Stereoselective Synthesis of Boron-Containing sp^3-Rich Building Blocks

Luis M. Nóvoa Rodríguez

Doctoral Thesis

Supervised by:

Prof. Mariola Tortosa Manzanares

Dr. Alejandro Parra Sánchez

Departamento de Química Orgánica

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Memoria presentada por

Luis M. Nóvoa Rodríguez

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A mi familia

Siempre veía este momento demasiado lejano. Lo que no me imaginaba al principio es que esta tesis doctoral ocurriría en medio de una pandemia (con confinamiento incluido), ni que *Filomena* colapsaría totalmente Madrid en enero de 2021. Pero, a pesar de todas las incidencias encontradas por el camino, esta etapa llega a su fin y es el momento de agradecer a todas las personas que me acompañaron en este viaje.

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¡Muchas gracias a todos!

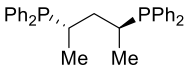

Bpin

Table of Contents

Ac	Acetate
acac	Acetylacetone
APCI$^+$	Atmospheric Pressure Chemical Ionization
aq	Aqueous
Ar	Aryl
BINAP	2,2′-bis(diphenylphosphino)-1,1′-binaphthyl
Bn	Benzyl
Boc	*tert*-Butoxycarbonyl
B_2pin_2	Bis(pinacolato)diboron
br	Broad
BTEAC	Benzyltriethylammonium chloride
dba	Dibenzylideneacetone
COSY	COrrelated SpectroscopY
cod	Cyclooctadiene
d	Doublet
dba	Dibenzylideneacetone
dbu	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCC	Dicyclohexylcarbodiimide
DCE	1,2-Dichloroethane
DCM	Dichloromethane
(+)-DET	(+)-Diethyl L-tartrate
DFT	Density Functional Theory
DM-Segphos	5,5′-Bis(diphenylphosphino)-4,4′-bi-1,3-benzodioxole
DMA	*N,N*-Dimethylacetamide
DMAP	4-(Dimethylamino)pyridine
DME	Dimethoxyethane
DMF	Dimethylformamide
DMI	*N*,*N*′-Dimethylethyleneurea

DMP	Dess-Martin Periodinane
DMAP	4-Dimethylaminopyridine
DMSO	Dimethyl sulfoxide
DPEPhos	Bis[(2-diphenylphosphino)phenyl] ether
dppBz	1,2-Bis(diphenylphosphino)benzene
dppf	1,1′-Bis(diphenylphosphino)ferrocene
dppp	1,3-Bis(diphenylphosphino)propane
dr	Diastereomeric ratio
E^+	Electrophile
ee	Enantiomeric excess
EI^+	Electronic Impact
equiv	Equivalents
er	Enantiomeric Ratio
ESI^+	Electrospray Ionization
EWG	Electron-Withdrawing Group
HBpin	Pinacolborane
HMBC	Heteronuclear Multiple Bond Correlation
HMPA	Hexamethylphosphoramide
HOMO	Highest Occupied Molecular Orbital
HPLC	High-Performance Liquid Cromatography
HRMS	High Resolution Mass Spectrometry
L	Ligand
NOE	Nuclear Overhouser Effect
Ph	Phenyl
pin	Pinacol

q	Quartet
Quinap	1-(2-Diphenylphosphino-1-naphthyl)isoquinoline
QuinoxP	2,3-Bis(tert-butylmethylphosphino)quinoxaline
quint	Quintuplet
rt	Room temperature
RuPhos	2-Dicyclohexylphosphino-2′,6′-diisopropoxybiphenyl
s	Singlet
SET	Single Electron Tranfer
sept	Septuplet
SPhos	2-Dicyclohexylphosphino-2′,6′-dimethoxybiphenyl
SPS	Solvent Purification System
t	Triplet
***t*Bu**	*tert*-Butyl
TBHP	tert-Butyl hydroperoxide
Tf	Triflate
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
TLC	Thin Layer Chromatography
TMEDA	1,2-Bis(dimethylamino)ethane
TMS	Trimethylsilyl
Ts	Tosyl
xantphos	4,5-Bis(diphenylphosphino)-9,9-dimethylxanthene
XPhos	2-Dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl



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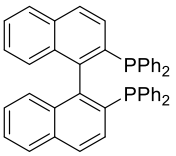

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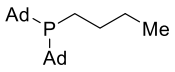

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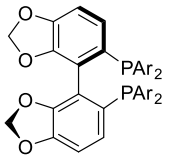

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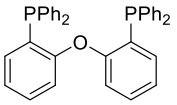

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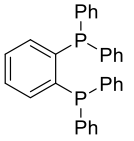

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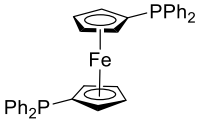

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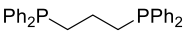

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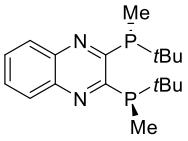
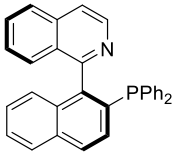
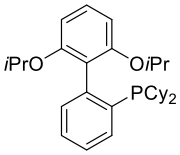


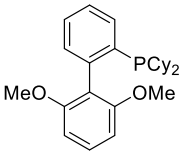
(*R*,*R*) QuinoxP®



(*S*)-Quinap



RuPhos



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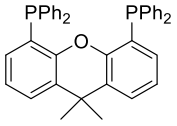
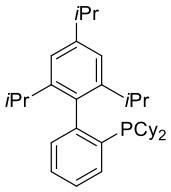
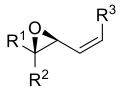


Xantphos



XPhos

List of Molecules



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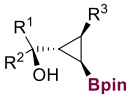

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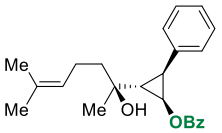

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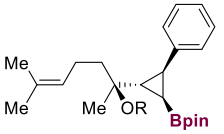

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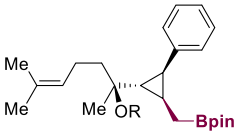

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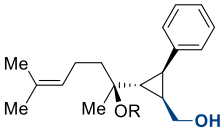

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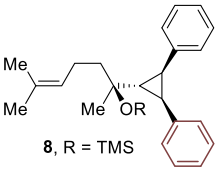

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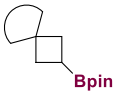

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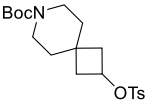

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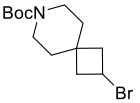

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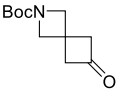

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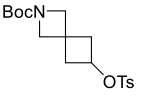

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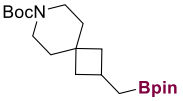

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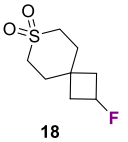

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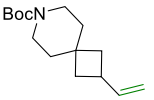

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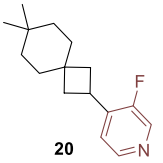

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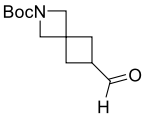

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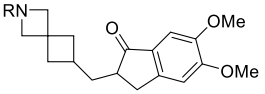

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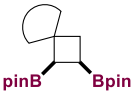

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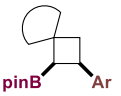

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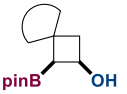

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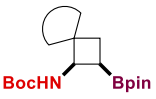

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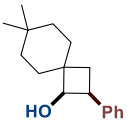

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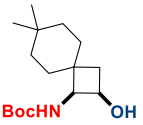

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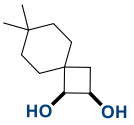

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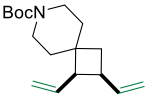

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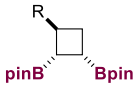

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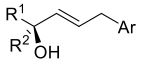

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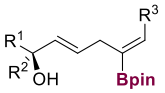

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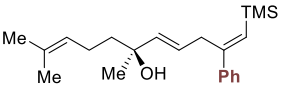

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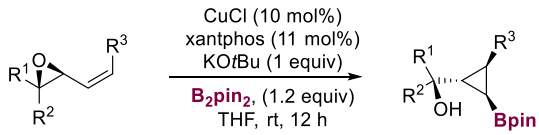
Abstract

In this doctoral thesis we have focused on the development of novel approaches to obtain borylated cyclopropanes and spirocyclobutanes. These scaffolds are privileged structures in medicinal chemistry as the strained ring provides rigidity and at the same time three-dimensionality. These two properties, make them ideal fragments to explore new areas of chemical space. Moreover, the versatility of the C–B bond allows for the synthesis of a wide range of molecules from a common intermediate.

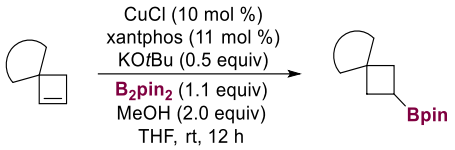
In the first chapter, we reported a new route to synthetize chiral α-hydroxy cyclopropylboronates from vinyl epoxides using a copper(I) salt and a commercially available phosphine ligand. We demonstrated that our method is stereospecific and cyclopropanes with four contiguous stereocenters can be obtained by proper selection of the structural features of the starting material (Scheme 1).



Scheme 1. Stereospecific synthesis of α-hydroxy cyclopropylboronates.

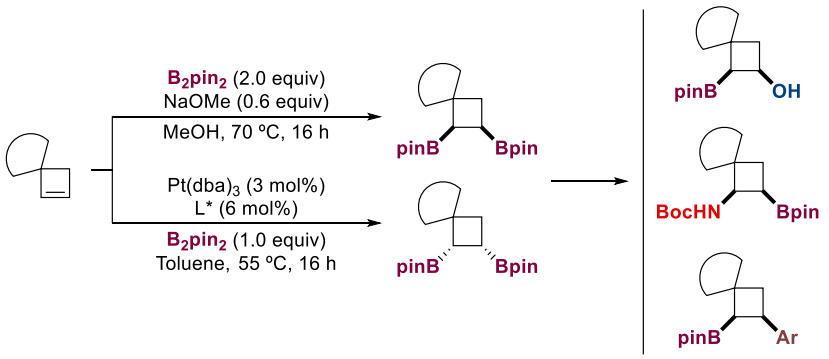
In the second chapter, we described the regioselective hydroboration of spirocyclobutenes. The combination of a commercially available phosphine ligand with an inexpensive copper(I) salt provided access to different spirocyclobutylboronates as single regioisomers (Scheme 2). Moreover, the versatility of the products was demonstrated through

different functionalizations of the C–B bond. Additionally, we developed a synthetic route to prepare a bioisostere of the approved drug Donepezil.



Scheme 2. Regioselective hydroboration of spirocyclobutenes.

In the third chapter, we developed two approaches for the preparation of chiral spirocycles trough the diboration of spirocyclobutenes. First, we developed a transition-metal-free diboration to prepare spirocycles in a diastereoselective fashion. Then, we stablished an asymmetric version to obtain optically active spirocycles using a platinum catalyst and a phosphonite chiral ligand. Moreover, selective functionalization of the boryl moieties in the products (Suzuki-Miyaura cross-coupling, oxidation and amination) allows unique control on the directionality and nature of the substituents on the spirocycle framework and provides access to a wide variety of spirocyclobutanes from a common intermediate (**Scheme 3**).

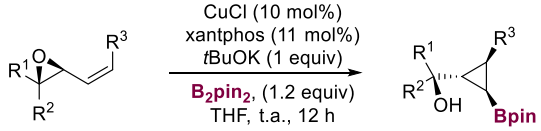


Scheme 3. Stereoselective diboration of spirocyclobutenes.

Resumen

En esta tesis doctoral nos hemos centrado en el desarrollo de nuevos procedimientos para la síntesis de ciclopropanos y espirociclobutanos borilados. Estos fragmentos son de gran importancia en el campo de la química médica, ya que el anillo tensionado aporta rigidez y al mismo tiempo tridimensionalidad a la molécula. Estas dos propiedades, los convierten fragmentos ideales para explorar nuevas regiones del espacio químico. Además, la versatilidad que presenta el enlace C–B permite la síntesis de numerosos derivados a partir de un intermedio sintético común.

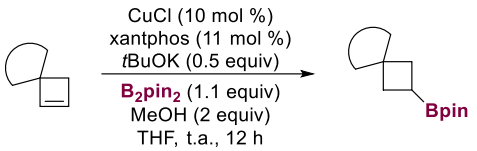
En el primer capítulo, presentamos una nueva ruta para la síntesis de α-hidroxiciclopropilboronatos quirales a partir de epóxidos vinílicos, usando una sal de cobre(I) y una fosfina comercial. Demostramos que el método era estereoespecífico y que, mediante la adecuada elección de las características geométricas de los sustratos de partida, diferentes ciclopropanos con cuatro centros quirales contiguos pueden ser sintetizados (**Esquema 1**).



Esquema 1. Síntesis estereoespecífica de α-hidroxiciclopropilboronatos.

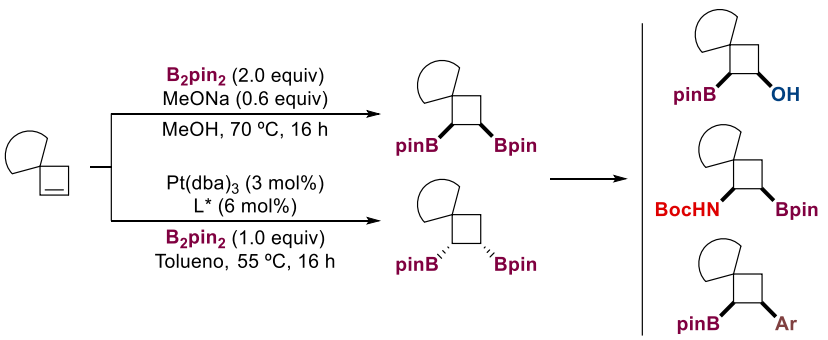
En el segundo capítulo, describimos la hidroboración regioselectiva de espirociclobutenos. La combinación de una fosfina comercial con un catalizador de cobre(I) económico permitió la síntesis de diferentes

sistemas espirocíclicos borilados como únicos regioisómeros (Esquema 2). Además, la versatilidad de los productos fue demostrada a través de diferentes funcionalizaciones del enlace C–B. Finalmente, desarrollamos una ruta para preparar un bioisóstero del fármaco comercial Donepezilo.



Esquema 2. Hidroboración regioselectiva de espirociclobutenos.

En el tercer capítulo, desarrollamos dos procedimientos para llevar a cabo la diborilación de espirociclobutenos. En primer lugar, desarrollamos la diborilación diastereoselectiva catalizada por una base de Lewis. Más tarde, nos centramos en desarrollar una versión asimétrica para obtener espirociclos ópticamente activos, utilizando un catalizador de platino y un ligando (fosfonito) quiral. Además, la funcionalización selectiva de los productos diborilados (acoplamiento de Suzuki-Miyaura, oxidación y aminación) permite el control en la direccionalidad y la naturaleza de los sustituyentes del espirociclo (Esquema 3).



Esquema 3. Diborilación estereoselectiva de espirociclobutenos.

Introduction

Introduction

1. General Overview of Organoboron Compounds

Boron is a chemical element that in the ground state has three valence electrons ($1s^2 2s^2 2p^1$). Typically, boron forms trivalent compounds with a trigonal planar geometry in which the boron atom is sp^2 hybridized with an empty *p*-orbital (**Figure 1**). For that, these compounds have an electrophilic character and are isoelectronic with carbocations.[1]

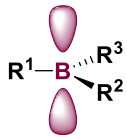


Figure 1. General structure of organoboron compounds.

Organoboron compounds are those that presents a C–B bond in their structure. This type of bonds is not present in nature, so they must be synthetized in the laboratory.

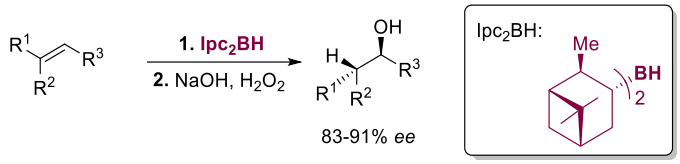
[1] Ingleson, M. J. Fundamental and Applied Properties of Borocations. In *Synthesis and Application of Organoboron Compounds;* Fernández, E., Whiting, A. Ed.; Springer International Publishing: Switzerland, 2015; pp 39–71.

It was in 1860 when Fankland and Duppa prepared and isolated the first boronic acids. However, organoboron compounds did not have application until the beginning of the 20th century.

In 1912, Alfred Stock[2] developed pioneering experimental vacuum techniques to prepare volatile and potentially explosive boron hydrides such as B_2H_6, B_4H_{10}, B_5H_9, B_5H_{11} and B_6H_{10}. Half a century later, in 1972, Lipscomb studied the borane structures through X-ray diffraction analysis. These studies gave rise to a new theory of chemical bonding, based on the formation of bonds with three centers and two electrons.[3] The work of Lipscomb was recognized with the Nobel Prize in Chemistry in 1976.

In the second half of the 20th century took place the first applications of boron hydrides in the organic chemistry field. In 1956, Herbert C. Brown published the first hydroboration reaction of alkenes[4] and, since then, many borylation reactions have been reported. Moreover, boron chemistry also played a key role in the development of modern asymmetric synthesis. In 1961, Brown reported the hydroboration of *cis*-2-butene with diisopinocampheylborane. The stereoselectivity obtained in the hydroboration with Icp_2BH was comparable to that obtained in some enzymatic processes (**Scheme 4**).[5]

[2] Stock, A.; Massenez, C. *Eur. J. Inorg. Chem.* **1912**, *45*, 3539–3568.
[3] Lipscomb, W. N. *Pure. Appl. Chem.* **1972**, *29*, 493–511.
[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.



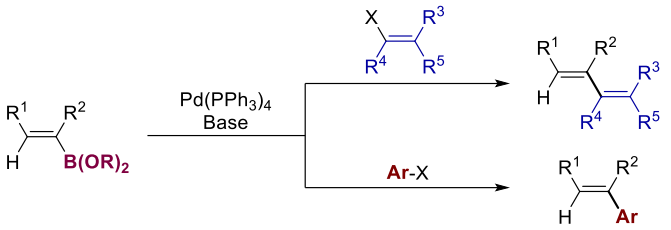
Scheme 4. Asymmetric synthesis of alcohols via hydroboration.

Brown developed an impressive work for the preparation of organoboranes and demonstrated that they were highly versatile intermediates. The C–B bond can be converted into C–O, C–N, C–C and C–X, allowing the access to a wide variety of new organic compounds from a common intermediate.[6] Due to his invaluable contributions in the field of boron chemistry, Professor Brown was awarded with the Nobel Prize in Chemistry in 1979.

In that moment, an important challenge found was the use of alkenyl boranes in cross-coupling reactions. These compounds could be synthetized through the hydroboration of alkynes, but the synthesis of conjugated dienes from alkenyl boranes in the presence of palladium and alkenyl halides was unsuccessful. One possible reason may be the weak carbanion character of organic groups in organoboranes which makes not possible the transmetalation process between R-PdX intermediates and alkenyl boranes. In 1979, Professor Akira Suzuki realized that using organoborates, formed from alkenyl boranes and a base, the transmetalation step took place smoothly. Moreover, he found that the use of boronic acids and esters presented several advantages over the use of boranes due to the fact that they are more stable and less reactive (**Scheme 5**). The Suzuki-Miyaura cross-coupling reaction represented a great

[6] Brown, H. C. *Organic Syntheses via Boranes*; Wiley: New York, 1975.

advance in organic synthesis and nowadays is an essential synthetic tool in academia and industry.[7] In 2010, Professors Akira Suzuki, Richard Heck and Ei-ichi Negishi received the Nobel Prize in Chemistry for their contribution in the development of palladium catalyzed cross-coupling reactions.



Scheme 5. Suzuki-Miyaura cross-coupling reaction.

Beyond their useful synthetic applications, boronic acid derivatives also are playing an important role in drug discovery programs. Nowadays, there are a wide number of boron-containing molecules in advanced clinical trials and others are already approved; for example, the anticancer agent Velcade®, the fungicide Kerydin® or Vabomere®, a β-lactamase inhibitor based on a cyclic boronic acid pharmacophore with antibacterial activity used for the treatment of complicated urinary tract infections **(Figure 2)**.

[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)** Almond-Thynne, J.; Blakemore, D. C.; Prydeb, D. C.; Spivey, A. C. *Chem. Sci.* **2017**, *8*, 40-62. **(g)** Sydnes, M. O. *Catalysts* **2017**, *7*, 35−48. **(h)** Hooshmand, S. E.; Heidari, B.; Sedghi, R.; Varma, R. S. *Green Chem.* **2019**, *21*, 381−405. **(i)** Jiang, S.-P.; Dong, X.-Y.; Gu, Q.-S.; Ye, L.; Li, Z.-L.; Liu, X.-Y. *J. Am. Chem. Soc.* **2020**, *142*, 19652−19659. **(j)** Zhu, Z.; Wang, Z.; Jian, Y.; Sun, H.; Zhang, G.; Lynam, J. M.; McElroy, C. R.; Burden, T. J.; Inight, R. L.; Fairlamb, I. J. S.; Zhang, W.; Gao, Z. *Green Chem.* **2021**, *23*, 920−926.

Boron containing molecules are also playing important roles in nanoscience,[8] polymer chemistry,[9] and neutron capture therapy (^{10}B).[10]

Figure 2. Approved boron-containing drugs.

2. Boronic Acids and Derivatives

Boronic acids are trivalent boron-containing molecules with two hydroxyl groups and one carbon-based substituent (the carbon atom could be sp^3, sp^2 or sp-hybridized). When the boron center is attached to a carbon atom and two alkoxides, the molecules are called boronic esters or boronates and they are key intermediates in organic synthesis.[11]

Boronic esters are more stable, less polar and easier to handle than boronic acids, because they are less prone to generate hydrogen bonds. In

[8] Aung, Y.-Y.; Kristanti, A. N.; Lee, H. V.; Zakki Fahmi, M. Z. *ACS Omega* **2021**, *6*, 17750−17765.

[9] **(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. **(d)** Brooks, W. L. A.; Sumerlin, B. S. *Chem. Rev.* **2016**, *116*, 3, 1375−1397.

[10] **(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. **(c)** Hu, K.; Yang, Z.; Zhang, L.; Xie, L.; Wang, L.; Xu, H.; Josephson, L.; Liang, S. H.; Zhang, M.-R. *Coord. Chem. Rev.* **2020**, *405*, 213139.

[11] **(a)** Meng, F.; McGrath, K. P.; Hoveyda, A. H. *Nature* **2014**, *513,* 367−374. **(b)** António, J. P. M.; Russo, R.; Carvalho, C. P.; Cal, P. M. S. D.; Gois, P. M. P. *Chem. Soc. Rev.* **2019**, *48*, 3513−3536.

organic synthesis we can find a wide variety of boronic esters. In addition, boronates bearing a chiral alkoxide have been used as asymmetric inductors in stereoselective reactions.[12] The commonly most used boronic esters are derived from ethylenglycol (Beg), pinacol (Bpin), neopentyl glycol (Bnep), hexylene glycol (Bheg), pinanediol (Bpnd) and cathecol (Bcat) (**Figure 3**).[13] Bcat esters are sensitive boronates prone to hydrolysis due to the conjugation between the benzene ring and the oxygen that increases the Lewis acidity of the boron center. On the other hand, diethanolamine (BDEA), *N*-methyliminodiacetic acid (BMIDA) and 1,8-diaminonaphthalene (Bdan) have been employed as alternative protecting groups due to their high stability.

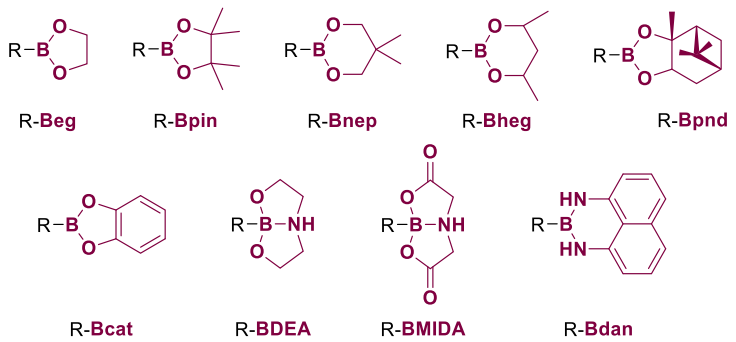
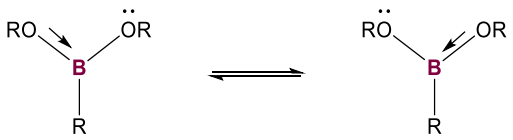


Figure 3. Most commonly used boronic esters.

[12] **(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. *J. Org. Chem.* **2013**, 78, 10009−10023.

[13] **(a)** Hall, D. G. *Boronic Acids: Preparation and Application in Organic Synthesis, Medicine and Materials*, 2nd ed.; Wiley-VCH: Boston, 2011. **(b)** Gulyás, H.; Fernández, E. The Influence of the Borane Reagent Structures on Catalytic Synthesis of Organoboranes. In *Boron: Compounds, Production and Application*, 1st ed.; Nova Science Publishers, 2011; pp. 177−220. **(c)** Fernández, E.; Whiting, A. *Synthesis and Application of Organoboron Compounds: Topics in Organometallic Chemistry*, 1st ed.; Springer, 2015.

