Synthesis of Cyclopropylboronates and Allylic Alcohols via Copper-Catalyzed Borylation Reactions

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Doctoral Thesis

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A Javi. Por todo.

This Doctoral Thesis has been developed in the Organic Chemistry Department at Universidad Autónoma de Madrid, under supervision of Dr. Mariola Tortosa Manzanares.
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LIST OF ABBREVIATIONS

Ac	Acetate
acac	Acetylacetone
ACPA	2-Arylcyclopropylamine
Ad	Adamantyl
Ar	Aryl
*t*AmylOH	*tert*-Amyl alcohol
BARF	tetrakis[3,5-bis(trifluoromethyl)phenyl]borate
BINAP	2,2'-Bis(difenilfosfino)-1,1'-binaftilo
BIPHEP	Biphenylphosphine
Bn	Benzyl
B_2pin_2	Bis(pinacolato)diboron
BPO	Benzoyl Peroxide
*t*Bu	*tert*-Butyl
*t*BuOMe	*tert*-Butyl methyl ether
Bz	Benzoyl
COD	1,5-Cyclooctadiene
Cy	Cyclohexyl
dba	Dibenzylideneacetone
DCC	*N*,*N*′-Dicyclohexylcarbodiimide
DCE	1,2-Dichloroethene
(+)-DET	(+)-Diethyl L-tartrate
DFT	Density Functional Theory
DMAP	4-(Dimethylamino)pyridine
DMF	Dimethylformamide
(*R*)-DM-Segphos	(*R*)-(+)-5,5′−Bis[di(3,5-xylyl)phosphino]-4,4′-bi-1,3-benzodioxole
diglyme	Bis(2-methoxyethyl) ether

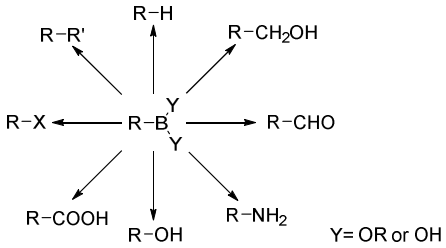
DMP	Dess-Martin Periodinane
DMSO	Dimethyl Sulfoxide
DPEPhos	(Oxydi-2,1-phenylene)bis(diphenylphosphine)
dppBz	1,2-Bis(diphenylphosphino)benzene
dppf	1,1′-Bis(diphenylphosphino)ferrocene
(*R*)-DTBM-Segphos	(*R*)-(−)-5,5′-Bis[di(3,5-di-*tert*-butyl-4-methoxyphenyl)phosphino]-4,4′-bi-1,3-benzodioxole
ee	Enantiomeric excess
EI	Electronic Impact
eq	Equation
equiv	Equivalents
er	Enantiomeric Ratio
ESI	Electrospray Ionization
EWG	Electron Withdrawing Group
E^+	Electrophile
Hal	Halide
HBcat	Catecolborane
HBpin	Pinacolborane
HMPA	Hexamethylphosphoramide
HPLC	High Pressure Liquid Cromatography
HRMS	High Resolution Mass Spectrometry
ICy	*N*,*N*′-Bis(cyclohexylimidazol)-2-ylidene
IMes	*N*,*N*′-Bis(2,4,6-trimethylphenyl)imidazol)-2-ylidene
(*R*,*R*)-*i*Pr-DUPHOS	(+)-1,2-Bis[(2*R*,5*R*)-2,5-diisopropylphospholano]benzene
JohnPhos	(2-Biphenyl)di-*tert*-butylphosphine
KHMDS	Potassium bis(trimethylsilyl)amide
L	Ligand

L*	Quiral Ligand
LDA	Lithium diisopropylamide
MALDI	Matrix-Assisted Laser Desorption/Ionization
(*R*,*R*)-Me-DuPhos	(–)-1,2-Bis[(2*R*,5*R*)-2,5-dimethylphospholano]benzene
Mes	Mesityl
MIRC	Michael Initiated Ring Closure
MRSA	*Methicillin-Resistant* S*taphylococcus Aureus*
Ms	Mesylate
MS	Mass Spectrometry
nap	Naphthyl
NHC	*N*-Heterocyclic Carbene
NMR	Nuclear Magnetic Resonance
NSMD	*N*-sulfinyl metallodienamine
Nu^-	Nucleophile
Ph	Phenyl
Phen	Phenanthroline
PPTS	Pyridinium *p*-toluenesulfonate
Py	Pyridine
pin	Pinacol
QuinoxP*	(*R*,*R*)-(–)-2,3-Bis(tert-butylmethylphosphino)quinoxaline
rt	Room Temperature
(*R*)-Segphos	(*R*)-(+)-5,5′-Bis(diphenylphosphino)-4,4′-bi-1,3-benzodioxole
SFC	Supercritical Fluid Chromatography
SPhos	2-Dicyclohexylphosphino-2′,6′-dimethoxybiphenyl
SPS	Solvent Purification System

(*R*,*R*)-Taniaphos	(R_P)-1-[(*R*)-α-(Dimethylamino)-2-(diphenylphosphino)benzyl]-2-diphenylphosphinoferrocene
TBDMS	*tert*-Butyldimethylsilyl
TBHP	*tert*-Butyl hydroperoxide
TC	Thiophene-2-carboxylate
TEBAC	Benzyltriethylammonium chloride
Tf	Triflyl
THF	Tetrahydrofuran
TLC	Thin Layer Chromatography
Tol	Tolyl
(*R*)-*p*-Tol-BINAP	(*R*)-(+)-2,2′-Bis(di-*p*-tolylphosphino)-1,1′-binaphthyl
TMEDA	N,N,N′,N′-Tetramethylethylenediamine
TMS	Trimethylsilyl
TES	Triethylsilyl
(*R*)-C_3-TunePhos	(*R*)-1,13-Bis(diphenylphosphino)-7,8-dihydro-6*H*-dibenzo[f,h][1,5]dioxonin
xantphos	4,5-Bis(diphenylphosphino)-9,9-dimethylxanthene

SUMMARY

Boronic esters are very useful synthetic intermediates, due to the versatility of the C-B bond. The carbon-boron bond can be easily transformed into C-O, C-N and C-C bonds, allowing access to a wide range of organic compounds (*Scheme 1*).

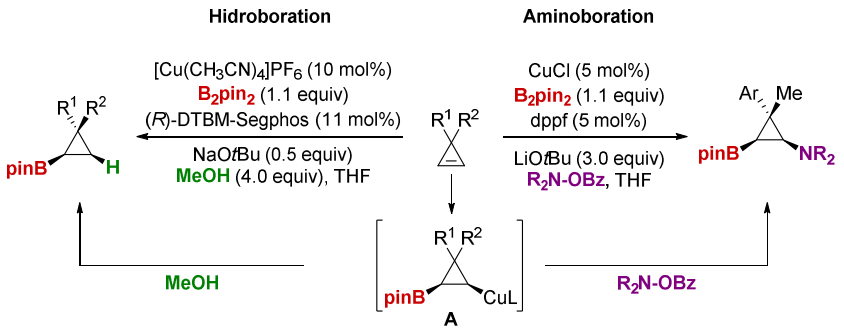


Scheme 1. Functionalization of the C-B bond.

Moreover, boronic esters are playing an increasing role in drug discovery, with the anticancer agent Velcade® and the fungicide Kerydin® being the two first approved drugs in the market bearing a boronic acid unit. Therefore, the development of new synthetic methods that allow the formation of new carbon-boron bonds is still a field of interest in organic chemistry. In the last decades, copper(I)-catalyzed borylation reactions have emerged as a powerful tool to synthesize these interesting molecules. In fact, the increasing number of publications in this field over the last ten years confirms the importance of this transformation. The low cost and toxicity of copper compared to other transition metals, as well as the unique reactivity that copper-boron complexes present, are some of the advantages that make these transformations very attractive synthetic tools.

The nucleophilicity of these boron species allows the formation of C-B bonds that were inaccessible via traditional methods.

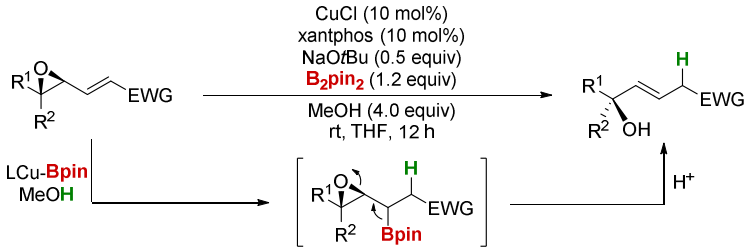
In this context, in this doctoral thesis we have focused on the development of novel borylation reactions using copper catalysis. In the second chapter, we reported the first diastereo- and enantioselective copper(I)-catalyzed hydroboration of cyclopropenes. This method allows for the synthesis of enantiomerically enriched cyclopropylboronates with a quaternary stereocenter and represents the first enantioselective copper(I)-catalyzed desymmetrization of cyclopropenes. Our approach nicely complemented the few existing methods to synthesize non-racemic cyclopropylboronates and gave new insights into the enantioselective metal-catalyzed desymmetrization of cyclopropenes (*Scheme 2*). Additionally, the capture of the cyclopropyl copper intermediate **A** with electrophilic amines highlights the synthetic potential of this approach and opens a new way to synthesize highly functionalized cyclopropanes (*Scheme 2*).



Scheme 2. Desymmetrization of cyclopropenes.

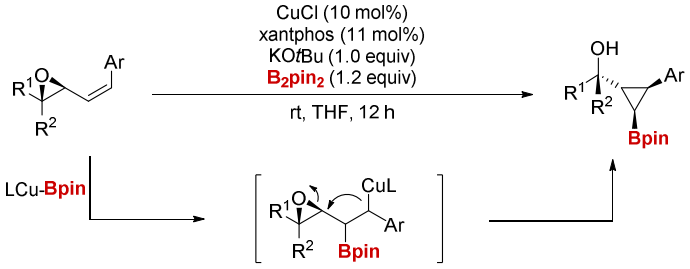
In the third chapter, we developed a formal reduction of allylic epoxides through a copper(I)-catalyzed traceless borylation-elimination (*Scheme 3*). This transformation takes place through regioselective borylation of the double bond of the allylic epoxide, followed by

spontaneous and stereoselective elimination of the α-epoxy boronate. Our method represents a mild alternative to the use of stoichiometric amounts of strong reductants for the reductive ring opening of allylic epoxides.



Scheme 3. Formal reduction of allylic epoxides.

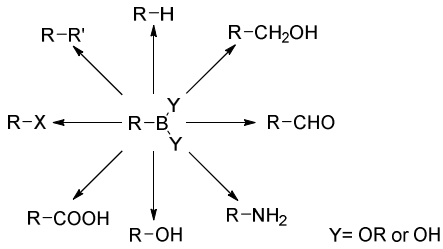
In chapter four, we applied this strategy to the synthesis of ciclopropylboronates. When the transformation described in *Scheme 3* was performed in the absence of an electrophile, an intramolecular substitution preceded the elimination to afford ciclopropylboronates with four contiguous stereocenters (*Scheme 4*). The borylation and the cyclization took place with complete stereoselectivity to afford a single diastereomer. The chirality was completely transferred from the epoxides to the products.



Scheme 4. Synthesis of cyclopropylboronates.

RESUMEN

Los ésteres borónicos son intermedios sintéticos muy versátiles. Junto con las conocidas reacciones de acoplamiento catalizadas por metales, el enlace C-B se puede transformar en C-O, C-N, C-C, permitiendo el acceso a una amplia variedad de compuestos orgánicos (*Esquema 1*).

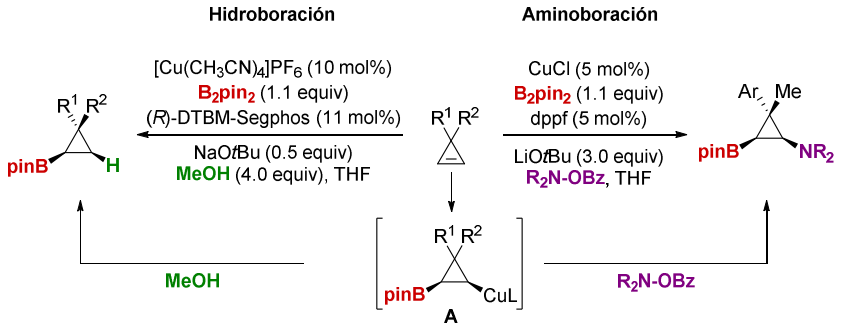


Esquema 1.Posibles transformaciones del enlace C-B.

Además, en los últimos años los ésteres borónicos han ganado importancia fuera del campo de la química orgánica sintética. La reciente salida al mercado del antitumoral Velcade®, el primer fármaco comercializado que contiene una unidad de ácido borónico en su estructura, ha suscitado un interés creciente en la industria farmacéutica por estos compuestos. Por lo tanto, el desarrollo de nuevos métodos sintéticos que permitan generar enlaces C-B de forma eficiente es un área de creciente interés en química orgánica. En la última década, las reacciones de borilación catalizadas por cobre se han convertido en una herramienta sintética muy potente para la formación de enlaces C-B. De hecho, el creciente número de publicaciones en este campo de la química durante los últimos años, confirma la importancia de este tipo de transformaciones. El bajo coste y toxicidad del cobre comparado con otros

metales de transición, junto con la reactividad única que presentan los complejos de cobre-boro, convierten estas reacciones en transformaciones muy atractivas. El carácter nucleófilo de las especies de boro intermedias permite crear enlaces C-B no accesibles utilizando métodos más tradicionales en los que el boro presenta un marcado carácter electrófilo.

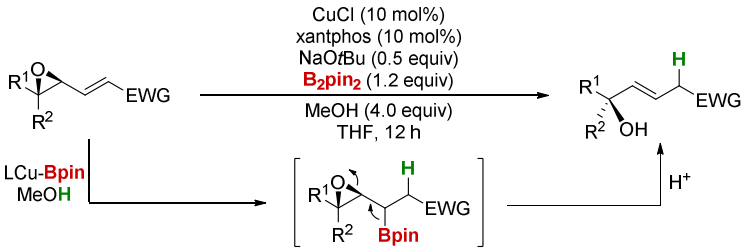
En este contexto, en esta tesis doctoral hemos profundizado en el desarrollo de nuevas reacciones de borilaciones catalizadas por cobre. En el segundo capítulo, hemos desarrollado la primera hidroboración enantio- y diastereoselectiva catalizada por cobre(I) de ciclopropenos. Aparte de complementar los pocos métodos existentes para la síntesis de ciclopropilboronatos enantioméricamente enriquecidos, este método representa la primera desimetrización enantioselectiva de ciclopropenos catalizada por cobre(I) (*Esquema 2*). Además, el intermedio ciclopropil cobre **A** formado se puede capturar con aminas electrófilas para formar ciclopropilaminoboronatos de forma diastereoselectiva (*Esquema 2*).



Esquema 2. Desimetrización de ciclopropenos.

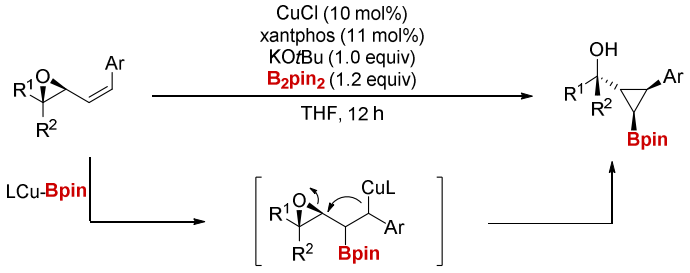
En el tercer capítulo, se encontró de forma inesperada un método de reducción formal de epóxidos alílicos, utilizando condiciones de borilación catalizadas por cobre(I). La reacción transcurre a través de una adición regioselectiva del complejo de cobre-boro al doble enlace del epóxido, seguida de una eliminación espontánea y estereocontrolada del

α-epoxy boronato formado, para generar el correspondiente alcohol alílico (*Esquema 3*). Este método representa una alternativa al uso de cantidades estequiométricas de reductores fuertes para la apertura reductora de epóxidos alílicos.



Esquema 3.Reducción de epoxidos alílicos.

En el cuarto capítulo, hemos utilizado esta estrategia para la preparación de ciclopropilboronatos altamente funcionalizados. Cuando la transformación descrita en el *Esquema 3* se lleva a cabo en ausencia de una fuente de protones, una sustitución intramolecular entre el intermedio de alquil cobre y el epóxido, precede a la reacción de eliminación. Los productos son ciclopropilboronatos con cuatro centros estereogénicos contiguos, difícilmente accesibles mediante métodos descritos en la bibliografía (*Esquema 4*). La adición y la sustitución se producen de forma estereocontrolada generándose un solo diastereoisómero y la quiralidad se transfiere totalmente de los epóxidos a los productos.



Esquema 4. Síntesis de ciclopropilboronatos.

Chapter 1

INTRODUCTION

1. INTRODUCTION

1.1. General Overview

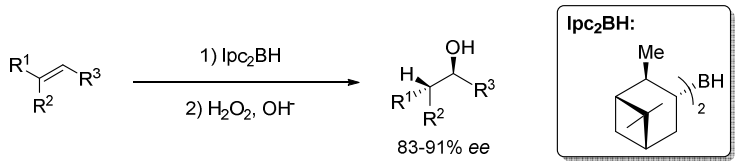
Boron is the fifth element of the periodic table. It has three valence electrons and a ground state electron configuration of $1s^2 2s^2 2p^1$. Boron typically forms trivalent neutral compounds in which the boron atom is sp^2 hybridized and has an empty *p*-orbital. These types of compounds are electron-deficient and are isoelectronic with carbocations.[1]

The history of boron is as rich and versatile as this element has proven to be. Around 1912, Alfred Stock started to establish borane chemistry.[2] He developed the experimental techniques which were required for the preparation of the volatile and potentially explosive boron hydrides such as B_2H_6, B_4H_{10}, B_5H_9, B_5H_{11} and B_6H_{10}. Intrigued by these compounds, William N. Lipscomb deciphered the molecular structures of boranes by X-ray diffraction and led to a reasonable basis for a theory of chemical bonding, which was different from the typical bonding in carbon chemistry.[3] These studies were essential to understand the polyhedral-like nature of boron hydrides and were recognized with the Nobel Prize in Chemistry awarded to Lipscomb in 1976.

In the second part of the 20th century boron increasingly adopted an organic face. In 1956 Professor Herbert C. Brown published the first

[1] Ingleson, M. J. Fundamental and Applied Properties of Borocations. In *Synthesis and Application of Organoboron Compounds;* Fernández, E., Whiting, A. Ed.; Springer International Publishing: Switzerland, 2015; pp 39-71.
[2] Stock, A.; Massenez, C. *Eur. J. Inorg. Chem.* **1912**, *45*, 3539-3568.
[3] Lipscomb, W. N. *Pure. Appl. Chem.* **1972**, *29*, 493-511.

hydroboration reaction of simple olefins[4] and, since then, a large number of new reactions have been developed. Boron chemistry played a key role in the development of modern asymmetric synthesis. Reagent control was essentially born in 1961 with the discovery of the hydroboration of cis-2-butene with diisopinocampheylborane. This was one the first chemical processes that gave enzyme-levels of selectivity (*Scheme I-1*).[5]



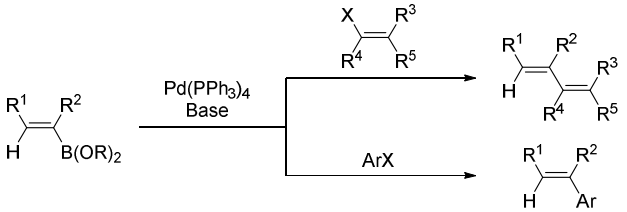
Scheme I-1. Asymmetric synthesis of alcohols via hydroboration.

Brown built a large toolbox for the preparation of organoboranes and demonstrated that they were highly versatile intermediates. The C-B bond can be transformed into C-O, C-N, C-C and C-X, allowing the access to a wide variety of organic compounds.[6] Professor Brown received the Nobel Prize in Chemistry in 1979 for his invaluable contributions in this field.

When the hydroboration reaction was applied to alkynes, stereodefined alkenyl diorganoboranes could be synthetized. Soon after, several groups tried to use these vinylboranes in palladium catalyzed cross-coupling reactions with alkenyl halides, but without succeed. One possible reason was that the transmetalation process between RPdX species and alkenylboranes does not occur smoothly due to the weak carbanion character of the organic groups in organoboranes. Professor Akira Suzuki reasoned that if organoborates, formed from alkenylboranes, and a base

[4] (a) Brown, H. C.; Rao, B. C. S. *J. Am. Chem. Soc.* **1956**, *78*, 5694-5695. (b) Wang, Z. Brown Hydroboration. In *Comprehensive Organic Name Reactions and Reagents*; John Wiley & Sons: Hoboken, 2009; pp 536-543.
[5] Brown, H. C.; Zweifel, G. *J. Am. Chem. Soc.* **1961**, *83*, 486-487.
[6] Brown, H. C. *Organic Syntheses via Boranes*; Wiley: New York, 1975.

were used instead of alkenylboranes, there was a possibility for the transmetalation to take place. That was indeed true, although eventually he discovered that the use of boronic acids and esters presented several advantages over the use of boranes. Aryl boronic acids could be also used as partners, providing access to a broad number of synthetic intermediates (*Scheme I-2*). Since then, numerous research groups have worked on this transformation that has become an essential synthetic tool in academia and industry.[7] In 2010, Professors Suzuki, Heck and Negishi received the Nobel Prize in Chemistry for the development of palladium catalyzed cross-coupling reactions in organic chemistry.



Scheme I-2. Suzuki cross-coupling reaction.

With three Nobel Prizes behind it, boron chemistry might appear as a mature field. However, the increasing number of publications clearly indicates a new renaissance of boron chemistry. In the last twenty years, boron has found new interesting applications beyond the synthetic chemistry field. There is no doubt that boronic acid derivatives are playing an increasing role in drug discovery. An example of this is the approval of

[7] (a) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457-2483. (b) Suzuki, A. *J. Organomet. Chem.* **1999**, *576*, 147-168. (c) Martin, R.; Buchwald, S. L. *Acc. Chem. Res.* **2008**, *41*, 1461-1473. (d) Sun, H. Y.; Hall, D. G. At the Forefront of the Suzuki-Miyaura Reaction: Advances in Stereoselective Cross-Couplings. In *Synthesis and Application of Organoboron Compounds;* Fernández, E., Whiting, A. Ed.; Springer International Publishing: Switzerland, 2015; pp 221-242. (e) Hussain, I.; Capricho, J.; Yawer, M. A. *Adv. Synth. Catal.* **2016**, *358*, 3320-3349. (f) Das, P.; Linert, W. *Coord. Chem. Rev.* **2016**, *311*, 1-23. (g) Almond-Thynne, J.; Blakemore, D. C.; Prydeb, D. C.; Spivey, A. C. *Chem. Sci.* **2017**, *8*, 40-62. (h) Sydnes, M. O. *Catalysts* **2017**, *7*, 35-48.

the anticancer agent Velcade® or the fungicide Kerydin® (*Figure I-1*), which are the two first drugs in the market that contain a boronic acid unit in their structure. Boron derivatives are also present in functional polymers,[8] nanotubes or in ^{10}B carriers for neutron capture therapy.[9]

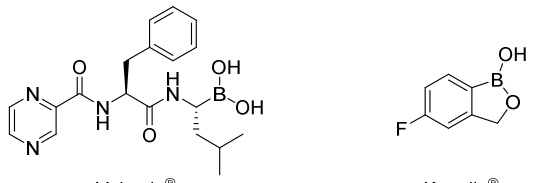


Figure I-1. Commercial drugs containing boron.

This burst in novel applications indicates that Professor Brown's words are today more actual than ever:[6] *"A new continent has been discovered – it requires settlers to develop its riches to contribute to mankind."*

1.2. Boronic Acids and Derivatives

Boronic acids are very important synthetic intermediates in organic chemistry.[10] They are trivalent boron-containing compounds that possess one carbon-based substituent and two hydroxyl groups. In the case of boronic esters, also known as boronates, the boron atom is bonded to a carbon atom and two alkoxides.

In general, boronates are easier to handle and less polar than boronic acids, due to the loss of the hydrogen bond donor capability. There is a wide selection of boronic esters that can be commonly found in organic

[8] (a) Matsumi, N.; Naka, K.; Chujo Y. *J. Am. Chem. Soc.* **1998**, *120*, 5112-5113. (b) Matsumi, N.; Naka, K.; Chujo Y. *J. Am. Chem. Soc.* **1998**, *120*, 10776-10777. (c) Entwistle, C. D.; Marder, T. B. *Angew. Chem. Int. Ed.* **2002**, *41*, 2927-2931.

[9] (a) Barth, R. F.; Soloway, A. H.; Brugger, R. M. *Cancer Invest.* **1996**, *14*, 534-550. (b) Yura, Y.; Fujita, Y. *Oral Science International* **2013**, *10*, 9-14.

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

synthesis. Moreover, some of them are chiral compounds that have been used as inducers in stereoselective reactions.[11] The most common boronic esters are ethylenglycol (Beg), pinacol (Bpin), neopentyl glycol (Bnep), hexylene glycol (Bheg), pinanediol (Bpnd) and cathecol (Bcat) derivatives (*Figure I-2*).[12] Cathecolboronic esters are sensitive species, as the opposite conjugation between the oxygen atom and the benzene ring confers them particular Lewis acidity, and therefore they are prone to hydrolysis. Usually, the stability of hindered cyclic boronates is higher than their unhindered or acyclic analogues, which can easily undergo hydrolysis. Beyond these, recently diethanolamine (BDEA) and *N*-methyliminodiacetic acid (BMIDA) have been employed as alternative protecting groups. Moreover, 1,8-diaminonaphthalene (Bdan) has also been used, providing a less Lewis acidic boron atom.

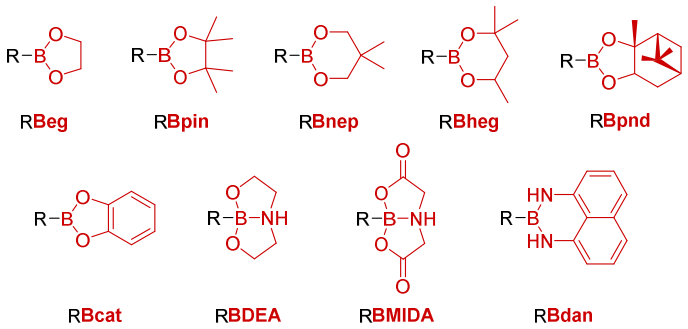


Figure I-2. Most common boronic esters.

The B-O bond (130 Kcal/mol) is stronger than C-O bond (92 Kcal/mol).[13] This energetic difference can be explained by the partial

[11] (a) Ramachandran, P. V.; Brown, H. C. Recent Advances in Borane Chemistry. In *Organoboranes for Syntheses*, ACS Symposium Series 783; American Chemical Society: Washington, DC, 2001; pp 1-15. (b) Matteson, D. S. *Tetrahedron*, **1998**, *54*, 10555-10607.

[12] Hall, D. G. *Boronic Acids: Preparation and Application in Organic Synthesis, Medicine and Materials*, 2nd ed.; Wiley-VCH: Boston, 2011.

[13] Sana, M.; Leroy, G.; Wilante, C. *Organometallics* **1991**, *10*, 264-270.

donation of the oxygen electron pair to the vacant *p*-orbital of the boron atom, what confers a partially double bond character. Thus, the B-O bonds are considered sigma bonds augmented with a π dative bond from the oxygen to the boron atom. When the boron atom has two oxygen-containing substituents, the vacancy on the boron atom is not enough to allow two simultaneous π dative bonds. Then, the electronic structure is an intermediate between two resonance forms (*Scheme I-3*).[12]

Scheme I-3. Resonance forms of π dative bond intermediates.

Since the interest on these species has potentially increased, several approaches have been reported to synthesize boronic esters. In this context, the development of novel metal-catalyzed transformations has been essential to make boronic esters more available compounds *(Scheme I-4)*. For many years, the classical approach to prepare aryl boronates involved the use of organolithium[14] or Grignard[15] reagents, prepared *in situ* from organo halides *(Scheme I-4a)*. Not surprisingly, the use of highly reactive nucleophiles presented serious functional group compatibility issues. In 1995, Miyaura and co-workers described the palladium-catalyzed cross-coupling reaction of B_2pin_2 and arylbromides or iodides to afford aryl boronic esters *(Scheme I-4b)*.[16] This strategy offered a wide

[14] Brown, H. C.; Cole, T. E. *Organometallics* **1983**, *2*, 1316-1319.

[15] (a) Gilman, H.; Vernon, C. *J. Am. Chem. Soc.* **1926**, *48*, 1063-1066. (b) Clary, J. W.; Rettenmaier, T. J.; Snelling, R.; Bryks, W.; Banwell, J.; Wipke, W. T.; Singaram, B. *J. Org. Chem.* **2011**, *76*, 9602-9610.

[16] (a) Ishiyama, T.; Murata, M.; Miyaura, N. *J. Org. Chem.* **1995**, *60*, 7508-7510. (b) Ishiyama, T.; Itoh, Y.; Kitano, T.; Miyaura, N. *Tetrahedron Lett.* **1997**, *38*, 3447-3450. (c) Ishiyama, T.; Miyaura, N. *J. Organomet. Chem.* **2000**, *611*, 392-402. (d) Miyaura, N. *Bull. Chem. Soc. Jpn.* **2008**, *81*, 1535-1553. (e) Ishiyama, T.; Miyaura, N. *Chem. Rec.* **2004**, *3*, 271-280.

structural scope and great tolerance of different functional groups. Vinyl,[17] aryl,[18] allyl[19] or benzyl[20] halides or triflates were found to be suitable substrates on this transformation.

The metal-catalyzed hydroboration[21] and addition of diboron compounds to different unsaturated substrates is another useful way to prepare alkyl and alkenylboronic esters *(Scheme I-4c)*. Platinum complexes have generally proven to be the most effective and general catalysts for diboration reactions, although other metals, such as gold,[22] rhodium,[23] iridium,[24] or palladium,[25] are also feasible metals to catalyze this transformation. The substrate scope for this reaction is quite extensive including alkynes,[26] alkenes,[23,27] allenes,[28] carbonyls,[29] and imines.[30]

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

[18] (a) Ishiyama, T.; Itoh, Y.; Kitano, Y.; Miyaura, N. *Tetrahedron Lett.* **1997**, *38*, 3447-3450. (b) Fürstner, A.; Seidel, G. *Org. Lett*. **2002**, *4*, 541-543. (c) Billingsley, K. L.; Barder, T. E.; Buchwald, S. L. *Angew. Chem. Int. Ed*. **2007**, *46*, 5359-5363.

[19] Zhang, P.; Roundtree, I. A.; Morken, J. P. *Org. Lett*. **2012**, *14*, 1416-1419.

[20] Ishiyama, T.; Oohashi, Z.; Ahiko, T.-A.; Miyaura, N. *Chem. Lett*. **2002**, 780-781.

[21] (a) Beletskaya, I.; Pelter, A. *Tetrahedron* **1997**, *53*, 4957-5026. (b) Crudden, C. M.; Edwards, D. *Eur. J. Org. Chem*. **2003**, 4695-4712.

[22] Baker, R. T.; Nguyen, P.; Marder, T. B.; Westcott, S. A. *Angew. Chem., Int. Ed.* **1995**, *34*, 1336-1338.

[23] Nguyen, P.; Coapes, R. B.; Woodward, A. D.; Taylor, N. J.; Burke, J. M.; Howard, J. A. K.; Marder, T. B. *J. Organomet. Chem.* **2002**, *652*, 77-85.

[24] Xu, L.; Zhang, S.; Li, P. *Chem. Soc. Rev*. **2015**, *44*, 8848-8858.

[25] Yang, F.-Y.; Cheng, C.-H.*J. Am. Chem. Soc.* **2001**, *123*, 761-762.

[26] Ishiyama, T.; Matsuda, N.; Miyaura, N.; Suzuki, A. *J. Am. Chem. Soc.* **1993**, *115*, 11018-11019.

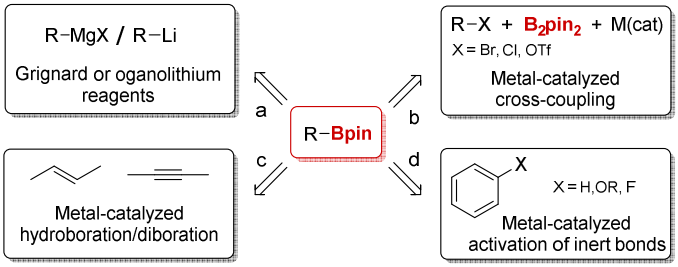
[27] (a) Ishiyama, T.; Yamamoto, M.; Miyaura, N. *Chem. Commun*. **1996**, 2073-2074. (b) Ishiyama, T.; Yamamoto, M.; Miyaura, N. *Chem. Commun.* **1997**, 689-690. (c) Iverson, C. N.; Smith, M. R. *Organometallics* **1997**, *16*, 2757-2759.

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

[29] Lawson, Y. G.; Lesley, M. J. G.; Norman, N. C.; Rice, C. R.; Marder, T. B. *Chem. Commun.* **1997**, 2051-2052.

[30] Cameron, T. M.; Baker, R. T.; Westcott, S. A. *Chem. Commun.* **1998**, 2395-2396.

More recently, the metal catalyzed C-H borylation has emerged as a promising approach to prepare aryl boronates *(Scheme I-4d)*.[31] This atom economic technique is quite attractive due to the use of simple arenes instead of the previously needed aryl halides. Iridium is the most employed metal in C-H borylation,[32] although rhodium,[33] palladium[34] and rhenium[35] can also be used. Moreover, novel metal-catalyzed activation of inert entities, such as fluoroarenes or anisole derivatives, has also been reported *(Scheme I-4d)*.[36]



Scheme I-4. Synthesis of boronic esters.

[31] (a) Ishiyama, T.; Miyaura, N. *J. Organomet. Chem.* **2003**, *680*, 3-11. (b) Mkhalid, I. A. I.; Barnard, J. H.; Marder, T. B.; Murphy, J. M.; Hartwig, J. F. *Chem. Rev.* **2010**, *110*, 890-931. (c) Neeve, E. C.; Geier, S. J.; Mkhalid, I. A. I.; Westcott, S. A.; Marder, T. B. *Chem. Rev.* **2016**, *116*, 9091-9161. (d) Ros, A.; Fernández, R.; Lassaletta, J. M. *Chem. Soc. Rev.* **2014**, *43*, 3229-3243.

[32] (a) Iverson, C. N.; Smith, M. R., III. *J. Am. Chem. Soc.* **1999**, *121*, 7696-7697. (b) Cho, J. Y.; Iverson, C. N.; Smith, M. R. III. *J. Am. Chem. Soc.* **2000**, *122*, 12868-12869. (c) Cho, J.-Y.; Tse, M. K.; Holmes, D.; Maleczka, R. E., Jr.; Smith, M. R., III. *Science* **2002**, *295*, 305-308. (d) Ishiyama, T.; Takagi, J.; Ishida, K.; Miyaura, N.; Anastasi, N. R.; Hartwig, J. F. *J. Am. Chem. Soc.* **2002**, *124*, 390-391. (e) Ishiyama, T.; Takagi, J.; Yonekawa, Y.; Hartwig, J. F.; Miyaura, N. *Adv. Synth. Catal.* **2003**, *345*, 1103-1106. (f) Coventry, D. N.; Batsanov, A. S.; Goeta, A. E.; Howard, J. A. K.; Marder, T. B.; Perutz, R. N. *Chem. Commun.* **2005**, 2172-2174. (g) Kikuchi, T.; Nobuta, Y.; Umeda, J.; Yamamoto, Y.; Ishiyama, T.; Miyaura, N. *Tetrahedron* **2008**, *64*, 4967-4971.

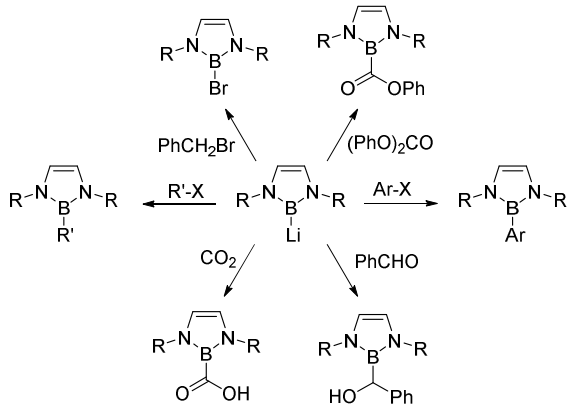
[33] Chen, H. Y.; Schlecht, S.; Semple, T. C.; Hartwig, J. F. *Science* **2000**, *287*, 1995-1997.

[34] Ishiyama, T.; Ishida, K.; Takagi, J.; Miyaura, N. *Chem. Lett.* **2001**, *30*, 1082-1083.

[35] Chen, H.; Hartwig, J. F. *Angew. Chem. Int. Ed.* **1999**, *38*, 3391-3393.

[36] (a) Liu, X. W.; Echavarren, J.; Zarate, C.; Martin, R. *J. Am. Chem. Soc.* **2015**, *137*, 12470-12473. (b) Zarate, C.; Manzano, R.; Martin, R. *J. Am. Chem. Soc.* **2015**, *137*, 6754-6757. (c) Mao, L.; Szabó, K. J.; Marder, T. B. *Org. Lett.* **2017**, *19*, 1204-1207.

Despite the large amount of publications reported for the synthesis of boronic esters, most of them are based on the electron-deficient nature of boron. In 2006, Segawa, Yamashita and Nozaki established that some boryl complexes can act as nucleophiles.[37] They reported the first isolation of a boryl lithium compound and its characterization by X-ray crystallography. The B-Li bond was highly polarized and the boron center had anionic character. They also studied the reaction of the boryl lithium species in the presence of a variety of electrophiles, indicating that the boryl anion acts as a strong nucleophile (*Scheme I-5*). Although this study represented a breakthrough in boron chemistry, the synthetic utility was hampered by the instability of the boryl lithium species. Later, the group of Nozaki converted boryl lithium reagents in boryl magnesium compounds by treatment with magnesium bromide.[38]



Scheme I-5. Reactivity of boryl lithium compounds.

[37] (a) Segawa, Y.; Yamashita, M.; Nozaki, K. *Science* **2006**, *314*, 113-115. (b) Marder, T. B. *Science* **2006**, *314*, 69-70. (c) Braunschweig , H. *Angew. Chem. Int. Ed.* **2007**, *46*, 1946-1948. (d) Segawa, Y.; Suzuki, Y.; Yamashita, M.; Nozaki, K. *J. Am. Chem. Soc.* **2008**, *130*, 16069-16079. (e) For theoretical studies, see: Cheung, M. S.; Marder, T. B.; Lin, Z. *Organometallics* **2011**, *30*, 3018-3028.

[38] Yamashita, M.; Suzuki, Y.; Segawa, Y.; Nozaki K. *J. Am. Chem. Soc*. **2007**, *129*, 9570-9571.

This concept of the generation of nucleophilic boron species opened a new pathway to form carbon-boron bonds, broadening the tool box for the synthesis of organic boronic esters.[39] Indeed, several approaches have been reported to generate *in situ* nucleophilic boron species,[40] but the use of copper-catalysis has proven to be the most versatile.

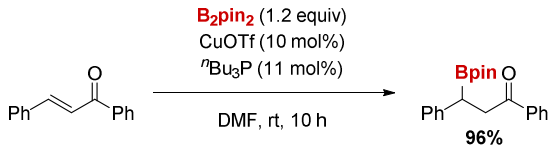
1.3. Copper-Catalyzed Borylation Reactions

In 2000, Hosomi reported the first copper-catalyzed β-borylation of α,β-unsaturated ketones using B_2pin_2 (*Scheme I-6*).[41] This reaction offered a new strategy to synthesize boron-containing compounds. The catalytic activity of copper(I) was disclosed for the first time for this type of transformations and addition of phosphine ligands was found to improved dramatically the results. To demonstrate the utility of this novel copper-catalyzed borylation, different enones were tested and the oxidation of the C-B bond was successfully performed.

[39] (a) Dang, L.; Lin, Z.; Marder, T. B. *Chem. Commun*. **2009**, 3987-3995. (b) Cid, J.; Gulyás, H.; Carbó, J. J.; Fernández, E. *Chem. Soc. Rev*. **2012**, *41*, 3558-3570. (c) Yamashita, M.; Nozaki K. Boryl Anions. In *Synthesis and Application of Organoboron Compounds;* Fernández, E., Whiting, A. Ed.; Springer International Publishing: Switzerland, 2015; pp 1-38.

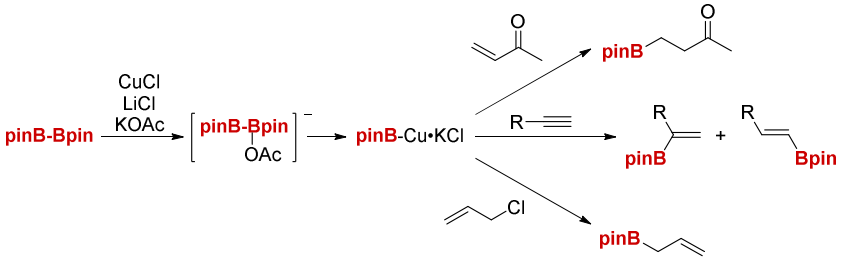
[40] For the activation of diboron compounds with Lewis bases, see: (a) Lee, K. S.; Zhugralin, A. R.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2009**, *131*, 7253-7255. (b) Bonet, A.; Gulyás, H.; Fernández, E. *Angew. Chem. Int. Ed.* **2010**, *49*, 5130-5134. (c) Bonet, A.; Pubill-Ulldemolins, C.; Bo, C.; Gulyás, H.; Fernández, E. Angew. *Chem. Int. Ed.* **2011**, *50*, 7158-7161. (d) Cid, J.; Gulyás, H.; Carbó, J. J.; Fernández, E. *Chem. Soc. Rev.* **2012**, *41*, 3558-3570. (e) Wu, H.; Radomkit, S.; O'Brien, J. M.; Hoveyda, A. H. *J. Am. Chem. Soc.*, **2012**, *134*, 8277-8285. (f) Kleeberg, C.; Crawford, A. G.; Batsanov, A. S.; Hodgkinson, P.; Apperley, D. C.; Cheung, M. S.; Lin, Z.; Marder, T. B. *J. Org. Chem.*, **2013**, *77*, 785-789. (g) Sanz, X.; Lee, G. M.; Pubill-Ulldemolins, C.; Bonet, A.; Westcott, S. A.; Gulyás, H.; Bo, C.; Fernández, E. *Org. Biomol. Chem.* **2013**, *11*, 7004-7010.

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



Scheme I-6. Hosomi's copper-catalyzed borylation.

Later, Miyaura reported the copper promoted heterolytic cleavage of the B-B bond in diboron reagents by the aid of KOAc.[42] Hence, by mixing B_2pin_2 and CuCl in the presence of LiCl and KOAc, they proposed the *in situ* formation of $[B_2pin_2OAc]^-$ required to afford copper-boryl species, which underwent β-borylation of α,β-unsaturated carbonyls, monoborylation of alkynes and allylic substitution (*Scheme I-7*).



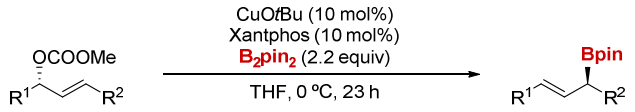
Scheme I-7. Miyaura's copper-catalyzed borylation.

Although both reports used slightly different conditions, they both agreed in the *in situ* generation of copper-boryl complexes that behaved as formal boron nucleophiles.

It was not until 2005, when Sawamura reported the copper-catalyzed borylation of allylic carbonates, that the synthetic potential of copper-catalyzed borylation reactions was revealed.[43] The *in situ* formed copper-boryl complex could catalyze the S_N2' borylation of allylic carbonates affording allylboron compounds via γ-selective and stereospecific

[42] (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.
[43] Ito, H.; Kawakami, C.; Sawamura, M. *J. Am. Chem. Soc.* **2005**, *127*, 16034-16035.

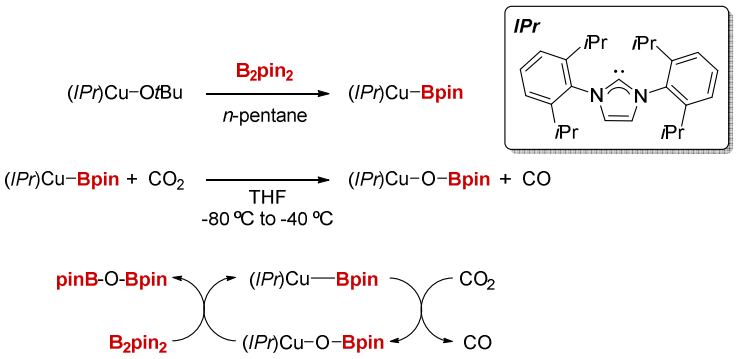
substitution reaction. Moreover, the reaction of the enantioenriched allylic carbonates with an α-stereogenic center underwent α-to-γ chirality transfer with *anti*-stereochemistry, leading to optically active allylboronates (*Scheme I-8*).



Scheme I-8. Copper-catalyzed borylation of allylic carbonates.

Simultaneously, Sadighi and co-workers presented the catalytic reduction of CO_2 to CO in homogeneous solution.[44] In this interesting work, they reported the isolation and characterization, via X-ray crystal structure, of the copper(I) boryl complex [(*IPr*)Cu-Bpin] by reaction of (*IPr*)Cu-O*t*Bu with CO_2 (*Scheme I-9*). The (*IPr*)Cu(Bpin) complex deoxygenates CO_2 rapidly and quantitatively, affording CO and the borate complex [(*IPr*)Cu(OBpin)]. The boryl complex [(*IPr*)Cu-Bpin] may be regenerated by treatment with the diboron compound B_2pin_2, giving the stable by product pinB-O-Bpin. Moreover, encouraged by these interesting results, Sadighi envisioned the copper-catalyzed 1,2-diboration of aldehydes, affording α-hydroxyalkyl anion equivalents.[45]

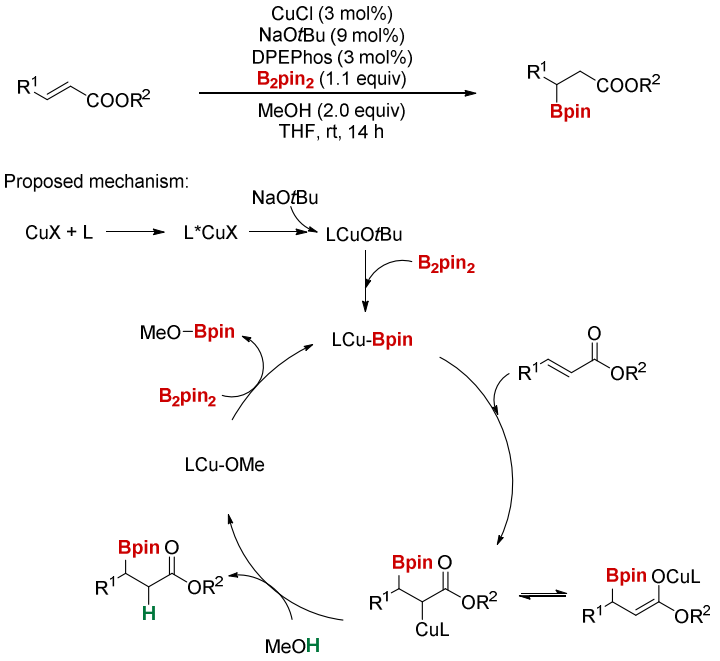
[44] Laitar, D. S.; Mueller, P.; Sadighi, J. P. *J. Am. Chem. Soc.* **2005**, *127*, 17196-17197.
[45] Laitar, D. S.; Tsui, E. Y.; Sadighi, J. P. *J. Am. Chem. Soc.* **2006**, *128*, 11036-11037.



Scheme I-9. The synthesis of copper alkoxides.

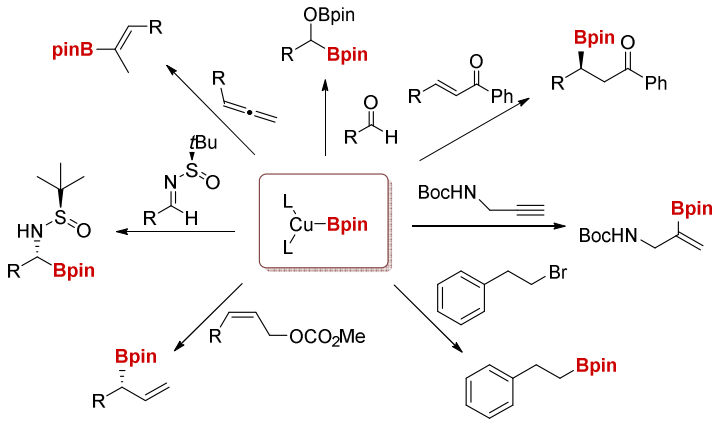
Soon after these two publications, Yun reported an efficient protocol for the copper-catalyzed conjugate addition of B_2pin_2 to α,β-unsaturated carbonyl compounds (*Scheme I-10*).[46] There were two important features in this publication. The first one was the use of alcohols as additives to increase the rate of the reaction. After the insertion step, a copper enolate is generated. In the absence of methanol, the generation of copper methoxide from this enolate is very slow. The addition of methanol allows the protonation of the copper enolate, forming copper methoxide that starts over the catalytic cycle. The second important feature was the *in situ* generation of the sensitive copper alkoxide by reaction of copper chloride and sodium *tert*-butoxide, which made the reaction much more convenient from the experimental point of view. These two findings were crucial for the subsequent development of novel copper-catalyzed borylation reactions.

[46] Mun, S.; Lee, J. E.; Yun, J. *Org. Lett.* **2006**, *8*, 4887-4889.



Scheme I-10. Conjugate addition of B_2pin_2 to α,β-unsaturated carbonyl compounds.

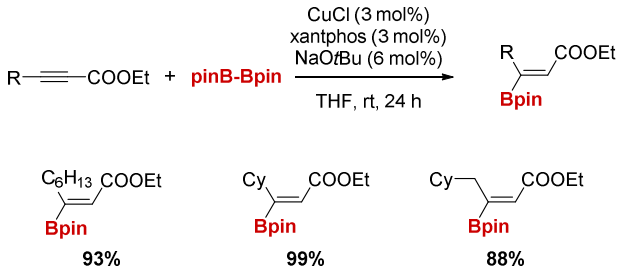
After these publications, many catalytic borylation reactions have been reported involving copper-boryl species as key intermediates. Many groups have contributed to demonstrate that most of the chemistry previously done with organocopper species can be applied to form C-B bonds instead of C-C bonds (*Scheme I-11*). These species react with a wide variety of electrophiles such as aldehydes, imines, α,β-unsaturated compounds, alkynes, alkenes and allenes. The field has grown so much in the last ten years that a comprehensive review of the literature exceeds the scope of the introduction of this doctoral thesis. Therefore, only selective examples of each transformation will be included in the next sections.



Scheme I-11. The use of copper-boryl intermediates in organic synthesis.

1.3.1. Copper-Catalyzed Borylation of Alkynes

After the pioneering work reported by Miyaura[42] on copper-mediated borylation reactions, Yun introduced the use of bulky copper(I) complexes in the borylation of ynoates. The transformation took place with excellent regio- and stereoselectivity (*Scheme I-12*).[47]

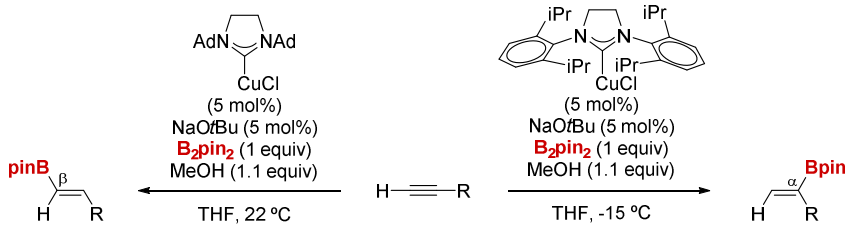


Scheme I-12. Copper-catalyzed formal hydroboration of ynoates.

A few years later, Hoveyda developed the regiodivergent synthesis of vinylboronates via copper-catalyzed hydroboration of terminal alkynes.[48]

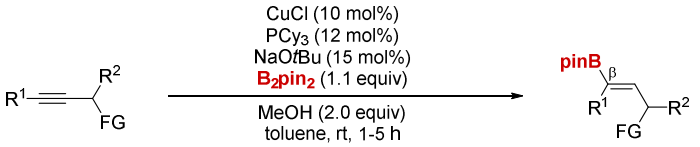
[47] Lee, J.-E.; Kwon, J.; Yun, J. *Chem. Commun.* **2008**, 733-734.
[48] Jang, H.; Zhugralin, A. R.; Lee, Y.; Hoveyda, A. H.; *J. Am. Chem. Soc.* **2011**, *133*, 7859-7871.

The use of different *N*-heterocyclic carbene (NHC) complexes of copper allowed the control of the site selectivity to produce α- or β-vinylboronic esters (*Scheme I-13*). Propargylic amines, amides, alcohols and the derived silyl ethers as well as a wide range of aryl-substituted terminal alkynes were particularly effective substrates.



Scheme I-13. Copper-catalyzed site selective hydroboration of terminal alkynes.

Then, Carretero and Arrayás reported the copper-catalyzed hydroboration of propargyl-substituted internal alkynes (*Scheme I-14*).[49] The presence of a propargylic polar substituent (OH, OR, SAr, SO_2Ar, or NHTs), in combination with PCy_3 as ligand, allowed maximizing the reactivity and site-selectivity to afford β-borylated products.

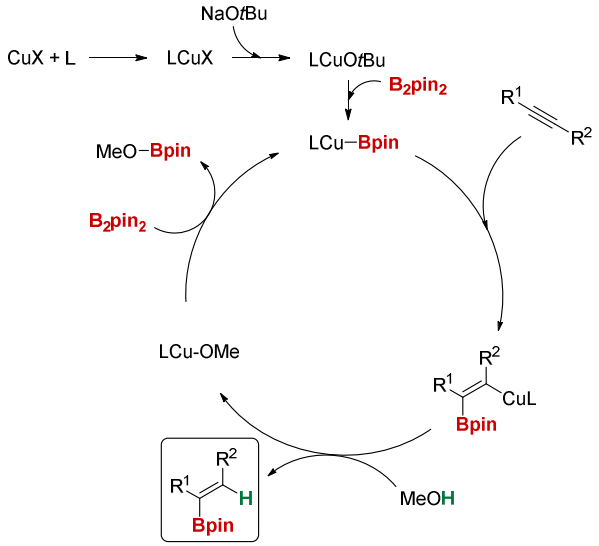


Scheme I-14. Copper-catalyzed hydroboration of propargyl-substituted alkynes.

The detailed reaction mechanism for the copper(I)-catalyzed borylation of internal alkynes has been recently studied by experiments and DFT

[49] (a) Moure, A. L.; Arrayás, R. G.; Cárdenas, D. J.; Alonso, I.; Carretero, J. C. *J. Am. Chem. Soc.* **2012**, *134*, 7219-7222. (b) Moure, A. L.; Mauleón, P.; Arrayás, R. G.; Carretero, J. C. *Org. Lett.* **2013**, *15*, 2054-2057.

calculations.[50] A catalytic cycle has been proposed for this transformation (*Scheme I-15*), similar to the one proposed by Yun for the α,β-unsaturated substrates. In the hydroboration reaction, the treatment of a copper complex in the presence of a base affords a copper alkoxide, and then a copper-boryl species is generated by σ bond metathesis between this copper alkoxide and the diborane reagent. The addition of the catalytic active species [LCu-Bpin] to the alkyne provides vinyl copper intermediate. Next, protonation of the alkenylcopper intermediate with MeOH generates efficiently the desired product and copper methoxide that starts over the catalytic cycle.



Scheme I-15. Proposed mechanism on the copper-catalyzed hydroboration of alkynes.

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

Other groups have reported copper-catalyzed borylation of triple bonds.[51] Yoshida used pinB-Bdan for the borylation of propiolates.[52] Moreover, thioacetylenes[53] were found to be suitable substrates, as well as silylalkynes,[54] alkynamides[55] and conjugated diynes.[56]

The mechanism involved in the copper-catalyzed borylation is very specific for copper. It is different from other metal-catalyzed hydroborations because the C-H bond is not formed through a reductive elimination step from a metal-hydride but it is formed through a protonation. This fact opens the possibility to trap the vinyl copper intermediate with electrophiles different than proton, in a catalytic fashion. Tortosa and co-workers were the first ones to prove that this was indeed possible. They developed the copper-catalyzed formal carboboration of alkynes, in which a C-B bond and a C-C bond were created in a single step (*Scheme I-16*).[57] Through this process, highly functionalized vinyl boronic esters could be prepared from readily available starting materials.

---

[51] (a) Kim, H. R.; Yun, J. *Chem. Commun.* **2011**, *47*, 2943-2945. (b) Jung, H. Y.; Feng, X.; Kim, H.; Yun, J. *Tetrahedron* **2012**, *68*, 3444-3449. (c) Semba, K.; Fujihara, T.; Terao, J.; Tsuji, Y. *Chem. Eur. J.* **2012**, *18*, 4179-4184. (d) Yun, J. *Asian J. Org. Chem.* **2013**, *2*, 1016-1025. (e) Fujihara, T.; Semba, K.; Terao, J.; Tsuji, Y. *Catal. Sci. Technol.* **2014**, *4*, 1699-1709. (f) Tai, C. C.; Yu,M. S.; Chen, Y. L.; Chuang, W. H.; Lin, T. H.; Yap, G. P. A.; Ong, T. G. *Chem. Commun.* **2014**, *50*, 4344-4346. (g) Semba, K.; Fujihara, T.; Terao, J.; Tsuji, Y. *Tetrahedron* **2015**, *71*, 2183-2197. (h) Yoshida, H. *ACS Catal.* **2016**, *6*, 1799-1811. (i) Liu, s.; Zeng, X.; Xu, B. *Tetrahedron Lett.* **2016**, *57*, 3706-3710. (j) Kojima, C.; Lee, K. H.; Lin, Z.; Yamashita, M. *J. Am. Chem. Soc.* **2016**, *138*, 6662-6669. (k) Xuan, Q. Q.; Wei, Y. H.; Song, Q. L. *Chin. Chem. Lett.* **2017**, *28,* 1163-1166. (l) Szadkowska, A.; Zaorska, E.; Staszko, S.; Pawłowski, R.; Trzybiński, D.; Woźniak, K. *Eur. J. Org. Chem.* **2017**, 4074-4084. (m) Bai, T.; Yang, Y.; Han, C. *Tetrahedron Lett.* **2017**, *58*, 1523-1527

[52] Yoshida, H.; Takemoto, Y.; Takaki, K. *Chem. Commun.* **2014**, *50*, 8299-8302.

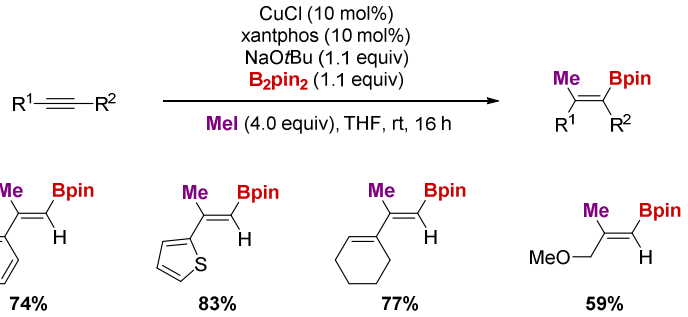
[53] Zhu, G.; Kong, W.; Feng, H.; Qian, Z. *J. Org. Chem.* **2014**, *79*, 1786-1795.

[54] (a) Kubota, K.; Yamamoto, E.; Ito, H. *Adv. Synth. Catal.* **2013**, *355*, 3527-3531 (b) Chae, Y. M.; Bae, J. S.; Moon, J. H.; Lee, J. Y.; Yun, J. *Adv. Synth. Catal.* **2014**, *356*, 843-849.

[55] He, G.; Chen, S.; Wang, Q.; Huang, H.; Zhang, Q.; Zhang, D.; Zhang, R.; Zhu, H. *Org. Biomol. Chem.* **2014**, *12*, 5945-5953.

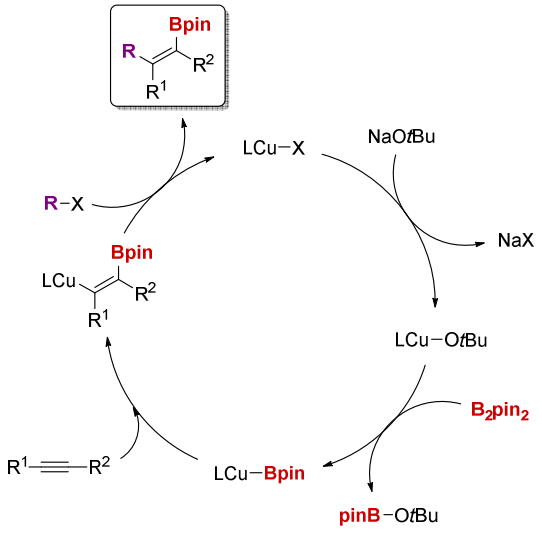
[56] Li, D.; Kim, Y. E.; Yun, J. *Org. Lett.* **2015**, *17*, 860-863.

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



Scheme I-16. Copper-catalyzed carboboration of alkynes.

The proposed mechanism for carboboration is slightly different than the one for the hydroboration (*Scheme I-17*). After the insertion step, the vinyl copper intermediate reacts with the alkyl halide to form the carboboration product and a copper halide. In the carboboration reaction, at least one equivalent of base is needed to transform the copper halide into a copper alkoxide, which can start over the catalytic cycle.

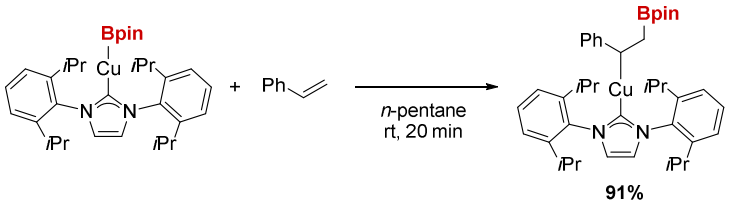


Scheme I-17. Proposed mechanism on the copper-catalyzed carboboration of alkynes.

After this publication, other groups have also contributed to make this transformation in a very robust and general way to access trisubtituted vinyl boronates.[58]

1.3.2. Copper-Catalyzed Borylation of Alkenes

Alkenes are also suitable substrates for the copper(I)-catalyzed hydroboration,[59] following the same pattern than alkynes. In 2006, Sadighi and co-workers isolated the boroalkyl complexes formed by insertion of alkenes into an (NHC)copper(I) boryl complex (*Scheme I-18*).[60]



Scheme I-18. Isolated boroalkyl complex.

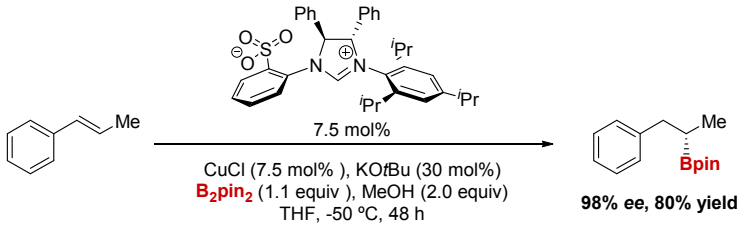
[58] (a) Okuno, Y.; Yamashita, M.; Nozaki, K. *Angew. Chem. Int. Ed.* **2011**, *50*, 920-923. (b) Okuno, Y.; Yamashita, M.; Nozaki, K. *Eur. J. Org. Chem.* **2011**, 3951-3958. (c) Yoshida, H.; Kageyuki, I.; Takaki, K. *Org. Lett.* **2013**, *15*, 952-955. (d) Zhou, Y.; You, W.; Smith, K. B.; Brown, M. K. *Angew. Chem. Int.* Ed. **2014**, *53*, 3475-3479. (e) Bidal, Y. D.; Lazreg, F.; Cazin, C. S. J. *ACS Catal.* **2014**, *4*, 1564-1569. (f) Bin, H. Y.; Wei, X.; Zi, J.; Zuo, Y. J.; Wang, T. C.; Zhong, C. M. *ACS Catal.* **2015**, *5*, 6670-6679. (g) Itoh, T.; Shimizu, Y.; Kanai, M. *J. Am. Chem. Soc.* **2016**, *138*, 7528-7531.

[59] (a) Cano, R.; Ramon, D. J.; Yus, M. *J. Org. Chem.* **2010**, *75*, 3458-3460. (b) Cano, R.; Ramon, D. J.; Yus, M. *J. Org. Chem.* **2010**, *75*, 3458-3460. (c) Noh, D.; Yoon, S. K.; Won, J.; Lee, J. Y.; Yun, J. *Chem. Asian J.* **2011**, *6*, 1967-1969. (d) Iwasaki, H.; Teshima, Y.; Yamada, Y.; Ishikawa, R.; Koga, Y.; Matsubara, K. *Dalton Trans.* **2016**, *45*, 5713-5719. (e) Xi, Y.; Hartwig, J. F. *J. Am. Chem. Soc.* **2016**, *138*, 6703-6706. (f) Jang, W. J.; Song, s. M.; Moon, J. H.; Lee, J. Y.; Yun, J. *J. Am. Chem. Soc.* **2017**, *139*, 13660-13663. (g) Iwamoto, H.; Kubota, K.; Ito, H. *Chem. Commun.* **2016**, *52*, 5916-5919.

[60] Laitar, D. S.; Tsui, E. Y.; Sadighi, J. P. *Organometallics*, **2006**, *25*, 2405-2408.

One year later, Marder published the computational study of the insertion reaction of alkenes into copper(I)-boryl complexes.[61] DFT calculations supported the expected mechanism where the insertion of an alkene substrate molecule into a Cu-B bond involved nucleophilic attack of the boryl ligand to the alkene.

However, interest into copper-catalyzed hydroboration of alkenes increased in 2009, when Hoveyda and co-workers reported the asymmetric β-borylation of vinyl arenes catalyzed by copper-(I)-NHC complexes (*Scheme I-19*).[62] This contribution to catalytic asymmetric hydroboration provided further impetus for improving the scope. In 2013, they expanded this methodology to aryl- and alkyl-substituted vinylsilanes to synthesize a wide range of borosilanes.[63]

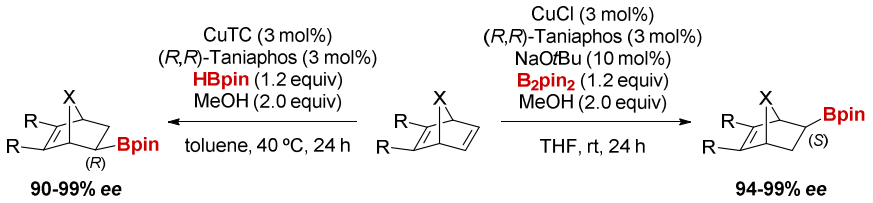


Scheme I-19. Copper(I)-catalyzed asymmetric hydroboration.

Yun explored the borylation of strained alkenes in 2015, and she reported an enantiodivergent copper(I)-catalyzed hydroboration of bicyclic substrates (*Scheme I-20*).[64] Excellent enantioselectivities were obtained for bicyclic alkenes including oxa- and azabicyclic compounds, using (*R*,*R*)-Taniaphos as chiral ligand. Furthermore, different boron sources were tested and it was found that the use of B_2pin_2 generated the

[61] Dang, L.; Zhao, H.; Lin, Z.; Marder, T. B. *Organometallics* **2007**, *26*, 2824-2832.
[62] (a) Lee, Y.; Hoveyda, a. H. *J. Am. Chem. Soc.* **2009**, *131*, 3160-3161. (b) Guiry, P. J. *ChemCatChem* **2009**, *1*, 233-235. (c) Corberán, R.; Mszar, N. W.; Hoveyda, A. H. *Angew. Chem. Int. Ed.* **2011**, *50*, 7079-7082.
[63] Meng, F. K.; Jang, H. J.; Hoveyda, A. H. *Chem. Eur. J.* **2013**, *19*, 3204-3214.
[64] Lee, H.; Lee, B. Y.; Yun, J. *Org. Lett.* **2015**, *17*, 764-766.

(*S*)-enantiomer, while the opposite enantiomer was obtained when HBpin was used. Further studies demonstrated that *N*-heterocyclic carbenes were also suitable ligands.[65]



Scheme I-20. Enantiodivergent copper-catalyzed hydroboration of bicyclic alkenes.

The alkylcopper intermediate formed in these reactions has been also trapped with electrophiles different than proton such as alkyl halides[66] and mesylates,[67] electrophilic amines,[68] ketones,[69] imines[70] or acyl chlorides.[71]

[65] Ondrusek, B. A.; Opalka, S. M.; Hietsoi, O.; Shatruk, M.; McQuade, D. T. *Synlett* **2013**, *24*, 1211-1214.

[66] (a) Kubota, K.; Yamamoto, E.; Ito, H. *J. Am. Chem. Soc.* **2013**, *135*, 2635-2640. (b) Kageyuki, I.; Yoshida, H.; Takaki, K. *Synthesis* **2014**, *46*, 1924-1932. (c) Parra, A.; López, A.; Díaz-Tendero, S.; Amenós, L.; Garcia-Ruano, J. L.; Tortosa, M. *Synlett* **2015**, *26*, 494-500. (d) Iwamoto, H.; Akiyama, S.; Hayama, K.; Ito, H. *Org. Lett.* **2017**, *19*, 2614-2617. (e) Cui, J.; Wang, H.; Song, J.; Chi, X.; Meng, L.; Liu, Q.; Zhang, D.; Dong, Y.; Liu, H. *Org. Biomol. Chem.* **2017**, *15*, 8508-8512.

[67] (a) Ito, H.; Toyoda, T. Sawamura, M. *J. Am. Chem. Soc.* **2010**, *132*, 5990-5992. (b) Zuo, Y. J.; Chang, X. T.; Hao, Z. M.; Zhong, C M. *Org. Biomol. Chem.* **2017**, *15*, 6323-6327.

[68] (a) Matsuda, N.; Hirano, K.; Satoh, T.; Miura, M. *J. Am. Chem. Soc.* **2013**, *135*, 4934-4937. (b) Sakae, R.; Matsuda, N.; Hirano, K.; Satoh, T.; Miura, M. *Org. Lett.* **2014**, *16*, 1228-1231. (c) Sakae, R.; Hirano, K.; Satoh, T.; Miura, M. *Angew. Chem. Int. Ed.* **2015**, *54*, 613-617. (d) Sakae, R.; Hirano, K.; Miura, M. *J. Am. Chem. Soc.* **2015**, *137*, 6460-6463. (e) Jiang, H. C.; Tang X. Y.; Shi, M. *Chem. Commun.* **2016**, *52*, 5273-5276.

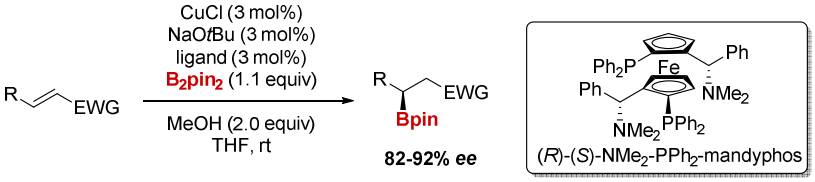
[69] Yamamoto, E.; Kojima, R.; Kubota, K.; Ito, H. *Synlett*, **2016**, *27*, 272-276.

[70] Smith, J. J.; Best, D.; Lam, H. W. *Chem. Commun.* **2016**, *52*, 3770-3772.

[71] Huang, Y.; Smith, K. B.; Brown, M. K. *Angew. Chem. Int. Ed.* **2017**, *56*, 13314-13318.

1.3.3. Copper-Catalyzed Borylation of α,β-Unsaturated Compounds

The borylation of α,β-unsaturated compounds is one of the most studied transformations using copper catalysis. After Yun reported the role of the protic additives in the reaction rate, a dramatic progress was observed to develop an asymmetric version of this transformation. In 2008, Yun and co-workers published the first enantioselective borylation of α,β-unsaturated esters and nitriles (*Scheme I-21*).[72]



Scheme I-21. Enantioselective borylation of α,β-unsaturated esters, nitriles and ketones.

Almost simultenously, Pérez and Fernández studied the enantioselective β-borylation of α,β-unsaturated esters and aldehydes using chiral *N*-heterocyclic carbene ligands.[73] A few years later, Hoveyda reported excellent enantiocontrol in the copper-catalyzed borylation of α,β-unsaturated carboxylic esters, ketones, and thioesters, also using chiral *N*-heterocyclic carbene ligands.[74] Additionally, Kanai and Shibasaki developed the copper-catalyzed asymmetric hydroboration of cyclic α,β-unsaturated ketones to produce enantiomerically enriched tertiary organoboronates (*Scheme I-22*).[75]

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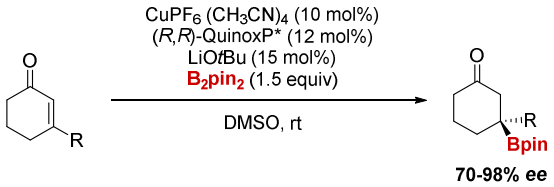
[72] Lee, J. E.; Yun, J. *Angew. Chem. Int. Ed.* **2008**, *47*, 145-147.
[73] Lillo, V.; Prieto, A.; Bonet, A.; Díaz-Requejo, M. M.; Ramírez, J.; Pérez, P. J.; Fernández, E. *Organometallics* **2009**, *28*, 659-662.
[74] O'Brien, J. M; Lee, K. S.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2010**, *132*, 10630-10633.
[75] (a) Chen, I. H.; Yin, L.; Itano, W.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2009**, *131*, 11664-11665. (b) Chen, I. H.; Kanai, M.; Shibasaki, M. *Org. Lett.* **2010**, *12*, 4098-4101.



Scheme I-22. Asymmetric synthesis of chiral tertiary organoboronic esters.

Encouraged by this work, several research groups have expanded this methodology[76] to the hydroboration of aldehydes,[77] amides,[78] γ-imino boronates,[79] α,β-unsaturated sulfones,[80] β-boronylacrylates,[81] α,β-unsaturated phosphine oxides[82] and γ-amidoacrylates.[83] Even heterocycles, such as indole-2-carboxylates, are suitable substrates.[84]

[76] For more examples of copper-catalyzed borylation of α,β-unsaturated ketones, see: (a) Sim, H. S.; Feng, X.; Yun, J. *Chem. Eur. J.* **2009**, *15*, 1939-1943. (b) Feng, X.; Yun, *J. Chem. Commun.* **2009**, 6577-6579. (c) Hong, B.; Ma, Y.; Zhao, L.; Duan, W.; He, F.; Song, C. *Tetrahedron: Asymmetry* **2011**, *22*, 1055-1062. (d) Radomkit, S.; Hoveyda, A. H. *Angew. Chem. Int. Ed.* **2014**, *53*, 3387-3391. (e) Jian, Q.; Guo, T.; Yu, Z. *ChemCatChem* **2015**, *7*, 660-665. (f) Wang, Q. D.; Yang, J. M.; Fang, D.; Ren, J.; Dong, B.; Zhou, B.; Zeng, B. B. *Tetrahedron Lett.* **2016**, 57, 2587-2590. (g) Zhou, J.; Liu, X.; Sun, Z. *Heterocycles*, **2016**, *92*, 944-953.
For more examples of copper-catalyzed borylation of α,β-unsaturated ketones, see: (a) Park, J. K.; Lackey, H. H.; Rexford, M. D.; Kovnir, K.; Shatruk, M.; McQuade, D. T. *Org. Lett.* **2010**, *12*, 5008-5011. (b) Feng, X.; Yun, J. *Chem. Eur. J.* **2010**, *16*, 13609-13612. (c) Zhang, J. L.; Chen, L. A.; Xu, R. B.; Wang, C. F.; Ruan, Y. P.; Wang, A. E.; Huang, P. Q. *Tetrahedron: Asymmetry* **2013**, *24*, 492-498. (d) He, Z. T.; Zhao, Y. S.; Tian, P.; Wang, C. C.; Dong, H. Q.; Lin, G. Q. *Org. Lett.* **2014**, *16*, 1426-1429. (e) Jiang, Q.; Guo, T.; Yu, Z. *J. Org. Chem.* **2017**, *82*, 1951-1960.

[77] Pujol, A.; Calow, A. D. J.; Batsanov, A. S.; Whiting, A. *Org. Biomol. Chem.* **2015**, *13*, 5122-5130.

[78] Chea, H.; Sim, H. S.; Yun, J. *Adv. Synth. Catal.* **2009**, *351*, 855-858.

[79] Solé, C.; Fernndez, E. *Chem. Asian J.* **2009**, *4*, 1790-1793. (b) Solé, C.; Whiting, A.; Gulys, H.; Fernandez, E. *Adv. Synth. Catal.* **2011**, *353*, 376-384. (c) Solé, C.; Tatla, A.; Mata, J. A.; Whiting, A.; Gulys, H.; Fernndez, E. *Chem. Eur. J.* **2011**, *17*, 14248-14257.

[80] Moure, A. L.; Gómez-Arráyas, R.; Carretero, J. C. *Chem. Commun.* **2011**, *47*, 6701-6703.

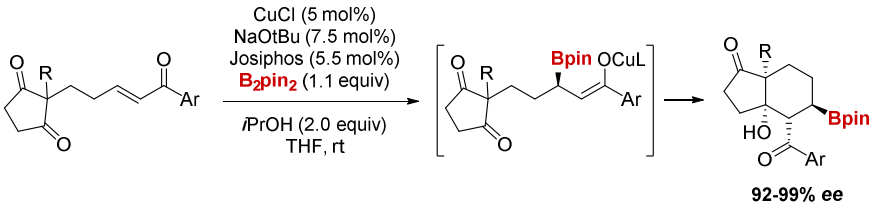
[81] Lee, J. C. H.; McDonald, R.; Hall, D. G. *Nat. Chem.* **2011**, *3*, 894-899.

[82] Hornillos, V.; Vila, C.; Otten, E.; Feringa, B. L. *Angew. Chem. Int. Ed.* **2015**, *54*, 7867-7871.

[83] (a) Chen, L.; Zou, X.; Zhao, H.; Xu, S. *Org. Lett.* **2017**, *19*, 3676-3679. (b) López, A.; Clark, T. B.; Parra, A.; Tortosa, M. *Org. Lett.* Accepted Manuscript.

[84] Kubota, K.; Hayama, K.; Iwamoto, H.; Ito; H. *Angew. Chem. Int. Ed.* **2015**, *54*, 8809-8813.

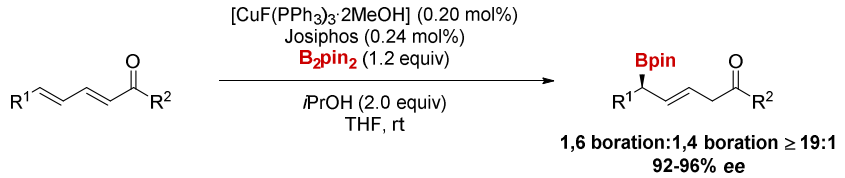
Beyond the large amount of reported hydroboration examples of α,β-unsaturated compounds, some other variants have been studied regarding this transformation. In 2012, it was developed the first asymmetric borylative/aldol cyclization by trapping the metal enolate, generated during the copper-catalyzed conjugate borylation, with a ketone (*Scheme I-23*).[85] The resulting intramolecular reaction leads to enantiomerically enriched bicyclic products containing multiple stereocenters.



Scheme I-23. Enantioselective borylative/aldol cyclization.

Furthermore, the enantioselective copper-catalyzed 1,6-boration of acyclic α,β,γ,δ-unsaturated esters and ketones was described by Lam in 2014 (*Scheme I-24*).[86] The reaction proceeded with high regioselectivity for the 1,6- over the 1,4-boration, without a "blocking" substituent at the β-carbon. Later, Liao[87] and Tortosa[88] extended this methodology to the use of *p*-quinone methides, affording enantioenriched dibenzylic boronates through copper-catalyzed asymmetric 1,6-borylation.

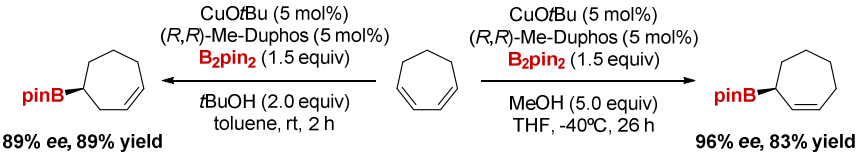
[85] Burns, A. R.; González, J. S.; Lam, H. W. *Angew. Chem. Int. Ed.* **2012**, *51*, 10827-10831.
[86] Luo, Y.; Roy, I. D.; Madec, A. G. E.; Lam, H. W. *Angew. Chem. Int. Ed.* **2014**, *53*, 4186-4190.
[87] Lou, Y.; Cao, P.; Jia, T.; Zhang, Y.; Wang, M.; Liao, J. *Angew. Chem. Int. Ed.* **2015**, *54*, 12134-12138.
[88] Jarava-Barrera, C.; Parra, A.; López, A.; Cruz-Acosta, F.; Collado-Sanz, D.; Cárdenas, D. J.; Tortosa, M. *ACS Catal.* **2016**, *6*, 442-446.



Scheme I-24. 1,6-Boration of acyclic α,β,γ,δ-unsaturated esters and ketones.

1.3.4. Copper-Catalyzed Borylation of Dienes, Enynes, and Allenes

The regio- and enantioselective copper(I)-catalyzed borylation of cyclic 1,3-dienes was studied by Ito and co-workers (*Scheme I-25*).[89] They reported the asymmetric synthesis of homoallylic and allylic boronates with excellent regio- and stereocontrol. They found that the regioselectivity of the reaction could be controlled just modifying the proton source.



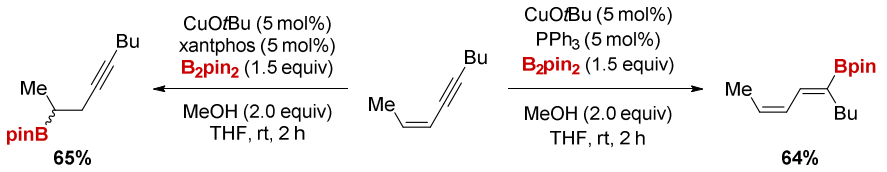
Scheme I-25. Regio- and enantioselective hydroboration of cyclic 1,3-dienes.

Moreover, *in situ* dearomatized pyridines were found to be suitable dienes to undergo copper-catalyzed borylation reaction to achieve enantioselective functionalized piperidines.[90]

The same group also investigated the regioselectivity in the copper(I)-catalyzed monoborylation of 1,3-enynes (*Scheme I-26*).[91] Borylcupration

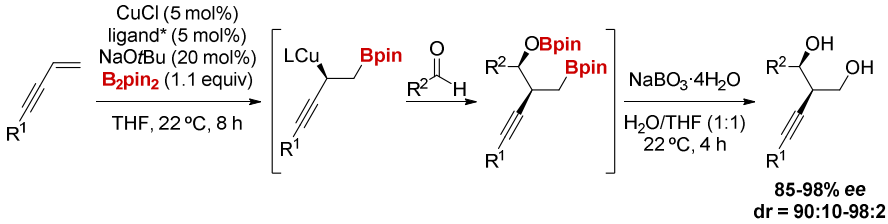
[89] Sasaki, Y.; Zhong, C.; Sawamura, M.; Ito, H. *J. Am. Chem. Soc.* **2010**, *132*, 1226-1227.
[90] (a) Kubota, K.; Watanabe, Y.; Hayama, K.; Ito, H. *J. Am. Chem. Soc.* **2016**, *138*, 4338-4341. (b) Kubota, K.; Watanabe, Y.; Ito, H. *Adv. Synth. Catal.* **2016**, *358*, 15, 2379-2384.
[91] Sasaki, Y.; Horita, Y.; Zhong, C.; Sawamura, M.; Ito, H. *Angew. Chem. Int. Ed.* **2011**, *50*, 2778-2782.

took place at the double bond when steric hindrance on the olefin was not significant, while the copper-boryl addition was produced into the alkyne in the case of highly substituted olefins. However, if steric demand around the double bond was moderate, the ligand would play an important role on this reaction, as the regioselectivity could also be controlled by changing the phosphine. This methodology was extended to the synthesis of dienylboronic esters bearing a hydroxyl or amino group.[92]



Scheme I-26. Regioselective hydroboration of 1,3-enynes.

Further work from Hoveyda and co-workers described a copper-catalyzed enantioselective multicomponent process involving B_2pin_2, 1,3-enynes, and aldehydes (*Scheme I-27*).[93] The resulting copper intermediate, generated *in situ* in the borylation reaction, reacted with the aldehyde and after oxidative work-up 1,3-diol derivatives were prepared.

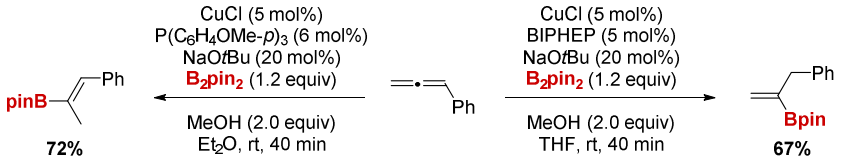


Scheme I-27. Synthesis of 1,3-diol derivatives.

Copper-catalyzed hydroboration of allenes affords vinyl boronates, which are very useful intermediates for subsequent transformations into

[92] Xu, H. D.; Wu, H.; Jiang, C.; Chen, P.; Shen, M. H. *Tetrahedron Lett.* **2016**, *57*, 2915-2918.
[93] Meng, F. K.; Haeffner, F.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2014**, *136*, 11304-11307.

more complex structures. The highly selective borylcupration of allenes was reported by Ma in 2013, this reaction produced two different types of alkenylboranes depending on the employed ligand (*Scheme I-28*).[94] In the presence of a monodentate phosphine, the borylcupration occurred at the less substituted C=C bond with exclusive *Z*-geometry, while bidentate ligands gave opposite regioselectivity, reacting the internal double bond.



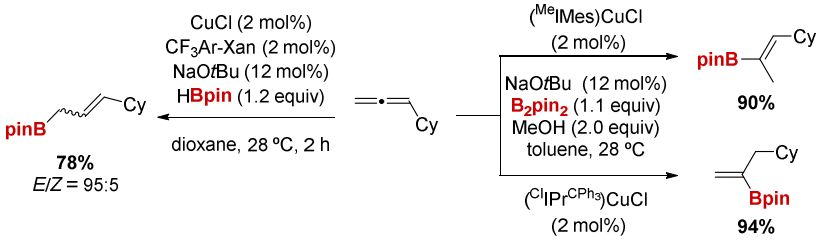
Scheme I-28. Regioselective hydroboration of allenes.

Hoveyda also realized about the importance of the steric hindrance of the ligand, when he developed the selective copper(I)-catalyzed borylation of allenes with *N*-heterocyclic carbenes.[95] He presented mechanistic basis for the observed selectivity and he applied this novel methodology to natural product synthesis. The same group published the enantioselective hydroboration of 1,1-disubstituted allenes to afford enantiomerically enriched alkenylboronates with an allylic stereocenter.[96]

Around the same time, Tsuji and co-workers reported a related hydroboration of allenes catalyzed by copper(I).[97] As Hoveyda, they controlled the regioselectivity of the insertion choosing the appropiate ligand. Two different kinds of vinyl boronic esters were prepared using a monodentate phosphine or an NHC-ligand (*Scheme I-29*). Additionally,

[94] Yuan, W.; Ma, S. *Adv. Synth. Catal.* **2012**, *354*, 1867-1872.
[95] Meng, F.; Jung, B.; Haeffner, F.; Hoveyda, A. H. *Org. Lett.* **2013**, *15*, 1414-1417.
[96] Jang, H.; Jung, B.; Hoveyda, A. H. *Org. Lett.* **2014**, *16*, 4658-4661.
[97] Semba, K.; Shinomiya, M.; Fujihara, T.; Terao, J.; Tsuji, Y. *Chem. Eur. J.* **2013**, *19*, 7125-7132.

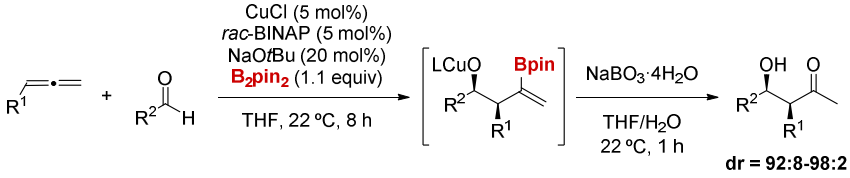
allylboronates were selectively prepared when HBpin was used instead of B_2pin_2. Tsuji also developed the boration of α-alkoxyallenes with B_2pin_2.[98]



Scheme I-29. Selective synthesis of alkenyl- and allylboronates from allenes.

In addition, Ma has recently developed a highly regio- and stereoselective hydroboration of substituted 2,3-allenamides,[99] as well as the enantioselective borylation of allenylsilanes.[100]

In 2013, Hoveyda was able to trap the alkylcopper intermediate formed after borylation of an allene with aldehydes, through a chemo-, diastereo and enantioselective transformation (*Scheme I-30*).[101]



Scheme I-30. Selective synthesis of 2-borylated homoallylic alkoxide intermediates.

Recently, Procter presented a similar copper-catalyzed borylative cross-coupling reaction using allenes, B_2pin_2 and imines to afford

[98] Semba, K.; Fujihara, T.; Terao, J.; Tsuji, Y. *Angew. Chem. Int. Ed.* **2013**, *52*, 12400-12403

[99] Yuan, W.; Zhang, X.; Yu, Y.; Ma, S. *Chem. Eur. J.* **2013**, *19*, 7193-7202.

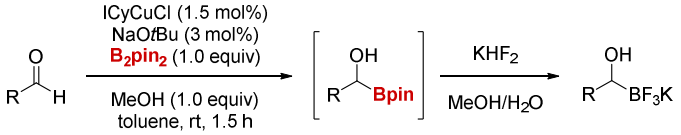
[100] Yuan, W.; Song, L.; Ma, S. *Angew. Chem. Int. Ed.* **2016**, *55*, 3140-3143.

[101] Meng, F. K.; Jang, H.; Jung, B.; Hoveyda, A. H. *Angew. Chem. Int. Ed.* **2013**, *52*, 5046-5051.

branched α,β-substituted-γ-boryl homoallylic amines.[102] Moreover, the alkyl copper intermediate has been trapped with acyl fluorides, generating β-boryl β,γ-unsaturated ketones possessing a quaternary center.[103]

1.3.5. Copper-Catalyzed Borylation of Aldehydes, Ketones and Imines

As aforementioned, in 2006, Sadighi reported the 1,2-diboration of aldehydes under copper-catalyzed borylation conditions.[45] Inspired by this work, Molander envisioned the synthesis of potassium 1-(hydroxy)alkyltrifluoroborates through a copper-catalyzed diboration of aldehydes. The α-hydroxyboronates intermediates were treated with KHF_2 to form the trifluoroborate salts (*Scheme I-31*).[104] In addition, they reported the palladium-catalyzed Suzuki-Miyaura cross-coupling of the products to obtain protected secondary alcohols in high yields.

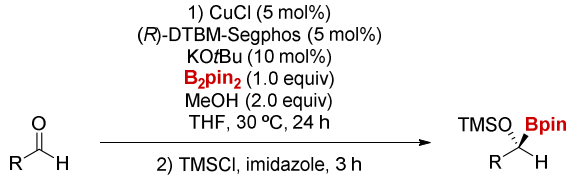


Scheme I-31. Synthesis of potassium 1-(hydroxy)alkyltrifluoroborates.

Then, Ito developed the first enantioselective borylation of aldehydes to give the corresponding optically active α- alkoxyorganoboronate esters with excellent enantioselectivities through a borylation-protection sequence (*Scheme I-32*).[105] This transformation provided attractive

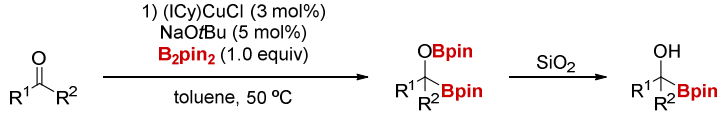
[102] Rae, J.; Yeung, K.; McDouall, J. J. W.; Procter, D. J. *Angew. Chem. Int. Ed.* **2016**, *55*, 1102-1107.
[103] Boreux, A.; Indukuri, K.; Gagosz, F.; Riant O. *ACS Catal.* 2017, Just Accepted Manuscript, DOI: 10.1021/acscatal.7b02938.
[104] Molander, G. A.; Wisniewski, S. R. *J. Am. Chem. Soc.* **2012**, *134*, 16856-16868.
[105] Kubota, K.; Yamamoto, E.; Ito, H. *J. Am. Chem. Soc.* **2015**, *137*, 420-424.

intermediates for the synthesis of useful enantioenriched functionalized alcohols.



Scheme I-32 Synthesis of enantiomerically enriched α-alkoxyorganoboronate esters.

Analogous ketones were also suitable substrates, as it was described by Clark in 2010, when he reported the first diboration of ketones to achieve tertiary α-hydroxyboronate esters (*Scheme I-33*).[106] Recently, Ito has reported the asymmetric version of this transformation, providing access to enantioenriched α-hydroxyboronic esters via copper-catalyzed borylation of ketones.[107]



Scheme I-33. Synthesis of tertiary α-hydroxyboronate esters.

Ellman and co-workers demonstrated that Sadighi's catalyst could be used in combination with a chiral auxiliary to achieve the asymmetric diboration of *tert*-butanesulfinylaldimines (*Scheme I-34*).[108] The synthesis of enantioenriched α-amino boronates was a breakthrough in this field, as these compounds present high biological importance. The application to the synthesis of the anticancer drug Velcade® confirmed the great utility of this methodology.

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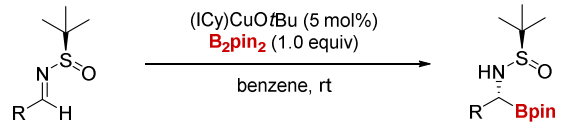
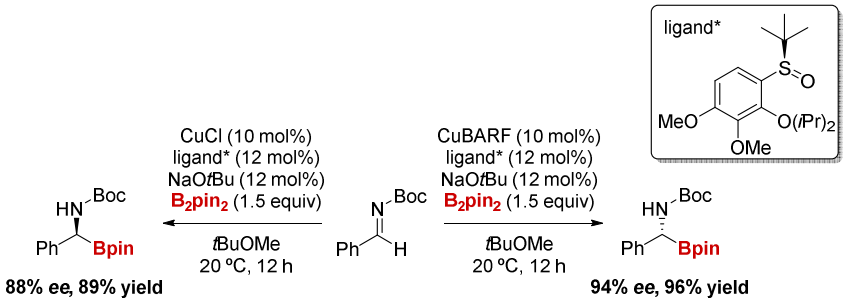
[106] McIntosh, M. L.; Moore, C. M.; Clark, T. B. *Org. Lett.* **2010**, *12*, 1996-1999.
[107] Kubota, K.; Osaki, S.; Jin, M.; Ito, H. *Angew. Chem. Int. Ed.* **2017**, *56*, 6646-6650.
[108] Beenen, M. A.; An, C.; Ellman, J. A. *J. Am. Chem. Soc.* **2008**, *130*, 6910-6911.



Scheme I-34. Copper-catalyzed asymmetric diboration of *tert*-butanesulfinylaldimines.

