ESCOLA DE DOUTORAMENTO
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Novel synthetic methodologies via synergistic bimetallic catalysis

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TESE DE DOUTORAMENTO

NOVEL SYNTHETIC METHODOLOGIES VIA SYNERGISTIC BIMETALLIC CATALYSIS

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ESCOLA DE DOUTORAMENTO INTERNACIONAL DA UNIVERSIDADE DE SANTIAGO DE COMPOSTELA

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Novel synthetic methodologies via synergistic bimetallic catalysis

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ABBREVIATIONS AND ACRONYMS

δ	Chemical shift
Ac	Acyl
AcOEt	Ethyl acetate
Ad	Adamantly
APCI	Atmosphere-pressure chemical ionization
Ar	Aryl
aq.	Aqueous
BINAP	(2,2’-bis(diphenylphosphino)-1,1’-binaphthyl)
Bn	Benzyl
Boc	*tert*-Butyloxycarbonyl
BrettPhos	2-(Dicyclohexylphosphino)3,6-dimethoxy-2’,4’,6’-triisopropyl-1,1’-biphenyl
t-BuXPhos-Pd-G3	[(2-Di-tert-butylphosphino-2’,4’,6’-triisopropyl-1,1’-biphenyl)-2-(2’-amino-1,1’-biphenyl)] palladium(II) methanesulfonate
cat.	Catalyst
Conv.	Conversion
d	doublet
dba	Dibenzylideneacetone
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DIBAL-H	Diisobutylaluminium hydride
DMA	Dimethylacetamide
DMAP	4-Dimethylaminopyridine
DMF	Dimethylformamide
DMSO	Dimethyl sulfoxide
DIOP	(2,3-O-isopropylidene-2,3-dihydroxy-1,4-bis(diphenylphosphino)butane)
DPEPhos	Bis[(2-diphenylphosphino)phenyl] ether
dppbz	1,2-Bis(diphenylphosphino)benzene
dppe	1,2-Bis(diphenylphosphino)ethane
dppf	1,1’-Bis(diphenylphosphino)ferrocene
dppm	Bis(diphenylphosphino)methane
dppp	1,3-Bis(diphenylphosphino)propane
dr	Diastereomeric ratio
DTBM	3,5-di-tert-butyl-4-methoxyphenyl
DuPhos	2-Dicyclohexylphosphino-2’,6’-diisopropoxybiphenyl
E	electrophile
EDG	electron-donating group
EI	Electron ionization
equiv	Equivalent
er	enantiomeric ratio
EWG	electron-withdrawing group
FG	functional group
GC-MS	Gas chromatography mass spectroscopy
hex	Hexyl
(Het)Ar	Heteroaromatic
HOMO	Highest-occupied molecular orbital
HRMS	High resolution mass spectrometry
IMes	1,3-Bis(2,4,6-trimethylphenyl)-1,3-dihydro-2H-imidazol-2-ylidene
IPr	1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene
J	Coupling constant

L	Ligand
LG	Leaving group
LUMO	Lowest-unoccupied molecular orbital
m	multiplet
M	Molar
M	Metal
Mes	Mesityl
m/z	Mass charge relation
NBS	N-bromosuccinimide
n.d.	not determined
NHC	N-heterocyclic carbene
NMR	nuclear magnetic resonance
NOE	Nuclear Overhauser effect
Nu	nucleophile
p	Pentet
Ph	Phenyl
pin	Pinacol
Piv	Pivalic acid
ppm	Parts per million
Pr	Propyl
PTSA	p-Toluenesulfonic acid
PXPd	Dichlorobis(chlorodi-tert-butylphosphine)palladium(II)
q	Quadruplet
QuinoxP*	2,3-Bis(tert-butylmethylphosphino)quinoxaline
Ref.	Reference
r.t.	Room temperature
RuPhos	2-Dicyclohexylphosphino-2',6'-diisopropoxybiphenyl
SN	Nucleophilic Substitution
SEGPhos	5,5'-Bis(diphenylphosphino)-4,4'-bi-1,3-benzodioxole
SFC	super fluid chromatography
SIMes	1,3-Bis(2,4,6-trimethylphenyl)-4,5-dihydroimidazol-2-ylidene
SIPr	1,3-Bis(2,6-di-i-propylphenyl)imidazolidin-2-ylidene
SPhos	2-Dicyclohexylphosphino-2',6'-dimethoxybiphenyl
T	Temperature
TBAF	Tetra-n-butylammonium fluoride
TBDMS	Tert-Butyldimethylsilyl
TBS	Tert-Butyldimethylsilyl
TC	Thiophene-2-carboxylate
TCCA	Trichloroisocyanuric acid
TEMPO	(2,2,6,6-Tetramethylpiperidin-1-yl)oxyl
TES	Triethylsilane
Tf	Triflate
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
TIB	2,4,6-triisopropylbenzoate
TIPS	Triisopropylsilyl
TM	Transition metal
TMS	Trimethylsilyl
UV	Ultraviolet
Xantphos	4,5-Bis(diphenylphosphino)-9,9-dimethylxanthene
XPhos	2-Dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl


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GENERAL OBJECTIVES

The general objective of this thesis project is the development of new methodologies through bimetallic catalysis that allow the synthesis of borylated dienes from simple and abundant molecules, avoiding the generation of metal residues. Such methodologies will involve the chemoselective activation of an hydrocarbon (alkynes or allenes), an alkenyl or allyl substrate and bis(pinacolato)diboron by the cooperative action of two different transition metal complexes to afford 1,3-, 1,4-, or 1,5-borylated dienes with complete control over the process selectivity.

Classical methods to prepare these complex molecules via transition metal catalysis typically require the use of stoichiometric amount of alkenyl-metal reagents. These methodologies are limited to the availability and reactivity profiles of the alkenyl reagent. Additionally, the use of this pre-functionalized reagents entails the stoichiometric formation of inorganic salts as side reaction products. In order to avoid the use of stoichiometric amounts and previously preparation of organometallic reagents, an alternative would be the formation of the C(sp^2) or C(sp^3) nucleophile promoted by a transition metal catalyst. Particularly, the insertion of alkynes and allenes to CuBpin complexes has become a powerful tool for the generation of nucleophilic boryl alkenyl- or allylcopper complexes.

One of the main objectives of this thesis is to synthesize borylated 1,3-, 1,4-, and 1,5-dienes under a synergistic catalysis regime, using simple alkynes and allenes as a transient functionalized alkenyl- or allylcopper species in a stereo- and regioselective (and enantioselective where appropriate) allylic substitution or alkenylboration. Furthermore, the chemo-, regio- and stereoselectivity in these processes has to be controlled with both transition metal catalysis in order to avoid the formation of isomeric mixtures.

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CHAPTER I: Introductioon

1. Bimetallic catalysis

Catalysis is one of the most efficient and powerful strategies for the discovery of new chemical reactions. During the last decades, a wide range of catalytic reactions employing a single transition metal catalyst allowed the discovery of new transformations. In these strategies, a single metal catalyst activates a substrate to promote a particular transformation. However, some transformations, such as multicomponent reactions, are still challenging due to the impossibility of using a single catalyst.

In order to address these challenges, several types of multicatalytic systems have been developed. These transformations include bifunctional, double activation, cascade or synergistic catalysis.

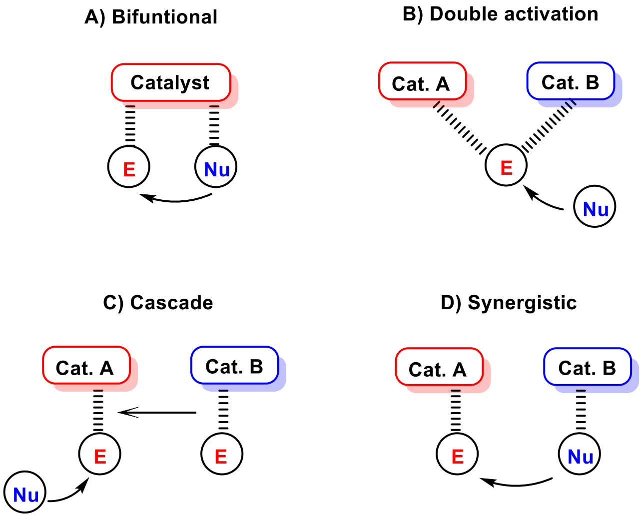

Figure 1. Classification of multicatalytic systems

- *Bifunctional catalysis*: The nucleophile and electrophile are activated separately on the same catalyst (*Fig. 1A*)
- *Double activation catalysis*: Both catalysts activate only one of the reacting partners (*Fig. 1B*)
- *Cascade catalysis*: Both catalysts activate the same reacting partner in a sequential maner (*Fig. 1C*)
- *Synergistic catalysis:* The nucleophile and electrophile are simultaneously activated by two different catalysts (*Fig. 1D*)

This PhD dissertation deals with the development of new synthetic transformations based on synergistic transition metal catalysis. Thus, an introduction to this concept and an overview of the main transformation involving this type of catalysis will be given in the following.

1.1.1 Synergistic catalysis

Synergistic catalysis is becoming popular for being a powerful tool to increase the variety of transformations, to improve previously reported methods or to new reactions that are not possible to achieve by single metal catalysis.[1]

This type of transformations involve a simultaneous activation of the electrophile (**E**) by one catalyst (**cat1**) and the activation of the nucleophile (**Nu**) by the other cocatalyst (**cat2**). This activation creates species with a lower LUMO (Lowest Unoccupied Molecular Orbital) (**A'**) and the other one with a higher HOMO (Highest Occupied Molecular Orbital) (**B'**) (Figure 2). These activated species can couple in an easier manner thus allowing chemical reactions that are impossible or inefficient using traditional single-catalyst methodologies to be carried out with high efficiency.

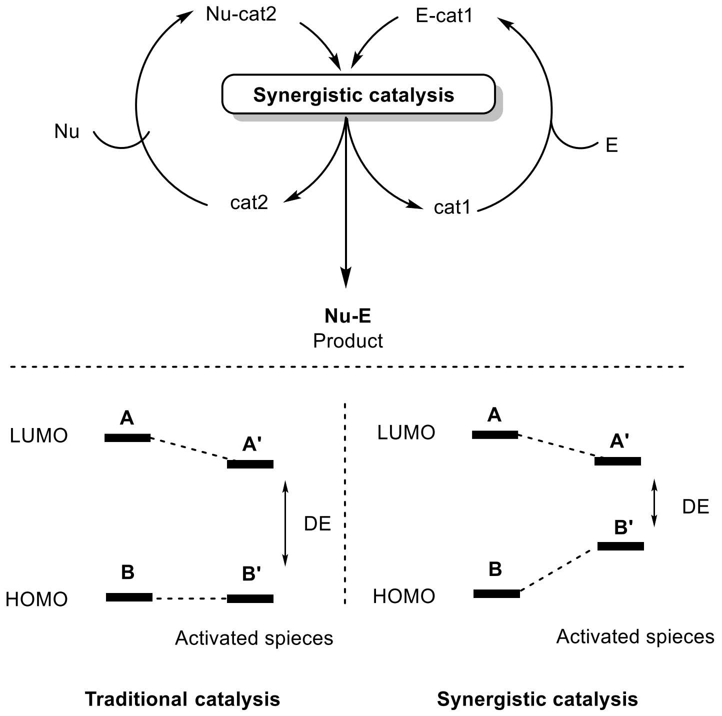

Figure 2. Concept of dual synergistic catalysis

The use of synergistic catalysis, in which two different catalysts activate two different substrates, presents several challenges, associated in most cases with the complexity of the system. The main challenges are:

a) Compatibility: both active catalytic species must be compatible, as they can interact with each other resulting in self-quenching, which renders both catalysts inactive.
b) Chemoselectivity control: each catalyst must react with the appropiate substrate in a selective manner, avoiding side reactions.

---

[1] For a review see: (a) Allen, A.; MacMillan, D. *Chem. Sci*. **2012**, *3*, 633-658. (b) Pye, D. R.; Mankad, N. P. *Chem. Sci*. **2017**, *8*, 1705-1718. (c) Gandeepan, P.; Ackermann, L. *Chem* **2018**, *4*, 199-222. (d) Kim, U B.; Jung, D. J.; Jeon, H. J.; Rathwell, K.; Lee, S.-g. *Chem. Rev*. **2020**, *120*, 13382-13433. (e) Wu, Y.; Huo, X.; Zhang, W. *Chem. Eur. J*. **2020**, *26*, 4895-4916.

c) Kinetics: both catalysts should have compatible activation rates to make the two catalytic cycles kinetically compatible.

An overview of the reactions reported using synergistic dual transition metal catalysis, indicate that palladium (which is usually used to activate the electrophilic coupling partner) show a broad range of catalyst compatibility with a wide number of transition metal catalyst such as Cu, Au, Ru, Rh, Ni, V and Ag.[1d]

Additionally, copper (usually used to activates the nucleophilic counterpart) can also be compatible with Fe, Ru, Mn, Ni, Rh, Re.[1d] There are other reported combinations of transition metal catalysts such as Rh/Ag, Ru/Ti, Au/Fe or Ti/Ni. However, is important to highlight that the most outstanding combination is between palladium and copper.

1.1.2 Sonogashira cross coupling

The first example of Cu/Pd cooperative catalysis was reported in 1975 by Sonogashira and co-workers. In this work, they reported the cross-coupling of acetylene gas with (hetero)aryl iodides or vinyl bromides (Scheme 1).[2] In this transformation catalytic amounts of copper iodide and $Pd(PPh_3)_2Cl_2$ were used. The addition of a catalytic amount of the copper salt allowed the use of conditions milder than reported in previous methodologies, which also implies a better group tolerance. This transformation consists in the in-situ generation of the nucleophilic copper acetylide under the presence of a weak base. The active Pd(0) complex is involved in the oxidative addition step with the halide. Then transmetalation between the resulting R^2-Pd(II) intermediate and the copper acetylide followed by reductive elimination, provides the coupled product.

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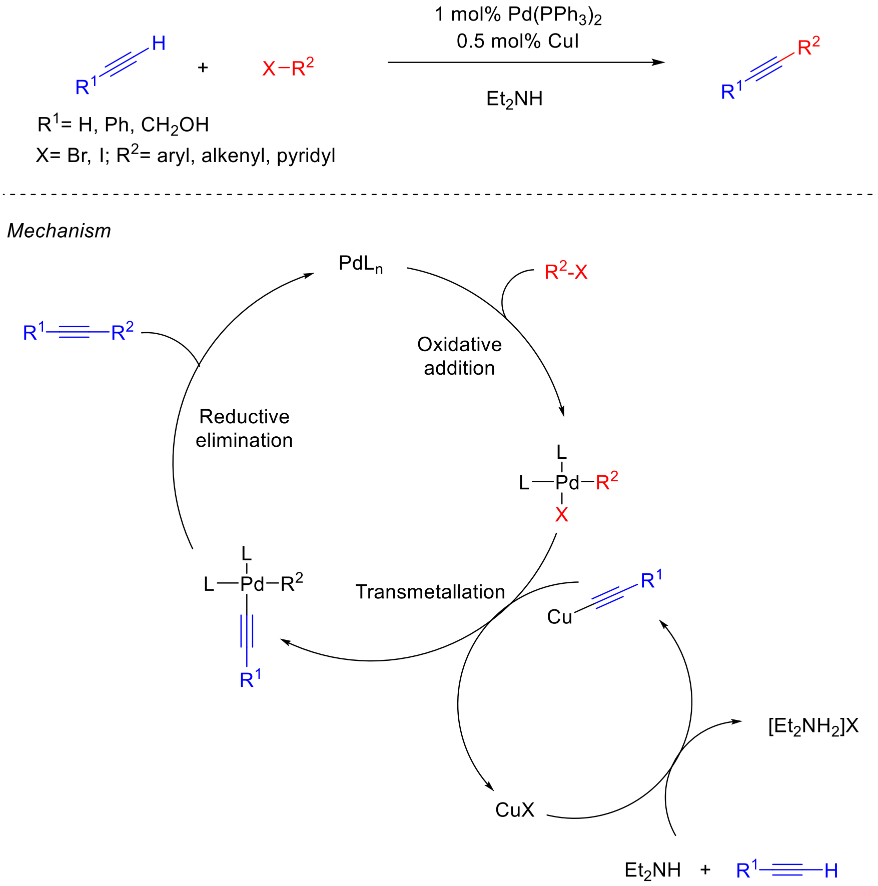
[2] Sonogashira, K.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett*. **1975**, *16*, 4467-4470.



Scheme 1. First example of Sonogashira coupling

After this pioneering work by Sonogashira and coworkers, several research groups focused into the Cu/Pd dual catalytic system which has a wide potential to improve or create new chemical transformations. Some of these strategies are shown below.

1.1.3 Decarboxylative cross-coupling

Decarboxylative cross-coupling between haloarenes and aromatic carboxylic acids has been used as an alternative to traditional methods for the synthesis of biaryl structures. This strategy allows to avoid the use of stoichiometric amounts of organometallic reagents as well as the generation of stoichiometric amount of metal salts as a side product. In this type of transformations, the palladium is used as the cross-coupling catalyst and copper or silver as the decarboxylative catalyst.

In this contest, in 2006, the group of Gooβen[3] reported the use of a copper catalyst to facilitate the decarboxylative cupration of 2-nitrobenzoic acids to form a nucleophilic aryl copper complex which can undergo a coupling reaction with an aryl palladium(II) complex. In this transformation, the arylcopper intermediate (**I**), which is generated in situ, transmetalates with arylpalladium intermediate (**II**) to give a diaryl palladium complex (**III**), which after a reductive elimination gives rise to the corresponding coupled product and regenerate the active Pd(0)

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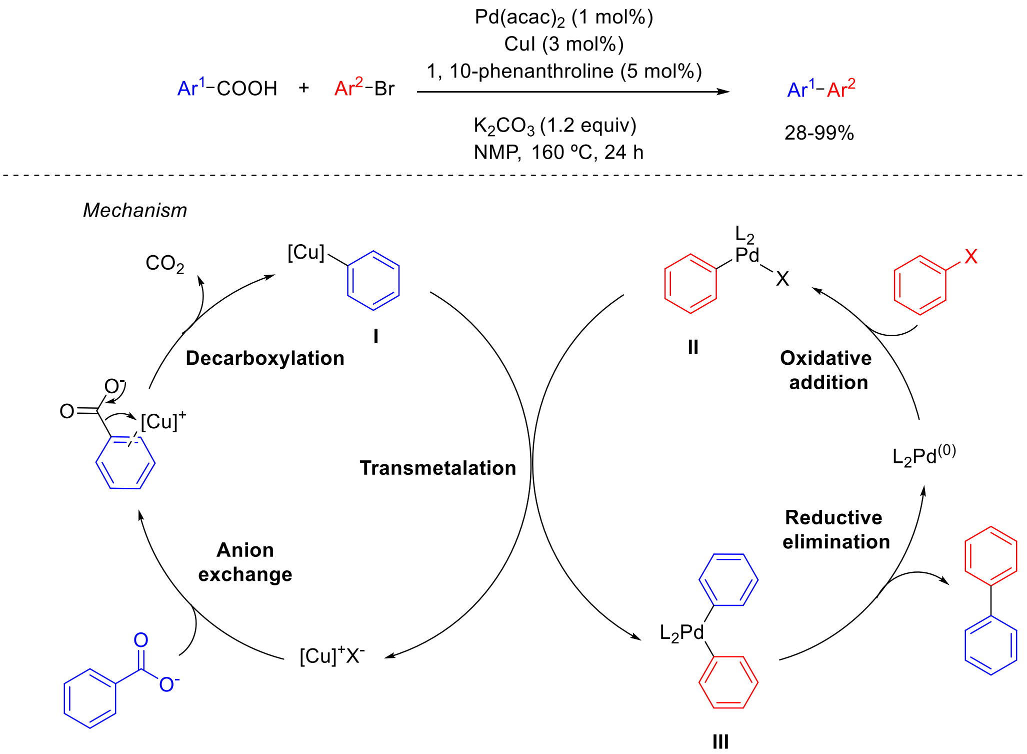
[3] Gooβen, L. J.; Deng, G.; Levy, L. M. *Science* **2006**, *313*, 662-664.

spieces (Scheme 2). Both, electron rich and electron poor electrophiles can be used to give rise to different products with different steric demand and functional groups.



Scheme 2. Cu/Pd-catalyzed decarboxylative cross coupling.

1.1.4 Cross-coupling via C-H activation

Aryl-substituted heterocycles are present in a wide range of pharmaceuticals and natural products. Due to this fact, several synthetic methodologies to achieve this kind of compounds, such as the direct arylation of heteroarenes, have been reported. However, most of them are associated with the use of high catalyst loadings, harsh reaction conditions or even selectivity problems.[4] To solve these issues, the group of Miura, found in 1998, that the use of CuI promotes the Pd-catalyzed arylation of thiazoles and thiophene derivatives.[5]

In 2010, the group of Huang reported a highly efficient method for the direct arylation of heteroarenes using a Cu/Pd catalytic system (Scheme 3).[6] They found that the combination of an air-stable Pd dichloride (PXPd) complex with Cu(XantPhos) iodide forms an excellent dual catalyst system. For this transformation, a mechanism in which the copper catalyst takes part in the critical transmetalation step, being responsible for the high reactivity, is proposed. This process involves the formation of intermediate **II** and its subsequent deprotonation/rearrangement afford **III**. Then, transmetalation of the resulting benzothiazole-

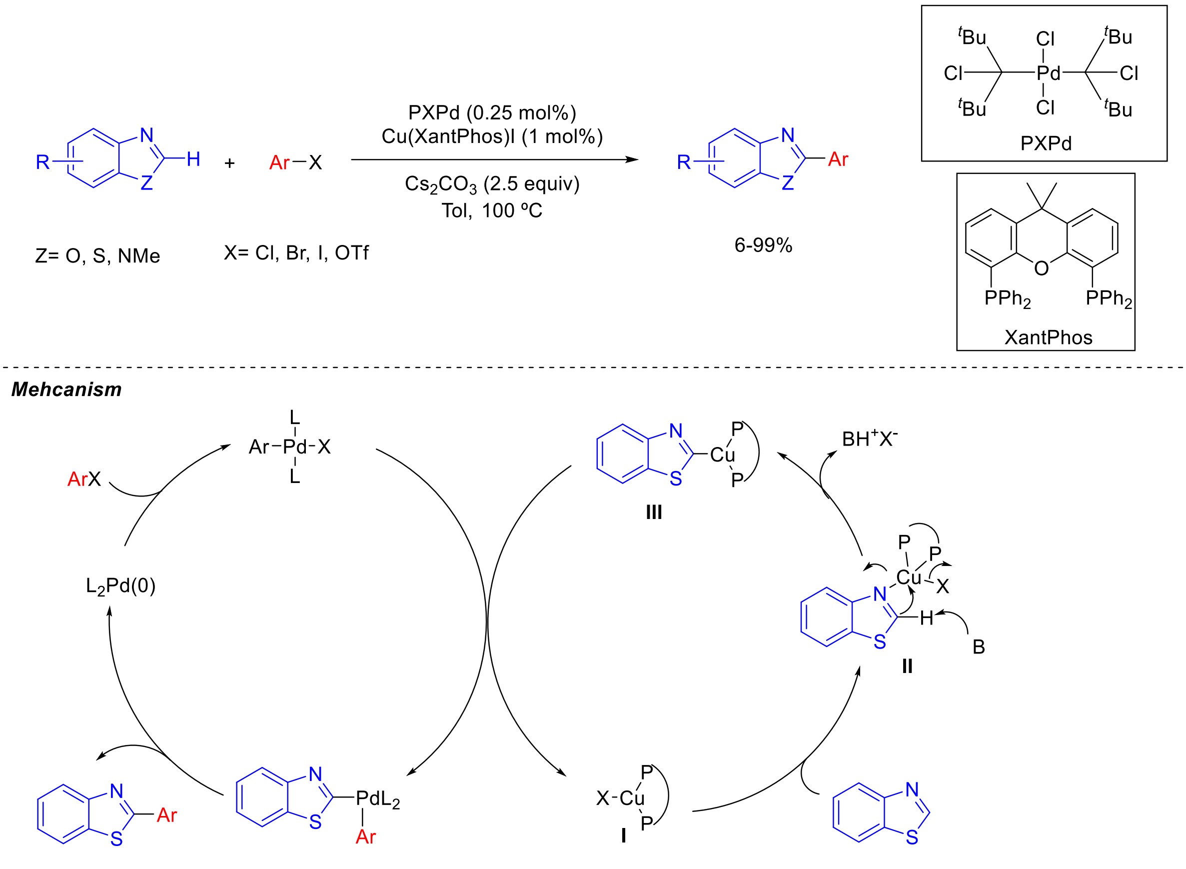
---

[4] a) Dyker, G. *Angew. Chem. Int. Ed.* **1999**, *38*, 1698–1712; b) Jia, C.; Kitamura, T.; Fujiwara, Y. *Acc. Chem. Res.* **2001**, *34*, 633–639.

[5] Pivsa-Art, S.; Satoh, T.; Kawamura, Y.; Miura, M.; Nomura, M. *Bull. Chem. Soc. Jpn.* **1998**, *71*, 467-473.

[6] Huang, J.; Chan, J.; Chen, Y.; Borths, C. J.; Baucom, K. D.; Larsen, R. D.; Faul, M. M. *J. Am. Chem. Soc.* **2010**, *132*, 3674-3675.

copper species (**III**) to the aryl-Pd(II) intermediate, followed by reductive elimination gives rise to the desired product and releases both catalysts.



L= *t*-Bu$_2$PCl; X= I, Br, Cl, OTf; B=CO_3^{2-}

Scheme 3. Pd/Cu co-catalyst system for direct arylation of heteroarenes

In 2015, using a similar strategy, the group of Cazin reported the use of a dual Cu/Pd system involving [Pd(Cl)(cin)(NHC)] and [Cu(Cl)(NHC) to perform the direct arylation of C-H bonds without the presence of a directing group.[7] The mechanistic studies that they carried out, indicate that the copper species performs an acid-base activation to generate the reactive (hetero)arylcopper intermediate (Scheme 4).

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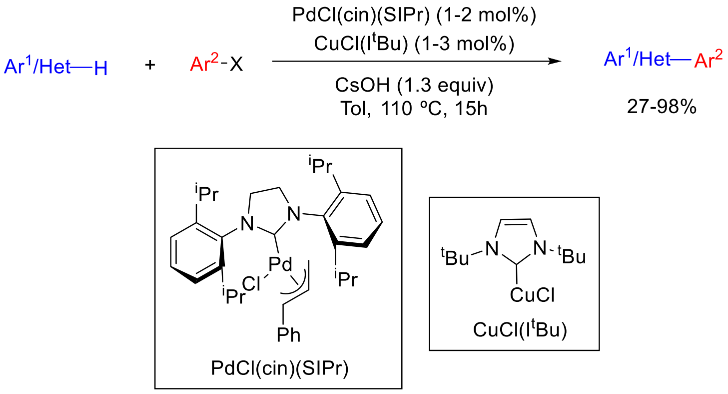
[7] Lesieur, M.; Lazreg, F.; Cazin, C. S. J. *Chem. Commun.* **2014**, *50*, 8927-8929.



Scheme 4. Direct C-H bond arylation using Cu/Pd synergistic catalysis.

1.1.5 Synergistic Cu/Pd-catalyzed enantioselective α-allylation of carbonyl compounds

In 2017, the group of Shibasaki reported the enantioselective α-allylation of α-CF_3 amide with allylic carbonates through synergistic Cu/Pd catalysis to afford γ,δ-unsaturated amides bearing a CF_3 unit at the stereogenic center (Scheme 5a).[8]

This strategy is based on the enolization of α-CF_3 amide with a chiral Cu(I) complex in the presence of a base to generate a chelated Cu enolate **II**. Then, this intermediate reacts with the π-allylPd(II) complex **IV** which was generated from the oxidative addition of the allylic carbonate to de Pd(0), to afford the α-allylated product. The sterocontrol of the transformation is due to the presence of (R,R_P)-Walphos chiral ligand on copper catalyst, giving rise to high levels of asymmetric induction. In the transformation, the Cu-enolate act as soft nucleophile to attack the π-allylPd(II) intermediate **IV** from the opposite side of Pd(II). In this step, the chiral environment of Cu(I) complex is crucial for the steocontrol of the reaction.

Several cinnamyl carbonate derivatives with different substitution patterns and functional groups afforded the desired α-allylated amides in good yields and enantioselectivities. However, for the use of less reactive aliphatic allyl carbonates, the increase of the catalytic loading was necessary.

The use of diastereomerically pure *syn* allyl carbonates afforded the selective formation of *syn* products in a stereospecific manner. This fact suggests that this transformation may proceed via a net stereoretentive outer-sphere mechanism involving a stereoinvertive oxidative addition and followed by stereoinvertive nucleophilic addition (Scheme 5b).

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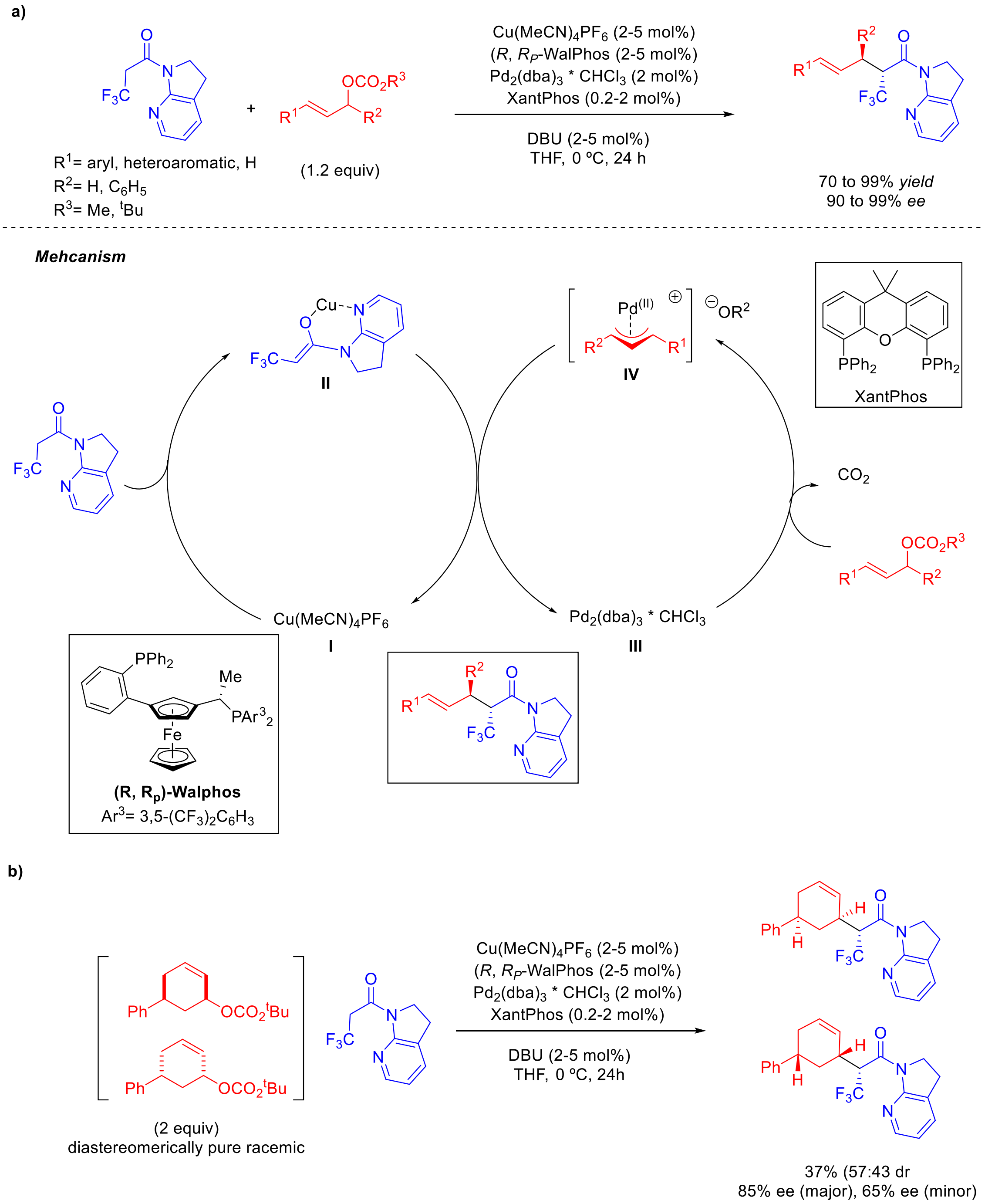
[8] Saito, A.; Kumagai, N.; Shibasaki, M. *Angew. Chem., Int. Ed.* **2017**, *56*, 5551–5555.



Scheme 5. Asymmetric α-allylation of an α-CF_3 amide via Cu/Pd dual catalysis.

In 2017 Zhang and co-workers reported an enantioselective Pd-catalyzed asymmetric allylation of aldimine Schiff base using synergistic Cu/Pd catalysis (Scheme 6).[9] This catalytic system was applied for the asymmetric synthesis of non-natural α,α-dialkyl α-AAs and to the stereoselective access to *N*-terminal α-allylation of small peptides. In this transformation, the aldimine Schiff base could be transformed into a five-membered N,O-bidentate metalated azomethine ylide in a simple manner under the presence of a copper catalyst and a weak base. The rigid structure of this five-membered ylide **I** facilitates the asymmetric induction from the

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[9] Huo, X.; He, R.; Fu, J.; Zhang, J.; Yang, G.; Zhang, W. *J. Am. Chem. Soc.* **2017**, *139*, 9819–9822.

chiral ligand. Furthermore, the use of two chiral reactive species such as **I** and allyl-palladium intermediate **III**, proved to be essential to achieve high stereoinduction since the use of achiral ligand in either the copper or palladium complex gave rise to racemic mixtures of desired product. The transformation tolerates a wide range of allylic acetates with arenes bearing EDG or EWD to afford the products in good yields and enantioselectivities.

Almost simultaneously, Wang and co-workers reported a similar transformation through the use of chiral Cu(I) complex derived from an aldimine Schiff base and an achiral Pd(0) complex derived from an allylic carbonate to afford enantiopure allylation products (Scheme 6b).[10]

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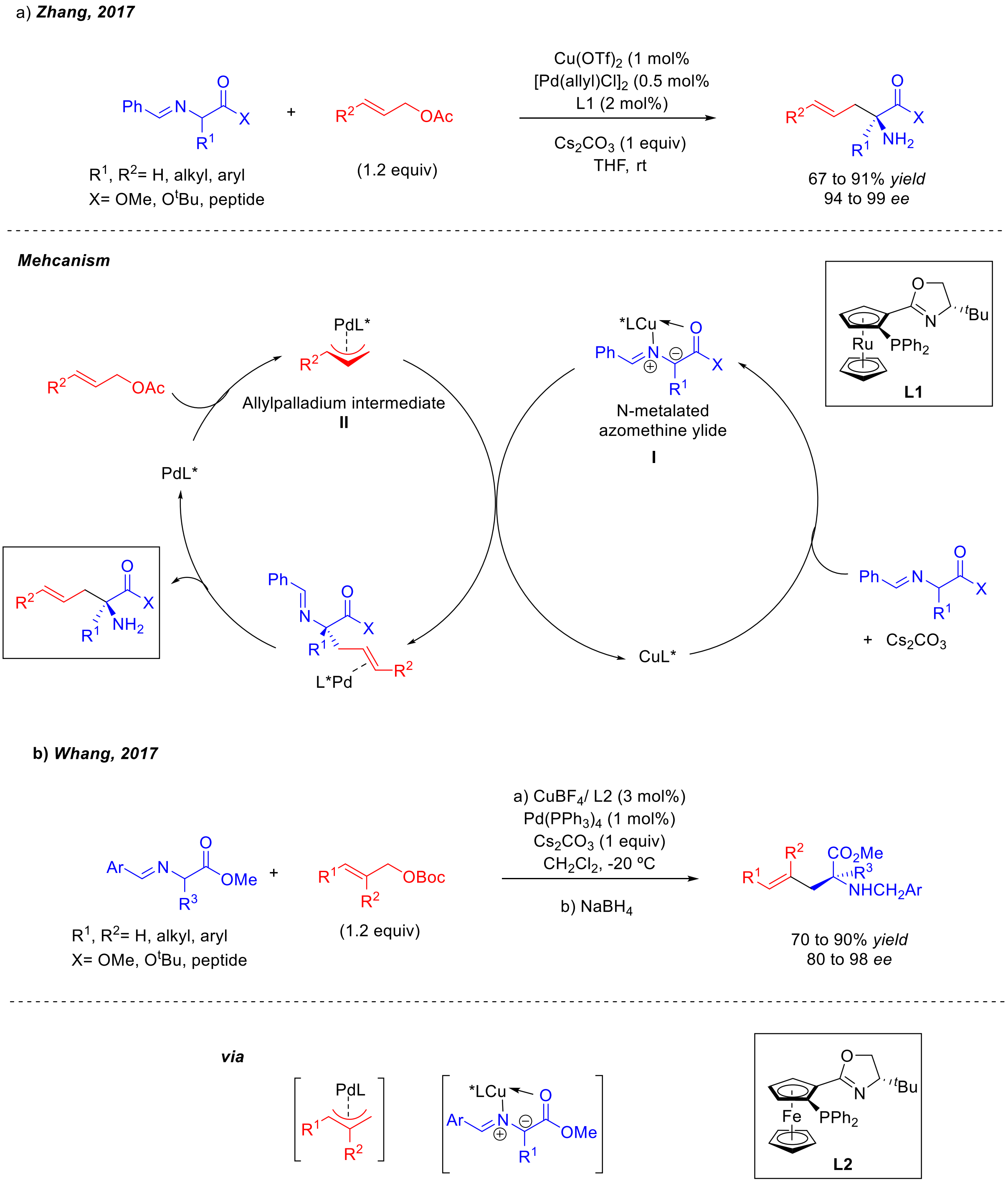
[10] Wei, L.; Xu, S.-M.; Zhu, Q.; Che, C.; Wang, C.-J. *Angew. Chem., Int. Ed.* **2017**, *56*, 12312–12316.



Scheme 6. Synergistic Cu/Pd-catalyzed enantioselective α-allylic alkylation of aldimine esters.

1.1.6 Synergistic CuH/Pd catalysis

Until the synthesis of “Striker’s reagent in 1988,[11] CuH chemistry remained underdeveloped. However, the use of this phosphine-stabilized copper hexamer, $[(Ph_3P)CuH]_6$ allowed the development of highly regioselective reductions of different carbonyl compounds under mild

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[11] Deutsch, C.; Krause, N.; Lipshutz, B. H. *Chem. Rev.* **2008**, *108*, 2916-2927.

conditions and good functional group tolerance. Despite the several difficulties associated with the catalytic generation of copper (I) hydrides, this metodology (catalytic in copper and based on dihydrogen or mild hydrilic sylanes as stoichiometric reducing agents) represents a powerful tool for the developing of enantioselective C-H bond forming reactions in a catalytic manner. In this section several recent advances in this area will be presented.

a) α-Allylation of carbonyl compounds

In 2013, Riant and co-workers successfully reported an asymmetric tandem 1,4-reduction/allylation of α,β-unsaturated ketones using CuH/Pd synergistic catalysis for the synthesis of optically active allylated ketones (Scheme 7).[12]

In this process, a copper hydride is generated from reaction between a Cu(I) chloride and a hydrosilane. The regioselective conjugate hydride addition to a cyclic α,β-unsaturated ketone affords a Cu(I) enolate, which can react with a π-allylPd(II) complex, generated from oxidative addition of an allyl carbonate into a Pd(0) complex. Formation of the *O*-allylation product can take place at room temperature. However, the α-allylated product is selectively formed at slightly higher temperatures. It was shown that the silyl enolate does not react with π-allylPd(II) without the presence of a copper co-catalyst thus demonstrating that copper enolate **A** is essential for this transformation. With this methodology several enantioenriched ketones bearing a quaternary center could be easily formed in moderate to good yields and high enantioselectivities. Additionally, this dual catalytic system also was reported for the α-allylation of α,β-unsaturated malonates and coumarins.[13]

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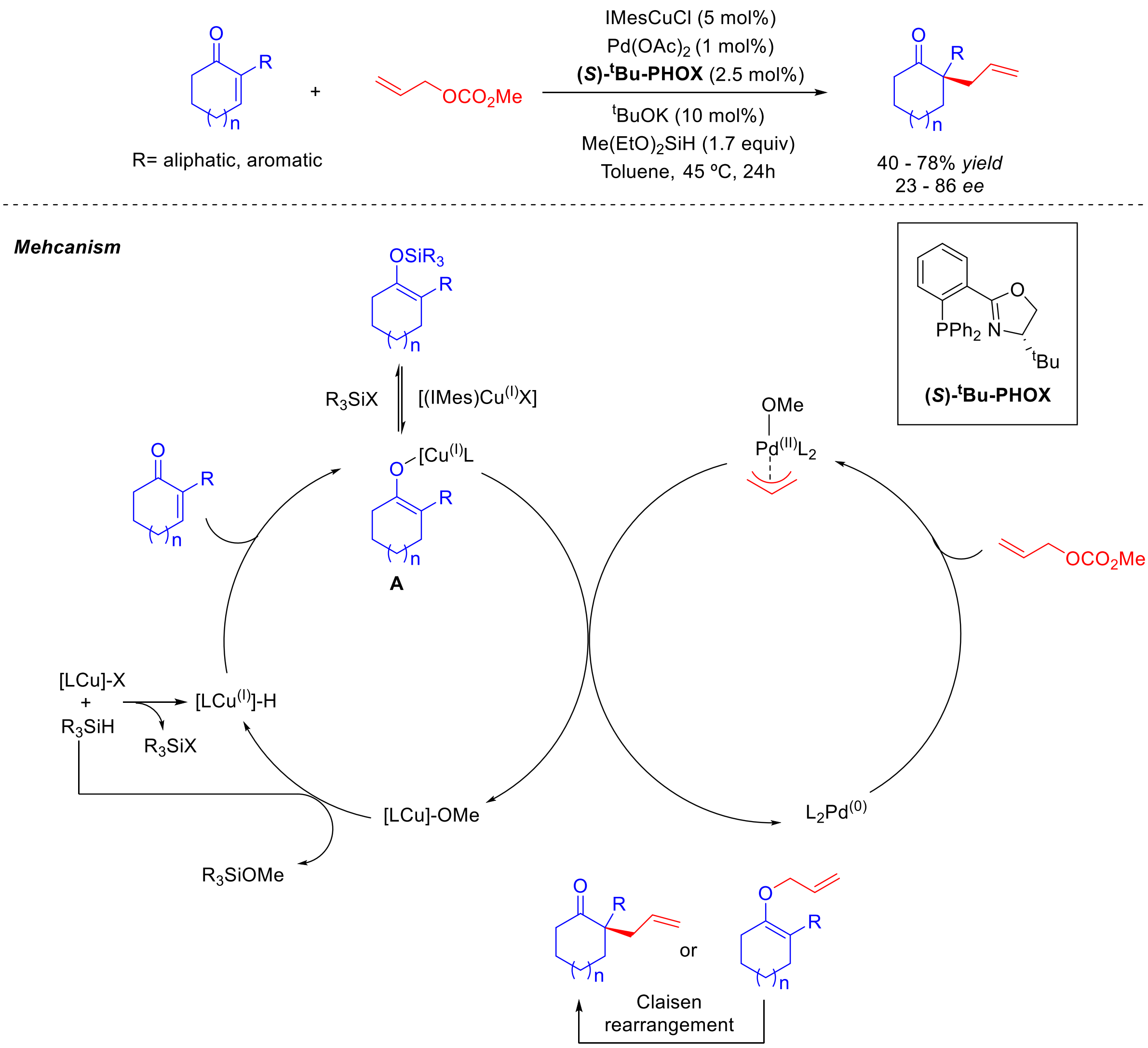
[12] Nahra, F.; Macé, Y.; Lambin, D.; Riant, O. *Angew. Chem. Int. Ed*. **2013**, *52*, 3208-3212.

[13] Nahra, F.; Macé, Y.; Boreux, A.; Billard, F.; Riant, O. *Chem. - Eur. J.* **2014**, *20*, 10970−10981.



Scheme 7. Synergistic Cu/Pd-catalyzed enantioselective α-allylation of unsaturated ketones

b) Enantioselective hydroarylation of vinylarenes

An asymmetric synthesis of 1,1-diarylalkanes, important intermediates of pharmaceutical drug agents and natural products, was reported in 2016 by Buchwald using synergistic Cu/Pd catalysis (Scheme 8).[14] The proposed mechanism for this transformation is shown in Scheme 8. First, in the copper catalytic cycle, the formation of active CuH catalyst **I** would occur through the use of Cu(I) or Cu(II) in combination with a metal alkoxide base, a chiral ligand and a hydrosilane. Then, a regio- and enantioselective hydro-cupration of the corresponding olefin forms stereodefined Cu(I) benzylic intermediate **III**. The palladium catalytic cycle starts with the oxidative addition of aryl bromide to Pd(0) to afford complex **VI**. Then, the both catalytic cycles converge via a stereospecific transmetalation of organocopper intermediate **III** with **VI** to afford chiral alkyl-aryl Pd(II) intermediate **V**. Finally, a stereoretentive reductive elimination affords the enantioenriched diarylalkane and regenerates both catalysts.

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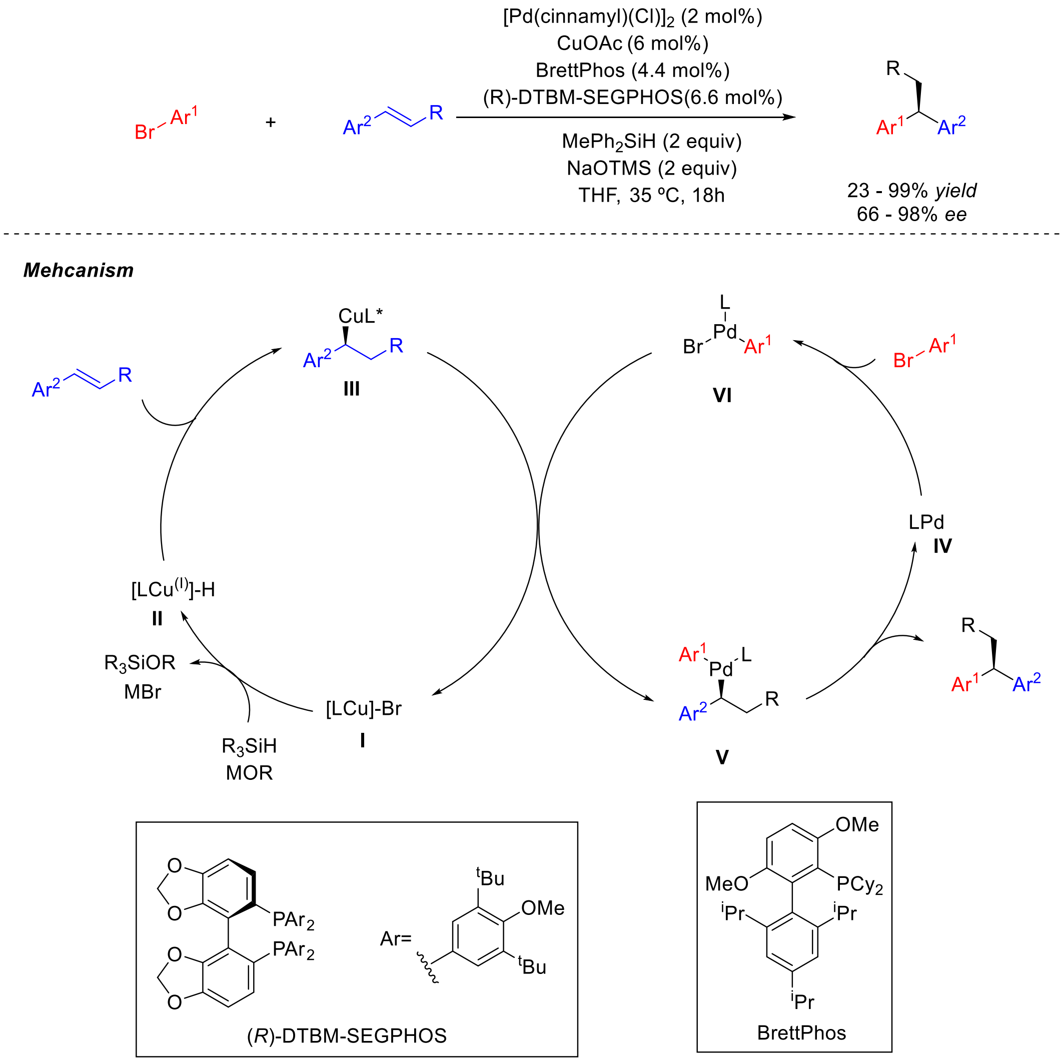
[14] Friis, S. D.; Pirnot, M. T.; Buchwald, S. L., *J. Am. Chem. Soc.* **2016**, *138*, 8372-8375.

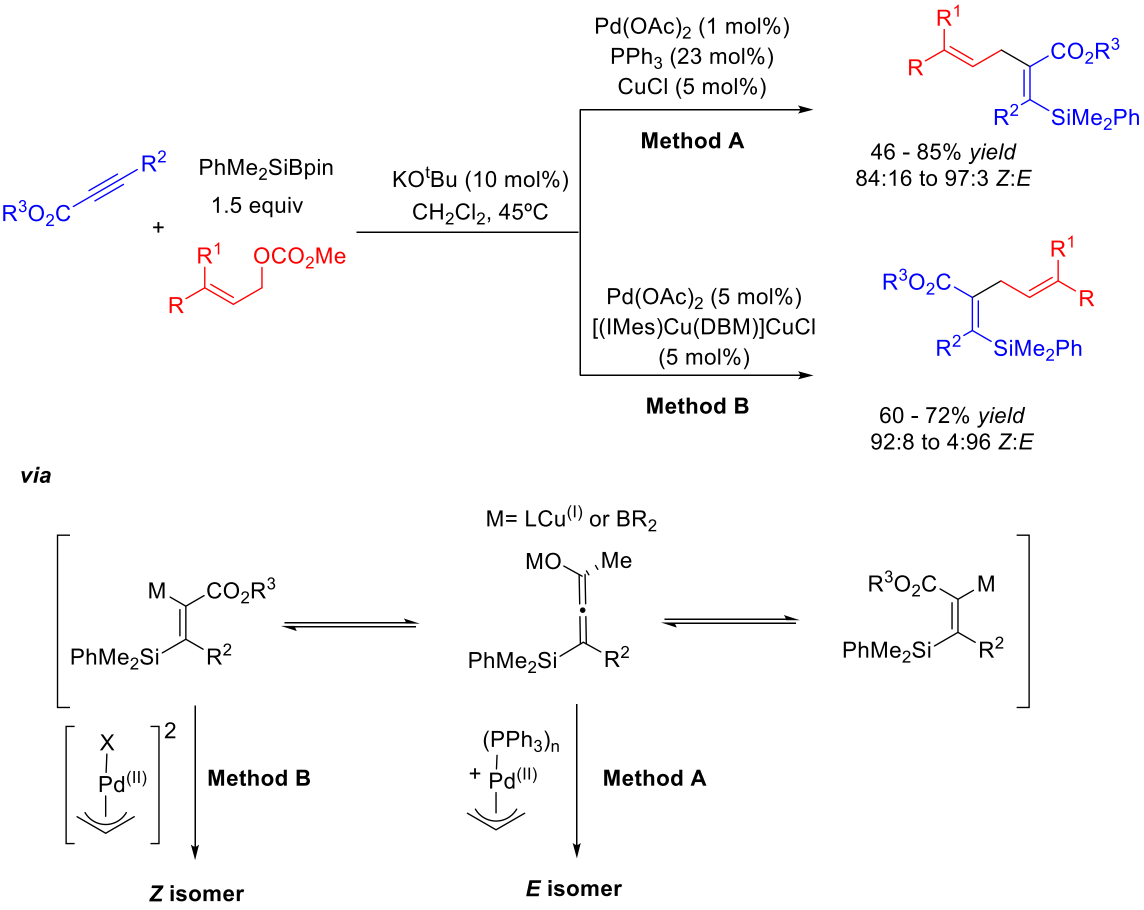
It was found that the best conditions involved a chiral Cu/(*R*)-DTBM-SEGPHOS complex in combination with a Pd/BrettPhos co-catalyst. Under this synergistic catalysis regime, different aryl bromides afforded the corresponding1,1-diarylalkanes in good yields and excellent enantioselectivities. Moreover, a wide range of vinylarenes, such as *ortho*- and β-substituted styrenes were shown to be efficient for the transformation.



Scheme 8. Enantioselective Pd/Cu-catalyzed hydroarylation of styrenes for the synthesis of 1,1-diarylalkanes.

1.1.7 Synergistic Cu-Si and Pd catalysis

Silylcupration of unsaturated compounds is a simple methodology for the catalytically generation of active silyl organocopper intermediates.[15] This strategy can be used in combination with Pd-catalyzed cross-coupling transformations. In 2014, Riant and co-workers reported the use of silylcopper(I) species, generated by silylcupration of propynoates, combined with a Pd-catalyzed allylic alkylation to afford highly substituted and functionalized vinylsilanes (Scheme 9a).[16] The synthetic strategy entailed the Cu-mediated *syn* silyl-cupration across the alkyne followed by a Pd-catalyzed allylation. The reaction afforded (*Z*) isomer when PPh_3 was used. However, when PPh_3 was not used, isomer (*E*) was obtained. The selectivity of the process is associated with the reactivity between the π-allylPd(II) species formed under the two diverging conditions. As is shown in scheme 9, when no phosphine was used, dimeric π-allylPd(II) intermediate is formed by oxidative addition of Pd(0) in the allyl carbonate. This intermediate directly undergoes transmetalation with alkenyl copper to afford the *Z* isomer. In other way, when PPh_3 was used, π-allylPd(II)[PPh3]$_n$ complex is formed. Moreover, the presence of the phosphine ligand inhibits the direct transmetalation pathway, giving rise to isomerization of alkenyl copper into allenoate, which then reacts from the less hindered side with the allyl-palladium intermediate to afford the (*E*) isomer.



Scheme 9. Cu/Pd catalyzed allylsililation of alkynes.

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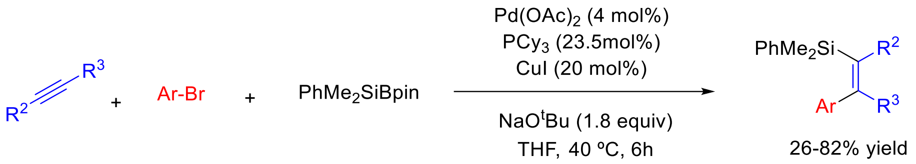
[15] Oestreich, M.; Hartmann, E.; Mewald, M. *Chem. Rev*. **2013**, *113*, 402– 441.

[16] Vercruysse, S.; Cornelissen, L.; Nahra, F.; Collard, L.; Riant, O. *Chem. Eur. J.* **2014**, *20*, 1834-1838.

The Cu/Pd-catalyzed arylsylilation of alkynes through a three component reaction has been reported by Nozaki and co-workers. By employing an alkyne silylcupration strategy, the authors developed a methodology in which the silylilate alkenylcopper interemdiate that results from the alkyne silylcupration is efficiently cross-coupled with an aryl?-Pd(II) complex. This transformation gives access to 1,2-disubstituted 2-arylethenylsilanes (Scheme 10).[17]



Scheme 10. Cu/Pd-catalyzed arylsilylation of alkynes

Besides transformations involving silylcupration of unsaturated hydrocarbons, another interesting synthetic methodology to access silylated structures is the used of catalytically generated alkoxyalkyl copper(I) species generated from aldehydes. In this regard, Ohmiya reported the use of α-alkoxyalkyl copper(I) species in Pd-catalyzed cross coupling reactions.[18] In this transformation the α-alkoxyalkyl copper(I) is generated in situ from aldehydes via the addition of silylcopper(I) species followed by a 1,2-Brook rearrangement. Then, the resulting organocopper intermediate is trapped by the catalytic Pd(II) complex (Scheme 11a). By using a chiral fluorinated NHC/Cu complex they could render this reaction enantioselective (Scheme 11b).[19]

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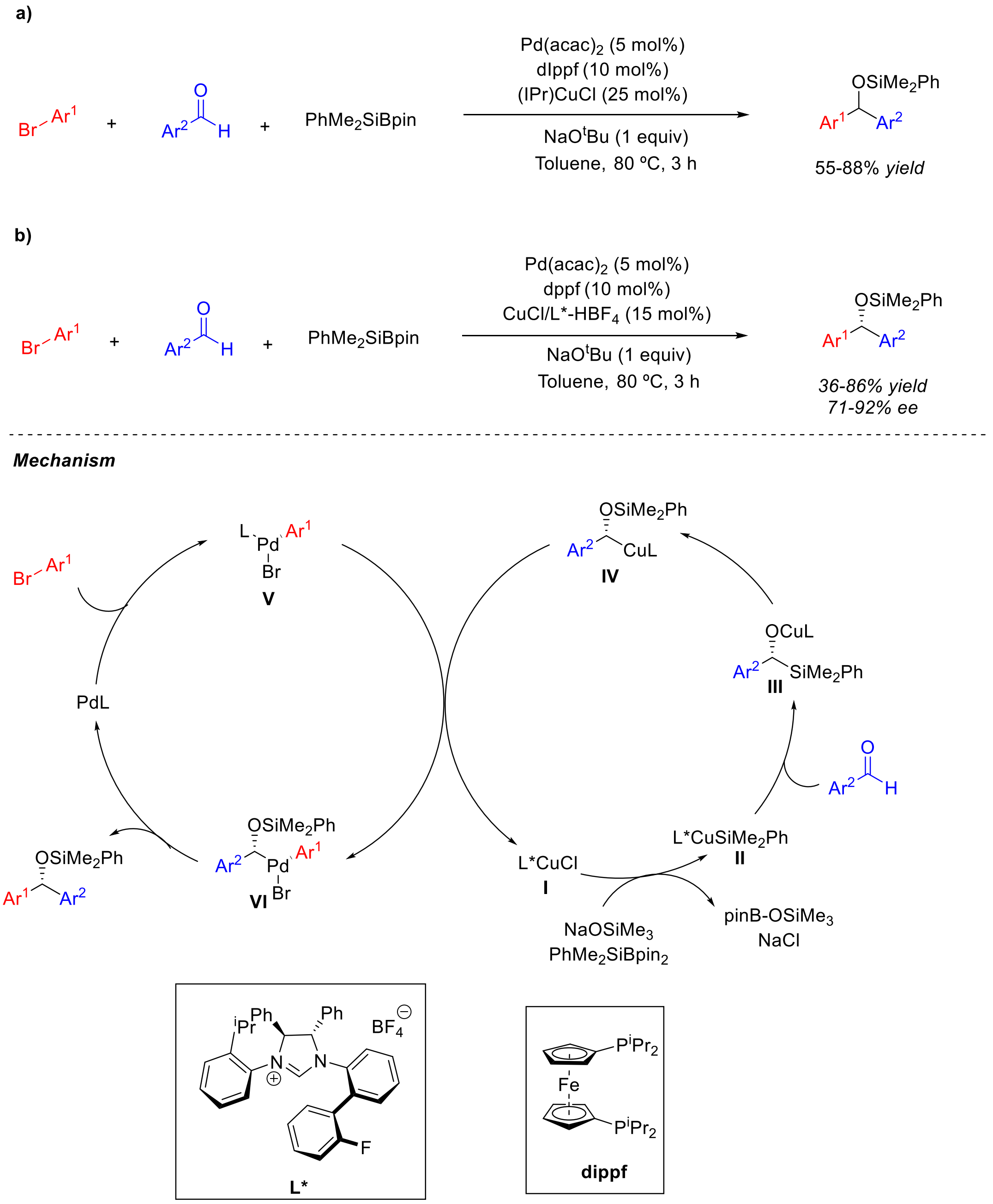
[17] Shintani, R.; Kurata, H.; Nozaki, K. *J. Org. Chem.* **2016**, *81*, 3065-3069.

[18] Takeda, M.; Yabushita, K.; Yasuda, S.; Ohmiya, H. *Chem. Commun*. **2018**, *54*, 6776–6779.

[19] Yabushita, K.; Yuasa, A.; Nagao, K.; Ohmiya, H. *J. Am. Chem. Soc.* **2019**, *141*, 113-117.

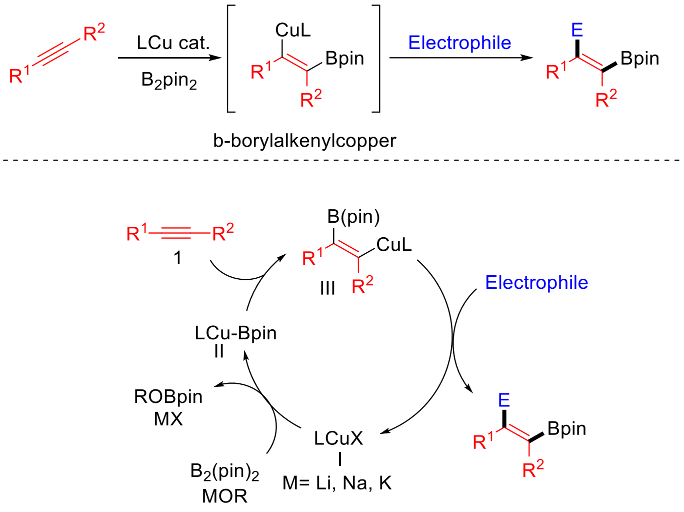


Scheme 11. Cu/Pd-catalyzed coupling of aldehydes, aryl bromides, and Suginome reagent.

The chiral induction arises from the stereoselective addition of chiral silylcopper species to the aldehydes. Then, the chiral addition product undergoes a stereoinvertive 1,2-Brook rearrangement to afford a stereodefined α-silyloxybenzyl copper species **IV**. This species undergoes stereoretentive transmetalation with the arylpalladium intermediate to afford palladium complex **VI**. Finally, reductive elimination affords the enantioenriched product (Scheme 11c).

1.1.8 Synergistic Cu/Pd bimetallic catalysis for carboboration of unsaturated hydrocarbons

In the recent years, Cu-catalyzed carboboration of unsaturated hydrocarbons such as alkynes, alkenes or allenes has become a powerful tool for their conversion into versatile alkenylboronates.[20] The use of this organic pro-nucleophiles represents an alternative to the use of stoichiometric reagents in cross-coupling reactions, as well as the need to preform and isolate the nucleophile. In scheme 12 is shown the mechanism for Cu-catalyzed carboboration of alkynes. This transformation entails the catalytic formation of a nucleophilic β-boryl substituted alkenylcopper intermediate **III** and subsequent electrophilic trapping. The process starts with the insertion of the alkyne into a borylcopper complex **II**, which is previously generated by σ-bond metathesis reaction between a copper alkoxide and a diboron reagent.[21] These boryl-substituted organocopper complexes can directly couple with different carbon electrophiles.



Scheme 12. Copper-catalyzed carboboration of alkynes.

In some cases, due to the reduced nucleophilicity of the organocopper regent, the use of a co-catalyst is necessary to activate the electrophile and facilitate the trapping. Moreover, the presence of a second catalyst also offers an alternative selectivity to copper in the cross-coupling step (e.g. S_N2' vs S_N2 regioselectivity in allylic substitution transformation). In this context, synergistic Cu/Pd bimetallic catalysis has become a powerful tool for the selective carboboration of unsaturated substrates, such as alkynes, alkenes, or dienes.

A general mechanism for this type of transformation is shown in Scheme 13. In the copper cycle, the first step is the formation of the active boryl-copper species (**I**) which then undergoes borocupration of the unsaturated hydrocarbon to provide beta-boryl substituted organocopper intermediate **II**. In the second catalytic cycle, the first step is the oxidative addition

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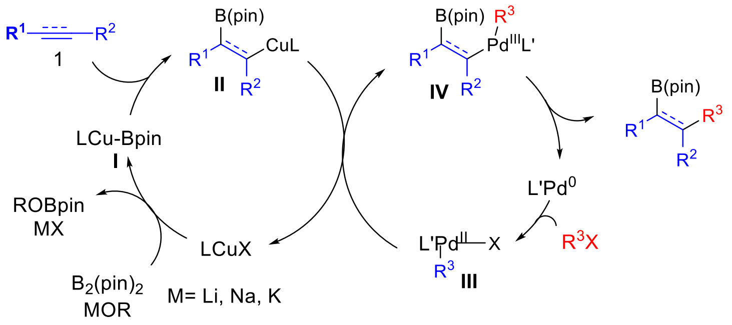
[20] a) K. Semba, K.; Fujihara, T.; Terao, J.; Tsuji, Y. *Tetrahedron*, **2015**, *71*, 2183-2197; b) Yoshida, H. *ACS Catal.* **2016**, *6*, 1799-1811; c) Neeve, E. C.; Geier, S. J.; Mkhalid, I. A.: Westcott, S. A.; Marder, T. B. *Chem. Rev.* **2016**, *116*, 9091-9161; d) Whyte, A.; Torelli, A.; Mirabi, B.; Zhang, A.; Lautens, M. *ACS Catal*. **2020**, *10*, 11578–11622.

[21] Ito, H.; Yamanaka, H.; Tateiwa, J.; Hosomi, A. *Tetrahedron Lett.* **2000**, *41*, 6821-6825.

of the corresponding electrophile to Pd(0) to generate Pd(II) complex **III**. Then, transmetallation between intermediates **II** and **III** gives rise to intermediate **IV.** Finally, a reductive elimination releases the corresponding product and both transition metal catalysts are regenerated.



Scheme 13. General mechanism for the Cu/Pd catalyzed carboboration of unsaturated substrates.

These borylative couplings require the control of several issues: 1) competitive borylation of the electrophile, that can be catalyzed by both catalysts. This process must be suppressed with the efficient formation of LCu-Bpin catalyst and its chemoselective reaction with the unsaturated hydrocarbon; 2) Ligand exchange must be suppressed; and 3) Kinetics of both catalytic cycles must be compatible to avoid formation of undesired products.

Using this synergistic catalysis regime, several carboboration reactions of unsaturated compounds have been reported and they are outlined below.[22]

1.1.8.1 Cu/Pd catalyzed carboboration of alkenes

a) Arylboration of alkenes

Semba/Nakao[23] and Brown[24], reported independently in 2014, the use of transient β-borylalkylcopper intermediates in coupling reactions of styrene derivatives with aromatic bromides and B_2pin_2 using synergistic Cu/Pd catalysis. This transformation led to the formation of 2-boryl-1,1-diarylethanes in good yields, chemo- and regioselectivities (Scheme 14). The mechanism for this transformation consists in two individual cycles involving Cu and Pd catalysis. The palladium cycle is initiated by the oxidative addition of the corresponding aryl halide to Pd(0) to afford intermediate **VI**. In other hand, the copper catalytic cycle starts with the formation of borylcopper intermediate **III** which is generated by the reaction of copper alkoxide **II** with B_2pin_2. Then, the addition of the borylcopper across the alkene afforded the intermediate **IV**, that after a transmetalation step with **VI** and reductive elimination afforded the corresponding product and regenerate both catalytic cycles.

Brown further demonstrated that his methodology can be applied to the use of cyclic styrene derivatives to obtain the *trans*-diastereomer as the major product. This selectivity is due to the fact that although the insertion of the alkene into the boryl copper complex occurs with *syn* selectivity (intermediate **IV**), it was proposed that the formation of *trans*-diastereomer results

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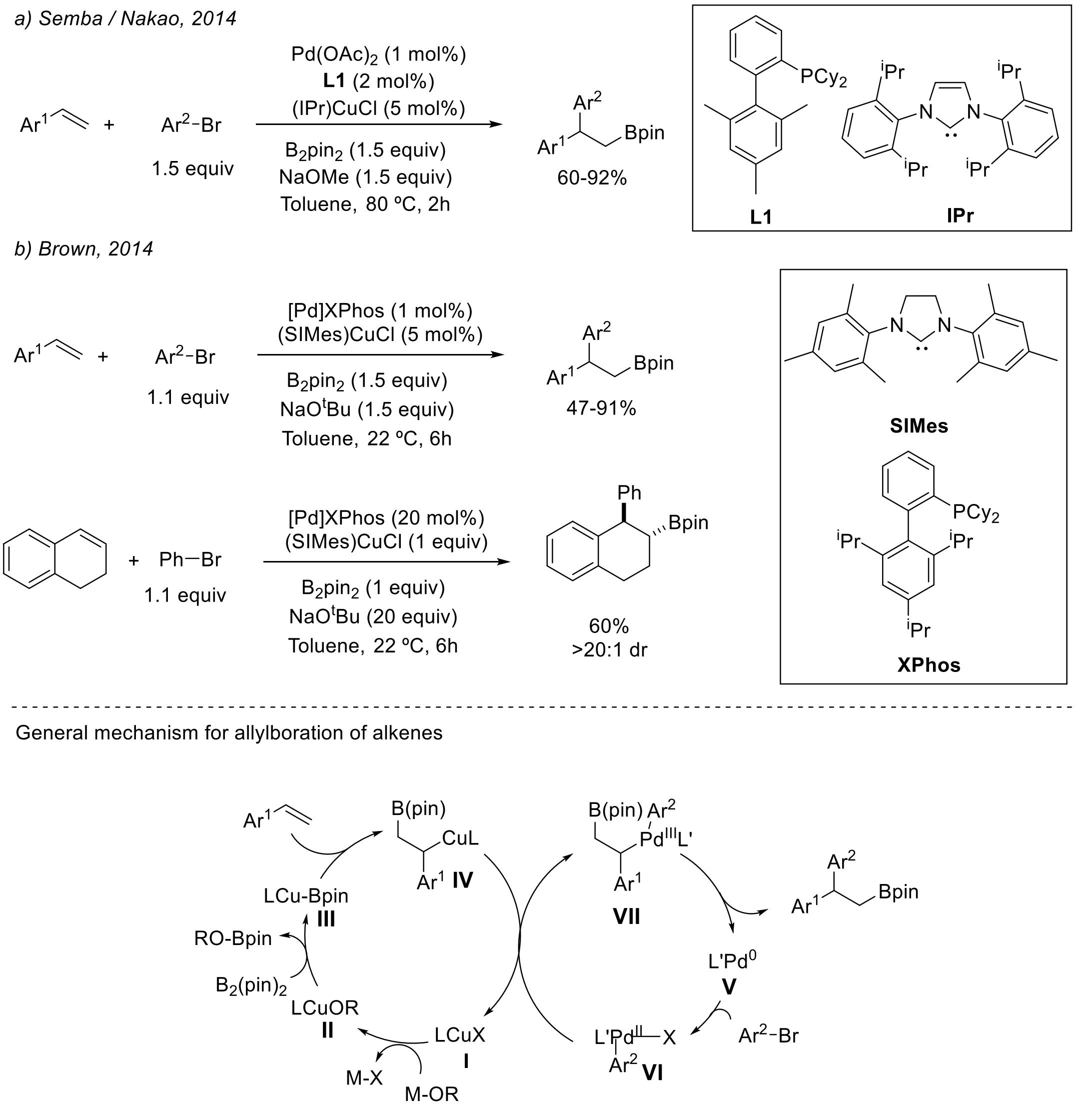
[22] For a review, see: Rivera-Chao, E.; Fra, L.; Fañanás-Mastral, M. *Synthesis* **2018**, *50*, 3825–3832.
[23] Semba, K.; Nakao, Y. *J. Am. Chem. Soc.* **2014**, *136*, 7567-7570.
[24] Smith, K. B.; Logan, K. M.; You, W.; Brown, M. K. *Chem. Eur. J.* **2014**, *20*, 12032-12036.

from a Cu-Pd transmetallation which proceeds with inversion of configuration, followed by a stereoretentive reductive elimination (Scheme 14b).



Scheme 14. Cu/Pd-catalyzed arylboration of styrene derivatives.

Later, the group of Brown reported a modified method for the arylboration of acyclic styrene derivatives, which provides selective access to both *syn* and *anti*-diastereomers (Scheme 15).[25] The use of RuPhos as ligand in the palladium catalyst and SIMes-CuCl in THF (conditions A) afforded the *syn* product in modereate to good yields and high diastereoselectivities. However, when P^{i}Bu was used instead of RuPhos, and base and solvent were changed to NaO^{t}Amyl and toluene (conditions B), the *anti-* diastereomer was obtained selectively. Thus, control over the diastereoselectivity is due to the effect of solvent and ligand in the palladium complex. In order to better understand this transformation they carried out the reaction in a stepwise manner (Scheme 14b). After the formation of C (sp^3)-Cu complex **I** they submitted to reaction conditions A to afford selectively the *syn* product. They proposed that the stereoretentive transmetalation step proceed through transition state **II**. On the other hand, when they submitted the copper complex A to reaction conditions B to afford the anti- product, they proposed the formation of

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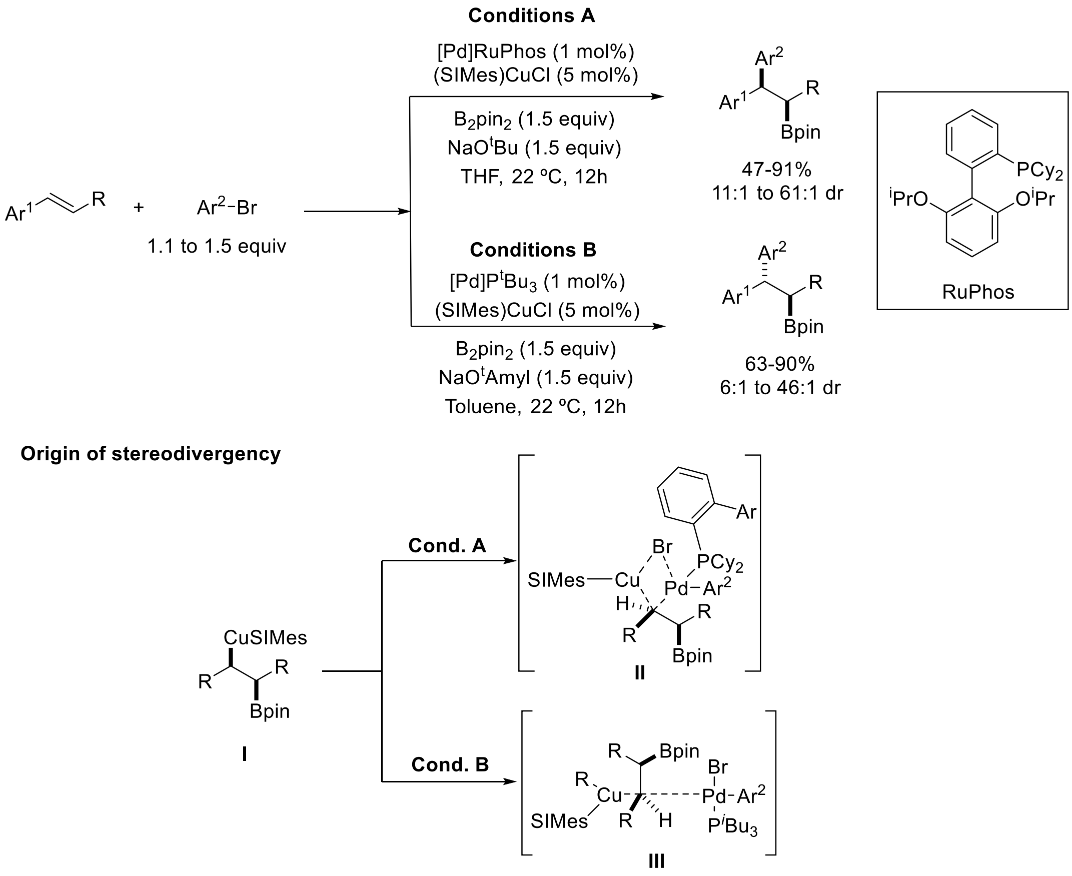
[25] Logan, K. M.; Smith, K. B.; Brown, M. K. *Angew. Chem. Int. Ed.* **2015**, *54*, 5228-5231.

the putative transition state **III** for the stereoinvertive transmetalation. A requirement of this model is the coordination of the copper atom with an external nucleophile to facilitate transmetalation.



Scheme 15. Diastereoselective Cu/Pd-catalyed arylboration of styrene derivatives

The enantioselective arylboration of styrenes combining the use of a chiral copper catalyst with an achiral palladium co-catalyst was also described. In this context, Logan and Brown[26] reported the enantioselective arylboration of alkenylarenes using chiral Cu-NHC complex **C1.** The reaction works well for a variety of alkenylarenes, providing access to biologically active molecules from simple starting materials (Scheme 16a). A similar strategy was used by Liao and co-workers.[27] They reported a three component enantioselective Cu/Pd-catalyzed borylative coupling of styrene derivatives with aryl or alkenyl iodides. For this transformation they used a copper catalyst bearing a chiral phosphine-sulfoxide ligand *(R)*-SOP-1 in combination with an achiral Pd(dppf)Cl_2 co-catalyst (Scheme 16b).

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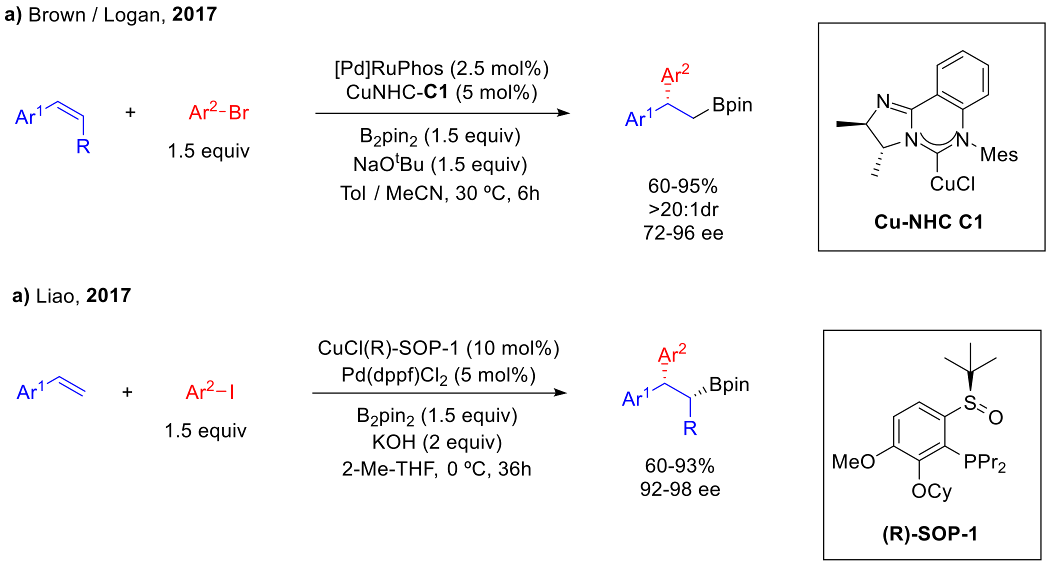
[26] Logan, K.; Brown, K. *Angew.Chem.Int. Ed.* **2017**, *56*, 851–855.

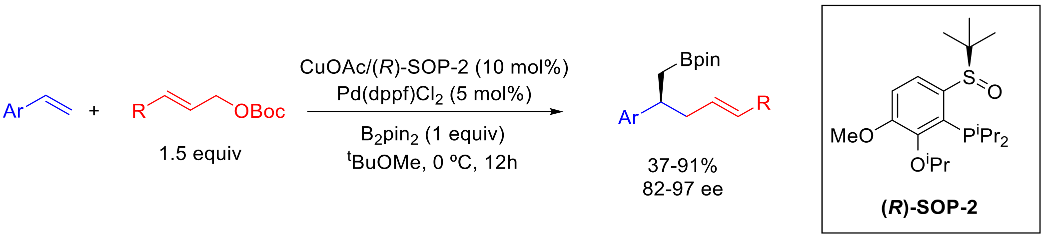
[27] Chen, B.; Cao, P.; Yin, X.; Liao, Y.; Jiang, L.; Ye, J.; Wang, M.; Liao, J. *ACS Catal.* **2017**, *7*, 2425-2429.



Scheme 16. Asymmetric Cu/Pd catalyzed arylboration of styrene derivatives.

b) Allylboration of alkenes

The group of Liao reported a similar strategy for the allylboration of styrenes also using a chiral Cu/SOP complex (Scheme 17).[28] In this case, the chiral organocopper intermediate generated by the enantioselective borylcupration of styrene undergoes a transmetalation reaction with a π-allylpalladium complex, generated through oxidative addition of the allylic carbonate into the Pd(0) catalyst in to a stereochemically retentive manner. This method represents the first example of asymmetric intermolecular 1,2-carboboration of alkenes in which the desired products were obtained in good levels of yield and enantioselectivities. Moreover, a broad functional group tolerance was observed.



Scheme 17. Enantioselective Cu/Pd-catalyzed allylboration of styrenes.

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[28] Jia, T.; Cao, P.; Wang, B.; Lou, Y.; Yin, X.; Wang, M.; Liao, J. *J. Am. Chem. Soc.* **2015**, *137*, 13760-13763.

1.1.8.2 Cu/Pd catalyzed carboboration of alkynes

a) **Arylboration of alkynes**

The groups of Semba/Nakao[29] and Cazin[30] independently reported the regio- and stereoselective synthesis of tetrasubstituted alkenyl boronates using a Cu/Pd-catalyzed arylboration of alkynes. In this transformation alkynes were used as $C(sp^2)$ pro-nucleophiles in a Pd-catalyzed cross-coupling with an aryl halide (Scheme 18a). The method reported by Cazin is based on the use of Cu-NHC and Pd-NHC catalysts and is limited to the use of alkyl(aryl)acetylenes (Scheme 17a). On the other hand, the work reported by Semba and Nakao is based on the use of a biaryl phosphine such as RuPhos as ligand for both metals. This protocol allows for the arylboration of diarylacetylenes, dialkylacetylenes and alkyl(aryl)acetylenes (Scheme 18b). However, the use of unsymmetrical diaryl alkynes afforded practically equimolar amount of α- and β-borylated isomers. The use of terminal alkynes is not possible in both transformations.

The group of Brown reported de Cu/Pd-catalyzed (hetero)arylboration of alkynes (Scheme 18c).[31] In this transformation, they reported the use of piridylidene-Cu complex **A** which efficiently promotes heteroarylboration of alkenes. [32] The combination of this copper complex and APhosPdG3 afforded good results with alkyl(aryl)alkynes, dialkyl- and diarylalkynes. Heteroaryl bromides such as indoles, furans or pyridines can be coupled with different hetoaryl-substituted alkynes to afford α-α-bis(hetero)arylalkenes in good yield and with total selectivity towards the β-borylated product.

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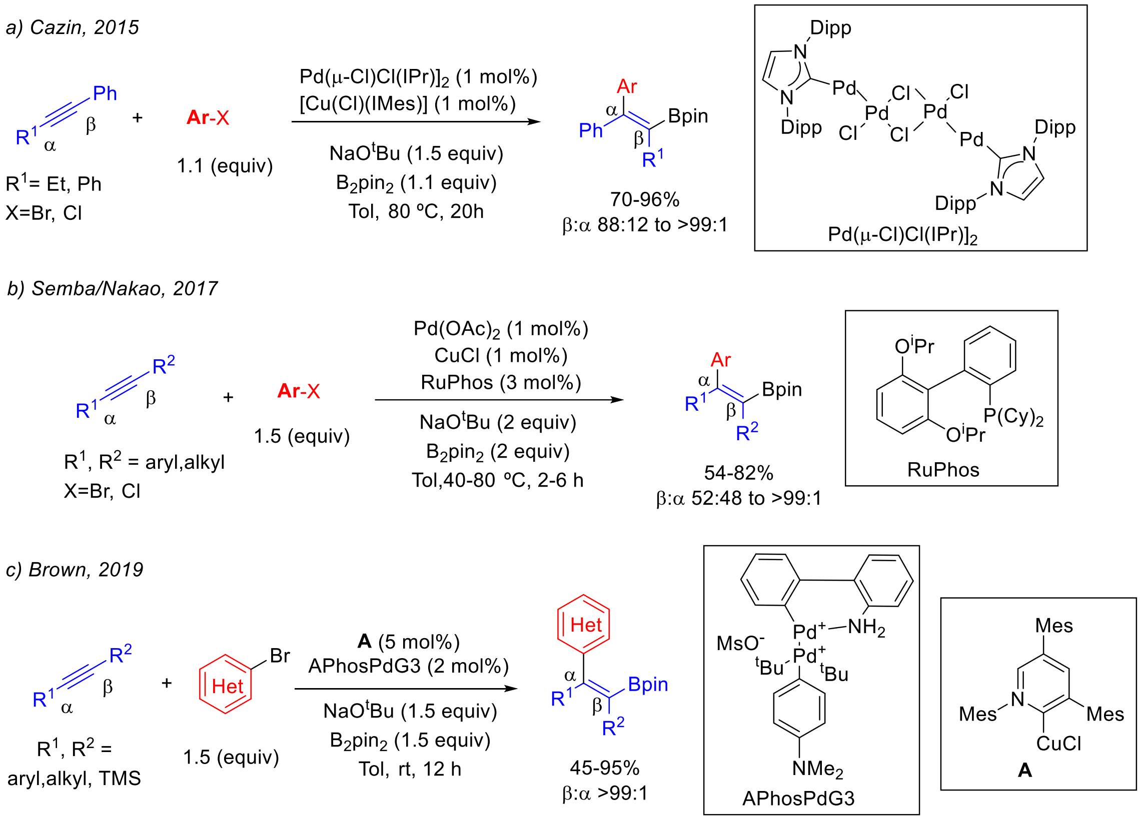
[29] Semba, K.; Nakao, Y. *Bull. Chem. Soc. Jpn*. **2017**, *90*, 1340-1343.

[30] Lesieur, M.; Bidal, Y. D.; Lazreg, F.; Nahra, F.; Cazin, C. S. J. *ChemCatChem* **2015**, *7*, 2108-2112.

[31] Huang, Y.; Bergmann, A. M.; Brown, M. K. *Org. Biomol. Chem*. **2019**, *17*, 5913-5915.

[32] Huang, Y. Brown, M. K. *Angew. Chem. Int. Ed*. **2019**, *58*, 6048-6052.



Scheme 18. Synergistic Cu/Pd-catalyzed arylboration of alkynes.

b) Allylboration of alkynes

In our group, we reported a synergistic Cu/Pd-catalyzed allylboration of alkynes (Scheme 19).[33] It is a three-component coupling between alkynes, B_2pin_2 and allylic carbonates and represents the first example of the use of a catalytically generated β-borylalkenylcopper species in palladium catalyzed allylic substitution. This methodology is based on the use of CuCl-PCy_3 and Pd(dba)$_2$-dppf as catalytic system and affords borylated 1,4-skipped dienes in very good yields and selectivities. In this process the β-borylated product is selectively formed in a S_N2 type allylic substitution.

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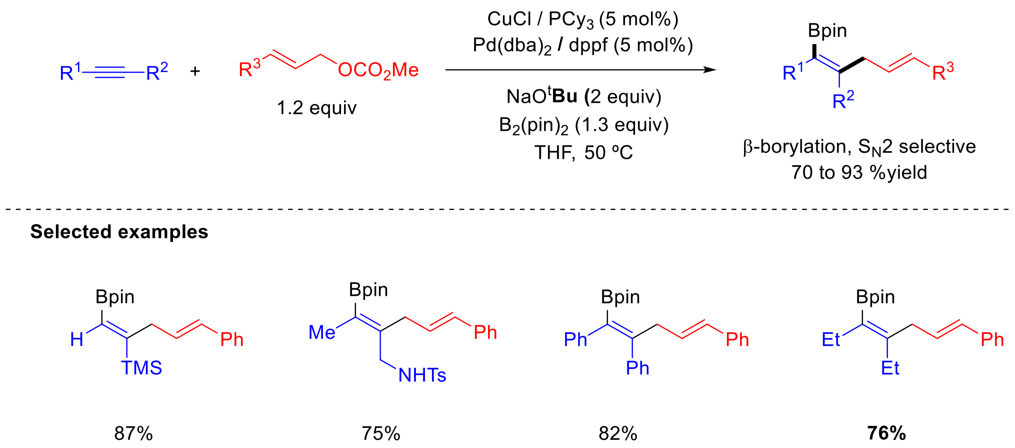
[33] Mateos, J.; Rivera-Chao, E.; Fañanás-Mastral, M. *ACS Catal.* **2017**, *7*, 5340-5344.

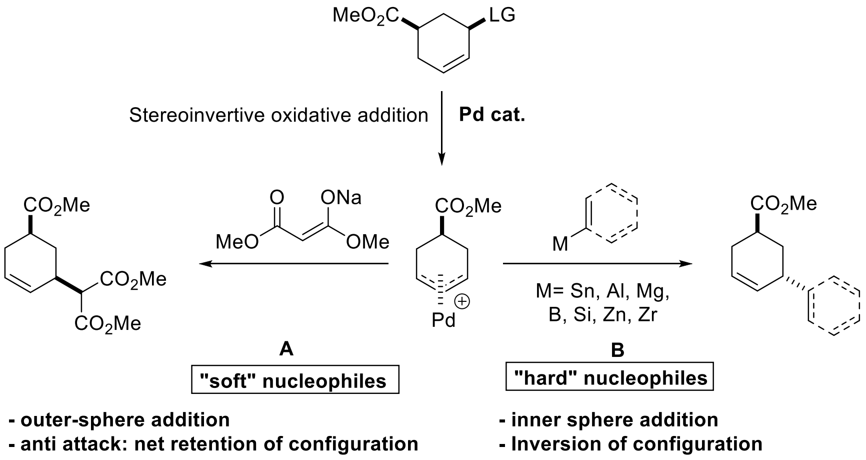


Scheme 19. Cu/Pd catalyzed allylboration of alkynes.

The reaction tolerates several functional groups such as sulfonamide, chloro, trimethylsilyl, or ester groups. Internal alkynes with both aromatic or aliphatic substitution proved to be efficient for this transformation. Terminal alkynes were also efficient despite the acidity of the terminal proton. Moreover, the synthetic potential of this transformation has been illustrated with the synthesis of *(Z,E)*-α-homofarnesene and isosesquilavandulyl alcohol from simple starting materials.

Given the mechanistic complexities of this three component transformation, we wanted to elucidate what type of reaction takes place between the key organometallic intermediates, i.e. alkenylcopper and allylpalladium complexes. It is known, that organocopper reagents usually act as "*soft*" nucleophiles in their direct reactions with allylic substrates.[34] However, their nucleophilic nature in Pd-catalyzed allylation reactions was not well studied.

Clasically, nucleophiles classified as "soft" undergo external anti attack to the π-allyl-Pd(II) intermediate, which is generated via stereoinvervite oxidative addition, resulting in a net retention of configuration (Scheme 20a). In other hand, "hard" nucleophiles usually lead to an overall inversion of configuration as a result of a transmetalation to the palladium center followed by reductive elimination (Scheme 20b).



Scheme 20. Stereochemical outcome depending on the type of nucleophile in Pd-catalyzed allylic substitution.

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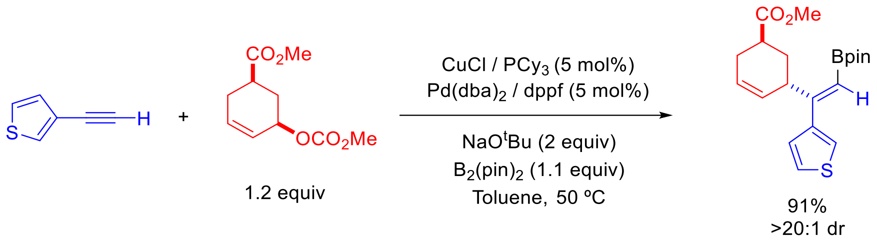
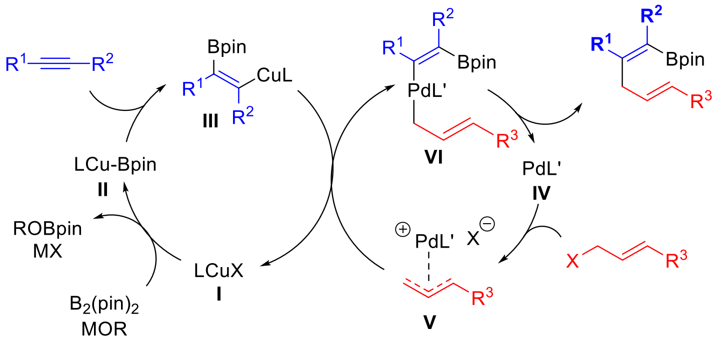
[34] (a) Breit, B.; Demel, P. In *Modern Organocopper Chemistry*; Krause, N., Ed.; Wiley-VCH: Weinheim, 2002; pp 188-223; (b) Yoshikai, N.; Nakamura, E. *Chem. Rev*. **2012**, *112*, 2339-2372.

To determine whether the catalytically generated alkenylcopper species act as "*soft*" or "*hard*" nucleophile in Pd-catalyzed allylic substitution, 3-ethynylthiophene was reacted with a diastereomerically pure *cis* allyl carbonate and B_2pin_2. The product was obtained as a single *trans* diastereomer with excellent diastereocontrol (Scheme 21).[35] This result suggests that the catalytically generated β- borylalkenylcopper intermediate act as "*hard*" nucleophile in this transformation.



Scheme 21. Allylboration of alkynes with a diastereomerically pure *cis* cyclic allyl carbonate.

In view of the results, the dual catalytic mechanism depicted in Scheme 22 is proposed for this transformation. The mechanism starts with a regio- and stereoselective borylcupration of the alkyne with LCu-Bpin complex **II** to generate the β-boryl alkenylcopper(I) intermediate **III**. In the palladium catalytic cycle, a cationic π-allyl Pd(II) complex is formed by oxidative addition of the allyl substrate to Pd(0). Then, the reaction between intermediates **III** and **V** elapses through an inner-sphere transmetalation step to afford **VI** and regenerate copper complex **I**. In this step, the regioselectivity of the allylic substitution is controlled by palladium catalyst, and the borylated 1,4-diene is obtained after reductive elimination in which Pd(0) complex **IV** is regenerated. Before the transmetalation step, isomerization to a σ-allylpaladium intermediate can take place to generate a vacant site in the palladium. The control of the regioselectivity might arise from the formation of this σ-allylPd complex in which the palladium atom is in the less substituted position of the allyl substrate.



Scheme 22. Mechanism of Cu/Pd-catalyzed allylboration of alkynes.

Based on our Cu/-catalyzed allylboration of alkynes, Gong and Fu recently studied the incorporation of fluorinated moieties using Cu/Pd-catalyzed allylboration of alkynes (Scheme 23).[36] They proposed the use of 3,3-difluoro-substituted allylic carbonates as electrophiles in a Cu/Pd-catalyzed boryldifluoroallylation of alkynes (Scheme 23a). With this strategy, they managed to access skipped *gem*-difluorodiene motifs with high levels of regio- and

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[35] Mateos, J.; Fuentes-Vara, N.; Fra, L.; Rivera-Chao, E.; Vázquez-Galiñanes, N.; Chaves-Pouso, A.; Fañanás-Mastral, M. *Organometallics* **2020**, *39*, 740-745

[36] (a) Zhuo, K.-F.; Xu, W.-Y.; Gong, T.-J.; Fu, Y., *Chem. Commun.* **2020**, *56*, 2340–2343. (b) Suliman, A. M. Y.; Ahmed, E.-A. M. A.; Gong, T.-J.; Fu, Y., *Org. Lett.* **2021**, *23*, 3259–3263.

stereoselectivity with great functional group tolerance and broad scope of alkynes. However, the scope of *gem*-difluoroallyl carbonates is limited to the use of 2-aryl substituted ones.

Gem-difluorinated cyclopropanes have been described to undergo C-C bond activation and C-F bond cleavage using palladium catalyst, in which is formed an allylpalladium(II) complex.[37] This group used this strategy to develop a Cu/Pd-catalyzed cis-borylfluoroallylation of alkynes (Scheme 23b). This transformation allows the synthesis of monofluorinated 1,4-dienes using IMesCuCl and ^{t}BuXPhos-PdG3 as catalyst with high functional group tolerance. Several terminal and internal alkynes were used affording the corresponding products with excellent levels of regio- and stereoselectivity. Nevertheless, the reaction is limited to 2-aryl substituted *gem*-difluorinated cyclopropanes.

The mechanism for these transformations starts with the catalytically formation of β-borylalkenylcopper intermediate **III.** Meanwhile, Pd(II) π-allylic complex is formed via oxidative addition of an allylic substrate to Pd(0) species. Finally, transmetalation between intermediates **III** and **V** connect both cycles and leads to intermediate VI which gives rise to the final product after reductive elimination (Scheme 23c).

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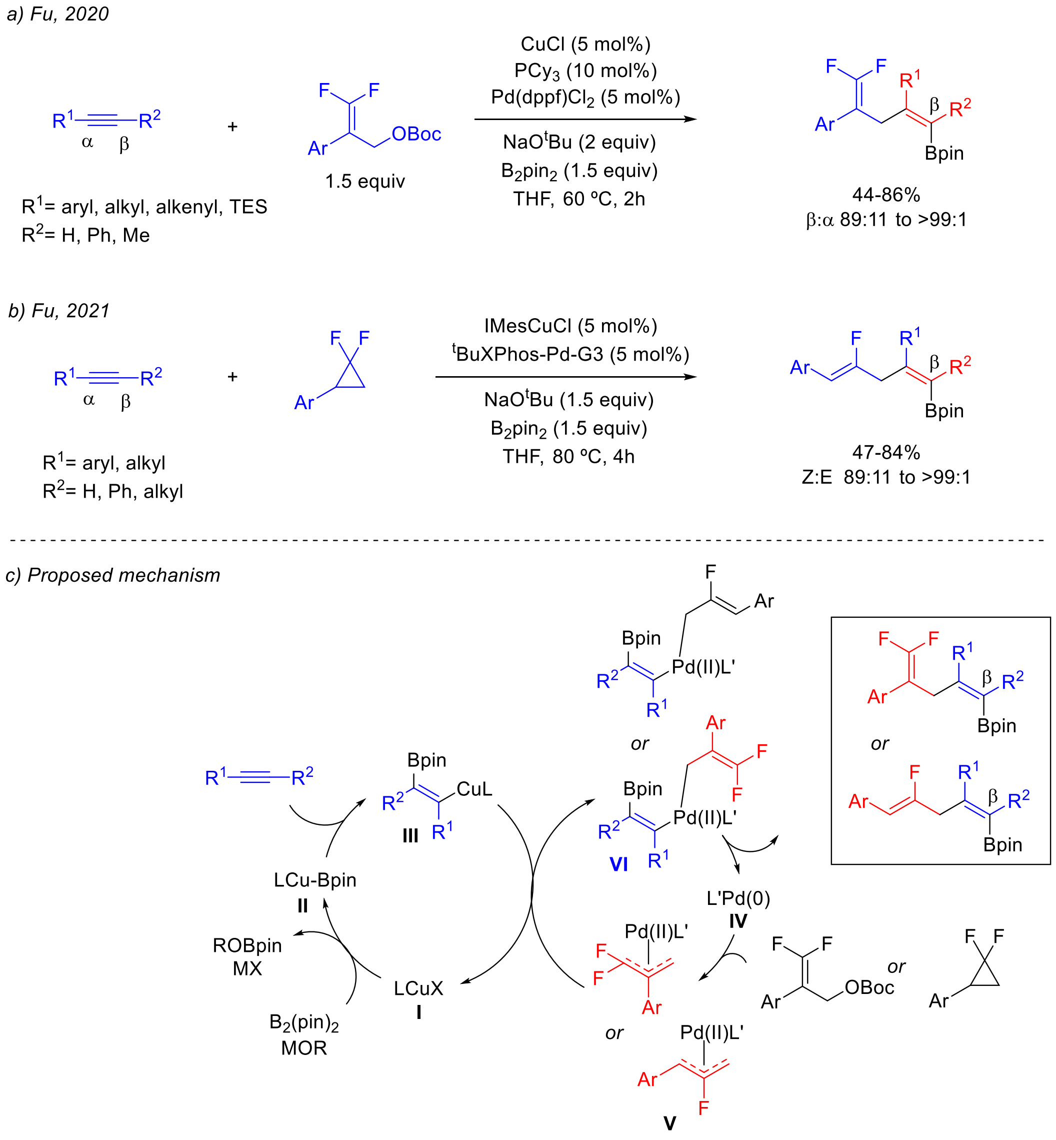
[37] (a) Xu, J.; Ahmed, E.-A.; Xiao, B.; Lu, Q.-Q.; Wang, Y.-L.; Yu, C.-G.; Fu, Y. *Angew. Chem., Int. Ed.* **2015**, *54*, 8231– 8235. (b) Ahmed, E.-A. M. A.; Suliman, A. M. Y.; Gong, T.-J.; Fu, Y. *Org. Lett*. **2019**, *21*, 5645–5649. (c) Ahmed, E.-A. M. A.; Suliman, A. M. Y.; Gong, T.-J.; Fu, Y. *Org. Lett.* **2020**, *22*, 1414–1419.



Scheme 23. Synthesis of *gem*-difluoroalkenes and monofluoroalkenes through Cu/Pd-catalyzed allylboration of alkynes.

c) Borylallenylation of alkynes

In 2020, the group of Yu reported the Cu/Pd-catalyzed boryallenylation of alkynes (Scheme 24).[38] This transformation is based in the coupling of propargylic carbonates and alkynes, using IMesCuCl and Pd(dppf)Cl_2 as catalytic system. The use of this kind of carbonates under palladium catalysis allows the formation of allenyl palladium intermediate **V** via a SN2'-type oxidative addition. The reaction gave rise to β-borylated ene-allene products in a regioselective manner and high efficiency for aryl, alkenyl, alkyl and silyl substituted terminal alkynes. In addition, the hexasubstituted boryl ene-alenes could be synthesized using this methodology.

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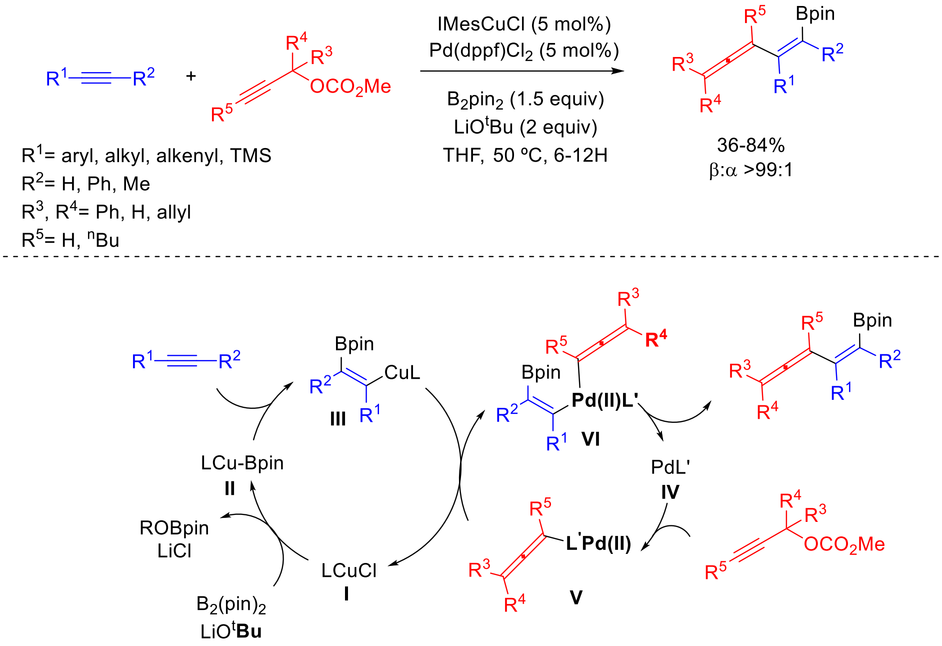
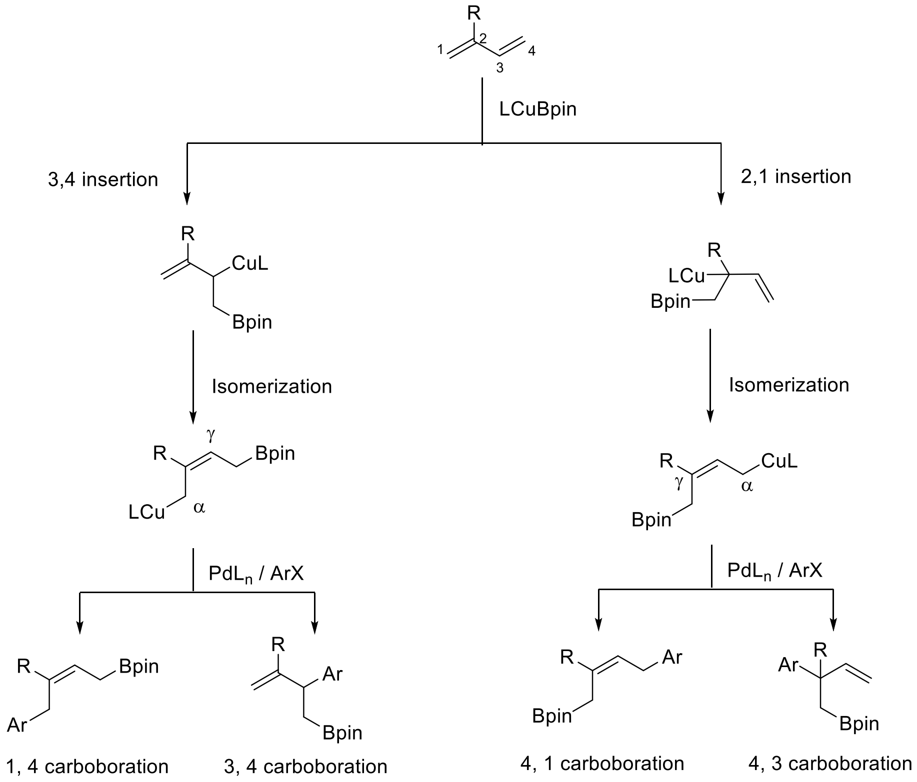
[38] Yu, S.-H.; Gong, T.-J.; Fu, Y. *Org. Lett*. **2020**, *22*, 2941-2945.



Scheme 24. Synergistic Cu/Pd-catalyzed borylallenylation of alkynes

1.1.8.3 Cu/Pd catalyzed carboboration of 1,3-dienes.

The use of 1,3-dienes as pronucleophiles in borylative couplings entails an additional challenge. In this case,the migratory insertion into the borylcopper intermeditate can potentially give rise to regioisomeric allylcopper species. This species tend to isomerize to 1,4-complexes, which are more stable. Then, these interemdiates can undergo transmetalation to the Pd(II) intermediate through the α- or γ- position, thus potentially leading to the possible formation of several different carboboration products (Scheme 25).



Scheme 25. Possible intermediates in the Cu/Pd-catalyzed carboboration of 1,3-dienes.

The group of Brown reported a method for the regioselective arylboration of isoprene derivatives.[39] They observed that the use of similar conditions as the ones previously reported by the Cu/Pd-catalyzed arylboration of styrenes [25]afforded mixtures of products. However, the use of a bulkier copper complex such as (I^{t}Bu)CuBr, facilitated the control over the regioselectivity of the borylcupration step. The use of [Pd]QPhos complex allows for an efficient arylation to obtain 1,4-arylboration products with high *Z*-selectivity (Scheme 26a). Moreover, the use of an additive such as 4-dimethylaminopyridine (DMAP) in combination with a bulkier phosphine in the palladium complex, allowed to change the regioselectivity of the process, obtaining 2,1-arylboration products bearing a quaternary stereogenic center (Scheme 26b). Cyclic 1,2-disubstituted dienes also proved to be efficient in this type of transformation, in which the *anti*-diastereomer is formed with high levels of selectivity (Scheme 26c).