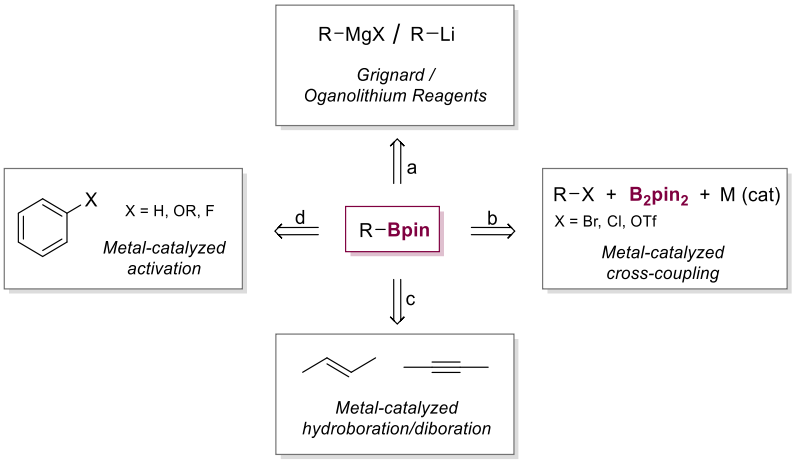
The partial π dative electron donation of the lone pair of the oxygen to the empty *p*-orbital of the boron atom confers the B–O bond (130 Kcal/mol) partial double bond character, making it stronger than the C–O bond (92 Kcal/mol).[14] When the boron center is attached to two oxygen-containing substituents, only one of them can give electron donation because the vacant *p*-orbital of the boron atom does not allow two simultaneous π dative bonds. For that reason, the electronic structure can be explained by two different resonance forms (**Scheme 6**).[13]



Scheme 6. Resonance forms of π dative bond of a boronic ester.

Due to the increased interest and their potential applications, several approaches have been reported to obtain boronic esters. In this context, the development of metal-catalyzed transformations has been the most important advance to make them available (**Scheme 7**).

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



Scheme 7. Synthesis of boronic esters.

The classical approach to synthetize aryl boronates requires the use of organolithium[15] or Grignard reagents[16] (**Scheme 7a**). The use of highly reactive nucleophiles makes this approach not compatible with several functional groups. In 1995, Miyaura reported the palladium-catalyzed cross-coupling reaction of B_2pin_2 and arylbromides or iodides to afford aryl boronic esters (**Scheme 7b**).[17] This new strategy offered a wide functional

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

[16] **(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.

[17] **(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)** Fürstner, A.; Seidel, G. *Org. Lett*. **2002**, *4*, 541–543. **(e)** Ishiyama, T.; Miyaura, N. *Chem. Rec.* **2004**, *3*, 271–280. **(f)** Billingsley, K. L.; Barder, T. E.; Buchwald, S. L. *Angew. Chem. Int. Ed*. **2007**, *46*, 5359–5363.

group compatibility and vinyl,[18] allyl[19] or benzyl[20] halides or triflates can be transformed to the corresponding boronates using this methodology.

Other useful method to prepare alkyl and alkenylboronic esters is the metal-catalyzed hydroboration and addition of diboron reagents to unsaturated substrates (Scheme 7c).[21]

More recently, the C–H borylation catalyzed by transition metals has emerged as a promising tool to synthetize aryl boronates (Scheme 7d).[22] This atom-economic strategy presents the possibility to use simple arenes instead of aryl halides. Iridium complexes are the most employed catalysts in this transformation,[23] although other metals such as rhodium,[24]

[18] **(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.

[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)** Crudden, C. M.; Edwards, D. *Eur. J. Org. Chem*. **2003**, 4695–4712. **(b)** Neeve, E. C.; Geier, S. J.; Mkhalid, I. A. I.; Westcott, S. A.; Marder, T. B. *Chem. Rev.* **2016**, *116*, 9091–9161. **(c)** Hemmings, D.; Fritemeier, R.; Westcott, S. A.; Santos, W. L.; Steel, P. G. *Chem. Soc. Rev.* **2018**, *47*, 7477–7494.

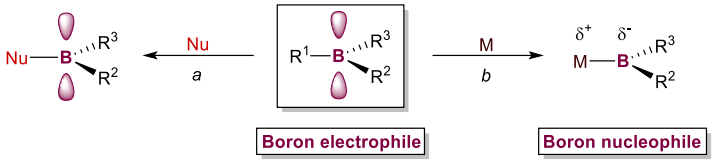
[22] **(a)** Ishiyama, T.; Miyaura, N. *J. Organomet. Chem.* **2003**, *680*, 3–11. **(b)** Mkhalid, I. A. I.; Barnard, J. H.; Marder, T. B.; Murphy, J. M.; Hartwig, J. F. *Chem. Rev*. **2010**, *110*, 890–931. **(c)** Ros, A.; Fernández, R.; Lassaletta, J. M. ***Chem. Soc. Rev.*** **2014**, ***43***, 3229–3243.

[23] **(a)** Cho, J.-Y.; Tse, M. K.; Holmes, D.; Maleczka, R. E., Jr.; Smith, M. R., III *Science* **2002**, *295*, 305–308. **(b)** Ishiyama, T.; Takagi, J.; Ishida, K.; Miyaura, N.; Anastasi, N. R.; Hartwig, J. F. *J. Am. Chem. Soc.* **2002**, *124*, 390–391. **(c)** Ros, A.; Estepa, B.; Lopez-Rodriguez, R.; Alvarez, E.; Fernandez, R.; Lassaletta, J. M. *Angew. Chem. Int. Ed.* **2011**, *50*, 11724–11728. **(d)** Kuninobu, Y.; Ida, H.; Nishi, M.; Kanai, M. *Nat. Chem.* **2015**, *7*, 712–717. **(e)** Wang, G.; Liu, L.; Ding, Y. S.; Zhou, J.; Mao, S.; Li, P. *J. Am. Chem. Soc.* **2017**, *139*, 91–94. **(f)** Zeng, J.; Naito, M.;Torigoe, T.; Yamanaka, M.; Kuninobu, Y. *Org. Lett.* **2020**, *22*, 3485–3489.

[24] **(a)** Chen, H. Y.; Schlecht, S.; Semple, T. C.; Hartwig, J. F. *Science* **2000**, *287*, 1995–1997. **(b)** Kawamorita, S.; Miyazaki, T.; Ohmiya, H.; Iwai, T.; Sawamura, M. *J. Am. Chem. Soc.* **2011**, *133*, 19310–19313. **(c)** Tanaka, J.; Nagashima, Y.; Dias, A. J. A.; Tanaka, K. *J. Am. Chem. Soc.* **2021**, *143*, 11325–11331.

palladium[25] and rhenium[26] are suitable for this transformation. Additionally, other inert bonds, such as C–F[27] or C–OR[28] also can be used in metal-catalyzed borylation reactions (**Scheme 7d**).

Most of approaches to synthetize boronic esters are based on the electrophilic nature of the boron atom (**Scheme 8a**). However, in 2006, Yamashita and Nozaki studied some boryl-lithium complexes that can act as nucleophiles, changing the classical reactivity of the boron center (**Scheme 8b**).[29] The B–Li bond is highly polarized, and the boron center gains anionic character.



Scheme 8. Different reactivity of boron compounds.

[25] **(a)** Ishiyama, T.; Ishida, K.; Takagi, J.; Miyaura, N. *Chem. Lett.* **2001**, *30*, 1082–1083. **(b)** Dai, H. X.; Yu, J. Q. *J. Am. Chem. Soc.* **2012**, *134*, 134–137. **(c)** Kuninobu, Y.; Iwanaga, T.; Omura, T.; Takai, K. *Angew. Chem. Int. Ed.* **2013**, *52*, 4431–4434.

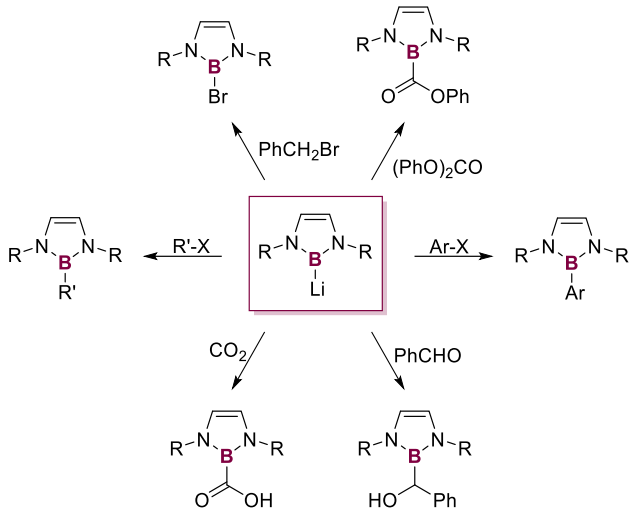
[26] **(a)** Chen, H.; Hartwig, J. F. *Angew. Chem. Int. Ed.* **1999**, *38*, 3391–3393. **(b)** Donnelly, L. J.; Faber, T.; Morrison, C. A.; Nichol, G. S.; Thomas, S. P.; Love, J. B. *ACS Catal.* **2021**, *11*, 12, 7394–7400.

[27] **(a)** Liu, X. W.; Echavarren, J.; Zarate, C.; Martin, R. *J. Am. Chem. Soc.* **2015**, *137*, 12470–12473. **(b)** Tian, Y. M.; Guo, X. N.; Kuntze-Fechner, M. W.; Krummenacher, I.; Braunschweig, H.; Radius, U.; Steffen, A.; Marder, T. B. *J. Am. Chem. Soc.* **2018**, *140*, 17612–17623.

[28] **(a)** Zarate, C.; Manzano, R.; Martin, R. *J. Am. Chem. Soc.* **2015**, *137*, 6754–6757. **(b)** Mao, L.; Szabó, K. J.; Marder, T. B. *Org. Lett.* **2017**, *19*, 1204–1207.

[29] **(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)** Cheung, M. S.; Marder, T. B.; Lin, Z. *Organometallics* **2011**, *30*, 3018–3028.

They also studied the reactivity of boryl lithium reagents with different electrophiles, demonstrating their strong nucleophilicity (**Scheme 9**). In 2007, the same authors reported the transformation of boryl lithium reagents into boryl magnesium compounds using magnesium bromide.[30] These studies represented a breakthrough in boron chemistry. However, the synthetic utility is quite limited due to the instability of the boryl lithium species.



Scheme 9. Reactivity of boryl lithium compounds with different electrophiles.

The *umpolung* strategy to generate nucleophilic boron species opened a new window for the formation of carbon–boron bonds.[31]

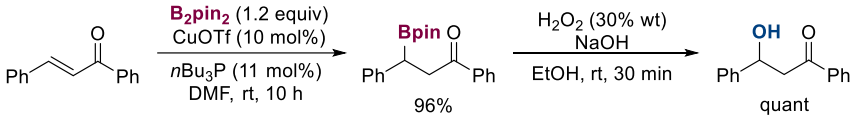
[30] Yamashita, M.; Suzuki, Y.; Segawa, Y.; Nozaki K. *J. Am. Chem. Soc*. **2007**, *129*, 9570–9571.

[31] **(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. **(d)** Neeve, E. C.; Geier, S. J.; Mkhalid, I. A. I.; Westcott, S. A.; Marder, T. B. *Chem. Rev.* **2016**, *116*, 9091–9161.

Among the different approaches that have been published to generate nucleophilic boron species, the use of copper-catalysis has emerged as a particularly attractive alternative due to its versatility. Moreover, copper catalysts are less expensive and toxic than other metal sources.

3. Copper-Catalyzed Borylation Reactions

The first borylation using copper-catalysis was carried out by Hosomi in 2000. This group reported the borylation of α,β-unsaturated ketones with a copper(I) salt and B_2pin_2 as a boron source (**Scheme 10**).[32] This reaction led to a new area of research to synthetize alkylboronic esters. They also found that the addition of phosphine ligands improved drastically the results. The oxidation of the C–B bonds shows the utility of the Cu(I)-catalyzed borylation reaction for the synthesis of β-hydroxy ketones.



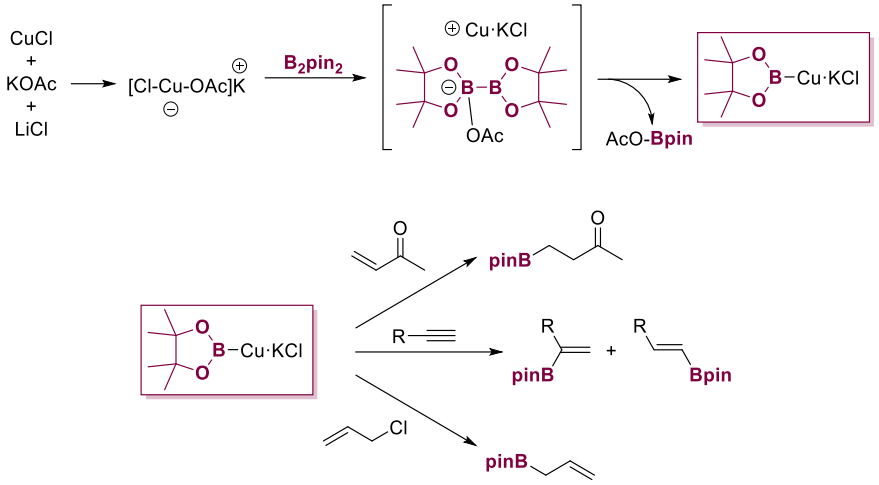
Scheme 10. Copper-catalyzed borylation of α,β-unsaturated ketones.

Then, Professor Miyaura reported the hydroboration of different unsaturated bonds.[33] The authors proposed the *in situ* formation of $[B_2pin_2OAc]^-$ mixing B_2pin_2 and CuCl in the presence of LiCl and KOAc. The

[32] Ito, H.; Yamanaka, H.; Tateiwa, J.; Hosomi, A. *Tetrahedron Lett.* **2000**, *41*, 6821–6825.
[33] **(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.

formation of this complex is required to generate the copper-boryl complexes that behaved as formal boron nucleophiles.

Using this methodology, the β-borylation of α,β-unsaturated carbonyl compounds, monoborylation of alkynes and allylic substitution of allyl chloride are described (Scheme 11).

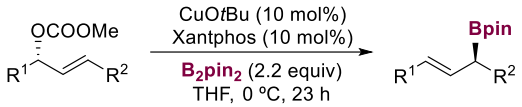


Scheme 11. Miyaura's copper-catalyzed borylation.

Five years later, in 2005, Sawamura reported the first stereospecific copper-catalyzed borylation of allylic carbonates. This approach reveled the synthetic potential of copper-catalyzed borylation reactions.[34] The copper-boryl complex generated *in situ* could catalyze the formal S_N2' borylation of enantioenriched allylic carbonates. The reaction underwent α-to-*γ* chirality transfer with *anti*-stereoselectivity, affording enantiomerically enriched

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

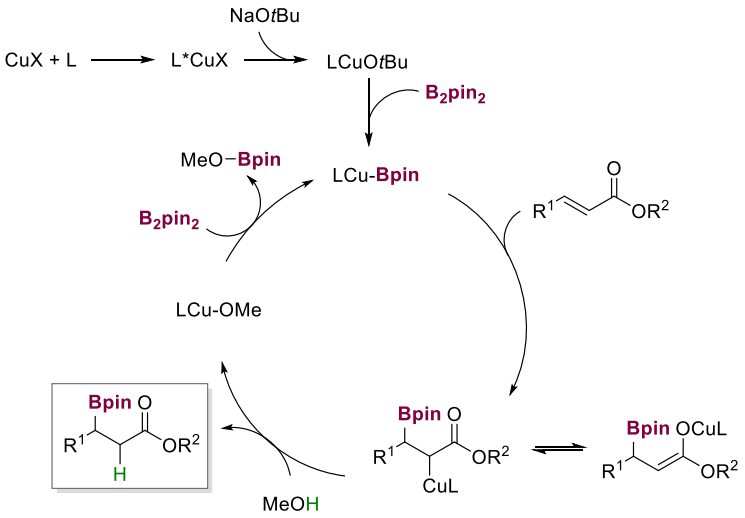
allyl-boronates, a useful class of compounds that can react with aldehydes to afford enantioenriched homoallylic alcohols (Scheme 12).



Scheme 12. Copper-catalyzed borylation of allylic carbonates.

In 2006, Yun and co-workers reported an efficient protocol for the copper-catalyzed borylation of α,β-unsaturated carbonyl compounds (Scheme 13).[35] In this investigation, the authors found that the use of a proton source such as an alcohol increased drastically the reaction rate. Methanol let the protonation of the copper enolate to afford the product and copper methoxide, needed to regenerate the catalytic cycle. Without methanol, the regeneration of the copper-boryl complex is very slow. In this work they also reported the *in situ* generation of the highly sensitive copper alkoxide by reaction of copper(I) chloride and sodium *tert*-butoxide. These two finding were crucial for the subsequent development of novel copper-catalyzed borylation reactions.

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



Scheme 13. Proposed mechanism for the β-borylation of α,β-unsaturated carbonyl compounds.

In the last twenty years, the number of reported publications that involve copper-boryl species as key intermediates has dramatically increased. Copper-boryl complexes can react with a wide variety of

electrophiles such as α,β-unsaturated compounds,[36] alkynes,[37] alkenes,[38] allenes[39] and also aldehydes[40] and imines[41] (**Scheme 14**). A comprehensive

[36] *Selected examples*: **(a)** Lee, J. E.; Yun, J. *Angew. Chem. Int. Ed*. **2008**, *47*, 145–147. **(b)** Chen, I. H.; Yin, L.; Itano, W.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc*. **2009**, *131*, 11664–11665. **(c)** O'Brien, J. M; Lee, K. S.; Hoveyda, A. H. *J. Am. Chem. Soc*. **2010**, *132*, 10630–10633. **(d)** Moure, A. L.; Gómez-Arráyas, R.; Carretero, J. C. *Chem. Commun*. **2011**, *47*, 6701–6703. **(e)** Solé, C.; Whiting, A.; Gulyás, H.; Fernandez, E. *Adv. Synth. Catal*. **2011**, *353*, 376–384. **(f)** Hornillos, V.; Vila, C.; Otten, E.; Feringa, B. L. *Angew. Chem. Int. Ed.* **2015**, *54*, 7867–7871.

[37] *Selected examples*: **(a)** Jang, H.; Zhugralin, A. R.; Lee, Y.; Hoveyda, A. H.; *J. Am. Chem. Soc.* **2011**, *133*, 7859–7871. **(b)** Moure, A. L.; Arrayás, R. G.; Cárdenas, D. J.; Alonso, I.; Carretero, J. C. *J. Am. Chem. Soc*. **2012**, *134*, 7219–7222. **(c)** Moon, J. H.; Jung, H.-Y.; Lee, Y. J.; Lee, S. W.; Yun, J.; Lee, J. Y. *Organometallics* **2015**, *34*, 2151–2159. *For carboboration of akynes see*: **(a)** Alfaro, R.; Parra, A.; Aleman, J.; García-Ruano, J. L.; Tortosa, M. *J. Am. Chem Soc.* **2012**, *134*, 15165–15168. **(b)** Kim-Lee, S. H.; Alonso, I.; Mauleón, P.; Gómez-Arrayás, R.; Carretero, J. C. *ACS Catal.* **2018**, *8*, 8993–9005. **(c)** Li, Z.; Sun, J. *Org. Lett.* **2021**, *23*, 3706–3711.

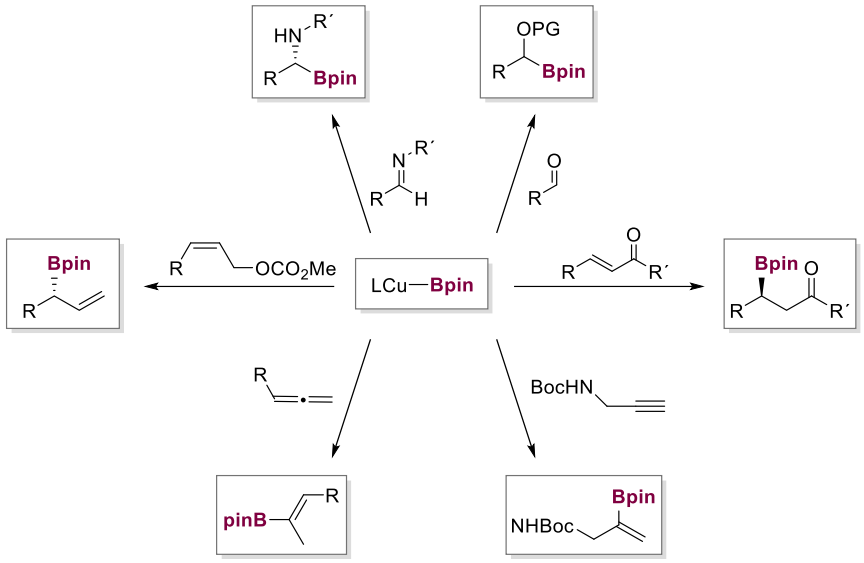
[38] *Selected examples:* **(a)** Laitar, D. S.; Tsui, E. Y.; Sadighi, J. P. *Organometallics* **2006**, *25*, 2405–2408. **(b)** Dang, L.; Zhao, H.; Lin, Z.; Marder, T. B. *Organometallics* **2007**, *26*, 2824–2832. **(c)** Lee, Y.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2009**, *131*, 3160–3161. **(d)** Corberán, R.; Mszar, N. W.; Hoveyda, A. H. *Angew. Chem. Int. Ed.* **2011**, *50*, 7079–7082. **(e)** Meng, F. K.; Jang, H. J.; Hoveyda, A. H. *Chem. Eur. J*. **2013**, *19*, 3204–3214. **(f)** Parra, A.; Amenos, L.; Guisan-Ceinos, M.; López, A.; García-Ruano, J. L.; Tortosa, M. *J. Am. Chem. Soc*. **2014**, *136*, 15833–15836. **(g)** Xi, Y.; Hartwig, J. F. *J. Am. Chem. Soc.* **2016**, *138*, 6703–6706. **(h)** Iwamoto, H.; Kubota, K.; Ito, H. *Chem. Commun.* **2016**, *52*, 5916–5919. **(i)** Guisan-Ceinos, M.; Parra, A.; Martin-Heras, V.; Tortosa, M. *Angew. Chem. Int. Ed.* **2016**, *55*, 6969–6972. **(j)** Jang, W. J.; Song, s. M.; Moon, J. H.; Lee, J. Y.; Yun, J. *J. Am. Chem. Soc.* **2017**, *139*, 13660–13663.

[39] *Selected examples*: **(a)** Semba, K.; Fujihara, T.; Terao, J.; Tsuji, Y. *Angew. Chem. Int. Ed.* **2013**, *52*, 12400–12403. **(b)** Meng, F. K.; Jang, H.; Jung, B.; Hoveyda, A. H. *Angew. Chem. Int. Ed*. **2013**, *52*, 5046–5051. **(c)** Jang, H.; Jung, B.; Hoveyda, A. H. *Org. Lett*. **2014**, *16*, 4658–4661. **(d)** Yuan, W.; Song, L.; Ma, S. *Angew. Chem. Int. Ed*. **2016**, *55*, 3140–3143. **(e)** Han, J.; Zhou, W.; Zhang,P.-C.; Wang, H.; Zhang, R.; Wu, H.-H.; Zhang, J. *ACS Catal.* **2019**, *9*, 6890–6895.

[40] *Selected examples*: **(a)** Molander, G. A.; Wisniewski, S. R. *J. Am. Chem. Soc*. **2012**, *134*, 16856–16868. **(b)** Kubota, K.; Yamamoto, E.; Ito, H. *J. Am. Chem. Soc*. **2015**, *137*, 420–424. **(c)** Wang, L.; Zhang, T.; Sun, W.; He, Z.; Xia, C.; Lan, Y.; Liu, C. *J. Am. Chem. Soc.* **2017**, *139*, 5257–5264. **(d)** Taguchi, J.; Takeuchi, T.; Takahashi, R.; Masero, F.; Hajime Ito, H. *Angew. Chem. Int. Ed.* **2019**, *58*, 7299–7303.

[41] *Selected examples*: **(a)** Beenen, M. A.; An, C.; Ellman, J. A. *J. Am. Chem. Soc.* **2008**, *130*, 6910–6911. **(b)** Wang, D.; Cao, P.; Wang, B.; Jia, T.; Lou, Y. Z.; Wang, M.; Liao, J. *Org. Lett*. **2015**, *17*, 2420–2423. **(c)** Li, Z.; Zhang, L.; Nishiura, M.; and Hou, Z. *ACS Catal.* **2019**, *9*, 4388–4393. **(d)** Li, Z.; Zhang, L.; Nishiura, M.; Luo, G.; Luo, Y.; Hou, Z. *J. Am. Chem. Soc.* **2020**, *142*, 1966–1974. **(e)** Wu, F.-P.; Wu, X.-F. *Angew. Chem. Int. Ed.* **2021**, *60*, 695–700. **(f)** Kubota, K.; Miura, D.; Takeuchi, T.; Osaki, S.; Ito, H. *ACS Catal.* **2021**, *11*, 6733–6740.

review of this literature exceeds the scope of this chapter, therefore, only selected examples of copper-catalyzed borylation of allylic electrophiles will be discussed in *Chapter I*.



Scheme 14. The use of copper-boryl complexes in organic synthesis.

