TESE DE DOUTORAMENTO

NEW SYNTHETIC ROUTES TOWARDS 1,4-DIENYLBORONATES VIA CATALYTIC ALKYNE ALLYLBORATION REACTIONS.

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A mi familia

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Abbreviations and Acronyms

ºC	degree Celsius	DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
δ	chemical shift	DCE	dichloroethane
9-BBN	9-Borabicyclo[3.3.1]nonane	DEM	Diethyl malonate
Å	Angstrom	DFT	Density functional theory
Ac	acyl	DIAD	Diisopropyl azodicarboxylate
acac	Acetylacetone	DIBAL-H	Diisobutylaluminium hydride
AcOEt	ethyl acetate	diglyme	Bis (2-metoxietil) éter
Ad	adamantly	DMA	Dimethylacetamide
APCI	Atmosphere-pressure chemical ionization	DMAP	4-Dimethylaminopyridine
APhosPdG3	[4-(Di-tert-butylphosphino)-N,N-dimethylaniline-2-(2'-aminobiphenyl)]palladium(II) methanesulfonate	DMF	Dimethylformamide
Ar	Aryl	dmpd	Dimethylpentanediol
aq.	Aqueous	DMSO	Dimethyl sulfoxide
BenzP*	1,2-Bis(t-butylmethylphosphino)benzene	DIOP	(2,3-O-isopropylidene-2,3-dihydroxy-1,4-bis(diphenylphosphino)butane)
BINAP	(2,2′-bis(diphenylphosphino)-1,1′-binaphthyl)	DPEPhos	Bis[(2-diphenylphosphino)phenyl] ether
Bn	Benzyl	dppbz	1,2-Bis(diphenylphosphino)benzene
Boc	*tert*-Butyloxycarbonyl	dppe	1,2-Bis(diphenylphosphino)ethane
		dppf	1,1′-Bis(diphenylphosphino)ferrocene
BQ	1,4-Benzoquinone	dppm	Bis(diphenylphosphino)methane
BrettPhos	2-(Dicyclohexylphosphino)3,6-dimethoxy-2′,4′,6′-triisopropyl-1,1′-biphenyl	dppp	1,3-Bis(diphenylphosphino)propane
Bu	butyl	dr	Diastereomeric ratio
t-BuXPhos-Pd-G3	[(2-Di-tert-butylphosphino-2′,4′,6′-triisopropyl-1,1′-biphenyl)-2-(2′-amino-1,1′-biphenyl)] palladium(II) methanesulfonate	DTDA	Diene transmissive Diels-Alder
CAAC	Cyclic(alkyl)(amino)carbene	DTBM	3,5-di-tert-butyl-4-methoxyphenyl
cat	catechol	DuPhos	2-Dicyclohexylphosphino-2′,6′-diisopropoxybiphenyl
cat.	catalyst	E	electrophile
CI	chemical ionization	EDG	electron-donating group
Cp*	1,2,3,4,5-pentamethylcyclopentadienyl	*ee*	enantiomeric excess
Cy	cyclohexyl	EI	Electron ionization
Cyp	cyclopentyl	equiv	Equivalent
COD	1,5-Cyclooctadiene	er	enantiomeric ratio
Conv.	Conversion	Et	Ethyl
CPME	cyclopentylmethylether	Et_2O	diethyl ether
d	doublet	Et_3N	triethyl amine
dan	1,8-Diaminonaphthalene	EWG	electron-withdrawing group
dba	Dibenzylideneacetone	FG	functional group
DBAD	Dibenzyl azodicarboxylate	GC-MS	Gas chromatography mass spectroscopy

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h	hours
hex	Hexyl
(Het)Ar	Heteroaromatic
HG-II	(1,3-Bis-(2,4,6-trimethylphenyl)-2-imidazolidinylidene)dichloro(o-isopropoxyphenylmethylene)ruthenium
HOMO	Highest-occupied molecular orbital
HRMS	High resolution mass spectrometry
Hz	Hertz
IMes	1,3-Bis(2,4,6-trimethylphenyl)-1,3-dihydro-2H-imidazol-2-ylidene
IMS	1,3-dimethylimidazoline-2-thione
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
Me	Methyl
Mes	Mesityl
MIDA	*N*-methyliminodiacetic acid
min	mintutes
Mp	Melting point
MS	Molecular sieves
m/z	Mass charge relation
NBS	*N*-bromosuccinimide
n.d.	not determined
neop	neopentyl glycolato
NHC	*N*-heterocyclic carbene
NIS	*N*-iodosunccinimide
NMR	nuclear magnetic resonance
NOE	Nuclear Overhauser effect
Nu	nucleophile
p	Pentet
pai	Pinanediolato
pent	pentyl
Ph	Phenyl
Phth	Phthaloyl
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
S_E	Electrophilic substitution
S_N	nucleophilic substitution
SEGPhos	5,5′-Bis(diphenylphosphino)-4,4′-bi-1,3-benzodioxole
SET	Single electron transfer
SFC	super fluid chromatography
Sia	Disiamylborane
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
TaniaPhos	(2*S*)-1-[(*R*)-(Dimethylamino)[2-(diphenylphosphino)phenyl]methyl]-2-(diphenylphosphino)ferrocene
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
TFP	Tri(2-furyl)phosphine
THF	Tetrahydrofuran
TIB	2,4,6-triisopropylbenzoate
TIPS	Triisopropylsilyl
TM	Transition metal
TMDS	1,1,3,3-Tetramethyldisiloxane
TMS	Trimethylsilyl
TPGS-750-M	DL-α-Tocopherol methoxypolyethylene glycol succinate
Ts	Tosyl
TS	transition state
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 metallic and/or bimetallic catalysis that allow the synthesis of borylated 1,4-dienes from simple molecules abundant in nature, avoiding the generation of metal residues. Such methodologies will involve the chemoselective activation of a hydrocarbon, an allylic substrate and bis(pinacolato)diboron (either by a single transition metal or by the cooperative action of two different transition metal complexes), so that these molecules can react through an allylic substitution reaction to form borylated 1,4-dienes with complete control over the process selectivity.

Classical methods to prepare 1,4-dienes via transition metal-catalyzed alkenylation of allylic substrates require stoichiometric amount of alkenyl metal reagents. These methodologies are inherently limited to the availability and reactivity profiles of the alkenyl reagent. In addition, the use of these pre-functionalized reagents entails the formation of a stoichiometric amount of inorganic salt as a reaction by-product. To avoid the use of stoichiometric amounts and the prior preparation of the organometallic reagent, an excellent alternative would be the transient formation of the C(sp^2) nucleophile promoted by a transition metal catalyst.

One of the main objectives of this thesis is to synthesize borylated 1,4-dienes by using simple alkynes as a transient functionalized alkenylmetal species in a stereo- and regioselective (and enantioselective where appropriate) allylic substitution. Furthermore, the regioselectivity of the allylic substitution has to be controlled with transition metal catalysis in order to avoid the formation of mixture of isomers.

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CHAPTER I: INTRODUCTION

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1. ORGANOBORON COMPOUNDS

Organoboron chemistry has been a focus of attention for organic chemists for a long time and still is on the present day. The exciting discoveries and the enormous potential of this chemistry keep the synthesis and reactivity of organoboron compounds at the forefront of our science.

Organoboron compounds are usually trivalent neutral compounds with trigonal planar geometry. Trivalent boron atom is sp^2 hybridized and has an empty p orbital, which makes organoboron compounds electron-deficient and Lewis acidic species.[1] This electron deficiency and the Lewis acidity provide organoboron compounds a versatile reactivity. Tetravalent boron compounds, which feature a tetrahedral geometry, can also be formed by addition of a nucleophile to the electrophilic boron center. Furthermore, due to the low polarity of the C-B bond, these compounds are generally more stable than other organometallic species. This also results in a lower basicity and reactivity which make them tolerant to a broad range of functional groups.

Organoboron compounds can be classified according to the substitution of the boron atom. Some of the more common types of organoboron compounds are boranes, boron hydrides, boronic acids, boronic esters, trifluoroborate salts, boronamides or tetravalent boron 'ate' complexes among others (Figure 1).

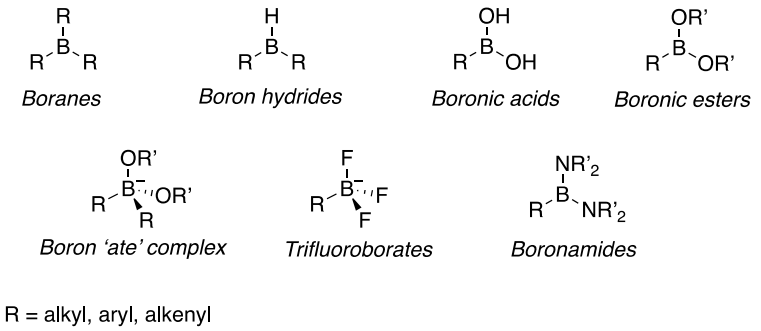

Figure 1. Common types of organoboron compounds.

Owing to the above-mentioned properties, organoboron reagents are some of the most versatile compounds in organic synthesis. C-B bond can be transformed into, C-C, C-O, C-N, C-halogen, among others (see section 1.2, chapter I). Some of the most common synthetic transformation involving organoboron compounds are illustrated in Scheme 1.

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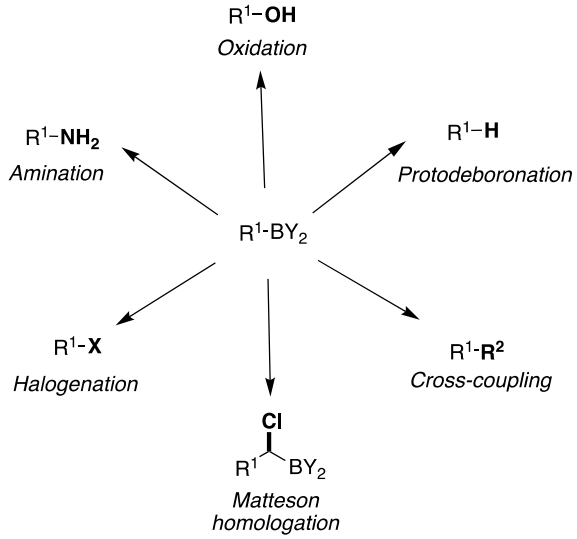
[1] Defrancesco, H.; Dudley, J.; Coca, A. Boron Chemistry: An Overview. In *Boron reagents in Synthesis*; Coca, A., Ed.; ACS Symposium Series 1236; American Chemical Society: Washington, DC, 2016; pp 1-25.



Scheme 1. Examples of the reactivity of organoboron compounds.

Pioneering work of H. C. Brown on hydroboration reactions revolutionized synthetic organic chemistry. Brown's group discovered that unsaturated hydrocarbons could undergo addition of borohydrides to readily obtain organoboron compounds.[2] These achievements, together with his investigation on borohydride compounds as reducing agents, led him to win the Nobel Prize in Chemistry in 1979. Later on, remarkable contributions by Matteson,[3] Suzuki and Miyaura,[4] Aggarwal[5] and others[6] have led to new research and new uses of organoboron compounds in organic chemistry.

Besides their importance in organic synthesis, there is an increasing interest of these compounds in medicinal chemistry and material science. In the past centuries, boron chemistry did not receive special attention in medicine probably due to the lack of boron containing natural products.[7] However, in last years the use of boron in drug design is becoming more popular. Bioactive boron-containing products have been shown to

[2] (a) Brown, H. C.; Rao, B. C. S. *J. Am. Chem. Soc.* **1956**, *78*, 5694-5695. (b) Brown, H. C.; Tsukamoto, A.; Bigley, D. B. *J. Am. Chem. Soc.* **1960**, *82*, 4703-4707. (c) Brown, H. C. *Tetrahedron* **1961**, *12*, 117-138.

[3] (a) Matteson, D. S.; Mah, R. W. H. *J. Org. Chem.* **1963**, *28*, 2171-2174. (b) Matteson, D. S.; Mah, R. W. H. *J. Am. Chem. Soc.* **1963**, *85*, 2599-2603.

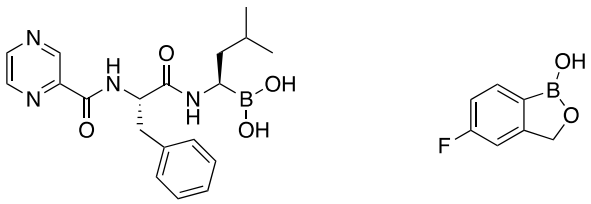
[4] (a) Miyaura, N.; Yamada, K.; Suzuki, A. *Tetrahedron Lett.* **1979**, *20*, 3437-3440. (b) Miyaura, N.; Suzuki, A. *J. Chem. Soc., Chem. Commun.* **1979**, 866-867.

[5] (a) Stymiest, J. L.; Bagutski, V.; French, R. M.; Aggarwal, V. K. *Nature* **2008**, *456,* 778-782. (b) Burns, M.; Essafi, S.; Bull, S. P.; Webster, M. P.; Balieu, S.; Dale, J. W.; Butts, C. P.; Harvey J. N.; Aggarwal, V. K. *Nature* **2014**, *513*, 183-188. (c) Balieu, S.; Hallett, G. E.; Burns, M.; Bootwicha, T.; Studley, J.; Aggarwal, V. K. *J. Am. Chem. Soc.* **2015**, *137*, 4398-4403.

[6] (a) Fernández, E.; Whiting, A. *Top. Organomet. Chem.* **2015**, *49*, 1-37. (b) Fyfe, J. W. B.; Watson, A. J. B. *Chem.* **2017**, *3*, 31-55.

[7] Few examples of tetravalent boron-containing natural products have been isolated: (a) Hutter, R.; Keller-Schierlein, W.; Knusel, F.; Prelog, V.; Rodgers, G. C., Jr.; Suter, P.; Vogel, G.; Voser, W.; Zahner, H. *Helv. Chim. Acta* **1967**, *50*, 1533-1539. (b) Chen, X.; Schauder, S.; Potier, N.; Van Dorsselaer, A.; Pelczer, I.; Bassler, B. L.; Hughson, F. M. *Nature* **2002**, *415,* 545-549. (c) Dembitsky, V. M.; Smoum, R.; Al-Quntar, A.A.; Ali, H. A.; Pergament, I.; Srebnik, M. *Plant. Sci.* **2002**, *163*, 931-942. No examples of trivalent boronic acids or esters containing natural products have been reported so far.

possess interesting properties for biological targeting and therapeutic uses (Figure 2).[8] Boron compounds also play an important role in material science, for example as luminescent materials, optoelectronics or nanomaterials for drug delivery.[9]



Bortezomib
(anticancer drug)

Tavaborole
(antifungal)

Figure 2. Example of boron-containing approved drugs.

1.1. SYNTHESIS OF ORGANOBORON COMPOUNDS

In this section, the most common methods to prepare organoboron compounds are going to be summarized, emphasizing the synthesis of alkenylboronic esters, for being more relevant to the work reported in this thesis.

Since Brown's first synthesis of organoboron compounds by alkene and alkyne hydroboration, great efforts have been done in the development of efficient methodologies for the synthesis of this type of compounds. Besides hydroboration of unsaturated compounds, classical methods to synthesize organoboron compounds have typically involved the use of hard organometallic reagents, such as organolithium or Grignard compounds, and its transmetalation with boron alkoxides (Scheme 2).[10] The use of such reactive organometallic reagents trigger limited functional group tolerance and usually involve multistep procedures, making these protocols poorly efficient in terms of step-economy. Next sections will be focused on milder and more efficient methodologies, mainly relying on transition metal catalysis, that avoids the use of stoichiometric amounts of hard organometallic reagents.

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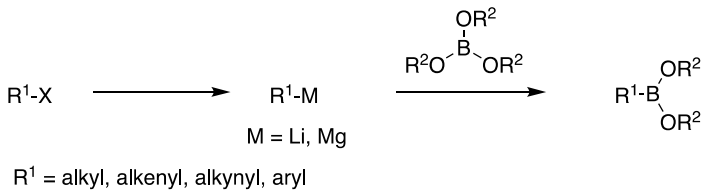
[8] (a) Issa, F.; Kassiou, M.; Rendina, L. M. *Chem. Rev*. **2011**, *111*, 5701-5722. (b) Ban, H. S.; Nakamura, H. *Chem. Rec*. **2015**, *15*, 616-635. (c) Diaz, D. B.; Yudin, A. K. *Nat. Chem*. **2017**, *9*, 731-742.

[9] (a) Entwistle, C. D.; Marder, T. B. *Chem. Mater*. **2004**, 16, 4574-4585. (b) Mukherjee, S.; Thilagar, P. *J. Mater. Chem. C*. **2016**, *4*, 2647-2662. (c) Stubelius, A.; Lee, S.; Almutairi, A. *Acc. Chem. Res*. **2019**, *52*, 3108-3119.

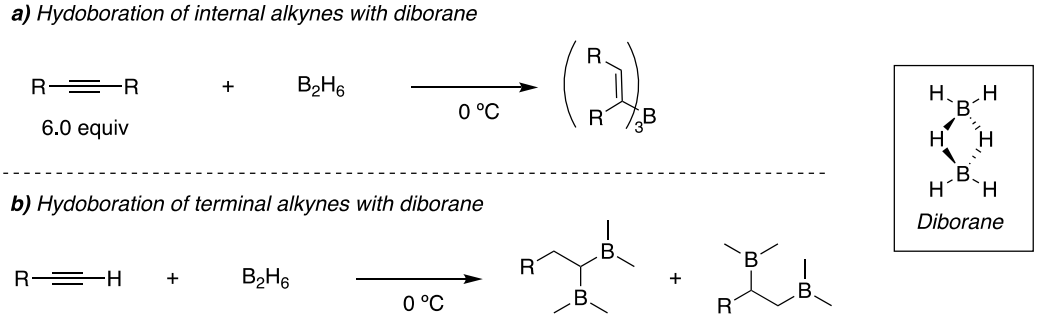
[10] (a) Brown, H. C.; Cole, T. E. *Organometallics* **1983**, *2*, 1316-1319. (b) Brown, H. C.; Bhat, N. G.; Srebnik, M. *Tetrahedron Lett*. **1988**, *29*, 2631-2634.



Scheme 2. Traditional synthesis of organoboron compounds by transmetalation with organolithium or Grignard reagents.

1.1.1. Synthesis of alkenylboron compounds by uncatalyzed hydroboration of alkynes

Alkenylboranes could be synthetized using Brown's procedure for hydroboration of alkynes. This procedure involves the addition of a B-H bond into an alkyne. Initially, these reactions were performed at 0 ºC with diborane (B_2H_6) and internal alkynes. This reaction provides trialkenylboranes (Scheme 3a).[11] Selective monoborylation of terminal alkynes could not be achieved under these conditions and mixtures of diborylated aliphatic products were obtained in those cases (Scheme 3b).[12]



Scheme 3. Uncatalyzed hydroboration of alkynes with diborane.

The use of dialkylboranes such as disiamylborane (Sia_2BH) and 9-Borabicyclo[3.3.1]nonane (9-BBN; Scheme 4a) in the hydroboration of alkynes helped to circumvent these selectivity issues, thus, enabled selective monoborylation of terminal alkynes (Scheme 4b).[13,14,15] The reaction between terminal alkynes with 9-BBN at room temperature provides the dihydroborated product. However, excellent yields of monohydroborated alkenylboranes can be obtained by lowering the temperature and increasing the equivalents of the alkyne. The reaction with internal alkynes readily proceeds at room temperature leading exclusively to the monoborylated product (Scheme 4c). The steric hindrance of these dialkylboranes also helps to improve the regioselectivity of the addition to unsymmetrical dialkylalkynes, compared with the smaller diborane (Scheme 4d).

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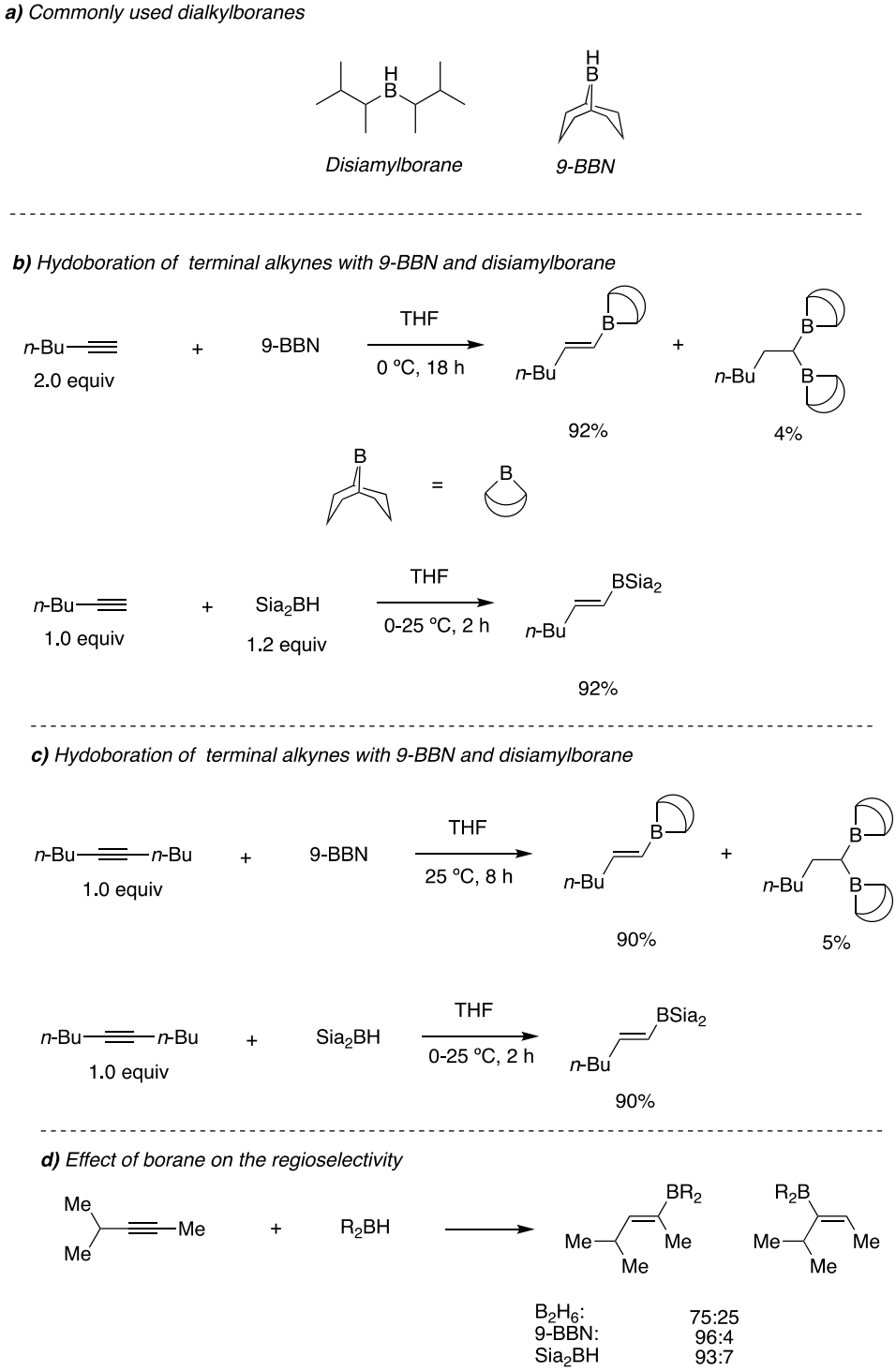
[11] Brown, H. C.; Zweifel, G. *J. Am. Chem. Soc.* **1959**, *81*, 1512-1512.
[12] Zweifel, G.; Arzoumanian, H. *J. Am. Chem Soc*. **1967**, *89*, 291-295.
[13] Brown, H. C.; Zweifel, G. *J. Am. Chem. Soc*. **1961**, *83*, 3834-3840.
[14] Brown, H. C.; Lane, C. F. *Heterocycles* **1977**, *7*, 453-485.
[15] Brown, H. C.; Scouten, C. G.; Liotta, R. *J. Am. Chem. Soc*. **1979**, *101*, 96-99.

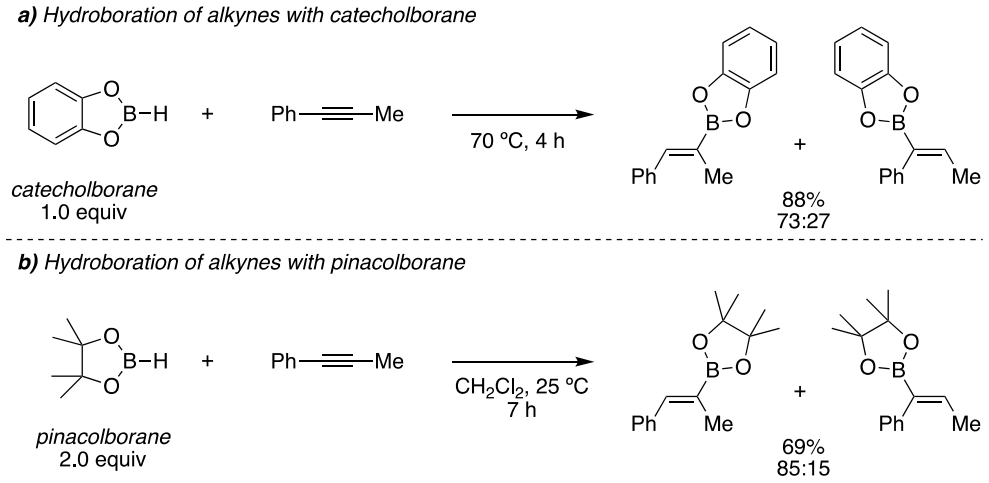


Scheme 4. Hydroboration of alkynes with 9-BBN and disiamylborane.

Although great advances have been done in this chemistry, safety considerations must be bear in mind, as diborane and other dialkylboranes are flammable and air and moisture sensitive. Further discoveries have led to methodologies that allow the use of more stable, thus less reactive, boronic esters such as catecholborane (HBcat)[16] and

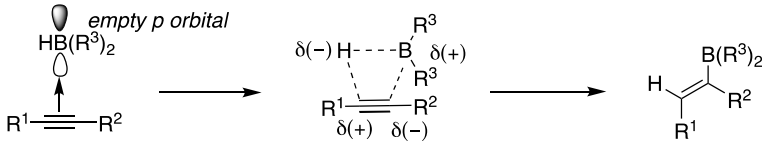
[16] (a) Brown, H. C.; Gupta, S. K. *J. Am. Chem. Soc*. **1972**, *94,* 4370-4371. (b) Brown, H. C.; Gupta, S. K. *J. Am. Chem. Soc*. **1975**, *97*, 5249-5255.

pinacolborane (HBpin) [17] as hydroboration reagents (Scheme 5). Due to the lower reactivity of catecholborane, higher temperatures are needed (70 ºC) and mixture of regioisomers are obtained after the hydroboration of alkynes (Scheme 5a). Alkenyl catecholboronic esters are water sensitive and are usually hydrolyzed to the corresponding boronic acid for their easier handling. The use of pinacolborane enables hydroboration of alkynes in milder conditions (25 ºC) and better regioselectivities than catecholborane (Scheme 5b). Moreover, it gives rise to bench stable alkenyl pinacol boronic esters, which can be usually isolated by column chromatography.



Scheme 5. Uncatalyzed hydroboration with catechol and pinacolborane.

The mechanism of this uncatalyzed reaction gets initiated by the coordination of triple bond to the empty orbital of the boron atom. Then, addition of the boron atom proceeds into the less substituted or into the more nucleophilic carbon atom, leading to a carbocation type intermediate positioned in the more stable position. Overall, a *syn* anti-Markovnikov addition of HBR_2 in obtained. (Scheme 6).



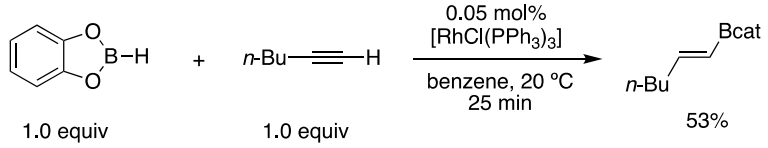
Scheme 6. Mechanism of uncatalyzed hydroboration of unsaturated compounds.

1.1.2. Transition metal-catalyzed hydroboration of alkynes

It was not until the 1980s, when first examples of transition metal-catalyzed hydroboration of alkynes with boranes were reported. Those methodologies were based on rhodium and cobalt catalysis, which improve the efficiency and enable the use of milder conditions.[18] The use of a transition metal catalyst increases the rate of the addition of the B-H bond into the unsaturated compound. A methodology reported by Männig and

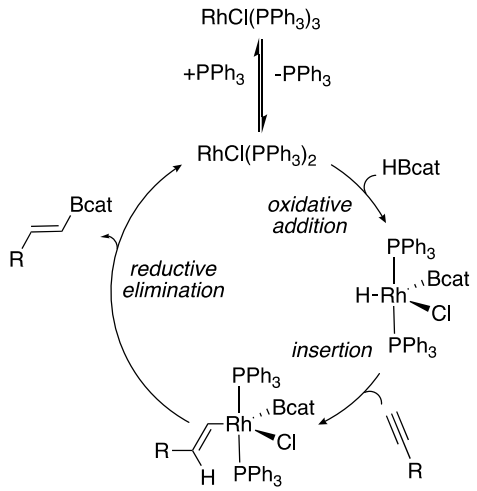
[17] Tucker, C. E.; Davidson, J.; Knochel, P. *J. Org. Chem*. **1992**, *57*, 3485-3487.
[18] (a) Wilczynski, R.; Sneddon, L. G. *J. Am. Chem. Soc*. **1980**, *102*, 2857-2858. (b) Männig, D.; Nöth, H. *Angew. Chem. Int. Ed.* **1985,** *24*, 878-879.

Nöth, based on the use of catalytic amount of a rhodium complex ($RhCl(PPh_3)_3$), enabled the use of catecholborane (HBcat) with milder conditions than uncatalyzed additions (20 ºC).[18b] Under these mild conditions, hydroboration of 1-hexyne could be performed with full selectivity although in only moderate yield (Scheme 7).



Scheme 7. First report of rhodium-catalyzed hydroboration of 1-hexyne with catecholborane.

The mechanism of this reaction was suggested to proceed via initial loss of a phosphine by the rhodium complex and oxidative addition of the B-H bond. Insertion of the alkene into the Rh-H bond and subsequent reductive elimination afford the hydroborated product (Scheme 8).



Scheme 8. Rhodium-catalyzed hydroboration of alkynes.

Since this initial report, the use of transition metal catalysis opened up new possibilities to control the stereoselectivity, which can be complementary to those obtained from the uncatalyzed reaction. In this sense, there was an increasing interest in catalyzed hydroboration reactions and numerous methodologies involving precious metal-catalysts (mainly based on rhodium catalysis) and earth abundant metals were reported (Scheme 9).[19]

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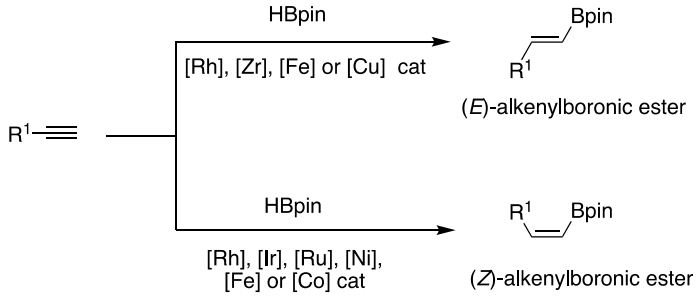
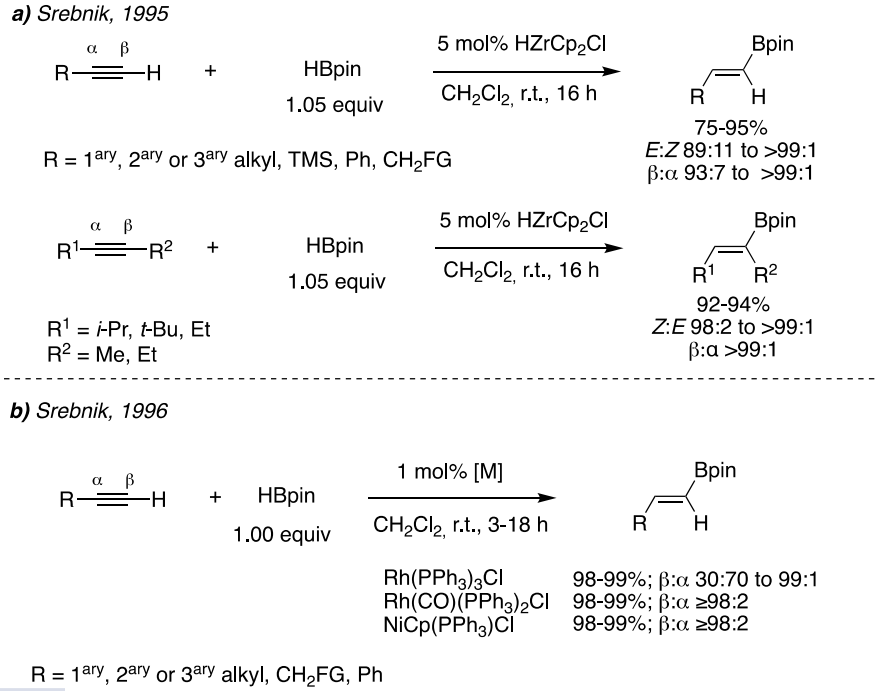
[19] For reviews see: (a) Burgess, K.; Ohlmeyer, M. *Chem. Rev.* **1991**, *9*1, 1179-1191. (b) Vogels, C.; Westcott, S. *Curr. Org. Chem*. **2005**, *9*, 687-699. (c) Obligacion, J. V.; Chirik, P. J. *Nat. Rev. Chem*. **2018**, *2*, 15-34. (d) Yoshida, H. *ACS Catal*., **2016**, *6*, 1799-1811.



Scheme 9. Transition metals used to catalyze *cis* and *trans* hydoboration of alkynes with pinacolborane.

1.1.2.1. Transition metal-catalyzed *cis*-hydoboration of alkynes

Early reports of *cis* hydroboration of alkynes were based in the use of Schwartz reagent (Cp_2ZrHCl) and HBpin. This reaction provides *E*-alkenylboronic esters with very good selectivity and yield with terminal alkyl and aryl alkynes and with internal dialkyl alkynes (Scheme 10a).[20] Shortly after, a methodology to perform a hydroboration of alkynes with pinacolborane using rhodium ([$Rh(PPh_3)_3Cl$] and [$Rh(CO)(PPh_3)_2Cl$]) and nickel ([$NiCp(PPh_3)Cl$]) catalysis afforded the olefinic products in quantitative yields (Scheme 10b).[21] However, $Rh(PPh_3)Cl$ provide mixtures of β and α borylated products in most of the cases.



Scheme 10. Early examples of transition metal-catalyzed hydroboration of alkynes.

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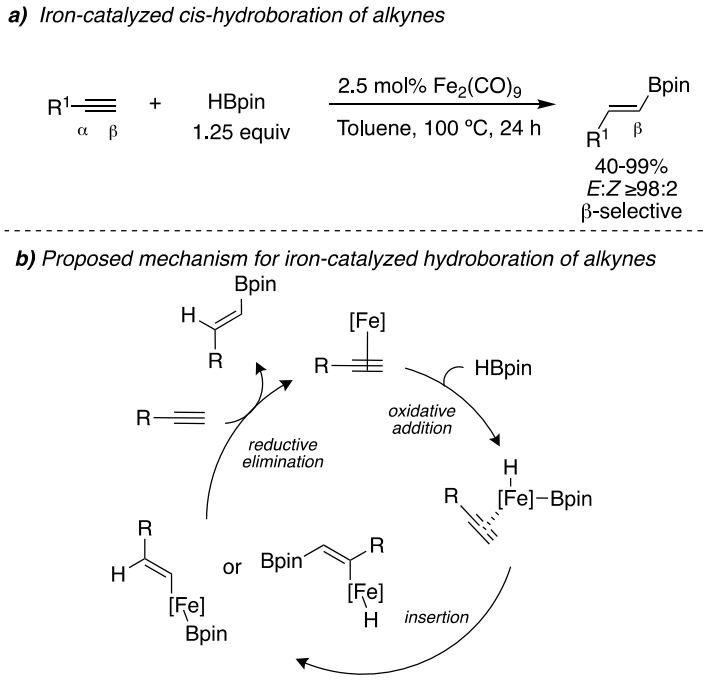
[20] Pereira, S.; Srebnik, M. *Organometallics* **1995**, *14*, 3127-3128.
[21] Pereira, S.; Srebnik, M. *Tetrahedron Lett*. **1996**, *37*, 3283-3286.

Iron catalysis was explored for the hydroboration of terminal alkynes with HBpin.[22] Enthaler proved the utility of $Fe_2(CO)_9$ in the hydroboration of alkynes with pinacolborane, upon thermal activation (100 ºC) (Scheme 11a).[22a] Under these conditions, terminal alkyl and arylalkynes exclusively provide the β borylated *E* isomer in very high yields in nearly all cases. Nonetheless, the use of internal alkynes gives rise to lower selectivity, leading to a mixture of up to four isomers (α-*E,* α-*Z*, β-*E* and β-*Z* isomers). The proposed mechanism for the iron-catalyzed *E* selective hydroboration of alkynes (Scheme 11b) involves the initial coordination of the alkyne to the iron catalyst followed by oxidative addition with HBpin. It has not been elucidated whether if the alkyne insertion takes places into the Fe-H or Fe-Bpin bond. However, reductive elimination of each of these two intermediates would lead to the formation of the β-borylated vinylboronic ester.



Scheme 11. Iron-catalyzed *cis*-hydroboration of alkynes.

Copper catalysis have also been described to undergo formal *cis*-hydroboration with pinacolborane (Scheme 12a). [23] This reaction is based on the use of cyclic(alkyl)(amino)carbene (CAAC) as ligand and provides good results with terminal aryl and alkyl alkynes. The mechanism of this transformation if proposed go through the formation of a copper-acetylide (Scheme 12b).

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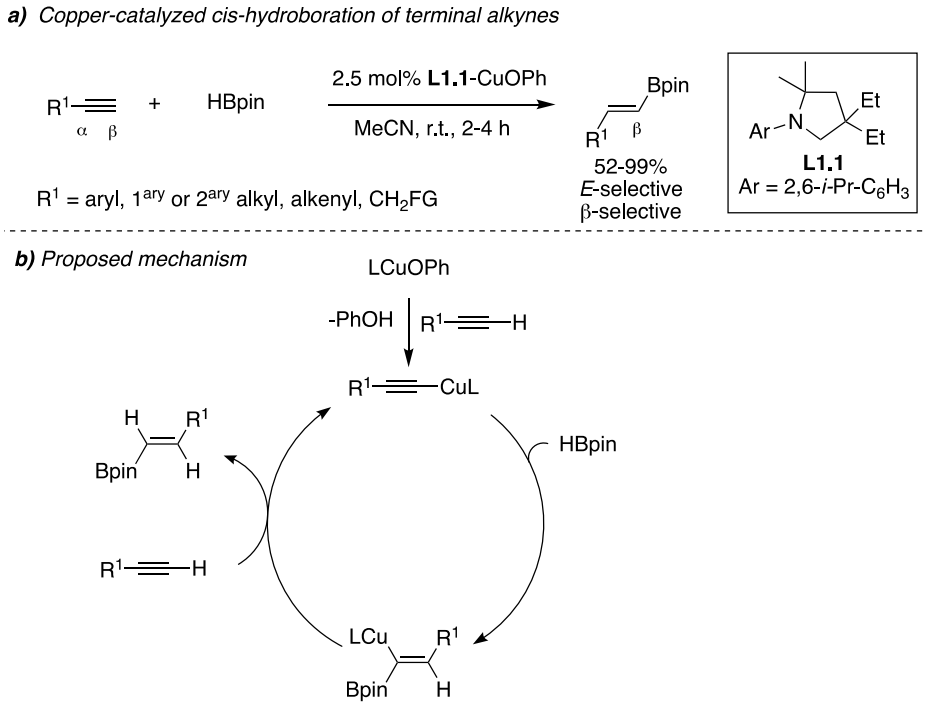
[22] (a) Haberberger, M.; Enthaler, S. *Chem. Asian J.* **2013**, *8*, 50-54. (b) Nakajima, K.; Kato, T.; Nishibayashi, Y. *Org. Lett*. **2017**, *19*, 4323-4326.

[23] Romero, E. A.; Jazzar, R.; Bertrand, G. *J. Organomet. Chem*. **2017**, *829*, 11-13.



Scheme 12. Copper-catalyzed hydroboration of terminal alkynes with pinacolborane.

Hydroboration of internal alkynes with copper catalysis and pincacolborane leads to the formation of the α-borylated product.[24] The group of Tsuji reported that the use of Xantphos-derived bulky biarylphosphines in combination with CuCl efficiently catalyzed the α selective *E*-hydroboration of internal alkynes (Scheme 13a).[24b] The alkyne substituent (G) induces an electronic bias in the triple bond in such a way that the addition of the hydride takes place into the β-carbon (more electrophilic). The proposed mechanism for the copper-catalyzed hydroboration of triple bonds is represented in Scheme 13b. Initially a LCu-H complex is formed after a σ-bond metathesis of LCuO*t*-Bu complex and HBpin. Then, the unsaturated bond inserts into the Cu-H bond to provide an alkenylcopper intermediate. Finally, a σ-bond metathesis between the alkenylcopper complex and HBpin affords the borylated product and regenerates the LCuH catalyst.

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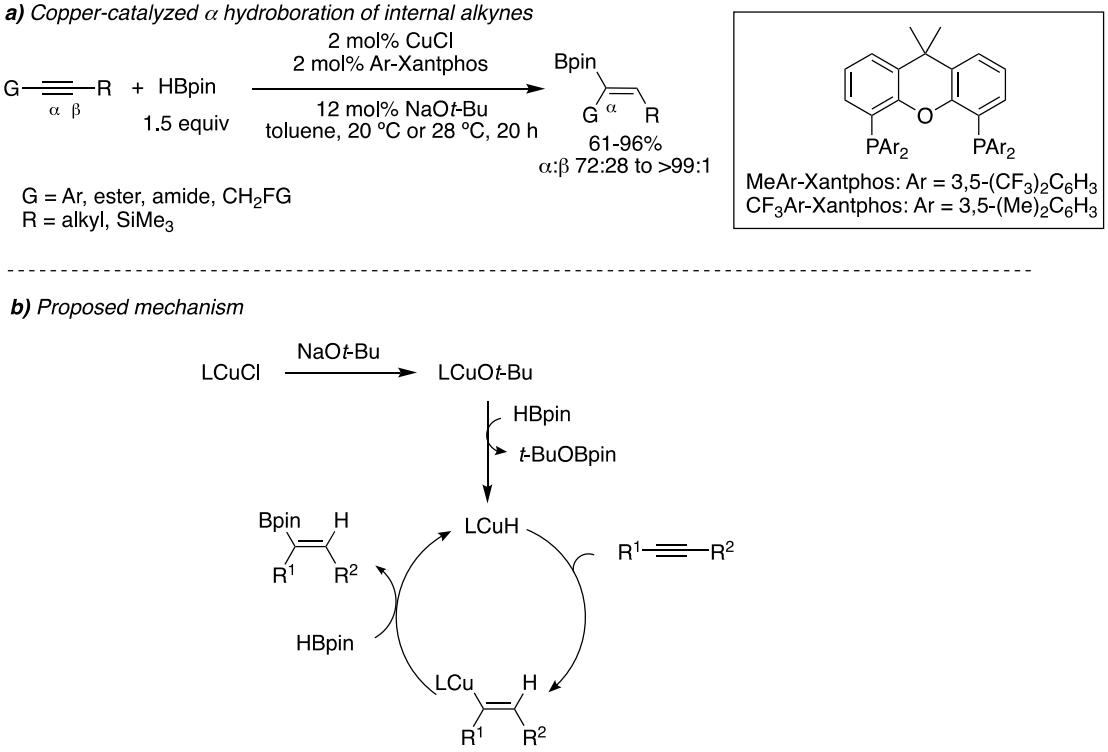
[24] (a) Lipshutz, B. H.; Boskovic Z. V.; Aue, D. H. *Angew. Chem. Int. Ed*. **2008**, *47*, 10183-10186. (b) Semba, K.; Fujihara, T.; Terao, J.; Tsuji, Y. *Chem. Eur. J.* **2012**, *18*, 4179-4184. (c) Bidal, Y. D.; Lazreg, F.; Cazin, C. S. J. *ACS Catal*. **2014**, *4*, 1564-1569.



Scheme 13. **a)** Copper-catalyzed α hydroboration of internal alkynes and **b)** proposed mechanism for copper-catalyzed hydroboration of alkynes.

Selective α-borylation of terminal alkynes was recently achieved using a cobalt catalyst and pincacolborane (Scheme 14).[25] This transformation is challenging due to that, usually, the insertion of the alkyne into the [M]-H bond leads to the metal positioned in the terminal carbon. However, in this case, the insertion of the alkyne into the Co-H bond leads to the α-alkenylcobalt complex with the use of a *N,N,N*-tridentate ligand **L1.2**. Then, σ-bond metathesis between the cobalt complex and pinacolborane give rise to the branched alkenylborante and restores the Co-H catalyst.

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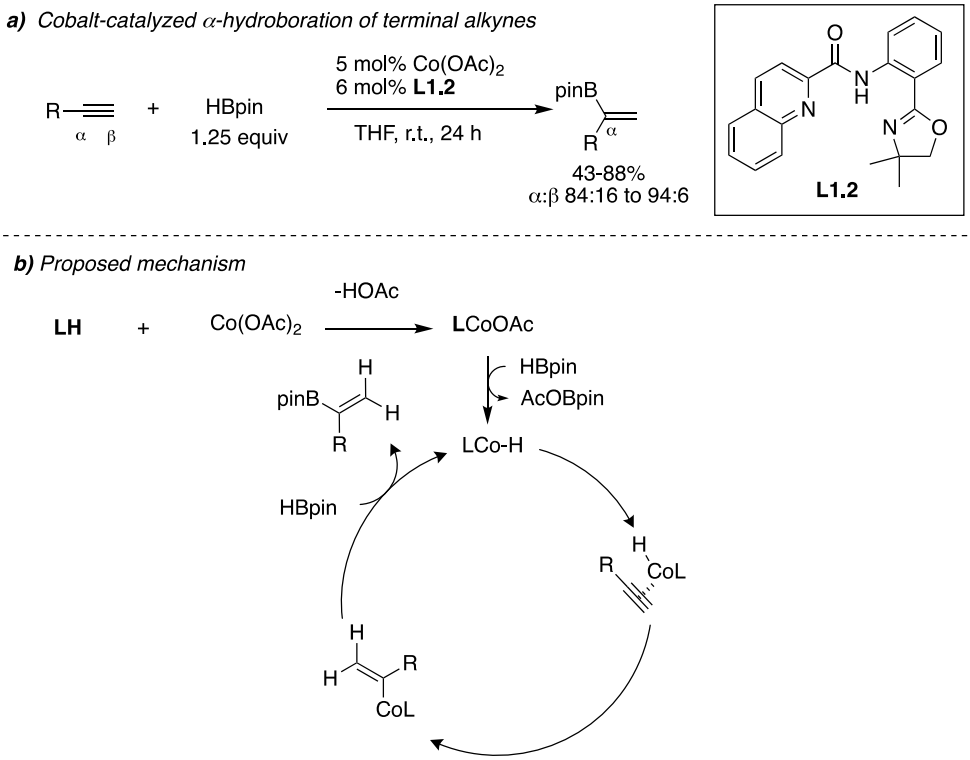
[25] Chen, J.; Shen, X.; Lu, Z. *Angew. Chem. Int. Ed.* **2021**, *60*, 690-694.



Scheme 14. Cobalt-catalyzed hydroboration of terminal alkynes.

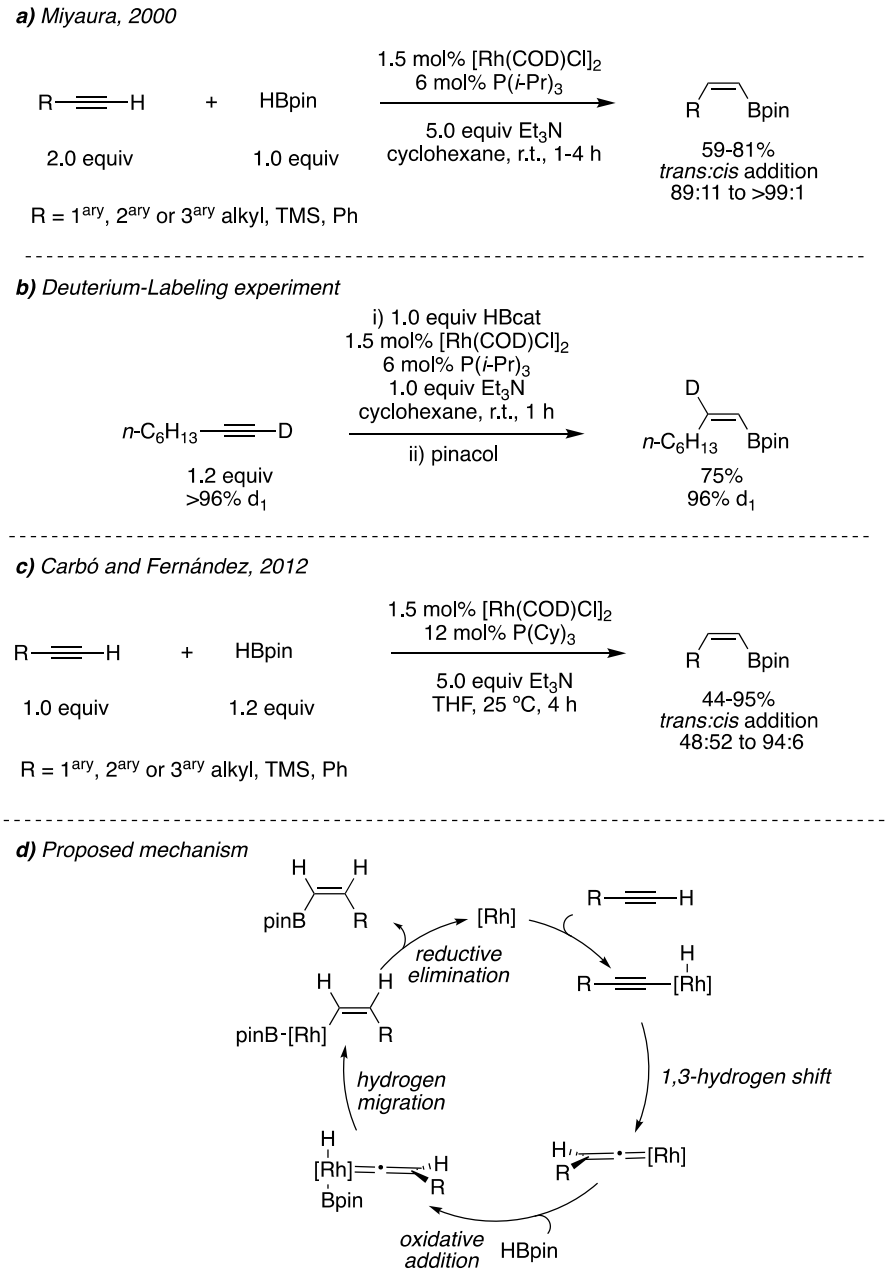
1.1.2.2. Transition metal-catalyzed *trans*-hydroboration of alkynes

Trans-hydroboration of alkynes with pinacolborane has been accomplished with different transition metal catalyst: rhodium[26] and iridium,[27] ruthenium,[28] iron[29] and cobalt.[30]

Miyaura and co-workers reported a rhodium-catalyzed *trans*-hydroboration of alkynes with pinacolborane (Scheme 15a).[27] Using a [{Rh(cod)Cl}$_2$]/P(*i*-Pr)$_3$ catalytic system they were able to obtain excellent *trans* selectivity. They observed, by deuterium-labeling experiments, that the acetylenic proton ended in the β-position of the alkenylboronate product (Scheme 15b) and a mechanism involving the formation of a rhodium vinylidene complex was proposed. A theoretical and experimental study of the rhodium catalyzed *trans*-hydroboration of alkynes was later reported by Fernández group to elucidate the mechanism of this transformation (Scheme 15c and d).[26] They found that the more plausible mechanistic pathway would consist in the insertion of the rhodium complex into the acetylenic C-H bond, followed by isomerization to the rhodium vinylidene complex. Then, oxidative addition of pinacolborane followed by vinylidene

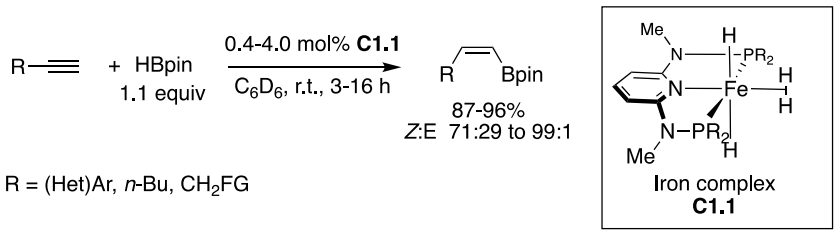
[26] Cid, J.; Carbó, J. J.; Fernández, E. *Chem. Eur. J.* **2012**, *18*, 1512-1521.
[27] Ohmura, T.; Yamamoto, Y.; Miyaura N. *J. Am. Chem. Soc.* **2000**, *122*, 4990-4991.
[28] Gunanathan, C.; Hölscher, M.; Pan, F.; Leitner, W. *J. Am. Chem. Soc*. **2012**, *134*, 14349-14352.
[29] Gorgas, N.; Alves, L. G.; Stöger, B.; Martins, A. M.; Veiros, L. F.; Kirchner, K. *J. Am. Chem. Soc*. **2017**, *139*, 8130-8133.
[30] Obligacion, J. V.; Neely, J. M.; Yazdani, A. N.; Pappas, I.; Chirik, P. J. *J. Am. Chem. Soc*. **2015**, *137*, 5855-5858.

insertion into the Rh-H bond and final reductive elimination would afford the *Z*-alkenylboronate.



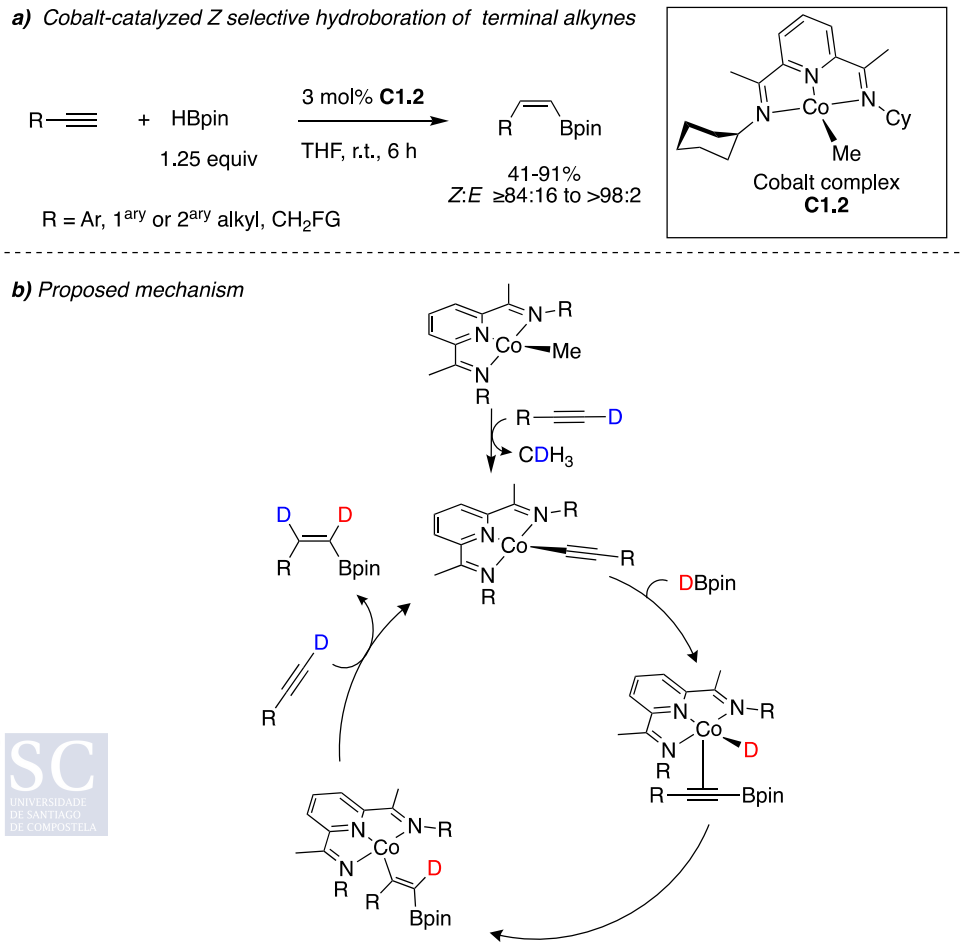
Scheme 15. Rhodium-catalyzed *trans*-hydroboration of alkynes.

More recently, an iron(II) polyhydride complex bearing a PNP pincer ligand was reported to catalyze the *Z* selective hydroboration of terminal alkynes (Scheme 16).[29] The *Z* vinylboronates are obtained in excellent yield, at room temperature and with generally high stereoselectivity. The *Z* selectivity is also believed to be originated after the formation of vinylidene intermediates.



Scheme 16. Iron-catalyzed hydroboration of terminal alkynes.

Cobalt catalysis provided in many cases, similar reactivity than iron complexes, and same type of ligands are usually applied. Chirik *et al.* reported a methodology based on the use of bis(imino)pyridine cobalt catalyst for the *Z*-selective hydroboration of terminal alkynes (Scheme 17a). Deuteration labeling experiments were performed to elucidate the reaction mechanism. In contrast to other metal-ctalyzed *Z*-selective hydroboration reacitons which operate through the formation of vinylidene intermediate, bis(iminimo)pyridine cobalt methyl complex **C1.2** reacts with terminal alkynes to generate methane and a cobalt acetylide (Scheme 17b). Oxidative addition of HBpin and reductive elimination provides alkynylboronate product. *Syn*-hydrometalation of this alkyne generates the (*Z*)-cobalt vinyl intermediate, which reacts with the terminal alkyne to afford the (*Z*)-alkenylboronic ester and regenerates the cobalt acetylide complex.



Scheme 17. a) *Z*-selective cobalt-catalyzed hydroboration of alkynes and **b)** proposed mechanism for cobalt-catalyzed *trans* hydroboration of alkynes.

1.1.3. Diboron compounds

Diboron compounds were discovered in 1925,[31] however, it was not until two decades ago, when the chemistry of these compounds started to be extensively explored and proved to be very versatile and extremely useful reagents in many synthetic transformations.[32] The number of publications involving the use of diboron compounds as reactants or reagents is increasing every year (Figure 3), demonstrating the importance of these compounds in current organic chemistry.

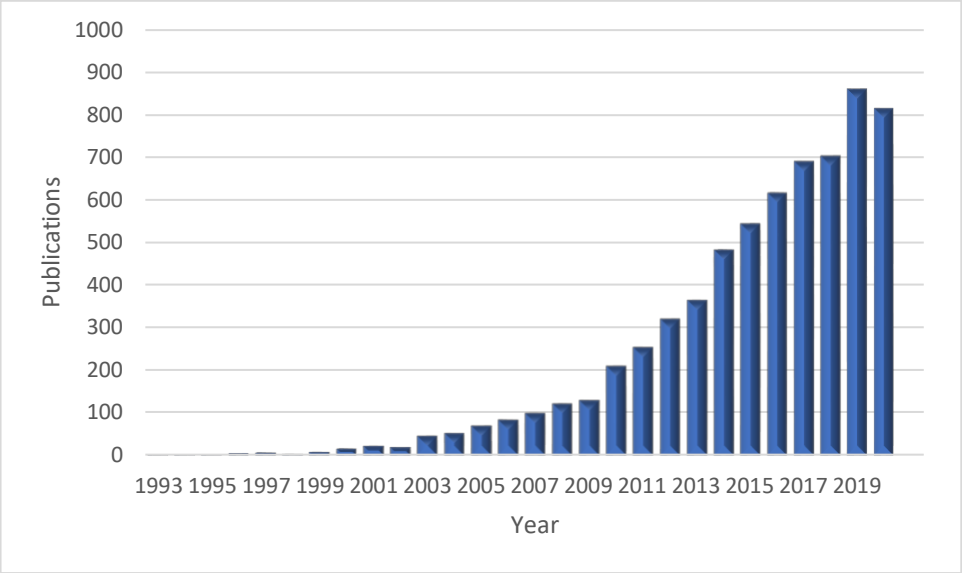


Figure 3. Number of publications per year in journals including bis(pinacolato)diboron as reactant or reagent (Scifinder).

The first type of diboron compounds reported were the diboron tetrahalides (with formula $X_2B\text{-}BX_2$), in particular, B_2Cl_4. Similar to diborane and hydroboranes, these compounds can react with alkynes to afford borylated compounds and uncatalyzed addition of diboron tetrahalides to unsaturated substrates has been studied.[33] This reaction generally gives the *syn*-1,2-addition, however, due to the high reactivity of these species, low temperatures are needed (-80 ºC) and compounds with B-Cl bonds are usually moisture and air sensitive (Scheme 18). Moreover, the difficulty associated with the manipulation of diboron tetrahalides (they react violent with oxygen and moisture) and the harsh conditions needed for the synthesis of B_2X_4 limited the utility of this method.

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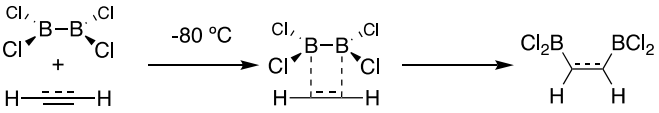
[31] Stock, A.; Brandt, A.; Fischer, H. *Ber. Dtsch. Chem. Ges. B* **1925**, *58*, 643-657.

[32] Neeve, E. C.; Geier, S. J.; Mkhalid, I. A. I.; Westcott, S. A.; Marder, T. B. *Chem. Rev*. **2016**, *116*, 9091-9161.

[33] (a) Urry, G.; Kerrigan, J.; Parsons, T. D.; Schlesinger, H. I. *J. Am. Chem. Soc*. **1954**, *76*, 5299-5301. (b) Ceron, P.; Finch, A.; Frey, J.; Kerrigan, J.; Parsons, T. D. Urrya, G.; Schlesinger, H. I. *J. Am. Chem. Soc*. **1959**, *81*, 6368-6371.



Scheme 18. Uncatalyzed addition of B_2Cl_4 to unsaturated bonds.

The use of compounds with alkoxide or amino substitution (i.e. $B_2(OR)_4$ or $B_2(NR_2)_4$; Figure 4), provides more stable products and an easier preparation of these reagents. Nevertheless, these reagents feature a diminished reactivity and, in most cases, the use of transition metal catalysis is necessary to make them effective in reactions with alkynes. Among the commonly used diboron compounds, bis(pinacolato)diboron (B_2pin_2) has been extensively studied due to its greater stability and availability.

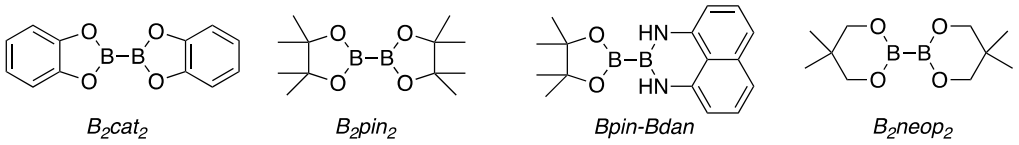


Figure 4. Representative examples of diboron compounds.

The higher stability of these compounds is due to the π-type overlap between the full p orbital of oxygen or nitrogen atoms with the empty p orbital of boron, making tetra(amino)diboron compounds the more stable ones (Figure 5). Less reactive diboron compounds have then lower Lewis acidity. Thus, the stability decreases in the following order: $B_2(NR_2)_4$> $(OR_2)_2B$-$B(NR_2)_2$> $B_2(OR_2)_4$>>$B_2(R)_4$, B_2Cl_4.

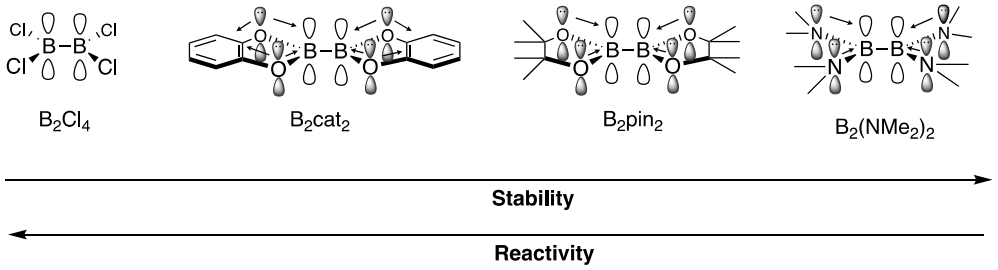


Figure 5. Comparation of reactivity and stability of B_2Cl_4, B_2cat_2, B_2pin_2 and $B_2(NMe_2)_4$.

The mode of activation of the B-B bond in B_2pin_2 with transition metals catalysts depends on the metal and ligand of choice.[34] The activation of B_2pin_2 with a metal can generally undergo two mechanisms: oxidative addition of the B-B into the metal center or σ-bond metathesis between a M-X bond and the B-B bond (Figure 6).

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[34] Westcott, S. A.; Fernandez, E. *Adv. Organomet. Chem*. **2015**, *63*, 39-89.

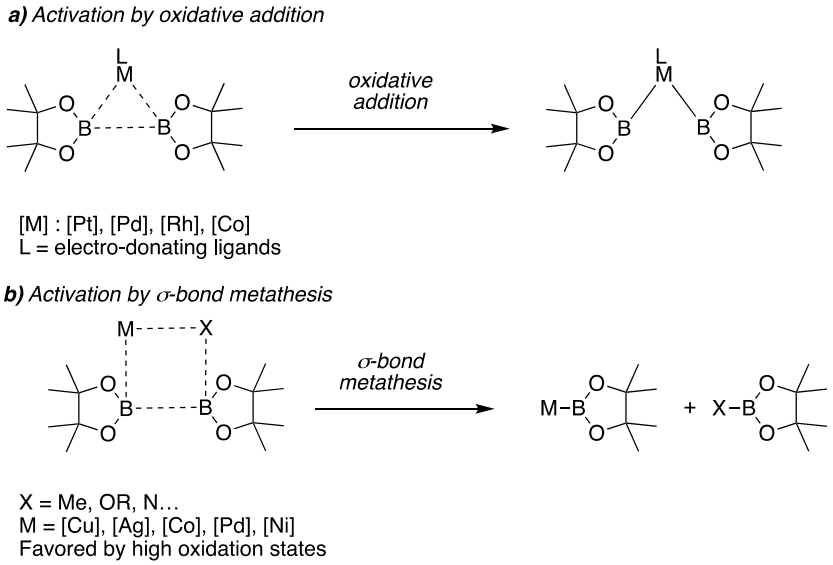
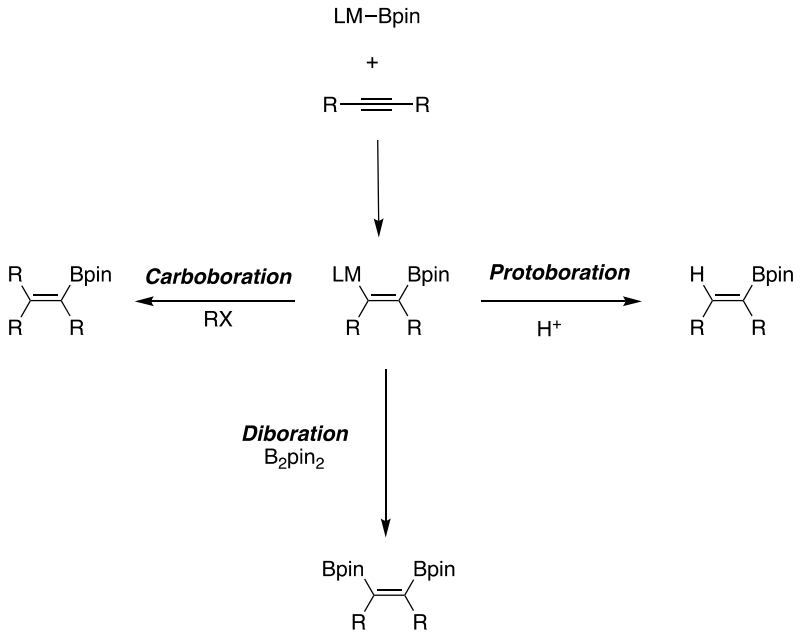


Figure 6. Transition metal activation of B_2pin_2.

The mode of B-B activation is important since it somewhat dictated the type of reaction that the diboron compound is going to undergo with the unsaturated hydrocarbon. The oxidative addition of the B_2pin_2 into a metal center (to form B-M-B) usually leads to diborylations reactions. The *syn*-insertion of an alkyne into one M-B bond and subsequent reductive elimination would give rise to the corresponding diborylated products. This transformation was mostly exploited with platinum catalysis.[35] In contrast, M-Bpin complexes generated after σ-bond metathesis usually undergo a *syn*-insertion of an unsaturated compound giving rise to a nucleophilic C-M intermediate that can be trapped by and electrophile thus, giving the opportunity of performing a difunctionalization of alkynes, without the incorporation of the hydride moiety that is implied with the use of boron hydrides (Scheme 19). These transformations can be classified upon the electrophile used and are typically named as protoboration reaction (when a protic source is used),[36] as carboboration reaction (when a carbon electrophile is used) and, diboration reaction (when Bpin group is incorporated).[32]

[35] (a) Ishiyama, T.; Yamamoto, M.; Miyaura, N. *Chem. Commun.* **1997**, 689-690. (b) Kilman, L. T.; Mlynarski, S. N.; Morken, J. P. *J. Am. Chem. Soc*. **2009**, *131*, 13210-13211. (c) Ishiyama, T.; Matsuda, N.; Miyaura, N.; Suzuki, A. *J. Am. Chem. Soc*. **1993**, *115*, 11018-11019. (d) Thomas, R. L.; Souza, F. E. S.; Marder, T. B. *J. Chem. Soc., Dalton Trans*. **2001**, 1650-1656.

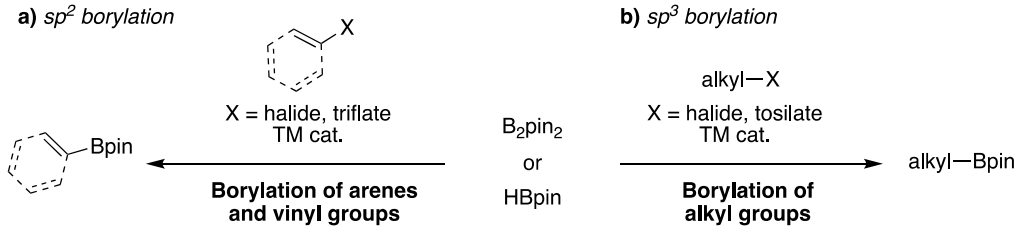
[36] Although these reactions are commonly called hydroboration reactions, we believe that it is more accurate to name them protoboration reactions since in this case, a proton (rather than a hydride) is added to the unsaturated hydrocarbon. This terminology will be used in this thesis.



Scheme 19. Reactivity M-Bpin complexes with alkynes.

1.1.4. Synthesis of organoboron compounds by C-Br borylation

Besides hydroboration or metaloboration of unsaturated compounds, transition metal-catalyzed borylation of organic halides has been also deeply studied as a tool for the synthesis of organoboron compounds (Scheme 20).[37] Most representative examples of this chemistry rely on the use of HBpin or B_2pin_2.

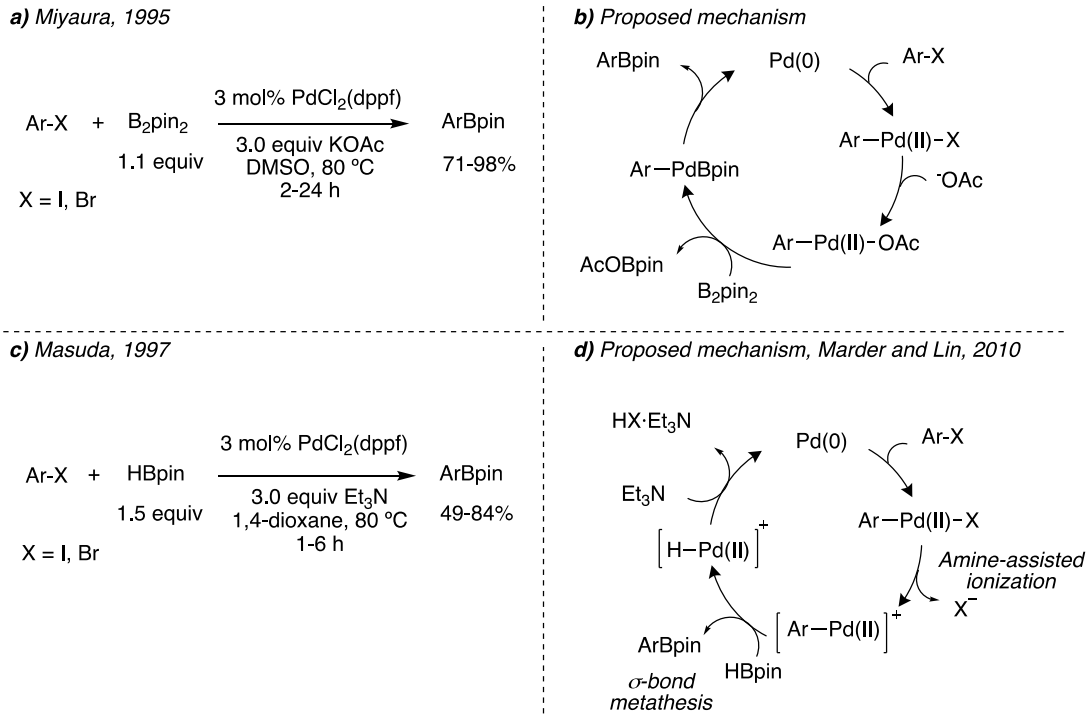


Scheme 20. Borylations of organic halides.

In 1995, Miyaura and co-workers reported the palladium-catalyzed borylation of haloarenes with bis(pinacolato)diboron (Scheme 21a).[38] Since then, this type of reaction is known as Miyaura borylation and is widely used for borylation of a large variety of aromatic halides and pseudohalides (e.g. triflates or tosylates). The reaction consists in the oxidative addition of the aryl halide into a Pd(0) complex, transmetalation with B_2pin_2 and reductive elimination of the resulting intermediate (Scheme 21b). The group of Masuda described the borylation of aromatic halides with HBpin as boron source (Scheme 21c).[39] The mechanism of this transformation is slightly different (Scheme 21d).

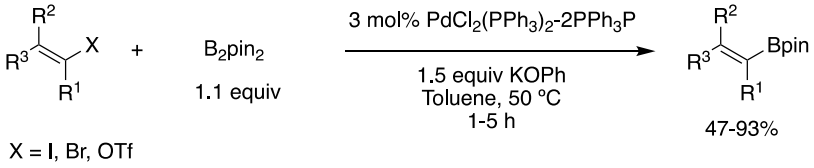
[37] For reviews see: (a) Murata, M. *Heterocycles*. **2012**, *85*, 1795-1819. (b) Chow, W. K.; Yuen, O. Y.; Choy, P. Y.; So, C. M.; Lau, C. P.; Wong, W. T.; Kwong, F. Y. *RSC Adv*. **2013**, *3*, 12518-12539.
[38] Ishiyama, T.; Murata, M.; Miyaura, N. *J. Org. Chem*. **1995**, *60*, 7508-7510.
[39] Murata, M.; Watanabe, S.; Masuda, Y. *J. Org. Chem*. **1997**, *62*, 6458-6459.

Lin and Marder proposed a mechanism involving a cationic pathway, through an amine-assisted ionization followed by σ-bond metathesis to generate ArBpin and $[LPd(II)H]^+$.[40] Then, the palladium(II) complex gets deprotonated by triethylamine to regenerate the Pd(0) catalyst.



Scheme 21. Palladium-catalyzed borylation of aryl halides.

The group of Miyaura also reported conditions for the palladium-catalyzed borylation of alkenyl halides and triflates. This reaction resulted in an efficient method for the synthesis of alkenyl boronates (Scheme 22).[41]



Scheme 22. Miyaura borylation of vinyl halides and triflates.

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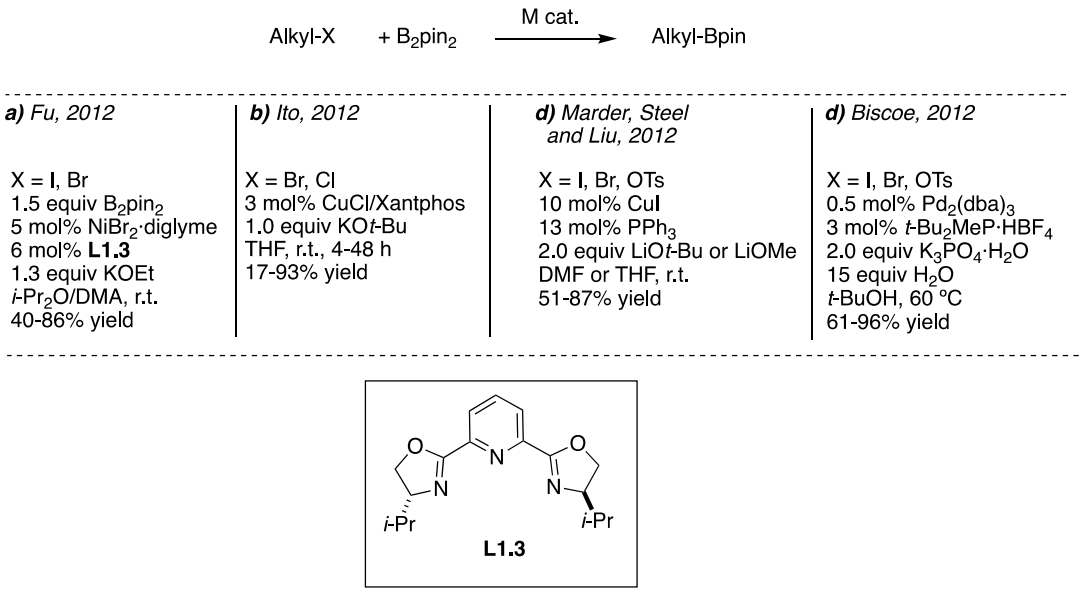
[40] Lam, K. C.; Marder, T. B.; Lin, Z. *Organometallics* **2010**, *29*, 1849-1857.

[41] (a) Takahashi, K.; Takagi, J.; Ishiyama, T.; Miyaura, N. *Chem. Lett*. **2000**, *29*, 126-127. (b) Takagi, J.; Takahashi, K.; Ishiyama, T.; Miyaura, N. *J. Am. Chem. Soc*. **2002**, *124*, 8001-8006.

The Miyaura borylation of more challenging unactivated alkyl halides was less explored. It was not until early 2010's when C(sp^3) borylations using Ni,[42] Cu[43] or Pd[44] catalysis were reported (Scheme 23).



Scheme 23. Miyaura borylation of alkyl halides and tosylates.

1.1.5. Synthesis of organoboron compounds by C-H activation

The construction of C-B bonds via C-H activation is a very interesting approach for the synthesis of organoboron compounds since the pre-installation of the organic halide functionality is not required, thus reducing the steps of the procedure.[45]

The group of Hartwig was one of the main contributors to the development of C-H borylation and reported, in 1995, the first example of borylation of arenes and alkenes (Scheme 24).[46] Aryl- and alkenylboronates could be prepared by irradiation of a stoichiometric amount of $(CO)_5$Fe-Bcat in the presence of an arene or an alkene.

Scheme 24. Early examples of C-H borylations of arenes and alkenes.

[42] Dudnik, A. S.; Fu, G. C. *J. Am. Chem. Soc*. **2012**, *134*, 10693-10697.

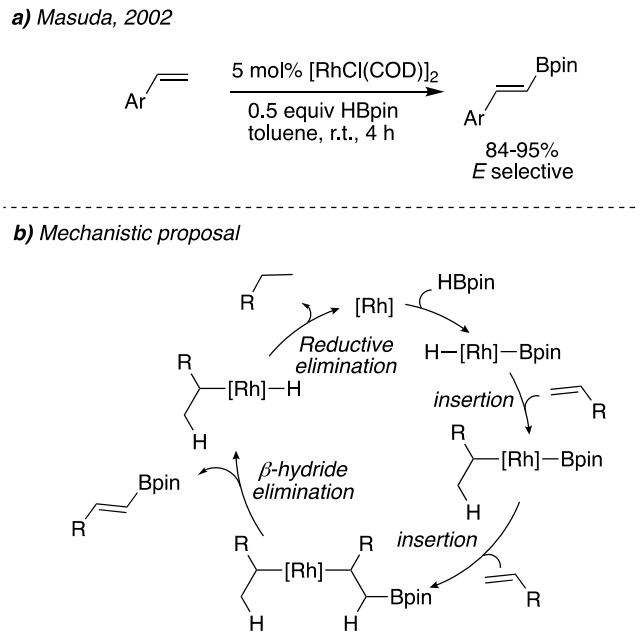
[43] (a) Ito, H.; Kubota, K. *Org. Lett*. **2012**, *14*, 890-893. (b) Yang, C.-T.; Zhang, Z.-Q.; Tajuddin, H.; Wu, C.-C.; Liang, J.; Lui, J.-H.; Fu, Y.; Czyzewska, M.; Steel, P. G.; Marder, T. B.; Liu, L. *Angew. Chem. Int. Ed.* **2012**, *51*, 528-532.

[44] Joshi-Pangu, A.; Ma, X.; Diane, M.; Iqbal, S.; Kribs, R. J.; Huang, R.; Wang, C.-Y.; Biscoe, M. R. *J. Org. Chem.* **2012**, *77*, 6629-6633.

[45] (a) Mkhalid, I. A. I.; Barnard, J. H.; Marder, T. B.; Murphy, J. M.; Hartwig, J. F. *Chem. Rev*. **2010**, *110*, 890-931. (b) Xu, L.; Wang G.; Zhang, S.; Wang, H.; Wang, L.; Liu, L.; Jiao, J.; Li, P. *Tetrahedron* **2017**, *73*, 7123-7157.

[46] Waltz, K. M.; He, X.; Muhoro, C.; Hartwig, J. F. *J. Am. Chem. Soc*. **1995**, *117*, 11357-11358.

The catalytic C-H borylation of alkenes was initially studied mainly with rhodium complexes and using HBpin and B_2pin_2 as borylating reagents.[47] Masuda *et al.* reported an efficient $[RhCl(cod)]_2$ catalyzed *E* selective dehydrogenative borylation of vinylarenes with pinacolborane (Scheme 25).[47b] The mechanism proposed for this transformation involves initial oxidative addition of HBpin into the rhodium complex followed by insertion of the alkene into the M-H bond.[48] A second molecule of the alkene would insert into the M-B bond to produce a dialkyl rhodium complex. Then, β-hydride elimination would afford the vinylboronate and a subsequent reductive elimination would lead to the formation of the hydrogenated alkene and the regeneration of the catalyst. Thus, these methodologies usually require the use of a sacrificial equivalent of the alkene. In this context, Miyaura and Murakami have recently reported the use of norbornene as a hydrogen acceptor in a rhodium-catalyzed dehydrogenative borylation.[47d]



Scheme 25. Rhodium-catalyzed dehydrogenative borylation of alkenes.

Catalytic C-H borylation of arenes was initially reported with rhodium catalysis (Scheme 26a).[49] However, more efficient transformations were achieved later by using iridium catalysis in the reaction with B_2pin_2.[50] The use of bipyridine-ligated iridium

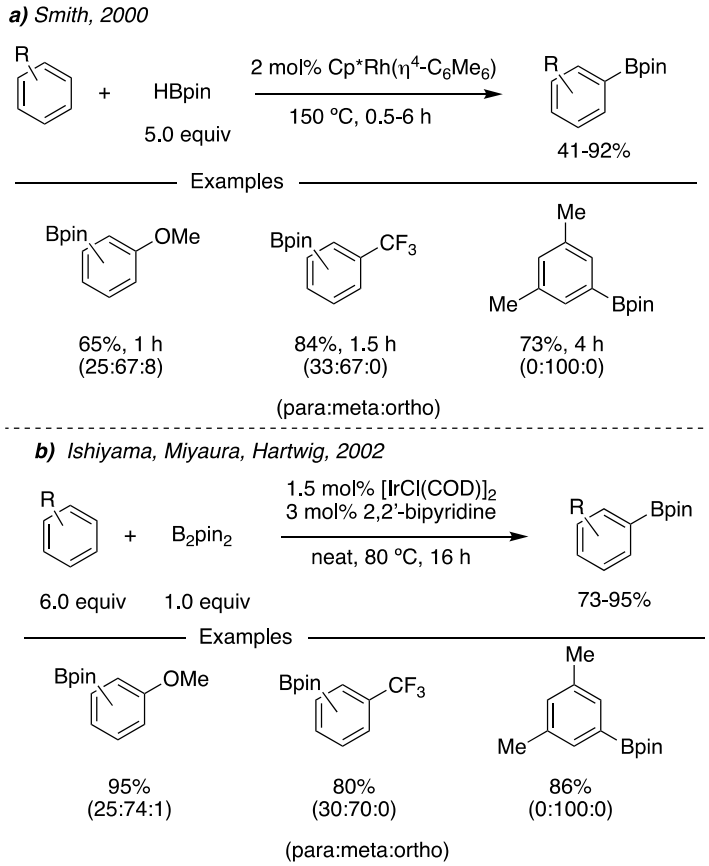
[47] (a) Murata, M.; Watanabe, S.; Masuda, Y. *Tetrahedron Lett.* **1999**, *40*, 2585-2588. (b) Murata, M.; Kawakita, K.; Asana, T.; Watanabe, S.; Masuda, Y. *Bull. Chem. Soc. Jpn*. **2002**, *75*, 825-829. (c) Coapes, R. B.; Souza, F. E. S.; Thomas, R. Ll.; Hall, J. J.; Marder, T. B. *Chem. Commun*. **2003**, 614-615. (d) Morimoto, M.; Miura, T.; Murakami, M. *Angew. Chem. Int. Ed*. **2015**, *54*, 12659-12663. For a review see: (e) Geier, S. J.; Westcott, S. A. *Rev. Inorg. Chem*. **2015**, *35*, 69-79.

[48] Due to the similitude of the mechanism, hydroboration of the alkene is usually a competitive side reaction.

[49] Cho, J.-Y.; Iverson, C. N.; Smith, M. R. III *J. Am. Chem. Soc*. **2000**, *122*, 12868-12869.

[50] (a) Cho, J.-Y.; Tse, M. K.; Holmes, D.; Maleczka Jr., R. E.; Smith, M. R. III *Science* **2002**, *295*, 305-308. (b) Boller, T. M.; Murphy, J. M.; Hapke, M.; Ishiyama, T.; Miyaura, N.; Hartwig, J. F. *J. Am. Chem. Soc.* **2002**, *124*, 390-391. (c) Boebel, T. A.; Hartwig, J. F. *J. Am. Chem. Soc*. **2008**, *130*, 7534-7535.

catalyst with B_2pin_2 allowed the use of milder temperatures higher yields and slightly improved meta-selectivity (Scheme 26b).



Scheme 26. Rhodium and iridium-catalyzed C-H borylation of arenes.

Hartwig also described the selective catalytic C-H borylation of alkanes. Photochemical borylation was developed with rhenium complexes (Scheme 27a) and thermal borylation was achieved with rhodium catalysis (Scheme 27b) and with ruthenium catalysis (Scheme 27c) with B_2pin_2, with high selectivity towards the borylation at the terminal C-H bond.[51]

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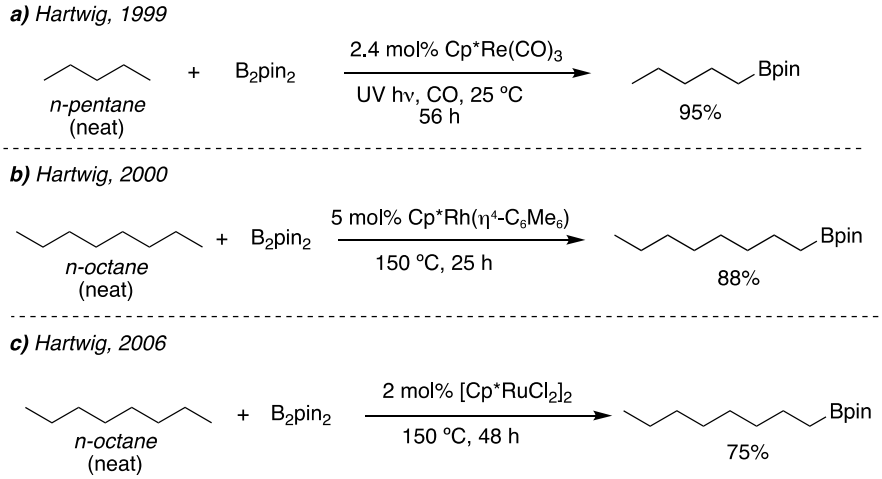
[51] (a) Chen, H.; Hartwig, J. F. *Angew. Chem. Int. Ed*. **1999**, *38*, 3391-3393. (b) Chen, H.; Schlecht, S.; Semple, T. C.; Hartwig, J. F. *Science* **2000**, *287*, 1995-1997. (c) Murphy, J. M.; Lawrence, J. D.; Kawamura, K.; Incarvito, C.; Hartwig, J. F. *J. Am. Chem. Soc*. **2006**, *128*, 13684-13685.



Scheme 27. a) Rhenium, **b)** Rhodium and **c)** Ruthenium-catalyzed C-H borylation of alkanes.

1.1.6. Synthesis of organoboron compounds by allylic substitution

Allylic boronic esters feature unique and versatile reactivity (See section 1.2.7, chapter I). One common method for the preparation of these moieties relies on the transition metal-catalyzed allylic substitution with boron-based nucleophiles. With this approach, allylboron species can be synthesized in a regio- and stereoselective manner, and selectivity can be modified by choosing the appropriate catalytic system. Based on their Pd-catalyzed borylation of aromatic compounds, the group of Miyaura developed a palladium-catalyzed borylation of allylic acetates (Scheme 28a).[52] The reaction works in an efficient manner without the use of any phosphine ligand (the addition of phosphine ligand slows down the reaction rate), however, small amount of dimerization of the allylic substrate is typically formed as byproduct. The mechanism consists in an oxidative addition of the allylic substrate to a Pd(0) complex to form a π-allylpalladium(II) acetate (Scheme 28b). Transmetalation with B_2pin_2 and subsequent reductive elimination provide the formation of the allylboronate and regeneration of the catalyst. The allyl palladium complex can also transmetallate with the allylboron compound that is formed, to obtain a bis-allyl palladium complex. In this case, the formation of the dimer would occur.

When disubstituted allylic substrates are used (with substitution in the α or γ position with respect to the leaving group), the borylation takes place selectively at the less hindered position of the allyl moiety and with an *E* stereochemistry, regardless the stereochemistry of the initial allylic acetate.

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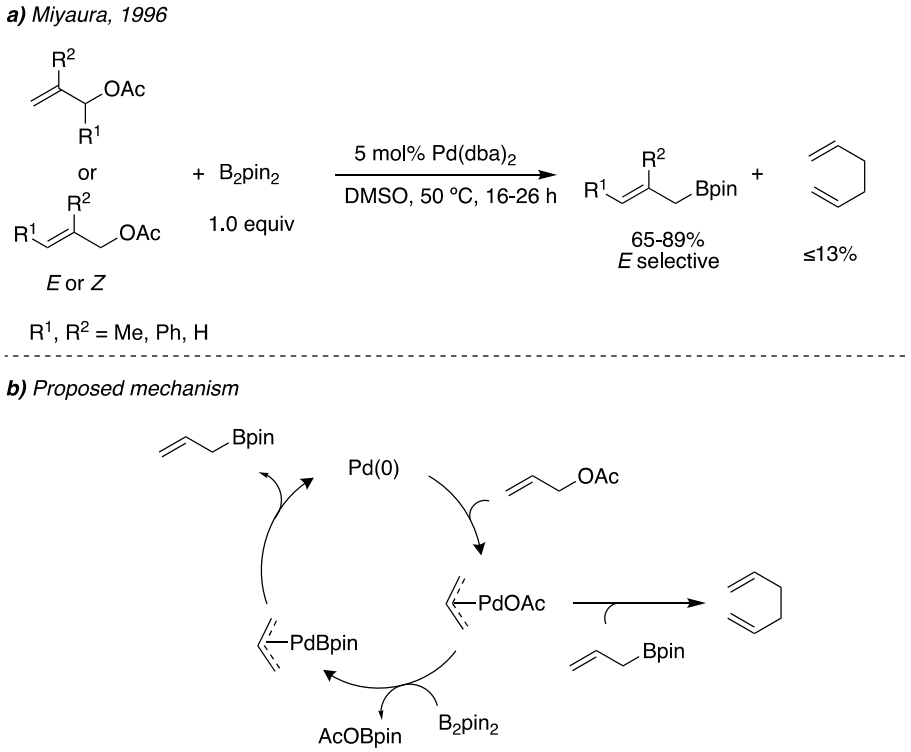
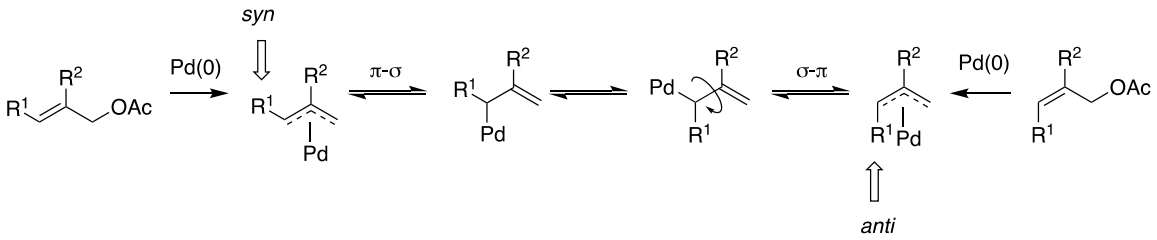
[52] Ishiyama, T.; Ahiko, T.-A.; Miyaura, N. *Tetrahedron Lett*. **1996**, *37*, 6889-6892.



Scheme 28. Palladium-catalyzed Miyaura borylation of allylic acetates.

The formation of the *E* product can be reasoned by the isomerization of *anti*-allylpalladium complex, which would be formed after oxidative addition of the *Z*-allylic substrate into the palladium catalyst, to the more stable *syn*-complex (Scheme 29).

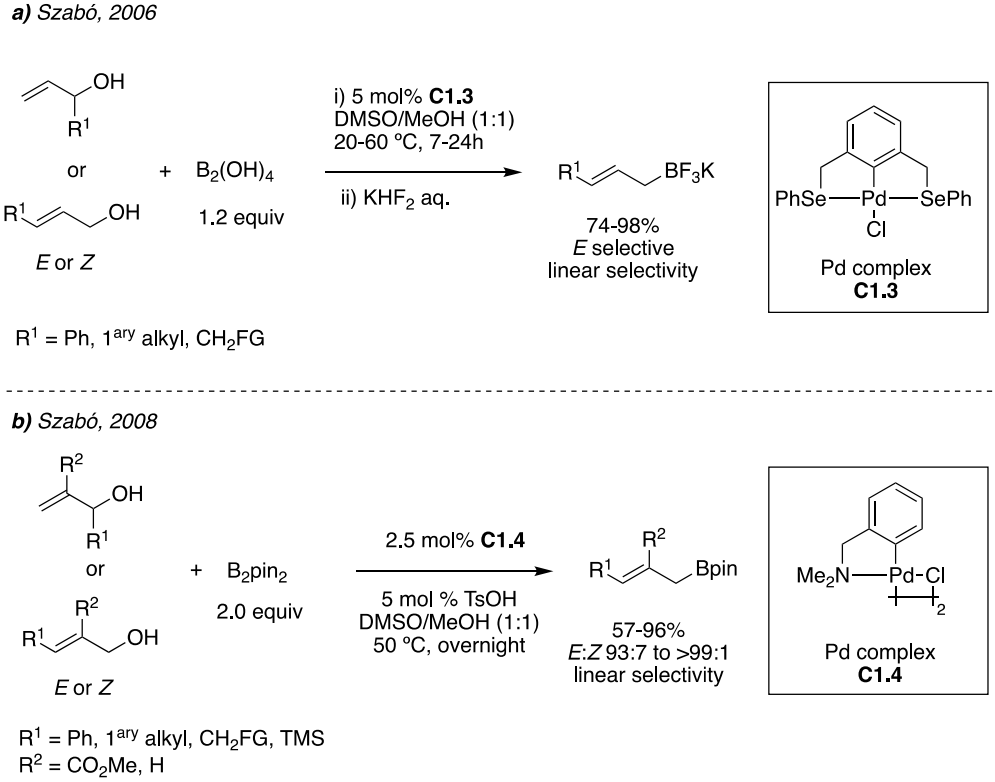


Scheme 29. *Syn-anti* isomerization.

Allyl substrate dimerization could be overcome by using allylic alcohols and a palladium pincer complex as reported by Szabó. Under these conditions, the formation of the bis-allyl palladium complex is avoided.[53] In 2006, Szabó described a borylation of cyclic and acyclic allylic alcohols with tetrahydroxydiboron using palladium pincer complex **C1.3** as catalyst (Scheme 30a).[53a] Nonetheless, allyl boronic acids that were obtained are unstable and had to be transformed to the corresponding potassium trifluoroborate salts by addition of KHF_2. In the same way than reported by Miyaura, the use of branched or linear alcohols (*E* or *Z*) provides in all cases the linear *E* product. Later

[53] (a) Olsson, V. J.; Sebelius, S.; Selander, N.; Szabó, K. J. *J. Am. Chem. Soc*. **2006**, *128*, 4588-4589. (b) Dutheuil, G.; Selander, N.; Szabó, K. J.; Aggarwal, V. *Synthesis* **2008**, *14*, 2293-2297.

on, in a collaboration with the group of Aggarwal, it was reported that the use of B_2pin_2 in this allylation reaction was enabled by using palladium catalyst **C1.4,** and by adding *p*-toluenesulfonic acid as co-catalyst (Scheme 30b).[53b]



Scheme 30. Borylation of allylic alcohols with palladium complexes.

The regioselectivity of the allylic borylation can be switched with the use of copper catalysis to perform a formal S_N2' allylic substitution. In 2005, Ito and Sawamura reported the first copper-catalyzed S_N2'-selective borylation of allylic carbonates with a CuO*t*-Bu/Xantphos system (Scheme 31a).[54] Linear and branched allyl boron compounds can be accessed with the use of branched and linear allylic carbonates, respectively. This transformation involves the regioselective addition of the Cu-B bond across the C-C double bond. Orbital interactions between the $\sigma^*(C_\alpha\text{-O})$ and the $\sigma(\text{Cu-C}_\beta)$ control the regioselectivity of the addition of the Cu-B into the alkene. This would form a β-copper intermediate that would undergo a β-alkoxy elimination to afford the final product (Scheme 31b).

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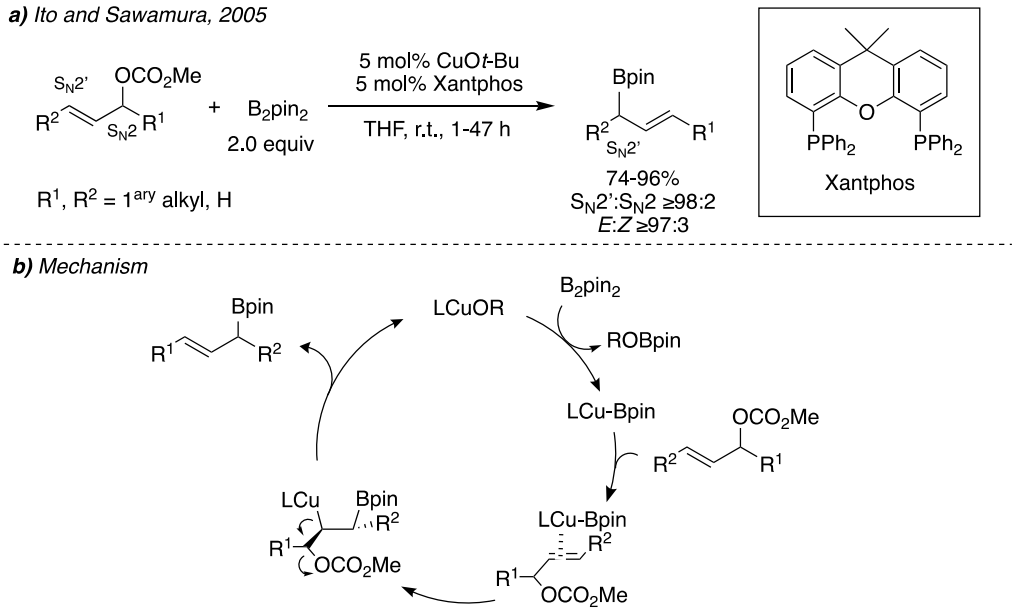
[54] Ito, H.; Kawakami, C.; Sawamura, M. *J. Am. Chem. Soc.* **2005**, *127*, 16034-16035.



Scheme 31. Copper-catalyzed borylation of allylic carbonates.

The asymmetric reaction could be achieved with the use of CuO*t*-Bu and (*R,R*)-QuinoxP*. This methodology was, however, limited to *Z*-allylic carbonates (Scheme 32a).[55] *E*-allylic carbonates provided allylic boronates in excellent yield, although a dramatic decrease of the enantiomeric excess was observed for these substrates. Moreover, the use of *E*-allylic substrate gave rise to the opposite enantiomer. This fact could be reasoned by the authors by comparing the steric hindrance of the transition state of the Cu-B addition for both stereoisomers, which is the enantiodiscrimitating step (Scheme 32b). When a *Z*-allylic carbonate is used, the Cu-B addition to the double bond is clearly favored by one face of the allylic substrate. However, with the use of *E*-allylic carbonates, both transition states have steric repulsion and thus, the energies are more similar. This causes a decrease in the enantioselectivity.

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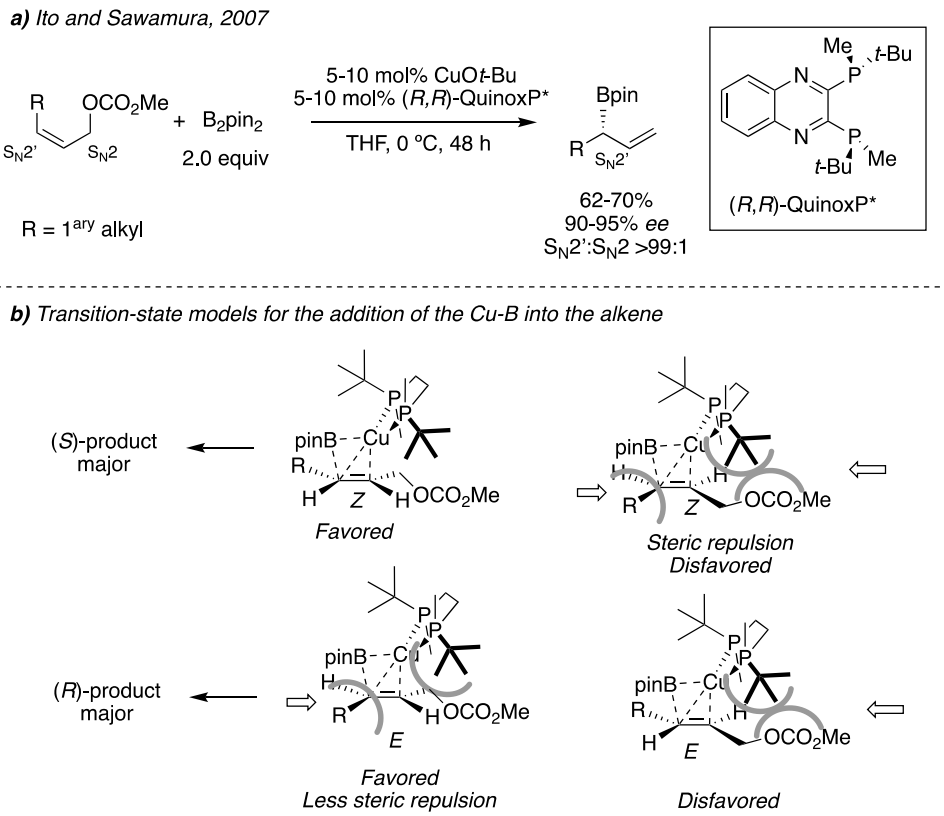
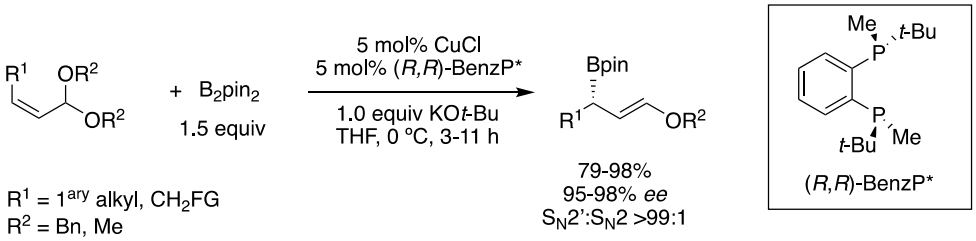
[55] Ito, H.; Ito, S.; Sasaki, Y.; Matsuura, K.; Sawamura, M. *J. Am. Chem. Soc*. **2007**, *129*, 14856-14857.



Scheme 32. Copper-catalyzed asymmetric borylation of allylic carbonates.

Ito and coworkers also reported the asymmetric copper-catalyzed borylation of cyclic and acyclic *Z*-allylic ethers using as chiral ligands, (*R,R*)-QuinoxP* and (*R,R*)-BenzP* respectively (Scheme 33).[56]



Scheme 33. Copper-catalyzed borylation of Z-allylic ethers.

Hoveyda and co-workers reported a copper-catalyzed asymmetric borylation of γ,γ-disubstituted (*E* and *Z*) allylic carbonates (Scheme 34a).[57] The use of a chiral sulfonate bearing NHC ligated copper complex allowed the synthesis of enantioenriched boron substituted quaternary stereogenic carbons in good yields with excellent enantioselectivity in most of the cases. The borylation of *E* and *Z* allylic substrates leads to the formation of a different enantiomer. For an easier isolation of the product, they performed an *in situ* oxidation to afford the tertiary allylic alcohol. Authors proposed that,

[56] (a) Ito, H.; Kunii, S.; Sawamura, M. *Nat. Chem*. **2010**, *2*, 972-976. (b) Yamamoto, E.; Takenouchi, Y.; Ozaki, T.; Miya, T.; Ito, H. *J. Am. Chem. Soc*. **2014**, *136*, 16515-16521.

[57] Guzman-Martinez, A.; Hoveyda, A. H. *J. Am. Chem. Soc*. **2010**, *132*, 10634-10637.

with these disubstituted allylic substrates and this particular catalyst, the mechanism would consist in the oxidative addition of the allyl moiety into the copper complex to afford a π-allyl Cu(III) complex. The formation of a 20% of the of the S_N2 isomer, which could not be formed through an addition-elimination mechanism, when γ-ethyl–γ-phenyl substituted allylic carbonate is used, supports this mechanistic proposal.

Soon thereafter, McQuade *et al.* reported an NHC-copper-catalyzed stereoconvergent borylation of an *E/Z* mixture of allylic aryl ethers (Scheme 34b).[58] Same enantiomer is obtained from the *E* and *Z* allylic ether, in contrast with the previous mentioned examples with allylic carbonates (Scheme 32b). In this case, the most favorable transition state for both the *E* and *Z* allylic substrates conducts to the formation of the same enantiomer.

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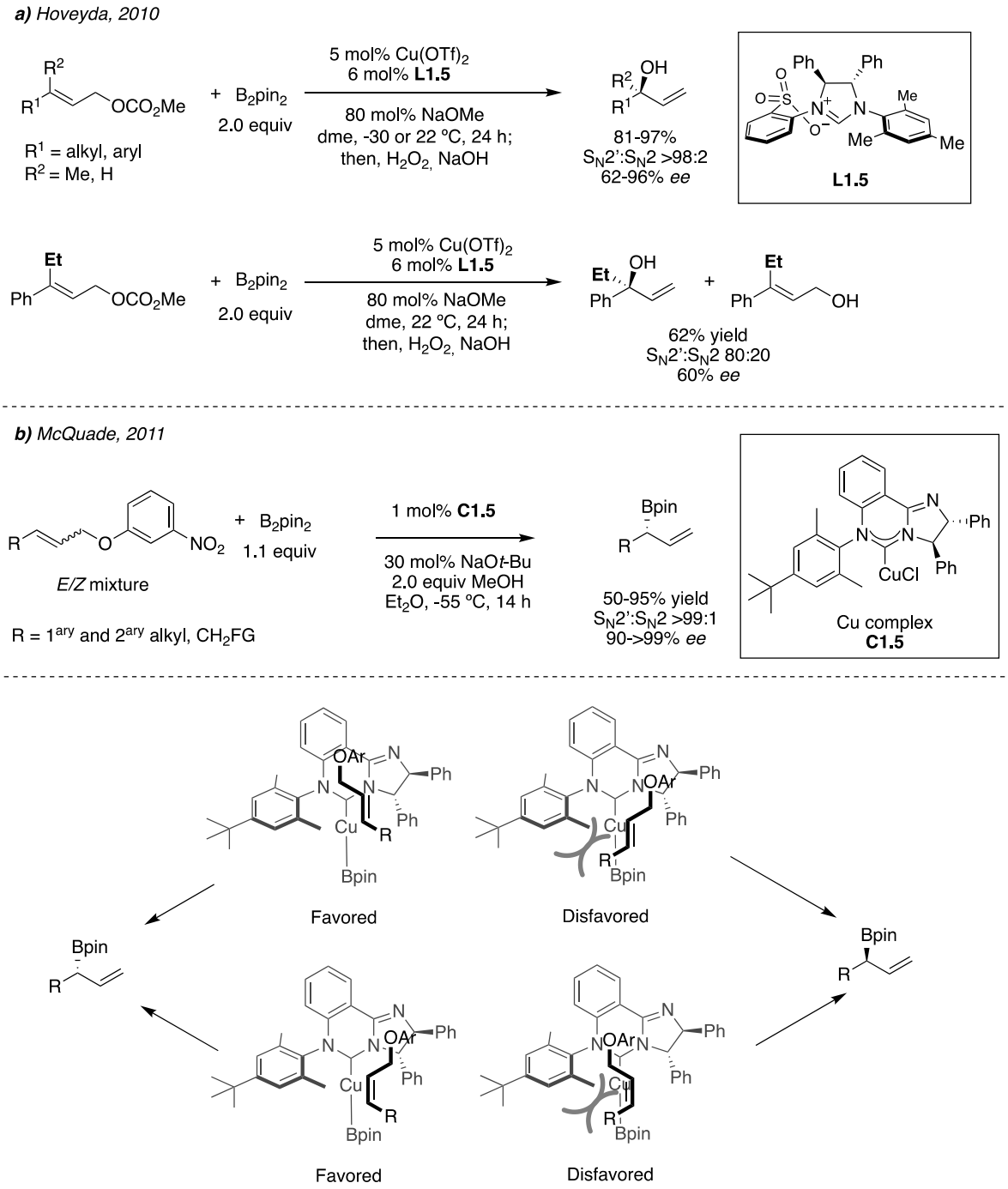
[58] Park, J. K.; Lackey, H. H.; Ondrusek, B. A.; McQuade, D. T. *J. Am. Chem. Soc*. **2011**, *133*, 2410-2413.



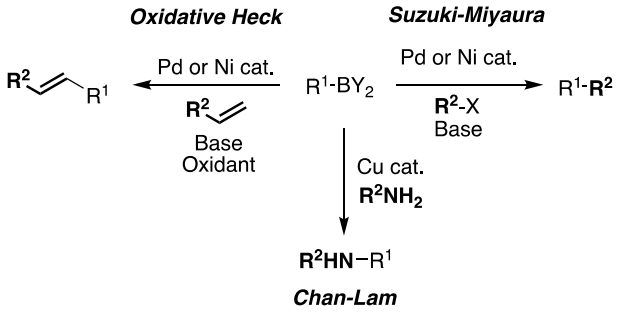
Scheme 34. Copper-catalyzed asymmetric borylation of allylic carbonates and allylic ethers.

1.2. REACTIVITY OF ORGANOBORON COMPOUNDS

As mentioned before, organoboron compounds present very versatile reactivity. In next sections, the most relevant transformations of organoboron compounds are discussed.

1.2.1. Organoboron compounds in cross-coupling reactions

Cross-coupling reactions are, by definition, those in which two different starting materials react together to form a new bond with help of a metal catalyst. This type of reactions is one of the most reliable and widely utilized method to prepare new C-C bonds. Among the different cross-coupling reactions, the Suzuki-Miyaura cross-coupling, oxidative Heck coupling and Chan-Lam coupling are the most representative examples of the ones that involve the use of organoboron compounds (Scheme 35).



Scheme 35. Cross-coupling reactions involving organoboron compounds.

1.2.2. Suzuki-Miyaura cross-coupling

Probably, the most representative application of organoboron reagents in organic synthesis is the Pd-catalyzed Suzuki-Miyaura cross-coupling (Scheme 36a).[4] This reaction was first reported in 1979 and led Akira Suzuki to win the 2010 Nobel Prize in Chemistry together with Richard F. Heck and Ei-ichi Negishi for their work on palladium-catalyzed cross couplings in organic synthesis.[59] This reaction consists in the coupling of an organoboron reagent (boronic esters, boronic acids or trifluoroborates) and an organic (pseudo)halide, and represents an extremely powerful method for the formation of C-C bonds with a remarkable functional group tolerance. The proposed mechanism involves the oxidative addition of the organic halide into a Pd(0) catalyst, subsequent alkoxide-assisted transmetalation with the boronic acid (ester) and final reductive elimination (Scheme 36b). Although great advances have been achieved in this field, studies on new versions of Suzuki-Miyaura cross-coupling are still an important part of current synthetic chemistry, for example, greener versions, expansion of substrate scope or new applications.[60]

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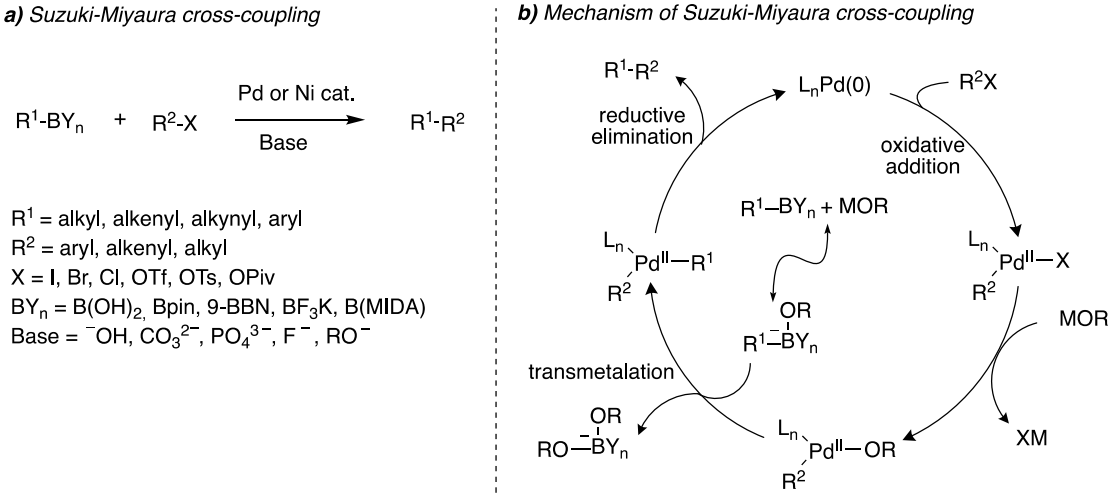
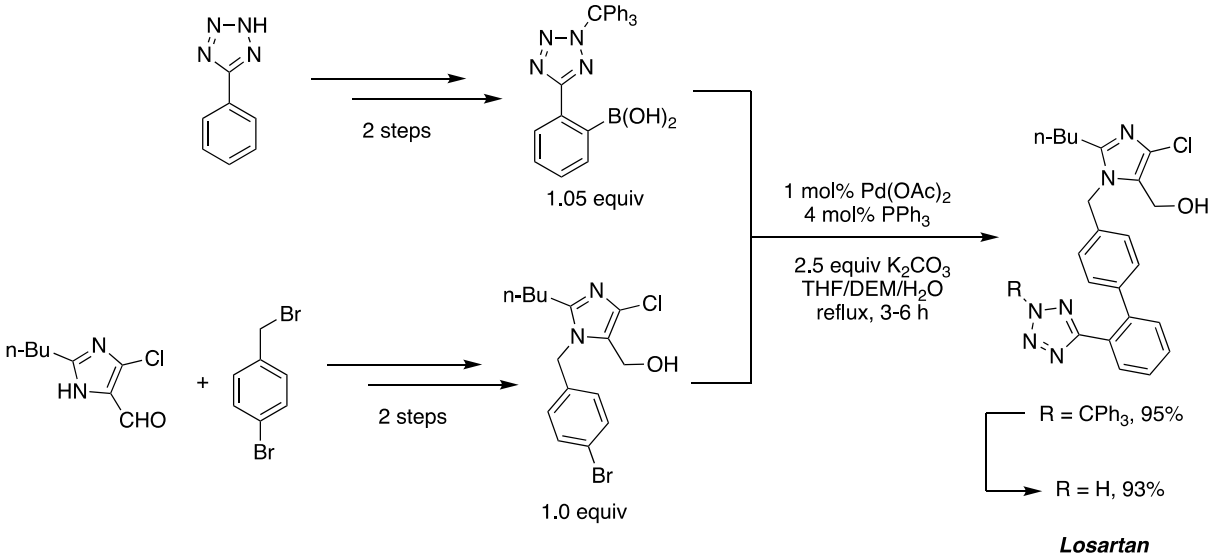
[59] Suzuki, A. *Angew. Chem. Int. Ed*. **2011**, *50*, 6722-6737.

[60] (a) Xu, L.; Zhang, S.; Li, P. *Chem. Soc. Rev*. **2015**, *44*, 8848-8858. (b) Hooshmand, S. E.; Heidari, B.; Sedghi, R.; Varma, R. S. *Green Chem*. **2019**, *21*, 381-405. (c) Gillis, E.P.; Burke, M. D. *J. Am. Chem. Soc*. **2007**, *129*, 6716-6717. (d) Li, Y.; Luo, Y.; Peng, L.; Li, Y.; Zhao, B.; Wang, W.; Pang, H.; Deng, Y.; Bai, R.; Lan, Y.; Yin, G. *Nat. Commun*. **2020**, *11*, 417.



Scheme 36. Suzuki-Miyaura cross-coupling.

Due to the mild conditions and available starting material, in addition to the efficiency of this method, the Suzuki-Miyaura coupling is one of the most used cross-coupling reactions in industrial applications.[61] For example, Suzuki-Miyaura cross-coupling is involved as a key step in the industrial multi-kg synthesis of Losartan (Scheme 37), which is a drug used for the treatment of high blood pressure and heart failure.[62]



Scheme 37. Total synthesis of Losartan.

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[61] Budarin, V. L.; Shuttleworth, P. S.; Clark, J. H.; Luque R. *Curr. Org. Synth*. **2010**, *7*, 614-627.

[62] (a) Larsen, R. D.; King, A. O.; Chen, C. Y.; Corley, E. G.; Foster, B. S.; Roberts, F. E.; Yang, C. H.; Lieberman, D. R.; Reamer, R. A.; Tschaen, D. M.; Verhoeven, T. R.; Reider, P. J. *J. Org. Chem*. **1994**, *59*, 6391-6394. (b) Campbell Jr., G.; Dwivedi, A.; Levorse, D.; Mccauley, J.; Raghavan, K. (Merck & Co., Inc., E. I. Du Pont de Nemours & Company, The DuPont Merck Pharmaceutical Company), US 5,608,075, 1997.

1.2.3. Oxidative Heck coupling

Another classical and very relevant reaction for organic chemistry is the Heck reaction (or Mizokori-Heck reaction). This reaction was reported independently by Mizokori[63] and Heck[64] and involves the coupling between and alkene and an organic halide with Pd(0) catalysis (Scheme 38a). An excellent complementary tool for this reaction is the oxidative Heck coupling, which allows to couple the alkene with an organometallic compound (usually organoboron compounds) instead of the organic halide (Scheme 38b). Oxidative Heck coupling (or boron Heck) stands out for being efficient, air and moisture tolerant and for proceeding under mild conditions, thus allowing a great functional group tolerance. The first example was reported in a stoichiometric manner by Heck *et al.* in 1975[65] and the first catalytic version was developed by Uemura *et al.* in 1994.[66] It was further studied by other groups improving versatility and providing enantioselective variants.[67] This approach requires the use of Pd(II) catalyst and an oxidant, which is typically used in stoichiometric amount. The mechanistic proposal consists in an initial transmetalation of the organoboron compound with a Pd(II) complex, followed by a migratory insertion of the alkene (Scheme 38c). After the insertion of the alkene, the Pd atom is positioned at the more hindered position of the double bond when electron-deficient alkenes are used. However, when electron-rich alkenes are used, the Pd complex occupies the terminal position. Then, *syn* β-H elimination affords the product, and finally, reductive elimination occurs to remove HX and regenerate the catalytic active Pd(II) species after oxidation.

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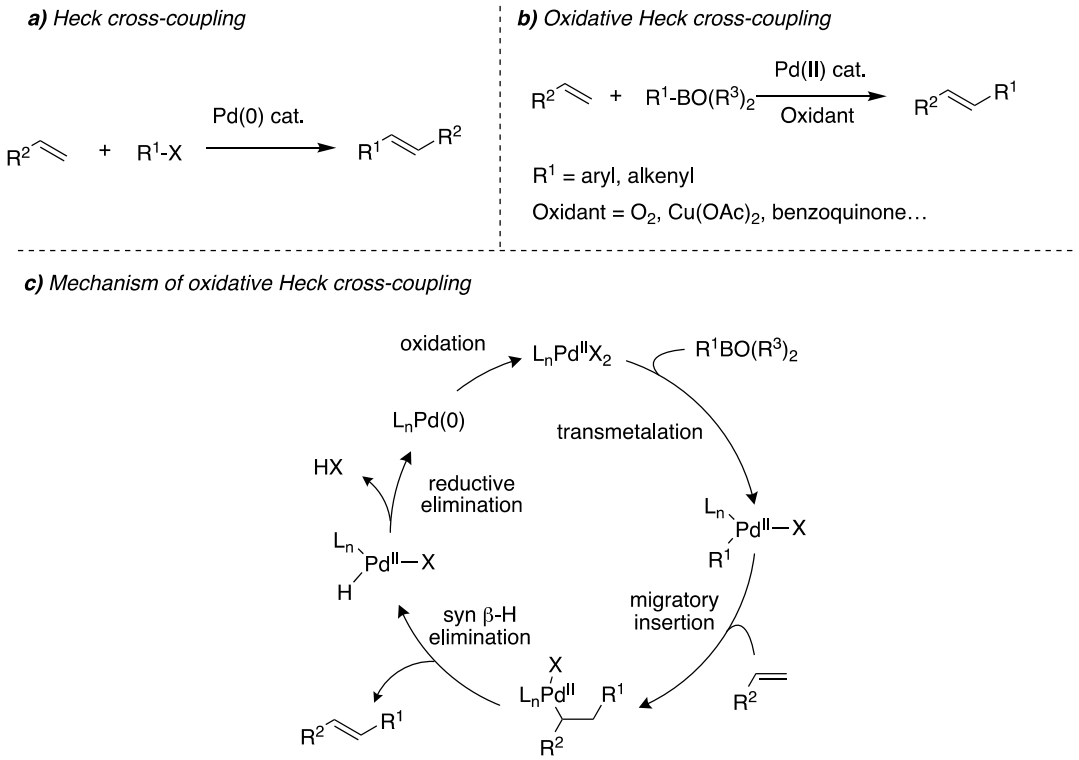
[63] Mizoroki, T.; Mori, K.; Ozaki, A. *Bull. Chem. Soc. Jpn*. **1971**, *44*, 581-581.
[64] Heck, R. F.; Nolley, J. P. Jr. *J. Org. Chem*. **1972**, *37*, 2320-2322.
[65] Dieck, H. A.; Heck, R. F. *J. Org. Chem*. **1975**, *40*, 1083-1090.
[66] Cho, C. S.; Uemura, S. *J. Organomet. Chem*., **1994**, *465*, 85-92.
[67] For reviews see: (a) Su, Y.; Jiao, N. *Curr. Org. Chem*. **2011**, *15*, 3362-3388. (b) Lee, A.-L. *Org. Biomol. Chem*. **2016**, *14*, 5357-5366.



Scheme 38. Heck vs oxidative Heck cross-coupling.

1.2.4. Chan-Lam coupling

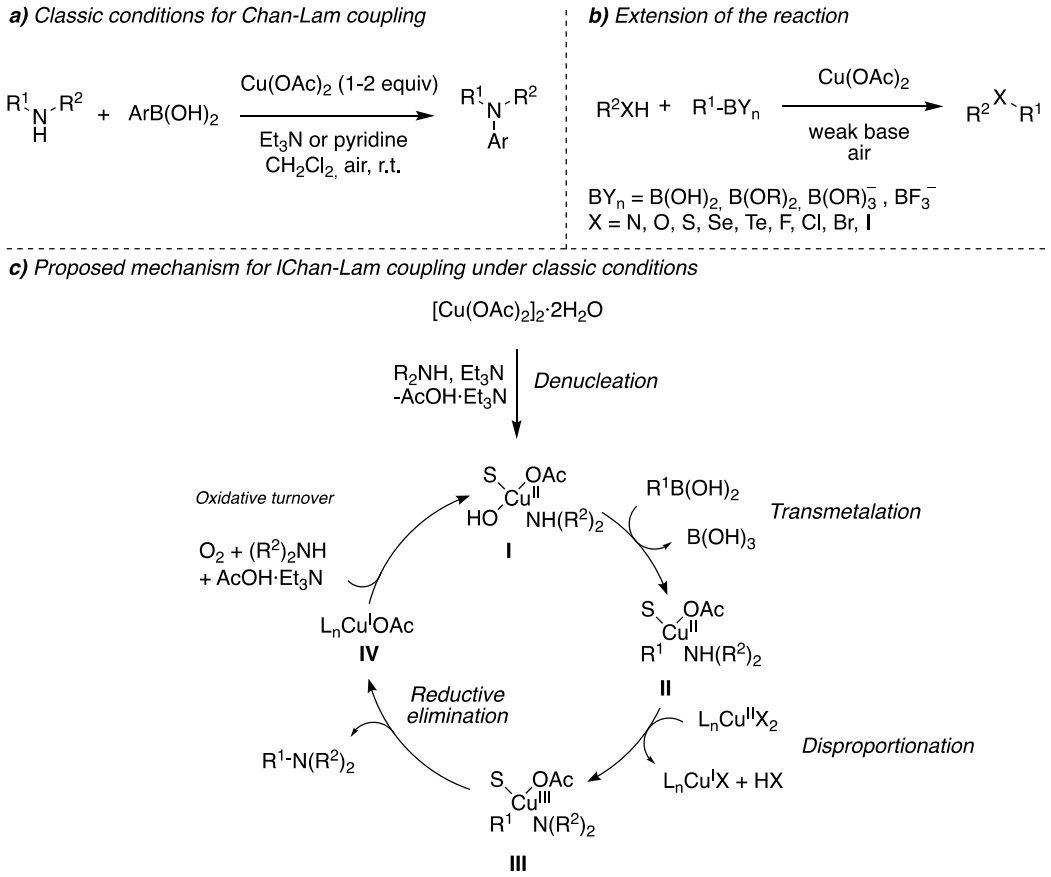
Besides C-C bond formation, formation of C-N bonds is very interesting especially for the synthesis of bioactive molecules. Organoboron compounds can also be used for the formation of C-N or C-O bonds via a copper promoted oxidative coupling, widely known as Chan-Lam coupling (or Chan-Evans-Lam coupling, Scheme 39).[68] This transformation has typically involved the use of stoichiometric amounts of $Cu(OAc)_2$, however nowadays, catalytic methodologies have been reported, although they usually require higher temperatures or additives.[69] Although the mechanism is still a focus of debate and it is suggested to change depending on the reaction conditions, a general proposed mechanism for this transformation under "classic conditions" is shown in Scheme 39b (Classic conditions: $Cu(OAc)_2$ and Et_3N as base; for a detailed review of the mechanism see ref. 70). The initial step of the mechanism is the denucleation of the dimeric $[Cu(OAc)_2]_2$ complex to form a monomeric complex **I** by the amine followed by transmetalation with the boronic acid to provide Cu(II) complex **II**. This Cu(II) complex has to be oxidized to Cu(III) complex **III** prior to reductive elimination. This oxidation is suggested to occur through a disproportionation step with a different Cu(II) species. Reductive elimination ocurrs with complex **III** to afford the product and a Cu(I) complex

[68] (a) Chan, D. M. T.; Monaco, K. L.; Wang, R.-P.; Winters, M. P. *Tetrahedron Lett*. **1998**, *39*, 2933-2936. (b) Evans, D. A.; Katz, J. L.; West, T. R. *Tetrahedron Lett*. **1998**, *39*, 2937-2940. (c) Lam, P. Y. S.; Clark, C. G.; Saubern, S.; Adams, J.; Winters, M. P.; Chan, D. M. T.; Combs, A. *Tetrahedron Lett*. **1998**, *39*, 2941-2944.

[69] For a review see: Chen, J. Q.; Li, J. H.; Dong, Z. B. *Adv. Synth. Catal*. **2020**, *362*, 3311-3331.

[70] West, M. J.; Fyfe, J. W. B.; Vantourout, J. C.; Watson, A. J. B. *Chem. Rev*. **2019**, *119*, 12491-12523.

IV which is reoxidized to Cu(II) by oxygen. As can be seen for the mechanism, 2 equivalents of $Cu(OAc)_2$ for each equivalent of product would be needed for the reaction to occur without an oxidant.



Scheme 39. General Chan-Lam coupling.

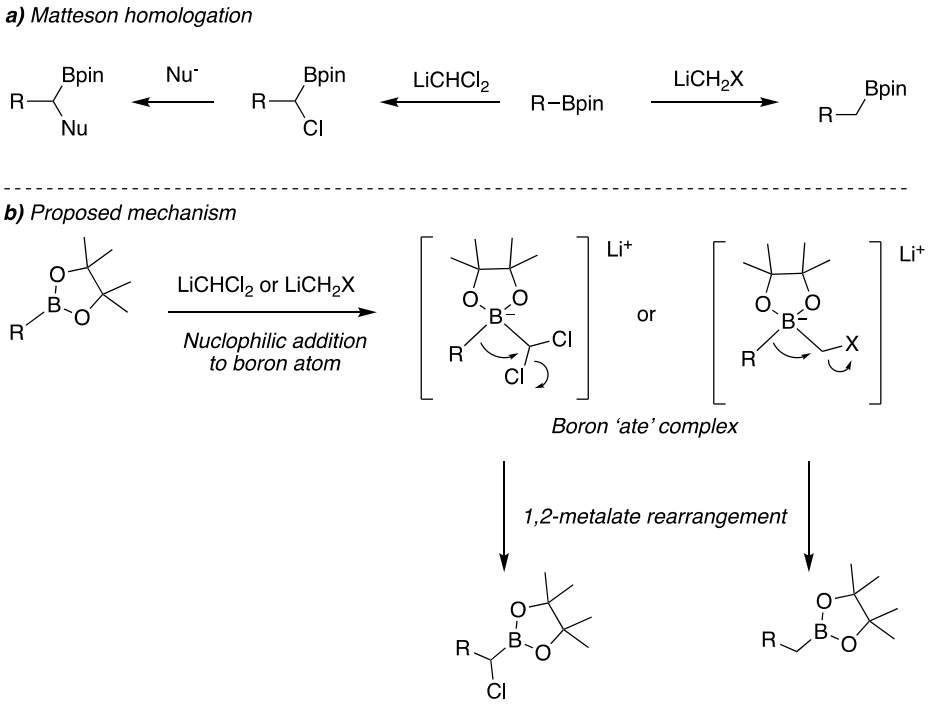
1.2.5. 1,2-Metallate rearrangements of organoboron compounds

1.2.5.1. Matteson homologation

Reactions involving a 1,2-metallate rearrangements from boron 'ate' complexes represent a very important part of organoboron chemistry. In 1980, D. S. Matteson reported a convenient method to synthesize α-haloboronic esters which consists in a homologation of boronic esters with dichloromethyllithium, nowadays known as Matteson homologation (Scheme 40a).[71] The mechanism of this transformation consists in the initial formation of a boron 'ate' complex through addition of a nucleophilic $LiCHCl_2$ to the empty p orbital of boron (Scheme 40b). Then, removal of the leaving group (Cl) occurs through a 1,2-metallate rearrangement step. An interesting feature of this transformation is that the α-haloboronic esters can be further functionalized by nucleophilic substitution of the chlorine atom while maintaining the boron functionality. The incorporation of a methylene unit is also possible with the use of $LiCH_2X$ (X = Cl,

[71] Matteson, D. S.; Majumdar, D. *J. Am. Chem. Soc*. **1980**, *102*, 7588-7591.

or Br) species that can be formed from halogen-lithium exchange of CH_2XY (Y = Br or I) with *n*-BuLi (Scheme 40b).[72]



Scheme 40. a) Matteson homologation of boronic esters and **b)** the proposed mechanism.

The reaction can be performed in an enantiospecific manner with the use of chiral boronic esters (substrate control, Scheme 41a) or chiral reagents (reagent control, Scheme 41b). Common chiral reagents to develop enantiospecific homologations are the chiral lithiated carbamates. Hoppe and coworkers developed a chiral lithiated carbamate with (-)-sparteine as chiral auxiliary which has been widely used in this type of homologations (Scheme 41c).[73]

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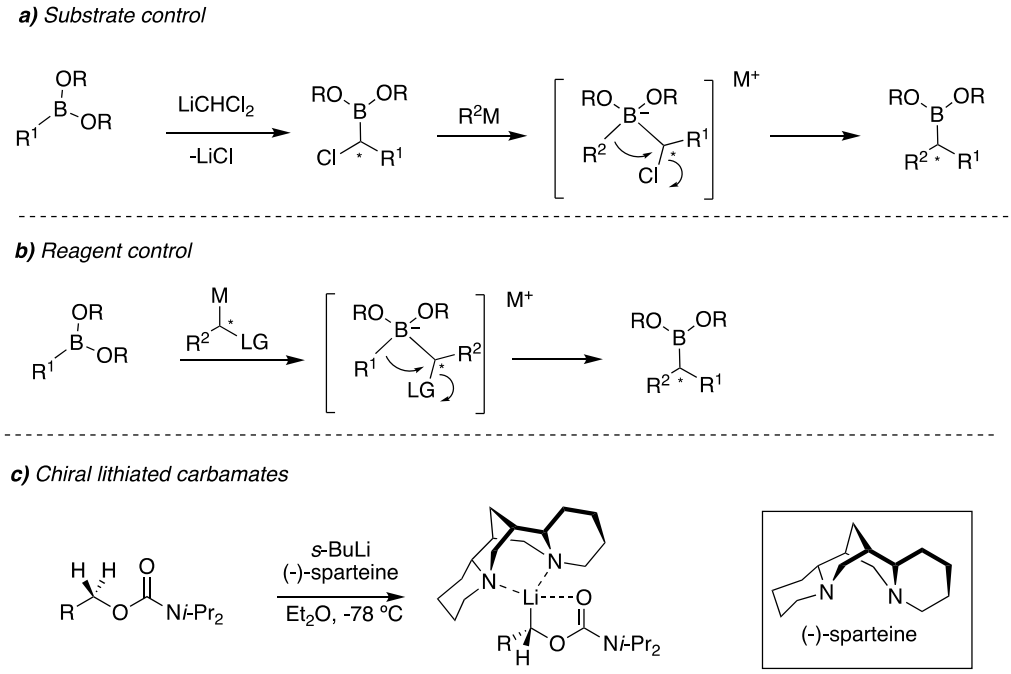
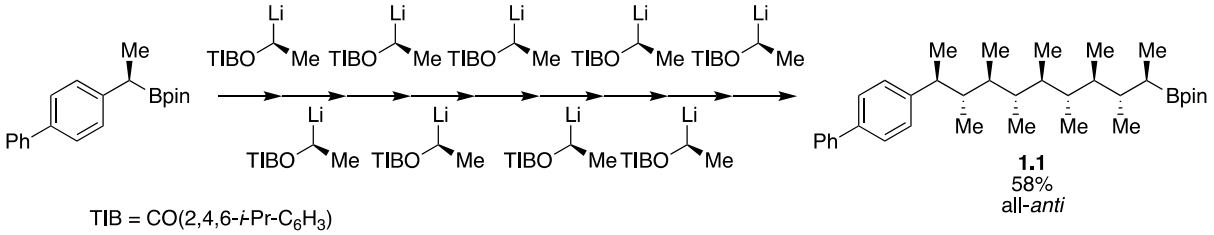
[72] (a) Sadhu, K. M.; Matteson, D. S. *Organometallics* **1985**, *4*, 1687-1689. (b) Michnick, T. J.; Matteson, D. S. *Synlett* **1991**, 631-632. (c) Soundararajan, R.; Li, G.; Brown, H. C. *Tetrahedron Lett*. **1994**, *35*, 8957-8960.

[73] (a) Hoppe, D.; Hense, T. *Angew. Chem. Int. Ed*. **1997**, *36*, 2282-2316. (b) Beckmann, E.; Desai, V.; Hoppe, D. *Synlett* **2004**, 2275-2280.



Scheme 41. a) and **b)** Alternative routes for the enantiospecific synthesis of chiral boronates and **c)** synthesis of chiral lithiated carbamates using (-)-sparteine as chiral auxiliary.

The potential of this reaction has been proved by the application of this homologation/alkylation methodology in a great number of natural product syntheses.[74] In particular, Aggarwal has reported important contributions with the synthesis of complex natural products by iteratively chain elongation, with complete stereocontrol, through reagent controlled enantiospecific homologations of boronic esters.[5] As an example, the synthesis of product **1.1** after nine iterative homologations with complete stereocontrol, requiring only two aqueous work up and one purification (Scheme 42).[5b]



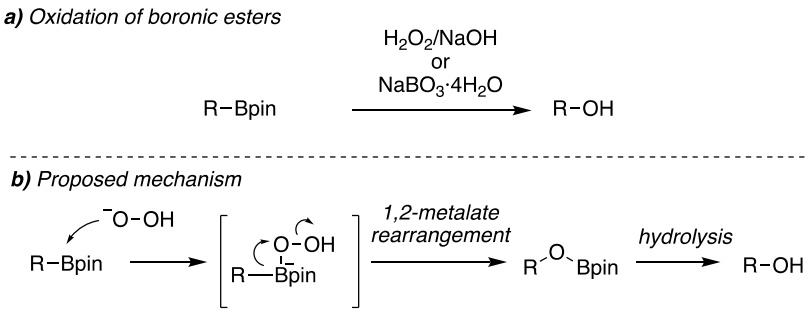
Scheme 42. Example of synthesis of complex products with stereocontrol through iterative homologations.

1.2.5.2. Oxidation and amination of organoboron compounds

Transformation of C-B bonds to C-O and C-N bonds can be also carried out based on 1,2-metallate rearrangements. Brown and co-workers developed in 1961 the oxidation

[74] (a) Matteson, D. S.; Man, H.-W.; Ho, O. C. *J. Am. Chem. Soc*. **1996**, *118*, 4560-4566. (b) Hiscox, W. C.; Matteson, D. S. *J. Organomet. Chem*. **2000**, *614-615*, 314-317. (c) Thomas, S. P.; French, R. M.; Jheengut, V.; Aggarwal, V. K. *Chem. Rec*. **2009**, *9*, 24-39.

of organoboranes with hydrogen peroxide, which can be also applied to boronic esters (Scheme 43a).[75] Besides hydrogen peroxide, sodium perborate is the second most common reagent for the oxidation of boronic esters. Compared to hydrogen peroxide, it grants the use of milder conditions and higher functional group tolerance (Scheme 43b).[76] In this reaction, the peroxide attacks the boron atom and then, the resulting boron 'ate' complex undergoes 1,2-metallate rearrangement with migration of the R group to the oxygen atom. Then, the O-B bond can be cleaved through hydrolysis.