In 2013, Tian and Lin described the enantioselective copper(I)-catalyzed hydroboration of *N*-benzoyl aldimines, using bulky chiral imidazolium salt NHC precursor as ligand, to prepare α-amido boronic esters.[109] Sun enhanced the access to α-aminoboronates from *N-tert*-butanesulfinyl aldimines and ketimines by tuning the *N*-heterocyclic carbene employed and preforming the carbene-copper complex.[110] These conditions avoided the need of glove box to perform the reaction. Then, Liao extended this methodology to the borylation of *N*-Boc-imines, in the presence of a chiral sulfoxide-dialkylphosphine ligand, to afford α-aminoboronate esters with high enantioselectivities (*Scheme I-35*).[111] This selective borylation offered the possibility of synthesizing both enantiomers through an achiral counteranion switch.



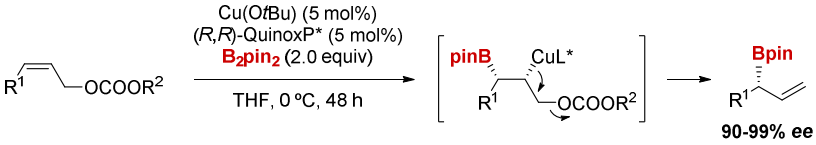
Scheme I-35. Copper(I)-catalyzed hydroboration of *N*-Boc-imines.

[109] Zhang, S. S.; Zhao, Y. S.; Tian, P.; Lin, G. Q. *Synlett* **2013**, *24*, 437-442.
[110] (a) Wen, K.; Wang, H.; Chen, J.; Zhang, H.; Cui, X.; Wei, C.; Fan, E.; Sun, Z. *J. Org. Chem.* **2013**, *78*, 3405-3409. (b) O'Brien, J. M.; Lee, K. S.; Hoveyda, A. H. *RSC Adv.* **2014**, *4*, 21131-21133.
[111] Wang, D.; Cao, P.; Wang, B.; Jia, T.; Lou, Y. Z.; Wang, M.; Liao, J. *Org. Lett.* **2015**, *17*, 2420-2423.

Besides, *N*-phosphinylimines were shown to be suitable substrates to undergo copper-catalyzed enantioselective borylation to obtain α-aminoboronates ester.[112]

1.3.6. Copper-Catalyzed Borylation of Allylic and Propargylic Electrophiles

In 2007, Ito and Sawamura described a novel method for the synthesis of α-chiral allylboronates via copper-catalyzed enantioselective borylation of allylic carbonates (*Scheme I-36*).[113] This methodology involved a S_N2' type reaction that allowed for the access of optically active allylboronates. The synthesized boronic esters bearing a stereogenic carbon at the α-position of the boryl group are very useful synthetic intermediates, as they offer a nearly perfect chirality transfer in allylation reactions. Later, McQuade reported a steroconvengent version using mixtures of *E*/*Z* allylic ethers and a chiral NHC.[114]



Scheme I-36. Copper-catalyzed enantioselective synthesis of α-allylboronates.

In 2008, Ito and Sawamura extended the previous copper-catalyzed borylation reaction to the use of propargylic carbonates, affording allenyl

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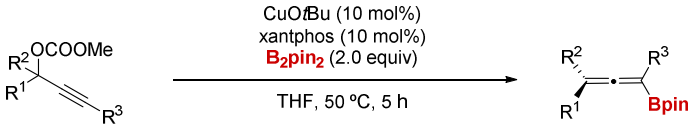
[112] Xie, J. B.; Luo, J.; Winn, T. R.; Cordes, D. B.; Li, G. G. *Beilstein J. Org. Chem.* **2014**, *10*, 746-751.

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

[114] (a) Park, J. K.; Lackey, H. H.; Ondrusek, B. A.; McQuade, T. *J. Am. Chem. Soc.* **2011**, *133*, 2410-2413. (b) Takenouchi, Y.; Kojima, R.; Momma, R.; Ito, H. *Synlett* **2017**, *28*, 270-274.

boronates in a high regio- and stereoselective manner (*Scheme I-37*).[115] The combination of copper *tert*-butoxide and xantphos was found to be effective to prepare a wide variety of allenyl boronic esters. Moreover, they succeeded on the synthesis of optically active allenyl boronates from enantioenriched carbonates with complete chirality transfer.

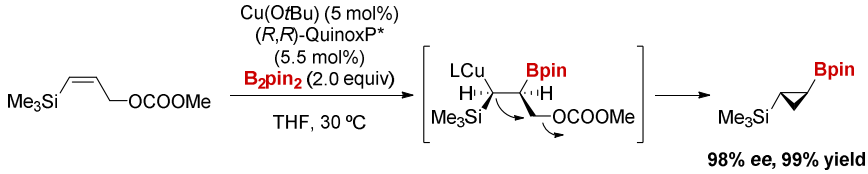


Scheme I-37. Selective synthesis of allenyl boronic esters.

Regarding these substrates, Szabó has recently published the selective synthesis of allenylboronates and alkenyl diboronates from propargyl cyclopropanes via copper-catalyzed borylative ring-opening reaction.[116]

In 2008, Ito and Sawamura envisioned a new asymmetric route for the synthesis of boron-silicon bifunctional cyclopropane derivatives through the copper(I)-catalyzed hydroboration of allylic carbonates using a chiral bisphosphine ligand (*Scheme I-38*).[117] The reaction involved the addition of a copper-boryl intermediate to the alkene, followed by the intramolecular substitution between the resulting alkylcopper(I) moiety and the carbonate. The regioselectivity in the insertion step was unexpected and this was due to the stereoelectronic effect of the silyl group.

[115] Ito, H.; Sasaki, Y.; Sawamura, M. *J. Am. Chem. Soc.* **2008**, *130*, 15774-15775.
[116] Zhao, J.; Szabó K. J. *Angew. Chem. Int. Ed.* **2016**, *55*, 1502-1506.
[117] Ito, H.; Kosaka, Y.; Nonoyama, K.; Sasaki, Y.; Sawamura, M. *Angew. Chem. Int. Ed.* **2008**, *47*, 7424-7427.

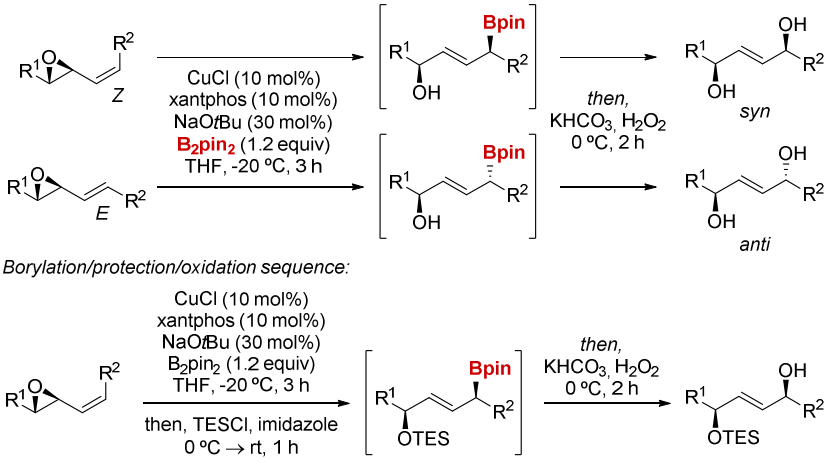


Scheme I-38. Enantioselective synthesis of 1-silyl-2-borylcyclopropanes.

Furthermore, they developed a highly enantioselective copper(I)-catalyzed synthesis of *trans*-2-aryl- and -heteroaryl-substituted cyclopropylboronates from (*Z*)-allylic phosphates.[118]

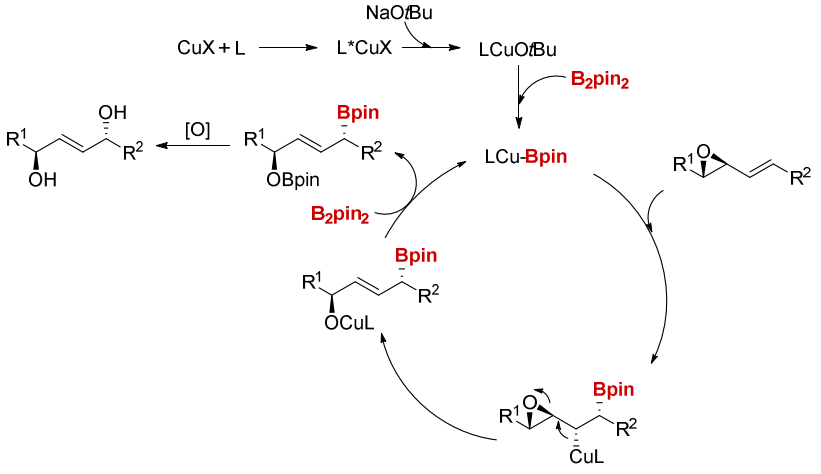
In 2011, Tortosa reported the copper-catalyzed S_N2' addition of diboronates to allylic epoxides.[119] The products, after C-B bond oxidation, are stereodefined 1,4-diols, which are present in a high number of biologically active compounds (*Scheme I-39*). The method allows for the preparation of both *syn* and *anti* 1,4-diols by proper choice of the double-bond and oxirane geometries of the allylic epoxide (*Scheme I-39*). If protection of the hydroxyl of the 1,4-hydroxyboronate takes place prior to C-B bond oxidation, orthogonally protected 1,4-diols can be prepared.

[118] Zhong, C.; Kunii, S.; Kosaka, Y.; Sawamura, M.; Ito, H. *J. Am. Chem. Soc.* **2010**, *132*, 11440-11442.
[119] Tortosa, M. *Angew. Chem. Int. Ed.* **2011**, *50*, 3950-3953.



Scheme I-39. Diastereoselective synthesis of *syn* and *anti* 1,4-diols.

The observed stereochemistry could be explained by an *anti* addition of the copper-boryl complex to the allylic epoxide. A mechanistic proposal is shown in *Scheme I-40*. Addition of the Cu-B bond across the alkene would afford the β-borylalkyl copper intermediate that would undergo β-oxygen elimination to release the allyl boronate, forming a copper alkoxide that would react with B_2pin_2 to regenerate the catalytic cycle.



Scheme I-40. Mechanistic proposal.

Chapter 2

SYNTHESIS OF CYCLOPROPYLBORONATES BY COPPER-CATALYZED DESYMMETRIZATION OF CYCLOPROPENES

2. SYNTHESIS OF CYCLOPROPYLBORONATES BY COPPER-CATALYZED DESYMMETRIZATION OF CYCLOPROPENES

2.1. Background

2.1.1. Importance of Cyclopropanes in Organic Chemistry

Cyclopropanes are three membered rings that present unique steric and electronic properties due to its rigid and highly strained structure. They represent common structural motifs that can be found in a wide variety of natural products and biologically active molecules (*Figure II-1*).[1]

Additionally, cyclopropanes have been used as key intermediates to access medium-sized rings or highly functionalized molecules.[2] Therefore, the development of novel methodologies that allow for the

[1] For some examples of natural products containing cyclopropanes, see: (a) Ringer, S. M.; Greenough, R. C.; Roemer, S.; Connor, D.; Gutt, A. L.; Blair, B.; Kanter, G; von Stradtmann, M. *J. Antiobiot.* **1977**, *30*, 371-375. (b) Connor, D. T.; Greenough, R. C.; von Stradtmann, M. *J. Org. Chem.* **1977**, *42*, 3664-3669. (c) Elliot, M.; Janes, N. F. *Chem. Soc. Rev.* **1978**, *7*, 473-505. (d) Kazlauskas, R.; Murphy, P. T.; Wells, R. J.; Blount, J.-F. *Tetrahedron Lett.* **1978**, *19*, 4155-4158. (e) Epstein, W. W.; Gaudioso, L. A.; Brewster, G. B. *J. Org. Chem.* **1984**, *49*, 2748-2754.

[2] For recent examples of total synthesis involving cyclopropanation, see: (a) Donaldson, W. A. *Tetrahedron* **2001**, *57*, 8589-8627. (b) Wessjohann, L. A.; Brandt, W. Thiemann, T. *Chem. Rev.* **2003,** *103,* 1625-1647. (c) Reichelt, A.; Martin, S. F. *Acc. Chem. Res.* **2006**, *39*, 433-442. (d) Chen, D. Y. K.; Pouwer R. H.; Richard, J. A. *Chem. Soc. Rev.* **2012**, *41*, 4631-4642. (e) Gaydou, M.; Miller, R.; Delont, N.; Ceccon, J.; Echavarren, A. M. *Angew. Chem. Int. Ed.* **2013**, *52*, 6396-6399. (f) Homs, A.; Muratore, M. E.; Echavarren, A. M. *Org. Lett.* **2015**, *17*, 461-463. (g) Kirillova, M. S.; Muratore, M. E.; Dorel, R.; Echavarren, A. M. *J. Am. Chem. Soc.* **2016**, *138*, 3671-3674. (h) Ebner, C.; Carreira, E. M. *Chem. Rev.* **2017**, *117*, 11651-11679.

enantioselective preparation of functionalized cyclopropanes has become a very active research area.[3]

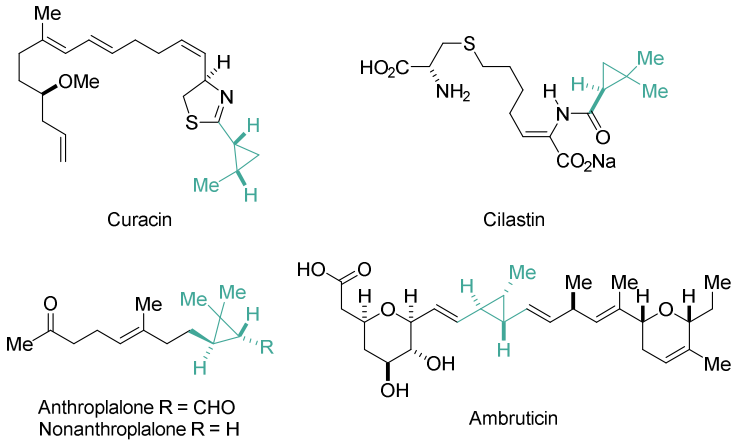


Figure II-1. Some natural products containing cyclopropanes in their structure.

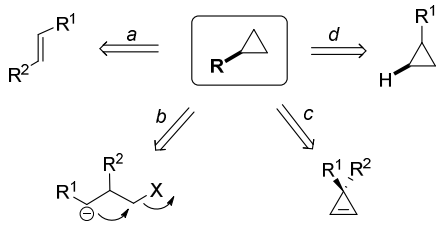
The classical approach to prepare enantioenriched cyclopropanes has been for many years the cyclopropanation of olefins, through *in situ* formation of Simmons-Smith carbenoids[4] or metal carbenes[5] (*Scheme II-*

[3] (a) Salaun, J. *Chem. Rev.* **1989**, *89*, 1247-1270. (b) Lebel, H.; Marcoux, J.-F.; Molinaro, C.; Charette, A. B. *Chem. Rev.* **2003**, *103*, 977-1050. (c) Pellissier, H. *Tetrahedron* **2008**, *64*, 7041-7095.

[4] (a) Simmons, H. E.; Smith, R. D. *J. Am. Chem. Soc.* **1958**, *80*, 5323-5324. (b) Simmons, H. E.; Smith, R. D. *J. Am. Chem. Soc.***1959**, *81*, 4256-4264. (c) Simmons, H. E. *Org. React.* **1973**, *20*, 1-133. (d) Ukaji, Y.; Nishimura, M.; Fujisawa, T. *Chem. Lett.* **1992**, *21*, 61-64. (e) Charette, A. B.; Lemay, J. *Angew. Chem. Int. Ed.* **1997**, *36*, 1090-1092. (f) Charette, A. B.; Beauchemin, A. *Org. React.* **2001**, *58*, 1-85. (g) Charette, A. B.; Gagnon, A.; Fournier, J.-F. *J. Am. Chem. Soc.* **2002**, *124*, 386-387. (h) Zimmer, L. E.; Charette, A. B. *J. Am. Chem. Soc.* **2009**, *131*, 15624-15626. (i) Lévesque, E.; Goudreau, S. R.; Charette, A. B. *Org. Lett.* **2014**, *16*, 1490-1493.

[5] (a) Evans, D. A.; Woerpel, K. A.; Hinman, M. M.; Faul, M. M. *J. Am. Chem. Soc.* **1991**, *113* , 726-728. (b) Davies, H. M. L.; Bruzinski, P. R.; Lake, D. H.; Kong, N.; Fall, M. J. *J. Am. Chem. Soc.* **1996**, *118*, 6897-6907. (c) Doyle, M. P.; Peterson, C. S.; Parker Jr., D. L. *Angew. Chem. Int. Ed.* **1996**, *35*, 1334-1336. (d) Böhm, C.; Reiser, O. *Org. Lett.* **2001**, *3*, 1315-1318. (c) López, S.; Herrero-Gómez, E.; Pérez-Galán, P.; Nieto-Oberhuber, C.; Echavarren, A. M. *Angew. Chem. Int. Ed.* **2006**, *45*, 6029-6032. (e) Chen, Y.; Ruppel, J. V.; Zhang, X. P. *J. Am. Chem. Soc.* **2007**, *129*, 12074-12075. (f) Suematsu, H.; Kanchiku, S.; Uchida, T.; Katsuki, T. *J. Am. Chem. Soc.* **2008**, *130*, 10327-10337. (g) Lindsay, V. N. G.; Lin, W.; Charette, A. B. *J. Am. Chem. Soc.* **2009**, *131*, 16383-16385. (h) Ito, J. I.; Ujiie, S.; Nishiyama, H. *Chem. Eur. J.* **2010**, *16*, 4986-4990. (i) Voituriez, A.; Zimmer, L. E.; Charette, A. B.; *J. Org. Chem.* **2010**, *75*, 1244-1250. (j) Herlé, B.; Holstein, P. M.; Echavarren, A. M. *ACS Catal.* **2017**, *7*, 3668-3675.

1a). This outcome is changing rapidly and novel catalytic methods involving ring closing reactions (*Scheme II-1b*),[6] functionalization of cyclopropenes (*Scheme II-1c*) and C-H functionalization of cyclopropanes (*Scheme II-1d*),[7] have become attractive alternatives.



Scheme II-1. Some methodologies to synthesize functionalized cyclopropanes.

Among them, the stereoselective functionalization of cyclopropenes has proven to be an ideal approach to prepare functionalized cyclopropanes. Although successful diastereoselective approaches[8] have been developed, in this chapter we will describe only enantioselective desymmetrization.

---

[6] (a) Kolsaker, P.; Storesund, H. J. *J. Chem. Soc., Chem. Commun.* **1972**, 375-375. (b) Little, R. D.; Dawson, J. R. *J. Am. Chem. Soc.* **1978**, *100*, 4607- 4609. (c) Verhe, R.; De Kimpe, N.; De Buyck, L.; Courtheyn, D.; Schamp, N. *Synthesis* **1978**, 530-532. (d) Ukaji, Y.; Nishimura, M.; Fujisawa, T. *Chem. Lett.* **1992**, *21*, 61-64. (e) Norsikian, S.; Marek, I.; Klein, S.; Poisson, J. F.; Normant, J. F. *Chem. Eur. J.* **1999**, *5*, 2055-2068. (f) Majumdar, S.; de Meijere, A.; Marek, I. *Synlett* **2002**, 423-426.

[7] (a) Wasa, M.; Engle, K. M.; Lin, D. W.; Yoo, E. J.; Yu, J. Q. *J. Am. Chem. Soc.* **2011**, *133*, 19598-19601. (b) Roman, D. S.; Charette, A. B. *Org. Lett.* **2013**, *15*, 4394-4397. (c) Chan, K. S. L.; Fu, H. Y.; Yu, J. Q. *J. Am. Chem. Soc.* **2015**, *137*, 2042-2046. (d) Kim, J.; Sim, M.; Kim, N.; Hong, S. *Chem. Sci.* **2015**, *6*, 3611-3616.

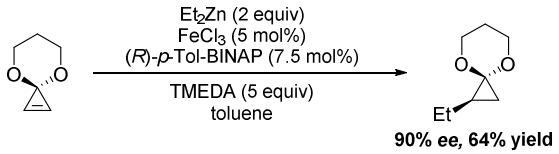
[8] For selected examples of diastereoselective functionalization of cyclopropenes, see: (a) Rubina, M.; Rubin, M.; Gevorgyan, V. *J. Am. Chem. Soc.* **2002**, *124*, 11566-11567. (b) Yin, J.; Chisholm, J. D. *Chem. Commun.* **2006**, 632-634. (c) Trofimov, A.; Rubina, M.; Rubin, M.; Gevorgyan, V. *J. Org. Chem.* **2007**, *72*, 8910-8920. (d) Yan, N.; Liu, X.; Fox, J. M. *J. Org. Chem.* **2008**, *73*, 563-568. (e) Levin, A.; Marek, I. *Chem. Commun.* **2008**, 4300-4302. (f) Tarwade, V.; Liu, X.; Yan, N.; Fox, J. M. *J. Am. Chem. Soc.* **2009**, *131*, 5382-5383. (g) Tenaglia, A.; Jeune, K. L.; Giordano, L.; Buono, G. *Org. Lett.* **2011**, *13*, 636-639. (h) Xie, X.; Fox, J. M. *Synthesis* **2013**, 1807-1814. (i) Didier, D.; Delaye, P. O.; Simaan, M.; Island, B.; Eppe, G.; Eijsberg, H.; Kleiner, A.; Knochel, P.; Marek, I. *Chem. Eur. J.* **2014**, *20*, 1038-1048. (j) Simaan, M.; Delaye, P. O.; Shi, M.; Marek, I. *Angew. Chem. Int. Ed.* **2015**, *54*, 12345-12348. (k) Zhu, P. L.; Zhang, Z.; Tang, X. Y.; Marek, I.; Shi, M. *ChemCatChem* **2015**, *7*, 595-600. (l) Zeng, X. P.; Cao, A. Y.; Wang, Y. H.; Zhou, F.; Zhou, J. *Chem. Rev.* **2016**, *116*, 7330-7396.

2.1.2. Enantioselective Desymmetrization of Cyclopropenes

Cyclopropenes possess significant strain, which makes these species highly energetic compounds and extremely reactive molecules. This offers a large spectrum of remarkable transformations that extend far beyond the simple olefin reactions. Besides, these conformationally constrained molecules have very pronounced steric, stereoelectronic, and directing effects, which make them versatile substrates to study stereoselective transformations.

As mention above, the enantioselective functionalization of symmetric cyclopropenes represents an attractive alternative for the preparation of polisubstituted cyclopropanes.

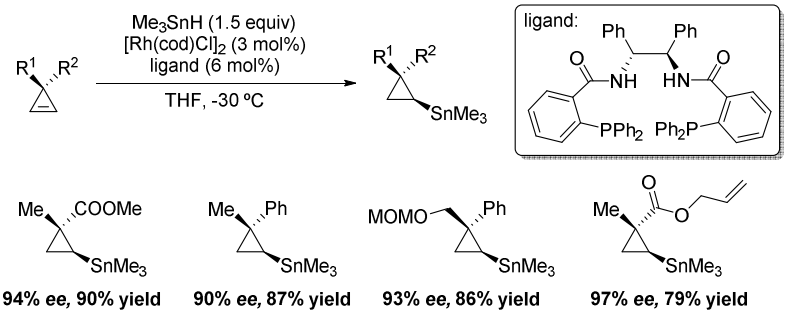
In 2000, Nakamura described the first iron-catalyzed asymmetric carbometalation of an alkene (*Scheme II-2*).[9] Moreover, it also represents the first catalytic enantioselective desymmetrization of a cyclopropene. Cyclopropanes functionalized with an acetal moiety were prepared in moderate yields and good enantioselectivities starting from cyclopropenone acetals and dialkylzinc reagents. The presence of a soft/hard phosphine/diamine ligand (TMEDA) for the iron/zinc bimetallic reagent was essential to achieve high yields and good levels of diastereocontrol.



Scheme II-2. Iron-catalyzed carbometalation of cyclopropenone acetals.

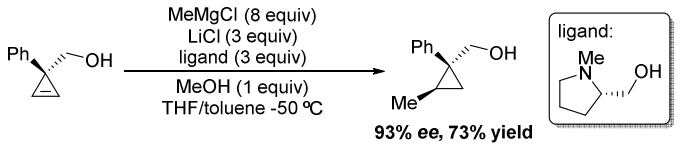
[9] (a) Nakamura, M.; Hirai, A.; Nakamura, E. *J. Am. Chem. Soc.* **2000**, *122*, 978-979. (b) Nakamura, E.; Yoshikai, N. *J. Org. Chem.* **2010**, *75*, 6061-6067.

Later, in 2004, Gevorgyan developed the first transition metal-catalyzed asymmetric hydrostannation of cyclopropenes. A rhodium(I) complex bearing a chiral diamide-based phosphine ligand was employed (*Scheme II-3*).[10] This route allowed for the synthesis of synthetically useful cyclopropyltin derivatives as single diastereomers in good yields and high levels of enantioselectivity.



Scheme II-3. Rhodium(I)-catalyzed asymmetric hydrostannation of cyclopropenes.

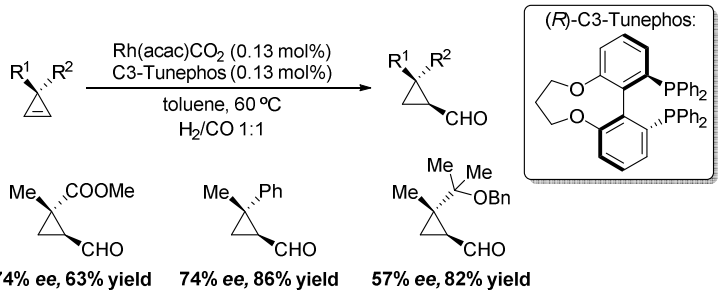
Fox published the enantioselective addition of carbon nucleophiles to 3-hydroxymethylcyclopropenes (*Scheme II-4*).[11] The process built up new stereocenters in a tandem addition/capture sequence. Enantiomerically enriched cyclopropanes with a quaternary stereocenter were prepared in good yields and excellent stereocontrol. One of the limitations is the need to use 3 equivalents of a chiral ligand.



Scheme II-4. Enantioselective carbomagnesation of cyclopropenes.

[10] Rubina, M.; Rubin, M.; Gevorgyan, V. *J. Am. Chem. Soc.* **2004**, *126*, 3688-3689.
[11] Liu, X.; Fox, J. M. *J. Am. Chem. Soc.* **2006**, *128*, 5600-5601.

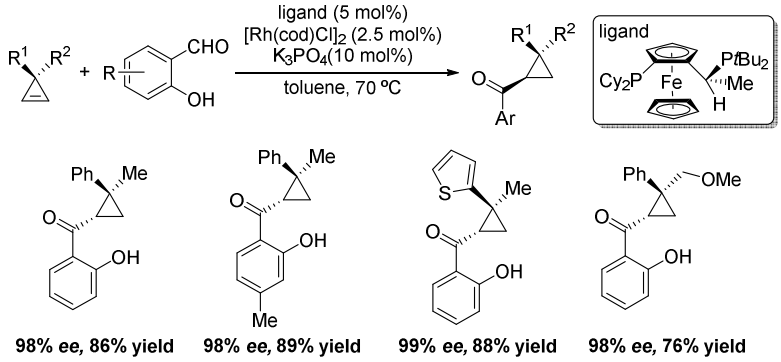
The first catalytic diastereo- and enantioselective hydroformylation of cyclopropenes was reported by Rubin in 2008 (*Scheme II-5*).[12] The reaction proceeded efficiently under mild conditions and low loadings of Rh(I)-catalyst. Moreover, this efficient catalytic carbonylative transformation offered a new atom-economic approach toward the synthesis of optically active cyclopropylcarboxaldehydes.



Scheme II-5. Rhodium(I)-catalyzed asymmetric hydroformylation of cyclopropenes.

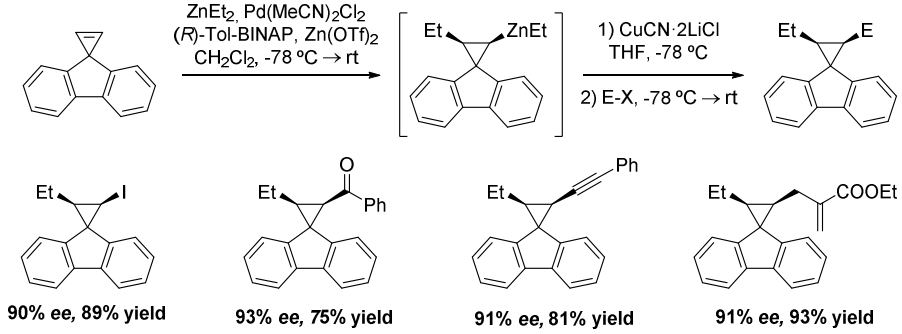
In 2010, Dong developed the enantioselective desymmetrization of cyclopropenes by rhodium-catalyzed hydroacylation (*Scheme II-6*).[13] This catalytic method allowed for the formation of cyclopropylketones with complete diastereocontrol and excellent enantiomeric excess.The method is limited to use of aromatic aldehydes with an *ortho* hydroxyl group.

[12] Sherrill, W. M.; Rubin, M. *J. Am. Chem. Soc.* **2008**, *130*, 13804-13809.
[13] Phan, D. H. T.; Kou, K. G. M.; Dong, V. M. *J. Am. Chem. Soc.* **2010**, *132*, 16354-16355.



Scheme II-6. Enantioselective Rh-catalyzed hydroacylation of cyclopropenes.

Then, Lautens presented a novel enantio- and diastereoselective palladium-catalyzed carbozincation of cyclopropenes.[14] The cyclopropylzinc could be successfully trapped with a range of electrophiles, although transmetalation to copper was necessary to succeed in the last step.



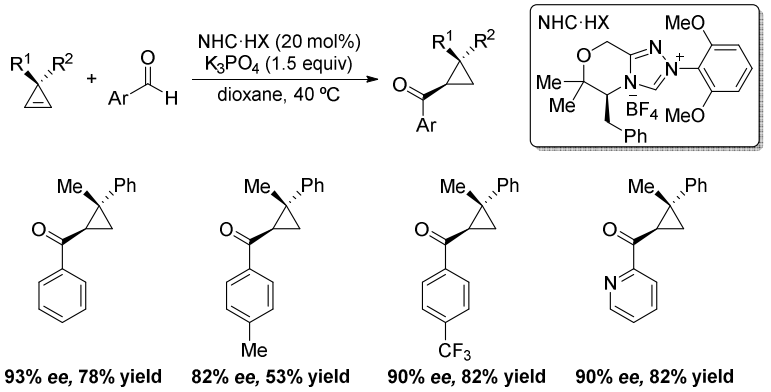
Scheme II-7. Palladium-catalyzed carbozincation of cyclopropenes.

Later, Glorius developed the asymmetric hydroacylation of cyclopropenes catalyzed by *N*-heterocyclic carbenes (NHCs), which are powerful organocatalysts in asymmetric reactions (*Scheme II-8*).[15] They

[14] Krämer, K.; Leong, P.; Lautens, M. *Org. Lett.* **2011**, *13*, 819-821.

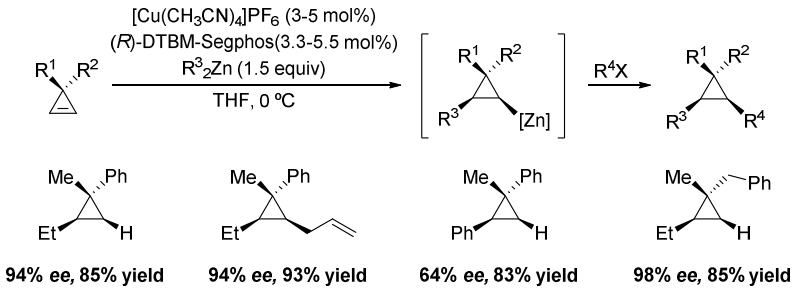
[15] (a) Liu, F.; Bugaut, X.; Schedler, M.; Fröhlich, R.; Glorius, F. *Angew. Chem. Int. Ed.* **2011**, *50*, 12626 -12630. (b) Bugaut, X.; Liu, F.; Glorius, F. *J. Am. Chem. Soc.* **2011**, *133*, 8130-8133. (c) Schedler, M.; Fröhlich, R.; Daniliuc, C. G.; Glorius, F. *Eur. J. Org. Chem.* **2012**, 4164-4171.

designed an *ortho,ortho'*-disubstituted electron-rich triazolium salt that was suitable for the preparation of enantiomerically enriched acylcyclopropanes.



Scheme II-8. Metal-free enantioselective hydroacylation of cyclopropenes.

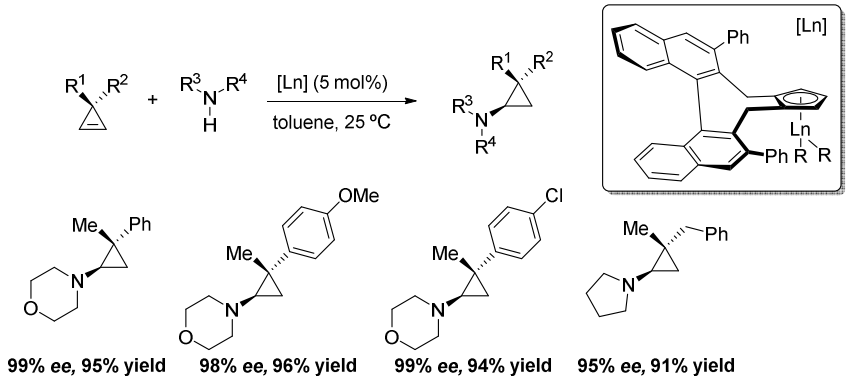
In 2015, subsequent to the investigation described in this chapter, Marek developed the enantioselective synthesis of tri- and tetrasubstituted cyclopropanes via copper-catalyzed carbozincation of cyclopropenes with diorganozinc reagents (*Scheme II-9*).[16] The cyclopropylzinc intermediate could be easily functionalized with a broad range of electrophiles.



Scheme II-9. Cu(I)-catalyzed enantioselective hydrozincation of cyclopropenes.

[16] Müller, D. S.; Marek, I. *J. Am. Chem. Soc.* **2015**, *137*, 15414-15417.

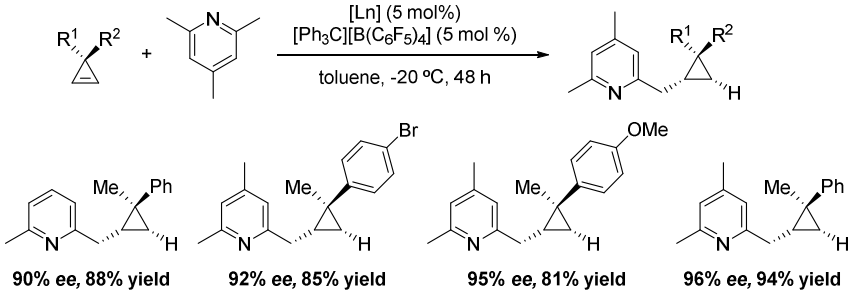
More recently, Hou proposed an atom efficient route for the synthesis of chiral aminocyclopropane derivatives (*Scheme II-10*).[17] They reported the enantioselective hydroamination of substituted cyclopropenes by chiral half-sandwich rare-earth metal complexes. This method allowed for the synthesis of a variety of chiral α-aminocyclopropanes in high yields and excellent diastereo- and enantioselectivities under mild reaction conditions.



Scheme II-10. Enantioselective hydroamination of substituted cyclopropenes.

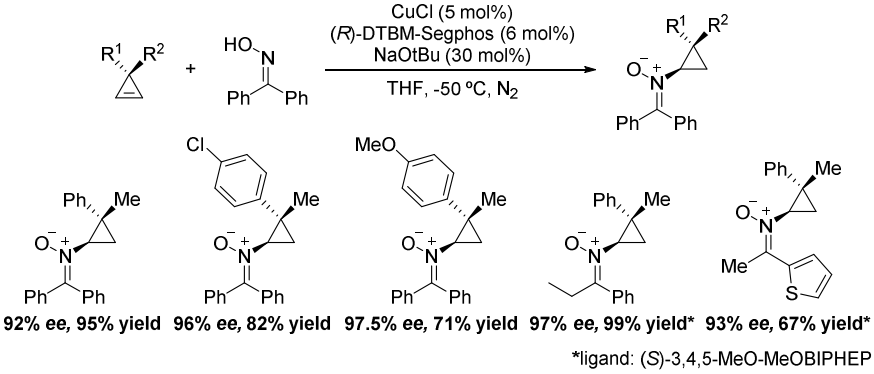
The same group applied this approach to develop the first enantioselective C(sp^3)-H bond addition of 2-methyl azaarenes to various cyclopropenes (*Scheme 11*).[18] This process allowed for the formation of chiral pyridylmethyl-functionalized cyclopropane derivatives with excellent enantioselectivity in an atom-efficient manner.

[17] Teng, H. L.; Luo, Y.; Wang, B.; Zhang, L.; Nishiura, M.; Hou, Z. *Angew. Chem. Int. Ed.* **2016**, *55*, 15406 -15410.
[18] Luo, Y.; Teng, H. L.; Nishiura, M.; Hou, Z. *Angew. Chem. Int. Ed.* **2017**, *56*, 9207-9210.



Scheme II-11. Enantioselective addition of 2-methyl azaarenes to cyclopropenes.

This year, Zhang reported the first access to valuable chiral nitrones through an intermolecular Cope-type hydroamination process of oximes using copper catalysis (*Scheme 12*).[19] This asymmetric cyclopropene "hydronitronylation" was found to be high enantio- and diastereoselective, due to the remarkable ligand directed stererocontrol.



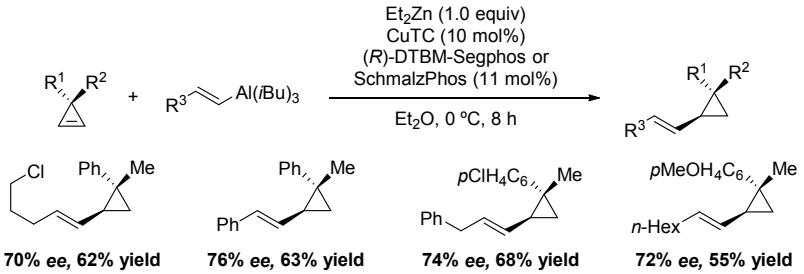
Scheme II-12. Enantioselective hydronitronylation of cyclopropenes.

Recently, Marek developed a general procedure for the enantioselective tandem hydroalumination-vinylmetalation reaction employing copper salts and commercially available chiral phosphines (*Scheme 13*).[20] This challenging process allowed for the use of a wide

[19] Li, Z.; Zhao, J.; Sun, B.; Zhou, T.; Liu, M.; Liu, S.; Zhang, M.; Zhang, Q. *J. Am. Chem. Soc.* **2017**, *139*, 11702-11705.

[20] Müller, D. S.; Werner, V.; Akyol, S.; Schmalz, H. G.; Marek, I. *Org. Lett.* **2017**, *19*, 3970-3973.

range of vinyl nucleophiles and cyclopropene substrates, affording interesting vinylcyclopropane derivatives. Moreover, this strategy was later extended to the use of Grignard reagents, providing access to the asymmetric copper-catalyzed carbomagnesiation of cyclopropenes.[21]



Scheme II-13. Enantioselective hydronitronylation of cyclopropenes.

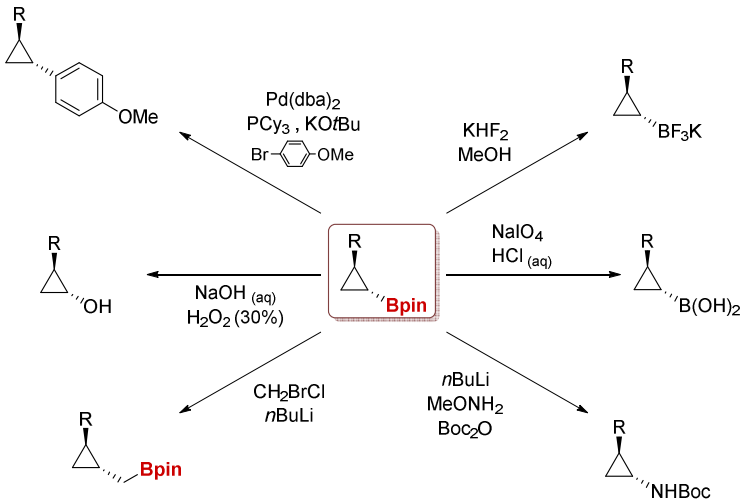
2.1.3. Synthesis of Cyclopropylboronates

As mentioned above, stereodefined small rings with multiple stereocenters are gaining increasing attention because they provide rigidity and at the same time three-dimensionality, both valuable attributes in drug discovery. In this context, chiral cyclopropanes with boron containing stereocenters are expected to be promising synthetic intermediates. They present high configurational stability at the C-B bonds and provide a synthetic handle for further stereospecific transformations.[22] Oxidation, amination, homologation, olefination and

[21] Dian, L.; Müller, D. S.; Marek, I. *Angew. Chem. Int. Ed.* **2017**, *56*, 6783-6787.

[22] (a) Utimoto, K.; Tamura, M.; Tanol, M.; Sisido, K. *Tetrahedron* **1972**, *28*, 5697-5702. (b) Fontani, P.; Carboni, B.; Vaultier, M.; Carrié, R. *Tetrahedron Lett*. **1989**, *30*, 4815-4818 (c) Fontani, P.; Carboni, B.; Vaultier, M.; Maas, G. *Synthesis* **1991**, *8*, 605-609 (d) Hildebrand, J. P.; Marsden, S. P. *Synlett* **1996**, 893-894. (e) Löhr, S.; Meijere, A. *Synlett* **2001**, *4*, 489-492. (f) Marko, I. E.; Giard, T.; Sumida, S.; Gies, A. E. *Tetrahedron Lett.* **2002**, *43*, 2317-2320. (g) Fujioka, Y.; Amii, H. *Org. Lett*. **2008**, *10*, 769-772. (h) Hall, D. G. *Boronic Acids: Preparation and Applicationin Organic Synthesis, Medicine and Materials*, 2nd ed.; Wiley-VCH: Boston, 2011. (i) Sandford, C.; Aggarwal, V. K. *Chem. Commun.* **2017**, *53*, 5481-5494.

cross-coupling reactions offer the possibility to access structurally diverse cyclopropanes from common intermediates *(Scheme II-14*).



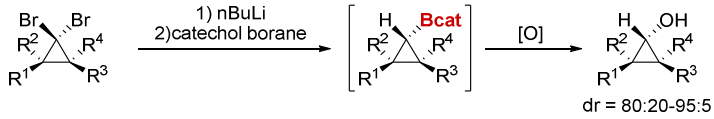
Scheme II-14. Some possible derivatizations from cyclopropylboronates.

Despite the synthetic potential of cyclopropylboronates, the stereoselective methods reported for their preparation are still limited. In this section, we will distinguish between diastereoselective methods and enantioselective approaches for the synthesis of cyclopropylboronates. The first one describes synthetic methods that do not allow for the preparation of enantiomerically enriched compounds. The second section compiles the existing enantioselective methodologies for the preparation of cyclopropylboronates.

2.1.3.1. Diastereoselective Synthesis of Cyclopropylboronates

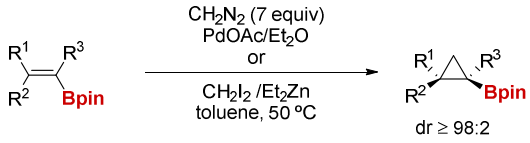
The first stereoselective synthesis of a cyclopropylboronate was published by Danheiser and Savoca in 1985. Starting from dibromocyclopropane (*Scheme II-15*), lithium-halogen exchange followed by reaction with catecholborane formed cyclopropylboronate through a

Matteson-Pasto rearrangement. Unfortunately, the authors were not able to isolate the bcyclopropylboronates. Instead, they *in situ* oxidized the C-B bond to isolate cyclopropanols with excellent diastereoselectivity.[23]



Scheme II-15. Stereoselective synthesis of a cyclopropylboronate.

Vinyl boronic esters have been extensively used to prepare stereodefined cyclopropylboronates. In 1991, Carboni developed a diastereoselective cyclopropanation of vinyl boronates using diazomethane and a palladium catalyst or typical Simmon-Smith conditions (*Scheme II-16*). Cyclopropylboronates were formed with complete stereospecificity.[24] Interestingly, the methodology was also applied for the synthesis of bifuctionalized cyclopropanes. This example represents the first stereoselective synthesis of a cyclopropane substituted with boryl substituents. Several groups have studied the Suzuki-Miyaura cross-coupling reaction of cyclopropylboronates prepared through this methodology.[25]

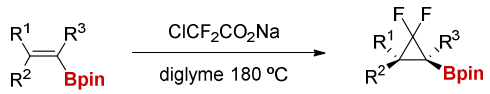


Scheme II-16. Diastereoselective cyclopropanation of vinyl boronates.

For the synthesis of *gem*-difluorocyclopropanes, Amii reported the cyclopropanation of vinylboronates with a difluorocarbene generated *in*

[23] Danheiser, R. L.; Savoca, A. C. *J. Org. Chem.* **1985**, *50*, 2401-2403.
[24] Fontani, P.; Carboni, B.; Vaultier, M.; Maas, G. *Synthesis* **1991**, 605-609.
[25] (a) Hildebrand, J.P.; Marsden, S. P. *Synlett* **1996**, 893. (b) Rossi, R.; Carpita, A.; Ribecai, A.; Mannina, L. *Tetrahedron* **2001**, *57*, 2847-2856.

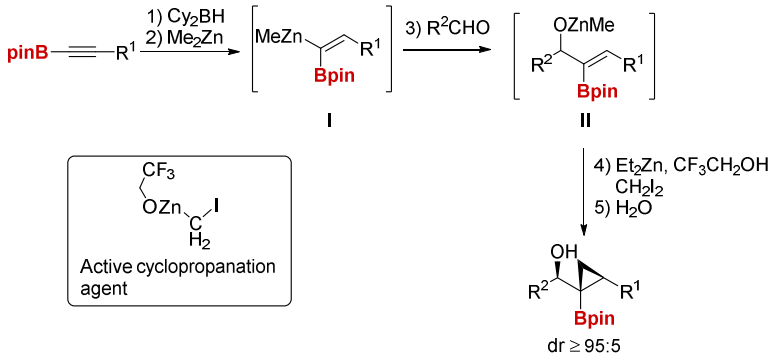
situ from sodium chlorodifluoroacetate in diglyme at 180 °C (*Scheme II-17*). A series of interesting *gem*-difluorocyclopropanes were prepared with excellent diastereoselectivity.[26] Both, *cis* and *trans* cyclopropanes were prepared by the appropriate choice of the geometry of the starting alkenes.



Scheme II-17. Synthesis of *gem*-difluorocyclopropanes.

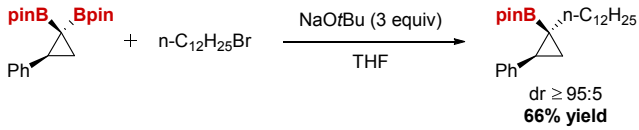
α-Hydroxy vinyl boronic esters have been also used in cyclopropanation reactions (*Scheme II-18*). Walsh developed a tandem carbonyl addition/alkoxide-directed cyclopropanation. The sequence started by generation of a boron-zinc heterobimetallic compound **I**[27] through regioselective hydroboration of an alkynyl boronic ester with dicyclohexylborane followed by selective transmetallation of the Cy_2B-C bond. Reaction of this intermediate with an aldehyde at the Zn-C position, afforded an allylic zinc alkoxide **II** that underwent stereoselective cyclopropanation. The active cyclopropanation reagent was formed by reaction of Et_2Zn, CH_2I_2 and trifluoroethanol. α-Hydroxy cyclopropylboronates were prepared in good yields and high diastereoselectivities.[28]

[26] Fujioka, Y.; Amii, H. *Org. Lett.* **2008**, *10*, 769-772.
[27] (a)Waas, J. R.; Sidduri, A.; Knochel, P. *Tetrahedron Lett.* **1992**, *33*, 3717-3720. (b) Deloux, L.; Skrzypczak-Jankun, E.; Cheesman, B. V.; Srebnik, M.; Sabat, M. *J. Am. Chem. Soc.* **1994**, *116*, 10302-10303. (c) Deloux, L.; Srebnik, M. *J. Org. Chem.* **1994**, *59*, 6871-6873. (d) Deloux, L.; Srebnik, M.; Sabat, M. *J. Org. Chem.* **1995**, *60*, 3276-3277. (e) Molander, G. A.; Ellis, N. M. *J. Org. Chem.* **2008**, *73*, 6841-6844.
[28] Hussain, M. M.; Li, H.; Hussain, N.; Ureña, M.; Carroll, P. J.; Walsh, P. J. *J. Am. Chem. Soc.* **2009**, *131*, 6516-6524.



Scheme II-18. Synthesis of α-hydroxy cyclopropylboronates.

In an elegant work, Morken has used 1,1-bis(pinacolboronate) esters as precursors of α-boryl carbanions, which can react with a variety of alkyl electrophiles (*Scheme II-19*). In one of the examples, the authors used the readily available geminal bis(boryl)cyclopropane for this purpose, obtaining outstanding levels of stereocontrol in the final cyclopropylboronate.[29] It is noteworthy the formation of a tertiary sp^3 boron-containing stereocenter.

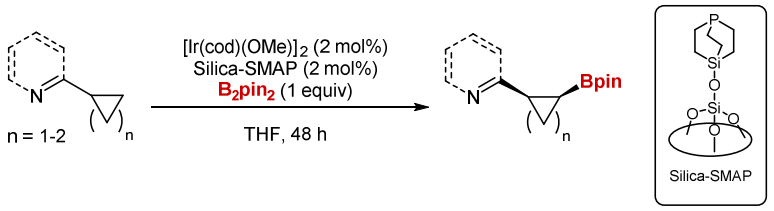


Scheme II-19. Synthesis of cyclopropylboronates from geminal bis(boryl)cyclopropane.

Sawamura studied the C-H activation of cyclopropanes carrying nitrogen-containing substituents.[30] Using a silica-suported monophosphane-Ir catalyst, *cis* cyclopropylboronates were prepared with excellent diastereocontrol (*Scheme II-20*). Pyridines, oxazoles and imines served as directing groups in this transformation. Both the

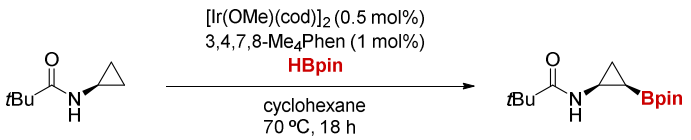
[29] Hong, K.; Liu, X.; Morken, J. P. *J. Am. Chem. Soc.* **2014**, *136*, 10581-10584.
[30] Murakami, R.; Tsunoda, K.; Iwai, T.; Sawamura, M. *Chem. Eur. J.* **2014**, *20*, 13127-13131.

bis(pinacolato)diboron and the pinacolborane produced *in situ* can act as borylating agents



Scheme II-20. Synthesis of *cis* cyclopropylboronates.

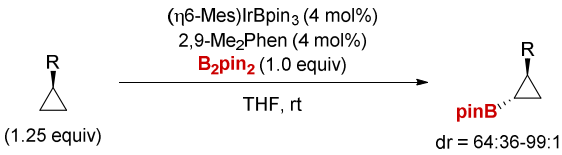
A method for the synthesis of 2-arylcyclopropylamines (ACPAs) was developed by Itami through sequencial C-H borylation and Suzuki-Miyaura coupling (*Scheme II-21*).[31] Starting from readily available *N*-cyclopropylpivalamide, they obtained the *cis* C-H borylation product in high yield using an iridium catalyst and a phenantroline type ligand.



Scheme II-21. Ir-catalyzed C-H borylation of *N*-cyclopropylpivalamide.

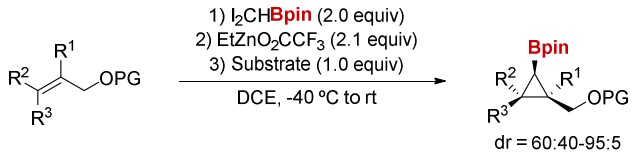
In 2013, Hartwig proposed the synthesis of cyclopropylboronates by C-H activation (*Scheme II-22*).[32] The iridium-catalyzed borylation of cyclopropanes yielded the desired products with high diasteroselectivity. The borylation occurred selectively at the methylene C-H bonds of the cyclopropane ring. Besides, the versatile cyclopropylboronates could be converted into trifluoroborate salts, boronic acids, cyclopropylarenes, cyclopropylamines, and cyclopropanols.

[31] Miyamura, S.; Araki, M.; Suzuki, T.; Yamaguchi, J.; Itami, K. *Angew. Chem. Int. Ed.* **2015**, *54*, 846-851.
[32] Liskey, C. W.; Hartwig, J. F. *J. Am. Chem. Soc.* **2013**, *135*, 3375-3378.



Scheme II-22. Ir-catalyzed C-H borylation of cyclopropanes.

Recently, borocyclopropanation of (*E*)- and (*Z*)-allylic ethers and styrene derivatives via the Simmons-Smith reaction was achieved by Charette using a novel boromethylzinc carbenoid (*Scheme II-23*).[33] 1,2,3-Substituted borocyclopropanes could be afforded in high yields and diastereoselectivities and several post-functionalization reactions illustrated their versatility. Although simple styrenes are suitable compounds for the reaction, the results are not as remarkable as for those protected allylic alcohols, so the scope was quite limited.



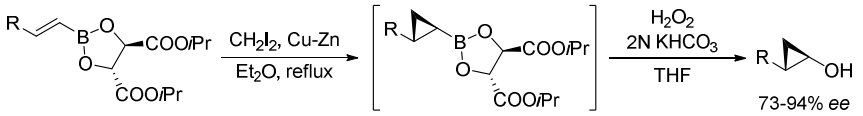
Scheme II-23. Diastereoslective borocyclopropanation.

2.1.3.2. Asymmetric Synthesis of Cyclopropylboronates

The first approach towards the synthesis of optically active cyclopropyl boronates was published in 1990. The asymmetric cyclopropanation of alkenylboronic esters was carried out by diastereofacial selective Simmons-Smith reaction (*Scheme II-24*).[34] The use of boronic esters modified by enantiomerically pure diols provided a chiral auxiliary in the alkene capable to control the selectivity on the

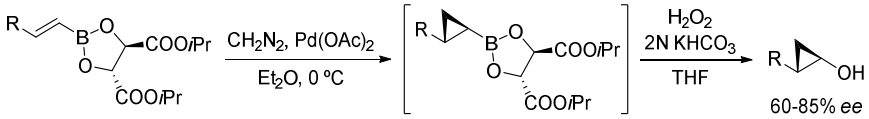
[33] Benoit, G.; Charette, A. B. *J. Am. Chem. Soc.* **2017**, *139*, 1364-1367.
[34] Imai, T.; Mineta, H.; Nishida, S. *J. Org. Chem.* **1990**, *55*, 4986-4988.

cyclization. The cyclopropylboronates were not isolated and subsequent oxidation gave optically active cyclopropanols.



Scheme II-24. First synthesis of enantioeriched cyclopropyl boronates.

Later, the group of Pietruszka reported the cyclopropanation of enantioenriched alkenylboronic esters in presence of diazoamethane and palladium(II) acetate, to afford optically active cyclopropylboronates in excellent yield and good diastereomeric ratio (*Scheme II-25*).[35] Furthermore, this methodology was applied to the synthesis of cyclopropyl analogues of combretastatin A4.[36]



Scheme II-25. Cyclopropanation of optically pure alkenylboronates.

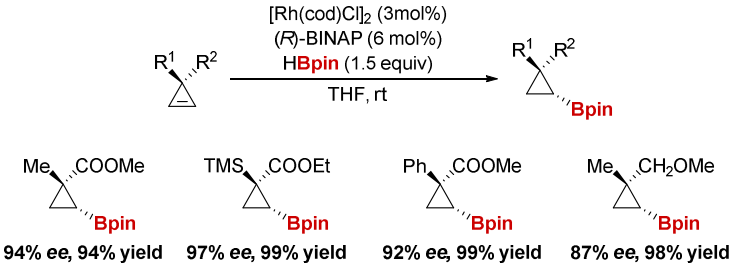
In 2003, Gevorgyan described the first catalytic enantioselective hydroboration of cyclopropenes.[37] This desymmetrization of cyclopropenes, via rhodium-catalyzed hydroboration, provided a facile method for the synthesis of cyclopropylboronates with very high degrees of diastereo- and enantioselectivity using the readily available chiral

[35] (a) Pietruszka, J.; Widenmeyer, M. *Synlett* **1997**, 977-979. (b) Luithle, J. E: A.; Pietruszka, J.; Witt, A. *Chem. Commun.* **1998**, 2651-2652. (c) Zhou, S. M.; Deng, M. Z.; Xia, L. J.; Tang, M. H. *Angew. Chem. Int. Ed.* **1998**, *37*, 2845-2847. (d) Luithle, J. E. A.; Pietruszka, J. *J. Org. Chem.* **1999,** *64,* 8287-8297. (e) Luithle, J. E. A.; Pietruszka, J. *Eur. J. Org. Chem.* **2000**, 2557-2562. (f) Pietruszka, J.; Witt, A.; Frey, W. *Eur. J. Org. Chem.* **2003**, 3219-3229. (g) Pietruszka, J.; Witt, A. *Synlett* **2003**, *1*, 91-94. (h) Lin, H.; Tian, L.; Krauss, I. J. *J. Am. Chem. Soc.* **2015**, *137*, 13176-13182.

[36] Ty, N.; Pontikis, R.; Chabot, G. G.; Devillers, E.; Quentin, L.; Bourg, S.; Florent, J. C. *Bioorg. Med. Chem.* **2013**, *21*, 1357-1366.

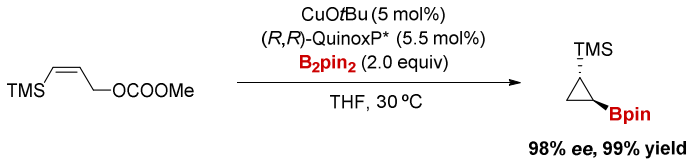
[37] Rubina, M.; Rubin, M.; Gevorgyan, V. *J. Am. Chem. Soc.* **2003**, *125*, 7198-7199.

ligand (*R*)-BINAP (*Scheme II-26*). The limitation of this method was the requirement of an ester or alkoxymethyl substituent on the molecule as directing groups to achieve high degrees of diastereo- and enantiocontrol.



Scheme II-26. Rhodium-catalyzed asymmetric hydroboration of cyclopropenes.

The synthesis of optically active boron-silicon bifunctional cyclopropane derivatives was accomplished by Ito and Sawamura (*Scheme II-27*).[38] The reaction of silicon substituted allylic carbonates with a diboron reagent gave cyclopropylboronates through enantioselective copper(I)-catalyzed borylation. This novel transformation presented unexpected regioselectivity. First, the hydroboration of the alkene takes place, followed by intramolecular nucleophilic attack occurs at the β-position of the leaving group to afford the desired products.

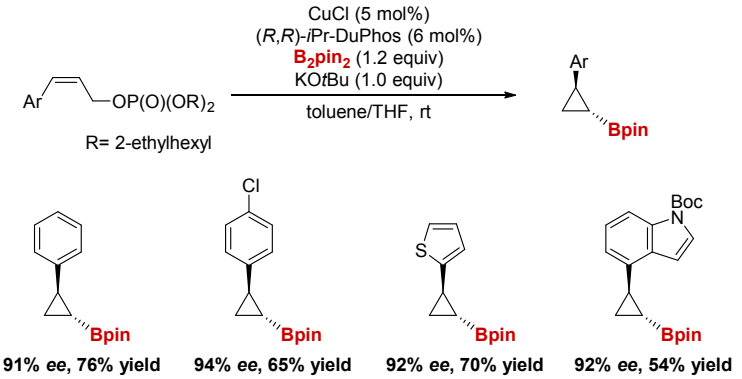


Scheme II-27. Synthesis of enantioenriched boron-silicon cyclopropane derivatives.

Encouraged by these results, they extended this methodology to the use of aryl substituted allylic phosphates. In 2011, they described a new asymmetric route for the synthesis of *trans*-2-aryl- and heteroaryl-

[38] Ito, H.; Kosaka, Y.; Nonoyama, K.; Sasaki, Y.; Sawamura, M. *Angew. Chem. Int. Ed.* **2008**, *47*, 7424 -7427.

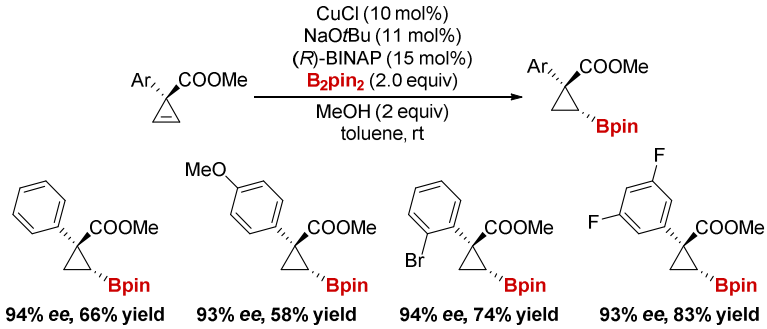
substituted cyclopropylboronates (*Scheme II-28*).[39] Under mild reaction conditions, the reaction afforded optically active arylcyclopropane derivatives in a highly enantioselective manner.



Scheme II-28. Synthesis of enantioenriched cyclopropanes from allylic phosphates.

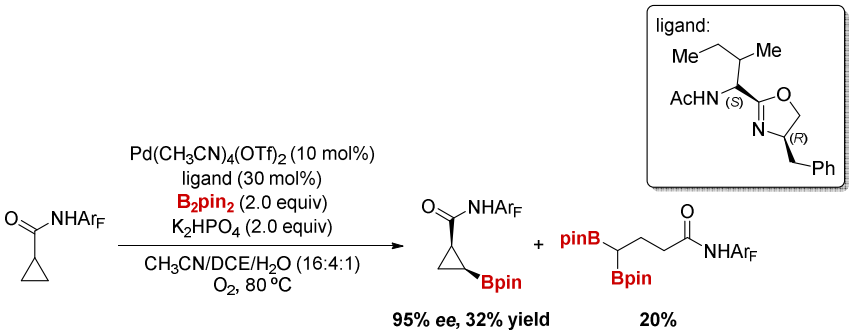
Concurrently to our work, Lin envisioned the synthesis of cyclopropylboronic derivatives from the asymmetric hydroboration of cyclopropenes with an ester group (*Scheme II-29*).[40] Copper(I)-catalyzed enantioselective hydroboration afforded cyclopropylboronates with excellent enantioselectivities in moderate to high yields, through desymmetrization of cyclopropenes. The non-directing effect of the ester group was observed by the formation of *trans*-isomer as single product.

[39] Zhong, C.; Kunii, S.; Kosaka, Y.; Sawamura, M.; Ito, H. *J. Am. Chem. Soc.* **2010**, *132*, 11440-11442.
[40] Tian, B.; Liu, Q.; Tong, X.; Tian, P.; Lin, G. Q. *Org. Chem. Front.* **2014**, *1*, 1116-1122.



Scheme II-29. Copper-catalyzed enantioselective hydroboration of cyclopropenes.

Recently, Yu described the palladium(II)-catalyzed enantioselective C-H borylation (*Scheme II-30*).[41] The formation of new carbon-boron bond by C-H activation was performed for the first time using chiral acetyl-protected aminomethyl oxazoline ligands. This reaction was compatible with a wide variety of substrates, although only one example using cyclopropanes has been documented.

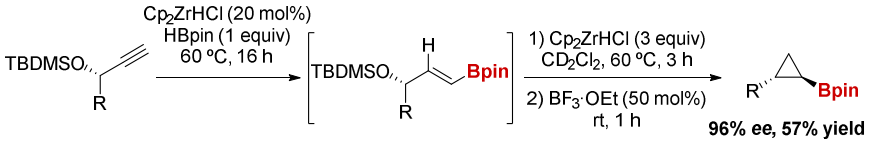


Scheme II-30. Pd(II)-catalyzed C-H borylation of cyclopropanes.

Talbot just published the one-pot, three-step synthesis of cyclopropylboronic esters from propargylic silyl ethers (*Scheme II-31*).[42] The use of enantioenriched propargylic silyl-protected alcohols enabled the Lewis acid-mediated cyclization to afford cyclopropylboronic esters in

[41] He, J.; Shao, Q.; Wu, Q.; Yu, J. Q. *J. Am. Chem. Soc.* **2017**, *139*, 3344-3347.
[42] Spencer, J. A.; Jamieson C.; Talbot, E. P. A. *Org. Lett.* **2017**, *19*, 3891-3894.

moderate diasteremoreic ratio and high enantiopurity. First, zirconium catalyzed hydroboration provided the formation of the corresponding alkenylboronate that underwent hydrozirconation followed by Lewis acid-mediated cyclization to achieve the cyclopropylboronates.



Scheme II-31. Synthesis of cyclopropylboronic esters from propargylic silyl ethers.

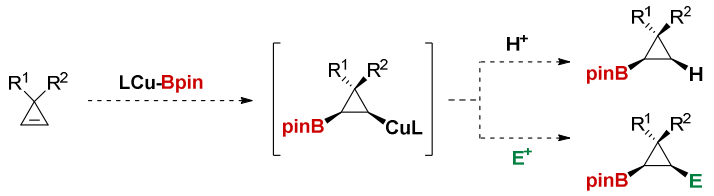
2.2. Synthesis of Cyclopropylboronates through Copper-Catalyzed Desymmetrization of Cyclopropenes

2.2.1. Copper(I)-Catalyzed Borylation

2.2.1.1. Introduction and Objectives

At the beginning of this doctoral thesis, there were only three reports in the literature to prepare enantiomerically enriched cyclopropylboronates (*Schemes II-26*, *II-27* and *II-28*).[37,38,39] Motivated by these limited examples, we decided to explore the possibility of preparing stereodefined cyclopropylboronates through the copper(I)-catalyzed borylation of cyclopropenes. We envisioned that the use of bulky ligands could provide an opportunity to access cyclopropylboronates with control of the diastereo- and enantioselectivity, independently of the substituents on the cyclopropane (*Scheme II-32*). If successful, our approach would be an improvement over Gevorgyan's method, avoiding the use of expensive rhodium catalysts and the need of a directing group on the cyclopropene.

Besides the importance of the products, we were also intrigued about the reactivity of cyclopropenes under copper-catalyzed borylation conditions. Before our investigation, only alkenes with strong electronwithdrawing groups and styrene derivatives had been used in this kind of transformations. The reason is that the HOMO of the copper-boryl complex must interact with a sufficiently low LUMO of an alkene. We reasoned that strain could be a way to lower the LUMO in alkenes that are not electronically biased. Moreover, due to the mechanism involved in the copper-catalyzed borylation of alkenes, we could explore the possibility of trapping the cyclopropylcopper intermediate with electrophiles different than proton (*Scheme II-32*).



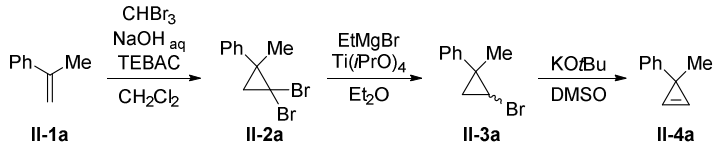
Scheme II-32. Goals of this chapter.

2.2.1.2. Synthesis of a Model Substrate

To start our study, we chose cyclopropene **II-4a** as model substrate (*Scheme II-33*). Our goal was to develop a general method, avoiding the use of directing groups to control the stereoselectivity. Therefore, we looked for susbtituents that could provide some steric differentiation, but without coordinating functional groups.

Cyclopropene **II-4a** was prepared following reported procedures.[43] The synthetic strategy followed to prepare these substrates starts from styrene derivatives (*Scheme II-33*). First, dibromocyclopropanes **II-2a** were synthesized by cyclopropanation of methyl styrene **II-1a** with a dibromocarbene generated *in situ* under phase transfer conditions. [44] Then, the partial reduction of dibromocyclopropanes **II-2a** took place by reaction with ethyl magnesium bromide and catalytic amounts of titanium isopropoxide to afford monobromocyclopropane **II-3a**.[45] Finally, the synthesis of cyclopropene **II-4a** from monobromocyclopropane **II-3a** was carried out in anhydrous DMSO in presence of slight excess of KO*t*Bu.

[43] (a) Rubin, M.; Gevorgyan, V. *Synthesis* **2004**, *5*, 796-800. (b) Sherrill, W. M.; Kim, R.; Rubin, M. *Tetrahedron* **2008**, *64*, 8610-8617.
[44] Makosza, M.; Waurzynienioz, Y. *Tetrahedron Lett.* **1969**, *53*, 4659-4662.
[45] Al Dulayymi, J. R.; Baird, M. S.; Bolesov, I. G.; Nizovtsev, A. V.; Tverezovsky, V. V. *J. Chem. Soc., Perkin Trans.* **2000**, *2*, 1603-1617.



Scheme II-33. Synthesis of (1-methylcycloprop-2-en-1-yl)benzene **II-4a**.

2.2.1.3. Copper-Catalyzed Borylation of Cyclopropenes Using non-Chiral Ligands: Screening of Conditions

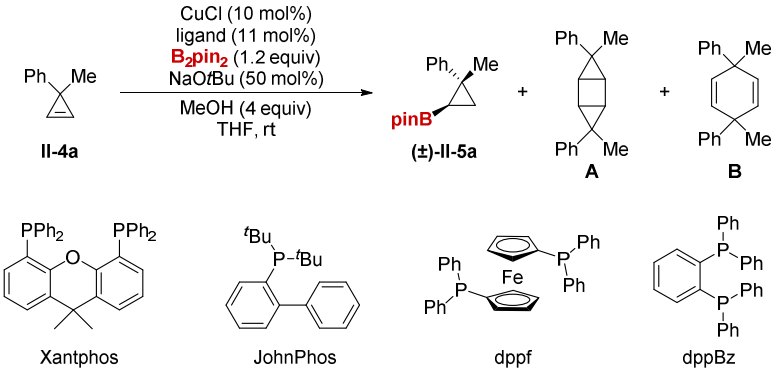
With cyclopropene **II-4a** in hand, we studied first the reactivity under copper(I)-catalyzed borylation conditions using non-chiral ligands (Table 1). We started using conditions previously employed in our group for the borylation of allylic epoxides and alkynes. Treatment of **II-4a** with CuCl (10 mol%), xantphos (11 mol%), NaO*t*Bu (50 mol%), B_2pin_2 (1.1 equiv) and 4 equivalents of MeOH, in THF at room temperature, afforded the desired product **(±)-II-5a** with excellent diastereoselectivity but only moderate yield (*entry 1, Table II-1*). The low yield was due to the formation of dimers **A** and **B**, as byproducts in the reaction. Compound **A** came from the [2+2] cycloaddition of cyclopropene **II-4a**, most likely catalyzed by the metal, and cyclohexadiene **B** derived from the electrocyclic ring opening of **A**.[46] This result was not very surprising since dimerization is one of the most common undesired pathways in transition-metal-catalyzed reactions with cyclopropenes.[12]

For a while we were stuck on that problem. When we carried out the reaction at -20 ºC, we observed a slight improvement in the yield. However, further lowering the temperature, changing the copper salt, the solvent, the ligand and the proton source did not improve over that result (*entry 2, Table II-1*). Although the yield increased, the formation of the undesired dimers was not completely avoided. After extensive

[46] Binger, P.; Biedenbach, B. *Chem. Ber.* **1987**, *120*, 601-605.

experimentation, we observed that addition of cyclopropene **II-4a** and MeOH to a -78 °C solution of the preformed xantphos-copper-boryl complex, followed by warming to -20 °C afforded **(±)-II-5a** in excellent yield as a single diastereoisomer (*entry 3, Table II-1*). Once the optimized temperature was found, different phosphines were tested (*entries 4-8, Table II-1*).We observed that the yield and the diastereoselectivity were highly dependent on the ligand. In the absence of ligand (*entry 9, Table II-1*) dimers **A** and **B** were obtained as major products.

Table II-1. Optimization of the diastereoselective borylation of cyclopropenes.



Entry[a]	ligand	T (ºC)	dr[b]	yield (%)[c]
1	xantphos	23	95:5	30-40
2	xantphos	-20	≥98:2	60
3[d]	***xantphos***	***-20***	***≥98:2***	***90***
4[d]	JohnPhos	-20	86:14	41
5[d]	PPh_3	-20	85:15	43
6[d]	PCy_3	-20	82:18	18
7[d]	dppf	-20	≥98:2	14
8[d]	dppBz	-20	75:25	29
9	-	-20	97:3	10[e]

[a]Reaction conditions: **II-4a** (0.2 mmol), B_2pin_2 (0.22 mmol), NaO*t*Bu (0.1 mmol), CuCl (10 mol%), ligand (11 mol%), MeOH (0.8 mmol), THF (0.33 M). [b]Determined by ^{1}H NMR analysis. [c]Yield of isolated **II-5a**. [d]Cyclopropene **II-4a** and MeOH were added at -78 ºC and then warmed up to -20 ºC. [e]An inseparable mixture of **A** and **B** was obtained in 90% yield.

2.2.1.4. Copper-catalyzed Borylation of Cyclopropenes Using Chiral Ligands: Screening of Conditions

Although we were pleased about the results obtained in the diastereoselective approach, our ultimate goal was to control, not only the diastereoselectivity but also the enantioselectivity of the reaction. We started testing several commercially available ligands with different steric and electronic properties using the previously optimized conditions for xantphos (*Table II-2*). Ligands with a central chirality at the phosphorus atom (**L1** and **L2**), ferrocenyl derivatives (**L3** and **L4**) and ligand with C2 symmetry (**L5**-**L8** and **L12**-**L14**) were used in the screening. Among them, the Segphos family (**L9**-**L11**) was found to be more suitable for this transformation. The bulkiest (*R*)-DTBM-Segphos (**L11**) was found to be superior controlling the diastereo and enantioselectivity of the process, affording cyclopropane (*R*,*R*)-**II-5a** in 71% yield and 92:8 enantiomeric ratio (*entry 11, Table II-2*).

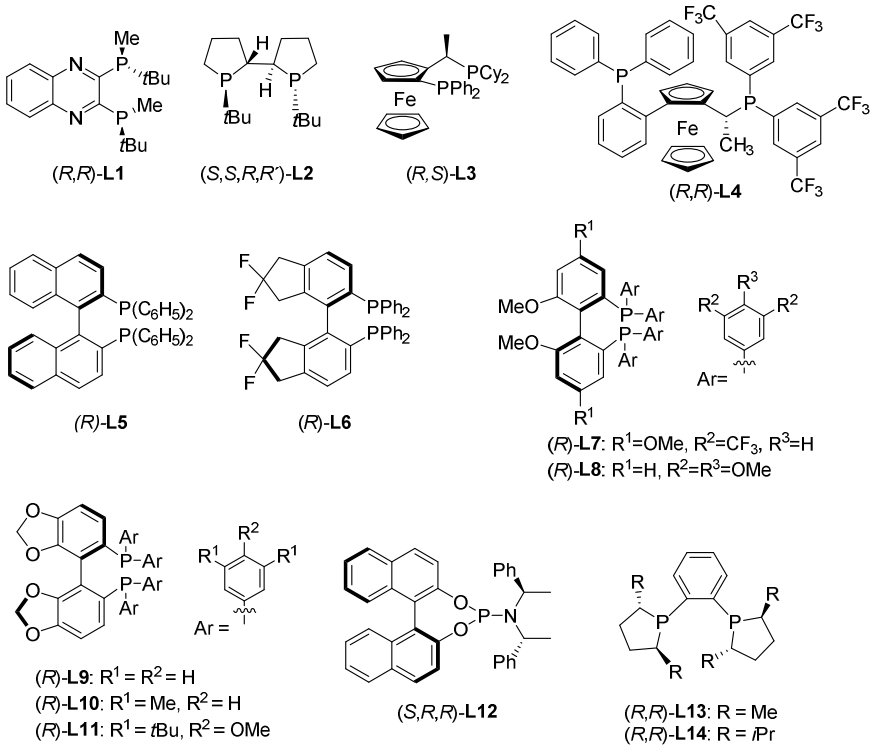
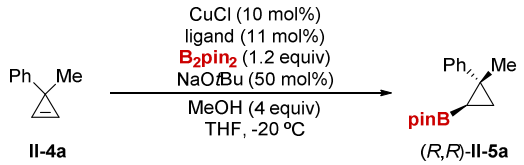


Figure 2. List of tested chiral ligands.

Table II-2. Screening of chiral ligands.



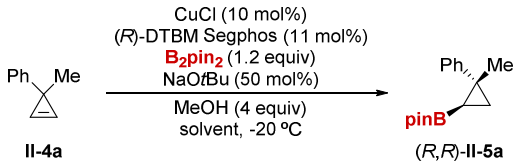
II-4a (*R*,*R*)-**II-5a**

Entry[a,b]	ligand*	dr[c]	*er*[d]	yield[e] (%)
1	**L1**	70:30	77:23	70
2	**L2**	-	-	traces
3	**L3**	91:9	42:58	65
4	**L4**	95:5	28:72	60
5	**L5**	96:4	78:22	49
6	**L6**	85:15	80:20	93
7	**L7**	77:33	55:45	33
8	**L8**	≥98:2	71:29	43
9	**L9**	89:11	81:19	55
10	**L10**	94:6	82:18	70
11	***L11***	***≥98:2***	***92:8***	***71***
12	**L12**	97:3	53:47	45
13	**L13**	95:5	60:40	15
14	**L14**	95:5	36:64	20

[a]Reaction conditions: **II-4a** (0.2 mmol), B_2pin_2 (0.22 mmol), NaO*t*Bu (0.1 mmol), CuCl (10 mol%), ligand (11 mol%), MeOH (0.8 mmol), THF (0.33 M). [b]Cyclopropene **II-4a** and MeOH were added at -78 °C; the reaction mixture was then warmed up to -20 °C. [c]Determined by ^{1}H NMR analysis. [d]*er* determined by chiral SFC. [e]Yield of isolated **II-5a**.

Once we had the optimal ligand, we study the reaction in a wide variety of aprotic solvents (*entries 1-10, Table II-3*). The best results were observed using THF. Other ethers were also tested (*entries 11-13, Table II-3*), but none of them improved the results obtained with THF.

Table II-3. Screening of solvents.

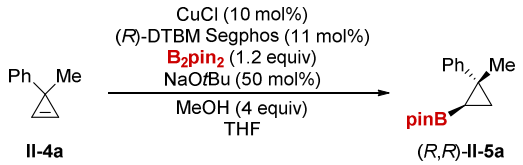


Entry[a,b]	solvent	dr[c]	*er*[d]	yield (%)[e]
1	***THF***	***≥98:2***	***92:8***	***71***
2	Toluene	90:10	75:25	30
3	CH_2Cl_2	93:7	72:28	31
4	CH_3CN	97:3	81.5:18.5	62
5	CH_3Cl	-	-	NR[f]
6	DCE	≥98:2	60:39	84
7	DME	90:10	82:18	58
8	DMF	94:6	66:34	27
9	EtOAc	≥98:2	82:12	68
10	*t*BuOAc	93:7	80:20	39
11	Et_2O	88:22	75:25	14
12	2-Me-THF	≥98:2	84:16	74
13	*t*BuOMe	90:10	71:29	62

[a]Reaction conditions: **II-4a** (0.2 mmol), B_2pin_2 (0.22 mmol), NaO*t*Bu (0.1 mmol), CuCl (10 mol%), (*R*)-DTBM-Segphos (11 mol%), MeOH (0.8 mmol), solvent (0.33 M). [b]Cyclopropene **II-4a** and MeOH were added at -78 °C; the reaction mixture was then warmed up to -20 °C. [c]Determined by ^{1}H NMR analysis. [d]*er* determined by chiral SFC. [e]Yield of isolated **II-5a**. [f]NR: no reaction.

Then, we found that the effect of the temperature did not follow a linear progress. The optimal result was obtained at -20 ºC and the yield and stereoselectivity dropped down at lower or higher temperatures (*entries 1-6, Table II-4*).

Table II-4. Screening of temperature and concentration.



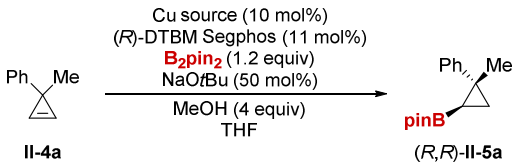
Entry[a,b]	Concentration	T (ºC)	dr[c]	*er*[d]	yield (%)[e]
1	0.33	23	≥98:2	87:13	55
2	0.33	0	96:4	80:20	68
3	0.33	-10	95:5	92:8	70
4	***0.33***	***-20***	***≥98:2***	***92:8***	***71***
5	0.33	-40	94:6	82:16	78
6	0.33	-78	≥98:2	85:15	73

[a]Reaction conditions: **II-4a** (0.2 mmol), B_2pin_2 (0.22 mmol), NaO*t*Bu (0.1 mmol), Cu(I) (10 mol%), (*R*)-DTBM-Segphos (11 mol%), MeOH (0.8 mmol), THF. [b]Cyclopropane **II-4a** and MeOH were added at -78 °C; the reaction mixture was then warmed up to the corresponding temperature. [c]Determined by ^{1}H NMR analysis. [d]*er* determined by chiral SFC.[e]Yield of isolated (*R,R*)- **II-5a**.

After significant screening of conditions, we found the best results using CuCl (10 mol%), (*R*)-DTBM Segphos (11 mol%), B_2pin_2 (1.2 equiv) and MeOH (4 equiv). However, we observed that the enantiomeric ratio was hard to reproduce, with values varying inconsistently from 85:15 to 92:8. Trying to solve this problem, we performed the reaction with different copper sources (*Table II-5*). $Cu(OAc)_2$, Cu(OAc), CuBr and CuTC afforded the desired compound with lower stereocontrol. Interestingly, $Cu(OAc)_2$ gave the opposite enantiomer as the major compound, although with low yield (*entries 2-5, Table II-5*). A first attempt using $[Cu(CH_3CN)_4]PF_6$ (*entry 6, Table II-5*) afforded (*R,R*)-**II-5a** with high diastereoselectivity but only moderate yield and enantioselectivity. Gratifyingly, when the acetonitrile was removed in vacuo after phosphine-copper complex formation (*entry 7, Table II-5*), the desired compound was consistently obtained in high yield (74%) with excellent diastereo- and enantioselectivity (dr = 97:3, *er* = 95:5). We also

tried to decrease the catalyst loading, although the use of 5 mol % of $[Cu(CH_3CN)_4]PF_6$ resulted in lower yield and poorer enantioselectivity (*entry 8, Table II-5*). Finally, no reaction was observed in the absence of a copper salt, ruling out a possible metal-free borylation through phosphine or base activation of the diboron compound (*entry 9, Table II-5*).[47]

Table II-5. Screening of copper sources.



Entry[a,b]	Cu source	dr[c]	*er*[d]	yield (%)[e]
1	CuCl	≥98:2	92:8	71
2	$Cu(OAc)_2$	90:10	24:75	36
3	CuBr	96:4	87:13	76
4	CuTC[f]	96:4	90:10	76
5	CuOAc	93:7	89:11	72
6	$[Cu(CH_3CN)_4]PF_6$	96:4	82:18	58
7	***$[Cu(CH_3CN)_4]PF_6$***	***97:3***	***95:5***	***74***[g]
8	$[Cu(CH_3CN)_4]PF_6$	95:5	90:10	50[h]
9	-	-	-	NR[i]

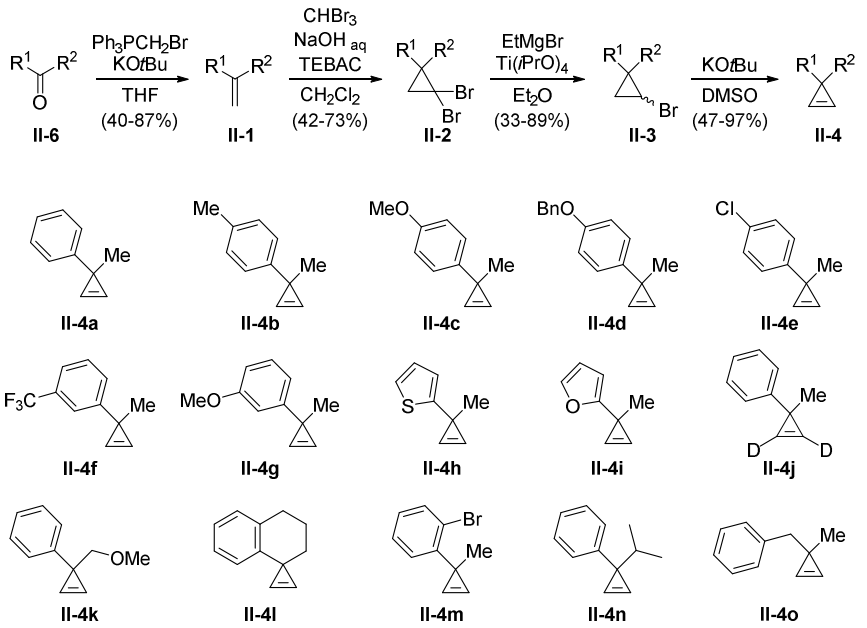
[a]Reaction conditions: **II-4a** (0.2 mmol), B_2pin_2 (0.22 mmol), NaO*t*Bu (0.1 mmol), Cu(I) (10 mol%), (*R*)-DTBM-Segphos (11 mol%), MeOH (0.8 mmol), THF (0.33 M). [b]Cyclopropane **II-4a** and MeOH were added at -78 °C; the reaction mixture was then warmed up to the corresponding temperature. [c]Determined by ^{1}H NMR analysis. [d]*er* determined by chiral SFC. [e]Yield of isolated (*R,R*)-**II-5a**. [f]CuTC: Copper(I)-thiophene-2-carboxylate. [g]CH_3CN was removed in vacuum after phosphine-copper complex formation. [h]5% of $[Cu(CH_3CN)_4]PF_6$ was used. [i]NR: no reaction.

[47] (a) Bonet, A.; Lillo, A.; Ramírez, J.; Díaz-Requejo, M.; Fernandez, E. *Org. Biomol. Chem*, **2009**, *7*, 1533-1535. (b) Pubill-Ulldemolins, C.; Bonet, A.; Bo, C.; Gulys, H.; Fernandez, E. *Chem. Eur. J.* **2012**, *18*, 1121-1126.

2.2.1.5. Scope of the Reaction

To study the scope of the reaction a wide variety of (3,3-disubstituted) cyclopropenes (**II-4**) were synthesized (*Scheme II-34*), using the same synthetic sequence as for **II-4a**. In some cases, the starting alkene was not commercially available and one more step was required.

In case of non-commercial styrene derivatives, we started from the corresponding ketone **II-6** (*Scheme II-34*), which underwent Wittig olefination after treatment with methyl triphenylphosphonium salt in the presence of KO*t*Bu. Subsequent cyclopropene **II-4** was prepared. Then, dibromocyclopropane **II-2** were synthesized by cyclopropanation of methyl styrene **II-1** with a dibromocarbene generated *in situ*.[44] Partial reduction of dibromocyclopropanes **II-2** by reaction with ethyl magnesium bromide and catalytic amounts of titanium isopropoxide afforded monobromocyclopropane **II-3**.[45] Finally, cyclopropene **II-4** was achieved from monobromocyclopropane **II-3a** in the presence of slight excess of KO*t*Bu in anhydrous DMSO.



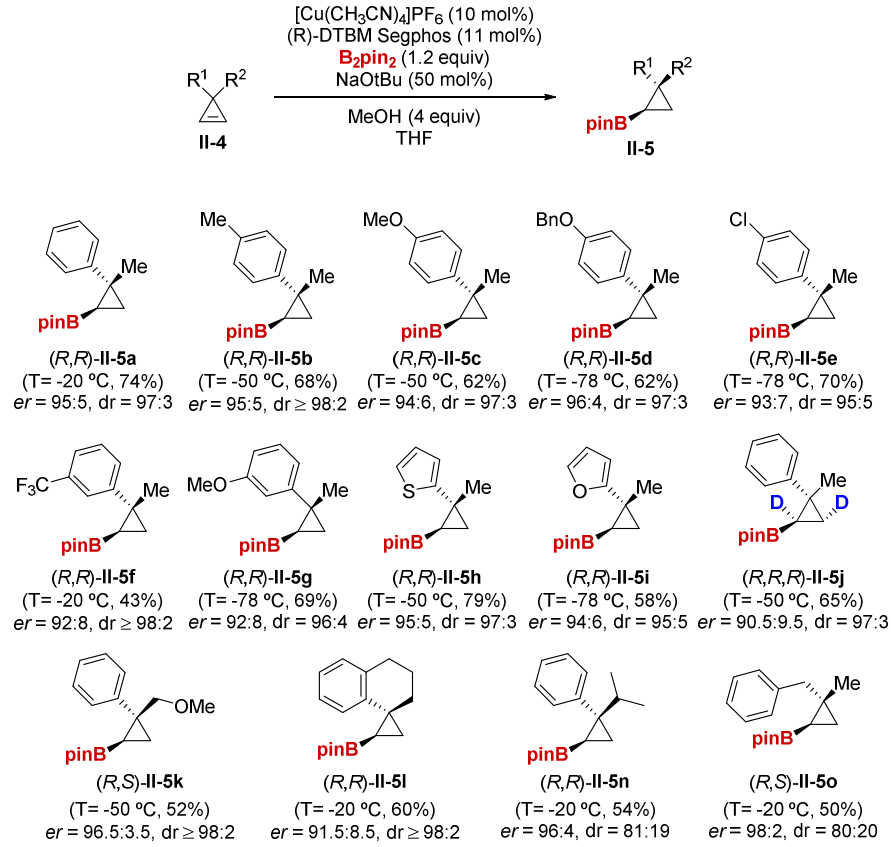
Scheme II-34. Synthesis of (3,3-disubstituted) cyclopropenes (**II-4**).

Next, we applied the optimized copper-catalyzed borylation conditions to the synthesized cyclopropenes (*Scheme II-35*). In some cases, the reaction was carried out at -20, -50 or -78 °C to optimize the enantiomeric ratio.

Compounds bearing electron-donating groups (**II-4b**, **II-4c** and **II-4d**) on the phenyl ring afforded the corresponding cyclopropylboronates (*R*,*R*)-**II-5b**, (*R*,*R*)-**II-5c** and (*R*,*R*)-**II-5d** with similar efficiency to the model substrate (*R*,*R*)-**II-5a**. Cyclopropenes with electron-deficient aryl groups underwent the borylation in good yields and high diastereoselectivities although slightly lower enantiomeric ratios (compounds (*R*,*R*)-**II-5e** and (*R*,*R*)-**II-5f**). Moreover, substitution at the *meta* position of the aryl group also seemed to have little effect on the enantioselectivity (*R*,*R*)-**II-5g** (*para* 94:6 vs *meta* 92:8). Compounds bearing an heterocylic ring, as (*R*,*R*)-**II-5h** and (*R*,*R*)-**II-5i**, were also prepared in good yields and high stereocontrol. Starting from dideuterated

II-4j, compound (*R*,*R*,*R*)-**II-5j** with three contiguous stereocenters was successfully achieved.

Additionally, coordinating groups (CH_2OMe) were also compatible with the hydroboration conditions and compound (*R*,*S*)-**II-5k** was obtained with excellent results. Cyclopropane (*R*,*R*)-**II-5l**, bearing a spiro-quaternary stereocenter, was also synthesized with high levels of stereocontrol. As expected, bulkier groups on the cyclopropene (R^2 = *i*Pr, (*R*,*R*)-**II-5n**) decreased the diastereoselectivity but the enantiocontrol was still excellent. Likewise, cyclopropane (*R*,*S*)-**II-5o** bearing two alkyl groups (R^1 = Bn, R^2 = Me) was successfully obtained with lower diastereoselectivity than (*R*,*R*)-**II-5a** but high enantioselectivity.

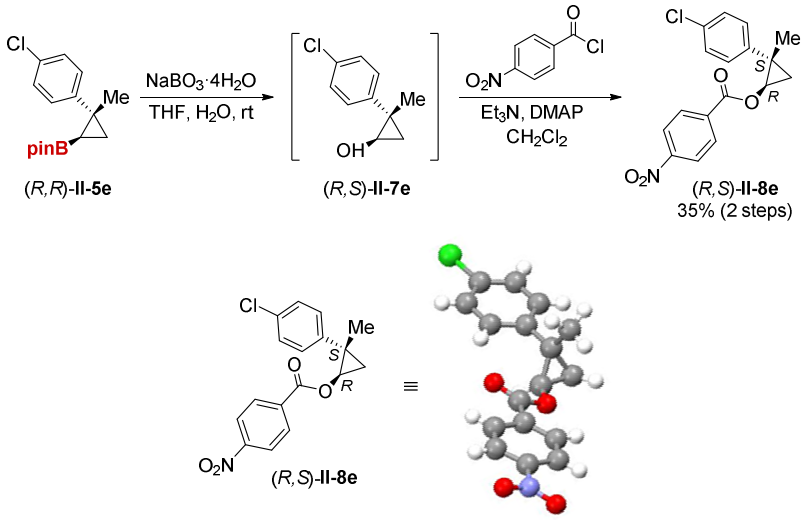


Scheme II-35. Scope of the enantioselective hydroboration.[48]

The absolute configuration of (*R*,*R*)-**II-5e** was determined from single crystal X-ray crystallography of a *p*-nitrobenzoate (*R*,*S*)-**II-8e** derivative (*Scheme II-36*). Oxidation of the carbon-boron bond with sodium perborate,[49] followed by benzoylation with 4-nitrobenzoyl chloride afforded compound (*R*,*S*)-**II-8e**. The absolute configuration of all the other cyclopropylboronates was assigned by analogy.

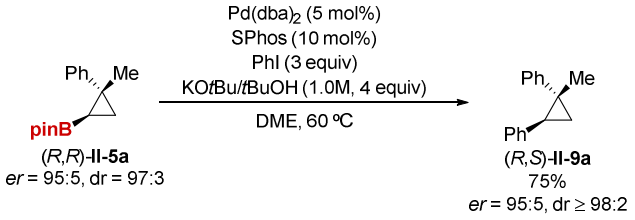
[48] Reaction conditions: **II-4** (0.2 mmol), B_2pin_2 (0.22 mmol), NaO*t*Bu (0.1 mmol), CuCl (10 mol %), (*R*)-DTBM-Segphos (11 mol %), MeOH (0.8 mmol), THF (0.33 M). Yield of isolated **II-5**; er determined by chiral SFC and dr determined by ^{1}H NMR analysis.

[49] Kabalka, G. W.; Shoup, T. M.; Goudgaon, N. M. *Tetrahedron Lett.* **1989**, *30*, 1483-1486.



Scheme II-36. Determination of absolute configuration by X-ray structure of (*R*,*S*)-**II-8e**.

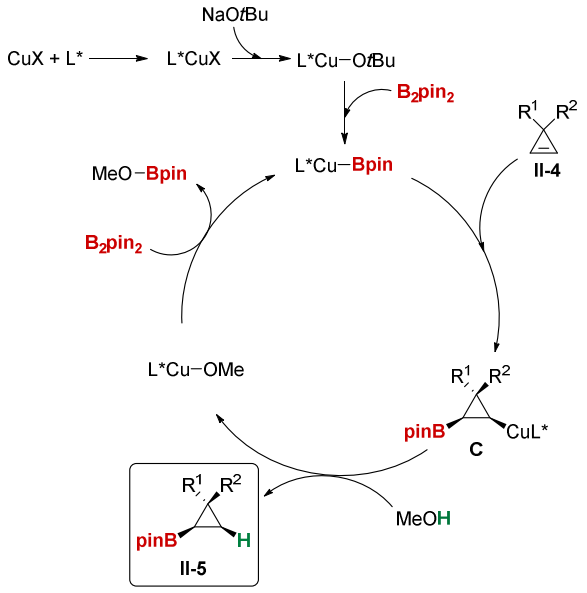
To further demonstrate the utility of the cyclopropylboronates we studied the palladium-catalyzed Suzuki-Miyaura cross-coupling between (*R*,*R*)-**II-5a** and iodobenzene (*Scheme II-37*).[38] Treatment of (*R*,*R*)-**II-5a** and iodobenzene in the presence of $Pd(dba)_2$, SPhos as ligand and a solution of KO*t*Bu in *t*BuOH afforded the cross-coupling product in good yield. Importantly, the (*R*,*S*)-**II-9a** was obtained with complete stereoretention.