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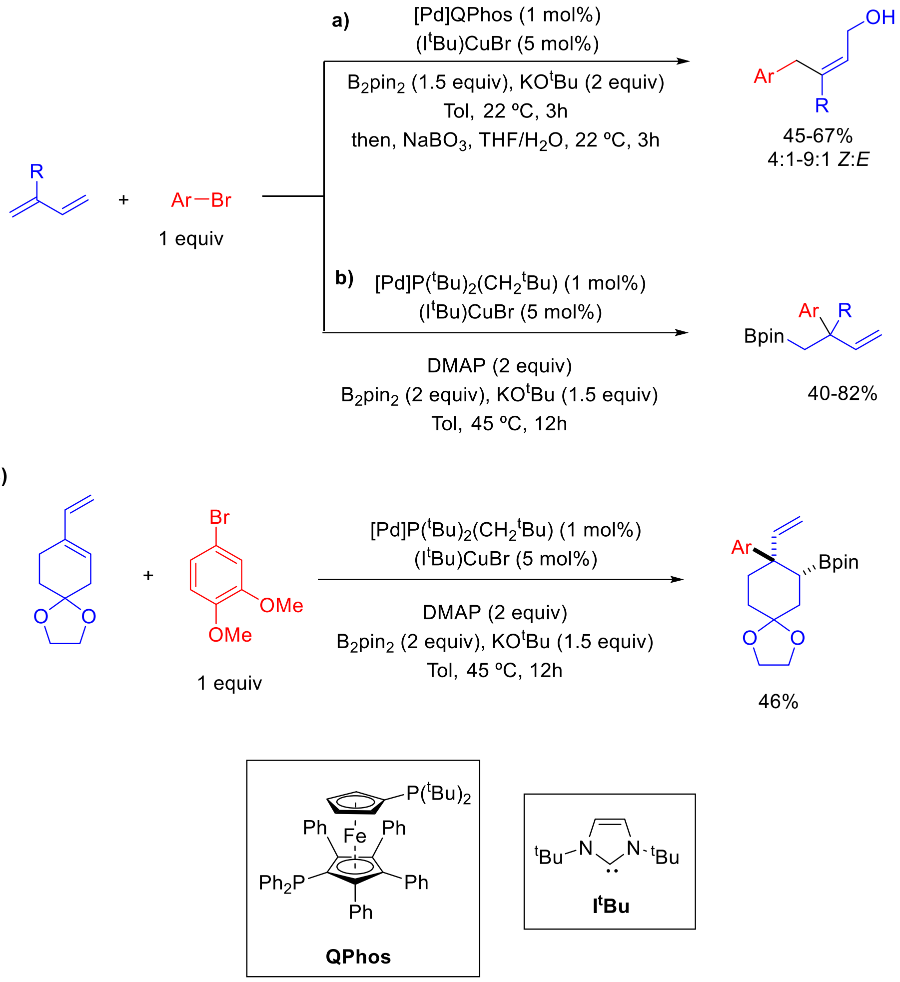
[39] Smith, K. B.; Brown, M. K. *J. Am. Chem. Soc.* **2017**, *139*, 7721-7724.



Scheme 26. Regioselective Cu/Pd-catalyzed arylboration of isoprene derivatives

Subsequent work from the same group led to the development of a Cu/Pd-catalyzed arylboration of 1-aryl-1,3-dienes (Scheme 27).[40] They observed that the use of sterically demanding IPrCuCl in combination with Pd-PAd$_2{}^n$Bu G3 in the presence of a base and B$_2$pin$_2$ afforded the corresponding 1,2-arylated product in good yields and selectivities (Scheme 27a). Several aryl bromides with EDG and EWG and functional groups were tolerated. Moreover, a variety of aryl bromides functioned well for this transformation. However, when more sterically demanding aryl bromides were used, they found that Pd-P^{t}Bu$_3$ allowed the product formation in slightly better yields and regioselectivities. It is important to note that although starting dienes were used as mixtures of *E* and *Z* isomers, the obtained product was isolated as a single isomer (>20:1 *E*:*Z*). Remarkably, the use of modified conditions, such as the use of more electrophilic palladium complex (JackiePhos) favor the formation of 1,4-arylated product in moderate yields (Scheme 27b). For this evidence, they proposed the formation of a single allylcopper intermediate, and that regiodivergency is given by the selectivity in the transmetalation step.

For the 1,2-arylboration process they proposed the mechanism shown in Scheme 27c. The process starts by the treatment of the butadiene with the in situ prepared IPrCuBpin to afford the allylcopper intermediate **I** as a single *Z* isomer, may be due to the formation of thermodynamically more stable complex or a kinetically favored insertion to an s-*cis*-diene. Then, this intermediate, is treated with Pd-Pad$_2{}^n$Bu G3 and aryl bromide to yield the expected 1,2-arylated product with high regioselectivity. Many factors can control the regioselectivity of this transformation. If transmetalation is the determining step for the selectivity, two different

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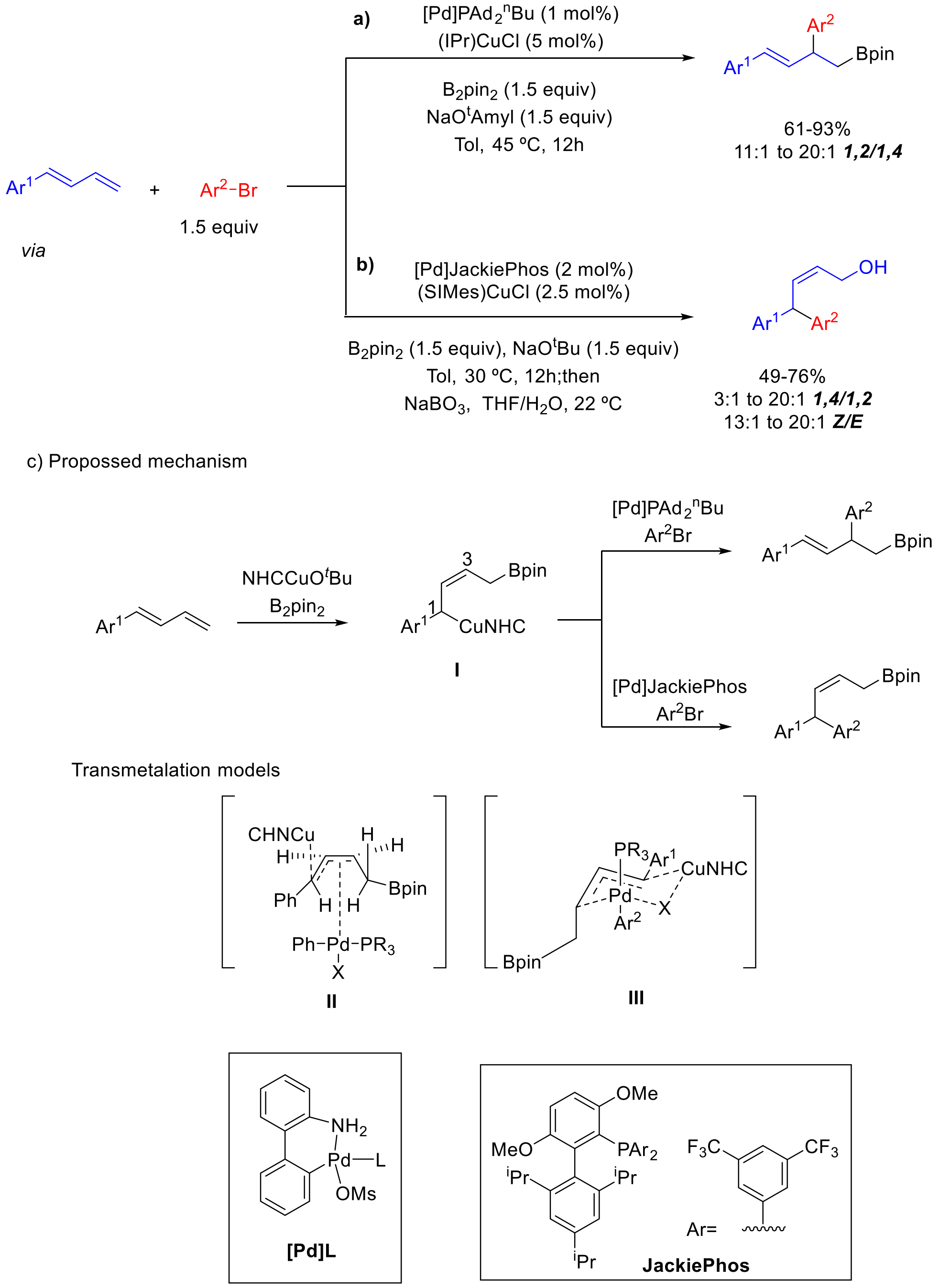
[40] Sardini, S. R.; Brown, M. K. *J. Am. Chem. Soc.* **2017**, *139*, 9823-9826.

possibilities of reaction between intermediate **I** and ArPdBrLn are possible (intermediates **II** and **III**). Their hypothesis pointed to the formation of intermediate **II**. For the formation of the 1,4-arylation product, the use of less bulky and more electrophilic palladium complex favors the transmetalation at the Cu-C1 bond instead at the Cu-C1, giving rise to the desired product. Furthermore, the desired arylboration product should be the Z-alkene isomer (Scheme 25d)



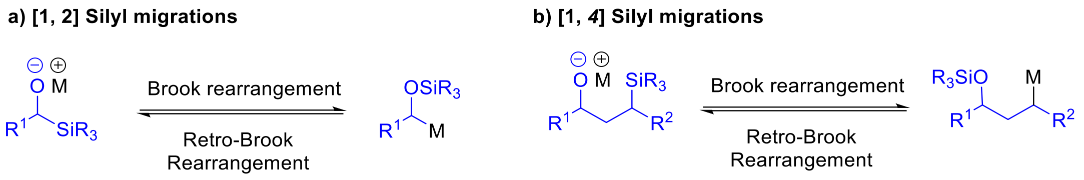
Scheme 27. Regiodivergent Cu/Pd-catalyzed arylboration of 1-aryl-1,3-dienes.

CHAPTER II: Merging Brook rearrangement and allylic substitution via synergistic Cu/Pd catalysis

1.1 Brook rearrangement

Brook rearrangement was described for the first time in the late 1950s by the Canadian chemist Adrian Gibbs Brook.[41] This transformation consists in an intramolecular anionic migration of silyl groups from a carbon to an oxygen atom promoted by the presence of a base, that can be an amine, sodium hydride, an organolithium reagent or an alkali metal alloy. Aza-[42] or thia-[43] variants involving silyl shifts from C to N or S, have been reported too. However, these types of migrations are not as well studied as the previous ones.

Usually, the Brook rearrangement refers to [1,2] anionic silyl migration. However, the migratory aptitude of the silyl group was found to be more general, including a family of [1,n]-carbon to oxygen silyl migrations (Scheme 28). Additionally, the silyl substituents can be aliphatic or aromatic and the alcohol can be secondary or tertiary with aryl or aliphatic groups.



Scheme 28. Anionic silyl migrations.

The transformation is based on the great capacity of silicon to form of a stronger and more stable silicon-oxygen bond. Besides this general trend, oxygen to carbon migrations, so called retro-Brook rearrangements, are also known.[44] A very interesting use of the Brook rearrangement is its use in tandem reactions that involve C-C bons forming reactions before and after the rearrangement.

The [1,2] anionic silyl migration has been used for the regio- and stereoselective formation of silyl enol ethers. These anionic migrations can be induced in different ways, including photolytically, thermally or using basic/acid conditions. This transformation involves a nucleophilic attack to an acyl silane to generate an oxy-anion which then attacks the silicon atom to afford a hypervalent pentacoordinate silyl species. Then subsequent ring opening and irreversible fast protonation of the resulting carbanion afford the corresponding silyl ether. As is shown in Scheme 29, the formation of cyclic pentavalent silicon species is a key step in all described types of Brook rearrangement

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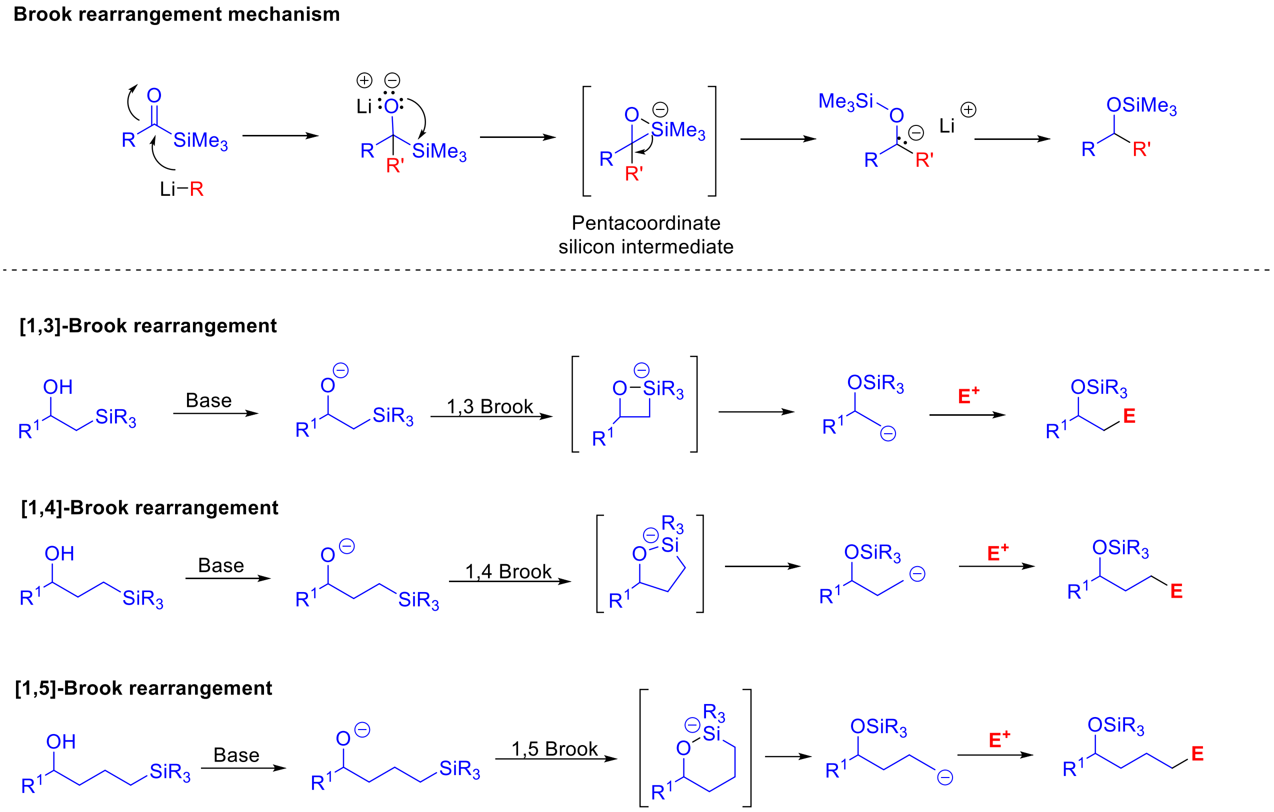
[41] a) Brook, A. G. *J. Am. Chem. Soc.* **1958**, 80, 1886-1889; b) Brook, A. G., Warner, C. M., McGriskin, M. E. *J. Am. Chem. Soc.* **1959**, 81, 981-983.

[42] Brook, A. G. *Acc. Chem. Res.* **1974**, *7*, 77–84; b) Moser,W. H. *Tetrahedron* **2001**, *57*, 2065–2084.

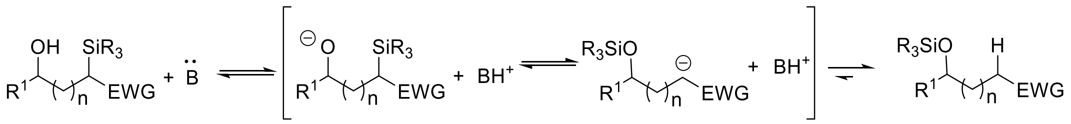
[43] Brook, A. G.; Duff, J. M. *J. Am. Chem. Soc.* **1974**, *96*, 4692–4693. (b) Honda, T.; Mori, M. *J. Org. Chem.* **1996**, *61*, 1196–1197.

[44] [a] R. West, R.; Gornowicz, G. A., J. *Organomet. Chem.* **1971**, *28*, 25–35; [b] A. N. Thadani, A. N.; Huang, Y.; Rawal, V. H., *Org. Lett.* **2007**, *9*, 3873–3876.



Scheme 29. Brook rearrangement mechanism.

The main challenge associated with the use of Brook rearrangements in tandem reactions is the control of the rate and direction of the silyl migration. In this way, when catalytic amount of base is used to facilitate the rearrangement, the relative stability of the silyl ethers and the starting neutral silyl carbinols govern the equilibrium position. The presence of an electron-withdrawing group in the carbon attached to the silicon atom kinetically facilitates the carbanion formation, providing enough driving force for the complete conversion of α-, β- and γ-silyl carbinols into the corresponding silyl ethers. The fast and irreversible protonation of the carbanion, renders this method ineffective for strategies oriented towards the further formation of a C-C bond (Scheme 30).

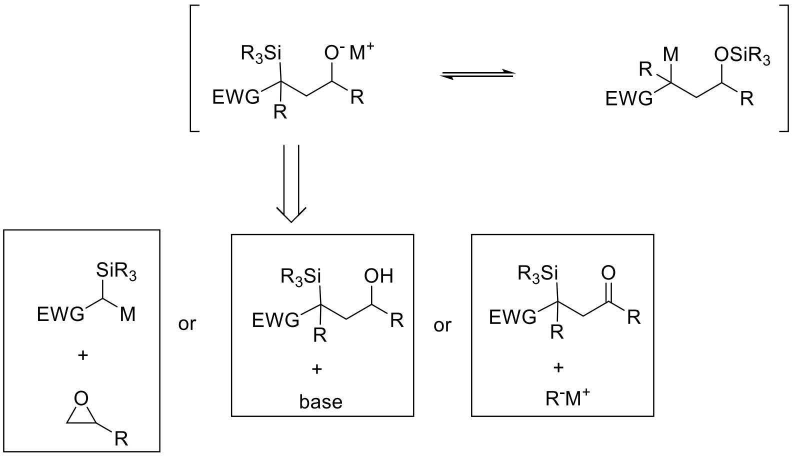


Scheme 30. Anionic silyl migration as an equilibrium process

In this chapter we will focus on transformations that involve the [1,4] intramolecular anionic C to O silyl migration.

1.1.1 [1,4] Silyl migration

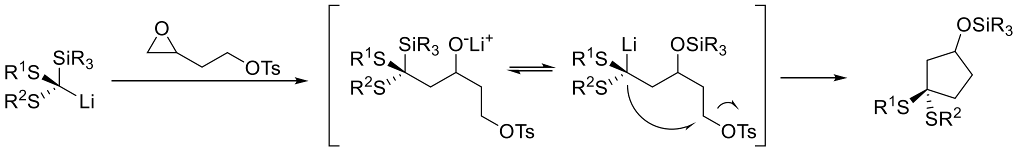
This type of transformation requires the initial formation of the γ-silyl-substituted oxy-anion. This structure can be accessed by several methodologies which include nucleophilic opening of epoxides with α-silyl metalated reagents bearing an EWG, by deprotonation of γ-silyl carbinols or by organometallic addition to β-silyl aldehydes or ketones (Scheme 31).



Scheme 31. Synthetic methods to initiate anionic 1,4-silyl migrations

1.1.1.1 Silyl migration/intramolecular alkylation

A common strategy for this sequence is the nucleophilic ring opening of stabilized epoxides with silyl-substituted alkyllithium reagents, followed by the [1,4] Brook rearrangement and an intramolecular S_N2 attack to form the new cyclic product. Schaumann and co-workers employed this strategy in a formal (4+1) synthesis of substituted cyclopentanols (Scheme 32).[45]



Scheme 32. Formal [4+1] cycloaddition approach to cyclic systems

1.1.1.2 Silyl migration/intermolecular alkylation

Several examples of tandem nucleophilic addition and [1,4] Brook rearrangement in an intermolecular alkylations have also been reported, starting from stabilized α-silyl carbanions. Matsuda and co-workers employed this strategy to obtain 1,5-diols derivatives via a transformation that involves the addition of the stabilized carbanion to an epoxide, 1,4 Brook rearrangement and trapping of the resulting carbanion with a second molecule of the epoxide (Scheme 33) .[46]

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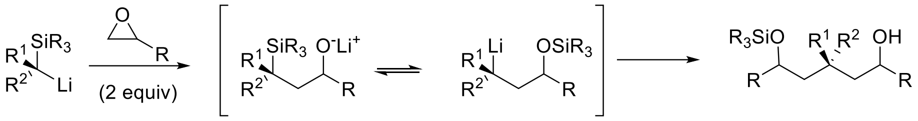
[45] (a) Fischer, M. R.; Kirschning, A.; Michel, T.; Schaumann, E. *Angew. Chem., Int. Ed. Engl*. **1994**, *33*, 217. (b) Brauer, N.; Michel, T.; Schaumann, E. *Tetrahedron* **1998**, *54*, 11481.

[46] Matsuda, I.; Murata, S.; Ishii, Y. *J. Chem. Soc., Perkin Trans.1* **1979**, 26.

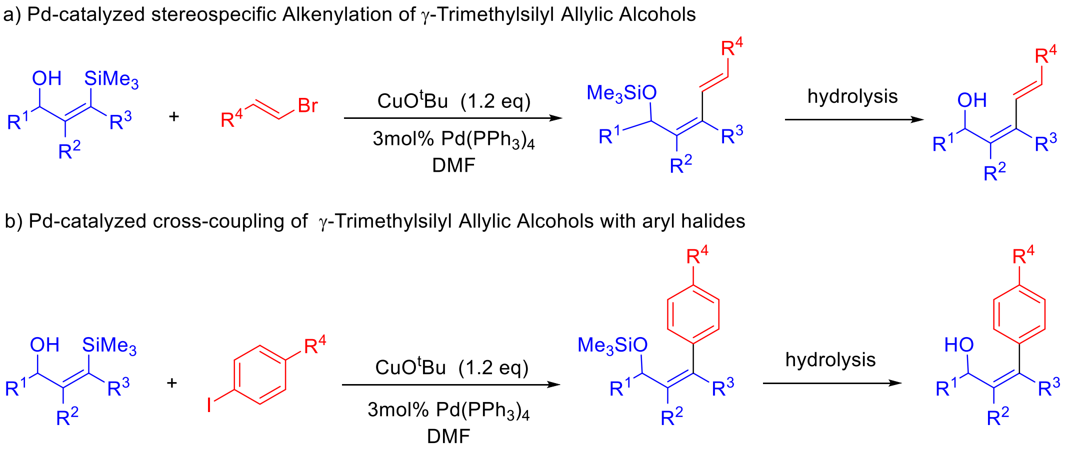


Scheme 33. Symmetrical bis-alkylations of silyl-stabilized carbanions

1.2 The merger of [1,4] Brook rearrangement and Pd-catalyzed cross-coupling.

The use of vinyl copper species generated through C^{sp2} -to- O silyl migration promoted by copper *tert*-butoxide has been used in different couplings with several electrophiles. In this regard, Takeda and co-workers reported in 2002 the use of vinyl copper species in Pd-catalyzed stereoespecific cross coupling reactions with aryl and vinylic halides (Scheme 34).[47]

They observed that the treatment of the γ-silyl allylic alcohols with several aryl and vinyl halides in the presence of stoichiometric CuO^tBu and catalytic $Pd(PPh_3)_4$ afforded the final products in good yields with high selectivities and complete retention of configuration. In addition, it was confirmed that no reaction takes place when no palladium catalyst was added.



Scheme 34. Pd-catalyzed cross-coupling transformations.

The use of alkyl halides in this kind of transformations was also reported by the same group (Scheme 35a).[48] They studied the reaction between (*Z*)-trimethylsilyl-susbtituted allylic alcohol derivatives and benzyl bromide or bromo(methoxy)methane under the presence of an excess of CuO^tBu. Then, after the silyl ether hydrolysis with TBAF they could obtained tri- or tetrasubstituted olefins with totally retention of configuration. It is of special interest that the alkylation of vinyl copper species generated through C^{sp2} -to- O silyl migration proceeds even when primary alkyl iodides were used (Scheme 35b). However, in some cases, the use of additional equivalents of lithium iodide was necessary to improve the reaction yield.

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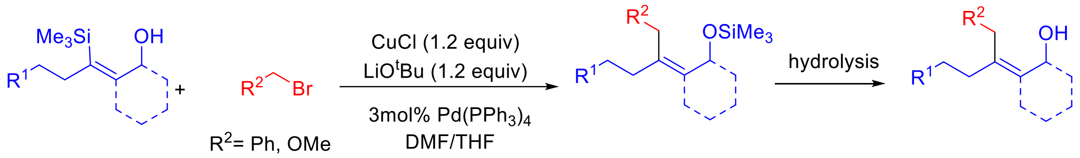
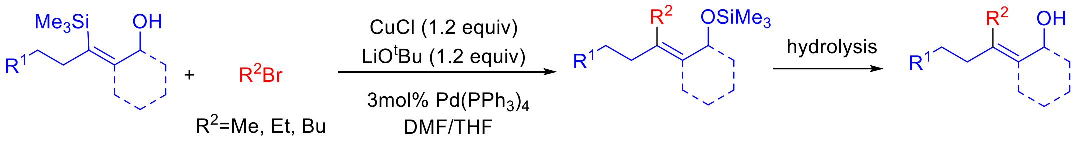
[47] Taguchi, H.; Ghoroku, K.; Tadaki, M.; Tsubouchi, A.; Takeda, T. *J. Org. Chem.* **2002**, *67*, 8450-8456.

[48] Taguchi, H.; Tsubouchi, A.; Takeda, T. *Tetrahedron Lett.* **2003**, *44*, 5205–5207

a) Reaction of the γ-silylallylic alcohols with reactive alkyl halides



b) Reaction of the γ-silylallylic alcohols with primary alkyl iodides

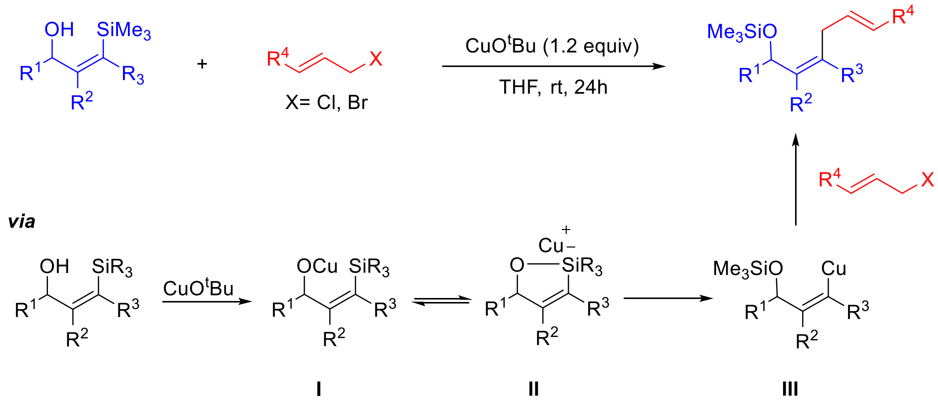


Scheme 35. Stereospecific alkylation of β-hydroxymethylvinylsilanes with alkyl halides

1.3 The merger of [1,4] Brook rearrangement and allylic substitution

In contrast to 1,4 C^{sp3}-to-O silyl migrations, 1,4 C^{sp2}-to-O silyl migration has been less studied. Takeda's group used the 1,4 C^{sp2}-to-O silyl migration of silyl allylic alcohols in allylic substitution reactions.

Transmetalation of organosilicon compound trough Brook rearrangement represents an attractive approach to produce reactive organometallic species. In 2001, Takeda and co-workers reported the stereospecific allylation of (*Z*)-γ-trimethylsilyl allylic alcohols trough a 1,4 C^{sp2}-to-O silyl migration promoted by the use of a stoichiometric amount of copper(I) *tert*-butoxide (Scheme 36).[49]



Scheme 36. Stereospecific allylation of trimethylsilyl allylic alcohols promoted by copper(I) tert-butoxide.

In this transformation, CuO^{t}Bu, synthesized in situ by the reaction of CuI and LiO^{t}Bu,reacts with the corresponding trimethylsilyl-substituted allylic alcohol forming copper alkoxide **I** which is in equilibrium with the pentavalent silicon intermediate **II**. This pentacoordinated silicon compound undergoes a Brook-type rearrangement to afford vinylcopper species **III**. which reacts with the allylic halide to produce a skipped diene with retention of configuration. Finally, a hydrolysis process using tetrabutylammonium fluoride is performed to render the corresponding more stable alcohol.

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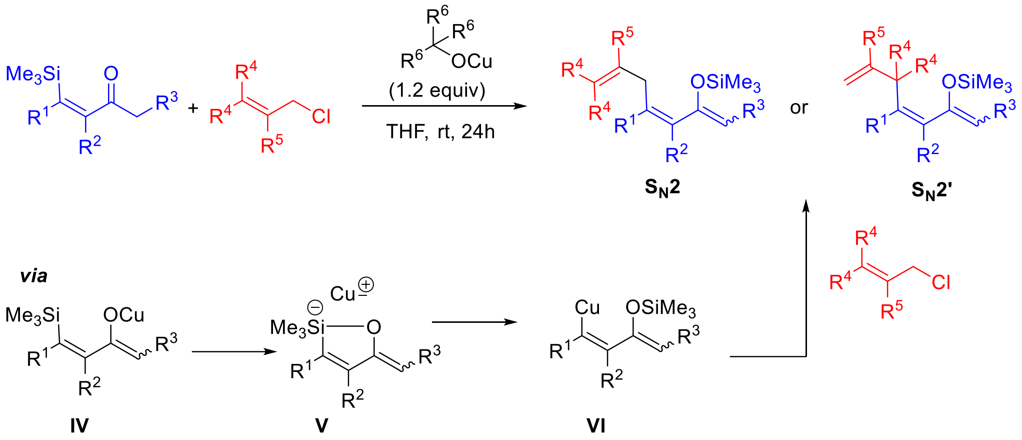
[49] Taguchi, H.; Ghoroku, K.; Tadaki, M.; Tsubouchi, A.; Takeda, T. *Org. Lett.* **2001**, *3*, 3811-3814.

This methodology is limited to the use of primary allyl chlorides or bromides. In addition, it is necessary that the olefin has a defined stereochemistry, since Brook rearrangement only takes place when the double bond has a *Z* stereochemistry. This fact was confirmed when the reaction was carried out with an (*E*)-allylic alcohol and no formation of the corresponding dienyl alcohol was observed. In this way, the key role of intramolecular coordination in 1,4 C^{sp2}-to-O silyl migration becomes clear. Moreover, the use of stoichiometric amounts of copper *tert*-butoxide represents a limitation of their use.

The anionic [1,4]-silyl migration from carbon to oxygen involvingα,β-unsaturated ketones was also reported (Scheme 37).[50] In this work, formation of a Cu(I) enolates promoted by copper (I) *tert*-alkoxide proceeds the Brook rearrangement and the subsequent electrophilic trapping. This, usually to afford the formal S_N2 product. However, it is important to remark that when prenyl chloride was used as allylic partner, the attack takes places at the γ-carbon to produce the formal S_N2' substitution product.



Scheme 37. Anionic silyl migration from sp^2 carbon to carbonyl oxygen

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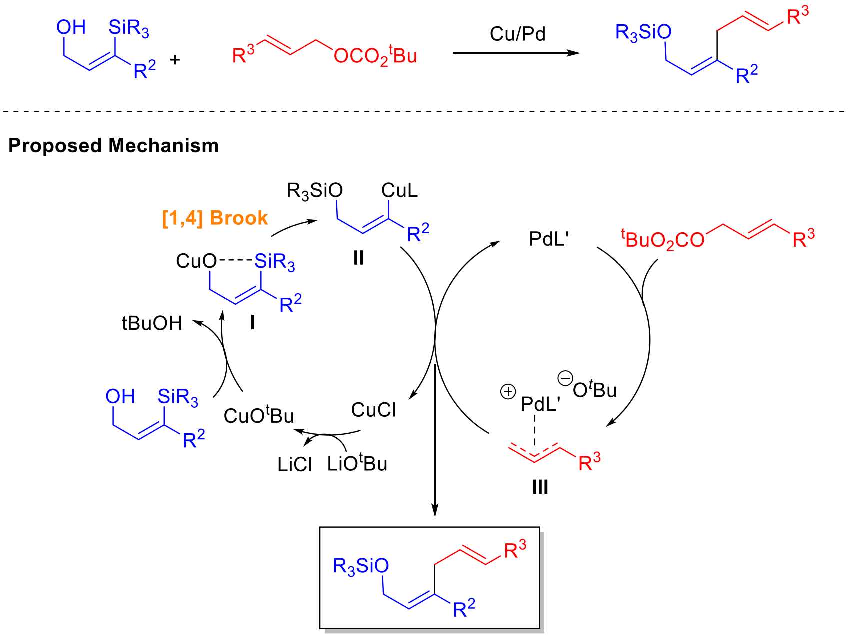
[50] Taguchi, H.; Miyashita, H.; Tsubouhi, A.; Takeda, T. *Chem. Commun*. **2002**, 2218-2219.

2. OBJECTIVE

As shown above, the work of Takeda relies on the use of superstoichiometric amounts of CuO^{t}Bu to perform the [1,4] Brook rearrangement/ allylic substitution processes (see section 1.3). The main objective of this chapter is the development of a new catalytic methodology that allows to perform a tandem Brook rearrangement /allylic substitution using catalytic amounts of both copper and palladium complexes. The proposed strategy is based on the use of synergistic catalysis as a synthetic strategy to achieve the synthesis of chiral skipped dienes using silyl alkenylmetal equivalents in asymmetric allylic substitution reactions (Scheme 38).



Scheme 38. [1,4] Brook rearrangement and allylic substitution using Cu/Pd synergistic catalysis

This approach lies on the merger of a catalytic cycle in which a silyl-substituted compound is activated as the nucleophile through a Brook rearrangement by a copper catalyst, with a second catalytic cycle in which a palladium catalyst activates the electrophilic allylic substrate. The designed synergistic catalysis not only provides simultaneous activation of both the nucleophile and the electrophile of this C-C bond formation, but also serves as a key mechanism to promote the Brook rearrangement in a catalytic manner.

Besides the control of the direction and/or rate of the silyl migration, the key to successfully performing a C-C bond formation involving a catalytic Brook rearrangement lies on developing a system in which 1) the trapping of the vinylmetal intermediate generated in the C(sp^2)-to-O silyl migration is faster than its protonation and 2) the metal species responsible for Brook rearrangement is regenerated in that crucial step.
In the proposed design (Scheme 11), exemplified for a transformation involving a 1,4-Brook rearrangement, a catalytic amount of copper(I) *tert*-butoxide will deprotonate a γ-trimethylsilyl allylic alcohol forming copper alkoxide **I**. This intermediate will experience a Csp^2-to-O silyl migration generating alkenylcopper species **II**. In a second catalytic cycle a cationic π-allyl metal complex **III** will be formed by decarboxylative oxidative addition of an allyl carbonate to a palladium(0) complex. The connection of the two catalytic cycles will be the crucial step of this

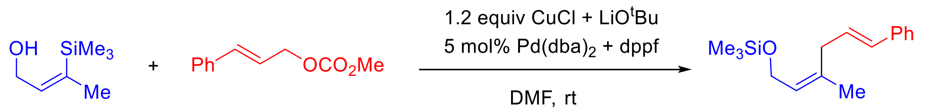
approach. It will promote the formation of the C-C bond, and will regenerate both catalysts. The activation of the allyl substrate is essential to favor the C-C bond formation versus the protonation of the alkenylcopper species. Moreover, the nature of the cationic allyl-Pd complex has a direct impact on the regeneration of the copper catalyst as the counter-anion which is originally in this complex ends up in the first catalytic cycle as part of the copper catalyst.

2. RESULTS AND DISCUSSION

2.1 Optimization

At the outset of our investigation, we selected the reaction involving (*Z*)-3-(trimethylsilyl)but-2-en-1-ol (**2.1**) and *tert*-butyl cinnamyl carbonate (**2.2**). We initially evaluated the stoichiometric ratio between the starting materials (Table 1). For this screening, we used lithium *tert*-butoxide as base, CuCl as copper source and Pd(dba)$_2$ and dppf as palladium source. Dimethylformamide was selected as solvent. We first focused on the initial assessment of the reaction using a stoichiometric amount of copper with the idea to tranfer the optimized result to a process catalytic in copper. The initial experiment already showed that the use of 1.6 equivalents of **2.1** afforded the desired product in 52% yield (Table 1, entry 1). When we tried to decrease the amount of the silylated alcohol **2.1** (Table 1, entry 2) similar results were obtained. However, when an excess of *tert*-butyl cinnamyl carbonate (**2.2**) was used, lower yield was obtained (Table 1, entry 3).

Table 1. Study of starting material stoichiometric. [a]



2.1 **2.2** **2.3**

Entry	2.1 (Equiv)	2.2 (Equiv)	Conv. 2.1 (%) [b]	Conv. 2.2 (%) [b]	Yield 2.3 (%) [b]
1	1.6	1	Full	Full	51
3	1	1	Full	Full	50
4	1	1.5	Full	62	43

[a] Reactions run on a 0.2 mmol scale, [b] Determined by ^{1}H-NMR analysis using Trimethyl benzene-1,3,5-tricarboxylate as internal standard.

Then, using an equimolar amount of both starting materials, we evaluated different solvents (Table 2). Fortunately, we observed that the use of dimethylacetamide (Table 2, entry 2), slightly increased the yield of the transformation, affording the corresponding product in 60% yield. However, the use of more polar solvents, such as hexamethylphosphoramide (Table 2, entry 3) slightly decreased the efficiency of the transformation. Finally, the combination of HMPA with THF (Table 2, entry 4) did not yield the product **2.3**. It is important to remark, that in some cases it was necessary to carry out a hydrolysis with 2 equivalents of tetra-*n*-butylammonium fluoride in order to facilitate the analysis of the crude NMR spectra.

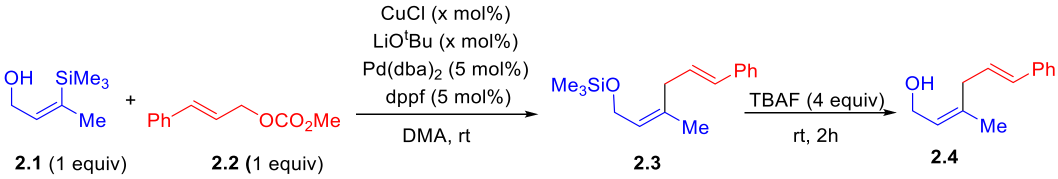
Table 2. Screening of solvents. [a]

Entry	**Solvent**	**Conversion (%)** [b]		**Yield 2.3 (%)**[b]	**Yield 2.4 (%)** [b]
		2.1	**2.2**		
1	DMF	Full	Full	50	nd
2	DMA	Full	Full	n.d.	60
3	HMPA	60	55	40	nd
4	HMPA/THF	31	65	-	-

[a] Reactions run on a 0.2 mmol scale, [b] Determined by ^{1}H-NMR analysis using Trimethyl benzene-1,3,5-tricarboxylate as internal standard.

The effect of CuO^{t}Bu amount that was used was also studied (Table 3). As we commented in section 2, our initial goal was to carry out the reaction catalytically. Thus, we tried to decrease de amount of CuCl and LiO^{t}Bu added to the reaction. Gratifyingly, we observed that the use of 70 mol% of CuCl and LiO^{t}Bu (Table 3, entry 2) gave rise to the formation of the desired product in a similar yield. Remarkably, this transformation could be successfully carried out by using 50 mol% of CuO^{t}Bu, which the same efficiency of the reaction (Table 3, entry 3). However, the use of less amount of copper *tert*-butoxide (Table 3, entry 4) only afforded traces of product **2.3** with recovery of the starting materials.

Table 3. Effect of CuO^{t}Bu amount. [a]



Entry	**CuO^{t}Bu (equiv)**	**Conversion (%)** [b]		**Yield 2.3 (%)** [b]	**Yield 2.4 (%)** [b]
		1	**2**		
1	1.2	Full	Full	n.d	60
2	0.7	Full	Full	n.d.	56
3	0.5	90	90	n.d.	58
4	0.3	SM was recovered		n.d.	Traces

[a] Reactions run on a 0.2 mmol scale, [b] Determined by ^{1}H-NMR analysis using trimethyl benzene-1,3,5-tricarboxylate as internal standard.

Finally, we did a screening of different ligands both on copper and palladium complexes. We observed that the employment of different NHC ligands on copper as well as different Pd/dppf derivatives had a detrimental effect on the reaction and observing no product formation, in those cases.

2.2 Reaction scope

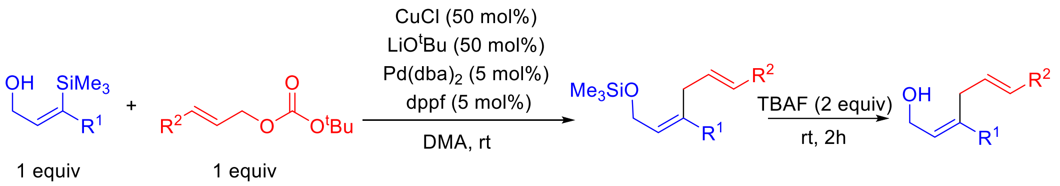
Having established the optimal conditions for the Cu/Pd catalyzed Brook rearrangement /allylic substitution reaction (Table 3, entry 3), we set out to investigate the scope of the reaction (Table 4).

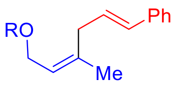
The use of an allylic alcohol bearing a more electron withdrawing phenyl group in the carbon attached to the silyl unit (i.e.) (*Z*)-3-phenyl-3-(trimethylsilyl)prop-2-en-1-ol) provided a similar result and afforded the silylated product **2.5** in 33% yield. A slight improvement in the reaction yield was observed when this compound was directly converted in a two step procedure to the corresponding alcohol by treatment with TBAF.

Different cinnamyl carbonate derivatives bearing both electro withdrawing and electrodonating groups were also tested. A similar outcome than the one observed for cinnamyl carbonate was observed. However, the use of more electrodonating or electrowithdrawing *para*-substituted cinnamyl carbonate did not afford the corresponding product

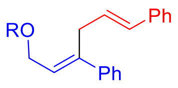
Due to the low efficiency of the reaction and the impossibility to reduce the amount of copper, this project was stopped at this point.

Table 4. Scope of the transformation[a]

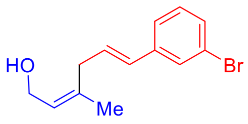




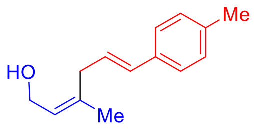
2.3, R= $SiMe_3$, 42%
2.4,R= H, 58%[b]



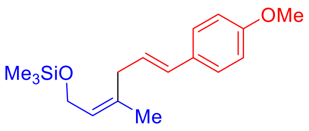
2.5, R= $SiMe_3$, 33%
2.6,R= H, 36%[b]



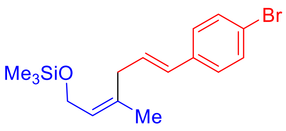
2.7, 45%[b]



2.8, 41%[b]



2.9, 0%



2.10, 0%

[a] Reactions run on a 0.2 mmol scale, [b] Two steps isolated yield

3. CONCLUSIONS

We have studied a methodology for the synthesis of silylated 1,4-dienes, through a novel synergistic Cu/Pd catalyzed reaction between allylic carbonates and (*Z*)-silyl-substituted allyl alcohols.

However, we were not able to reduce the copper *tert*-butoxide amount by more than 50 mol % in order to guarantee the reaction efficiency. Furthermore, the reaction is not useful and efficient for the use of other different silyl-substituted allyl alcohols either allylic carbonates.

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CHAPTER III: Stereoselective synthesis of borylated 1,3-dienes by synergistic Cu/Pd catalysis.

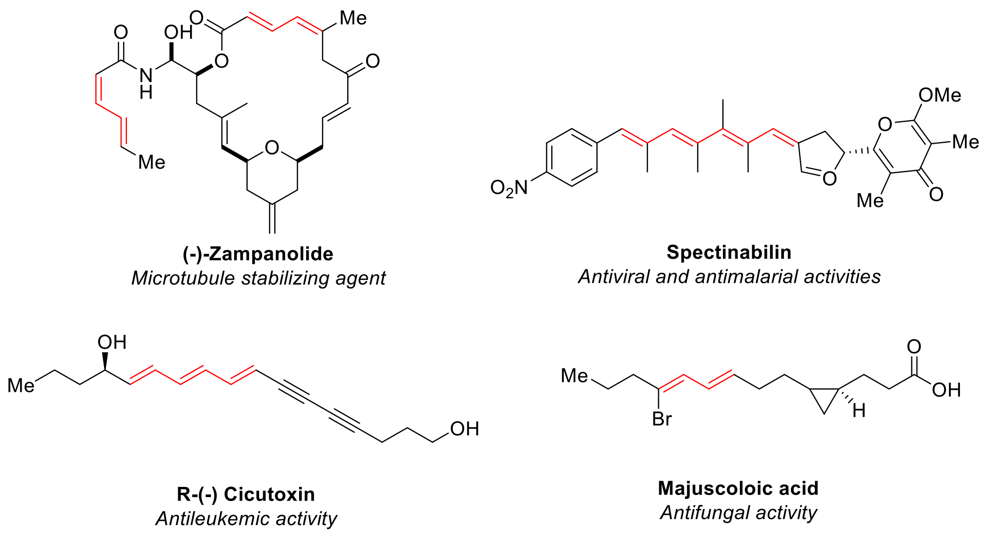
Chapter adapted from:

Vázquez-Galiñanes, N.;[a] Fañanás-Mastral, M.[a] *ChemCatChem* **2018**, *10*, 4817-4820.

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

1. INTRODUCTION

1,3-dienes are an important class of structures which are present in many natural products and bioactive molecules. Some examples of natural products containing the 1,3-diene motif are shown in Figure 1.



(-)-Zampanolide
Microtubule stabilizing agent

Spectinabilin
Antiviral and antimalarial activities

R-(-) Cicutoxin
Antileukemic activity

Majuscoloic acid
Antifungal activity

Figure 3. Examples of natural products containing 1, 3-dienes.

Examples including (-)-Zampanolide,[51] a potent microtubule-stabilizing agent, Spectinabilin,[52] an antiviral and antimalarial agent, *R*-(-)-Cicutoxin,[53] which has antileukemic activity or Majuscoloic acid, an antifungal agent, are present in this family of structures.

Traditional methods to prepare 1,3-dienes involve Pd-catalyzed cross-coupling reactions,[54] Wittig reaction[55] or Horner Wadsworth-Emmons[56] transformations. However, these methodologies are associated with the use of stoichiometric amount of metal and most of them are not stereoselective processes.

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[51] Diaz, J. F. *et. al. Chemistry and Biology*, **2012**, *19*, 686-698.

[52] Kakinuma, K.; Hanson, C. A.; Rinehart, L., *Tetrahedron*, **1976**, *32*, 217-222.

[53] Gung, B.; Omollo, A. Eur. *J. Org. Chem*., **2009**, *8*, 1136–1138.

[54] Liu, C.; Yuan, J.; Gao, M.; Tang, S.; Li, W.; Shi, R.; Lei, A. *Chem. Rev.* **2015**, *115*, 12138

[55] Maryanoff, B. E.; Reitz, A. B. *Chem. Rev.* **1989**, *89*, 863-871.

[56] Bisceglia, J. Á.; Orelli, L. R. Curr. *Org. Chem*. **2012**, *16*, 2206.

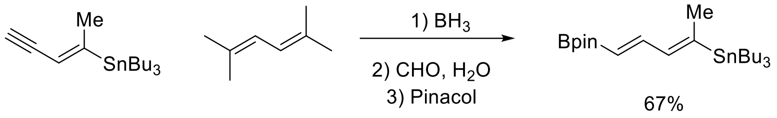
1.1 Boron-substituted 1,3-dienes

Boron-substituted 1,3-dienes represent an important class of compounds which serve as key building blocks in the synthesis of a wide range of bioactive natural products and organic materials. The preparation of polyene frameworks by metal-catalyzed cross-coupling reactions[57] or Diels-Alder cycloadditions which render a versatile cyclic allyl-boron intermediate[58] illustrate the synthetic utility of these organoboron compounds. Notably, these transformmations require the use of stereodefined borylated 1,3-dienes to access structurally unique molecular architectures.

1.1.1 Methodologies for the synthesis of *anti*- borylated 1,3-dienes

Most of the reported methodologies for the synthesis of borylated 1,3-dienes give access to the isomer in which the boron atom is in *anti* disposition to the second olefinic unit. These examples include hydroboration,[59] carboboration[60] and borostannylation of enynes,[61] cross-metathesis of vinylboronates with 1,3-butadienes,[62] Heck coupling,[63] Negishi coupling[64] or Takai olefination.[65] Some of these examples will be shown below.

In 2008 the group of Tortosa reported the Total Synthesis of (+)-Superstolide A. In this transformation was involved the use of hydroboration of an enyne using Snieckus' procedure[66] for the synthesis of a bimetallic 1,3 diene intermediate (Scheme 39).



Scheme 39. Hydroboration of enynes for the synthesis of *anti* 1,3-borylated dienes

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[57] Cornil, J.; Guérinot, A.; Cossy, J. *Org. Biomol. Chem*. **2015**, *13*, 4129-4142.

[58] G. Hilt, P. Bolze, Synthesis 2005, 2091–2115; b) B. B. Tour_, D. G. Hall, Chem. Rev. 2009, 109, 4439–4486.

[59] L. Garnier, B. Plunian, J. Mortier, M. Vaultier, *Tetrahedron Lett*. **1996**, *37*, 6699–6700; b) M. Tortosa, N. A. Yakelis, W. R. Roush, *J. Am. Chem. Soc.* **2008**, *130*, 2722–2723; Pd catalysis: c) Y. Matsumoto, M. Naito, T. Hayashi, *Organometallics* **1992**, *11*, 2732–2734; Zr catalysis: d) X. Gao, D. G. Hall, *Tetrahedron Lett*. **2003**, *44*, 2231–2235; Cu catalysis: e) Y. Sasaki, Y. Horita, C. Zhong, M. Sawamura, H. Ito, *Angew. Chem. Int. Ed*. **2011**, *50*, 2778–2782; Ag catalysis: f) H. Yoshida, I. Kageyuki, K. Takaki, *Org. Lett.* **2014**, *16*, 3512–3215.

[60] Alfaro, R.; Parra, A.; Alemán, J.; García-Ruano, J. L.; Tortosa, M. *J. Am. Chem.Soc.* **2012**, *134*, 15165-15168.

[61] R. R. Singidi, T. V. RajanBabu, *Org. Lett.* **2010**, *12*, 2622–2625.

[62] T. W. Funk, J. Efskind, R. H. Grubbs, *Org. Lett.* **2005**, *7*, 187–190; For a single example of Z-selective cross-metathesis, see: b) E. T. Kiesewetter, R. V. O'Brien, E. C. Yu, S. J. Meek, R. R. Schrock, A. H. Hoveyda, *J. Am. Chem. Soc.* **2013**, *135*, 6026–6029.

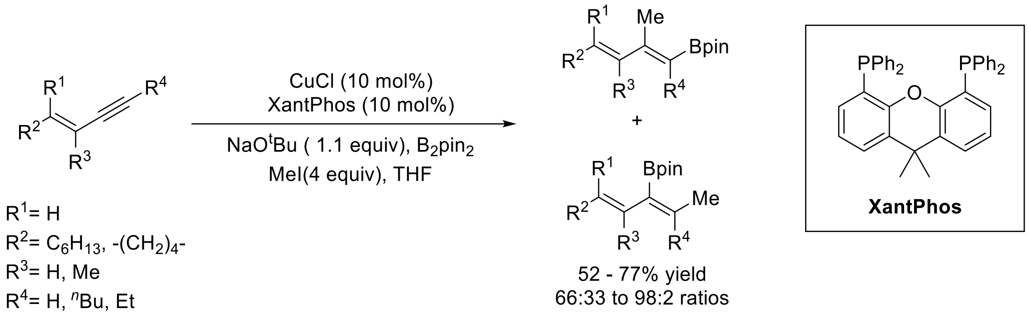
[63] A. P. Lightfoot, S. J. R. Twiddle, A. Whiting, *Org. Biomol. Chem*. **2005**, *3*, 3167–3172; b) J. J. Molloy, C. P. Seath, M. J. West, C. McLaughlin, N. J. Fazakerley, A. R. Kennedy, D. J. Nelson, A. J. B. Watson, *J. Am. Chem. Soc.* **2018**, *140*, 126–130.

[64] Mazal, C.; Vaultier, M. *Tetrahedron Lett.* **1994**, *35*, 3089–3090; b) Lee, S. J.; Gray, K. C.; Paek, J. S.; Burke, M. D. *J. Am. Chem. Soc*. **2008**, *130*, 466–468.

[65] a) Coleman, R. S.; Walczak, M. C. *Org. Lett.* **2005**, *7*, 2289–2291; b) R. S. Coleman, R. S.; Walczak, M. C.; Campbell, E. L. *J. Am. Chem. Soc*. **2005**, *127*, 16038–16039.

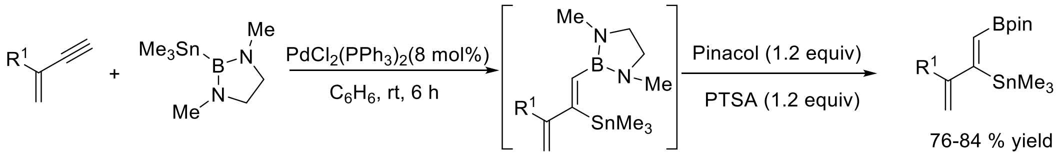
[66] Kalinin, A. V.; Scherer, S.; Snieckus, V. *Angew. Chem., Int. Ed.* **2003**,*42*, 3399-3404.

The same group reported years latter, the Cu-catalyzed carboboration of 1, 3-enynes with MeI (Scheme 40).[60] However, in this transformation they obtained poor selectivities and regioisomeric mixtures, making this methodology inefficient for the selective synthesis of this type of substrates.



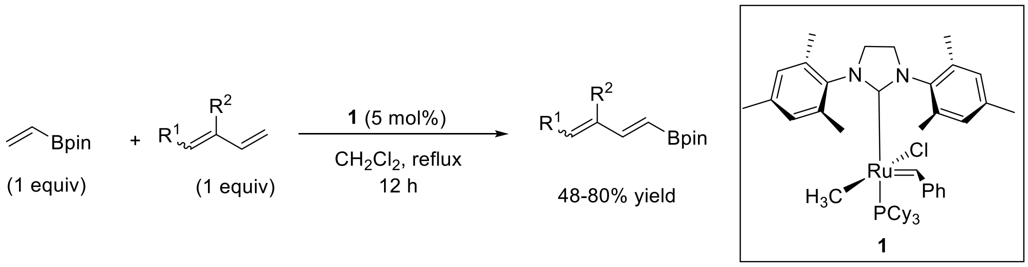
Scheme 40. Cu-catalyzed carboboration of 1, 3-enynes.

Pd-catalyzed borostannylation of enynes was also reported by the group of RajanBabu.[61] In this work, the 1,3-enynes undergoes the addition reaction with high levels of stereo-, chemo- and regioselectivity obtaining a single *Z* isomer with a terminal boronate (Scheme 41).



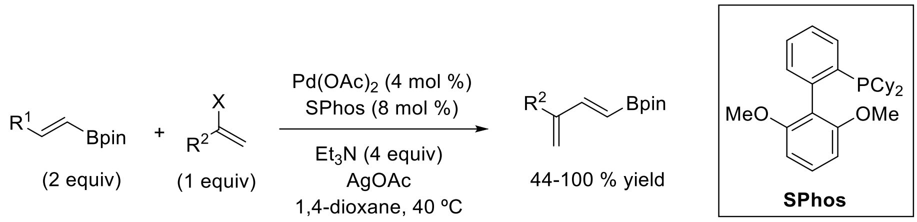
Scheme 41. Pd-catalyzed borostannylation of enynes

Cross-metathesis of vinylboronates with 1,3-butadienes also represents an alternative for the synthesis of *anti*-borylated 1,3-dienes (Scheme 42). In this work, reported by the group of Grubbs, they proposed the use of a ruthenium benzylidene catalyst **1** for the conversion of a butadiene in to stereodefined borylated diene in moderate yield.



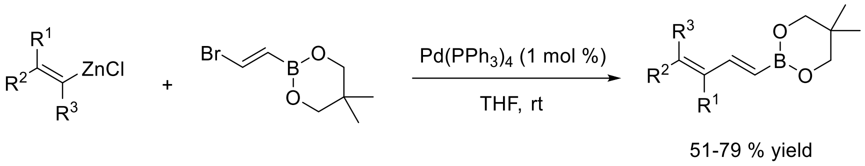
Scheme 42. Cross metathesis of vinylboronates with 1,3-dienes.

Pd-catayzed Heck cross-coupling transformations were also used for the synthesis of *anti*-borylated 1,3-dienes (Scheme 43). In this transformation, the use of a biaryl phosphine such as SPhos, under palladium catalysis in the presence of Et_3N as a base selectively afforded the desired products in good yields.



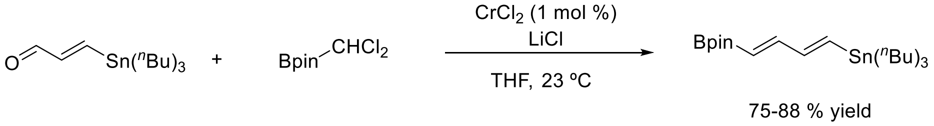
Scheme 43. Heck coupling of alkenyl halides with vinyl Bpin.

The use of vinylzinc chlorides in combination with alquenylboronates in Neghishi cross coupling transformation was possible for the synthesis of 1 -(dialkoxyboryl)- 1.3-dicnes (Scheme x). In this transformation, the stereochemical of both (*E*)-bromoboronate and vinylzinc is maintaining during the outcome of the transformation, allowing the access to [*E*, *E*] and [*Z*, *E*]-1,3-dienylboronic esters.



Scheme 44. Pd-catalyzed Neghishi cross-coupling of vinylzinc chlorides and alkenylboronates.

Finally, the synthesis of hetero-bis-metalated 1,3-butadiene was possible using a Takai olefination transformation between β-stannylacrolein and a dichloromethylborinate to afford the final butadiene in high yields. Then, this versatile structure can be converted into more complex molecules through Stille or Suzuki-Miyaura cross-coupling reactions.



Scheme 45. Use of Takai olefination for the synthesis of hetero-bis-metalated 1,3-dienes

1.1.2 Methodologies for the synthesis of *syn*- borylated 1,3-dienes.

However, methodologies that selectively afford the *syn* isomer are scarce and give rise to limited substitution patterns. In particular, some representative examples of the synthesis of *syn*-1-boron-1,3-dienes will be presented below.

Ito and co-workers reported a regio- and stereoselective Ni-catalyzed silaborative dimerization of alkynes that provides *syn* borylated 1,3-dienes (Scheme 46).[67] For this transformation, they proposed that the silyl(boryl)Ni(II) intermediate **A**, generated by oxidative addition of the Si-B bond in the Ni(0) complex, undergoes *cis*-insertion of alkyne into the B-Ni bond with high regioselective formation of Ni-C bond at the internal alkynyl carbon to afford the Ni(II) intermediate **B.** The second insertion into Si-Ni bond of intermediate **B** takes place with

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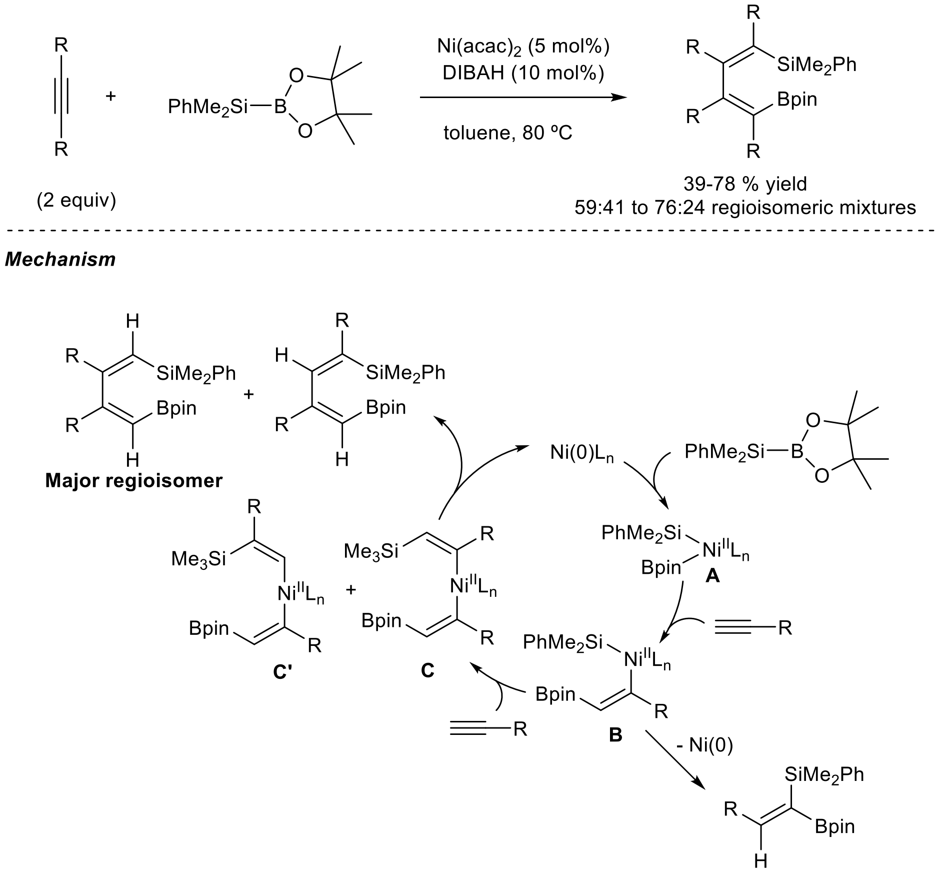
[67] Suginome, M.; Matsuda, T.; Ito, Y. *Organometallics* **1998**, *17*, 5233-5235.

moderate regiochemical preference, affording intermediates **C** and **C'.** Finally, a reductive elimination afforded the silaborative dimerization products.

However, this method is non selective for cross-dimerization of two different alkynes. In these cases, mixtures of the cross-dimerization product with the homodimerization ones are obtained, decreasing the versatility of the methodology.



Scheme 46. Ni-catalyzed silaborative dimerization of alkynes

In 2009, the group of Negishi reported a regio- and stereoselective synthesis of (*Z*)-trisubstituted alkenes via propyne bromoboration and tandem Pd-catalyzed cross-coupling with an alkenylzinc reagent (Scheme 47).[68] During this process, a stereochemical unstable bromo-alkenyldibromoborane **A** is formed, and is necessary to convert it into the pinacolboronate **B**. Then, the boronate must be isolated and purified before the Pd-catalyzed cross-coupling transformation with an alkenyl Zinc reagent to afford the corresponding 1,3-borylated diene. This transformation results in a multi-step methodology in which the isolation and purification of one of the intermediates is necessary.

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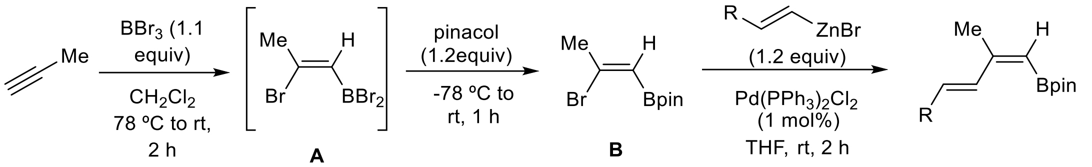
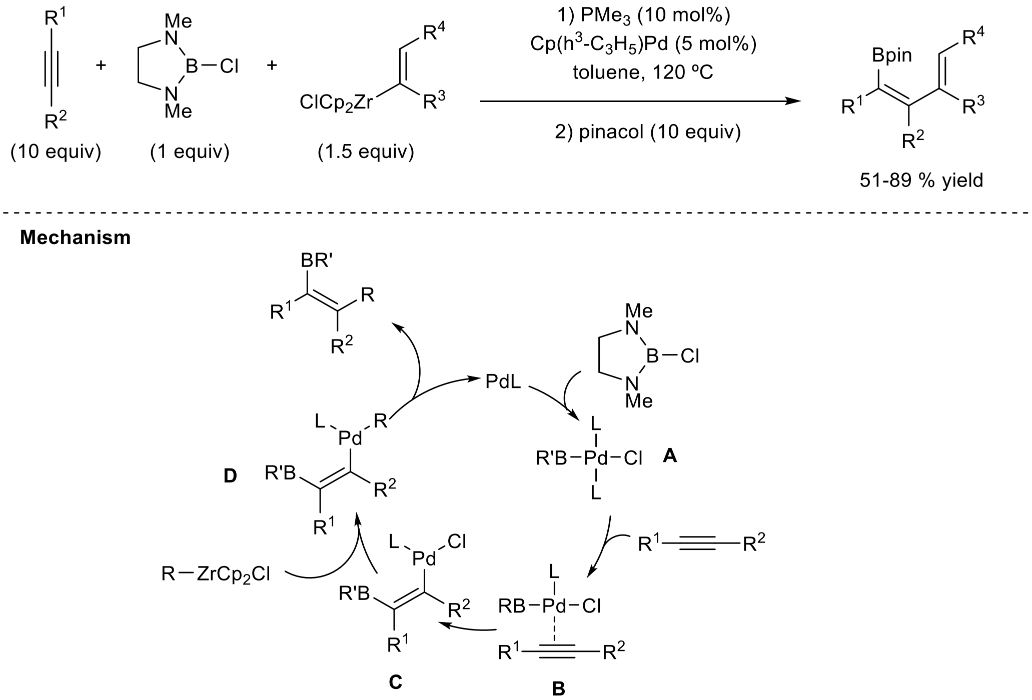
[68] Wang, C.; Tobrman, T.; Xu, Z.; Negishi, E. *Org. Lett.* **2009**, *11*, 4092-4095.



Scheme 47. Bromoboration/Negishi coupling of alkynes

Suginome and Daini reported a Pd-catalyzed transmetalative carboboration of alkynes (Scheme 48).[69] They proposed that this transformation starts with the oxidative addition of the B-Cl bond to palladium to afford intermediate **A**, followed by the insertion of the alkyne in the B-Pd bond to afford a β-borylalkenyl)chloropalladium (II) intermediate **C**. Then, intermediate **C** reacts with the organozirconium compound resulting in the formation of diorganopalladium intermediate **D**. Finally, after reductive elimination, the carboboration product is formed. This transformation requires the use of an air-sensitive chloroborane, alkenylzirconium reagents and a large excess of the alkyne. Moreover, the use of an organometallic compound under harsh conditions limits the functional group tolerance.



Scheme 48. Transmetalative carboboration of alkynes

The trans-selective hydroboration of enynes represents an alternative to the use of organometallic reagents (Scheme 49).[70] Liu and co-workers reported the use of this methodology for the synthesis of *syn*-1-boron-1,3-dienes under palladium catalysis in which the use of monobenzofused 1,4-azaborine-base phosphine ligands play an important role. They found that the use of this Pd(0) complexes catalyzed *trans*-hydroboration of both terminal and

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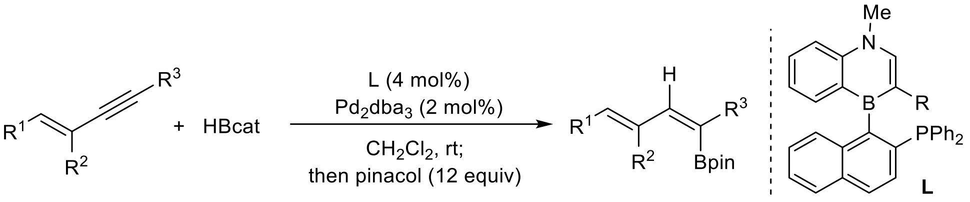
[69] Daini, M.; Suginome, M. *Chem. Commun*. **2008**, 5224–5226.

[70] Xu, S.; Zhang, Y.; Li, B.; Liu, S.-Y. *J. Am. Chem. Soc.* **2016**, *138*, 14566–14569.

internal *E*-1,3-enynes with high stereoselectivity under mild conditions. However, its reductive nature precludes the challenging formation of highly substituted 1,3-dienes.

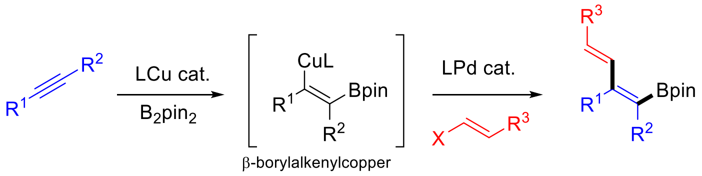


Scheme 49: Trans-hydroboration of enynes

Despite the adnaces shown above, a catalytic transformation which provides rapid and stereoselective access to highly substituted *syn*-borylated 1,3-dienes from simple and abundant starting materials was still highly desirable.

2. OBJECTIVE

Based on previous work in our group, and that of Semba/Nakao and Cazin (See section 1.1.8, Chapter I) on the use of synergistic Cu/Pd catalysis for the carboboration of alkynes, the objective of the present chapter is the development of a catalytic method that provides rapid and stereoselective access to highly substituted *syn*-borylated 1, 3-dienes, using simple and abundant starting materials (Scheme 50).



Scheme 50. Proposed synergistic Cu/Pd alkenylation of alkynes.

We envisioned that a catalytically generated β-borylalkenylcopper intermediate can be used in a Pd-catalyzed cross-coupling transformation with an alkenyl halide under cooperative catalysis regime. This approach provides different advantages with respect to the reported methods. 1) *Syn*-selectivity would result from a *syn*-selective alkyne borocupration; 2) the use of alkynes as pro-nucleophiles avoids the stoichiometric use of an alkenyl metal reagent; 3) activation of the alkenyl halide using a Pd co-catalyst would facilitate the coupling under mild conditions; 4) a single operation allows the assembly of three different components.

The use of alkenyl (pseudo)halides in alkyne carboboration reactions to afford *syn*-selective formation of 1-borylated 1, 3-dienes has not been reported, since the employment of this type of electrophiles entails an extra challenge. There is potential for competitive migratory insertion of the LCu-Bpin intermediate across the alkenyl bromide.

In order to successfully implement this idea, several challenges associated whit the use of copper and palladium synergistic catalysis as well as the substrates must be overcome:

- ***Chemoselectivity***:

To avoid parallel reactions, each catalyst must react with each substrate in a chemoselective manner.
For example, reactions such as the Pd-catalyzed Miyaura borylation of alkenyl halides[71] and the alkyne protoboration must be precluded (Scheme 51).[72]

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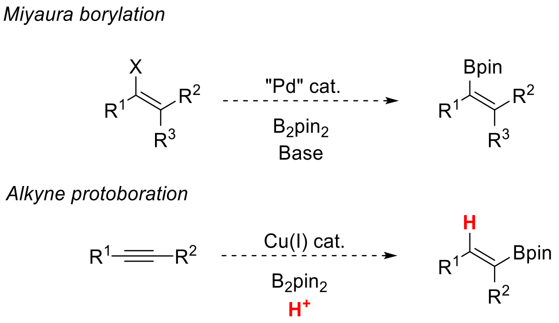
[71] Takagi, J.; Takahashi, K.; Ishiyama, T.; Miyaura, N, . *J.Am. Chem. Soc.* **2002**, *124*, 8001-8006.

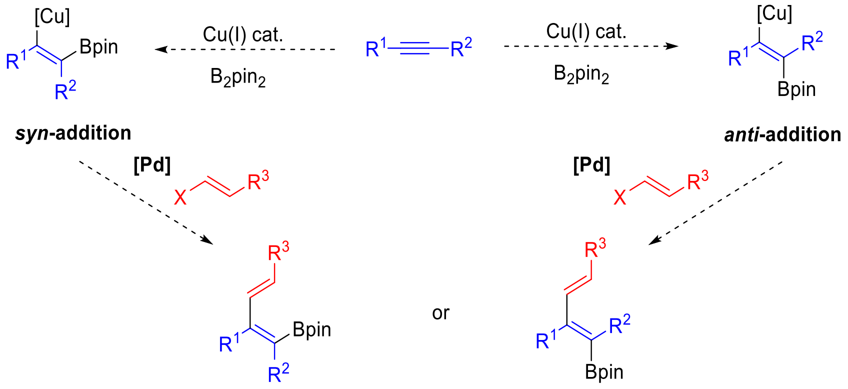
[72] Takahashi, K.; Ishiyama, T.; Miyaura, N. *Chem. Lett.* **2000**, *29*, 982-983.



Scheme 51. Possible side reactions

- ***Stereoselectivity***:

To obtain the desired borylated syn 1,3-diene alkyne insertion into the borylcopper complex (Cu-Bpin) must occur in a *syn*-fashion. This is usually the case for this step. However, isomerization of the alkenylcopper complex can provide the formation of an *anti*-addition product.[73] This fact has been observed in the case of phenylacetylene derivatives (Scheme 52).



Scheme 52. Possible formation of *syn* and *anti* stereoisomers after the addition of Cu-Bpin to the alkyne.

- ***Regioselectivity:***

Insertion of unsymmetrical alkynes can take place in two different ways giving access to the α or β borylated regioisomer (Scheme 53).

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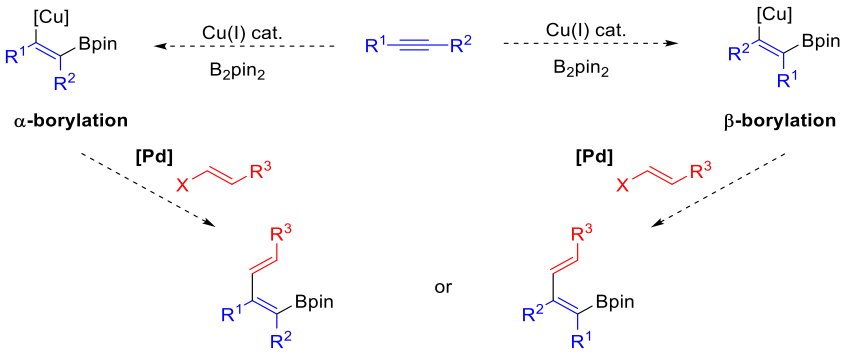
[73] Jang, W. J.; Lee, W. L.; Moon, J. H.; Lee, J. Y.; Yun, J. *Org. Lett*. **2016**, *18*, 1390-1393.



Scheme 53. Copper catalyzed borocupration of alkynes

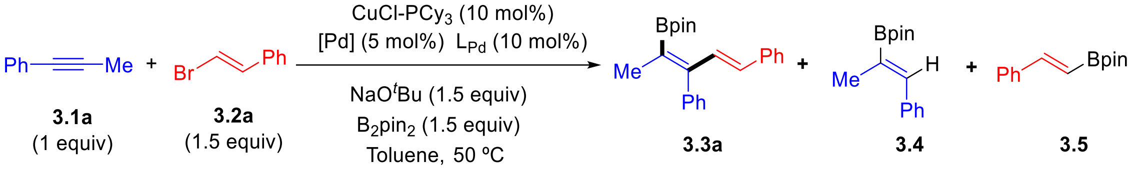
3. RESULTS AND DISCUSSION

3.1 Optimization studies

We started our study by investigating the reaction between B_2pin_2, 1-phenyl-1-propyne (**3.1a**) and b-bromostyrene (**3.2a**) to evaluate the feasibility of the proposed transformation.

We initially evaluated the effect of the ligand in the palladium catalyst (Table 5). For this screening we used sodium *tert*-butoxide as a base, different combinations of Pd/L_{Pd} and CuCl/PCy_3 as the catalytic system. We observed that the use of PCy_3 as ligand for both metals afforded the desired product **3.3a** in 50% yield, obtaining also alkyne protoboration product **3.4** and Miyaura borylation product **3.5**. The use of less basic and/or bidentate phosphines (Table 5, entries 2 and 3) afforded the product in lower ^{1}H-NMR yields and selectivities. Then, we investigate the use of different biarylphosphines (Table 5, entries 4-12). We observed that in most cases the reaction was carried out obtaining good yields for the desired product, obtaining very low yields for the formation of alkyne protoboration or Miyaura borylation product. However, the use of more sterically demanding ligands such as BrettPhos (Table 5, entry 10) did not lead to the formation of **3**.**3a** likely due to a non-efficient rate of transmetalation. The use of less sterically hindered biarylphosphines such as SPhos (Table 5, entry 8) and XPhos (Table 5, entry 9) afforded the best results until the moment. We observed that the yield decreases dramatically when a different palladium source such as $Pd(OAc)_2$ (Table 5, entry 14), $Pd(PPh_3)_2Cl_2$ (Table 5, entry 13) or PEPPSI-^{i}Pr (Table 5, entry 15) was used. The use of a premade catalyst such as XPhos-Pd G3, (Table 5, Entry 16) reduced the ^{1}H-NMR yield until 40%, being slightly increased when we added 10% of free XPhos phosphine (Table 5, entry 17). We conclude that the use of a proper biarylphosphine is key for the process efficiency.

Table 5. Screening of ligands for palladium catalyst.[a]



Entry	**Pd** source	**L$_{Pd}$**	**Conv. (%)**	**^{1}H-NMR yield (%)^b**		
				3.3a	**3.4**	**3.5**
1	Pd(dba)$_2$	PCy$_3$	96	50	25	Traces
2	Pd(dba)$_2$	DPEPhos	90	63	8	10
3	Pd(dba)$_2$	dppf	70	46	19	18
4	Pd(dba)$_2$	CyJohnPhos	Full	60	13	10
5	Pd(dba)$_2$	MePhos	95	70	12	Traces
6	Pd(dba)$_2$	DavePhos	84	52	15	10
7	Pd(dba)$_2$	RuPhos	Full	52	45	-
8	Pd(dba)$_2$	SPhos	Full	71	11	Traces
9	Pd(dba)$_2$	XPhos	96	80	12	Traces
10	Pd(dba)$_2$	BrettPhos	45	Traces	37	-
11	Pd(dba)$_2$	^{t}BuXPhos	98	40	36	-
12	Pd(dba)$_2$	JohnPhos	Full	76	20	-
13	Pd(PPh$_3$)$_2$Cl$_2$	93	16	20	22	
14	Pd(OAc)$_2$	XPhos	76	20	10	18
15	PEPPSI-^{i}Pr		84	37	Traces	18%
16	XPhos-Pd G3		82	40	18	14
17	XPhos-Pd G3	XPhos	Full	54	23	Traces

[a] Reactions performed on a 0.5 mmol scale, [b] Determined by ^{1}H-NMR analysis using 1,3,5-trimethoxybenzene as internal standard.

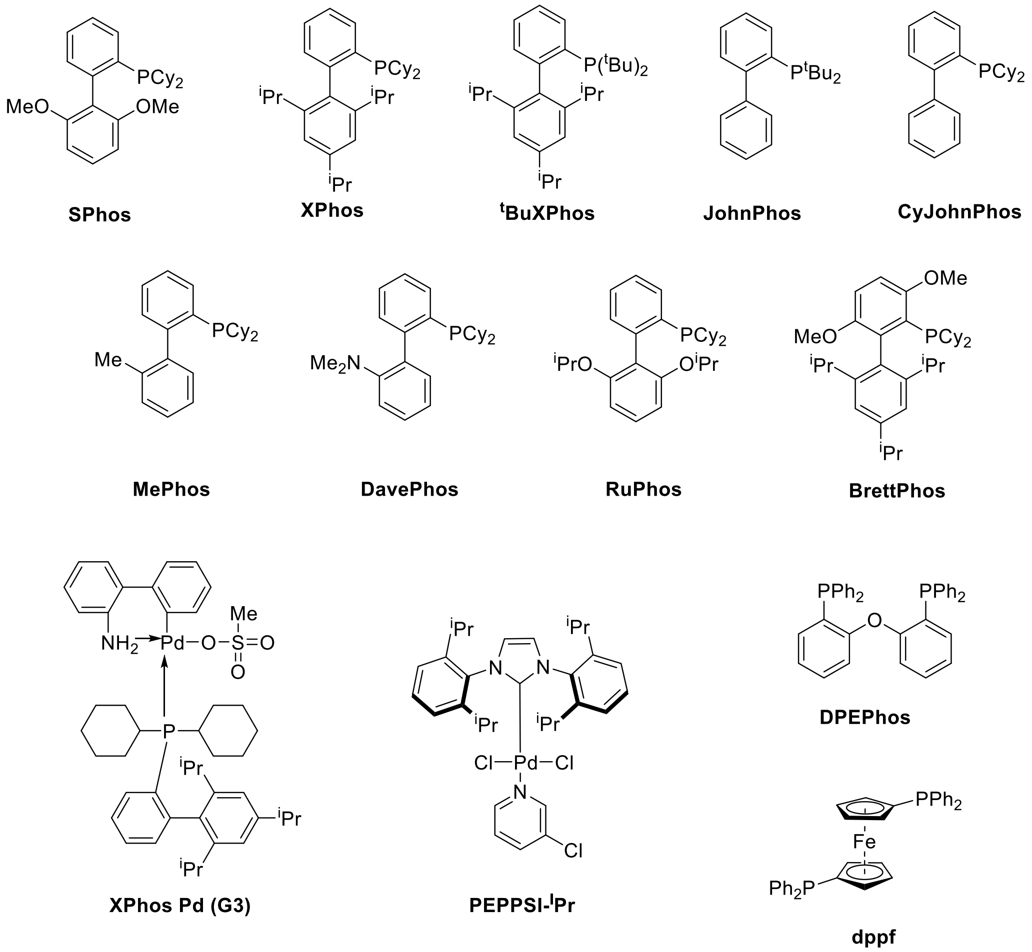
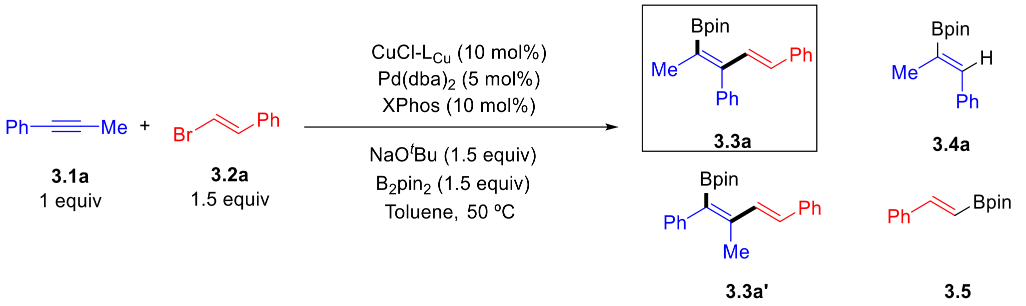


Figure 4. List of ligands for palladium catalyst.

Next, we evaluate the effect of the ligand in the copper catalyst (Table 6). The use of different NHCs ligands (Table 6, entries 2-4) led to the formation of the desired product in moderate yields. However, in these cases, the formation of the regioisomer **3.3a'** was also observed and the formation of **4a** and **5** was increased. The use of the same biaryl phosphine such as XPhos in both metals only afford 15% of desired product (Table 6, entry 5).

Table 6. Screening of ligands for copper catalyst.[a]

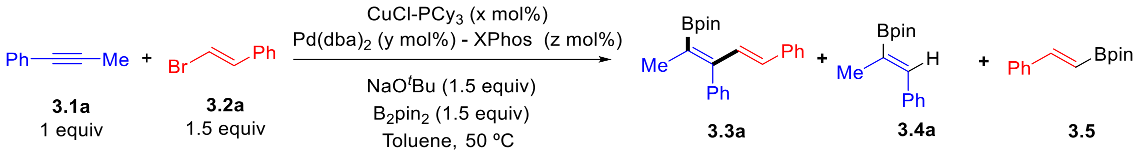


Entry	L$_{Cu}$	Conv. 3.1a (%)[b]	Yield (%)[b]			
			3.3a	3.3a'	3.4	3.5
1	PCy$_3$	96	80	-	12	Traces
2	IMes	Full	43	6	24	Traces
3	SIMes	78	43	Traces	15	25
4	IPr	95	35	10	12	-
5	XPhos	85	15	-	13	Traces

[a] Reactions performed on a 0.5 mmol scale, [b] Determined by ^{1}H-NMR analysis using 1,3,5-trimethoxybenzene as internal standard.

Having established Pd(dba)$_2$/XPhos and CuCl/PCy$_3$ as the optimal catalytic system, we examined the ratio of both catalysts and ligands (Table 7). When using 5:1 or 1:1 Cu/Pd ratio (Table 7, entries 1 and 5) substantial decrease of yield was observed (40 and 48% NMR yield). This shows the importance of matched kinetics in synergistic catalysis, a 2:1 Cu/Pd ratio being necessary to achieve a good result (Table 7, entries 2-4). Another important factor to consider is the amount of L$_{Pd}$. We observed that it is necessary to have a 1:2 Pd/L$_{Pd}$ ratio (Table 7, entries 2 and 4). It is important to highlight that the reaction is totally inhibited in the absence of copper catalyst, obtaining only Miyaura borylation product in trace amount (Table 7, entry 7). Under single copper catalysis only 13% NMR yield of **3.3a** was observed, even at higher temperatures (Table 7, entry 8). Notably, catalysts loading could be reduced to 5 mol% of copper and 2.5 mol% of palladium catalysts (Table 7, entry 4) providing the borylated diene **3.3a** in a slightly increased NMR yield.

Table 7. Evaluation of Cu/Pd catalysts molar ratio.[a]

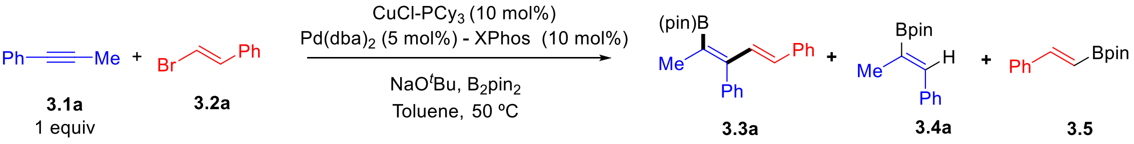


Entry	CuCl (x mol%)[b]	PCy$_3$ (x mol%)[b]	Pd(dba)$_2$ (y mol%)[b]	XPhos (z mol%)[b]	Conv. (%)[b]	Yield (%)[b]		
						3.3a	3.4a	3.5
1	10	10	2	4	88	40	16	8
2	10	10	5	10	96	80	12	Traces
3	8	8	4	8	Full	89	7	-
4	5	5	2.5	5	Full	87	12	-
5	5	5	5	10	90	48	20	-
6	5	5	2.5	2.5	86	45	15	6
7	-	-	5	10	35	-	-	6
8	10	10	-	-	80	13(19)[c]	49(50)[c]	-(13)[c]

[a] Reactions performed on a 0.5 mmol scale, [b] Determined by ^{1}H-NMR analysis using 1,3,5-Trimethoxybenzene as internal standard, [c] Results at 80 °C shown in brackets.

Evaluation of reagents/reactants was also done (Table 8). Initially we observed that the use of 2 equiv. of base is key in this transformation. When we tried to reduce the amount of NaO^{t}Bu, the yield decreased or no reaction was observed (Table 8, entries 2 and 3). A reduction in the amount of β-bromostyrene and base resulted in a slightly higher yield (Table 8, entry 4). Unfortunately, it was no possible to decrease the amount of B$_2$pin$_2$ (Table 8, entry 5).

Table 8. Evaluation of reagent/reactants stoichiometry.[a]

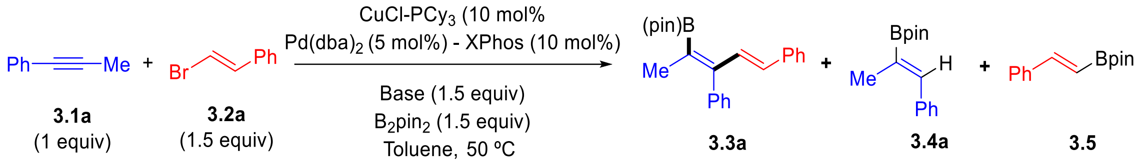


Entry	3.2a (equiv)	NaO^{t}Bu (equiv)	B$_2$pin$_2$ (equiv)	Conv. (%)[b]	NMR yield (%)[b]		
					3.3a	3.4a	3.5
1	1.5	2	1.5	Full	80	9	Traces
2	1.5	1.2	1.5	94	50	23	Traces
3	1.5	0.2	1.5	-	-	-	-
4	1.2	1.5	1.5	Full	84	12	Traces
5	1.2	1.5	1.2	92	65	7	Traces

[a] Reactions performed on a 0.5 mmol scale, [b] Determined by ^{1}H-NMR analysis using 1,3,5-Trimethoxybenzene as internal standard.

We next screened the effect of base (Table 9). We initially observed that changing the cation of the base has an impact in the outcome of the reaction (Table 9, entries 1-3). KO^{t}Bu and LiO^{t}Bu led to **3.3a** in lower yield. Other type of bases such as NaOMe or LiOMe provided very little or no formation of product (Table 9, entries 4 and 5).

Table 9. Effect of base.[a]

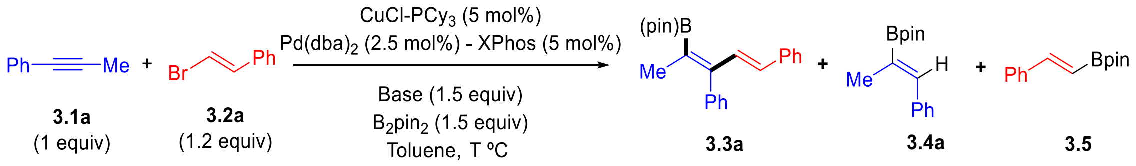


Entry	Base	Conv. (%)[b]	Yield (%)[b]		
			3.3a	**3.4a**	**3.5**
1	NaO^{t}Bu	96	80	12	Traces
2	KO^{t}Bu	98	65	25	Traces
3	LiO^{t}Bu	84	60	20	Traces
4	NaOMe	82	27	31	7
5	LiOMe	No reaction			

[a] Reactions performed on a 0.5 mmol scale, [b] Determined by ^{1}H-NMR analysis using 1,3,5-Trimethoxybenzene as internal standard.

Finally combining the best conditions for this transformation until the moment, we tried to low the temperature (Table 10) and similar results were observed at 50 °C or 30 °C.

Table 10. Effect of temperature. [a]



Entry	Temperature (°C)	Conv. (%)	Yield (%)[b]		
			3.3a	**3.4a**	**3.5**
1	50	Full	87	12	-
2	30	98	86(78)[c]	10	-

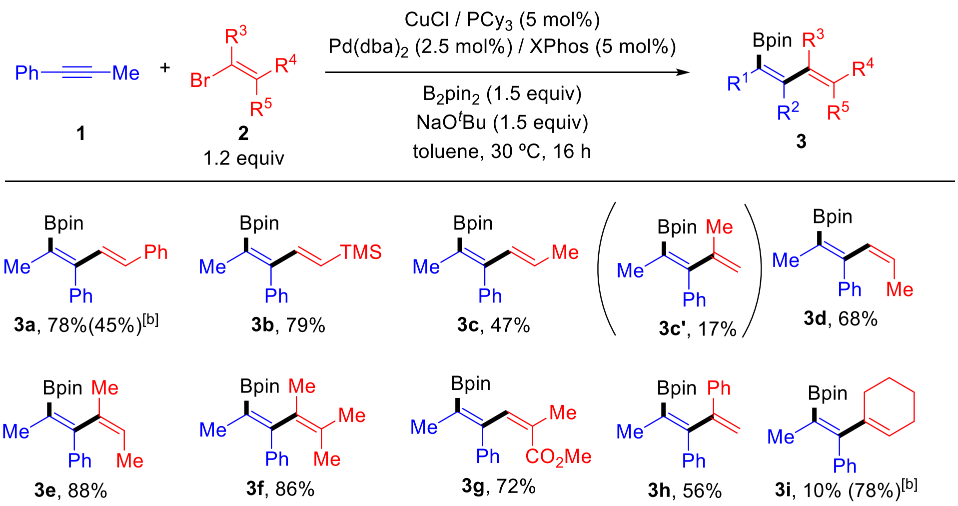
[a] Reactions performed on a 0.5 mmol scale, [b] Determined by ^{1}H-NMR analysis using 1,3,5-Trimethoxybenzene as internal standard. [c] Isolated yield shown in brackets.

3.2 Scope of the reaction

Having established the optimized conditions for the Cu/Pd-catalyzed alkenylboration of alkynes (Table 10, entry 2), we set out to investigate the scope of the reaction (Tables 11 and 12). Importantly, the estereoretentive nature of this process preserves the stereochemical information of the catalytically generated β-borylcopper intermediate and the alkenyl bromide, affording stereomerically pure diene structures.

Different alkenyl bromides featuring all types of substitution pattern were used obtaining in all cases the corresponding borylated dienes **3.3a–h** with total chemo- regio- and *syn*-stereoselectivity (Table 11). Alkenyl triflates were also compatible substrates with this transformation. While acyclic triflates provided diminished yield, as illustrated in the synthesis of **3.3a**, 1-cyclohexenyl triflate proved to be much more efficient for the synthesis of product **3.3i** than the corresponding cyclic bromide. Importantly, the stereoretentive nature of this process preserves the stereochemical information of both the catalytically generated β-boryl alkenylcopper intermediate and the alkenyl bromide, thus providing stereomerically pure diene structures. Partial erosion of the alkenyl bromide structure was only observed when *trans*-1-bomo-1-propene **3.2c** was used. In this case diene **3.3c** was obtained together with a small amount of isomer **3.3c’** which probably results from coupling of in-situ formed 2-bromo-1-propene. Noteworthy are the reactions with alkenyl bromides bearing functional groups such as trimethylsilyl and ester moieties that give stereoselective access to bifunctionalized dienes **3.3b** and **3.3g** which can serve as versatile linchpin reagents in the construction of polyene frameworks.

Table 11. Alkenyl bromides scope.[a]

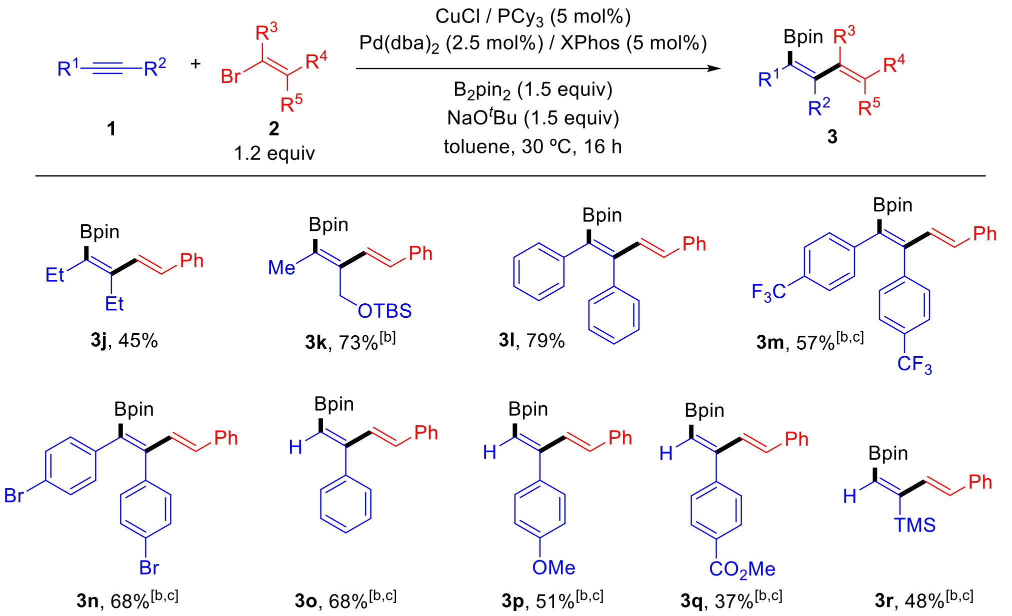


[a]Reactions performed on a 0.5 mmol scale and yields refer to isolated products. [b] The corresponding alkenyl triflate was used.

Regarding the alkyne partner, internal alkynes bearing both aromatic or aliphatic substituents proved to be very efficient substrates affording the corresponding products **3.3j–n** in good yields (Table 12). Remarkably, in the case of **3.3n**, there was no evidence of borylation of the aryl bromide further highlighting the high chemoselectivity of this dual catalytic system. Terminal alkynes showed slightly diminished reactivity and required the use of a more elevated temperature (50 °C) and higher catalyst loading. However, under these conditions dienes **3.3o**–

q could be obtained in competitive yields. It is important to note that the use of trimethylsilylacetylene not only provides bifunctionalized diene **3.3r** but also opens the possibility to access less substituted borylated dienes by desilylation. Thus, 1-boron-1,3-dienes featuring all type of substitution patterns, ranging from simple 1,4-disubtituted structures to the challenging hexasubstituted systems which are difficult to access by other methods, are available by this novel Cu/Pd-catalyzed alkenylboration reaction.

Table 12. Scope of alkynes [a]

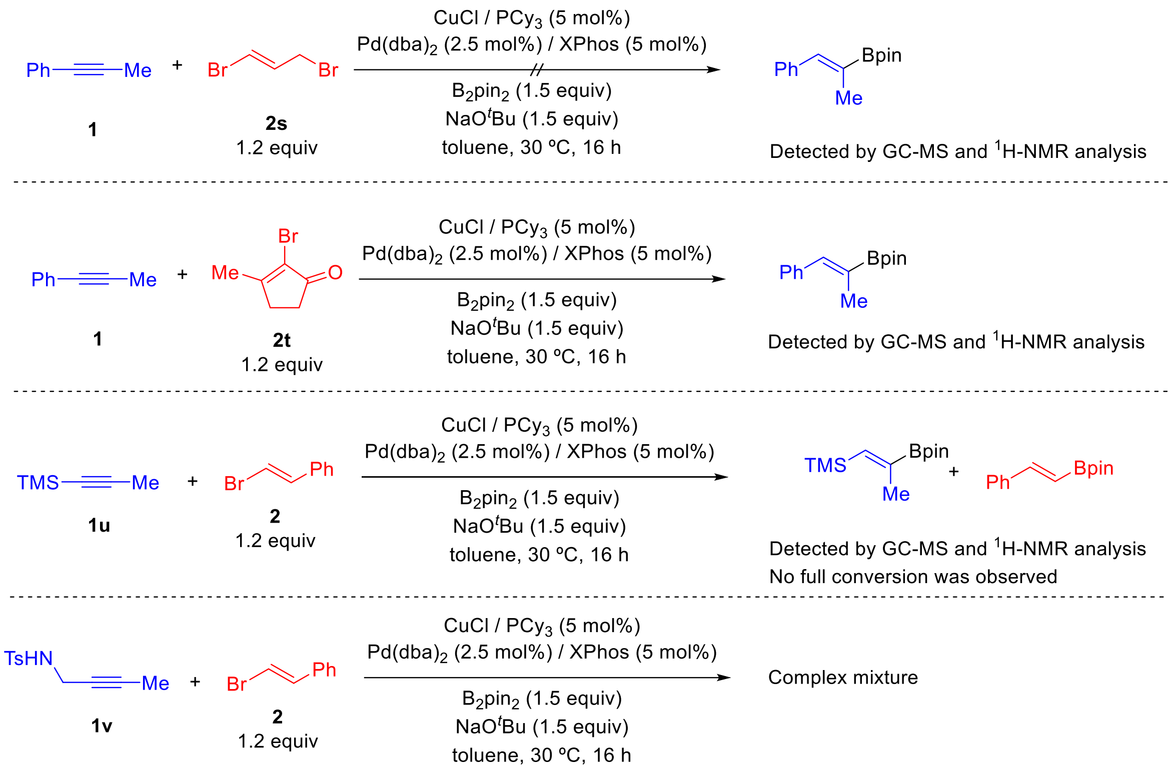


[a] Reactions performed on a 0.5 mmol scale and yields refer to isolated products, [b] Reaction performed at 50 °C. [c] Use of CuCl/PCy3 (10 mol%), Pd(dba)2 (5 mol%), XPhos (10 mol%).

3.2.1 Scope limitations

Although the transformation showed a high tolerance for several functional groups and different substitution patterns, some substrates resulted unreactive under optimal standard conditions (Scheme 54). (*E*)-1,3-dibromoprop-1-ene, **3.2s** decomposed under standard conditions and only alkyne protoboration product was observed in that case.

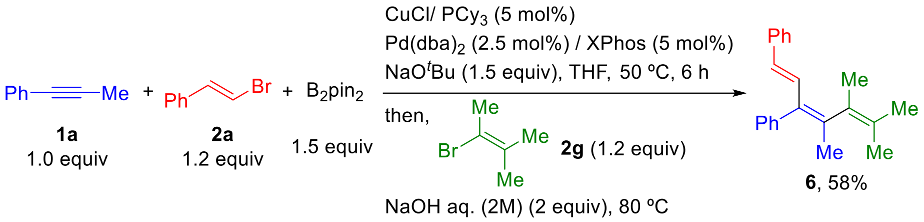
In the case of the cyclic functionalized alkenyl bromide **3.2t** similar outcome was observed. Regarding alkynes, internal alkyne **3.1u**, did not afford the desired product an only alkyne protoboration and Miyaura borylation of the β-bromostyrene was observed. In the case of the alkyne **3.1v**, a complex mixture of products was observed by GC-MS and ^{1}H-NMR analysis.



Scheme 54. Unreactive substrates for Cu/Pd catalyzed synthesis of *syn*- 1,3-borylated dienes.

3.3 Product derivatization

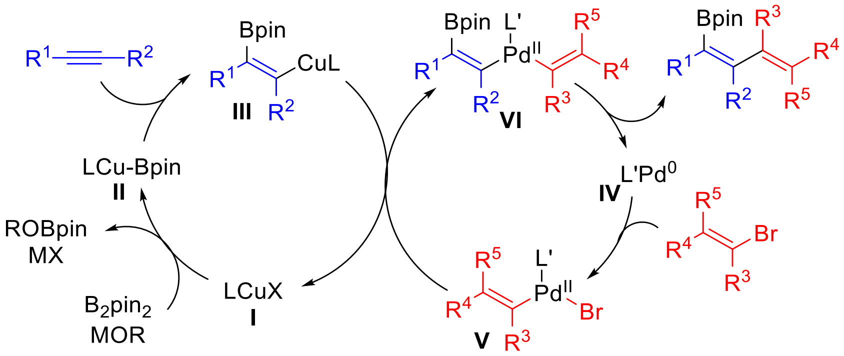
An interesting feature of this methodology is the synthetic versatility of the boronic ester group that can be exploited in combination with the initial catalyst to stereoselectively access triene structures in a one-pot alkenylboration/Suzuki coupling. This formal alkyne dialkenylation was illustrated by the synthesis of triene **3.6** (Scheme 55). Thus, treatment of alkyne **3.1a** with alkenylbromide **3.2a** and B_2pin_2 under modified optimized conditions and subsequent addition of alkenyl bromide **3.2g** and NaOH aqueous solution led to triene **3.6** in 58% yield. For this transformation was necessary the use of THF as solvent, which is perfect compatible with the alkenylboration reaction. Was necessary to achieve high efficiency in the Suzuki coupling, since the use of toluene did not afford full conversion of the borylated 1, 3-diene.



Scheme 55. Synthesis of triene 6 by one-pot alkenylboration/Suzuki coupling

3.4 Mechanistic proposal

In sight of the experimental results, we propose a dual catalytic mechanism (Scheme 56) that consists in a regio- and stereoselective borylcupration of the alkyne with LCu-Bpin complex **II** to generate the β-boryl alkenylcopper (I) intermediate **III**. The second catalytic cycle starts with the oxidative addition of the alkenyl substrate to a Pd(0) complex **IV** to afford the alkenylpalladium (II) intermediate **V**. Then, a transmetalation step between intermediates **III** and **V** afford intermediate **VI**. Finally, a reductive elimination process releases the desired product and recovered both catalytic active spieces.



Scheme 56. Mechanistic proposal for the Cu/Pd catalyzed alkenylboration of alkynes.

4. CONCLUSIONS

We have developed an efficient methodology for the synthesis of borylated 1,3-dienes, through a novel palladium and copper synergistically catalyzed alkenylboration of alkynes under mild conditions.

One of the main features of the catalytic system are the remarkable high levels of chemo-, regio-, and stereoselectivity for the synthesis of *syn*-1-boron-1,3-dienes. Side reactions such as Miyaura borylation of alkenylbromide and alkyne protoboration are completely precluded or reduced to not significant levels.

The use of bench stable and readily available starting materials under mild conditions makes the method practical and straightforward. Additionally, stereodefined conjugated trienes can also be accessed via a one-pot alkenylation/Suzuki coupling in which the initial palladium complex act as a two-fold catalyst.

CHAPTER IV: Bifunctional skipped dienes through Cu/Pd-catalyzed allylboration of alkynes with B_2pin_2 and vinyl epoxides

Chapter adapted from: Vázquez-Galiñanes, N.; Velo-Heleno, I.; Fañanás-Mastral, M. *Org. Lett.* **2022**, 24, 8244–8248.

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

1. INTRODUCTION

1.1 Vinyl epoxides as reagents

Vinyl epoxides represent a versatile class of substrates since they can be used in a number of synthetic transformations.[74] The presence of an oxirane group next to a carbon-carbon double bond is key to provide a high synthetic versatility to these molecules.

Nucleophilic ring opening is the most common transformation for this type of substrates. Due to the strain of the oxirane, intermolecular attack has been observed at all four possible positions (Figure 5). Usually, soft nucleophiles prefer the formation of S_N2' product which is formed through a 1,4-addition (pathway a), while hard ones prefer the 1,2-addition (pathway b). The attack in the position c is an alternative S_N2 transformation that takes places when this reaction site is unhindered in comparison to attack in position b, when the size of the ring disfavors pathway b, or when there are directing groups. The fourth possibility (pathway d) involves the alkene functionalization. This is a rare and it has only been observed for substrates where R is and electron-withdrawing group that competes with the epoxide reactivity.

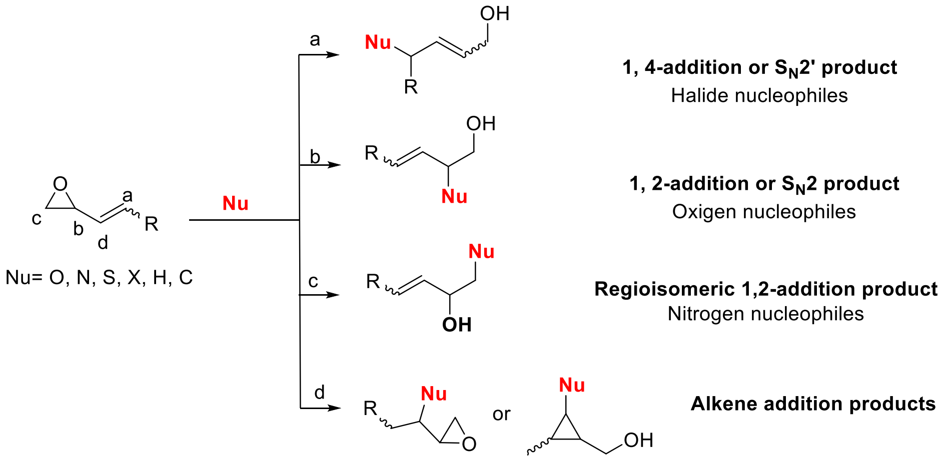


Figure 5. Nucleophilic ring-opening pathways of vinyl epoxides

Besides the reactions involving a nucleophilic ring opening, vinyl epoxides have also been used in in different rearrangements, such as pericyclic reactions, radical reactions or different cycloaddition transformations.[74]

Given their inherent reactivity, vinyl epoxides have also served as versatile substrates in transition metal catalysis. Among the different transformations, the metal-catalyzed allylic alkylation of vinyl epoxides is of main interest since it allows the concomitant formation of a C-C bond and an allylic alcohol which can be used for further functionalization. [75] Several carbon nucleophiles have been used in Pd-catalyzed alkylation of vinyl epoxides.

In this type of transformations, a zwitterionic η^3-allyl-Pd(II) complex is formed by oxidative addition of the vinyl epoxide to the Pd(0) species. Then, nucleophilic attack to this electrophilic Pd species can take place through a 1,2 or 1,4-addition. Control over the regioselectivity in this step represents the key challenge in this type of reactions (Scheme 57).