Scheme 43. Methods and mechanism for the oxidation of boronic esters.

Aggarwal *et al.* reported a stereospecific protocol for the synthesis of tertiary amines starting from boronic esters (Scheme 44a).[77] This protocol consists in the prior formation of the potassium trifluoroborate salt with KHF_2 and subsequent treatment with $SiCl_4$ and BnN_3 and final hydrolysis. A direct one step protocol was described by Morken and co-workers for the amination of alkyl and aryl pinacol boronic esters with lithiated alkoxyamines (Scheme 44b).[78] In these examples, the nucleophilic nitrogen attacks the p empty orbital of the boron atom to form a boron 'ate' complex. Then, migration of the R group to the nitrogen atom and subsequent hydrolysis of the N-B bond provides the amine.

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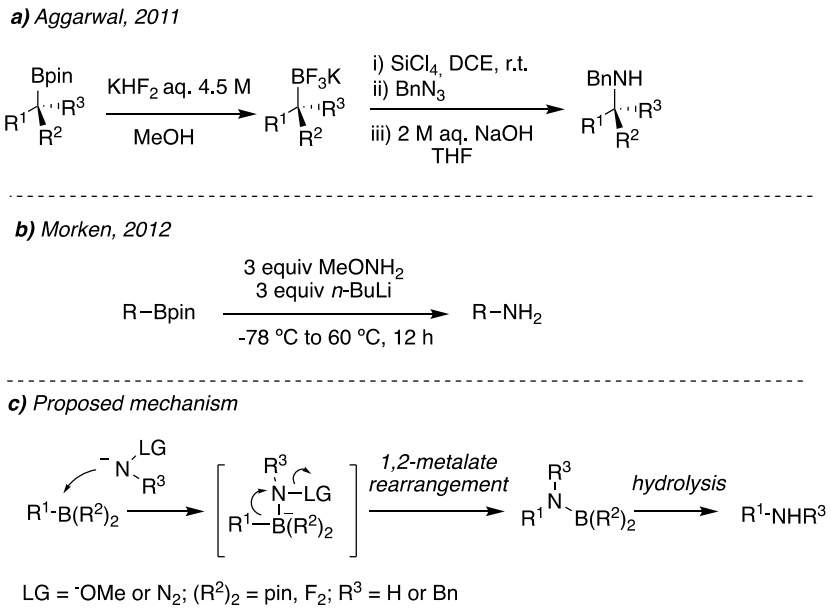
[75] Brown, H. C.; Zweifel, G. *J. Am. Chem. Soc*. **1961**, *83*, 2544-2551.
[76] Kabalka, G. W.; Shoup, T. M.; Goudgaon, N. M. *Tetrahedron Lett*. **1989**, *30*, 1483-1486.
[77] Bagutski, V.; Elford, T. G.; Aggarwal, V. K. *Angew. Chem. Int. Ed*. **2011**, *50*, 1080-1083.
[78] Mlynarski, S. N.; Karns, A. S; Morken, J. P. *J. Am. Chem. Soc.* **2012**, *134*, 16449-16451.



Scheme 44. Methods and mechanism for the amination of boronic esters.

1.2.5.3. Zweifel olefination

The Zweifel olefination is a powerful alternative to other olefination methods allowing the coupling between vinyl boronic esters and organolithium or Grignard reagents, or alkenylmetal and alkylboronic esters, in a stereoinvertive fashion (Scheme 45a).[79] This reaction involves boron 'ate' complex formation after addition of a Grignard or organolithium reagent to the boron center. Iodination of the double bond is followed by 1,2-metallate rearrangement with migration of the R^3 group into the adjacent carbon. In the presence of hydroxide base, the resulting boronic ester suffers hydroxide-assisted *anti*-deiodoborylation to afford the alkene with inversion of the configuration (Scheme 45b).

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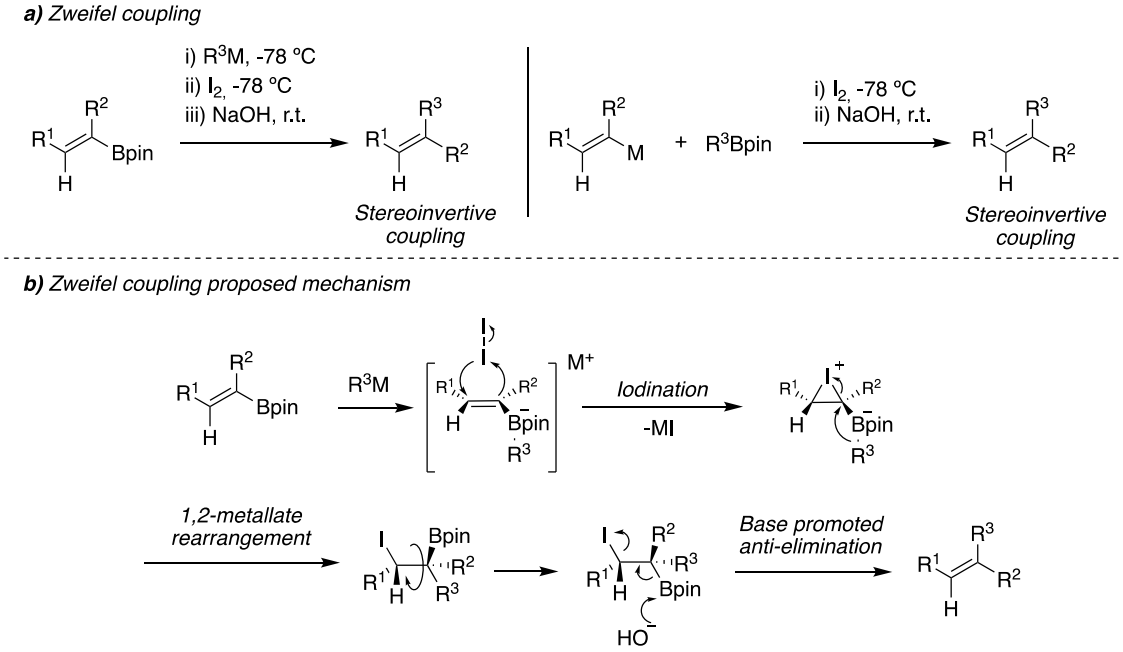
[79] (a) Zweifel, G.; Arzoumanian, H.; Whitney, C. C. *J. Am. Chem. Soc*. **1967**, *89*, 3652-3653. (b) Xu, S.; Lee, C.-T.; Rao, H.; Negishi, E. *Adv. Synth. Catal*. **2011**, *353*, 2981-2987. (c) Armstrong, R. J.; Aggarwal, V. K. *Synthesis* **2017**, *49*, 3323-3336.



Scheme 45. Zweifel olefination.

1.2.6. Electrophilic substitution of boron 'ate' complexes: halogenation and protodeboronation

Besides 1,2-metallate rearrangements, boron 'ate' complexes can also undergo electrophilic substitution. This reactivity was explored in first instance by the group of Brown, when they observed that, by treatment with a base (usually NaOH or NaOMe), and addition of I_2 or Br_2, they could convert trialkylboranes into the alkyl halides (Scheme 46a).[80] They observed inversion of the configuration during the reaction suggesting a S_E2 type electrophilic substitution pathway. Halogenation of alkenyl boronic esters is discussed more in detail in chapter V.

Later on, Aggarwal *et al.* exploited this chemistry using boron 'ate' complexes as chiral organometallic nucleophilic reagents.[81] They could trap this intermediate with a wide variety of electrophiles. They were able to perform iodination, bromination, fluorination and formation of C-N, C-O and C-C bonds (Scheme 46b). Racemization of the product arises in some cases from competing radical (SET) mechanism (Scheme 46c).

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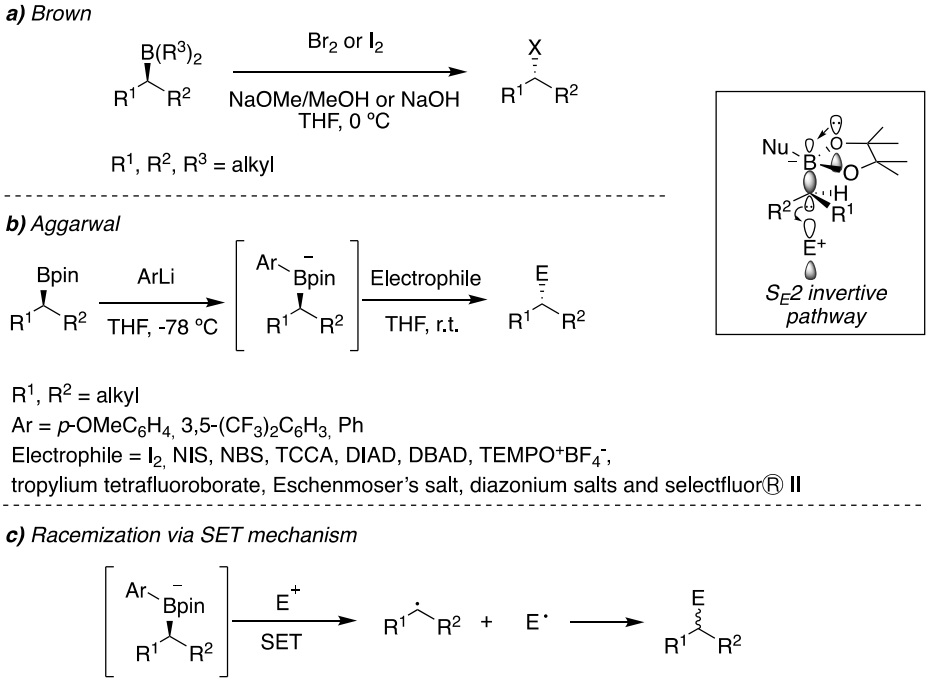
[80] (a) Brown, H. C.; Rathke, M. W.; Rogi, M. M. *J. Am. Chem. Soc*. **1968**, *90*, 5038-5040. (b) Brown, H. C.; Lane, C. F. *J. Am. Chem. Soc*. **1970**, *92*, 6660-6661. (c) Brown, H. C.; Lane, C. F. *J. Chem. Soc. D*, **1971**, 521-522. (d) Brown, H. C.; De Lue, N. R.; Kabalka, G. W.; Hedgecock, H. C. *J. Am. Chem. Soc*. **1976**, *98*, 1290-1291. (e) Brown, H. C.; Lane, C. F. *Tetrahedron*, **1988**, *44*, 2763-2772.

[81] (a) Larouche-Gauthier, R.; Elford, T. G.; Aggarwal, V. K. *J. Am. Chem. Soc*. **2011**, *133*, 16794-16797. (b) Sandford, C.; Rasappan, R.; Aggarwal, V. K. *J. Am. Chem. Soc*. **2015**, *137*, 10100-10103



Scheme 46. Electrophilic substitution of boron 'ate' complexes.

Electrophilic substitution can be also accomplished with a proton source. In this case the C-B bond is replaced by a C-H bond, in a process known as protodeboronation.[82] Protodeboronation has been typically considered as an undesired side reaction. As a result of this, it was not deeply explored until recent days. Moreover, classical conditions for protodeboronation require harsh conditions such as the use of strong acids or bases or high temperatures. This transformation was typically applied for reduction of alkenes and alkynes in hydroboration/protodeboronation sequences (Scheme 47a).[83] Nowadays, milder conditions have been found and its use has been extended, for example, to the synthesis of tertiary carbon stereocenters (Scheme 47b)[84] or selective protodeboronation of arene compounds, where a boronic acid or ester can serve as a removable directing group (Scheme 47c).[85] The common used methodology for protodeboronation involves the use of a base promoter (usually $CsCO_3$, CsF or TBAF), however, methodologies with

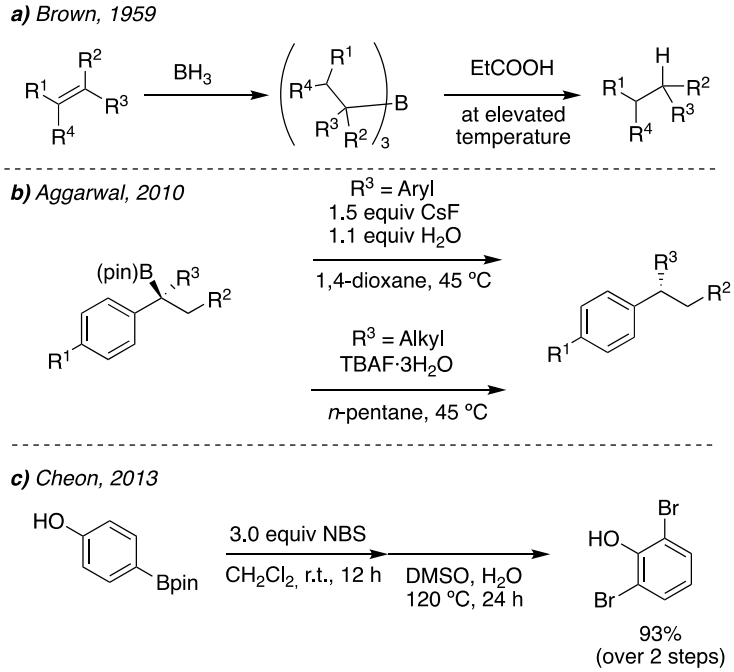
[82] For reviews see: (a) Lee, C.-Y.; Cheon, C.-H. Development of Organic Transformations Based on Protodeboronation. In *Boron reagents in Synthesis*; Coca, A., Ed.; ACS Symposium Series 1236; American Chemical Society: Washington, DC, 2016; pp 483-523. (b) Kuang, Z.; Yang, K.; Zhou, Y.; Song, Q. *Chem. Commun*. **2020**, *56*, 6469-6479.

[83] (a) Brown, H. C.; Murray, K. J. *J. Am. Chem. Soc*. **1959**, *81*, 4108-4109. (b) Brown, H. C.; Murray, K. J. *Tetrahedron* **1986**, *42*, 5497-5504.

[84] (a) Nave, S.; Sonawane, R. P.; Elford, T. G.; Aggarwal, V. K. *J. Am. Chem. Soc*. **2010**, *132*, 17096-17098. (b) Elford, T. G.; Nave, S.; Sonawane, R. P.; Aggarwal, V. K. *J. Am. Chem. Soc*. **2011**, *133*, 16798-16801.

[85] (a) Lozada, J.; Liu, Z.; Perrin, D. M. *J. Org. Chem*. **2014**, *79*, 5365-5368. (b) Lee, C.-Y.; Ahn, S.-J.; Cheon, C.-H. *J. Org. Chem*. **2013**, *78*, 12154-12160. (c) Ihara, H.; Suginome, M. *J. Am. Chem. Soc*. **2009**, *131*, 7502-7503.

transition metal catalysis have been also reported.[86]. Incorporation of deuterium has also been achieved with deuterodeboronation methods.[87]



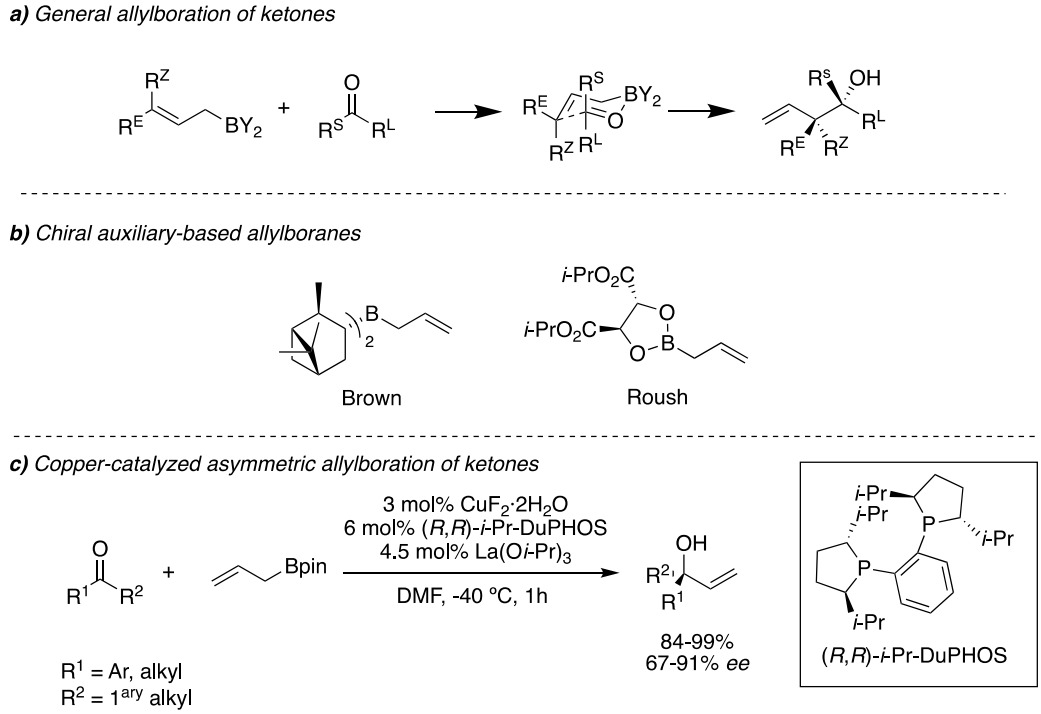
Scheme 47. Protodeboronation reactions **a)** by using propionic acid at elevated temperature and **b)** fluoride-based reagents, **c)** after using Bpin as a removable directing group.

1.2.7. Allylboration of carbonyl compounds

The addition of allylic boron reagents to carbonyl compounds represents a very useful transformation in organic chemistry for the synthesis, often in an asymmetric fashion, of a wide variety of tertiary and quaternary enantioenriched homoallylic alcohols.[88] This transformation usually involves a rigid chair-like transition state, which allows for a good control over the stereoselectivity (Scheme 48a). Due to the importance of this reaction, a large number of works have been reported so far. Initially, most asymmetric transformations relied on the use of chiral allylboron species. Brown reported in 1983 the use of α-pinene (Scheme 48b) as chiral auxiliary for allylboration of carbonyl compounds, and, since then, it became a very popular and successful chiral auxiliary which provides efficient reactions with very good levels of enantio- and

[86] (a) Liu, C.; Li, X.; Wu, Y.; Qiu, J. *RSC Adv*. **2014**, *4*, 54307-54311. (b) Shen, F.; Tyagarajan, S.; Perera, D.; Krska, S. W.; Maligres, P. E.; Smith, M. R., III; Maleczka, R. E., Jr. *Org. Lett*. **2016**, *18*, 1554-1557.
[87] (a) Brown, H. C.; Murray, K. J. *J. Org. Chem*. **1961**, *26*, 631-632. (b) Kallepalli, V. A.; Gore, K. A.; Shi, F.; Sanchez, L.; Chotana, G. A.; Miller, S. L.; Maleczka, R. E., Jr.; Smith, M. R., III. *J. Org. Chem*. **2015**, *80*, 8341-8353. (c) Barker, G.; Webster, S.; Johnson, D. G.; Curley, R.; Andrews, M.; Young, P. C.; Macgregor, S. A.; Lee, A.-L. *J. Org. Chem*. **2015**, *80*, 9807-9816.
[88] For reviews see: (a) Jonnalagadda, S. C.; Suman, P.; Patel, A.; Jampana, G.; Colfer, A. Allylboration. In *Boron reagents in Synthesis*; Coca, A., Ed.; ACS Symposium Series 1236; American Chemical Society: Washington, DC, 2016; pp 67-122. (b) Diner, C.; Szabó, K. J. *J. Am. Chem. Soc*. **2017**, *139*, 2-14.

diastereoselectivity.[89] Roush and co-workers reported a significant contribution to this field with the development of useful allylboronate reagents derived from tartrate esters (Scheme 48b).[90] More recently, methodologies have been described for the asymmetric allylboration of achiral substrates with the use of chiral catalysts (Scheme 48c).[91]



Scheme 48. a) General reaction of enantio- and diastereoselective addition of allylic boronates to carbonyl compound. **b)** Commonly used chiral allylboranes for asymmetric allylboration of ketones. **c)** Copper-catalyzed asymmetric allylboration of ketones.

1.2.8. Rhodium-catalyzed conjugate addition of boronic acids

Boronic acids have also proved to be versatile reagents in the asymmetric conjugate addition to α,β-unsaturated carbonyl compounds. The first example of transition metal-catalyzed addition of an arylboronic acid to an α,β-unsaturated compound was reported in 1995 by Uemura.[92] This reaction proceeds with a catalytic amount of $Pd(OAc)_2$ and without ligand. In 1997, Miyaura and co-workers reported a rhodium-catalyzed

[89] (a) Brown, H. C.; Jadhav, P. K. *J. Am. Chem. Soc*. **1983**, *105*, 2092-2093. (b) Brown, H. C.; Ramachandran, P. V. *J. Organomet. Chem*. **1995**, *500*, 1-19.

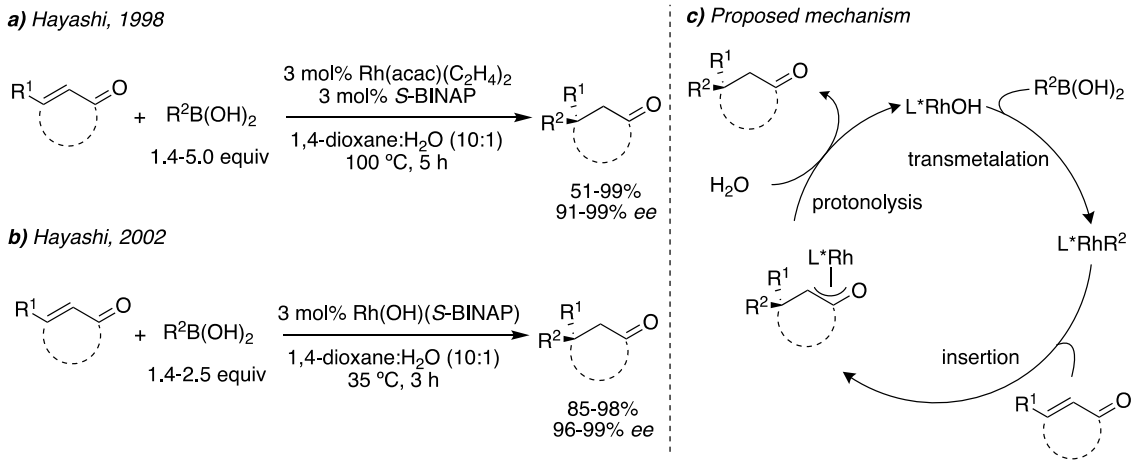
[90] (a) Roush, W. R.; Walts, A. E.; Hoong, L. K. *J. Am. Chem. Soc*. **1985**, *107*, 8186-8190. (b) Roush, W. R.; Halterman, R. L. J. Am. Chem. Soc. **1986**, 108, 294-296. (c) Roush, W. R.; Banfi, L. *J. Am. Chem. Soc*. **1988**, *110*, 3979-3982.

[91] (a) Wada, R.; Oisaki, K.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc*. **2004**, *126*, 8910-8911. (b) Jain, P.; Antilla, J. C. *J. Am. Chem. Soc*. **2010**, *132*, 11884-11886. (c) Barnett, D. S.; Moquist, P. N.; Schaus, S. E. *Angew. Chem. Int. Ed*. **2009**, *48*, 8679-8682. (d) Kobayashi, S.; Endo, T.; Ueno, M. *Angew. Chem. Int. Ed*. **2011**, *50*, 12262-12265. (e) Alam, R.; Vollgraff, T.; Eriksson, L.; Szabó, K. J. *J. Am. Chem. Soc*. **2015**, *137*, 11262-11265. (f) van der Mei, F. W.; Qin, C.; Morrison, R. J.; Hoveyda, A. H. *J. Am. Chem. Soc*. **2017**, *139*, 9053-9065.

[92] Cho, C.S.; Motofusa, S.; Ohe, K.; Uemura, S. *J. Org. Chem*. **1995**, *60*, 883-888.

conjugated addition of aryl and alkenyl boronic acids to enones. They found that the use of a rhodium complex [Rh(acac)(CO)$_2$] and a bisphosphine ligand (dppb) allowed the desired Michael product to be obtained in good yield. This reaction could be also extended to the use of alkenyl boronic acids.[93] Important advances in this chemistry arose when Hayashi and Miyaura described the first enantioselective version in 1998.[94] For this transformation, they used a Rh/*S*-BINAP system which allows addition of aromatic and alkenyl boronic acids to cyclic and acyclic enones in good yields and excellent enantioselectivity (Scheme 49a). The use of Rh(OH)(*S*-BINAP) allows to run the reaction at lower temperature than Rh(acac)(*S*-BINAP) and also, it showed higher yield and enantioselectivity (Scheme 49b).[95] The catalytic cycle involves transmetalation of the Rh(I) and boronic acid, insertion of unsaturated compounds into the carbon-rhodium bond followed by hydrolysis to form the product and regenerate a hydroxorhodium complex (Scheme 49c).

In the last decades great advances have been made in this field which have brought a plethora of conditions to run this reaction with excellent efficiency and enantioselectivity.[96]



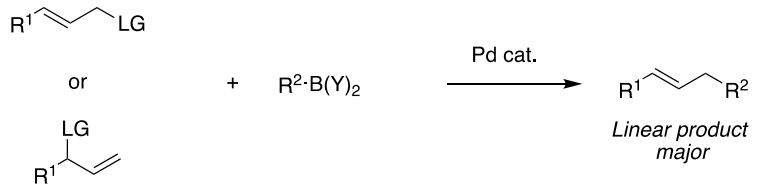
Scheme 49. Rhodium-catalyzed addition of organoboron compounds to α,β-unsaturated bonds.

1.2.9. Organoboron compounds in asymmetric copper catalyzed allylic substitution

The use of organoboron compounds as organometallic hard nucleophiles for allylic substitution was explored with different transition metals.[97] Palladium catalysts are one

[93] Sakai, M.; Hayashi, T.; Miyaura, N. *Organometallics* **1997**, *16*, 4229-4231.
[94] Takaya, Y.; Ogasawara, M.; Hayashi, T.; Sakai, M.; Miyaura, N. *J. Am. Chem. Soc*. **1998**, *120*, 5579-5580.
[95] Hayashi, T.; Takahashi, M.; Takaya, Y.; Ogasawara, M. *J. Am. Chem. Soc*. **2002**, *124*, 5052-5058.
[96] For reviews see: (a) Hayashi, T.; Yamasaki, K. *Chem. Rev*. **2003**, *103*, 2829-2844. (b) Edwards, H. J.; Hargrave, J. D.; Penrose, S. D.; Frost, C. G. *Chem. Soc. Rev*. **2010**, *39*, 2093-2105.
[97] Pigge, F. C. *Synthesis* **2010**, *11*, 1745-1762.

of the most explored catalysts for this transformation. Aryl,[98] alkenyl[99] and allylboron[100] compounds have been used in combination with a variety of allylic substrates such as, allylic acetates, bromides, chlorides or unactivated allylic alcohols. These reactions provide in most of the cases, the linear product as major or exclusive product (Scheme 50).



R^1 = Ar, H, 1^{ary} alkyl
R^2 = Ar, alkenyl, allyl

LG = Br, OAc, OH, OBoc…
[Pd] = $Pd(dba)_2$, $[PdCl_2(TFP)_2]$, $Pd(PPh_3)_4$, $PdCl_2(dppf)$…
$B(Y)_2$ = $B(OH)_2$, $B(Sia)_2$, BF_3K…

TFP = tri(2-furyl)phosphine

Scheme 50. General palladium-catalyzed allylic substitution with organoboron reagents.

Due to the ability of copper to promote S_N2'-selective allylic substitution, this metal was explored for allylic substitution with organoboron reagents. First examples were reported independently by Ohmiya and Sawamura[101] and Lalic[102] using arylboronates. Ohmiya and Sawamura reported a S_N2'-selective enantiospecific copper-catalyzed coupling between enantioenriched α,γ-disubstituted-(*Z*)-allylic phosphates and neopentyl glycol arylboronic esters (Scheme 51a). The products were obtained without erosion of the enantiomeric excess, with perfect S_N2' selectivity and with *E*-stereochemistry. The authors proposed a mechanism for this transformation involving in first instance, the transmetalation between the organoboron compound and the LCuOR complex. An oxidative addition of the allylic phosphate into the copper complex with *anti*-stereochemistry with respect to the phosphate, and subsequent reductive elimination at the S_N2' position provides the product and regenerates the CuOR complex (Scheme 51b).

On the other hand, Lalic *et al.* reported a copper-catalyzed S_N2'-selective substitution of allyl chlorides with pinacol arylboronic esters with IMesCuO*t*-Bu (Scheme 51c). Products were obtained with high yield and excellent regioselectivity.

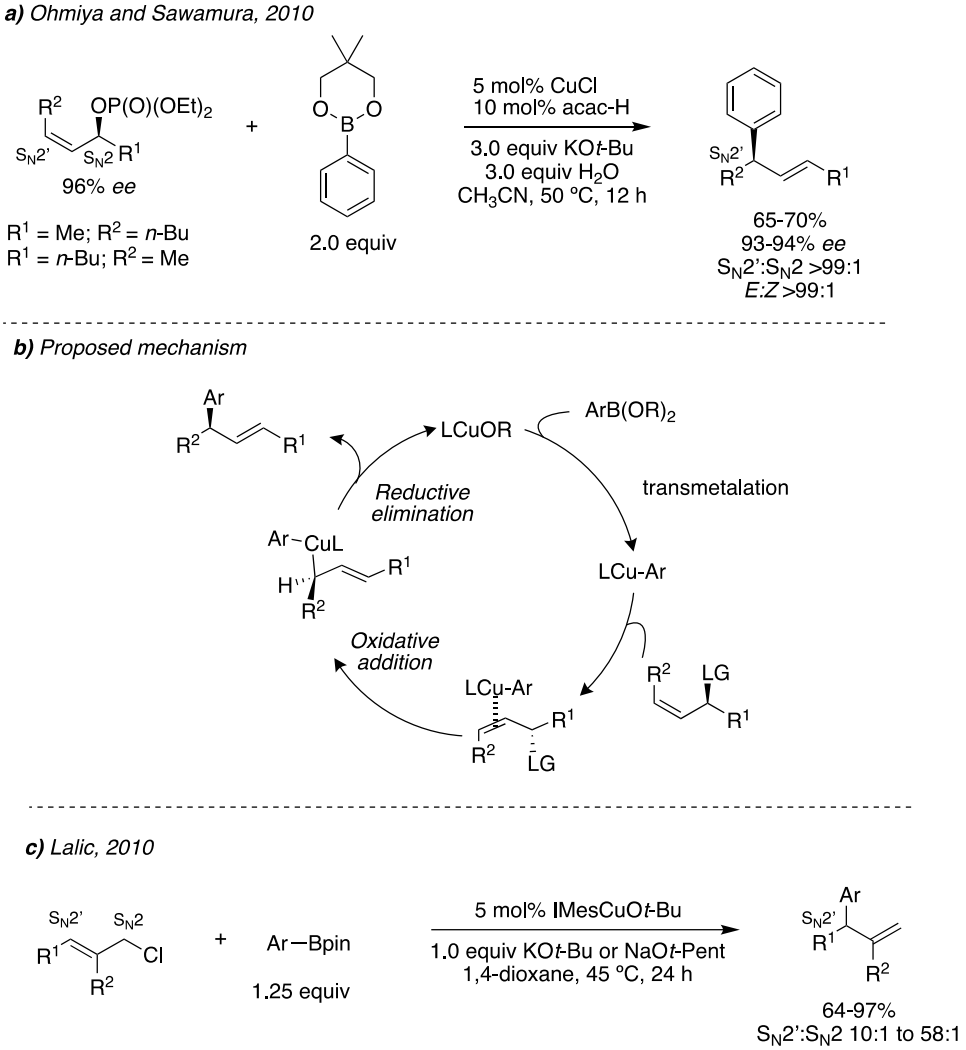
[98] (a) Moreno-Mañas, M.; Pajuelo, F.; Pleixats, R. *J. Org. Chem.* **1995**, *60*, 2396-2397. (b) Bouyssi, D.; Gerusz, V.; Balme, G. *Eur. J. Org. Chem.* **2002**, 2445-2448. (c) Tsukamoto, H.; Sato, M.; Kondo, Y. *Chem. Commun*. **2004**, 1200-1201. (d) Tsukamoto, H.; Uchiyama, T.; Suzuki, T.; Kondo, Y. *Org. Biomol. Chem.* **2008**, *6*, 3005-3013.

[99] (a) Miyaura, N.; Yano, T.; Suzuki, A. *Tetrahedron Lett*. **1980**, *21*, 2865-2868. (b) Kabalka, G. W.; Al-Masum, M. *Org. Lett.* **2006**, *8*, 11-13.

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

[101] Ohmiya, H.; Yokokawa, N.; Sawamura, M. *Org. Lett*. **2010**, *12*, 2438-2440.

[102] Whittaker, A. M.; Rucker, R. P.; Lalic, G. *Org. Lett*. **2010**, *12*, 3216-3218.



Scheme 51. First examples of copper-catalyzed allylic substitution with arylboronates.

The first example of the use of boronic esters as organometallic partner in enantioselective allylic substitution catalyzed by copper was reported by the group of Hayashi (Scheme 52a).[103] In this example, aryl boronic esters were coupled with allylic phosphates by using a chiral sulfonate-bearing NHC-Cu complex. Tertiary and quaternary carbon stereogenic centers were formed in good yield with good regio- and enantiomeric excess. After this initial example, asymmetric copper-catalyzed allylic substitution with organoboron compounds was mainly explored by the group of Hoveyda. Chiral NHC-copper complexes resulted to be excellent catalysts for the allylic substitution of allenyl, [104] alkenyl[105] and propargylic[106] boronic esters (Scheme 52b-d).

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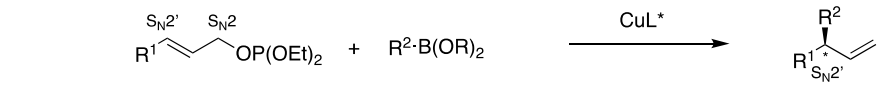
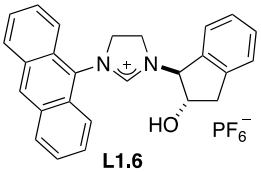
[103] Shintani, R.; Takatsu, K.; Takeda, M.; Hayashi, T. *Angew. Chem. Int. Ed*. **2011**, *50*, 8658-8659.
[104] Jung, B.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2012**, *134*, 1490-1493.
[105] (a) Gao, F.; Carr, J. L.; Hoveyda, A. H. *Angew. Chem. Int. Ed*. **2012**, *51*, 6613-6617. (b) Gao, F.; Carr, J. L.; Hoveyda, A. H. *J. Am. Chem. Soc*. **2014**, *136*, 2149-2161.
[106] Shi, Y.; Jung, B.; Torker, S.; Hoveyda, A. H. *J. Am. Chem. Soc*. **2015**, *137*, 8948-8964.



a) *Hayashi, 2011*

Ar—Bneop 2.0 equiv

Conditions: 5 mol% CuCl
5.5 mol% **L1.6**
2.0 equiv NaOMe
THF, 30 ºC, 16 h
74-95%
68-96% *ee*
$S_N2':S_N2$ 85:15 to >99:1



L1.6

b) *Hoveyda, 2012*

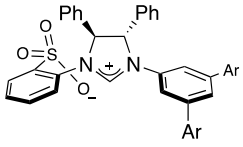
1.5 equiv

Conditions: 10 mol% CuCl
11 mol% **L1.7**
2.0 equiv NaOMe
THF, 30 ºC, 16 h
64-92%
81-98% *ee*
$S_N2':S_N2$ 77:23 to >98:2

c) *Hoveyda, 2014*

2.0 equiv

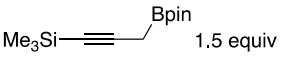
Conditions: 5 mol% CuCl
5.5 mol% **L1.7**
2.0 equiv NaOMe
THF, 22 ºC, 8 h
74-96%
74-98% *ee*
$S_N2':S_N2$ ≥98:2



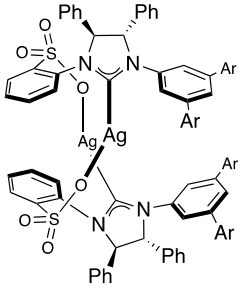
Ar = 2,4,6-(*i*-Pr)$_3$C$_6$H$_2$

L1.7

d) *Hoveyda, 2015*



Conditions: 5 mol% CuCl
2.75 mol% **C1.6**
2.0 equiv NaOMe
THF, 22 ºC, 8 h
75-95%
64-98% *ee*
$S_N2':S_N2$ 87:13 to >98:2



Ar = 2,4,6-(*i*-Pr)$_3$C$_6$H$_2$

C1.6

Scheme 52. Examples of copper catalyzed allylic substitution with boronic esters.

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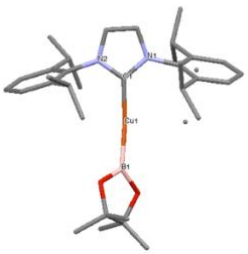
2. COPPER-CATALYZED BORYLATIVE TRANSFORMATIONS OF ALKYNES

Copper was one of the first transition metals to be widely used for catalysis in organic chemistry and, to this day, is one of the most common metals in organic transformations due to their high versatility and their high abundance in the earth crust, which makes copper cheap and easy to obtain.

As mentioned in section 1.1.6 (chapter I), borylcopper complexes have been proved to be very useful for the synthesis of allylboron compounds and, in general, borylcopper species have emerged as one of the most important species in the history of boryl anions from a synthetic point of view.

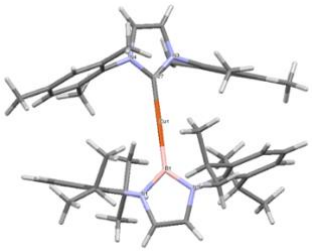
Borylcopper complexes bearing NHC ligands have been isolated and characterized by X-Ray crystallography by the groups of Sadighi,[107] Nozaki[108] and Tsuji[109] (Figure 7), and more recently, an example with a phosphine ligand was isolated by the group of Kleeberg.[110]

a) *Sadighi, 2005*



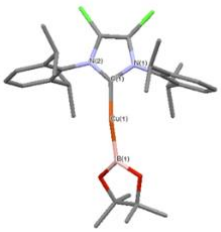
IPrCuBpin complex

b) *Nozaki, 2007*



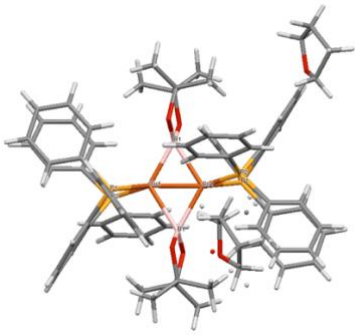
IMesCuB(RNCH=CHNR)
(R = 2,6-*i*-$Pr_2C_6H_3$)

c) *Tsuji, 2013*



^{Cl}IPrCuBpin complex

d) *Kleeberg, 2017*



[(dppbz)Cu-Bpin]$_2$

Figure 7. Examples of isolated LCu-B complexes. Crystallographic data obtained free of charge from The Cambridge Crystallographic Data Centre.

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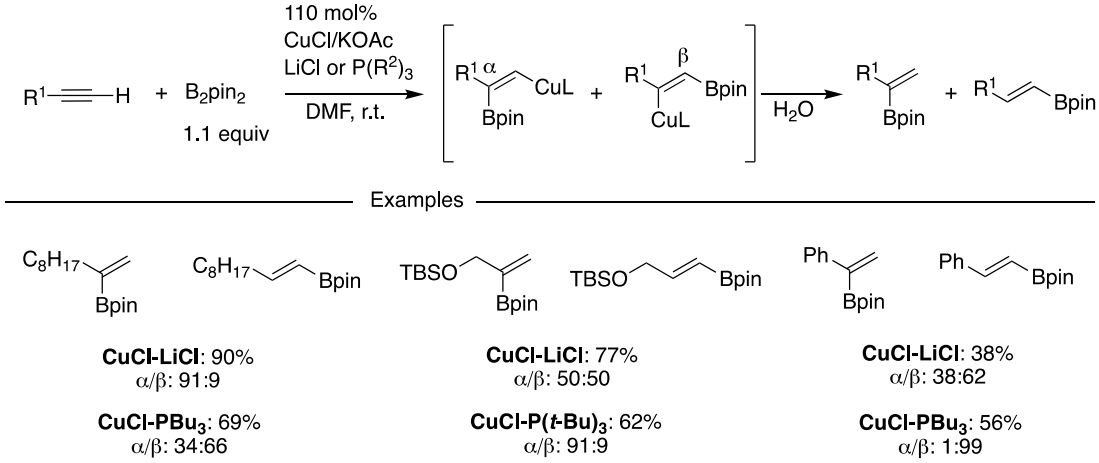
[107] Laitar D. S.; Müller, P.; Sadighi, J. P. *J. Am. Chem. Soc*. **2005**, *127*, 17196-17197.
[108] Segawa, Y.; Yamashita, M.; Nozaki, K. *Angew. Chem. Int. Ed*. **2007**, *46*, 6710-6713.
[109] Semba, K.; Shinomiya, M.; Fujihara, T.; Terao, J.; Tsuji, Y. *Chem. Eur. J*. **2013**, *19*, 7125-7132.
[110] Borner, C.; Anders, L.; Brandhorst, K.; Kleeberg, C. *Organometallics* **2017**, *36*, 4687-4690.

In 2000, Ito and Hosomi[111] and the group of Miyaura[112] independently reported the use of borylcopper species for the borylation of α,β-unsaturated carbonyl compounds and alkynes, the latter being the first example of a copper-mediated protoboration of an unsaturated hydrocarbon. To date, borylcupration of various unsaturated hydrocarbons such as alkenes, 1,3-dienes, alkynes or allenes has been extensively studied.[113] Within the context of this thesis, next sections are focused on the borylcupration of alkynes and its subsequent trapping with electrophiles towards the synthesis of alkenyl boronates.

2.1. COPPER(I)-CATALYZED PROTOBORATION OF ALKYNES WITH DIBORON COMPOUNDS

As mentioned above, Miyaura and co-workers reported the *syn* addition of borylcopper species to terminal alkynes, efficiently promoted by stoichiometric amounts of CuCl/KOAc/LiCl. The reaction proceeded in DMF at room temperature giving rise to the protoboration product after hydrolytic work-up.[112] In this work, however, they obtained mixtures of *syn* terminal (β) and internal (α) borylation products (Scheme 53). They observed that both the nature of the substituent of the alkyne and the ligand on the copper complex have an influence on the regioselectivity, however, a general correlation was not found.



Scheme 53. Miyaura's stoichiometric addition of borylcopper species to terminal alkynes.

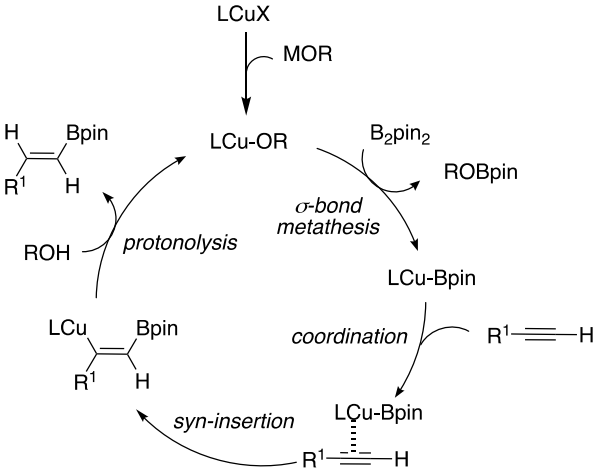
After this pioneering work reported by Miyaura, the development of catalytic methods to perform copper-catalyzed protoboration of alkynes in a regioselective manner was sought after.

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

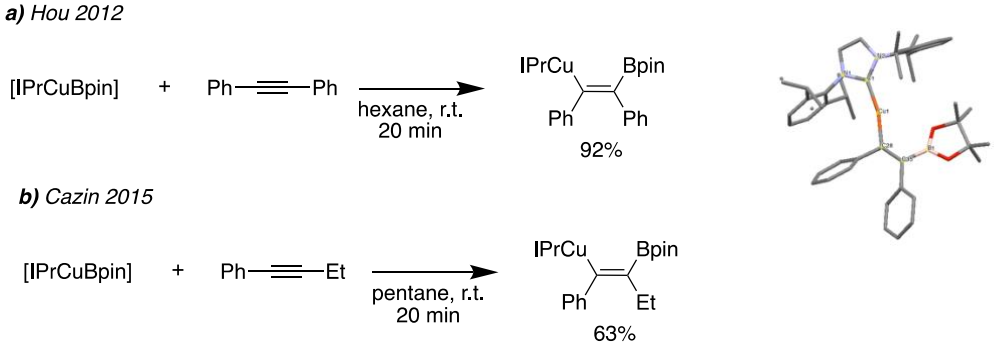
[112] (a) Takahashi, K.; Ishiyama, T.; Miyaura, N. *Chem. Lett.* **2000**, *29*, 982-983. (b) Takahashi, K.; Ishiyama, T.; Miyaura, N. *J. Organomet. Chem*. **2001**, *625*, 47-53.

[113] (a) Hemming, D.; Fritzemeier, R.; Westcott, S. A.; Santos, W. L.; Steel, P. G. *Chem. Soc. Rev*. **2018**, *47*, 7477-7494. (b) Whyte, A.; Torelli, A.; Mirabi, B.; Zhang, A.; Lautens, M. *ACS Catal*. **2020**, *10*, 11578-11622.

The general proposed mechanism for a protoboration of alkynes in shown in Scheme 54. Initially, copper alkoxide is formed by reaction of LCuX complex and an alkoxide base. Then, reaction of this complex with B_2pin_2 through σ-bond metathesis provide the LCuBpin complex. The alkyne coordinates the copper complex and a *syn*-insertion into the Cu-B bond leads to generating a nucleophilic β-boryl alkenylcopper complex. Final protonation affords the borylated product and regenerates the active LCuOR complex. The insertion step was demonstrated by isolation of β-boryl alkenylcopper(I) intermediates by Hou[114] and Cazin[115] (Scheme 55).



Scheme 54. Proposed mechanism for protoboration of alkynes.



Scheme 55. Isolation of copper(I) β-borylalkenyl intermediates.

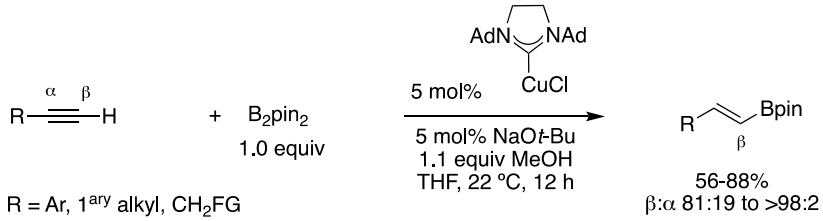
2.1.1. Protoboration of terminal alkynes

Following the initial report on Miyaura *et al.* great efforts have been done in the development of efficient and regioselective Cu(I)-catalyzed methodologies for the protoboration of terminal alkynes, and also, to understand the factors that determine the regioselectivity.

In 2011, the group of Hoveyda reported an NHC-copper-catalyzed protoboration of terminal alkynes.[116] The regioselectivity of the process could be controlled by fine tuning the properties of the ligand. Regioselectivity of this transformation is marked by steric

[114] Zhang, L.; Cheng, J.; Carry, B.; Hou, Z. *J. Am. Chem. Soc*. **2012**, *134*, 14314-14317.
[115] Lesieur, M.; Bidal, Y. D.; Lazreg, F.; Nahra, F.; Cazin, C. S. J. *ChemCatChem* **2015**, *7*, 2108-2112.
[116] Jang, H.; Zhugralin, A. R.; Lee, Y.; Hoveyda, A. H. *J. Am. Chem. Soc*. **2011**, *133*, 7859-7871.

and electronic attributes of NHC ligands and steric and electronic properties of the terminal alkyne, and subtle differences determine the borylation site selectivity. The formation of the β-borylated alkene is usually favored upon addition of LCu-Bpin complex to an alkyne. Due to the higher electrophilicity and lower steric hindrance of the β-carbon atom (comparing to the α-carbon), bulky Bpin anion would preferentially attack this carbon. The use of a strong σ-donating and sterically hindered NHC ligand, *N*-adamantyl substituted NHC, provides the β borylation of propargylic ethers and amines and aryl and alkyl substituted alkynes (Scheme 56). Aryl alkynes bearing both electron-donating and electron-withdrawing groups provide very high β:α ratios.



Scheme 56. β-selective protoboration of terminal alkynes.

Authors proposed an irreversible insertion step, in such a way that either the coordination or the insertion step would be the regiodetermining step. DFT calculations revealed that coordination of the copper complex with the alkyne is the actual regiodetermining step. Frontier orbital study with strongly electron-donating NHC complexes shows that the strongest interaction in the coordination step is the back-donation from the copper complex to the alkyne (Figure 8). In this case, electronic factors play a more important role on the regioselectivity control. These NHC-Cu-Bpin complexes have a slightly bent structure, due to the high *trans* effect of the NHC ligand. This fact allows the alkyne to approach copper in an *anti* manner to the NHC. As the C_β has a larger LUMO, this carbon would be positioned *trans* to the NHC providing a more advanced Cu-C_β bond in the transition state, and thus favoring β selectivity.

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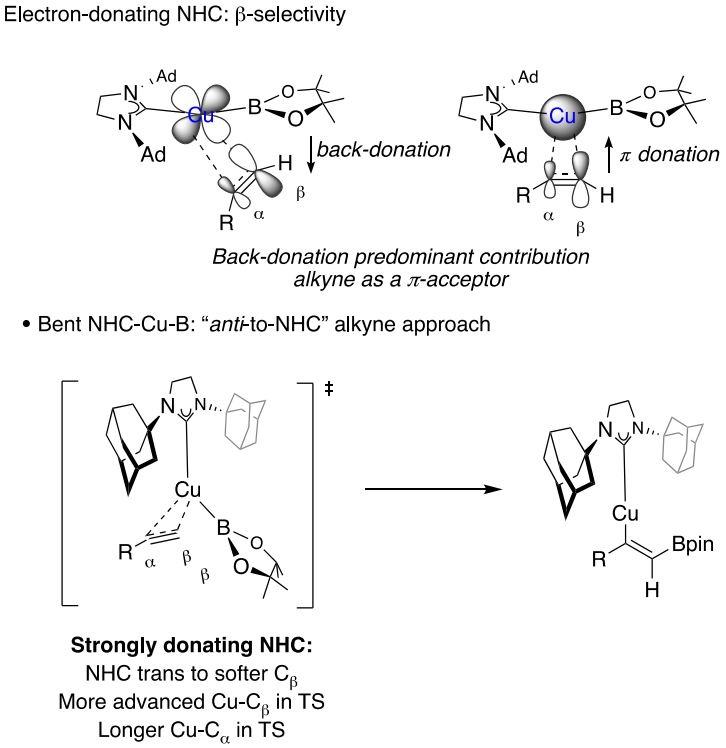

Figure 8. Explanation for the β-selectivity.

The more challenging α-isomer could be obtained with the use of less donating aryl-substituted NHC ligands. Terminal propargylic ethers or amines, and terminal aryl alkynes could be selectively borylated at the α position by running the reaction at -50 ºC and -15 ºC respectively (Scheme 57). In the case of aryl-substituted alkynes, electron-donating substituents on the aryl ring cause an erosion on the α regioselectivity control. Moreover, this approach is not feasible for terminal alkyl alkynes, which afford β-borylated alkene as major product with SIMesCuCl. Authors proposed that with these substrates, in the absence of an electron-withdrawing group proximal to the alkyne, the insertion step might be the regiodetermining step.

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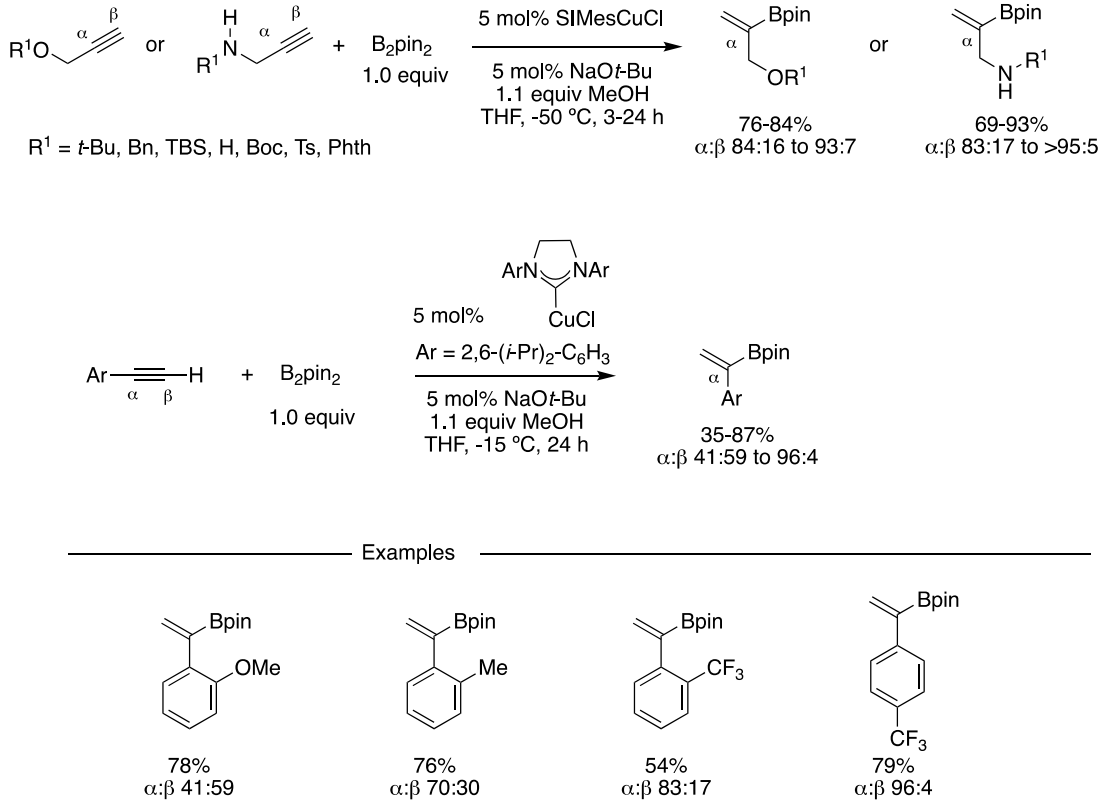

Scheme 57. Regioselective protoboration of terminal alkynes.

In Figure 9, factors involving the α-selectivity are presented. By a frontier orbitals study, the authors could observe that with less donating aryl-substituted NHC ligands, π donation from alkyne to copper and back-donation from copper to the alkyne have similar contribution in the coordination step. This results in a practically symmetrical transition state where sterics play a major role for the regioselectivity control (intermediate **I** vs **II)**. With aryl alkynes bearing electron-withdrawing groups there is a slightly higher electron density at α carbon. This favors a more advanced Cu-C_α bond in the transition state. However, in aryl alkynes bearing an electron-donating group there is a higher electron density at the C_β, which implies a shorter Cu-C_β bond in the transition states. This makes modes of coordination **I** and **III** similar in energy, thus, a diminished regioselectivity is obtained.

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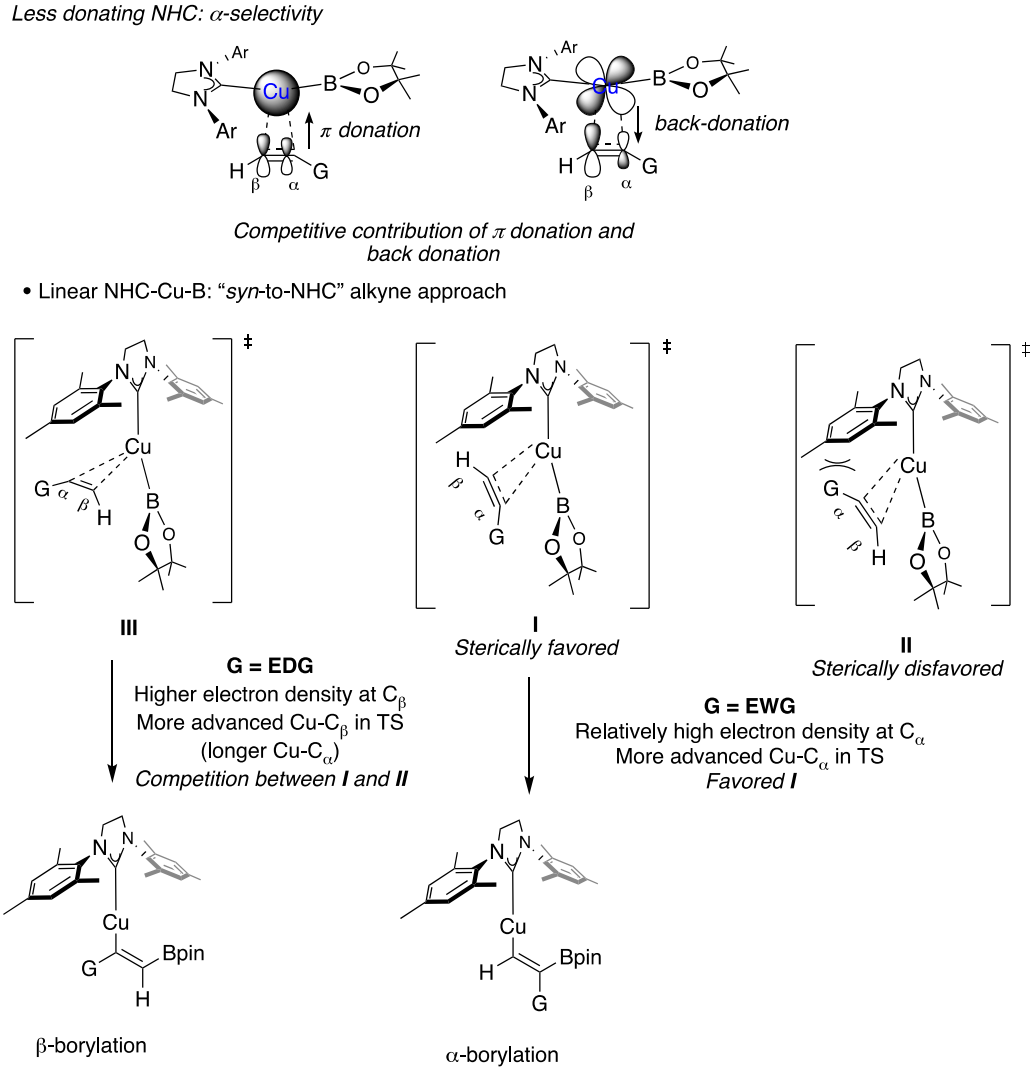

Figure 9. Explanation of the α-selectivity.

Recently, Engle *et al.* reported the use of cyclic(alkyl)(amino)carbene (CAAC) ligands for the α borylation of terminal alkynes.[117] These ligands are stronger σ donors than analogous NHC ligands. This reaction can be applied to alkyl and aryl substituted alkynes with very good levels of regioisomeric ratio, improving those reported in Hoveyda's work[116] for aryl alkynes (Scheme 58). They observed that comparing different CAAC ligands with comparable steric hindrance, an increase in the σ donor ability promotes higher α selectivity. Comparison of steric effect of CAAC ligands with comparable electronic properties indicates that decreasing steric hindrance also favors α selectivity. With these ligands, the electronic nature of the alkynes has less influence on the regioselective outcome than with classical NHC ligands. The only limitation that was found in this work was the use of *tert*-butyl substituted acetylene. The steric hindrance of

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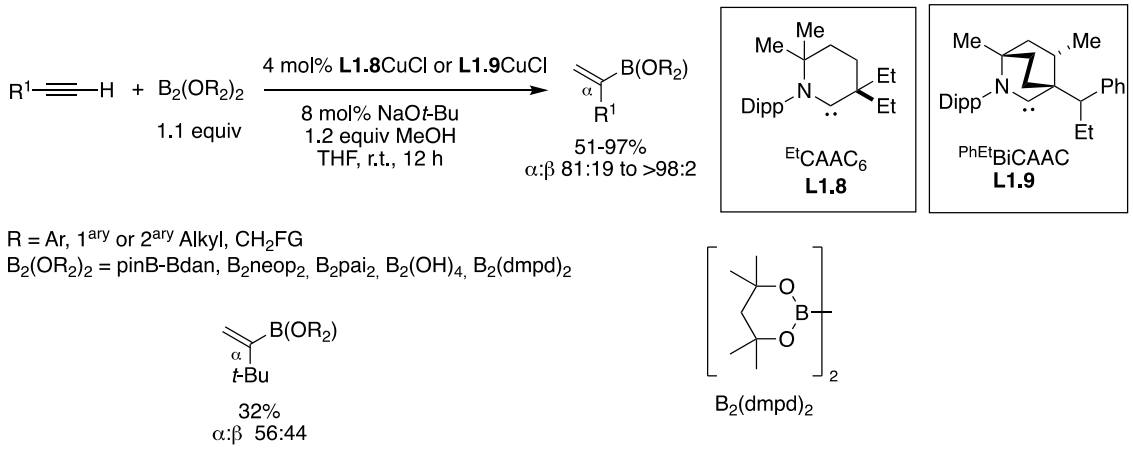
[117] Gao, Y.; Yazdani, S.; Kendrick, A.; Junor, G. P.; Kang, T.; Grotjahn, D. B.; Bertrand, G.; Jazzar, R.; Engle, K. M. *Angew. Chem. Int. Ed*. **2021**, *60*, 19871-19878.

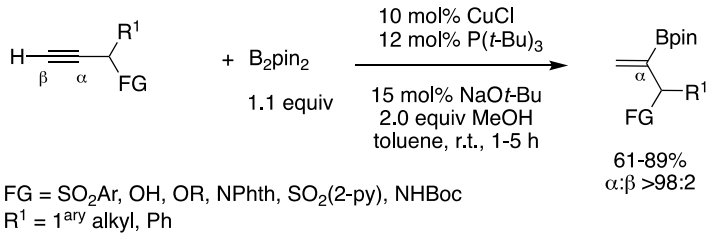
this substrate entails a dramatic decrease on the regioselectivity, obtaining nearly an equimolar mixture of α and β borylated products.



Scheme 58. Cu(I)-catalyzed α-selective protoboration of terminal alkynes with cyclic(alkyl)(amino)carbene ligands.

Control over the regioselectivity in the borylation of terminal alkynes has been also accomplished by using propargylic groups, such as 2-$PySO_2$, that proved to be useful to control the regioselectivity towards the α-borylated product.[118] Carretero reported the use of this functional group as a removable propargylic directing group together with CuP*t*-Bu as catalyst (Scheme 59). Under these conditions, the reaction also works with complete control on the regioselectivity with other propargylic functional groups such as, SO_2Ph, OH, OAc or NHBoc.

Authors claimed that, due to the similar σ-donor ability character of *t*-Bu_3P and IMes, and also their similar steric bulk,[119] the hypothesis developed by the group of Hoveyda to explain α-selectivity with the latter Cu complex (Figure 9)[116] could be also applied to this catalytic system.

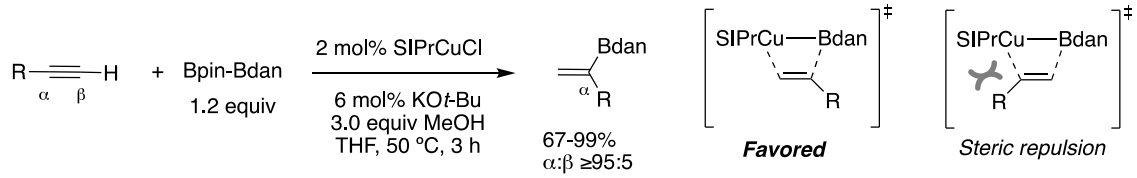


Scheme 59. Cu(I)-catalyzed α-protoboration of terminal alkynes with a propargylic directing group.

Another approach for the synthesis of α-vinylboronates is the use of (pin)B-B(dan) and SIPrCuCl as reported by Yoshida.[120] When unsymmetrical diboron compounds are

[118] Moure, A. L.; Mauleón, P.; Gómez Arrayás, R.; Carretero, J. C. *Org. Lett*. **2013**, *15*, 2054-2057.
[119] Balogh, J.; Slawin, A. M. Z.; Nolan, S. P. *Organometallics* **2012**, *31*, 3259-3263.
[120] Yoshida, H.; Takemoto, Y.; Takaki, K. *Chem. Commun*. **2014**, *50*, 8299-8302.

used, the less Lewis acidic boron atom forms the Cu-B bond after the σ-bond metathesis.[121] Thus, SiPrCuBdan complex is the active catalytic species in this transformation. The lower Lewis acidity of Bdan (compared with Bpin) affects the regioselectivity of the insertion of the alkyne. In general, in a Cu-Bpin addition to terminal alkynes, the Lewis acidic Bpin moiety tends to add to the less substituted carbon atom (to generate the more stable carbocationic transition state). This behavior would be negligible lowering the Lewis acidity of the boron atom (as in the Bdan moiety). Therefore, the electronic factors are diminished in the interaction with the SIPrCu-Bdan and the terminal alkyne, leading to a scenario in which regioselectivity is controlled by the steric repulsion of the bulky SIPr ligand and the substituent of the alkyne (Scheme 60). This approach offers excellent results in terms of yield and regioselectivity (α:β ≥95:5).



R = Ar, 1^{ary} or 3^{ary} alkyl, CH_2FG, TMS

Scheme 60. α-selective protoboration of terminal alkynes with SIPrCu-Bdan.

2.1.2. Protoboration of internal alkynes

The copper-catalyzed borylation of internal alkynes is more challenging due to the lower reactivity of these substrates. Nonetheless, the use of internal alkynes provides the stereoselective synthesis of trisubstituted alkenyl boronates.

Copper-catalyzed β-selective *syn*-protoboration of internal propyonates could be accomplished with the use of a bidentate phosphine Xantphos as ligand (Scheme 61).[122] Primary and secondary alkyl substituted, or even terminal α,β-acetylenic esters are well tolerated, obtaining just the *syn*-addition β-borylated products. However, when a bulky group, e.g. *tert*-butyl group, is present in the β-position, mixtures of *syn* and *trans* addition products are observed. This is proposed to happen by isomerization of the copper enolate intermediate, which occurs likely due to the steric repulsion of the *t*-Bu and the carboxylic ester groups. The regioselectivity outcome can be explained by the high electronic bias that imparts the electron-withdrawing ester group, making the β-carbon more susceptible to the attack of the nucleophilic boron atom.

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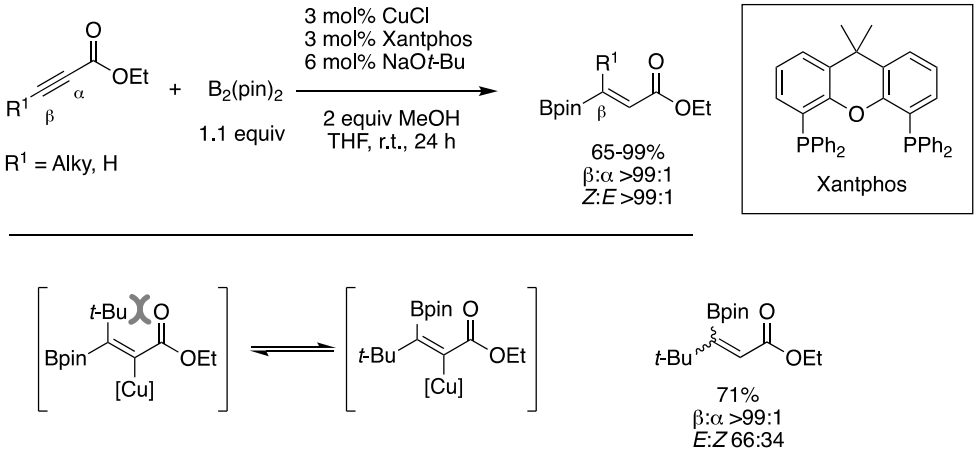
[121] Higher Lewis acidity, i.e. more available p orbital at Bpin moiety favors interaction of the boron atom with the lone pair of electrons of the oxygen of the *tert*-butoxy group and thus favors formation of Cu-Bdan.
[122] Lee, J.-E.: Kwon, J.; Yun, J. *Chem. Commun*. **2008**, 733-734.



Scheme 61. β-Selective *syn*-protoboration of α,β-acetylenic esters.

The protoboration of less reactive internal (alkyl)arylalkynes, in a stereo- and regioselective manner, was initially based on the use of a IMS (1,3-dimethylimidazole-2-thione)/CuCl catalytic system (Scheme 62a).[123] Electron-withdrawing substituents in the aromatic group led to a better yield than electron-donating substituents. This suggests that the more important step is the nucleophilic addition of the boron atom to the alkynes, rather the initial coordination of the alkyne to the copper. Sterics also play an important role on the efficiency of the reaction, since bulkier alkyl groups led to diminished conversion. The regioselectivity is governed by the electron-withdrawing effect of the aryl moiety, favoring the nucleophilic addition of the boron atom in the β position.

The limitation with the alkyl substituent of Yun's previous transformation could be overcome by using a (*p*-tolyl)$_3$PCuCl complex as catalyst (Scheme 62b).[124] β-Selective *syn*-protoboration of a variety of (alkyl)arylalkynes was achieved with this catalyst. Diphenylacetylene was also tolerated providing excellent yield. Interestingly, when sterically demanding *tert*-butyl alkynes are subjected to these conditions, the reaction proceeds slower and the α-borylated product was obtained as a unique isomer, resulting in a complete inversion of the regioselectivity. These results could be explained by an insertion step governed by steric factors rather than electronics (in contrast with previous mentioned examples).

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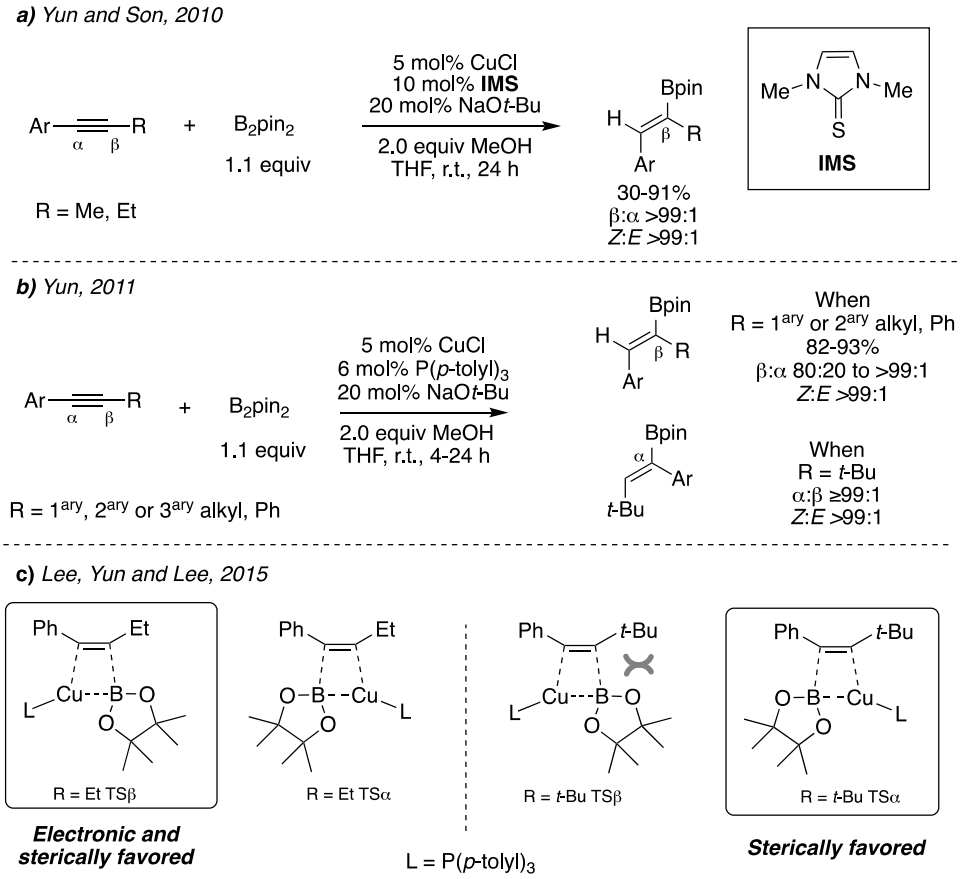
[123] Kim, H. R.; Jung, I. G.; Yoo, K.; Jang, K.; Lee, E. S.; Yun, J.; Son, S. U. *Chem. Commun*. **2010**, *46*, 758-760.
[124] Kim, H. R.; Yun, J. *Chem. Commun*. **2011**, *47*, 2943-2945.



Scheme 62. Regioselective protoboration of internal alkynes and **c)** study of the regioselectivity determining factors.

A DFT study of the effect of the R group of the internal alkynes on the regioselectivity of the process was performed by Lee.[125] For this purpose, they studied different 1-phenyl 2-alkyl acetylene bearing several alkyl substituents, using (*p*-tolyl)$_3$PCuCl as catalyst (Scheme 62c). They found that electronic factors play an important role when R group is smaller than Ph group (R = Et). In this case, higher electrophilicity is observed for C$_\beta$ and the boryl group acts as a nucleophile, preferentially attacking at this carbon. However, when R group is larger than Ph (R = *t*-Bu), the steric hindrance between the R group and the boryl group strongly influences the regioselectivity of the process, the formation of the α isomer being the most favorable pathway. The behavior of other ligands, SIMes and PH$_3$, was also studied by DFT and same regioselectivity preference was observed for Et and *t*-Bu groups, suggesting a low influence of the size of the ligand on the regioselectivity in this case.

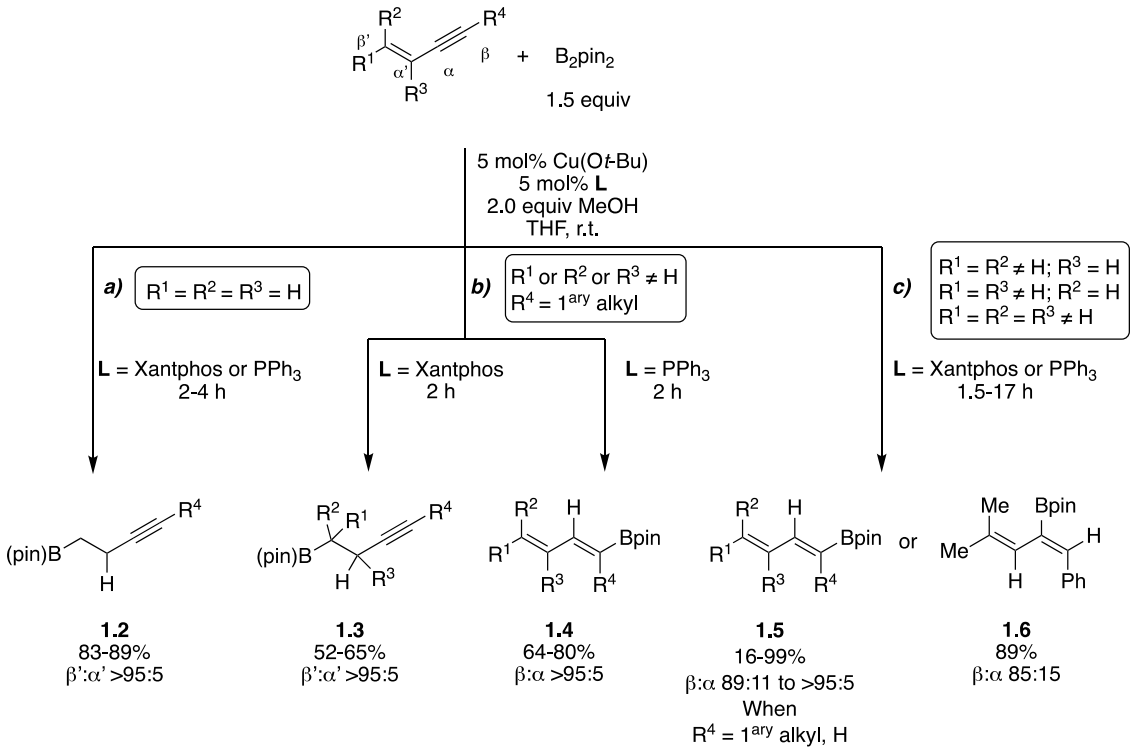
Ito and co-workers reported a copper(I)-catalyzed chemoselective protoboration of internal 1,3-enynes.[126] Although in selected cases the regioselectivity can be modulated by either choosing Xantphos or PPh$_3$ as ligand, the degree of substitution of the alkene moiety plays a crucial role on the control of the chemoselectivity (Scheme 63): When a

[125] Moon, J. H.; Jung, H.-Y.; Lee, Y. J.; Lee, S. W.; Yun, J.; Lee, J. Y. *Organometallics* **2015**, *34*, 2151-2159.

[126] Sasaki, Y.; Horita, Y.; Zhong, C.; Sawamura, M.; Ito, H. *Angew. Chem. Int. Ed*. **2011**, *50*, 2778-2782.

terminal double bond is used (Scheme 63a), protoboration occurs at the alkene group to obtain products **1.2**, regardless the ligand used. The regioselectivity with enynes containing an alkene with substitution at the 1- or 2- position, can be controlled by switching the catalytic system (Scheme 63b). XantphosCuO*t*-Bu selectively provides protoboration of the alkene moiety, leading to products **1.3**, while the selective protoboration of the triple bond can be accomplished by using Ph_3PCuO*t*-Bu as catalyst, products **1.4**. In the case of tri- or tetra-substituted double bonds (Scheme 63c), the protoboration takes place selectively at the alkyne moiety no matter the ligand used (products **1.5** and **1.6**).

Orbital population analysis showed that the alkene moiety has a larger contribution to the LUMO of the molecule, thus, borylcopper complex (HOMO) would add preferentially in this position when there is not significant steric perturbation. However, when steric hindrance around the olefin increases, the addition of the borylcopper complex into the alkyne is favored.

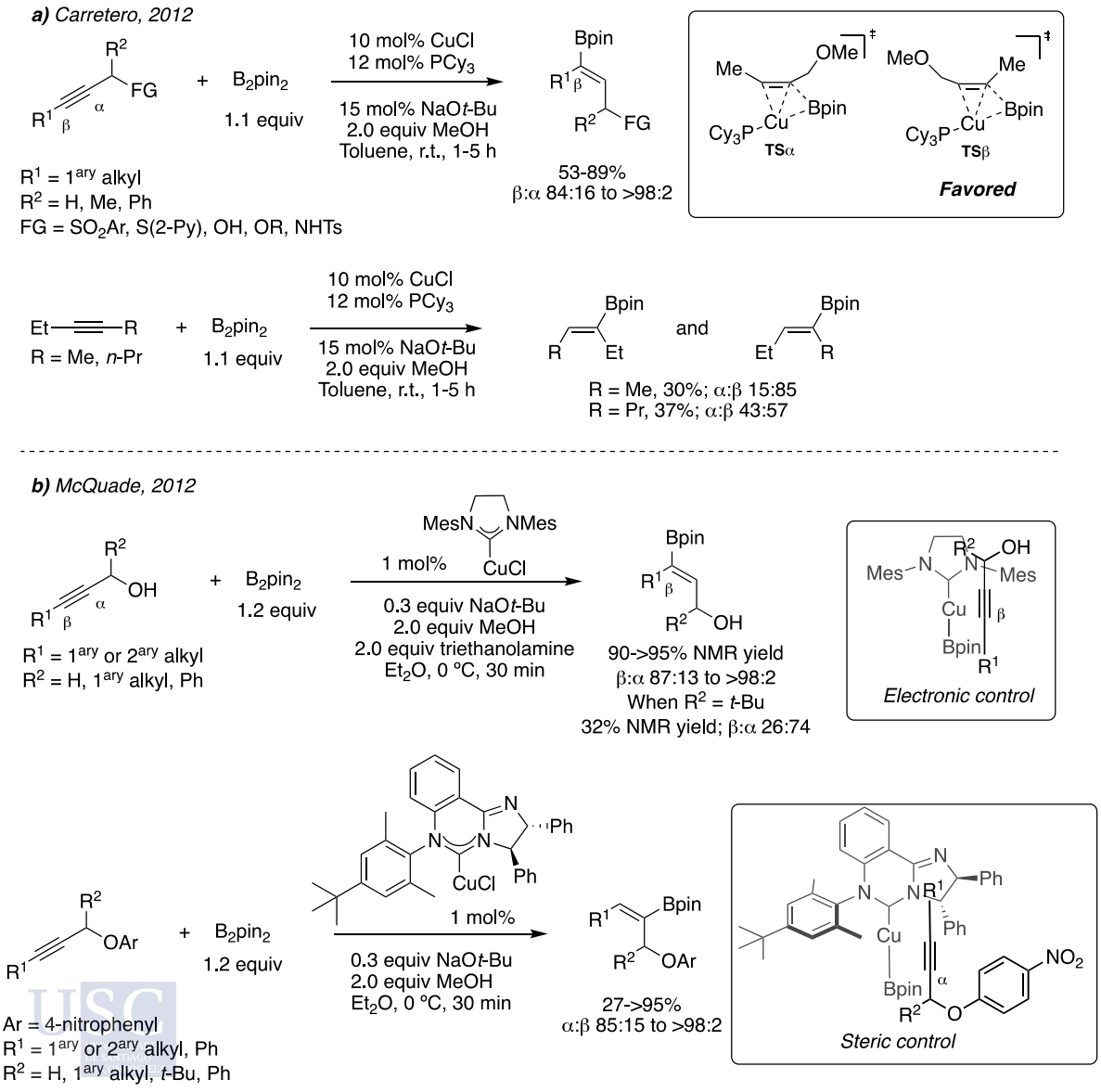


Scheme 63. Copper(I)-catalyzed protoboration of 1,3-enynes.

Dialkyl alkynes are more challenging substrates due to the lack of a strong electronic bias in the alkyne moiety. In 2012, the group of Carretero[127] and the group of McQuade[128] independently reported a regiocontrolled copper-catalyzed borylation of propargylic-functionalized internal dialkyl alkynes (Scheme 64). In the work developed by Carretero, they found that an electron-rich monodentate phosphine as PCy_3 provides selective

[127] Moure, A. L.; Gómez Arrayás, R.; Cárdenas, D. J.; Alonso, I.; Carretero, J. C. *J. Am. Chem. Soc*. **2012**, *134*, 7219-7222.
[128] Park, J. K.; Ondrusek, B. A.; McQuade, D. T. *Org. Lett*. **2012**, *14*, 4790-4793.

borylation at the β position (Scheme 64a). Under these conditions a variety of propargyl alcohol derivatives such as sulfones, ethers and amines or even the free alcohol could be efficiently borylated with high levels of β regioselectivity. The regiocontrol is governed by the subtle electronic bias of the propargylic functional group. In examples where this propargyl functional group is missing, such as 2-pentyne or 3-heptyne, a dramatic decrease of reaction yield and regioselectivity was observed, only the small difference in the size of the two alkyl substituents being the source of regioselectivity. DFT calculations of the activation energies of both transition states for the insertion of the alkyne into the Cu-B bond indicates that the **TSβ** is favored (6.1 kcal mol^{-1} vs 10.6 kcal mol^{-1} for **TSα**), further highlighting that the regioselectivity of this method is controlled by the subtle electronic bias that cause the propargylic functional group of the alkyne.

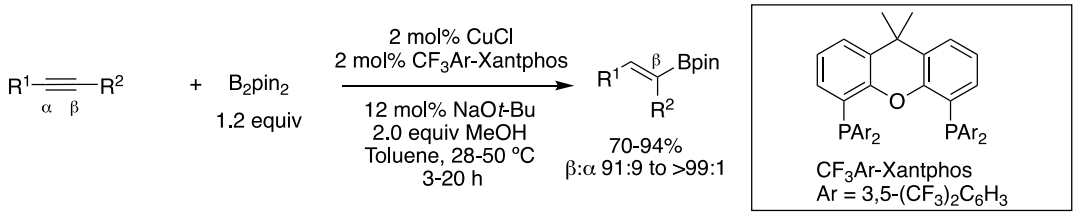


Scheme 64. Copper(I)-catalyzed protoboration of dialkyl alkynes.

A similar regioselectivity outcome was reported by McQuade for the use of SIMesCuCl as catalyst in the copper-catalyzed borylation of free propargylic alcohols

(Scheme 64b). In this case, they also proposed an electronic control. The use of a more sterically demanding substitution in the propargylic position (R^2 = *t*-Bu) provides α selectivity, likely due do the steric repulsion between the *t*-Bu group and the ligand. In the same way, with the use of a bulky protecting group (Ar = 4-nitrophenyl) and a more sterically demanding NHC-Cu catalyst, selectivity is dominated by steric effects providing the borylation at the α position. In this case steric interaction between these two bulky systems favors borylcupration in such a way that the copper atom lies far from the nitrophenyl group.

The regioselectivity of the copper-catalyzed borylation of internal alkynes can be also controlled on the basis of the nature of the boron source. It was mentioned in section 1.1.2.1 (chapter I) that Tsuji and co-workers reported a copper-catalyzed α-selective protoboration of internal alkynes with pinacolborane (see Scheme 13 and ref. 24b). In the mentioned work, they were able to change the regioselectivity of the process by using B_2pin_2 instead of HBpin. The use of B_2pin_2 generates a Cu-Bpin complex instead of a Cu-H. Thus, in the first case the Bpin is installed in in the insertion step, in contrast to the Cu-H catalysis where the Bpin is installed in the last step of the reaction, i.e. the electrophilic trapping of the alkenylcopper intermediate. This methodology, based on the use of CF_3Ar-Xantphos/CuCl, provides a wide functional group tolerance, amide, amine, ester, aromatic and heteroaromatic functionalities were well tolerated providing excellent yield and β regioselectivity (Scheme 65).



R^1 = Ar, CH_2FG, ester, amide, alkenyl
R^2 = 1^{ary} or 2^{ary} alkyl

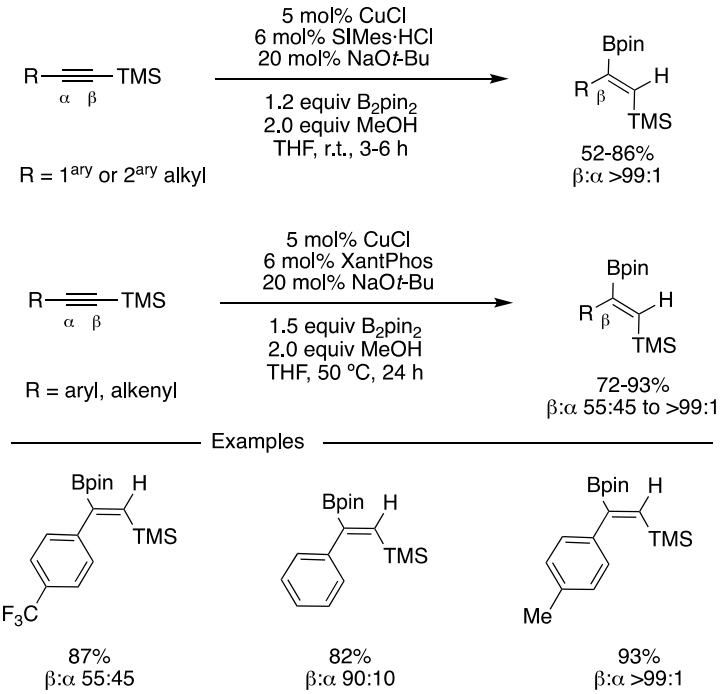
Scheme 65. Cu(I)-catalyzed protoboration of internal alkynes with CF_3Ar-Xantphos.

A similar control over the regioselectivity of this transformation was reported by Cazin and co-workers who described a more environmentally friendly and air tolerant α and β borylation of internal alkynes.[24c] In this case, IMesCuCl turned out to be an efficient catalyst for both transformations which could be run with a less expensive base (NaOH) and in a greener solvent (CPME).

Protoboration of internal silyl-substituted alkynes was studied by the group of Lee and Yun.[129] The products of this reaction, (β-borylalkenyl)silanes are very versatile and useful building blocks due to its orthogonal reactivity (Scheme 66). β-Borylation of alkyl-substituted silylated alkynes could also be achieved with the of SIMes·HCl as ligand. DFT calculations revealed that C_β has a larger contribution to the LUMO of the alkyne, thus, Bpin would be transferred to this carbon atom preferentially. This means that regioselectivity operates under electronic control. Silylated alkynes with electron-

[129] Chae, Y. M.; Bae, J. S.; Moon, J. H.; Lee J. Y.; Yun, J. *Adv. Synth. Catal.* **2014**, *356*, 843-849.

withdrawing aryl substituents led to a decrease on the regioselectivity due to a competing electronic effect between electron poor aryl group and the silicon group.



Scheme 66. Copper-catalyzed protoboration of internal silyl-substituted alkynes.

Yoshida *et al.* investigated the use of an unsymmetrical diboron compound, pinB-Bdan, in the protoboration of internal alkynes to synthetize alkenyl-Bdan compounds (Scheme 67).[130] α and β selectivity were achieved, respectively, with the use of SIPrCuCl or $Cu(PPh_3)_3$ in the protoboration of 1-phenyl-1-propyne. α-Selectivity with SIPrCuCl is proposed to be obtain as a result of steric repulsion between the bulky copper complex and the phenyl group. It is proposed that the use of a less sterically demanding copper complex, such as $(Ph_3P)_3CuCl$, would lead to diminished steric repulsion, thus, the selectivity would be governed by electronic factors. The electronic directing effect of the phenyl group lead the addition of the copper in the α position.

The $(Ph_3P)_3CuCl$-catalyzed protoboration of internal alkynes could be extended to other alkyl(aryl)alkynes, which provided good results in terms of yield and regioselectivity. However, the use of unsymmetrical internal dialkyl or diaryl alkynes led to a low control of the regioselectivity.

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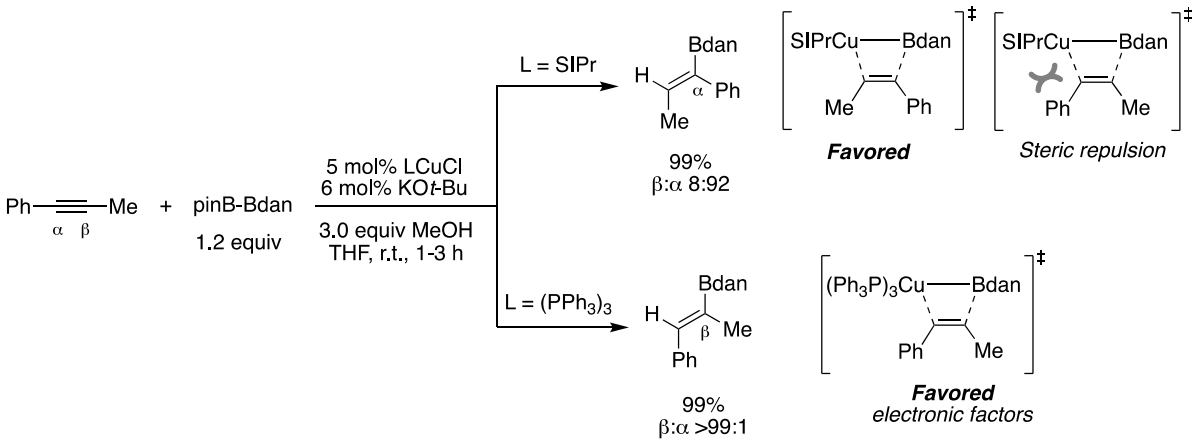
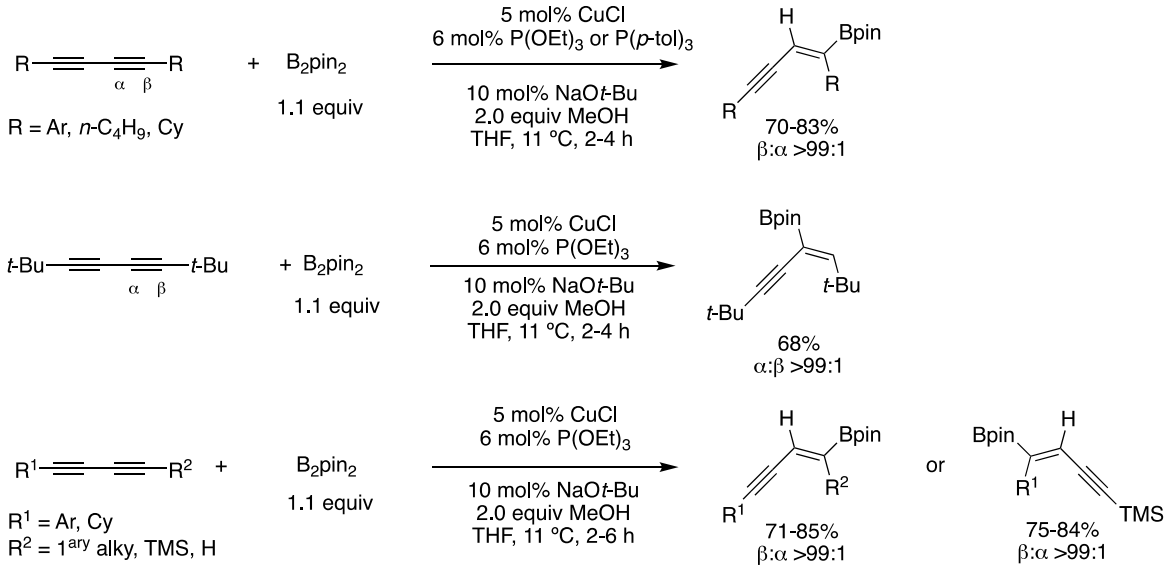
[130] Yoshida, H.; Takemoto, Y.; Takaki, K. *Asian J. Org. Chem*. **2014**, *3*, 1204-1209.



Scheme 67. Copper(I)-catalyzed protoboration of internal alkynes with unsymmetrical Bpin-Bdan.

The group of Yun also reported the copper-catalyzed protoboration of conjugated diynes to afford boron-substituted enynes (Scheme 68).[131] Classical hydrometalation reactions are reported to provide the metalation at the internal positions of the enyne.[132] In this case, the use of CuCl in combination with $P(OEt)_3$ or $P(p\text{-tolyl})_3$ drove the borylation selectivity towards the external position. Symmetrical diaryl and primary and secondary alkyl diynes were well tolerated.



Scheme 68. Cu(I)-catalyzed monoborylation of diynes.

The use of a bulkier substituent, *t*-Bu, provide the borylation at the internal position due to the steric repulsion between the *t*-Bu and the Bpin groups. Unsymmetrical substituted diynes with an aryl and an alkyl substitution led to the external borylation

[131] Li, D.; Kim, Y. E.; Yun, J. *Org. Lett*. **2015**, *17*, 860-863.

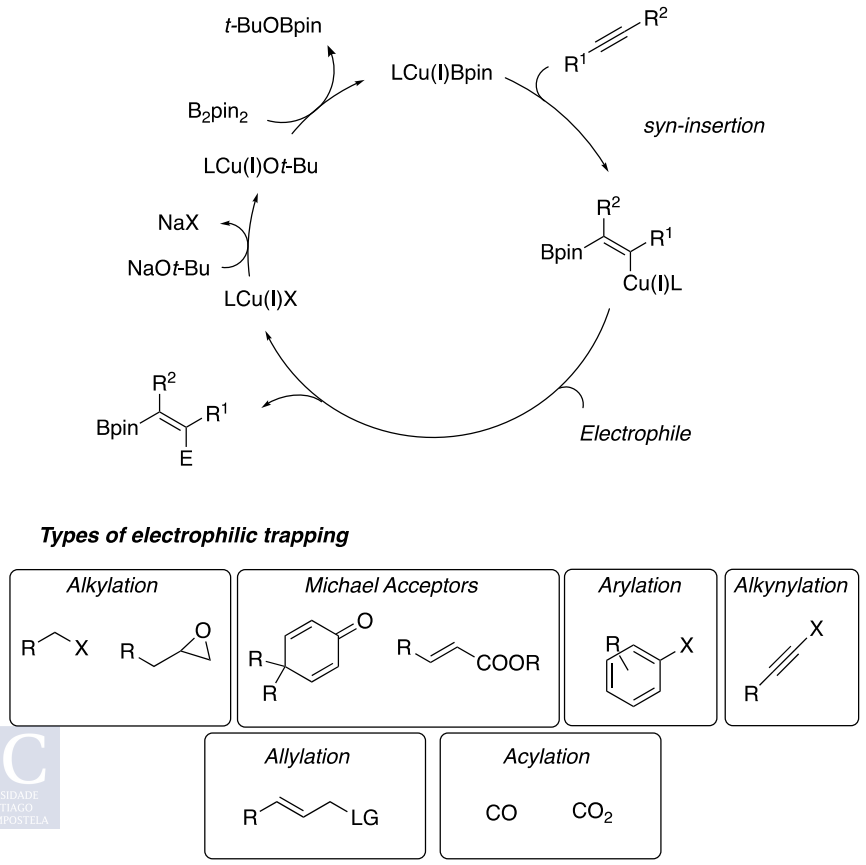
[132] (a) Zweifel, G.; Polston, N. L. *J. Am. Chem. Soc*. **1970**, *92*, 4068-4071. (b) Alonso, F.; Buitrago, R.; Moglie, Y.; Sepúlveda-Escribano, A.; Yus, M. *Organometallics* **2012**, *31*, 2336-2342. (c) Zhang, H. X.; Guibé, F.; Balavoine, G. *J. Org. Chem*. **1990**, *55*, 1857-1867.

close to the alkyl group. In the case of silyl-substituted diynes, the borylation takes place at the external carbon positioned away from the silyl group.

2.2. COPPER(I)-CATALYZED CARBOBORATION OF ALKYNES WITH DIBORON COMPOUNDS

The trapping of the β-boryl alkenylcopper intermediate with a carbon electrophile instead of a proton leads to a formal alkyne carboboration reaction in which a new C-B and C-C bond are established in a single operation. These multicomponent reactions are a powerful methodology to access tri- and tetrasubstituted alkenylboronates.

The general mechanism for a carboboration reaction is shown in Scheme 69. Initially, copper halide species are transformed to the catalytically active LCuO*t*-Bu. The B_2pin_2 reacts with this complex via σ-bond metathesis to obtain the LCu-Bpin complex. Regio- and stereoselective insertion of the alkyne into the Cu-Bpin bond leads to the formation of the nucleophilic β-boryl alkenylcopper complex, which reacts with the carbon electrophile to form the alkenyl boronate with concomitant regeneration of the catalyst. The type of reaction that occurs in this last step mainly depends on the nature of the electrophile.



Scheme 69. General mechanism for the copper-catalyzed carboboration of alkynes.

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Besides control over the stereo- and regioselectivity, there are extra challenges associated with these transformations in comparison with the protoboration reaction: 1) competitive borylation of the carbon electrophile must be avoided and 2), protonation of the organocopper intermediate must be precluded (especially when terminal alkynes are used). Unlike protoboration reactions, stoichiometric amount of base (generally sodium or potassium *tert*-butoxide) is usually needed in carboboration reactions to regenerate the catalyst since an inactive CuX species is generated in the electrophilic trapping. LCuOR has to be generated in the catalytic cycle to undergo σ-bond metathesis with bis(pinacolato)diboron to obtain the active catalytic species LCuBpin.

2.2.1. Copper-catalyzed alkylboration of alkynes

Tortosa *et al.* reported the first copper-catalyzed *syn* alkylboration of simple alkynes. (Scheme 70a).[133] This method, which comprises the use of Xantphos/CuCl as catalyst, 1.1 equiv of NaO*t*-Bu and methyl iodide as the electrophile, provided complete levels of regio- and stereoselectivity towards the formation of the β-alkenylboronates. A big excess of methyl iodide (4.0 equiv) is needed in order to avoid the formation of the protoboration product. Terminal arylalkynes and terminal alkynes bearing an ether moiety in the propargylic position react at room temperature in THF under these conditions providing a single product. However, unactivated terminal alkyl alkynes did not afford the reaction. P(*p*-tolyl)$_3$ improved the reaction with internal alkynes, which also require to increase the temperature to 60 ºC in toluene.

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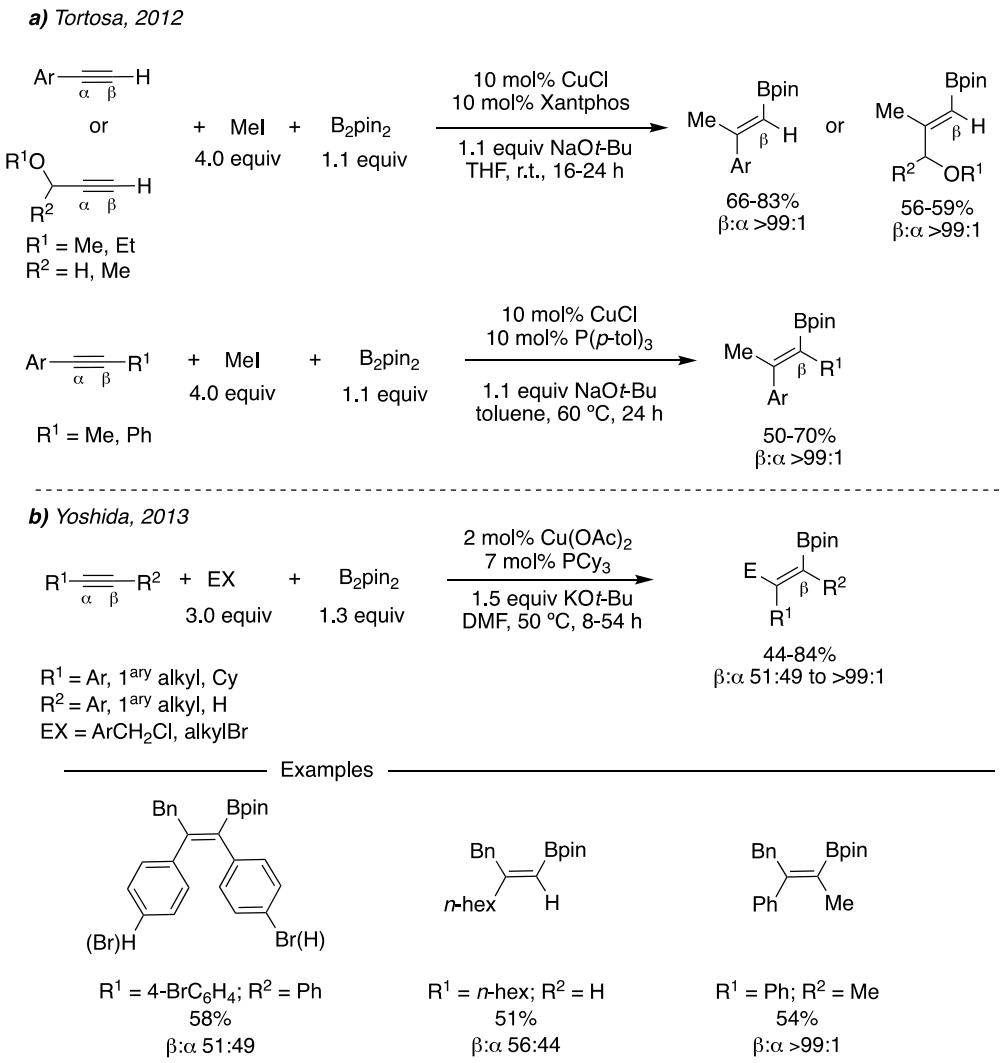
[133] Alfaro, R.; Parra, A.; Alemán, J.; García Ruano, J. L.; Tortosa, M. *J. Am. Chem. Soc*. **2012**, *134*, 15165-15168.



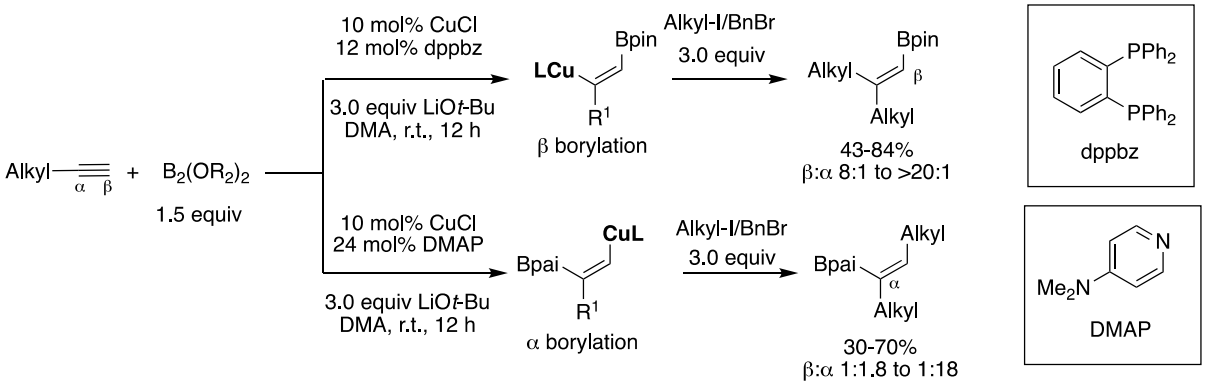
Scheme 70. Early examples of copper catalyzed alkylboration of alkynes.

A year later, Yoshida *et al.* reported an alkylboration of alkynes with benzyl chlorides catalyzed by a $CuPCy_3$ system in DMF (Scheme 70b).[134] This approach allows the benzylboration of alkyl(aryl)alkynes and phenylacetylene in a regioselective manner (β:α >99:1). However, nearly equimolar mixtures of α and β borylated isomers were obtained when unsymmetrical diaryl alkynes and terminal alkyl alkynes were used.

As mentioned for the protoboration reaction, control of the regioselectivity in the carboboration depends on several factors. In the aforementioned alkylboration protocols, regioselectivity control was mainly dictated by an electronic bias of the aryl alkyne substituents. The use of alkyl alkynes adds an additional challenge since there is not a strong electronic bias. In this context, Fu *et al.* reported a regiodivergent alkylboration of terminal alkyl alkynes (Scheme 71).[135] They found that the use of bisphosphine ligands (such as dppbz) promotes selective β borylation. Interestingly, the use of nitrogenated ligands (such as DMAP) switches the regioselectivity in favor of the α borylation product.

[134] Yoshida, H.; Kageyuki, I.; Takaki, K. *Org. Lett*. **2013**, *15*, 952-955.
[135] Su, W.; Gong, T.-J.; Zhang, Q.; Zhang, Q.; Xiao, B.; Fu, Y. *ACS Catal*. **2016**, *6*, 6417-6421.

Furthermore, α selectivity can be improved with the use of B_2pai_2 as boron source instead of B_2pin_2. Secondary alkyl electrophiles provided sluggish reactions.



Scheme 71. Regiodivergent carboboration of unactivated alkyl alkynes.

Alkylboration of dialkylalkynes is more challenging than diarylakynes due to the lower reactivity of the former. Due to this lack of reactivity, borylation of the alkyl halide results in a major competitive reaction. Alkylboration of dialkylalkynes was accomplished by Kanai and co-workers in 2016 (Scheme 72).[136] Common ligands for other alkyne carboboration reactions (dppbz, Xantphos, or IMesCuCl) failed in this transformation and mainly provided the borylation of the alkyl halide. This chemoselectivity issue was overcome with the use of a strong π accepting ligand such as ^{NQ}IMes in which the π accepting ability is enhanced by conjugation of the *N*-heterocyclic carbene with the π-system of the electron-withdrawing quinone. Authors hypothesized that the π accepting NHC-Cu catalyst would have more affinity towards the π electrons of the alkyne (through a π donation from the alkyne to the copper center; see ref. 116) thus favoring the reaction of the copper complex with the alkynes instead with the alkyl halide. Under these conditions, a variety of trialkylsubstituted alkenyl boronates were obtained in good yields. However, the control of the regioselectivity is very difficult with these substrates due to the lack of electronic bias and similar steric environments of both alkyl substituents of the alkyne, providing in some cases low regioisomeric ratio. The use of propargylic functional groups or increasing the steric hindrance of the substituents of the alkynes led to an increase in the β:α ratio. Functional groups such as amide, amines, esters or ethers were well tolerated. Primary alkyl iodides, together with benzyl bromide and ethyl bromoacetate were efficient electrophiles for this transformation. However, secondary alkyl iodides were unreactive.

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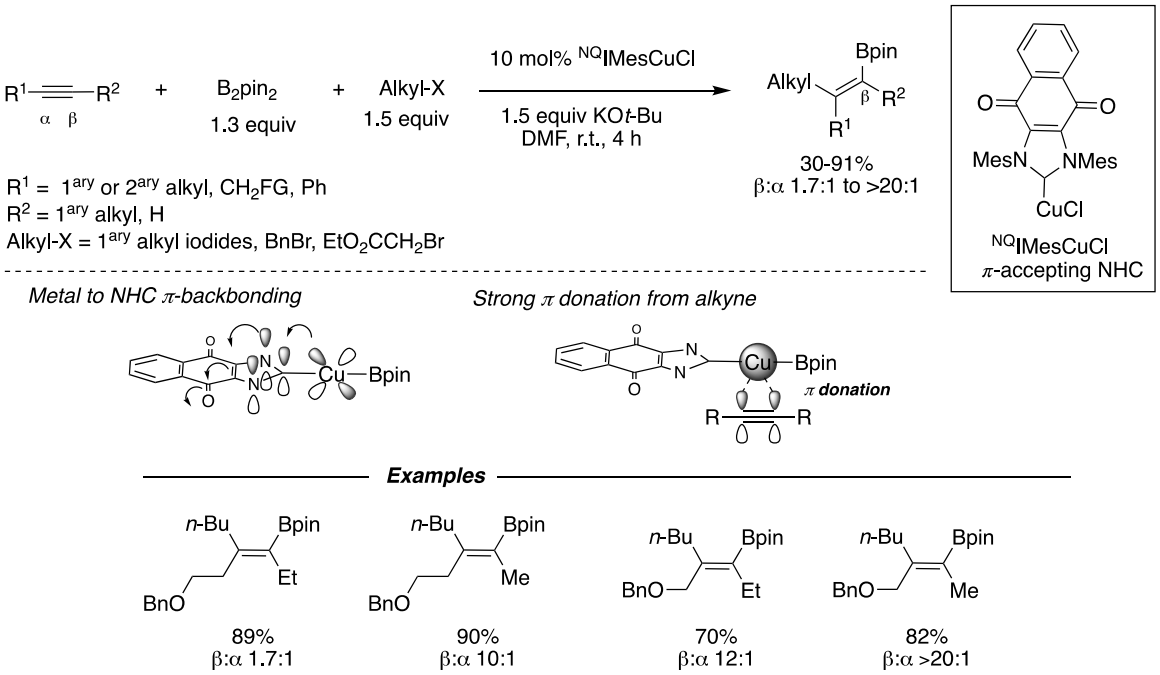
[136] Itoh, T.; Shimizu, Y.; Kanai, M. *J. Am. Chem. Soc*. **2016**, *138*, 7528-7531.



Scheme 72. NQIMesCuCl catalyzed alkylboraton of alkynes.

As mentioned above, secondary alkyl halides have been traditionally poorly efficient substrates in alkylboration reactions. Recently, Carretero *et al.* have reported a novel dynamic multiligand copper-catalyzed alkylboration of alkynes, based on a polar to radical crossover strategy, that allows the use of secondary alkyl iodides and bromides (Scheme 73).[137] Moreover, this reaction has a very broad scope of alkynes (mainly relying on alkyl(aryl)alkynes) and provides the corresponding tri- or tetra-substituted alkenylbornates in good yields and with excellent regioselectivity in nearly all cases. The proposed mechanism for this transformation consists in a phosphine-Cu(I) catalyzed regio- and stereoselective borylcupration of the alkyne. Then, a ligand exchange occurs to give the phenanthroline-Cu alkenyl complex, which enables the oxidation of Cu(I) to Cu(II) by halogen atom transfer to generate the alkyl radical. The free radical collapses with the Cu(II) complex to afford the tetrasubstituted alkenyl boronate and the Cu(phenanthroline)X complex. This complex then undergoes ligand exchange with the phosphine ligand to restart the catalytic cycle.

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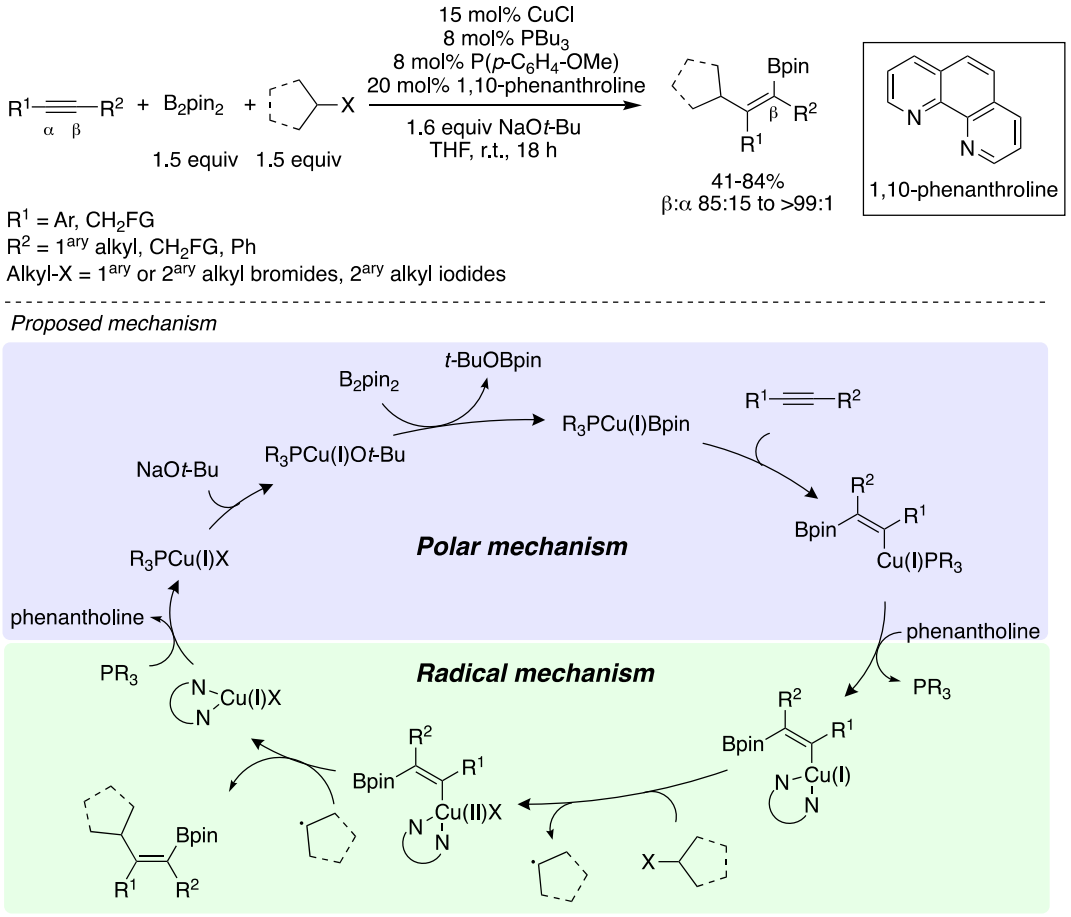
[137] Kim-Lee, S.-H.; Mauleón, P.; Gómez Arrayás, R.; Carretero, J. C. *Chem* **2021**, *7*, 2212-2226.



Scheme 73. Dynamic multiligand copper-catalyzed alkylboration of alkynes.

Alkylboration of alkynes for the synthesis of cyclic structures trough intramolecular cyclization has been also explored. Ito *et al.* reported a copper-catalyzed alkylboration of silicon-tethered internal alkynes bearing an alkyl bromide (Scheme 74a).[138] As it was already mentioned,[139] the presence of silicon atom establishes an electronic bias in which a partial positive charge is stabilized at the β carbon. Due to this effect, high regioselectivity can be achieved in borylcupration of silyl-substituted alkynes. Thus, by using IMesCuCl as catalyst several silicon-heterocycles could be obtained in very good yields and with perfect level of regio- and stereoselectivity.

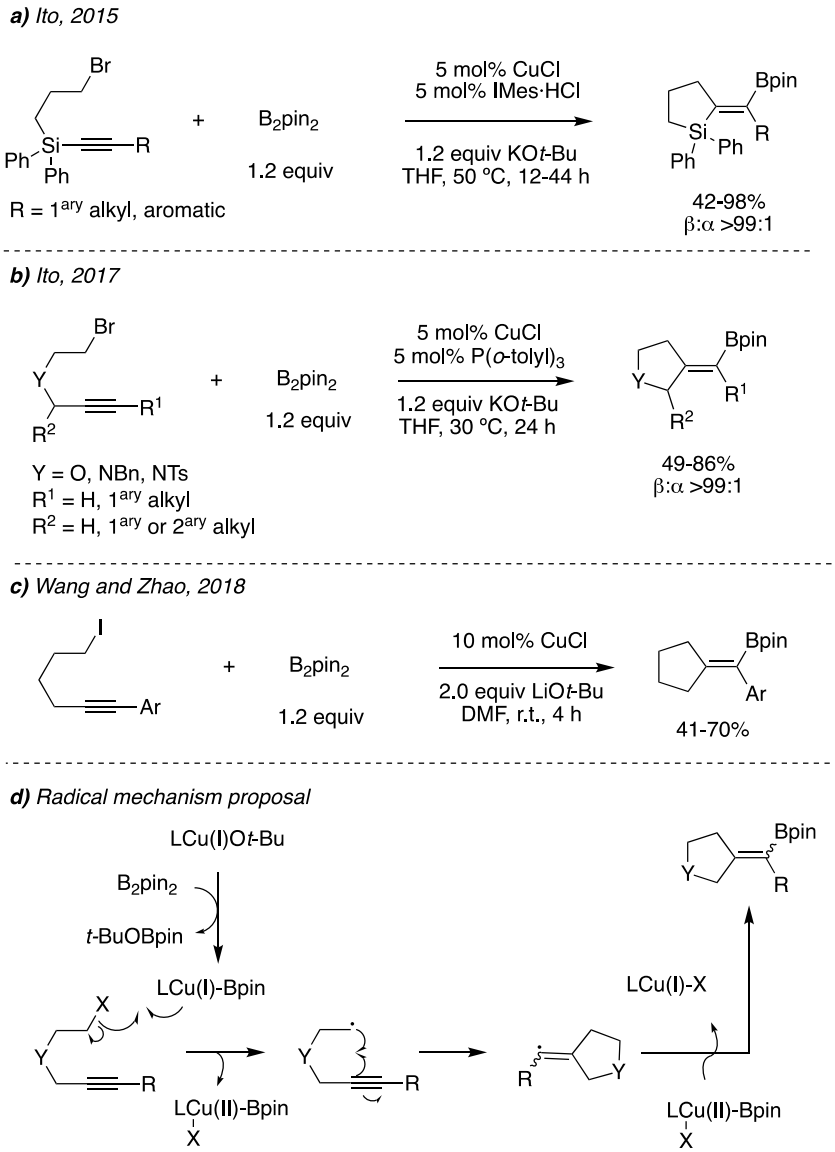
In addition to silyl-substituted alkynes, Ito described an intramolecular alkylboration of propargylic ethers and amines bearing an alkyl bromide, which provides access to densely functionalized *O*- and *N*-heterocycles (Scheme 74b).[140] In this case, the use of P(*o*-tolyl)$_3$ as ligand was necessary to obtain the products in moderate to good yields with complete levels of regio- and stereoselectivity. The mechanism proposed for this transformation consists in the initial insertion of the alkyne into the borylcopper complex followed by intramolecular substitution of the bromide. When R^1 is a bulky group

[138] Kubota, K.; Iwamoto, H.; Yamamoto, E.; Ito, H. *Org. Lett*. **2015**, *17*, 620-623.

[139] For a detailed study of the electronic effect of the silyl substituent see section 2.1.2 (chapter I), Scheme 66, ref. 129.

[140] Iwamoto, H.; Ozawa, Y.; Kubota, K.; Ito, H. *J. Org. Chem*. **2017**, *82,* 10563-10573.

(isopropyl or *tert*-butyl), mixture of *E*/*Z* isomers are obtained. Based on this fact, the authors proposed a radical mechanism in the cases when a bulky group hinders insertion of the alkyne into the boryl-copper complex (Scheme 74d). According to their proposed mechanism, Cu(I)-Bpin complex is oxidized to Cu(II)Bpin by single electron transfer generating an alkyl radical. The alkyl radical undergoes radical cyclization to obtain a more stable alkenyl radical, which can easily isomerize to obtain *E:Z* mixtures. This radical reacts with Cu(II) complex to afford the products and to regenerate the Cu(I) active catalyst.



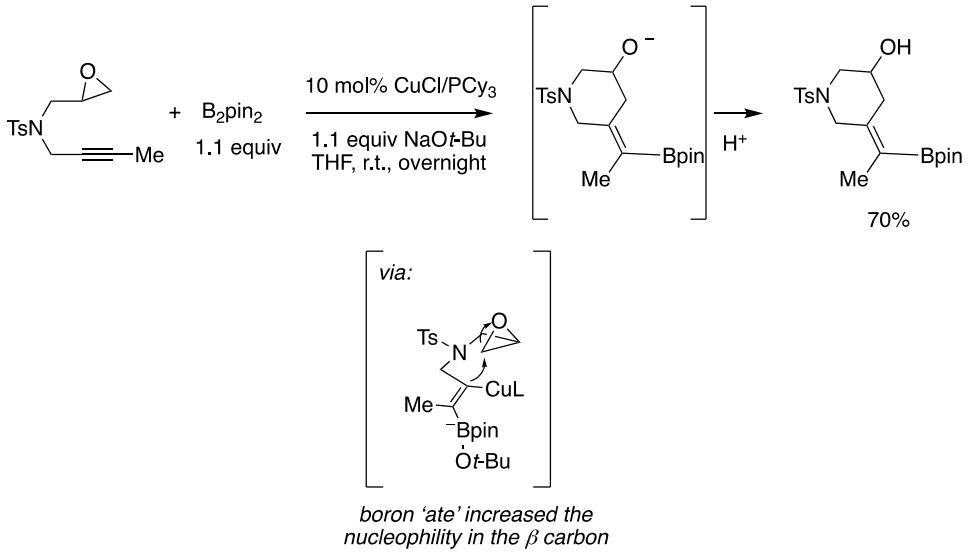
Scheme 74. Copper-catalyzed intramolecular alkylboration of alkynes.

A similar mechanism was proposed for the copper(I)-catalyzed intramolecular alkylboration of alkyl(aryl)alkynes bearing a pendant aliphatic alkyl iodide (Scheme 74c).[141] Interestingly, this reaction proceeds in the absence of ligand, no formation of the product was observed in the presence of a phosphine ligand. Radical trapping experiments

[141] Zhou, S.; Yuan, F.; Guo, M.; Wang, G.; Tang, X.; Zhao, W. *Org. Lett*. **2018**, *20*, 6710-6714.

showed complete inhibition of the reaction in the presence of TEMPO, thus suggesting radical mechanism similar to the one proposed by Ito.

In 2018, within a mechanistic study of the copper-catalyzed carboboration of alkynes, Carretero *et al.* reported a reaction involving alkyne borylcupration and subsequent intramolecular epoxide ring opening (Scheme 75).[142] The use of CuCl/PCy_3 as catalyst, allowed to efficiently convert a propargyl amine bearing an epoxide into the corresponding piperidine. Interestingly, the authors observed that a stoichiometric amount of NaO*t*-Bu is required despite a copper-alkoxide is formed after the electrophilic trapping. Moreover, the isolated β-borylalkenylcopper intermediate does not undergo nucleophilic attack to the epoxide unless an extra equivalent of external sodium *tert*-butoxide is added. Based on these experiments, ^{11}B NMR analysis and DFT calculations the authors proposed a boron 'ate' complex as the active nucleophilic intermediate.



Scheme 75. Copper(I)-catalyzed carboboration of alkynes involving intramolecular epoxide ring opening.

2.2.2. Copper-catalyzed alkyne carboboration involving conjugate-additions

Unsaturated carbonyl compounds have also been used as electrophilic agents to intramolecularly trap catalytically generated alkenylcopper intermediates. Lin and co-workers reported in 2013 a copper(I)-catalyzed asymmetric borylative cyclization of cyclohexadienone-containing 1,6-enynes to afford enantioenriched *cis*-hydrobenzofuran frameworks in moderate yields and good regio- and enantioselectivity (Scheme 76).[143] They proposed that the regioselective β borylation is achieved by coordination of the copper with the propargylic oxygen which directs alkyne insertion. The resulting

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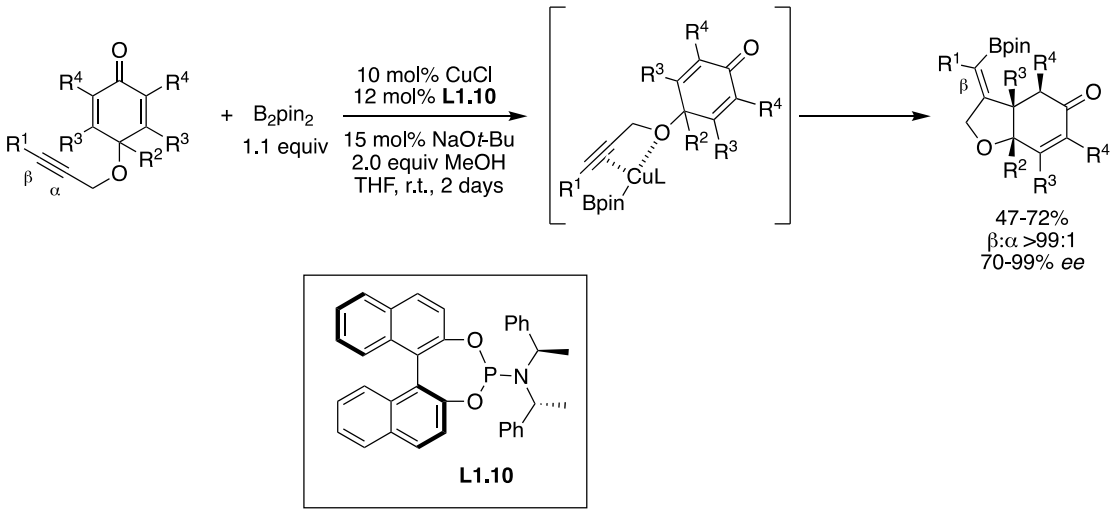
[142] Kim-Lee, S.-H.; Alonso, I.; Mauleón, P.; Gómez Arrayás R.; Carretero, J. C. *ACS Catal*. **2018**, *8*, 8993-9005.

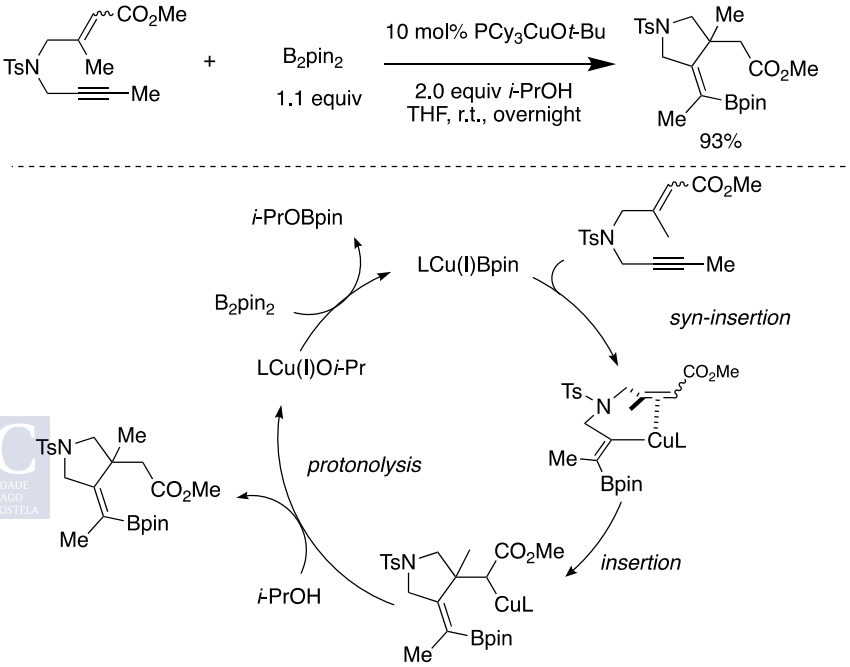
[143] Liu, P.; Fukui, Y.; Tian, P.; He, Z.-T.; Sun, C.-Y.; Wu, N.-Y.; Lin, G.-Q. *J. Am. Chem. Soc*. **2013**, *135*, 11700-11703.

alkenylcopper intermediate undergoes an asymmetric conjugated addition to the enone. Phosphoramidite ligand **L1.10** provided the best results.



Scheme 76. Asymmetric borylative cyclization.

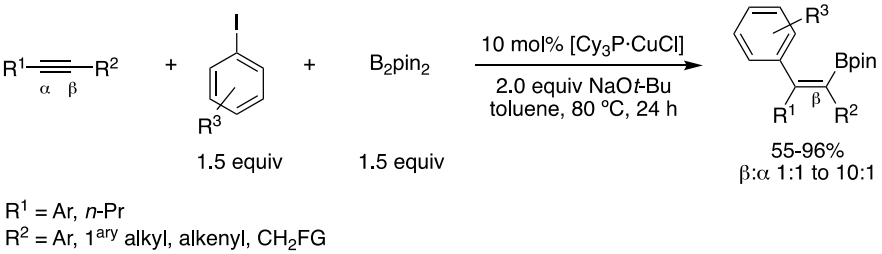
Carretero *et al.* also reported a methodology for the borylative annulation of propargylic amines bearing an β-substituted methyl acrylate moiety (Scheme 77). In contrast with the epoxide trapping (described in previous section), this reaction can operate with catalytic amount of base.[142] In this case, after the formation of the β-boryl alkenylcopper species, the copper atom coordinates to the alkene followed by migratory insertion across the β,β-disubstituted olefin, instead of a S_N2 type reaction. Then, protonation with *iso*-propyl alcohol takes places to generate the product and to regenerate the LCuOR. Due to the different mechanistic differences, in this case, the formation of the boron 'ate' complex is not needed, thus, catalytic amount of base is enough.



Scheme 77. Copper(I)-catalyzed borylative annulation.

2.2.3. Copper-catalyzed aryl- and alkynylboration of alkynes

Carboboration reactions involving $C(sp^2)$-$C(sp^2)$ bond formation have also been reported. Brown *et al.* described a copper-catalyzed arylboration of alkynes with aryl iodides obtaining tetrasubstituted vinyl boronates in moderate to good yields (Scheme 78).[144] Indeed, they found that *in situ* generated β-boryl alkenylcopper reagents can undergo cross-coupling reaction with aryl iodides although high temperature is required due to the low reactivity of the organocopper intermediate. Consequently, only moderate regioselectivity was observed with alkyl(aryl)alkynes and low regioselectivity with the use of unsymmetrical diarylalkynes. Moreover, the efficiency of the reaction was lower with the use of dialkylalkynes.



Scheme 78. Copper(I)-catalyzed arylboration of alkynes.

To overcome this limitation regarding the low reactivity of alkenylcopper reagents under these conditions, the use of bimetallic catalysis emerged as a tool to improve the efficiency and versatility of this reaction. This is discussed in Chapter II, section 1.3.

Copper-catalyzed alkynylborylation of terminal and internal alkynes has also been reported. This approach represents a valuable manner to synthesize boron-containing fully substituted enynes. In 2018, Yu reported the first example of coupling of a vinyl copper species and C(sp) based electrophiles (Scheme 79a).[145] They described that IMesCuCl selectively catalyzes the reaction between internal alkynes, B_2pin_2 and silylated alkynyl bromides as electrophiles. Shortly after, Gong and Fu, developed a similar methodology for the use of terminal alkynes (Scheme 79b).[146]

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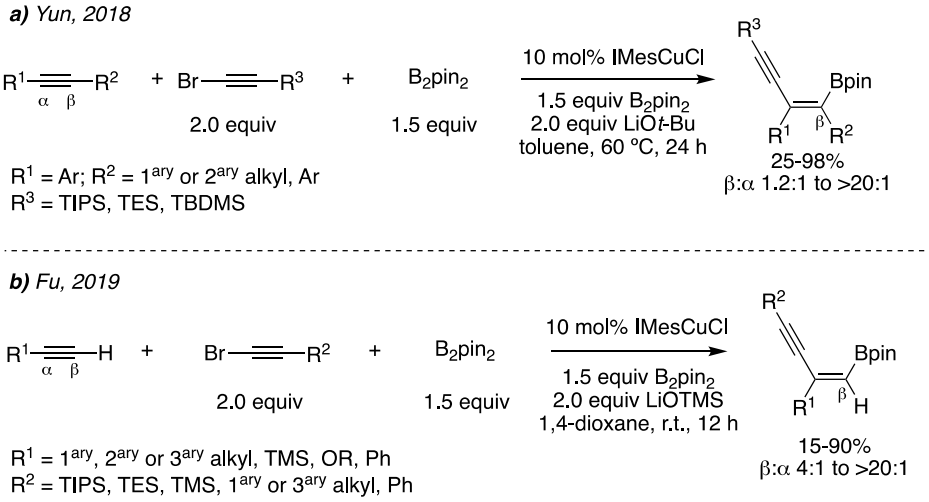
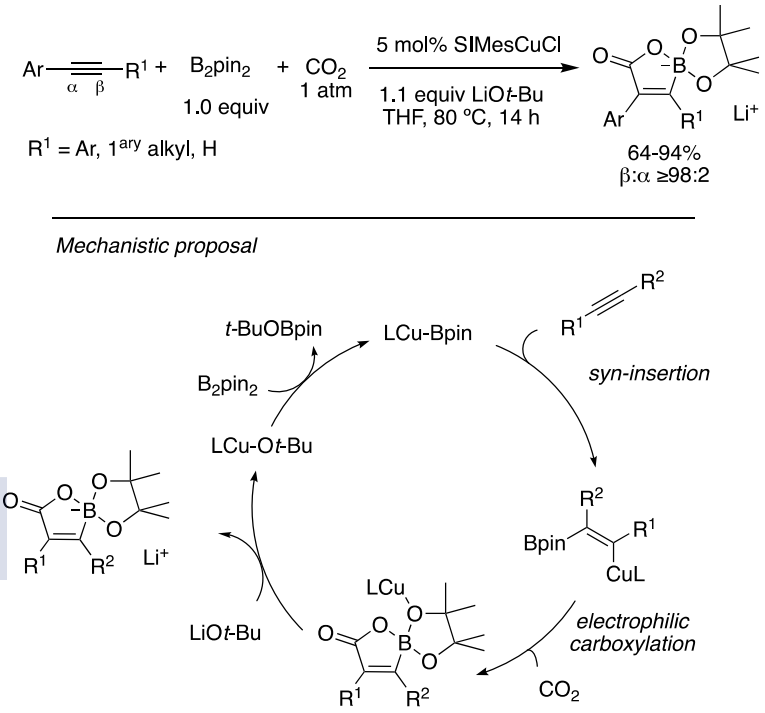
[144] Zhou, Y.; You, W.; Smith, K. B.; Brown, M. K. *Angew. Chem. Int. Ed*. **2014**, *53*, 3475-3479.
[145] Han, J. T.; Yun, J. *Org. Lett*. **2018**, *20*, 2104-2107.
[146] Li, K.; Yu, S.-H.; Zhuo, K.-F.; Lu, X.; Xiao, B.; Gong, T.-J.; Fu, Y. *Adv. Synth. Catal*. **2019**, *361*, 3937-3942.



Scheme 79. Copper(I)-catalyzed alkynylboration of alkynes.

2.2.4. Copper-catalyzed acylboration of alkynes

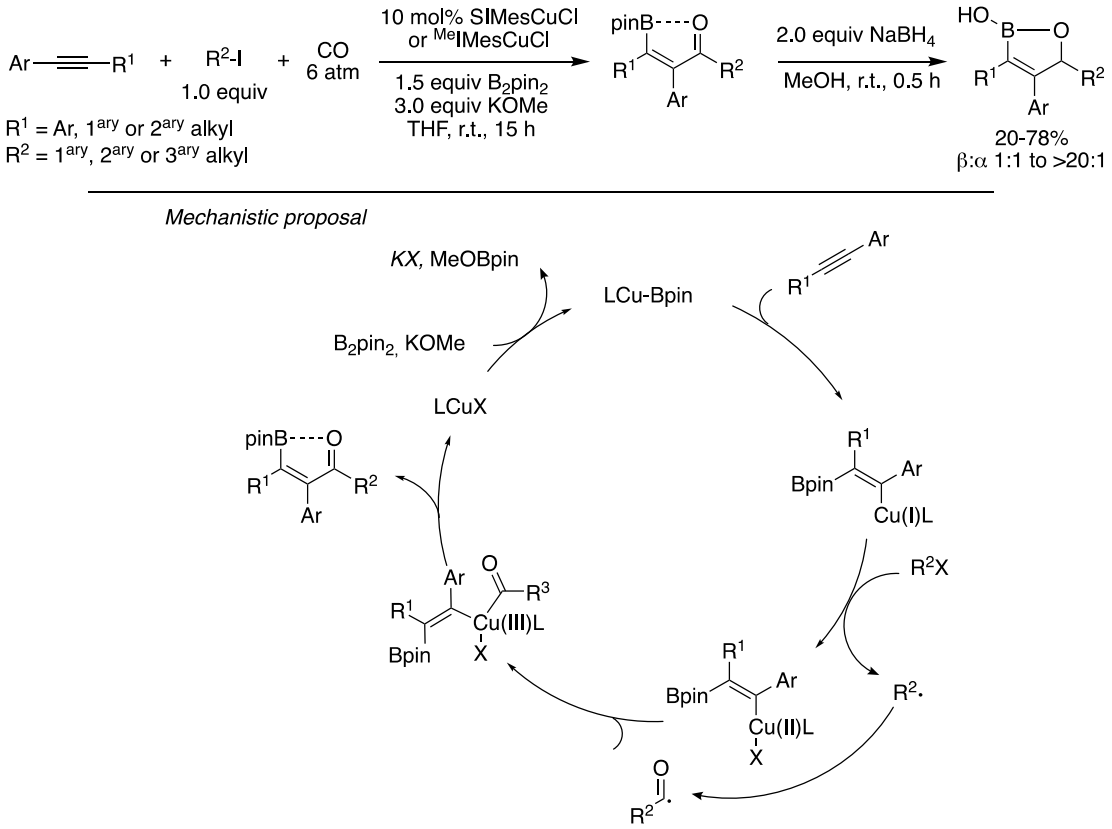
Copper(I)-catalyzed boracarboxylation of alkynes was accomplished by the group of Hou (Scheme 80).[114] The methodology was based on the use of SIMesCuCl and provided good results with diaryl alkynes, 1-phenyl-1-propyne, 1-phenyl-1-butyne and phenylacetylene with complete levels of regioselectivity. Mechanistic studies revealed that, after formation of the β-boryl alkenylcopper complex through *syn*-insertion of the alkyne into Cu-B bond, nucleophilic addition of the alkenylcopper to the CO_2 would render the formation of a β-boralactone with the copper complex coordinated to one of the oxygens of the Bpin. Transmetalation between the copper complex and LiO*t*-Bu would generate the product and regenerate the SIMesCuO*t*-Bu.



Scheme 80. Copper-catalyzed boracarboxylation of alkynes.

Few years later, a copper-catalyzed boracarbonylation of alkynes using CO as a C1 source was reported by the group of Mankad (Scheme 81).[147] This methodology affords tetrasubstituted α,β-unsaturated β-boryl ketones and represents the first tetracomponent reaction involving the formation of two C-C and a C-B bonds in a single step. Since the reaction products are not stable in silica gel, reduction to the oxaborole was necessary to isolate the products in good yield. Although the reaction resulted to be efficient with diaryl and alkyl aryl substituted alkynes, it fails with dialkyl alkynes, which were unreactive under these conditions, or terminal alkynes, which provide full conversion however, formation of product was not detected.

The mechanism of this reaction consists in the *syn* borocupration of the alkyne. Then, the reaction between the alkenylcopper and the alkyl halide generates the alkyl radical and the Cu(II). The alkyl radical undergoes carbonylation to give an acyl radical that collapses with the copper complex, to generate a Cu(III) intermediate. The Cu(III) intermediate undergoes reductive elimination to afford the final product.



Scheme 81. Copper(I)-catalyzed tetracomponent reaction.