Scheme II-37. Suzuki-Miyaura cross-coupling between (*R*,*R*)-**II-5a** and iodobenzene.

2.2.1.6. Mechanistic Proposal

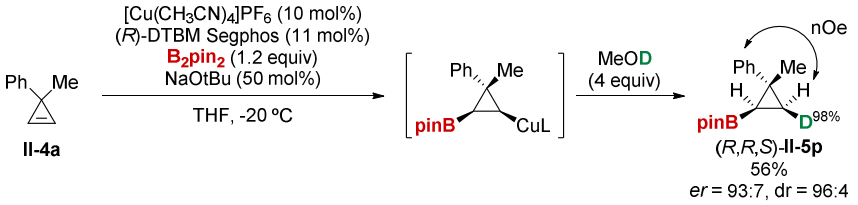
A possible mechanism for the copper(I)-catalyzed borylation of cyclopropenes is proposed in *Scheme II-38*. First, a copper alkoxide is formed by reaction of the ligand, the copper salt and sodium *tert*-butoxide. This alkoxide (L*Cu-O*t*Bu) could undergo a σ-bond methatesis reaction with bis(pinacolato)diboron to form a chiral copper-boryl complex (L*Cu-Bpin). Then, insertion of the cyclopropene would afford a cyclopropyl copper intermediate **C**. Reaction with MeOH would provide the hydroboration product and copper-methoxide (L*Cu-OMe) that would start over the catalytic cycle.



Scheme II-38. Proposed mechanism for copper-catalyzed borylation.

To account for the formation of a cyclopropylcopper intermediate **C** we performed the reaction in the presence of MeOD (*Scheme II-39*). Compound (*R*,*R*,*S*)-**II-5p** was obtained in good yield and high stereoselectivity (*er* = 93:7, dr = 96:4, >98% D incorporation). This

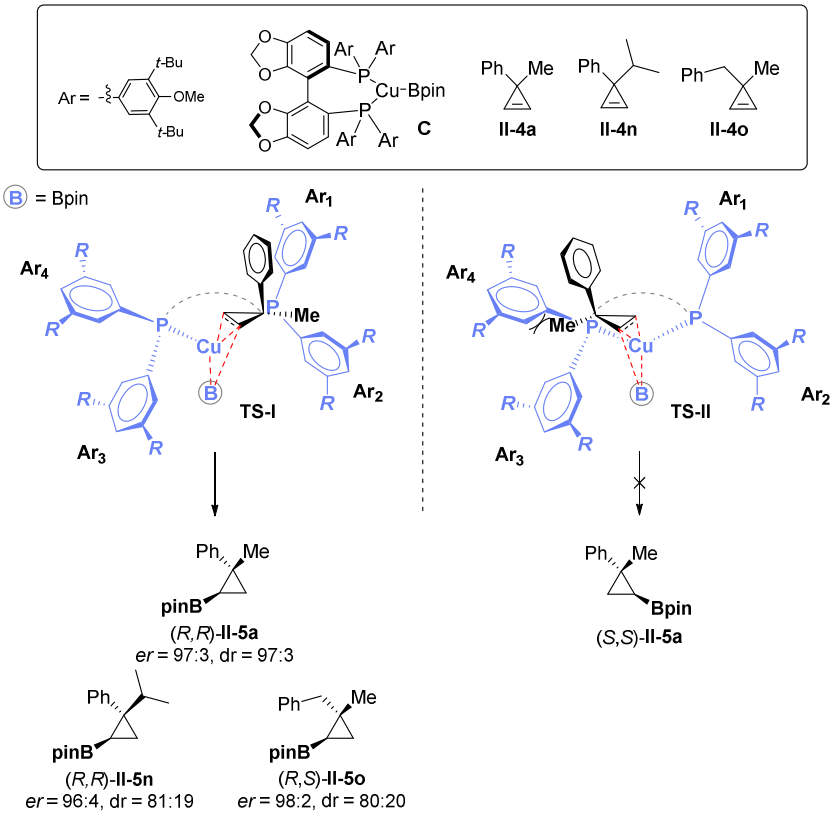
experiment demonstrated the *syn* insertion of the cyclopropene in the copper-boryl complex. The *syn* relationship between the deuterium and the boron atom was confirmed by nOe experiments of (*R*,*R*,*S*)-**II-5p**.



Scheme II-39. Deuteration experiment.

2.2.1.7. Proposed Transition-State Models for the Copper-Catalyzed Hydroboration of Cyclopropenes

The following rational, based on molecular mechanics modeling (AMBER), was used to explain the diastereo- and enantioselectivity of the reaction (*Scheme II-40*). The biphenyl backbone in complex **A** is crucial to fix the conformation of $\mathbf{Ar_1}$-$\mathbf{Ar_4}$ on the phosphorous atoms and to effectively block one of the faces of complex **A**, but does not ultimately determine the cyclopropene approach. Therefore, to simplify the drawings of **TS-I** and **TS-II** we have only shown the part of the copper-boryl complex **A** that interacts directly with the cyclopropene. For clarification, in **TS-I** and **TS-II** the cyclopropene is approaching the catalyst complex from above the plane.



Scheme II-40. Proposed transition-state models.

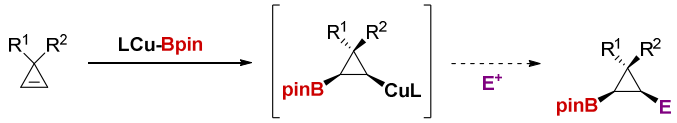
We proposed that the diastereoselectivity is controlled by steric interactions between the Me and Ph substituents of the cyclopropene and the **Ar** rings of the chiral phosphine. The diastereoselectivity of the reaction is determined by approach of the cyclopropene with either the Me or Ph group facing toward the boryl copper phosphine complex. In the case of Me and Ph, the clear steric difference between these groups affords consistently excellent diastereoselectivity. However, when either group is changed to reduce the steric differentiation {e.g., *i*Pr for Me [(*R*,*R*)-**II-5n**] or Bn for Ph [(*R*,*S*)-**II-5o**]} a noticeable reduction in the selectivity is observed (81:19 and 80:20, respectively).

The absolute stereochemistry of the reaction can be explained by comparison of the transition states during the insertion of the cyclopropene into the Cu-B bond (**TS-I** and **TS-II**). Transition state **TS-I** is free from steric repulsion between the methyl group and $\mathbf{Ar_1}$-$\mathbf{Ar_2}$ of the chiral ligand, affording (*R,R*)-**II-4a** as the major enantiomer. However, **TS-II** is destabilized by steric repulsion between the methyl group and $\mathbf{Ar_4}$.

2.2.2. Copper(I)-Catalyzed Aminoboration

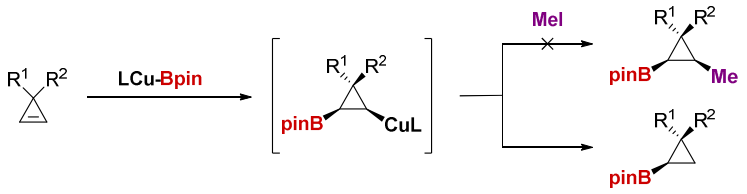
2.2.2.1. Introduction and Objectives

One of the attractive features for developing a copper-catalyzed borylation of cyclopropenes, was the possibility of trapping the cyclopropylcopper intermediate with electrophiles different than proton (*Scheme II-41*).



Scheme II-41. Proposed reaction by the use of different elctrophiles.

First, we tried the use of alkyl halides, such as methyl iodide, in analogy to the copper(I)-catalyzed carboboration of alkynes, previously developed in our group. Unfortunately, the reaction failed under these conditions, affording just the hydroboration product in low yield (*Scheme II-42*).



Scheme II-42. First attempt for copper(I)-catalyzed carboboration.

Then, we turned our attention to electrophilic *O*-benzoyl-*N*,*N*-dialkylhydroxylamines,[50] which had been successfully used in copper-catalyzed transformations, but never before for the desymmetrization of cyclopropenes.[51]

The expected products would be cyclopropylaminoboronates with three contiguous stereocenters, difficult to prepare by known methods. In addition, cyclopropylamines are interesting compounds present in a wide number of biologically active compounds.[52]

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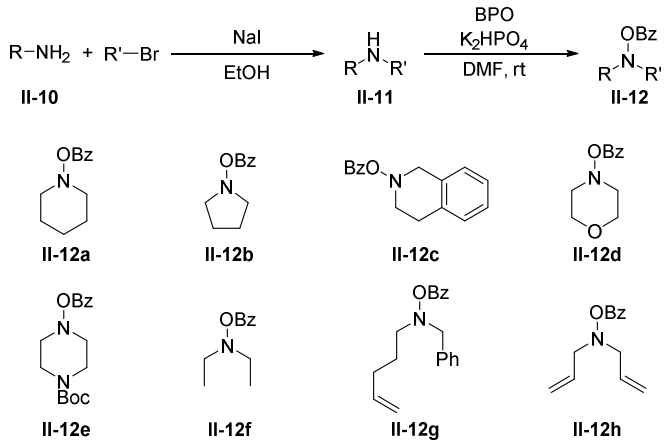
[50] Berman, A. M.; Johnson, J. S. *J. Am. Chem. Soc.* **2004**, *126* , 5680-5681

[51] 1) For copper-catalyzed electrophilic amination reaction, see: (a) Berman, A. M.; Johnson, J. S. *J. Org. Chem.*, **2006**, *71*, 219-224. (b) Hirano, K.; Satoh, T.; Miura, M. *Org. Lett.* **2011**, *13*, 2395-2397. (c) Matsuda, N.; Hirano, K.; Satoh, T.; Miura, M. *Org. Lett.* **2011**, *13*, 2860-2863. (d) Matsuda, N.; Hirano, K.; Satoh, T.; Miura, M. *J. Org. Chem.* **2012**, *77*, 617-625. (e) Matsuda, N.; Hirano, K.; Satoh, T.; Miura, M. *Synthesis* **2012**, *12*, 1792-1797. (f) Matsuda, N.; Hirano K.; Satoh, T.; Miura, M. *Angew. Chem. Int. Ed.* **2012**, *51*, 3642-3645. (g) Matsuda, N.; Hirano, K.; Satoh, T.; Miura, M. *Angew. Chem. Int. Ed.* **2012**, *51*, 11827-11831. (h) Miki, Y.; Hirano, K.; Satoh, T.; Miura, M. *Org. Lett.* **2013**, *15*, 172-175. (i) Sakae, R.; Hirano, K.; Satoh, T.; Miura, M. *Chem. Lett.* **2013**, *42*, 1128-1130. (j) Zhu, S.; Niljianskul, N.; Buchwald, S. L. *J. Am. Chem. Soc.* **2013**, *135*, 15746-15749. (k) Miki, Y.; Hirano, K.; Satoh, T.; Miura, M. *Angew. Chem. Int. Ed.* **2013**, *52*, 10830-10834. (l) Zhu, S.; Buchwald, S. L. *J. Am. Chem. Soc.* **2014**, *136*, 15913–15916. (m) Niljianskul, N.; Zhu, S.; Buchwald, S. L. *Angew. Chem. Int. Ed.* **2015**, *54*, 1638-1641. (n) Shi, S. L.; Buchwald, S. L. *Nat. Chem.* **2015**, *7*, 38-44. (o) Niu, D.; Buchwald, S. L. *J. Am. Chem. Soc.* **2015**, *137*, 9716-9721. (p) Yang, Y.; Shi, S. L.; Niu, D.; Liu, P.; Buchwald, S. L. *Science* **2015**, *349*, 62-66. (q) Bandar, J. S.; Pirnot, M. T.; Buchwald, S. L. *J. Am. Chem. Soc.* **2015**, *137*, 14812-14818. (r) Pirnot, M. T.; Wang, Y. M.; Buchwald, S. L. *Angew. Chem. Int. Ed.* **2016**, 55, 48-57.
2) For copper-catalyzed aminoboration reaction, see: (a) Matsuda, N.; Hirano, K.; Satoh, T.; Miura, M. *J. Am. Chem. Soc.* **2013**, *135*, 4934-4937. (b) Sakae, R.; Matsuda, N.; Hirano, K.; Satoh, T.; Miura, M. *Org. Lett.* **2014**, *16*, 1228-1231. (c) Sakae, R.; Hirano, K.; Miura, M. *J. Am. Chem. Soc.* **2015**, *137*, 6460-6463. (d) Sakae, R.; Hirano, K.; Satoh, T.; Miura, M. *Angew. Chem. Int. Ed.* **2015**, *54*, 613-617. (e) Jiang, H. C.; Tang X. Y.; Shi, M. *Chem. Commun.* **2016**, *52*, 5273-5276.

[52] (a) Hargrave, K. D.; Proudfoot, J. R.; Grozinger, K. G.; Cullen, E.; Kapadia, S. R.; Patel, U. R.; Fuchs, V. U.; Mauldin, S. C.; Vitous, J.; Behnke, M. L.; Klunder, J. M.; Pal, K.; Skiles, J. W.; McNeil, D. W.; Rose, J. M.; Chow, G. C.; Skoog, M. T.; Wu, J. C.;

2.2.2.2. Synthesis of Starting Materials

To explore this approach, we prepared a series of *O*-benzoyl-*N*,*N*-dialkylhydroxylamines following reported procedures. The synthetic sequence to prepare these hydroxyl amines derivatives starts with the synthesis of a secondary amine **II-11** by alkylation reaction of a primary amine **II-10** (*Scheme II-44*).[53] In most cases, dialkylamines **II-11** were commercially available so this step was omitted. Then, oxidation of amine **II-11** in presence of benzoyl peroxide and dibasic potassium phosphate, in dimethylformamide, afforded hydroxylamine derivatives **II-12**.[54]



Scheme II-44. Synthesis of hydroxylaminederivatives **II-12**.

Schmidt, G.; Engel, W. W.; Eberlein, W. G.; Saboe, T. D.; Campbell, S. J.; Rosenthal, A. S.; Adams, J. *J. Med. Chem.* **1991**, *34*, 2231-2241. (b) Kelly, T. A.; Patel, U. R. *J. Org. Chem.* **1995**, *60*, 1875-1878. (c) Asai, A.; Tsujita, T.; Sharma, S. V.; Yamashita, Y.; Akinaga, S.; Funakoshi, M.; Kobayashi, H.; Mizukami, T. *Biochem. Pharmacol.* **2004**, *67*, 227-234.

[53] Gribkov, D. V.; Hultzsch, K. C. *Angew. Chem. Int. Ed.* **2004**, *43*, 5542-5546.

[54] Berman, A. M.; Johnson, J. S. *J. Org. Chem.* **2006**, *71*, 219-224.

2.2.2.3. Copper-Catalyzed Aminoboration of Cyclopropenes: Screening of conditions

As we did for the hydroboration reaction, we started our study using non-chiral phosphines. Unfortunately, the conditions found for the diastereoselective hydroboration of cyclopropene **II-4a** (*entry 1*, *Table II-6*) were not optimal for the aminoboration reaction.Although the formation of cyclopropylaminoboronate **II-13d** was observed, several unknown byproducts were also produced and the diastereoselectivity was poorer. One undesired pathway was the reaction between the base, NaO*t*Bu, and the electrophilic amine. This problem was solved by changing the base to LiO*t*Bu. We then studied the effect of the ligand in the transformation. We used ferrocenyl type ligands as well as mono and bidentate phosphines (*entries 1-6*, *Table II-6*). The best results were observed when1,1′-ferrocenediyl-bis(diphenylphosphine) (dppf) was employed.

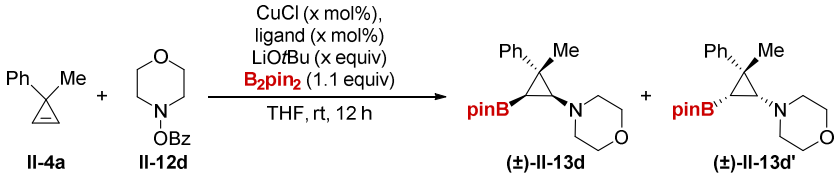
The ^{1}H NMR of the crude product showed a clean conversion, but the product was isolated in low yield after column chromatography on silica (*entry 6*, *Table II-6*). Finally, we were pleased to find that purification through florisil® gave compound (±)-**II-13d** with an acceptable isolated yield.

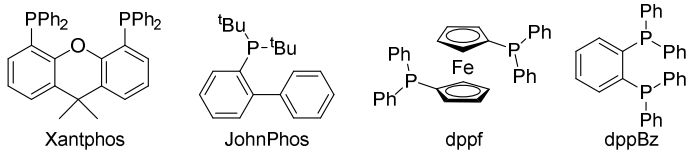
With the optimal ligand in hand, we tried to decrease the amount of base, but unfortunately lower yield was observed (*entry 7*, *Table II-6*). Gratifyingly, when lower loading of catalyst was used (5 mol%) the yield was slightly improved (*entry 8*, *Table II-6*).

Thus, the use of CuCl/dppf (5 mol %) and LiO*t*Bu (3.0 equiv) in THF in the presence of **II-4a**, **II-12d** and B_2pin_2, allowed for the synthesis of cyclopropylaminoboronate (±)-**II-13d** in good yield and excellent diastereomeric ratio (*entry 8*, *Table II-6*). Surprisingly, the reaction was

carried out at room temperature without observing significant amounts of dimerization products **A** and **B**.

Table II-6. Screening of achiral phosphines





Entry[a]	CuCl (mol%)	LiO*t*Bu (equiv)	Ligand(mol%)	dr[b]	Conversion (yield %)[c,d]
1	10	3.0	xantphos (10)	88:12	100
2	10	3.0	dppbz (10)	52:48	100
3	10	3.0	JohnPhos (10)	64:36	100
4	10	3.0	PCy_3 (10)	76:24	100
5	10	3.0	PPh_3 (10)	76:24	100
6	10	3.0	dppf (10)	97:3	100 (61)
7	10	2.0	dppf (10)	97:3	100 (53)
8	***5***	***3.0***	***dppf (5)***	***97:3***	***100 (62)***

[a]Reaction conditions: **II-4a** (0.2 mmol), **II-12h** (0.3 mmol), B_2pin_2 (0.22 mmol), THF (0.2 M). [b]ratio**II-13d:II-13d'**, determined by ^{1}H NMR analysis. [c]Conversion determined by ^{1}H NMR analysis. [d]Yield of isolated **II-13d** is shown within brackets.

Unfortunately, the diastereoselectivity of the reaction was highly dependent on the ligand, which made very difficult the development of an enantioselective version. We tried several structurally different chiral ligands, but in all cases the diastereomeric ratio was inferior to that observed with dppf. Moreover, we could not separate the diastereomers by column chromatography and the products seemed to decompose through chiral HPLC columns. Consequently, we were not able to measure yields

orenantiomeric ratios. At this point we decided to study the scope just in the racemic series.

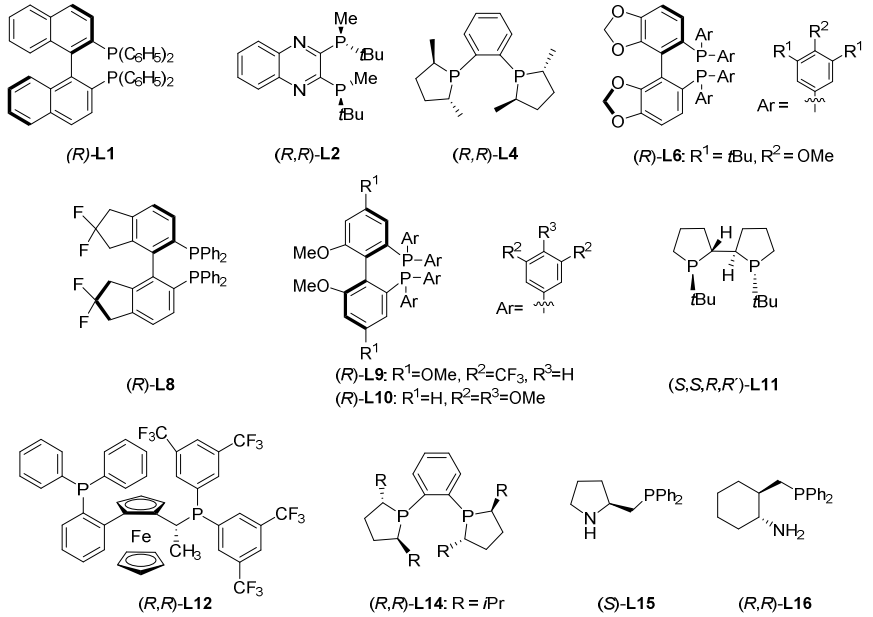
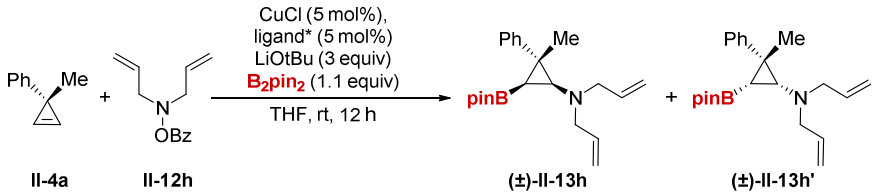


Figure 3. List of tested chiral ligands

Table II-7. Screening of chiral phosphines



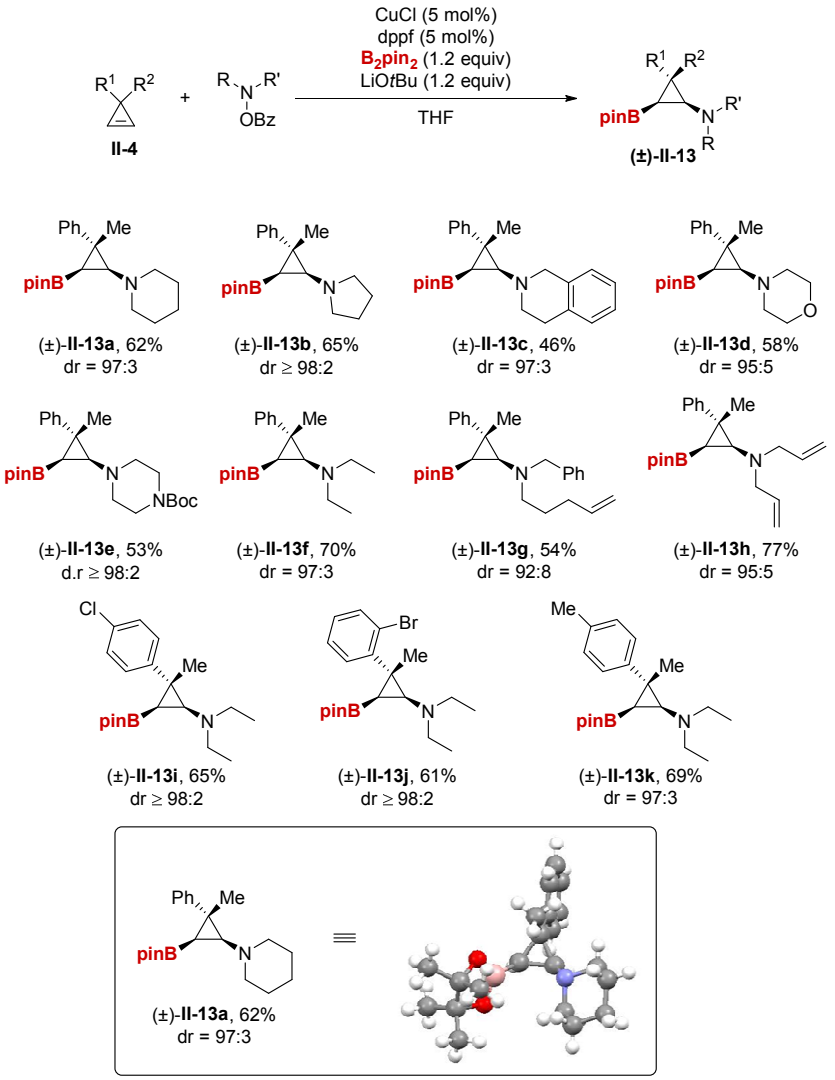
Entry[a]	Chiral ligand	dr[b] (**II-13h**:**II-13h'**)
1	**L1**	77:23
2	**L2**	94:6
3	**L4**	66:34
4	**L6**	61:39
5	**L8**	77:23
6	**L9**	73:27
7	**L10**	73:27
8	**L11**	75:25
9	**L12**	68:32
10	**L14**	66:34
11	**L15**	90:10
12	**L16**	90:10

[a]Reaction conditions: **II-4a** (0.2 mmol), **II-12h** (0.3 mmol), B_2pin_2 (0.22 mmol), CuCl (0.01 mmol), ligand (0.01 mmol), LiO*t*Bu (0.6 mmol), THF (0.2 M). [b]Determined by ^{1}H NMR analysis.

2.2.2.4. Scope of the Reaction

The optimized conditions found for the preparation of **(±)-II-13d** were tested with a variety of *O*-benzoyl-*N*,*N*-dialkylhydroxylamines to determine the scope of the aminoboration. Piperidine, pyrrolidine, tetrahydroisoquinoline, morpholine, and piperazine derivatives (±)-**II-13a-e** (*Scheme II-45*) were synthesized in high yields and excellent diastereocontrol. Moreover, cyclopropylaminoboronates bearing an

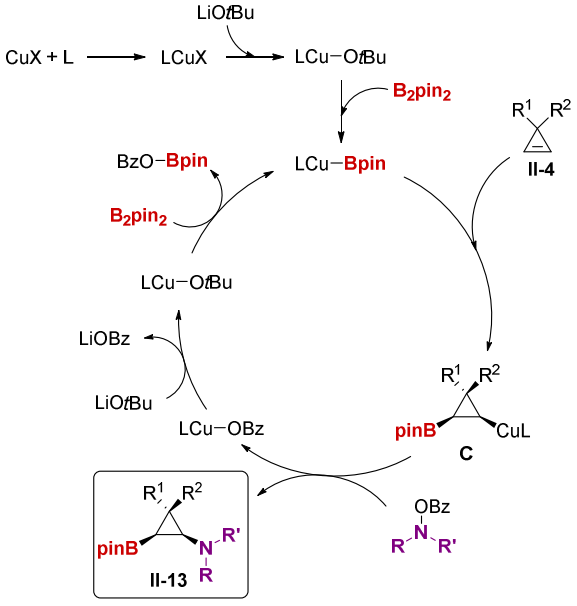
acyclic *N*,*N*-dialkylaminemoiety were alsoprepared through this method [compounds (±)-**II-13f**, (±)-**II-13g** and (±)-**II-13h**]. Additionally, we performed the reaction with cyclopropenes bearing different substituents on the aromatic ring. Halogenated susbtituents in *ortho* and *para* positions as well as a methyl group in *para* were well tolerated. Compounds (±)-**II-13i**, (±)-**II-13j** and (±)-**II-13k** were prepared with almost perfect diastereocontrol. In all cases, *syn* orientation of nitrogen and boron substituents was obtained. The relative configuration of the products was confirmed by X-ray crystal analysis of (±)-**II-13a** (*Scheme II-45*).



Scheme II-45. Scope of the diastereoselective aminoboration.

2.2.2.5. Mechanistic proposal

We proposed the following catalytic cycle for the synthesis of cyclopropylaminoboronates (*Scheme II-46*). As for the hydroboration reaction, the cycle starts with the formation of copper alkoxide (LCu-O*t*Bu) that later undergoes σ-bond methatesis reaction with bis(pinacolato)diboron to form a copper-boryl complex (LCu-Bpin). Then, insertion of cyclopropene allows for the formation of a cyclopropyl copper intermediate **C** that can be trapped by the electrophilic amine to afford cyclopropylaminoboronates **II-13**.



Scheme II-46. Proposed mechanism for copper-catalyzed aminoboration.

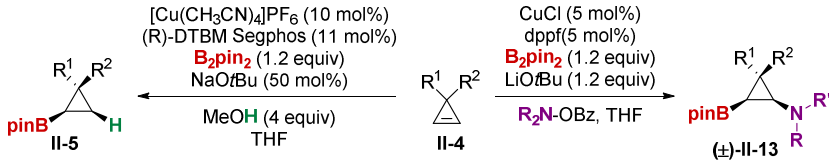
2.2.3. Conclusions

In this chapter, we describe the first diastereo- and enantioselective copper-catalyzed hydroboration of cyclopropenes. This method allows for the synthesis of enantiomerically enriched cyclopropylboronates with a quaternary stereocenter and represents the first enantioselective copper-catalyzed desymmetrization of cyclopropenes (*Scheme II-47*).

Finding the optimal conditions was not easy and several problems, such as dimerization of the cyclopropenes and reproducibility issues were successfully overcome.

Our approach nicely complements the few existing methods to synthesize non-racemic cyclopropylboronates and gives new insights into the enantioselective metal-catalyzed desymmetrization of cyclopropenes.

Additionally, the capture of the cyclopropylcopper intermediate with electrophilic amines highlights the synthetic potential of this approach and opens a new way to synthesize functionalized cyclopropanes.



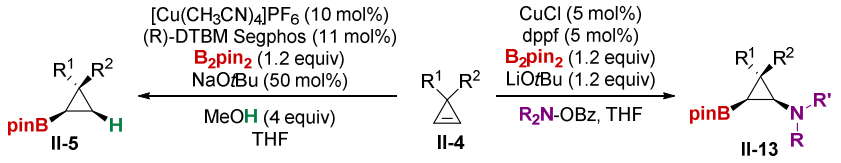
Scheme II-47. Copper(I)-catalyzed hydro- and aminoboration.

2.2.4. Conclusiones

En este capítulo hemos descrito la primera hidroboración diastereo- y enantioselectiva de ciclopropenos catalizada por cobre(I). Este método permite la síntesis de ciclopropilboronatos enantioméricamente enriquecidos con un estereocentro cuaternario y representa la primera desimetrización enantioselectiva de ciclopropenos catalizada por cobre (*Esquema II-44*).

Encontrar las condiciones óptimas no fue sencillo, ya que diversos problemas surgieron a lo largo de la optimización, como por ejemplo la formación del producto de dimerización y dificultades en la reproducibilidad de los resultados obtenidos.

Esta aproximación complementa los pocos métodos existentes para la síntesis de ciclopropilboronatos enantioméricamente enriquecidos. Además, el intermedio ciclopropil cobre formado se ha podido capturar con aminas que presentan carácter electrófilo. Esto junto con las diversas funcionalizaciones que se llevaron a cabo demuestra el potencial sintético de esta transformación.



Esquema II-44. Hidro- y aminoboración catalizadas por cobre(I).

2.3. Supplementary data

2.3.1. General Experimental Details

Tetrahydrofuran, toluene, acetonitrile and dichloromethanewere purified by passing through a Pure Solv™ column drying system from Innovative Technology, Inc. Additionally, THF and methanol were degassed through three consecutive freeze-pump-thaw cycles. Diethyl ether, chloroform, dichloroethane, dimethoxyethane, ethylacetate, dibutyl ether, *tert*-butylacetate, *tert*-butylmethyl ether and 2-methyltetrahydrofuran weredried using activated 4Å molecular sieves and stored under argon. Dry-DMSO and dry-DMF were acquired from comercial sources. Unless indicated otherwise, all reactions were conducted under an argon atmosphere using flame-dried glassware with standard vacuum-line techniques.

NMR spectra were acquired on a Bruker 300 spectrometer, running at 300, and 75 MHz for ^{1}Hand ^{13}C, respectively. Chemical shifts (δ) are reported in ppm relative to residual solvent signals ($CDCl_3$, 7.26 ppm for ^{1}H NMR and 77.2 ppm for ^{13}C NMR respectively). ^{13}C NMR spectra were acquired on a broad band decoupled mode. The following abbreviations are used to describe peak patterns when appropriate: s (singlet), d (doublet), t (triplet), q (quartet), quint (quintet), m (multiplet), br (broad). Analytical thin layer chromatography (TLC) was performed using pre-coated aluminum-backed plates (Merck Kieselgel 60 F254) and visualized by ultraviolet irradiation or phosphomolybdic acid dip or potassium permanganate dip. Purification of reaction mixtures was carried out by flash chromatography (FC) using silica gel Merck-60 or Florisil® 100-200 mesh from Aldrich. Optical rotations were measured on a Perkin-Elmer 241 polarimeter. The enantiomeric ratio (*er*) of the products was determined by stationary phase SFC using chiral columns. Mass

Spectrometry (MS) and High Resolution Mass Spectrometry (HRMS) were registered in a spectrometer *GCT Agilent Technologies 6890N*using Electronic Impact (EI) techniques at 70 eV. Melting points were determined in a *GallenKamp*apparatus in open capillary tubes.

All ligands, $[Cu(CH_3CN)_4]PF_6$, benzoyl peroxide, piperidine, pyrrolidine, tetrahidroisolquinoline, morpholine, diehtylamine, diallylamine, *N*-BOC-piperazine, benzylamine, α-methylstyrene, 4-chloro-α-methylstryene, NaO*t*Bu (2.0 M solution in THF), LiO*t*Bu (solid)and all arylmethylketoneswere acquired from comecial sources and were used without further purification.

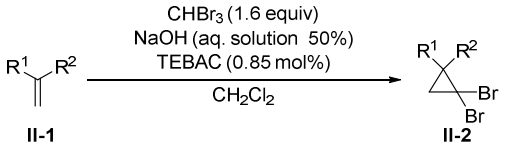
CuCl was washed with acetic acid, filtered and washed with ethanol and ethyl ether twice and dried under vacuum before used.[55] Bis(pinacolato)diboron was recrystrallized in *n*-pentane before used.

Styrenes **II-1a** and **II-1e** were commercially available, styrene derivatives (**II-1b**,[43] **II-1c**,[43] **II-1d**,[43] **II-1f**,[43] **II-1g**,[56] **II-1h**,[13] **II-1i**,[13] **II-1l**,[13] **II-1n**[57] and **II-1o**[58]), benzoyl amines (**II-12a,**[54] **II-12b,**[54] **II-12c,**[52] **II-12d,**[54] **II-12e,**[52] **II-12f**[54] and **II-12h**,[54]) and cyclopropene **II-4k**[13] were prepared following reported procedures.

[55] Perrin, D. D. Armarego, W. L. *Purification of Laboratory Chemicals,* 3rd Ed.; Pergamon Press: Oxford, 1988.
[56] Lebel, H.; Davis, M.; Díez-González, S.; Nolan, S. P. *J. Org. Chem.* **2007**, *72*, 144-149.
[57] Kiefer, G.; Jeanbourquin, L.; Severin, K. *Angew. Chem. Int. Ed.* **2013**, *52*, 6302-6305.
[58] Baralle, A.; Fensterbank, L.; Goddard, J. P.; Ollivier C. *Chem. Eur. J.* **2013**, *19*, 10809-10813.

2.3.2. Synthesis of Starting Materials

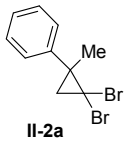
2.3.2.1. General Procedure for the Synthesis of Dibromocyclopropanes, **II-2**



II-1 **II-2**

To a solution of alkene **II-1** (1.0 equiv), bromoform (1.6 equiv), TEBAC (0.85 mol%) in dichloromethane (4 mL/mmol **II-1**), was added dropwise a solution of 50% NaOH (2.86 mL/mmol **II-1**) and left stirring at 30-35 °C until full conversion was observed by TLC (1-3 days). Water and CH_2Cl_2 were added. The aqueous phase was extracted with CH_2Cl_2 (x3). The combined organic phases were washed with saturated NaCl solution, dried over Na_2SO_4 and the solvent removed under reduced pressure. The reaction mixture was purified by flash column chromatography using hexanes as eluent**.**

(2,2-dibromo-1-methylcyclopropyl)benzene, II-2a

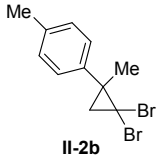


II-2a

From **II-1a** (13.2 mL, 0.1 mol), following the general procedure described above, compound **II-2a** (24.6 g, 85 mmol) was obtained in 85% yield.

The spectral data for **II-2a** matched those previously reported for this compound.[43] **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.47-7.32 (m, 5H), 2.23 (d, *J* = 7.5 Hz, 1H), 1.84 (d, *J* = 7.5 Hz, 1H), 1.78 (s, 3H).

1-(2,2-dibromo-1-methylcyclopropyl)-4-methylbenzene, II-2b

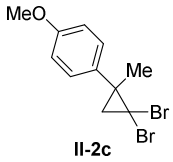


II-2b

From **II-1b** (3.8 g, 29 mmol), following the general procedure described above, compound **II-2b** (6.45 g, 21 mmol) was obtained in 72% yield.

The spectral data for **II-2b** matched those previously reported for this compound.[43] **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.20-7.13 (m, 4H), 2.34 (s, 3H), 2.14 (d, *J* = 7.5 Hz, 1H), 1.75 (d, *J* = 7.5 Hz, 1H), 1.69 (s, 3H).

1-(2,2-dibromo-1-methylcyclopropyl)-4-methoxybenzene, II-2c

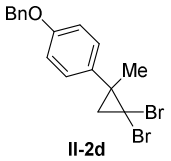


II-2c

From **II-1c** (3.5 g, 23.6 mmol), following the general procedure described above, compound **II-2c** (5.7 g, 17.8 mmol) was obtained in 75% yield.

The spectral data for **II-2c** matched those previously reported for this compound.[43] **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.25 (d, *J* = 8.6 Hz, 2H), 6.92 (d, *J* = 8.6 Hz, 2H), 3.84 (s, 3H), 2.15 (d, *J* = 7.6 Hz, 1H), 1.78 (d, *J* = 7.6 Hz, 1H), 1.73 (s, 3H).

1-(Benzyloxy)-4-(2,2-dibromo-1-methylcyclopropyl)benzene, II-2d

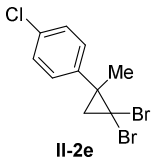


II-2d

From **II-1d** (3.74 g, 16.7 mmol, 1.0 equiv), following the general proceduredescribed above, compound **II-2d** (4.0 g, 10 mmol) was obtained in 60% yield as a white solid. $\mathbf{R}_f$ = 0.5 (5% EtOAc/hexanes).

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.45-7.28 (m, 5H), 7.21 (d, *J* = 8.7 Hz, 2H), 6.95 (d, *J* = 8.7 Hz, 2H), 5.04 (s, 2H), 2.11 (d, *J* = 7.5 Hz, 1H), 1.73 (d, *J* = 7.6 Hz, 1H), 1.68 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 158.0, 137.0, 134.9, 129.6, 128.6, 128.0, 127.6, 114.7, 70.1, 37.4, 35.2, 33.9, 27.7. **mp=** 98-100 °C.

1-chloro-4-(2,2-dibromo-1-methylcyclopropyl)benzene, II-2e

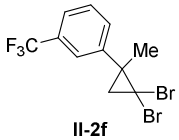


II-2e

From **II-1e** (3.1 g, 20.3 mmol), following the general procedure described above, compound **II-2e** (5.1 g, 15.7 mmol) was obtained in 77% yield.

The spectral data for **II-2e** matched those previously reported for this compound.[43] **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.36 (d, *J* = 8.0 Hz, 2H), 7.26 (d, *J* = 8.0 Hz, 2H), 2.15 (d, *J* = 7.6 Hz, 1H), 1.81 (d, *J* = 7.6 Hz, 1H), 1.72 (s, 3H)

1-(2,2-dibromo-1-methylcyclopropyl)-3-(trifluoromethyl)benzene, II-2f

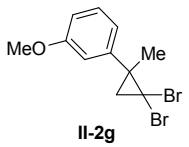


II-2f

From **II-1f** (3.0 g, 16.1 mmol), following the general procedure described above, compound **II-2f** (4.2 g, 11.7 mmol) was obtained in 73% yield.

The spectral data for **II-2f** matched those previously reported for this compound.[43] **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.60-7.45 (m, 4H), 2.18 (d, *J* = 7.7 Hz, 1H), 1.83 (t, *J* = 8.4 Hz, 1H), 1.73 (s, 3H).

1-(2,2-Dibromo-1-methylcyclopropyl)-3-methoxybenzene, II-2g

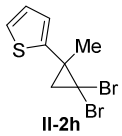


II-2g

From **II-1g** (2.8 g, 18.9 mmol),following the general procedure described above, compound **II-2g** (2.5 g, 7.9 mmol) was obtained in 42% yield as a pale yellow solid. $\mathbf{R}_f$ = 0.7 (10% EtOAc/hexanes).

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.31 (dd, *J* = 10.5, 5.9 Hz, 1H), 6.93 (d, *J* = 7.7 Hz, 1H), 6.87 (d, *J* = 6.1 Hz, 2H), 3.87 (s, 3H), 2.19 (d, *J* = 7.5 Hz, 1H), 1.81 (d, *J* = 7.5 Hz, 1H), 1.75 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 159.6, 143.9, 129.4, 120.9, 114.5, 112.4, 55.3, 36.6, 35.8, 33.9, 27.7. **HRMS (EI$^+$)** calculated for $C_{11}H_{12}Br_2O$ $[M]^+$:317.9255, found:317.9265. **mp**= 40-42 °C.

2-(2,2-dibromo-1-methylcyclopropyl)thiophene, II-2h

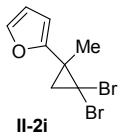


II-2h

From **II-1h** (3.5 g, 28.2 mmol), following the general procedure described above, compound **II-2h** (3.3 g, 11.3 mmol) was obtained in 40% yield.

The spectral data for **II-2h** matched those previously reported for this compound.[13] **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.22 (dd, *J* = 5.1, 1.2 Hz, 1H), 6.97-6.91 (m, 1H), 6.90-6.84 (m, 1H), 2.26 (d, *J* = 7.8 Hz, 1H), 1.85 (d, *J* = 7.8 Hz, 1H), 1.80 (s, 3H).

2-(2,2-dibromo-1-methylcyclopropyl)furan, II-2i

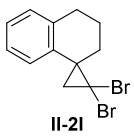


II-2i

From **II-1i** (2.8 g, 25.9 mmol), following the general procedure described above, compound **II-2i** (2.2 g, 7.8 mmol) was obtained in 30% yield.

The spectral data for **II-2i** matched those previously reported for this compound.[13] **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.35 (d, *J* = 1.1 Hz, 1H), 6.37-6.33 (m, 1H), 6.20 (d, *J* = 3.2 Hz, 1H), 2.33 (d, *J* = 7.7 Hz, 1H), 1.71-1.77 (m, 4H).

2,2-dibromo-3',4'-dihydro-2'*H*-spiro[cyclopropane-1,1'-naphthalene], II-2l

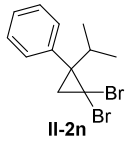


II-2l

From **II-1l** (4.0 g, 27.9 mmol), following the general procedure described above, compound **II-2l** (5.5 g, 17.4 mmol) was obtained in 62% yield.

The spectral data for **II-2l** matched those previously reported for this compound.[13] **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.34-7.15 (m, 3H), 6.99 (d, *J* = 7.8 Hz, 1H), 3.06-2.84 (m, 2H), 2.45 (d, *J* = 8.2 Hz, 1H), 2.36-2.19 (m, 1H), 2.19-2.08 (m, 2H), 1.99-1.90 (m, 1H), 1.84 (d, *J* = 8.2 Hz, 1H).

(2,2-Dibromo-1-isopropylcyclopropyl)benzene, II-2n

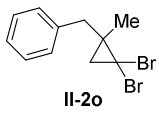


II-2n

From **II-1n** (4.5 g, 30.6 mmol, 1.0 equiv), following the general procedure described above, compound **II-2n** (4.7 g, 14.8 mmol) was obtained in 48% yield as a pale yellow solid. $\mathbf{R}_f$ = 0.65 (hexanes).

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.48-7.26 (m, 4H), 7.06 (s, 1H), 1.94 (d, *J* = 7.2 Hz, 1H), 1.94-1.80 (m, 1H), 1.77 (d, *J* = 7.2 Hz, 1H), 1.10 (d, *J* = 6.8 Hz, 3H), 0.86 (d, *J* = 6.8 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 136.9, 132.5, 130.8, 128.0, 127.4, 127.0, 44.2, 38.0, 37.0, 35.5, 20.3, 19.1. **HRMS (EI$^+$)** calculated for $C_{12}H_{14}Br_2$ $[M]^+$: 315.9462, found: 315.9462. **mp**= 58-60 °C.

[(2,2-Dibromo-1-methylcyclopropyl)methyl]benzene, II-2o

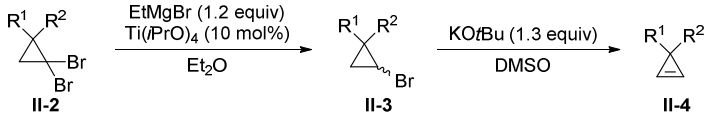


II-2o

From **II-1o** (1.6 g, 12 mmol, 1.0 equiv), following the general procedure described above, compound **II-2o** (2.2 g, 7.3 mmol) was obtained in 61% yield as a yellow oil. $\mathbf{R}_f$ = 0.6 (hexanes).

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.38-7.20 (m, 5H), 3.06 (d, *J* = 14.8 Hz, 1H), 2.97 (d, *J* = 14.8 Hz, 1H), 1.69 (d, *J* = 7.4 Hz, 1H, 1.51 (d, *J* = 7.4 Hz, 1H), 1.28 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 138.7, 129.3, 128.6, 126.7, 44.0, 39.4, 34.5, 30.6, 23.1. **HRMS (EI$^+$)** calculated for $C_{11}H_{12}Br_2$ $[M]^+$:301.9306, found: 301.9313.

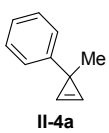
2.3.2.2. General Procedure for the Synthesis of 3,3-Disubstituted Cyclopropenes, **II-4**



To a solution of dibromocyclopropane **II-2** (1.0 equiv) and Ti(*i*PrO)$_4$ (10 mol%) in anhydrous Et_2O, under an argon atmosphere, was added a 3.0 M solution of EtMgBr in Et_2O (1.2 equiv) dropwise. The mixture was stirred at room temperature for 2 h and then water and a solution of 10% H_2SO_4 (1.5 mL/mmol of **II-2**) were added. The phases were separated and the aqueous phase was extracted with Et_2O (x3). The combined organic phases were washed with saturated $NaHCO_3$ and saturated NaCl solution, dried over Na_2SO_4 and filtered. The solvent was removed under reduced pressure and the crude product was purified by flash column chromatography using hexanes as eluent.

To a solution of monobromocyclopropane **II-3** (1.0 equiv) in anhydrous DMSO (0.55 mL/ 1 mmol of **II-3**), KO*t*Bu (1.3 equiv) was added under an argon atmosphere and stirred at room temperature for 12 h. Water was added, the phases were separated and the aqueous phase was extracted with Et_2O (x3). The combined organic phases were washed with saturated NaCl solution, dried over Na_2SO_4 and filtered. The solvent was removed under reduced pressure and the crude product was purified by flash column chromatography using pentane as eluent.

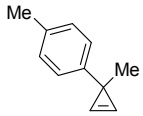
(1-methylcycloprop-2-en-1-yl)benzene, II-4a



From **II-2a** (4.0 g, 14.0 mmol), following the general procedure described above, compound **II-4a** (1.0 g, 7.7 mmol) was obtained in 55% yield.

The spectral data for **II-4a** matched those previously reported for this compound.[43] **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.40-7.15 (m, 6H), 1.68 (s, *J* = 1.3 Hz, 3H).

1-methyl-4-(1-methylcycloprop-2-en-1-yl)benzene, II-4b

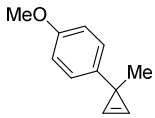


II-4b

From **II-2b** (6.45 g, 21 mmol), following the general procedure described above, compound **II-4b** (2.0 g, 13.9 mmol) was obtained in 66% yield.

The spectral data for **II-4b** matched those previously reported for this compound.[43] **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.30 (s, 2H), 7.15 (s, 4H), 2.37 (s, 3H), 1.66 (s, 3H).

1-methoxy-4-(1-methylcycloprop-2-en-1-yl)benzene, II-4c

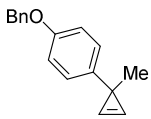


II-4c

From **II-2c** (5.7 g, 17.8 mmol), following the general procedure described above, compound **II-4c** (1.4 g, 8.7 mmol) was obtained in 48% yield.

The spectral data for **II-4c** matched those previously reported for this compound.[43] **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.33 (s, 2H), 7.20 (d, *J* = 8.8 Hz, 2H), 6.91 (d, *J* = 8.8 Hz, 2H), 3.85 (s, 3H), 1.69 (s, 3H).

1-(Benzyloxy)-4-(1-methylcycloprop-2-en-1-yl)benzene, II-4d



II-4d

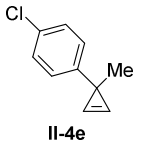
From **II-2d** (4.0 g, 10 mmol, 1 equiv), following the general procedure described above, compound **II-3d** (1.8 g, 5.6 mmol) was obtained in 56% yield as a white solid. $\mathbf{R}_f$ = 0.5 (5% EtOAc/hexanes).

From **II-3d** (1.8 g, 5.6 mmol, 1 equiv), following the general procedure described above, compound **II-4d** (877 mg, 3.7 mmol) was obtained in 66% yield as a white solid. $\mathbf{R}_f$ = 0.5 (5% EtOAc/hexanes).

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.46-7.29 (m, 5H), 7.12 (d, *J* = 8.8 Hz, 2H), 6.91 (d, *J* = 8.8 Hz, 2H), 5.05 (s, 2H), 1.61 (s, 3H). **^{13}C NMR** (75

MHz, $CDCl_3$): δ 156.6, 142.5, 137.3, 128.6, 127.9, 127.4, 127.0, 116.1, 114.3, 70.1, 25.7, 21.3. **HRMS (EI$^+$)** calculated for $C_{17}H_{16}O$ $[M]^+$: 236.1201, found: 236.1208. **mp=** 48-50 °C.

1-chloro-4-(1-methylcycloprop-2-en-1-yl)benzene, II-4e

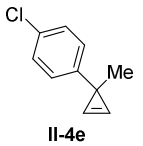


II-4e

From **II-2e** (5.1 g, 15.7 mmol), following the general procedure described above, compound **II-4e** (1.5 g, 9.1 mmol) was obtained in 58% yield.

The spectral data for **II-4e** matched those previously reported for this compound.[43] **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.28 (d, *J* = 8.6 Hz, 2H), 7.28 (s, 2H), 7.17 (d, *J* = 8.6 Hz, 2H), 1.65 (s, 3H).

1-chloro-4-(1-methylcycloprop-2-en-1-yl)benzene, II-4f

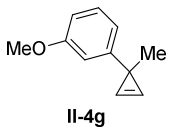


II-4e

From **II-2f** (5.1 g, 15.7 mmol), following the general procedure described above, compound **II-4f** (1.5 g, 9.1 mmol) was obtained in 58% yield.

The spectral data for **II-4f** matched those previously reported for this compound.[43] **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.28 (d, *J* = 8.6 Hz, 2H), 7.28 (s, 2H), 7.17 (d, *J* = 8.6 Hz, 2H), 1.65 (s, 3H).

1-Methoxy-3-(1-methylcycloprop-2-en-1-yl)benzene, II-4g



II-4g

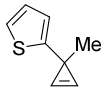
From **II-2g** (3.2 g, 10.0 mmol), following the general procedure described above, compound **II-3g** (1.7 g, 7.0 mmol) was obtained in 70% yield as a white solid. $\mathbf{R}_f$ = 0.6 (5% EtOAc/hexanes).

From **II-3g** (1.7 g, 7.0mmol, 1.0equiv), following the general procedure described above, compound **II-4g** (715 mg, 4.5 mmol) was obtained in 64% yield as a colorless oil. $\mathbf{R}_f$ = 0.6 (10% EtOAc/hexanes).

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.27 (m, 3H), 6.87 (d, *J* = 7.7 Hz, 1H), 6.80 (m, 1H), 6.75 (m, 1H), 3.85 (s, 3H), 1.66 (s, 3H). **^{13}C NMR** (75

MHz, $CDCl_3$): δ 159.6, 152.0, 128.8, 118.7, 115.4, 112.3, 110.3, 55.2, 25.5, 21.9. **HRMS (EI$^+$)** calculated for $C_{17}H_{16}O$ $[M]^+$:160.0888, found:160.0887.

2-(1-methylcycloprop-2-en-1-yl)thiophene, II-4h

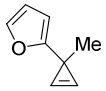


II-4h

From **II-2h** (3.3 g, 11.3 mmol), following the general procedure described above, compound **II-4h** (492.5 mg, 3.6 mmol) was obtained in 32% yield.

The spectral data for **II-4h** matched those previously reported for this compound.[13] **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.28 (s, 2H), 7.07 (d, *J* = 5.0 Hz, 1H), 6.98-6.93 (m, 1H), 6.77 (d, *J* = 3.3 Hz, 1H), 1.65 (s, 3H).

2-(1-methylcycloprop-2-en-1-yl)furan, II-4i

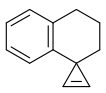


II-4i

From **II-2i** (2.2 g, 7.8 mmol), following the general procedure described above, compound **II-4i** (432.5 mg, 3.6 mmol) was obtained in 46% yield.

The spectral data for **II-4i** matched those previously reported for this compound.[13] **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.27 (s, 2H), 7.23-7.25 (m, 1H), 6.31 (m, 1H), 5.96 (dd, *J* = 3.2, 0.4 Hz, 1H), 1.52 (s, 3H).

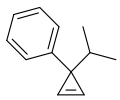
3',4'-dihydro-2'*H*-spiro[cyclopropane-1,1'-naphthalen]-2-ene, II-4l


II-4l

From **II-2l** (5.5 g, 17.4 mmol), following the general procedure described above, compound **II-4l** (734 mg, 4.7 mmol) was obtained in 27% yield.

The spectral data for **II-4l** matched those previously reported for this compound.[13] **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.18 (s, 2H), 7.14-7.08 (m, 3H), 6.87-6.79 (m, 1H), 2.91 (t, *J* = 6.2 Hz, 2H), 2.05-1.95 (m, 2H), 1.87-1.79 (m, 2H).

(1-Isopropylcycloprop-2-en-1-yl)benzene, II-4n

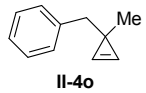

II-4n

From **II-2n** (4.7 g, 14.8 mmol), following the general procedure described above, compound **II-3n** (1.4 g, 5.9 mmol) was obtained in 40% yield as a colorless oil. $\mathbf{R}_f$ = 0.6 (hexanes).

From **II-3n** (1.4 g, 5.9 mmol), following the general procedure described above, compound **II-4n** (300 mg, 1.9 mmol) was obtained in 33% yield as a colorless oil. $\mathbf{R}_f$ = 0.7 (hexanes).

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.29 (s, 2H), 7.28-7.17 (m, 4H), 7.17-7.09 (m, 1H), 2.59 (sept, *J* = 6.7 Hz, 1H), 0.74 (d, *J* = 6.7 Hz, 6H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 148.9, 128.0, 127.0, 125.2, 113.7, 33.6, 30.1, 20.8. **HRMS (EI$^+$)** calculated for $C_{12}H_{14}$ $[M]^+$: 158.1096, found: 158.1102.

[(1-Methylcycloprop-2-en-1-yl)methyl]benzene, II-4o



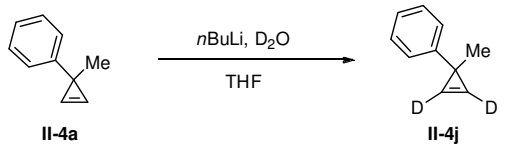
II-4o

From **II-2o** (2.1 g, 7.0 mmol), following the general procedure described above, compound **II-3o** (940 mg, 4.2 mmol) was obtained in 60% yield as a colorless oil. $\mathbf{R}_f$ = 0.6 (hexanes).

From **II-3o** (900 mg, 4 mmol), following the general procedure described above, compound **II-4o** (315 mg, 2.2 mmol) was obtained in 55% yield as a colorless oil. $\mathbf{R}_f$ = 0.7 (hexanes).

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.33 (s, 2H), 7.30-7.11 (m, 4H), 7.07 (d, *J* = 7.3 Hz, 1H), 2.76 (s, 2H), 1.19 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 141.2, 129.4, 128.2, 125.7, 122.2, 47.9, 27.0, 21.8. **HRMS (EI$^+$)** calculated for $C_{11}H_{12}$ $[M]^+$: 144.0939, found: 144.0954.

2.3.2.3. Synthesis of (1-methylcycloprop-2-en-1-yl-2,3-*d*2)benzene, **II-4j**

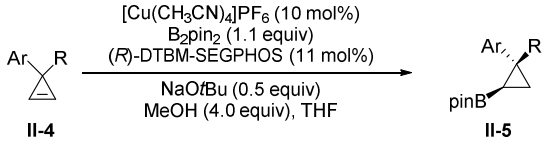


To a stirred solution of cyclopropene **II-4a** (678 mg, 5.2 mmol) in anhydrous THF (7 mL) at -30 ºC was added a solution of *n*-butyllithium (2.5 M in hexane, 5.2 mL, 13.0 mmol, 2.5 equiv). The mixture was stirred for 30 min at 0 ºC and quenched with deuterium oxide (0.9 mL, 50.5 mmol, 9.7 equiv). The organic phase was separated, dried over $MgSO_4$, filtered and concentrated. The residue was distilled to afford **II-4j** (330.5 mg, 2.5 mmol) in 48% yield.

The spectral data for **II-4j** matched those previously reported for this compound.[59] **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.37-7.15 (m, 5H), 1.67 (s, 3H).

2.3.3. Enantioselective Hydroboration of Cyclopropenes

2.3.3.1. General Procedure for the Synthesis of Chiral Cyclopropylboronates, **II-5**.

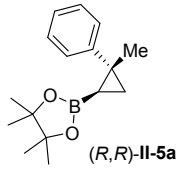


An oven-dried vial was charged with $[Cu(CH_3CN)_4]PF_6$ (7.5 mg, 0.02 mmol, 10.0mol%) and (*R*)-DTBM-Segphos (26 mg, 0.022 mmol, 11.0 mol%) and sealed with a septum. The vial was connected to an argon-vacuum line, evacuated and backfilled with argon (x3). THF (1.0 mL/0.2

[59] Alnasleh, B.K.; Sherrill, W.M.; Rubin, M. *Org. Lett.* **2008**, *10*, 3231-3234.

mmol of **II-4**) was added and the mixture was stirred for 30 min at room temperature. With the vial still connected to the double line, the solvent was removed to dryness. Then, a solution of B_2pin_2 (1.1 equiv) in THF (0.6 mL/0.2 mmol of **II-4**) was added and the mixture was stirred for 10 min. A 0.2 M NaO*t*Bu solution in THF (50 µL, 0.1 mmol, 0.5 equiv) was then added dropwise and the dark brown solution was stirred for 10 min. The reaction mixture was cooled at -78 °C for 10 min and the corresponding cyclopropene **II-4** (0.2 mmol, 1.0 equiv) was added followed by methanol (32 µL, 0.8 mmol, 4.0 equiv). Then, the reaction mixture was stirred overnight at the optimized temperature for each case (-20, -50 or -78 ºC). Et_2O and water were added and the layers were separated. The aqueous phase was extracted with Et_2O (x3) and the combined organic layers were washed with saturated NaCl solution, dried over Na_2SO_4, filtered and concentrated. The crude product was purified by flash-column chromatography (0-5% Et_2O/pentane) to afford cyclopropylboronate **II-5**.

4,4,5,5-Tetramethyl-2-[(1*R*,2*R*)-2-methyl-2-phenylcyclopropyl]-1,3,2-dioxaborolane, (*R,R*)-II-5a



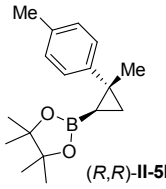
(*R,R*)-**II-5a**

From **II-4a** (29 µL, 0.2 mmol), following the general procedure described above (-20 °C, 12 h), compound (*R,R*)-**II-5a** (38.2 mg, 0.15 mmol, dr = 97:3) was obtained in 74% yield as a colorless oil. $\mathbf{R_f}$ **=** 0.5 (5% EtOAc/hexanes).

The spectral data for (*R,R*)-**II-5a** matched those previously reported for (±)-**II-5a** except for the optical rotation.[9] **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.25-7.03 (m, 5H), 1.42 (s, 3H), 1.20 (d, *J* = 5.1 Hz, 12H), 1.11 (dd, *J* = 9.7, 3.6 Hz, 1H), 0.98-0.90 (m, 1H), 0.29 (dd, *J* = 9.7, 7.3 Hz, 1H).Compound (*R,R*)-**II-5a** was obtained with a 95:5 enantiomeric ratio

determined by SFC using Chiralpak-IC column [CO_2/MeOH (99:1), 1.0 mL/min]: τ_{major}= 6.4 min, τ_{minor}= 7.4 min. $[\alpha]^{20}_{D}$= -109.4 (*c*= 1.20, $CHCl_3$).

4,4,5,5-Tetramethyl-2-[(1*R*,2*R*)-2-methyl-2-(4-methylphenyl)cyclopropyl]-1,3,2-dioxaborolane, (*R,R*)-II-5b

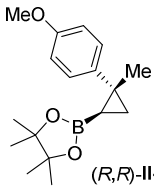


(*R,R*)-**II-5b**

From **II-4b** (28 µL, 0.2 mmol), following the general procedure described above (-50 °C, 36 h), compound (*R,R*)- **II-5b** (37 mg, 0.14 mmol, dr ≥ 98:2) was obtained in 68% yield as a colorless oil. $\mathbf{R}_f$ **=** 0.7 (5% EtOAc/hexanes).

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.23-7.03 (m, 4H), 2.30 (s, 3H), 1.47 (s, 3H), 1.28 (s, 6H), 1.26 (s, 6H), 1.14 (dd, *J* = 9.7, 3.5 Hz, 1H), 0.98 (dd, *J* = 7.2, 3.5 Hz, 1H), 0.34 (dd, *J* = 9.7, 7.2 Hz, 1H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 145.3, 135.1, 128.8, 127.1, 83.1, 26.6, 25.2, 24.6, 23.2, 20.9, 20.1. [note: the carbon attached to boron was not observed due to quadrupole broadening caused by the ^{11}B nucleus]. **HRMS (EI$^+$)** calculated for $C_{17}H_{25}BO_2$ $[M]^+$: 272.1948, found: 272.1945.Compound(*R,R*)- **II-5b** was obtained with a 95:5 enantiomeric ratio determined by SFC using Chiralpak-IC column [CO_2/MeOH (99:1), 0.5 mL/min]: τ_{major}= 10.8 min, τ_{minor}= 13.9 min. $[\alpha]^{20}_{D}$= -117.1 (*c* = 1.04, $CHCl_3$).

2-[(1*R*,2*R*)-2-(4-Methoxyphenyl)-2-methylcyclopropyl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane, (*R,R*)-II-5c

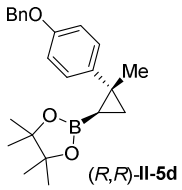


(*R,R*)-**II-5c**

From **II-4c** (32 µL, 0.2 mmol), following the general proceduredescribed above (-50 °C, 36 h), compound (*R,R*)-**II-5c** (35.7 mg, 0.12 mmol, dr = 97:3) was obtained in 62% yield as a colorless oil. $\mathbf{R}_f$ **=** 0.6 (5% EtOAc/hexanes).

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.22 (d, *J* = 8.8 Hz, 2H), 6.80 (d, *J* = 8.8 Hz, 2H), 3.78 (s, 3H), 1.46 (s, 3H), 1.28 (s, 1H), 1.26 (s, 1H), 1.12 (dd, *J* = 9.7, 3.5 Hz, 1H), 0.96 (dd, *J* = 7.2, 3.5 Hz, 1H), 0.31 (dd, *J* = 9.7, 7.2 Hz, 1H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 157.8, 140.7, 128.5, 113.7, 83.4, 55.5, 26.6, 25.4, 24.8, 23.6, 20.2. [note: the carbon attached to boron was not observed due to quadrupole broadening caused by the ^{11}B nucleus]. **HRMS (EI$^+$)** calculated for $C_{17}H_{25}BO_3$ $[M]^+$: 288.1897, found: 288.1892.Compound(*R,R*)-**II-5c** was obtained with a 94:6 enantiomeric ratio determined by SFC using Chiralpak-IC column [CO_2/MeOH (99:1), 1.0mL/min]: τ_{major}= 11.3 min, τ_{minor}= 13.8 min. **[α]$^{20}_D$**= -97.9 (*c*= 1.31, $CHCl_3$).

2-[(1*R*,2*R*)-2-(4-(Benzyloxy)phenyl)-2-methylcyclopropyl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane, (*R,R*)-II-5d



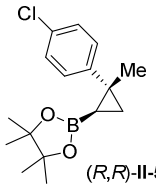
(*R,R*)-**II-5d**

From **II-4d** (47.3 mg, 0.2 mmol), following the general procedure described above (-50 °C, 36 h), compound (*R,R*)-**II-5d** (45 mg, 0.123 mmol, dr = 97:3) was obtained in 62% yield as a colorless oil. $\mathbf{R}_f$ =0.5 (5% EtOAc/Cy)

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.46-7.29 (m, 6H), 7.23 (d, *J* = 8.7 Hz, 2H), 6.88 (d, *J* = 8.7 Hz, 2H), 5.04 (s, 2H), 1.47 (s, *J* = 7.2 Hz, 3H), 1.29 (s, 6H), 1.27 (s, 6H), 1.14 (dd, *J* = 9.7, 3.5 Hz, 1H), 0.98 (dd, *J* = 7.2, 3.5 Hz, 1H), 0.32 (dd, *J* = 9.7, 7.2 Hz, 1H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ157.0, 140.9, 137.4, 128.7, 128.3, 128.0, 127.6, 114.6, 83.3, 70.2, 26.5, 25.3, 24.7, 23.5, 20.2. [note: the carbon attached to boron was not observed due to quadrupole broadening caused by the ^{11}B nucleus]. **HRMS (EI$^+$)** calculated for $C_{23}H_{29}BO_3$ $[M]^+$:364.2210, found: 364.2202. Compound(*R,R*)-**II-5d** was obtained with a 96:4 enantiomeric ratio determined by SFC using Chiralpak-IC column[CO_2/MeOH (95:5), 1.0

mL/min]: τ_{major}= 12.4 min, τ_{minor}= 13.8 min. $[\alpha]^{20}_{D}$= -86.76 (*c* = 1.16, $CHCl_3$).

2-[(1*R*,2*R*)-2-(4-Chlorophenyl)-2-methylcyclopropyl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane, (*R,R*)-II-5e

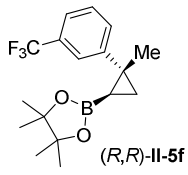


(*R,R*)-**II-5e**

From **II-4e** (26 µL, 0.2 mmol), following the general procedure described above (-78 °C, 60 h), compound (*R,R*)-**II-5e** (41 mg, 0.14 mmol, dr = 95:5) was obtained in 70% yield as a colorless oil. $\mathbf{R_f}$ **=** 0.5 (5% EtOAc/hexanes).

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.21 (s, 4H), 1.46 (s, 3H), 1.28 (s, 6H), 1.26 (s, 6H), 1.14 (dd, *J* = 9.7, 3.8 Hz, 1H), 1.01 (dd, *J* = 7.2, 3.7 Hz, 1H), 0.31 (dd, *J* = 9.8, 7.2 Hz, 1H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 147.0, 131.6, 128.8, 128.5, 83.6, 26.6, 25.5, 24.9, 23.2, 20.6. [note: the carbon attached to boron was not observed due to quadrupole broadening caused by the ^{11}B nucleus]. **HRMS(EI$^+$)** calculated for $C_{16}H_{22}BClO_2$ $[M]^+$: 292.1400, found: 292.1400. Compound (*R,R*)-**II-5e** was obtained with a 93:7 enantiomeric ratio determined by SFC using Chiralpak-IC column [CO_2/MeOH (99:1), 1.0 mL/min]: τ_{major}= 7.1 min, τ_{minor}= 9.0 min. $[\alpha]^{20}_{D}$= -102.6 (*c* = 1.88, $CHCl_3$).

4,4,5,5-Tetramethyl-2-[(1*R*,2*R*)-2-methyl-2-(3-(trifluoromethyl)phenyl)cyclopropyl]-1,3,2-dioxaborolane, (*R,R*)-II-5f

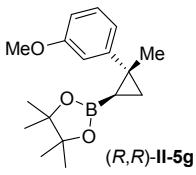


(*R,R*)-**II-5f**

From **II-4f** (29 µL, 0.2 mmol), following the general procedure described above (-20 °C, 12 h), compound (*R,R*)-**II-5f** (28 mg, 0.09 mmol, dr ≥ 98:2) was obtained in 43% yield as a colorless oil. $\mathbf{R_f}$ **=** 0.5 (5% EtOAc/hexanes).

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.44 (s, 1H), 7.32 (m, 3H), 1.43 (s, 3H), 1.21 (s, 6H), 1.19 (s, 6H), 1.12 (dd, *J* = 9.8, 3.8 Hz, 1H), 1.00 (dd, *J* = 7.3, 3.8 Hz, 1H), 0.30 (dd, *J* = 9.7, 7.3 Hz, 1H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 149.1, 130.44 (q, $J_{C\text{-}F}$ = 31.9 Hz), 130.4, 128.5, 124.3 (q, $J_{C\text{-}F}$ = 272.4 Hz), 123.7 (q, $J_{C\text{-}F}$ = 3.8 Hz), 122.4 (q, $J_{C\text{-}F}$ = 4.0 Hz), 83.4, 26.5, 25.2, 24.5, 22.6, 20.4. [note: the carbon attached to boron was not observed due to quadrupole broadening caused by the ^{11}B nucleus]. **HRMS (EI$^+$)** calculated for $C_{17}H_{22}BF_3O_2$ $[M]^+$: 326.1665, found: 326.1656. Compound (*R,R*)-**II-5f** was obtained with a 92:8 enantiomeric ratio determined by SFC using Chiralpak-IC column [CO_2/MeOH (99.5:0.5), 1.0 mL/min]: τ_{major}= 4.4 min, τ_{minor}= 5.3 min. **[α]$^{20}_D$**= -70.1 (*c*= 0.75, $CHCl_3$).

2-[(1*R*,2*R*)-2-(3-Methoxyphenyl)-2-methylcyclopropyl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane, (*R,R*)-II-5g

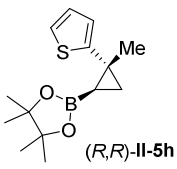


(*R,R*)-**II-5g**

From **II-4g** (31 μL, 0.2 mmol), following the general procedure described above (-78 °C, 60 h), compound (*R,R*)-**II-5g** (39.8 mg, 0.14 mmol, dr = 96:4) was obtained in 69% yield as a colorless oil. $\mathbf{R}_f$ = 0.5 (5% EtOAc/hexanes).

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.20-7.12 (m, 1H), 6.91-6.81 (m, 2H), 6.72-6.65 (m, 1H), 3.79 (s, 2H), 1.49 (s, 2H), 1.28 (s, 6H), 1.26 (s, 6H), 1.18 (dd, *J* = 9.8, 3.6 Hz, 1H), 0.99 (dd, *J* = 7.2, 3.6 Hz, 1H), 0.37 (dd, *J* = 9.7, 7.3 Hz, 1H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 159.6, 150.0, 129.2, 119.6, 113.1, 111.0, 83.3, 55.3, 26.9, 25.3, 24.7, 23.0, 20.5. [note: the carbon attached to boron was not observed due to quadrupole broadening caused by the ^{11}B nucleus]. **HRMS (EI$^+$)** calculated for $C_{17}H_{25}BO_3$ $[M]^+$: 288.1897, found: 288.1907. Compound (*R,R*)-**II-5g** was obtained with a 92:8 enantiomeric ratio determined by SFC using Chiralpak-IC column [CO_2/MeOH (99:1), 1.0 mL/min]: τ_{major}= 11.2 min, τ_{minor}= 12.1 min. **[α]$^{20}_D$**= -93.7 (*c*= 1.96, $CHCl_3$).

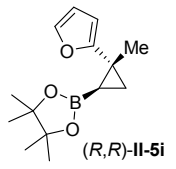
4,4,5,5-Tetramethyl-2-[(1*R*,2*R*)-2-methyl-2-(thiophen-2-yl)cyclopropyl]-1,3,2-dioxaborolane, (*R,R*)-II-5h



From **II-4h** (31 μL, 0.2 mmol), following the general procedure described above (-50 °C, 36 h), compound (*R,R*)-**II-5h** (41.7 mg, 0.16 mmol, dr = 97:3) was obtained in 79% yield as a colorless oil. $\mathbf{R}_f$ **=** 0.6 (5% EtOAc/hexanes).

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.02 (dd, *J* = 5.1, 1.2 Hz, 1H), 6.85 (dd, *J* = 5.1, 3.5 Hz, 1H), 6.78 (dd, *J* = 3.5, 1.2 Hz, 1H), 1.59 (s, 3H), 1.27 (s, 6H), 1.25 (s, 6H), 1.22 (d, *J* = 3.7 Hz, 1H), 1.11 (dd, *J* = 7.5, 3.7 Hz, 1H), 0.51 (dd, *J* = 9.9, 7.5 Hz, 1H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 154.6, 126.8, 122.3, 122.2, 83.6, 25.5, 24.9, 23.7, 23.5, 22.7. [note: the carbon attached to boron was not observed due to quadrupole broadening caused by the ^{11}B nucleus]. **HRMS (EI$^+$)** calculated for $C_{14}H_{21}BO_2S$ $[M]^+$: 264.1355, found: 264.1343. Compound(*R,R*)-**II-5h** was obtained with a 95:5 enantiomeric ratio determined by SFC using Chiralpak-IC column [CO_2/MeOH (99:1), 1.0 mL/min]: τ_{major}= 7.6 min, τ_{minor}= 9.0 min. **[α]$^{20}_D$**= -102.6 (*c*= 1.88, $CHCl_3$).

2-[(1*R*,2*R*)-2-(furan-2-yl)-2-methylcyclopropyl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane, (*R,R*)-II-5i

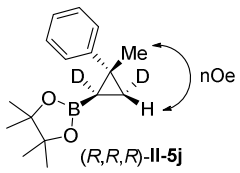


From **II-4i** (26 μL, 0.2 mmol), following the general procedure described above (-78 ºC, 60 h), compound (*R,R*)-**II-5i** (33 mg, 0.116 mmol, dr = 95:5) was obtained in 58% yield as a colorless oil. $\mathbf{R}_f$ **=** 0.5 (5% EtOAc/hexanes).

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.19 (d, *J* = 0.8 Hz, 1H), 6.24 (dd, *J* = 2.9, 1.6 Hz, 1H), 5.98 (d, *J* = 3.2 Hz, 1H), 1.49 (s, 3H), 1.32 (dd, *J* = 9.8, 3.3 Hz, 1H), 1.25 (s, 6H), 1.24 (s, 6H), 0.96 (dd, *J* = 7.5, 3.3 Hz, 1H), 0.59 (dd, *J* = 9.7, 7.7 Hz, 1H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 160.2, 140.0,

110.2, 103.1, 83.3, 25.2, 24.6, 20.9, 19.7, 18.9. [note: the carbon attached to boron was not observed due to quadrupole broadening caused by the ^{11}B nucleus]. **HRMS (EI$^+$)** calculated for $C_{14}H_{21}BO_3$ $[M]^+$:284.1584, found:248.1591. Compound (*R,R*)-**II-5i** was obtained with a 94:6 enantiomeric ratio determined by SFC using Chiralpak-IC column [CO_2/MeOH (99:1), 1.0 mL/min]: τ_{major}= 7.0 min, τ_{minor}= 8.5 min. **[α]$^{20}_D$**= -123.14 (*c*= 0.69, $CHCl_3$).

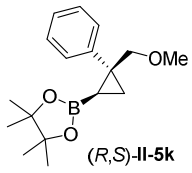
4,4,5,5-Tetramethyl-2-[(1*R*,2*R*,3*R*)-2-methyl-2-phenylcyclopropyl-1,3-*d*$_2$]-1,3,2-dioxaborolane, (*R,R,R*)-II-5j



From **II-4j** (29 µL, 0.2 mmol), following the general procedure described above (-50 °C, 36 h), compound (*R,R,R*)-**II-5j** (33.8 mg, 0.13 mmol, dr = 97:3) was obtained in 65% yield as a colorless oil. **R$_f$ =** 0.5 (5% EtOAc/hexanes). The relative configuration was confirmed by nOe analysis.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.25-7.13 (m, 5H), 7.09-7.03 (m, 1H), 1.42 (s, 3H), 1.20 (s, 6H), 1.18 (s, 6H), 0.90 (s, 1H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 148.2, 128.2, 127.1, 125.7, 83.3, 26.7, 25.3, 24.7, 23.0, 20.0 (t, $J_{C\text{-}D}$=24.7). [note: the carbon attached to boron was not observed due to quadrupole broadening caused by the ^{11}B nucleus]. **HRMS (EI$^+$)** calculated for $C_{16}H_{21}D_2BO_2$ $[M]^+$:260.1917, found: 260.1913. Compound (*R,R,R*)-**II-5j** was obtained with a 90.5:9.5 enantiomeric ratio determined by SFC using Chiralpak-IC column [CO_2/MeOH (99:1), 1.0 mL/min]: τ_{major}= 6.4 min, τ_{minor}= 7.4 min. **[α]$^{20}_D$**= -102.6 (*c*= 1.85, $CHCl_3$).

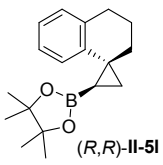
2-[(1*R*,2*S*)-2-(Methoxymethyl)-2-phenylcyclopropyl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane, (*R,S*)-**II-5k**



From **II-4k** (25 mg, 0.16 mmol), following the general procedure described above (-50 °C, 36 h), compound (*R,S*)-**II-5k** (30 mg, 0.10 mmol, dr ≥ 98:2) was obtained in 52% yield as a colorless oil. $\mathbf{R}_f$ = 0.5 (5% EtOAc/hexanes).

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.38-7.32 (m, 1H), 7.30-7.22 (m, 3H), 7.20-7.13 (m, 1H), 3.74 (d, *J* = 9.8 Hz, 1H), 3.54 (d, *J* = 9.8 Hz, 1H), 3.26 (s, 3H), 1.28 (s, 6H), 1.27 (s, 6H), 1.18 (dd, *J* = 9.5, 3.7 Hz, 1H), 1.10 (dd, *J* = 7.3, 3.7 Hz, 1H), 0.43 (dd, *J* = 9.5, 7.3 Hz, 1H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 145.0, 128.5, 128.2, 126.2, 83.4, 77.6, 58.6, 32.1, 25.1, 24.8, 18.1. [note: the carbon attached to boron was not observed due to quadrupole broadening caused by the ^{11}B nucleus]. **HRMS (EI$^+$)** calculated for $C_{17}H_{25}BO_3$ $[M]^+$: 288.1897, found: 288.1898. Compound (*R,S*)-**II-5k** was obtained with a 96.5:3.5 enantiomeric ratio determined by SFC using Chiralpak-IC column[CO_2/MeOH (99:1), 1.0 mL/min]: τ_{major}= 13.6 min, τ_{minor}= 16.4 min. **$[\alpha]^{20}_D$**= -73.9 (*c*= 1.02, $CHCl_3$).

2-[(1*R*,2*R*)-3',4'-Dihydro-2'H-spiro[cyclopropane-1,1'-naphthalen]-2-yl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane, (*R,R*)-**II-5l**

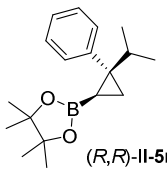


From **II-4l** (28 µL, 0.2 mmol), following the general procedure described above (-20 °C, 12 h), compound (*R,R*)-**II-5l** (34.1 mg, 0.12 mmol, dr ≥ 98:2) was obtained in 60% yield as a white solid. $\mathbf{R}_f$ **=** 0.4 (5% EtOAc/hexanes).

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.10-6.97 (m, 3H), 6.73 (d, *J* = 7.0 Hz, 1H), 2.93-2.83 (m, 2H), 1.94-1.80 (m, 4H), 1.35 (dd, *J* = 9.7, 4.0 Hz, 1H), 1.26 (s, 6H), 1.25 (s, 6H), 1.10 (dd, *J* = 7.7, 4.0 Hz, 1H), 0.41 (dd, *J* = 9.6,

7.7 Hz, 1H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 142.3, 137.7, 129.1, 126.4, 125.1, 121.9, 83.5, 31.8, 31.1, 26.2, 25.4, 24.9, 22.9, 22.7. [note: the carbon attached to boron was not observed due to quadrupole broadening caused by the ^{11}B nucleus]. **HRMS (EI$^+$)** calculated for $C_{18}H_{25}BO_2$ $[M]^+$: 284.1948, found: 284.1958. Compound (*R,R*)-**II-5l** was obtained with a 91.5:8.5 enantiomeric ratio determined by SFC using Chiralpak-IC column [CO_2/MeOH (99:1), 1.0 mL/min]: τ_{major}= 11.0 min, τ_{minor}= 19.1 min. **[α]$^{20}_D$**= -121.9 (*c*= 1.19, $CHCl_3$). **mp**= 67-71 °C.

2-[(1*R*,2*R*)-2-Isopropyl-2-phenylcyclopropyl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane, (*R,R*)-**II-5n**



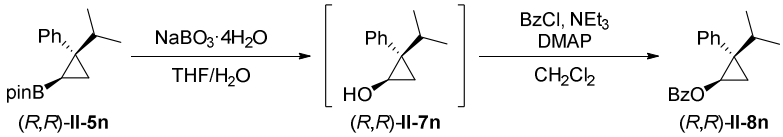
(*R,R*)-**II-5n**

From **II-4n** (35 µL, 0.2 mmol), following the general procedure described above (-20 °C, 12 h), compound (*R,R*)-**II-5n** (31.5 mg, 0.11 mmol, dr ≥ 81:19) was obtained in 54% yield as a colorless oil. **R_f =** 0.5 (5% EtOAc/hexanes).

^{1}H NMR (300 MHz, $CDCl_3$): δ7.26-7.06 (m, 5H), 1.53 (sept, *J* = 6.7 Hz, 1H), 1.22 (s, 6H), 1.19 (s, 6H), 1.02-0.96 (m, 1H), 0.88-0.82 (m, 1H), 0.80 (d, *J* = 6.7 Hz, 3H), 0.78 (d, *J* = 6.7 Hz, 3H), 0.21 (dd, *J* = 9.3, 7.0 Hz, 1H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 143.1, 131.8, 127.2, 126.2, 83.1, 39.2, 34.0, 33.8, 25.2, 24.6, 20.8, 20.5, 18.7. [note: the carbon attached to boron was not observed due to quadrupole broadening caused by the ^{11}B nucleus]. **HRMS (EI$^+$)** calculated for $C_{18}H_{27}BO_2$ $[M]^+$: 286.2104, found: 286.2112.

Compound (*R,R*)-**II-5n** was transformed into (*R,R*)-**II-8n** through oxidation followed by benzoylation to determine the enantiomeric ratio as described below.

(1*R*,2*R*)-2-Isopropyl-2-phenylcyclopropyl benzoate, (*R,R*)-II-8n



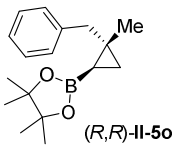
$NaBO_3 \cdot 4H_2O$ (4.0 equiv) was added to a solution of cyclopropylboronate (*R,R*)-**II-5n** (62 mg, 0.22 mmol) in THF/H_2O (1:1). The reaction mixture was stirred overnight at room temperature. Then it was quenched with H_2O, extracted with Et_2O (x3), combined organic phases were washed with brine, dried over Na_2SO_4, filtered and concentrated in vacuum to afford alcohol (*R,R*)-**II-7n**. This compound was used in the next step without further purification.

To a solution of alcohol (*R,R*)-**II-7n** in CH_2Cl_2, 4-dimethylaminopyridine (DMAP), triethylamine (3.0 equiv) and benzyl chloride (2.0 equiv) were added. The reaction mixture was stirred for 30 min and then quenched with H_2O. The aqueous layer was extracted with Et_2O (x3) and the combined organic phases were washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (eluent 5% EtOAc/hexanes) to afford compound (*R,R*)-**II-8n** (55 mg, 0.2 mmol) in 60% yield as a pale yellow solid. $\mathbf{R_f}$ **=** 0.7 (5% EtOAc/hexanes). Through this sequence, the major diastereomer was selectively oxidized and (*R,R*)-**II-8n** was obtained as a single diastereomer.

^{1}H NMR (300 MHz, $CDCl_3$): δ 8.10-8.05 (m, 2H), 7.59 (t, *J* = 7.4 Hz, 1H), 7.53-7.40 (m, 4H), 7.36-7.21 (m, 3H), 4.63 (dd, *J* = 7.2, 3.6 Hz, 1H), 1.77 (sept, *J* = 6.8 Hz, 1H), 1.35-1.29 (m, 1H), 1.08 (dd, *J* = 6.1, 3.6 Hz, 1H), 0.99 (d, *J* = 6.8 Hz, 3H), 0.83 (d, *J* = 6.8 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ167.7, 140.1, 133.1, 131.5, 130.1, 129.6, 128.5, 127.8, 126.8, 60.2, 36.7, 31.5, 20.2, 20.0, 18.7. **HRMS (EI$^+$)** calculated for $C_{12}H_{25}O$ $[M\text{-}Bz]^+$:175.1123, found: 175.1123. **mp=** 69-71°C. Compound (*R,R*)-**II-8n** was obtained with a 96:4 enantiomeric ratio determined by

SFC using Chiralpak-IC column [CO_2/MeOH (99:1), 1.0 mL/min]: τ_{major}= 14.2 min, τ_{minor}= 17.7 min. $[\alpha]^{20}_{D}$= -44.1 (*c* = 1.05, $CHCl_3$).

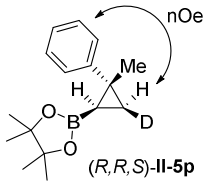
2-[(1*R*,2*S*)-2-Benzyl-2-methylcyclopropyl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane, (*R*,*S*)-II-5o



From **II-4o** (28 µL, 0.2 mmol), following the general procedure described above (-20 °C, 12 h), compound (*R*,*S*)-**II-5o** (27 mg, 0.1mmol, dr = 80:20) was obtained in 50% yield as a colorless oil. $\mathbf{R}_f$ = 0.45 (5% EtOAc/hexanes). Preparative thin layer chromatography (2% Et_2O/Pentane) afforded pure (*R*,*S*)-**II-5o**.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.31-7.24 (m, 4H), 7.22-7.12 (m, 1H), 2.82 (d, *J* = 14.7 Hz, 1H), 2.76 (d, *J* = 14.7 Hz, 1H), 1.22 (s, 6H), 1.18 (s, 6H), 1.01 (s, 3H), 0.88 (dd, *J* = 6.7, 3.5 Hz, 1H), 0.69 (dd, *J* = 9.3, 3.5 Hz, 1H), -0.07 (dd, *J* = 9.3, 6.7 Hz, 1H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 141.4, 129.1, 128.0, 125.7, 83.1, 41.6, 25.1, 24.9, 24.6, 23.4, 19.3. [note: the carbon attached to boron was not observed due to quadrupole broadening caused by the ^{11}B nucleus]. **HRMS (EI$^+$)** calculated for $C_{17}H_{25}BO_2$ $[M]^+$:272.1948, found: 272.1953. Compound (*R*,*S*)-**II-5o** was obtained with a 98:2 enantiomeric ratio determined by SFC using Chiralpak-IC column [CO_2/MeOH (99.5:0.5), 1.0 mL/min]: τ_{major}= 6.9 min, τ_{minor}= 7.6 min. $[\alpha]^{20}_{D}$= -44.3 (*c* = 1.15, $CHCl_3$).

4,4,5,5-Tetramethyl-2-[(1*R*,2*R*,3*S*)-2-methyl-2-phenylcyclopropyl-3-*d*]-1,3,2-dioxaborolane, (*R*,*R*,*S*)-II-5p



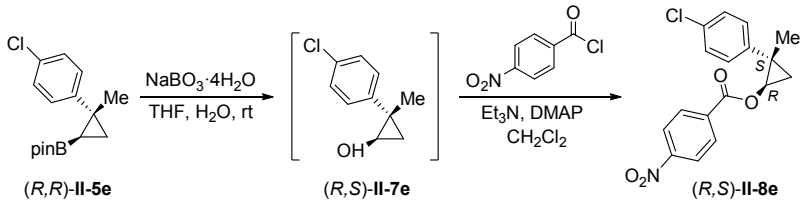
From **II-4p** (29 µL, 0.2 mmol), following the general procedure described above (MeOD, -20 °C, 36 h), compound (*R*,*R*,*S*)-**II-5p** (29 mg, 0.11 mmol, dr = 96:4) was obtained in 56% yield as a colorless oil. $\mathbf{R}_f$

= 0.5 (5% EtOAc/hexanes).The relative configuration was confirmed by nOe analysis.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.25-7.15 (m, 4H), 7.07 (t, *J* = 6.8 Hz, 1H), 1.42 (s, 3H), 1.21 (s, 6H), 1.19 (s, 6H), 1.10 (d, *J* = 9.7 Hz, 1H), 0.28 (d, *J* = 9.7 Hz, 1H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 148.1, 128.1, 127.0, 125.6, 83.2, 26.7, 25.2, 24.6, 22.9, 19.9 (t, $J_{C\text{-}D}$=24.6). [note: the carbon attached to boron was not observed due to quadrupole broadening caused by the ^{11}B nucleus]. **HRMS (EI$^+$)** calculated for $C_{16}H_{22}DBO_2$ $[M]^+$:259.1854, found: 259.1852. Compound (*R*,*R*,*S*)-**II-5p** was obtained with a 93:7 enantiomeric ratio determined by SFC using Chiralpak-IC column [CO_2/MeOH (99:1), 1.0 mL/min]: τ_{major}= 7.8 min, τ_{minor}= 8.9 min. **[α]$^{20}_D$**= -87.9 (*c*= 0.46, $CHCl_3$).

2.3.3.2. Synthesis of (1*R*,2*S*)-2-(4-Chlorophenyl)-2-methylcyclopropyl 4-nitrobenzoate, (*R*,*S*)-**II-8e**

The crystal structure of (*R*,*S*)-**II-8e** was obtained from the derived benzoate of (*R*,*R*)-**II-5e** using the following reaction sequence:

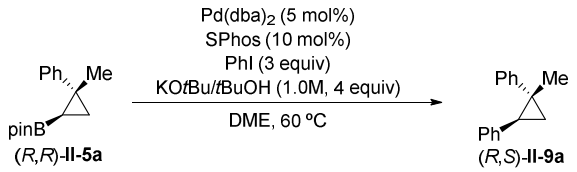


(*R*,*R*)-**II-5e** (*R*,*S*)-**II-7e** (*R*,*S*)-**II-8e**

$NaBO_3·4H_2O$ (4 equiv) was added to a solution of cycloropylboronate (*R*,*R*)-**II-5e** (33.6 mg, 0.13 mmol) in THF/H_2O (1:1). The reaction mixture was stirred overnight at room temperature and then quenched with H_2O and extracted with Et_2O (x3). The combined organic phases were washed with brine, dried over Na_2SO_4, filtered and concentrated in vacuum to afford compound (*R*,*S*)-**II-7e**. This compound was used in the next step without further purification.

To a solution of alcohol (*R,S*)-**II-7e** in CH_2Cl_2, 4-dimethylaminopyridine (DMAP) (27 mol%), triethylamine (3 equiv) and 4-nitrobenzoyl chloride (2.0 equiv) were added. The reaction mixture was stirred for 30 min at room temperature and then quenched with H_2O. The aqueous layer was extracted with Et_2O (x3) and the combined organic phases were washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (eluent 5% EtOAc/hexanes) to afford compound (*R,S*)-**II-8e** in 35% yield (two steps) as a white solid.
^{1}H NMR (300 MHz, $CDCl_3$): δ 8.37-8.29 (m, 2H), 8.28-8.21 (m, 2H), 7.43-7.35 (m, 2H), 7.35-7.28 (m, 2H), 4.41 (dd, *J* = 7.3, 3.7 Hz, 1H), 1.48 -1.37 (m, 4H), 1.17 (dd, *J* = 6.7, 3.8 Hz, 1H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 165.7, 150.7, 142.8, 135.0, 132.48, 130.7, 129.4, 128.8, 123.7, 60.1, 26.1, 20.3, 18.9. **mp**= 89-92 ºC (hexane:*i*PrOH, 1:1). **HRMS (MALDI):** calculated for $C_{17}H_{14}ClNO_4$ $[M]^+$: 331.0611, found 331.0598. **$[\alpha]^{20}_D$**= -98.2 (*c* = 0.92, $CHCl_3$).

2.3.3.3. Synthesis of [(1*R*,2*S*)-1-Methylcyclopropane-1,2-diyl]dibenzene, (*R,S*)-**II-9a**

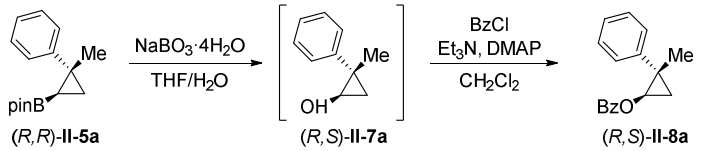


To a solution of (*R,R*)-**II-5a** (38.7 mg, 0.15 mmol), iodobenzene (3.0 equiv), $Pd(dba)_2$ (5 mol%), 2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl (S-Phos) (10 mol%) in dry dimethoxyethane, a *t*BuOH solution of KO*t*Bu (1.0 M, 4.0 equiv) was added. The reaction mixture was stirred for 16 h at 60°C. After the reaction was complete (TLC), water and hexane were added, and then the organic layer was separated. The aqueous layer was extracted twice with hexane. The

combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (hexanes) to afford (*R,S*)-**II-9a** (23.4 mg, 0.11 mmol) in 75% yield as a colorless oil. Spectroscopic data of (*R,S*)-**9a** are in agreement with those described for racemic **(±)-II-9a**,[60] except for the optical rotation.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.45-7.22 (m, 10H), 2.45 (dd, *J* = 8.8, 6.4 Hz, 1H), 1.49 (dd, *J* = 8.8, 5.1 Hz, 1H), 1.28 (dd, *J* = 6.4, 5.1 Hz, 1H), 1.16 (s, 3H). Compound (*R,S*)-**II-9a** was obtained with a 95:5 enantiomeric ratio determined by SFC using Chiralpak-IA column [CO_2/MeOH (99.5:0.5), 1.0 mL/min]: τ_{major}= 12.8 min, τ_{minor}= 14.1 min. **[α]$^{20}_D$**= -156.5 (*c* = 1.08, $CHCl_3$).

2.3.3.4. Synthesis of (1*R*,2*S*)-2-Methyl-2-phenylcyclopropyl benzoate, (*R,S*)-**II-8a**



$NaBO_3 \cdot 4H_2O$ (4 equiv) was added to a solution of cycloropylboronate (*R,R*)-**II-5a** (33.6 mg, 0.13 mmol) in THF/H_2O (1:1). The reaction mixture was stirred overnight at room temperature and then quenched with H_2O and extracted with Et_2O (x3). The combined organic phases were washed with brine, dried over Na_2SO_4, filtered and concentrated in vacuum to afford compound (*R,S*)-**II-7a**. This compound was used in the next step without further purification.