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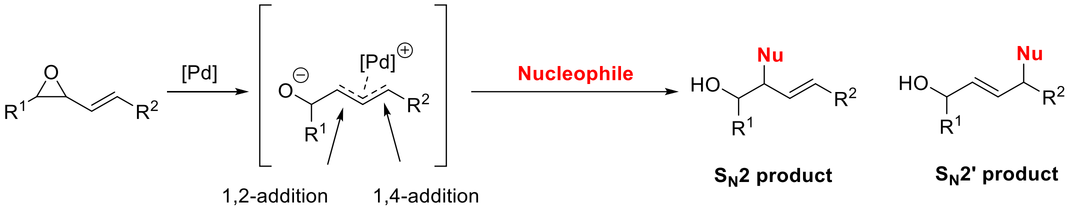
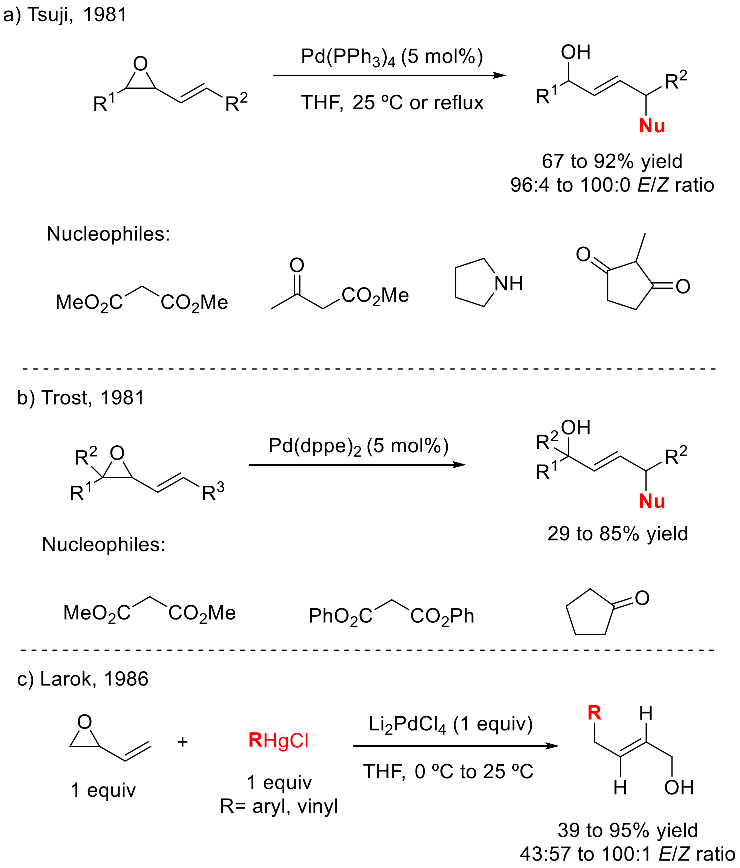
[74] For review see: He, J.; Ling, J.; Chiu, P. *Chem. Rev.* **2014**, *114*, 8037-8128.

[75] a) Tsuji, J.; Kataoka, H.; Kobayashi, Y. *Tetrahedron Lett.* **1981**, *22*, 2575-2578. (b) Trost, B. M.; Molander, G. A. *J. Am. Chem. Soc.* **1981**, *103*, 5969-5972. (c) Trost, B. M.; Warner, R. W. *J. Am. Chem. Soc.* **1983**, *105*, 5940-5942. (d) Larock, R. C.; Ilkka, S. J. *Tetrahedron Lett.* **1986**, *27*, 2211-2214 (e) Trost, B. M.; Granja, J. R. *J. Am. Chem. Soc.* **1991**, *113*, 1044-1046.



Scheme 57. Pd-catalyzed reactions via Zwitterionic allylpalladium intermediates

In 1981 Tsuji and co-workers reported the regioselective 1,4-addition of different stabilized nucleophiles such as malonate, cyclic ketones or pyrrolidine to 1,3-diene monoepoxides using palladium catalysis under neutral conditions to afford selectively 1,4-adducts (Scheme 58a).[75a] At the same time, the group of Trost reported a similar strategy for the regioselective formation of the 1,4-addition product using a different Pd catalyst (Scheme 58b).[75b] Some years later, Larock and co-workers reported a regio- and steroselective synthesis of functionally substituted allylic alcohols via 1,4- organopalladium additions to unsaturated epoxides (Scheme 58c).[75d]



Scheme 58. Pd-catalyzed allylic alkylation of vinyl epoxides

1.2 Pd-catalyzed alkenylation of vinyl epoxides with alkenyl nucleophiles

However, although several carbon nucleophiles have been used in this reaction, examples regarding the use of alkenyl nucleophiles in Pd-catalyzed cross-couplings are mainly limited with the use of alkenylstannanes[76] and alkenylboranes.[77]

Stille and co-workers reported in 1988 the palladium-catalyzed coupling of vinyl epoxides with organostannanes (Scheme 59a).[76a] In this transformation, the vinyl epoxides undergo oxidative addition to Pd(0) and coupled with different organostannanes in a 1,4-addition or 1,2-addition manner. The reaction takes place in the presence of a weakly ligated palladium catalyst $(CH_3CN)_2PdCl_2$, in a polar solvent such as DMF and under mild conditions of temperature. Usually, the Pd-catalyzed coupling of organostannanes with other type of electrophiles are insensitive to water. However, in this case, the use of water gave rise to higher yields of final products than when the reaction was run under dry conditions. Moreover, in the presence of water, the selectivity of the reaction is affected, obtaining high regioselectivity to the 1,4-allylic alcohol product and more effective *E*/*Z* ratios. Although regioisomeric mixtures were formed, high regioselectivity to the 1,4-allylic alcohol product was observed. The ratio of allylic to homoallylic alcohols (1,4: 1,2) is affected by the substitution pattern on the vinyl epoxide. Regarding with the scope, several alkenyl coupling partner such as vinyl, phenyl and styryl groups were transferred affording the corresponding products. The same group reported the use of cyclic vinyl epoxides using the same conditions (Scheme 59b).[76b] They observed that several vinyl epoxides derived from cyclic 1,3-dienes afforded stereoselectively the desired products in moderate to good yields. Moreover, although both 1,4 and 1,2-regioisomers were obtained, only the *trans*- substituted isomer was observed.

The use of bisnucleophiles in Pd-catalyzed alkenylation of vinyl epoxides have also been reported in 2001 (Scheme 59c).[76c] For this transformation they used palladium complexes without strongly coordinating ligands in order to favor the Pd/Sn transmetalation step. Thus, the use of palladium complexes with MeCN, dba or COD as the ligands selectively afford the corresponding product in good yields and *E*/*Z* selectivities, favoring the *E* isomer. The use of a phosphine as ligand, do not promote the transmetalation may be due to the reduced electophilicity of the (ŋ^3-allyl) palladium complex, leading to the nucleophilic attack of the malonate-type anion.

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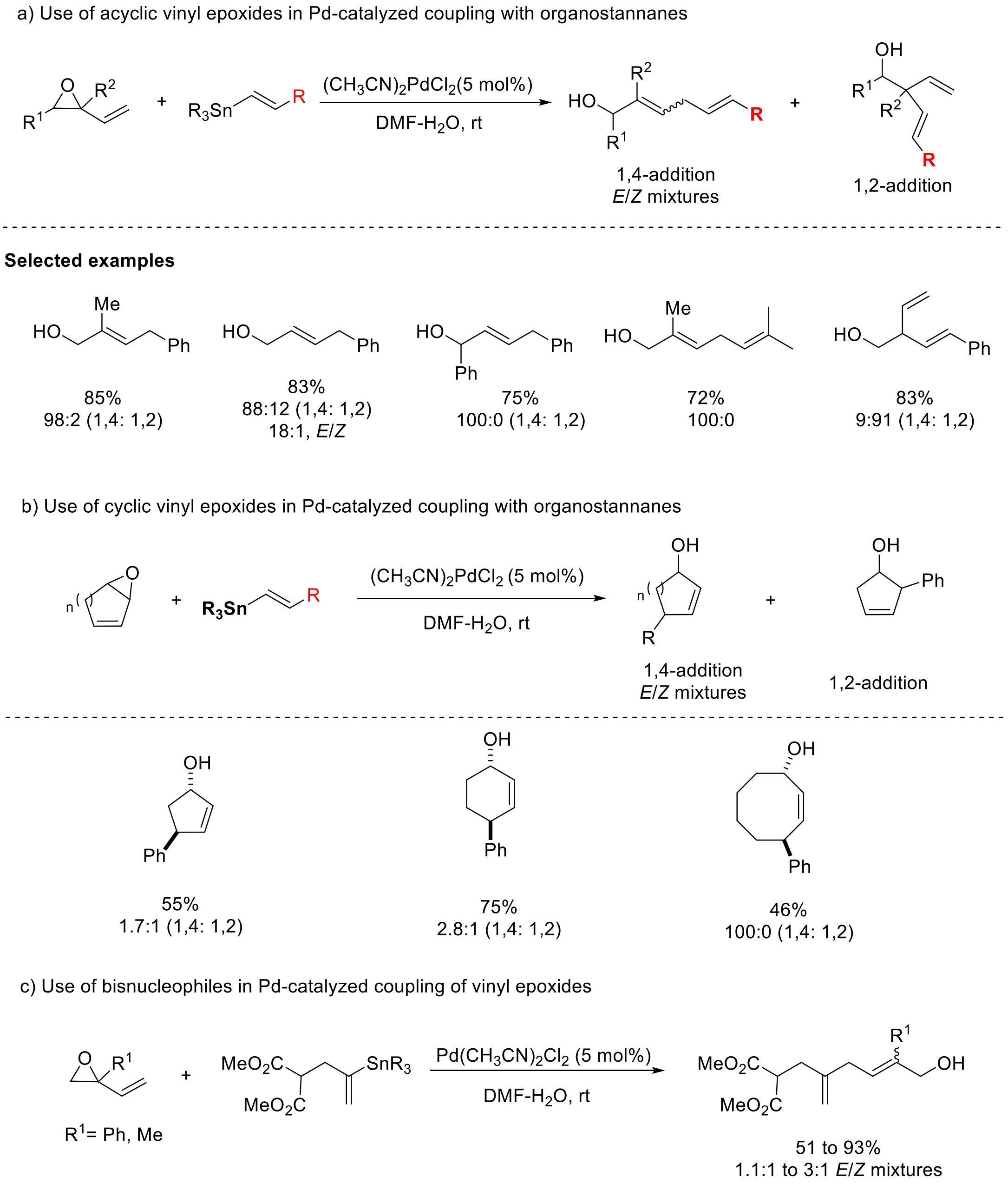
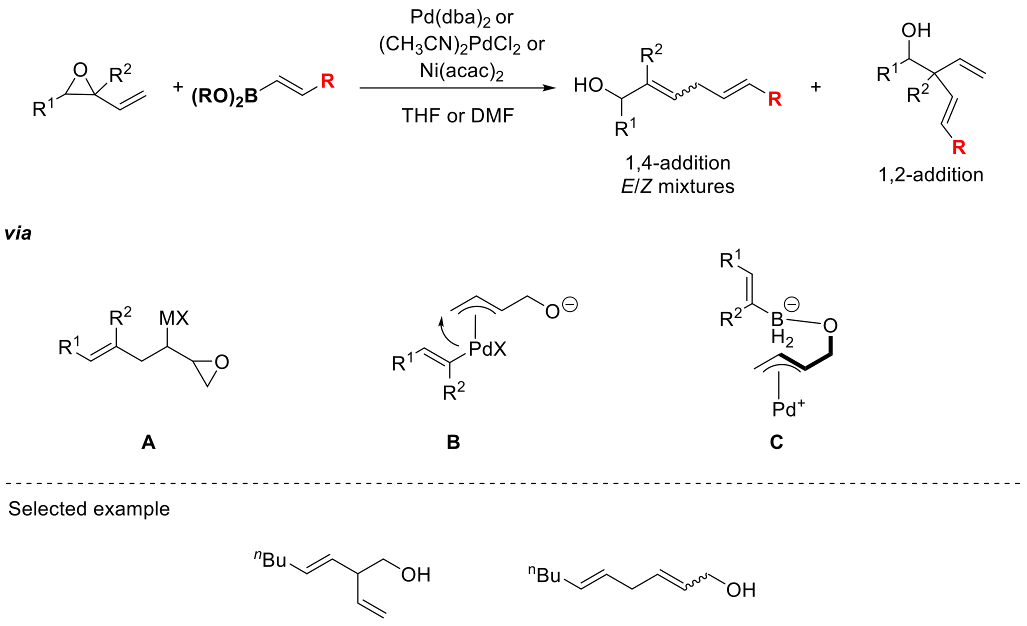
[76] (a) Echavarren, A. M.; Tueting, D. R.; Stille, J. K.*, J. Am. Chem. Soc.* **1988**, *110*, 4039-4041. (b) Tueting, D. R.; Echavarren, A. M.; Stille, J. K., *Tetrahedron* **1989**, *45*, 979-992. (c) Castaño, A. M.; Méndez, M.; Ruano, M.; Echavarren, A. M., *J. Org. Chem.* **2001,** *66,* 589-593.

[77] (a) Miyaura, N.; Tanabe, Y.; Suginome, H.; Suzuki, A., *J. Organomet. Chem.* **1982**, *233*, C13-C16. (b) Kjellgren, J.; Aydin, J.; Wallner, O. A.; Saltanova, I. V.; Szabó, K. J., *Chem. Eur. J.* **2005**, *11*, 5260–5268.



Scheme 59. Pd-catalyzed coupling of vinyl epoxides with organostannanes.

Miyaura and co-workers reported the cross-coupling of vinyl epoxides with alkenylboranes (Scheme 60).[77a] In this case the reaction took place either in the presence of a Pd or a Ni catalyst, and the regioselectivity highly depended on the nature of the transition metal catalyst and in the nature of the alkenyl borane. Thus, the formation of 1,4-addition product was predominant when $PdCl_2(PhCN)_2$ or $Ni(acac)_2$ were used, while the formation of 1,2-addition product was predominant when metal complexes such as $Pd(dba)_2$, $Pd(PPh_3)_4$ or $Ni(PPh_3)_4$ were used. They proposed that two different competitive mechanisms take place to explain the regioselectivity. They proposed that the 1,4-addition product could be formed when metal complexes are in oxidation state II, either though opening of epoxide ring in an intermediate **A** or through reductive elimination of π-allylallylmetal complex **B**, formed by addition of alkenylmetal (II) complexes, generated from transmetalation between metal (II) complexes and alkenylboronates to vinyl epoxide. The alkenyl group would be linked with the less sterically hindered atom when complexes **B** collapses. On the other hand, 1,2-addition product could be formed by catalysis of Pd(0) complexes through an intermediate such as **C**, formed by a coordination of an alkenylborane to the oxygen of a zwitterionic π-allylcomplex. Then, the alkenyl group in intermediate **C** attack the more hindered atom of the π-allyl unit to afford the 1,2-addition product preferentially.



Pd(dba) inTHF, rt	92% (74:26)
PdCl$_2$(PhCN)$_2$ in THF, rt	51% (22:78)
Ni(acac)$_2$ in DMF, rt	85% (16:24), (96:24) *E,E*/ *Z,E*
Pd(dba)$_2$ in THF, 80 °C	70% (24:76)

Scheme 60. Pd and Ni-catalyzed coupling of vinyl epoxides with pregenerated alkenylboronate compounds

However, besides the drawbacks associated with the stoichiometric use of premade alkenylmetal reagents, control over the regioselectivity (1,4- vs 1,2-addition) and stereoselectivity (*E* vs *Z* isomer) has represented a major issue in both cases.

1.3 Ni-catalyzed three-component coupling

Similar type of products of the ones obtained from Pd-catalyzed alkenylation of vinyl epoxides with organoestannanes or alkenylboronates can be accessed by the Ni-catalyzed three-component coupling of a vinyl epoxide, an alkyne and dimethylzinc reported by Kimura (Scheme 61).[78] They observed that this transformation takes place under the use of Ni(acac)$_2$ as catalyst in the absence of ligand and THF as solvent. Internal alkynes attack the terminal carbon of the vinyl group to afford the corresponding 1,4-addition product in a *E*/*Z* mixture via transfer of the methyl group from the ZnMe$_2$. However, when terminal alkynes were used mixtures of

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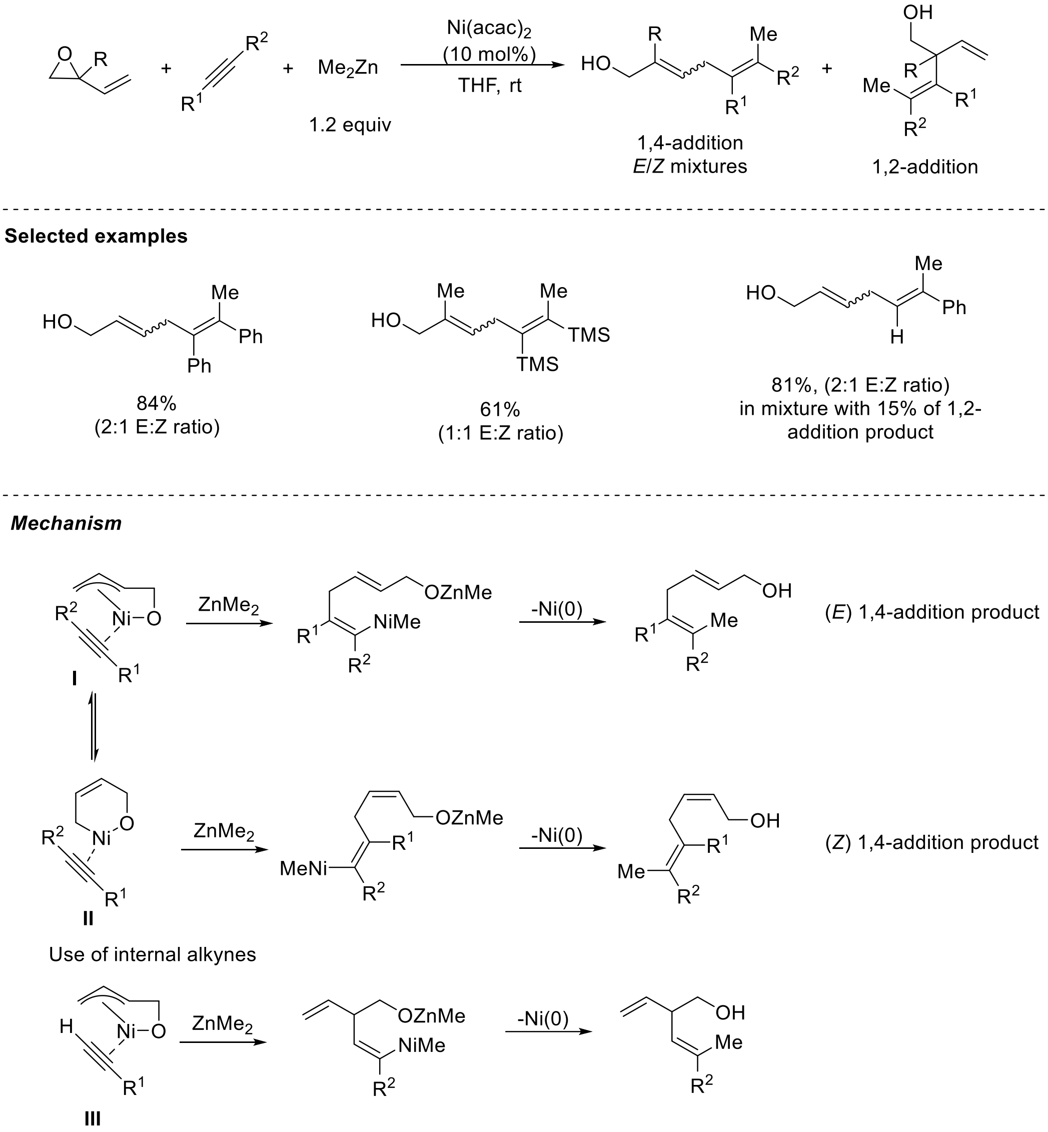
[78] Mori, T.; Nakamura, T.; Kimura, M. *Org. Lett.* **2011**, *13*, 2266–2269.

regioisomers were obtained. For this transformation they proposed the mechanism shown in Scheme 61. The origin of the low diastereoselectivity could be originated from the formation of π-allyloxanickelacycle intermediate **I**, wich is in equilibrium with the oxanickelacycle **II**. Then, a methyl group transfer from the Zn to the Ni center, afforded C-C bond formation as a mixture of stereoisomers. In the case of the use of terminal alkynes, the terminal carbon attack on the allylic position of the vinyloxacyclopropane leading to the branched regioisomer owing to less steric repulsion between the allylic moiety of intermediate **III** and the H atom of the terminal alkyne.

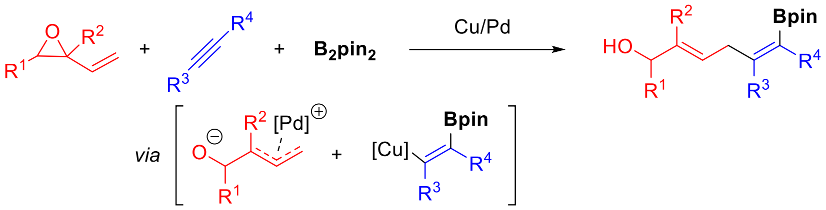


Scheme 61. Ni-catalyzed coupling of vinyl epoxide, alkyne and dimethylzinc.

Moreover, in this three-component transformation, also the use of stoichiometric amounts of organometallic reagents as well as lower selectivities represents a limitation for their use.

2. OBJECTIVE

Based on previous work on the Cu/Pd-catalyzed allylboration of alkynes with allylic carbonates (See Chapter 1, section 1.1.8),[33] we envisaged the development of a three-component catalytic process involving vinyl epoxides, alkynes and B_2pin_2. The use of this strategy would result in a bifunctional skipped diene bearing two orthogonal functionalities such and allylic alcohol and an alkenylboronate (Scheme 62).



Scheme 62. Cu/Pd-catalyzed allylboration of alkynes.

Besides the control over the regio- and stereoselectivity, the success of our proposed strategy also requires a high level of chemoselectivity since competitive addition of B_2pin_2 to the vinyl epoxide must be suppressed. Additionally, trapping of the allylpalladium complex by the alkenylcopper intermediate should be fast.

This method is significant from previous hydrocarbon carboboration reactions since it would be the first example that allows for the use of vinyl epoxides. It is also important to note that this new methodology provides unique access to these bifunctional dienol boronates which can be transformed into a variety of structures in a stereocontrolled manner.

In order to successfully implement this idea, several challenges must be overcome:

- ***Chemoselectivity***:

To avoid side reactions, each catalyst must react with each substrate in a chemoselectivity manner. Competitive addition of B_2pin_2 to the vinyl epoxide[79] must be suppressed (Scheme 63a). Moreover, trapping of the allyl-Pd complex by the alkenylcopper intermediate should be faster than potentially competitive rearrangement to the corresponding carbonyl compound (Scheme 63b).[80]

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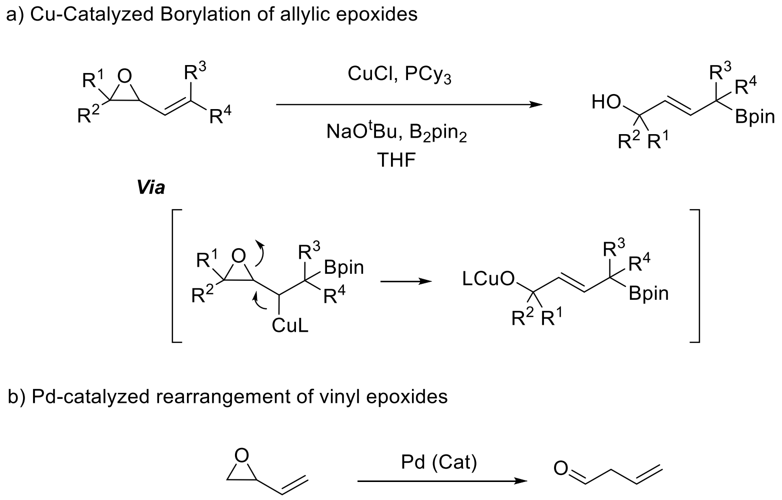
[79] (a) Tortosa, M. *Angew. Chem. Int. Ed.* **2011**, *50*, 3950 –3953. (b) Sanz, X.; Lee, G. M.; Pubill-Ulldemolins, C.; Bonet, A.; Gulyás, H.; Westcott, S. A.; Bo, C.; Fernández, E. *Org. Biomol. Chem.* **2013**, *11*, 7004-7010. (c) Amenos, L.; Trulli, L.; Novoa, L.; Parra A.; Tortosa, M. *Angew. Chem. Int. Ed.* **2019**, *58*, 3188-3192.

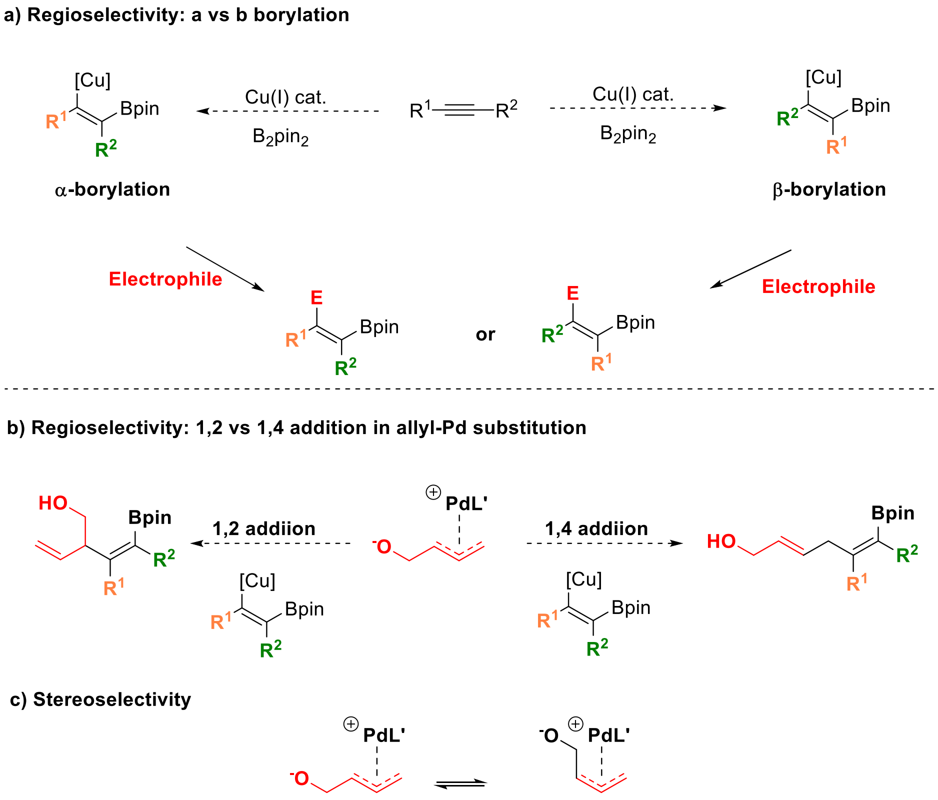
[80] Suzuki, M.; Oda, Y.; Noyori, R. *J. Am. Chem. Soc.* **1979**, *101*, 1623-1625.



Scheme 63. Copper and Palladium-catalyzed side reactions of allylic epoxides.

- ***Regio- and stereoselectivity:***

Insertion of unsymmetrical alkynes can occur in two different manners giving either to the α- or β-borylated regioisomer (Scheme 64a). Moreover, regio- and stereoselectivity of the allylic substitution also has to be controlled, in order to avoid side reactions (Scheme 64b and c).



Scheme 64. Regio- and stereoselectivity issues.

3. RESULTS AND DISCUSSION

3.1 Optimization

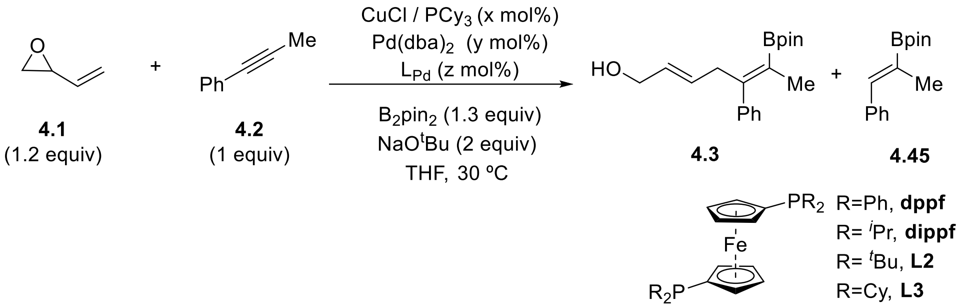
At the outset of our investigation, we selected a reaction involving B_2pin_2, 1-phenyl-1-propyne and 2-vinyloxirane to evaluate both the feasibility and selectivity of the process.

We initially evaluated the effect of the ligand in palladium. For this screening we selected CuCl/PCy_3 (5 mol%), $Pd(dba)_2/L_{Pd}$(5 mol%) as catalytic system and NaO^tBu (2 equiv) as base (Table 13). The initial experiment already showed the challenging nature of this multicomponent reaction since diene **4.3** was obtained in only 10% yield as a 1:1 mixture of *E*,*Z* and *Z*,*Z* isomers (Table 13, entry 1). The use of different bisphosphines (Table 13, entries 2 and 3) did not afford the desired product, obtaining only the alkyne protoboration product **4.45**. The use of PPh_3 as ligand using different palladium sources (Table 13, entries 4 and 5) gave rise to similar results regarding to conversion and yield. The use of bis(acetonitrile)dichloropalladium(II) (table 13, entry 6) only afford 5% of yield for the product **4.3**.

Then, we decided to decrease the temperature to 30 °C and test several triphenylphosphine derivatives (Table 13, entries 7-10), however, no improvement was observed. Interestingly, although **4.3** was obtained in similar yield when the reaction was run at 30 °C, it was obtained as the pure (*Z*)-alkenylboronate and (*E*) -allylic alcohol (Table 13, entry 11). Increasing the Cu/Pd molar ratio from 1:1 to 2:1 produced a slight improvement, although the yield of 3 was still far from satisfactory (Table 13, entry 12).

Careful analysis of the reaction mixtures revealed that the low yield of **4.3** was accompanied by total consumption **4.1**, which likely occurred through direct borylation pathways. In order to minimize these non-productive reactions, we reasoned that keeping a lower concentration of **1** in the reaction medium should result in the formation of a larger amount of the desired diene **4.3**. Accordingly, we found that slow addition of the vinyl epoxide **1** in 0.3 ml of THF during 3 h produced a significant enhancement of the reaction yield, obtaining 56% of isolated yield for product **4.3** (Table 13, entry 13). Finally, we tried several dppf derivatives under these conditions (Table 13, entries 14-17) although no improvement was observed.

Table 13. Screening of palladium catalyst ligand. [a]

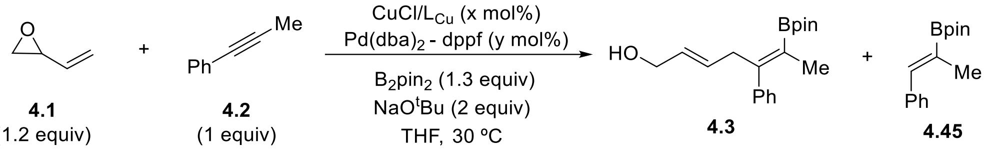


Entry	T (°C)	x:y:z Ratio	Pd source	L_{Pd}	Conv 4.2 (%)[b]	Yield 4.3 (%)[b]	Yield 4.45 (%)[b]
1	50	5:5:5	$Pd(dba)_2$	dppf	nd	10[c]	29
2	50	5:5:5	$Pd(dba)_2$	dppe	95	-	38
3	50	5:5:5	$Pd(dba)_2$	dppm	70	-	31
4	50	5:5:5	$Pd(dba)_2$	PPh_3	82	24	traces
5	50	5:5:5	$Pd_2(dba)_3$	PPh_3	86	16	15
6	50	5:5	$Pd(CH_3CN)Cl_2$		90	5	10
7	30	5:5:5	$Pd(dba)_2$	PPh_3	Full	18	26
8	30	5:5:5	$Pd(dba)_2$	P(*p*-F-$C_6H_4)_3$	92	traces	14
9	30	5:5:5	$Pd(dba)_2$	P(*p*-OMe-$C_6H_4)_3$	90	-	19
10[d]	30	5:5:10	$Pd_2(dba)_3$	PPh_3	79	19	26
11	30	5:5:5	$Pd(dba)_2$	dppf	94	10(13)[e]	63(70)[e]
12	30	10:5:5	$Pd(dba)_2$	dppf	90	19	9
13[f]	30	10:5:5	$Pd(dba)_2$	dppf	95	47(56)[e]	32
14[f]	30	10:5:5	$Pd(dba)_2$	dippf	52	traces	-
15[f]	30	10:5:5	$Pd(dba)_2$	L2	85	traces	60
16[f]	30	10:5:5	$Pd(dba)_2$	L3	82	traces	48
17[f]	30	10:5	Pd-dppf G3		74	15	52

[a]Reactions performed on a 0.3 mmol scale. [b]Determined by ^{1}H-NMR using 1,3,5-trimethoxybenzene as internal standard. [c]1:1 mixture of *Z,E*:*Z,Z* isomers. [d]Use of 10 mol% of PPh_3. [e]Yield of isolated product shown in brackets. [f]Slow addition of 0.36 mmol of **1** in 0.3 ml of THF added over 3 h.

We next screened the effect of ligand in the copper catalyst (Table 14). The use of different *N*-heterocyclic carbene ligands (Table 14, entries 1-3) keeping Pd(dba)$_2$/dppf as the palladium catalyst did not afford the formation of desired product **4.3**, obtaining the alkyne proboboration **4.45** as the single reaction product. Similar results were obtained when triphenylphosphine was used (Table 14, entry 4). These results further demonstrated that tricyclohexylphosphine was the best ligand on copper for this transformation. We next studied the copper / palladium catalyst ratio. As mentioned above, we observed that the use of 10 mol% of CuCl-PCy$_3$ and 5 mol% of Pd(dba)$_2$/dppf (table 14, entry 6) slightly improved the yield of the transformation, isolating product **4.3** in 56% yield. However, the use of other catalyst molar ratios (Table 14, entries 9 and 10) led to a significant loss of effciency.

Table 14. Screening of copper catalyst ligand.[a]

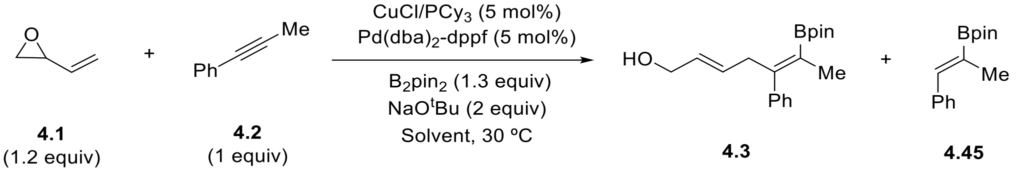


Entry	x:y ratio	L$_{Cu}$	Conv 4.2 (%) [b]	Yield 4.3 (%) [b]	Yield 4.45 (%) [b]
1	5:5	IPr	40	-	9
2	5:5	IMes	63	-	44
3	5:5	SIMes	75	-	54
4	5:5	PPh$_3$	63	-	44
5	5:5	PCy$_3$	92	40	16
6	10:5	PCy$_3$	95	47(56)[c]	32
7	10:5	BINAP	87	22(20)[c]	56
8	10:5	P(*p*-OMe-C$_6$H$_4$)$_3$	64	traces	58
9	10:2	PCy$_3$	83	8	11
10	5:10	PCy$_3$	Full	-	51

[a] Reactions performed on a 0.3 mmol scale with slow addition of **1** in 0.3 ml of THF added over 3 h. [b] Determined by ^{1}H-NMR using 1,3,5-trimethoxybenzene as internal standard. [c] Yield of isolated product shown in brackets.

The effect of solvent was also evaluated (Table 15). For this screening we selected CuCl/PCy$_3$ (5 mol%) and Pd(dba)$_2$/dppf (5 mol%) as catalytic system and NaO^{t}Bu (2 equiv) as base. Fortunately, under these conditions we observed moderate yield (40% NMR yield) for the desired product **4.3** and only 16% NMR yield for the formation of the alkyne protoboration product (Table 15, entry 1). However, the use of other solvents such as toluene (Table 15, entry 2) disfavored the outcome of the reaction. When more polar solvents such as DMF and DMA were used (Table 15, entries 3 and 4), no reaction was observed.

Table 15. Screening of solvents.[a]

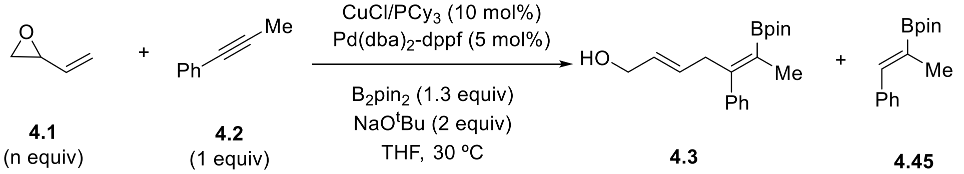


Entry	Solvent	Conv. 4.2 (%)[b]	Yield 4.3 (%)[b]	Yield 4.45 (%)[b]
1	THF	92	40	16
2	Toluene	87	14	26
3	DMF	69	-	25
4	DMA	80	-	-

[a] Reactions performed on a 0.3 mmol scale with slow addition of **1** (dissolved in 0.3 ml of THF) over 3 h. [b] Determined by ^{1}H-NMR using 1,3,5-trimethoxybenzene as internal standard.

We next investigated the slow addition time (Table 16). We observed that the time of the addition as well as the concentration of the vinyl epoxide played an important role in this transformation. Fine adjustment of these two parameters produced a significant enhancement of the reaction yield and revealed that the addition of 2 equivalents of **4.1** in 0.5 ml of THF during 1 hour were the optimal conditions. Using this protocol, product **4.3** could be obtained as a single isomer in 65% yield (Table 16, entry 7).

Table 16. Effect of slow addition time.[a]

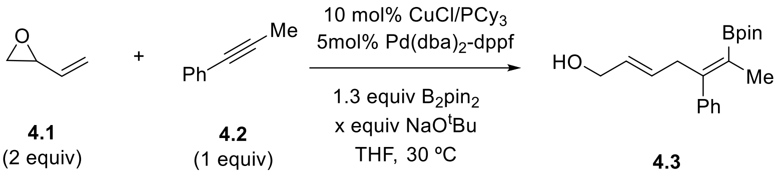


Entry	Slow addition time (h)	Vol. THF for the addition (ml)	4.1 (Equiv)	Conv 4.2 (%)[b]	Yield 4.3 (%)[b]	Yield 4.45 (%)[b]
1	3	0.3	1.2	95	52(56)[c]	32
2	1	0.3	1.2	75	32(28)[c]	15
3	3	0.3	2	84	41(34)[c]	24
4	5	0.5	2	95	35	53
6	3	0.5	2	91	34	39
7	1	0.5	2	90	70(65)[c]	10

[a]Reactions performed on a 0.3 mmol scale. [b]Determined by ^{1}H-NMR using 1,3,5-trimethoxybenzene as internal standard. [c]Yield of isolated product shown in brackets.

Finally, the effect of the nature and amount of the base was evaluated (Table 17). We initially found that an increase in the amount of NaO^tBu (Table 17, entry 1) produced a slight decrease of the yield (66% NMR yield). Remarkably, this transformation could be successfully carried out by using a catalytic amount of NaO^tBu, which even improved the efficiency of the reaction (Table 17, entry 3). Finally, we observed that changing the cation of the *tert*-butoxide base (Table 17, entries 4 and 5) has not a big impact in the outcome of the reaction, obtaining similar yield with NaO^tBu and LiO^tBu. The use of a bigger cation in the base (Table 17, entry 7) afforded the product in a slightly lower yield.

Table 17. Base effect.[a]



Entry	Base	Base equivalents	Conv 4.2 (%)[b]	Yield 4.3 (%)[b]
1	NaO^tBu	3	66	15
2	NaO^tBu	2	90	70(65)[c]
3	NaO^tBu	0.2	Full	75(70)[c]
4	LiO^tBu	0.2	Full	74
5	KO^tBu	0.2	Full	56

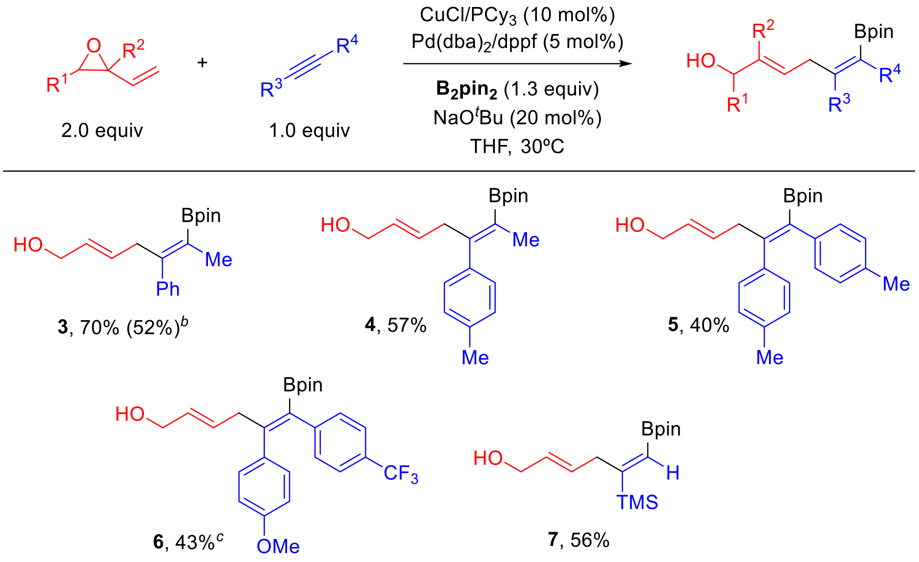
[a] Reactions performed on a 0.3 mmol scale with slow addition of 0.6 mmol of **1** in 0.5 ml of THF added in 1h. [b] Determined by ^1H-NMR using 1,3,5-trimethoxybenzene as internal standard. [c] Yield of isolated product shown in brackets.

3.2 Scope of the reaction

Having established the optimized conditions (Table 17, entry 3), we set out to investigate the scope of the reaction (Table 18). Remarkably, reactions proceeded with total stereo- and regioselectivity and furnished exclusively the 1,4-addition product with excellent *E,Z*-selectivity in nearly all cases.

Internal aryl alkyl alkynes and 1,2-diarylakynes proved to be efficient substrates and reacted with epoxide **4.1** and B_2pin_2 affording the corresponding bifunctional dienes **4.3**-**4.6** in good yields. A terminal alkyne such as trimethylsilylacetylene also worked well in this transformation providing the trifunctionalized skipped diene **4.7** in 56% yield.

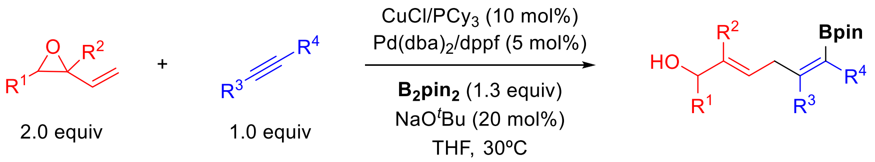
Table 18. Scope of alkynes[a]

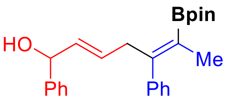


[a]Conditions: see Table 17, entry 3. Yield values refer to isolated products. [b]Reaction run at 1 mmol scale. [c]Obtained as a 2:1 mixture of regioisomers (only major isomer is shown).

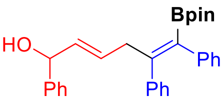
More substituted vinyl epoxides were also evaluated under these dual Cu/Pd catalytic conditions (Table 19). 1,2-disubstituted epoxides required a slightly higher temperature (50 °C) but also worked well and afforded products **4.8**-**4.18** in moderate to good yields. Notably, these secondary allylic alcohols were obtained with perfect regio- and stereoselectivity despite using diastereomeric *cis*/*trans* mixtures of the corresponding starting vinyl epoxides. It is reported that a diastereomeric mixture of 2-phenyl-3-vinyloxirane give rise to to *E*/*Z* mixtures of stereoisomers in the Pd-catalyzed reaction with alkenylstannanes.[76a] Heteroaromatic substituents were well-tolerated at either the alkyne (**4.16** and **4.17**) or the vinyl epoxide structure (**4.18**). Isoprene monoepoxide proved also to be efficient for this transformation and provided dienes **4.19** and **4.20**, which feature both a tetra- and a tri-substituted double bond, with excellent selectivity. 2-Phenyl-2-vinyloxirane could also be used, although in this case the corresponding product **4.21** was obtained in low yield and as a 1:1 *E,Z*:*Z,Z* mixture. It is important to note that this synergistic Cu/Pd catalysis provides access to skipped dienols bearing a tetra-substituted alkenyl boronate (cf. **4.3**-**4.6**, **4.8**-**4.21**) that cannot be synthesized from any other current methodology. To the best of our knowledge, the only method to access this class of bifunctional dienes is the ruthenium-catalyzed Alder-ene reaction between alkynylboronates and homoallylic alcohol derivatives, which is limited to the synthesis of trisubstituted alkenyl boronates.[81]

Table 19. Scope of vinyl epoxides.[a]

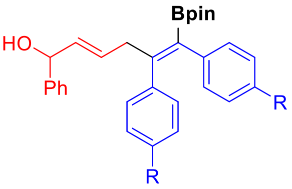




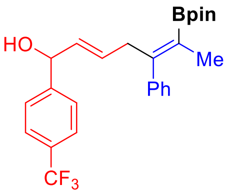
8, 71%[b,c]



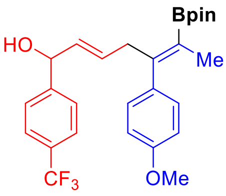
9, R= 46%[b,c]



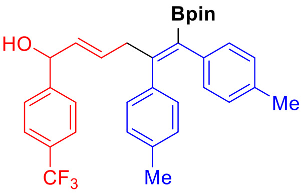
10, R= Br, 26%[b,c]
11, R = Me, 59%[b,c]
12, R = CF_3, 46%[b,c]



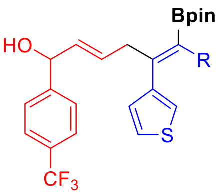
13, R= H, 83%[b,d]



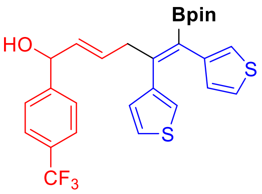
14, R= OMe, 67%[b,d]



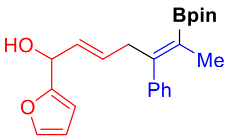
15, 63%[b,d]



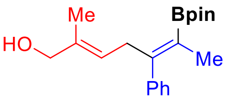
16,R= Me, 43%[b,d]



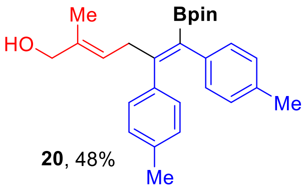
17, R= 39%[b,d]



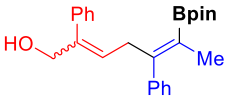
18, 29%[b,d]



19, 36%



20, 48%



21, 28%[e]

[a]Conditions: see Table 17, entry 3. Yield values refer to isolated products. [b]Reaction run at 50 °C. [c]Vinyl epoxide used as a 2:1 *cis/trans* mixture. [d]Vinyl epoxide was used as a 5:1 *cis/trans* mixture. [e]Obtained as a 1:1 *E,Z*:*Z,Z* mixture.

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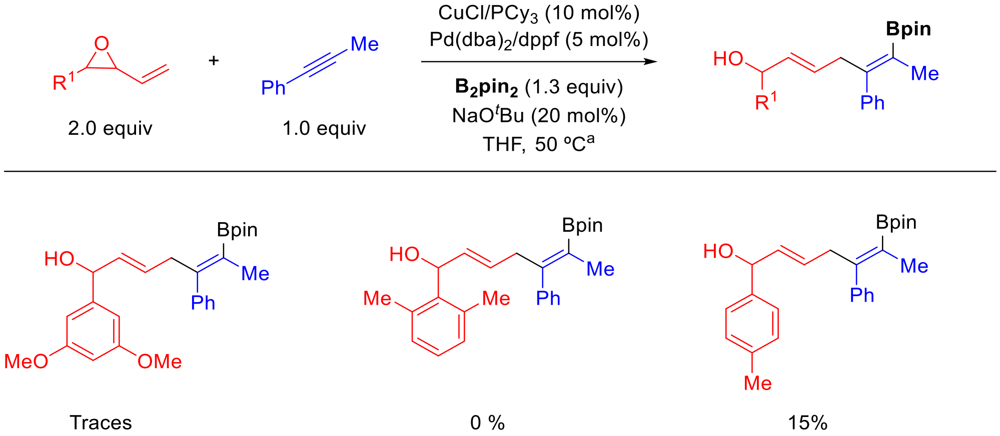
[81] Hansen, E. C.; Lee, D. *J. Am. Chem. Soc*. **2005**, *127*, 3252– 3253.

3.2.1 Scope limitations

Although the transformation tolerated well a range of functional groups as well as different substitution patterns, some substrates resulted unreactive under standard conditions(Scheme 14). The use of vinyl epoxides bearing electron rich aryl groups did not give rise to the desired product or only traces were detected by ^{1}H-NMR or GC-MS analysis. In these cases, full conversion of alkyne and vinyl epoxide was not achieved, being the alkyne protoboration the major product in all cases.

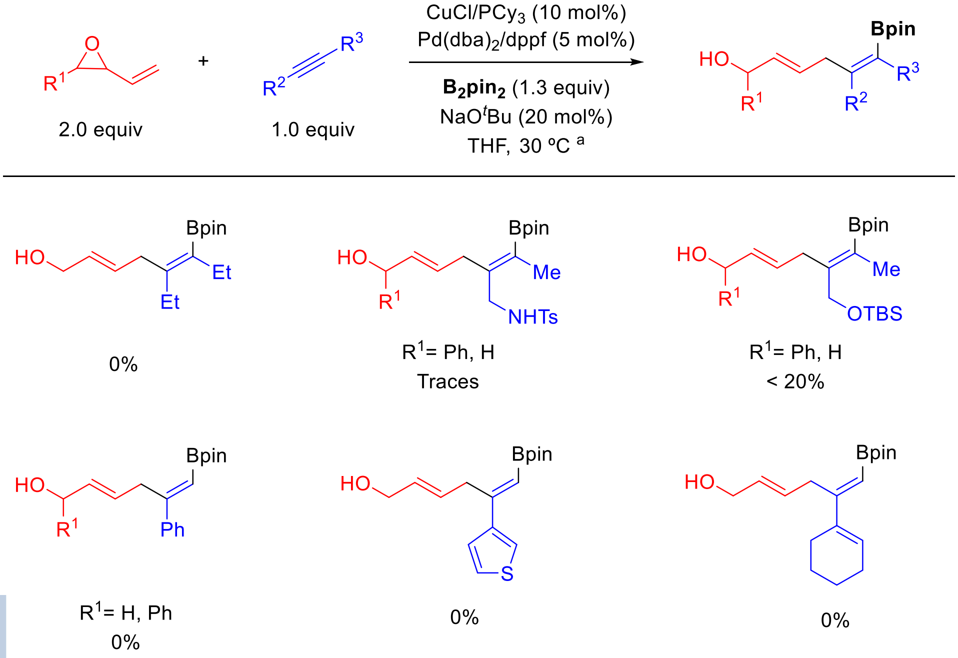
Table 20. Unsuccessful alkynes in Cu/Pd-catalyzed allylboration with vinyl epoxides.[a]



[a]Reactions performed under optimized conditions (Table 17, entry 3) at 50 °C.

The use of alkyl, alkyl alkynes did not give rise to the desired product, or only produced traces of it (Table 21). Moreover, when we tried to carry out the reaction with terminal alkynes different than trimethylsilylacetylene, only the corresponding protoboration product was formed.

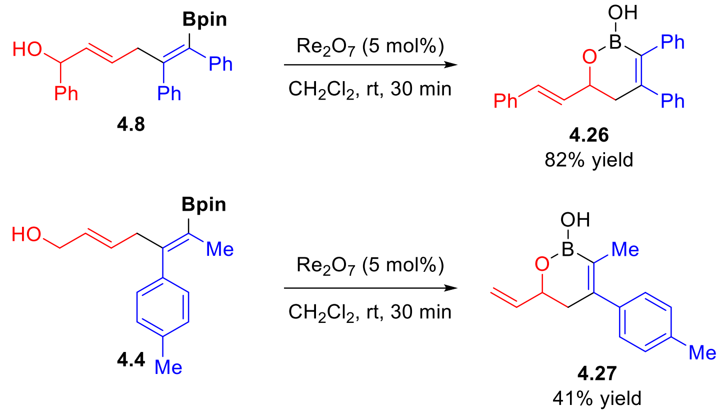
Table 21. Unsuccessful vinyl epoxides in Cu/Pd-catalyzed allylboration of alkynes.[a]



[a]Reactions performed under optimized conditions (Table 17, entry 3).

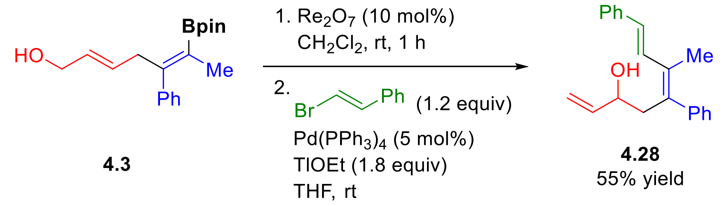
3.3 Synthetic modifications

An attractive feature of this new allylboration reaction with vinyl epoxides is the functional group diversity present in the products which makes them highly versatile building-blocks. Notably, the rhenium-catalyzed allylic [1,3]-transposition[82] of bifunctional dienes **4.4** and **4.8** resulted in an efficient synthesis of cyclic boronic acids **4.26** and **4.27** (Scheme 65). These boracycles are important structures since they are valuable synthetic intermediates[83] and have recently gained increased interest in the drug discovery process of pharmaceutical industry.[84]



Scheme 65. Re-catalyzed allylic [1,3]-transposition

Furthermore, triene **4.28** could be obtained from **4.3** in a stereocontrolled manner via a one-pot allylic [1,3]-transposition/Suzuki cross-coupling (Scheme 66).[85]



Scheme 66. One-pot allylic [1,3]-transposition/Suzuki cross-coupling

The presence of the alkenylboronate unit also offers a synthetic handle to easily convert the products into 6- hydroxy-2-aryl ketones by treatment with sodium perborate, as illustrated with the synthesis of compound **4.29** (Scheme 67a).

This oxidation protocol was also employed to elucidate the structure of compounds **4.6** and **4.6'** (relative position of the two different aryl groups). Thus, after oxidation of a 2:1 mixture of compounds **4.6** and **4.6'**, the formation of a 2:1 mixture of ketone **4.40** and **4.40'** was observed.

---

[82] (a) Morrill, C.; Grubbs, R. H. *J. Am. Chem. Soc*. **2005**, *127*, 2842-2843. (b) Hansen, E. C.; Lee, D. *J. Am. Chem. Soc.* **2006**, *128*, 8142-8143.

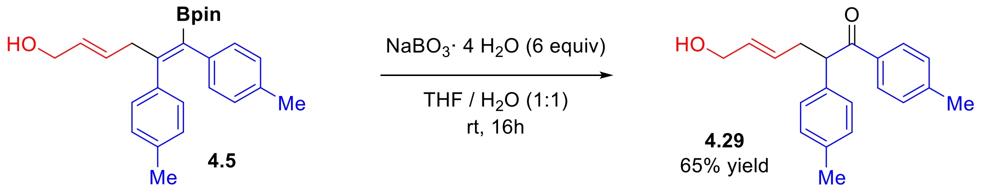
[83] (a) Körner, C.; Starkov, P.; Sheppard, T. D. *J. Am. Chem. Soc.* **2010**, *132*, 5968–5969. (b) Nogami, M.; Hirano, K.; Kanai, M.; Wang, C.; Saito, T.; Miyamoto, K.; Muranaka, A.; Uchiyama, M. *J. Am. Chem. Soc.* **2017**, *139*, 12358 –12361.

[84] Delost, M. D.; Smith, D. T.; Anderson, B. J.; Njardarson, J. T. *J. Med. Chem.* **2018**, *61*, 10996–11020.

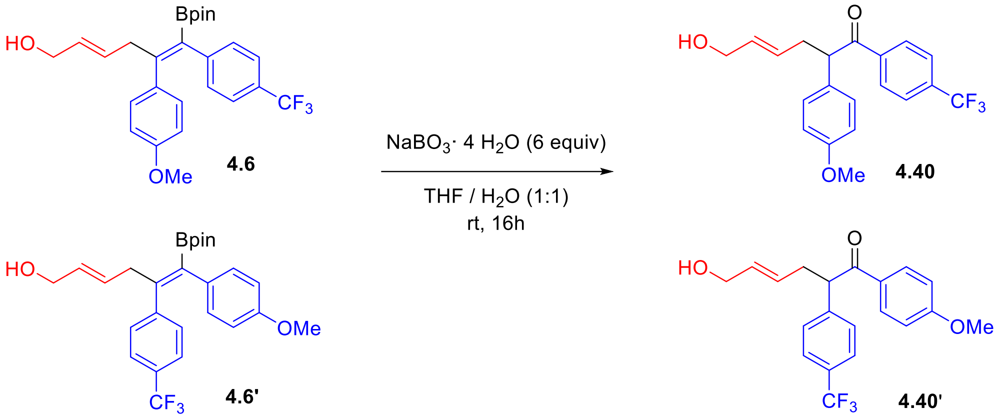
[85] Frank, S. A.; Chen, H.; Kunz, R. K.; Schnaderbeck, M. J.; Roush, W. R. *Org. Lett.* **2000**, *2*, 2691-2694.

Isolation of major ketone **4.40** was possible by column chromatography. Characterization of its structure help to elucidate the major isomer of the allylboration reaction (See experimental section).

a) Oxidation of difunctionalized skipped diene 4.**5**



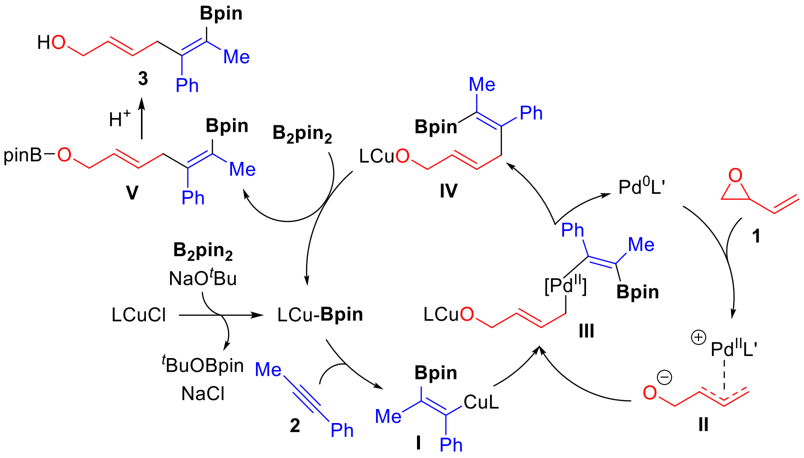
b) Oxidation of difuntionalized skipped diene 4.**6** and 4.**6'** for regiochemistry determination



Scheme 67. Oxidation of Bpin moiety.

3.4 Mechanistic proposal

On the basis of our experimental observations and our previous investigations, we propose the following mechanism for the Cu/Pd-catalyzed alkyne allylboration with vinyl epoxides (Scheme 68). A regio- and stereoselective addition of LCu-Bpin complex across alkyne **4.2** would generate β-boryl-alkenylcopper(I) intermediate **I**. In the second catalytic cycle, zwitterionic η^3-allyl-Pd complex **II** would be formed by oxidative addition of the vinyl epoxide **4.1** to the L'Pd(0) complex. Transmetalation between these two organometallic species would give rise to bimetallic intermediate **III** which undergoes reductive elimination with concomitant regeneration of the Pd(0) catalyst and formation of copper alkoxide **IV**. This intermediate would be reactive enough to undergo σ-bond metathesis with B_2pin_2 which results in the recovery of the active LCu-Bpin complex and the formation of intermediate **V** which would lead to bifunctional diene **4.3** by protonation. Reaction between intermediate **IV** and B_2pin_2 would explain the viability of performing this reaction with catalytic amount of NaO^{t}Bu.



Scheme 68. Proposed mechanism for the Cu/Pd-catalyzed allylboration of alkynes.

4. CONCLUSIONS

We have developed an efficient methodology for the synthesis of bifunctional skipped dienes, through a novel synergistic Cu/Pd-catalyzed three-component reaction of alkynes, B_2pin_2 and vinyl epoxides.

One of the main features of this system is the remarkable regio- and stereoselectivity. Side reactions such as direct borylation of vinyl epoxides and alkyne protoboration are reduced to not significant levels.

These multifunctional products display very diverse reactivity which makes them very attractive building-blocks for chemical synthesis.

The use of bench stable and readily available starting materials under mild conditions makes this method practical. Additionally, several boracyles, ketones and more complex molecules such as triene **4.28** can also be accessed via one-pot allylic [1,3]-transposition/Suzuki cross-coupling.

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CHAPTER V: Synergistic Cu/Pd catalysis as a handle for regioselectivity switch in allyl-allyl cross-coupling.

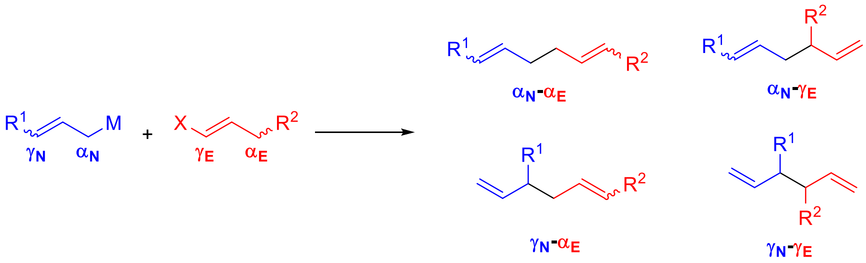
1. INTRODUCTION

1.1 Allyl-allyl cross coupling

Allyl-allyl coupling between allyl electrophiles and allyl nucleophiles is a powerful synthetic tool for providing direct access to 1,5-dienes. This structures are present in many natural products and serve as a versatile building blocks in organic synthesis.[86] Moreover, cross-coupling reactions between an allyl metal reagent and an allylic electrophile is an attractive method due to the possibility to establish two new stereocenters with concomitant formation of a C(sp^3)-C(sp^3) bond.

This type of C-C coupling has been traditionally carried out by using stoichiometric amounts on allyl metal reagents such allyl lithium,[87] magnesium,[88] tin,[89] boron,[90] silicon[91] and indium[92] nucleophiles were reactive with allyl electrophiles. However, these methods are typically confined to the introduction of simple allyl fragments.

When unsymmetrical allyl reagents are used, the coupling can potentially occur at either the α or γ position of the nucleophile and the electrophile. In this way, up to four possible regioisomers can be obtained, and more isomers may be formed if stereoisomers are also considered (Scheme 69).



Scheme 69. Potential isomers in the allyl-allyl cross-coupling.

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[86] a) Breitmaier, E. *Terpenes, Flavors, Fragrances, Pharmaca, Pheromones*; Wiley-VCH: Weinheim, 2006. b) *Medicinal Natural Products: A Biosynthetic Approach*; Dewick, P. M., Ed.; Wiley: Chichester, 2002.

[87] a) Yamamoto, Y.; Maruyama, K. *J. Am. Chem. Soc.* **1978**, *100*, 6282 – 6284; b) Yamamoto, Y.; Yatagai, H.; Maruyama, K. *J. Am. Chem. Soc*. **1981**, *103*, 1969 – 1975.

[88] a) Goliaszewski, A.; Schwartz, J. *J. Am. Chem. Soc.* **1984**, *106*, 5028 – 5030; b) Goliaszewski, A.; Schwartz, J. *Tetrahedron* **1985**, *41*, 5779 – 5789; c) Yanagisawa, A.; Nomura, N.; Yamamoto, H. *Synlett* **1993**, 689 – 690; d) Yanagisawa, A.; Nomura, N.; Yamamoto, H. *Tetrahedron* **1994**, *50*, 6017 – 6028; e) Karlström, A.; Bäckvall, J.-E. *Chem. Eur. J.* **2001**, *7*, 1981 – 1989; f) Hornillos, V.; Pérez, M.; Fañanás-Mastral, M.; Feringa, B. L. *J. Am. Chem. Soc.* **2013**, *135*, 2140 – 2143.

[89] a) Trost, B. M.; Keinan, E. *Tetrahedron Lett.* **1980**, *21*, 2595 – 2598; b) Godschalx, J.; Stille, J. K. *Tetrahedron Lett.* **1980**, *21*, 2599 – 2602.

[90] a) Flegeau, E. F.; Schneider, U.; Kobayashi, S. *Chem. Eur. J.* **2009**, *15*, 12247 – 12254; b) Jiménez-Aquino, A.; Flegeau, E. F.; Schneider, U.; Kobayashi, S. *Chem. Commun*. **2011**, *47*, 9456 – 9458; c) Zhang, P.; Brozek, L. A.; Morken, J. P. *J. Am. Chem. Soc*. **2010**, *132*, 10686 – 10688; d) Brozek, L. A.; Ardolino, M. J.; Morken, J. P. *J. Am. Chem. Soc*. **2011**, *133*, 16778 – 16781.

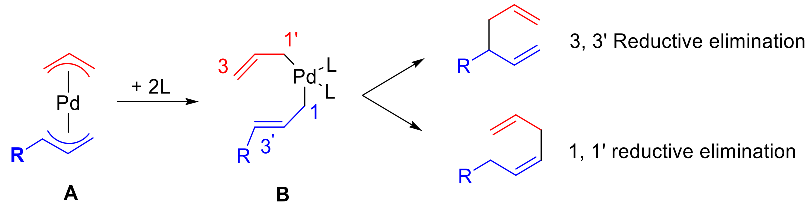
[91] Murakami, M. Kato, T.; Mukaiyama, T. *Chem. Lett*. **1987**, 1167 – 1170.

[92] Lee, P. H.; Sung, S.-Y.; Lee, K.; Chang, S. *Synlett* **2002**, 146 – 148.

Stereoselective allyl-allyl cross-coupling has been achieved through Pd,[93] Cu[94] or Ni[3a] and Ir[95]-catalyzed coupling of stoichiometric allyl-metal reagents with several allylic electrophiles.[96] Copper- and palladium-catalyzed cross couplings will be covered in this chapter.

1.1.1 Pd-catalyzed allyl-allyl cross-coupling

Palladium is probably the most useful metal in organic synthesis. Several complexes and salts act as catalyst or pre-catalyst in a wide range of different transformations.[97] As mentioned above, reactions involving the formation of C-C bonds through Pd-catalyzed allyl-allyl cross-coupling between allyl electrophiles and allyl nucleophiles are of particular interest. In this transformation, catalytic allyl-Pd complexes are key intermediates and play an important role. η^3 allyl-palladium complexes being the most common ones (**A** in scheme 70). However, depending on the saturation degree of the metal and the nature of the ancillary ligands, they may be in equilibrium with η^1 coordinate mode species (**B** in scheme 70).[98] These intermediates are usually formed by oxidative addition of allyl halides, esters or carbonates into Pd(0) species. Bis(allyl)palladium intermediate **B** can undergo either 3,3' or 1,1' reductive elimination. The 3,3' reductive elimination, as described by Echavarren,[99] operates when coordination of a ligand to a bis(allyl)metal species causes both allyl groups to adopt the η^1 bonding mode (as in **B** in Scheme 2) instead of the more common η^3 mode (as in **A**).



Scheme 70. Formation of bis-allyl palladium intermediates.

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[93] a) Flegeau, E. F.; Schneider, U.; Kobayashi, S. *Chem. Eur. J.* **2009**, *15*, 12247 – 12254; b) Lee, P. H.; Sung, S.-Y.; Lee, K.; Chang, S. *Synlett* **2002**, 146 – 148.

[94] Yanagisawa, A.; Nomura, N.; Yamamoto, H. *Synlett* **1993**, 689 – 690; f) Yanagisawa, A.; Nomura, N.; Yamamoto, H. *Tetrahedron* **1994**, 50, 6017 – 6028; g) Karlstrçm, A. S. E.; Bäckvall, J.-E. *Chem. Eur. J.* **2001**, 7, 1981 – 1989.

[95] a) Hamilton, J. Y.; Hauser, N.; Sarlah, D.; Carreira, E. M. *Angew. Chem. Int. Ed.* **2014**, *53*, 10759-10762 b) Zheng, Y.; Yue, B.-B.; Wei, K.; Yang, Y.-R. *Org. Lett.* **2018**, *20*, 8035-8038.

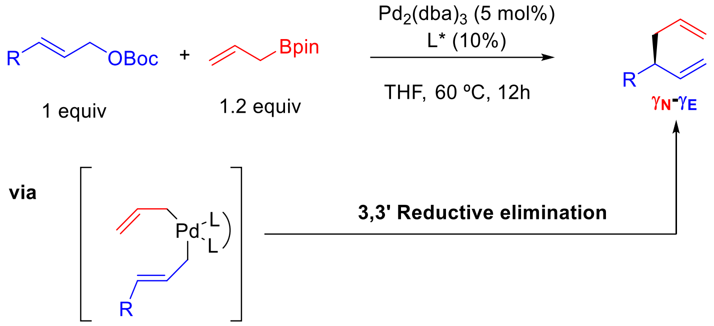
[96] Ravichandiran, V.;Jana, A. ***Org. Chem. Front.***, **2023**,***10***, 267-281

[97] a) *Metal-catalyzed Cross-coupling Reactions*, eds. F. Diederich and P. J. Stang, Wiley-VCH, Weinheim, **1998**; b) *Palladium Reagents and Catalysts: Innovations in Organic Synthesis*, ed. J. Tsuji, Wiley, Chichester, **1997**; c) *Handbook of Organopalladium Chemistry for Organic Synthesis*,ed. E. Negishi, Wiley, New York, **2002**.

[98] Solin, N.; Szabó, K. J. *Organometallics*, **2001**, *20*, 5464-5471.

[99] a) Méndez, M.; Cuerva, J. M.; Gómez-Bengoa, E.; Cárdenas, D. J.; Echavarren, A. M. *Chem. Eur. J.* **2002**, *8*, 3620; b) Cárdenas, D. J.; Echavarren, A. M. *New J. Chem.* **2004**, *28*, 338-347.

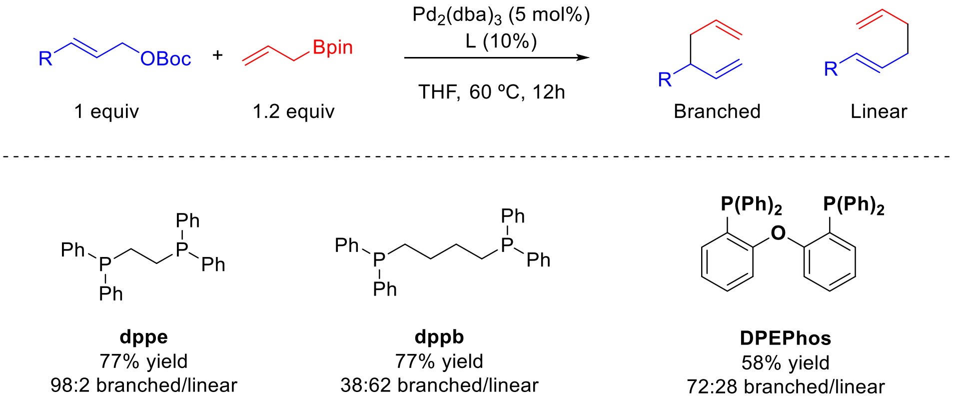
Morken and co-workers reported the Pd-catalyzed regio- and enantioselective cross-coupling of allylboronates and allylic carbonates to afford selectively γ_N- γ_E products (Scheme 71).[100]



Scheme 71. Pd-Catalyzed Branched-Selective Cross-Coupling.

The regiochemical outcome of this transformation is consistent with a pathway involving a 3,3' reductive elimination of bis(allyl)Pd complexes, as proposed by Echavarren.[99] Importantly, the nature of the ligand plays a key role in the regioselectivity of the transformation.

They observed that the use of smaller bite angle ligands, favor the branched product. However, when larger bite angle ligand such as dppb or DPEPhos were used, they obtained mixtures of linear and branched products (Scheme 72). This is consistent with a reaction proceeding through an intermediate such as **B** (Scheme 70), since increasing C1-C1' distance (small angle bite ligands) may disfavor the 1,1' reductive elimination pathway.



Scheme 72. Pd-catalyzed allyl-allyl cross-coupling.

Based on these preliminary studies, the group of Morken developed the enantioselective version of this transformation by using 2,2'-bis(difurylphosphino)-6,6'-dimethoxybiphenyl as chiral ligand (Scheme 73). Under these conditions, different allyl carbonates react with allyl-Bpin leading the branched product with excellent regio- and enantioselectivity. However, the use of a different ligand such as QUINOX-P* was necessary when aliphatic substrates were used in order to improve the yield and selectivities.

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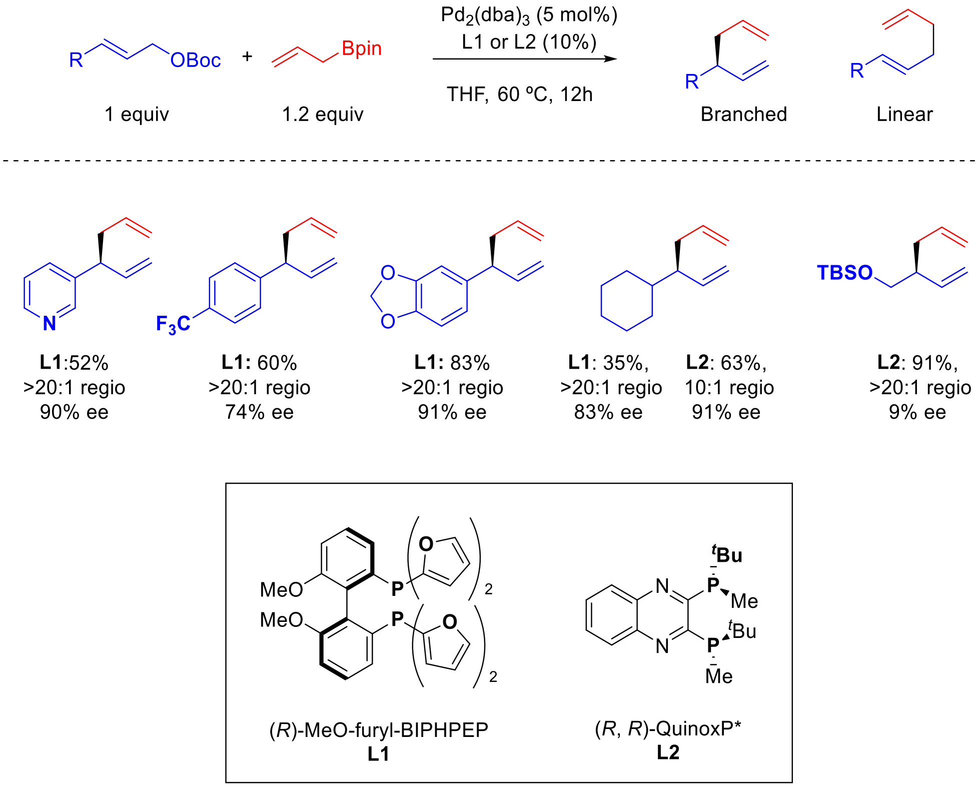
[100] Zhang, P.; Brozek, L. A.; Morken, J. P. *J. Am.Chem.Soc.*, **2010**, *132*, 10686-10688.



Scheme 73. Enantioselective Pd-catalyzed allyl-allyl cross-coupling.

The same group could expand this transformation to the coupling of substituted prochiral allylboronates and allyl chlorides (Scheme 74).[101] In this case, the use of γ-substituted allylboronates leads to the formation of products bearing adjacent tertiary stereocenters with control over both the diastereoselectivity and also the enantioselectivity.

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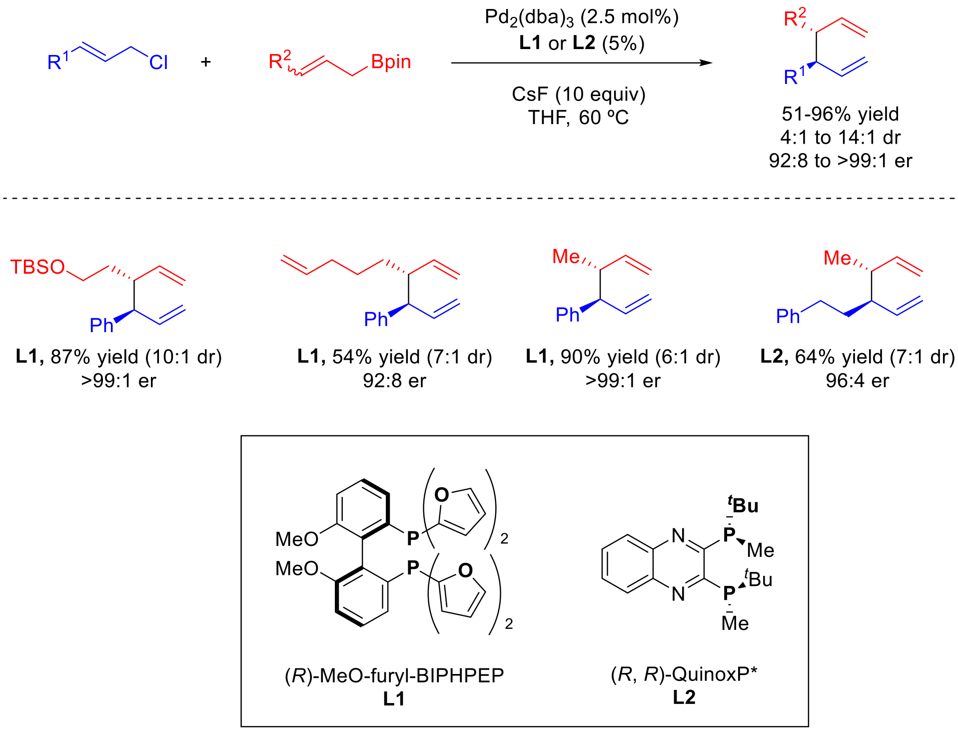
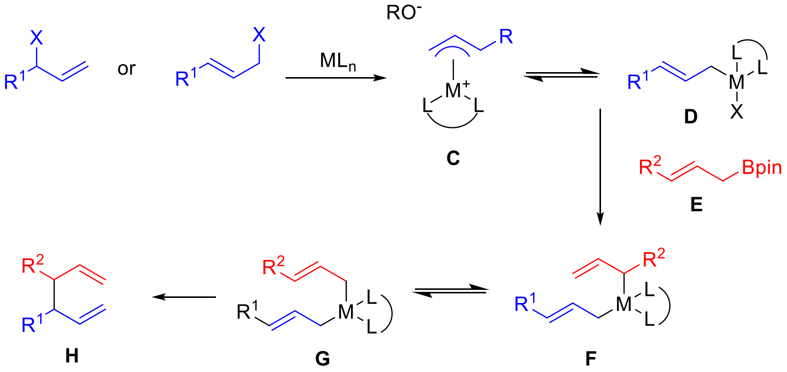
[101] Brozek, L.; Arldolino, M.; Morken, J.P. *J. Am. Chem. Soc*. **2011**, 133, 16778-16781.



Scheme 74. Enantioselective Pd-catalyzed allyl allyl cross-coupling.

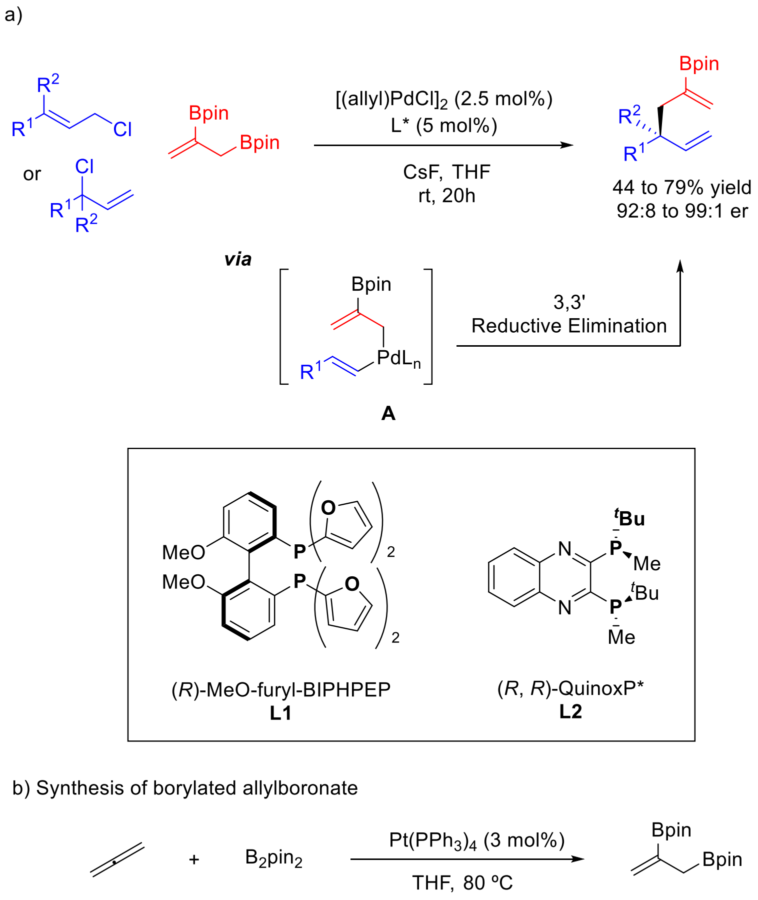
For this transformation, they proposed the mechanism shown in Scheme 75. After CsF-assisted transmetalation between allylboronate **E** and palladium chloride complex **D**, the boronate-derived allyl fragment undergoes isomerization to minimize steric effects to give **G** prior to stereochemistry-determining reductive elimination to give **H**. Interestingly, the use of *cis* and *trans* boronates react selectively for the formation of desired product.



Scheme 75. Proposed mechanism for the Pd-catalyzed allyl-allyl cross-coupling.

A similar methodology could be applied to the enantioselective allyl-allyl cross-coupling of diborylated compound with allyl chlorides to afford borylated chiral 1,5-hexadienes (Scheme

76).[102] However, to carry out this transformation was necessary to synthesized the borylated allylboronate by diboration of allene using catalytic amounts of Pt(PPh₃)₄ (Scheme 76b).[103]



Scheme 76. Use of borylated allylboronate in Pd-catalyzed allyl-allyl cross coupling

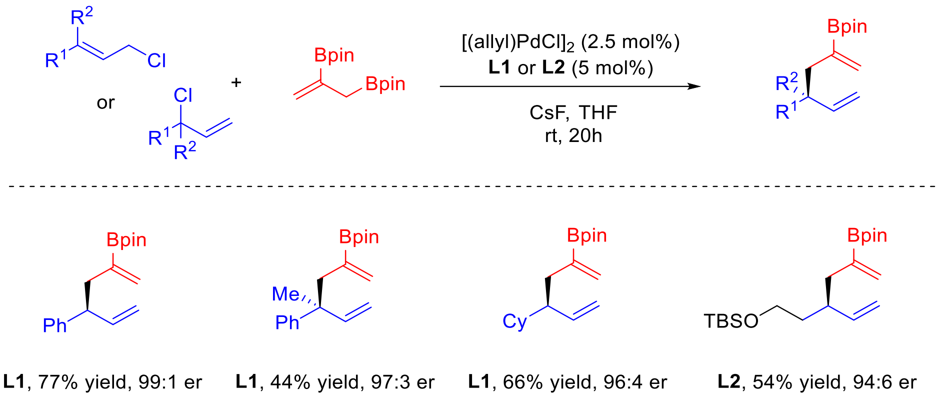
It is also important to highlight in this transformation that the level of enantioselectivity decreases when unsubstituted allylB(pin) and cinnamyl electrophiles were used, which showed the relevance of the presence of Bpin moiety in the bis(allyl)palladium intermediate (Scheme 77). Several electron-rich and -poor aromatic substrates afforded the corresponding products in good levels of yield and enantioselectivities under reaction conditions. Importantly, the use of stereoisomeric mixtures of allyl chlorides can be used in the coupling providing high yields of single products.

However, although aliphatic substrates such as cyclohexyl-substituted allylic chlorides reacted to afford the corresponding product, when other aliphatic substrates were used, elimination to 1,3 dienes was the predominant side reaction, by β-hydride elimination from π-allyl complex intermediates. The use of (R,R)-QuinoxP* as ligand and THF/H_2O as solvent minimized β-hydride elimination and allowed the formation of desired products.

---

[102] Le, H.; E. Kyne, R.; Brozek, L. A.; Morken, J. *Org. Lett*. **2013**, *15*, 1432-1435.

[103] Ishiyama, T.; Kitano, T.; Miyaura, N. *Tetrahedron Lett*. **1998**, 39, 2357-2360.

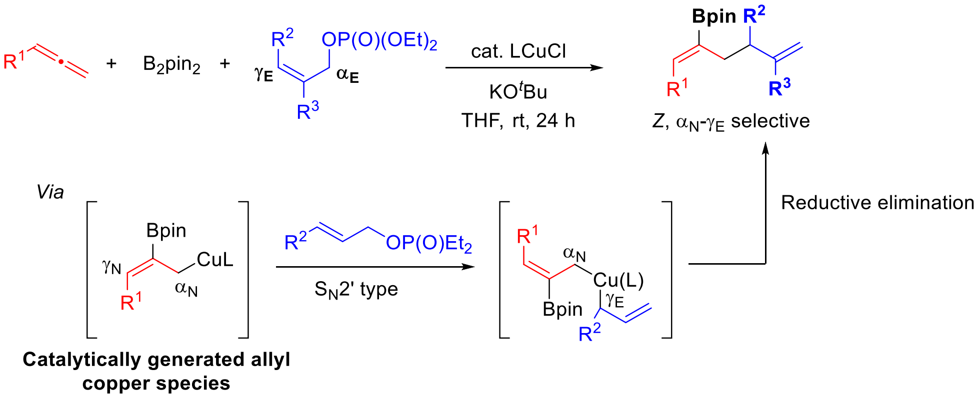


Scheme 77. Selected examples of Pd-catalyzed borylative allyl-allyl cross-coupling.

1.1.2 Cu-catalyzed borylative allyl-allyl cross-coupling

Previously reported methods as well as many other, employ stoichiometric amounts of allyl-metal reagents. Thus, the copper catalyzed borylative allyl-allyl cross coupling represents and alternative that supposes the use of catalytic amounts of allyl-metal.

In 2014, Tsuji and coworkers reported the first copper catalyzed borylative allyl-allyl cross-coupling between allenes, bis(pinacolato)diboron and allyl phosphates (Scheme 78).[104]



Scheme 78. Cu-catalyzed borylative allyl–allyl coupling.

The reaction affords a wide variety of boryl-substituted 1,5-dienes via the formation of β-boryl(*Z*)-σ-allyl copper species as a key catalytic species. In this transformation, the allyl copper species bearing a boryl functionality in the β_N position is generated catalytically [105]and reacts with allyl phosphate through a S_N2' type substitution providing the α_N-γ_E product with excellent regio- and stereoselectivity.

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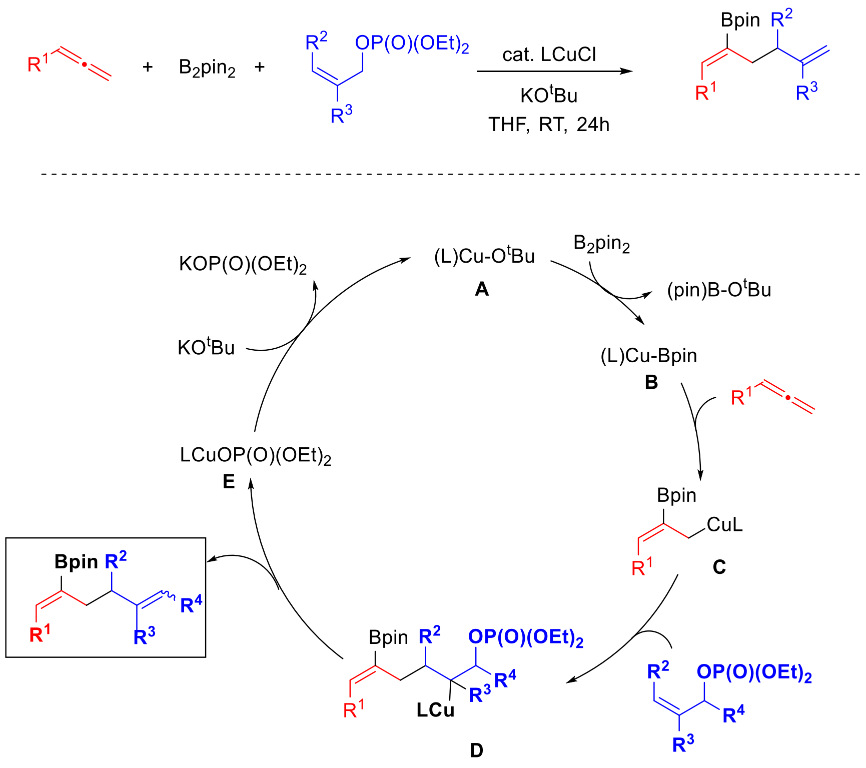
[104] Semba, K.; Bessho, N.; Fujihara, T.; Terao, J.; Tsuji, Y., *Angew. Chem. Int. Ed*. **2014**, 53, 9007-9011.

[105] a) Pulis, A. P.; Yeung, K.; Procter, D. J. *Chem. Sci.* **2017**, *8*, 5240-5247; b) Fujihara, T.; Tsuji, Y. *Synthesis* **2018**, *50*, 1737-1749; c) Whyte, A.; Torelli, A.; Mirabi, B.; Zhang, A.; Lautens, M. *ACS Catal.* **2020**, *10*, 11578-11622.

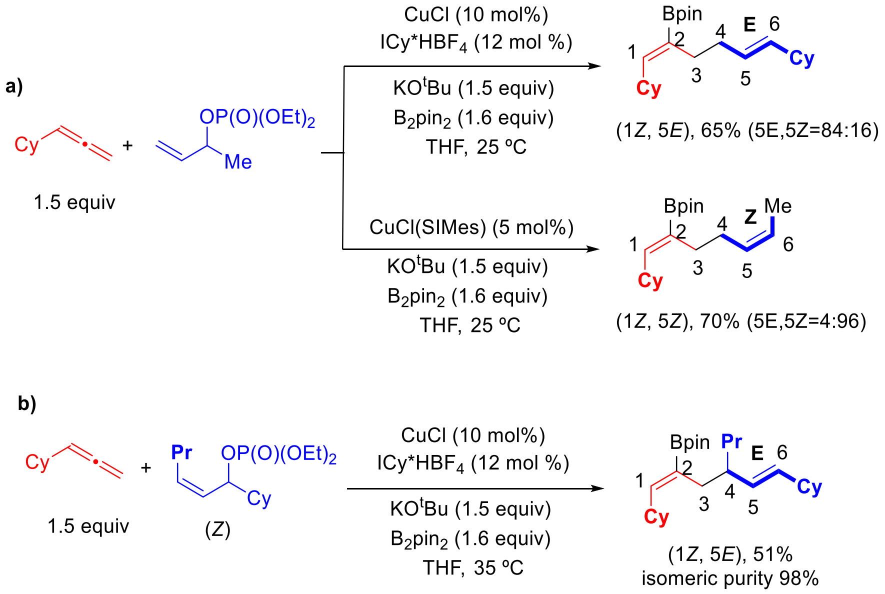
The mechanism depicted in Scheme 79 is proposed for this transformation. First, catalytically generated CuO^{t}Bu species **A** reacts with B$_2$pin$_2$ to afford borylcopper species **B**. Then the allene reacts with **B** to generate the β-boryl(Z)-σ-allyl copper intermediate **C** in a regio- and stereoselective manner. Then, addition of **C** to the double bond of the allyl phosphate give rise to intermediate **D**. Subsequently, stereoselective β-elimination releases the copper phosphate and yielded the final product. Finally, the reaction of **E** with KO^{t}Bu regenerates CuO^{t}Bu and the catalytic cycle is completed.



Scheme 79. Proposed mechanism.

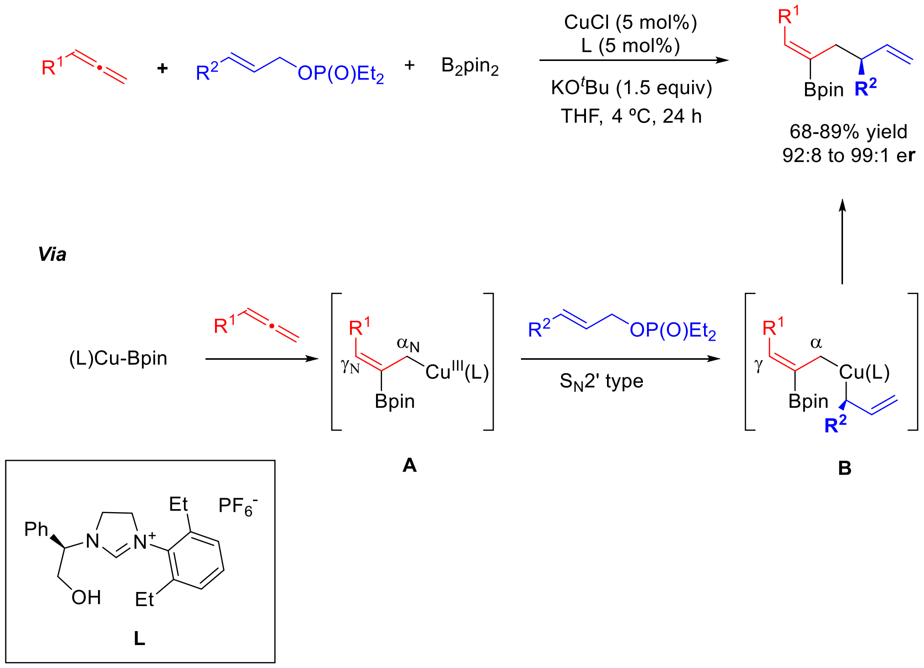
They tried several NHC ligands such as SIMes, IMes or ^{Me}IMes. However, they found that the use of ICy was crucial for the outcome of the reaction. The use of phosphines such as dppp, dppe or XantPhos provided the product in much lower yields and lower selectivities. It is also important to highlight that the use of *E* allyl phosphate instead of the *Z* gave rise to the same product in a slightly moderate yield although the same selectivity. Another factor to take into account in this transformation is the nature of the leaving group, since the use of allyl bromide, acetate or carbonate only gave rise to traces of product, or no reaction was observed.

Regarding to the use of secondary α-substituted allyl phosphates it is important to remark that they were able to reverse the reaction stereoselectivity by using different ligands (Scheme 80a). Moreover, α,γ-substituted allyl phosphates afford selectively the 1*Z*,5*E* product when ICy was used as ligand under standard conditions. Surprisingly, when SIMes was used as ligand, the stereoselectivity was switched to *5E* to *5Z* (Scheme 12a). Furthermore, the use of (*Z*) α, γ-disubstituted allyl phosphates afforded the corresponding product with 98% isomeric purity (Scheme 80b).



Scheme 80. Use of α-substituted allyl phosphates.

Concomitantly with the work of Tsuji, the group of Hoveyda reported the enantioselective version of the copper-catalyzed borylative allyl-allyl cross-coupling between allenes and allyl phosphates (Scheme 81).[106] In this case, they proposed the formation of a σ-allyl Cu(II) intermediate **A**. Then a S_N2' oxidative addition type gave rise the intermediate **B**, to finally, a reductive elimination afforded the final product. For this transformation was essential the use of a chiral NHC-Cu complex to guide the catalytic cycle along the desired pathway. It is also important to highlight that this transformation only tolerates the presence of aliphatic substitution in the allene moiety.



Scheme 81. Enantioselective Cu-catalyzed borylative allyl-allyl cross coupling.

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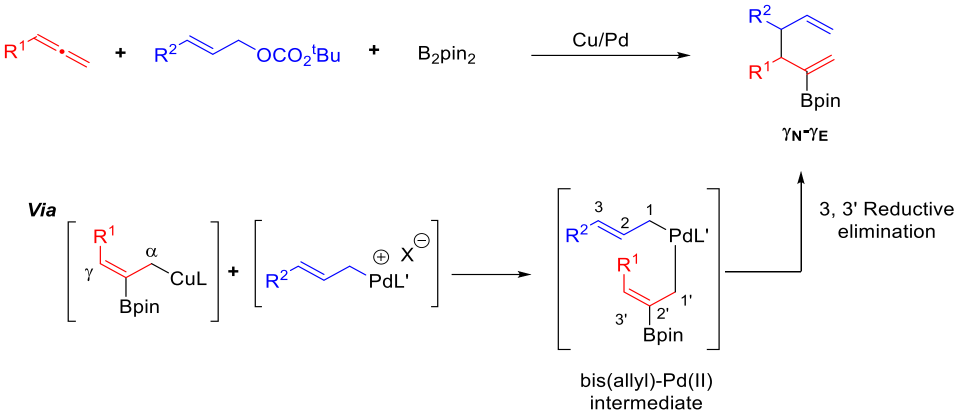
[106] Meng, F.; McGrath, K. P.; Hoveyda, A. H. *Nature* **2014**, *513*, 367-374.

2. OBJECTIVE

As shown in section 1, the copper-catalyzed borylative coupling between allenes and allylic phosphates described by Tsuji[105] and Hoveyda[106] provides the α_N,γ_E coupling product. However, only one regioisomer out of the possible four can be obtained from this reaction. Access to other regioisomers represents a desirable goal and would broaden the product chemical space of borylative couplings. With this idea in mind, and based on our previous work in Cu/Pd catalyzed allylboration of alkynes with allylic carbonates (See chapter 1, section 1.1.8),[33] we envisioned that the use of synergistic Cu/Pd catalysis may serve as a platform to achieve a selectivity switch in this borylative allyl-allyl coupling, thus providing a new tool to access borylated 1,5-dienes with a different connectivity (Scheme 82).



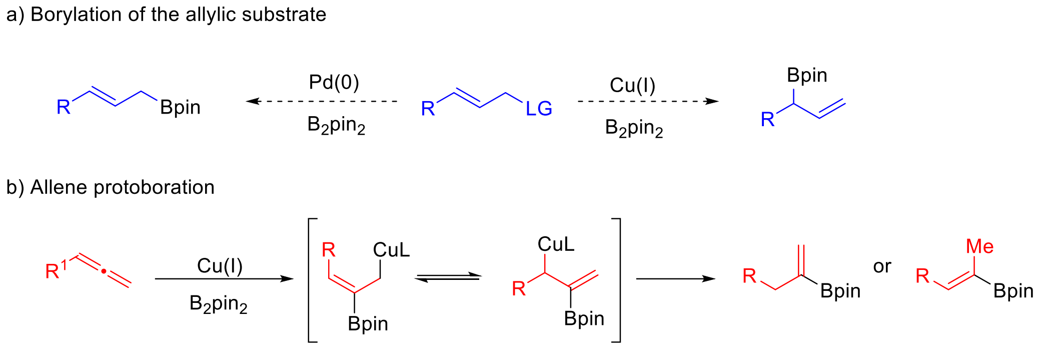
Scheme 82. Proposed strategy for the Cu/Pd catalyzed allyl-allyl cross coupling of allenes and allylic carbonates.

In our mechanistic hypothesis, the allylcopper species catalytically generated from the borylcupration of the allene would undergo transmetalation with an allyl-Pd(II) complex generated by oxidative addition of an allyl substrate to a Pd(0) catalyst. Controlled evolution of the resulting bis(allyl)-Pd(II) intermediate would provide 1,5-borylated diene.

In order to successfully implement this idea, several challenges must be overcome:

- **Chemoselectivity**

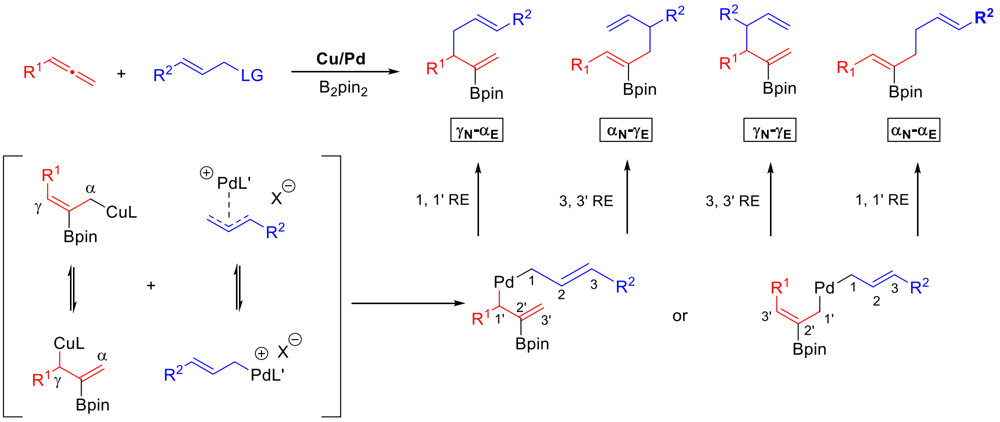
To avoid side reactions, each catalyst must react with each substrate in a chemoselectivity manner. For example, direct borylation of allylic substrate has been described with both copper and palladium catalysis (Scheme 83a). Furthermore, boryl allylcopper intermediates can potentially react with protic sources to produce protoboration product (Scheme 83b).



Scheme 83. Possible side reactions with copper and palladium catalysis

- **Regioselectivity**

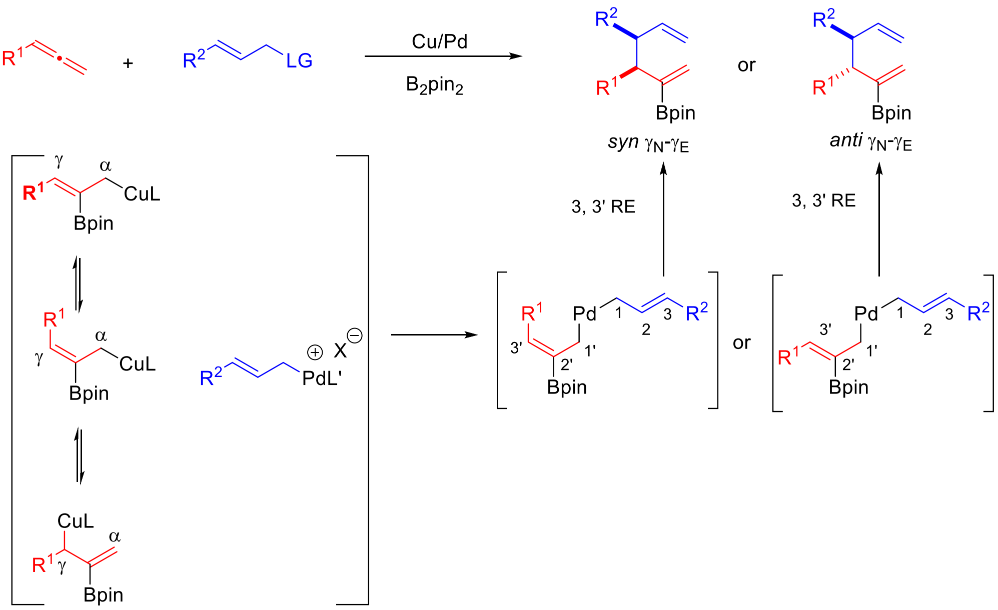
The proposed transformation involves a big regioselelctivity challenge. The allyl-Cu(I) intermediate can exist in two different resonance forms, which can react with the allyl-Pd(II) species either by a S_E2 or by a S_E2' mechanism. Moreover, the resulting bis(allyl)Pd(II) intermediate can evolve via 1,1'- or 3,3'-reductive elimination pathways (Scheme 16).



Scheme 84. Possible formation of regioisomers in Cu/Pd catalyzed allyl-allyl cross-coupling.

- **Stereoselectivity**

Since the allyl-Cu(I) intermediate can exist in equilibrium between the two possible regioisomeric structures, controlled transmetalation should be achieved since the final relative configuration of the two carbon stereogenic centers may be influenced by the stereochemistry in the borylated allyl substituent (Scheme 85).



Scheme 85. Diastereoselectivity control in Cu/Pd catalyzed allyl-allyl cross-coupling.

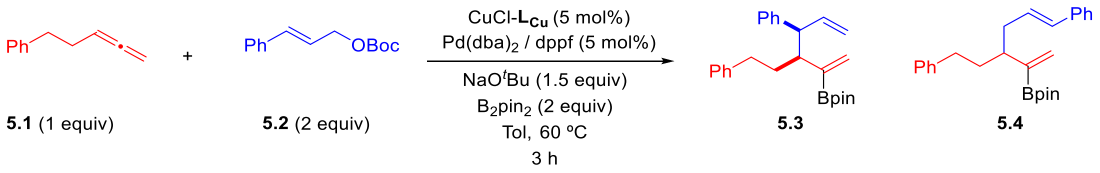
3. RESULTS AND DISCUSSION

3.1 Optimization

At the outset of our investigation, we selected a reaction involving B_2pin_2, penta-3,4-dien-1-ylbenzene **5.1** and *tert*-butyl cinnamyl carbonate **5.2** to evaluate both the feasibility and selectivity of the process.

We initially evaluated the effect of the ligand in copper. For this screening we selected $Pd(dba)_2$/dppf (5 mol%) and CuCl/L_{Cu} (5 mol%) as catalytic system and NaO^tBu (1.5 equiv) as base (Table 22). The initial experiment using BINAP as ligand (Table 22, entry 1) afforded the product **5.3** in 60% yield and good diastereomeric ratio (8:1). When we use other different bisphosphine such as BIPHEP (Table 22, entry 2), we were able to increase the yield and at the same time the diastereomeric ratio up to 14:1. However, the use of XantPhos, DPEPhos and dppf (Table 22, entries 3-5) gave rise to the product **5.3** in lower yields and diastereoselectivity. Interestingly, the use of dppe (Table 22, entry 6) afforded a mixture of isomers **5.3** and **5.4** in which the major product was **5.4**. Moreover, the use of monodentate phosphines such as PPh_3 (Table 22, entry 7) also gave rise to mixtures of isomers and lower yields. With the use of NHC ligands (Table 22, entries 8,9), the diastereomeric ratio and yield decreased dramatically.

Table 22. Screening of ligand on copper in the Cu/Pd catalyzed allyl-allyl cross-coupling.[a]

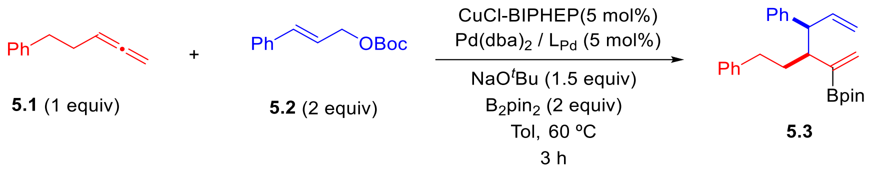


Entry	L_{Cu}	5.3 yield (%)[b]	5.3 dr	Yield 5.4 (%)[b]
1	BINAP	60	8:1	-
2	BIPHEP	76	14:1	-
3	XantPhos	77	5:1	-
4	DPEPhos	54	3:1	-
5	dppf	45	6:1	-
6	dppe	18	3:1	36
7	PPh_3	6	18:1	9
8	IMes	46	7:1	-
9	SIMes	12[c]	n.d.	-

[a] Reactions performed in a 0.2 mmol scale. [b] Yield of isolated product.

We next screened the effect of the ligand in palladium catalyst keeping CuCl/BIPHEP as the copper catalyst. The use of PPh_3 (Table 23, entry 2) led to the formation of the desired product **5.3** as a single diastereoisomer, however we observed a significant decrease in yield. Gratifyingly, the use of BIPHEP ligand for both metals gave rise to the desired product in good yield and selectivity (Table 23, entry 3). Similar results were observed when BINAP was used (Table 23, entry 4). Finally, the use of other bidentate phosphine such as DPEPhos (Table 23, entry 5) afforded the product in moderate yield and lower diastereoselectivity.

Table 23. Screening of ligand on palladium catalyst in the Cu/Pd catalyzed allyl-allyl cross-coupling.[a]

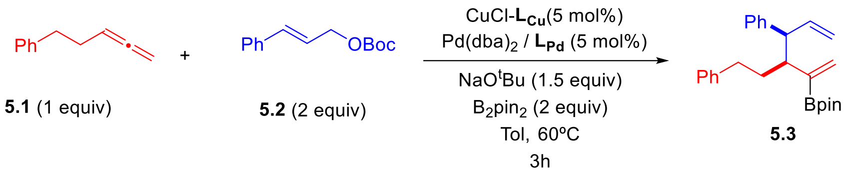


Entry	L_{Pd}	Yield 5.3 (%) [b]	dr[b]
1	dppf	76	14:1
2 [c]	PPh_3	40	>20:1
3	BIPHEP	75	14:1
4	BINAP	63	17:1
5	DPEPhos	60	6:1

[a] Reactions performed in a 0.2 mmol scale. [b] Isolated yields. [c] 10 mol% was used.

After having carried out these screening of ligands (Table 22 and 23) several studies were carried out to probe if a ligand exchange takes places during the progress of the reaction (Table 24). However, we could only conclude that the diastereoselectivity depends on both metals.