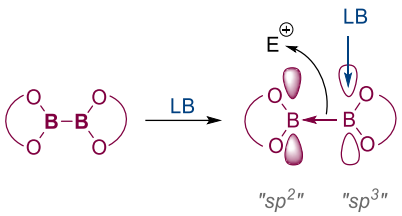
4. Transition-Metal-Free Borylation Reactions

Nowadays, the development of catalytic processes that do not require the use of metal complexes is critical for the development of modern organic synthesis because they avoid the use of expensive catalysts and make the synthetic process greener.[42] In the borylation field, the activation

[42] Sun, C.-L.; Shi, Z.-J. *Chem. Rev.* **2014**, *114*, 9219–9280.

of diboron(4) compounds with Lewis bases offer an alternative to the use of transition-metal complexes to obtain organoboron compounds.[43]

Tetra(alkoxy)diboron reagents are bifunctional Lewis acids, which can interact with Lewis bases to afford sp^2-sp^3 Lewis acid-base adducts (**Scheme 15**). Upon formation of these complexes, the boron–boron bond becomes strongly polarized and the non-quaternized boryl moiety B(sp^2) gains a strong nucleophilic character. Simple Lewis bases can transform electrophilic, non-polar diboranes into nucleophilic synthetics equivalents of boryl anions that can react with appropriate organic electrophiles.



Scheme 15. Generation of sp^2-sp^3 diboron adducts with a simple Lewis base.

The first evidence of the formation of a sp^2-sp^3 Lewis acid-base adduct was reported in 1949 by Schlesinger and co-workers. The authors described that B_2Cl_4 forms a ''liquid monoetherate'' or a ''solid dietherate'' upon addition of different amounts of diethyl ether.[44] In the following years, several studies were published describing the coordination of different Lewis bases with diboron(4) compounds,[45] but it wasn't until 1984 when

[43] Wen, Y.; Deng, C.; Xie, J.; Kang, X. *Molecules* **2019**, *24*, 101.
[44] Wartik, T.; Moore, R.; Schlesinger, H. I. *J. Am. Chem. Soc.* **1949**, *71*, 3265–3266.
[45] **(a)** Finch, A.; Schlesinger, H. I. *J. Am. Chem. Soc.* **1958**, *80*, 3573–3574. **(b)** Wartik, T.; Apple, E. F. *J. Am. Chem. Soc.* **1958**, *80*, 6155–6158. **(c)** Taft, R. W.; Carten, J. W. *J. Am. Chem. Soc.* **1964**, *86*, 4199–4200. **(d)** Kirk, R. W.; Smith, D. L.; Airey, W.; Timms, P. L. *J. Chem. Soc. Dalton Trans.* **1972**, 1392–1396.

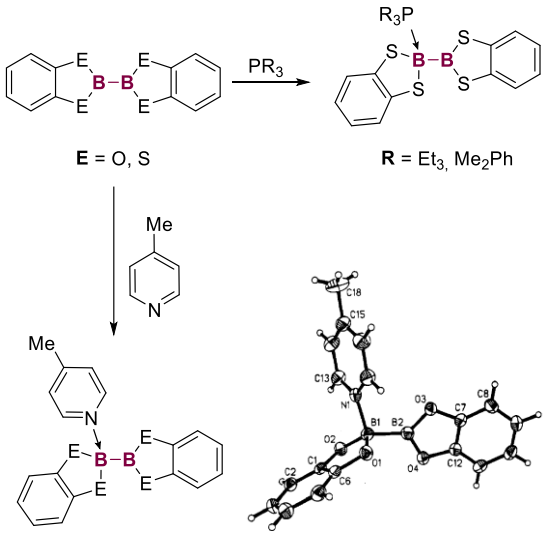
the first cyclic sp^2-sp^3 diborane was fully and unequivocally characterized by Haubold and co-workers (**Figure 4**).[46] The structurally characterization showed a characteristic planar and tetrahedral boron atoms, as well as a B–N dative bond. This structural authentication was also supported by ^{11}B and ^{1}H NMR experiments and elemental analysis data.

Figure 4. Structure of the first characterized cyclic sp^2-sp^3 diborane.

More than 10 years later, Marder and Norman reported the first structural characterization of acyclic sp^2-sp^3 diboranes formed by addition of pyridyl and phosphine Lewis bases to bis(catecholato) and bis(thiocatecholato)diboron.[47] The authors reported the significant stabilizing effect of the π-donation from the oxygen and sulfur atoms to the empty *p* orbital of the boron center. Moreover, the comparation of the structural data of the B_2cat_2 (B–B length = 1.678 Å) and the corresponding pyridine complex (B–B length = 1.713 Å) showed that the B–B bond is lengthened upon mono-quaternization (**Scheme 16**).

[46] Haubold, W.; Hrebicek, J.; Sawitzki, G. *Z. Naturforsch. B: Anorg. Chem., Org. Chem.* **1984**, *39*, 1027–1031.

[47] **(a)** Nguyen, P.; Dai, C.; Taylor, N. J.; Power, W. P.; Marder, T. B.; Pickett, N. L.; Norman, N. C. *Inorg. Chem.* **1995**, *34*, 4290–4291. **(b)** Clegg, W.; Dai, C.; Lawlor, F. J.; Marder, T. B.; Nguyen, P.; Norman, N. C.; Pickett, N. L.; Power, W. P.; Scott, A. J. *J. Chem. Soc. Dalton Trans.* **1997**, 839–846.



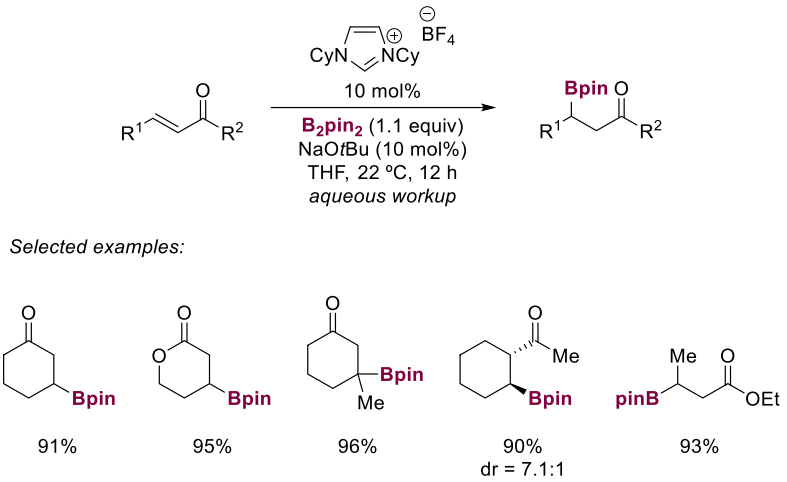
Scheme 16. Structural characterization of acyclic sp^2–sp^3 diboryl complexes.

In 2009, Marder and co-workers reported the first copper-catalyzed borylation of aryl halides in the presence of bis(pinacolato) diboron and potassium *tert*-butoxide. In this work, a control reaction in the absence of the copper catalyst resulted in the formation of traces of the borylated product.[48] The authors suggested that the formation of a sp^2-sp^3 adduct formed by reaction of B_2pin_2 with the base provided a nucleophilic boryl source capable of borylating the aryl electrophile directly, although very slowly.

The same year, Hoveyda group reported the first transition-metal-free borylation of α,β-unsaturated ketones and esters.[49] The authors proposed that the imidazolium salts were deprotonated leading to *in situ* generation

[48] Kleeberg, C.; Dang, L.; Lin, Z.; Marder, T. B. *Angew. Chem. Int. Ed.* **2009**, *48*, 5350–5354.
[49] Lee, K.; Zhugralin, A. R.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2009**, *131*, 7253–7255.

of *N*-heterocyclic carbenes (NHCs). The reaction of these species with B_2pin_2 generates the nucleophilic boron source that smoothly react with the Michael acceptors (**Scheme 17**). Although the sp^2-sp^3 complex was not isolated, DFT calculations, revealed that their increased reactivity over B_2pin_2 could be due to the charge differences on the boron atoms and its longer B–B bond length. Finally, in 2012 the [B_2pin_2·NHC] complex was isolated and fully characterized by Marder and co-workers.[50] Years later, the same research group reported the enantioselective diboration of unsaturated carbonyls esters, ketones, amides and aldehydes in the presence of a chiral NHC, MeOH and dbu.[51]



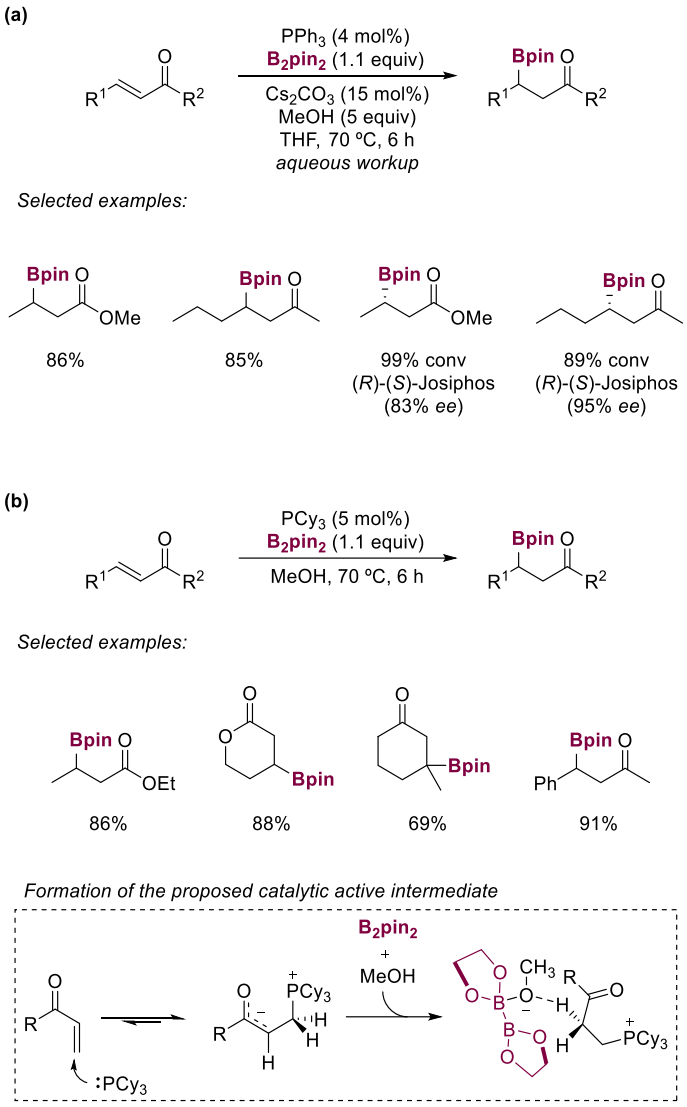
Scheme 17. Transition-metal-free borylation of α,β-unsaturated ketones and esters catalyzed by NHC complexes.

[50] Kleeberg, C.; Crawford, A. G.; Batsanov, A. S.; Hodgkinson, P.; Apperley, D. C.; Cheung, M. S.; Lin, Z.; Marder, T. B. *J. Org. Chem.* **2012**, *77*, 785–789.

[51] Wu, H.; Radomkit, S.; O'Brien, J. M.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2012**, *134*, 8277-8285.

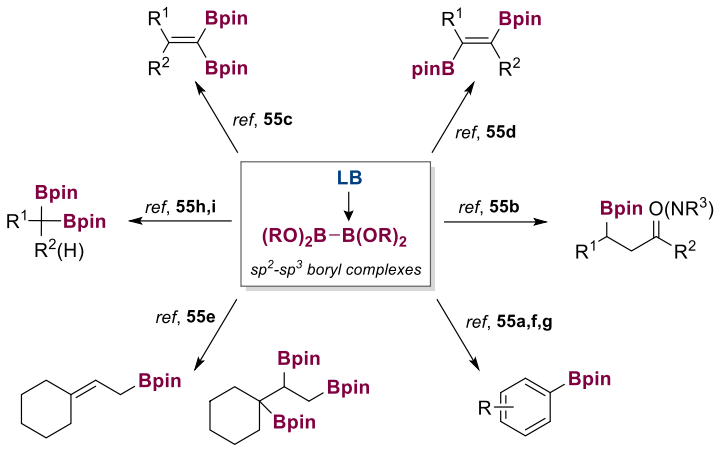
In 2010, Fernández, presented a complementary method to carried out the borylation of α,β-unsaturated compounds in the absence of transition metals. Initial investigations showed that B_2pin_2 in the presence of phosphine ligands, a catalytic amount of base and MeOH as additives could facilitate the borylation of different enones. Moreover, they found that some chiral phosphines could induce some degree of enantioselectivity (Scheme 18a).[52] This work represents the first example of an enantioselective transition-metal-free borylation reaction. The proposed reaction mechanism involves a direct coordination of the phosphine with one of the boron atoms that promotes the B–B bond cleavage after interaction with the unsaturated substrate. Further studies[53] demonstrated that the use of Brönsted bases was not required to promote the β-borylation and the reaction occurs using only the phosphine in the presence of the alcohol. The new proposed catalytic cycle, supported by NMR experiments, DFT calculations and stoichiometric experiments, suggests that the phosphine plays a key role by interaction with the substrate to generate a zwitterionic phosphonium enolate. This intermediate can further deprotonate the MeOH in the presence of B_2pin_2 and the resulting methoxide activates the diboron reagent to generate the ion pair $[\alpha\text{-(H)},\beta\text{-}(PR_3)\text{-ketone}]^+\text{-}[B_2pin_2\cdot OMe]^-$ that is proposed as the active catalyst for this transformation (Scheme 18b).

[52] Bonet, A.; Gulyás, H.; Fernández, E. *Angew. Chem. Int. Ed.* 2010, *49*, 5130–5134.
[53] Pubill-Ulldemolins, C.; Bonet, A.; Gulyás, H.; Bo, C.; Fernández, E. *Org. Biomol. Chem.* 2012, *10*, 9677–9682.



Scheme 18. Phosphine promoted organocatalytic β-borylation reactions reported by Fernández and co-workers.

More recently, different sp^2-sp^3 diboryl complexes were characterized[54] and their applications have been demonstrated in the synthesis of boron containing organic molecules (**Scheme 19**).[55] A complete review of this literature exceeds the scope of this chapter. Therefore, only the transition-metal-free 1,2-diboration of alkenes will be discussed in *Chapter III*.



Scheme 19. Different applications of sp^2-sp^3 boryl complexes.

[54] **(a)** Grigsby, W. J.; Power, P. *Chem. Eur. J.* **1997**, *3*, 368–375. **(b)** Neu, A.; Mennekes, T.; Paetzold, P.; Englert, U.; Hofmann, M.; Schleyer, P v. R. *Inorg. Chim. Acta* **1999**, *289*, 58–69. **(c)** Gao, M.; Thorpe, S. B.; Santos, W. L. *Org. Lett.* **2009**, *11*, 3478–3481. **(d)** Kleeberg, C.; Dang, L.; Lin, Z.; Marder, T. B. *Angew. Chem. Int. Ed.* **2009**, *48*, 5350–5354. **(e)** Gao, M.; Thorpe, S. B.; Kleeberg, C.; Slebodnick, C.; Marder, T. B.; Santos, W. L. *J. Org. Chem.* **2011**, *76*, 3997–4007. **(f)** Thorpe, S. B.; Guo, X.; Santos, W. L. *Chem. Commun.* **2011**, *47*, 424–426. **(g)** Pietsch, S.; Neeve, E. C.; Apperley, D. C.; Bertermann, R.; Mo, F.; Qiu, D.; Cheung, M. C.; Dang, L.; Wang, J.; Radius, U.; Lin, Z.; Kleeberg, C.; Marder, T. B. *Chem. Eur. J.* **2015**, *21*, 7082–7099. **(h)** Zheng, J.; Wang, Y.; Li, Z. H.; Wang, H. *Chem. Commun.* **2015**, *51*, 5505–5508.

[55] *Selected examples:* **(a)** Yamamoto, E.; Izumi, K.; Horita, Y.; Ito, H. *J. Am. Chem. Soc.* **2012**, *134*, 19997–20000. **(b)** Pubill-Ulldemolins, C.; Bonet, A.; Bo, C.; Gulyás, H.; Fernández, E. *Chem. Eur. J.* **2012**, *18*, 1121–1126. **(c)** Morinaga, A.; Nagao, K.; Ohmiya, H.; Sawamura, M. *Angew. Chem. Int. Ed.* **2015**, *54*, 15859–15862. **(d)** Nagao, K.; Ohmiya, H.; Sawamura, M. *Org. Lett.* **2015**, *17*, 1304–1307. **(e)** Miralles, N.; Alam, R.; Szabý, K. J.; Fernández, E. *Angew. Chem. Int. Ed.* **2016**, *55*, 4303–4307. **(f)** Candish, L.; Teders, M.; Glorius, F. *J. Am. Chem. Soc.* **2017**, *139*, 7440–7443. **(g)** Zhang, L.; Jiao, L. *J. Am. Chem. Soc.* **2017**, *139*, 607–610. **(h)** Nallagonda, R.; Padala, K.; Masarwa, A. *Org. Biomol. Chem.* **2018**, *16*, 1050–1064. **(i)** Salvado, O.; Gava, R.; Fernández, E. *Org. Lett.* **2019**, *21*, 9247–9250.

Chapter I

Stereospecific Synthesis of

α-Hydroxy Cyclopropylboronates

from Vinyl Epoxides

Chapter I. Stereospecific Synthesis of α-Hydroxy Cyclopropylboronates from Vinyl Epoxides

1. Introduction

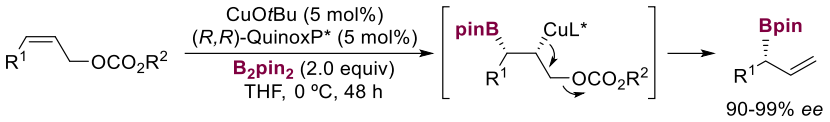
1.1 Copper-Catalyzed Borylation of Allylic Electrophiles

Among the different substrates that have been employed to obtain boronic esters through copper-catalyzed borylation reactions, allylic electrophiles represent an important subclass.

In 2007, Ito and Sawamura reported the synthesis of α-chiral allylboronates from allylic carbonates using a copper catalyst and a commercially available chiral phosphine ligand (**Scheme 20**).[56] This methodology involved a formal S_N2' type reaction that allowed for the access of optically active allylboronates. The obtained boronic esters are very useful synthetic intermediates in organic chemistry, due to their highly efficient chirality transfer in allylation reactions. Years later, McQuade described a steroconvengent version using mixtures of *E*/*Z* allylic ethers and a chiral carbene.[57]

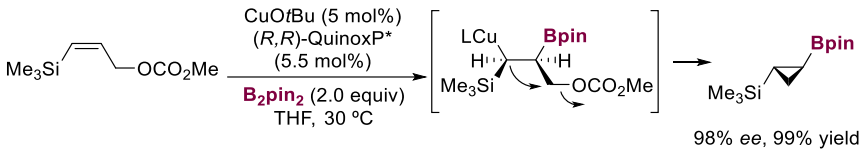
[56] Ito, H.; Ito, S.; Sasaki, Y.; Matsuura, K.; Sawamura, M. *J. Am. Chem. Soc.* **2007**, *129*, 14856−14857.

[57] **(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.



Scheme 20. Enantioselective copper-catalyzed borylation of allylic carbonates.

In 2008, Ito and Sawamura published a copper(I)-catalyzed diastereo- and enantioselective route to convert γ-silylated allylic carbonates into optically active B–Si bifunctional cyclopropane derivatives using a chiral bidentate phosphine ligand (**Scheme 21**).[58] The silyl group changed the expected regioselectivity in the insertion step due to stereoelectronic effects.



Scheme 21. Enantioselective synthesis of 1-silyl-2-borylcyclopropanes.

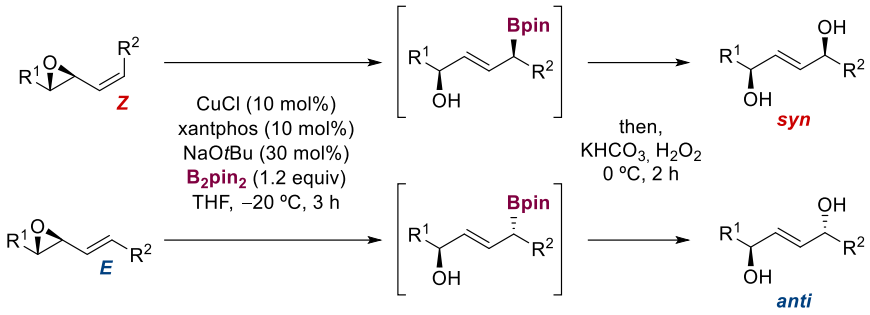
In 2010, the same authors developed a new asymmetric route for the synthesis of *trans*-2-aryl and heteroaryl-substituted cyclopropylboronates using (*Z*)-allylic phosphates as starting materials.[59]

In 2011, Tortosa described the synthesis of stereodefined 1,4-diols through a copper-catalyzed formal S_N2' addition of diboronates to vinyl

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

[59] Zhong, C.; Kunii, S.; Kosaka, Y.; Sawamura, M.; Ito, H. *J. Am. Chem. Soc.* **2010**, *132*, 11440–11442.

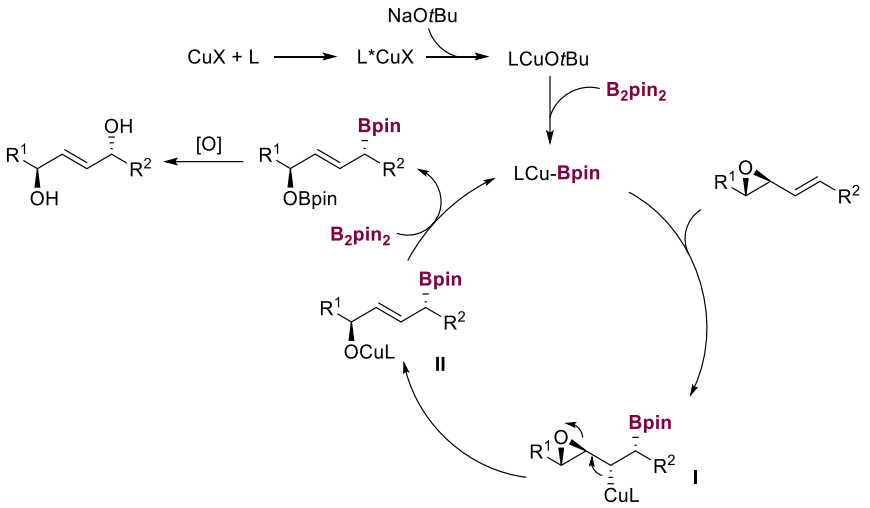
epoxides (**Scheme 22**).[60] This scaffold is present in a wide number of biologically active compounds like ingramycin or palmerolide A. *Syn* and *anti* 1,4-diols can be prepared by tuning the geometry of the epoxide and/or the double-bond.



Scheme 22. Diastereoselective synthesis of *syn* and *anti* 1,4-diols.

The observed stereochemical outcome could be explained by an *anti*-attack of the copper-boryl intermediate to the vinyl epoxide in an *s-trans* conformation.[61] Insertion of the alkene into the Cu–B bond would afford the β-borylalkyl copper intermediate **I**, followed by β-oxygen elimination and ring opening to form copper alkoxide **II**. Finally, reaction of **II** with B_2pin_2 allows the regeneration of the catalytic cycle (**Scheme 23**).

[60] Tortosa, M. *Angew. Chem. Int. Ed*. **2011**, *50*, 3950–3953.
[61] Marshall, J. A. *Chem. Rev.* **1989**, *89*, 1503–1511.



Scheme 23. Proposed mechanism for the synthesis of 1,4-diols.

1.2 Synthesis of α-Hydroxy Cyclopropanes

Cyclopropanes are three membered carbocycles that present unique steric and electronic properties. Their rigidity and strain (approximately 27 kcal/mol) lead to significant challenges for their construction and manipulation.[62]

Stereodefined cyclopropanes are increasingly important scaffolds in drug discovery programs. The introduction of the cyclopropyl ring into lead compounds started in the 1960s and it has demonstrated to improve their pharmacokinetic properties and reduce some secondary effects.[63] Among biologically active cyclopropane derivatives, the α-hydroxy cyclopropyl

[62] Ebner, C.; Carreira, E. M. *Chem. Rev.* **2017**, *117*, 11651−11679.

[63] **(a)** Taylor, R. D.; MacCoss, M.; Lawson, A. D. G. *J. Med. Chem.* **2014**, *57*, 5845−5859. **(b)** Talele, T. T. *J. Med. Chem.* **2016**, *59*, 8712−8756.

fragment represents a prevalent core structure (**Figure 5**). Moreover, limited approaches have been reported for the synthesis of this scaffold.