To a solution of alcohol (*R,S*)-**II-7a** in CH_2Cl_2, 4-dimethylaminopyridine (DMAP) (27 mol%), triethylamine (3 equiv) and benzoyl chloride (2.0 equiv) were added. The reaction mixture was stirred

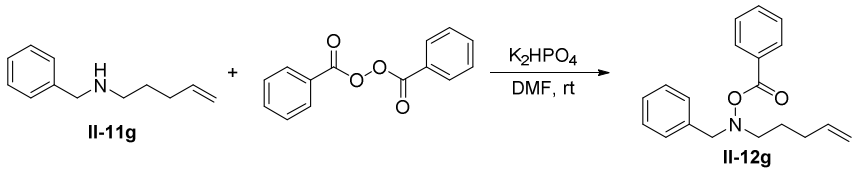
[60] Berkessel, A.; Kaiser, P.; Lex, J. *Chem. Eur. J.* **2003**, *9*, 4746-4756.

for 30 min at room temperature and then quenched with H_2O. The aqueous layer was extracted with Et_2O (x3) and the combined organic phases were washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (eluent 5% EtOAc/hexanes) to afford compound (*R,S*)-**II-8a** (15.7 mg, 0.06 mmol) in 48% yield (two steps) as a colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ 8.09 (d, *J* = 7.7 Hz, 2H), 7.59 (t, *J* = 7.4 Hz, 1H), 7.51-7.42 (m, 4H), 7.33 (t, *J* = 7.4 Hz, 2H), 7.25-7.18 (m, 1H), 4.42 (dd, *J* = 7.2, 3.7 Hz, 1H), 1.46 (s, 3H), 1.44-1.35 (m, 1H), 1.11 (dd, *J* = 6.3, 3.7 Hz, 1H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 167.6, 144.9, 133.2, 130.0, 129.67, 128.6, 128.5, 128.0, 126.5, 59.5, 26.4, 20.4, 19.1. Compound (*R,S*)-**4a** was obtained with a 95:5 enantiomeric ratio determined by SFC using Chiralpak-IC column [CO_2/MeOH (99:1), 1.0 mL/min]: τ_{major}= 18.1 min, τ_{minor}= 19.9 min. **[α]$^{20}_D$**= -71.6 (*c* = 0.96, $CHCl_3$).

2.3.4. Diastereoselective Aminoboration of Cyclopropenes

2.3.4.1. Synthesis of *O*-Benzoyl-*N*-benzyl-*N*-(pent-4-en-1-yl)hydroxylamine, **II-12g**

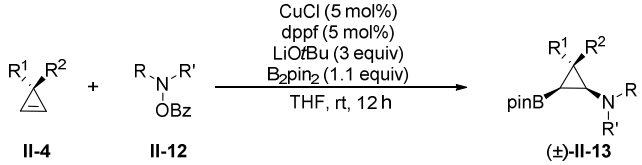


To a solution of benzoyl peroxide (815 mg, 3.4 mmol), dipotassium hydrogen phosphate (888 mg, 5.1 mmol), and *N,N*-dimethyl formamide (125 mL), *N*-benzylpent-4-en-1-amine, **II-11g** (648.0 mg, 3.7 mmol) was added in one portion. The reaction mixture was stirred overnight at room temperature. Water (20 mL) was added and stirred vigorously for several

minutes until all solids were dissolved. The reaction mixture was extracted with ethyl acetate (2 x 20 mL). The organic phase was collected and washed with saturated aq. $NaHCO_3$ solution. All of the organic fractions were combined and washed with water, brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The resulting crude product was purified by flash column chromatography (3% EtOAc/hexanes) to afford the desired product **II-12g** (498 mg, 1.7 mmol) in 50% yield as a yellow oil. $\mathbf{R}_f$ = 0.9 (50% EtOAc/hexanes).

^{1}H NMR (300 MHz, $CDCl_3$): δ 8.01-7.93 (m, 2H), 7.56 (ddd, *J* = 6.7, 2.5, 1.3 Hz, 1H), 7.49-7.39 (m, 4H), 7.37-7.26 (m, 3H), 5.81 (ddt, *J* = 16.9, 10.2, 6.6 Hz, 1H), 5.08-4.92 (m, 2H), 4.22 (s, 2H), 3.10-3.01 (m, 2H), 2.18 (m, 2H), 1.82-1.70 (m, 2H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ165.2, 138.1, 135.8, 133.0, 129.7, 129.4 (2C), 128.42, 128.36, 127.7, 115.1, 63.7, 57.9, 31.3, 26.2. **HRMS (EI$^+$)** calculated for $C_{19}H_{21}NO_2$ $[M+H]^+$: 296.1650, found: 296.1643.

2.3.4.2. General Procedure for the Synthesis of Chiral Cyclopropylamino Boronates, (±)-II-13

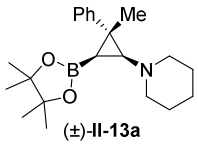


II-4 **II-12** **(±)-II-13**

An oven-dried vial was charged with CuCl (2 mg, 0.01 mmol, 0.05 equiv), LiO*t*Bu (96 mg, 1.2 mmol, 3 equiv) and dppf (11 mg, 0.01 mmol, 0.05 equiv) and sealed with a septum. After the vial was connected to an argon-vacuum line, it was evacuated and backfilled with argon (x3). THF (1.0 mL/0.4 mmol of **II-4**) was added and the mixture was stirred for 15 minutes at room temperature. Then, a solution of B_2pin_2 (112 mg, 0.44 mmol, 1.1 equiv), cyclopropene **II-4** (0.4 mmol, 1.0 equiv) and amine **II-12**(1.52 equiv) in THF (1mL/0.4 mmol of **II-4**) was added and the mixture

was stirred overnight at room temperature. Et_2O and water were added and the layers were separated. The aqueous phase was extracted with Et_2O (x3) and the combined organic layers were washed with saturated NaCl solution, dried over Na_2SO_4, filtered and concentratedunder reduced pressure. Product (±)-**II-13** was purified by flash column chromatographyusing florisil® (eluent is indicated in each case).

1-[(1*S,2*R**,3*S**)-2-Methyl-2-phenyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)cyclopropyl]piperidine,** (±)-**II-13a**

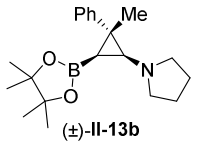


(±)-**II-13a**

From **II-4a** (58 µL, 0.4 mmol) and piperidin-1-yl benzoate (124 mg, 0.6 mmol), following the general procedure described above, compound (±)-**II-13a** was obtained. Purification by flash column chromatography (10%-30% EtOAc/hexanes) afforded (±)-**II-13a** (84.6 mg, 0.25 mmol, 62%, dr = 97:3) as a white solid. $\mathbf{R}_f$ = 0.2 (30% EtOAc/hexanes).

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.17 (d, *J* = 4.3 Hz, 4H), 7.09 - 7.02 (m, 1H), 2.44 (d, *J* = 12.8 Hz, 4H), 2.00 (d, *J* = 8.3 Hz, 1H), 1.56-1.43 (m, 4H), 1.50 (s, 3H), 1.42-1.31 (m, 2H), 1.18 (s, 12H), 0.37 (d, *J* = 8.3 Hz, 1H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 149.0, 128.2, 127.7, 125.7, 82.7, 56.3, 54.9, 32.5, 26.0, 25.1, 24.9, 24.7, 18.2. [note: the carbon attached to boron was not observed due to quadrupole broadening caused by the ^{11}B nucleus]. **HRMS (EI$^+$)** calculated for $C_{21}H_{32}BNO_2$ $[M]^+$: 341.2526, found: 341.2535. **mp=** 75-77 °C.

1-[(1*S,2*R**,3*S**)-2-Methyl-2-phenyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)cyclopropyl]pyrrolidine,** (±)-**II-13b**

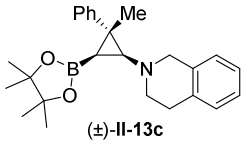


(±)-**II-13b**

From **II-4a** (58 µL, 0.4 mmol) and pyrrolidin-1-yl benzoate, (116 mg, 0.6 mmol), following the general procedure described above, compound (±)-**II-13b** was obtained. Purification by flash column chromatography (10%-30% EtOAc/hexanes) afforded (±)-**II-13b** (43.2 mg, 0.13 mmol, 65%, dr ≥ 98:2) as a colorless oil. $\mathbf{R}_f$ **=** 0.2 (30% EtOAc/hexanes).

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.18 (d, *J* = 4.3 Hz, 4H), 7.07 (dd, *J* = 8.5, 4.3 Hz, 1H), 2.59 (t, *J* = 8.0 Hz, 4H), 2.00 (d, *J* = 8.3 Hz, 1H), 1.72-1.63 (m, 4H), 1.52 (s, 3H), 1.19 (s, 6H), 1.18 (s, 6H), 0.43 (d, *J* = 8.3 Hz, 1H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 148.9, 128.3, 127.7, 125.7, 82.8, 54.1, 32.2, 25.1, 24.8, 24.1, 18.6. [note: the carbon attached to boron was not observed due to quadrupole broadening caused by the ^{11}B nucleus]. **HRMS (EI$^+$)** calculated for $C_{20}H_{30}BNO_2$ $[M]^+$: 327.2370, found:327.2379.

2-[(1*S,2*R**,3*S**)-2-Methyl-2-phenyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)cyclopropyl]-1,2,3,4-tetrahydroisoquinoline,**(±)-**II-13c**



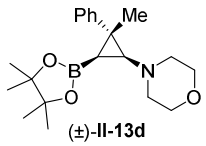
(±)-**II-13c**

From **II-4a** (58 µL, 0.4 mmol) and 3,4-dihydroisoquinolin-2(1*H*)-yl benzoate (143 mg, 0.6 mmol), following the general procedure described above, compound (±)-**II-13c** was obtained. Purification by flash column chromatography (10%-30% EtOAc/hexanes) afforded (±)-**II-13c** (71.6 mg, 0.18 mmol, 46%, dr = 97:3) as a colorless oil. $\mathbf{R}_f$ **=** 0.8 (33% EtOAc/hexanes).

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.27-7.20 (m, 4H), 7.18 (d, *J* = 1.0 Hz, 1H), 7.07-6.99 (m, 4H), 3.74 (s, 2H), 2.98-2.65 (m, 4H),2.22 (d, *J* = 8.3 Hz, 1H), 1.55 (s, 3H), 1.16 (s, 6H), 1.15 (s, 6H),0.50 (d, *J* = 8.2 Hz, 1H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 148.6, 135.7, 135.1, 128.8, 128.4, 127.7, 126.6, 125.9, 125.9, 125.5, 82.9, 56.3, 55.6, 51.2, 32.7, 29.4, 25.1, 24.9, 18.3. [note: the carbon attached to boron was not observed due to quadrupole broadening caused by the ^{11}B nucleus]. **HRMS (EI$^+$)** calculated for $C_{25}H_{33}BNO_2$ $[M+H]^+$: 390.2604, found: 390.2596.

4-[(1*S,2*R**,3*S**)-2-Methyl-2-phenyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)cyclopropyl]morpholine,** (±)-**II-13d**

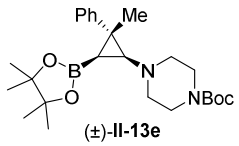


(±)-**II-13d**

From **II-4a** (58 μL, 0.4 mmol) and morpholino benzoate (126 mg, 0.6 mmol), following the general procedure described above, compound (±)-**II-13d** was obtained. Purification by flash column chromatography (10%-30% EtOAc/hexanes) afforded (±)-**II-13d** (79.6 mg, 0.23 mmol, 58%, dr = 95:5) as a colorlessoil. **R_f =** 0.7 (33% EtOAc/hexanes).

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.21-7.16 (m, 4H), 7.13-7.04 (m, 1H), 3.69-3.59 (m, 4H), 2.68-2.43 (m, 4H), 2.07 (d, *J* = 8.2 Hz, 1H), 1.51 (s, 3H), 1.18 (s, 12H), 0.41 (d, *J* = 8.2 Hz, 1H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 148.4, 128.3, 127.6, 125.9, 82.8, 67.1, 55.4, 53.9, 32.3, 25.1, 24.9, 18.3. [note: the carbon attached to boron was not observed due to quadrupole broadening caused by the ^{11}B nucleus]. **HRMS (EI$^+$)** calculated for $C_{20}H_{30}BNO_3$ $[M]^+$: 343.2319, found: 343.2326.

***tert*-Butyl 4-[(1*S**,2*R**,3*S**)-2-methyl-2-phenyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)cyclopropyl)piperazine-1-carboxylate],** (±)-**II-13e**



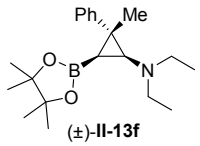
(±)-**II-13e**

From **II-4a** (58 μL, 0.4 mmol) and *tert*-butyl 4-(benzoyloxy)piperazine-1-carboxylate (186.3 mg, 0.6 mmol), following the general procedure described above, compound (±)-**II-13e** was obtained. Purification by

flash column chromatography (10%-30% EtOAc/hexanes) afforded (±)-**II-13e** (93.8 mg, 0.21mmol, 53%, dr ≥ 98:2) as a colorless oil. $\mathbf{R_f}$ **=** 0.5 (10% EtOAc/hexanes).

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.21-7.15 (m, 4H), 7.12-7.03 (m, 1H), 3.42-3.30 (m, 4H), 2.60-2.35 (m, 4H), 2.05 (d, *J* = 8.2 Hz, 1H), 1.50 (s, 3H), 1.40 (s, 9H), 1.18 (s, 12H), 0.42 (d, *J* = 8.2 Hz, 1H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 155.1, 148.3, 128.3, 127.6, 125.9, 82.8, 79.5, 55.0, 53.1, 32.4, 28.6, 28.3, 25.1, 24.9, 18.3. [note: the carbon attached to boron was not observed due to quadrupole broadening caused by the ^{11}B nucleus]. **HRMS (EI$^+$)** calculated for $C_{25}H_{39}BN_2O_4$ $[M]^+$: 442.3003, found: 442.3017.

(1*S,2*R**,3*S**)-*N*,*N*-Diethyl-2-methyl-2-phenyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)cyclopropan-1-amine,** (±)-**II-13f**

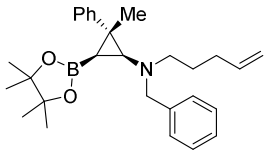


(±)-**II-13f**

From **II-4a** (58 µL, 0.4 mmol) and *O*-benzoyl-*N*,*N*-diethylhydroxylamine (117 mg, 0.6 mmol), following the general procedure described above, compound (±)-**II-13f** was obtained. Purification by flash column chromatography (10%-30% EtOAc/hexanes) afforded (±)-**II-13f** (92.2 mg, 0.28 mmol, 70%, dr = 97:3) as a colorless oil. $\mathbf{R_f}$ **=** 0.15 (33% EtOAc/hexanes).

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.18 (d, *J* = 4.1 Hz, 4H), 7.10-7.03 (m, 1H), 2.81-2.52 (m, 4H), 2.34 (d, *J* = 8.6 Hz, 1H), 1.51 (d, *J* = 2.0 Hz, 3H), 1.18 (s, 12H), 0.95 (t, *J* = 7.2 Hz, 6H), 0.43 (d, *J* = 8.4 Hz, 1H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 148.9, 128.3, 127.3, 125.7, 82.8, 54.5, 46.6, 33.7, 25.0, 24.9, 18.4, 10.9. [note: the carbon attached to boron was not observed due to quadrupole broadening caused by the ^{11}B nucleus]. **HRMS (EI$^+$)** calculated for $C_{20}H_{32}BNO_2$ $[M]^+$: 329.2526, found: 329.2516.

(1*S,2*R**,3*S**)-*N*-Benzyl-2-methyl-*N*-(pent-4-en-1-yl)-2-phenyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)cyclopropan-1-amine,** (±)-**II-13g**

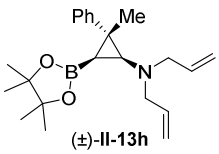


(±)-**II-13g**

From **II-4a** (58 µL, 0.4 mmol) and *O*-benzoyl-*N*-benzyl-*N*-(pent-4-en-1-yl)hydroxylamine (179 mg, 0.6 mmol), following the general procedure described above, compound (±)-**II-13g** was obtained. Purification by flash column chromatography (10% EtOAc/hexanes) afforded (±)-**II-13g** (93.2 mg, 0.22 mmol, 54%, dr = 92:8) as a colorless oil. $\mathbf{R}_f$ **=** 0.5 (33% EtOAc/hexanes).

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.49 (d, *J* = 6.8 Hz, 2H), 7.38-7.18 (m, 8H), 5.81 (ddt, *J* = 16.8, 10.0, 6.6 Hz, 1H), 5.11-4.88 (m, 2H), 3.96 (d, *J* = 14.0 Hz, 1H), 3.78 (d, *J* = 14.0 Hz, 1H), 2.71-2.51 (m, 2H), 2.57 (d, *J* = 8.4 Hz, 1H), 2.01 (m, 2H), 1.72 (s, 3H), 1.69-1.59 (m, 2H), 1.31 (s, 12H), 0.67 (d, *J* = 8.4 Hz, 1H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 148.6, 139.4, 138.9, 129.3, 128.3, 127.9, 127.3, 126.7, 125.8, 114.4, 82.9, 58.2, 55.1, 53.2, 34.4, 32.0, 25.2, 24.8, 24.4, 18.4. [note: the carbon attached to boron was not observed due to quadrupole broadening caused by the ^{11}B nucleus]. **HRMS (EI$^+$)** calculated for $C_{28}H_{38}BNO_2$ $[M]^+$: 431.2996, found: 431.3001.

(1*S,2*R**,3*S**)-*N*,*N*-Diallyl-2-methyl-2-phenyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)cyclopropan-1-amine,** (±)-**II-13h**

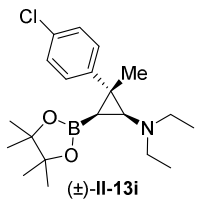


(±)-**II-13h**

From **II-4a** (58 µL, 0.4 mmol) and *N,N*-diallyl-*O*-benzoylhydroxylamine, 132 mg, 0.6 mmol), following the general procedure described above, compound (±)-**II-13h** was obtained. Purification by flash column chromatography (10%-30% EtOAc/hexanes) afforded (±)-**II-13h** (108.8 mg, 0.31 mmol, 77%, dr = 95:5) as a colorless oil. $\mathbf{R}_f$ **=** 0.7 (33% EtOAc/hexanes).

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.29-7.23 (m, 4H), 7.19-7.10 (m, 1H), 5.95 (ddt, *J* = 17.0, 10.2, 6.6 Hz, 2H), 5.12 (dd,*J* = 25.2, 16.1 Hz, 4H), 3.41-3.16 (m, 4H), 2.50 (d, *J* = 8.3 Hz, 1H), 1.60 (s, 3H), 1.26 (s, 12H), 0.52 (d, *J* = 8.3 Hz, 1H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ148.7, 135.5, 128.3, 127.6, 125.8, 117.3, 82.9, 56.2, 53.8, 34.2, 25.1, 25.0, 18.5. [note: the carbon attached to boron was not observed due to quadrupole broadening caused by the ^{11}B nucleus]. **HRMS (EI$^+$)** calculated for $C_{22}H_{32}BNO_2$ $[M]^+$: 353.2526, found: 353.2530.

(1*,2*R,3*S**)-2-(4-chlorophenyl)-*N*,*N*-diethyl-2-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)cyclopropan-1-amine,** (±)-**II-13i**

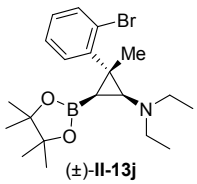


(±)-**II-13i**

From **II-4e** (52 µL, 0.4 mmol) and *O*-benzoyl-*N*,*N*-diethylhydroxylamine (117 mg, 0.6 mmol), following the general procedure described above, compound (±)-**II-13i** was obtained. Purification by flash column chromatography (10%-30%EtOAc/hexanes) afforded (±)-**II-13i** (94.6 mg, 0.26 mmol, 65%, dr ≥ 98:2) as a colorless oil. **R_f =** 0.15 (33% EtOAc/hexanes).

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.19-7.07 (m, 4H), 2.73-2.50 (m, 4H), 2.29 (d, *J* = 8.5 Hz, 1H), 1.47 (s, 3H), 1.18 (s, 12H), 0.94 (t, *J* = 7.2 Hz, 6H), 0.38 (d, *J* = 8.5 Hz, 1H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 147.4, 131.3, 128.7, 128.3, 82.9, 54.5, 46.5, 33.1, 25.0, 24.9, 18.3, 10.9. [note: the carbon attached to boron was not observed due to quadrupole broadening caused by the ^{11}B nucleus]. **HRMS (EI$^+$)** calculated for $C_{20}H_{31}BClNO_2$ $[M^+]$: 363.2136, found: 363.2140.

(1*S,2*R**,3*S**)-2-(2-Bromophenyl)-*N*,*N*-diethyl-2-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)cyclopropan-1-amine,** (±)-**II-13j**

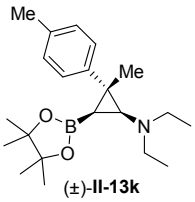


(±)-**II-13j**

From **II-4m** (68 µL, 0.4 mmol) and *O*-benzoyl-*N*,*N*-diethylhydroxylamine (117 mg, 0.6 mmol), following the general procedure described above, compound (±)-**II-13j** was obtained. Purification by flash column chromatography (10%-30%EtOAc/hexanes) afforded (±)-**II-13j** (99.6 mg, 0.24 mmol, 61%, dr ≥ 98:2) as a colorless oil. $\mathbf{R}_f$ **=** 0.3 (33% EtOAc/hexanes).

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.41 (dd, *J* = 7.9, 0.9 Hz, 1H), 7.25-7.06 (m, 2H), 7.01-6.86 (m, 1H), 2.69 (q, *J* = 7.1 Hz, 4H), 2.47 (d, *J* = 8.5 Hz, 1H), 1.47 (s, 3H), 1.19 (s, 12H), 0.99 (t, *J* = 7.1 Hz, 6H), 0.25 (d, *J* = 8.5 Hz, 1H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 147.7, 133.3, 131.1, 127.6, 127.4, 125.6, 82.8, 53.1, 45.8, 36.0, 25.0, 24.9, 16.8, 10.7. [note: the carbon attached to boron was not observed due to quadrupole broadening caused by the ^{11}B nucleus]. **HRMS (EI$^+$)** calculated for $C_{20}H_{31}BBrNO_2$ $[M]^+$: 407.1631, found: 407.1640.

(1*R,2*S**,3*R**)-*N*,*N*-Diethyl-2-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2-(*p*-tolyl)cyclopropan-1-amine,** (±)-**II-13k**



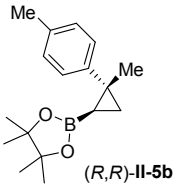
(±)-**II-13k**

From **II-4b** (56 µL, 0.4 mmol) and *O*-benzoyl-*N*,*N*-diethylhydroxylamine (117 mg, 0.6 mmol), following the general procedure described above, compound (±)-**II-13k** was obtained. Purification by flash column chromatography (10%-30%EtOAc/hexanes) afforded (±)-**II-13k** (94.8 mg, 0.28 mmol, 69%, dr = 97:3) as a colorless oil. $\mathbf{R}_f$ **=** 0.2 (33% EtOAc/hexanes).

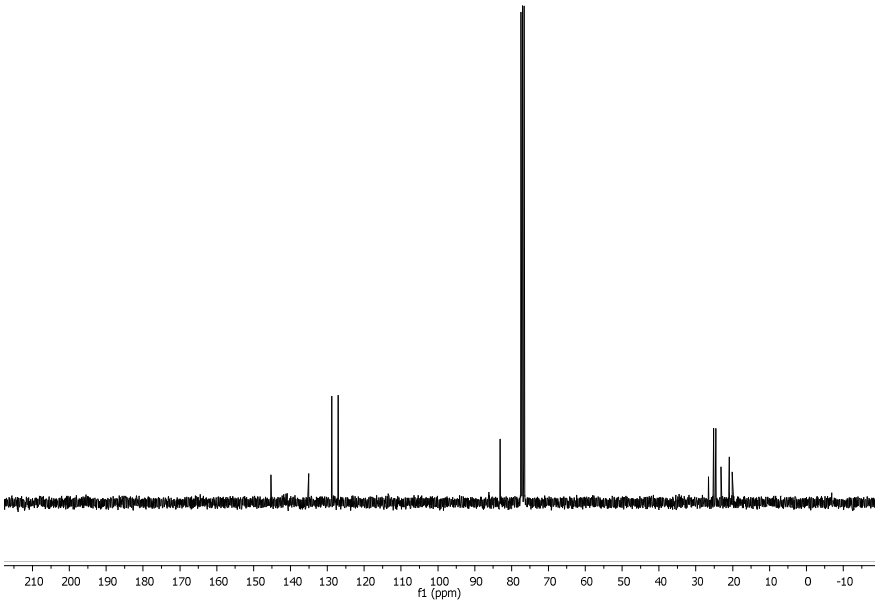
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.17 (d, *J* = 8.1 Hz, 2H), 7.09 (d, *J* = 8.1 Hz, 2H), 2.86-2.61 (m, 4H), 2.40 (d, *J* = 8.5 Hz, 1H), 2.32 (s, 3H), 1.58 (s, 3H), 1.27 (s, 12H), 1.04 (t, *J* = 7.1 Hz, 6H), 0.50 (d, *J* = 8.5 Hz, 1H). **^{13}C**

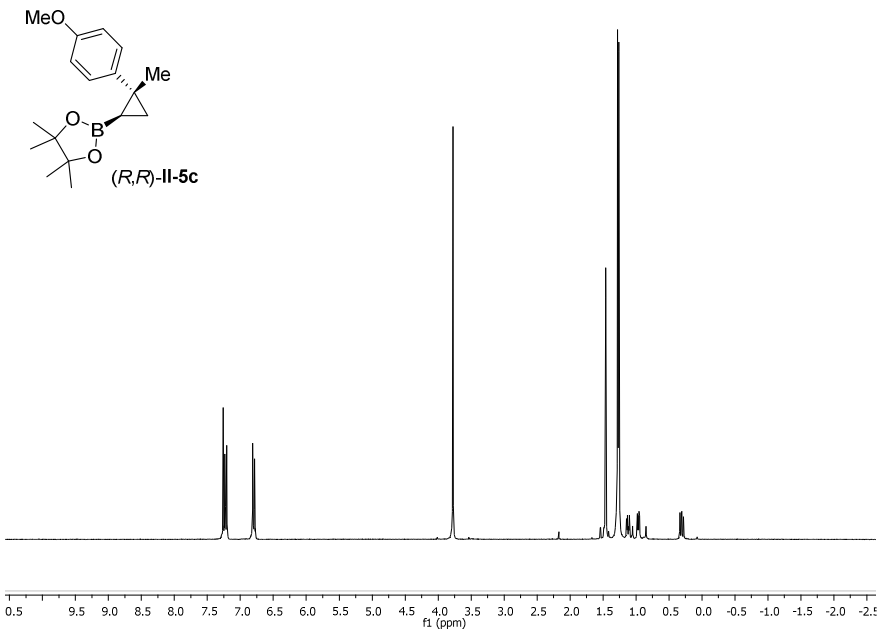
NMR (75 MHz, $CDCl_3$): δ 145.9, 135.0, 128.8, 127.1, 82.6, 54.4, 46.4, 33.3, 24.9, 24.8, 20.9, 18.4, 10.8. [note: the carbon attached to boron was not observed due to quadrupole broadening caused by the ^{11}B nucleus]. **HRMS (EI$^+$)** calculated for $C_{21}H_{34}BNO_2$ $[M]^+$: 343.2683, found: 343.2680.

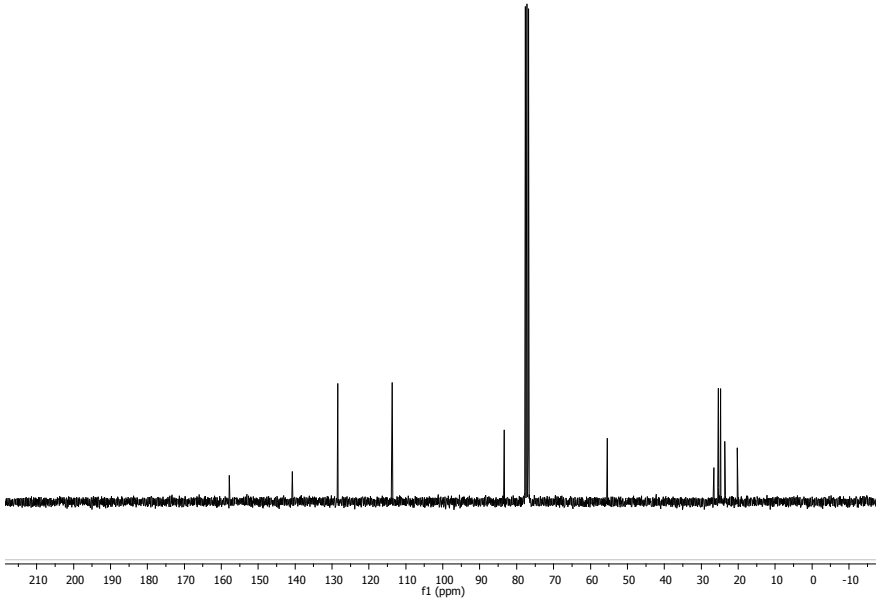
2.4. NMR spectra

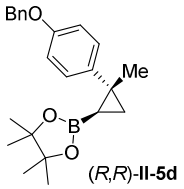


(*R*,*R*)-**II-5b**



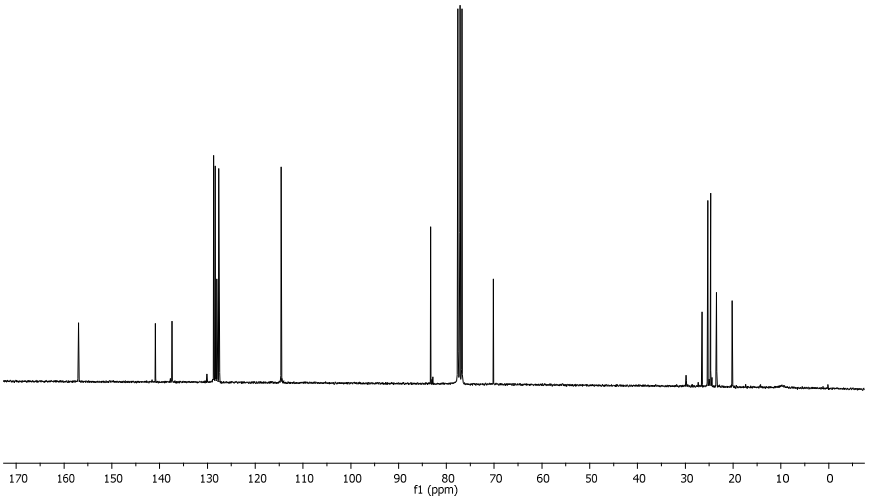

MeO
Me
O
B
O
(*R*,*R*)-**II-5c**
0.5 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0 -1.5 -2.0
f1 (ppm)

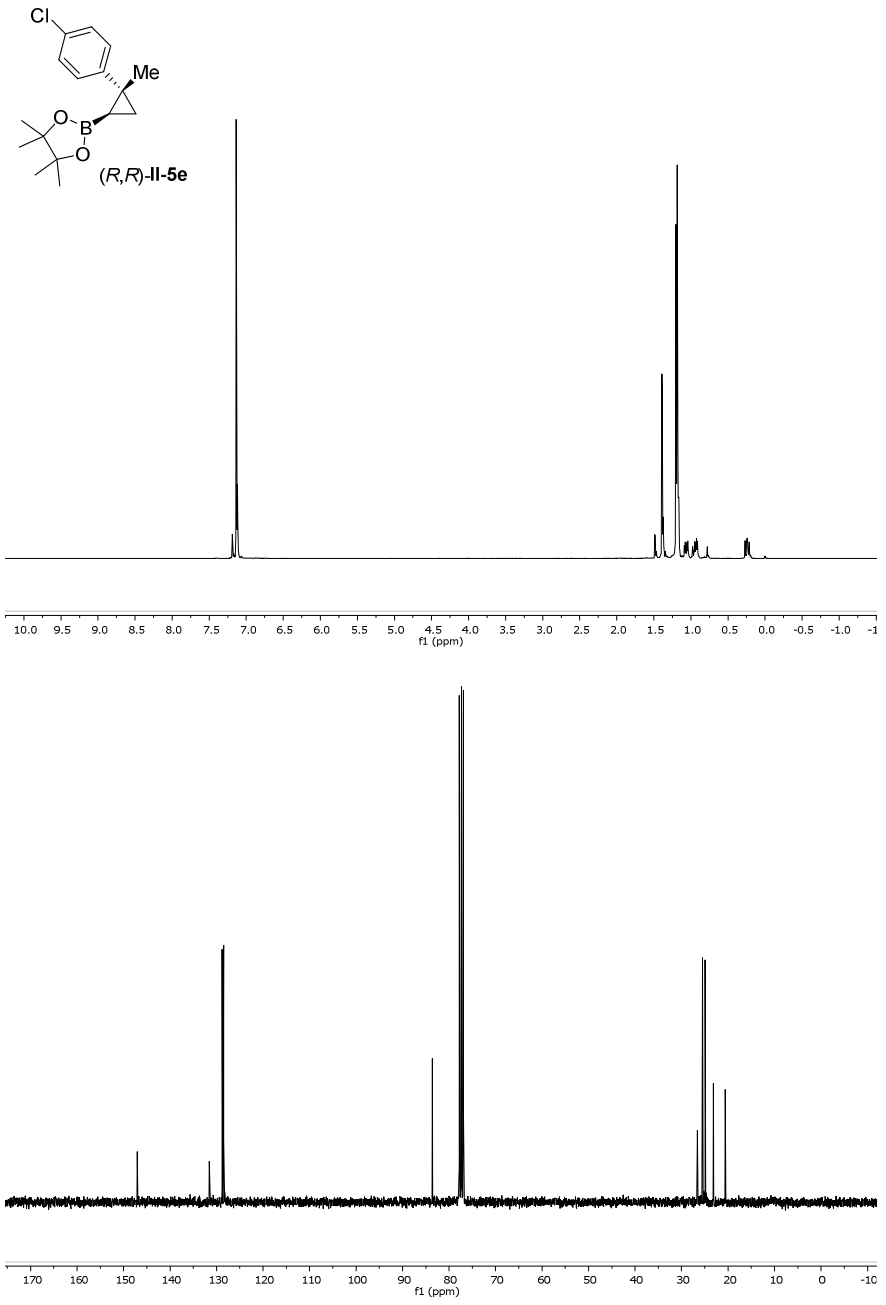

210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

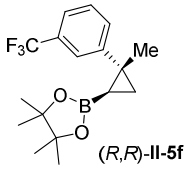

BnO
Me
O
B
O

(*R*,*R*)-**II-5d**

8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)

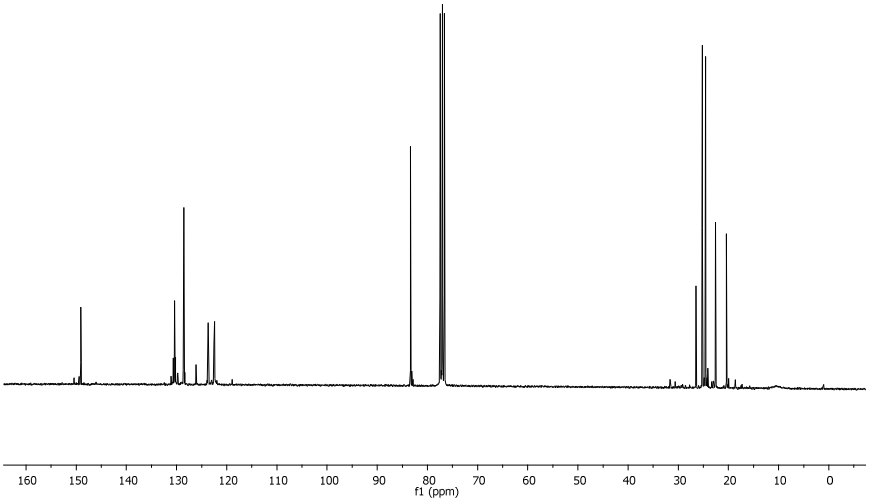

170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

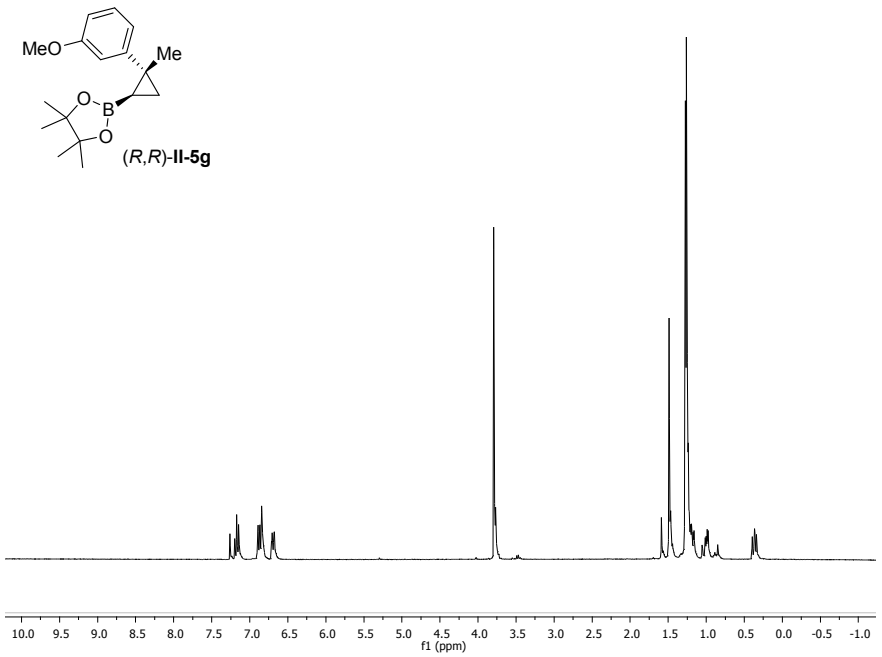

Cl
Me
O
B
O
(*R*,*R*)-**II-5e**
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0
f1 (ppm)
170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


F3C
Me
O
B
O

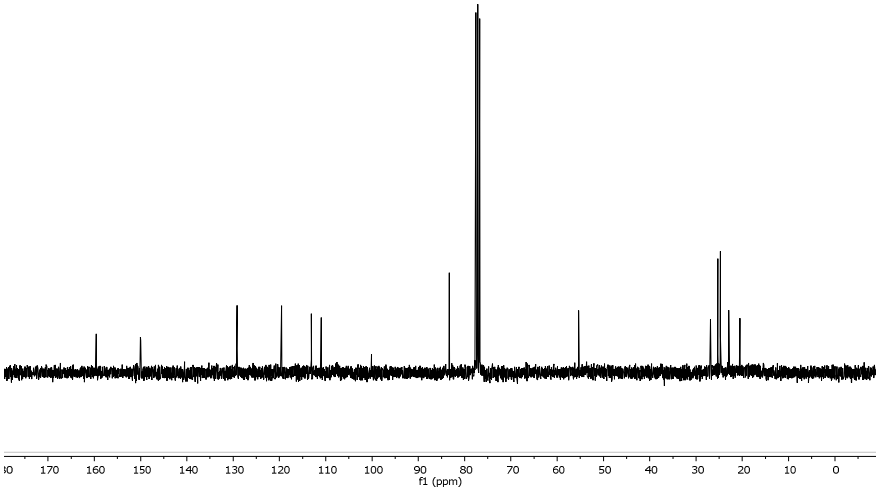
(*R*,*R*)-**II-5f**

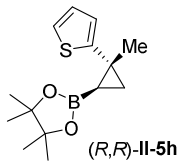
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


MeO
Me
O
B
O
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0
f1 (ppm)

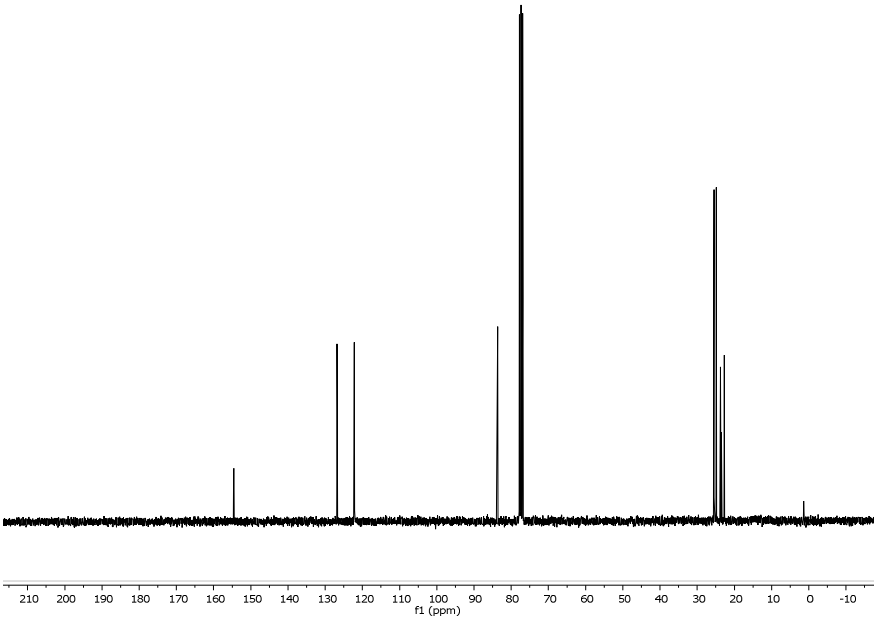
(*R*,*R*)-**II-5g**

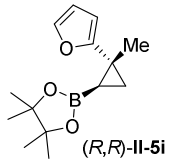

170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


S
Me
O
B
O

(*R*,*R*)-**II-5h**

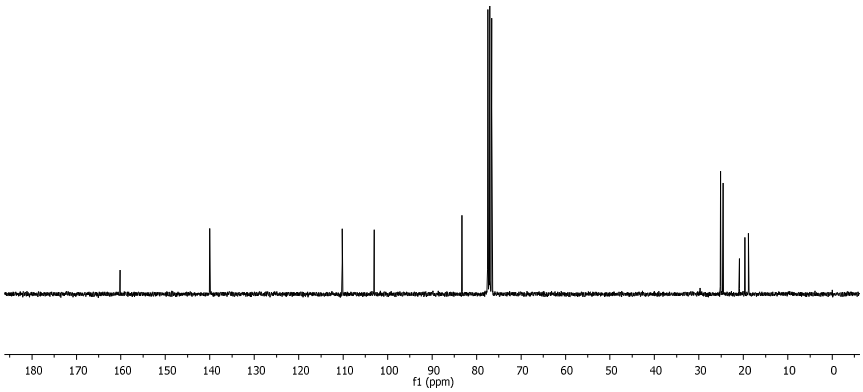
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0 -1
f1 (ppm)

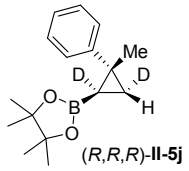

210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


Me
O
O
B
O

(*R*,*R*)-**II-5i**

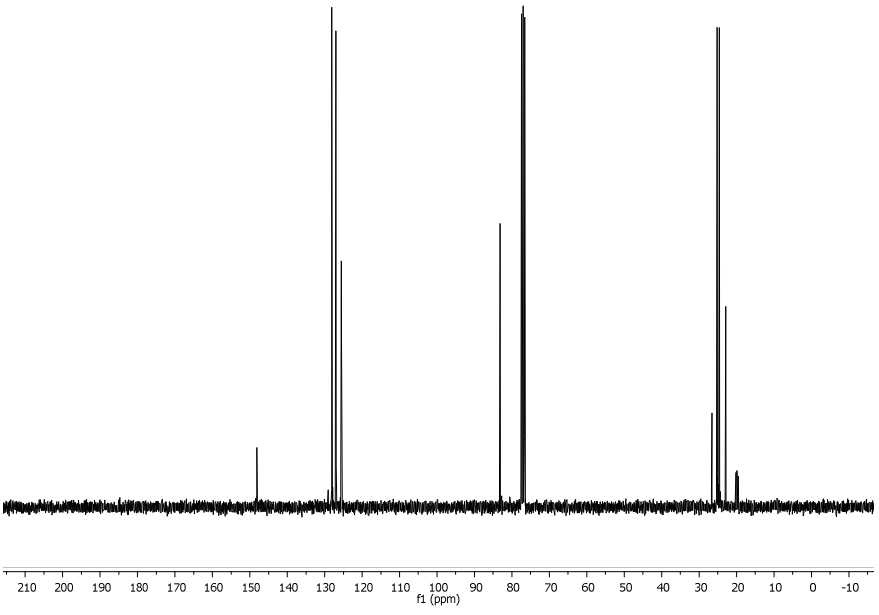
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)

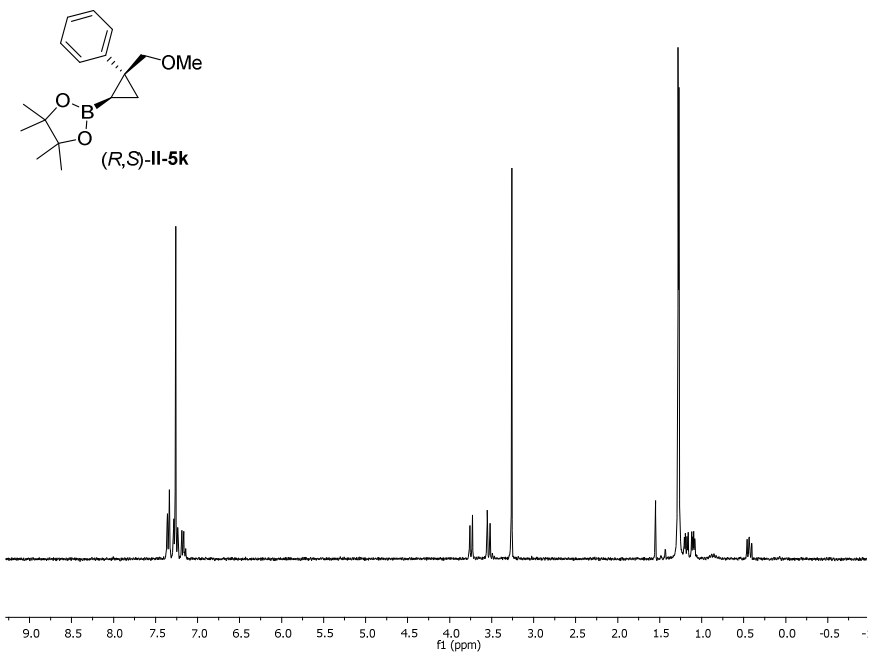

180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

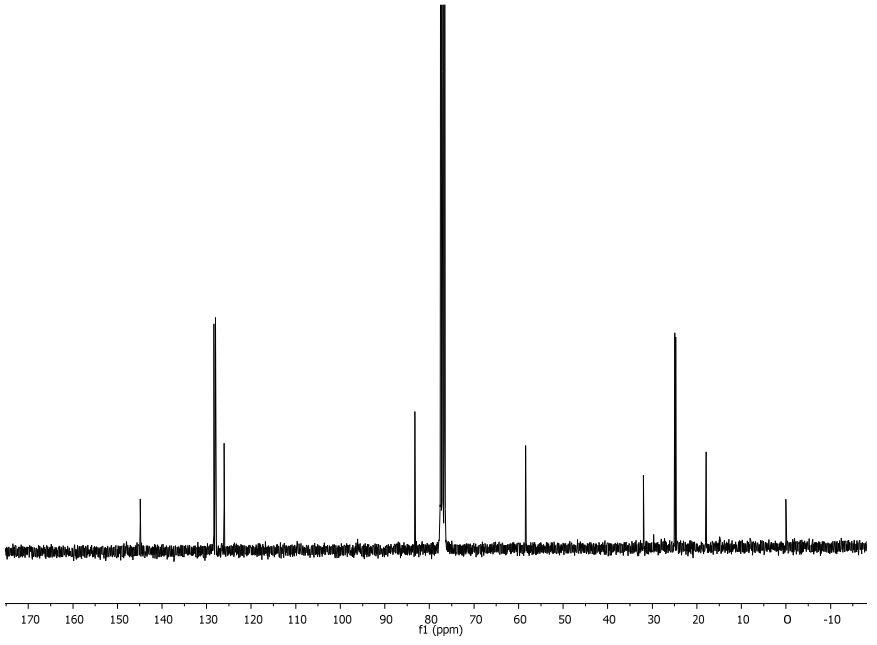

Me
D
D
O
B
O
H

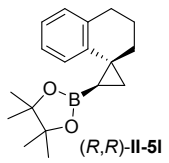
(*R*,*R*,*R*)-**II-5j**

9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0 -1.5
f1 (ppm)


210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

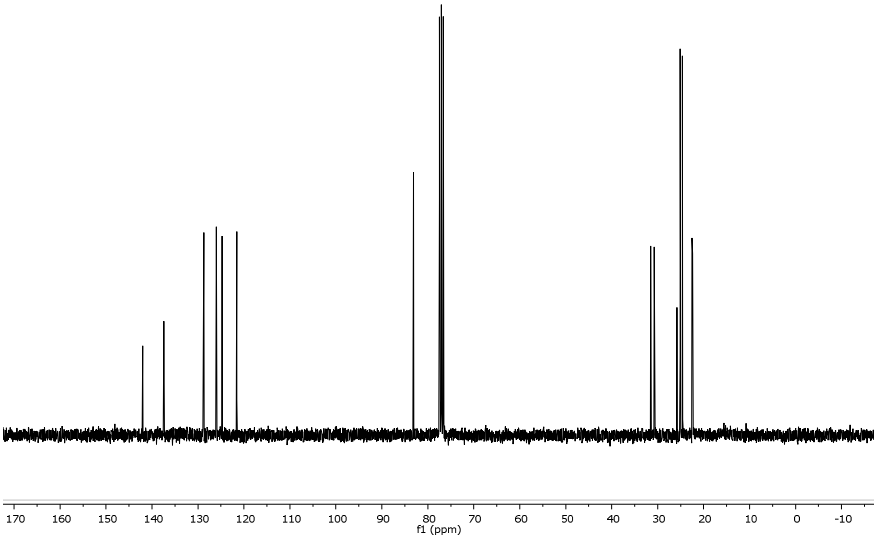

OMe
O
B
O
(*R*,*S*)-**II-5k**
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)


170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


O
B
O

(*R*,*R*)-**II-5l**

8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)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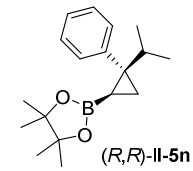
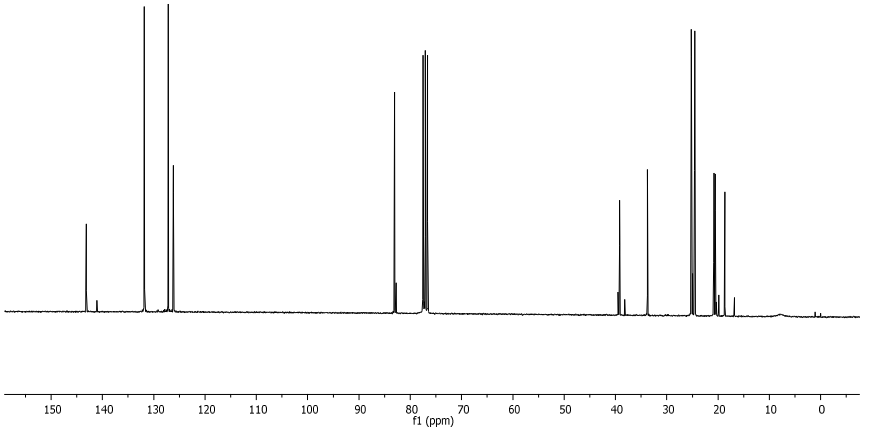
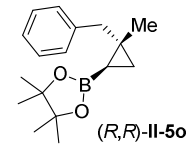
f1 (ppm)


O
B
O

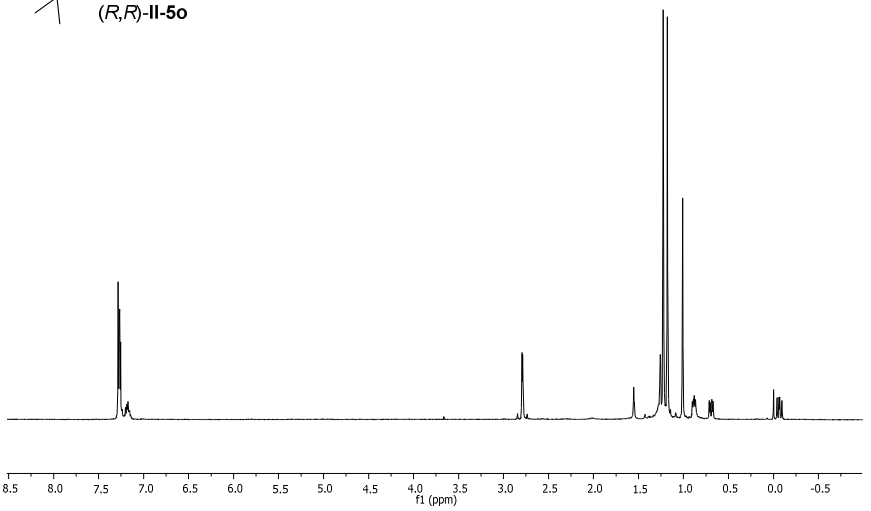
(*R*,*R*)-**II-5n**

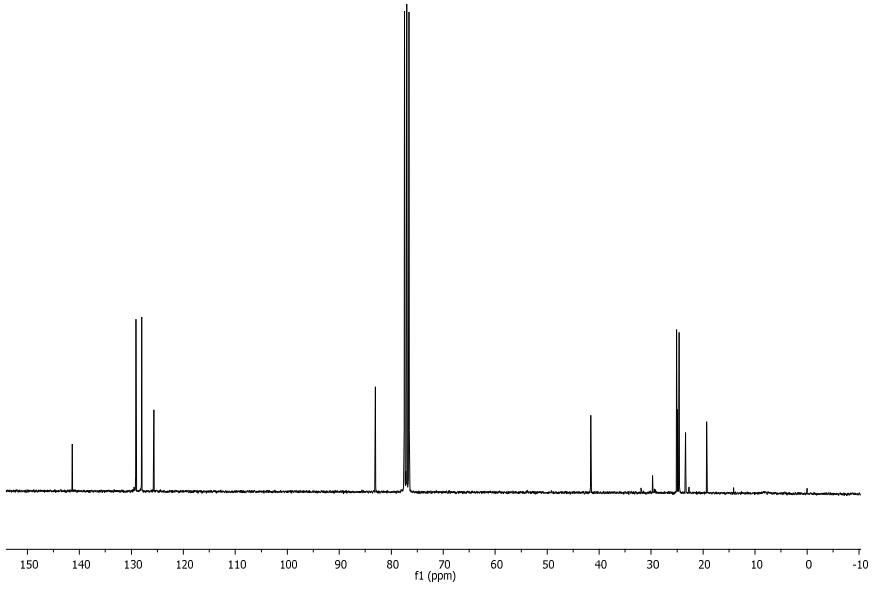
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

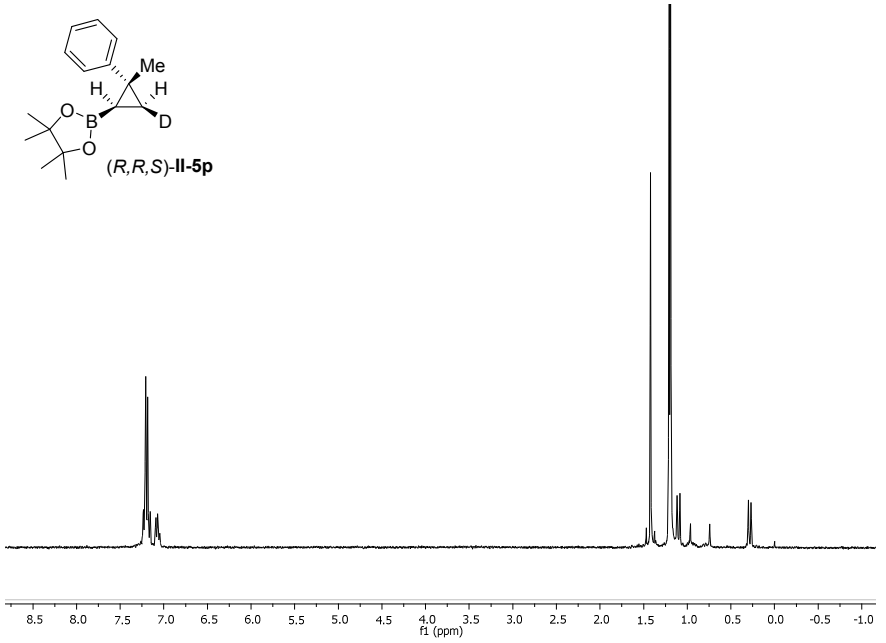

150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

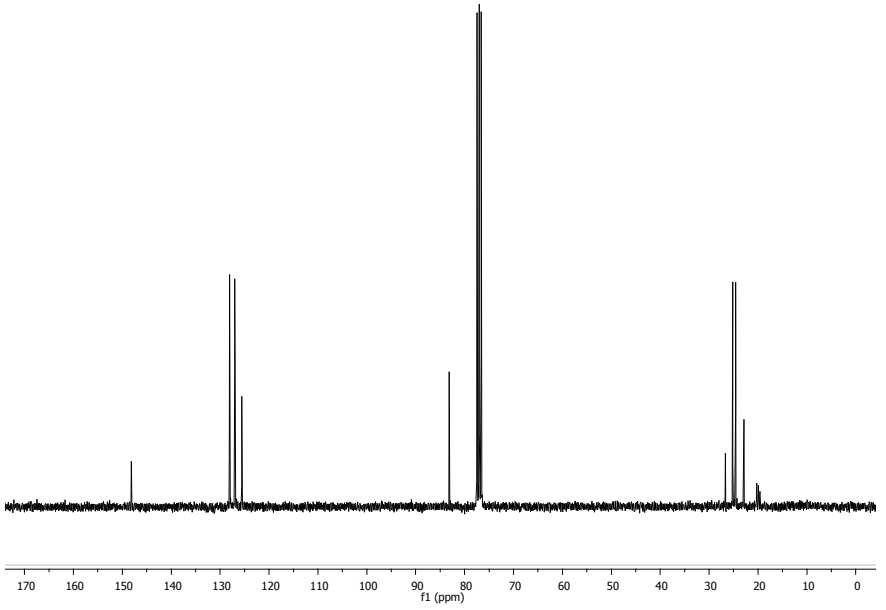

Me
O
B
O

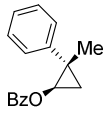
(*R*,*R*)-**II-5o**


8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)

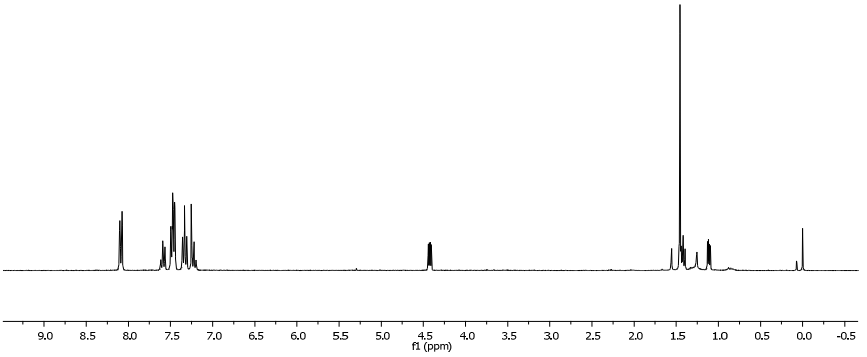

150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

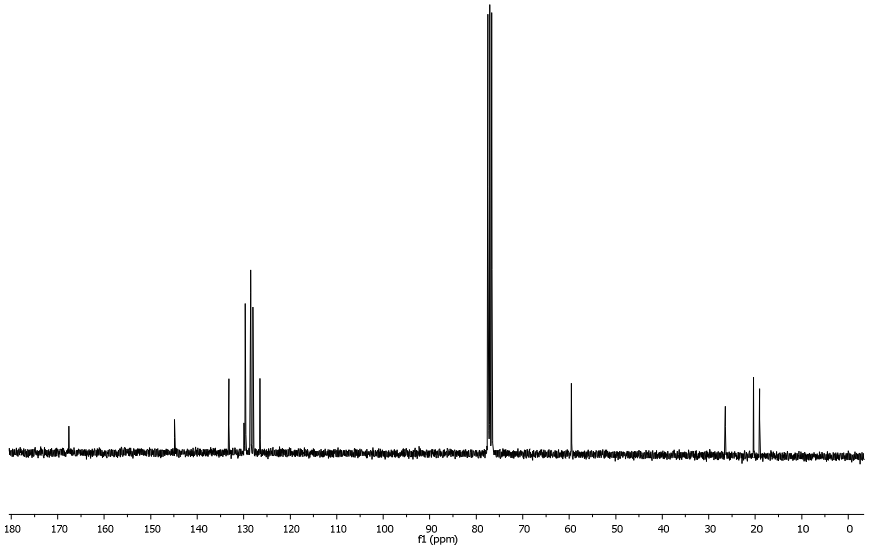

Me
H
H
O
B
D
O
(*R*,*R*,*S*)-**II-5p**
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0
f1 (ppm)

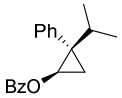

170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


Me
BzO

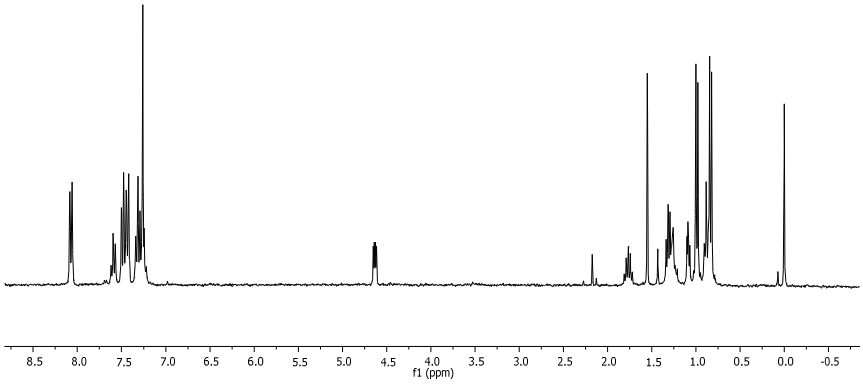
(*R,S*)-**II-8a**

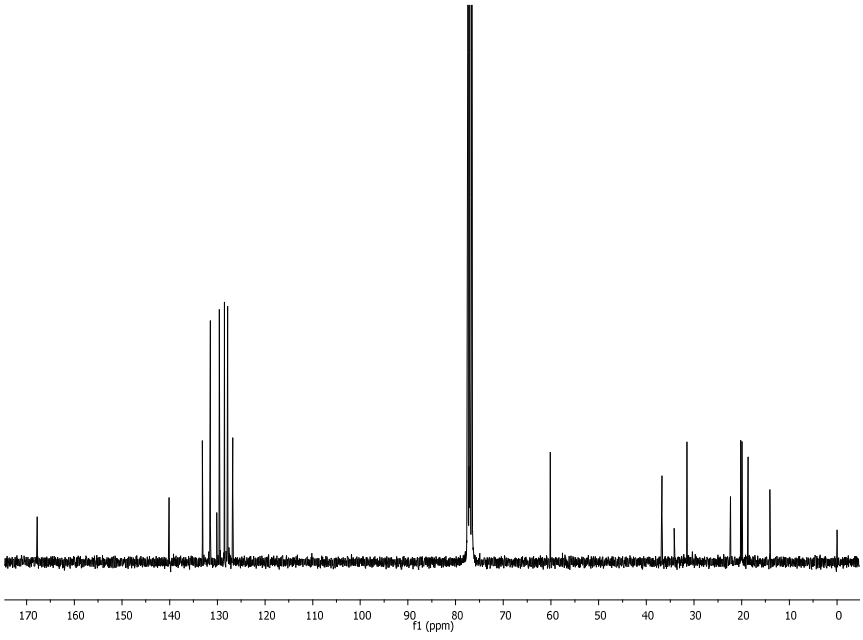

9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)

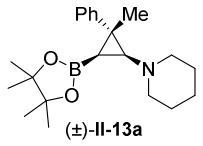

180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


Ph
BzO

(*R*,*R*)-**II-8n**

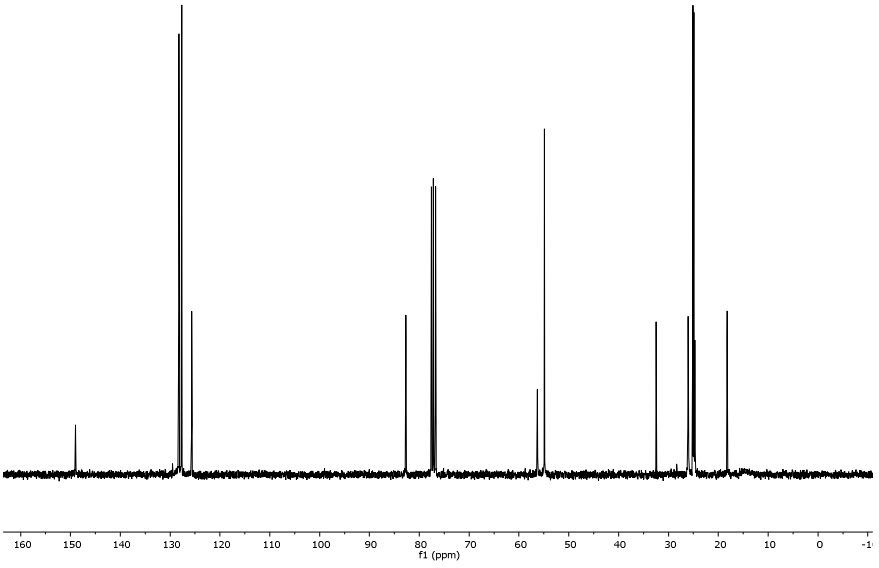

8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)

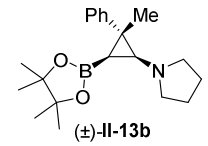

170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


Ph
Me
O
B
O
N

(±)-**II-13a**

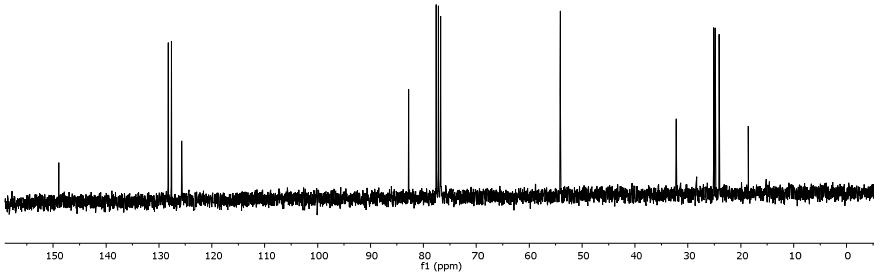
8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

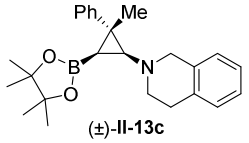

160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


Ph
Me
O
B
O
N

(±)-**II-13b**

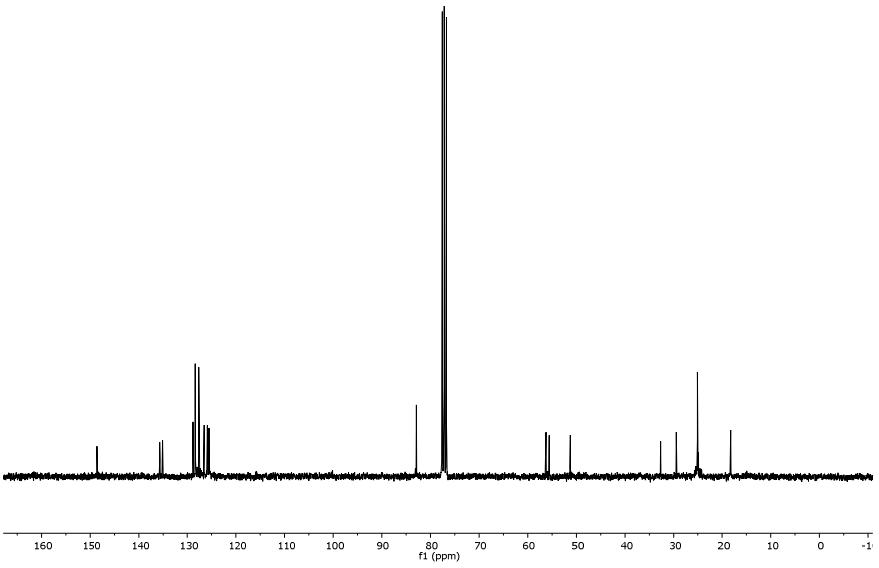
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0
f1 (ppm)

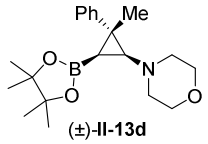

150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


Ph
Me
O
B
O
N

(±)-**II-13c**

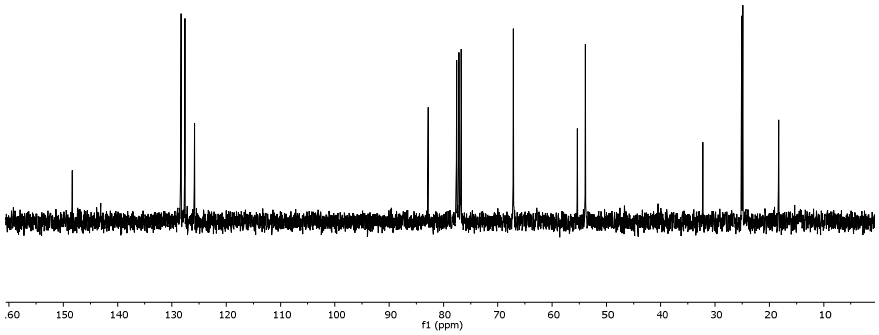
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)

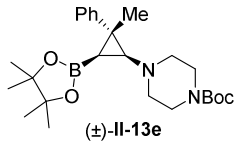

160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


Ph
Me
O
B
O
N
O

(±)-**II-13d**

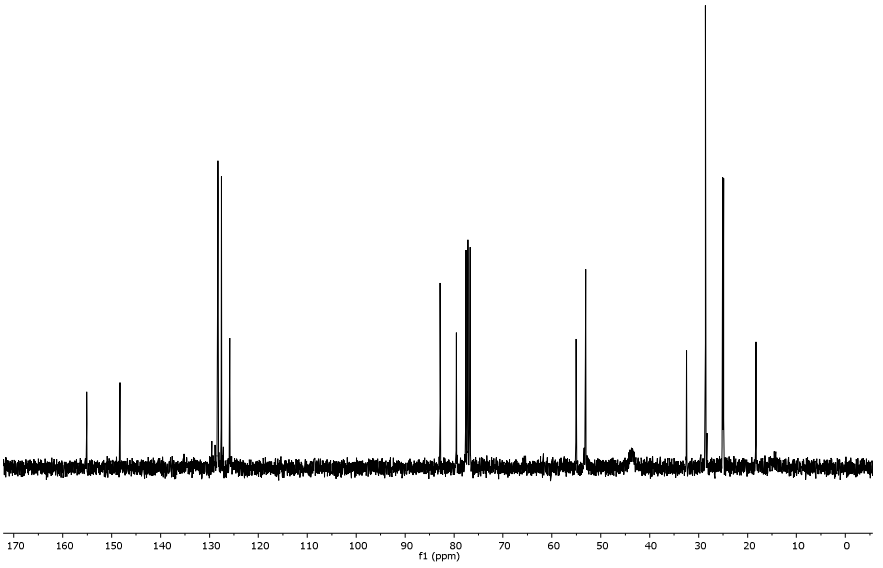
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

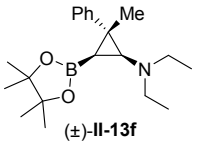

150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)


Ph
Me
O
B
O
N
NBoc

(±)-**II-13e**

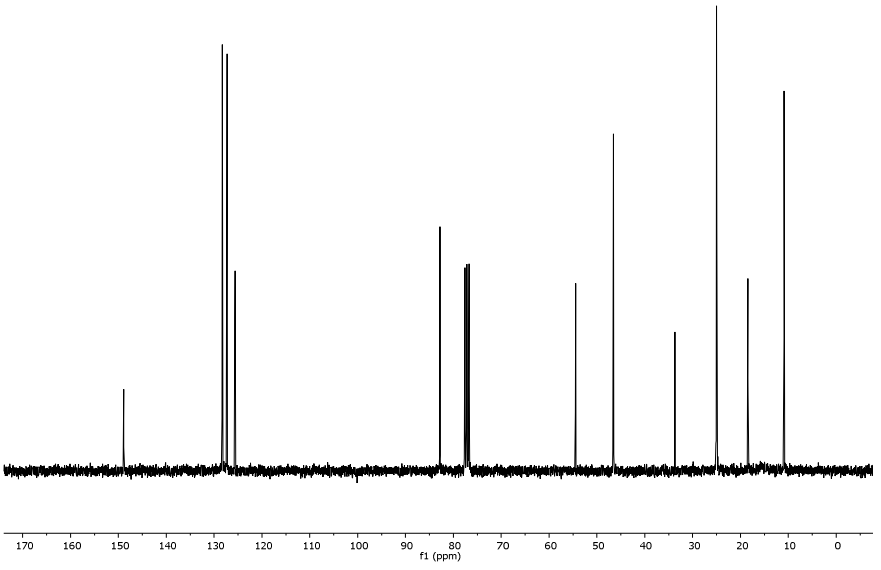
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

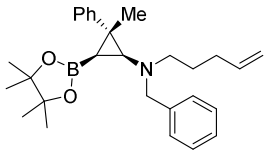

170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


Ph
Me
O
B
O
N

(±)-**II-13f**

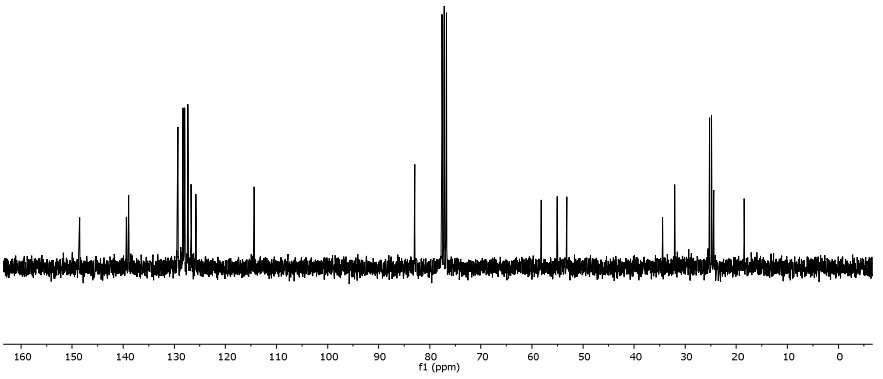
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)

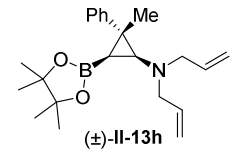

170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


Ph
Me
O
B
O
N

(±)-**II-13g**

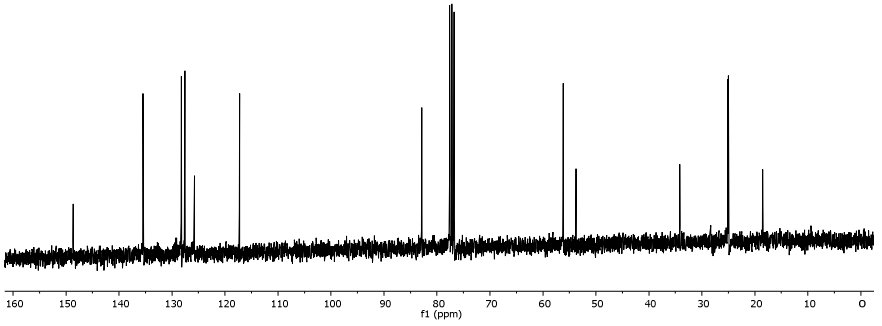
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

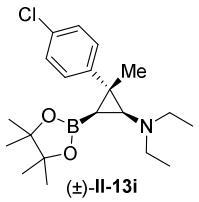

160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


Ph
Me
O
B
O
N

(±)-**II-13h**

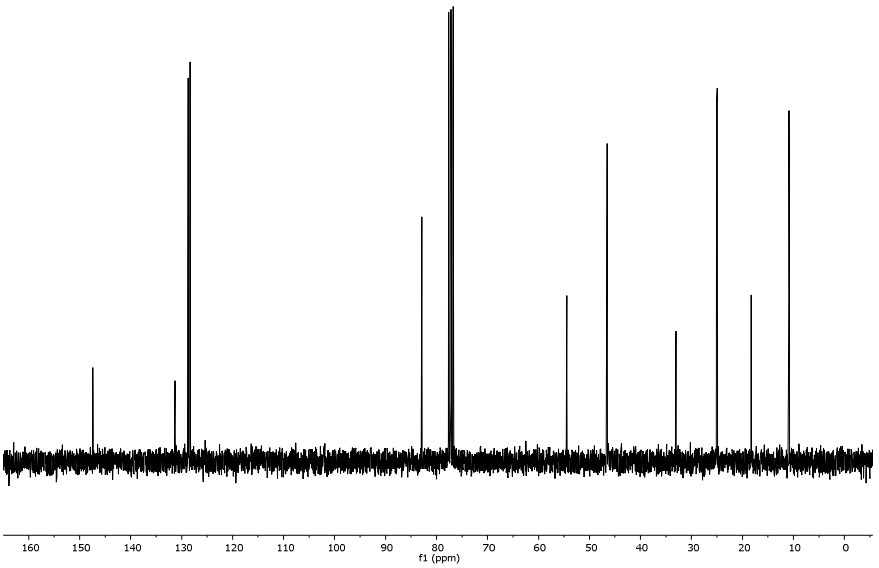
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

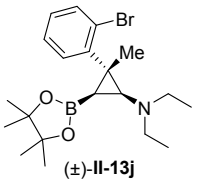

160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


Cl
Me
O
B
O
N

(±)-**II-13i**

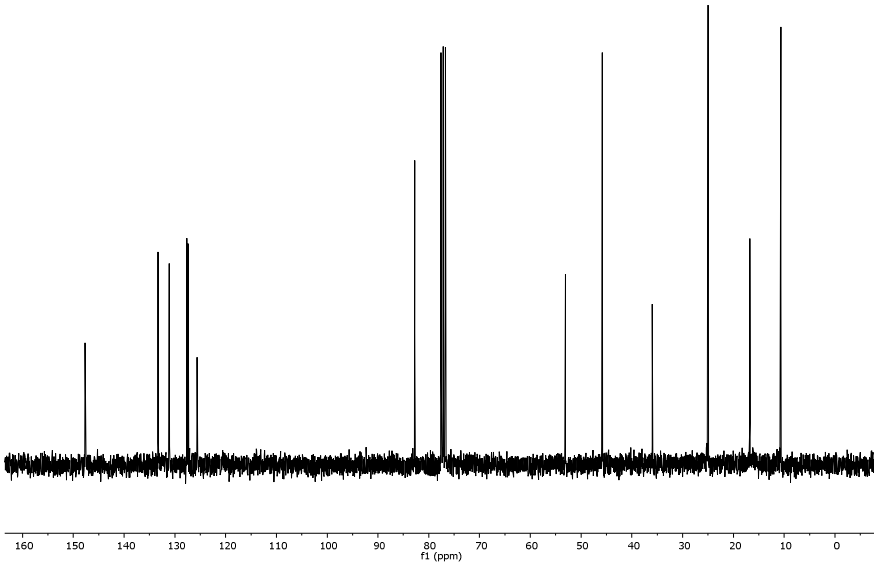
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

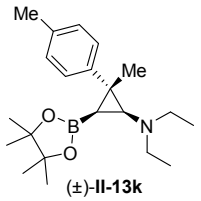

160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


Br
Me
O
B
O
N

(±)-**II-13j**

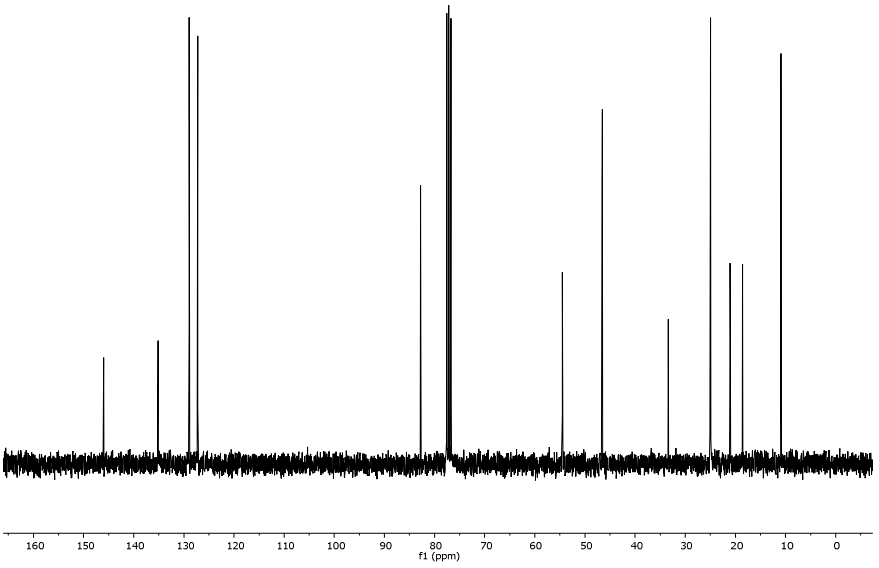
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

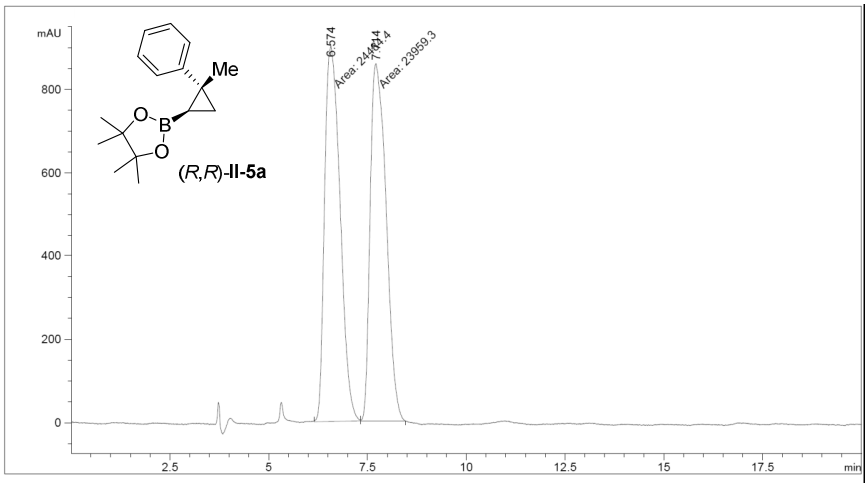

Me
Me
O
B
O
N

(±)-**II-13k**

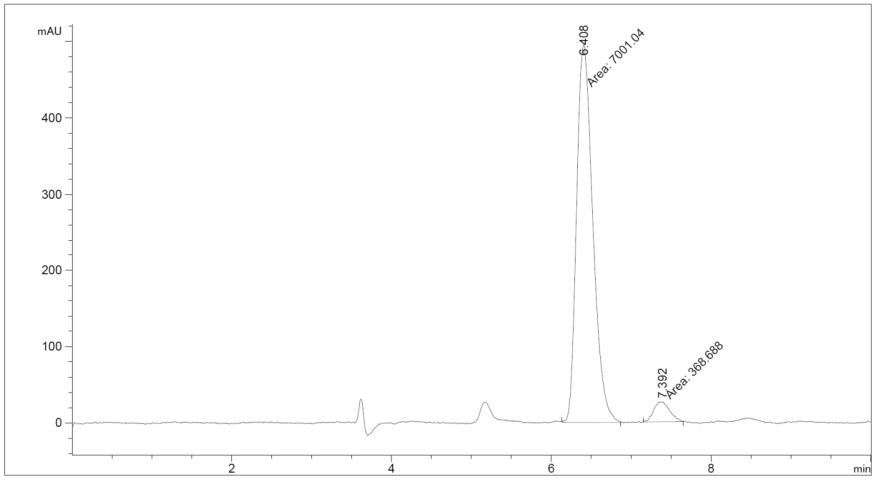
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

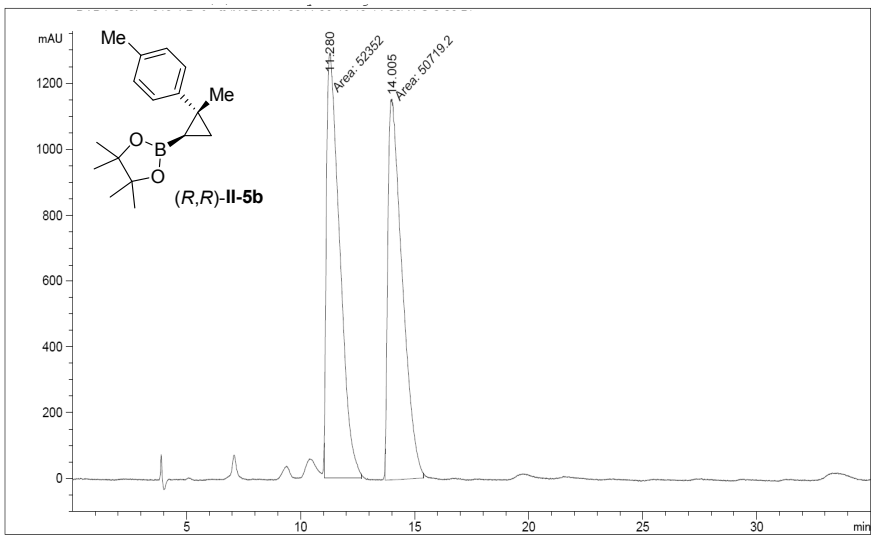
2.5. HPLC Chromatogram



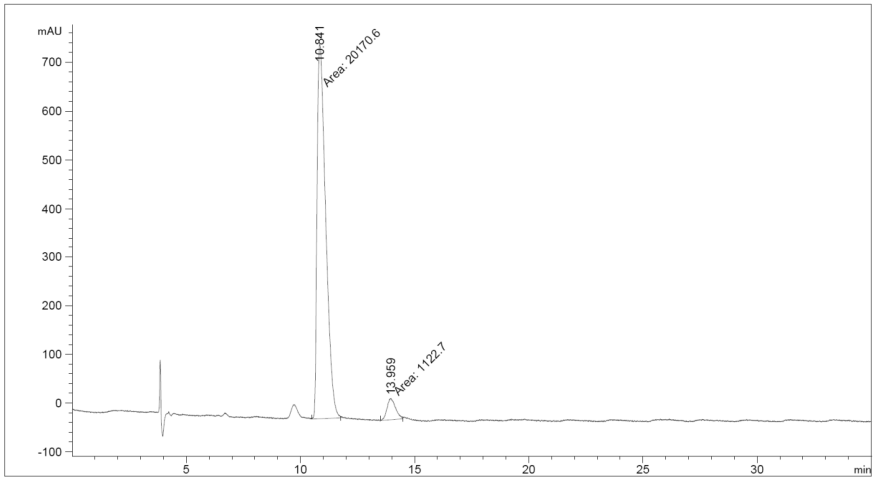
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	6.574	MM	0.4530	2.44844e4	900.83038	50.5420
2	7.714	MM	0.4657	2.39593e4	857.38440	49.4580



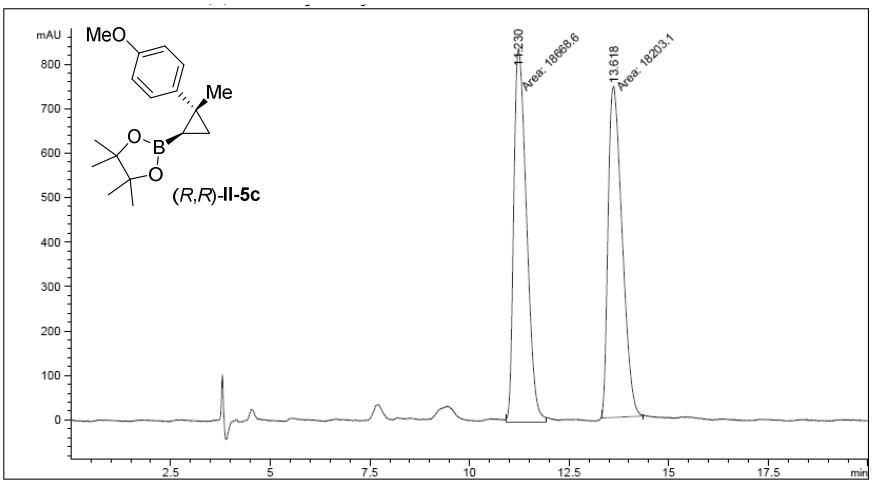
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	6.408	MM	0.2355	7001.03516	495.39816	94.9973
2	7.392	MM	0.2330	368.68814	26.36850	5.0027



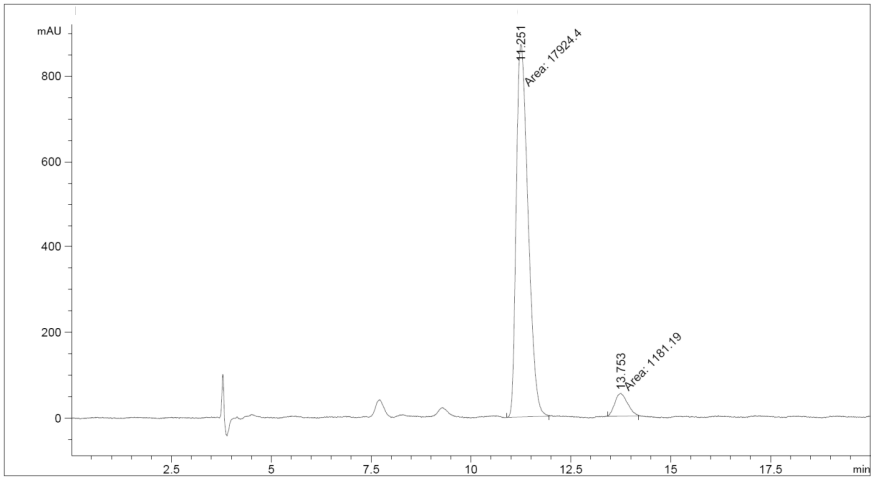
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	11.280	MM	0.6764	5.23520e4	1289.92798	50.7921
2	14.005	MM	0.7309	5.07192e4	1156.52844	49.2079



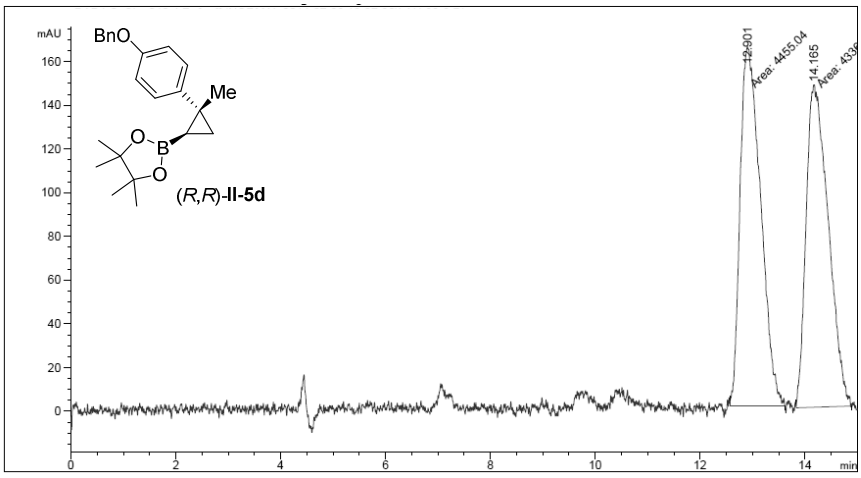
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	10.841	MM	0.4373	2.01706e4	768.79736	94.7274
2	13.959	MM	0.4259	1122.70386	43.92964	5.2726



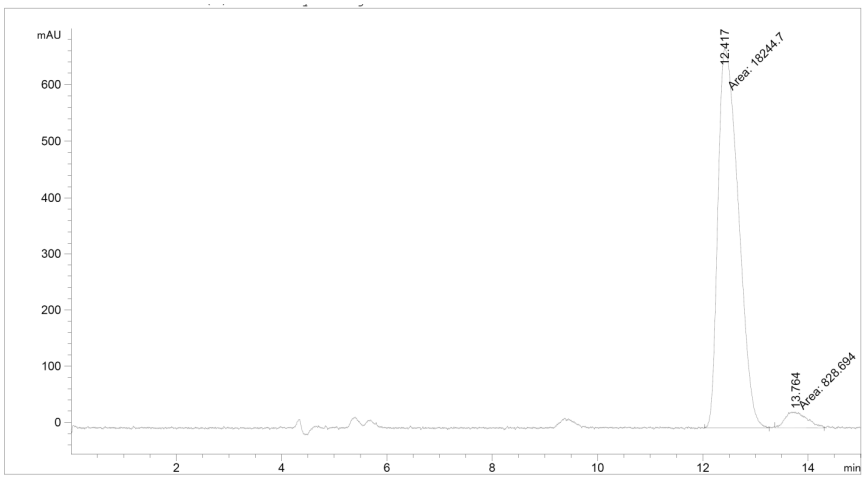
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	11.230	MM	0.3706	1.86686e4	839.53943	50.6313
2	13.618	MM	0.4074	1.82031e4	744.68756	49.3687



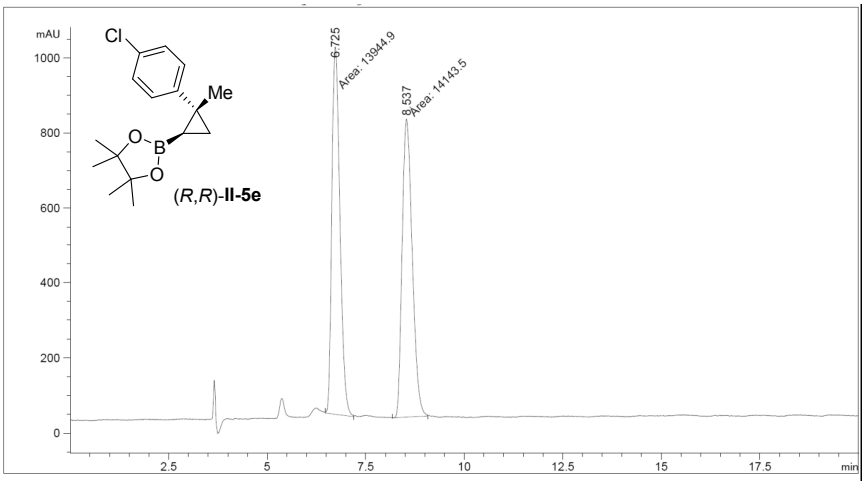
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	11.251	MM	0.3427	1.79244e4	871.68665	93.8176
2	13.753	MM	0.3686	1181.18896	53.41341	6.1824