Table 24. Ligand exchange study between copper and palladium.[a]

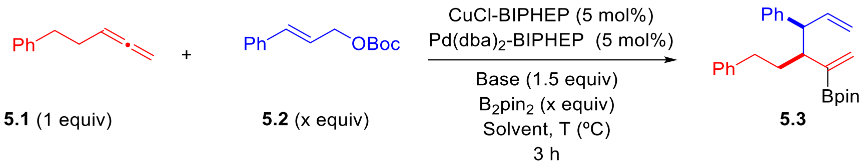


Entry	CuCl / L_{Cu}	$Pd(dba)_2$/ L_{Pd}	Yield 5.3 (%)[b]	dr
1	BIPHEP	BIPHEP	75	14:1
2	BIPHEP	dppf	76	14:1
3	dppf	dppf	45	6:1
4	dppf	BIPHEP	59	10:1
5 [c]	-	5 mol%	-	-
6 [d]	5 mol%	-	-	-

[a] Reactions performed in a 0.2 mmol scale. [b] Yield of isolated product. [c] Starting material was recovered and 24% of allene protoboration product was obtained. [d] Decomposition of allyl carbonate **5.2** was observed.

Temperature, reagents stoichiometry, effect of the base and leaving group were also evaluated (Table 25). We observed that a decrease in temperature and in the equivalents of **5.2** gave rise to a similar yield and the diastereomeric ratio reached up to 20:1 (Table 25, entry 2). However, the use of catalytic amounts of base, only afforded **5.3** in 45% yield although high selectivity (Table 25, entry 3). We next evaluated the effect of the nature of the base in the transformation. We initially found that the use of a bigger cation such as KO^{t}Bu (Table 25, entry 4) produced a decrease of the yield although the diastereomeric ratio was maintained. However, the use of LiO^{t}Bu (Table 25, entry 5) produced a significant decrease in the reaction efficiency and product **5.3** was only obtained in 14% NMR yield. The effect of leaving group was also evaluated, and we observed that the use of *tert*-butyl carbonate is essential, since the use of other groups did not afford the desired product (Table 25, entries 6 and 7). Finally the use of THF, one of the most common solvents in carboboration transformations was tested (Table 25, entry 8). However, no improvement of the transformation was observed.

Table 25. Screening of reaction conditions.[a]



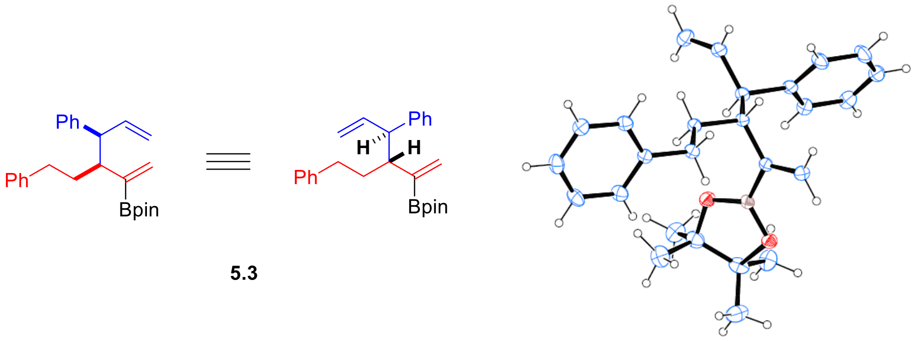
5.1 (1 equiv) **5.2** (x equiv) **5.3**

Entry	**Solvent**	**T (°C)**	**Base**	**Leaving group**	**5.2 (Equiv)**	**Yield 5.3 (%)[b]**	**dr**
1	Toluene	60	NaO^{t}Bu	OCO$_2{}^t$Bu	2	76	14:1
2	Toluene	30	NaO^{t}Bu	OCO$_2{}^t$Bu	1.5	70	>20:1
3[c]	Toluene	30	NaO^{t}Bu	OCO$_2{}^t$Bu	1.5	45	>20:1
4	Toluene	30	KO^{t}Bu	OCO$_2{}^t$Bu	1.5	43	19:1
5	Toluene	30	LiO^{t}Bu	OCO$_2{}^t$Bu	1.5	14[b]	-
6	Toluene	30	NaO^{t}Bu	OCO$_2$Me	1.5	-	-
7	Toluene	30	NaO^{t}Bu	Cl	1.5	-	-
8	THF	30	NaO^{t}Bu	OCO$_2{}^t$Bu	1.5	43	>20:1

[a] Reactions performed in a 0.2 mmol scale. [b] Yield of isolated product. [c] Use of 20 mol% of base.

3.2 Scope of the reaction

Having stablished the optimized conditions (Table 25, entry 2), we set out to investigate the scope of the reaction (Table 26). Remarkably, reactions proceeded with total stereo- and regioselectivity to afford the corresponding products. The use of allene **5.1** and allyl carbonate **5.2** afforded the product **5.3** in high yield and diastereoselectivity. Furthermore, it is important to note that the reaction gave rise to the same results using the branched starting carbonate **5.2'** to afford the corresponding product **5.3**. The stereochemistry of these products was confirmed by X-ray analysis of diene **5.3** (Figure 1).



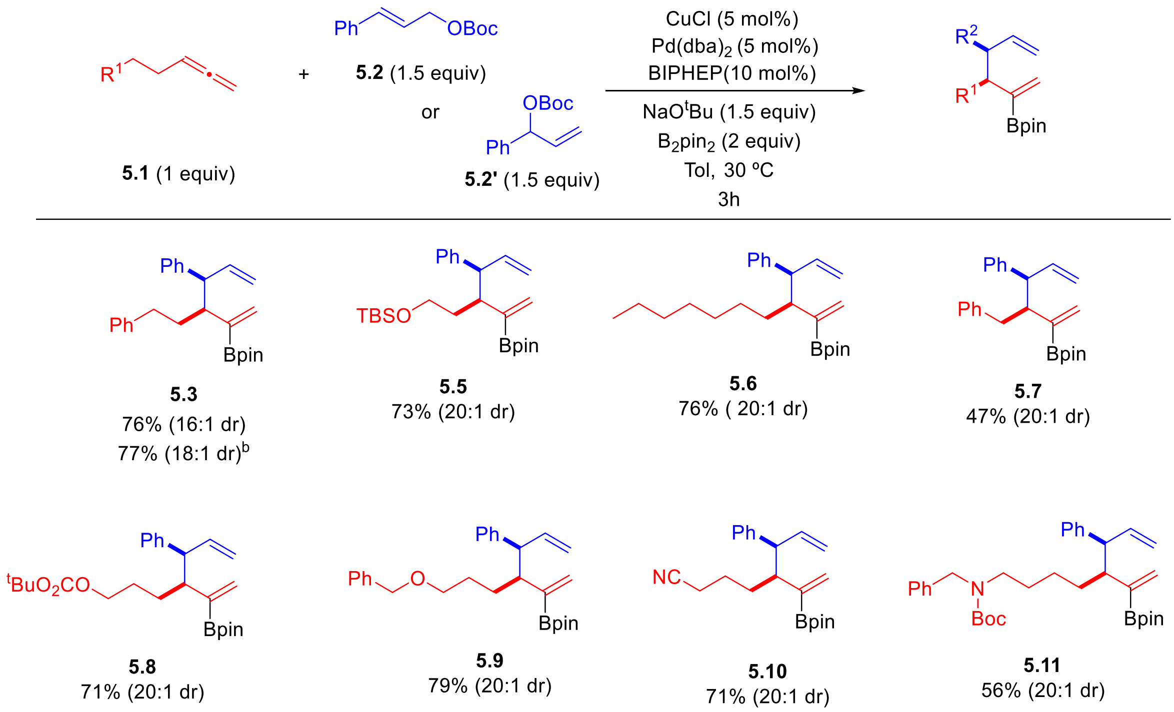
5.3

Figure 6. X-ray analysis of product **5.3**

We observed that the diastereoselectivity of our process is the opposite of that obtained by Morken and co-workers in Pd-catalyzed allyl-allyl cross-coupling, obtaining in our case de *syn* diastereoisomer.

Several allenes were tested in this transformation (Table 26). Allenes with an aliphatic chain proved to be efficient substrates and reacted with cinnamyl *tert*-butylcarbonate **5.2** and B_2pin_2 affording the corresponding 1,5-borylated dienes **5.5-5.11** in good yields and with high diastereoselectivity levels. Functional groups such as silyl ether (**5.5**), protected amine (**5.11**), or cyanide group (**5.10**) were well tolerated.

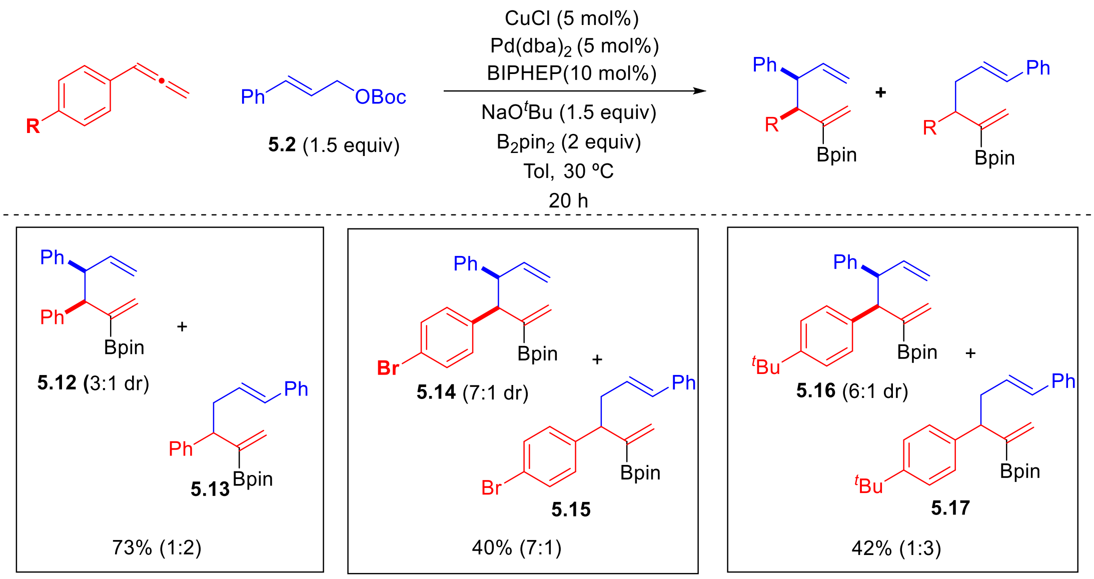
Table 26. Scope of allenes[a]



[a] Reactions performed in a 0.2 mmol scale, [b] Use of branched allylic carbonate **5.2'.**

The use of aromatic allenes led to regioisomeric mixtures and low diastereoselectivity (Table 27).

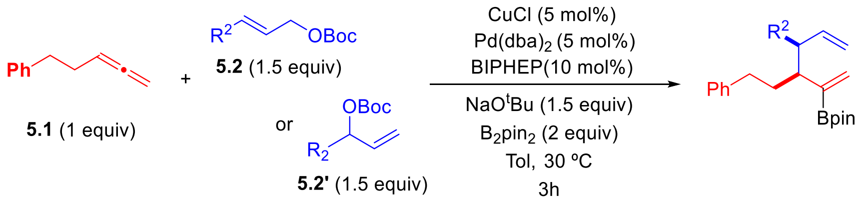
Table 27. Use of aromatic allenes.[a]

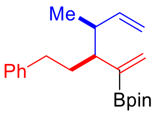


[a] Reactions performed in a 0.2 mmol scale.

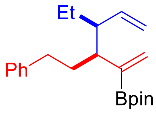
Several allylic carbonates were also evaluated under these dual Cu/Pd catalytic conditions (Table 28). Different cinnamyl carbonate derivatives with different substitution patterns, proved also to be efficient for this transformation and provided dienes **5.23** - **5.27** in good yields and with excellent diastereoselctivity. (*E*)-*tert*-Butyl (3-(4-methoxyphenyl)allyl) carbonate turned out to be less reactive in this transformation, so it was necessary to carry out the reaction at 60 °C to afford the product **5.27** which was still obtained with good selectivity. Aliphatic substituted allyl carbonates gave rise to the formation of the desired product in good yields, although low diastereoselectivity was observed (**5.18** - **5.20**) in these cases. The use of *Z* allylic carbonate in the formation of **5.19** was also possible. Similarly, 1,3-disubstituted allylic carbonates led to products **5.21** and **5.22** in good yields albeit with low diastereoselectivity ranging from 1.1 to 1.5:1. Simple allyl carbonate provided **5.29** in good yield. The use of branched allyl carbonate afforded the corresponding product **5.28** in high levels of yield and selectivity (10:1, γ_N-α_E). In this case, it is important to highlight that due to the extra conjugation of the starting allyl carbonate there is the possibility of formation of side products that were not observed. Surprisingly, when an allylic carbonate bearing a bulky tert-butyl groups was used, regioselectivity was switched and γ_N-α_E regioisomer **5.30** was obtained in 50% yield as the sole reaction product.

Table 28. Scope of allyl carbonates [a]

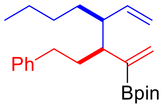




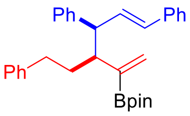
5.18
76% (1.5:1 dr)
40% (1.3:1 dr)[c]



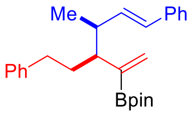
5.19[b]
73% (3:1 dr)



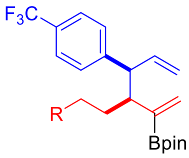
5.20[c]
74% (3:1 dr)



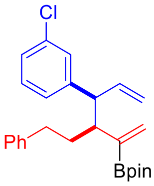
5.21[d]
70% (1.5:1 dr)



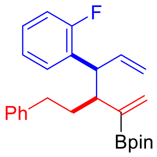
5.22[d]
71% (1:1 dr)



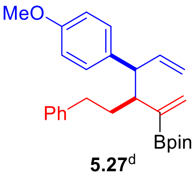
5.23, R= Ph, 80% (20:1 dr)
5.24, R= OTBS, 80% (20:1 dr)



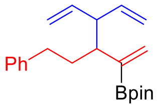
5.25
71% (20:1 dr)



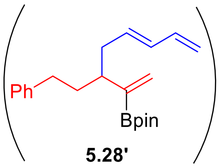
5.26
67% (20:1 dr)



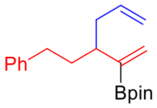
5.27[d]
78% (13:1 dr)



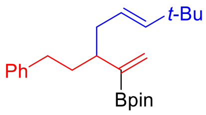
5.28[c,e]
73%



5.28'



5.29
78%



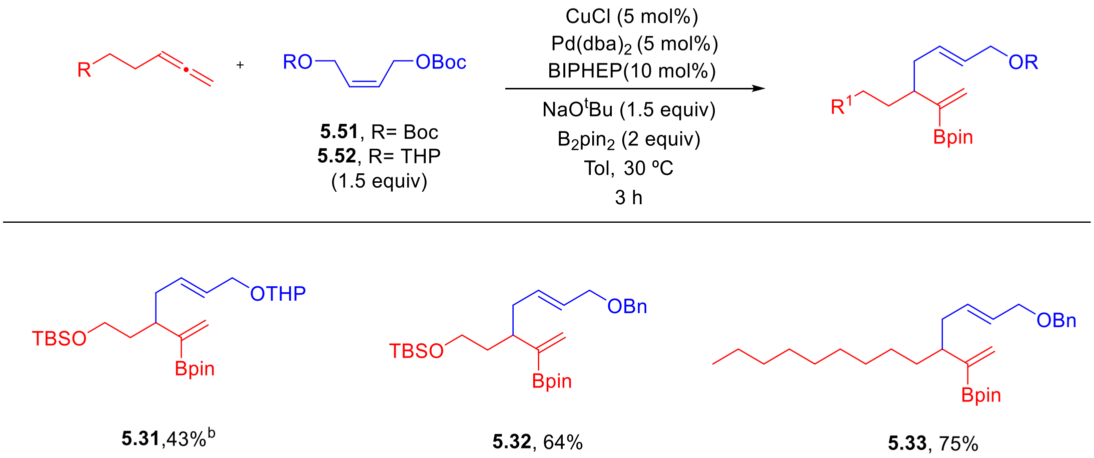
5.30
50%

[a] Reactions performed in a 0.2 mmol scale, [b] From *Z* allylic carbonate, [c] From branched allylic carbonate, [d] Run at 60 °C, [e] Isolated inmixture with **5.28'** (γ_N-α_E selectivity, 10:1 dr) from the branched allyl carbonate were R^2=$CHCH_2$.

3.2.1 Use of linear α-functionalized allyl carbonates.

Surprisingly, when we used α-functionalized allylic carbonates **5.51** and **5.52**, we observed a regioselectivity switch, obtaining selectively the γ_N-α_E products **5.31** - **5.33** (Table 29).

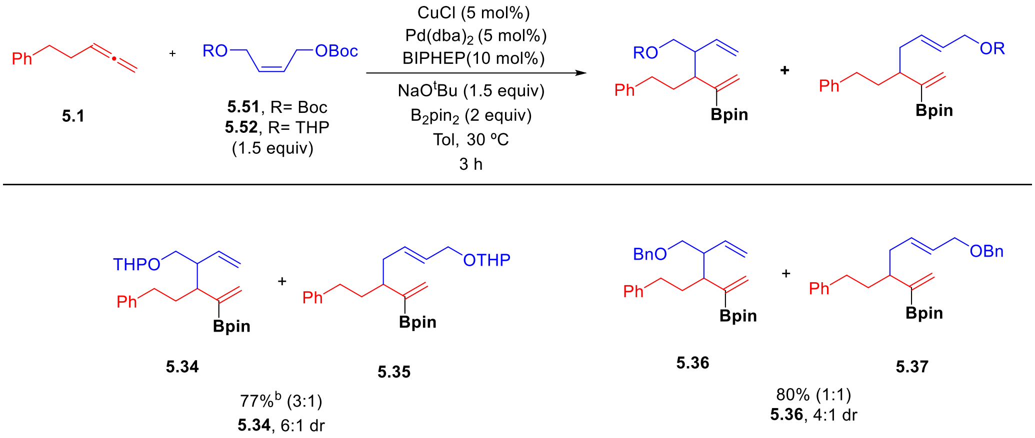
Table 29. Use of linear functionalized allylic carbonates in Cu/Pd catalyzed allyl-allyl cross-coupling [a]



[a] Reactions performed in a 0.2 mmol scale, [b] Diastereomeric ratio arise from the presence of THP group can not seen in NMR and are not be consider

Moreover, we observed that the selective formation of these regioisomers not only depends on the nature of the allyl carbonate. The use of penta-3,4-dien-1-ylbenzene **5.1** led to the formation of regioisomeric mixtures. Although good yields were obtained, the diastereoselectivities for the γ_N-γ_E products were lower, obtaining values between 4:1 to 6:1 for products **5.34** and **5.36** (Table 30).

Table 30. Cu/Pd-catalyzed borylative coupling bewteen linear functionalized allylic carbonates and allene **5.1**.[a]

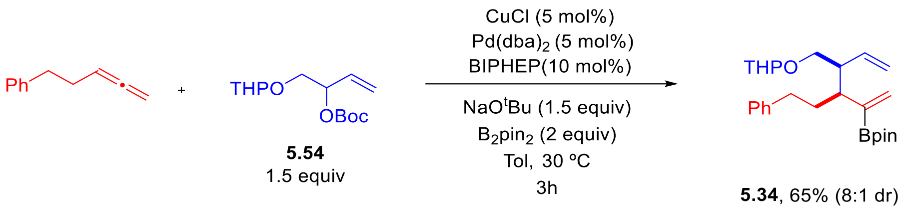


[a] Reactions performed in a 0.2 mmol scale, [b] Diastereomeric ratio arise from the presence of THP group can not seen in NMR and are not be consider.

3.2.2 Use of functionalized branched allyl carbonates

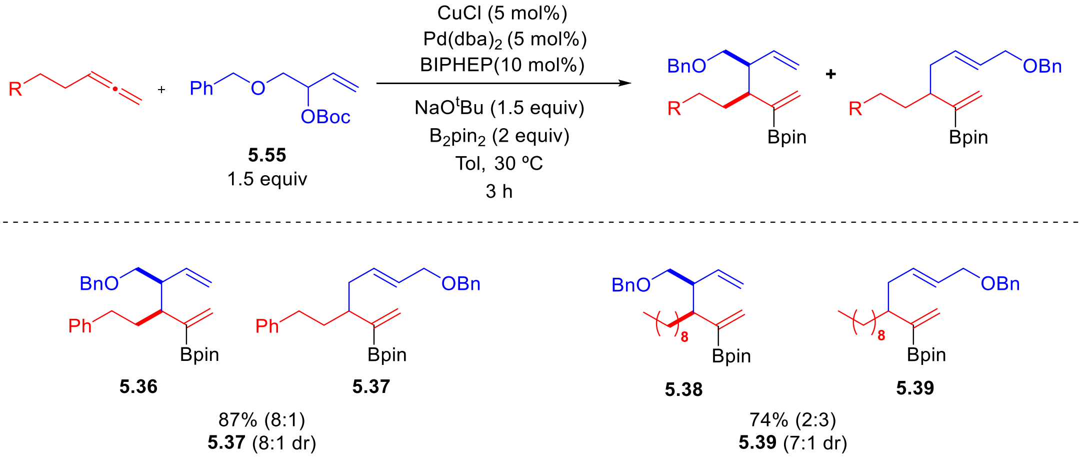
As mentioned above, the use of branched or linear allyl carbonates in reactions involving aromatic or aliphatic allylic carbonates afforded the same product. However, a different behavior was observed when branched allylic carbonates containing an alkoxy group such as THP or benzyl group in alpha position, were used (Scheme 86). The reaction between allene **5.1** and THP-protected allylic carbonate **5.54** afforded selectively the product **5.38** in 65% yield and 8:1 diastereomeric ratio.

Scheme 86. Use of functionalized branched allylic carbonate **5.54** in Cu/Pd catalyzed allyl-allyl coupling.



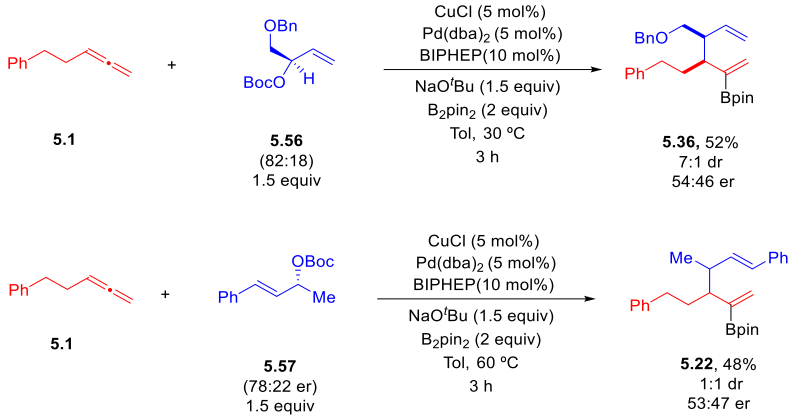
Similar effect was observed with benzyl protected allyl carbonate **5.55**, although regioselectivity was slightly lower in those cases, obtaining mixtures of γN-γE and γN-αE products (Table 31).

Table 31. Use of branched allyl carbonate **5.55** in in Cu/Pd catalyzed allyl-allyl coupling.



3.2.3 Use of enantioenriched allylic carbonates

To better understand the reaction outcome, two experiments were carried out using enantioenriched allylic carbonates (Scheme 87). It was observed that with the use of this type of substrates, the chiral information is lost, obtaining nearly racemic mixtures of the corresponding products **5.39** and **5.22**.

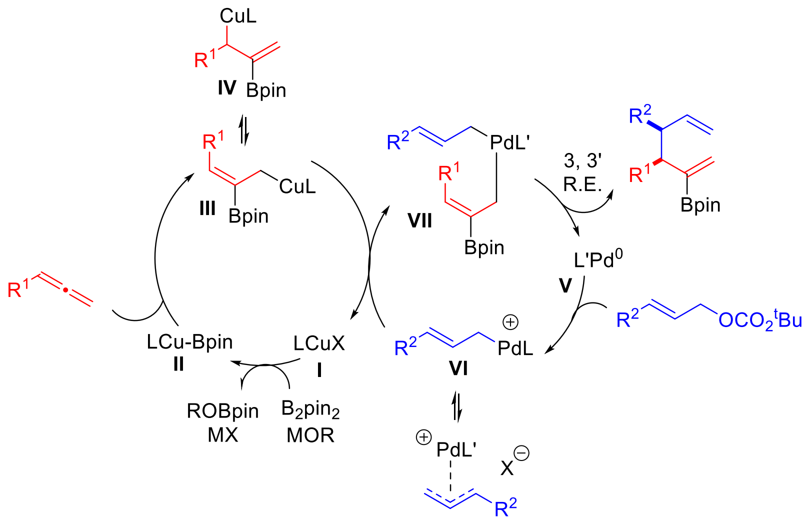


Scheme 87. Use of enantioenriched allylic carbonates.

3.3 Proposal mechanism

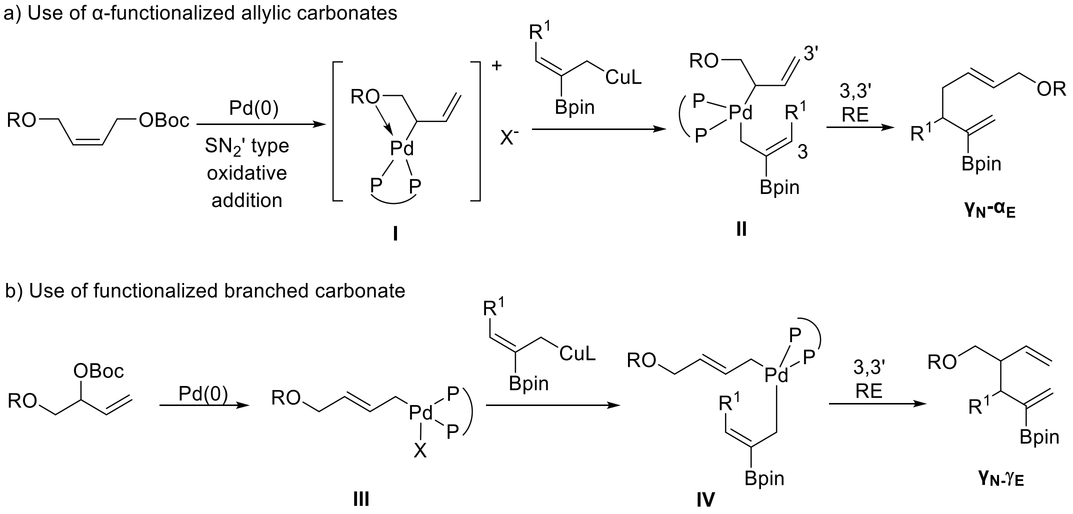
On the basis of our experimental observations and our previous investigations, we propose the following mechanism for the Cu/Pd catalyzed borylative coupling between allenes and allyl carbonates (Scheme 88).

The catalytic cycle starts with the generation of *tert*-butoxy copper species **I**, which reacts with B_2pin_2 to afford borylcopper species **II**. Insertion of the allene into complex **II** generates β-boryl-(*Z*)-allyl copper intermediate **III** which can be in equilibrium with **IV**. In a second catalytic cycle, oxidative addition of the allyl carbonate to the LPd(0) complex afford the intermediate **VI**. Transmetalation between organometallic species **III** and **VI** would form bis-allyl palladium intermediate **VII**. Finally, a 3,3’ reductive elimination would give rise to the desired product and both catalytic cycles were regenerated.



Scheme 88. Proposed mechanism for the Cu/Pd catalyzed borylative coupling between allenes and allyl carbonates.

As was mentioned in previous section, the use of α-functionalized allylic carbonates **5.51** and **5.52** gave rise to a regioselectivity switch of the transformation, obtaining selectively the γ_N-α_E. This fact could be explained through the mechanistic proposal shown below (Scheme 89a). For that, we proposed a SN_2’ type oxidative addition of the allyl carbonate to Pd(0) to afford the intermediate **I**, in which the oxygen could be coordinated to the Pd center. Then, transmetalation with the allylcopper afforded the bis-allyl Pd intermediate **II**. Finally, a 3,3’ reductive elimination afforded the the γ_N-α_E product. In other hand, the use of branched functionalized allyl carbonate could give rise to a different type of mechanism, in which a different regioisomer could be obtained (Scheme 89b). We proposed the formation of intermediate **III** after the oxidative addition of the allylcarbonate to Pd(0). Then, transmetalation with allyl-copper takes place to afford the intermediate **IV**, that after a 3,3’ reductive elimination afforded the xx product γ_N-γ_E.

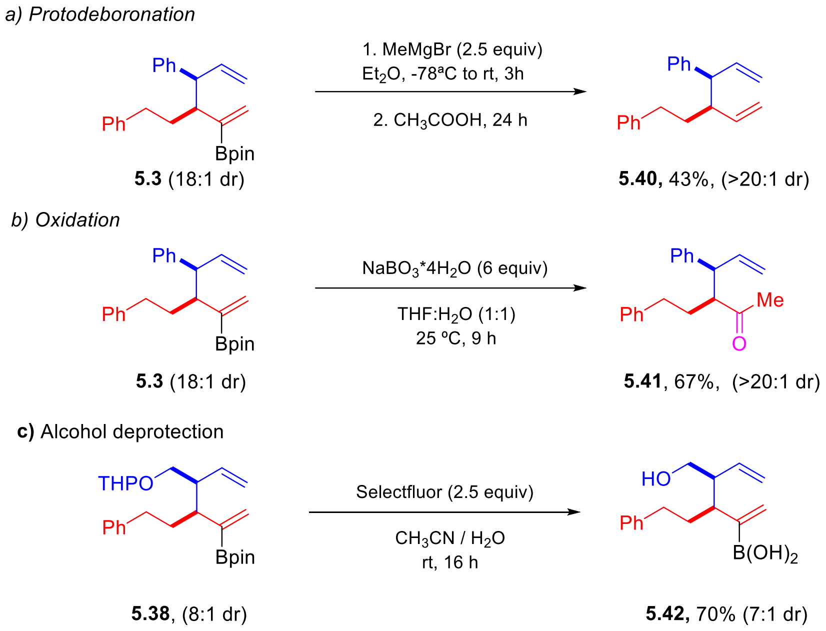


Scheme 89. Regioselectivity switch and memory effect.

3.4 Synthetic modifications

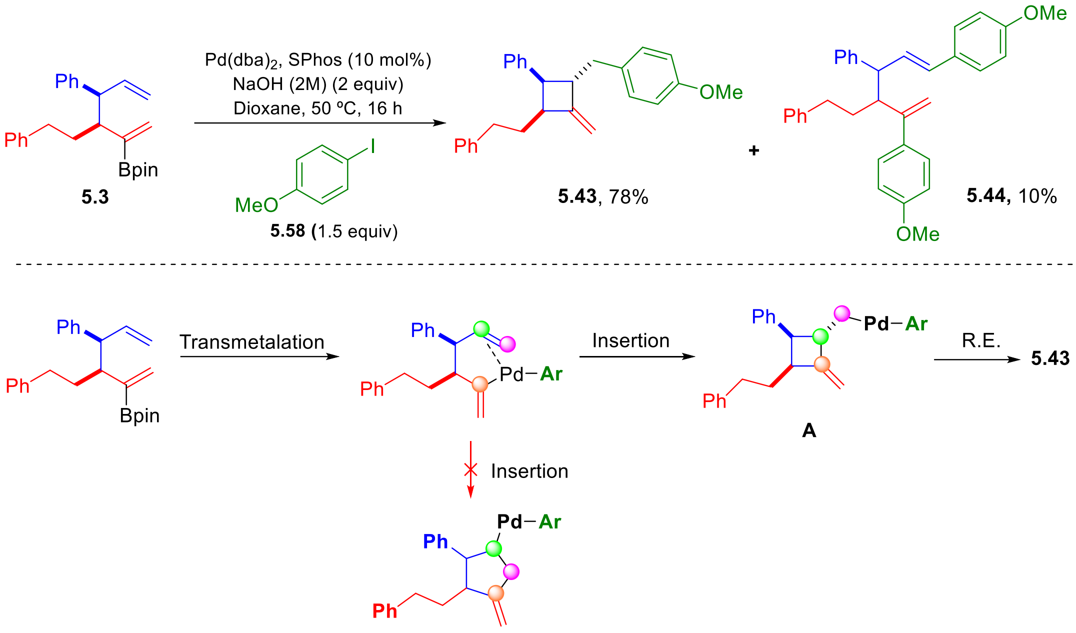
To illustrate the synthetic utility of the present synergistic Cu/Pd-catalyzed borylative allyl-allyl coupling, we targeted the synthesis of different structures from the borylated 1,5-diene core.

Protodeboronation of compound **5.3** was carried out to give rise to product **5.43** in a moderate yield after treatment with methyl magnesium bromide, thus accessing the opposite diastereoisomer to that obtained by Morken in Pd-catalyzed allyl-allyl cross-coupling (Scheme 90a). The synthesis of the methyl ketone **5.44** was also possible from 1,5-borylated dienes after an oxidation process with $NaBO_3$ (Scheme 90b). Finally, after treatment of **5.38** with Selectfluor to carry out the alcohol deprotection, the boronic acid **5.45** was obtained (Scheme 90c).



Scheme 90. Synthetic modifications of **5.3** and **5.38**.

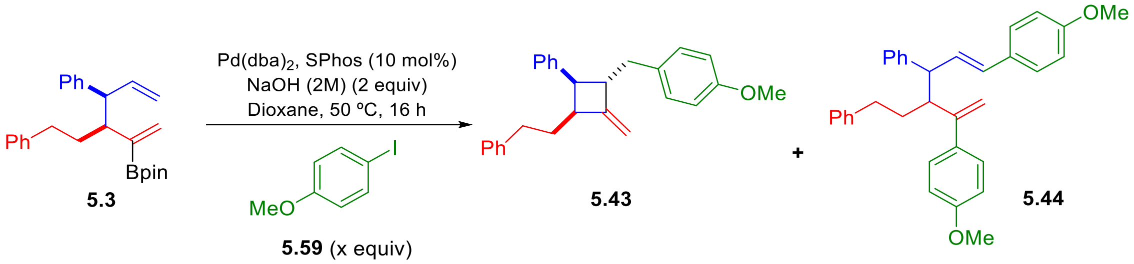
Furthermore, we attempted to carry out a Suzuki cross coupling of compound **5.3**. Surprisingly, when **5.3** was treated with $Pd(dba)_2$, SPhos and an aqueous solution of sodium hydroxide under the presence of 1-iodo-4-methoxybenzene in dioxane, no tractable amount of Suzuki cross-coupled product was observed. Nevertheless, methylenecyclobutane **5.46** was obtained in 78% yield. We propose that the reaction proceeds through the mechanism depicted in Scheme 91. After transmetalation between the boronic ester and the aryl-Pd(II) intermediate, generated by oxidative addition of the aryl iodide to the palladium(0) catalyst, the resulting Pd(II) intermediate would undergo a regio- and stereoselective insertion of vinyl group into the C-Pd bond leading to intermediate **A** which would give rise to product **5.46** via reductive elimination. Besides formation of the methylenecyclobutane, **5.47** was obtained in 10% yield. Formation of this product could be explained through a tandem Heck-Suzuki cross-coupling.



Scheme 91. Stereoselective synthesis of methylenecyclobutane **5.43**.

To better understand this transformation, a preliminary screening of conditions was carried out. First, we studied the stoichiometry of the transformation in order to improve the selectivity of the reaction (Table 32). We observed that a decrease in the amount of iodoarene gave rise to the selective formation of the cyclic product **5.46**, although lower yields were observed. Moreover, the use of 3 equivalents of **5.59** afforded an equimolar mixture of **5.46** and **5.47**. Notably, the use of 1-bromo-4-methoxybenzene, afforded selectively the formation of product **5.47** in 32% yield (Table 32, entry 5).

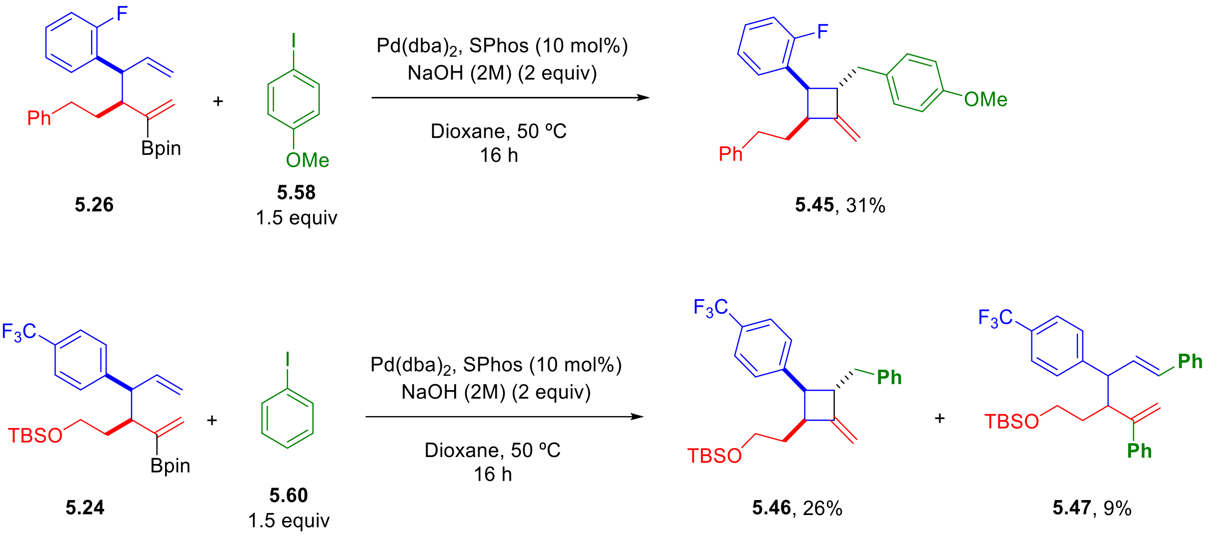
Table 32. Screening of stoichiometry.[a]



Entry	5.59 (Equiv)	Conversion 5.3 (%)[b]	Yield 5.46 (%)[b]	Yield 5.47 (%)[b]
1	1.5	Full	78	10
2	1.3	90	45	-
3	1.1	85	42	-
4	3	Full	23	23
5[c]	1.5	Full	-	32

[a] Reactions performed in a 0.2 mmol scale. [b] Measured in isolated product, [c] Use of 1-bromo-4-methoxybenzene instead of **5.59**.

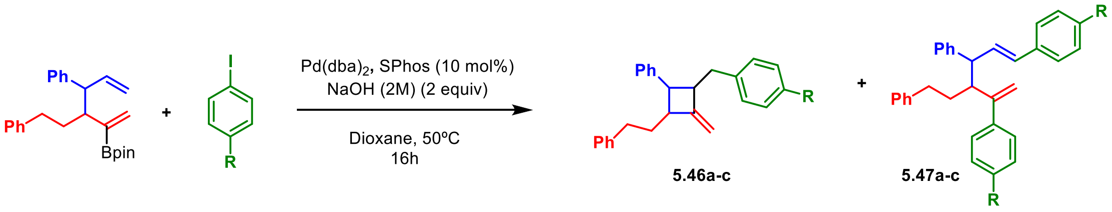
Different borylated 1,5-dienes proved to undergo a similar transformation when reacted with iodoarenes under these reaction conditions (Scheme 92). The use of 1,5-borylated diene **5.26** in combination with iodoanisole **5.59**, afforded selectively methylenecyclobutane **5.48** in 31% yield although full conversion was not achieved, recovering 31% of starting material after column chromatography. Similarly, iodobenzene could be coupled with diene **5.24** to produce a mixture of cyclobutane **5.49** and Suzuki-Heck double coupled product **5.50** in moderate yields.



Scheme 92. Stereoselective synthesis of methylenecyclobutanes **5.45** and **5.46**.

However, when other iodoarenes were evaluated, no product formation was observed (Table 33).

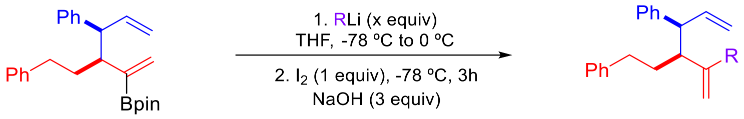
Table 33. Use of different iodoarenes for the synthesis of cyclobutanes [a]



Entry	R	Conversion 5.3 (%)[b]	Yield 5.46a-c (%)[b]	Yield 5.47a-c (%)[b]
1	NO_2	Full	-	Traces
2	CF_3	Full	-	-
3	CO_2Et	75	-	-

[a]Reactions performed in a 0.2mmol scale. [b]Determined by ^{1}H-NMR using 1,3,5-trimethoxybenzene as internal standard.

Finally, direct arylation or methylation of borylated 1,5-dienes could be achieved by means of a Zweifel coupling.[107] Using this strategy, diene **5.3** could be coupled with PhLi and MeLi to access products **5.51** and **5.52** in good yields (Scheme 93).



5.3

5.48, (Use of 1.5 equiv PhLi) R = Ph; 47%
5.49, (Use of 2.5 equiv MeLi) R = Me; 62%

Scheme 93. Zweifel coupling of **5.3**

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[107] (a) Zweifel, G.; Arzoumanian, H.; Whitney, C. C. *J. Am. Chem. Soc*. **1967**, *89*, 3652-3653. (b) Xu, S.; Lee, C.-T.; Rao, H.; Negishi, E. *Adv. Synth. Catal*. **2011**, *353*, 2981-2987. (c) Armstrong, R. J.; Aggarwal, V. K. *Synthesis* **2017**, *49*, 3323-3336.

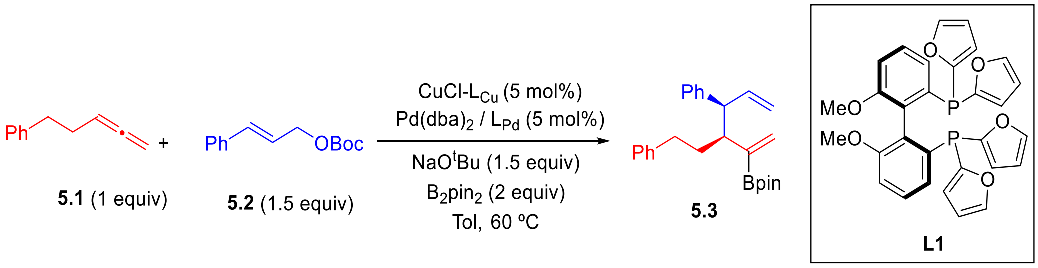
4. Enantioselective Cu/Pd-catalyzed borylative allyl-allyl cross-coupling

In view of the precedents mentioned in the introduction and our work reported in this chapter about the racemic Cu/Pd-catalyzed allylboration of allenes, we devised to move one step further and attempt to develop an enantioselective version of this transformation.

4.1 Optimization

We first assessed the necessity of using a chiral ligand in both transition metals (Table 34). To do this, we first run the reaction between allene **5.1** and allyl carbonate **5.2** using both chiral complexes Cu/**L1** and Pd/**L1** under the optimal conditions for the racemic transformation (Table 34, entry 1), however, no reaction was observed. Pleasantly, we observed high levels of regio- and enantioselectivity, in the formation of **5.3** when we increased the temperature reaction to 60 °C (Table 34, entry 2). Interestingly, a catalytic system comprising the non-chiral Cu/BIPHEP complex and chiral Pd/L1 complex led to a similar yield, although with a significant decrease in selectivity and especially affecting the enantioselectivity of the reaction (Table 34, entry 3). By reversing the situation, i.e. using chiral Cu/L1 complex and non-chiral Pd/BIPHEP complex, diastereoseelctivity value was recovered although product **5.3** was obtained as a racemic mixture(Table 34, entry 4). In order to evaluate a possible ligand exchange scenario in the previous entries, the reaction was run with a combination of Pd/**L1** and a Cu/NHC complex in which the strong Cu-C bond hampers ligand scrambling (Table 34, entry 5). Under these conditions, the product was obtained in moderate yield albeit with lower er than the one observed when L1 was used for both Pd and Cu catalysts (87:13 vs 97:3 er). Finally, the use of Cu/**L1** and Pd/***enant*-L1** led to a significant decrease of the enantioselectivity. Taken together, these results demonstrate the necessity of using the same chiral ligand in both transition metal complexes to achieve high enantioselectivity. Moreover, they suggest that both metal complexes are involved in the enantiodetermining step of the process, although a possible ligand exchange scenario cannot be discarded at this point.

Table 34. Screening of chiral ligands in copper and palladium catalysts[a]

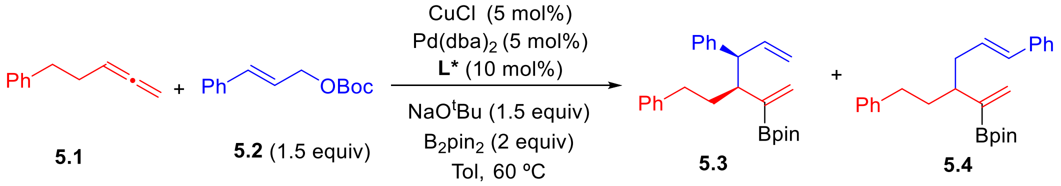


Entry	**L$_{Cu}$**	**L$_{Pd}$**	**5.3* (% yield)[b]**	**dr**	**e.r.**
1[c]	L1	L1	-	-	-
2	L1	L1	23	>20:1	97:3[d]
3	BIPHEP	L1	28	13:1	66:34[e]
4	L1	BIPHEP	47	>20:1	49:51[e]
5	IMes	L1	49	5:1	87:13[e]
6	L1	*enant*-L1	25	>20:1	62:38[e]

[a]Reactions performed in a 0.2mmol scale. [b] Isolated yield, [c] Reacction run at 30 °C, [d] Determined by HPLC analysis after oxidation of **5.3**. [e] Determined by SFC analysis of **5.3**.

Having observed that the presence of a chiral ligand in both metals is necessary, a screening of different chiral MeOBIPHEP ligands was subsequently carried out (Table 35). The use of ligand bearing phenyl groups at the phosphorous atom instead of the furyl rings afforded the product in higher yield although the reaction was not satisfactory in terms of regio- and diastereoselectivity (Table 35, entry 2). In addition, a decrease in the enantioselectivity of the transformation was observed. The use of a phosphine featuring more hindered 3,5-dimethylphenyl rings (Table 35, entry 3) did not afford the product **5.3**, allene protoboration being the single reaction product. The diastereo- and enantioselectivity were recovered when *para*-methylphenyl-substituted bisphosphine **L5** was used, although reaction was not regioselective and a 1:1 mixture of products **5.3** and **5.4** was obtained (Table 35, entry 4). Comparison between results shown in entries 1,2 and 4 suggest that the presence of electron donating groups on the ligand phosphorous atom is detrimental for this transformation. Accordingly, no product formation was observed when aliphatic phosphine ligand L6 was used (Table 35, entry 5). Considering the importance of the electronic effects in this transformation, a ligand bearing a chlorine atom in the biphenyl structure led to excellent regioselectivity, although diastereo- and enantioselectivity were non satisfactory (Table 35, entry 6). As shown in entries 7-12, other types of chiral bisphosphines ligands were tested none of them led to improved results.

Table 35. Screening of chiral ligands in Cu/Pd catalyzed allyl-allyl cross-coupling[a]



Entry	L*	5.3 (% yield, dr)	5.3 (er)	5.3: 5.4 ratio	5.4 (er)
1	**L1**	23 (>20:1)	97:3[b]	1:0	-
2	**L3**	59 (12:1)	92:8[c]	5:1	64:36[c]
3	**L4**	-	-	-	-
4	**L5**	32 (11:1)	89:11[c]	1:1	54:46[c]
5	**L6**	-	-	-	-
6	**L7**	43 (10:1)	79:2[b]	>20:1	n.d.
7	Quinox P*	-	-	-	-
8	*R*- SegPhos	53(11:1)	91:9[c]	2:1	73:27[c]
9	*S*, DM- SegPhos	37 (7:1)	n.d	1:5	68:32
10	*S*-BINAP	49 (13:1)	83:17[b]	4:1	64:36[b]
11	*S*, Ph-GarPhos	50 (9:1)	93:7[c]	1:1.5	59:41[c]
12	DuanPhos	-		-	-

[a]Reactions performed in a 0.2mmol scale. [b] Enantiomeric ratio was measured using HPLC analysis after oxidatitacion of corresponding product [c] Enantiomeric ratio was measured using SFC in the corresponding borylated product.

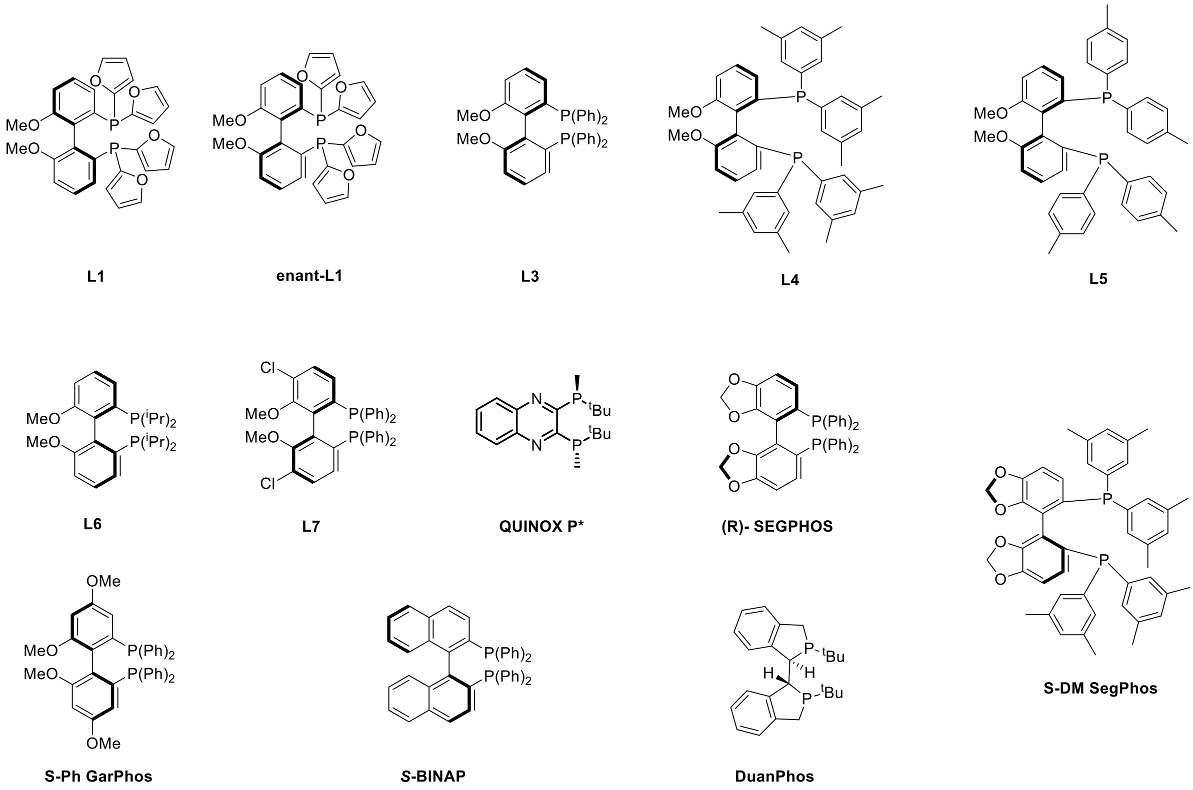
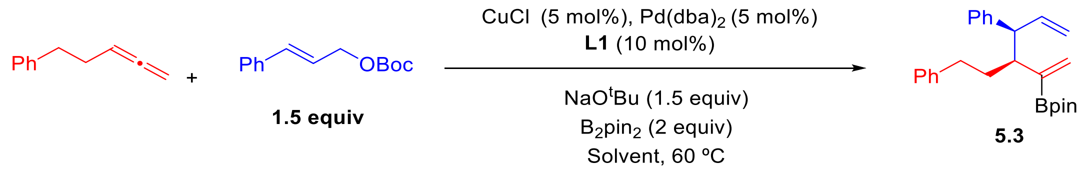


Figure 7. Chiral ligands used in enantioselective borylative allyl-allyl coupling of allenes and allyl carbonates.

Evaluation of solvents was also carried out (Table 36). We observed that the use of a polar aprotic solvent such as THF (Table 36, entry 1) afforded similar results to toluene. However, when we use 1,4-dioxane we observed a slight deterioration in the diastereoselectivy of the transformation, although no formation of regioisomer **5.4** was observed.

Table 36. Screening of solvents for the enantioselective Cu/Pd catalyzed cross-coupling of allenes and allyl carbonates.[a]

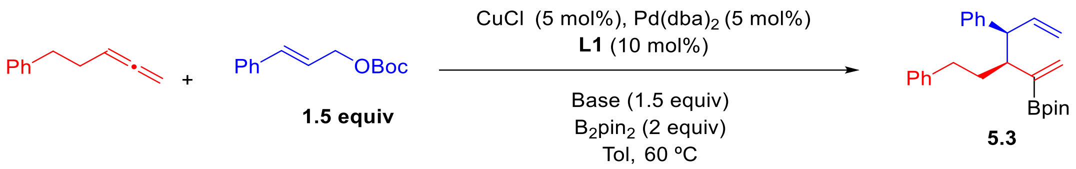


Entry	Solvent	5.3* (% yield)[a]	dr	e.r.[b]
1	Toluene	23	>20:1	97:3
2	THF	17	>20:1	97:3
3	1,4-Dioxane	23	12:1	96:4

[a]Reactions performed in a 0.2mmol scale. [b] er measured using HPLC analysis after oxidation of product **5.3**.

The use of different bases was also evaluated (Table 37). Although the enantioselectivity was not highly affected by the use of different bases, the use of a smaller metal cation in the base (Table 37, entry 3) resulted in a diminished diastereoselectivity.

Table 37. Screening of bases.[a]



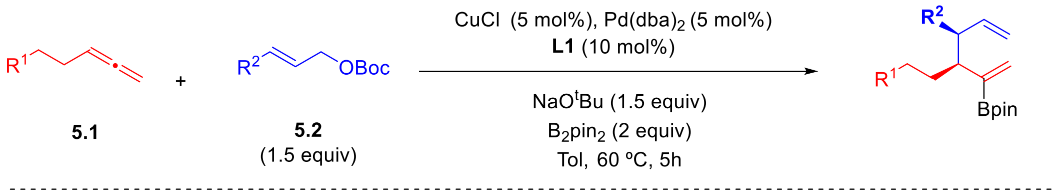
Entry	Base	Yield 5.3 (%)	dr	er[b]
1	NaO^{t}Bu	23	>20:1	97:3
2	KO^{t}Bu	19	>20:1	95:5
3	LiO^{t}Bu	16	12:1	98:2

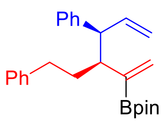
[a]Reactions performed in a 0.2mmol scale. [b] er measured using HPLC analysis after oxidation of **5.3**.

4.2 Scope

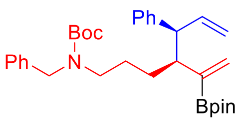
Having established the best conditions for the enantioselectieve Cu/Pd-catalyzed borylative allyl-allyl coupling, we set out to investigate the scope of the reaction (Table 37, entry 1). Remarkably, reactions proceeded with total stereo- and regioselectivity and furnished exclusively the γ_N-γ_E product with good regio-, diastereo- and enantioselectivity in all cases. Although the observed yields were generally low, we observed that the use of allylic carbonates bearing electron withdrawing groups led to a significant increase in reaction yield while keeping excellent levels of selectivity.

Table 38. Enantioselective Cu/Pd catalyzed allyl-allyl cross-coupling scope [a]

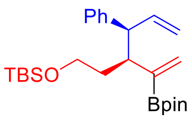




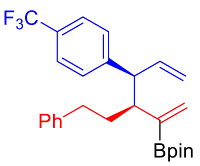
5.53, 23%
97:3 e.r.[b]



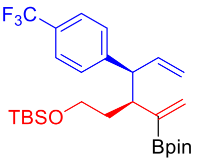
5.54, 32%
92:8 e.r.[c]



5.55, 28%
95:5 e.r.[c]



5.56,41%
96:4 e.r.[b]



5.57,48%
96:4 e.r.[c]

[a]Reactions performed in a 0.2 mmol scale, [b] er measured using HPLC analysis after oxidation of **5.3**., [c] er measured using SFC analysis of borylated product.

5. CONCLUSIONS

We have developed an efficient methodology for the synthesis of borylated 1,5-dienes through a novel synergistic Cu/Pd catalyzed three-component allyl-allyl cross-coupling between allenes, allyl carbonates and B_2pin_2.

One of the main features of this system is the remarkable diastereo- and regioselectivitiy. Due to the use of synergistic bimetallic catalysis, it was possible to change the regioselectivity of this type of transformations, giving access to a 1,5-borylated diene with a different connectivity than the one obtained by single copper catalysis. Furthermore, this strategy allows the use of allylic carbonates, unlike previously reported methodologies.

These borylated products display different reactivity which makes them very attractive building-blocks for chemical synthesis. Several transformations such as protodeboronation, oxidation, Zweifel coupling or stereoselective synthesis of methylenecyclobutanes can be effceintly carried out with these 1,5-borylated dienes. The synthesis of this type of compound remains under study.

An enantioselective version of this transformation has been developed. Although products are obtained in moderate yield, high diastereo- and enantioselectivities were obtained.

GENERAL CONCLUSIONS

We have developed efficient methodologies for the synthesis of 1, 3-, 1, 4- and 1, 5- borylated dienes via synergistic Cu/Pd-catalyzed alkenylboration of alkynes, and allylboration of alkynes or allenes. In addition, in chapter II we have tried to develop a novel Cu/Pd catalyzed methodology for the synthesis of silylated 1, 4-dienes from allylic carbonates and (*Z*)-silyl substituted allyl alcohols. However, the study of the reaction was stopped because it could not be carried out under catalytic conditions.

In chapter III we were able to synthesized *syn*-1-boron-1,3-dienes trough Cu/Pd catalyzed alkenylboration of alkynes. This transformation showed high levels of chemo-, regio-, and stereoselectivity. The use of bench stable and readily available starting materials under mild conditions makes this method practical. Moreover, stereodefined conjugated dienes can be also accessed via a one-pot alkenylation/Suzuki coupling using the initial palladium complex.

In chapter IV we have developed an efficient methodology for the synthesis of bifunctional 1,4-borylated dienes trough synergistic Cu/Pd-catalyzed three-component reaction between alkynes, B_2pin_2 and vinyl epoxides. The formation of this multifunctional products displays diverse reactivity which makes them very attractive builing-blocks for organic synthesis. Additionally, several boracycles, ketones and more complex molecules such as triene can also be accessed via one-pot allylic [1,3]-transposition/Suzuki cross-coupling.

Finally, in chapter V, an efficient methodology for the synthesis of borylated 1,5-dienes trough bimetallic Cu/Pd catalysis has been described. This transformation consists in a three-component allyl-allyl cross-coupling between B_2pin_2, allenes and allyl carbonates. One of the main features of this system was the remarkable diastereo- and regioselectivity. Also the use of synergistic bimetallic catalysis made possible the access to a 1,5-borylated diene with a different connectivity than the one obtained by single copper catalysis. Several transformations such as protodeboronation, oxidation, Zweifel coupling or stereoselective synthesis of methylenecyclobutanes can be efficeintly carried out with these 1,5-borylated dienes. Additionally, an enantioselective version of this transformation has been developed. However, although products were obtained in moderate yield, high diastereo- and enantioselectivities were observed.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RESUMO

Nesta tese doutoral móstrase a investigación levada a cabo no ámbito da catálise bimetálica sinerxística empregando cobre e paladio, para a obtención de moléculas complexas.

En concreto, no capítulo I recóllese unha revisión dos métodos máis relevantes nos que se emprega catálise bimetálica e a súa importancia no ámbito da química sintética. No capítulo II, descríbese o emprego do reagrupamento de Brook e sustitución alílica grazas o emprego de catálise bimetálica de Cu/Pd para a síntese de 1, 4-dienos sililados. No capítulo III descríbese a síntese estereoselectiva de 1,3-dienos borilados a partir de unha reacción tricompoñente entre alquinos, bromuros de alquenilo e B_2pin_2 catalizada por cobre e paladio. No capítulo IV descríbese a síntese de 1,4-dienos borilados a partir de unha reacción de alilboracion de alquinos con vinil epóxidos catalizada por cobre e paladio. Por último, no capítulo V, descríbese o emprego de catálise sinerxística de cobre e paladio para levar a cabo un cambio de rexioselectividade nun proceso de acoplamento cruzado entre dúas sustancias alílicas. A continuación faise un breve resumo do contido descrito nos capítulos mencionados anteriormente.

Capítulo I: Introdución

A catálise é unha das estratexias máis poderosas e eficientes para o descubrimento de novas reaccións químicas. Nas últimas décadas, un amplio rango de reaccións catalíticas que empregan un único catalizador metálico permitiron o descubrimento de novas transformacións. Neste tipo de estratexias, un único catalizador activa o sustrato para promover unha transformación. Sin embargo, algunhas transformacións como as reaccións multicompoñente continúan sendo un reto debido á imposibilidade de usar un único catalizador. Para abordar estes desafíos, desenvolvéronse varios tipos de sistemas multicatalíticos. Estas transformacións inclúen a catálise bifuncional, dobre activación, en cascada ou sinérxica. Esta tese de doutoramento trata sobre o desenvolvemento de novas transformacións sintéticas baseadas na catálise sinérxica de metais de transición. Así, neste capítulo dase unha introdución a este concepto e unha visión xeral da principal transformación que implica este tipo de catálise.

A catálise sinérxica estase facendo popular por ser unha poderosa ferramenta para aumentar a variedade de transformacións, para mellorar os métodos previamente descritos ou para novas reaccións que non son posibles mediante a catálise dun único metal. Este tipo de transformacións implican unha activación simultánea do electrófilo (E) por un catalizador (cat1) e a activación do nucleófilo (Nu) polo outro cocatalizador (cat2). Esta activación crea especies cun LUMO máis baixo (Orbital Molecular Desocupado Baixo) (A’) e a outra cun HOMO (Orbital Molecular Maior Ocupado) (B’) máis alto (Figura 1). Estas especies activadas poden acoplarse dun xeito máis sinxelo permitindo así que as reaccións químicas imposibles ou ineficientes mediante as metodoloxías tradicionais dun só catalizador se realicen con alta eficiencia.

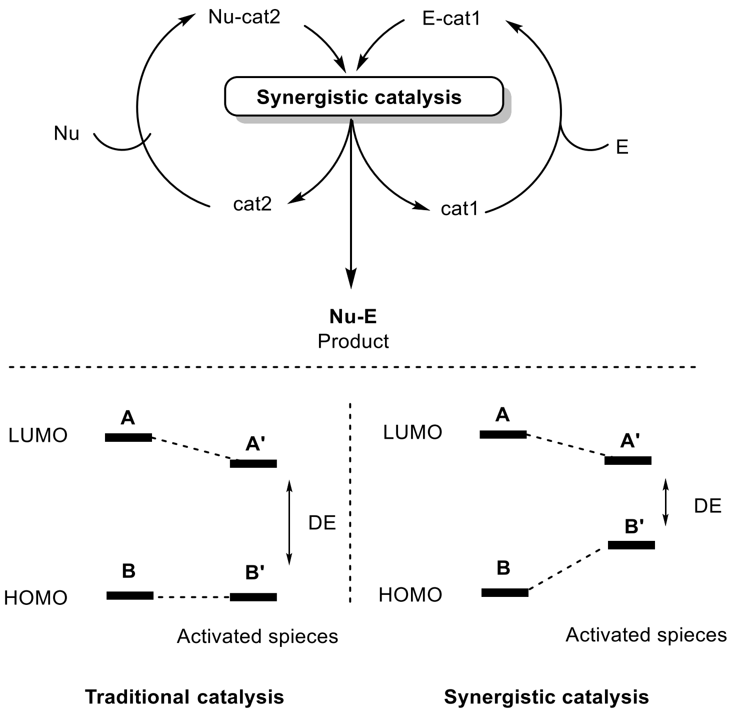


Figura 1. Concepto de catálise sinérxica dual.

O uso da catálise sinérxica, na que dous catalizadores diferentes activan dous substratos diferentes, presenta varios retos, asociados na maioría dos casos á complexidade do sistema. Os principais retos son:

a) Compatibilidade: ambas especies catalíticas activas deben ser compatibles, xa que poden interactuar entre sí, o que fai que ambos catalizadores sexan inactivos.

b) Control da quimioselectividade: cada catalizador debe reaccionar co substrato apropiado de forma selectiva, evitando a formación de productos indesexados a través de reaccións secundarias.

c) Cinética: ambos catalizadores deben ter enerxías de activación compatibles para facer os dous ciclos catalíticos compatibles cinéticamente.

Unha visión xeral das reaccións descritas mediante a catálise sinérxica de metais de transición indica que o paladio (que normalmente se usa para activar o electrofílico) mostra unha ampla gama de compatibilidade con unha gran cantidade de catalizadores de metais de transición como Cu, Au, Ru , Rh, Ni, V e Ag. Ademais, o cobre (xeralmente usado para activar o nucleófilo) tamén pode ser compatible con Fe, Ru, Mn, Ni, Rh, Re. Hai outras combinación de catalizadores metálicos descritas como Rh/Ag, Ru/Ti, Au/Fe ou Ti/Ni. Non obstante, é importante salientar que a combinación máis utilizada é entre o paladio e o cobre.

O primeiro exemplo de catálise cooperativa de Cu/Pd foi informado en 1975 por Sonogashira e os seus colaboradores. Neste traballo, describen o acoplamento cruzado de gas acetileno con ioduros de (hetero)arilo ou bromuros de vinilo. Despois deste traballo pioneiro, varios grupos de investigación centráronse no emprego deste sistema catalítico dual entre cobre e paladio debido o seu gran potencial para crear novas transformacións químicas ou mellorar as previamente descritas. Algunhas destas estratexias móstranse ó longo deste capítulo:

- Acoplamento cruzado descarboxilativo.

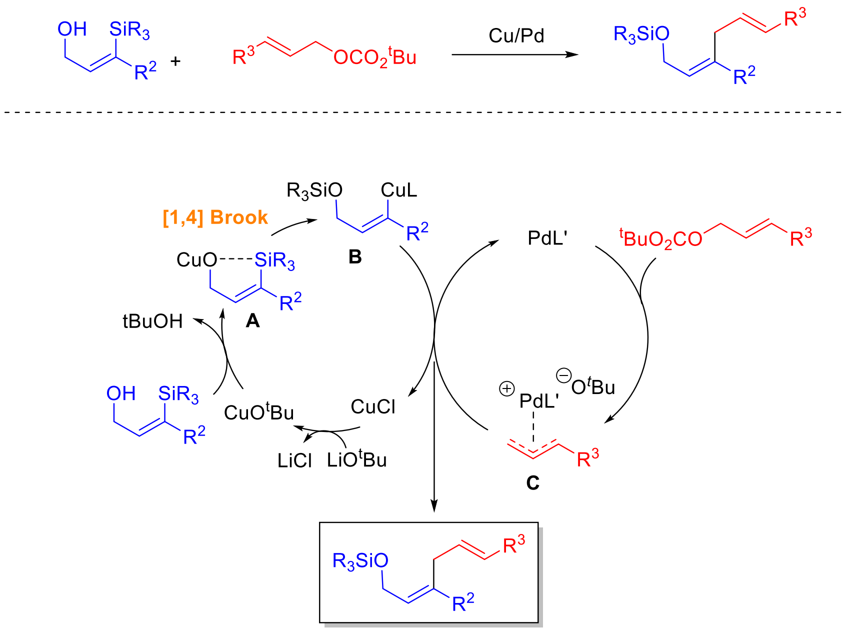
- Acoplamento cruzado mediante activación C-H.
- Alilación α enantioselectiva catalizada por Cu/Pd sinérxica de compostos carbonílicos
- α-alilación enantioselectiva de compostos carbonílicos catalizada por Cu/Pd
- Catálise sinérxica de CuH/Pd
- Catálise sinérxica de Cu-Si e Pd
- Catálise bimetálica sinérxica de Cu/Pd para a carboboración de hidrocarburos insaturados.

Capítulo II: Reordenamento Brook e sustitución alílica mediante catálise sinérxica de Cu/Pd.

O reordenamento de Brook foi descrito por primeira vez a finais dos anos 50 polo químico canadense Adrian Gibbs Brook. Esta transformación consiste nunha migración aniónica intramolecular de grupos sililo dun carbono a un átomo de osíxeno promovida pola presenza dunha base, que pode ser unha amina, hidruro de sodio, un reactivo de organolitio ou unha aliaxe de metal alcalino. Normalmente, o reordenamento de Brook refírese á migración aniónica de sililo [1,2]. A migración aniónica de sililo [1,2] utilizouse para a formación rexio- e estereoselectiva de éteres de silil enol. Estas migracións aniónicas poden ser inducidas de diferentes xeitos, incluíndo fotolíticamente, térmicamente ou utilizando condicións básicas/ácidas. Neste capítulo centrámonos nas transformacións que implican a migración aniónica [1,4] intramolecular de C a O.

A fusión de reagrupamento de Brook [1,4] e acoplamento cruzado catalizado por Pd supón unha estratexia para a formación de novas estructuras. Neste ámbito, o uso de especies vinílicas de cobre xeradas mediante a migración do grupo sililo dende un Csp^2 ao O promovida polo *terc*-butóxido de cobre utilizouse en diferentes acoplamentos con varios electrófilos. Neste sentido, Takeda e os seus colaboradores informaron en 2002 do uso de especies vinílicas de cobre en reaccións de acoplamento cruzado estereoespecífico catalizadas por Pd con haluros arilo e vinilo. Por outra banda, o uso de haluros de alquilo neste tipo de transformacións tamén foi descrito polo mesmo grupo. Sen embargo, o emprego do reordenamento [1,4] de Brook e a substitución alílica foi menos estudada, aínda que o grupo de Takeda, describiu a alilación estereoespecífica de alcoholes alílicos γ-sililados (*Z*) mediante unha migración [1,4] Brook promovida por unha cantiade estequiómetrica de CuO^tBu.

Como se mostra anteriormente, o traballo de Takeda baséase no uso de cantidades superestequiométricas de CuO^tBu para realizar os procesos de reordenación/substitución alílica [1,4] Brook .O obxectivo principal deste capítulo é o desenvolvemento dunha nova metodoloxía catalítica que permita realizar unha reordenación tándem de Brook/substitución alílica utilizando cantidades catalíticas de complexos de cobre e paladio. A estratexia proposta está baseada no uso da catálise sinérxica como estratexia sintética para lograr a síntese de 1,4-dienos utilizando silil alquenilmetais en reaccions de sustitución alílica (Esquema 1). Este enfoque reside na fusión dun ciclo catalítico no que un composto silil sustituído é activado como nucleófilo a través dunha reordenación Brook por un catalizador de cobre, cun segundo ciclo catalítico no que un catalizador de paladio activa o substrato alílico electrófilo. A catálise sinérxica deseñada non só proporciona a activación simultánea tanto do nucleófilo como do electrófilo desta formación de enlaces C-C, senón que tamén serve como mecanismo clave para promover a reordenación de Brook de forma catalítica.



Esquema 1. Proposta mecanística para o reagrupamentp [1,4] Brook e sustitución alílica empregando catálise sinérxica de Cu/Pd.

No deseño proposto, que implica unha reordenación de 1,4-Brook, unha cantidade catalítica de CuO^{t}Bu desprotonará o alcohol alílico γ-sililado formando alcóxido de cobre **A**. Este intermedio experimentará a migración de silicio de Csp^2-a-O xerando especies de alquenilcobre **B**. Nun segundo ciclo catalítico formarase un complexo metálico π-alilo catiónico **C** pola adición oxidatante descarboxilativa dun carbonato alílico a un complexo de paladio(0). A conexión dos dous ciclos catalíticos será o paso crucial deste enfoque. Favorecerá a formación do enlace C-C e rexenerará ambos catalizadores. A activación do substrato alilo é esencial para favorecer a formación do enlace C-C fronte á protonación da especie alquenilcobre. Ademais, a natureza do complexo alil-Pd catiónico ten un impacto directo na rexeneración do catalizador de cobre xa que o contraanión que se atopa orixinalmente neste complexo acaba no primeiro ciclo catalítico como parte do catalizador de cobre.

Tras levar a cabo un intenso estudo de condicions de reacción, non puidemos reducir a cantidade de CuO^{t}Bu en máis dun 50 mol % para garantir a eficiencia da reacción. Intentouse levar a cabo un estudo do alcance da transformación, sen embargo, observamos que non se puido obter mellores resultados.

Capítulo III: Síntese estereoselectiva de 1,3-dienos borilados mediante catálise sinérxica de Cu/Pd.

Hoxe en día, a creación de novas metodoloxías químicas máis eficientes e respectuosas co medio ambiente é de vital importancia. Neste contexto, o desenvolvemento de metodoloxías sintéticas que den acceso a estruturas moleculares complexas a través de procesos con alta eficiencia atómica e redución da xeracion de residuos representa un dos grandes retos da química actual.

Neste eido, cabe destacar o desenvolvemento de sistemas catalíticos capaces de activar substratos sinxelos e abundantes na natureza e combinalos de unha forma selectiva para a súa transformación en moléculas máis complexas que conteñan un alto grado de funcionalización para poder levar a cabo posteriores modificacións.

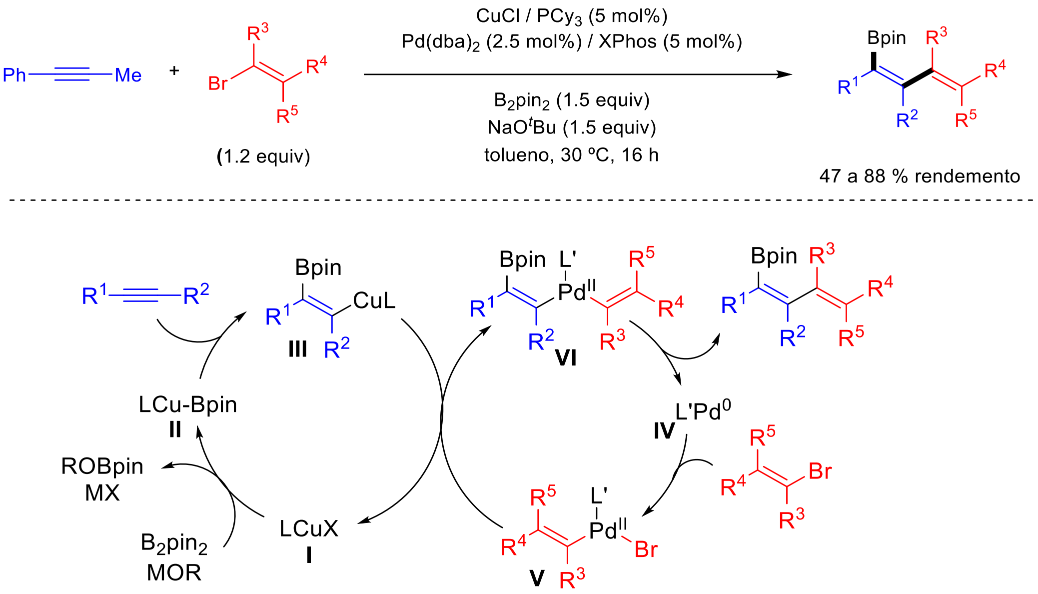
Os 1,3-dienos son unha clase importante de estruturas que están presentes en moitos produtos naturais e moléculas bioactivas. Trátase de moléculas con gran actividade biolóxica, pois son empregados como axentes antivirais, ou antifúnxicos entre outros. Os métodos tradicionais para sintetizar 1,3-dienos implican reaccións de acoplamento cruzado catalizadas por Pd, reacción de Wittig ou transformacións de Horner Wadsworth-Emmons. Non obstante, estas metodoloxías están asociadas ao uso de cantidades estequiométrica de metal e a maioría delas non son procesos estereoselectivos. Por outra banda, os 1,3-dienos substituídos con boro representan unha clase importante de compostos que serven como bloques fundamentais na síntese dunha ampla gama de produtos naturais bioactivos e materiais orgánicos. A maioría das metodoloxías descritas ata o momento para a síntese deste tipo de dienes dan acceso ao isómero no que o átomo de boro está en disposición *anti* á segunda unidade olefínica. Metodoloxías que permitan a síntese selectiva do isómero *syn* son escasas e proporcionan patróns de sustitución limitados. Sen embargo, é desexada unha transformación catalítica que proporcione acceso rápido e estereoselectivo a 1,3-dienos *syn*- borilados altamente substituídos a partir de sustancias de partida sinxelas e abundantes.

Nos últimos anos, a carboboración de alquinos catalizada por cobre converteuse nunha poderosa ferramenta para a súa conversión en alquenilboronatos. Deste xeito, en base ós traballos descritos anteriormente sobre o uso da catálise sinérxica de cobre e paladio para a carboboración de alquinos, o obxectivo do presente capítulo é o desenvolvemento dun método catalítico que proporcione un acceso rápido e estereoselectivo a 1,3-dienos *syn*-borilados altamente substituídos, utilizando materiais de partida sinxelos e abundantes.

Propoñemos que un intermediario β-borilalquenilcobre xerado catalíticamente pode usarse nunha transformación de acoplamento cruzado catalizada por Pd con un haluro de alquenilo en réxime de catálise cooperativa. Este enfoque ofrece diferentes vantaxes con respecto aos métodos descritos con anterioridade, entres os cales se encontran: 1) A selectividade *syn* resultaría dunha borocupación de alquino *syn*-selectiva; 2) o uso de alquinos como pronucleófilos evita o uso estequiométrico dun reactivo de alquenilmetal; 3) a activación do haluro de alquenilo usando un co-catalizador de Pd facilitaría o acoplamento en condicións suaves; 4) unha única operación permite a ensamblaxe de tres compoñentes diferentes.

Ata o momento o emprego de (pseudo)haluros de alquenilo nas reaccións de carboboración de alquinos para dar lugar á formación selectiva de 1, 3-dienos borilados non foi descrita, xa que o emprego deste tipo de electrófilos supón un desafío adicional. Para implementar con éxito esta idea, hai que superar varios retos asociados ao uso da catálise sinérxica de cobre e paladio así como os substratos. Para evitar reaccións paralelas, cada catalizador debe reaccionar con cada substrato dun xeito quimioselectivo. Por exemplo, débense excluír reaccións como a borilación de haluros de alquenilo de Miyaura catalizada por Pd e a protoboración de alquino. Para obter selectivamente o dieno 1,3- *syn* borilado, a inserción do alquino desexado no complexo de borilcobre (Cu-Bpin) debe producirse de forma *syn*. Por último, a inserción de alquinos asimétricos pode ter lugar de dúas formas diferentes dando acceso ao rexioisómero borilado α ou β.

Na metodoloxía descrita neste capítulo, propoñemos un mecanismo catalítico dual (Esquema 1) que consiste nunha borilcupación rexio- e estereoselectiva do alquino co complexo LCu-Bpin **II** para xerar o intermedio β-boril alquenilcobre (I) **III**. O segundo ciclo catalítico comeza coa adición oxidativa do substrato de alquenilo ó complexo **IV** de Pd(0) para obter o intermedio de alquenilpaladio (II) **V**. Despois, unha etapa de transmetalación entre os intermedios **III** e **V** dá lugar o intermedio **VI**. Finalmente, un proceso de eliminación redutora libera o produto desexado e recupera ambas especies catalíticas activas.



Esquema 2. Proposta mecanística para a alquenilboración de alquinos catalizada por Cu/Pd.

Unha das principais características deste sistema catalítico son os notables altos niveis de quimio-, rexio- e estereoselectividade para a síntese de *syn*-1-boro-1,3-dienos. As reaccións secundarias como a borilación de Miyaura e a protoboración de alquinos están completamente excluídas ou redúcense a niveis non significativos. Por outra banda, o emprego de condicións de reacción suaves e sustancias de partida estables e fácilmente dispoñibles, fai que esta metodoloxía sexa prática e sinxela.

Ademais de poder acceder a un amplo número de 1,3-dienos borilados altamente sustituíods, grazas a esta transformación foi posible acceder a trienos estereodefinidos conxugados mediante un acoplamento de alquenilación seguido dun acoplamento de Suzuki, no que o complexo de paladio inicial actúa como un catalizador dobre.

Capítulo IV: Síntese de 1,4-dienos bifuncionais mediante alilboración de alquinos con epóxidos vinílicos catalizada por Cu/Pd

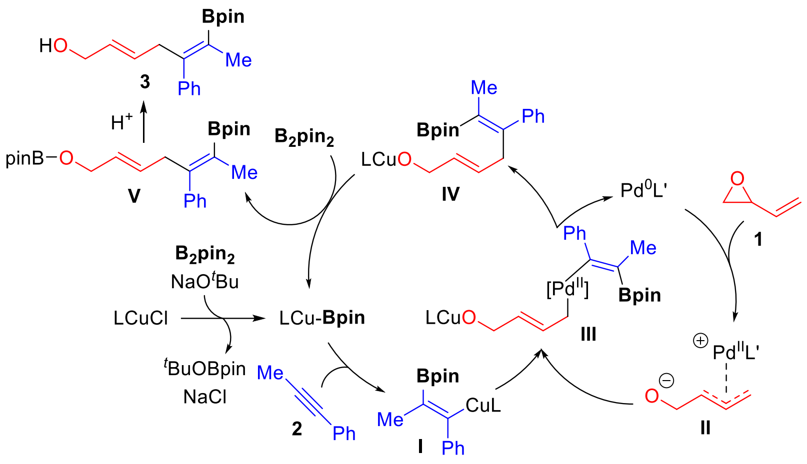
Na actualidade, deséxanse métodos sintéticos que permitan a ensamblaxe de moléculas orgánicas complexas a partir de materiais de partida sinxelos e facilmente dispoñibles. En particular, as reaccións multicompoñentes que proporcionan acceso estereoselectivo a moléculas altamente funcionalizadas aínda representan un gran desafío e son particularmente valiosas para acadar a diversidade molecular mediante diferentes modificacións sintéticas.

Os epóxidos vinílicos son unha clase versátil de substratos, xa que poden participar nunha serie de transformacións sintéticas. A alquilación alílica de epóxiods de vinilo catalizada por metais é de principal interese xa que permite a formación dun enlace C−C e un alcohol alílico, que se pode utilizar para unha posterior funcionalización. Aínda que se utilizaron varios nucleófilos de carbono nesta tipo de reacción, os exemplos relativos ao uso de nucleófilos alqueníllicos limítanse principalmente a acoplamentos con alquenilstananos e alquenilboranos. Por outra banda, pódese acceder a un tipo similar de produtos mediante o acoplamento de tres componentes, un epóxido de vinilo, un alquino e unha especie dimetilcinc, catalizados por Ni. Non obstante, ademais dos inconvenientes asociados ao uso estequiométrico de reactivos organometálicos, o control da rexioselectividade (adición 1,4- vs 1,2) e a estereoselectividade (formación de isómero *E* frente ao isómero *Z*) representa un problema importante en ambos os casos.

Como foi comentado nos anteriores capítulos, nos últimos anos, o noso grupo de investigación e o de Gong e Fu exploraron unha estratexia complementaria cara á alquenilación alílica estereoselectiva catalizada por Paladio. Este enfoque baséase nun mecanismo catalítico sinérxico que implica a xeración catalítica dun nucleófilo C(sp2) estereodefinido mediante a adición de LCu−Bpin a través dun alquino seguido dunha substitución alílica catalizada por Pd para proporcionar formalmente un produto de carboboración. Este proceso é atractivo xa que se emprega un alquino simple como pronucleófilo, permitindo así que a concentración das especies reactivas se manteña baixa, ademáis de xerarse dous novos enlaces C−C e C−B nunha única operación. Baseándonos nos nosos estudos anteriores, imaxinamos que a alilboración dun alquino usando un epóxido de vinilo como compoñente alílico daría lugar a un dieno bifuncional con dúas funcionalidades ortogonais, como un alcohol alílico e un alquenilboronato. Dada a ampla reactividade de ambos grupos funcionais, esta transformación proporcionaría unha estructura moi versátil. Ademais do control sobre a rexio- e estereoselectividade, o éxito da nosa estratexia proposta tamén require un alto nivel de quimioselectividade xa que a adición competitiva de B_2pin_2 ao epóxido de vinilo debe ser suprimida. Ademais, o atrapado do complexo de alilpaladio polo intermedio alquenilcobre debería ser máis rápida que a reordenación potencialmente competitiva do composto carbonilo correspondente.

Neste capítulo mostramos a implementación exitosa desta idea e, polo tanto, do desenvolvemento dun proceso catalítico de tres compoñentes que permite a síntese rexio-, estereo- e quimioselectiva de dienos bifuncionais. Este método é distinto das reaccións de carboboración de hidrocarburos descritas ata o momento xa que é o primeiro exemplo que permite o uso de epóxidos de vinilo. Tamén é importante ter en conta que esta nova metodoloxía proporciona un acceso único a estes dienol boronatos bifuncionais, que poden transformarse nunha variedade de estruturas dunha maneira estereocontrolada. Unha vez levados a cabo diversos estudos de optimización da reacción, chegamos á obtención de unhas condicións óptimas para o desenvolvemento desta metodoloxía.

En base as nosas observacións experimentais e das nosas investigacións anteriores, propoñemos o seguinte mecanismo para a alilboración de alquinos catalizada por Cu/Pd con epóxidos de vinilo (Esquema 2). Unha adición rexio- e estereoselectiva do complexo LCu-Bpin a través do alquino xeraría o β-boril-alquenilcobre (I) intermedio **I**. No segundo ciclo catalítico, o complexo zwitteriónico **II** η3-alil-Pd formaríase pola adición oxidante do epóxido de vinilo ao complexo L'Pd(0). A transmetalación entre estas dúas especies organometálicas daría lugar ao intermediario bimetálico **III** que tras un proceso de eliminación redutora rexenera o catalizador Pd(0) e a formación do alcóxido de cobre **IV**. Este intermediario sería o suficientemente reactivo como para sufrir metátese de enlace σ con B_2pin_2 o que resulta na recuperación do complexo activo LCu-Bpin e na formación do intermedio **V** que levaría ao 1,4-dieno bifuncionalizado por protonación. A reacción entre o intermedio **IV** e B_2pin_2 explicaría a viabilidade de realizar esta reacción con unha cantidade catalítica de NaO^tBu.



Esquema 3. Mecanismo proposto para a alilboración de alquinos catalizada por Cu/Pd.

O uso de materiais de partida estables e facilmente dispoñibles así como o emprego de condicións de reacción suaves fai que este método sexa práctico. Ademais, grazas o desenvolvemento desta metodoloxía, foi posible o acceso a varios compostos cíclicos de boro, cetonas e moléculas máis complexas como a formación dun trieno mediante transposición alílica [1,3]/acoplamento cruzado Suzuki.

Capítulo V: Emprego de catálise sinérxica de Cu/Pd para un cambio na rexioselectividade en acoplamentos cruzados entre duas sustancias alílicas.

O acoplamento entre dous alilos, donde un deles actúa como nucleófilo e o outro electrófilo é unha poderosa ferramenta sintética para proporcionar acceso directo aos 1,5-dienos. Estas estruturas están presentes en moitos produtos naturais e serven como estruturas de partida para a síntese orgánica de moléculas máis complexas. Ademais, as reaccións de acoplamento cruzado entre un reactivo dun metal alílico e un electrófilo alílico son un método atractivo debido á posibilidade de establecer dous novos estereocentros coa formación concomitante dun enlace C(sp3)-C(sp3). Este tipo de acoplamento C-C realizouse tradicionalmente mediante o uso de cantidades estequiométricas en reactivos metálicos alílicos, como os nucleófilos de alil-litio, magnesio, estaño, boro, silicio ou indio que reaccionaban con electrófilos alílicos. Non obstante, estes métodos adoitan limitarse á introdución de fragmentos de alilo sinxelos. O acoplamento estereoselectivo de dúas sustancias alílicas ten lugar mediante catálise de Pd, Cu ou Ni e Ir. Neste capítulo tratanse os acoplamentos cruzados catalizados por cobre e paladio.

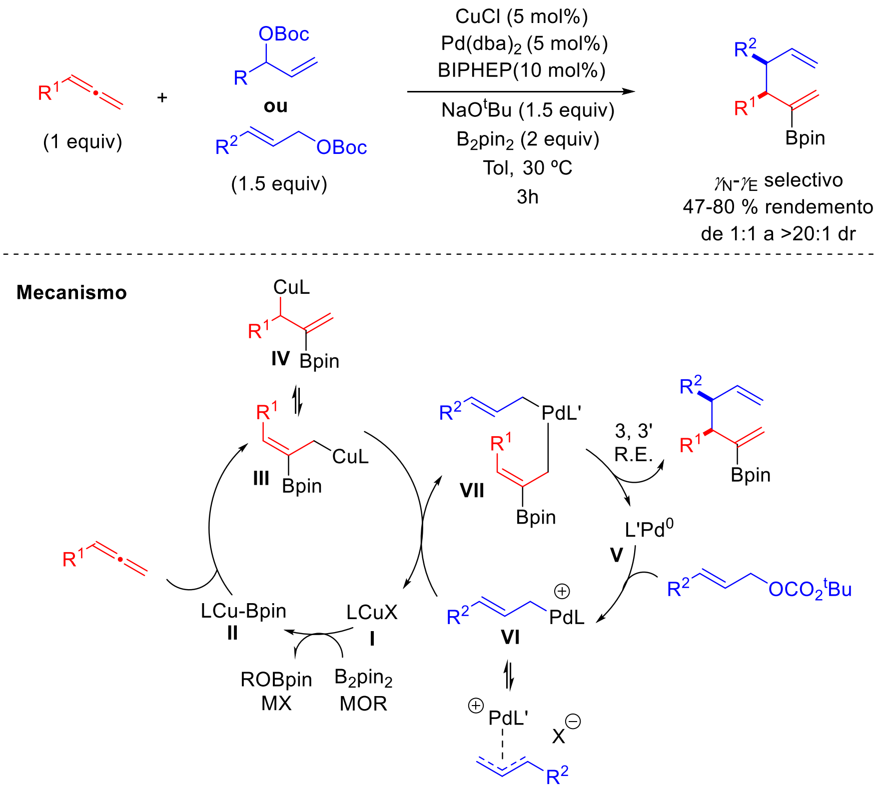
O paladio é probablemente o metal máis útil na síntese orgánica. Varios complexos e sales deste metal actúan como catalizadores ou precatalizadores nunha ampla gama de transformacións diferentes. Como se mencionou anteriormente, son de especial interese as reaccións que implican a formación de enlaces C-C a través do acoplamento cruzado entre electrófilos e nucleófilos alílicos catalizado por Pd. Nesta transformación, os complexos catalíticos alil-Pd son intermediarios clave e xogan un papel importante. Os complexos de alil-paladio η^3 son os máis común, non obstante, dependendo do grao de saturación do metal e da natureza dos ligandos auxiliares, poden estar en equilibrio coas especies en modo de coordinación η^1. Estes intermedios bis(alil)paladio fórmanse normalmente pola adición oxidante de haluros de alilo, ésteres ou carbonatos en especies Pd(0) e poden sufrir unha eliminación redutora 3,3’ ou 1,1’. Utilizando esta estratexia, Morken e os seus colaboradoress informaron do acoplamento cruzado rexio- e enantioselectivo catalizado por paladio entre alilboronatos e carbonatos alílicos, no cal obteñen seletivamente os productos γ_N-γ_E. Por outra banda, o grupo de investigación de Tsuji, describeu o primeiro acoplamento borilativo cruzado entre dous alilos alil-alilo empregando catálise de cobre. Trátase dunha reacción tricompoñente entre alenos, bis(pinacolato)diboro e os fosfatos alílicos. De forma paralela e independente, Hoveyda e colaboradores deseñaron unha versión enantioselectiva deste tipo de transformación, catalizada tamén por paladio. En ambas transformacións, os productos finais obtidos teñen unha selectividade α_N-γ_E.

O acceso a outros rexioisómeros representa un obxectivo desexable e ampliaría a versatilidade química do produto dos acoplamentos borilativos. Con esta idea en mente, e baseándonos no noso traballo anterior na alilboración catalizada de Cu/Pd de alquinos con carbonatos alílicos, imaxinamos que o uso da catálise sinérxica de Cu/Pd pode servir como plataforma para lograr un cambio de selectividade neste acoplamento borilativo entre dous alilos, proporcionando así unha nova ferramenta para acceder a 1,5-dienos borilados cunha conectividade diferente. Na nosa hipótese mecanística, as especies de alilcobre xeradas cataliticamente a partir da borilcupación do aleno sufrirían transmetalación cun complexo alílico de Pd(II), xerado pola adición oxidante dun substrato alílico a un catalizador de Pd(0). A evolución controlada do intermedio bis(alil)-Pd(II) resultante proporcionaría o dieno 1,5-borilado desexado. Trátase dunha transformación que trae asociados diversos retos para evitar a formación de reacción secundarias. Cada catalizador debe reaccionar con cada substrato dun xeito quimioselectivo. Por exemplo, describiuse a borilación directa do substrato alílico tanto con catálise de cobre como de paladio. Ademais, os intermedios de boril alil-cobre poden reaccionar potencialmente con fontes próticas para producir produto de protoboración. Ademais a transformación proposta implica un gran reto de rexioselectividade. O intermedio alil-Cu(I) pode existir en dúas formas de resonancia diferentes, que poden reaccionar coa especie alil-Pd(II) ben por un mecanismo S_E2 ou por un mecanismo S_E2'. Ademais, o intermedio bis(alil)Pd(II) resultante pode evolucionar por vías de eliminación redutoras 1,1' ou 3,3'. Por último, débese conseguir unha transmetalación controlada, xa que a configuración relativa final dos dous novos centros estereoxénicos pode estar influenciada pola estereoquímica do substituente no intermedio alílico borilado.

Tras un estudo exhaustivo de diversas condicións de reacción, conseguimos atopar unhas condición óptimas para esta transformación (Esquema 3). Foi posible o emprego de diversos alenos sustituídos con cadeas alifáticas e diferentes funcionalidades. Sen embargo, o emprego de alenos aromáticos deu lugar a mesturas de rexioisómeros. Ademáis, unha variedade de carbonatos alílicos foron empregados para a síntese de dienos 1,5-borilados con selectividade γ_N-γ_E.

Estes produtos borilados mostran unha reactividade diferente o que os converte en estructuras moi atractivas para a síntese química. Con estes dienos 1,5-borilados pódense realizar de forma eficaz diversas transformacións como a protodeboración, a oxidación, o acoplamento Zweifel ou a síntese estereoselectiva de metilenciclobutanos.

Sobre a base das nosas observacións experimentais e dos traballos anteriores levados a cabo no noso grupo de investigación, propoñemos o seguinte mecanismo para o acoplamento borilativo entre alenos e carbonatos alílicos catalizado por Cu/Pd (Esquema 4). O ciclo catalítico comeza coa xeración da especie **I**, que reacciona con B_2pin_2 para producir a especie borilcobre **II**. A inserción do aleno no complexo **II** xera o intermedio de cobre β-boril-(*Z*)-alílico **III** que pode estar en equilibrio co intermedio **IV**. Nun segundo ciclo catalítico, a adición oxidante do carbonato alílico ao complexo LPd(0) proporciona o intermedio **VI**. A transmetalación entre as especies organometálicas **III** e **VI** formaría o intermediario bis(alil)Pd **VII**. Finalmente, unha eliminación redutora 3,3’ daría lugar ao produto desexado e á rexeneración dos dous ciclos catalíticos.



Esquema 4. Mecanismo proposto para o acoplamento borilativo entre alenos e carbonatos alílicos catalizado por Cu/Pd.

Ademais, desenvolveuse unha versión enantioselectiva desta transformación, na que o emprego dun ligando quiral para os dous metais deu lugar a productos con altas diastereo- e enantioselectividades. Sen embargo, estes productos obtivéronse en rendementos moderados.

Como conclusión xeral deste capítulo, podemos decir que unha das principais características deste sistema é a notable diastereo- e rexioselectividade. Debido ao uso da catálise bimetálica sinérxica, foi posible modificar a rexioselectividade deste tipo de transformacións, dando acceso a un dieno 1,5-borilado cunha conectividade diferente á obtida por catálise de cobre. Ademais, esta estratexia permite o uso de carbonatos alílicos, a diferenza das metodoloxías descritas anteriormente.

EXPERIMENTAL PART

1. General procedures

- All reactions were performed under argon atmosphere using oven dried glassware and using standard Schlenk techniques. Solvents were dried using an MBraun SPS 800 system. All chemicals, copper and palladium complexes were purchased from Acros Organics Ltd., Aldrich Chemical Co. Ltd., Alfa Aesar, Apollo, Strem Chemicals Inc., Fluorochem Ltd. or TCI Europe N.V. chemical companies and used without further purification, unless otherwise noted.

- Analytical thin layer chromatography was carried out on silica-coated aluminium plates (silica gel 60 F254 Merck) and components were visualized by UV light, I_2 and KMnO4 staining. Flash column chromatography was performed on silica gel 60 (Merck, 230-400 mesh) without previous deactivation, unless otherwise stated.

- GC-MS analyses were performed in a Agilent instrument GC-6890N equipped with Chemical Ionization (CI) MS-5973 detector or Agilent instrument GC-8890 equipped with Chemical Ionization (CI) MS-5977B detector.

- High Resolution Mass spectrometry was carried out on a Bruker microTOF spectrometer using CI, ESI or APCI.

- ^{1}H- and ^{13}C-NMR experiments were carried out using a Varian Inova 500MHz or a Varian Mercury 300 MHz NMR spectrometers. Chemical shift values are reported in ppm with the solvent resonance as the internal standard (CHCl3: δ 7.26 for ^{1}H, δ 77.0 for ^{13}C). Coupling constants *J* are given in Hertz (Hz). Multiplicities are reported as follows: s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, m = multiplet or as a combination of them.

- Because of quadrupolar relaxation, in most of cases the carbon directly attached to the boron atom was not detected by 13C NMR technique.

- Optical rotation was determined in a Jasco P-2000 Polarimeter.

- Enantiomeric ratios were determined by Supercritical Fluid Chromatography (SFC) analysis in a Jasco Series 4000 instrument.

- In order to preclude side protoboration reactions, commercial alkynes and B2pin2 were dried over Na2SO4 prior to being used.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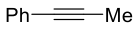
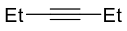
2. CHAPTER III

2.1 List of starting materials

Alkynes **3.1a**, **3.1b**, **3.1g-j**, alkenyl pseudo-halides 3.**2a, 3.2b-f, 3.2h, 3.2i-OTf** and $B_2(pin)_2$ were obtained from commercial sources and used without further purification. Alkynes **1c**[108], **1d**-**1f**,[109] alkenyl bromides **3.2g**[110], **3.2i**[111] and alkenyl triflate **3.2a-OTf**[112] were prepared following described procedures.

- Alkynes


3.1a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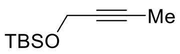
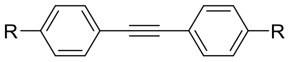
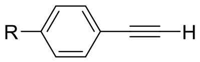
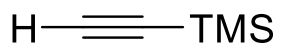
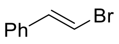

3.1c

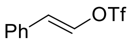

R= H **3.1d**
R= CF_3 **3.1e**
R= Br **3.1f**

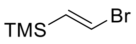

R= H **3.1g**
R= OMe **3.1h**
R= CO_2Me **3.1i**

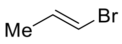

3.1j

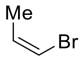
- Alkenyl (pseudo-) halides.

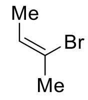

2a


2a-OTf


2b


2c


2d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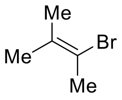
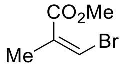
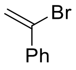
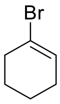
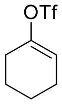

2f


2g


2h


2i


2i-OTf

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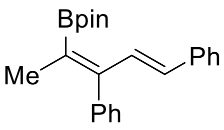
[108] Hesse, M. H.; Butts, C. P.; Willis, C. L.; Aggarwal, V. K. *Angew. Chem. Int. Ed.* **2012**, *51*, 12444-12448.
[109] Miio, M.; Kopel, L. C.; Braun, J.B.; Gadzikwa, T. L.; Hull, K. L.; Brisbois, R. G.; Markworth, C. J.; Grieco, P. A. *Org. Lett.* **2002**, *4*, 3199-3202.
[110] Yuang, Y.; Dai, W. *Eur. J. Org. Chem.* **2014**, 323-330.
[111] Zhang, F.; Liang, G. *Angew. Chem. Int. Ed.* **2013**, *52*, 1266-1269.
[112] Suero, M. G.; Bayle, E. D.; Collins, B. S. L.; Gaunt, M. J. *J. Am. Chem. Soc.* **2013**, 135, 5332-5335.

2.2 General procedure for the Cu/Pd-catalyzed synthesis of 1,3-borylated dienes

CuCl (5 mol%, 0.025 mmol) and tricyclohexylphosphine (5 mol%, 0.025 mmol) were suspended in dry toluene (0.5 mL), stirred during 15 minutes at r.t. After this time the alkyne **1** (1 equiv, 0.5 mmol) was added over the previous solution. The final solution was added to the reaction vial containing B_2pin_2 (1.5 equiv, 0.75 mmol) and NaO^tBu (1.5 equiv, 0.075 mmol) to afford a red suspension. In a separate vial $Pd(dba)_2$ (2.5 mol%, 0.0125 mmol) and XPhos (5 mol%, 0.025 mmol) were stirred in dry toluene (0.5mL) for 15 minutes at r.t. and over this solution the alkenyl bromide **2** (1.2 equiv, 0.6mmol) was added. Finally, this solution was added to the reaction vial and heated during 16 hours at 30 ^oC. After this time, the reaction was quenched by addition of saturated aqueous solution of NH_4Cl (10 mL) and extracted with Et_2O (2x10 mL). The organic layer was dried over Na_2SO_4, filtered and solvent was removed under vacuum. The final product was purified by silica gel column chromatography using the indicated mixture of eluents for each case.

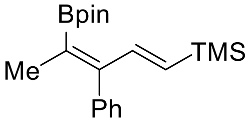
2.3 Compound characterization

2-((2*Z*,4*E*)-3,5-Diphenylpenta-2,4-dien-2-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (3.3a)



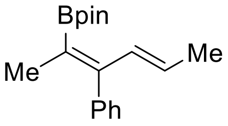
Obtained from **3.1a**, **3.2a** as a yellow oil after column chromatography (hexane/CH_2Cl_2 5:1) following the general procedure in 78% yield. When 2a-OTf was used, 3a was obtained in 45% yield. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.04 (d, *J* = 15.9 Hz, 1H), 7.44 – 7.40 (m, 2H), 7.37 – 7.25 (m, 5H), 7.23 – 7.10 (m, 3H), 5.99 (d, *J* = 15.9 Hz, 1H), 1.68 (s, 3H), 1.42 (s, 12H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 153.6 (C), 142.4 (C), 140.2 (C), 138.1 (C), 132.2 (CH), 129.0 (CH), 128.5 (CH), 128.1(CH), 127.1 (CH), 126.6 (CH), 126.5 (CH), 83.5 (2C), 25.0 ($4CH_3$), 19.0 (CH_3). **^{11}B NMR** (160 MHz, $CDCl_3$): δ 29.7 ppm. **HRMS (APCI)** Calc. for $C_{23}H_{27}BO_2[M+H^+]$: 346.2100, found 346.2103.

Trimethyl((1*E*,3*Z*)-3-phenyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)penta-1,3-dien-1-yl)silane (3.3b).



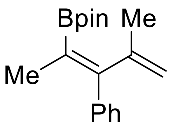
Obtained from **3.1a**, **3.2b** as a yellow oil after column chromatography using deactivated silica (Et_3N) following the general procedure in 79% yield. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.67 – 7.56 (d, *J* = 18.5 Hz, 1H), 7.42 – 7.27 (m, 3H), 7.08 – 7.00 (d, *J* = 7.9 Hz, 2H), 5.35 (d, *J* = 18.5 Hz, 1H), 1.62 (s, 3H), 1.37 (s, 12H), 0.11 – 0.01 (s, 9H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 154.3 (C), 146.2 (CH), 139.9 (C), 133.0 (CH), 129.2 (2CH), 127.6 (2CH), 126.4 (CH), 83.4 (2C), 24.9 ($4CH_3$), 18.9 (CH_3), -1.2 ($3CH_3$). **^{11}B NMR** (160 MHz, $CDCl_3$): δ 29.6 ppm. **HRMS (APCI)** Calc. for $C_{20}H_{32}BO_2Si[M+H^+]$: 342.2202, found 342.2206.

((2*Z*,4*E*)-3-Phenylhexa-2,4-dien-2-yl) 4,4,5,5-tetramethyl-1,3,2-dioxaborolane (3.3c).



Obtained from **3.1a**, **3.2c** as a yellow oil after column chromatography (hexane/CH_2Cl_2 5:1) following the general procedure in 47% yield. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.41 – 7.26 (m, 3H), 7.17 – 7.10 (m, 1H), 7.09 – 7.04 (m, 2H), 5.14 (dq, *J* = 14.2, 6.9 Hz, 1H), 1.73 (d, *J* = 6.8 Hz, 4H), 1.57 (s, 3H), 1.38 (t, *J* = 1.5 Hz, 15H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 153.4 (C), 141.0 (2C), 134.3 (CH), 130.0 (CH), 128.9 (2CH), 127.9 (2CH), 126.3 (CH), 83.3 (2C), 25.0 ($4CH_3$), 18.6 (CH_3), 18.59 (CH_3). **^{11}B NMR** (160 MHz, $CDCl_3$) δ 22.4 ppm. **HRMS (APCI)** Calc. for $C_{18}H_{26}BO_2[M+H^+]$: 285.2020, found 285.2022.

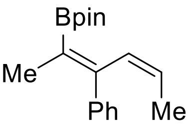
(*Z*)-4,4,5,5-Tetramethyl-2-(4-methyl-3-phenylpenta-2,4-dien-2-yl)-1,3,2-dioxaborolane (3.3c')



3c'

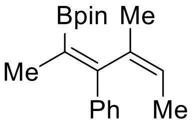
Obtained from **3.1a**, **3.2c** as a yellow oil after column chromatography (hexane/CH_2Cl_2 5:1) following the general procedure in 17% yield as a 1:1.5 mixture of **3.4a**:**3.3c'** (**4a**, Protoboration product) that could not be separated by column chromatography. Yield calculated by ^{1}H-NMR analysis of the isolated mixture. **^{1}H NMR** δ 7.36 (d, *J* = 7.5 Hz, 3H), 7.21 (d, *J* = 7.5 Hz, 2H), 5.02 (s, 1H), 4.89 (s, 1H), 1.72 (s, 3H), 1.38 (s, 3H), 1.31 (s, 12H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 142.4 (C), 129.4 (2CH), 128.0, 127.1 (2CH),126.9 (CH), 114.6 (CH_2), 83.5 (2C), 31.6 (CH_3), 24.9 ($4CH_3$), 15.9 (CH_3). **^{11}B NMR** (160 MHz, $CDCl_3$) δ 22.6 ppm. **HRMS (APCI)** Calc. for $C_{18}H_{26}BO_2[M+H^+]$: 285.2020, found 285.2022.

4,4,5,5-Tetramethyl-2-((2*Z*,4*Z*)-3-phenylhexa-2,4-dien-2-yl)-1,3,2-dioxaborolane (3.3d).



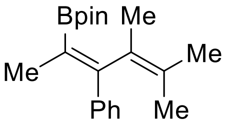
Obtained from **3.1a**, **3.2d** as a yellow oil after column chromatography (hexane/CH_2Cl_2 5:1) following the general procedure in 68% yield. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.34 (t, *J* = 7.2 Hz, 2H), 7.26 (d, *J* = 7.1 Hz, 1H), 7.18 (d, *J* = 6.8 Hz, 2H), 6.64 (d, *J* = 11.7 Hz, 1H), 5.53 (dq, *J* = 14.5, 7.3 Hz, 2H), 1.71 (s, 3H), 1.34 (s, 12H), 1.20 (d, *J* = 7.2 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 149.9 (C), 142.2 (C), 132.0 (CH), 128.9 (CH), 128.0 (2CH), 127.2 (2CH), 126.4 (CH), 83.3 (2C), 24.8 ($4CH_3$), 18.1 (CH_3), 14.6 (CH_3). **^{11}B NMR** (160 MHz, $CDCl_3$) δ 22.4 ppm **HRMS (APCI)** Calc. for $C_{18}H_{26}BO_2[M+H^+]$: 285.2020, found 285.202.

4,4,5,5-Tetramethyl-2-((2*Z*,4*Z*)-4-methyl-3-phenylhexa-2,4-dien-2-yl)-1,3,2-dioxaborolane (3.3e).



