echavarren, A. M. *Chem. Eur. J.* **2007**, *13*, 1358–1373. (c) Toups, K. L.; Liu, G. T.; Widenhoefer, R. A. *J. Organomet. Chem.* **2009**, *694*, 571–575 (d) Zhu, P.-L.; Zhang, Z.; Tang, X.-Y.; Marek, I.; Shi, M. *ChemCatChem* **2015**, *7*, 595–600.
19. Brand, J. P.; Charpentier, J.; Waser, J. *Angew. Chem. Int. Ed.* **2009**, *48*, 9346–9349.
20. de Haro, T.; Nevado, C. *J. Am. Chem. Soc.* **2010**, *132*, 1512–1513.



Scheme 3.8. Gold(I)-catalyzed alkynylation of indoles with hypervalent iodine reagent.

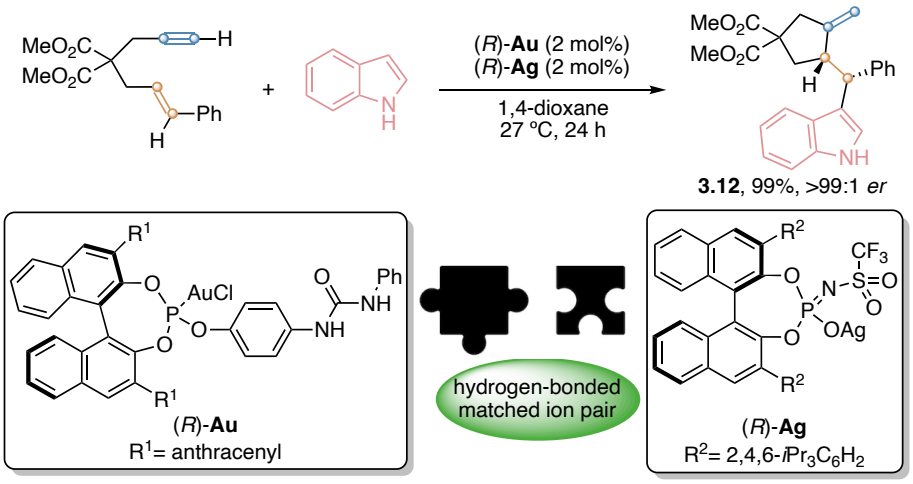
Gold catalysis has been also successfully applied to the functionalization of indoles through cycloaddition and cascade reactions.[21] Particularly, our group reported in 2007 that indoles could be employed as external carbon nucleophiles in the cycloisomerization of 1,6-enynes (Scheme 3.9). The reaction can take place through a *5-exo*-dig or a 6-*endo*-dig cyclization where the cyclopropyl gold(I) carbene is trapped by the indole nucleophile.[22]



Scheme 3.9. Indoles as nucleophiles in the cycloisomerization of 1,6- enynes.

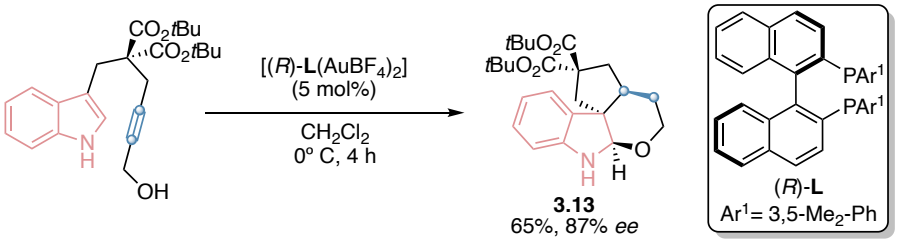
21. (a) Xu, S.; Zhou, Y.; Xu, J.; Jiang, H.; Liu, H. *Green Chem.* **2013**, *15*, 718–726. (b) Rossi, E.; Abbiati, G.; Pirovano, V. *Eur. J. Org. Chem.* **2017**, 4512–4529.
22. (a) Amijs, C. H. M.; Ferrer, C.; Echavarren, A. M. *Chem. Commun.* **2007**, *7*, 698–700. (b) Amijs, C. H. M.; López-Carrillo, V.; Raducan, M.; Pérez-Galán, P.; Ferrer, C.; Echavarren, A. M. *J. Org. Chem.* **2008**, *73*, 7721–7730.

Enantioselective functionalization reactions of indoles have also been deeply studied. In this context, in 2023, our group reported the enantioselective nucleophilic addition of indoles using a chiral catalyst in combination with a matched gold(I) phosphitourea and phosphoramidate (Scheme 3.10). [23] The reaction afforded the carbocyclization products (**3.12** as an example) in excellent yields and enantioselectivities.



Scheme 3.10. Gold(I)-enantioselective cycloaddition of indoles.

Many other examples of enantioselective gold(I)-catalyzed functionalization of indoles have been presented in the past years.[24] One of the first examples of these transformations was reported by Bandini and co-workers in 2012 where they presented the synthesis of enantioenriched tetracyclic fused indolines through gold(I)-catalyzed hydroindolination of propargylic alcohols (Scheme 3.11).[25]



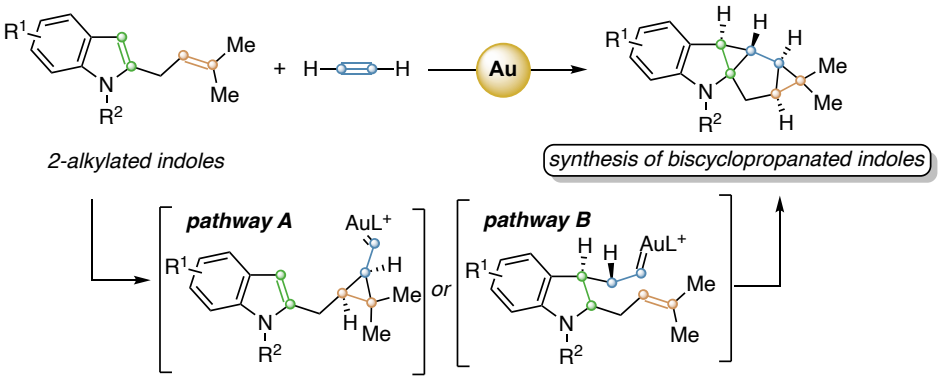
Scheme 3.11. Enantioselective gold(I)-catalyzed synthesis of polycyclic indolines.

Undeniably, the combination of homogeneus gold catalysis and indole chemistry has become a broadly explored field in the past decades. However, due to the excellent capability of gold(I)-catalysts to promote cascade reactions, efforts should be dedicated to the synthesis of complex polycyclic indoles.

23. Martí, À.; Ogalla, G.; Echavarren, A. M. *ACS Catal.* **2023**, *13*, 10217–10223.
24. Milcendeau, P.; Sabat, N.; Ferry, A.; Guinchard, X. *Org. Biomol. Chem.* **2020**, *18*, 6006–6017.
25. Cera, G.; Chiarucci, M.; Mazzanti, A.; Mancinelli, M.; Bandini, M. *Org. Lett.* **2012**, *14*, 1350–1353.

Objectives

The aim of the research summarized in this Chapter was the development of a gold(I)-catalyzed biscyclopropanation reaction of 2-alkylated indoles in the presence of acetylene gas. This unprecedented transformation could take place through two plausible mechanistic pathways depending on which alkene reacts first with (η^2-acetylene) gold(I) complex. In this sense, additional computational studies will be carried out to elucidate the reaction mechanism.[26]



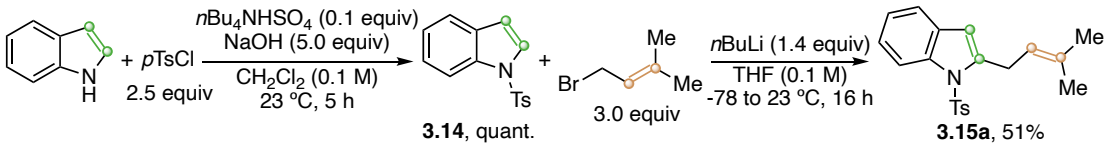
Scheme 3.12. Gold(I)-catalyzed biscyclopropanation of indoles with acetylene gas.

26. Part of the experiments described in this section were performed jointly with Dr. Anna Sadurní, Dr. L. Anders Hammarback, Jennifer Tamayo and Mathéo La Torre.

Results and Discussion

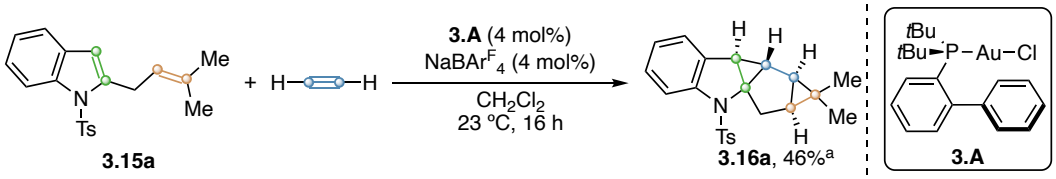
Synthesis of Biscyclopropanated Indoles with Acetylene Gas

We decided to start our work with the synthesis of indole **3.15a** (Scheme 3.13). This substrate was prepared by a two-step synthetic route based on a *N*-tosyl protection followed by the 2-alkylation of the indole using prenyl bromide and organolithium reagents.



Scheme 3.13. Synthesis of starting indole **3.15a**.

Alkylated indole **3.15a** was submitted to the gold(I) catalysis in the presence of acetylene gas (Scheme 3.14). We were delighted to confirm the formation of biscyclopropanated product **3.16a** in a moderate yield using commercially available JohnPhosAuCl (**3.A**) as gold(I) catalyst. The structure and stereochemistry of the product were determined by X-ray diffraction analysis (Figure 3.2).



[a]Yield determined by ^{1}H NMR spectroscopy using 1,4-diacetylbenzene as internal standard.

Scheme 3.14. First attempt of gold(I)-catalyzed biscyclopropanation of indole **3.15a**.

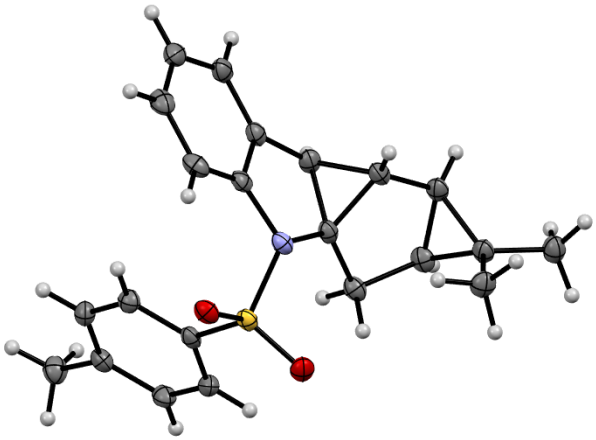
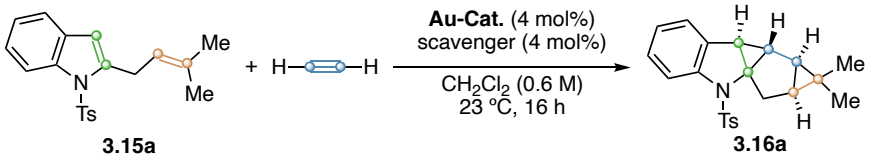


Figure 3.2. X-ray structure of product **3.16a**.

After this promising result, we moved to the optimization of the reaction conditions (Table 3.1). Changing JohnPhosAuCl (Table 3.1, entry 1) to other phosphine-based ligands as catalysts had a detrimental effect in the yield of the reaction (Table 3.1, entry 2). Neither employing a *N*-heterocyclic carbene type catalyst or phosphite-based complex led to any improvement of the yield of the product **3.16a** (Table 3.1, entries 3–5). The use of different chloride scavengers was also studied and $AgSbF_6$ and $AgNTf_2$ gave the best results, affording product **3.16a** in 50% and 51% yield, respectively (Table 3.1, entries 6, 9). In view of these results, we tested cationic gold(I) complex **3.F** and confirmed that the yield of **3.16a** was maintained (Table 3.1, entry 10).

After identifying **3.F** as the best catalyst for the reaction we tested different catalyst loadings and concentrations, but we could not improve the yield beyond 50%.

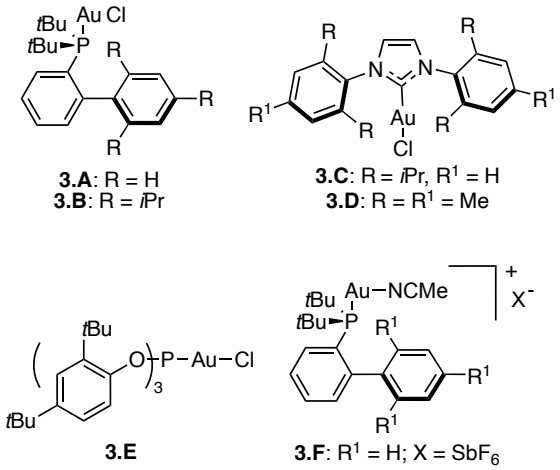
Table 3.1. Optimization of the reaction conditions.



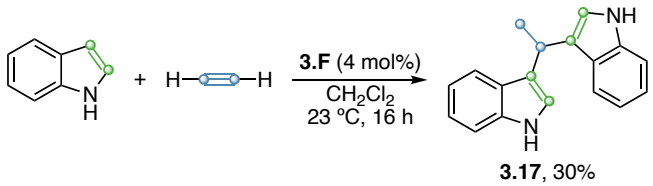
3.15a 3.16a

Entry	Au-Cat.	Scavenger	Yield 3.16a (%)[a]
1	**3.A**	$NaBAr^F_4$	46
2	**3.B**	$NaBAr^F_4$	38
3	**3.C**	$NaBAr^F_4$	10
4	**3.D**	$NaBAr^F_4$	43
5	**3.E**	$NaBAr^F_4$	37
6	**3.A**	$AgSbF_6$	50
7	**3.A**	$AgPF_6$	11
8	**3.A**	$AgNTf_2$	51
9	**3.A**	AgOTf	4
10[b]	**3.F**	-	52

[a]Yield determined by ^{1}H NMR spectroscopy using 1,4-diacetylbenzene as internal standard. [b]Cationic gold(I) complex used directly without chloride scavenger.



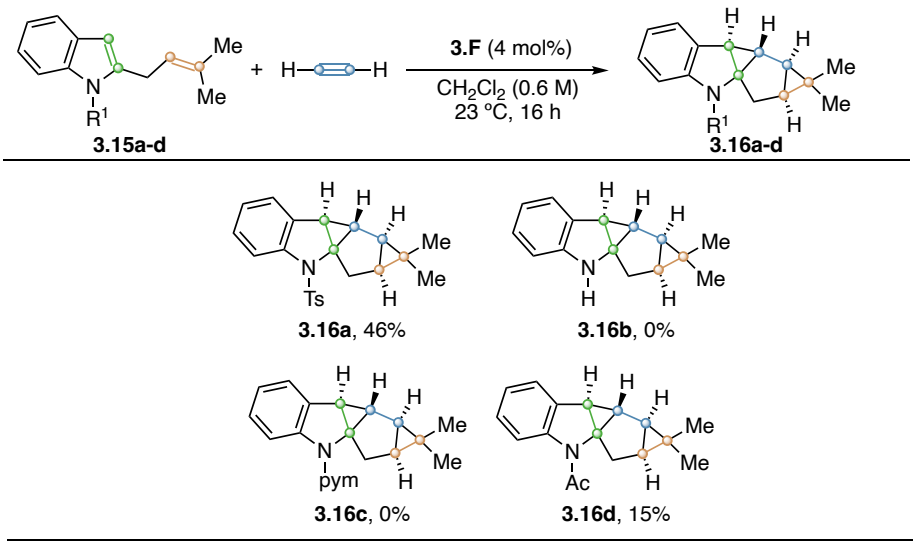
Additionally, we performed a control test using 1*H*-indole and acetylene gas in the presence of catalyst **3.F**. In this case, we didn't observe a cyclopropanation reaction, as expected, but, instead, the only product detected was the double addition of indole to the acetylene moiety (Scheme 3.15). This type of reactivity has been described before using gold(I) catalysis and aryl alkynes in combination with propiolates.[27]



Scheme 3.15. Gold(I)-catalyzed double addition of indole to acetylene gas.

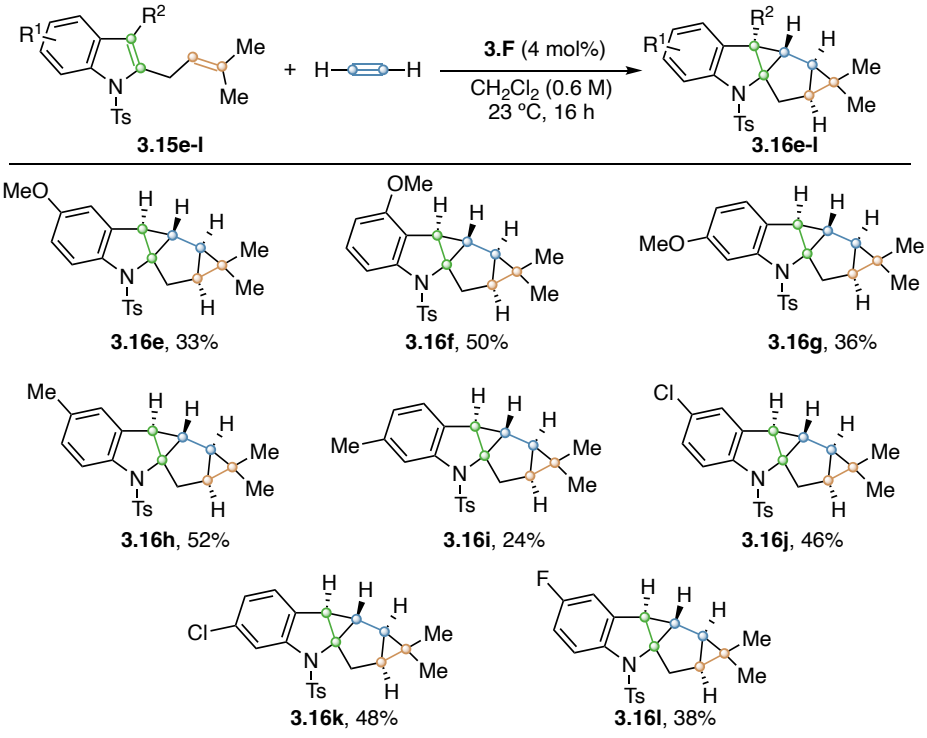
Moving on to the evaluation of the scope of the reaction, we tested free 2-alkylated indole **3.15b** but, unfortunately, the biscyclopropanated indole product was not formed. Instead, only products of side oligomerization reaction were detected by ^{1}H NMR spectroscopy. Next, the influence of other nitrogen protecting groups was tested. When 2-pyrimidyl group was employed, no conversion of the starting material (**3.15c**) was observed whereas acetylated indole **3.15d** afforded the desired product **3.16d** in low yield (Scheme 3.16).

27. (a) Li, Z.; Shi, Z.; He, C. *J. Organomet. Chem.* **2005**, *690*, 5049–5054. (b) Ferrer, C.; Amijs, C. H. M.; Echavarren, A. M. *Chem. Eur. J.* **2007**, *13*, 1358–1373.



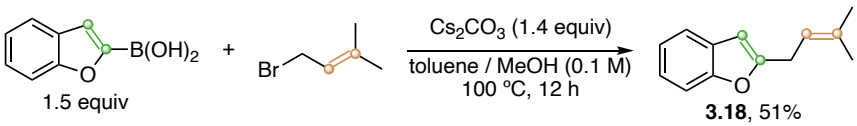
Scheme 3.16. Scope of indole protecting groups.

In view of these results, we decided to study the influence of the substitution pattern in the aryl ring of the indole moiety (Scheme 3.17). Electron-donating groups were well tolerated in different positions of the aryl ring (**3.16e-i**). However, when electron-rich substituents were placed at the C6 position, the corresponding cyclized products **3.16g** and **3.16i** were obtained in lower yields. The use of halogen-substituted indoles led to the desired products in moderate yields (46% and 48% yield for chlorinated products **3.16j** and **3.16k** and 38% yield for fluorinated product **3.16l**).



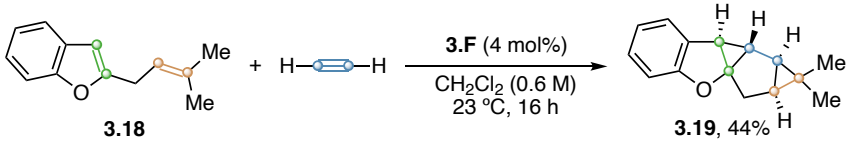
Scheme 3.17. Scope of aryl-substituted indoles.