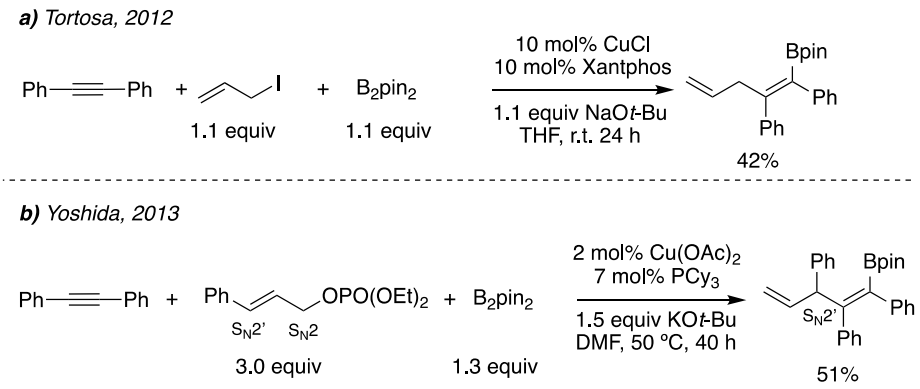
2.2.5. Copper-catalyzed allylboration of alkynes

Preliminary results on alkyne allyboration substrates with simple allylic substrates was reported by Tortosa[133] in her work of alkylboration of alkynes (Scheme 82a).

The use of more complex 1,3-disubstituted allyl phosphates leads to the generation of another point of selectivity, since the allylic substitution can occur either in S_N2 or

[147] Cheng, L.-J.; Mankad, N. P. *Angew. Chem. Int. Ed*. **2018**, *57*, 10328-10332.

S_N2' position to the leaving group. A single example was reported in the work of Yoshida[134] (Scheme 82b) which shows perfect S_N2' selectivity in the Cu/PCy_3 catalyzed allylboration of diphenylacetylene with cinnamyl phosphate.



Scheme 82. Preliminary results of copper-catalyzed allylboration of alkynes.

In 2015 Zhong and co-workers expanded the study of this transformation and reported a methodology for the synthesis of skipped dienyl boronates by copper-catalyzed allylboration of alkynes with several allylic phosphates.[148] The methodology is based on the use of phosphine ligands ((±)-BINAP, PPh_3 or PCy_3). Nonetheless, the conditions of the reaction (ligand, solvent and temperature) had to be optimized for every alkyne substitution pattern. Importantly, the regioselectivity of the allylic substitution step operates under substrate control.

Secondary allylic phosphates in combination with terminal aryl, internal diaryl and alkyl(aryl)alkynes led to the formation the S_N2' product using (±)-BINAP or PPh_3 as ligand. In combination with internal dialkyl alkynes, these allylic substrates led to mixtures of regioisomers using PCy_3 as ligand (Scheme 83a). The formal S_N2 allylboration of alkynes led to the formation of the *Z* product.

For primary allylic phosphates, their reaction with internal diaryl alkynes provided the S_N2 isomer as the major product (Scheme 83b). However, use of dialkylalkynes led to the opposite regioisomer and internal alkyl(aryl)alkynes to mixtures of both.

The use of terminal alkylalkynes led to a poor control in the α:β regioselectivity and high amounts of protoboration products were obtained.

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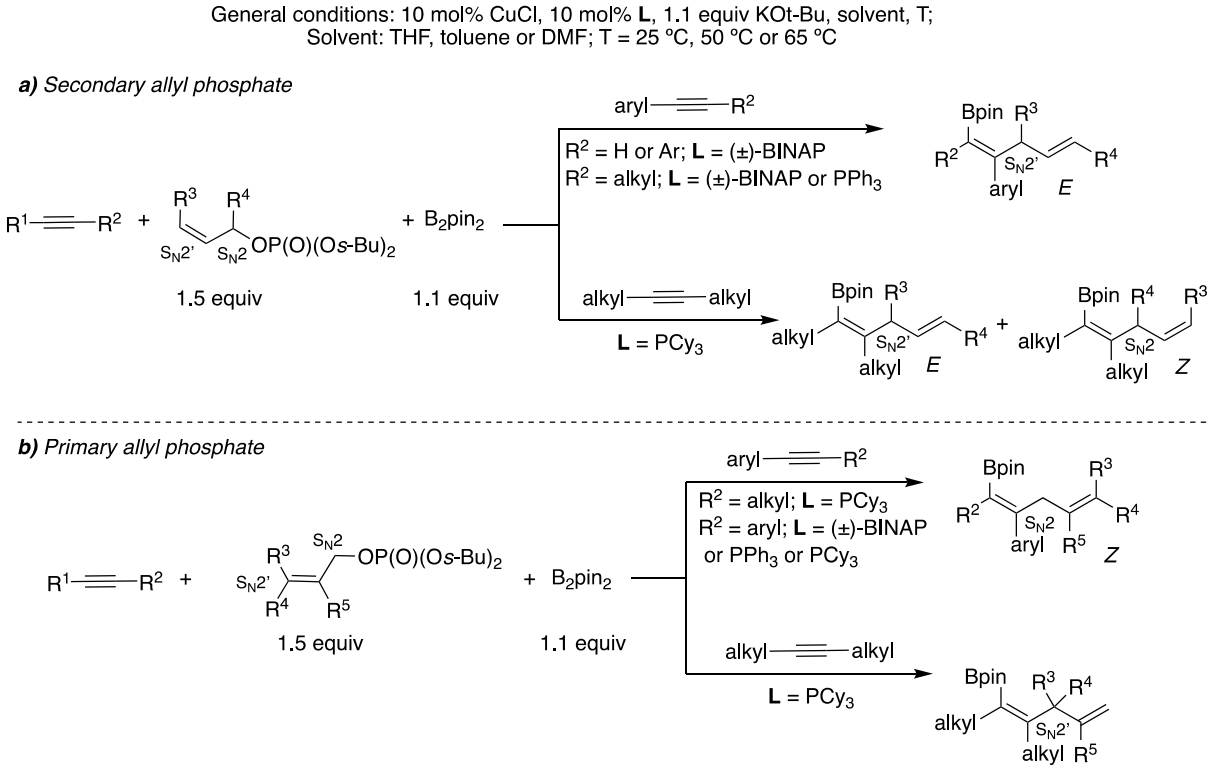
[148] Bin, H.-Y.; Wei, X.; Zi, J.; Zuo, Y.-J.; Wang, T.-C.; Zhong, C.-M.; *ACS Catal*. **2015**, *5*, 6670-6679.



Scheme 83. Copper(I)-catalyzed allylboration of alkynes with allylic phosphates.

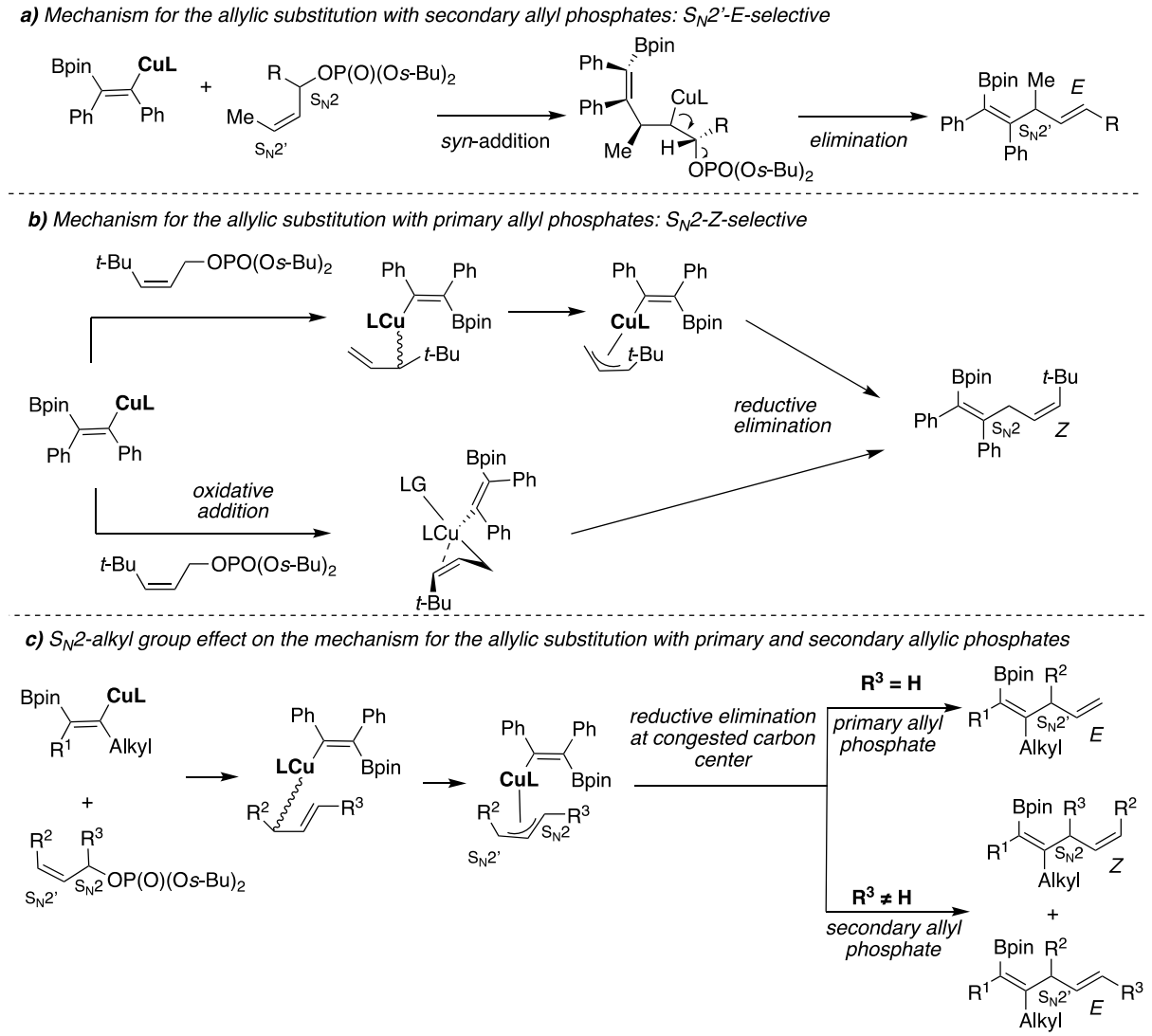
Different mechanistic pathways were proposed to explain the observed regiodiversity. Authors proposed a mechanism involving a *syn*-addition of the aryl alkenylcopper complex into the double bond of secondary allylic phosphates followed by stereoselective *anti*-β-elimination of the leaving group to afford *E*-S$_N$2' isomer (Scheme 84a).[149]

For the reaction between alkenylcopper complexes arising from aryl substituted alkynes and primary allylic phosphates, in which S$_N$2 products are obtained, authors proposed an oxidative addition of the alkenylcopper species into the allylic phosphate in a S$_N$2' manner. Then, the allylcopper species generated might suffer a σ-π-σ isomerization, which would need to be much faster than the σ-bond rotation to preserve *Z* stereochemistry of the allylic phosphate after reductive elimination. As alternative pathway based on an S$_N$2 type oxidative addition of the (*Z*)-allylic phosphate over the copper center followed by reductive elimination was also proposed (Scheme 84b).

Authors assumed that different regioselectivity afforded with alkenylcopper complex derived from dialkylalkynes is due to the electron-donating effect and small size of the alkyl groups. An S$_N$2' type oxidative addition of the allylic phosphate over the copper center would occur. Then, rapid σ-π isomerization could be proposed followed by reductive elimination at the more hindered carbon atom. This mechanism would give rise

[149] This type of mechanism has been proposed for copper-catalyzed allylic substitution with allylic phosphates with carbon nucleophiles: (a) Ohmiya, H.; Yokobori, U.; Makida, Y.; Sawamura, M. *J. Am. Chem. Soc.* **2010**, *132*, 2895-2897. (b) Nagao, K.; Yokobori, U.; Makida, Y.; Ohmiya, H.; Sawamura, M. *J. Am. Chem. Soc*. **2012**, *134*, 8982-8987.

to the S_N2' isomer when primary allylic phosphates are used. However, when secondary allylic phosphates are used, due to the similar steric environments of the S_N2' and S_N2 positions, mixture of isomers are obtained.



Scheme 84. Different proposed mechanistic pathways to explain regiodivergency in copper-catalyzed allylboration of alkynes with allylic phosphates.

An intramolecular version of this transformation was reported by Bai and Zhu.[150] By using Cu/PPh_3 as catalyst a series of enynyl phosphates can be converted into heterocycles of different sizes via a copper-catalyzed reaction with B_2pin_2 (Scheme 85). A mechanism involving an addition-elimination pathway was proposed for the allylic substitution step.

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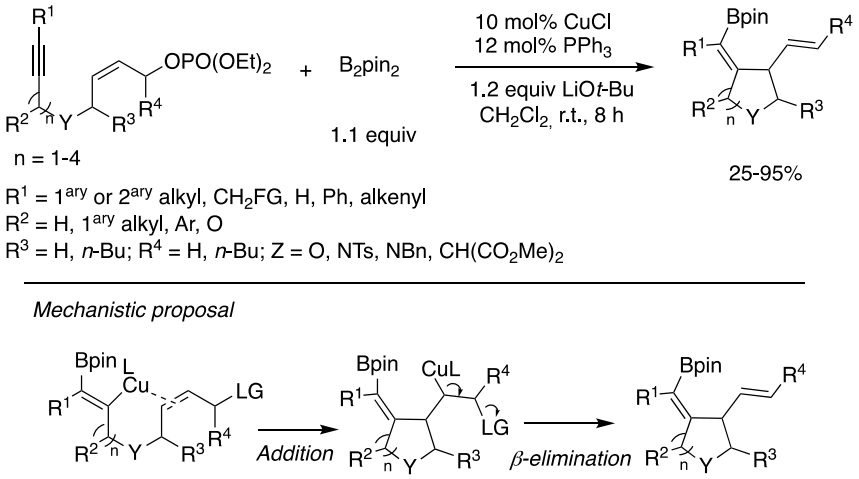
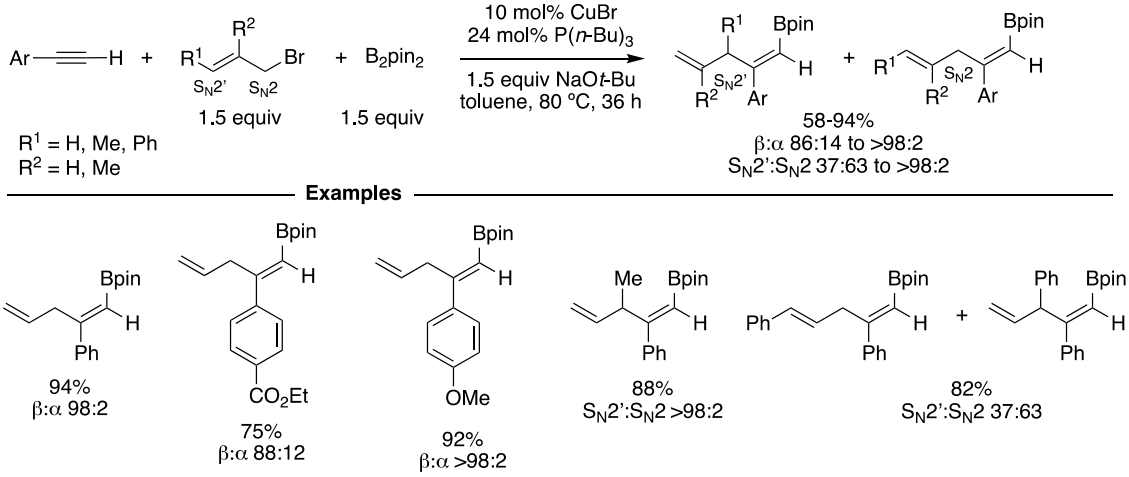
[150] Zhang, F.; Wang, S.; Liu, Z.; Bai, Y.; Zhu, G. *Tetrahedron Lett*. **2017**, *58*, 1448-1452.



Scheme 85. Intramolecular copper-catalyzed allylboration of 1,n-enynyl phosphates.

Copper-catalyzed allylboration of alkynes with allylic bromides has also been investigated (Scheme 86).[151] The use of CuBr and P*t*-Bu$_3$ as catalyst provides skipped dienyl boronates in good yield although reaction is limited to terminal aryl alkynes and variable mixtures of α and β isomers are obtained when 1,3-disubstituted allylic bromides are used. Moreover, high temperature (80 ºC) and long reaction times (36 h) are required.



Scheme 86. Copper(I)-catalyzed allylboration of alkynes with allylic bromides.

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[151] Jing, H.; Feng, X.; Guo, M.; Zhou, S.; Li, Y.; Zhang, J.; Zhao, W.; Tang, X.; Wang, G. *Asian J. Org. Chem.* **2017**, *6*, 1375-1379.

CHAPTER II: SYNERGISTIC COPPER/PALLADIUM CATALYSIS FOR THE REGIO- AND STEREOSELECTIVE SYNTHESIS OF BORYLATED SKIPPED DIENES

Chapter adapted from:

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

Rivera-Chao, E.[a]; Fra, L.[a]; Fañanás-Mastral, M.[a] *Synthesis* **2018**, *50*, 3825-3832.

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

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

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1. INTRODUCTION

1.1. SKIPPED DIENES

1,4-Dienes, also known as skipped dienes, are important structural motifs present in a wide variety of natural products,[152,153] and bioactive molecules.[154] In Figure 10, some examples of natural products containing the 1,4-diene structure are presented.

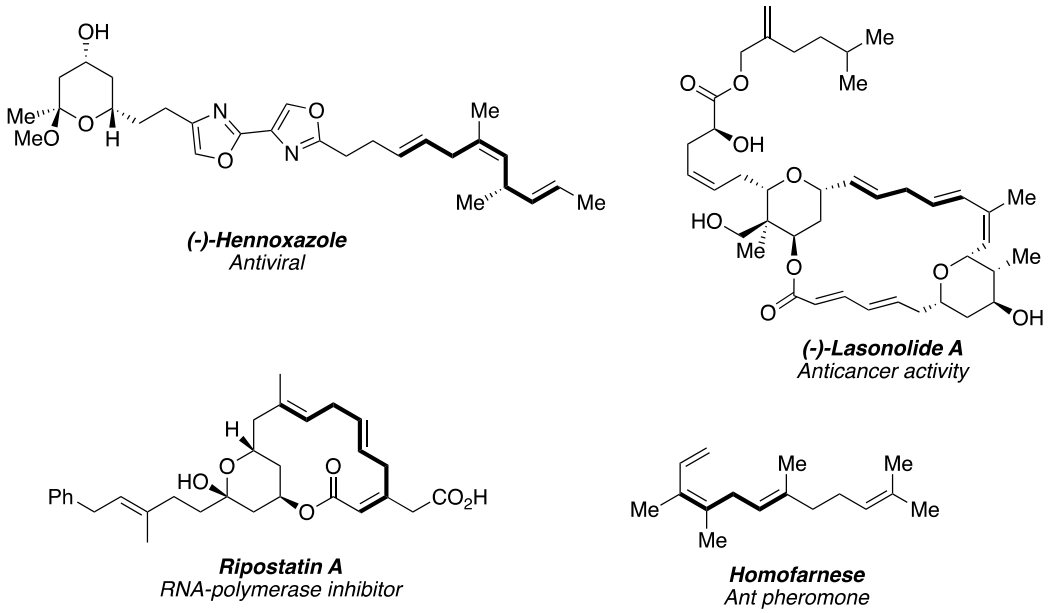

Figure 10. Examples of natural products containing 1,4-dienes.

Examples include (-)-hennoxazole,[155] which is an antiviral marine natural product, (-)-lasonolide A,[156] which is a potent anticancer agent, ripostatin A,[157] which is a RNA-polymerase inhibitor, and (*Z*,*E*)-α-Homofarnesene,[158] which is a component of a trial pheromone for the fire ant. A common feature in these products is that the stereochemical identity of the non-conjugated diene unit imparts unique properties to each compound.

[152] Petruncio, G.; Shellnutt, Z.; Elahi-Mohassel, S.; Alishetty, S.; Paige, M. *Nat. Prod. Rep.* **2021**; DOI: 10.1039/d1np00012h.

[153] Jie, M. S. F. L. K.; Pasha, M. K.; Syed-Rahmatullah, M. S. K. *Nat. Prod. Rep*. **1997**, *14*, 163-189.

[154] (a) Fürstner, A.; Nevado, C.; Waser, M.; Tremblay, M.; Chevrier, C.; Teplý, F.; Aïssa, C.; Moulin, E.; Müller, O. *J. Am. Chem. Soc*. **2007**, *129*, 9150-9161. (b) Wilson, M. C.; Nam, S.-J.; Gulder, T. A. M.; Kauffman, C. A.; Jensen, P. R.; Fenical, W.; Moore, B. S. *J. Am. Chem. Soc*. **2011**, *133*, 1971-1977.

[155] Yokokawa, F.; Asano, T.; Shioiri, T. *Org. Lett*. **2000**, *2*, 4169-4172.

[156] Trost, B. M.; Stivala, C. E.; Fandrick, D. R.; Hull, K. L.; Huang, A.; Poock, C.; Kalkofen, R. *J. Am. Chem. Soc.* **2016**, *138*, 11690-11701.

[157] Tang, W.; Prusov, E. V. *Org. Lett*. **2012**, *14*, 4690-4693.

[158] (a) Wilson, E. O. *Science* **1959**, *129*, 643-644. (b) Alvarez, F. M.; Vander Meer, R. K.; Lofgren, C. S. *Tetrahedron* **1987**, *43*, 2897-2900. (c) Chou, S.-S. P.; Lee, W.-H. *Synthesis* **1990**, *1990*, 219-220.

Consequently, general methods that allow for the efficient and stereoselective preparation of skipped dienes are in high demand.

1.1.1. Synthesis of skipped dienes

Common methods to prepare 1,4-dienes involve olefination, cross-coupling, allylic alkylation, hydrovinylation or Alder-ene-type strategies among others.[152,159] In particular, some representative examples of synthesis of 1,4-dienes are presented in Scheme 87. Micalizio reported a methodology based on the titanium-mediated cross-coupling between vinylcyclopropanes and vinylsilanes with high control over the double bonds stereochemistry (Scheme 87a).[159a] RajanBabu reported a cobalt-catalyzed hydrovinylation of 1,3-dienes with a chiral ligand ((*R*,*R*)-DIOP) that allows the synthesis of 1,4-dienes, with a central stereogenic center, with high levels of enantiomeric excess (Scheme 87b).[159b] The synthesis of skipped dienes bearing a central stereogenic center was also reported by Feringa through a copper-catalyzed alkylation of dienyl bromides with Grignard reagents (Scheme 87c).[159c] 1,4-dienes were obtained with a very high enantiomeric excess and high regioselectivity. A multicomponent procedure was reported by the group of Sigman, that consists in the stereoselective palladium-catalyzed 1,4-difunctionalization of butadiene with an alkenyl triflate and a boronic acid (Scheme 87d).[159d] Another example was later reported by the group of Montgomery, which consists in a nickel-catalyzed reductive coupling between enones and alkynes (Scheme 87e).[159e] This methodology is promoted by a Lewis acid, Ti(O*i*-Pr)$_4$ and a silane, and proceeds through a deoxygenative C-C bond formation obtaining the skipped dienes without the carbonyl group.

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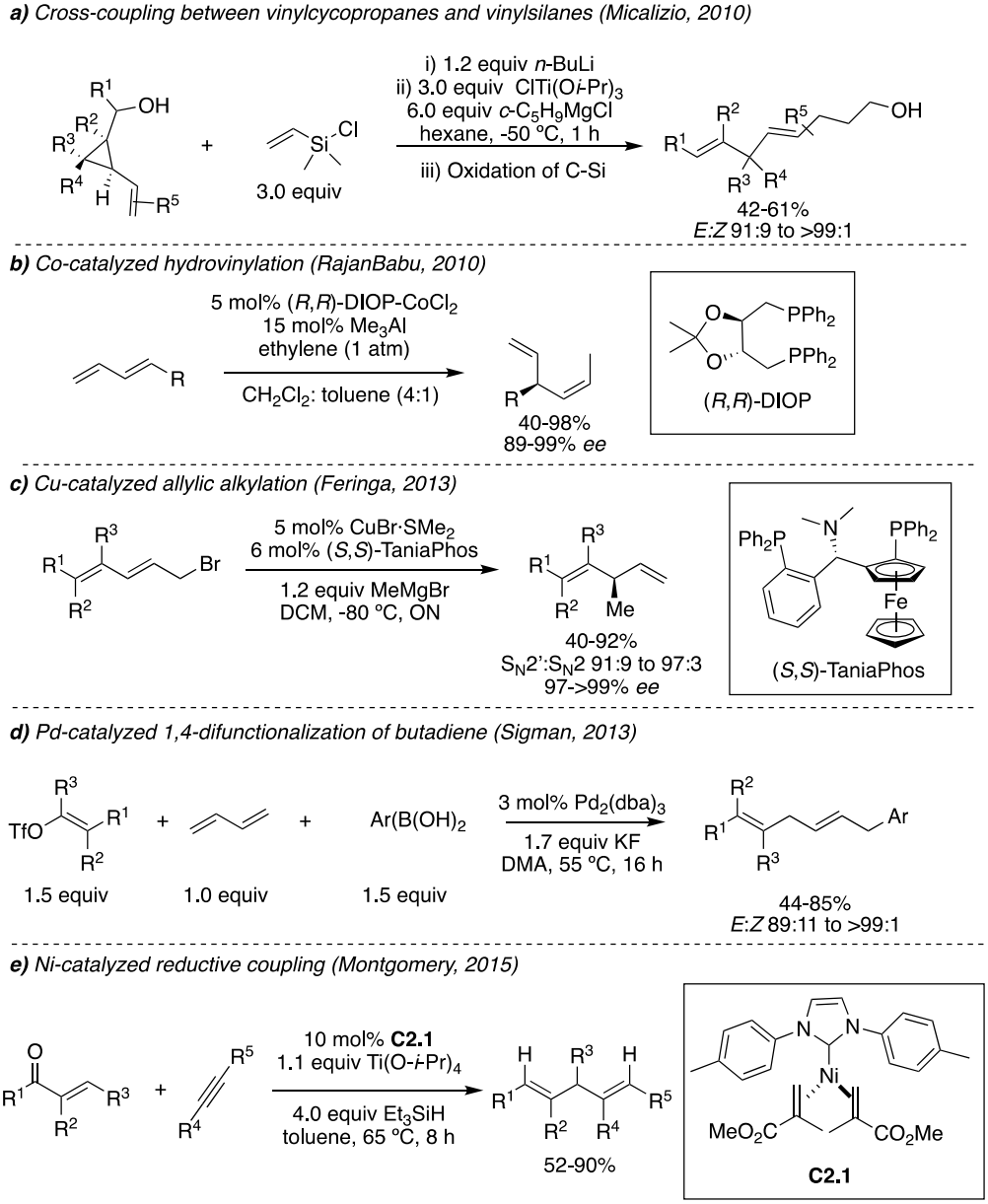
[159] (a) Macklin, T. K.; Micalizio, G. C. *Nat. Chem*. **2010**, *2*, 638-643. (b) Sharma, R. K.; RajanBabu, T. V. *J. Am. Chem. Soc*. **2010**, *132*, 3295-3297. (c) Huang, Y.; Fañanás-Mastral, M.; Minnaard, A. J.; Feringa, B. L. *Chem. Commun*. **2013**, *49*, 3309-3311. (d) McCammant, M. S.; Liao, L.; Sigman, M. S. *J. Am. Chem. Soc*. **2013**, *135*, 4167-4170. (e) Todd, D. P.; Thompson, B. B.; Nett, A. J.; Montgomery, J. *J. Am. Chem. Soc*. **2015**, *137*, 12788-12791.



Scheme 87. Selected examples of synthesis of 1,4-dienes.

Among the different strategies for the construction of skipped dienes, the transition metal-catalyzed allylic alkenylation represents a powerful alternative. Traditional methodologies for the incorporation of an alkenyl moiety rely on the use of stoichiometric amount of an alkenylmetal reagent (Li, MgBr, Al, Zn, Sn). Beyond other metals, palladium catalysis outstands in S_N2-type allylic substitution. Examples of S_N2 allylic substitution with alkenyl aluminum,[160] alkenyl tin,[161] alkenyl boron[99] or alkenyl silanes[162] compounds have been reported (Scheme 88).

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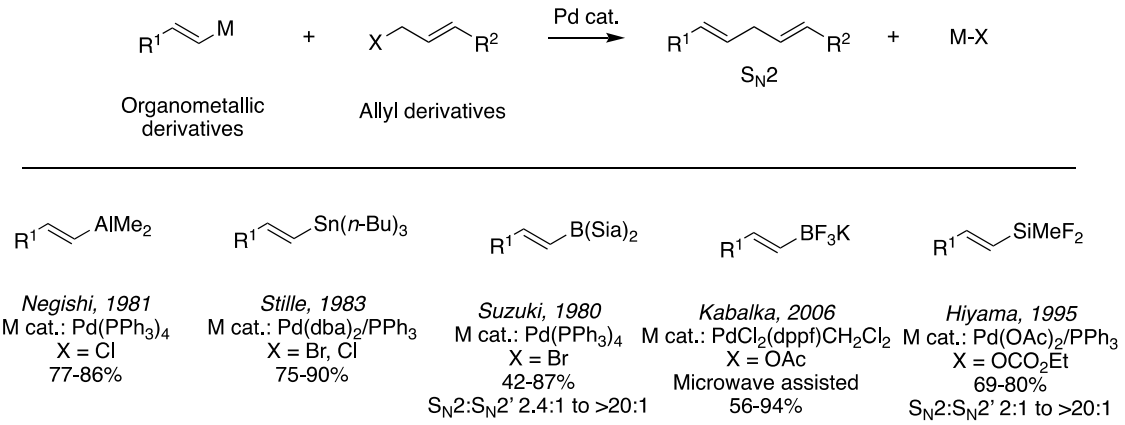
[160] Matsushita, H.; Negishi, E. *J. Am. Chem. Soc*. **1981**, *103*, 2882-2884.
[161] Sheffy, F. K.; Stille, J. K. *J. Am. Chem. Soc*. **1983**, *105*, 7173-7175.
[162] Matsuhashi, H.; Hatanaka, Y.; Kuroboshi, M.; Hiyama, T. *Tetrahedron Lett*. **1995**, *36*, 1539-1540.



Scheme 88. Palladium-catalyzed S_N2 allylic substitution with alkenyl metal reagents.

1.2. PALLADIUM CATALYZED ALLYLIC SUBSTITUTION

In 1965, Tsuji and co-workers found that electrophilic palladium-allyl complexes undergo substitution under the presence of nucleophiles.[163] Catalytic regio-, stereo- and enantioselective methodologies did not take long to appear, to a large extent, thanks to the work of the group of Trost,[164] who has developed some of the most useful catalysts for the enantioselective palladium-catalyzed allylic substitution. These pioneering works are the origin of the reaction widely known as the Tsuji-Trost allylation.[165]

Generally, the reaction of an allylic electrophile with a nucleophile can provide two regioisomers, the S_N2-type substitution product of or the S_N2'-type substitution product (Scheme 89).

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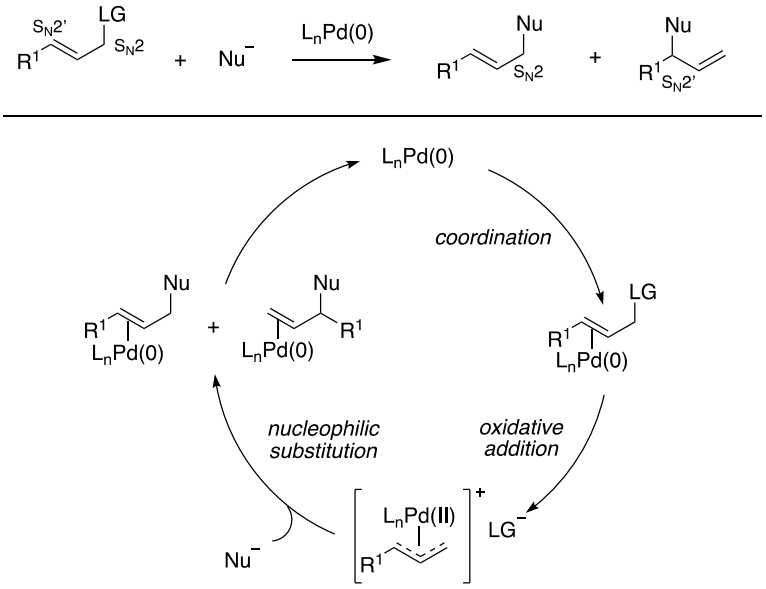
[163] Tsuji, J.; Takahashi, H.; Morikawa, M. *Tetrahedron Lett* **1965**, *6*, 4387-4388.

[164] (a) Trost, B. M.; Fullerton, T. J. *J. Am. Chem. Soc*. **1973**, *95*, 292-294. (b) Trost, B. M.; Strege, P. E. *J. Am. Chem. Soc.* **1977**, *99*, 1649-1651.

[165] For reviews see: (a) Trost, B. M.; Crawley, M. L. *Chem. Rev.* **2003**, *103*, 2921-2943. (b) Poli, G.; Prestat, G.; Liron, F.; Kammerer-Pentier, C. *Top. Organomet. Chem.* **2012**, *34*, 1-64.



Scheme 89. Mechanism for the Palladium-catalyzed allylic substitution.

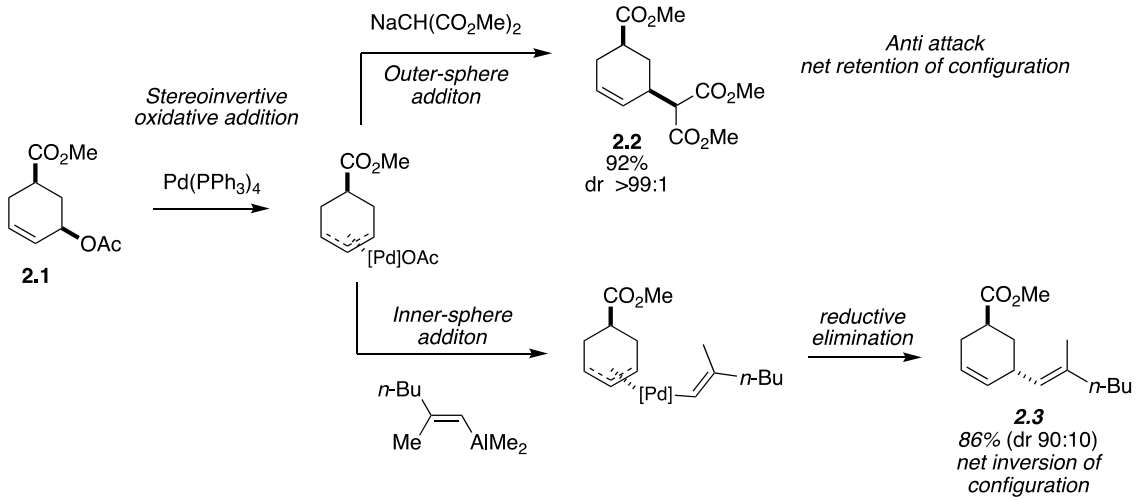
The general mechanism for this transformation is shown in Scheme 89. Initially, the palladium catalyst coordinates to the allyl group. Then, an oxidative addition occurs to form a η^3-allylpalladium(II) complex. The final step is a nucleophilic substitution, which is the product-determining step. The palladium catalysis provides, in most of the cases, the allylic substitution at the less hindered allylic termini.

Several different allylic electrophiles have been proved to work in these reactions, allyl acetates and carbonates being the most commonly used. Regarding the nucleophiles, two different types of nucleophiles can be used, "*soft"* nucleophiles, that are stabilized nucleophiles with conjugated acids with pK_a lower than 25 (usually the anion of a β-carbonyl compound), and "*hard"* nucleophiles, which are non-stabilized nucleophiles with conjugated acids with pK_a higher than 25 (usually organometallic reagents). Examples of palladium-catalyzed allylic substitution with *"hard"* nucleophiles have been reported, however, *"soft"* nucleophiles have been by far more explored in this transformation.

The type of nucleophile has an important role in the stereochemistry of the reaction when secondary allylic substrates are used. When *"soft"* nucleophiles are used, retention on configuration is observed. This is explained by an outer-sphere mechanism. Oxidative addition of the allylic substrate to the palladium(0) complex adds *anti* to the leaving group thus resulting in an inversion of the configuration (Scheme 90). "*Soft"* nucleophiles attack one of the allylic termini of the allyl-Pd following an outer-sphere mechanism, thus, this attack takes place *anti* to the palladium center thus providing a second inversion of the configuration (respect to the palladium complex), which results in a final net retention of the configuration. This behavior was observed by Trost in the palladium-catalyzed addition of the sodium salt of dimethylmalonate to diastereomerically pure *cis* cyclohexenyl acetate **2.1**.[166] They observed the formation of *cis* product **2.2** as a single isomer.

[166] Trost, B. M.; Verhoeven, T. R. *J. Org. Chem*. **1976**, *41*, 3215-3216.

In contrast, *"hard"* nucleophiles react with the allyl-palladium complex through transmetalation, following an inner-sphere mechanism. The resulting Pd complex undergoes a stereoretentive, reductive elimination, providing net inversion of the configuration. This stereochemical trend was observed by Negishi in the addition of (*E*)-(2-methylhex-1-enyl)dimethylalane to *cis*-allylic acetate **2.1**.[167] They observed in this case, formation of the *trans* product **2.3** as a major isomer.



Scheme 90. Stereochemical outcome depending on the type of nucleophile in palladium-catalyzed allylic substitution.

1.3. SYNERGISTIC CATALYSIS

Catalytic reactions employing a single catalyst have allowed the discovery of a wide range of new transformations. However, they become limited at some extend for some transformations, mostly in multicomponent reactions, that are difficult or not possible with the use of a unique catalyst. Synergistic catalysis is becoming popular for being a powerful tool to increase the variety of transformations, improve existing methods or create or improve stereocontrol on the reactions.[168] This type of catalysis implies the activation of the electrophile (**E**) by one catalyst (**cat1**) and simultaneously activation of the nucleophile (**Nu**) by a different catalyst (**cat2**). This activation creates species with a lower LUMO (lowest unoccupied molecular orbital) and the other one with a higher HOMO (highest occupied molecular orbital) (Figure 11).

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[167] Matsushita, H.; Negishi, E. *J. Chem. Soc., Chem. Commun*. **1982**, 160-161.

[168] 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.

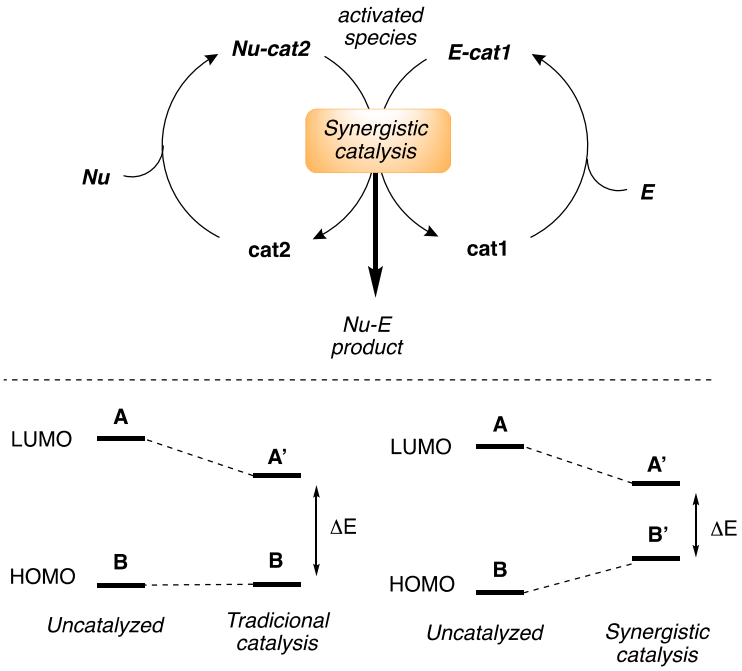


Figure 11. Mode of activation and concept of synergistic catalysis.

It is important to note that the term synergistic catalysis should be used only for the mechanism outlined above. Other types of multicatalyst systems include:

- *Bifunctional catalysis*: a single catalyst activates simultaneously two substrates.
- *Double activation catalysis*: a single substrate is activated simultaneously by two different catalytic species.
- *Cascade catalysis*: a single substrate is activated sequentially by two different catalytic species.

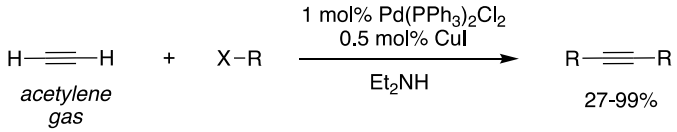
The use of two different catalytic systems to activate two different substrates presents several challenges which must be overcome in order to achieve an efficient transformation. These main challenges are: i) Compatibility: the two catalytic species must be compatible, as they can interact with each other given a self-quenching, which renders catalyst inactivation. ii) Control of the chemoselectiviy: each catalyst must react with the appropriate substrate in a selective manner in order to avoid side reactions. iii) Kinetics: catalysts should have comparable and compatible activation rates to make both catalytic cycles kinetically compatible.

In terms of synergistic dual transition metal catalysis, the most common combination of metals is palladium (usually to activate the electrophile) and copper (to activate the nucleophile).

Sonogashira and co-workers reported in 1975 the first example of Cu/Pd cooperative catalysis.[169] In this work, they reported the cross-coupling of acetylene gas with bromoalkenes, iodoarene and bromopyridines (Scheme 91). The use of a catalytic amount

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

of copper iodide allowed the use of milder conditions than previously reported methodologies, which also implies greater functional group tolerance. In this transformation, the acetylene is converted into a nucleophilic copper acetylide under the assistance of a copper complex and a weak base.



Scheme 91. First example of Sonogashira coupling.

After this pioneering work by Sonogashira, numerous research groups have turned their attention into the Cu/Pd dual catalytic system which has an enormous potential, as shown in the previous example, to improve or to create new chemical transformations.[168d,e] In this context, combining the ability of palladium to perform allylic or propargyl substitution, or carbonylative coupling, with hydrocarbon or carbonyl activation by copper chemistry, offers multiple possibilities. For example, combining copper catalyzed C-H activation followed by Pd-catalyzed cross-coupling led to the efficient arylation of heteroarenes (Scheme 92a),[170] or a decarboxylative coupling for the synthesis of biaryl compounds enabled by the transient formation of a nucleophilic aryl copper complex from a carboxylic acid, followed by coupling with an aryl palladium complex (Scheme 92b). [171] Combination of CuH and Pd catalysis has enabled enantioselective α-allylation of α,β-unsaturated ketones [172] or enantioselective hydroarylation of alkenes (Scheme 92c and d).[173] In the same way, the combination of Pd and Cu catalysis in carbosylilation and carboboration reactions has become popular in the last years. Next section will be focused on the synergistic Cu/Pd catalyzed carboboration of alkynes.

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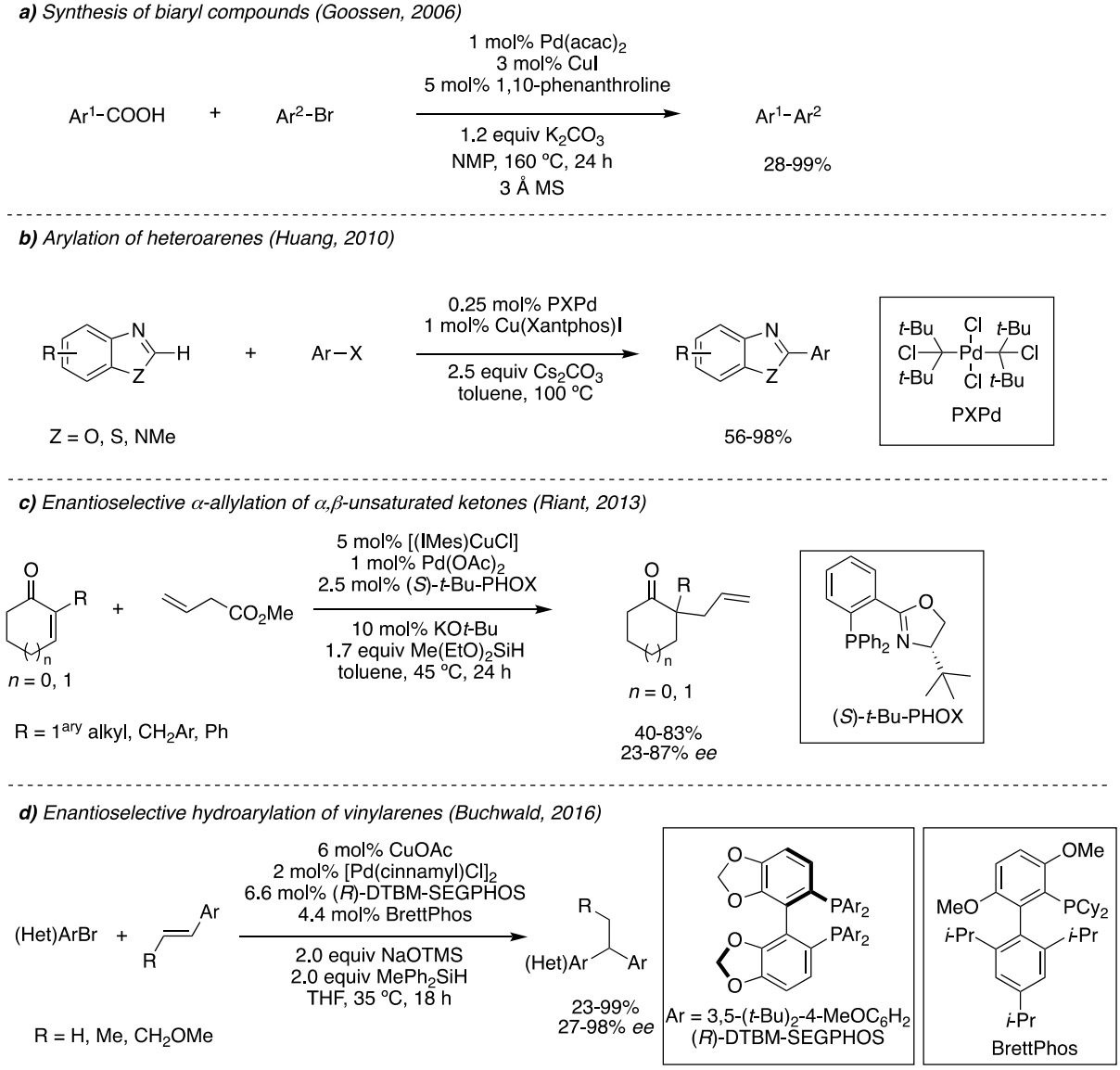
[170] Huang, J.; Chan, J.; Chen, Y.; Borths, C. J.; Baucom, K. D.; Larsen, R. D.; Faul, M. M. *J. Am. Chem. Soc.* **2010**, *132*, 3674-3675.
[171] Goosen, L. J.; Deng, G.; Levy, L. M. *Science* **2006**, *313*, 662-664.
[172] Nahra, F.; Macé, Y.; Lambin, D.; Riant, O. *Angew. Chem. Int. Ed*. **2013**, *52*, 3208-3212.
[173] Friis, S. D.; Pirnot, M. T.; Buchwald, S. L. *J. Am. Chem. Soc*. **2016**, *138*, 8372-8375.

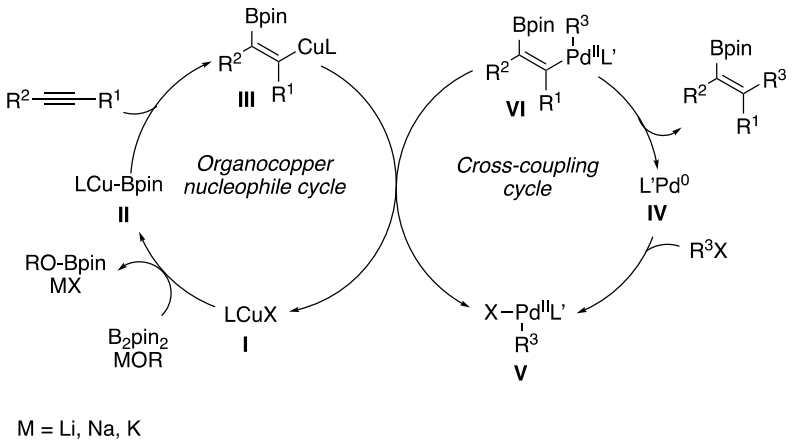


Scheme 92. Examples of applications of synergistic Cu/Pd catalysis.

1.3.1. Synergistic Cu/Pd catalysis for carboboration of alkynes

As mentioned in section 2 of chapter I, alkynes readily insert into borylcopper complexes leading to β-boryl alkenylcopper complexes. If this transient intermediate is trapped with a carbon electrophile the reaction formally constitutes an alkyne carboboration. However, these alkenylcopper complexes display a moderate reactivity, something which somewhat limits this type of reaction to very reactive carbon electrophiles or to the use of harsh conditions. Thus, the use of a Pd co-catalyst to activate the organic electrophile can facilitate this trapping and provide an efficient carboboration process. A general mechanism of this transformation is shown in Scheme 93. The first step in the palladium catalytic cycle is the oxidative addition of the electrophile to Pd(0) to generate Pd(II) complex **V**. On the other hand, the copper catalytic cycle starts with the formation of the active catalyst LCuBpin **II**, which then undergoes borocupration of the alkyne to provide β-boryl alkenylcopper(I) intermediate **III**. Transmetalation between

alkenylcopper(I) intermediate **III** and palladium(II) complex **V** gives rise to complex **VI** and regenerates copper complex **I**. Reductive elimination affords the product and allows regeneration of the Pd(0) catalyst **IV**.



Scheme 93. General mechanism of a synergistic palladium and copper catalyzed carboboration of alkynes.

Using this strategy, the groups of Semba/Nakao [174] and Cazin[115] independently reported the regio- and stereoselective synthesis of tetrasubstituted alkenyl boronates via an alkyne arylboration, in which alkynes serve as C(sp^2) pro-nucleophiles in a Pd-catalyzed cross-coupling with an aryl bromide or chloride (Scheme 94). The method reported by Cazin, based on the use of Cu-NHC and Pd-NHC catalysts, is limited to the use of alkyl(aryl)acetylenes (Scheme 94a). On the other hand, the protocol described by Semba and Nakao is based on the use of the phosphine ligand RuPhos for both catalysts, and allows for the arylboration of diarylacetylenes, alkyl(aryl)acetylenes, and dialkylacetylenes (Scheme 94b). However, when unsymmetrical diarylalkynes are used, the nearly equimolar amount of β and α borylation isomers is obtained. In both cases terminal alkynes are not tolerated.

In 2019, Brown reported a Pd/Cu catalyzed (hetero)arylboration of alkynes (Scheme 94c).[175] The use of piridylidene-Cu complexes (**C2.2**) had been reported by the same authors in a previous work to efficiently promote heteroarylboration of alkenes.[176] Pyridylidenes have been reported to be more strongly donating than other common NHC ligands. Thus, authors proposed the use of pyridylidenes-Cu complex could prevent the coordination of the Lewis basic heteroatoms of the heteroaryl substrates to the copper center, which could deactivate the catalyst. Combination of Cu-pyridylidene (Cu-complex **C2.2**) and APhosPdG3 furnished good results with alkyl(aryl)alkynes, diarylalkynes and dialkylalkynes. Heteroaryl bromides such as pyridines, indoles, furan or carbazoles can be used in combination with heteroaryl-substituted alkynes to obtain

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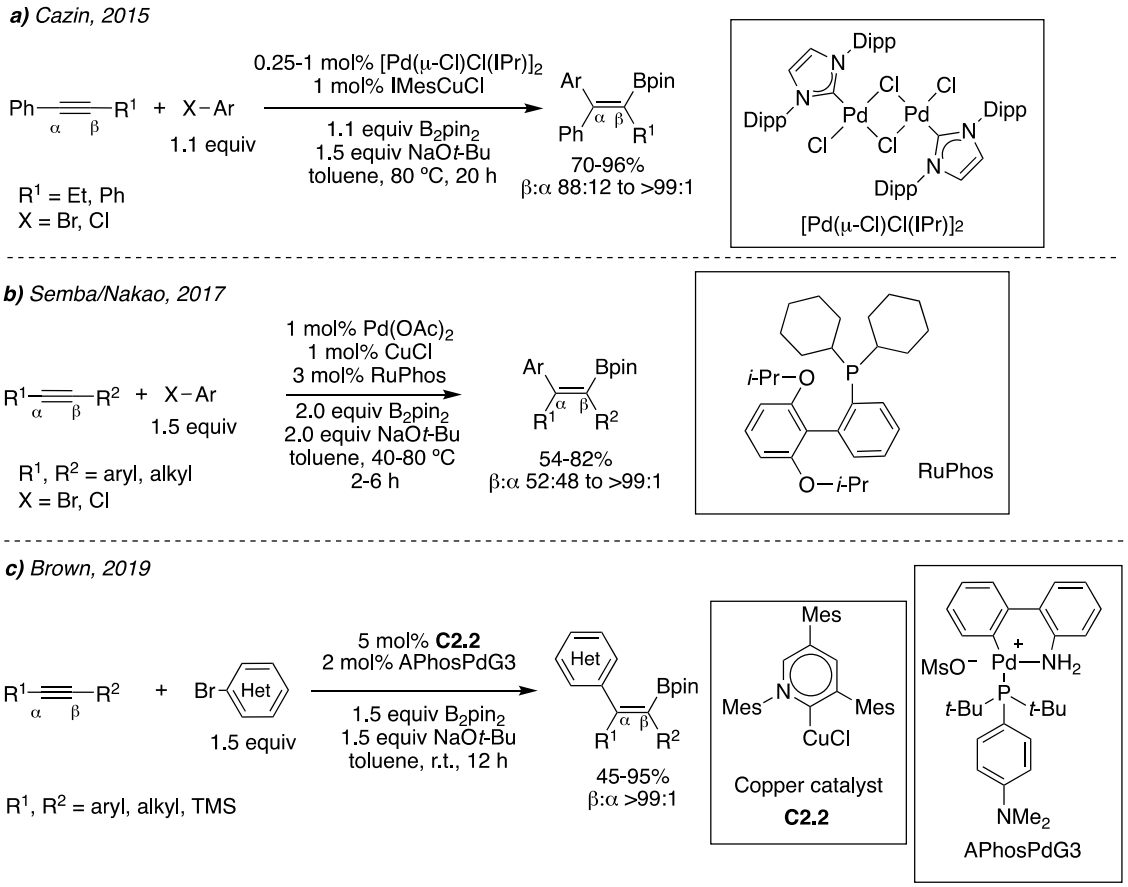
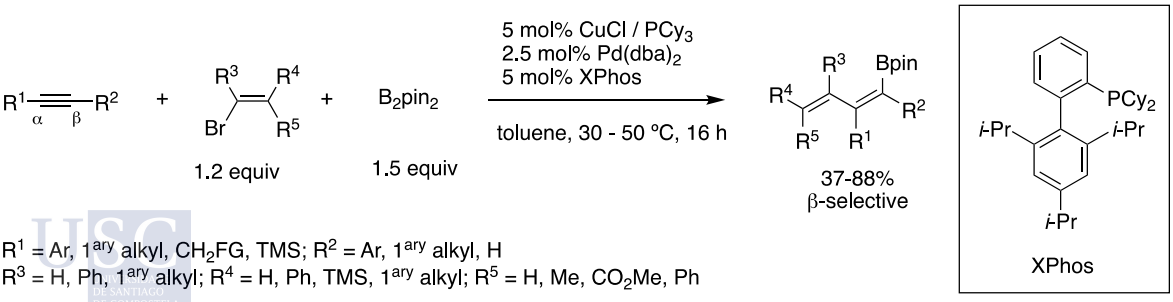
[174] Semba, K.; Nakao, Y. *Bull. Chem. Soc. Jpn*. **2017**, *90*, 1340-1343.
[175] Huang, Y.; Bergmann, A. M.; Brown, M. K. *Org. Biomol. Chem*. **2019**, *17*, 5913-5915.
[176] Huang, Y. Brown, M. K. *Angew. Chem. Int. Ed*. **2019**, *58*, 6048-6052.

the corresponding α,α-bis(hetero)arylalkenes in good yield and complete selectivity towards the β-borylated product.



Scheme 94. Synergistic Cu/Pd catalyzed arylboration of alkynes.

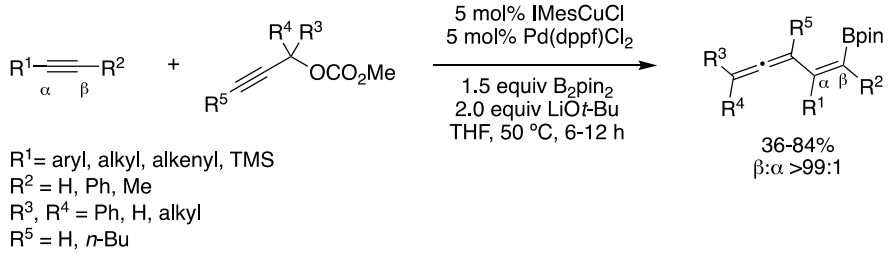
We have recently reported in our group a synergistic Cu/Pd-catalyzed alkenylboration of alkynes (Scheme 95).[177] This methodology is based on the use of $CuPCy_3$ and PdXPhos as catalytic system and allows the synthesis of up to hexasubtituted borylated 1,3-dienes in good to excellent yield with a variety of substrates. Moreover, the reaction proceeds with excellent levels of chemo-, regio- and stereoselectivity.

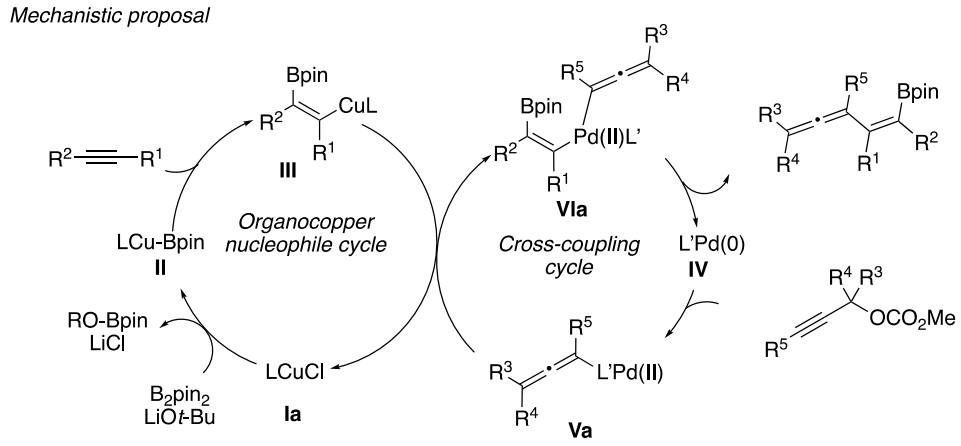


Scheme 95. Synergistic Cu/Pd-catalyzed alkenylboration of alkynes.

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

After the publication of the work that is described in this chapter on the allylboration of alkynes, related works have been published. Cu/Pd-catalyzed borylallenylation of alkynes was described by Yu (Scheme 96).[178] The methodology is based on the coupling of propargylic carbonates and alkynes using IMesCuCl and $Pd(dppf)Cl_2$ as catalytic system. The use of propargylic carbonates under palladium catalysis led to the formation of allenyl palladium intermediate **Va**. The reaction furnishes complete regioselectivity towards the formation of the β-borylated ene-allene products and high efficiency for aryl, alkenyl, alkyl and silyl substituted terminal alkynes. Up to hexasubstituted boryl ene-allenes could be synthesized





Scheme 96. Synergistic Cu/Pd catalyzed borylallenylation of alkynes.

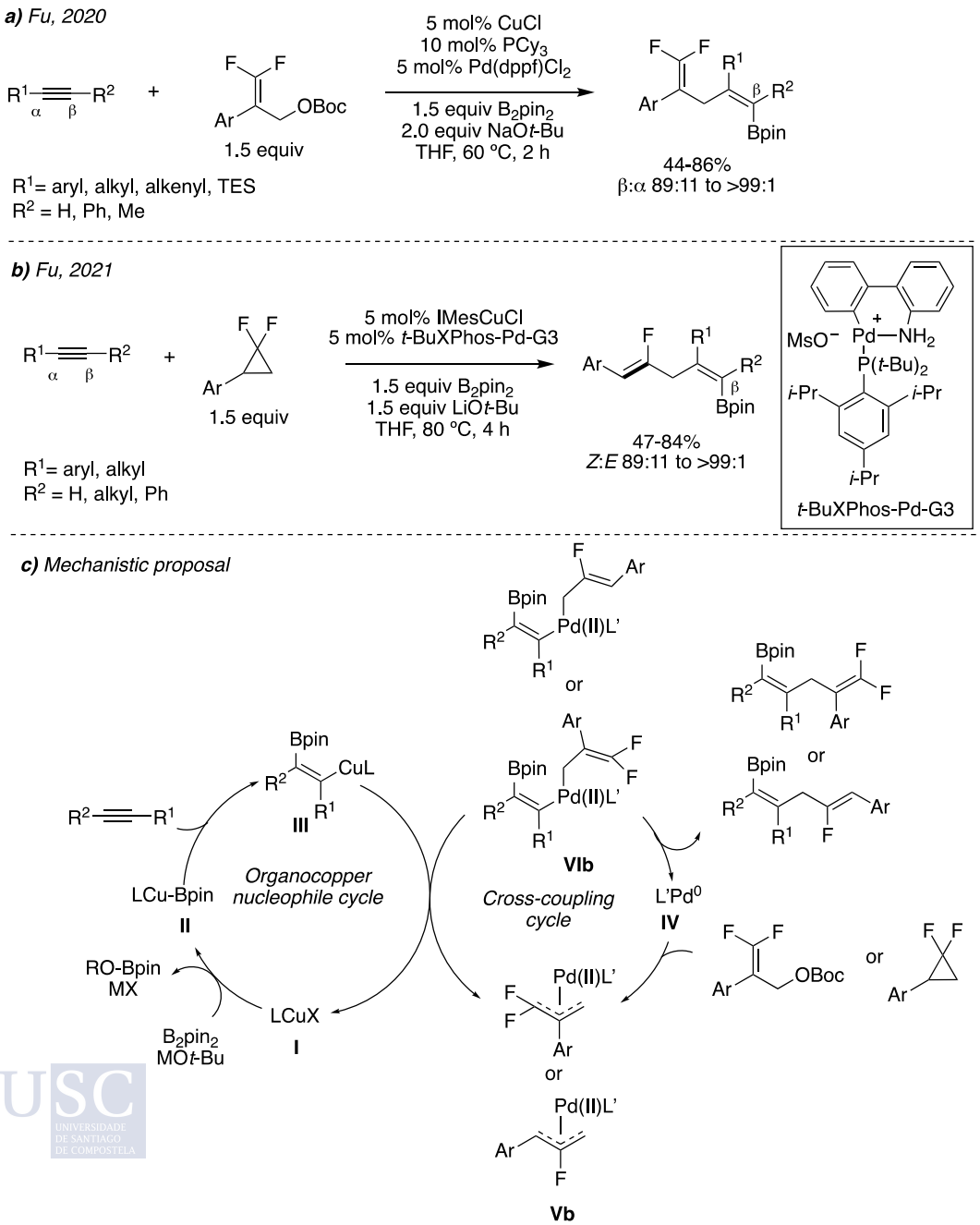
Introduction of fluorine substitution in organic molecules it is very interesting for medicinal chemistry. In particular, the incorporation of *gem*-difluoroalkene is important since is bioisostere of the carbonyl group. Fu recently investigated the incorporation of fluorinated moieties via Cu/Pd catalyzed carboboration of alkynes (Scheme 97).[179] The use of *gem*-difluoroallyl carbonates under $CuPCy_3$ and $Pd(dppf)Cl_2$ catalysis, allows the synthesis of *gem*-difluoro 1,4-dienes with a great functional group tolerance and a broad scope of alkynes (Scheme 97a). However, the scope of *gem*-difluoroallyl carbonates is limited to 2-aryl substituted ones.

Gem-difluorinated cyclopropanes have been described to undergo C-C bond activation and C-F bond cleavage with Pd(0) complexes to lead to the formation of an allylpalladium(II) complex. This strategy was used by Fu to develop a Cu/Pd-catalyzed

[178] Yu, S.-H.; Gong, T.-J.; Fu, Y. *Org. Lett*. **2020**, *22*, 2941-2945.
[179] (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.

cis-borylfluoroallylation of alkynes (Scheme 97b). This protocol allows the synthesis of monofluorinated 1,4-dienes under IMesCuCl and *t*-Bu-XPhos-PdG3 catalysis with a very good functional group tolerance. Wide variety of internal and terminal alkynes were used with excellent regio- and stereoselectivity. However, is also limited to 2-aryl substituted *gem*-difluorinated cyclopropanes.

The mechanism of these two protocols consists in the activation of the fluorinated compounds with the palladium catalysis through oxidative addition to obtain and Pd(II) π-allylic intermediate, followed by transmetalation with the alkenylcopper intermediate and final reductive elimination affords the fluorinated 1,4-diene (Scheme 97c).

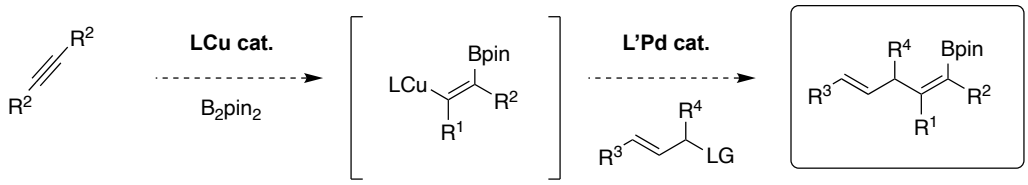


Scheme 97. Synergistic Cu/Pd catalyzed synthesis of *gem*-difluoroalkenes and monofluoroalkenes.

2. OBJECTIVE

As mentioned above, one of the best ways to synthesized linear 1,4-dienes consists in a transition metal-catalyzed allylic substitution with alkenyl metal reagents. These methodologies are inherently limited to the availability and reactivity profiles of the alkenyl reagent. In addition, the use of these pre-functionalized reagents entails the formation of a stoichiometric amount of inorganic salt as a reaction by-product. To avoid the use of stoichiometric amounts and the prior preparation of the organometallic reagent, an excellent alternative would be the transient formation of the C(sp^2) nucleophile promoted by a transition metal catalyst.

The objective of the present chapter is the development of a catalytic method for the synthesis of 1,4-dienes, using simple alkynes as a transient functionalized alkenylmetal species in a stereo- and regioselective allyic substitution. To overcome the selectivity issues observed by Zhong in his copper-catalyzed transformation,[148] we envisaged a strategy based on the generation of a β-alkenylcopper intermediate via an insertion of the alkyne to a boryl-copper complex and its reactivity towards a Pd-catalyzed allylic substitution under synergistic catalysis. The combination of copper and palladium catalyst would allow for concomitant activation of both the alkyne and allyl substrate and would provide total control over the different selectivity factors associated with this transformation, giving access to regio- and stereodefined skipped dienes bearing a Bpin group which can be further functionalized in several ways (Scheme 98).



Scheme 98. Proposed dual Cu/Pd-catalyzed allylboration of alkynes.

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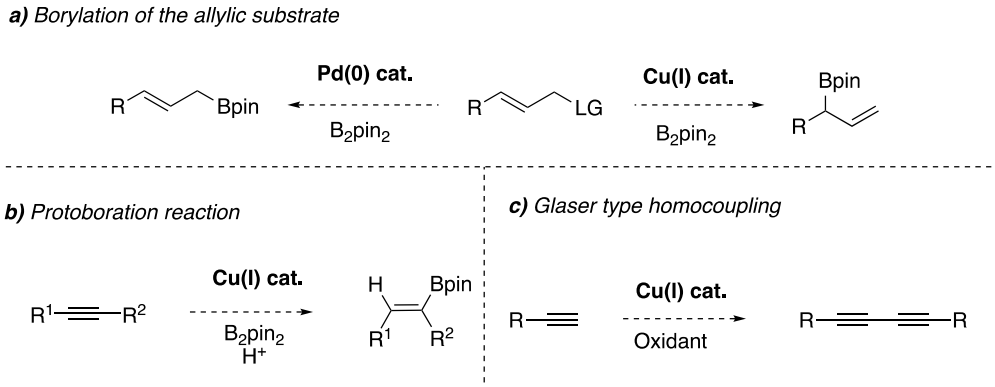
3. RESULTS AND DISCUSSION

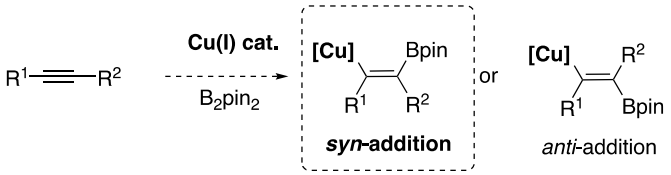
In order to successfuly implement this idea, several challenges associated with the use of synergistic catalysis and the substrates must be overcome:

- *Chemoselectivity*: To avoid side reactions, each catalyst must react with each substrate in a chemoselective manner. For example, direct borylation of allylic substrate has been described with both copper and palladium catalysis[52-58] (see section 1.1.6, chapter I). Furthermore, β-boryl alkenylcopper intermediates can potentially react with protic sources to produce the protoboration product (see section 2.1, chapter I). Moreover, Glaser type homocoupling of terminal alkynes could occur.[180]



Scheme 99. Possible side reactions with copper and palladium catalysis.

- *Stereoselectivity*: (Scheme 100) Alkyne insertion into the Cu-Bpin complex generally occurs in a *syn*-fashion, although isomerization of the resulting alkenylcopper complexes to provide an *anti*-addition product has also been observed for phenylacetylene derivatives and cannot be discarded.[181]

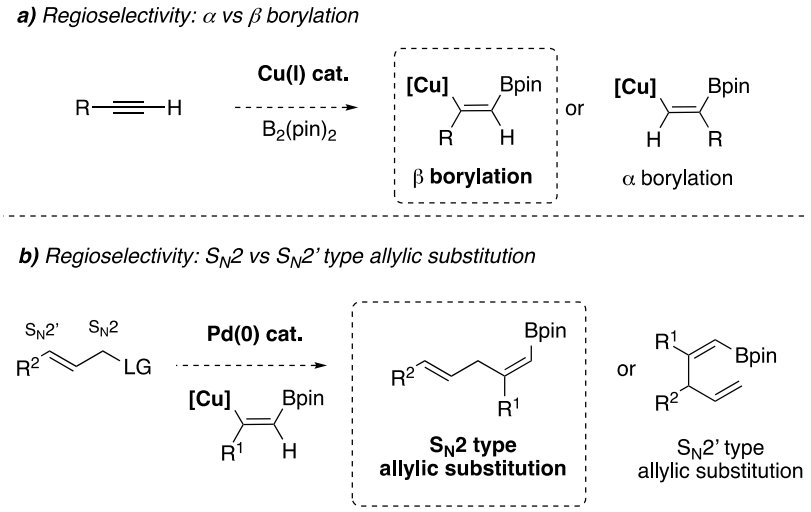


Scheme 100. Potential *syn* and *anti* stereoisomers that can be formed after addition of Cu-Bpin to the alkyne.

- *Regioselectivity*: Insertion of unsymmetrical alkynes can occur in two different manners giving either to the α or β borylated regioisomer. Moreover,

[180] Glaser, C. *Ber. Dtsch. Chem. Ges*. **1869**, *2*, 422-424.
[181] Jang, W. J.; Lee, W. L.; Moon, J. H.; Lee, J. Y.; Yun, J. *Org. Lett*. **2016**, *18*, 1390-1393.

regioselectivity of the allylic substitution also has to be controlled when 1,3-disubstituted substrates are used (Scheme 101).



Scheme 101. Regioselectity issues of **a)** copper-catalyzed borocupration of alkynes and **b)** palladium-catalyzed allylic alkenylation.

Taking all together, besides the formation of side products arising from competing reactions, up to eight possible isomers could be formed in the proposed allylboration reaction.

3.1. OPTIMIZATION

At the outset of our investigation, we selected a reaction involving B_2pin_2, 1-phenyl-1-butyne (**2.4**) and *tert*-butyl cinnamyl carbonate (**2.5**) to evaluate both the feasibility and selectivity of the process. We initially evaluated the effect of the solvent (Table 1). For this screening, we used a combination of $CuCl/PCy_3$ and $Pd(dba)_2$/dppe as catalytic system, and sodium *tert*-butoxide (1.3 equiv) as base. Gratifyingly, under these conditions all the solvents tested provided product **2.7** as unique isomer. This product arises from *syn* borylcupration, selective β borylation and S_N2 allylic substitution, with the alkyne protoboration product **2.8** being the only side product.

The evaluation of the solvent revealed that THF provided the best results, affording **2.7** in 57% NMR yield, together with 25% of **2.8** (Table 1, entry 1). The use of toluene and dichloromethane led to product **2.7** in a slightly lower yield (49% and 47% NMR yield respectively), and 18% and 20% NMR yield of **2.8** (Table 1, entries 2 and 3). Lastly, dichloroethane triggered virtually no conversion of **2.4** (Table 1, entry 4).

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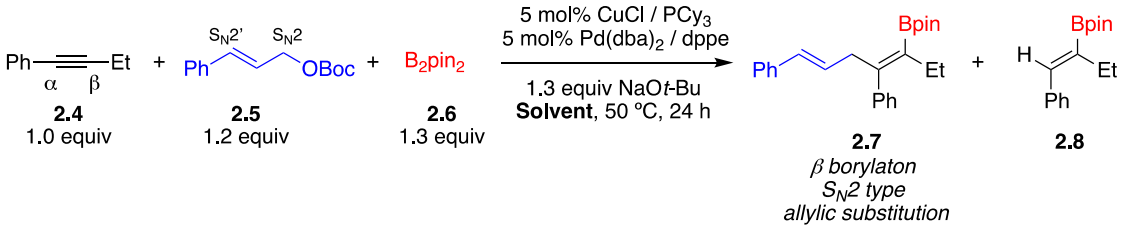
Table 1. Effect of solvent

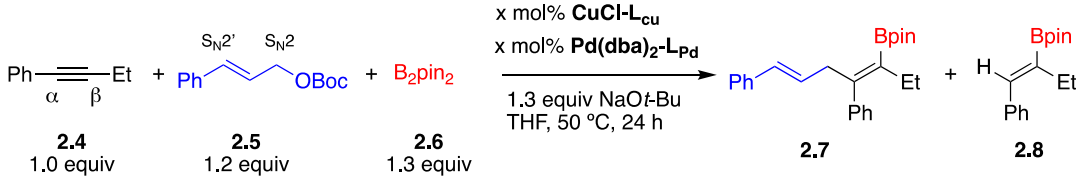


Entry[a]	Solvent	Conv. **2.4** (%)[b]	**2.7**/**2.8** (%)[b]	β/α (%)[b]	S_N2/S_N2' (%)[b]
1	**THF**	82	57/25	>99:1	>99:1
2	**Toluene**	67	49/18	>99:1	>99:1
3	**CH_2Cl_2**	67	47/20	>99:1	>99:1
4	**DCE**	13	8/5	>99:1	>99:1

[a] Reaction conditions: 0.2 mmol scale (0.1 M). [b] Determined by GC-MS analysis and ^{1}H NMR of the crude using Ph_3CH as internal standard.

We next screened the effect of the ligand on both, the palladium and the copper catalysts (Table 2). Evaluation of different bisphosphine ligands in the palladium catalyst (Table 2, entries 1-4), keeping $CuPCy_3$ as the copper catalyst, allowed us to improve the efficiency of the reaction by using dppf as ligand. Under these conditions, **2.7** was obtained in 70% NMR yield, although a considerable amount of side product **2.8** (30% NMR yield) was still obtained (entry 4). Regarding the copper catalyst, the use of other less electron-rich monodentate phosphines led to diminished yields of **2.7** (Table 2, entries 5-7). The use of IMesCuCl provided **2.7** in moderate 45% yield and SIMesCuCl led to no conversion of **2.4** (Table 2, entries 8 and 9).

Table 2. Evaluation of Pd and Cu catalyst.



Entry[a]	L_{Pd} (x mol%)	L_{Cu} (x mol%)	Conv. **2.4** (%)[b]	**2.7**/**2.8** (%)[b]
1	**dppe** (5 mol%)	PCy_3 (5 mol%)	82	57/25
2	**dppm** (5 mol%)	PCy_3 (5 mol%)	-	n.d.
3	**dppp** (5 mol%)	PCy_3 (5 mol%)	-	n.d.
4	**dppf** (5 mol%)	**PCy_3** (5 mol%)	>99	70/30
5	dppf (5 mol%)	**PPh_3** (5 mol%)	35	15/20
6	dppf (5 mol%)	**P(*o*-tolyl)$_3$** (5 mol%)	27	15/12

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7	dppf (5 mol%)	**P(*p*-OMeC$_6$H$_4$)$_3$** (5 mol%)[c]	95	55/39
8	dppf (5 mol%)	**IMes** (5 mol%)[d]	70	45/25
9	dppf (5 mol%)	**SIMes** (5 mol%)[e]	<5	n.d.
10[f]	dppf **(10 mol%)**	PCy_3 (5 mol%)	35	30/5
11[f]	dppf (5 mol%)	PCy_3 **(10 mol%)**	25	25/n.d.
12[f]	-	PCy_3 (5 mol%)	16	-/16
13[f]	dppf (5 mol%)		-	-/-

[a] Reaction conditions: 0.2 mmol scale (0.1 M), β/α: >99:1 and S_N2: S_N2' >99:1 unless otherwise noted. [b] Determined by GC-MS analysis and ^{1}H NMR of the reaction crude using Ph_3CH as internal standard. [c] β/α: 95:5 mixture of borylated products. [d] Using IMesCuCl. [e] SIMesCuCl *in situ* generated from the imidazolium salt $SIMesBF_4$ and CuCl. [f] 2.0 equivalents of NaO*t*-Bu. dppe = 1,2-bis (diphenylphosphinoethane). dppf = 1,1′-bis(diphenylphosphinoferrocene). IMes = 1,3-dimesitylimidazolidinium chloride. SIMes = 1,3-bis(mesityl)imidazolium chloride. n.d. = not determined-

Having established $Pd(dba)_2$/dppf and CuCl/PCy_3 as the optimal catalytic system, we examined the ratio of the two catalysts. When using a 2:1 or 1:2 Cu/Pd ratio (Table 2, entries 10 and 11) substantial decrease of yield was observed (30 and 25% NMR yield of **2.7**), thus, showing the importance of matched kinetics in bimetallic catalysis. It is important to highlight that the reaction is totally inhibited in the absence of any of the metal catalysts (Table 2, entries 12 and 13).

Evaluation of the nature of the base and the leaving group of the allylic substrate was also carried out (Table 3). We initially observed that changing the cation of the *tert*-butoxide base has a big impact in the outcome of the reaction (Table 3, entries 1-3). KO*t*-Bu and LiO*t*-Bu led to **2.7** in considerably lower yield. Other type of bases such as KOH or NaOMe did not provide formation of product **2.7** (Table 3, entries 4 and 5). We also found that catalytic amount of base did not provide the reaction in an efficient manner (Table 3, entry 6). Importantly, an increase in the amount of NaO*t*-Bu (2.0 equiv) afforded **2.7** in an excellent 94% NMR yield almost precluding the formation of **2.8** (Table 3, entry 7). The use of bigger amount of NaO*t*-Bu (3.0 equiv) provided partial decomposition of the product **2.7** by protodeboronation, thus decreasing the yield (Table 3, entry 8).

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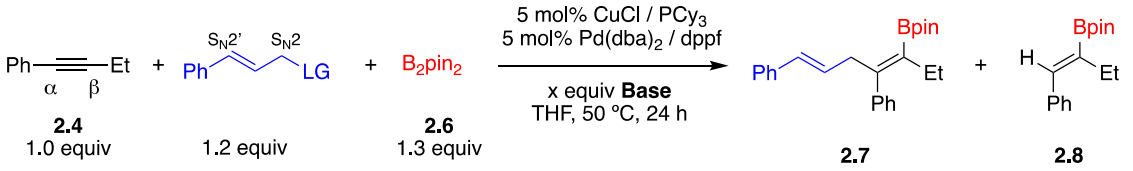
Table 3. Evaluation of base and leaving group.



Entry[a]	Base	Equiv (x)	LG	Conv. **2.4** (%)[b]	**2.7**/**2.8** (%)[b]
1	**NaO*t*-Bu**	1.3	OBoc	>99	70/30
2	**LiO*t*-Bu**	1.3	OBoc	41	34/7
3	**KO*t*-Bu**	1.3	OBoc	58	41/17
4	**KOH**	1.3	OBoc	<5	n.d.
5	**NaOMe**	1.3	OBoc	<5	n.d.
6[c]	NaO*t*-Bu	**0.2**	OBoc	11	8/3
7[d]	NaO*t*-Bu	**2.0**	OBoc	>99	94/6
8[e]	NaO*t*-Bu	**3.0**	OBoc	>99	85/5
9[d]	NaO*t*-Bu	2.0	**OCO_2Me**	>99	93/7
10	NaO*t*-Bu	2.0	**$OP(O)(OEt)_2$**	38	21/17
11	NaO*t*-Bu	2.0	**OAc**	15	15/-
12	NaO*t*-Bu	2.0	**Br**	-	n.d.

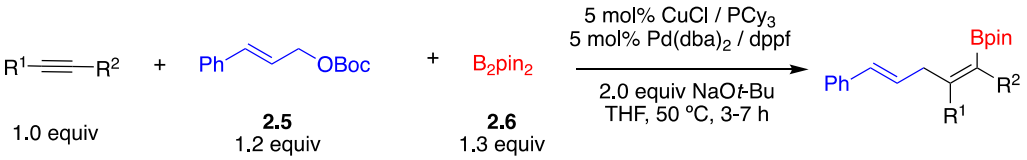
[a] Reaction conditions: 0.2 mmol scale (0.1 M), β/α: >99:1 and S_N2/ S_N2': >99:1 unless otherwise noted. [b] Determined by GC-MS analysis and ^1H NMR of the crude using Ph_3CH as internal standard. [c] 10 mol% of both catalyst, toluene as solvent and dppe as ligand for Pd. [d] Reaction completed in 5 hours. [e] Deborylation product observed at longer times of reaction. n.d. = not determined

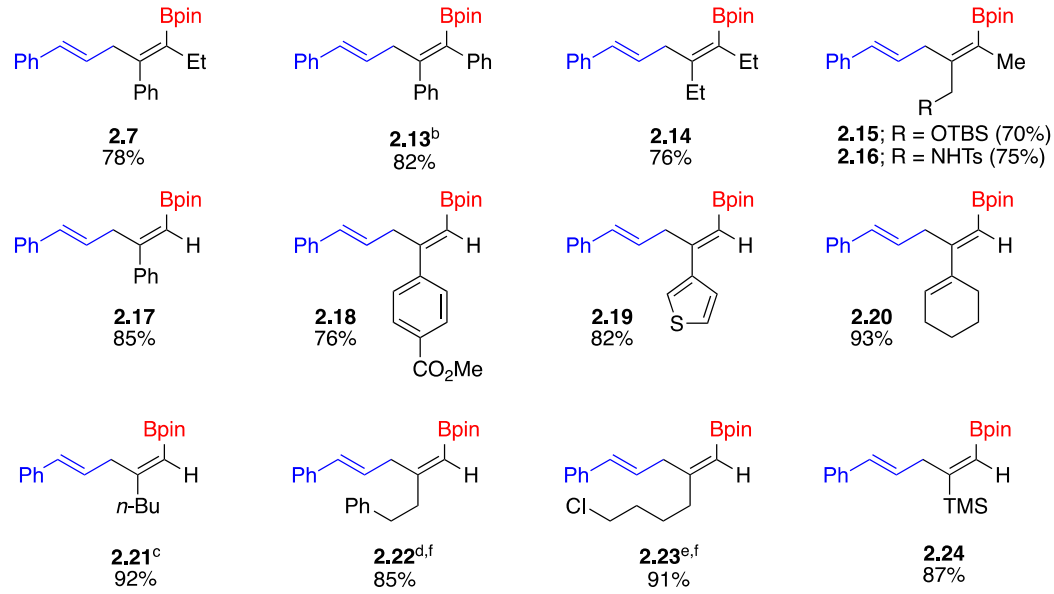
Cinnamyl methyl carbonate (**2.9**) provided comparable results to those obtained with **2.5** under the optimized conditions (Table 3, entry 9). On the other hand, cinnamyl phosphate (**2.10**), acetate (**2.11**), and bromide (**2.12**) were not efficient substrates for this transformation (Table 3, entries 10-12).

3.2. SCOPE OF THE REACTION

Having established the optimized conditions for the Cu/Pd-catalyzed allylboration of alkynes (Table 3, entry 7), we set out to investigate the scope of the reaction. First, we explored this new transformation by using different alkynes (Table 4).

Table 4. Scope of alkynes[a]





[a] Reactions performed on a 0.5 mmol scale. β/α and S_N2/ S_N2' ratios >99:1 unless otherwise noted. Yields refer to isolated pure products. Regioselectivity determined by GC and ^{1}H NMR analysis of the reaction crude. [b] Structure was confirmed by X-ray analysis. [c] β/α = 95:5. [d] β/α = 90:10. [e] β/α = 82:18. [f] Combined yield of both α and β regioisomers.

Reactions proceeded with total stereo- and regioselectivity and furnished exclusively the corresponding dienes in nearly all cases. Moreover, several functional groups such as silyloxy, sulfonamide, chloro, ester and trimethylsilyl groups were well tolerated. Internal alkynes bearing both aromatic or aliphatic substituents proved to be very efficient substrates affording the corresponding products **2.7**, **2.13-2.16** in very good yields. Interestingly, dialkylalkynes **2.15** and **2.16** without a strong electronic bias[127] to control the borylcupration step exhibited complete regioselectivity. Terminal alkynes were also efficient partners for this transformation despite the acidity of the terminal proton. Aryl and heteroaryl-substituted alkynes and an enyne gave rise to the corresponding products **2.17-2.20** in very good yields without any trace of the corresponding protoboration products. Remarkably, alkyl-substituted terminal alkynes, which exhibited poor regioselectivity in copper-catalyzed allylboration[148] and alkylboration reactions,[134] showed high levels of selectivity under our dual Cu/Pd catalytic conditions. Borylated diene **2.21** was obtained from 1-hexyne with near-perfect selectivity in 92% yield. The presence of a phenyl or a chloro group in the alkyl substituent caused a slight decrease on the β/α selectivity but products **2.22** and **2.23** were still obtained in good yields with

perfect S_N2 type selectivity. Noteworthy is the reaction with trimethylsilylacetylene[182] which gives stereoselective access to dienes (**2.24**) featuring Bpin and TMS substituents which allow for further orthogonal functionalization of the diene.

Different allyl carbonates were evaluated under the standard conditions (Table 5). Both electron-rich and electron-deficient cinnamyl substrates worked well and afforded products **2.25**-**2.27** in good yields with perfect S_N2 type substitution. Remarkably, in the case of **2.26**, the catalytic system tolerated the presence of an aromatic bromide. There was no evidence of borylation of the aryl bromide,[38] thus demonstrating the extremely high chemoselectivity of this dual catalytic system. Terminal and aliphatic allyl carbonates were also suitable substrates for this transformation showing good reactivity with both terminal and internal alkynes (**2.28**-**2.30**). When (*Z*)-tert-butyl pent-2-en-1-yl carbonate (*Z*)-**2.37** was used, inversion of the configuration of the allyl double bond took place and the corresponding diene **2.30** was obtained as pure (*Z,E*) isomer. Inversion of the allyl double bond configuration might arise from π-σ isomerization and C−C bond rotation of the allyl-Pd(II) intermediate. The reaction was also compatible with the use of secondary cyclic and acyclic allylic carbonates (**2.31**-**2.34**) with toluene being the most efficient solvent in these cases. Interestingly, complete S_N2 selectivity was still observed in the formation of dienes **2.33** and **2.34** from unsymmetrical secondary allyl carbonate **2.38**. The use of trisubstituted allylic carbonates was exemplified by using geraniol (**2.39**) and nerol (**2.40**) derivatives. In both cases the corresponding products **2.35** and **2.36** were obtained in excellent yield and with complete regio- and stereoselectivity and total retention of the configuration of the double bond of the starting allylic substrate. Stereochemical retention of the double bond geometry would be the result of a slow π−σ−π isomerization of the corresponding trisubstituted allyl-Pd(II) intermediate. These results show that synergistic Cu/Pd catalysis allows for an efficient allylboration of alkynes which features total S_N2-type regioselectivity enabled by the Pd catalytic cycle. This is in sharp contrast with the copper-catalyzed allylboration of alkynes with allyl phosphates reported by Zhong,[148] in which, regioselectivity is governed by substrate control and formal S_N2 or S_N2' substitution products, or mixtures of both, are obtained depending on the nature of the alkyne and the allyl phosphate.

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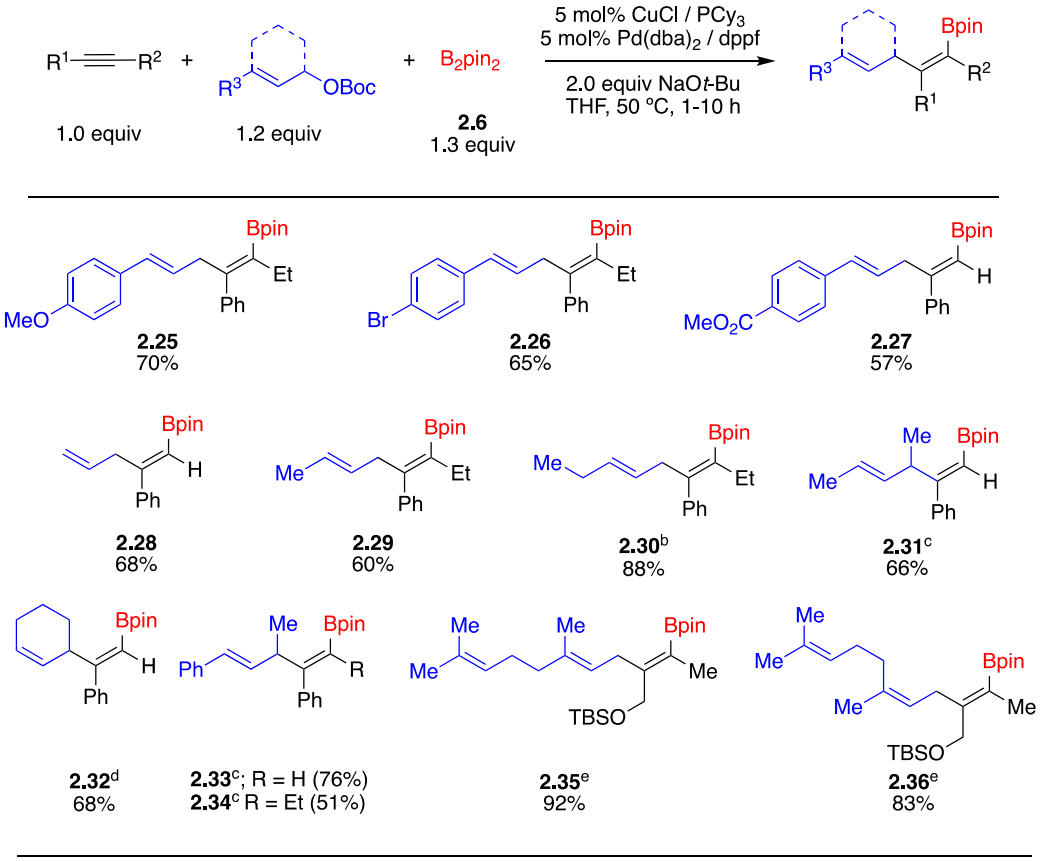
[182] Trimethylsilylacetylene has shown to be a reluctant partner in copper-catalyzed allylboration (ref 148) and protoboration reactions (ref 129).

Table 5. Scope of allyl substrates[a]



[a] Reactions performed on a 0.5 mmol scale. β/α and S_N2/ S_N2' >99:1 in all cases. Yields refer to isolated pure products. Regioselectivity determined by ^{1}H NMR analysis of the reaction crude. [b] (*Z*)-**2.37** used at 60 °C. [c] In toluene at 50 °C. [d] In toluene at 75 °C. [e] THF reflux using 1.1 equiv of B_2pin_2.

The stereochemistry of these products was confirmed by X-ray analysis of diene **2.13** (Figure 12).

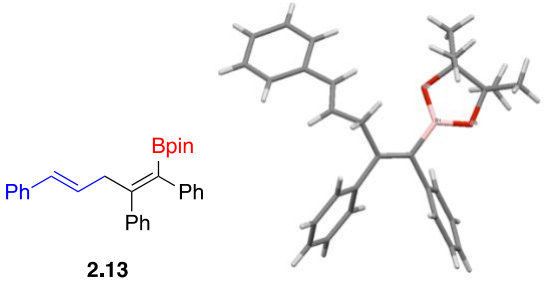
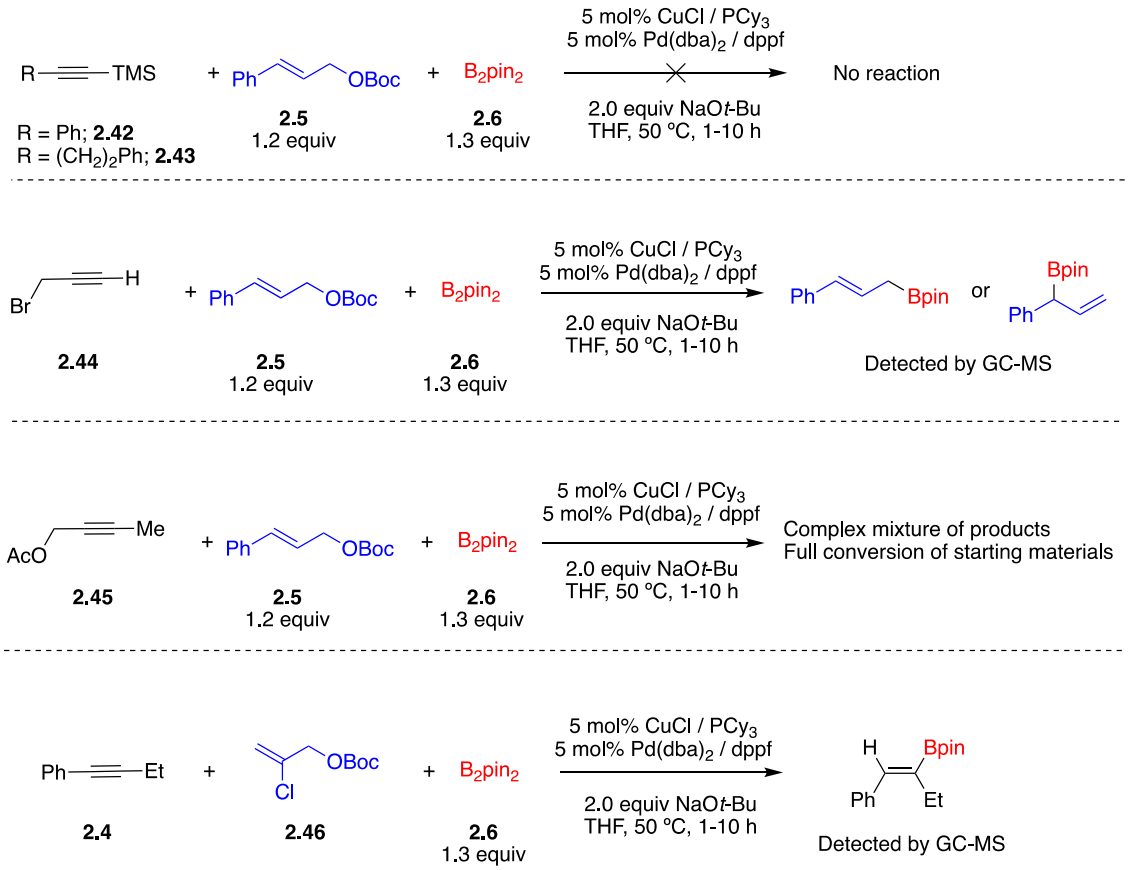


Figure 12. X-ray analysis of product **2.13**.

3.2.1. Limitations of the scope

Although the protocol showed up a broad functional group tolerance, some substrates resulted unreactive or not selective under standard conditions. In Figure 13, substrates that resulted unreactive or provided undesired products are shown. In the optimized conditions, alkyne **2.42** and **2.43** did not provide the formation of any product, conversion of starting materials was not observed. With propargylic alkyne **2.44** the formation of

borylated allyl substrate and remaining starting cinnamyl *tert*-butyl carbonate were detected by GC-MS, full conversion of the alkyne was observed by ^{1}H NMR analysis. Using alkyne **2.45**, a complex mixture of products was observed by ^{1}H NMR analysis, no starting alkyne or cinnamyl *tert*-butyl carbonate was detected. Regarding the allylic substrates, the allylic carbonate **2.46** did not provide the allylboration product when it was reacted with 1-phenyl-1-propyne, or with phenylacetylene.



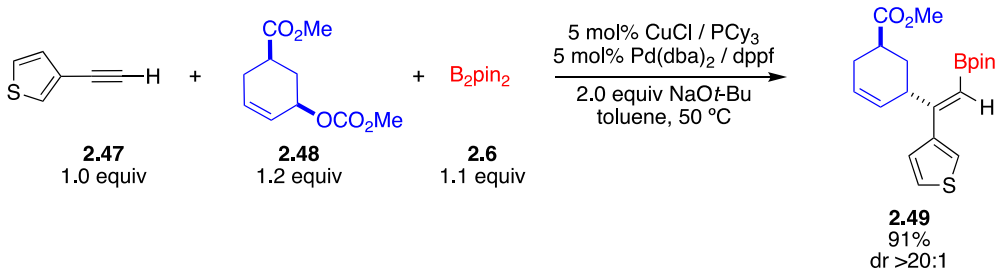
Scheme 102. Unsuccessful substrates.

3.3. MECHANISTIC PROPOSAL

Among the mechanistic intricacies of this transformation, we wanted to elucidate what type of reaction occurs between the key organometallic intermediates, i.e. the alkenylcopper and the allylPd complexes. Organocopper reagents have been identified as *"soft"* nucleophiles in their direct reactions with allylic substrates,[183] however, little is known about their nucleophilic nature in Pd-catalyzed allylation reactions. To assess whether the catalytically generated alkenylcopper species behave as *"soft"* or *"hard"* nucleophile in the Pd-catalyzed allylation event, alkyne **2.47** were reacted with diastereomerically pure *cis* allyl carbonates **2.48** and B2pin2 **2.6**. Excellent diastereocontrol was observed providing the corresponding product **2.49** as single *trans*

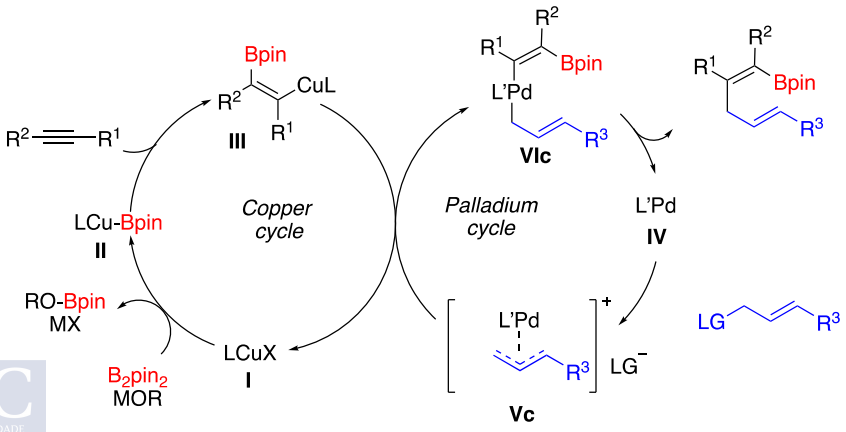
[183] (a) Breit, B.; Demel, P. In *Modern Organocopper Chemistry*; Krause, N., Ed.; Wiley-VCH: Weinheim, 2002; pp 188-223; (b) Yoshikai, N.; Nakamura, E. *Chem. Rev*. **2012**, *112*, 2339-2372.

diastereomers in 95% yield. This result clearly indicates that the catalytically generated β-borylalkenylcopper intermediate behaves as a *"hard"* nucleophile in this transformation.



Scheme 103. Allylboration reaction of phenylacetylene with a diastereomerically pure *cis* cyclic allyl carbonate **2.48**.

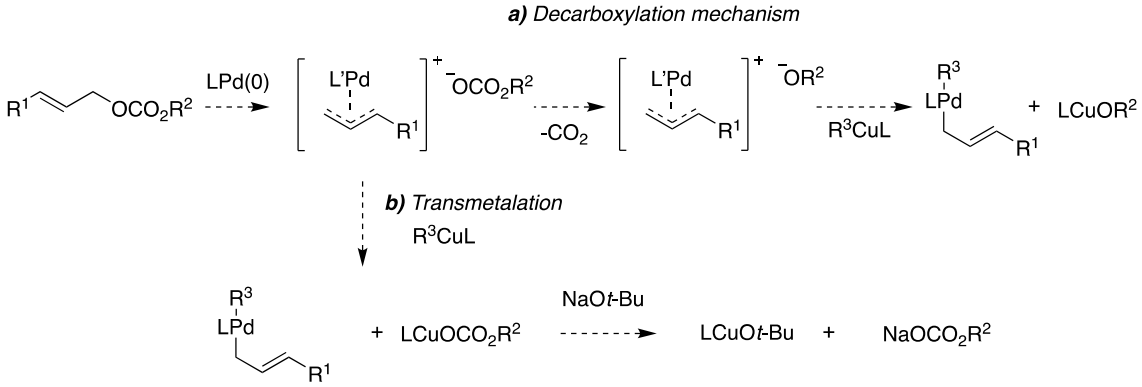
In sight of the experiment shown in Scheme 103, we can propose a dual catalytic mechanism (Scheme 104) that would consist in a regio- and stereoselective borylcupration of the alkyne with LCu-Bpin complex **II** to generate the β-boryl alkenylcopper(I) intermediate **III**. In the second catalytic cycle, a cationic π-allyl Pd(II) complex **Vc** would be formed by oxidative addition of the allyl substrate to a Pd(0) complex **IV**. Reaction between intermediates **III** and **Vc** elapses through an inner-sphere transmetalation step, to form the intermediate **VIc** and to regenerate copper complex **I**. In this step, the palladium catalyst controls the regioselectivity of the allylic substitution, and skipped diene would be obtained after reductive elimination to regenerate palladium(0) complex **IV**. Before the transmetalation step, isomerization to a σ-allylpalladium complex would occur to generate a vacant site at the Pd atom. Regioselectivity control might arise from the formation of the the σ-allylpalladium complex with the palladium atom positioned in the less substituted position of the allylic substrate.



Scheme 104. Mechanistic proposal for the Cu/Pd catalyzed allylboration of alkynes.

As we observed during the screening of the reaction, stoichiometric amount of base is needed for the reaction to work in an efficient manner (Table 3, entry 6 vs 7). After the oxidative addition of the allylic carbonate into the palladium(0) center, the carbonate

released could undergo decarboxylation to provide an alkoxide (Scheme 105a). This alkoxide could regenerate the Cu-OR after the transmetalation step. However, if the decarboxylation step is slow,[184] the transmetalation step could be faster, generating a carbonate copper complex which would need to react with NaO*t*-Bu to regenerate the active catalytic species (Scheme 105b).



Scheme 105. Possible palladium complexes formed before transmetalation step.

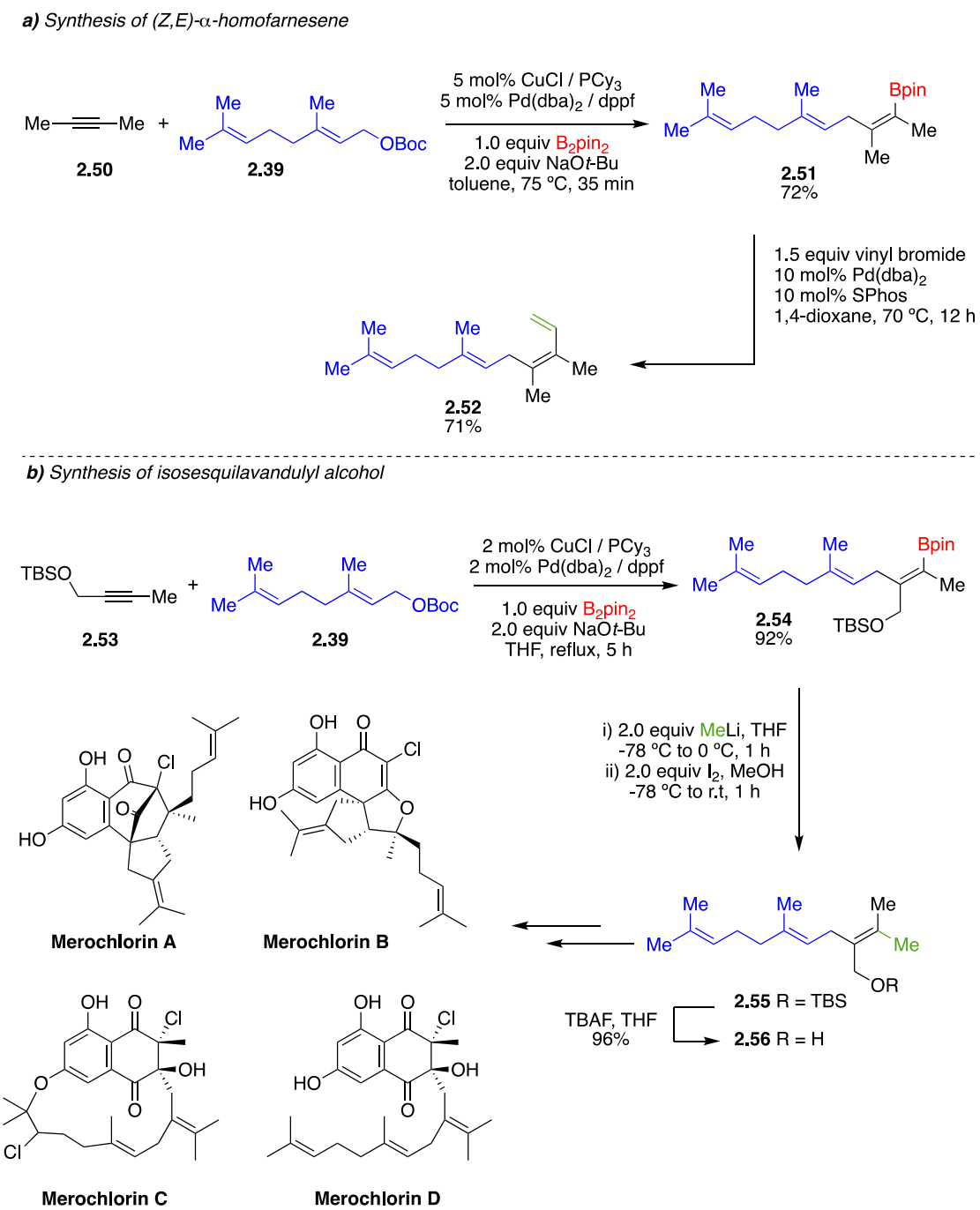
3.4. SYNTHETIC APPLICATIONS

To illustrate the synthetic utility of the present catalytic methodology, we targeted the synthesis of two natural products (Scheme 106). (*Z*,*E*)-α-Homofarnesene **2.52**, a component of the trail pheromone of the fire-ant,[158] could be obtained in two steps via Cu/Pd-catalyzed allylboration of 2-butyne **2.50** with allyl carbonate **2.39** and subsequent Suzuki coupling with vinyl bromide (Scheme 106a). This new synthetic route reduces significantly the number of steps and provides a single stereoisomer in contrast to previous syntheses which afforded mixtures of the (*Z*,*E*) and (*E*,*E*) homofarnesenes.[158b,c] We also applied our methodology to the synthesis of isosesquilavandulyl alcohol **2.56** (Scheme 106b), a key intermediate in the synthesis of Merochlorins A-D which are marine meroterpenoid secondary metabolites with potent antibiotic activity.[185] Synthesis of **2.54** was executed on larger scale (3 mmol) using a reduced catalyst loading (2 mol % of both copper and palladium catalysts) and still furnished the product without erosion of yield (92%). Conversion of the C-Bpin to a C-Me bond was performed by reaction with MeLi and iodine,[5b,79b] affording **2.55** in 87% yield. Final cleavage of the TBS group delivered isosesquilavandulyl alcohol **2.56** in 77% overall yield. This route not only gives

[184] p-allylpalladium(II) carbonate complexes have been isolated and reported to not undergo a fast decarboxylation in certain cases: (a) Ozawa, F.; Son, T.; Ebina, S.; Osakada, K.; Yamamoto, A. *Organometallics* **1992**, *11*, 171-176. (b) Amatore, C.; Gamez, S.; Jutand, A.; Meyer, G.; Moreno-Mañas, M.; Morral, L.; Pleixats, R. *Chem. Eur. J.* **2000**, *6*, 3372-3376.

[185] (a) Kaysser, L.; Bernhardt, P.; Nam, S.-J.; Loesgen, S.; Ruby, J. G.; Skewes-Cox, P.; Jensen, P. R.; Fenical, W.; Moore, B. S. *J. Am. Chem. Soc.* **2012**, *134*, 11988-11991. (b) Pepper, H. P.; George, J. H. *Angew. Chem. Int. Ed*. **2013**, *52*, 12170-12173. (c) Meier, R.; Strych, S.; Trauner, D. *Org. Lett*. **2014**, *16*, 2634-2637. (d) Teufel, R.; Kaysser, L.; Villaume, M. T.; Diethelm, S.; Carbullido, M. K.; Baran, P. S.; Moore, B. S. *Angew. Chem. Int. Ed*. **2014**, *53*, 11019-11022.

straightforward access to **2.56** but also offers the possibility of synthesizing artificial analogs of Merochlorins by alternative functionalization (e.g., trifluoromethylation, fluorination) of the C-Bpin bond.



Scheme 106. a) Total synthesis of homofarnesene and **b)** formal synthesis of merochlorins A-D via Cu/Pd catalyed allylboration of alkynes.

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4. CONCLUSIONS

We have developed an efficient methodology for the synthesis of borylated linear 1,4-dienes, through a novel palladium and copper synergistically catalyzed allylboration of alkynes under mild conditions.

One of the main features of the catalytic system is the high levels of chemoselectivity shown. Competing reactions such as borylation of the allylic substrate and protoboration of the alkyne are completely precluded or reduced to not significant levels.

Optimized conditions provided perfect levels of regio- and stereoselectivity for this transformation. Upon the eight isomers that can emerged from this reaction, in the optimized conditions the formation of just one product was observed in nearly all cases.

We have demonstrated that the alkenylcopper(I) reagents act as *"hard"* nucleophile, providing the allylic substitution through an inner-sphere transmetalation mechanism with complete inversion of configuration when a diastereomerically pure allyl substrate is used.

The versatility of the methodology was demonstrated by the total synthesis of (*Z*,*E*)-α-Homofarnesene, a trial pheromone of the fire ant, in two steps (previously described in 4 steps). We could also perform the synthesis of isosesquilavandulyl alcohol, which is a key intermediate in the synthesis of Merochlorins A-D, which are marine meroterpenoid secondary metabolites with potent antibiotic activity.

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CHAPTER III: SYNTHESIS OF STEREODEFINED BORYLATED DENDRALENES THROUGH COPPER-CATALYZED ALLYLBORATION OF ALKYNES

Chapter adapted from:
Rivera-Chao, E.[a]; Fañanás-Mastral, M.[a] *Angew. Chem. Int. Ed.* **2018**, *57*, 9945-9949.

[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)

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1. INTRODUCTION

1.1. DENDRALENES

Polyenes can be classified in two groups: conjugated and cross-conjugated systems. Among conjugated polyenes, we can distinguish between linear polyenes and annulenes, which are conjugated endocyclic alkenes. Regarding cross-conjugated polyenes, we can differentiate three classes: radialenes, which consist in entirely exocyclic double bonds, fulvenes, a mixture of exocylic and endocylic double bonds, and dendralenes, that are polyenes with geminal connections between the double bonds (Figure 13).

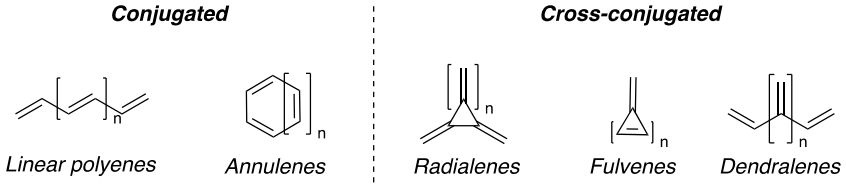


Figure 13. Different types of polyenes.

Conjugated polyenes are common scaffolds in organic chemistry and have been extensively studied and synthetized.[186] Nonetheless, the chemistry of cross-conjugated polyenes have been less explored, although the interest on these systems has been growing up in the last decades.[187] In particular, dendralenes have been neglected for a long time, likely due to the lack of efficient methods to synthesized them. Moreover, dendralenes were assumed to be too unstable to handle. After decades of obscurity, pioneering work by Hopf, and more recently the Sherburn group, has brought dendralenes to the forefront of organic chemistry.[188] Dendralenes have recently attracted much

[186] (a) *The Chemistry of Dienes and Polyenes*; Rappoport, Z., Ed.; Wiley: Chichester, U.K., 1997. (b) *The Chemistry of Dienes and Polyenes*, 2nd ed.; Rappoport, Z., Ed.; Wiley: Chichester, U.K., 2000. (c) Thirsk, C.; Whiting, A. *J. Chem. Soc., Pekin Trans*. **2002**, *1*, 999-1023. (d) Spitler, E. L.; Johnson, C. A.; Haley M. M. *Chem. Rev.* **2006**, *106*, 5344-5386.

[187] *Cross Conjugation: Modern Dendralene, Radialene and Fulvene Chemistry*; Hopf, H.; Sherburn, M. S, Eds. Wiley-VCH, Weinheim: 2016.

[188] For reviews see: (a) Hopf, H.; *Angew. Chem. Int. Ed*. **1984**, *23*, 948-959. (b) Hopf, H. *Angew. Chem. Int. Ed*. **2001**, *40*, 705-707. (c) Gholami, M.; Tykwinski, R. R. *Chem. Rev*. **2006**, *106*, 4997-5027. (d) Mackay, E. G.; Sherburn, M. S. *Pure Appl. Chem.* **2013**, *85*, 1227-1239.

attention due to their important role in polymer[189] and synthetic chemistry,[190] as well as their occurrence in a number of natural products (Figure 14).[191]

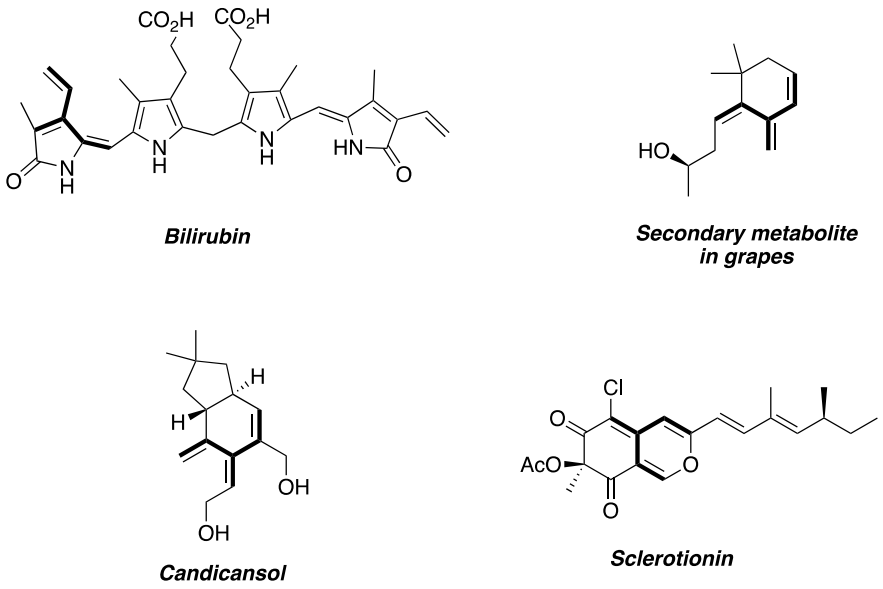


Figure 14. Natural occurring dendralenes.

Dendralenes are named after the number of cross-conjugated double bonds present in their structure. This number is given in brackets before the word dendralene. Some examples of parent dendralenes that have been reported so far are depicted in Figure 15.

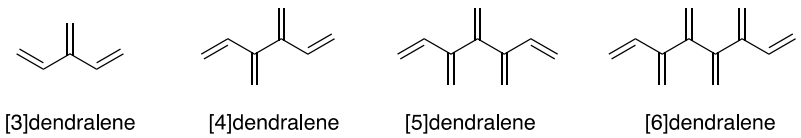


Figure 15. Nomenclature of dendralenes.

1.1.1. Synthesis of dendralenes

Classical methodologies for the synthesis of dendralenes involve thermal rearrangements, elimination or Wittig reactions. However, they usually require very high

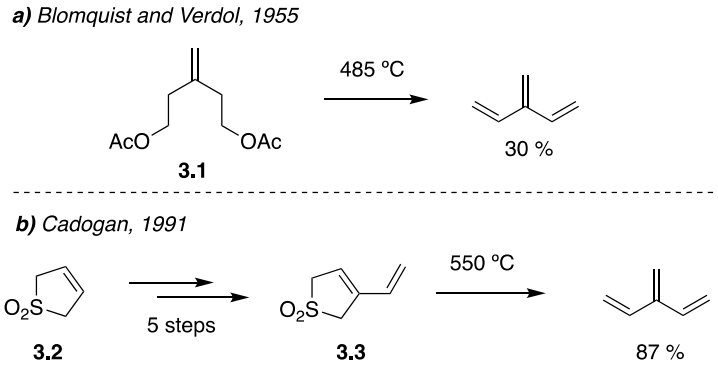
[189] (a) Diakoumakos, C. D.; Mikroyannidis, J. A. *J. Appl. Polym. Sci*. **1994**, *53*, 201-212. (b) Takenaka, K.; Amamoto, S.; Takeshta, H.; Miya, M.; Shiomi, T. *Macromolecules* **2013**, *46*, 7282-7289. (c) Takamura, Y.; Takenaka, K.; Toda, T.; Takeshita, H.; Miya, M.; Shiomi, T. *Macromol. Chem. Phys*. **2018**, *219*, 1700046. (e) Takagi, T.; Toda, T.; Miya, M.; Takenaka, K. *Macromolecules* **2021**, *54*, 4326-4332.

[190] (a) Naidu, G. S.; Singh, R.; Ghosh, S. K. *Synlett*. **2018**, *29*, 282-295. (b) Newton, C. G.; Sherburn, M. S. Cross-conjugation in synthesis in *Cross Conjugation: Modern Dendralene, Radialene and Fulvene Chemistry*; Hopf, H.; Sherburn, M. S, Eds. Wiley-VCH, Weinheim: 2016; pp. 413-444. (c) Hopf, H.; Sherburn, M. S. *Angew. Chem. Int. Ed*. **2012**, *51*, 2298-2338.

[191] (a) Maccurin, T.; Reilly, J. *Nature* **1940**, 146, 335. (b) Bonnett, R.; Davies, J. E.; Hursthouse, M. B. *Nature* **1976**, *262*, 326-328. (c) Tattje, D. H. E.; Bos, R.; Bruins, A. *P. Planta Med*. **1980**, *38*, 79-85. (d) Montanarella, L.; Bos, R.; Fischer, F. C. *Planta Med*. **1986**, *52*, 332-334. (e) A. Arnone, R. Cardillo, V. Dimodugno, G. Nasini, *J. Chem. Soc. Perkin Trans. 1,* **1989**, 1995-2000. (f) Sefton, M. A.; Francis, I. L.; Williams, P. J. *J. Food Sci*. **1994**, *59*, 142-147.

temperatures and most of these methods do not provide dendralenes in a productive manner or require the use of not readily available precursors.[192]

An example of this type of transformations consists in the thermal elimination of diacetate **3.1** at 485 ºC, that provides the parent [3]dendralene in 30% yield (Scheme 107a).[192a] The group of Cadogan reported a more efficient synthesis of [3]dendralene by pyrolysis of 3-vinyl-3-sulfone **3.3** (Scheme 107b).[192f] Although more efficient, this method requires the synthesis of **3.3**, which involves 5 steps from sulfone **3.2**.



Scheme 107. Early syntheses of [3]dendralene.

The work of Cadogan inspired the Sherburn group to develop a synthetic methodology for the synthesis of higher dendralenes.[193] They could obtain dendralenes by thermal cheletropic elimination with sulfone-masked dendralenes, which were obtained via Stille couplings (Scheme 108). This represented the first example for the synthesis of dendralenes higher than [4]dendralene.

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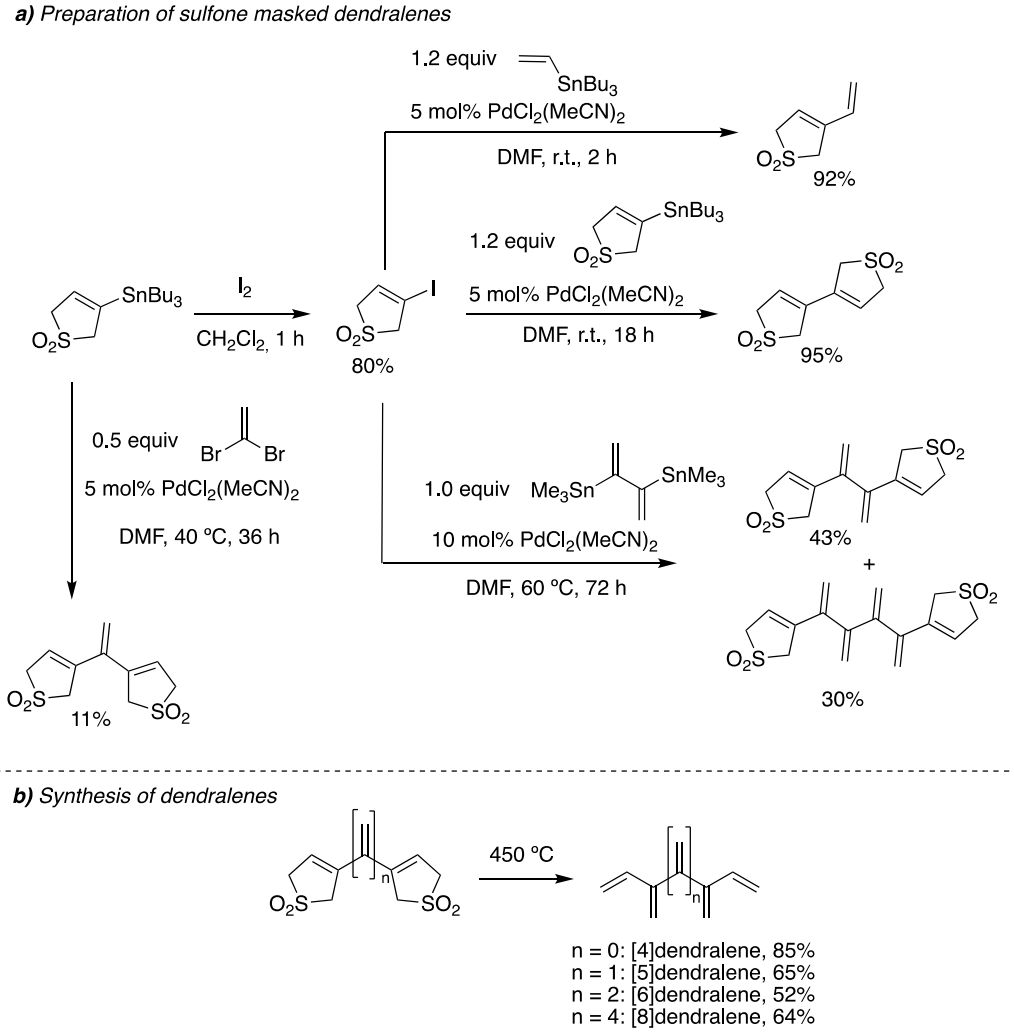
[192] (a) Blomquist, A. T.; Verdol, J. A. *J. Am. Chem. Soc*. **1955**, *77*, 81-83. (b) Bailey, W. J.; Economy, J. *J. Am. Chem. Soc*. **1955**, *77*, 1133-1136. (c) Blomquist, A. T.; Verdol, J. A. *J. Am. Chem. Soc*. **1955**, *77*, 1806-1809. (d) Bailey, W. J.; Cunov, C. H.; Nicholas, L. *J. Am. Chem. Soc*. **1955**, *77*, 2787-2790. (e) Priebe, H.; Hopf, H. *Angew. Chem. Int. Ed*. **1982**, *21*, 286-287. (f) Cadogan, J. I. G.; Cradock, S.; Gillam, S.; Gosney, I. *Chem. Commun*. **1991**, 114-115.

[193] Fielder, S.; Rowan, D. D.; Sherburn, M. S. *Angew. Chem. Int. Ed*. **2000**, 39, 4331-4333.

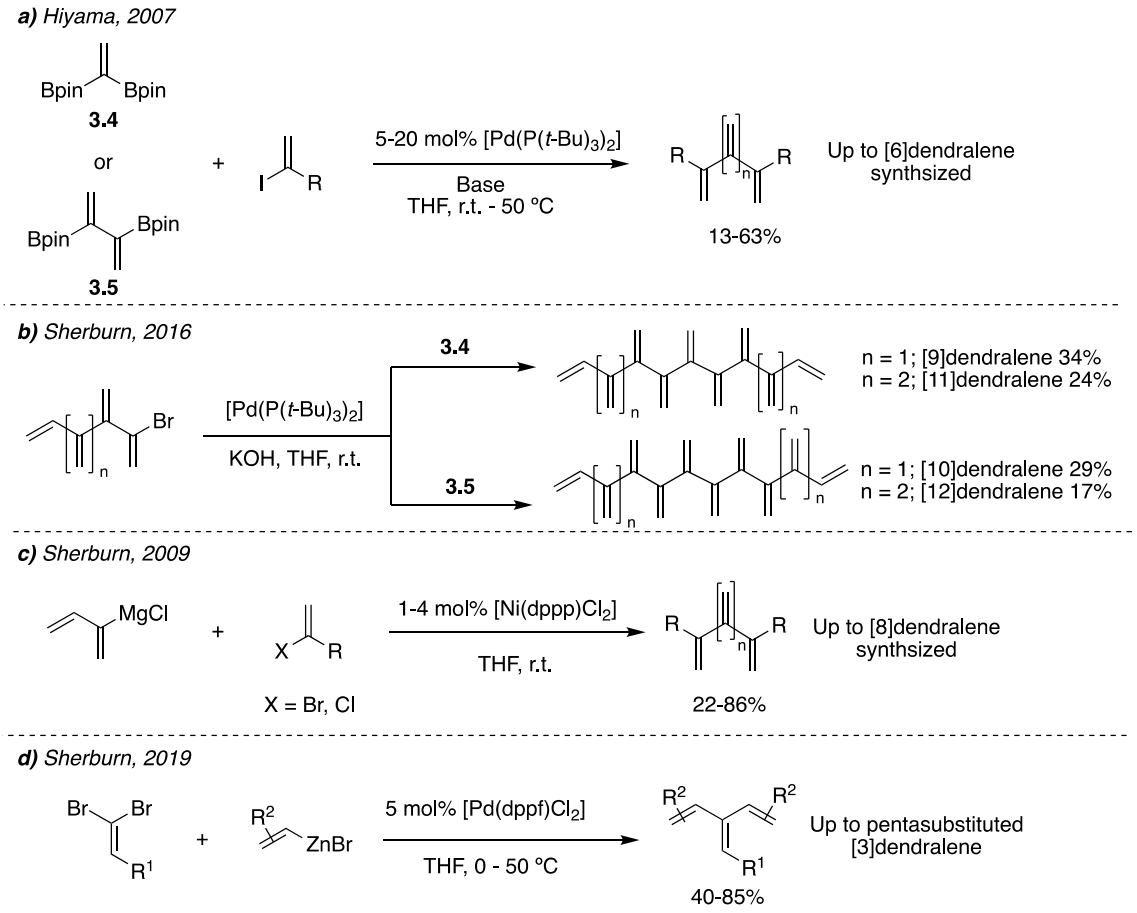


Scheme 108. First synthesis of [5] to [8]dendralenes.

The high value of dendralenes and the growing interest in their chemistry calls for efficient synthetic methods. Modern methodologies are based in transition metal catalysis and they mainly rely on Ni- and Pd-catalyzed cross-coupling of alkenyl metal reagents with (bis)haloalkenes (Scheme 109).[194] Based on this transformation, the retrosynthesis of dendralenes could be envisioned in two ways: 1) a double cross-coupling with a 1,1-bis(halo)-alkene and an alkenyl metal reagent, and 2) the other way around, a reaction between a 1,1-bis(metal)alkene with an haloalkene. Based on the latter strategy, Hiyama reported in 2007 the synthesis of [n]dendralenes (n = 3-6) via a palladium-catalyzed Suzuki-Miyaura cross-coupling between 1,1-diborylalkene **3.4** and 2,3-diborylbutadiene **3.5** and iodoalkenes (Scheme 109a).[194b] They were able to prepare unsymmetrical

[194] (a) Shimizu, M.; Nakamaki, C.; Shimono, K.; Schelper, M.; Kurahashi, T.; Hiyama, T. *J. Am. Chem. Soc*. **2005**, *127*, 12506-12507. (b) Shimizu, M.; Kurahashi, T.; Shimono, K.; Tanaka, K.; Nagao, I.; Kiyomoto, S.-I.; Hiyama, T. *Chem. Asian J*. **2007**, *2*, 1400-1408. (c) Bradford, T. A.; Payne, A. D.; Willis, A. C.; Paddon-Row, M. N.; Sherburn, M. S. *Org. Lett*. **2007**, *9*, 4861-4864. (d) Payne, A. D.; Bojase, G.; Paddon-Row, M. N.; Sherburn, M. S. *Angew. Chem. Int. Ed*. **2009**, *48*, 4836-4839. (e) Saglam, M. F.; Fallon, T.; Paddon-Row, M. N.; Sherburn, M. S. *J. Am. Chem. Soc*. **2016**, *138*, 1022-1032. (f) George, J.; Ward, J. S.; Sherburn, M. S. *Chem. Sci*. **2019**, *10*, 9969-9973.

substituted dendralenes performing a two-step sequence of cross-coupling with different alkenyl iodides. However, the yields are generally low, and the protocol requires the previous synthesis of the diborylalkenes. The discovery of these double nucleophiles, **3.4** and **3.5**, for the synthesis of dendralenes, allowed Sherburn and co-workers to achieve the first synthesis of [9] to [12]dendralenes in a work published in 2016 (Scheme 109b).[194e]



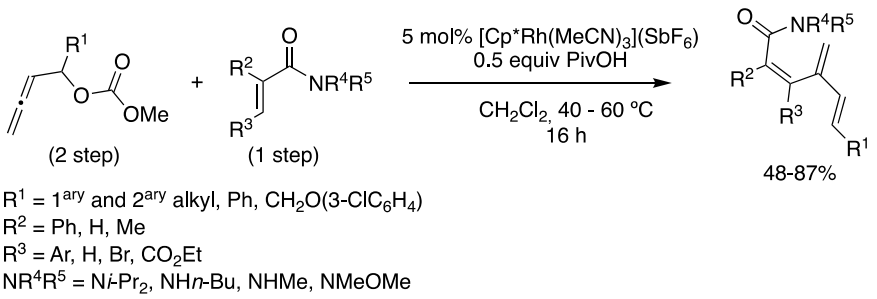
Scheme 109. Synthesis of dendralenes by Palladium or Nickel-catalyzed cross-coupling reactions.

A protocol based on Kumada-Tamao-Corriu and Negishi couplings was reported by Sherburn to synthesize [3]-[8] dendralenes in a more efficient manner using nickel catalysis (Scheme 109c).[194d] Recently, the same group reported the synthesis of multisubstituted [3]dendralenes via palladium-catalyzed Negishi coupling (Scheme 109d).[194f]

Aside from these transformations, other elegant catalytic alternatives for the synthesis of dendralenes involve Rh-catalyzed C-H-activation.[195] For instance, the rhodium catalyzed coupling of allenyl carbonates with acryl amides reported by Glorius [195a], allows the synthesis of highly substituted [3]dendralenes (Scheme 110). Although

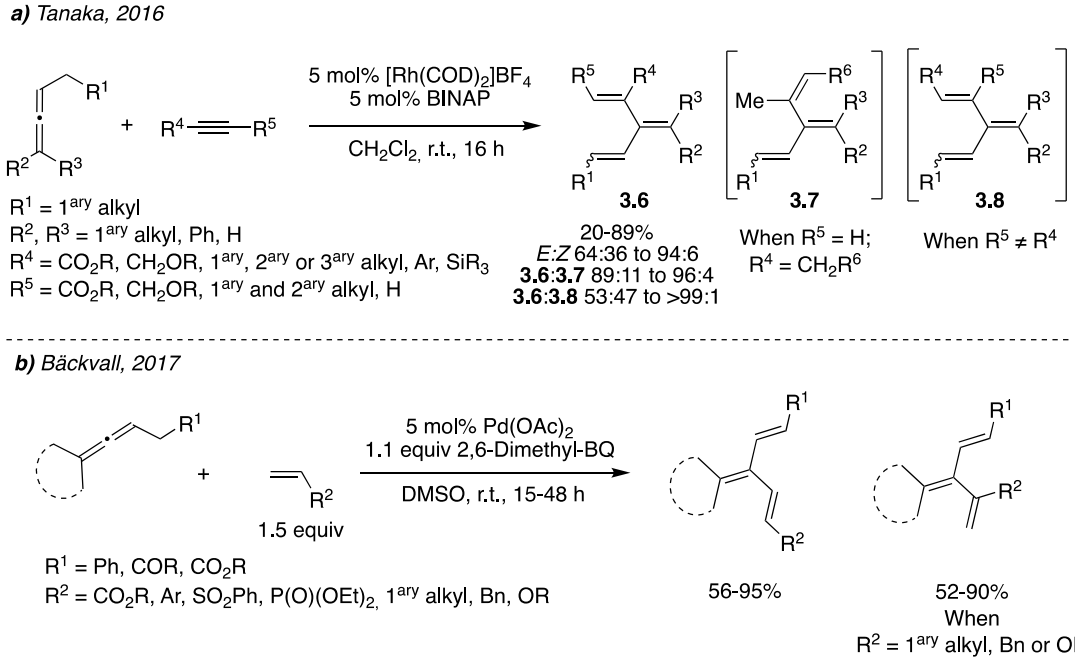
[195] (a) Wang, H.; Beiring, B.; Yu, D.; Collins, K. D.; Glorius, F. *Angew. Chem. Int. Ed*. **2013**, *52*, 12430-12434. (b) Gong, T.-J.; Su, W.; Liu, Z.-J.; Cheng, W.-M.; Xiao, B.; Fu, Y. *Org. Lett*. **2014**, *16*, 330-333.

efficient and versatile, this methodology implies the prior preparation of both the starting material the acrylamide.



Scheme 110. Example of the synthesis of [3]dendralenes via rhodium-catalyzed C-H activation of allenyl carbonates.

Pd- and Rh-catalyzed coupling of allenes have also proved to be useful for the synthesis of [3]dendralenes. [196] , [197] Tanaka reported a rhodium-catalyzed cross-dimerization of allenes and alkynes that provides [3]dendralenes with substitution in up to the 3 double bonds (Scheme 111a).[196] However, depending on the substitution of the starting material, selectivity issues can appear and mixtures of up to three isomers are obtained in certain cases.



Scheme 111. Synthesis of [3]dendralenes via rhodium- and palladium-catalyzed coupling of allenes with alkynes and alkenes.

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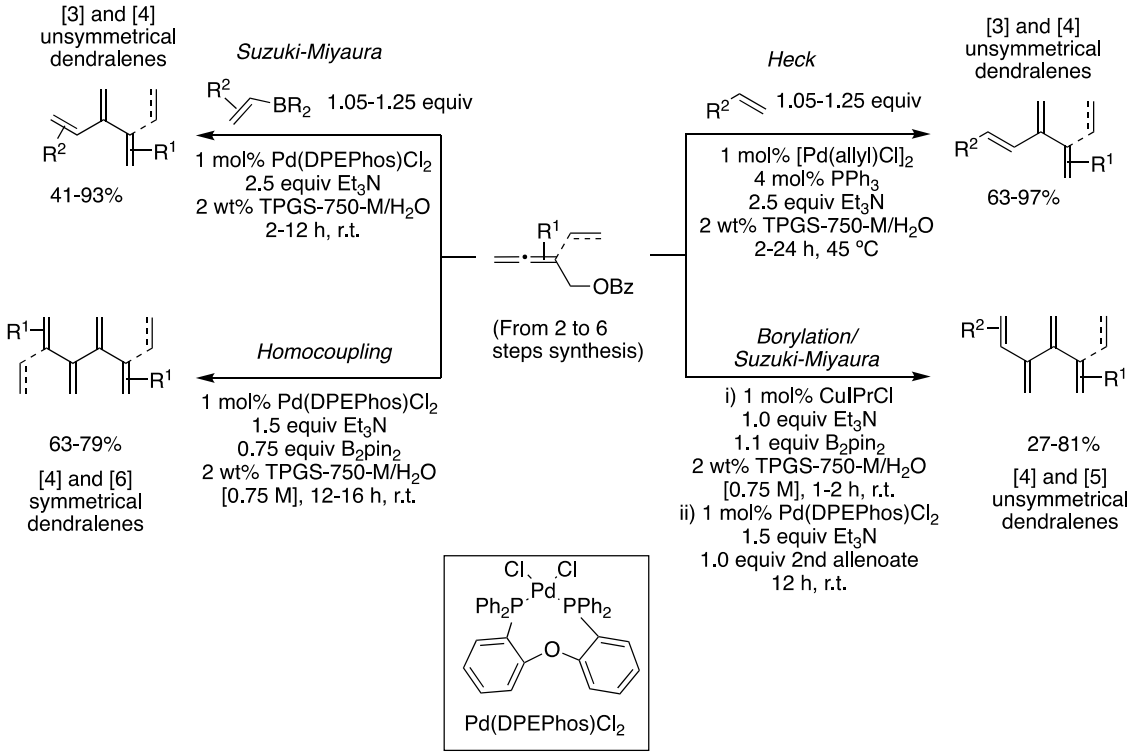
[196] Sakashita, K.; Shibata, Y.; Tanaka, K. *Angew. Chem. Int. Ed*. **2016**, *55*, 6753-6357.

[197] (a) Qiu, Y.; Posevins, D.; Bäckvall, J.-E. *Angew. Chem. Int. Ed*. **2017**, *56*, 13112-13116. (b) Lippincott, D. J.; Linstadt, R. T. H.; Maser, M. R.; Lipshutz, B. H. *Angew. Chem. Int. Ed*. **2017**, *56*, 847-850. (c) Mao, M.; Zhang, L.; Chen, Y.; Zhu, J.; Wu, L. *ACS Catal*. **2017**, *7*, 181-185.

Bäckvall reported a similar methodology using palladium catalysis which involves the coupling of allenes and alkenes with a great functional group tolerance.[197a] The regioselectivity outcome highly depends on the nature of the alkene R^2 group (Scheme 111b).

Lipshutz reported the synthesis of dendralenes by using different types of cross-coupling disconnections (Scheme 112).[196b] They exploited palladium-catalyzed Suzuki-Miyaura, Heck and tandem borylations/cross-coupling reactions to obtain a wide variety of dendralenes. Nonetheless, the allenoates used for these syntheses are not readily accessible, requiring 2 steps for the synthesis of the simpler ones to 6 steps for the more complex substrates.



Scheme 112. Synthesis of [3], [4], [5] and [6]dendralenes by palladium-catalyzed cross-coupling of allenoates.

Another alternative for the synthesis of dendralenes involves the Ru-catalyzed elimination from 1,3-dienic allylic carbonates reported by the group of Bruneau (Scheme 113).[198] Similar to other above mentioned methods, this protocol requires very specific substrates and the substitution pattern of the resulting dendralenes is limited.