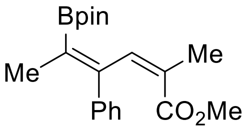
Obtained from **3.1a**, **3.2e** as a yellow oil after column chromatography (hexane/CH_2Cl_2 5:1) following the general procedure in 88% yield. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.35 – 7.28 (m, 2H), 7.24 – 7.19 (m, 3H), 5.41 – 5.32 (m, 1H), 1.82 (d, *J* = 1.0 Hz, 3H), 1.75 (dt, *J* = 6.6, 1.3 Hz, 3H), 1.72 – 1.70 (m, 3H), 1.28 (s, 12H). **^{13}C-NMR** (75 MHz, $CDCl_3$) δ 149.3 (C), 141.2 (C), 139.9 (C), 128.8 (CH), 127.8 (CH), 126.7 (CH), 121.9 (CH), 83.0 (2 x C), 24.5 (4 CH_3), 23.5 (CH_3), 17.4 (CH_3), 15.2 (CH_3). **^{11}B NMR** (160 MHz, $CDCl_3$) δ 22.5 ppm **HRMS (APCI)** Calc. for $C_{19}H_{28}BO_2$ $[M+H^+]$: 299.2177, found 299.2182.

(*E*)-2-(4,5-Dimethyl-3-phenylhexa-2,4-dien-2-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (3.3f).



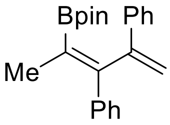
Obtained from **3.1a**, **3.2f** as yellow oil after column chromatography (hexane/CH_2Cl_2 5:1) following the general procedure in 86% yield. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.36 – 7.28 (m, 2H), 7.21 (d, *J* = 7.7 Hz, 3H), 1.86 (s, 3H), 1.79 (s, 3H), 1.71 (s, 3H), 1.65 (s, 3H), 1.26 (s, 12H), **^{13}C NMR** (75 MHz, $CDCl_3$) δ 152.1 (C), 140.4 (C), 134.2 (C), 128.9 (2CH), 127.8 (2CH), 126.6 (CH), 82.9 (2C), 24.7 ($4CH_3$), 22.4 (CH_3), 19.9 (CH_3), 18.4 (CH_3), 17.4 (CH_3). **^{11}B NMR** (160 MHz, $CDCl_3$) δ 22.42 ppm **HRMS (APCI)** Calc. for $C_{20}H_{30}BO_2$ $[M+H^+]$: 313.2334, found 313.233.

Methyl (2*Z*,4*Z*)-2-methyl-4-phenyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)hexa-2,4-dienoate (3.3g).



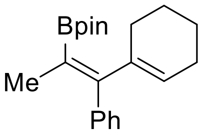
Obtained from **3.1a**, **3.2g** as yellow oil after column chromatography (hexane/AcOEt 8:2) following the general procedure using 10 mol% of CuCl/PCy$_3$ and 5 mol% of Pd(dba)$_2$ / 10 mol% of XPhos in 72% yield. ^{1}**H NMR** (300 MHz, CDCl$_3$) δ 7.92 – 7.88 (m, 1H), 7.40 – 7.26 (m, 3H), 7.11 (dt, *J* = 8.0, 1.9 Hz, 2H), 3.75 (d, *J* = 2.1 Hz, 3H), 1.76 (d, *J* = 3.0 Hz, 3H), 1.36 (d, *J* = 2.1 Hz, 15H) ^{13}**C NMR** (75 MHz, CDCl$_3$) δ 169.7 (C), 148.3 (C), 141.0 (C) , 140.3 (CH), 128.9 (2CH), 128.3 (2CH), 127.5 (C), 127.0 (CH), 83.8 (2C), 51.6 (CH$_3$), 24.8 (4CH$_3$), 18.6 (CH$_3$), 13.7 (CH$_3$). ^{11}**B NMR** (160 MHz, CDCl$_3$) δ 22.4 ppm **HRMS (APCI)** Calc. for $C_{21}H_{27}BO_4$[M+H$^+$]: 343.2089, found 343.2080.

(*E*)-2-(3,4-Diphenylpenta-2,4-dien-2-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (3.3h).



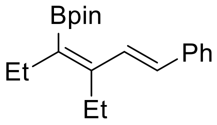
Obtained from **3.1a**, **3.2h** as yellow oil after column chromatography (hexane: CH$_2$Cl$_2$ 5:1) following general procedure in 56% yield. ^{1}**H NMR** (300 MHz, CDCl$_3$) δ 7.48 – 7.43 (m, 3H), 7.29 (m, 4H), 7.25 – 7.19 (m, 3H), 5.51 (d, *J* = 2.0 Hz, 1H), 5.37 (d, *J* = 2.0 Hz, 1H), 1.94 (s, 2H), 1.24 (s, 12H). ^{13}**C NMR** (75 MHz, CDCl$_3$) δ 152.3 (C), 150.5 (C), 140.4 (C), 139.9 (C), 129.2 (2CH), 127.9 (2CH), 127.7 (2CH), 127.6 (2CH), 127.1 (CH), 126.7 (CH), 115.9 (CH$_2$), 83.3 (2C), 24.5 (4CH$_3$), 18.3 (CH$_3$). ^{11}**B NMR** (160 MHz, CDCl$_3$) δ 22.4 ppm **HRMS (APCI)** Calc. for $C_{23}H_{28}BO_2$[M+H$^+$]: 347.2168, found 347.2177.

(*Z*)-2-(1-(Cyclohex-1-en-1-yl)-1-phenylprop-1-en-2-yl)-4,4,5,5-tetramethyl-1,3,2 dioxaborolane (3.3i).



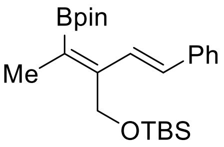
Obtained from **3.1a**, **3.2i** as yellow oil after column chromatography (hexane: CH$_2$Cl$_2$ 5:1) following the general procedure in 78% yield as 3.5:1 mixture of **3.3i:3.4a** that could not be separated by column chromatography. Yield calculated by ^{1}H-NMR analysis of the isolated mixture. ^{1}**H NMR** (300 MHz, CDCl$_3$) δ 7.32 – 7.23 (m, 3H), 7.17 (d, *J* = 8.2 Hz, 2H), 5.67 (s, 1H), 2.08 (s, 2H), 1.87 (s, 2H), 1.59 – 1.51 (m, 4H), 1.28 (s, 12H). ^{13}**C NMR** (75 MHz, CDCl$_3$) δ 154.2 (C), 142.4 (CH),140.2 (C), 137.9 (C) 129.4 (2CH), 129.1, 128.1 (2CH), 127.1 (CH) , 83.5 (2C), 27.9 (CH$_2$), 25.6 (CH$_2$), 24.9 (4CH$_3$), 22.8 (CH$_2$), 22.2 (CH$_2$), 15.9 (CH$_3$). ^{11}**B NMR** (160 MHz, CDCl$_3$) δ 29.1 ppm.

2-((3*E*,5*E*)-4-Ethyl-6-phenylhexa-3,5-dien-3-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (3.3j).



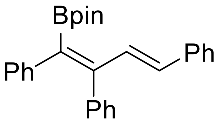
Obtained from **3.1b**, **3.2a** as yellow oil after column chromatography (hexane: CH$_2$Cl$_2$ 5:1) following the general procedure in 45% of yield as a 1:1.5 mixture of protoboration product **3.4b** and **3.3j** that could not be separated by column chromatography. Yield calculated by ^{1}H-NMR analysis of the isolated mixture. ^{1}**H NMR** (300 MHz, CDCl$_3$) δ 7.61 (d, *J* = 16.2 Hz, 1H), 7.42 (d, *J* = 7.7 Hz, 3H), 7.36 – 7.27 (m, 2H), 6.61 (d, *J* = 16.2 Hz, 1H), 2.46 (q, *J* = 7.5 Hz, 2H), 2.32 (q, *J* = 7.5 Hz, 2H), 1.35 (s, 12H), 1.11 – 1.06 (t, 3H), 1.01 (t, *J* = 7.3 Hz, 3H). ^{13}**C NMR** (75 MHz, CDCl$_3$) δ 151.1 (C), 138.6 (C), 128.5 (2CH), 127.5 (CH), 126.9 (2CH), 126.4 (2CH), 82.9 (2C), 24.7 (4CH$_3$), 21.6 (CH$_3$), 20.9 (CH$_2$), 14.8 (CH$_3$), 13.8 (CH$_2$). **HRMS (APCI)** Calc. for $C_{20}H_{30}BO_2$[M+H$^+$]: 312.2326, found 312.2329.

***tert*-Butyldimethyl(((*Z*)-2-((*E*)-styryl)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)but-2-en-1-yl)oxy)silane (3.3k)**



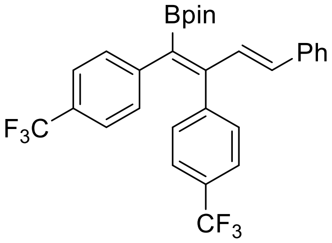
Obtained from **3.1c**, **3.2a** as yellow oil after column chromatography (hexane: CH_2Cl_2 5:1) following the general procedure in 73% yield. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.71 (d, *J* = 16.2 Hz, 1H), 7.43 (d, *J* = 7.7 Hz, 2H), 7.32 (t, *J* = 7.6 Hz, 2H), 6.81 (d, *J* = 16.3 Hz, 1H), 4.53 (s, 2H), 1.97 (s, 3H), 1.34 (s, 12H), 0.93 (d, *J* = 5.5 Hz, 9H), 0.14 (s, 6H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 148.7 (C), 138.6 (C), 130.4 (CH), 128.9 (CH), 128.5 (CH), 126.9 (CH), 126.4 (CH), 83.3 (2C), 58.6 (CH_2), 26.0 (CH_3), 24.9 ($4CH_3$), 18.4(CH_3), 17.0 (CH_3). **^{11}B NMR** (160 MHz, $CDCl_3$) δ 22.6ppm. **HRMS (APCI)** Unstable product.

4,4,5,5-Tetramethyl-2-((1Z,3E)-1,2,4-triphenylbuta-1,3-dien-1-yl)-1,3,2-dioxaborolane (3.3l).



Obtained from **3.1d**, **3.2a** as yellow solid after column chromatography (hexane: CH_2Cl_2 5:1) following the general procedure in 79% yield. **^{1}H-NMR** (300 MHz, $CDCl_3$) δ 7.89 (d, *J* = 15.8, 1.4 Hz, 1H), 7.44 (d, *J* = 8.1 Hz, 2H), 7.40 – 7.33 (m, 2H), 7.29 – 7.23 (m, 4H), 7.17 – 7.12 (m, 3H), 7.05 (td, *J* = 8.1, 3.4 Hz, 3H), 6.41 (d, *J* = 15.7 Hz, 1H), 1.48 (d, *J* = 1.5 Hz, 12H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 151.9 (C), 141.5 (C), 139.4 (C), 137.8 (C), 134.0 (CH), 132.2 (CH), 130.5 (2CH), 129.6 (2CH), 128.6 (2CH), 127.7 (2CH), 127.6 (2CH), 127.4 (CH), 126.7 (2CH), 125.5 (CH), 84.0 (2C), 24.9 ($3CH_3$). **^{11}B NMR** (160 MHz, $CDCl_3$) δ 22.9 ppm**.** **HRMS** (APCI) Calc. for $C_{28}H_{30}BO_2$[M+H$^+$]: 409.2333, found 409.2336

4,4,5,5-Tetramethyl-2-((1*Z*,3*E*)-4-phenyl-1,2-bis(4-(trifluoromethyl)phenyl)buta-1,3-dien-1-yl)-1,3,2-dioxaborolane (3.3m).

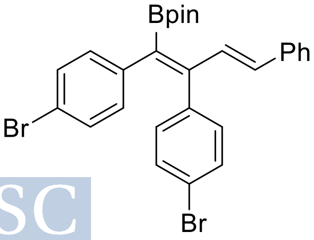


Obtained from **3.1e**, **3.2a** as yellow solid after column chromatography (hexane: AcOEt 8:2) following the general procedure using 10 mol% of CuCl/PCy_3 and 5 mol% of $Pd(dba)_2$ / 10 mol% of XPhos at 50 ^{0}C in 57% yield**.** **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.87 (d, *J* = 15.9 Hz, 1H), 7.47 (d, *J* = 8.1 Hz, 2H), 7.37 – 7.29 (m, 7H), 7.15 (d, *J* = 8.0 Hz, 2H), 7.04 – 6.98 (m, 2H), 6.21 (d, *J* = 15.9 Hz, 1H), 1.40 (s, 12H). **$_{13}$C NMR (75 MHz, $CDCl_3$)*** δ 152.2 (C), 144.9 (C), 142.8 (C), 137.1 (C), 135.4 (CH), 130.7 (2CH), 129.9 (CH), 129.7 (2CH), 128.7 (2CH), 128.2 (CH), 126.8 (CH), 125.1 (CH, q, *J* = 3.8 Hz), 124.5 (CH, q, *J* = 3.8 Hz), 84.3 (2C), 24.9 ($4CH_3$). **19F NMR** (282 MHz, $CDCl_3$) δ -62.53, -62.61. **HRMS (APCI)** Calc. for $C_{30}H_{28}BF_6O_2$[M+H$_+$]: 545.2081, found 545.2086.

19F NMR (282 MHz, $CDCl_3$) δ -62.53, -62.61**.** **HRMS** (APCI) Calc. for $C_{30}H_{28}BF_6O_2$[M+H$^+$]: 545.2081, found 545.2086.

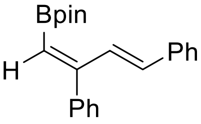
*Quaternary C heterocoupled with F could not be seen.

2-((1*Z*,3*E*)-1,2-Bis(4-bromophenyl)-4-phenylbuta-1,3-dien-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (3.3n).



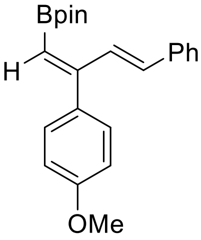
Obtained from **3.1f**, **3.2a** as yellow solid after column chromatography (hexane: CH_2Cl_2 5:1) following the general procedure, using 10 mol% of CuCl/PCy_3 and 5 mol% of $Pd(dba)_2$ / 10 mol% of XPhos at 50 ^{0}C, in 68% yield. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.81 (d, *J* = 15.9 Hz, 1H), 7.41 – 7.20 (m, 9H), 6.97 – 6.90 (m, 2H), 6.85 – 6.79 (m, 2H), 6.28 (d, *J* = 15.9 Hz, 1H), 1.41 (s, 12H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 151.4 (C), 140.1 (C), 138.0 (C), 137.4 (C), 134.7 (CH), 132.1 (2CH), 131.4 (CH), 131.1 (2CH), 131.2 (2CH), 130.7 (2CH), 128.7 (2CH), 127.9 (CH), 126.8 (2CH), 121.0 (C), 119.8 (C), 84.2 (2C), 24.9 (4CH$_3$). ^{11}**B NMR** (160 MHz, CDCl$_3$) δ 29.4ppm. **HRMS** (APCI) Calc. for $C_{28}H_{28}BBr_2O_2[M+H^+]$: 565.0544, found 565.0545.

2-((1*E*,3*E*)-2,4-Diphenylbuta-1,3-dien-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (3o).



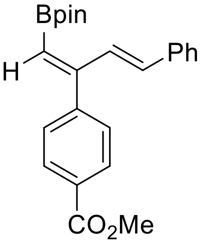
Obtained from **3.1g**, **3.2a** as yellow solid after column chromatography (hexane: CH$_2$Cl$_2$ 5:1) following the general procedure, using 10 mol% of CuCl/PCy$_3$ and 5 mol% of Pd(dba)$_2$ / 10 mol% of XPhos at 50 ^{0}C, in 68% yield. ^{1}**H NMR** (300 MHz, CDCl$_3$) δ 8.02 (d, *J* = 16.2 Hz, 1H), 7.38 (m, 10H), 6.48 (d, *J* = 16.2 Hz, 1H), 5.51 (s, 1H), 1.36 (s, 12H). ^{13}**C NMR** (75 MHz, CDCl$_3$) δ 160.1 (C), 149.5 (C), 142.7 (C), 137.5 (CH), 134.9 (CH), 129.8 (CH), 128.6 (2CH), 128.5 (2CH), 128.0 (2CH), 127.8 (CH), 127.6 (CH), 126.9 (2CH), 83.2 (2C), 24.9 (4CH$_3$). ^{11}**B NMR** (160 MHz, CDCl$_3$) δ 23.4 ppm**. HRMS (APCI)** Calc. for $C_{22}H_{26}BO_2[M+H^+]$: 332.1921, found 332.1923.

2-((1*E*,3*E*)-2-(4-Methoxyphenyl)-4-phenylbuta-1,3-dien-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (3.3p).



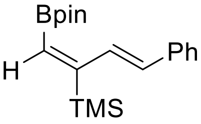
Obtained from **3.1h**, **3.2a** as yellow oil after column chromatography (hexane: AcOEt 9:1) following the general procedure, using 10 mol% of CuCl/PCy$_3$ and 5 mol% of Pd(dba)2 / 10 mol% of XPhos at 50 ^{0}C, in in 51% yield. ^{1}**H NMR** (300 MHz, CDCl$_3$) δ 7.48 – 7.24 (m, 5H), 6.90 – 6.83 (m, 3H), 6.02 (d, *J* = 18.4 Hz, 1H), 3.81 (s, 3H), 1.31 (s, 12H). ^{13}**C NMR** (75 MHz, CDCl$_3$) δ 137.6 (C), 134.7 (C), 129.7 (2CH), 129.5 (C), 128.6 (2CH), 127.8 (CH), 126.9 (2CH), 126.5 (CH), 113.6 (CH), 113.4 (2CH), 83.2 (2C), 55.3 (CH$_3$), 24.9 (4CH$_3$). ^{11}**B NMR** (160 MHz, CDCl$_3$) δ 29.1ppm. **HRMS (APCI)** Calc. for $C_{23}H_{28}BO_3[M+H^+]$: 362.2127, found 362.2129.

Methyl 4-((1E,3E)-4-phenyl-1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)buta-1,3-dien-2-yl)benzoatexaborolane (3.3q).



Obtained from **3.1i**, **3.2a** as yellow oil after column chromatography (hexane: AcOEt 9:1) following the general procedure, using 10 mol% of CuCl/PCy$_3$ and 5 mol% of Pd(dba)$_2$ / 10 mol% of XPhos at 50 ^{0}C, in 37% yield. ^{1}**H NMR** (300 MHz, CDCl$_3$) δ 8.04 (d, *J* = 9.3 Hz, 2H), 7.46 – 7.38 (m, 5H), 7.32 (s, 3H), 6.39 (d, *J* = 17.0 Hz, 1H), 5.52 (s, 1H), 3.94 (s, 3H), 1.36 (s, 12H). ^{13}**C NMR** (75 MHz, CDCl$_3$) δ 159.0 (C), 137.2 (C), 135.2 (C), 129.4 (2CH), 129.3 (2CH), 128.6 (2CH), 128.6 (2CH), 128.1 (CH), 126.9 (2CH), 83.4 (2C), 52.1 (CH$_3$), 24.9 (4CH$_3$). ^{11}**B NMR** (160 MHz, CDCl$_3$) δ 24.8ppm **(APCI)** Calc. for $C_{24}H_{28}BO_4[M+H^+]$: 391.2075, found 391.2080.

Trimethyl((1*E*,3*E*)-4-phenyl-1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)buta-1,3-dien-2-yl)silane (3.3r).



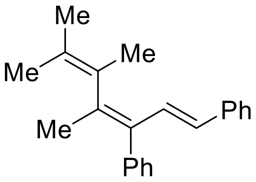
Obtained from **3.1j**, **3.2a** as yellow oil after column chromatography (hexane: CH$_2$Cl$_2$ 5:1) following the general procedure, using 10 mol% of CuCl/PCy$_3$ and 5 mol% of Pd(dba)$_2$ / 10 mol% of XPhos at 50 ^{0}C, in 48% yield. ^{1}**H NMR** (300 MHz, CDCl$_3$) δ 7.88 (d, *J* = 16.5 Hz, 1H), 7.47 (d, *J* = 7.6 Hz, 2H), 7.37 (t, *J* = 7.4 Hz, 3H), 6.73 (d, *J* = 16.5 Hz, 1H), 6.02 (s, 1H), 1.35 (s, 12H), 0.28 (s, 9H). ^{13}**C NMR** (75 MHz, CDCl$_3$) δ 164.0 (C), 138.0 (C), 133.2 (CH), 133.1 (CH), 128.6 (2CH), 127.5 (2CH), 126.6 (2CH), 83.3 (2C), 29.7 (CH$_3$), 24.9 (4CH$_3$), 24.6 (CH$_3$), -0.23 (CH$_3$). ^{11}**B NMR** (160 MHz, CDCl$_3$) δ 27.57. **HRMS (APCI).** Calc. for $C_{19}H_{30}BO_2Si[M+H^+]$: 329.2103, found 329.2106.

2.4 Product derivatization

CuCl (5 mol%, 0.025 mmol) and tricyclohexylphosphine (5 mol%, 0.025 mmol) were suspended in the corresponding solvent (0.5 mL), stirred during 15 minutes at r.t. After this time the 1-phenyl-1-propyne **3.1a** (1 equiv, 0.5 mmol) was added over the previous solution. The final solution was added to the reaction vial containing B_2pin_2 (1.5 equiv, 0.75 mmol) and NaO^tBu (1.5 equiv, 0.075 mmol) to afford a red suspension. In a separate vial $Pd(dba)_2$ (2.5 mol%, 0.0125 mmol), L_{Cu} (5 mol%, 0.025 mmol), (*E*)-(2-bromovinyl)benzene **3.2a** (1.2 equiv, 0.6 mmol) were stirred in THF* (0.5 mL) for 15 minutes at r.t. This solution was finally added to the reaction vial and heated at 50 ^{0}C for 16 hours. After the reaction ends, 2-bromo-3-methylbut-2-ene **3.2g** (1.2 equiv, 0.6 mmol) and a solution of NaOH (2M, 2 equiv) were added to the vial reaction and heat at 80 ^{0}C for 16 hours. After this time, the reaction was quenched by addition of saturated aqueous solution of NH_4Cl (10 mL) and extracted with Et_2O (2x10 mL). The organic layer was dried over Na_2SO_4, filtered and solvent was removed under vacuum. The final product was purified by silica gel column chromatography.

*When the reaction was run using toluene as solvent, we did not observe full conversion of the intermediate **3.3a** (40% conv.)

((1*E*,3*E*)-4,5,6-Trimethylhepta-1,3,5-triene-1,3-diyl)dibenzene (3.6).



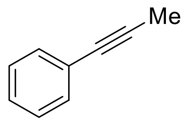
Obtained from **3.1a**, **3.2a** and **3.2g** as colorless oil after column chromatography (hexane: CH_2Cl_2 5:1) in 58% yield. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.48 – 7.41 (m, 3H), 7.39 – 7.34 (m, 1H), 7.29 (s, 2H), 7.27 (d, *J* = 1.5 Hz, 2H), 7.26 – 7.17 (m, 2H), 7.15 (d, *J* = 12.6 Hz, 1H), 5.90 (d, *J* = 16.1 Hz, 1H), 1.90 (q, *J* = 1.3 Hz, 3H), 1.86 (d, *J* = 1.1 Hz, 3H), 1.72 (q, *J* = 1.4 Hz, 3H), 1.65 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 141.7 (C), 140.1 (C), 138.4 (C), 135.4 (C), 130.2 (CH), 130.0 (2CH), 129.3 (CH), 128.5 (2CH), 128.2 (2CH), 126.8 (CH), 126.5 (CH), 126.2 (2CH), 21.4 (CH_3), 19.8 (CH_3), 19.7 (CH_3), 17.8 (CH_3). **HRMS** (APCI) Calc. for $C_{22}H_{25}$ [M+H$^+$]: 289.1951 found 289.1950.

3. CHAPTER IV

3.1 List of starting materials

Alkynes **4.2**, **4.29-4.30**, vinyl epoxides **4.1**, **4.37**-**4.38**, vinyl cyclic carbonate **4.19** and $B_2(pin)_2$ were obtained from commercial sources and used without further purification. Alkynes **4.27-4.28**,[113] **4.31**-**4.34**,[6] vinyl epoxides **4.35**-**4.36**[114] and vinyl cyclic carbonate **4.20**[115] were prepared following described procedures.

- **Alkynes**



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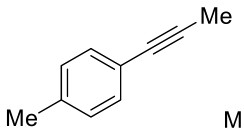

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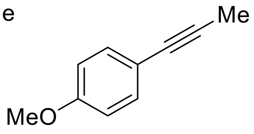

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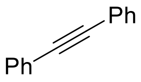

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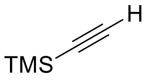
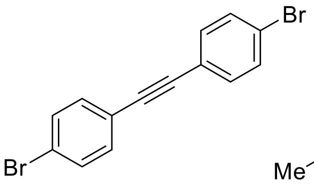


4.30



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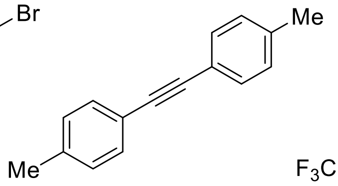

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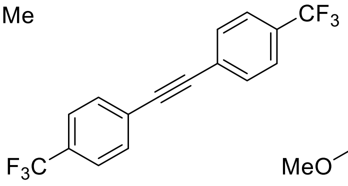

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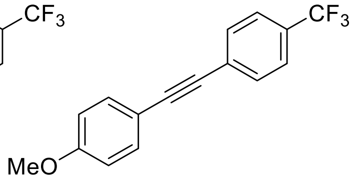
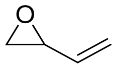
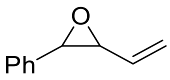


4.34

- **Vinyl epoxides**

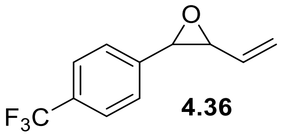


4.1



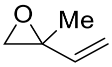
4.35

2:1 cis/trans

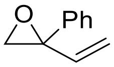


4.36

5:1 cis/trans



4.37



4.38

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[113] Miio, M.; Kopel, L. C.; Braun, J.B.; Gadzikwa, T. L.; Hull, K. L.; Brisbois, R. G.;. Markworth, C. J.; Grieco, P. A. *Org. Lett*. **2002**, 4, 3199-3202.

[114] Yoshida, Y.; Takesh, E. *Polym. Chem*., **2016***, 7*, 6770-6778.

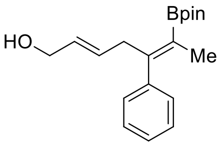
[115] Deng, L.; Kleij, A.W.; Yang, W. *Chem. Eur. J*. **2018**, *24*, 19156-19161.

3.2 General procedure for the Cu/Pd allylboration of alkynes with vinyl epoxides.

In a dry vial CuCl (10 mol%, 3 mg, 0.1 mmol,) and Tricyclohexylphosphine (10 mol%, 23.8 mg, 0.1 mmol) were suspended in dry THF (0.3 mL) and stirred during 15 minutes at room temperature. After this time the corresponding alkyne (1 equiv, 0.3 mmol) was added over the previous solution. The final solution was added to the reaction vial containing B_2pin_2 (1.3 equiv, 99.1 mg, 0.39 mmol) and NaO^tBu (20 mol%, 5.8 mg, 0.06 mmol) to afford a red suspension. In a separate vial $Pd(dba)_2$ (5 mol%, 8.62 mg, 0.015 mmol) and dppf (5 mol%, 8.32 mg, 0.015 mmol) were stirred in dry THF (0.3 mL) for 15 minutes at room temperature and added to the reaction vial. Then, a solution of vinyl epoxide (2 equiv, 0.6 mmol) in dry THF (0.5 ml) was added dropwise over 1 hour using a syringe pump. When the addition was completed, the mixture was stirred for additional 14 h at 30 °C. After this time, the reaction was quenched by addition of saturated aqueous solution of NH_4Cl (10 mL) and extracted with EtOAc (2 x 10 mL). The organic layer was dried over Na_2SO_4, filtered and solvent was removed under vacuum. The final product was purified by silica gel column chromatography using the indicated mixture of eluents for each case.

3.3 Compound characterization

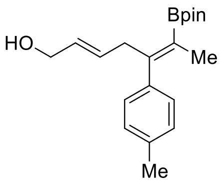
(2*E*,5*Z*)-5-Phenyl-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)hepta-2,5-dien-1-ol (4.3)



Synthesized from **4.1**, **4.2** and B_2pin_2 according to general procedure A. Yellow oil obtained in 70% yield (65.8 mg) after column chromatography (Hexane / EtOAc 4:1). 1 mmol scale: 52% yield (165 mg).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34 – 7.29 (m, 2H), 7.23 – 7.18 (m, 1H), 7.09 – 7.02 (m, 2H), 5.59 – 5.54 (m, 2H), 3.99 (d, *J* = 4.7 Hz, 2H), 3.43 – 3.38 (d, d, *J* = 4.7 Hz, 2H), 1.58 (s, 3H), 1.32 (s, 12H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 152.4 (C), 142.9 (C), 131.4 (CH) 129.80 (CH), 128.1 (2 x CH), 127.9 (2 x CH), 126.40 (CH), 83.2 (2 x C), 63.8 (CH_2), 40.8 (CH_2), 24.9 (4 x CH_3), 18.3 (CH_3) **^{11}B NMR** (160 MHz, $CDCl_3$) δ 31.45. **HRMS** (APCI) Calc. for $C_{19}H_{26}BO_2$ [M-H_2O+H^+]: 297.2020; found 297.2022.

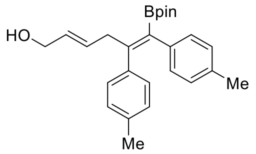
(2*E*,5*Z*)-6-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)-5-(p-tolyl)hepta-2,5-dien-1-ol (4.4)



Synthesized from **4.1**, **4.27** and B_2pin_2 according to general procedure A. Yellow oil obtained in 57% yield (65.8 mg) after column chromatography (Hexane / EtOAc 4:1).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.15 – 7.13 (m, 2H), 7.00 – 6.98 (m, 2H), 5.61 – 5.58 (m, 2H), 4.03 – 4.00 (m, 2H), 3.43 – 3.40 (m, 2H), 2.36 (s, 3H), 1.61 (s, 3H), 1.34 (s, 12H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 152.3 (C), 139.9 (C), 135.9 (C), 131.6 (CH), 129.6 (CH), 128.6 (2 x CH), 128.0 (2 x CH), 83.2 (2 x C), 63.8 (CH_2), 40.8 (CH_2), 24.9 (4 x CH_3), 21.2 (CH_3), 18.4 (CH_3). **^{11}B NMR** (160 MHz, $CDCl_3$) δ 31.42. **HRMS (APCI)** Calc. for $C_{20}H_{28}BO_2$[M-H_2O+H^+]: 311.2177; found 311.2181.

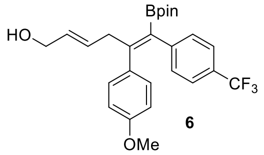
(2*E*,5*Z*)-6-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)-5,6-di-p-tolylhexa-2,5-dien-1-ol (4.5)



Synthesized from **4.1**, **4.37** and B$_2$pin$_2$ according to general procedure A. Yellow oil obtained in 40% yield (56.0 mg) after column chromatography (Hexane / EtOAc 4:1).

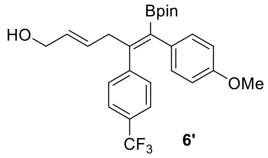
^{1}H NMR (500 MHz, CDCl$_3$) δ 6.88 – 6.71 (m, 8H), 5.60 – 5.56 (m, 2H), 3.93 (d, *J* = 4.5 Hz, 2H), 3.38 (d, *J* = 4.4 Hz, 2H), 2.16 (s, 3H), 2.13 (s, 3H), 1.24 (s, 12H).**^{13}C NMR** (75 MHz, CDCl$_3$) δ 149.9 (C), 138.9 (C), 138.4 (C) 135.9 (C), 134.7 (C), 130.9 (CH), 130.3 (CH), 129.5 (2 x CH), 129.1 (2 x CH), 128.4 (2 x CH), 128.3 (2 x CH), 83.68 (2 x C), 63.7 (CH$_2$), 41.4 (CH$_2$), 29.70, 24.8 (4 x CH$_3$), 21.1 (CH$_3$), 21.1 (CH$_3$). **^{11}B NMR** (160 MHz, CDCl$_3$) δ 30.80. **HRMS(APCI)** Calc. for $C_{26}H_{32}BO_2$ [M-H$_2$O+H$^+$]: 387.2490; found 387.2492.

(2*E*,5*Z*)-5-(4-Methoxyphenyl)-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-6-(4-(trifluoromethyl)phenyl)hexa-2,5-dien-1-ol (4.6) and (2*E*,5*Z*)-6-(4-Methoxyphenyl)-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5-(4-(trifluoromethyl)phenyl)hexa-2,5-dien-1-ol (4.6’)



6

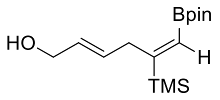
Synthesized from **4.1**, **4.34** and B$_2$pin$_2$ according to general procedure A. Yellow oil obtained in 43% yield (61.0 mg) after column chromatography (Hexane / EtOAc 4:1) as a 2:1 mixture of regioisomers **4.6** and **4.6’**.



6'

^{1}H NMR (300 MHz, CDCl$_3$) δ 7.38 (d, *J* = 8.0 Hz, 2H, **6’**), 7.33 (d, *J* = 8.1 Hz, 2H, **4.6**), 7.11 (d, *J* = 8.3 Hz, 2H, **4.6’**), 7.05 (d, *J* = 8.0 Hz, 2H, **6**), 6.90 – 6.82 (m, 2H, **4.6** +**4.6’**), 6.70 – 6.57 (m, 2H, **6** + **6’**), 5.73 – 5.55 (m, 2H, **4.6** + **4.6’**), 4.17 – 3.96 (m, 2H, **4.6** + **4.6’**), 3.74 (s, 3H, **4.6**), 3.72 (s, 3H, **4.6’**), 3.58 – 3.46 (m, 2H, **4.6** + **4.6’**), 1.35 (s, 12H, **4.6’**), 1.34 (s, 12H, **4.6**). **^{13}C NMR** (75 MHz, CDCl$_3$) δ 158.3 (C, **4.6**), 157.7 (C, **4.6’**), 153.0 (C, **4.6** + **4.6’**), 148.2 (C, **4.6’**), 145.9 (C, **4.6**), 135.2 (**4.6’**), 133.6 (C, **4.6**), 132.9 (C, **4.6’**), 132.2 (CH, **4.6’**), 130.9 (CH, **4.6’**), 130.6 (CH, **4.6**), 130.3 (CH, **4.6**), 129.9 (2 x CH, **4.6**), 129.8 (2 x CH, **4.6’**), 129.5 (2 x CH, **4.6**), 124.66 (q, *J* = 3.8 Hz, 2 x CH, **4.6’**), 124.4 (q, *J* = 3.8 Hz, 2 x CH, **4.6)**, 113.2 (2 x CH, **4.6**), 83.9 (2 x C, **4.6’**), 83.8 (2 x C, **4.6**), 63.6 (CH$_2$, **4.6**), 63.4 (CH$_2$, **4.6’**), 55.05 (CH$_3$, **4.6**), 55.0 (CH$_3$, **4.6’**), 41.1 (CH$_2$, **4.6**), 40.9 (CH$_2$, **4. 6’**), 24.7 (4 x CH$_3$, **4. 6** +**4. 6’**). **^{19}F NMR** (282 MHz, CDCl$_3$) δ -62.26 (**4.6**), -62.44 (**4.6’**). **^{11}B NMR** (160 MHz, CDCl$_3$) δ 31.29. **HRMS (APCI)** Cal. for $C_{26}H_{29}BF_3O_3$ [M-H$_2$O+H$^+$]: 457.2156; found 457.2168.

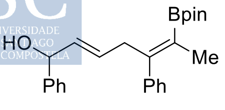
(2*E*,5*E*)-6-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)-5-(trimethylsilyl)hexa-2,5-dien-1-ol (4.7)



Synthesized from **4.1**, **4.30** and B$_2$pin$_2$ according to general procedure A. Yellow oil obtained in 56% yield (49.5 mg) after column chromatography (Hexane / EtOAc 4:1).

^{1}H NMR (500 MHz, CDCl$_3$) δ 5.93 (s, 1H), 5.67 – 5.64 (m, 2H), 4.08 (d, *J* = 3.9 Hz, 2H), 3.31 – 3.28 (m, 2H), 1.28 (s, 12H), 0.08 (s, 9H). **^{13}C NMR** (126 MHz, CDCl$_3$) δ 168.2 (C), 132.7 (CH), 129.5 (CH), 83.0 (2 x C), 63.9 (CH$_2$), 37.5 (CH$_2$), 24.9 (4 X CH$_3$), 1.2 (3 x CH$_3$). **^{11}B NMR** (160 MHz, CDCl$_3$) δ 28.80. **HRMS(APCI)** Calc. for $C_{15}H_{28}BO_2Si$ [M-H$_2$O+H$^+$]: 279.1946; found 279.1941.

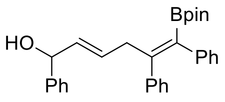
(2*E*,5*Z*)-1,5-Diphenyl-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)hepta-2,5-dien-1-ol (4.8)



Synthesized from **4.2**, **4.35** and B$_2$pin$_2$ according to general procedure A at 50 °C. Yellow oil obtained in 71% yield (83 mg) after column chromatography (Hexane / EtOAc 4:1).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.26 – 7.18 (m, 5H), 7.16 – 7.11 (m, 3H), 6.99 – 6.93 (m, 2H), 5.58 (dtd, *J* = 14.9, 6.9, 1.0 Hz, 1H), 5.49 – 5.41 (m, 1H), 4.99 (d, *J* = 7.0 Hz, 1H), 3.43 – 3.28 (m, 2H), 1.51 (s, 3H), 1.23 (s, 12H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 152.4 (C), 143.1 (C), 142.9 (C), 133.3 (CH), 128.3 (2 x CH), 128.1 (2 x CH), 127.9 (2 x CH), 127.3 (CH), 126.3 (CH), 126.2 (2 x CH), 83.2 (2 x C), 74.9 (CH), 40.7 (CH_2), 24.9 (4 x CH_3), 18.4 (CH_3). **^{11}B NMR** (160 MHz, $CDCl_3$) δ 32.49. **HRMS (APCI)** Calc. for $C_{25}H_{30}BO_2$ [M-H_2O+H^+]: 373.2333; found 373.2348.

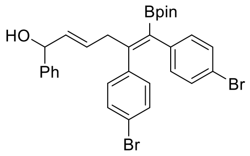
(2*E*,5*Z*)-1,5,6-Triphenyl-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)hexa-2,5-dien-1-ol (4.9)



Synthesized from **4.29**, **4.35** and B_2pin_2 according to general procedure A at 50 °C. Yellow oil obtained in 46% yield (62.4 mg) after column chromatography (Hexane / EtOAc 4:1).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.32 – 7.19 (m, 5H), 7.10 – 6.95 (m, 10H), 5.73 (ddd, *J* = 34.4, 15.3, 7.7 Hz, 2H), 5.11 (d, *J* = 6.5 Hz, 1H), 3.55 (dd, *J* = 6.02, 2.3, 2H), 1.35 (s, 12H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 151.0 (C), 141.9(C), 141.4 (C), 134.0 (C), 129.9 (CH), 129.7 (2 x CH), 129.3 (2 x CH), 128.3 (2 x CH), 127.7 (2 x CH), 127.5 (2 x CH), 127.4 (CH), 126.4 (CH), 126.3 (2 x CH), 125.5 (CH), 83.8 (2 x C), 74.7 (CH), 41.3 (CH_2), 24.8 (4 x CH_3). **^{11}B NMR** (160 MHz, $CDCl_3$) δ 30.5. **HRMS (APCI)** Calc. for $C_{30}H_{32}BO_2$ [M-H_2O+H^+]: 435.2490; found 435.2496.

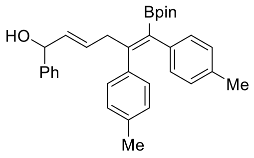
(2*E*,5*Z*)-5,6-Bis(4-bromophenyl)-1-phenyl-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)hexa-2,5-dien-1-ol (4.10)



Synthesized from **4.31**, **4.35** and B_2pin_2 according to general procedure A at 50 °C. Yellow oil obtained in 26% yield (47.4 mg) after column chromatography (Hexane / EtOAc 4:1).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.26 – 7.05 (m, 9H), 6.73 – 6.68 (m, 3H), 5.67 – 5.47 (m, 2H), 5.01 (dd, *J* = 6.7, 3.2 Hz, 1H), 3.41 (qd, *J* = 14.5, 6.6 Hz, 2H), 1.21 (s, 11H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 149.9 (C), 141.8 (C), 139.4 (C), 139.1 (C), 133.4 (CH), 130.3 (2 x CH), 130.0 (2 x CH), 129.8 (2 x CH), 129.8 (2 x CH), 128.0 (CH), 127.4 (2 x CH), 126.5 (CH), 125.1 (2 x CH), 119.7 (C), 118.7 (C), 82.9 (2 x C), 73.7 (CH), 39.9 (CH_2), 23.7 (4 x CH_3).**^{11}B NMR** (160 MHz, $CDCl_3$) δ 30.97. **HRMS (APCI)** Calc. for $C_{30}H_{30}BBr_2O_2$ [M-H_2O+H^+]: 591.0700; found 591.0693.

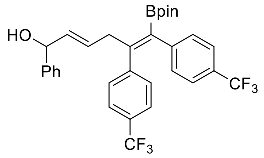
(2*E*,5*Z*)-1-Phenyl-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5,6-di-p-tolylhexa-2,5-dien-1-ol (4.11)



Synthesized from **4.32**, **4.35** and B_2pin_2 according to general procedure A at 50 °C. Yellow oil obtained in 59% yield (73.9 mg) after column chromatography (Hexane / EtOAc 4:1).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34 – 7.15 (m, 4H), 6.96 – 6.81 (m, 9H), 5.85 – 5.57 (m, 2H), 5.09 (d, *J* = 6.7 Hz, 1H), 3.50 (d, *J* = 5.7 Hz, 2H), 2.26 (s, 3H), 2.23 (s, 3H), 1.32 (s, 12H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 150.1 (C), 143.1 (C), 138.9 (C), 138.5 (C), 135.8 (C), 134.7 (C), 133.8 (CH), 130.2 (CH), 129.5 (2 x CH), 129.2 (2 x CH), 128.4 (2 x CH), 128.3 (2 x CH), 128.2 (2 x CH), 127.3 (CH), 126.3 (2 x CH), 83.7 (2 x C), 74.8 (CH), 41.4 (CH_2), 24.8 (4 x CH_3), 21.13 (2 x CH). **^{11}B NMR** (160 MHz, $CDCl_3$) δ 30.35. **HRMS (APCI)** Calc. for $C_{32}H_{36}BO_2$ [M-H_2O+H^+]: 463.2803; found 463.2803.

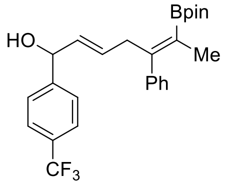
(2*E*,5*Z*)-1-Phenyl-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5,6-bis(4-(trifluoromethyl)phenyl)hexa-2,5-dien-1-ol (4.12)



Synthesized from **4.33**, **4.35** and B_2pin_2 according to general procedure A at 50 °C. Yellow oil obtained in 46% yield (81.2 mg) after column chromatography (Hexane / EtOAc 4:1).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.61 – 7.21 (m, 5H), 7.17 (d, *J* = 9.5 Hz, 1H), 7.03 (d, *J* = 7.2 Hz, 4H), 5.82 – 5.55 (m, 2H), 5.11 (d, *J* = 6.1 Hz, 1H), 3.69 – 3.48 (m, 2H), 1.33 (s, 12H).**^{13}C NMR** (75 MHz, $CDCl_3$) δ 151.9 (C), 145.2 (C), 144.9 (C), 142.9 (C), 134.8 (CH), 129.8 (2 x CH), 129.4 (2 x CH), 128.5 (CH), 128.4 (2 x CH), 127.6 (CH), 126.1 (2 x CH), 124.7 (q, *J* = 4.0 Hz, 2 x CH), 124.61 (q, *J* = 4.0 Hz, 2 x CH), 84.1 (2 x C), 74.7 (CH_2), 40.9 (CH_2), 24.7 (4 x CH_3). **^{19}F NMR** (282 MHz, $CDCl_3$) δ -62.39, -62.51. **^{11}B NMR** (160 MHz, $CDCl_3$) δ 30.31 **HRMS (APCI)** Calc. for $C_{32}H_{30}BF_6O_2$ $[M-H_2O+H^+]$: 571.2238; found 571.2245.

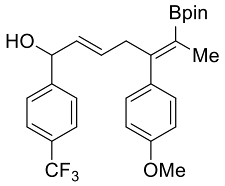
(2*E*,5*Z*)-5-Phenyl-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1-(4 (trifluoromethyl)phenyl)hepta-2,5-dien-1-ol (4.13).



Synthesized from **4.2**, **4.36** and B_2pin_2 according to general procedure A at 50 °C. Yellow oil obtained in 83% yield (114 mg) after column chromatography (Hexane / EtOAc 4:1).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.58 – 7.52 (m, 2H), 7.35 – 7.23 (m, 5H), 7.08 – 7.02 (m, 2H), 5.74 – 5.64 (m, 1H), 5.47 (ddt, *J* = 15.2, 7.2, 1.3 Hz, 1H), 5.11 (d, *J* = 7.57 Hz, 1H), 3.56 – 3.35 (m, 2H), 1.61 (s, 3H), 1.31 (s, 12H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 152.0 (C), 146.9 (C), 142.7 (C), 132.7 (CH), 131.8 (CH), 128.1 (2 x CH), 128.0 (2 x CH), 126.5 (CH) 126.4 (2 X CH), 126.4 (CH), 125.1 (q, *J* = 3.4 Hz, 2 x CH), 83.3 (2 x C), 74.4 (CH), 40.6 (CH_2), 24.8 (4 x CH_3), 18.4 (CH_3). **^{19}F NMR** (282 MHz, $CDCl_3$) δ -62.90. **^{11}B NMR** (160 MHz, $CDCl_3$) δ 30.93. **HRMS (APCI)** Calc. $C_{26}H_{29}BF_3O_2$ $[M-H_2O+H^+]$: 441.2211; found 441.2213

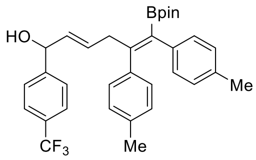
(2*E*,5*Z*)-5-(4-Methoxyphenyl)-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1-(4-(trifluoromethyl)phenyl)hepta-2,5-dien-1-ol (4.14)



Synthesized from **4.28**, **4.36** and B_2pin_2 according to general procedure A at 50 °C. Yellow oil obtained in 67% yield (98 mg) after column chromatography (Hexane / EtOAc 4:1).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.55 – 7.52 (m, 2H), 7.32 – 7.29 (m, 2H), 6.99 – 6.96 (m, 2H), 6.84 – 6.82 (m, 2H), 5.67 (dtd, *J* = 15.0, 6.9, 0.9 Hz, 1H), 5.46 (ddt, *J* = 15.2, 7.3, 1.4 Hz, 1H), 5.11 (d, *J* = 7.3 Hz, 1H), 3.80 (s, 3H), 3.49 (dd, *J* = 14.1, 6.6 Hz, 1H), 3.40 – 3.34 (m, 1H), 1.63 (s, 3H), 1.30 (s, 12H). **^{13}C NMR** (126 MHz, $CDCl_3$**)** δ 158.1 (C), 151.6 (C), 146.9 (C), 134.9 (C), 132.6 (CH, 131.9 (CH), 129.3 (2 x CH), 126.4 (2 x CH), 125.1 (q, *J* = 3.8 Hz, 2 x CH), 113.3 (2 x CH), 83.2 (2 x C), 74.4 (CH), 55.1 (CH_3), 40.8 (CH_2), 24.8 (4 x CH_3), 18.5 (CH_3). **^{19}F NMR** (282 MHz, $CDCl_3$) δ -62.54. **^{11}B NMR** (160 MHz, $CDCl_3$) δ 30.84. **HRMS (APCI)** Calc. for $C_{27}H_{31}F_3O_3$ $[M-H_2O+H^+]$: 471.2313; found 471.2315.

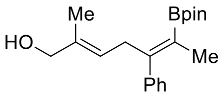
(2*E*,5*Z*)-6-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)-5,6-di-p-tolyl-1-(4-(trifluoromethyl)phenyl)hexa-2,5-dien-1-ol (4.15)



Synthesized from **4.32**, **4.36** and B_2pin_2 according to general procedure A at 50 °C. Yellow oil obtained in 63% yield (104 mg) after column chromatography (Hexane / EtOAc 4:1).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.49 (d, *J* = 8.0 Hz, 2H), 7.27 (d, *J* = 7.8 Hz, 2H), 6.91 – 6.86 (m, 8H), 5.76 (dt, *J* = 13.9, 6.6 Hz, 1H), 5.55 (dd, *J* = 15.3, 7.2 Hz, 1H), 5.10 (d, *J* = 7.3 Hz, 1H), 3.59 – 3.45 (m, 2H), 2.27 (s, 3H), 2.25 (s, 3H), 1.34 (s, 12H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 149.7 (C), 146.9 (C), 138.8 (C), 138.3 (C), 135.9 (C), 134.8 (C), 133.3 (CH), 129.5 (2 x CH), 129.2 (2 x CH), 128.4 (2 x CH), 128.4 (2 x CH), 126.5 (2 x CH), 125.1 (q, *J* = 3.8 Hz, 2 x CH), 83.7 (2 x C), 74.3 (CH), 41.3 (CH_2), 24.7 (4 x CH_3), 21.1 (2 x CH_3).**^{19}F NMR** (282 MHz, $CDCl_3$) δ -62.45. **^{11}B NMR** (160 MHz, $CDCl_3$) δ 30.91. **HRMS (APCI)** Cal. for $C_{33}H_{35}BF_3O_2$ [M-H_2O+H^+]: 531.2677; found 531.2687.

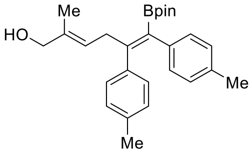
(2*E*,5*Z*)-2-Methyl-5-phenyl-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)hepta-2,5-dien-1-ol (4.16)



Synthesized from **4.2**, **4.37** and B_2pin_2 according to general procedure A. Yellow oil obtained in 36% yield (35.5 mg) after column chromatography (Hexane / EtOAc 4:1).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34 – 7.31 (m, 2H), 7.25 – 7.22 (m, 1H), 7.10 – 7.06 (m, 2H), 5.31 (t, *J* = 6.3, 1H), 3.91 (s, 2H), 3.45 (d, *J* = 7.4 Hz, 2H), 1.59 (s, 3H), 1.51 (s, 3H), 1.35 (s, 12H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 153.2 (C), 143.1 (C), 135.0 (C), 128.0 (2 x CH), 127.9 (2 x CH), 126.3 (CH), 124.6 (CH), 83.2 (2 x C), 69.1 (CH_2), 36.4 (CH_2), 24.9 (4 x CH_3), 18.3 (CH_3), 13.7 (CH_3). **^{11}B NMR** (160 MHz, $CDCl_3$) δ 31.42. **HRMS (APCI)** Calc. for $C_{20}H_{28}BO_2$ [M-H_2O+H^+]: 311.2153; found 311.2159.

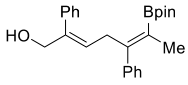
(2*E*,5*Z*)-2-Methyl-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5,6-di-p-tolylhexa-2,5-dien-1-ol (4.17)



Synthesized from **4.32**, **4.37** and B_2pin_2 according to general procedure A. Yellow oil obtained in 48% yield (60.2 mg) after column chromatography (Hexane / EtOAc 4:1).

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.96 – 6.79 (m, 8H), 5.39 (t, *J* = 6.3, 1H), 3.92 (s, 2H), 3.49 (d, *J* = 6.9 Hz, 2H), 2.25 (s, 3H), 2.23 (s, 3H) 1.61 (s, 3H), 1.34 (s, 12H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 150.9 (C), 139.1 (C), 138.6 (C), 135.7 (C), 135.4 (C), 134.6 (C), 129.5 (2 x CH), 129.0 (2 x CH), 128.3 (2 x CH), 128.2 (2 x CH), 124.5 (CH), 83.6 (2 x C), 69.0 (CH_2), 37.2 (CH_2), 24.8 (4 x CH_3), 21.1 (CH_3), 13.9 (CH_3).**HRMS (APCI)** Calc. for $C_{27}H_{34}BO_2$ [M-H_2O+H^+]: 401.2646; found 401.2659.

(2*E*,5*Z*)-2,5-Diphenyl-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)hepta-2,5-dien-1-ol (4.18) and **(2*Z*,5*Z*)-2,5-diphenyl-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)hepta-2,5-dien-1-ol (4.18')**



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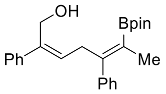
+



18'

Synthesized from **4.2**, **4.38** and B_2pin_2 according to general procedure A. Yellow oil obtained in 28% yield (32.8 mg) after column chromatography (Hexane / EtOAc 4:1) as a 1:1 mixture of stereoisomers **4.18** and **4.18’**.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38 – 7.19 (m, *J* = 8.0 Hz, 12H, **4.18** +**4.18’**), 7.13 (d, *J* = 7.0 Hz, 2H), 7.00 (d, *J* = 8.3 Hz, 2H), 6.89 (d, *J* = 7.7 Hz, 2H), 5.79 (t, *J* = 7.8 Hz, 1H, **4.18’**), 5.62 (s, 1H, **4.18**), 4.36 (d, *J* = 5.1 Hz, 2H, **4.18’**), 4.22 (s, 2H, **4.18**), 3.68 (d, *J* = 7.8 Hz, 2H, **4.18’**), 3.41 (d, *J* = 7.1 Hz, 2H, **4.18**), 1.61 (s, 3H, **4.18’**), 1.58 (s, 3H, **4.18**), 1.38 (s, 12H), 1.25 (s, 12H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 152.7 (C), 152.7 (C), 142.8 (C), 142.6 (C), 141.6 (C), 140.3 (C), 139.0 (C), 138.2 (C), 129.54 (CH), 128.7 (2 x CH), 128.3 (2 x CH), 128.2 (2 x CH), 128.1 (2 x CH), 128.1 (2 x CH), 127.9 (2 x CH), 127.3 (CH), 126.9 (2 x CH), 126.7 (CH), 126.3 (CH), 126.2 (2 x CH), 83.5 (CH), 83.2 (CH), 68.3 (CH_2), 59.8 (CH_2) , 37.5 (CH_2), 37.3 (CH_2), 24.8 (4 x CH_3), 24.7 (4 x CH_3), 18.5 (CH_3), 18.3 (CH_3). **^{11}B NMR** (160 MHz, $CDCl_3$) δ 30.81. **HRMS (APCI)** Calc. for $C_{25}H_{30}BO_2$ [M-H_2O+H^+]: 373.2333; found 373.2335.

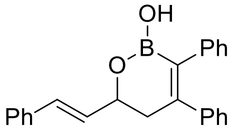
3.4 Product derivatization

3.4.1 Rhenium-catalyzed allylic [1,3] transposition: synthesis of dihydroborininols

Following described procedures for the rhenium-catalyzed [1, 3]-transposition of allylic alcohols, a solution of the corresponding bifunctional skipped diene (0.2 mmol, 1 equiv) in 1 ml of dry dichloromethane was stirred in the presence of Re_2O_7 (4.85 mg, 5 mol%) under Argon atmosphere for 30 minutes. After this time, the solvent was evaporated, and the mixture was filtered through a small portion of silica gel to afford the corresponding dihydroborininol.

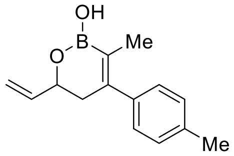
Note: these compounds were not stable enough for HRMS analysis.

(*E*)-5,6-Diphenyl-3-styryl-3,4-dihydroborinin-1(2H)-ol (4.23)



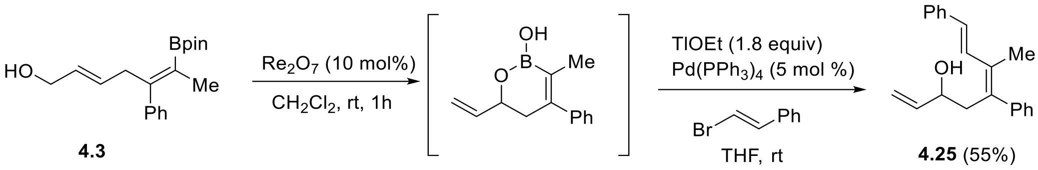
Obtained from diene **4.8** as a brown oil (57.7 mg, 82% yield).
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.47 – 7.34 (m, 5H), 7.26 – 7.16 (m, 5H), 7.12 – 7.02 (m, 5H), 6.79 (d, *J* = 15.9 Hz, 1H), 6.41 (dd, *J* = 15.9, 5.8 Hz, 1H), 5.05 (dt, *J* = 10.4, 5.1 Hz, 1H), 3.06 – 2.82 (m, 2H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 153.6 (C), 141.1 (C), 139.9 (C), 136.7 (C), 130.8 (CH), 130.4 (C) 129.8 (CH), 129.4 (2 x CH), 128.6 (2 x CH), 128.3 (2 x CH), 128.2 (2 x CH), 127.9 (2 x CH), 127.7 (CH) 127.4 (CH), 126.6 (2 x CH), 126.1 (CH), 73.68 (CH), 40.5 (CH_2). **^{11}B NMR** (160 MHz, $CDCl_3$) δ 22.45.

3-Methyl-4-(p-tolyl)-6-vinyl-5,6-dihydro-2H-1,2-oxaborinin-2-ol (4.24)



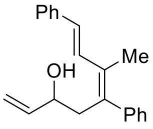
Obtained from diene **4** as a brown oil (19 mg, 41% yield).
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.21 – 7.19 (m, 2H), 7.13 – 7.11 (m, 2H), 5.99 (ddd, *J* = 17.2, 10.5, 5.6 Hz, 1H), 5.37 – 5.32 (ddd, *J* = 17.2, 10.5, 5.6 Hz, 1H), 5.19 (dt, *J* = 10.5, 1.4 Hz, 1H), 4.71 – 4.66 (m, 1H), 4.27 – 4.19 (m, 1H), 2.68 – 2.54 (m, 2H), 2.39 (s, 3H), 1.78 (dd, *J* = 2.2, 1.3 Hz, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 152.1 (C), 138.9 (CH), 138.6 (C), 136.9 (C), 130.9 (C), 128.83 (2 x CH), 127.5 (2 x CH), 115.3 (CH_2), 74.1 (CH), 40.12 (CH_2), 21.21 (CH_3), 14.9 (CH_3). **^{11}B NMR** (160 MHz, $CDCl_3$) δ 27.95.

3.4.2 One-pot allylic [1,3] transposition/Suzuki cross-coupling



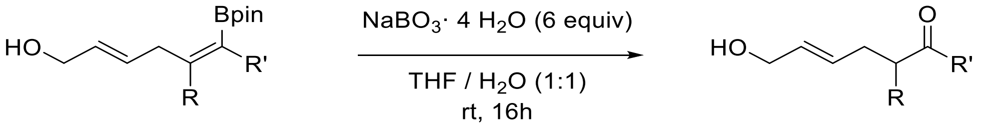
A solution of the difunctionalized diene **4.3** (62.8 mg, 0.2 mmol, 1 equiv) in 1 ml of dry dichloromethane was stirred in the presence of Re_2O_7 (9.7 mg, 10 mol%) under Argon atmosphere for 1 h. After this time, the solvent was evaporated under vacuum. Then, a solution of β-bromostyrene (43.95 mg, 0.24 mmol, 1.2 equiv) in 1 ml of THF/H_2O (3:1) was added, followed by the addition of $Pd(PPh_3)_4$ (11.56 mg, 5 mol%) and TlOEt (89.8 mg, 0.36 mmol, 1.8 equiv). The resulting solution was stirred at room temperature under argon atmosphere for 1 h. After this time, the mixture was diluted in EtOAc and washed with brine. The organic layer was dried, filtered and the solvents were evaporated under vacuum. The final product was purified by SiO_2 column chromatography using a mixture of Hexane : AcOEt (8:2) as eluent to afford the product **4.23** as a yellow oil in 55% yield (32.0 mg).

(5*E*,7*E*)-6-Methyl-5,8-diphenylocta-1,5,7-trien-3-ol (4.25).



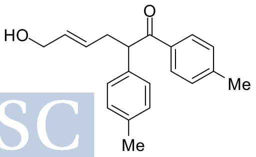
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.50 – 7.47 (m, 1H), 7.45 (d, *J* = 15.9 Hz, 1H), 7.40 – 7.34 (m, 4H), 7.31 – 7.28 (m, 1H), 7.26 – 7.23 (m, 1H), 7.21 – 7.18 (m, 2H), 6.73 (d, *J* = 15.9 Hz, 1H), 5.91 (ddd, *J* = 17.2, 10.5, 5.8 Hz, 1H), 5.23 (dt, *J* = 17.2, 1.5 Hz, 1H), 5.10 (dt, *J* = 10.5, 1.4 Hz, 1H), 4.12– 4.07 (m, 1H), 3.04 (dd, *J* = 13.9, 8.2 Hz, 1H), 2.82 (dd, *J* = 13.9, 8.2 Hz, 1H), 1.85 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 142.2 (C), 139.3 (CH), 136.9 (C), 136.4 (C), 131.1 (C), 128.6 (CH), 127.9 (2 x CH), 127.6 (2 x CH), 127.2 (2 x CH), 126.7 (CH), 126.4 (CH), 125.7 (CH), 125.5 (2 x CH), 113.7 (CH_2), 70.4 (CH), 40.9 (CH_2), 15.8 (CH_3). **HRMS (APCI)** Calc. for $C_{21}H_{21}$ [M-H_2O+H$^+$]: 273.1614; found 273.1610.

3.4.3 Oxidation: Synthesis of 6-hydroxy-ketones



A solution of the corresponding borylated diene (0.2 mmol, 1 equiv) in 1 ml of THF and 1 ml of water was stirred in the presence of $NaBO_3·4H_2O$ (1.2 mmol, 6 equiv) over 16 hours. After this time, the reaction mixture was diluted in Et_2O and washed with brine. The organic layer was dried, filtered and the solvents were evaporated under vacuum. The final product was purified by SiO_2 column chromatography using Hexane / AcOEt (4:1) as eluent to afford the corresponding ketone.

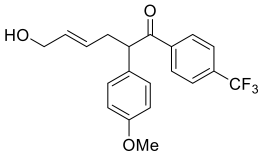
(*E*)-6-Hydroxy-1,2-di-p-tolylhex-4-en-1-one (4.26)



Obtained from diene **4.5** as a yellow oil (38.3 mg, 65% yield). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.87 (d, *J* = 8.1 Hz, 2H), 7.18 (d, *J* = 8.7 Hz, 4H), 7.10 (d, *J* = 8.1 Hz, 2H) 5.71 – 5.56 (m, 2H), 4.58 (t, *J* = 7.5 Hz, 1H), 4.03 (s, 2H), 3.02 – 2.87 (m, 1H), 2.60 – 2.54 (m, 1H), 2.36 (s, 3H), 2.29 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 198.8 (C), 143.7 (C), 136.7 (C), 136.2 (C), 134.1 (C), 131.1, 130.4 (CH), 129.6 (2 x CH), 129.2 (2 x CH), 128.9 (2 x CH), 128.0 (2 x CH), 63.6

(CH_2), 53.1 (CH), 36.6 (CH_2), 21.6 (CH_3), 21.0 (CH_3). **HRMS (APCI)** Calc. for $C_{20}H_{21}O$ [M-H_2O+H^+]: 277.1587; found 277.1587.

(*E*)-6-Hydroxy-2-(4-methoxyphenyl)-1-(4-(trifluoromethyl)phenyl)hex-4-en-1-one (4.42).



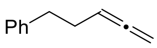
Synthesized from a 2:1 mixture of compounds **6** and **6'**. Formation of a 2:1 mixture of ketones **4.42** and **4.42'** was observed by NMR analysis of the reaction crude. After column chromatography, it was possible to isolate the pure major product **4.42** as a yellow oil in 22% yield (15.0 mg) (see section 9 for further information).

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.04 (d, *J* = 8.1 Hz, 2H), 7.67 (d, *J* = 8.2 Hz, 2H), 7.25 – 7.15 (m, 2H), 6.86 (d, *J* = 8.6 Hz, 2H), 5.67 (q, *J* = 4.9 Hz, 2H), 4.55 (t, *J* = 7.3 Hz, 1H), 4.06 (d, *J* = 4.2 Hz, 2H), 3.78 (s, 3H), 2.95 (dt, *J* = 13.2, 6.3 Hz, 1H), 2.57 (dt, *J* = 13.3, 6.2 Hz, 1H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 198.3 (C), 158.9 (C), 131.5 (CH), 130.2 (CH), 129.6 (CH), 129.2 (C), 128.9 (C), 125.6 (d, *J* = 3.8 Hz, 2 x CH), 114.6 (2 x CH), 63.5 (CH_2), 55.2 (CH_3), 53.4 (CH), 36.4 (CH_2). **^{19}F NMR** (282 MHz, $CDCl_3$) δ -63.22. **HRMS (APCI)** Calc. for $C_{20}H_{18}F_3O_2$ [M-H_2O+H^+]: 347.1253, found 347.1246.

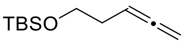
4. CHAPTER V

4.1 List of starting materials

Allenes **5.1-5.50-5.59**, allyl cyclic carbonates were synthesized following described procedures.



5.1



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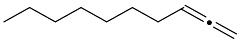
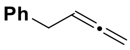


5.51



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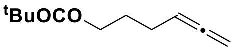
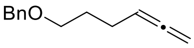


5.53



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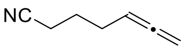

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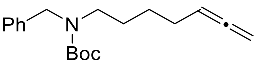
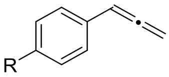
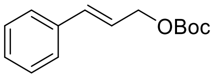


5.56

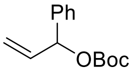


R= H, **5.57**
R= Br, **5.58**
R=^{t}Bu, **5.59**

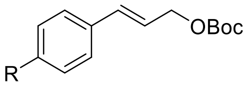
Allylic carbonates



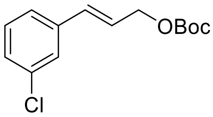
5.2



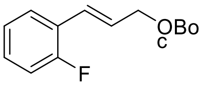
5.2'



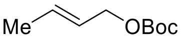
5.60 R= CF_3
5.61 R= OMe



5.62



5.63



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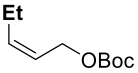
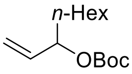
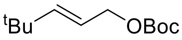


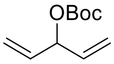
5.65



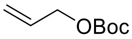
5.66



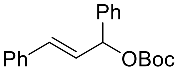
5.67



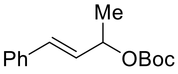
5.68



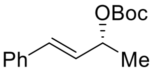
5.69



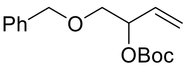
5.70



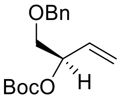
5.71



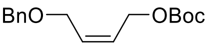
enant-5.71



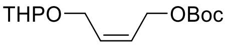
5.72



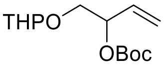
enant-5.72



5.73

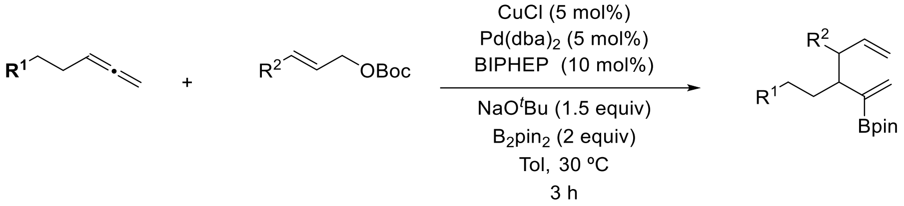


5.74



5.75

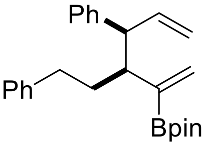
4.2 General procedure for the Cu/Pd catalyzed synthesis of 1, 5-borylated dienes.



In a Schlenk flask which contains B_2pin_2 (2 equiv, 0.8 mmol), NaO^tBu (1.5 equiv, 0.6 mmol), CuCl (5 mol%, 0.02 mmol), $Pd(dba)_2$ (5 mol%, 0.02 mmol) and BIPHEP (10 mol%, 0.04mmol) was added a solution of (0.3 mmol) in 2ml of dry toluene and **5.2** (1.5 equiv, 0.6 mmol) in 2 ml of dry toluene. The final solution was stirred at 30 °C during 3 hours. After this time, the final mixture was filtered through a small amount of silica and solvent was removed under vacuum. The final product was purified by silica gel column chromatography (80:20, Hexane : DCM).

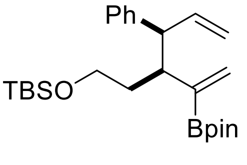
4.3 Compound characterization

4,4,5,5-tetramethyl-2-((3S,4S)-3-phenethyl-4-phenylhexa-1,5-dien-2-yl)-1,3,2-dioxaborolane (5.3).



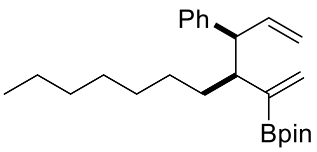
Synthesized from **5.1**, **5.2** and B_2pin_2 according to general procedure. Yellow oil obtained in 76% yield (>20:1 dr) after column chromatography (Hexane/CH_2Cl_2 4:1). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.38 – 7.13 (m, 10H), 6.14 – 5.93 (m, 1H), 5.84 (d, *J* = 3.4 Hz, 1H), 5.49 (d, *J* = 3.4 Hz, 1H), 5.18 – 5.06 (m, 2H), 3.61 (t, *J* = 9.7 Hz, 1H), 2.74 – 2.42 (m, 3H), 2.20 – 1.85 (m, 2H), 1.33 (s, 6H), 1.30 (s, 6H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 144.3, 143.2, 141.8, 132.1, 128.5, 128.4, 128.3, 128.2, 125.6, 83.1, 55.4, 51.0, 34.3, 34.2, 24.8, 24.7.**^{11}B NMR** (160 MHz, $CDCl_3$) δ 30.5, **HRMS (APCI)** Calc. for $C_{28}H_{34}BO_2$ [M+H$^+$]: 389.2646, found 389.2657.

Tert-butyldimethyl(((3S,4S)-4-phenyl-3-(1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)vinyl)hex-5-en-1-yl)oxy)silane (5.4).



Synthesized from **5.50**, **5.2** and B_2pin_2 according to general procedure. Yellow oil obtained in 73% yield (>20:1 dr) after column chromatography (Hexane/CH_2Cl_2 4:1). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.29 – 7.19 (m, 2H), 7.15 – 7.07 (m, 3H), 6.03 – 5.88 (m, 1H), 5.68 (d, *J* = 3.5 Hz, 1H), 5.39 (d, *J* = 3.5 Hz, 1H), 5.15 – 5.02 (m, 2H), 3.66 – 3.40 (m, 3H), 2.64 (td, *J* = 10.7, 3.1 Hz, 1H), 2.00 (dtd, *J* = 13.4, 8.0, 3.1 Hz, 1H), 1.80 – 1.62 (m, 1H), 1.25 (s, 6H), 1.21 (s, 6H), 0.92 (s, 9H), 0.05 (d, *J* = 1.9 Hz, 6H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 144.1, 141.7, 131.7, 128.3, 128.1, 125.7, 115.2, 83.0, 61.8, 54.9, 47.6, 34.9, 26.0, 24.8, 24.6, -5.2. **^{11}B NMR** (160 MHz, $CDCl_3$) δ 31.3, **HRMS (APCI)** Calc. for $C_{26}H_{44}BO_3Si$ [M+H$^+$]: 443.3147, found 443.3157.

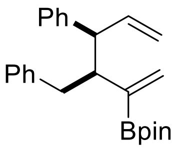
4,4,5,5-tetramethyl-2-(3-(1-phenylallyl)dec-1-en-2-yl)-1,3,2-dioxaborolane (5.6).



Synthesized from **5.51**, **5.2** and B_2pin_2 according to general procedure. Yellow oil obtained in 76% yield (>20:1 dr) after column chromatography (Hexane/CH_2Cl_2 4:1).

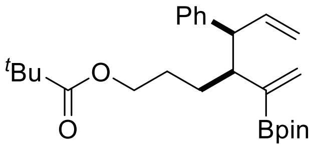
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30 – 7.19 (m, 2H), 7.16 – 7.08 (m, 3H), 5.98 (dtd, *J* = 17.0, 9.8, 2.3 Hz, 1H), 5.73 – 5.65 (m, 1H), 5.37 – 5.34 (m, 1H), 5.14 – 5.00 (m, 2H), 3.59 – 3.45 (m, 1H), 2.50 (ddd, *J* = 13.8, 9.6, 3.3 Hz, 1H), 1.29 (d, *J* = 6.2 Hz, 12H), 1.25 (s, 6H), 1.22 (s, 6H), 0.91 (t, *J* = 6.7, 3H).**^{13}C NMR** (75 MHz, $CDCl_3$) δ 144.5, 142.1, 131.3, 128.4, 128.0, 125.6, 114.9, 82.9, 55.4, 50.9, 32.1, 29.7, 29.6, 29.4, 24.8, 24.5, 22.7, 14.1. **^{11}B NMR** (160 MHz, $CDCl_3$) δ 30.5, **HRMS (APCI)** Calc. for $C_{25}H_{40}BO_2$[M+H$^+$]:, found 397.3299.

2-((3S,4S)-3-benzyl-4-phenylhexa-1,5-dien-2-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (5.7).



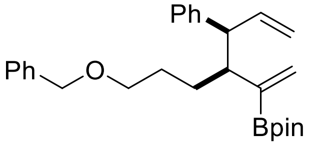
Synthesized from **5.52**, **5.2** and B_2pin_2 according to general procedure. Yellow oil obtained in 47% yield (>20:1 dr) after column chromatography (Hexane/CH_2Cl_2 4:1). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.30 – 7.10 (m, 10H), 6.22 – 6.03 (m, 1H), 5.61 – 5.53 (m, 1H), 5.30 – 5.10 (m, 3H), 3.68 (t, *J* = 9.7 Hz, 1H), 3.22 (d, *J* = 12.9, 1H), 2.96 – 2.64 (m, 2H), 1.25 (s, 6H), 1.23 (s, 6H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 143.9, 142.0, 141.6, 132.4, 129.4, 128.3, 128.2, 127.9, 125.8, 125.4, 115.5, 83.0, 55.4, 52.9, 39.2, 24.85, 24.62. **HRMS (APCI)** Calc. for $C_{25}H_{32}BO_2$ [M+H$^+$]: 375.2490, found 375.2504.

(4S,5S)-5-phenyl-4-(1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)vinyl)hept-6-en-1-yl pivalate (5.8)



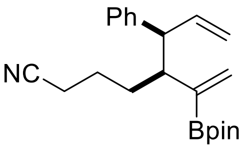
Synthesized from **5.53**, **5.2** and B_2pin_2 according to general procedure. Yellow oil obtained in 71% yield (>20:1 dr) after column chromatography (Hexane/CH_2Cl_2 4:1). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.20 (d, *J* = 7.2 Hz, 2H), 7.10 (dt, *J* = 6.2, 2.7 Hz, 3H), 5.94 (dt, *J* = 16.6, 9.6 Hz, 1H), 5.71 (d, *J* = 3.3 Hz, 1H), 5.39 (d, *J* = 3.3 Hz, 1H), 5.13 – 5.00 (m, 2H), 4.04 (t, *J* = 6.2 Hz, 2H), 3.51 (t, *J* = 9.8 Hz, 1H), 2.52 (td, *J* = 10.4, 3.2 Hz, 1H), 1.87 – 1.74 (m, 1H), 1.70 – 1.40 (m, 4H) , 1.24 (s, 9H), 1.21 (s, 12H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 178.6, 144.1, 141.7, 131.8, 128.3, 128.1, 125.7, 115.2, 83.1, 64.4, 55.3, 50.4, 28.3, 27.2, 26.9, 24.8, 24.6. **HRMS (APCI)** Calc. for $C_{26}H_{40}BO_4$ [M+H$^+$]: 427.3014, found 427.3029.

2-((3S,4S)-3-(3-(benzyloxy)propyl)-4-phenylhexa-1,5-dien-2-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (5.9).



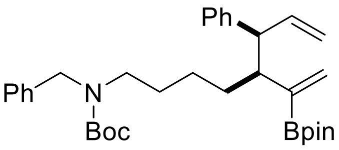
Synthesized from **5.54**, **5.2** and B_2pin_2 according to general procedure. Yellow oil obtained in 79% yield (>20:1 dr) after column chromatography (Hexane/CH_2Cl_2 4:1). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.42 – 7.23 (m, 7H), 7.18 – 7.11 (m, 3H), 6.01 (dt, *J* = 17.0, 9.6 Hz, 1H), 5.74 (d, *J* = 3.4 Hz, 1H), 5.41 (d, *J* = 3.4 Hz, 1H), 5.20 – 5.03 (m, 2H), 4.54 (s, 1H), 3.61 – 3.48 (m, 3H), 2.56 (td, *J* = 10.4, 3.3 Hz, 1H), 1.94 – 1.83 (m, 1H), 1.71 – 1.50 (m, 3H), 1.27 (s, 6H), 1.24 (s, 6H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 144.3, 141.9, 138.9, 128.4, 128.3, 128.1, 127.6, 127.4, 125.7, 115.1, 83.0, 72.7, 70.5, 55.5, 50.7, 28.5, 27.9, 24.9, 24.61. **^{11}B NMR** (160 MHz, $CDCl_3$) δ 31.70 **HRMS (APCI)** Calc. for $C_{28}H_{38}BO_3$ [M+H$^+$]: 433.2909, found 433.2917.

(5S,6S)-6-phenyl-5-(1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)vinyl)oct-7-enenitrile (5.10).



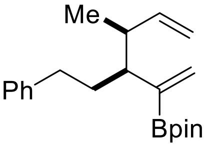
Synthesized from **5.55**, **5.2** and B$_2$pin$_2$ according to general procedure. Yellow oil obtained in 71% yield (>20:1 dr) after column chromatography (Hexane/CH$_2$Cl$_2$ 4:1). **^{1}H NMR** (300 MHz, CDCl$_3$) δ 7.27 – 7.19 (m, 3H), 7.10 (dd, *J* = 7.9, 1.4 Hz, 2H), 5.96 (dt, *J* = 17.0, 9.8 Hz, 1H), 5.72 (d, *J* = 3.2 Hz, 1H), 5.40 (d, *J* = 3.3 Hz, 1H), 5.16 – 5.04 (m, 2H), 3.50 (t, *J* = 9.8 Hz, 1H), 2.51 (td, *J* = 10.4, 3.3 Hz, 1H), 2.44 – 2.20 (m, 2H), 1.92 – 1.45 (m, 4H), 1.25 (s, 6H), 1.22 (s, 6H). **^{13}C NMR** (75 MHz, CDCl$_3$) **^{11}B NMR** (160 MHz, CDCl$_3$) δ 31.1 **HRMS (APCI)** Calc. for C$_{22}$H$_{31}$BNO$_2$ [M+H$^+$]: 352.2442, found 352.2453.

tert-butyl benzyl((5S,6S)-6-phenyl-5-(1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)vinyl)oct-7-en-1-yl)carbamate (5.11)



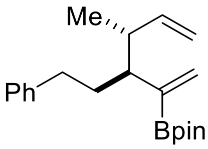
Synthesized from **5.56**, **5.2** and B$_2$pin$_2$ according to general procedure. Yellow oil obtained in 56% yield (>20:1 dr) after column chromatography (Hexane/CH$_2$Cl$_2$ 4:1). **^{1}H NMR** (300 MHz, CDCl$_3$) δ 7.37 – 7.17 (m, 5H), 7.14 – 7.07 (m, 3H), 5.94 (dt, *J* = 17.0, 9.7 Hz, 1H), 5.66 (d, *J* = 3.4 Hz, 1H), 5.33 (d, *J* = 3.5 Hz, 1H), 5.11 – 4.99 (m, 2H), 4.43 (bs, 2H), 3.47 (t, *J* = 9.8 Hz, 1H), 3.12 (bs, 2H), 2.45 (td, *J* = 10.6, 3.4 Hz, 1H), 1.48 (s, 15H), 1.23 (s, 6H), 1.19 (s, 6H). **^{13}C NMR** (75 MHz, CDCl$_3$) δ 144.3, 141.9, 131.5, 128.4, 128.3, 128.1, 127.0, 125.7, 115.0, 82.9, 79.4, 55.4, 31.7, 28.5, 25.0, 24.8, 24.5. **^{11}B NMR** (160 MHz, CDCl$_3$) δ 30.4 **HRMS (APCI)** Calc. for C$_{34}$H$_{49}$BNO$_4$ [M+H$^+$]: 546.3749, found 546.3760.

4,4,5,5-tetramethyl-2-((3S,4S)-4-methyl-3-phenethylhexa-1,5-dien-2-yl)-1,3,2-dioxaborolane (5.18) + 4,4,5,5-tetramethyl-2-((3S,4R)-4-methyl-3-phenethylhexa-1,5-dien-2-yl)-1,3,2-dioxaborolane (5.18’).



5.19

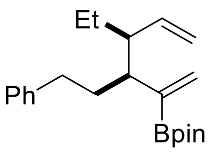
+



5.19'

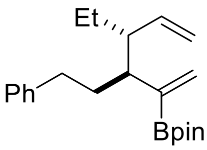
Synthesized from **5.1**, **5.64** and B$_2$pin$_2$ according to general procedure. Yellow oil obtained in 76% yield (1.5:1 dr) after column chromatography (Hexane/CH$_2$Cl$_2$ 4:1). **^{1}H NMR** (300 MHz, CDCl$_3$) δ 7.32 – 7.11 (m, 5H **5.18**+ 5H **5.18’**), 5.96 (bs, 1H **5.18** + 1H **5.18’**), 5.74 – 5.54 (m, 2H **5.18** + 2H **5.18’**), 5.02 – 4.85 (m, 2H **5.18**+ 2H **5.18’**), 2.68 – 2.51 (m, 1H **5.18** +1H **5.18’**), 2.43 – 2.26 (m, 2H **5.18** +2H **5.18’**), 2.05 – 1.73 (m, 3H **5.18** + 3H **5.18’**), 1.29 (s, 12H **5.18** + **5.18’**), 0.99 (d, *J* = 6.9 Hz, 3H **5.18’**), 0.89 (d, *J* = 6.9, 3H **5.18**).**^{13}C NMR** (75 MHz, CDCl$_3$) δ 144.2 (**5.18**), 143.9 (**5.18’**), 143.4 (**5.18** + **5.18’**), 130.8 (**5.18**), 130.6 (**5.18’**), 128.4 (**5.18** + **5.18’**), 128.2 (**5.18’**), 128.1 (**5.18**), 125.4 (**5.18’**), 125.3 (**5.18**) 113.5 (**5.18**), 112.8 (**5.18’**), 83.1 (**5.18** + **5.18’**), 51.8 (**5.18**), 51.3 (**5.18’**), 42.1 (**5.18**), 41.8 (**5.18’**), 34.3 (**5.18’**), 34.4 (**5.18**) 33.8 (**5.18**), 32.9 (**5.18’**), 24.7 (**5.18**), 24.7 (**5.18’**), 19.2 (**5.18**), 17.9 (**5.18’**). **^{11}B NMR** (160 MHz, CDCl$_3$) δ 31.1 **HRMS (APCI)** Calc. for C$_{21}$H$_{32}$BO$_2$ [M+H$^+$]: 327.2490, found 327.2494.

2-((3S,4S)-4-ethyl-3-phenethylhexa-1,5-dien-2-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (5.19) + 2-((3S,4R)-4-ethyl-3-phenethylhexa-1,5-dien-2-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (5.19')



5.20

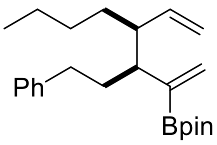
+



5.20'

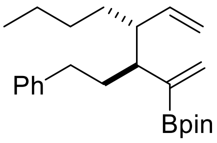
Synthesized from **5.1**, **5.65** and B_2pin_2 according to general procedure. Yellow oil obtained in 73% yield (3:1 dr) after column chromatography (Hexane/CH_2Cl_2 4:1). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.34 – 7.15 (m, 5H, **5. 19** + **5. 19'**), 5.99 (d, *J* = 3.6 Hz, 1H, **5. 19**), 5.93 (d, *J* = 3.5 Hz, 1H, **5. 19'**), 5.63 (d, *J* = 3.5 Hz, 1H, **5. 19**), 5.59 (d, *J* = 3.6 Hz, 1H, **5. 19'**), 5.57 – 5.37 (m, 1H **5. 19** +**5. 19'**), 5.10 – 4.94 (m, 2H, **5. 19** + **5. 19'**), 2.70 – 2.17 (m, 4H **5. 19** + **5. 19'**), 2.15 – 1.73 (m, 4H, **5. 19** + **5. 19'**), 1.32 (s, 12H **5. 19** + **5. 19**), 0.99 (t, *J* = 7.4 Hz, 3H, **5. 19**), 0.82 (t, *J* = 7.3 Hz, 3H, **5. 19**). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 143.4, 143.3, 142.1, 141.7, 133.1, 130.8, 130.5, 129.6, 128.5, 128.2, 128.1, 127.9, 125.5, 125.4, 115.7, 114.9, 83.1, 50.5, 50.2, 50.1, 49.8, 38.0, 35.6, 34.2, 33.8, 25.7, 24.8, 24.7, 14.1, 11.9, 11.6. **^{11}B NMR** (160 MHz, $CDCl_3$) δ 31.1

4,4,5,5-tetramethyl-2-((3S,4S)-3-phenethyl-4-vinyloct-1-en-2-yl)-1,3,2-dioxaborolane (5.20) + 4,4,5,5-tetramethyl-2-((3S,4R)-3-phenethyl-4-vinyloct-1-en-2-yl)-1,3,2-dioxaborolane (5.20')



5.20

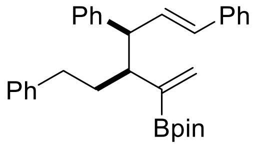
+



5.20'

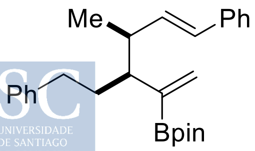
Synthesized from **5.1**, **5.66** and B_2pin_2 according to general procedure at 60 °C . Yellow oil obtained in 74% yield (3:1 dr) after column chromatography (Hexane/CH_2Cl_2 4:1). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.33 – 7.25 (m, 2H **5.20** + **5.20'**), 7.24 – 7.15 (m, 3H **5.20**+ **5.20'**), 5.99 (d, *J* = 3.6 Hz, 1H **5.20**), 5.93 (d, *J* = 3.5 Hz, 1H **5.20'**), 5.63 (d, *J* = 3.5 Hz, 1H **5.20**), 5.59 (d, *J* = 3.5 Hz, 1H, **5.20'**), 5.56 – 5.35 (m, 1H **5.20** + **5.20'**), 5.07 – 4.87 (m, 1H **5.20** + **5.20'**), 2.70 – 1.73 (m, 6H **5.20** + **5.20'**), 1.32 (d, *J* = 1.4 Hz, 12H **5.20** + **5.20'**), 0.96 – 0.85 (m, 3H **5.20** + **5.20'**). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 143.4, 143.4, 143.3, 142.5, 141.9, 131.5, 130.9, 130.5, 129.6, 128.9, 128.5, 128.4, 128.2, 128.1, 125.4, 125.4, 115.4, 114.7, 83.1, 50.8, 49.9, 48.2, 46.2, 38.0, 35.62, 34.39, 34.3, 33.9, 33.7, 33.7, 32.6, 32.3, 32.1, 31.8, 29.7, 29.5, 24.8, 24.7, 24.69, 22.86, 22.64, 14.14, 13.9.

(E)-4,4,5,5-tetramethyl-2-(3-phenethyl-4,6-diphenylhexa-1,5-dien-2-yl)-1,3,2-dioxaborolane (5.21)

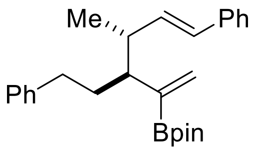


Synthesized from **5.1**, **5.70** and B_2pin_2 according to general procedure at 60 °C. Yellow oil obtained in 70% yield (1:1.5 dr) after column chromatography (Hexane/CH_2Cl_2 4:1).

4,4,5,5-tetramethyl-2-((3S,4S,E)-4-methyl-3-phenethyl-6-phenylhexa-1,5-dien-2-yl)-1,3,2-dioxaborolane (5.22) + 4,4,5,5-tetramethyl-2-((3S,4R,E)-4-methyl-3-phenethyl-6-phenylhexa-1,5-dien-2-yl)-1,3,2-dioxaborolane (5.22')



5.22

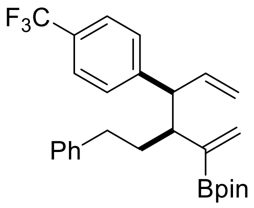


5.22'

Synthesized from **5.1**, **5.71** and B_2pin_2 according to general procedure at 60 °C . Yellow oil obtained in 71% yield (1:1 dr) after column chromatography (Hexane/CH_2Cl_2 4:1). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.39 – 7.08 (m, 20H

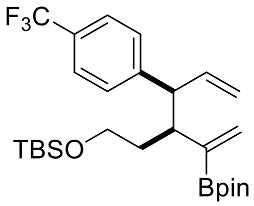
5.22 + **5.22’**), 6.35 (d, *J* = 15.8 Hz, 1H, **5.22**), 6.27 (d, *J* = 15.9 Hz, 1H, **5.22’**), 6.14 – 6.01 (m, 2H **5.22** +**5.22’**), 5.99 (d, *J* = 3.7 Hz 1H, **5.22**), 5.97 (d, *J* = 4.1 Hz, 1H, **5.22’**), 5.64 (d, *J* = 3.7 Hz, 1H, **5.22**), 5.61 (d, *J* = 3.6 Hz, 1H, **5.22**), 2.70 – 1.77 (m, 12H **5.22** +**5.22’**), 1.28 (d, 12H, **5.22**) 1.25 (d, *J* = 3.8 Hz 12H, **5.22’**), 1.07 (d, *J* = 6.7 Hz, 3H, **5.22**), 0.97 (d, *J* = 6.7 Hz, 3H, **5.22’**). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 143.3, 143.3, 138.2, 138.1, 136.3, 136.1, 131.2, 131.1, 129.1, 128.5, 128.5, 128.5, 128.4, 128.3, 128.2, 126.7, 126.6, 126.1, 125.5, 125.5, 83.2, 83.2, 52.3, 51.6, 41.6, 41.3, 34.4, 34.4, 34.0, 33.4, 24.9, 24.8, 24.8, 24.7, 24.7, 19.71, 18.58. **^{11}B NMR** (160 MHz, $CDCl_3$) δ 30.5 **HRMS (APCI)** Calc. for $C_{27}H_{36}BO2$ [$M+H^+$]: 403.2803, found 403.2814.

4,4,5,5-tetramethyl-2-((3S,4S)-3-phenethyl-4-(4-(trifluoromethyl)phenyl)hexa-1,5-dien-2-yl)-1,3,2-dioxaborolane (5.23).



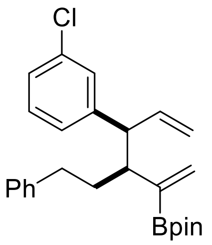
Synthesized from **5.1**, **5.60** and B_2pin_2 according to general procedure. Yellow oil obtained in 80% yield (>20:1 dr) after column chromatography (Hexane/CH_2Cl_2 4:1). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.47 (d, *J* = 8.0 Hz, 2H), 7.33 – 7.12 (m, 7H), 5.90 (dt, *J* = 17.0, 9.7 Hz, 1H), 5.78 (d, *J* = 3.3 Hz, 1H), 5.44 (d, *J* = 3.3 Hz, 1H), 5.14 – 5.00 (m, 2H), 3.59 (t, *J* = 9.8 Hz, 1H), 2.70 – 2.32 (m, 2H), 2.12 – 1.75 (m, 2H), 1.23 (d, *J* = 8.8 Hz, 12H). **^{19}F NMR** (282 MHz, $CDCl_3$) δ -62.05. **^{11}B NMR** (160 MHz, $CDCl_3$) δ 31.70 **HRMS (APCI)** Calc. for $C_{27}H_{33}BF_3O2$ [$M+H^+$]: 457.2520, found 457.2522.

tert-butyldimethyl(((3S,4S)-3-(1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)vinyl)-4-(4-(trifluoromethyl)phenyl)hex-5-en-1-yl)oxy)silane (5.24).



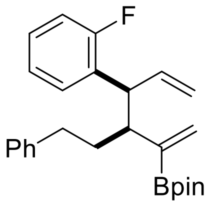
Synthesized from **5.50**, **5.60** and B_2pin_2 according to general procedure. Yellow oil obtained in 80% yield (>20:1 dr) after column chromatography (Hexane/CH_2Cl_2 4:1). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.48 (d, *J* = 8.6 Hz, 2H), 7.23 (d, *J* = 7.9 Hz, 2H), 5.94 (ddd, *J* = 16.9, 10.1, 9.1 Hz, 1H), 5.71 (d, *J* = 3.4 Hz, 1H), 5.42 (d, *J* = 3.4 Hz, 1H), 5.17 – 5.06 (m, 2H), 3.67 – 3.42 (m, 3H), 2.68 (td, *J* = 10.8, 3.0 Hz, 1H), 2.08 – 1.63 (m, 2H), 1.24 (s, 6H), 1.21 (s, 6H), 0.95 – 0.90 (s, 9H), 0.05 (d, *J* = 2.0 Hz, 6H). **^{11}B NMR** (160 MHz, $CDCl_3$) δ 30.2 **^{19}F NMR** (282 MHz, $CDCl_3$) δ -62.07.

2-((3S,4S)-4-(3-chlorophenyl)-3-phenethylhexa-1,5-dien-2-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (5.25)



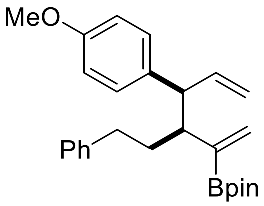
Synthesized from **5.1**, **5.62** and B_2pin_2 according to general procedure. Yellow oil obtained in 71% yield (>20:1 dr) after column chromatography (Hexane/CH_2Cl_2 4:1). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.34 – 7.25 (m, 2H), 7.23 – 7.07 (m, 7H), 6.96 (d, *J* = 7.4 Hz, 1H), 5.88 (dt, *J* = 16.7, 9.6 Hz, 1H), 5.77 (d, *J* = 3.3 Hz, 1H), 5.43 (d, *J* = 3.4 Hz, 1H), 5.12 – 5.01 (m, 2H), 3.52 (t, *J* = 9.9 Hz, 1H), 2.70 – 2.33 (m, 3H), 2.05 (dtd, *J* = 13.9, 6.9, 3.4 Hz, 1H), 1.81 (qd, *J* = 11.3, 4.9 Hz, 1H), 1.26 (d, *J* = 10.6 Hz, 12H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 146.7, 143.3, 141.3, 134.1, 132.8, 129.7, 128.9, 128.8, 128.6, 126.7, 126.2, 125.9, 116.2, 83.5, 55.3, 34.4, 25.2, 24.9. **^{11}B NMR** (160 MHz, $CDCl_3$) δ 31.50. **HRMS (APCI)** Calc. for $C_{26}H_{33}BClO_2$ [$M+H^+$]: 423.2257, found 423.2272.

2-(4-(2-fluorophenyl)-3-phenethylhexa-1,5-dien-2-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (5.26).



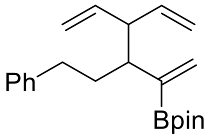
Synthesized from **5.1**, **5.63** and B_2pin_2 according to general procedure. Yellow oil obtained in 67% yield (>20:1 dr) after column chromatography (Hexane/CH_2Cl_2 4:1). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.35 – 7.23 (m, 2H), 7.23 – 7.02 (m, 5H), 7.04 – 6.84 (m, 2H), 6.08 – 5.90 (m, 1H), 5.74 (d, *J* = 3.3 Hz, 1H), 5.49 (d, *J* = 3.6 Hz, 1H), 5.17 – 4.98 (m, 2H), 3.79 (t, *J* = 10.0 Hz, 1H), 2.73 – 2.53 (m, 2H), 2.48 – 2.32 (m, 1H), 2.12 – 1.80 (m, 2H), 1.24 (d, *J* = 10.5, 12H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 143.2, 140.1, 132.1, 130.1 (d, *J* = 5.8 Hz), 128.4, 128.2, 127.3 (d, *J* = 8.4 Hz), 125.5, 123.6 (d, *J* = 3.2 Hz), 116.0, 115.5, 115.2, 83.1, 49.8 (d, *J* = 16.8 Hz), 34.3, 24.9, 24.5. **^{11}B NMR** (160 MHz, $CDCl_3$) δ 31.30 **^{19}F NMR** (282 MHz, cdcl$_3$) δ -116.13.

2-(4-(4-methoxyphenyl)-3-phenethylhexa-1,5-dien-2-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (5.27).



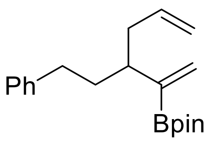
Synthesized from **5.1**, **5.61** and B_2pin_2 according to general procedure. Yellow oil obtained in 78% yield (>20:1 dr) after column chromatography (Hexane/CH_2Cl_2 4:1). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.27 (d, *J* = 7.1 Hz, 3H), 7.17 (d, *J* = 7.6 Hz, 3H), 7.06 – 6.97 (m, 2H), 6.81 – 6.72 (m, 2H), 5.92 (dt, *J* = 16.9, 9.5 Hz, 1H), 5.77 (d, *J* = 3.5 Hz, 1H), 5.42 (d, *J* = 3.4 Hz, 1H), 5.11 – 4.95 (m, 2H), 3.77 (s, 2H), 3.49 (t, *J* = 9.8 Hz, 1H), 2.76 – 2.33 (m, 3H), 2.11 – 1.79 (m, 2H), 1.26 (d, *J* = 8.6 Hz, 12H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 157.9, 143.5, 142.3, 136.7, 132.3, 129.5, 128.8, 125.8, 115.2, 113.9, 83.4, 55.4, 54.7, 51.4, 34.6, 34.5, 25.2, 24.9. **^{11}B NMR** (160 MHz, $CDCl_3$) δ 31.70 **HRMS (APCI)** Calc. for $C_{27}H_{36}BO_3$ [M+H$^+$]: 419.2752, found 419.2755.

4,4,5,5-tetramethyl-2-(3-phenethyl-4-vinylhexa-1,5-dien-2-yl)-1,3,2-dioxaborolane (5.28).



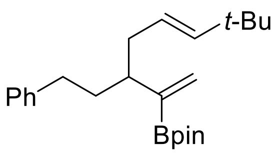
Synthesized from **5.1**, **5.68** and B_2pin_2 according to general procedure. Yellow oil obtained in 73% yield after column chromatography (Hexane/CH_2Cl_2 4:1). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.34 – 7.27 (m, 2H), 7.23 – 7.17 (m, 3H), 6.01 (d, *J* = 3.5 Hz, 1H), 5.71 (m, 2H), 5.63 (d, *J* = 3.5 Hz, 1H), 5.11 – 5.02 (m, 2H), 5.02 – 4.94 (m, 2H), 3.00 (q, *J* = 8.5 Hz, 1H), 2.65 (ddd, *J* = 13.4, 9.9, 5.6 Hz, 1H), 2.48 – 2.21 (m, 2H), 1.96 – 1.85 (m, 2H), 1.32 (d, *J* = 2.0 Hz, 12H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 143.2, 140.8, 140.4, 131.2, 128.5, 128.2, 125.5, 115.3, 114.4, 83.1, 52.9, 50.2, 34.1, 33.4, 24.9, 24.7. **^{11}B NMR** (160 MHz, $CDCl_3$) δ 30.90 **HRMS (APCI)** Calc. for $C_{22}H_{32}BO_2$ [M+H$^+$]: 339.2490, found 339.2493.

4,4,5,5-tetramethyl-2-(3-phenethylhexa-1,5-dien-2-yl)-1,3,2-dioxaborolane (5.29).



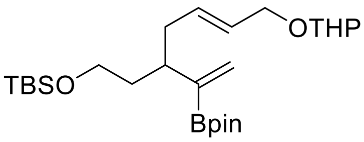
Synthesized from **5.1**, **5.69** and B_2pin_2 according to general procedure. Yellow oil obtained in 78% yield after column chromatography (Hexane/CH_2Cl_2 4:1). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.30 – 7.22 (m, 2H), 7.20 – 7.13 (m, 2H), 5.90 (d, *J* = 3.4 Hz, 1H), 5.72 (ddt, *J* = 16.8, 10.2, 6.7 Hz, 1H), 5.60 (d, *J* = 3.4 Hz, 1H), 5.02 – 4.91 (m, 2H), 2.67 – 2.39 (m, 2H), 2.27 (td, *J* = 9.8, 6.1 Hz, 3H), 1.92 – 1.71 (m, 2H), 1.28 (s, 12H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 143.5, 138.1, 130.1, 128.7, 128.5, 125.8, 115.6, 83.5, 46.1, 39.6, 36.0, 34.2, 25.0. **^{11}B NMR** (160 MHz, $CDCl_3$) δ 31.50.

(E)-2-(7,7-dimethyl-3-phenethylocta-1,5-dien-2-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (5.30).



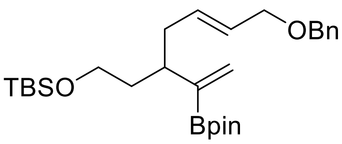
Synthesized from **5.1**, **5.67** and B$_2$pin$_2$ according to general procedure. Yellow oil obtained in 50% yield after column chromatography (Hexane/CH$_2$Cl$_2$ 4:1). **^{1}H NMR** (300 MHz, CDCl$_3$) δ 7.34 – 7.22 (m, 2H), 7.22 – 7.14 (m, 3H), 5.91 (d, *J* = 3.5 Hz, 1H), 5.60 (d, *J* = 3.6 Hz, 1H), 5.44 (dd, *J* = 15.7, 3.3 Hz, 1H), 5.26 (dt, *J* = 16.3, 5.8 Hz, 1H), 2.68 – 2.43 (m, 2H), 2.31 – 2.12 (m, 3H), 1.89 – 1.75 (m, 2H), 1.35 – 1.25 (m, 12H), 1.05 – 0.94 (m, 9H). **^{13}C NMR** (75 MHz, CDCl$_3$) δ 143.3, 142.7, 129.6, 128.4, 128.2, 125.4, 123.4, 83.1, 46.2, 37.8, 35.4, 33.9, 32.8, 29.9, 24.8. **^{11}B NMR** (160 MHz, CDCl$_3$) δ 30.2 **HRMS (APCI)** Calc. for C$_{24}$H$_{38}$BO$_2$ [M+H$^+$]: 369.2959, found 369.2973

(E)-tert-butyldimethyl((7-((tetrahydro-2H-pyran-2-yl)oxy)-3-(1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)vinyl)hept-5-en-1-yl)oxy)silane (5.31)



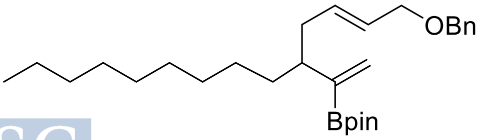
Synthesized from **5.50**, **5.74** and B$_2$pin$_2$ according to general procedure. Yellow oil obtained in 43% yield after column chromatography (Hexane/CH$_2$Cl$_2$ 4:1). **^{1}H NMR** (300 MHz, CDCl$_3$) δ 5.81 (d, *J* = 3.5 Hz, 1H), 5.68 – 5.47 (m, 3H), 4.62 (dd, *J* = 4.4, 2.8 Hz, 1H), 4.20 – 4.12 (m, 1H), 3.97 – 3.83 (m, 2H), 3.66 – 3.44 (m, 3H), 2.51 – 2.13 (m, 3H), 1.92 – 1.46 (m, 9H), 1.25 (s, 12H), 0.90 (s, 9H), 0.07 – 0.03 (s, 6H). **^{13}C NMR** (75 MHz, CDCl$_3$) δ 133.8, 133.6, 129.9, 129.8, 127.2, 127.2, 97.7, 97.5, 83.2, 67.9, 67.8, 62.4, 61.8, 42.9, 42.8, 37.8, 37.7, 36.9, 36.8, 30.8, 26.2, 26.1, 25.7, 24.9, 24.9, 24.9, 19.7, 18.5, -5.1. **^{11}B NMR** (160 MHz, CDCl$_3$) δ 30.30

(E)-((7-(benzyloxy)-3-(1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)vinyl)hept-5-en-1-yl)oxy)(tert-butyl)dimethylsilane (5.32).



Synthesized from **5.50**, **5.73** and B$_2$pin$_2$ according to general procedure. Yellow oil obtained in 64% yield after column chromatography (Hexane/CH$_2$Cl$_2$ 4:1). **^{1}H NMR** (300 MHz, CDCl$_3$) δ 7.37 – 7.28 (m, 4H), 5.85 (d, *J* = 3.5 Hz, 1H), 5.70 – 5.51 (m, 2H), 4.49 (s, 2H), 4.00 – 3.96 (m, 2H), 3.66 – 3.49 (m, 2H), 2.42 – 2.19 (m, 3H), 1.73 (tdt, *J* = 11.3, 7.6, 4.2 Hz, 2H), 1.27 (d, *J* = 1.0 Hz, 13H), 0.91 (s, 8H), 0.05 (s, 6H). **^{13}C NMR** (75 MHz, CDCl$_3$) δ 138.6, 133.9, 128.3, 127.8, 127.4, 127.2, 83.1, 71.5, 70.9, 61.6, 42.8, 37.7, 36.8, 26.0, 24.8, 24.7, 18.3, -5.2. **^{11}B NMR** (160 MHz, CDCl$_3$) δ 31.20 **HRMS (APCI)** Calc. for C$_{28}$H$_{48}$BO$_4$Si [M+H$^+$]: 487.3409, found 487.3425

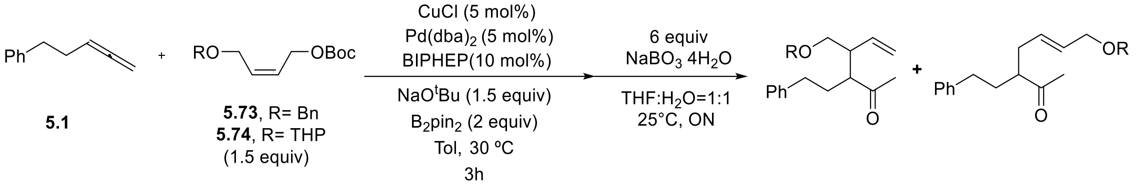
(E)-2-(3-(4-(benzyloxy)but-2-en-1-yl)dodec-1-en-2-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (5.33).



Synthesized from **5.51**, **5.73** and B$_2$pin$_2$ according to general procedure. Yellow oil obtained in 75% yield after column chromatography (Hexane/CH$_2$Cl$_2$ 4:1). **^{1}H NMR** (300 MHz, CDCl$_3$) δ 7.40 – 7.27 (m, 5H), 5.85 (d, *J* = 3.5 Hz, 1H), 5.67 – 5.53 (m, 2H), 4.50 (s, 2H), 3.99 (d, *J* = 5.4 Hz, 2H), 2.34 – 2.19 (m, 3H), 1.46 (dt, *J* = 11.0, 5.1 Hz, 2H), 1.28 (s, 24H), 0.94 – 0.87 (t, *J* = 7.04 Hz, 3H). **^{13}C NMR** (75 MHz, CDCl$_3$) δ 138.6, 134.3, 129.3, 128.3, 127.8, 127.5, 126.9, 83.1, 71.5, 70.9, 46.0, 37.6, 33.9, 31.9, 29.8, 29.6, 29.3, 27.5, 24.8, 24.7, 22.7, 14.1. **^{11}B NMR** (160 MHz, $CDCl_3$) δ 31.60 **HRMS (APCI)** Calc. for $C_{28}H_{46}BO_3$ [$M+H^+$]: 441.3535, found 441.3547.

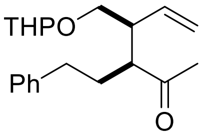
4.3.1 Use of linear α-functionalized allyl carbonates

As was explain in chapter V, the use of linear functionalized allyl carbonates, gave rise to regioisomeric mixtures. To better analyzed the mixture of products, an oxidation was carried out to obtain the corresponding ketones, as is shown below.