We then envisioned to extend this methodology to other heterocycles. We successfully prepared in one step alkylated benzofuran **3.18** in good yield (Scheme 3.18)



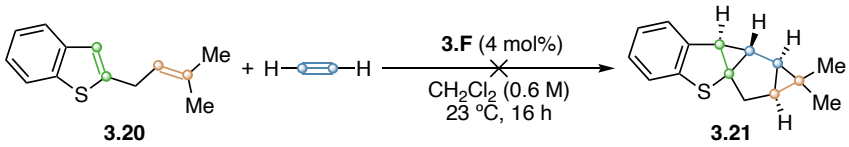
Scheme 3.18. Synthesis of 2-prenyl benzofuran **3.18**.

We tested the reactivity of this new substrate in the gold(I)-catalyzed cyclopropanation reaction with acetylene gas (Scheme 3.19). We were glad to confirm the formation of polycyclic compound **3.19** as a single product in moderate yield.



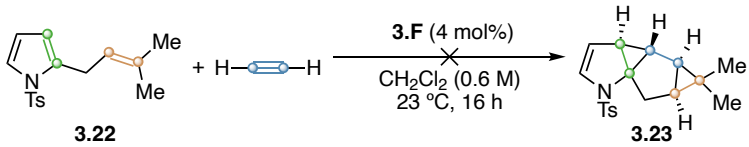
Scheme 3.19. Gold(I)-catalyzed biscyclopropanation of alkylated benzofuran **3.19** with acetylene gas.

Furthermore, we evaluated the reactivity of 2-alkylated benzothiophene **3.20** but, unfortunately, in this case, no reaction was observed as only the starting benzothiophene was recovered after the reaction (Scheme 3.20).



Scheme 3.20. Test with 2-alkylated benzothiophene **3.20**.

Additionally, 2-alkykated pyrrole derivate **3.22** was submitted to the optimized reaction conditions but no conversion towards the expected product was observed (Scheme 3.21).



Scheme 3.21. Test with 2-alkylated pyrrole derivate **3.22**.

Due to their ring strain, cyclopropanes usually undergo ring-opening reactions.[28] This reactivity makes cyclopropanes highly interesting for the synthesis and functionalization of building blocks.[29] In this context, we wanted to explore the possibility of model substrate **3.16a** to engage in a ring-opening reaction to afford product **3.24** (Scheme 3.22).

Scheme 3.22. Cyclopropane ring-opening reaction of **3.16a**.

Several conditions for the cyclopropane opening were tested and can be summed in Table 3.2.

Firstly, we tried the ring-opening reaction using gold(I) catalysis since similar transformations involving the opening of cyclopropane rings have been reported before.[30] Commercially available JohnPhosAuCl (**3.A**) as catalyst was tested at 40 ºC and 70 ºC but no conversion was achieved in any case (Table 3.2, entries 1–2). Increasing the temperature up to 110 ºC and changing the solvent to toluene did not show any conversion either (Table 3.2, entry 3). The use of $AuCl_3$ as catalyst led to the decomposition of the starting material and no product could be detected after the reaction (Table 3.2, entry 4). Additionally, we tested different Lewis acids but only starting **3.16a** could be recovered after 16 h (Table 3.2, entry 6).

Table 3.2. Tests for the cyclopropane ring-opening reaction.

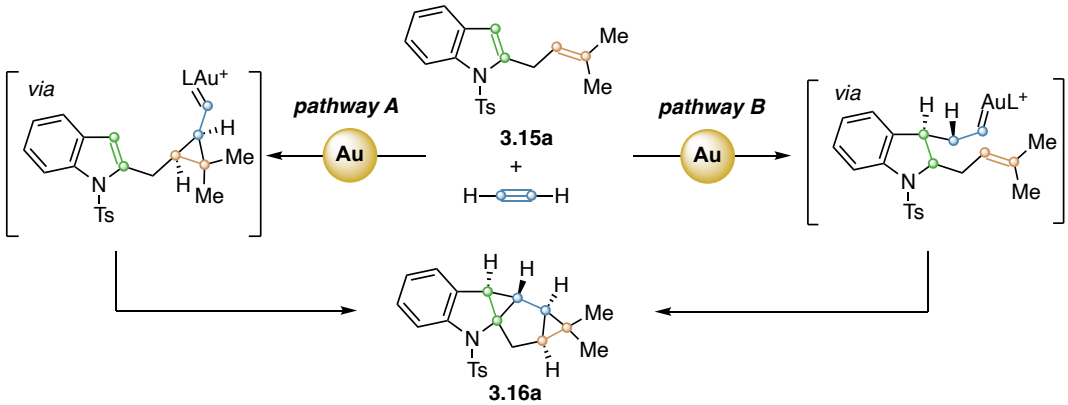
Entry	Conditions	Outcome
1	JohnPhosAuCl, $NaBAr^F_4$ 1,2-DCE, 40 ºC, 16 h	no conversion
2	JohnPhosAuCl, $NaBAr^F_4$ 1,2-DCE, 70 ºC, 16 h	no conversion
3	JohnPhosAuCl, $NaBAr^F_4$ toluene, 110 ºC, 16 h	no conversion
4	$AuCl_3$ 1,2-DCE, 70 ºC, 16 h	decomposition
5	$HClO_4$ CH_2Cl_2, 23 ºC, 1 h	no conversion
6	*p*TsOH·H_2O toluene, 110 ºC, 16 h	no conversion

28. (a) Sivanandan, S. T.; Bharath Krishna, R.; Baiju, T. V.; Mohan, C. *Eur. J. Org. Chem.* **2021**, *48*, 6781–6805. (b) Pirenne, V.; Muriel, B.; Waser, J. *Chem. Rev.* **2021**, *121*, 227–263.
29. de Meijere, A. *Angew. Chem. Int. Ed.* **1979**, *18*, 809–826.
30. Fang, W.; Shi, M. *Chem. Eur. J.* **2018**, *24*, 9998–10005.

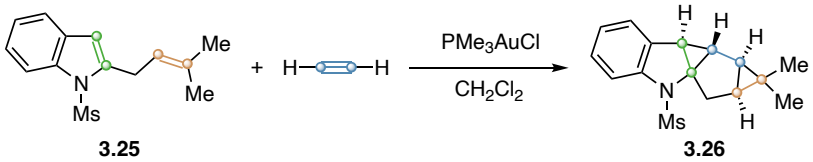
DFT Calculations

To gain insights into the reaction mechanism, DFT calculations were performed. We envisioned two possible mechanistic pathways for the biscyclopropanation reaction depending on which alkene reacts first. If the reaction follows pathway A (Scheme 3.23, left), upon coordination of acetylene to the gold(I) catalyst, the alkene (orange) would attack first to the (η^2-alkyne) gold(I) complex forming the corresponding cyclopropyl gold(I) carbene. However, if the reaction follows pathway B instead (Scheme 3.23, right), then, upon coordination of the gold center to the alkyne, it would be the indole (green) which would attack first to form the cyclopropyl gold(I) carbene.

Scheme 3.23. Possible mechanistic pathways for the biscyclopropanation of indoles.



To elucidate the reaction mechanism, we calculated the energies of the intermediates and the transition states for both possible routes (Scheme 3.24).[31]



Scheme 3.24. Reaction scheme for DFT studies.

31. DFT calculations were performed using *N*-methanesulfonyl as protecting group instead of *N*-toluenesulfonyl and with PMe_3 as gold ligand for simplification reasons.

Model *N*-Methanesulfonyl Indole 3.25: Pathway A (Figure 3.3)

Starting from **Int1** two possible mechanistic pathways were envisioned. Following pathway A, the formation of the *syn* cyclopropyl gold(I) carbene takes place with an energy barrier of 13.8 kcal mol^{-1}. Then, intramolecular attack of the *syn* cyclopropyl gold(I) carbene to the indole lead to the formation of six-membered ring **Int3**. This process (**TS_{2-3}**) was found to be energetically favored with an activation barrier of only 3.9 kcal mol^{-1}. Finally, the ring contraction of **Int3** afforded the desired product **Int4** with an activation barrier of 3.3 kcal mol^{-1}.

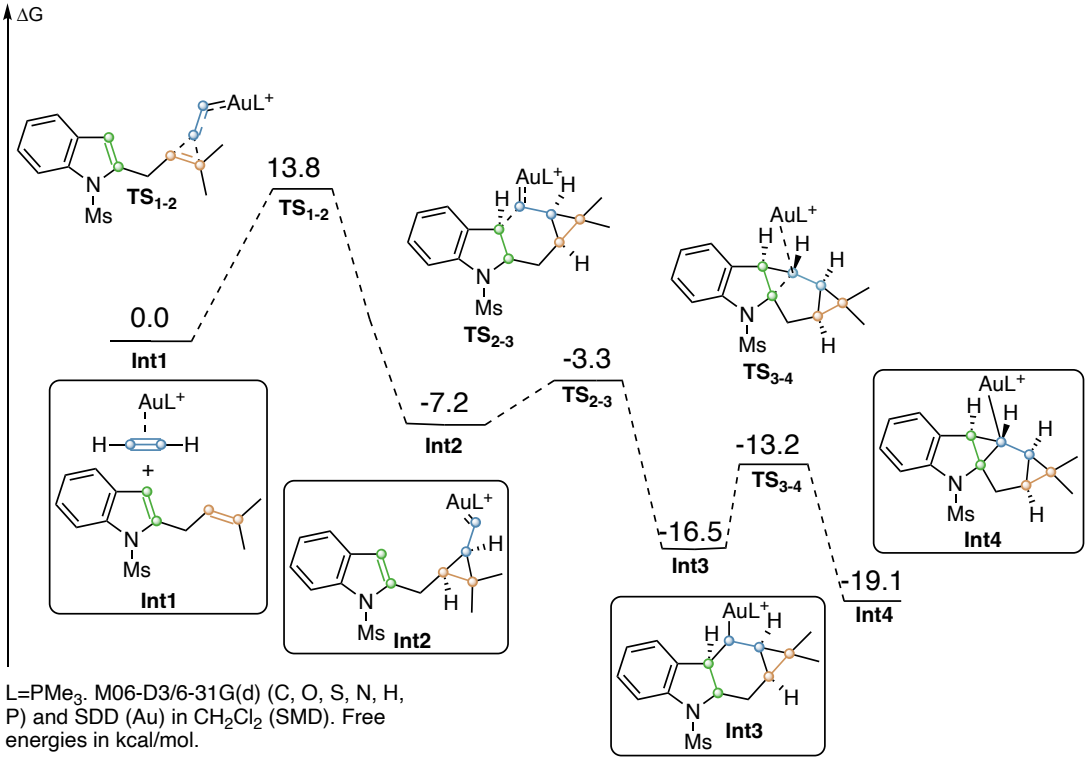


Figure 3.3. DFT calculations for *N*-methanesulfonyl indole **3.25** (pathway A).

Model *N*-Methanesulfonyl Indole 3.25: Pathway B (Figure 3.4)

As in pathway A, the reaction mechanism begins with the formation of **Int1** followed by the nucleophilic attack of the alkene. In this case, the cyclopropyl gold(I) carbene (**Int5**) is formed upon reaction of the alkene of the indole with the acetylene gold(I) complex (**TS_{1-5}**). The energy barrier for the formation of this cyclopropyl gold(I) carbene is 15.7 kcal mol^{-1}, almost 2 kcal mol^{-1} higher than the energy barrier for pathway A (13.8 kcal mol^{-1}). These values support the reaction going through pathway A instead of pathway B since the energy barrier for the first transition state is lower.

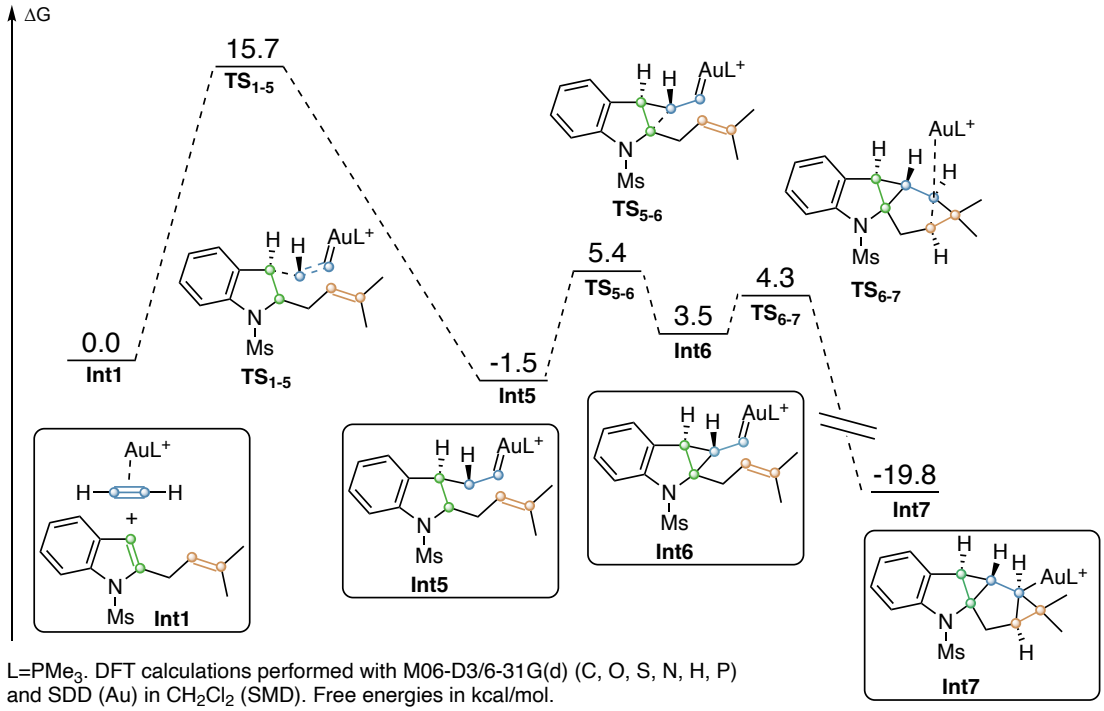
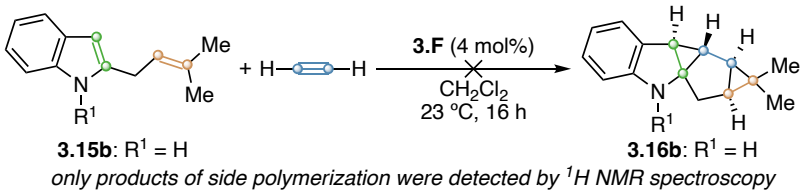


Figure 3.4. DFT calculations for *N*-methanesulfonyl indole **3.25** (pathway B).

We hypothesize that this preference could be due to the diminished reactivity of the alkene of the indole. This lack of reactivity could be attributed to the presence of an electron-withdrawing group close to the alkene group (tosyl group in the nitrogen atom α to the double bond of the indole) that makes this alkene less nucleophilic.

Furthermore, we were intrigued about the possibility of justifying the different reaction outcome when free indole (**3.15b**) was employed (Scheme 3.25).



Scheme 3.25. Reaction outcome for indoles **3.15b**.

For substrate **3.15b**, both possible mechanistic pathways were calculated (Figure 3.5). Even though the energy barrier for the first transition state ($\mathbf{TS_{8\text{-}9}}$) is similar to the one calculated for substrate **3.15a** (14.3 kcal mol^{-1} for **3.15b** *vs* 13.8 kcal mol^{-1}for **3.15a**), for substrate **3.15b**, pathway B is preferred. DFT calculations show that, in this case, the nucleophilic attack of the indole is more energetically favored by almost 2 kcal mol^{-1} ($\mathbf{TS_{8\text{-}11}}$ = 12.7 kcal mol^{-1}). Likely, this is a result of the absence of an electron-withdrawing group in the nitrogen of the heterocycle. However, despite being energetically feasible, we could not calculate the transition state to afford the biscyclopropanated product (**Int12**). All our tests resulted in the protodeauration of **Int11**.

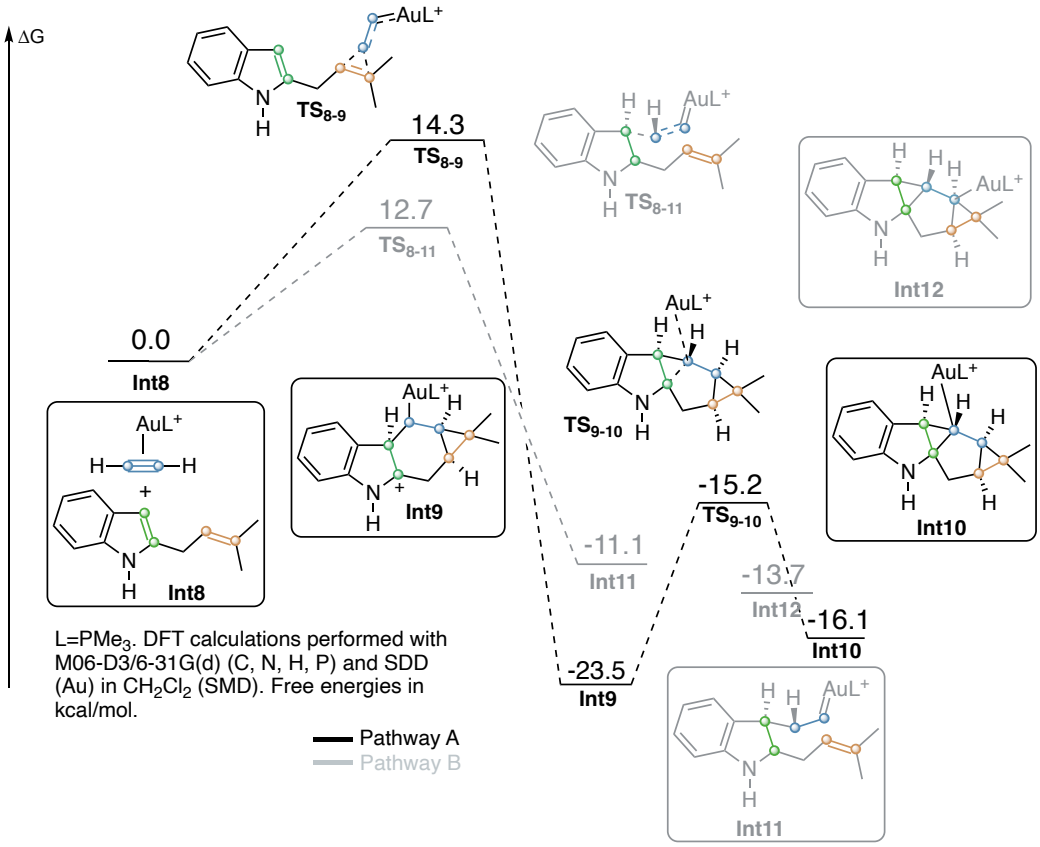


Figure 3.5. DFT calculations for the reaction of free indole **3.15b**.

These DFT calculation do not explain why, in the case of substrate **3.15b**, only oligomerization products are observed. To explain this outcome, the oligomerization rate of the corresponding substrate and products should be calculated.

Moreover, DFT calculations were performed for a model substrate (*N*-methyl indole) and the results obtained were the same as for substrate **3.15b** (Figure 3.6). Like in the case of the free indole, for this substrate, pathway B is more energetically favored ($\mathbf{TS_{13\text{-}14}}$ = 12.0 kcal mol^{-1} for pathway A *vs* $\mathbf{TS_{13\text{-}17}}$ = 9.3 kcal mol^{-1} for pathway B).