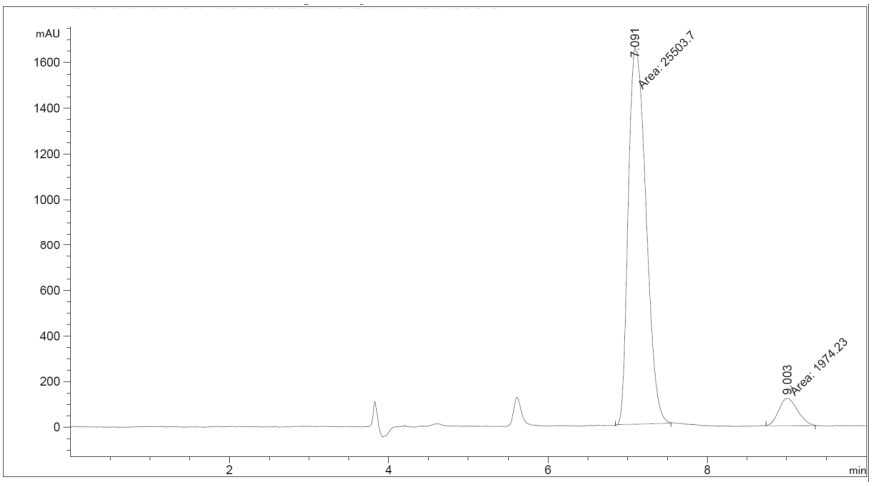
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	12.901	MM	0.4510	4455.04053	164.63686	50.6760
2	14.165	MM	0.4898	4336.18750	147.54567	49.3240



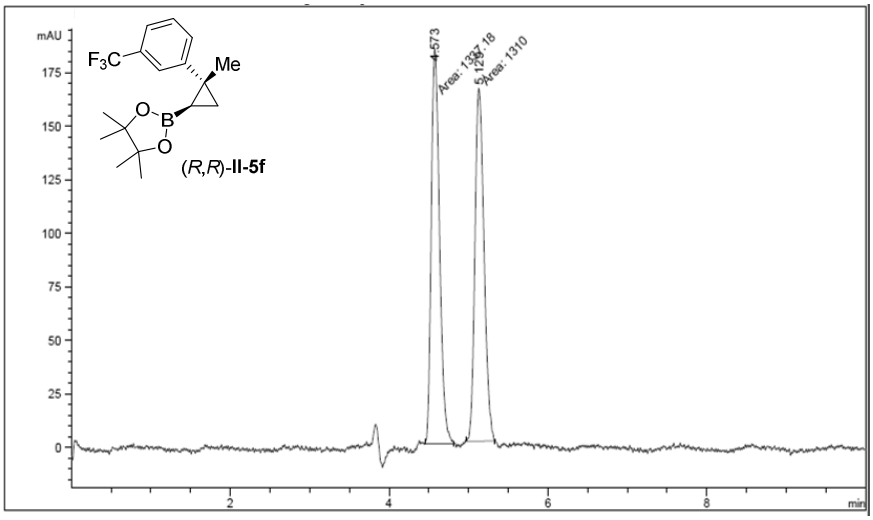
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	12.417	MM	0.4506	1.82447e4	674.77197	95.6552
2	13.764	MM	0.4877	828.69366	28.32075	4.3448



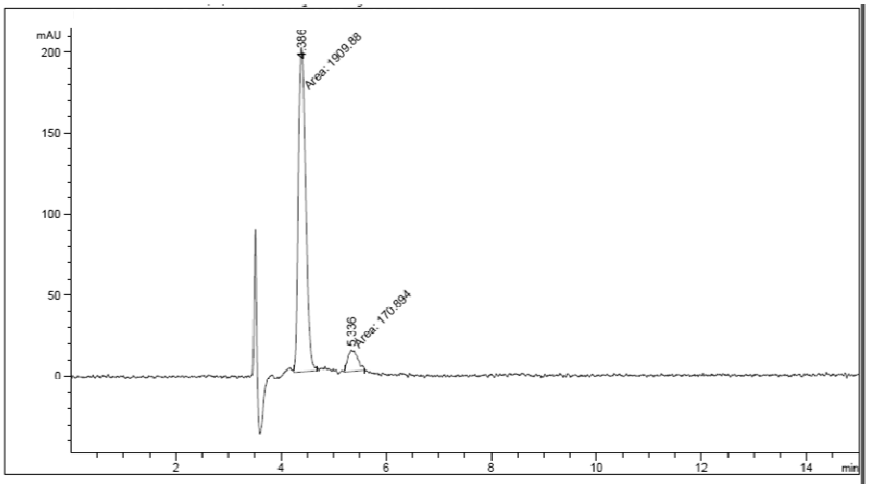
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	6.725	MM	0.2373	1.39449e4	979.23431	49.6464
2	8.537	MM	0.2967	1.41435e4	794.51312	50.3536



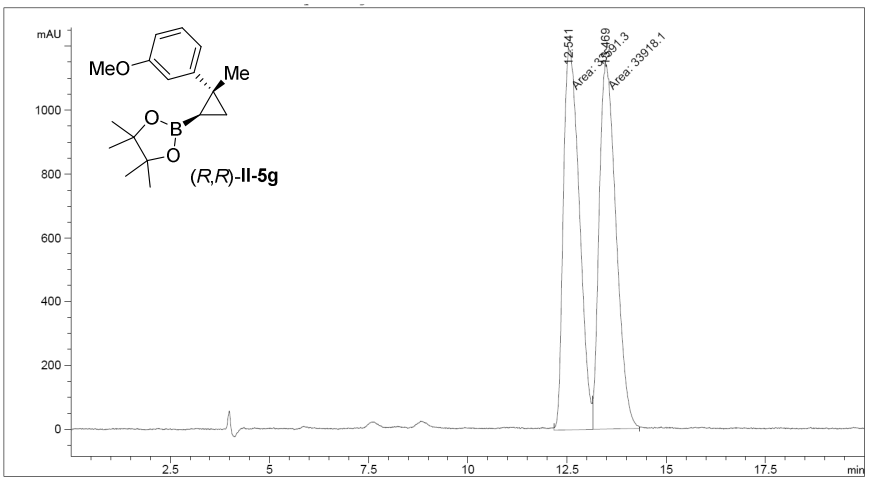
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	7.091	MM	0.2566	2.55037e4	1656.41138	92.8152
2	9.003	MM	0.2719	1974.23218	121.01965	7.1848



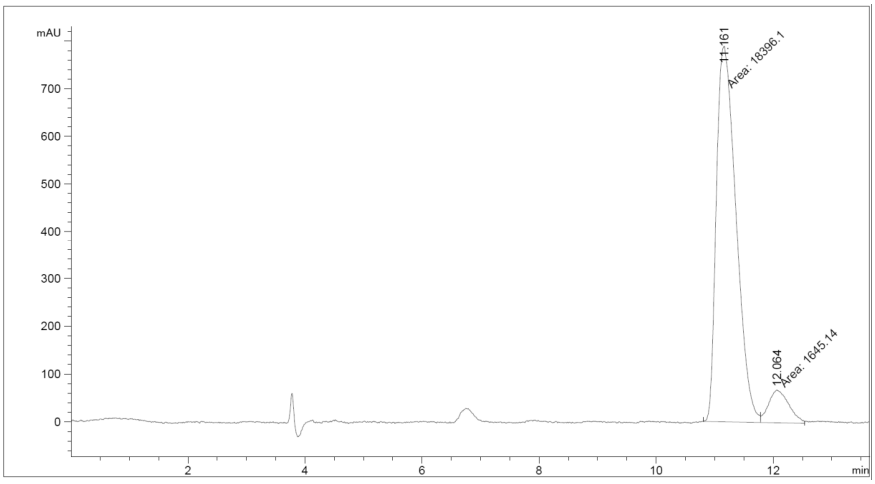
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	4.573	MM	0.1210	1337.17688	184.18233	50.5132
2	5.129	MM	0.1324	1310.00391	164.84259	49.4868



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	4.386	MM	0.1592	1909.88232	199.90544	91.7870
2	5.336	MM	0.2149	170.89444	13.25645	8.2130



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	12.541	MF	0.4677	3.35913e4	1197.03967	49.7579
2	13.469	FM	0.4910	3.39181e4	1151.44128	50.2421



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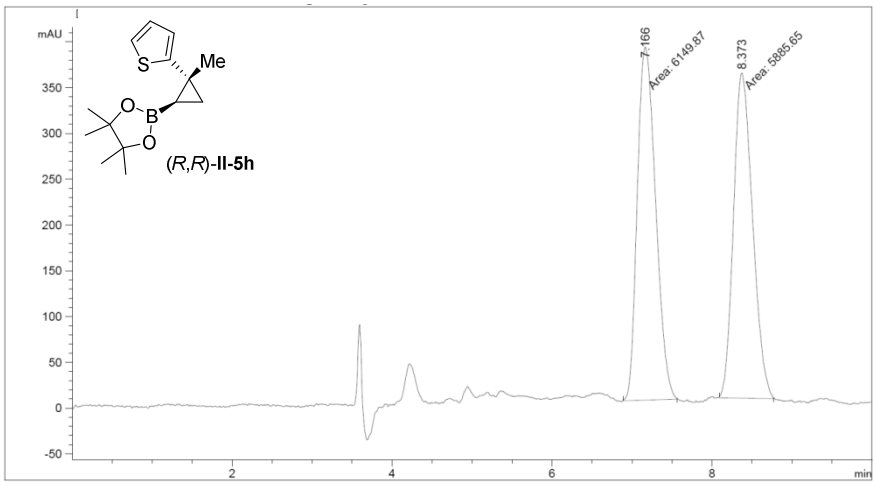
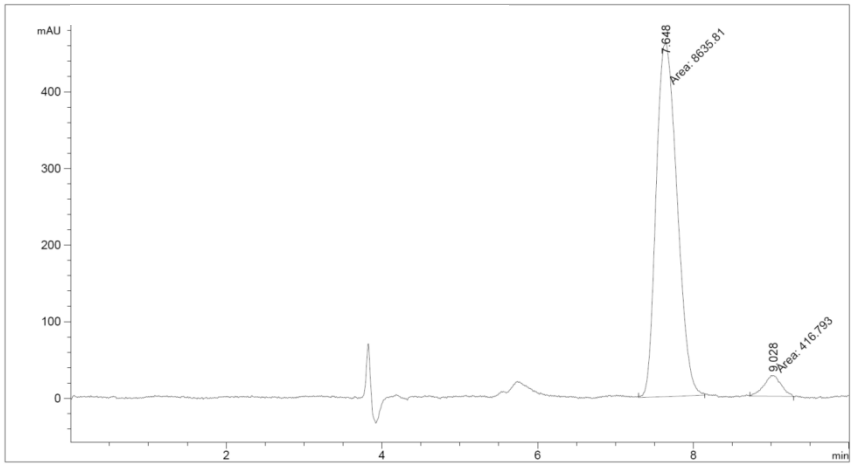
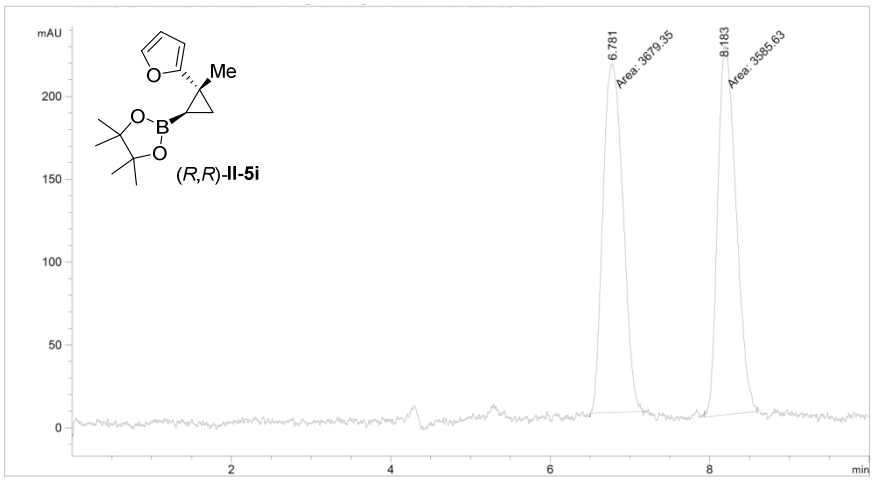
1	11.161	MF	0.3883	1.83961e4	789.62115	91.7912
2	12.064	FM	0.3999	1645.14441	68.55850	8.2088



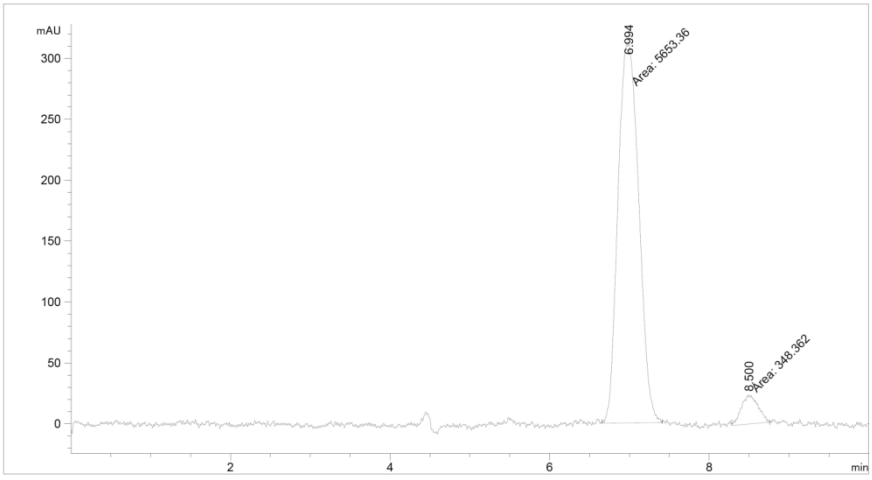
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	7.166	MM	0.2657	6149.87207	385.75143	51.0977
2	8.373	MM	0.2761	5885.64648	355.31253	48.9023



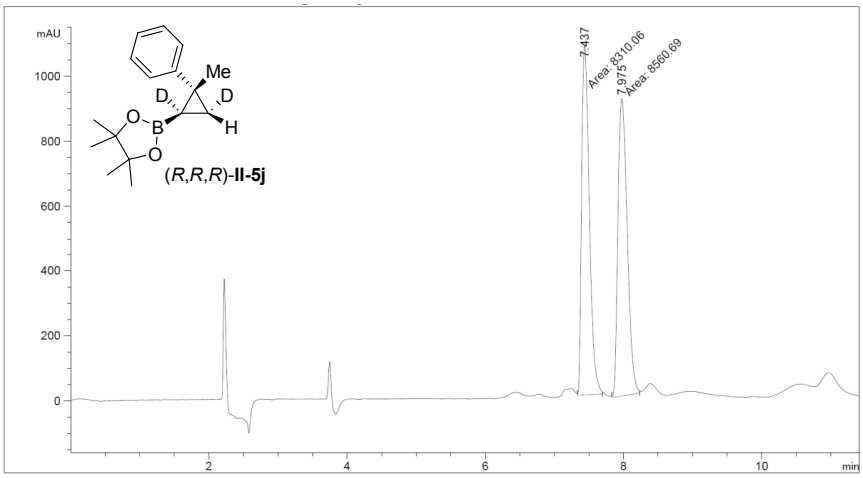
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	7.648	MM	0.3120	8635.81055	461.25302	95.3959
2	9.028	MM	0.2530	416.79254	27.45133	4.6041



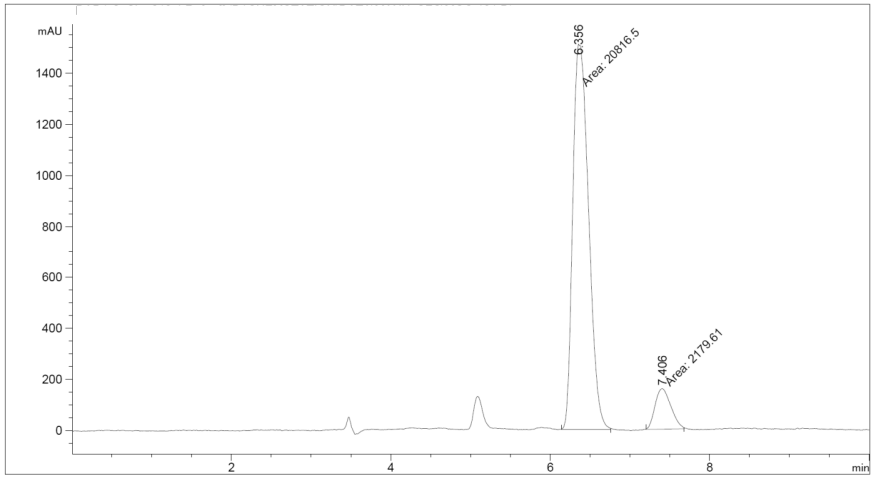
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	6.781	MM	0.2911	3679.34668	210.69267	50.6450
2	8.183	MM	0.2683	3585.62622	222.71022	49.3550



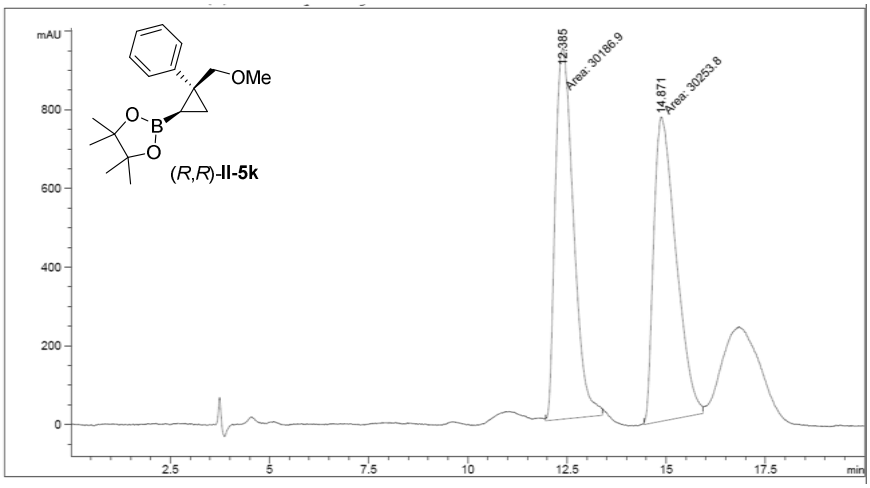
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	6.994	MM	0.3026	5653.36328	311.40594	94.1956
2	8.500	MM	0.2419	348.36206	24.00359	5.8044



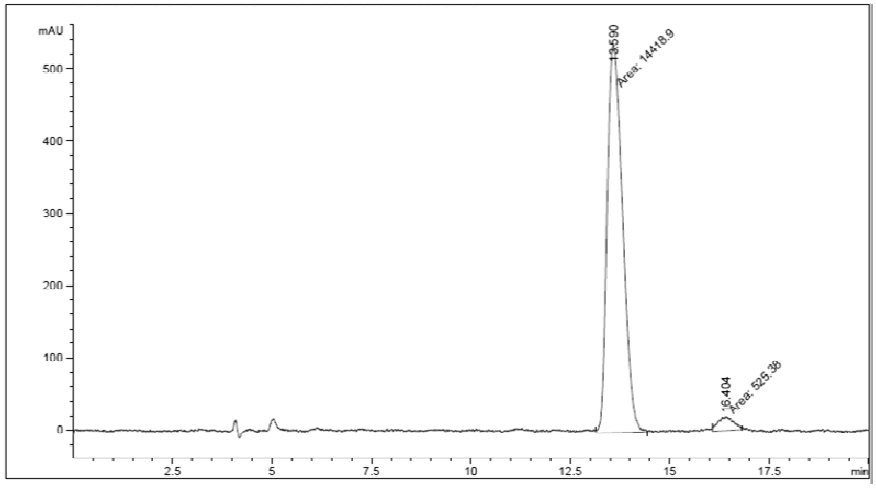
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	7.437	MM	0.1290	8310.05762	1073.35095	49.2572
2	7.975	MM	0.1557	8560.69141	916.47552	50.7428



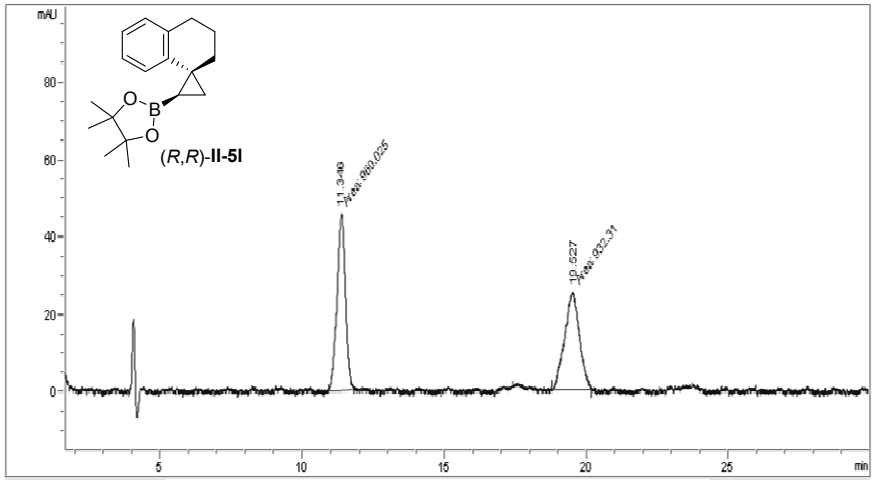
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	6.356	MM	0.2297	2.08165e4	1510.16125	90.5218
2	7.406	MM	0.2297	2179.61353	158.14557	9.4782



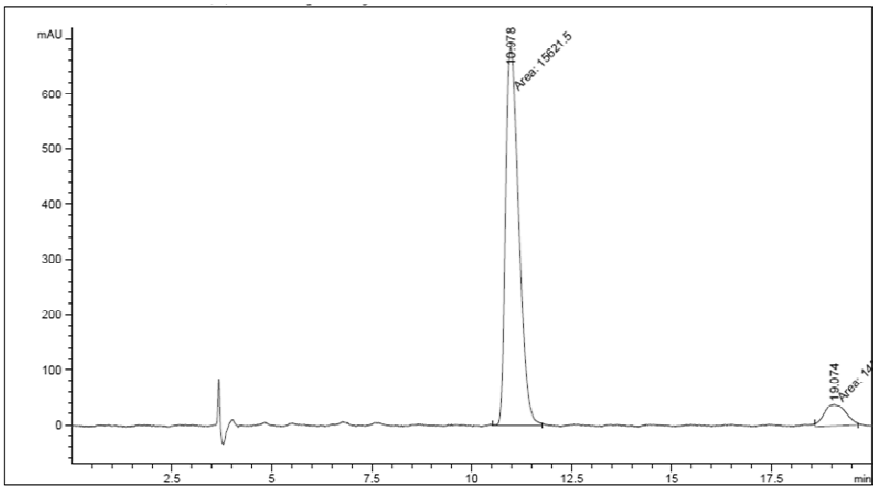
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	12.385	MM	0.5331	3.01869e4	943.71118	49.9447
2	14.871	MM	0.6514	3.02538e4	774.10846	50.0553



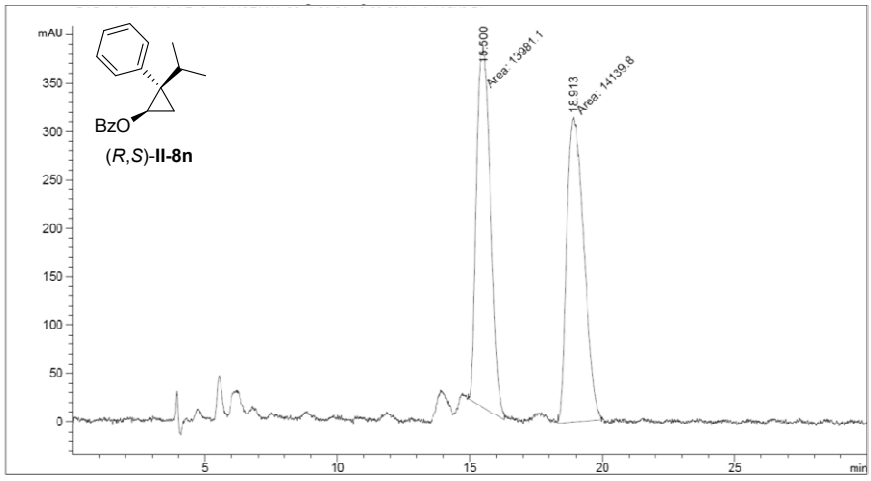
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	13.590	MF	0.4478	1.44189e4	536.68567	96.4844
2	16.404	MM	0.4505	525.38043	19.43849	3.5156



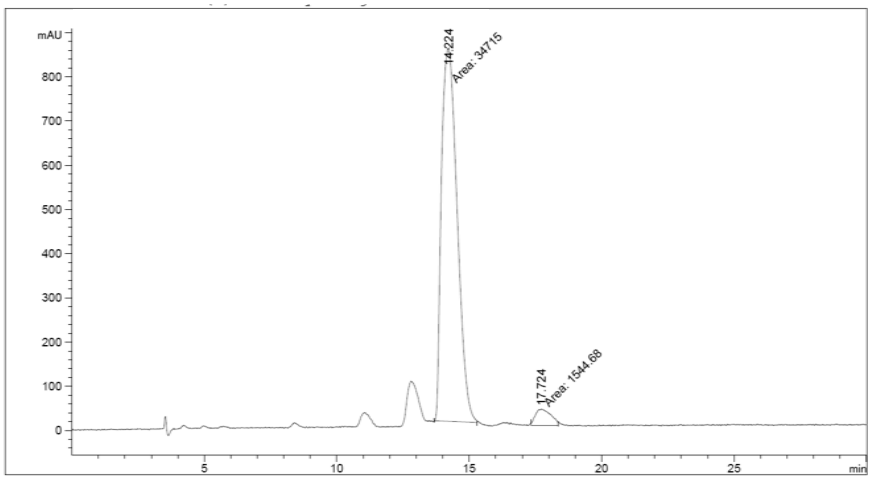
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	11.346	MM	0.3490	960.02496	45.84128	50.7323
2	19.527	MM	0.6117	932.31006	25.40182	49.2677



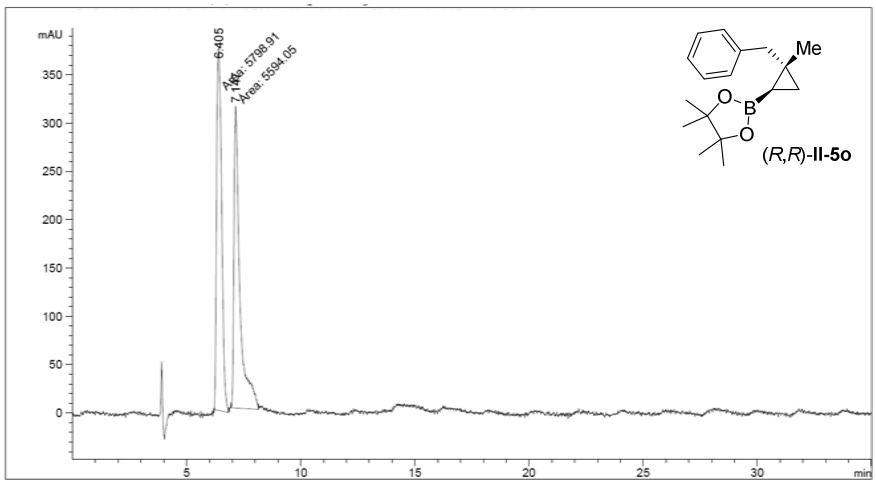
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	10.978	MM	0.3810	1.56215e4	683.41278	91.4987
2	19.074	MM	0.6168	1451.41003	39.21825	8.5013



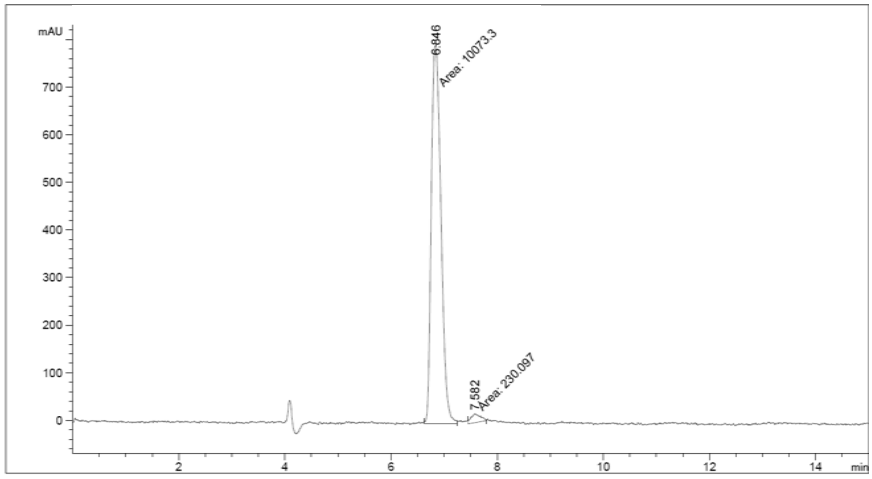
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	15.500	MM	0.6228	1.39811e4	374.14224	49.7179
2	18.913	MM	0.7459	1.41398e4	315.93918	50.2821



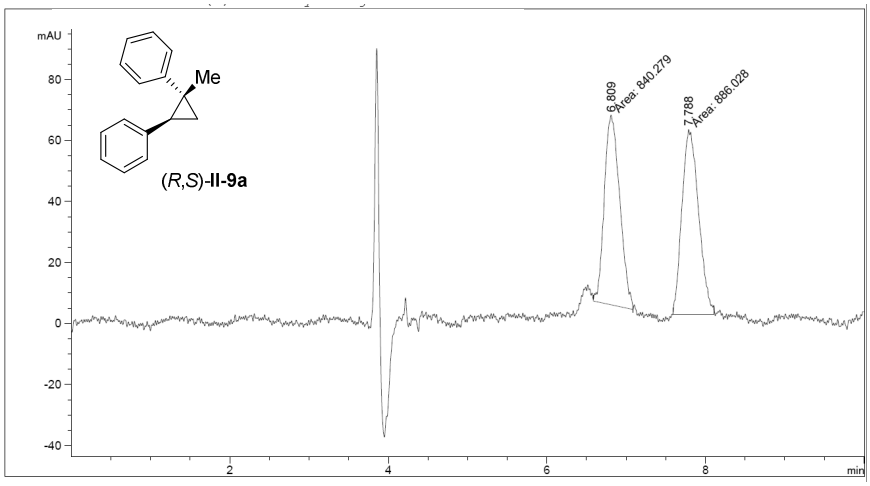
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	14.224	MM	0.6848	3.47150e4	844.86041	95.7399
2	17.724	MM	0.6802	1544.68188	37.85035	4.2601



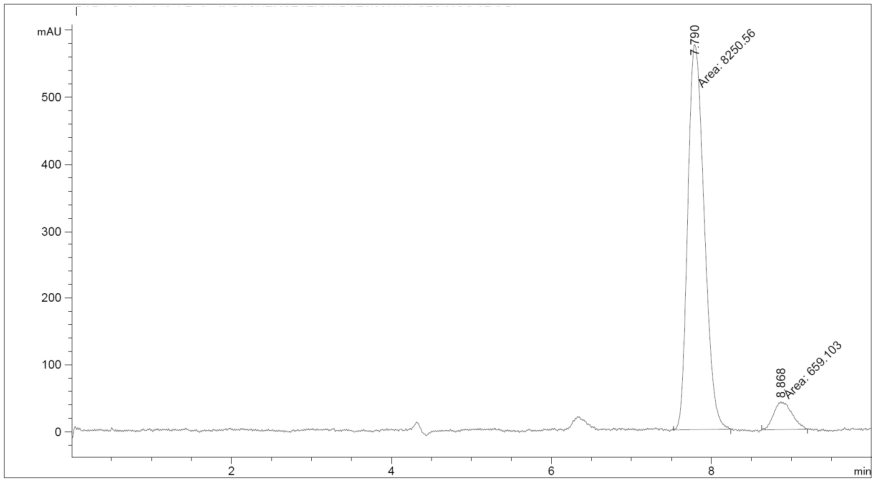
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	6.405	MM	0.2573	5798.90576	375.61420	50.8990
2	7.147	MM	0.2985	5594.05469	312.31778	49.1010



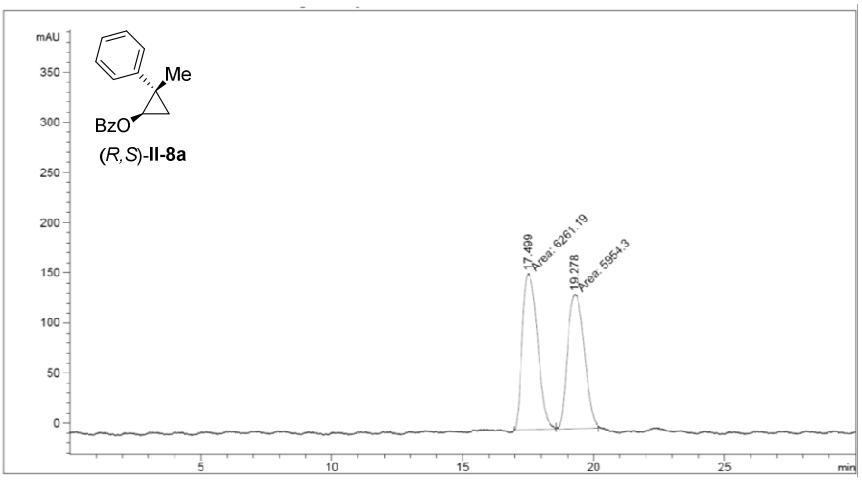
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	6.846	MM	0.2105	1.00733e4	797.41229	97.7668
2	7.582	MM	0.2009	230.09674	19.08639	2.2332



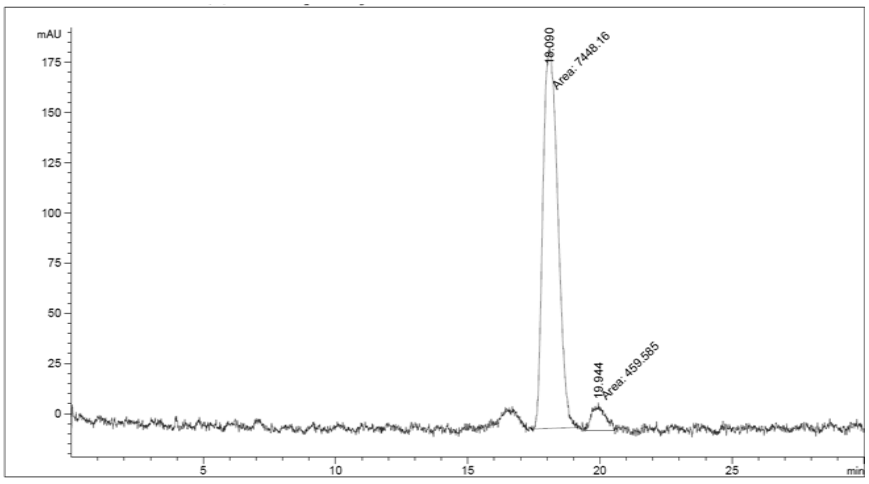
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	6.809	MM	0.2251	840.27881	62.22195	48.6750
2	7.788	MM	0.2433	886.02753	60.68904	51.3250



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	12.788	MM	0.3219	2.99012e4	1548.31653	94.9909
2	14.086	MM	0.3224	1576.76111	81.51219	5.0091



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	17.499	MF	0.6709	6261.18848	155.54517	51.2562
2	19.278	FM	0.7396	5954.29688	134.18076	48.7438



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	18.090	MM	0.6537	7448.16406	189.88968	94.1882
2	19.944	MM	0.5460	459.58453	14.03004	5.8118

Chapter 3

TOWARDS THE TOTAL SYNTHESIS OF ALBOCYCLINE: UNPRECENTED REARRANGMENT OF α-BORYL EPOXIDES

3. TOWARDS THE TOTAL SYNTHESIS OF ALBOCYCLINE: UNPRECENTED REARRANGMENT OF α-BORYL EPOXIDES

3.1. Background

3.1.1. Albocycline

Albocycline, also known as Ingramycin, was isolated in 1967 from the fermentation broth of *Streptomyces*,[1] which were originally isolated from soil samples collected at various places throughout Japan.

The complete characterization and absolute configuration of this new antibiotic were confirmed by X-ray crystallography in 1982.[2]

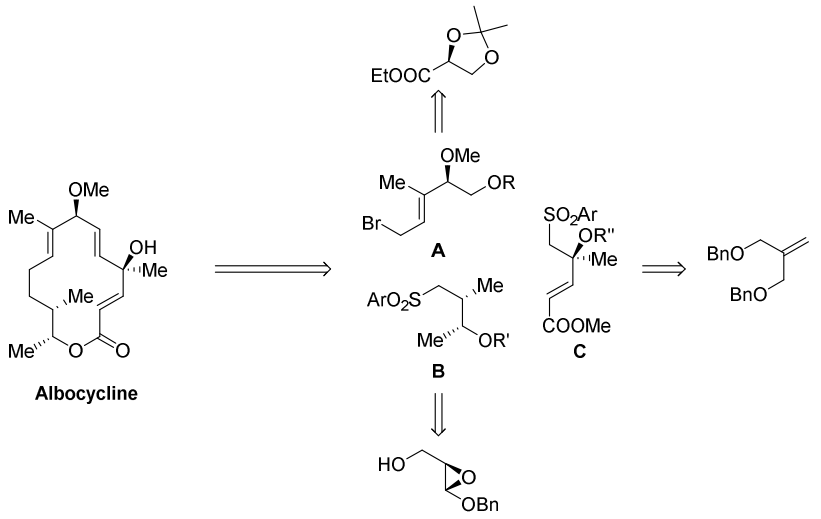
The biological activity of albocycline has been studied by several research groups and it was found to be an inhibitor of nicotinate biosynthesis,[3] melanogenesis[4] and human prolyl endopeptidases.[5] Moreover, in 2013, Tomoda and co-workers observed that this compound presented high potential against *methicillin-resistant staphylococcus aureus* (MRSA). This is a bacterium that causes infections in different parts

[1] (a) Nagahama, N.; Suzuki, M.; Awataguchi, S.; Okuda, T. *J. Antibiot.* **1967**, *20*, 261-266. (b) Furumai, T.; Nagahama, N.; Okuda, T. *J. Antibiot.* **1968**, *21*, 85-90.
[2] (a) Thomas, R. C.; Chidester, C. G. *J. Antibiot.* **1982**, *35*, 1658-1664. (b) Furusaki, A.; Matsumoto, T.; Harada, K.; Suzuki, M.; Kinoshita, K.; Hayashi, M.; Nakatsu, K. *Bull. Chem. Soc. Jpn.* **1983**, *56*, 3042-3046.
[3] Reusser, F. *J. Bacteriol.* **1969**, *100*, 11-13.
[4] Takamatsu, S.; Kim, Y. P.; Hayashi, M.; Komiyama, K.; Imokawa, G.; Omura, S. *J. Antibiot.* **1996**, *49*, 485-486.
[5] Christner, C.;Kullertz, G.; Fischer, G. *J. Antibiot.* **1998**, *51*, 368-371.

of the body and it is tougher to treat than most strains of *staphylococcus aureus* because it is resistant to most of the commonly used antibiotics.

The effectiveness of this natural product against MRSA is due to the mechanism of action of albocycline, which was found to be different from that of representative macrolide antibiotics.[6] The potent antibacterial activity and architectural complexity conferred unique properties to this compound.

Albocycline is a 14-membered macrolactone that contains four stereogenic centers and three (*E*)-alkenes (*Scheme III-1*). In 1987, Tanner and Somfai reported the first total synthesis of albocycline in 40 total steps (21 the longest linear sequence).[7]



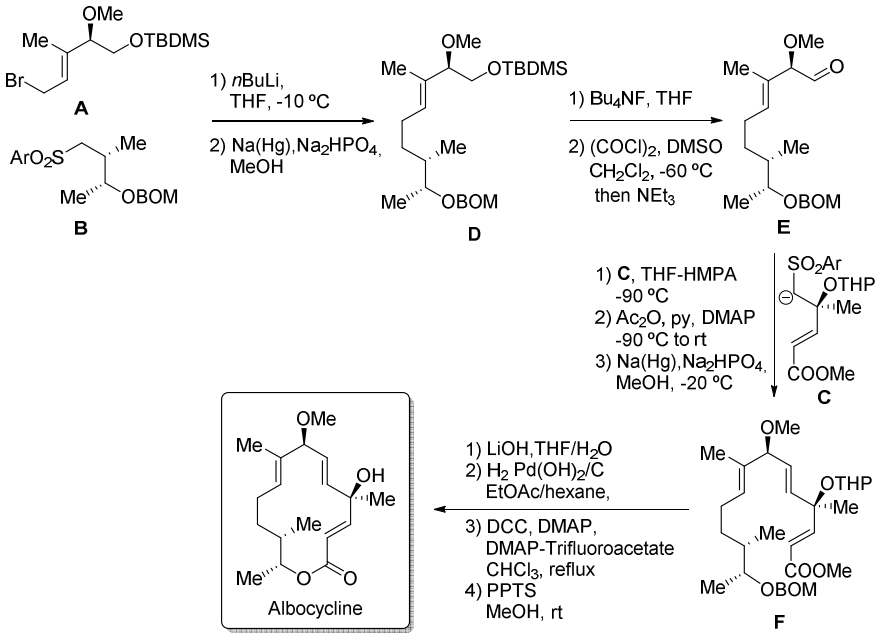
Scheme III-1. Retrosynthetic analysis of Albocycline.

The retrosynthetic analysis proposed by Tanner is outlined in *Scheme III-1*. They envisioned the synthesis of albocycline from three chiral fragments **A**, **B** and **C**. Fragment **A** could be prepared from *L*-serine,

[6] Koyama, N.; Yotsumoto, M.; Onaka, H.; Tomoda, H. *J. Antibiot.* **2013**, *66*, 303-304.
[7] Tanner, D.; Somfai, P. *Tetrahedron* **1987**, *43*, 4395-4406.

whereas sulfones **B** and **C** could be synthesized through Sharpless asymmetric epoxidation protocol of allylic alcohols.

From fragments **A**, **B** and **C**, the authors accomplished the total synthesis of albocycline. S_N2 reaction of the sulfone anion derived from **B** and allylic bromide **A**, followed by desulfonylation, gave fragment **D** that was further deprotected and oxidized to get aldehyde **E** (*Scheme III-2*). Then, Julia olefination between fragments **E** and **C**, followed by desulfonylation afforded fragment **F**. Finally, hydrolysis of the ester and benzyloxymethyl ether deprotection, allowed for macrolactonization providing the natural product.

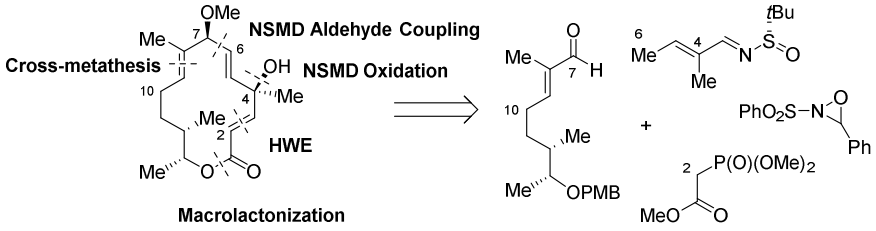


Scheme III-2. Last steps on the synthesis of albocycline.

That was the only reported total synthesis until date. However, recently, it has been published a new route towards the synthesis of albocycline.[8] The proposed retrosynthetic analysis disconnected the molecule in 4 different

[8] Chatare, V. K.; Andrade, R. B. *Angew. Chem. Int. Ed.* **2017**, *56*, 5909 -5911.

fragments (*Scheme III-3*). N-(*S*)-*tert*-butanesulfinylenamine, derived from the metalation of enolizable N-(*S*)-*tert*-butanesulfinylimine, can react with the aldehyde in a 1,2-fashion to prepare the C7 carbinol. Subsequent metalation and oxidation with the Davis oxaziridine could allow for the regio- and stereoselectively access of the tertiary carbinol at C4. Reduction of the resulting imine to the aldehyde, followed by Horner-Wadsworth-Emmons olefination would deliver the (*E*)-enoate precursor to the requisite seco acid. Finally, Keck macrolactonization of protected seco acid, a tactic used by Tanner and Somfai in their synthesis, would access the 14-membered ring.



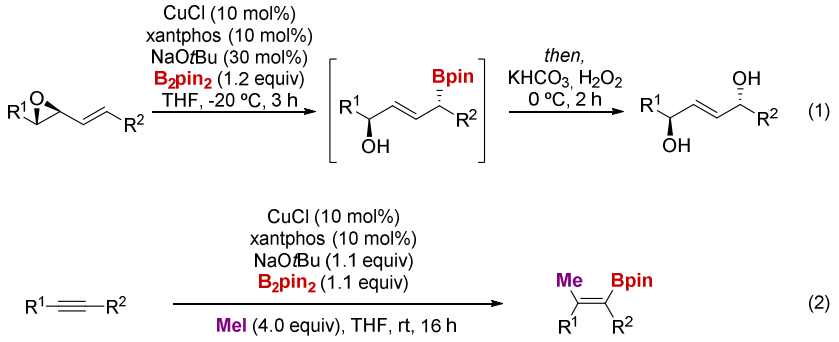
Scheme III-3. Retrosynthetic analysis.

3.2. Towards the Total Synthesis of Albocycline through Copper-Catalyzed Borylations: Unexpected Change of Course

3.2.1. Introduction and Objectives

At the beginning of this investigation, there was only one total synthesis of albocycline reported in the literature in 1987. Since then, the field of organic chemistry has evolved notably, providing chemist with the tools to develop a more efficient route towards this natural product.

As described in the introduction of this manuscript, Tortosa and co-workers developed the copper-catalyzed borylation of allylic epoxides (*Scheme III-4, eq 1*).[9] This method allows for the preparation of *syn* or *anti* 1,4-diols via a 1,4-hydroxyboronate intermediate. They also described the copper-catalyzed carboboration of alkynes to prepare stereodefined trisubstituted vinyl boronates (*Scheme III-4, eq 2*).[10] At the beginning of this thesis, we envisioned that these two methodologies were perfectly suited for the preparation of the northern fragment of albocycline.

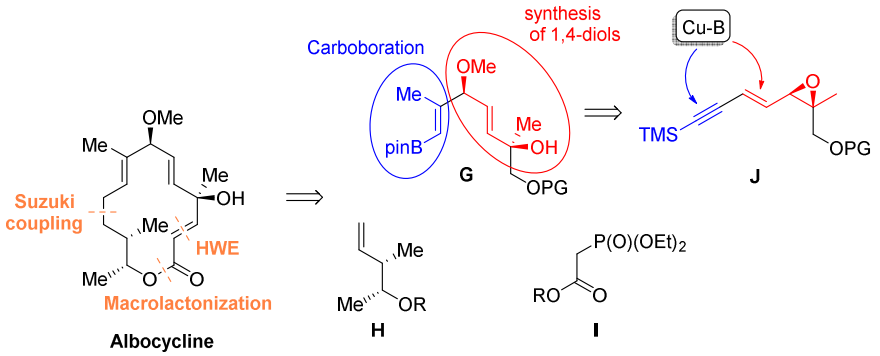


Scheme III-4. Copper-catalyzed borylation reactions developed by Tortosa's group.

[9] Tortosa, M. *Angew. Chem. Int. Ed.* **2011**, *50*, 3950-3953.
[10] Alfaro, R.; Parra, A.; Aleman, J.; García-Ruano, J. L.; Tortosa, M. *J. Am. Chem Soc.* **2012**, *134*, 15165-15168.

We proposed three main disconnections to assemble the macrolide: an alkyl Suzuki cross-coupling to couple fragments **G** and **H**, previous transformation of the boronic ester into a vinyl halide, a Horner-Wadsworth-Emmons olefination, and a macrolactonization reaction (*Scheme III-5*). Our initial goal in this doctoral thesis was to synthesize fragment **G** using two copper-catalyzed borylation reactions previously developed in our group.

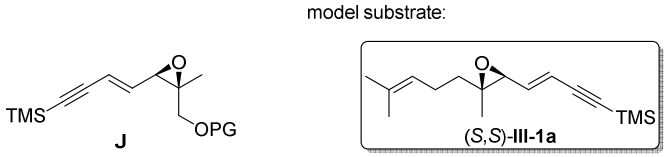
We thought that the 1,4-diol moiety could be introduced through the copper-catalyzed borylation of an allylic epoxide **J**. On the other hand, the trisubstituted vinylboronate could be installed using a copper-catalyzed carboboration technique. Both methods required the *in situ* generation of a copper-boryl complex that could react with the alkene of the epoxide or with the triple bond. Therefore, this proposal presented an important challenge: the control of the chemoselectivity in the borylation events. Ideally, we wanted the borylation of the epoxide to take place first, followed by the carboboration of the triple bond.



Scheme III-5. Copper-catalyzed borylations for the synthesis of albocycline.

3.2.2. Synthesis of a Model Substrate

To test out this hypothesis we prepared a simplified model compound (*S*,*S*)-**III-1a** that contained all the structural requirements of fragment **J** (trisubstituted epoxyenyne), and could be easily prepared from geraniol (*Scheme III-6*).



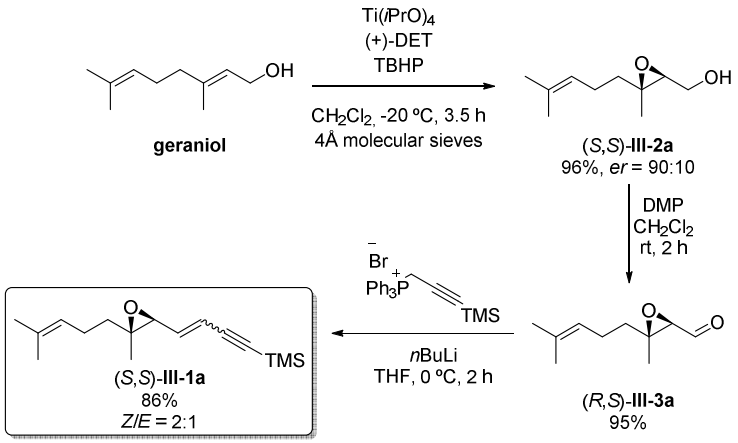
Scheme III-6. Model substrate for fragment **J**.

The synthetic sequence to prepare epoxyenyne (*S*,*S*)-**III-1a** started from Sharpless epoxidation[11] of geraniol to obtain the enantiomerically enriched epoxy alcohol (*S*,*S*)-**III-2a** (*Scheme III-7*). Then, (*S*,*S*)-**III-2a** was oxidized through with Dess-Martin periodinane[12] to obtain aldehyde (*R*,*S*)-**III-3a** that underwent Wittig olefination[13] in the presence of a propargylic phosphonium salt. We introduced a trimethylsilyl group at the terminal position of the alkyne to block the borylation of the triple bond. Epoxyenyne (*S*,*S*)-**III-1a** was obtained as a 2:1 *Z*/*E* mixture. The low *Z*/*E* selectivity was not a problem at this point because we just wanted to explore first the chemoselectivity in the copper-catalyzed borylation.

[11] (a) Katsuki, T.; Sharpless, K. B. *J. Am. Chem. Soc.* **1980**, *102*, 5974-5976. (b) Gao, Y.; Hanson, R. M.;Klunder, J. M.;Ko, S. Y.; Nasamune, H.; Sharpless, K. B. *J. Am. Chem. Soc.* **1987**, *109*, 5765-5780.

[12] (a) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155-4156. (b) Bratz, M.; Bullock, W. H.; Overman, L. E.; Takemoto,T. *J. Am. Chem. Soc.* **1995**, *117*, 5958-5966.

[13] Maercker, A. *Org. React.* **1965**, *14*, 270-490.

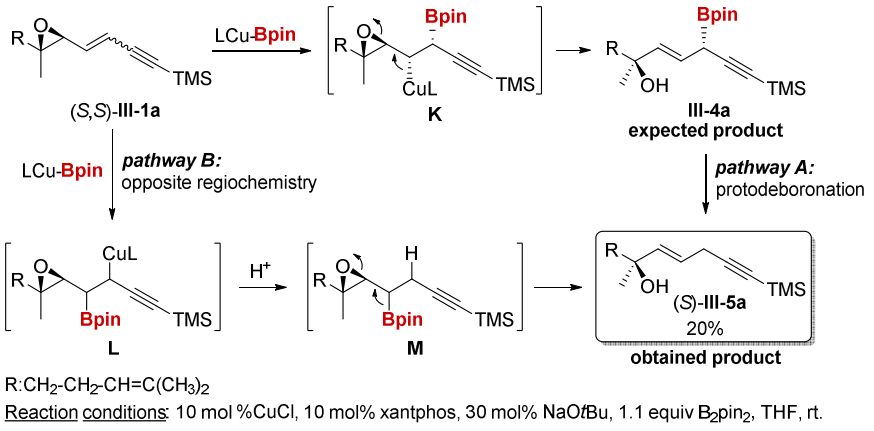


Scheme III-7. Synthesis of the model substrate.

With epoxyenyne (*S*,*S*)-**III-1a** in hand we applied the conditions previously developed in our group for copper-catalyzed borylation of allylic epoxide (*Scheme III*-8). Treatment of (*S*,*S*)-**III-1a** with CuCl (10 mol%), xantphos (10 mol%), NaO*t*Bu (30 mol%) and B_2pin_2 (1.2 equiv) did not afford the desired compound **III-4a**. Instead, 20% of allylic alcohol (*S*)-**III-5a**, which did not contain the boryl moiety, was observed. We envisioned two possible pathways for the formation of (*S*)-**III-5a** (*Scheme III-8*). *Pathway A* would involve the expected 1,4-borylation followed by protodeboronation of a potentially unstable allylic and propargylic boronic ester (**III-4a**).[14] *Pathway B* would involve an initial borylation of the alkene with the opposite regiochemistry in the insertion step,[15] followed by spontaneous and unprecedented rearrangement of an α-epoxy boronate.

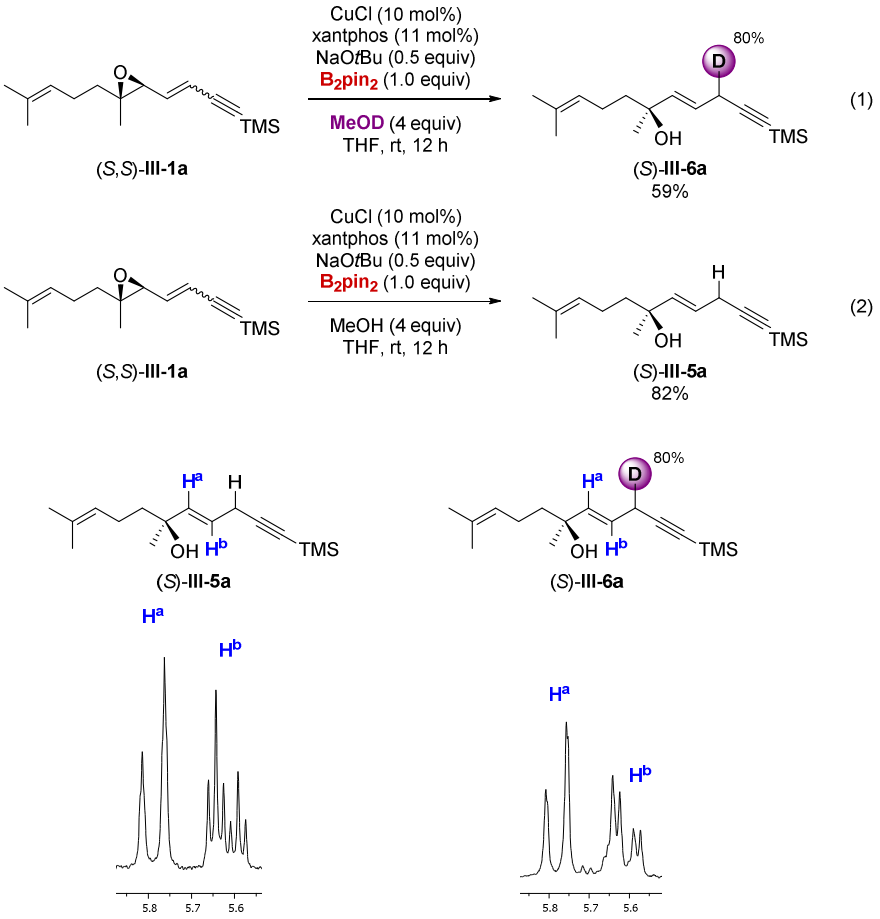
[14] (a) Nave, S.; Sonawane, R. P.; Elford, T. G.; Aggarwal V. K. *J. Am. Chem. Soc.* **2010**, *132*, 17096-17098. (b) Lee, C. Y.; Cheon C. H. Development of Organic Transformations Based on Protodeboronation. In *Boron Reagents in Synthesis*; Coca, A., Ed.; Oxford University Press: Washington DC, 2016; pp 483-523.

[15] For copper-catalyzed borylation of a simple enyne, see: (a) Sasaki, Y.; Horita, Y.; Zhong, C.; Sawamura, M.; Ito, H. *Angew. Chem.* **2011**, *123*, 2830-2834. (b) Meng, F.; Haeffner, F. Hoveyda, A. H. *J. Am. Chem. Soc.* **2014**, *136*, 11304-11307.



Scheme III-8. First attempt under copper(I)-catalyzed borylation conditions.

To verify which pathway led to alcohol (*S*)-**III-5a**, a deuterium-labelling experiment was performed (*Scheme III-9, eq 1*). When four equivalents of deuterated methanol were added to the reaction mixture, product (*S*)-**III-6a** was obtained. We observed a clear change in the multiplicity of the ^{1}H NMR signals at 5.62 ppm from a double triplet to double doublet (*Scheme III-9*). This experiment confirmed that pathway B was taking place, with formation of intermediate **L**. The yield for (*S*)-**III-6a** was significantly higher than that observed for (*S*)-**III-5a** (20 mol%) in the absence of deuterated methanol. This result revealed the importance of a proton source to achieve high conversions. Indeed, when epoxide (*S*,*S*)-**III-1a** was treated under the same conditions as before but in the presence of 4 equivalents of methanol, compound (*S*)-**III-5a** was obtained in 82% yield (*Scheme III-9, eq 2*).



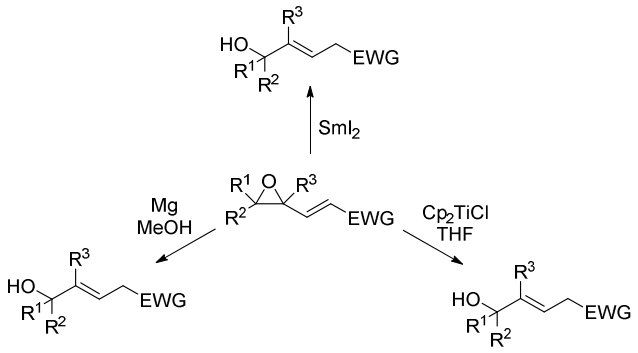
Scheme III-9. Deuterated experiments.

Although we were disappointed by these preliminary results, the unexpected outcome was interesting for several reasons. Overall, the transformation represented a formal reductive opening of an allylic epoxide under very mild conditions, using methanol as the formal "hydride source".

We found that previous published strategies to get 1,4- reduction of electron poor vinyl epoxides required stoichiometric amounts of strong reductant, such as samarium iodide,[16] magnesium in methanol[17] or

[16] (a) Molander, G. A.; La Belle, B. E.; Hahn, G. *J. Org. Chem.* **1986**, *51*, 5259-5264. (b) Otsubo, K.; Inanaga, J.; Yamaguchi, M. *Tetrahedron Lett.* **1987**, *28*, 4437-4440.

titanium salts[18] (*Scheme III-10*). However, these conditions have not been applied to epoxyenynes and their use could present compatibility issues.



Scheme III-10. 1,4-Reduction of vinyl epoxides.

Moreover, the spontaneous rearrangement of an α-epoxy boronate, such as intermediate **M** (*Scheme III-8*), was unprecedented and stereospecific, since only the *E* allylic alcohol was observed. At this point, we found this transformation worth of studying more deeply and we changed the direction in our research.

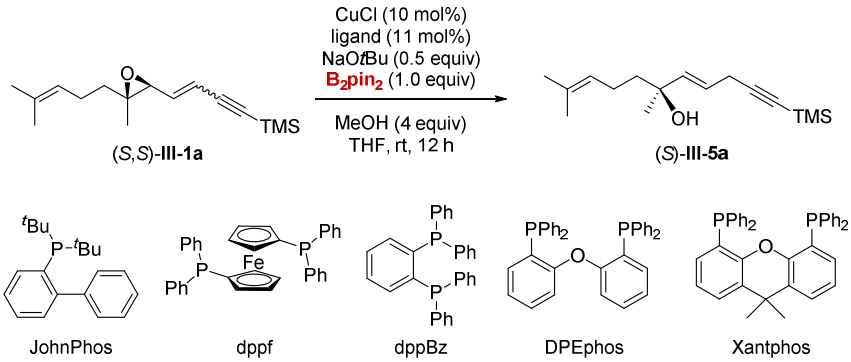
[17] (a) Pak, C. S.; Lee, E.; Lee, G. H.; *J. Org. Chem.* **1993**, *58*, 1523-1530. (b) Poldy, J.; Peakall, R.; Barrow, R. A. *Eur. J. Org. Chem.* **2012**, 5818-5827. (c) Oe, K.; Ohfune, Y.; Shinada, T. *Org. Lett.* **2014**, *16*, 2550-2553.

[18] Yadav, J. S.; Shekharam, I.; Srinivas, D. *Tetrahedron Lett.* **1992**, *33*, 7973-7976.

3.2.3. Copper-Catalyzed Formal Reduction of Vinyl Epoxides: Screening of Conditions

Starting from our preliminary result with xantphos (*Scheme III-9*) we first explore the influence of the ligand in the copper-catalyzed formal reduction (*Table III-1*). Monodentate phosphines with different stereoelectronic properties afforded the allylic alcohol in moderate yields (*entries 2-5, Table III-1*). Also, ferrocenyl-based ligand was tested and good results were observed (*entry 6, Table III-1*). 1,2-Bis(diphenylphosphino)benzene (dppBz), a bidentate phosphine with smaller bite angle than xantphos, showed poor conversion (*entry 7, Table III-1*). However, DPEPhos, with a bite angle closer to xantphos, provided good yield (*entry 8, Table III-1*).

Table III-1. Screening of ligands and copper(I) sources.

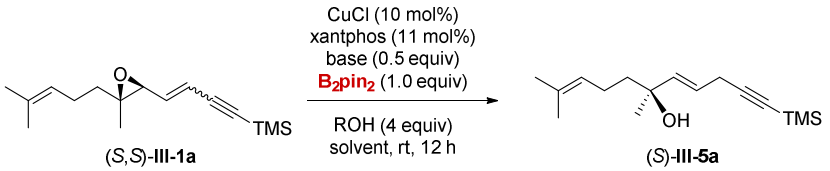


Entry[a]	ligand	Yield (%)
1	***xantphos***	***82***[b]
2	PPh_3	57[c]
3	PCy_3	37[c]
4	P(*t*Bu)$_3$	44[c]
5	JohnPhos	33[c]
6	dppf	65[c]
7	dppBz	18[c]
8	DPEPhos	74[b]

[a]Reaction conditions: (*S*,*S*)-**III-1a** (0.2 mmol), B_2pin_2 (0.22 mmol), NaO*t*Bu (0.1 mmol), Cu(I) (10 mol%), ligand (11 mol%), MeOH (0.8 mmol), THF (0.2 M).[b]Yield of isolated (*S*)-**III-5a**. [c]Determined by ^{1}H NMR analysis.

We also studied the effect of the solvent in the reaction (*entries 1-5, Table III-2*) but none of them proved to be superior to THF. The use of bulkier alcohols as proton sources provided lower yields (*entries 6-7, Table III-2*). Moreover, among different bases (*entries 8-11, Table III-2*), the best results were observed using sodium *tert*-butoxide (*entry 5, Table III-2*).

Table III-2. Screening of solvents, proton sources and bases.



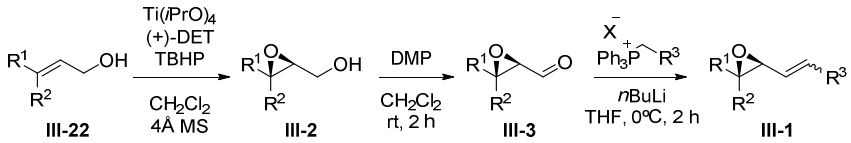
(*S*,*S*)-**III-1a** (*S*)-**III-5a**

Entry[a]	solvent	Alcohol	base	Yield
1	CH_2Cl_2	MeOH	NaO*t*Bu	78[b]
2	toluene	MeOH	NaO*t*Bu	63[b]
3	CH_3CN	MeOH	NaO*t*Bu	49[b]
4	Et_2O	MeOH	NaO*t*Bu	74[b]
5	***THF***	***MeOH***	***NaOtBu***	***82***[c]
6	THF	*i*PrOH	NaO*t*Bu	57[b]
7	THF	*t*BuOH	NaO*t*Bu	32[b]
8	THF	MeOH	KO*t*Bu	65[b]
9	THF	MeOH	LiOMe	35[b]
10	THF	MeOH	NaOPh	70[b]

[a]Reaction conditions: (*S*,*S*)-**III-1a** (0.2 mmol), B_2pin_2 (0.22 mmol), base (0.1 mmol), CuCl (10 mol%), xantphos (11 mol%), ROH (0.8 mmol), solvent (0.2 M). [b]Determined by ^{1}H NMR analysis. [c]Yield of isolated (*S*)-**III-5a**.

3.2.4. Scope of the Reaction

To study the scope of the transformation, we synthesized several allylic epoxides with different substitution patterns. We followed the same synthetic sequence previously used for the model substrate. Sharpless asymmetric epoxidation of allylic alcohols **III-22** afforded enantioenriched epoxides **III-2**,[11] which were oxidized to aldehydes **III-3** using the Dess-Martin periodinane.[12] Finally, a Wittig olefination provided the desired vinyl oxiranes **III-1** (*Scheme III-11*).[13]



Scheme III-11. Synthesis of Starting Materials.

We first synthesized different epoxyenynes to study the scope of the copper(I)-catalyzed formal reduction in these systems (*Figure III-1a*). However, we also wanted to explore the transformation with vinyl epoxides carrying different substituents at the allylic position. We looked for functional groups that could provide the regiochemistry observed for the enynes in the insertion step. Therefore, we prepared vinyl oxiranes with aromatic and heteroaromatic substituents as well as ketone, cyano and ester groups (*Figure III-1b*).

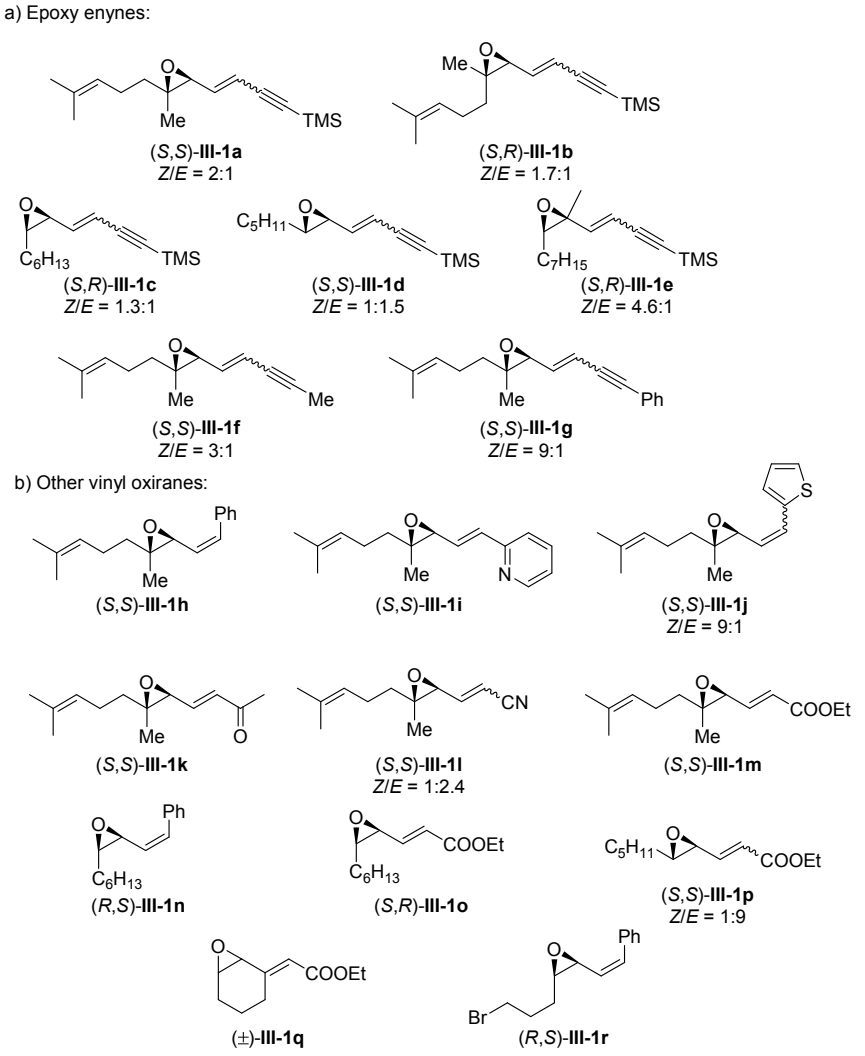
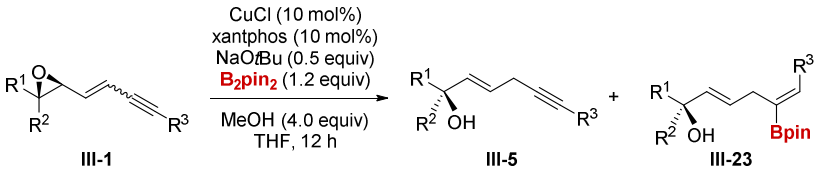


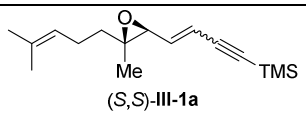
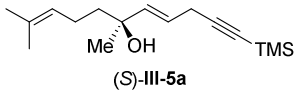
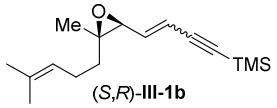
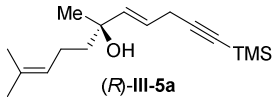
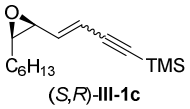
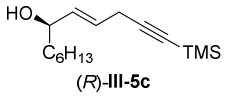
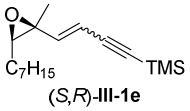
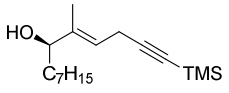
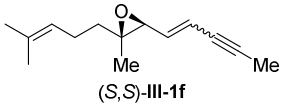
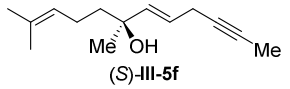
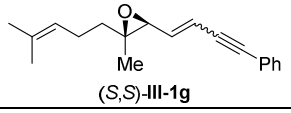
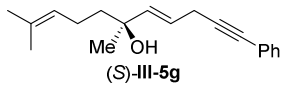
Figure III-1. Synthesized Starting Materials.

With the optimal conditions in hand, we next explored the scope of the method. When we applied these conditions to vinyl epoxide (*S*,*R*)-**III-1b** we observed the formation of (*R*)-**III-5a** in good yield (*entry 2, Table III-3*). However, when we used disubstituted epoxide (*S*,*R*)-**III-1c**, compound (*R*)-**III-5c** was obtained in 51% yield at room temperature. The lower yield can be explained by formation of byproduct **III-23**, resulting from the borylation of the propargylic moiety. Gratifingly, we observed that

low temperature avoided the formation of vinyl boronate **III-23**. Overall, yields were improved modulating the optimal temperature for each substrate. Allylic alcohol (*R*)-**III-5c** was obtained in 74% yield when the reaction was performed at 0 ºC (*entry 3, Table III-3*). Then, epoxide (*S*,*R*)-**III-1e**, that presented a different substitution pattern on the epoxide, gave allylic alcohol (*R*)-**III-5e** in moderate yield at -20ºC. The competition between the mono and the diborylated product is in this case higher due to the steric hindrance around the alkene in (*S*,*R*)-**III-1e**, that makes more difficult the first insertion step (*entry 4, Table III-3*). Methyl substituted epoxyenyne (*S*)-**III-5f**, was also prepared in 50% yield at 0 ºC (*entry 5, Table III-3*). Finally, epoxyenyne (*S*,*S*)-**III-1g** bearing a phenyl substituent on the alkyne, afforded alcohol (*S*)-**III-5g** in 58% yield. This substrate was found to be more reactive towards the second borylation, due to the electronic properties of the phenylacetylene moiety, and the reaction had to be performed at -20 ºC to minimize the formation of **III-23** (*entry 6, Table III-3*).

Table III-3. Copper-catalyzed borylation of epoxyenynes.



Entry[a]	Epoxyenyne	Allylic alcohol	yield (%)
1	 (*S*,*S*)-**III-1a**	 (*S*)-**III-5a**	82[b]
2	 (*S*,*R*)-**III-1b**	 (*R*)-**III-5a**	70[b]
3	 (*S*,*R*)-**III-1c**	 (*R*)-**III-5c**	74[c]
4	 (*S*,*R*)-**III-1e**	 (*R*)-**III-5e**	55[d,e]
5	 (*S*,*S*)-**III-1f**	 (*S*)-**III-5f**	50[c]
6	 (*S*,*S*)-**III-1g**	 (*S*)-**III-5g**	58[d,f]

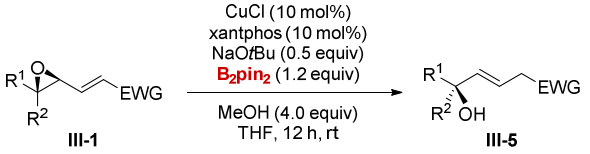
[a]Reaction conditions: **III-1** (0.15 mmol), B_2pin_2 (0.18 mmol), NaO*t*Bu (50 mol%), CuCl (10 mol%), xantphos (11 mol%), MeOH (0.6 mmol), THF (0.2 M). [b]The reaction was carried out at room temperature. [c]The reaction was carried out at 0 ºC. [d]The reaction was carried out at -20 ºC. [e]Ratio of products observed in the crude mixture by ^{1}H NMR: **III-5e**/**III-23e** = 6:1. [e]Ratio of products observed in the crude mixture by ^{1}H NMR: **III-5g**/**III-23g** = 5:1.

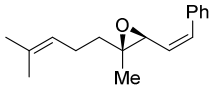
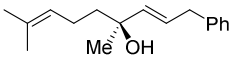
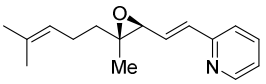
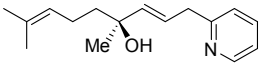
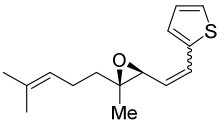
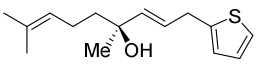
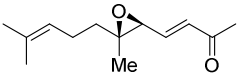
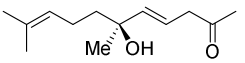
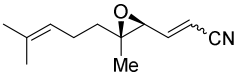
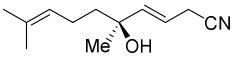
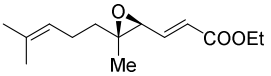
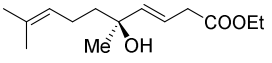
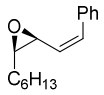
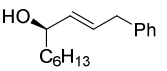
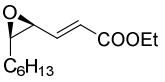
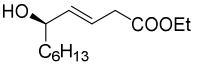
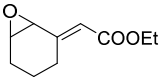
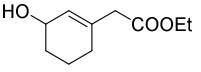
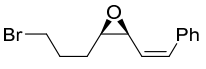
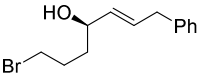
Then we studied the transformation with allylic epoxides bearing different electron withdrawing groups on the double bond. Gratifyingly, phenyl substituted epoxide (*S*,*S*)-**III-1h** afforded alcohol (*S*)-**III-5h** (*entry 1, Table III-4*). Heteroaromatic rings, such as pyridine (*S*,*S*)-**III-1i** and thiohene (*S*,*S*)-**III-1j** (*entries 2-3, Table III-4*), gave moderate yields and higher charge of copper was needed, due to the possible coordination of the copper with the heteroatom. Furthermore, ketones (*S*,*S*)-**III-1k**, nitriles

(*S*,*S*)-**III-1l** and esters (*S*,*S*)-**III-1m** were suitable functional groups for this transformation (*entries4-6, Table III-4*). Good results were observed when disubstituted epoxides (*R*,*S*)-**III-1n** and (*S*,*R*)-**III-1o** were used (*entries 7-8, Table III-4*). Cyclic epoxide (±)-**III-1q** was also successfully transformed into (±)-**III-5q** (*entry 9, Table III-4*). Finally, epoxy alkene (*R*,*S*)-**III-1r** bearing an alkyl halide afforded allylic alcohol (*R*)-**III-5r** in 53% yield (*entry 10, Table III-4*). The chemoselectivity in this last example is remarkable since alkyl bromides are known to undergo borylation at the C-Br bond under similar reaction conditions.[19]

[19] (a) Kleeberg, C.; Dang, L.; Lin, Z.; Marder, T. B. *Angew. Chem. Int. Ed.* **2009**, *48*, 5350-5354. (b) Ito, H.; Kubota, K. *Org. Lett.* **2012**, *14*, 890-893. (c) Iwamoto, H.; Kubota, K.; Yamamoto, E.; Ito, H. *Chem. Commun.* **2015**, *51*, 9655-9658.

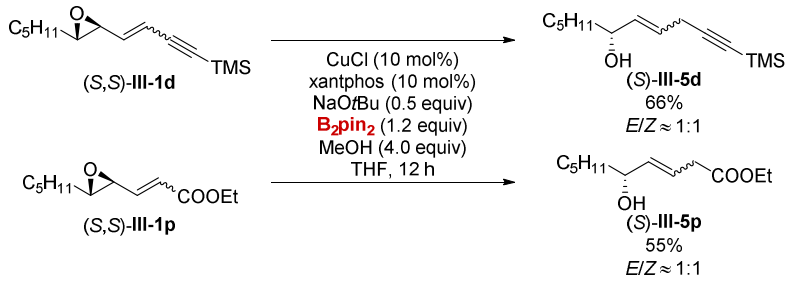
Table III-4. Scope of vinyl epoxides.



Entry[a]	Vinyl epoxide	Allylic alcohol	yield (%)
1	 (*S*,*S*)-**III-1h**	 (*S*)-**III-5h**	78[b]
2	 (*S*,*S*)-**III-1i**	 (*S*)-**III-5i**	51[c]
3	 (*S*,*S*)-**III-1j**	 (*S*)-**III-5j**	60[c]
4	 (*S*,*S*)-**III-1k**	 (*S*)-**III-5k**	52
5	 (*S*,*S*)-**III-1l**	 (*S*)-**III-5l**	61
6	 (*S*,*S*)-**III-1m**	 (*S*)-**III-5m**	77
7	 (*R*,*S*)-**III-1n**	 (*R*)-**III-5n**	73[b]
8	 (*S*,*R*)-**III-1o**	 (*R*)-**III-5o**	74
9	 (±)-**III-1q**	 (±)-**III-5q**	83
10	 (*S*,*S*)-**III-1r**	 (*R*)-**III-5r**	53

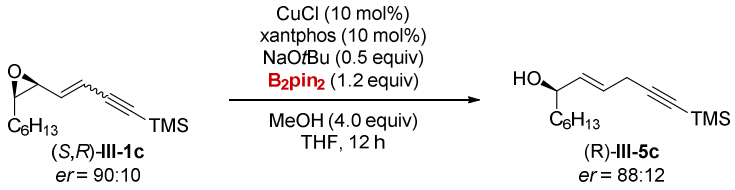
[a]Reaction conditions: **III-1** (0.15 mmol), B_2pin_2 (0.18 mmol), NaO*t*Bu (50 mol%), CuCl (10 mol%), xantphos (11 mol%), MeOH (0.6 mmol), THF (0.2 M).[b] 2.0 equiv of B_2pin_2were added. [c]Higher loading of CuCl (20 mol%) and xantphos (20 mol%) were needed.

Unfortunately, when the reaction was performed with *trans* epoxides (*S*,*S*)-**III-1d** and (*S*,*S*)-**III-1p**, under the optimal reaction conditions, mixtures of *E*/*Z* products were obtained (*Scheme III-12*).



Scheme III-12. Hydroboration of *trans* epoxides.

The enantiomeric ratio of chiral alcohol (*R*)-**III-5c** was measured to demonstrate that the copper(I)-catalyzed reduction of vinyl epoxides takes places with excellent chirality transfer (*Scheme III-13*).[20]



Scheme III-13. Evaluation of the chirality transfer.

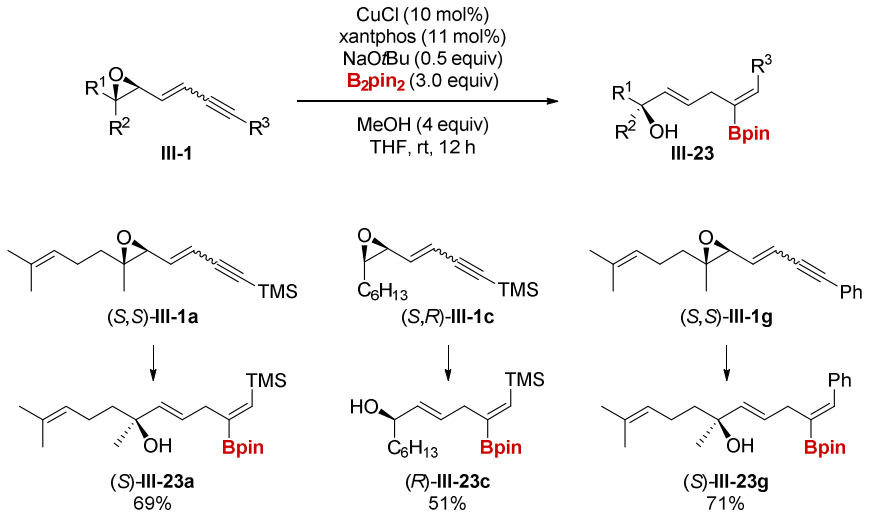
[20] All enantiomeric excesses were determined by ^{1}H NMR analysis of the derived α-methoxyphenylacetic ester, following reported procedures: (a) Latypov, s. K.; Seco, J. M.; Quiñoá, E.; Riguera R. *J. Org. Chem.* **1996**, *61*, 8569-8577. (b) Seco, J. M.; Quiñoá, E.; Riguera R. *Chem. Rev.* **2004**, *104*, 17-118.

3.2.5. Double Borylation Reaction: Synthesis of Functionalized Skipped Dienes

In some of the examples described in *Table III-3*, we consistently observed significant amounts of skipped diene **III-23**, which is formed through a second borylation of the alkyne in allylic alcohol **III-5**. Although initially undesired, compounds **III-23** are very interesting functionalized skipped dienes that could be used as synthetic intermediates in the preparation of complex molecules. Therefore, we tried to optimize the formation of these dienes increasing the amount of the borylating reagent at room temperature. Indeed, from epoxide (*S*,*S*)-**III-1a**, using 3 equivalents of B_2pin_2 at room temperature, compound (*S*)-**III-23a** was obtained in 69% yield as a single stereo- and regioisomer (*Scheme III-14*).

The same conditions were applied to epoxides (*S*,*R*)-**III-1c** and (*S*,*S*)-**III-1g** to prepare skipped dienes (*R*)-**III-23c** and (*S*)-**III-23g** in 51% and 71% yield respectively (*Scheme III-14*). Compounds **III-23a** and **III-23c** are specially interesting because they have a bifunctional alkene, with a Bpin and a TMS group, that could be used in orthogonal cross-coupling reactions.[21]

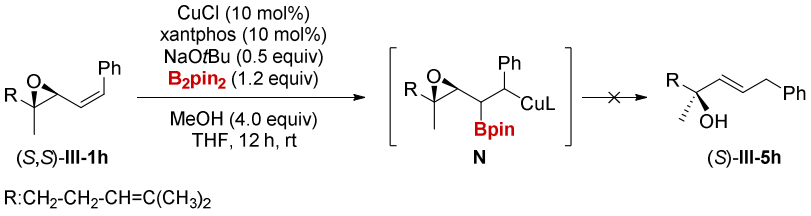
[21] (a) Suginome, M.; Matsuda, T.; Nakamura, H.; Ito, Y. *Tetrahedron*, **1999**, *55*, 8787-8800. (b) PraveenGanesh, N.; Candia, C.; Memboeuf, A.; Lendvay, G.; Gimbert, Y.; Chavant, P. Y. *J. Organomet. Chem.* **2010**, *695*, 2447-2454. (c) Saito, N.; Saito, K.; Sato, H.; Sato, Y. *Adv. Synth. Catal.* **2013**, *355*, 853-856. (d) Chae, Y. M.; Bae, J. S.; Moon, J. H.; Lee, J. Y.; Yun, J. *Adv. Synth. Catal.* **2014**, *356*, 843-849.



Scheme III-14. Synthesis of functionalized skipped dienes.

3.2.6. Stereochemical Outcome and Mechanistic Proposal

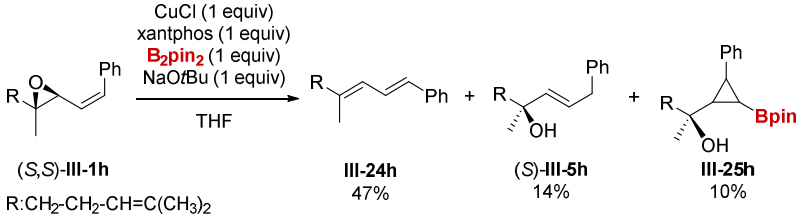
To gain further insight into the mechanism of this transformation we carried out some NMR controlled experiments. When we monitored the reaction by ^{1}H NMR, under the optimized conditions, we could not identify copper intermediate **N** (*Scheme III-15*), and only the formation of the final product (*S*)-**III-5h** was observed.[22] On the other hand, ^{11}B-NMR experiments were also performed, but were inconclusive.



Scheme III-15. ^{1}H NMR controlled experiment.

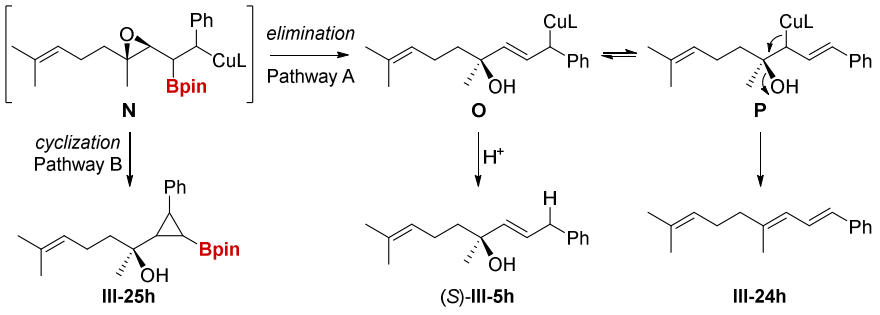
[22] We decided to use (*S*,*S*)-**III-1h,** to carry out these mechanistic studies, in order to simplify the reaction, as skipped dienes cannot be obtained with this substrate.

Then, we performed an experiment using a stoichiometric amount of copper salt, ligand and base, in absence of proton source, to try to stop the reaction at the copper-boryl intermediate **N** (*Scheme III-15*). However, we observed the formation of a mixture of three compounds, being the major one diene **III-24h** (*Scheme III-16*). Allylic alcohol (*S*)-**III-5h** and cyclopropane **III-25h** were also formed in 14 and 10% yield respectively.



Scheme III-16. Stoichiometric experiment.

These three species could be formed from the same intermediate **N**, that undergoes different reaction pathways (*Scheme III-17*). If the elimination takes place before the cyclization (pathway A), a σ-allyl copper **O** would be formed, that could be in equilibrium with σ-allyl copper **P** through a π-allyl copper complex. Protonation of **O** would afford allylic alcohol (*S*)-**III-5h** and protonation of **P** would provide diene **III-24h**. If the cyclization takes place before the elimination (pathway B), cyclopropane **III-25h** would be formed.



Scheme III-17. Proposed pathways for the synthesis of cyclopropanes and dienes.

Cyclopropylboronate **III-25h** was further characterized to determine the relative and absolute configuration of the four stereogenic centers. The X-ray crystal structure provided the relative stereochemistry. The absolute stereochemistry was assigned as shown in *Figure III-2* considering the absolute stereochemistry of the starting material (*S*,*S*)-**III-1h**.

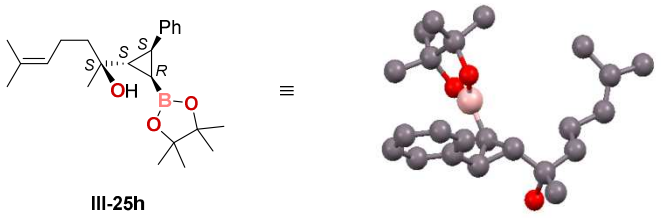
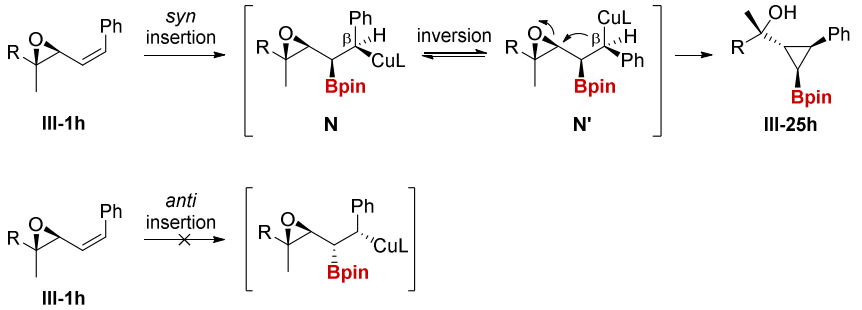


Figure III-2. Absolute configuration

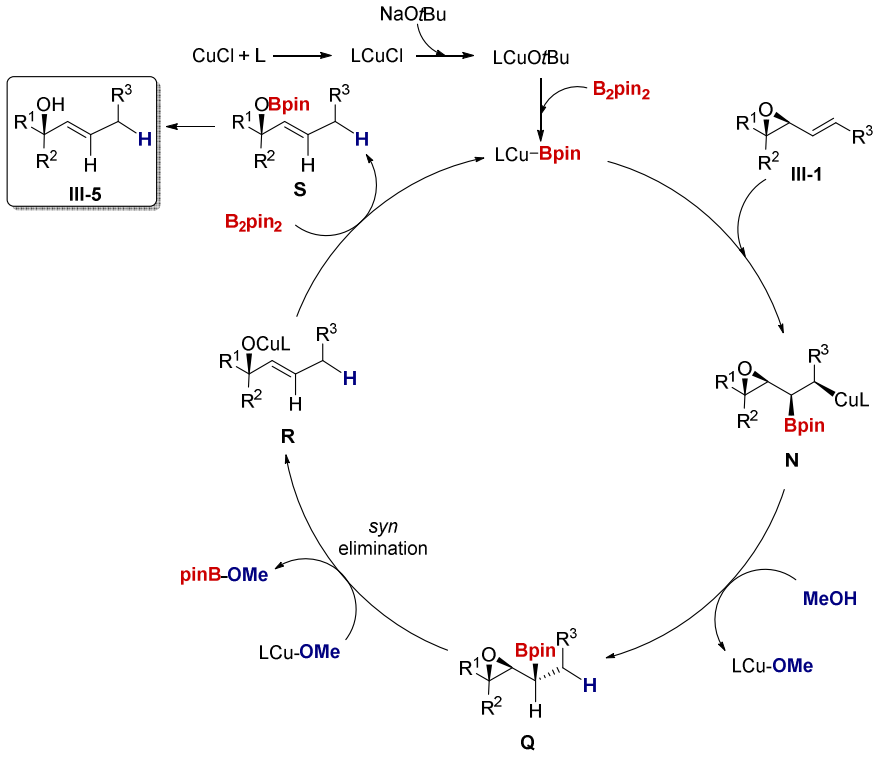
The relative configuration of the stereocenters in **III-25h** gave us also information about the mechanism. To account for the observed stereochemistry the insertion step must take place *syn* to the epoxide, drawn as in *Scheme III-18*, to provide intermediate **N**, in which the boron sp^3 stereocenter has been fixed. The copper-carbon stereocenter is not configurationally stable and inversion of the configuration of C(β) occurs before the cyclization takes place. This conclusion is derived from the *cis* disposition of the phenyl group and the boryl moiety in the final product (*Scheme III-18*). Additionally, the formation of allylic alcohol (*S*)-**III-5h** from intermediate **N** must take place through a *syn* elimination process to account for the *E* geometry of the double bond in the final product.



Scheme III-18. *Syn* and *anti* insertion.

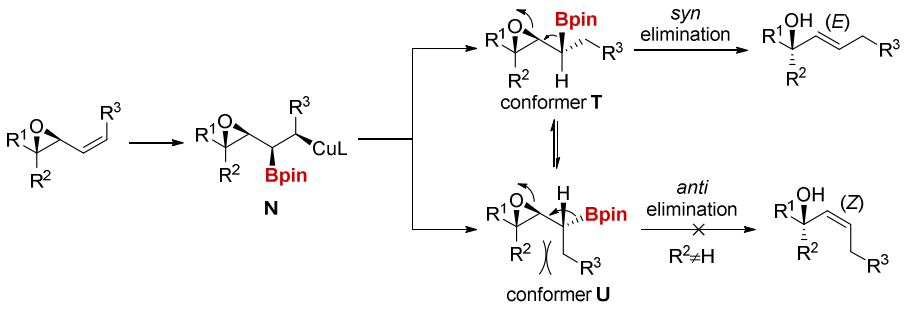
According to the experimental observations, we proposed the following mechanistic pathway (*Scheme III-19*). First copper(I) chloride is coordinated to the ligand and in the presence of NaO*t*Bu, a copper alkoxide is formed. Then, reaction with B_2pin_2 generates the copper-boryl complex through sigma bond metathesis reaction. Insertion of the alkene from vinyl epoxide **III-1** affords the copper-boryl intermediate **N** that can be protonated by MeOH. Intermediate **Q** undergoes a quickly rearrangement with ring opening, through a *syn* elimination pathway to provide **R**. Finally, copper alkoxide **R** reacts with B_2pin_2 to afford **S** that can evolve to allylic alcohol **III-5**.[23]

[23] Although the dual role of copper has not been proven in this reaction, we can assume a similar mechanism than the one observed for the recently developed synthesis of allenols from propargylic epoxides: Jarava-Barrera, C.; Parra, A.; Amenós, L.; Arroyo, A.; Tortosa, M. *Chem. Eur. J.* **2017**, Accepted, DOI: 10.1002/chem.201705019.



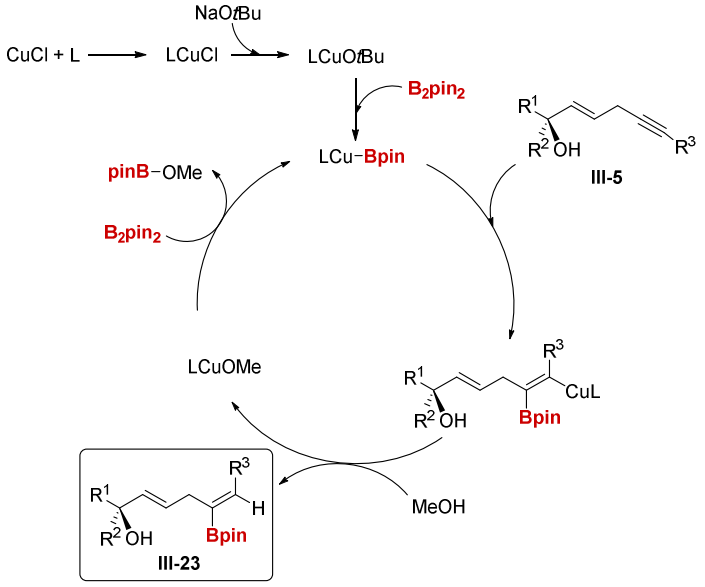
Scheme III-19. Mechanistic proposal for the formal reduction of vinyl oxiranes.