For that, a solution of the corresponding mixture of borylated dienes (0.2 mmol, 1 equiv) in 1 ml of THF and 1 ml of water was stirred in the presence of $NaBO_3{\cdot}4H_2O$ (1.2 mmol, 6 equiv) over 16 hours. After this time, the reaction mixture was diluted in Et_2O and washed with brine. The organic layer was dried, filtered and the solvents were evaporated under vacuum. The final product was purified by SiO_2 column chromatography using Hexane / AcOEt (4:1) as eluent to afford the corresponding ketone.

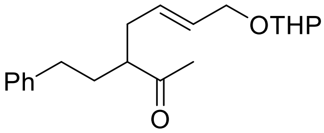
(3S,4S)-3-phenethyl-4-(((tetrahydro-2H-pyran-2-yl)oxy)methyl)hex-5-en-2-one (5.34’).



Synthesized from a regioisomeric (3:1) mixuture of **5.34** (6:1, dr) and **5.35** in 6:1 diastereomeric ratio.

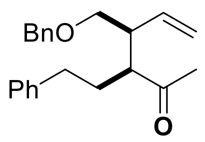
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30 – 7.23 (m, 2H), 7.22 – 7.10 (m, 3H), 5.71 – 5.51 (m, 1H), 5.15 – 5.07 (m, 2H), 4.55 – 4.44 (m, 1H), 3.86 – 3.61 (m, 3H), 3.55 – 3.33 (m, 3H), 2.77 – 2.37 (m, 3H), 2.19 (d, *J* = 1.9 Hz, 3H), 1.94 – 1.48 (m, 8H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 211.6, 211.4 141.8, 141.7, 136.6, 136.5, 128.4, 125.9, 117.79, 117.7, 117.0, 99.2, 98.7, 69.5, 69.0, 62.3, 62.1, 53.8, 53.4, 46.2, 33.5, 33.4, 25.4, 19.5, 19.3.

(E)-3-phenethyl-7-((tetrahydro-2H-pyran-2-yl)oxy)hept-5-en-2-one (5.35)



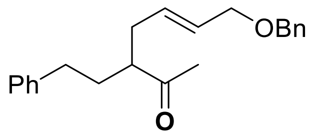
Synthesized from a regioisomeric (3:1) mixuture of **5.34** (6:1, dr) and **5.35.** **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.32 – 7.24 (m, 2H), 7.23 – 7.08 (m, 3H), 5.62 (ddd, *J* = 5.9, 3.6, 2.1 Hz, 2H), 4.60 (d, *J* = 4.4 Hz, 1H), 4.23 – 4.11 (m, 1H), 3.97 – 3.81 (m, 2H), 3.50 (dt, *J* = 10.6, 4.7 Hz, 1H), 2.57 (dt, *J* = 9.3, 6.4 Hz, 3H), 2.39 (dd, *J* = 15.4, 5.7 Hz, 1H), 2.30 – 2.17 (m, 1H), 2.12 (d, *J* = 1.1 Hz, 3H), 2.04 – 1.90 (m, 1H), 1.87 – 1.69 (m, 3H), 1.65 – 1.49 (m, 4H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 211.4 (C), 141.5 (C), 130.3 (CH), 128.9 (CH), 128.4 (2 x CH), 128.3 (2 x CH), 126.0 (CH), 97.8 (CH), 67.4 (CH_2), 62.3 (CH_2), 51.9 (CH), 34.2 (CH_2), 33.4 (CH_2), 32.5 (CH_2), 30.6 (CH_2), 29.3 (CH_3), 25.4 (CH_2), 19.5 (CH_2).

(3S,4S)-4-((benzyloxy)methyl)-3-phenethylhex-5-en-2-one (5.36’).



Synthesized from a regioisomeric (1:1) mixuture of **5.36** (4:1, dr) and **5.37**. **^{1}H NMR** (300 MHz, CDCl$_3$) δ 7.38 – 7.23 (m, 7H), 7.21 – 7.10 (m, 3H), 5.63 (ddd, *J* = 16.4, 10.4, 8.4 Hz, 1H), 5.16 – 5.06 (m, 2H), 4.44 (s, 2H), 3.42 (qd, *J* = 9.4, 4.9 Hz, 2H), 2.78 – 2.66 (m, 2H), 2.64 – 2.38 (m, 2H), 2.14 (d, *J* = 1.6 Hz, 3H), 1.98 – 1.71 (m, 1H). **^{13}C NMR** (75 MHz, CDCl$_3$) δ 211.6 (C), 141.7 (C), 138.1 (C), 136.7 (CH), 128.4 (CH), 127.7 (CH), 127.6 (CH), 125.9 (CH), 117.7 (CH), 73.1 (CH), 72.2 (CH), 53.3 (CH$_2$), 46.3 (CH$_2$), 33.5 (CH), 30.8 (CH$_3$), 30.3 (CH$_2$). **HRMS (APCI)** Calc. for $C_{22}H_{27}O_2$ [M+H$^+$]: 323.2006, found 323.2005.

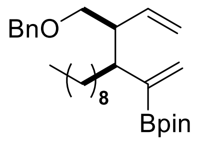
(E)-7-(benzyloxy)-3-phenethylhept-5-en-2-one (5.37’).



Synthesized from a regioisomeric (1:1) mixuture of **5.36** (4:1, dr) and **5.37.** **^{1}H NMR** (300 MHz, CDCl$_3$) δ 7.37 – 7.13 (m, 10H), 5.63 (td, *J* = 5.0, 3.1 Hz, 2H), 4.49 (s, 2H), 3.97 (d, *J* = 4.0 Hz, 2H), 2.60 (qd, *J* = 8.4, 5.9 Hz, 3H), 2.46 – 2.34 (m, 1H), 2.27 (q, *J* = 6.9 Hz, 1H), 2.13 (s, 3H), 1.99 (dtd, *J* = 17.1, 8.6, 6.5 Hz, 1H), 1.82 – 1.69 (m, 1H). **^{13}C NMR** (75 MHz, CDCl$_3$) δ 211.3 (C), 141.5 (C), 138.3 (C), 130.5 (CH), 129.0 (CH), 128.4 (2 x CH), 128.4 (2 x CH), 128.3 (2 x CH), 127.7 (2 x CH), 127.6 (CH), 126.0 (CH), 71.9 (CH$_2$), 70.4 (CH$_2$), 51.9 (CH), 34.2 (CH$_2$), 33.4 (CH$_2$), 32.5 (CH$_2$), 29.22 (CH$_3$). **HRMS (APCI)** Calc. for $C_{22}H_{27}O_2$ [M+H$^+$]: 323.2006, found 323.2005.

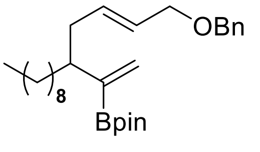
Use of functionalized branched allyl carbonates

2-((S)-3-((S)-1-(benzyloxy)but-3-en-2-yl)dodec-1-en-2-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (5.38)



^{1}H NMR (300 MHz, CDCl$_3$) δ 7.38 – 7.23 (m, 5H), 5.85 (d, *J* = 3.6 Hz, 1H), 5.79 – 5.64 (m, 1H), 5.56 (d, *J* = 3.6 Hz, 1H), 5.15 – 5.07 (m, 2H), 4.45 (d, *J* = 4.0 Hz, 2H), 3.48 – 3.26 (m, 2H), 2.62 – 2.50 (m, 1H), 2.13 (td, *J* = 10.2, 3.8 Hz, 1H), 1.58 – 1.37 (m, 2H), 1.24 (d, *J* = 2.4 Hz, 23H), 0.89 (t, *J* = 6.7 Hz, 3H). **^{13}C NMR** (75 MHz, CDCl$_3$δ 140.5 (CH), 138.9 (C), 130.4 (CH$_2$), 128.2 (2 x CH), 127.5 (2 x CH), 127.2 (CH), 116.1 (CH$_2$), 83.0 (2 x C), 72.9 (CH$_2$), 72.7 (CH$_2$), 48.1 (CH), 47.7 (CH), 31.9 (CH$_2$), 31.4 (CH$_2$), 29.6 (CH$_2$), 29.6 (CH$_2$), 29.3 (CH$_2$), 27.6 (CH$_2$), 24.75 (4 x CH$_3$), 22.7 (CH$_2$), 14.1 (CH$_3$).

(E)-2-(3-(4-(benzyloxy)but-2-en-1-yl)dodec-1-en-2-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (5.39).

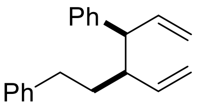


^{1}H NMR (300 MHz, CDCl$_3$) δ 7.37 – 7.25 (m, 5H), 5.83 (d, *J* = 3.4 Hz, 1H), 5.65 – 5.53 (m, 2H), 4.48 (s, 2H), 3.97 (d, *J* = 5.4 Hz, 2H), 2.24 (ttd, *J* = 10.8, 6.6, 3.6 Hz, 2H), 1.52 – 1.41 (m, 2H), 1.30 – 1.19 (m, 12H), 0.93 – 0.86 (m, 3H). **^{13}C NMR** (75 MHz, CDCl$_3$) δ 138.6 (C), 134.3 (CH), 129.2 (CH$_2$), 128.2 (2 x CH), 127.8 (2 x CH), 127.45 (CH), 126.9(CH), 83.04 (2 x C), 71.4 (CH), 70.9 (CH$_2$), 45.9 (CH$_2$), 37.6 (CH$_2$), 33.9 (CH$_2$), 31.9 (CH$_2$), 29.8 (CH$_2$), 29.6 (CH$_2$), 29.3 (CH$_2$), 27.51 (CH$_2$), 24.74 (4 x CH$_3$), 22.67 (CH$_2$), 14.1 (CH$_3$).

4.4 Derivatization product.

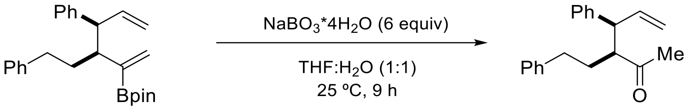
a) Protodeboronation

((3R,4S)-3-vinylhex-5-ene-1,4-diyl)dibenzene (5.40).



^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35 – 7.09 (m, 10H), 6.02 (dt, *J* = 17.6, 9.3 Hz, 1H), 5.54 – 5.38 (m, 1H), 5.12 –5.03 (m, 2H), 4.97 – 4.83 (m, 2H), 3.76 – 3.49 (m, 2H), 3.21 (t, *J* = 8.5 Hz, 2H), 2.62 – 2.46 (m, 1H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ 142.3 (C), 141.5 (C), 140.9 (CH), 140.3 (CH), 128.9 (2 x CH), 128.82(2 x CH), 128.6 (2 x CH), 128.3 (2 x CH), 127.27 (CH), 126.46 (CH), 116.39 (CH_2), 115.85 (CH_2), 49.06 (CH), 48.66 (CH), 33.9 (CH_2), 32.8 (CH_2).

b) Oxidation

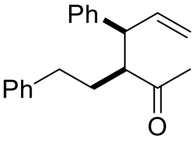


5.3
(18:1 dr)

5.41,
67%, (>20:1 dr)

A solution of borylated diene **5.3** (0.2 mmol, 1 equiv) in 1 ml of THF and 1 ml of water was stirred in the presence of $NaBO_3{\cdot}4H_2O$ (1.2 mmol, 6 equiv) over 16 hours. After this time, the reaction mixture was diluted in Et_2O and washed with brine. The organic layer was dried, filtered and the solvents were evaporated under vacuum. The final product was purified by SiO_2 column chromatography using Hexane / AcOEt (4:1) as eluent to afford the corresponding ketone.

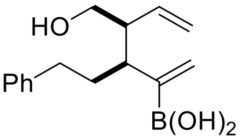
(3S,4S)-3-phenethyl-4-phenylhex-5-en-2-one (5.41).



^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34 – 7.14 (m, 10H), 5.92 (dt, *J* = 16.9, 9.7 Hz, 1H), 5.17 – 5.08 (m, 2H), 3.47 (t, *J* = 9.8 Hz, 1H), 3.03 – 2.93 (m, 1H), 2.70 – 2.44 (m, 2H), 2.06 – 1.95 (m, 2H), 1.80 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 212.2, 142.1, 139.7, 139.1, 128.9, 128.9, 128.7, 127.9, 126.9, 126.4, 117.2, 59.7, 53.7, 37.6, 33.1. **HRMS (APCI)** Calc. for $C_{20}H_{23}O$ [$M+H^+$]: 279.1743, found 279.1742.

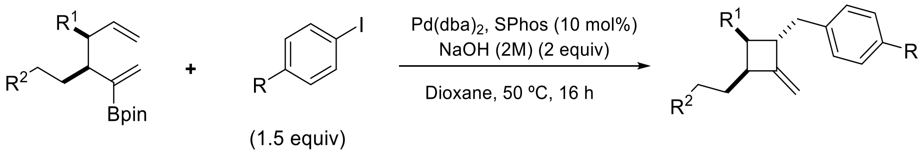
c) Alcohol deprotection

((3S,4S)-4-(hydroxymethyl)-3-phenethylhexa-1,5-dien-2-yl)boronic acid (5.42).



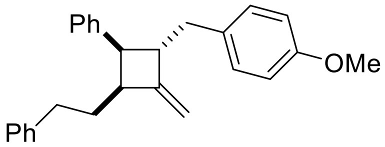
A solution of borylated diene **5.38** (0.1 mmol) and Selectfluor (0.25 mmol) was diluted in 2 ml of CH_3CN and 0.1 ml of water. The mixture was stirring at room temperature for 5 hours. The final product was purified by SiO_2 column chromatography using Hexane / AcOEt (4:1) as eluent to afford the product **5.42**. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.23 – 7.19 (m, 2H), 7.13 – 7.08 (m, 3H), 5.92 (dd, *J* = 3.0, 1.4 Hz, 1H), 5.70 – 5.58 (m, 2H), 5.11 – 5.02 (m, 2H), 4.13 (dd, *J* = 11.5, 3.4 Hz, 1H), 3.89 (dd, *J* = 11.5, 4.5 Hz, 1H), 2.63 – 2.46 (m, 2H), 2.36 – 2.25 (m, 2H), 1.85 – 1.63 (m, 2H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 142.4 (C), 138.4 (2 x CH), 128.8 (CH_2), 128.4 (2 x CH), 125.8 (CH), 116.4 (CH_2), 66.1 (CH_2), 45.10 (CH), 44.8 8 (CH), 34.9 (CH_2), 32.2 (CH_2).

d) Stereoselective synthesis of methylenecyclobutanes.



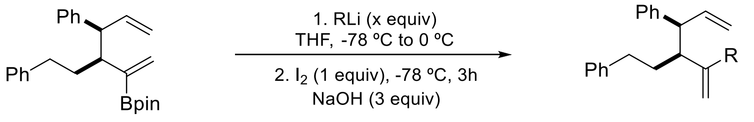
In a Schlenk flask, Pd(dba)2 (10 mol%, 0.02 mmol) and SPhos (10 mol%, 0.02 mmol) were added. Then, the corresponding 1,5-borylated diene (0.2 mmol) was added in 1,4-dioxane (2.0 ml), followed by the addition of the iodoarene (1.5 equiv 0.3 mmol) and aq. NaOH (2.0 M, 2.0 equiv, 0.4 mmol). The reaction was stirred at 50 °C for 16 h. After this time, the resulting crude was diluted in Et_2O (15 ml) and washed with H2O (2x10 ml). The organic layer was dried over Na_2SO_4 and filtered. The residue was purified by column chromatography (Hex/CH_2Cl_2, 8:2) affording the desired product as a yellow oil.

1-methoxy-4-(((1S,3S,4R)-2-methylene-3-phenethyl-4 phenylcyclobutyl)methyl)benzene (5.43).



Synthesized from **5.3**, **and 5.?** as a yellow oil obtained in 78% yield (>20:1 dr) after column chromatography (Hexane/CH_2Cl_2 4:1). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.20 – 7.16 (m, 2H), 7.13 – 7.06 (m, 4H), 7.04 – 7.00 (m, 2H), 6.86 – 6.82 (m, 2H), 6.72 – 6.69 (m, 2H), 4.80 (t, *J* = 2.2 Hz, 1H), 4.73 (t, *J* = 2.3 Hz, 1H), 3.69 (s, 3H), 3.40 (dtp, *J* = 7.2, 4.9, 2.6 Hz, 1H), 3.30 (dd, *J* = 9.2, 7.0 Hz, 1H), 2.84 (dd, *J* = 7.2, 2.3 Hz, 2H), 2.39 – 2.16 (m, 2H), 1.50 – 1.31 (m, 2H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 158.2 (C), 155.4 (C), 142.7 (C), 140.9 (C), 132.6 (C), 130.2 (CH), 128.6 (CH), 128.6 (CH), 128.5 (CH), 128.3 (CH), 126.3 (CH), 125.8 (CH), 113.7 (CH), 105.2 (CH_2), 55.5 (CH_3), 48.9 (CH), 46.2 (CH), 45.8 (CH), 39.5 (CH_2), 33.8 (CH_2), 32.2 (CH_2).

d) Zweifel coupling

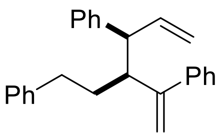


5.3

5.48, (Use of 1.5 equiv PhLi) R = Ph; 47%
5.49, (Use of 2.5 equiv MeLi) R = Me; 62%

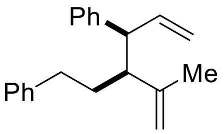
In a Schlenk dry flask, the borylated diene **5.3** (0.2 mmol) was diluted in Et_2O (0.8 ml) and cooled to -78 °C. Then PhLi (1.5 equiv) or MeLi (2.5 equiv) was added. After 30 min, the reaction was warmed to 0 °C and stirred during 1h. After this time, solvents were evaporated under vacuum and a solution of I_2 (0.2 mmol) in dry MeOH (0.4 ml) was added at -78 °C. After 3h, a solution of NaOH 3M (0.6 mmol) was added and diluted with Et_2O (15 ml). The organic layer was dried over Na_2SO_4 and filtered. The residue was purified by column chromatography (Hex: AcOEt 4:1) affording the desired product as a yellow oil.

((3S,4S)-3-phenethylhexa-1,5-diene-2,4-diyl)dibenzene (5.48)



^{1}H NMR (300 MHz, CDCl$_3$) δ 7.35 – 7.04 (m, 15H), 6.09 – 5.94 (m, 1H), 5.32 (bs, 1H), 5.14 – 5.02 (m, 3H), 3.39 (t, *J* = 9.0 Hz, 1H), 3.06 (td, *J* = 9.5, 3.2 Hz, 1H), 2.84 (ddd, *J* = 15.0, 11.1, 4.6 Hz, 1H), 2.58 (ddd, *J* = 13.4, 10.4, 6.5 Hz, 1H), 2.22 – 1.82 (m, 2H). **^{13}C NMR** (75 MHz, CDCl$_3$) δ 150.2, 143.6, 143.4, 142.5, 139.9, 128.4, 128.3, 128.1, 128.0, 126.9, 126.8, 125.9, 125.7, 115.9, 114.7, 55.2, 48.9, 33.4, 33.4.

((3S,4S)-3-(prop-1-en-2-yl)hex-5-ene-1,4-diyl)dibenzene (5.49).



^{1}H NMR (300 MHz, CDCl$_3$) δ 7.37 – 7.12 (m, 10H), 5.91 (ddd, *J* = 16.9, 10.0, 9.2 Hz, 1H), 5.10 – 5.00 (m, 2H), 4.72 (bs, 1H), 4.62 (bs, 1H), 3.23 (t, *J* = 9.9 Hz, 1H), 2.67 (ddd, *J* = 15.1, 10.6, 4.8 Hz, 1H), 2.49 (dtd, *J* = 13.8, 7.3, 3.4 Hz, 2H), 2.06 (dtd, *J* = 14.0, 6.9, 3.4 Hz, 1H), 1.69 – 1.59 (m, 1H), 1.56 (s, 3H). **^{13}C NMR** (75 MHz, CDCl$_3$) δ 144.7, 143.6, 142.7, 141.4, 128.5, 128.3, 128.2, 127.9, 126.0, 125.6, 115.3, 114.4, 54.9, 51.4, 33.9, 32.5, 18.6. **HRMS (APCI)** Calc. for $C_{21}H_{25}$ [M+H$^+$]: 277.1951, found 277.1941.

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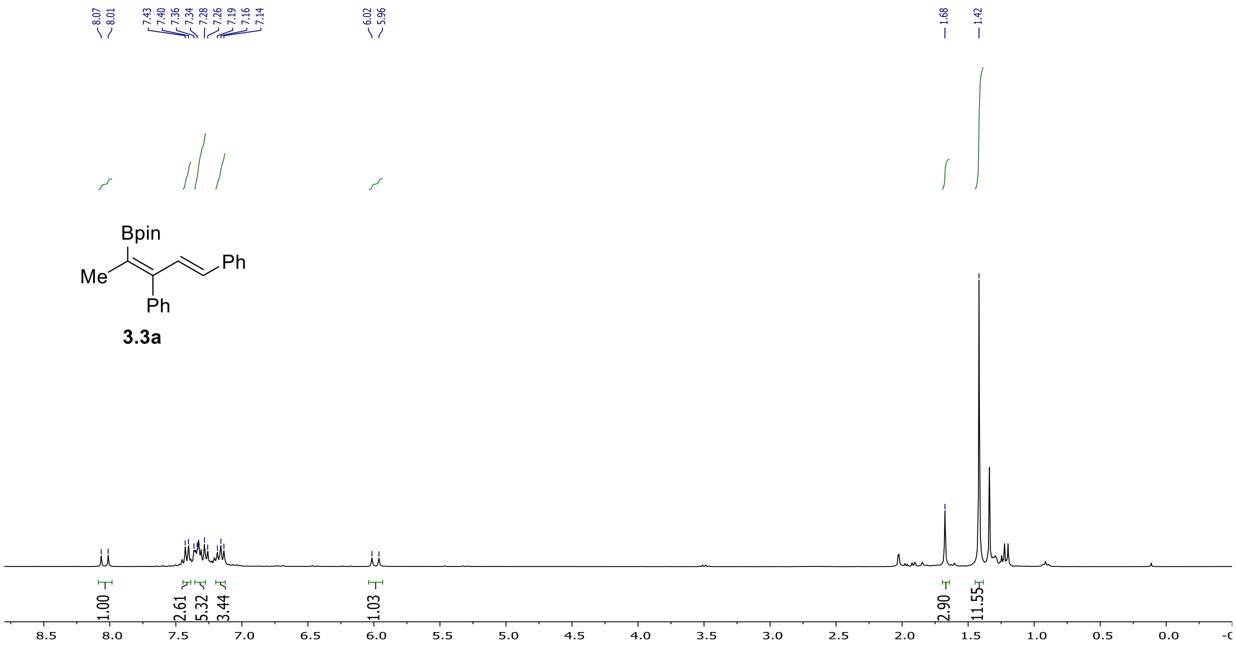
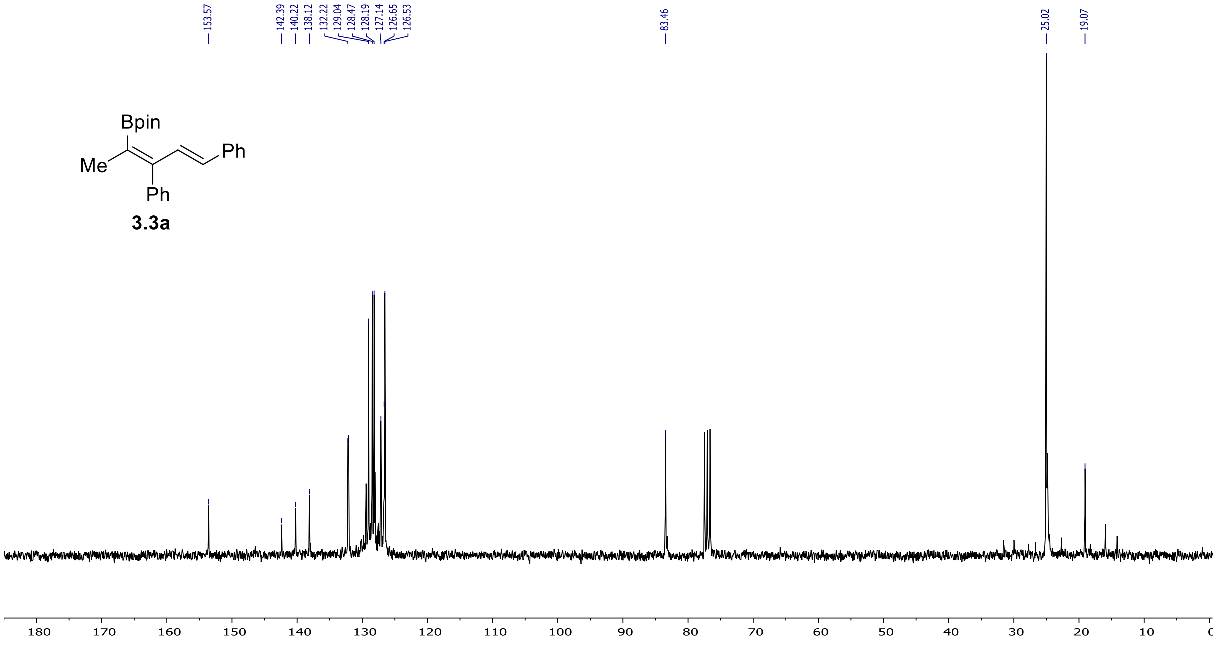
SELECTED NMR SPECTRA

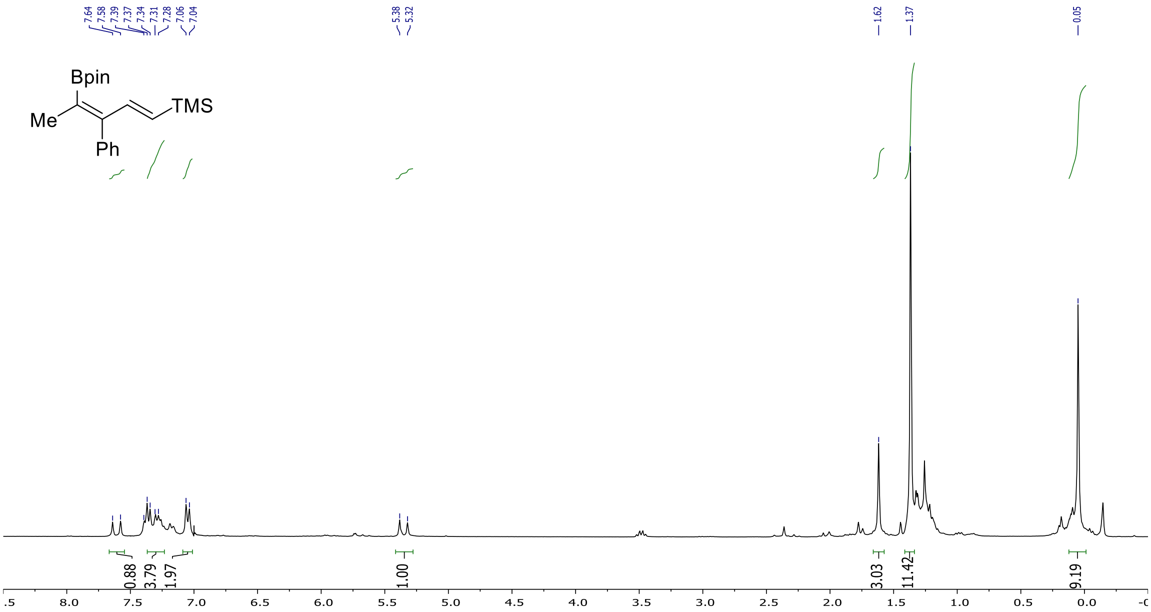
NMR (300 MHz, $CDCl_3$)



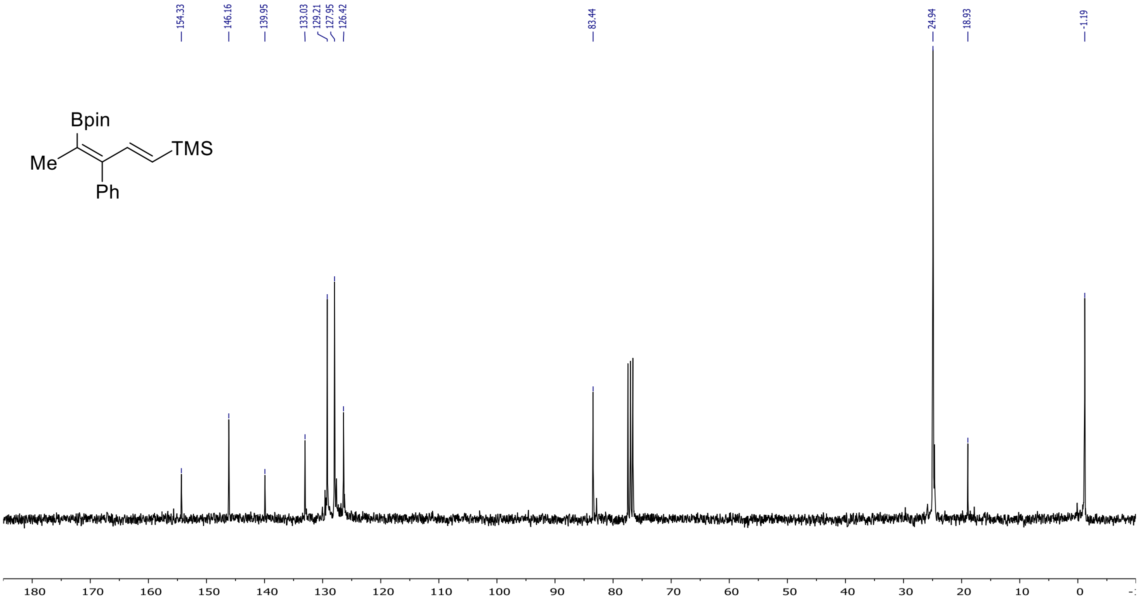
^{13}C NMR (75 MHz, $CDCl_3$)



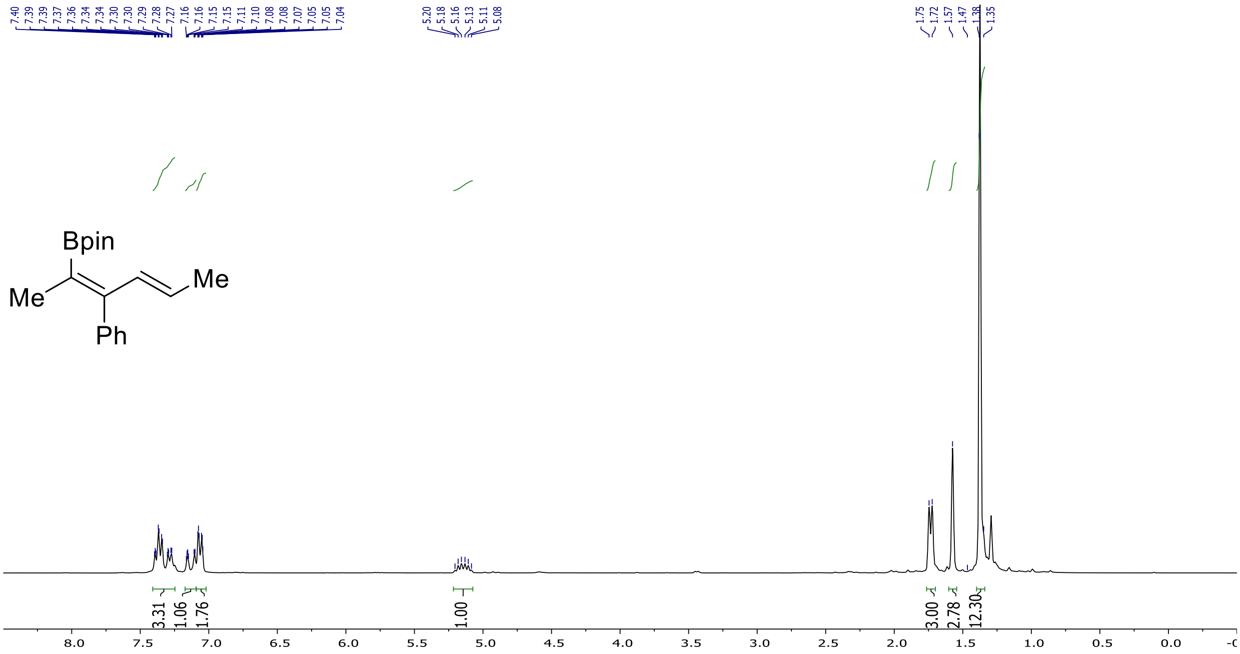
H NMR (300 MHz, $CDCl_3$)



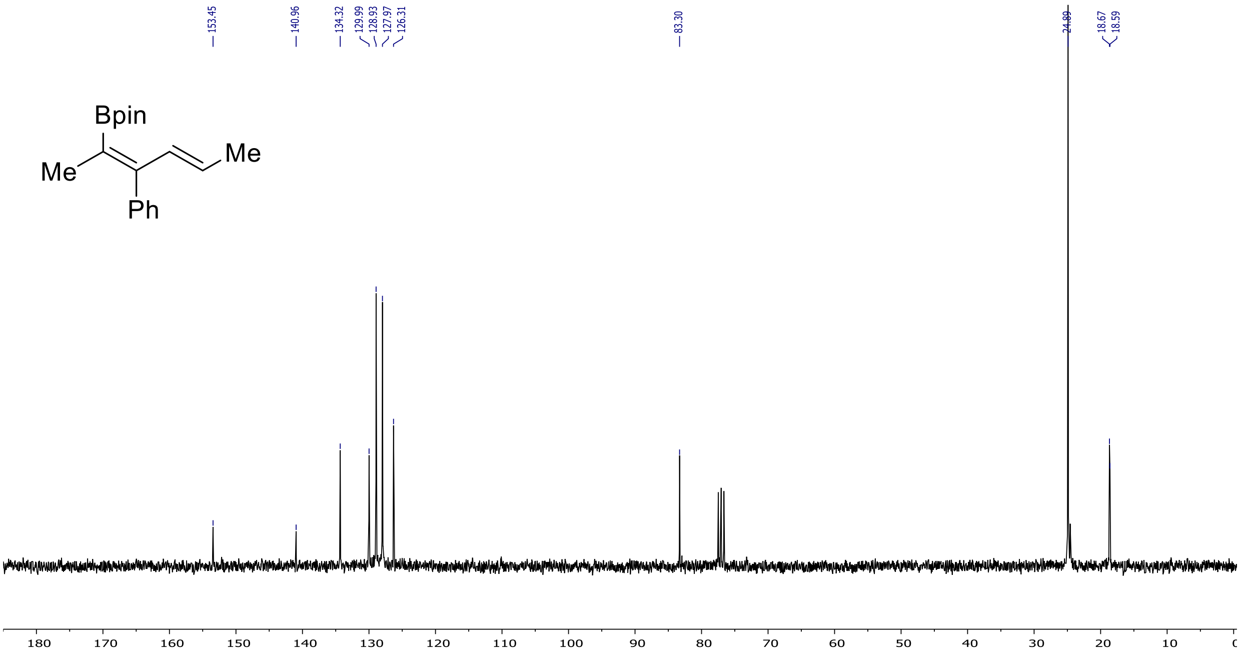
^{13}C NMR (75 MHz, $CDCl_3$)



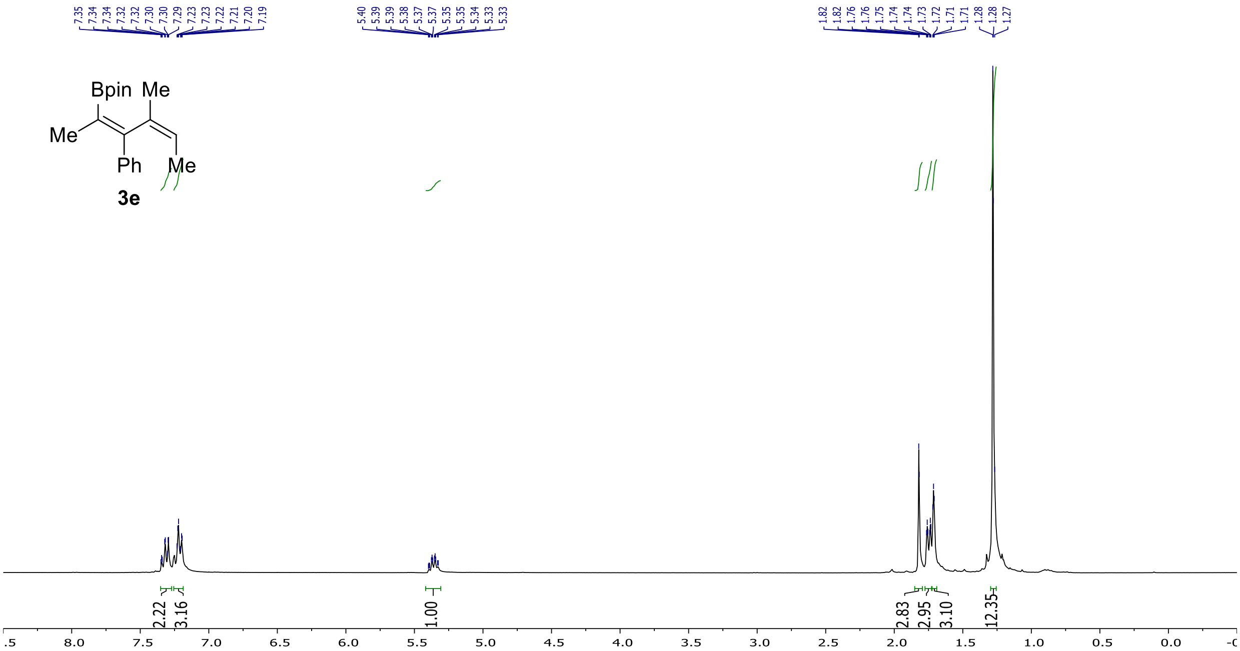
^{1}H NMR (300 MHz, CDCl$_3$)



^{13}C NMR (75 MHz, CDCl$_3$)



^{1}H NMR (300 MHz, CDCl$_3$)



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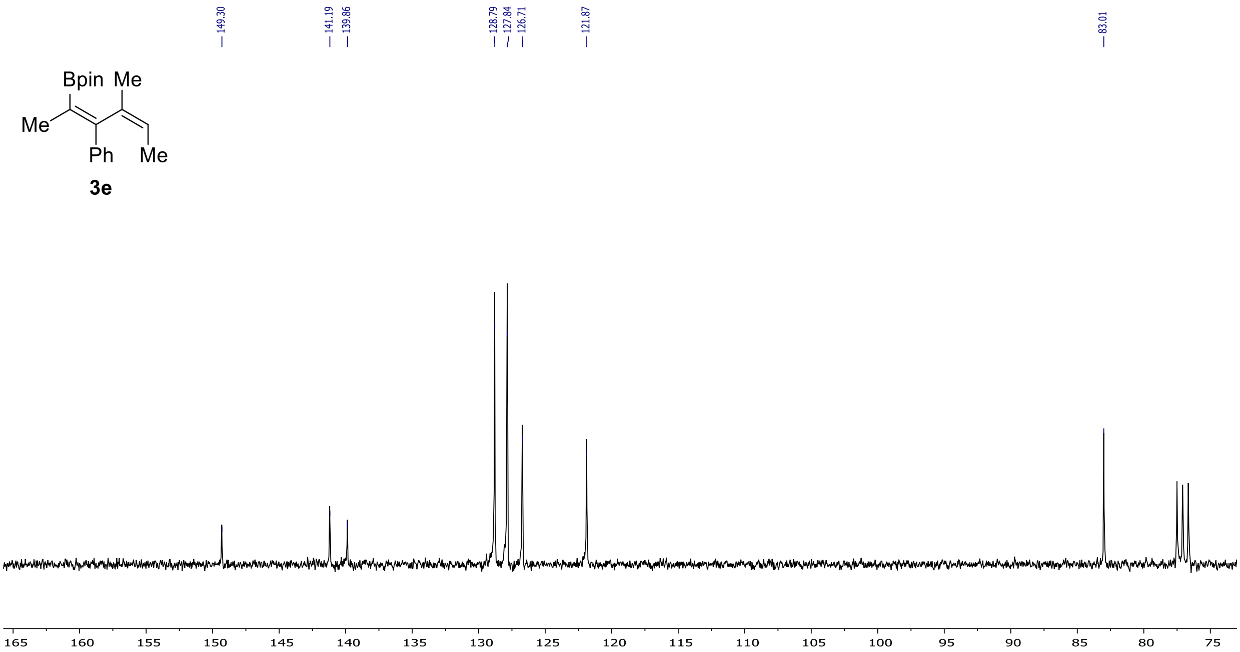
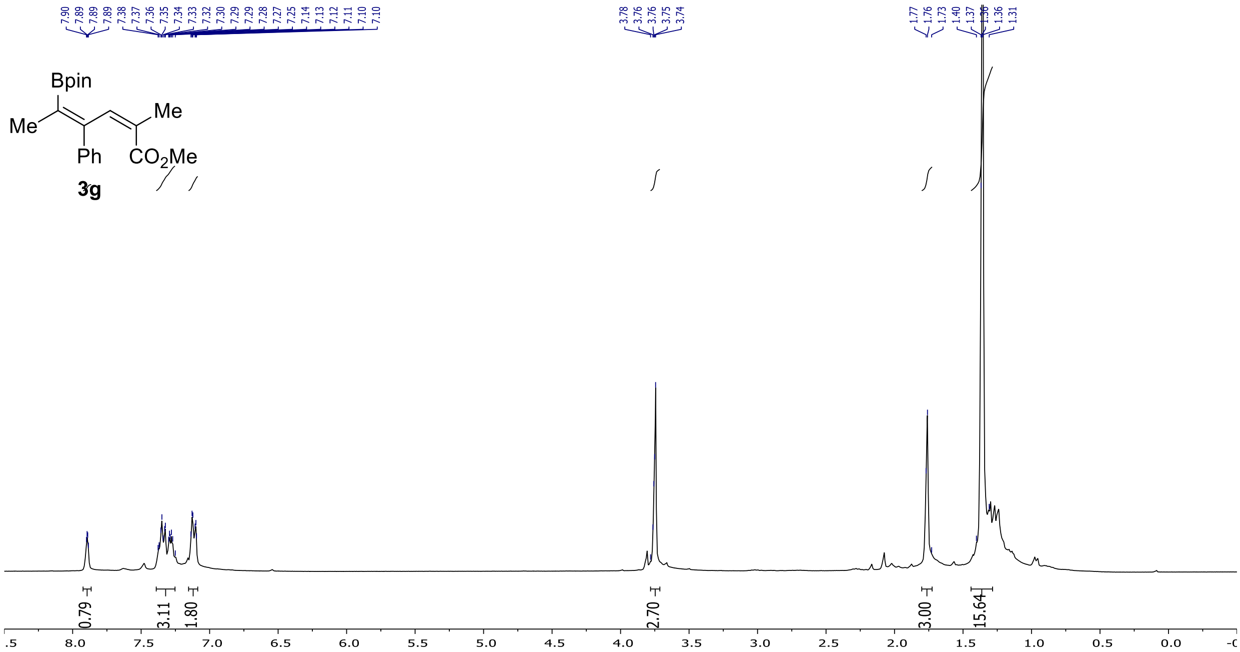
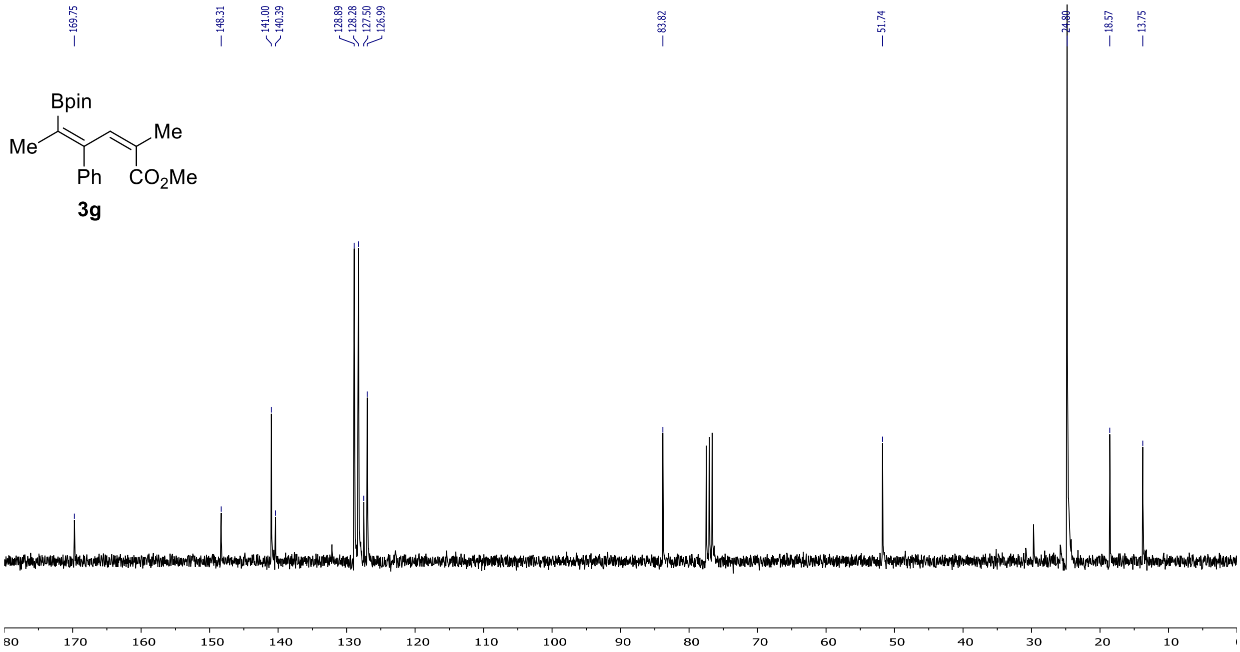


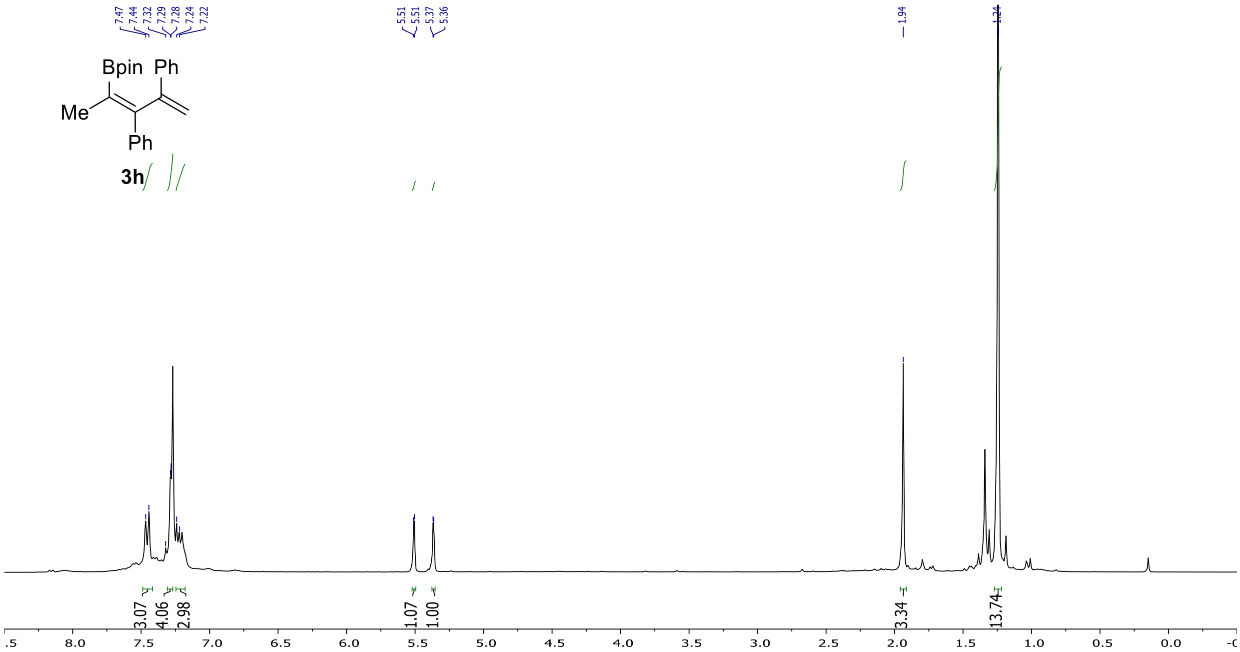
^{1}H NMR (300 MHz, CDCl$_3$)



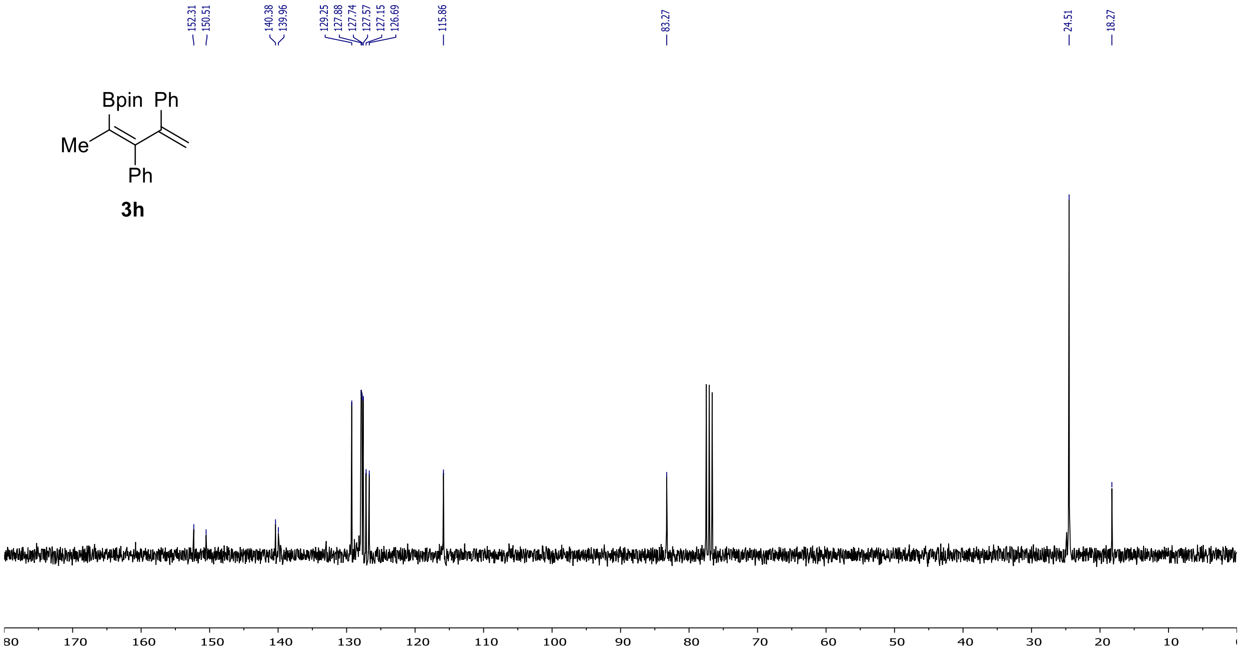
^{13}C NMR (75 MHz, CDCl$_3$)



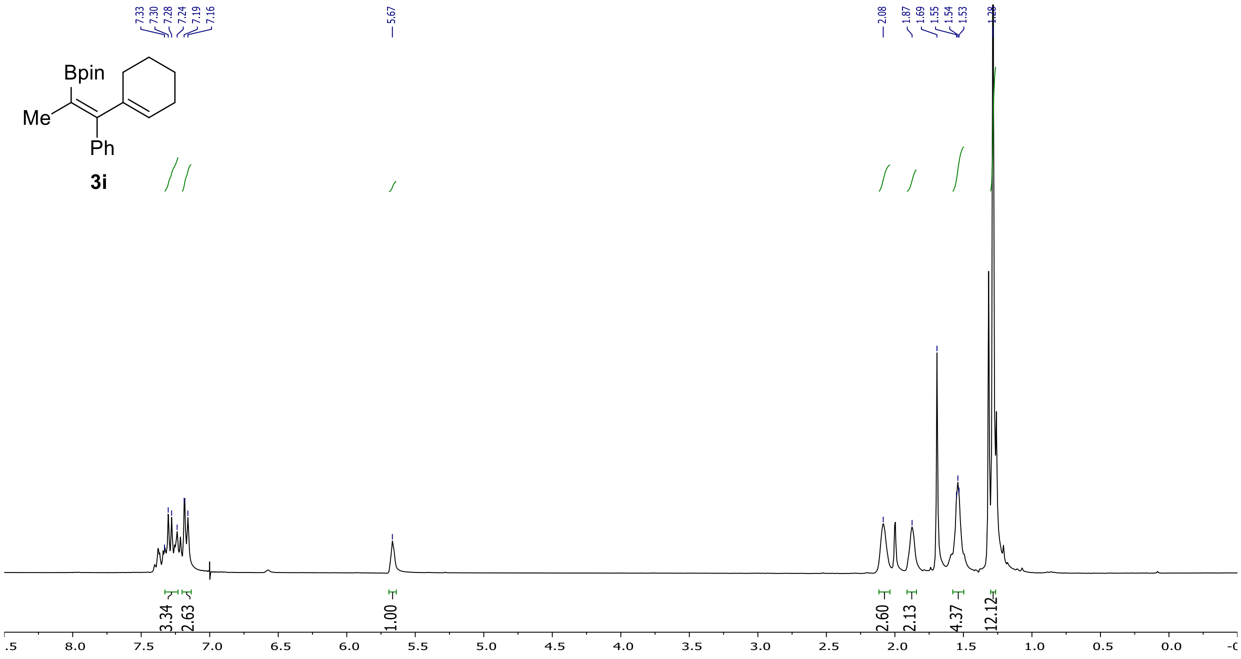
^{1}H NMR (300 MHz, CDCl$_3$)



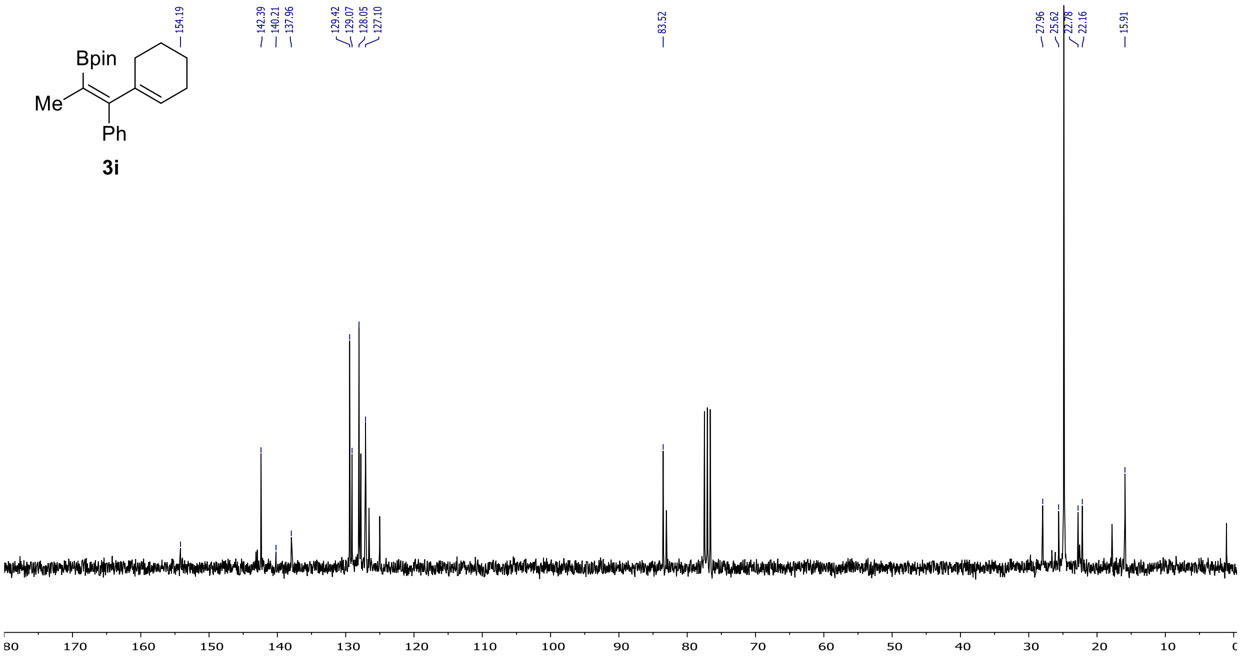
^{13}C NMR (75 MHz, CDCl$_3$)



^{1}H NMR (300 MHz, CDCl$_3$



^{13}C NMR (75 MHz, CDCl$_3$)



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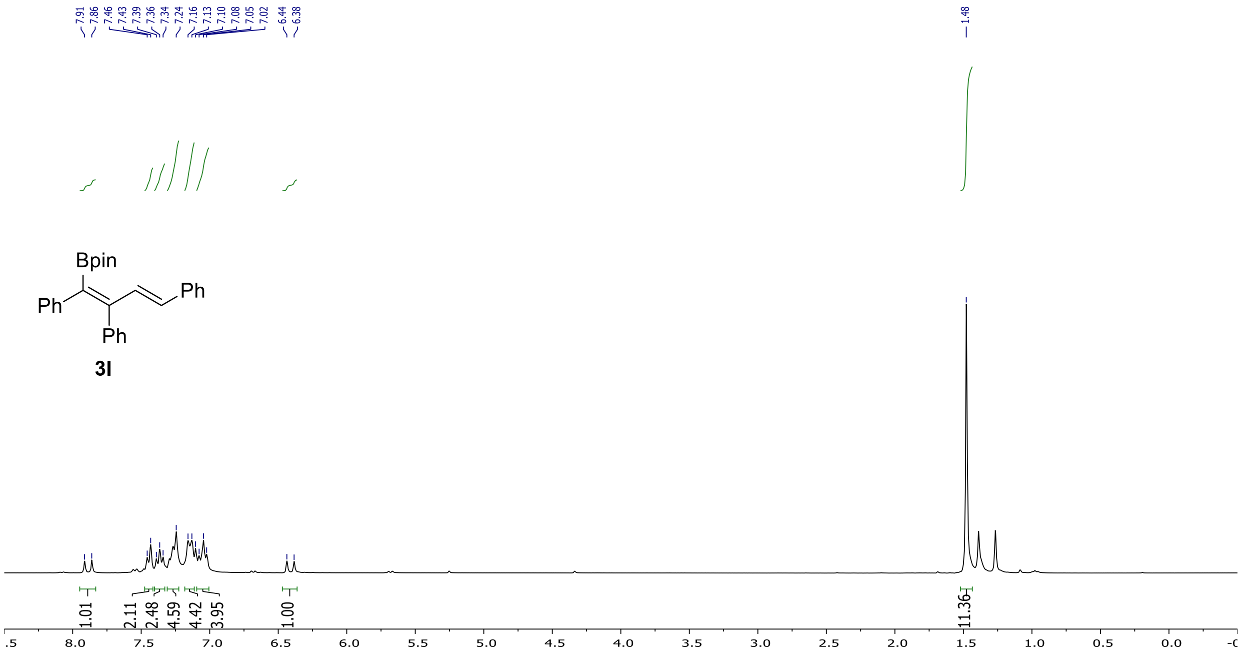
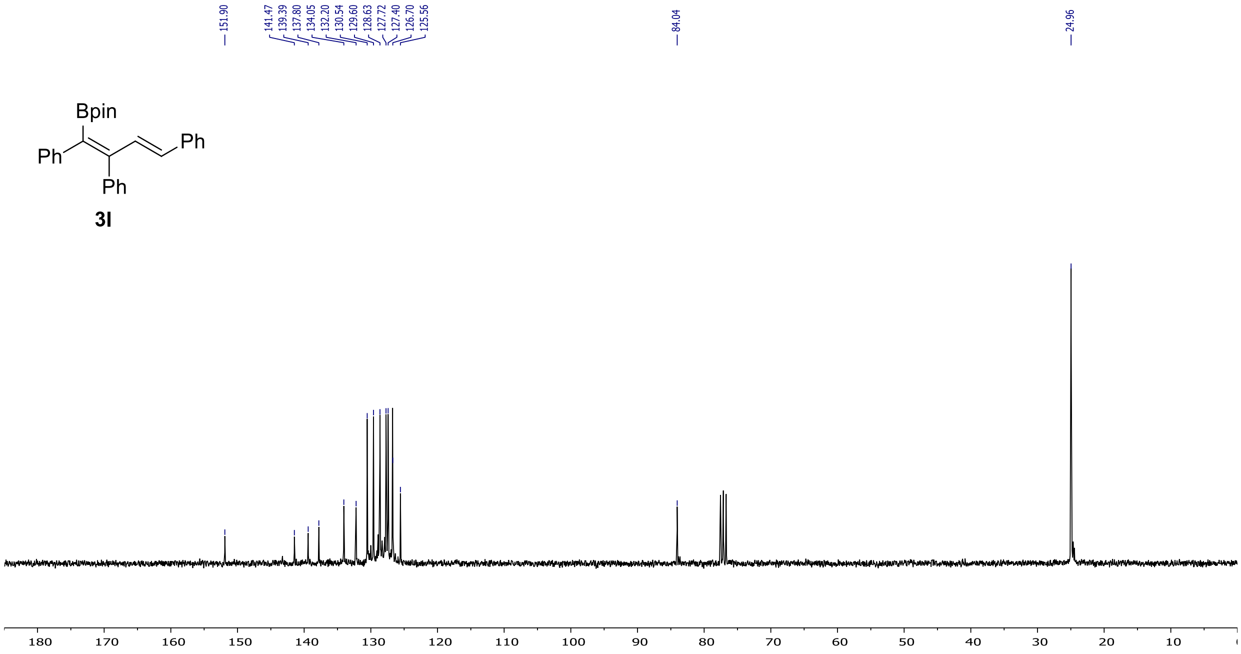


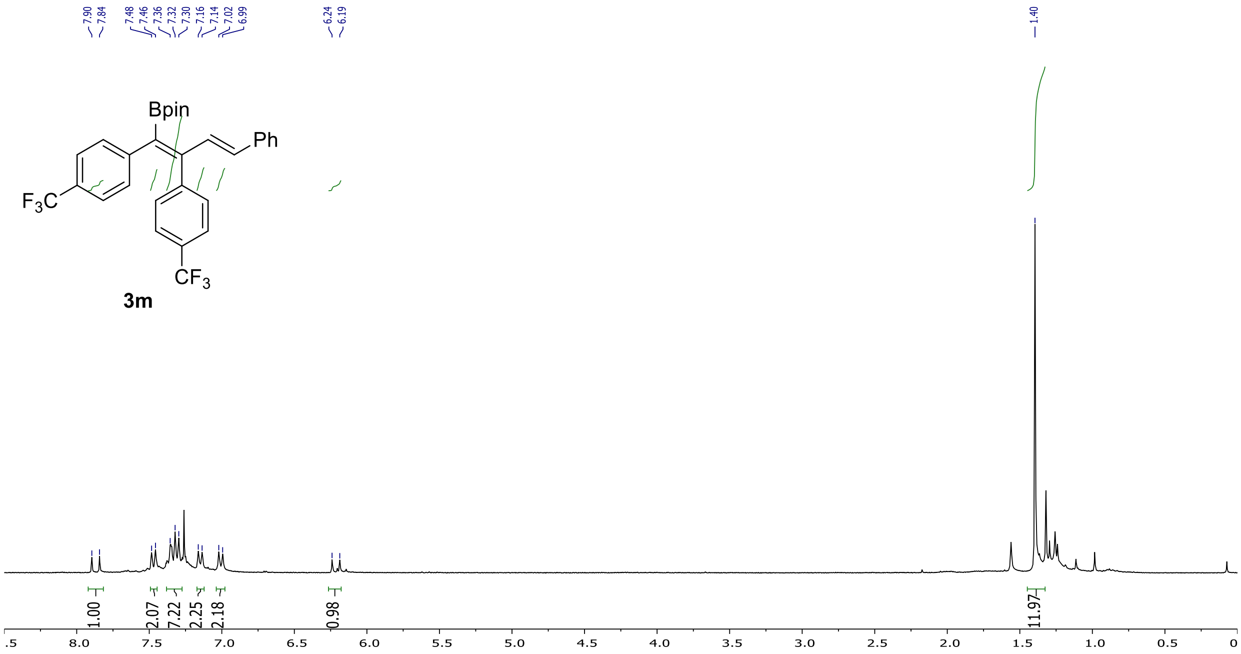
3l

^{13}C NMR (75 MHz, CDCl$_3$)

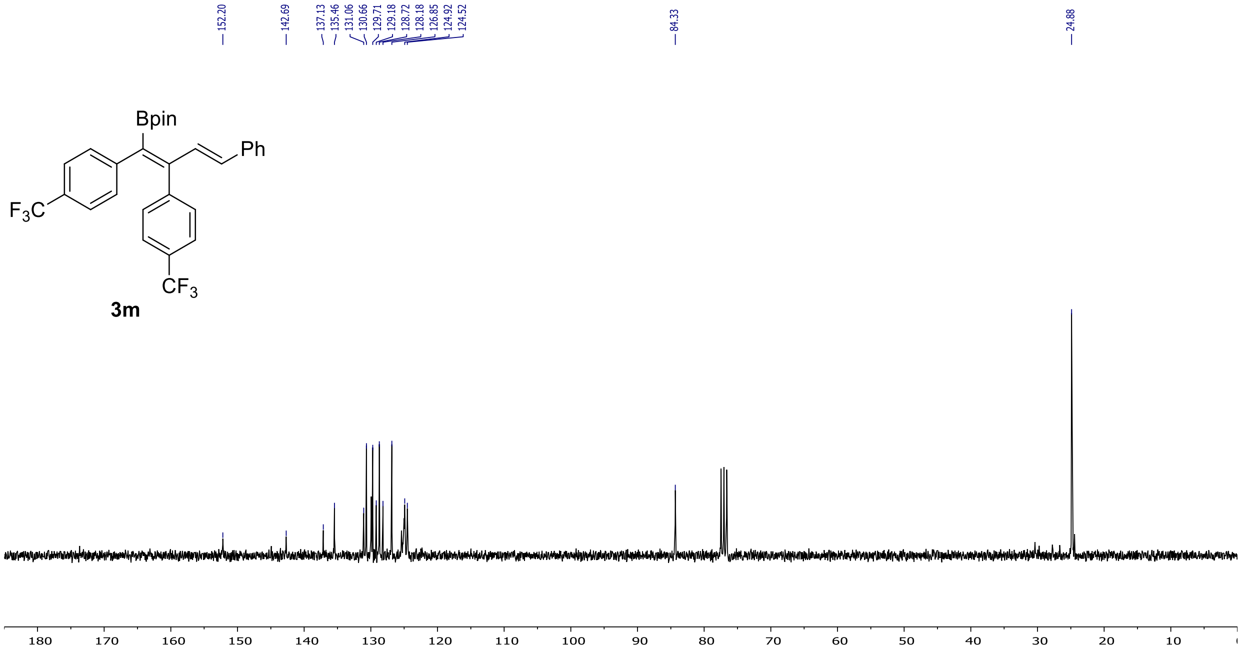


3l

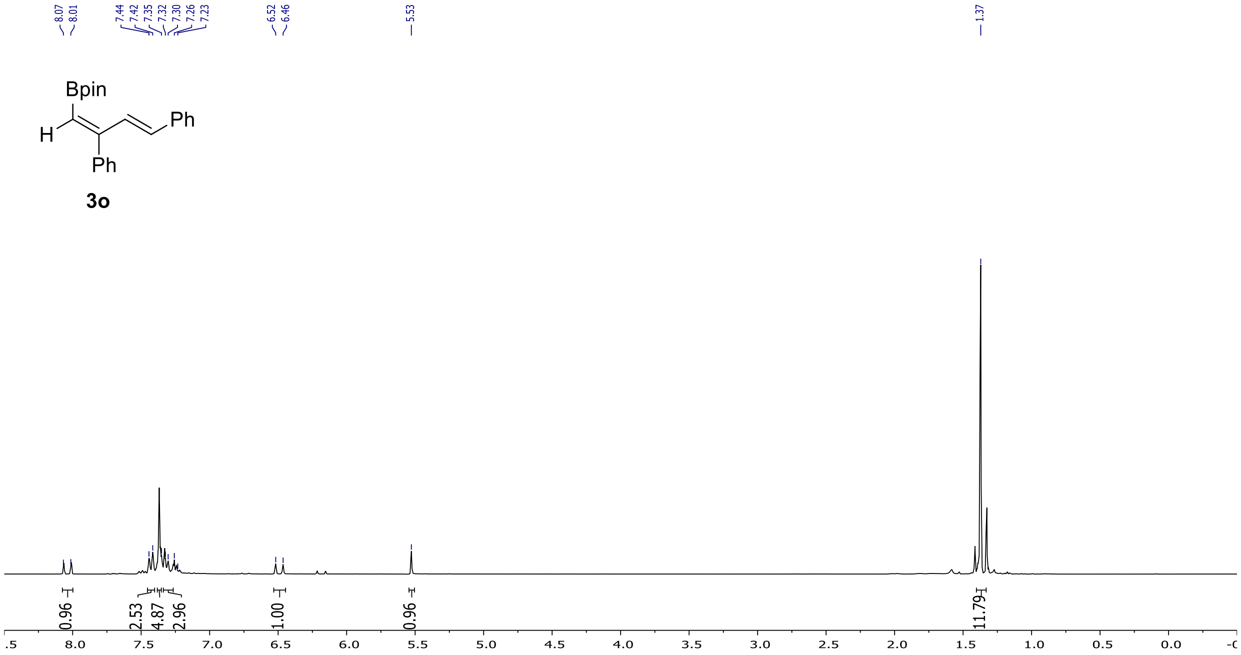
^{1}H NMR (300 MHz, $CDCl_3$)



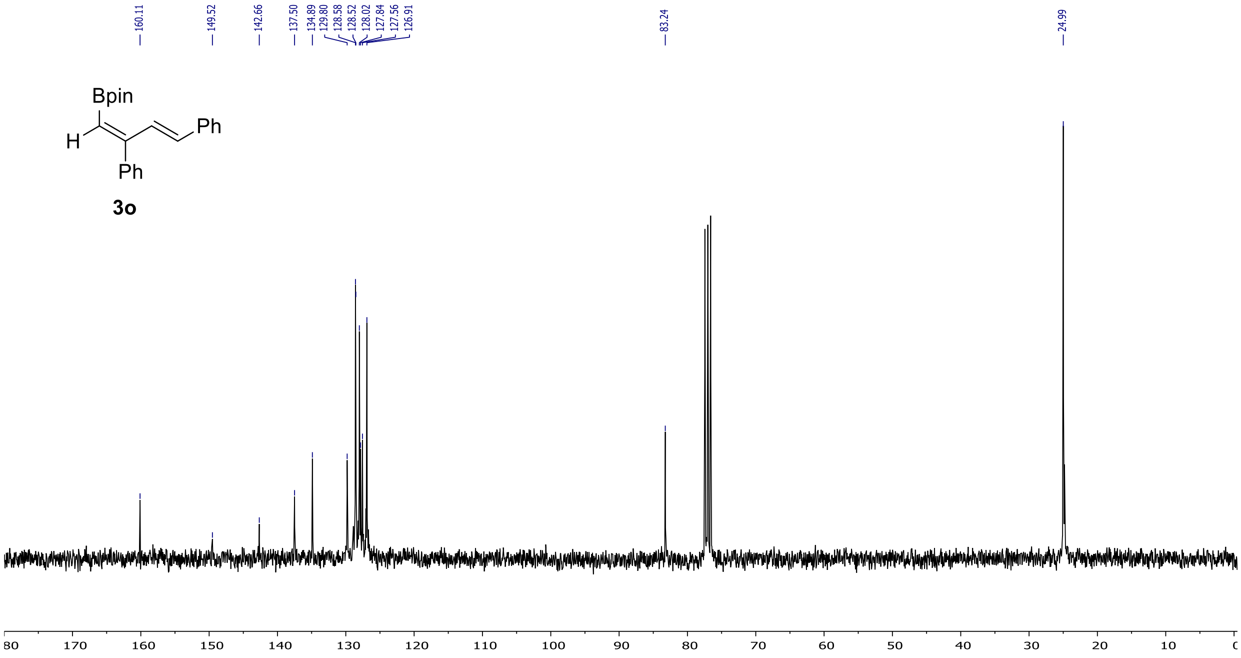
^{13}C NMR (75 MHz, $CDCl_3$)



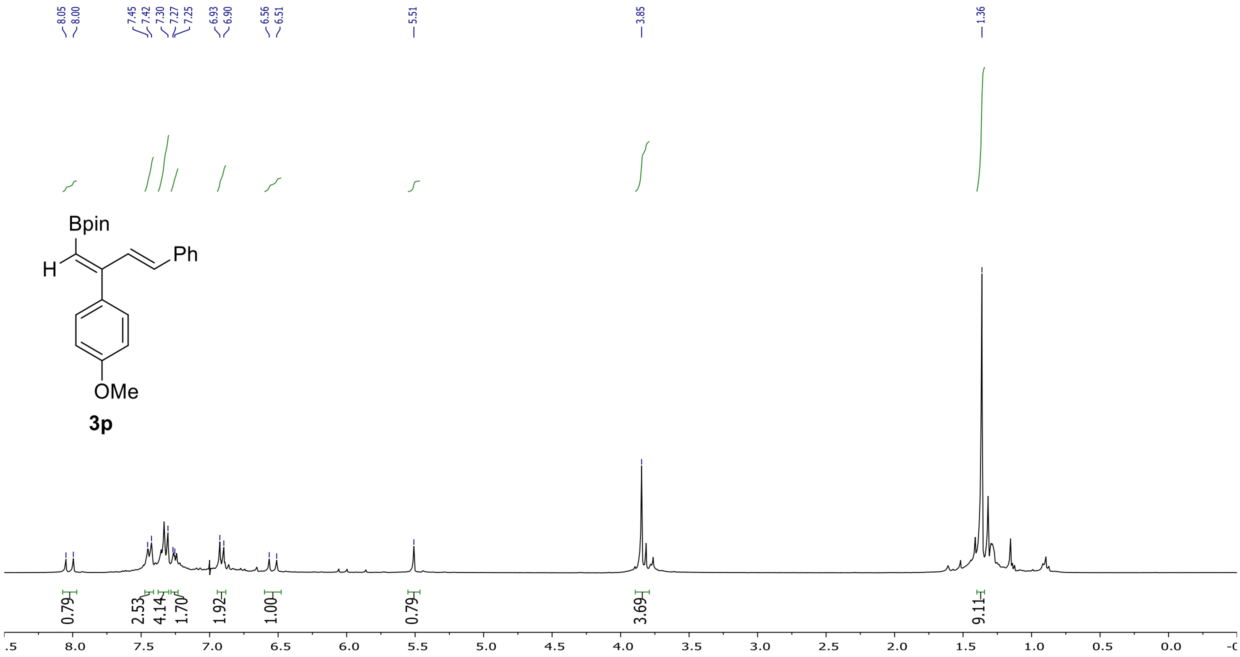
^{1}H NMR (300 MHz, CDCl$_3$)



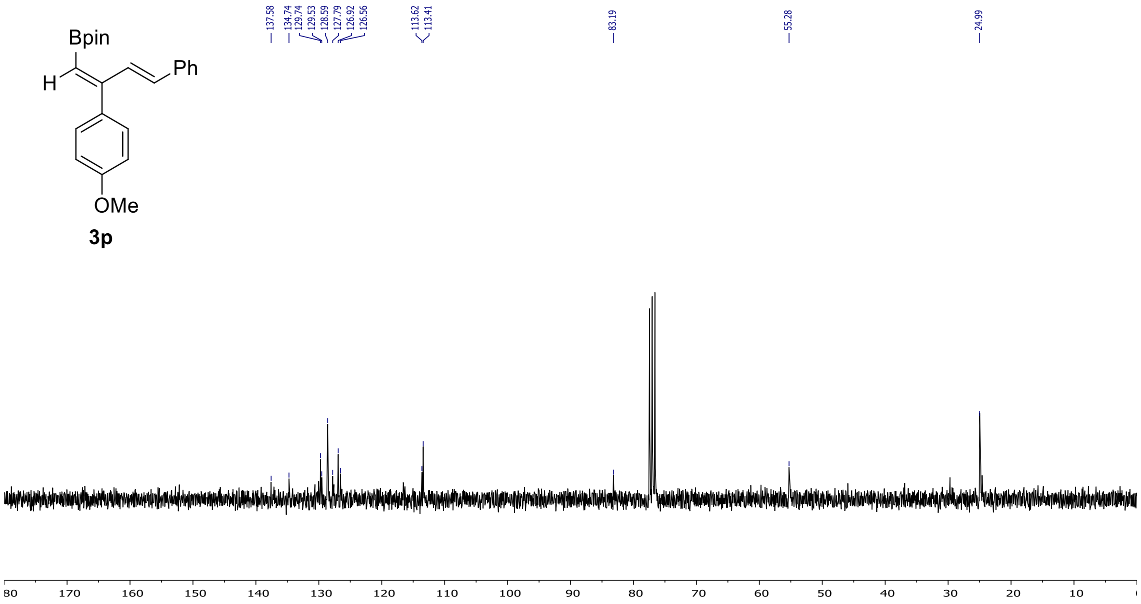
^{13}C NMR (75 MHz, CDCl$_3$)



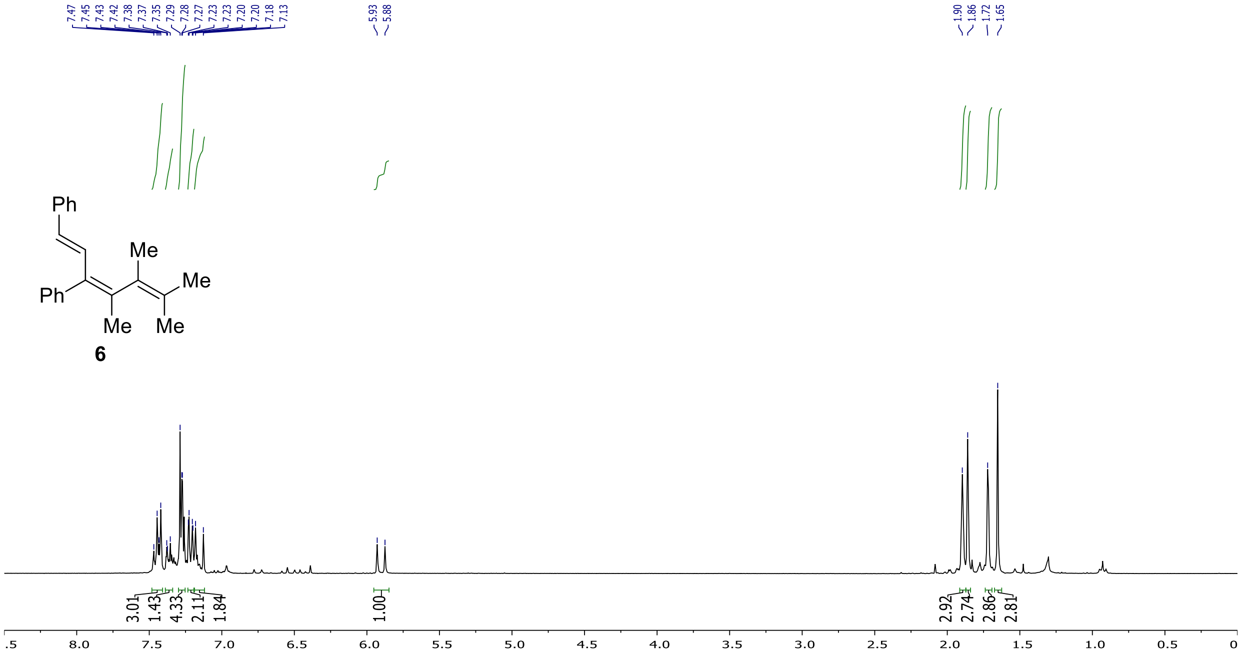
^{1}H NMR (300 MHz, $CDCl_3$)



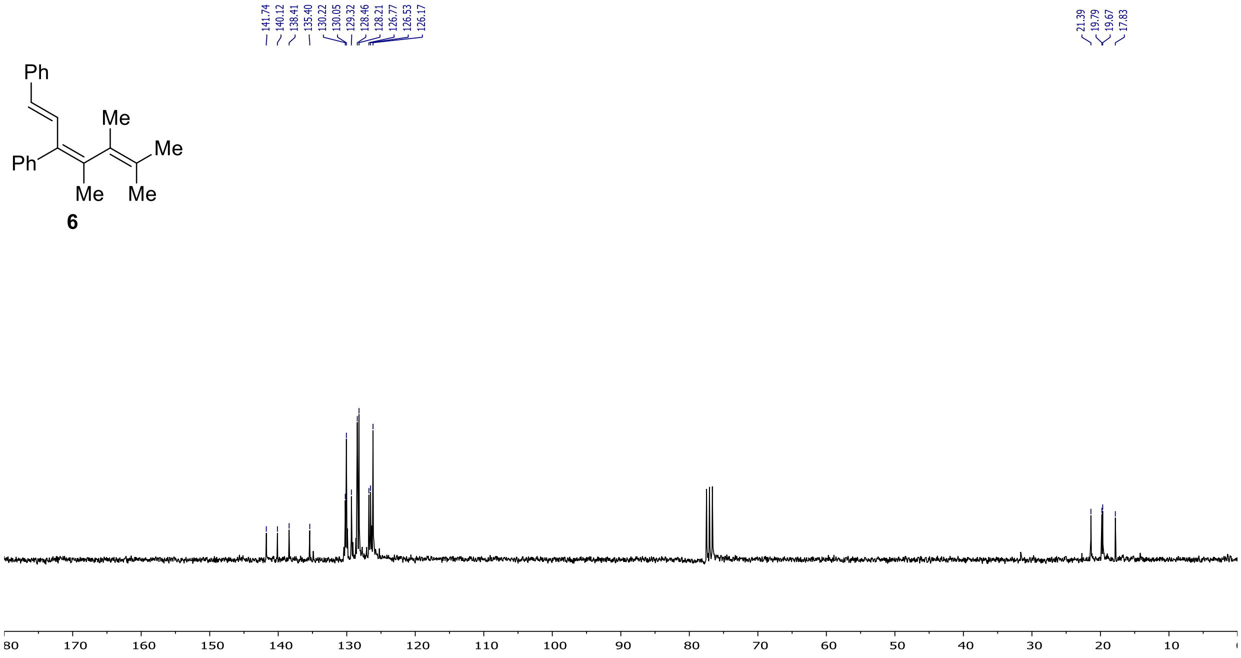
^{13}C NMR (75 MHz, $CDCl_3$)



^{1}H NMR (300 MHz, $CDCl_3$)



^{13}C NMR (75 MHz, $CDCl_3$)

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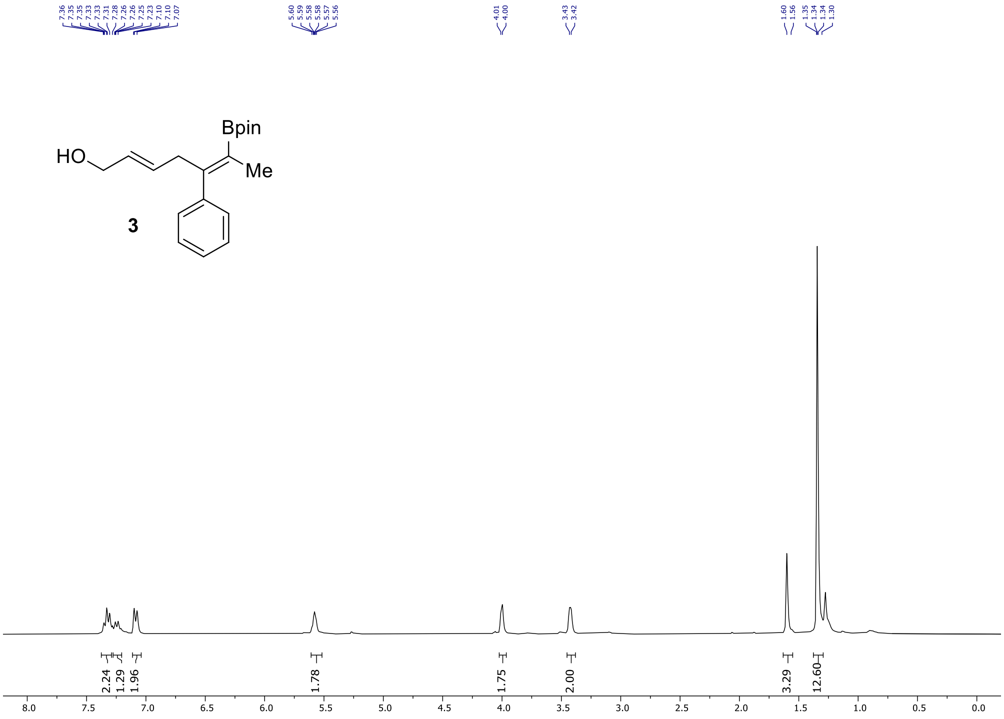
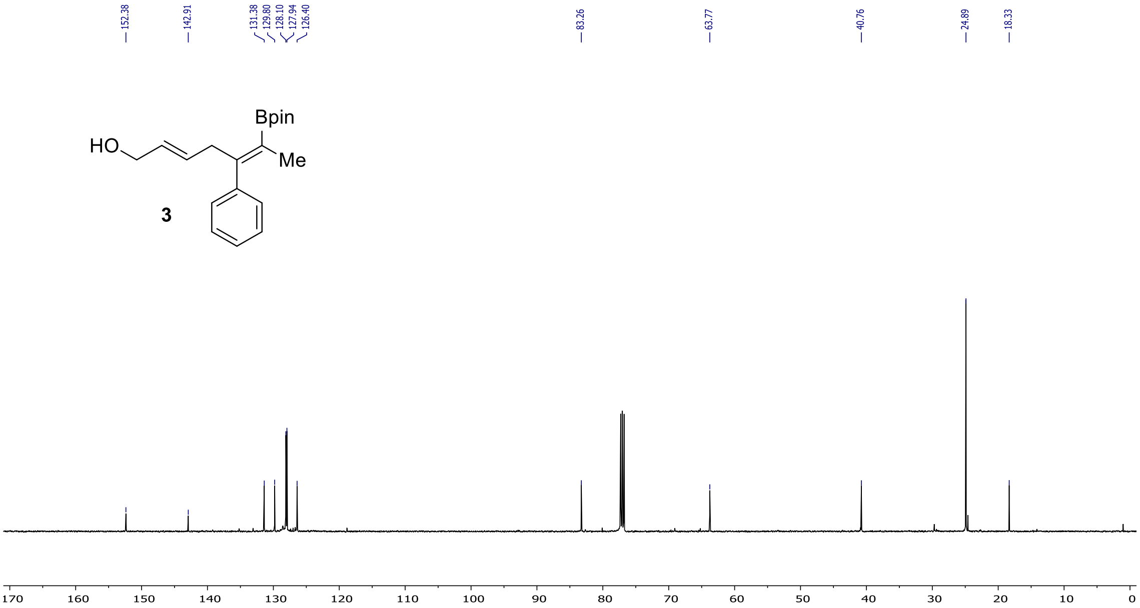
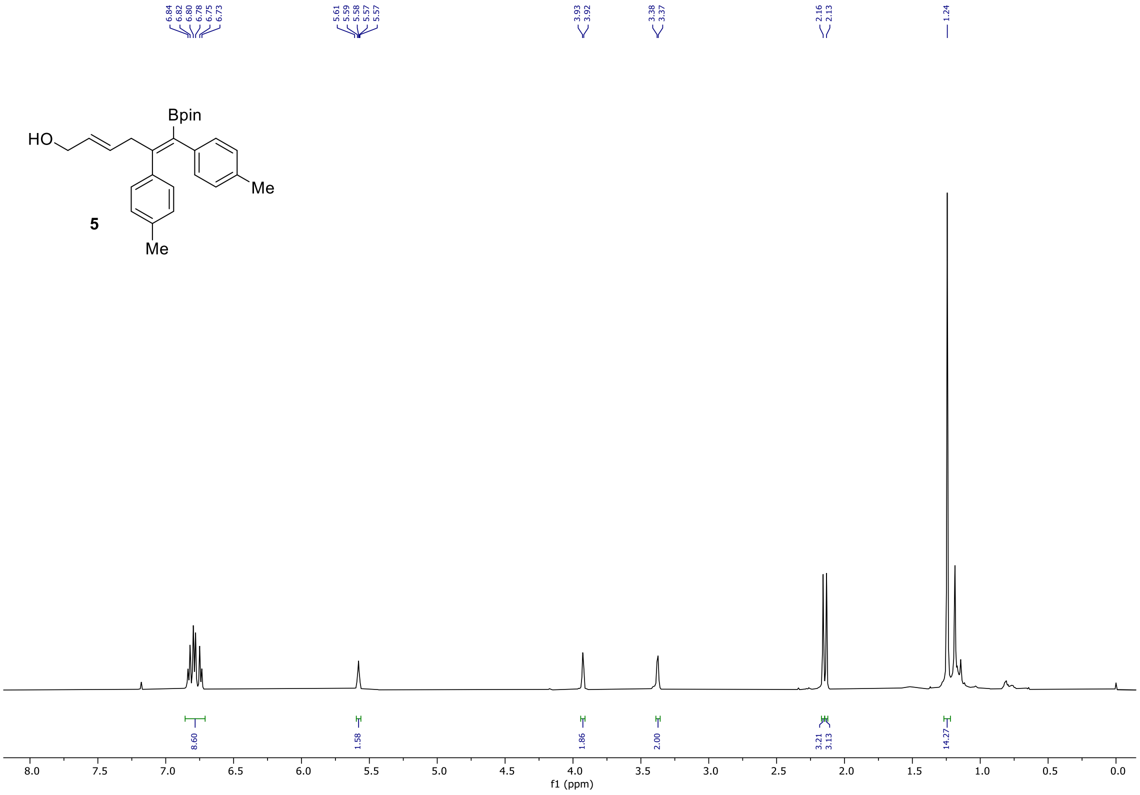
^{1}H NMR (500 MHz, CDCl$_3$)



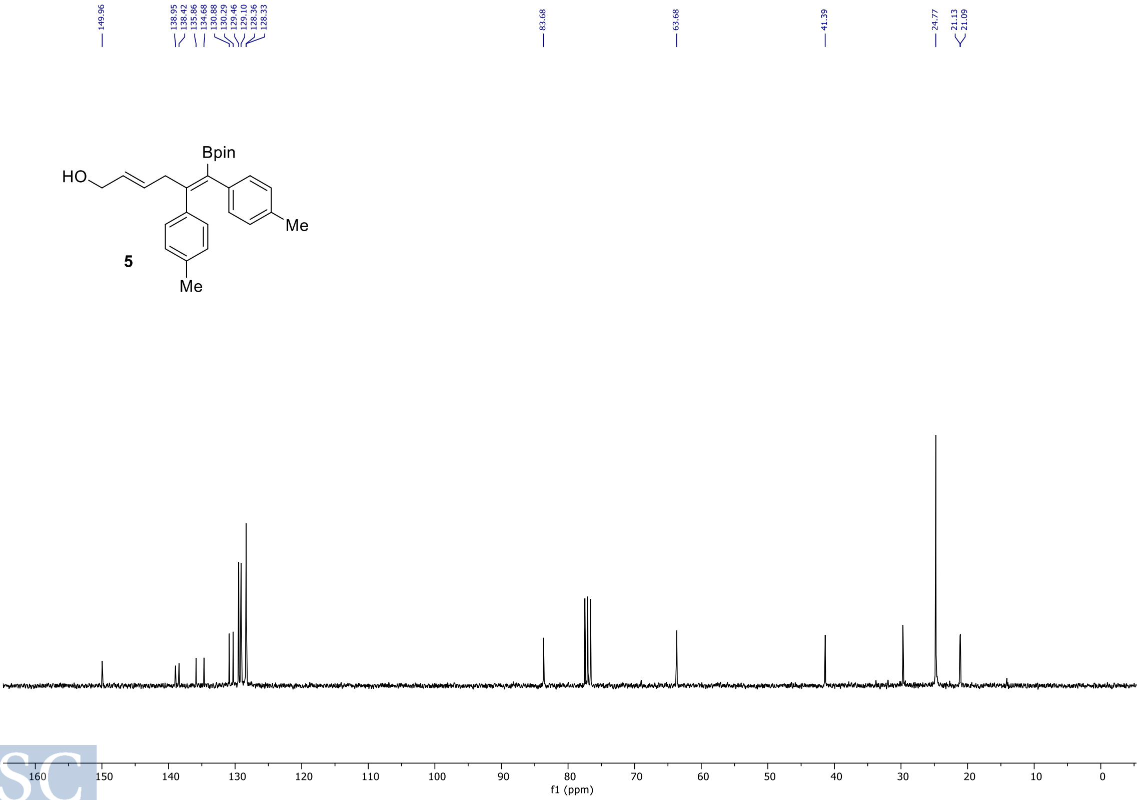
^{13}C NMR (126 MHz, CDCl$_3$)



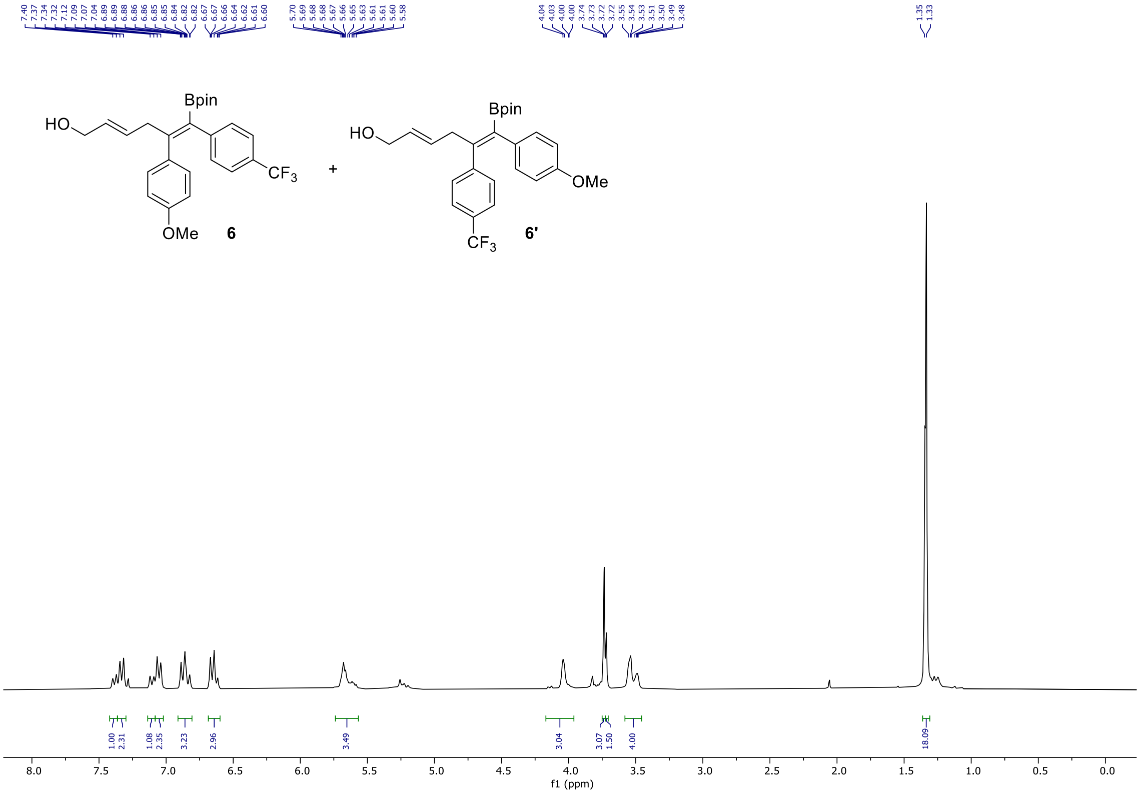
^{1}H NMR (500 MHz, CDCl$_3$)



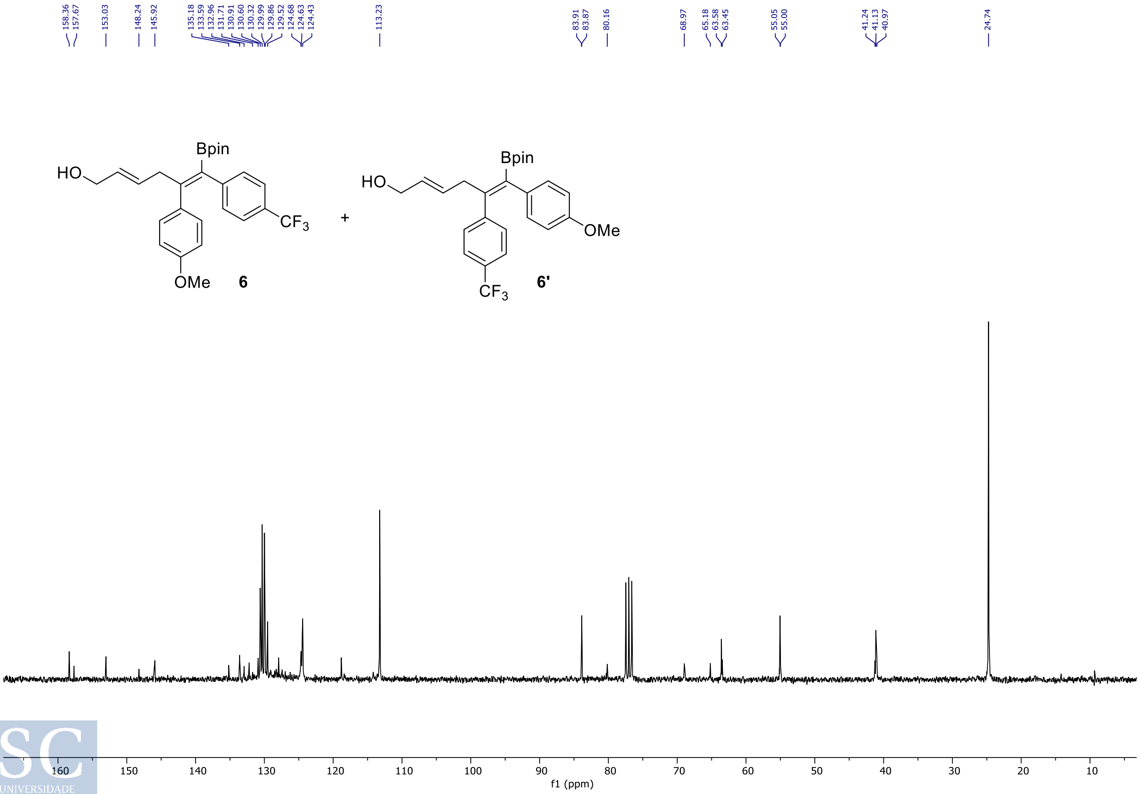
^{13}C NMR (75 MHz, CDCl$_3$)



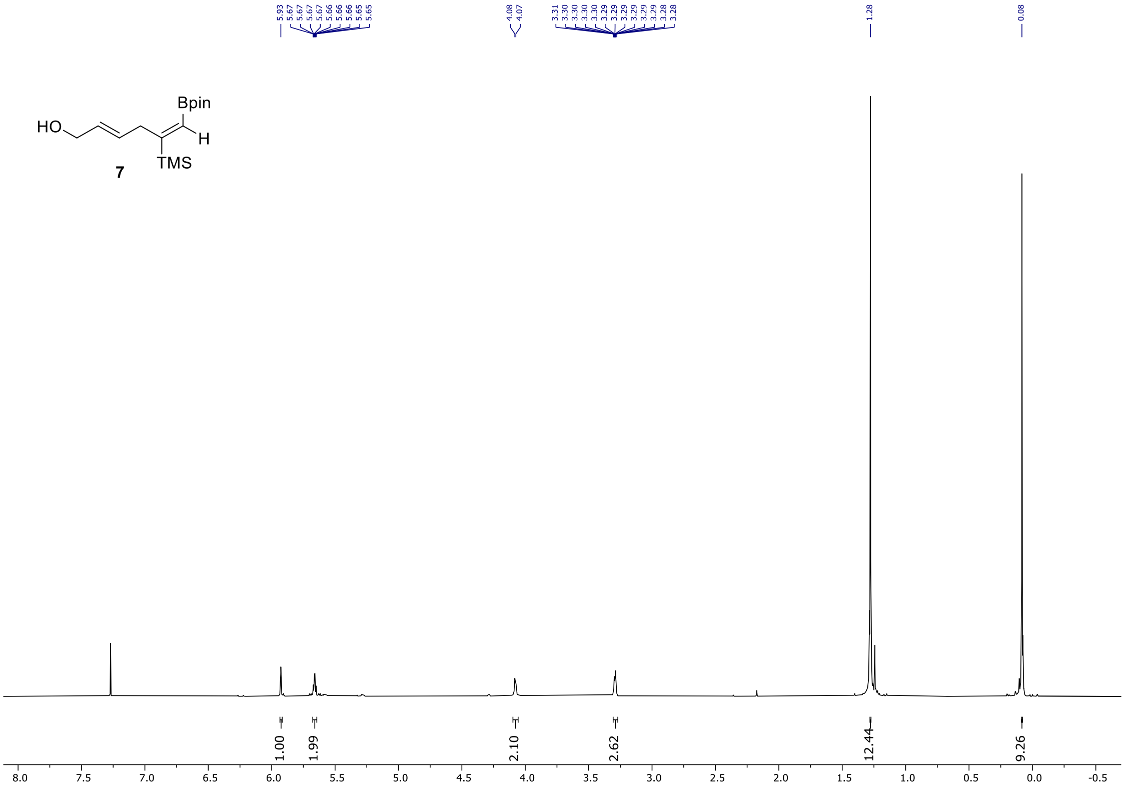
^{1}H NMR (300 MHz, CDCl$_3$)



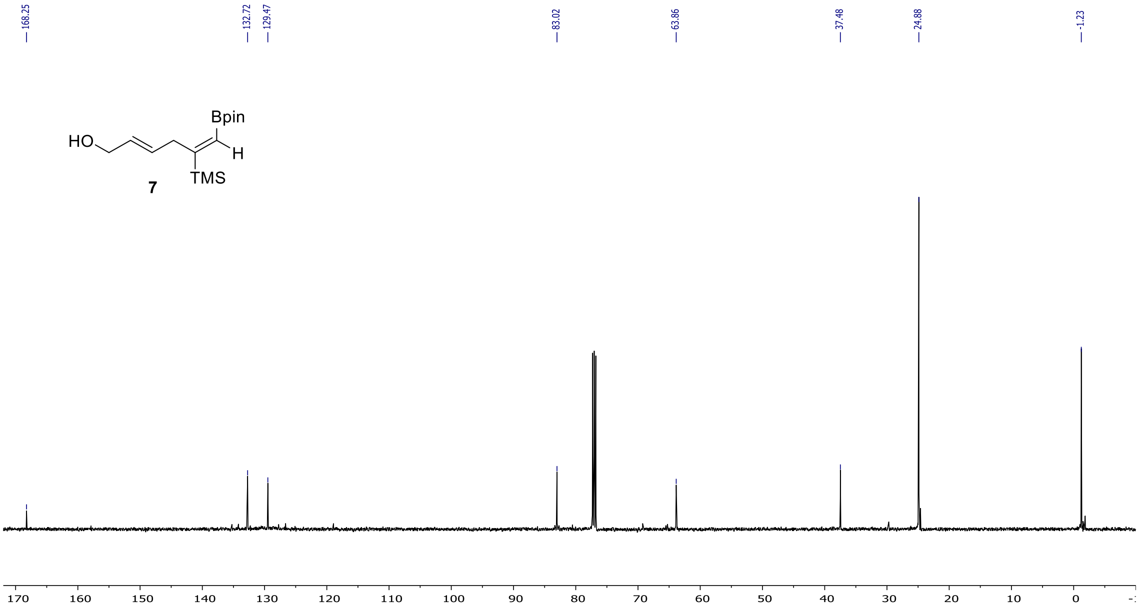
^{13}C NMR (75 MHz, CDCl$_3$)



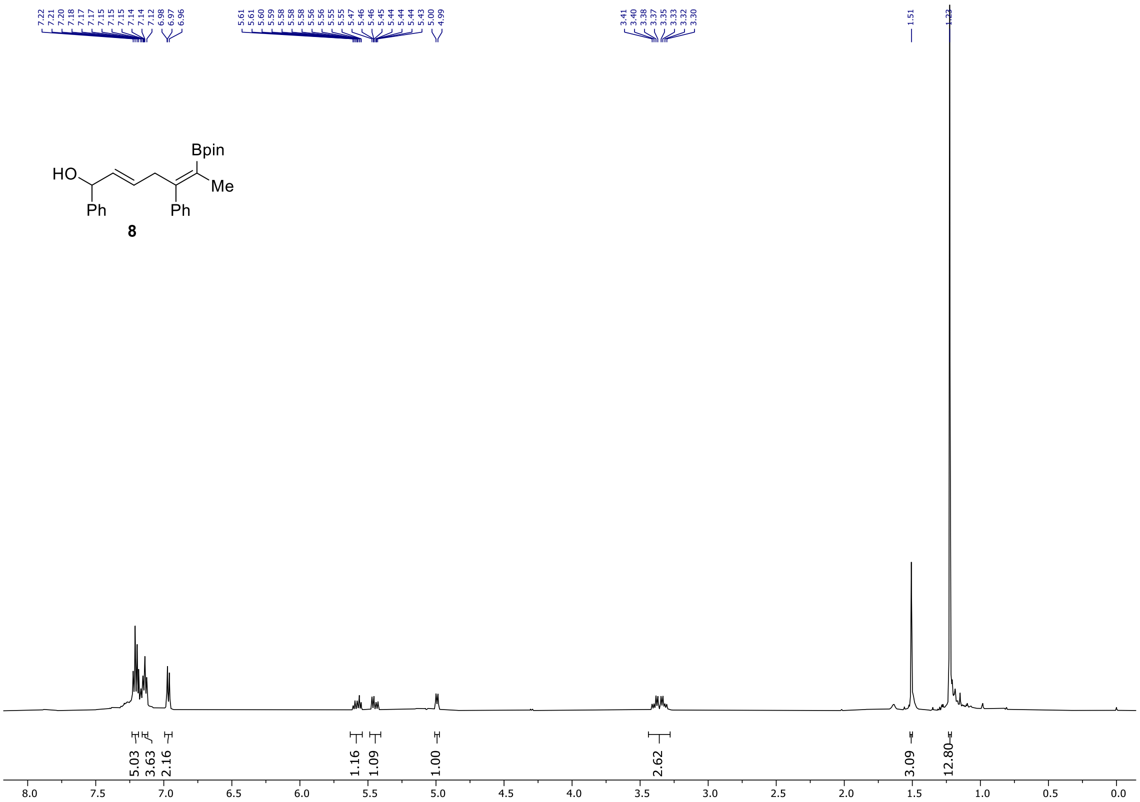
^{1}H NMR (500 MHz, $CDCl_3$)



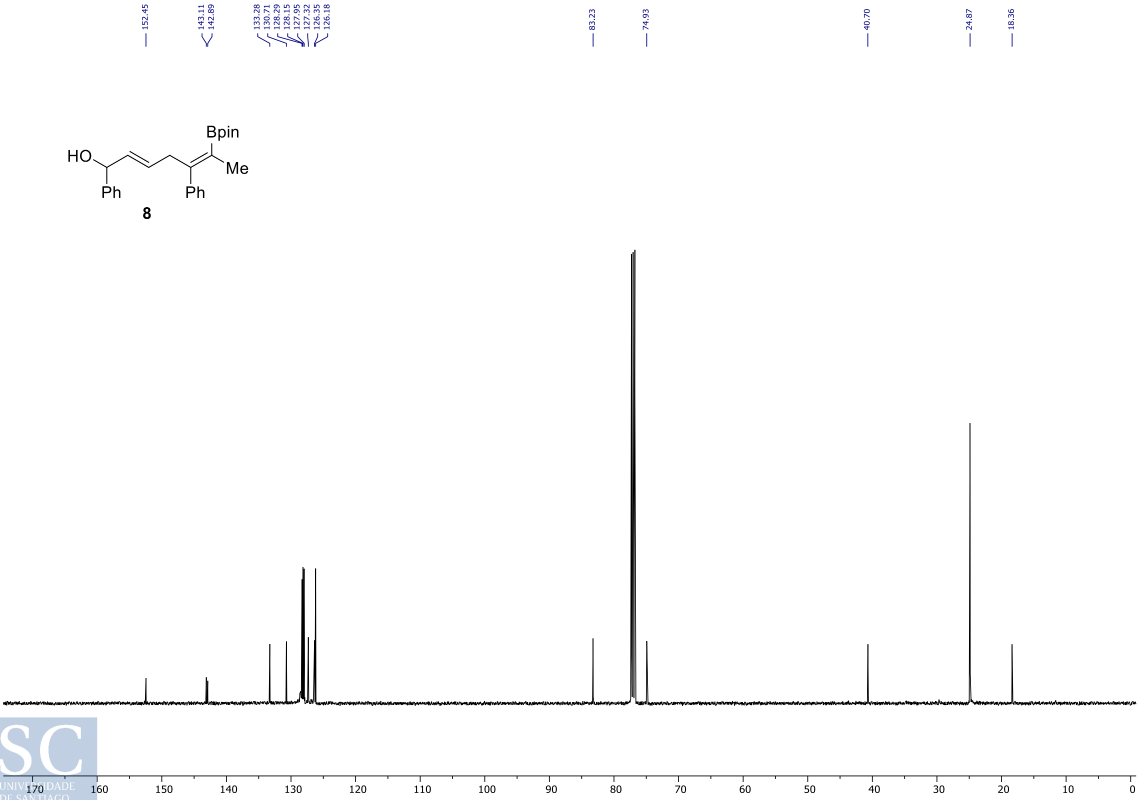
^{13}C NMR (126 MHz, $CDCl_3$)