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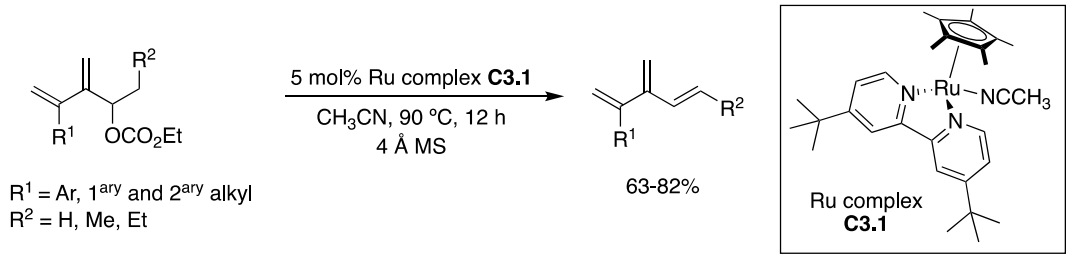
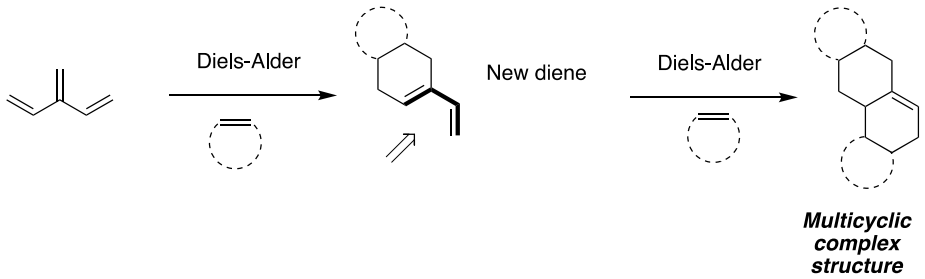
[198] Beydoun, K.; Zhang, H.-J.; Sundararaju, B.; Demerseman, B.; Achard, M.; Xi, Z.; Bruneau, C. *Chem. Commun*. **2009**, 6580-6582.



Scheme 113. Examples of synthesis of dendralenes via ruthenium-catalyzed reaction.

1.1.2. Reactivity of dendralenes

Probably, the most attractive and mostly applied synthetic feature of dendralenes is their ability to engage in diene-transmissive Diels-Alder reaction (DTDA). DTDA involves the cycloaddition between a dienophile and a dendralene, generating a new conjugated diene ready to undergo a second Diels-Alder reaction with the dienophile (Scheme 114). The degree of complexity which can be achieved with this transformation is clearly illustrated with the DTDA reaction of the simplest [3]dendralene, which generates four new C-C bonds, 2 new cycles and up to eight stereocenters.



Scheme 114. Diene transmissive Diels-Alder reaction of [3]dendralene.

The first example of a dendralene cycloaddition reaction was reported in the early 1950s.[192] However, it was not until the work of Tsuge and co-workers in 1983 when the term of Diene-Transmisive Diels-Alder (DTDA) was coined and it started to gain importance. Initial experiments involved a multiple Diel-Alder reaction between dendralene **3.9** and dimethyl acetylenedicarboxylate to provide 5-8-dihydro-1-naphtol derivative **3.10** (Scheme 115).[199] Following on this initial study, the group of Tsuge has applied the DTDA to numerous synthetic transformations.[200]

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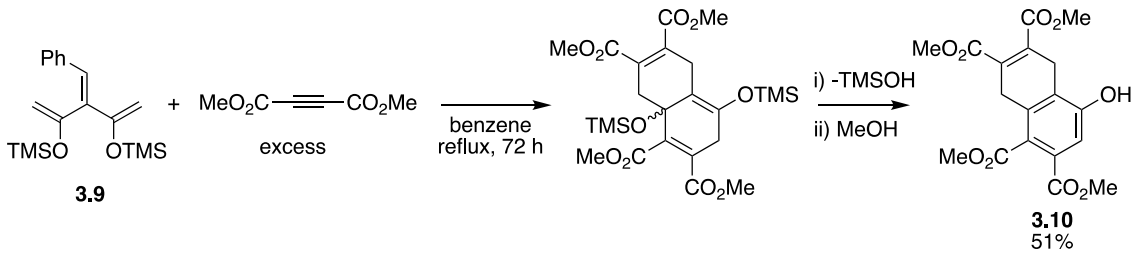
[199] Tsuge, O.; Wada, E.; Kanemasa, S. *Chem. Lett*. **1983**, *12*, 239-242.

[200] (a) Tsuge, O.; Wada, E.; Kanemasa, S.; Sakoh, H. *Bull. Chem. Soc. Jpn*. **1984**, *57*, 3221-3233. (b) Tsuge, O.; Kanemasa, S.; Sakoh, H.; Wada, E. *Chem. Lett*. **1984**, 273-276. (c) Kanemasa, S.; Sakoh, H.; Wada, E.; Tsuge, O. *Bull. Chem. Soc. Jpn*. **1986**, *59*, 1869-1876.



Scheme 115. Initial example of DTDA.

Due to the ability to achieve complex multicyclic structures with a high step- and atom-economy by the DTDA reaction, it is not a surprise that this transformation has been widely used for the synthesis of natural products[201] and complex polycycles.[190a,202] Some examples of polycyclic frameworks synthesized through DTDA protocols and some of the most common used dienophiles in this transformation shown in Figure 16.

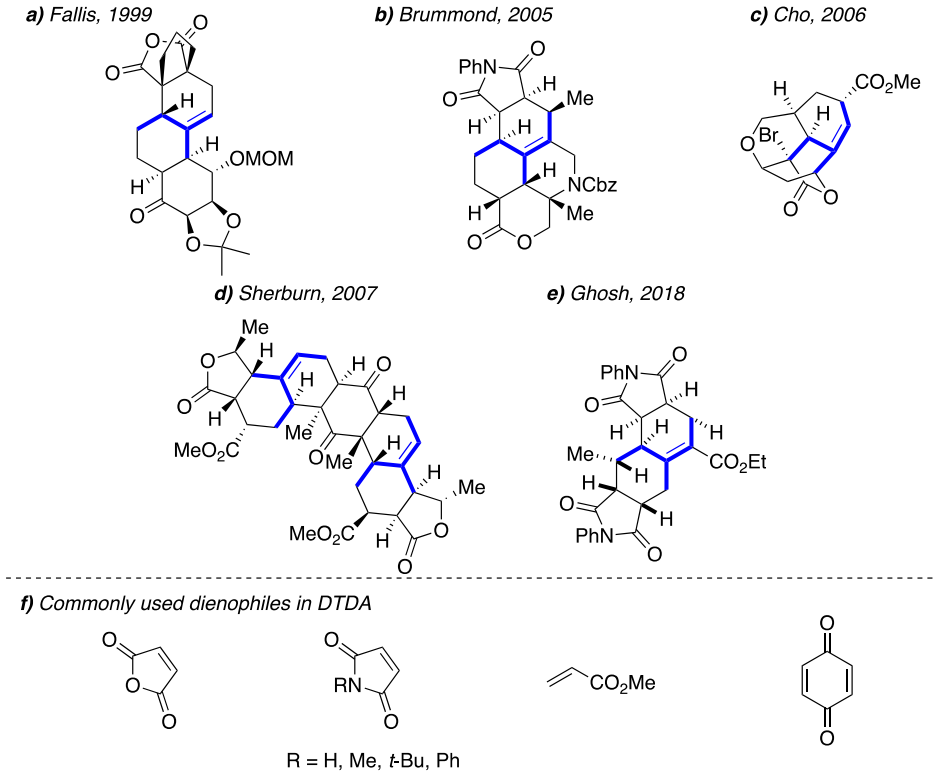
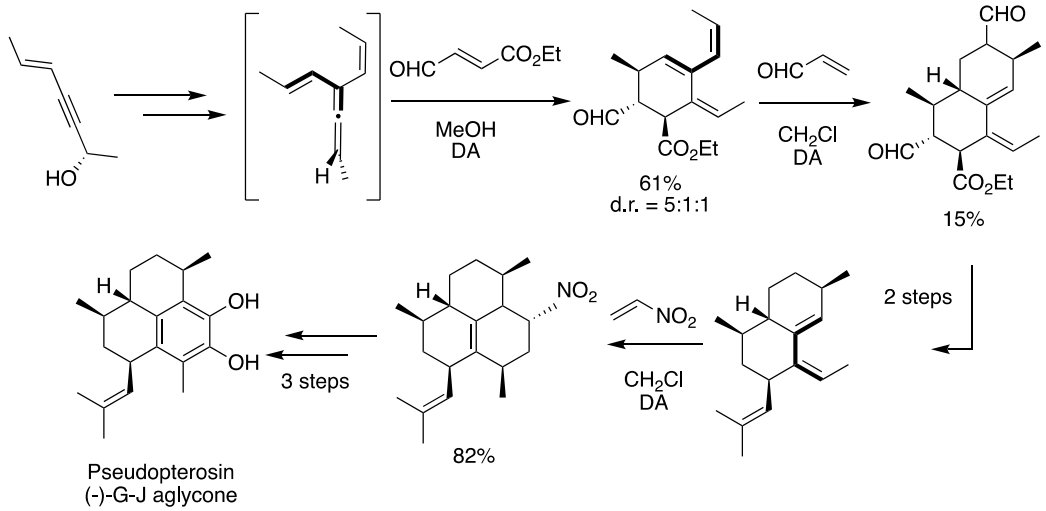


Figure 16. Examples of complex multicyclic structures synthesized by DTDA with [3]dendralenes (initial dendralene bonds in blue) and **f)** commonly used dienophiles for these transformations.

[201] (a) Miller, N. A.; Willis, A. C.; Sherburn, M. S. *Chem. Commun*. **2008**, 1226-1228. (b) Pronin, S. V.; Shenvi, R. A. *J. Am. Chem. Soc*. **2012**, *134*, 19604-19606. (c) Newton, C. G.; Drew, S. L.; Lawrence, A. L.; Willis, A. C.; Paddon-Row, M. N.; Sherburn, M. S. *Nat. Chem*. **2015**, *7*, 82-86.

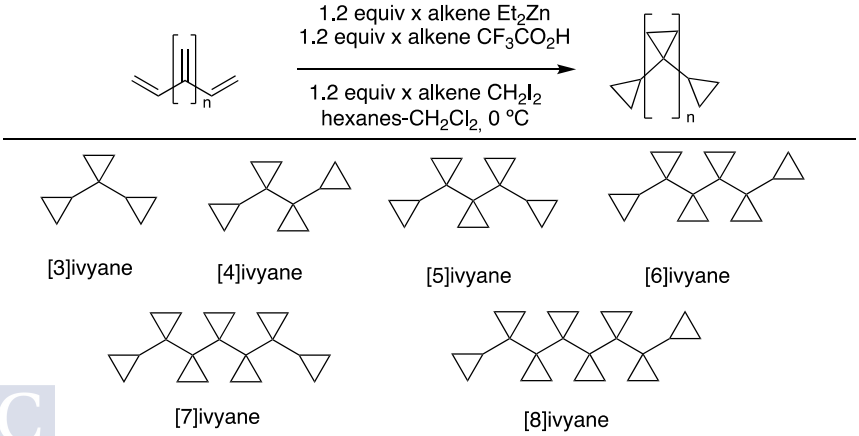
[202] (a) Woo, S.; Legoupy, S.; Parra, S.; Fallis, A. G. *Org. Lett*. **1999**, *1*, 1013-1016. (b) Brummond, K. M.; You, L. *Tetrahedron* **2005**, *61*, 6180-6185. (c) Chung, S.-I.; Seo, J.; Cho, C.-G. *J. Org. Chem*. **2006**, *71*, 6701-6704. (d) Miller, N. A.; Willis, A. C.; Paddon-Row, M. N.; Sherburn, M. S. *Angew. Chem. Int. Ed.* **2007**, *46*, 937-940. (e) Souweha, M. S.; Arab, A.; ApSimon, M.; Fallis, A. *Org. Lett*. **2007**, *9*, 615-618. (f) Naidu, G. S.; Singh, R.; Kumar, M.; Ghosh, S. K. *J. Org. Chem*. **2017**, *82*, 3648-3658.

Among these examples, one of the most remarkable applications is the total synthesis of pseudopterosin (-)-G-J aglycone, a diterpene marine natural product which presents anti-inflammatory and analgesic propierties, reported by the group of Sherburn (Scheme 116).[201c] Starting from an allenic [3]dendralene they performed three consecutive Diels-Alder reactions with different dienophiles, which allows the formation of three new carbocycles and 6 new stereocenters with good diastereoselectivity.



Scheme 116. Total synthesis of pseudopterosin (-)-G-J aglycone via DTDA.

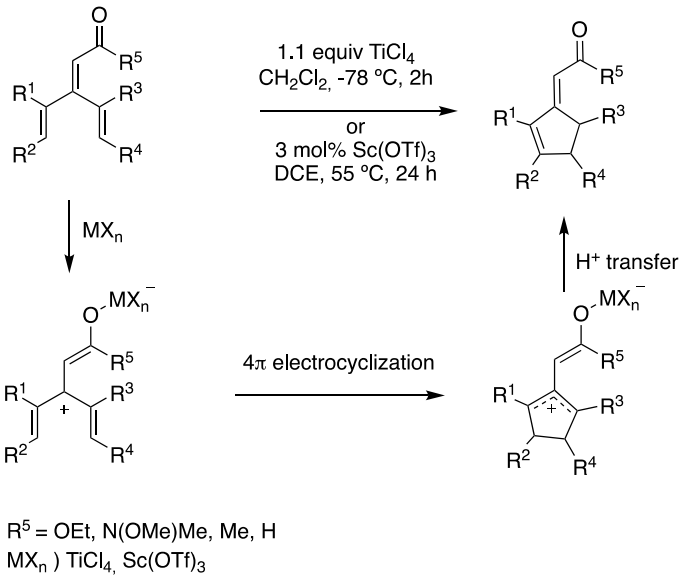
Besides DTDA reactions, dendralenes have been also described to participate in other interesting transformations. Dendralenes can form 1,1-oligocyclopropanes[203] (also called ivyanes) through a variation of a Simmons-Smith cyclopropanation (Scheme 117).[204] This represents an important transformation since ivyanes have interesting properties. For instance, [6]ivyane, has one of the highest reported experimental combustion heat of any hydrocarbon and it is currently being studied as rocket fuel by the NASA.



Scheme 117. Synthesis of [3] to [8] ivyane.

[203] Bojase, G.; Nguyen, T. V.; Payne, A. D.; Willis, A. C.; Sherburn, M. S. *Chem. Sci.* **2011**, *2*, 229-232.
[204] Yang, Z.; Lorenz, J. C.; Shi, Y. *Tetrahedron Lett*. **1998**, *39*, 8621-862

[3]Dendralenes can also undergo vinylogous Nazarov reactions as reported by West in the Lewis acid mediated synthesis of cyclopentenones from [3]dendralenes bearing different carbonyl groups (Scheme 118).[205] Coordination of a Lewis acid to the carbonyl group generates a cationic intermediate which undergoes electrocyclization to provide a cyclopentene with an exocyclic double bond.



Scheme 118. First example of vinylogous Nazarov reaction.

Tricarbonyliron complexes have been used to improve the stability and selectivity of [3]dendralenes (Scheme 119a).[206] The tricarbonyliron complex of [3]dendralene is stable at room temperature (in contrast with the free parent [3]dendralene) and can undergo reactions that are not possible with the free compound. The complexation with the $Fe(CO)_3$ complex makes one diene moiety less accessible, allowing selective functionalization of the terminal double bond. Using this strategy, selective mono-propanation of the terminal double bond under Simons-Smith conditions (Scheme 119b) and selective cross-metathesis reaction could be performed (Scheme 119c). Importantly, previous attempts to perform a cross-metathesis reaction with the naked [3]dendralene were unsuccessful due to the rapid homodimerization of parent [3]dendralene through Diels-Alder reaction.[207]

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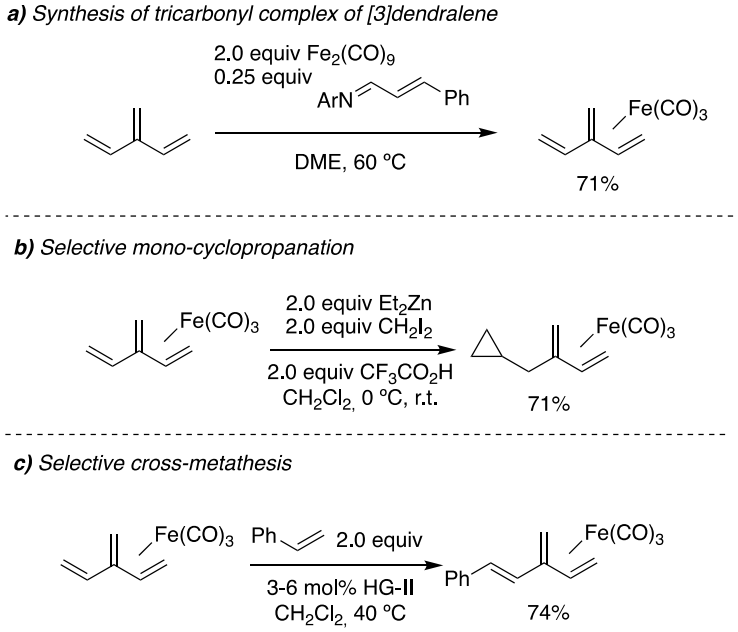
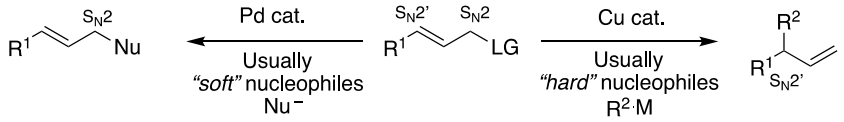
[205] Rieder, C. J.; Winberg, K. J.; West, F. G. *J. Am. Chem. Soc*. **2009**, *131*, 7504-7505.
[206] Toombs-Ruane, H.; Osinski, N.; Fallon, T.; Wills, C.; Willis, A. C.; Paddon-Row, M. N.; Sherburn, M. S. *Chem. Asian J.* **2011**, *6*, 3243-3250.
[207] Toombs-Ruane, H.; Pearson, E. L.; Paddon-Row, M. N.; Sherburn, M. S. *Chem. Commun*. **2012**, *48*, 6639-6641.



Scheme 119. a) Synthesis of tricarbonyliron complex of [3]dendralene, **b)** selective mono-propanation and **c)** selective cross-metathesis with styrene.

1.2. COPPER-CATALYZED ALLYLIC SUBSTITUTION

In contrast to palladium-catalyzed allylic substitution, copper-catalyzed allylic substitution has been typically carried out with *"hard"* nucleophiles (usually organometallic compounds) and usually provides the formal S_N2' selectivity (Scheme 120).



Scheme 120. Palladium-catalyzed vs copper-catalyzed allylic substitution.

As a result of this selectivity a new carbon stereocenter is formed next to a terminal double bond. This results in an excellent choice to develop enantioselective allylic substitution reactions when a chiral catalyst is used (see chapter IV). Common

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organometallic reagents that have been used in copper-catalyzed allylic substitution are: organozinc,[208] organoaluminium,[209] organolithium[210] or Grignard reagents.[211,212]

The general proposed mechanism for this transformation starts with the initial transmetalation of an organometallic reagent with a copper(I) salt, to form a nucleophilic organocopper complex. Then, coordination of the organocopper intermediate to the allylic electrophile to form a η^2-π-complex occurs (Scheme 121). Then, oxidative addition occurs to generate a Cu(III) σ-allyl complex with the copper atom in γ position to the leaving group. The regioselectivity was explained by the orbital interaction during the oxidative addition step.[213] Copper(I) filled d^{10} orbital (HOMO) interacts with the LUMO of the allylic substrate at the γ carbon (π^*) but also, with the σ^*antibonding orbital of the C-X bond. The organocopper complex would then attack the allylic substrate in *anti* to the leaving group. The γ carbon has a higher contribution to the LUMO thus, the copper atom would interact in higher extent with this carbon, providing the branched σ-allylcopper(III) complex. Reductive elimination affords the branched product, however, isomerization to the π-allylcopper(III) could also occur prior to reductive elimination which would lead to the isomerization to the less sterically hindered terminal σ-allylcopper(III) complex, that would afford the linear product after reductive elimination.

[208] Selected examples: (a) Sekiya, K.; Nakamura, E. *Tetrahedron Lett.* **1988**, *29*, 5155-5156. (b) Dübner, F.; Knochel, P. *Angew. Chem Int. Ed*. **1999**, *38*, 379-381. (c) Bertozzi, F.; Crotti, P.; Macchia, F.; Pineschi, M.; Feringa, B. L. *Angew. Chem. Int. Ed*. **2001**, *40*, 930-932. (d) Murphy, K. E.; Hoveyda, A. H. *J. Am. Chem. Soc*. **2003**, *125*, 4690-4691. (e) Larsen, A. O.; Leu, W.; Oberhuber, C. N.; Campbell, J. E.; Hoveyda, A. H. *J. Am. Chem. Soc*. **2004**, *126*, 11130-11131.

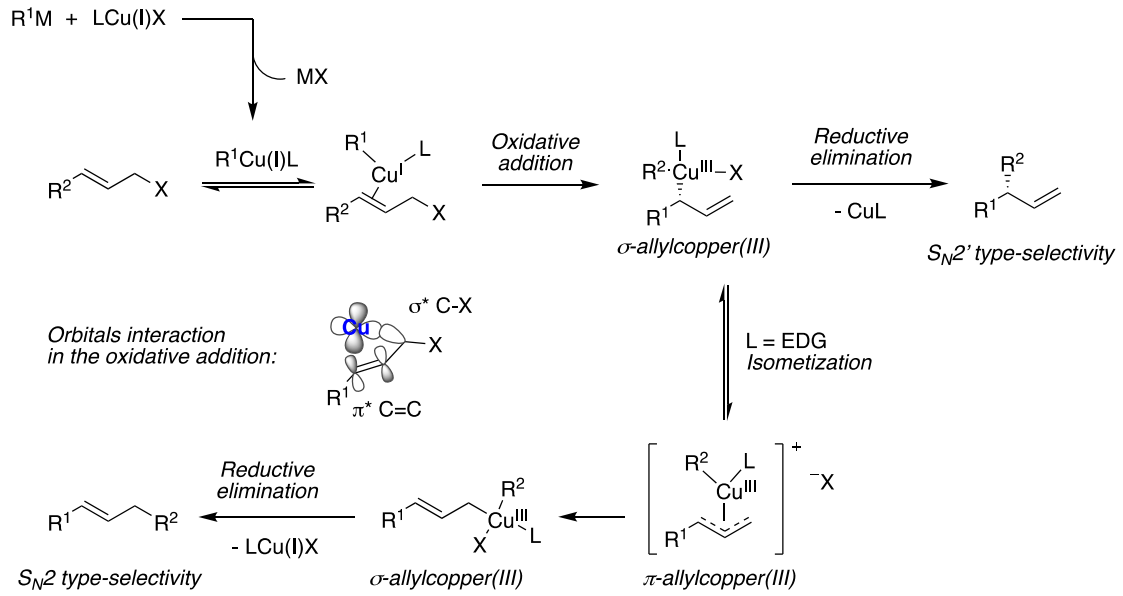
[209] Selected examples: (a) Akiyama, K.; Gao, F.; Hoveyda, A. H. *Angew. Chem. Int. Ed*. **2010**, *49*, 419-423. (b) Gao, F.; Lee, Y.; Mandai, K.; Hoveyda, A. H. *Angew. Chem. Int. Ed*. **2010**, *49*, 8370-8374. (c) Dabrowski, J. A.; Gao, F.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2011**, *133,* 4778-4781.

[210] Selected examples: (a) Pérez, M.; Fañanás-Mastral, M.; Bos, P. H.; Rudolph, A.; Harutyunyan, S. R.; Feringa, B. L. *Nat. Chem*. **2011**, *3*, 377-381. (b) Fañanás-Mastral, M.; Pérez, M.; Bos, P. H.; Rudolph, A.; Harutyunyan, S. R.; Feringa, B. L. *Angew. Chem. Int. Ed*. **2012**, *51*, 1922-1925. (c) Guduguntla, S.; Gualtierotti, J.-B.; Goh, S. S.; Feringa, B. L. *ACS Catal.* **2016**, *6*, 6591-6595.

[211] Selected examples: (a) van Klaveren, M.; Persson, E. S. M.; del Villar, A.; Grove, D. M.; Bäckvall, J. E.; van Koten, G. *Tetrahedron Lett*. **1995**, *36*, 3059-3062. (b) Tissot-Croset, K.; Polet, D.; Alexakis, A. *Angew. Chem. Int. Ed*. **2004**, *43*, 2426-2428. (c) Geurts, K.; Fletcher, S. P.; Feringa, B. L. *J. Am. Chem. Soc.* **2006**, *128*, 15572-15573. (d) Selim, K. B.; Matsumoto, Y.; Yamada, K.-i.; Yomioka, K. *Angew. Chem. Int. Ed.* **2009**, 48, 8733-8735. (e) Giannerini, M.; Fañanás-Mastral, M.; Feringa, B. L. *J. Am. Chem. Soc.* **2012**, *134*, 4108-4111. (f) Hornillos, V.; Pérez, M.; Fañanás-Mastral, M.; Feringa, B. L. *J. Am. Chem. Soc.* **2013**, *135*, 2140-2143.

[212] For reviews see: (a) Yorimitsu, H.; Oshima, K. *Angew. Chem. Int. Ed.* **2005**, *44*, 4435-4439. (b) Harutyunyan, S. R.; den Hartog, T.; Geurts, K.; Minnaard, A. J.; Feringa, B. L. *Chem. Rev*. **2008**, *108*, 2824-2852 (c) Alexakis, A.; Bäckvall, J. E.; Krause, N.; Pàmies, O.; Diéguez, M. *Chem. Rev*. **2008**, *108*, 2796-2823. (d) Hornillos, V.; Gualtierotti, J.-B.; Feringa, B. L. *Top. Organomet. Chem*. **2016**, *58*, 1-40.

[213] Corey, E. J.; Boaz, N. W. *Tetrahedron Lett*. **1984**, *25*, 3062-3066.



Scheme 121. Proposed mechanism for copper-catalyzed allylic substitution.

Although copper has the tendency to provide the S_N2' type substituted products, there are some factors that can affect the regioselectivity of the process like the identity of the electrophile, the solvent, the temperature of the reaction, and the source of the organometallic nucleophile.

Electron-withdrawing and bulky ligands favors the rapid reductive elimination to obtain S_N2' type product, thus, avoiding isomerization to the π-allylcopper(III). However, if the σ-allylcopper(III) is stabilized, for example with the use of electron-donating ligands, the lower tendency to provide a fast reductive elimination can provide the σ-π-σ isomerization to the less sterically hindered σ-allylcopper(III) and provide the S_N2 type allylic substitution.

The most commonly used allylic substrates for the copper-catalyzed allylic substitution are allylic acetates, allylic halides and allylic phosphates. A particular type of allylic substrates are the 1,4-dihalo-2-butenes, which are simple, cheap and commercially available starting materials (Scheme 122). Alexakis showed that these substrates show perfect levels of regioselectivity towards the formation of the branched S_N2' type product in their reaction with Grignard reagents.[214] In this transformation a chiral copper complex is used to obtain chiral tunable synthons, which can be further functionalized. Both 1,4-dibromo-2-butene and 1,4-dichloro-2-butene provided high enantiomeric excess when a chiral phosphoramidite ligand is used.

To rationalize this perfect selectivity, the authors proposed a stabilizing interaction via a donation of electron density from the filled orbitals of the halide, that is in ε position, to the empty d orbital of the copper(III) atom (Scheme 122).

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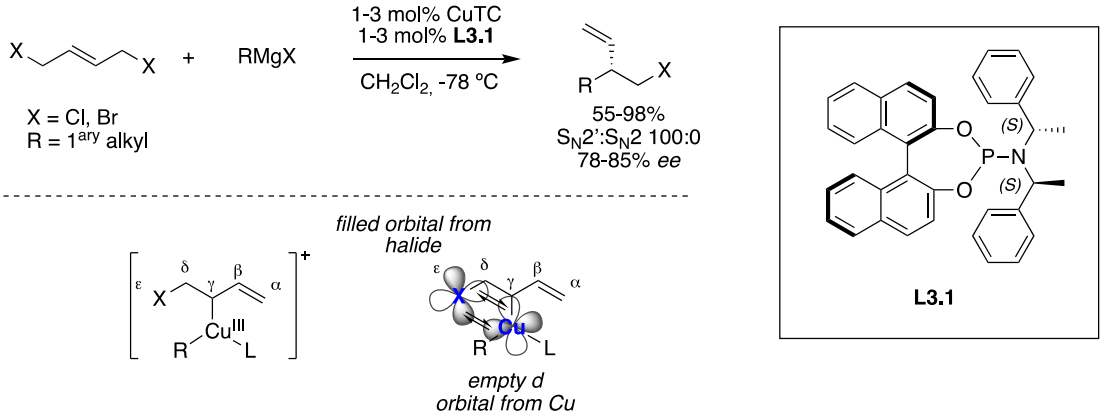
[214] (a) Falciola, C. A.; Alexakis, A. *Angew. Chem. Int. Ed*. **2007**, *46*, 2619-2622. (b) Falciola, C. A.; Alexakis, A. *Chem. Eur. J*. **2008**, *14*, 10615-10627.



Scheme 122. Copper-catalyzed allylic substitution with 1,4-dihalo-2-butenes.

Besides improving the regioselectivity, the use of 1,4-dihalo-2-butenes gives rise to a product with a halide functionality, which provide excellent versatility for downstream transformations.

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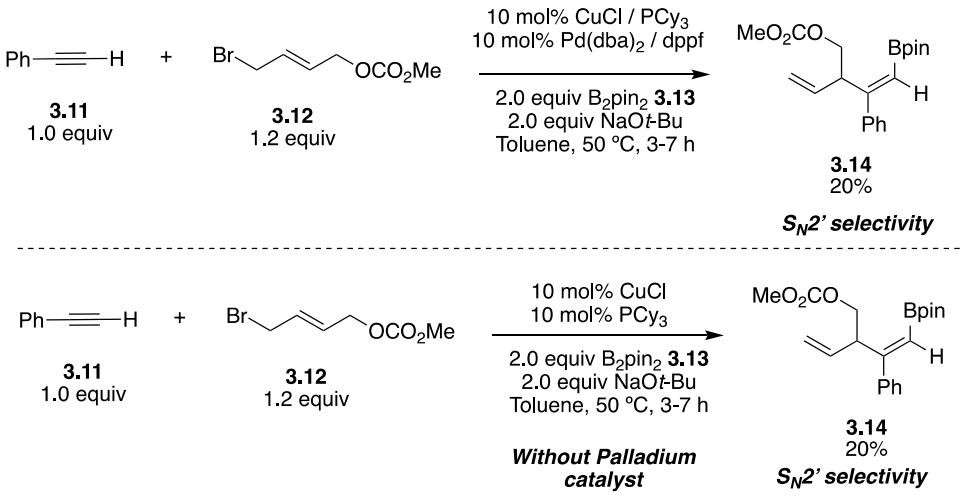
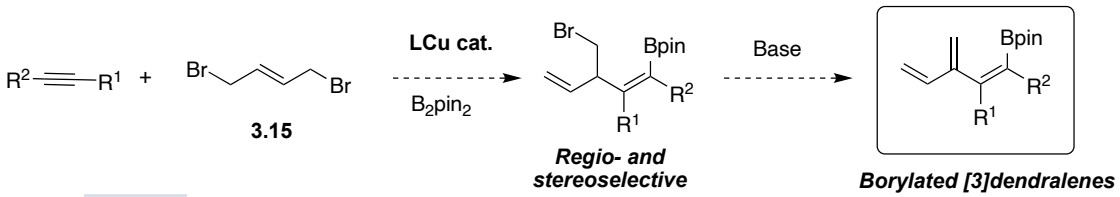
2. OBJECTIVE

During our studies on the Cu/Pd allylboration of alkynes shown in chapter II, we observed that 4-bromo-1-allylcarbonate **3.12** provided product 3.14 which arises from substitution of the bromide in a S_N2' fashion. Same result was obtained in the absence of the palladium catalyst (Scheme 123).



Scheme 123. Preliminary results with difunctional allylic substratres.

Based on these preliminary results, we envisioned that the use of commercially available 1,4-dihalo-2-butene **3.15** would be an excellent allylic substrate for the synthesis of bromo- and boron-substituted multifunctional 1,4-dienes through allylboration of alkynes (Scheme 124). Moreover, we envisaged that these 1,4-dienes could be readily transformed into borylated [3]dendralenes through a base promoted dehydrohalogenation. It is important to note, that this type of organoboron compounds did not have any precedent in the literature and the structural combination of the boron functionality with the dendralenic scaffold resulted in an attractive novel structure to study.



Scheme 124. Proposed synthesis of borylated [3]dendralenes.

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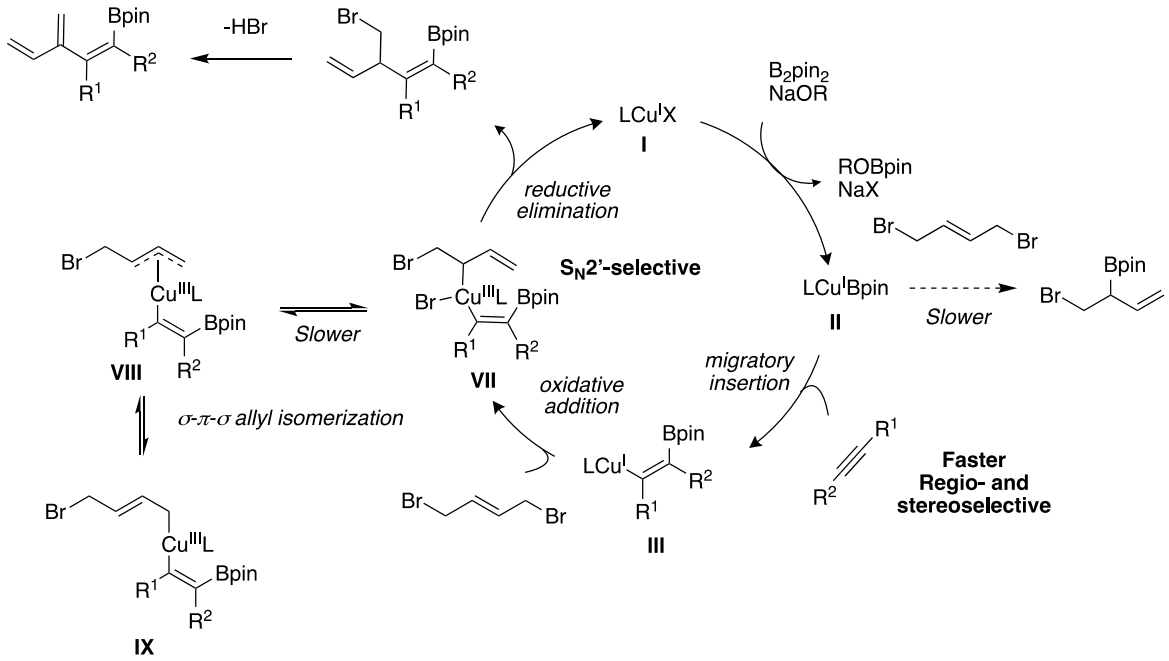
3. RESULT AND DISCUSSION

3.1. MECHANISTIC PROPOSAL

Successful implementation of this transformation demands a multitasking copper catalyst capable of promoting several steps with high levels of chemo-, regio-, and stereoselectivity (Scheme 125). Notably, the rate of the borylcupration of the alkyne, which has to occur in a regio- and stereoselective manner, must be faster than direct allylation of the LCu-Bpin complex to avoid undesired side reactions (see section 1.1.6, chapter I). Moreover, the resulting alkenylcopper species **III** must be reactive enough towards 1,4-dibromo-2-butene, via oxidative addition, to give rise to intermediate **VII**. This complex must undergo a facile reductive elimination to afford the branched 1,4-diene and regenerate the catalyst, avoiding isomerization to π-allyl complex **VIII**, that could give rise to an erosion of regioselectivity.



Scheme 125. Proposed mechanism for Cu-catalyzed allylboration of alkynes.

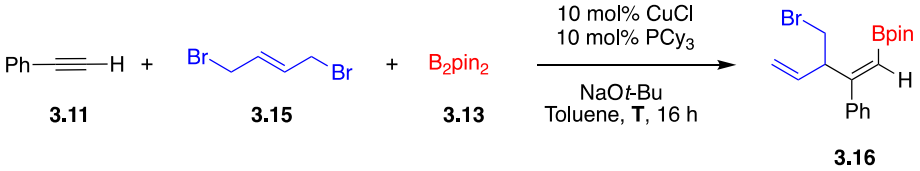
3.2. OPTIMIZATION

We first focused on the optimization of the copper-catalyzed allylboration of alkynes with 1,4-dibromo-2-butene that would provide straightforward access to the dendralene precursor.

We selected a model reaction involving commercially available phenylacetylene (**3.11**), 1,4-dibromo-2-butene (**3.15**), and bis(pinacolato)diboron (**3.13**, B_2pin_2) and using sodium *tert*-butoxide as base and toluene as solvent. Under the conditions shown in

Scheme 123, that involves the use of 2 equivalents of bis(pinacolato)diboron and 2 equivalents of sodium *tert*-butoxide in toluene at 50 ºC, we obtained product **3.16** in 60% yield (Table 6, entry 1). We soon observed that competing addition of LCu-Bpin to **3.15** was an important side reaction. Indeed, **3.15** readily reacts with B_2pin_2 in the absence of the alkyne (Table 6, entry 2). In view of this, we first evaluated the reagents stoichiometry. Increasing the amount of **3.15** to 2.0 equivalents led to a decrease of yield (**3.16,** 25%) (Table 6, entry 3). On the other hand, when we used 1.0 equivalent of **3.15** and 2.0 equivalents of alkyne **3.11**, product **3.16** was obtained in 70% yield (Table 6, entry 4). Afterwards, we evaluated the effect of the temperature (Table 6, entries 4-6) and we observed a slightly improved yield at 30 ºC (75% yield vs 70% yield at 50 ºC). In order to avoid the competitive borylation of **3.15**, we anticipated that slow addition of the allylic bromide to the reaction media could be beneficial for the chemoselectivity of the process. Indeed, slow addition of **3.15** allowed to increase the yield of **3.16** to 91% and reduce the amount of alkyne to 1.1 equivalents (Table 6, entries 7 and 8).

Table 6. Evaluation of reagents stoichiometry and reaction conditions



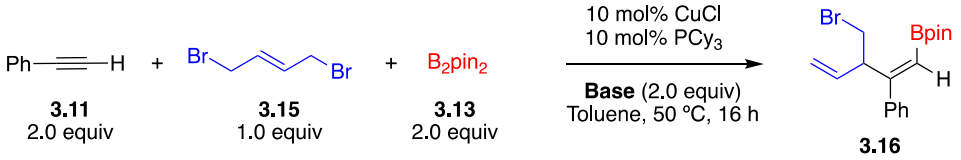
3.11 **3.15** **3.13** **3.16**

Entry[a]	**3.11** (n equiv)	**3.15** (n equiv)	NaO*t*-Bu (n equiv)	B_2pin_2 (n equiv)	T (ºC)	Conv. **3.15** (%)[b]	**3.16** (%)[b]
1	1.0	1.2	2.0	2.0	50	n.d.	60
2	---	1.0	2.0	2.0	50	>99	---
3	1.0	2.0	2.0	2.0	50	n.d.	25
4	2.0	1.0	2.0	2.0	50	>99	70
5	2.0	1.0	2.0	2.0	60	>99	61
6	2.0	1.0	2.0	2.0	30	>99	75
7	1.1	1.0[c]	2.0	2.0	30	>99	91
8	1.1	1.0[d]	2.0	2.0	30	>99	91 (82%)[e]

[a] Reaction conditions: 0.2 mmol scale (0.13 M concentration). [b] Analyzed by GC-MS and ^{1}H-NMR. 1.0 equiv of 1,3,5-trimethoxybenzene as internal standard. β/α borylation >99:1 and S_N2'/S_N2 >99:1 in all the cases. [c] Added with syringe pump over 10 h. [d] Added with syringe pump over 5 h. [e] Yield of isolated product.

We next evaluated the effect of the base (Table 7). The nature of the cation of the *tert*-butoxide base had a big impact in the outcome of the reaction (Table 7, entries 1-3). Changing sodium for potassium or lithium led to a considerable decrease of the yield (28 and 44% respectively). The use of other type of bases such as KOH and NaOMe did not lead to the formation of product **3.16**.

Table 7. Evaluation of the effect of base

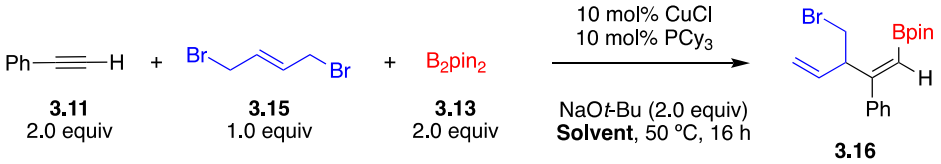


Entry[a]	Base	Conv. **3.15** (%)[b]	**3.16** (%)[b]
1	NaO*t*-Bu	>99	75
2	KO*t*-Bu	>99	28
3	LiO*t*-Bu	81	44
4	KOH	>99	---
5	NaOMe	>99	---

[a] Reaction conditions: 0.2 mmol scale (0.13 M concentration). [b] Analyzed by GC-MS and ^{1}H-NMR. 1.0 equiv of 1,3,5-trimethoxybenzene as internal standard. β/α borylation >99:1 and S_N2'/S_N2 >99:1 in all the cases.

Evaluation of other solvents showed that the use of more polar media also provided full conversion of **3.15** but favored competitive LCu-Bpin allylation, leading to diminished yields (Table 8).

Table 8. Evaluation of the effect of solvent



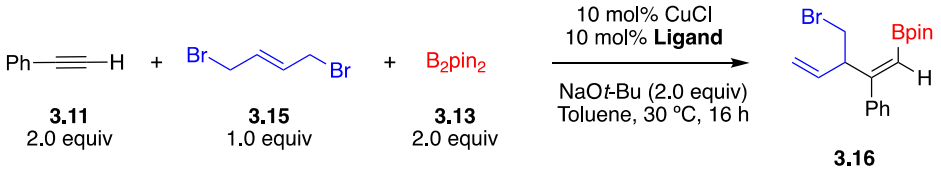
Entry[a]	**3.11** (n equiv)	**3.15** (n equiv)	Solvent	Conv. (%)	**3.16** (%)[b]
1	1.0	1.2	Toluene	n.d.	60
2	1.0	1.2	CH_2Cl_2	n.d.	---
3	1.0	1.2	1,4-Dioxane	n.d.	33
4	2.0	1.0	Toluene	>99	75
5	2.0	1.0	THF	>99	40
6	2.0	1.0	DMF	>99	---

[a] Reaction conditions: 0.2 mmol scale (0.13 M concentration). [b] Analyzed by GC-MS and ^{1}H-NMR. 1.0 equiv of 1,3,5-trimethoxybenzene as internal standard. β/α borylation >99:1 and S_N2'/S_N2 >99:1 in all the cases. CH_2Cl_2 = dichloromethane. THF = tetrahydrofuran. DMF = *N*,*N*-dimethylformamide.

The nature of the ligand also played a key role in the outcome of the reaction. While copper complexes from electron-rich monodentate phosphines proved to efficiently catalyze the allylboration reaction (Table 9, entries 1-2), the use of less Lewis basic and

bidentate phosphines led to a decrease in chemoselectivity (Table 9, entries 3-9), thus providing **3.16** in poor yields. Similarly, NHC ligands were inefficient in terms of both reactivity and selectivity (Table 9, entries 10-11).

Table 9. Ligand screening



3.11 2.0 equiv | **3.15** 1.0 equiv | **3.13** 2.0 equiv | **3.16**

Entry[a]	Ligand	Conv. **3.15** (%)	**3.16** (%)[b]
1	PCy_3	>99	75
2	$PCyp_3$	>99	61
3	PPh_3	76	12
4	$P(OMe)_3$	91	27
5	P(*p*-OMe-C_6H_4)$_3$	>99	32
6	P(2,6-OMe-C_6H_3)$_3$	92	13
7	Xantphos	92	21
8	*rac*-BINAP	82	18
9	dppf	75	22
10	IMes	>99	23
11	SIMes	>99	14[c]

[a] Reaction conditions: 0.2 mmol scale (0.13 M concentration). [b] Analyzed by GC-MS and ^{1}H-NMR. 1.0 equiv of 1,3,5-trimethoxybenzene as internal standard. β/α borylation >99:1 and S_N2'/S_N2 >99:1 unless otherwise noted. [c] β/α borylation 62:38. IMes = 1,3-Bis(2,4,6-trimethylphenyl)-1,3-dihydro-2H-imidazol-2-ylidene. SIMes = 1,3-Bis(2,4,6-trimethylphenyl)-4,5-dihydroimidazol-2-ylidene. Xantphos = 4,5-Bis(diphenylphosphino)-9,9-dimethylxanthene. BINAP = 2,2'-Bis(diphenylphosphino)-1,1'-binaphthyl. Dppf = 1,1'-ferrocenediyl-bis(diphenylphosphine). Cy = cyclohexyl. Cyp = cyclopentyl.

3.3. SCOPE OF THE REACTION

Having established optimized conditions, we set out to explore the scope of this novel allylboration reaction (Table 10).

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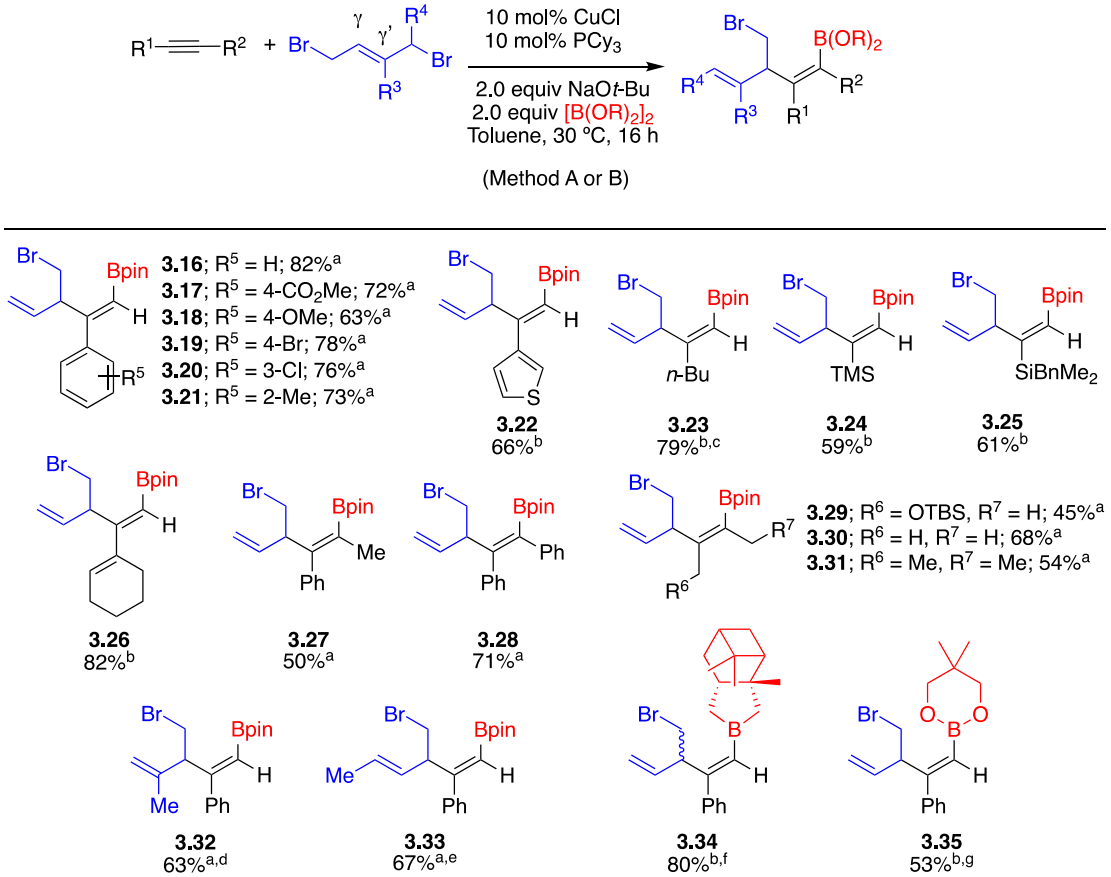
Table 10. Scope for the synthesis of skipped dienes.

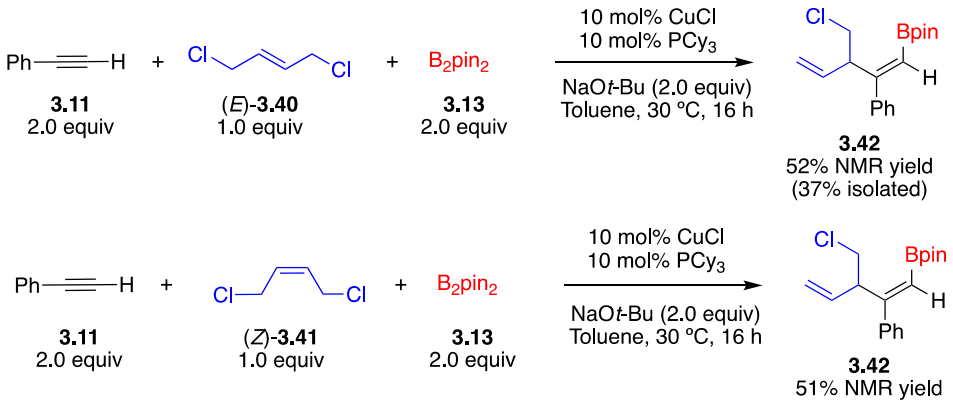


[a] Method A: conditions as entry 8, Table 6. [b] Method B: conditions as entry 6, Table 6. [c] The reaction provided an 80:20 mixture of β- and α- borylated products, which could be separated by column chromatography. [d] **3.36**, R^3 = Me, R^4 = H. [e] **3.37**, R^3 = H, R^4 = Me. [f] **3.38**, B_2pai_2 = Bis[(+)-pinanediolato]diboron; dr 1:1 [g] **3.39**, B_2neop_2 = Bis(neopentyl glycolato)diboron.

Remarkably, the allylboration reactions proceeded with complete stereo- and site selectivity (>99% β borylation and S_N2' allylic substitution), generating exclusively skipped dienes regardless the nature of the alkyne. Moreover, functional groups such as ester, halide, silyloxy, and trialkylsilyl groups were well tolerated. The reaction proved to be very efficient with terminal alkynes bearing ortho-, meta-, and para-substituted aromatic groups (**3.16-3.21**), as well as heteroaromatic (**3.22**), aliphatic (**3.23**) and trialkylsilyl (**3.24-3.25**) and alkenyl (**3.26**) groups. Notably, products **3.22-3.26** could be obtained in very good yields without slow addition of **3.14**. Internal alkynes showed slightly diminished reactivity and slow addition was necessary to avoid undesired Cu-Bpin allylation. With this optimized protocol, skipped dienes **3.27-3.31** were obtained with excellent levels of selectivity even when unsymmetrical substrates were used. Interestingly, reaction with trisubstituted and unsymmetrical (*E*)-1,4-dibromo-2-methylbut-2-ene **3.36** (R^3 = Me, R^4 = H), which adds an extra point of selectivity (γ vs. γ' substitution), provided product **3.32** as a single isomer arising from a formal S_N2'-selective allylic substitution at the less hindered position of the olefin. Similarly, the use of (*E*)-1,4-dibromopent-2-ene **3.37** (R^3 = H, R^4 = Me), which features both a primary and a secondary bromide, led exclusively to the regio- and stereoselective substitution of

the more substituted bromide to afford **3.33** as a single *E*,*E* isomer. Finally, the reaction tolerates the use of other diborons such as B_2pai_2 (**3.38**) and $B_2(neop)_2$ (**3.39**), which afforded products **3.34** and **3.35** in good yields with excellent selectivity.

We also studied the feasibility of using 1,4-dichloro-2-butene and we studied the effect of using the *E* or *Z* substrate under optimized conditions (Scheme 126). The use of chlorine as leaving group led to a decrease of the product yield, however, both (*E*)-**3.40** and (*Z*)-**3.41** provided the product **3.42** in the same yield (52 and 51% NMR yield).



Scheme 126. Evaluation of (*E*)-1,4-dichloro-2-butene and (*Z*)-1,4-dichloro-2-butene.

To our delight, skipped dienes could be easily transformed into borylated dendralenes by DBU-promoted dehydrohalogenation, based on previously reported methods for dehydrohalogenation of 4-bromoalkenes to obtain 1,3-butadienes (Table 11).[215]

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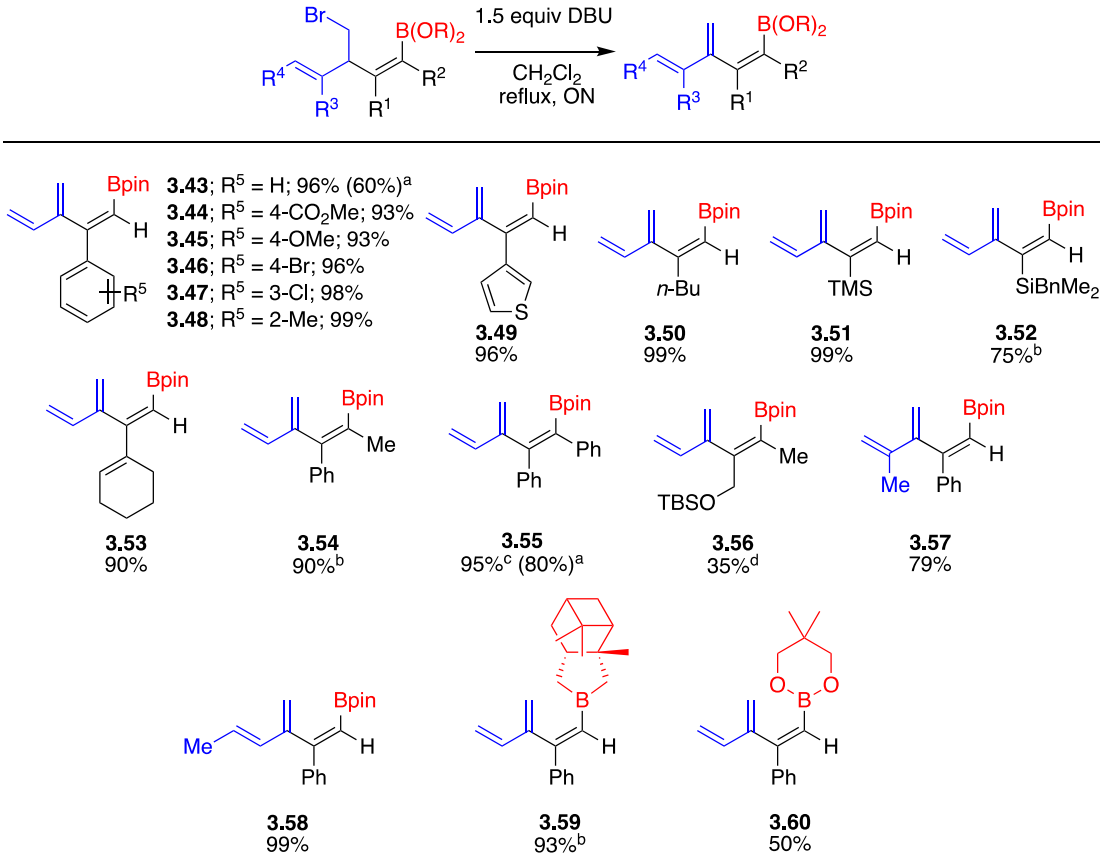
[215] Sen, S.; Singh, S.; Siebuth, S. McN. *J. Org. Chem*. **2009**, *74*, 2884-2886.

Table 11. Transformation skipped dienes into borylated dendralenes.



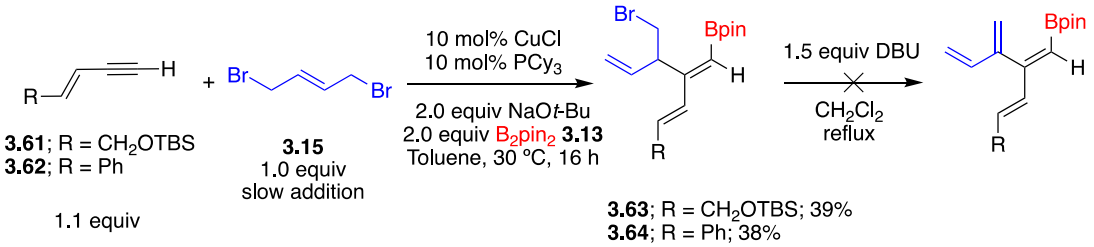
[a] Method A, then DBU (1.5 equiv), 30 ºC. [b] DBU (3 equiv). [c] Run at 30 ºC. [d] DBU (3 equiv), toluene, 45 ºC. DBU = 1,8-Diazabicyclo[5.4.0]undec-7-ene.

Several points regarding substrate scope are noteworthy: 1) The presence of the boronic ester and the other substituents on the dendralenic framework imparted enough stability to the products, thus allowing their isolation in very good yields. Importantly, borylated dendralenes can also be efficiently prepared directly from the commercially available substrates in a one-pot operation, as shown for **3.43** and **3.55**. 2) Borylated dendralenes with several different substitution patterns can be obtained by simply switching the starting materials. 3) Given the stereoselectivity of the allylboration reaction, dendralenes are obtained with a fully stereodefined structure. 4) As illustrated by the synthesis of **3.53**, borylated [4]dendralenes can also be accessed by using an enyne as starting material. 5) Dendralenes **3.51** and **3.52**, featuring Bpin and a trialkylsilyl groups, offer multiple functionalization options, including the synthesis of the parent borylated [3]dendralene by desilylation or access to higher dendralenes by Hiyama couplings.[216] 6) Chiral dendralenes such as **3.59** can be obtained by using a chiral diboron source.

[216] (a) Trost, B. M.; Machacek, M. R.; Ball, Z. T. *Org. Lett.* **2003**, *5*, 1895-1898. (b) Nakao, Y.; Hiyama,

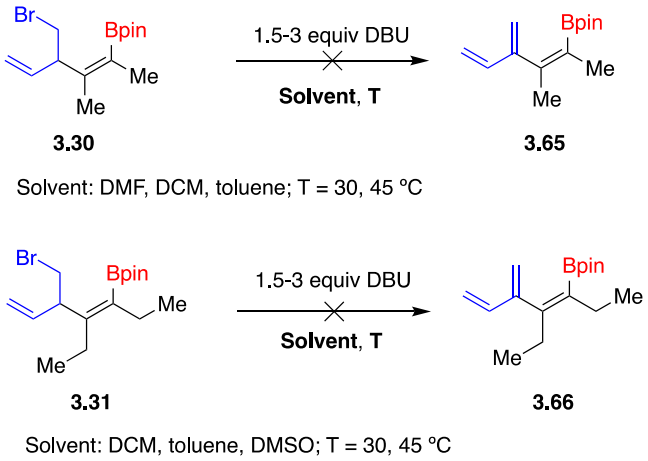
3.3.1. Scope Limitations

Enynes **3.61** and **3.62** led to **3.63** and **3.64** in moderate yields, likely due to the instability of these substrates (Scheme 127). Moreover, their transformation into the corresponding dendralenes could not be achieved also probably to the high instability of these compounds.



Scheme 127. Unsuccessful synthesis of dendralenes from enynes.

Attempts to transform compounds **3.30** and **3.31** into the corresponding dialkylsubstituted [3]dendralenes **3.65** and **3.66** did not provide good results (Scheme 128). We could observe the formation of the products in traces by ^{1}H-NMR and GC-MS analysis of the reaction crude, however, after screening of several reaction conditions, we could not obtain the products in productive yields.



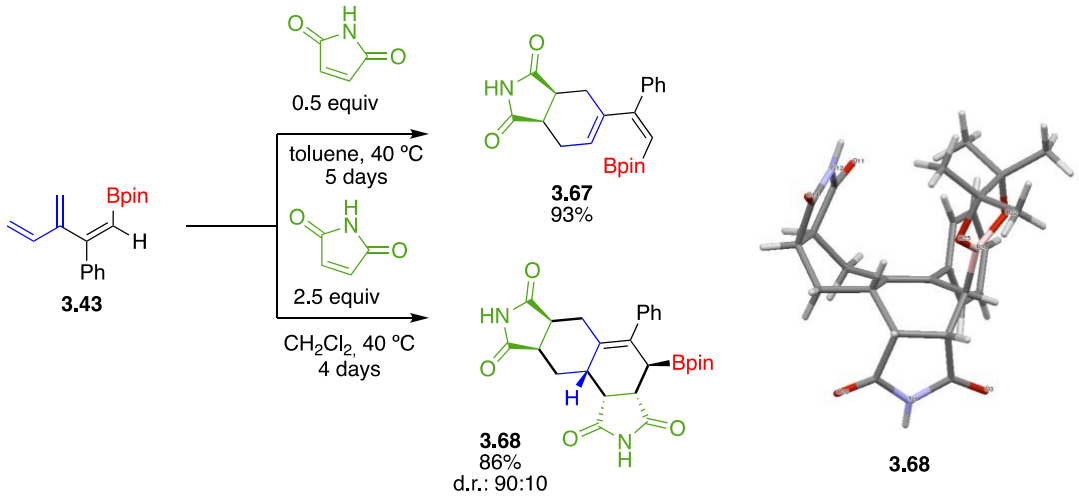
Scheme 128. Attempts for the synthesis of **3.65** and **3.66**.

3.4. SYNTHETIC APPLICATIONS

Having developed an efficient method to access borylated dendralenes, we then explored the synthetic potential of combining the reactivity of the dendralenic structure

T. *Chem. Soc. Rev*. **2011**, *40*, 4893-4901. Access to higher dendralenes would most probably involve a sequential Suzuki-Hiyama coupling: (c) McLaughlin, M.G.; McAdam, C. A.; Cook, M. J. *Org. Lett*. **2015**, *17*, 10-13.

and organoboron chemistry. In view of the high synthetic potential of the diene-transmissive Diels-Alder (DTDA) with dendralenes to synthetize complex multicyclic structures, we decided to explore this reactivity. Interestingly, either single or double (diene-transmissive) Diels-Alder could be selectively carried out to give organoboronates **3.67** and **3.68** in very good yields, with the first cycloaddition reaction taking place exclusively at the less sterically hindered diene moiety (Scheme 129). Notably, under these conditions the DTDA reaction proceeded with high *endo* selectivity delivering a compound which features 6 new defined stereocenters and which structure could be confirmed by X-ray analysis. Furthermore, the presence of a chiral boronic ester opens new possibilities for the transformation of the decalin system through stereospecific couplings.[217]



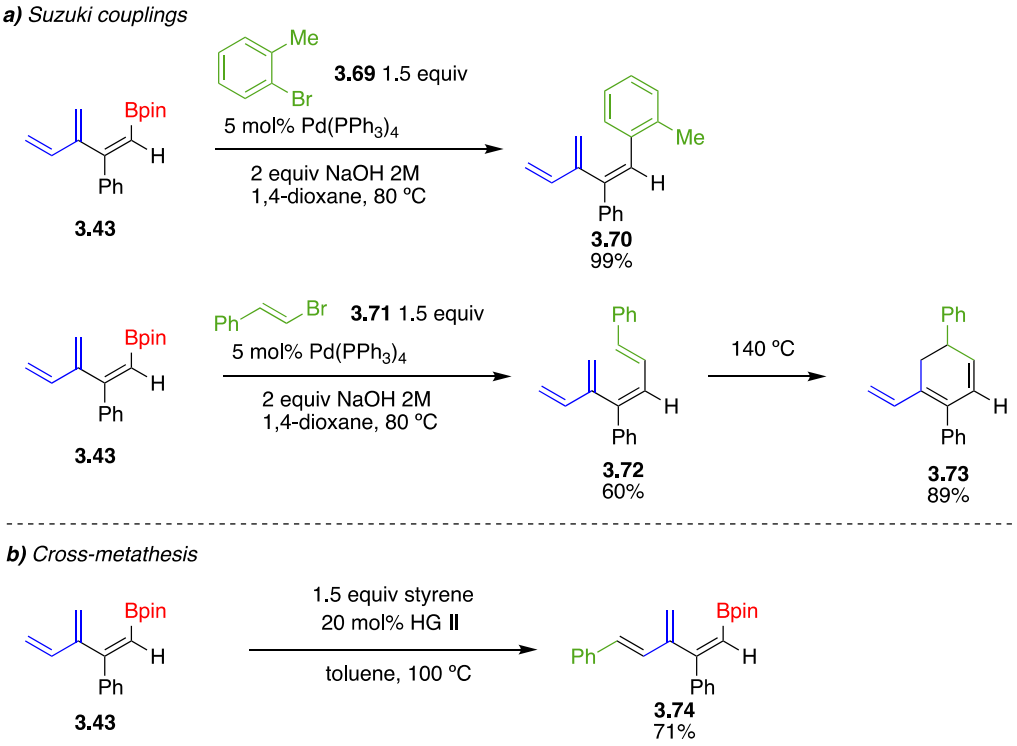
Scheme 129. Diels-Alder and DTDA reactions between **3.43** and N-H-maleimide.

Another interesting feature of the borylated dendralene framework is that new dendralenes can be readily accessed from a same precursor by exploiting the reactivity of the C-B bond. This was exemplified by the synthesis of compounds **3.70** and **3.72** using Pd-catalyzed stereoretentive Suzuki cross-coupling with 2-bromotoluene **3.69** and β-bromostyrene **3.71** (Scheme 130a). Given from the stereochemical outcome of the copper-catalyzed allylboration, tetraene **3.72** displays a proper structure to undergo thermal 6π-electrocyclization as showcased by the preparation of trisubstituted cyclohexadiene **3.73**. Structural variations of this important nucleus are easily accessible by this approach, which further highlights the synthetic versatility of this new class of organoboronates.

Additionally, the boronic ester group imparted enough stability to facilitate the synthesis of borylated dendralene **3.74** by selective functionalization at the C5 position of **3.43** by cross-metathesis with styrene (Scheme 130b). This approach constitutes a versatile alternative to access 5-substituted borylated dendralenes and represents, to the

[217] (a) Leonori, D.; Aggarwal, V. K. *Angew. Chem. Int. Ed*. **2015**, *54*, 1082-1096. (b) Rygus, J. P. G.; Crudden, C. M. *J. Am. Chem. Soc*. **2017**, *139*, 18124-18137.

best of our knowledge, the first example of a direct cross-metathesis of an acyclic dendralenic framework.



Scheme 130. Dendralene to dendralene transformations.

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4. CONCLUSIONS

In conclusion, we have developed an efficient methodology for the synthesis of borylated branched 1,4-dienes through a copper-catalyzed allylboration of alkynes with *trans*-1,4-dibromo-2-butene under mild conditions. This methodology is complementary, in terms of regioselectivity, to the methodology reported in chapter II.

The multitasking copper catalyst showed high levels of 1) chemoselectivity, reducing the amount of borylation of the allylic substrate to not significant levels, 2) regio- and stereoselectivity providing, in the optimized conditions, the formation of a single product in nearly all the cases.

Borylated dendralenes, which are a new type of organoboron compounds, could be easily synthesized from the multifunctional 1,4-dienes through a simple base promoted dehydrohalogenation, that allows the synthesis of these products in excellent yields and featuring diverse substitution patterns.

Additionally, we have shown that this new type of organoboronates present very versatile reactivity and offer exciting new opportunities in organic synthesis. We have proved the versatility of these products in a DTDA reaction, which features a multicyclic product with 6 new defined stereocenters and the presence of a chiral boronic ester. Moreover, the presence of the boronic ester in the dendralenic moiety allows for dendralene to dendralene transformation, showcased by Suzuki-couplings and a metathesis reaction.

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CHAPTER IV: COPPER-CATALYZED ENANTIOSELECTIVE ALLYLBORATION OF ALKYNES: SYNTHESIS OF HIGHLY VERSATILE MULTIFUNCTIONAL BUILDING BLOCKS

Chapter adapted from:

Rivera-Chao, E.[a]; Mitxlena, M.[a]; Varela, J. A.[a]; Fañanás-Mastral, M.[a] *Angew. Chem. Int. Ed.* **2019**, *58*, 18230-18234.

[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)

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1. INTRODUCTION

Synthetic methods that enable the catalytic and enantioselective assembly of complex organic molecules from simple and readily available materials are highly sought after. In particular, asymmetric multicomponent reactions that provide efficient access to chiral, densely functionalized building blocks capable of undergoing a variety of chemical transformations still represent a formidable challenge and are particularly valuable in the quest to accelerate the drug discovery process by diversity-oriented synthesis.[218] Moreover, chiral 1,4-dienes are interesting scaffolds due to their wide presence in natural products and bioactive molecules and to their unique properties (see section 1, chapter II).

Among the methodologies available for the asymmetric synthesis of branched 1,4-dienes, enantioselective transition metal-catalyzed asymmetric allylic alkenylation has become a powerful tool. Transition metal-catalyzed asymmetric allylic substitution with arylmetal and alkylmetal reagents have been developed in high extend, nonetheless, the use of alkenylmetal reagents has been less explored.

1.1. TRANSITION METAL-CATALYZED ASYMMETRIC ALLYLIC ALKENYLATION

The group of Hoveyda pioneered the use of alkenylmetal reagents in copper-catalyzed asymmetric allylic alkylation reactions. They initially studied the enantioselective copper-catalyzed addition of alkenylaluminum reagents to allylic phosphates.[209a, 219] In 2008, a methodology involving the *in situ* formation of alkenylaluminum reagents through the reaction between terminal alkyl-substituted alkynes and DIBAL-H was reported (Scheme 131a).[219a] This transformation was based in the use of a chiral NHC-Cu complex bearing a sulfonate group. Although the yields and selectivity are generally high, the preparation of the alkenylaluminum presented some limitations. Aryl-substituted alkynes were not tolerated since the addition of DIBAL-H did not work with these substrates. Moreover, the method is limited to the synthesis of *trans* alkenes since the alkyne insertion into the Al-H bond occurs in a *syn* fashion.

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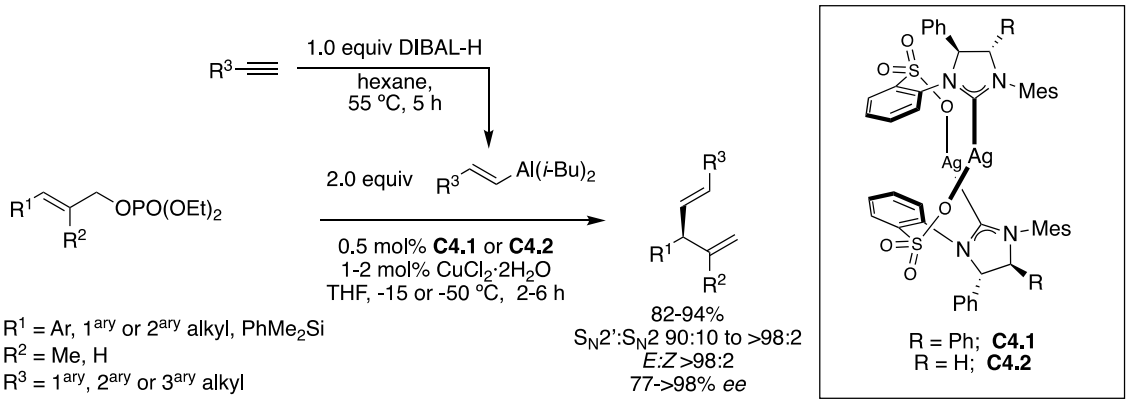
[218] (a) Ramón, D. J.; Yus, M. *Angew. Chem. Int. Ed*. **2005**, *44*, 1602-1634. (b) Galloway, W. R. J. D.; Isidro-Llobet, A.; Spring, D. R. *Nat. Commun*. **2010**, *1*, 80. (c) de Graaff, C.; Ruijter, E.; Orru, R. V. A. *Chem. Soc. Rev*. **2012**, *41*, 3969-4009. (d) Eppe, G.; Didier, D.; Marek, I. *Chem. Rev*. **2015**, *115*, 9175-9206.

[219] (a) Lee, Y.; Akiyama, K.; Gillingham, D. G.; Brown, M. K.; Hoveyda, A. H. *J. Am. Chem. Soc*. **2008**, *130*, 446-447. (b) Gao, F.; McGrath, K. P.; Lee, Y.; Hoveyda, A. H. *J. Am. Chem. Soc*. **2010**, *132*, 14315-14320.



Scheme 131. Copper-catalyzed asymmetric alkenylation of allylic phosphates with alkyl-substituted alkenylaluminum reagents.

These limitations could be partially overcome with the use of 1-silyl-2-aryl-substituted alkynes (Scheme 132).[219b] Addition of DIBAL-H to these compounds efficiently generates the alkenylaluminum reagent. In this case, the *E*- and *Z*-alkenylaluminum reagents could be accessed. Due to the steric hindrance of the sterically demanding silyl and aryl groups, *Z*-alkenylaluminum compounds tend to isomerize to the less congested *E* isomer under the reaction in hexane. However, addition of THF to the reaction inhibits the isomerization since the Lewis basic THF coordinates to the aluminum atom. In this way, both *cis* and *trans* aryl-substituted alkenylaluminum reagents could be obtained (silyl group could be further removed by TFA addition). Sulfonate bearing NHC-Cu complex **C4.3** was the best catalyst for the reaction with *E*-alkenylaluminum and **C4.4** for the reaction with *Z*-alkenylaluminum. The sterically demanding silyl aryl substituted alkynes failed in the allylic alkenylation of more congested γ,γ-disubstituted allylic phosphates.

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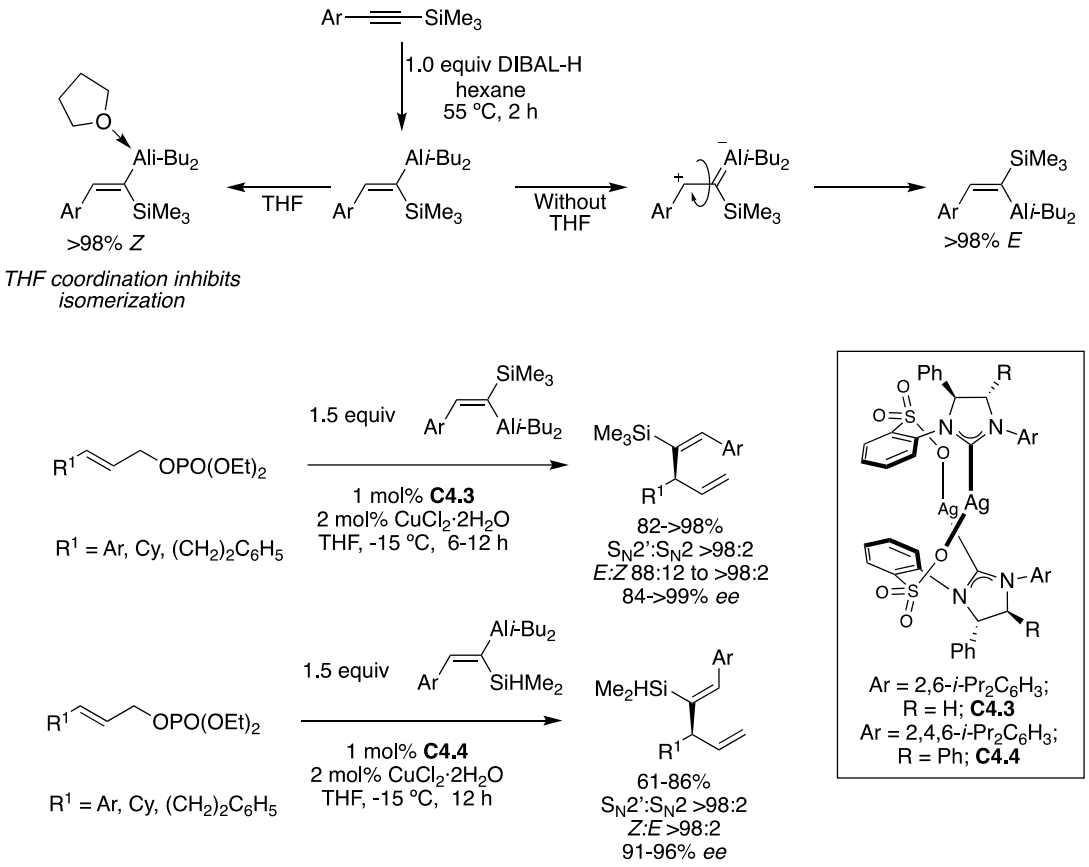
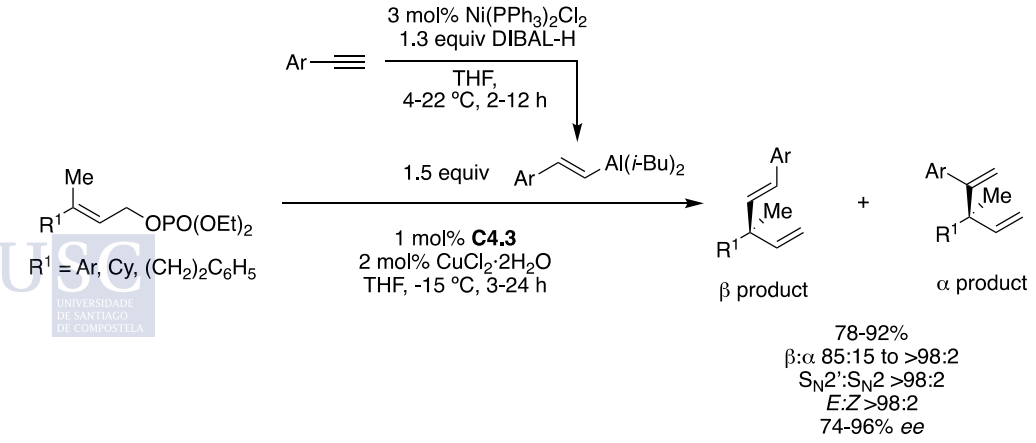


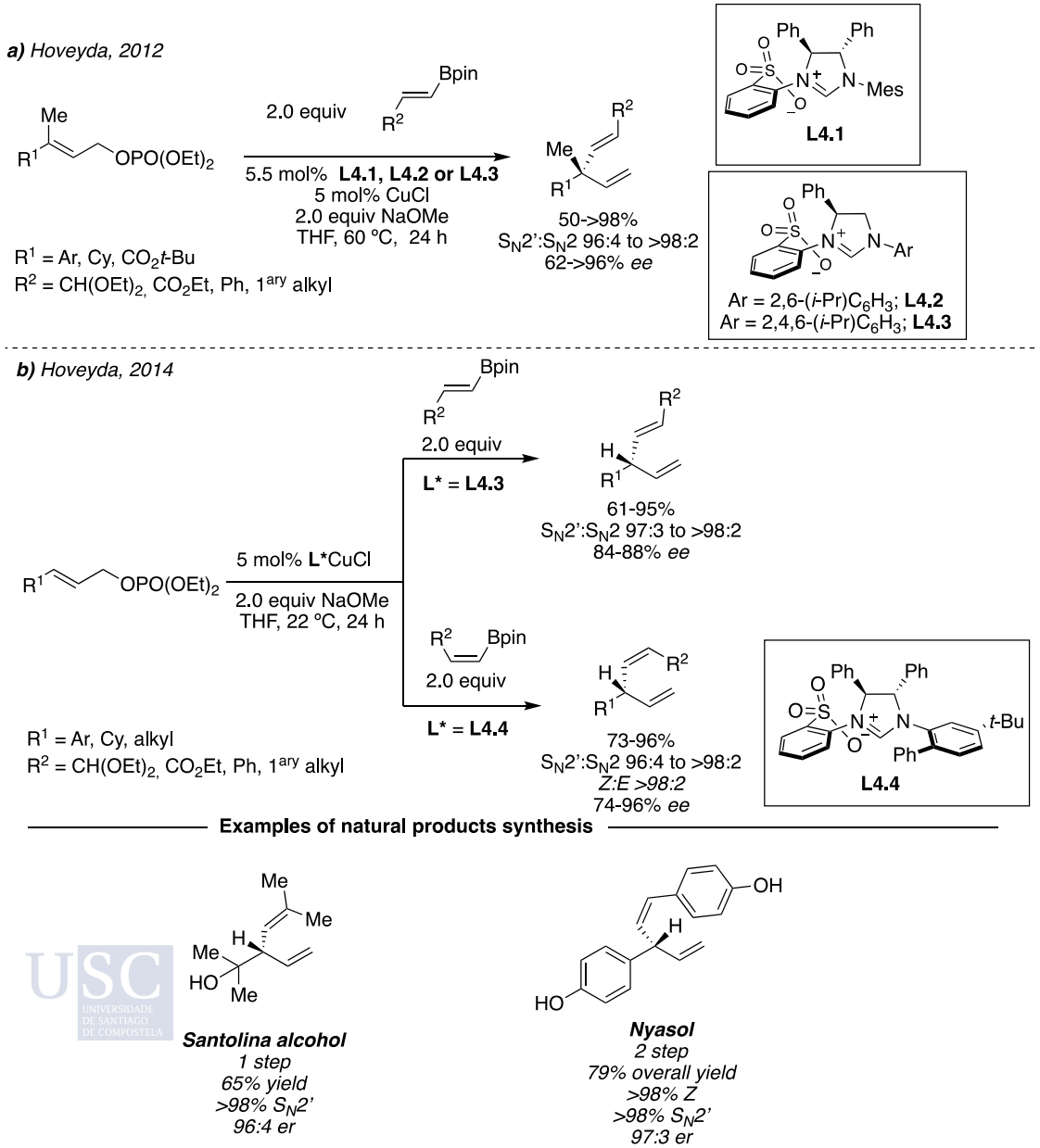
Scheme 132. Copper-catalyzed asymmetric alkenylation of allylic phosphates with aryl-substituted alkenylaluminum reagents.

Shortly after, Hoveyda reported the use of nickel catalysis to prepare aryl-substituted alkenylaluminum reagents. The use of this nickel catalyst makes aryl-substituted alkynes reactive towards the addition of DIBAL-H, avoiding the need of the silyl group. Moreover, the absence of the silyl group enables the participation of the aryl-substituted alkenylaluminum reagents in the copper-catalyzed alkenylation of γ,γ-disubstituted allylic phosphates, which generates an all-carbon quaternary stereogenic center (Scheme 133).[219c]



Scheme 133. Asymmetric copper-catalyzed allylic alkenylation of γ,γ-disubstituted allylic phosphates with aryl-substituted alkenylaluminum reagents.

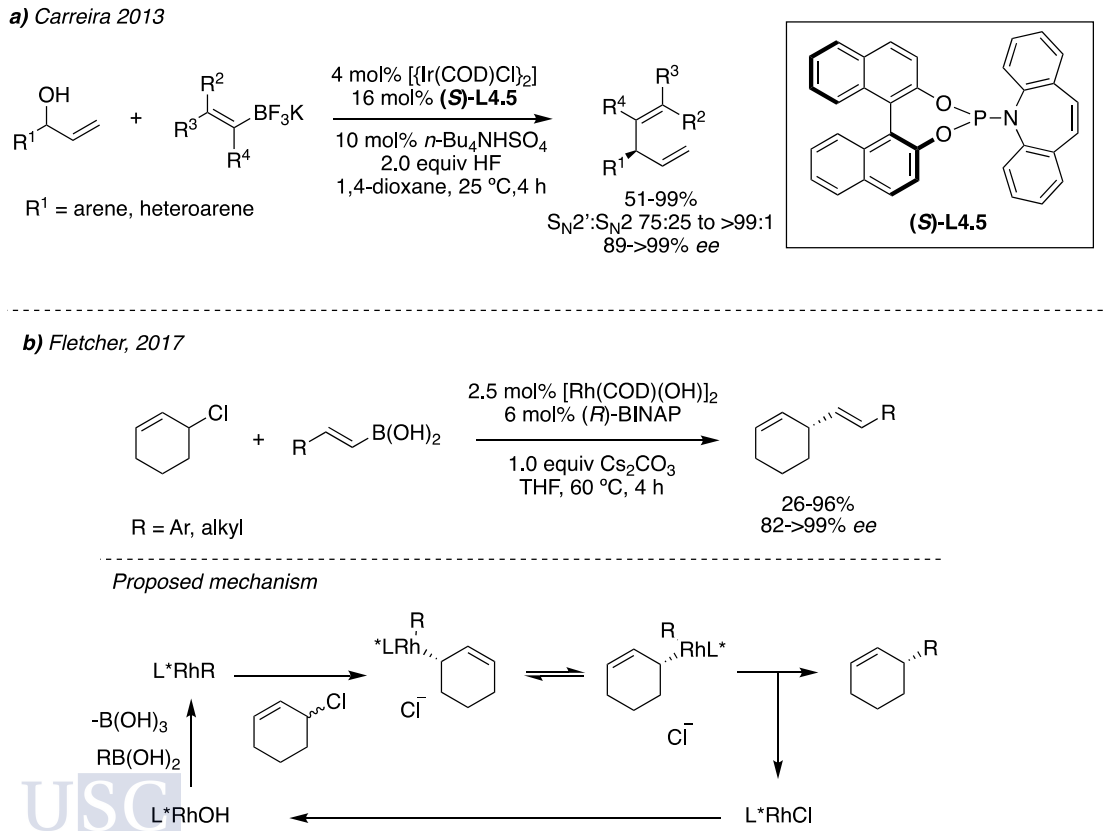
The use alkenylaluminum reagents although efficient, implies limitations related to the functional group tolerance. Thus, the use of more accessible and stable alkenyl reagents was preferable. In this context, methodologies relying on the use of alkenyl boron compounds emerged. The group of Hoveyda reported the use of very accessible alkenylboronic esters in a copper-catalyzed S_N2' type asymmetric allylic substitution of mono- and disubstituted allylic phosphates (Scheme 134).[105] Several chiral 1,4-dienes bearing an all carbon stereogenic center were obtained in good yield with high selectivity and excellent functional group tolerance by using different chiral NHC ligands (Scheme 134a). Enantioselective allylic substitution with monosubstituted allylic phosphates was also accomplished with both *E*- and *Z*-alkenylboronic esters by using **L4.3** or **L4.4** as ligand (Scheme 134b). Moreover, the utility of the method was demonstrated by the synthesis of several small natural products.



Scheme 134. Copper-catalyzed alkenylation of allylic phosphates with alkenylboron reagents.

Besides copper catalysis, other transition metal catalysts have been used to promote the asymmetric allylic alkenylation with different alkenylmetal reagents. Carreira developed a method for the asymmetric allylic substitution of simple allylic alcohols with potassium alkenyltrifluoroborates salts using chiral phosphoramidite-iridium catalysis (Scheme 135a).[220] The transformation has perfect levels of regioselectivity and very high enantioselectivity. Nonetheless, alkenylboronic acids and boronic esters were unreactive under these conditions and two equivalents of HF were needed to activate the alkenyltrifluoroborate salts. *N*-Bu_4NHSO_4 was used as a Brønsted acid for the activation of the allylic alcohol, and also, as a phase transfer catalyst to improve solubility of potassium trifluoroborates salts.

Fletcher recently reported an enantioselective rhodium-catalyzed Suzuki-Miyaura cross-coupling between alkenylboronic acids and cyclic allylic halides (Scheme 135b).[221] This strategy is based on the use of a chiral rhodium catalyst to obtain enantioenriched 1,4-dienes from racemic allylic substrates. A mechanism involving transmetalation of the boronic acids with the L*RhOH complex followed by oxidative addition of the allylic chloride and 1,3-isomerization of the resulting Rh(III) allylic species was proposed to explain this enantioconvergent transformation. Reductive elimination was proposed as the rate- and enantiodetermining step.

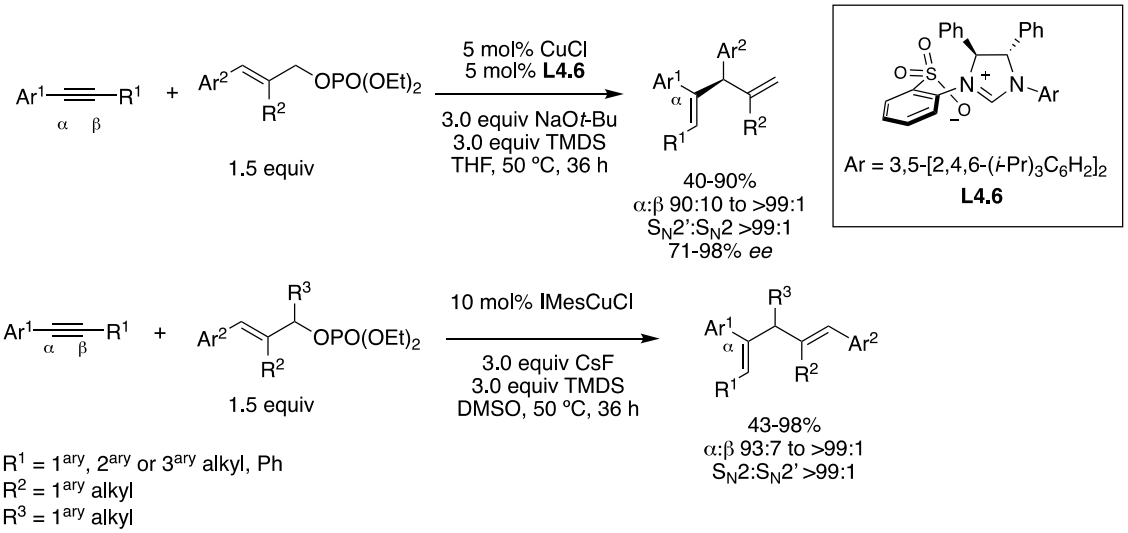


Scheme 135. a) Iridium- and **b)** Rhodium-catalyzed asymmetric allylic alkenylation.

[220] Hamilton, J. Y.; Sarlah, D.; Carreira, E. M. *J. Am. Chem. Soc*. **2013**, *135*, 994-997.
[221] Schäfer, P.; Palacin, T.; Sidera, M.; Fletcher, S. P. *Nat. Commun*. **2017**, *8*, 15762.

The above mentioned methodologies resulted very useful strategies for the asymmetric synthesis of branched 1,4-dienes and a big step forward in the addition of alkenylmetal reagents to allylic substrates. However, all of them share in common the requirement of the stoichiometric use of organometallic reagents, and most of them, their prior preparation.

An alternative to the use of stoichiometric amount of alkenylmetals reagents was reported in 2017 by Xiong through a copper-catalyzed alkyne hydroallylation. This approach involves a catalytic Cu-H addition to an alkyne forming a nucleophilic alkenylcopper intermediate, which then undergoes addition to an allylic phosphate (Scheme 136).[222] Control over the regioselectivity of the process can be achieved by changing the copper catalyst. By using a chiral NHC ligand bearing a sulfonate group, S_N2' type selectivity is obtained in an enantioselective manner. On the other hand, the use of a monodentate NHC ligand, such as IMes, together with a change in reaction conditions (CsF as base instead of NaO*t*-Bu and DMSO as solvent instead of THF) promotes the S_N2-type selective allylic substitution.



Scheme 136. Ligand-controlled regiodivergent and enantioselective copper-catalyzed hydroallylation of alkynes.

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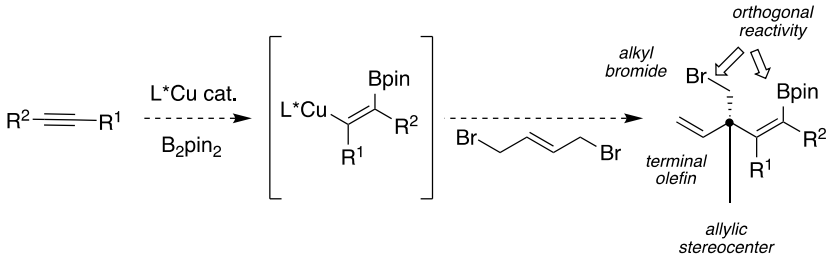
[222] Xu, G. Zhao, H.; Fu, B.; Cang, A.; Zhang, G.; Zhang, Q.; Xiong, T.; Zhang, Q. *Angew. Chem. Int. Ed*. **2017**, *56*, 13130-13134.

2. OBJECTIVE

In view of the precedents mentioned in the introduction and our work reported in chapter III about racemic copper-catalyzed allylboration of alkynes with difunctional allylic substrates, we devised to move one step further and attempt to develop an enantioselective copper-catalyzed allylboration of alkynes. We envisioned that the use of 1,4-dihalo-2-butene would give rise to densely functionalized chiral skipped dienes, bearing several orthogonal functionalities. Thus, the products obtained with this methodology would possess a great potential to exploit their synthetic versatility towards the synthesis of a variety of non-racemic molecules.



Scheme 137. Initial reaction proposal.

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3. RESULTS AND DISSCUSION

3.1. OPTIMIZATION

We first surveyed the performance of different types of chiral ligands in the reaction between phenylacetylene (**4.1**), *trans*-1,4-dibromo-2-butene (**4.2**) and bis(pinacolato)diboron (B_2pin_2, **4.3**) (Table 12). In this case, we needed a catalyst capable of controlling the chemo-, regio- and stereoselecivity (see Chapter II and III) and in addition, to promote enantioselective allylic substitution. The use of mono- (**L4.7**) or bisphosphine ligands (**L4.8**-**L4.11**) provided 1,4-diene **4.4** in negligible or modest yields, and as a nearly racemic mixture in all cases (Table14, entries 1-5). A similar outcome was observed for Quinox-type ligand **L4.12** (Table 12, entry 6). We then turned our attention to the use of NHC ligands which were formed *in situ* from the corresponding salts. Small increase in the enantioselectivity was observed when ligands **L4.13**, **L4.14** and **L4.15** were used although their efficiency was still far from satisfactory (Table 12, entries 7-9). Low yields were typically associated with the formation of competing LCu-Bpin allylation by-products. A major increase on the efficiency and the enantioselectivity was achieved when sulfonate-bearing NHC ligand **L4.1** was used (Table 12, entry 10). The chiral NHC-Cu catalyst derived from this ligand afforded **4.4** as a single isomer in 88% yield and with an excellent 97:3 enantiomeric ratio. The complete levels of regioselectivity (β-borylation and S_N2'-allylation) are also noteworthy, with the chemoselectivity being especially remarkable since the copper complex derived from ligand **L4.1** was described to readily promote the direct Bpin allylation when reacted with allylic phosphates.[223] Incorporation of a 3,5-di-*tert*-butyl substituted aromatic unit (**L4.16**) instead of the mesityl group, gave rise to a decrease on both the efficiency and enantioselectivity of the reaction (Table 12, entry 11). Interestingly, the Cu/**L4.1** catalyst loading could be reduced to 5 mol% still obtaining the product in good yield while keeping perfect levels of selectivity (Table 12, entry 12).

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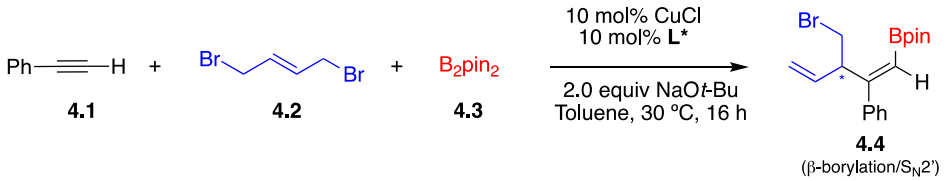
[223] Meng, F.; McGrath, K. P.; Hoveyda, A. H. *Nature* **2014**, *513*, 367-374.

Table 12. Screening of ligands.



Entry[a]	Ligand	Conv. **4.2** (%)[b]	Yield **4.4** (%)[c]	er[d]
1	**L4.7**	37	5	n.d.[e]
2	**L4.8**	73	18	51:49
3	**L4.9**	>99	25	66:34
4	**L4.10**	>99	50	47:53
5	**L4.11**	78	43	52:48
6	**L4.12**	48	8	n.d.[e]
7	**L4.13**	>99	35	61:39
8	**L4.14**	90	15	59:41
9	**L4.15**	88	33	64:36
10	**L4.1**	>99	88	97:3
11	**L4.16**	25	25	64:36
12[f]	**L4.1**	>99	73	97:3

[a] Reaction conditions: **4.1** (1.1 equiv), **4.2** (0.2 mmol, 1.0 equiv, added by syringe pump), **4.3** (2.0 equiv), CuCl (10 mol%), Ligand (10 mol%), NaO*t*-Bu (2.0 equiv), toluene (1.5 ml) at 30 ºC. [b] Conversion (**4.2** consumption) was determined by ^{1}H-NMR using 1,3,5-trimethoxybenzene as internal standard. [c] Yield of isolated **4.4**. Selectivity β/α >99:1 and S_N2': S_N2 >99:1 in all the cases. [d] Enantioselectivity determined by SFC analysis. [e] n.d. = not determined. [f] CuCl (5 mol%), **L4.1** (5 mol%).

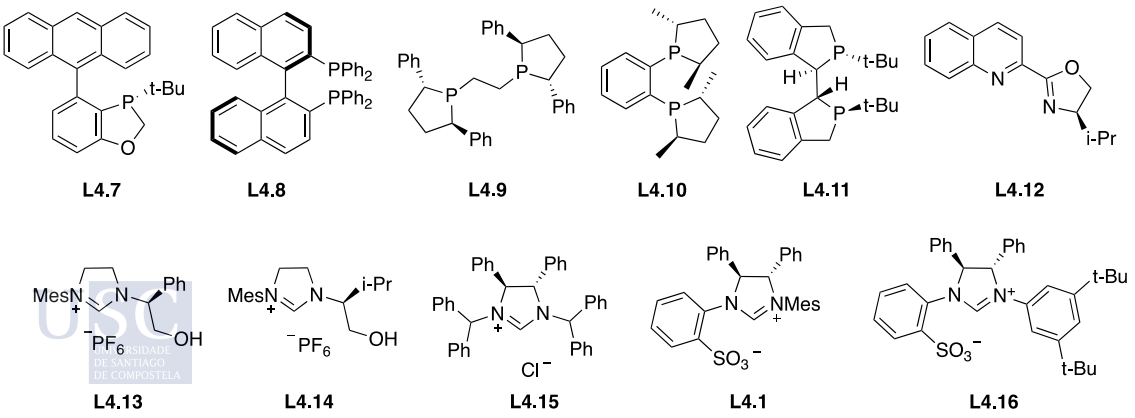
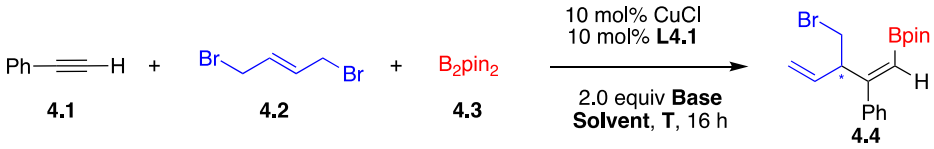


Figure 17. Structure of ligands tested in the optimization.

Further investigations using **L4.1** as ligand revealed that both the solvent and the metal alkoxide also play an important role in the reaction outcome (Table 13). Good selectivity levels were achieved when reaction was run in hexane although lower conversion was observed likely due to poor solubility of reagents and catalyst (Table 13, entry 2). Conversely, the use of a more polar solvent such as THF led to lower levels of chemo- and enantioselectivity (Table 13, entry 3). Regarding the metal alkoxide, a significant drop in enantioselectivity was observed when LiO^{t}Bu was used (Table 13, entry 4). The 97:3 er could be restored by using KO^{t}Bu although it was less efficient than NaO^{t}Bu (**4.4**, 55% vs 88% yield) (Table 13, entry 5). Finally, the temperature of the reaction was decreased to 0 ºC and a dramatic drop of the reaction efficiency was observed (**4.4**, 23% vs 88%) while maintaining the excellent enantiomeric ratio (Table 13, entry 6).

Table 13. Optimization of reaction conditions.



Entry[a]	Solvent	Base	T (º C)	Conv. **4.2** (%)[b]	Yield **4.4** (%)[c]	er[d]
1	toluene	NaO*t*-Bu	30	>99	88	97:3
2	hexane	NaO*t*-Bu	30	60	60	95:5
3	THF	NaO*t*-Bu	30	85	31	92:8
4	toluene	LiO*t*-Bu	30	94	35	90:10
5	toluene	KO*t*-Bu	30	>99	55	97:3
6	toluene	NaO*t*-Bu	0	80	23	97:3

[a] Reaction conditions: **4.1** (1.1 equiv), **4.2** (0.2 mmol, 1.0 equiv, added by syringe pump), **4.3** (2.0 equiv), CuCl (10 mol%), **L4.10** (10 mol%), NaO*t*-Bu (2.0 equiv), toluene (1.5 ml) at 30 ºC. [b] Conversion (**4.2** consumption) was determined by ^{1}H-NMR using 1,3,5-trimethoxybenzene as internal standard. [c] Yield of isolated **4.4**. Selectivity β/α >99:1 and S_N2': S_N2 >99:1 in all cases. [d] Enantioselectivity determined by SFC analysis.

3.2. SCOPE OF THE REACTION

Having established optimized conditions for the asymmetric allylboration of alkynes, we set out to explore the scope of the reaction (Table 14). The Cu/**L4.1** catalyst proved to be remarkably effective with a range of aryl alkynes. Products **4.4**-**4.10** were obtained in good yields with excellent regio- and enantioselectivity regardless of the electronic properties and position of the substituent on the aromatic ring (60-88% yield, >99% β-borylation, >99% S_N2', 93:7 to >99:1 er).

Functional groups such as ether, ester, halogen, and trifluoromethyl groups were well tolerated. Similarly, terminal alkynes bearing heteroaromatic (**4.11**), alkenyl (**4.12**), or cyclopropyl (**4.13**) groups provided the corresponding products in good yields with excellent levels of selectivity. The reaction with 1-hexyne suffered from a slightly lower site selectivity (β/α-borylation 78:22), although **4.14** was still obtained as a pure product with perfect S_N2' selectivity and high er. Importantly, allylic alkynylation[224] was never observed with terminal alkynes. The use of internal alkynes was illustrated with diphenylacetylene, which turned out to be less reactive, leading to incomplete conversion. Although **4.15** was only obtained with 80:20 er, it is important to note that, to the best of our knowledge, this represents the first example of an enantioselective alkenyl allylation using a tetrasubstituted alkenyl nucleophile. Gratifyingly, we observed that this new method can be extended to other types of allylic substrates. (*E*)-1,4-Dichloro-2-butene (**4.17**) was equally efficient for this transformation and gave rise to the chloro-substituted product **4.16** in 90%yield and 98:2 er. Importantly, the use of (*Z*)-**4.18** afforded **4.16** in very good yield but with only 76:24 er, thus showing that the enantioselectivity of the reaction is influenced by the *E*/*Z* configuration of the allylic starting material. A bifunctional allylic substrate in the form of a phenyl ether was also well tolerated and provided product **4.19** with perfect site selectivity and 93:7 er. Cinnamyl-type substrates also proved to be efficient partners for this transformation, providing the corresponding products **4.20**-**4.23** in good yields and with high enantioselectivities except for allylic bromides bearing sterically demanding substituents. Remarkably, the S_N2' selectivity was as high as that obtained with 1,4-dihalo-2-butenes, despite the absence of a coordinating unit in the allyl substrate.[214]

Cinnamyl phosphate and chloride could also be used for the asymmetric allylboration of phenylacetylene (**4.20**), although they proved to be less efficient than cinnamyl bromide. We also investigated the asymmetric allylboration with crotyl bromide, which has been scarcely used in catalytic asymmetric allylic substitution reactions involving organometallic nucleophiles likely because of the challenging enantiotopic differentiation caused by the small size of the methyl substituent.[106] To our delight, the reaction of crotyl bromide with phenylacetylene and B_2pin_2 afforded methyl-substituted product **4.26** in 88% yield with very high regioselectivity (S_N2'/S_N2 94:6) and enantioselectivity (95:5 er), further highlighting the efficiency of the catalytic system.

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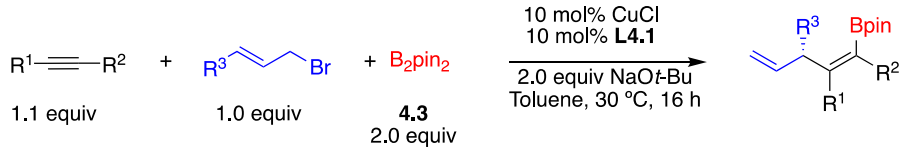
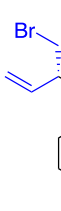
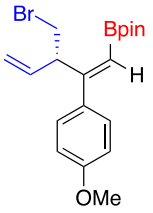
[224] Harada, A.; Makida, Y.; Sato, T.; Ohmiya, H.; Sawamura, M. *J. Am. Chem. Soc*. **2014**, *136*, 13932-13939.

Table 14. Scope of the copper-catalyzed enantioselective allylboration of alkynes.

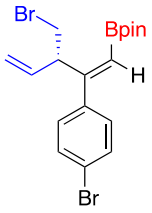




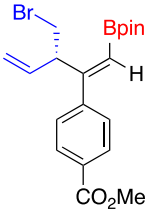
4.4
88% yield
97:3 e.r.



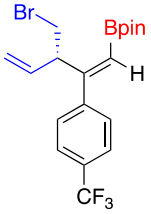
4.5
60% yield
93:7 e.r.



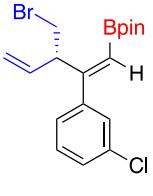
4.6
84% yield
93:7 e.r.



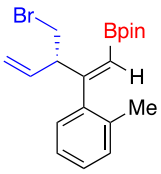
4.7
83% yield
>99:1 e.r.



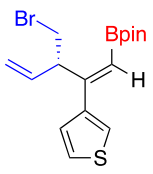
4.8
70% yield
94.5:5.5 e.r.



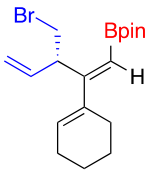
4.9[a]
60% yield
98.5:1.5 e.r.



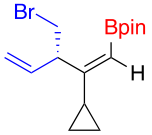
4.10
48% yield
94:6 e.r.



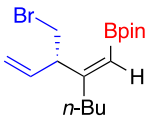
4.11
51% yield
97:3 e.r.



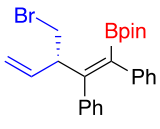
4.12[b]
50% yield
97:3 e.r.



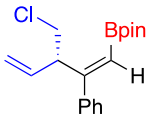
4.13[b]
66% yield
92:8 e.r.



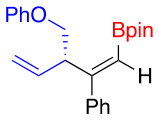
4.14[c]
44% yield
95:5 e.r.



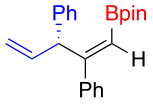
4.15[b]
33% yield
80:20 e.r.



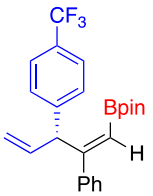
4.16[d]
from (*E*)-**4.17**: 90% yield, 98:2 e.r.
from (*Z*)-**4.18**: 99% yield, 76:24 e.r.



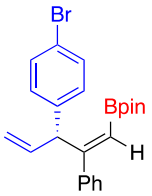
4.19[d]
67% yield
93:7 e.r.



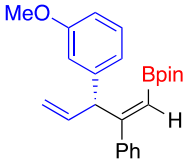
4.20
82% yield, 96.5:3.5 e.r.
64% yield, 96:4 e.r.[e]
40% yield, 93:7 e.r.[f]



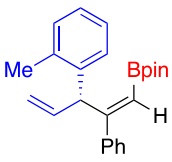
4.21
59% yield
93:7 e.r.



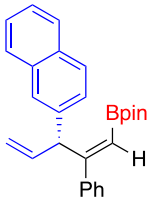
4.22
60% yield
95:5 e.r.



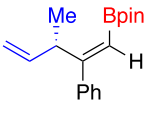
4.23
63% yield
92:8 e.r.



4.24
92% yield
85.5:14.5 e.r.



4.25
98% yield
87.5:12.5 e.r.



4.26[d,g]
88% yield
95:5 e.r.

Conditions reported in Table 12, entry 10. Selectivity >99% unless otherwise noted. [a] At 40 ºC. [b] At 50 ºC. [c] β-borylation/α-borylation 78:22. [d] Slow addition of the allyl bromide was not required. [e] Diethyl cinnamyl phosphate used instead of cinnamyl bromide. [f] Cinnamyl chloride used instead of cinnamyl bromide. [g] S_N2'/S_N2 94:6.

Absolute configuration of these products was determined by X-ray diffraction analysis of products **4.15** and **4.20** (Figure 18).

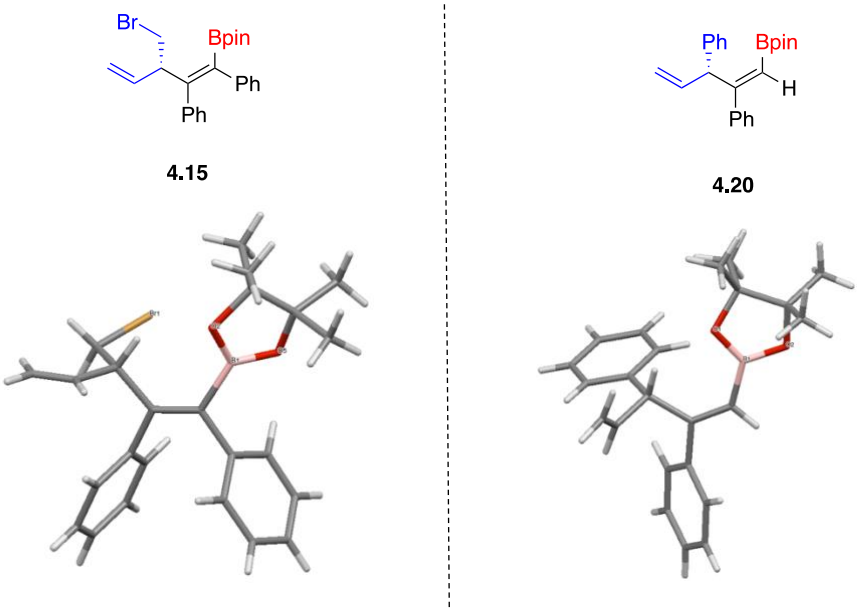


Figure 18. X-ray analysis of compounds **4.15** and **4.20**.

3.2.1. Limitations of the scope

Trimethylsilylacetylene **4.27** and internal alkynes such as **4.28** and **4.29** were not efficient substrates for the copper-catalyzed asymmetric allylboration. No productive amount of the desired borylated 1,4-dienes was obtained, neither under optimized conditions, nor increasing the temperature of the reaction. When **4.27** was reacted with **4.2** and B_2pin_2 under optimized conditions the corresponding 1,4-diene product was obtained in only 17% yield while observing full conversion of **4.2**. At higher temperatures no improvement was observed.

Alkynes **4.28** and **4.29** only led to mixture of alkyne protoboration products and unreacted alkynes. In both cases full conversion of **4.2** was observed

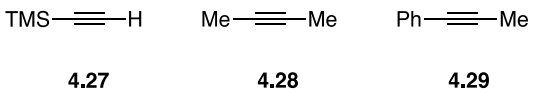
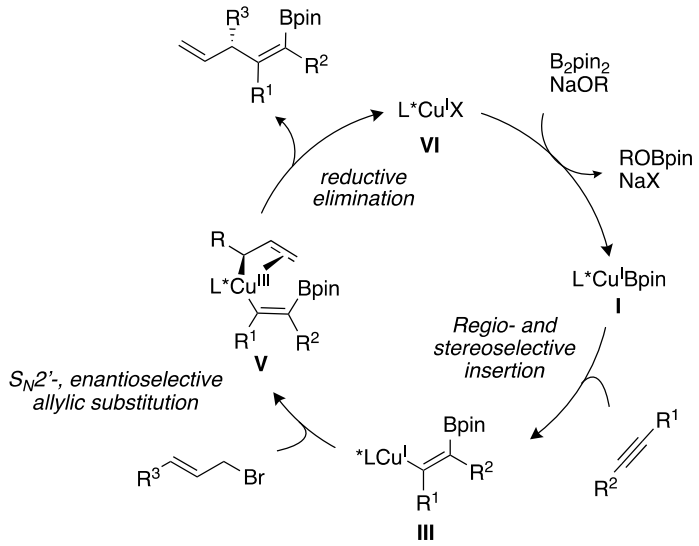


Figure 19. Unsuccessful alkynes in the copper-catalyzed asymmetric allylboration reaction.

3.3. MECHANISTIC INSIGHTS

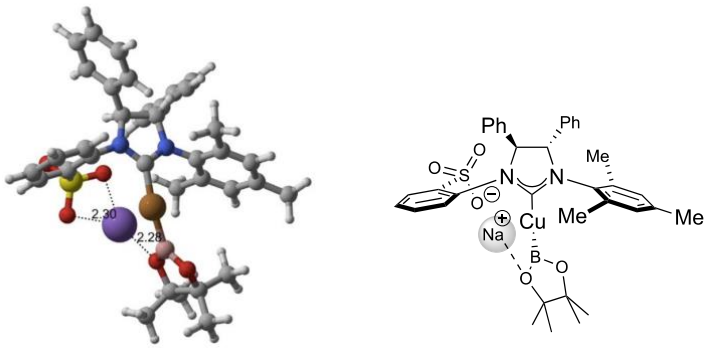
The proposed catalytic cycle for the copper-catalyzed asymmetric alkyne allyboration is depicted in Scheme 138. Initially the formation of the active catalytic species **I** occurs by reaction between L*CuX, NaO*t*-Bu and B_2pin_2. Regio- and stereoselective insertion of the alkyne into this complex would give rise to the nucleophilic β-boryl alkenylcopper(I) complex **III**. An S_N2'-type selective oxidative addition of the allylic bromide into this intermediate leads to Cu(III) complex **V**. During the oxidative addition, one of the prochiral faces of the allyl substrate has to be selectively

recognize in order to obtain an enantioselective transformation. Complex **V** would then undergo facile reductive elimination to afford the branched borylated 1,4-diene.



Scheme 138. Proposed mechanism for enantioselective copper-catalyzed allylboration of alkynes.

To gather insight about the high levels of selectivity achieved in this new transformation, DFT calculations were performed using formation of **4.26** (see Table 14) as model reaction. We initially found that the most favored conformation for the Cu-Bpin complex **I** arises from a coordination of the sodium cation with one oxygen atom of the pinacolato group (Figure 20).



I (ΔG_{sol} = 0.0 kcal/mol)

Figure 20. Optimized structure for complex **I**.

This situation favors coordination of the alkyne on the opposite side to the NHC's sulfonate group (front side) providing either isomeric Cu complexes **II** or **II'**. Transition state **TS** leading to the β-boryl substituted alkenyl-Cu complex **III** (blue path) was found to be 6.6 kcal/mol more favorable than **TS'** associated to the α-borylation pathway to **III'** (red path, Figure 21). The coordination of the alkyne from the opposite side, providing $\mathbf{II_{conf2}}$ was also studied (green path). However, transition state $\mathbf{TS_{con2}}$ leading to alkenyl-Cu complex $\mathbf{III_{conf2}}$ was found to be 2.5 kcal/mol less favored than the **II** to **III** pathway.

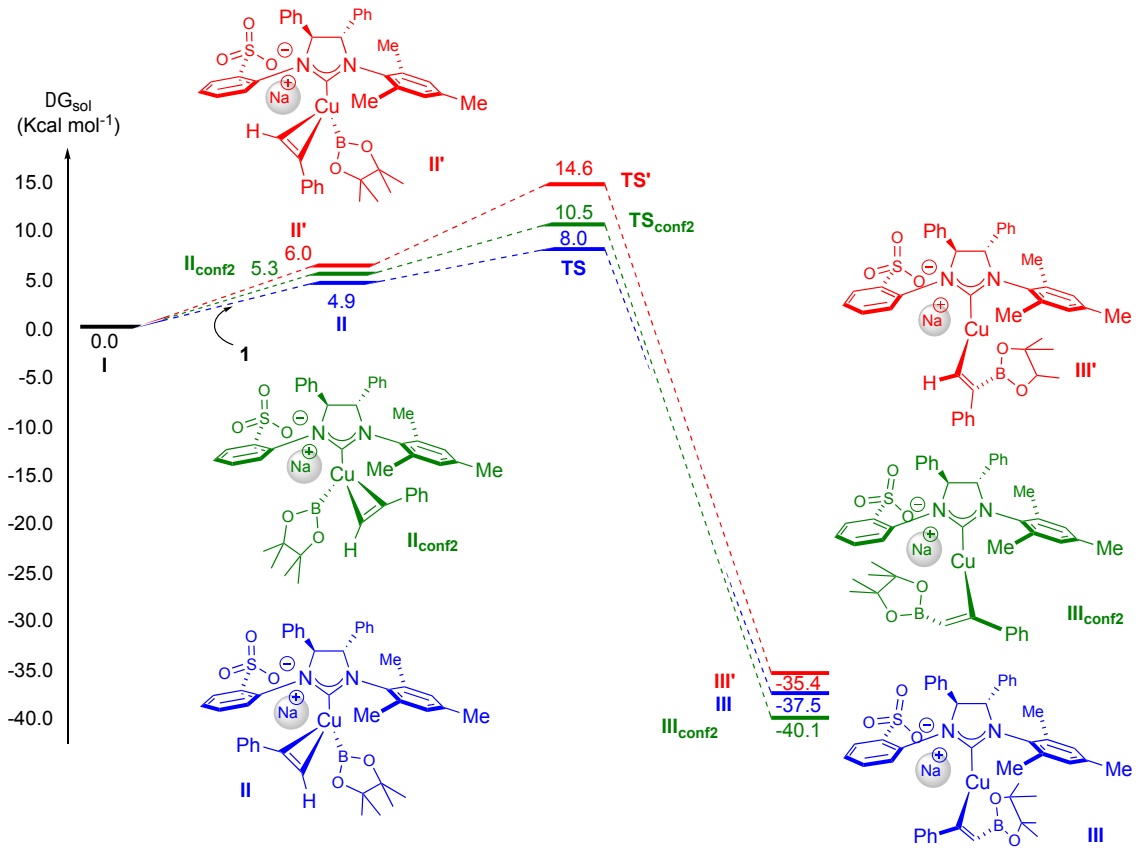
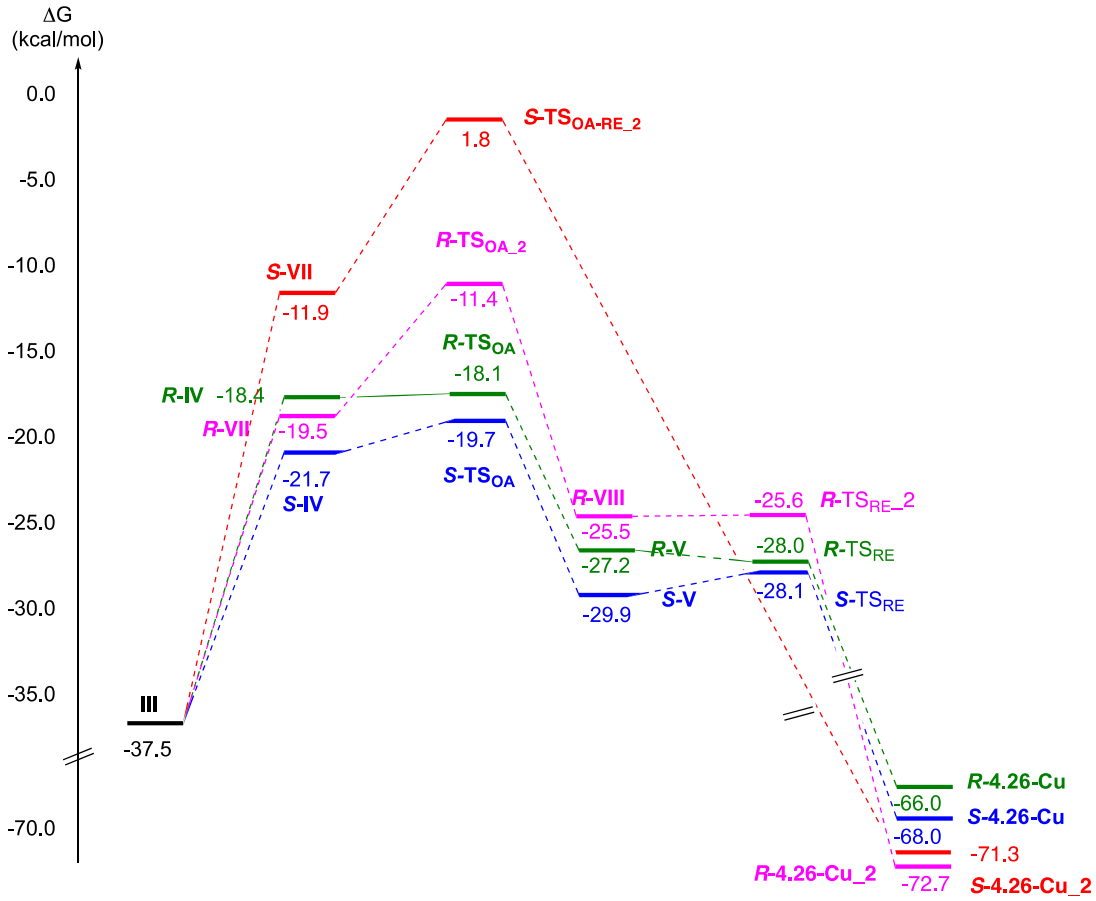


Figure 21. Free energy profile calculated at the ωB97XD/Def2-TZVPP$_{tol(SMD)}$//ωB97XD/6-31G(d) level for the alkyne borylcupration step.

The energy profile of next steps of the reaction suggests the oxidative addition step as the stereochemistry-determining step. Reductive elimination steps from ***S*-V** and ***R*-V** to final coordinated products ***S*-4.26-Cu** and ***R*-4.26-Cu** were found to be almost barrierless. Based on our findings, a stereochemical model for oxidative addition step, where the allyl bromide approaches complex **III** so that a sodium cation bridge is established between the NHC's sulfonate group and the bromide unit, may be proposed.[225] Four modes of coordination were investigated, and it was found that the pathways featuring the allyl bromide approaching in the same side that the sizable NMes unit (red and pink pathways) are higher in energy comparing to those ones featuring the allyl bromide opposite to the NMes unit (green and blue pathways). As shown in Figure 22, the relative energy for transition state ***S*-TS$_{OA}$** (pathway to the major *S* enantiomer) is 1.6 kcal/mol lower than of ***R*-TS$_{OA}$**, consistent with the observed 95:5 er. In the pathway leading to the minor enantiomer, the Me substituent in the allylic substrate would engender a repulsive interaction with the Bpin unit (Figure 23). The higher enantioselectivity observed in non-polar solvents (see Table 13, entries 1-3), where the ion pairing would be stronger thus leading to a more rigid transition state, is in accordance with a key supramolecular interaction between the sodium cation and the bromide. In this

[225] Lee, J.; Torker, S.; Hoveyda, A. H. *Angew. Chem. Int. Ed.* **2017**, *56*, 821-826.

context, the lower er observed when LiO^{t}Bu was used (Table 13, entry 4) might arise from a less efficient interaction due to the smaller size of the Li cation.



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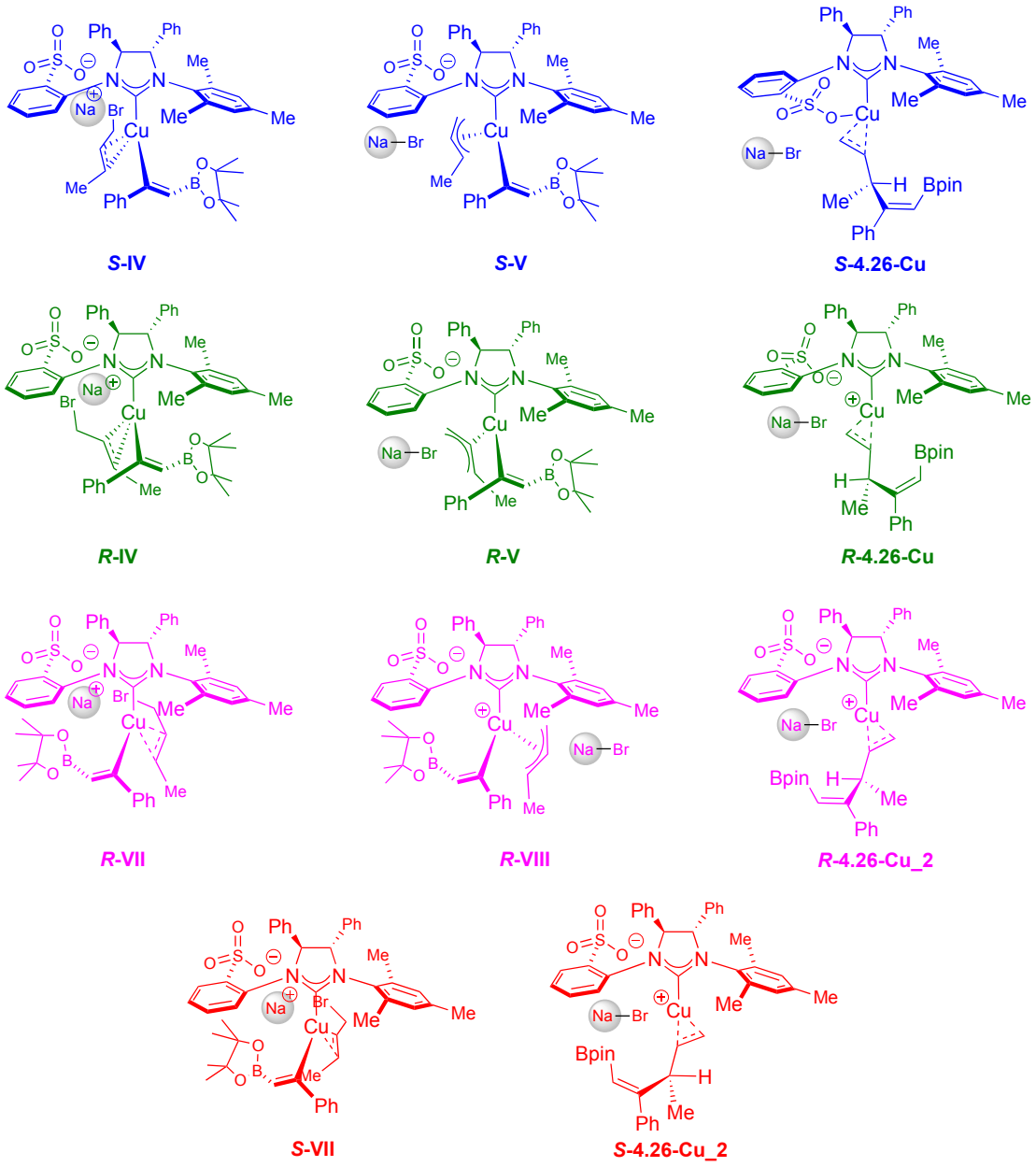

Figure 22. Free energy profile calculated at the ωB97XD/Def2-TZVPP$_{tol(SMD)}$//ωB97XD/6-31G(d) level for the formation of (*S*)-4.26-Cu, (*R*)-4.26-Cu, (*R*)-4.26-Cu_2 and (*S*)-4.26-Cu_2.

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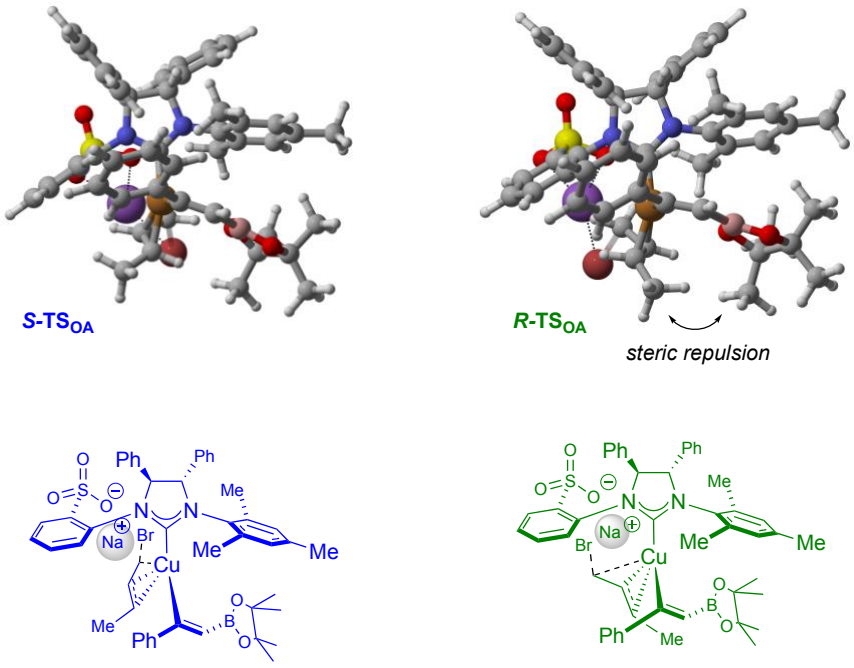

Figure 23. Optimized structures for *S*-TS$_{OA}$ and *R*-TS$_{OA}$.

3.4. SYNTHETIC APPLICATIONS

An attractive feature of this new asymmetric allylboration reaction is the functional group diversity present in the products, which makes them highly versatile non-racemic building blocks for the synthesis of a wide variety of non-racemic molecules.

3.4.1. Stereoselective synthesis of cyclopropanes

Cyclopropanes are important structural motifs that are present in a range of natural products and pharmaceuticals,[226] and are also valuable synthetic intermediates (Figure 24).[227] Examples of drugs containing a cyclopropane ring are Tasimelteon, which is a melatonin receptor antagonist used for sleep disorders, Tranylcypromine, which is an antidepressant and Milnacipran, which is a serotonin-norephrine reuptake inhibitor used for the treatment of fribromyalgia. *Trans*-chrysanthemic acid is a natural occurring compound in which, the cyclopropane ring contributes to its insecticidal properties.

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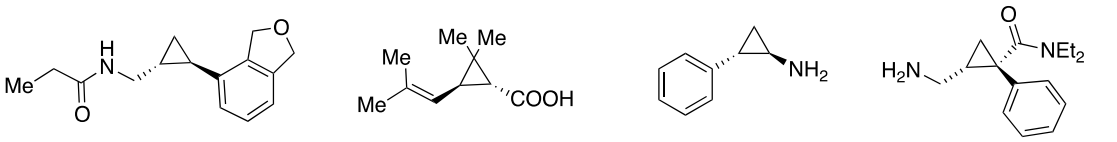
[226] (a) Faust, R. *Angew. Chem. Int. Ed*. **2001**, *40*, 2251-2253. (b) Talele, T. T. *J. Med. Chem*. **2016**, *59*, 8712-8756.

[227] (a) Rubin, M.; Rubina, M.; Gevorgyan, V. *Chem. Rev*. **2007**, *107*, 3117-3179. (b) Souillart, L.; Cramer, N. *Chem. Rev*. **2015**, *115*, 9410-9464. (c) Meazza, M.; Guo, H.; Rios, R. *Org. Biomol. Chem*. **2017**, *15*, 2479-2490. (d) Bruffaerts, J.; Pierrot, D.; Marek, I. *Nat. Chem*. **2018**, *10*, 1164-1170.



Tasimelteon *Melatonin receptor antagonist*

Trans-Chrysanthemic acid *Insecticide*

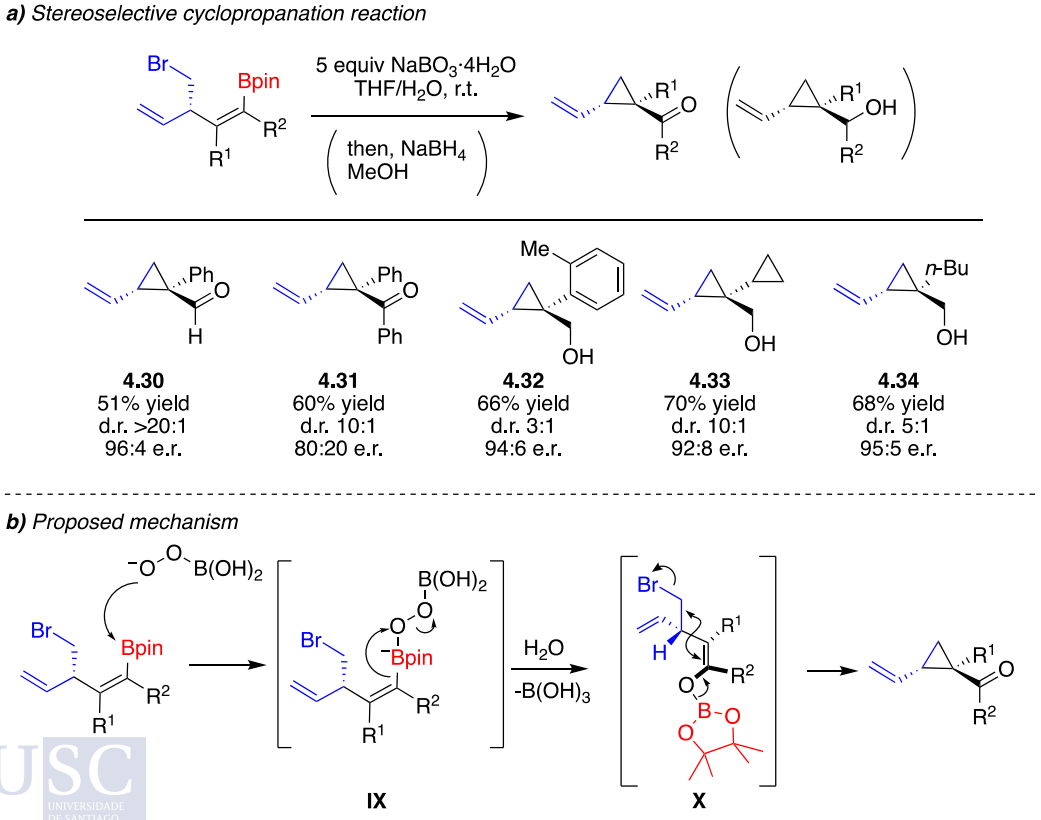
Tranylcypromine *Antidepressant*

L-Milnacipran *Serotonin–norepinephrine reuptake inhibitor*

Figure 24. Example of cyclopropane containing natural products and drugs.

Treatment of bromo-substituted dienyl boronates with sodium perborate resulted in a new stereoselective cyclopropanation reaction [228] for the asymmetric synthesis of functionalized vinylcyclopropanes. Vinylcyclopropane carbaldehydes (or carbinols after reduction) **4.30-4.34**, bearing a newly generated all-carbon quaternary center next to the tertiary stereocenter, were formed with generally high diastereoselectivity, and without any loss in the er.

The mechanism of this reaction likely involves the attack of the sodium perborate to the boron atom to form a boron 'ate' intermediate **IX**, which could undergo 1,2-metallate rearrangement to provide boron enolate **X**. Then, an intramolecular trapping, where the sizable OBpin unit would be placed *anti* to the vinyl group would take place to obtain the vinylcyclopropane carbaldehydes with high diastereoselectivity (Scheme 139).

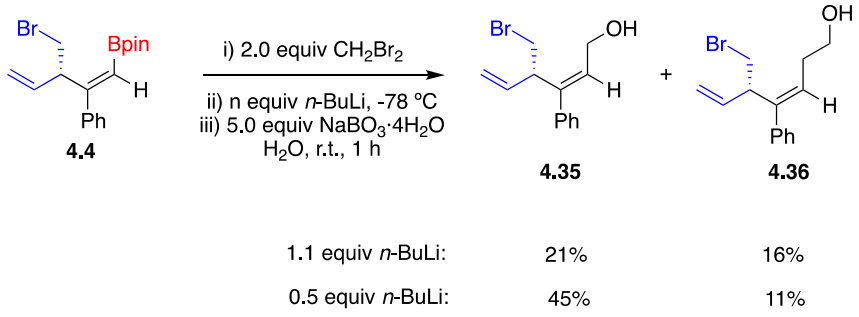


Scheme 139. a) Stereoselective cyclopronation reaction and **b)** mechanistic proposal.

[228] (a) Lebel, H.; Marcoux, J. F.; Molinaro, C.; Charette, A. B. *Chem. Rev*. **2003**, *103*, 977-1050. (b) Bartoli, G.; Bencivenni, G.; Dalpozzo, R. *Synthesis* **2014**, *46*, 979-1029.

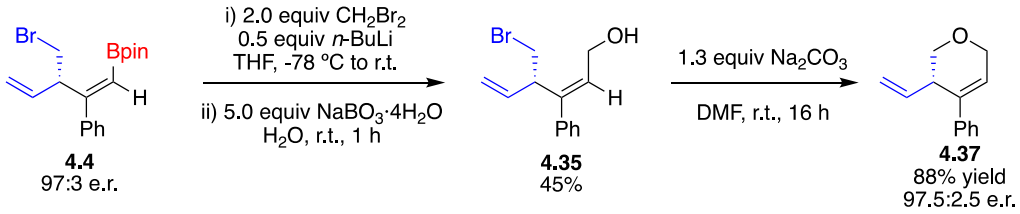
3.4.2. Synthesis of chiral non-racemic heterocycles through Matteson homologation

We also envisioned the synthesis of chiral heterocycles by a sequence of a Matteson homologation/oxidation/cyclization. Transformation of **4.4** to **4.35** via Matteson homologation was challenging due to the high reactivity of the allyl-Bpin formed as intermediate before oxidation. Homoallylic alcohol was detected as an important side-product (**4.36**). The equivalents of *n*-BuLi had to be adjusted to 0.5 equiv to increase the **4.35**/**4.36** ratio to 4:1 (Scheme 140), and thus, the yield of the product **4.35**, which could be isolated pure after column chromatography.



Scheme 140. Optimization of Matteson homologation with **4.4**.

Once the Matteson homologation was optimized, we could perform the synthesis of vinyl-substituted dihydropyran **4.37** in two steps. As mentioned above, the route consists in the Matteson homologation followed by an oxidation of the resulting allyl-Bpin compound with sodium perborate. Then, product **4.35** easily undergoes intramolecular cyclization under basic conditions to afford product **4.37** in good yield and with total stereochemical retention (Scheme 141).

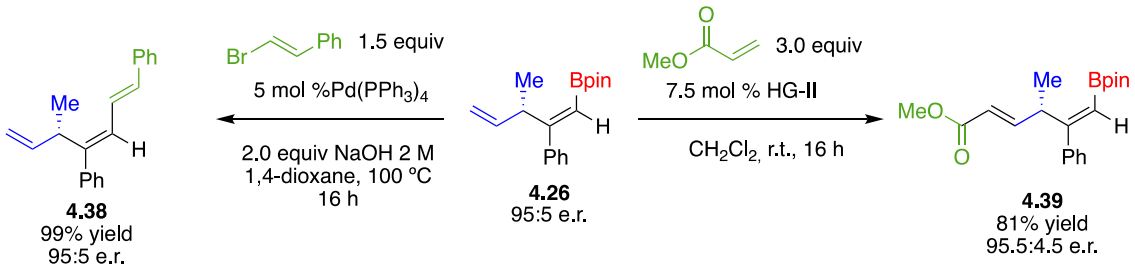


Scheme 141. Synthesis of non-racemic heteocycles.

3.4.3. Chemo- and stereoselective modification of methyl-substituted skipped dienes

The presence of both a terminal olefin and an alkenyl boronate offers the possibility of chemo- and stereoselective modification of both termini of the skipped diene skeleton. Thus, methyl-substituted skipped diene **4.26** could be selectively modified by Suzuki cross-coupling (**4.38**) or cross-metathesis (**4.39**; Scheme 142). This strategy represents a versatile tool to access structurally diverse chiral skipped dienes bearing a methyl-

substituted central stereogenic carbon atom, which are common structural motifs in a range of biologically active compounds.[229]



Scheme 142. Chemo- and stereoselective modification of methyl-substituted skipped dienes.

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[229] Ref. 154 and 159c.

4. CONCLUSIONS

We have developed the first asymmetric allylboration of alkynes. The use of a sulfonate bearing chiral NHC-copper catalyst enables the efficient synthesis of branched borylated 1,4-dienes with high levels of chemo-, stereo-, regio- and enantioselectivity under mild conditions. Furthermore, this methodology provides excellent results with a wide variety of substrates.