After the insertion and protonation step, the *syn* elimination would take place through conformer **T** and the *anti* elimination through conformer **U** (*Scheme 20*). When $R^2 \neq H$, the *syn* elimination pathway is favored over the *anti* due to the steric hindrance between R^2 and the $-CH_2R^3$ chain in conformer **S**. When $R^2 = H$ (*trans* epoxides) that steric hindrance is not so high and the *anti* pathway competes with the *syn*.



Scheme III-20. Conformers in equilibrium generated in s*yn* and *anti* elimination.

Finally, skipped dienes **III-23** would be formed through a second borylation reaction following the typical catalytic cycle for a copper-catalyzed borylation shown in *Scheme III-21*.



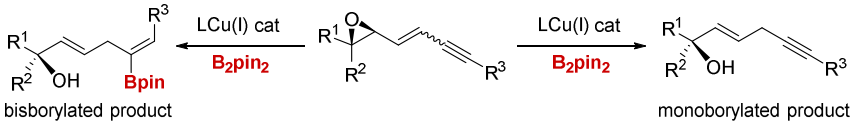
Scheme III-21. Mechanistic proposal for the synthesis of skipped dienes.

3.2.7. Conclusions

We have developed a novel formal reduction of enantioenriched vinyl oxiranes under mild conditions that avoids the use of stoichiometric amount of a strong reductant (*Scheme III-22*). The scope of the reaction is broad for vinyl epoxides bearing electron withdrawing groups on the double bond.

The reaction takes place through an initial borylation of the alkene, with unexpected regiochemisty, followed by an unprecedented *syn* elimination to provide the product of formal reduction.

Moreover, reductive ring-opening and borylation of the alkyne can be achieved just using two equivalents of B_2pin_2. The products are highly functionalized skipped dienes that would be difficult to synthesize by known methods.

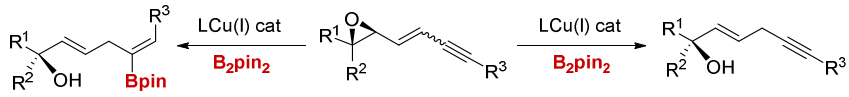


Scheme III-22. Synthesis of allylic alcohols and skipped dienes.

3.2.8. Conclusiones

Se ha desarrollado un nuevo método de reducción formal de epóxidos alílicos en condiciones suaves de reacción, sin utilizar cantidades estequiométricas de un reductor (*Esquema III-23*). El alcance estructural de la reacción es amplio para epóxidos vinílicos con sustituyentes electroatractores en el doble enlace. La reacción transcurre a través de una borilación inicial del doble enlace, con regioquímica opuesta a la esperada, seguida de un proceso de eliminación-apertura del epóxido sin precedentes.

Adicionalmente, en el caso de utilizar epoxieninos, se puede controlar la mono- o doble borilación mediante el número de equivalentes de B_2pin_2. En el caso de la doble borilación, se obtienen dienos no conjugados altamente funcionalizados (*Esquema III-23*).



Esquema III-23. Sintesis de alcoholes alílicos y vinilboronatos.

3.3. Supplementary data

3.3.1. General Experimental Details

Tetrahydrofuran, toluene, acetonitrile and dichloromethane were purified by passing through a Pure Solv™ column drying system from Innovative Technology, Inc. Additionally, THF and methanol were degassed through three consecutive freeze-pump-thaw cycles. Diethyl ether was dried using activated 4Å molecular sieves and stored under argon. Unless indicated otherwise, all reactions were conducted under an argon atmosphere using flame-dried glassware with standard vacuum-line techniques.

NMR spectra were acquired on a Bruker 300 spectrometer, running at 300, and 75 MHz for ^{1}H and ^{13}C, respectively. Chemical shifts (δ) are reported in ppm relative to residual solvent signals ($CDCl_3$, 7.26 ppm for ^{1}H NMR and 77.16 ppm for ^{13}C NMR respectively). ^{13}C NMR spectra were acquired on a broad band decoupled mode. The following abbreviations are used to describe peak patterns when appropriate: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), br (broad). Analytical thin layer chromatography (TLC) was performed using pre-coated aluminum-backed plates (Merck Kieselgel 60 F254) and visualized by ultraviolet irradiation or phosphomolybdic acid dip. Purification of reaction mixtures was carried out by flash chromatography (FC) using silica gel Merck-60 or Florisil® 100-200 mesh from Aldrich. Optical rotations were measured on a Perkin-Elmer 241 polarimeter. Mass Spectrometry (MS) and High Resolution Mass Spectrometry (HRMS) were registered in a spectrometer *GCT Agilent Technologies 6890 N* using Electronic Impact (EI^+) techniques at 70 eV and electrospray (ESI^+).

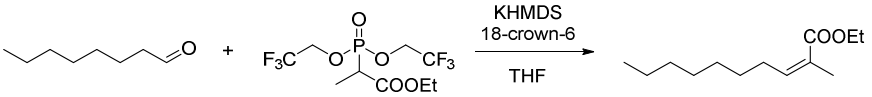
All ligands, NaO*t*Bu (2.0 M solution in THF), LiOMe, KO*t*Bu and NaOPh were acquired from comercial sources and were used without further purification.

(+)-Diethyl tartrate (DET) and titanium tetraisopropoxide were freshly distilled before used at Sharpless epoxidation. Dess-Martin periodinane[12a] was synthesized following reported procedures.

CuCl was washed with acetic acid, filtered and washed with ethanol and diethyl ether twice and dried under vacuum before used.[24] Bis(pinacolato)diboron was recrystrallized in *n*-pentane before used.

3.3.2. Synthesis of Starting Materials

3.3.2.1. Synthesis of Ethyl (*Z*)-2-Methyldec-2-enoate

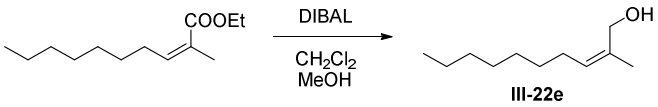


A solution of ethyl 2-(bis(2,2,2-trifluoroethoxy)phosphoryl) propanoate (1.23 g, 3.6 mmol, 1.3 equiv), 18-crown-6 (2.9 g, 11 mmol, 4 equiv) in 55 mL of anhydrous THF was cooled to -78 ºC under argon and treated with KHMDS (6.6 mL, 3.3 mmol, 1.2 equiv, 0.5M in toluene). Octanal (352.6 mg, 2.75 mmol, 1 equiv) was then added and the resulting mixture was stirred for 30 min at -78 ºC. Saturated NH_4Cl was added and layers were separated. The product was extracted with diethyl ether and organic phases were dried over Na_2SO_4, filtered and concentrated. Finally, the crude product was purified by flash column chromatography on silica gel (2% EtOAc/Cyclohexane) to afford (*Z*)-2-methyldec-2-enoate (356.2 mg, 1.68 mmol) in 61% yield.

[24] Perrin, D. D. Armarego, W. L. *Purification of Laboratory Chemicals,* 3rd Ed.; Pergamon Press: Oxford, 1988.

The spectral data for (*Z*)-2-methyldec-2-enoate matched those previously reported for this compound.[25] **^{1}H NMR** (300 MHz, $CDCl_3$): δ 5.91 (t, *J* = 7.4 Hz, 1H), 4.18 (q, *J* = 7.1 Hz, 2H), 2.54-2.36 (m, 2H), 1.88 (s, 3H), 1.43-1.17 (m, 13H), 0.87 (t, *J* = 6.4 Hz, 3H).

3.3.2.2. Synthesis of Ethyl (*Z*)-2-Methyldec-2-en-1-ol, **III-22e**

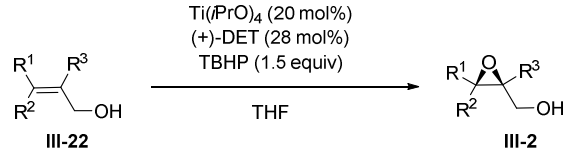


To a -78 ºC solution of (*Z*)-2-methyldec-2-enoate (339.7 mg, 1.6 mmol, 1 equiv) in 9 mL of anhydrous CH_2Cl_2, DIBAL (3.6 mL, 3.6 mmol, 2.3 equiv, 1M in CH_2Cl_2) was added. The reaction mixture was stirred for 1.5h and then, quenched with MeOH (3.5 mL) and diluted with an aqueous solution of Rochelle's salt (13 mL). The resulting slurry was allowed to warm to room temperature for 2 h. Layers were separated, aqueous phase was extracted with CH_2Cl_2 (x3) and combined organic phases were dried over $MgSO_4$, filtered and concentrated. Finally, the residue was purified by flash column chromatography on silica gel (10% EtOAc/Cyclohexane) to **III-22e** (253.4 mg, 1.49 mmol) in 93% yield.

The spectral data for **III-22e** matched those previously reported for this compound.[26] **^{1}H NMR** (300 MHz, $CDCl_3$): δ 5.29 (t, *J* = 7.3 Hz, 1H), 4.11 (s, 2H), 2.13-1.93 (m, 2H), 1.78 (s, 3H), 1.36-1.19 (m, 10H), 0.87 (t, *J* = 6.6 Hz, 3H).

[25] Ando, K. *J. Org. Chem.* **1998**, *63*, 8411-8416.
[26] Ely, R. J.; Morken, J. P. *J. Am. Chem. Soc.* **2010**, *132*, 2534-2535.

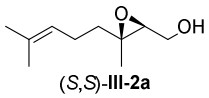
3.3.2.3. General Procedure for the Synthesis of Epoxy Alcohols via Sharpless epoxidation, **III-2**



III-22 **III-2**

An oven dried flask equipped with a magnetic stirbar, was charged with 4Å powdered activated molecular sieves (28 mg/mmol **III-22**) and dry CH_2Cl_2 (0.6 mL/mmol **III-22**). The flask was cooled to -20 ºC. L-(+)-Diethyl tartrate (28 mol%) and Ti(*i*PrO)$_4$, (20 mol%, via syringe) were added sequentially. The reaction mixture was stirred at -20 ºC while TBHP (1.5 equiv, 5.5 in decanes) was added dropwise. The resulting mixture was stirred at -20 ºC for 30 min. Alcohol **III-22** (1 equiv), dissolved in dry CH_2Cl_2 (0.15 mL/mmol **III-22**), was then added dropwise. The mixture was stirred for an additional 24 h at -20 ºC. After the reaction mixture was warmed to 0 ºC, water was added and the mixture was stirred for 30min, while allowing it to warm to room temperature. Then, 30% aqueous solution of NaOH was added and stirring vigorously for 20 min. The resulting solution was transferred to a separatory funnel and extracted with CH_2Cl_2 (x3), the combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by flash column chromatography on silica gel to achieve compound **III-2**.

[(2*S*,3*S*)-3-Methyl-3-(4-methylpent-3-en-1-yl)oxiran-2-yl]methanol, (*S*,*S*)-III-2a



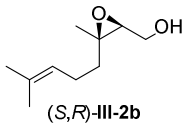
(*S*,*S*)-**III-2a**

From alcohol **III-22a** (2.0 g, 13.0 mmol) following the general procedure described above, compound (*S*,*S*)-**III-2a** (2.13 g, 12.5 mmol) was obtained in 96 % yield.

The spectral data for (*S*,*S*)-**III-2a** matched those previously reported for this compound.[27] **^{1}H NMR** (300 MHz, $CDCl_3$): δ 5.07 (t, *J* = 6.9 Hz, 1H), 3.82 (ddd, *J* = 11.7, 7.2, 4.2 Hz, 1H), 3.67 (ddd, *J* = 11.6, 6.7, 4.6 Hz, 1H), 2.97 (dd, *J* = 6.6, 4.3 Hz, 1H), 2.14-2.02 (m, 2H), 1.76- 1.63 (m, 2H), 1.68 (s, 3H), 1.60 (s, 3H), 1.29 (s, 3H).

The enantiomeric ratio of the product was determined to be 90:10 by ^{1}H NMR analysis of its methoxy phenyl acetates, prepared by reaction of (±)- and (-)-methoxyphenyl acid and DCC in CH_2Cl_2.[20]

[(2*S*,3*R*)-3-Methyl-3-(4-methylpent-3-en-1-yl)oxiran-2-yl]methanol, (*S*,*R*)-III-2b



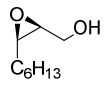
(*S*,*R*)-**III-2b**

From alcohol **III-22b** (2.0 g, 13.0 mmol) following the general procedure described above, compound (*S*,*R*)-(*S*,*R*)-**III-2b** (1.91 g, 11.2 mmol) was obtained in 86 % yield.

The spectral data for (*S*,*R*)-**III-2b** matched those previously reported for this compound.[27] **^{1}H NMR** (300 MHz, $CDCl_3$): δ 5.10-4.95 (m, 1H), 3.83-3.67 (m, 1H), 3.64-3.52 (m, 1H), 2.93 (dd, *J* = 7.0, 4.3 Hz, 1H), 2.13-1.93 (m, 2H), 1.63 (s, 3H), 1.55 (s, 3H), 1.42 (ddd, *J* = 13.7, 10.1, 7.0 Hz, 1H), 1.23 (s, 3H).

The enantiomeric ratio of the product was determined to be 86:14 by ^{1}H NMR analysis of its methoxy phenyl acetates, prepared by reaction of (±)- and (-)-methoxyphenyl acid and DCC in CH_2Cl_2.[20]

[(2*S*,3*R*)-3-Hexyloxiran-2-yl]methanol, (*S*,*R*)-III-2c



(*S*,*R*)-**III-2c**

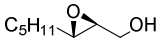
From alcohol **III-22c** (1.42 g, 10.0 mmol) following the general procedure described above, compound (*S*,*R*)-**III-2c** (901.9 mg, 5.7 mmol) was obtained in 57 % yield.

[27] Noji, M.; Kobayashi, T.; Uechi, Y.; Kikuchi, A.; Kondo, H.; Sugiyama, S.; Ishii, K. *J. Org. Chem.* **2015**, *80*, 3203-3210.

The spectral data for (*S*,*R*)-**III-2c** matched those previously reported for this compound.[28] **^{1}H NMR** (300 MHz, $CDCl_3$): δ 3.83-3.70 (m, 1H), 3.64-3.50 (m, 1H), 3.15-3.04 (m, 1H), 2.96 (d, *J* = 4.4 Hz, 1H), 1.56-1.39 (m, 2H), 1.33-1.11 (m, 8H), 0.81 (t, *J* = 6.4 Hz, 3H).

The enantiomeric ratio of the product was determined to be 90:10 by ^{1}H NMR analysis of its methoxy phenyl acetates, prepared by reaction of (±)- and (-)-methoxyphenyl acid and DCC in CH_2Cl_2.[20]

[(2*S*,3*S*)-3-Pentyloxiran-2-yl]methanol, (*S*,*S*)-III-2d



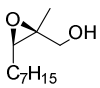
(*S*,*S*)-**III-2d**

From alcohol **III-22d** (2.0 g, 15.6 mmol) following the general procedure described above, compound (*S*,*S*)-**III-2d** (1.33 g, 9.2 mmol) was obtained in 59 % yield.

The spectral data for (*S*,*S*)-**III-2d** matched those previously reported for this compound.[28] **^{1}H NMR** (300 MHz, $CDCl_3$): δ 3.91 (ddd, *J* = 12.3, 7.6, 4.0 Hz, 1H), 3.71-3.56 (ddd, *J* = 12.3, 7.2, 4.1 Hz, 1H), 3.02-2.88 (m, 2H), 1.58-1.53 (m, 2H), 1.50-1.38 (m, 2H), 1.37-1.22 (m, 4H), 0.89 (t, *J* = 6.8 Hz, 3H).

The enantiomeric ratio of the product was determined to be 92:8 by ^{1}H NMR analysis of its methoxy phenyl acetates, prepared by reaction of (±)- and (-)-methoxyphenyl acid and DCC in CH_2Cl_2.[20]

[(2*S*,3*R*)-3-Heptyl-2-methyloxiran-2-yl]methanol, (*S*,*R*)-III-2e



(*S*,*R*)-**III-2e**

From alcohol **III-22e** (348.2mg, 2.0 mmol) following the general procedure described above, compound (*S*,*R*)-**III-2e** (326.7mg, 1.75 mmol) was obtained in 88 % yield.

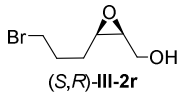
The spectral data for (*S*,*R*)-**III-2e** matched those previously reported for this compound.[29] **^{1}H NMR** (300 MHz, $CDCl_3$): δ 3.64 (t, *J* = 5.0 Hz, 2H),

[28] Wang, C.; Yamamoto, H. *J. Am. Chem. Soc.* **2014**, *136*, 1222-1225.
[29] Kumar, H.; Reddy, A. S.; Yadav, J. S.; Reddy, B. V. S. *Synlett* **2013**, *24*, 1415-1419.

2.82 (t, *J* = 6.2 Hz, 1H), 1.59-1.53 (m, 2H), 1.36 (s, 3H), 1.33-1.20 (m, 10H), 0.86 (t, *J* = 6.7 Hz, 3H).

The enantiomeric ratio of the product was determined to be 67:33 by ^{1}H NMR analysis of its methoxy phenyl acetates, prepared by reaction of (±)- and (-)-methoxyphenyl acid and DCC in CH_2Cl_2.[20]

[(2*S*,3*R*)-3-(3-Bromopropyl)oxiran-2-yl]methanol, (*S*,*R*)-III-2r



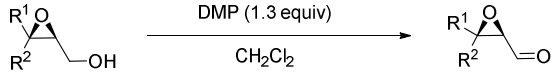
(*S*,*R*)-**III-2r**

From alcohol **III-22r** (1.96 g, 10.9 mmol) following the general procedure described above, compound (*S*,*R*)-**III-2r** (1.23g, 6.3 mmol) was obtained in 58 % yield, as a white oil. $\mathbf{R}_f$ = 0.1 (20% EtOAc/Cyclohexane).

^{1}H NMR (300 MHz, $CDCl_3$): δ 3.89-3.78 (m, 1H), 3.73-3.63 (m, 1H), 3.53-3.38 (m, 2H), 3.15 (dt, *J* = 6.6, 4.3 Hz, 1H), 3.03 (dt, *J* = 7.5, 4.8 Hz, 1H), 2.29 (br s, 1H), 2.15-1.91 (m, 2H), 1.85-1.57 (m, 2H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 60.8, 56.9, 56.4, 33.1, 30.0, 26.6. **HRMS (ESI$^+$)**: calculated for $C_6H_{11}O_2NaBr$ $[M+Na]^+$: 216.9834; found: 216.9826. **$[\alpha]^{20}_D$**= + 1.0 (*c*=1.0, $CHCl_3$).

The enantiomeric ratio of the product was determined to be 88:12 by ^{1}H NMR analysis of its methoxy phenyl acetates, prepared by reaction of (±)- and (-)-methoxyphenyl acid and DCC in CH_2Cl_2.[20]

3.3.2.4. General Procedure for the Synthesis of Epoxy Aldehydes via Dess-Martin oxidation, **III-3**

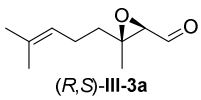


III-2 **III-3**

The Dess-Martin periodinane (1.3 equiv) was added to a stirring solution of epoxy alcohol **III-2** (1 equiv) in CH_2Cl_2 (10 mL/mmol) at 0 ºC. Then the reaction mixture was stirred at room temperature for 1h. Finally, the reaction was quenched by cooling the solution to 0 ºC followed by

addition of hexanes. The resulting solution was filtered through florisil (eluting with a solvent mixture 1:1 Et_2O/cyclohexane) and compound **III-3** was obtained.

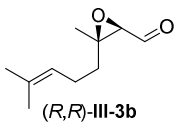
(2*R*,3*S*)-3-Methyl-3-(4-methylpent-3-en-1-yl)oxirane-2-carbaldehyde, (*R*,S)-III-3a



From epoxy alcohol (*S*,*S*)-**III-2a** (1.0 g, 5.9 mmol) following the general procedure described above, compound (*R*,*S*)-**III-3a** (942.1 mg, 5.6 mmol) was obtained in 95 % yield.

The spectral data for (*R*,*S*)-**III-3a** matched those previously reported for this compound.[30] **^{1}H NMR** (300 MHz, $CDCl_3$): δ 9.45 (d, *J* = 4.9 Hz, 1H), 5.05 (t, *J* = 6.7 Hz, 1H), 3.17 (d, *J* = 4.9 Hz, 1H), 2.16-2.02 (m, 2H), 1.80-1.47 (m, 2H), 1.68 (s, 3H), 1.59 (s, 3H), 1.43 (s, 3H).

(2*R*,3*R*)-3-Methyl-3-(4-methylpent-3-en-1-yl)oxirane-2-carbaldehyde, (*R*,*R*)-III-3b



From epoxy alcohol (*S*,*R*)-**III-2b** (2.0 g, 13.0 mmol) following the general procedure described above, compound (*R*,*R*)-**III-3b** (1.91 g, 11.2 mmol) was obtained in 86 % yield.

The spectral data for (*R*,*R*)-**III-3b** matched those previously reported for this compound.[30] **^{1}H NMR** (300 MHz, $CDCl_3$): δ 9.41 (d, *J* = 5.1 Hz, 1H), 5.03 (t, *J* = 6.7 Hz, 1H), 3.16 (d, *J* = 5.1 Hz, 1H), 2.27-1.99 (m, 2H), 1.91-1.79 (m, 1H), 1.66 (s, *J* = 6.2 Hz, 3H), 1.58 (s, 3H), 1.42 (s, 3H).

[30] Nacro, K.; Batlas, M.; Escudier, J. M.; Gorrichon, L. *Tetrahedron* **1996**, *52*, 9047-9056.

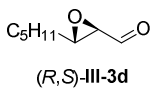
(2*R*,3*R*)-3-Hexyloxirane-2-carbaldehyde, (*R*,*R*)-III-3c


(*R*,*R*)-**III-3c**

From epoxy alcohol (*S*,*R*)-**III-2c** (901.9 mg, 5.7 mmol) following the general procedure described above, compound (*R*,*R*)-**III-3c** (843.6 mg, 5.4 mmol) was obtained in 95 % yield.

The spectral data for (*R*,*R*)-**III-3c** matched those previously reported for this compound.[31] **^{1}H NMR** (300 MHz, $CDCl_3$): δ 9.45 (d, *J* = 5.0 Hz, 1H), 3.31 (dd, *J* = 5.0, 4.9 Hz, 1H), 3.24-3.14 (m, 1H), 1.82-1.19 (m, 10H), 0.87 (t, *J* = 6.6 Hz, 3H).

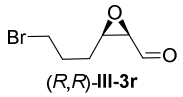
(2*R*,3*S*)-3-pentyloxirane-2-carbaldehyde, (*R*,*S*)-III-3d


(*R*,*S*)-**III-3d**

From epoxy alcohol (*S*,*S*)-**III-2d** (1.33 g, 9.2 mmol) following the general procedure described above, compound (*R*,*S*)-**III-3d** (924.3mg, 6.5 mmol) was obtained in 71 % yield.

The spectral data for (*R*,*S*)-**III-3d** matched those previously reported for this compound.[32] **^{1}H NMR** (300 MHz, $CDCl_3$): δ 9.01 (d, *J* = 6.3 Hz, 1H), 3.22 (td, *J* = 5.7, 1.9 Hz, 1H), 3.13 (dd, *J* = 6.3, 1.9 Hz, 1H), 1.74-1.17 (m, 8H), 0.90 (t, *J* = 7.0 Hz, 3H).

(2*R*,3*R*)-3-(3-Bromopropyl)oxirane-2-carbaldehyde, (*R*,*R*)-III-3r.


(*R*,*R*)-**III-3r**

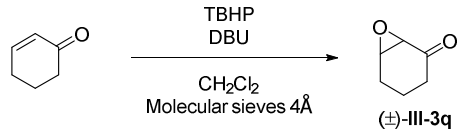
From epoxy alcohol (*S*,*R*)-**III-2r** (1.08g, 5.2 mmol) following the general procedure described above, compound (*R*,*R*)-**III-3r** (933.3 mg, 4.8 mmol) was obtained in 93 % yield, as a white oil. $\mathbf{R}_f$ = 0.3 (20% EtOAc/Cyclohexane).

^{1}H NMR (300 MHz, $CDCl_3$): δ 9.48 (d, *J* = 5.0 Hz, 1H), 3.50-3.40 (m, 2H), 3.37 (t, *J* = 4.8 Hz, 1H), 3.31-3.23 (m, 1H), 2.22-1.91 (m, 2H), 1.90-1.79 (m, 2H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 198.6, 58.2, 57.8, 32.5, 29.8,

[31] Davis, R. L.; Jensen, K. L.; Gschwend, B.; Jorgensen, K. A. *Chem. Eur. J.* **2014**, *20*, 64-67.
[32] Mori, K.; Osada, K.; Amaike, M. *Tetrahedron: Asymmetry* **2015**, *26*, 861-867.

26.8. **HRMS (ESI$^+$)**: calculated for $C_6H_9O_2NaBr$ $[M+Na]^+$: 214.9638; found: 214.9633. **[α]$^{20}_D$**= +18.6 (*c*= 1.1, $CHCl_3$).

3.3.2.5. Synthesis of 7-Oxabicyclo[4.1.0]heptan-2-one, (±)-**III-3q**



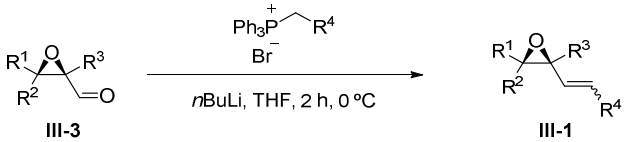
(±)-**III-3q**

A dichloromethane solution (10 mL) of cyclohex-2-en-1-one (0.5 mL, 5.16 mmol, 1 equiv) was added to a solution of DBU (0.93 mL, 6.2 mmol, 1.2 equiv) and anhydrous *tert*-butyl hydroperoxide (TBHP) (1.9 mL, 10.3 mmol, 2 equiv, 5.5M solution in decanes) in 10 mL of dichloromethane (2.0 ml) at 0°C. The reaction mixture was stirred overnight at room temperature. The workup involved dilution with $CHCl_3$, addition of water and solid sodium metasulphite and stirring for 15 min. Then, layers were separated; organic phase was dried over Na_2SO_4, filtered and concentrated. The residue was purified by filtration through florisil (10% EtOAc/cyclohexane) to afford (±)-**III-3q** (500 mg, 4.46 mmol) in 86% yield.

The spectral data for (±)-**III-3q** matched those previously reported for this compound.[33] **^{1}H NMR** (300 MHz, $CDCl_3$): δ 3.64-3.56 (m, 1H), 3.23 (d, *J* = 3.9 Hz, 1H), 2.65-2.48 (m, 1H), 2.36-2.23 (m, 1H), 2.16-2.03 (m, 1H), 2.00-1.89 (m, 2H), 1.78-1.65 (m, 1H).

[33] Welker, M.; Woodward, S.; Alexakis, A. *Org. Lett.* **2010**, *12*, 576-579.

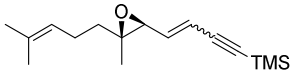
3.3.2.6. General Procedure for the Synthesis of Vinyl Epoxides **III-1** via Wittig Olefination



III-3 **III-1**

Under argon atmosphere, to a suspension of phosphonium salt (1.72 equiv) in anhydrous THF (16 mL/mmol of **III-3**) was added *n*-BuLi (1.6M, 1.3 equiv) dropwise at -50 ºC. The resulting mixture was maintained at -50 ºC for 30 min and then cooled to -78 ºC. A solution of epoxy aldehyde **III-3** (1 equiv) in anhydrous THF (2 mL/mmol of **III-3**) was then added dropwise. The resulting solution was maintained at 0 ºC for 2h and then diluted with hexanes, washed with brine, dried over Na_2SO_4 and concentrated. The residue was purified by flash column chromatography on silica gel (5% EtOAc/Cyclohexane) to afford the desired product **III-1**.

Trimethyl (4-[(2*S*,3*S*)-3-methyl-3-(4-methylpent-3-en-1-yl)oxiran-2-yl]but-3-en-1-yn-1-yl)silane, (*S*,*S*)-III-1a



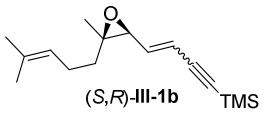
(*S*,*S*)-**III-1a**

From aldehyde (*R*,*S*)-**III-3a** (109 mg, 0.65 mmol, 1 equiv) and triphenyl(3-(trimethylsilyl)prop-2-yn-1-yl)phosphonium bromide (503 mg, 1.11 mmol, 1.72 equiv), following the general proceduredescribed above, compound (*S*,*S*)-**III-1a** (148 mg, 0.56 mmol) was obtained in 86 % yield, as a colorless oil. $\mathbf{R}_f$ = 0.85 (20% EtOAc/Cyclohexane).

Isomeric mixture *Z*/*E* = 2:1; **^{1}H NMR** (300 MHz, $CDCl_3$): δ (Z isomer) 5.87-5.70 (m, 2H), 5.23-5.02 (m, 1H), 3.76 (d, *J* = 6.3 Hz, 1H), 2.18-2.02 (m, 2H), 1.77-1.41 (m, 2H), 1.69 (s, 3H), 1.61 (s, 3H), 1.29 (s, 3H), 0.19 (s, 9H); (E isomer) 6.05 (dd, *J* = 15.9, 7.0 Hz, 1H), 5.87-5.70 (m,1H), 5.23-5.02 (m, 1H), 3.20 (d, *J* = 6.9 Hz, 1H), 2.18-2.02 (m, 2H), 1.77-1.41

(m, 2H), 1.69 (s, 3H), 1.61 (s, 3H), 1.26 (s, 3H), 0.19 (s, 9H). **^{13}C NMR**(75 MHz, $CDCl_3$): δ (isomeric mixture *Z/E*) 139.6, 139.4, 134.0, 133.7, 132.3, 132.2, 123.5, 123.4, 114.27, 114.25, 102.9, 101.2, 100.8, 96.4, 63.7, 63.4, 62.7, 60.8, 38.7, 38.6, 25.8, 23.9, 23.8, 17.8, 17.6, 16.8, 0.0. **HRMS (EI$^+$)**: calculated for $C_{16}H_{26}OSi$ $[M]^+$: 262.1753; found: 262.1758. **[α]$^{20}_D$**= +75.2 (*c*= 1.0, $CHCl_3$).

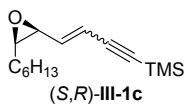
Trimethyl (4-[(2*S*,3*R*)-3-methyl-3-(4-methylpent-3-en-1-yl)oxiran-2-yl]but-3-en-1-yn-1-yl)silane, (*S*,*R*)-III-1b



From aldehyde (*R*,*R*)-**III-3b** (200 mg, 1.19 mmol, 1 equiv) and triphenyl(3-(trimethylsilyl)prop-2-yn-1-yl)phosphonium bromide (928 mg, 2.04 mmol, 1.72 equiv), following the general procedure described above, compound (*S*,*R*)-**III-1b** (247 mg, 0.94 mmol) was obtained in 79 % yield, as a colorless oil. $\mathbf{R}_f$ = 0.85 (20% EtOAc/Cyclohexane).

Isomeric mixture *Z/E* = 1.7:1; **^{1}H NMR** (300 MHz, $CDCl_3$): δ (<u>*Z* isomer</u>) 5.84-5.73 (m, 2H), 5.06 (t, *J* = 6.3 Hz, 1H), 3.69 (d, *J*= 5.1 Hz, 1H), 2.18-1.98 (m, 2H), 1.66 (s, 3H), 1.59 (s, 3H), 1.52-1.39 (m, 2H), 1.36 (s, 3H), 0.19 (s, 9H); (<u>*E* isomer</u>) 6.04 (dd, *J* = 15.9, 6.9 Hz, 1H), 5.82-5.70 (m, 1H), 5.06 (t, *J* = 5.0 Hz, 1H), 3.17 (d, *J* = 6.9 Hz, 1H), 2.18-2.00 (m, 2H), 1.66 (s, 3H), 1.59 (s, 3H), 1.51-1.40 (m, 2H), 1.33 (s, 3H), 0.17 (s, 9H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ (isomeric mixture *Z*/*E*) 139.7, 139.3, 132.4, 132.2, 123.6, 123.5, 114.2, 114.1, 103.0, 101.4, 100.9, 96.3, 63.8, 63.6, 63.4, 61.9, 34.0, 33.0, 25.8, 24.2, 22.2, 22.1, 17.71, 17.66, -0.1. **HRMS (EI$^+$)**: calculated for $C_{16}H_{26}OSi$ $[M]^+$: 262.1753; found: 262.1747. **[α]$^{20}_D$**= +94.6 (*c*= 1.2, $CHCl_3$).

(4-[(2*S*,3*R*)-3-Hexyloxiran-2-yl]but-3-en-1-yn-1-yl)trimethylsilane, (*S*,*R*)-III-1c

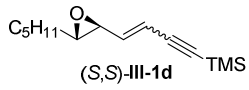


(*S*,*R*)-**III-1c**

From aldehyde (*R*,*R*)-**III-3c** (85 mg, 0.54 mmol, 1 equiv) and triphenyl(3-(trimethylsilyl)prop-2-yn-1-yl)phosphonium bromide (424 mg, 0.94 mmol, 1.72equiv), following the general procedure described above, compound (*S*,*R*)-**III-1c** (126 mg, 0.50 mmol) was obtained in 93 % yield, as a colorless oil. $\mathbf{R}_f$ = 0.85 (20% EtOAc/Cyclohexane).

Isomeric mixture *Z*/*E* =1.3:1; **^{1}H NMR** (300 MHz, $CDCl_3$): δ (Z isomer) 5.74 (d, *J* = 11.2 Hz, 1H), 5.66 (dd, *J* = 11.2, 8.3 Hz, 1H), 3.87 (dd, *J*= 8.3, 4.4 Hz, 1H), 3.13-3.07(m, 1H), 1.58-1.16 (m, 10H), 0.83 (t, *J* = 6.3 Hz, 3H), 0.14 (s, 9H); (E isomer) 5.96 (dd, *J* = 15.9, 7.0 Hz, 1H), 5.79 (d, *J* = 15.9 Hz, 1H), 3.33 (dd, *J* = 7.0, 4.3 Hz, 1H), 3.07-3.00 (m, 1H), 1.58-1.16 (m, 10H), 0.83 (t, *J* = 6.3 Hz, 3H), 0.13 (s, 9H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ (isomeric mixture *Z*/*E*) 138.5, 138.4, 114.9, 114.7, 102.8, 101.3, 100.6, 96.4, 59.6, 59.3, 56.4, 54.7, 31.8, 29.14, 29.09, 28.6, 27.78, 26.5, 26.4, 22.6, 14.1, -0.1. **HRMS (EI$^+$)**: calculated for $C_{15}H_{26}OSi$ $[M]^+$: 250.1753; found: 250.1747. **$[\alpha]^{20}_D$**= +75.4 (*c*= 1.2, $CHCl_3$).

Trimethyl(4-[(2*S*,3*S*)-3-pentyloxiran-2-yl]but-3-en-1-yn-1-yl)silane, (*S*,*S*)-III-1d



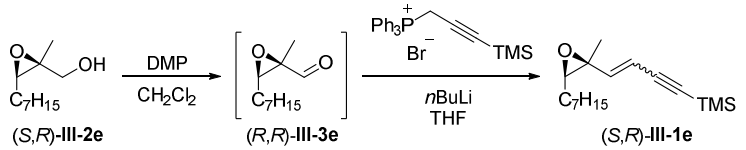
(*S*,*S*)-**III-1d**

From aldehyde (*R*,*S*)-**III-3d** (300 mg, 2.10 mmol, 1equiv) and triphenyl(3-(trimethylsilyl)prop-2-yn-1-yl)phosphonium bromide (1.65 g, 3.63 mmol, 1.72equiv), following the general procedure described above, compound (*S*,*S*)-**III-1d** (445 mg, 1.88 mmol) was obtained in 90 % yield, as a colorless oil. $\mathbf{R}_f$ = 0.85 (20% EtOAc/Cyclohexane).

Isomeric mixture *Z*/*E* =1:1.5; **^{1}H NMR** (300 MHz, $CDCl_3$): δ (Z isomer) 5.70 (d, *J* = 11.0 Hz, 1H), 5.54 (dd, *J* = 11.0, 8.7 Hz, 1H), 3.64 (d, *J* = 8.7 Hz, 1H), 2.87 (t, *J* = 5.4 Hz, 1H), 1.65-1.22 (m, 8H), 0.89 (t, *J* = 6.7 Hz,

3H), 0.19 (s, 9H); (*E* isomer) 5.91 (dd, *J* = 15.9, 6.6 Hz, 1H), 5.81 (d, *J* = 15.9 Hz, 1H), 3.07 (d, *J* = 6.6 Hz, 1H), 2.79 (t, *J* = 5.4 Hz, 1H), 1.65-1.22 (m, 8H), 0.88 (t, *J* = 5.0 Hz, 3H), 0.16 (s, 9H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ (isomeric mixture *Z/E*) 141.5, 141.4, 113.7, 113.1, 102.7, 101.0, 100.7, 96.5, 61.3, 60.3, 57.7, 56.1, 32.02, 31.96, 31.7, 25.59, 25.57, 22.6, 14.1, -0.1. **HRMS (EI$^+$)**: calculated for $C_{14}H_{24}OSi$ $[M]^+$: 236.1596; found: 236.1597. **$[\alpha]^{20}_D$**= +3.2 (*c*= 1.2, $CHCl_3$).

(4-[(2*S*,3*R*)-3-Heptyl-2-methyloxiran-2-yl]but-3-en-1-yn-1-yl)trimethylsilane, (*S*,*R*)-III-1e



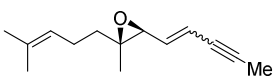
The Dess-Martin periodinane (298mg, 0.70 mmol, 1.3 equiv) was added to a stirring solution of epoxy alcohol (*S*,*R*)-**III-2e** (100 mg, 0.54 mmol, 1 equiv) in CH_2Cl_2 (20 mL/mmol (*S*,*R*)-**III-2e**) at 0 ºC. The reaction mixture was stirred at room temperature. After 1 h, the reaction was cooled again to 0 ºC and diluted with cyclohexane. Then the resulting solution was filtered through florisil eluted with a 1:1 mixture cyclohexane/Et_2O. Concentration provided pure aldehyde (*S*,*R*)-**III-2e** (69 mg, 0.37 mmol) in 69% yield as a colorless oil. $\mathbf{R}_f$ = 0.4 (20% EtOAc/Cyclohexane). Aldehyde (*R*,*R*)-**III-3e** could not be fully characterized and had to be used immediately on the following step. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 9.37 (s, 1H), 3.11-3.01 (m, 1H), 1.79-1.60 (m, 2H), 1.39 (s, 3H), 1.35-1.16 (m, 10H), 0.86 (t, *J* = 6.4 Hz, 3H).

From aldehyde (*R*,*R*)-**III-3e** (69 mg, 0.37 mmol, 1 equiv) and triphenyl(3-(trimethylsilyl)prop-2-yn-1-yl)phosphonium bromide (293 mg, 0.65 mmol, 1.72 equiv), following the general procedure described

above, compound (*S*,*R*)-**III-1e** (91 mg, 0.33 mmol) was obtained in 89 % yield, as a colorless oil. $\mathbf{R}_f$ = 0.8 (20% EtOAc/Cyclohexane).

Isomeric mixture *Z*/*E* = 4.6:1; **^{1}H NMR** (300 MHz, $CDCl_3$): δ (Z isomer) 5.88 (d, *J* = 11.7 Hz, 1H), 5.65 (d, *J* = 11.7 Hz, 1H), 2.87 (t, *J* = 5.5 Hz, 1H), 1.58 (s, 3H), 1.48 (m, 2H), 1.35-1.21 (m, 10H), 0.87 (t, *J* = 6.6 Hz, 3H), 0.18 (s, 9H); (E isomer) 6.12 (d, *J* = 16.1 Hz, 1H), 5.71 (d, *J* = 16.1 Hz, 1H), 2.92-2.82 (m, 1H), 1.58 (s, 3H), 1.48 (m, 2H), 1.36-1.22 (m, 10H), 0.87 (t, *J* = 6.6 Hz, 3H), 0.17 (s, 9H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ (isomeric mixture *Z*/*E*) 142.6, 142.0, 112.6, 111.9, 107.9, 103.7, 103.1, 102.0, 101.5, 67.0, 66.2, 60.6, 60.1, 31.9, 30.0, 29.6, 29.4, 29.34, 29.30, 28.2, 26.6, 26.5, 22.8, 22.0, 21.7, 14.2, 0.0, -0.2. **HRMS (EI$^+$)**: calculated for $C_{17}H_{30}OSi$ $[M]^+$: 278.2066; found: 278.2069. **[α]$^{20}_D$**= +114.2 (*c*= 1.0, $CHCl_3$).

(2*S*,3*S*)-2-Methyl-2-(4-methylpent-3-en-1-yl)-3-(pent-1-en-3-yn-1-yl)oxirane, (*S*,*S*)-III-1f



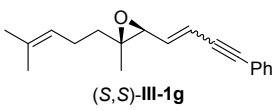
(*S*,*S*)-**III-1f**

From aldehyde (*S*,*R*)-**III-3a** (200 mg, 1.19mmol, 1 equiv) and but-2-yn-1-yltriphenylphosphonium bromide (810 mg, 2.05mmol, 1.72 equiv), following the general procedure described above, compound (*S*,*S*)-**III-1f** (138 mg, 0.68mmol) was obtained in 57 % yield, as a colorless oil. $\mathbf{R}_f$ = 0.85 (20% EtOAc/Cyclohexane).

Isomeric mixture *Z*/*E* =3:1; **^{1}H NMR** (300 MHz, $CDCl_3$): δ (Z isomer) 5.81-5.70 (m, 1H), 5.63 (dd, *J* = 10.8, 8.3 Hz, 1H), 5.13 (t, *J* = 7.1 Hz, 1H), 3.73 (d, *J* = 8.3 Hz, 1H), 2.16-2.04 (m, 2H), 2.00 (s, 3H), 1.69 (s, 3H), 1.62 (s, 3H), 1.79-1.45 (m, 2H), 1.28 (s, 3H); (E isomer) 5.90 (dd, *J* = 15.9, 7.0 Hz, 1H), 5.80-5.71 (m, 1H), 5.11-5.05 (m, 1H), 3.20 (d, *J* = 7.0 Hz, 1H), 2.16-2.04 (m, 2H), 1.96 (s, 3H), 1.69 (s, 3H), 1.61 (s, 3H), 1.79-1.46 (m, 2H), 1.26 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ (isomeric mixture *Z*/*E*) 136.9, 134.0, 133.8, 132.2, 128.8, 128.7, 128.6, 123.7, 123.5,

115.0, 92.3, 75.8, 63.1, 63.0, 60.9, 38.8, 38.6, 25.8, 23.9, 17.7, 17.5, 16.8, 4.6, 4.4. **HRMS (EI$^+$)**: calculated for $C_{14}H_{20}O$ $[M]^+$: 204.1514; found: 204.1509. **[α]$^{20}_D$**= +70.7 (*c*= 1.1, $CHCl_3$).

(2*S*,3*S*)-2-Methyl-2-(4-methylpent-3-en-1-yl)-3-(4-phenylbut-1-en-3-yn-1-yl)oxirane, (*S*,*S*)-III-1g

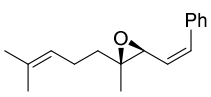


(*S*,*S*)-**III-1g**

From aldehyde (*R*,*S*)-**III-3a** (178 mg, 1.06 mmol, 1equiv) and triphenyl(3-phenylprop-2-yn-1-yl)phosphonium bromide (832 mg, 1.82mmol, 1.72equiv), following the general procedure described above, compound (*S*,*S*)-**III-1g** (205 mg, 0.77 mmol) was obtained in 73 % yield, as a yellow oil. **R$_f$** = 0.9 (20% EtOAc/Cyclohexane).

Isomeric mixture *Z*/*E*=9:1; **^{1}H NMR** (300 MHz, $CDCl_3$): δ (Z isomer) 7.50-7.39 (m, 2H), 7.39-7.29 (m, 3H), 6.00 (d, *J*= 11.0 Hz, 1H), 5.79 (dd, *J* = 11.0, 8.6 Hz, 1H), 5.13 (t, *J* = 7.0 Hz, 1H), 3.85 (d, *J* = 8.6 Hz, 1H), 2.20-2.09(dt, *J* = 7.6, 7.4 Hz, 2H), 1.66 (s, 3H), 1.82-1.49 (m, 2H), 1.59 (s, 3H), 1.33 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ (Z isomer) 138.2, 132.3, 131.6, 128.6, 128.5, 123.5, 123.2, 114.3, 95.6, 85.4, 63.4, 61.0, 38.7, 25.8, 23.9, 17.7, 17.5. **HRMS (EI$^+$)**: calculated for $C_{19}H_{22}O$ $[M]^+$: 266.1671; found: 266.1663. **[α]$^{20}_D$**= +144.2 (*c*= 1.1, $CHCl_3$).

(2*S*,3*S*)-2-Methyl-2-(4-methylpent-3-en-1-yl)-3-[(*Z*)-styryl]oxirane, (*S*,*S*)-III-1h

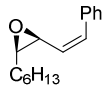


(*S*,*S*)-**III-1h**

From aldehyde (*R*,*S*)-**III-3a** (250 mg, 1.49 mmol, 1equiv) and benzyltriphenylphosphonium bromide (1.11 g, 2.56 mmol, 1.72 equiv) following the general procedure described above, compound (*S*,*S*)-**III-1h** (184 mg, 0.76 mmol) was obtained in 51 % yield, as a yellow oil. **R$_f$** = 0.85 (20% EtOAc/Cyclohexane).

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.35-7.16 (m, 5H), 6.67 (d, *J* = 11.9 Hz, 1H), 5.50 (dd, *J* = 11.9, 7.5 Hz, 1H), 5.05 (t, *J* = 7.1 Hz, 1H), 3.51 (d, *J* = 7.5 Hz, 1H), 2.13-2.00 (m, 2H), 1.61 (s, 3H), 1.70-1.47 (m, 2H), 1.55 (s, 3H), 1.27 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 136.6, 134.6, 132.2, 128.9, 128.4, 127.7, 127.6, 123.7, 63.1, 60.2, 38.4, 25.8, 23.7, 17.7, 17.6. **HRMS (ESI$^+$)**: calculated for $C_{17}H_{22}ONa$ $[M+Na]^+$: 265.1562; found: 265.1562. **[α]$^{20}_D$**= +166.1 (*c*= 1.2, $CHCl_3$).

(2*R*,3*S*)-2-Hexyl-3-[(*Z*)-styryl]oxirane, (*R*,*S*)-III-1n



(*R*,*S*)-**III-1n**

From aldehyde (*R*,*R*)-**III-3c** (760 mg, 4.86 mmol, 1 equiv) and benzyltriphenylphosphonium bromide (3.62 g, 8.35 mmol, 1.72equiv) following the general procedure described above, compound (*R*,*S*)-**III-1n** (681 mg, 2.96 mmol) was obtained in 61 % yield, as a yellow oil. **R**$_f$ = 0.85 (20% EtOAc/Cyclohexane).

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.39-7.08 (m, 5H), 6.68 (d, *J* = 11.8 Hz, 1H), 5.46 (dd, *J* = 11.8, 7.9 Hz, 1H), 3.68 (dd, *J* = 7.9, 4.3 Hz, 1H), 3.17-3.05 (m, 1H), 1.65-1.14 (m, 10H), 0.79 (t, *J* = 6.4 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ136.4, 135.1, 128.9, 128.4, 127.6, 126.7, 59.4, 54.0, 31.8, 29.2, 28.7, 26.5, 22.6, 14.1. **HRMS (ESI$^+$)**: calculated for $C_{16}H_{22}ONa$ $[M+Na]^+$: 253.1562; found: 253.1560. **[α]$^{20}_D$**= +189.9 (*c*= 1.1, $CHCl_3$).

(2*R*,3*S*)-2-(3-Bromopropyl)-3-[(*Z*)-styryl]oxirane, (*R*,*S*)-III-1r

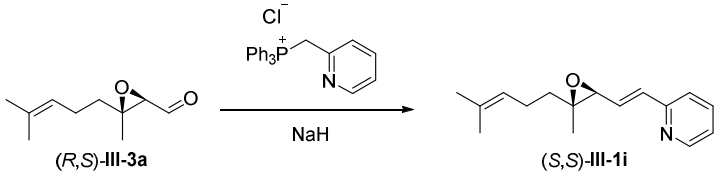
(*R*,*S*)-**III-1r**

From aldehyde (*R*,*R*)-**III-3r** (872 mg, 4.5 mmol, 1equiv) and benzyltriphenylphosphonium bromide (3.35 g, 7.74 mmol, 1.72 equiv) following the general procedure described above, compound (*R*,*S*)-**III-1r** (428 mg, 1.6 mmol) was obtained in 36 % yield, as a colorless oil. **R**$_f$ = 0.55 (from 20% to 40% EtOAc/Cyclohexane).

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.34-7.03 (m, 5H), 6.71 (d, *J* = 11.8 Hz, 1H), 5.46 (dd, *J* = 11.8, 7.8 Hz, 1H), 3.71 (ddd, *J* = 7.8, 4.3, 1.0 Hz, 1H),

3.45-3.29 (m, 2H), 3.16-3.08 (m, 1H), 2.11-1.84 (m, 2H), 1.80-1.60 (m, 2H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 136.3, 135.7, 128.9, 128.5, 127.8, 126.1, 58.4, 54.0, 33.2, 29.9, 27.5. **HRMS (APCI$^+$)**: calculated for $C_{13}H_{16}BrO$ $[M+H]^+$: 267.0379; found: 267.0384. **$[\alpha]^{20}_D$**= +112.7 (*c*= 0.6, $CHCl_3$).

3.3.2.7. Synthesis of 2-[(*E*)-2-((2*S*,3*S*)-3-Methyl-3-(4-methylpent-3-en-1-yl)oxiran-2-yl)vinyl]pyridine, (*S*,*S*)-**III-1i**

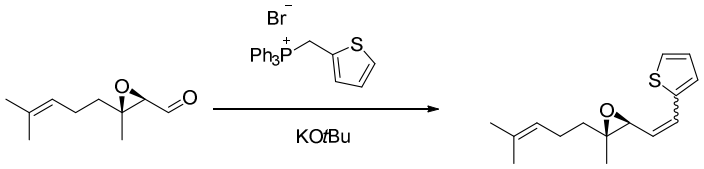


Triphenyl(pyridin-2-ylmethyl)phosphonium (632 mg, 1.62 mmol, 1 equiv) chloride was dissolved in 30 mL THF under argon and cooled to 0 ºC, sodium hydride (78 mg, 4.62 mmol, 1.2 equiv) was added portion-wise and the solution was stirred for 1h. Aldehyde (*R*,*S*)-**III-3a** (300 mg, 1.78 mmol, 1.1 equiv) in 5.0 mL THF was then added and the reaction was warmed to room temperature and stirred overnight. The solution was diluted by addition of EtOAc and biphasic system was extracted with EtOAc (x3), combined organic phases were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (gradient from 10% to 20% EtOAc/Cyclohexane) to afford (*S*,*S*)-**III-1i** (255 mg, 1.05 mmol) in 59% yield. $\mathbf{R}_f$ = 0.45 (20% EtOAc/Cyclohexane).

^{1}H NMR (300 MHz, $CDCl_3$): δ 8.56 (ddd, *J* = 4.8, 1.7, 0.8 Hz, 1H), 7.63 (td, *J* = 7.7, 1.7 Hz, 1H), 7.27 (d, *J* = 7.9 Hz, 1H), 7.14 (ddd, *J* = 7.5, 4.8, 1.1 Hz, 1H), 6.80 (d, *J* = 15.8 Hz, 1H), 6.64 (dd, *J* = 15.8, 6.9 Hz, 1H), 5.17-5.07 (m, 1H), 3.42 (d, *J* = 6.9 Hz, 1H), 2.19-2.06 (m, 2H), 1.81-1.72 (m, 1H), 1.70 (s, 3H), 1.62 (s, 3H), 1.60-1.49 (m, 1H), 1.35 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 154.8, 149.8, 136.7, 134.3, 132.3, 129.7,

123.6, 122.5, 122.0, 63.7, 63.3, 38.8, 25.9, 24.0, 17.8, 17.0. **HRMS (APCI$^+$)**: calculated for $C_{16}H_{22}NO$ $[M+H]^+$: 244.1696; found: 244.1699. **[α]$^{20}_D$**= -19.2 (*c*= 1.1, $CHCl_3$).

3.3.2.8. Synthesis of (2*S*,3*S*)-2-Methyl-2-(4-methylpent-3-en-1-yl)-3-((*Z*)-2-(thiophen-2-yl)vinyl)oxirane, (*S*,*S*)-**III-1j**

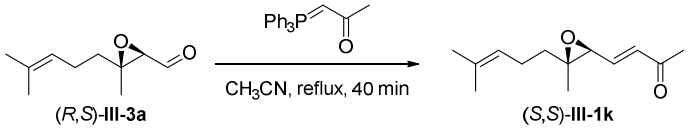


(*R*,*S*)-**III-3a** (*S*,*S*)-**III-1j**

Under argon atmosphere, KO*t*Bu (445 mg, 3.95 mmol, 2.22 equiv) was added to the solution of triphenyl(thiophen-2-ylmethyl)phosphonium bromide(956 mg, 2.18 mmol, 1.22 equiv)in anhydrous THF (8.0 mL) at room temperature and the solution turned red. Aldehyde (*R*,*S*)-**III-3a** (300 mg, 1.78 mmol, 1.0 equiv) in anhydrous THF (4.0 mL) was added dropwise. The reaction mixture was stirred overnight at room temperature and poured into water. The organic layers were separated, dried over Na_2SO_4 and solvent was removed. The residue was purified by flash column chromatography on silica gel (gradient from 5% to 10% EtOAc/Cyclohexane) to afford (*S*,*S*)-**III-1j** (259.6 mg, 1.05 mmol) in 59% yield, as a yellow oil. $\mathbf{R}_f$ = 0.65 (20% EtOAc/Cyclohexane).

Isomeric mixture *Z*/*E*=9:1; **^{1}H NMR** (300 MHz, $CDCl_3$): δ (Z isomer) 7.34-7.28 (m, 1H), 7.07-7.01 (m, 2H), 6.79 (dd, *J* = 11.8, 1.1 Hz, 1H), 5.48 (dd, *J* = 11.8, 6.8 Hz, 1H), 5.20-5.10 (m, 1H), 3.77 (dd, *J* = 6.8, 1.3 Hz, 1H), 2.19 (dt, *J* = 8.7, 7.0 Hz, 2H), 1.78-1.72 (m, 2H), 1.70 (s, 3H), 1.64 (s, 3H), 1.30 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ (Z isomer) 139.7, 132.2, 128.4, 127.4, 126.3, 126.1, 125.9, 123.8, 63.4, 60.5, 38.4, 25.8, 23.7, 17.8, 17.7. **HRMS (APCI$^+$)**: calculated for $C_{15}H_{21}OS$ $[M+H]^+$: 249.1308; found: 249.1311. **[α]$^{20}_D$**= +32.0 (*c*= 1.0, $CHCl_3$).

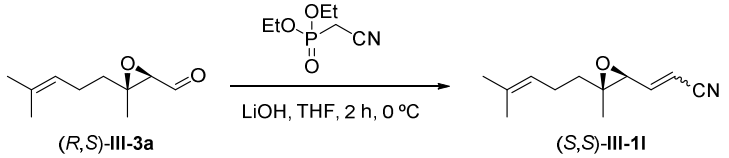
3.3.2.9. Synthesis of (*E*)-4-[(2*S*,3*S*)-3-Methyl-3-(4-methylpent-3-en-1-yl)oxiran-2-yl]but-3-en-2-one, (*S*,*S*)-**III-1k**



Under argon atmosphere, a solution of epoxy aldehyde (*R*,*S*)-**III-3a** (200 mg, 1.18 mmol, 1 equiv) and acetylmethylene-triphenylphosphorane (398 mg, 1.25 mmol, 1.05equiv) in anhydrous CH_3CN (4.2 mL/mmol of (*R*,*S*)-**III-3a**) was refluxed for 40 min before concentration. The residue was filtered using diethyl ether and the filtrate was concentrated. The residual oil was subjected to column chromatography on silica gel (5% EtOAc/Cyclohexane) to obtain compound (*S*,*S*)-**III-1k** (169 mg, 0.81mmol) in 69 % yield, as a colorless oil. $\mathbf{R}_f$ = 0.65 (20% EtOAc/Cyclohexane).

^{1}H NMR (300 MHz, $CDCl_3$): δ 6.62 (dd, *J* = 16.0, 6.4 Hz, 1H), 6.32 (d, *J* = 16.0 Hz, 1H), 5.06 (t, *J* = 6.7 Hz, 1H), 3.31 (d, *J* = 6.4 Hz, 1H), 2.26 (s, 3H), 2.16-2.02 (m, 2H), 1.67 (s, 3H), 1.79-1.46 (m, 2H), 1.59 (s, 3H), 1.25 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 197.0, 141.7, 133.3, 132.2, 123.1, 64.1, 61.4, 38.4, 27.3, 25.6, 23.6, 17.6, 16.6. **HRMS (EI$^+$)**: calculated for $C_{13}H_{20}O_2$ $[M]^+$: 208.1463; found: 208.1453. **$[\alpha]^{20}_D$**= -0.3 (*c*= 1.0, $CHCl_3$).

3.3.2.10. Synthesis of (*E*)-3-[(2*S*,3*S*)-3-Methyl-3-(4-methylpent-3-en-1-yl)oxiran-2-yl]acrylonitrile, (*S*,*S*)-**III-1l**

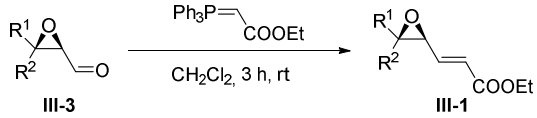


Under argon atmosphere, a solution of diethyl cyanomethyl phosphonate (232 mg, 1.31 mmol, 1.1 equiv) and LiOH (34 mg, 1.43 mmol, 1.2 equiv) in anhydrous THF (10 mL/mmol of (R,S)-**III-3a**) was

stirred for 30 min at 70 ºC and then cooled to room temperature. Epoxy aldehyde (*R*,*S*)-**III-3a** (200 mg, 1.19 mmol, 1 equiv) was then added dropwise. The resulting solution was controlled by TLC. Finally it was quenched with water, extracted with diethyl ether (x3), washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (5% EtOAc/Cyclohexane) to afford compound (*S*,*S*)-**III-1l** (191 mg, 0.56mmol) in 47 % yield, as a colorless oil. $\mathbf{R}_f$ = 0.7 (20% EtOAc/Cyclohexane).

Isomeric mixture *Z*/*E* =1:2.4; **^{1}H NMR** (300 MHz, $CDCl_3$): δ (*Z* isomer) 6.30 (dd, *J* = 11.2, 8.3 Hz, 1H), 5.57 (d, *J* = 11.2 Hz, 1H), 5.08 (t, *J* = 7.9 Hz, 1H), 3.63 (d, *J* = 8.3 Hz, 1H), 2.12 (dt, *J* = 7.9, 7.6 Hz, 2H), 1.68 (s, 3H), 1.82-1.47 (m, 2H), 1.60 (s, 3H), 1.31 (s, 3H); (*E* isomer) 6.65 (dd, *J* = 16.2, 5.3 Hz, 1H), 5.59 (d, *J* = 16.2 Hz, 1H), 5.06 (t, *J* = 7.9 Hz, 1H), 3.30 (d, *J* = 5.3 Hz, 1H), 2.10 (dt, *J* = 7.9, 7.6 Hz, 2H), 1.68 (s, 3H), 1.83-1.49 (m, 2H), 1.60 (s, 3H), 1.23 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ (isomeric mixture *Z*/*E*) 149.9, 149.4, 132.74, 132.69, 123.0, 116.8, 115.2, 103.2, 102.9, 65.0, 64.3, 61.4, 60.4, 38.4, 38.3, 25.8, 23.7, 17.8, 17.4, 16.3. **HRMS (EI$^+$)**: calculated for $C_{12}H_{17}NO$ $[M]^+$: 191.1310; found: 191.1309. **[α]$^{20}_D$**= +43.6 (*c*= 1.1, $CHCl_3$).

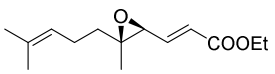
3.3.2.11. Synthesis of Epoxy Acrylates, **III-1**



Under argon atmosphere, a suspension of ethyl (triphenylphosphoranylidene)acetate (1.2 equiv) in anhydrous CH_2Cl_2 (6 mL/mmol of **III-3**) was stirred for 15 min. The solution was cooled to 0 ºC and a solution of the corresponding epoxy aldehyde **III-3** (1 equiv) in anhydrous CH_2Cl_2 (2.5 mL/mmol of **III-3**) was added. The reaction

mixture was stirred for 3h at room temperature and monitored by TLC. Then, hexanes were added and the organic phase was washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (5% EtOAc/Cyclohexane) to obtain the desired product **III-1**.

Ethyl (*E*)-3-[(2*S*,3*S*)-3-methyl-3-(4-methylpent-3-en-1-yl)oxiran-2-yl]acrylate, (*S*,*S*)-III-1m

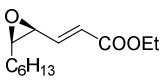


(*S*,*S*)-**III-1m**

From aldehyde (*R*,*S*)-**III-3a** (200.2 mg, 1.19 mmol, 1 equiv) following the general procedure described above, compound (*S*,*S*)-**III-1m** (231.2 mg, 0.97 mmol) was obtained in 82 % yield.

The spectral data for (*S*,*S*)-**III-1m** matched those previously reported for this compound.[34] **^{1}H NMR** (300 MHz, $CDCl_3$): δ 6.80 (dd, *J* = 15.7, 6.5 Hz, 1H), 6.06 (dd, *J* = 15.7, 0.9 Hz, 1H), 5.06 (t, *J* = 7.1 Hz, 1H), 4.19 (q, *J* = 7.1 Hz, 2H), 3.29 (d, *J* = 6.5 Hz, 1H), 2.07 (dt, *J* = 13.9, 7.1 Hz, 2H), 1.67 (s, 3H), 1.80-1.45 (m, 2H), 1.59 (s, 3H), 1.28 (t, *J* = 7.1 Hz, 3H), 1.26 (s, 3H).

Ethyl (*E*)-3-[(2*S*,3*R*)-3-hexyloxiran-2-yl]acrylate, (*S*,*R*)-III-1o



(*S*,*R*)-**III-1o**

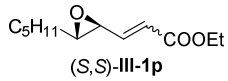
From aldehyde (*R*,*R*)-**III-3c** (200 mg, 1.28 mmol, 1 equiv) following the general procedure described above, compound (*S*,*R*)-**III-1o** (222 mg, 0.98 mmol) was obtained in 77 % yield, as a colorless oil. $\mathbf{R}_f$ = 0.75 (20% EtOAc/Cyclohexane).

^{1}H NMR (300 MHz, $CDCl_3$): δ 6.78 (dd, *J* = 15.7, 6.6 Hz, 1H), 6.10 (dd, *J* = 15.7, 1.0 Hz, 1H), 4.19 (q, *J* = 7.1 Hz, 2H), 3.48 (ddd, *J*= 6.6, 4.4, 1.0 Hz, 1H), 3.19-3.12 (m, 1H), 1.61-1.20 (m, 13H), 0.86 (t, *J* = 6.8 Hz, 3H).

[34] Yu, X.-Q.; Yoshimura, F.; Tanino, K.; Miyashita, M. *Tetrahedron* **2008**, *49*, 7442-7446.

^{13}C NMR (75 MHz, $CDCl_3$): δ 165.7, 142.2, 125.3, 60.7, 59.8, 55.3, 31.8, 29.0, 27.7, 26.4, 22.6, 14.3, 14.1. **HRMS (ESI$^+$)**: calculated for $C_{13}H_{22}O_3Na$ $[M+Na]^+$: 249.1461; found: 249.1459. **$[\alpha]^{20}_D$**= +37.3 (*c*= 1.2, $CHCl_3$).

Ethyl (*E*)-3-[(2*S*,3*S*)-3-pentyloxiran-2-yl]acrylate, (*S*,*S*)-III-1p

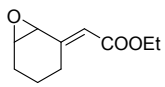


(*S*,*S*)-**III-1p**

From aldehyde (*R*,*S*)-**III-3d** (300 mg, 2.1 mmol, 1 equiv) following the general procedure described above, compound (*S*,*S*)-**III-1p** (280 mg, 1.32mmol) was obtained in 63 % yield, as a colorless oil. $\mathbf{R}_f$ = 0.8 (20% EtOAc/Cyclohexane).

Isomeric mixture *Z*/*E* =1:9; **^{1}H NMR** (300 MHz, $CDCl_3$): δ (*E* isomer) 6.65 (dd, *J* = 15.7, 7.1 Hz, 1H), 6.09 (d, *J* = 15.7 Hz, 1H), 4.17 (q, *J* = 6.9 Hz, 2H), 3.17 (dd, *J* = 7.0, 1.9 Hz, 1H), 2.85 (td, *J* = 5.5, 1.9 Hz, 1H), 1.65-1.17 (m, 11H), 0.87 (t, *J* = 6.9 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ (*E* isomer) 165.76, 144.91, 123.60, 61.56, 60.61, 56.39, 31.97, 31.59, 25.56, 22.60, 14.28, 14.01. **HRMS (EI$^+$)**: calculated for $C_{12}H_{20}O_3$ $[M]^+$: 212.1412; found: 212.1410. **$[\alpha]^{20}_D$**= -5.2 (*c*= 1.0, $CHCl_3$).

Ethyl (*E*)-2-(7-oxabicyclo[4.1.0]heptan-2-ylidene)acetate, (±)-III-1q



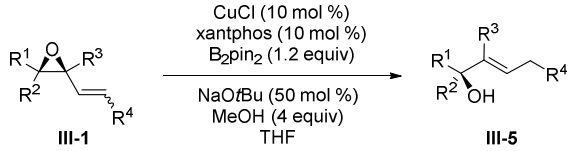
(±)-**III-1q**

From aldehyde (±)-**III-3q** (500 mg, 4.45 mmol, 1 equiv) following the general procedure described above, compound (±)-**III-1q** (532 mg, 2.92 mmol) was obtained in 66 % yield.

The spectral data for (±)-**III-1q** matched those previously reported for this compound.[35] **^{1}H NMR** (300 MHz, $CDCl_3$): δ 5.88 (s, 1H), 4.63 (d, *J* = 3.9 Hz, 1H), 4.18-4.06 (m, 2H), 3.44-3.35 (m, 1H), 2.38-2.27 (m, 1H), 2.11-1.92 (m, 2H), 1.88-1.72 (m, 1H), 1.66-1.51 (m, 1H), 1.51-1.34 (m, 1H), 1.23 (t, *J* = 7.1 Hz, 3H).

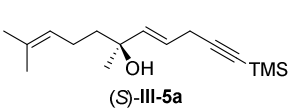
[35] Bensel, N.; Höhn, J.; Marschall, H.; Weyerstahl, P. *Chem. Ber.* **1979**, *112*, 2256-2277.

3.3.3. General Procedure for the Synthesis of Enantioenriched Allylic Alcohols, **III-5**



An oven-dried vial was charged with CuCl (1.5 mg, 0.015 mmol, 10 mol%), B_2pin_2 (45.7 mg, 0.18mmol, 1.2 equiv) and ligand (8.7 mg, 0.015 mmol, 10 mol%) and sealed with a septum. The vial was connected to an argon-vacuum line, evacuated and backfilled with argon (x3). THF (0.5 mL/0.15 mmol of **III-1**) was added and the mixture was stirred for 15 minutes at room temperature. A 0.2 M NaO*t*Bu solution in THF (38µL, 0.075 mmol, 50 mol%) was added dropwise and the dark brown solution was stirred for 10 min. Then, the corresponding epoxide **III-1** (1.0 equiv) in THF (0.2 mL/0.15 mmol of **III-1**) was added followed by methanol (24 µL, 0.6 mmol, 4 equiv). Finally, the reaction mixture was stirred overnight at the indicated temperature (room temperature, 0 ºC or -20 ºC). Water and CH_2Cl_2 were added and the layers were separated. The aqueous phase was extracted with CH_2Cl_2 (x3) and the combined organic layers were washed with saturated NaCl solution, dried over Na_2SO_4, filtered and concentrated. The crude product was purified by flash column chromatography on silica gel (2-5% EtOAc/Cyclohexane).

(*S*,*E*)-6,10-Dimethyl-1-(trimethylsilyl)undeca-4,9-dien-1-yn-6-ol, (*S*)-III-5a

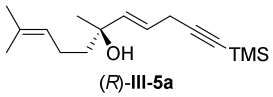


(*S*)-**III-5a**

From epoxyenyne (*S*,*S*)-**III-1a** (32.8 mg, 0.125 mmol, 1 equiv) following the general procedure described above at room temperature, compound (*S*)-**III-5a** (27.2 mg, 0.103 mmol) was obtained in 82% yield, as a colorless oil. $\mathbf{R}_f$ = 0.3 (5% EtOAc/Cyclohexane).

^{1}H NMR (300 MHz, $CDCl_3$): δ 5.78 (d, *J* = 15.5 Hz, 1H), 5.61 (dt, *J* = 15.5, 5.3 Hz, 1H), 5.12 (t, *J* = 6.5 Hz, 1H), 3.00 (d, *J* = 5.3 Hz, 2H), 2.11-1.96 (m, 2H), 1.68 (s, 3H), 1.62-1.52 (m, 2H), 1.60 (s, 3H), 1.28 (s, 3H), 0.16 (s, 9H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 138.8, 132.1, 124.5, 121.9, 104.2, 86.8, 73.2, 42.5, 28.3, 25.9, 23.0, 22.9, 17.9, 0.2. **HRMS (ESI$^+$)**: calculated for $C_{16}H_{28}ONaSi$ $[M+Na]^+$: 287.1801; found: 287.1810. **[α]$^{20}_D$**= -6.3 (*c*= 1.2, $CHCl_3$).

(*R*,*E*)-6,10-Dimethyl-1-(trimethylsilyl)undeca-4,9-dien-1-yn-6-ol, (*R*)-III-5a

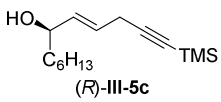


(*R*)-**III-5a**

From epoxyenyne (*S*,*R*)-**III-1b** (39.4 mg, 0.150 mmol, 1 equiv) following the general procedure described above at 0 ºC, compound (*R*)-**III-5a** (27.9 mg, 0.105 mmol) was obtained in 70% yield, as a colorless oil. **R$_f$** = 0.5 (20% EtOAc/Cyclohexane).

^{1}H NMR (300 MHz, $CDCl_3$): δ 5.79 (d, *J* = 15.5 Hz, 1H), 5.61 (dt, *J* = 15.5, 5.3 Hz, 1H), 5.12 (t, *J* = 7.1 Hz, 1H), 3.04-2.97 (m, 2H), 2.11-1.96 (m, 2H), 1.68 (s, 3H), 1.61 (s, 3H), 1.59-1.53 (m, 2H), 1.28 (s, 3H), 0.16 (s, 9H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 138.8, 132.1, 124.5, 121.9, 104.2, 86.8, 73.2, 42.5, 28.3, 25.9, 23.0, 22.9, 17.9, 0.2. **HRMS (ESI$^+$)**: calculated for $C_{16}H_{28}ONaSi$ $[M+Na]^+$: 287.1801; found: 287.1810. **[α]$^{20}_D$**= +2.0 (*c*= 1.0, $CHCl_3$).

(*R*,*E*)-1-(Trimethylsilyl)dodec-4-en-1-yn-6-ol, (*R*)-III-5c



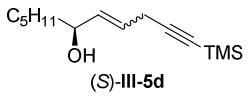
(*R*)-**III-5c**

From epoxyenyne (*S*,*R*)-**III-1c** (37.6 mg, 0.150 mmol, 1 equiv) following the general procedure described above at 0 ºC, compound (*R*)-**III-5c** (28.0 mg, 0.111 mmol) was obtained in 74 % yield as a colorless oil. **R$_f$** = 0,5 (20% EtOAc/Cyclohexane).

^{1}H NMR (300 MHz, $CDCl_3$): δ 5.76 (dd, *J* = 15.3, 6.4 Hz, 1H), 5.62 (dt, *J* = 15.3, 5.0 Hz, 1H), 4.16-4.07 (m, 1H), 3.00 (d, *J* = 5.0 Hz, 2H), 1.62-1.43 (m, 4H), 1.36-1.19 (m, 6H), 0.87 (t, *J*= 6.7 Hz, 3H), 0.16 (s, 9H). **^{13}C NMR** (75 MHz, $CDCl_3$):δ 135.1, 125.1, 103.9, 87.0, 72.7, 37.4, 32.0, 29.4, 25.5, 22.9, 22.7, 14.2, 0.2. **HRMS (ESI$^+$)**: calculated for $C_{15}H_{27}OSi$ $[M-H]^+$: 251.1825; found: 251.1819. **$[\alpha]^{20}_D$**= -1.9 (*c*= 1.1, $CHCl_3$).

The enantiomeric ratio of the product was determined to be 88:12 by ^{1}H NMR analysis of its methoxy phenyl acetates, prepared by reaction of (±)- and (-)-methoxyphenyl acid and DCC in CH_2Cl_2.[20]

(*S*)-1-(Trimethylsilyl)undec-4-en-1-yn-6-ol, (*S*)-III-5d

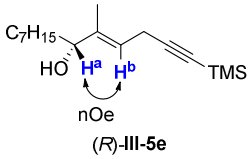


(*S*)-**III-5d**

From epoxyenyne (*S*,*S*)-**III-1d** (31.8 mg, 0.150 mmol, 1 equiv) following the general procedure described above at room temperature, compound (*S*)-**III-5d** (23.6 mg, 0.099 mmol) was obtained in 66 % yield, as a colorless oil. $\mathbf{R}_f$ = 0.5 (20% EtOAc/Cyclohexane).

Isomeric mixture *Z*/*E* = 1:2; **^{1}H NMR** (300 MHz, $CDCl_3$): δ (<u>*Z* isomer</u>) 5.62-5.43 (m, 2H), 4.49-4.40 (m, 1H), 3.06-3.01 (m, 2H), 1.66-1.43 (m, 2H), 1.39-1.27 (m, 6H),0.89 (t, *J* = 5.2 Hz, 3H), 0.14 (s, 9H); (<u>*E* isomer</u>) 5.81-5.71 (m, 1H), 5.68-5.63 (m, 1H), 4.18-4.06 (m, 1H), 3.02-2.97 (m, 2H), 1.66-1.43 (m, 2H), 1.39-1.27 (m, 6H), 0.89 (t, *J* = 5.2 Hz, 3H), 0.16 (s, 9H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ (isomeric mixture *Z*/*E*) 135.1, 134.9, 126.0, 125.1, 104.8, 103.9, 87.0, 83.7, 72.7, 67.7, 37.4, 37.3, 31.92, 31.89, 25.2, 25.1, 22.9, 22.8, 18.9, 14.2, 0.23, 0.15. **HRMS (ESI$^+$)**: calculated for $C_{14}H_{26}ONaSi$ $[M+Na]^+$: 261.1645; found: 261.1653. **$[\alpha]^{20}_D$**= -13.4 (*c*= 1.0, $CHCl_3$).

(*R*,*E*)-5-Methyl-1-(trimethylsilyl)tridec-4-en-1-yn-6-ol, (*R*)-III-5e

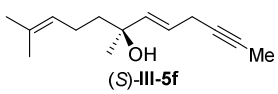


(*R*)-**III-5e**

From epoxyenyne (*S*,*R*)-**III-1e** (41.8 mg, 0.150mmol, 1equiv) following the general procedure described above at -20 ºC, compound (*R*)-**III-5e** (23.3 mg, 0.083 mmol) was obtained in 55 % yield, as a colorless oil. $\mathbf{R}_f$ = 0.5 (20% EtOAc/Cyclohexane). The *E* geometry of the double bond was established by nOe experiments, which showed coupling between $\mathbf{H}^a$ and $\mathbf{H}^b$.

^{1}H NMR (300 MHz, $CDCl_3$): δ 5.44 (t, *J* = 6.7 Hz, 1H), 4.00 (t, *J* = 6.6 Hz, 1H), 2.97 (d, *J* = 6.7 Hz, 2H), 1.61 (s, 3H), 1.58-1.43 (m, 2H), 1.36-1.18 (m, 10H), 0.88 (t, *J* = 6.7 Hz, 3H), 0.15 (s, 9H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 139.7, 120.8, 105.3, 84.4, 77.5, 35.0, 32.0, 29.7, 29.4, 25.9, 22.8, 18.9, 14.2, 11.5, 0.3. **HRMS (ESI$^+$)**: calculated for $C_{17}H_{31}OSi$ [M-H]$^+$:279.2144; found:279.2169. **[α]$^{20}_D$**= +3.5 (*c*= 1.0, $CHCl_3$).

(*S*,*E*)-2,6-Dimethyldodeca-2,7-dien-10-yn-6-ol, (*S*)-III-5f

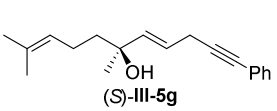


(*S*)-**III-5f**

From epoxyenyne (*S*,*S*)-**III-1f** (30.6 mg, 0.150 mmol, 1 quiv) following the general procedure described above at 0 ºC, compound (*S*)-**III-5f** (15.5 mg, 0.075 mmol) was obtained in 50% yield, as a colorless oil. $\mathbf{R}_f$ = 0.3 (5% EtOAc/Cyclohexane).

^{1}H NMR (300 MHz, $CDCl_3$): δ 5.78 (d, *J* = 15.5 Hz, 1H), 5.62 (dt, *J* = 15.5, 5.2 Hz, 1H), 5.13 (t, *J* = 6.3 Hz, 1H), 2.94-2.89 (m, 2H), 2.12-1.93 (m, 2H), 1.82 (s, 3H), 1.69 (s, 3H), 1.61 (s, 3H), 1.60-1.50 (m, 2H), 1.28 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 138.8, 138.2, 132.1, 124.6, 123.0, 121.9, 73.2, 42.6, 28.3, 25.9, 23.0, 21.8, 17.8, 3.7. **HRMS (EI$^+$)**: calculated for $C_{14}H_{22}ONa$ [M+Na]$^+$: 229.1562; found: 229.1554. **[α]$^{20}_D$**= -3.7 (*c*= 0.4, $CHCl_3$).

(*S*,*E*)-6,10-Dimethyl-1-phenylundeca-4,9-dien-1-yn-6-ol, (*S*)-III-5g

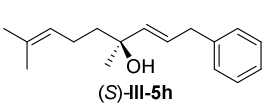


(*S*)-**III-5g**

From epoxyenyne (*S*,*S*)-**III-1g** (40.0 mg, 0.150 mmol, 1 equiv) following the general procedure described above at -20 ºC and adding just 1 equivalent of B_2pin_2, compound (*S*)-**III-5g** (23.4 mg, 0.087 mmol) was obtained in 58% yield, as a yellow oil. $\mathbf{R}_f$ = 0.5 (20% EtOAc/Cyclohexane).

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.45-7.39 (m, 2H), 7.33-7.28 (m, 3H), 5.87 (d, *J* = 15.5 Hz, 1H), 5.71 (dt, *J* = 15.5, 5.2 Hz, 1H), 5.14 (t, *J* = 6.6 Hz, 1H), 3.20 (d, *J* = 5.2 Hz, 2H), 2.13-1.99 (m, 2H), 1.68 (s, 3H), 1.61 (s, 3H), 1.64-1.55 (m, 2H), 1.30 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 138.9, 132.2, 131.8, 128.5, 128.0, 124.6, 124.0, 122.3, 87.4, 82.8, 73.4, 42.7, 28.4, 25.9, 23.2, 22.6, 18.0. **HRMS (ESI$^+$)**: calculated for $C_{19}H_{24}NaO$ $[M+Na]^+$: 291.1725; found: 291.1704. $[\alpha]^{20}_D$= -5.3 (*c*= 1.2, $CHCl_3$).

(*S*,*E*)-4,8-Dimethyl-1-phenylnona-2,7-dien-4-ol, (*S*)-III-5h

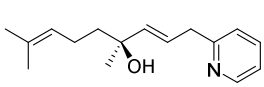


(*S*)-**III-5h**

From epoxide (*S*,*S*)-**III-1h** (48.5 mg, 0.200 mmol, 1 equiv) following the general procedure described above at room temperature and adding 2 equiv of B_2pin_2, compound (*S*)-**III-5h** (38.2 mg, 0.156 mmol) was obtained in 78 % yield, as a yellow oil. $\mathbf{R}_f$ = 0.5 (20% EtOAc/Cyclohexane).

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.32-7.24 (m, 2H), 7.24-7.16 (m, 3H), 5.79 (dt, *J* = 15.5, 6.7 Hz, 1H), 5.60 (d, *J* = 15.5 Hz, 1H), 5.12 (t, *J* = 7.1 Hz, 1H), 3.38 (d, *J* = 6.7 Hz, 2H), 2.09-1.97 (m, 2H), 1.68 (s, 3H), 1.58 (s, 3H), 1.58-1.47 (m, 2H), 1.29 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 140.6, 138.5, 132.0, 128.7, 128.6, 126.9, 126.2, 124.5, 73.2, 42.6, 38.8, 28.3, 25.8, 23.1, 17.8. **HRMS (ESI$^+$)**: calculated for $C_{17}H_{24}ONa$ $[M+Na]^+$: 267.1719; found: 267.1724. $[\alpha]^{20}_D$= -0.2 (*c*= 1.0, $CHCl_3$).

(*S*,*E*)-4,8-dimethyl-1-(pyridin-2-yl)nona-2,7-dien-4-ol, (*S*)-III-5i

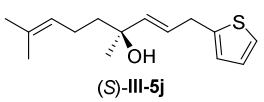


(*S*)-**III-5i**

From epoxide (*S*,*S*)-**III-1i** (48.7 mg, 0.200 mmol, 1 equiv) following the general procedure described above at room temperature with 20 mol% CuCl and 20 mol% of xantphos, compound (*S*)-**III-5i** (25.0 mg, 0.102 mmol) was obtained in 51% yield, as a pale yellow oil. $\mathbf{R}_f$ = 0.35 (20% EtOAc/Cyclohexane).

^{1}H NMR (300 MHz, $CDCl_3$): δ 8.49 (br s, 1H), 7.61 (t, *J* = 7.6 Hz, 1H), 7.22-7.07 (m, 2H), 5.70-5.44 (m, 2H), 5.21-5.08 (m, 1H), 3.83 (d, *J* = 7.5 Hz, 2H), 2.30-1.96 (m, 2H), 1.67 (s, 3H), 1.61 (s, 3H), 1.64-1.48 (m, 2H), 1.35 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 160.6, 148.9, 139.5, 137.3, 131.3, 125.1, 124.9, 123.4, 121.4, 73.9, 44.1, 36.1, 30.4, 25.8, 23.2, 17.8. **HRMS (APCI$^+$)**: calculated for $C_{16}H_{24}ON$ $[M+H]^+$: 246.1852; found: 246.1857. $[\alpha]^{20}_D$= +28.2 (*c*= 1.1, $CHCl_3$).

(*S*,*E*)-4,8-dimethyl-1-(thiophen-2-yl)nona-2,7-dien-4-ol, (*S*)-III-5j

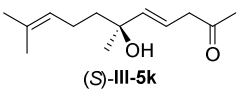


(*S*)-**III-5j**

From epoxide (*S*,*S*)-**III-1j** (49.7 mg, 0.200 mmol, 1 equiv) following the general procedure described above at room temperature with 20 mol% CuCl and 20 mol% of xantphos, compound (*S*)-**III-5j** (30.1 mg, 0.120 mmol) was obtained in 60% yield, as a pale yellow oil. $\mathbf{R}_f$ = 0.4 (20% EtOAc/Cyclohexane).

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.14 (dd, *J* = 5.1, 1.2 Hz, 1H), 6.93 (dd, *J* = 5.1, 3.4 Hz, 1H), 6.80 (dd, *J* = 3.4, 1.2 Hz, 1H), 5.82 (dt, *J* = 15.5, 6.6 Hz, 1H), 5.66 (dt, *J* = 15.5, 1.2 Hz, 1H), 5.19-5.08 (m, 1H), 3.57 (d, *J* = 6.6 Hz, 2H), 2.16-1.95 (m, 2H), 1.69 (s, 3H), 1.60 (s, 3H), 1.59-1.52 (m, 2H), 1.30 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 143.7, 138.9, 132.1, 127.0, 126.1, 124.6, 124.5, 123.7, 73.1, 42.6, 32.8, 28.3, 25.8, 23.1, 17.8. **HRMS (ESI$^+$)**: calculated for $C_{15}H_{22}ONaS$ $[M+Na]^+$: 273.1283; found: 273.1280. $[\alpha]^{20}_D$= +2.5 (*c*= 1.1, $CHCl_3$).

(*S*,*E*)-6-Hydroxy-6,10-dimethylundeca-4,9-dien-2-one, (*S*)-III-5k

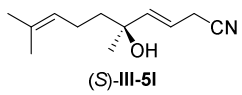


(*S*)-III-5k

From epoxide (*S*,*S*)-**III-1k** (31.2 mg, 0.150 mmol, 1 equiv) following the general procedure described above at room temperature, compound (*S*)-**III-5k** (16.3 mg, 0.078 mmol) was obtained in 52 % yield, as a colorless oil. $\mathbf{R}_f$ = 0.3 (20% EtOAc/Cyclohexane).

^{1}H NMR (300 MHz, $CDCl_3$): δ 5.75 (dt, *J* = 15.5, 6.7 Hz, 1H), 5.62 (d, *J* = 15.5 Hz, 1H), 5.10 (t, *J* = 7.0 Hz, 1H), 3.16 (d, *J* = 6.7 Hz, 2H), 2.15 (s, 3H), 2.08-1.93 (m, 2H), 1.67 (s, 3H), 1.59 (s, 3H), 1.61-1.51 (m, 2H), 1.28 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 207.1, 141.5, 132.1, 124.4, 119.9, 73.1, 47.3, 42.4, 29.6, 28.1, 25.8, 23.0, 17.8. **HRMS (ESI$^+$)**: calculated for $C_{13}H_{22}O_2Na$ $[M+Na]^+$: 233.1512; found: 233.1515. **[α]$^{20}_D$**= -0.6 (*c*= 1.2, $CHCl_3$).

(*S*,*E*)-5-Hydroxy-5,9-dimethyldeca-3,8-dienenitrile, (*S*)-III-5l

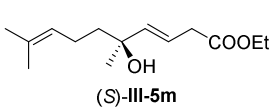


(*S*)-III-5l

From epoxide (*S*,*S*)-**III-1l** (28.7 mg, 0.150mmol, 1equiv) following the general procedure described above at room temperature, compound (*S*)-**III-5l** (17.7 mg, 0.092mmol) was obtained in 61 % yield, as a colorless oil (column chromatography was carried out using 2-5% acetone/CH_2Cl_2 as eluent). $\mathbf{R}_f$ = 0.3 (20% EtOAc/Cyclohexane).

^{1}H NMR (300 MHz, $CDCl_3$): δ 5.91 (d, *J* = 15.5 Hz, 1H), 5.62 (dt, *J* = 15.5, 5.4 Hz, 1H), 5.11 (t, *J* = 7.2 Hz, 1H), 3.12 (d, *J* = 5.4 Hz, 2H), 2.15-1.93 (m, 2H), 1.68 (s, 3H), 1.60 (s, 3H), 1.62-1.53 (m, 2H), 1.29 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 142.3, 132.5, 124.1, 117.6, 115.5, 73.2, 42.3, 28.4, 25.8, 22.9, 20.3, 17.9. **HRMS (ESI$^+$)**: calculated for $C_{12}H_{19}NONa$ $[M+Na]^+$: 216.1358; found: 216.1363. **[α]$^{20}_D$**= +2.3 (*c*= 1.1, MeOH).

Ethyl (*S*,*E*)-5-hydroxy-5,9-dimethyldeca-3,8-dienoate, (*S*)-III-5m

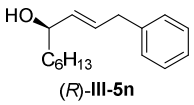


(*S*)-**III-5m**

From epoxide (*S*,*S*)-**III-1m** (30.8 mg, 0.150 mmol, 1 equiv) following the general procedure described above at room temperature, compound (*S*)-**III-5m** (27.8 mg, 0.116 mmol) was obtained in 77 % yield, as a colorless oil. $\mathbf{R}_f$ = 0.5 (20% EtOAc/Cyclohexane).

^{1}H NMR (300 MHz, $CDCl_3$): δ 5.75 (dt, *J* = 15.6, 6.5 Hz, 1H), 5.65 (d, *J* = 15.6 Hz, 1H), 5.11 (t, *J* = 7.2 Hz, 1H), 4.14 (q, *J* = 7.1 Hz, 2H), 3.06 (d, *J* = 6.5 Hz, 2H), 2.10-1.93 (m, 2H), 1.67 (s, 3H), 1.59 (s, 3H), 1.57-1.49 (m, 2H), 1.28 (s, 3H), 1.25 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 172.0, 141.0, 132.1, 124.5, 119.9, 73.1, 60.8, 42.4, 37.9, 28.1, 25.8, 23.0, 17.8, 14.3. **HRMS (ESI$^+$)**: calculated for $C_{14}H_{24}O_3Na$ $[M+Na]^+$: 263.1617; found: 263.1609. **[α]$^{20}_D$**= +2.4 (*c*= 1.2, $CHCl_3$).

(*R*,*E*)-1-Phenyldec-2-en-4-ol, (*R*)-III-5n

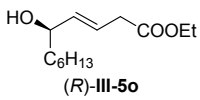


(*R*)-**III-5n**

From epoxide (*R*,*S*)-**III-1n** (34.5 mg, 0.150mmol, 1 equiv) following the general procedure described above at -20 ºC (60h) and adding 2 equiv of B_2pin_2, compound (*R*)-**III-5n** (25.3 mg, 0.109 mmol) was obtained in 73 % yield, as a yellow oil. $\mathbf{R}_f$ = 0.5 (20% EtOAc/Cyclohexane).

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.34-7.25 (m, 2H), 7.24-7.15 (m, 3H), 5.80 (dt, *J* = 15.6, 6.7 Hz, 1H), 5.55 (dd, *J* = 15.6, 6.9 Hz, 1H), 4.09 (dt, *J* = 6.9, 6.4 Hz, 1H), 3.38 (d, *J* = 6.7 Hz, 2H), 1.62-1.40 (m, 2H), 1.38-1.23 (m, 8H), 0.89 (t, *J* = 6.8 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$):δ140.3, 134.7, 130.5, 128.7, 128.6, 126.3, 73.1, 38.8, 37.5, 32.0, 29.4, 25.6, 22.7, 14.2. **HRMS (ESI$^+$)**: calculated for $C_{16}H_{24}ONa$ $[M+Na]^+$: 255.1719; found: 255.1721. **[α]$^{20}_D$**= +3.6 (*c*= 1.2, $CHCl_3$).

Ethyl (*R*,*E*)-5-hydroxyundec-3-enoate, (*R*)-III-5o

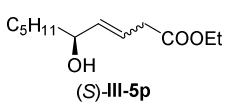


(*R*)-**III-5o**

From epoxide (*S*,*R*)-**III-1o** (34.0 mg, 0.150 mmol, 1 equiv) following the general procedure described above at room temperature, compound (*R*)-**III-5o** (25.3 mg, 0.111 mmol) was obtained in 74 % yield, as a colorless oil. $\mathbf{R}_f$ = 0.4 (20% EtOAc/Cyclohexane).

^{1}H NMR (300 MHz, $CDCl_3$): δ 5.75 (dt, *J* = 15.0, 6.8 Hz, 1H), 5.60 (dd, *J* = 15.0, 6.6 Hz, 1H), 4.13 (q, *J* = 7.1 Hz, 2H), 4.22-4.01 (m, 1H), 3.06 (d, *J* = 6.8 Hz, 2H), 1.58-1.43 (m, 2H), 1.39-1.19 (m, 11H), 0.87 (t, *J* = 6.6 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 171.8, 137.3, 123.0, 72.7, 60.8, 37.8, 37.2, 31.9, 29.3, 25.5, 22.7, 14.3, 14.2. **HRMS (ESI$^+$)**: calculated for $C_{13}H_{24}O_3Na$ $[M+Na]^+$: 251.1617; found: 251.1619. **$[\alpha]^{20}_D$**= -2.8 (*c*= 1.2, $CHCl_3$).

Ethyl (*S*)-5-hydroxydec-3-enoate, (*S*)-III-5p

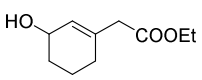


(*S*)-**III-5p**

From epoxide (*S*,*S*)-**III-1p** (35.5 mg, 0.150 mmol, 1 equiv) following the general procedure described above at room temperature, compound (*S*)-**III-5p** (19.6 mg, 0.082 mmol) was obtained in 55 % yield, as a colorless oil. $\mathbf{R}_f$ = 0.45 (20% EtOAc/Cyclohexane).

The spectral data for (*S*)-**III-5p** matched those previously reported for this compound.[16a] Isomeric mixture *Z*/*E* = 1:3. **^{1}H NMR** (300 MHz, $CDCl_3$): δ (*E* isomer) 5.83-5.71 (m, 1H), 5.62 (dd, *J* = 17.2, 6.7 Hz, 1H), 4.21-4.07 (m, 3H), 3.14-3.03 (m, 2H), 1.59-1.20 (m, 11H), 0.94-0.85 (d, *J* = 6.5 Hz, 3H).

Ethyl 2-(3-hydroxycyclohex-1-en-1-yl)acetate, (±)-III-5q

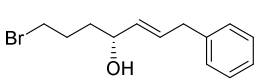


(±)-**III-5q**

From epoxide (±)-**III-1q** (27.3 mg, 0.150 mmol, 1 equiv) following the general procedure described above at room temperature, compound (±)-**III-5q** (22.8 mg, 0.124 mmol) was obtained in 83 % yield, as a colorless oil. $\mathbf{R}_f$ = 0.35 (20% EtOAc/Cyclohexane).

The spectral data for (±)-**III-5q** matched those previously reported for this compound.[16a] **^{1}H NMR** (300 MHz, $CDCl_3$): δ 5.74-5.60 (m, 1H), 4.27-4.20 (m, 1H), 4.13 (q, *J* = 7.1 Hz, 2H), 2.98 (s, 2H), 2.09-1.54 (m, 6H), 1.25 (t, *J* = 7.1 Hz, 3H).

(*R*,*E*)-7-Bromo-1-phenylhept-2-en-4-ol, (*R*)-III-5r

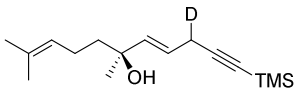


(*R*)-**III-5r**

From epoxide (*R*,*S*)-**III-1r** (53.4 mg, 0.200 mmol, 1 equiv) following the general procedure described above at room temperature, compound (*R*)-**III-5r** (28.5 mg, 0.106 mmol) was obtained in 53% yield, as a pale yellow oil. $\mathbf{R}_f$ = 0.3 (20% EtOAc/Cyclohexane).