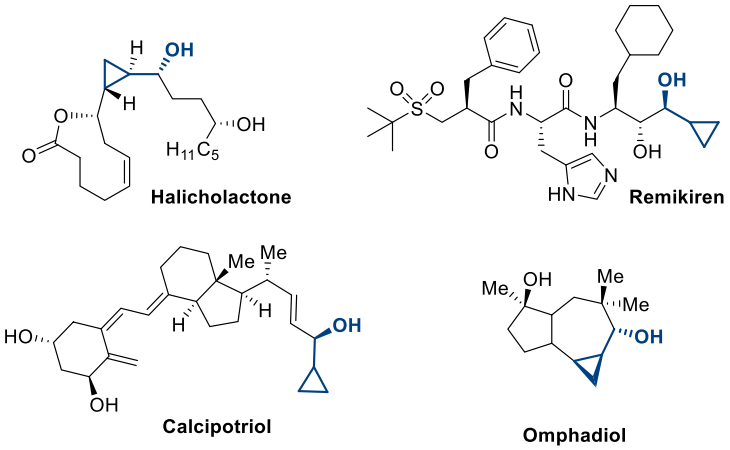
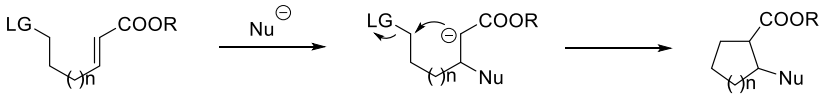


Figure 5. α-Hydroxy cyclopropanes in natural products and drugs.

The term "Michael Initiated Ring Closure reaction" (MIRC) was defined by Little and Dawson in 1980 as "a general 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 24**).[64]

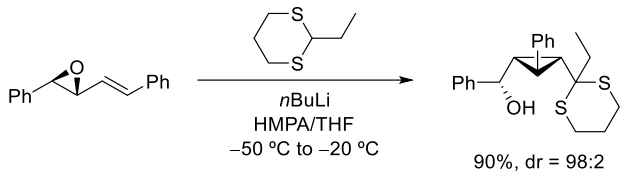


Scheme 24. A general MIRC reaction.

[64] Little, R. D.; Dawson, J. R. *Tetrahedron Lett.* **1980**, *21*, 2609–2612.

Among the wide number of examples that have been reported using this methodology, the MIRC reaction represents a very useful and elegant method to prepare cyclopropanes.[65] Several electrophiles are suitable to undergo this nucleophilic addition/ring-closing process, and allylic epoxides are among them.

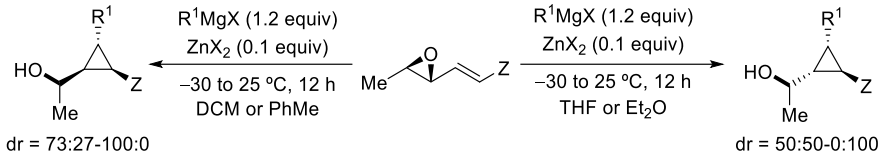
In 2005, Pan described the synthesis of 1,2,3-trisubstituted cyclopropanes from unactivated phenyl-vinyl epoxides as Michael acceptors (**Scheme 25**).[66] A tandem conjugated addition and epoxide-opening sequence afforded trisubstituted cyclopropanes with high diastereoselectivity.



Scheme 25. MIRC reaction with dithianillithium derivatives and allylic epoxides.

In 2013, Dieter found that organozincates and Grignard reagents in the presence of zinc catalysts also undergo MIRC reaction (**Scheme 26**) to yield 1,2,3-trisubstituted cyclopropanes.[67] This reaction was diastereodivergent, and just by changing the reaction solvent both diastereomers can be prepared.

[65] Lebel, H.; Marcoux, J.-F.; Molinaro, C.; Charette, A. B. *Chem. Rev.* **2003**, *103*, 977–1050.
[66] Xie, X.; Yue, G.; Tang, S.; Huo, X.; Liang, Q. She, X.; Pan, X. *Org. Lett.* **2005**, *7*, 4057–4059.
[67] Dhakal, R. C.; Dieter, R. K. *J. Org. Chem.* **2013**, *78*, 12426–12439.



Scheme 26. Diastereoselective synthesis of 1,2,3-trisubstituted cyclopropanes.

1.3 Synthesis of Cyclopropylboronates

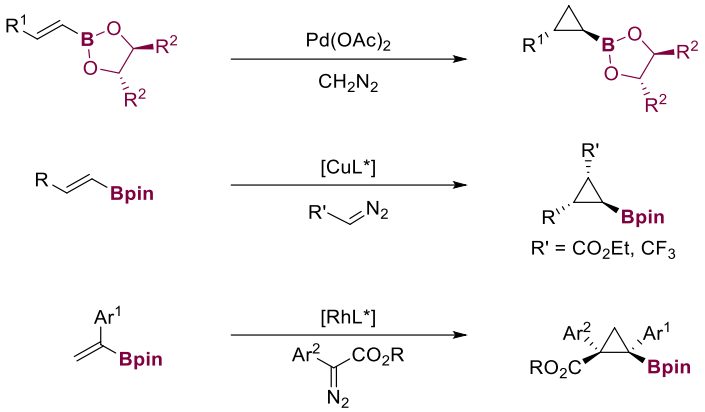
Due to the importance of cyclopropanes, the incorporation of a boronic ester in their structure could be useful to obtain different cyclopropyl derivatives from a common intermediate or for their incorporation into complex molecules through the C–B bond functionalization. The carbon–boron bond is configurationally stable and the boryl moiety offers a handle for further functionalization.[68]

Different diastereoselective approaches have been reported to provide cyclopropylboronates.[69] Additionally, optically active cyclopropylboronates

[68] **(a)** Leonori, D.; Aggarwal, V. K. *Angew. Chem. Int. Ed.* **2015**, *54*, 1082–1096. **(b)** Sandford, C.; Aggarwal, V. K. *Chem. Commun*. **2017**, *53*, 5481–5494.

[69] *For recent diastereoselective methods to obtain cyclopropylboronates see*: **(a)** Hussain, M. M.; Li, H.; Hussain, N.; Ureña, M.; Carroll, P. J.; Walsh, P. J. *J. Am. Chem. Soc.* **2009**, *131*, 6516–6524. **(b)** Liskey, C. W.; Hartwig, J. F. *J. Am. Chem. Soc.* **2013**, *135*, 3375–3378. **(c)** Miyamura, S.; Araki, M.; Suzuki, T.; Yamaguchi, J.; Itami, K. *Angew. Chem. Int. Ed.* **2015**, *54*, 846–851. **(d)** He, J.; Jiang, H.; Takise, R.; Zhu, R.-Y.; Chen, G.; Dai, H.-X.; Dhar, T. G. M.; Shi, J.; Zhang, H.; Cheng, P. T. W. Yu, J.-Q. *Angew. Chem. Int. Ed.* **2016**, *55*, 785–789. **(e)** Benoit, G.; Charette, A. B. *J. Am. Chem. Soc.* **2017**, *139*, 1364–1367. **(f)** Murai, M.; Mizuta, C.; Taniguchi, R.; Takai, K. *Org. Lett.* **2017**, *19*, 6104–6107. **(g)** Sayes, M.; Benoit, G.; Charette, A. B. *Angew. Chem. Int. Ed.* **2018**, *57*, 13514–13518. **(h)** Ohtani, T.; Tsuchiya, Y.; Uraguchi, D.; Ooi, T. *Org. Chem. Front.* **2019**, *6*, 1734–1737. **(i)** Liu, Y.; Zhou, Y.; Li, D.; Chen, H.; Zhao, J.; Qu, J. *Org. Chem. Front.* **2019**, *6*, 983–988 **(j)** Wu, F.-P.; Luo, X.; Radius, U.; Marder, T. B.; Wu, X.-F. *J. Am. Chem. Soc.* **2020**, *142*, 14074–14079. **(k)** Mizoguchi, H.; Seriu, M.; Sakakura, A. *Chem. Commun.* **2020**, *56*, 15545–15548.

have been prepared through different methodologies. The most studied approach is based on the cyclopropanation of chiral vinyl boronates and asymmetric cyclopropanation using copper or rhodium chiral catalysts (Scheme 27).[70]



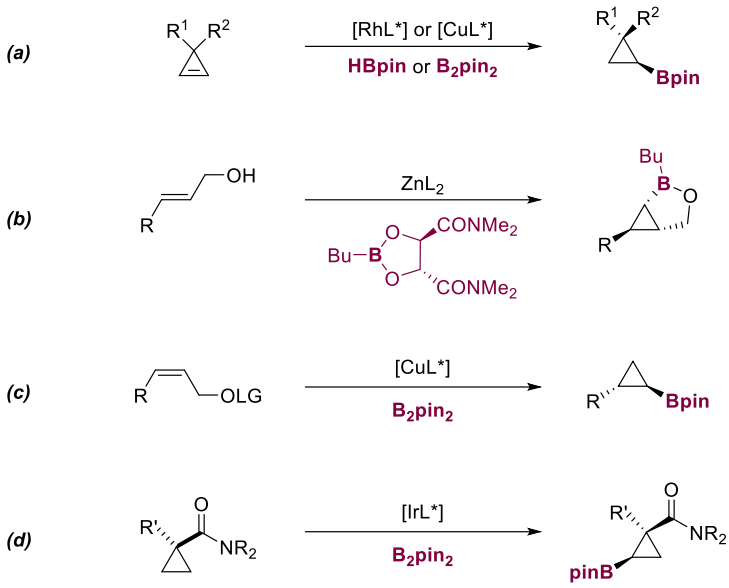
Scheme 27. Enantioselective Simmons-Smith type cyclopropanation.

Other reported approaches consist in the hydroboration of cyclopropenes with copper or rhodium catalyst in the presence of chiral ligands (Scheme 28a),[71] cyclopropanation of allylic alcohols using chiral

[70] **(a)** Imai, T.; Mineta, H.; Nishida, S. *J. Org. Chem.* **1990**, *55*, 4986–4988. **(b)** Zhou, S.-M., Deng, M.-Z., Xia, L.-J. and Tang, M.-H. *Angew. Chem. Int. Ed.* **1998**, *37*, 2845–2847. **(c)** Luithle, J. E. A.; Pietruszka, J.; Witt, A. *Chem. Commun.* **1998**, 2651–2652. **(d)** Luithle, J. E. A.; Pietruszka, J. *J. Org. Chem.* **1999**, *64*, 8287–8297. **(e)** Pietruszka, J.; Witt, A. *J. Chem. Soc. Perkin Trans. 1* **2000**, 4293–4300. **(f)** Luithle, J. E. A.; Pietruszka, J. *Eur. J. Org. Chem.* **2000**, 2557–2562. **(g)** Luithle, J. E. A.; Pietruszka, J. *J. Org. Chem.* **2000**, *65*, 9194–9200. **(h)** Pietruszka, J.; Witt, A.; Frey, W. Eur. *J. Org. Chem.* **2003**, 3219–3229. **(i)** Carreras, J.; Caballero, A.; Pérez, P. J. *Angew. Chem. Int. Ed.* **2018**, *57*, 2334–2338. **(j)** Sun, X.; Gu, P.; Qin, J.; Yan Su, Y. *Chem. Commun.* **2020**, *56*, 12379–12382. **(k)** Altarejos, J.; Sucunza, D.; Vaquero, J. J.; Carreras, J. *Org. Lett.* **2021**, *23*, 6174–6178.

[71] **(a)** Rubina, M.; Rubin, M.; Gevorgyan, V. *J. Am. Chem. Soc.* **2003**, *125*, 7198–7199. **(b)** Parra, A.; Amenós, L.; Guisán-Ceinos, M.; López, A.; García-Ruano, J. L.; Tortosa, M. *J. Am. Chem. Soc.* **2014**, *136*, 15833–15836. **(c)** Tian, B.; Liu, Q.; Tong, X.; Tian, P.; Lin, G.-Q. *Org. Chem. Front.* **2014**, *1*, 1116–1122.

boron sources (**Scheme 28b**)[72], borylative ring closure of allylic carbonates and phosphates using chiral copper-boryl complexes (**Scheme 28c**)[73] or C–H borylation of cyclopropanes using iridium complexes. (**Scheme 28d**).[74]



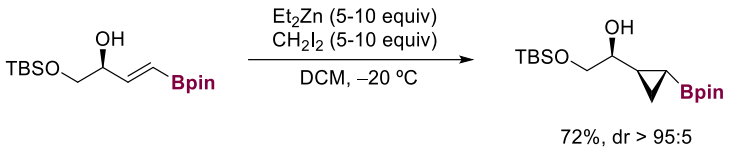
Scheme 28. Other approaches to obtain optically active cyclopropylboronates.

Despite the significant efforts to obtain enantioenriched cyclopropyl-boronates, an important subclass of cyclopropylboronates that is still underdeveloped is that containing a secondary α-hydroxy group. The introduction of a boryl moiety into this fragment would provide a modular platform to incorporate α-hydroxy cyclopropanes into more complex

[72] Zimmer, L. E.; Charette, A. B. *J. Am. Chem. Soc.* **2009**, *131*, 15624–15626.
[73] **(a)** Ito, H.; Kosaka, Y.; Nonoyama, K.; Sasaki, Y.; Sawamura, M. *Angew. Chem. Int. Ed.* **2008**, *47*, 7424–7427. **(b)** Zhong, C.; Kunii, S.; Kosaka, Y.; Sawamura, M.; Ito, H. *J. Am. Chem. Soc.* **2010**, *132*, 11440–11442.
[74] Shi, Y.; Gao, Q.; Xu, S. *J. Am. Chem. Soc.* **2019**, *141*, 10599–10604.

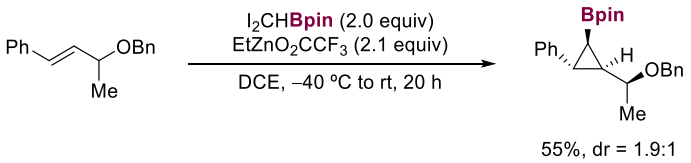
molecules. In the literature only two examples to build this scaffold were reported at the outset of this doctoral thesis.

One approach is based on the diastereoselective cyclopropanation of *trans*-disubstituted vinylboronates (**Scheme 29**). This strategy presents limitations in the structural scope and the stereoselectivity, therefore, only *trans*-disubstituted products can be formed.[75]



Scheme 29. Cyclopropanation of α-hydroxy vinylboronates.

In 2017, Charette reported the borocyclopropanation of allylic ethers using boronate-substituted zinc carbenoids generated *in situ* (**Scheme 30**). They obtained good diastereoselectivities when the starting material has a primary protected alcohol. However, with a secondary one the product was obtained as a 1.9:1 mixture of diastereomers.[76]



Scheme 30. Synthesis of α-hydroxy cyclopropylboronates from allylic alcohols.

[75] **(a)** Pietruszka, A.; Witt, A. *Synlett* **2003**, 91. **(b)** Murray, S. A.; Luc, E. C. M.; Meek, S. *J. Org. Lett.* **2018**, *20*, 469–472.
[76] Benoit, G.; Charette, A. B. *J. Am Chem. Soc.* **2017**, *139*, 1364–1367.

2. Previous Work in Our Research Group

Enantiomerically enriched vinyl epoxides are attractive building blocks in organic synthesis. They can be easily prepared from α-epoxy alcohols through an oxidation-olefination sequence or from dienes through asymmetric epoxidation.[77] The unique conjugation of the oxirane ring and the double bond makes them very versatile electrophiles that had been used in metal-catalyzed transformations to prepare enantiomerically enriched molecules through stereospecific transformations.[78]

As mentioned before, years ago our research group decided to explore the reactivity of vinyl epoxides in the presence of nucleophilic copper-boryl complexes. They found that allylic epoxides are suitable substrates to build 1,4-diols in a stereospecific manner. Modulating the geometry of the epoxide and the alkene, *syn* or *anti*-1,4 diols could be obtained.[60] Dr. Laura Amenós found during her PhD studies that one of the limitations of this method was that vinyl epoxides with aromatic substituents in the double bond did not provide the expected 1,4-diol, instead a complex mixture of products was obtained. However, she could identify the formation of cyclopropylboronate **2a** as a single diastereomer (**Scheme 33**).

Driven by the interest in the synthesis of functionalized small rings, our research group started the optimization process to obtain α-hydroxy cyclopropylboronates from enantiomerically enriched vinyl epoxides.

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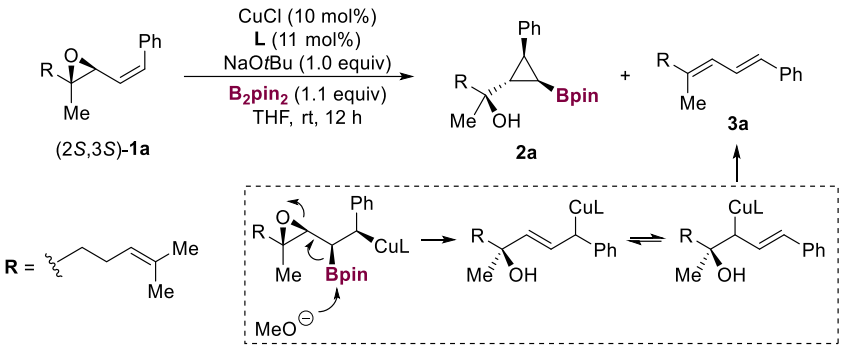
[77] Berkessel, A.; Engler, H.; Leuther, T. M. In *Science of Synthesis: Catalytic Oxidation in Organic Synthesis*; Muñiz, K., Ed.; Thieme: Stuttgart, 2017, Chapter 5, pp 245–307.

[78] *For a review, see*: **(a)** Pineschi, M.; Bertolini, F.; Di Bussolo, V.; Crotti, P. *Curr. Org. Synth.* **2009**, *6*, 290–324. **(b)** He, J.; Ling, J.; Chiu, P. *Chem. Rev.* **2014**, *114*, 8037–8128.

Vinyl epoxide **1a**, was tested under the conditions previously developed for the synthesis of 1,4-diols (**Scheme 33**), affording cyclopropylboronate **2a** in 30% yield. Using 1 equivalent of the base, the yield increased up to 77% (**Table 1**, **entry 1**) and the formation of diene **3a** also was detected. This undesired product could be formed after the insertion step through elimination of the boryl moiety and subsequent ring opening followed by isomerization of the resulting allyl copper intermediate and β-oxygen elimination (**Table 1**).

Different ligands and bases were tested to optimize the process that was shown to be highly dependent on the ligand. The use of PCy_3, failed to deliver cyclopropylboronate **2a** and only the formation of diene **3a** was observed (**Table 1**, **entry 2**). The use of a bidentate phosphine with a small bite angle, dppBz (β_n = 83°), favored the formation of **3a**, and only a small amount of cyclopropane **2a** could be detected (**Table 1**, **entry 3**). Increasing the bite angle of the ligand favored the formation of **2a**. DPEPhos (β_n = 102°) afforded cyclopropane **2a** and diene **3a** in almost a 1:1 mixture (**Table 1**, **entry 4**). The previous results, obtained with xantphos, with a bigger bite angle (β_n = 111°) afforded the best result. Finally, changing the counterion of the base from sodium to lithium resulted in lower yield of cyclopropane **2a** (**Table 1**, **entry 5**). On the contrary, KO*t*Bu allowed to completely suppress the formation of diene **3a** (**Table 1, entry 6**). When the amount of base was reduced (**Table 1**, **entry 7**) the yield for **2a** dropped down significantly.

Table 1. Reaction optimization.[a]



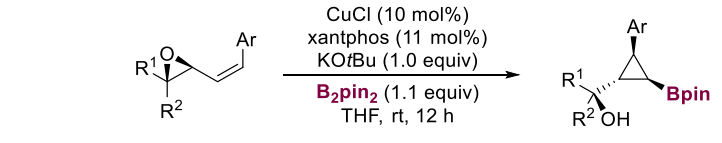
Entry[a]	Ligand	Change	Yield 2a (%)[b]	Yield 3a (%)[b]
1	xantphos	NaO*t*Bu	77	8
2	PCy_3	-	-	56
3	dppBz	-	4	60
4	DPEPhos	-	26	30
5	xantphos	Using LiO*t*Bu	33	8
6	**xantphos**	**Using KO*t*Bu**	**85 (81)**[c]	-
7	xantphos	Using KO*t*Bu (0.5 equiv)	29	7

[a]Reaction conditions: **1** (0.2 mmol), B_2pin_2 (0.24 mmol), base (0.2 mmol), CuCl (10 mol%), **L** (11 mol%), THF (0.2 M). [b]Yield calculated by ^1H NMR using 1,4-diacetylbenzene as internal standard. [c]Isolated yield.

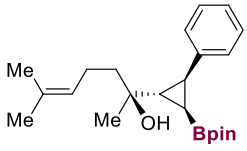
Cyclopropane **2a** was obtained as a single diastereomer, indicating that the insertion step took place with complete diastereocontrol. The relative configuration for the four contiguous stereocenters was determined from single-crystal X-ray crystallography of **2a**.

The substrate scope (**Scheme 31**) includes modifications in the stereoelectronic effects of the aryl group on the alkene. The reaction

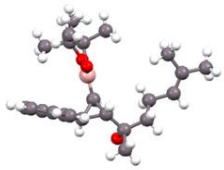
showed good tolerance to *ortho*- (**2b**), *para*- (**2c**-**2f**) and *meta*- (**2g**-**2h**) substitution including electron withdrawing and electron donating groups. In all cases, cyclopropanes **2** were obtained as single diastereomers. Additionally, epoxide **1i**, with a *cis* geometry in the oxirane ring, gave diastereomer **2i**, with a different relative stereochemistry between the oxygenated carbon and the three stereocenters on the cyclopropyl ring.



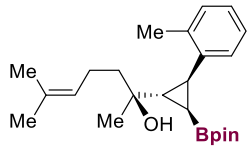
1 **2**



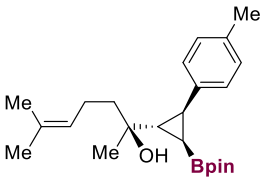
2a, 81%
dr ≥ 98:2



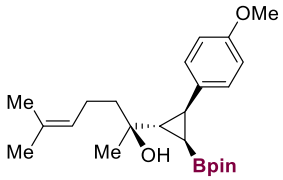
X-Ray structure ***2a***



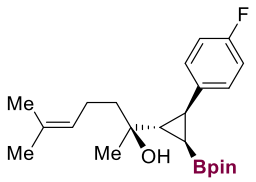
2b, 43%
dr ≥ 98:2



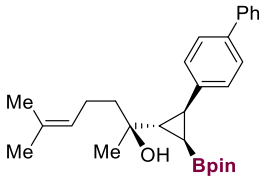
2c, 82%
dr ≥ 98:2



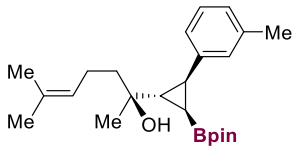
2d, 54%
dr ≥ 98:2



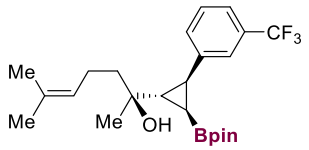
2e, 94%
dr ≥ 98:2



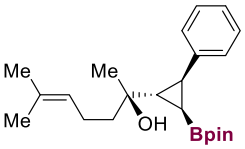
2f, 42%
dr ≥ 98:2



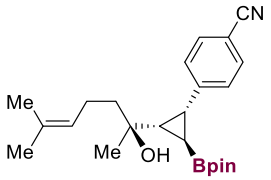
2g, 92%
dr ≥ 98:2



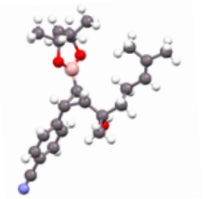
2h, 88%
dr ≥ 98:2



2i, 67%
dr ≥ 98:2



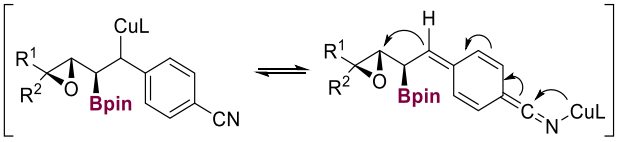
2j, 76%
dr ≥ 98:2



X-Ray structure ***2j***

Scheme 31. Scope of the reaction.

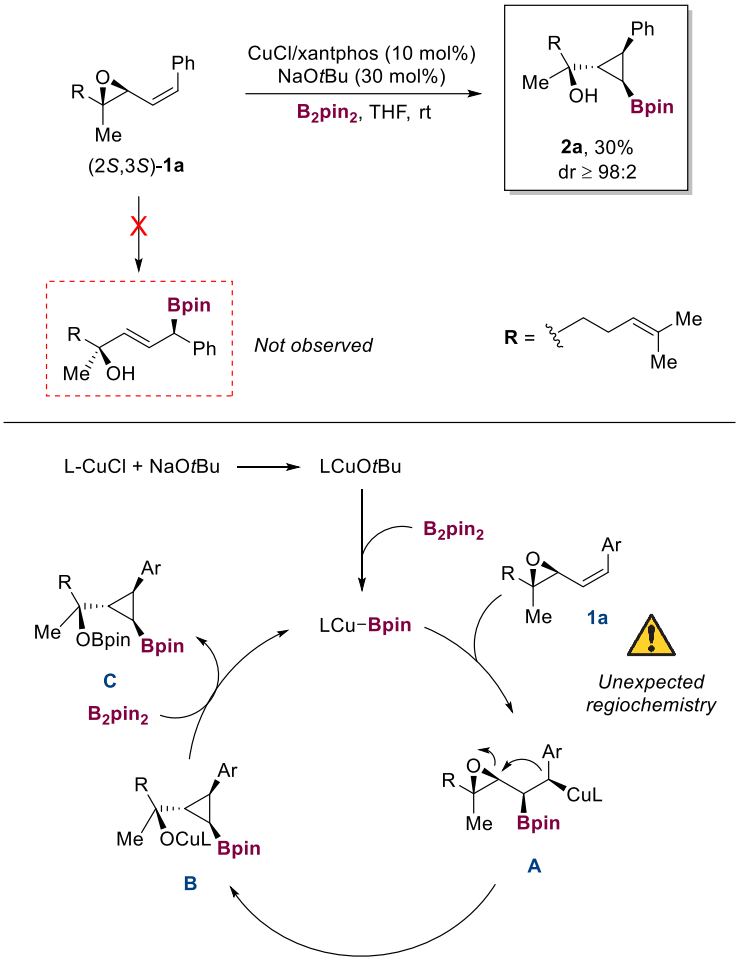
Surprisingly, epoxide **1j**, with a *para*-cyano group, afforded cyclopropylboronate **2j**, with the boronic ester and the aromatic ring in a *trans* relationship. The ^{1}H NMR of **2j** showed a clear change on the shift and multiplicity of the proton next to the boryl moiety compared to the rest of cyclopropanes. Indeed, single-crystal X-ray crystallography analysis revealed the formation of a different diastereomer. This unexpected result could be explained by formation of a *para*-quinone dimethide intermediate (**Scheme 32**), favored by the electron-deficient aryl group.[79]



Scheme 32. Formation of the possible *para*-quinone dimethide intermediate.