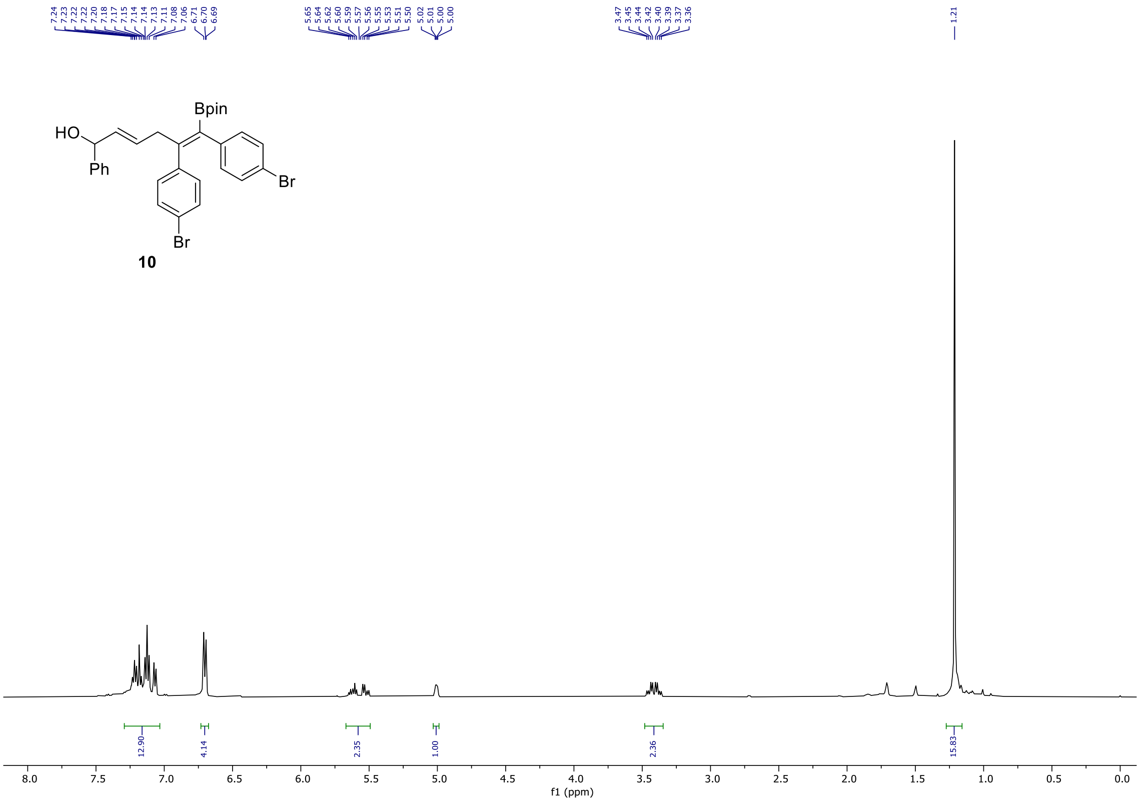
^{1}**H NMR** (500 MHz, CDCl$_3$)



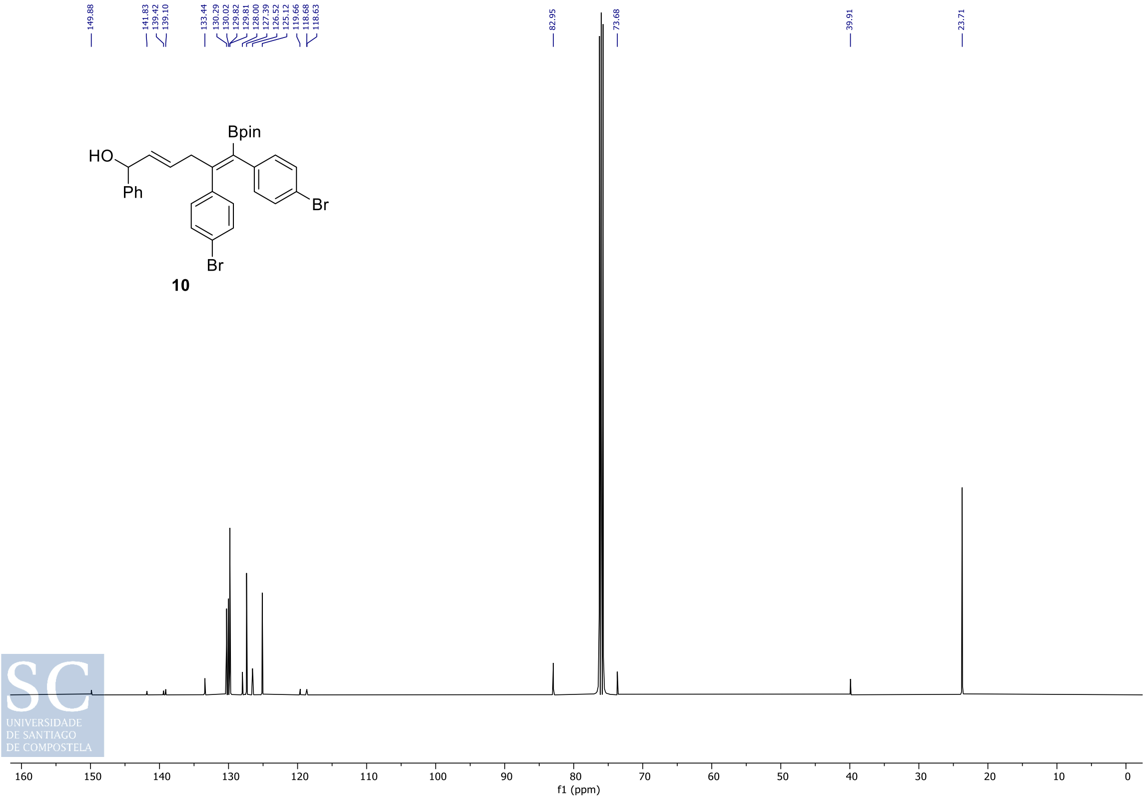
^{13}**C NMR** (126 MHz, CDCl$_3$)



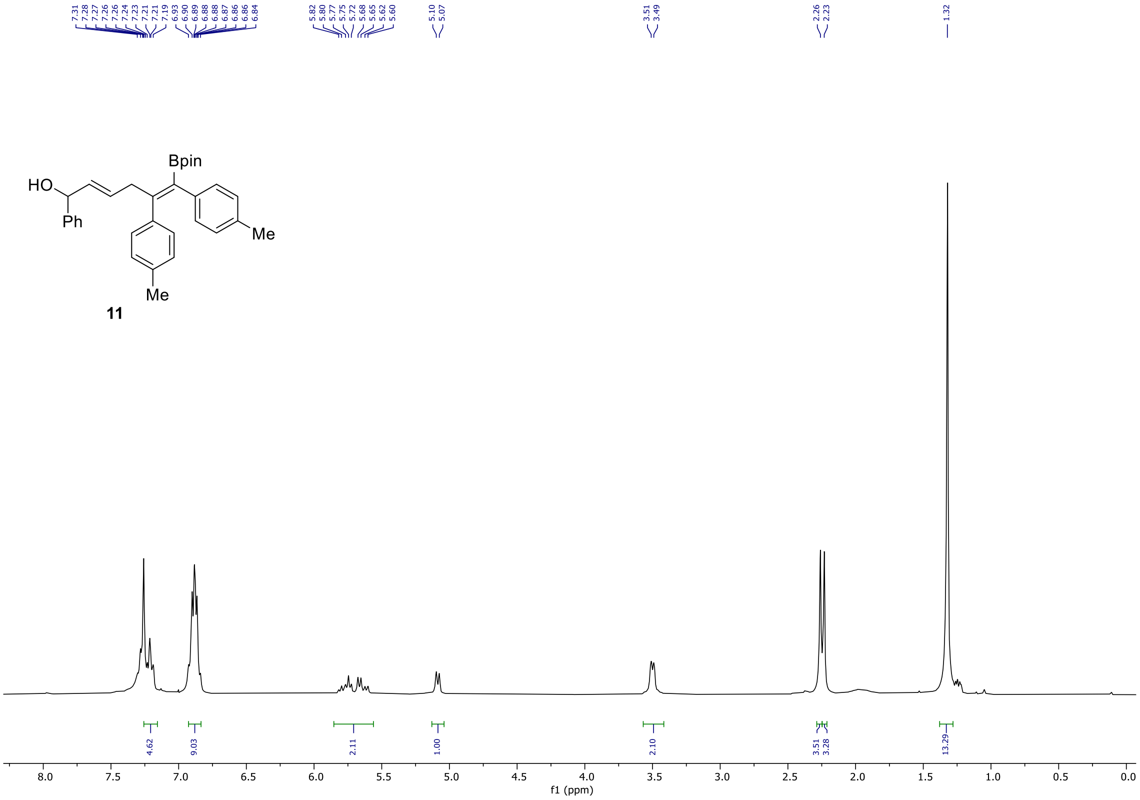
^{1}H NMR (500 MHz, CDCl$_3$)



^{1}H NMR (126 MHz, CDCl$_3$)

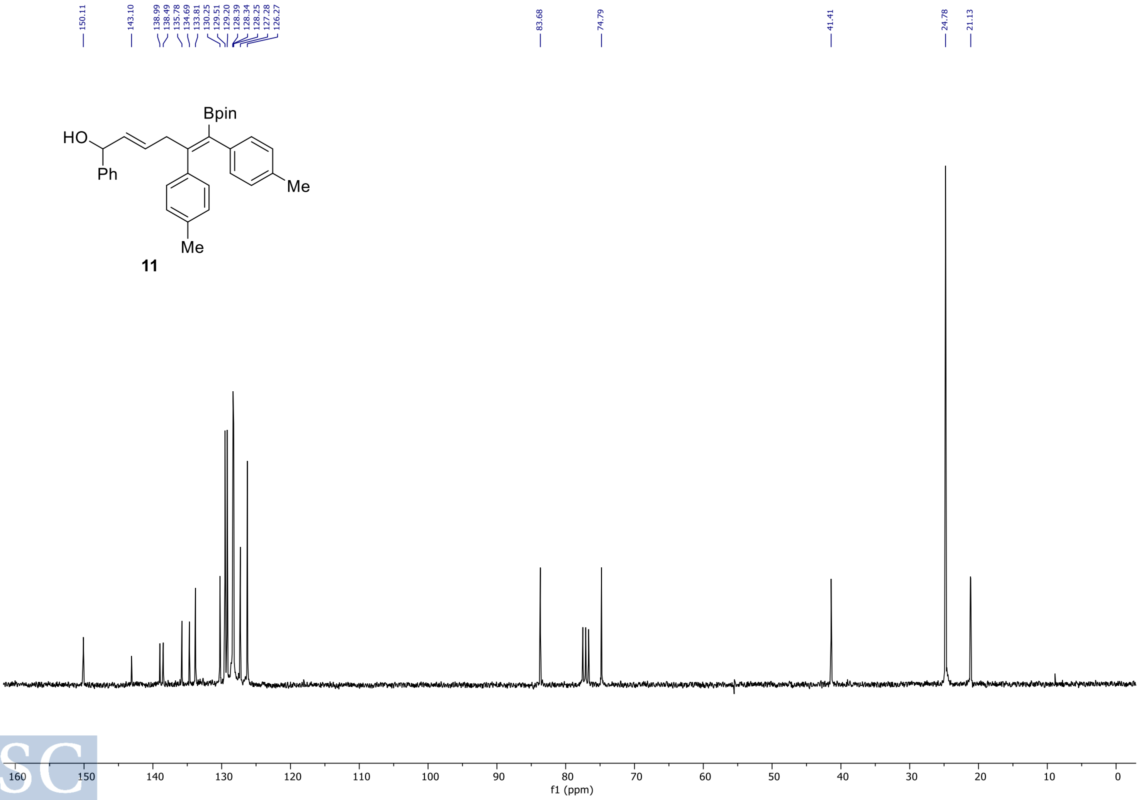


^{1}**H NMR** (300 MHz, CDCl$_3$)



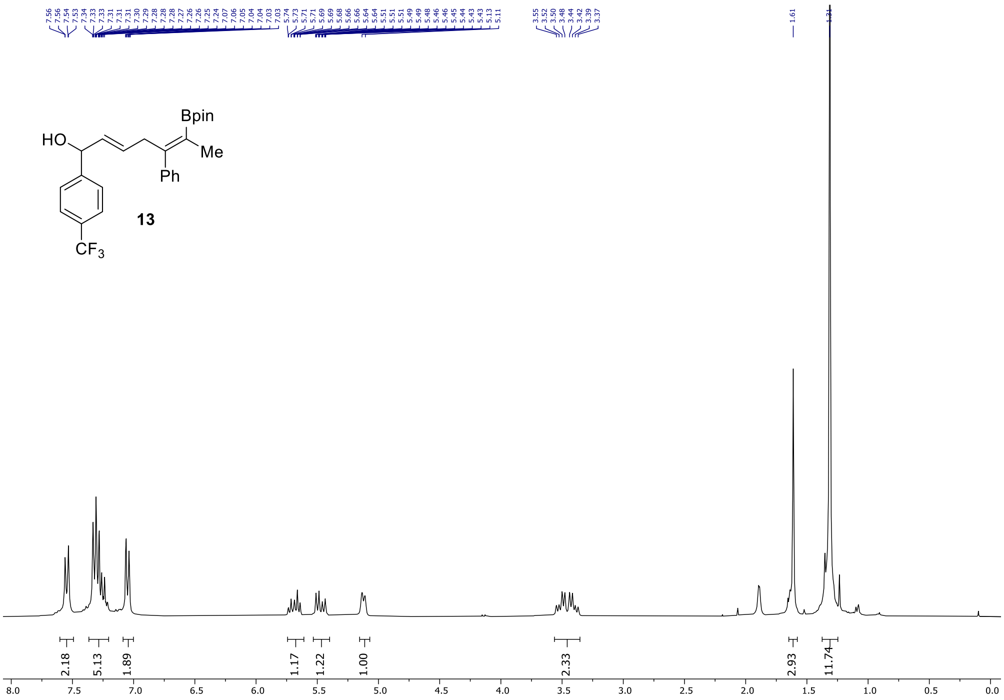
11

^{13}**C NMR** (75 MHz, CDCl$_3$)

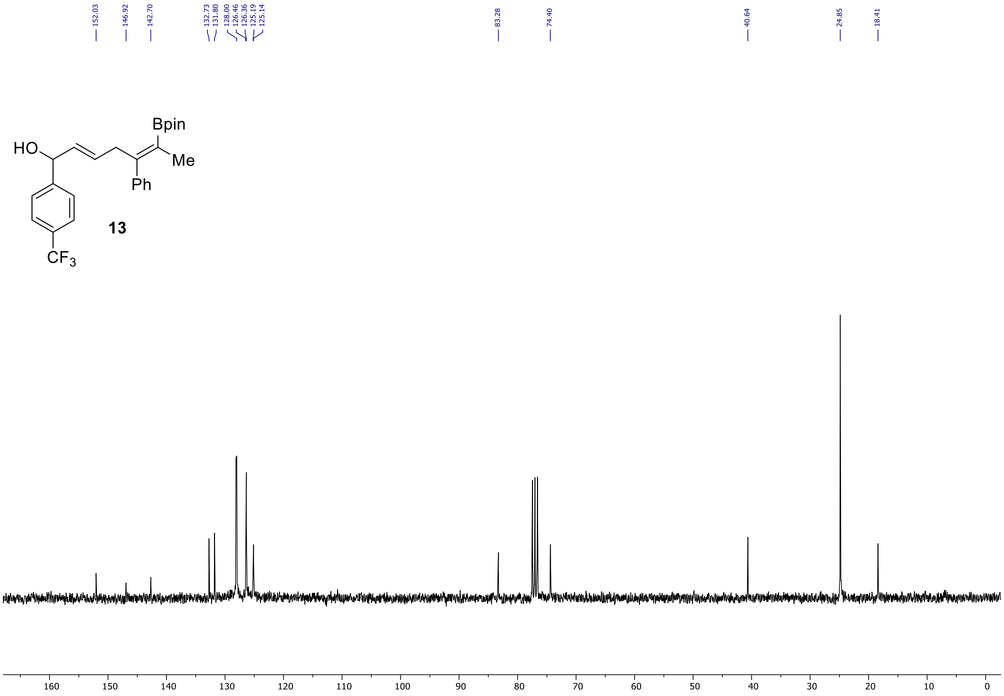


11

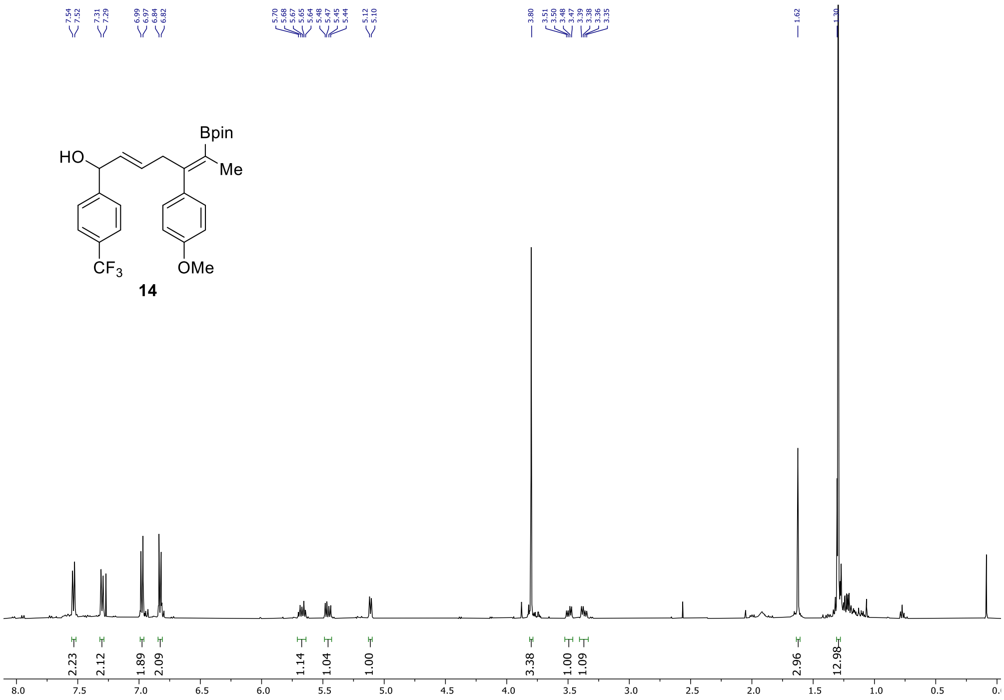
^{1}H NMR (500 MHz, $CDCl_3$)



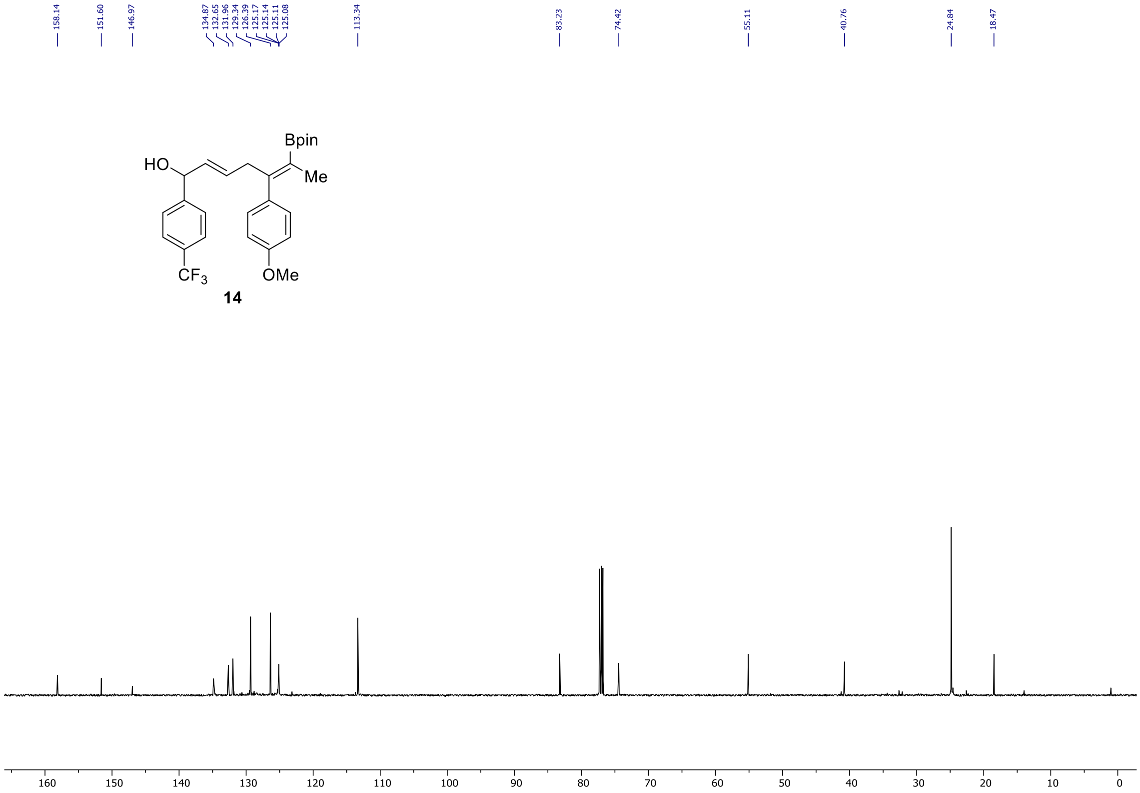
^{13}C NMR (162 MHz, $CDCl_3$)



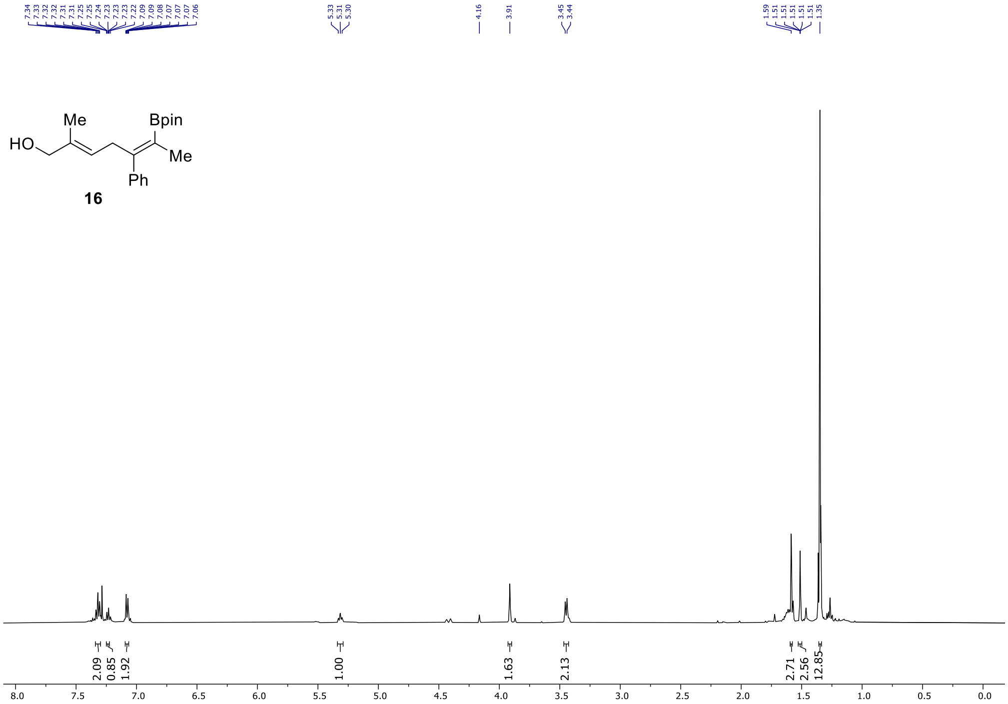
^{1}H NMR (500 MHz, $CDCl_3$)



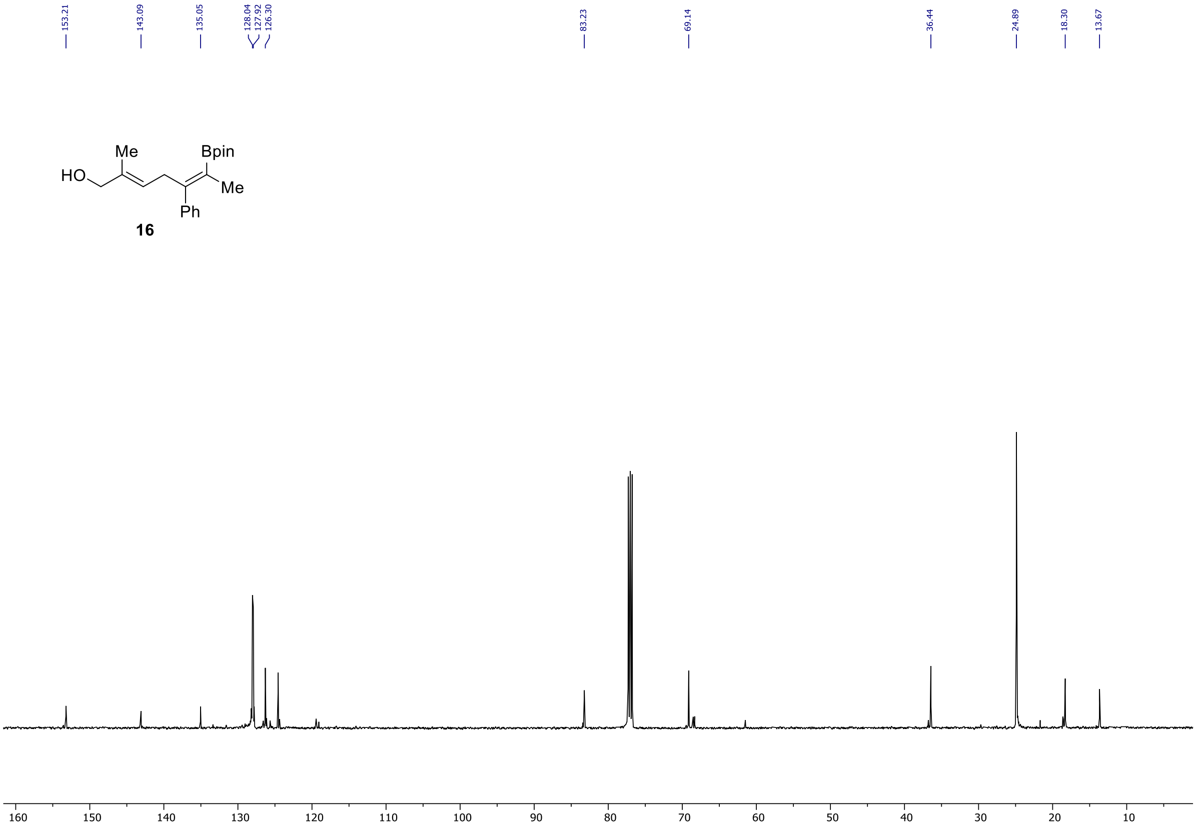
^{13}C NMR (162 MHz, $CDCl_3$)



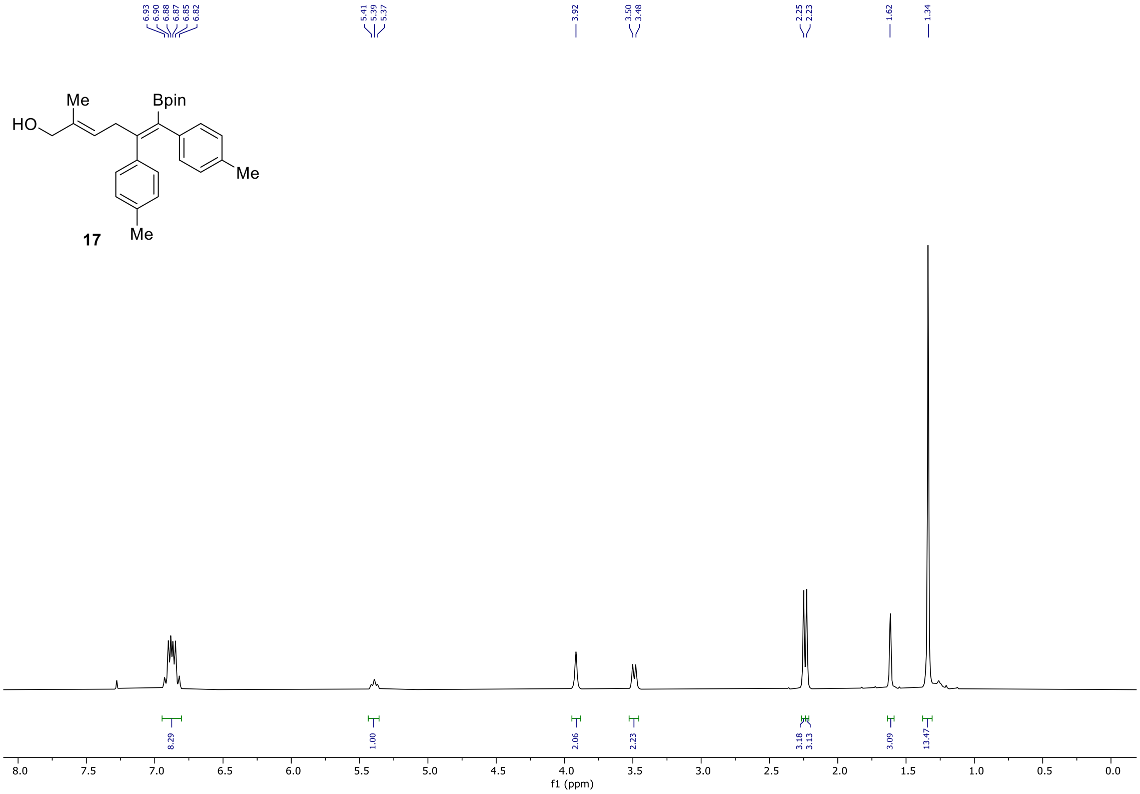
^{1}H NMR (500 MHz, $CDCl_3$)



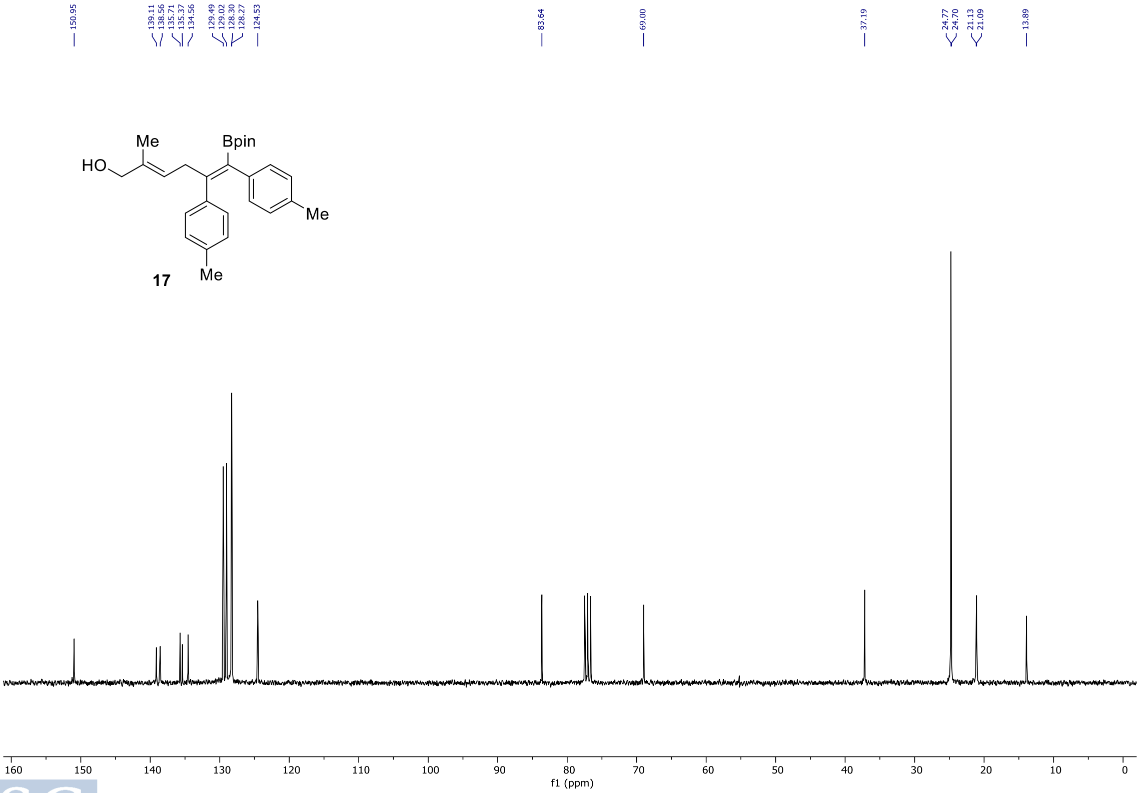
^{13}C NMR (126 MHz, CDCl$_3$)



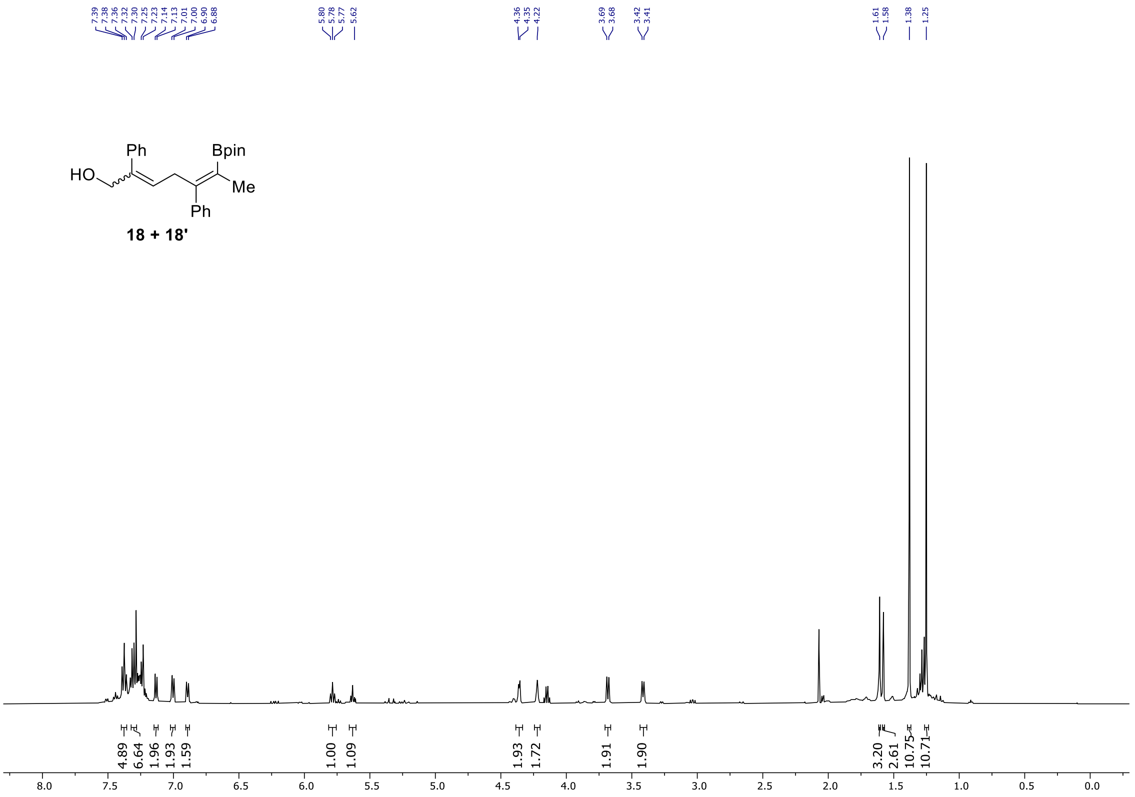
^{1}H NMR (500 MHz, CDCl$_3$)



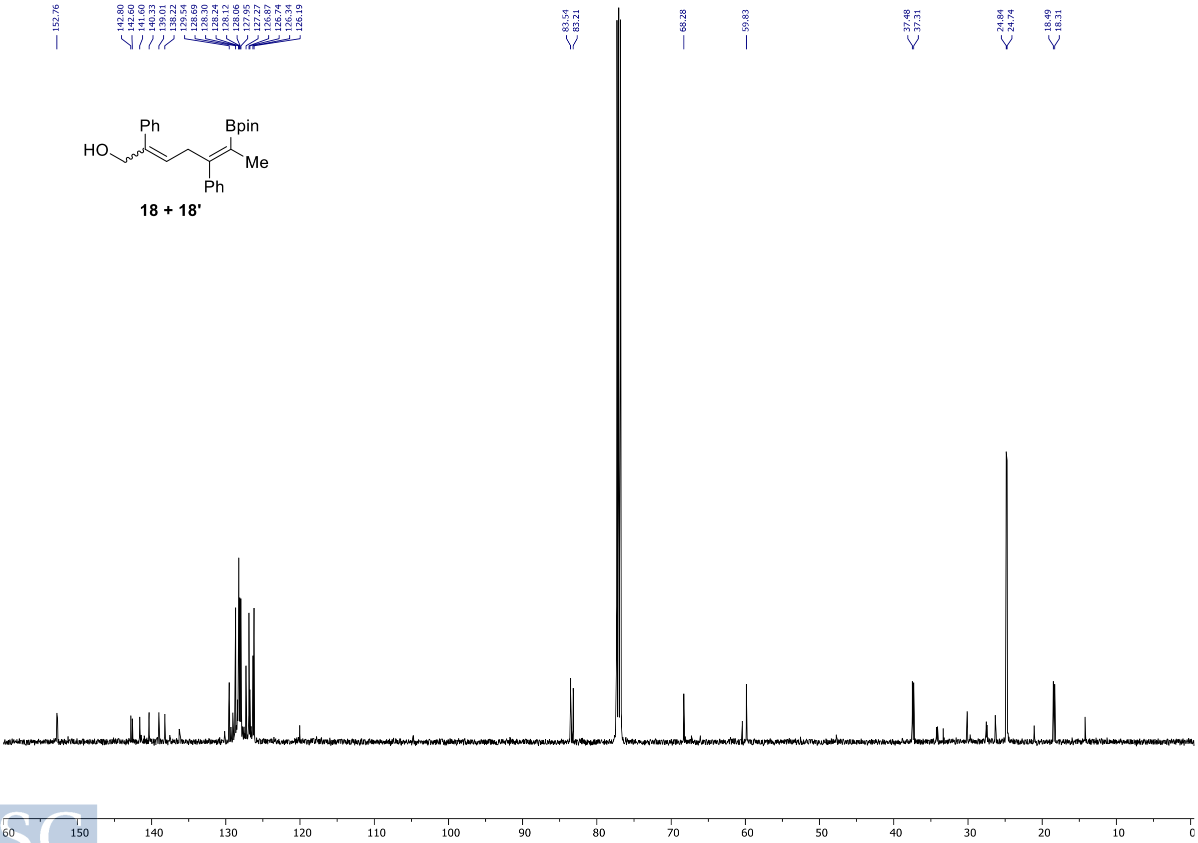
^{13}C NMR (162 MHz, $CDCl_3$)



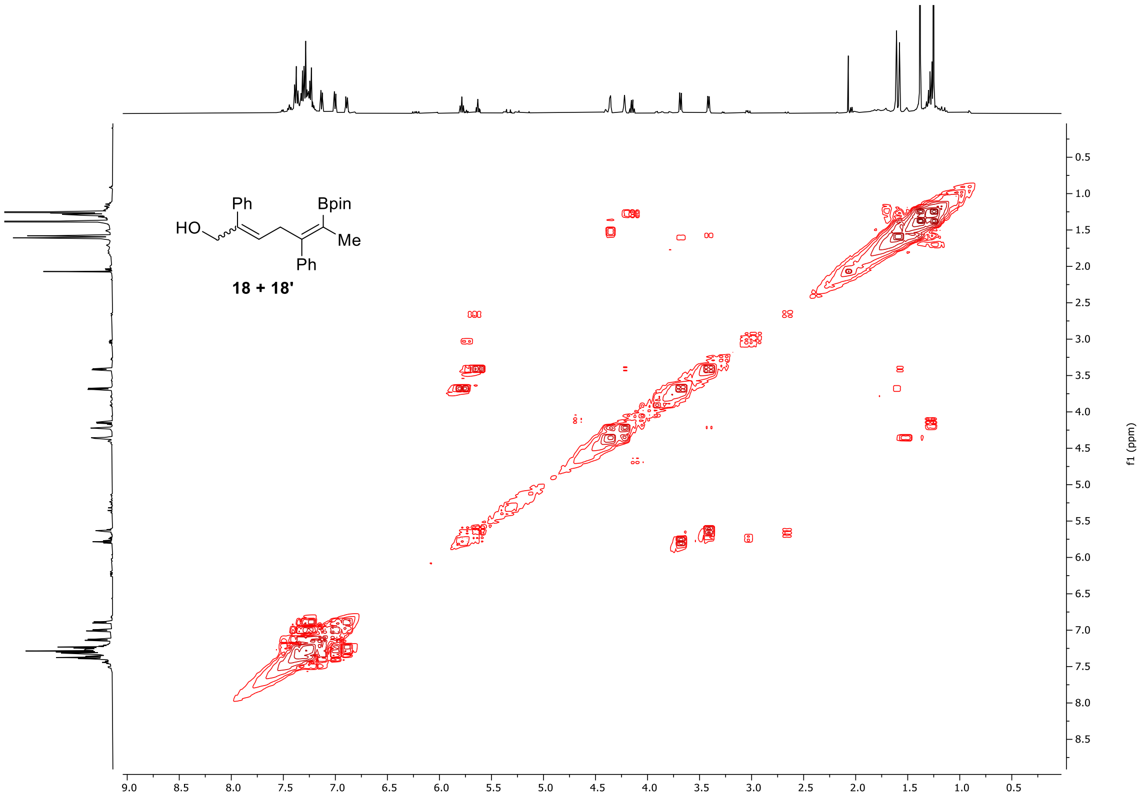
^{1}H NMR (500 MHz, $CDCl_3$)



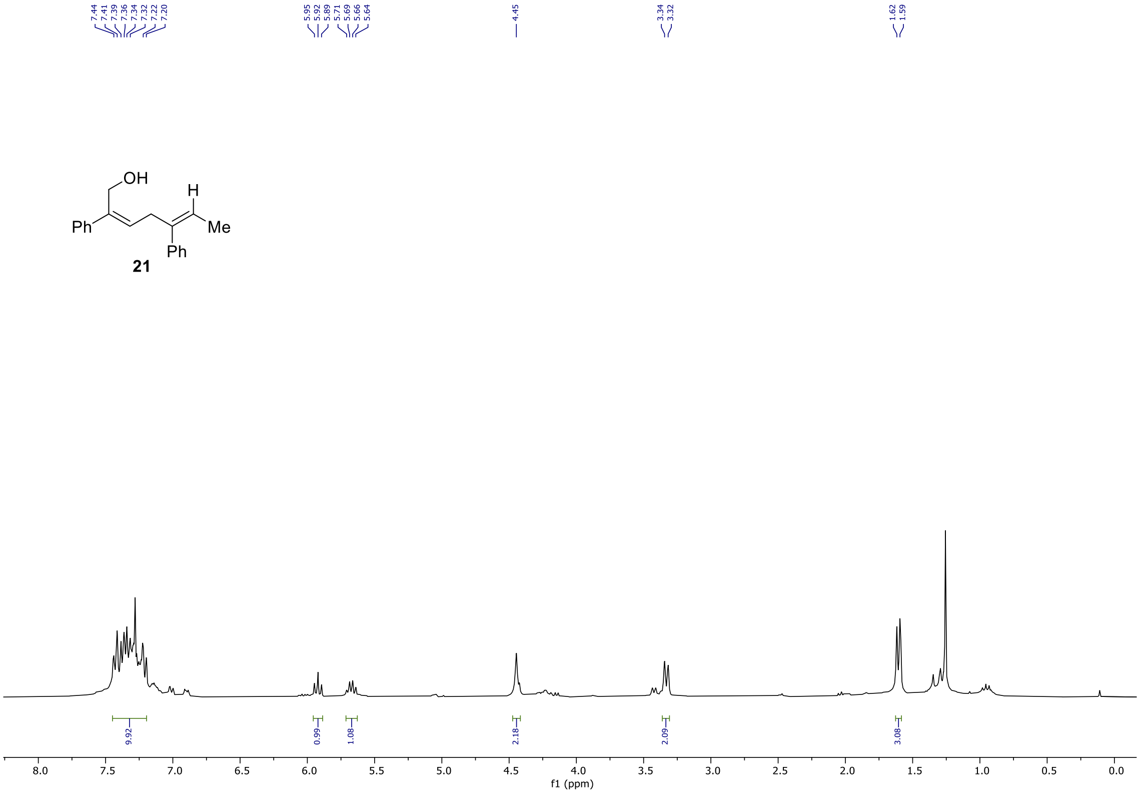
^{13}C NMR (126 MHz, CDCl$_3$)



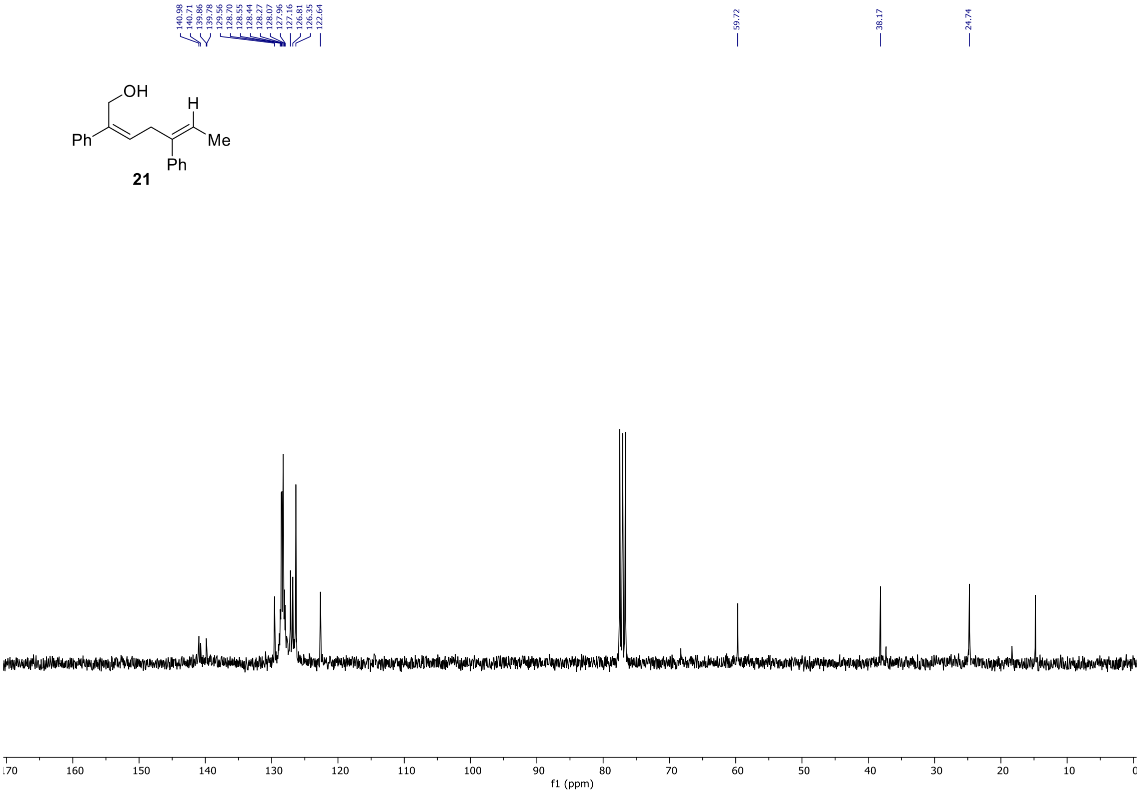
COSY



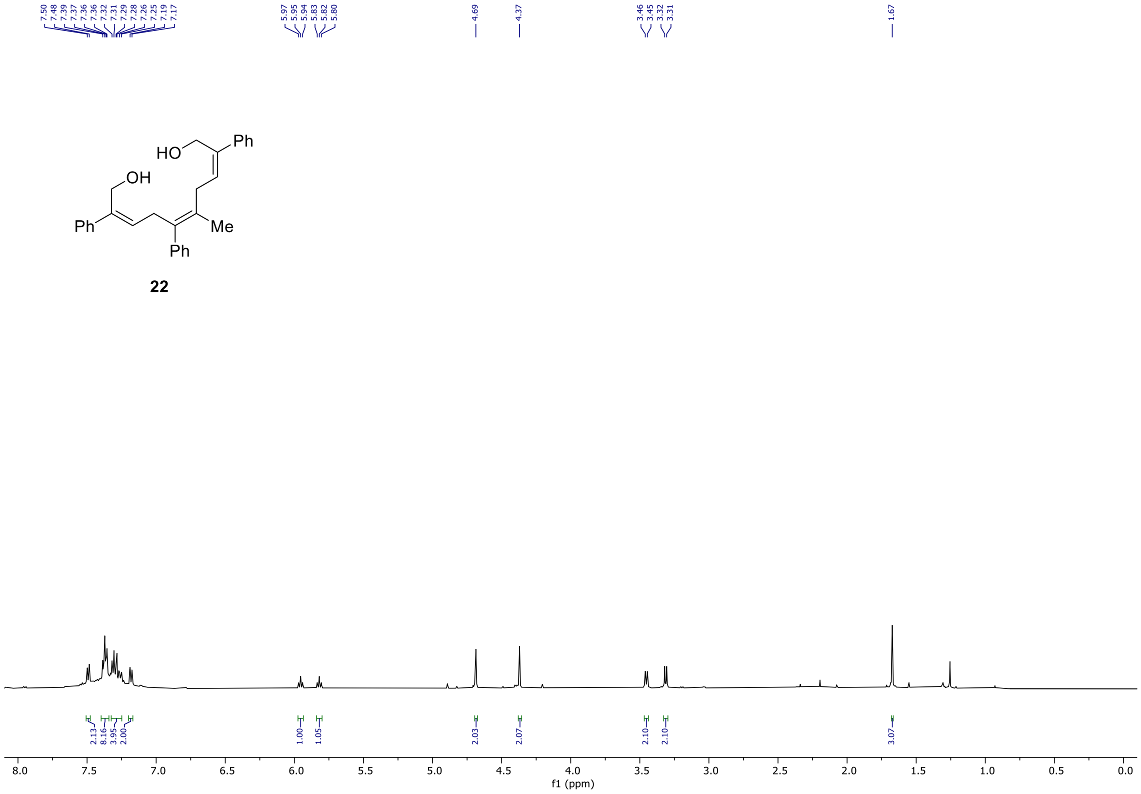
^{1}H NMR (500 MHz, CDCl$_3$)



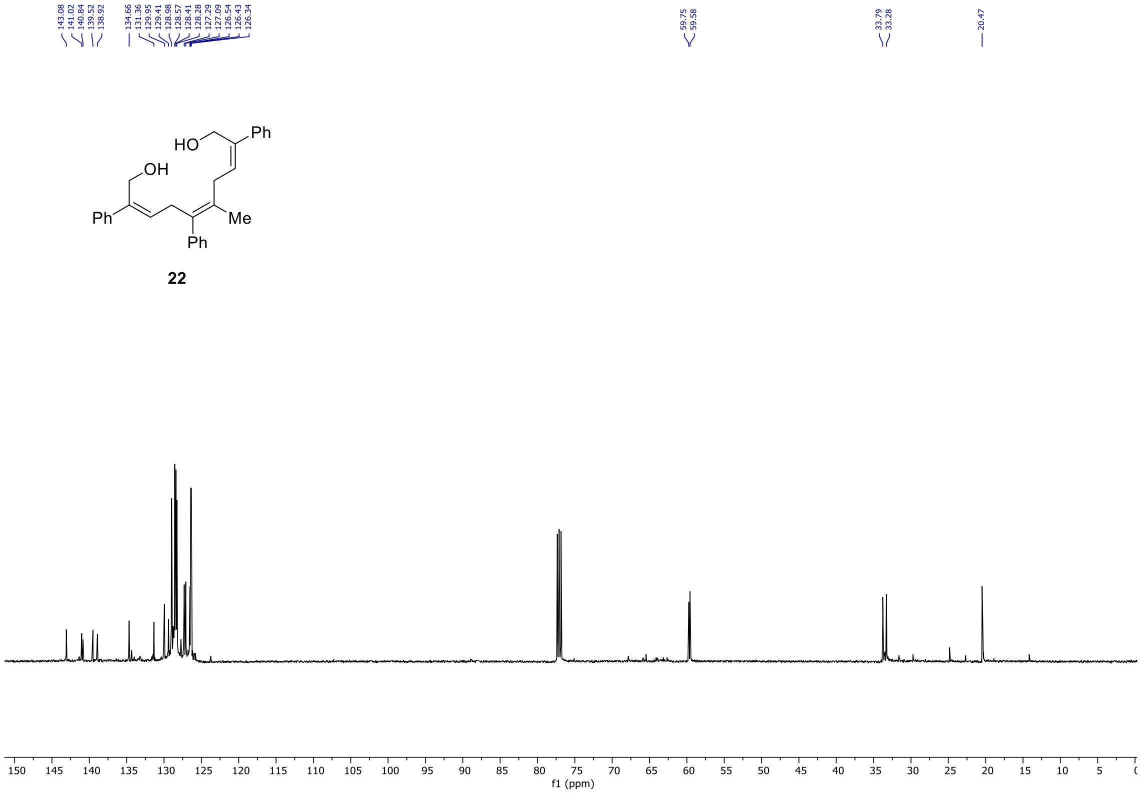
^{13}C NMR (126 MHz, $CDCl_3$)



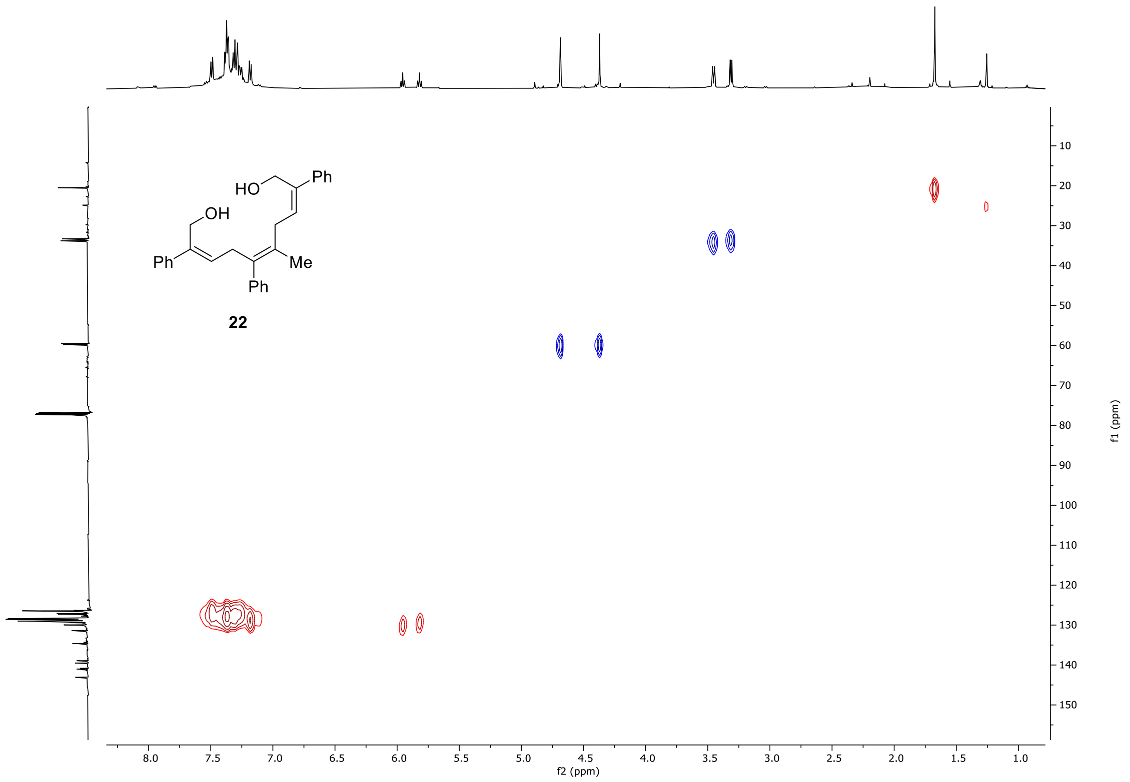
^{1}H NMR (300 MHz, $CDCl_3$)



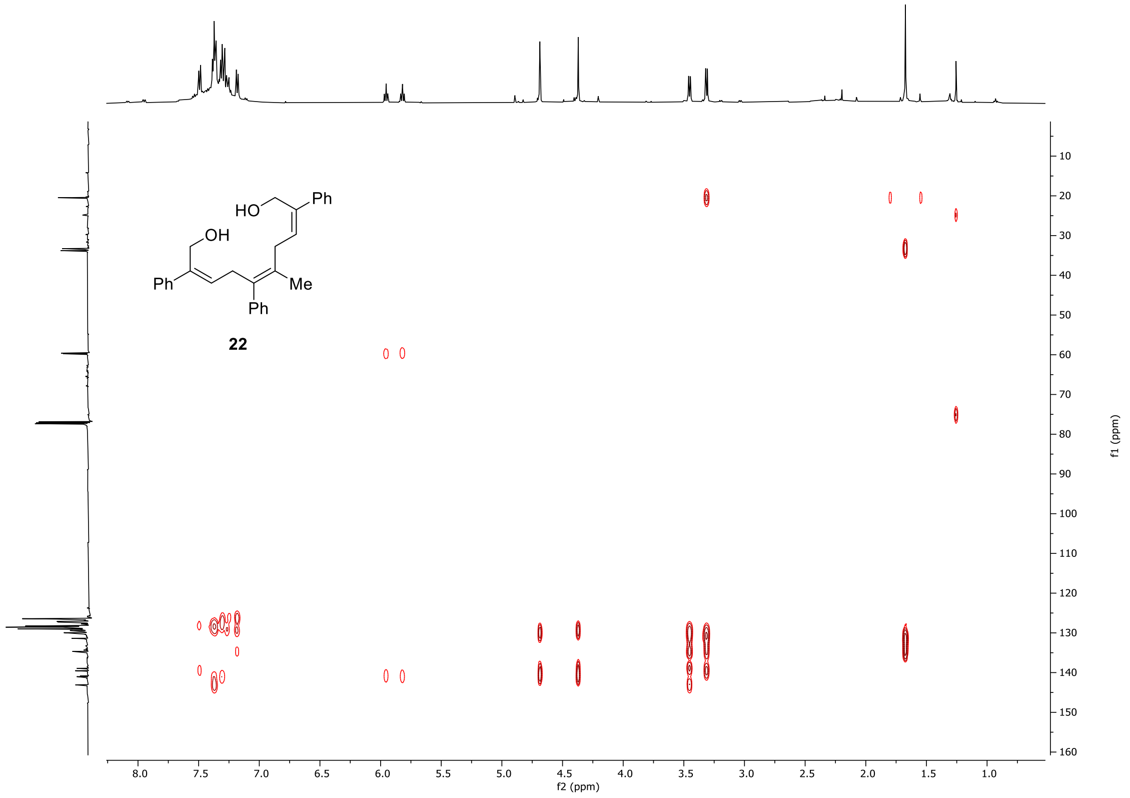
^{13}C NMR (126 MHz, $CDCl_3$)



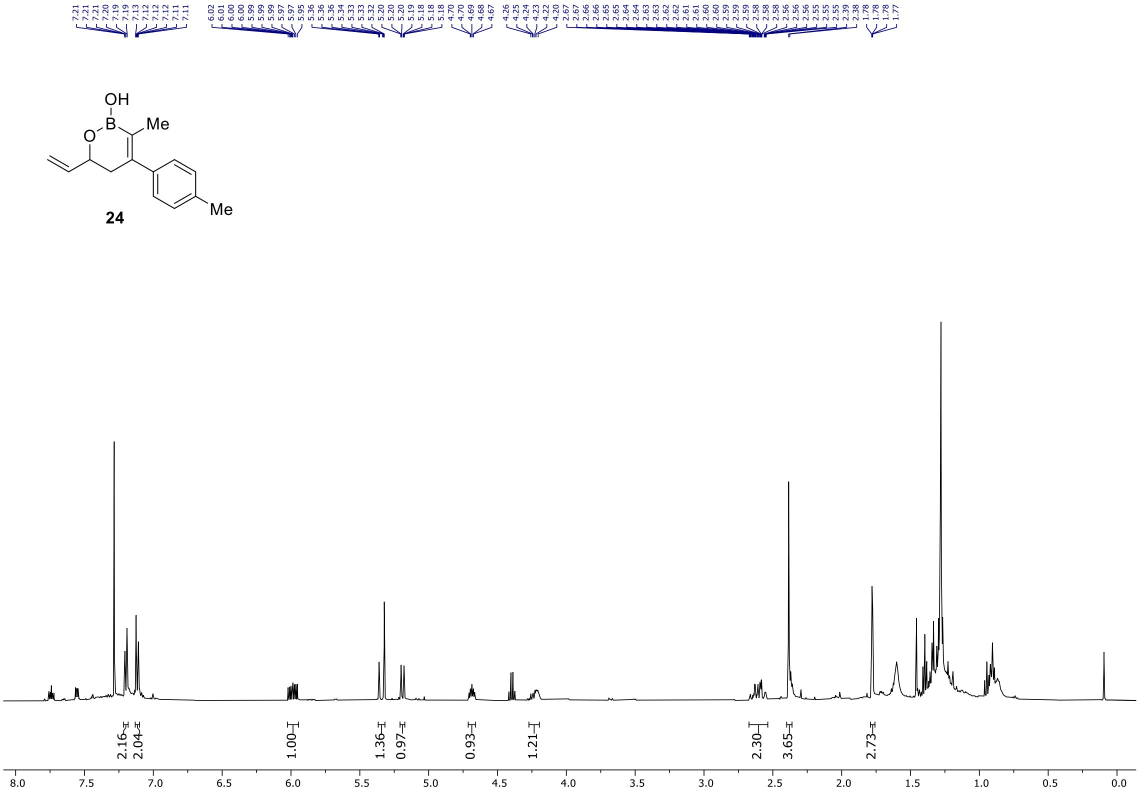
HSQC



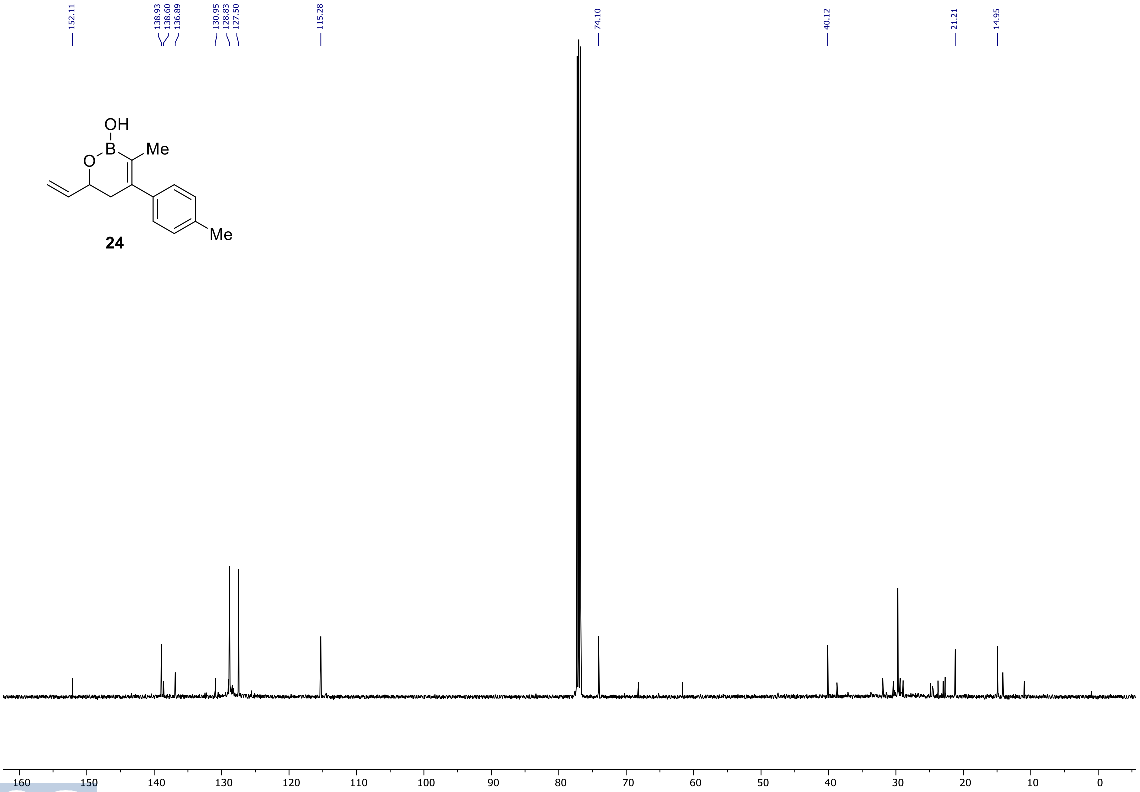
HMBC



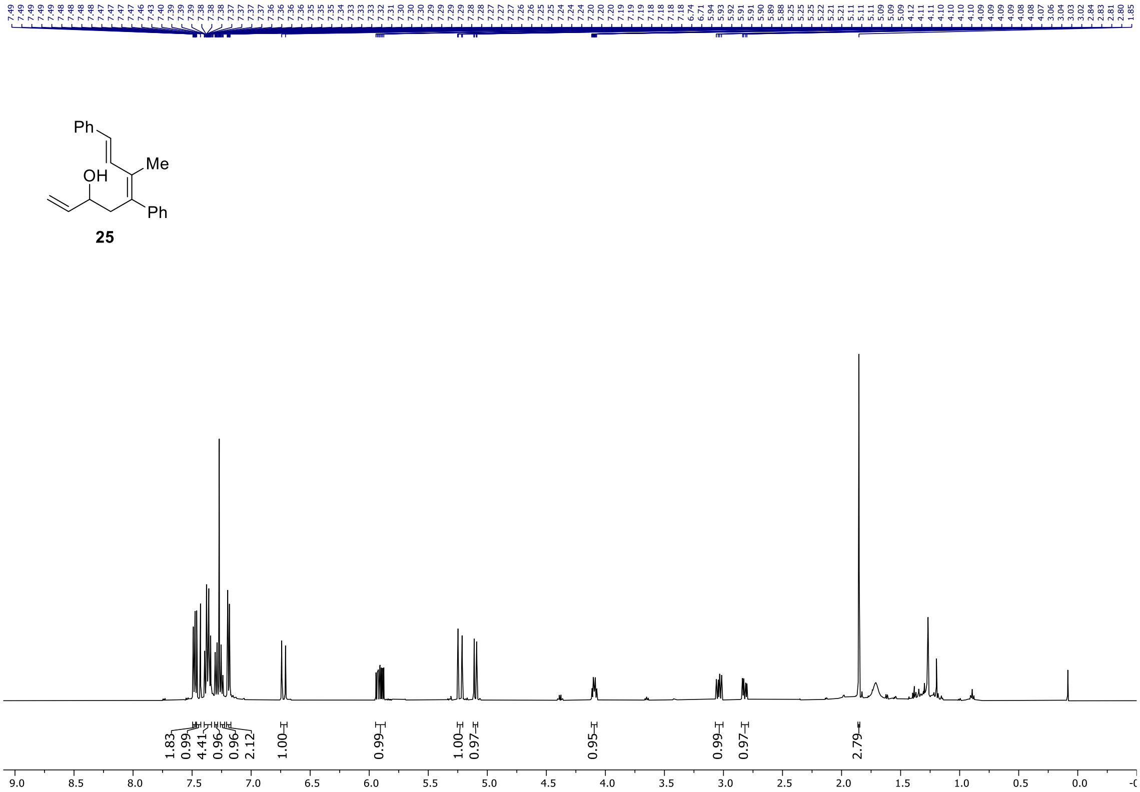
^{1}H NMR (500 MHz, CDCl$_3$)



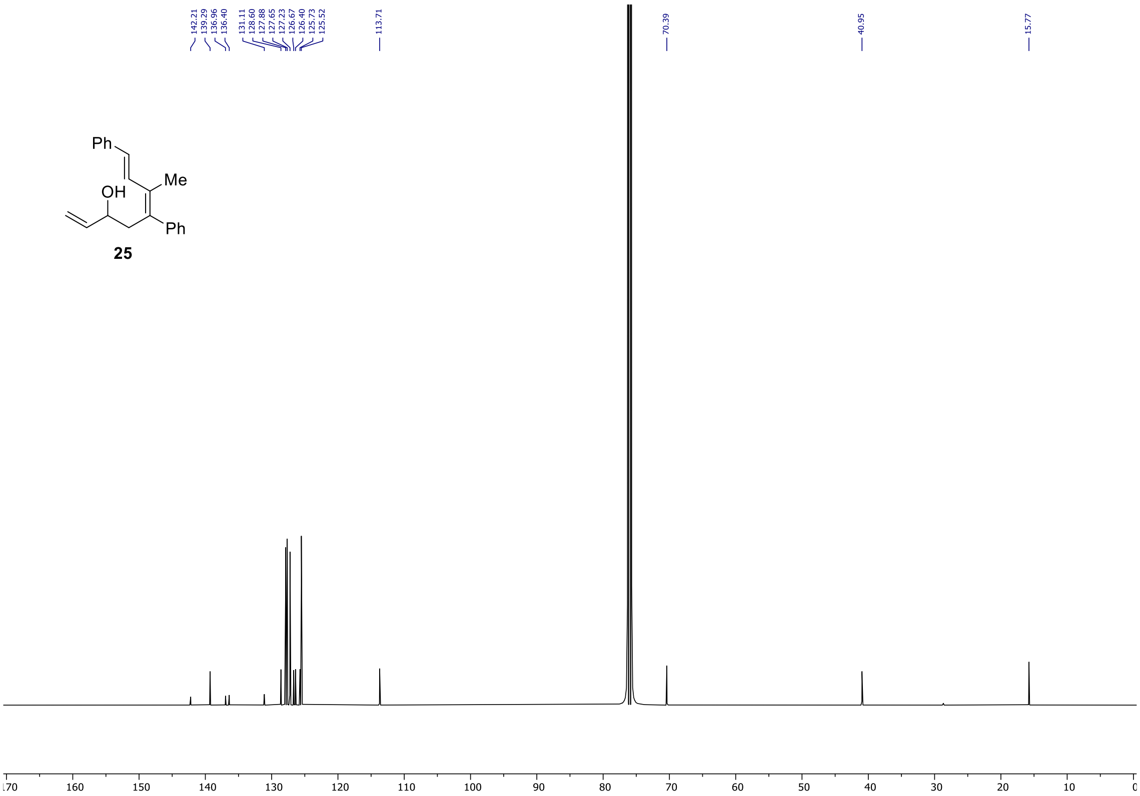
^{13}**C NMR** (126 MHz, $CDCl_3$)



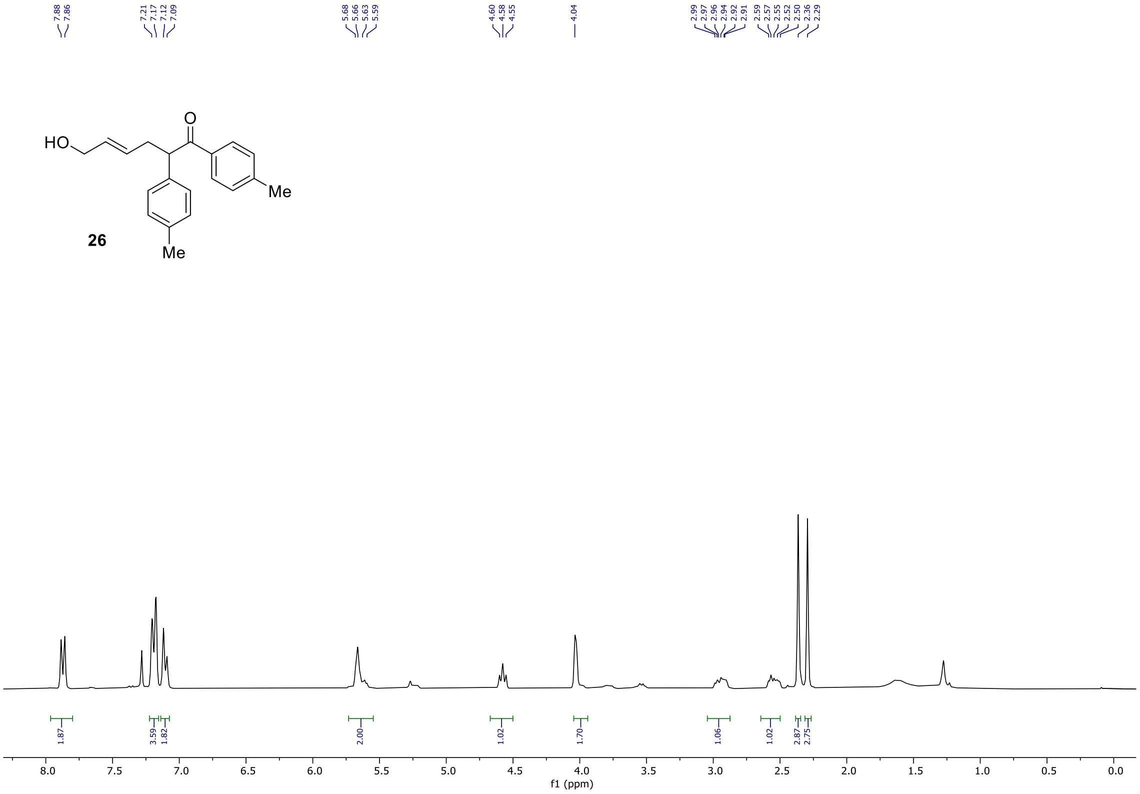
^{1}**H NMR** (500 MHz, $CDCl_3$)



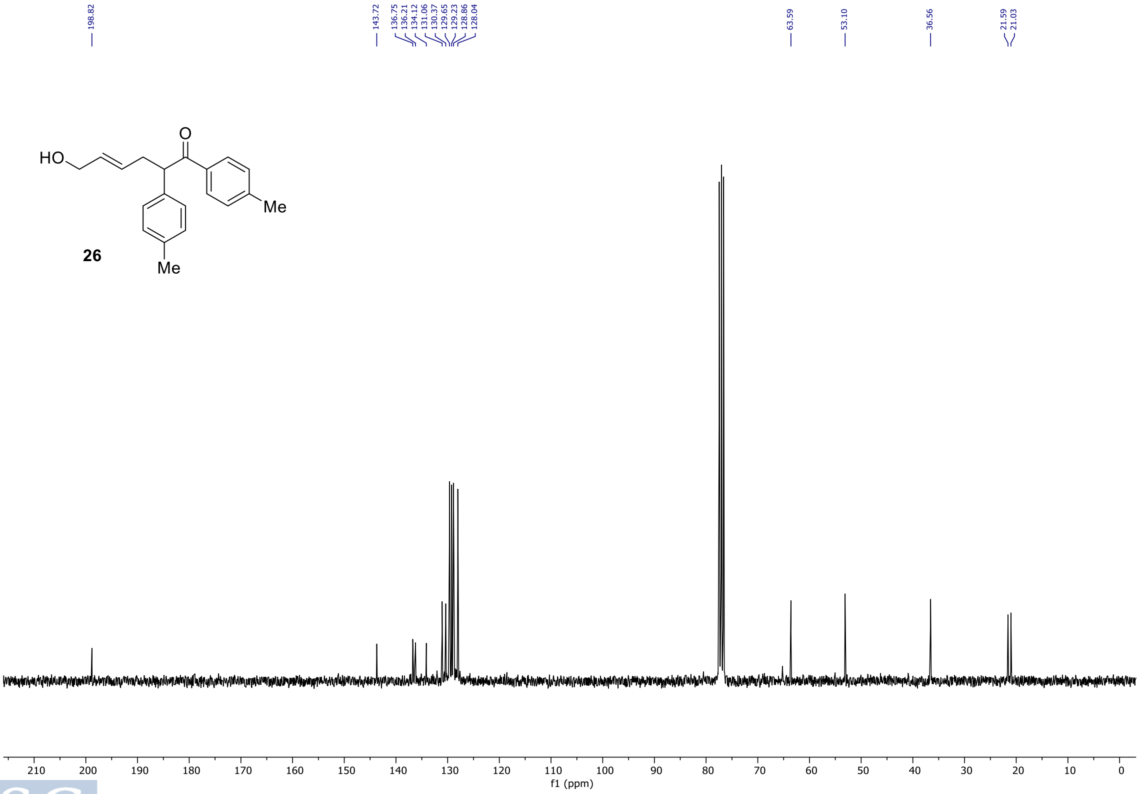
^{13}C-NMR (126 MHz, CDCl$_3$)



^{1}H NMR (300 MHz, CDCl$_3$)

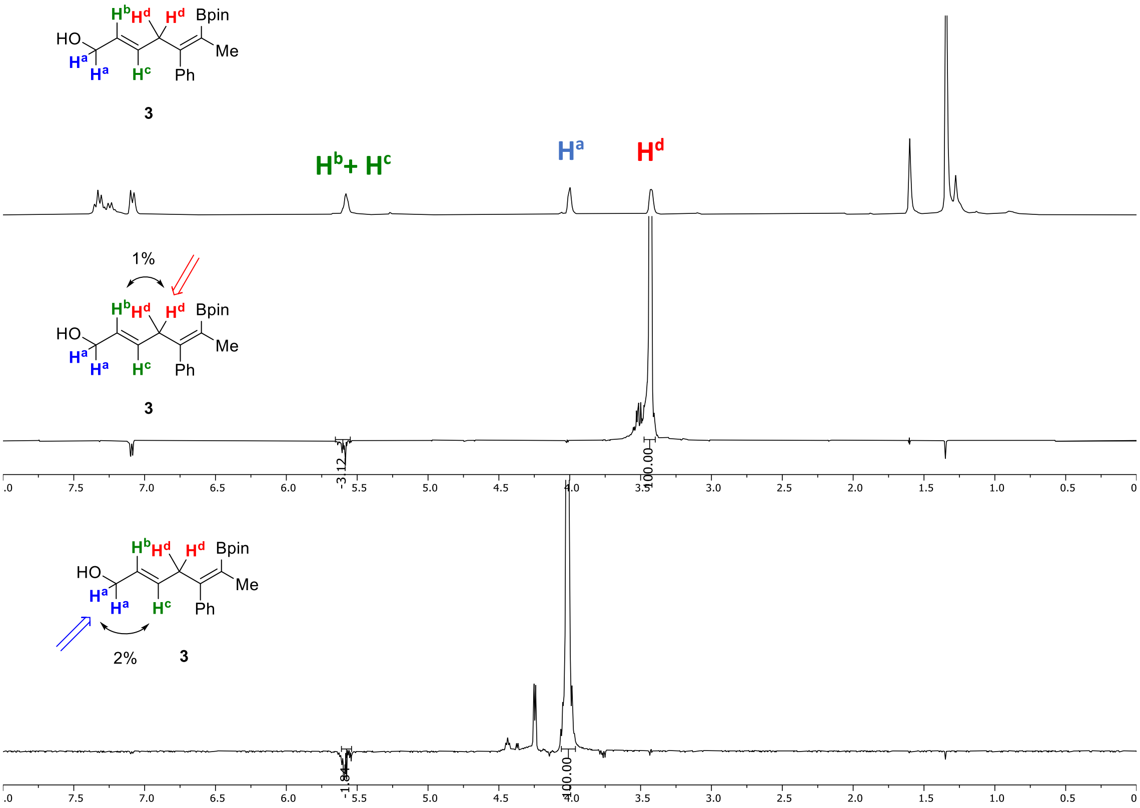


^{13}C NMR (75 MHz, $CDCl_3$)



Stereochemistry determination

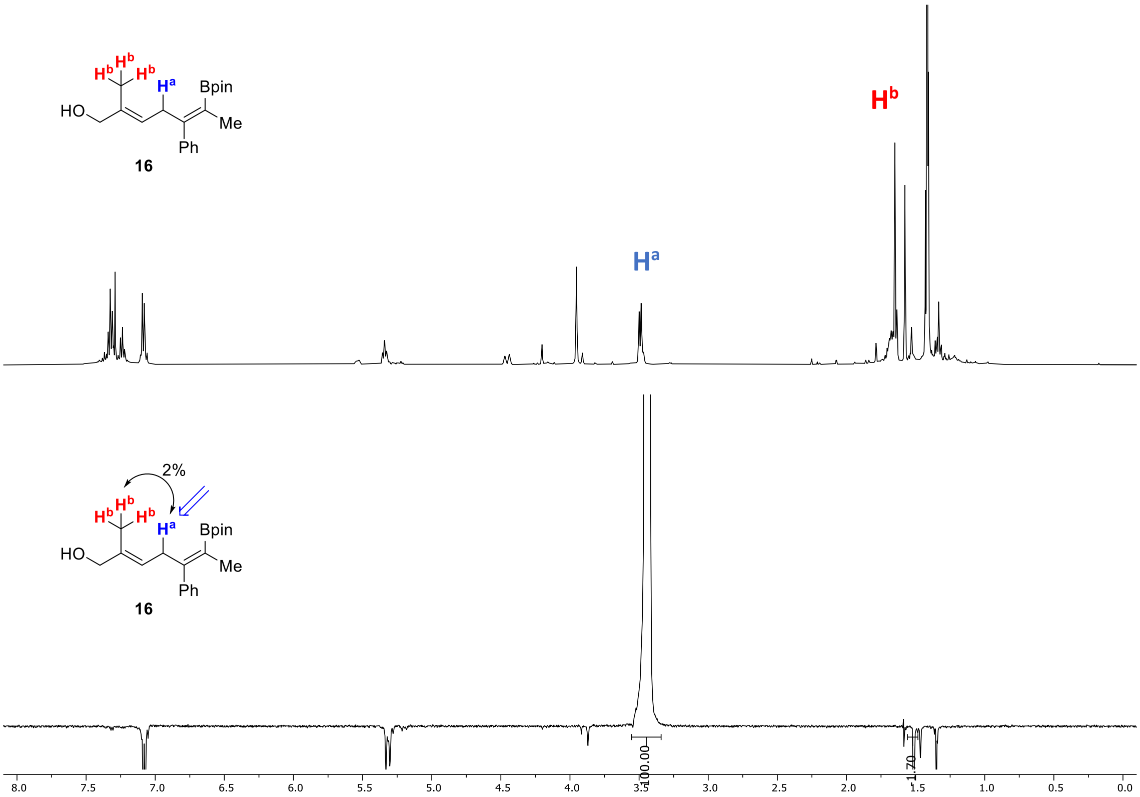
- **Compound 4.3**



The irradiation at CH$_2$ signal (H^d) induces a NOE response on the CH corresponding to (H^b and H^c) and not on the CH$_2$ corresponding to (H^a).

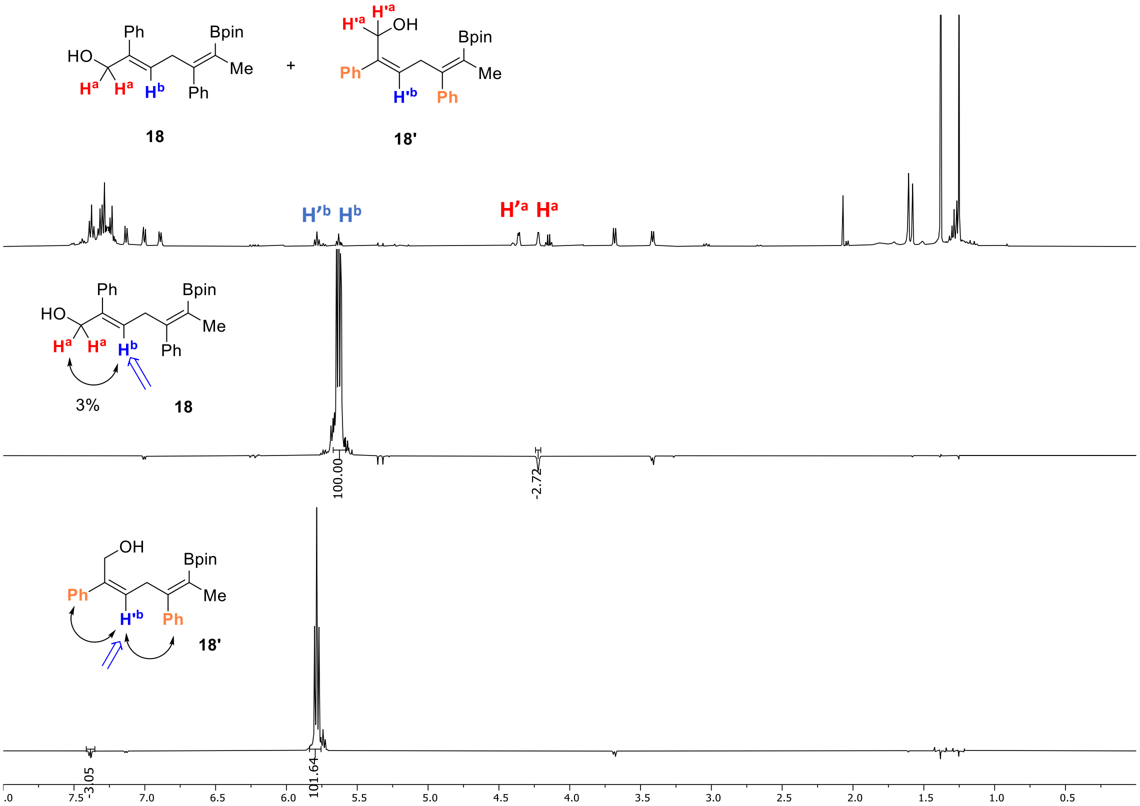
Similarly, irradiation at CH$_2$ signal (H^a) induces a NOE response on the CH corresponding to (H^b and H^c) and not on the CH$_2$ corresponding to (H^d).

- **Compound 4.16**



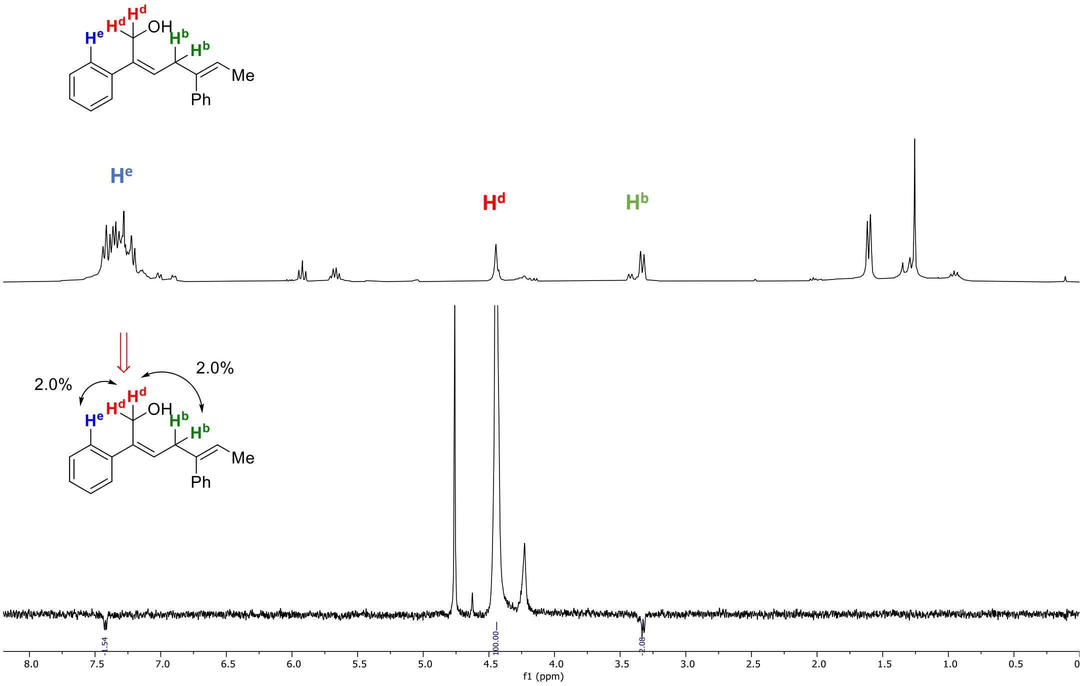
The irradiation at CH_2 signal (H^a) induces a NOE response on the CH_3 corresponding to (H^b).

- **Compounds 4.18 and 4.18’**



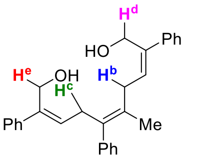
The irradiation at CH signal (H^b) induces a NOE response on the CH$_2$ corresponding to (H^a).

The irradiation at CH signal (H$'^b$) induces a NOE response on the CH corresponding to phenyl group (H^{Ph}).

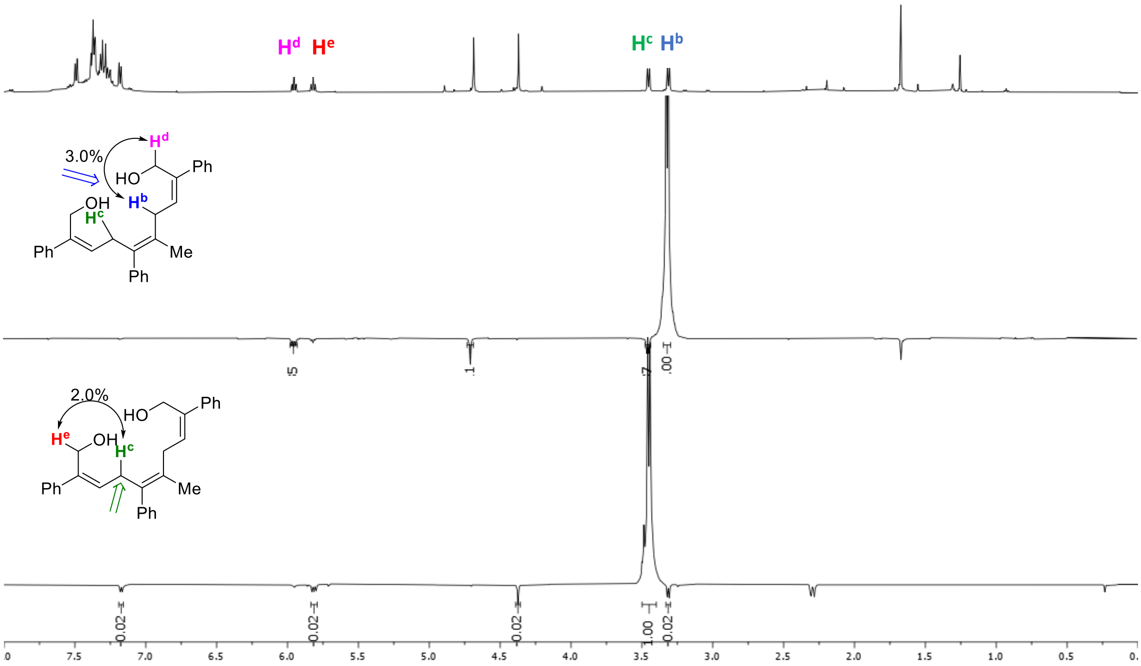


The irradiation at CH_2 signal (**H^d**) induces a NOE response on the CH_2 corresponding to (**H^b**) and on the CH corresponding to (**H^e**).

- **Compound 4.22**



22



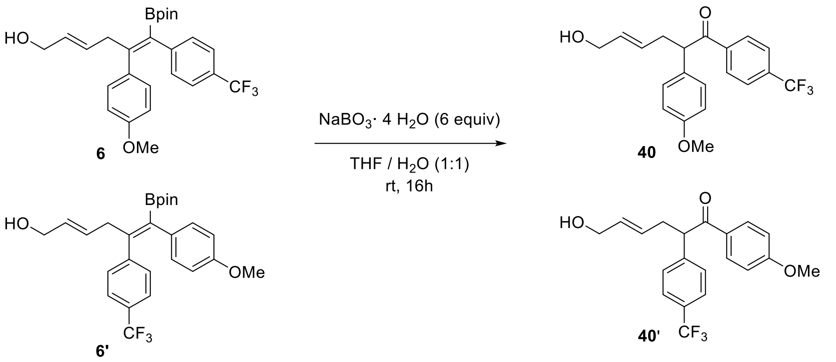
The irradiation at CH_2 signal (H^b) induces a NOE response on the CH_2 corresponding to (H^d and $H^{d'}$) and on the CH_2 corresponding to (H^c).

The irradiation at CH_2 signal (H^c) induces a NOE response on the CH_2 corresponding to (H^e).

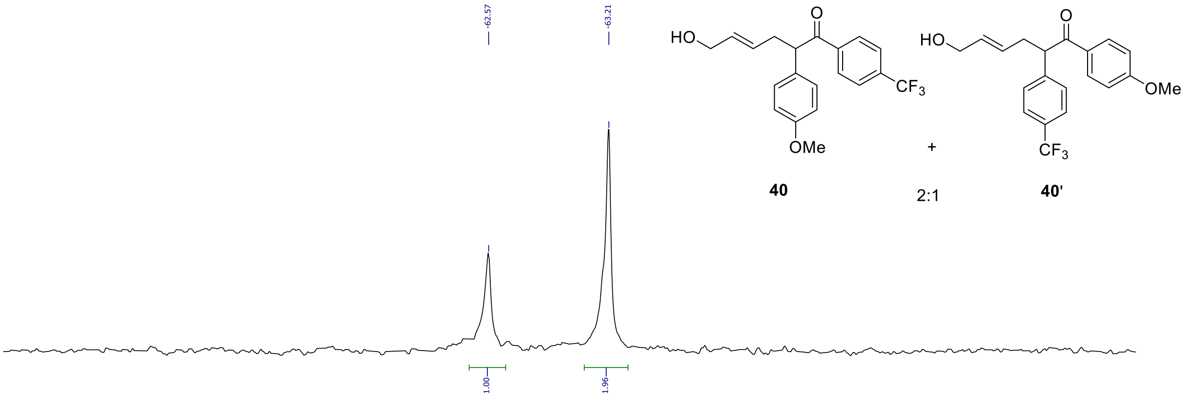
Regiochemistry determination for compound 4.40 (and 4.6 and 4.6')

The structure of compounds **6** and **6’** (relative position of the two different aryl groups) could be determined by carrying out the following experiment.

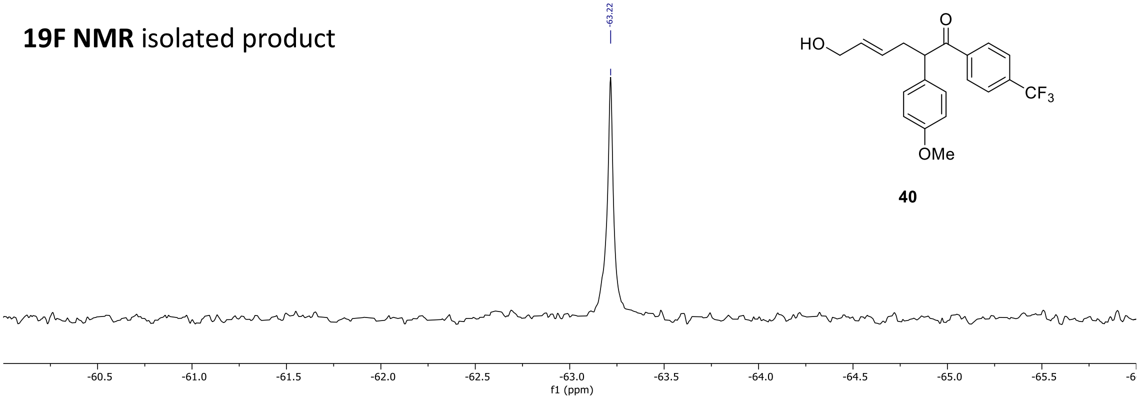
After oxidation of a 2:1 mixture of compounds **6** and **6’** following the procedure described in section 6.3, the formation of a 2:1 mixture of ketone **40** and **40’** was observed by ^{19}F NMR. After column chromatography, it was possible to isolate the pure major product **40**, which structure was elucidated by bidimensional NMR analysis (see below).