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.39-7.08 (m, 5H), 5.86 (dt, *J* = 15.3, 6.7 Hz, 1H), 5.58 (dd, *J* = 15.3, 6.8 Hz, 1H), 4.16 (dt, *J* = 6.8, 6.5 Hz, 1H), 3.59-3.31 (m, 4H), 2.15-1.88 (m, 2H), 1.81-1.65 (m, 2H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 140.0, 134.1, 131.1, 128.7, 128.7, 126.3, 72.2, 38.7, 35.8, 33.9, 29.0. **HRMS (ESI$^+$)**: calculated for $C_{13}H_{17}BrONa$ $[M+Na]^+$: 291.0354; found: 291.0346. **$[\alpha]^{20}_D$**= +1.94 (*c*= 0.6, $CHCl_3$).

(4*S*,*E*)-4,8-Dimethyl-1-phenylnona-2,7-dien-1-*d*-4-ol, (*S*)-III-6a



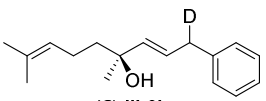
(*S*)-**III-6a**

From epoxide (*S*,*S*)-**III-1a** (36.3 mg, 0.150 mmol, 1equiv) following the general procedure described above at room temperature with

MeOD, compound (*S*)-**III-6a** (23.9 mg, 0.09 mmol) was obtained in 60% yield with 80% deuteration degree, as a yellow oil. $\mathbf{R}_f$ = 0.5 (20% EtOAc/Cyclohexane).

^{1}H NMR (300 MHz, $CDCl_3$): δ 5.78 (d, *J* = 15.5 Hz, 1H), 5.61 (dd, *J* = 15.5, 5.3 Hz, 1H), 5.12 (t, *J* = 7.1 Hz, 1H), 2.99 (d, *J* = 5.3 Hz, 1H), 2.13-1.90 (m, 2H), 1.68 (s, 3H), 1.60 (s, 3H), 1.58-1.48 (m, 2H), 1.28 (s, 3H), 0.16 (s, 9H). **^{13}C RMN** (75 MHz, $CDCl_3$): δ 138.8, 132.1, 124.5, 121.9, 104.2, 86.8, 73.2, 42.5, 28.3, 25.8, 23.0, 17.9, 0.2. **HRMS (ESI$^+$)**: calculated for $C_{16}H_{27}DONaSi$ $[M+Na]^+$: 288.1864; found: 288.1862.

(4*S*,*E*)-4,8-Dimethyl-1-phenylnona-2,7-dien-1-*d*-4-ol, (*S*)-III-6h

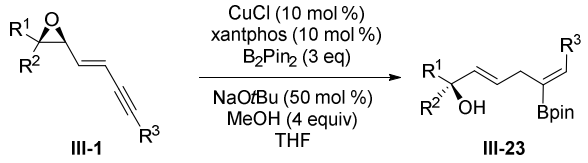


(*S*)-**III-6h**

From epoxide (*S*,*S*)-**III-1h** (36.3 mg, 0.150mmol, 1equiv) following the general procedure described above at room temperature with MeOD, compound (*S*)-**III-6h** (19.3 mg, 0.079mmol) was obtained in 53% yield with 80% deuteration degree, as a yellow oil. $\mathbf{R}_f$ = 0.5 (20% EtOAc/Cyclohexane).

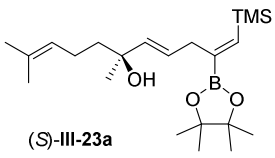
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.41-7.31 (m, 2H), 7.31-7.18 (m, 3H), 5.85 (dd, *J* = 15.5, 6.4 Hz, 1H), 5.66 (d, *J* = 15.5 Hz, 1H), 5.19 (t, *J* = 6.5 Hz, 1H), 3.44 (d, *J* = 6.4 Hz, 1H), 2.21-1.98 (m, 2H), 1.74 (s, 3H), 1.65 (s, 3H), 1.68-1.53 (m, 2H), 1.35 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 140.6, 138.5, 132.0, 128.7, 128.6, 126.8, 126.2, 124.5, 73.2, 42.7, 38.5(t, $J_{C\text{-}D}$=19.7), 28.3, 25.8, 23.1, 17.8. **HRMS (ESI$^+$)**: calculated for $C_{17}H_{23}DONa$ $[M+Na]^+$: 268.1782; found: 268.1789. **$[\alpha]^{20}_D$**= +1.1 (*c*= 1.1, $CHCl_3$).

3.3.4. General Procedure for the Synthesis of Skipped Dienes, **III-23**



An oven-dried vial was charged with CuCl (1.5 mg, 0.015 mmol, 10 mol%), B_2pin_2 (114.3 mg, 0.45 mmol, 3equiv) and ligand (8.7 mg, 0.015 mmol, 10 mol%) and sealed with a septum. The vial was connected to an argon-vacuum line, evacuated and backfilled with argon (x3). THF (0.5 mL/0.15 mmol of **III-1**) was added and the mixture was stirred for 15 min at room temperature. A 0.2 M NaO*t*Bu solution in THF (38µL, 0.075 mmol, 50 mol%) was added dropwise and the dark brown solution was stirred for 10 min. Then the corresponding epoxide **III-1** (1.0 equiv) in THF (0.2 mL/0.15 mmol of **III-1**) was added followed by methanol (24 µL, 0.6 mmol, 4 equiv). Finally, the reaction mixture was stirred overnight at room temperature. Water and CH_2Cl_2 were added and the layers were separated. The aqueous phase was extracted with CH_2Cl_2 (x3) and the combined organic layers were washed with saturated NaCl solution, dried over Na_2SO_4, filtered and concentrated. The crude product was purified by flash column chromatography (2-5% EtOAc/Cyclohexane) to obtain compound **III-23**.

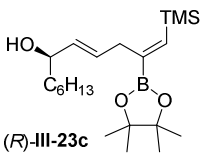
(*S*,1*Z*,4*E*)-6,10-Dimethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1-(trimethylsilyl)undeca-1,4,9-trien-6-ol, (*S*)-III-23a



From epoxyenyne (*S*,*S*)-**III-1a** (52.4 mg, 0.200 mmol) following the general procedure described above, compound (*S*)-**III-23a** (53.9 mg, 0.137 mmol) was obtained in 69% yield, as a colorless oil. $\mathbf{R}_f$ = 0.45 (20% EtOAc/Cyclohexane).

^{1}H NMR (300 MHz, $CDCl_3$): δ 6.57 (s, 1H), 5.69 (dt, *J* = 15.7, 6.1 Hz, 1H), 5.49 (d, *J* = 15.7 Hz, 1H), 5.10 (t, *J* = 7.1 Hz, 1H), 3.01 (d, *J* = 6.0 Hz, 2H), 2.10-1.90 (m, 2H), 1.67 (s, 3H), 1.60 (s, 3H), 1.57-1.47 (m, 2H), 1.25 (s, 12H), 1.24 (s, 3H), 0.14 (s, 9H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 147.55, 137.48, 131.85, 126.81, 124.68, 83.65, 73.23, 42.59, 37.41, 29.86, 28.29, 25.84, 24.94, 23.07, 17.90, 0.35. [note: the carbon attached to boron was not observed due to quadrupole broadening caused by the ^{11}B nucleus]. **HRMS (ESI$^+$)**: calculated for $C_{22}H_{41}BO_3NaSi$ $[M+Na]^+$: 415.2810; found: 415.2794. **[α]$^{20}_D$**= -6.1 (*c*= 1.5, $CHCl_3$).

(*R*,1*Z*,4*E*)-2-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)-1-(trimethylsilyl)dodeca-1,4-dien-6-ol, (*R*)-III-23c

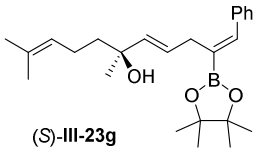


(*R*)-**III-23c**

From epoxyenyne (*S*,*R*)-**III-1c** (50.1 mg, 0.200 mmol, 1 equiv) following the general procedure described above, compound (*R*)-**III-23c** (38.8 mg, 0.102 mmol) was obtained in 51% yield as a colorless oil. $\mathbf{R}_f$ = 0.45 (20% EtOAc/Cyclohexane).

^{1}H NMR (300 MHz, $CDCl_3$): δ 6.57 (s, 1H), 5.69 (dt, *J* = 15.2, 6.0 Hz, 1H), 5.44 (dd, *J* = 15.4, 7.1 Hz, 1H), 4.09-3.97 (m, 1H), 2.99 (d, *J* = 6.0 Hz, 2H), 1.61-1.23 (m, 10H), 1.25 (s, 12H), 0.87 (t, *J* = 6.1 Hz, 3H), 0.13 (s, 9H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 147.7, 133.9, 130.8, 83.7, 73.4, 37.5, 37.4, 32.0, 29.4, 25.6, 24.93, 24.91, 22.8, 14.2, 0.3. [note: the carbon attached to boron was not observed due to quadrupole broadening caused by the ^{11}B nucleus]. **HRMS (ESI$^+$)**: calculated for $C_{21}H_{41}BO_3NaSi$ $[M+Na]^+$: 403.2810; found: 403.2800. **[α]$^{20}_D$**= +2.9 (*c*= 1.0, $CHCl_3$).

(*S*,1*Z*,4*E*)-6,10-Dimethyl-1-phenyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)undeca-1,4,9-trien-6-ol, (*S*)-III-23g

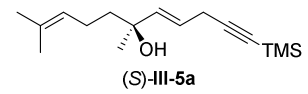


(*S*)-**III-23g**

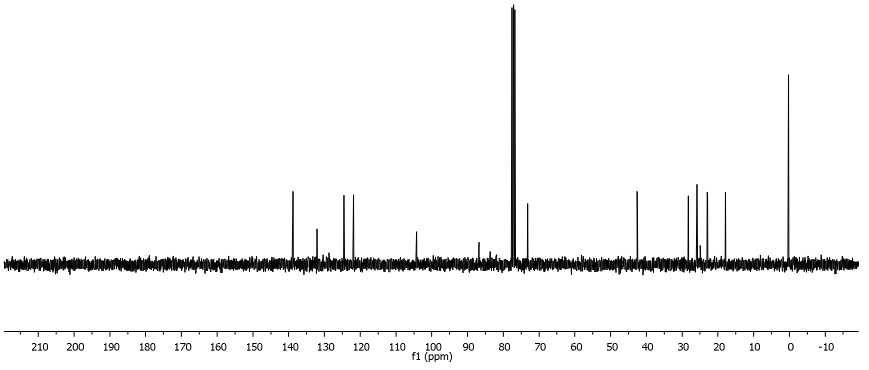
From epoxyenyne (*S*,*S*)-**III-1g** (53.3 mg, 0.200 mmol) following the general procedure described above, compound (*S*)-**III-23g** (56.2 mg, 0.142 mmol) was obtained in 71% yield, as a yellow oil. $\mathbf{R}_f$ = 0.45 (20% EtOAc/Cyclohexane).

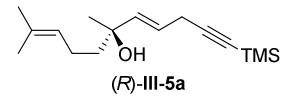
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.39-7.18 (m, 6H), 5.81 (dt, *J* = 15.7, 5.6 Hz, 1H), 5.54 (d, *J* = 15.7 Hz, 1H), 5.10 (t, *J* = 6.5 Hz, 1H), 3.11 (d, *J* = 5.3 Hz, 2H), 2.13-1.91 (m, 2H), 1.66 (s, 3H), 1.62-1.48 (m, 5H), 1.29 (s, 12H), 1.26 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 143.3, 137.7, 137.3, 131.9, 129.0, 128.2, 127.5, 126.6, 124.7, 83.6, 73.4, 42.6, 32.2, 28.5, 25.8, 25.0, 24.9, 23.1, 17.9. [note: the carbon attached to boron was not observed due to quadrupole broadening caused by the ^{11}B nucleus]. **HRMS (ESI$^+$)**: calculated for $C_{25}H_{37}BO_3Na$ $[M+Na]^+$: 419.2727; found: 419.2716. **$[\alpha]^{20}_D$**= -1.5 (*c*= 1.0, $CHCl_3$).

3.4. NMR spectra



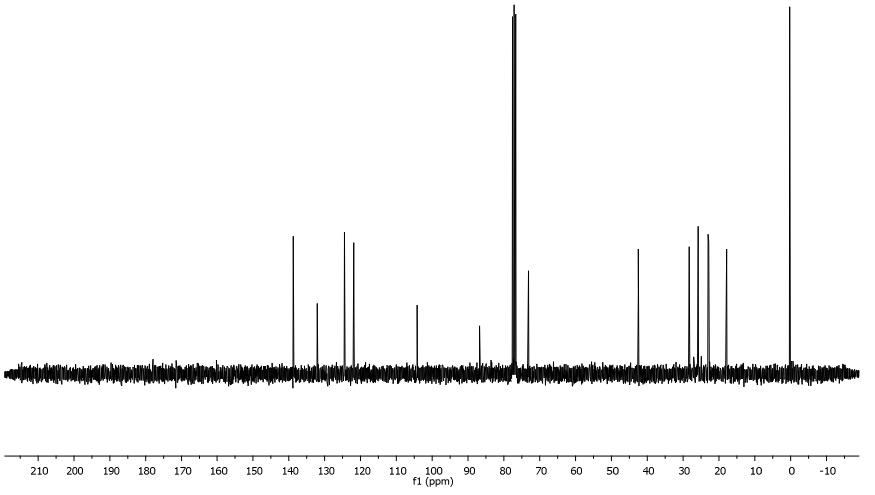
(*S*)-**III-5a**

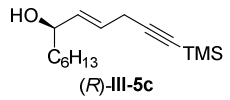



OH
TMS

(*R*)-**III-5a**

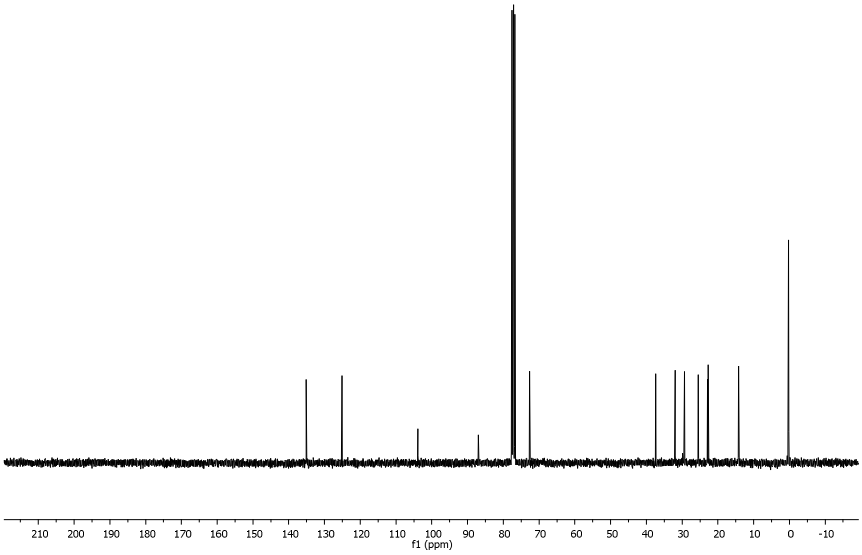
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0 -1.5
f1 (ppm)

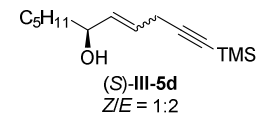

210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


HO
C6H13
TMS

(*R*)-**III-5c**

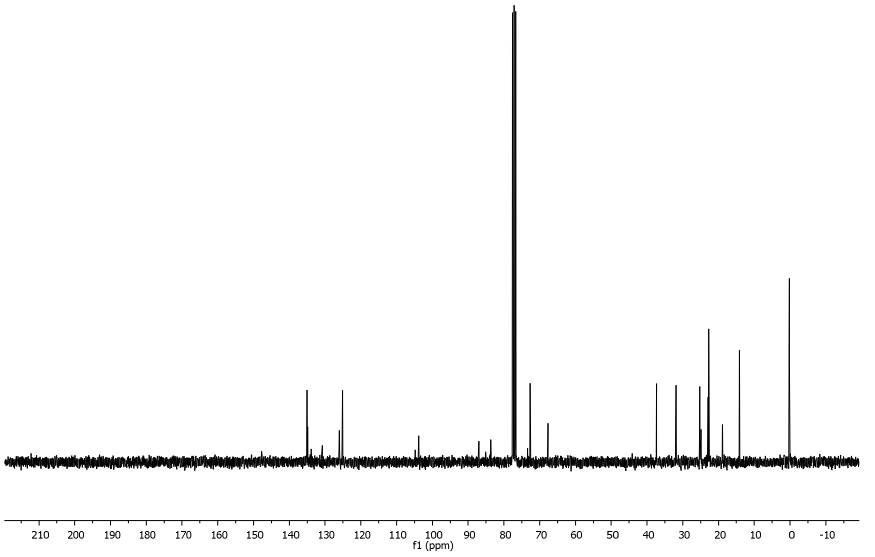
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0
f1 (ppm)

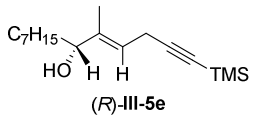

210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


C5H11
OH
TMS

(*S*)-**III-5d**
Z/*E* = 1:2

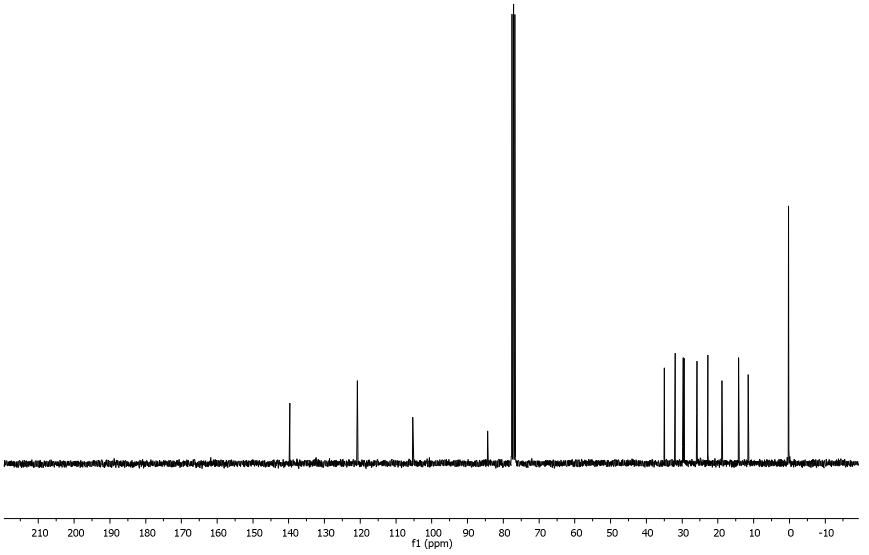
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0 -1.5
f1 (ppm)

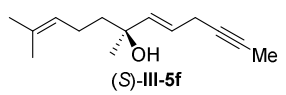

210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


C7H15
HO
H
H
TMS

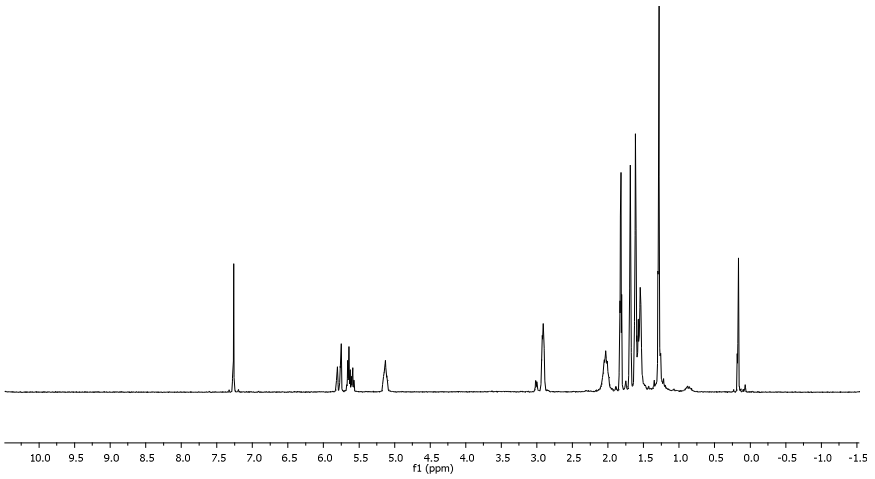
(*R*)-**III-5e**

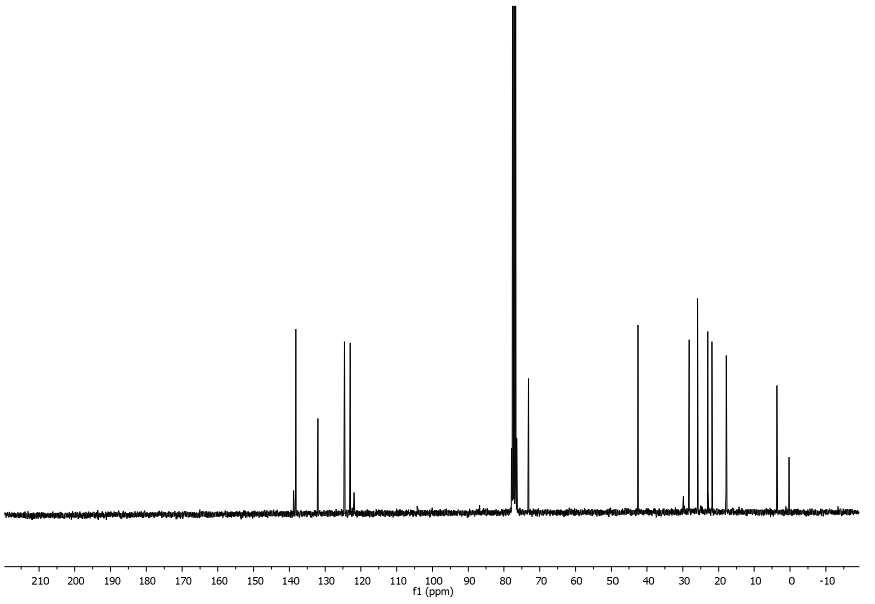
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0 -1.5
f1 (ppm)

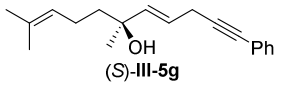

210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


OH
Me

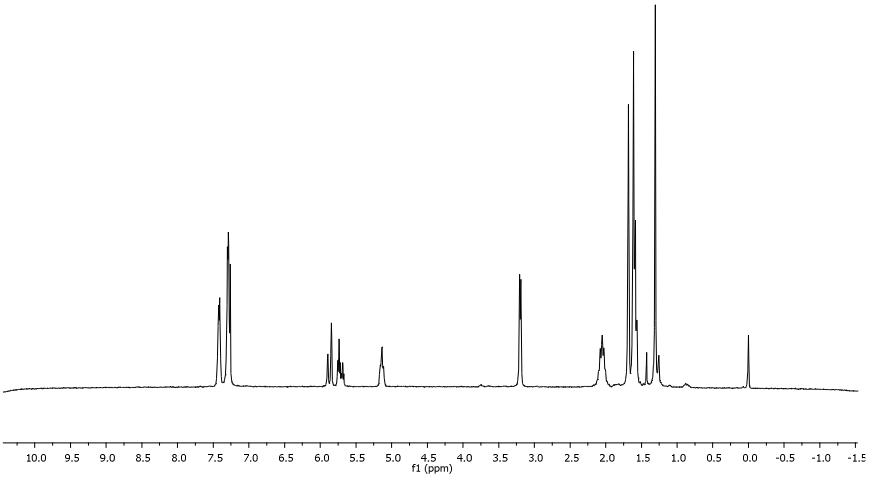
(*S*)-**III-5f**

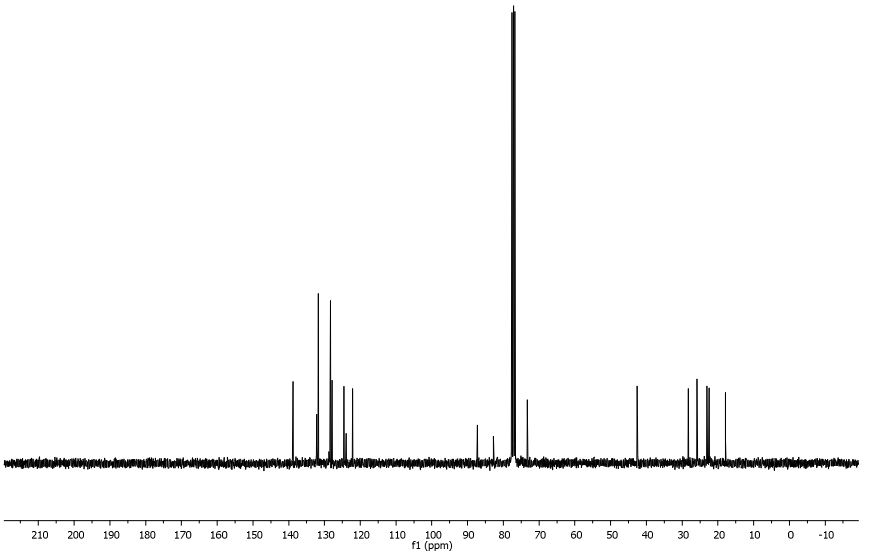

10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0 -1.5
f1 (ppm)

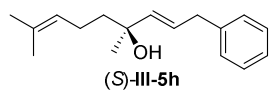

210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


OH
Ph

(*S*)-**III-5g**

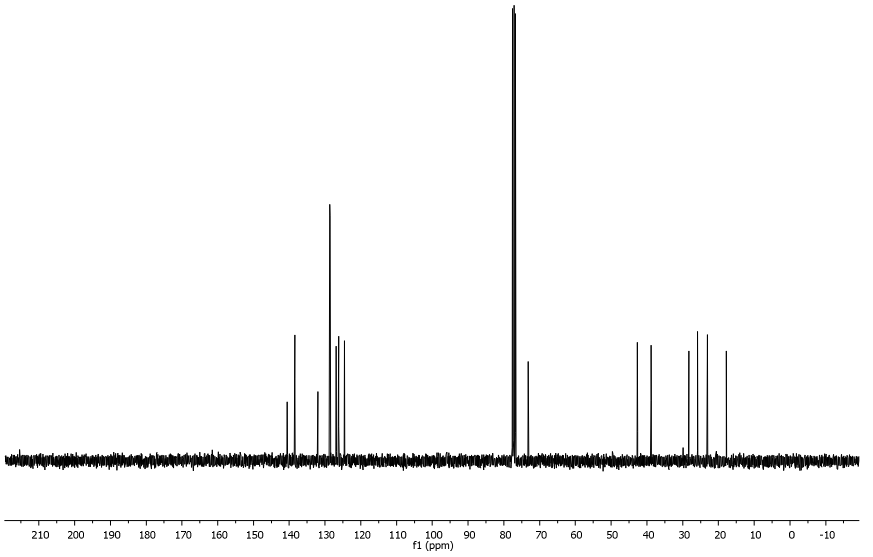

10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0
f1 (ppm)

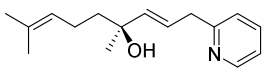

210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


OH

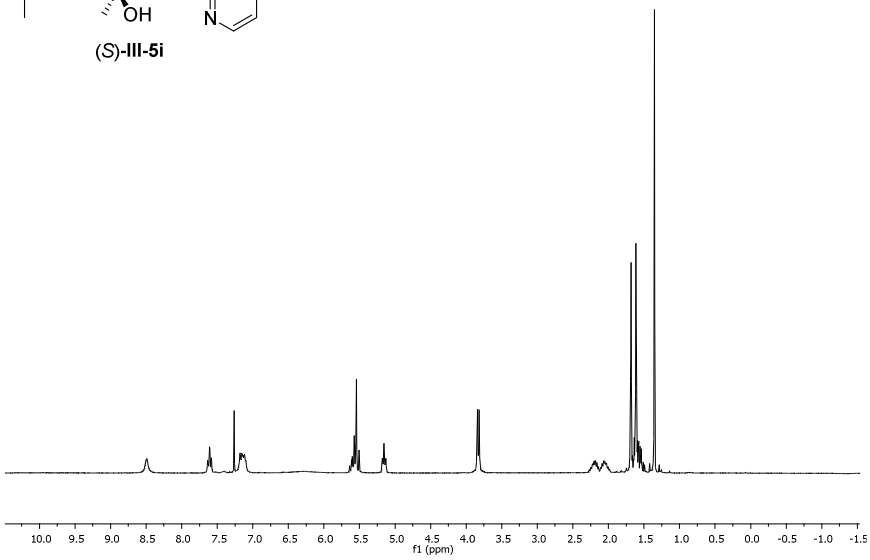
(*S*)-**III-5h**

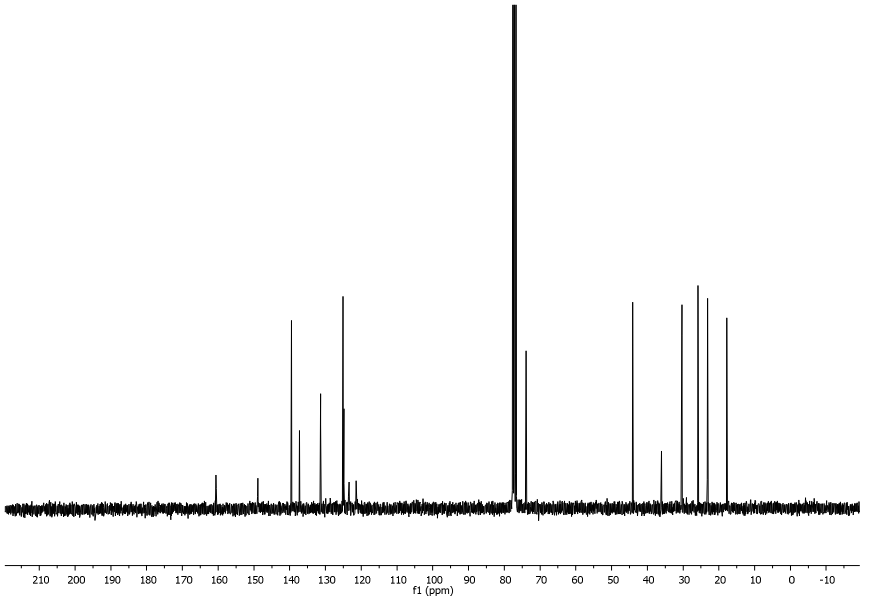
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0 -1.5
f1 (ppm)

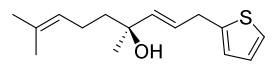

210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


OH
N

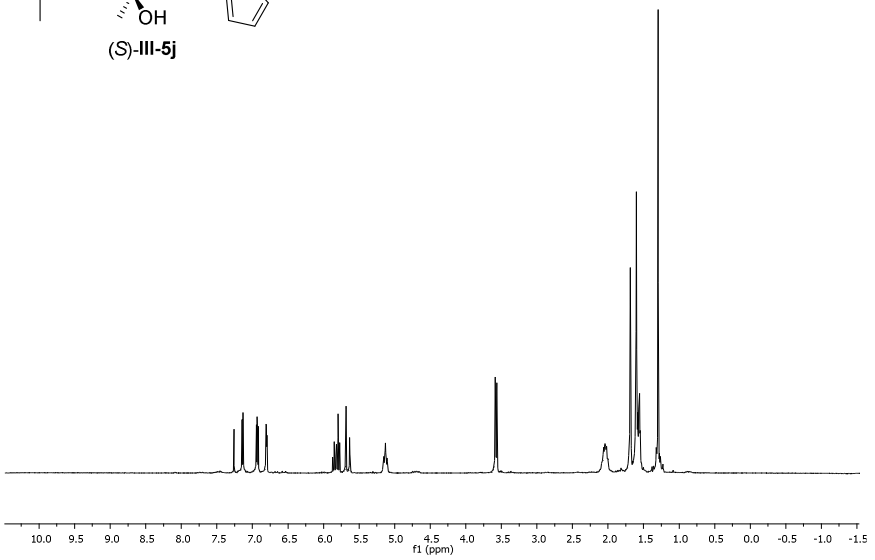
(*S*)-**III-5i**

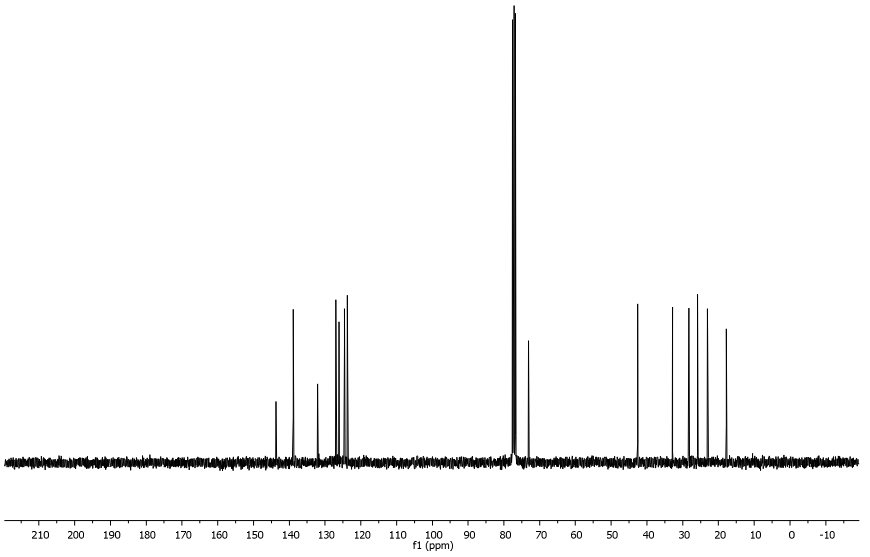

10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0 -1.5
f1 (ppm)

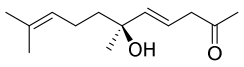

210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


S
OH

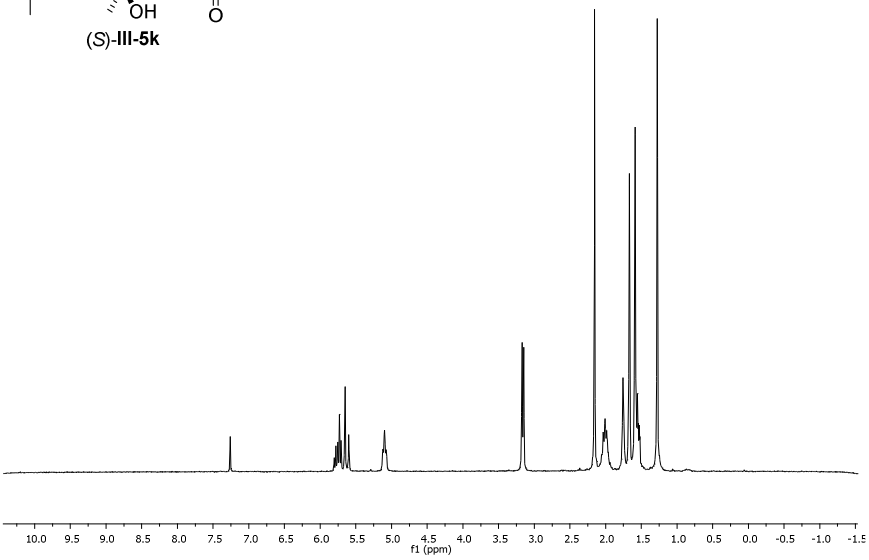
(*S*)-**III-5j**

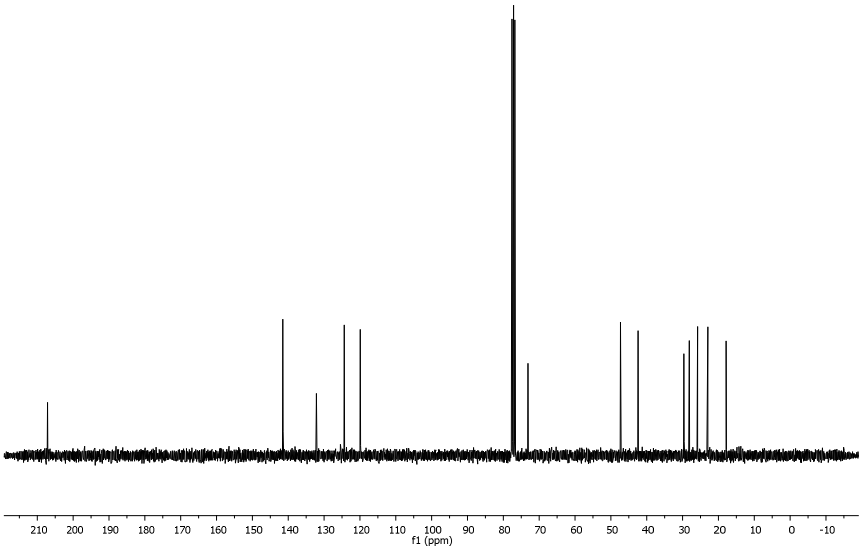

10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0 -1.5
f1 (ppm)

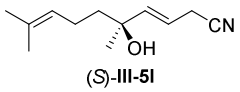

210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


OH
O

(*S*)-**III-5k**

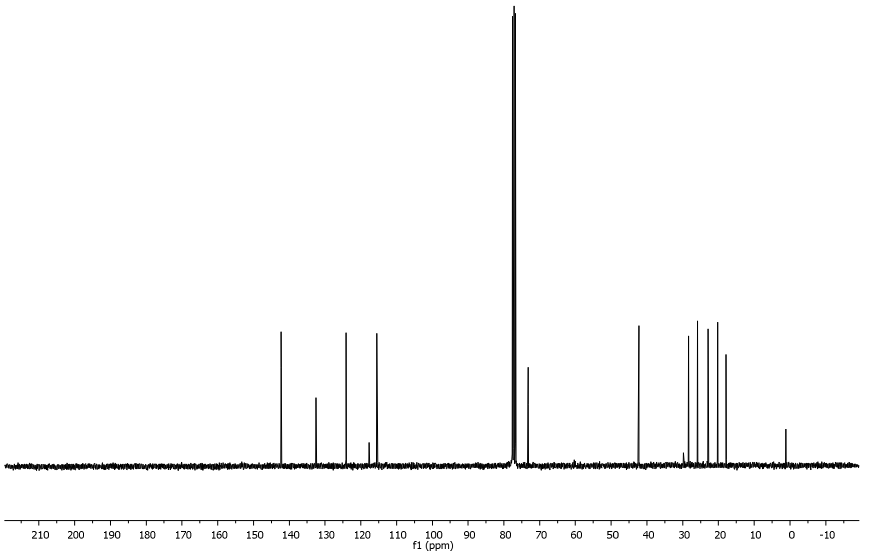

10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0
f1 (ppm)

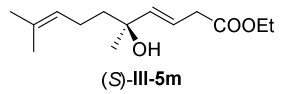

210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


CN
OH

(*S*)-**III-5l**

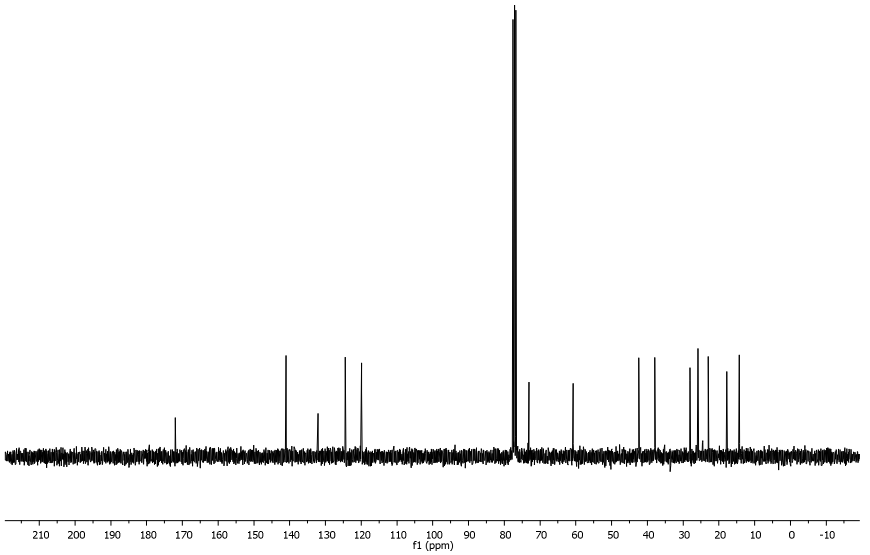
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0 -1.5
f1 (ppm)

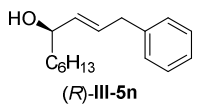

210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


COOEt
OH

(*S*)-**III-5m**

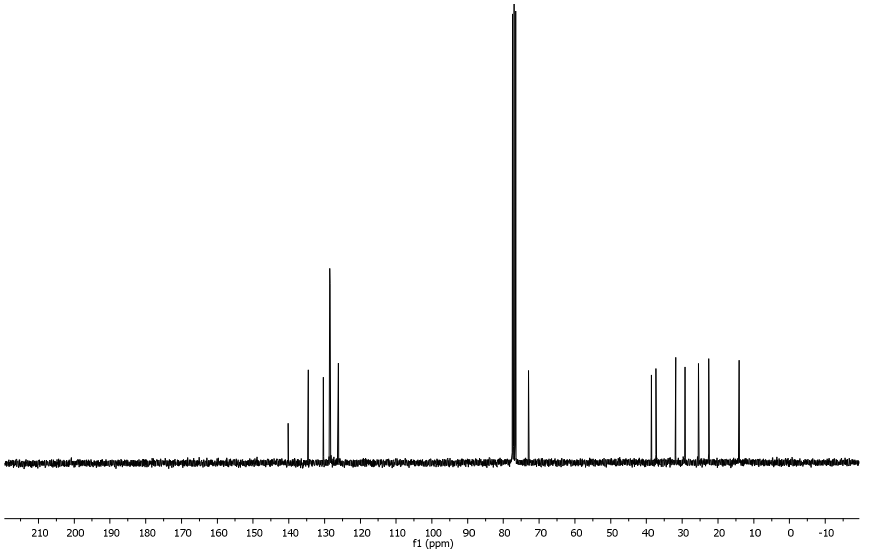
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0 -1.5
f1 (ppm)

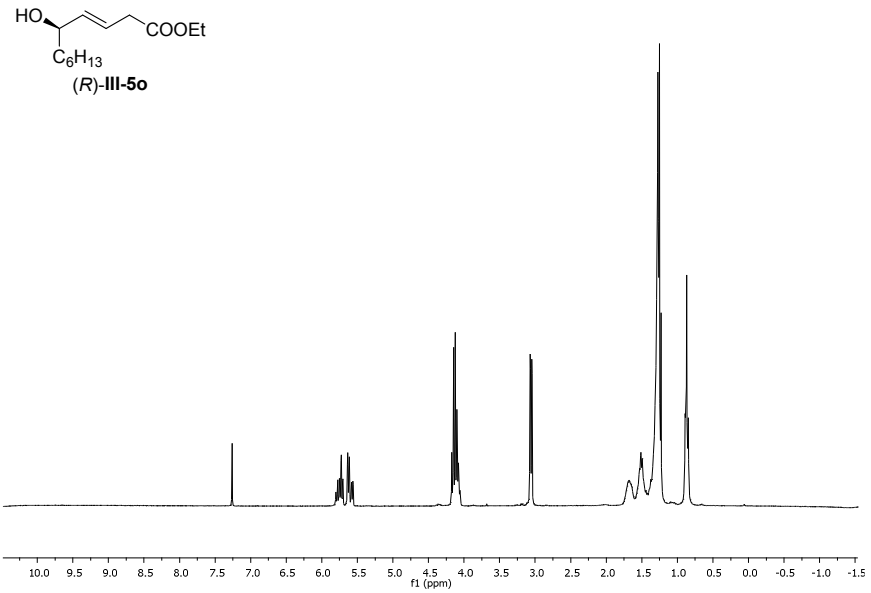

210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

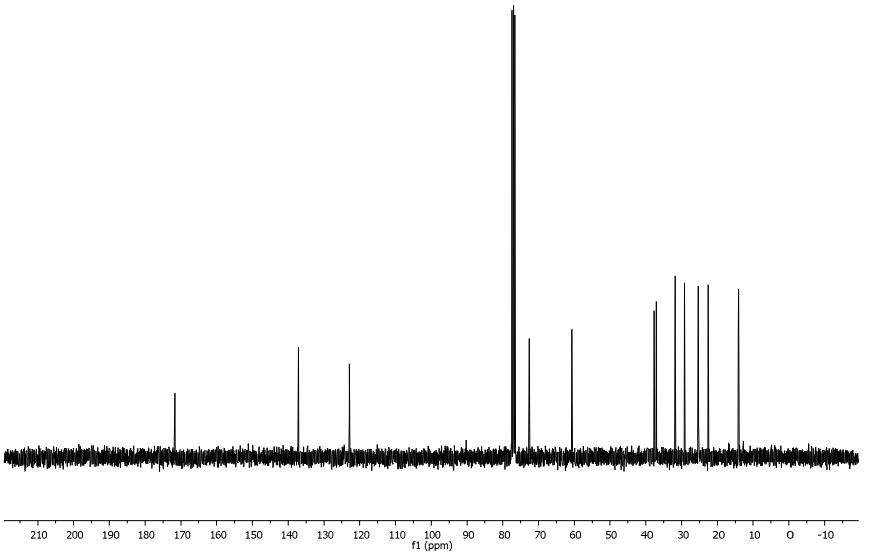

HO
C6H13

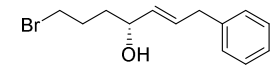
(*R*)-**III-5n**

10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0 -1.5
f1 (ppm)

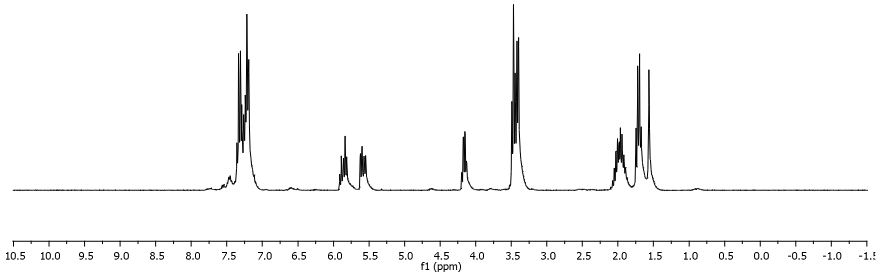

210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

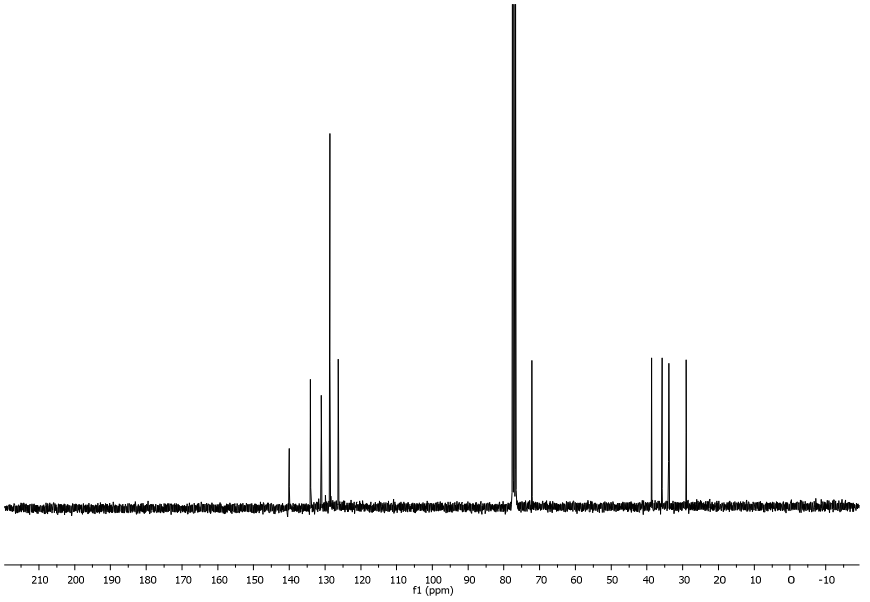

HO
COOEt
C_6H_{13}
(*R*)-**III-5o**
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0 -1.5
f1 (ppm)

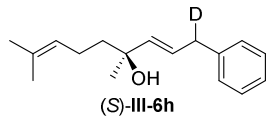

210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


Br
OH

(*R*)-**III-5r**

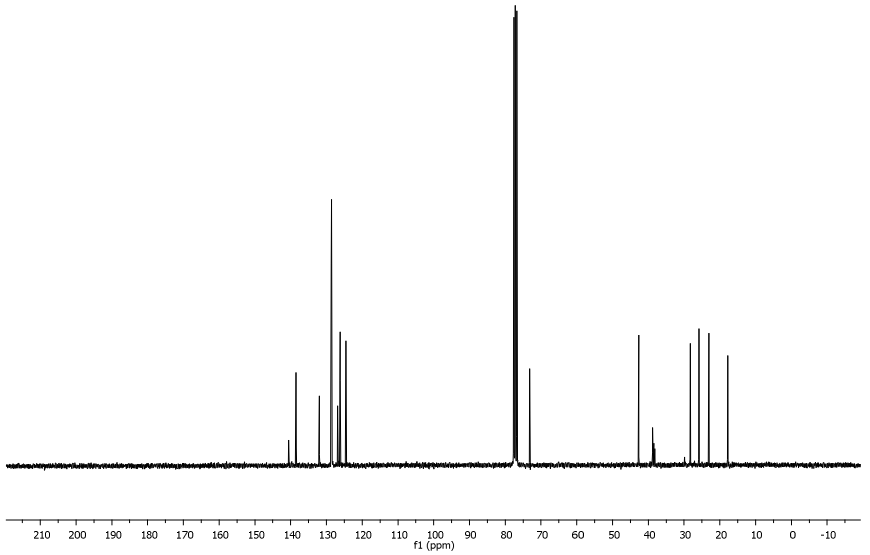

10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0
f1 (ppm)

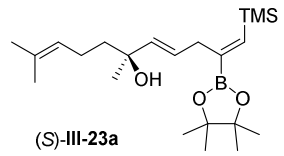

210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


D
OH

(*S*)-**III-6h**

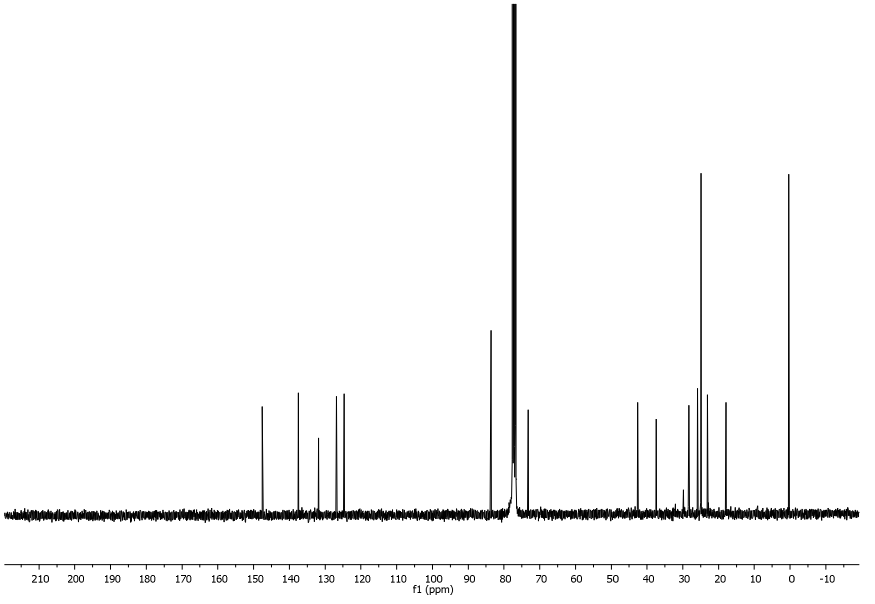
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0
f1 (ppm)

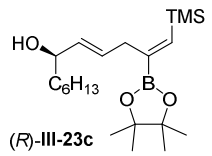

210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


TMS
OH
B
O
O

(*S*)-**III-23a**

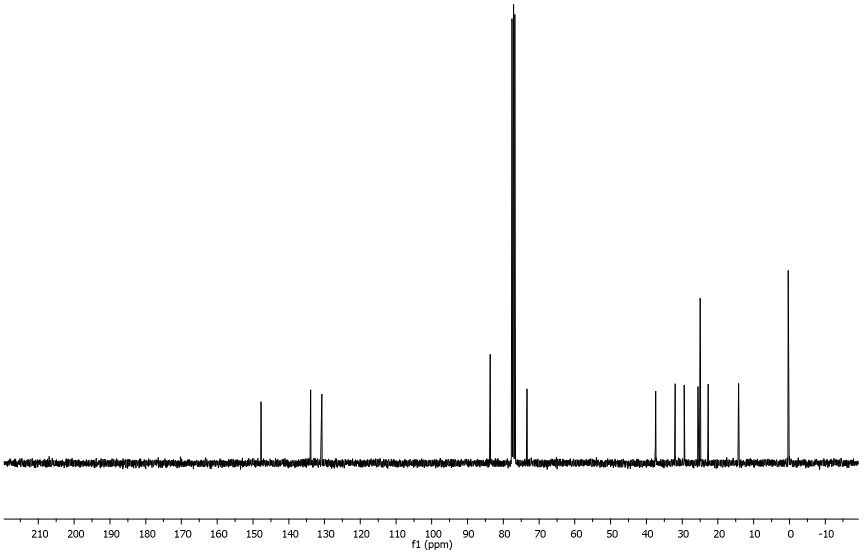
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0 -1.5
f1 (ppm)

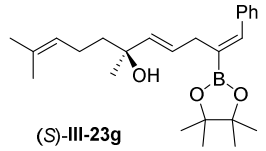

210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


TMS
HO
C_6H_{13}
B
O
O

(*R*)-**III-23c**

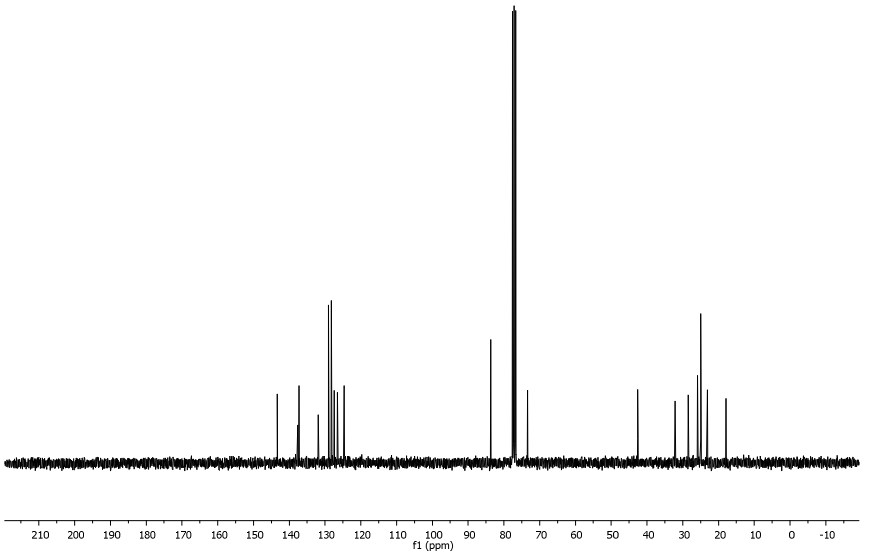
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0 -1.5
f1 (ppm)


210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


Ph
OH
B
O
O

(*S*)-**III-23g**

10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0 -1.5
f1 (ppm)


210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

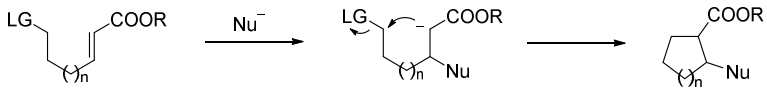
Chapter 4

SYNTHESIS OF CYCLOPROPYLBORONATES VIA MICHAEL INITIATED RING CLOSURE (MIRC) REACTION

4. SYNTHESIS OF CYCLOPROPYLBORONATES VIA MICHAEL INITIATED RING CLOSURE (MIRC) TYPE REACTION

4.1. Michael Initiated Ring Closure (MIRC)

In 1980, Little and Dawson defined the term MIRC (Michael Initiated Ring Closure) reaction as "a genera1 set of transformations which are initiated by a conjugate addition to an α,β-unsaturated ester or ketone to produce an enolate which subsequently undergoes intramolecular ring closure" (*Scheme IV-1*).[1]



Scheme IV-1. General Scheme for MIRC reactions.

Many synthetically useful examples have been reported using this methodology. In fact, the Michael Initiated Ring Closure (MIRC) reaction represents an elegant approach to obtain cyclopropane rings,[2] carbocyclic compounds,[3] and small/medium sized nitrogen[4] or oxygen[5] containing

[1] Little, R. D.; Dawson, J. R. *Tetrahedron Lett.* **1980**, *21*, 2609-2612.
[2] Lebel, H.; Marcoux, J.-F.; Molinaro, C.; Charette, A. B. *Chem. Rev.* **2003**, *103*, 977-1050.
[3] (a) Little, R. D.; Verhe, R.; Monte, W. T.; Nugent, S.; Dawson, J. R. *J. Org. Chem.* **1982**, *47*, 362-364. (b) Nugent, S. T.; Baizer, M. M.; Little R. D. *Tetrahedron Lett.* **1982**, *23*, 1339-1342. (c) Dumez, E.; Durand, A.-C.; Guillaume, M.; Roger, P.-Y.; Faure, R.; Pons, J.-M.; Herbette, G.; Dulcére, J.-P.; Bonne, D.; Rodriguez, J. *Chem. Eur. J.* **2009**, *15*, 12470-12488. (d) Yamaguchi, M.; Tsukamoto, M.; Hirao, I. *Tetrahedron Lett.* **1985**, *26*, 1723-1726.

heterocyclic compounds. This transformation can be considered a one-pot multicomponent reaction, which means that it occurs in a single pot and it exhibits high atom-economy and selectivity. All these features make Michael Initiated Ring Closure (MIRC) reactions a very attractive tool to develop modern synthetic organic chemistry.

There are two categories of MIRC reactions.[6] "Type I", in which the leaving group (LG) is attached to the Michael acceptor (*Scheme IV-2*), and a variety of nucleophiles can be used, such as alkoxides, thiolates, cyanides, enolates, Grignard reagents, hydrides, phosphites, and phosphonites.[7] On the other hand, reactions in which the leaving group is on the nucleophile, are called "Type II" (*Scheme IV-2*).[8] These nucleophiles can be α-halocarbanions, although the most effective reagents are the heteroatom-derived ylides, such as sulfur, phosphorus, arsenium, and telluronium ylides.

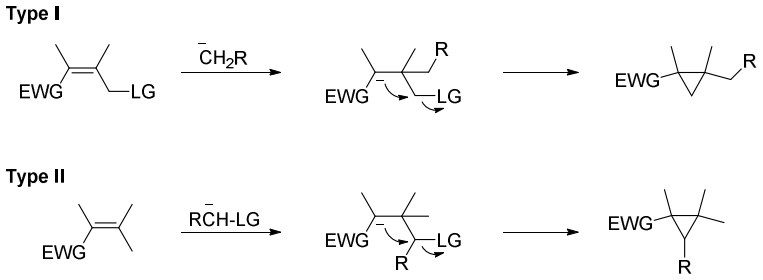
[4] (a) Fioravanti, S.; Morreale, A.; Pellacani, L.; Tardella, P. A. *Eur J. Org. Chem.* **2003**, 4549-4552. (b) Fioravanti, S.; Marchetti, F.; Morreale, A.; Pellacani, L.; Ranieria, L.; Tardella, P. *Tetrahedron: Asymmetry* **2008**, *19*, 231-236. (c) Fioravanti, S.; Morea, S.; Morreale, A.; Pellacani, L.; Tardella, P. A. *Tetrahedron* **2009**, *65*, 484-492. (d) Khan, A. T.; Das, D. K. *Tetrahedron Letters* **2012**, *53*, 2345-2351.

[5] (a) Wang, Q.-F.; Hou, H.; Hui, L.; Yan, C.-G. *J. Org. Chem.* **2009**, *74*, 7403-7406. (b) Dumez, E.; Durand, A.-C.; Guillaume, M.; Roger, P.-Y.; Faure, R.; Pons, J.-M.; Herbette, G.; Dulcére, J.-P.; Bonne, D.; Rodriguez, J. *Chem. Eur. J.* **2009**, *15*, 12470-12488. (c) Altieri, E.; Cordaro, M.; Grassi, G.; Risitano, F.; Scala, A. *Tetrahedron* **2010**, *66*, 9493- 496.

[6] Casey, M.; Claire M. Keaveney, C. M.; Walker, A. J. *ARKIVOC* **2002**, 91-103.

[7] Caine, D. *Tetrahedron* **2001**, *57*, 2643-2684.

[8] (a) Artaud, I.; Seyden-Penne, J.; Viout, P. *Synthesis* **1980**, 34-36. (b) Shibata, I.; Mori, Y.; Yamasaki, H.; Baba, A.; Matsuda, H. *Tetrahedron Lett.* **1993**, *34*, 6567-6570. (c) Rodios, N. A.; Bojilova, A.; Terzis, A.; Raptopoulou, C. P. *J. Heterocycl. Chem.* **1994**, *31*, 1129-1133. (d) Escribano, A.; Pedregal, C.; González, R.; Fernández, A.; Burton, K.; Stephenson, G. A. *Tetrahedron* **2001**, *57*, 9423-9427.



Scheme IV-2. Categories of MIRC reations.

4.1.1. Cyclopropanation via "Type I" MIRC Reactions from Allylic Epoxides

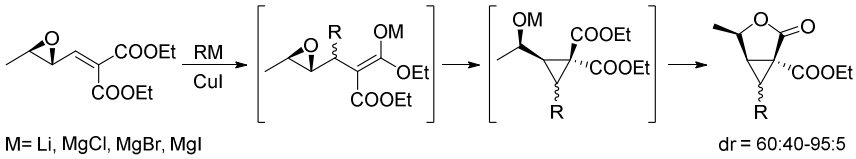
Different products can be obtained via Michael Initiated Ring Closure (MIRC) reaction, although cyclopropanes are the most representative group.[9] Amongst the wide range of suitable electrophiles to undergo this nucleophilic addition/ring-closing tandem process, in this chapter we will focus our attention on the use of allylic epoxides.

The synthesis of cyclopropane bearing lactones using a MIRC reaction was reported by Kasatkin.[10] Treatment of diethyl (2,3-epoxybutylidene)malonate with either a Grignard or an organolithium reagent in the presence of catalytic amounts of copper iodide led to cyclopropanation reaction through one pot conjugate addition-annulation-

[9] (a) Ratney, R. S.; English Jr, J. *J. Org. Chem.* **1960**, *25*, 2213-2215. (b) Kolsaker, P.; Storesund, H. J. *J. Chem. Soc., Chem. Commun.* **1972**, 375-375. (c) Torii, S.; Tanaka, H.; Nagai, Y. *Bull. Chem. Soc. Jpn* **1977**, *50*, 2825-2826. (d) Little, R. D.; Dawson, J. R. *J. Am. Chem. Soc.* **1978**, *100*, 4607- 4609. (e) Verhe, R.; De Kimpe, N.; De Buyck, L.; Courtheyn, D.; Schamp, N. *Synthesis* **1978**, 530-532. (f) Ghera, E.; Ben-David, Y. *Tetrahedron Lett.* **1979**, *47*, 4603-4606. (g) Joucla, M.; El Goumzili, M.; Fouchet, B. *Tetrahedron Lett.* **1986**, *27*, 1677-1680. (h) Cooke Jr, M. P.; Jaw, J. Y. *J. Org. Chem.* **1986**, *51*, 758-760. (i) Zindel, J.; Meijere, A. *Synthesis* **1994**, 190-194. (j) Funaki, I.; Roel, P. L. B.; Lambertus, T.; Zwanenburg, B. *Tetrahedron* **1996**, *52*, 12253-12274. (k) Toru, T.; Nakamura, S.; Takemoto, H.; Ueno, Y. *Synlett* **1997**, 449-450. (l) Norsikian, S.; Marek, I.; Klein, S.; Poisson, J. F.; Normant, J. F. *Chem. Eur. J.* **1999**, *5*, 2055-2068. (m) Majumdar, S.; de Meijere, A.; Marek, I. *Synlett* **2002**, 423-426. (n) Kurniawan, Y. D.; Hou, D. R. *J. Pure App. Chem. Res.* **2016**, 5, 9-18.

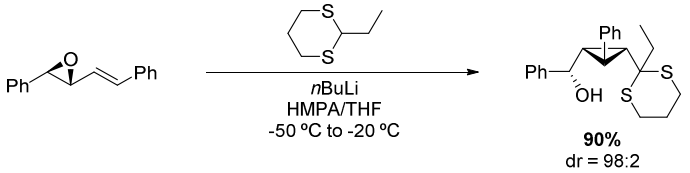
[10] Kasatkin, A. N.; Kulak, A. N.; Biktimirov, R. Kh.; Tolstikov, G. A. *Tetrahedron Lett.* **1990**, *31*, 4915-4916.

lactonization process (*Scheme IV-3*). The diastereoselectivities varied from moderate to good. Then, a quite similar strategy was used with dithianyllithium reagents as nucleophiles,[11] however no addition of copper was necesssary to undergo MIRC reaction.



Scheme IV-3. Synthesis of cyclopropane bearing lactones.

Moreover, in 2005 a method to synthesize 1,2,3-trisubstituted cyclopropanes with high diastereoselectivity was described using unactivated phenylvinyl epoxides as the Michael acceptors (*Scheme IV-4*).[12] This unexpected reaction allowed for the development of a highly diastereoselective process for the synthesis of cyclopropane derivatives with three contiguous stereocenters. A tandem conjugated addition and epoxide-opening sequence led to these interesting cyclopropyl moieties.

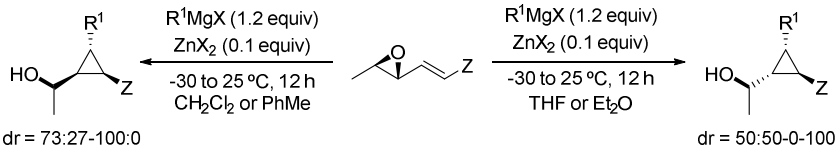


Scheme IV-4. MIRC reaction with dithianillithium derivatives and allylic epoxides.

Recently, the use of organozincates or Grignard reagents in the presence of zinc catalysts has been reported to undergo Michael initiated ring closure (MIRC) reaction with different activated substrates (*Scheme*

[11] Tang, S.; Xie, X.; Huo, X.; Liang, Q.; She, X.; Pan, X. *Tetrahedron Lett.* **2006**, *47*, 205-208.
[12] Xie, X.; Yue, G.; Tang, S.; Huo, X.; Liang, Q. She, X.; Pan, X. *Org. Lett.* **2005**, *7*, 4057-4059.

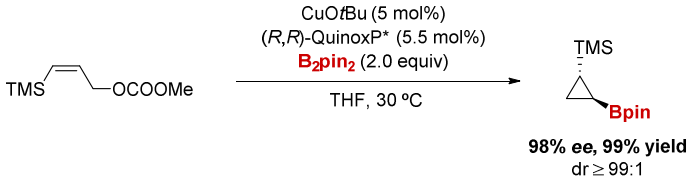
IV-5).[13] 1,2,3-Trisubstituted cyclopropanes can be easily prepared from γ,δ-epoxy-α,β-enoates, enones, enesulfones, and enamides. This reaction was diastereodivergent, as the formation of both diastereomers can be controlled just by changing the reaction solvent.



Scheme IV-5. Diastereoselective synthesis of 1,2,3-trisubstituted cyclopropanes.

4.1.2. Synthesis of Cyclopropylboronates via "Type I" MIRC Type Reactions

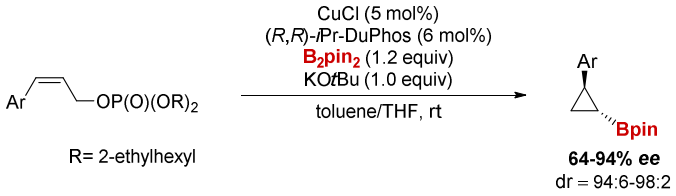
The synthesis of cyclopropylboronates from allylic carbonates was accomplished for the first time by Ito and Sawamura (*Scheme IV-6*).[14] This copper(I)-catalyzed borylation-cyclopropanation process took place with complete stereoselctivity. Primary allylic carbonates, with a silyl substituent on the double bond, underwent a regio- and enantioselective borylation followed by cyclization to give 1,2-disubstituted cyclopropane derivatives.



Scheme IV-6. Synthesis of enantioenriched boron-silicon cyclopropane derivatives.

[13] Dhakal, R. C.; Dieter, R. K. *J. Org. Chem.* **2013**, *78*, 12426-12439.
[14] Ito, H.; Kosaka, Y.; Nonoyama, K.; Sasaki, Y.; Sawamura, M. *Angew. Chem. Int. Ed.* **2008**, *47*, 7424 -7427.

Later, they developed a similar methodology to get aryl and heteroaryl substituted cyclopropylboronates (*Scheme IV-7*). This new asymmetric route used allylic phosphonates to afford optically active arylcyclopropane derivatives under mild conditions.[15]



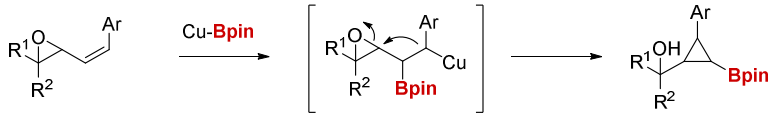
Scheme IV-7. Synthesis of enantioenriched cyclopropanes from allylic phosphates.

[15] Zhong, C.; Kunii, S.; Kosaka, Y.; Sawamura, M.; Ito, H. *J. Am. Chem. Soc.* **2010**, *132*, 11440-11442.

4.2. Synthesis of Cyclopropylboronates via MIRC Type Reaction

4.2.1. Introduction and Objectives

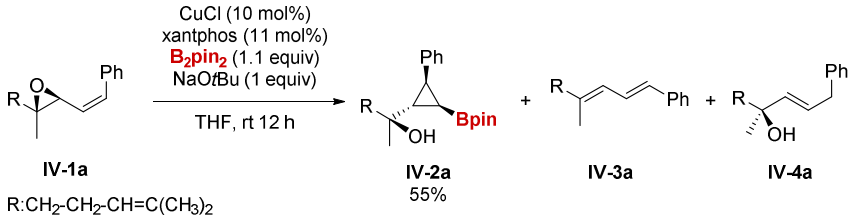
The only precedents for cyclopropylboronate formation using a MIRC reaction were reported by Ito with primary allylic carbonates and phosphonates. In that case, disubstituted cyclopropanes were obtained and the stereoselectivity was ligand-controlled. However, the use of boryl nucleophiles in MIRC reactions with allylic epoxides had not been studied before. Here, we were hoping to take advantage of the stereochemistry of the epoxide to control the diastereoselectivity of the process. We would access to trisubstituted functionalized cyclopropanes, with four contiguous stereocenters in a single synthetic step (*Scheme IV-8*).



Scheme IV-8. Proposed synthesis of cyclopropylboronates via MIRC reaction.

4.2.2. Screening of Conditions

We decided to start trying the conditions found for the copper-catalyzed formal reduction of allylic epoxides (chapter III) in the absence of a proton source to promote the cyclization. The first attempt was performed with enantioenriched epoxide **IV-1a** in the presence of 10 mol% copper chloride, 11 mol% of xantphos, 1 equivalent of sodium *tert*-butoxide and 1.1 equivalents of B_2pin_2 in THF (*Scheme IV-9*).

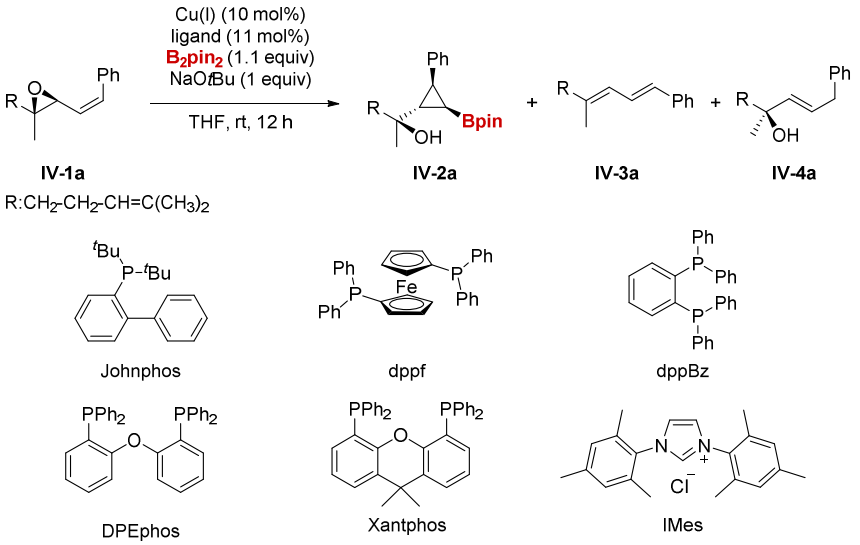


Scheme IV-9. First attempt to get cyclopropane derivatives.

A mixture of three different products was obtained in a ratio **IV2a**:**IV3a**:**IV4a** = 80:16:4 (*Scheme IV-9*). The major product was found to be cyclopropane **IV-2a**, which was formed as a single diastereomer. Diene **IV-3a** and allylic alcohol **IV-4a** were also observed in the ^{1}H-NMR.

To find the optimal conditions, we started testing different ligands, from simple monodentate phosphines (*entries2-4, Table IV-1*) to bulkier bidentate phosphines (*entries 5-8, Table IV-1*), including *N*-heterocyclic carbenes (*entry 8, Table IV-1*). Surprisingly, the cyclopropane formation was highly dependent on the ligand. Only DPEphos (*entry 7, Table IV-1*) and xantphos (*entry 1, Table IV-1*) afforded the cyclized product **IV-2a**. Most ligands gave diene **IV-3a** as major product and some mixtures of starting material and allylic alcohol **IV-4a**. When tetrakis(acetonitrile)copper(I) hexafluorophosphate was used as copper source (*entry 9, Table IV-1*), lower yield was observed.

Table IV-1. Screening of ligands and copper(I) sources.



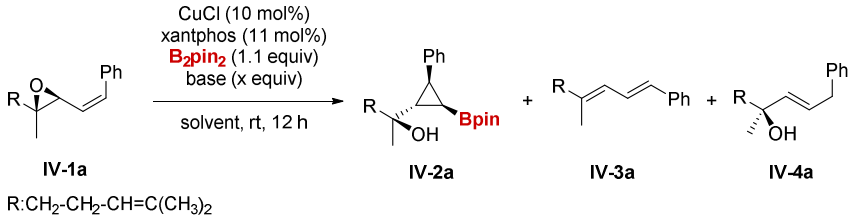
Entry[a]	Ligand	Copper source	Yield **IV-2a**[b]	Yield **IV-3a**[b]	Yield **IV-4a**[b]
1	***Xantphos***	***CuCl***	***77%***	***6%***	**-**
2	PPh_3	CuCl	-	25%	10%
3	PCy_3	CuCl	-	56%	8%
4	JohnPhos	CuCl	-	24%	12%
5	dppf	CuCl	-	85%	15%
6	dppBz	CuCl	4%	60%	-
7	DPEphos	CuCl	26%	30%	4%
8[c]	IMes	CuCl	-	30%	38%
9	Xantphos	$[Cu(CH_3CN)_4]PF_6$	39%	6%	6%

[a]Reaction conditions: **IV-1a** (0.2 mmol), B_2pin_2 (0.22 mmol), NaO*t*Bu (0.2 mmol), copper source (10 mol%), ligand (11 mol%), THF (0.2 M). [b]Determined by ^1H NMR analysis. [c]Excess of base (1.2 equiv) was needed to form the carbene *in situ* from the corresponding commercial salt.

Then, the use of different solvents was evaluated (*entries 1-5, Table IV-2*) and THF was the best choice. Moreover, different bases were tested (*entries 6-7, Table IV-2*) and the best results were obtained using

potassium *tert*-butoxide (*entry 5, Table IV-2*). Finally, we proved that one equivalent of base was required to shift the reaction towards cyclopropanation (*entries 7-9, Table IV-2*).

Table IV-2. Screening of solvents and bases.



Entry[a]	Solvent	Base (equiv)	Yield **IV-2a**[b]	Yield **IV-3a**[b]	Yield **IV-4a**[b]
1	THF	NaO*t*Bu (1)	77%	6%	-
2	CH_2Cl_2	NaO*t*Bu (1)	-	31%	17%
3	Toluene	NaO*t*Bu (1)	-	12%	9%
4	CH_3CN	NaO*t*Bu (1)	3%	2%	22%
5	Et_2O	NaO*t*Bu (1)	17%	9%	3%
6	THF	LiO*t*Bu (1)	33%	8%	-
7	***THF***	***KOtBu (1)***	***85%***	**-**	**-**
8	THF	KO*t*Bu (0.5)	29%	7%	**-**
9	THF	KO*t*Bu (0.2)	-	30%	37%

[a]Reaction conditions: **IV-1a** (0.2 mmol), B_2pin_2 (0.22 mmol), Base (x mmol), CuCl (10 mol%), Xantphos (11 mol%), solvent (0.2 M). [b]Determined by ^{1}H NMR analysis.

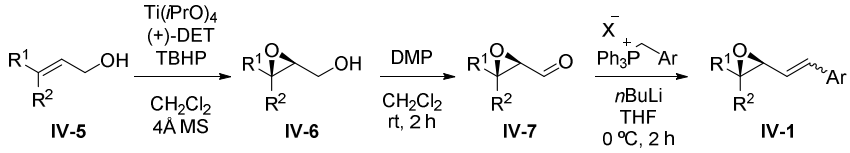
We observed that cyclopropylboronates **IV-2a** decomposed through column chromatography on silica gel. The ^{1}H NMR of the crude product was extremely clean but the best yield obtained was 62%. Therefore, we tried different purification techniques to get higher yields.

Flash column cromatography on alumina gave poor results, affording 56% yield. Then, silica deactivated with 10% of triethylamine was also used and 71% yield was obtained. Using silica deactivated with 30% of

water the yield was improved to 79%. Finally, filtration through florisil was found to be the most appropriate choice, obtaining 81% yield.

4.2.3. Scope of the Reaction

The starting materials to study the scope of the reaction were prepared following the same strategy used to synthesize the model substrate. First Sharpless epoxidation[16] allowed the synthesis of enantioenriched epoxyalcohols **IV-6** from allylic alcohols **IV-5**. Then, oxidation with Dess-Martin periodinane[17] afforded the corresponding aldehydes **IV-7**. Finally, Wittig olefination[18] provided the desired allylic epoxide **IV-1** (*Scheme IV-10*).



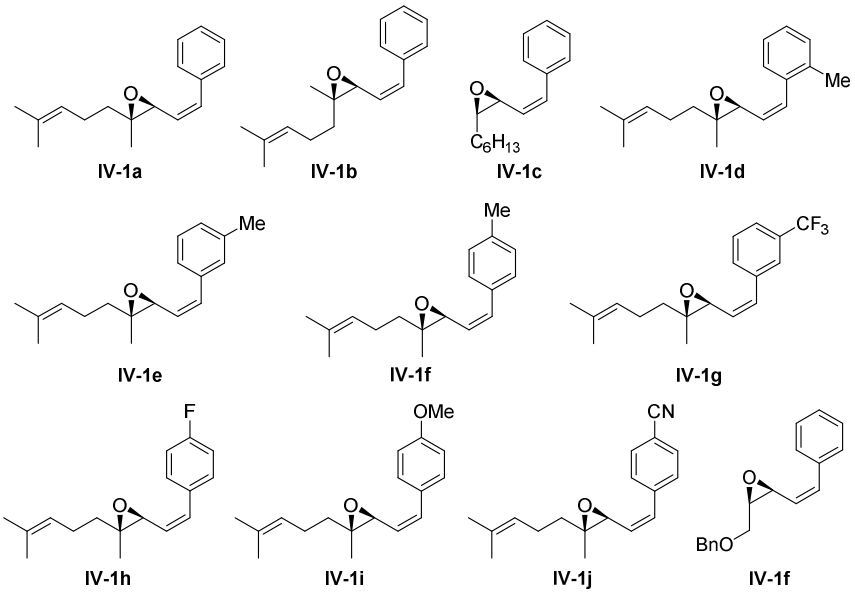
Scheme IV-10. Synthesis of Starting Materials.

Following this route epoxides **IV-1a-k** were prepared and tested in the cyclopropanation reaction (*Scheme IV-11*).

[16] (a) Katsuki, T.; Sharpless, K. B. *J. Am. Chem. Soc.* **1980**, *102*, 5974-5976. (b) Gao, Y.; Hanson, R. M.;Klunder, J. M.;Ko, S. Y.; Nasamune, H.; Sharpless, K. B. *J. Am. Chem. Soc.* **1987**, *109*, 5765-5780.

[17] (a) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155-4156. (b) Bratz, M.; Bullock, W. H.; Overman, L. E.; Takemoto,T. *J. Am. Chem. Soc.* **1995**, *117*, 5958-5966.

[18] Maercker, A. *Org. React.* **1965**, *14*, 270-490.



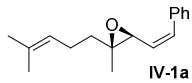
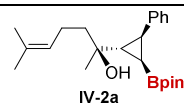
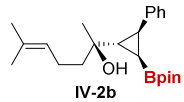
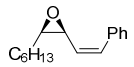
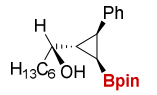
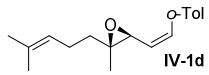
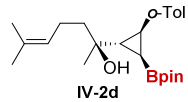
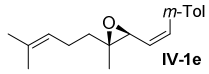
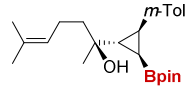
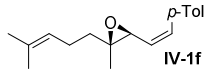
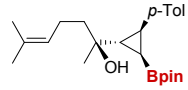
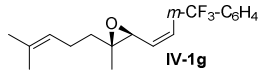
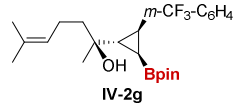
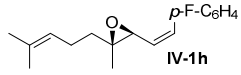
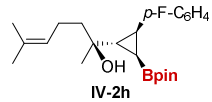
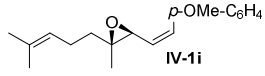
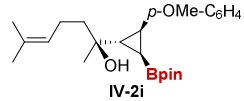
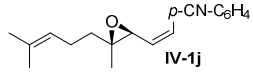
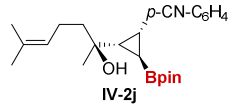
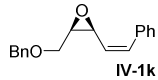
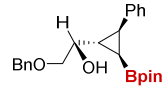
Scheme IV-11. Synthesized allylic epoxides **IV-1**.

Nerol derivative **IV-1b** and disubstituted epoxide **IV-1c** afforded cyclopropylboronates **IV-2b** and **IV-2c** in good yield as single diastereomers (*entries 1-3, Table IV-3*). Furthermore, different substituents on the aryl group were evaluated. Although, an *ortho*-methyl substituted phenyl ring resulted in moderate yields (*entry 4, Table IV-3*), *meta*- and *para*-methyl groups were well tolerated (*entries 5-6, Table IV-3*). The boracupration-cyclization sequence worked well with aryl groups bearing electron withdrawing (*entries 7-8, Table IV-3*) and electron donating groups (*entry 9, Table IV-3*).

Surprisingly, epoxide **IV-1j**, with a *para*-cyano group, afforded the diastereoisomer **IV-2j**, with the opposite stereochemistry at C2 on the cyclopropane ring (*entry 10, Table IV-3*). Although X-ray crystal structure confirmed the absolute configuration of **IV-2j**, first evidences were detected by ^{1}H-NMR when it was observed a clear change on the multiplicity of the proton at C3 position. Finally, vinyl epoxide **IV-1k**,

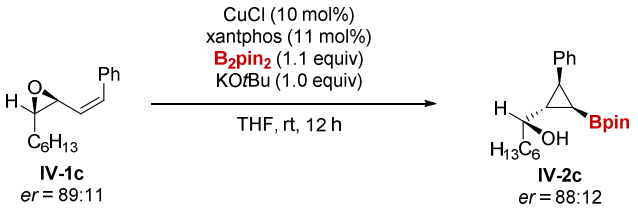
bearing a protected alcohol, afforded cyclopropylboronate **IV-2k** in moderate yield (*entry 11, Table IV-3*).

Table IV-3. Scope of vinyl epoxides.

Entry[a]	Vinyl epoxide	Cyclopropane	Yield(%)
1	 **IV-1a**	 **IV-2a**	81
2	 **IV-1b**	 **IV-2b**	67
3	 **IV-1c**	 **IV-2c**	91
4	 **IV-1d**	 **IV-2d**	43
5	 **IV-1e**	 **IV-2e**	92
6	 **IV-1f**	 **IV-2f**	82
7	 **IV-1g**	 **IV-2g**	88
8	 **IV-1h**	 **IV-2h**	94
9	 **IV-1i**	 **IV-2i**	54
10	 **IV-1j**	 **IV-2j**	76
11	 **IV-1k**	 **IV-2k**	39

[a]Reaction conditions: **IV-I** (0.2 mmol), B_2pin_2 (0.22 mmol), KO*t*Bu (0.2 mol), CuCl (10 mol%), xantphos (11 mol%), THF (0.2 M).

The enantiomeric ratio was measured for **IV-2c** to demonstrate that there is complete chirality transfer through the process (*Scheme IV-12*).



Scheme IV-12. Evaluation of the chirality transfer.

Moreover, the absolute configuration of cyclopropyl boronic esters **IV-2a** and **IV-2j** was determined by X-ray crystal structure (*Figure IV-1*).

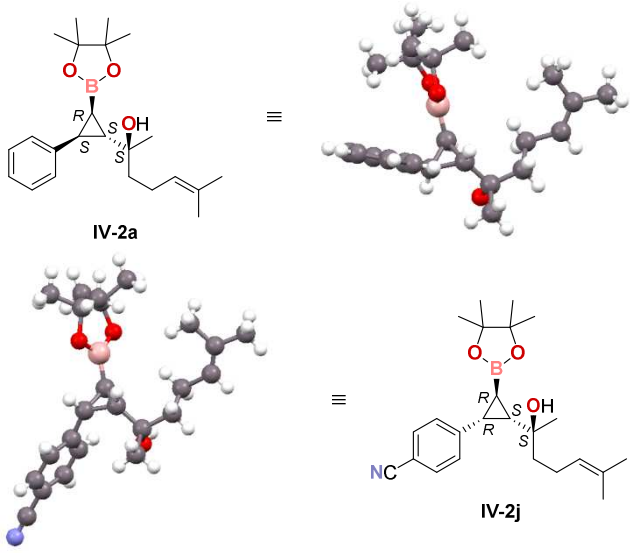
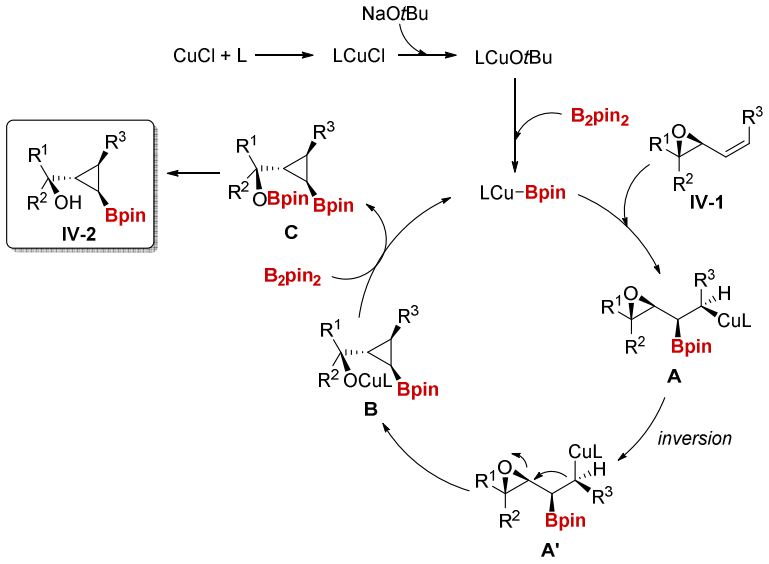


Figure IV-1. Absolute configuration

4.2.4. Mechanistic Proposal

We propose the following catalytic cycle for the formation of cyclopropylboronates via MIRC type reaction (*Scheme IV-13*). Reaction between copper chloride, the ligand and potassium *tert*-butoxide affords a copper alkoxide. This complex undergoes a σ-bond metathesis reaction in the presence of B_2pin_2 to form the catalytically active species. Insertion of the alkene moiety from vinyl oxirane **IV-1** into the Cu-B bond would afford an alkyl copper intermediate **A** that could undergo intramolecular substitution to give cyclopropyl boronic ester **B**. The copper alkoxide moiety in **B**, could react with another molecule of B_2pin_2 to regenerate the catalytic cycle releasing **C**. Then, after work-up, the desired cyclopropylboronate **IV-2** would be obtained. Considering the configuration of the carbon attached to the boryl moiety in the final products, the stereochemical pathway for the insertion must be *syn* relative to the epoxide. For most of the studied examples, the intramolecular substitution proceeded with inversion of the stereochemistry to give a *cis* orientation between the aryl group and the Bpin. The relatively low configurational stability of the copper carbon stereocenter allows this inversion. With a cyano substituent in the *para* positions of the aromatic ring, the substitution reaction took place with retention of the stereochemistry to give the *trans* diastereomer. We still do not have a clear answer to this behavior. The detailed rationale for these differences requires further mechanistic studies.



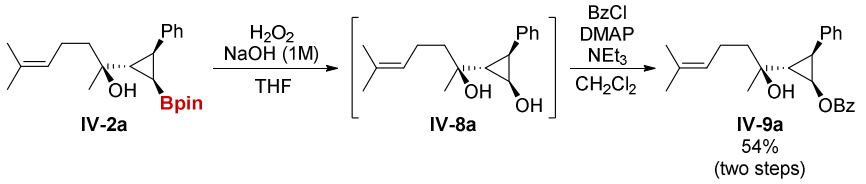
Scheme IV-13. Proposed mechanism for the synthesis of cyclopropylboronates.

4.2.5. Functionalization of the C-B Bond

To demonstrate the versatility of the Bpin group, we studied different functionalizations of the C-B bond.

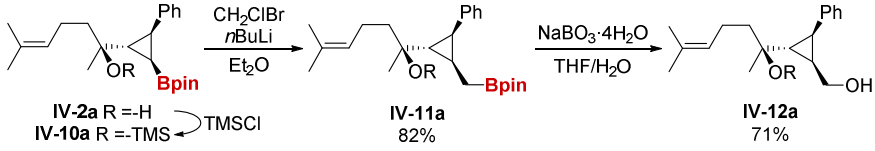
The oxidation-benzoylation sequence was performed in 54% yield for two steps (*Scheme IV-14*). First, oxidation[19] of cyclopropylboronate **IV-2a** with hydrogen peroxide and sodium hydroxide was found to be quantitative and alcohol **IV-8a** was used without further purification in the presence of benzoyl chloride to afford the corresponding benzoate **IV-9a**.[20]

[19] Liskey, C. W.; Hartwig, J. F. *J. Am. Chem. Soc.* **2013**, *135*, 3375-3378.
[20] Parra, A.; Amenós, L.; Guisán-Ceinos, M.; López, A.; Garcia Ruano, J. L.; Tortosa, M. *J. Am. Chem. Soc.* **2014**, *136*, 15833-15836.



Scheme IV-14. Oxidation-benzoylation sequence.

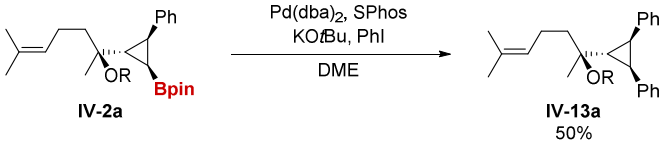
To explore the Matesson homologation of the C-B bond, we first protected the free alcohol in **IV-2a** with a trimethylsilyl group. Treatment of cyclopropane **IV-2a** with trimethylsilyl chloride afforded trimethylsilyl ether **IV-10a** (*Scheme IV-15*).[21] Then, homologation to add one more carbon was successfully achieved with bromochloromethane in the presence of butyllithium, obtaining **IV-11a**.[22] Additionally, the resulting product **IV-11a** could be easily oxidized under mild conditions to afford diol **IV-12a**.[20]



Scheme IV-15. Protection-homologation-oxidation sequence.

Finally, the palladium-catalyzed Suzuki-Miyaura cross-coupling with phenyl iodide afforded diphenyl substituted cyclopropane **IV-13a** in moderate yield (*Scheme IV-16*).[20]

[21] Rüedi, G.; Nagel, M.; Hansen, H. J. *Org. Lett.* **2004**, *6*, 2989-2991.
[22] Jarava-Barrera, C.; Parra, A.; López, A.; Cruz-Acosta, F.; Collado-Sanz, D.; Cárdenas, D. J.; Tortosa, M. *ACS Catal.* **2016**, *6*, 442-446.



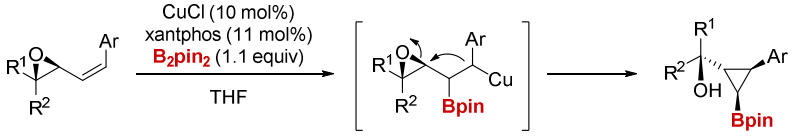
Scheme IV-16. Suzuki-Miyaura cross-coupling reaction.

4.2.6. Conclusions

We have developed a new route to synthesize cyclopropyl boronic esters via MIRC (Michael Initiated Ring Closure) type reaction from simple vinyl epoxides (*Scheme IV-17*).

First, copper(I)-catalyzed borylation reaction takes place on the alkene moiety, affording an alkyl copper intermediate that undergoes spontaneous cyclization to produce cyclopropylboronates with excellent diastereoselectivity in high yields. The products are highly functionalized cyclopropanes with four contiguous stereocenters, difficult to prepare by known methods.

Moreover, the functionalization of the C-B bond through oxidation, homologation and Suzuki cross-coupling allowed access to highly functionalized 3-membered rings.



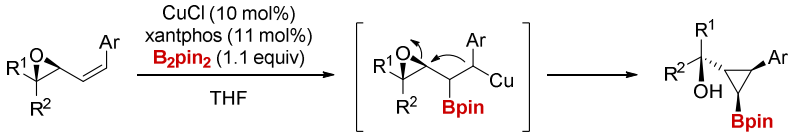
Scheme IV-17. Synthesis of cyclopropylboronates via MIRC reaction.

4.2.7. Conclusiones

En este capítulo hemos conseguido desarrollar una nueva ruta para sintetizar ciclopropilboronatos a partir de vinil oxiranos, a través de una reacción de cierre de anillo tipo MIRC (Michael Initiated Ring Closure).

Primero tiene lugar la reacción de borilación catalizada por cobre en el doble enlace del epóxido alílico, produciendo así un intermedio alquil-cobre (*Esquema IV-18*). Este intermedio reacciona de manera espontáneaa través de una reacción de sustitución intramolecular para dar los correspondientes ésteres borónicos con rendimientos elevados y excelente diastereoselectividad. Los productos son ciclopropilboronatos, con cuatro centros estereogénicos contiguos, díficiles de preparar mediante otros métodos.

Además, la funcionalización del enlace C-B mediante oxidación, homologación o acoplamiento de Suzuki, permite la preparación de diferentes ciclopropanos altamente funcionalizados.



Esquema IV-18. Síntesis de ciclopropilboronatos a través de una reacción tipo MIRC.