A change in the regiochemistry in the insertion step, promoted by the presence of the aromatic ring, could explain the formation of this unexpected product. This outcome could be favoured by coordination of the oxygen of the epoxide to the boron atom. From **B**, α-hydroxy cyclopropylboronate **C** would be formed through an intramolecular S_N2 reaction (**Scheme 33**).

[79] *For the formation of a related extended copper-enolate from a benzylic intermediate, see*: Lee, J.; Radomkit, S.; Torker, S.; del Pozo, J.; Hoveyda, A. H. *Nat. Chem.* **2018**, *10*, 99–108.



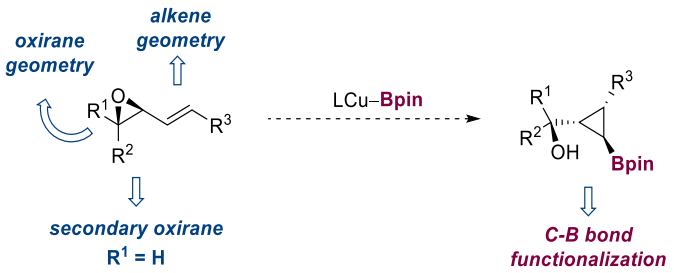
Scheme 33. Proposed mechanism for the formation of **2a**.

3. Expanded Scope of the Methodology

3.1 Objectives

Based on the previous results obtained by Dr. Laura Amenós in this PhD thesis we decided to complete this study tackling some questions that had not been previously answered.

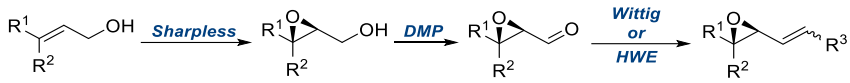
First, we decided to expand the scope of the reaction (Scheme 34). In particular, we wanted to test the influence of the geometry of the double bond and the geometry of the epoxide in the transformation. To do that, we planned to synthetize a series of vinyl epoxides with modifications in the geometry of both the double bond and the oxirane ring. If the reaction was stereospecific different isomers could be obtaining by appropriate modulation of the geometry of the starting materials. Moreover, we wanted to know if our methodology could be used with disubstituted epoxides. If successful, we could obtain cyclopropylboronates bearing a secondary hydroxy group. Finally, we also proposed to study the feasibility of different functionalizations of the C–B bond to demonstrate the versatility of the final products.



Scheme 34. Objectives of *Chapter I*.

3.2 Synthesis of the New Starting Materials

To expand the scope of our method, we synthetized several vinyl epoxides with different modifications. The synthetic sequence followed to prepare the vinyl epoxides started from the Sharpless epoxidation of the corresponding allylic alcohols, followed by Dess-Martin oxidation. Finally, a Wittig olefination was used to afford the alkenes with *Z* geometries. *E*-alkenes were synthetized from the corresponding enantioenriched vinyl aldehydes and diethyl benzyl-phosphonate derivatives through a Horner-Wadsworth-Emmons reaction (**Scheme 35**).

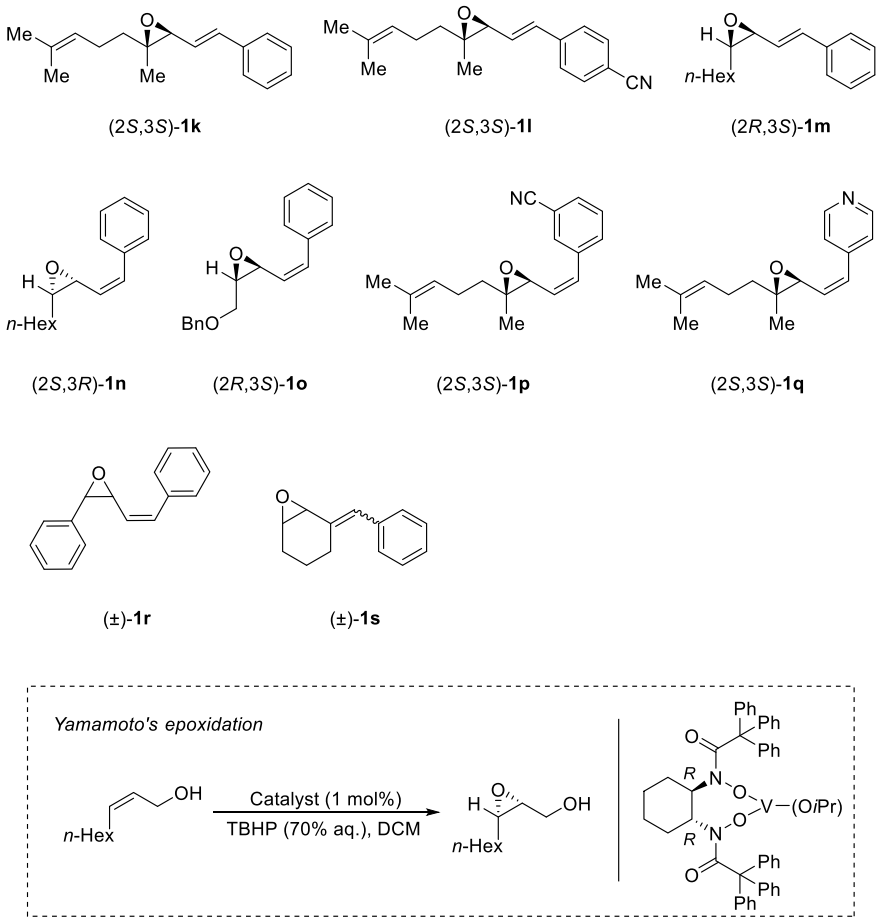


Scheme 35. Strategy for the synthesis of vinyl epoxides.

Following this synthetic sequence, we obtained different vinyl epoxides with *E* geometries (**1k**-**1m**) to study the influence of the geometry of the double bond in the stereochemical outcome of the transformation. Moreover, two disubstituted (instead of trisubstituted) epoxides were synthetized (**1m-1o**), to explore their compatibility under the optimized reaction conditions. Epoxide **1n** was synthetized from the corresponding allylic alcohol using the methodology described by Yamamoto.[80] The reported chiral vanadium complex offers some advantages over the

[80] Zhang, W.; Basak, A.; Kosugi, Y.; Hoshino, Y.; Yamamoto, H. *Angew. Chem. Int. Ed.* **2005**, *44*, 4389–4391.

classical Sharpless epoxidation like the use of higher temperatures, shorter reaction times and the use of aqueous TBHP as oxidant. Moreover, the method offers higher enantioselectivities for *cis* and *trans* olefins. Using this alternative approach, we expected to increase the enantiomeric ratio of the starting material to obtain cyclopropylboronates with higher enantiomeric excesses. Using the (*R*,*R*) catalyst, the (2*S*,3*R*) epoxide was obtained. Vinyl epoxide **1p** was prepared to observe the influence of the cyano group in *meta* position. Epoxide **1q** bearing a pyridine ring attached to the double bond was prepared to test their compatibility of this heterocycle under the reaction conditions. Finally, epoxide **1r** with an aromatic ring attached to the epoxide and cyclic epoxide **1s** were synthetized to further expand the scope of the transformation (Scheme 36).



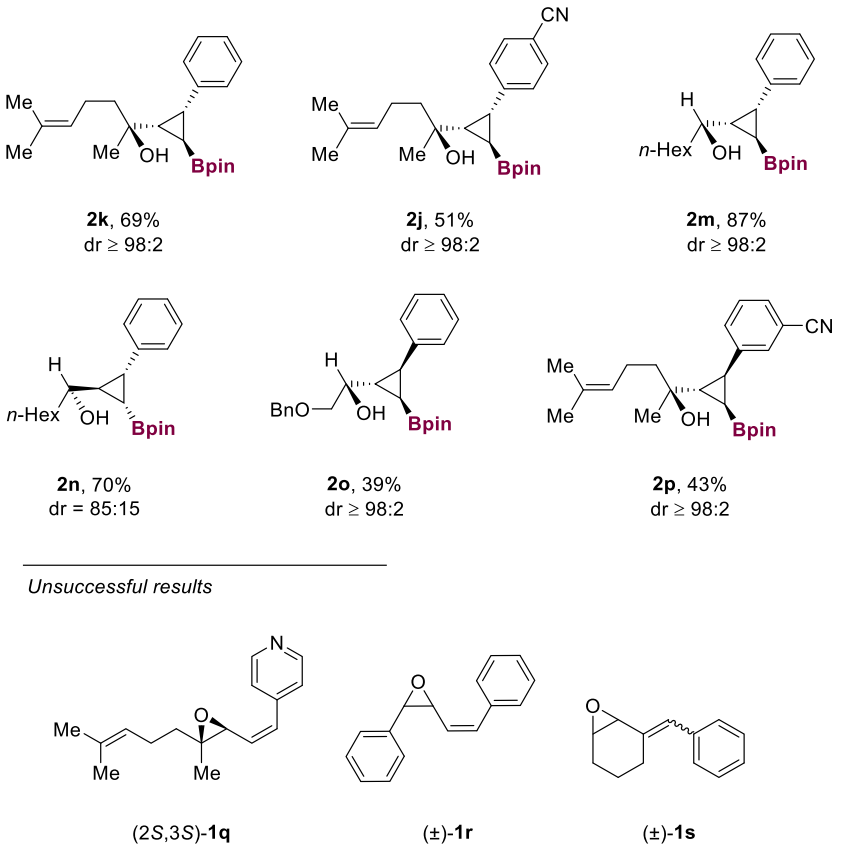
Scheme 36. New synthetized vinyl epoxides.

3.3 Study of the Structural Scope

With the optimal conditions in hand, we explored the reactivity of the newly synthetized compounds. Vinyl epoxides **1k** and **1l** afforded cyclopropylboronates **2k** and **2j** respectively, in moderate yield with a *trans* arrangement between the aromatic ring and the Bpin groups (**Scheme 37**). These results proved that the relative configuration of the stereocenters in the cyclopropane can be controlled by the appropriate selection of the geometry of the double bond in the starting material. *Cis*-disubstituted epoxides **1m**-**1o**, provided cyclopropylboronates **2m**, **2n** and **2o** in good to moderate yields. Cyclopropylboronate **2m** showed again that *trans* arrangement between the phenyl ring and the Bpin groups is possible starting from a vinyl epoxide with an *E*-double bond. Additionally, with these examples we proved that disubstituted vinyl epoxides are compatible with our reaction conditions. The diastereoselectivity observed for epoxide **1n** was slightly lower (85:15 dr) but compound **2n** was obtained as a single diastereomer after purification by flash column chromatography. Finally, we synthetized vinyl epoxide **1p** to observe the effect of the cyano- group in *meta* position. The product was obtained with the expected *cis* relative configuration between the Bpin group and the aromatic ring. In contrast with compound **1j** (**Scheme 32**), the isomerization does not occur with the -CN group in a *meta* position.

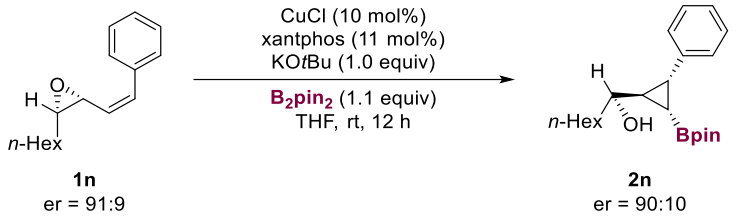
Unfortunately, epoxides (**1q**-**1s**) did not afford the desired cyclopropylboronates. Vinyl epoxide **1r**, bearing a pyridine ring at the double bond, afforded a complex mixture of products that could not be identified. Vinyl epoxide **1q** afforded the desired cyclopropylboronate

along with a mixture of unidentified byproducts. However, when we tried to isolate it by flash column chromatography only decomposition of the product was observed. Finally, cyclic epoxide **1s** proved to be unreactive under the reaction condition, and only starting material was recovered (Scheme 37).



Scheme 37. Scope of the new synthetized cyclopropylboronates.

To demonstrate that the process takes place with chirality transfer, we measured the enantiomeric ratio of compound **2n** (**Scheme 38**). The enantiomeric ratio of the product was determined by ^{1}H NMR analysis of its methoxy phenyl acetates, prepared by reaction of (±)-methoxyphenyl acetic and (-)-methoxyphenyl acetic acids with DCC.[81]



Scheme 38. Evaluation of the chirality transfer.

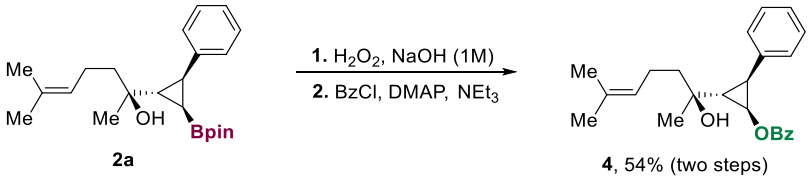
With all this information we can conclude that our method is stereospecific, and the relative configuration of the products can be controlled by appropriate selection of the geometries of the oxirane and the double bond in the starting materials. Starting from optically active vinyl epoxides, enantioenriched α-hydroxy cyclopropylboronates could be synthetized with excellent chirality transfer.

[81] **(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.

3.4 Functionalization of the C–B Bond

To demonstrate the versatility of the obtained cyclopropylboronates, different functionalizations of the C–B bond have been developed.

First, oxidation[82] of cyclopropylboronate **2a** with hydrogen peroxide and sodium hydroxide afforded the corresponding cyclopropanol in quantitative yield. The crude was used without further purification in the presence of benzoyl chloride to yield benzoate **4** in 54% yield (two steps) (**Scheme 39**).[83]

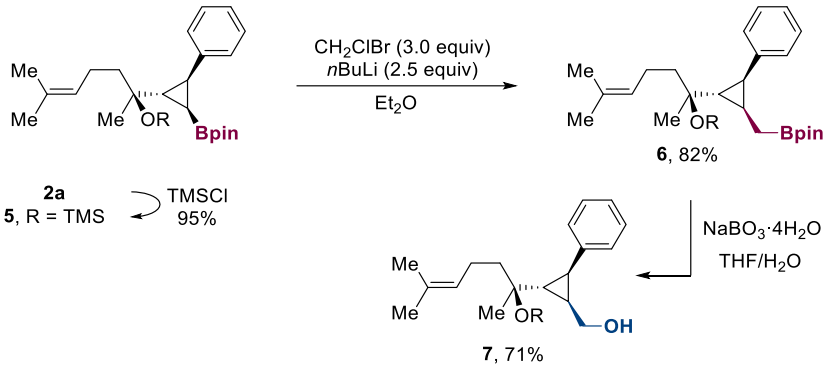


Scheme 39. Oxidation-benzoylation sequence.

To explore the Matesson homologation of the C–B bond, we first protected the free alcohol in **2a**. Treatment of **2a** with trimethylsilyl chloride afforded trimethylsilyl ether **5** (**Scheme 40**).[84] Then, homologation was successfully achieved with bromochloromethane in the presence of *n*-butyllithium, obtaining boronate **6** in excellent yield.[85] Additionally, the

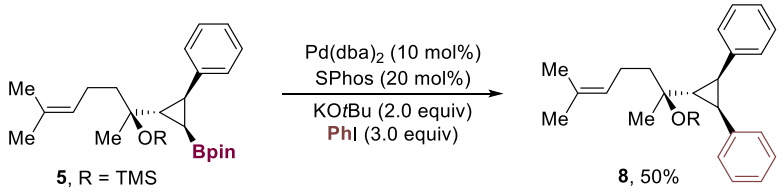
[82] Liskey, C. W.; Hartwig, J. F. *J. Am. Chem. Soc.* **2013**, *135*, 3375–3378.
[83] Parra, A.; Amenós, L.; Guisán-Ceinos, M.; López, A.; Garcia Ruano, J. L.; Tortosa, M. *J. Am. Chem. Soc.* **2014**, *136*, 15833–15836.
[84] Rüedi, G.; Nagel, M.; Hansen, H. J. *Org. Lett.* **2004**, *6*, 2989–2991.
[85] Jarava-Barrera, C.; Parra, A.; López, A.; Cruz-Acosta, F.; Collado-Sanz, D.; Cárdenas, D. J.; Tortosa, M. *ACS Catal.* **2016**, *6*, 442–446.

resulting product **6** could be easily oxidized under mild conditions to afford diol **7** (**Scheme 40**).[83]



Scheme 40. Homologation-oxidation sequence.

Finally, the palladium-catalyzed Suzuki-Miyaura cross-coupling with phenyl iodide afforded diphenyl-substituted cyclopropane **8** in moderate yield (**Scheme 41**).[83]

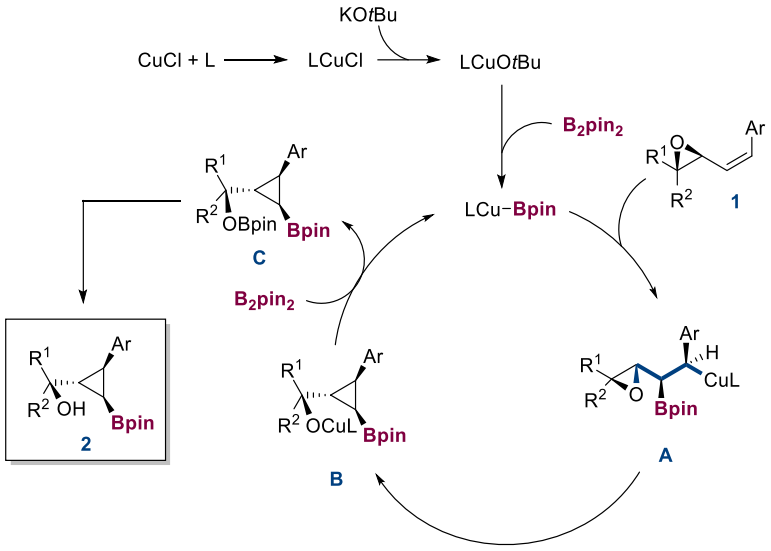


Scheme 41. Suzuki-Miyaura cross-coupling of **5**.

3.5 Proposed Reaction Mechanism

Based on our observations and the literature precedents, we propose the following catalytic cycle for the stereospecific formation of α-hydroxy cyclopropylboronates through copper-catalysis (**Scheme 42**). First, reaction between copper chloride, the ligand and potassium *tert*-butoxide affords the copper(I)-alkoxide. This intermediate undergoes a σ-bond metathesis reaction with the diboron compound to afford the catalytically active copper(I)-boryl complex.[86] Then, insertion of the alkene **1** into the copper-boron bond takes place. In this stereo-determining step intermediate **A** is formed. The observed stereochemical outcome could be explained by a *syn* approach of the copper(I)-boryl complex to a vinyl epoxide in an *s-trans* conformation. This *syn* approach could be directed by coordination of the oxygen of the epoxide to the boron atom. From **A**, intramolecular S_N2 type reaction would afford cyclopropylboronate **B**. The *cis* relationship between the boryl moiety and the aryl group may result from a W-shaped transition state.[87] This relationship would be *trans* starting from an *E* vinyl epoxide through a similar transition state. Finally, the copper alkoxide **B** could react with another molecule of B_2pin_2 to form cyclopropylboronate **C** and the copper-boryl complex, necessary to regenerate the catalytic cycle. Then, after hydrolysis of the O–B bond, the desired α-hydroxy cyclopropylboronate **2** is formed.

[86] Dang, L.; Zhao, H.; Lin, Z.; Marder, T. B. *Organometallics* **2007**, *26*, 2824–2832.
[87] Norsikian, S.; Marek, I.; Poisson, J.-F.; Normant, J. F. *J. Org. Chem*. **1997**, *62*, 4898–4899.

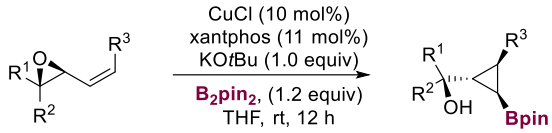


Scheme 42. Proposed catalytic cycle.

3.6 Conclusions/Conclusiones

In summary, we have studied a new route to synthetize chiral α-hydroxy cyclopropylboronates. Starting from readily available vinyl epoxides, we have developed a catalytic and stereospecific method for the preparation of enantioenriched α-hydroxy cyclopropylboronates with control of four contiguous stereocenters. Using a copper(I) salt and a commercially available phosphine ligand excellent diastereoselectivities are observed. Structural changes of the geometry of the epoxide and the double bond in the starting material allows the selective synthesis of different diastereomers.

Moreover, we have demonstrated that the functionalization of the C–B bond in the products allows access to highly functionalized cyclopropanes.

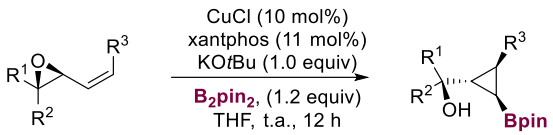


Scheme 43. Stereospecific synthesis of α-hydroxy cyclopropylboronates from vinyl epoxides.

Conclusiones

En este capítulo, hemos desarrollado una nueva ruta para la síntesis de α-hidroxiciclopropilboronatos a partir de epóxidos vinílicos. El método desarrollado es estereoespecífico y permite la síntesis de ciclopropanos con control en cuatro centros estereogénicos contiguos. Utilizando una sal de cobre(I) y una fosfina comercial se obtuvieron los productos con altos niveles de diastereoselectividad. Modulando la geometría del epóxido y del doble enlace podemos obtener diferentes diastereoisómeros (**Esquema 4**).

Además, demostramos que podemos sintetizar ciclopropanos altamente funcionalizados a través de la funcionalización del enlace C–B.



Esquema 4. Síntesis estereoespecífica de α-hidroxiciclopropilboronatos a partir de epóxidos vinílicos.

4. Supplementary Data

4.1 General Experimental Details

Tetrahydrofuran and dichloromethane were purified by passing through a Pure Solv™ column drying system from Innovative Technology, Inc. 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 precoated aluminum-backed plates (Merck Kieselgel 60 F_{254}) 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^+).

Dess-Martin periodinane was synthesized following reported procedures.[88]

The enantiomeric ratio of the products was determined by ^{1}H NMR analysis of its methoxy phenyl acetate, prepared by reaction of (-)-methoxyphenyl acid and DCC in DCM.[89]

[88] Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155–4156.

[89] **(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.

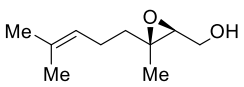
4.2 General Procedure for the Synthesis of Vinyl Epoxides, 1

Sharpless Asymmetric Epoxidation of Allylic Alcohols, SI-1

SI-1

An oven dried flask equipped with a magnetic stir bar, was charged with 4Å powdered activated molecular sieves (28 mg/mmol) and dry DCM (0.6 mL/mmol). The flask was cooled to −20 °C. L-(+)-Diethyl tartrate (28 mol%) and Ti(*i*PrO)$_4$, (20 mol%) *via* syringe were added sequentially. The reaction mixture was stirred at −20 °C while TBHP (1.5 equiv, 5.5 in decanes) was added dropwise. The resulting mixture was stirred at –20 °C for 30 min. Solution of allylic alcohol (1 equiv) in dry DCM (0.15 mL/mmol), was then added dropwise and stirring was continued at the same temperature for several hours. The process of epoxidation was monitored by TLC. After the reaction mixture was warmed to 0 °C, water was added and the mixture was stirred for 30 min, 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 DCM (x3), the combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated. The residue was purified by flash column chromatography on silica gel to achieve the desired **SI-1** compound. The enantiomeric ratio of the epoxides was determined by ^{1}H NMR analysis of its methoxy phenyl acetate, prepared by reaction of (-)-methoxyphenyl acid and DCC in DCM.

[(2*S*,3*S*)-3-Methyl-3-(4-methylpent-3-en-1-yl)oxiran-2-yl]methanol, (*S*,*S*)-**SI-1a**

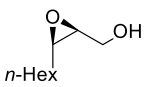


(*S*,*S*)-**SI-1a**

From geraniol (2.0 g, 13.0 mmol) following the general procedure described above, compound (*S*,*S*)- **SI-2a** (2.13 g, 12.5 mmol) was obtained in 96% yield (*er* = 90:10). The spectral data for (*S*,*S*)-**SI-1a** matched those previously reported for this compound.[90]

^{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).