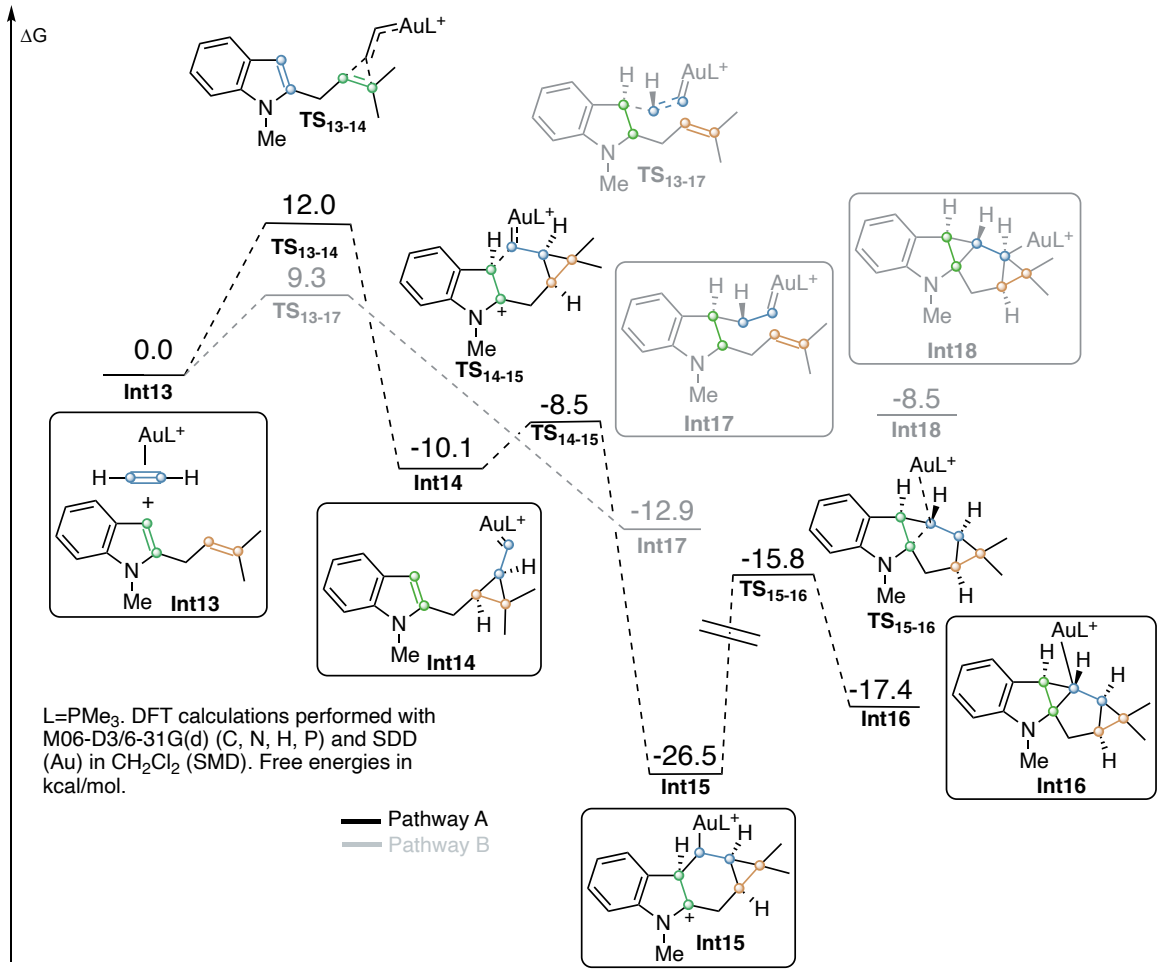


Figure 3.6. DFT calculations for the reaction of *N*-methyl indole.

We also calculated the energy profile for the benzofuran analogue **3.18** (Figure 3.7). Both mechanistic pathways were calculated and as expected, pathway A (where the alkene reacts first) is more energetically favored than pathway B by more than 4 kcal mol^{-1} ($\mathbf{TS_{19\text{-}20}}$ =13.7 kcal mol^{-1} *vs* $\mathbf{TS_{19\text{-}23}}$ = 17.9 kcal mol^{-1}). As in the case of substrate **3.15a**, DFT calculations support the formation of **Int25** from the nucleophilic attack of the indole to form the cyclopropyl gold(I) carbene.

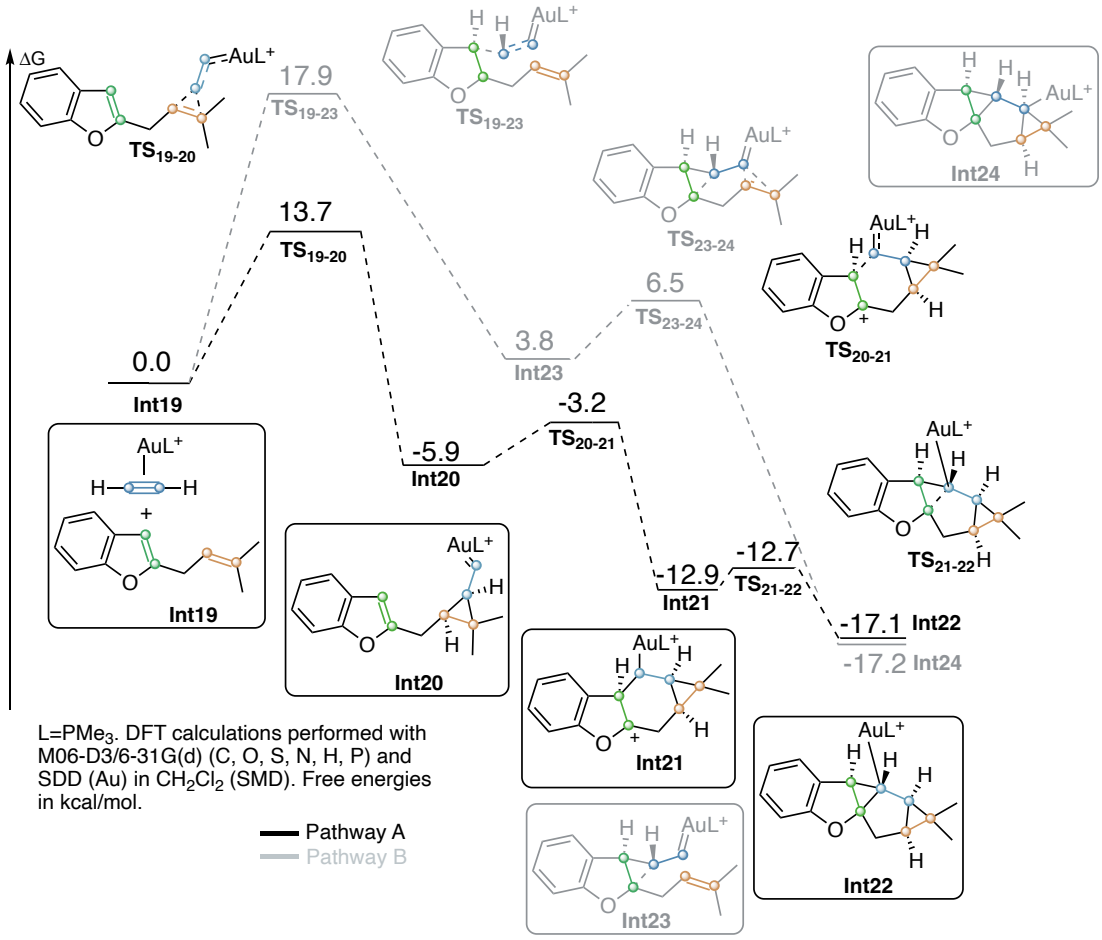
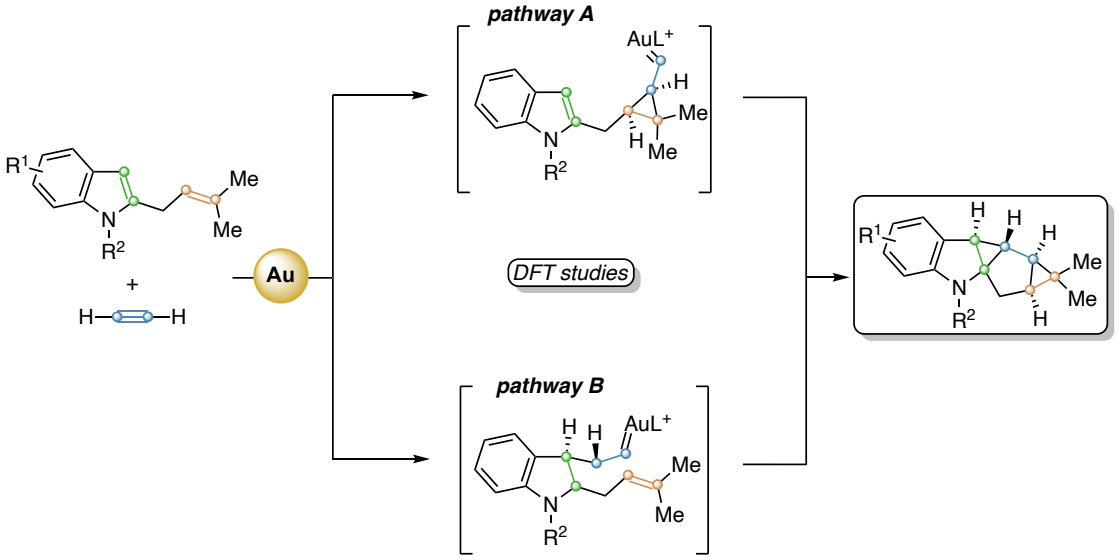


Figure 3.7. DFT studies on the possible mechanistic pathways for the synthesis of benzofuran **3.19**.

Conclusions

We have developed the gold(I)-catalyzed reaction between 2-alkylated indoles and acetylene gas to afford biscyclopropanated indoles in moderate to good yields. DFT studies were performed to gain insights into the reaction mechanism. When sulfonamides are used as protecting groups for the indole, calculations show that the alkene reacts firsts to form the cyclopropyl gold(I)-carbene that, eventually, gives rise to the biscyclopropanated products.



Scheme 3.26. Mechanistic insights into the gold(I)-catalyzed biscyclopropanation of indoles.

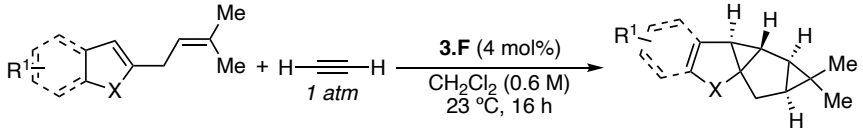
Experimental Section

General Methods

The general information has been provided in the experimental section of Chapter I.

Synthetic Procedures and Analytical Data

General procedure A: Gold(I)-catalyzed biscyclopropanation of 2-substituted indoles



X = NTs, **3.15a-l**
X = O, **3.18**

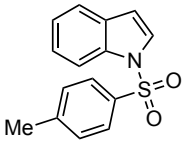
X = NTs, **3.16a-l**
X = O, **3.19**

A reaction tube was charged with substrate **3.15** or **3.18** (1.0 equiv) and **3.F** (4 mol%) in HPLC grade CH_2Cl_2 (0.6 M). The tube was introduced in a HEL reactor under 1 atm of acetylene gas. The reaction mixture was stirred at 23 ºC for 24 h and after emptying the remaining gas, the reaction was quenched by the addition of 3 drops of Et_3N and concentrated under reduced pressure. The crude product was purified as described in the individual procedures affording the biscyclopropanated products **3.16** and **3.19**.

Synthesis of Starting Indoles (3.15)

1-Tosyl-1*H*-indole (3.27)

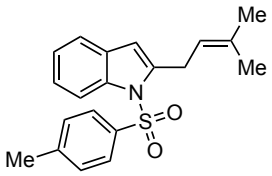
Freshly pulverized NaOH (1.40 g, 35.0 mmol, 5.0 equiv) was added to a mixture of 1*H*-indole (820 mg, 7.00 mmol, 1.0 equiv) and nBu_4NHSO_4 (238 mg, 0.70 mmol, 0.1 equiv) in anhydrous CH_2Cl_2 (70.0 mL, 0.1 M) at 23 ºC for 5 min. Then, *p*-toluenesulfonyl chloride (3.34 g, 17.5 mmol, 2.5 equiv) was added portion wise at 23 ºC and the mixture was stirred for 5 additional hours. Upon completion, it was quenched with sat. aq. Na_2CO_3 (40 mL) and extracted with CH_2Cl_2 (3 x 40 mL). The combined organic layers were washed with brine (50 mL), dried over anhydrous $MgSO_4$, filtered and concentrated under vacuo. The crude was purified by flash column chromatography (SiO_2, cyclohexane/EtOAc 100:0, *v/v*) and the product **3.27** was obtained as a colorless oil (1.90 g, 7.00 mmol, quantitative).



^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 (dq, *J* = 8.3, 0.9 Hz, 1H), 7.79–7.75 (m, 2H), 7.57 (d, *J* = 3.7 Hz, 1H), 7.53 (ddd, *J* = 7.8, 1.3, 0.8 Hz, 1H), 7.31 (ddd, *J* = 8.4, 7.2, 1.3 Hz, 1H), 7.25–7.18 (m, 3H), 6.65 (dd, *J* = 3.7, 0.8 Hz, 1H), 2.33 (s, 3H).The characterization data matches those reported in the literature.[32]

32. Leclair, A.; Wang, Q.; Zhu, J. *ACS Catal.* **2022**, *12*, 1209–1215.

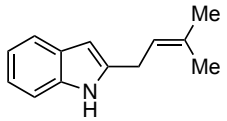
2-(3-Methylbut-2-en-1-yl)-1-tosyl-1*H*-indole (3.15a)



Freshly titrated *n*BuLi (2.48 mL, 6.19 mmol, 1.4 equiv, 2.5 M) was added dropwise to a solution of 1-tosyl-1*H*-indole **3.27** (1.20 g, 4.42 mmol, 1.0 equiv) in anhydrous THF (44.2 mL, 0.1 M) at –78 ºC. The reaction mixture was stirred for 45 min and 3,3-dimethylallylbromide (1.54 mL, 1.98 g, 13.3 mmol, 3.0 equiv) was added in one portion. The resulted solution was stirred for another 15 min at –78 ºC and then slowly warmed to 23 ºC and stirred for 16 h. Upon completion, it was quenched by the addition of sat. aq. NH_4Cl (35 mL) and extracted with CH_2Cl_2 (3 x 40 mL). The combined organic layers were washed with brine (50 mL), dried over anhydrous $MgSO_4$, filtered and concentrated under vacuo. The crude was purified by flash column chromatography (SiO_2, cyclohexane/EtOAc 100:0 to 80:20, *v/v*) and the product **3.15a** was obtained as a yellow oil (761 mg, 4.42 mmol, 51% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.21 (dq, *J* = 8.4, 0.9 Hz, 1H), 7.69–7.65 (m, 2H), 7.41 (ddd, *J* = 7.6, 1.4, 0.7 Hz, 1H), 7.29–7.26 (m, 1H), 7.24–7.20 (m, 1H), 7.20–7.16 (m, 2H), 6.38 (q, *J* = 1.2 Hz, 1H), 5.42 (dddd, *J* = 7.2, 5.8, 2.9, 1.5 Hz, 1H), 3.71 (d, *J* = 7.2 Hz, 2H), 2.33 (d, *J* = 3.4 Hz, 3H), 1.81 (d, *J* = 1.4 Hz, 3H), 1.65 (d, *J* = 1.4 Hz, 3H).The characterization data matches those reported in the literature.[33]

2-(3-Methylbut-2-en-1-yl)-1*H*-indole (3.15b)



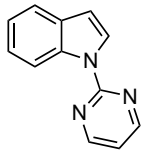
In a round-bottom flask under air, 2-(3-methylbut-2-en-1-yl)-1-tosyl-1*H*-indole **3.15a** (3.00 g, 8.84 mmol, 1.0 equiv) was dissolved in MeOH (17.7 mL, 0.5 M). Activated Mg (3.87 g, 159 mmol, 18.0 equiv) was added, and the mixture was sonicated without magnetic stirring at 23 °C during 1 h. The reaction was then stirred without sonication at 23 °C for 1 h. The reaction mixture was filtered and washed with 1M HCl (15 mL), sat. aq. $NaHCO_3$ (10 mL) and H_2O (10 mL). The aqueous phase was extracted three times with CH_2Cl_2 (3 x 15 mL). The combined organic layers were washed with brine (20 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The crude residue was purified by flash column chromatography (neutralized SiO_2 with 5% Et_3N in cyclohexane, cyclohexane/Et_2O 100:0 to 80:20, *v/v*) to afford **3.15b** as a pale-yellow solid (982 mg, 5.30 mmol in 60% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.86 (s, 1H), 7.56–7.52 (m, 1H), 7.32–7.29 (m, 1H), 7.13 (ddd, *J* = 8.1, 7.1, 1.4 Hz, 1H), 7.08 (ddd, *J* = 8.2, 7.1, 1.2 Hz, 1H), 6.27–6.24 (m, 1H), 5.44–5.39 (m, 1H), 3.52–3.49 (m, 2H), 1.82 (d, *J* = 1.3 Hz, 3H), 1.76 (d, *J* = 1.4 Hz, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 138.8, 136.1, 134.7, 129.1, 121.1, 120.3, 119.9, 119.7, 110.5, 99.6, 27.3, 25.9, 18.0. The characterization data matches those reported in the literature.[34]

33. Bock, J.; Daniliuc, C. G.; Hennecke, U. *Org. Lett.* **2019**, *21*, 1704–1707.
34. Wagger, J.; Svete, J.; Stanovnik, B. *Synthesis* **2008**, *2008*, 1436–1442.

1-(Pyrimidin-2-yl)-1*H*-indole (3.28)

To a stirred solution of 1*H*-indole (400 mg, 3.41 mmol, 1.0 equiv) in anhydrous DMF (8.5 mL, 0.4 M)

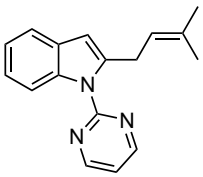


was added NaH (205 mg, 60% Wt, 5.12 mmol, 1.5 equiv) in one portion at 0 ºC under argon atmosphere. After stirring for 30 minutes, pyrimidin-2-yl chloride (469 mg, 4.10 mmol, 1.2 equiv) was added and the mixture was stirred at 130 ºC in a metallic heating block for 18 h. Upon completion, the reaction was cooled down to 23 ºC, poured into H_2O (8 mL) and extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with brine (15 mL), dried over anhydrous $MgSO_4$, filtered and concentrated under vacuo. The crude was purified by flash column chromatography (SiO_2, cyclohexane/EtOAc 100:0 to 90:10, *v/v*) and the product **3.28** was obtained as a white solid (549 mg, 2.81 mmol, 82% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.84 (dq, *J* = 8.4, 0.9 Hz, 1H), 8.69 (d, *J* = 4.8 Hz, 2H), 8.30 (d, *J* = 3.7 Hz, 1H), 7.70–7.62 (m, 1H), 7.43–7.37 (m, 1H), 7.30–7.25 (m, 1H), 7.02 (t, *J* = 4.8 Hz, 1H), 6.73 (dd, *J* = 3.7, 0.8 Hz, 1H). The characterization data matches those reported in the literature.[35]

2-(3-Methylbut-2-en-1-yl)-1-(pyrimidin-2-yl)-1*H*-indole (3.15c)

AgOTf (33 mg, 0.123 mmol, 0.10 equiv) was added inside the glovebox to a mixture of



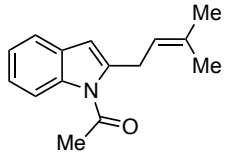
carbonyldiiodo(pentamethylcyclopentadienyl)cobalt(III) (Cp*Co(CO)I_2) (31 mg, 0.064 mmol, 0.05 equiv), AgOAc (21 mg, 0.128 mmol, 0.10 equiv) and 1-(pyrimidin-2-yl)-1*H*-indole **3.28** (250 mg, 1.28 mmol, 1.0 equiv) in anhydrous 1,2-dichloroethane (12.8 mL, 0.1 M). The mixture was taken outside the glovebox and 3-hydroxy-3-methyl-1-butyne (201 µL, 165 mg, 1.92 mmol, 1.5 equiv) was added and the mixture was stirred at 60 ºC in a metallic heating block for 16 h. The crude was quenched by the addition of sat. aq. NH_4Cl (8 mL) and extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were washed with brine (10 mL), dried over anhydrous $MgSO_4$, filtered and concentrated under vacuo. The crude was purified by flash column chromatography (SiO_2, cyclohexane/EtOAc 100:0 to 90:10, *v/v*) and the product **3.15c** was obtained as a white solid (262 mg, 1.00 mmol, 78% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.79 (d, *J* = 4.8 Hz, 2H), 8.23 (ddt, *J* = 8.2, 1.3, 0.7 Hz, 1H), 7.52 (ddd, *J* = 7.4, 1.6, 0.7 Hz, 1H), 7.21 (ddd, *J* = 8.2, 7.1, 1.5 Hz, 1H), 7.17 (td, *J* = 7.4, 1.3 Hz, 1H), 7.14 (t, *J* = 4.8 Hz, 1H), 6.46 (q, *J* = 1.1 Hz, 1H), 5.33 (tdq, *J* = 7.3, 3.0, 1.4 Hz, 1H), 3.88 (dq, *J* = 7.2, 1.1 Hz, 2H), 1.72 (q, *J* = 1.3 Hz, 3H), 1.70–1.68 (m, 3H). The characterization data matches those reported in the literature.[36]

35. Leitch, J. A.; McMullin, C. L.; Mahon, M. F.; Bhonoah, Y.; Frost, C. G. *ACS Catal*. **2017**, *7*, 2616–2623.
36. Suzuki, Y.; Sun, B.; Sakata, K.; Yoshino, T.; Matsunaga, S.; Kanai, M. *Angew. Chem. Int. Ed.* **2015**, *54*, 9944–9947.