Key to achieving this selectivity is the use of a catalyst featuring a sulfonate-bearing chiral NHC ligand capable of establishing substrate-cation bridging interactions in different catalytic steps. As suggested by DFT calculations, the allyl bromide approaches to the alkenylcopper complex next to the sulfonate group by means of sodium cation bridge. Another important feature is the steric repulsion between the substituent of the allyl substrate and the mesityl group, enabling the enantiotopic differentiation of one of the faces of the allyl compound.

Another strength of this method is the access to the synthesis of densely functionalized molecules from simple starting materials. The high degree of functionalization provides to these compounds a highly versatile reactivity. Vinylcyclopropane carbaldehydes in which a new all-carbon quaternary center is generated could be accessed in a highly estereoselective manner through simple oxidation of the chiral bromo-substituted borylated 1,4-dienes. Moreover, the high versatility of this methodology was also illustrated by the synthesis of vinyl dihydropyran and diverse chiral skipped dienes bearing a methyl-substituted stereogenic carbon atom.

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CHAPTER V: STEREOSELECTIVE SYNTHESIS OF HIGHLY SUBSTITUTED 1,3-DIENES VIA 'À LA CARTE' MULTIFUNCTIONALIZATION OF BORYLATED DENDRALENES

Chapter adapted from:
Rivera-Chao, E.[a]; Fañanás-Mastral, M.[a] *Angew. Chem. Int. Ed.* **2021**, *60*, 16922-16927.

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[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)

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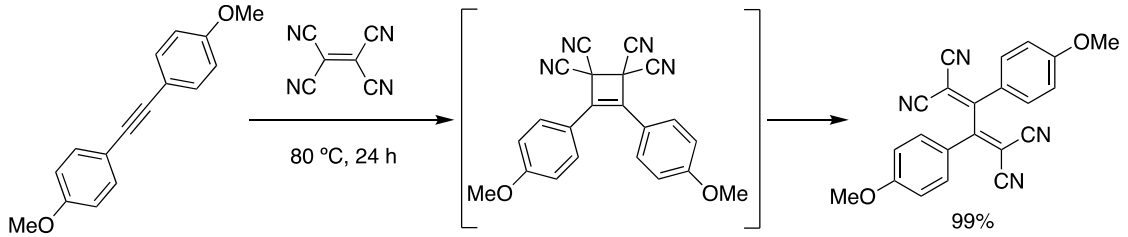
1. INTRODUCTION

1.1. SYNTHESIS OF HIGHLY SUBSTITUTED 1,3-DIENES

1,3-Dienes represent an important class of compounds owing to their versatile application in chemical synthesis[230] and their ubiquitous presence in a wide range of biologically active natural products, [231] and functional materials and devices. [232] Accordingly, a number of methods for the preparation of conjugated dienes have been developed.[233] Despite the effectiveness of these methods, the stereoselective construction of tetra- or more highly substituted 1,3-dienes is still scarce. Recent advances in the synthesis of highly substituted 1,3-dienes include a [2+2] cycloaddition-retroelectrocyclization reaction between tetracyanoethylene and electron rich alkynes (Scheme 143).[234] This methodology enables the synthesis of hexasubstituted 1,3-dienes, which are the most difficult to synthesize. However, this method is restricted to electron-rich aryl alkynes and to tetracyanoethylene, which implies a lack of versatility.



Scheme 143. Synthesis of hexasubstituted 1,3-dienes via [2+2] cycloaddition-retroelectrocyclization.

[230] Ref. 186.; (a) Nicolaou, K. C.; Snyder, S. A.; Montagnon, T.; Vassilikogiannakis, G. E. *Angew. Chem. Int. Ed.* **2002**, *41*, 1668-1698. (b) Cornil, J.; Guérinot, A.; Cossy, J. *Org. Biomol. Chem*. **2015**, *13*, 4129-4142. (c) Perry, G. J. P.; Jia, T.; Procter, D. J. *ACS Catal*. **2020**, *10*, 1485-1499.

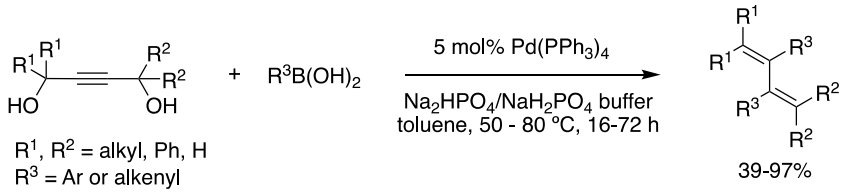
[231] (a) Cereghetti, D. M.; Carreira, E. M. *Synthesis* **2006**, 914-942. (b) Madden, K. S.; Mosa, F. A.; Whiting, A. *Org. Biomol. Chem*. **2014**, *12*, 7877-7899.

[232] (a) Guo, Y.; Feng, X.; Han, T.; Wang, S.; Lin, Z.; Dong, Y.; Wang, B. *J. Am. Chem. Soc*. **2014**, *136*, 15485-15488. (b) Lv, S.; Han, L.; Xiao, J.; Zhu, L.; Shi, J.; Wei, H.; Xu, Y.; Dong, J.; Xu, X.; Li, D.; Wang, S.; Luo, Y.; Meng, Q.; Li, X. *Chem. Commun*. **2014**, *50*, 6931-6934.

[233] Olefination of unsaturated carbonyl compounds: (a) van Staden, L. F.; Gravestock, D.; Ager, D. J. *Chem. Soc. Rev*. **2002**, *31*, 195-200. (b) Cui, H.; Li, Y.; Zhang, S. *Org. Biomol. Chem*. **2012**, *10*, 2862-2869, and references cited therein.; Elimination/isomerization reactions: (c) Trost, B. M.; Schmidt, T. A. *J. Am. Chem. Soc*. **1988**, *110*, 2301-2303. (d) Crouch, I. T.; Dreier, T.; Frantz, D. E. *Angew. Chem. Int. Ed*. **2011**, 50, 6128-6132.; Metathesis reactions: (e) Funk, T. W.; Efskind, J.; Grubbs, R. H. *Org. Lett.* **2005**, *7*, 187-190. (f) Diver, S. T.; Giessert, A. J. *Chem. Rev*. **2004**, *104*, 1317-1382.; Transition metal-catalyzed cross-coupling reactions: (g) Molander, G. A.; Felix, L. A. *J. Org. Chem*. **2005**, *70*, 3950-3956. (h) Ebran, J. P.; Hansen, A. L.; Gøgsig, T. M.; Skrydstrup, T. *J. Am. Chem. Soc*. **2007**, *129*, 6931-6942. (i) Xu, Q.; Zheng, B.; Zhou, X.; Pan, L.; Liu, Q.; Li, Y. *Org. Lett*. **2020**, *22,* 1692-1697.

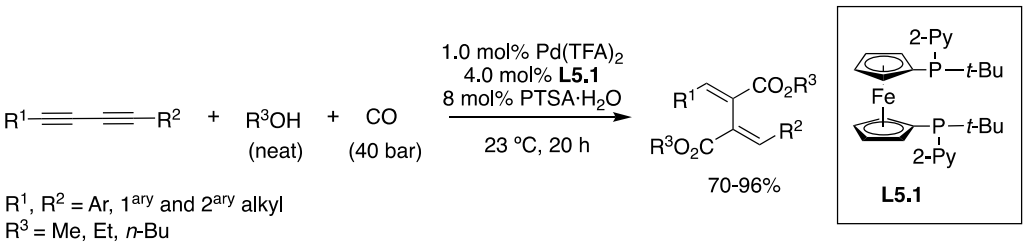
[234] Chiu, M.; Tchitchanov, B. H.; Zimmerli, D.; Sanhueza, I. A.; Schoenebeck, F.; Trapp, N.; Schweizer, W. B.; Diederich, F. *Angew. Chem. Int. Ed*. **2015**, *54*, 349-354.

Another interesting methodology for the synthesis of highly substituted 1,3-dienes is a palladium-catalyzed coupling of propargylic diols with arylboronic acids reported by the group of Sherburn (Scheme 144).[235] This methodology allows the synthesis of hexasubstituted 1,3-dienes in good to excellent yields in most of the cases, however, symmetrical products are obtained in most of the examples.



Scheme 144. Palladium-catalyzed cross-coupling of propargylic diols and boronic acids.

The palladium-catalyzed carbonylation of 1,3-diynes reported by the group of Beller allows tetrasubstituted 1,3-dienes to be synthesized in high yields and with excellent stereoselectivity (Scheme 145).[236]



Scheme 145. Palladium-catalyzed carbonylation of 1,3-diynes.

As mentioned above, these methods somewhat lack the possibility to install structurally diverse substituents at the different positions of the diene core. Moreover, besides the challenge associated to the substitution pattern, the synthesis of 1,3-dienes bearing substituents at all four positions imposes another big selectivity issue since every double bond must be constructed stereoselectively while substituents being incorporated in a regioselective manner. Thus, the development of new methodologies, particularly those that allow the stereoselective synthesis of highly substituted conjugated dienes with 'à la carte' introduction of diverse substituents remains a challenge.

1.2. CARBOLITHIATION OF DENDRALENES

Carbolithiation of unsaturated hydrocarbons provides an interesting pathway for the synthesis of new C-C bonds.[237] This reaction consists in the addition of an organolithium

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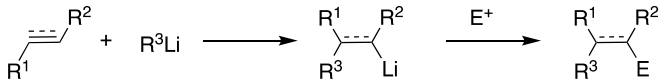
[235] Green, N. J.; Willis, A. C.; Sherburn, M. S. *Angew. Chem. Int. Ed*. **2016**, *55*, 9244-9248.
[236] Liu, J.; Yang, J.; Baumann, W.; Jackstell, R.; Beller, M. *Angew. Chem. Int. Ed*. **2019**, *58*, 10683-10687.
[237] (a) Clayden, J. Regio- and Stereoselective Addition Reactions of Organolithiums in *Organolithiums: Selectivity for Synthesis*; Tetrahedron Organic Chemistry Series, Vol. 23; Pergamon Press: Oxford, U.K.,

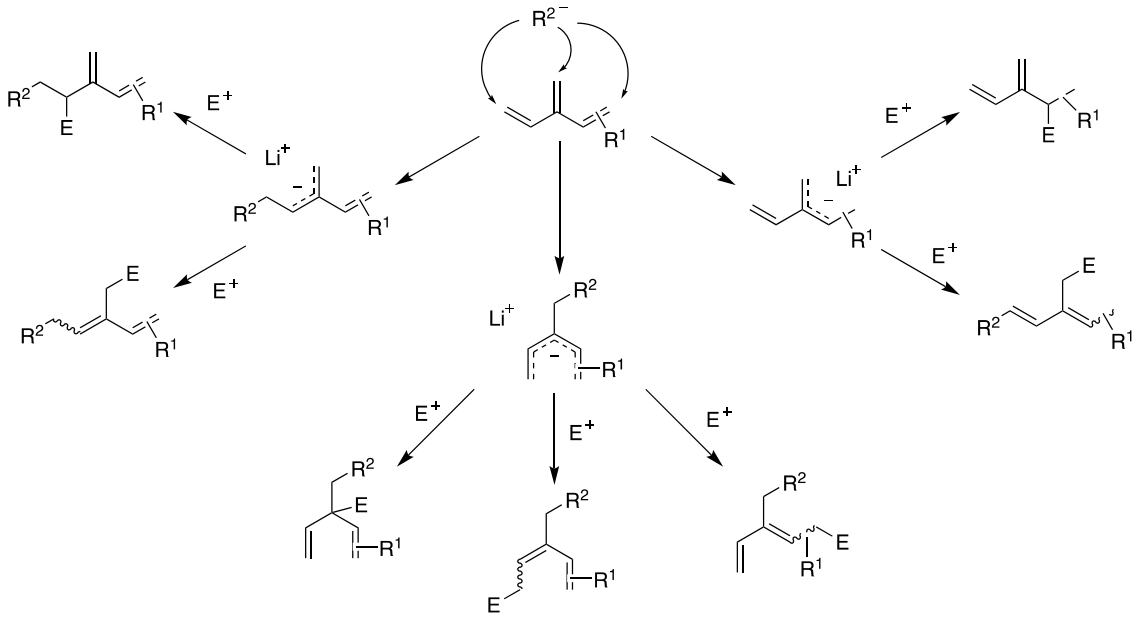
reagent to a non-activated double or triple bond. This addition results in a new organolithium intermediate, which gets trapped with an electrophile, offering the possibility to incorporate an extra functionalization on the molecule (Scheme 146).



Scheme 146. Carbolihitation of unsaturated substrates.

These are thermodynamically driven processes, thus, reaction proceeds if the generated organolithium is more stable than the starting reagent. Hence, the reactivity of organolithium reagents can be classified upon their stability, being methyl, aryl and vinyl lithium reagents less reactive than alkyllithiums. Organolithiums are also widely used as initiators for anionic polymerization processes.[238]

In contrast to the widely explored carbolitihation of alkenes and alkynes (and conjugated 1,3-dienes), the carbolithiation of dendralenes has been less explored. In this case, different isomeric products can be formed from the addition of the organolithium to the dendralene. As depicted in Scheme 147, different allyl or pentadienyl lithium intermediates can potentially form after organolithium addition. Moreover, the electrophilic trapping can occur at different positions and its stereochemical outcome can also represent an issue



Scheme 147. Potential isomers that can be formed from [3]dendralene carbolithiation.

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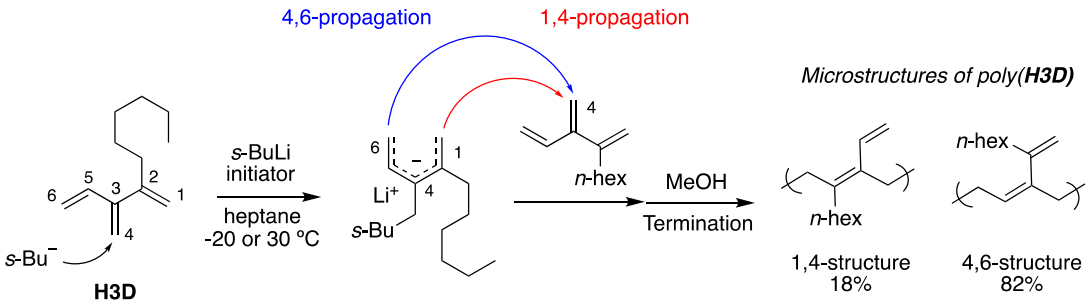
2002; pp. 273-335. (b) Hogan, A.-M. L.; O'Shea, D. F. *Chem. Commun*. **2008**, 3839-3851. (c) Minko, Y.; Marek, I. *Advances in Carbolithiation in Lithium Compounds in Organic Synthesis: From Fundamentals to Applications* 1st ed.; Luisi, R., Capriati, V., Eds.; Wiley-VCH: Weinheim, 2014; pp. 329-350. (d) Marsico, G.; Scafato, P.; Belviso, S.; Superchi, S. *RSC Adv*. **2020**, *10*, 32581-32601.

[238] Baskara, D.; Muller, A. H. *Anionic Vinyl Polymerization in Controlled and living polymerizations: from mechanisms to applications*, Wiley-VCH Verlag GmbH & Co. KgaA, Weinheim, 2010.

One of the few examples or carbanion addition to [3]dendralenes is related to anionic polymerization proccesses. The group of Takenaka explored this polymerization using potassium naphthalenide, lithium naphthalenide or *sec*-butyllithium as initiators.[189c,d,e] In particular, the polymerization of dendralene **H3D** was explored using *s*-BuLi as initiators and methanol as the electrophilic trapping agent (Scheme 148).[189d] After the analysis of the polymeric structure of poly(**H3D**) they observed that, among the microstuctures which can be formed, 1,4- and 4,6-connection are formed exclusively, being the latter more abundant. The formation of these microstructures would imply the initial nucleophilic attack of *s*-BuLi to the central olefin (carbon 4), to provide a pentadienyl lithium intermediate. The propagation of the anion can occur from carbon 1 or from carbon 6, leading to a 1,4-propagation or to a 4,6-propagation respectively. Authors proposed that the propension to provide the 4,6-structure is related to the steric hindrance of the hexyl chain, thus, the propagation of the polymerization of the less-hindered 4,6-anion is favored.



Scheme 148. Anionic polymerization of [3]dendralenes.

Besides anionic polymerization reactions, carbolitihation of cyclic [3]dendralenes has been also studied.[239] These studies proved that the addition of the organolithium reagent occurs in the central double bond as a result of the formation of a more stabilized pentadienyl lithium intermediate. In the example reported by Williams, Baik and co-workers,[239b] the pentadienyl lithium intermediate suffers an intramolecular electrocyclization to afford an allyl lithium which undergoes electrophilic trapping with a wide variety of electrophiles, in a process where three new bonds are formed in a single step (Scheme 149). The carbolithiation step with secondary and tertiary alkyllithium reagents occurs in Et_2O within minutes. However, primary alkyllithium reagents require the use of hexane as solvent and an equivalent of a diamine ligand (TMEDA or (-)-sparteine) to promote effective carbolithiation. Nonetheless, phenyl-, vinyl-, allyl- and methyllithium reagents did not provide carbolithiation under these conditions.

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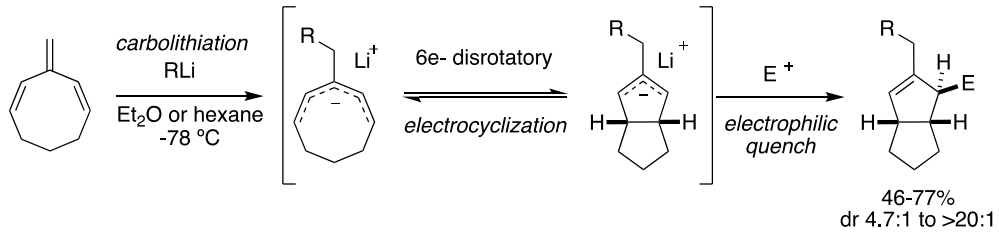
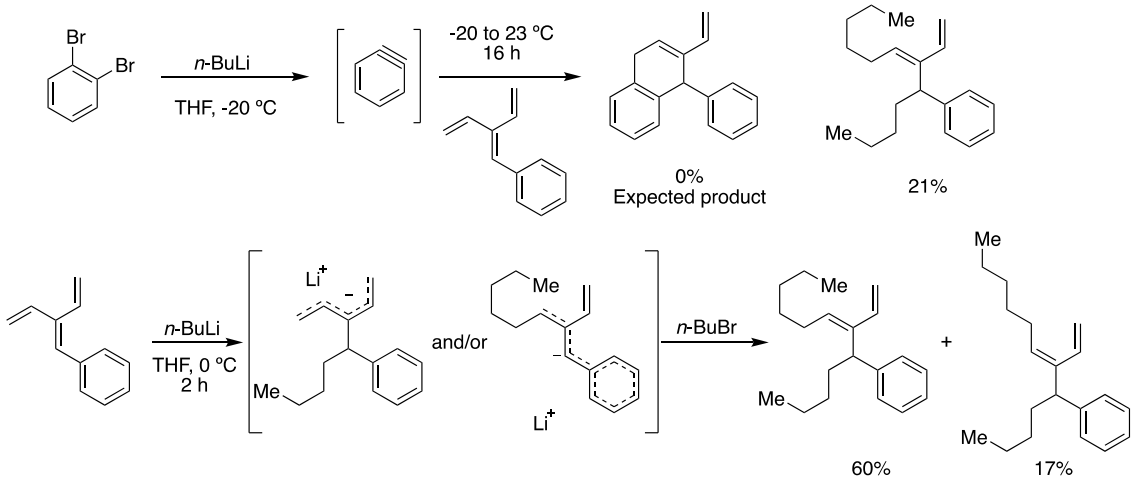
[239] (a) Hallden-Abberton, M.; Engelman, C.; Fraenkel, G. *J. Org. Chem* **1981**, *46*, 538-546. (b) Williams, D. R.; Reeves, J. T.; Nag, P. P.; Pitcock, W. H.; Baik, M.-H. *J. Am. Chem. Soc*. **2006**, *128*, 12339-12348.



R = *t*-Bu, *i*-Pr, Cy, *n*-Bu, TIPSO$(CH_2)_5$
E^+ = R_2CO, PhCHO, PhSSPh, PhCOCl, alkyl-I, CO_2, $PhMe_2SiCl$, CH_2O, epoxide electrophiles

Scheme 149. Carbolithiation of cyclic [3]dendralenes.

A single example of carbolithiation of acyclic of dendralenes has been reported so far. Within a study on DTDA reaction between acyclic [3]dendralenes and *in situ* generated benzynes, Sherburn and co-workers observed that under the conditions to generate benzyne, using 1,2-dibromobenzene and *n*-BuLi in THF, an unexpected product after the addition of [3]dendralene was formed.[240] Instead of the expected Diels-Alder product, the product of the addition of two *n*-butyl units to the dendralene was obtained in 21% yield. The yield could be increased to 60% with the use of bromobutane instead of 1,2-dibromobenzene (Scheme 150). To explain the formation of this product, a nucleophilic addition of *n*-BuLi to dendralene, to form a stabilized pentadienyl lithium intermediate, and subsequent trapping with bromobutane was proposed.



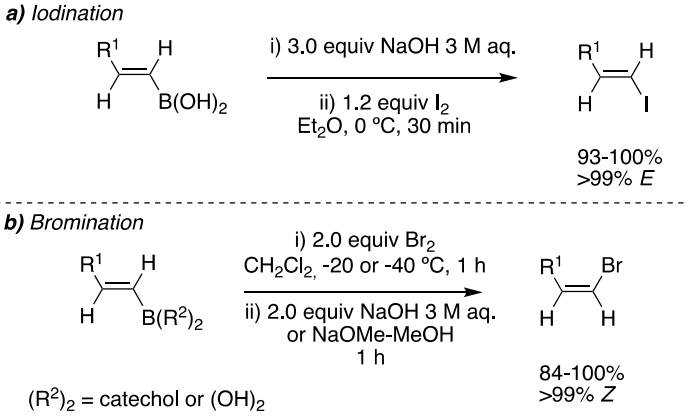
Scheme 150. Carbolithiation of acyclic [3]dendralene and subsequent electrophilic trapping with *n*-BuBr.

1.3. HALODEBORONATION OF ALKENYL BORONATES

As introduced in chapter I, section 1.2.6, C-B bonds can undergo electrophilic substitution due to the nucleophilic character of the carbon attached to the boron atom. Halodeboronation of alkenyl boron compounds was initially studied by the group of

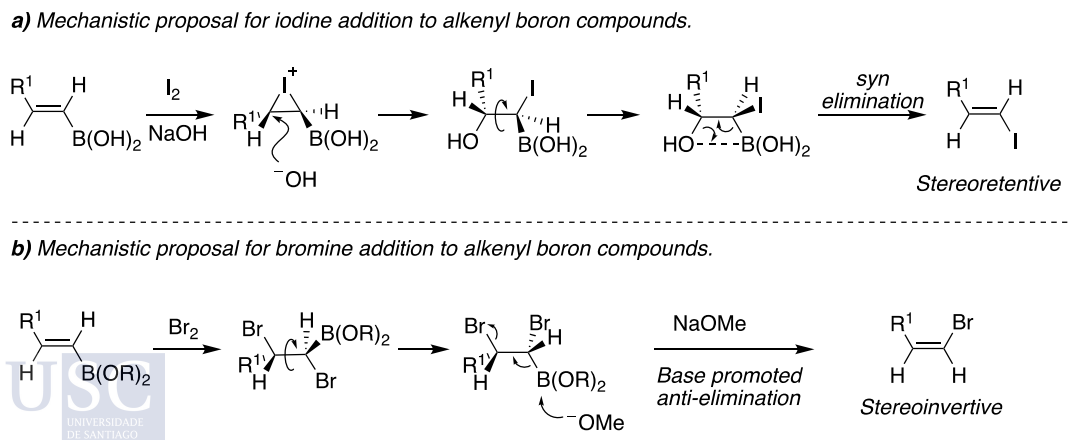
[240] George, J.; Ward, J. S.; Sherburn, M. S. *Org. Lett*. **2019**, *21*, 7529-7533.

Brown.[241] These reactions involved the addition of iodine or bromine to alkenyl boronic acids or catechol boronic esters, using NaOH or NaOMe as base at low temperatures (Scheme 151). Importantly, the addition of iodine provides alkenyl iodide with retention of configuration of the double bond, while the addition of bromine provides inversion of the double bond configuration. It was observed that the order of addition of Br_2 and base was important for the stereochemical outcome.



Scheme 151. First examples of iodination and bromination of alkenylboron compounds.

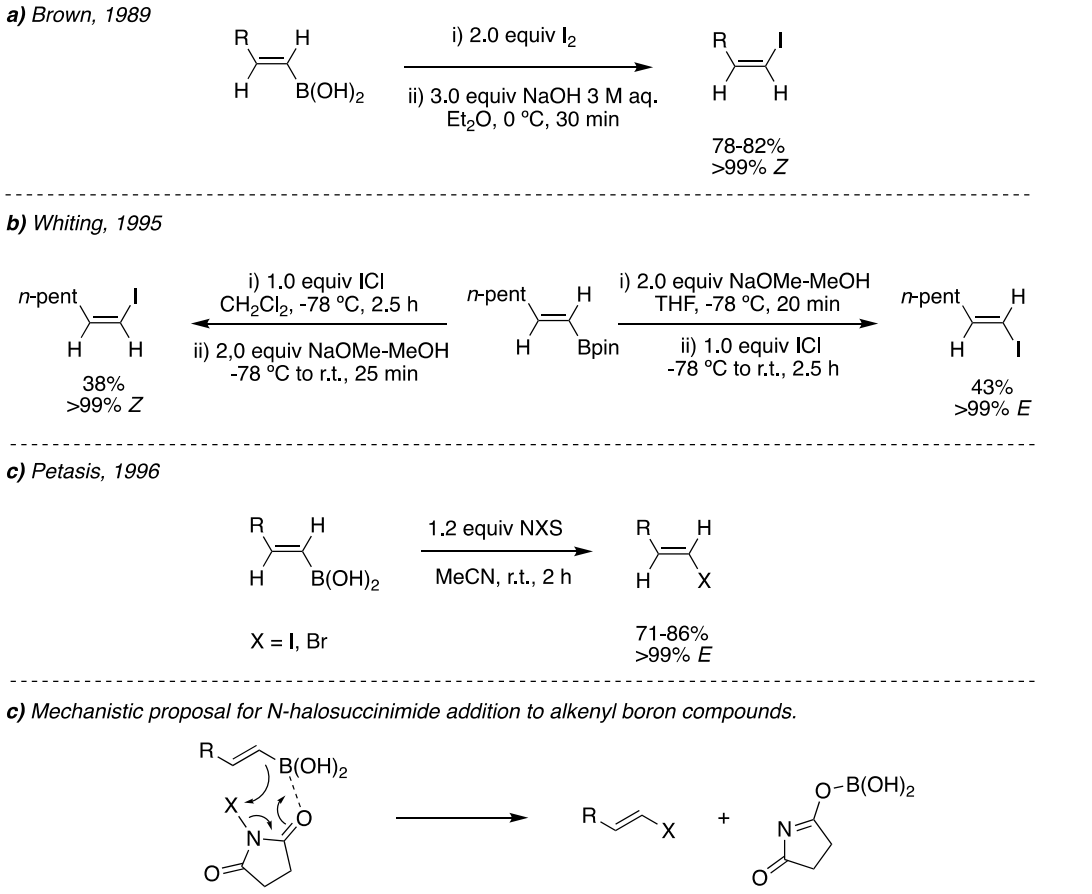
To explain the outcome of these reactions the authors proposed a tentative mechanism for the addition of I_2 and Br_2 to alkenyl boronic acids under basic conditions (Scheme 152a and b). When Iodine is added, a three membered iodonium intermediate would be formed. The hydroxide ion would attack the β-carbon (from the boron atom) and, after rotation of the single bond, a *syn* elimination would afford the iodoalkene with stereoretention of the double bond configuration. In the case of bromine, addition of the Br-Br bond to the double bond provides the dibrominated intermediate, which would undergo base-promoted *anti* elimination. This mechanism would give rises to the bromoalkene with inversion of configuration of the double bond.



Scheme 152. Mechanistic proposal for the halogenation of alkenylboron compounds.

[241] (a) Brown, H. C.; Hamaoka, T.; Ravindran, N. *J. Am. Chem. Soc*. **1973**, *95*, 5786-5788. (b) Brown, H. C.; Hamaoka, T.; Ravindran, N. *J. Am. Chem. Soc*. **1973**, *95*, 6456-6457.

Later on, it was found that the stereochemistry of the final product is sensitive to the reagent used for iodination or bromination and also to the order of addition of the base.[242] Brown found that the addition of iodine prior to the addition of the base leads to the formation of the product with inversion of configuration (Scheme 153a). The use of ICl also leads to the formation of the iodinated products and both *E* and *Z* isomers can be obtained by changing the order of the addition of the reagents. Furthermore, *N*-halosuccinimides (NIS and NBS) were described to promote direct electrophilic trapping with total stereoretention (Scheme 153c).[243] This latter transformation does not require the use of base and can be performed at room temperature. In contrast to the mechanism proposed for halogens, which involves an electrophilic addition of the halogen to the double bond, the mechanism for *N*-halosuccinimides is proposed to undergo a direct migration of the alkenyl moiety to the halide after coordination of the succinimide with the boron atom (Scheme 153d).



Scheme 153. Examples of conditions and reagents explored for the halogenation of alkenylboron compounds.

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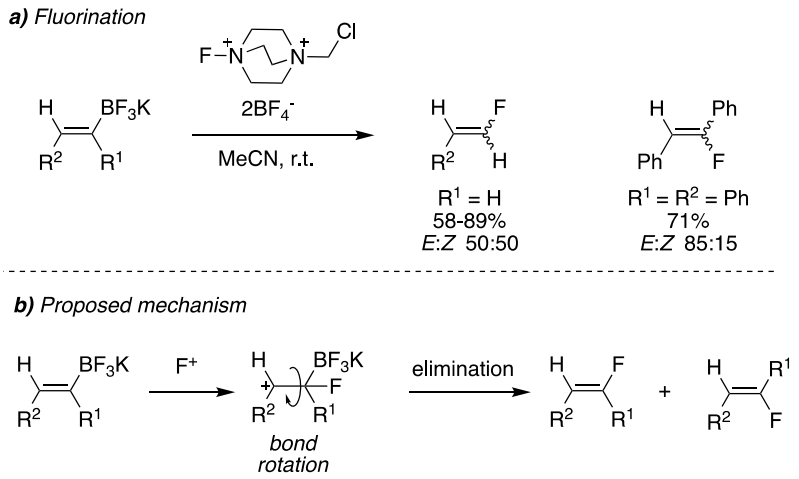
[242] (a) Brown, H. C.; Subrahmanyam, C.; Hamaoka, T.; Ravindran, N.; Bowman, D. H.; Misumi, S.; Unni, M. K.; Somayaji, V.; Bhat, N. *J. Org. Chem*. **1989**, *54*, 6068-6075. (b) Stewart, S. K.; Whiting, A. *Tetrahedron Lett.* **1995**, 36, 3929-3932. (d) Lightfoot, A. P.; Twiddle, S. J. R.; Whiting, A. *Org. Biomol. Chem.* **2005**, *3*, 3167-3172. (e) Szyling, J.; Franczyk, A.; Pawluć, P.; Marciniec, B.; Walkowiak, J. *Org. Biomol. Chem*. **2017**, *15*, 3207-3215.

[243] Petasis, N. A.; Zavialov, I. A. *Tetrahedon Lett*. **1996**, *37*, 567-570.

Fluorination of alkenylboron compounds has been less explored than iodination or bromination.[244] Metal-free fluorination with Selectfluor®[245] of alkenyl trifluoroborates was described by Olah and Prakash (Scheme 154a).[246] Stereochemistry cannot be controlled in this case, obtaining in most of cases equimolar *E*:*Z* mixtures. This transformation was proposed to occur through the generation of a β-fluorocarbocation intermediate (Scheme 154b). Thus, after the formation of this intermediate, bond rotation can occur which could lead to both *E* and *Z* stereoisomers.[247]



Scheme 154. Fluorination of alkenyl trifluoroborates with Selectfluor®.

1.4. CONJUNCTIVE FUNCTIONALIZATION OF ALKENYL BORON 'ATE' COMPLEXES WITH ELECTROPHILES

The group of Aggarwal reported a three-component conjunctive functionalization of alkenyl boronic esters (Scheme 155).[248] In this case an organolithium reagent attacks the boron atom, to form a boron 'ate' complex. Then, an electrophile activates the double bond triggering a 1,2-metallate rearrangement (similar to Zweifel olefination, see section 1.2.5.3, chapter I). In contrast with the halogenation of vinylboronic esters, in this example a nucleophile and an electrophile are incorporated to the molecules and the boronic ester functionality is maintained. A variety of organolithium reagents were tested using PhSeCl as the electrophile. The products were obtained in good yields and excellent *anti* diastereoselectivity with *E*-alkenyl boronates, and *syn* diastereoselectivity with

[244] For a review of fluorination of organoboron compounds see: Pattison, G. *Org. Biomol. Chem*. **2019**, *17*, 5651-5660.

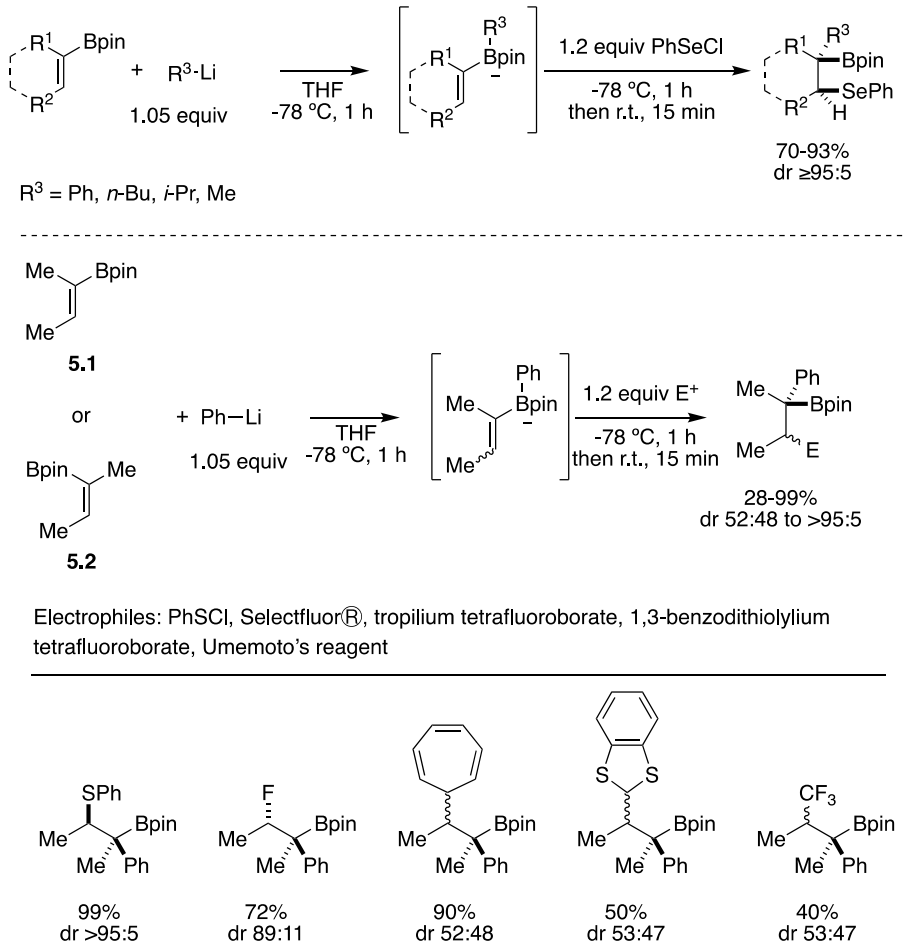
[245] Selectfluor®, a trademark of Air Products and Chemicals, Inc., or 1-Chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate) is a widely use reagent for electrophilic fluorination, which was discovered in 1992: Banks, R. E.; Mohialdin-Khaffaf, S. N.; Lal, G. S.; Sharif, I.; Syvret, R. G. *J. Chem. Soc., Chem. Commun*. **1992**, 595-596.

[246] Petasis, N.; Yudin, A.; Zavialov, I.; Prakash, G.; Olah, G. *Synlett* **1997**, *1997*, 606-608.

[247] Liu, G. Fluorination of Alkenes and Alkynes for Preparing Alkyl Fluorides. In *Fluorination*; Hu, J. Umemoto, T. Eds.; Springer Nature Singapore Pte Ltd., 2018, pp. 1-35.

[248] Armstrong, R. J.; Sandford, C.; García-Ruiz, C.; Aggarwal, V. K. *Chemm. Commun*. **2017**, *53*, 4922-4925.

Z-alkenyl boronates. The scope of electrophiles was investigated with alkenyl boronates **5.1** and **5.2** and PhLi and they observed that high levels of diastereoselectivity were only achieved when electrophiles that form three-membered ring intermediates (PhSeCl or PhSCl). With carbon electrophiles, nearly equimolar mixtures of diastereoisomers were obtained (Scheme 155). Inversion of the diastereoselectivity was achieved with selecfluor®, produced by *syn* migration.



Scheme 155. Three-component conjunctive functionalization of alkenyl boronic esters.

In the case of β,β-disubstituted alkenyl boronic esters, mixtures of products **5.3** and **5.4** were obtained. Authors proposed that, with these substrates, the C_β-Se bond lengthens due to the ability of the tertiary β-carbon to build up a partial positive charge, thus, favoring the elimination of PhBpin. Using a mixture of THF and DMF they could improve the selectivity of the reaction towards the 1,2-metallate rearrangement pathway.

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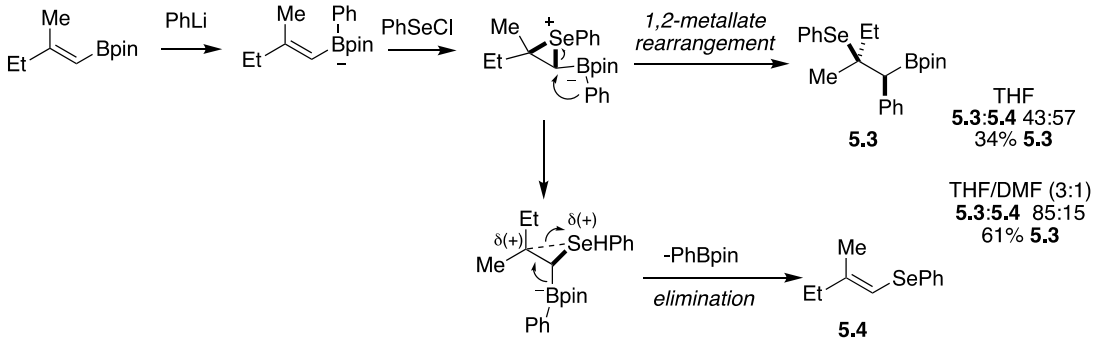

Scheme 156. Mechanistic proposal for the formation of **5.3** and **5.4**.

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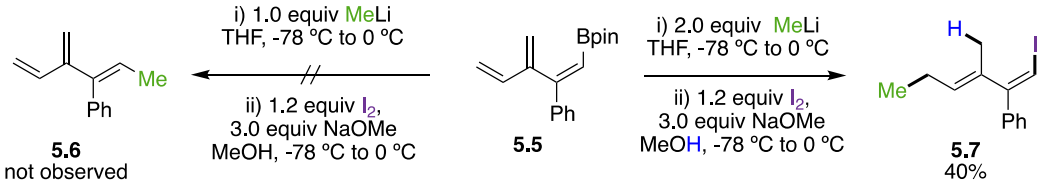
2. OBJECTIVE

Within the study on the functionalization of borylated dendralenes (chapter III), we attempted to transform compound **5.5** into methyl-substituted dendralene **5.6** through a Zweifel olefination. This transformation should involve boron 'ate' complex formation, 1,2-metallate rearrangement and deiodoborylation.[249] Surprisingly, when **5.5** was sequentially treated with 1 equivalent of MeLi and iodine, no tractable amount of Zweifel coupling product **5.6** was detected. By using 2 equivalents of MeLi, the only reaction product was the unexpected 1,2,3,4-tetrasubstituted *E,E*-diene **5.7** where three new C-C, C-H and C-I bonds were formed (Scheme 157).



Scheme 157. Preliminary results.

Considering the high relevance of tetrasubstituted 1,3-dienes and the scarcity of methods to access multisubstituted conjugated dienes, we decided to study this tetracomponent reaction with the aim to develop a stereoselective transformation that enables the synthesis of multifunctional tetrasubstituted 1,3-dienes in a single one-pot operation.

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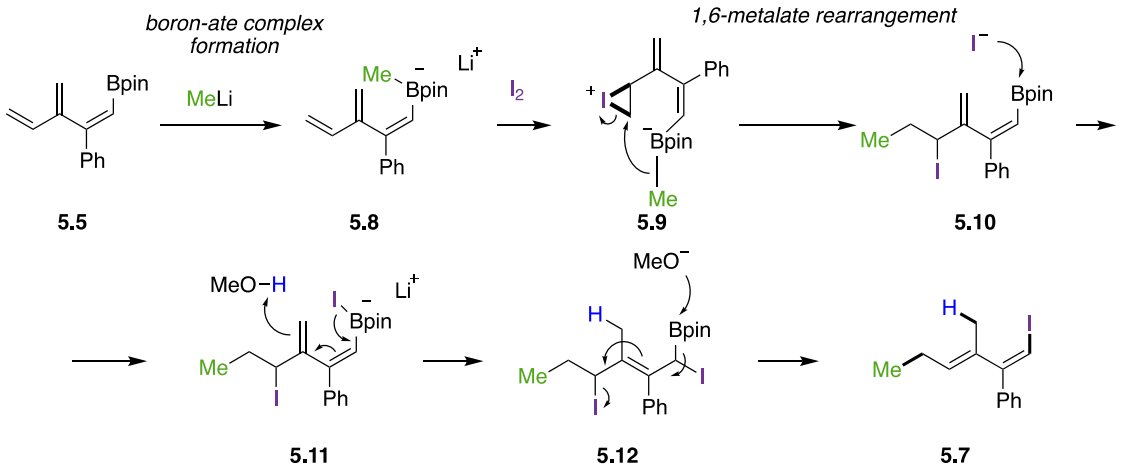
[249] See section 1.2.5.3, chapter I, and ref. 79.

3. RESULTS AND DISCUSSION

3.1. MECHANISM INVESTIGATION AND REACTION OPTIMIZATION

In order to optimize and extend the scope of this reaction, we first decided to get insight on the mechanism of this new transformation. Initially, two possible mechanistic scenarios for the formation of the product **5.7** were considered. One mechanistic pathway would consist in the initial formation of the boron 'ate' complex with MeLi and activation of the more accessible terminal double bond with iodine to give the intermediate **5.9** (Scheme 158). Then, the methyl group would suffer an intramolecular 1,6-metallate rearrangement to afford intermediate **5.10**. The generated iodine anion would attack the boron center to obtain **5.11**, followed by 1,2-iodine migration and electrophilic trapping with MeOH to generate intermediate **5.12**. This intermediate would give rise to product **5.7** after a base promoted elimination.



Scheme 158. Possible mechanistic pathway via 1,6-metallate rearrangement.

An alternative mechanistic pathway is shown in Scheme 159. This one would consist in the formation of the boron 'ate' complex and subsequent intermolecular carbolithiation of the terminal olefin of the dendralene to generate allyllithium **5.13**. Subsequent electrophilic trapping with methanol of the allyllithium formed would provide boron 'ate' **5.14**. Iodination of the double bond next to the boron followed by iododeboronation would lead to product **5.7**.

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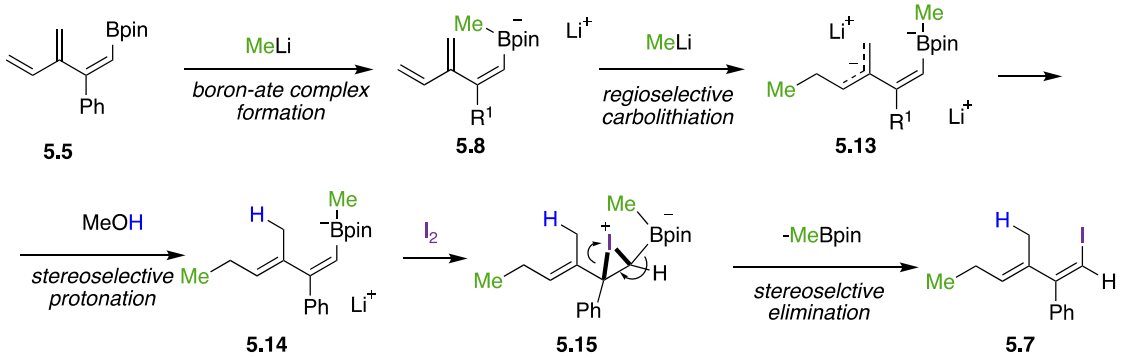

Scheme 159. Possible mechanistic pathway via intermolecular carbolithiation.

To elucidate the mechanism of this novel transformation, we analyzed the nature of the reaction intermediates by ^{11}B and ^{1}H NMR spectroscopy (Figures 25 and 26).

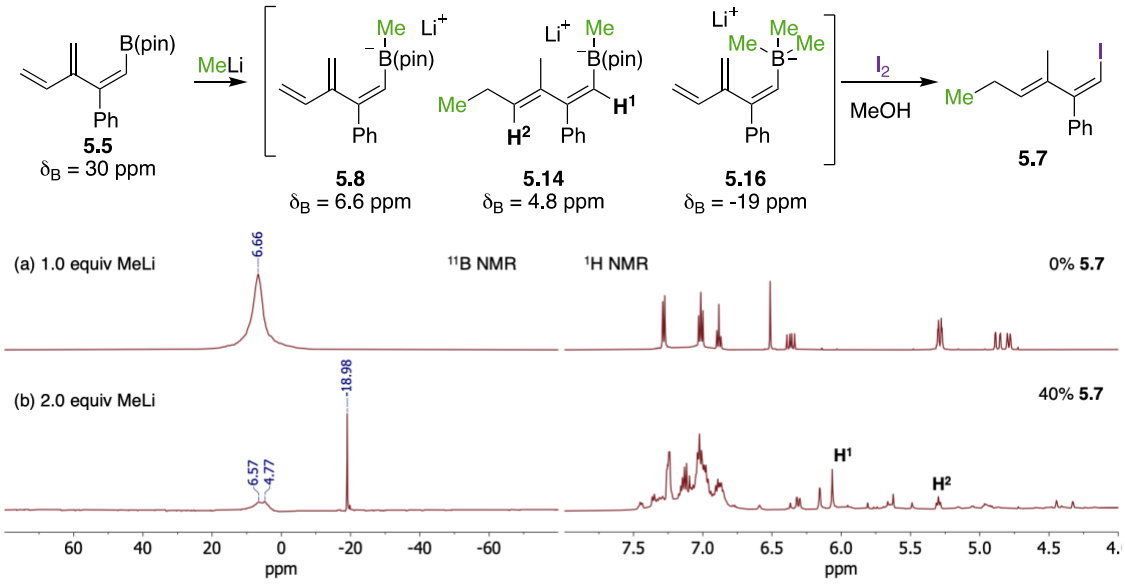

Figure 25. ^{1}H and ^{11}B NMR studies of the intermediates of addition of MeLi to **5.5**.

Upon addition of 1 equivalent of MeLi to **5.5** we observed quantitative formation of boronate complex **5.8**. This fact is corroborated by the signal at 6.6 ppm in the ^{11}B NMR (Figure 25a; also complete disappearance of the signal at 30 ppm corresponding to **5.5** was observed) and the signals of the ^{1}H NMR match with a dendralene moiety. As expected from our preliminary result (Scheme 157), treatment of this intermediate with iodine did not afford the 1,2-metallate rearrangement product **5.6** nor 1-iodo-1,3-diene **5.7**. Addition of 2 equivalents of MeLi to **5.5** led to formation of two different boron 'ate' complexes (6.6 and 4.8 ppm) along with a new boron species featuring a sharp singlet at -19.0 ppm, which is consistent with a trimethyl boron 'ate' complex **5.16**[250] (Figure 25b). Addition of a solution of iodine in methanol to this mixture provided iododiene **5.7** in 40% yield. Interestingly, ^{1}H NMR analysis of the mixture generated by addition of 2 equiv of MeLi revealed the presence of **5.14** as the major component of this mixture,

[250] Armstrong, R. J.; Niwetmarin, W.; Aggarwal, V. K. *Org. Lett.* **2017**, *19*, 2762-2765.

somewhat discarding a 1,6-metallate rearrangement pathway. Formation of **5.14** might arise from nucleophilic attack at the vinyl group of boron 'ate' complex **5.8** and subsequent stereoselective protonation of the resulting allyllithium intermediate. Considering that the presence of multiple boron species was probably not the best situation to achieve an efficient transformation, we decided to use PhLi instead of MeLi. Addition of 1 equivalent of PhLi to **5.5** quantitatively provided dendralenic boron 'ate' complex **5.17** (Figure 26a). Gratifyingly, addition of a second equivalent of PhLi followed by protonation cleanly generated a single boron 'ate' complex (**5.18**, 7.2 ppm, Figure 26b), which afforded tetrasubstituted diene **5.19** in 65% yield upon treatment with of a solution of iodine (1.2 equiv) in methanol (Figure 26c). We could also observe the formation of PhBpin as a byproduct, which could be isolated in 57% yield.

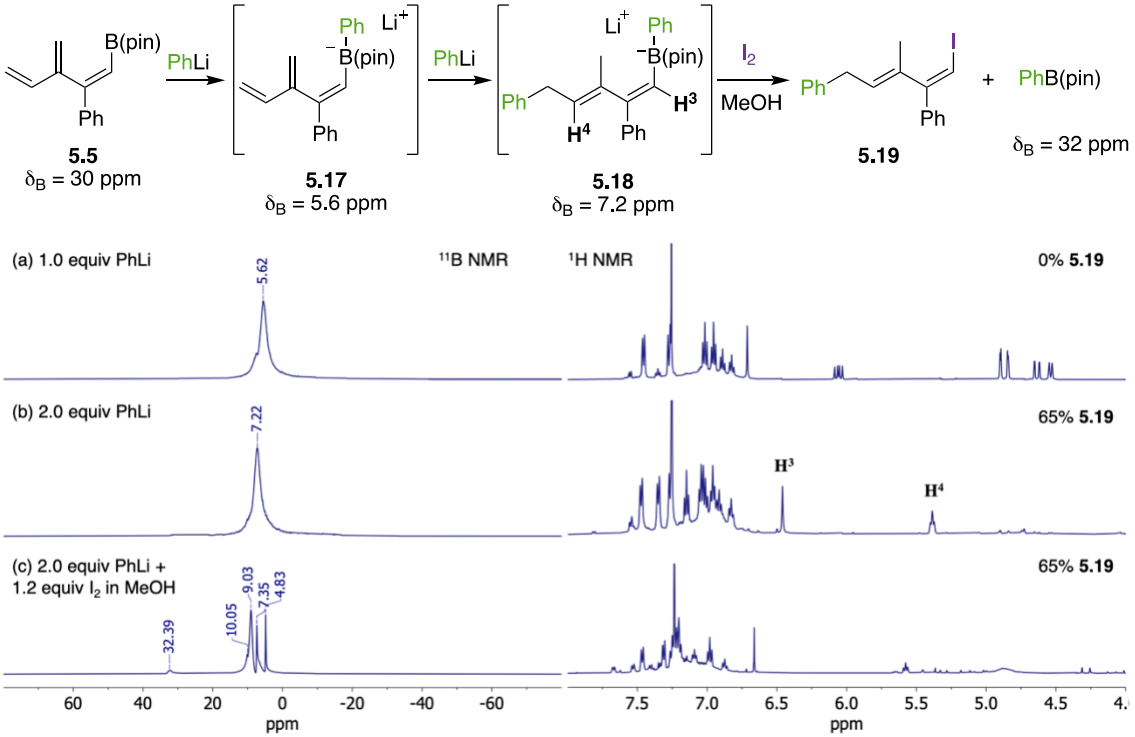

Figure 26. ^{1}H and ^{11}B NMR studies of the intermediates of addition of PhLi to **5.5**

To further prove a direct carbolithiation mechanism, boron 'ate' complex **5.17** was sequentially treated with 1 equivalent of MeLi and iodine/methanol and the reaction exclusively afforded diene **5.7** in an improved 54% yield (vs 40% yield with 2 equivalents of MeLi). Similarly, addition of PhLi to boron 'ate' complex **5.8** followed by treatment with iodine and methanol led to the selective formation of diene **5.19** (Scheme 160).

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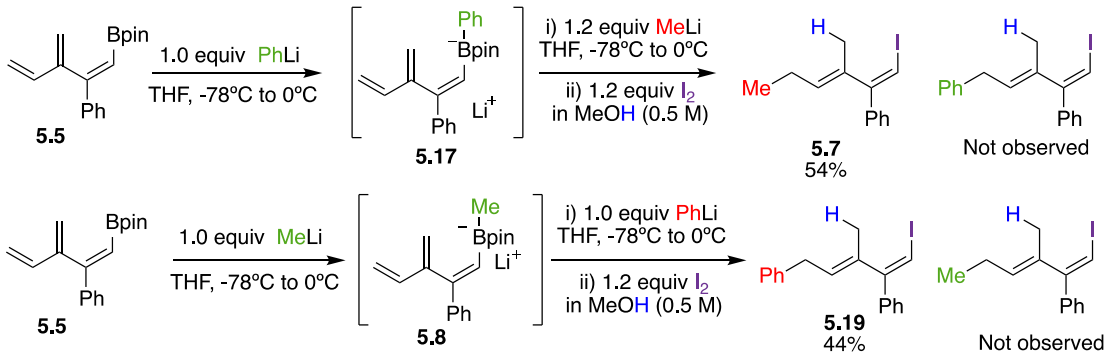


Scheme 160. Experiments supporting a carbolithiation pathway.

As mentioned in the introduction of this chapter, few examples of carbolithiation of dendralenes have been described. Interestingly, in our system, carbolithiation occurs via a regioselective addition of the organolithium reagent to the terminal vinyl moiety of the borylated dendralene which generates an allyllithium intermediate. This is in sharp contrast with previous examples where dendralene carbolithiation generates a stabilized pentadienyllithium intermediate. We hypothesized that the presence of the polarized C-B bond in our system might hamper both the formation of the pentadienyllithium intermediate and the carbolithiation at the alkenyl boronate moiety, thus providing a favored scenario for nucleophilic addition at the vinylic terminus. Another important feature of the carbolithiation step is the high level of regio- and stereoselectivity achieved after the electrophilic trapping. Given that allyllitium species tend to rapidly equilibrate, this high selectivity might likely arise from the formation of the thermodynamically most stable *E*-isomer after electrophilic attack at the less hindered allylic terminus.[251]

As mentioned above, during the mechanistic studies we also observed the formation, by ^{1}H NMR and GC-MS analysis, of PhBpin together with phenyl boron 'ate' complexes, which might be originated from reaction between *in situ* generated LiOMe and the phenyl boronic ester, after iodine addition (Figure 26c). This suggests that C-B to C-I transformation would occur through a two-step iodonium formation/elimination sequence. Overall, on the basis of these experiments, we concluded that this transformation might follow the mechanism proposed in Scheme 159.

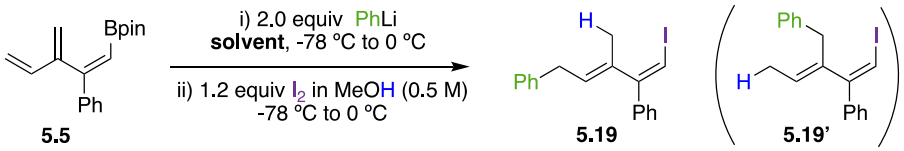
3.2. EVALUATION OF SOLVENT

We tested different solvents for this reaction (Table 15). Less polar ethereal solvents, such as Et_2O, 1,4-dioxane and CPME provided a substantial decreased of the reaction effciency, leading to 1,3-diene **5.19** in 38%, 20% and 36% yield respectively (Table 15, entries 2-3 and 5). The use of a more environmentally responsible solvent such as

[251] (a) Fraenkel, G.; Halasa, A. F.; Mochel, V.; Stumpe, R.; Tate, D. *J. Org. Chem*. **1985**, *50*, 4563-4565. (b) Winchester, W. W.; Bauer, W.; Schleyer, P. v. R. *J. Chem. Soc., Chem. Commun.* **1987**, 177-179. (c) Fraenkel, G.; Gallucci, J.; Liu, H. *J. Am. Chem. Soc.* **2006**, *128*, 8211-8216.

2-Me-THF led to similar yield of **5.19** than with THF. However, a slight decrease on the regioselectivity towards the carbolithiation step was observed (93:7).

Table 15. Evaluation of solvents in the addition of PhLi to **5.5**.



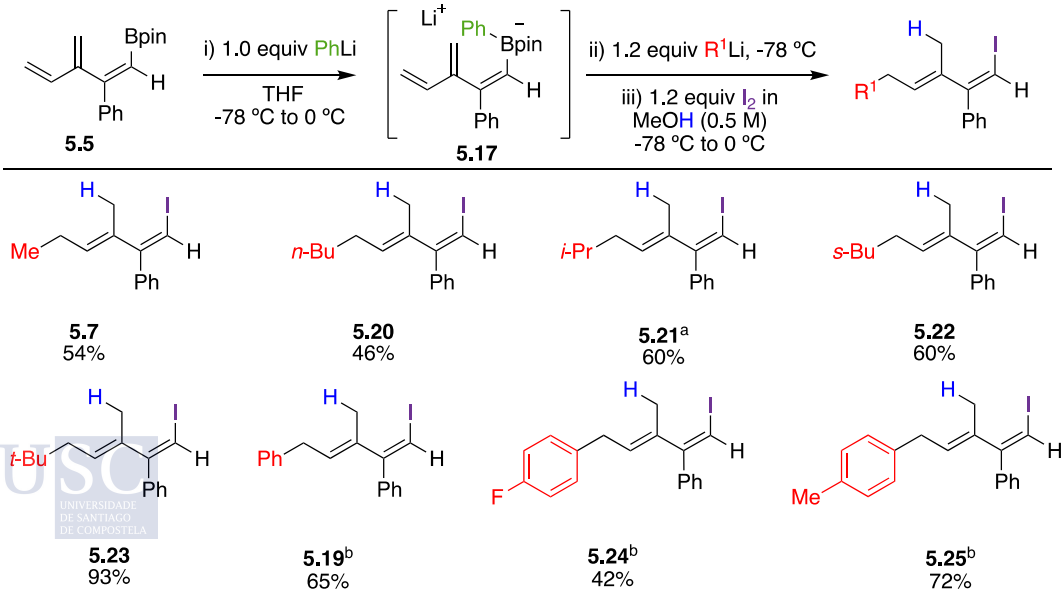
Entry	solvent	Yield **5.19** (%)[a]
1	THF	68
2	Et_2O	38
3	1,4-Dioxane	20
4	2-MeTHF	69[b]
5	CPME	36

[a] NMR yield. 1,3,5-Trimethoxybenzene was used as internal standard. [b] The product was obtained as a 93:7 mixture of regioisomers **5.19**:**5.19'**.

3.3. SCOPE OF THE REACTION

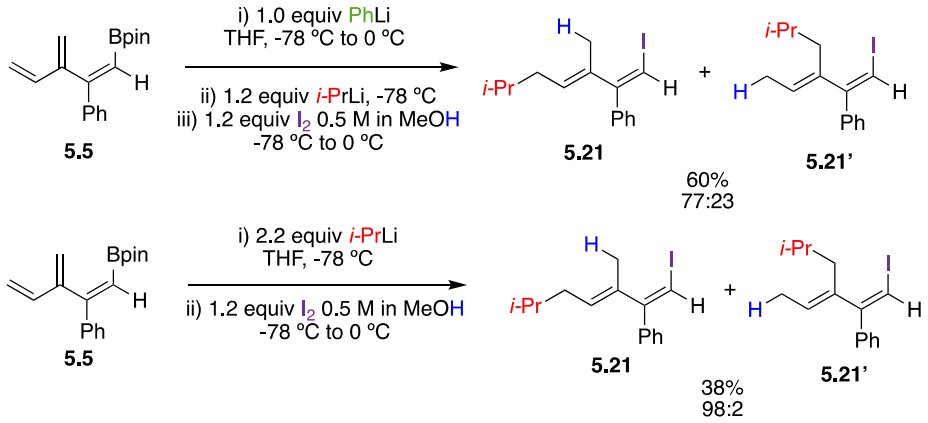
Having disclosed the mechanistic intricacies of this tetracomponent reaction, we set out to explore the scope of this transformation (Table 16-19).

Table 16. Scope of organolithium reagents.



Reactions conditions: dendralene **5.5** (1.0 equiv, 0.2 mmol) in 1.0 ml of dry THF, PhLi (1.0 equiv), -78 ºC to 0 ºC and stirred for 5 min; then, R^1Li (1.2 equiv), -78 ºC, then, I_2 (1.2 equiv) 0.5 M in MeOH, -78 ºC to 0 ºC and stirred for 30 min. [a] Obtained as a mixture of regioisomers of carbolithiation step (see Scheme 161). [b] PhLi (or ArLi, 2.2 equiv), -78 ºC to 0 ºC, then I_2 0.5 M in MeOH.

We first investigated the behavior of different organolithium compounds (Table 16). Primary, secondary, and tertiary alkyllithium reagents all proved to be efficient for this transformation. With those nucleophiles, carbolithiation took place at -78 ºC and subsequent quenching with MeOH and iodine provided the corresponding tetra-substituted dienes **5.7**, **5.20-5.23** in good yield with complete levels of regio- and stereoselectivity in nearly all cases. Only when *i*-PrLi was used, a 77:23 mixture of isomers **5.21** and **5.21'** was obtained in a 60% combined yield (Scheme 161). The addition of 2.2 equiv *i*-PrLi to **5.5** led to a better 98:2 ratio between **5.21**:**5:21'**, however the yield dropped to 38%.



Scheme 161. Mixture of isomers obtained with i-PrLi.

Interestingly, aryllitihium reagents which failed to provide carbometalation with other dendralenes,[239b] worked well in this transformation albeit warming to 0 ºC was necessary to achieve full carbolithiation. Under these conditions, dienes **5.19**, **5.24** and **5.25** were obtained in good yield and with excellent selectivity.

The nucleophilicity of the allyllithium intermediate also enabled efficient trapping of different carbon electrophiles thus providing a handle for the elongation of the 3-substituent of the dienic core through a second C-C bond formation. Use of iodomethane, benzyl bromide, 1- bromobutane or benzaldehyde, instead of MeOH, resulted in efficient two C-C, one C-I forming processes (Table 17, **5.26-5.33**).

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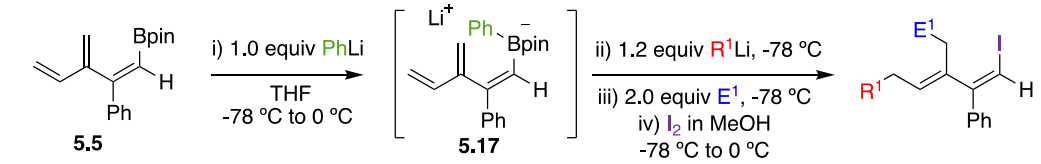
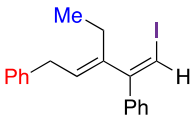
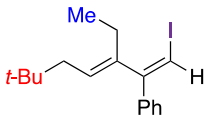
Table 17. Scope of first electrophile.

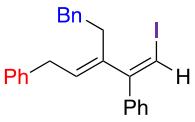




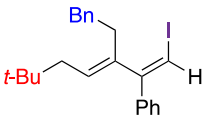
5.26[a,b]
63%
(E^1 = MeI)



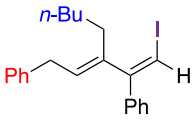
5.27[b]
70%
(E^1 = MeI)



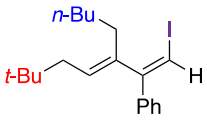
5.28[a,c,d]
48%
(E^1 = BnBr)



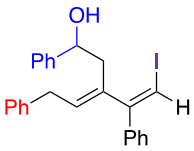
5.29[c]
57%
(E^1 = BnBr)



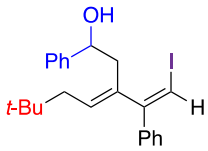
5.30[a,e]
46%
(E^1 = n-BuBr)



5.31[e]
51%
(E^1 = n-BuBr)



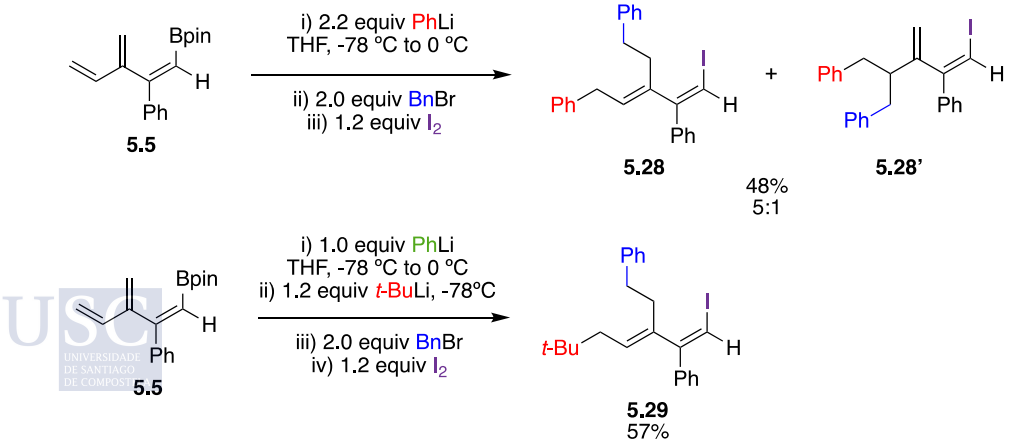
5.32[a,f]
38%
(E^1 = PhCHO)



5.33[f]
46%
(E^1 = PhCHO)

Reactions conditions: dendralene **5.5** (1.0 equiv, 0.2 mmol) in 1.0 ml of dry THF, PhLi (1.0 equiv), -78 ºC to 0 ºC and stirred for 5 min; then, R^1Li (1.2 equiv), -78 ºC, then, E^1 (2.0 or 4.0 equiv) at -78 ºC and I_2 (1.2 equiv), -78 ºC to 0 ºC and stirred for 30 min. [a] PhLi (or ArLi, 2.2 equiv), -78 ºC to 0 ºC, then E^1 and I_2; [b] MeI (E^1, 2 equiv), -78 ºC to 0 ºC; then, I_2 (1.2 equiv); [c] BnBr (E^1, 2 equiv), 0 ºC; then, I_2 (1.2 equiv); [d] Obtained as a mixture of regioisomers of the electrophilic trapping; [e] *n*-BuBr (E^1, 2 equiv), -78 ºC to 0 ºC; then, I_2 (1.2 equiv); [f] PhCHO (E^1, 2 equiv), -78 ºC to 0 ºC; then, I_2 (1.2 equiv) 0.5 M in MeOH.

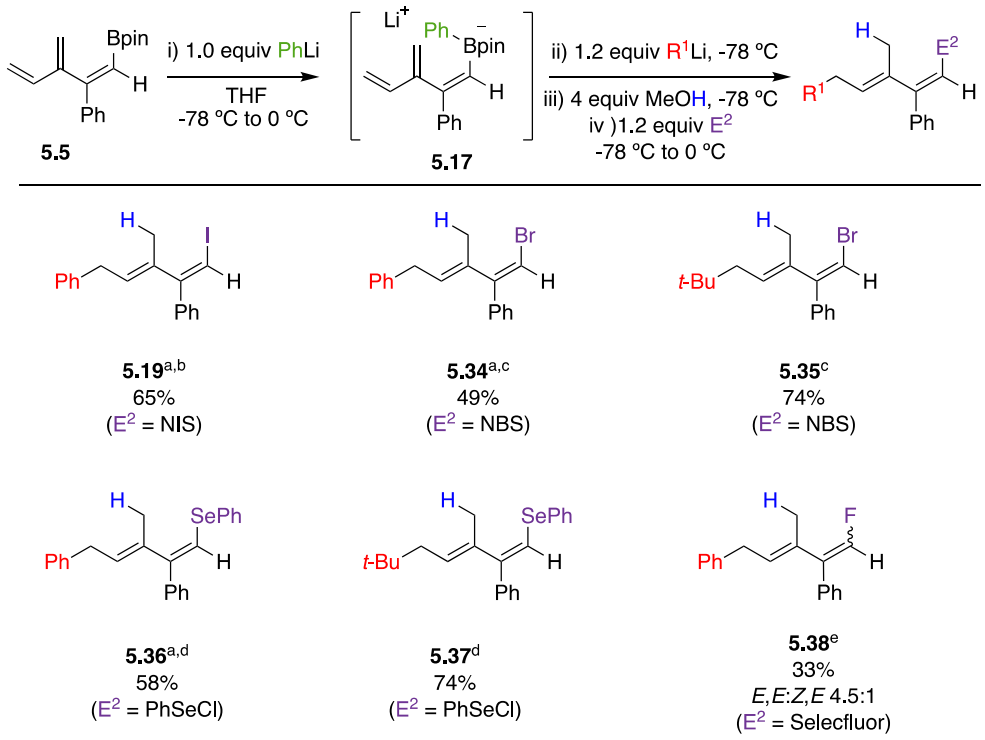
When the allyllithium intermediate generated after addition of 2 equiv of PhLi is trapped with benzylbromide, a 5:1 mixture of isomers **5.28** and **5.28'** are obtained (Scheme 162). However, when the carbolithiation is performed with *t*-BuLi, the electrophilic trapping with BnBr gives rise only to product **5.29**.



Scheme 162. Mixture of isomers obtained with BnBr.

The intermediate dienyl boron 'ate' complex generated after the carbolithiation/electrophilic trapping step could also be exploited in other electrophilic couplings to incorporate different functionalization on the diene structure. For this purpose, a series of electrophiles rather than iodine were investigated in reactions involving carbolithiation with PhLi or *t*-BuLi (Table 18). We found that the use of NIS is equally effective than iodine to afford iododiene **5.19**. With NBS and PhSeCl the reactions also proceeded with total regio- and stereoselectivity, producing 1-bromo-1,3- dienes **5.34** and **5.35** and 1,3- dienyl selenides **5.36** and **5.27**, respectively, as single *E*,*E* isomers in very good yields. Interestingly, in sharp contrast with the conjunctive functionalization of β,β-disubstituted vinyl boronate complexes with PhSeCl reported by Aggarwal,[248] no formation of 1,2-migration products was observed in these cases.

Table 18. Scope of second electrophile.



Reactions conditions: dendralene **5.5** (1.0 equiv, 0.2 mmol) in 1.0 ml of dry THF, PhLi (1.0 equiv), -78 ºC to 0 ºC and stirred for 5 min; then, R^1Li (1.2 equiv), -78 ºC, then, E^2 (1.2 equiv) 0.5 M MeOH, -78 to 0 ºC and stirred for 30 min. [a] PhLi (or ArLi, 2.2 equiv), -78 ºC to 0 ºC, then E^2 0.5 M MeOH; [b] MeOH (4 equiv), then NIS (E^2, 1.2 equiv) instead of I_2/MeOH; [c] MeOH (4 equiv), then NBS (E^2, 1.2 equiv) instead of I_2/MeOH; [d] MeOH (4 equiv), then PhSeCl (E^2, 1.2 equiv, 0.5 M in THF) instead of I_2/MeOH; [e] MeOH (4 equiv), -78 ºC to rt; solvent evaporation, then, MeCN (1.0 ml), Selectfluor® (E^2, 1.5 equiv), rt.

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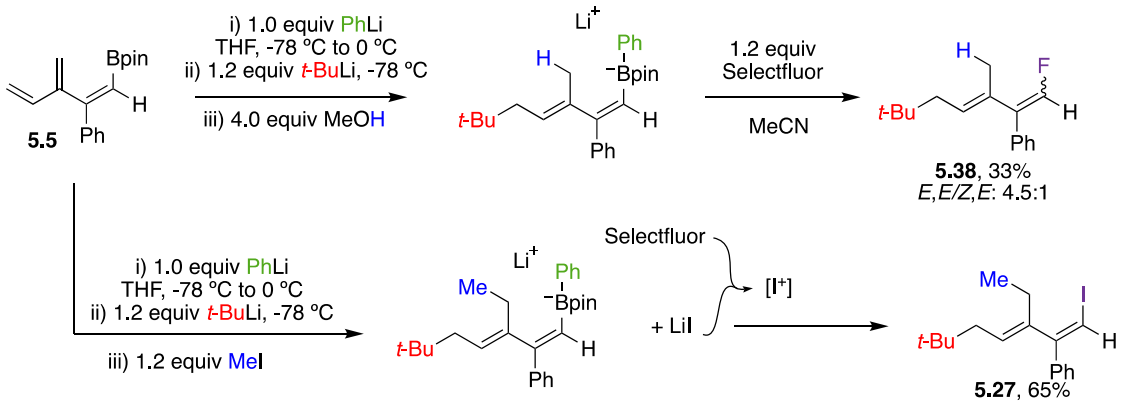
We next investigated a transformation involving a carbolithiation/protonation/fluorination process. Subsequent treatment of borylated dendralene **5.5** with PhLi, *t*-BuLi, MeOH and Selectfluor®, afforded 1-fluoro-1,3-diene **5.38** in moderate yield with excellent regioselectivity although with slightly diminished stereoselectivity (*E*,*E*:*E*,*Z* = 4.5:1). These results suggest that the formation of a closed three-membered intermediate prior to the elimination step is important to achieve

stereochemical retention. Interestingly, when a carbolithiation/alkylation/fluorination process was attempted by using MeI instead of MeOH, 1-iodo-1,3-diene **5.27** was exclusively obtained (Scheme 163). In this case, formation of **5.27** may be explained by the presence of LiI which is generated in the first electrophilic trapping and may be oxidized by Selectfluor® to the iodine cation,[252] which might promote the electrophilic iodination of the dienylboron 'ate' intermediate.



Scheme 163. Effect of first electrophile in the reaction with Selectfluor®.

Finally, we explored the outcome of different borylated dendralenes in the carbolithiation/protonation/iodination reaction (Table 19). Both electron-withdrawing (**5.39**) and electron-donating groups (**5.40**) were tolerated at the aromatic substituent in the 2 position, although reaction turned out to be more efficient with the latter. Gratifyingly, substrates bearing heteroaromatic and aliphatic substituents also worked well and afforded the corresponding tetrasubstituted dienes **5.41** and **5.42** in good yield with excellent regio- and stereoselectivity. Noteworthy, reaction with a borylated [4]dendralane, which adds an extra point of regioselectivity in the carbolithiation step, afforded iododendralene **5.43** as a single product in 82% yield. Surprisingly, when a borylated dendralene bearing a TMS group in the 2 position was used in combination with PhLi and *t*-BuLi, products **5.44** and **5.45** arising from a Zweifel-type 1,2-metallate rearrangement-elimination sequence were obtained instead of the expected 1-iodo-1,3-dienes. Products **5.44** and **5.45** were obtained as *E*,*E*:*Z*,*E* mixtures although they isomerized to a single *E*,*E* isomer. A similar behavior was observed for a borylated dendralene bearing substituents both at 1 and 2 positions (formation of **5.46**). Formation of isomeric *E*,*E*:*Z*,*E* mixtures in products **5.44-5.46** is likely due to *syn*- and *anti*-elimination pathways which would operate concomitantly.

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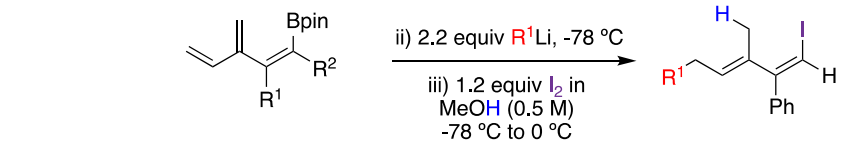
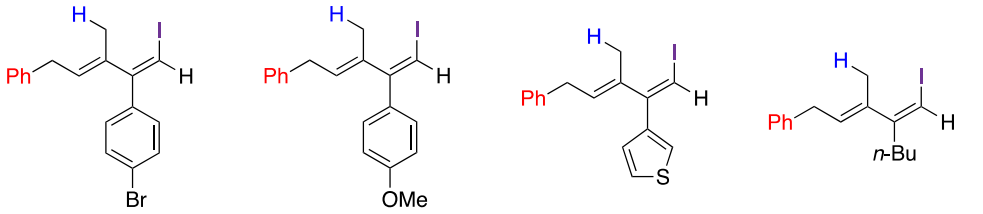
[252] Nyffeler, P. T.; Gonzalez Durón, S.; Burkart, M. D.; Vincent, S. P.; Wong, C.-H. *Angew. Chem. Int. Ed.* **2005**, *44*, 192-212.

Table 19. Scope of dendralenes.



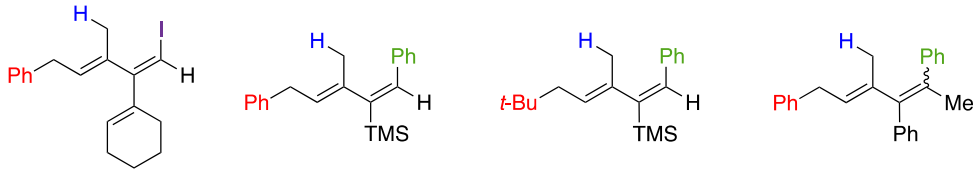


5.39 34%

5.40 74%

5.41 72%

5.42 54%



5.43 82%

5.44 53%

5.45[a] 64%

5.46 32%
E,*E*:*Z*,*E* 1.5:1

Reactions conditions: dendralene (1.0 equiv, 0.2 mmol) in 1.0 ml of dry THF, PhLi (2.2 equiv), -78 ºC to 0 ºC and stirred for 5 min; then, I_2 (1.2 equiv) 0.5 M in MeOH, -78 ºC to 0 ºC and stirred for 30 min. [a] PhLi (1.0 equiv), -78 ºC to 0 ºC and stirred for 5 min; then, *t*-BuLi (1.2 equiv), -78 ºC to 0 ºC, then, I_2 (1.2 equiv) 0.5 M in MeOH), at 0 ºC and stirred for 30 min.

A plausible mechanistic rationale accounting for this divergency observed for products **5.44**-**5.46** is outlined in Scheme 164. After the carbolithiation/protonation step, treatment of the resulting diene boron 'ate' complex with iodine would form a zwitterionic iodonium intermediate. This species can either eliminate to afford the iododiene along with PhBpin or undergo a 1,2-rearrangement of the phenyl group. The commonly observed elimination may arise from a partial positive charge stabilization at the β carbon, likely due to the β,β-disubstitution, which would allow lengthening of the C(β)-I bond thus favoring this pathway (Scheme 164a; see section 1.4, chapter V). However, the presence of a TMS group in the β position may rather stabilize positive charge at the α carbon,[253] facilitating the 1,2-migration of the phenyl group (Scheme 164b). Similarly, the presence of an extra substituent at the α position would also provide a good scenario to build up partial positive charge at that carbon.

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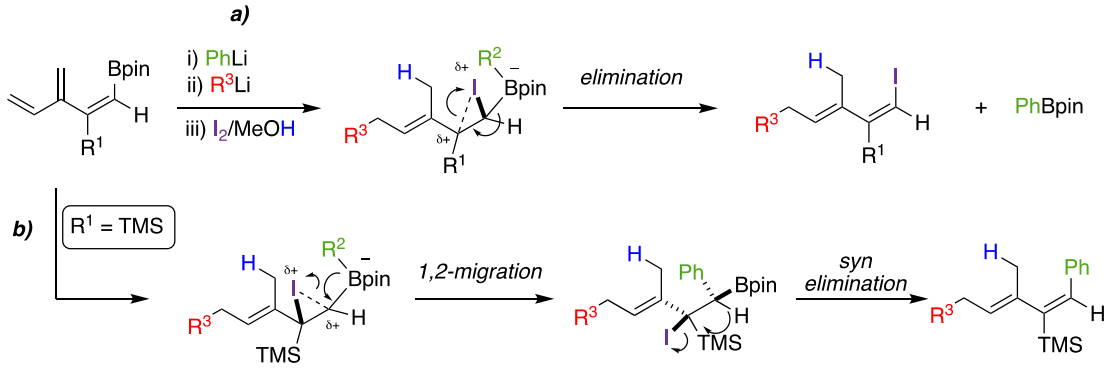
[253] Lambert, J. B.; Wang, G.; Finzel, R. B.; Teramura, D. H. *J. Am. Chem. Soc.* **1987**, *109*, 7838-7845.



Scheme 164. Mechanistic rationale for the divergent elimination pathways.

3.4. SYNTHETIC APPLICATIONS

An attractive feature of this new tetracomponent reaction is the functional group diversity that can be installed in the diene core which allows to access more complex dienic structures (Scheme 165). Formation of PhBpin as side product could be exploited to perform an *in situ* Suzuki-Miyaura coupling with the 1-iodo-1,3-diene product just by adding a Pd catalyst and aq. K_2CO_3 to the reaction mixture. The synthesis of diene **5.47** showcases a route to incorporate the aryl group from the organolithium used to generate the initial dendralenic boronate complex into the final product. The obtained 1-iodo-1,3-dienes also served as good precursors to prepare stereodefined polyconjugated systems as illustrated with the synthesis of dienyne **5.48** by Sonogashira coupling. Moreover, the versatile reactivity of the C-I bond can also be used to perform lithium/halogen exchange to generate a dienyllithium reagent which can react with a carbon electrophile (e.g. MeI) to establish a new $C(sp^2)$-$C(sp^3)$ bond as shown for the synthesis of **5.49**.

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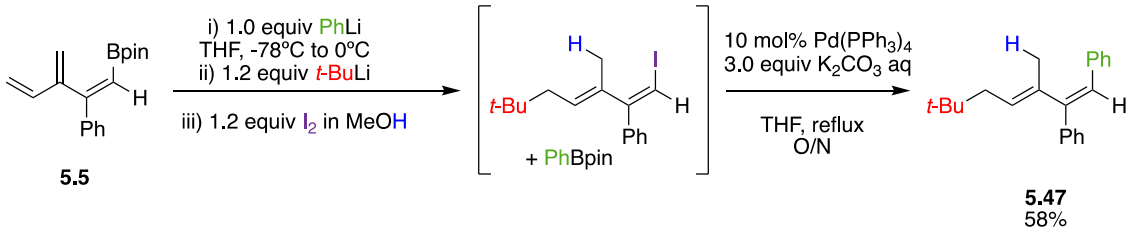
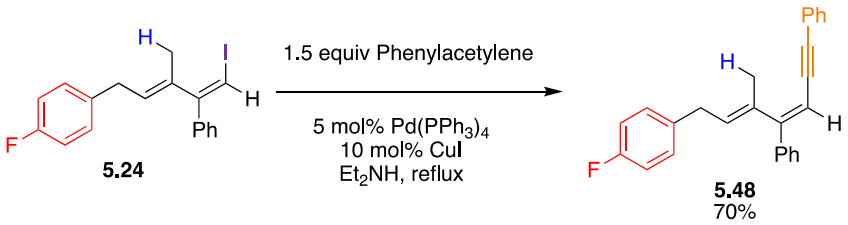
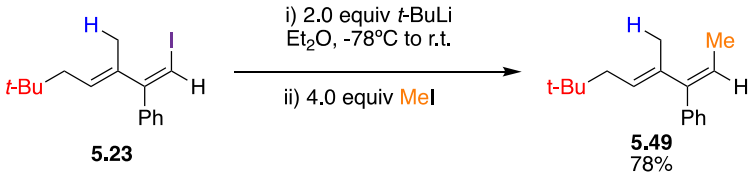
a) *In situ Suzuki-Miyaura coupling*



b) *Synthesis of 1,3,5-dienyne by Sonogashira coupling*



c) *C(sp^2)-C(sp^2) coupling via lithium-iodide exchange/electrophilic trapping*



Scheme 165. Synthetic transformations of products.

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4. CONCLUSIONS

We have developed an efficient tetracomponent reaction that allows the synthesis of 1,2,3,4-substituted 1-iodo-1,3-dienes, otherwise difficult to obtain. Three new bonds, up to two C-C and a C-X bonds are formed in a single one-pot protocol, with total regio- and stereoselectivity in almost all cases.

A mechanism which entails the *in situ* formation of a dendralenic boronate complex, its regioselective carbolithiation and two subsequent stereoselective electrophilic trappings has been proposed based on NMR studies and experimental tests. The presence of the Bpin moiety in the dendralenic moiety is crucial for the regiochemical outcome and provides the formation of an allyllithium intermediate which has not been observed for other dendralenes.

The synthetic versatility of 1-iodo-1,3-dienes obtained through this methodology has been demonstrated by the formation of new $C(sp)^2$-C(sp), $C(sp)^2$-$C(sp)^2$ and $C(sp)^2$-$C(sp)^3$ bonds, respectively, by means of a Sonogashira coupling, an *in situ* Suzuki-coupling and lithium/halogen exchange, followed by trapping by and electrophile (e.g. MeI).

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General Conclusions

We have developed efficient methodologies for the synthesis of borylated 1,4-dienes via transition metal-catalyzed allylboration of alkynes. In chapter II we have performed the synthesis of linear borylated 1,4-dienes, through a novel palladium and copper synergistically catalyzed allylboration of alkynes under mild conditions, with high levels of chemo-, stereo- and regioselectivity. We have also demonstrated that the alkenylcopper(I) reagents act as *"hard"* nucleophile, providing the allylic substitution through an inner-sphere transmetalation mechanism, with complete inversion of configuration when a diastereomerically pure allyl substrate is used. We could demonstrate the utility of this methodology by the synthesis of two natural products.

In chapter III we were able to synthesize borylated branched 1,4-dienes through a copper-catalyzed allylboration of alkynes with *trans*-1,4-dibromo-2-butene under mild conditions. The multitasking copper catalyst showed high levels chemo-, stereo- and regioselectivity. Moreover, borylated dendralenes, which are a new type of organoboron compounds, could be easily synthesized from the multifunctional 1,4-dienes through a simple base promoted dehydrohalogenation.

In chapter IV the enantioselective version of the copper-catalyzed allylboration of alkynes described in chapter III was achieved. This reaction represent the first example of asymmetric allylboration of alkynes. The use of a sulfonate bearing chiral NHC-copper catalyst enables the efficient synthesis of branched borylated 1,4-dienes with high levels of chemo-, stereo-, regio- and enantioselectivity under mild conditions. Furthermore, this methodology provides excellent results with a wide variety of substrates. This method gives access to the synthesis of densely functionalized molecules from simple starting materials. The high degree of functionalization provides to these compounds a highly versatile reactivity.

Finally, in chapter V, we have developed an efficient tetra-component reaction that allows the synthesis of 1,2,3,4-substituted 1-iodo-1,3-dienes from the borylated dendralenes described in chapter III. Three new bonds, up to two C-C and a C-X bonds are formed in a single one-pot protocol, with total regio- and stereoselectivity in almost all cases, by combining borylated dendralenes, organolithium reagents and two different

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electrophiles. The mechanism of this transformation was elucidated by NMR studies, which led to the suggestion of a direct carbolithiation mechanism.

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Resumo

Nesta tese doutoral móstrase a investigación levada a cabo para a síntese de 1,4-dienil boronatos a través de procesos con catálise metálica e o estudo da súa reactividade. Estes procesos sintéticos están baseados na reacción dun alquino pro-nucleófilo con complexos de tipo LCu-Bpin.

En concreto, no capítulo I recóllese unha revisión da importancia dos compostos organoboro, dos métodos máis relevantes para sintetizalos e a súa versatilidade sintética. No capítulo II descríbese a síntese de 1,4-dienos lineais borilados a través dunha alilboración de alquinos catalizada por cobre e paladio. No capítulo III descríbese a síntese de 1,4-dienos ramificados e multifuncionalizados, a través dunha alilboración de alquinos catalizada por cobre. Ademais, estes produtos permítennos sintetizar dendralenos borilados, que son un novo tipo de compostos organoboro. No capítulo IV desenvólvese a versión enantionselectiva da alilboración de alquinos presentada no capítulo III cun complexo quiral de cobre. Por último, no capítulo V descríbese unha reacción de multifuncionalización dos dendralenos borilados obtidos no capítulo III para a síntese á carta de 1,3-dienos densamente funcionalizados.

A continuación, faise un breve resumo do contido descrito nos capítulos mencionados anteriormente.

Capítulo I: Introdución

A química dos compostos de organoboro, é dicir, aqueles compostos que conteñen un enlace carbono-boro, volveuse moi popular en diferentes ámbitos da química, como por exemplo, en química de materiais (ex.: introdución de átomos de boro en materiais optoelectrónicos ou luminiscentes); en química biolóxica, (novos medicamentos conteñen boro na súa estrutura); ou en química orgánica sintética. Esta última foi a máis explorada ata o de agora debido a que as propiedades do átomo de boro confiren unha versatilidade sintética moi ampla. Os compostos de organoboro son compostos trigonais nos que o átomo de boro presenta unha hibridación sp^2 e un orbital p baleiro, o que fai estes compostos electro deficientes e ácidos de Lewis e, por tanto, moi reactivos cara o ataque dun nucleófilo. Tras o ataque dun nucleófilo, fórmase un produto nucleofílico de boro tetravalente, que pode reaccionar con compostos electrófilos. A día de hoxe, o estudo da química deses compostos desenvolveuse enormemente e o enlace C-B conseguiuse converter en enlaces C-C, C-O, C-N, C-halóxeno e C-H entre outros.

Debido á utilidade destes compostos, desenvolvéronse numerosas metodoloxías para a súa síntese. En particular, a hidroboración de alquinos con hidroboranos descuberta por Brown resultou ser unha poderosa maneira para sintetizar compostos alquenil-boro. Por mor deste descubrimento, desenvolvéronse metodoloxías co uso dun catalizador metálico, que permiten levar a cabo esta transformación de forma máis eficiente e mediante o uso de reactivos máis suaves que os hidroboranos, como son os boronatos (o máis empregado é o bis(pinacolato)diboro, B_2pin_2).

Neste contexto, o uso de complexos de cobre como catalizadores empregouse abundantemente para a borilación de hidrocarburos insaturados, e en particular, na borilación de alquinos con B_2pin_2. Ademais da hidroboración, na que un enlace C-H e un enlace C-B son formados, tamén se poden levar a cabo reacciones de carboboración de alquinos, nas que se forma un enlace C-C e un enlace C-B, mediante a reacción dun alquino, un diboronato e un electrófilo. Nesta transformación o alquino insírese no enlace M-B, formado co catalizador metálico e o diboronato. Esta inserción dá lugar a un complexo alquenil metal nucleófilo, que pode ser atrapado por diferentes carbonos electrófilos. Isto permite obter alquenos tetrasubstituídos e unha maior versatilidade sintética.

Dentro deste contexto, esta Tese baseouse no desenvolvemento de metodoloxías, selectivas e sostibles, baseadas en reaccións de alilboración de alquinos catalizadas por cobre ou cobre/ paladio para a obtención de dienil-boronatos e ao estudo da reactividade dos mesmos.

Capítulo II: Catálise sinérxica de cobre e paladio para a síntese rexio- e estereoselectiva de 1,4- dienos borilados

No marco actual dunha procura de condicións máis sostibles, a creación de novas tecnoloxías químicas eficientes e respectuosas co medio ambiente é de vital importancia. Neste contexto, o desenvolvemento de metodoloxías sintéticas que permitan a formación de estruturas moleculares complexas con alta eficiencia atómica e con mínima xeración de residuos representa un dos maiores retos da química. De especial importancia son aquelas metodoloxías sintéticas baseadas no emprego de substratos sinxelos abundantes na natureza e/ou de fácil acceso. Neste sentido, o desenvolvemento de sistemas catalíticos capaces de activar este tipo de substratos e combinalos dunha forma selectiva é crucial para a súa transformación en moléculas máis complexas que posúan un alto grao de funcionalización.

A estrutura de 1,4-dieno está presente nun amplo número de produtos naturais con importantes actividades biolóxicas, sendo algúns deles potentes antibióticos, axentes antimicóticos ou citotóxicos. Nestes compostos a unidade de 1,4-dieno e a estereoquímica das dobres enlaces confírenlles propiedades únicas. Por tanto, o desenvolvemento de metodoloxías sintéticas para a preparación estereoselectiva de moléculas con esta estrutura, que poidan ser utilizadas como intermedios clave para a síntese de produtos naturais ou análogos, é un reto de gran relevancia para a comunidade científica. Unha das estratexias sintéticas máis directas para a preparación de 1,4-dienos é a substitución alílica cun reactivo vinílico. Tradicionalmente, estes procesos leváronse a cabo a través de metodoloxías sintéticas que requiren o emprego estequiométrico de reactivos organometálicos, o cal limita estas transformacións á dispoñibilidade, estabilidade e reactividade de devanditos compostos. Ademais, o uso destes reactivos dá lugar á formación como subprodutos de reacción de compostos inorgánicos potencialmente tóxicos. Por tanto, a procura de metodoloxías para a síntese destes compostos dunha maneira catalítica, con control na estereoquímica dos dous dobres enlaces e con substratos sinxelos e fáciles de obter é de gran interese.

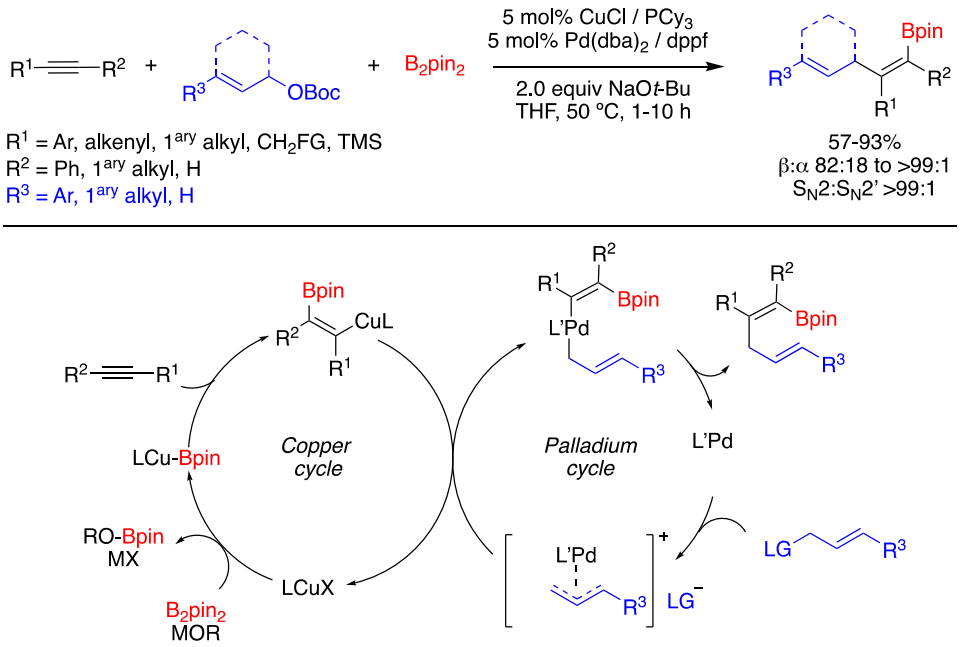
O uso de alquinos, que son substratos sinxelos e fáciles de obter, como pro-nucleófilos, para formar de maneira catalítica un reactivo alquenil metal que evite a necesidade de usar cantidades estequiométricas dun reactivo organometálico, supón un gran avance para reducir as limitacións que implican o uso destes substratos e para reducir os residuos asociados a estes.

No capítulo II desta tese descríbese o desenvolvemento dunha reacción de alilboración de alquinos con carbonatos alílicos e bis(pinacolato)diboro catalizada sinérxicamente por cobre e paladio para obter 1,4-dienos borilados.

A catálise cooperativa ten o potencial de mellorar a eficiencia de reaccións descritas, posibilitar transformacións que non son accesibles cun único catalizador ou cambiar a selectividade do proceso. Por iso, hoxe en día, o interese na catálise cooperativa está a aumentar. Estas reaccións consisten na activación de dous substratos diferentes, simultánea e selectivamente, con dous catalizadores diferentes. No noso caso, dous catalizadores metálicos. Con todo, o uso de dous catalizadores metálicos de maneira cooperativa tamén ten uns retos asociados: os metais teñen que interaccionar de maneira selectiva cun único substrato para evitar a formación de reaccións secundarias e os dous ciclos catalíticos teñen que ser compatibles e ter cinéticas parecidas.

Na metodoloxía descrita neste capítulo xérase un intermedio alquenil cobre β-borilado de forma catalítica mediante a inserción dun alquino nun complexo LCuBpin (xerado con bis(pinacolato)diboro, unha sal de cobre e un ligando; Esquema 166). Os aspectos clave da formación deste intermedio son a rexio- e estereoselectividade, xa que o alquino pódese inserir posicionando o grupo Bpin no carbono α ou no carbono β do alquino. Neste caso, a inserción está controlada por factores fundamentalmente electrónicos que dirixen o átomo de boro á posición β do alquino. Doutra banda, a adición do enlace Cu-B ao alquino podería darse de forma *syn* ou *anti*. A adición *syn* é a máis común, sendo a que observamos no noso caso. Ademais, a presenza de maneira catalítica deste intermedio no medio de reacción favorece a diminución de reaccións secundarias, xa que a concentración do reactivo é máis baixa. Doutra banda, o catalizador de paladio é o encargado de activar o substrato alílico. A reacción do carbonato alílico co complexo de paladio ten lugar a través dunha adición oxidante para formar un complexo de π-alil-paladio intermedio. Os ciclos catalíticos do cobre e do paladio únense mediante unha etapa de transmetalación proporcionando un complexo σ-alil-paladio e a rexeneración do catalizador de cobre. O complexo σ-alil-paladio sofre finalmente unha eliminación redutora para dar lugar ao 1,4-dieno borilado e a rexeneración do catalizador de paladio.

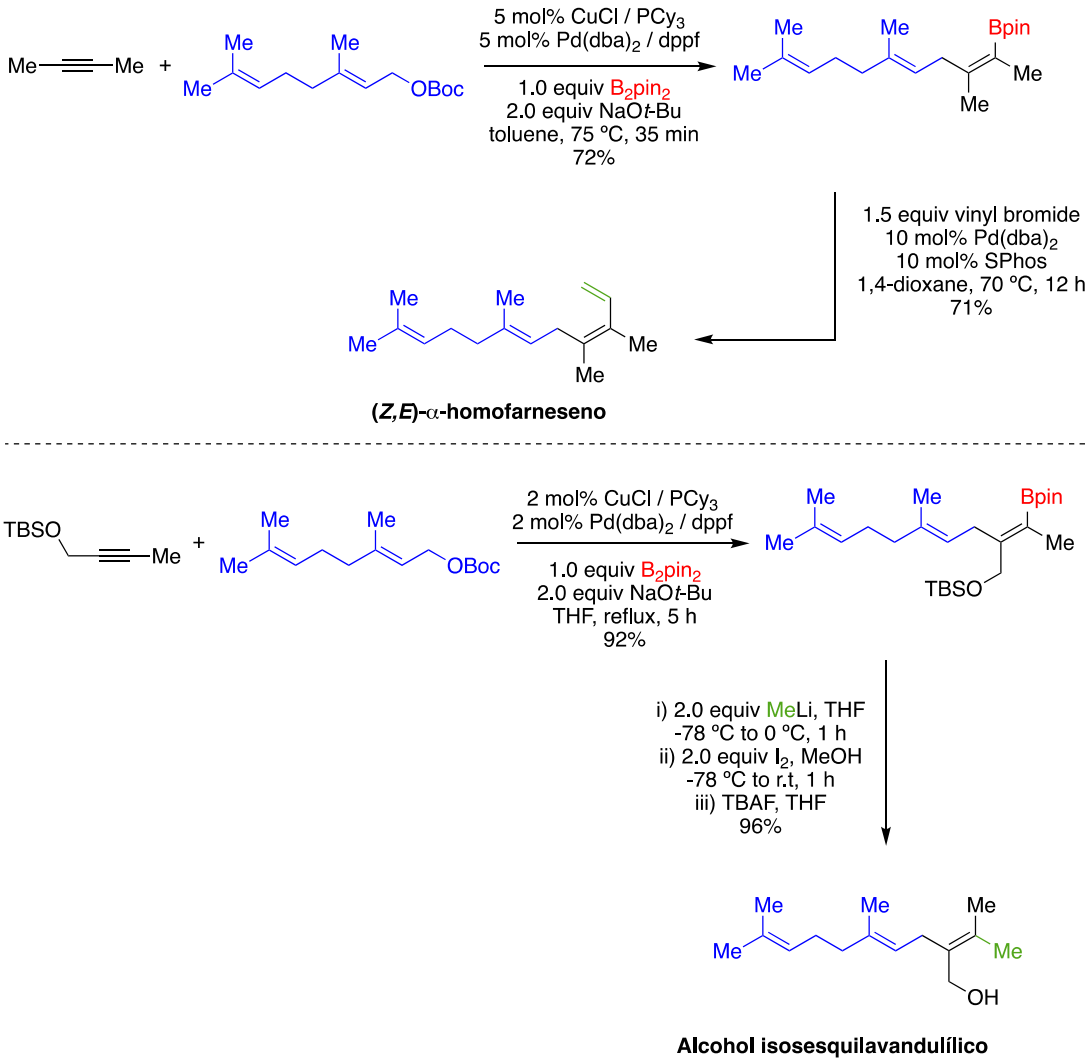
O uso de paladio como catalizador permite ter un control total da rexioselectividade na substitución alílica, favorecendo a substitución na posición menos impedida do carbonato alílico para obter 1,4-dienos lineais. O feito de que esta metodoloxía opere baixo un control do sistema catalítico é de especial relevancia xa que en traballos anteriores enfocados na obtención de 1,4-dienos borilados mediante catálise de cobre a rexioselectividade do proceso era controlada polo tipo de substrato utilizado, obtendo substitución tipo S_N2, S_N2' ou a mestura de ambos os isómeros dependendo da natureza dos reactivos.



Esquema 166. Reacción de alilboración de alquinos catalizada por cobre e paladio e o mecanismo proposto.

O uso da catálise cooperativa con cobre e paladio permite usar unha gran variedade de alquinos e carbonatos alilílicos, para obter diversos produtos dunha forma eficiente, baixo condicións suaves e con control total da rexio- e estereoselectividade. Ademais, a reacción tolera a presenza de diferentes grupos funcionais como -CO_2R, -OR, -SiR_3, -NHR, -Cl ou -Br.

A utilidade deste método foi demostrada mediante a síntese de dous produtos naturais (Esquema 167). En primeiro lugar, o (*Z,E*)-α-homofarneseno, que é unha feromona producida pola formiga de lume, púidose sintetizar en dous pasos desde o 2-butino e o carbonato alílico derivado do xeraniol. O primeiro paso consistiu nunha reacción de alilboración do alquino con catálise de cobre e paladio, seguido por unha reacción Suzuki-Miyaura de acoplamento cruzado estereoretentiva, catalizada por paladio, con bromuro de vinilo. Con esta secuencia, fomos capaces de sintetizar o homofarneseno en bo rendemento e con control total na estereoselectivitidade. É importante destacar que os métodos previos para a síntese deste composto requirían máis pasos e, ademais, producían mesturas de estereoisómeros. Doutra banda, levamos a cabo a síntese dun terpenoide, o alcohol isosesquilavandulílico, precursor das Meroclorinas A-D, que son axentes con potente actividade como antibióticos e metabolitos secundarios que se extraen de esponxas mariñas. O primeiro paso da síntese foi a alilboración do 2- butin-1-ol protexido cun grupo *tert*-butildimetilsililo, catalizada por cobre e paladio, co carbonato alílico derivado do xeraniol e bis(pinacolato)diboro. Despois, levouse a cabo un paso de conversión do enlace C-B a través dunha reacción de olefinación de Zweifel, utilizando MeLi e iodo. Esta reacción dá lugar á transformación do enlace C-B a C-Me con inversión na configuración do dobre enlace. Por último, tras unha etapa de desprotección do alcohol, puidemos obter o alcohol isoesquilavandulílico nun bo rendemento global.



Esquema 167. Síntese de produtos naturais a través da alilboración de alquinos catalizada por cobre e paladio.

Capítulo III: Síntese de dendralenos borilados estereodefinidos a través de alilboración de alquinos catalizada por cobre

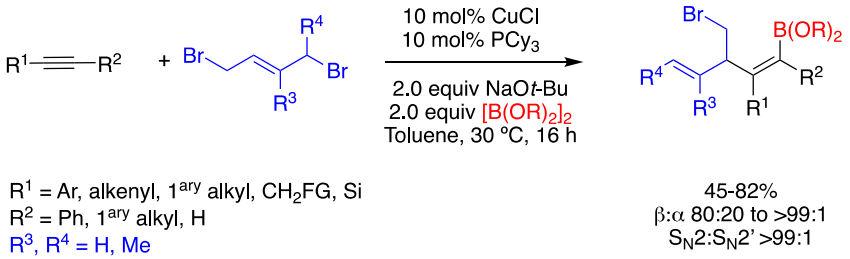
Durante o estudo da reacción anterior de alilboración de alquinos catalizada por cobre e paladio, observamos que co uso dun substrato difuncionalizado cun carbonato e un bromuro alílico, o produto obtido proviña da substitución alílica tipo SN2' do bromuro, permanecendo o carbonato de *tert*-butilo na molécula. Ao repetir a mesma reacción unicamente co catalizador de cobre, o resultado que obtivemos foi idéntico, polo que se concluíu que a catálise de paladio non é necesaria para o uso deste tipo de substratos.

En vista deste resultado preliminar, decidimos estudar esta reacción en maior detalle co obxectivo de desenvolver unha metodoloxía complementaria á descrita no capítulo anterior, traballo que se recolle no capítulo III desta tese. Para levar a cabo este estudo usamos como substrato alílico o 1,4-dibromo-2-buteno, un substrato sinxelo e comercial, que nos permite obter 1,4-dienos borilados substituídos cun bromuro achegando unha

versatilidade sintética aínda máis ampla. Para a obtención destes produtos utilízase un catalizador de cobre capaz de acoplar o *trans*-1,4-dibromo-2-buteno cun alquino e un composto diboronato con altos niveis de quimio-, rexio- e estereoselectividade. Neste caso, a reacción iniciaríase igualmente coa inserción do alquino no complexo LCuBpin de maneira rexio- e esteroselectiva, para dar lugar a un complexo nucleofílico de alquenil cobre β-borilado. O bromuro alílico reacciona con este complexo a través dunha adición oxidante para dar lugar a un complexo σ-alilcobre(III), co cobre situado na posición γ respecto ao grupo saínte. Por último, o complexo σ-alilcobre(III) sufriría unha eliminación redutora para xerar o produto e rexenerar o catalizador de cobre. De acordo con traballos anteriores baseados no uso deste tipo de substratos en alquilación alílica con reactivos de Grignard catalizada por cobre, proponse unha estabilización do complexo intermedio σ-alilcobre(III) a través dunha doazón electrónica dos orbitais cheos do bromo presente no complexo cara os orbitais baleiros do átomo de cobre. Esta estabilización facilitaría o control da regioselectividade cara a obtención do produto con substitución tipo S_N2'.

Tras unha extensa optimización das condicións de reacción, atopamos que o uso dun ligando de tipo monofosfina σ-dadora, en concreto a triciclohexilfosfina, conduciu aos mellores resultados proporcionando un único isómero e bos rendementos na maioría dos casos (Esquema 168). É importante destacar que, na maioría dos casos, a adición lenta do *trans*-1,4-dibromo-2-buteno ao medio de reacción supuxo unha mellora na eficiencia da transformación, xa que unha das reaccións secundarias máis importantes é a borilación directa do bromuro alílico co complexo LCuBpin.

A metodoloxía para a alilboración de alquinos catalizada por cobre foi aplicada a unha gran variedade de alquinos baixo condicións suaves, sendo tolerante con diversos grupos funcionais como -CO_2R, -OR, -SiR_3, -Cl ou -Br, dando lugar aos 1,4-dienos borilados en bos rendementos e control total na rexio- e estereoselectividade en practicamente todos os casos.

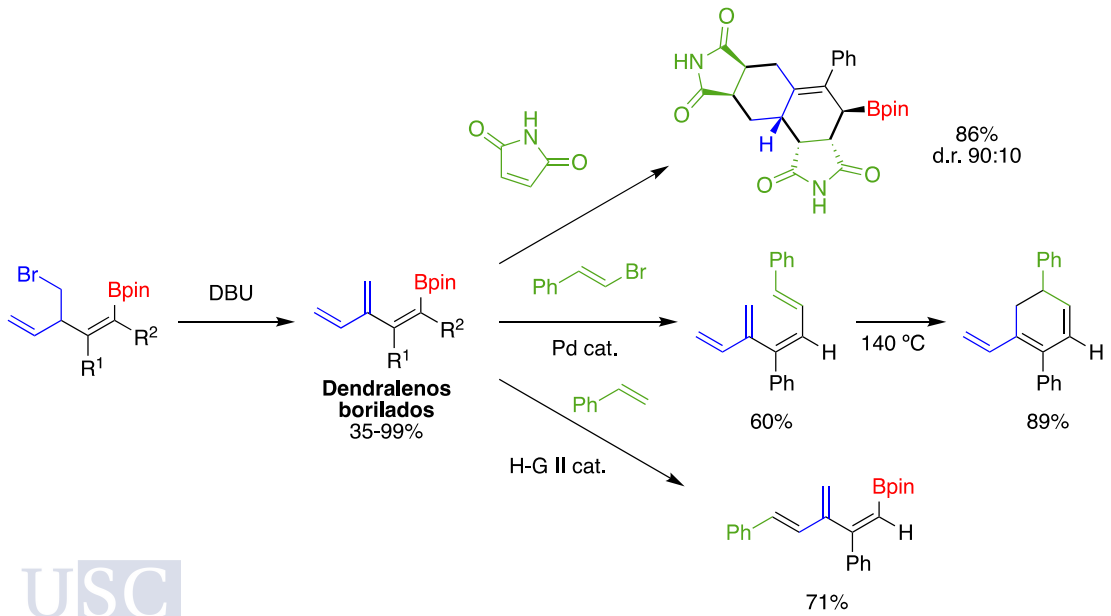


Esquema 168. Reacción de alilboración de alquinos catalizada por cobre.

Ademais, atopamos que estes 1,4-dienos borilados substituídos con bromo son excelentes precursores para a síntese de dendralenos borilados tras unha reacción de dehidrohaloxenación promovida por unha base (Esquema 169). Os dendralenos son un tipo de polienos acíclicos con conxugación cruzada que teñen un gran potencial en síntese orgánica e en química de polímeros e tamén, atópanse presentes nun gran número de produtos naturais. A pesar deste gran potencial, foron moi pouco estudados debido á falta

de métodos eficaces para sintetizalos. Por isto, o desenvolvemento dunha metodoloxía que permita a síntese destes compostos dunha forma fácil e rápida é de gran interese.

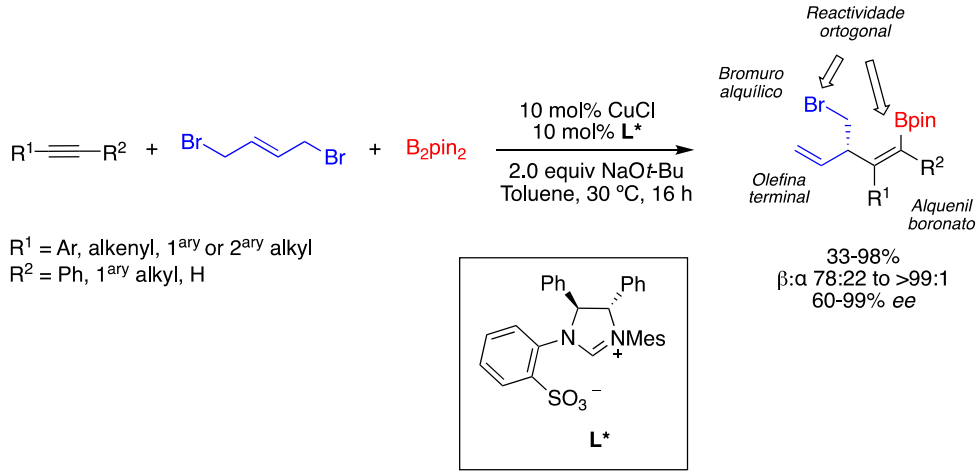
No noso traballo descríbese un método catalítico, simple e eficiente para a síntese de dendralenos borilados, partindo desde substratos sinxelos e comerciais. Trátase da primeira metodoloxía para a preparación dunha nova familia de compostos organoboro, o que lle suma relevancia a este traballo. Cabe destacar o amplo alcance da reacción o que permite unha alta diversificación do esqueleto dendralénico. Un dos principais atractivos desta nova estrutura é a combinación do esqueleto dendralénico coa presenza dun grupo éster borónico que achega unha gran versatilidade sintética a estes novos compostos, a cal tamén foi estudada neste traballo (Esquema 169). Dentro deste estudo púidose observar que os dendralenos borilados experimentan de forma selectiva reaccións de Diels-Alder ou " Diene Transmissive Diels-Alder" (DTDA), nas cales, ademais da excelente rexioselectividade, hai que destacar que se obteñen estruturas multicíclicas boriladas nas que se crean 6 novos centros estereoxénicos cunha diastereoselectividade moi alta. Tamén demostramos a versatilidade da presenza do boro que nos permite levar a cabo acoplamentos de Suzuki para xerar novos enlaces carbono-carbono podendo así obter diferentes dendralenos partindo dos nosos substratos. Debido á gran estereoselectividade da reacción de alilboración, pódense xerar tetraenos cunha estereoquímica adecuada para levar a cabo reacciones de electrociclación que dan lugar a ciclohexadienos vinil-substituídos con alto rendemento. Ademais, levamos a cabo a primeira reacción de metátese que se realiza nun dendraleno acíclico. Isto foi posible debido á estabilización que produce o éster borónico no esqueleto dendralénico e que impide a súa dimerización mediante unha reacción homo-Diels-Alder.



Esquema 169. Síntese de dendralenos borilados e a súa versatilidade sintética.

Capítulo IV: Síntese de "building blocks" altamente versátiles e multifuncionais a través de alilboración de alquinos enantioselectiva catalizada por cobre

O traballo descrito no capítulo IV baséase no desenvolvemento da versión enantioselectiva da alilboración de alquinos catalizada por cobre descrita no capítulo III. As metodoloxías catalíticas enantioselectivas que permiten a conversión de materiais de partida abundantes e simples en produtos quirales multifuncionais e complexos, dunha maneira fácil e sostible, están moi demandadas na actualidade. Neste contexto, desenvolvemos a primeira alilboración de alquinos asimétrica catalizada por cobre para a síntese de 1,4-dienos borilados quirales multifuncionalizados (Esquema 170). Esta reacción procede cunha excelente quimio-, estereo-, rexio- e enantioselectividade co uso dun complexo de cobre cun ligando tipo carbeno *N*-heterocíclico quiral que contén un grupo sulfonato. A reacción pódese levar a cabo en condicións suaves, o que permite o uso dunha gran variedade de alquinos e bromuros alílicos con gran tolerancia cara a grupos funcionais, como -CO_2R, -OR, -CF_3, -Cl ou -Br, obtendo os produtos con moi bos rendementos, control completo da rexioselectividade en prácticamente todos os casos e, ademais, excelentes excesos enantioméricos.

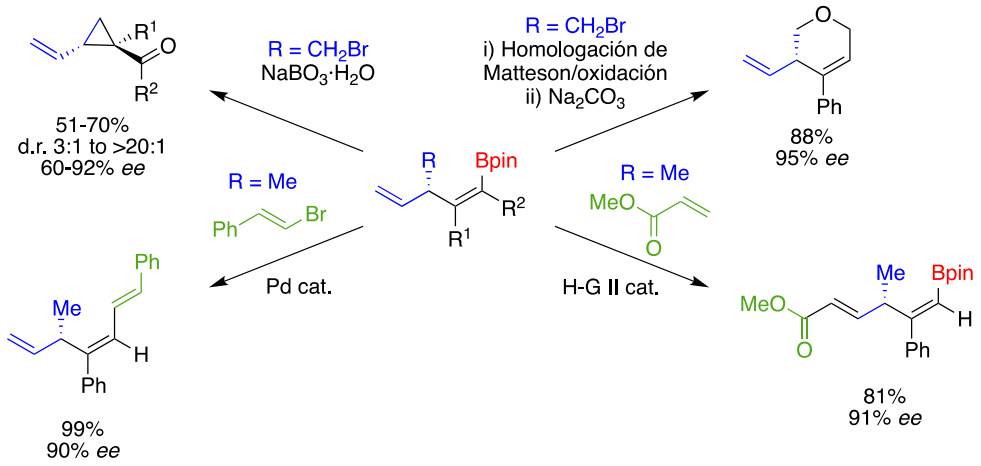


Esquema 170. Reacción de alilboración de alquinos asimétrica catalizada por cobre.

A través dun estudo de cálculos DFT puidemos esclarecer os aspectos clave que levan aos excelentes niveis de rexio- e enantioselectividade. A presenza dunha ponte de sodio entre o grupo sulfonato do ligando quiral tipo NHC e o bromuro alílico é clave á hora de obter boa selectividade, de tal maneira que facilita a formación dun estado de transición ríxido na etapa enantiodiscriminante que se corresponde coa adición oxidante do bromuro alílico ao intermedio alquenilcobre. Neste estado de transición o impedimento estérico entre o substituínte do alilo e o grupo mesitilo voluminoso que contén o ligando tipo NHC, favorece a enantiodiferenciación dunha das dúas caras do alilo.

Ademais do amplo alcance da reacción, unha das propiedades máis interesantes dos produtos é a súa gran versatilidade sintética derivada do seu alto grao de funcionalización (Esquema 170). Desta maneira, puidemos transformar varios 1,4-dienos borilados substituídos con bromo en ciclopropanos, estruturas importantes para farmacoloxía e

química biolóxica, a través dunha reacción de oxidación do enlace C-B con perborato de sodio. Esta oxidación xera un intermedio enolato de boro, que pode atacar intramolecularmente ao bromo da molécula. Esta ciclación intramolecular dá acceso á síntese de vinilciclopropano carbaldehídos quirales, nos que se forma un centro estereogénico cuaternario á beira dun centro terciario cunha alta diastereoselectividade. Ademais da síntese de vinilciclopropanos, puidemos explorar a versatilidade sintética de dienos borilados quirales coa síntese en dous pasos dun vinil pirano, a través dunha homologación de Matteson seguida por unha oxidación da enlace C-B e ciclación consecutiva. Por último, tamén avaliamos a reactividade do grupo Bpin cara a unha reacción de Suzuki-Miyaura de acoplamento cruzado catalizada por paladio e a reactividade do grupo vinílico terminal cara a unha reacción de metátese cruzada catalizada por rutenio.

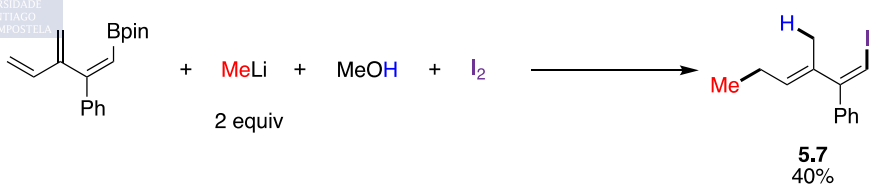


Esquema 171. Versatilidade sintética dos 1,4-dienos borilados quirais.

Capítulo V: Síntese estereoselectiva á carta de 1,3-dienos a través da multifuncionalización de dendralenos borilados

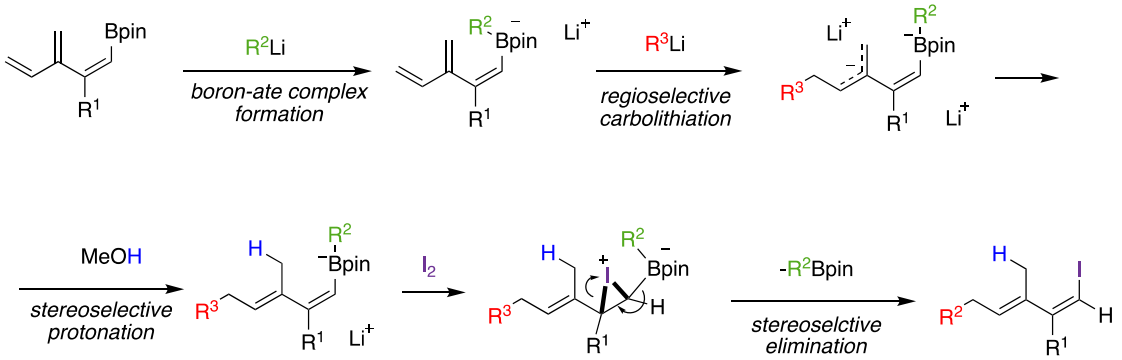
No capítulo V levamos a cabo unha ampliación do estudo da reactividade dos dendralenos borilados descritos no capítulo III, a través do desenvolvemento dunha nova reacción tetracomponente para a multifuncionalización de [3] e [4]dendralenos borilados, con reactivos organolíticos e diferentes electrófilos.

Esta reacción foi atopada durante o intento de levar a cabo unha olefinación de Zweifel nun dendraleno borilado. Curiosamente, inicialmente observamos que a reacción non ocorría cun equivalente de metil litio e, ao aumentar a cantidade de MeLi a dous equivalentes, con iodo e metanol observamos a formación do produto **5.7** (Esquema 172).



Esquema 172. Resultado preliminar da multifuncionalización de dendralenos borilados.

Debido á novidade da transformación, estudamos o mecanismo de reacción mediante resonancia magnética nuclear (RMN). O primeiro paso da reacción consiste no ataque do nucleófilo, é dicir, o composto organolítico, ao átomo de boro para formar un complexo boron 'ato' tetravalente. Propuxéronse dous posibles mecanismos a partir deste complexo de boro tetravalente para a formación do 1,3-dieno. Xa que neste complexo hai tres dobres enlaces que poderían ser activados polo iodo, a primeira proposta involucraba a activación con iodo da dobre enlace terminal, seguido por un reordenamento 1,6 do substituinte unido ao boro. Doutra banda, unha reacción de carbolitiación directa cun segundo equivalente de organolítico podería ser posible. Grazas aos estudos de RMN puidemos observar que a reacción procede mediante unha carbolitiación rexio- e estereoselectiva do complexo dendralenico boron 'ato' no dobre enlace terminal do polieno, para formar un intermedio alil litio (Esquema 173). Este intermedio é despois atrapado por un electrófilo, neste caso o protón do metanol, que forma un complexo dienil boron 'ato'. Por último, o iodo provoca unha halodeboronación estereoretentiva para obter os produtos.



Esquema 173. Mecanismo da reacción de multifuncionalización de dendralenos borilados.

Esta metodoloxía prové acceso a 1,3-dienos tetrasubstituidos con niveis excelentes de rexio- e estereoselectividade a través da reacción entre dendralenos borilados, un reactivo organolítico e dous electrófilos (Esquema 174). Unha vez elucidado o mecanismo da reacción, estudouse o alcance da mesma. Ademais de diferentes dendralenos borilados e unha gran variedade de reactivos organolíticos, puidemos empregar diferentes electrófilos para o atrapado do alil litio intermedio, como MeI, *n*-BuBr, BnBr ou benzaldehído. A substitución electrófila do grupo boron 'ato' tamén se puido realizar con electrófilos diferentes ao iodo como *N*-bromosuccinimida, PhSeCl ou selectfluor®.

Esquema 174. Esquema xeral da multifuncionalización de dendralenos borilados cun reactivo organolítico e dous electrófilos.

A importancia deste método destácase pola facilidade na que podemos obter dienos estruturalmente complexos e altamente substituídos. A estrutura do 1,3-dieno é moi importante por estar presente en multitude de produtos naturais, materiais funcionais e dispositivos optoelectrónicos. Debido a isto, púxose moito esforzo no desenvolvemento de metodoloxías para a síntese destes compostos. Con todo, a síntese de 1,3-dienos con substitución en todos os carbonos do dieno é moi complexa, xa que hai que controlar o lugar onde se introducen as diferentes funcionalidades ademais da estereoquímica de dous dobres enlaces. As metodoloxías máis recentes e destacables, aínda que son eficientes e permiten a síntese de dienos con altos graos de funcionalización, fallan na introdución de substituintes con diversas funcionalidades no dieno. Por iso, a introdución á carta de substituintes no esqueleto do dieno supón unha gran relevancia neste campo. Por ultimo, puidemos transformar a enlace $C(sp^2)$-I presente nos produtos en enlaces $C(sp^2)$-$C(sp^3)$, $C(sp^2)$-$C(sp^2)$ e $C(sp^2)$-C(sp), demostrando a utilidade desta metodoloxía.

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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 $KMnO_4$ 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 ($CHCl_3$: 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 ^{13}C NMR technique.
- Melting points were determined using a Buchi-M565 apparatus.
- 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 hydroboration reactions, commercial alkynes and B_2pin_2 were dried over Na_2SO_4 prior to being used.

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2. CHAPTER II:

2.1. LIST OF STARTING MATERIAL

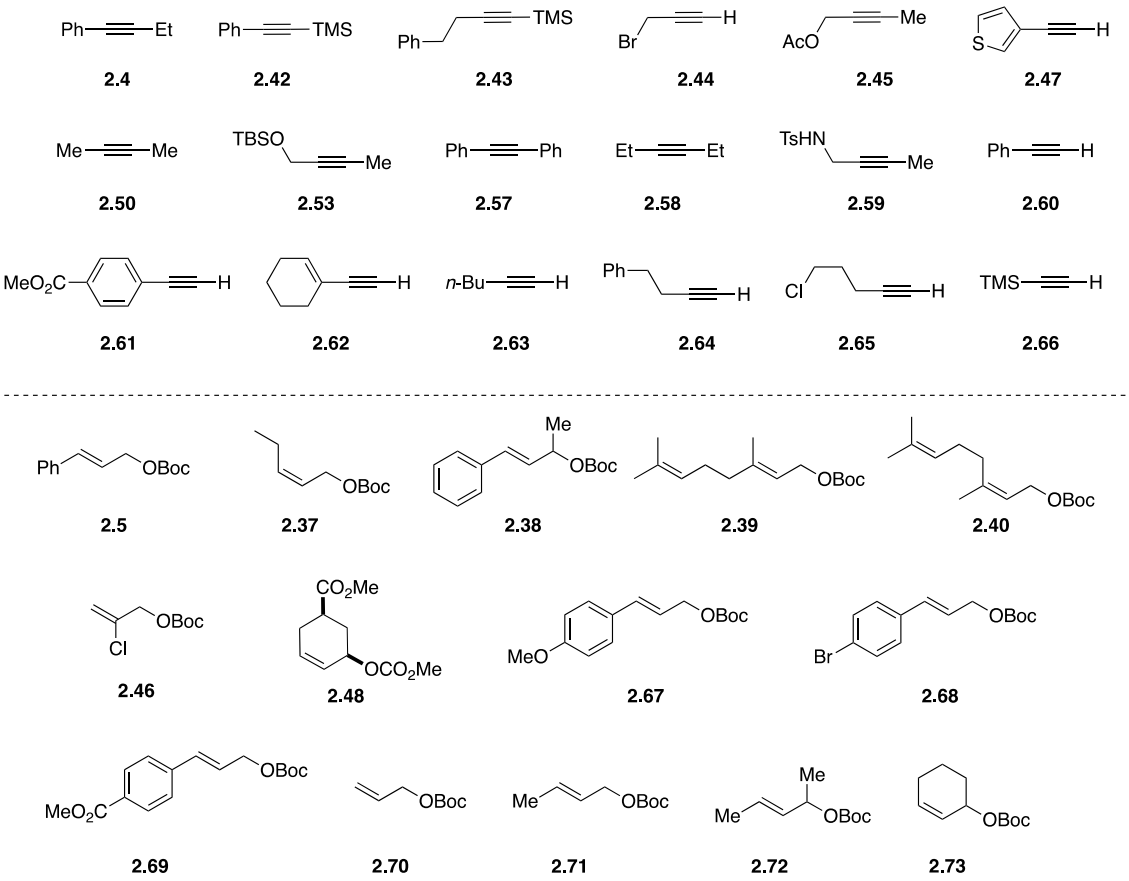

Figure 27. List of starting material.

Alkynes **2.4**, **2.44**, **2.47**, **2.50**, **2.57**, **2.58** and **2.60-2.66** were obtained from commercial sources. Alkynes **2.42**, [373] **2.43**, [374] **2.45**, [375] **2.53** [376] and **2.59** [377] were synthesized according to previously described methodologies. Allyl carbonates **2.5**, and

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[373] Huang, H.; Zhang, G.; Gong, L.; Zhang, S.; Chen, Y. *J. Am. Chem. Soc*. **2014**, *136*, 2280-2283.
[374] Kubota, K.; Yamamoto, E.; Ito, H. *Adv. Synth. Catal.* **2013**, *355*, 3527-3531.
[375] Rooke, D. A.; Ferreira, E. M. *Angew. Chem. Int. Ed.* **2012**, *51*, 3225-3230.
[376] Hesse, M. J.; Butts, C. P.; Willis, C. L.; Aggarwal, V. K. *Angew. Chem. Int. Ed.* **2012**, *51*, 12444-14448.
[377] Serpier, F.; Flamme, B.; Brayer, J.-L.; Folléas, B.; Darses, S. *Org. Lett.* **2015**, *17*, 1720-1723.

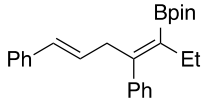
2.73,[378] **2.37**, **2.39-2.40**, **2.70** and **2.72**, [379] **2.46, 2.67-2.68** and **2.71**,[380] **2.48**,[381] **2.69**[106,382] and **2.38**,[383] were synthesized according to previously described methodologies.

2.2. GENERAL PROCEDURE FOR THE CU/PD-CATALYZED SYNTHESIS OF SKIPPED DIENES.

CuCl (5 mol%, 0.025 mmol, 2.5 mg) and tricyclohexylphosphine (5 mol%, 0.025 mmol, 7.0 mg) were suspended in dry THF (2 mL), stirred during 15 minutes at r.t. and added to the reaction vial containing B_2pin_2 (1.3 equiv, 0.65 mmol, 165.1 mg) and NaO*t*-Bu (2.0 equiv, 1.0 mmol, 96.2 mg) to afford a red suspension. In a separate vial $Pd(dba)_2$ (5 mol%, 0.025 mmol, 14.3 mg), dppf (5 mol%, 0.025 mmol, 13.8 mg), 1-phenyl-1-butyne **2.4** (1.0 equiv, 0.5 mmol, 65.1 mg) and *tert*-butyl cinnamyl carbonate **2.5** (1.2 equiv, 0.6 mmol, 140.6 mg) were stirred in THF (3 mL) for 15 minutes at r.t. This solution was finally added to the reaction vial and heated at 50 ºC for the indicated time. After this time, the reaction was quenched by addition of saturated aqueous solution of NH_4Cl (10 mL), extracted with Et_2O (2x10 mL) and washed with water (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, or filtered over silica gel when no chromatography was necessary.

2.3. COMPOUND CHARACTERIZATION

2-((3*Z*,6*E*)-4,7-Diphenylhepta-3,6-dien-3-yl)-4,4,5,5-tetramethyl-1,3,2 dioxaborolane (2.7)



Obtained from **2.4**, **2.5** and B_2pin_2 as yellow oil after column chromatography (hexane/CH_2Cl_2, 4:1) in 78% yield (146.0 mg). Reaction time: 5 h. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.35 - 7.15 (m, 8H), 7.09 (ddd, *J* = 7.9, 1.6, 0.8 Hz, 2H), 6.32 - 6.24 (d, *J* = 15.8 Hz, 1H), 6.12 (dt, *J* = 15.8, 6.8 Hz, 1H), 3.50 (d, *J* = 6.9 Hz, 2H), 1.99 (q, *J* = 7.5 Hz, 2H), 1.35 (s, 12H), 0.89 (t, *J* = 7.5 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 151.2, 143.2, 138.1, 130.7, 129.1, 128.4, 128.1, 128.0, 126.8, 126.4, 126.1, 83.3, 41.9, 25.8, 25.1, 15.1. **^{11}B NMR** (160 MHz, $CDCl_3$) δ 31.3 ppm. **HRMS (CI)** Calc. for $C_{25}H_{31}BO_2$ [M^+]: 374.2417, found 374.2419.

[378] Trost, B. M.; Malhotra, S.; Olson, D. E.; Maruniak, A.; Du Bois, J. *J. Am. Chem. Soc*. **2009**, *131*, 4190-4191.
[379] Trost, B. M.; Luan, X.; Miller, Y. *J. Am. Chem. Soc*. **2011**, *133*, 12824-12833.
[380] Yuan, Q.; Yao, K.; Liu, D.; Zhang, W. *Chem. Commun.* **2015**, *51*, 11834-11836.
[381] Misale, A.; Niyomchon, S.; Luparia, M.; Maulide, N. *Angew. Chem. Int. Ed.* **2014**, *53*, 7068-7073.
[382] Liu, J.; Cao, C.-G.; Sun, H.-B.; Zhang, X.; Niu, D. *J. Am. Chem. Soc.* **2016**, *138*, 13103-16106.
[383] Li, C.; Xing, J.; Zhao, J.; Huynh, P.; Zhang, W.; Jiang, P.; Zhang, Y. J. *Org. Lett.* **2012**, *14*, 390-393.

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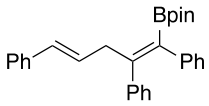
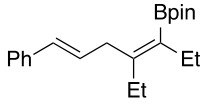
4,4,5,5-Tetramethyl-2-((1*Z*,4*E*)-1,2,5-triphenylpenta-1,4-dien-1-yl)-1,3,2-dioxaborolane (2.13)



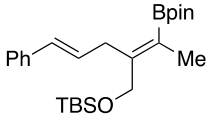
Obtained from **2.57**, **2.5** and B_2pin_2 as a white solid after column chromatography (hexane/CH_2Cl_2, 5:1) in 82% yield (173.0 mg). Reaction time: 7 h. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.28 - 7.26 (m, 5H), 7.10 - 6.92 (m, 10H), 6.41 (d, *J* = 15.8 Hz, 1H), 6.21 (dt, *J* = 15.7, 6.7 Hz, 1H), 3.64 (d, *J* = 6.7 Hz, 2H), 1.32 (s, 12H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 151.5, 142.5, 141.8, 138.0, 131.4, 129.9, 129.4, 128.8, 128.6, 127.8, 127.7, 127.1, 126.6, 126.6, 125.6, 83.9, 42.1, 24.9. **^{11}B NMR** (160 MHz, $CDCl_3$) δ 31.2 ppm. **HRMS (CI)** Calc. for $C_{29}H_{31}BO_2$ [M^+]: 422.2417, found 422.2416. **Mp (°C):** 65-68.

2-((3*E*,6*E*)-4-Ethyl-7-phenylhepta-3,6-dien-3-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (2.14)



Obtained from **2.58**, **2.5** and B_2pin_2 as colorless oil after column chromatography (hexane/CH_2Cl_2, 5:1) in 76% (123.9 mg). Reaction time: 7 h. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.35 - 7.28 (m, 4H), 7.21 - 7.15 (m, 1H), 6.40 (d, *J* = 15.8 H, 1H), 6.18 (dt, *J* = 15.8, 6.9 Hz, 1H), 3.23 (d, *J* = 6.9 Hz, 2H), 2.24 - 2.09 (m, 4H), 1.29 (s, 12H), 1.06 - 0.92 (m, 6H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 152.9, 138.2, 130.7, 130.4, 128.6, 126.9, 126.2, 83.0, 39.4, 25.0, 24.9, 24.1, 15.4, 13.5. **^{11}B NMR** (160 MHz, $CDCl_3$) δ 22.1 ppm. **HRMS (CI)** Calc. for $C_{21}H_{31}BO_2$ [M^+]: 326.2417, found 326.2416.

***tert*-Butyldimethyl(((2*Z*,4*E*)-5-phenyl-2-(1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)ethylidene)pent-4-en-1-yl)oxy)silane (2.15)**

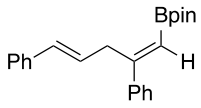


Obtained from **2.53**, **2.5** and B_2pin_2 as yellow oil after column chromatography (hexane/CH_2Cl_2, 4:1) in 70% yield (149.9 mg). Reaction time: 7 h. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.35 - 7.24 (m, 4H), 7.20 - 7.13 (m, 1H), 6.41 (d, *J* = 15.7 Hz, 1H), 6.27 (dd, *J* = 15.7, 6.9 Hz, 1H), 4.27 (s, 2H), 3.40 (d, *J*= 6.9 Hz, 2H), 1.73 (s, 2H), 1.29 (s, 12H), 0.93 (s, 9H), 0.08 (s, 6H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 152.1, 138.4, 130.6, 130.3, 128.7, 126.8, 126.2, 111.3, 83.2, 61.6, 35.9, 26.0, 24.9, 18.4, 15.7, -5.3. **^{11}B NMR** (160 MHz, $CDCl_3$) δ 22.5 ppm. **HRMS (CI)** Calc. for $C_{19}H_{26}BO_2$ [M^+-OTBS]: 297.2026, found 297.2026.

4-Methyl-*N*-((2*Z*,4*E*)-5-phenyl-2-(1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)ethylidene)pent-4-en-1-yl)benzenesulfonamide (2.16)

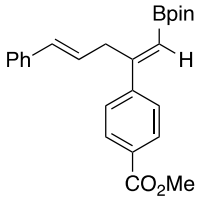
Obtained from **2.59**, **2.5** and B_2pin_2 as yellow oil after column chromatography (hexane/CH_2Cl_2, 4:1) in 75% yield (175.1 mg). Reaction time: 7 h. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.71 (d, J = 8.2 Hz, 2H), 7.31 - 7.21 (m, 7H), 6.41 (d, J = 15.9 Hz, 1H), 6.21 - 6.11 (m, 1H), 5.97 (dt, J = 15.9, 6.7 Hz, 1H), 3.99 - 3.88 (m, 4H), 2.42 (s, 3H), 1.63 (s, 3H), 1.22 (s, 12H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 143.1, 139.3, 137.4, 136.3, 133.8, 129.6, 128.5, 127.8, 127.3, 126.4, 124.1, 83.4, 49.7, 44.7, 24.7, 21.5, 14.1. **^{11}B NMR** (160 MHz, $CDCl_3$) δ 22.5 ppm. **HRMS (CI)** Calc. for $C_{25}H_{35}BNO_4S$ [M^++H]: 468.2380, found 468.2386.

2-((1*E*,4*E*)-2,5-Diphenylpenta-1,4-dien-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (2.17)



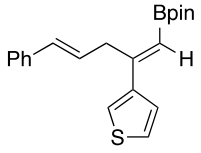
Obtained from **2.60**, **2.5** and B_2pin_2 as a yellow oil after column chromatography (hexane/CH_2Cl_2, 6:1) in 85% yield (147.2 mg). Reaction time: 3 h. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.56 - 7.48 (m, 2H), 7.36 - 7.20 (m, 8H), 6.46 (d, *J* = 15.8 Hz, 1H), 6.22 (dt, *J* = 15.8, 6.7 Hz, 1H), 5.80 (s, 1H), 3.82 (dd, *J* = 6.6, 1.6 Hz, 2H), 1.32 (s, 12H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 160.1, 142.9, 137.9, 130.7, 129.4, 128.4, 128.2, 128.0, 126.8, 126.4, 126.0, 111.1, 83.0, 36.9, 24.7. **^{11}B NMR** (160 MHz, $CDCl_3$) δ 22.5 ppm. **HRMS (CI)** Calc. for $C_{23}H_{27}BO_2$ [M^+]: 346.2104, found 346.2100.