4.3. Supplementary data

4.3.1. General Experimental Details

Tetrahydrofuran, toluene, acetonitrile and dichloromethane were purified by passing through a Pure Solv™ column drying system from Innovative Technology, Inc. Additionally, THF was degassed through three consecutive freeze-pump-thaw cycles. Diethyl ether was dried using activated 4Å molecular sieves and stored under argon. All borylation reactions were set up in the glove box Inert PURELAB PL-HE-2GB. The rest of reactions that required inert atmosphere were conducted under an argon using flame-dried glassware with standard vacuum-line techniques.

NMR spectra were acquired on a Bruker 300 spectrometer, running at 300, and 75 MHz for ^{1}H and ^{13}C, respectively. Chemical shifts (δ) are reported in ppm relative to residual solvent signals ($CDCl_3$, 7.26 ppm for ^{1}H NMR and 77.16 ppm for ^{13}C NMR respectively). ^{13}C NMR spectra were acquired on a broad band decoupled mode. The following abbreviations are used to describe peak patterns when appropriate: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), br (broad). Analytical thin layer chromatography (TLC) was performed using pre-coated aluminium-backed plates (Merck Kieselgel 60 F254) and visualized by ultraviolet irradiation or phosphomolybdic acid dip. Purification of reaction mixtures was carried out by flash chromatography (FC) using silica gel Merck-60 or Florisil® 100-200 mesh from Aldrich. Optical rotations were measured on a Perkin-Elmer 241 polarimeter. Mass Spectrometry (MS) and High Resolution Mass Spectrometry (HRMS) were registered in a spectrometer *GCT Agilent Technologies 6890 N*using Electronic Impact (EI^+) techniques at 70 eV and electrospray (ESI^+).

All ligands, $[Cu(CH_3CN)_4]PF_6$, Li*O*t*Bu*, Na*O*t*Bu* and K*O*t*Bu* were acquired from comercial sources and were used without further purification.

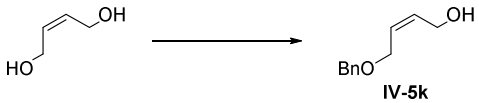
(+)-Diethyl tartrate (DET) and titanium tetraisopropoxide were freshly distilled before used at Sharpless epoxidation. Dess-Martin periodinane[17] was synthesized following reported procedures.

CuCl was washed with acetic acid, filtered and washed with ethanol and diethyl ether twice and dried under vacuum before used.[23] Bis(pinacolato)diboron was recrystrallized in *n*-pentane before used.

Compounds **IV-6a** (**III-2a**), **IV-6b** (**III-2b**), **IV-6c** (**III-2c**), **IV-7a** (**III-3a**), **IV-7b** (**III-3b**), **IV-7c** (**III-3c**), **IV-1a** (**III-1h**) and **IV-1c** (**III-1n**) have been reported in the previous chapter. Their identification number in chapter III is indicated within brackets.

4.3.2. Synthesis of Starting Materials

4.3.2.1. Synthesis of (*Z*)-4-(benzyloxy)but-2-en-1-ol, **IV-5k**



IV-5k

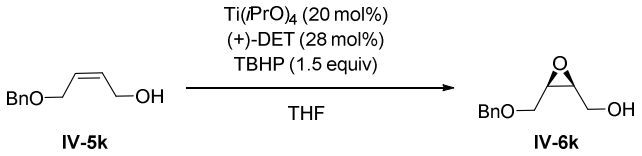
To a stirred solution of cis-2-butene-1,4-diol (3.0 g, 34.0 mmol) in THF (12 mL) was added sodium hydride (60% in mineral oil, 964.9 mg, 16.0 mmol) at 0 °C. After being stirred for 30 min at room temperature, benzyl bromide (1.4 mL, 16.0 mmol) was added, and the resulting mixture was stirred at reflux for 1 h. The reaction mixture was diluted at room temperature by the addition of saturated aqueous NH_4Cl solution at 0 °C. Water was added until the white solid was dissolved. The layers were separated, and the aqueous phase was extracted with CH_2Cl_2 (x3). The

[23] Perrin, D. D. Armarego, W. L. *Purification of Laboratory Chemicals,* 3rd Ed.; Pergamon Press: Oxford, 1988.

combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (10% to 50% EtOAc/cyclohexane) to afford alcohol **IV-5k** (5.1 g, 26.6 mmol) in 34% yield.

The spectral data for **IV-5k** matched those previously reported for this compound.[24] **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.32-7.18 (m, 5H), 5.84-5.59 (m, 2H), 4.45 (s, 2H), 4.09 (d, *J* = 5.8 Hz, 2H), 4.01 (d, *J* = 6.1 Hz, 2H).

4.3.2.2. Synthesis of {(2*S*,3*R*)-3-[(benzyloxy)methyl]oxiran-2-yl}methanol, (*S*,*R*)-**IV-6k**



IV-5k **IV-6k**

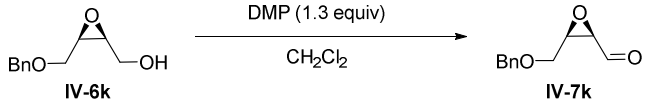
An oven dried flask equipped with a magnetic stirbar, was charged with 4Å powdered activated molecular sieves (28 mg/mmol **IV-5k**) and dry CH_2Cl_2 (0.6 mL/mmol **IV-5k**). The flask was cooled to -20 ºC. L-(+)-Diethyl tartrate (28 mol%) and Ti(*i*PrO)$_4$, (20 mol%, via syringe) were added sequentially. The reaction mixture was stirred at -20 ºC while TBHP (1.5 equiv, 5.5 in decanes) was added dropwise. The resulting mixture was stirred at -20 ºC for 30 min. Alcohol **IV-5k** (3.46 g, 19.4 mmol, 1 equiv), dissolved in dry CH_2Cl_2 (0.15 mL/mmol **IV-5k**), was then added dropwise. The mixture was stirred for an additional 24 h at -20 ºC. After the reaction mixture is warmed to 0 ºC, water was added and the mixture is stirred for 30min, while allowing it to warm to room temperature. Then, 30% aqueous solution of NaOH was added and stirring vigorously for 20 min. The resulting solution was transferred to a separatory funnel and extracted with CH_2Cl_2 (x3), the combined organic

[24] Becker, J.; Butt, L.; von Kiedrowski, V.; Mischler, E.; Quentin, F.; Hiersemann, M. *J. Org. Chem.* **2014**, *79*, 3040-3051.

layers were washed with brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by flash column chromatography on silica gel to achieve compound (*S*,*R*)-**IV-6k** (2.45 g, 12.6 mmol) was obtained in 65 % yield (*er* = 89:11). The enantiomeric ratio of the product was determined to be 89:11 by ^{1}H NMR analysis of its methoxy phenyl acetate, prepared by reaction of (-)-methoxyphenyl acid and DCC in DCM.[25]

The spectral data for (*S*,*R*)-**IV-6k** matched those previously reported for this compound.[26] **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.35-7.21 (m, 5H), 4.55 (d, *J* = 11.8 Hz, 1H), 4.46 (d, *J* = 11.8 Hz, 1H), 3.73-3.58 (m, 4H), 3.27-3.19 (m, 1H), 3.18-3.09 (m, 1H).

4.3.2.3. Synthesis of (2*R*,3*R*)-3-[(benzyloxy)methyl]oxirane-2-carbaldehyde, (*R*,*R*)-**IV-7k**



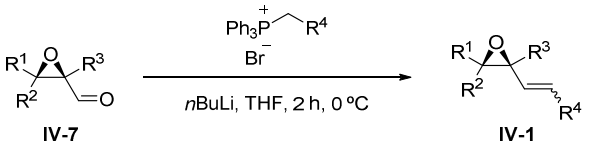
IV-6k **IV-7k**

The Dess-Martin periodinane (1.3 equiv) was added to a stirring solution of epoxy alcohol (*S*,*R*)-**IV-6k** (1.75 g, 9.0 mmol, 1 equiv) in CH_2Cl_2 (10 mL/1 mmol) at 0 ºC. Then the reaction mixture was stirred at room temperature for 1h. Finally, the reaction was quenched by cooling the solution to 0 ºC followed by addition of hexanes. The resulting solution was filtered through florisil (eluting with a solvent mixture 1:1 Et_2O/cyclohexane) and compound (*R*,*R*)-**IV-7k** (1.46 g, 7.6 mmol) was obtained in 84 % yield.

[25] (a) Latypov, s. K.; Seco, J. M.; Quiñoá, E.; Riguera R. *J. Org. Chem.* **1996**, *61*, 8569-8577. (b) Seco, J. M.; Quiñoá, E.; Riguera R. *Chem. Rev.* **2004**, *104*, 17-118.
[26] Okado, Y.; Shigetomi, K.; Mitsuhashi, S.; Ubukata, M. *J. Antibiot.* **2015**, *68*, 721-724.

The spectral data for (*R*,*R*)-**IV-7k** matched those previously reported for this compound.[27] **^{1}H NMR** (300 MHz, $CDCl_3$): δ 9.46 (d, *J* = 4.6 Hz, 1H), 7.46-7.24 (m, 5H), 4.58 (s, 2H), 3.91-3.74 (m, 2H), 3.58-3.50 (m, 1H), 3.49-3.40 (m, 1H).

4.3.2.4. General Procedure for the Synthesis of Vinyl Epoxides via Wittig Olefination, **IV-1**

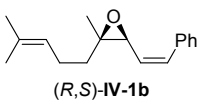


IV-7 **IV-1**

Under argon atmosphere, to a suspension of phosphonium salt (1.72 equiv) in anhydrous THF (16 mL/mmol of **IV-7**) was added *n*-BuLi (1.6M, 1.3 equiv) dropwise at -50 ºC. The resulting mixture was maintained at -50ºC for 30 min and then cooled to -78 ºC. A solution of epoxy aldehyde **IV-7** (1 equiv) in anhydrous THF (2 mL/mmol of **IV-7**) was then added dropwise. The resulting solution was maintained at 0 ºC for 2h and then diluted with hexane, washed with brine, dried over Na_2SO_4 and concentrated. The residue was purified by flash column chromatography on silica gel (5% EtOAc/Cyclohexane) to afford the desired product **IV-1**.

[27] Ley, S. V.; Tackett, M. N.; Maddess, M. L.; Anderson, J. C.; Brennan, P. E.; Cappi, M. W.; Heer, J. P.; Helgen, C.; Kori, M.; Kouklovsky, C.; Marsden, S. P.; Norman, J.; Osborn, D. P.; Palomero, M.; Pavey, J. B. J.; Pinel, C.; Robinson, L- A.; Schnaubelt, J.; Scott, J. S.; Spilling, C. D.; Watanabe, H.; Wesson, K. E.; Willis, M. C. *Chem. Eur. J.* **2009**, *15*, 2874-2914.

(2*R*,3*S*)-2-methyl-2-(4-methylpent-3-en-1-yl)-3-[(*Z*)-styryl]oxirane, (*R*,*S*)-**IV-1b**

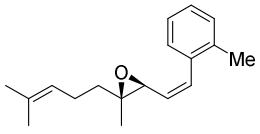


(*R*,*S*)-**IV-1b**

From aldehyde (*R*,*R*)-**IV-7b** (501.8 mg, 2.98 mmol, 1 equiv) and benzyltriphenylphosphonium bromide (2.22 g, 5.13 mmol, 1.72 equiv) following the general procedure described above, compound (*R*,*S*)-**IV-1b** (333.4 mg, 1.38 mmol) was obtained in 46 % yield, as a yellow oil. $\mathbf{R}_f$ = 0.85 (20% EtOAc/Cyclohexane).

^{1}H NMR (300 MHz, $CDCl_3$): 7.34-7.13 (m, 5H), 6.64 (d, *J* = 11.9 Hz, 1H), 5.51 (dd, *J* = 11.9, 7.5 Hz, 1H), 5.11-4.97 (m, 1H), 3.46 (d, *J* = 7.5 Hz, 1H), 2.15-1.98 (m, 2H), 1.56 (s, 3H), 1.70-1.40 (m, 2H), 1.51 (s, 3H), 1.32 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 136.6, 134.3, 132.1, 128.9, 128.4, 127.7, 127.6, 123.7, 63.3, 61.5, 34.1, 25.8, 24.3, 21.8, 17.7. **HRMS (ESI$^+$)**: calculated for $C_{17}H_{22}ONa$ $[M+Na]^+$: 265.1562; found: 265.1560. **[α]$^{20}_D$**= +238.7 (*c*= 1.0, $CHCl_3$).

(2*S*,3*S*)-2-methyl-2-(4-methylpent-3-en-1-yl)-3-[(*Z*)-2 methylstyryl]oxirane, (*S*,*S*)-**IV-1d**



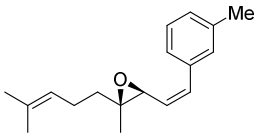
(*S*,*S*)-**IV-1d**

From aldehyde (*R*,*S*)-**IV-7a** (800 mg, 4.8 mmol, 1equiv) and (2-methylbenzyl) (triphenyl)phosphonium bromide (3.29 g, 8.18 mmol, 1.72 equiv) following the general procedure described above, compound (*S*,*S*)-**IV-1d** (729.6 mg, 2.9 mmol) was obtained in 60 % yield, as a yellow oil. $\mathbf{R}_f$ = 0.75 (20% EtOAc/Cyclohexane).

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.37-7.18 (m, 4H), 6.90 (d, *J* = 11.7 Hz, 1H), 5.68 (dd, *J* = 11.7, 8.0 Hz, 1H), 5.22-5.11 (m, 1H), 3.48 (t, *J* = 8.0 Hz, 1H), 2.38 (s, 3H), 2.17 (q, *J* = 7.7 Hz, 2H), 1.75 (s, 3H), 1.68 (s, 3H), 1.73-1.52 (m, 2H), 1.45 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 136.2, 135.4, 133.8, 131.7, 129.9, 129.1, 127.7, 127.7, 125.4, 123.6, 62.7, 59.9,

38.4, 25.6, 23.6, 19.8, 17.5, 17.3. **HRMS (EI$^+$)**: calculated for $C_{18}H_{24}O$ $[M]^+$: 256.1827; found: 256.1821. **[α]$^{20}_D$**= +187.4 (*c*= 1.0, $CHCl_3$).

(2*S*,3*S*)-2-methyl-2-(4-methylpent-3-en-1-yl)-3-[(*Z*)-3-methylstyryl]oxirane, (*S*,*S*)-**IV-1e**

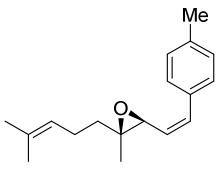


(*S*,*S*)-**IV-1e**

From aldehyde (*R*,*S*)-**IV-7a** (800 mg, 4.8 mmol, 1 equiv) and (3-methylbenzyl) (triphenyl)phosphonium bromide (3.29 g, 8.18 mmol, 1.72 equiv) following the general procedure described above, compound (*S*,*S*)-**IV-1e** (256.2 mg, 1.0 mmol) was obtained in 21 % yield, as a yellow oil. $\mathbf{R}_f$ = 0.75 (20% EtOAc/Cyclohexane).

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.41-7.05 (m, 4H), 6.77 (d, *J* = 11.9 Hz, 1H), 5.59 (dd, *J* = 11.9, 7.5 Hz, 1H), 5.20-5.13 (m, 1H), 3.63 (dd, *J* = 7.5, 1.0 Hz, 1H), 2.40 (s, 3H), 2.24-2.13 (m, 2H), 1.72 (s, 3H), 1.79-1.61 (m, 2H), 1.66 (s, 3H), 1.39 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 138.0, 136.6, 134.7, 132.2, 129.7, 128.4, 128.3, 127.6, 126.0, 123.7, 63.1, 60.4, 38.4, 25.8, 23.8, 21.6, 17.8, 17.6. **HRMS (EI$^+$)**: calculated for $C_{18}H_{24}O$ $[M]^+$: 256.1827; found: 256.1822. **[α]$^{20}_D$**= +186.4 (*c*= 1.0, $CHCl_3$).

(2*S*,3*S*)-2-methyl-2-(4-methylpent-3-en-1-yl)-3-[(*Z*)-4-methylstyryl]oxirane, (*S*,*S*)-**IV-1f**



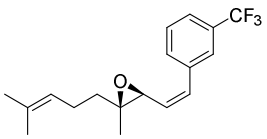
(*S*,*S*)-**IV-1f**

From aldehyde (*R*,*S*)-**IV-7a** (319.6 mg, 1.9 mmol, 1 equiv) and (4-methylbenzyl) (triphenyl)phosphonium bromide (1.48 g, 3.3 mmol, 1.72 equiv) following the general procedure described above, compound (*S*,*S*)-**IV-1f** (279.8 mg, 1.1 mmol) was obtained in 58 % yield, as a yellow oil. $\mathbf{R}_f$ = 0.75 (20% EtOAc/Cyclohexane).

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.20-7.06 (m, 4H), 6.64 (d, *J* = 11.9 Hz, 1H), 5.44 (dd, *J* = 11.9, 7.5 Hz, 1H), 5.05 (t, *J* = 7.1 Hz, 1H), 3.51 (d, *J* =

7.5 Hz, 1H), 2.28 (s, 3H), 2.12-2.01 (m, 2H), 1.61 (s, 3H), 1.67-1.50 (m, 2H), 1.55 (s, 3H), 1.27 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 137.5, 134.6, 133.8, 132.2, 129.2, 128.9, 126.9, 123.8, 63.2, 60.5, 38.5, 25.8, 23.8, 21.4, 17.8, 17.6. **HRMS (EI$^+$)**: calculated for $C_{18}H_{24}O$ $[M]^+$: 256.1827; found: 256.1832. **[α]$^{20}_D$**= +151.0 (*c*= 1.1, $CHCl_3$).

(2*S*,3*S*)-2-methyl-2-(4-methylpent-3-en-1-yl)-3-[(*Z*)-3-(trifluoromethyl)styryl]oxirane, (*S*,*S*)-**IV-1g**

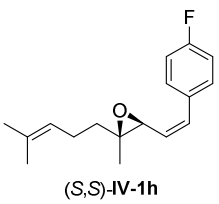


(S,S)-**IV-1g**

From aldehyde (*R*,*S*)-**IV-7a** (300 mg, 1.78 mmol, 1 equiv) and [3-(trifluoromethyl)benzyl] triphenylphosphonium bromide (1.4 g, 3.1 mmol, 1.72 equiv) following the general procedure described above, compound (*S*,*S*)-**IV-1g** (184.8 mg, 0.6 mmol) was obtained in 33 % yield, as a yellow oil. R_f = 0.7 (20% EtOAc/Cyclohexane).

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.65-7.43 (m, 4H), 6.75 (d, *J* = 11.8 Hz, 1H), 5.69 (dd, *J* = 11.8, 7.4 Hz, 1H), 5.19-5.05 (m, 1H), 3.51 (dd, *J* = 7.4, 1.1 Hz, 1H), 2.21-2.06 (m, 2H), 1.75-1.56 (m, 2H), 1.67 (s, 3H), 1.61 (s, 3H), 1.35 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 137.3, 133.0, 132.3, 132.0, 131.0 (q, J_{CF} = 32.3 Hz), 129.7, 128.9, 125.5 (q, J_{CF} = 3.8 Hz), 124.3 (q, J_{CF} = 3.7 Hz), 124.2 (q, J_{CF} = 272.4 Hz), 123.5, 63.3, 59.8, 38.1, 25.7, 23.6, 17.7, 17.6. **^{19}F NMR** (282 MHz, $CDCl_3$): δ -62.76. **HRMS (EI$^+$)**: calculated for $C_{18}H_{21}OF_3$ $[M]^+$: 310.1545; found: 310.1540. **[α]$^{20}_D$**= +159.4 (*c*= 1.0, $CHCl_3$).

(2*S*,3*S*)-3-[(*Z*)-4-fluorostyryl]-2-methyl-2-(4-methylpent-3-en-1-yl)oxirane, (*S*,*S*)-**IV-1h**

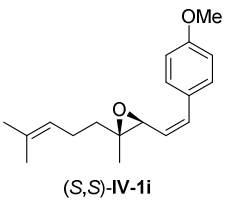


(*S*,*S*)-**IV-1h**

From aldehyde (*R*,*S*)-**IV-7a** (200 mg, 1.2 mmol, 1 equiv) and (4-fluorobenzyl) (triphenylphosphonium bromide (854.5 mg, 2.1 mmol, 1.72 equiv) following the general procedure described above, compound (*S*,*S*)-**IV-1h** (197.3 mg, 0.76 mmol) was obtained in 64 % yield, as a yellow oil. $\mathbf{R}_f$ = 0.75 (20% EtOAc/Cyclohexane).

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.31-7.16 (m, 2H), 7.03-6.91 (m, 2H), 6.63 (d, *J* = 11.9 Hz, 1H), 5.48 (dd, *J* = 11.9, 7.5 Hz, 1H), 5.10-4.98 (m, 1H), 3.44 (d, *J* = 7.5 Hz, 1H), 2.05 (dd, *J* = 15.2, 7.6 Hz, 2H), 1.60 (s, 3H), 1.70-1.45 (m, 2H), 1.54 (s, 3H), 1.26 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 162.2 (d, J_{CF} = 247.4 Hz), 133.7, 132.7 (d, J_{CF} = 3.4 Hz), 130.6 (d, J_{CF} = 8.0 Hz), 127.5 (d, J_{CF} = 1.3 Hz), 132.3, 123.6, 115.4 (d, J_{CF} = 21.5 Hz), 63.2, 60.1, 38.4, 25.8, 23.8, 17.8, 17.6. **^{19}F NMR** (282 MHz, $CDCl_3$): δ -114.11. **HRMS (ESI$^+$)**: calculated for $C_{17}H_{21}FONa$ $[M+Na]^+$: 283.1468; found: 283.1466. **$[\alpha]^{20}_D$**= +146.1 (*c*= 1.0, $CHCl_3$).

(2*S*,3*S*)-3-[(*Z*)-4-methoxystyryl]-2-methyl-2-(4-methylpent-3-en-1-yl)oxirane, (*S*,*S*)-**IV-1i**



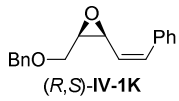
(*S*,*S*)-**IV-1i**

From aldehyde (*R*,*S*)-**IV-7a** (300 mg, 1.78 mmol, 1 equiv) and (4-methoxylbenzyl) (triphenylphosphonium bromide (1.28 g, 3.1 mmol, 1.72 equiv) following the general procedure described above, compound (*S*,*S*)-**IV-1i** (201.7 mg, 0.74 mmol) was obtained in 42 % yield, as a yellow oil. $\mathbf{R}_f$ = 0.55 (20% EtOAc/Cyclohexane).

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.20 (d, *J* = 9.0 Hz, 2H), 6.81 (d, *J* = 9.0 Hz, 2H), 6.60 (d, *J* = 11.8 Hz, 1H), 5.40 (dd, *J* = 11.8, 7.4 Hz, 1H), 5.09-5.01 (m, 1H), 3.74 (s, 3H), 3.50 (dd, *J* = 7.4, 1.0 Hz, 1H), 2.07 (dd, *J* =

15.5, 7.6 Hz, 2H), 1.61 (s, 3H), 1.66-1.50 (m, 2H), 1.55 (s, 3H), 1.26 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 159.2, 134.2, 132.2, 130.2, 129.4, 125.8, 123.8, 113.9, 63.2, 60.5, 55.4, 38.5, 25.8, 23.8, 17.8, 17.6. **HRMS (EI$^+$)**: calculated for $C_{18}H_{24}O_2$ $[M]^+$: 272.1776; found: 272.1765. **[α]$^{20}_D$**= +126.7 (*c*= 1.1, $CHCl_3$).

(2*R*,3*S*)-2-[(benzyloxy)methyl]-3-[(*Z*)-styryl]oxirane, (*R*,*S*)-**IV-1k**

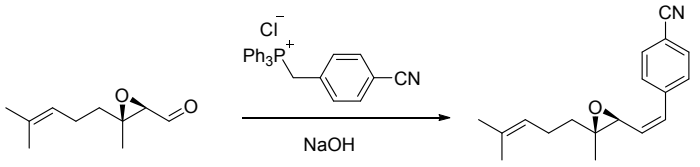


(*R*,*S*)-**IV-1K**

From aldehyde (*R*,*R*)-**IV-7k** (1.46 g, 7.6 mmol, 1 equiv) and benzyltriphenylphosphonium bromide (5.65 g, 13.1 mmol, 1.72 equiv) following the general procedure described above, compound (*R*,*S*)-**IV-1k** (829.9 mg, 3.12 mmol) was obtained in 41 % yield, as a pale yellow oil. $\mathbf{R}_f$ = 0.2 (5% EtOAc/Cyclohexane).

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.44-7.29 (m, 10H), 6.80 (dd, *J* = 11.8, 1.2 Hz, 1H), 5.55 (dd, *J* = 11.8, 7.7 Hz, 1H), 4.69 (d, *J* = 11.9 Hz, 1H), 4.59 (d, *J* = 11.9 Hz, 1H), 3.89 (ddd, *J* = 7.7, 4.3, 1.2 Hz, 1H), 3.79 (dd, *J* = 11.2, 4.3 Hz, 1H), 3.67 (dd, *J* = 11.2, 6.3 Hz, 1H), 3.55-3.47 (m, 1H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 137.8, 136.1, 135.7, 128.9, 128.8 128.5, 128.4, 127.9, 127.8, 125.6, 73.4, 68.7, 57.6, 53.0. **HRMS (ESI$^+$)**: calculated for $C_{18}H_{18}O_2Na$ $[M+Na]^+$: 289.1199; found: 289.1193. **[α]$^{20}_D$**= +59.4 (*c*= 1.0, $CHCl_3$).

4.3.2.5. Synthesis of 4-{(*Z*)-2-[(2*S*,3*S*)-3-methyl-3-(4-methylpent-3-en-1-yl)oxiran-2-yl]vinyl}benzonitrile, (*S*,*S*)-**IV-1j**

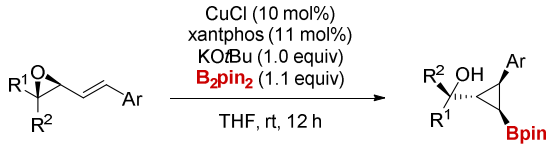


(*R*,*S*)-**IV-7a** (*S*,*S*)-**IV-1j**

A mixture of (4-cyanobenzyl)triphenylphosphonium chloride (811 mg, 1.96 mmol, 1.1 equiv) and aldehyde (*R*,*S*)-**IV-7a** (300 mg, 1.78 mmol, 1 equiv) in 3.5 mL of $CHCl_3$ was stirred vigorously 0 ºC. To this suspension, 1.15 mL of NaOH (50% aqueous solution) was added dropwise very slowly. After stirring vigorously for 1h at room temperature, the mixture was washed with three portions of water. The organic layer was dried over $MgSO_4$ and the solvent was removed. The residue was purified by flash column chromatography on silica gel (eluent 10% to 20% EtOAc/cyclohexane) to afford compound (*S*,*S*)-**IV-1j** (379.7 mg, 1.42 mmol) in 80% yield, as a yellow oil. $\mathbf{R}_f$ = 0.55 (20% EtOAc/Cyclohexane).

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.61 (d, *J* = 8.3 Hz, 2H), 7.40 (d, *J* = 8.3 Hz, 2H), 6.71 (d, *J* = 11.9 Hz, 1H), 5.70 (dd, *J* = 11.9, 7.5 Hz, 1H), 5.10-5.03 (m, 1H), 3.37 (dd, *J* = 7.5, 1.0 Hz, 1H), 2.09 (dd, *J* = 15.4, 7.5 Hz, 2H), 1.64 (s, 3H), 1.74-1.51 (m, 2H), 1.58 (s, 3H), 1.31 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 141.0, 132.9, 132.2, 132.1, 130.9, 129.3, 123.4, 118.7, 111.0, 63.3, 59.5, 38.2, 25.7, 23.6, 17.7, 17.4. **HRMS (EI$^+$)**: calculated for $C_{18}H_{21}NO$ $[M]^+$: 267.1623; found: 267.1615. **$[\alpha]^{20}_D$**= +176.1 (*c*= 1.0, $CHCl_3$).

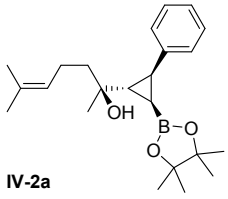
4.3.3. General Procedure for the Synthesis of enantioenriched cyclopropylboronates, **IV-2**



IV-1 **IV-2**

An oven-dried vial was charged with CuCl (2 mg, 0.02 mmol, 10 mol%), B_2pin_2 (55.9 mg, 0.22 mmol, 1.1 equiv), KO*t*Bu (22.4 mg, 0.2 mmol, 1.0 equiv) and xantphos (12.7 mg, 0.022 mmol, 11 mol%) in the glove box and sealed with a septum. The vial was connected to an argon-vacuum line and backfilled with argon. Anhydrous THF (0.5 mL/0.2 mmol of **IV-1**) was added and the mixture was stirred for 15 min at room temperature. Then the corresponding epoxide **IV-1** (1.0 equiv) in THF (0.5 mL/0.2 mmol of **IV-1**) was added. Finally, the reaction mixture was stirred overnight at room temperature. The resulting solution was filtered through a pad of celite (eluted with Et_2O) and concentrated under reduced pressure. The crude product was purified filtering through florisil (20% EtOAc/Cyclohexane) to afford cyclopropylboronate **IV-2**.

(*S*)-6-methyl-2-[(1*S*,2*S*,3*R*)-2-phenyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)cyclopropyl]hept-5-en-2-ol, IV-2a



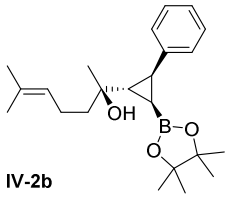
IV-2a

From epoxide **IV-1a** (48.5 mg, 0.200 mmol) following the general procedure described above, compound **IV-2a** (60.0 mg, 0.162 mmol) was obtained in 81 % yield, as a white solid. $\mathbf{R}_f$ = 0.4 (20% EtOAc/Cyclohexane).

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.25-7.00 (m, 5H), 5.12-5.03 (m, 1H), 2.27 (dd, *J* = 10.5, 6.0 Hz, 1H), 2.09 (dd, *J* = 15.9, 7.5 Hz, 2H), 1.74 (dd, *J* = 7.1, 6.0 Hz, 1H), 1.62 (s, 3H), 1.60-1.56 (m, 2H), 1.55 (s, 3H), 1.20 (s, 3H), 0.95 (s, 6H), 0.83 (s, 6H), 0.51 (dd, *J* = 10.5, 7.1 Hz, 1H). **^{13}C NMR**

(75 MHz, $CDCl_3$): δ 140.8, 131.9, 129.0, 127.8, 125.9, 124.7, 83.1, 71.0, 43.3, 32.7, 27.0, 25.8, 24.9, 24.7, 24.6, 23.0, 17.8. [note: the carbon attached to boron was not observed due to quadrupole broadening caused by the ^{11}B nucleus]. **HRMS (ESI$^+$)**: calculated for $C_{23}H_{35}BO_3Na$ $[M+Na]^+$: 393.2571; found: 393.2562. **[α]$^{20}_D$**= +39.3 (*c*= 1.0, $CHCl_3$). **mp** = 75-77 ºC

(*R*)-6-methyl-2-[(1*S*,2*S*,3*R*)-2-phenyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)cyclopropyl]hept-5-en-2-ol, IV-2b

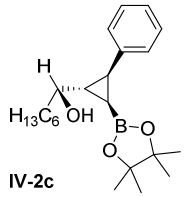


IV-2b

From epoxide **IV-1b** (48.5 mg, 0.200 mmol) following the general procedure described above, compound **IV-2b** (49.6 mg, 0.134 mmol) was obtained in 67 % yield, as a pale yellow solid. $\mathbf{R}_f$ = 0.45 (20% EtOAc/Cyclohexane).

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.27-6.96 (m, 5H), 5.15-4.98 (m, 1H), 2.33 (dd, *J* = 10.5, 6.0 Hz, 1H), 2.08 (dd, *J* = 16.0, 7.5 Hz, 2H), 1.74 (dt, *J* = 14.2, 7.1 Hz, 1H), 1.59 (s, 3H), 1.61-1.54 (m, 2H), 1.50 (s, 3H), 1.16 (s, 3H), 0.95 (s, 6H), 0.83 (s, 6H), 0.44 (dd, *J* = 10.5, 7.2 Hz, 1H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 140.6, 131.9, 129.0, 127.8, 125.9, 124.7, 83.1, 71.1, 43.0, 32.8, 26.9, 25.8, 25.1, 24.9, 24.5, 23.0, 17.8. [note: the carbon attached to boron was not observed due to quadrupole broadening caused by the ^{11}B nucleus]. **HRMS (ESI$^+$)**: calculated for $C_{23}H_{35}BO_3Na$ $[M+Na]^+$: 393.2571; found: 393.2569. **[α]$^{20}_D$**= +39.8 (*c*= 1.0, $CHCl_3$). **mp** = 74-76 ºC

(*R*)-1-[(1*S*,2*S*,3*R*)-2-phenyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)cyclopropyl]heptan-1-ol, IV-2c

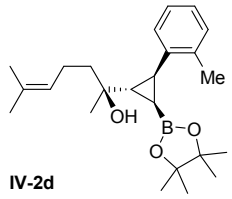


IV-2c

From epoxide **IV-1c** (46.1 mg, 0.200 mmol) following the general procedure described above, compound **IV-2c** (65.1 mg, 0.182 mmol, *er* = 88:12) was obtained in 91 % yield, as a colorless oil. $\mathbf{R}_f$ = 0.45 (20% EtOAc/Cyclohexane). The enantiomeric ratio of the product was determined to be 88:12 by ^{1}H NMR analysis of its methoxy phenyl acetate, prepared by reaction of (-)-methoxyphenyl acid and DCC in DCM.[25]

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.23-7.01 (m, 5H), 3.17 (dd, *J* = 13.4, 6.4 Hz, 1H), 2.23 (dd, *J* = 10.5, 5.7 Hz, 1H), 1.76 (td, *J* = 6.9, 5.7 Hz, 1H), 1.58 (dd, *J* = 13.8, 7.8 Hz, 2H), 1.34-1.15 (m, 8H), 0.95 (s, 6H), 0.83 (s, 6H), 0.80 (d, *J* = 6.8 Hz, 3H), 0.37 (dd, *J* = 10.5, 6.9 Hz, 1H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 140.2, 128.9, 127.9, 126.0, 83.2, 75.8, 37.3, 32.0, 29.6, 29.5, 26.7, 25.8, 24.9, 24.5, 22.7, 14.2. [note: the carbon attached to boron was not observed due to quadrupole broadening caused by the ^{11}B nucleus]. **HRMS (ESI$^+$)**: calculated for $C_{22}H_{35}BO_3Na$ $[M+Na]^+$: 381.2571; found: 381.2569. **[α]$^{20}_D$**= +40.4 (*c*= 1.0, $CHCl_3$).

(*S*)-6-methyl-2-[(1*S*,2*S*,3*R*)-2-(*o*-tolyl)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)cyclopropyl]hept-5-en-2-ol, IV-2d



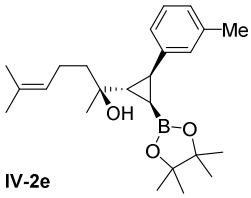
IV-2d

From epoxide **IV-1d** (51.3 mg, 0.200 mmol) following the general procedure described above, compound **IV-2d** (33.1 mg, 0.086 mmol) was obtained in 43 % yield, as a white solid. $\mathbf{R}_f$ = 0.5 (20% EtOAc/Cyclohexane).

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.21-7.14 (m, 1H), 7.10-7.05 (m, 3H), 5.17 (t, *J* = 7.1 Hz, 1H), 2.40 (s, 3H), 2.30-2.12 (m, 3H), 1.91 (t, *J* = 6.4 Hz, 1H), 1.70 (s, 3H), 1.74-1.61 (m, 2H), 1.64 (s, 3H), 1.31 (s, 3H), 0.97

(s, 6H), 0.76 (s, 6H), 0.65 (dd, *J* = 10.5, 6.8 Hz, 1H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 138.8, 132.1, 129.4, 128.2, 126.1, 125.3, 124.6, 82.9, 71.1, 43.4, 31.9, 27.2, 25.9, 24.7, 24.3, 23.2, 23.1, 19.7, 17.9. [note: the carbon attached to boron was not observed due to quadrupole broadening caused by the ^{11}B nucleus]. **HRMS (ESI$^+$)**: calculated for $C_{24}H_{37}BO_3Na$ $[M+Na]^+$: 407.2727; found: 407.2717. **[α]$^{20}_D$**= +60.4 (*c*= 0.9, $CHCl_3$). **mp** = 115-117 ºC

(*S*)-6-methyl-2-[(1S,2*S*,3*R*)-2-(*m*-tolyl)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)cyclopropyl]hept-5-en-2-ol, IV-2e

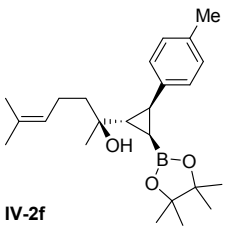


IV-2e

From epoxide **IV-1e** (51.3 mg, 0.200 mmol) following the general procedure described above, compound **IV-2e** (70.7 mg, 0.184 mmol) was obtained in 92 % yield, as a pale yellow solid. **R**$_f$ = 0.5 (20% EtOAc/Cyclohexane).

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.04-6.94 (m, 3H), 6.88-6.78 (m, 1H), 5.13-4.97 (m, 1H), 2.30-2.17 (m, 1H), 2.19 (s, 3H), 2.06 (dd, *J* = 15.5, 7.4 Hz, 2H), 1.76-1.65 (m, 1H), 1.59 (s, 3H), 1.61-1.49 (m, 2H), 1.53 (s, 3H), 1.16 (s, 3H), 0.93 (s, 6H), 0.81 (s, 6H), 0.47 (dd, *J* = 10.5, 7.2 Hz, 1H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 140.6, 137.2, 131.9, 129.5, 127.8, 126.6, 126.1, 124.6, 83.1, 71.0, 43.3, 32.6, 27.0, 25.8, 25.1, 24.9, 24.5, 23.0, 21.5, 17.8. [note: the carbon attached to boron was not observed due to quadrupole broadening caused by the ^{11}B nucleus]. **HRMS (ESI$^+$)**: calculated for $C_{24}H_{37}BO_3Na$ $[M+Na]^+$: 407.2727; found: 407.2710. **[α]$^{20}_D$**= +34.6 (*c*= 1.0, $CHCl_3$). **mp** = 80-82 ºC

(*S*)-6-methyl-2-[(1*S*,2*S*,3*R*)-2-(*p*-tolyl)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)cyclopropyl]hept-5-en-2-ol, IV-2f

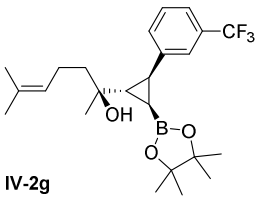


IV-2f

From epoxide **IV-1f** (51.3 mg, 0.200 mmol) following the general procedure described above, compound **IV-2f** (63.0 mg, 0.164 mmol) was obtained in 82 % yield, as a white solid. $\mathbf{R}_f$ = 0.5 (20% EtOAc/Cyclohexane).

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.16 (d, *J* = 8.0 Hz, 2H), 7.01 (d, *J* = 8.0 Hz, 2H), 5.15 (t, *J* = 7.1 Hz, 1H), 2.33-2.25 (m, 4H), 2.22-2.09 (m, 2H), 1.77 (t, *J* = 6.5 Hz, 1H), 1.69 (s, 3H), 1.72-1.56 (m, 2H), 1.63 (s, 3H), 1.26 (s, 3H), 1.04 (s, 6H), 0.92 (s, 6H), 0.55 (dd, *J* = 10.5, 7.2 Hz, 1H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 137.6, 135.3, 132.0, 128.8, 128.5, 124.6, 83.1, 71.0, 43.3, 32.7, 27.0, 25.9, 24.9, 24.5, 24.3, 23.0, 21.1, 17.9. [note: the carbon attached to boron was not observed due to quadrupole broadening caused by the ^{11}B nucleus]. **HRMS (ESI$^+$)**: calculated for $C_{24}H_{37}BO_3Na$ $[M+Na]^+$: 407.2732; found: 407.2732. **$[\alpha]^{20}_D$**= +30.9 (*c*= 1.1, $CHCl_3$). **mp** = 73-75 ºC

(*S*)-6-methyl-2-{(1*S*,2*S*,3*R*)-2-[3-(trifluoromethyl)phenyl]-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)cyclopropyl}hept-5-en-2-ol, IV-2g



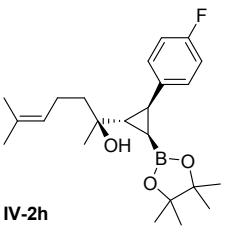
IV-2g

From epoxide **IV-1g** (62.1 mg, 0.200 mmol) following the general procedure described above, compound **IV-2g** (77.2 mg, 0.176 mmol) was obtained in 88 % yield, as a pale yellow solid. $\mathbf{R}_f$ = 0.45 (20% EtOAc/Cyclohexane).

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.63-7.28 (m, 4H), 5.22-5.07 (m, 1H), 2.38 (dd, *J* = 10.5, 6.0 Hz, 1H), 2.15 (dd, *J* = 15.4, 7.7 Hz, 2H), 1.83 (dd, *J* = 7.1, 6.0 Hz, 1H), 1.69 (s, 3H), 1.72-1.57 (m, 2H), 1.62 (s, 3H), 1.29 (s, 3H), 1.02 (s, 6H), 0.90 (s, 6H), 0.65 (dd, *J* = 10.5, 7.1 Hz, 1H). **^{13}C NMR**

(75 MHz, $CDCl_3$): δ 142.0, 132.7, 132.1, 130.2 (q, J_{CF} = 31.9 Hz), 128.2, 125.4 (q, J_{CF} = 3.8 Hz), 124.5 (q, J_{CF} = 272.2 Hz), 124.4, 122.7 (q, J_{CF} = 3.8 Hz), 83.3, 70.8, 43.2, 33.1, 27.3, 25.8, 24.7, 24.5, 24.4, 23.0, 17.8. **^{19}F NMR** (282 MHz, $CDCl_3$): δ -62.53. [note: the carbon attached to boron was not observed due to quadrupole broadening caused by the ^{11}B nucleus]. **HRMS (ESI$^+$)**: calculated for $C_{24}H_{34}BF_3O_3Na$ $[M+Na]^+$: 461.2450; found: 461.2464. **[α]$^{20}_D$**= +32.9 (*c*= 1.1, $CHCl_3$). **mp** = 66-68 ºC

(*S*)-2-[(1*S*,2*S*,3*R*)-2-(4-fluorophenyl)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)cyclopropyl]-6-methylhept-5-en-2-ol, IV-2h

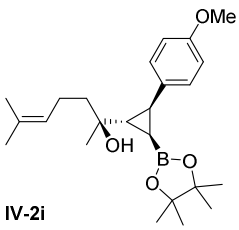


IV-2h

From epoxide **IV-1h** (52.1 mg, 0.200 mmol) following the general procedure described above, compound **IV-2h** (33.1 mg, 0.086 mmol) was obtained in 94 % yield, as a colorless oil. **R**$_f$ = 0.35 (20% EtOAc/Cyclohexane).

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.31-7.20 (m, 2H), 6.97-6.86 (m, 2H), 5.22-5.11 (m, 1H), 2.31 (dd, *J* = 10.5, 5.9 Hz, 1H), 2.15 (dd, *J* = 15.9, 7.5 Hz, 2H), 1.80-1.73 (m, 1H), 1.69 (s, 3H), 1.67-1.60 (m, 2H), 1.63 (s, 3H), 1.28 (s, 3H), 1.05 (s, 6H), 0.93 (s, 6H), 0.57 (dd, J = 10.5, 7.1 Hz, 1H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 161.47 (d, J_{CF} = 243.3 Hz), 136.5 (d, J_{CF} = 3.0 Hz), 132.0, 130.4 (d, J_{CF} = 7.8 Hz), 124.6, 114.5 (d, J_{CF} = 21.2 Hz), 83.2, 70.9, 43.3, 33.0, 27.1, 25.8, 24.9, 24.6, 23.9, 23.0, 17.8. **^{19}F NMR** (282 MHz, $CDCl_3$): δ -117.80. [note: the carbon attached to boron was not observed due to quadrupole broadening caused by the ^{11}B nucleus]. **HRMS (ESI$^+$)**: calculated for $C_{23}H_{34}BFO_3Na$ $[M+Na]^+$: 411.2477; found: 411.2475. **[α]$^{20}_D$**= +37.0 (*c*= 1.0, $CHCl_3$).

(*S*)-2-[(1*S*,2*S*,3*R*)-2-(4-methoxyphenyl)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)cyclopropyl]-6-methylhept-5-en-2-ol, IV-2i

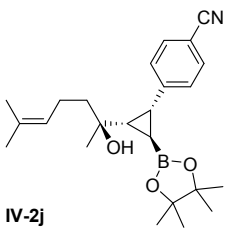


IV-2i

From epoxide **IV-1i** (54.5 mg, 0.200 mmol) following the general procedure described above, compound **IV-2i** (43.2 mg, 0.108 mmol) was obtained in 54 % yield, as a pale yellow oil. $\mathbf{R}_f$ = 0.3 (20% EtOAc/Cyclohexane).

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.19 (d, *J* = 8.6 Hz, 2H), 6.76 (d, *J* = 8.6 Hz, 2H), 5.19-5.09 (m, 1H), 3.76 (s, 3H), 2.28 (dd, *J* = 10.4, 5.9 Hz, 1H), 2.15 (dd, *J* = 15.7, 7.3 Hz, 2H), 1.75 (dd, *J* = 7.1, 5.9 Hz, 1H), 1.68 (s, 3H), 1.67-1.59 (m, 2H), 1.62 (s, 3H), 1.26 (s, 3H), 1.04 (s, 6H), 0.92 (s, 6H), 0.53 (dd, *J* = 10.4, 7.1 Hz, 1H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 158.0, 133.0, 131.9, 130.0, 124.7, 113.3, 83.1, 71.0, 55.5, 43.3, 32.8, 27.0, 25.8, 25.0, 24.6, 23.9, 23.0, 17.8. [note: the carbon attached to boron was not observed due to quadrupole broadening caused by the ^{11}B nucleus]. **HRMS (ESI$^+$)**: calculated for $C_{24}H_{37}BO_4Na$ $[M+Na]^+$: 423.2682; found: 423.2663. $[\alpha]^{20}_D$= +31.7 (*c*= 1.0, $CHCl_3$).

4-{(1*R*,2*S*,3*R*)-2-[(*S*)-2-hydroxy-6-methylhept-5-en-2-yl)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl]cyclopropyl}benzonitrile, IV-2j



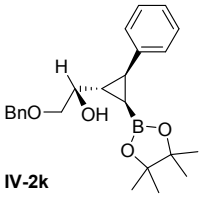
IV-2j

From epoxide **IV-1j** (53.5 mg, 0.200 mmol) following the general procedure described above, compound **IV-2j** (60.1 mg, 0.152 mmol) was obtained in 76 % yield, as a pale yellow solid. $\mathbf{R}_f$ = 0.45 (20% EtOAc/Cyclohexane).

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.53 (d, *J* = 8.3 Hz, 2H), 7.43 (d, *J* = 8.3 Hz, 2H), 5.14-5.03 (m, 1H), 2.41-2.30 (m, 1H), 2.06 (dd, *J* = 15.6, 7.9 Hz, 2H), 1.67 (s, 3H), 1.61 (s, 3H), 1.54-1.41 (m, 2H), 1.24 (s, 12H), 1.07 (s, 3H), 0.99 (t, *J* = 7.2 Hz, 1H), 0.44 (s, 1H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 145.3, 131.9, 131.7, 130.6, 124.4, 119.2, 109.7, 83.6, 72.0, 44.4, 36.1,

28.0, 26.8, 25.8, 24.9, 24.9, 22.7, 17.8. [note: the carbon attached to boron was not observed due to quadrupole broadening caused by the ^{11}B nucleus]. **HRMS (ESI$^+$)**: calculated for $C_{24}H_{34}BNO_3Na$ $[M+Na]^+$: 418.2523; found: 418.2519. **[α]$^{20}_D$**= +102.8 (*c*= 1.1, $CHCl_3$).

(*S*)-2-(benzyloxy)-1-[(1*S*,2*S*,3*R*)-2-phenyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)cyclopropyl]ethan-1-ol, IV-2k

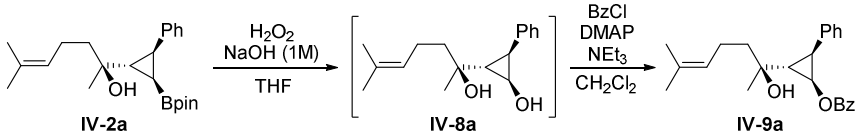


IV-2k

From epoxide **IV-1k** (53.3 mg, 0.200 mmol) following the general procedure described above, compound **IV-2k** (30.8 mg, 0.078 mmol) was obtained in 39 % yield, as a yellow oil. **R**$_f$ = 0.3 (20% EtOAc/Cyclohexane). **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.30-7.00 (m, 10H), 4.51 (s, 2H), 3.65-3.56 (m, 1H), 3.52-3.41 (m, 2H), 2.32 (dd, *J* = 10.5, 5.4 Hz, 1H), 1.73 (dd, *J* = 12.0, 5.7 Hz, 1H), 0.93 (s, 6H), 0.81 (s, 6H), 0.40 (dd, *J* = 10.5, 6.7 Hz, 1H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 140.1, 138.3, 129.0, 128.6, 127.9, 127.8, 126.0, 83.2, 74.4, 73.6, 73.5, 26.4, 25.0, 24.9, 24.6. [note: the carbon attached to boron was not observed due to quadrupole broadening caused by the ^{11}B nucleus]. **HRMS (ESI$^+$)**: calculated for $C_{24}H_{31}BO_4Na$ $[M+Na]^+$: 417.2212; found: 417.2210. **[α]$^{20}_D$**= +37.0 (*c*= 1.1, $CHCl_3$).

4.3.4. Functionalization of the C-B Bond

4.3.4.1. Synthesis of (1*R*,2*R*,3*S*)-2-[(*S*)-2-hydroxy-6-methylhept-5-en-2-yl]-3-phenylcyclopropyl benzoate, **IV-9a**



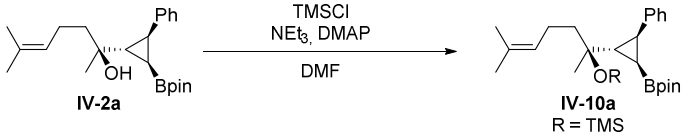
To cyclopropylboronate **IV-2a** (37 mg, 0.10 mmol, 1.0 equiv) in THF (0.2 mL), an aqueous solution of NaOH (0.10 mL, 0.10 mmol, 1M) was added, and the reaction mixture was cooled to 0 ºC. Then, a solution of H_2O_2 (0.020 mL, 30% (w/w), 2.0 equiv) was added dropwise. A white precipitate was formed within 10 min. After 30 min, full conversion was checked by TLC. Water was added and the mixture was extracted with Et_2O (x3). The combined organic layers were washed with brine, dried with $MgSO_4$, filtered and concentrated in vacuum to afford compound **IV-8a** . This compound was used in the next step without further purification.

To a solution of alcohol **IV-8a** in CH_2Cl_2 (0.85 mL), 4-dimethylaminopyridine (DMAP) (3.3 mg, 0.027 mmol, 27 mol%), triethylamine (30 µl, 0.3 mmol, 3 equiv) and benzyl chloride (23 µl, 0.2 mmol, 2.0 equiv) were added. The reaction mixture was stirred for 1 hour at room temperature and then quenched with H_2O. The aqueous layer was extracted with Et_2O (x3) and the combined organic phases were washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (5% EtOAc/hexanes) to afford compound **IV-9a** (19.7 mg, 0.054 mmol) in 54% yield (two steps) as a yellow oil. $\mathbf{R}_f$ = 0.5 (20% EtOAc/Cyclohexane).

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.78-7.69 (m, 2H), 7.48-7.08 (m, 9H), 5.17-5.07 (m, 1H), 4.50 (dd, *J* = 7.4, 3.5 Hz, 1H), 2.42 (t, *J* = 7.4 Hz, 1H), 2.14 (dd, *J* = 15.4, 7.7 Hz, 2H), 1.78-1.67 (m, 3H), 1.61 (s, 3H), 1.54 (s,

3H), 1.20 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 167.5, 136.4, 133.2, 132.2, 129.8, 129.6, 128.9, 128.4, 128.3, 126.5, 124.4, 70.7, 55.9, 42.8, 35.1, 26.1, 25.8, 25.7, 23.0, 17.8. **HRMS (ESI$^+$)**: calculated for $C_{24}H_{28}O_3Na$ $[M+Na]^+$: 387.1930; found: 387.1939. **[α]$^{20}_D$**= +25.9 (*c*= 1.0, $CHCl_3$).

4.3.4.2. Synthesis of trimethyl {[(*S*)-6-methyl-2-((1*S*,2*S*,3*R*)-2-phenyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)cyclopropyl)hept-5-en-2-yl]oxy}silane, **IV-10a**

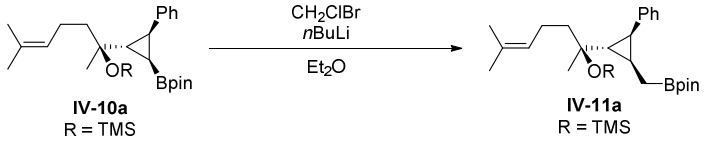


To a solution of cyclopropylboronate **IV-2a** (148 mg, 0.4 mmol, 1.0 equiv), DMAP (8 mg, 0.06 mmol, 15 mol%) and triethylamine (80 µl, 0.6 mmol, 1.5 equiv) in DMF (1.6 mL) at 0ºC, trimethylsilyl chloride (64 µl, 0.48 mmol, 1.2 equiv) was added via syringe. The resulting cloudy solution was stirred for 1 hour at room temperature and then poured into a separatory funnel containing Et_2O and saturated NH_4Cl. The organic layer was separated and the aqueous phase was extracted with Et_2O (x3). The combined organic phases were washed with saturated NH_4Cl and brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (5% EtOAc/hexanes) to afford compound **IV-10a** (167.8 mg, 0.38 mmol) in 95% yield as a white solid. $\mathbf{R}_f$ = 0.8 (20% EtOAc/Cyclohexane).

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.21-6.97 (m, 5H), 5.07-4.99 (m, 1H), 2.13 (dd, *J* = 10.5, 5.7 Hz, 1H), 2.02 (dd, *J* = 16.8, 7.2 Hz, 2H), 1.59 (s, 3H), 1.64-1.45 (m, 2H), 1.51 (s, 3H), 1.22 (s, 3H), 0.93 (s, 6H), 0.81 (s, 6H), 0.59 (dd, *J* = 10.5, 7.0 Hz, 1H), -0.00 (s, 9H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 141.4, 131.1, 129.1, 127.8, 125.7, 125.1, 83.0, 73.9, 44.5, 32.8, 28.3, 25.8, 24.9, 24.6, 24.5, 23.3, 17.8, 2.6. [note: the carbon attached to

boron was not observed due to quadrupole broadening caused by the ^{11}B nucleus]. **HRMS (ESI$^+$)**: calculated for $C_{26}H_{43}BO_3SiNa$ $[M+Na]^+$: 465.2972; found: 465.2960. **[α]$^{20}_D$**= +39.0 (*c*= 0.8, $CHCl_3$). **mp** = 44-46 ºC

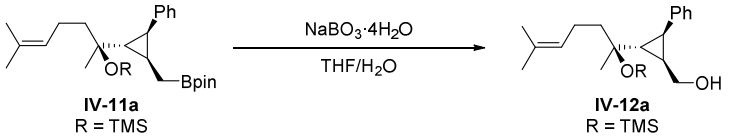
4.3.4.3. Synthesis of trimethyl{[(*S*)-6-methyl-2-((1*S*,2*S*,3*R*)-2-phenyl-3-((4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)methyl)cyclopropyl)hept-5-en-2-yl]oxy}silane, **IV-11a**



To a solution of cyclopropylboronate **IV-10a** (44.3 mg, 0.1 mmol, 1.0 equiv) and bromochloromethane (16 µL, 3.0 equiv) in anhydrous diethyl ether (0.5 mL) at -78 ºC, *n*BuLi (1.6 M in hexanes, 0.2 mL, 2.5 equiv) was added dropwise. The mixture was stirred for 20 min at -78 ºC, and then it was warmed to room temperature and stirred overnight. The reaction mixture was filtered through silica gel using a fritted filter and solvent was removed under reduced pressure to give **IV-11a** (37.5 mg, 0.082 mmol) in 82% yield as a pale yellow oil. **R$_f$** = 0.75 (20% EtOAc/Cyclohexane).

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.18-6.96 (m, 5H), 5.08-4.97 (m, 1H), 2.00 (dd, *J* = 16.5, 7.5 Hz, 2H), 1.92 (dd, *J* = 9.4, 5.7 Hz, 1H), 1.57 (s, 3H), 1.50 (s, 3H), 1.53-1.45 (m, 2H), 1.26-1.21 (m, 1H), 1.16 (s, 3H), 1.05 (s, 6H), 1.03 (s, 6H), 0.92 (t, *J* = 5.6 Hz, 1H), 0.61 (dd, *J* = 16.6, 6.8 Hz, 1H), 0.38 (dd, *J* = 16.6, 7.8 Hz, 1H), -0.00 (s, 9H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 140.1, 131.0, 129.5, 127.9, 125.5, 125.2, 83.0, 74.6, 44.1, 36.1, 27.8, 25.8, 25.0, 24.9, 24.1, 23.4, 17.8, 17.7, 2.7. [note: the carbon attached to boron was not observed due to quadrupole broadening caused by the ^{11}B nucleus]. **HRMS (ESI$^+$)**: calculated for $C_{27}H_{45}BO_3SiNa$ $[M+Na]^+$: 479.3129; found: 479.3130. **[α]$^{20}_D$**= +25.7 (*c*= 1.0, $CHCl_3$).

4.3.4.4. Synthesis of {(1*R*,2*R*,3*S*)-2-[(*S*)-6-methyl-2-((trimethylsilyl)oxy)hept-5-en-2-yl]-3-phenylcyclopropyl}methanol, **IV-12a**



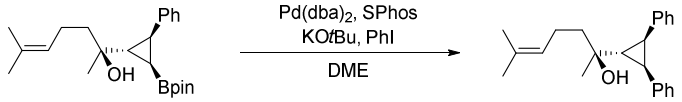
IV-11a
R = TMS

IV-12a
R = TMS

$NaBO_3 \cdot 4H_2O$ (22 mg, 0.14 mmol, 4 equiv) was added to a solution of cyclopropylboronate **IV-11a** (16 mg, 0.035 mmol) in 0.3 mL of THF/H_2O (1:1). The biphasic mixture was stirred vigorously overnight at room temperature and then quenched with H_2O and extracted with Et_2O (x3). The combined organic phases were washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (5% EtOAc/cyclohexane) to afford **IV-12a** (8.5 mg, 0.025 mmol) in 71% yield as a colorless oil. $\mathbf{R}_f$ = 0.6 (20% EtOAc/Cyclohexane).

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.29-7.08 (m, 5H), 5.05 (t, *J* = 7.3 Hz, 1H), 3.55 (dd, *J* = 11.5, 5.7 Hz, 1H), 3.22 (dd, *J* = 11.5, 9.1 Hz, 1H), 2.16 (dd, *J* = 9.1, 5.7 Hz, 1H), 2.05 (dd, *J* = 16.4, 7.5 Hz, 2H), 1.63 (s, 3H), 1.59-1.51 (m, 2H), 1.55 (s, 3H), 1.27 (s, 3H), 1.23-1.17 (m, 2H), 0.05 (s, 9H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 138.9, 131.5, 129.1, 128.5, 126.2, 124.8, 73.7, 62.3, 44.3, 32.0, 28.3, 25.9, 24.7, 23.3, 23.2, 17.8, 2.6. **HRMS (ESI$^+$)**: calculated for $C_{21}H_{34}O_2SiNa$ $[M+Na]^+$: 369.2258; found: 369.2262. **$[\alpha]^{20}_D$**= +47.4 (*c*= 1.0, $CHCl_3$).

4.3.4.5. Synthesis of (*S*)-2-[(1*R*,2*R*,3*S*)-2,3-diphenylcyclopropyl]-6-methylhept-5-en-2-ol, **IV-13a**

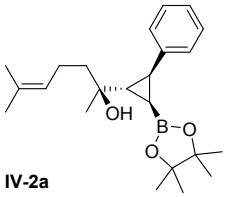


IV-2a **IV-13a**

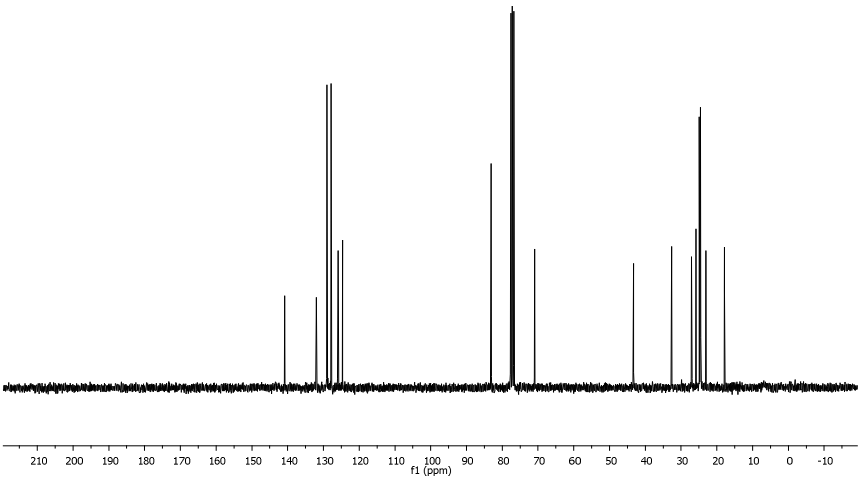
To a solution of cyclopropane **IV-2a** (37mg, 0.1 mmol), phenyliodide (34 µl, 0.3 mmol, 3.0 equiv), $Pd(dba)_2$ (5.8 mg, 0.01 mmol, 10 mol%) and SPhos (8.2 mg, 0.02 mmol, 20 mol%) in dry dimethoxyethane (0.4 mL), a solution of KO*t*Bu in *t*BuOH (1.0 M, 0.2 mL, 2.0 equiv) was added. Then, water and hexane were added, and the organic layer was separated. The aqueous layer was extracted twice with hexane. Finally, the combined organic phases were washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (5% to 10% EtOAc/cyclohexane) to afford **IV-13a** (16 mg, 0.05 mmol) in 50% yield as an orange oil. $\mathbf{R}_f$ = 0.6 (20% EtOAc/Cyclohexane).

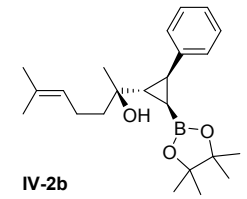
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.16-6.90 (m, 10H), 5.16 (t, *J* = 6.5 Hz, 1H), 2.65-2.52 (m, 2H), 2.20 (dd, *J* = 15.6, 7.3 Hz, 2H), 1.84 (t, *J* = 6.2 Hz, 1H), 1.79 – 1.71 (m, 2H), 1.68 (s, 3H), 1.57 (s, 3H), 1.40 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 138.4, 138.3, 132.2, 129.3, 129.0, 127.9, 125.8, 125.7, 124.5, 71.1, 43.0, 35.4, 27.5, 27.3, 27.2, 25.8, 23.0, 17.8. **HRMS (ESI$^+$)**: calculated for $C_{23}H_{28}ONa$ $[M+Na]^+$: 343.2032; found: 343.2037. **$[\alpha]^{20}_D$**= -13.2 (*c*= 1.0, $CHCl_3$).

4.4. NMR spectra



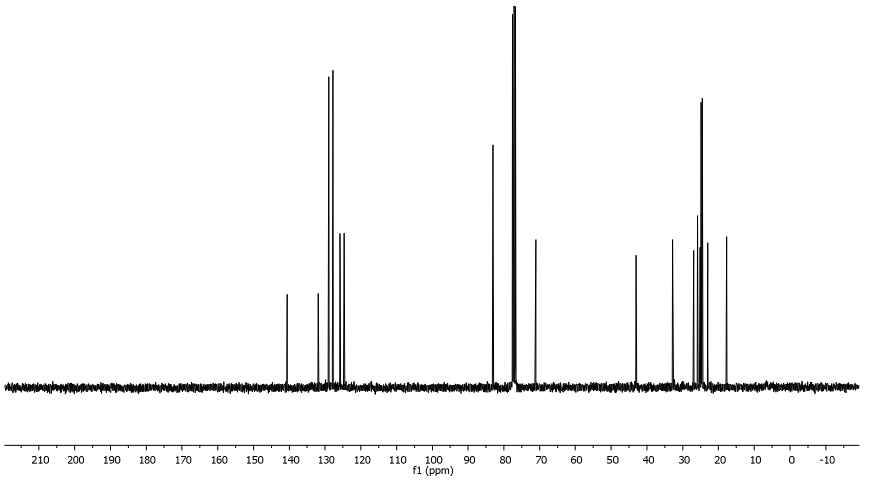
IV-2a

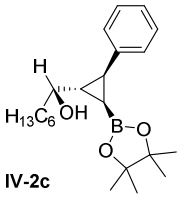



OH
B
O
O

IV-2b

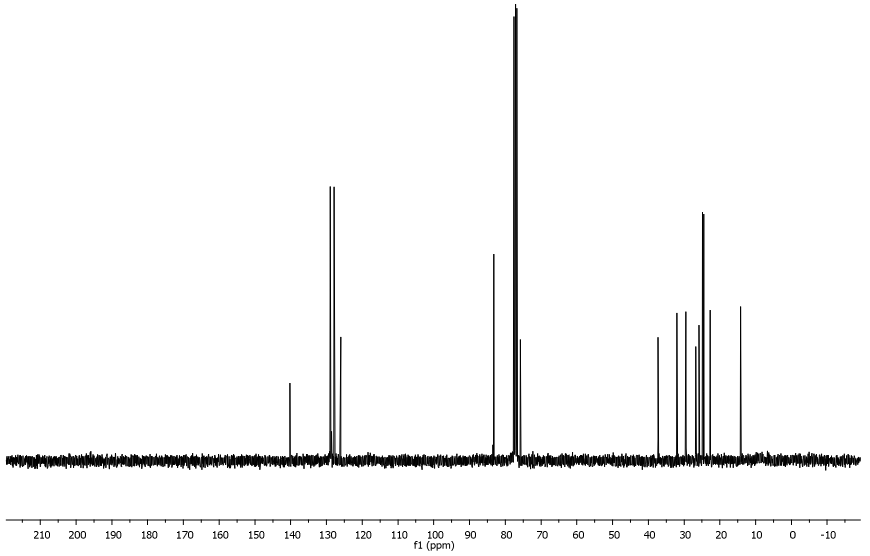
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0 -1.5
f1 (ppm)

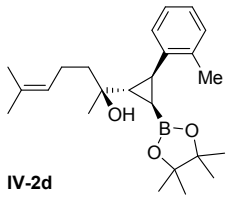

210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


H
H13C6
OH
B
O
O

IV-2c

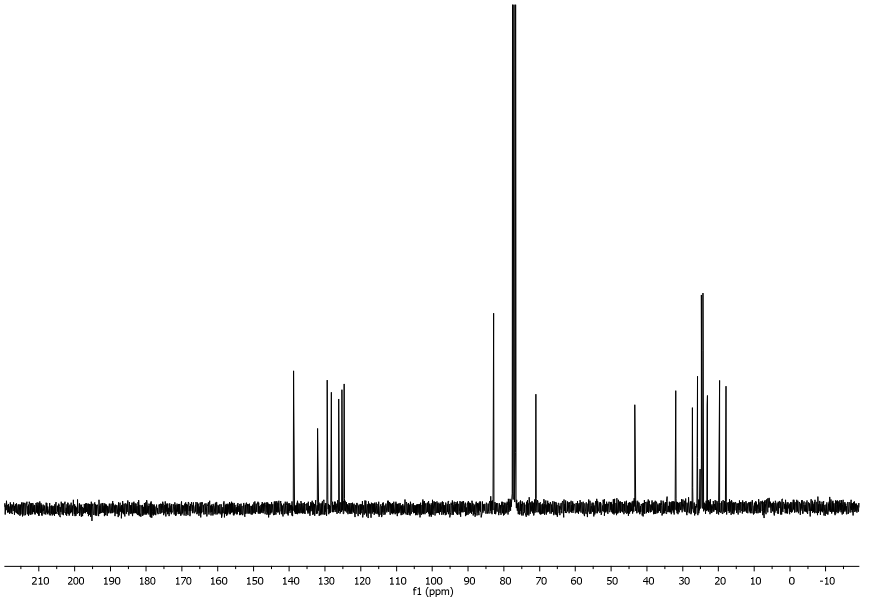
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0 -1.5
f1 (ppm)


210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


Me
OH
B
O
O

IV-2d

10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0 -1.5
f1 (ppm)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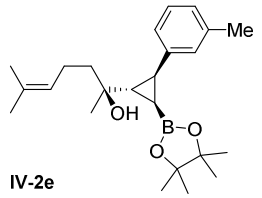
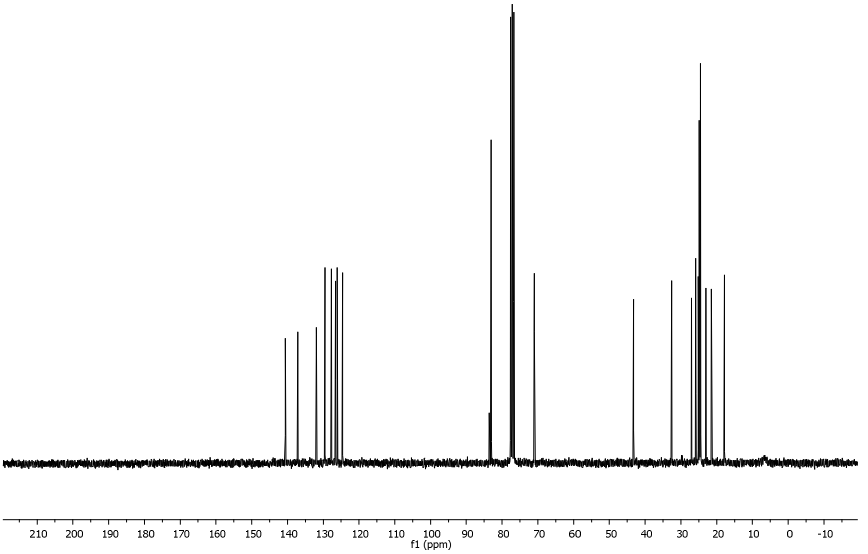
f1 (ppm)


Me
OH
B
O
O

IV-2e

10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0 -1.5
f1 (ppm)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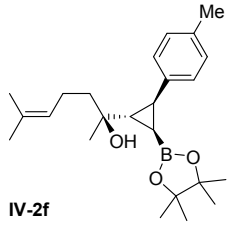
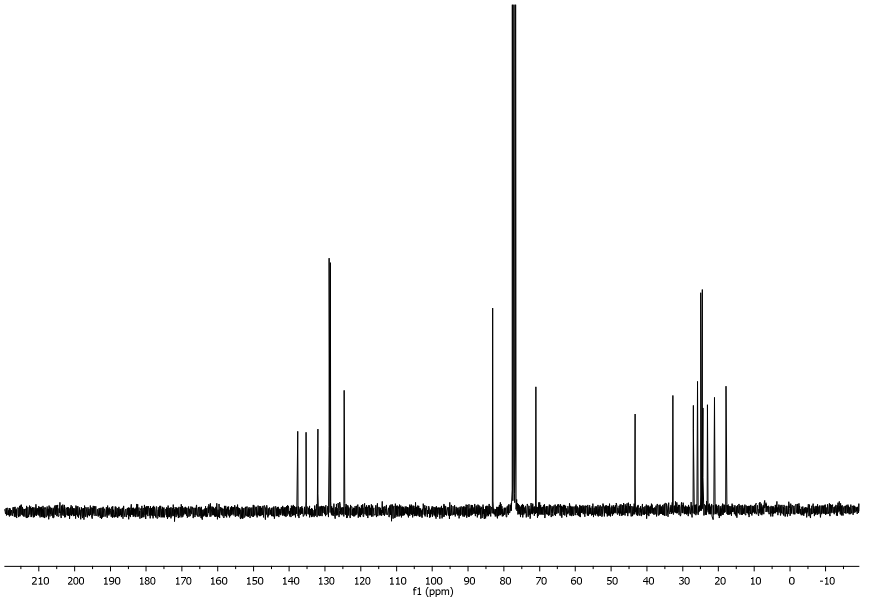
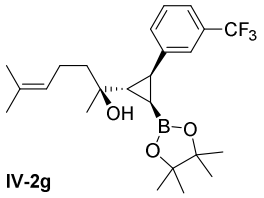
f1 (ppm)


Me
OH
B
O
O

IV-2f

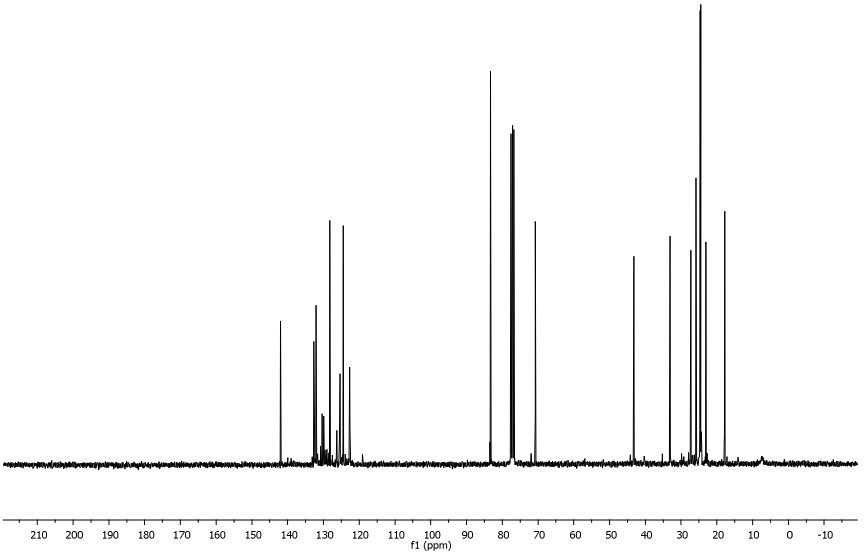
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0 -1.5
f1 (ppm)

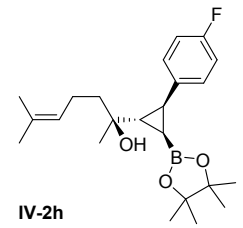

210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


CF3
OH
B
O
O

IV-2g

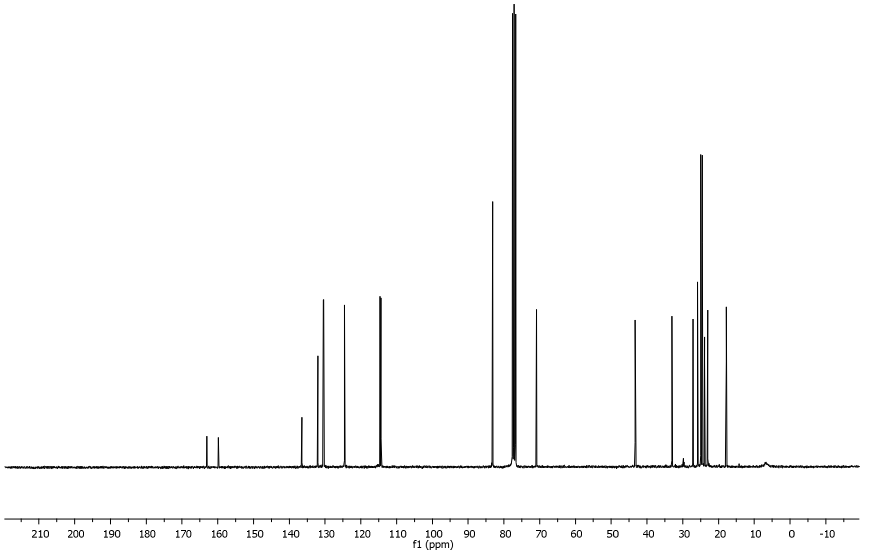
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0 -1.5
f1 (ppm)

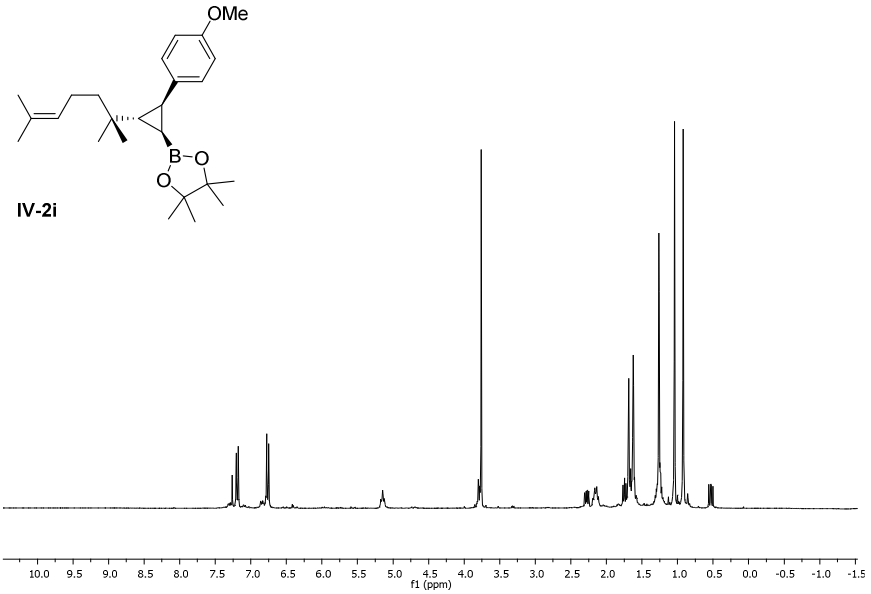

210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

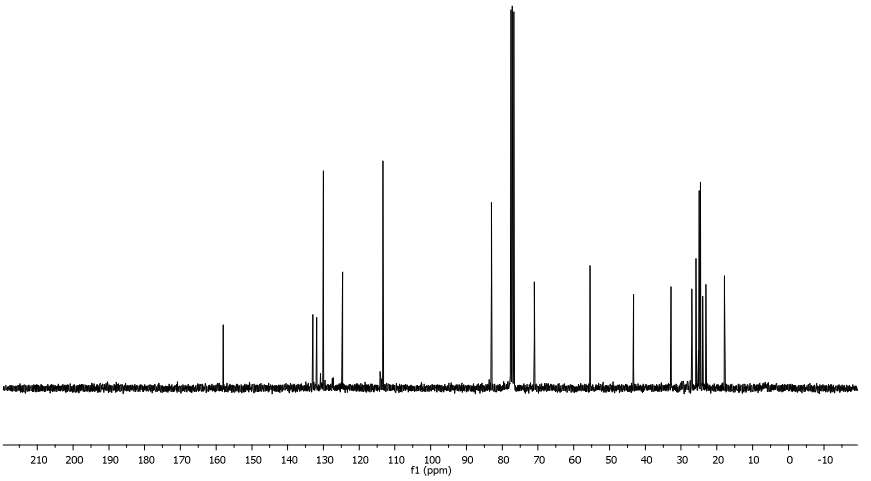

F
OH
B
O
O

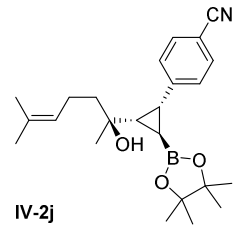
IV-2h

10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0 -1.5
f1 (ppm)


210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

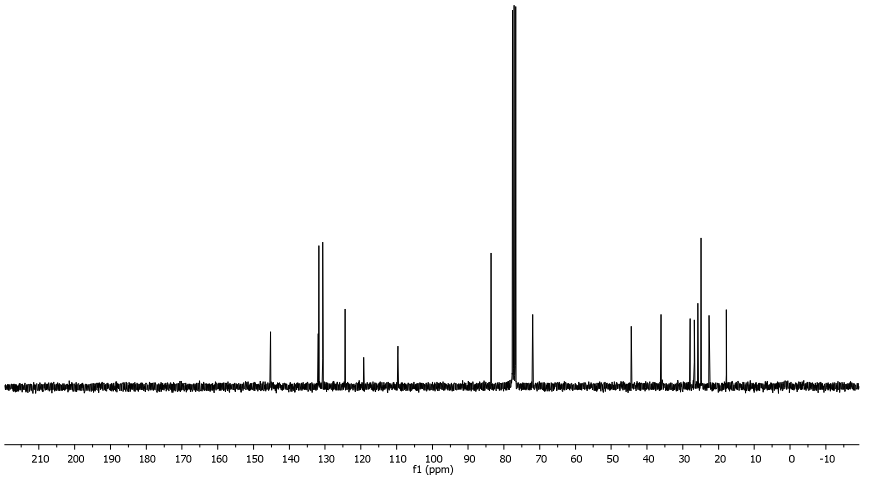

OMe
B
O
O
IV-2i
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0 -1.5
f1 (ppm)

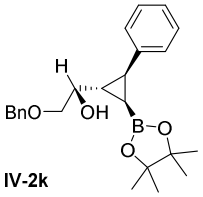

210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


CN
OH
B
O
O

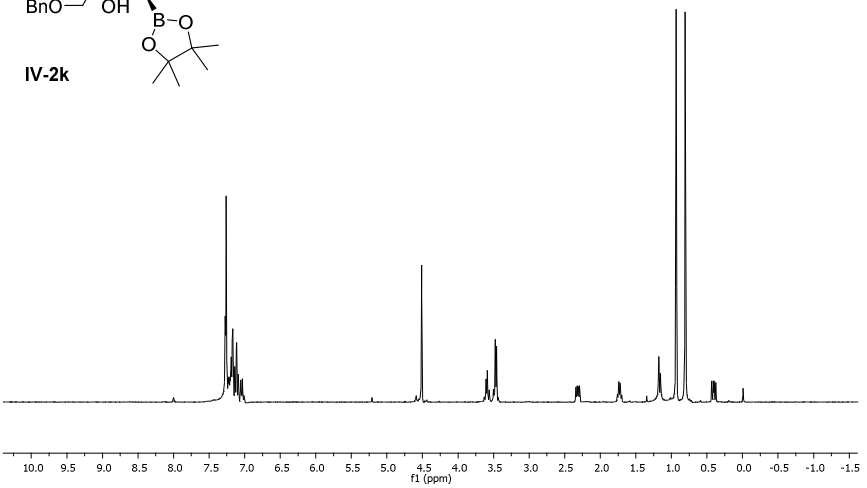
IV-2j

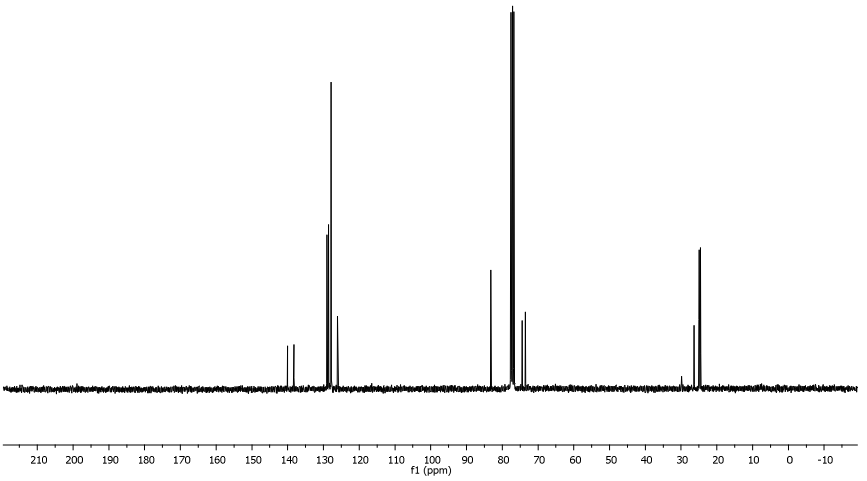
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0 -1.5
f1 (ppm)

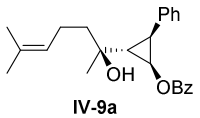

210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


H
BnO
OH
B
O
O

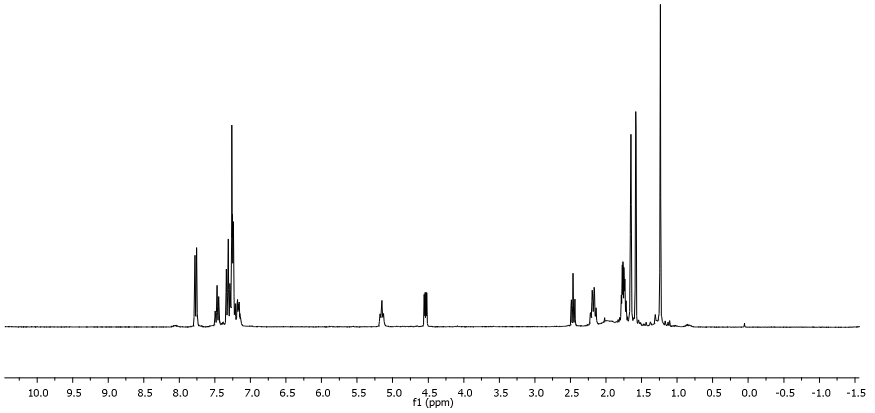
IV-2k

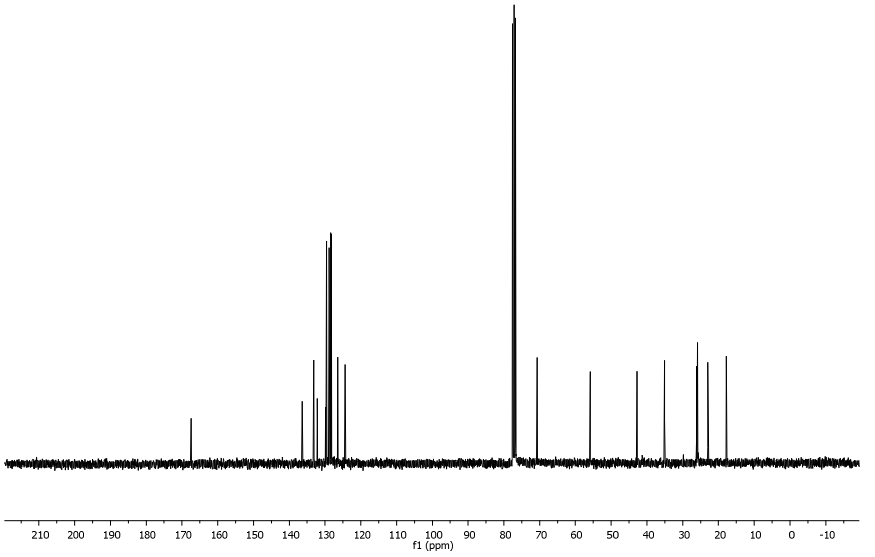

10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0 -1.5
f1 (ppm)

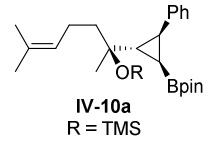

210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


Ph
OH
OBz

IV-9a

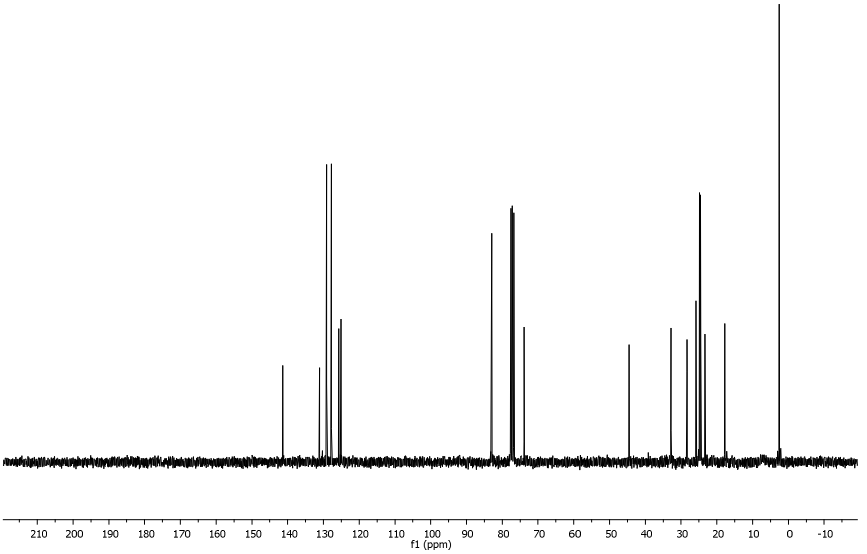

10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0 -1.5
f1 (ppm)

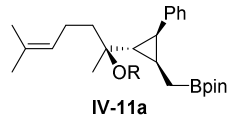

210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


Ph
OR
Bpin

IV-10a
R = TMS

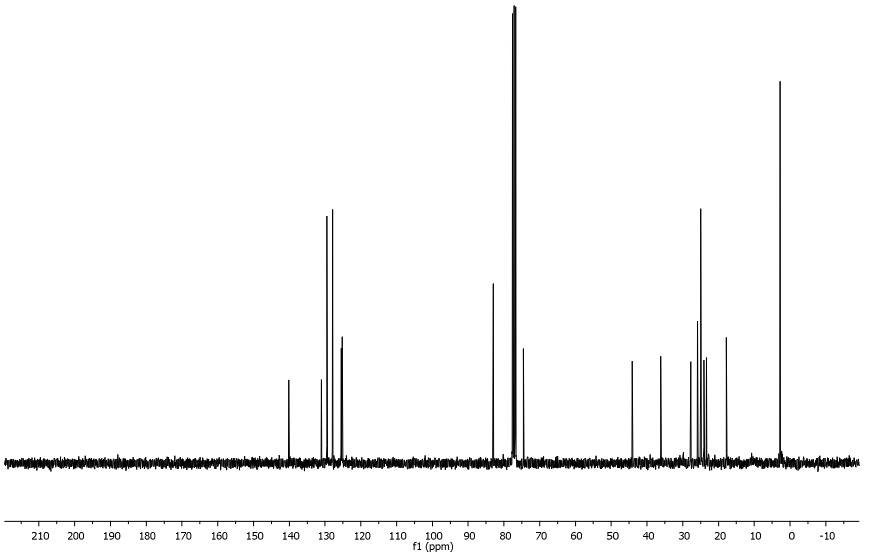
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0 -1.5
f1 (ppm)

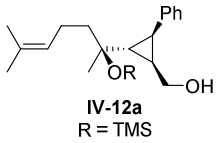

210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


Ph
OR
Bpin

IV-11a
R = TMS

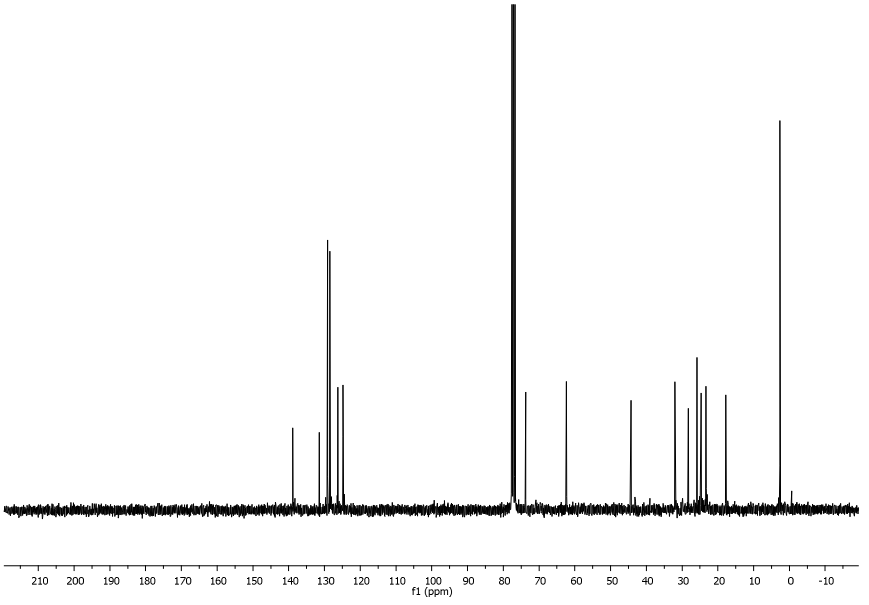
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0 -1.5
f1 (ppm)

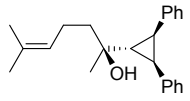

210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


Ph
OR
OH

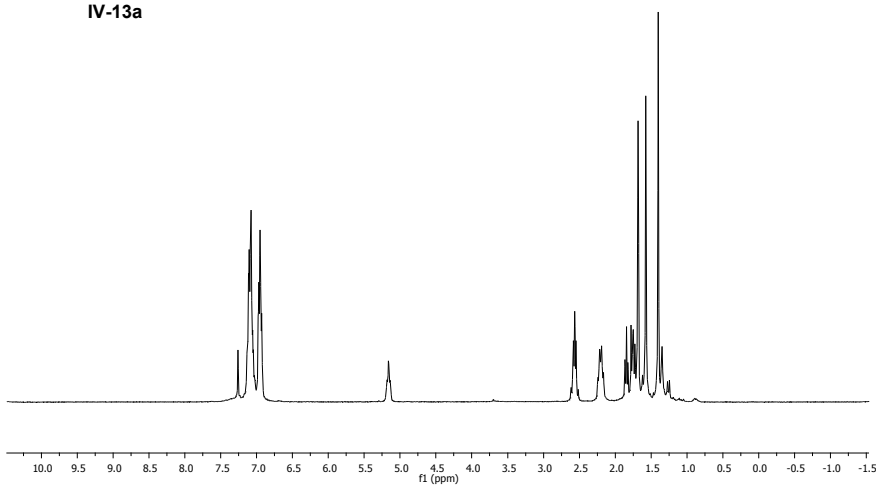
IV-12a
R = TMS

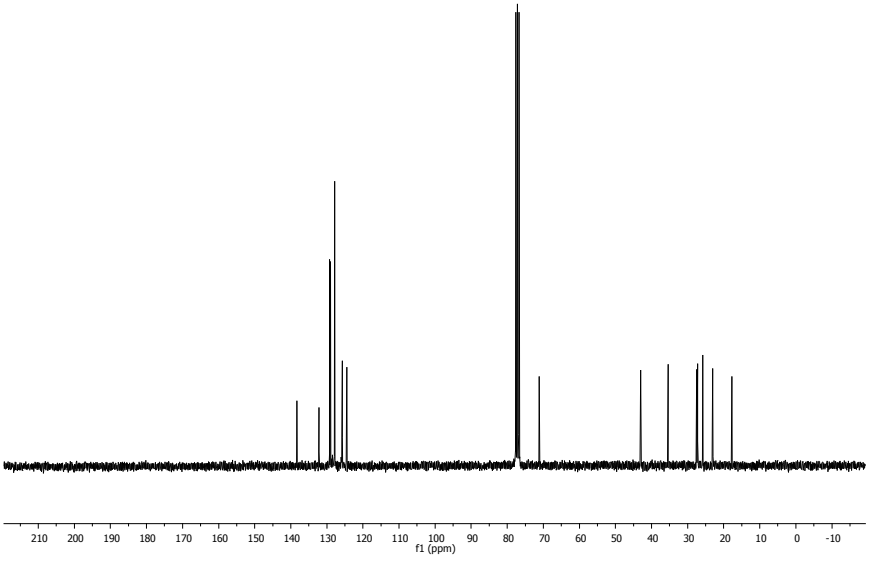
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0 -1.5
f1 (ppm)


210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


Ph
OH
Ph

IV-13a


10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0 -1.5
f1 (ppm)


210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)