1-(2-(3-Methylbut-2-en-1-yl)-1*H*-indol-1-yl)ethenone (3.15d)

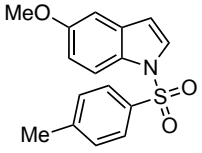
In a two-neck round-bottom flask, 2-(3-methylbut-2-en-1-yl)-1*H*-indole **3.15b** (200 mg, 1.08 mmol, 1.0 equiv) was dissolved in anhydrous deoxygenated DMF (4.3 mL, 0.25 M). NaH (65 mg, 60% Wt, 1.62 mmol, 1.2 equiv) was added portionwise at 0 °C and the solution was stirred for 30 min at this temperature. Subsequently, acetyl chloride (3.3 mL, 45.7 mmol, 2.0 equiv) was added dropwise, and the reaction mixture was stirred for additional 16 h at 23 °C. The reaction was quenched with sat. aq. $NaHCO_3$ (3 mL) and the aqueous phase was extracted three times with CH_2Cl_2 (3 x 5 mL). The combined organic layers were washed with brine (8 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The crude residue was purified by flash column chromatography (neutralized SiO_2 with 5% Et_3N in cyclohexane, cyclohexane/Et_2O 100:0 to 70:30, *v/v*) yielding **3.15d** as a yellow oil (125 mg, 0.55 mmol in 51% yield).



^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90–7.85 (m, 1H), 7.49–7.45 (m, 1H), 7.26–7.18 (m, 2H), 6.42–6.39 (m, 1H), 5.42–5.36 (m, 1H), 3.70 (d, *J* = 7.0 Hz, 2H), 2.77 (s, 3H), 1.80 (d, *J* = 1.3 Hz, 3H), 1.70 (d, *J* = 1.4 Hz, 3H).

5-Methoxy-1-tosyl-1*H*-indole (3.29)

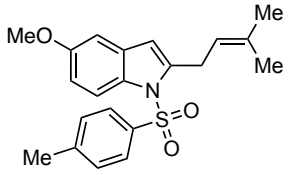
Freshly pulverized NaOH (500 mg, 12.5 mmol, 5.0 equiv) was added to a mixture of 5-methoxy-1*H*-indole (368 mg, 2.50 mmol, 1.0 equiv) and *n*Bu_4NHSO_4 (85 mg, 0.250 mmol, 0.1 equiv) in anhydrous CH_2Cl_2 (25.0 mL, 0.1 M) and the reaction was stirred at 23 ºC for 5 min. Then, *p*-toluenesulfonyl chloride (1.19 g, 6.25 mmol, 2.5 equiv) was added portion wise at 23 ºC and the mixture was stirred for 5 additional hours. Upon completion, it was quenched with sat. aq. Na_2CO_3 (25 mL) and extracted with CH_2Cl_2 (3 x 25 mL). The combined organic layers were washed with brine (30 mL), dried over anhydrous $MgSO_4$, filtered and concentrated under vacuo. The crude was purified by flash column chromatography (SiO_2, cyclohexane/EtOAc 100:0 to 80:20, *v/v*) and the product **3.29** was obtained as a yellow solid (486 mg, 1.61 mmol, 65% yield).



^{1}H NMR (500 MHz, $CDCl_3$) δ 7.87 (dt, *J* = 9.0, 0.7 Hz, 1H), 7.75–7.70 (m, 2H), 7.51 (dd, *J* = 3.6, 0.5 Hz, 1H), 7.23–7.19 (m, 2H), 6.96 (d, *J* = 2.5 Hz, 1H), 6.92 (ddd, *J* = 9.0, 2.5, 0.5 Hz, 1H), 6.57 (dd, *J* = 3.7, 0.8 Hz, 1H), 3.80 (s, 3H), 2.33 (s, 3H). The characterization data matches those reported in the literature.[37]

37. Arisawa, M.; Terada, Y.; Takahashi, K.; Nakagawa, M.; Nishida, *J. Org. Chem.* **2006**, *71*, 4255–4261.

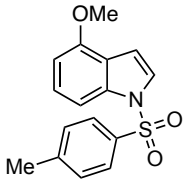
5-Methoxy-2-(3-methylbut-2-en-1-yl)-1-tosyl-1*H*-indole (3.15e)



Freshly titrated *n*BuLi (239 µL, 0.597 mmol, 1.5 equiv, 2.5 M) was added dropwise to a solution of 5-methoxy-1-tosyl-1*H*-indole **3.29** (120 mg, 0.398 mmol, 1.0 equiv) in anhydrous THF (4.0 mL, 0.1 M) at –78 ºC: The reaction mixture was stirred for 45 min and 3,3-dimethylallylbromide (139 µL, 178 mg, 1.19 mmol, 3.0 equiv) was added in one portion. The resulted solution was stirred for another 15 min at –78 ºC and then slowly warmed to 23 ºC and stirred for 16 h. Upon completion, it was quenched by the addition of sat. aq. NH_4Cl (3 mL) and extracted with CH_2Cl_2 (3 x 4 mL). The combined organic layers were washed with brine (6 mL), dried over anhydrous $MgSO_4$, filtered and concentrated under vacuo. The crude was purified by two flash column chromatography (SiO_2, cyclohexane/EtOAc 100:0 to 80:20, *v/v*) and the product **3.15e** was obtained as a yellow oil (129 mg, 0.365 mmol, 10% yield) as an inseparable mixture with the starting material (45%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.09–8.04 (m, 1H), 7.65–7.57 (m, 2H), 7.21–7.16 (m, 2H), 6.89–6.83 (m, 2H), 6.28 (q, *J* = 1.2 Hz, 1H), 5.37 (dddd, *J* = 7.3, 5.8, 2.9, 1.4 Hz, 1H), 3.80 (s, 3H), 3.65 (d, *J* = 7.3 Hz, 2H), 2.33 (s, 3H), 1.78 (q, *J* = 1.2 Hz, 3H), 1.62 (d, *J* = 1.3 Hz, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 156.6, 144.7, 142.2, 136.3, 134.9, 132.1, 130.9, 129.9, 126.4, 119.8, 115.7, 112.3, 109.2, 103.0, 55.7, 28.1, 25.8, 21.7, 17.9. **HRMS** (ESI +) calculated for $C_{21}H_{23}NNaO_3S$ $[M+Na]^+$: 392.1291; found: 392.1294.

4-Methoxy-1-tosyl-1*H*-indole (3.30)



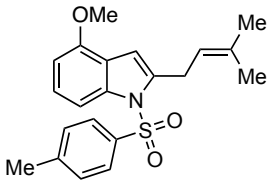
Freshly pulverized NaOH (1.00 g, 25.0 mmol, 5.0 equiv) was added to a mixture of 4-methoxy-1*H*-indole (736 mg, 5.00 mmol, 1.0 equiv) and nBu_4NHSO_4 (170 mg, 0.500 mmol, 0.1 equiv) in anhydrous CH_2Cl_2 (50.0 mL, 0.1 M) and the reaction was stirred at 23 ºC for 5 min. Then, *p*-toluenesulfonyl chloride (2.38 g, 12.5 mmol, 2.5 equiv) was added portion wise at 23 ºC and the mixture was stirred for 5 additional hours. Upon completion it was quenched with sat. aq. Na_2CO_3 (40 mL) and extracted with CH_2Cl_2 (3 x 50 mL). The combined organic layers were washed with brine (50 mL), dried over anhydrous $MgSO_4$, filtered and concentrated under vacuo. The crude was purified by flash column chromatography (SiO_2, cyclohexane/EtOAc 100:0 to 80:20, *v/v*) and the product **3.30** was obtained as a white solid (1.50 g, 4.93 mmol, 99% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.77–7.73 (m, 2H), 7.60–7.58 (m, 1H), 7.46 (d, *J* = 3.7 Hz, 1H), 7.24–7.19 (m, 3H), 6.76 (dd, *J* = 3.7, 0.8 Hz, 1H), 6.64 (d, *J* = 8.0 Hz, 1H), 3.89 (s, 3H), 2.33 (s, 3H).The characterization data matches those reported in the literature.[38]

38. Hawkins, P. M. E.; Tran, W.; Nagalingam, G.; Cheung, C.-Y.; Giltrap, A. M.; Cook, G. M.; Britton, W. J.; Payne, R. J. *Chem. Eur. J.* **2020**, *26*, 15200–15205.

4-Methoxy-2-(3-methylbut-2-en-1-yl)-1-tosyl-1*H*-indole (3.15f)

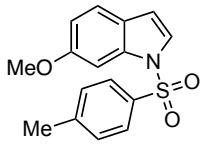
Freshly titrated *n*-BuLi (1.33 mL, 3.32 mmol, 1.5 equiv, 2.5 M) was added dropwise to a solution of 4-methoxy-1-tosyl-1*H*-indole **3.30** (1.00 g, 3.32 mmol, 1.0 equiv) in anhydrous THF (33.2 mL, 0.1 M) at –78 ºC: The reaction mixture was stirred for 45 min and 3,3-dimethylallylbromide (2.30 mL, 2.97 g, 19.9 mmol, 6.0 equiv) was added in one portion. The resulted solution was stirred for another 15 min at –78 ºC and then slowly warmed to 23 ºC and stirring for 16 h. Upon completion, it was quenched by the addition of sat. aq. NH_4Cl (20 mL) and extracted with CH_2Cl_2 (3 x 30 mL). The combined organic layers were washed with brine (30 mL), dried over anhydrous $MgSO_4$, filtered and concentrated under vacuo. The crude was purified by flash column chromatography (SiO_2, cyclohexane/EtOAc 100:0 to 70:30, *v/v*) and the product **3.15f** was obtained as a yellow oil (883 mg, 2.39 mmol, 72% yield).



^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (d, *J* = 8.4 Hz, 1H), 7.67– 7.62 (m, 2H), 7.21–7.15 (m, 3H), 6.65 (d, *J* = 8.0 Hz, 1H), 6.48– 6.45 (m, 1H), 5.38 (dddd, *J* = 7.3, 5.8, 2.9, 1.5 Hz, 1H), 3.88 (s, 3H), 3.65 (d, *J* = 7.3 Hz, 2H), 2.34 (s, 3H), 1.77 (d, *J* = 1.5 Hz, 3H), 1.62 (d, *J* = 1.4 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 152.3, 144.7, 139.9, 138.7, 136.5, 134.9, 129.9, 126.5, 124.7, 120.0, 119.9, 108.0, 105.7, 103.9, 55.5, 28.1, 25.9, 21.7, 17.9. **HRMS** (ESI+) calculated for $C_{21}H_{23}NNaO_3S$ $[M+Na]^+$ 392.1291 *m/z*, found 392.1303 *m/z.*

6-Methoxy-1-tosyl-1*H*-indole (3.31)

Freshly pulverized NaOH (1.00 mg, 25.0 mmol, 5.0 equiv) was added to a mixture of 6-methoxy-1*H*-indole (736 mg, 5.00 mmol, 1.0 equiv) and nBu_4NHSO_4 (170 mg, 0.500 mmol, 0.1 equiv) in anhydrous CH_2Cl_2 (50.0 mL, 0.1 M) and the reaction was stirred at 23 ºC for 5 min. Then, *p*-toluenesulfonyl chloride (2.38 g, 12.5 mmol, 2.5 equiv) was added portion wise at 23 ºC and the mixture was stirred for 5 additional hours. Upon completion, it was quenched with sat. aq. Na_2CO_3 (40 mL) and extracted with CH_2Cl_2 (3 x 50 mL). The combined organic layers were washed with brine (50 mL), dried over anhydrous $MgSO_4$, filtered and concentrated under vacuo. The crude was purified by flash column chromatography (SiO_2, cyclohexane/EtOAc 100:0 to 80:20, *v/v*) and the product **3.31** was obtained as a yellow solid (1.50 g, 4.97 mmol, 99% yield).

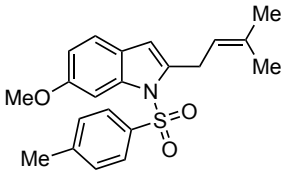


^{1}H NMR (500 MHz, $CDCl_3$) δ 7.76–7.73 (m, 2H), 7.53 (dd, *J* = 2.2, 0.7 Hz, 1H), 7.44 (d, *J* = 3.7 Hz, 1H), 7.38 (dd, *J* = 8.6, 0.5 Hz, 1H), 7.23–7.20 (m, 2H), 6.85 (dd, *J* = 8.6, 2.3 Hz, 1H), 6.57 (dd, *J* = 3.7, 0.8 Hz, 1H), 3.87 (s, 3H), 2.34 (s, 3H). The characterization data matches those reported in the literature.[39]

39. Tayu, M.; Watanabe, R.; Isogi, S.; Saito, N. A C *Adv. Synth. Cat.* **2021**, *363*, 1147–1151.

6-Methoxy-2-(3-methylbut-2-en-1-yl)-1-tosyl-1*H*-indole (3.15g)

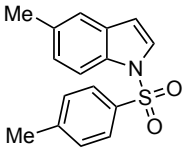
Freshly titrated *n*-BuLi (1.33 mL, 3.32 mmol, 1.5 equiv, 2.5 M) was added dropwise to a solution of 6-methoxy-1-tosyl-1*H*-indole **3.31** (1.00 g, 3.32 mmol, 1.0 equiv) in anhydrous THF (33.2 mL, 0.1 M) at –78 ºC: The reaction mixture was stirred for 45 min and 3,3-dimethylallylbromide (2.30 mL, 2.97 g, 19.9 mmol, 6.0 equiv) was added in one portion. The resulted solution was stirred for another 15 min at –78 ºC and then slowly warmed to 23 ºC and stirred for 16 h. Upon completion, it was quenched by the addition of sat. aq. NH_4Cl (20 mL) and extracted with CH_2Cl_2 (3 x 30 mL). The combined organic layers were washed with brine (30 mL), dried over anhydrous $MgSO_4$, filtered and concentrated under vacuo. The crude was purified by flash column chromatography (SiO_2, cyclohexane/EtOAc 100:0 to 80:20, *v/v*) and the product **3.15g** was obtained as a yellow oil (797 mg, 2.16 mmol, 65% yield).



^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 (d, *J* = 2.3 Hz, 1H), 7.65–7.61 (m, 2H), 7.27–7.24 (m, 1H), 7.21–7.17 (m, 2H), 6.83 (dd, *J* = 8.5, 2.3 Hz, 1H), 6.27–6.25 (m, 1H), 5.36 (ddq, *J* = 8.6, 5.7, 1.4 Hz, 1H), 3.87 (s, 3H), 3.62 (d, *J* = 7.2 Hz, 2H), 2.34 (s, 3H), 1.77 (d, *J* = 1.5 Hz, 3H), 1.61 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 157.4, 144.8, 140.1, 138.5, 136.5, 134.8, 129.9, 126.4, 123.7, 120.6, 120.0, 112.4, 108.8, 99.7, 56.0, 28.1, 25.8, 21.7, 17.9. **HRMS** (ESI+) calculated for $C_{21}H_{23}NNaO_3S$ $[M+Na]^+$ 392.1291 *m/z*, found 392.1281 *m/z*.

5-Methyl-1-tosyl-1*H*-indole (3.32)

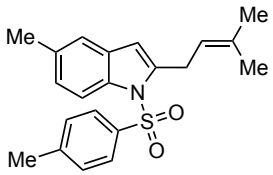
Freshly pulverized NaOH (1.4 g, 35.0 mmol, 5.0 equiv) was added to a mixture of 5-methyl-1*H*-indole (918 mg, 7.00 mmol, 1.0 equiv) and nBu_4NHSO_4 (238 mg, 0.70 mmol, 0.1 equiv) in anhydrous CH_2Cl_2 (70.0 mL, 0.1 M) and the reaction was stirred at 23 ºC for 5 min. Then, *p*-toluenesulfonyl chloride (3.34 g, 17.5 mmol, 2.5 equiv) was added portion wise at 23 ºC and the mixture was stirred for 5 additional hours. Upon completion, it was quenched with sat. aq. Na_2CO_3 (50 mL) and extracted with CH_2Cl_2 (3 x 60 mL). The combined organic layers were washed with brine (60 mL), dried over anhydrous $MgSO_4$, filtered and concentrated under vacuo. The crude was purified by flash column chromatography (SiO_2, cyclohexane/EtOAc 100:0 to 80:20, *v/v*) and the product **3.32** was obtained as a yellow solid (1.1 g, 3.89 mmol, 56% yield).



^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 (d, *J* = 8.5 Hz, 1H), 7.78–7.71 (m, 2H), 7.51 (d, *J* = 3.7 Hz, 1H), 7.35–7.28 (m, 1H), 7.24–7.17 (m, 2H), 7.12 (dd, *J* = 8.5, 1.7 Hz, 1H), 6.57 (dd, *J* = 3.7, 0.8 Hz, 1H), 2.40 (s, 3H), 2.33 (s, 3H). The characterization data matches those reported in the literature.[40]

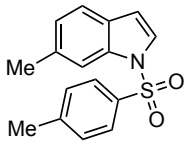
40. Song, S.; Huang, M.; Li, W.; Zhu, X.; Wan, Y. *Tetrahedron* **2015**, *71*, 451–456.

5-Methyl-2-(3-methylbut-2-en-1-yl)-1-tosyl-1*H*-indole (3.15h)



Freshly titrated *n*BuLi (688 µL, 1.72 mmol, 1.5 equiv, 2.5 M) was added dropwise to a solution of 5-methyl-1-tosyl-1*H*-indole **3.32** (327 mg, 1.15 mmol, 1.0 equiv) in anhydrous THF (11.5 mL, 0.1 M) at –78 ºC. The reaction mixture was stirred for 45 min and 3,3-dimethylallylbromide (400 µL, 512 mg, 3.44 mmol, 3.0 equiv) was added in one portion. The resulted solution was stirred for another 15 min at –78 ºC and then slowly warmed to 23 ºC and stirred for 16 h. Upon completion, it was quenched by the addition of sat. aq. NH_4Cl (10 mL) and extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were washed with brine (10 mL), dried over anhydrous $MgSO_4$, filtered and concentrated under vacuo. The crude was purified by preparative TLC plate (SiO_2, cyclohexane/EtOAc 4:1, *v/v*) followed by flash column chromatography (SiO_2, cyclohexane/EtOAc 100:0 to 80:20, *v/v*). The product **3.15h** could only be obtained with a purity of 70% due to the presence of an impurity probably from the 3,3-dimethylallylbromide (24 mg, 0.07 mmol, 3% yield, ^{1}H NMR signals of impurity at 4.77 and 3.1 ppm). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.04 (d, *J* = 8.5 Hz, 1H), 7.67–7.61 (m, 2H), 7.22–7.15 (m, 3H), 7.08–7.04 (m, 1H), 6.33–6.22 (m, 1H), 5.38 (ddq, *J* = 8.6, 5.8, 1.4 Hz, 1H), 3.65 (d, *J* = 7.2 Hz, 2H), 2.39 (s, 3H), 2.33 (d, *J* = 2.9 Hz, 3H), 1.78 (q, *J* = 1.2 Hz, 3H), 1.62 (d, *J* = 1.4 Hz, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 144.6, 141.4, 136.5, 135.7, 134.9, 133.1, 130.1, 129.9, 126.4, 125.2, 120.2, 119.9, 114.5, 108.9, 28.1, 25.8, 21.7, 21.3, 17.9. **HRMS** (ESI +) calculated for $C_{21}H_{23}NNaO_2S$ $[M+Na]^+$: 376.1342; found: 376.1340.