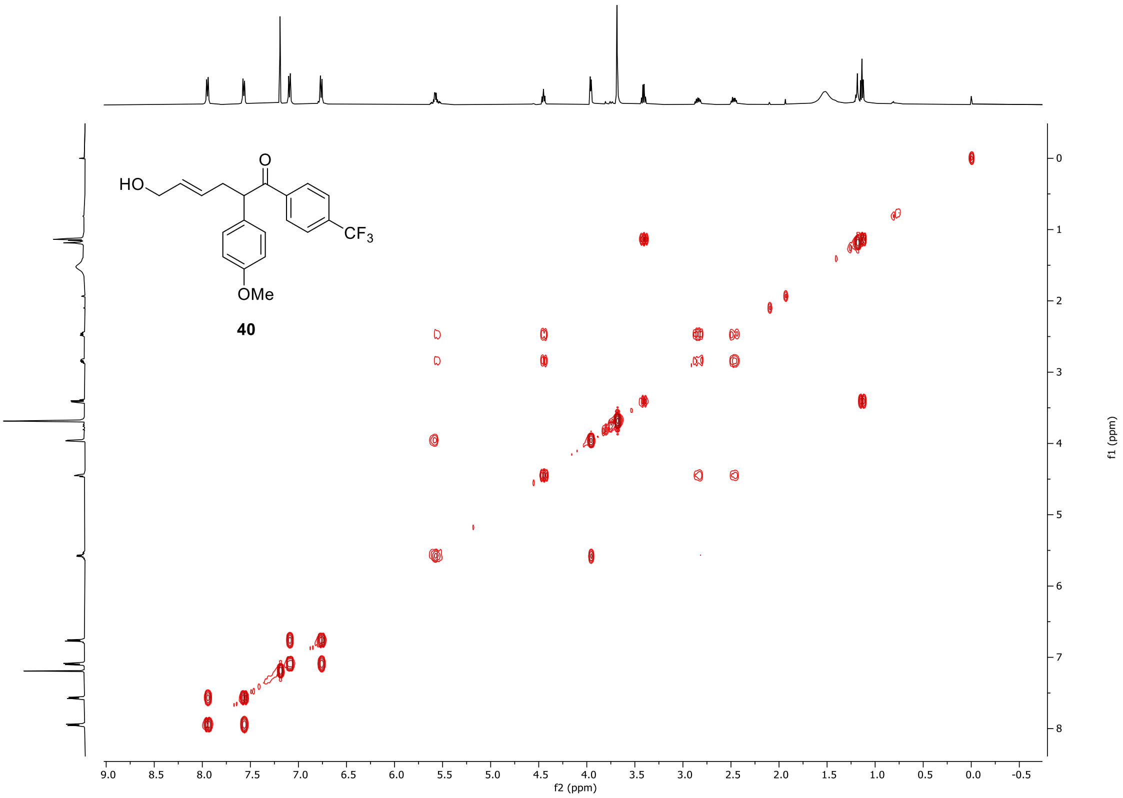
^{19}F NMR crude product after oxidation



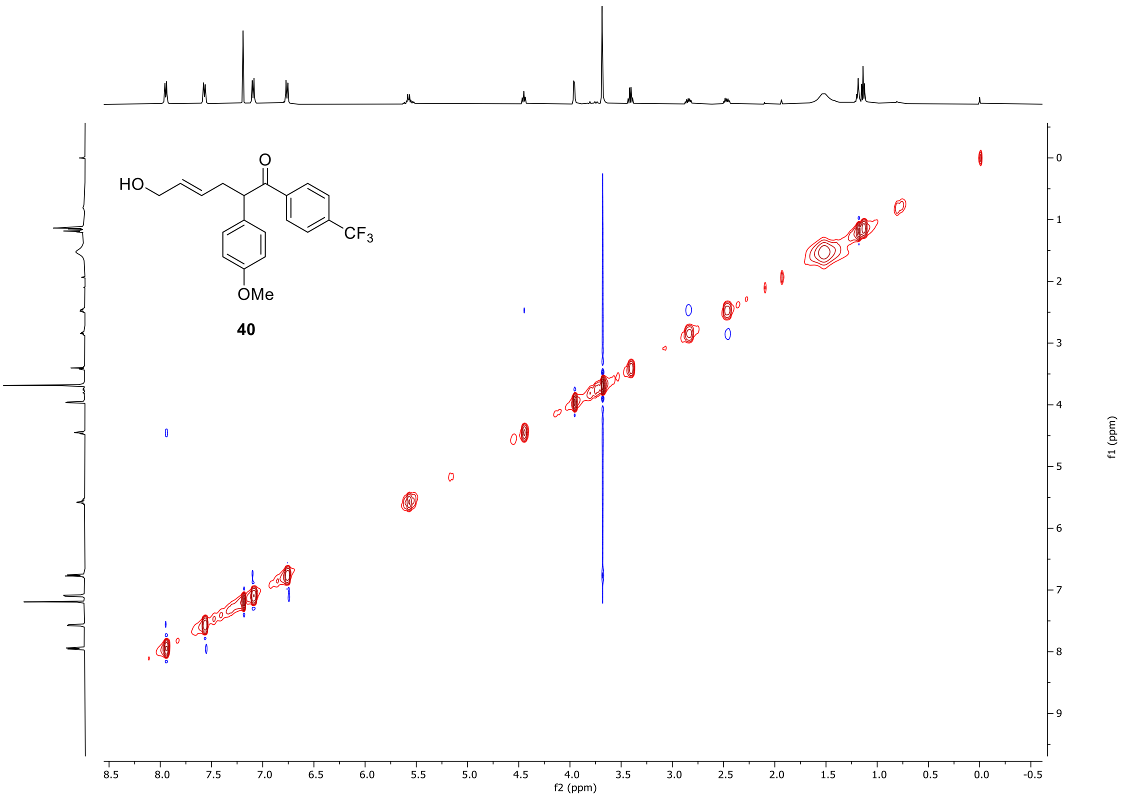
19F NMR isolated product



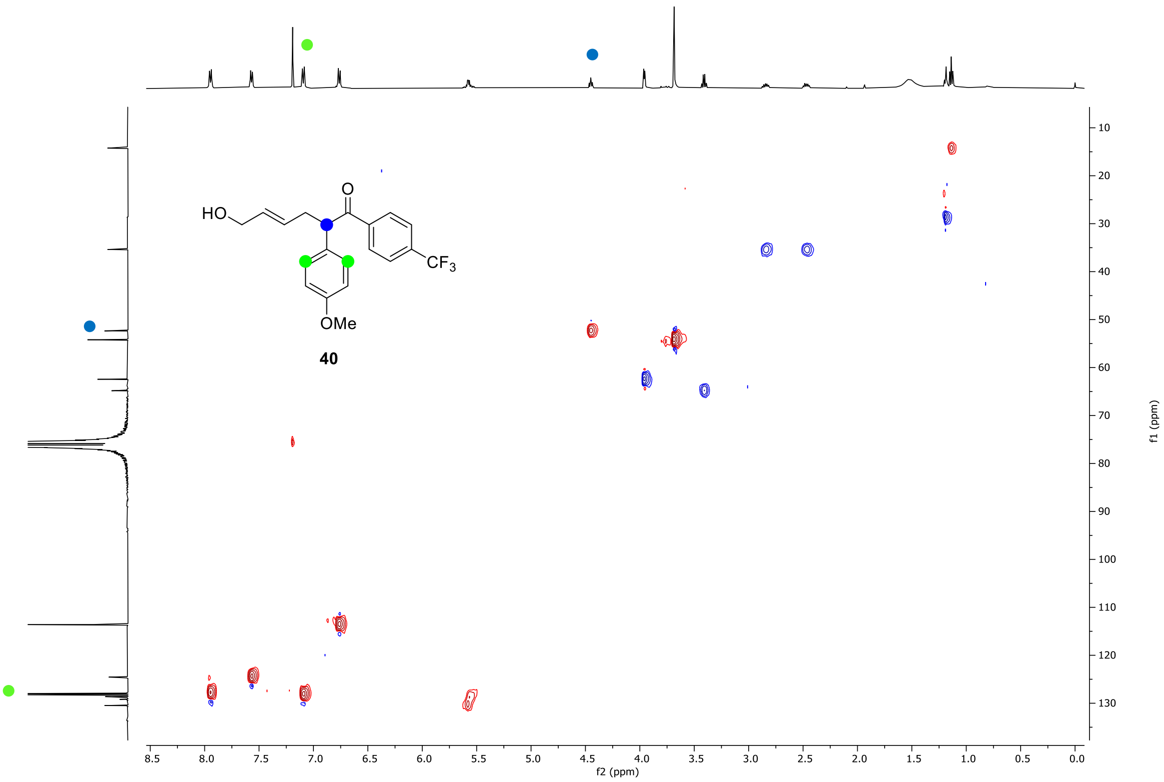
COSY


HO
O
CF3
OMe
40
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f2 (ppm)
0
1
2
3
4
5
6
7
8
f1 (ppm)

NOESY


HO
O
CF3
OMe
40
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f2 (ppm)
0
1
2
3
4
5
6
7
8
9
f1 (ppm)

HSQC


HO
O
CF$_3$
OMe
40
f2 (ppm)
f1 (ppm)
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8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
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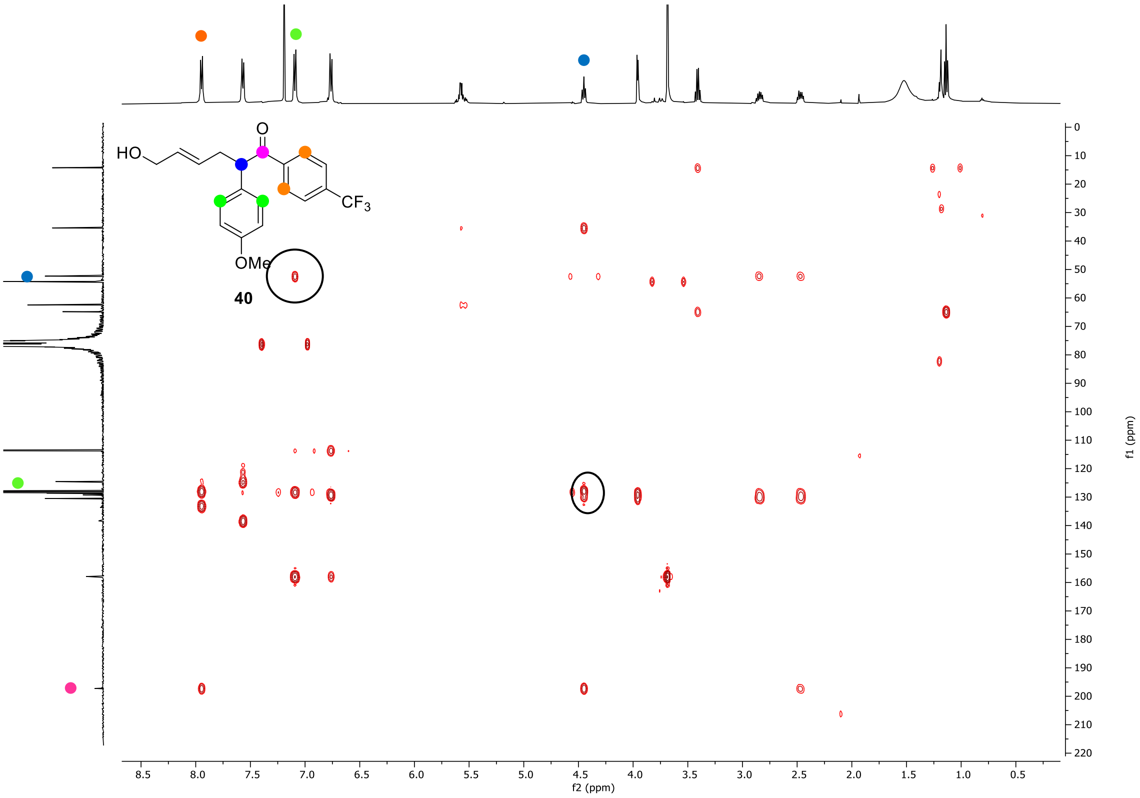
130

HMBC


HO
O
CF$_3$
OMe
40
f2 (ppm)
f1 (ppm)
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8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
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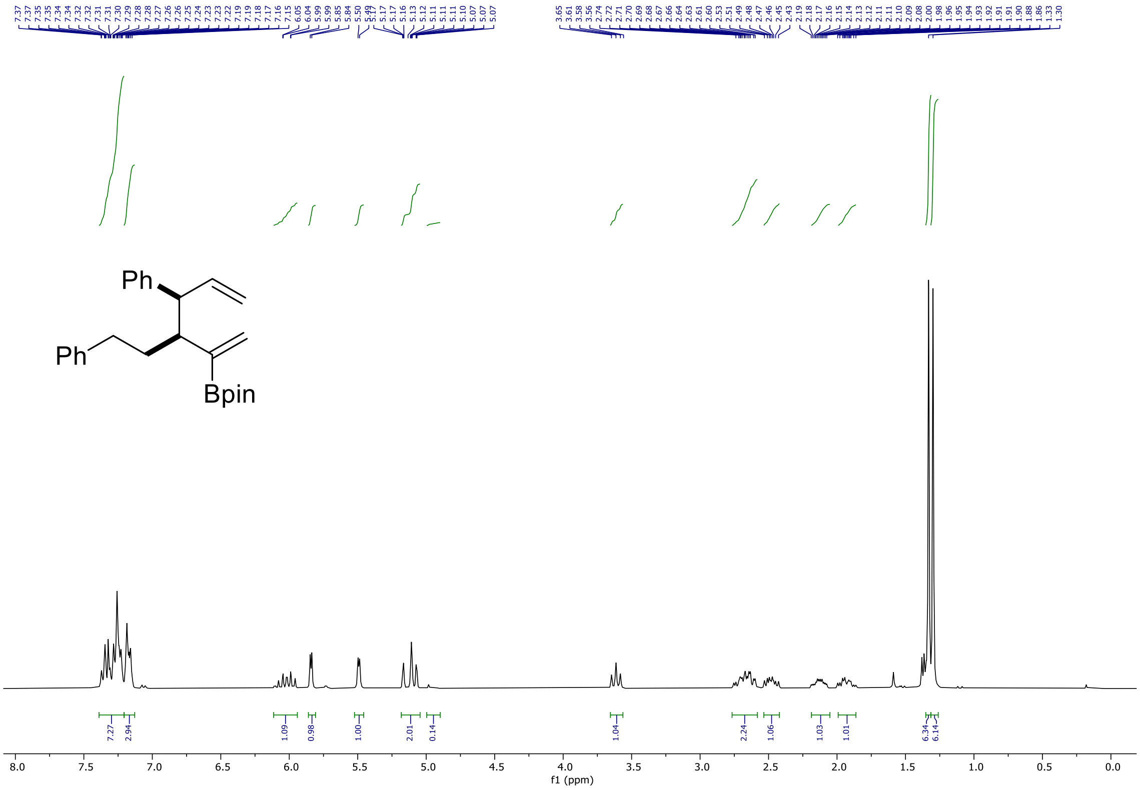
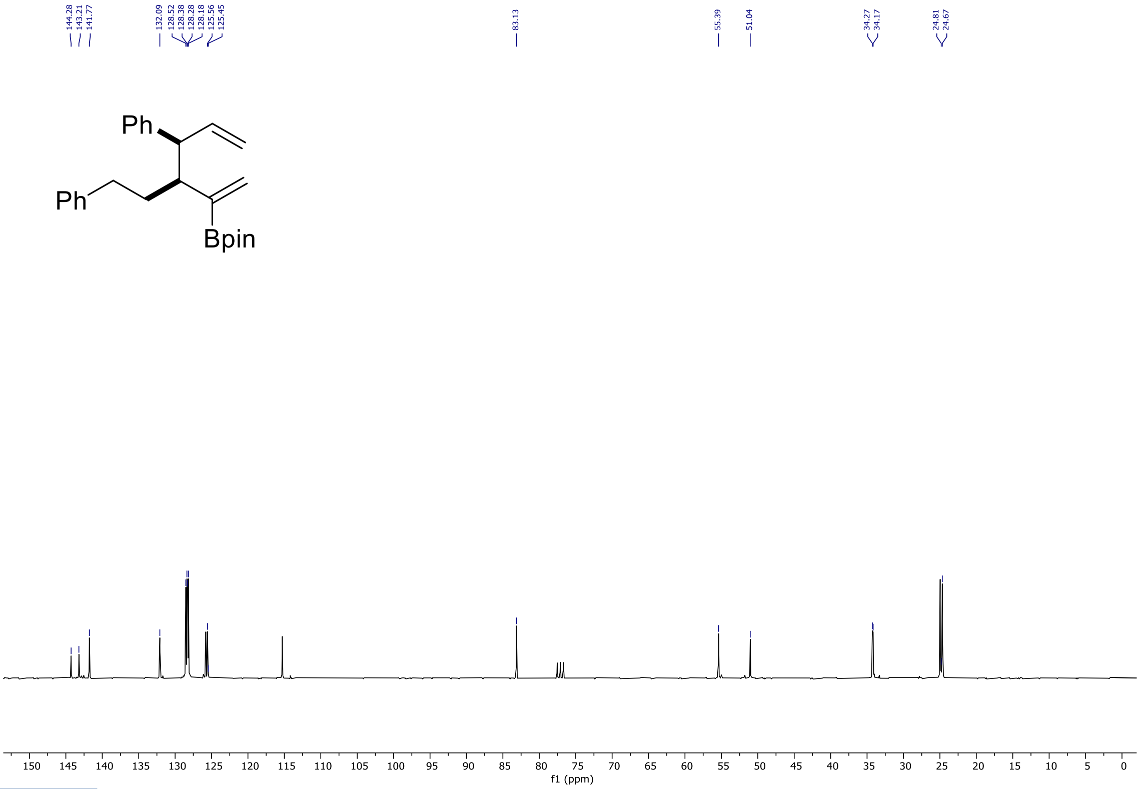
200
210
220

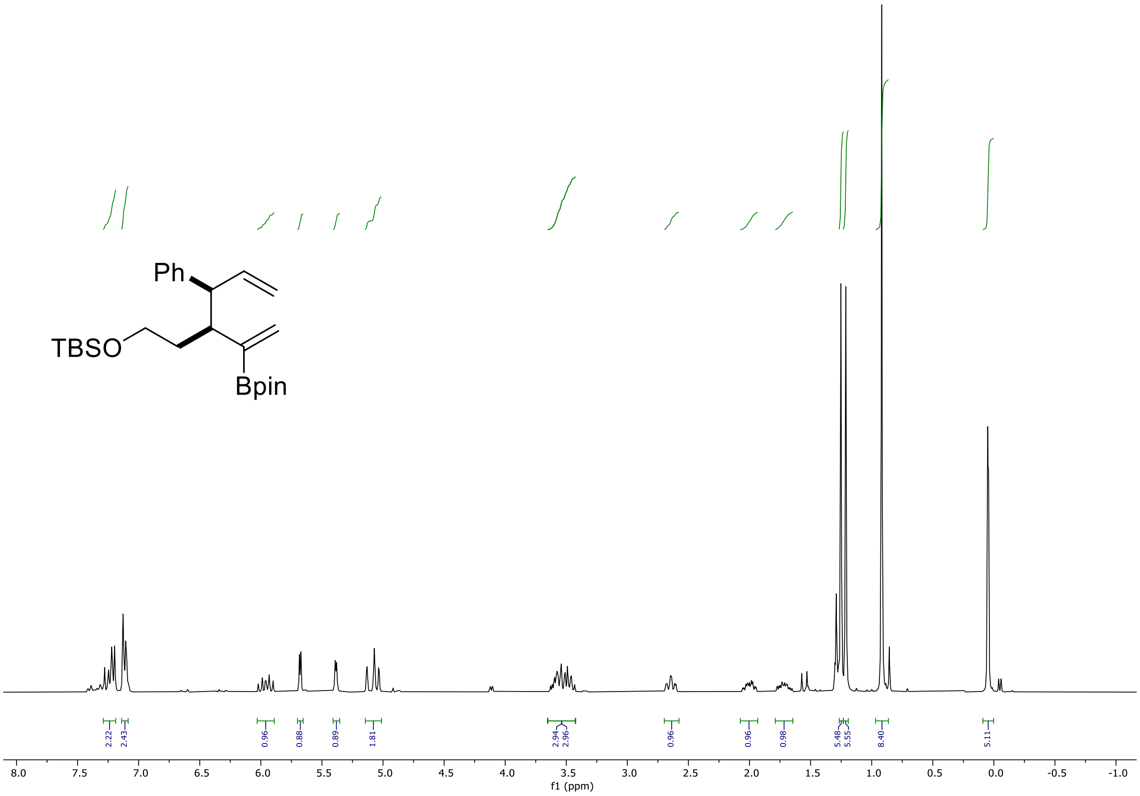
^{1}**H NMR** (300 MHz, CDCl$_3$)



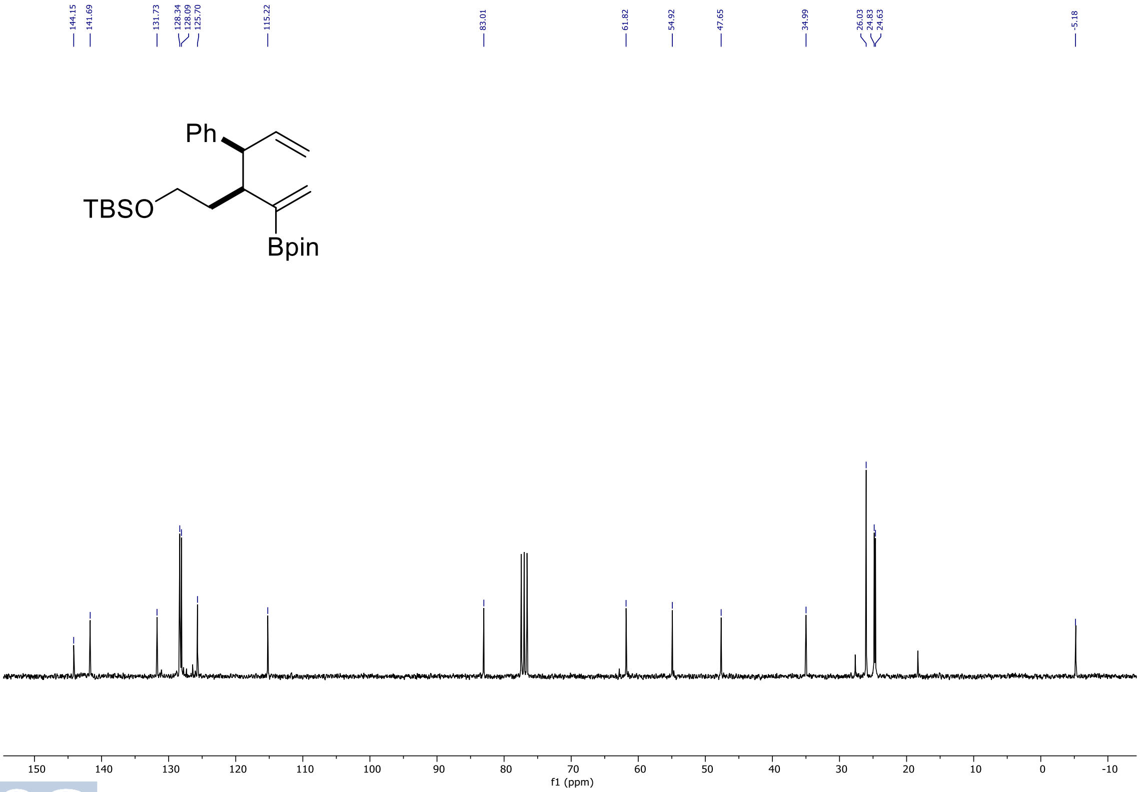
^{13}**C NMR** (75 MHz, CDCl$_3$)



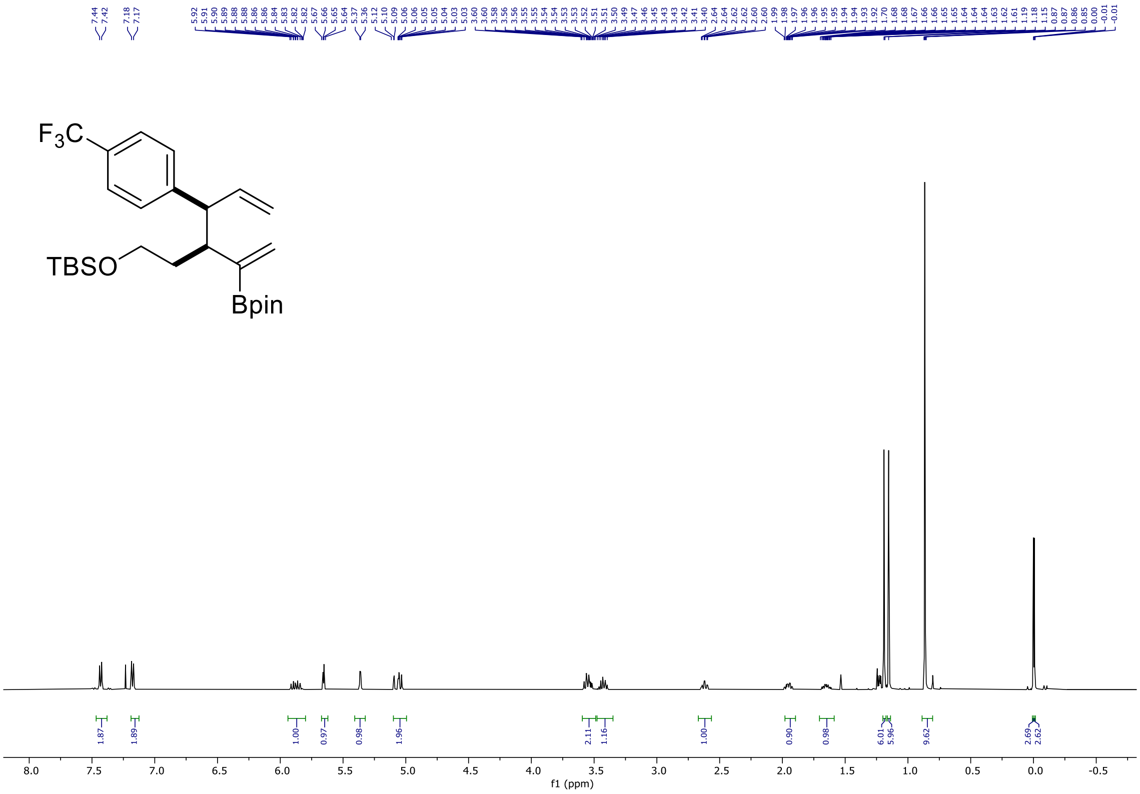
^{1}**H NMR** (300 MHz, CDCl$_3$)



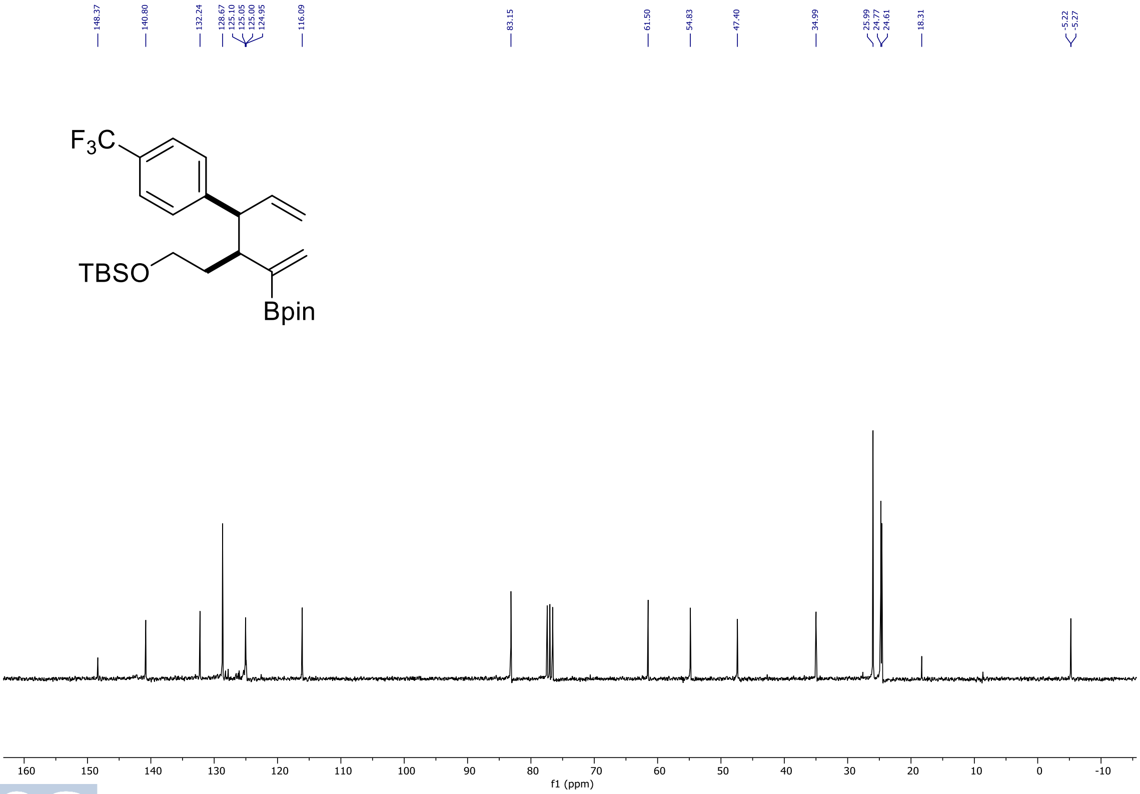
^{13}C NMR (75 MHz, $CDCl_3$)



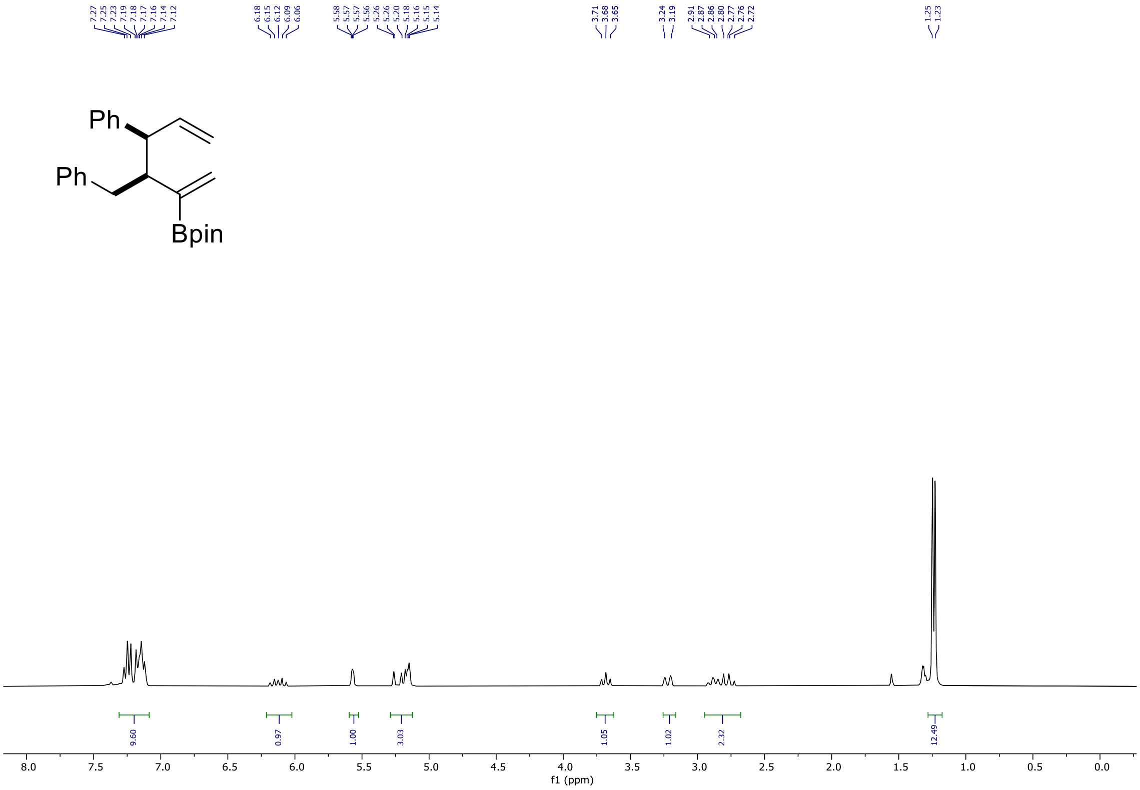
^{1}H NMR (300 MHz, $CDCl_3$)



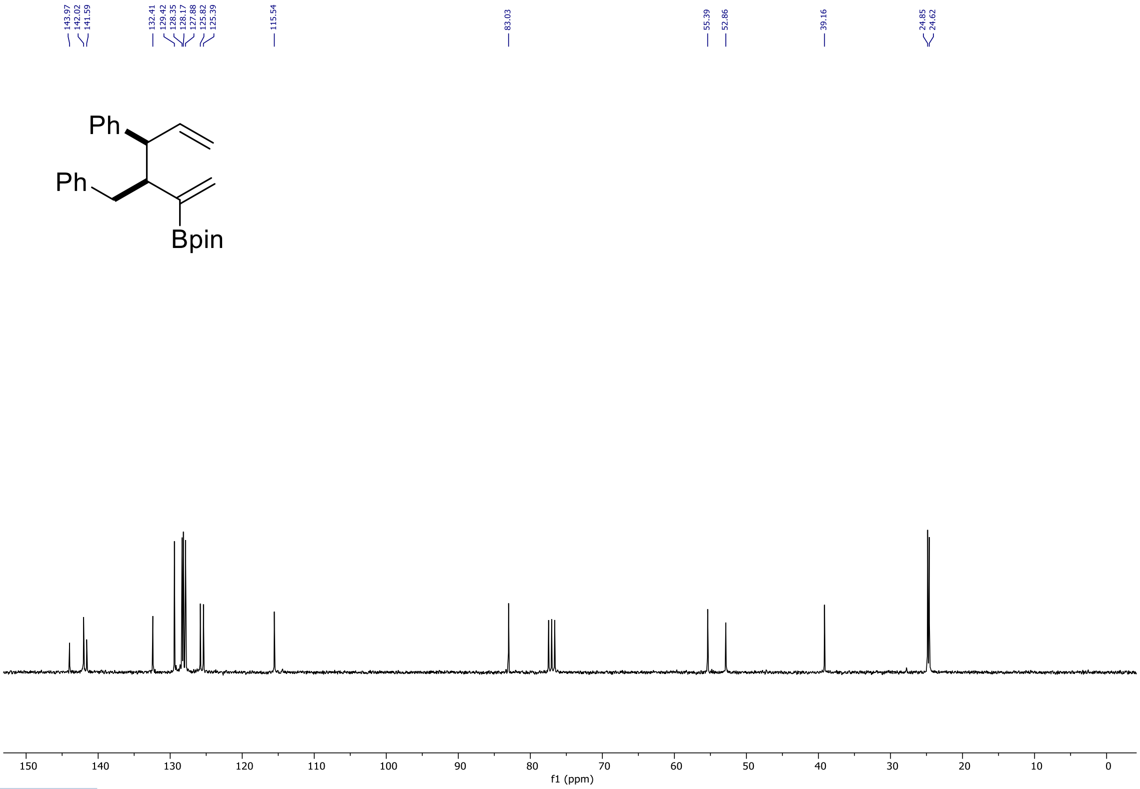
^{13}C NMR (75 MHz, $CDCl_3$)



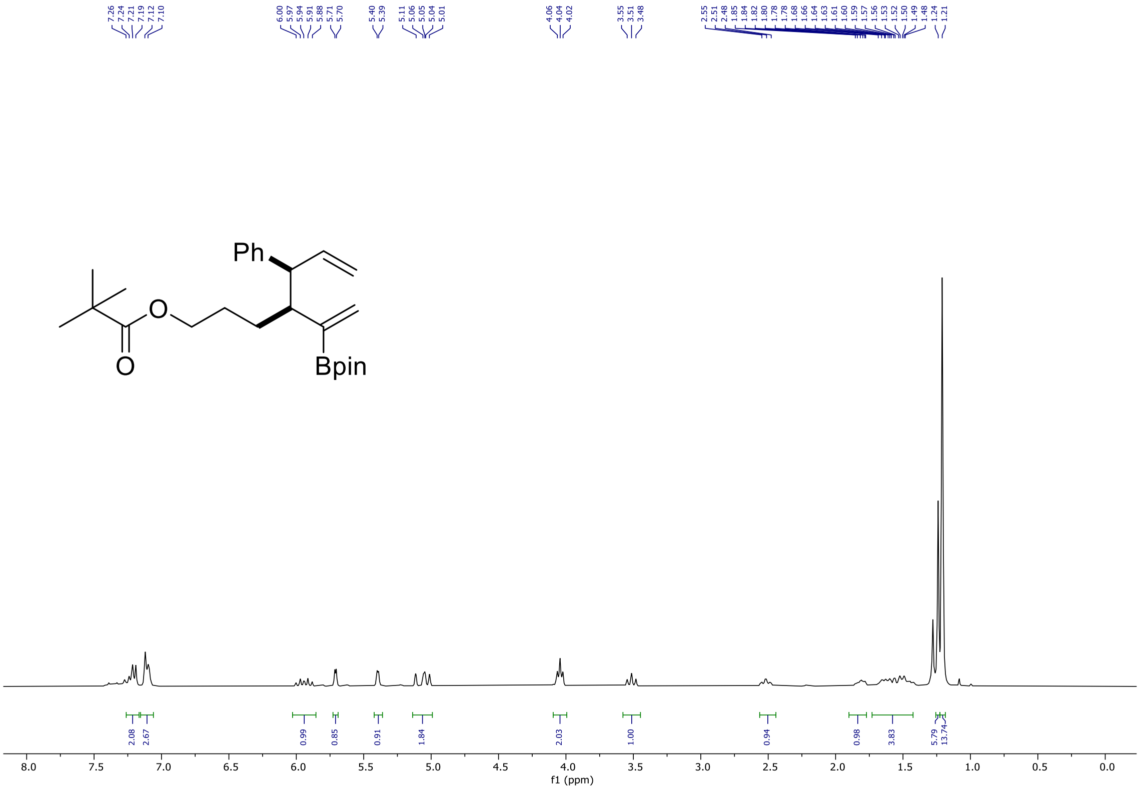
^{1}H NMR (300 MHz, CDCl$_3$)



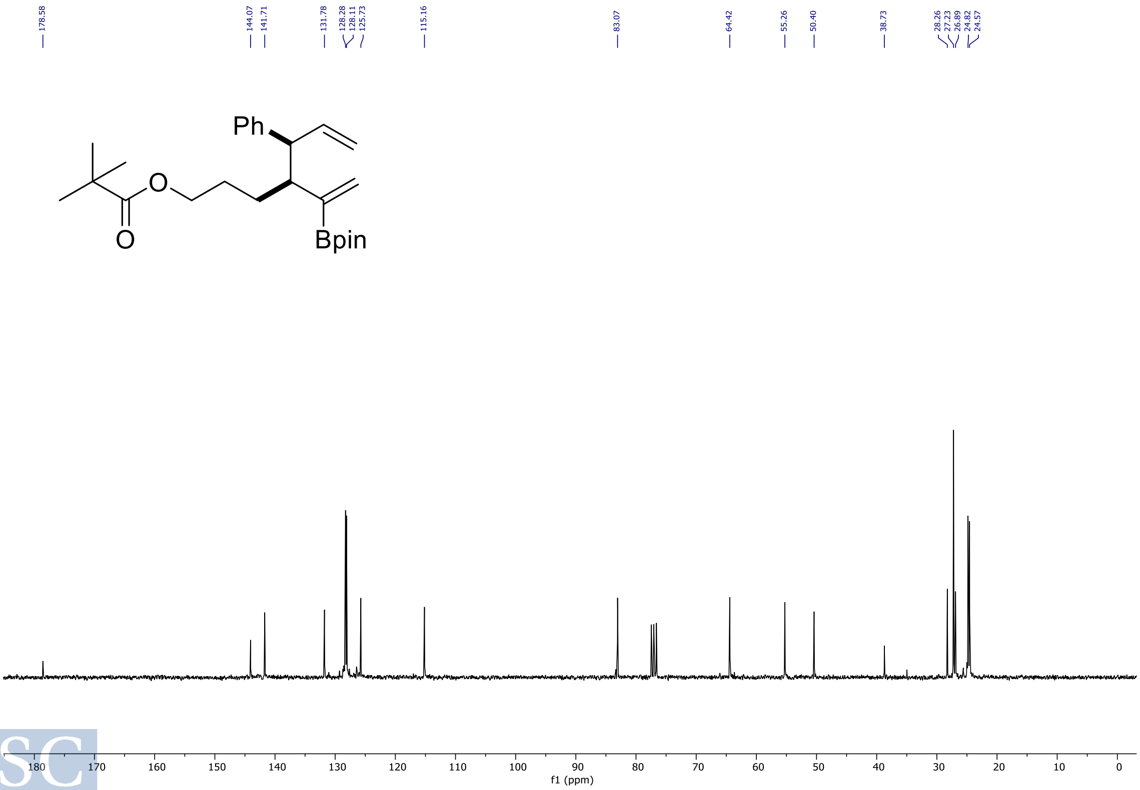
^{13}C NMR (75 MHz, CDCl$_3$)



^{1}**H NMR** (300 MHz, $CDCl_3$)



^{13}**C NMR** (75 MHz, $CDCl_3$)



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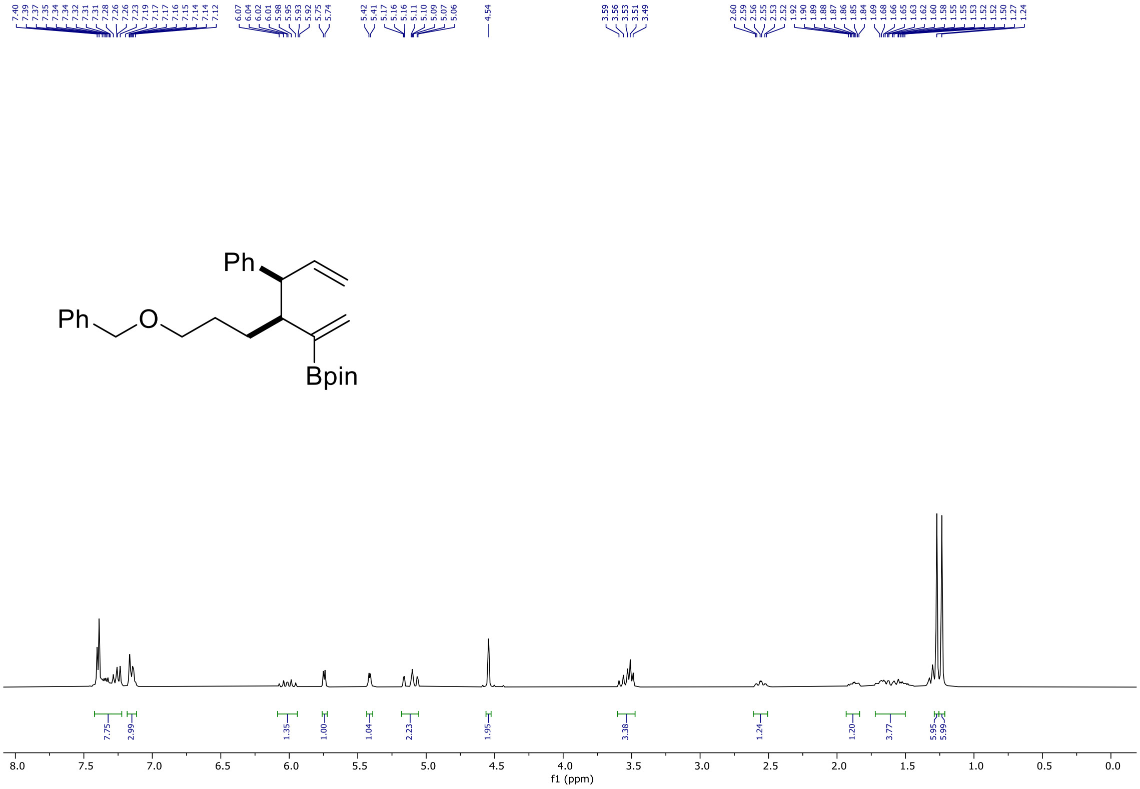
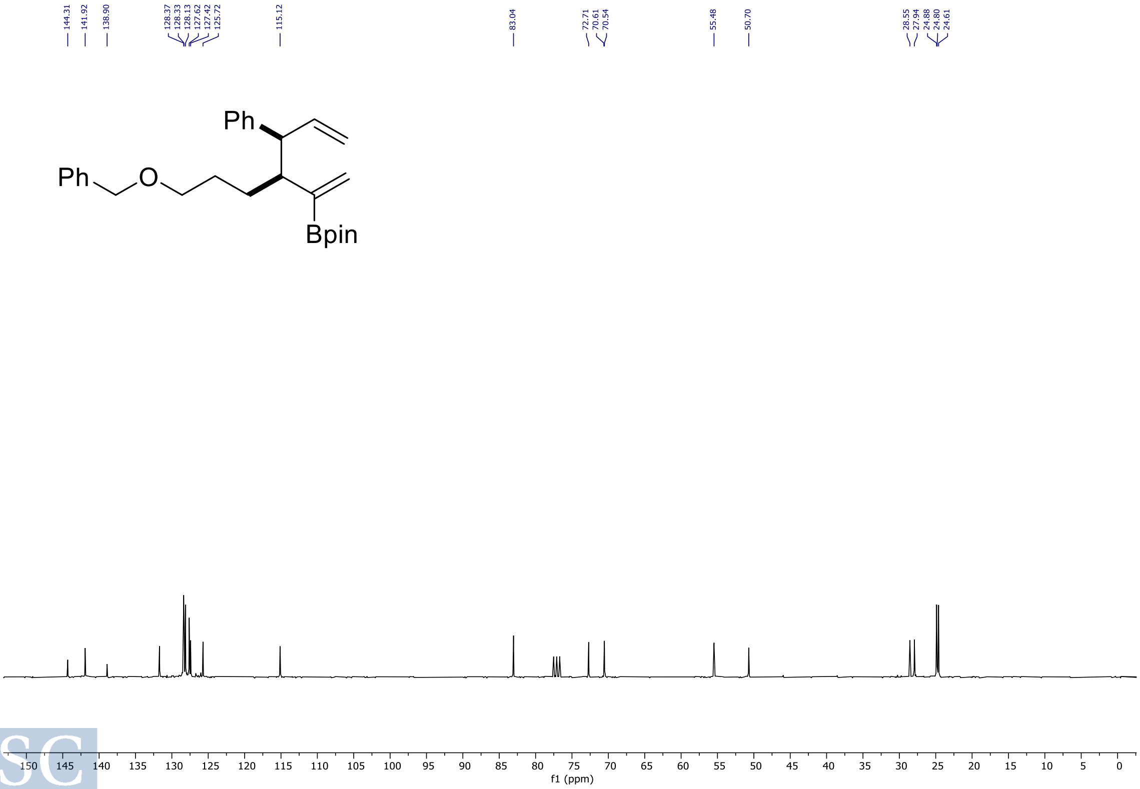
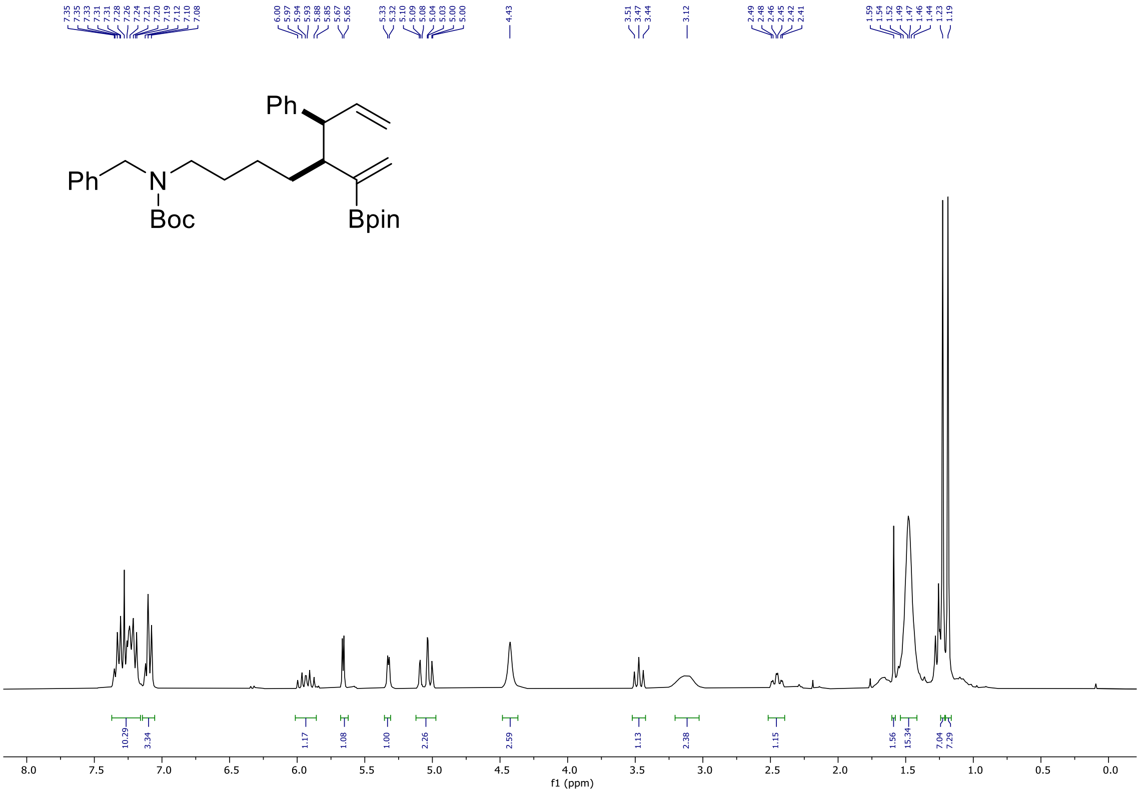


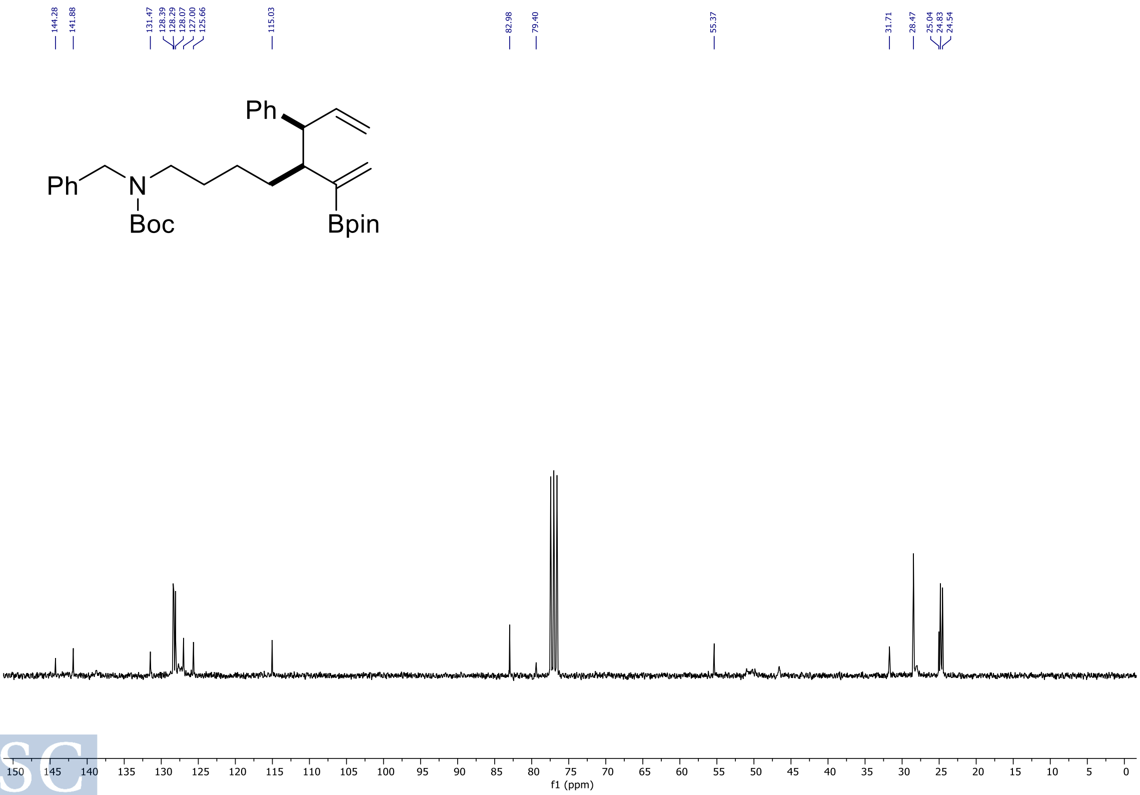
^{13}C NMR (75 MHz, CDCl$_3$)



^{1}H NMR (300 MHz, CDCl$_3$)



^{13}C NMR (75 MHz, CDCl$_3$)



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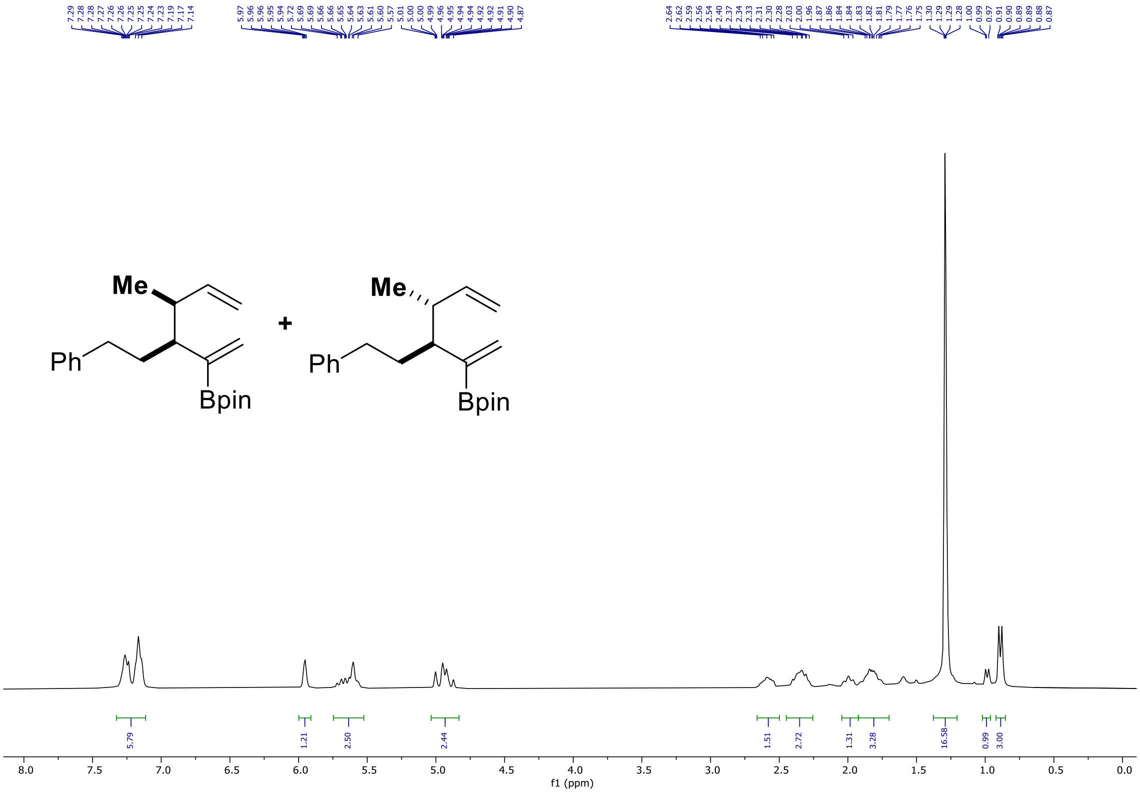

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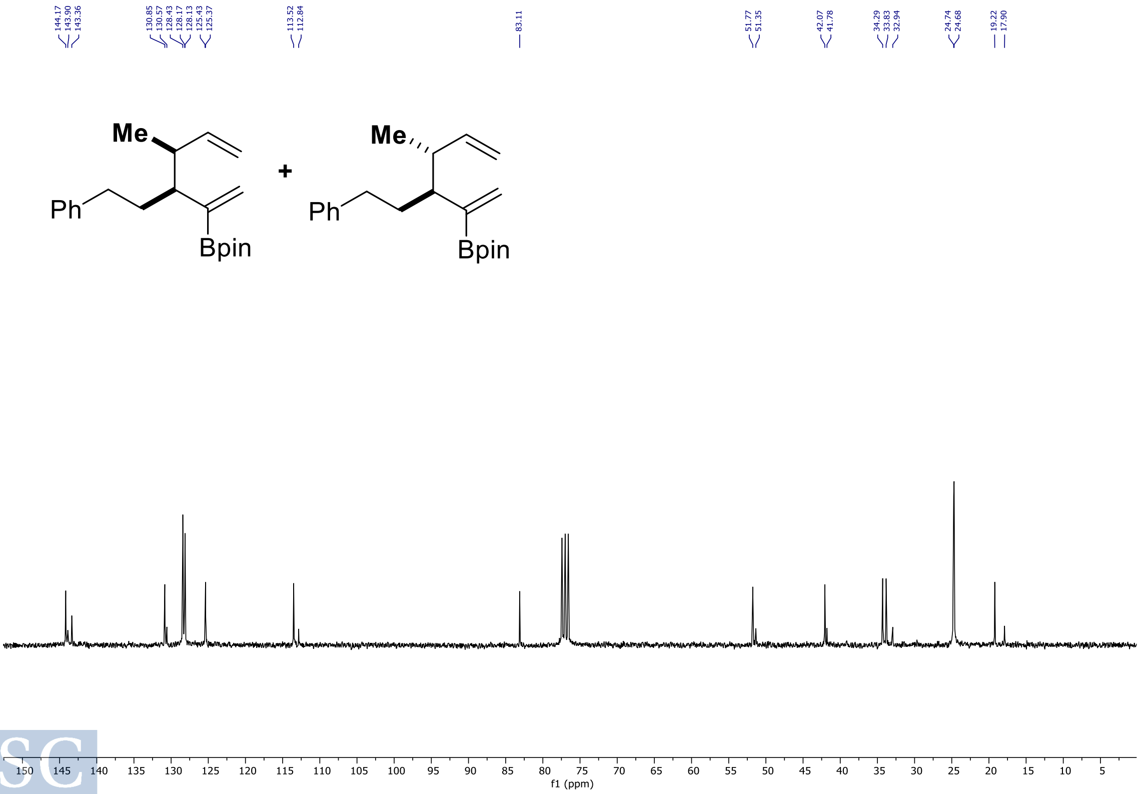

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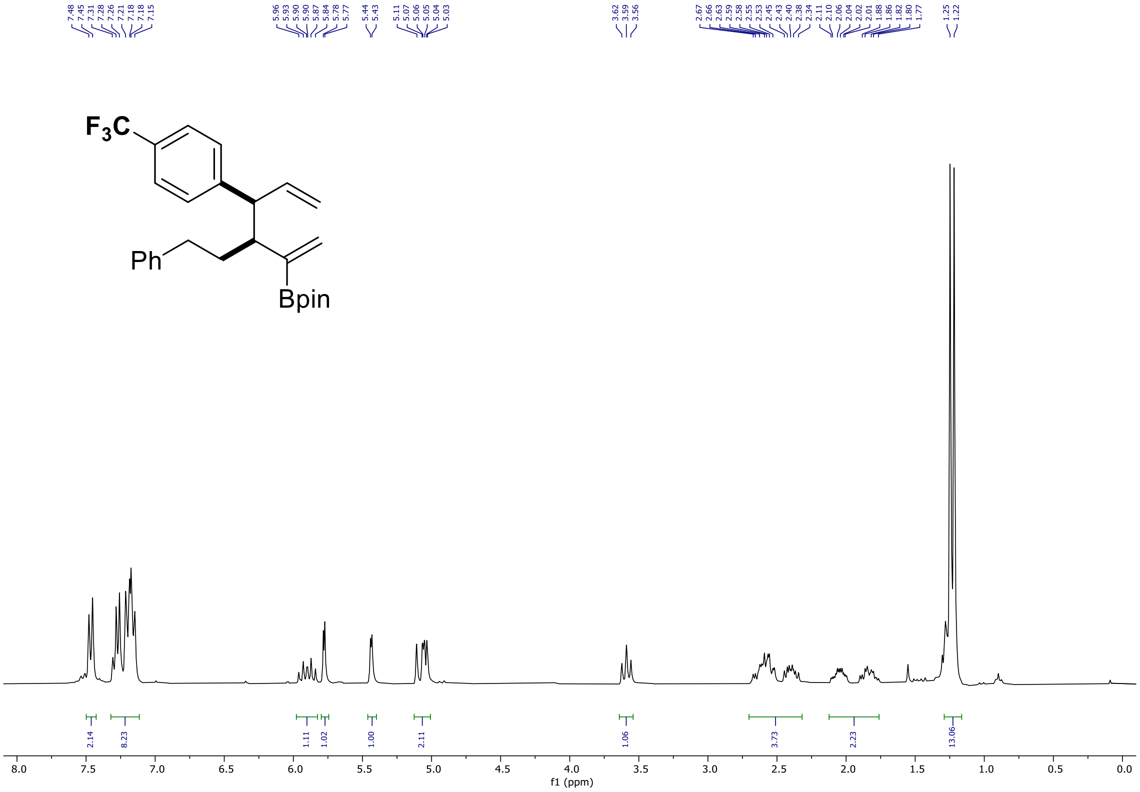

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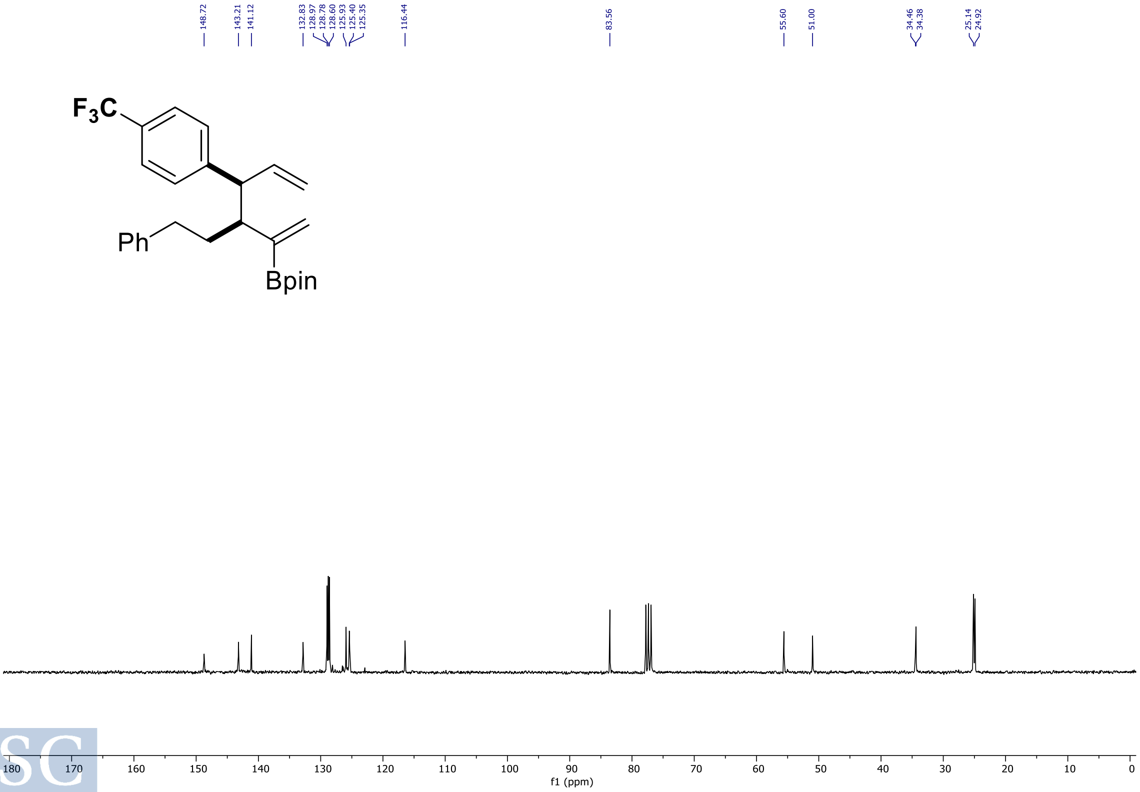

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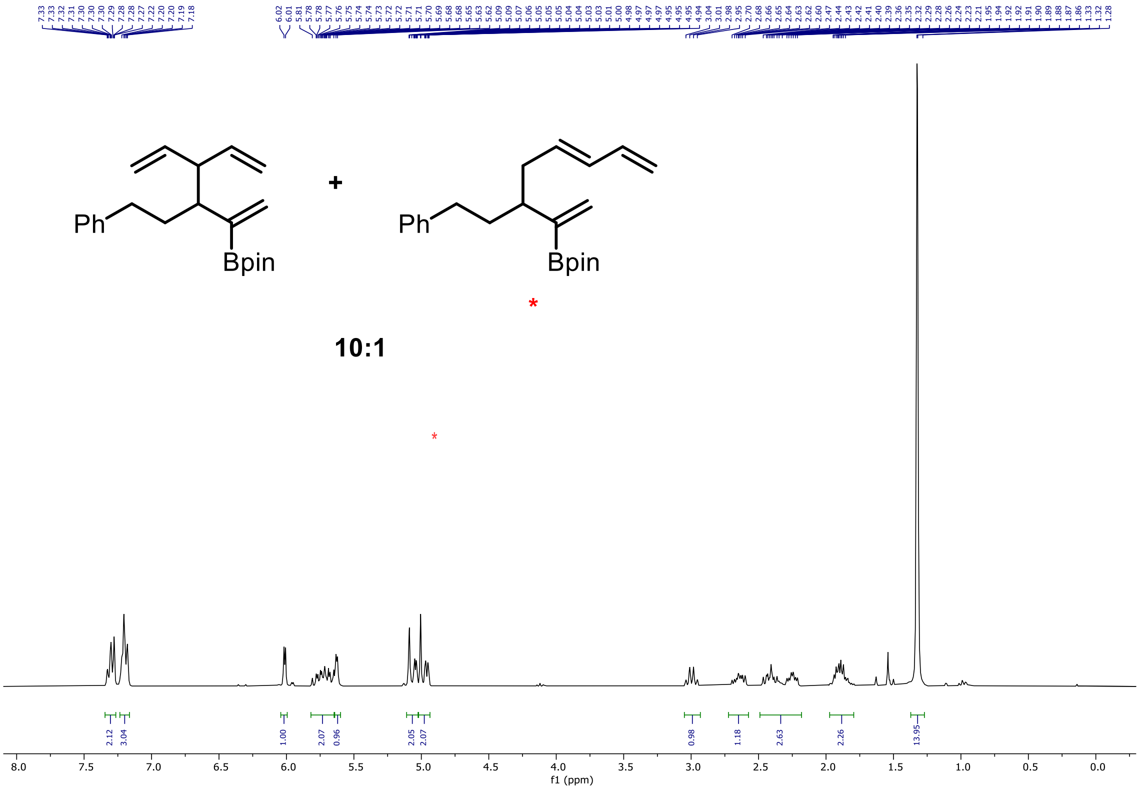
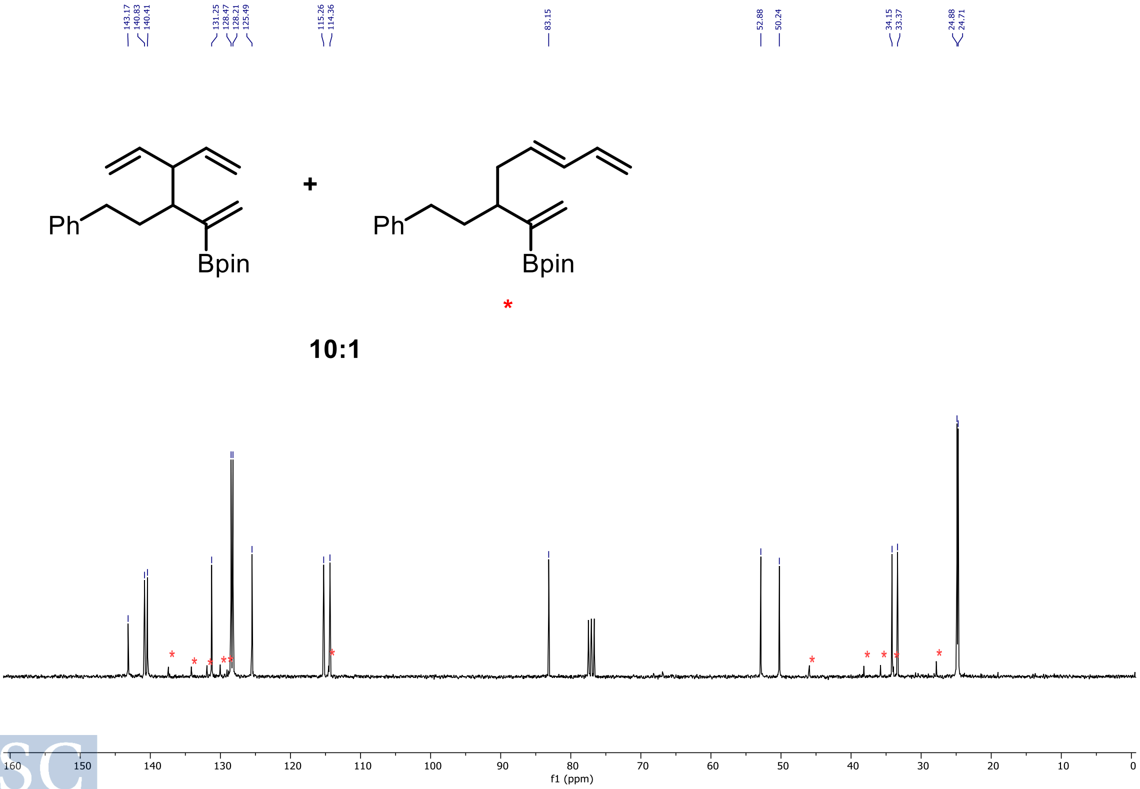
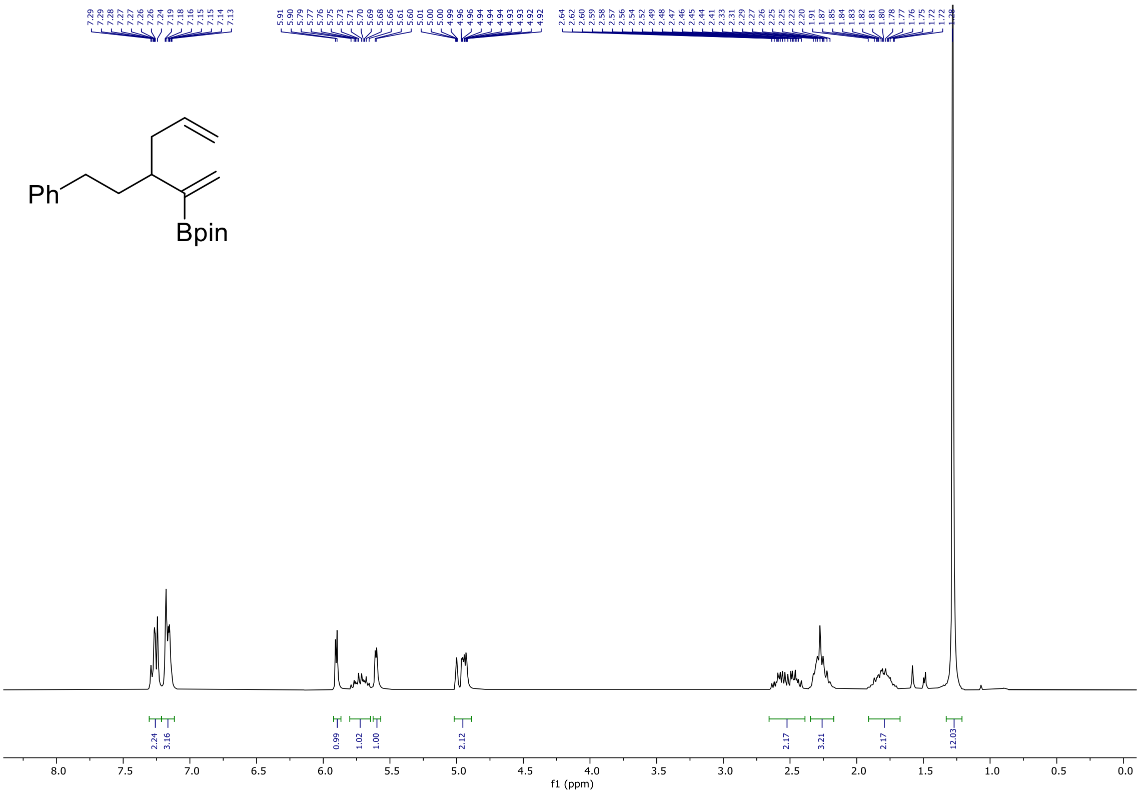


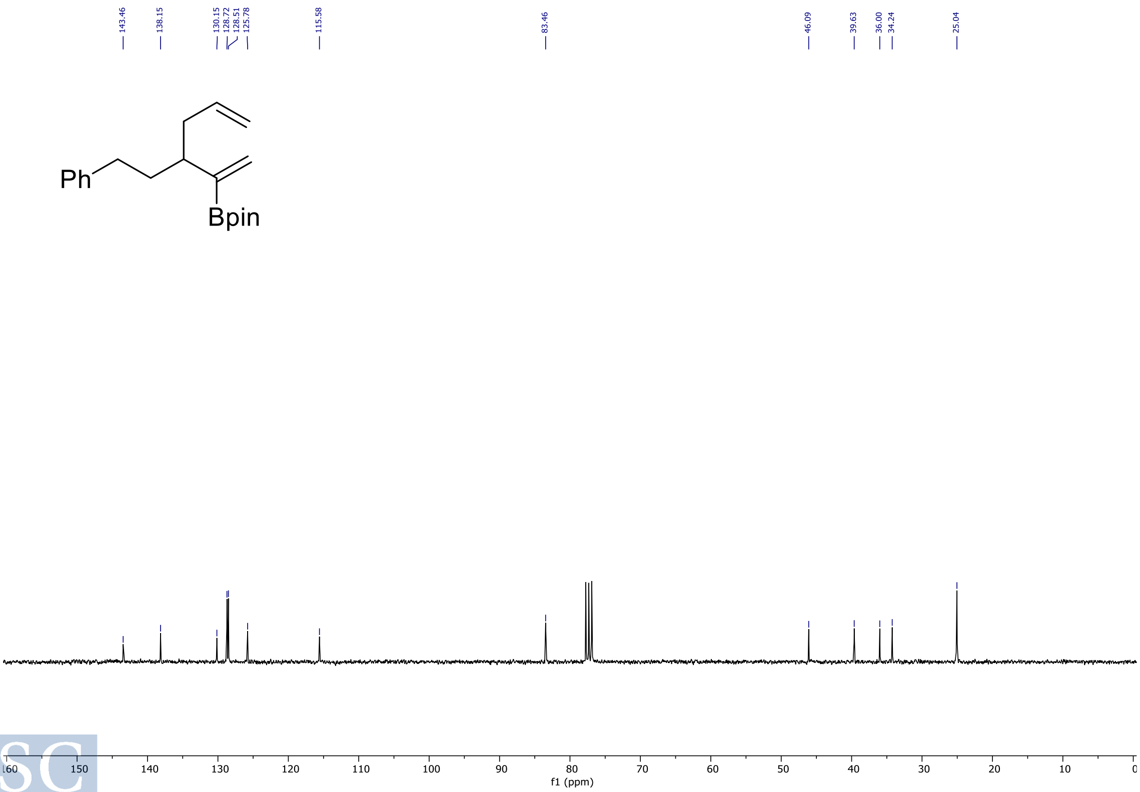
^{13}C NMR (75 MHz, CDCl$_3$)



^{1}**H NMR** (300 MHz, CDCl$_3$)



^{13}**C NMR** (75 MHz, CDCl$_3$)



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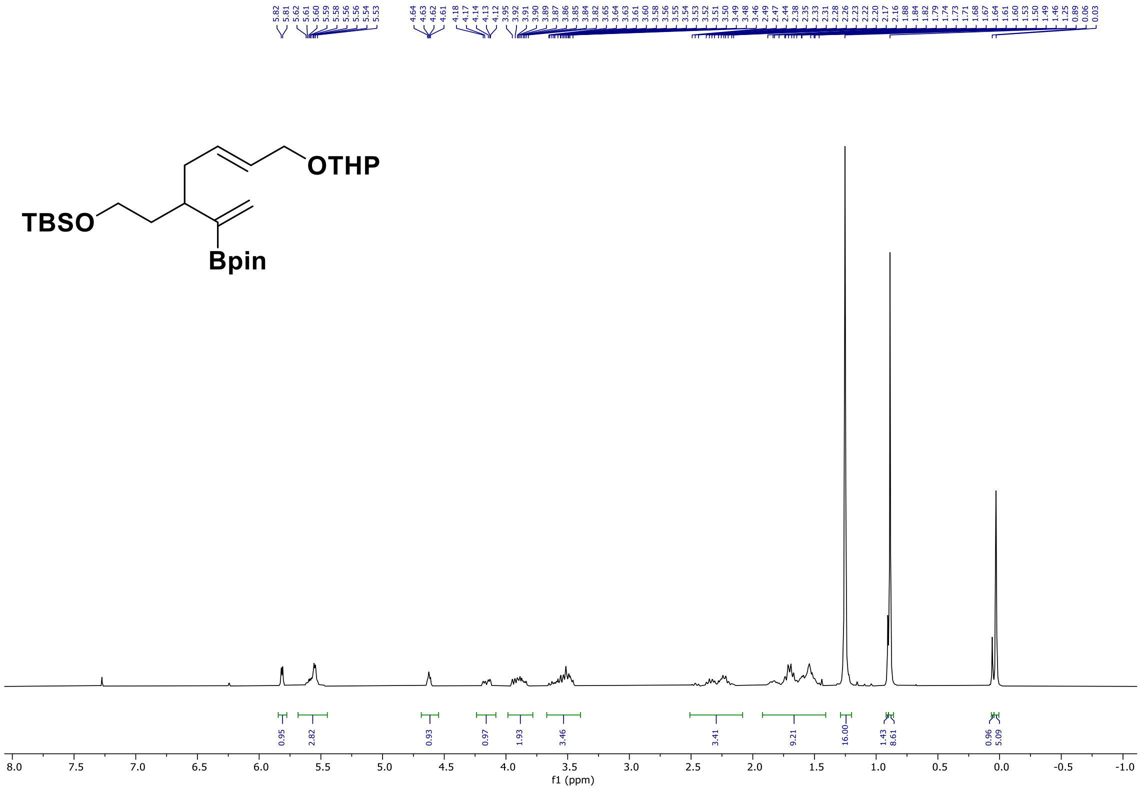
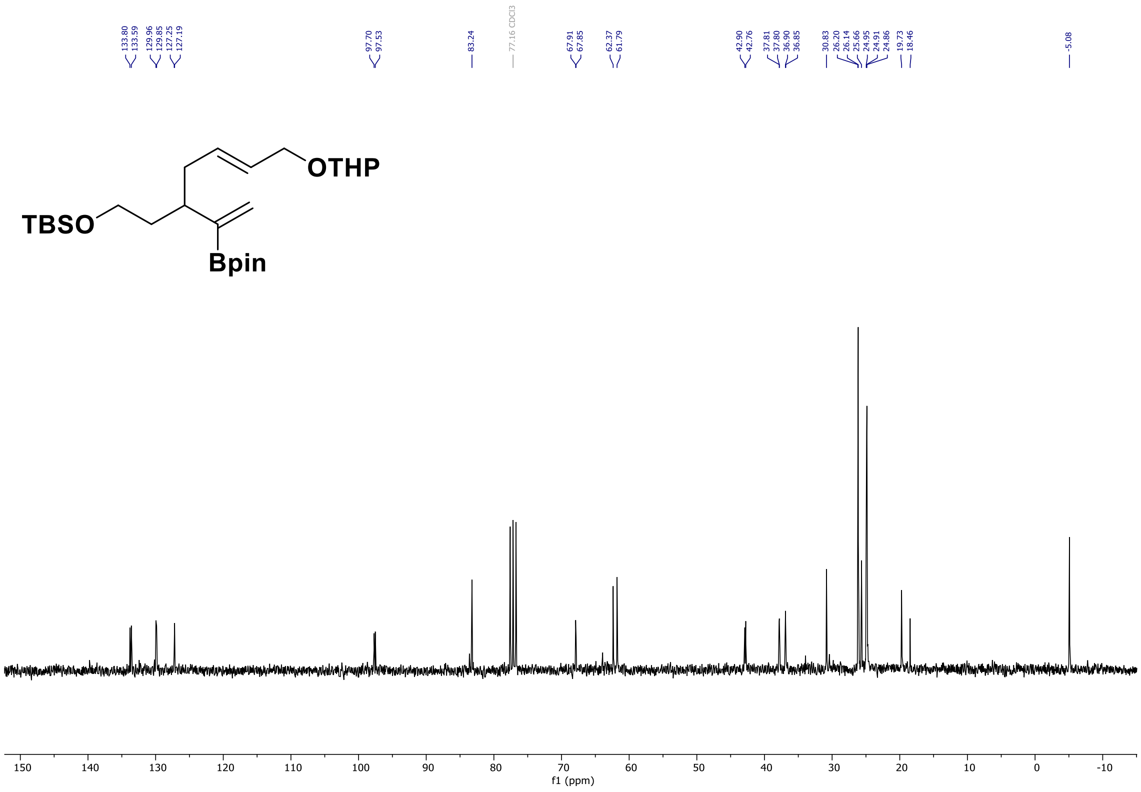


^{13}C NMR (75 MHz, CDCl$_3$)



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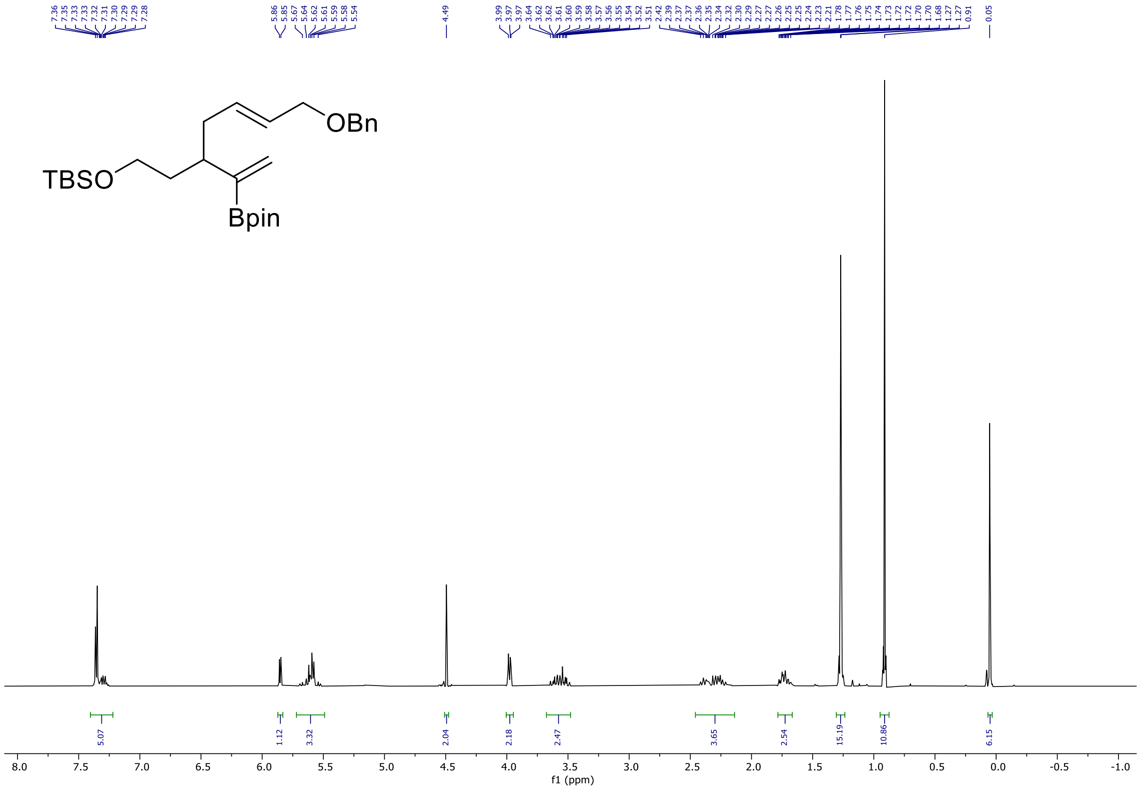
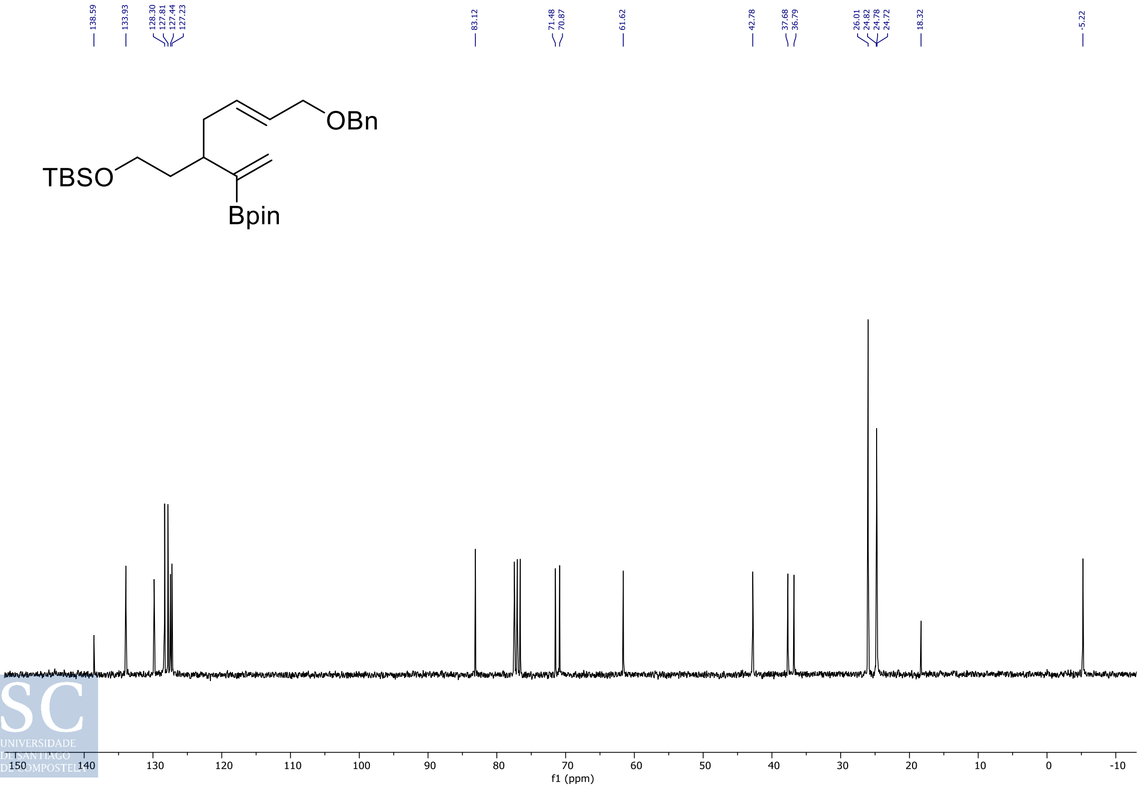
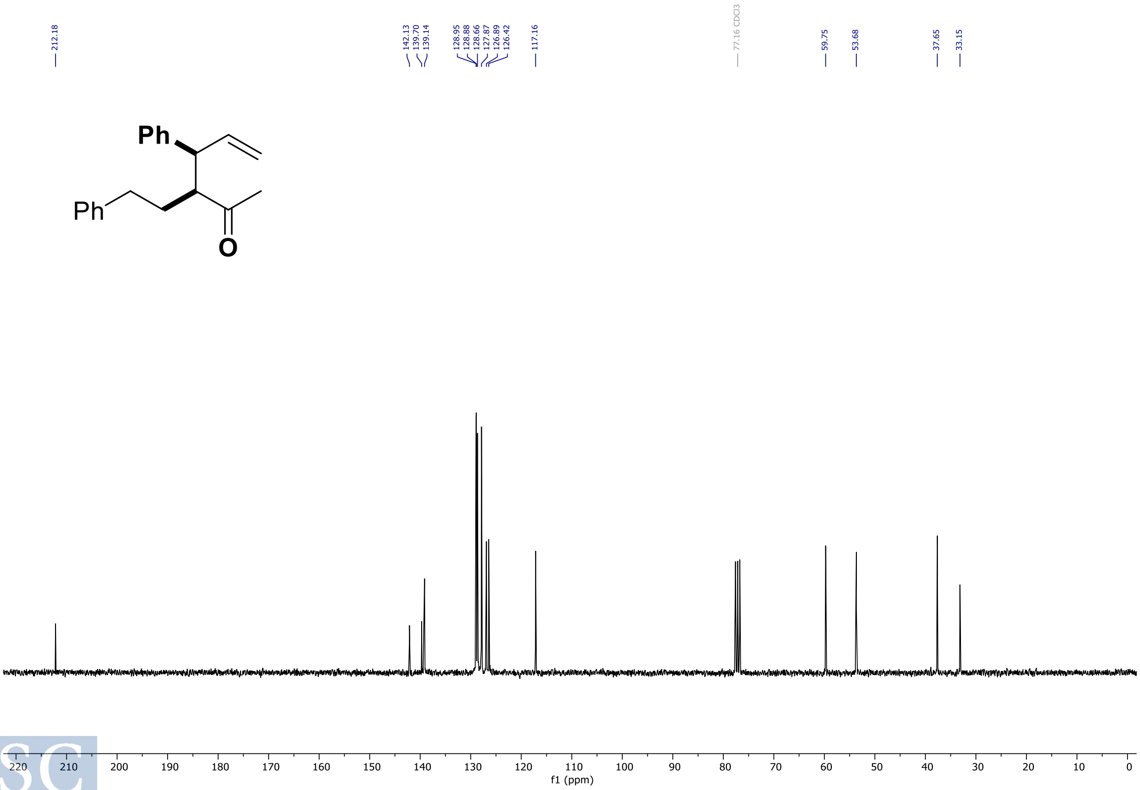


^{13}C NMR (75 MHz, CDCl$_3$)



^{1}H NMR (300 MHz, $CDCl_3$)

^{13}C NMR (75 MHz, $CDCl_3$)



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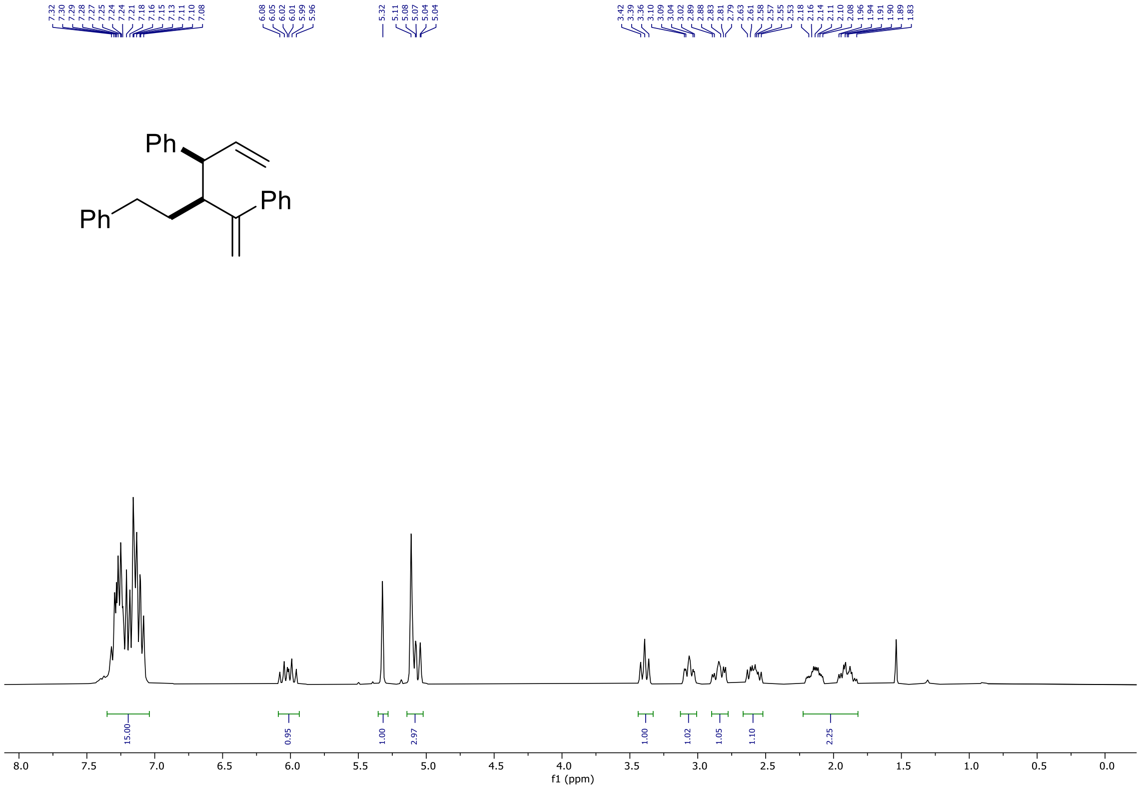
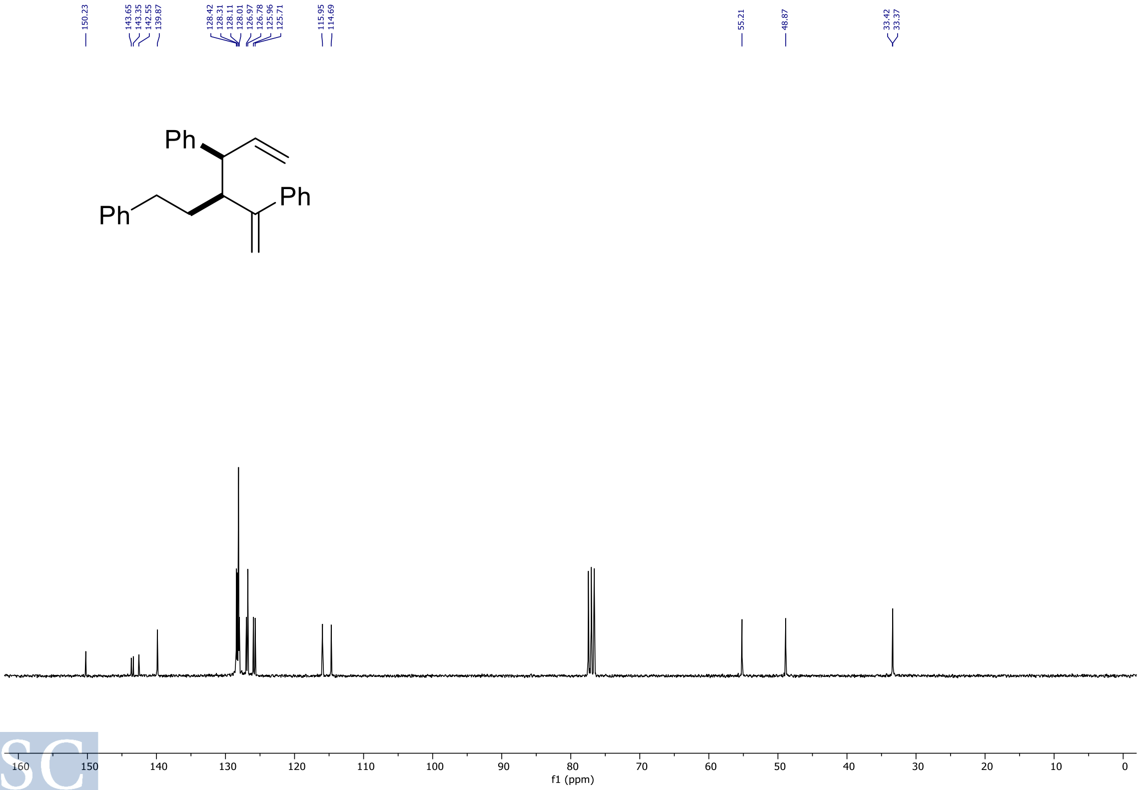
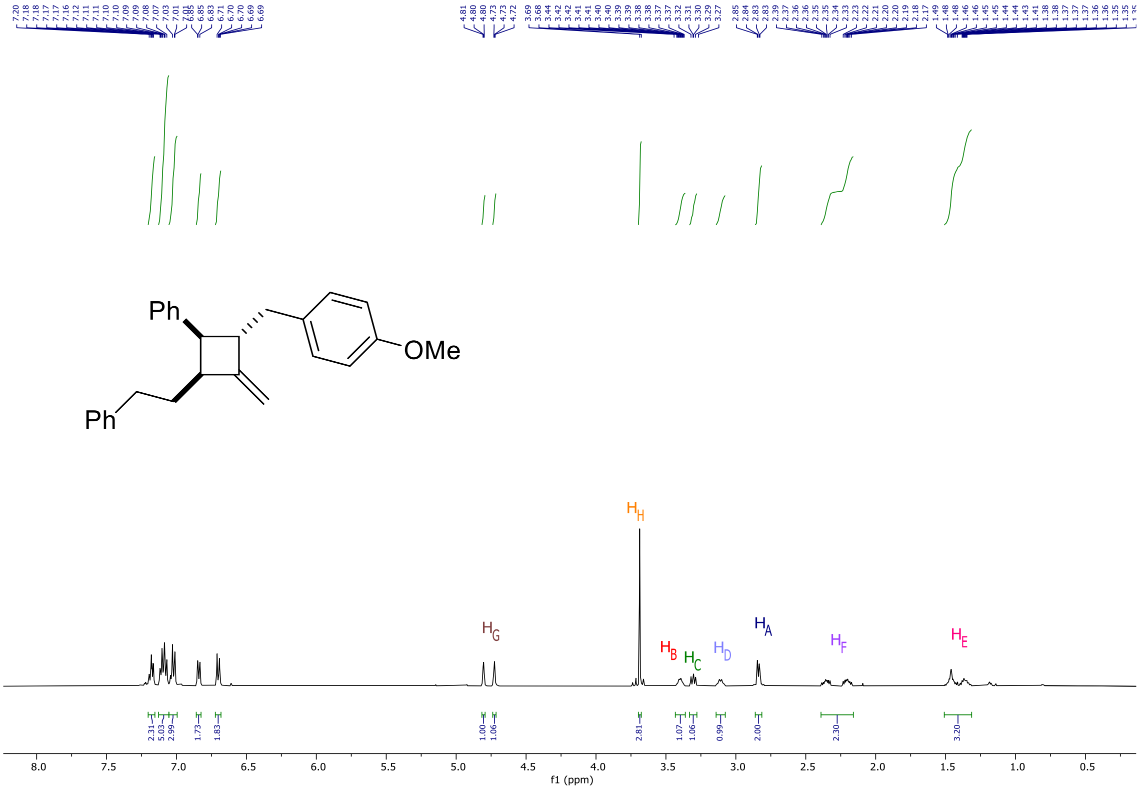


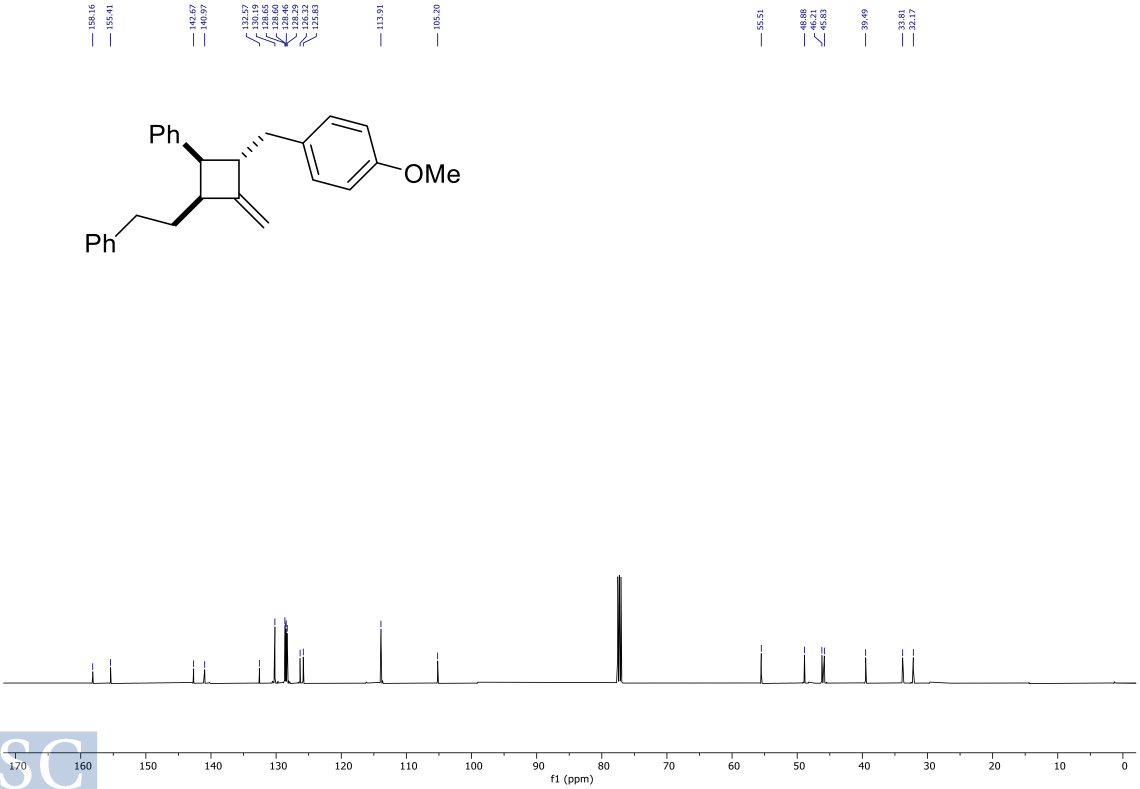
^{13}C NMR (75 MHz, $CDCl_3$)



^{1}H NMR (500 MHz, CDCl$_3$)



^{13}C NMR (126 MHz, CDCl$_3$)



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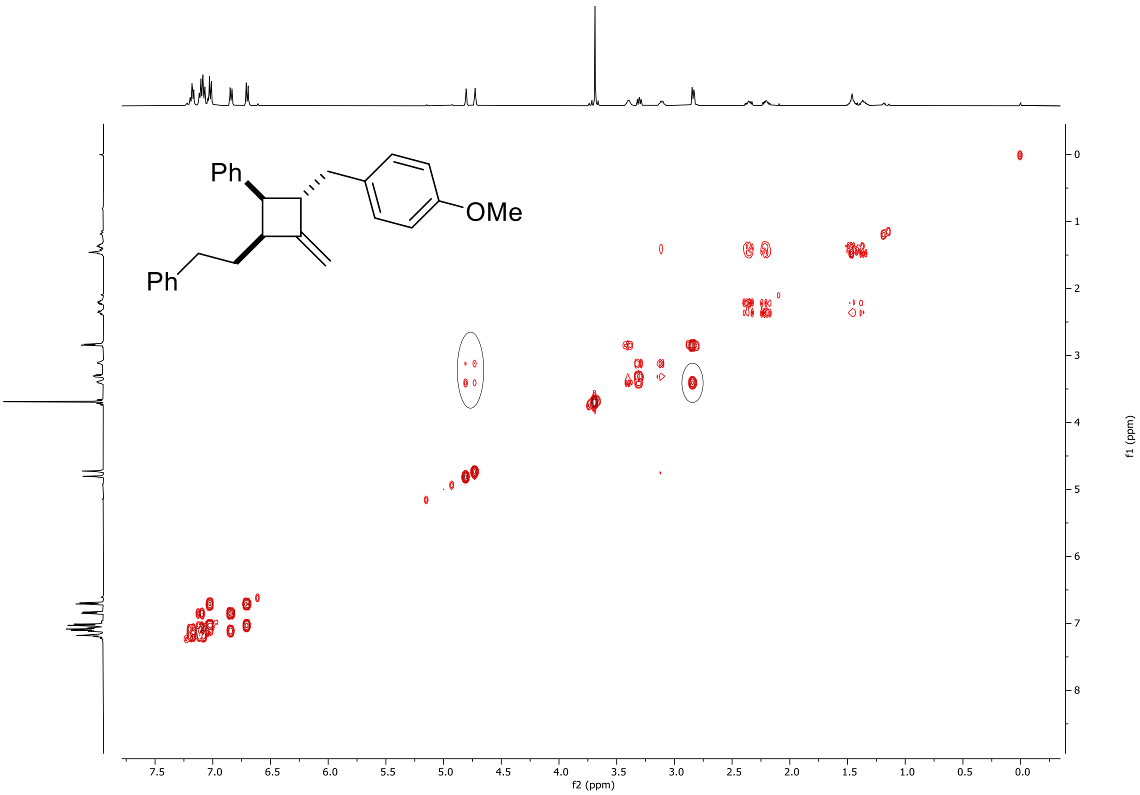
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Ph
OMe
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6.5
6.0
5.5
5.0
4.5
4.0
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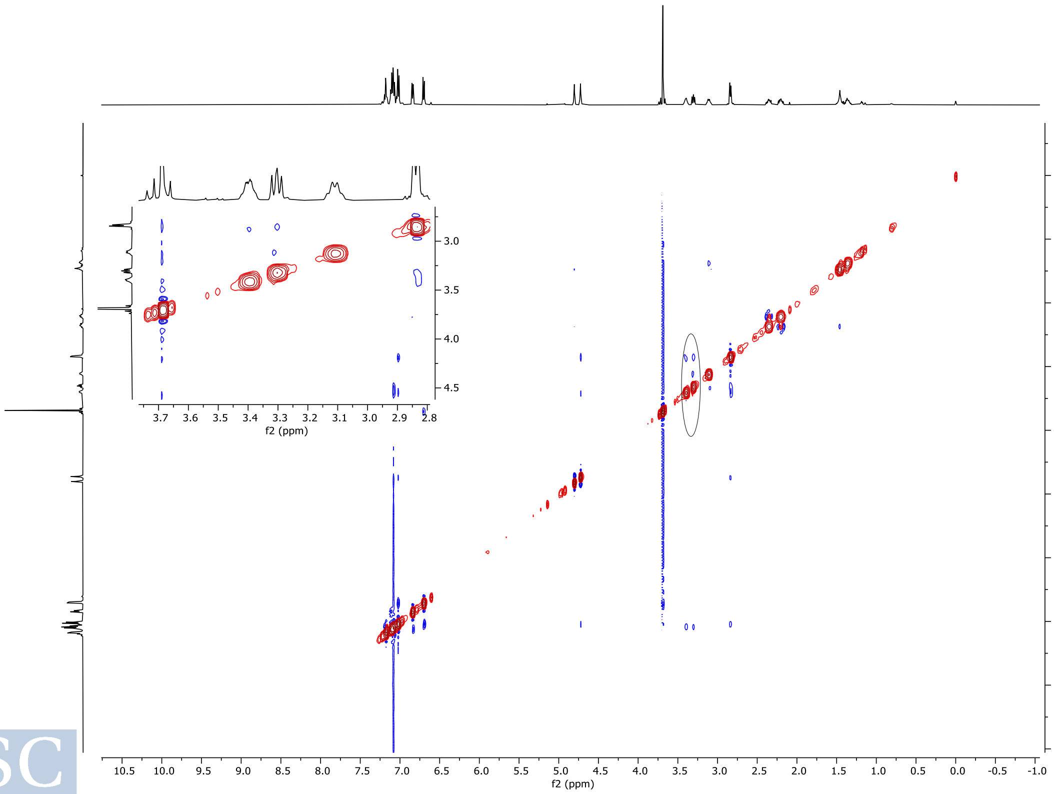
2.5
2.0
1.5
1.0
0.5
0.0
f2 (ppm)
0
1
2
3
4
5
6
7
8
f1 (ppm)

NOESY


3.7
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3.2
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3.5
4.0
4.5
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
-1.0
f2 (ppm)
0
1
2
3
4
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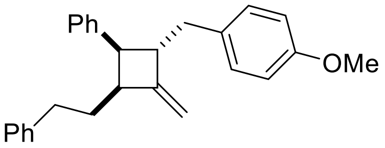
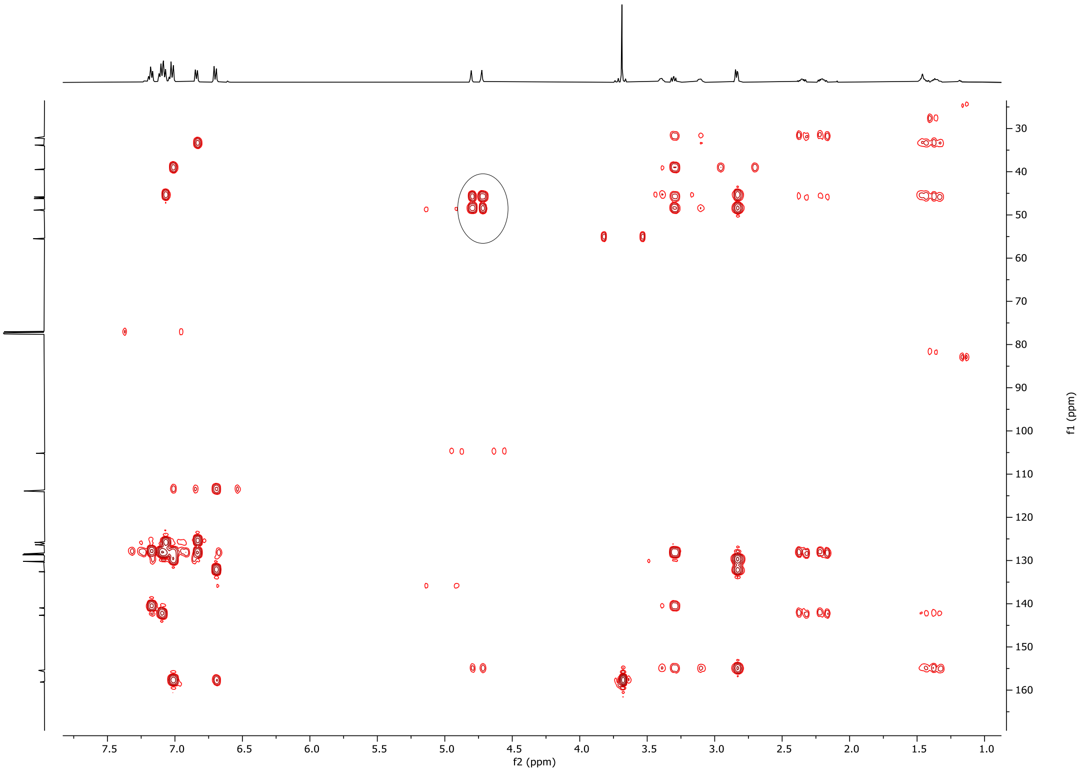
6
7
8
9


Ph
OMe
Ph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5.5
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1.5
1.0
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40
50
60
70
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100
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120
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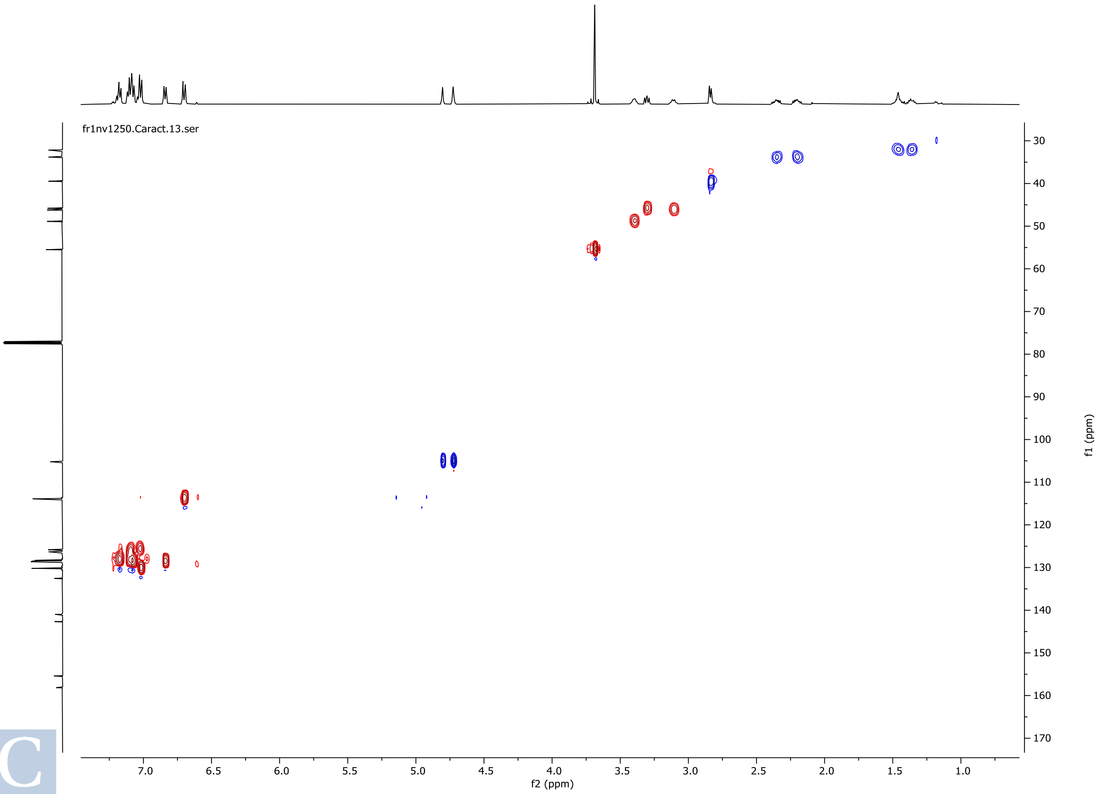
140
150
160
f1 (ppm)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6.0
5.5
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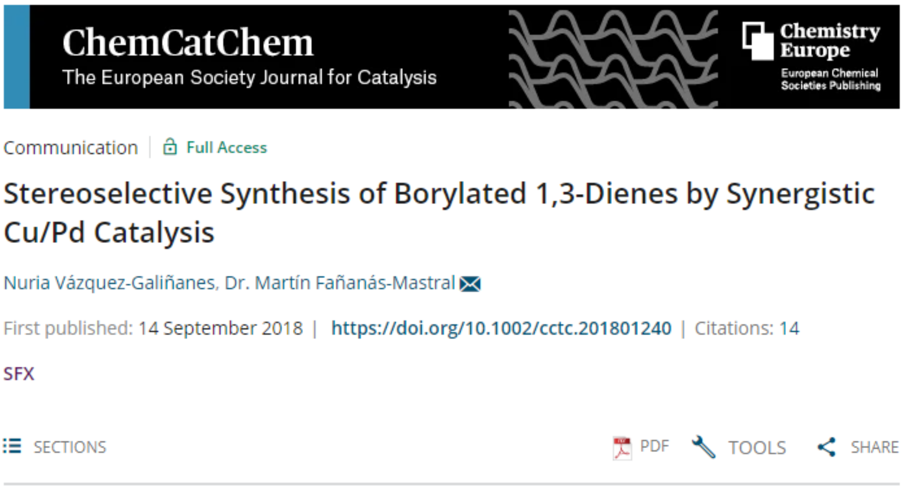
4.0
3.5
3.0
2.5
2.0
1.5
1.0
f2 (ppm)
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
f1 (ppm)

LIST OF PUBLICATIONS

Title: Stereoselective Synthesis of Borylated 1, 3-Dienes by Synergistic Cu/Pd Catalysis

Authors:	**Nuria Vázquez Galiñanes and Martín Fañanás Mastral**
Publication year	**2018**
Journal	**ChemCatChem**
Volumen, pages	**10, 4817-4820**
Impact factor	**5.497**
PhD student contribution	**Synthesis of starting materials; Synthesis and characterization of borylated 1,3-dienes and derivatives**



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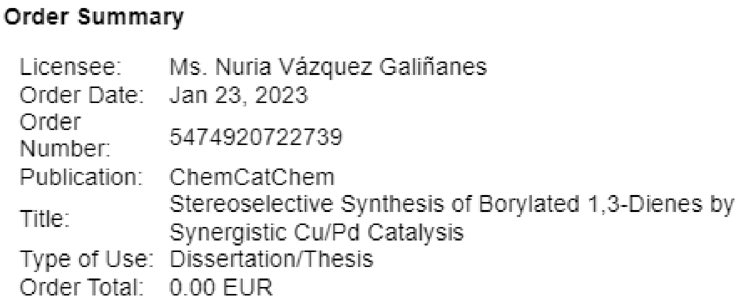
Stereoselective Synthesis of Borylated 1,3-Dienes by Synergistic Cu/Pd Catalysis

Nuria Vázquez-Galiñanes, Dr. Martín Fañanás-Mastral

First published: 14 September 2018 | https://doi.org/10.1002/cctc.201801240 | Citations: 14



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Licensee: Ms. Nuria Vázquez Galiñanes
Order Date: Jan 23, 2023
Order Number: 5474920722739
Publication: ChemCatChem
Title: Stereoselective Synthesis of Borylated 1,3-Dienes by Synergistic Cu/Pd Catalysis
Type of Use: Dissertation/Thesis
Order Total: 0.00 EUR

Title: ***Bifunctional Skipped Dienes through Cu/Pd-Catalyzed Allylboration of Alkynes with B_2pin_2 and Vinyl Epoxides***

Authors:	**Nuria Vázquez Galiñanes, Isabel Velo Heleno and Martín Fañanás Mastral**
Publication year	**2022**
Journal	**Organic Letters**
Volumen, pages	**24, 8244–8248**
Impact factor	**6.005**
PhD student contribution	**Synthesis of starting materials; Synthesis and characterization of borylated 1,4-dienes.**

Bifunctional Skipped Dienes through Cu/Pd-Catalyzed Allylboration of Alkynes with B_2pin_2 and Vinyl Epoxides

Nuria Vázquez-Galiñanes, Isabel Velo-Heleno, and Martín Fañanás-Mastral*

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Publication Date: November 3, 2022
https://doi.org/10.1021/acs.orglett.2c03390
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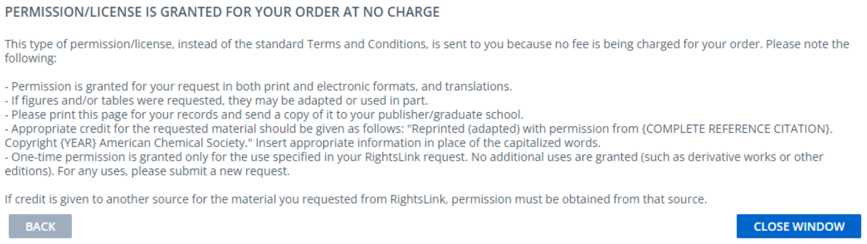
SUBJECTS: Chemical reactions, Ethers,



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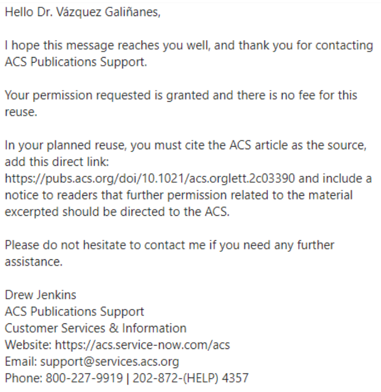

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In this PhD thesis we have developed methodologies to synthesize functionalized dienes using synergistic Cu/Pd catalysis. The first approach involves the synthesis of silylated 1,4- dienes from allylic carbonates and (Z)-silyl substituted allyl alcohols. The next approach is a Cu/Pd catalyzed three component alkenylboration of alkynes. Using this strategy was possible to synthesized stereofedined syn-1-boron-1,3- dienes. Furthermore, we have developed a three-component transformation between alkynes, bis(pinacolato)diboron and vinyl epoxides for the synthesis of bifunctional 1,4-borylated dienes. Finally, an efficient methodology for the synthesis of borylated 1,5-dienes has been described. This transformation consists in a borylative allyl-allyl cross-coupling between allenes and allylic carbonates.