Methyl-4-((*1E,4E*)-5-phenyl-1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)penta-1,4-dien-2-yl)benzoate (2.18)



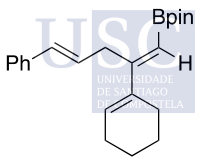
Obtained from **2.61**, **2.5** and B_2pin_2 as a yellow oil after column chromatography (hexane/AcOEt, 10:1) in 76% yield (153.6 mg). Reaction time: 3 h. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.99 (d, *J* = 8.4 Hz, 2H), 7.57 (d, *J* = 8.4 Hz, 2H), 7.41 - 7.13 (m, 9H), 6.45 (d, *J* = 15.8, 1H), 6.20 (dt, *J* = 15.8, 6.6 Hz, 1H), 5.87 (s, 1H), 3.90 (s, 2H), 3.83 (d, *J* = 6.6 Hz, 1H), 1.33 (s, 12H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 166.8, 158.8, 148.1, 147.4, 137.6, 131.0, 129.6, 128.7, 128.4, 127.0, 126.4, 126.0, 83.3, 52.0, 36.9, 24.9. **^{11}B NMR** (160 MHz, $CDCl_3$) δ 22.5 ppm. **HRMS (CI)** Calc. for $C_{25}H_{29}BO_4$ [M^+]: 404.2159 found 404.2150.

4,4,5,5-Tetramethyl-2-((1*E*,4*E*)-5-phenyl-2-(thiophen-3-yl)penta-1,4-dien-1-yl)-1,3,2-dioxaborolane (2.19)



Obtained from **2.47**, **2.5** and B_2pin_2 as orange oil after column chromatography (hexane/CH_2Cl_2, 6:1) in 82% yield (144.4 mg). Reaction time: 5 h. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.42 (dd, *J* = 2.9, 1.4 Hz, 1H), 7.33 (dd, *J* = 5.2, 1.4 Hz, 2H), 7.30 - 7.22 (m, 5H), 6.51 (d, *J* = 15.8 Hz, 1H), 6.29 (dt, *J* = 15.8, 6.7 Hz, 1H), 5.86 (s, 1H),3.77 (dd, *J* = 6.6, 1.6 Hz, 2H), 1.31 (s, 11H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 154.2, 144.5, 138.0, 131.0, 129.7, 128.6, 127.1, 126.3, 126.2, 125.7, 122.8, 111.3, 83.2, 37.2, 24.9. **^{11}B NMR** (160 MHz, $CDCl_3$) δ 22.5 ppm. **HRMS (CI)** Calc. for $C_{21}H_{25}BO_2S$ [M^+]: 352.1668, found 352.1663.

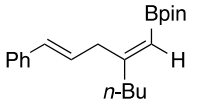
2-((1*E*,4*E*)-2-(Cyclohex-1-en-1-yl)-5-phenylpenta-1,4-dien-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (2.20)



Obtained from **2.62**, **2.5** and B_2pin_2 as yellow oil after column chromatography (hexane/CH_2Cl_2, 5:1) in 93% yield (162.8 mg). Reaction time: 5 h. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.34 - 7.24 (m, 4H), 7.20 - 7.14 (m, 1H), 6.44 (d, *J* = 15.9 Hz, 1H), 6.30 - 6.17 (m, 2H), 5.44 (s, 1H), 3.59 (dd, *J* = 6.6, 1.5 Hz, 2H), 2.24 - 2.12 (m, 4H), 1.73 - 1.53 (m, 4H), 1.29 (s, 12H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 160.6, 138.4, 137.7, 131.0, 130.1, 128.6, 128.4,

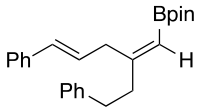
126.9, 126.2, 83.0, 34.9, 26.3, 26.1, 24.9, 23.0, 22.1. **^{11}B NMR** (160 MHz, $CDCl_3$) δ 22.5 ppm. **HRMS (CI)** Calc. for $C_{23}H_{31}BO_2$ [M^+]: 350.2417, found 350.2417.

2-((*Z*)-2-Cinnamylhex-1-en-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (2.21)



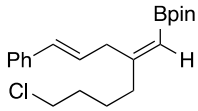
Obtained from **2.63**, **2.5** and B_2pin_2 as yellow oil after column chromatography (hexane/CH_2Cl_2, 6:1) in 92% yield (150.1 mg). Reaction time: 7h. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.38 - 7.24 (m, 4H), 7.21 (m, 1H), 6.44 (d, *J* = 15.5 Hz, 1H), 6.19 (dt, *J* = 15.5, 7.0 Hz, 1H), 3.32 (d, *J* = 7.0 Hz, 2H), 2.15 (t, *J*=7.2 Hz, 2H), 1.52 - 1.41 (m, 4H), 1.28 (s, 12H), 0.89 (t, *J* = 7.2 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 164.7, 137.9, 130.7, 129.5, 128.5, 126.8, 126.0, 82.6, 38.6, 38.5, 29.6, 24.7, 22.3, 13.8. **^{11}B NMR** (160 MHz, $CDCl_3$) δ 22.6 ppm. **HRMS (CI)** Calc. for $C_{21}H_{31}BO_2$ [M^+]: 326.2417, found 326.2416.

4,4,5,5-Tetramethyl-2-((1*Z*,4*E*)-2-phenethyl-5-phenylpenta-1,4-dien-1-yl)-1,3,2-dioxaborolane (2.22)



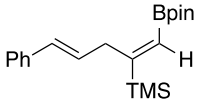
Obtained from **2.64**, **2.5** and B_2pin_2 as dark orange oil as 91:9 mixture of β/α regioisomers. Reaction time: 3 h. No column chromatography was necessary. Purification was performed by addition of 10 ml of cold hexane, keeping the mixture into an ice bath for 30 minutes and removing the resulting black solid by simple filtration through cotton. Solvents were removed under vacuum, affording the desired diene **2.22** in 85% yield (159.0 mg). Spectroscopic data for major product: **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.40 - 7.19 (m, 10H), 6.49 (d, *J* = 15.7 Hz, 1H), 6.31 - 6.19 (m, 1H), 5.37 (s, 1H), 3.41 (d, *J* = 7.1 Hz, 2H), 2.90 - 2.72 (m, 2H), 2.50 (m, 2H), 1.33 (s, 12H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 163.6, 142.1, 137.8, 131.1, 129.2, 128.6, 128.4, 127.0, 126.4, 126.1, 125.9, 82.9, 40.9, 39.1, 34.4, 25.0. **^{11}B NMR** (160 MHz, $CDCl_3$) δ 22.5 ppm. **HRMS (CI)** Calc. for $C_{25}H_{31}BO_2$ [M^+]: 374.2417, found 374.2417.

2-((*Z*)-6-Chloro-2-cinnamylhex-1-en-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (2.23)



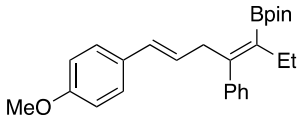
Obtained from **2.65**, **2.5** and B_2pin_2 as a dark yellow oil as 80:20 mixture of β/α regioisomers. Reaction time: 3 h. No column chromatography was necessary. Purification was performed by addition of 10 ml of cold hexane, keeping the mixture into an ice bath for 30 minutes and removing the resulting black solid by simple filtration through cotton. Solvents were removed under vacuum, affording the desired diene **2.23** in 91% yield (163.8 mg). Spectroscopic data for major product: **^{1}H NMR** (300 MHz, $CDCl_3$): 7.36-7.26 (m, 5H), 6.45 (d, *J* = 15.9 Hz, 1H), 6.20 (m, 1H), 5.24 (s, 1H), 3.53 (m, 2H), 3.33 (d, *J* = 7.1 Hz, 2H), 2.19 (t, *J* = 7.4 Hz, 2H), 1.83 - 1.60 (m, 4H), 1.29 (s, 12H).**^{13}C NMR** (75 MHz, $CDCl_3$) δ 163.4, 137.7, 130.9, 129.1, 128.5, 126.9, 126.0, 83.0, 44.9, 38.6, 38.0, 32.2, 27.7, 24.9. **^{11}B NMR** (160 MHz, $CDCl_3$) δ 22.5 ppm. **HRMS (CI)** Calc. for $C_{21}H_{30}BO_2$ [M^+]: 360.2027, found 360.2028.

Trimethyl((1*E*,4*E*)-5-phenyl-1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)penta-1,4-dien-2-yl)silane (2.24)



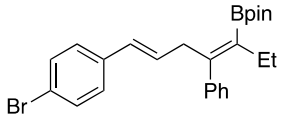
Obtained from **2.66**, **2.5** and B_2pin_2 as colorless oil after column chromatography (hexane/CH_2Cl_2, 6:1, SiO_2 deactivated with 3% Et_3N) in 87% yield (148.2 mg). Reaction time: 5 h. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.36 - 7.17 (m, 5H), 6.39 (d, *J* = 15.8 Hz, 1H), 6.16 (dt, *J* = 15.8, 6.9 Hz, 1H), 5.97 (s, 1H), 3.45 (d, *J* = 6.8 Hz, 2H), 1.29 (s, 12H), 0.10 (s, 9H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 168.8, 138.3, 130.7, 130.5, 128.7, 127.0, 126.2, 83.2, 38.3, 25.0, -1.2. **^{11}B NMR** (160 MHz, $CDCl_3$) δ 22.5 ppm. **HRMS (CI)** Calc. for $C_{29}H_{28}BO_2Si$ [M^+-CH_3]: 327.1952, found 327.2080.

4,4,5,5-Tetramethyl-2-((3*Z*,6*E*)-7-(4-methoxyphenyl)-4-phenylhepta-3,6-dien-3-yl)-1,3,2-dioxaborolane (2.25)



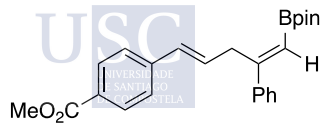
Obtained from **2.4**, **2.67** and B_2pin_2 as a white solid after column chromatography (hexane/AcOEt, 20:1) in 70% yield (141.4 mg). Reaction time: 5 h. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.34 - 7.16 (m, 5H), 7.08 (d, *J* = 6.7 Hz, 2H), 6.80 (d, *J* = 8.6 Hz, 2H), 6.21 (d, *J* = 15.8 Hz, 1H), 5.97 (dt, *J* = 15.8, 7.0 Hz, 1H), 3.78 (s, 1H), 3.46 (d, *J* = 7.0 Hz, 2H), 1.98 (q, *J* = 7.5 Hz, 2H), 1.35 (s, 12H), 0.88 (t, *J* = 7.5 Hz, 3H).**^{13}C NMR** (75 MHz, $CDCl_3$) δ 158.7, 151.4, 143.3, 131.0, 130.1, 128.1, 128.0, 127.2, 127.0, 126.4, 114.0, 83.4, 55.4, 42.0, 25.8, 25.0, 15.2. **^{11}B NMR** (160 MHz, $CDCl_3$) δ 31.2 ppm. **HRMS (CI)** Calc. for $C_{26}H_{33}BO_3$ [M^+]: 404.2523, found 404.2529. **Mp** (°C): 89-92.

4,4,5,5-Tetramethyl-2-((3*Z*,6*E*)-7-(4-bromophenyl)-4-phenylhepta-3,6-dien-3-yl)-1,3,2-dioxaborolane (2.26)



Obtained from **2.4**, **2.68** and B_2pin_2 as a white solid after column chromatography (hexane/AcOEt, 20:1) in 65% yield (146.9 mg). Reaction time: 5 h. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.42 - 7.18 (m, 5H), 7.17 - 7.05 (m, 4H), 6.26 - 6.05 (m, 2H), 3.50 (d, *J* = 6.4 Hz, 2H), 2.00 (q, *J* = 7.5 Hz, 2H), 1.36 (s, 12H), 0.90 (t, *J* = 7.5 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 150.8, 143.1, 137.0, 131.5, 130.0, 129.6, 128.1, 128.0, 127.7, 126.5, 120.5, 83.4, 41.9, 25.8, 25.1, 15.2. **^{11}B NMR** (160 MHz, $CDCl_3$) δ 31.2 ppm. **HRMS (CI)** Calc. for $C_{25}H_{30}BBrO_2$ [M^+]: 452.1522, found 452.1513. **Mp** (°C): 109-111.

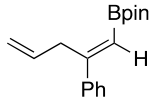
Methyl 4-((1*E*,4*E*)-4-phenyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)penta-1,4-dien-1-yl)benzoate (2.27)



Obtained from **2.60**, **2.69** and B_2pin_2 as a yellow oil after column chromatography (hexane/CH_2Cl_2, 8:2) in 57% yield (115.1 mg). Reaction time: 18 h. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.91 (d, *J* = 8.4 Hz, 2H), 7.54 - 7.47 (m, 2H), 7.35 - 7.29 (m, 5H), 6.50 (d, *J* = 15.9 Hz, 2H), 6.37 (dt, *J* = 15.8, 6.3 Hz, 2H), 5.83 (s, 1H), 3.88 (s, 3H), 3.85 (d, *J* = 6.3 Hz, 2H), 1.32 (s, 12H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 166.9, 159.4, 142.7, 142.3, 132.3, 128.3, 128.1, 126.4, 125.8, 83.1, 52.0, 37.0, 24.9. **^{11}B NMR** (160 MHz,

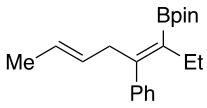
$CDCl_3$) δ 22.6 ppm. **HRMS (CI)** Calc. for $C_{25}H_{30}BO_4$ [M+H$^+$]: 405.2159, found 405.2236.

(*E*)-4,4,5,5-Tetramethyl-2-(2-phenylpenta-1,4-dien-1-yl)-1,3,2-dioxaborolane (2.28)



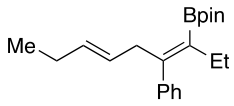
Obtained from **2.60**, **2.70** and B_2pin_2 as yellow oil after column chromatography (hexane/CH_2Cl_2, 7:1) in 68% yield (91.8 mg). Reaction time: 10 h. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.50 - 7.44 (m, 2H), 7.34 - 7.25 (m, 3H), 5.89 - 5.78 (m, 1H), 5.76 (s, 1H), 5.08 (dq, *J* = 17.1, 1.8 Hz, 1H), 4.95 (dq, *J* = 10.1, 1.8 Hz, 1H), 3.68 (dt, *J* = 6.5, 1.8 Hz, 2H), 1.31 (s, 12H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 160.1, 143.1, 137.5, 128.3, 128.3, 128.1, 126.6, 115.6, 83.2, 38.1, 25.0. **^{11}B NMR** (160 MHz, $CDCl_3$) δ 22.5 ppm. **HRMS (CI)** Calc. for $C_{17}H_{23}BO_2$ [M$^+$]:270.1791, found 270.1820.

4,4,5,5-Tetramethyl-2-((3*Z*,6*E*)-4-phenylocta-3,6-dien-3-yl)-1,3,2-dioxaborolane (2.29)



Obtained from **2.4**, **2.71** and B_2pin_2 as colorless oil after column chromatography (hexane/CH_2Cl_2, 7:1) in 60% yield (93.7 mg). Reaction time: 10 h. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.33 - 7.17 (m, 3H), 7.05 (m, 2H), 5.31 (m, 2H), 3.28 - 3.20 (m, 2H), 1.95 (q, *J* = 7.5 Hz, 2H), 1.62 - 1.52 (m, 3H), 1.33 (s, 12H) 0.86 (t, *J* = 7.5 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 151.7, 143.4, 129.4, 128.2, 127.9, 126.3, 125.9, 83.3, 41.8, 25.8, 25.1, 18.1, 15.2. **^{11}B NMR** (160 MHz, $CDCl_3$) δ 31.4 ppm. **HRMS (CI)** Calc. for $C_{20}H_{29}BO_2$ [M$^+$]: 312.2261, found 312.2257.

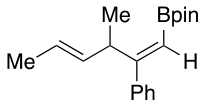
4,4,5,5-Tetramethyl-2-((3*Z*,6*E*)-4-phenylnona-3,6-dien-3-yl)-1,3,2-dioxaborolane (2.30)



Obtained from **2.4**, **2.37** and B_2pin_2 as yellow oil after column chromatography (hexane/AcOEt, 20:1) in 88% yield (143.1 mg). Reaction time 15 h.* **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.31 - 7.26 (m, 2H), 7.23 - 7.17 (m, 1H), 7.05 (d, *J* = 8.3 Hz, 2H), 5.35 - 5.25 (m, 2H), 3.26 (d, *J* = 5.2 Hz, 2H), 1.99 - 1.86 (m, 4H), 1.34 (s, 12H), 0.89 - 0.85 (m, 6H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 152.0, 143.3, 133.2, 128.2, 127.8, 127.1, 126.2, 83.3, 41.6, 25.7, 25.7, 25.0, 24.7, 15.1, 14.0. **^{11}B NMR** (160 MHz, $CDCl_3$) δ 31.4 ppm. **HRMS (CI)** Calc. for $C_{21}H_{31}BO_2$ [M$^+$]: 326.2417, found 326.2419.

*Reaction performed at 60 °C. When reaction was performed at 50 °C a *Z,E*/*Z,Z* mixture (92:8) was obtained.

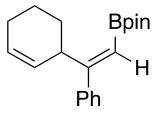
4,4,5,5-Tetramethyl-2-((1*E*,4*E*)-3-methyl-2-phenylhexa-1,4-dien-1-yl)-1,3,2-dioxaborolane (2.31)



Obtained in from of **2.60**, **2.72** and B_2pin_2 as yellow oil after column chromatography (hexane/CH_2Cl_2, 7:1) in 66% yield (98.4 mg). Reaction time: 2 h (toluene). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.30 - 7.22 (m, 5H), 5.67 - 5.50 (m, 2H), 5.37 (s, 1H), 4.23 - 4.05 (m, 1H), 1.69 (d, *J* = 5.8 Hz, 3H),

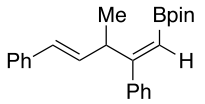
1.31 (s, 12H), 1.10 (d, J = 7.0 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 167.4, 143.7, 135.7, 127.6, 127.5, 126.9, 123.8, 83.0, 40.9, 24.9, 24.8, 19.3, 18.0. **^{11}B NMR** (160 MHz, $CDCl_3$) δ 22.4 ppm. **HRMS (CI)** Calc. for $C_{19}H_{27}BO_2$ [M^+]: 298.2104, found 298.2125.

(*E*)-2-(2-(Cyclohex-2-en-1-yl)-2-phenylvinyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (2.32)



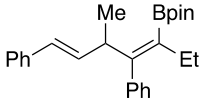
Obtained at from **2.60**, **2.73** and B_2pin_2 in toluene as a colorless oil after column chromatography (hexane/CH_2Cl_2, 7:1) in 68% yield (105.5 mg). Reaction time: 8 h (toluene 75 ºC) **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.41 - 7.35 (m, 2H), 7.25-7.22 (m, 3H), 5.77-5.70 (m, 2H), 5.50 (s, 1H), 4.12-4.05 (m, 1H), 2.05 - 1.98 (m, 2H), 1.87 - 1.72 (m, 2H), 1.70 - 1.56 (m, 2H), 1.30 (s, 12H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 166.4, 143.9, 131.6, 127.6, 127.3, 127.1, 127.1, 83.0, 42.0, 29.5, 24.8, 24.6, 22.4. **^{11}B NMR** (160 MHz, $CDCl_3$) δ 22.4 ppm. **HRMS (CI)** Calc. for $C_{20}H_{27}BO_2$ [M^+]:310.2104, found 310.2107.

4,4,5,5-Tetramethyl-2-((1*E*,4*E*)-3-methyl-2,5-diphenylpenta-1,4-dien-1-yl)-1,3,2-dioxaborolane (2.33)



Obtained in toluene from **2.60**, **2.38** and B_2pin_2 in toluene as yellow oil after column chromatography (hexane/CH_2Cl_2, 5:1) in 76% yield (136.9 mg). Reaction time: 2 h (toluene). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.41 - 7.19 (m, 10H), 6.53 - 6.34 (m, 2H), 5.47 (s, 1H), 4.43 - 4.31 (m, 1H), 1.33 (s, 12H), 1.23 (d, J = 7.0 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 166.7, 143.5, 138.0, 135.2, 128.6, 128.5, 127.6, 127.5, 127.1, 126.9, 126.1, 83.1, 41.1, 24.8, 19.1. **^{11}B NMR** (160 MHz, $CDCl_3$) δ 29.9 ppm. **HRMS (CI)** Calc. for $C_{24}H_{29}BO_2$ [M^+]: 360.2261, found 360.2260.

4,4,5,5-Tetramethyl-2-((*3Z,6E*)-5-methyl-4,7-diphenylhepta-3,6-dien-3-yl)-1,3,2-dioxaborolane (2.34)



Obtained in toluene from **2.4**, **2.38** and B_2pin_2 as 1:1 mixture of **2.34**:**2.8** that could not be separated by column chromatography. Yield (51%) calculated by NMR analysis of the isolated mixture. Reaction time: 5 h (toluene). The presence of side product **2.8** was detected in a 48% and could not be separated by column chromatography. Spectroscopic data collected only for product **2.34**. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.39 - 7.21 (m, 8H) (overlapped with Ar-H from **2.8**), 7.06 - 6.97 (m, 2H), 6.35 (d, J = 16.0 Hz, 1H), 6.16 (dd, J = 16.0, 7.0 Hz, 1H), 4.08 (p, J = 7.0 Hz, 1H), 1.87 (q, J = 7.5, 2H), 1.33 (s, 12H), 1.21 (d, J = 7.0 Hz, 3H), (overlapped with CH_3 from **2.8**), 0.86 (t, J = 7.5 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 155.6, 141.4, 140.0, 138.1, 128.9, 128.4, 128.1, 127.4, 127.0, 126.1, 83.3, 42.9, 24.8, 22.7, 14.6. **^{11}B NMR** (160 MHz, $CDCl_3$) δ 31.3 ppm.

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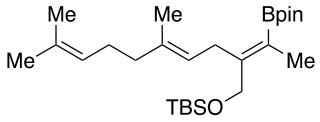
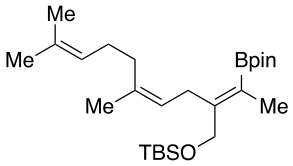
tert-Butyl(((2*Z*,4*E*)-5,9-dimethyl-2-(1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)ethylidene)deca-4,8-dien-1-yl)oxy)dimethylsilane (2.35)



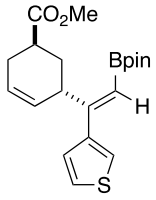
Obtained from **2.53**, **2.39** and B_2pin_2 as yellow oil, after filtration through a silica plunger without using CH_2Cl_2 as eluent, in 92% yield (206.3 mg). Reaction time: 5 h (THF reflux). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 5.18 - 5.03 (m, 2H), 4.18 (s, 2H), 3.19 (d, J = 6.9 Hz, 2H), 2.12 - 1.90 (m, 4H), 1.70 (s, 3H), 1.67 (s, 6H), 1.59 (s, 3H), 1.26 (s, 12H), 0.90 (s, 9H), 0.05 (s, 6H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 153.1, 135.0, 131.3, 124.7, 123.9, 83.1, 61.2, 40.0, 31.9, 26.9, 26.1, 25.9, 25.0, 18.5, 17.8, 16.4, 15.9, -5.2. **^{11}B NMR** (160 MHz, $CDCl_3$) δ 22.5 ppm. **HRMS (CI)** Calc. for $C_{20}H_{34}BO_2$ [M-TBS] 317.2652, found 317.2650.

tert-Butyl(((2*Z*,4*Z*)-5,9-dimethyl-2-(1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)ethylidene)deca-4,8-dien-1-yl)oxy)dimethylsilane (2.36)



Obtained from **2.53**, **2.40** and B_2pin_2 as a yellow oil, after filtration through a silica plunger using CH_2Cl_2 as eluent in 83% yield (185.9 mg). Reaction time: 5 h (THF reflux). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 5.19 - 5.07 (m, 2H), 4.18 (s, 2H), 3.18 (d, J = 7.1 Hz, 2H), 2.20 - 2.02 (m, 4H), 1.70 (s, 3H), 1.67 (s, 6H), 1.60 (s, 3H), 1.26 (s, 12H), 0.89 (s, 9H), 0.05 (s, 6H).**^{13}C NMR** (75 MHz, $CDCl_3$) δ 153.0, 135.3, 131.3, 124.8, 124.5, 83.1, 61.1, 32.1, 31.7, 26.8, 26.1, 25.9, 24.9, 23.6, 18.5, 17.8, 15.9, -5.2. **^{11}B NMR** (160 MHz, $CDCl_3$) δ 22.4 ppm. **HRMS (CI)** Calc. for $C_{20}H_{34}BO_2$ [M-TBS] 317.2652, found 317.2652.

Methyl (1*R,5*S**)-5-((*E*)-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1-(thiophen-3- yl)vinyl)cyclohex-3-ene-1-carboxylate (2.49)**



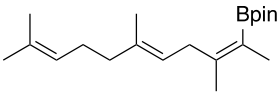
Obtained from **2.47**, **2.48** and B_2pin_2 as a yellow oil after column chromatography (hexane/Et_2O 5:1) in 90% yield. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.37 - 7.36 (m, 1H), 7.22 - 7.17 (m, 2H), 5.86 - 5.80 (m, 1H), 5.79 - 5.75 (m,1H), 5.66 (s, 1H), 4.12 - 4.06 (m, 1H), 3.69 (s, 3H), 2.76 - 2.71 (m, 1H), 2.46 - 2.40 (m, 1H), 2.28 - 2.22 (m, 1H), 2.14 - 2.08 (m, 1H), 1.99 - 1.92 (m, 1H), 1.28 (s, 12H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 175.8, 158.5, 143.9, 130.9, 127.6, 126.2, 124.7, 122.2, 83.3, 52.8, 38.7, 37.2, 30.1, 26.3, 25.02, 24.7. **^{11}B NMR** (300 MHz, $CDCl_3$): δ 30.16. **HRMS** (APCI) m/z: Calc. for $C_{20}H_{28}BO_4S$ [$M+H^+$] 375.1796, found 375.1800.

2.3.1. Synthesis of (*Z,E*)-α -homofarnesene (2.52)

4,4,5,5-Tetramethyl-2-((2*E*,5*E*)-3,6,10-trimethylundeca-2,5,9-trien-2-yl)-1,3,2-dioxaborolane (2.51)

According to the general procedure for the Cu/Pd-catalyzed allylboration of alkynes, *tert*-butyl geranyl carbonate **2.39** (508.7 mg, 2.0 mmol, 2-butyne **2.50** (649.1 mg, 12.0 mmol) and B_2pin_2 (2.0 mmol, 514.1 mg) were reacted in toluene (3 mL) at 75 °C for 35

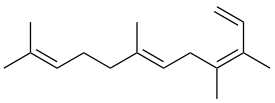
minutes. Toluene was removed from the reaction mixture under reduced pressure and the resulting crude mixture was diluted in Et_2O (10 mL), washed with aq. NH_4Cl (2 x 10 mL) and water (1 x 10 mL). The organic layer was dried over Na_2SO_4, filtered and taken to dryness. The residue was purified by column chromatography (hexane/CH_2Cl_2, 2:1) affording the desired product **2.52** as colorless oil (458.3 mg, 72%% yield).



^{1}H NMR (300 MHz, $CDCl_3$) δ 5.14 - 5.00 (m, 2H), 3.09 (d, *J* = 7.3 Hz, 2H), 2.10 - 1.95 (m, 4H), 1.66 (s, 12H), 1.59 (s, 3H), 1.25 (s, 12H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 151.5, 135.4, 131.4, 124.6, 123.6, 82.9, 40.0, 37.1, 27.9, 26.9, 25.9, 25.0, 18.9, 17.8, 16.8. **^{11}B NMR** (160 MHz, $CDCl_3$) δ 22.6 ppm. **HRMS (CI)** Calc. for $C_{20}H_{35}BO_2$ [M^+]:318.2730, found 318.2741.

(3*Z*,6*E*)-3,4,7,11-Tetramethyldodeca-1,3,6,10-tetraene ((*Z*,*E*)-α-homofarnesene) (2.52)

In a Schlenk tube, $Pd(dba)_2$ (19.6 mg, 0.03 mmol) and SPhos (13.9 mg, 0.03 mmol) were dissolved in 2 mL of 1,4-dioxane. Next, and in this order, product **2.51** (107.0 mg, 0.34 mmol), vinyl bromide 1.0 M in THF (0.5 mL, 0.50 mmol) and aq. NaOH 2.0 M (0.35 mL, 0.67 mmol) were added and the resulting mixture was heated at 70 °C for 12 h. The solvent was removed under vacuum and the residue was diluted in Et_2O (10 mL), washed with aq. NH_4Cl (2 x 5 mL) and water (1 x 5 mL). The organic layer was dried over Na_2SO_4, filtered and taken to dryness. The residue was purified by column chromatography (hexane) affording the desired product **2.52** as a colorless oil (52.7 mg, 71% yield).



^{1}H NMR (300 MHz, $CDCl_3$) δ 6.87 (dd, *J* = 17.2, 10.9 Hz, 1H), 5.13 (d, *J* = 17.2), 5.10-5.04 - (m, 2H), 4.95 (d, *J* = 10.9 Hz), 2.91 (d, *J* = 7.1 Hz, 2H), 2.11 - 1.91 (m, 4H), 1.78 (s, 3H), 1.77 (s, 3H), 1.67 (s, 6H), 1.61 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 135.8, 135.8, 135.3, 131.5, 126.9, 124.4, 122.6, 111.3, 39.9, 32.9, 26.8, 25.9, 19.9, 17.9, 16.3, 13.9. **HRMS (CI)** Calc. for $C_{16}H_{26}$ [M^+]: 218.2035, found 218.1925.

2.3.2. Synthesis of isosesquilavandulyl alcohol (2.56)

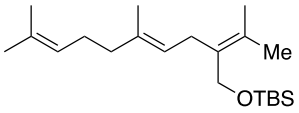
Synthesis of 2.54 on 3.0 mmol scale

CuCl (2 mol%, 0.06 mmol, 5.9 mg) and tricyclohexylphosphine (5 mol%, 0.06 mmol, 16.8 mg) were dissolved in dry THF (5 mL), stirred during 15 minutes at r.t. and added to a flask containing B_2pin_2 (1.0 equiv, 3.0 mmol, 761.8 mg) and NaO*t*-Bu (2.0 equiv, 6.0 mmol, 577.2 mg) to afford a red suspension. In a separate vial $Pd(dba)_2$ (2 mol%, 0.06 mmol, 34.5 mg) and dppf (2 mol%, 0.06 mmol, 33.2 mg), **2.53** (1.0 equiv, 3.0 mmol, 553.0 mg) and **2.39** (1.1 equiv, 3.3 mmol, 839.0 mg) were stirred in THF (5 mL) for 15 minutes at r.t. This solution was finally added to the reaction flask and heated at 75 °C for 3 h. After this time, the reaction was quenched by addition of saturated aqueous solution of NH_4Cl (10 mL), extracted with Et_2O (2 x 10 mL) and washed with water (2 x 10 mL). The organic layer was dried over Na_2SO_4, filtered and solvent was removed

under vacuum. The residue was dissolved in CH_2Cl_2 and filtration over a silica gel plunger afforded pure product in 92% yield (1.24 g).

(*E*)-*tert*-Butyl((5,9-dimethyl-2-(propan-2-ylidene)deca-4,8-dien-1-yl)oxy)dimethylsilane (2.55)

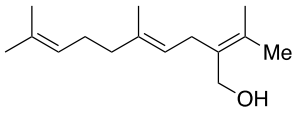
In a dry vial and under Ar atmosphere, a solution of **2.54** (90.0 mg 0.2 mmol) in THF (2 mL) was taken to -78 °C. MeLi (0.4 mmol, 0.25 mL 1.6 M in Et_2O) was then added and the mixture was allowed to reach r.t. and stirred at that temperature for 1 h. The reaction mixture was taken again to -78 °C and a solution of I_2 (101.5 mg, 0.4 mmol) in dry MeOH (3 mL) was added, letting reach r.t for 1 hour. The reaction was quenched by addition of $Na_2S_2O_3$ aq. (10 mL), washed with water and extracted to Et_2O. The organic layer was dried over Na_2SO_4, filtered and solvents were evaporated. The crude product was purified by column chromatography (Hexane/CH_2Cl_2, 4:1) to afford pure **2.55** as colorless oil (57 mg, 87% yield).



^{1}H NMR (300 MHz, $CDCl_3$) δ 5.19 - 4.95 (m, 2H), 4.12 (s, 2H), 2.85 (d, J = 7.0 Hz, 2H), 2.15 - 1.92 (m, 4H), 1.71 (s, 3H), 1.70 - 1.65 (m, 9H), 1.60 (d, J = 1.3 Hz, 3H), 0.91 (s, 9H), 0.06 (s, 6H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 134.8, 131.8, 131.3, 128.0, 124.6, 123.3, 62.0, 40.0, 28.7, 26.9, 26.2, 25.9, 20.8, 20.3, 18.6, 17.8, 16.2, -5.1. **HRMS (CI)** Calc. for $C_{21}H_{40}OSi$ [M^+]: 336.2848, found 336.2845.

(*E*)-5,9-Dimethyl-2-(propan-2-ylidene)deca-4,8-dien-1-ol (2.56)

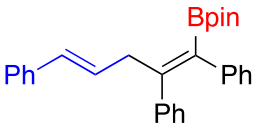
In a dry vial and under Ar atmosphere, 0.34 mL of TBAF 1.0 M in THF were added to a solution of **2.55** (57 mg, 0.17 mmol) in THF and the reaction mixture was stirred at r.t. for 3 h. The reaction mixture was then washed with aq. NH_4Cl (2 x 5 mL) and water (10 mL). The organic layer was dried over Na_2SO_4, filtered and taken to dryness to yield the desired product **2.56** (colorless oil, 36.1 mg, 96% yield).



^{1}H NMR (500 MHz, $CDCl_3$) δ 5.11 - 5.04 (m, 2H), 4.11 (s, 2H), 2.87 (d, *J* = 7.2 Hz, 2H), 2.11 - 2.05 (m, 2H), 2.03 - 1.98 (m, 2H), 1.76 (s, 3H), 1.72 (s, 3H), 1.70 - 1.65 (m, 6H), 1.60 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 136.0, 131.7, 131.6, 130.2, 124.4, 122.9, 62.5, 39.9, 29.9, 26.8, 25.8, 20.7, 20.4, 17.8, 16.2. **HRMS (CI)** Calc. for $C_{15}H_{26}O$ [M-OH]: 205.1956, found 205.1956.

2.3.3. X-ray diffraction analysis data of product 2.13

Product **2.13** was dissolved in CH_2Cl_2 and cold hexane was added, leaving to slow evaporation overnight to yield colorless needle type of crystals of an approximate dimensions 0.046 mm x 0.087 mm x 0.588 mm. The X-ray intensity data were measured on a κ-geometry diffractometer system equipped with a graphite monochromator and a MoKα sealed x-ray tube (λ = 0.71073 Å). The structure was solved and refined using the Bruker SHELXTL Software Package. CCDC number 1572585.



2.13

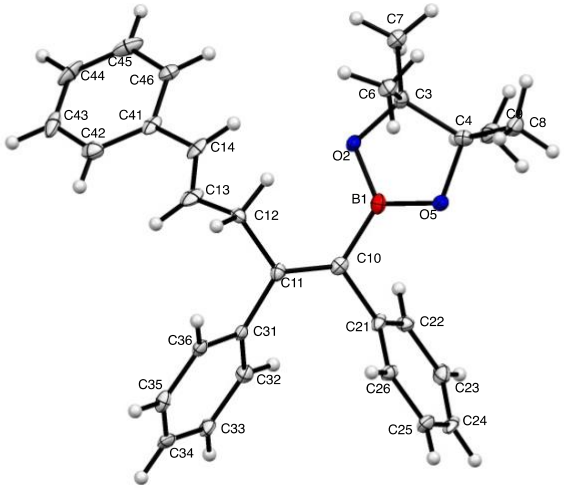


Figure 28. ORTEP plot of product **2.13** with 30% ellipsoids. Selected bond distances (Å) and angles (º): C14-C13 (1.288), C10-C11 (1.351), B1-C10 (1.553), C10-C21 (1.521), C14-C41 (1.499); C13-C12-C11 (111.3), C11-C10-B1 (125.3).

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3. CHAPTER III:

3.1. LIST OF STARTING MATERIALS

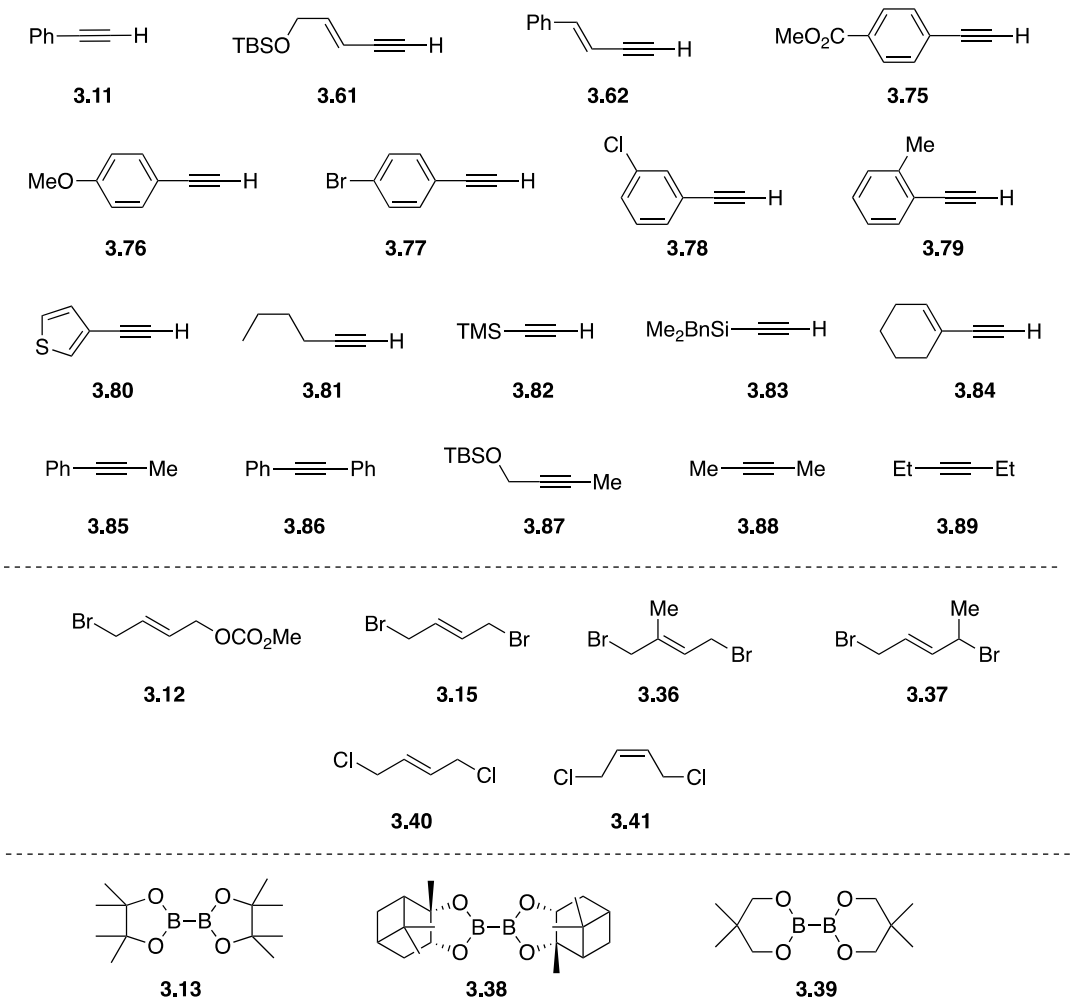


Figure 29. List of starting materials.

Alkynes **3.11**, **3.75-3.82, 3.84-3.86**, **3.88-3.89**, allyl derivates **3.15**, **3.40** and **3.41** and diboron compounds **3.13**, **3.38** and **3.39** were obtained from commercial sources. Alkynes **3.61,**[384] **3.62**,[385] **3.83**[386] and **3.87**,[387] and allyl derivates **3.12**,[388] **3.36**[389] and **3.37**[390] were prepared under described conditions.

[384] Mahapatra, S.; Carter, R. G. *J. Am. Chem. Soc.* **2013**, *135*, 10792-10803.
[385] Nakamura, S.; Hayama, D. *Angew. Chem. Int. Ed.* **2017**, *56*, 8785-8789.
[386] Denmark, S. E.; Tymonko, S. A. *J. Am. Chem. Soc.* **2005**, *127*, 8004-8005.
[387] Hesse, M. H.; Butts, C. P.; Willis, C. L.; Aggarwal, V. K. *Angew. Chem. Int. Ed.* **2012**, *51*, 1244-12448.
[388] (a) Kinoshita, M.; Takami, H.; Taniguchi, M.; Tamai, T. *Bull. Chem. Soc. Jpn.* **1987**, *60*, 2151-2161. (b) B. M. Trost, K. L. Sacchi, G. M. Schroeder, N. Asakawa, *Org. Lett.* **2002**, *4*, 3427-3430.
[389] A. C. Falciola, K. Tissot-Croset, H. Reyneri, A. Alexakis, *Adv. Synth. Catal.* **2008**, *350*, 1090-1100.
[390] C. Chiappe, D. Capraro, V. Conte, D. Pieraccini, *Org. Lett.* **2001**, *3*, 1061-1063.

3.2. GENERAL PROCEDURE FOR THE CU -CATALYZED SYNTHESIS OF SKIPPED DIENES AND DENDRALENES.

Method A. Cu-catalyzed allylboration of alkynes (with slow addition)

CuCl (10 mol%, 0.05 mmol) and tricyclohexylphosphine (10 mol%, 0.05 mmol) were suspended in dry toluene (1.0 mL), stirred during 15 min at r.t. and added to the reaction vial containing the diboron compound (2.0 equiv, 1.0 mmol) and NaO*t*-Bu (2.0 equiv, 1.0 mmol) to afford a red suspension. Alkyne (1.1 equiv, 0.55 mmol) in dry toluene (1.0 mL) was added and the mixture was stirred at 30 °C. A solution of the dibromobutene (1.0 equiv, 0.5 mmol) in dry toluene (1.0 mL) was added dropwise over 5 h using a syringe pump. When the addition was completed, the mixture was stirred for additional 11 h at 30 °C. Then, the reaction was filtered through a celite plunger and solvent was removed under vacuum. The final product was purified by SiO_2 column chromatography using the indicated mixture of eluents for each case.

Method B. Cu-catalyzed allylboration of alkynes

CuCl (10 mol%, 0.05 mmol) and tricyclohexylphosphine (10 mol%, 0.05 mmol) were suspended in dry toluene (1.0 mL), stirred during 15 min at r.t. and added to the reaction vial containing the diboron compound (2.0 equiv, 1.0 mmol) and NaO*t*-Bu (2.0 equiv, 1.0 mmol) to afford a red suspension. Alkyne (2.0 equiv, 1.0 mmol) and dibromobutene (1.0 equiv, 0.5 mmol) were added in dry toluene (2.0 mL) to the reaction mixture and heated at 30 ºC for 16 h. After this time, the reaction was filtered through a celite plunger and solvent was removed under vacuum. The final product was purified by SiO_2 column chromatography using the indicated mixture of eluents for each case.

Method C. One-pot synthesis of dendralenes

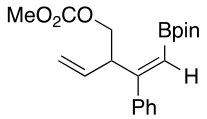
CuCl (10 mol%, 0.05 mmol) and tricyclohexylphosphine (10 mol%, 0.05 mmol) were suspended in dry toluene (1.0 mL), stirred during 15 minutes at r.t. and added to the reaction vial containing the diboron compound (2.0 equiv, 1.0 mmol) and NaO*t*-Bu (2.0 equiv, 1.0 mmol) to afford a red suspension. Alkyne (1.1 equiv, 0.55 mmol) in dry toluene (1.0 mL) was added and the mixture was stirred at 30 °C. A solution of the dibromobutene (1.0 equiv, 0.5 mmol) in dry toluene (1.0 mL) was added dropwise over 5 h using a syringe pump. When the addition was completed, the mixture was stirred for additional 11 h at 30 °C. Then, DBU (1.5 equiv, 0.75 mmol) was added to the solution and stirred at 30 °C for the indicated time. Then, the reaction was quenched by addition of saturated aqueous NH_4Cl solution (10 mL) and extracted with CH_2Cl_2 (2x10 mL). The organic layer was dried over Na_2SO_4, filtered and the solvent was removed under vacuum. The final product was purified by SiO_2 column chromatography using the indicated mixture of eluents for each case.

Method D. Dehydrohalogenation of skipped dienes

To a solution of the corresponding diene (1.0 equiv, 0.25 mmol) in dry CH_2Cl_2 (1.25 mL), DBU (1.5 or 3.0 equiv, 0.38 or 0.75 mmol) was added. The reaction was stirred at the indicated temperature for the indicated time. Then, the reaction was quenched by addition of saturated aqueous NH_4Cl solution (5 mL) and extracted with CH_2Cl_2 (2x5 mL). The organic layer was dried over Na_2SO_4, filtered and solvent was removed under vacuum. The final product was purified by SiO_2 filtration using CH_2Cl_2 as eluent or by SiO_2 column chromatography using the indicated mixture of eluents for each case.

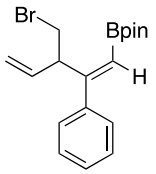
3.3. COMPOUND CHARACTERIZATION

(*E*)-methyl (3-phenyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2-vinylbut-3-en-1-yl) carbonate (3.14)



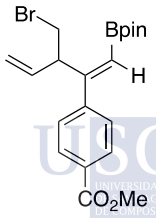
Obtained from **3.11**, **3.12** and **3.13** as a yellow oil after column chromatography (hexane/CH_2Cl_2, 9:1) in 35% yield, following method B. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.32 - 7.24 (m, 5H), 5.98 (ddd, *J* = 17.1, 10.4, 6.5 Hz, 1H), 5.57 (s, 1H), 5.23 (d, *J* = 16.9 Hz, 1H), 5.16 (d, *J* = 10.3 Hz, 1H), 4.46 - 4.30 (m, 2H), 4.18 (dd, *J* = 9.8, 7.0 Hz, 1H), 3.74 (s, 3H), 1.30 (s, 12H) ppm. **^{13}C NMR** (75 MHz, $CDCl_3$) δ 161.2, 155.7, 143.3, 137.2, 128.0, 127.6, 127.5, 116.9, 83.4, 69.1, 54.7, 47.6, 24.9 ppm.

(*E*)-2-(3-(Bromomethyl)-2-phenylpenta-1,4-dien-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (3.16)



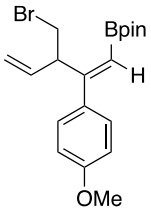
Obtained from **3.11**, **3.15** and **3.13** as a yellow oil after column chromatography (hexane/CH_2Cl_2, 9:1) in 82% yield, following method A. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.33-7.27 (m, 5H), 5.97 (ddd, J = 17.4, 10.3, 7.2 Hz, 1H), 5.56 (s, 1H), 5.33 - 5.11 (m, 2H), 4.43 (q, J = 7.2 Hz, 1H), 3.55 (dd, J = 9.8, 7.2 Hz, 1H), 3.43 (dd, J = 9.8, 7.2 Hz, 1H), 1.31 (s, 12H) ppm. **^{13}C NMR** (75 MHz, $CDCl_3$) δ 162.1, 142.8, 138.5, 128.0, 127.7, 117.1, 83.5, 50.9, 35.1, 24.9 ppm. **^{11}B NMR** (160 MHz, $CDCl_3$): δ 29.7 ppm **HRMS (CI)** Calc. for $C_{18}H_{25}BBrO_2$ $[M+H^+]$: 363.1131, found 363.1141.

(*E*)-Methyl 4-(3-(bromomethyl)-1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)penta-1,4-dien-2-yl)benzoate (3.17)



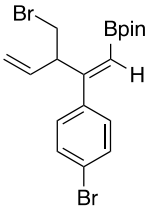
Obtained from **3.75**, **3.15** and **3.13** as a yellow oil after column chromatography (hexane/CH_2Cl_2, from 9:1 to 1:1) in 72% yield, following method A. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.95 (d, J = 8.3 Hz, 2H), 7.37 (d, J = 8.3 Hz, 2H), 5.94 (ddd, J = 17.3, 10.3, 7.0 Hz, 1H), 5.60 (s, 1H), 5.27 - 5.12 (m, 2H), 4.43 (dt, J = 9.0, 7.0 Hz, 1H), 3.90 (s, 3H), 3.53 (dd, J = 9.9, 7.0 Hz, 1H), 3.38 (dd, J = 9.9, 9.0 Hz, 1H), 1.31 (s, 12H) ppm. **^{13}C NMR** (75 MHz, $CDCl_3$) δ 167.0, 160.9, 147.5, 138.2, 129.4, 127.8, 117.3, 83.6, 52.2, 50.6, 34.5, 24.9 ppm. **^{11}B NMR** (160 MHz, CDCl3) δ 29.9 ppm. **HRMS (CI)** Calc. for $C_{20}H_{27}BBrO_4$ $[M+ H^+]$: 421.1186 found 421.1169.

(*E*)-2-(3-(Bromomethyl)-2-(4-methoxyphenyl)penta-1,4-dien-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (3.18)



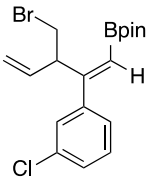
Obtained from **3.76**, **3.15** and **3.13** as a yellow oil after column chromatography (hexane/CH_2Cl_2, from 9:1 to 7:3) in 63% yield, following method A. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.27 (d, J = 8.7 Hz, 2H), 6.81 (d, J = 8.7 Hz, 2H), 6.01 (ddd, J = 17.3, 10.3, 7.9 Hz, 1H), 5.56 (s, 1H), 5.33 - 5.01 (m, 2H), 4.43 (q, J = 7.9 Hz, 1H), 3.79 (s, 3H), 3.58 (dd, J = 9.8, 7.9 Hz, 1H), 3.44 (dd, J = 9.8, 7.9 Hz, 1H), 1.30 (s, 12H) ppm. **^{13}C NMR** (75 MHz, $CDCl_3$) δ 161.6, 159.2, 138.7, 135.2, 128.8, 116.9, 113.4, 83.4, 55.3, 50.7, 35.1, 25.0 ppm. **^{11}B NMR** (160 MHz, $CDCl_3$) δ 30.6 ppm. **HRMS (CI)** Calc. for $C_{19}H_{27}BBrO_3$ [M+ H^+]: 393.1267 found 393.1238.

(*E*)-2-(3-(Bromomethyl)-2-(4-bromophenyl)penta-1,4-dien-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (3.19)



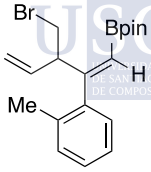
Obtained from **3.77**, **3.15** and **3.13** as a yellow oil after column chromatography (hexane/CH_2Cl_2, 9:1) in 78% yield, following method A. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.40 (d, *J* = 8.5 Hz, 2H), 7.18 (d, *J* = 8.5 Hz, 2H), 5.93 (ddd, *J* = 17.3, 10.3, 6.9 Hz, 1H), 5.55 (s, 1H), 5.30 - 5.07 (m, 2H), 4.43 (dt, *J* = 8.4, 6.9 1H), 3.53 (dd, *J* = 9.8, 6.9 Hz, 1H), 3.37 (dd, *J* = 9.8, 8.4 Hz, 1H), 1.30 (s, 12H) ppm. **^{13}C NMR** (75 MHz, $CDCl_3$) δ 160.6, 141.6, 138.2, 131.1, 129.3, 121.8, 117.2, 83.5, 50.4, 34.5, 24.9 ppm. **^{11}B NMR** (160 MHz, $CDCl_3$) δ 29.6 ppm. **HRMS (APCI)** Calc. for $C_{18}H_{24}BBr_2O_2$ [M+H^+]: 441.0231 found 441.0229.

(*E*)-2-(3-(bromomethyl)-2-(3-chlorophenyl)penta-1,4-dien-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (3.20)



Obtained from **3.78**, **3.15** and **3.13** as a yellow oil after column chromatography (From hexane to hexane/CH_2Cl_2 9:1) in 76% yield, following method A. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.24 - 7.13 (m, 4H), 5.89 (ddd, *J* = 17.3, 10.3, 7.1 Hz, 1H), 5.52 (s, 1H), 5.34 - 5.08 (m, 2H), 4.37 (dt, *J* = 8.5, 7.9 Hz, 1H), 3.52-3.42 (m, 1H), 3.35 (dd, *J* = 9.7, 8.7 Hz, 1H), 1.27 (s, 12H) ppm. **^{13}C NMR** (75 MHz, $CDCl_3$) δ 160.4, 144.6, 138.1, 133.9, 129.3, 127.8, 125.9, 117.4, 83.6, 50.6, 34.6, 24.9 ppm. **^{11}B NMR** (160 MHz, $CDCl_3$) δ 29.7 ppm. **HRMS (APCI)** Calc. for $C_{18}H_{24}BBrClO_2$ [M+H^+]: 397.0739 found 397.0740.

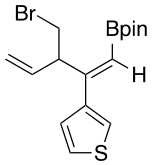
(*E*)-2-(3-(Bromomethyl)-2-(*o*-tolyl)penta-1,4-dien-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (3.21)



Obtained from **3.79**, **3.15** and **3.13** as a yellow oil after column chromatography (hexane/CH_2Cl_2, 9:1) in 73% yield, following method A. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.21 - 6.98 (m, 4H), 5.63 (ddd, *J* = 17.1, 10.1, 8.7 Hz, 1H), 5.35 (s, 1H), 5.23 (dd, *J* = 17.1, 1.7, 1H), 5.12 (dd, *J* = 10.1, 1.7, 1H), 4.35 (dt, *J* = 8.5, 7.2 Hz, 1H), 3.54 (dd, *J* = 9.7, 7.0 Hz, 1H), 3.44 (dd, *J* = 9.7, 8.4 Hz, 1H), 2.25 (s, 3H), 1.34 (s, 12H) ppm. **^{13}C NMR** (75 MHz, $CDCl_3$) δ 161.5, 142.2, 137.9, 135.1, 130.5, 127.7, 127.1, 125.0, 117.6, 83.5, 52.4, 35.6,

24.9, 20.7 ppm. **^{11}B NMR** (160 MHz, $CDCl_3$) δ 29.7 ppm. **HRMS (APCI)** Calc. for $C_{19}H_{27}BBrO_2$[M+H$^+$]: 377.1285 found 377.1282.

(*E*)-2-(3-(Bromomethyl)-2-(thiophen-3-yl)penta-1,4-dien-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (3.22)

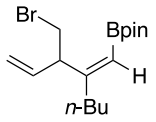


Obtained from **3.80**, **3.15** and **3.13** as a colorless oil after column chromatography (hexane/CH_2Cl_2, 9.5:0.5) in 66% yield, following method B. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.28 (dd, *J* = 2.9, 1.4 Hz, 1H), 7.23 (dd, *J* = 5.0, 3.0 Hz, 1H), 7.15 (dd, *J* = 5.0, 1.4 Hz, 1H), 6.06 (ddd, *J* = 17.1, 10.4, 6.8 Hz, 1H), 5.74 (s, 1H), 5.34 - 5.09 (m, 2H), 4.48 (dt, *J* = 7.7, 7.3 Hz, 1H), 3.63 (dd, *J* = 9.8, 7.4 Hz, 1H), 3.50 (dd, *J* = 9.8, 8.3 Hz, 1H), 1.30 (s, 12H) ppm. **^{13}C NMR** (75 MHz, $CDCl_3$) δ 156.1, 142.8, 138.5, 127.7, 125.2, 122.6, 117.1, 83.5, 50.3, 34.9, 25.0 ppm. **^{11}B NMR** (160 MHz, $CDCl_3$) δ 29.7 ppm. **HRMS (CI)** Calc. for $C_{16}H_{22}BBrO_2S$ [M$^+$]: 369.0695, found 369.0708.

(*Z*)-2-(2-(1-Bromobut-3-en-2-yl)hex-1-en-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (3.23) and (*E*)-2-(3-(Bromomethyl)nona-1,4-dien-5-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (3.23')

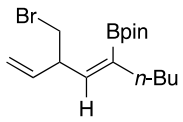
Obtained from **3.81**, **3.15** and **3.13** as a mixture of regioisomers (3.6:1) which can be separated by column chromatography (hexane/CH_2Cl_2, from 9:1) obtaining both as a colorless oil in 62 and 17% yield, respectively, following method B.

(*Z*)-2-(2-(1-Bromobut-3-en-2-yl)hex-1-en-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (3.23)



^{1}H NMR (300 MHz, $CDCl_3$) δ 5.85 (ddd, *J* = 17.5, 10.2, 7.6 Hz, 1H), 5.30 (s, 1H), 5.22 - 5.07 (m, 2H), 4.20 (q, *J* = 7.8 Hz, 1H), 3.53-3.45 (m, 2H), 2.05 (t, *J* = 7.7 Hz, 2H), 1.50-1.38 (m, 2H), 1.38-1.23 (m, 14H), 0.89 (t, *J* = 7.2 Hz, 3H).**^{13}C NMR** (75 MHz, $CDCl_3$) δ 164.1, 138.1, 116.9, 83.1, 51.2, 35.1, 33.8, 30.3, 24.9, 22.7, 14.2 ppm. **^{11}B NMR** (160 MHz, $CDCl_3$) δ 29.8 ppm. **HRMS (CI)** Calc. for $C_{16}H_{29}BO_2Br$ [M$^+$ H$^+$]: 343.1444 found 343.1450.

(*E*)-2-(3-(Bromomethyl)nona-1,4-dien-5-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (3.23')



^{1}H NMR (300 MHz, $CDCl_3$) δ 5.89 - 5.68 (m, 2H), 5.17 - 4.93 (m, 2H), 3.90 (p, *J* = 6.9 Hz, 1H), 3.44 - 3.30 (m, 2H), 2.13 (t, *J* = 6.8 Hz, 2H), 1.45-1.23 (m, 16H), 0.88 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 143.6, 139.1, 116.1, 83.3, 46.2, 38.0, 36.6, 32.4, 24.9, 22.4, 14.2 ppm.

(*E*)-(3-(Bromomethyl)-1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)penta-1,4-dien-2-yl)trimethylsilane (3.24)

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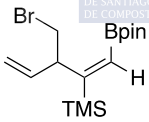
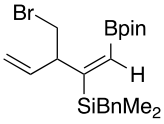


Obtained from **3.82**, **3.15** and **3.13** as a colorless oil after column chromatography (hexane/CH_2Cl_2, 9:1) in 59% yield, following method A. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 6.08 - 5.90 (m, 2H), 5.15-5.09 (m, 2H), 3.96 (q_{ap}, *J* = 8.3 Hz, 1H), 3.64 (t, *J* = 9.6 Hz, 1H), 3.45 (dd, *J* = 9.6, 6.1 Hz, 1H), 1.29 (s, 12H), 0.13 (s, 9H) ppm. **^{13}C NMR** (75 MHz, $CDCl_3$) δ 168.8, 138.9, 117.1, 83.6, 52.6,

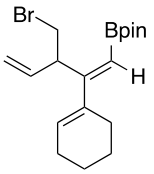
36.2, 24.9, -0.1 ppm. **^{11}B NMR** (160 MHz, $CDCl_3$) δ 28.9 ppm. **HRMS (CI)** Calc. for $C_{15}H_{29}BBrO_2Si$ [M+H$^+$]: 359.1213, found 359.1197.

(*E*)-Benzyl(3-(bromomethyl)-1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)penta-1,4-dien-2-yl)dimethylsilane (3.25)



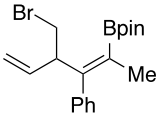
Obtained from **3.83**, **3.15** and **3.13** as a colorless oil after column chromatography (hexane/CH_2Cl_2, 9:1) in 61% yield, following method B. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.20 (t, *J* = 7.1 Hz, 2H), 7.07 (t, *J* = 7.3 Hz, 1H), 6.99 (d, *J* = 7.5 Hz, 2H), 6.06 - 5.92 (m, 2H), 5.17-5.12 (m, 1H), 3.98 (q_{ap}, *J* = 7.9 Hz, 1H), 3.64 (t, *J* = 9.3 Hz, 1H), 3.44 (dd, *J* = 9.5, 6.2 Hz, 1H), 2.21 (s, 2H), 1.31 (s, 12H), 0.08 (s, 6H) ppm. **^{13}C NMR** (75 MHz, $CDCl_3$) δ 167.1, 139.6, 138.8, 128.5, 128.3, 124.3, 117.3, 83.7, 52.4, 36.0, 26.3, 25.0, 24.9, -2.2, -2.3 ppm. **^{11}B NMR** (160 MHz, $CDCl_3$) δ 29.7 ppm. **HRMS (APCI)** Calc. for $C_{21}H_{33}BBrO_2Si$ [M+H$^+$]:435.1525, found 435.1518.

(*E*)-2-(3-(Bromomethyl)-2-(cyclohex-1-en-1-yl)penta-1,4-dien-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (3.26)



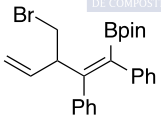
Obtained from **3.84**, **3.15** and **3.13** as a colorless oil after column chromatography (hexane/CH_2Cl_2, 9:1) in 82% yield, following method B. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 6.02 (ddd, *J* = 17.3, 10.3, 7.0 Hz, 1H), 5.86-5.79 (m, 1H), 5.39 (s, 1H), 5.21 - 5.03 (m, 2H), 4.17 (dt, *J* = 8.5, 7.0, 1H), 3.68 (dd, *J* = 9.6, 8.4 Hz, 1H), 3.56 (dd, *J* = 9.6, 7.0 Hz, 1H), 2.18 - 2.02 (m, 4H), 1.68-1.48 (m, 4H), 1.27 (s, 12H) ppm. **^{13}C NMR** (75 MHz, $CDCl_3$) δ 163.5, 139.1, 138.7, 126.5, 116.4, 83.3, 50.1, 36.0, 28.6, 25.7, 24.9, 23.1, 22.1 ppm. **^{11}B NMR** (160 MHz, $CDCl_3$) δ 29.9 ppm. **HRMS (APCI)** Calc. for $C_{18}H_{29}BBrO_2$ [M+H$^+$]: 367.1438, found 367.1439.

(*Z*)-2-(4-(Bromomethyl)-3-phenylhexa-2,5-dien-2-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (3.27)



Obtained from **3.85**, **3.15** and **3.13** as a colorless oil after column chromatography (hexane/CH_2Cl_2, 9.5:0.5) in 50% yield, following method A. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.37 - 7.26 (m, 3H), 7.06 - 6.99 (m, 2H), 5.62 (ddd, *J* = 17.4, 10.2, 8.2 Hz, 1H), 5.23 - 5.04 (m, 2H), 4.33 (q, *J* = 7.8 Hz, 1H), 3.30 (dd, *J* = 7.6, 1.3 Hz, 2H), 1.46 (s, 3H), 1.34 (s, 12H).**^{13}C NMR** (75 MHz, $CDCl_3$) δ 152.9, 139.4, 138.3, 129.0, 128.1, 126.8, 116.8, 83.6, 52.0, 35.6, 24.9, 18.3 ppm. **^{11}B NMR** (160 MHz, $CDCl_3$) δ 30.8 ppm. **HRMS (CI)** Calc. for $C_{19}H_{27}BO_2Br$ [M+H$^+$]: 377.1287 found 377.1305.

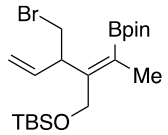
(*Z*)-2-(3-(Bromomethyl)-1,2-diphenylpenta-1,4-dien-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (3.28)



Obtained from **3.86**, **3.15** and **3.13** as a mixture of product **3.28** (71% NMR yield) and hydroboration product of alkyne (15% NMR yield), following method A. The side product could not be separated by column chromatography. Spectroscopic data collected only for product **3.28**. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.13 - 6.85 (m, 10H), 5.84 - 5.67 (m, 1H), 5.29 (d, *J* = 17.2 Hz, 1H), 5.22 (d, *J*

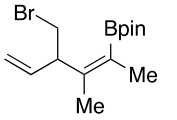
= 10.2 Hz, 1H), 4.13 (q, *J* = 7.9 Hz, 1H), 3.47 (ddd, *J* = 9.3, 7.3, 1.6 Hz, 1H), 3.37 (ddd, *J* = 9.8, 8.0, 1.8 Hz, 1H), 1.33 (s, 12H) ppm. **^{13}C NMR** (75 MHz, $CDCl_3$) δ 151.9, 140.8, 138.6, 137.8, 130.0, 129.3, 127.5, 127.5, 126.7, 125.6, 117.5, 84.1, 53.5, 35.3, 24.9 ppm. **^{11}B NMR** (160 MHz, $CDCl_3$) δ 30.8 ppm. **HRMS (APCI)** Calc. for $C_{24}H_{29}BBrO_2$ [M+H$^+$]: 439.1438 found 439.1444.

(*Z*)-((3-(Bromomethyl)-2-(1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)ethylidene)pent-4-en-1-yl)oxy)(*tert*-butyl)dimethylsilane (3.29)



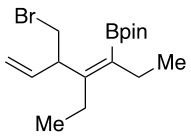
Obtained from **3.87**, **2.5** and **3.13** as a colorless oil after column chromatography (hexane/CH_2Cl_2, 9.5:0.5) in 45% yield, following method A. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 5.99 (ddd, *J* = 17.6, 9.8, 7.7 Hz, 1H), 5.17-5.11 (m, 2H), 4.31 (d, *J* = 12.1 Hz, 1H), 4.13 (d, *J* = 12.2 Hz, 1H), 4.06 (q, *J* = 7.8 Hz, 1H), 3.68 - 3.52 (m, 2H), 1.74 (s, 3H), 1.29 (s, 12H), 0.89 (s, 9H), 0.06 (s, 6H) ppm. **^{13}C NMR** (75 MHz, $CDCl_3$) δ 150.5, 138.7, 117.0, 83.6, 59.8, 52.2, 37.1, 26.1, 25.0, 24.9, 18.4, 16.3, -5.4.ppm. **^{11}B NMR** (160 MHz, $CDCl_3$) δ 30.0 ppm. **HRMS** could not be carried out due to the instability of the product.

(*E*)-2-(3-(Bromomethyl)-4-methyl-2-phenylpenta-1,4-dien-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (3.30)



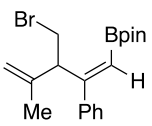
Obtained from **3.88**, **3.15** and **3.13** as a colorless oil after column chromatography (hexane/CH_2Cl_2, 9:1) in 63% yield, following method A. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.35 - 7.19 (m, 5H), 5.65 (s, 1H), 4.98 (s, 1H), 4.66 (s, 1H), 4.45 (dd, *J* = 9.7, 5.1 Hz, 1H), 3.68 (dd, *J* = 9.8, 5.3 Hz, 1H), 3.33 (t, *J* = 9.7 Hz, 1H), 1.88 (s, 3H), 1.31 (s, 12H) ppm. **^{13}C NMR** (75 MHz, $CDCl_3$) δ 160.4, 145.0, 142.2, 127.8, 127.6, 111.8, 83.3, 52.1, 34.0, 24.9, 22.9 ppm. **^{11}B NMR** (160 MHz, $CDCl_3$) δ 29.9 ppm. **HRMS (APCI)** Calc. for $C_{14}H_{25}BBrO_2$[M+H$^+$]: 315.1112 found 315.1125.

(*E*)-2-(5-(bromomethyl)-4-ethylhepta-3,6-dien-3-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (3.31)



Obtained from **3.89**, **3.15** and **3.13** as a mixture of product **3.31** (54% NMR yield) and protoboration product of alkyne (20% NMR yield), following method A. The side product could not be separated by column chromatography. Spectroscopic data collected only for product **3.31**. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 5.86 (ddd, J = 16.4, 11.0, 7.5 Hz, 1H), 5.28 - 4.92 (m, 2H), 3.94 (q, J = 7.6 Hz, 1H), 3.47 (d, J = 7.7 Hz, 2H), 2.15 (dq, J = 14.8, 7.4 Hz, 4H), 1.34 - 1.18 (m, 12H), 1.00 (t, J = 7.4 Hz, 6H) ppm. **^{13}C NMR** (75 MHz, $CDCl_3$) δ 151.8, 138.2, 116.9, 83.3, 52.9, 36.2, 29.9, 24.9, 24.1, 15.3, 14.8 ppm. **HRMS (APCI)** Calc. for $C_{16}H_{29}BBrO_2$ [M+H$^+$]: 343.1438, found 343.1439.

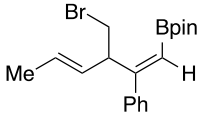
(*E*)-2-(3-(Bromomethyl)-4-methyl-2-phenylpenta-1,4-dien-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (3.32)



Obtained from **3.11**, **3.36** and **3.13** as a colorless oil after column chromatography (hexane/CH_2Cl_2, 9:1) in 63% yield, following method A. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.35 - 7.19 (m, 5H), 5.65 (s, 1H), 4.98 (s,

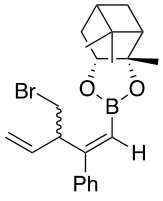
1H), 4.66 (s, 1H), 4.45 (dd, *J* = 9.7, 5.1 Hz, 1H), 3.68 (dd, *J* = 9.8, 5.3 Hz, 1H), 3.33 (t, *J* = 9.7 Hz, 1H), 1.88 (s, 3H), 1.31 (s, 12H) ppm. **^{13}C NMR** (75 MHz, $CDCl_3$) δ 160.4, 145.0, 142.2, 127.8, 127.6, 111.8, 83.3, 52.1, 34.0, 24.9, 22.9 ppm. **^{11}B NMR** (160 MHz, $CDCl_3$) δ 29.9 ppm. **HRMS (APCI)** Calc. for $C_{19}H_{27}BBrO_2$ [M+H$^+$]: 377.1282 found 377.1277.

2-((1*E*,4*E*)-3-(bromomethyl)-2-phenylhexa-1,4-dien-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (3.33)



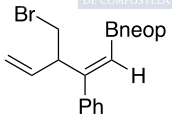
Obtained from **3.11**, **3.37** and **3.13** as a colorless oil after column chromatography (From hexane to hexane/CH_2Cl_2, 9:1) in 67% yield, following method B.**^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.42 - 7.14 (m, 5H), 5.76 - 5.41 (m, 3H), 4.36 (q, J = 7.6 Hz, 1H), 3.55 - 3.29 (m, 1H), 1.72 (d, J = 6.5 Hz, 3H), 1.31 (s, 12H) ppm. **^{13}C NMR** (75 MHz, $CDCl_3$) δ 162.8, 131.1, 128.2, 128.0, 127.9, 127.7, 127.5, 83.4, 50.1, 35.8, 24.9, 18.3 ppm. **HRMS (APCI)** Calc. for $C_{19}H_{27}BBrO_2$ [M+H$^+$]: 377.1282 found 377.1280.

(3a*S*,7a*R*, 3*R)-2-((*E*)-3-(Bromomethyl)-2-phenylpenta-1,4-dien-1-yl)-5,5,7a-trimethylhexahydro-4,6-methanobenzo[*d*][1,3,2]dioxaborole (3.34 and diast-3.34)**



Obtained from **3.11**, **3.15** and **3.38** as a yellow oil after column chromatography (hexane/CH_2Cl_2, 9:1) in 80% yield, following method B, as a 1:1 mixture of diastereomers (**3.34**+diast-**3.34**). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.35 - 7.27 (m, 5H **3.34** + 5H diast-**3.34**), 6.06 - 5.90 (m, 1H **3.34** + 1H diast-**3.34**), 5.64 - 5.57 (m, 1H **3.34** + 1H diast-**3.34**), 5.30 - 5.13 (m, 2H **3.34** + 2H diast-**3.34**), 4.45 (q, *J* = 7.1 Hz, 1H **3.34** + 1H diast-**3.34**), 4.38 (d, *J* = 7.4 Hz, 1H **3.34** + 1H diast-**3.34**), 3.61 - 3.49 (m, 1H **3.34** + 1H diast-**3.34**), 3.48 - 3.37 (m, 1H **3.34** + 1H diast-**3.34**), 2.45 - 2.32 (m, 1H **3.34** + 1H diast-**3.34**), 2.30 - 2.21 (m, 1H **3.34** + 1H diast-**3.34**), 2.11 (t, *J* = 5.4 Hz, 1H **3.34** + 1H diast-**3.34**), 2.01 - 1.86 (m, 2H **3.34** + 2H diast-**3.34**), 1.45 (s, 3H **3.34** + 3H diast-**3.34**), 1.31 (s, 3H **3.34** + 3H diast-**3.34**), 1.28 - 1.20 (m, *J* = 11.0, 2.8 Hz, 1H **3.34** + 1H diast-**3.34**), 0.88 (s, 3H **3.34** + 3H diast-**3.34**) ppm. **^{13}C NMR** (75 MHz, $CDCl_3$) δ 162.1 (**3.34** + diast-**3.34**), 142.8 (**3.34** + diast-**3.34**), 138.6 (**3.34**), 138.4 (diast-**3.34**), 128.0 (**3.34** + diast-**3.34**), 127.7 (**3.34** + diast-**3.34**), 117.1 (**3.34**), 117.0 (diast-**3.34**), 85.8 (**3.34**), 85.8 (diast-**3.34**), 78.0 (**3.34**), 77.9 (diast-**3.34**), 51.5 (**3.34** + diast-**3.34**), 50.9 (**3.34**), 50.8 (diast-**3.34**), 39.7 (**3.34** + diast-**3.34**), 38.3 (**3.34** + diast-**3.34**), 35.7 (**3.34** + diast-**3.34**), 35.0 (**3.34**), 34.9 (diast-**3.34**), 28.8 (**3.34**), 28.8 (diast-**3.34**), 27.2 (**3.34** + diast-**3.34**), 26.7 (**3.34** + diast-**3.34**), 24.2 (**3.34** + diast-**3.34**) ppm. **^{11}B NMR** (160 MHz, $CDCl_3$) δ 29.2 ppm. **HRMS (CI)** Calc. for $C_{22}H_{29}BO_2Br$ [M+H$^+$]: 415.1444 found 415.1428.

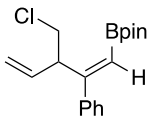
(*E*)-2-(3-(Bromomethyl)-2-phenylpenta-1,4-dien-1-yl)-5,5-dimethyl-1,3,2-dioxaborinane (3.35)



Obtained from **3.11**, **3.15** and **3.39** as an orange oil after column chromatography (hexane/CH_2Cl_2, 9:1) in 53% yield, following method B. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.33 - 7.25 (m, 5H), 5.98 (ddd, *J* = 17.3, 10.3, 6.9 Hz, 1H), 5.50 (s, 1H), 5.29 - 5.13 (m, 2H), 4.47 (q, *J* = 7.9 Hz, 1H), 3.70

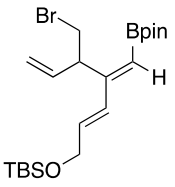
(s, 4H), 3.54 (dd, *J* = 9.7, 7.6 Hz, 1H), 3.42 (dd, *J* = 9.7, 8.0 Hz, 1H), 1.02 (s, 6H) ppm. **^{13}C NMR** (75 MHz, $CDCl_3$) δ 159.6, 143.1, 138.9, 127.9, 127.8, 127.4, 116.7, 72.3, 50.3, 35.2, 31.8, 22.0 ppm. **^{11}B NMR** (160 MHz, $CDCl_3$) δ 26.1 ppm. **HRMS (CI)** Calc. for $C_{17}H_{23}BO_2$ Br [M+H$^+$]: 349.0974 found 349.0966.

(*E*)-2-(3-(chloromethyl)-2-phenylpenta-1,4-dien-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (3.42)



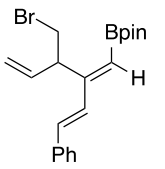
Obtained from **3.11**, **3.40** and **3.13** as a colorless oil after column chromatography (hexane/CH_2Cl_2, 9:1) in 37% yield, following method B. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.33-7.27 (m, 5H), 5.98 (ddd, *J* = 17.3, 10.3, 7.0 Hz, 1H), 5.57 (s, 1H), 5.25 (d, *J* = 17.3 Hz, 1H), 5.19 (d, *J* = 10.3 Hz, 1H), 4.38 (q, *J* = 7.0 Hz, 1H), 3.67 (dd, *J* = 10.6, 7.0 Hz, 1H), 3.57 (dd, *J* = 10.6, 7.0 Hz, 1H), 1.31 (s, 12H) ppm. **^{13}C NMR** (75 MHz, $CDCl_3$) δ 161.8, 143.0, 138.0, 128.0, 127.7, 117.1, 83.5, 51.0, 46.2, 25.0 ppm. **^{11}B NMR** (160 MHz, $CDCl_3$) δ 29.9 ppm. **HRMS (CI)** Calc. for $C_{18}H_{25}BClO_2$ [M+H$^+$]: 319.1636 found 319.1644.

(((2*E*,4*Z*)-5-(bromomethyl)-4-((4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)methylene)hepta-2,6-dien-1-yl)oxy)(*tert*-butyl)dimethylsilane (3.63)



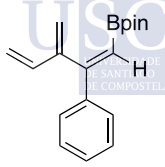
Obtained from **3.61**, **3.15** and **3.13** as a yellow oil after column chromatography (hexane/CH_2Cl_2 8:2) in 39% yield, following method A. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 6.19 (d, *J* = 15.8 Hz, 1H), 6.08 (dt, *J* = 15.8, 4.3 Hz, 1H), 5.93 (ddd, *J* = 17.3, 10.3, 7.0 Hz, 1H), 5.59 (s, 1H), 5.24 - 5.10 (m, 2H), 4.34 - 4.19 (m, 3H), 3.58 (dd, *J* = 9.8, 7.6 Hz, 1H), 3.48 (dd, *J* = 9.8, 7.9 Hz, 1H), 1.27 (s, 12H), 0.90 (s, 9H), 0.06 (s, 6H) ppm. **^{13}C NMR** (75 MHz, $CDCl_3$) δ 158.1, 138.0, 132.8, 129.2, 117.1, 83.3, 63.6, 48.9, 35.1, 26.0, 25.0, 24.9, 18.5, -5.1 ppm.

2-((*Z*)-3-(bromomethyl)-2-((*E*)-styryl)penta-1,4-dien-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (3.64)



Obtained from **3.62**, **3.15** and **3.13** as a yellow oil after column chromatography (hexane/CH_2Cl_2 75:25) in 38% yield, following method A. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.45 - 7.40 (m, 2H), 7.38 - 7.31 (m, 2H), 7.28 (td, *J* = 3.3, 2.1 Hz, 1H), 6.94 (d, *J* = 16.1 Hz, 1H), 6.71 (dd, *J* = 16.1, 0.8 Hz, 1H), 6.05 (ddd, *J* = 17.2, 10.4, 6.8 Hz, 1H), 5.81 (d, *J* = 0.8 Hz, 1H), 5.34 - 5.03 (m, 2H), 4.42 (tdt, *J* = 8.0, 6.8, 1.4 Hz, 1H), 3.69 (dd, *J* = 9.8, 7.5 Hz, 1H), 3.59 (dd, *J* = 9.9, 7.9 Hz, 1H), 1.32 (s, 12H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 158.2, 138.0, 137.0, 132.1, 128.9, 128.8, 128.2, 127.0, 117.3, 83.4, 48.8, 35.2, 25.0 ppm. **HRMS (APCI)** Calc. for $C_{20}H_{27}BO_2Br$ [M+H$^+$] 389.128199, found 389.128582.

(*E*)-4,4,5,5-Tetramethyl-2-(3-methylene-2-phenylpenta-1,4-dien-1-yl)-1,3,2-dioxaborolane (3.43)



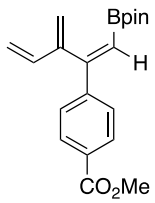
Obtained from **3.16** and 1.5 equiv of DBU under reflux for 13 h, following method D. Purified by SiO_2 filtration with CH_2Cl_2 obtaining the pure product as a yellow oil in 96% yield.

Obtained from **3.11**, **3.15** and **3.13** as a yellow oil after column chromatography (From hexane to hexane/CH_2Cl_2 8:2) in 60%, following method C.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.55 - 7.45 (m, 2H), 7.32 - 7.23 (m, 3H), 6.48 (dd, *J* = 17.4, 10.6 Hz, 1H), 6.03 (s, 1H), 5.35 (s, 1H), 5.16 (s, 1H), 5.06 - 4.96 (m, 2H), 1.24 (s,

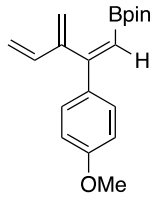
12H) ppm. **^{13}C NMR** (75 MHz, $CDCl_3$) δ 157.3, 147.8, 141.1, 138.2, 128.3, 128.1, 119.1, 83.1, 24.8 ppm. **^{11}B NMR** (160 MHz, $CDCl_3$) δ 30.6 ppm. **HRMS (APCI)** Calc. for $C_{18}H_{24}BO_2$ [M+H$^+$]: 283.1864 found 283.1862.

(*E*)-Methyl 4-(3-methylene-1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)penta-1,4-dien-2-yl)benzoate (3.44)



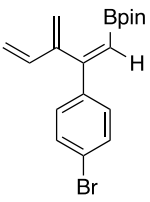
Obtained from **3.17** and 1.5 equiv of DBU under reflux for 4 h, following method D. Purified by SiO_2 filtration with CH_2Cl_2 obtaining the pure product as a yellow oil in 93% yield. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.95 (d, *J* = 8.9 Hz, 2H), 7.52 (d, *J* = 8.9 Hz, 2H), 6.47 (dd, *J* = 17.4, 10.6 Hz, 1H), 6.11 (s, 1H), 5.38 (s, 1H), 5.18 (s, 1H), 5.03 (d, *J* = 10.6 Hz, 1H), 4.94 (d, *J* = 17.4 Hz, 1H), 3.89 (s, 3H), 1.24 (s, 12H) ppm. **^{13}C NMR** (75 MHz, $CDCl_3$) δ 167.0, 156.0, 147.3, 145.5, 137.9, 129.7, 126.6, 119.6, 117.5, 83.4, 52.2, 24.8 ppm. **^{11}B NMR** (160 MHz, $CDCl_3$) δ 30.1 ppm. **HRMS (APCI)** Calc. for $C_{20}H_{26}BO_4$ [M+H$^+$]: 341.1922 found 341.1920.

(*E*)-2-(2-(4-Methoxyphenyl)-3-methylenepenta-1,4-dien-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (3.45)



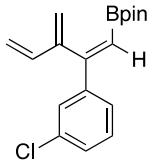
Obtained from **3.18** and 1.5 equiv of DBU under reflux for 4 h, following method D. Purified by SiO_2 filtration with CH_2Cl_2 obtaining the pure product as a yellow oil in 93% yield. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.44 (d, *J* = 8.8 Hz, 2H), 6.83 (d, *J* = 8.8 Hz, 2H), 6.49 (dd, *J* = 17.3, 10.7 Hz, 1H), 5.95 (s, 1H), 5.34 (s, 1H), 5.15 (s, 1H), 5.05-4.96 (m, 2H), 3.80 (s, 3H), 1.24 (s, 12H) ppm. **^{13}C NMR** (75 MHz, $CDCl_3$) δ 159.8, 156.9, 147.9, 138.3, 133.6, 128.0, 118.9, 117.0, 113.6, 83.0, 55.3, 24.8 ppm. **^{11}B NMR** (160 MHz, $CDCl_3$) δ 30.2 ppm. **HRMS (APCI)** Calc. for $C_{19}H_{26}BO_3$ [M+H$^+$]: 313.1973 found 313.1970.

(*E*)-2-(2-(4-Bromophenyl)-3-methylenepenta-1,4-dien-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (3.46)



Obtained from **3.19** and 1.5 equiv of DBU under reflux for 7 h, following method D. Purified by SiO_2 filtration with CH_2Cl_2 obtaining the pure product as a yellow oil in 96% yield. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.41 (d, *J* = 8.6 Hz, 2H), 7.34 (d, *J* = 8.6 Hz, 2H), 6.46 (dd, *J* = 17.4, 10.6 Hz, 1H), 6.01 (s, 1H), 5.35 (s, 1H), 5.15 (s, 1H), 5.04 (d, *J* = 10.6 Hz, 1H), 4.96 (d, *J* = 17.4 Hz, 1H), 1.23 (s, 12H) ppm. **^{13}C NMR** (75 MHz, $CDCl_3$) δ 156.0, 147.3, 140.1, 137.9, 131.4, 128.3, 122.3, 119.4, 117.4, 83.3, 24.8 ppm. **^{11}B NMR** (160 MHz, $CDCl_3$) δ 29.8 ppm. **HRMS (APCI)** Calc. for $C_{18}H_{23}BBrO_2$ [M+H$^+$]: 361.0972 found 361.0974.

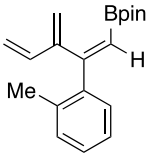
(*E*)-2-(2-(3-Chlorophenyl)-3-methylenepenta-1,4-dien-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (3.47)



Obtained from **3.20** and 1.5 equiv of DBU under reflux for 6 h, following method D. Purified by SiO_2 filtration with CH_2Cl_2 obtaining the pure product as a yellow oil in 98% yield. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.46 - 7.42 (m, 1H), 7.37 - 7.33 (m, 1H), 7.25 - 7.17 (m, 2H), 6.46 (dd, *J* = 17.4,

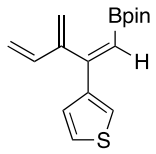
10.6 Hz, 1H), 6.02 (s, 1H), 5.36 (s, 1H), 5.16 (s, 1H), 5.05 (d, *J* = 10.6 Hz, 1H), 4.97 (d, *J* = 17.4 Hz, 1H), 1.23 (s, 12H) ppm. **^{13}C NMR** (75 MHz, $CDCl_3$) δ 155.6, 147.1, 142.9, 137.8, 134.2, 129.4, 128.0, 126.7, 124.7, 119.5, 117.4, 83.2, 24.7 ppm. **^{11}B NMR** (160 MHz, $CDCl_3$) δ 29.8 ppm. **HRMS (APCI)** Calc. for $C_{18}H_{23}BClO_2$ [M+H$^+$]: 317.1477 found 317.1479.

(*E*)-4,4,5,5-Tetramethyl-2-(3-methylene-2-(*o*-tolyl)penta-1,4-dien-1-yl)-1,3,2-dioxaborolane (3.48)



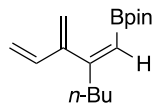
Obtained from **3.21** and 1.5 equiv of DBU under reflux for 13 h, following method D. Purified by SiO_2 filtration with CH_2Cl_2 obtaining the pure product as a yellow oil in 99% yield. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.39 - 7.32 (m, 1H), 7.32 - 7.20 (m, 3H), 6.54 (dd, *J* = 17.4, 10.8 Hz, 1H), 5.71 (s, 1H), 5.40 (s, 1H), 5.36 (d, *J* = 17.4 Hz, 1H), 5.23 (s, 1H), 5.17 (d, *J* = 10.8 Hz, 1H), 2.46 (s, 3H), 1.39 (s, 12H) ppm. **^{13}C NMR** (75 MHz, $CDCl_3$) δ 157.4, 148.6, 143.3, 138.1, 135.3, 130.6, 129.1, 127.3, 125.5, 118.6, 116.6, 83.3, 24.9, 20.8 ppm. **^{11}B NMR** (160 MHz, $CDCl_3$) δ 30.1 ppm. **HRMS (APCI)** Calc. for $C_{19}H_{26}BO_2$ [M+H$^+$]: 297.2020 found 297.2020.

(*E*)-4,4,5,5-Tetramethyl-2-(3-methylene-2-(thiophen-3-yl)penta-1,4-dien-1-yl)-1,3,2-dioxaborolane (3.49)



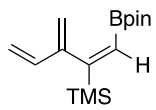
Obtained from **3.22** and 1.5 equiv of DBU under reflux for 3 h, following method D. Purified by SiO_2 filtration with CH_2Cl_2 obtaining the pure product as a yellow oil in 96% yield. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.33 - 7.29 (m, 1H), 7.29 - 7.22 (m, 2H), 6.54 (dd, *J* = 17.3, 10.5 Hz, 1H), 6.02 (s, 1H), 5.34 (s, 1H), 5.16 (s, 1H), 5.17 - 5.03 (m, 2H), 1.25 (s, 12H) ppm. **^{13}C NMR** (75 MHz, $CDCl_3$) δ 151.9, 147.7, 143.3, 138.1, 125.8, 125.4, 123.7, 118.0, 116.5, 83.0, 24.7 ppm. **^{11}B NMR** (160 MHz, $CDCl_3$) δ 32.7 ppm. **HRMS (APCI)** Calc. for $C_{16}H_{22}BO_2S$ [M+H$^+$]: 289.1431 found 289.1430.

(*Z*)-2-(2-(Buta-1,3-dien-2-yl)hex-1-en-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (3.50)



Obtained from **3.23** and 3 equiv of DBU under reflux for 16 h, following method D. Purified by SiO_2 filtration with CH_2Cl_2 obtaining the pure product as a yellow oil in 99% yield. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 6.37 (dd, *J* = 17.4, 10.6 Hz, 1H), 5.39 (s, 1H), 5.13 (d, *J* = 17.4 Hz, 1H), 5.10 - 5.00 (m, 2H), 4.91 (s, 1H), 2.21 (t, *J* = 7.6 Hz, 2H), 1.42 - 1.28 (m, 4H), 1.18 (s, 12H), 0.86 (t, *J* = 7.0 Hz, 3H) ppm. **^{13}C NMR** (75 MHz, $CDCl_3$) δ 160.9, 149.6, 138.3, 115.7, 82.8, 39.8, 30.1, 24.8, 22.4, 14.1 ppm. **^{11}B NMR** (160 MHz, $CDCl_3$) δ 30.1 ppm. **HRMS (APCI)** Calc. for $C_{16}H_{28}BO_2$ [M+H$^+$]: 263.2177 found 263.2179.

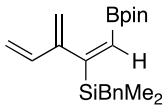
(*E*)-Trimethyl(3-methylene-1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)penta-1,4-dien-2-yl)silane (3.51)



Obtained from **3.24** and 1.5 equiv of DBU under reflux for 23 h, following method D. Purified by SiO_2 filtration with CH_2Cl_2 obtaining the pure product as a colorless oil in 99% yield. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 6.41

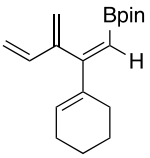
(dd, *J* = 17.2, 10.6 Hz, 1H), 6.12 (s, 1H), 5.15 - 4.83 (m, 3H), 4.71 (s, 1H), 1.19 (s, 12H), 0.06 (s, 9H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 165.8, 150.4, 139.2, 116.4, 113.4, 83.2, 24.8, -1.4 ppm. **HRMS (APCI)** Calc. for $C_{15}H_{28}BO_2Si$ [M+H$^+$]: 279.1949 found 279.1946.

(*E*)-Benzyldimethyl(3-methylene-1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)penta-1,4-dien-2-yl)silane (3.52)



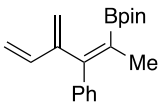
Obtained from **3.25** and 3.0 equiv of DBU at 30°C for 13 h, following method D. Purified by column chromatography (From hexane to hexane/CH_2Cl_2 1:1) obtaining the pure product as a colorless oil in 75% yield. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.19 (t, *J* = 7.5 Hz, 2H), 7.06 (d, *J* = 6.8 Hz, 1H), 6.98 (d, *J* = 7.4 Hz, 2H), 6.44 (dd, *J* = 17.3, 10.5 Hz, 1H), 6.18 (s, 1H), 5.10 - 4.98 (m, 3H), 4.74 (s, 1H), 2.16 (s, 2H), 1.21 (s, 12H), 0.00 (s, 6H) ppm. **^{13}C NMR** (75 MHz, $CDCl_3$) δ 13C NMR (75 MHz, cdcl3) δ 164.0, 150.1, 139.9, 128.4, 128.1, 124.0, 116.5, 113.6, 83.2, 25.1, 24.7, -3.7 ppm. **HRMS (APCI)** Calc. for $C_{21}H_{32}BO_2Si$ [M+H$^+$]: 355.2259 found 355.2261.

(*E*)-2-(2-(Cyclohex-1-en-1-yl)-3-methylenepenta-1,4-dien-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (5.53)



Obtained from **3.26** and 1.5 equiv of DBU under reflux for 13 h, following method D. Purified by column chromatography (From hexane to hexane/CH_2Cl_2 9:1) obtaining the pure product as a yellow oil in 90% yield. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 6.42 (dd, *J* = 17.3, 10.5 Hz, 1H), 5.96 (t, *J* = 4.2 Hz, 1H), 5.52 (s, 1H), 5.22 (s, 1H), 5.06 - 4.99 (m, 2H), 4.94 (s, 1H), 2.24 - 2.16 (m, 2H), 2.13 - 2.05 (m, 2H), 1.73 - 1.60 (m, 2H), 1.59 - 1.48 (m, 2H), 1.19 (s, 12H) ppm. **^{13}C NMR** (75 MHz, $CDCl_3$) δ 158.9, 148.0, 139.3, 136.9, 130.5, 118.0, 115.6, 82.9, 26.3, 25.5, 24.8, 23.1, 22.2 ppm. **^{11}B NMR** (160 MHz, $CDCl_3$) δ 30.8 ppm. **HRMS (APCI)** Calc. for $C_{18}H_{28}BO_2$ [M+H$^+$]: 287.2180 found 287.2181.

(*Z*)-4,4,5,5-Tetramethyl-2-(4-methylene-3-phenylhexa-2,5-dien-2-yl)-1,3,2-dioxaborolane (3.54)

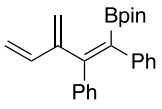


Obtained from **3.27** and 3.0 equiv of DBU at 30 °C for 15 h, following method D. Purified by column chromatography (From hexane to hexane/CH_2Cl_2 1:1) obtaining the pure product as a yellow oil in 90% yield. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.36 - 7.15 (m, 5H), 6.30 (dd, *J* = 17.5, 10.6 Hz, 1H), 5.22 - 5.10 (m, 3H), 5.02 (d, *J* = 10.6 Hz, 1H), 1.84 (s, 3H), 1.25 (s, 12H) ppm. **^{13}C NMR** (75 MHz, $CDCl_3$) δ 150.8, 148.7, 140.3, 138.0, 129.0, 127.9, 126.9, 118.5, 117.4, 83.4, 24.7, 18.1 ppm. **HRMS (APCI)** Calc. for $C_{19}H_{26}BO_2$ [M+H$^+$]: 297.2020 found 287.2024.

(*Z*)-4,4,5,5-Tetramethyl-2-(3-methylene-1,2-diphenylpenta-1,4-dien-1-yl)-1,3,2-dioxaborolane (3.55)

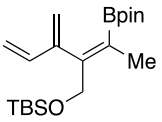
Obtained from **3.28** and 1.5 equiv of DBU at 30°C for 12 h, following method D. Purified by column chromatography (From hexane to hexane/CH_2Cl_2 8:2) obtaining the pure product as a white solid in 95% yield.

Obtained from **3.86**, **3.15** and **3.13** as a white solid after column chromatography (From hexane to hexane/CH_2Cl_2 8:2) in 80% yield, following method C.



^{1}H NMR (300 MHz, $CDCl_3$) δ 7.17 - 6.93 (m, 10H), 6.33 (dd, *J* = 17.5, 10.5 Hz, 1H), 5.41 (s, 1H), 5.34 (s, 1H), 5.19 (d, *J* = 17.5 Hz, 1H), 5.06 (d, *J* = 10.5 Hz, 1H), 1.26 (s, 12H) ppm. **^{13}C NMR** (75 MHz, $CDCl_3$) δ 150.2, 148.8, 140.8, 139.6, 137.0, 129.9, 129.5, 128.0, 127.7, 126.9, 126.0, 119.4, 118.1, 83.6, 24.5 ppm. **HRMS (APCI)** Calc. for $C_{24}H_{28}BO_2$ [M+H$^+$]: 359.2177 found 359.2181.

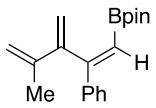
(*Z*)-*tert*-Butyldimethyl((3-methylene-2-(1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)ethylidene)pent-4-en-1-yl)oxy)silane (3.56)



Obtained from **3.29** and 3.0 equiv of DBU at 45°C in toluene for 17 h, following method D. Purified by column chromatography with SiO_2/Et_3N (From hexane to hexane/CH_2Cl_2 9.5:0.5) obtaining the pure product as a colorless oil in 35% yield.* **^{1}H NMR** (300 MHz, $CDCl_3$) δ 6.36 (dd, *J* = 17.4, 10.5 Hz, 1H), 5.18 (d, *J* = 17.4 Hz, 1H), 5.07 (d, *J* = 10.5 Hz, 1H), 5.01 (s, 1H), 4.95 (s, 1H), 4.21 (s, 2H), 1.83 (s, 3H), 1.19 (s, 12H), 0.85 (s, 9H), 0.07 (s, 3H), 0.01 (s, 3H) ppm. **^{13}C NMR** (75 MHz, $CDCl_3$) δ 13C NMR (75 MHz, cdcl3) δ 149.8, 147.9, 138.5, 117.3, 116.3, 83.1, 61.3, 29.9, 26.0, 24.7, 18.4, 15.9, -5.3 ppm. **HRMS (ESI)** Calc. for $C_{20}H_{38}BO_3Si$[M+H$^+$]: 365.2678 found 365.2678.

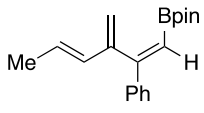
*The low yield of this reaction is due to the instability of **3.29** under reaction conditions.

(*Z*)-4,4,5,5-Tetramethyl-2-(4-methyl-3-methylene-2-phenylpenta-1,4-dien-1-yl)-1,3,2-dioxaborolane (3.57)



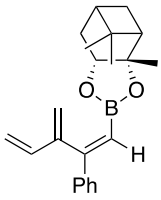
Obtained from **3.32** and 3.0 equiv of DBU under reflux for 24 h, following method D. Purified by column chromatography (From hexane to hexane/CH_2Cl_2 8:2) obtaining the pure product as a yellow oil in 79% yield. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.48 (d, *J* = 8.5 Hz, 2H), 7.34 - 7.18 (m, 3H), 6.01 (s, 1H), 5.39 (s, 1H), 5.08 (s, 1H), 4.94 (s, 1H), 4.91 (s, 1H), 1.97 (s, 3H), 1.23 (s, 12H) ppm. **^{13}C NMR** (75 MHz, $CDCl_3$) δ 159.4, 149.7, 142.8, 141.7, 128.3, 128.1, 126.7, 116.7, 115.4, 83.1, 24.8, 20.6. ppm. **HRMS (APCI)** Calc. for $C_{19}H_{26}BO_2$ [M+H$^+$]: 297.2020 found 297.2023.

4,4,5,5-tetramethyl-2-((1E,4E)-3-methylene-2-phenylhexa-1,4-dien-1-yl)-1,3,2-dioxaborolane (3.58)



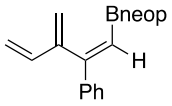
Obtained from **3.33** and 1.5 equiv of DBU under reflux for 16 h, following method D. Purified by SiO2 filtration with CH_2Cl_2 obtaining the pure product as a yellow oil in 99% yield. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.49 (d, J = 7.6 Hz, 2H), 7.33 - 7.22 (m, 3H), 6.18 (d, J = 15.6 Hz, 1H), 5.99 (s, 1H), 5.59 - 5.42 (m, 1H), 5.21 (s, 1H), 5.00 (s, 1H), 1.65 (d, J = 6.6 Hz, 3H), 1.24 (s, 12H) ppm. **^{13}C NMR** (75 MHz, $CDCl_3$) δ 157.8, 147.4, 144.1, 132.8, 128.7, 128.1, 127.8, 126.5, 116.1, 82.9, 24.6, 18.2 ppm.

(+)-(3a*S*,7a*R*)-3a,5,5-Trimethyl-2-((*E*)-3-methylene-2-phenylpenta-1,4-dien-1-yl)hexahydro-4,6-methanobenzo[*d*][1,3,2]dioxaborole (3.59)



Obtained from **3.34** and 1.5 equiv of DBU at 30°C for 16 h, following method D. Purified by SiO_2 filtration with CH_2Cl_2 obtaining the pure product as a yellow oil in 93% yield. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.49 (dd, *J* = 7.6, 2.1 Hz, 2H), 7.34 - 7.21 (m, 3H), 6.50 (dd, *J* = 17.4, 10.6 Hz, 1H), 6.06 (s, 1H), 5.36 (s, 1H), 5.15 (s, 1H), 5.07 - 4.93 (m, 2H), 4.29 (d, *J* = 8.7 Hz, 1H), 2.37 - 2.24 (m, 1H), 2.24 - 2.12 (m, 1H), 2.04 (t, *J* = 5.4 Hz, 1H), 1.93 - 1.76 (m, 2H), 1.37 (s, 3H), 1.27 (s, 3H), 1.16 (d, *J* = 10.8 Hz, 1H), 0.82 (s, 3H) ppm. **^{13}C NMR** (75 MHz, $CDCl_3$) δ 157.5, 147.9, 141.0, 138.2, 128.3, 128.2, 126.7, 119.0, 117.3, 85.4, 77.9, 51.4, 39.6, 38.3, 35.8, 35.5, 28.7, 27.2, 26.6, 24.2 ppm. **^{11}B NMR** (160 MHz, $CDCl_3$) δ 29.6 ppm. **HRMS (APCI)** Calc. for $C_{22}H_{28}BO_2$ [M+H$^+$]: 335.2181 found 335.2178. $[\alpha]_D^{30}$= + 3.15 (c = 0.66, $CHCl_3$).

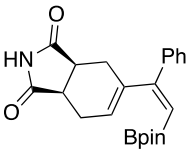
(*E*)-5,5-Dimethyl-2-(3-methylene-2-phenylpenta-1,4-dien-1-yl)-1,3,2-dioxaborinane (3.60)



Obtained from **3.35** and 3.0 equiv of DBU under reflux for 16 h, following method D. Purified by column chromatography with SiO_2/Et_3N (From hexane to hexane/AcOEt 8:2) obtaining the pure product as an orange oil in 50% yield. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.51 - 7.45 (m, 2H), 7.33 - 7.21 (m, 3H), 6.50 (dd, *J* = 17.1, 10.8 Hz, 1H), 5.99 (s, 1H), 5.34 (s, 1H), 5.14 (s, 1H), 5.09 - 4.96 (m, 2H), 3.61 (s, 4H), 0.96 (s, 6H) ppm. **^{13}C NMR** (75 MHz, $CDCl_3$) δ 155.2, 148.5, 141.6, 138.4, 128.3, 127.9, 126.7, 118.4, 117.0, 72.3, 22.1 ppm. **HRMS (APCI)** Calc. for $C_{17}H_{22}BO_2$ [M+H$^+$]: 269.1707 found 269.1704.

3.3.1. Diels-Alder reactions

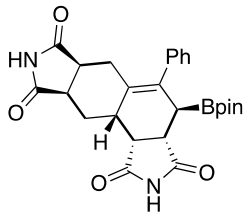
(3a*S,7a*R**)-5-((*E*)-1-Phenyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)vinyl)-3a,4,7,7a-tetrahydro-1*H*-isoindole-1,3(2*H*)-dione (3.67)**



Maleimide (1.0 equiv, 0.2 mmol) was added to a Schlenk flask. Then, **3.43** (2.0 equiv, 0.4 mmol) was added in dry toluene (1.0 ml). The reaction was stirred at 40°C for 5 days. Then, the solvent was removed under vacuum and the resulting crude was purified by column chromatography (hexane/AcOEt, 7:3) obtaining the product as a white solid in 93% yield. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.96 (s, 1H), 7.30 - 7.20 (m, 5H), 5.95 (t, *J* = 4.7 Hz, 1H), 5.63 (s, 1H), 3.20 - 3.04 (m, 2H), 2.63 - 2.27 (m, 4H), 1.24 (s, 12H) ppm. **^{13}C NMR** (75 MHz, $CDCl_3$) δ 180.3, 179.9, 161.0, 158.6, 140.8, 128.5, 128.3, 127.5, 126.7, 83.2, 40.8, 40.2, 27.6, 24.9, 24.1 ppm. **^{11}B NMR** (160 MHz, $CDCl_3$) δ 30.0 ppm. **HRMS (APCI)** Calc. for $C_{22}H_{27}BNO_4$ [M+H$^+$]: 380.2028 found 380.2036. **Mp** (°C): 70-72.

USC
DE SANTIAGO
DE COMPOSTELA

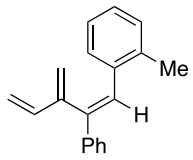
(3a*S,4*S**,6a*S**,9a*R**,10a*S**,10b*R**)-5-Phenyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)- 3a,4,6,6a,9a,10,10a,10b-octahydroisoindolo[5,6-*e*]isoindole-1,3,7,9(2*H*,8*H*)-tetraone (3.68)**



Maleimide (2.5 equiv, 0.5 mmol) was added to a Schlenk flask. Then, **3.43** (1.0 equiv, 0.2 mmol) was added in dry CH_2Cl_2 (1.0 ml). The reaction was stirred under reflux for 4 days. Then, the solvent was removed under vacuum and the resulting crude was purified by column chromatography (hexane/AcOEt, 1:1) obtaining the product as a 9:1 mixture of diastereomers, as a white solid in 86% yield. Spectroscopic data collected only for major isomer. **^{1}H NMR** (300 MHz, DMSO-d_6) δ 11.24 (s, 1H), 11.15 (s, 1H), 7.32 (t, *J* = 7.4 Hz, 2H), 7.24 (t, *J* = 7.4 Hz, 1H), 7.09 (d, *J* = 7.4 Hz, 1H), 3.23 (d, *J* = 8.8 Hz, 1H), 3.21 - 3.14 (m, 2H), 3.04 (ddd, *J* = 9.4, 6.8, 1.9 Hz, 1H), 2.68 (dd, *J* = 14.9, 1.9 Hz, 1H), 2.57 - 2.45 (m, 2H), 2.23 (dt, *J* = 13.1, 5.3, 1H), 2.10 (ddd, *J* = 14.9, 6.8, 2.5 Hz, 1H), 2.04 (dd, *J* = 15.4, 5.6 Hz, 1H), 1.17 (s, 12H) ppm. **^{13}C NMR** (126 MHz, DMSO-d_6) δ. 182.0, 181.6, 181.3, 179.7, 141.4, 136.3, 129.4, 128.4, 128.2, 126.9, 84.1, 45.1, 43.4, 40.3, 40.0, 33.9, 25.0, 25.0, 24.7, 23.4 ppm. **^{11}B NMR** (160 MHz, DMSO-d_6): 22.3 ppm. **HRMS (APCI)** Calc. for $C_{26}H_{30}BN_2O_6$[M+H$^+$]: 477.2191 found 477.2196. **Mp** (°C): Between 220-222 °C the product decomposes.

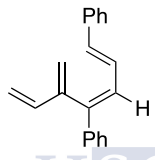
3.3.2. Suzuki cross-couplings

(*E*)-1-Methyl-2-(3-methylene-2-phenylpenta-1,4-dien-1-yl)benzene (3.70)



$Pd(PPh_3)_4$ (10 mol%, 0.04 mmol) was added to a Schlenk flask. Then, **3.43** (1.0 equiv, 0.4 mmol) was added in 1,4-dioxane (4.0 ml), followed by the addition of 2-bromotoluene **3.69** (1.5 equiv 0.6 mmol) and aq. NaOH (2.0 M, 2.0 equiv, 0.8 mmol). The reaction was stirred at 80 °C for 16 h. After this time, the resulting crude was diluted in Et_2O (15 ml) and washed with H_2O (2x10 ml). The organic layer was dried over Na_2SO_4, filtered and taken to dryness. The residue was purified by column chromatography (hexane/CH_2Cl_2, 8:2) affording the desired product **3.70** as a yellow oil in 99% yield. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.57 (d, *J* = 6.5 Hz, 2H), 7.46 (d, *J* = 7.5 Hz, 1H), 7.42 - 7.28 (m, 3H), 7.20 - 7.07 (m, 3H), 6.50 (dd, *J* = 17.4, 10.7 Hz, 1H), 5.39 (s, 1H), 5.29 - 5.02 (m, 3H), 2.37 (s, 3H) ppm. **^{13}C NMR** (75 MHz, $CDCl_3$) δ 146.1, 141.7, 140.9, 138.1, 137.0, 136.7, 129.8, 128.5, 128.3, 128.2, 127.6, 127.3, 126.7, 125.5, 120.9, 117.6, 20.4 ppm. **HRMS (APCI)** Calc. for $C_{19}H_{19}$[M+H$^+$]: 247.1481 found 247.1478.

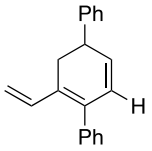
((1*E*,3*E*)-5-Methylenehepta-1,3,6-triene-1,4-diyl)dibenzene (3.72)



$Pd(PPh_3)_4$ (10 mol%, 0.04 mmol) was added to a Schlenk flask. Then, **3.43** (1.0 equiv, 0.4 mmol) was added in 1,4-dioxane (4.0 ml), followed by the addition of β-bromostyrene **3.72** (1.5 equiv 0.6 mmol) and aq. NaOH (2.0 M, 2.0 equiv, 0.8 mmol). The reaction was stirred at 80°C for 16 hours. Then, the resulting crude was diluted in Et_2O (15 ml) and washed with H_2O (2x10 ml). The organic layer was dried over Na_2SO_4, filtered and taken to dryness. The residue was purified by column chromatography (pentane) affording the desired product **3.72** as a yellow oil in 60% yield. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.61 - 7.16 (m, 10H), 7.03 (dd, *J* = 15.1, 10.8 Hz, 1H), 6.93 (d, *J* = 10.9 Hz, 1H), 6.73 (d, *J* = 15.1 Hz, 1H), 6.59 (dd, *J* = 17.3, 10.5 Hz, 1H), 5.63 (s, 1H), 5.23 (s, 1H), 5.17 - 4.97 (m, 2H) ppm. **^{13}C NMR** (75

MHz, $CDCl_3$) δ 145.8, 140.5, 140.1, 137.8, 137.7, 133.6, 128.7, 128.5, 127.7, 127.6, 127.4, 126.7, 126.5, 126.2, 120.6, 118.0 ppm. **HRMS (APCI)** Calc. for $C_{20}H_{19}[M+H^+]$: 259.1481 found 259.1476.

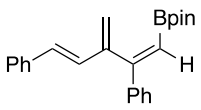
3'-Vinyl-1',2'-dihydro-1,1':4',1''-terphenyl (3.73)



3.72 (1.0 equiv, 0.1 mmol) was added to a sealed tube in dry toluene (2.5 ml). The reaction was stirred overnight at 140 °C. After this time, the solvent was removed under vacuum and the residue was purified by column chromatography (pentane) obtaining the product as a colorless oil in 89% yield. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.56 - 7.07 (m, 10H), 6.64 (dd, *J* = 17.4, 11.0 Hz, 1H), 6.27 (dd, *J* = 9.5, 2.6 Hz, 1H), 6.02 (dd, *J* = 9.5, 3.4 Hz, 1H), 5.30 (d, *J* = 17.4 Hz, 1H), 5.05 (d, *J* = 11.0 Hz, 1H), 3.76 (t, *J* = 11.0 Hz, 1H), 2.88 (dd, *J* = 16.3, 8.8 Hz, 1H), 2.61 (dd, *J* = 16.3, 13.3 Hz, 1H) ppm. **^{13}C NMR** (75 MHz, $CDCl_3$) δ 145.5, 140.5, 135.6, 135.3, 132.9, 131.1, 129.9, 129.2, 128.7, 128.3, 127.8, 127.1, 126.6, 113.6, 40.7, 32.1 ppm. **HRMS (APCI)** Calc. for $C_{20}H_{18}[M+H^+]$: 258.1403 found 258.1399.

3.3.3. Cross-metathesis reaction

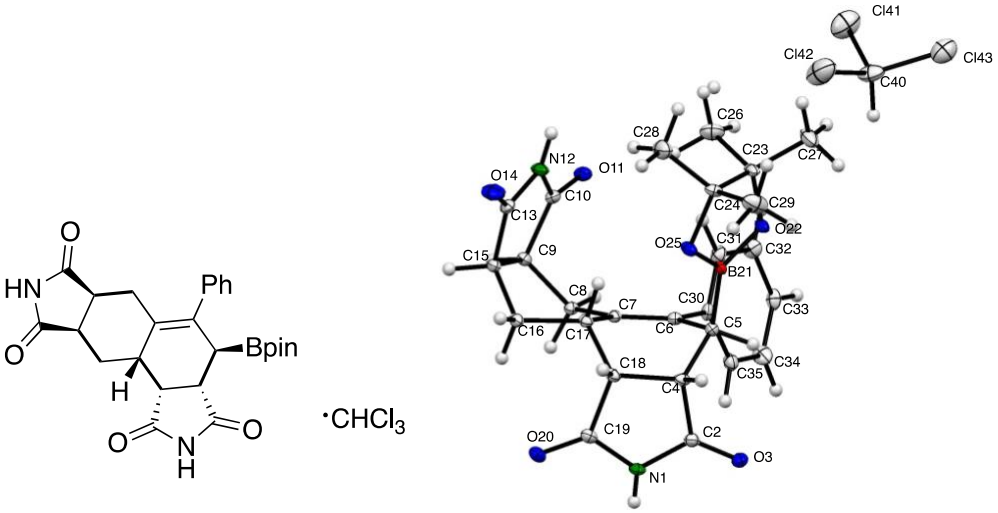
4,4,5,5-Tetramethyl-2-((1*E*,4*E*)-3-methylene-2,5-diphenylpenta-1,4-dien-1-yl)-1,3,2-dioxaborolane (3.74)



In a Schlenk flask, Hoveyda-Grubs 2nd generation catalyst (10 mol%, 0.04 mmol) was added. Styrene (1.5 equiv, 0.3 mmol) and **3.43** (1.0 equiv, 0.2 mmol) were added in dry toluene (2.0 ml) and the reaction was stirred at 100 °C for 2 days. Then, another 10 mol% of catalyst was added, and the reaction was stirred for 2 days more. Then, the solvent was removed under vacuum and the residue was purified by column chromatography (From hexane to hexane/CH_2Cl_2, 8:2) obtaining the product as a yellow oil in 71% yield. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.57 (d, *J* = 8.1, 2H), 7.42 - 7.16 (m, 8H), 6.97 (d, *J* = 16.1 Hz, 1H), 6.39 (d, *J* = 16.1 Hz, 1H), 6.14 (s, 1H), 5.51 (d, *J* = 2.0 Hz, 1H), 5.23 (d, *J* = 2.0 Hz, 1H), 1.23 (s, 12H) ppm. **^{13}C NMR** (75 MHz, $CDCl_3$) δ 157.5, 147.6, 141.2, 137.6, 131.6, 130.8, 128.6, 128.4, 128.2, 127.4, 126.8, 126.6, 119.3, 83.2, 24.8 ppm. **^{11}B NMR** (160 MHz, $CDCl_3$) 30.0 ppm. **HRMS (APCI)** Calc. for $C_{24}H_{28}BO_2[M+H^+]$: 359.2177 found 359.2181.

3.3.4. X-ray diffraction analysis data of compound 3.68

Product **3.68** was dissolved in $CHCl_3$ and leaving to slow evaporation overnight to yield clear colorless prism type of crystals of an approximate dimensions 0.129 mm x 0.157 mm x 0.263 mm. The X-ray intensity data were measured on a κ-geometry diffractometer system equipped with a graphite monochromator and a MoKα sealed x-ray tube (λ = 0.71073 Å). The structure was solved and refined using the Bruker SHELXTL Software Package. CCDC 1834677.



3.68

Figure 30. ORTEP plot of **3.68** with 30% ellipsoids. Selected bond distances (Å) and angles (°):C5-B21 (1.566), C6-C7 (1.336), C6-C30 (1.489), C10-O11 (1.220), C10-N12 (1.372; C6-C5-B21 (109.3).

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4. CHAPTER IV:

4.1. LIST OF STARTING MATERIALS

Alkynes **4.1**, **4.27-4.50** and allyl derivates **4.2**, **4.17-4.18**, **4.52** and **4.60** were obtained from commercial sources. Allyl derivates **4.51**,[391] **4.53**,[392] **4.54-4.59**[393] were prepared under described conditions. Ligands **L4.7-L4.12** were obtained from commercial sources. **L4.1**,[394] **L4.13-L4.14**,[395] **L4.15**[211d] and **L4.16**[396] were prepared under described conditions.

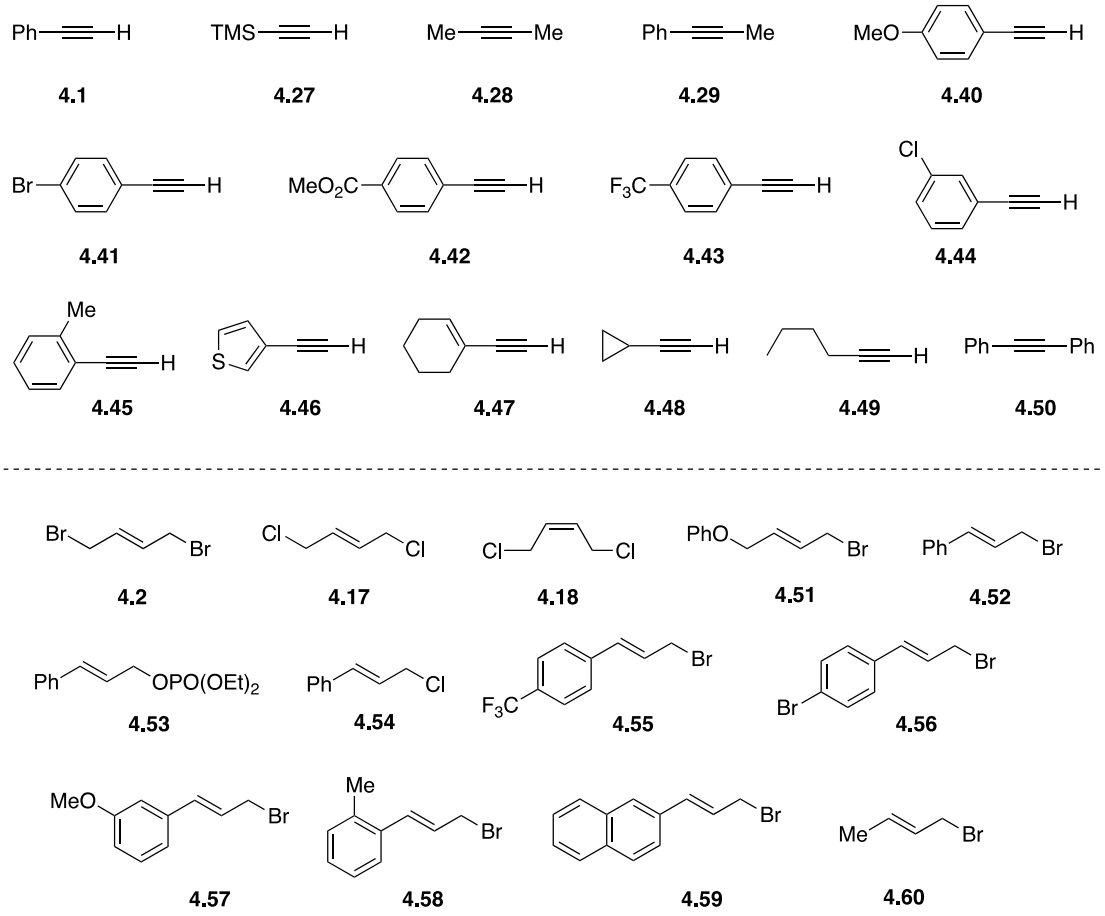

Figure 31. List of starting material.

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4.2. GENERAL PROCEDURE FOR THE CU -CATALYZED SYNTHESIS OF SKIPPED DIENES

Method A. Cu-catalyzed allylboration of alkynes (with slow addition)

CuCl (10 mol%, 0.02 mmol) and **L4.1** (12 mol%, 0.024 mmol) were suspended in dry toluene (0.5 mL), stirred during 30 min at r.t. and added to the reaction vial containing B_2pin_2 (2.0 equiv, 0.4 mmol) and NaO*t*-Bu (2.0 equiv, 0.4 mmol) to afford a red suspension. Alkyne (1.1 equiv, 0.22 mmol) in dry toluene (0.5 mL) was added and the mixture was stirred at 30 °C. A solution of the allyl derivative (1.0 equiv, 0.2 mmol) in dry toluene (0.5 mL) was added dropwise over 5 h using a syringe pump. When the addition was completed, the mixture was stirred for additional 11 h at 30 °C. After this time, the mixture was diluted in CH_2Cl_2 (2 mL) and washed with NH_4Cl (5 mL). Then the aqueous layer was extracted with 2 x CH_2Cl_2 (2 mL). The organic layer was dried, and the solvents were evaporated under vacuum. The final product was purified by SiO_2 column chromatography using the indicated mixture of eluents for each case.

Method B. Cu-catalyzed allylboration of alkynes

CuCl (10 mol%, 0.02 mmol) and **L4.1** (12 mol%, 0.024 mmol) were suspended in dry toluene (0.5 mL), stirred during 30 min at r.t. and added to the reaction vial containing B_2pin_2 (2.0 equiv, 0.4 mmol) and NaO*t*-Bu (2.0 equiv, 0.4 mmol) to afford a red suspension. Alkyne (1.1 equiv, 0.4 mmol) and allyl derivative (1.0 equiv, 0.2 mmol) were added in dry toluene (1.0 mL) to the reaction mixture and heated at 30 °C for 16h. After this time, the mixture was diluted in CH_2Cl_2 (2 mL) and washed with NH_4Cl (5 mL). Then the aqueous layer was extracted with 2 x CH_2Cl_2 (2 mL). The organic layer was dried, and the solvents were evaporated under vacuum. The final product was purified by SiO_2 column chromatography using the indicated mixture of eluents for each case.

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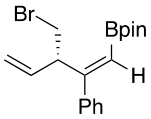
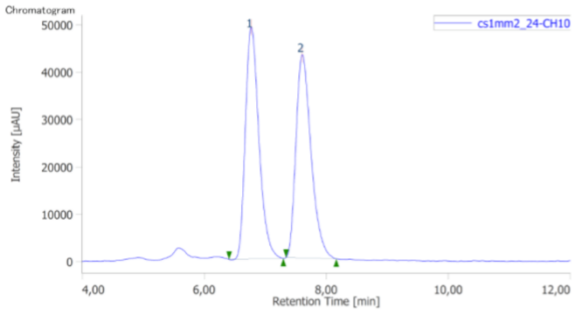
4.3. COMPOUND CHARACTERIZATION

(*S*,*E*)-2-(3-(Bromomethyl)-2-phenylpenta-1,4-dien-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (4.4)



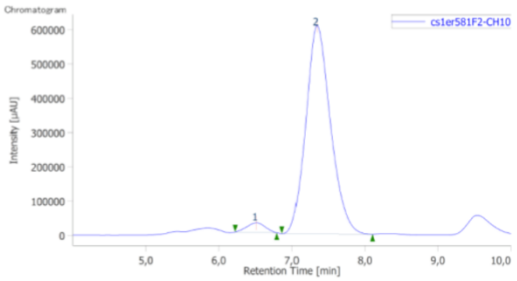
Obtained from **4.1** and **4.2** as a colorless oil after column chromatography (hexane/CH_2Cl_2, 9:1) in 88% yield and 97:3 er, following method A. The spectral data match with those previously described in chapter III, product **3.16**. **Optical rotation:** $[\alpha]_D^{22}$ +9.1 (*c* = 1.0, $CHCl_3$)

Enantiomeric purity was determined by chiral SFC analysis [Lux Amilose-1, 100 bar, T_{oven}: 40 °C, flow: 1 mL/min; 5% MeOH, λ = 220 nm, minor enantiomer t_R = 6.52 min, major enantiomer t_R = 7.34 min].



Peak Information

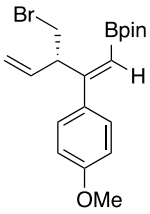
#	CH	tR [min]	Area [µV·sec]	Area%
1	10	6,770	754754	50,545
2	10	7,607	738471	49,455



Peak Information

#	CH	tR [min]	Area [µV·sec]	Area%
1	10	6,517	485647	3,300
2	10	7,340	14229417	96,700

(*S*,*E*)-2-(3-(Bromomethyl)-2-(4-methoxyphenyl)penta-1,4-dien-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (4.5)



Obtained from **4.40** and **4.2** as a yellow oil after column chromatography (hexane/CH_2Cl_2, from 9:1 to 7:3) in 60% yield and 93:7 er, following method A. The spectral data match with those previously described in chapter III, product **3.18**. **Optical rotation:** $[\alpha]_D^{22}$ +23.0 (*c* = 1.0, $CHCl_3$)

Enantiomeric purity was determined by chiral SFC analysis [Lux Amylose-1, 100 bar, T_{oven}: 40 °C, flow: 1 mL/min; 5% MeOH, λ = 250 nm, minor enantiomer t_R = 10.54 min, major enantiomer t_R = 12.11 min].

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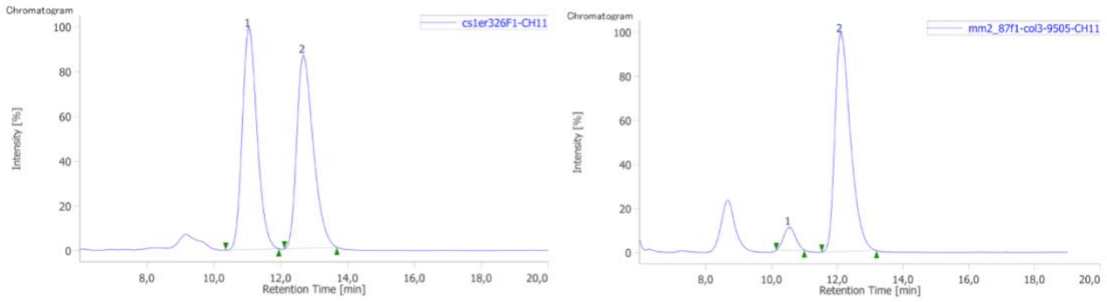


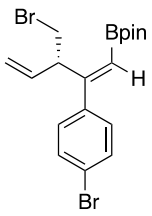
Peak Information

#	CH	tR [min]	Area [µV·sec]	Area%
1	11	11,050	6474226	50,563
2	11	12,680	6330118	49,437

Peak Information

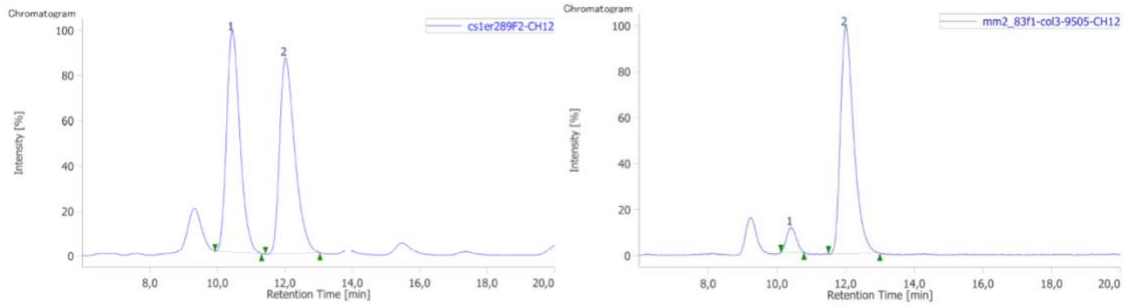
#	CH	tR [min]	Area [µV·sec]	Area%
1	11	10,543	681781	7,374
2	11	12,113	8563852	92,626

(*S*,*E*)-2-(3-(Bromomethyl)-2-(4-bromophenyl)penta-1,4-dien-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (4.6)



Obtained from **4.41** and **4.2** as a yellow oil after column chromatography (hexane/CH_2Cl_2, 9:1) in 84% yield and 93:7 er, following method A. The spectral data match with those previously described in chapter III, product **3.19**. **Optical rotation:** $[\alpha]_D^{22}$ +12.2 (*c* = 1.0, $CHCl_3$)

Enantiomeric purity was determined by chiral SFC analysis [Lux Amilose-1, 100 bar, T_{oven}: 40 °C, flow: 1 mL/min; 5% MeOH, λ = 275 nm, minor enantiomer t_R = 10.42 min, major enantiomer t_R = 12.00 min].



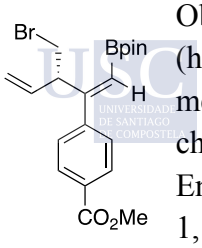
Peak Information

#	CH	tR [min]	Area [µV·sec]	Area%
1	12	10,437	4620397	49,789
2	12	12,013	4659634	50,211

Peak Information

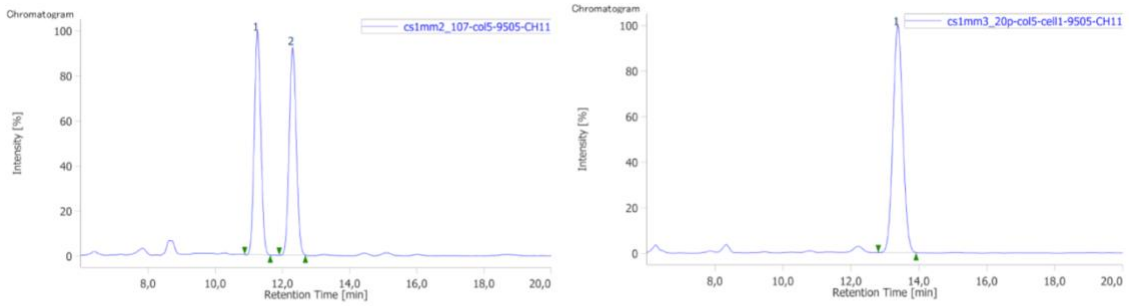
#	CH	tR [min]	Area [µV·sec]	Area%
1	12	10,417	97377	7,351
2	12	12,003	1227248	92,649

(*S*,*E*)-Methyl 4-(3-(bromomethyl)-1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)penta-1,4-dien-2-yl)benzoate (4.7)



Obtained from **4.42** and **4.2** as a yellow oil after column chromatography (hexane/CH_2Cl_2, from 9:1 to 1:1) in 83% yield and >99:1 er, following method A. The spectral data match with those previously described in chapter III, product **3.17**. **Optical rotation:** $[\alpha]_D^{22}$ +5.8 (*c* = 0.8, $CHCl_3$)

Enantiomeric purity was determined by chiral SFC analysis [Lux Celulose-1, 100 bar, T_{oven}: 40 °C, flow: 1 mL/min; 5% MeOH, λ = 250 nm, minor enantiomer t_R = 11.26 min, major enantiomer t_R = 13.38 min].



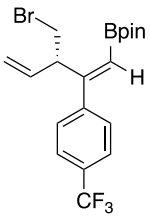
Peak Information

#	CH	tR [min]	Area [µV·sec]	Area%
1	11	11,257	875372	49,916
2	11	12,303	878322	50,084

Peak Information

#	CH	tR [min]	Area [µV·sec]	Area%
1	11	13,380	3776142	100,000

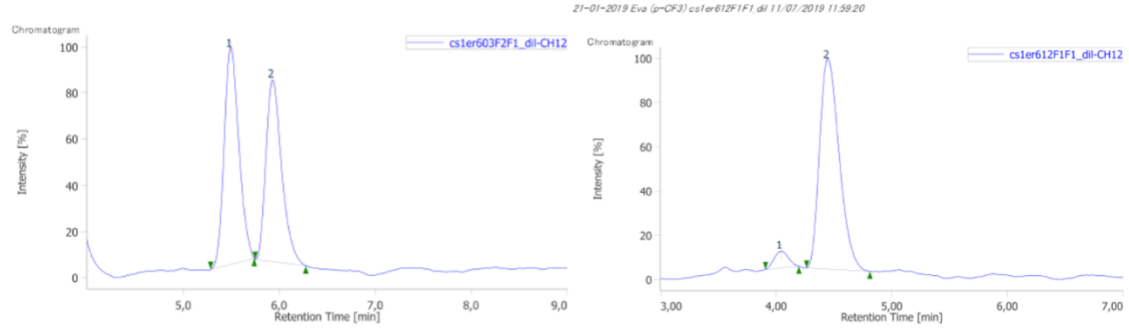
(*S*,*E*)-2-(3-(Bromomethyl)-2-(4-(trifluoromethyl)phenyl)penta-1,4-dien-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (4.8)



Obtained from **4.43** and **4.2** as a yellow oil after column chromatography (hexane/CH_2Cl_2, 9.5:0.5 to 1:1) in 70% yield and 94.5:5.5 er, following method A. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.55 (d, *J* = 8.1 Hz, 2H), 7.41 (d, *J* = 8.1 Hz, 2H), 5.93 (ddd, *J* = 17.3, 10.3, 7.0 Hz, 1H), 5.58 (s, 1H), 5.28 - 5.16 (m, 2H), 4.45 (q, *J* = 7.0 Hz, 1H), 3.53 (dd, *J* = 9.9, 7.0 Hz, 1H), 3.36 (dd, *J* = 9.9, 9.0 Hz, 1H), 1.32 (s, 12H) ppm. **^{13}C NMR** (75 MHz, $CDCl_3$) δ 160.5, 146.4, 138.1, 128.1, 125.0, 117.4, 83.7, 50.5, 34.4, 25.0 ppm. **^{11}B NMR** (160 MHz, $CDCl_3$) δ 29·6 ppm. **^{19}F NMR** (282 MHz, $CDCl_3$) δ -62.7 ppm. **HRMS (APCI)** Calc. for $C_{19}H_{24}BBrF_3O_2$ [M+H$^+$]: 431.1004 found 431.0999. **Optical rotation:** $[\alpha]_D^{22}$ +3.8 (*c* = 1.0, $CHCl_3$)

*Quaternary C heterocoupled with F could not be seen.

Enantiomeric purity was determined by chiral SFC analysis [Lux Amilose-1, 100 bar, T_{oven}: 40 °C, flow: 1 mL/min; 5% MeOH, λ = 275 nm, minor enantiomer t_R = 4.04 min, major enantiomer t_R = 4.45 min].



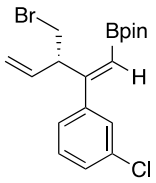
Peak Information

#	Peak Name	CH	tR [min]	Area [µV·sec]	Area%
1	Unknown	12	5,493	173948	52,762
2	Unknown	12	5,930	155739	47,238

Peak Information

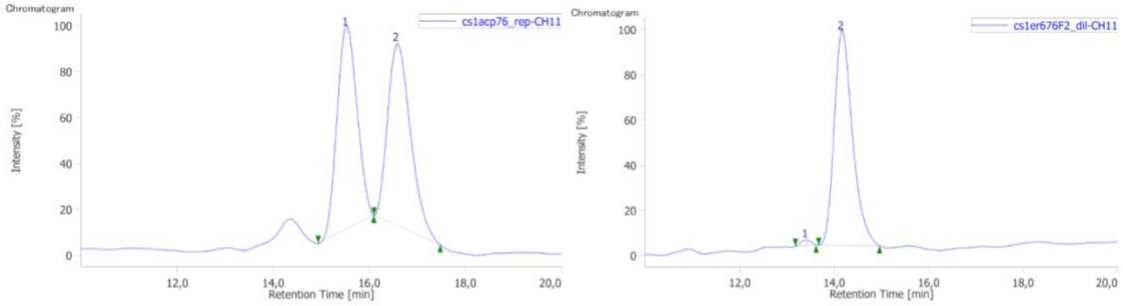
#	CH	tR [min]	Area [µV·sec]	Area%
1	12	4,040	12179	5,509
2	12	4,447	208896	94,491

(*S*,*E*)-2-(3-(Bromomethyl)-2-(3-chlorophenyl)penta-1,4-dien-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (4.9)



Obtained from **4.44** and **4.2** as a yellow oil after column chromatography (From hexane to hexane/CH_2Cl_2 9:1) in 60% yield and 98.5:1.5 er, following method A. The spectral data match with those previously described in chapter III, product **3.20**. **Optical rotation:** $[\alpha]_D^{23}$ +8.0 (*c* = 1.1, $CHCl_3$)

Enantiomeric purity was determined by chiral SFC analysis [Lux Amilose-1, 100 bar, T_{oven}: 40 °C, flow: 0.5 mL/min; 6% MeOH, λ = 250 nm, minor enantiomer t_R = 13.41 min, major enantiomer t_R = 14.16 min].



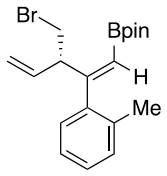
Peak Information

#	Peak Name	CH	tR [min]	Area [µV·sec]	Area%
1	Unknown	11	15,527	1182190	49,361
2	Unknown	11	16,580	1212813	50,639

Peak Information

#	CH	tR [min]	Area [µV·sec]	Area%
1	11	13,410	9897	1,429
2	11	14,163	682556	98,571

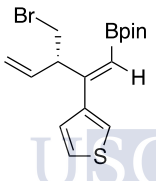
(*S*,*E*)-2-(3-(Bromomethyl)-2-(*o*-tolyl)penta-1,4-dien-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (4.10)



Obtained from **4.45** and **4.2** as a yellow oil after column chromatography (hexane/CH_2Cl_2, 9:1) in 48% yield and 94:6 er, following method AThe spectral data match with those previously described in chapter III, product **3.21**. **Optical rotation:** $[\alpha]_D^{21}$ -21.6 (*c* = 1.1, $CHCl_3$)

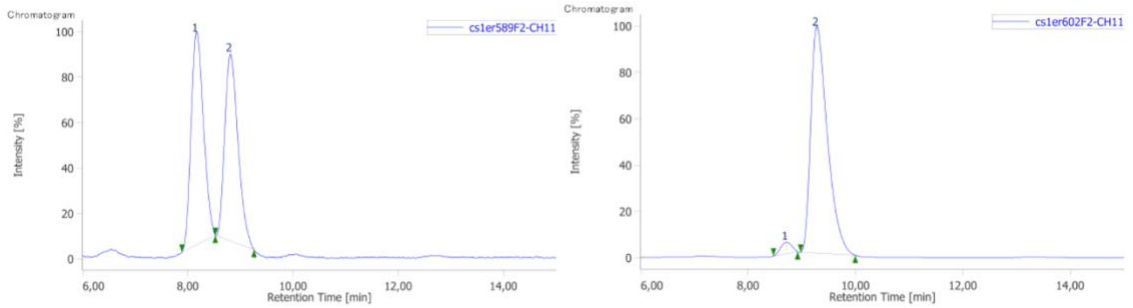
Enantiomeric purity was determined on cyclopropane product (see product **4.32**).

(*S*,*E*)-2-(3-(Bromomethyl)-2-(thiophen-3-yl)penta-1,4-dien-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (4.11)



Obtained from **4.46** and **4.2** as a colorless oil after column chromatography (hexane/CH_2Cl_2, 9.5:0.5) in 51% yield and 97:3 er, following method A. The spectral data match with those previously described in chapter III, product **3.22**. **Optical rotation:** $[\alpha]_D^{22}$ +38.5 (*c* = 0.5, $CHCl_3$)

Enantiomeric purity was determined by chiral SFC analysis [Lux Amilose-1, 100 bar, T_{oven}: 40 °C, flow: 1 mL/min; 5% MeOH, λ = 250 nm, minor enantiomer t_R = 8.71 min, major enantiomer t_R = 9.28 min].



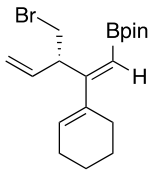
Peak Information

#	CH	tR [min]	Area [µV·sec]	Area%
1	11	8.167	1174351	51.432
2	11	8.810	1108947	48.568

Peak Information

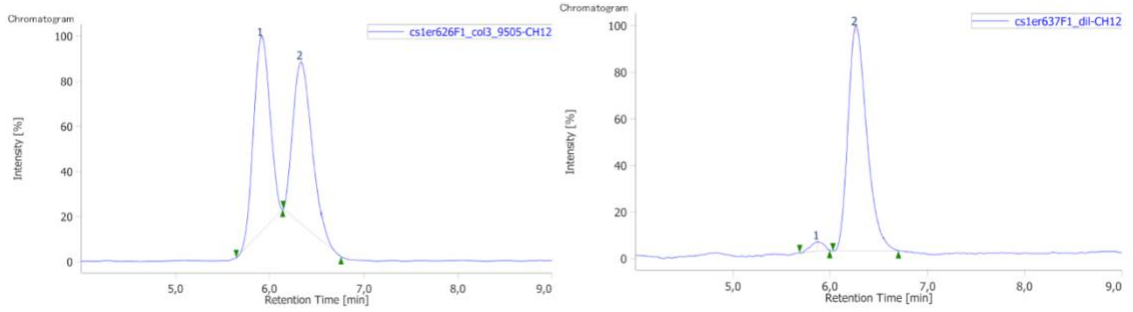
#	CH	tR [min]	Area [µV·sec]	Area%
1	11	8.713	727343	3.273
2	11	9.280	21496781	96.727

(*S*,*E*)-2-(3-(Bromomethyl)-2-(cyclohex-1-en-1-yl)penta-1,4-dien-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (4.12)



Obtained from **4.47** and **4.2** as a colorless oil after column chromatography (hexane/CH_2Cl_2, 9:1) in 50% yield and 97:3 er, following method A at 60 °C. The spectral data match with those previously described in chapter III, product **3.26**. **Optical rotation:** $[\alpha]_D^{22}$ +7.7 (*c* = 1.2, $CHCl_3$)

Enantiomeric purity was determined by chiral SFC analysis [Lux Amilose-1, 100 bar, T_{oven}: 40 °C, flow: 1 mL/min; 5% MeOH, λ = 275 nm, minor enantiomer t_R = 5.87 min, major enantiomer t_R = 6.27 min].