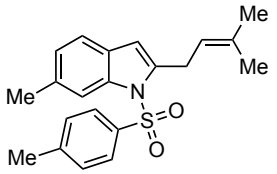
6-Methyl-1-tosyl-1*H*-indole (3.33)



Freshly pulverized NaOH (1.00 g, 25.0 mmol, 5.0 equiv) was added to a mixture of 6-methyl-1*H*-indole (656 mg, 5.00 mmol, 1.0 equiv) and nBu_4NHSO_4 (170 mg, 0.500 mmol, 0.1 equiv) in anhydrous CH_2Cl_2 (50.0 mL, 0.1 M) and the reaction was stirred at 23 ºC for 5 min. Then, *p*-toluenesulfonyl chloride (2.38 g, 12.5 mmol, 2.5 equiv) was added portion wise at 23 ºC and the mixture was stirred for 5 additional hours. Upon completion, it was quenched with sat. aq. Na_2CO_3 (40 mL) and extracted with CH_2Cl_2 (3 x 50 mL). The combined organic layers were washed with brine (50 mL), dried over anhydrous $MgSO_4$, filtered and concentrated under vacuo. The crude was purified by flash column chromatography (SiO_2, cyclohexane/EtOAc 100:0 to 90:10, *v/v*) and the product **3.33** was obtained as a white solid (1.40 g, 4.99 mmol, 100% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.80 (dq, *J* = 1.5, 0.8 Hz, 1H), 7.77– 7.74 (m, 2H), 7.48 (d, *J* = 3.7 Hz, 1H), 7.39 (d, *J* = 8.0 Hz, 1H), 7.23–7.20 (m, 2H), 7.05 (ddd, *J* = 8.0, 1.5, 0.7 Hz, 1H), 6.59 (dd, *J* = 3.7, 0.8 Hz, 1H), 2.47 (s, 3H), 2.34 (s, 3H). The characterization data matches those reported in the literature.[41]

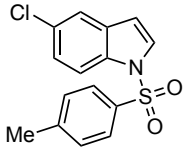
6-Methyl-2-(3-methylbut-2-en-1-yl)-1-tosyl-1*H*-indole (3.15i)



Freshly titrated *n*-BuLi (1.40 mL, 3.50 mmol, 1.5 equiv, 2.5 M) was added dropwise to a solution of 6-methoxy-1-tosyl-1*H*-indole **3.33** (1.00 g, 3.50 mmol, 1.0 equiv) in anhydrous THF (35.0 mL, 0.1 M) at –78 ºC: The reaction mixture was stirred for 45 min and 3,3-dimethylallylbromide (2.43 mL, 3.13 g, 21.0 mmol, 6.0 equiv) was added in one portion. The resulted solution was stirred for another 15 min at –78 ºC and then slowly warmed to 23 ºC and stirred for 16 h. Upon completion, it was quenched by the addition of sat. aq. NH_4Cl (20 mL) and extracted with CH_2Cl_2 (3 x 30 mL). The combined organic layers were washed with brine (30 mL), dried over anhydrous $MgSO_4$, filtered and concentrated under vacuo. The crude was purified by flash column chromatography (SiO_2, cyclohexane/EtOAc 100:0 to 80:20, *v/v*) and the product **3.15i** was obtained as a yellow oil (779 mg, 2.21 mmol, 63% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 (dq, *J* = 1.6, 0.8 Hz, 1H), 7.66–7.61 (m, 2H), 7.29–7.25 (m, 1H), 7.21–7.17 (m, 2H), 7.05–7.00 (m, 1H), 6.31–6.28 (m, 1H), 5.37 (tp, *J* = 7.2, 1.4 Hz, 1H), 3.63 (d, *J* = 7.2 Hz, 2H), 2.47 (s, 3H), 2.34 (s, 3H), 1.77 (d, *J* = 1.5 Hz, 3H), 1.61 (d, *J* = 1.4 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 144.7, 140.7, 138.0, 136.7, 134.8, 133.9, 129.9, 127.5, 126.4, 125.0, 119.9, 119.9, 115.0, 108.9, 28.1, 25.8, 22.2, 21.7, 17.9. **HRMS** (ESI+) calculated for $C_{21}H_{23}NNaO_2S$ $[M+Na]^+$ 376.1342 *m/z*, found 376.1332 *m/z*.

5-Chloro-1-tosyl-1*H*-indole (3.34)



Freshly pulverized NaOH (1.00 g, 25.0 mmol, 5.0 equiv) was added to a mixture of 5-chloro-1*H*-indole (758 mg, 5.00 mmol, 1.0 equiv) and *n*Bu_4NHSO_4 (170 mg, 0.500 mmol, 0.1 equiv) in anhydrous CH_2Cl_2 (50.0 mL, 0.1 M) and the reaction was stirred at 23 ºC for 5 min. Then, *p*-toluenesulfonyl chloride (2.38 g, 12.5 mmol, 2.5 equiv) was added portion wise at 23 ºC and the mixture was stirred for 5 additional hours. Upon completion, it was quenched with sat. aq. Na_2CO_3 (40 mL) and extracted with CH_2Cl_2 (3 x 50 mL). The combined organic layers were washed with brine (50 mL), dried over anhydrous $MgSO_4$, filtered and concentrated under vacuo. The crude was purified by flash column chromatography (SiO_2, cyclohexane/EtOAc 100:0 to 90:10, *v/v*) and the product **3.34** was obtained as a white solid (1.50 g, 4.77 mmol, 95% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.80 (dq, *J* = 1.5, 0.8 Hz, 1H), 7.77– 7.74 (m, 2H), 7.48 (d, *J* = 3.7 Hz, 1H), 7.39 (d, *J* = 8.0 Hz, 1H), 7.23–7.20 (m, 2H), 7.05 (ddd, *J* = 8.0, 1.5, 0.7 Hz, 1H), 6.59 (dd, *J* = 3.7, 0.8 Hz, 1H), 2.34 (s, 3H). The characterization data matches those reported in the literature.[41]

41. Chen, Z.; Shi, X.-X.; Ge, D.-Q.; Jiang, Z.-Z.; Jin, Q.-Q.; Jiang, H.-J.; Wu, J.-S. *Chin. Chem. Lett.* **2017**, *28*, 231–234.

5-Chloro-2-(3-methylbut-2-en-1-yl)-1-tosyl-1*H*-indole (3.15j)

In a two-neck round-bottom flask, anhydrous diisopropylamine (508 µL, 364 mg, 3.60 mmol, 1.1 equiv) and anhydrous deoxygenated THF (16.4 mL, 0.2 M) were added and cooled to −78 ºC. Freshly titrated *n*BuLi (1.38 mL, 3.27 mmol, 1.1 equiv, 2.37 M) was then added dropwise, and the resulting solution was stirred at this temperature for 30 min. This mixture was subsequently transferred dropwise to another two-neck round-bottom flask containing a solution of 5-chloro-1-tosyl-1*H*-indole **3.34** (1.00 g, 3.27 mmol, 1.0 equiv) in anhydrous deoxygenated THF (16.4 mL, 0.2 M) at −78 ºC. After stirring for 45 min at this temperature, 3,3-dimethylallylbromide bromide (1.13 mL, 1.46 g, 9.81 mmol, 3.0 equiv) was quickly added, and the mixture was stirred for an additional 2 h at −78 ºC. The solution was then gradually warmed to 23 ºC and stirred for 16 h. The reaction was quenched with sat. aq. NH_4Cl (20 mL), and the aqueous phase was extracted three times with CH_2Cl_2 (3 x 30 mL). The combined organic layers were washed with brine (30 mL), dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The crude residue was purified by flash column chromatography (neutralized SiO_2 with 5% Et_3N in cyclohexane, cyclohexane/Et_2O 100:0 to 90:10, *v/v*) to obtain **3.15j** as a yellow oil (587 mg, 1.57 mmol, 48% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10 (d, *J* = 8.9 Hz, 1H), 7.65–7.60 (m, 2H), 7.36 (d, *J* = 2.1 Hz, 1H), 7.23–7.18 (m, 3H), 6.29 (q, *J* = 1.2 Hz, 1H), 5.36 (tp, *J* = 7.2, 1.5 Hz, 1H), 3.65 (d, *J* = 7.2 Hz, 2H), 2.35 (s, 3H), 1.78 (d, *J* = 1.5 Hz, 3H), 1.62 (d, *J* = 1.4 Hz, 3H).**^{13}C NMR** (101 MHz, $CDCl_3$) δ 145.1, 143.0, 136.2, 135.8, 135.4, 131.1, 130.0, 129.2, 126.4, 124.0, 119.8, 119.4, 115.8, 108.3, 28.0, 25.8, 21.7, 17.9. **HRMS** (ESI+) calculated for $C_{20}H_{21}ClNO_2S$ $[M+H]^+$ 374.0976 *m/z*, found 374.0971 *m/z.*

6-Chloro-1-tosyl-1*H*-indole (3.35)

Freshly pulverized NaOH (1.00 g, 25.0 mmol, 5.0 equiv) was added to a mixture of 6-chloro-1*H*-indole (758 mg, 5.00 mmol, 1.0 equiv) and nBu_4NHSO_4 (170 mg, 0.500 mmol, 0.1 equiv) in anhydrous CH_2Cl_2 (50.0 mL, 0.1 M) and the reaction was stirred at 23 ºC for 5 min. Then, *p*-toluenesulfonyl chloride (2.38 g, 12.5 mmol, 2.5 equiv) was added portion wise at 23 ºC and the mixture was stirred for 5 additional hours. Upon completion, it was quenched with sat. aq. Na_2CO_3 (40 mL) and extracted with CH_2Cl_2 (3 x 50 mL). The combined organic layers were washed with brine (50 mL), dried over anhydrous $MgSO_4$, filtered and concentrated under vacuo. The crude was purified by flash column chromatography (SiO_2, cyclohexane/EtOAc 100:0 to 90:10, *v/v*) and the product **3.35** was obtained as a white solid (1.30 g, 4.11 mmol, 82% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02–8.00 (m, 1H), 7.79–7.74 (m, 2H), 7.54 (dd, *J* = 3.7, 0.7 Hz, 1H), 7.43 (dd, *J* = 8.4, 0.7 Hz, 1H), 7.28– 7.23 (m, 2H), 7.20 (ddd, *J* = 8.4, 1.9, 0.7 Hz, 1H), 6.62 (dd, *J* = 3.7, 0.9 Hz, 1H), 2.36 (s, 3H). The characterization data matches those reported in the literature.[42]

6-Chloro-2-(3-methylbut-2-en-1-yl)-1-tosyl-1*H*-indole (3.15k)

In a two-neck round-bottom flask, anhydrous diisopropylamine (508 μL, 364 mg, 3.60 mmol, 1.1 equiv) and anhydrous deoxygenated THF (16.4 mL, 0.2 M) were added and cooled to −78 ºC. Freshly titrated *n*BuLi (1.38 mL, 3.27 mmol, 1.1 equiv, 2.37 M) was then added dropwise, and the resulting solution was stirred at this temperature for 30 min. This mixture was subsequently transferred dropwise to another two-neck round-bottom flask containing a solution of 6-chloro-1-tosyl-1*H*-indole **3.35** (1.00 g, 3.27 mmol, 1.0 equiv) in anhydrous deoxygenated THF (16.4 mL, 0.2 M) at −78 ºC. After stirring for 45 min at this temperature, 3,3-dimethylallylbromide bromide (1.13 mL, 1.46 g, 9.81 mmol, 3.0 equiv) was quickly added, and the mixture was stirred for an additional 2 h at −78 ºC. The solution was then gradually warmed to 23 ºC and stirred for 16 h. The reaction was quenched with sat. aq. NH_4Cl (20 mL), and the aqueous phase was extracted three times with CH_2Cl_2 (3 x 30 mL). The combined organic layers were washed with brine (30 mL), dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The crude residue was purified by flash column chromatography (neutralized SiO_2 with 5% Et_3N in cyclohexane, cyclohexane/Et_2O 100:0 to 90:10, *v/v*) to obtain **3.15k** as a yellow oil (550 mg, 1.47 mmol, 45% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.21 (dt, *J* = 1.8, 0.6 Hz, 1H), 7.67–7.63 (m, 2H), 7.30 (dd, *J* = 8.3, 0.5 Hz, 1H), 7.25–7.21 (m, 2H), 7.17 (dd, *J* = 8.3, 1.9 Hz, 1H), 6.31 (td, *J* = 1.4, 0.8 Hz, 1H), 5.35 (dddd, *J* = 8.7, 5.8, 2.9, 1.4 Hz, 1H), 3.63 (d, *J* = 7.0 Hz, 2H), 2.36 (s, 3H), 1.78 (d, *J* = 1.3 Hz, 3H), 1.61 (d, *J* = 1.4 Hz, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 145.1, 142.1, 137.8, 136.2, 135.3, 130.1, 129.8, 128.3, 126.5, 124.1, 120.9, 119.4, 115.0, 108.5, 28.0, 25.8, 21.7, 17.9. **HRMS** (ESI+) calculated for $C_{20}H_{21}ClNO_2S$ $[M+H]^+$ 374.0976 *m/z*, found 374.0971 *m/z*.

5-Fluoro-1-tosyl-1*H*-indole (3.36)

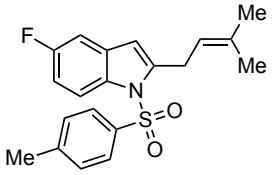
Freshly pulverized NaOH (518 mg, 12.9 mmol, 5.0 equiv) was added to a mixture of 5-fluoro-1*H*-indole (350 mg, 2.59 mmol, 1.0 equiv) and nBu_4NHSO_4 (87.9 mg, 0.259 mmol, 0.1 equiv) in anhydrous CH_2Cl_2 (25.9 mL, 0.1 M) and the reaction was stirred at 23 ºC for 5 min. Then, *p*-toluenesulfonyl chloride (1.23 g, 6.47 mmol, 2.5 equiv) was added portion wise at 23 ºC and the mixture was stirred for 5 additional hours. Upon completion it was quenched with sat. aq. Na_2CO_3 (20 mL) and extracted with CH_2Cl_2 (3 x 20 mL). The combined organic layers were washed with brine (20 mL), dried over anhydrous $MgSO_4$, filtered and concentrated under vacuo. The crude was purified by flash column chromatography (SiO_2, cyclohexane/EtOAc 100:0 to 80:20, *v/v*) and the product **3.36** was obtained as a yellow solid (528 mg, 1.82 mmol, 71% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.92 (ddt, *J* = 9.1, 4.4, 0.7 Hz, 1H), 7.78–7.72 (m, 2H), 7.59 (d, *J* = 3.7 Hz, 1H), 7.25–7.20 (m, 2H), 7.17 (ddd, *J* = 8.7, 2.6, 0.5 Hz, 1H), 7.03 (tdd, *J* = 9.1, 2.6, 0.5 Hz, 1H),

6.61 (dd, *J* = 3.7, 0.8 Hz, 1H), 2.35 (s, 3H). The characterization data matches those reported in the literature.[42]

5-Fluoro-2-(3-methylbut-2-en-1-yl)-1-tosyl-1*H*-indole (3.15l)

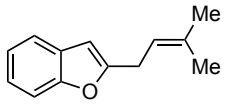
Freshly titrated *n*BuLi (968 µL, 2.33 mmol, 1.5 equiv, 2.4 M) was added dropwise to a solution of 5-fluoro-1-tosyl-1*H*-indole **3.36** (450 mg, 1.56 mmol, 1.0 equiv) in anhydrous THF (15.6 mL, 0.1 M) at–78 ºC: The reaction mixture was stirred for 45 min and 3,3-dimethylallylbromide (542 µL, 695 mg, 4.67 mmol, 3.0 equiv) was added in one portion. The resulted solution was stirred for another 15 min at –78 ºC and then slowly warmed to 23 ºC and stirring for 16 h. Upon completion, it was quenched by the addition of sat. aq. NH_4Cl (10 mL) and extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were washed with brine (10 mL), dried over anhydrous $MgSO_4$, filtered and concentrated under vacuo. The crude was purified by flash column chromatography (SiO_2, cyclohexane/EtOAc 100:0 to 80:20, *v/v*) and the product **3.15l** was obtained as a yellow oil (58 mg, 0.162 mmol, 10% yield).



^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12 (dd, *J* = 9.1, 4.5 Hz, 1H), 7.65–7.59 (m, 2H), 7.24–7.18 (m, 2H), 7.04 (dd, *J* = 8.7, 2.6 Hz, 1H), 6.97 (td, *J* = 9.1, 2.6 Hz, 1H), 6.31 (q, *J* = 1.2 Hz, 1H), 5.37 (tp, *J* = 7.2, 1.4 Hz, 1H), 3.66 (d, *J* = 7.2 Hz, 2H), 2.35 (s, 3H), 1.78 (d, *J* = 1.6 Hz, 3H), 1.62 (d, *J* = 1.4 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 161.0, 158.7, 145.0 (d, $J_{C–H}$= 177.3 Hz), 136.2, 135.3, 133.8, 130.9 (d, $J_{C–H}$= 10.3 Hz), 130.0, 126.4, 119.5, 115.9 (d, $J_{C–H}$= 9.1 Hz), 111.7 (d, $J_{C–H}$= 25.7 Hz), 108.9 f(d, $J_{C–H}$= 3.8 Hz), 105.9 (d, $J_{C–H}$= 26.0 Hz), 28.1, 25.8, 21.7, 17.9. **^{19}F NMR** (376 MHz, $CDCl_3$) δ -120.2. **HRMS** (ESI +) calculated for $C_{20}H_{20}FNNaO_2S$ $[M+Na]^+$: 380.1091; found: 380.1091.

2-(3-Methylbut-2-en-1-yl)benzofuran (3.18)

$Pd(PPh_3)_4$ (233 mg, 0.201 mmol, 0.10 equiv) was added to a mixture of benzofuran-2-ylboronic acid (489 mg, 3.02 mmol, 1.5 equiv), 3,3-dimethylallylbromide (234 µL, 300 mg, 2.01 mmol, 1.0 equiv), Cs_2CO_3 (918 mg, 2.82 mmol, 1.4 equiv) in anhydrous toluene (16.1 mL, 0.1 M) and MeOH (4.0 mL, 0.1 M). The reaction was heated at 100 ºC for 12 h and then quenched with sat. aq. NH_4Cl (10 mL). The mixture was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were washed with brine (10 mL), dried over anhydrous $MgSO_4$, filtered and concentrated under vacuo. The crude was purified by flash column chromatography (SiO_2, cyclohexane/EtOAc 100:0 to 70:30, *v/v*) and the product **3.18** was obtained as a colorless oil (189 mg, 1.01 mmol, 51% yield).

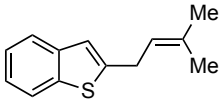


^{1}H NMR (500 MHz, $CDCl_3$) δ 7.49–7.44 (m, 1H), 7.43–7.39 (m, 1H), 7.22–7.15 (m, 2H), 6.36 (q, *J* = 1.1 Hz, 1H), 5.40 (tdt, *J* = 7.2, 2.9, 1.4 Hz, 1H), 3.48 (dq, *J* = 7.3, 1.1 Hz, 2H), 1.78 (t, *J* = 1.3 Hz, 3H),

42. Corbel, B.; Michaud, F.; Meijer, L.; Simon, G.; Couthon-Gourves, H.; Haelters, J.-P.; Kervarec, N. *J. Heterocycl. Chem.* **2007**, *44*, 793–801.

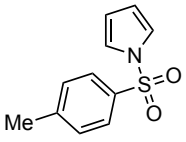
1.74–1.72 (m, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 123.2, 122.5, 120.3, 118.7, 110.9, 102.0, 27.7, 25.9, 17.9.[43] **HRMS** (ESI +) calculated for $C_{13}H_{14}O$ $[M+H]^+$: 185.0961; found: 185.0959.

2-(3-Methylbut-2-en-1-yl)benzo[*b*]thiophene (3.20)



Freshly titrated *n*BuLi (1.90 mL, 4.46 mmol, 1.0 equiv, 2.35 M) was added dropwise to a solution of benzo[b]thiophene (520 µL, 4.46 mmol, 1.0 equiv) in anhydrous THF (22.3 mL, 0.1 M) at –78 ºC: The reaction mixture was stirred for 45 min and 3,3-dimethylallylbromide (1.54 mL, 1.99 g, 13.4 mmol, 3.0 equiv) was added in one portion. The resulted solution was stirred for another 15 min at –78 ºC and then slowly warmed to 23 ºC and stirred for 16 h. After 16 h of reaction, distillation, and flash column chromatography, an inseparable mixture of **3.20** and the starting material was obtained (800 mg in total, 18% SM, 85 mg). This mixture was resubmitted to the reaction conditions and the crude residue was purified by flash column chromatography (neutralized SiO_2 with 5% Et_3N in cyclohexane, cyclohexane 100%, *v/v*) and **3.20** was obtained as a colorless oil (176 mg, 0.83 mmol, 19% yield) as an inseparable mixture with starting material (5%).
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.76–7.73 (m, 1H), 7.65 (dt, *J* = 7.9, 1.0 Hz, 1H), 7.32– 7.27 (m, 1H), 7.24 (ddd, *J* = 8.3, 7.1, 1.3 Hz, 1H), 7.00 (d, *J* = 1.0 Hz, 1H), 5.47–5.42 (m, 1H), 1.79 (d, *J* = 1.3 Hz, 3H), 1.74 (d, *J* = 1.4 Hz, 3H).