[(2*S*,3*R*)-3-Hexyloxiran-2-yl]methanol, (*S*,*R*)-**SI-1m**



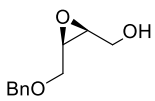
(*S*,*R*)-**SI-1m**

From *cis*-2-nonen-1-ol (1.42 g, 10.0 mmol) following the general procedure described above, compound (*S*,*R*)-**SI-1m** (902 mg, 5.7 mmol) was obtained in 57% yield (*er* = 90:10). The spectral data for (*S*,*R*)-**SI-1m** matched those previously reported for this compound.[91]

^{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).

[90] Noji, M.; Kobayashi, T.; Uechi, Y.; Kikuchi, A.; Kondo, H.; Sugiyama, S.; Ishii, K. *J. Org. Chem.* **2015**, *80*, 3203−3210.
[91] Wang, C.; Yamamoto, H. *J. Am. Chem. Soc.* **2014**, *136*, 1222−1225.

{(2*S*,3*R*)-3-[(benzyloxy)methyl]oxiran-2-yl}methanol, (*S*,*R*)-**SI-1o**

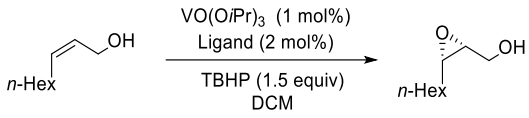


(*S*,*R*)-**SI-1o**

From (*Z*)-4-(benzyloxy)but-2-en-1-ol (3.46 g, 19.4 mmol) following the general procedure described above, compound (*S*,*R*)-**SI-1o** (2.45 g, 12.6 mmol) was obtained in 65% yield (*er* = 89:11). The spectral data for (*S*,*R*)-**SI-1o** matched those previously reported for this compound.[92]

^{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).

*Synthesis of [(2R,3S)-3-Hexyloxiran-2-yl]methanol, (R,S)-**SI-1n**[93]*



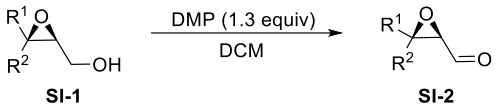
(*R*,*S*)-**SI-1n**

To a solution of (*R*,*R*)-*N*-Hydroxy-*N*-{2-[hydroxy-(3,3,3-triphenyl-propionyl)-amino]-cyclohexyl}-3,3,3-triphenylpropionamide (2 mol%) in dichloromethane (10 mL) was added $VO(OiPr)_3$ (1 mol%), and the mixture was stirred for 1 h at room temperature. The resulting solution was cooled to 0 °C, and then 70% aqueous TBHP (1.5 equiv) and allylic alcohol (1.42 g, 10.0 mmol) were added and stirring was continued at the same temperature for 6 hours. Saturated aqueous Na_2SO_3 was added, and the mixture was stirred for 1 h at 0 °C. The mixture was then allowed to warm to room temperature, extracted with Et_2O, dried over $MgSO_4$ and

[92] Okado, Y.; Shigetomi, K.; Mitsuhashi, S.; Ubukata, M. *J. Antibiot.* **2015**, *68*, 721–724.
[93] Zhang, W.; Basak, A.; Kosugi, Y.; Hoshino, Y.; Yamamoto, H. *Angew. Chem. Int. Ed.* **2005**, *44*, 4389–4391.

concentrated under reduced pressure. The remaining residue was purified by flash column chromatography (SiO_2, cyclohexane/EtOAc 80:20) to afford epoxy alcohol (*R*,*S*)-**SI-1n** (901 mg, 5.7 mmol) in 57% yield (*er* = 91:9).

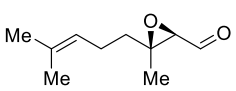
General Procedure for the Synthesis of Epoxy Aldehydes, ***SI-2***



SI-1 **SI-2**

Dess-Martin periodinane (1.3 equiv) was added to a stirring solution of epoxy alcohol **SI-1** (1 equiv) in DCM (10 mL/mmol) at 0 °C. Then the reaction mixture was stirred at room temperature for 1 h. Finally, the reaction was quenched by cooling the solution to 0 °C followed by addition of hexanes. The resulting solution was filtered through Florisil® (eluting with a solvent mixture 1:1 Et_2O/cyclohexane) to afford **SI-2**.

(2*R*,3*S*)-3-Methyl-3-(4-methylpent-3-en-1-yl)oxirane-2-carbaldehyde, *(R,S)*-**SI-2a**



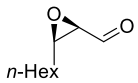
(*R*,*S*)-**SI-2a**

From epoxy alcohol (*S*,*S*)-**SI-1a** (1.0 g, 5.9 mmol) following the general procedure described above, compound (*R*,*S*)-**SI-2a** (942 mg, 5.6 mmol) was obtained in 95% yield. The spectral data for (*R*,*S*)-**SI-2a** matched those previously reported for this compound.[94]

^{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).

[94] Nacro, K.; Batlas, M.; Escudier, J. M.; Gorrichon, L. *Tetrahedron* **1996**, *52*, 9047–9056.

(2*R*,3*R*)-3-Hexyloxirane-2-carbaldehyde, (*R*,*R*)-**SI-2m**

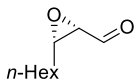


(*R*,*R*)-**SI-2m**

From epoxy alcohol (*S*,*R*)-**SI-1m** (902 mg, 5.7 mmol) following the general procedure described above, compound (*R*,*R*)-**SI-2m** (844 mg, 5.4 mmol) was obtained in 95% yield. The spectral data for (*R*,*R*)-**SI-2m** matched those previously reported for this compound.

^{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). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 199.2, 59.2, 57.9, 31.6, 28.9, 28.1, 26.6, 22.5, 14.0. **$[\alpha]_D^{20}$** = –105.1 (*c* = 1.1, $CHCl_3$).

(2*S*,3*S*)-3-Hexyloxirane-2-carbaldehyde, (*S*,*S*)-**SI-2n**

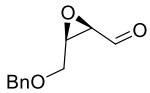


(*S*,*S*)-**SI-2n**

From epoxy alcohol (*R*,*S*)-**SI-1n** (800 mg, 5.06 mmol) following the general procedure described above, compound (*S*,*S*)-**SI-2n** (757 mg, 5.85 mmol) was obtained in 96% yield. The spectral data for (*S*,*S*)-**SI-2n** matched those previously reported for this compound.

^{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). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 199.2, 59.2, 57.9, 31.6, 28.9, 28.1, 26.6, 22.5, 14.0. **$[\alpha]_D^{20}$** = +103.8 (*c* = 1.0, $CHCl_3$).

(2*R*,3*R*)-3-[(Benzyloxy)methyl]oxirane-2-carbaldehyde, (*R*,*R*)-**SI-2o**



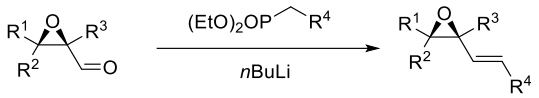
(*R*,*R*)-**SI-2o**

From epoxy alcohol (*S*,*R*)-**SI-1o** (1.77 g, 9.0 mmol) following the general procedure described above, compound (*R*,*R*)-S**I-3p** (1.5 g, 7.81 mmol) was obtained in 86% yield. The

spectral data for (*R*,*R*)-**SI-2o** matched those previously reported for this compound.[95]

^{1}H NMR (300 MHz, $CDCl_3$): δ 9.45 (d, *J* = 5.0 Hz, 1H), 7.35-7.26 (m, 5H), 4.56 (s, 2H), 3.81 (qd, *J* = 11.7, 3.8 Hz, 2H), 3.54-3.48 (m, 1H), 3.42 (t, *J* = 4.6 Hz, 1H).

General procedure for the Synthesis of (E)- Vinyl Epoxides, ***1***

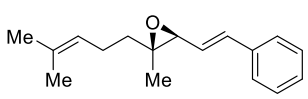


SI-2 **1**

Under argon atmosphere, to a suspension of diethyl benzylphosphonate derivative (1.72 equiv) in anhydrous THF (16 mL/mmol) was added *n*BuLi (1.6M, 1.3 equiv) dropwise at –78 °C. The resulting mixture was stirred at this temperature for 30 min and then it was allowed to warm at room temperature and stirred for further 30 min. A solution of epoxy aldehyde **SI-2** (1 equiv,) in anhydrous THF (2 mL/mmol) was then added dropwise. The resulting solution was maintained at room temperature for 2 h. Saturated NH_4Cl was added and the mixture extracted with EtOAc. The residue was purified by flash chromatography (SiO_2, cyclohexane/EtOAc 90:10) to afford the desired compound **1**.

[95] 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*S*,3*S*)-2-Methyl-2-(4-methylpent-3-en-1-yl)-3-((*E*)-styryl)oxirane, (*S*,*S*)-**1k**

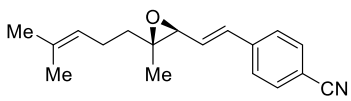


(*S*,*S*)-**1k**

From aldehyde (*R*,*S*)-**SI-2a** (500 mg, 3 mmol, 1.0 equiv) and diethyl benzylphosphonate (1.07 mL, 5.16 mmol, 1.72 equiv) following the general procedure described above, compound (*S*,*S*)-**1k** (166 mg, 0.68 mmol) was obtained in 23% yield, as a yellow oil. R_f = 0.83 (cyclohexane/EtOAc 80:20).

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.37-7.15 (m, 5H), 6.68 (d, *J* = 15.9 Hz, 1H), 6.03 (dd, *J* = 15.9, 7.4 Hz, 1H), 5.11-5.00 (m, 1H), 3.32 (d, *J* = 7.4 Hz, 1H), 2.19-1.97 (m, 2H), 1.64 (s, 3H), 1.74-1.42 (m, 2H), 1.56 (s, 3H), 1.28 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 136.6, 134.9, 132.2, 128.8, 128.0, 126.6, 125.0, 123.7, 63.7, 63.4, 38.7, 25.8, 23.9, 17.8, 17.0. **HRMS (EI$^+$)**: calculated for $C_{18}H_{22}O$ $[M]^+$: 242.1671; found: 242.1677. $[\alpha]_D^{20}$ = –78.0 (*c* = 0.5, $CHCl_3$).

4-((*E*)-2-((2*S*,3*S*)-3-Methyl-3-(4-methylpent-3-en-1-yl)oxiran-2-yl)vinyl)benzonitrile, (*S*,*S*)-**1l**



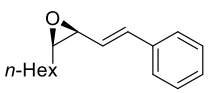
(*S*,*S*)-**1l**

From aldehyde (*R*,*S*)-**SI-2a** (300 mg, 1.78 mmol, 1.0 equiv) and diethyl (*p*-cyanobenzyl)phosphonate (760 mg, 3.0 mmol, 1.72 equiv) following the general procedure described above, compound (*S*,*S*)-**1l** (290 mg, 1.08 mmol) was obtained in 61% yield, as a yellow pale oil. R_f = 0.50 (cyclohexane/EtOAc 90:10).

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.69 (d, *J* = 8.4 Hz, 1H),7.50 (d, *J* = 8.4 Hz, 2H), 6.92 (d, *J* = 15.9 Hz, 1H), 6.34 (dd, *J* = 15.9, 7.3 Hz, 1H), 5.40-5.35 (m, 1H), 3.61 (d, *J* = 7.3 Hz, 1H), 1.96 (s, 3H), 1.88 (s, 3H), 2.04-1.75 (m, 2H), 1.59 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 135.4, 133.5, 132.1, 131.7, 128.0, 127.9,

125.8, 123.5, 121.7, 63.4, 63.3, 38.7, 25.7, 23.8, 17.7, 16.8. $[\alpha]_D^{20}$ = –15.3 (*c* = 1.1, $CHCl_3$).

(2*R*,3*S*)-2-Hexyl-3-((*E*)-styryl)oxirane, (*R*,*S*)-**1m**

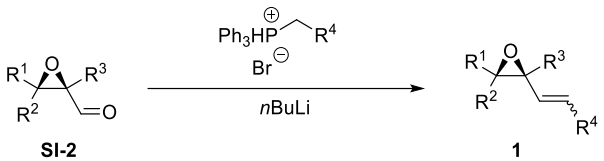


(*R*,*S*)-**1m**

From aldehyde (*R*,*S*)-**SI-2m** (300 mg, 2.11 mmol, 1.0 equiv) and diethyl benzylphosphonate (0.74 mL, 3.59 mmol, 1.72 equiv) following the general procedure described above, compound (*R*,*S*)-**1m** (125 mg, 1.08 mmol) was obtained in 27% yield, as a yellow pale oil. R_f = 0.80 (cyclohexane/EtOAc 90:10).

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.55-7.39 (m, 5H), 6.93 (d, *J* = 15.9 Hz, 1H), 6.21 (dd, *J* = 15.9, 7.6 Hz, 1H), 3.72 (dd, *J* = 7.5, 4.3 Hz, 1H), 3.38-3.26 (m, 1H), 1.85-1.44 (m, 10H), 1.02 (t, *J* = 6.6 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 136.4, 135.2, 128.6, 127.5, 126.4, 123.9, 59.4, 57.3, 31.7, 29.0, 27.9, 26.3, 22.5, 14.0. $[\alpha]_D^{20}$ = +15.3 (*c* = 1.1, $CHCl_3$).

*General Procedure for the Synthesis of (Z)-Vinyl Epoxides, **1***

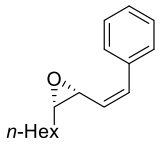


SI-2 **1**

Under argon atmosphere, to a suspension of phosphonium salt (1.72 equiv) in anhydrous THF (16 mL/mmol) was added *n*-BuLi (1.6M, 1.3 equiv) dropwise at –50 °C. The resulting mixture was maintained at –50 °C for 30 min and then cooled to −78 °C. A solution of epoxy aldehyde **SI-2** (1 equiv) in anhydrous THF (2 mL/mmol) was then added dropwise. The resulting solution was maintained at 0 °C for 2 h and then diluted with hexane, washed with brine, dried over $MgSO_4$ and concentrated. The residue was

purified by flash column chromatography (SiO_2, cyclohexane/EtOAc 95:5) to afford the desired product **1**.

(2*S*,3*R*)-2-Hexyl-3-[(*Z*)-styryl]oxirane, (S,*R*)-**1n**

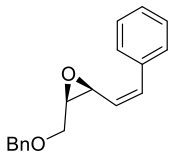


(*S*,*R*)-**1n**

From aldehyde (*S*,*S*)-**SI-2n** (760 mg, 4.86 mmol, 1 equiv) and benzyltriphenylphosphonium bromide (3.62 g, 8.35 mmol, 1.72 equiv) following the general procedure described above, compound (*S*,*R*)-**1n** (681 mg, 2.96 mmol) was obtained in 61% yield, as a yellow oil. R_f = 0.85 (cyclohexane/EtOAc 80:20).

^{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. **$[\alpha]_D^{20}$** = −172.6 (*c* = 1.5, $CHCl_3$).

(2*R*,3*S*)-2-[(benzyloxy)methyl]-3-[(*Z*)-styryl]oxirane, (*R*,*S*)-**1o**



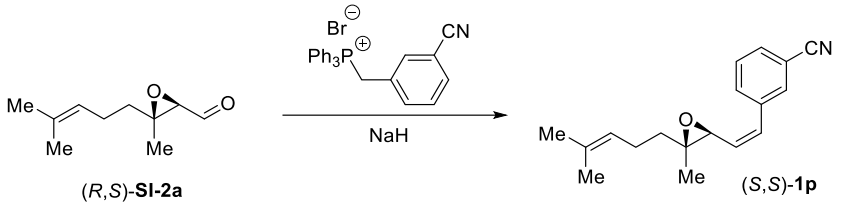
(*R*,*S*)-**1o**

From aldehyde (*R*,*R*)-**SI-2o** (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*)-**1o** (830 mg, 3.12 mmol) was obtained in 41% yield, as a pale yellow oil. R_f = 0.2 (cyclohexane/EtOAc 95:5).

^{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. $[\alpha]_D^{20}$ = +59.4 (*c* = 1.0, $CHCl_3$).

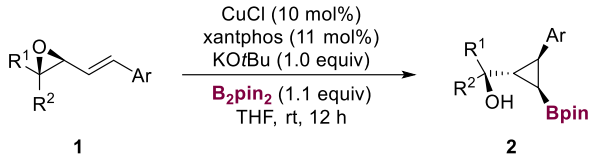
*Synthesis of 4-{(Z)-2-[(2S,3S)-3-Methyl-3-(4-methylpent-3-en-1-yl)oxiran-2-yl]vinyl}benzonitrile, (S,S)-**1p***



To a suspension of (3-ciano-benzyl)triphenylphosphonium salt (550 mg, 1.2 mmol, 1.0 equiv) in dry DMF (8 mL) at 0 °C under argon atmosphere, NaH (60% mineral oil, 58 mg, 1.4 mmol, 1.2 equiv) was added. The mixture was stirred at 0 °C for 15 minutes. Then, the aldehyde (*R*,*S*)-**SI-2a** in 2 mL of DMF was added to the solution. The resulting solution was maintained at 0 °C for 2 h and then diluted with hexane, washed with brine, dried over $MgSO_4$ and concentrated. The residue was purified by flash column chromatography (SiO_2, cyclohexane/EtOAc 95:5) to afford the desired compound (*S*,*S*)-**1p** (128 mg, 0.13 mmol) in 40% yield as a yellow oil. R_f = 0.36 (cyclohexane).

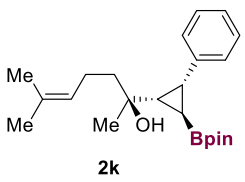
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.66-7.52 (m, 3H), 7.51-7.41 (m, 1H), 6.70 (d, *J* = 11.9 Hz, 1H), 5.70 (dd, *J* = 11.9, 7.4 Hz, 1H), 5.16-5.03 (m, 1H), 3.45 (dd, *J* = 7.4, 1.1 Hz, 1H), 2.12 (dd, *J* = 15.3, 7.5 Hz, 2H), 1.66 (s, 3H), 1.75-1.54 (m, 2H), 1.60 (s, 3H), 1.34 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 137.7, 133.0, 136.4, 132.2, 131.0, 130.3, 129.3, 123.4, 118.6, 112.8, 63.4, 59.6, 38.2, 25.8, 23.7, 17.8, 17.5. **HRMS (EI$^+$)**: calculated for $C_{18}H_{21}NO$ $[M]^+$: 267.1623; found: 267.1619. $[\alpha]_D^{20}$ = +142.5 (*c* = 1.1, $CHCl_3$).

4.3 General Procedure for the Synthesis of Cyclopropylboronates, 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 **1**) was added and the mixture was stirred for 15 min at room temperature. Then the corresponding epoxide **1** (1.0 equiv) in THF (0.5 mL/0.2 mmol of **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® (cyclohexane/EtOAc 80:20) to afford cyclopropylboronate **2**.

(*S*)-6-Methyl-2-[(1*S*,2*R*,3*R*)-2-phenyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)cyclopropyl]hept-5-en-2-ol, **2k**

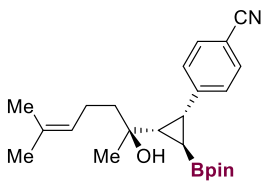


From epoxide **1k** (48.5 mg, 0.2 mmol) following the general procedure described above, compound **2k** (51 mg, 0.137 mmol) was obtained in 81% yield, as a white solid. R_f = 0.7 (cyclohexane/EtOAc 80:20).

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.38-7.14 (m, 5H), 5.13-5.07 (m, 1H), 2.46-2.30 (m, 1H), 2.07 (q, *J* = 7.9 Hz, 2H), 1.68 (s, 3H), 1.61 (s, 3H), 1.37-1.52 (m, 2H),

1.25 (s, 12H), 1.12 (s, 3H), 0.98 (t, *J* = 7.1 Hz, 1H), 0.43 (s, 1H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 138.2, 131.2, 129.7, 128.3, 126.3, 124.7, 83.1, 72.0, 43.7, 34.6, 28.0, 26.3, 25.7, 24.8, 24.7, 22.5, 17.6. [note: *the carbon attached to boron was not observed due to quadrupole broadening caused by the ^{11}B nucleus*]. **^{11}B NMR** (96 MHz, $CDCl_3$): δ 32.7. **HRMS (ESI$^+$)**: calculated for $C_{23}H_{35}BNaO_3$ $[M+Na]^+$: 393.2577; found: 393.2562. **$[\alpha]_D^{20}$** = +61.3 (*c* = 1.2, $CHCl_3$).

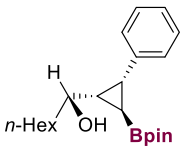
4-{(1*R*,2*S*,3*R*)-2-[(*S*)-2-Hydroxy-6-methylhept-5-en-2-yl)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl]cyclopropyl}benzonitrile, **2j** (from **1l**)



2j

From epoxide **1l** (53.5 mg, 0.2 mmol) following the general procedure described above, compound **2j** (40.3 mg, 0.101 mmol) was obtained in 51% yield, as a pale-yellow oil. **R_f** = 0.45 (cyclohexane/EtOAc 80:20).

1-((1*S*,2*R*,3*R*)-2-Phenyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)cyclopropyl)heptan-1-ol, **2m**



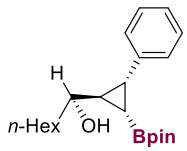
2m

From epoxide **1m** (48.5 mg, 0.2 mmol) following the general procedure described above, compound **2m** (49.6 mg, 0.134 mmol) was obtained in 87% yield, as a pale-yellow solid. R_f = 0.50 (cyclohexane/EtOAc 80:20).

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.32-7.22 (m, 5H), 3.00-2.90 (m, 1H), 2.46 (dd, *J* = 8.4, 6.7 Hz, 1H), 1.64-1.27 (m, 11H), 1.25 (s, 12H), 0.90-0.83 (m, 3H), 0.51 (t, *J* = 6.4 Hz, 1H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 138.2, 128.6, 126.7, 126.5, 83.5, 72.3, 37.1, 32.0, 31.9 29.6, 26.4, 25.7, 24.9, 24.8, 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

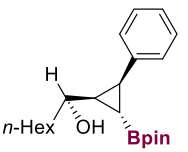
$C_{22}H_{35}BO_3Na$ $[M+Na]^+$: 381.2571; found: 381.2566. $[\alpha]_D^{20}$ = +60.0 (*c* = 0.9, $CHCl_3$).

(*S*)-1-[(1*R*,2*R*,3*S*)-2-phenyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)cyclopropyl]heptan-1-ol, **2n**



2n

From epoxide **1n** (46.1 mg, 0.2 mmol) following the general procedure described above, compound **2n** (50.2 mg, 0.140 mmol) was obtained in 70% yield as an 85:15 diastereomeric mixture. R_f = 0.45 (hexane/EtOAc 80:20). Further purification by flash column chromatography (SiO_2, hexane/EtOAc 98:2) gave **2n** as a single diastereomer. The enantiomeric ratio of product **2n** was determined to be 90:10 by ^{1}H NMR analysis of its methoxy phenyl acetates, prepared by reaction of (–)-methoxyphenyl acetic and (±)-methoxyphenyl acetic acids with dicyclohexylcarbodiimide in DCM. *This experiment proves that there is complete chirality transfer from the starting epoxide to the cyclopropylboronate.*

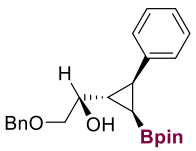


2n'

Data for 2n: ^{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*]. **^{11}B NMR** (96 MHz, $CDCl_3$): δ 31.3. **HRMS (ESI$^+$)**: calculated for $C_{22}H_{35}BO_3Na$ $[M+Na]^+$: 381.2571; found: 381.2569. $[\alpha]_D^{20}$ = –47.8 (*c* = 1.1, $CHCl_3$).

Data for 2n': ^{1}**H NMR** (300 MHz, $CDCl_3$): δ 7.47-7.26 (m, 5H), 3.08-2.96 (m, 1H), 2.55 (t, *J* = 7.5 Hz, 1H), 1.59-1.28 (m, 11H), 1.33 (s, 12H), 0.96-0.93 (m, 3H), 0.59 (t, *J* = 6.3 Hz, 1H).

(*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, **2o**

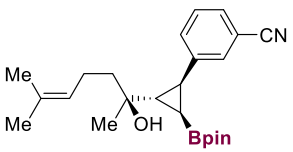


2o

From epoxide **1o** (53.3 mg, 0.2 mmol) following the general procedure described above, compound **2o** (30.8 mg, 0.078 mmol) was obtained in 39% yield, as a yellow oil. R_f = 0.3 (cyclohexane/EtOAc 80:20).

^{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*]. ^{11}**B NMR** (96 MHz, $CDCl_3$): δ 32.6. **HRMS (ESI$^+$)**: calculated for $C_{24}H_{31}BO_4Na$ $[M+Na]^+$: 417.2212; found: 417.2210. $[\alpha]_D^{20}$ = +37.0 (*c* = 1.1, $CHCl_3$).

3-{(1*S*,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, **2p**



2p

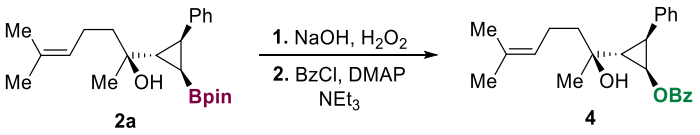
From epoxide **1p** (53.5 mg, 0.2 mmol) following the general procedure described above, compound **2p** (33.9 mg, 0.086 mmol) was obtained in 43% yield, as a pale-yellow solid.