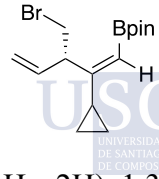
Peak Information

#	CH	tR [min]	Area [µV·sec]	Area%
1	12	5.917	896436	48.783
2	12	6.337	941168	51.217

Peak Information

#	CH	tR [min]	Area [µV·sec]	Area%
1	12	5.873	13376	2.841
2	12	6.267	457361	97.159

(*S*,*Z*)-2-(3-(Bromomethyl)-2-cyclopropylpenta-1,4-dien-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (4.13)



Obtained from **4.48** and **4.2** as a colorless oil after column chromatography (hexane/CH_2Cl_2, 9:1) in 66% yield and 92:8 er, following method A at 50 °C. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 5.95 (ddd, *J* = 17.4, 10.2, 7.6 Hz, 1H), 5.24 - 5.11 (m, 2H), 4.93 (s, 1H), 4.38 (q, *J* = 7.6 Hz, 1H), 3.60 (d, *J* = 7.6 Hz, 2H), 1.38 - 1.27 (m, 1H), 1.25 (s, 12H), 0.81 - 0.58 (m, 3H), 0.57 - 0.47 (m, 1H) ppm. **^{13}C NMR** (75 MHz, $CDCl_3$) δ 165.5, 138.2, 116.9, 83.0, 51.1, 35.2, 25.0, 14.1, 9.7, 7.4 ppm. **^{11}B NMR** (160 MHz, $CDCl_3$) δ 29.9 ppm. **HRMS (APCI)** Calc. for $C_{18}H_{29}BBrO_2$ $[M+H^+]$: 367.1438, found 367.1439. **Optical rotation:** $[\alpha]_D^{22}$ -16.7 (*c* = 1.2, $CHCl_3$)

Enantiomeric purity was determined on cyclopropane product (see product **4.33**).

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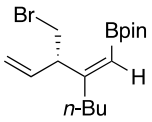
(*S*,*Z*)-2-(2-(1-Bromobut-3-en-2-yl)hex-1-en-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (4.14) and (S,*E*)-2-(3-(Bromomethyl)nona-1,4-dien-5-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (4.14')

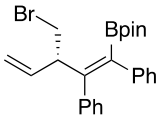
Obtained from **4.49** and **4.2** as a mixture of regioisomers (4:1) which can be separated by column chromatography (hexane/CH_2Cl_2, from 9:1) obtaining major isomer as a colorless oil in 34% yield and 95:5 er and the minor isomer in 10% yield, following method A.

(*S*,*Z*)-2-(2-(1-Bromobut-3-en-2-yl)hex-1-en-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (4.14)



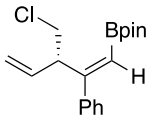
The spectral data match with those previously described in chapter III, product **3.23**. **Optical rotation:** $[\alpha]_D^{22}$ -24.3 (*c*=1.1, $CHCl_3$). Enantiomeric purity was determined on cyclopropane product (see product **4.34**).

(*S*,*Z*)-2-(3-(Bromomethyl)-1,2-diphenylpenta-1,4-dien-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (4.15)

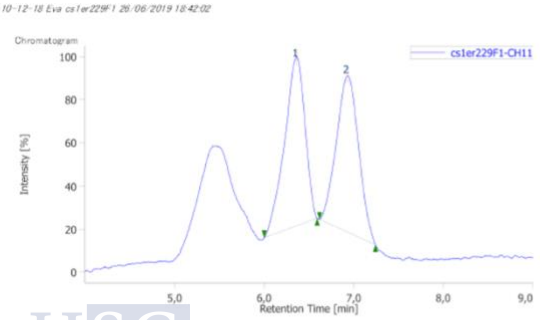


Obtained from **4.50** and **4.2** as a colorless oil after column chromatography (hexane/CH_2Cl_2, 9:1) in 33% yield and 80:20 er, following method A at 50°C. The spectral data match with those previously described in chapter III, product **3.28**. **Optical rotation:** $[\alpha]_D^{22}$ +9.42 (*c* = 1.1, $CHCl_3$)
Enantiomeric purity was determined on cyclopropane product (see product **4.31**).

(*S*,*E*)-2-(3-(Chloromethyl)-2-phenylpenta-1,4-dien-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (4.16)

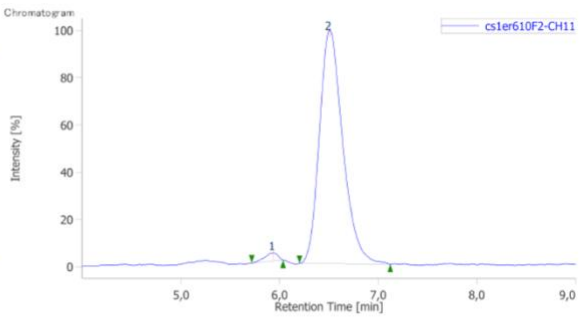


Obtained from **4.1** and **4.17** as a colorless oil after column chromatography (hexane/CH_2Cl_2, 9:1) in 90% yield and 98:2 er, following method B. The spectral data match with those previously described in chapter III, product **3.42**. **Optical rotation:** $[\alpha]_D^{22}$ +5.4 (*c* = 1.0, $CHCl_3$)
Enantiomeric purity was determined by chiral SFC analysis [Lux Amilose-1, 100 bar, T_{oven}: 40 °C, flow: 1 mL/min; 5% MeOH, λ = 220 nm, minor enantiomer t_R = 5.94 min, major enantiomer t_R = 6.51 min].



Peak Information

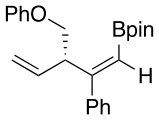
#	CH	tR [min]	Area [μV·sec]	Area%
1	11	6,363	251968	49,683
2	11	6,930	255182	50,317



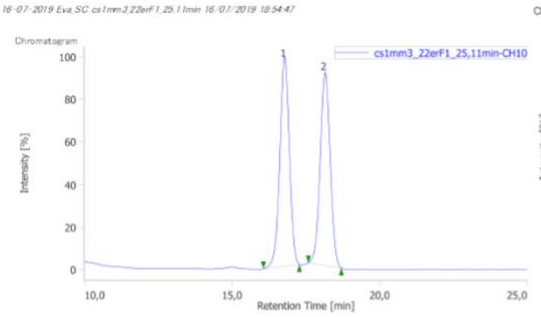
Peak Information

#	CH	tR [min]	Area [μV·sec]	Area%
1	11	5,937	23209	1,973
2	11	6,507	1153215	98,027

(*S*,*E*)-4,4,5,5-Tetramethyl-2-(3-(phenoxymethyl)-2-phenylpenta-1,4-dien-1-yl)-1,3,2-dioxaborolane (4.19)

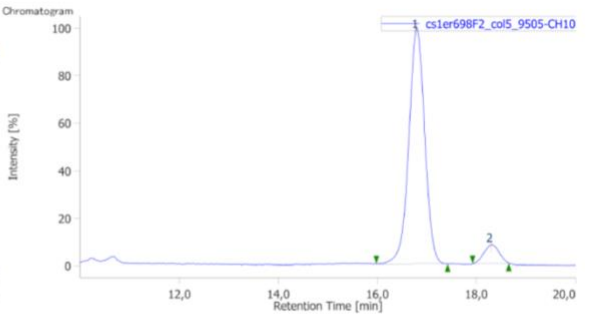


Obtained from **4.1** and **4.51** as a colorless oil after column chromatography (hexane to hexane/CH_2Cl_2 4:6) in 67% yield and 93:7 er, following method B. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.54 - 7.16 (m, 7H), 7.05 - 6.70 (m, 3H), 6.10 (ddd, *J* = 17.2, 10.4, 6.7 Hz, 1H), 5.60 (s, 1H), 5.30 (dt, *J* = 17.2, 1.6 Hz, 1H), 5.21 (dt, *J* = 10.4, 1.6 Hz, 1H), 4.59 (q, *J* = 7.3 Hz, 1H), 4.14 (dd, *J* = 9.4, 7.4 Hz, 1H), 4.05 (dd, *J* = 9.4, 7.5 Hz, 1H), 1.31 (s, 6H), 1.30 (s, 6H) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$) δ 162.3, 143.6, 138.0, 129.4, 127.9, 127.7, 127.5, 120.7, 116.5, 115.1, 83.3, 69.6, 48.0, 25.0 ppm. **^{11}B NMR** (160 MHz, $CDCl_3$) δ 30.0 ppm. **HRMS (APCI)** Calc. for $C_{24}H_{30}BO_3$ [M+H$^+$] 377.2283 found 347.2284. **Optical rotation:** $[\alpha]_D^{22}$ +8.6 (*c* = 2.4, $CHCl_3$)
Enantiomeric purity was determined by chiral SFC analysis [Lux Cellulose-1, 100 bar, T_{oven}: 40 °C, flow: 1 mL/min; 5% MeOH, λ = 220 nm, major enantiomer t_R = 16.79 min, minor enantiomer t_R = 18.29 min].



Peak Information

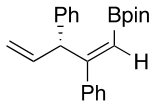
#	CH	tR [min]	Area [µV·sec]	Area%
1	10	16,780	12011224	50,910
2	10	18,147	11581940	49,090



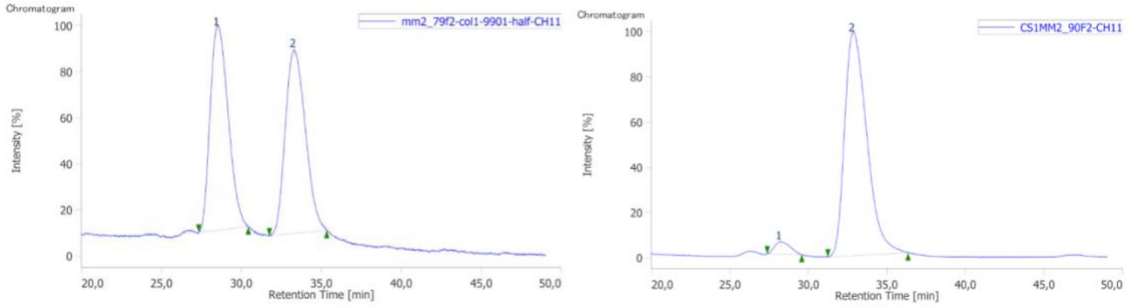
Peak Information

#	CH	tR [min]	Area [µV·sec]	Area%
1	10	16,790	5045687	92,979
2	10	18,293	380980	7,021

(*R*,*E*)-2-(2,3-Diphenylpenta-1,4-dien-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (4.20)



Obtained from **4.1** and **4.52** as a white solid after column chromatography (Hexane/CH_2Cl_2, 85:15) in 82% yield and 96.5:3.5 er, following method A. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.37 - 7.03 (m, 10H), 6.22 (dt, *J* = 17.9, 9.4 Hz, 1H), 5.71 (s, 1H), 5.60 (d, *J* = 9.4 Hz, 1H), 5.30 (d, *J* = 17.9 Hz, 1H), 5.21 (d, *J* = 9.4 Hz, 1H), 1.31 (s, 6H), 1.30 (s, 6H) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$) δ 163.6, 143.0, 142.7, 138.9, 128.3, 128.0, 127.9, 127.7, 126.1, 117.3, 83.3, 53.5, 24.9 ppm. **^{11}B NMR** (160 MHz, $CDCl_3$) δ 30.0 ppm **HRMS (APCI)** Calc. for $C_{23}H_{28}BO_2$ [M+H$^+$] 347.2177, found 347.2178. **Mp** (°C): 87-89. **Optical rotation:** $[\alpha]_D^{22}$ -12.7 (*c* = 1.0, $CHCl_3$)
Enantiomeric purity was determined by chiral SFC analysis [Lux Cellulose-2, 100 bar, T_{oven}: 40 °C, flow: 1 mL/min; 1% MeOH, λ = 250 nm, minor enantiomer t_R = 28.20 min, major enantiomer t_R = 32.85 min].



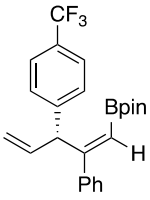
Peak Information

#	CH	tR [min]	Area [µV·sec]	Area%
1	11	28,520	811161	49,961
2	11	33,307	812414	50,039

Peak Information

#	CH	tR [min]	Area [µV·sec]	Area%
1	11	28,210	111425	3,553
2	11	32,853	3024319	96,447

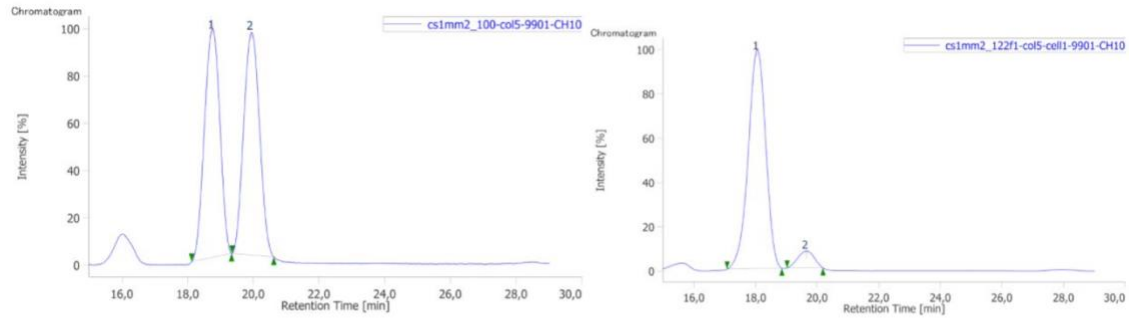
(*R*,*E*)-4,4,5,5-Tetramethyl-2-(2-phenyl-3-(4-(trifluoromethyl)phenyl)penta-1,4-dien-1-yl)-1,3,2-dioxaborolane (4.21)



Obtained from **4.1** and **4.55**. Purified through flash column chromatography on silica gel (Hexane/CH_2Cl_2 8:2) to afford the desired product in 59% yield and 93:7 er as colorless oil, following method A. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.53 (d, *J* = 8.2 Hz, 2H), 7.43 (d, *J* = 8.2 Hz, 2H), 7.26 - 7.11 (m, 3H), 7.06 (d, *J* = 6.0 Hz, 2H), 6.19 (dt, *J* = 18.1, 9.4 Hz, 1H), 5.74 (s, 1H), 5.58 (d, *J* = 8.5 Hz, 1H), 5.38 - 5.19 (m, 2H), 1.27 (d, *J* = 2.8 Hz, 12H) ppm. **^{13}C NMR** (75 MHz, $CDCl_3$) δ 162.6, 147.0, 142.6, 132.2, 128.2, 128.0, 127.8, 127.7, 125.2, 118.1, 83.5, 53.4, 25.0 ppm. **^{19}F (282 MHz, $CDCl_3$)** δ -62.7 ppm. **^{11}B NMR** (160 MHz, $CDCl_3$) δ 29.9 ppm. **HRMS (APCI)** Calc. for $C_{24}H_{27}BF_3O_2$ [M+H$^+$] 415.2051, found 415.2053. **Optical rotation:** $[\alpha]_D^{25}$ + 7.0 (*c* = 1.0, $CHCl_3$)

*Quaternary C heterocoupled with F could not be seen.

Enantiomeric purity was determined by chiral SFC analysis [Lux Cellulose-1, 100 bar, T_{oven}: 40 °C, flow: 1 mL/min; 1% MeOH, λ = 220 nm, minor enantiomer t_R = 18.06 min, major enantiomer t_R = 19.65 min].



Peak Information

#	CH	tR [min]	Area [µV·sec]	Area%
1	10	18,763	1497752	49,978
2	10	19,943	1499092	50,022

Peak Information

#	CH	tR [min]	Area [µV·sec]	Area%
1	10	18,057	9336367	93,242
2	10	19,653	676694	6,758

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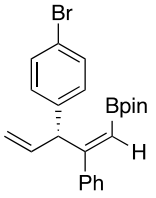
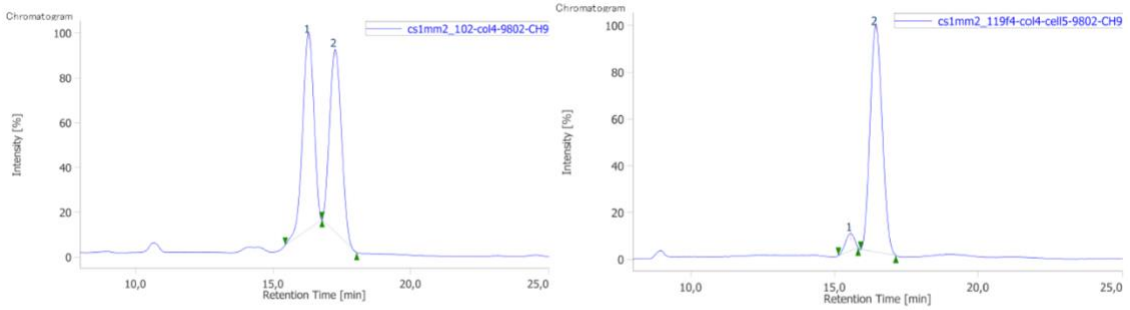
(*R*,*E*)-2-(3-(4-Bromophenyl)-2-phenylpenta-1,4-dien-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (4.22)



Obtained from **4.1** and **4.56** as a colorless oil after column chromatography (Hexane/CH_2Cl_2, 8:2) in 60% yield and 95:5 er, following method A. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.45 - 7.36 (m, 2H), 7.24 - 7.12 (m, 5H), 7.10 - 7.01 (m, 2H), 6.15 (ddd, *J* = 17.0, 10.0, 8.5 Hz, 1H), 5.71 (s, 1H), 5.50 (d, *J* = 8.5 Hz, 1H), 5.27 (dd, *J* = 17.0, 1.4 Hz, 1H), 5.20 (dd, *J* = 10.0, 1.4 Hz, 1H), 1.29 (s, 6H), 1.28 (s, 6H) ppm. **^{13}C NMR (75 MHz, $CDCl_3$)** δ 162.8, 142.5, 141.7, 138.3, 131.2, 129.6, 127.7, 127.4, 119.9, 117.7, 83.3, 52.8, 24.8 ppm. **^{11}B NMR** (160 MHz, $CDCl_3$) δ 30.1 ppm. **HRMS (APCI)** Calc. for $C_{23}H_{27}BBrO_2$ $[M+H^+]$ 425.1282, found 425.1282. **Optical rotation:** $[\alpha]_D^{25}$ + 25.7 (*c* = 1.0, $CHCl_3$)

Enantiomeric purity was determined by chiral SFC analysis [Lux Cellulose-5, 100 bar, T_{oven}: 40 °C, flow: 1 mL/min; 2% MeOH, λ = 205 nm, minor enantiomer t_R = 15.56 min, major enantiomer t_R = 16.44 min].



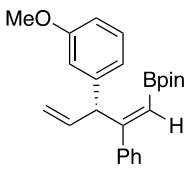
Peak Information

#	CH	tR [min]	Area [μV·sec]	Area%
1	9	16,293	6399176	50,463
2	9	17,257	6281750	49,537

Peak Information

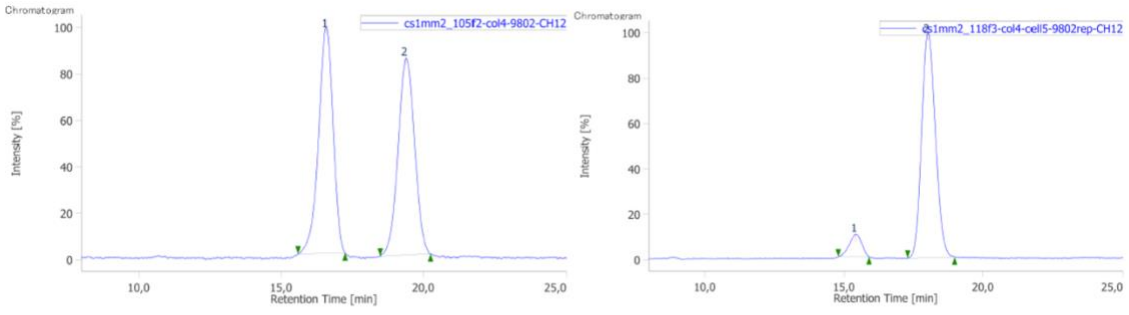
#	CH	tR [min]	Area [μV·sec]	Area%
1	9	15,563	230946	5,314
2	9	16,443	4114737	94,686

(*R*,*E*)-2-(3-(3-Methoxyphenyl)-2-phenylpenta-1,4-dien-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (4.23)



Obtained from **4.1** and **4.57** as a colorless oil after column chromatography (Hexane/CH_2Cl_2, 75:25) in 63% yield and 92:8 er, following method A. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.29 - 7.05 (m, 6H), 6.93 (d, *J* = 7.9 Hz, 2H), 6.77 (d, *J* = 8.0 Hz, 1H), 6.18 (ddd, *J* = 16.8, 10.1, 8.7 Hz, 1H), 5.71 (s, 1H), 5.55 (d, *J* = 8.7 Hz, 1H), 5.28 (dd, *J* = 16.8, 1.2 Hz, 1H), 5.20 (dd, *J* = 10.1, 1.2 Hz, 1H), 3.77 (s, 3H), 1.31 (s, 12H) ppm. **^{13}C NMR** (75 MHz, $CDCl_3$) δ 163.3, 159.6, 144.3, 138.7, 129.0, 127.8, 127.6, 127.3, 120.2, 117.3, 111.6, 83.2, 55.1, 53.3, 24.9, 24.8 ppm. **^{11}B NMR** (160 MHz, $CDCl_3$) δ 30.0 ppm. **HRMS (APCI)** Calc. for $C_{24}H_{30}BO_3$ $[M+H^+]$ 377.2283, found 377.2283. **Optical rotation:** $[\alpha]_D^{25}$ + 6.3 (*c* = 1.0, $CHCl_3$)

Enantiomeric purity was determined by chiral SFC analysis [Lux Cellulose-5, 100 bar, T_{oven}: 40 °C, flow: 1 mL/min; 2% MeOH, λ = 275 nm, minor enantiomer t_R = 15.42 min, major enantiomer t_R = 18.02 min].



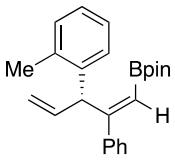
Peak Information

#	CH	tR [min]	Area [µV·sec]	Area%
1	12	16,590	1317869	50,263
2	12	19,380	1304054	49,737

Peak Information

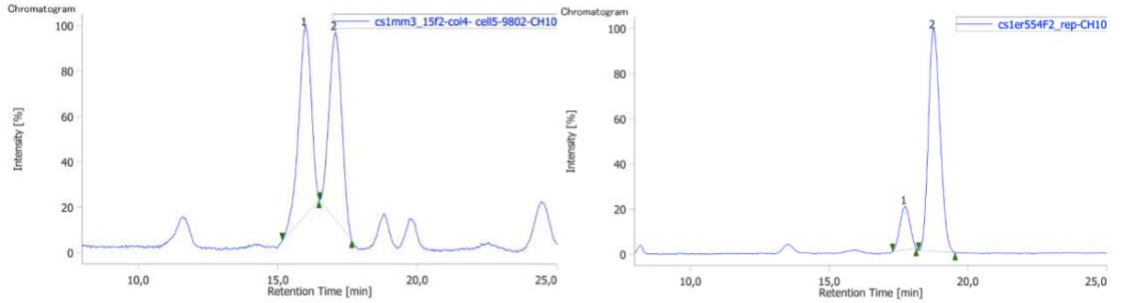
#	CH	tR [min]	Area [µV·sec]	Area%
1	12	15,420	133454	8,274
2	12	18,017	1479442	91,726

(*R*,*E*)-4,4,5,5-tetramethyl-2-(2-phenyl-3-(*o*-tolyl)penta-1,4-dien-1-yl)-1,3,2-dioxaborolane (4.24)



Obtained from **4.1** and **4.58** as a yellow oil after column chromatography (Hexane/CH_2Cl_2, 85:15) in 92% yield and 85.5:14.5 er, following method B. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.19 - 6.90 (m, 9H), 6.31 (ddd, J = 17.0, 10.2, 6.7 Hz, 1H), 5.67 (s, 1H), 5.65 (dt, J = 6.7, 1.7 Hz, 1H), 5.27 (dt, J = 17.0, 1.7 Hz, 1H), 5.20 (dt, J = 10.2, 1.7 Hz, 1H), 2.37 (s, 3H), 1.28 (s, 6H), 1.27 (s, 6H) ppm. **^{13}C NMR (**126 MHz, $CDCl_3$) δ 162.9, 143.7, 140.7, 140.2, 137.4, 130.2, 128.9, 128.1, 127.4, 127.1, 126.3, 125.6, 116.0, 83.2, 51.0, 25.0, 25.0, 20.0 ppm. **^{11}B NMR** (160 MHz, $CDCl_3$) δ 29.9 ppm. **HRMS (APCI)** Calc. for $C_{24}H_{30}BO_2$ $[M+H^+]$ 361.2333, found 361.2339. **Optical rotation:** $[\alpha]_D^{21}$ 23.9 (c = 0.88, $CHCl_3$)

Enantiomeric purity was determined by chiral SFC analysis [Lux Cellulose-5, 100 bar, T_{oven}: 40 °C, flow: 1 mL/min; 2% MeOH, λ = 220 nm, minor enantiomer t_R = 17.73 min, major enantiomer t_R = 18.76 min].



Peak Information

#	CH	tR [min]	Area [µV·sec]	Area%
1	10	15,987	1035558	50,301
2	10	17,060	1023181	49,699

Peak Information

#	Peak Name	CH	tR [min]	Area [µV·sec]	Area%
1	Unknown	10	17,733	821110	14,476
2	Unknown	10	18,757	4851288	85,524

(*R*,*E*)-4,4,5,5-Tetramethyl-2-(3-(naphthalen-2-yl)-2-phenylpenta-1,4-dien-1-yl)-1,3,2-dioxaborolane (4.25)

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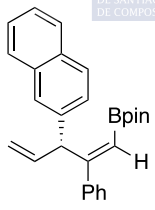
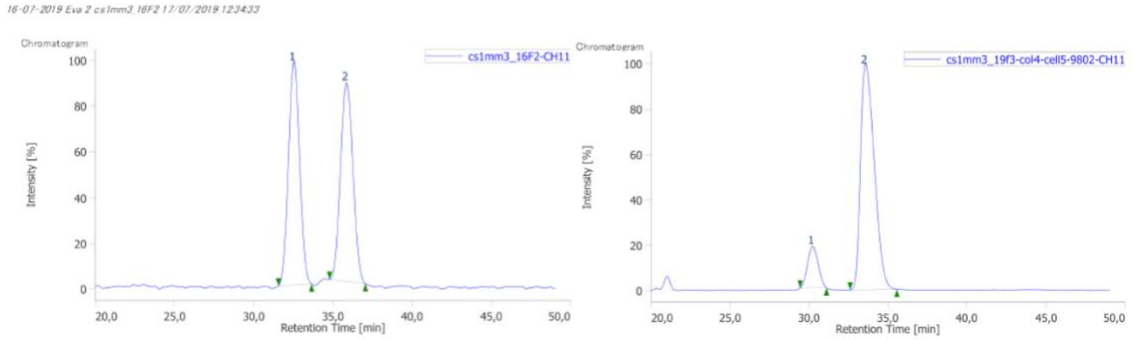


Obtained from **4.1** and **4.59**. Purified through flash column chromatography on silica gel (Hexane/CH_2Cl_2 75:25) to afford the desired product in 98% yield and 87.5:12.5 as colorless oil, following method A. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.87 - 7.69 (m, 4H), 7.57 - 7.41 (m, 3H), 7.19 - 7.06 (m, 5H), 6.29 (ddd, *J* = 17.0, 10.2, 8.7 Hz, 1H), 5.77 (s, 1H),

5.72 (d, *J* = 8.7 Hz, 1H), 5.34 (ddd, *J* = 17.0, 1.8, 0.9 Hz, 1H), 5.26 (dd, *J* = 10.2, 1.8 Hz, 1H), 1.28 (s, 6H), 1.27 (s, 6H) ppm. **^{13}C NMR** (75 MHz, $CDCl_3$) δ 163.3, 143.0, 140.4, 138.9, 133.7, 132.2, 128.0, 126.0, 127.8, 127.7, 127.5, 126.8, 126.1, 125.9, 125.5, 117.6, 83.8, 83.4, 53.6, 25.0, 24.9 ppm. **^{11}B NMR (**160 MHz, $CDCl_3$) δ 30.3 ppm. **HRMS (APCI)** Calc. for $C_{27}H_{29}BO_2$ [M+H$^+$] 397.2333, found 397.2338. **Optical rotation:** $[\alpha]_D^{24}$ +18.5 (*c* = 1.0, $CHCl_3$)

Enantiomeric purity was determined by chiral SFC analysis [Lux Cellulose-5, 100 bar, T_{oven}: 40 °C, flow: 1 mL/min; 2% MeOH, λ = 250 nm, minor enantiomer t_R = 30.23 min, major enantiomer t_R = 33.60 min].



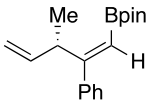
Peak Information

#	Peak Name	CH	tR [min]	Area [µV·sec]	Area%
1	Unknown	11	32.527	1850625	50.325
2	Unknown	11	35.853	1826729	49.675

Peak Information

#	CH	tR [min]	Area [µV·sec]	Area%
1	11	30.230	1604179	12.494
2	11	33.590	11235770	87.506

(*S*,*E*)-4,4,5,5-Tetramethyl-2-(3-methyl-2-phenylpenta-1,4-dien-1-yl)-1,3,2-dioxaborolane (4.26)



Obtained from **4.1** and **4.60**. Purified through flash column chromatography on silica gel (Hexane/CH_2Cl_2 85:15) to afford the desired product in 88% yield and 95:5 er as yellow oil, following method B. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.37 - 7.13 (m, 5H), 6.04 (ddd, *J* = 16.8, 10.3, 6.8 Hz, 1H), 5.43 (s, 1H), 5.12 (d, *J* = 16.8 Hz, 1H), 5.05 (d, *J* = 10.3 Hz, 1H), 4.20 (p, *J* = 6.8 Hz, 1H), 1.31 (s, 12H), 1.14 (d, *J* = 6.8 Hz, 3H) ppm. **^{13}C NMR** (75 MHz, $CDCl_3$) δ 166.6, 143.7, 143.3, 127.7, 127.2, 113.4, 83.2, 41.8, 25.0, 18.5 ppm. **^{11}B NMR** (160 MHz, $CDCl_3$) δ 30.0 ppm. **HRMS (APCI)** Calc. for $C_{18}H_{25}BO_2$ [M+H$^+$] 285.2020, found 285.2022. **Optical rotation:** $[\alpha]_D^{24}$ -25.5 (*c* = 1.0, $CHCl_3$)

Enantiomeric purity was determined on two derivatization products (see product **4.38** and product **4.39**).

4.3.1. Cyclopropanation reaction

Method A. Synthesis of aldehydes and ketones

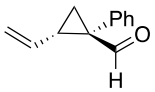
Diene (1.0 equiv) was dissolved in THF 1:1 H_2O (0.1 M). Sodium perborate tetrahydrate (5 equiv) was added and the reaction was stirred at room temperature upon complete conversion of starting material. After this time, the mixture was diluted in AcOEt (2 mL) and washed with aq. NaCl (5 mL). Then the aqueous layer was extracted with AcOEt (2 mL). The organic layer was dried, and the solvents were evaporated under vacuum. The

final product was purified by SiO_2 column chromatography using the indicated mixture of eluents for each case.

Method B. Synthesis of alcohols

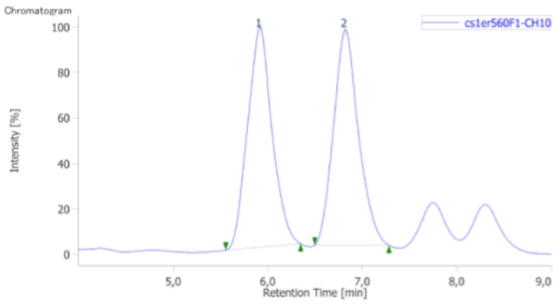
Diene (1.0 equiv) was dissolved in dry methanol (0.1 M). Sodium perborate tetrahydrate (5 equiv) was added and the reaction was stirred at room temperature upon complete conversion of starting material. After this time, $NaBH_4$ (1.5 equiv) was added and was stirred at room temperature upon complete conversion of starting material. After this time, the mixture was diluted in AcOEt (2 mL) and washed with aq. NaCl (5 mL). Then the aqueous layer was extracted with AcOEt (2 mL). The organic layer was dried, and the solvents were evaporated under vacuum. The final product was purified by SiO_2 column chromatography using the indicated mixture of eluents for each case.

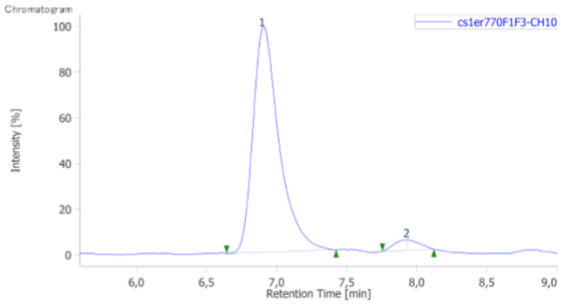
(1*R*,2*S*)-1-Phenyl-2-vinylcyclopropanecarbaldehyde (4.30)



Obtained from diene **4.4** and purified through flash column chromatography on silica gel (Hexane/CH_2Cl_2 9/1) to afford the desired product in 51% yield and 96:4 er as colorless oil. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 9.48 (s, 1H), 7.56 - 7.16 (m, 5H), 5.34 - 5.13 (m, 1H), 5.10 - 4.78 (m, 2H), 2.47 (td, *J* = 8.8, 6.7 Hz, 1H), 2.01 (dd, *J* = 8.8, 4.7 Hz, 1H), 1.66 (dd, *J* = 6.7, 4.7 Hz, 1H) ppm. **^{13}C NMR** (75 MHz, $CDCl_3$) δ 200.9, 135.7, 134.8, 131.1, 128.8, 127.9, 117.1, 44.2, 34.2, 21.1 ppm. **HRMS (APCI)** Calc. for $C_{12}H_{13}O$ [M+H$^+$] 173.0961, found 173.0959. **Optical rotation:** $[\alpha]_D^{21}$ -7.8 (*c* = 0.44, $CHCl_3$)

Enantiomeric purity was determined by chiral SFC analysis [Lux Amylose-1, 100 bar, T_{oven}: 40 °C, flow: 1 mL/min; 5% MeOH, λ = 220 nm, major enantiomer t_R = 6.91 min, major enantiomer t_R = 7.94 min].





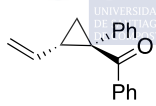
Peak Information

#	CH	tR [min]	Area [µV·sec]	Area%
1	10	5,920	5462456	49,999
2	10	6,820	5462596	50,001

Peak Information

#	Peak Name	CH	tR [min]	Area [µV·sec]	Area%
1	Unknown	10	6,907	1342971	95,699
2	Unknown	10	7,937	60364	4,301

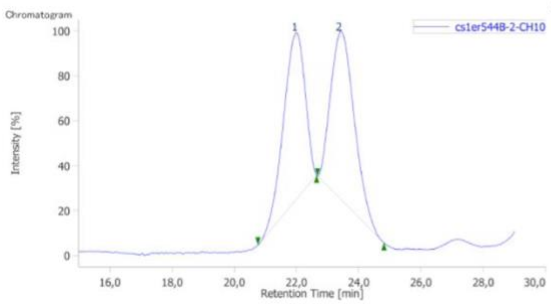
Phenyl((1*R*,2*S*)-1-phenyl-2-vinylcyclopropyl)methanone (4.31)



Obtained from **4.15**. Purified through flash column chromatography on silica gel (Hexane to hexane/CH_2Cl_2 80/20) to afford the desired product as a yellow oil in 60% yield and 80:20 er as a mixture 10:1 of diastereoisomers. NMR data of major diastereoisomer given. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.74 - 7.66 (m, 2H), 7.45 - 7.13 (m, 8H), 5.34 - 5.23 (m, 1H), 5.08 - 4.92 (m, 2H), 2.97 - 2.78 (m, 1H), 1.89 - 1.75 (m, 2H) ppm. **^{13}C NMR** (75 MHz, $CDCl_3$) δ 200.0,

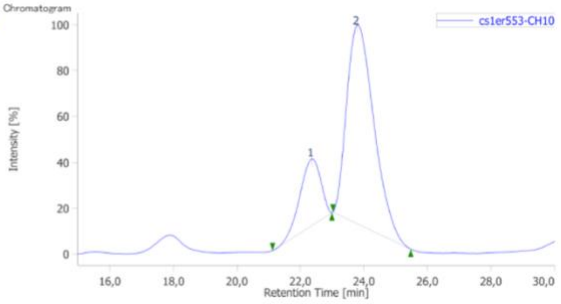
137.4, 137.1, 136.5, 131.8, 130.4, 129.3, 128.6, 128.0, 127.1, 116.4, 30.2, 21.5 ppm. **HRMS (APCI)** Calc. for $C_{18}H_{17}O$ [M+H$^+$] 249.1274, found 249.1270. **Optical rotation:** $[\alpha]_D^{23}$ -7.4 (*c* = 1.0, $CHCl_3$)

Enantiomeric purity of the major diastereoisomer was determined by chiral SFC analysis [Lux Amylose-1, 100 bar, T_{oven}: 40 °C, flow: 1 mL/min; 2% MeOH, λ = 220 nm, minor enantiomer t_R = 22.37 min, major enantiomer t_R = 23.80 min].



Peak Information

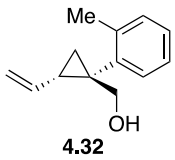
#	CH	tR [min]	Area [µV·sec]	Area%
1	10	21.987	3125522	47.560
2	10	23.407	3446193	52.440



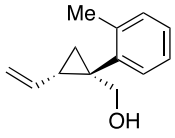
Peak Information

#	CH	tR [min]	Area [µV·sec]	Area%
1	10	22.367	4046628	20.403
2	10	23.800	15787088	79.597

(1*R*,2*S*)-1-(*o*-Tolyl)-2-vinylcyclopropyl)methanol and ((1*S*,2*S*)-1-(*o*-Tolyl)-2-vinylcyclopropyl)methanol (4.32 and 4.32')



4.32



4.32'

Obtained from **4.10**. Purified through flash column chromatography on silica gel (Hexane/AcOEt 90:10) to afford the desired product as a yellow oil in 66% yield and 94:6 er as a mixture 3:1 of diastereoisomers **4.32** and **4.32'**. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.39-7.23 (m, 3H **4.32'**), 7.21-7.11 (m, 13H (12H **4.32** and 1H **4.32'**)), 5.88 (ddd, *J* = 17.0, 10.2, 8.4 Hz, 1H **4.32'**), 5.31 (ddd, *J* = 17.0, 1.7, 0.9 Hz, 1H **4.32'**), 5.22-5.06 (m, 4H (3H **4.32** and 1H **4.32'**)), 4.99 (s, br, 3H **4.32**), 4.85 (s, br, 3H **4.32**), 4.09 (s, br, 3H **4.32**), 3.80-3.66 (m, 2H **4.32'**), 3.29-3.08 (m, 3H **4.32**), 2.41 (s, 3H **4.32'**), 2.40-2.34 (m, 9H **4.32**), 1.88 (m, 4H (3H **4.32** and 1H **4.32'**)), 1.37 (s, br, 3H **4.32**), 1.25-1.22 (m, 1H **4.32'**), 1.11 (dd, *J* = 5.9, 4.9 Hz, 1H **4.32'**), 0.96 (s, 3H) ppm. **^{13}C NMR** (160 MHz, $CDCl_3$) δ 140.9, 139.3, 138.7, 138.2, 136.8, 132.3, 132.0, 131.5, 130.9, 130.8, 127.4, 127.3, 126.0, 116.4, 115.3, 114.1, 69.2, 66.4, 34.1, 29.8, 28.4, 26.9, 21.2, 19.6, 19.5, 18.9 ppm. **HRMS (APCI)** Calc. for $C_{13}H_{17}O$ [M+H$^+$] 189.1274, found 189.1274. **Optical rotation:** $[\alpha]_D^{21}$ -2.4 (*c* = 0.55, $CHCl_3$)

Enantiomeric purity of major diastereoisomer was determined by chiral SFC analysis [Lux Amylose-1, 100 bar, T_{oven}: 40 °C, flow: 1 mL/min; 5% MeOH, λ = 220 nm, minor enantiomer t_R = 12.47 min, major enantiomer t_R = 14.30 min].

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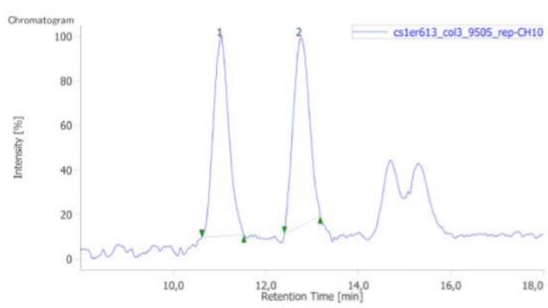
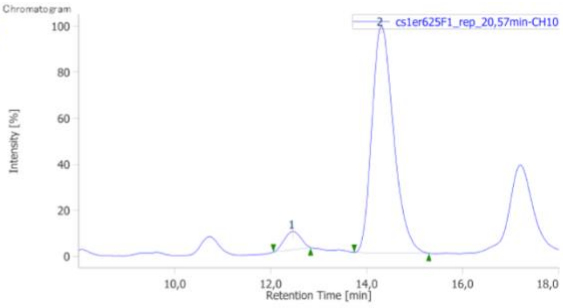


Peak Information

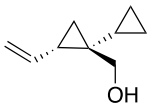
#	CH	tR [min]	Area [µV·sec]	Area%
1	10	11,033	194983	50,348
2	10	12,750	192288	49,652



Peak Information

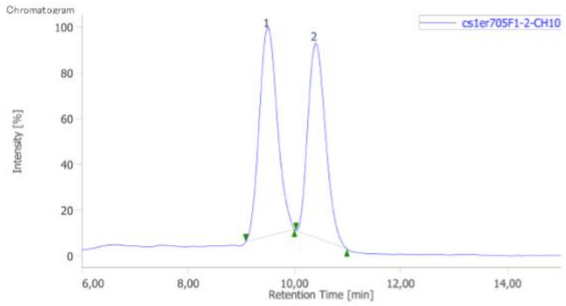
#	Peak Name	CH	tR [min]	Area [µV·sec]	Area%
1	Unknown	10	12,467	433669	5,868
2	Unknown	10	14,303	6957119	94,132

((1*S*,2*S*)-2-Vinyl-[1,1'-bi(cyclopropan)]-1-yl)methanol (4.33)



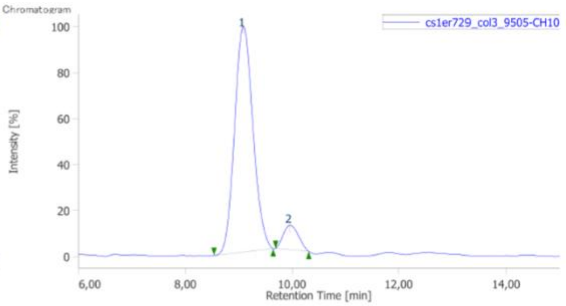
Obtained from **4.13**. Purified through flash column chromatography on silica gel (Hexane/AcOEt 90/10) to afford the desired product in 70% yield and 92:8 er as colorless oil with a 10:1 diastereomeric ratio. NMR data of major diastereoisomer given. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 5.69 (dt, *J* = 17.1, 9.8 Hz, 1H), 5.15 (dd, *J* = 17.1, 2.0 Hz, 1H), 4.97 (dd, *J* = 9.8, 2.0 Hz, 1H), 3.61 (d, *J* = 11.1 Hz, 1H), 3.33 (d, *J* = 11.1 Hz, 1H), 1.58 (m, 2H), 1.04 (tt, *J* = 8.3, 5.4 Hz, 1H), 0.58 (td, *J* = 8.8, 4.3 Hz, 2H), 0.53 - 0.40 (m, 1H), 0.34 (t, *J* = 5.2 Hz, 1H), 0.31 - 0.12 (m, 2H) ppm. **^{13}C NMR** (75 MHz, $CDCl_3$) δ 138.2, 114.2, 71.1, 30.3, 27.2, 14.1, 10.3, 3.9, 2.9 ppm. **HRMS (APCI)** Calc. for $C_9H_{15}O$ $[M+H^+]$ 139.1117, found 139.1114. **Optical rotation:** $[\alpha]_D^{21}$ +33.6 (*c* = 0.73, $CHCl_3$)

Enantiomeric purity was determined by chiral SFC analysis [Lux Amylose-1, 100 bar, T_{oven}: 40 °C, flow: 1 mL/min; 5% MeOH, λ = 220 nm, major enantiomer t_R = 9.09 min, minor enantiomer t_R = 9.96 min].



Peak Information

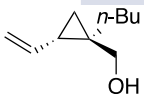
#	CH	tR [min]	Area [µV·sec]	Area%
1	10	9,497	1930123	52,244
2	10	10,397	1764295	47,756



Peak Information

#	CH	tR [min]	Area [µV·sec]	Area%
1	10	9,087	1601000	91,834
2	10	9,963	142361	8,166

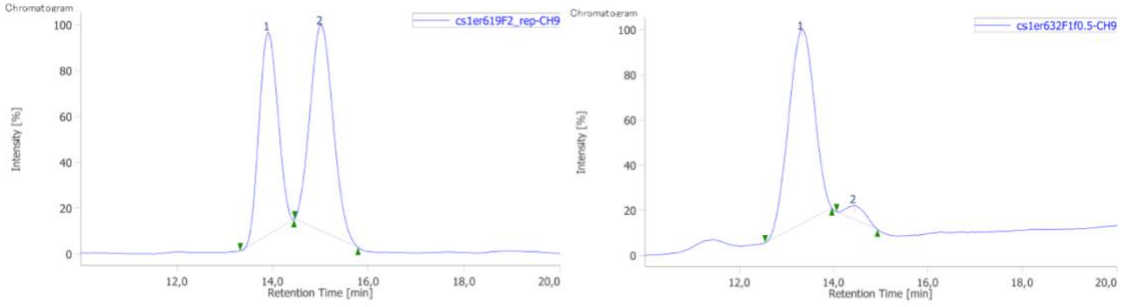
((1*R*,2*S*)-1-Butyl-2-vinylcyclopropyl)methanol (4.34)



Obtained from **4.14**. Purified through flash column chromatography on silica gel (Hexane/AcOEt 90/10) to afford the desired product in 68% yield and 95:5 er as colorless oil with a 5:1 diastereomeric ratio. NMR data of major diastereoisomer given. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 5.60 (ddd, *J* = 17.0, 10.2, 8.5 Hz, 1H), 5.10 (dd, *J* = 17.1, 1.3 Hz, 1H) 4.99 (dd, *J* = 10.3, 1.9 Hz, 1H), 3.44 (d, *J* =

11.2 Hz, 1H), 3.38 (d, *J* = 11.2 Hz, 1H), 1.52 - 1.14 (m, 7H), 0.88 (t, *J* = 7.1 Hz, 3H), 0.77 (dd, *J* = 8.6, 4.7 Hz, 1.H), 0.45 (t, *J* = 5.1 Hz, 1H) ppm. **^{13}C NMR** (75 MHz, $CDCl_3$) δ 137.7, 114.7, 68.9, 35.4, 29.4, 28.9, 25.9, 23.2, 17.6, 14.2 ppm. **HRMS (APCI)** Calc. for $C_{10}H_{19}O$ [M+H$^+$] 155.1430, found 155.1428. **Optical rotation:** $[\alpha]_D^{21}$ -2.0 (*c* = 0.3, $CHCl_3$)

Enantiomeric purity was determined by chiral SFC analysis [Lux Amylose-1, 100 bar, T_{oven}: 40 °C, flow: 0.5 mL/min; 5% MeOH, λ = 205 nm, major enantiomer t_R = 13.33 min, minor enantiomer t_R = 14.55 min].



Peak Information

#	Peak Name	CH	tR [min]	Area [µV·sec]	Area%
1	Unknown	9	13.910	7378666	44.428
2	Unknown	9	15.017	9229346	55.572

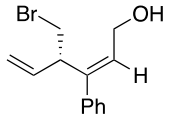
Peak Information

#	CH	tR [min]	Area [µV·sec]	Area%
1	9	13.330	1972046	94.913
2	9	14.447	105697	5.087

4.3.2. Synthesis of heterocycles

(*S*,*E*)-4-(Bromomethyl)-3-phenylhexa-2,5-dien-1-ol (4.35)

In a schlenk flask, **4.4** (2.0 equiv, 0.4 mmol) and CH_2Br_2 (4.0 equiv, 0.8 mmol) were dissolved in9bml of dry THF. *n*-BuLi (1.0 equiv, 0.2 mmol) were added at -78°C. The mixture was stirred 30 min at that temperature. After this time, the reaction was stirred at room temperature for 1 h and 30 min. After this time, $NaBO_3 \cdot 4H_2O$ (10 equiv, 2 mmol) was added dissolved in 2 ml of H_2O and let stirring for 1 h. After this time, the mixture was diluted in AcOEt (2 mL) and washed with NH_4Cl (5 mL). Then the aqueous layer was extracted with AcOEt (2 mL). The organic layer was dried, and the solvents were evaporated under vacuum. The final product was purified by SiO_2 column chromatography (Hexane/AcOEt 80/20) to afford a mixture of the desired product in 45% yield and the homoallylic alcohol (11%) that could not be separated.

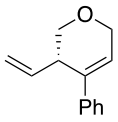


^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38 - 7.08 (m, 5H), 5.99 - 5.75 (m, 2H), 5.19 (d, 2H), 4.38 (dd, *J* = 13.0, 7.1 Hz, 1H), 4.28 (dd, *J* = 13.1, 6.5 Hz, 1H), 3.92 - 3.77 (m, 1H), 3.43 (dd, *J* = 10.3, 6.1 Hz, 1H), 3.35 - 3.24 (m, 1H) ppm. **^{13}C NMR** (75 MHz, $CDCl_3$) δ 142.3, 137.2, 131.7, 129.2, 128.1, 127.5, 117.4, 59.0, 47.9, 34.4 ppm. **HRMS (APCI)** Calc. for $C_{13}H_{14}Br$ [M-H_2O] 249.0273, found 249.0270. **Optical rotation:** $[\alpha]_D^{21}$ +23.8 (*c* = 2.4, $CHCl_3$)

(*S*)-4-Phenyl-3-vinyl-3,6-dihydro-2*H*-pyran (4.37)

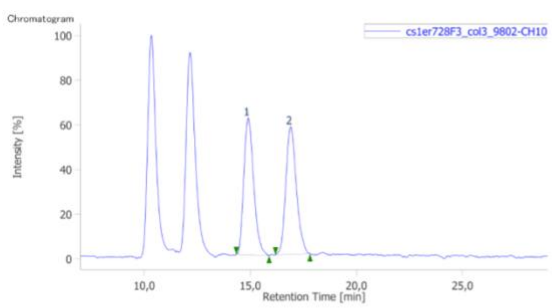
4.35 (1.0 equiv, 0.1 mmol) was dissolved in 1 ml of dry DMF and Na_2CO_3 was added and the reaction was left stirring overnight. After this time, the mixture was diluted in AcOEt (2 mL) and washed with aq. NaCl (5 mL). Then, the aqueous layer was extracted

with AcOEt (2 mL). The organic layer was dried, and the solvents were evaporated under vacuum. The final product was purified by SiO_2 column chromatography (Hexane/AcOEt 90/10) to afford the desired product in 88% yield and 97.5:2.5 er as colorless oil.



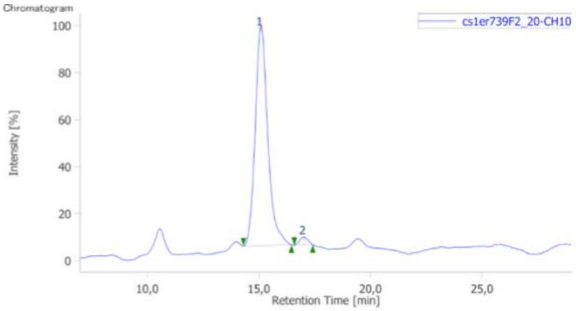
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.50 - 7.20 (m, 5H), 6.15 (t, *J* = 2.9 Hz, 1H), 5.90 (ddd, *J* = 17.5, 9.8, 7.4 Hz, 1H), 5.18 - 5.04 (m, 2H), 4.37 (q, *J* = 2.9, 2.5 Hz, 2H), 4.01 - 3.80 (m, 2H), 3.33 (s, 1H) ppm. **^{13}C NMR** (75 MHz, $CDCl_3$) δ 139.8, 138.3, 136.6, 128.5, 127.4, 125.8, 123.8, 117.2, 69.4, 66.3, 41.0 ppm. **HRMS (APCI)** Calc. for $C_{13}H_{15}O$ [M+H$^+$] 187.1117, found 187.1116. **Optical rotation:** $[\alpha]_D^{21}$ +104.8 (*c* = 0.73, $CHCl_3$)

Enantiomeric purity was determined by chiral SFC analysis [Lux Amylose-1, 100 bar, T_{oven}: 40 °C, flow: 1 mL/min; 2% MeOH, λ = 220 nm, major enantiomer t_R = 15.09 min, minor enantiomer t_R = 17.02 min].



Peak Information

#	CH	tR [min]	Area [µV·sec]	Area%
1	10	14,893	1676648	49,980
2	10	16,897	1677982	50,020



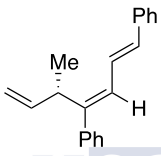
Peak Information

#	Peak Name	CH	tR [min]	Area [µV·sec]	Area%
1	Unknown	10	15,093	1667123	97,592
2	Unknown	10	17,023	41130	2,408

4.3.3. Synthesis of 4.38 by Suzuki coupling.

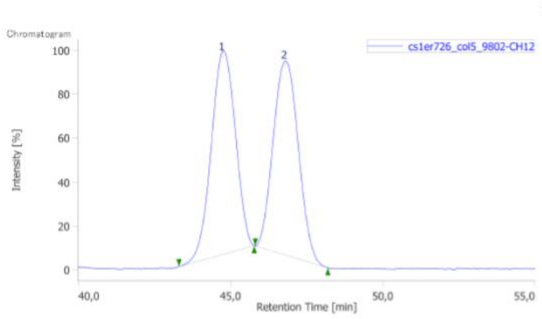
((*S*,1*E*,3*E*)-5-Methylhepta-1,3,6-triene-1,4-diyl)dibenzene (4.38)

$Pd(PPh_3)_4$ (10 mol%, 0.04 mmol) was added to a schlenk flask. Then, **4.26** (1.0 equiv, 0.4 mmol) was added in 1,4-dioxane (4.0 ml), followed by the adition of β-bromostyrene (1.5 equiv 0.6 mmol) and aq. NaOH (2.0 M, 2.0 equiv, 0.8 mmol). The reaction was stirred at 100°C for 16 hours. After this time, the resulting crude was diluted in Et_2O (15 ml) and washed with H_2O (2x10 ml). The organic layer was dried over Na_2SO_4, filtered and taken to dryness. The residue was purified by column chromatography (hexane) affording the desired product as a yellow oil in 99% yield and 95:5 er



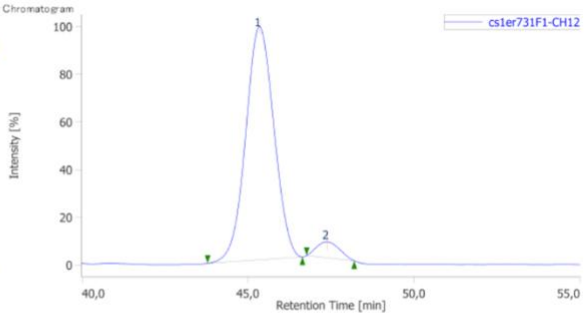
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.52 - 7.20 (m, 11H), 6.66 (d, *J* = 15.5 Hz, 1H), 6.42 (d, *J* = 11.3 Hz, 1H), 6.16 (ddd, *J* = 17.4, 10.4, 4.8 Hz, 1H), 5.31 - 5.14 (m, 2H), 4.05 - 3.86 (m, 1H), 1.34 (d, *J* = 7.2 Hz, 3H) ppm. **^{13}C NMR** (75 MHz, $CDCl_3$) δ 145.4, 142.9, 142.5, 137.8, 133.6, 129.5, 128.8, 128.0, 127.7, 127.7, 127.0, 126.5, 125.2, 113.8, 38.9, 18.6 ppm. **HRMS (APCI)** Calc. for $C_{20}H_{21}$ [M+H$^+$] 261.1638, found 261.1639. **Optical rotation:** $[\alpha]_D^{21}$ -40.9 (*c* = 1.0, $CHCl_3$)

Enantiomeric purity was determined by chiral SFC analysis [Lux Cellulose-1, 100 bar, T_{oven}: 40 °C, flow: 1 mL/min; 2% MeOH, λ = 275 nm, major enantiomer t_R = 45.35 min, minor enantiomer t_R = 47.39 min].



Peak Information

#	CH	tR [min]	Area [µV·sec]	Area%
1	12	44.757	3151787	50.138
2	12	46.810	3134407	49.862



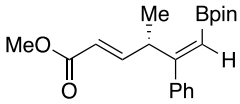
Peak Information

#	CH	tR [min]	Area [µV·sec]	Area%
1	12	45.347	9301834	94.728
2	12	47.387	517726	5.272

4.3.4. Synthesis of 4.39 by cross-metathesis.

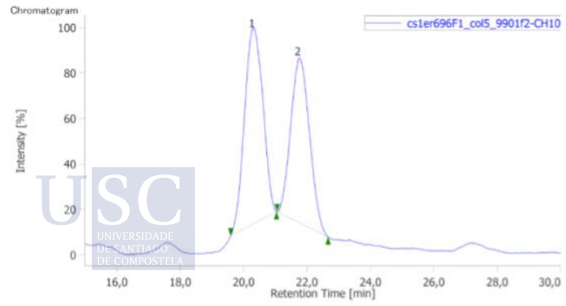
(*S*,2*E*,5*E*)-Methyl 4-methyl-5-phenyl-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)hexa-2,5-dienoate (4.39)

Hoveyda-Grubbs 2nd generation catalyst (7.5 mol%, 0.015 mmol) was added to a schlenk flask. Then, **4.26** (1.0 equiv, 0.2 mmol) was added in dry CH_2Cl_2 (0.4 ml), followed by the adition of methylacrylate (3 equiv, 1.0 mmol). The reaction was stirred at room temperature for 16 hours. After this time, the resulting crude was filtrated in SiO_2 using CH_2Cl_2 as eluent. The residue was purified by column chromatography (hexane to hexane/AcOEt 20:1) affording the desired product as a yellow oil in 81% yield and 95.5:4.5 er.



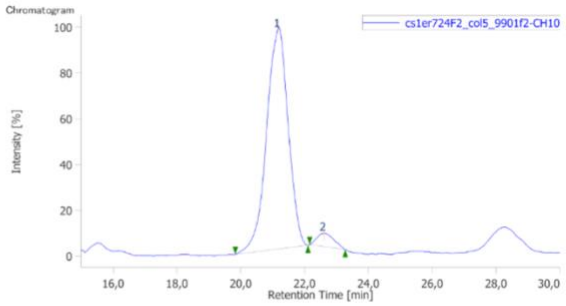
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37 - 7.13 (m, 6H), 5.93 (dd, *J* = 15.8, 2.0 Hz, 1H), 5.54 (s, 1H), 4.48 - 4.32 (m, 1H), 3.76 (s, 3H), 1.32 (s, 12H), 1.21 (d, *J* = 7.0 Hz, 3H) ppm. **^{13}C NMR** (75 MHz, $CDCl_3$) δ 167.5, 164.7, 153.7, 142.8, 128.0, 127.6, 127.5, 119.9, 83.4, 51.6, 40.8, 25.0, 24.9, 18.3 ppm. **HRMS (APCI)** Calc. for $C_{20}H_{28}BO_4$ [M+H$^+$] 343.2075, found 343.2081. **Optical rotation:** $[\alpha]_D^{21}$ -38.0 (*c* = 1.0, $CHCl_3$)

Enantiomeric purity was determined by chiral SFC analysis [Lux Cellulose-1, 100 bar, T_{oven}: 40 °C, flow: 2 mL/min; 1% MeOH, λ = 220 nm, major enantiomer t_R = 21.18 min, minor enantiomer t_R = 22.62 min].



Peak Information

#	CH	tR [min]	Area [µV·sec]	Area%
1	10	20.303	3447921	53.801
2	10	21.753	2960737	46.199

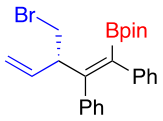


Peak Information

#	CH	tR [min]	Area [µV·sec]	Area%
1	10	21.183	4985428	95.486
2	10	22.617	235669	4.514

4.3.5. X-ray diffraction analysis data of product 4.15

Product **4.15** was dissolved in CH_2Cl_2 in hexane atmosphere and leaving to slow evaporation overnight to yield clear colorless plate type of crystals of an approximate dimensions 0.23 mm x 0.18 mm x 0.05 mm. The X-ray intensity data were measured on a Bruker D8 Venture Photon 100 CMOS diffractometer system equipped with a Incoatec HeliosTM multilayer optics monochromator and a MoKα sealed x-ray tube (λ = 0.71073 Å). The structure was solved and refined using the Bruker SHELXTL Software Package. Mixture of enantiomers crystalized with a 80% of the (*S*) enantiomer and a 20% of the (*R*) enantiomer. CCDC database number: 1947971



4.15

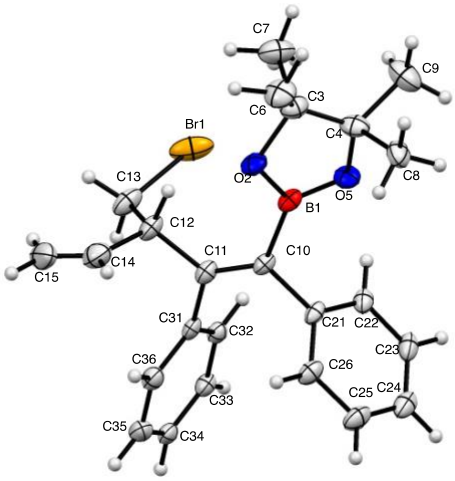


Figure 32. ORTEP plot of with 30% ellipsoids. Selected bond distances (Å) and angles (°): B1-C10 (1.642), C10-C11 (1.340), C10-C21 (1.515), C11-C12 (1.526), C14-C15 (1.196); C11-C10-B1 (123.6).

4.3.6. X-ray diffraction analysis data of product 4.20

Product **4.20** was dissolved in DCE in hexane atmosphere and leaving to slow evaporation overnight to yield clear colorless plate type of crystals of an approximate dimensions 0.08 mm x 0.07 mm x 0.06 mm. The X-ray intensity data were measured on a Bruker D8 VENTURE PHOTON III-14 diffractometer system equipped with a Incoatec multilayer mirror monochromator and a Cu Kα sealed x-ray tube (λ = 1.54178 Å). The structure was solved and refined using the Bruker SHELXTL Software Package. CCDC number 1947972.

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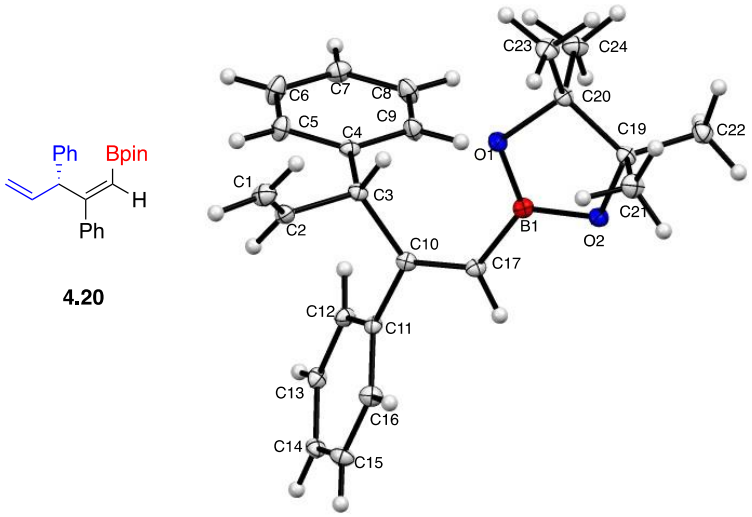

Figure 33. ORTEP plot of **4.20** with 30% ellipsoids. Selected bond distances (Å) and angles (°): C1-C2 (1.319), C17-B1 (1.558), C10-C17 (1.394), C10-C3 (1.531); C10-C17-B1 (128.9).

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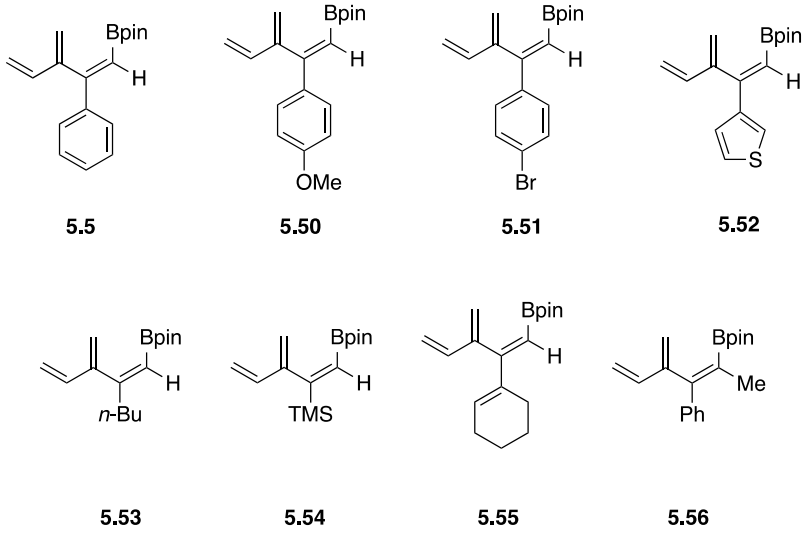
5. CHAPTER V:

5.1. LIST OF STARTING MATERIAL



5.5 **5.50** **5.51** **5.52**

5.53 **5.54** **5.55** **5.56**

Figure 34. List of starting material.

5.1.1. Preparation of 4-fluorophenyllithium and 4-methylphenyllithium

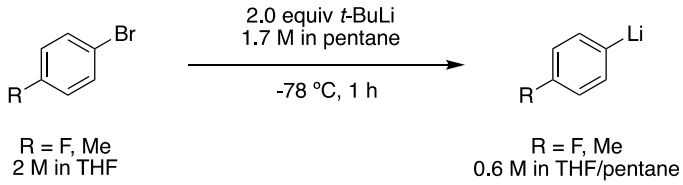


Figure 35. Preparation of aryllithium reagents.

In a dry Schlenk flask the corresponding bromide (1.0 equiv, 1.0 mmol) was dissolved in dry THF (0.5 mL) and the solution was cooled down to -78 °C. Then, *t*-BuLi (2.0 equiv, 1.7 M in pentane) was added slowly and the solution was stirred for 1 h. Then, the mixture was warmed to room temperature and the solution of the resulting organolithium compound (0.6 M) was directly used.

5.2. GENERAL PROCEDURE FOR MECHANISTIC STUDIES

Procedure for Figure 25a and 26a: 1.0 equiv RLi was added over a solution of dendralene **5.5** in THF (0.2 M) at -78 °C. The mixture was stirred for 15 min at that temperature and then it was warmed to room temperature and transferred to an NMR tube under argon atmosphere. Then, 1.2 equiv of I_2 in MeOH were added at 0 ºC.

Procedure for Figure 25b and 26b and c: 2.0 equiv RLi was added over a solution of dendralene **5.5** in THF (0.2 M) at -78 °C. The mixture was stirred for 15 min at that

temperature and then it was warmed to room temperature and transferred to an NMR tube under argon atmosphere. Then, 1.2 equiv of I_2 in MeOH were added at 0 ºC.

The formation of PhBpin was detected when RLi = PhLi by GC-MS and ^{1}H-NMR analysis of the reaction crude (Figure 36). PhBpin was isolated by flash column chromatography in 57% yield.

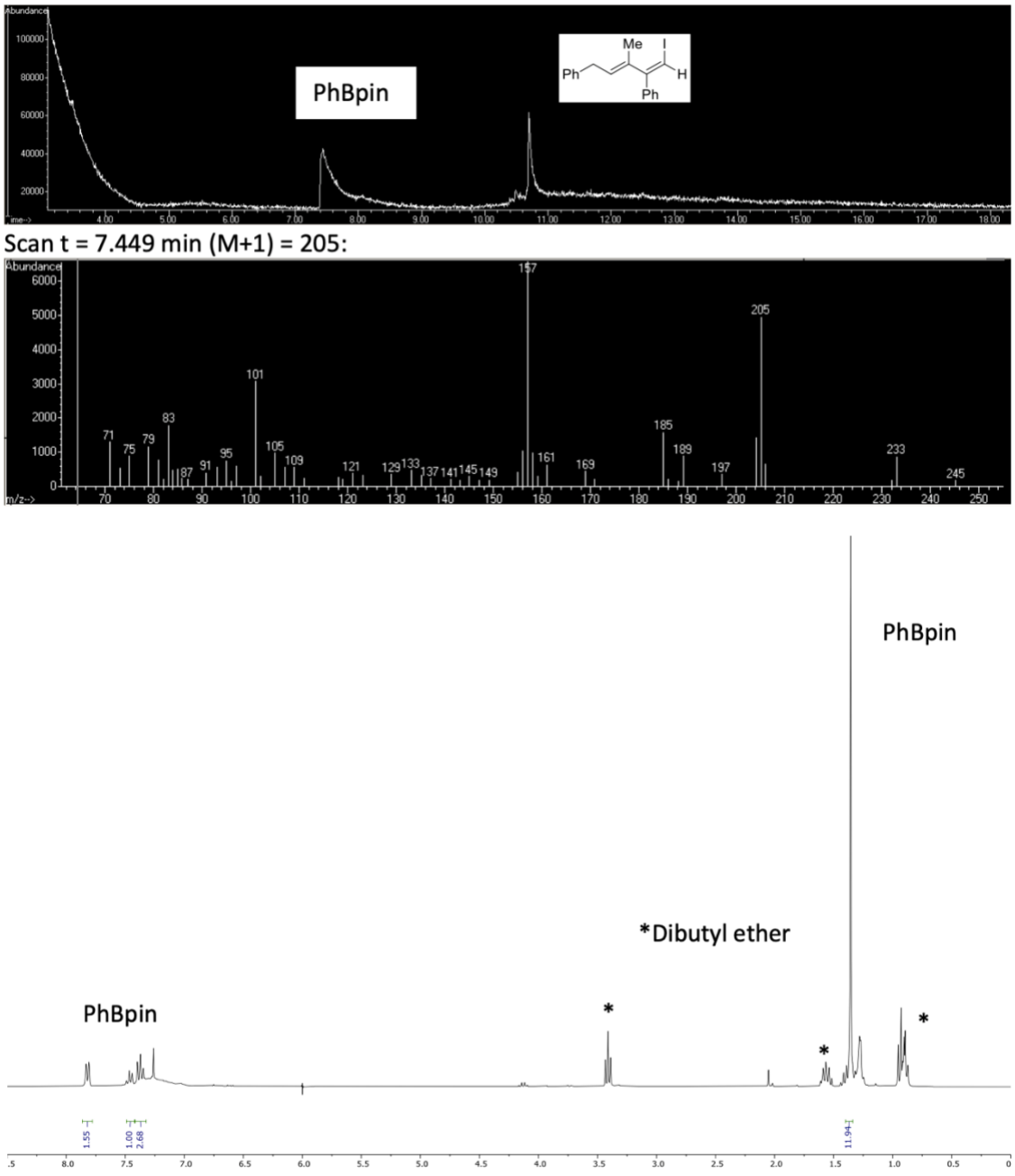


Figure 36. GC-MS analysis of the reaction crude and ^{1}H-NMR of isolated PhBpin.

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5.3. GENERAL PROCEDURES

General procedure A: A solution of the organolithium reagent RLi (2.2 equiv, 0.44 mmol) was added over a solution of the corresponding dendralene (1.0 equiv, 0.2 mmol)

in THF (0.2 M, 1 ml) at -78 °C. The mixture was then warmed to 0 °C and I_2 (1.2 equiv, 0.24 mmol) in MeOH (0.5 M, 0.5 ml) was added and stirred at that temperature for 30 min. After this time, the mixture was warmed to room temperature, solvent was evaporated under reduced pressure, and the product was purified by flash column chromatography.

General procedure B: PhLi (1.0 equiv, 0.2 mmol 1.9 M in Bu_2O) was added over a solution of the dendralene (1.0 equiv, 0.2 mmol) in THF (0.2 M, 1 ml) at -78 °C, warmed to 0 °C and stirred for 10 min. After this time, the mixture was cooled to -78 °C and RLi (1.2 equiv, 0.24 mmol) was added. At this temperature, I_2 (1.2 equiv, 0.24 mmol) in MeOH (0.5 M, 0.5 ml) was added, the mixture was warmed to 0 °C and stirred at that temperature for 30 min. After this time, the mixture was warmed to room temperature, solvent was evaporated under reduced pressure, and the product was purified by flash column chromatography.

General procedure C: RLi (2.2 equiv, 0.44 mmol) was added over a solution of the corresponding dendralene (1.0 equiv, 0.2 mmol) in THF (0.2 M, 1 ml) at -78 °C. The mixture was then warmed to 0 °C and electrophile E^1 (2.0 equiv, 0.4 mmol) was added, followed by subsequent addition of electrophile E^2 (1.2 equiv, 0.24 mmol). The resulting mixture was stirred at 0 °C for 30 min. After this time, the mixture was warmed to room temperature, solvent was evaporated under reduced pressure, and the product was purified by flash column chromatography.

General procedure D: PhLi (1.0 equiv, 0.2 mmol, 1.9 M in Bu_2O) was added over a solution of the corresponding dendralene (1.0 equiv, 0.2 mmol) in THF (0.2 M, 1 ml) at -78 °C. Then, the mixture was warmed to 0 °C and stirred for 10 min. After this time, the mixture was cooled to -78 °C and organolithium reagent RLi (1.2 equiv, 0.24 mmol) was added. At this temperature, electrophile E^1 (2.0 equiv, 0.4 mmol) was added, followed by subsequent addition of electrophile E^2 (1.2 equiv, 0.24 mmol). The resulting mixture was stirred at -78 °C for 30 min. After this time, the mixture was warmed to room temperature, solvent was evaporated under reduced pressure, and the product was purified by flash column chromatography.

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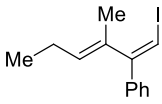
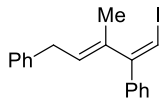
5.4. COMPOUND CHARACTERIZATION

((1*E*,3*E*)-1-Iodo-3-methylhexa-1,3-dien-2-yl)benzene (5.7)



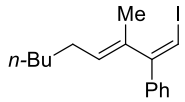
Obtained from dendralene **5.5** and MeLi (1.6 M in Et_2O) following method B after flash column chromatography (hexane) in 54% yield as a yellow oil. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.44 - 7.22 (m, 5H), 6.56 (s, 1H), 5.50 (t, *J* = 7.2 Hz, 1H), 2.21 (p, *J* = 7.5 Hz, 2H), 1.67 (s, 3H), 1.11 (t, *J* = 7.5 Hz, 3H) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$) δ 155.8, 139.3, 134.9, 134.4, 128.6, 128.1, 127.1, 76.8, 21.5, 15.2, 13.9 ppm. **HRMS (APCI)** Calc. for $C_{13}H_{16}I$ [M+H$^+$]: 299.0291 found 299.0286.

((2*E*,4*E*)-5-Iodo-3-methylpenta-2,4-diene-1,4-diyl)dibenzene (5.19)



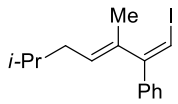
Obtained from dendralene **5.5** and PhLi (1.9 M in Bu_2O) following method A after flash column chromatography (hexane) in 65% yield as a yellow oil. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.39 - 7.21 (m, 10H), 6.59 (s, 1H), 5.71 (t, *J* = 7.4, 1H), 3.60 (d, *J* = 7.4 Hz, 2H), 1.82 (s, 3H) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$) δ 155.6, 140.6, 139.3, 136.8, 130.8, 128.8, 128.6, 128.6, 128.2, 127.1, 126.1, 77.0, 34.5, 15.7 ppm. **HRMS (APCI)** Calc. for $C_{18}H_{18}I$ [M+H$^+$]: 361.0448 found 361.0445.

((1*E*,3*E*)-1-Iodo-3-methylnona-1,3-dien-2-yl)benzene (5.20)



Obtained from **5.5** and *n*-BuLi (2.5 M in hexane) following method B after flash column chromatography (hexane) in 46% yield as yellow oil. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.40 - 7.27 (m, 5H), 6.55 (s, 1H), 5.51 (t, *J* = 7.4 Hz, 1H), 2.21 (q, *J* = 7.2 Hz, 2H), 1.67 (s, 3H), 1.59 - 1.22 (m, 8H), 0.93 (t, *J* = 7.2 Hz, 3H) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$) δ 155.6, 139.4, 135.4, 133.0, 128.6, 128.1, 127.1, 76.7, 32.22, 29.0, 28.1, 22.7, 15.4, 14.3 ppm. **HRMS (APCI)** Calc. for $C_{16}H_{22}I$ [M+H$^+$] 341.0761 found 341.0760.

((1*E*,3*E*)-1-Iodo-3,6-dimethylhepta-1,3-dien-2-yl)benzene (5.21)



Obtained from dendralene **5.5** and *i*-PrLi (0.7 M in pentane) following method B after flash column chromatography (hexane) as a 77:23 mixture of isomers **11:11'** in 60% yield as a yellow oil. Full regioselectivity can be obtained using method A obtaining **11** as a single product in 38% yield. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.39 - 7.28 (m, 5H), 6.55 (s, 1H), 5.53 (t, *J* = 7.5 Hz, 1H), 2.10 (t, *J* = 7.1 Hz, 2H), 1.81 (n, *J* = 6.7 Hz, 1H), 1.67 (s, 3H), 1.02 (d, *J* = 6.7 Hz, 6H) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$) δ 156.2, 139.5, 136.2, 131.8, 128.6, 128.1, 127.1, 76.4, 37.4, 28.9, 22.9, 15.6 ppm. **HRMS (APCI)** Calc. for $C_{15}H_{20}I$ [M+H$^+$]: 327.0604 found 327.0605.

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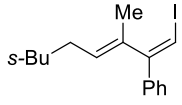
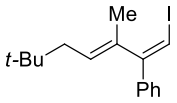
((1*E*,3*E*)-1-Iodo-3,6-dimethylocta-1,3-dien-2-yl)benzene (5.22)



Obtained from dendralene **5.5** and *s*-BuLi (1.4 M in cyclohexane) following method B after flash column chromatography (hexane) in 60% yield as a yellow oil. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.40 - 7.28 (m, 5H),

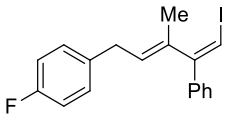
6.55 (s, 1H), 5.53 (t, *J* = 7.5 Hz, 1H), 2.21 (dt, *J* = 14.5, 6.6 Hz, 1H), 2.05 (dt, *J* = 14.5, 7.5 Hz, 1H), 1.67 (s, 3H), 1.65 - 1.42 (m, 2H), 1.27 (m, 1H), 1.00 (d, *J* = 6.5 Hz, 3H), 0.94 (t, *J* = 7.3 Hz, 3H) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$) δ 156.2, 139.5, 136.1, 131.8, 128.6, 128.1, 127.1, 76.6, 35.3, 35.1, 29.6, 19.7, 15.6, 11.7 ppm. **HRMS (APCI)** Calc. for $C_{16}H_{22}I$ [M+H$^+$] 341.0761 found 341.0757.

((1*E*,3*E*)-1-Iodo-3,6,6-trimethylhepta-1,3-dien-2-yl)benzene (5.23)



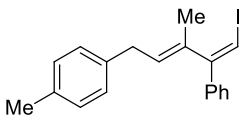
Obtained from dendralene **5.5** and *t*-BuLi (0.7 M in pentane) following method B after flash column chromatography (hexane) in 93% yield as a yellow oil. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.39 - 7.28 (m, 5H), 6.55 (s, 1H), 5.61 (t, *J* = 7.9 Hz, 1H), 2.12 (d, *J* = 7.9 Hz, 2H), 1.67 (s, 3H), 1.04 (s, 9H) ppm. **^{13}C NMR** (75 MHz, $CDCl_3$) δ 156.4, 139.6, 136.9, 130.2, 128.6, 128.1, 127.2, 76.5, 42.2, 32.3, 29.8, 15.6 ppm. **HRMS (APCI)** Calc for $C_{16}H_{22}I$ [M+H$^+$] 341.0761 found 341.0761.

1-Fluoro-4-((2*E*,4*E*)-5-iodo-3-methyl-4-phenylpenta-2,4-dien-1-yl)benzene (5.24)



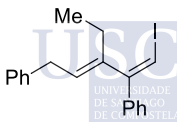
Obtained from dendralene **5.5** and 4-fluorophenyllithium following method A after flash column chromatography (hexane) in 42% yield as a yellow oil. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.39 - 7.26 (m, 7H), 7.02 (t, *J* = 8.7 Hz, 2H), 6.60 (s, 1H), 5.67 (t, *J* = 7.4 Hz, 1H), 3.57 (d, *J* = 7.4 Hz, 2H), 1.81 (s, 3H) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$) δ 162.5 - 160.6 (d, *J* = 243.7 Hz), 155.5, 139.2, 137.1, 136.2 - 136.2 (d, *J* = 3.2 Hz), 130.6, 130.2 - 130.1 (d, *J* = 7.4 Hz), 128.7, 128.3, 127.1, 115.4 - 115.2 (d, *J* = 21.2 Hz), 77.1, 33.7, 15.7 ppm. **^{19}F NMR** (282 MHz, $CDCl_3$) δ -118.0 (m) ppm**. HRMS (APCI)** Calc. for $C_{18}H_{17}FI$ [M+H$^+$] 379.0354 found 379.0349.

1-((2*E*,4*E*)-5-Iodo-3-methyl-4-phenylpenta-2,4-dien-1-yl)-4-methylbenzene (5.25)



Obtained from dendralene **5.5** and 4-methylphenyllithium following method A after flash column chromatography (hexane) in 72% yield as a yellow oil. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.39 - 7.36 (m, 2H), 7.34 - 7.30 (m, 3H), 7.24 (d, *J* = 8.0 Hz, 2H), 7.15 (d, *J* = 7.7 Hz, 2H), 6.59 (s, 1H), 5.70 (tq, *J* = 7.4, 1.5 Hz, 1H), 3.56 (d, *J* = 7.4 Hz, 2H), 2.36 (s, 3H), 1.82 (d, *J* = 1.5 Hz, 3H) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$) δ 155.6, 139.4, 137.5, 136.6, 135.6, 131.1, 129.2, 128.7, 128.6, 128.2, 127.1, 77.0, 34.1, 21.2, 15.7 ppm. **HRMS (APCI)** Calc. for $C_{19}H_{20}I$ [M+H$^+$] 375.0604 found 375.0604.

((2*E*,4*E*)-3-Ethyl-5-iodopenta-2,4-diene-1,4-diyl)dibenzene (5.26)



Obtained from dendralene **5.5,** PhLi (1.9 M in Bu_2O), MeI (**E^1**) and I_2 (**E^2**), following method C after flash column chromatography (hexane) in 46% yield as a yellow oil. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.46 - 7.20 (m, 10H), 6.66 (s, 1H), 5.74 (t, *J* = 7.5 Hz, 1H), 3.65 (d, *J* = 7.5 Hz, 2H), 2.28 (q, *J* = 7.6 Hz, 2H), 0.99 (t, *J* = 7.6 Hz, 3H) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$) δ 154.8, 141.9, 140.7, 139.9, 130.6, 128.8, 128.6, 128.6, 128.2, 127.2, 126.2, 78.7, 34.2, 22.8, 12.5 ppm. **HRMS (APCI)** Calc. for $C_{19}H_{20}I$ [M+H$^+$]: 375.0604 found 375.0604.

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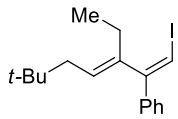
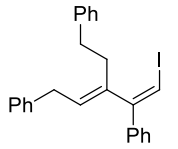
((1*E*,3*E*)-3-Ethyl-1-iodo-6,6-dimethylhepta-1,3-dien-2-yl)benzene (5.27).



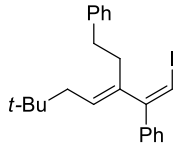
Obtained from dendralene **5.5**, *t*-BuLi (0.7 M in pentane), MeI (**E[1]**) and I_2 (**E[2]**), following method D after flash column chromatography (hexane) in 70% yield as a yellow oil. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.42 - 7.25 (m, 5H), 6.63 (s, 1H), 5.64 (t, *J* = 7.8 Hz, 1H), 2.16 (m, 4H), 1.08 (s, 9H), 0.91 (t, *J* = 7.6 Hz, 3H) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$) δ 155.6, 142.0, 140.1, 129.8, 128.6, 128.1, 127.3, 78.2, 41.9, 31.9, 29.8, 22.5, 12.3 ppm. **HRMS (APCI)** Calc. for $C_{17}H_{23}I$ [M+H$^+$]: 354.0839 found 354.0835.

((2*E*,4*E*)-5-Iodo-3-phenethylpenta-2,4-diene-1,4-diyl)dibenzene (5.28)



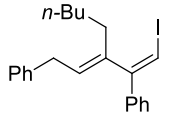
Obtained from dendralene **5.5**, PhLi (1.9 M in Bu_2O), BnBr (**E[1]**) and I_2 (**E[2]**), following method C after flash column chromatography (hexane) in 48% yield as a yellow oil as a 5:1 mixture of isomers **18:18'**. Characterization of the major isomer is given. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.42 - 7.32 (m, 9H), 7.32 - 7.15 (m, 7H), 7.11 (d, *J* = 6.8 Hz, 2H), 7.00 (d, *J* = 7.6 Hz, 1H), 6.68 (s, 1H), 5.85 (t, *J* = 7.4 Hz, 1H), 3.64 (d, *J* = 7.4 Hz, 2H), 2.69 (m, 2H), 2.59 - 2.49 (m, 2H) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$) δ 154.7, 142.1, 140.4, 139.9, 139.9, 131.8, 129.2, 128.8, 128.7, 128.6, 128.4, 128.4, 127.3, 126.2, 126.0, 78.8, 34.4, 34.3, 31.9 ppm. **HRMS (APCI)** Calc. for $C_{25}H_{24}I$ [M+H$^+$]: 451.0917 found 451.0914.

((3*E*,4*E*)-3-(3,3-Dimethylbutylidene)-5-iodopent-4-ene-1,4-diyl)dibenzene (5.29)



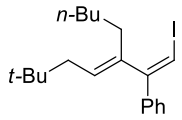
Obtained from dendralene **5.5**, *t*-BuLi (0.7 M in pentane), BnBr (**E[1]**) and I_2 (**E[2]**), following method D after flash column chromatography (hexane) in 57% yield as a yellow oil. Isolated with a 17% of 1,2-diphenylethane. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.26 (d, *J* = 2.0 Hz, 1H), 7.23 (dd, *J* = 5.0, 2.1 Hz, 2H), 7.19 (d, *J* = 6.9 Hz, 1H), 7.11 (t, *J* = 7.7 Hz, 4H), 7.04 (t, *J* = 7.4 Hz, 1H), 6.97 (d, *J* = 6.8 Hz, 2H), 6.54 (s, 1H), 5.63 (t, *J* = 7.8, 1H), 2.55 - 2.50 (m, 2H), 2.32 - 2.27 (m, 2H), 2.08 (d, *J* = 7.8 Hz, 2H), 0.97 (s, 9H) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$) δ 155.5, 142.4, 140.2, 140.1, 131.1, 128.7, 128.6, 128.5, 128.4, 128.4, 127.3, 78.4, 42.0, 34.2, 32.0, 31.7, 29.9 ppm. **HRMS (APCI)** Calc. for $C_{23}H_{28}I$ [M+H$^+$]: 431.1230 found 431.1229.

((2*E*,4*E*)-5-Iodo-3-pentylpenta-2,4-diene-1,4-diyl)dibenzene (5.30)



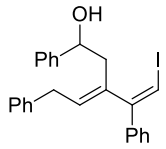
Obtained from dendralene **5.5**, PhLi (1.9 M in Bu_2O), *n*-BuBr (**E[1]**) and I_2 (**E[2]**), following method C after flash column chromatography (hexane) in 47% yield as a yellow oil. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.52 - 7.23 (m, 10H), 6.61 (s, 1H), 5.79 (t, *J* = 7.4 Hz, 1H), 3.65 (d, *J* = 7.4 Hz, 2H), 2.21 (t, *J* = 7.5 Hz, 2H), 1.52 - 1.16 (m, 7H), 0.94 - 0.77 (m, 3H). ppm. **^{13}C NMR** (126 MHz, $CDCl_3$) δ 155.1, 140.8, 140.7, 140.0, 131.3, 128.8, 128.6, 128.1, 127.3, 126.1, 78.3, 34.4, 32.1, 29.8, 27.7, 22.6, 14.1 ppm. **HRMS (APCI)** Calc. for $C_{22}H_{26}I$ [M+H$^+$]: 417.1074 found 417.1073.

((1*E*,3*E*)-3-(3,3-Dimethylbutylidene)-1-iodooct-1-en-2-yl)benzene (5.31)



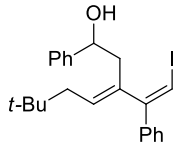
Obtained from dendralene **5.5**, *t*-BuLi (0.7 M in pentane), *n*-BuBr (**E**[1]) and I_2 (**E**[2]), following method D after flash column chromatography (hexane) in 51% yield as a yellow oil. **^{1}H NMR (500 MHz, CDCl$_3$)** δ 7.25 - 7.17 (m, 5H), 6.45 (s, 1H), 5.55 (t, *J* = 7.8 Hz, 1H), 2.04 (d, *J* = 7.8 Hz, 2H), 1.95 (t, *J* = 7.6 Hz, 2H), 1.23 - 1.14 (m, 2H), 1.14 - 1.08 (m, 4H), 0.94 (s, 9H), 0.72 (t, *J* = 6.9 Hz, 3H) ppm. **^{13}C NMR (126 MHz, CDCl$_3$)** δ 155.9, 141.0, 140.3, 130.6, 128.6, 128.1, 127.3, 77.8, 42.0, 32.1, 31.9, 29.9, 29.4, 27.5, 22.6, 14.1 ppm. **HRMS (APCI)** Calc. for $C_{20}H_{30}I$ [M+H$^+$]: 397.1387 found 397.1382.

(*E*)-3-((*E*)-2-Iodo-1-phenylvinyl)-1,5-diphenylpent-3-en-1-ol (5.32)



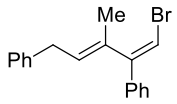
Obtained from dendralene **5.5**, PhLi (1.9 M in Bu_2O), benzaldehyde (**E**[1]) and I_2 (**E**[2]), following method C after flash column chromatography (hexane) in 38% yield as a yellow oil. **^{1}H NMR** (300 MHz, CDCl$_3$) δ 7.40 - 7.14 (m, 15H), 6.64 (s, 1H), 6.05 (t, *J* = 7.4 Hz, 1H), 4.70 (dt, *J* = 9.9, 3.0 Hz, 1H), 3.70 (d, *J* = 7.4 Hz, 2H), 2.84 (dd, *J* = 14.1, 10.0 Hz, 1H), 2.41 - 2.28 (dd, *J* = 15.2, 3.0 Hz 2H) ppm. **^{13}C NMR** (126 MHz, CDCl$_3$) δ 154.8, 143.7, 140.1, 139.5, 137.0, 136.2, 128.9, 128.8, 128.7, 128.6, 128.4, 127.5, 127.3, 126.4, 125.8, 79.2, 72.2, 40.1, 34.6 ppm. **HRMS (APCI)** Calc. for $C_{25}H_{22}I$ [M-OH]: 449.0761 found 449.0763.

(*E*)-3-((*E*)-2-Iodo-1-phenylvinyl)-6,6-dimethyl-1-phenylhept-3-en-1-ol (5.33)



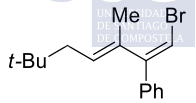
Obtained from dendralene **5.5**, *t*-BuLi (0.7 M in pentane), benzaldehyde (**E**[1]) and I_2 (**E**[2]), following method D after flash column chromatography (hexane) in 46% yield as a yellow oil. **^{1}H NMR** (500 MHz, CDCl$_3$) δ 7.25 (s, 5H), 7.21 - 7.10 (m, 5H), 6.55 (s, 1H), 5.90 (t, *J* = 7.6 Hz, 1H), 4.59 (d, *J* = 9.2 Hz, 1H), 2.63 (dd, *J* = 14.0, 10.4 Hz, 1H), 2.25 - 2.11 (m, 2H), 0.97 (s, 9H). ppm. **^{13}C NMR** (126 MHz, CDCl$_3$) δ 155.5, 143. 8, 139.7, 137.3, 135.7, 128.8, 128.5, 128.4, 127.4, 127.3, 125.7, 78.8, 72.2, 42.2, 40.0, 31.9, 29.8 ppm. **HRMS (APCI)** Calc. for $C_{23}H_{26}I$ [M-OH]: 429.1074 found 429.1074.

((2*E*,4*E*)-5-Bromo-3-methylpenta-2,4-diene-1,4-diyl)dibenzene (5.34)



Obtained from dendralene **5.5**, PhLi (1.9 M in Bu_2O), MeOH (4 equiv, **E**[1]) and *N*-bromosuccinimide (1.2 equiv, **E**[2]), following method C after flash column chromatography (hexane) in 49% yield as a colorless oil. **^{1}H NMR** (300 MHz, CDCl$_3$) δ 7.39 - 7.29 (m, 10H), 6.48 (s, 1H), 5.73 (t, *J* = 7.2 Hz, 1H), 3.58 (d, *J* = 7.2 Hz, 2H), 1.82 (s, 3H) ppm. **^{13}C NMR** (126 MHz, CDCl$_3$) δ 149.9, 140.7, 139.0, 134.0, 130.8, 128.7, 128.6, 128.2, 127.0, 126.1, 103.6, 34.5, 15.9 ppm. **HRMS (APCI)** Calc. for $C_{18}H_{17}Br$ [M+H$^+$]: 312.0508 found 312.0506.

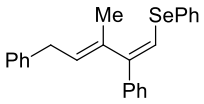
((1*E*,3*E*)-1-Bromo-3,6,6-trimethylhepta-1,3-dien-2-yl)benzene (5.35)



Obtained from dendralene **5.5**, *t*-BuLi (0.7 M in pentane), MeOH (4 equiv, **E**[1]) and *N*-bromosuccinimide (1.2 equiv, **E**[2]), following method D after flash column chromatography (hexane) in 74% yield as a colorless oil. **^{1}H NMR** (500 MHz, CDCl$_3$) δ 7.38 - 7.29 (m, 5H), 6.47 (s, 1H), 5.64 (tq, *J* = 8.0, 1.5 Hz, 1H), 2.11 (d, *J* = 7.9 Hz, 2H), 1.70 (s, 3H), 1.02 (s, 9H) ppm. **^{13}C NMR**

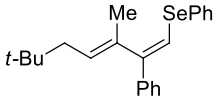
(126 MHz, $CDCl_3$) δ 150.6, 139.3, 134.0, 130.3, 128.6, 128. 1, 127.1, 103.2, 42.3, 32.3, 29.7, 15.7 ppm. **HRMS (APCI)** Calc. for $C_{16}H_{22}Br$ [M+H$^+$]: 293.0899 found 293.0894.

((1*E*,3*E*)-3-Methyl-2,5-diphenylpenta-1,3-dien-1-yl)(phenyl)selane (5.36)



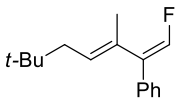
Obtained from dendralene **5.5**, PhLi (1.9 M in Bu_2O), MeOH (4 equiv, **E[1]**) and PhSeCl (1.2 equiv, **E[2]**), following method C after flash column chromatography (hexane) in 58% yield as a yellow oil. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.62 - 7.50 (m, 2H), 7.40 - 7.18 (m, 13H), 6.79 (s, 1H), 5.83 (t, *J* = 7.3 Hz, 1H), 3.63 (d, *J* = 7.3 Hz, 2H), 1.86 (s, 3H) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$) δ 146.4, 140.8, 139.6, 136.1, 132.6, 132.1, 131.1, 129.4, 128.7, 128.6, 128.6, 127.4, 127.3, 126.7, 126.2, 120.4, 34.6, 15.8 ppm. **HRMS (APCI)** Calc. for $C_{24}H_{23}Se$ [M+H$^+$]: 391.0959 found 391.0961.

Phenyl((1*E*,3*E*)-3,6,6-trimethyl-2-phenylhepta-1,3-dien-1-yl)selane (5.37)



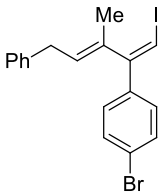
Obtained from dendralene **5.5**, *t*-BuLi (0.7 M in pentane), MeOH (4 equiv, **E[1]**) and PhSeCl (1.2 equiv, **E[2]**), following method D after flash column chromatography (hexane) in 74% yield as a yellow oil. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.67 - 7.59 (m, 2H), 7.40 - 7.31 (m, 7H), 7.30 - 7.22 (m, 1H), 6.79 (s, 1H), 5.74 (tq, *J* = 7.8, 1.4 Hz, 1H), 2.17 (d, *J* = 7.8 Hz, 2H), 1.75 (d, *J* = 1.4 Hz, 3H), 1.08 (s, 9H) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$) δ 147.2, 139.9, 136.3, 132.5, 132.3, 130.3, 129.3, 128.5, 127.3, 127.2, 126.7, 119.8, 42.4, 32.1, 29.87, 15.7 ppm. **HRMS (APCI)** Calc. for $C_{22}H_{27}Se$ [M+H$^+$]: 371.1272 found 371.1273.

((1*E*,3*E*)-1-Fluoro-3,6,6-trimethylhepta-1,3-dien-2-yl)benzene (5.38)



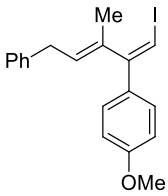
PhLi (1.0 equiv, 1.9 M in Bu_2O, 0.2 mmol) was added over the dendralene **5.5** (1.0 equiv, 0.2 mmol) in THF (0.2 M, 1 ml) at -78 °C and warmed to 0 °C and stirred for 10 min. After this time, the mixture was cooled to -78 °C and *t*-BuLi (1.2 equiv, 0.7 M in pentane, 0.24 mmol) was added. At this temperature, MeOH (4 equiv, 0.8 mmol) was added, and solvent was removed under vacuum. Then, the mixture was dissolved in dry MeCN (1 ml) followed by addition of selectfluor® (1.5 equiv, 0.3 mmol) at room temperature and it was stirred at that temperature for 30 min. After this time, solvent was evaporated under reduced pressure obtaining a 4.5:1 mixture of *E,E:E,Z* isomers. Both isomers could be separated by flash column chromatography (Hexane as eluent) obtaining the *E,E* isomer in 27% yield as a yellow oil. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.38 - 7.24 (m, 5H), 6.75 (d, *J* = 84.8 Hz, 1H), 5.59 (t, *J* = 7.9, 1H), 2.09 (d, *J* = 7.9 Hz, 2H), 1.80 (s, 3H), 0.96 (s, 9H) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$) δ 144.7 (d, *J* = 263.7 Hz), 136.7 (d, *J* = 8.5 Hz), 131.1 (d, *J* = 3.2 Hz), 130.3, 130.0 (d, *J* = 7.0 Hz), 128.5, 128.1 (d, *J* = 3.2 Hz), 127.6, 42.2, 32.1, 29.5, 16.4 (d, *J* = 3.2 Hz) ppm. **^{19}F NMR** (282 MHz, $CDCl_3$) δ -129.12 (d, *J* = 85.1 Hz) ppm. **HRMS (APCI)** Calc. for $C_{16}H_{21}F$ [M+H$^+$]: 232.1622 found 232.1622.

1-Bromo-4-((1*E*,3*E*)-1-iodo-3-methyl-5-phenylpenta-1,3-dien-2-yl)benzene (5.39)



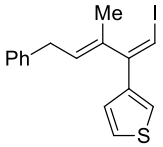
Obtained from dendralene **5.51** and PhLi (1.9 M in Bu_2O) following method A after flash column chromatography (hexane) in 34% yield as a yellow oil. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.48 - 7.40 (m, 2H), 7.35 - 7.29 (m, 4H), 7.25 - 7.18 (m, 3H), 6.61 (s, 1H), 5.68 (tq, *J* = 7.4, 1.5 Hz, 1H), 3.58 (d, *J* = 7.2 Hz, 1H), 1.79 (d, *J* = 1.4 Hz, 1H) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$) δ 154.5, 140.5, 138.2, 136.4, 131.8, 131.3, 128.8, 128.7, 128.6, 126.2, 122.3, 77.7, 34.5, 15.6 ppm. **HRMS (APCI)** Calc. for $C_{18}H_{17}BrI$ [M+H$^+$]: 438.9553 found 438.9548.

1-((1*E*,3*E*)-1-Iodo-3-methyl-5-phenylpenta-1,3-dien-2-yl)-4-methoxybenzene (5.40)



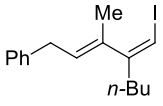
Obtained from dendralene **5.50** and PhLi (1.9 M in Bu_2O) following method A after flash column chromatography (hexane) in 74% yield as a yellow oil. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.40 - 7.24 (m, 7H), 6.87 (d, *J* = 8.7 Hz, 2H), 6.49 (s, 1H), 5.70 (t, *J* = 7.4 Hz, 1H), 3.84 (s, 3H), 3.62 (d, *J* = 7.5 Hz, 2H), 1.83 (s, 3H) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$) δ 159.7, 155.0, 140.7, 137.0, 131.9, 130.5, 128.8, 128.6, 128.3, 126.1, 114.0, 74.9, 55.4, 34.5, 15.7 ppm. **HRMS (APCI)** Calc. for $C_{19}H_{20}IO$ [M+H$^+$]: 391.0553 found 391.0554.

3-((1*E*,3*E*)-1-Iodo-3-methyl-5-phenylpenta-1,3-dien-2-yl)thiophene (5.41)



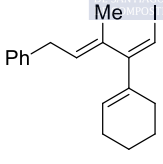
Obtained from dendralene **5.52** and PhLi (1.9 M in Bu_2O) following method A after flash column chromatography (hexane) in 72% yield as a yellow oil. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.37 - 7.05 (m, 8H), 6.66 (s, 1H), 5.64 (t, *J* = 7.4 Hz, 1H), 3.60 (d, *J* = 7.4 Hz, 2H), 1.92 (s, 3H). ppm. **^{13}C NMR** (126 MHz, $CDCl_3$) δ 150.3, 140.6, 140.6, 137.1, 129.8, 128.8, 128.6, 126.1, 125.7, 122.9, 76.7, 34.4, 15.8 ppm. **HRMS (APCI)** Calc. for $C_{16}H_{16}IS$ [M+H$^+$]: 367.0012 found 367.0013.

((2*E*,4*Z*)-4-(Iodomethylene)-3-methyloct-2-en-1-yl)benzene (5.42)



Obtained from dendralene **5.53** and PhLi (1.9 M in Bu_2O) following method A after flash column chromatography (hexane) in 46% yield as a yellow oil. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.35 - 7.09 (m, 5H), 5.89 (s, 1H), 5.38 (t, *J* = 7.4 Hz, 1H), 3.46 (d, *J* = 7.4 Hz, 2H), 2.24 (t, *J* = 7.3 Hz, 2H), 1.80 (s, 3H), 1.43 - 1.17 (m, 4H), 0.86 (t, *J* = 7.0 Hz, 3H) ppm. **^{13}C NMR** (75 MHz, $CDCl_3$) δ 156.2, 140.8, 137.4, 128.7, 128.5, 128.0, 126.0, 73.3, 37.6, 34.2, 30.1, 22.2, 15.1, 14.0 ppm. **HRMS (APCI)** Calc. for $C_{16}H_{22}I$ [M+H$^+$]: 341.0761 found 341.0755.

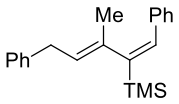
((2*E*,4*E*)-4-(Cyclohex-1-en-1-yl)-5-iodo-3-methylpenta-2,4-dien-1-yl)benzene (5.43)



Obtained from dendralene **5.55** and PhLi (1.9 M in Bu_2O) following method A after flash column chromatography (hexane) in 82% yield as a yellow oil. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.31 - 7.13 (m, 5H), 6.18 (s, 1H), 5.92 - 5.82 (m, 1H), 5.33 (t, *J* = 7.3 Hz, 1H), 3.49 (d, *J* = 7.4 Hz, 2H), 2.43 - 1.88 (m, 4H), 1.79 (s, 3H), 1.71 - 1.43 (m, 4H) ppm. **^{13}C NMR** (126

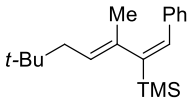
MHz, $CDCl_3$) δ 157.2, 141.0, 137.1, 135.4, 129.4, 129.3, 128.8, 128.5, 126.0, 75.5, 34.4, 26.2, 26.0, 22.9, 22.1, 16.3 ppm. **HRMS (APCI)** Calc. for $C_{18}H_{22}I$ [M+H$^+$]: 365.0761 found 365.0761.

Trimethyl((1*E*,3*E*)-3-methyl-1,5-diphenylpenta-1,3-dien-2-yl)silane (5.44)



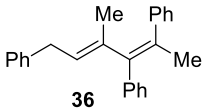
Obtained from dendralene **5.54** and PhLi (1.9 M in Bu_2O), following method A, after flash column chromatography (hexane) in 53% yield as a yellow oil. The product was initially obtained as a 2.3:1 *E,Z:E,E* mixture but it isomerized to a single *E,E* isomer. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.32 - 7.25 (m, 2H), 7.17 - 6.99 (m, 8H), 6.40 (s, 1H), 5.16 (tq, *J* = 7.5, 1.4 Hz, 1H), 3.31 (d, *J* = 7.7 Hz, 2H), 1.64 (d, *J* = 1.4, 3H), 0.00 (s, 9H) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$) δ 150.2, 141.5, 138.2, 137.3, 135.8, 129.0, 128.6, 128.5, 128.2, 127.1, 125.9, 123.7, 34.7, 17.4, -1.2 ppm. **HRMS (APCI)** Calc. for $C_{21}H_{27}Si$ [M+H$^+$]: 307.1877 found 307.1874.

Trimethyl((1*E*,3*E*)-3,6,6-trimethyl-1-phenylhepta-1,3-dien-2-yl)silane (5.45)

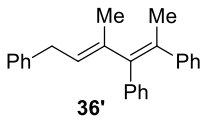


Obtained from dendralene **5.54** and *t*-BuLi (0.7 M in pentane) following method B after flash column chromatography (hexane) in 64% yield as a yellow oil. The product was initially obtained as a 1.7:1 *E,Z:E,E* mixture but it isomerized to a single *E,E* isomer. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.31 (dt, *J* = 6.6, 1.3 Hz, 2H), 7.13 - 7.02 (m, 2H), 7.04 - 6.97 (m, 1H), 6.38 (s, 1H), 5.02 (tq, *J* = 7.6, 1.4 Hz, 1H), 1.83 (d, *J* = 7.7 Hz, 2H), 1.51 (s, 3H), 0.76 (s, 9H), 0.00 (s, 9H) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$) δ 150.9, 138.3, 137.2, 135.4, 129.0, 128.2, 127.1, 123.0, 42.5, 32.1, 29.7, 17.3, -1.2 ppm. **HRMS (APCI)** Calc. for $C_{19}H_{31}Si$ [M+H$^+$]: 287.2190 found 287.2185.

((2*E*,4*E*)-3-Methylhexa-2,4-diene-1,4,5-triyl)tribenzene (5.46) and ((2*E*,4*Z*)-3-methylhexa-2,4-diene-1,4,5-triyl)tribenzene (5.46')



36

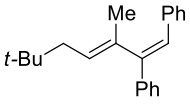


36'

Obtained from dendralene **5.56** and PhLi (1.9 M in Bu_2O) following method A after flash column chromatography (hexane) in 32% yield as a 1.5:1 mixture of *E,E:E,Z* isomers as a yellow oil (Signals of **5.46** - red, **5.46'** - orange peaks where diastereomers overlap/cannot be reliably assigned are colored purple). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.48 - 7.20 (m, 20H), 7.19 - 6.98 (m, 15H), 6.75 - 6.66 (m, 2H), 5.77 (t, *J* = 7.3 Hz, 1H), 5.34 (t, *J* = 7.5 Hz, 1H), 3.59 (d, *J* = 7.4 Hz, 2H), 3.24 (d, *J* = 7.4 Hz, 2H), 2.23 (s, 3H), 2.02 (s, 3H), 1.78 (s, 3H), 1.61 (s, 3H) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$) δ 145.4, 144.1, 143.3, 142.7, 141.9, 141.5, 141.2, 141.1, 137.8, 137.6, 133.9, 133.5, 130.3, 130.0, 129.5, 128.6, 128.4, 128.3, 128.3, 128.2, 128.2, 127.8, 127.5, 126.7, 126.1, 126.0, 126.0, 125.6, 34.7, 34.2, 23.1, 22.8, 17.3, 16.5 ppm. **HRMS (APCI)** Calc. for $C_{25}H_{25}$ [M+H$^+$]: 325.1951 found 325.1950.

Synthetic transformations of products

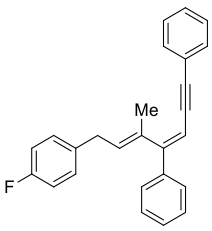
((1*E*,3*E*)-3,6,6-Trimethylhepta-1,3-diene-1,2-diyl)dibenzene (5.47)



PhLi (1.0 equiv, 1.9 M in Bu_2O, 0.2 mmol) was added over the dendralene **5.5** (1.0 equiv, 0.2 mmol) in THF (0.2 M, 1 ml) at -78 °C and warmed to 0 °C and stirred for 10 min. After this time, the mixture was

cooled to -78 °C and *t*-BuLi (1.2 equiv, 0.7 M in pentane, 0.24 mmol) was added. At this temperature, I_2 (1.2 equiv, 0.24 mmol) in MeOH (0.5M, 0.5 ml) was added, the mixture was warmed to 0 °C and stirred at that temperature for 30 min. After this time, the mixture was warmed to room temperature, followed by addition of $Pd(PPh_3)_4$ (0.1 equiv, 0.02 mmol) and aq. K_2CO_3 aq (3 equiv, 0.6 mmol). The reaction was left over night at 65 °C. After this time, the crude was washed with brine (5 ml) and extracted with CH2Cl2 (5 ml). The organic phase was dried over Na_2SO_4 and the solvent was evaporated under reduced pressure. The product was purified by flash chromatography (hexane) obtaining the pure product in 58% yield as a yellow oil. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.50 (d, *J* = 7.0 Hz, 2H), 7.46 (d, *J* = 7.4 Hz, 2H), 7.38 (t, *J* = 7.4 Hz, 2H), 7.35 - 7.27 (m, 3H), 7.20 (t, *J* = 7.4 Hz, 1H), 6.71 (s, 1H), 5.55 (t, *J* = 7.7 Hz, 1H), 2.05 (d, *J* = 7.4 Hz, 2H), 1.82 (s, 3H), 0.90 (s, 9H) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$) δ 147.1, 142.4, 138.3, 134.6, 130.2, 129.2, 128.4, 128.2, 127.5, 127.2, 126.6, 126.5, 42. 6, 32.1, 29.7, 17.0 ppm. **HRMS (APCI)** Calc. for $C_{22}H_{27}$ [M+H$^+$]: 291.2107 found 291.2108.

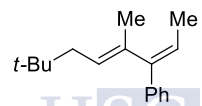
((3*E*,5*E*)-7-(4-Fluorophenyl)-5-methylhepta-3,5-dien-1-yne-1,4-diyl)dibenzene (5.48)



$Pd(PPh_3)_4$ (0.05 equiv, 0.007 mmol) and of CuI (0.1 equiv, 0.014 mmol) were diluted in Et_2NH (1 mL), then, product **35.24** (1.0 equiv, 0.14 mmol) and phenylacetylene (1.5 equiv, 0.21 mmol) were added. The reaction was left overnight under reflux. After this time, the crude was washed with water (5 ml) and extracted with AcOEt (3 x 5 mL). The combined organic phases were washed with water (5 ml) and brine (5 ml), the organic phase was dry over Na_2SO_4 and the solvent was evaporated under reduced pressure. The product was purified by flash chromatography (hexane) obtaining the pure product in 70% yield as a yellow oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34 - 7.30 (m, 2H), 7.29 - 7.14 (m, 10H), 6.76 (t, *J* = 8.7 Hz, 2H), 5.93 (s, 1H), 5.88 (tq, *J* = 7.5, 1.5 Hz, 1H), 3.50 (d, *J* = 7.1 Hz, 2H), 1.84 (m, 3H) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$) δ 161.5 (d, *J* = 243.4 Hz), 156.1, 139.8, 136.3 (d, *J* = 3.2 Hz), 134. 7, 131.5, 131.1, 130.0 (d, *J* = 7.7 Hz), 128.6, 128.4, 128.4, 128.1, 127.3, 123.9, 115.3 (d, *J* = 21.3 Hz), 105.7, 94.0, 88.9, 33. 9, 16.6 ppm. **^{19}F NMR** (282 MHz, $CDCl_3$) δ -118.13 (m) ppm. **HRMS (APCI)** Calc. for $C_{26}H_{22}F$ [M+H$^+$]: 353.1700 found 353.1702.

((2*E*,4*E*)-4,7,7-Trimethylocta-2,4-dien-3-yl)benzene (5.49)



Product **5.23**(1.0 equiv, 0.13 mmol) was diluted in dry Et_2O (0.5 ml) and *t*-BuLi (2.0 equiv, 0.7 M in pentane, 0.26 mmol) was added at -78 °C. After 20 min, the solution was warmed to room temperature and stirred for 10 additional minutes. After this time, MeI (4.0 equiv, 0.52 mmol) were added and the mixture was stirred for 1 hour. Then, solvent was evaporated under reduced pressure and the product was purified by flash chromatography (hexane) obtaining the pure product in 78% yield as a colourless oil. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.36 - 7.28 (m, 4H), 7.26 - 7.15 (m, 1H), 5.85 (q, *J* = 6.9 Hz, 1H), 5.45 (t, *J* = 7.8 Hz, 1H), 2.10 (d, *J* = 7.8 Hz, 2H), 1.83 (d, *J* = 6.9 Hz, 3H), 1.63 (s, 3H), 0.99 (s, 9H) ppm. **^{13}C NMR** (126

MHz, $CDCl_3$) δ 146.6, 141.5, 134.1, 128.4, 128.3, 126.7, 126.7, 121.8, 42.4, 32.1, 29.7, 16.6, 15.7 ppm. **HRMS (APCI)** Calc. for $C_{17}H_{25}$ [$M+H^+$]: 229.1951 found 229.1952.

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SELECTED NMR SPECTRA

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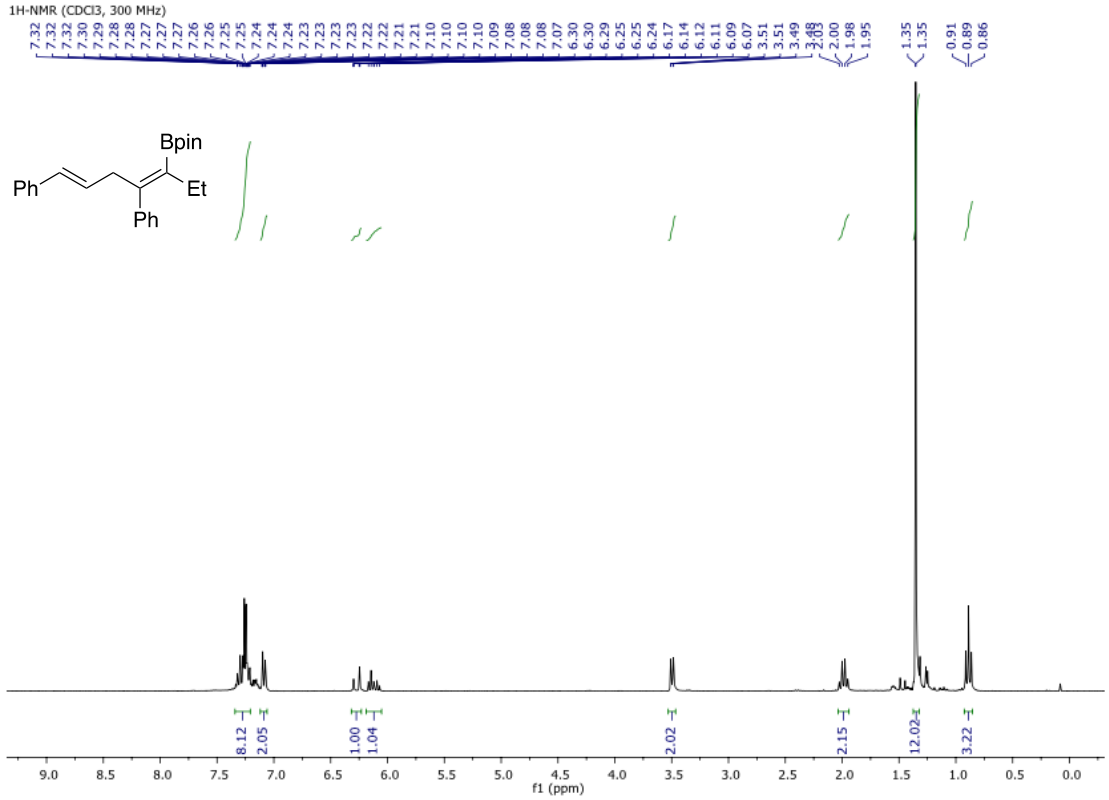
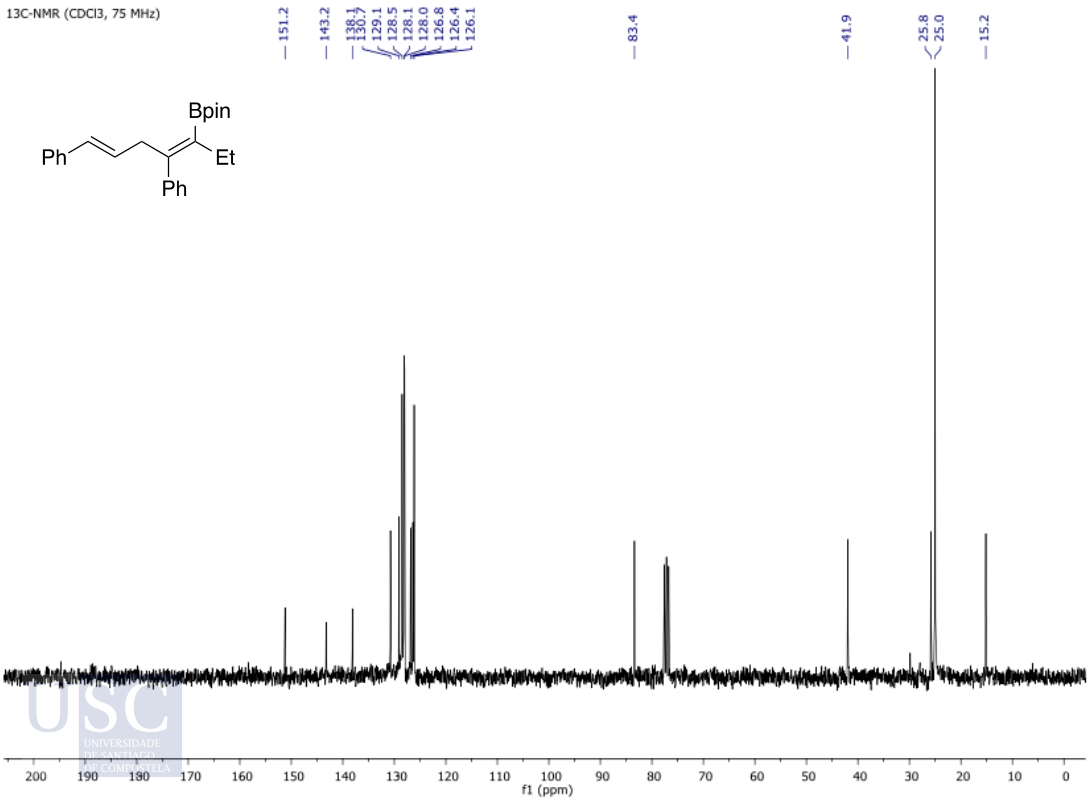
CHAPTER II:





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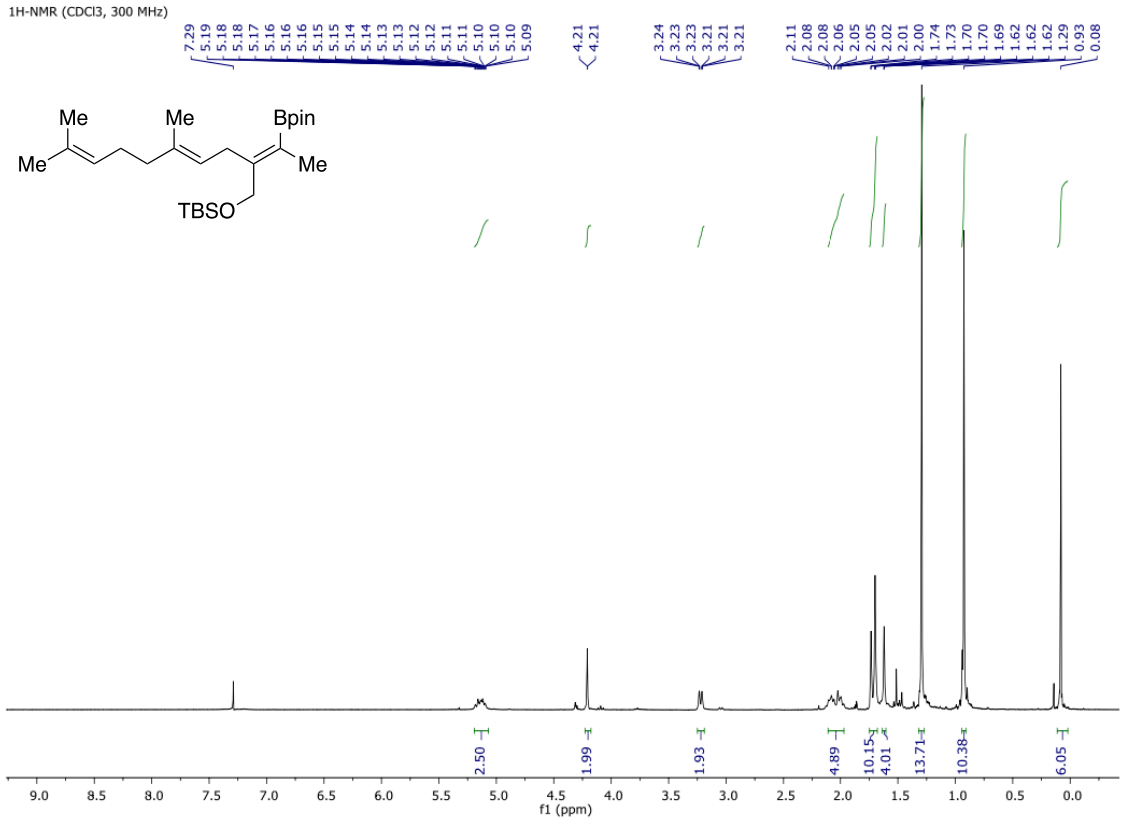

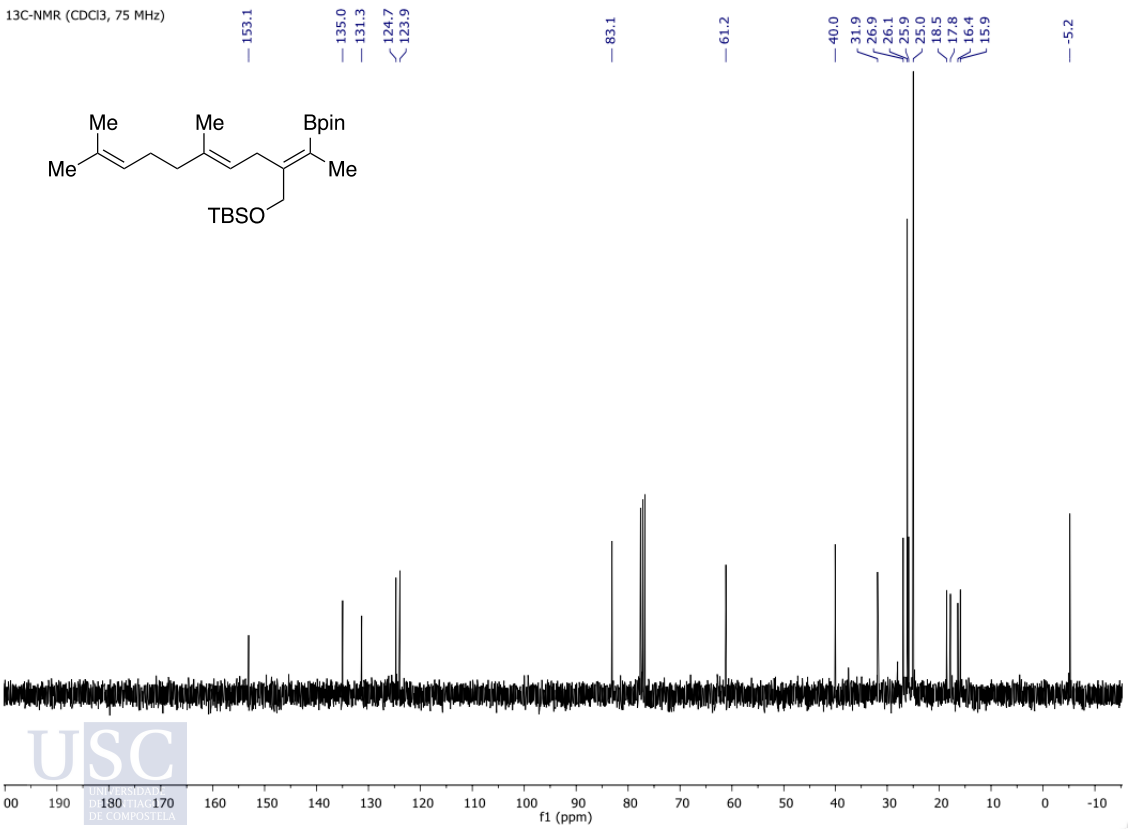

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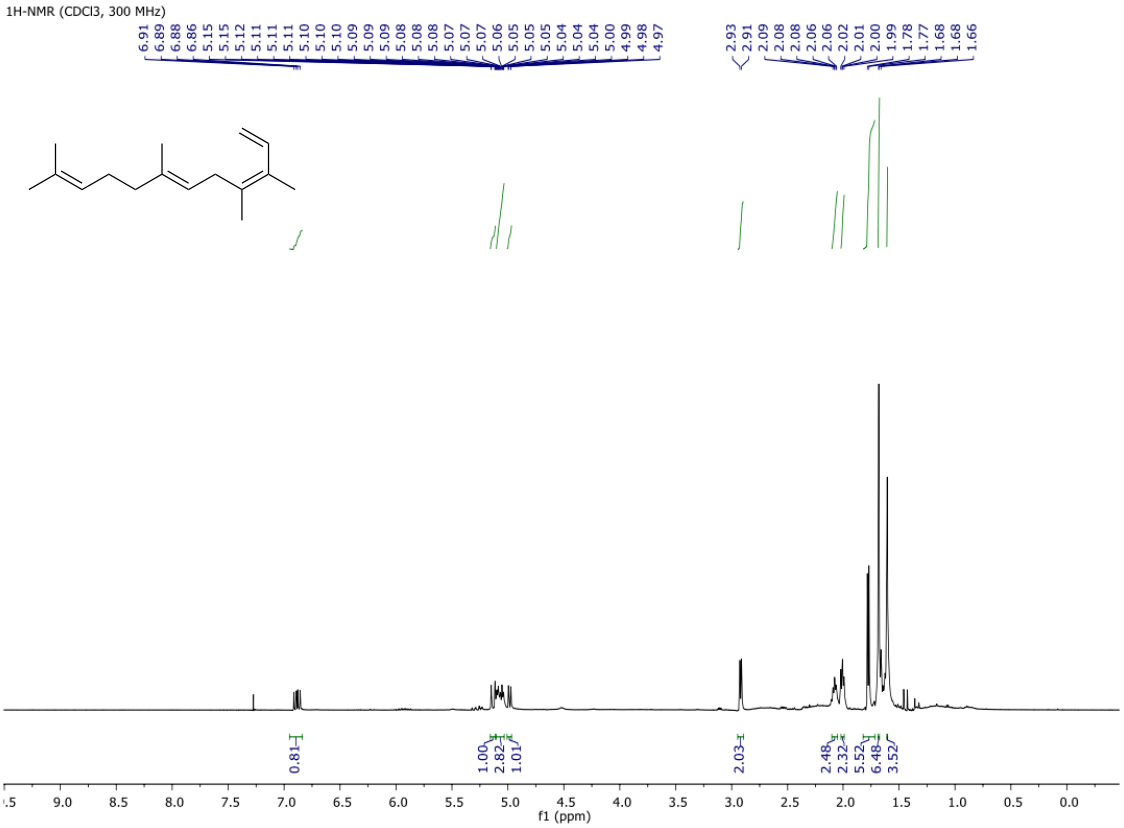

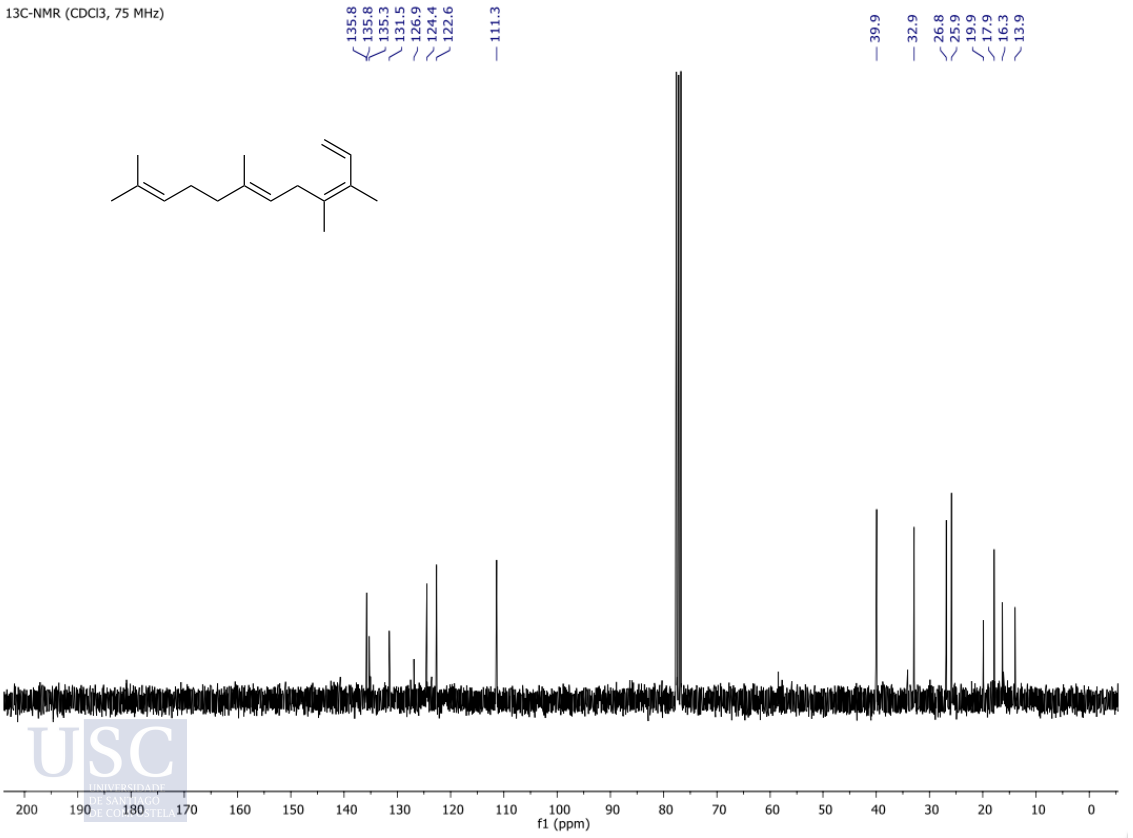

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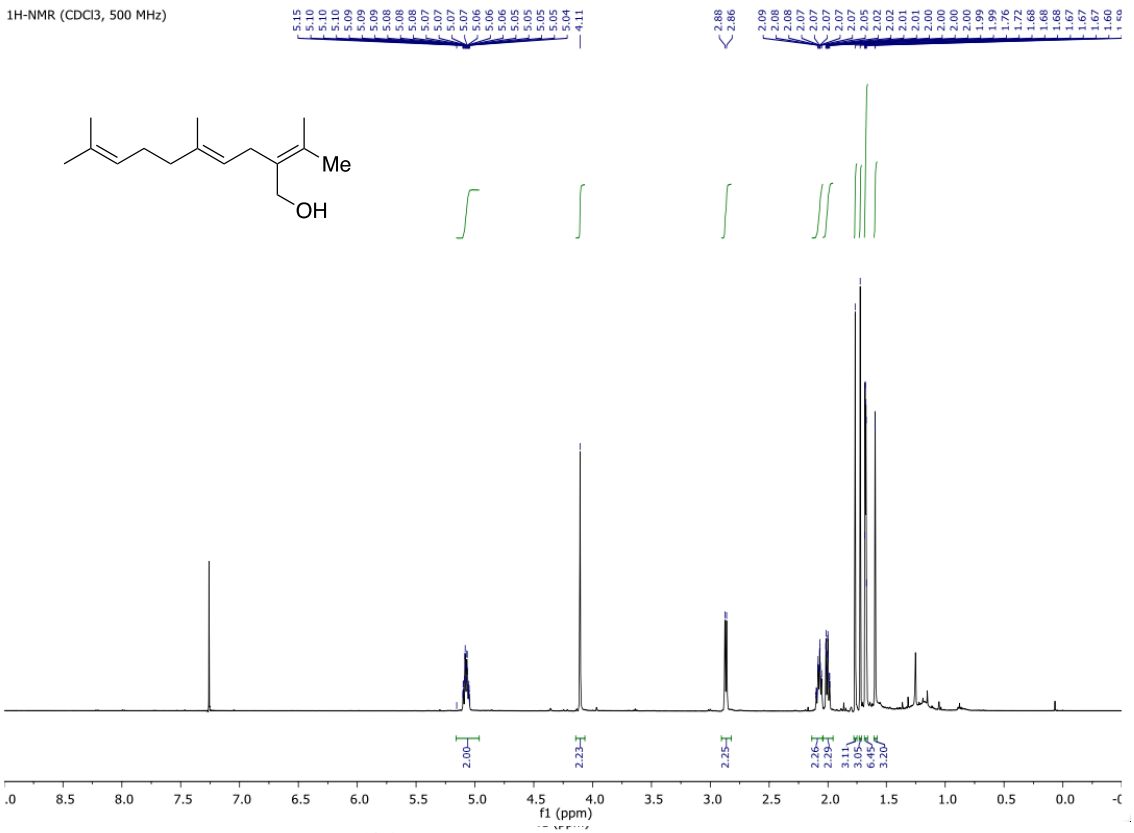