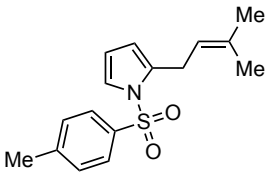
1-Tosyl-1*H*-pyrrole (3.37)



Freshly pulverized NaOH (1.00 g, 25.0 mmol, 5.0 equiv) was added to a mixture of 1*H*-pyrrole (347 µL, 335 mg, 5.00 mmol, 1.0 equiv) and nBu_4NHSO_4 (170 mg, 0.500 mmol, 0.1 equiv) in anhydrous CH_2Cl_2 (50.0 mL, 0.1 M) and the reaction was stirred at 23 ºC for 5 min. Then, *p*-toluenesulfonyl chloride (2.38 g, 12.5 mmol, 2.5 equiv) was added portion wise at 23 ºC and the mixture was stirred for 5 additional hours. Upon completion, it was quenched with sat. aq. Na_2CO_3 (40 mL) and extracted with CH_2Cl_2 (3 x 50 mL). The combined organic layers were washed with brine (50 mL), dried over anhydrous $MgSO_4$, filtered and concentrated under vacuo. The crude was purified by flash column chromatography (SiO_2, cyclohexane/EtOAc 100:0 to 90:10, *v/v*) and the product **3.37** was obtained as a white solid (1.2 g, 5.00 mmol, quantitative yield).
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.76–7.72 (m, 2H), 7.30–7.27 (m, 2H), 7.15 (dd, *J* = 2.4, 2.3 Hz, 2H), 6.28 (dd, *J* = 2.3, 2.3 Hz, 2H), 2.40 (s, 3H). The characterization data matches those reported in the literature.[44]

43. In the ^{13}C NMR spectra, four carbon signals are missing due to the sample being too diluted.
44. Ozaki, T.; Yorimitsu, H.; Perry, G. J. P. *Chem. Eur. J.* **2021**, *27*, 15387–15391.

2-(3-Methylbut-2-en-1-yl)-1-tosyl-1*H*-pyrrole (3.22)

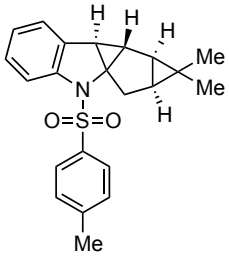


Freshly titrated *n*-BuLi (962 μL, 2.26 mmol, 1.0 equiv, 2.35 M) was added dropwise to a solution of 1-tosyl-1*H*-pyrrole **3.37** (500 mg, 2.26 mmol, 1.0 equiv) in anhydrous THF (22.6 mL, 0.1 M) at –78 ºC: The reaction mixture was stirred for 45 min and 3,3-dimethylallylbromide (783 μL, 1.01 g, 6.78 mmol, 3.0 equiv) was added in one portion. The resulted solution was stirred for another 15 min at –78 ºC and then slowly warmed to 23 ºC and stirring for 16 h. Upon completion, it was quenched by the addition of sat. aq. NH_4Cl (20 mL) and extracted with CH_2Cl_2 (3 x 30 mL). The combined organic layers were washed with brine (30 mL), dried over anhydrous $MgSO_4$, filtered and concentrated under vacuo. The crude was purified by flash column chromatography (SiO_2, cyclohexane/EtOAc 100:0 to 80:20, *v/v*) and the product **3.22** was obtained as a yellow oil (105 mg, 0.36 mmol, 16% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.66–7.63 (m, 2H), 7.30–7.27 (m, 3H), 6.18 (t, *J* = 3.3 Hz, 1H), 5.95–5.93 (m, 1H), 5.17 (dddd, *J* = 8.6, 5.7, 2.9, 1.4 Hz, 1H), 3.36 (d, *J* = 7.2 Hz, 2H), 2.40 (s, 3H), 1.69 (d, *J* = 1.3 Hz, 3H), 1.53 (d, *J* = 1.4 Hz, 3H).

Synthesis of Biscyclopropanated products (3.16 and 3.19)

1,1-Dimethyl-6-tosyl-1a,1b,1c,6,7,7a-hexahydro-1*H*
cyclopropa[3',4']cyclopenta[1',2':1,3]cyclopropa[1,2-*b*]indole (3.16a)

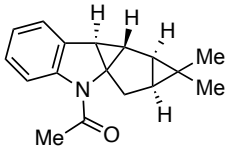


Prepared following general procedure A using 2-(3-methylbut-2-en-1-yl)-1-tosyl-1*H*-indole **3.15a** (42 mg, 0.125 mmol, 1.0 equiv), [JohnPhosAuNCMe]SbF_6 (4 mg, 0.005 mmol, 4 mol%) and 1 atm of acetylene gas in CH_2Cl_2 (0.21 mL, 0.6 M) at 23 ºC for 16 h. The crude was purified by flash column chromatography (SiO_2, cyclohexane/CH_2Cl_2 80:20 to 70:30, *v/v*) to afford the product **3.16a** as colorless oil (21 mg, 0.058 mmol, 46% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.71–7.65 (m, 1H), 7.65–7.59 (m, 2H), 7.25–7.22 (m, 1H), 7.19–7.16 (m, 2H), 7.16–7.11 (m, 1H), 6.99 (tt, *J* = 7.4, 0.8 Hz, 1H), 3.14 (d, *J* = 13.0 Hz, 1H), 2.35 (s, 3H), 2.34–2.28 (m, 2H), 1.33 (s, 3H), 1.10 (d, *J* = 7.2 Hz, 1H), 0.95 (s, 3H), 0.83–0.76 (m, 2H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 143.9, 143.8, 137.0, 132.0, 129.6, 127.3, 126.8, 124.5, 123.7, 116.0, 60.2, 34.4, 34.2, 29.3, 26.9, 26.1, 26.1, 22.8, 21.6, 15.6. **HRMS** (ESI +) calculated for $C_{22}H_{23}NNaO_2S$ $[M+Na]^+$: 388.1342; found: 388.1328.

1-((1a*S*,1b*S*,1c*R*,7a*S*)-1,1-Dimethyl-1,1a,1b,1c,7,7a-hexahydro-6*H*-cyclopropa[3',4']cyclopenta[1',2':1,3]cyclopropa[1,2-*b*]indol-6-yl)ethan-1-one (3.16d)

Prepared following general procedure A using 1-(2-(3-methylbut-2-en-1-yl)-1*H*-indol-1-yl)ethan-1-one

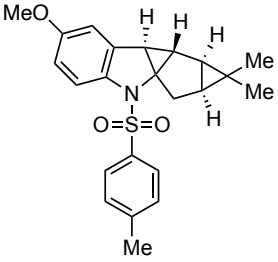


3.15d (28 mg, 0.125 mmol, 1.0 equiv), [JohnPhosAuNCMe]SbF_6 (4 mg, 0.005 mmol, 4 mol%) and 1 atm of acetylene gas in CH_2Cl_2 (0.21 mL, 0.6 M) at 23 ºC for 16 h. The crude was purified by flash column chromatography (SiO_2, cyclohexane/CH_2Cl_2 80:20 to 70:30, *v/v*) to afford the product **3.16d** as orange oil (5 mg, 0.019 mmol, 15% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 (dd, *J* = 7.4, 1.4 Hz, 1H), 7.28–7.22 (m, 1H), 7.12 (td, *J* = 7.9, 1.5 Hz, 1H), 6.99 (td, *J* = 7.4, 1.0 Hz, 1H), 3.40 (d, *J* = 12.8 Hz, 1H), 2.46 (s, 3H), 2.36 (d, *J* = 2.2 Hz, 1H), 2.24 (dd, *J* = 12.8, 6.5 Hz, 1H), 1.44 (s, 3H), 1.17 (d, *J* = 7.2 Hz, 1H), 1.01–0.96 (m, 4H), 0.87–0.84 (m, 1H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 169.7, 143.6, 132.4, 126.5, 125.1, 123.1, 114.9, 58.9, 34.2, 28.7, 27.9, 27.1, 27.0, 22.8, 15.7.

3-Methoxy-1,1-dimethyl-6-tosyl-1a,1b,1c,6,7,7a-hexahydro-1*H*-cyclopropa[3',4']cyclopenta[1',2':1,3]cyclopropa[1,2-*b*]indole (3.16e)

Prepared following general procedure A using 5-methoxy-2-(3-methylbut-2-en-1-yl)-1-tosyl-1*H*-indole

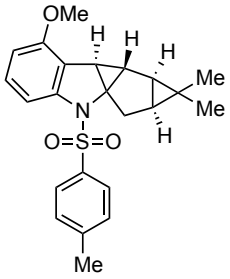


3.15e (125 mg, 55% purity, 0.192 mmol, 1.0 equiv), [JohnPhosAuNCMe]SbF_6 (6 mg, 0.008 mmol, 4 mol%) and 1 atm of acetylene gas in CH_2Cl_2 (0.32 mL, 0.6 M) at 23 ºC for 16 h. The crude was purified by flash column chromatography (SiO_2, cyclohexane/EtOAc 100:0 to 70:30, *v/v*) to afford the product **3.16e** as colorless oil (25 mg, 0.063 mmol, 33% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.65–7.59 (m, 1H), 7.58–7.54 (m, 2H), 7.16 (dd, *J* = 13.0, 8.1 Hz, 2H), 6.79 (d, *J* = 2.7 Hz, 1H), 6.71–6.65 (m, 1H), 3.83–3.75 (m, 3H), 3.12 (d, *J* = 13.2 Hz, 1H), 2.34 (d, *J* = 9.0 Hz, 3H), 2.28 (dd, *J* = 13.2, 6.6 Hz, 1H), 2.24 (d, *J* = 2.1 Hz, 1H), 1.31 (s, 3H), 1.07 (dd, *J* = 7.4, 0.9 Hz, 1H), 0.94 (s, 3H), 0.91–0.75 (m, 2H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 156.7, 143.8, 137.1, 136.7, 133.9, 129.5, 127.4, 117.3, 112.0, 110.1, 60.5, 55.7, 34.3, 34.0, 29.2, 27.2, 26.8, 26.1, 22.7, 21.6, 15.5. **HRMS** (ESI +) calculated for $C_{23}H_{25}NNaO_3S$ $[M+Na]^+$: 418.1447; found: 418.1444.

(1a*S*,1b*S*,1c*R*,7a*S*)-2-methoxy-1,1-dimethyl-6-tosyl-1a,1b,1c,6,7,7a-hexahydro-1*H*-cyclopropa[3',4']cyclopenta[1',2':1,3]cyclopropa[1,2-*b*]indole (3.16f)

Prepared following general procedure A using 4-methoxy-2-(3-methylbut-2-en-1-yl)-1-tosyl-1*H*-indole

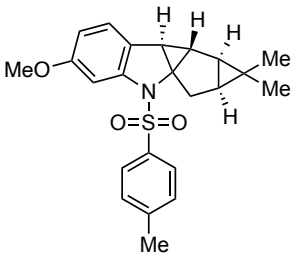


3.15f (46 mg, 0.125 mmol, 1.0 equiv), [JohnPhosAuNCMe]SbF_6 (4 mg, 0.005 mmol, 4 mol%) and 1 atm of acetylene gas in CH_2Cl_2 (0.21 mL, 0.6 M) at 23 ºC for 16 h. The crude was purified by flash column chromatography (SiO_2, cyclohexane/CH_2Cl_2 70:30 to 60:40, *v/v*) to afford the product **3.16f** as a yellow sticky solid (27 mg, 0.062 mmol, 50% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.67 – 7.62 (m, 2H), 7.32 (dt, *J* = 8.3, 0.6 Hz, 1H), 7.20 – 7.15 (m, 2H), 7.08 (t, *J* = 8.3 Hz, 1H), 6.54 (dd, *J* = 8.3, 0.7 Hz, 1H), 3.83 (s, 3H), 3.10 (d, *J* = 13.0 Hz, 1H), 2.36 (d, *J* = 2.2 Hz, 1H), 2.35 (s, 3H), 2.30 (ddd, *J* = 13.0, 6.5, 0.9 Hz, 1H), 1.43 (s, 1H), 1.33 (s, 3H), 1.16 (dd, *J* = 7.4, 0.9 Hz, 1H), 0.94 (s, 3H), 0.81 (dd, *J* = 2.2, 0.9 Hz, 1H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 156.1, 145.5, 143.9, 137.0, 129.6, 128.0, 127.3, 119.8, 108.8, 105.9, 60.3, 55.7, 34.2, 31.5, 29.6, 26.9, 26.0, 25.2, 22.8, 21.7, 15.6. **HRMS** (ESI+) calculated for $C_{23}H_{25}NNaO_3S$ $[M+Na]^+$ 418.1447 *m/z*, found 418.1458 *m/z.*

(1a*S*,1b*S*,1c*R*,7a*S*)-4-Methoxy-1,1-dimethyl-6-tosyl-1a,1b,1c,6,7,7a-hexahydro-1*H*-cyclopropa[3',4']cyclopenta[1',2':1,3]cyclopropa[1,2-*b*]indole (3.16g)

Prepared following general procedure A using 6-methoxy-2-(3-methylbut-2-en-1-yl)-1-tosyl-1*H*-

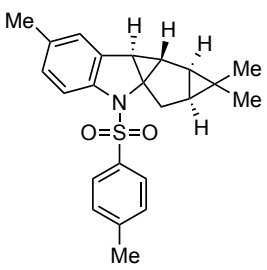


indole **3.15g** (46 mg, 0.125 mmol, 1.0 equiv), [JohnPhosAuNCMe]SbF_6 (4 mg, 0.005 mmol, 4 mol%) and 1 atm of acetylene gas in CH_2Cl_2 (0.21 mL, 0.6 M) at 23 ºC for 16 h. The crude was purified by flash column chromatography (SiO_2, cyclohexane/CH_2Cl_2 60:40 to 50:50, *v/v*) to afford the product **3.16g** a yellow oil (20 mg, 0.044 mmol, 36% yield) as an inseparable mixture with the monoaddition byproduct (13%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.66–7.62 (m, 2H), 7.30 (d, *J* = 2.4 Hz, 1H), 7.21–7.16 (m, 2H), 7.10 (d, *J* = 8.3 Hz, 1H), 6.54 (dd, *J* = 8.3, 2.4 Hz, 1H), 3.78 (s, 3H), 3.10 (d, *J* = 13.1 Hz, 1H), 2.36 (s, 3H), 2.29 (ddd, *J* = 13.0, 6.5, 0.9 Hz, 1H), 2.23 (d, *J* = 2.2 Hz, 1H), 1.31 (s, 3H), 1.06 (dd, *J* = 7.4, 0.9 Hz, 1H), 0.94 (s, 3H), 0.81 (dd, *J* = 2.1, 1.1 Hz, 1H), 0.77 (ddt, *J* = 7.4, 6.5, 1.0 Hz, 1H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 159.1, 145.1, 143.9, 137.1, 129.6, 127.3, 124.7, 124.2, 109.6, 102.3, 60.8, 55.8, 34.2, 33.7, 29.4, 26.9, 26.4, 26.0, 22.7, 21.7, 15.6.

1,1,3-Trimethyl-6-tosyl-1a,1b,1c,6,7,7a-hexahydro-1*H*-cyclopropa[3',4']cyclopenta[1',2':1,3]cyclopropa[1,2-*b*]indole (3.16h)

Prepared following general procedure A using 5-methyl-2-(3-methylbut-2-en-1-yl)-1-tosyl-1*H*-indole

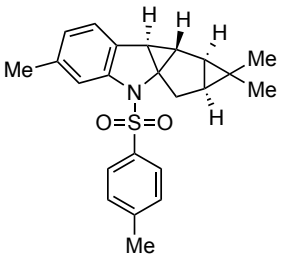


3.15h (24 mg, 0.453 mmol, 1.0 equiv, purity of 70%), [JohnPhosAuNCMe]SbF_6 (1 mg, 0.002 mmol, 4 mol%) and 1 atm of acetylene gas in CH_2Cl_2 (0.08 mL, 0.6 M) at 23 ºC for 16 h. The crude was purified by flash column chromatography (SiO_2, cyclohexane/EtOAc 100:0 to 70:30, *v/v*) to afford the product **3.16h** as colorless oil (8.9 mg, 0.023 mmol, 52% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.63–7.58 (m, 2H), 7.56 (d, *J* = 8.4 Hz, 1H), 7.18–7.14 (m, 2H), 7.04 (d, *J* = 1.9 Hz, 1H), 6.96–6.91 (m, 1H), 3.12 (d, *J* = 13.1 Hz, 1H), 2.35 (s, 3H), 2.29 (s, 3H), 2.24 (d, *J* = 2.2 Hz, 1H), 1.32 (s, 3H), 1.25 (d, *J* = 7.7 Hz, 2H), 1.07 (dd, *J* = 7.4, 0.9 Hz, 1H), 0.94 (s, 3H), 0.79–0.78 (m, 1H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 143.6, 141.4, 136.9, 133.3, 132.0, 129.4, 127.3, 127.2, 125.0, 115.7, 60.1, 34.2, 34.1, 29.2, 26.7, 26.3, 25.9, 22.6, 21.5, 20.9, 15.4. **HRMS** (ESI +) calculated for $C_{23}H_{25}NNaO_2S$ $[M+Na]^+$: 402.1498; found: 402.1497.

(1a*S*,1b*S*,1c*R*,7a*S*)-1,1,4-Trimethyl-6-tosyl-1a,1b,1c,6,7,7a-hexahydro-1*H*-cyclopropa[3',4']cyclopenta[1',2':1,3]cyclopropa[1,2-*b*]indole (3.16i)

Prepared following general procedure A using 6-methyl-2-(3-methylbut-2-en-1-yl)-1-tosyl-1*H*-indole

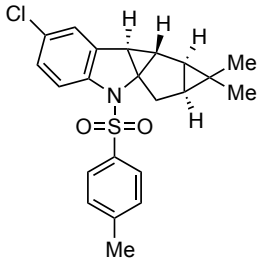


3.15i (44 mg, 0.125 mmol, 1.0 equiv), [JohnPhosAuNCMe]SbF_6 (4 mg, 0.005 mmol, 4 mol%) and 1 atm of acetylene gas in CH_2Cl_2 (0.21 mL, 0.6 M) at 23 ºC for 16 h. The crude was purified by flash column chromatography (SiO_2, cyclohexane/CH_2Cl_2 80:20 to 70:30, *v/v*) to afford the product **3.16i** as a yellow oil (13 mg, 0.032 mmol, 24% yield) as an inseparable mixture with the monoaddition byproduct (7%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.64–7.60 (m, 2H), 7.52 (dd, *J* = 1.6, 0.8 Hz, 1H), 7.19– 7.15 (m, 2H), 7.11 (d, *J* = 7.5 Hz, 1H), 6.80 (ddd, *J* = 7.6, 1.5, 0.8 Hz, 1H), 3.11 (d, *J* = 13.0 Hz, 1H), 2.36 (s, 3H), 2.33 (s, 3H), 2.31–2.26 (m, 1H), 2.25 (d, *J* = 2.2 Hz, 1H), 1.31 (s, 3H), 1.07 (dd, *J* = 7.3, 0.9 Hz, 1H), 0.94 (s, 3H), 0.80–0.75 (m, 2H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 144.1, 143.8, 137.2, 136.8, 129.6, 129.1, 127.3, 124.4, 124.1, 116.6, 60.3, 34.2, 34.1, 29.4, 26.9, 26.4, 26.1, 22.8, 21.9, 21.7, 15.6. **HRMS** ((ESI+) calculated for $C_{23}H_{25}NNaO_2S$ $[M+Na]^+$ 402.1498 *m/z*, found 402.1513 *m/z.*

(1a*S*,1b*S*,1c*R*,7a*S*)-3-Chloro-1,1-dimethyl-6-tosyl-1a,1b,1c,6,7,7a-hexahydro-1*H*-cyclopropa[3',4']cyclopenta[1',2':1,3]cyclopropa[1,2-*b*]indole (3.16j)

Prepared following general procedure A using 5-chloro-2-(3-methylbut-2-en-1-yl)-1-tosyl-1*H*-indole

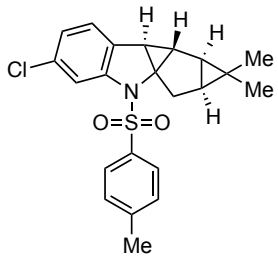


3.15j (47 mg, 0.125 mmol, 1.0 equiv), [JohnPhosAuNCMe]SbF_6 (4 mg, 0.005 mmol, 4 mol%) and 1 atm of acetylene gas in CH_2Cl_2 (0.21 mL, 0.6 M) at 23 ºC for 16 h. The crude was purified by flash column chromatography (SiO_2, cyclohexane/CH_2Cl_2 80:20 to 70:30, *v/v*) to afford the product **3.16j** as yellow oil (23 mg, 0.057 mmol, 46% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.63–7.57 (m, 3H), 7.21–7.17 (m, 3H), 7.09 (dd, *J* = 8.7, 2.3 Hz, 1H), 3.15–3.10 (m, 1H), 2.37 (s, 3H), 2.31–2.26 (m, 2H), 1.31 (s, 3H), 1.10 (dd, *J* = 7.4, 1.0 Hz, 1H), 0.95 (s, 3H), 0.81–0.77 (m, 2H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 144.2, 142.3, 136.7, 133.9, 129.7, 128.9, 127.3, 126.8, 124.7, 117.0, 60.8, 34.0, 33.9, 29.1, 26.8, 26.4, 26.1, 22.9, 21.7, 15.5.