^{1}**H NMR** (300 MHz, $CDCl_3$): δ 7.49-7.38 (m, 2H), 7.37-7.28 (m, 1H), 7.26-7.15 (m, 1H), 5.11-5.00 (m, 1H), 2.25 (dd, *J* = 10.4, 5.96 Hz, 1H), 2.11-1.96 (m,

2H), 1.68 (dd, *J* = 7.1, 6.0 Hz, 2H), 1.60 (s, 3H),), 1.56-1.50 (m, 2H), 1.53 (s, 3H), 1.20 (s, 3H), 0.95 (s, 6H), 0.84 (s, 6H), 0.57 (dd, *J* = 10.4, 7.2 Hz, 1H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 142.71, 133.9, 132.2, 132.2, 129.5, 128.6, 124.4, 119.2, 111.8, 83.4, 70.6, 43.2, 33.3, 27.5, 25.8, 24.9, 24.8, 24.6, 24.0, 23.0, 17.8. [note: *the carbon attached to boron was not observed due to quadrupole broadening caused by the ^{11}B nucleus*]. **^{11}B NMR** (96 MHz, $CDCl_3$): δ 32.8. **HRMS (ESI$^+$)**: calculated for $C_{24}H_{34}BNO_3Na$ $[M+Na]^+$: 418.2523; found: 418.2520. **$[\alpha]_D^{20}$** = +31.3 (*c* = 1.0, $CHCl_3$).

4.4 Functionalization of the C–B Bond

Oxidation-Benzoylation sequence**: Synthesis of (1R,2R,3S)-2-[(S)-2-hydroxy-6-methylhept-5-en-2-yl]-3-phenylcyclopropyl benzoate, **4



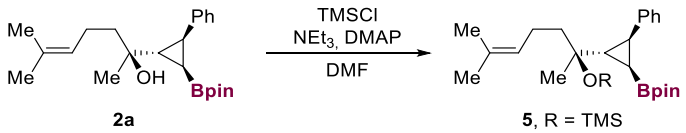
To cyclopropylboronate **2a** (37 mg, 0.10 mmol, 1.0 equiv) in THF (0.2 mL), an aqueous solution of NaOH (0.10 mL, 0.10 mmol, 1M) was added, and the reaction mixture was cooled to 0 °C. Then, a solution of H_2O_2 (20 µL, 30% (w/w), 2.0 equiv) was added dropwise. A white precipitate was formed within 10 min. After 30 min, full conversion was checked by TLC. Water was added and the mixture was extracted with Et_2O (3x). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure to afford the

corresponding cyclopropanol. This compound was used in the next step without further purification.

To a solution of the previous synthetized cyclopropanol in DCM (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 (3x) and the combined organic phases were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (hexane/EtOAc 95:5) to afford compound **4** (19.7 mg, 0.054 mmol) in 54% yield (two steps) as a yellow oil. R_f = 0.5 (cyclohexane/EtOAc 80:20).

^{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. **$[\alpha]_D^{20}$** = +25.9 (*c* = 1.0, $CHCl_3$).

Alcohol protection**: Synthesis of trimethyl {[(S)-6-methyl-2-((1S,2S,3R)-2-phenyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)cyclopropyl)hept-5-en-2-yl]oxy}silane, **5

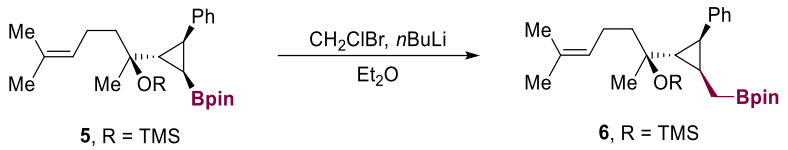


2a **5**, R = TMS

To a solution of cyclopropylboronate **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 0 °C, trimethylsilyl chloride (64 µl, 0.48 mmol, 1.2 equiv) was added dropwise. 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 (3x). 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 (hexane/EtOAc 95:5) to afford compound **5** (167.8 mg, 0.38 mmol) in 95% yield as a white solid. R_f = 0.8 (cyclohexane/EtOAc 80:20). **mp** = 44-46 °C.

^{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. **$[\alpha]_D^{20}$** = +39.0 (*c* = 0.8, $CHCl_3$).

Homologation**: Synthesis of trimethyl{[(S)-6-methyl-2-((1S,2S,3R)-2-phenyl-3-((4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2 yl)methyl)cyclopropyl)hept-5-en-2-yl]oxy}silane, **6

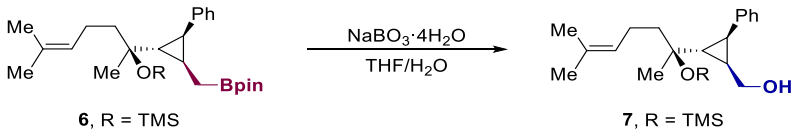


5, R = TMS **6**, R = TMS

To a solution of cyclopropylboronate **5** (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 °C, *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 °C, 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 **6** (37.5 mg, 0.082 mmol) in 82% yield as a pale yellow oil. R_f = 0.75 (cyclohexane/EtOAc 80:20).

^{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. **$[\alpha]_D^{20}$** = +25.7 (*c* = 1.0, $CHCl_3$).

Oxidation of 6**: Synthesis of {(1R,2R,3S)-2-[(S)-6-methyl-2-((trimethylsilyl)-oxy)hept-5-en-2-yl]-3-phenylcyclopropyl}methanol, **7

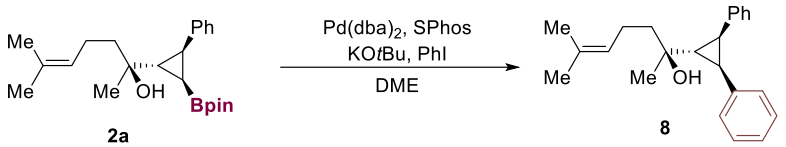


6, R = TMS **7**, R = TMS

$NaBO_3{\cdot}4H_2O$ (22 mg, 0.14 mmol, 4 equiv) was added to a solution of cyclopropylboronate **6** (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 (3x). 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 (cyclohexane/EtOAc 95:5) to afford **7** (8.5 mg, 0.025 mmol) in 71% yield as a colorless oil. R_f = 0.6 (cyclohexane/EtOAc 80:20).

^{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. **$[\alpha]_D^{20}$** = +47.4 (*c* = 1.0, $CHCl_3$).

Suzuki-Miyaura Cross-Coupling**: Synthesis of (S)-2-[(1R,2R,3S)-2,3-diphenyl-cyclopropyl]-6-methylhept-5-en-2-ol, **8



To a solution of cyclopropane **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 (cyclohexane/EtOAc 95:5 to 90:10) to afford **8** (16 mg, 0.05 mmol) in 50% yield as an orange oil. R_f = 0.6 (cyclohexane/EtOAc 80:20).

^{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. **$[\alpha]_D^{20}$** = −13.2 (*c* = 1.0, $CHCl_3$).

Chapter II

Copper-Catalyzed Regioselective Monoborylation of Spirocyclobutenes

Chapter II. Copper-Catalyzed Regioselective Monoborylation of Spirocyclobutenes

1. Introduction

1.1 Importance of Spirocycles in Medicinal Chemistry

Spirocycles are polycyclic compounds, in which two rings are fused through a single atom (usually a carbon). Among them, spirocyclobutanes containing stereocenters are particularly attractive scaffolds because the strained ring provides rigidity and rigorously shape their three-dimensionality.[96] These two properties, make them ideal scaffolds to explore new areas of chemical space in medicinal chemistry and therefore can bring new opportunities for intellectual property.[97]

The vast majority of compounds generated in pharmaceutical research contain aromatic or heteroaromatic rings that may be fused to reach the third dimension. By contrast, the nature of spirocycles is such that the exit vectors of a single spirocycle populate the third dimension (**Figure 6**). This

[96] Carreira, E. M.; Fessard, T. C. *Chem. Rev.* **2014**, *114*, 8257–8322.

[97] **(a)** Lipinski, C.; Hopkins, A. *Nature* **2004**, *432*, 855–861. **(b)** Lovering, F.; Bikker, J.; Humblet, C. *J. Med. Chem.* **2009**, *52*, 6752–6756. **(c)** Zheng, Y.-J.; Tice, C. M. *Expert Opin. Drug Discovery* **2016**, *11*, 831–834. **(d)** Voss, F.; Schunk, S.; Steinhagen, H. *RSC Drug Discovery Series* **2015**, 439–458. **(e)** Kirichok, A. A.; Shton, I.; Kliachyna, M.; Pishel, I.; Mykhailiuk, P. K. *Angew. Chem. Int. Ed.* **2017**, *56*, 8865–8869. **(f)** Kotha, S.; Panguluri, N. R.; Ali, R. *Eur. J. Org. Chem.* **2017**, 5316–5342. **(g)** Boström, J.; Brown, D. G.; Young, R. J.; Keserü, G. M. *Nat. Rev. Drug Discov.* **2018**, *17*, 709–727.

feature offers many more opportunities for covering the chemical space through an expanded set of exit vectors.[89]

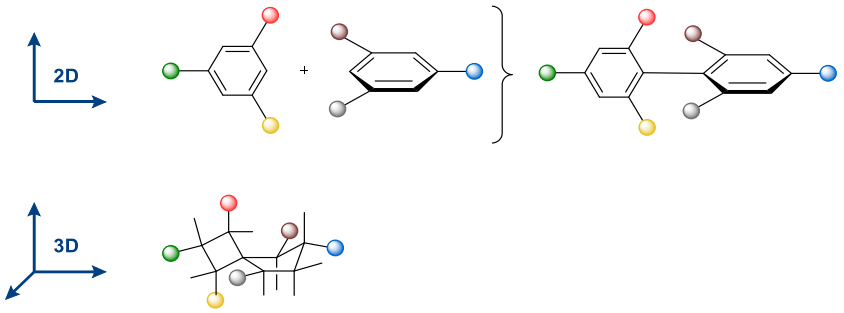


Figure 6. Comparison of covered chemical space of a biaryl and a spirocycle.

Moreover, they also provide an expanded toolbox to modulate physicochemical and pharmacokinetic properties in lead compounds such as lipophilicity, solubility, and metabolic stability. Furthermore, the sp^3 character of spirocycles is expected to favour their water solubility, and consequently to improve their bioavailability.[98]

[98] **(a)** Burkhard, J. A.; Wagner, B.; Fischer, H.; Schuler, F.; Müller, K.; Carreira, E. M. *Angew. Chem. Int. Ed.* **2010**, *49*, 3524–3527. **(b)** Zheng, Y.; Tice, C. M.; Singh, S. B. *Bioorg. Med. Chem. Lett.* **2014**, *24*, 3673–3682. **(c)** Muller, G.; Berkenbosch, T.; Benningshof, J. C. J.; Stumpfe, D.; Bajorath, J. *Chem. Eur. J.* **2017**, *23*, 703–710. **(d)** Kirichok, A. A.; Shton, I.; Kliachyna, M.; Pishel, I.; Mykhailiuk, P. K. *Angew. Chem. Int. Ed.* **2017**, *56*, 8865–8869.

1.2 Synthesis of 4-Membered Spirocycles

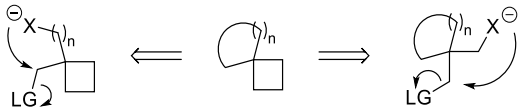
Spirocycles have been considered difficult to synthetize due to the presence of a quaternary centre in their structure and the need to control multiple stereocenters. The increased number of published articles in recent years describing different approaches for their synthesis suggest that these challenges are being addressed.

Most strategies for the synthesis of spirocycles rely on the use of starting materials incorporating a starter ring. The choice of what ring is constructed depends on the necessity of exit vectors or functionality onto the spirocyclic scaffold. It is noteworthy that the recent advances in the availability of four membered building blocks triggered the development of new strategies toward approaches in which a second ring is constructed onto an existing cyclobutane ring.

In this chapter, only selected examples of the main methods reported for the synthesis of spirocyclobutanes will be discussed.

The most classical strategy to obtain spirocyclobutanes involves an intramolecular S_N2 reaction to build either ring of the spirocycle framework (Scheme 44).[99] By modulating the extension of the carbon chain, the size of the new formed ring could be designed. One of the drawbacks of this approach is that it is linear, meaning that, for each spirocycle prepared, a different precursor is needed. Additionally, there is very little room to introduce substituents in the cyclobutane ring.

[99] Burkhard, J. A.; Guérot, C.; Knust, H.; Carreira, E. M. *Org. Lett.* **2012**, *14*, 66–69.

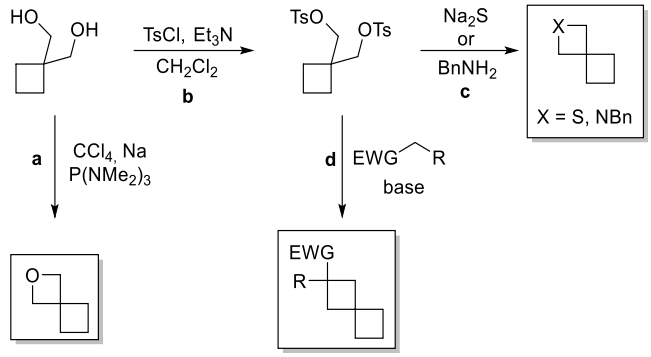


Scheme 44. Strategy for the synthesis of spirocycles through a S_N2 reaction.

The use of activated 1,3-diols is a common strategy for the generation of the cyclobutane ring. Starting from a common 1,3-diol different linear spirocycles could be obtained (**Scheme 45**).

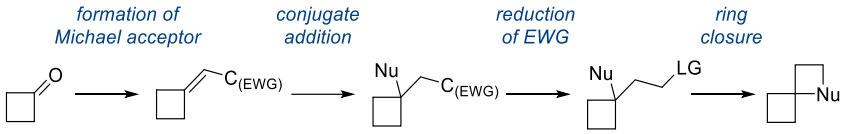
For example, treatment of the 1,3-diol with CCl_4, sodium and $P(NMe_2)_3$ afford selectively the activation at one of the two hydroxy groups. The generated oxiphosphonium intermediate is easily cyclized to afford 2-oxaspiro[3.3]heptane (**Scheme 45a**).[100] Activation of both alcohols with tosyl chloride yield the activated diol (**Scheme 45b**). This intermediate can react with different nucleophiles such as sodium sulfide[101] or piperonylamine[102] to afford the corresponding hetero-spirocyclobutanes (**Scheme 45c**). Finally, the double alkylative cyclization reactions with stabilized carbanions such as malonates or 2-phenylacetonitrile derivatives provides access to different spirocycles that could be functionalized at C6 (**Scheme 45d**).[103]

[100] Castro, B. R. *Org. React.* **1983**, *29*, 1–162.
[101] Lu, Y.; Wang, J.; Guo, J.; Tang, Y.; Zhang, S.; Tao, J.; Xiong, L.; Li, X.; Luo, J. *Heterocycl. Commun.* **2015**, *21*, 1–4.
[102] Burkhard, J. A.; Wagner, B.; Fischer, H.; Schuler, F.; Müller, K.; Carreira, E. M. *Angew. Chem. Int. Ed.* **2010**, *49*, 3524–3527.
[103] **(a)** Benincori, T.; Consonni, V.; Gramatica, P.; Pilati, T.; Rizzo, S.; Sannicolo, F. Todeschini, R.; Zotti, G. *Chem. Mater.* **2001**, *13*, 1665–1673. **(b)** Radchenko, D. S.; Grygorenko, O. O.; Komarov, I. V. *Tetrahedron: Asymmetry* **2008**, *19*, 2924–2930. **(c)** Tkachenko, A. N.; Radchenko, D. S.; Mykhailiuk, P. V.; Shishkin, O. V.; Tolmachev, A. A.; Komarova, I. V. *Synthesis* **2012**, *44*, 903–908.



Scheme 45. General synthesis of spirocycles through S_N2 reactions.

Alternatively, conjugate addition of heteroatomic nucleophiles to a cyclic Michael acceptor followed by reduction of the electron-withdrawing group, activation of the resulting alcohol, and ring-closing reaction affords angular spirocycles derivatives (**Scheme 46**).[104]

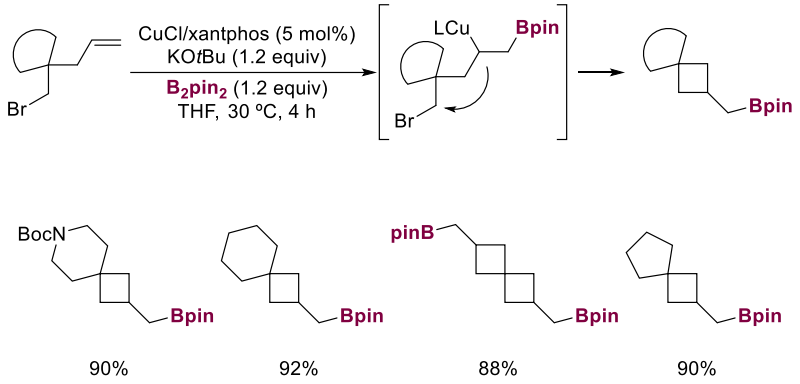


Scheme 46. General strategy for the synthesis of angular spirocycles.

More recently, new catalytic approaches have been developed to prepare spirocycles. In an elegant approach, Ito used alkenyl bromides to obtain spirocycles through a borylative *exo*-cyclization using copper-boryl complexes (**Scheme 47**). This method includes the regioselective borylation

[104] Burkhard, J. A.; Guérot, C.; Knust, H.; Rogers-Evans, M.; Carreira, E. M. *Org. Lett.* **2010**, *12*, 1944–1947.

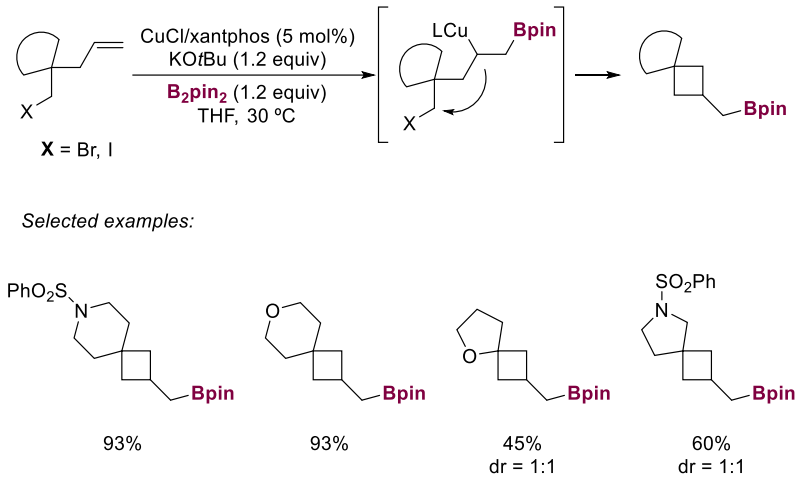
of unactivated terminal alkenes followed by intramolecular substitution of the resulting alkyl-copper intermediate. Different methylene boryl spirocyclobutanes have been obtained in moderate to excellent yields.[105]



Scheme 47. Synthesis of spirocycles trough copper catalysis.

A few years later, Fernandez and co-workers improved the scope of this approach preparing different hetero-spirocycles from alkyl bromides and iodides (**Scheme 48**).[106] Additionally, they carried out DFT calculations to explain the reaction outcome and propose a possible explanation for the favored formation of the strained ring. Moreover, the boronic ester present in the products allows access to a variety of synthetically valuable functional groups trough the C–B bond functionalization.

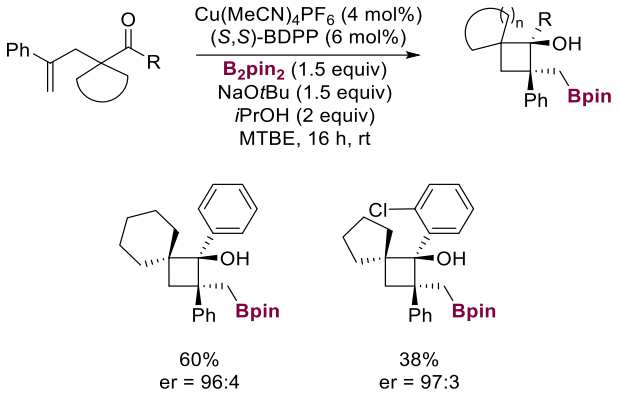
[105] Kubota, K.; Yamamoto, E.; Ito, H. *J. Am. Chem. Soc.* **2013**, *135*, 2635–2640.
[106] Royes, J.; Ni, S.; Farré, A.; La Cascia, E.; Carbó, J. J.; Cuenca, A. B.; Maseras, F.; Fernández, E. *ACS Catal.* **2018**, *8*, 2833–2838.



Scheme 48. Copper-catalyzed synthesis of spirocycles.

In 2019, Lautens reported the diastereo- and enantioselective synthesis of boryl-functionalized cyclobutanols from 1,1-disubstituted styrenes. The enantioselective borylcupration generates a chiral benzylic copper intermediate that is intercepted with a proximally tethered ketone. Using this methodology, spirocyclobutanols could be synthetized with moderate yields and excellent enantiomeric ratios (**Scheme 49**).[107]

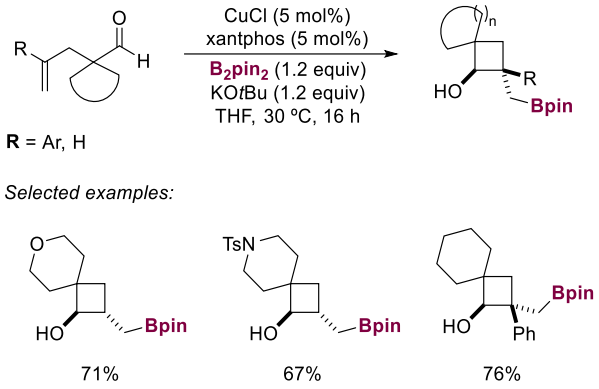
[107] Whyte, A.; Mirabi, B.; Torelli, A.; Prieto, L.; Bajohr, J.; Lautens, M. *ACS Catal.* **2019**, *9*, 9253–9258.



Scheme 49. Synthesis of spirocyclobutanols reported by Lautens.

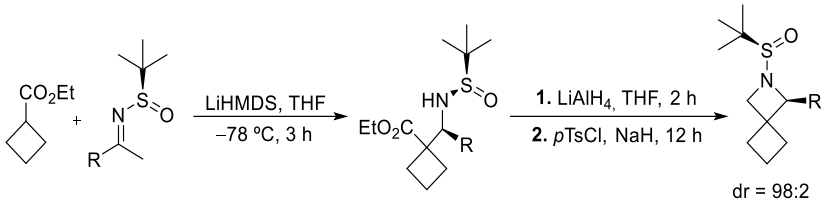
In 2020, Fernández and co-workers extended this approach reporting the diastereoselective borylative cyclization of γ-alkenyl aldehydes (Scheme 50). This method favored chemoselective borylcupration on the double bond and not at the carbonyl group. The cyclization took place with *anti*-diastereoselection. They also carried out DFT calculations to understand the key steps of the catalytic cycle that govern the chemo- and the diastereoselectivity. Different spirocyclobutanols were obtained in moderate to good yields.[108]

[108] Maza, R. J.; Royes, J.; Carbó, J. J.; Fernández, E. *Chem. Commun.* **2020**, *56*, 5973–5976.



Scheme 50. Synthesis of spirocyclobutanols reported by Fernández.

In 2019, Reddy and co-workers, published a method for the synthesis of 1-substituted 2-azaspiro[3.3]heptanes through the addition of ethyl cyclobutane-carboxylate anions to Davis–Ellman's imines. This approach allows the preparation of enantiomerically and diastereomerically pure spirocycles with yields up to 90% (**Scheme 51**).[109]

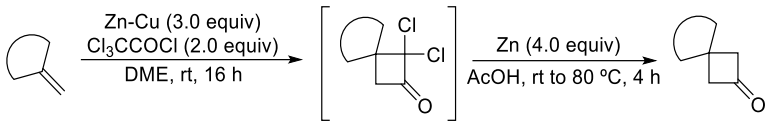


Scheme 51. Asymmetric synthesis of 1-substituted 2-azaspiro[3.3]heptanes.

[109] Reddy, L. R.; Waman, Y.; Kallure, P.; Nalivela, K. S.; Begum, Z.; Divya, T.; Kotturi, S. *Chem. Commun.* **2019**, *55*, 5068–5070.

A second strategy used to prepare spirocyclobutanes is the [2 + 2] or higher order cycloaddition reactions, starting from an exocyclic alkene.