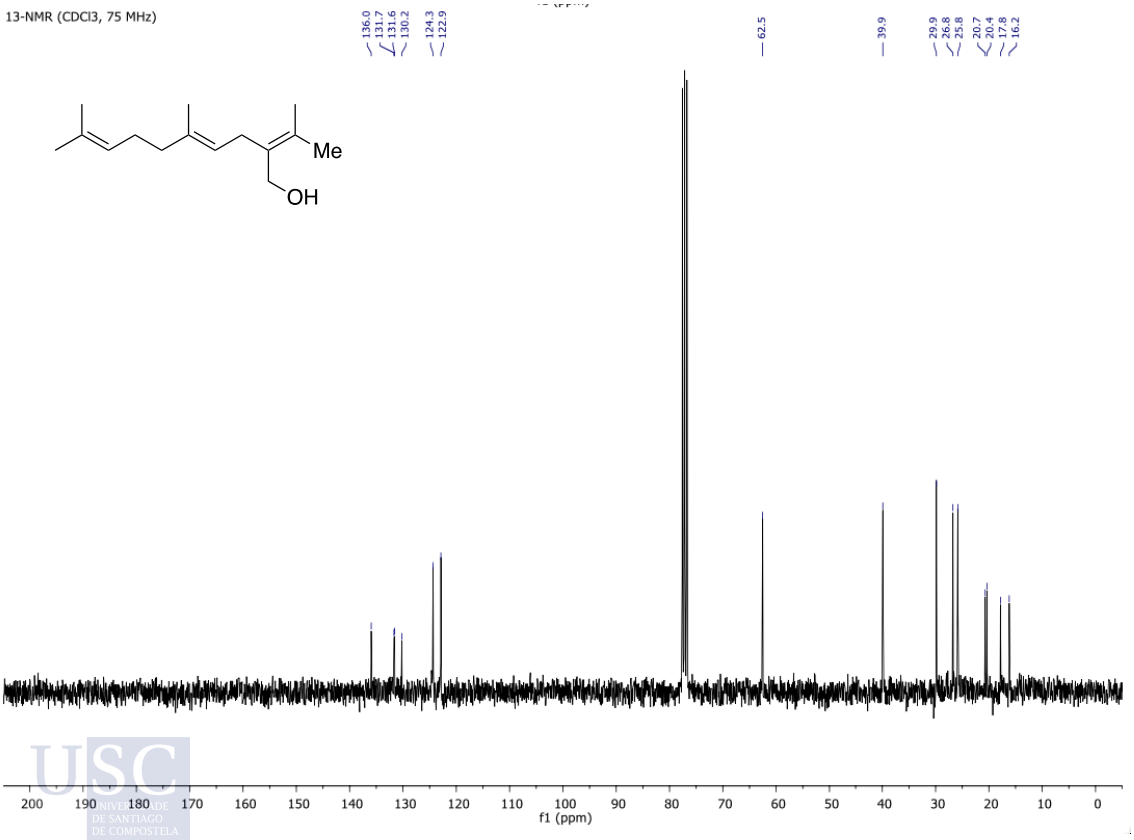

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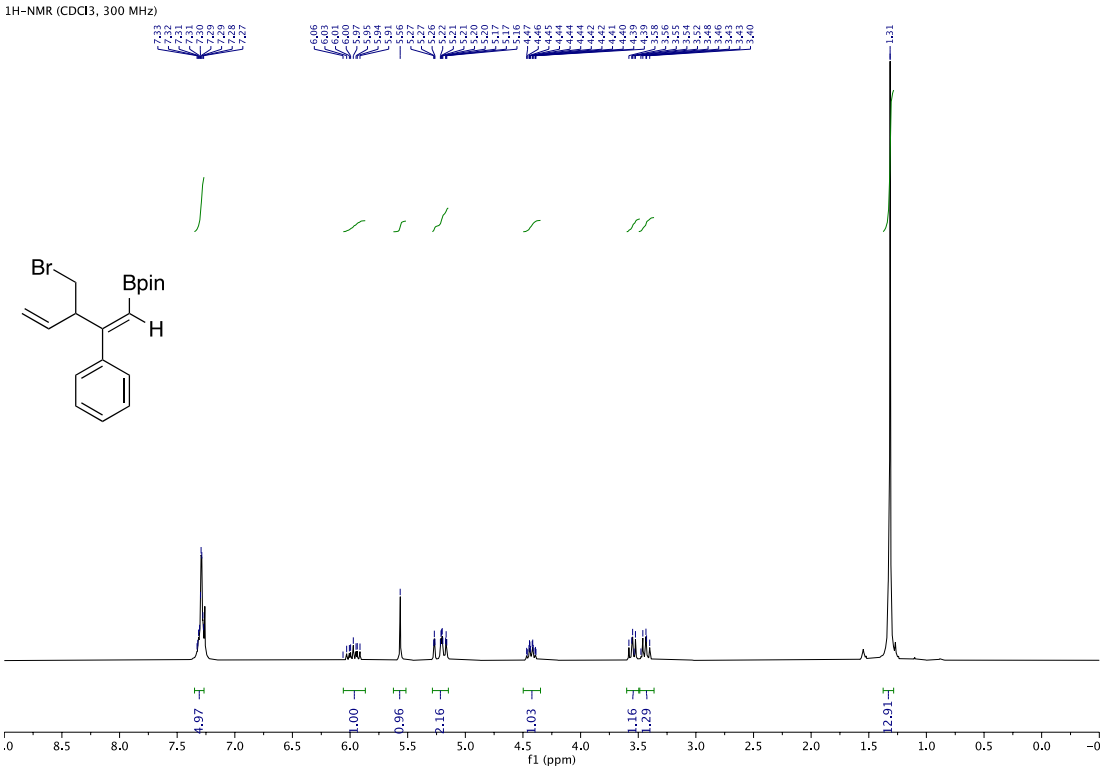
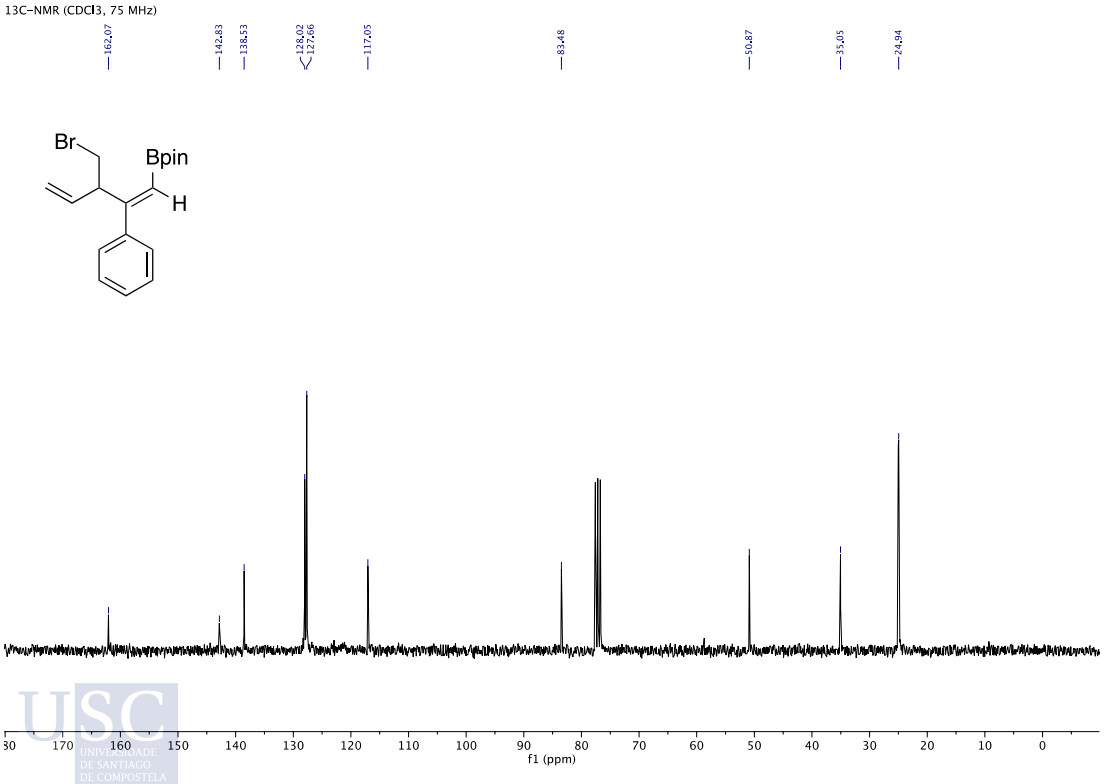
CHAPTER III:





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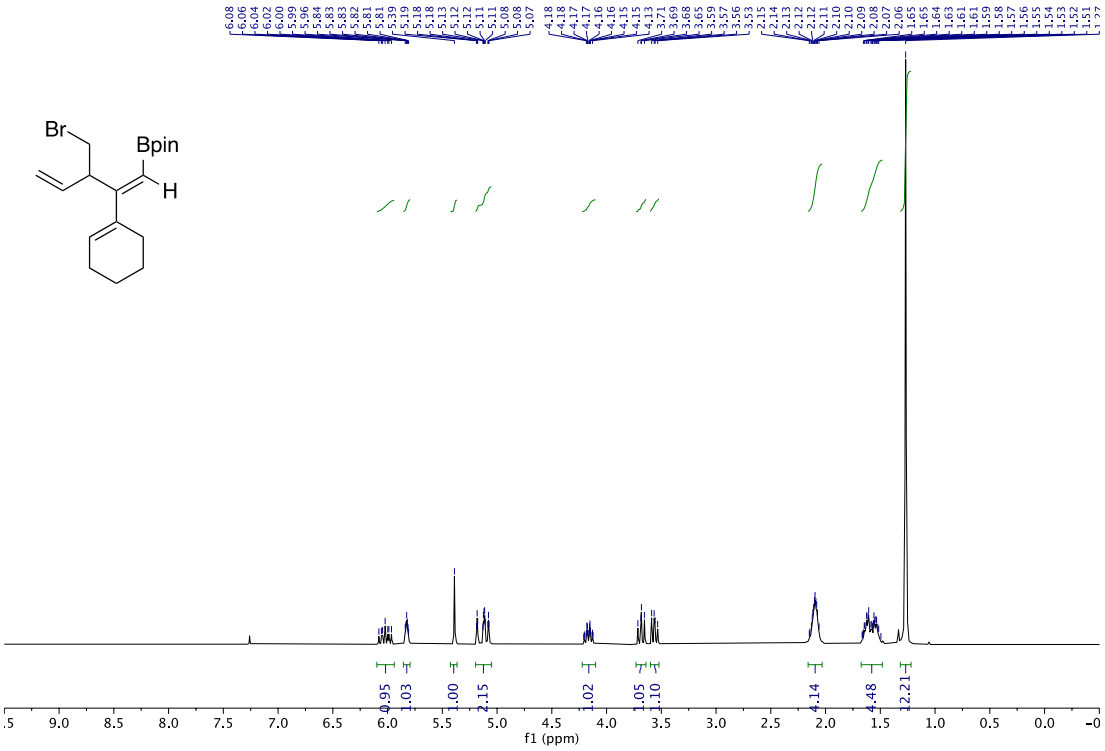
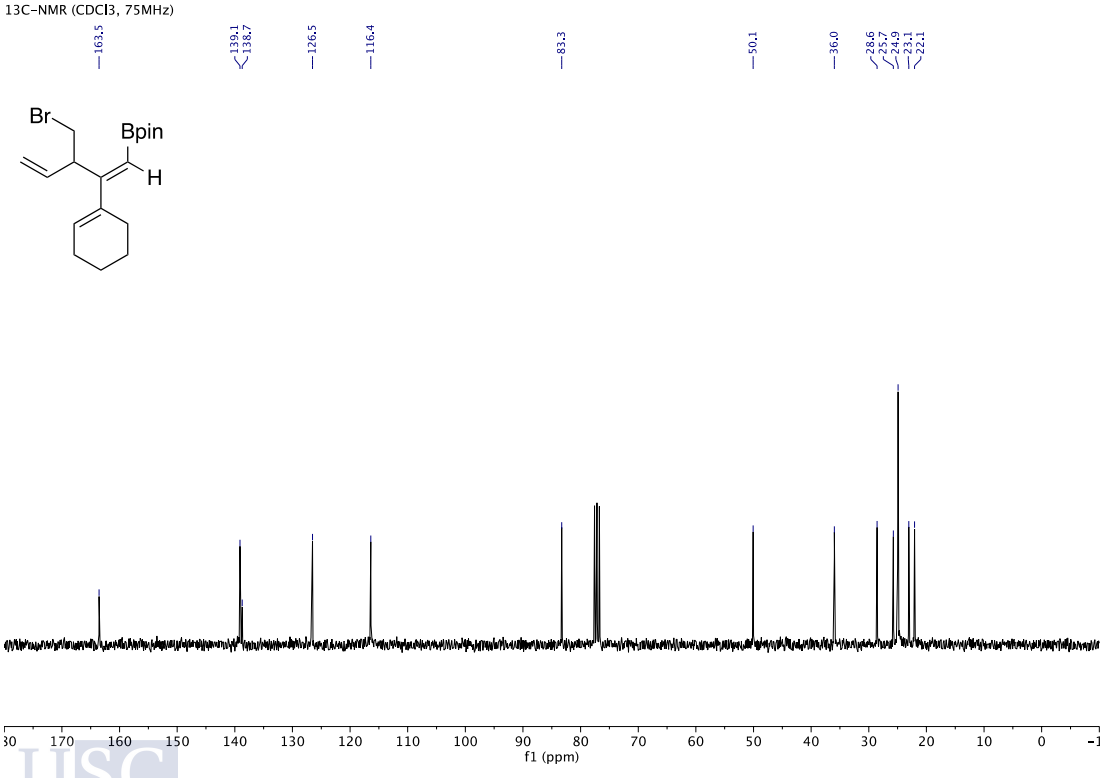
1H-NMR (CDCl3, 300MHz)



13C-NMR (CDCl3, 75MHz)



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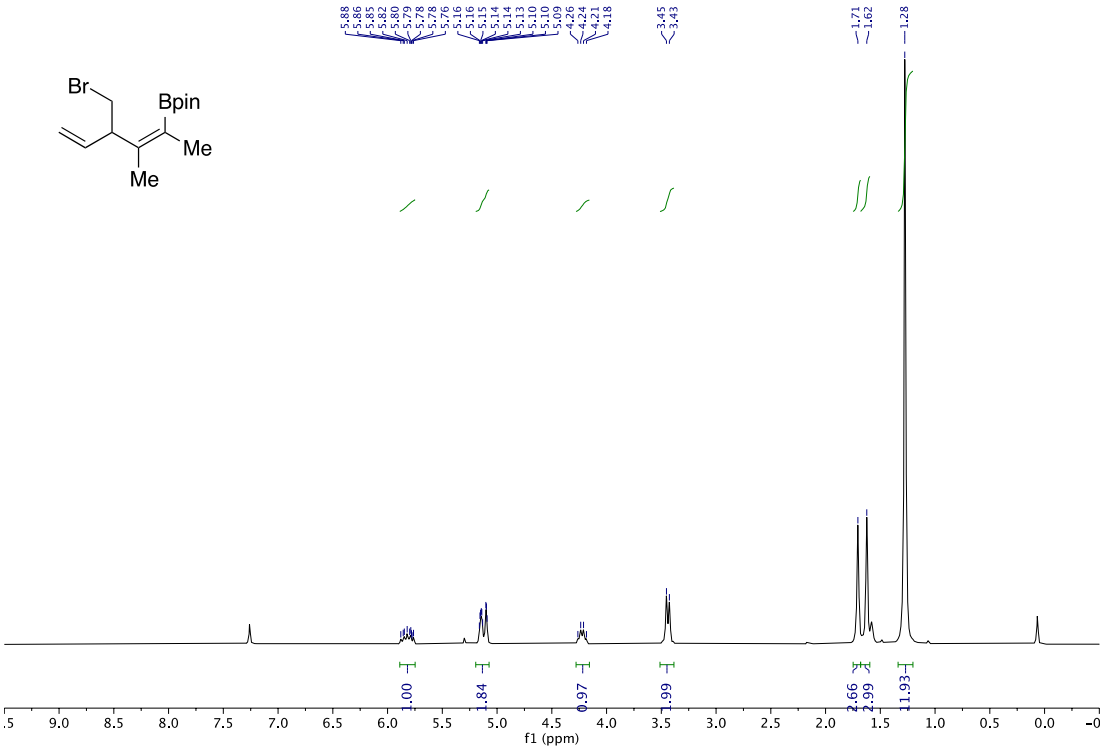
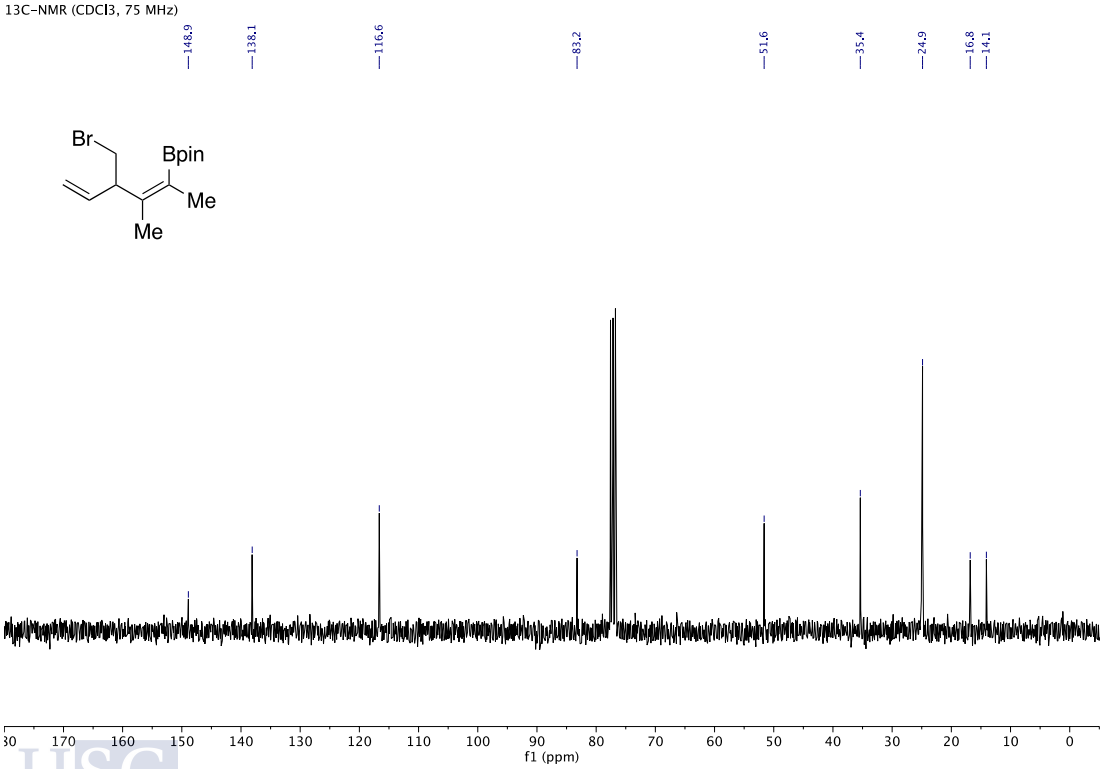
1H-NMR (CDCl3, 300 MHz)



13C-NMR (CDCl3, 75 MHz)



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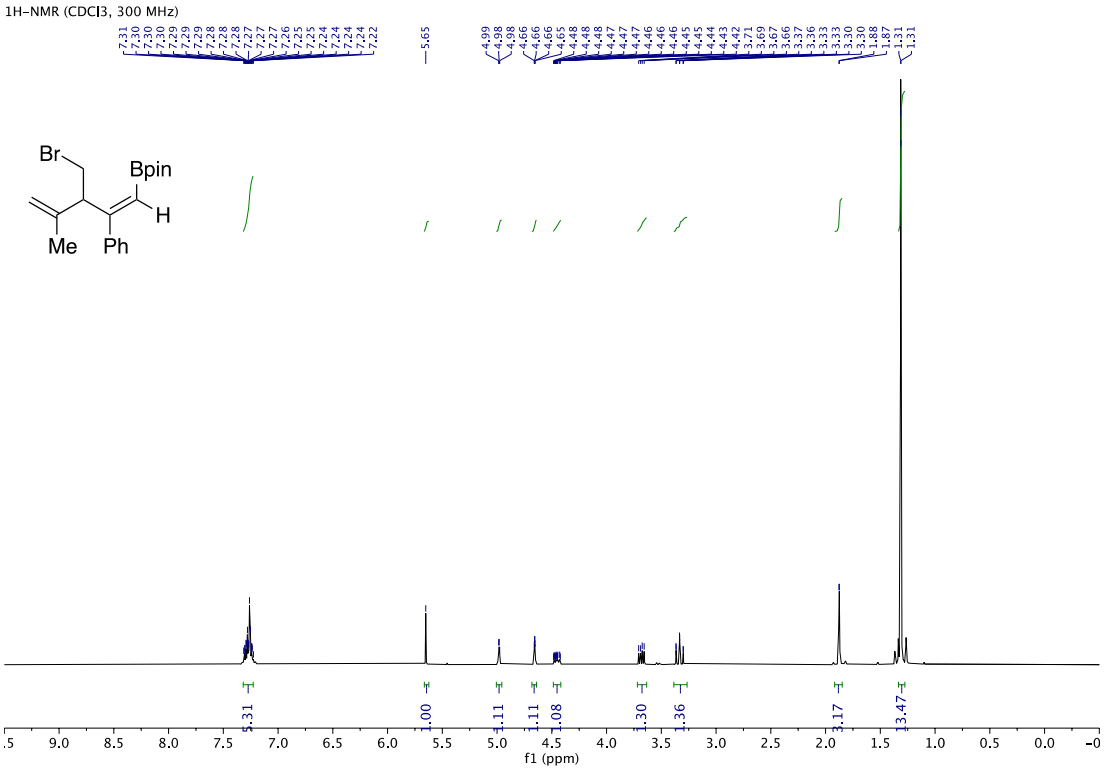

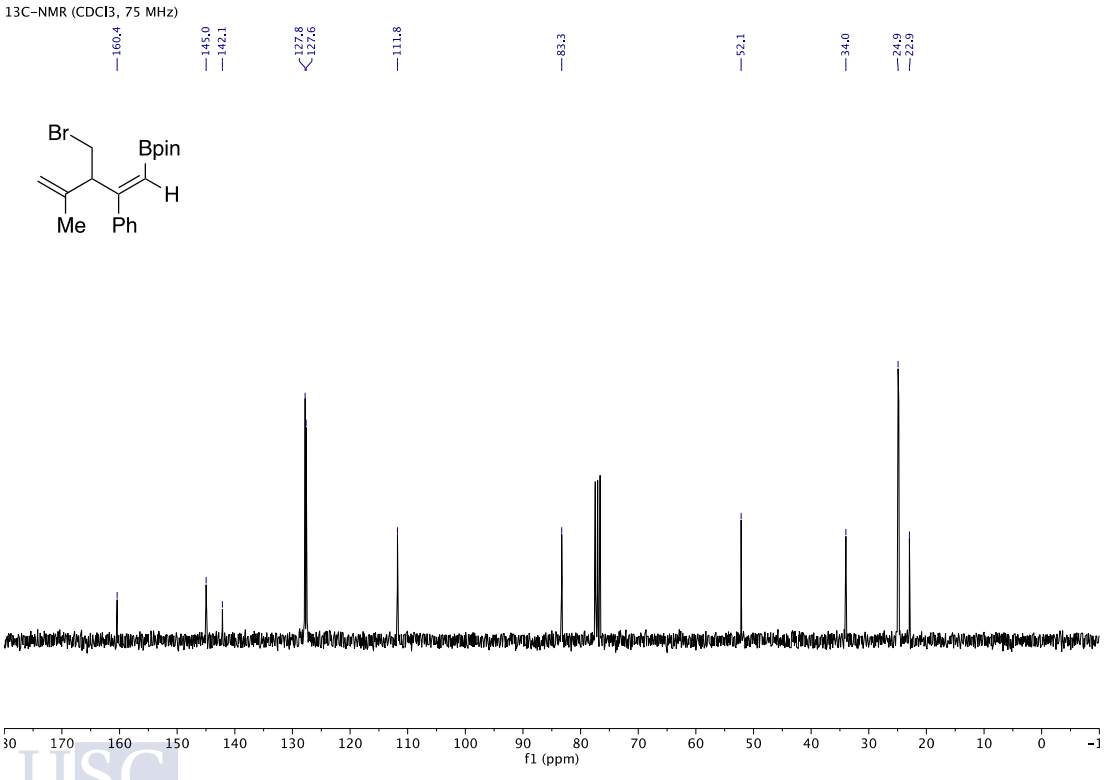

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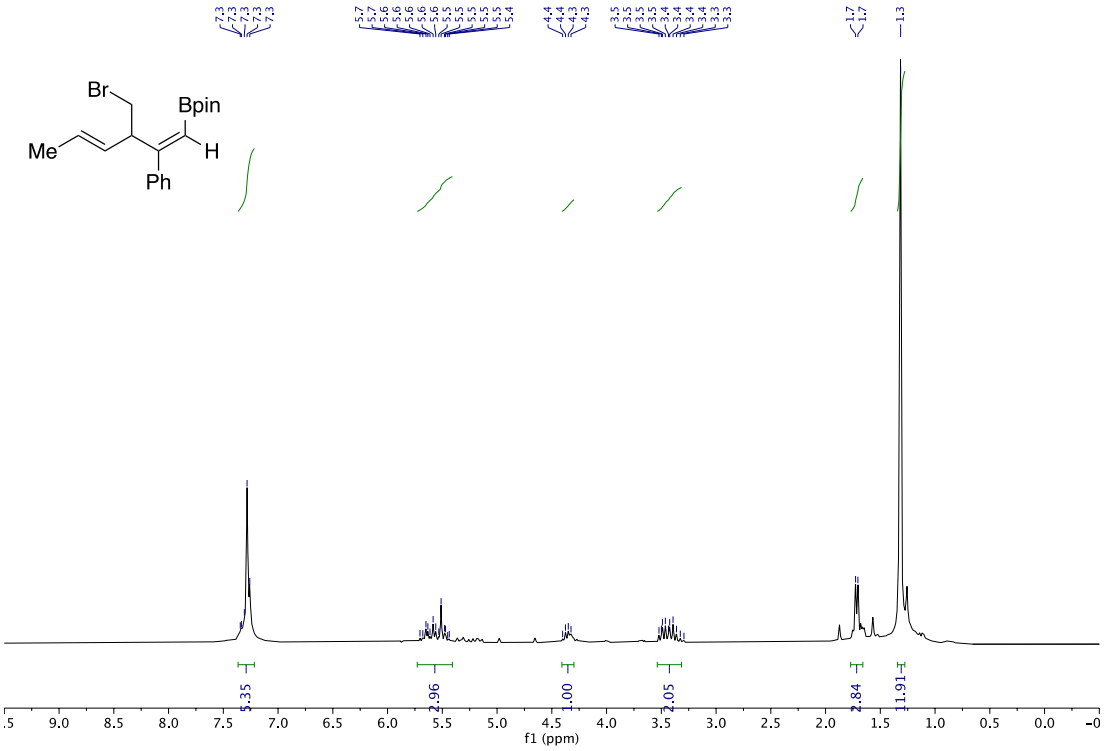
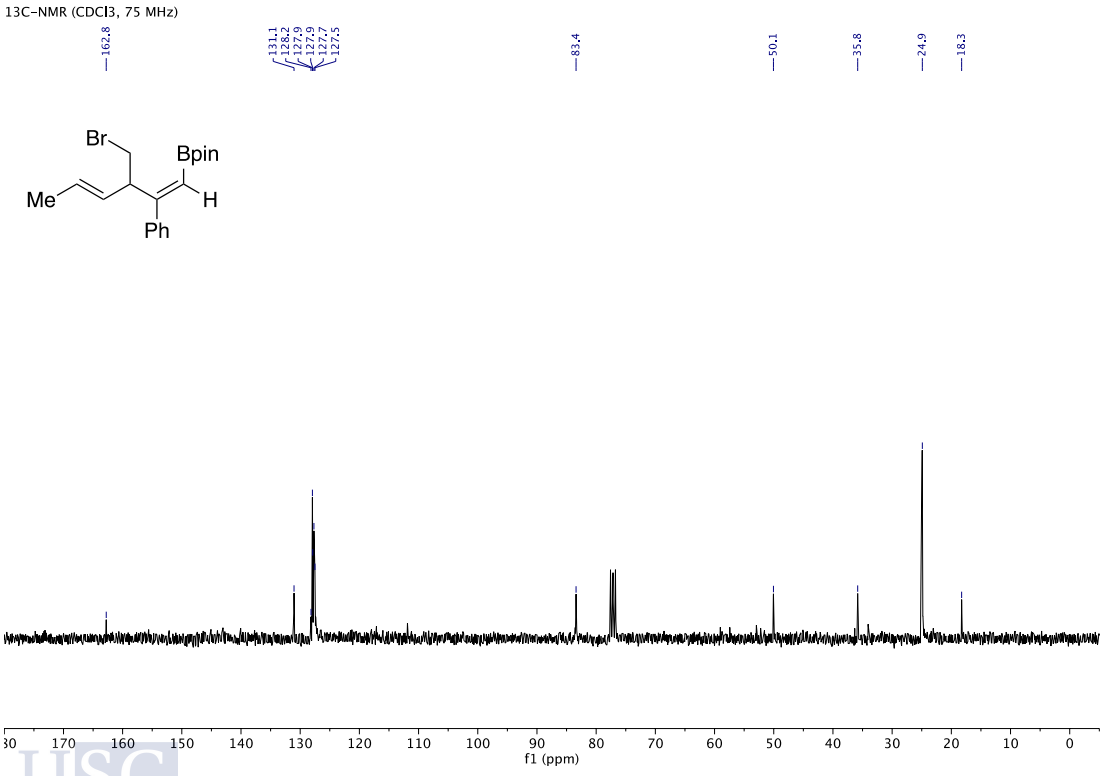
1H-NMR (CDCl3, 300 MHz)



13C-NMR (CDCl3, 75 MHz)



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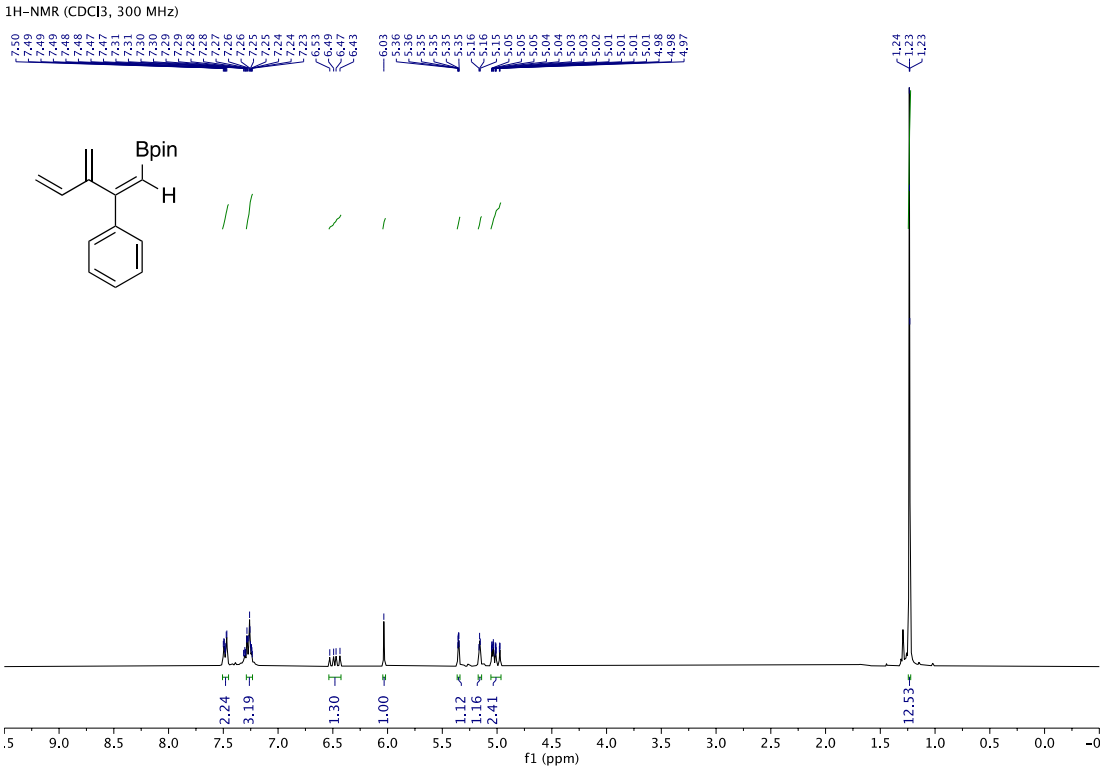

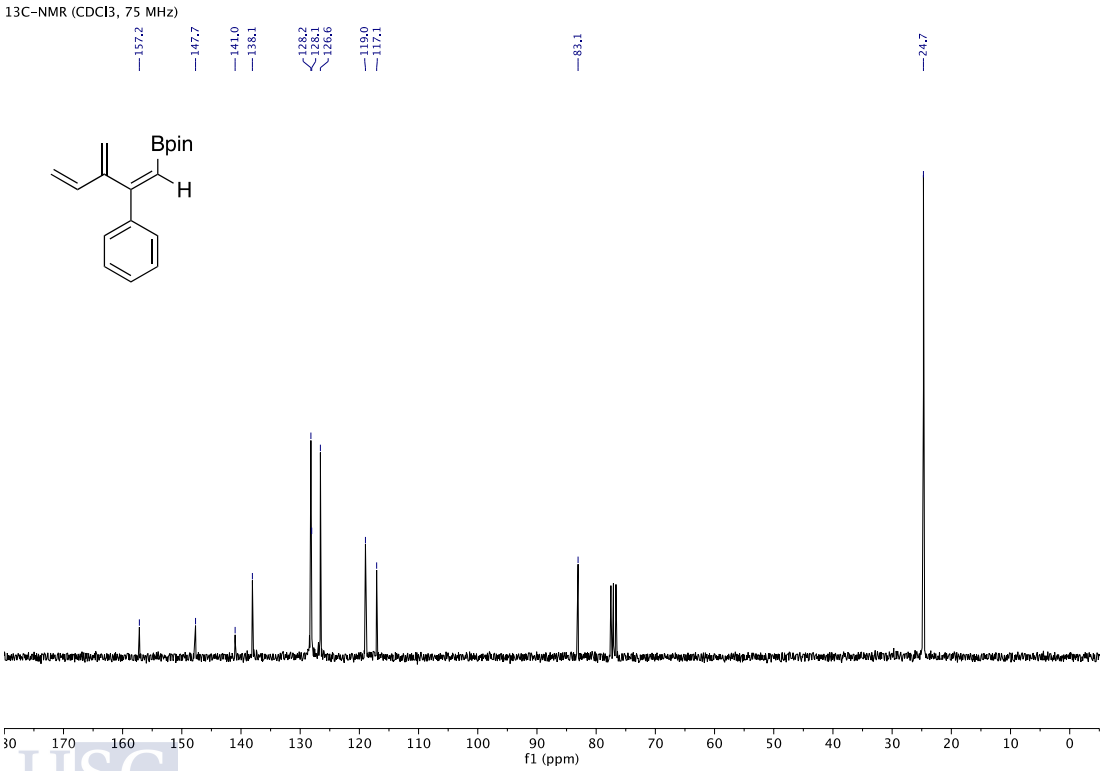

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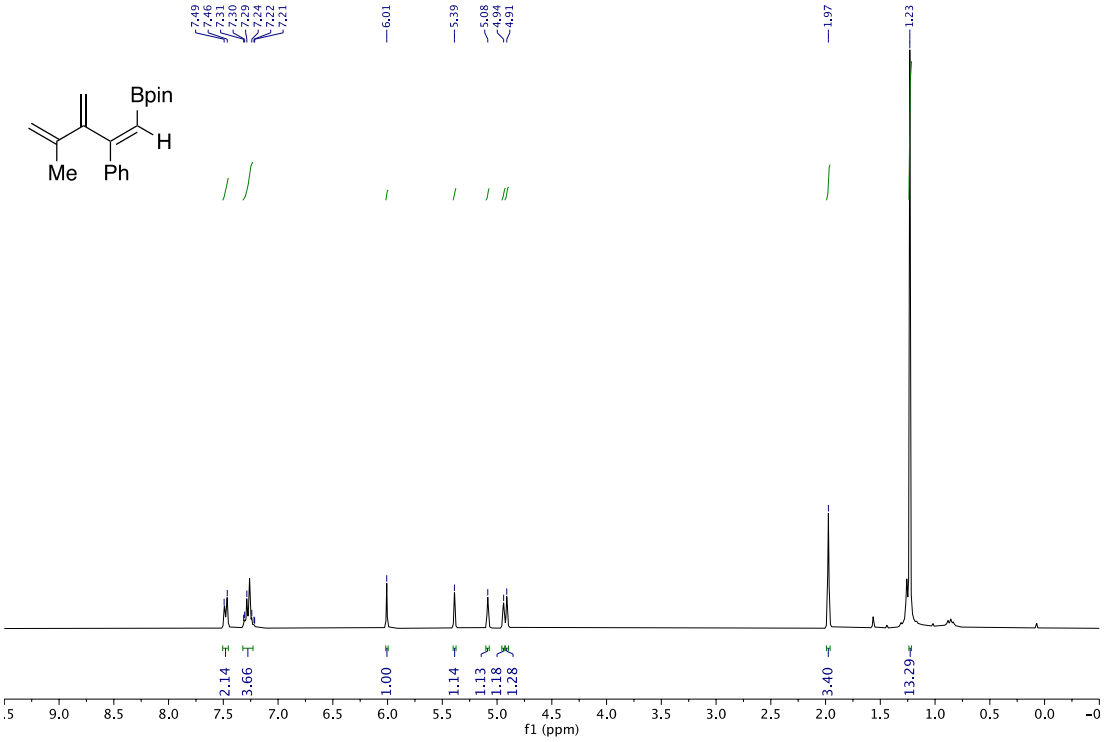
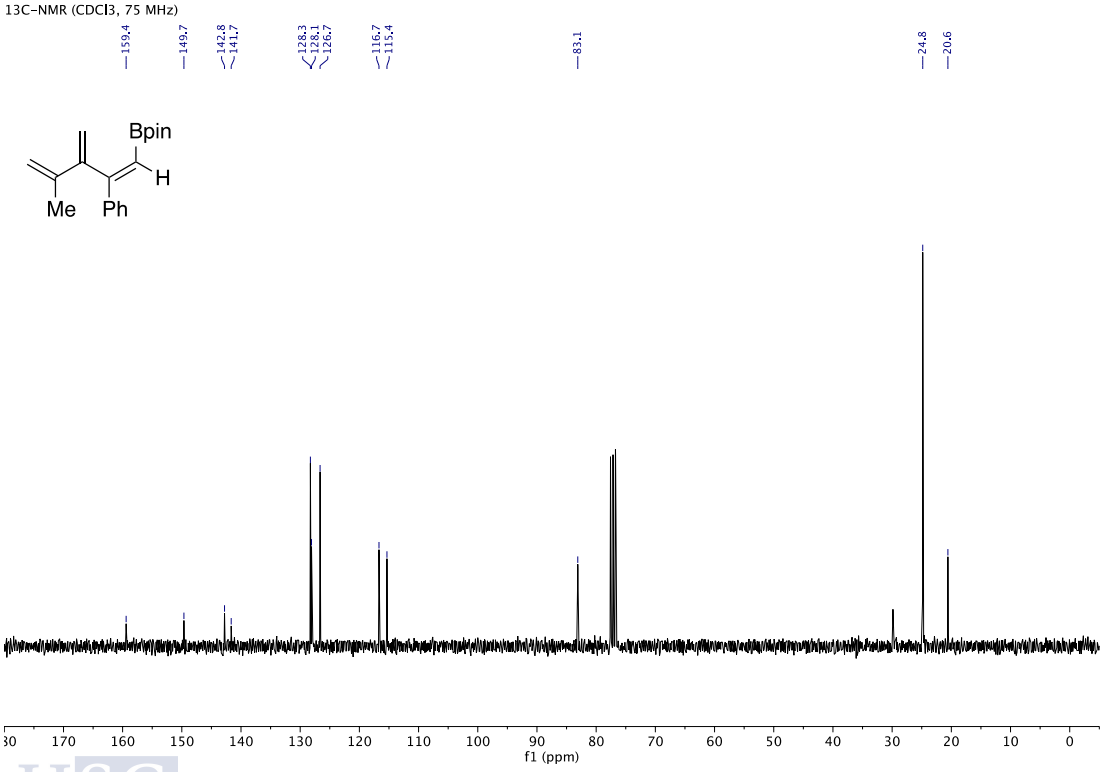
1H-NMR (CDCl3, 300 MHz)



13C-NMR (CDCl3, 75 MHz)



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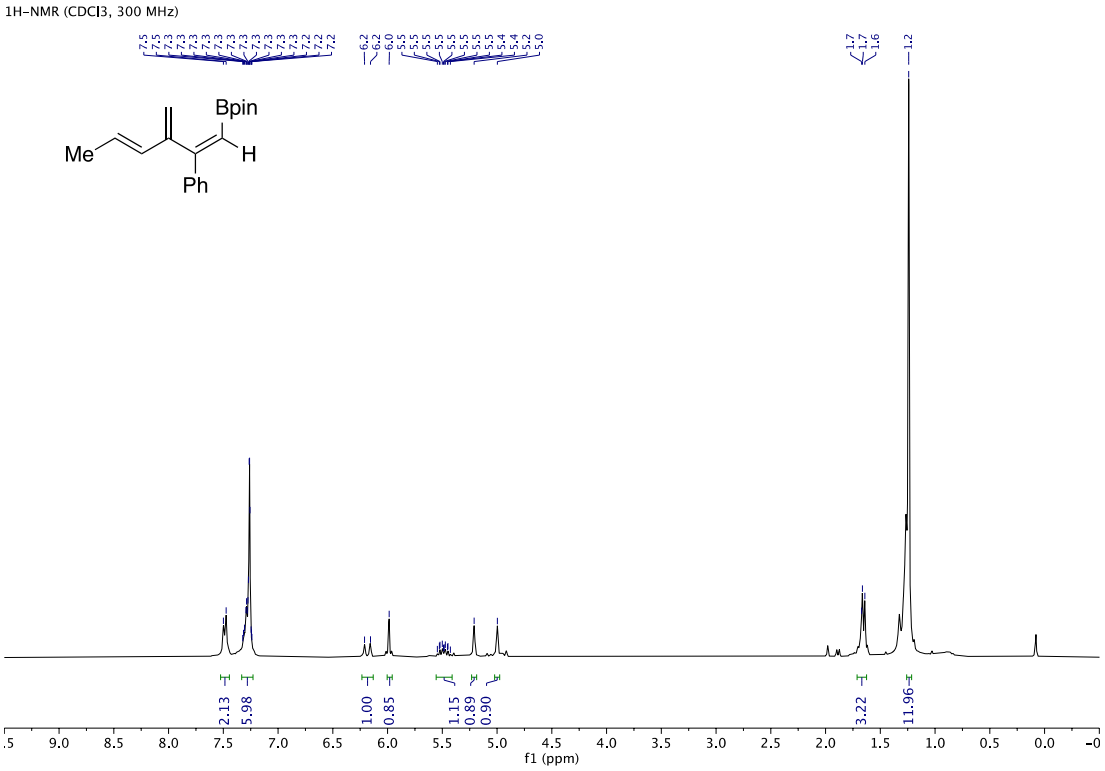

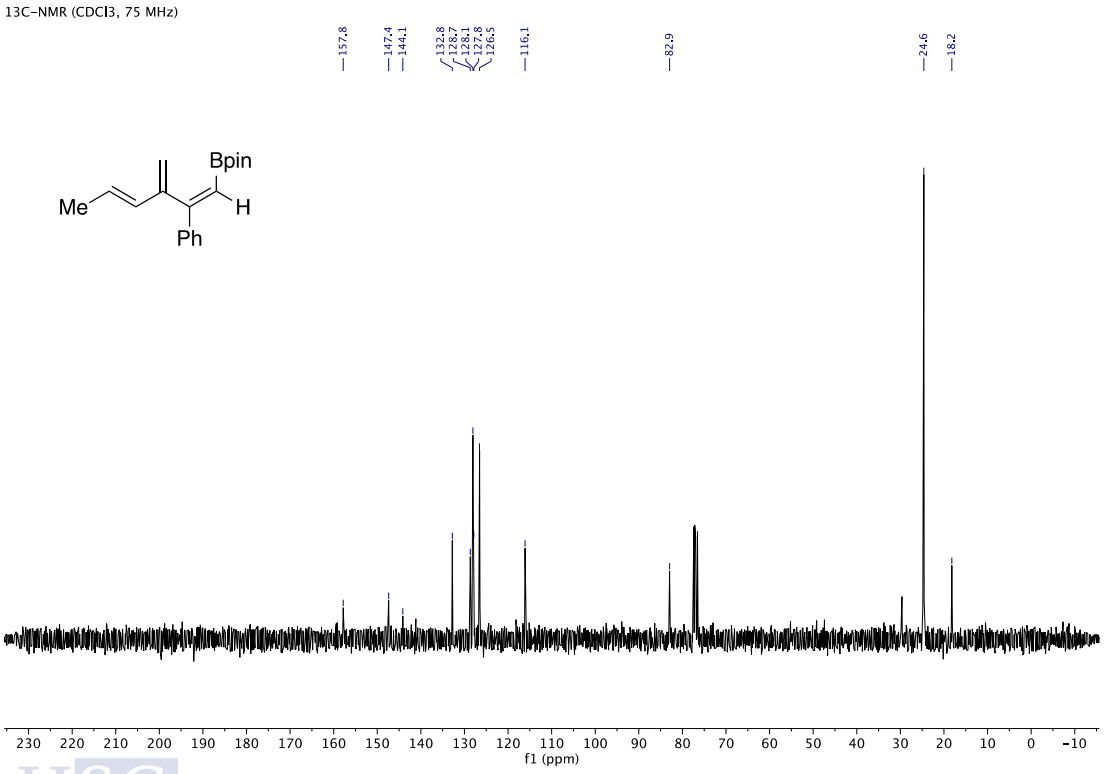

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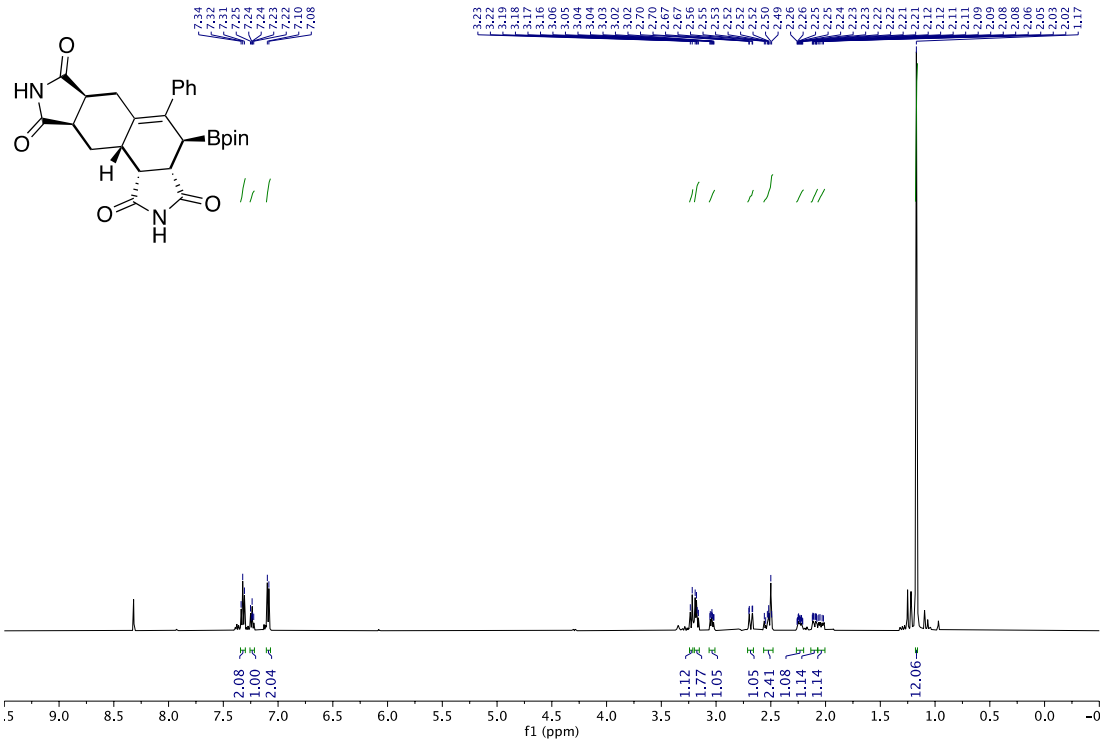
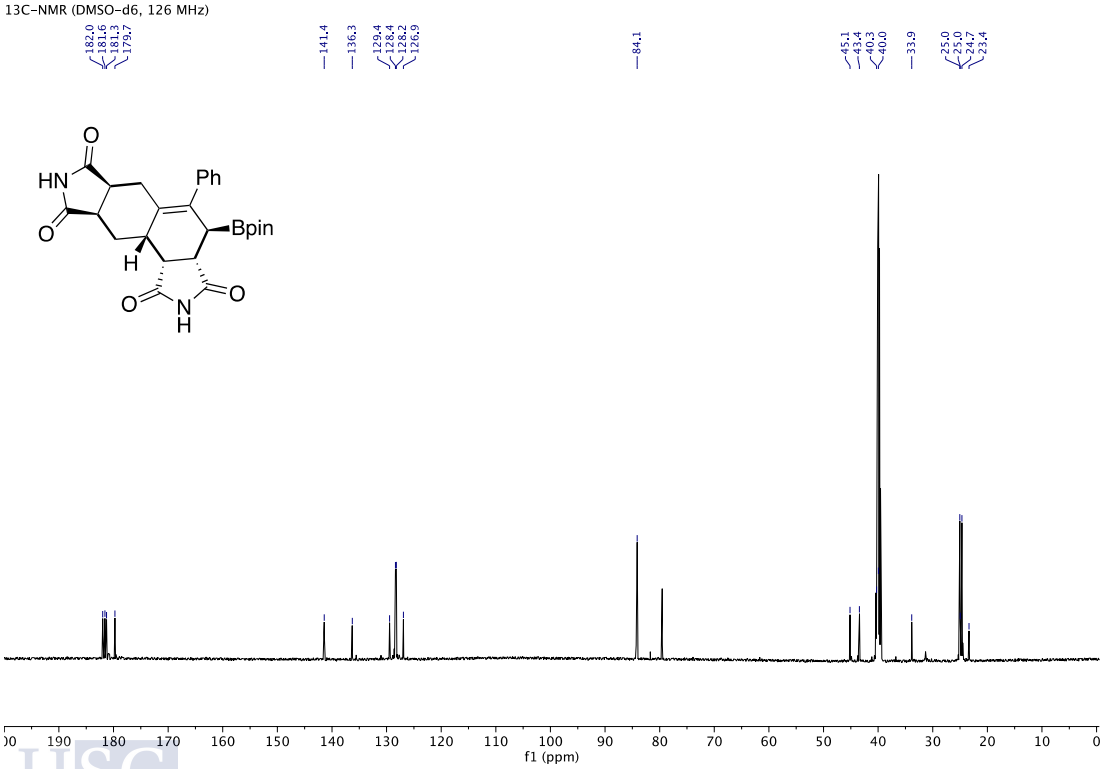
1H-NMR (DMSO-d6, 500 MHz)



13C-NMR (DMSO-d6, 126 MHz)



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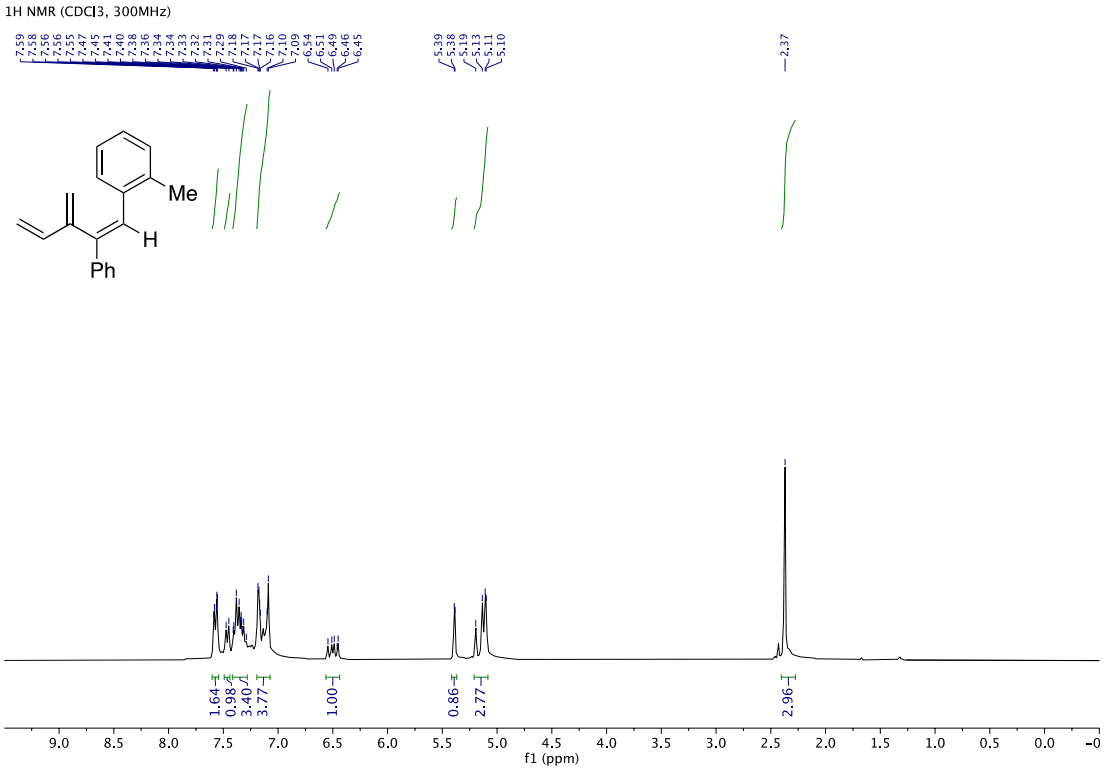

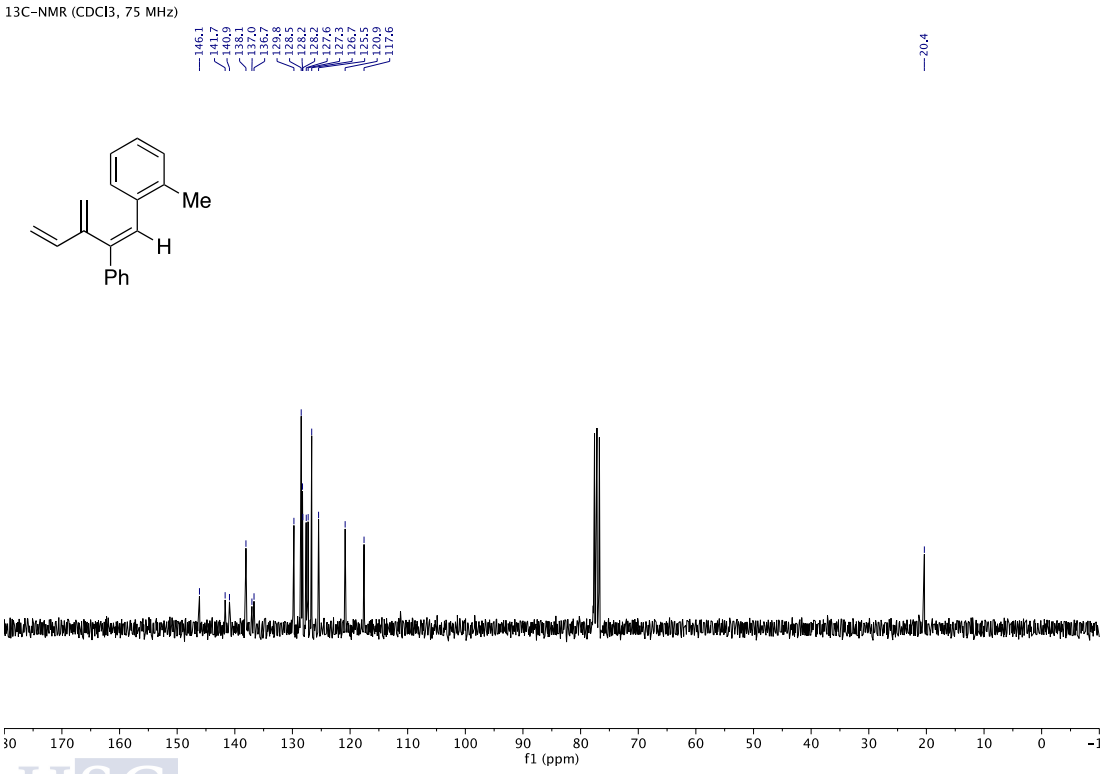

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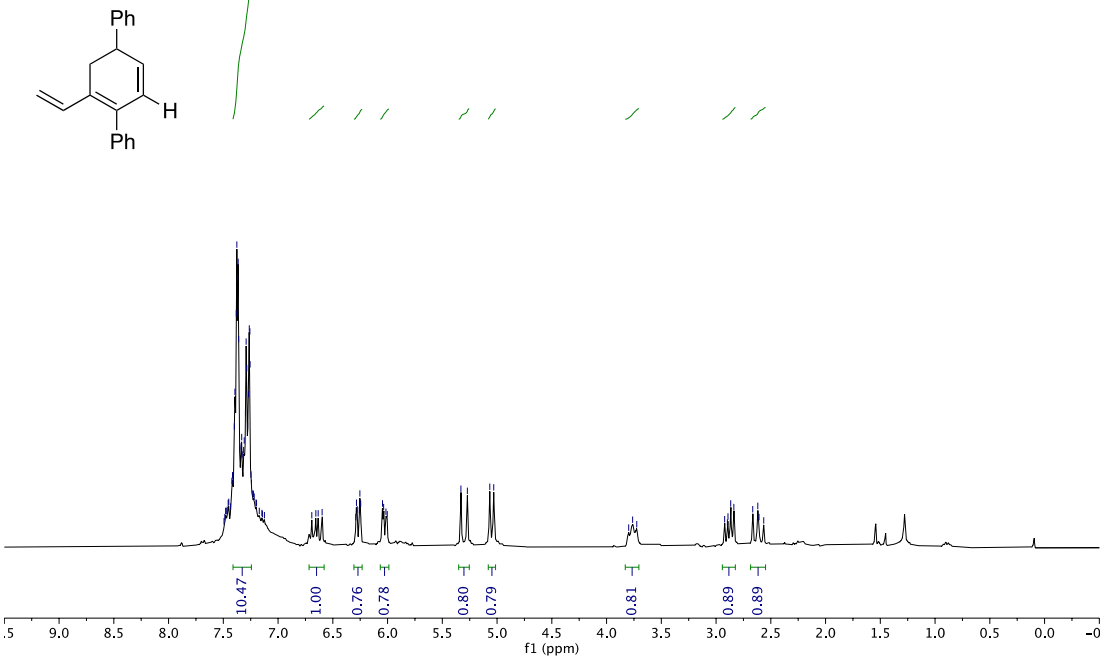
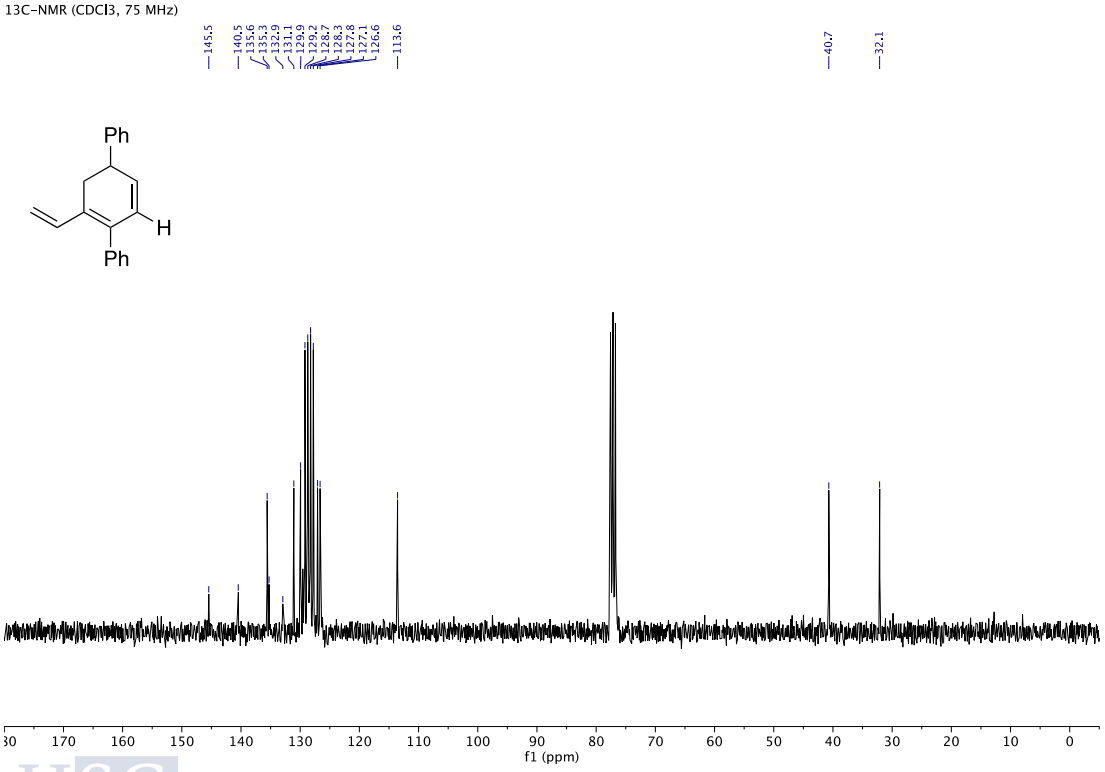
1H-NMR (CDCl3, 300 MHz)



13C-NMR (CDCl3, 75 MHz)



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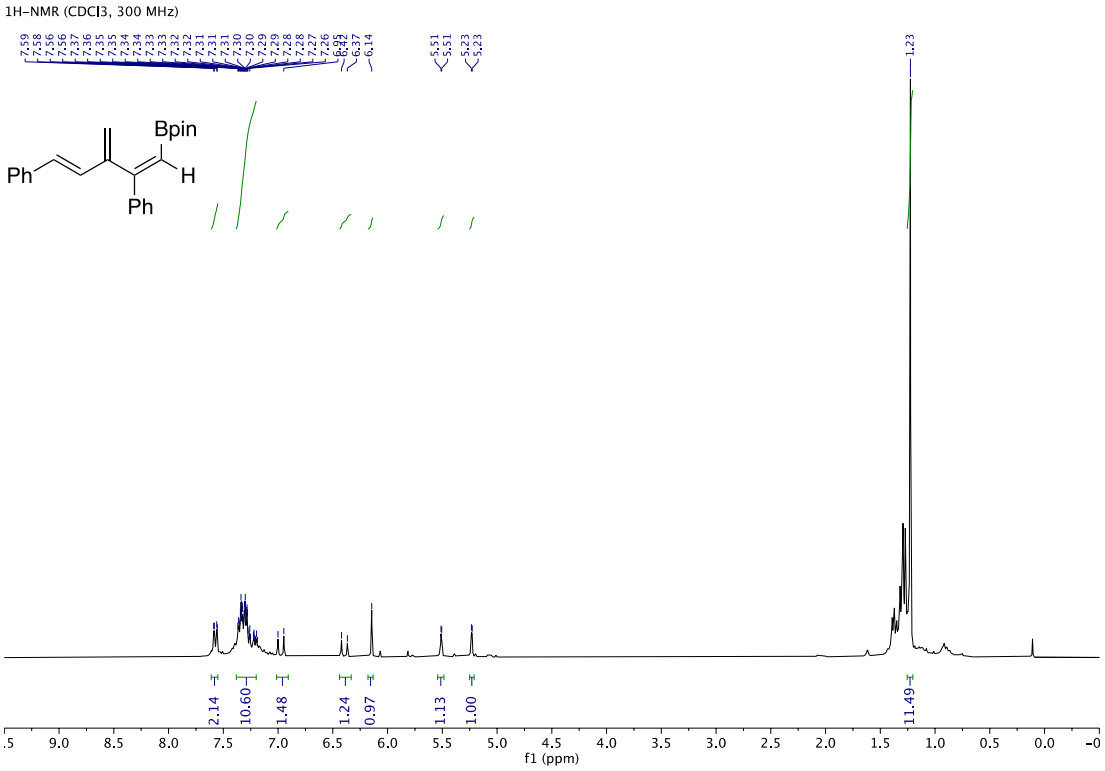

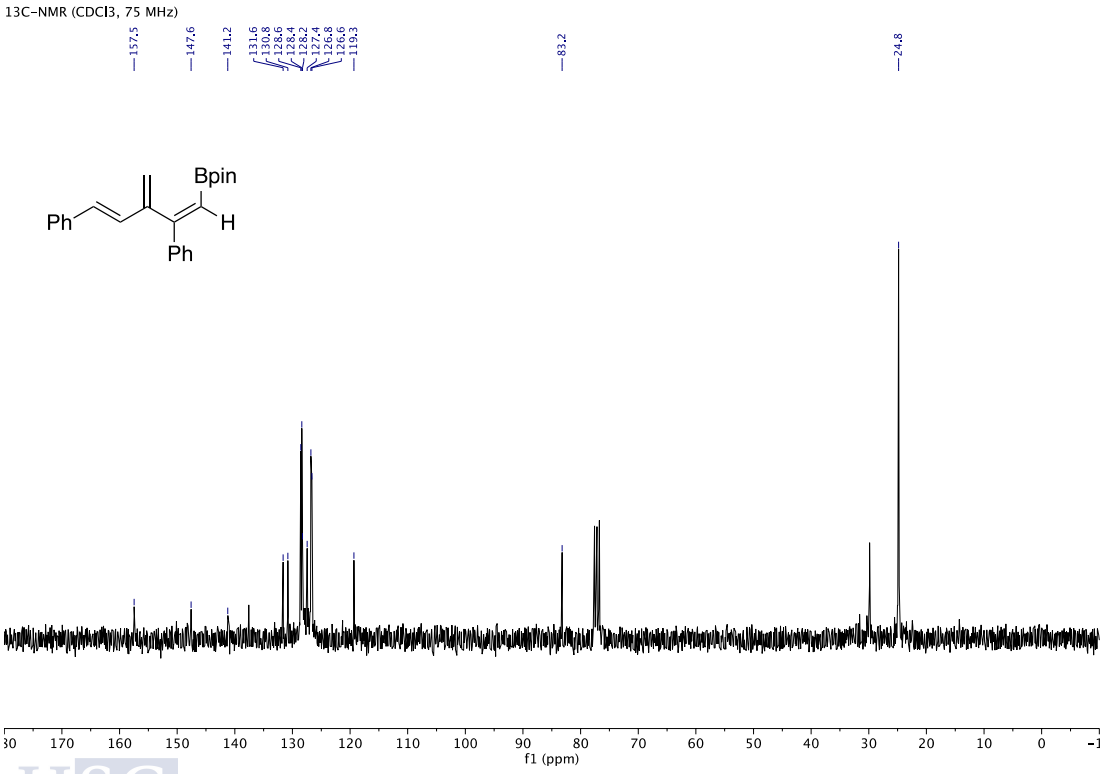

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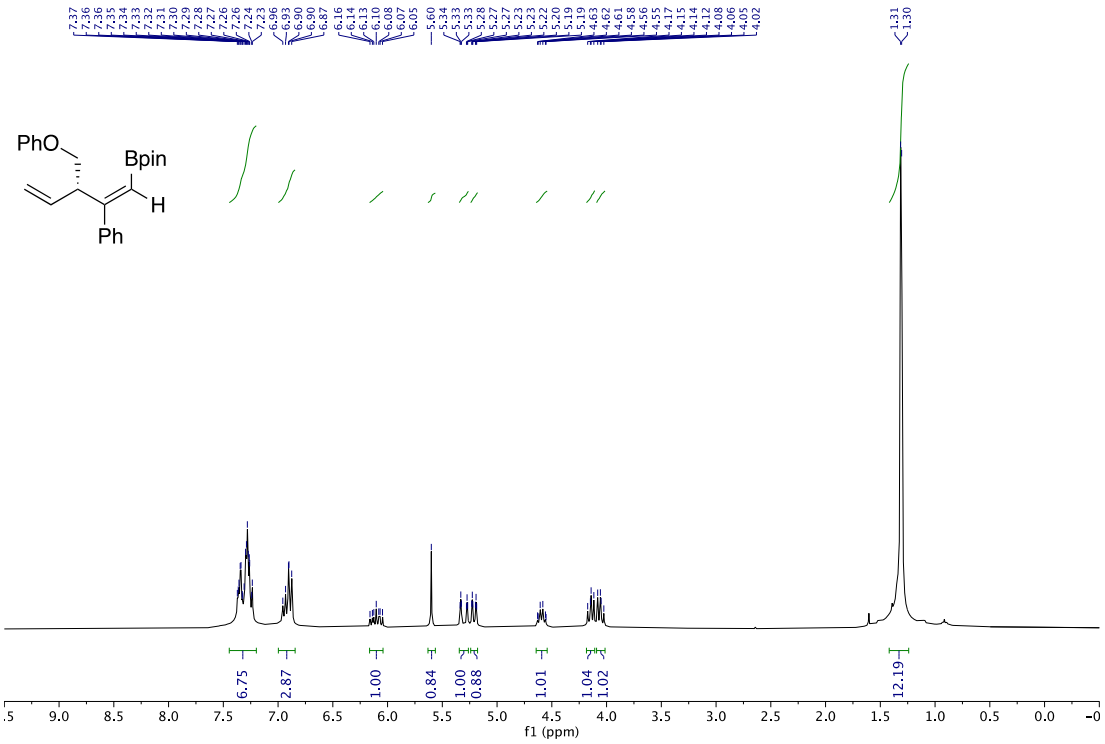
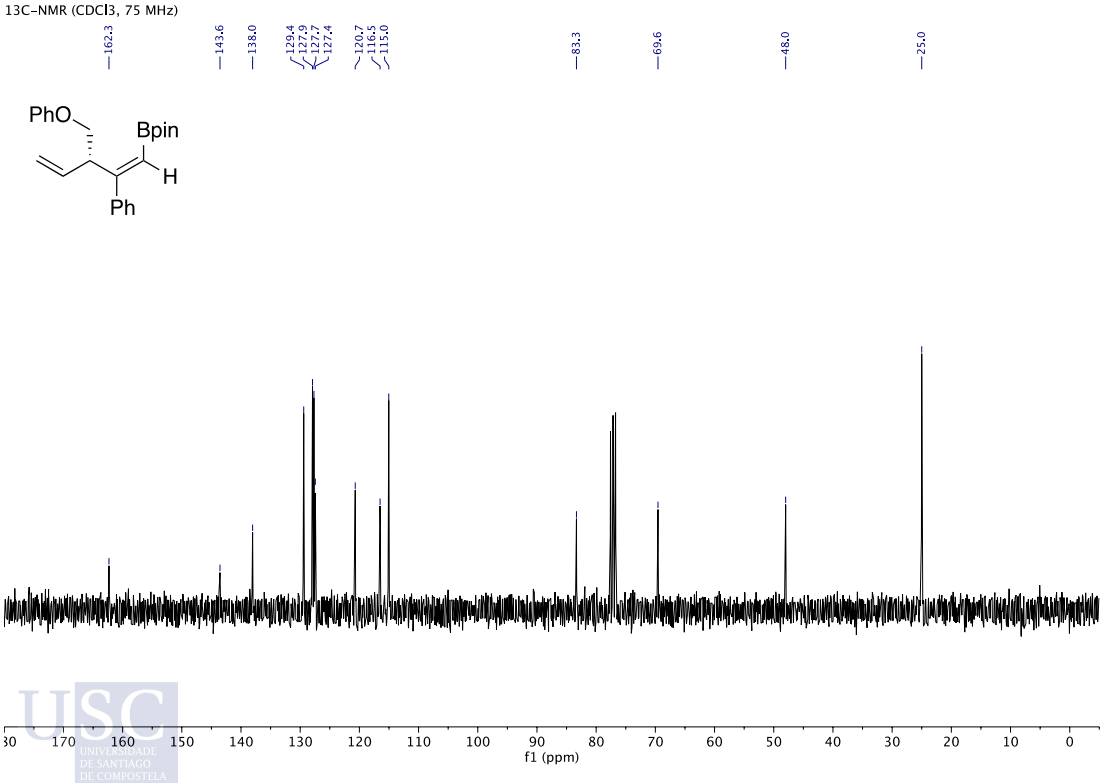
CHAPTER IV:

1H-NMR (CDCl3, 300 MHz)



13C-NMR (CDCl3, 75 MHz)



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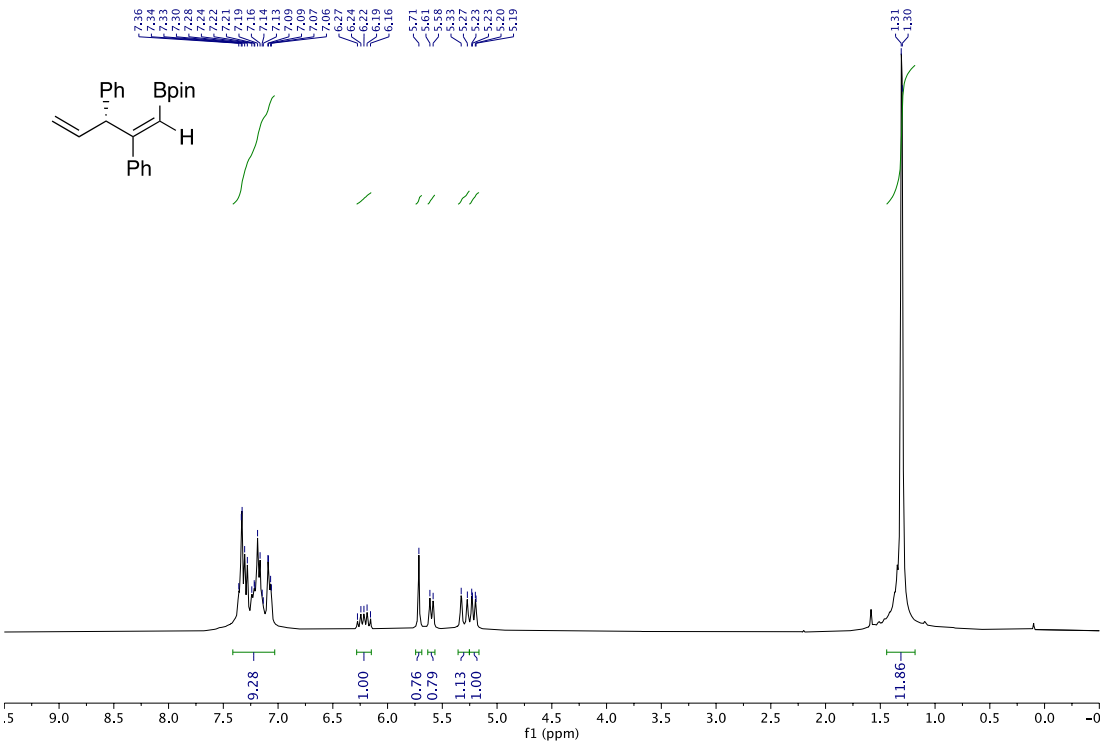
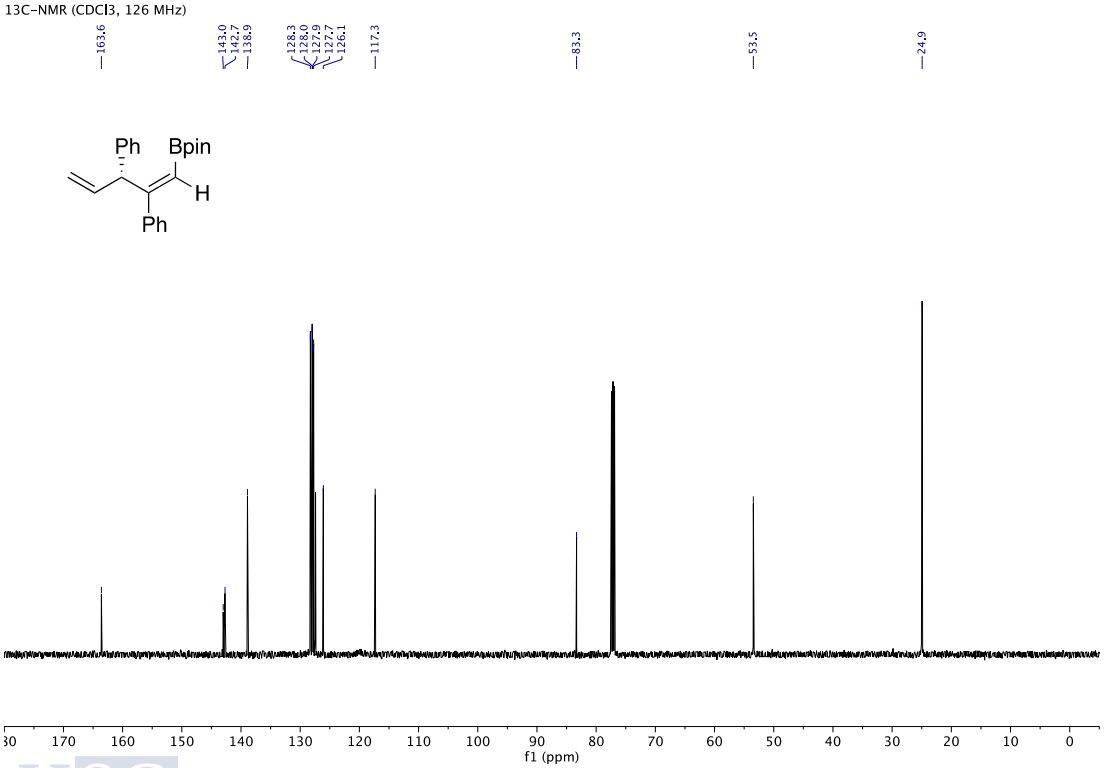
1H–NMR (CDCl3, 300 MHz)



13C–NMR (CDCl3, 126 MHz)



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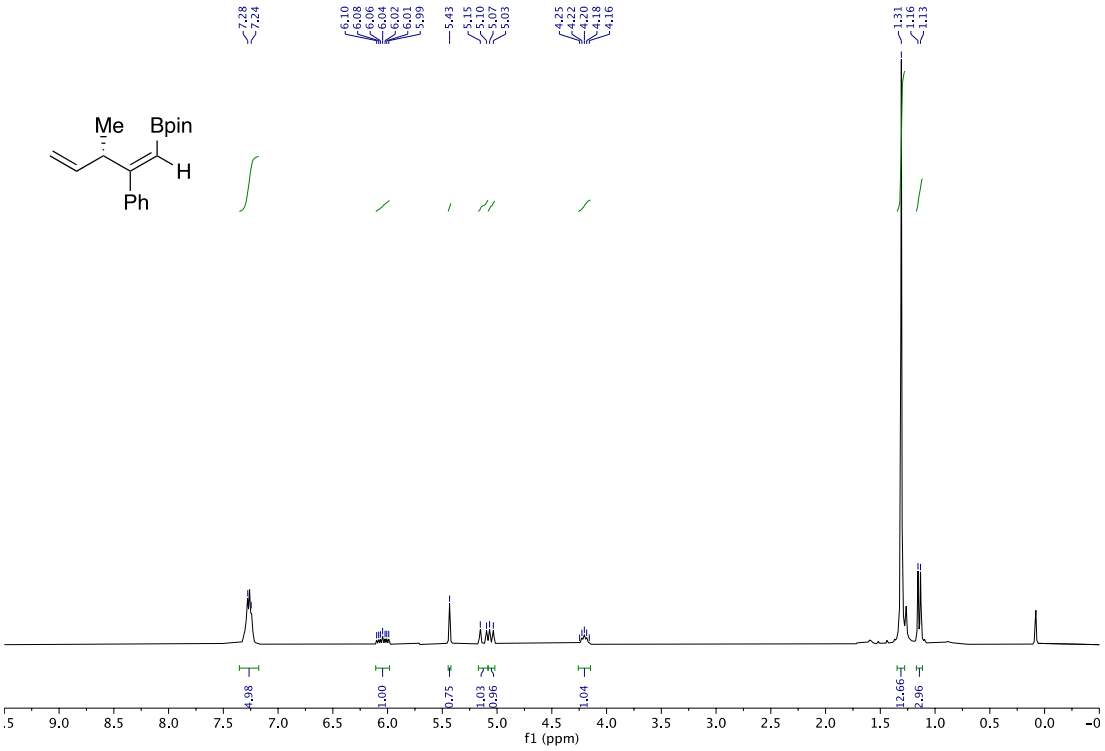
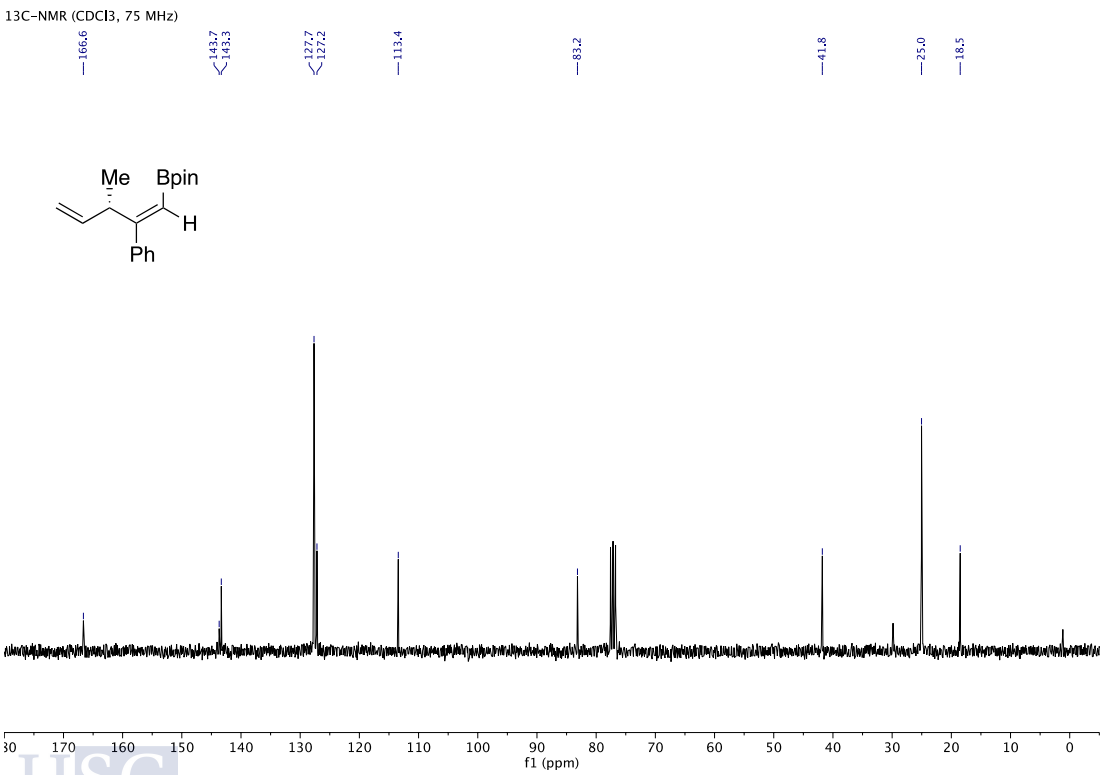
1H-NMR (CDCl3, 300 MHz)



13C-NMR (CDCl3, 75 MHz)



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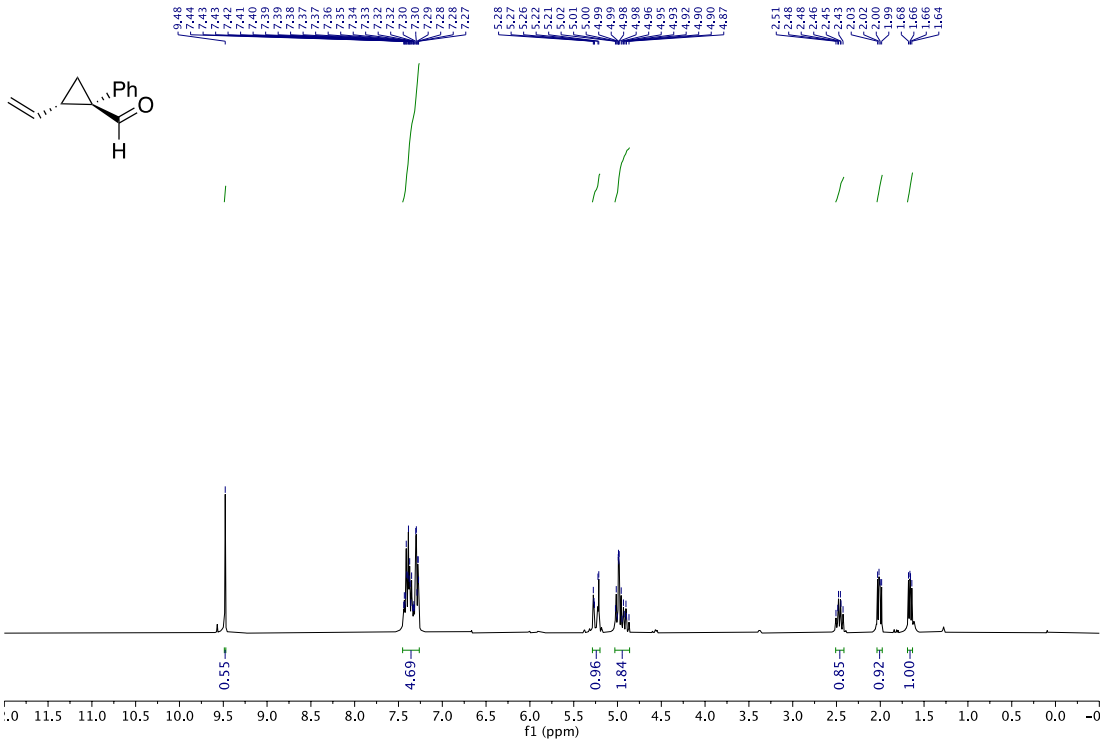
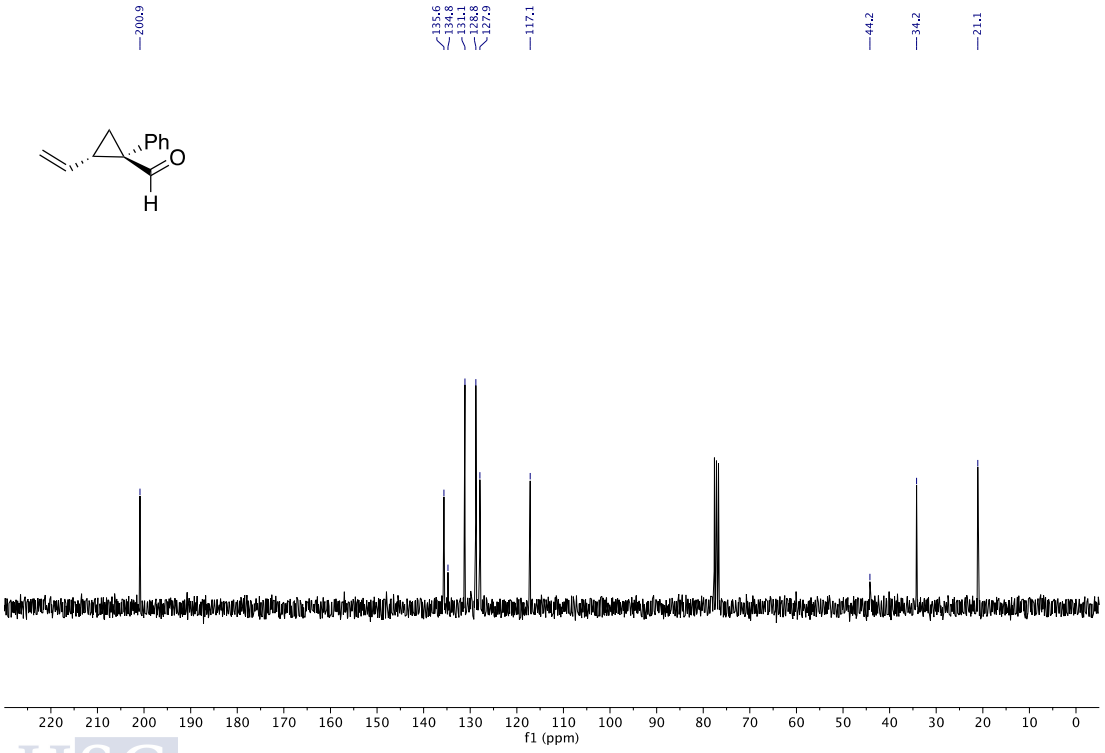
1H–NMR (CDCl3, 300 MHz)



13C–NMR (CDCl3, 75 MHz)



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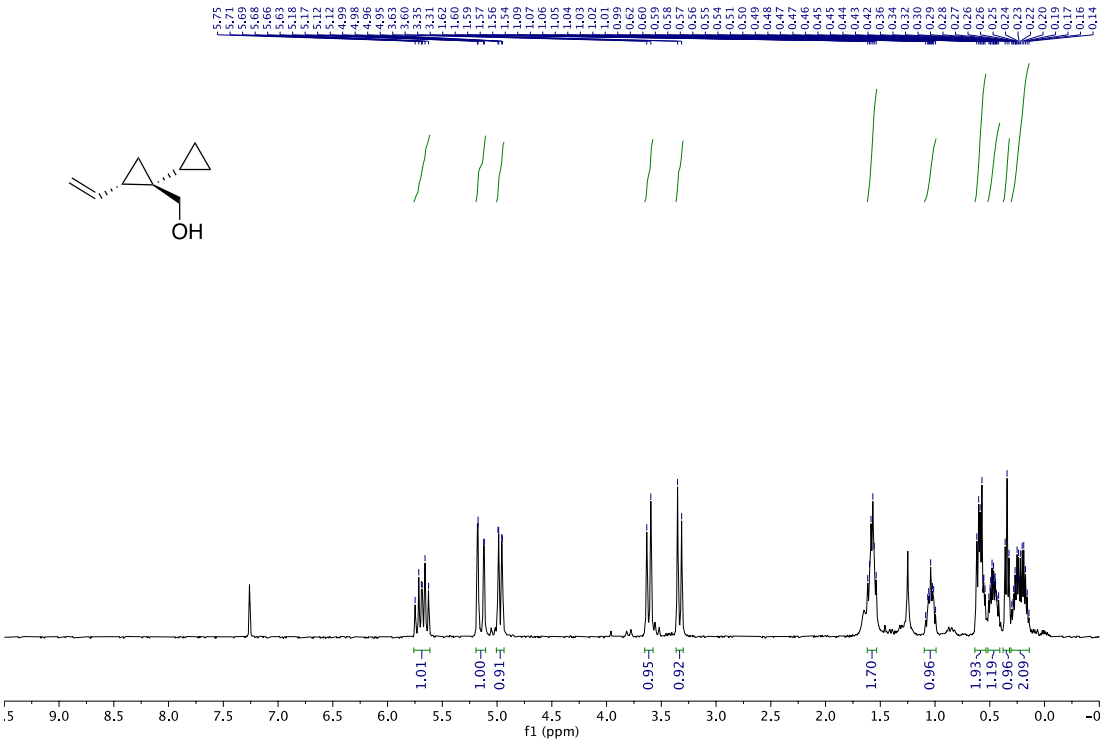
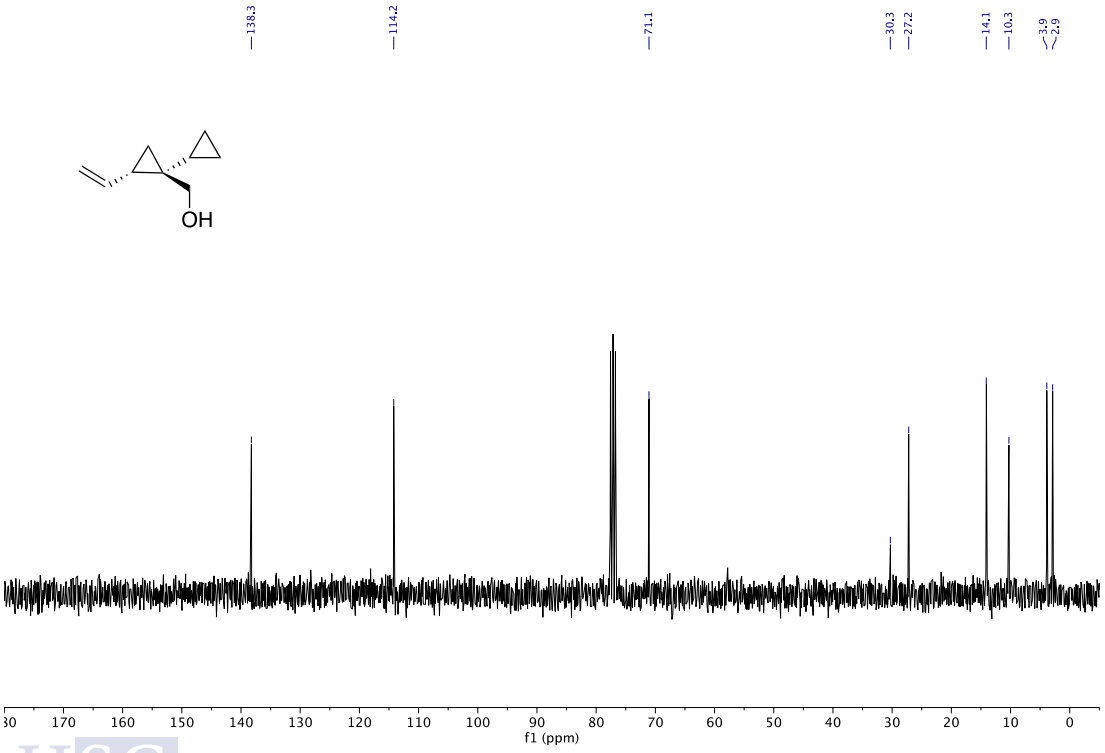
1H-NMR (CDCl3, 300 MHz)



13C-NMR (CDCl3, 75 MHz)



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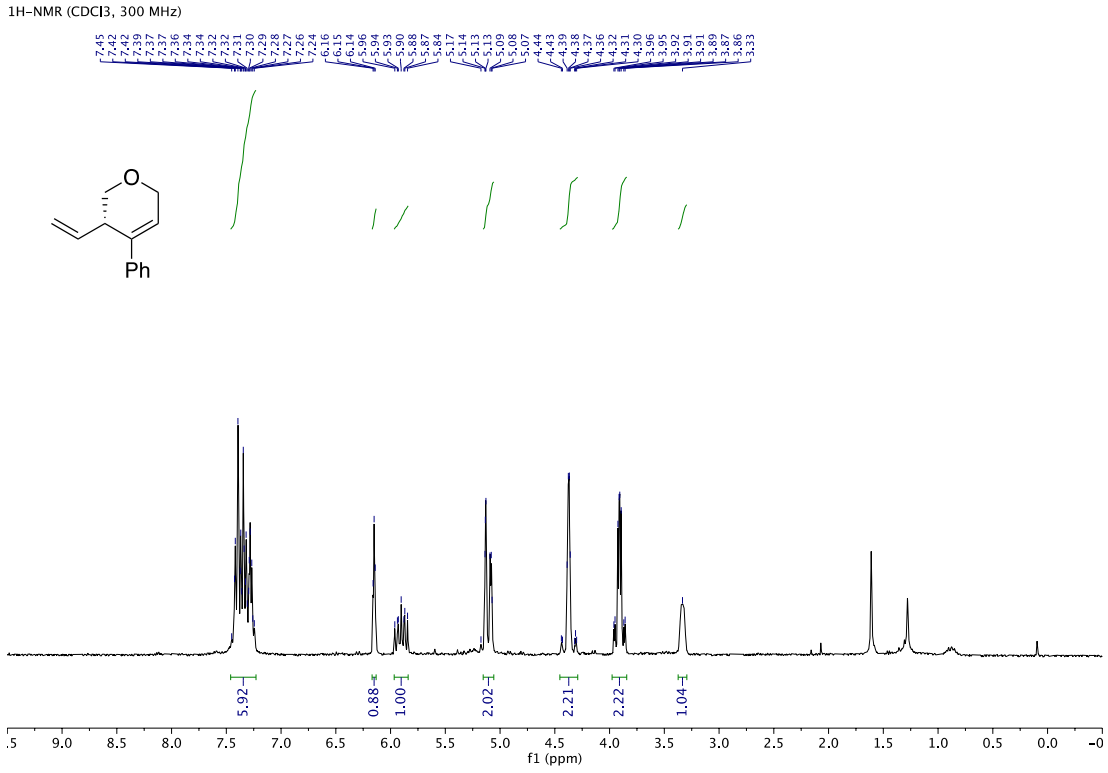

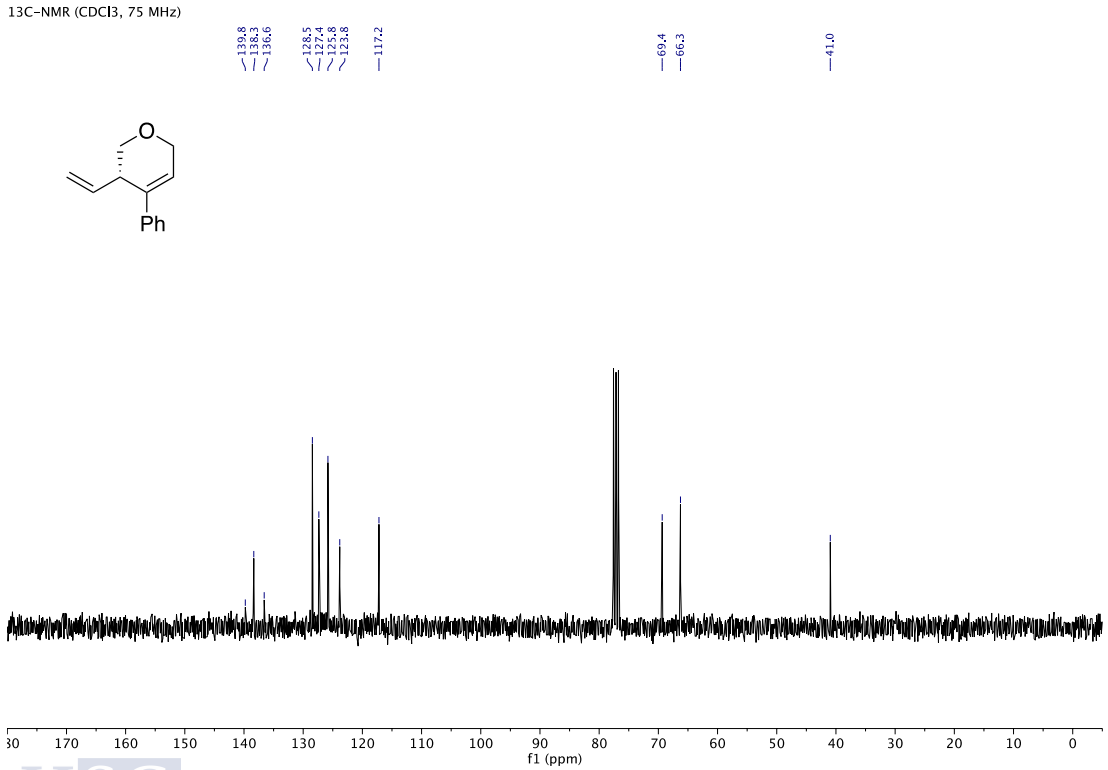

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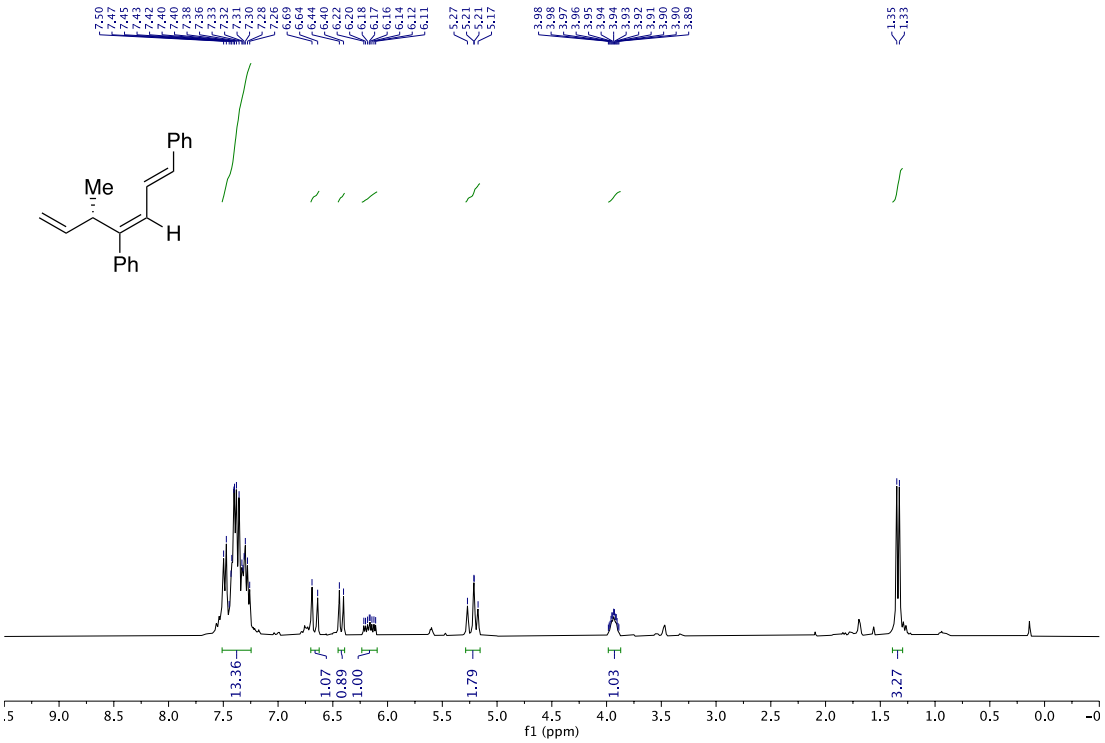
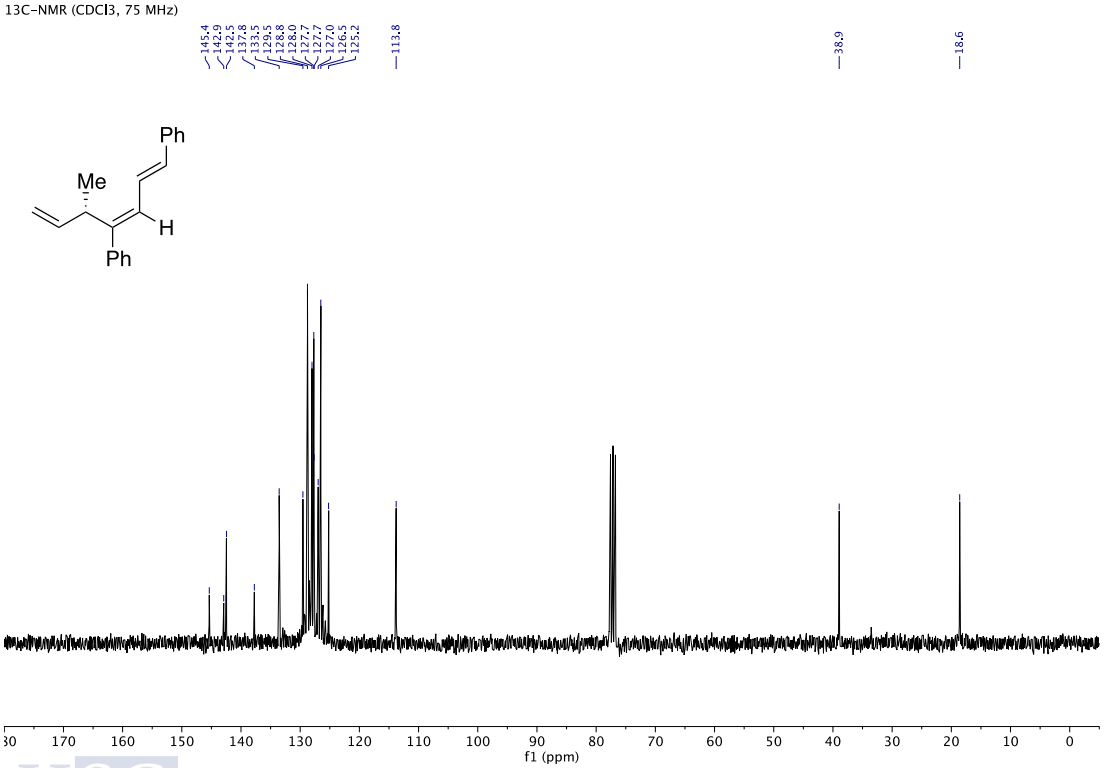
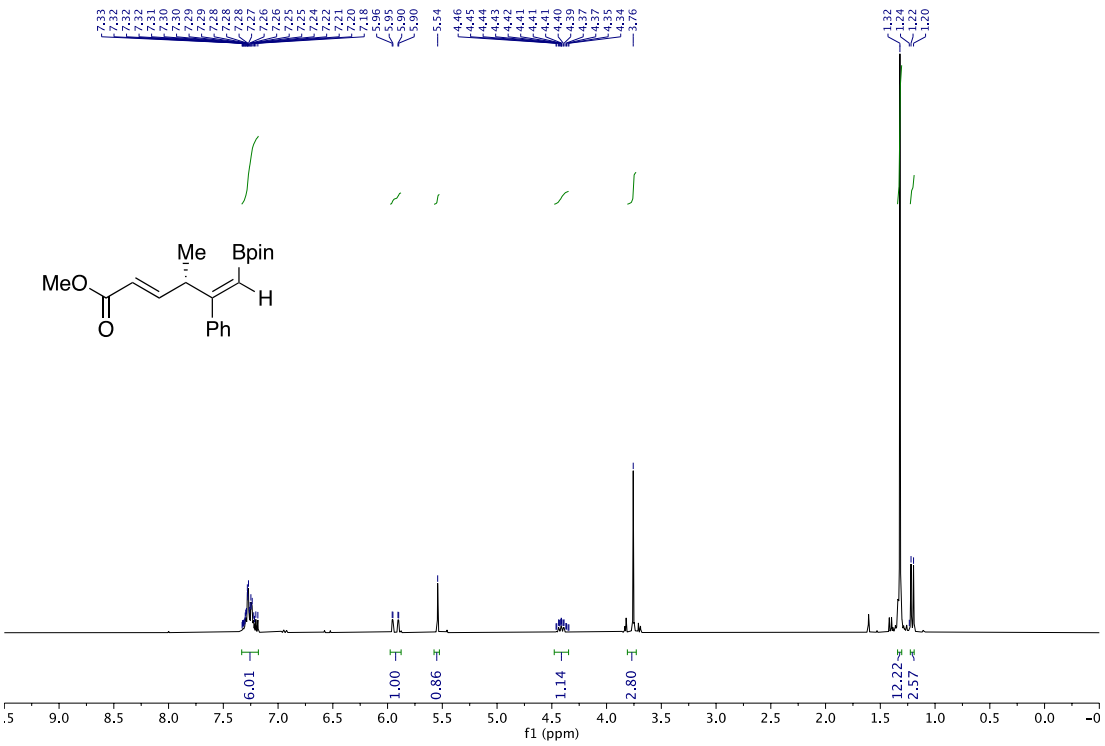
1H-NMR (CDCl3, 300 MHz)



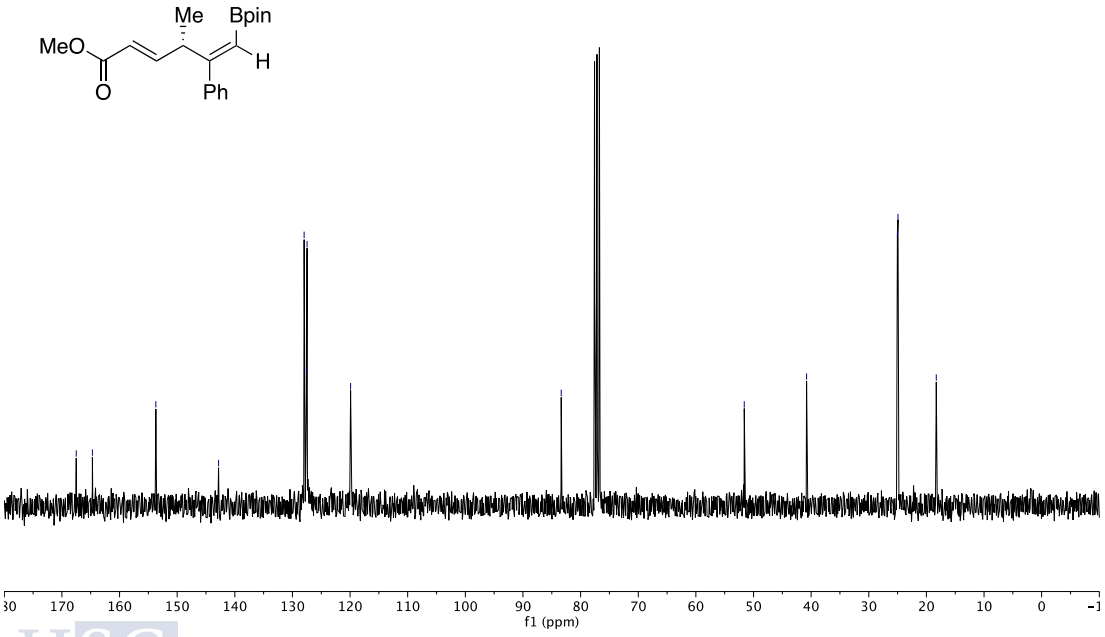
13C-NMR (CDCl3, 75 MHz)



1H-NMR (CDCl3, 300 MHz)



13C-NMR (CDCl3, 75 MHz)



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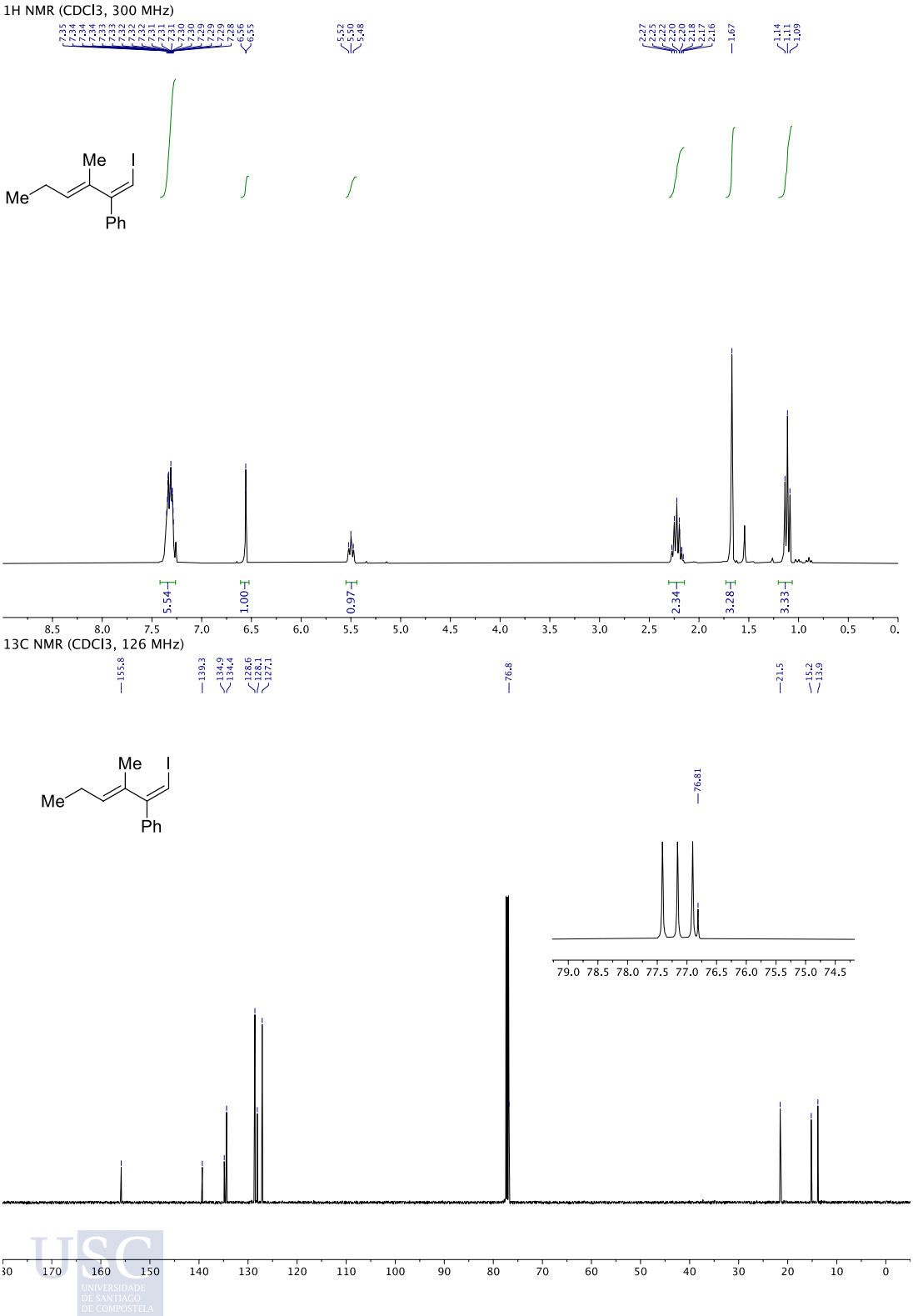
CHAPTER V:



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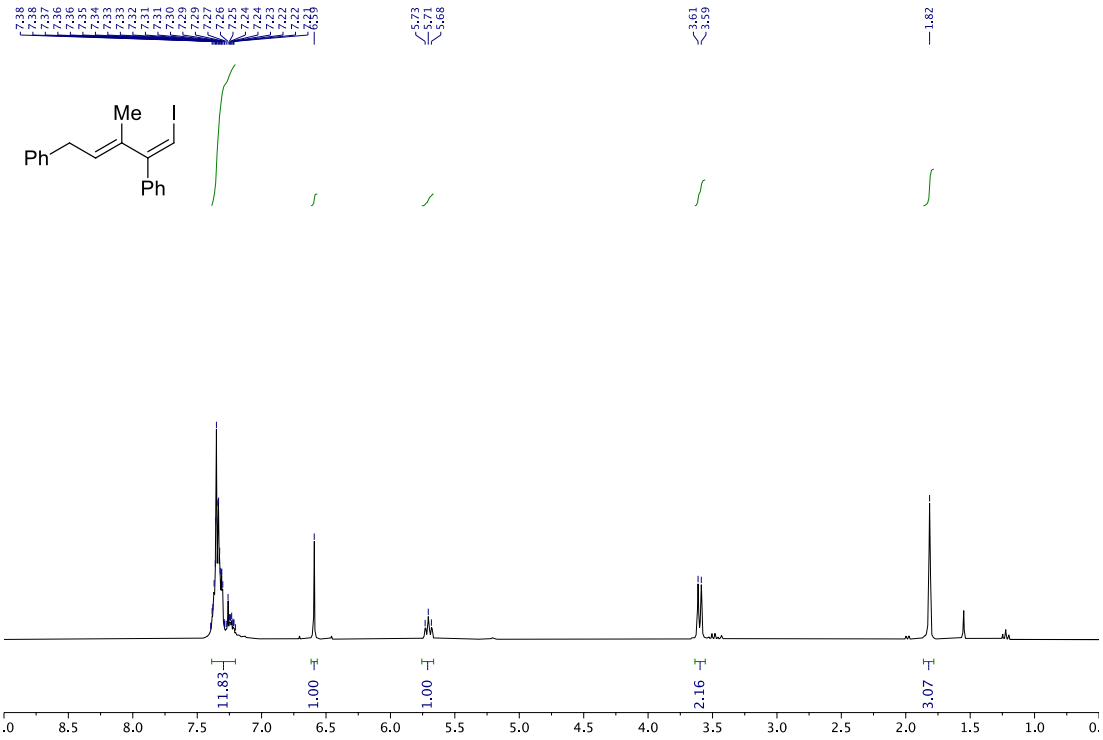
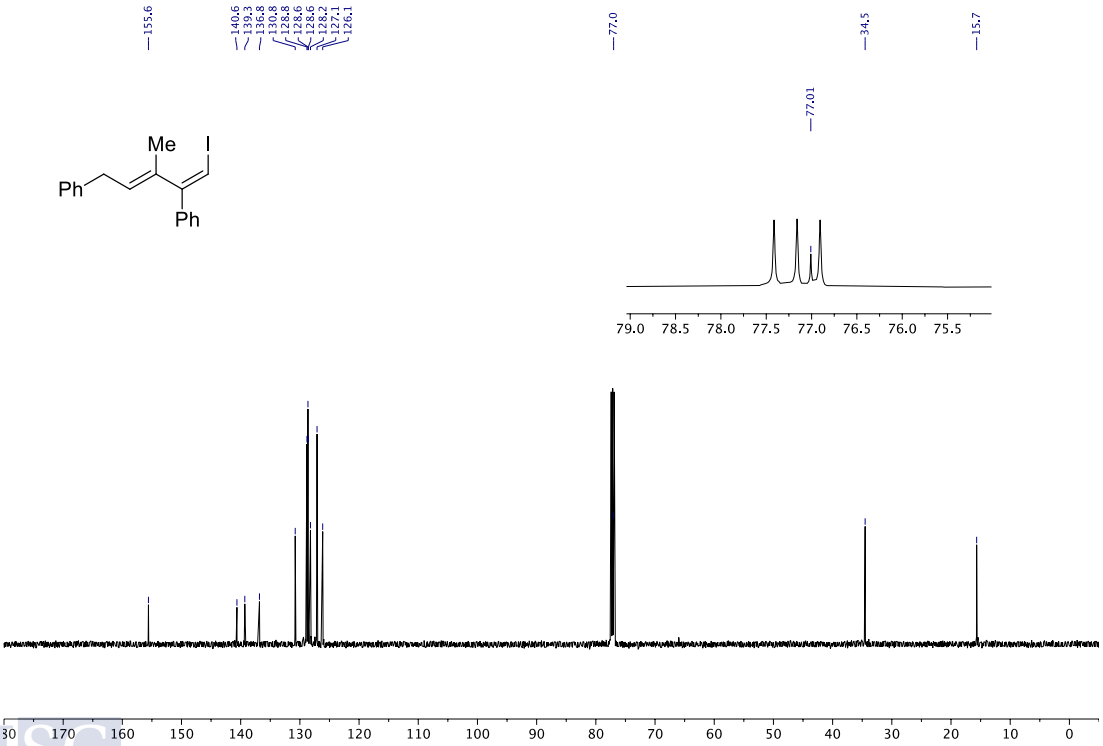
1H-NMR (CDCl3, 300 MHz)



13C-NMR (CDCl3, 126 MHz)



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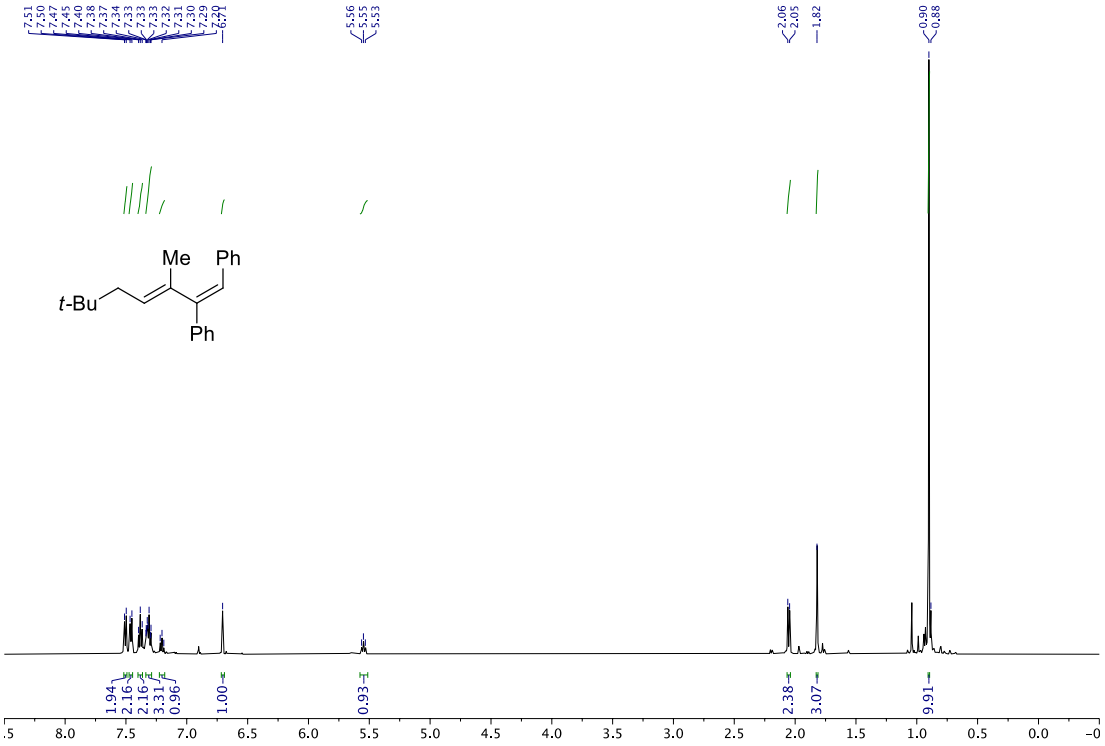
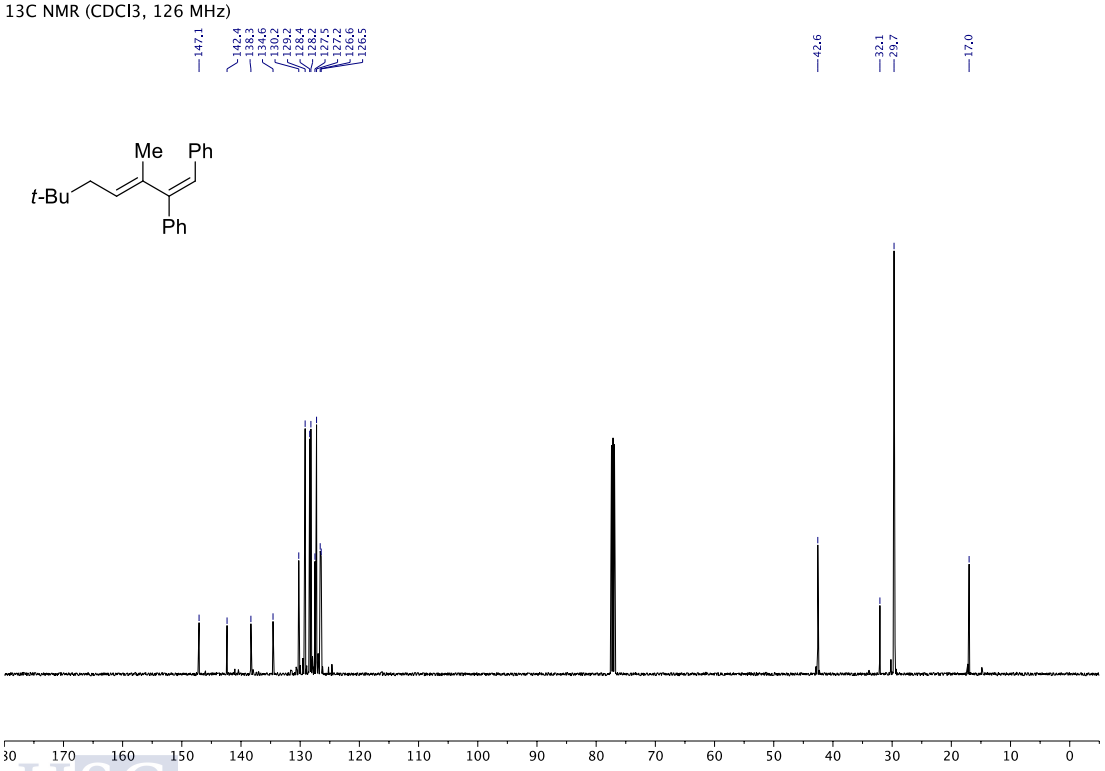
1H NMR (CDCl3, 500 MHz)



13C NMR (CDCl3, 126 MHz)



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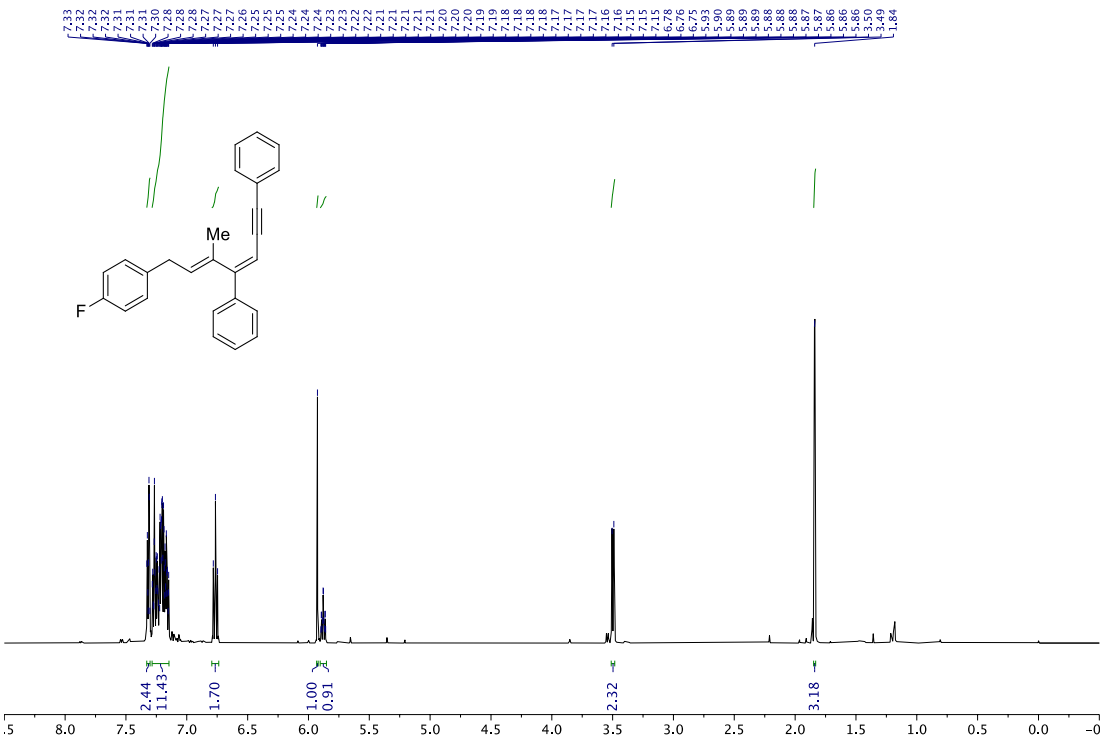
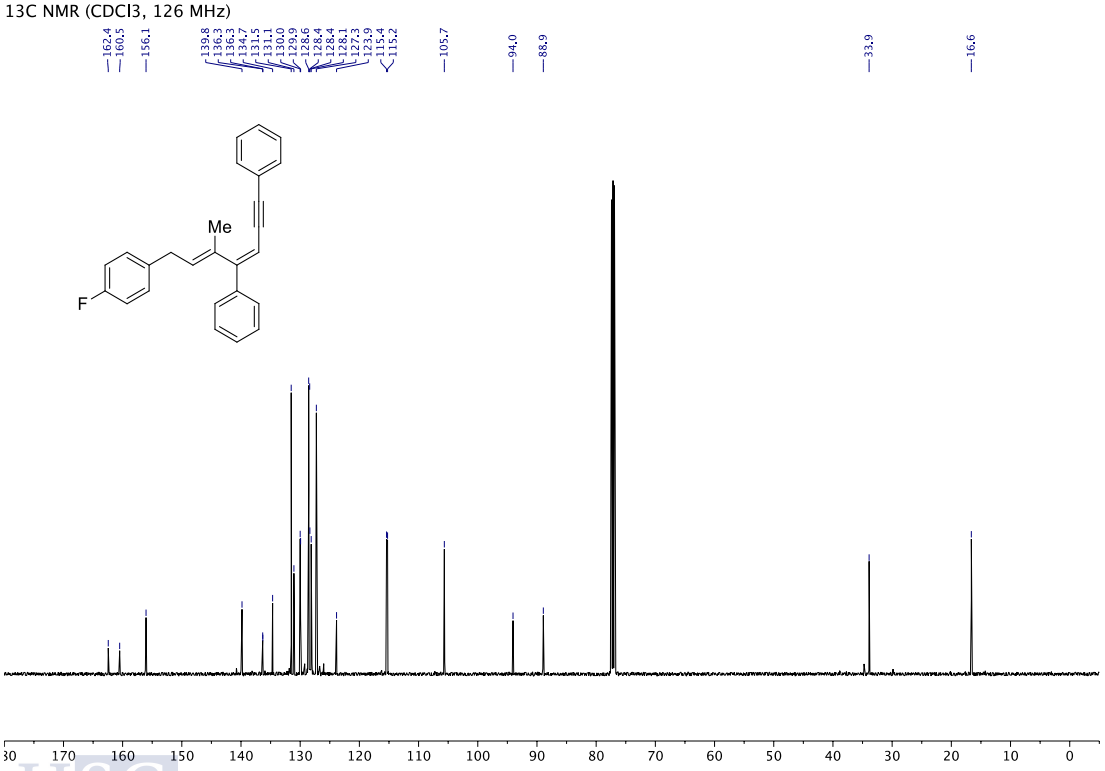
1H NMR (CDCl3, 500 MHz)



13C NMR (CDCl3, 126 MHz)



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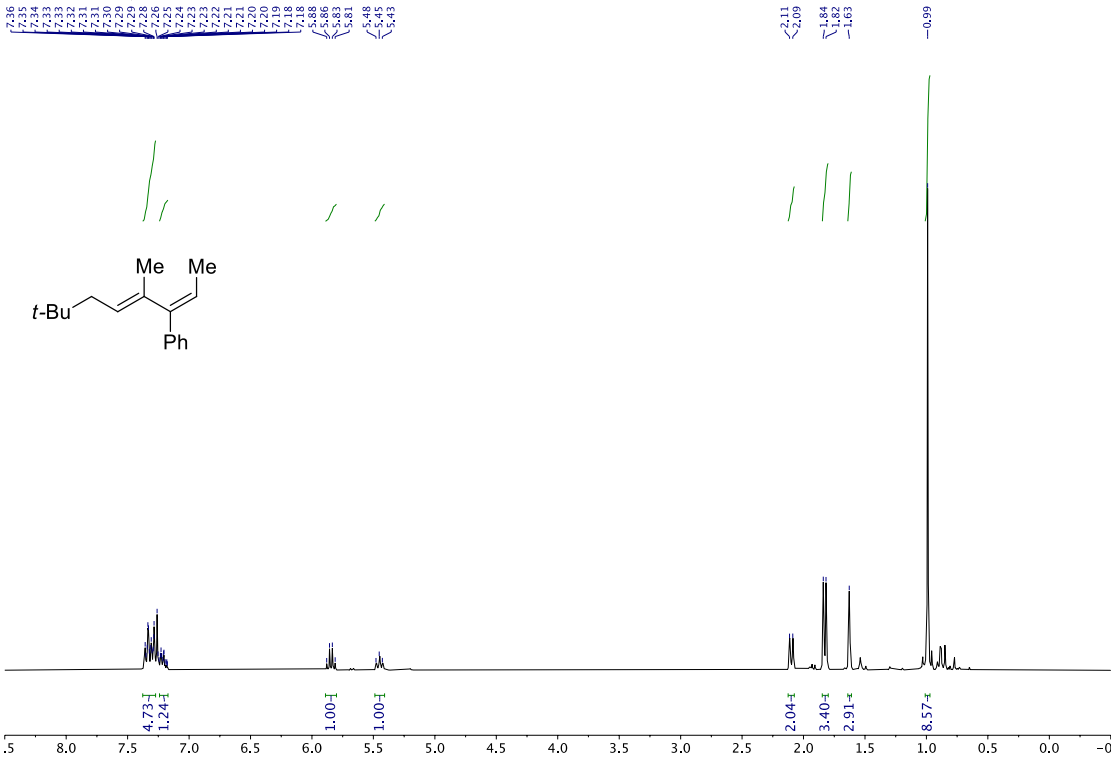
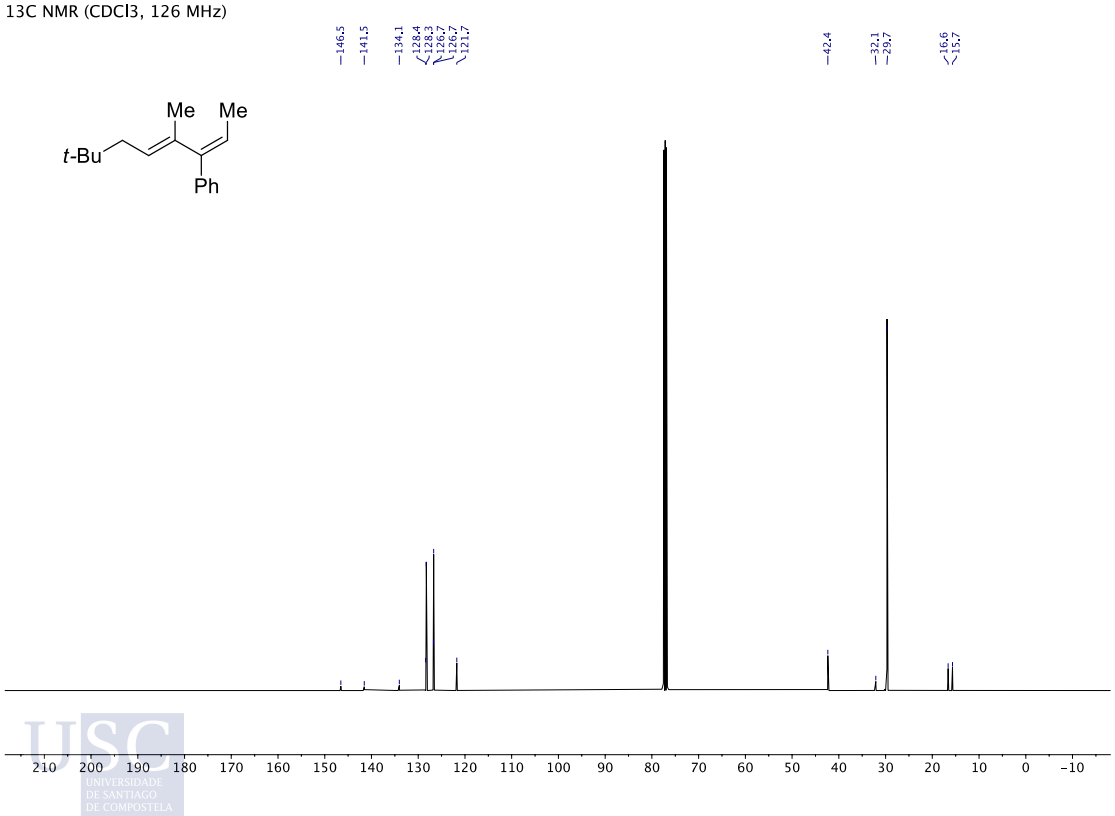
1H NMR (CDCl3, 300 MHz)



13C NMR (CDCl3, 126 MHz)



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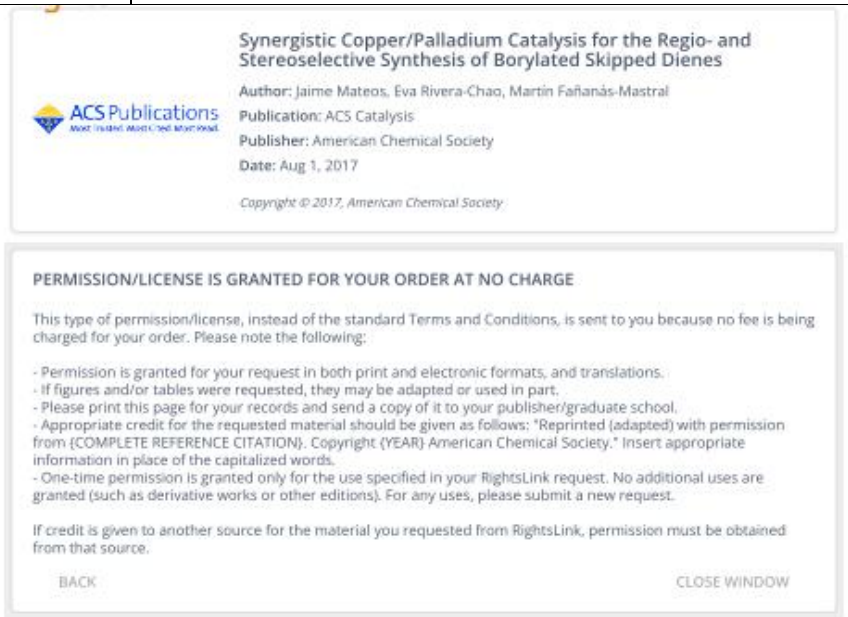
List of Publications

Title:	Synergistic Copper/Palladium Catalysis for the Regio- and Stereoselective Synthesis of Borylated Skipped Dienes
Authors:	Jaime Mateos, Eva Rivera Chao, and Martín Fañanás Mastral
Year:	2017
Journal:	ACS Catalysis
Volumen, pages:	7, 5340-5344
Impact Factor	13.084
PhD student contribution:	Synthesis of starting materials; Synthesis and characterization of a number of 1,4-borylated dienes.



ACS Publications

Synergistic Copper/Palladium Catalysis for the Regio- and Stereoselective Synthesis of Borylated Skipped Dienes

Author: Jaime Mateos, Eva Rivera-Chao, Martín Fañanás-Mastral
Publication: ACS Catalysis
Publisher: American Chemical Society
Date: Aug 1, 2017

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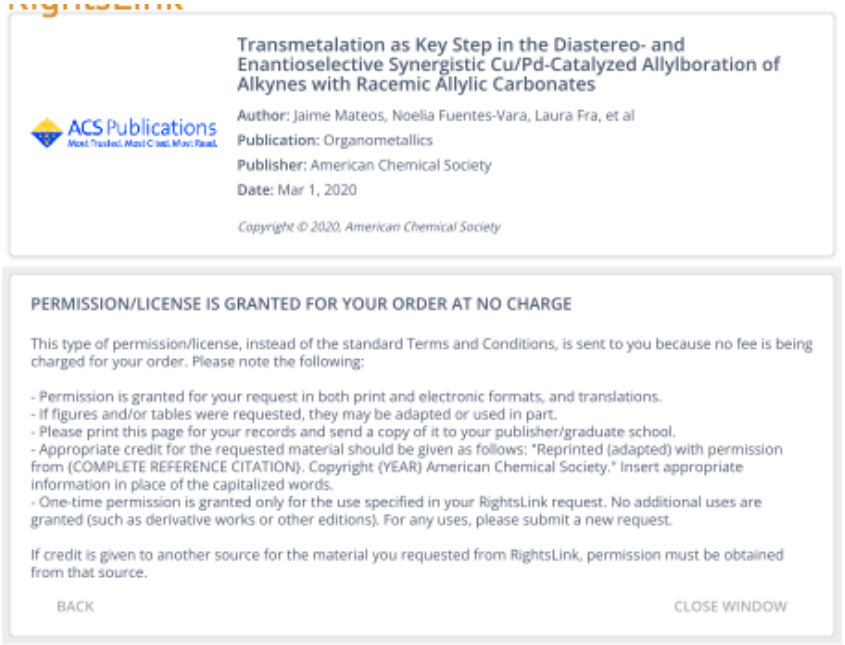
Title:	Transmetalation as Key Step in the Diastereo- and Enantioselective Synergistic Cu/Pd-Catalyzed Allylboration of Alkynes with Racemic Allylic Carbonates
Authors:	Jaime Mateos, Noelia Fuentes Vara, Laura Fra, Eva Rivera Chao, Nuria Vázquez Galiñanes, Andrea Chaves Pouso, and Martín Fañanás Mastral
Year:	2020
Journal:	Organometallics
Volumen, pages:	39, 740-745
Impact Factor	3.876
PhD student contribution:	Synthesis of starting materials; Synthesis of a number of 1,4-dienes.



Transmetalation as Key Step in the Diastereo- and Enantioselective Synergistic Cu/Pd-Catalyzed Allylboration of Alkynes with Racemic Allylic Carbonates

Author: Jaime Mateos, Noelia Fuentes-Vara, Laura Fra, et al
Publication: Organometallics
Publisher: American Chemical Society
Date: Mar 1, 2020

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Title:	Synergistic Bimetallic Catalysis for Carboboration of Unsaturated Hydrocarbons
Authors:	Eva Rivera Chao, Laura Fra and Martín Fañanás Mastral
Year:	2018
Journal:	Synthesis
Volumen, pages:	50, 3825-3832
Impact Factor	3.157
PhD student contribution:	Writing part of the review article.

Order Summary

Licensee: Eva Rivera Chao
Order Date: Oct 6, 2021
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USC UNIVERSIDADE DE SANTIAGO DE COMPOSTELA

Title:	Synthesis of Stereodefined Borylated Dendralenes through Copper-Catalyzed Allylboration of Alkynes
Authors:	Eva Rivera Chao, and Martín Fañanás Mastral
Year:	2018
Journal:	Angewandte Chemie International Edition
Volumen, pages:	57, 9945-9949
Impact Factor	15.336
PhD student contribution:	Optimization of the reaction conditions. Synthesis and characterization of the borylated dendralenes. Study of the reactivity of these products.

Order Summary

Licensee:	Eva Rivera Chao
Order Date:	Oct 4, 2021
Order Number:	5162071278776
Publication:	Angewandte Chemie International Edition
Title:	Synthesis of Stereodefined Borylated Dendralenes through Copper-Catalyzed Allylboration of Alkynes
Type of Use:	Dissertation/Thesis
Order Total:	0.00 EUR

USC UNIVERSIDADE DE SANTIAGO DE COMPOSTELA

Title:	Copper-Catalyzed Enantioselective Allylboration of Alkynes: Synthesis of Highly Versatile Multifunctional Building Blocks
Authors:	Eva Rivera Chao, Maider Mitxelena, Jesús A. Varela and Martín Fañanás Mastral
Year:	2019
Journal:	Angewandte Chemie International Edition
Volumen, pages:	58, 18230-18234
Impact Factor	15.336
PhD student contribution:	Part of the optimization of the reaction conditions. Synthesis and characterization of a number of chiral 1,4-borylated dienes. Study of the reactivity of the chiral 1,4-dienes.

Order Summary

Licensee:	Eva Rivera Chao
Order Date:	Oct 4, 2021
Order Number:	5162071345673
Publication:	Angewandte Chemie International Edition
Title:	Copper-Catalyzed Enantioselective Allylboration of Alkynes: Synthesis of Highly Versatile Multifunctional Building Blocks
Type of Use:	Dissertation/Thesis
Order Total:	0.00 USD

USC UNIVERSIDADE DE SANTIAGO DE COMPOSTELA

Title:	Stereoselective Synthesis of Highly Substituted 1,3-Dienes via 'à la carte' Multifunctionalization of Borylated Dendralenes
Authors:	Eva Rivera Chao and Martín Fañanás Mastral
Year:	2021
Journal:	Angewandte Chemie International Edition
Volumen, pages:	60, 16922-16927
Impact Factor	15.336
PhD student contribution:	Mechanistic experiments. Synthesis of characterization of the 1,3-dienes. Study of the reactivity of these compounds.

Order Summary

Licensee:	Eva Rivera Chao
Order Date:	Oct 4, 2021
Order Number:	5162071447571
Publication:	Angewandte Chemie International Edition
Title:	Stereoselective Synthesis of Highly Substituted 1,3-Dienes via "à la carte" Multifunctionalization of Borylated Dendralenes
Type of Use:	Dissertation/Thesis
Order Total:	0.00 USD

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