(1a*S*,1b*S*,1c*R*,7a*S*)-4-chloro-1,1-dimethyl-6-tosyl-1a,1b,1c,6,7,7a-hexahydro-1*H*-cyclopropa[3',4']cyclopenta[1',2':1,3]cyclopropa[1,2-*b*]indole (3.16k)

Prepared following general procedure A using 6-chloro-2-(3-methylbut-2-en-1-yl)-1-tosyl-1*H*-indole

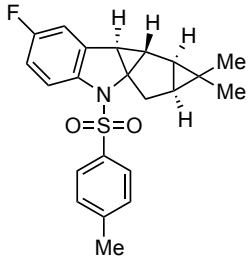


3.15k (47 mg, 0.125 mmol, 1.0 equiv), [JohnPhosAuNCMe]SbF_6 (4 mg, 0.005 mmol, 4 mol%) and 1 atm of acetylene gas in CH_2Cl_2 (0.21 mL, 0.6 M) at 23 ºC for 16 h. The crude was purified by flash column chromatography (SiO_2, cyclohexane/CH_2Cl_2 90:10, *v/v*) to afford the product **3.16k** as yellow oil (26 mg, 0.060 mmol, 48% yield) as an inseparable mixture with the monoaddition byproduct (6%) and starting material (3%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.70 (d, *J* = 1.9 Hz, 1H), 7.65–7.61 (m, 2H), 7.23–7.19 (m, 2H), 7.14 (d, *J* = 8.0 Hz, 1H), 6.95 (dd, *J* = 8.0, 1.9 Hz, 1H), 3.11 (dd, *J* = 13.0, 1.1 Hz, 1H), 2.37 (s, 3H), 2.31–2.25 (m, 2H), 1.31 (s, 3H), 1.09 (dd, *J* = 7.3, 0.9 Hz, 1H), 0.95 (s, 3H), 0.82–0.77 (m, 2H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 144.7, 144.3, 136.8, 132.5, 130.4, 129.7, 127.3, 125.2, 123.7, 116.1, 61.0, 34.0, 33.7, 29.2, 26.8, 26.2, 26.1, 22.9, 21.7, 15.5.

(1a*S*,1b*S*,1c*R*,7a*S*)-3-Fluoro-1,1-dimethyl-6-tosyl-1a,1b,1c,6,7,7a-hexahydro-1*H*-cyclopropa[3',4']cyclopenta[1',2':1,3]cyclopropa[1,2-*b*]indole (3.16l)

Prepared following general procedure A using 5-fluoro-2-(3-methylbut-2-en-1-yl)-1-tosyl-1*H*-indole

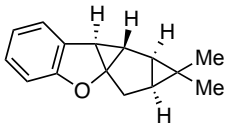


3.15l (48 mg, 0.133 mmol, 1.0 equiv), [JohnPhosAuNCMe]SbF_6 (4 mg, 0.005 mmol, 4 mol%) and 1 atm of acetylene gas in CH_2Cl_2 (0.22 mL, 0.6 M) at 23 ºC for 16 h. The crude was purified by flash column chromatography (SiO_2, cyclohexane/EtOAc 100:0 to 70:30, *v/v*) to afford the product **3.16l** as colorless oil (19 mg, 0.050 mmol, 38% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64 (dd, *J* = 9.0, 4.6 Hz, 1H), 7.61–7.53 (m, 2H), 7.22–7.13 (m, 2H), 6.93 (dd, *J* = 8.1, 2.8 Hz, 1H), 6.83 (td, *J* = 8.9, 2.8 Hz, 1H), 3.13 (d, *J* = 13.2 Hz, 1H), 2.36 (s, 3H), 2.27 (dd, *J* = 5.5, 1.5 Hz, 1H), 1.31 (s, 3H), 1.27–1.23 (m, 1H), 1.09 (dd, *J* = 7.4, 0.9 Hz, 1H), 0.95 (s, 3H), 0.81–0.77 (m, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 160.7, 158.3, 143.9, 139.4 ($J_{C–H}$= 2.4 Hz), 136.5, 134.1 ($J_{C–H}$= 8.6 Hz), 129.5, 127.2, 117.1 ($J_{C–H}$= 8.4 Hz), 113.3 ($J_{C–H}$= 22.7 Hz), 111.5, 60.7, 33.9, 33.8, 29.0, 26.6, 25.9, 22.7, 21.5, 15.3. **^{19}F NMR** (376 MHz, $CDCl_3$) δ -119.7. **HRMS** (ESI +) calculated for $C_{22}H_{23}FNO_2S$ $[M+H]^+$: 384.1428; found: 384.1423.

1,1-Dimethyl-1,1a,1b,1c,7,7a-hexahydrocyclopropa[3',4']cyclopenta[1',2':1,3]cyclopropa[1,2-*b*]benzofuran (3.19)

Prepared following general procedure A using 2-(3-methylbut-2-en-1-yl)benzofuran **3.18** (14 mg, 0.069 mmol, 1.0 equiv), [JohnPhosAuNCMe]SbF_6 (2 mg, 0.003 mmol, 4 mol%) and 1 atm of acetylene gas in CH_2Cl_2 (0.12 mL, 0.6 M) at 23 ºC for 16 h. The crude was purified by flash column chromatography (SiO_2, cyclohexane/EtOAc 100:0 to 70:30, *v/v*) to afford the product **3.19** as colorless oil (7 mg, 0.031 mmol, 44% yield).



^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30 (dt, *J* = 7.5, 1.0 Hz, 1H), 7.07 (ddd, *J* = 8.0, 7.5, 1.4 Hz, 1H), 6.87 (td, *J* = 7.5, 1.0 Hz, 1H), 6.80 (ddt, *J* = 8.1, 1.1, 0.6 Hz, 1H), 2.59–2.50 (m, 2H), 2.39 (dt, *J* = 13.3, 1.2 Hz, 1H), 1.21 (s, 3H), 1.11–1.05 (m, 1H), 1.00 (s, 3H), 0.84 (ddt, *J* = 7.2, 6.3, 1.0 Hz, 1H), 0.68 (dt, *J* = 1.8, 0.9 Hz, 1H) (soba 1H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 159.9, 130.3, 126.8, 124.3, 120.7, 110.2, 80.0, 32.2, 32.2, 28.7, 26.5, 26.0, 24.5, 22.1, 14.2. **HRMS** (ESI +) calculated for $C_{15}H_{17}O$ $[M+H]^+$: 213.1274; found: 213.1273.

DFT Calculations

Computational Methods

DFT calculations were performed by the Gaussian 09 suit.[45] All the calculations were carried out using B3LYP[46] functional that has provided suitable models in other DFT gold-catalyzed transformations.[47] The SDD basis set was used to describe Au. The 6-31G(d,p) basis set[48] was employed for all the other atoms (C, H, O, N, P and S). Full geometry optimizations were carried out in ethanol through a solvation model based (SMD).[49] The connectivity of the transition states was confirmed by the relaxation of each transition state towards both previous and next intermediates. All the energies are potential energies (E) and free energies (G) in solution at 298.15 K and 1 atm in kcal/mol. Optimized geometries were visualized using CYLView.[50]

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47. (a) Nieto-Oberhuber, C.; Pérez-Galan, P.; Herrero-Gómez, E.; Lauterbach, T.; Rodríguez, C.; López, S.; Bour, C.; Rosellón, A.; Cárdenas, D. J.; Echavarren, A. M. *J. Am. Chem. Soc.* **2008**, *130*, 269–279. (b) García-Morales, C.; Pei, X.-L.; Sarria Toro, J. M.; Echavarren, A. M. *Angew. Chem. Int. Ed.* **2019**, *58*, 3957–3961. (c) Scharnagel, D.; Escofet, I.; Armengol-Relats, H.; de Orbe, M. E.; Korber, J. N.; Echavarren, A. M. *Angew. Chem. Int. Ed.* **2020**, *59*, 4888–4891.
48. (a) Ditchfield, R.; Hehre, W. J.; Pople, J. A. *J. Phys. Chem.* **1971**, *54*, 724–728. (b) Hehre, W. J.; Ditchfield, R.; Pople, J. A. *J. Phys. Chem.* **1972**, *56*, 2257–2261.
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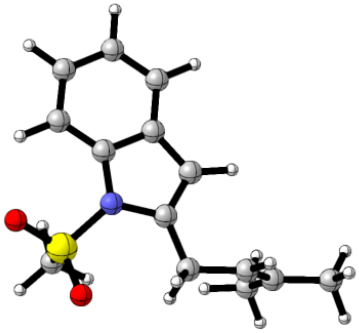
DFT Calculations for *N*-Methanesulfonyl Indole 3.25

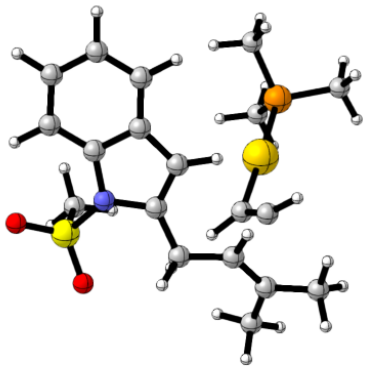
Pathway A

N-Methanesulfonyl Indole 3.25



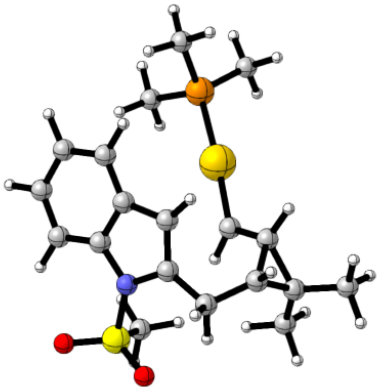
E = -1146.499926 Hartrees
G = -1146.259761 Hartrees

TS_{1-2}



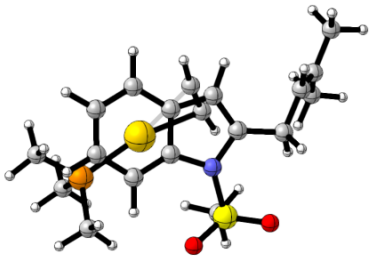
E = -1820.402785 Hartrees
G = -1820.037380 Hartrees

TS_{2-3}



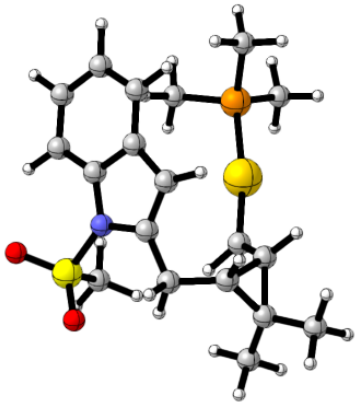
E = -1820.443314 Hartrees
G = -1820.064713 Hartrees

Int1



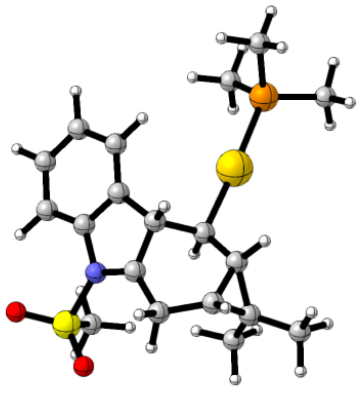
E = -1820.425105 Hartrees
G = -1820.054557 Hartrees

Int2



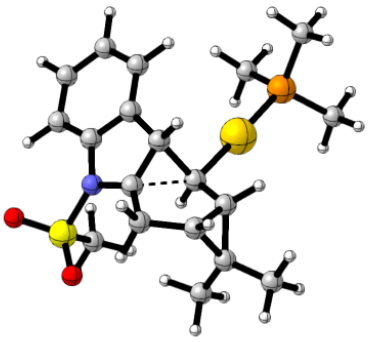
E = -1820.447396 Hartrees
G = -1820.070991 Hartrees

Int3



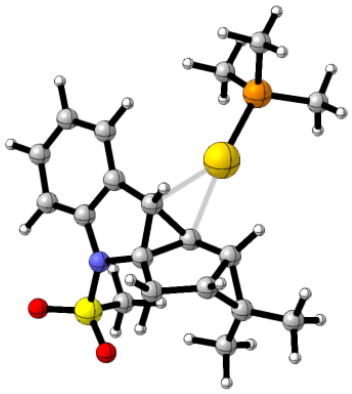
E = -1820.463642 Hartrees
G = -1820.085673 Hartrees

TS_{3-4}



E = -1820.458781 Hartrees
G = -1820.080467 Hartrees

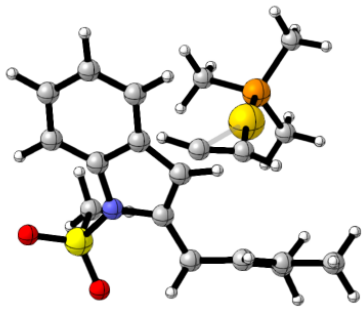
Int 4



E = -1820.468687 Hartrees
G = -1820.089865 Hartrees

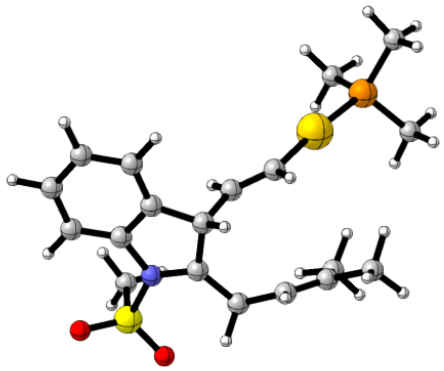
Pathway B

TS_{1-5}



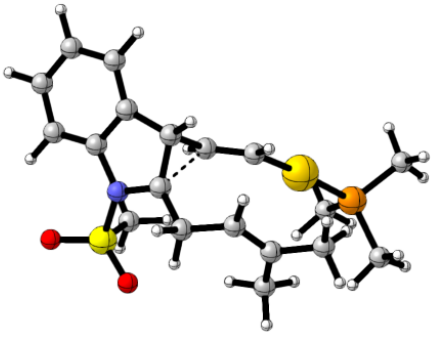
E = -1820.401481 Hartrees
G = -1820.034391 Hartrees

Int5



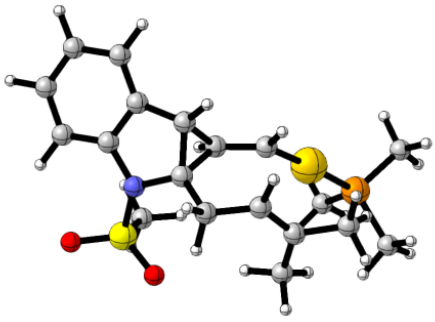
E = -1820.431166 Hartrees
G = -1820.061904 Hartrees

TS_{5-6}



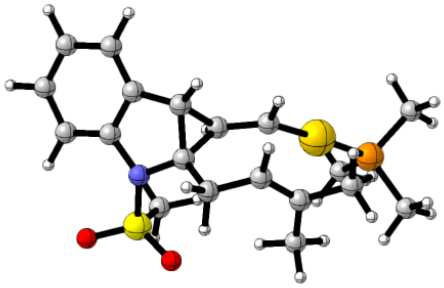
E = -1820.424855 Hartrees
G = -1820.050866 Hartrees

Int6



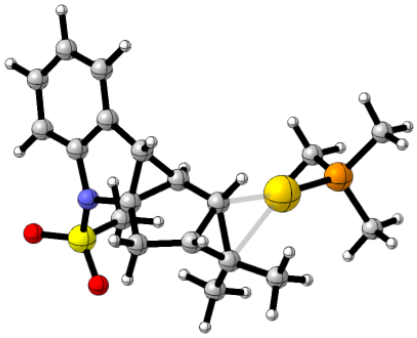
E = -1820.429070 Hartrees
G = -1820.053793 Hartrees

TS_{6-7}



E = -1820.429005 Hartrees
G = -1820.052541 Hartrees

Int

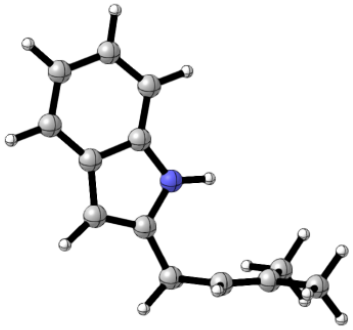


E = -1820.470894 Hartrees
G = -1820.091067 Hartrees

DFT Calculations for Indole 3.15b

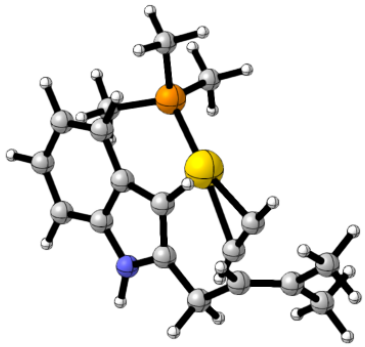
Pathway A

Indole 3.15b



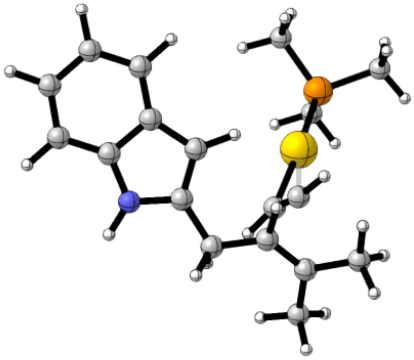
E = -558.7351846 Hartrees
G = -558.528131 Hartrees

Int8



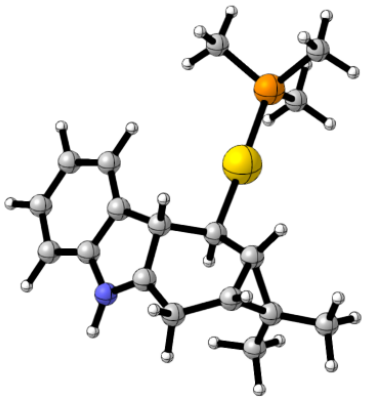
E = -1232.658024 Hartrees
G = -1232.325356 Hartrees

TS_{8-9}



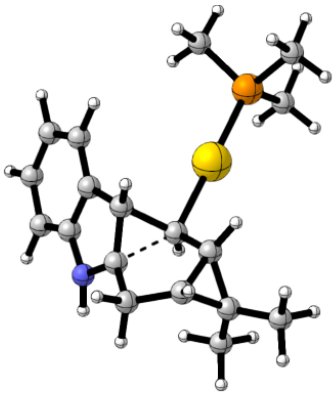
E = -1232.638573 Hartrees
G = -1232.305059 Hartrees

Int9



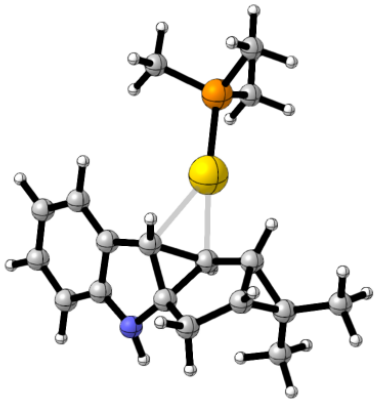
E = -1232.713182 Hartrees
G = -1232.365331 Hartrees

TS_{9-10}



E = -1232.697731 Hartrees
G = -1232.351990 Hartrees

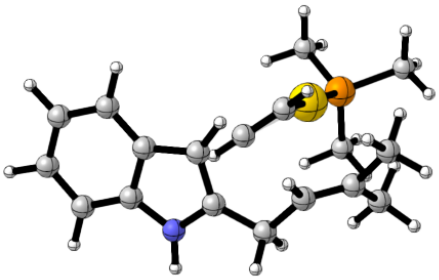
Int10



E = -1232.698850 Hartrees
G = -1232.353393 Hartrees

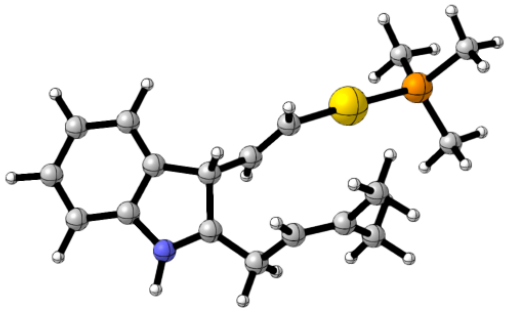
Pathway B

$TS_{8\text{-}11}$



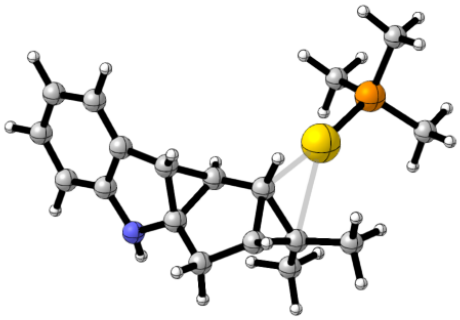
E = -1232.641329 Hartrees
G = -1232.307614 Hartrees

Int11



E = -1232.684783 Hartrees
G = -1232.345432 Hartrees

Int12

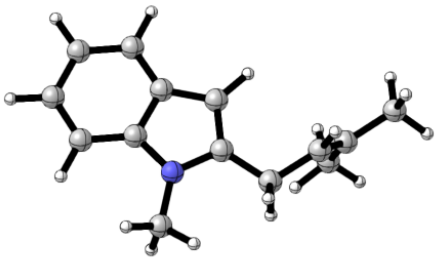


E = -1232.694130 Hartrees
G = -1232.349580 Hartrees

DFT Calculations for *N*-Me indole

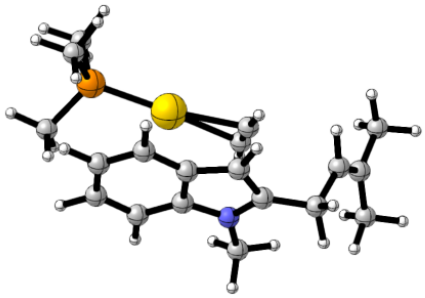
Pathway A

N-Me indole



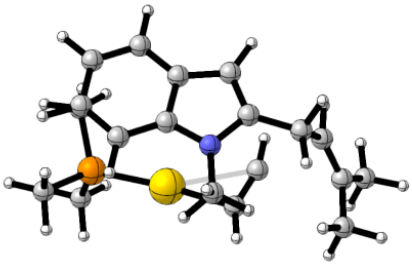
E = -598.011085 Hartrees
G = -597.777541 Hartrees

Int13



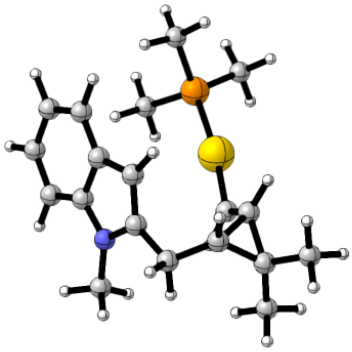
E = -1271.936749 Hartrees
G = -1271.574453 Hartrees

TS_{13-14}



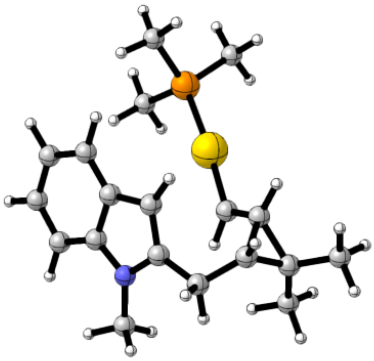
E = -1271.922465 Hartrees
G = -1271.558040 Hartrees

Int14



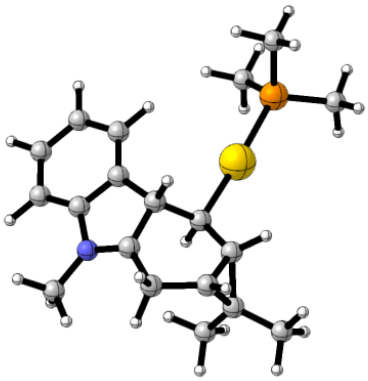
E = -1271.960556 Hartrees
G = -1271.593340 Hartrees

TS_{14-15}



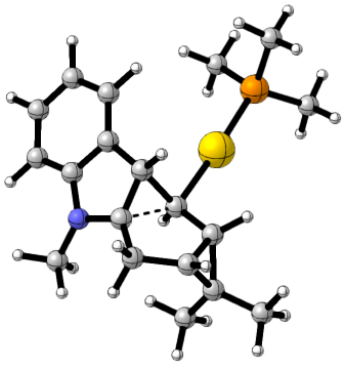
E = -1271.960495 Hartrees
G = -1271.590794 Hartrees

Int15



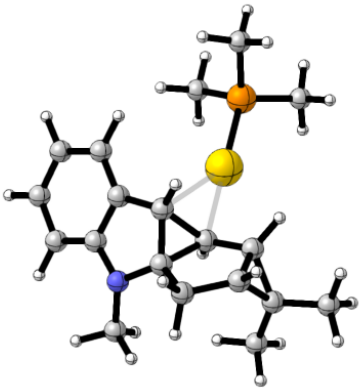
E = -1271.992563 Hartrees
G = -1271.619474 Hartrees

TS_{15-16}



E = -1271.974547 Hartrees
G = -1271.602448 Hartrees

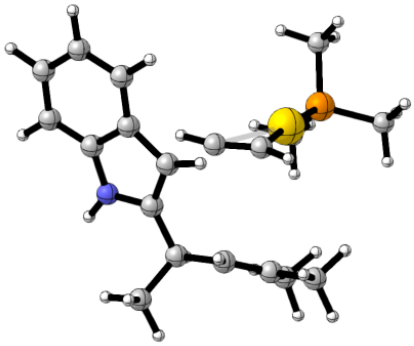
Int16



E = -1271.975943 Hartrees
G = -1271.604911 Hartrees

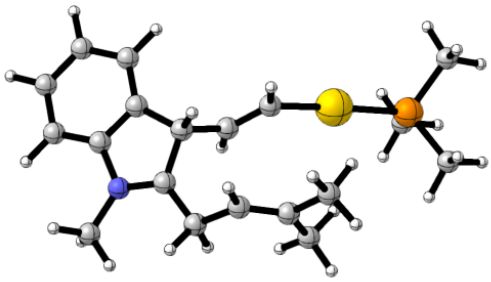
Pathway B

TS_{13-17}



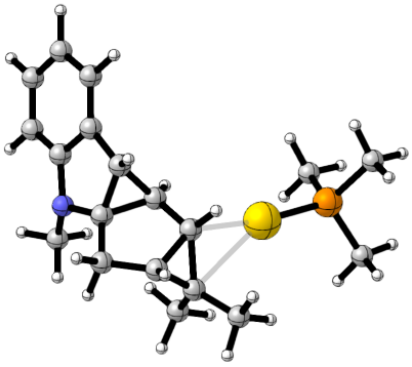
E = -1271.922739 Hartrees
G = -1271.562423 Hartrees

Int17



E = -1271.964485 Hartrees
G = -1271.597839 Hartrees

Int18

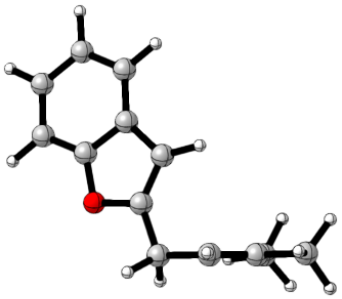


E = -1271.962030 Hartrees
G = -1271.590741 Hartrees

DFT Calculations for Benzofuran 3.18

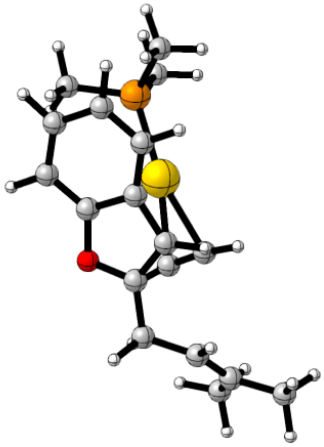
Pathway A

Benzofuran 3.18



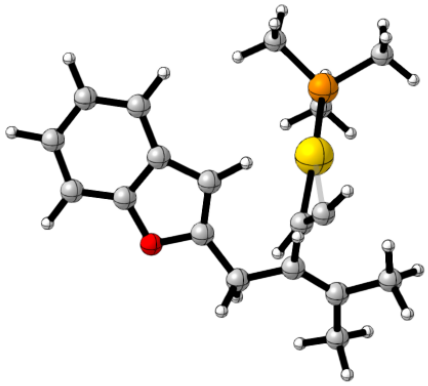
E = -578.5934285 Hartrees
G = -578.400232 Hartrees

Int19



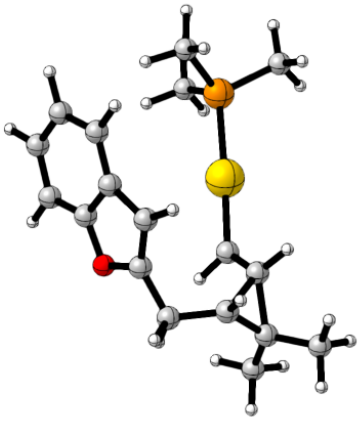
E = -1252.516363 Hartrees
G = -1252.196254Hartrees

$TS_{19\text{-}20}$



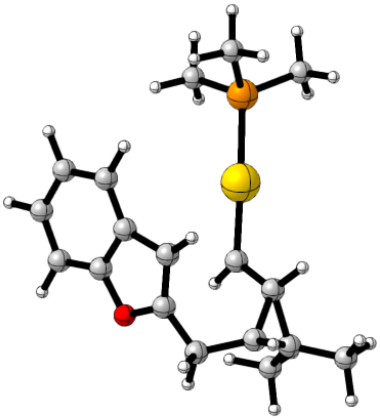
E = -1252.496617 Hartrees
G = -1252.178105 Hartree

Int20



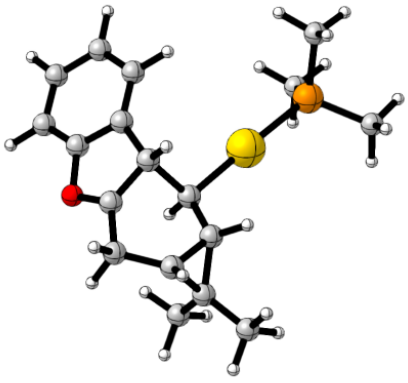
E = -1252.539628 Hartrees
G = -1252.209251 Hartrees

$TS_{20\text{-}21}$



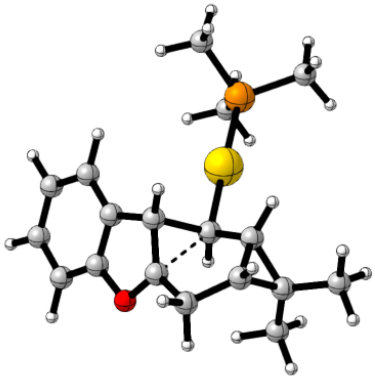
E = -1252.536937 Hartrees
G = -1252.204968 Hartrees

Int21



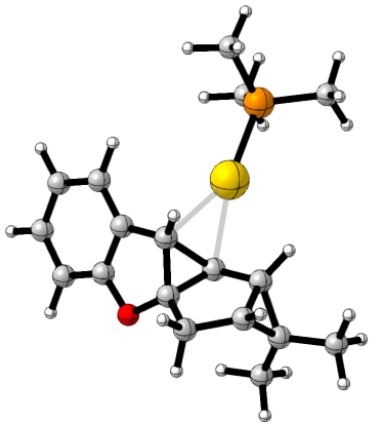
E = -1252.552900 Hartrees
G = -1252.220531 Hartrees

TS_{21-22}



E = -1252.551553 Hartrees
G = -1252.220221 Hartrees

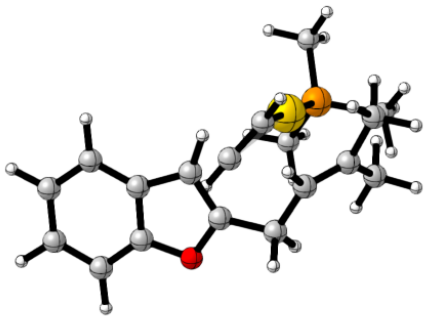
Int22



E = -1252.560996 Hartrees
G = -1252.227179 Hartrees

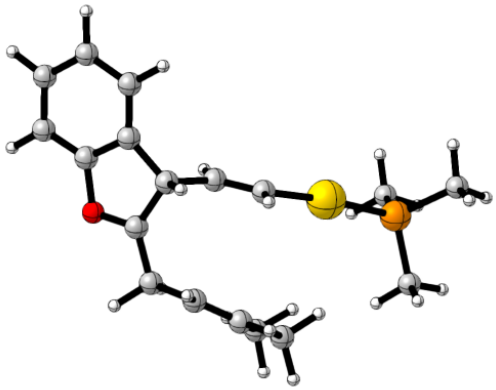
Pathway B

TS_{19-23}



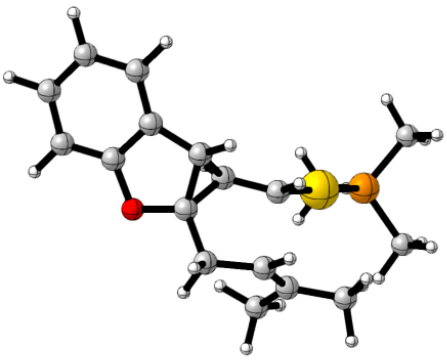
E = -1252.493901 Hartrees
G = -1252.171412 Hartrees

Int23



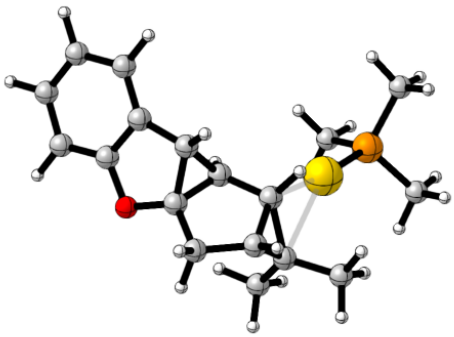
E = -1252.518918 Hartrees
G = -1252.193920 Hartrees

TS_{23-24}



E = -1252.519193 Hartrees
G = -1252.189514 Hartrees

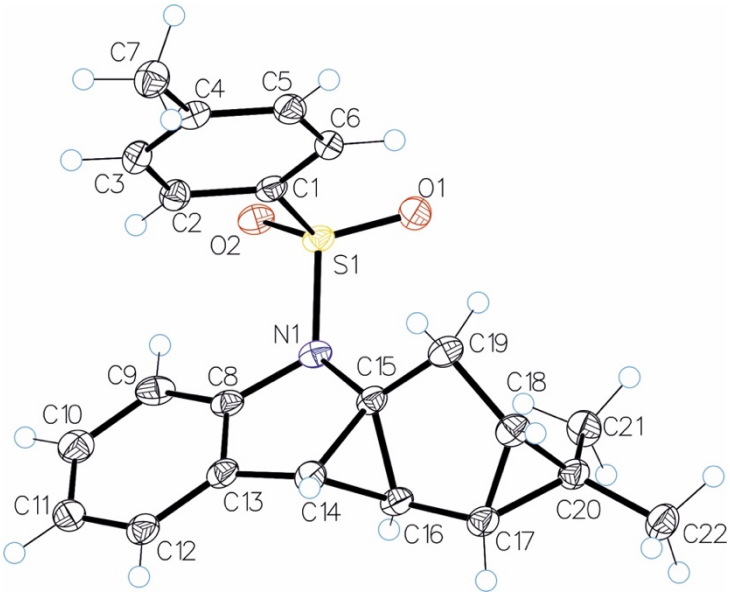
Int24

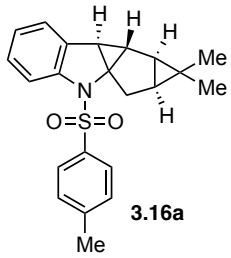


E = -1252.558699 Hartrees
G = -1252.227344 Hartrees

Crystallographic Data

(1a*S*,1b*S*,1c*R*,7a*S*)-1,1-Dimethyl-6-tosyl-1a,1b,1c,6,7,7a-hexahydro-1*H*-cyclopropa[3',4']cyclopenta[1',2':1,3]cyclopropa[1,2-*b*]indole (3.16a)





3.16a

Table 3.3. Crystal data and structure refinement for ASP-P1-068x.

Identification code	ASP-P1-068x
Empirical formula	$C_{22}H_{23}NO_2S$
Formula weight	365.47
Temperature/K	100
Crystal system	triclinic
Space group	P-1
a/Å	5.9416(2)
b/Å	10.0855(4)
c/Å	15.7827(4)
α/°	74.809(3)
β/°	86.923(3)
γ/°	81.707(3)
Volume/Å^3	903.05(5)
Z	2
ϱ_{calc}g/cm^3	1.344
μ/mm^{-1}	0.196
F(000)	388.0
Crystal size/mm^3	0.3 × 0.08 × 0.03

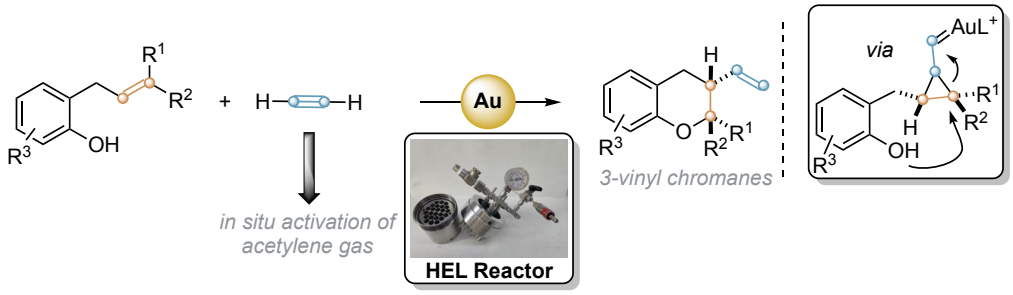
Radiation	Mo Kα (λ = 0.71073)
2Θ range for data collection/°	5.35 to 57.42
Index ranges	$-8 \leq h \leq 7$, $-13 \leq k \leq 13$, $-20 \leq l \leq 20$
Reflections collected	19817
Independent reflections	4173 [$R_{int} = 0.0459$, $R_{sigma} = 0.0408$]
Data/restraints/parameters	4173/0/238
Goodness-of-fit on F^2	1.040
Final R indexes [I>=2σ (I)]	$R_1 = 0.0423$, $wR_2 = 0.1033$
Final R indexes [all data]	$R_1 = 0.0598$, $wR_2 = 0.1109$
Largest diff. peak/hole / e $Å^{-3}$	0.37/-0.40

UNIVERSITAT ROVIRA I VIRGILIDevelopment of Gold(I)-Catalyzed Reactions Between Alkenes and Acetylene Gas
Tania Medina Gil

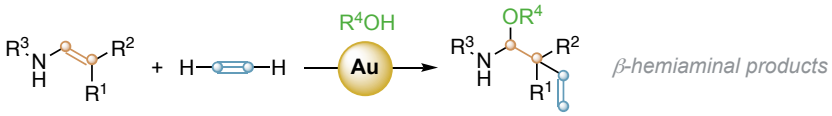
General Conclusions

In this Doctoral Thesis, the gold(I)-catalyzed activation of acetylene gas has been studied and three new transformations have been discovered, which will lead to further developments in an underexplored area of research.

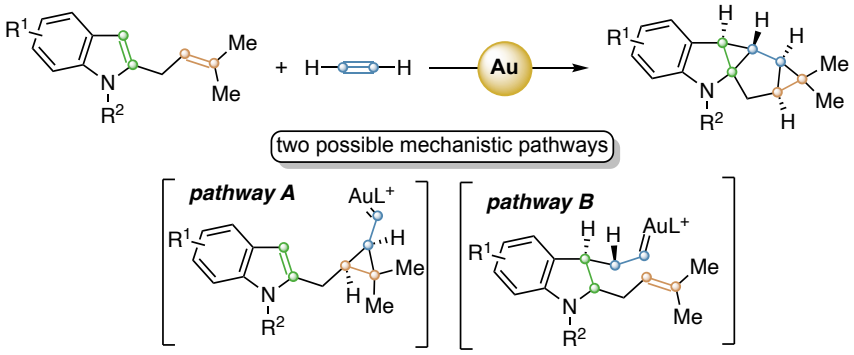
We have been able to successfully combine homogenous gold(I) catalysis and the use of acetylene gas for the development of an unprecedented aryloxyvinylation reaction of easily accessible *o*-allylphenols. The resulting products contain a chromane ring in their structure, a ubiquitous heterocyclic scaffold. We applied this methodology to the late-stage functionalization of lapachol natural product, a vitamin K derivate. Several diversifications of the model substrate were performed and preliminary results on the enantioselective version of these reaction were explored. Additionally, this chemistry could be extended to linear amines for the synthesis of pyrrolidines and piperidines containing products.



We have developed a fully intermolecular gold(I)-catalyzed alkoxyvinylation with acetylene gas where neither the alkyne, the alkene or the alcohol nucleophile are covalently linked. We found *N*-vinyl benzamides as suitable substrates for the synthesis of *β*-vinyl hemiaminal products. Furthermore, the competing oligomerization process was studied for the model reaction of *trans*-stilbene with acetylene.



Finally, we developed the gold(I)-catalyzed biscyclopropanation of 2-substituted indoles. This methodology was applied to the synthesis of a variety of polycyclic indoles. Additionally, DFT studies were performed to distinguish between two plausible mechanistic pathways. Calculations show a preference for pathway A when *N*-sulfonamide substituted indoles are employed whilst in the case of free and *N*-methyl indole the most energetically favored mechanism is pathway B.



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