The most vastly used strategy is the [2 + 2] cycloaddition between exocyclic alkenes and the *in situ* generated dichloroketene from trichloro acetyl chloride and zinc dust. The resulting dichlorocyclobutanone can be reduced in the presence of Zn dust in acetic acid to generate the corresponding spirocyclobutane (**Scheme 52**).[110] This approach is useful due to the presence of the ketone, that can be functionalized and let the introduction of exist vectors in the cyclobutane ring.[111]



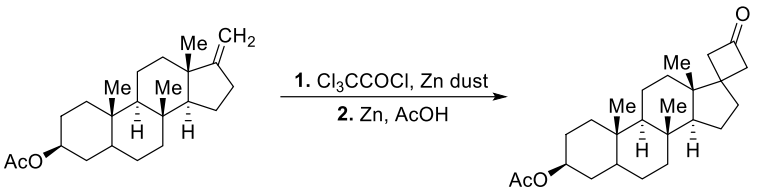
Scheme 52. Synthesis of spirocyclobutanones.

This approach has also been employed in the late-stage introduction of the spirocyclobutyl moiety into complex molecules. For example, in the synthesis of spirocyclic derivatives of steroids (**Scheme 53**).[112]

[110] **(a)** Meyers, M. J.; Muizebelt, I.; Wiltenburg, J.; Brown, D. L.; Thorarensen, A. *Org. Lett.* **2009**, *11*, 3523−3525. **(b)** Brown, D. G. *et al. J. Med. Chem.* **2014**, *57*, 733−758 **(c)** Nóvoa, L.; Trulli, L.; Parra, A.; Tortosa, M. *Angew. Chem. Int. Ed.* **2021**, *60*, 11763−11768.

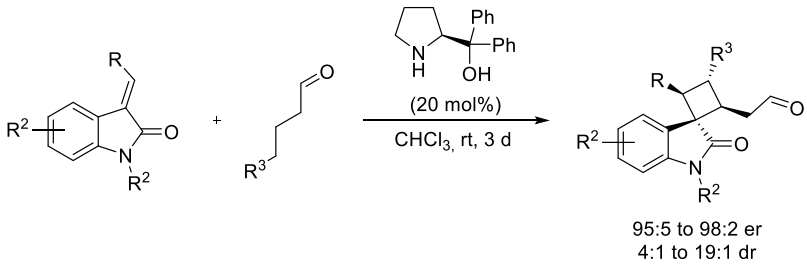
[111] **(a)** Kang, T.; Erbay, T. G.; Xu, K. L.; Gallego, G. M.; Burtea, A.; Nair, S. K.; Patman, R. L.; Zhou, R.; Sutton, S. C.; McAlpine, I. J.; Liu, P.; Engle, K. M. *ACS Catal.* **2020**, *10*, 13075−13083. **(b)** Yang, Y.; Tsien, J.; David, A. B.; Hughes, J. M. E.; Merchant, R. R.; Qin, T. *J. Am. Chem. Soc.* **2021**, *143*, 471−480.

[112] Paryzek, Z.; Blaszczyk, K. *Ann. Chem.* **1990**, *7*, 665−670.



Scheme 53. Synthesis of spirocyclic steroid derivatives.

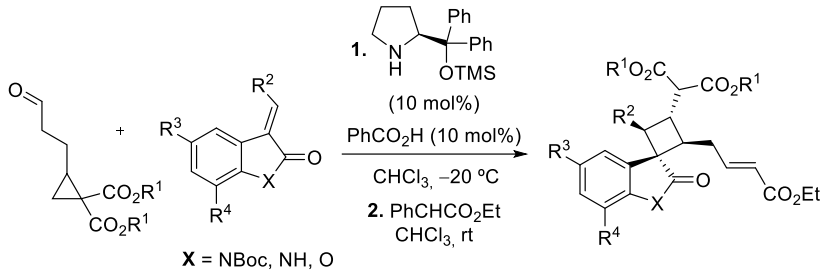
In 2014, Wang and co-workers reported the first organocatalytic asymmetric synthesis of a spirocyclobutyl oxindoles through a formal [2 + 2] cycloaddition (**Scheme 54**). The products, containing four contiguous stereocenters in the cyclobutane scaffold, were obtained in good yields (up to 83%) and with excellent stereocontrol (up to >19:1 dr and 97% *ee*).[113] This strategy allows the introduction of a high level of structural complexity in a single step, with the limitation that only provides access to very specific scaffolds.



Scheme 54. Organocatalytic synthesis of spirocyclobutyl oxindoles.

[113] Qi, L.-W.; Yang, Y.; Gui, Y.-Y.; Zhang, Y.; Chen, F.; Tian, F.; Peng, L.; Wang, L.-X. *Org. Lett.* **2014**, *16*, 6436−6439.

In 2015, Jørgensen reported the synthesis of spirocyclobutane-oxindoles and spirocyclobutane-benzofuranones using organo-catalytically activated cyclopropanes and 3-olefinic oxindoles or benzofuranones (Scheme 55). The biologically relevant spirocyclic derivatives were obtained in good yields, high diastereomeric ratios, and excellent enantiomeric excesses.[114]

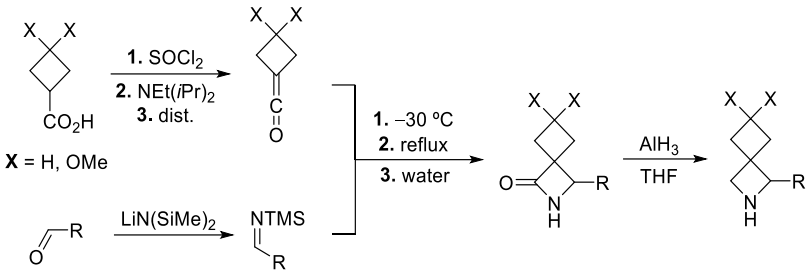


Scheme 55. Synthesis of spirocyclobutyl derivatives.

The Staudinger reaction has been applied to prepare azaspiro-[3.3]heptanes derivatives. Reaction between ketenes, that have easily been prepared from cyclobutane carboxylic acid and imines, has been used to synthetize 1-substituted 2-azaspiro[3.3]heptanes (Scheme 56). The spirocycles were obtained in moderate to good yields. These scaffolds are analogues of the 2-substituted piperidines that are important motifs present in several commercially available drugs.[115]

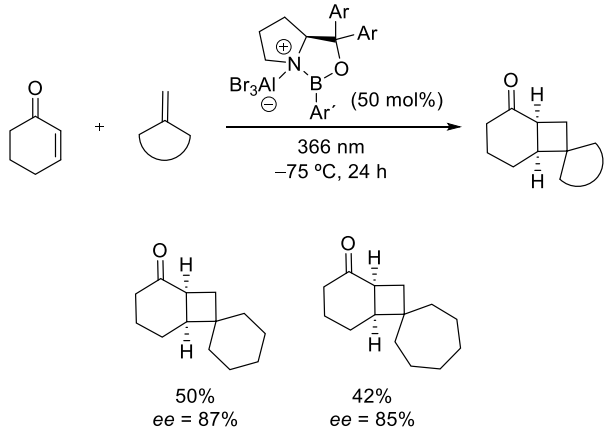
[114] Halskov, K. S.; Kniep, F.; Lauridsen, V. H.; Iversen, E. H.; Donslund, B. S.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2015**, *137*, 1685–1691.

[115] Kirichok, A. A.; Shton, I.; Kliachyna, M.; Pishel, I.; Mykhailiuk, P. K. *Angew. Chem. Int. Ed.* **2017**, *56*, 8865–8869.



Scheme 56. Synthesis of 1-substituted 2-azaspiro[3.3]heptanes.

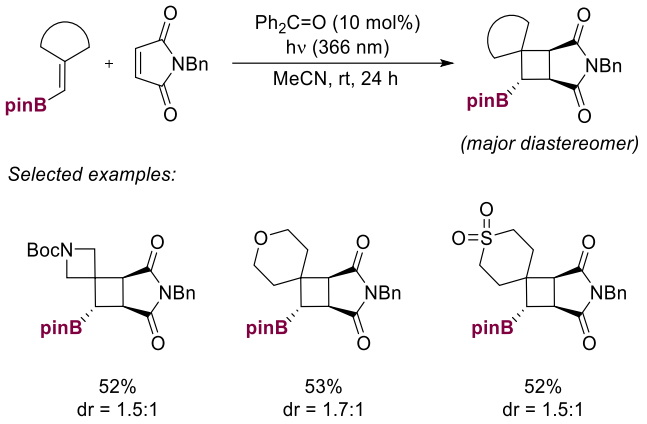
In 2018, Bach reported the intermolecular [2 + 2] photocycloaddition of cyclic α,β-unsaturated enones with olefins (**Scheme 57**). Using 1,1-substituted exocyclic alkenes as starting material, the method could be used to synthetize spirocyclobutanes. The products were obtained in moderate yields (42–59%) and with high levels of enantioselectivity (82%–87% *ee*).[116]



Scheme 57. [2 + 2] Cycloaddition of cyclic α,β-unsaturated enones with olefins.

[116] Poplata, S.; Bach, T. *J. Am. Chem. Soc.* **2018**, *140*, 3228–3231.

In 2020, Grygorenko and co-workers developed a methodology for the synthesis of 3-azabicyclo[3.2.0]heptyl boronic esters *via* the [2 + 2] photocycloaddition of the corresponding alkenyl boronic derivatives and maleimides (**Scheme 58**). The products were obtained with moderate to good yields and with moderate *exo* diastereoselectivity. Moreover, the utility of the products was demonstrated by different functionalization of the C–B bond.[117]

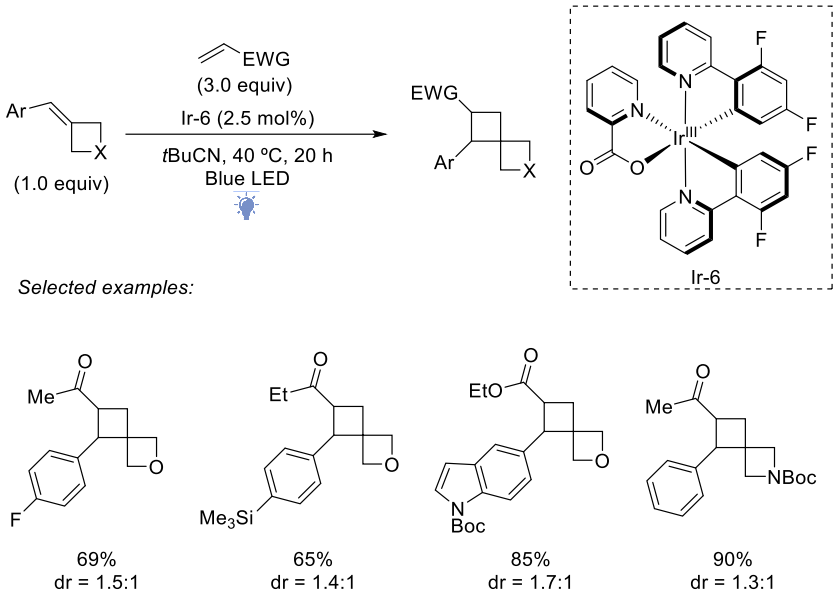


Scheme 58. Photochemical synthesis of 3-azabicyclo[3.2.0]heptanes.

Recently, Romanov-Michailidis, Knowles and co-workers described an intermolecular cross selective [2 + 2] photocycloaddition reaction of exocyclic arylidene oxetanes, azetidines, and cyclobutanes with electron-deficient alkenes (**Scheme 59**). The reaction works using a commercially available Ir(III) photosensitizer upon blue light irradiation. This

[117] Demchuk, O. P.; Hryshchuk, O. V.; Vashchenko, B. V.; Kozytskiy, A. V.; Tymtsunik, A. V.; Igor V. Komarov, I. V.; Grygorenko, O. O. *J. Org. Chem.* **2020**, *85*, 5927–5940.

transformation provides access to different polysubstituted spiro[3.3]heptane motifs with moderate to excellent yields.[118]

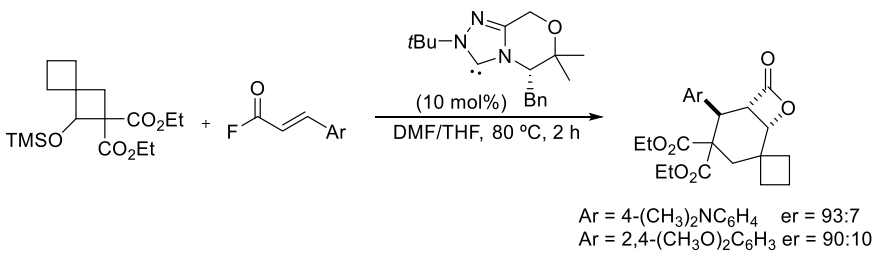


Scheme 59. Synthesis of spirocyclobutanes through [2 + 2] photocycloaddition.

In 2016, Lupton and co-workers reported in an elegant approach the [4 + 2] annulation of donor-acceptor cyclobutanes and unsaturated acyl fluorides using an *N*-heterocyclic carbene as catalyst. The method could be used to obtain four-membered spirocycles in excellent yields and enantiomeric ratios (**Scheme 60**).[119]

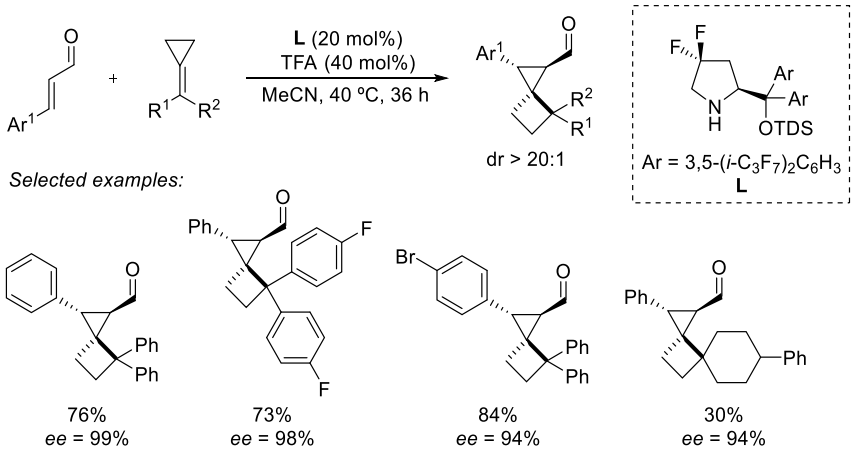
[118] Murray, P. R. D.; Bussink, W. M. M.; Davies, G. H. M.; van der Mei, F. W.; Antropow, A. H.; Edwards, J. T.; D'Agostino, L. A.; J. Ellis, M.; Hamann, L. G.; Romanov-Michailidis, F.; Knowles, R. R. *J. Am. Chem. Soc.* **2021**, *143*, 4055–4063.

[119] Levens, A.; Ametovski, A.; Lupton, D. W. *Angew. Chem. Int. Ed.* **2016**, *55*, 16136–16140.



Scheme 60. Enantioselective [4 + 2] annulation of donor-acceptor cyclobutanes.

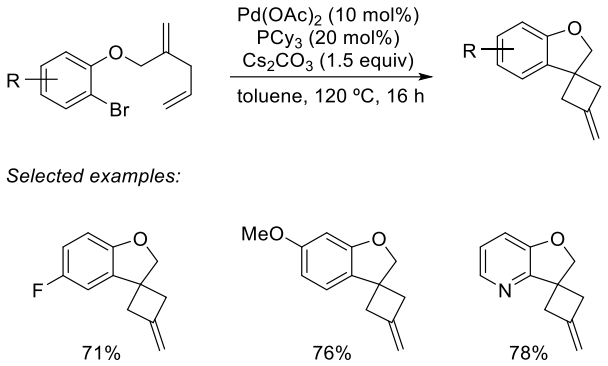
Other possibility consists in the use of cyclopropanes to build the four-membered ring through ring expansion. The products are highly strained spiro[2.3]hexane skeletons that are constructed from methylene-cyclopropanes and α,β-unsaturated aldehydes. The reaction proceeds through a Michael addition followed by ring expansion of methylene-cyclopropanes and enamine nucleophilic attack. Spirocycles were obtained with good yields and excellent enantiomeric excesses (**Scheme 61**).[120]



Scheme 61. Synthesis of spirocycles through a ring expansion approach.

[120] Zhao, C.-G.; Feng, Z.-T.; Xu, G.-Q; Gao, A.; Chen, J.-W.; Wang, Z.-Y.; Xu, P.-F. *Angew. Chem. Int. Ed.* **2020**, *59*, 3058–3062.

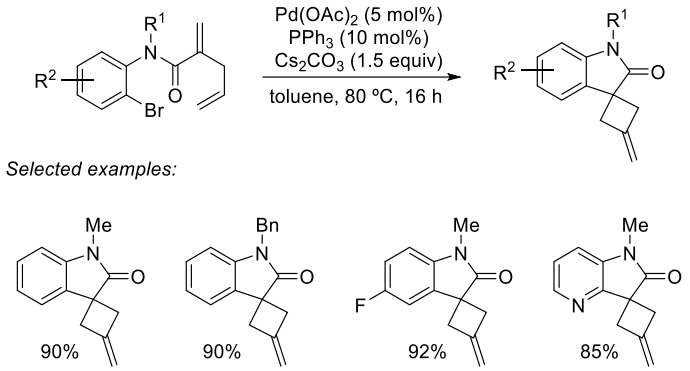
García-López studied the carbopalladation of skipped dienes to access different four membered spirocycles with biologically relevant structures. In 2019, this group disclosed a ligand-controlled cascade reaction to afford different spirocycles upon double carbopalladation of the starting substrate. The resulting products are dihydrobenzofuran spirocyclic derivatives that have been obtained in moderate to good yields (**Scheme 62**).[121]



Scheme 62. Synthesis of spirocycles through carbopalladation of skipped dienes.

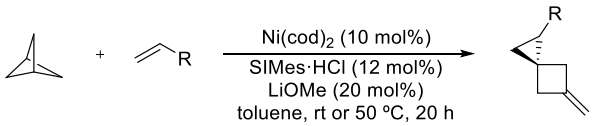
More recently, the same research group reported a complementary carbopalladation approach to synthetize spirooxindoles that are privileged structures present in many pharmaceuticals and natural products. In addition, the new generated exocyclic double bond can serve as platform to introduce modifications into the cyclobutane scaffold (**Scheme 63**).[122]

[121] Azizollahi, H.; Mehta, V. P.; García-López, J.-A. *Chem. Commun.* **2019**, *55*, 10281–10284.
[122] Azizollahi, H.; Pérez-Gómez, M.; Mehta, V. P.; García-López, J.-A. *Adv. Synth. Catal.* **2020**, *362*, 1899–1904.



Scheme 63. Synthesis of spirooxindoles through cascade double palladation.

Aggarwal and co-workers presented the synthesis of methylenspiro[2.3] hexanes from the highly strained tricyclic [1.1.1]propellane with a nickel(0) catalyst and different alkenes. The reaction offers high functional tolerance and when alkenyl boronic esters are used provide access to borylated methylenspiro[2.3]hexanes (**Scheme 64**).[123]

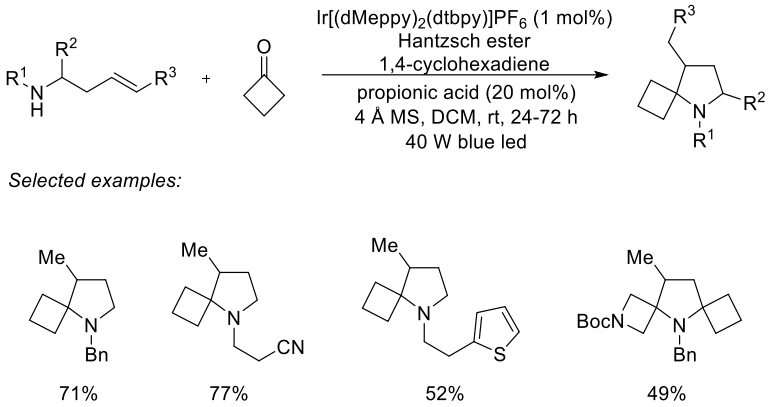


Scheme 64. Nickel-catalyzed cyclopropanation of [1.1.1]propallane.

In 2019, Gaunt group developed a general approach to construct complex C(sp^3)-rich *N*-heterospirocycles from commercially available aliphatic ketones and aldehydes with different alkene-containing secondary amines. The reaction is mediated by visible light using a highly

[123] Yu, S.; Noble, A.; Bedford, R. B.; Aggarwal, V. K. *J. Am. Chem. Soc.* **2019**, *141*, 20325–20334.

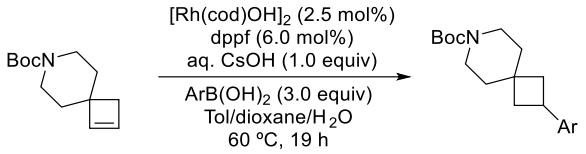
reducing iridium photocatalyst. This methodology provides access to different spirocyclic scaffolds displaying structural features relevant in medicinal chemistry programs (**Scheme 65**).[124]



Scheme 65. Photocatalytic synthesis of *N*-heterospirocycles.

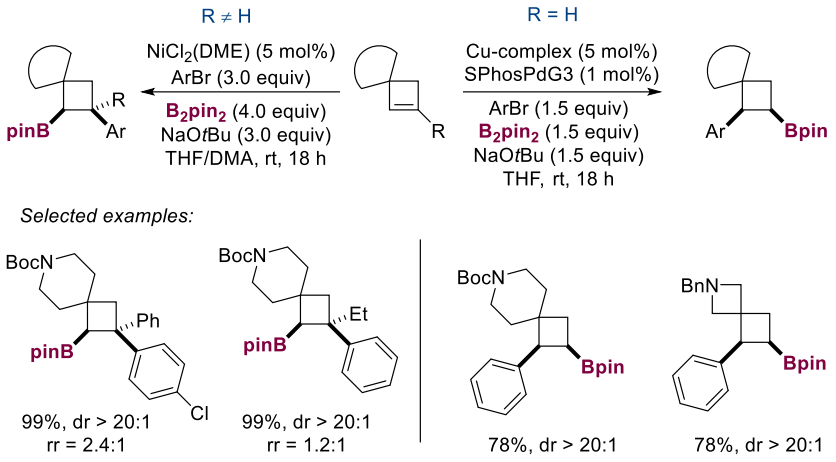
More recently, at the same time as the results from this thesis were published, Fletcher reported an elegant regioselective rhodium-catalyzed hydroarylation of cyclobutene-spirocyclic piperidine and pyrrolidine derivatives. The challenge of this approach was reaching high regioselectivity in non-symmetrical cyclobutenes. Using dppf as ligand and CsOH as base, complete regioselectivity was achieved with different boronic esters in the case of piperidine derivative. Pyrrolidine derivative afforded the desire product in a 4:1 regioisomeric mixture (**Scheme 66**).[125]

[124] Flodén, N. J.; Trowbridge, A.; Willcox, D.; Scarlett M. Walton, S. M.; Kim, Y.; Gaunt, M. J. *J. Am. Chem. Soc.* **2019**, *141*, 8426–8430.
[125] Goetzke, F. W.; Hell, A. M. L.; van Dijk, L.; Fletcher, S. P. *Nat. Chem.* **2021**, *13*, 880–886.



Scheme 66. Regioselective reductive Heck of spirocyclobutenes.

Recently, after the results presented in this doctoral thesis were reported, Brown and co-workers presented the catalytic arylboration of spirocyclobutenes. Depending on the substitution pattern of the cyclobutene ring, either a Cu/Pd or a Ni-catalyzed reaction was employed. The method afforded highly functionalized spirocyclobutanes in a single step. The products were obtained in moderate to good yields with excellent regioselectivity and diastereomeric ratios in the case of copper. However, using nickel as catalyst the products were obtained as a mixture of regioisomers (**Scheme 67**).[126]



Scheme 67. Arylboration of spirocyclobutenes.

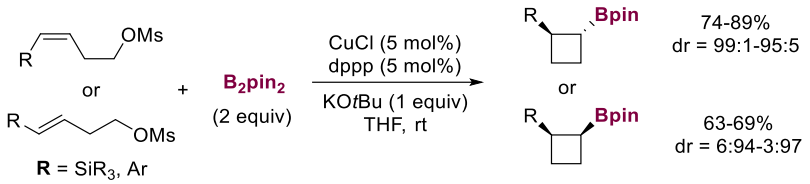
[126] Simlandy, A. K.; Lyu, M.-Y.; Brown, M. K. *ACS Catal.* **2021**, *11*, 12815−12820.

1.3 Synthesis of Cyclobutylboronates

Cyclobutylboronates are attractive rigid intermediates to prepare functionalized cyclobutanes. Boron-containing stereocenters are configurationally stable and the boryl moiety provides a handle for further functionalization through stereospecific transformations of the C–B bond.

In the literature, there are different approaches to prepare cyclobutylboronates. In this section, we will discuss the main approaches reported for the synthesis of cyclobutylboronates. Different diastereoselective and enantioselective methods have been developed for their synthesis and others offer access to symmetric cyclopropyl boronic esters.

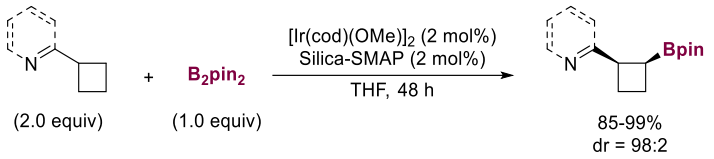
In 2010, Ito and co-workers, reported the stereospecific synthesis of cyclobutylboronates through a copper-catalyzed borylation of homoallylic sulfonates. The initially formed alkyl-copper intermediate cyclized to form a cyclobutylboronate. Both *syn* and *anti*-derivatives could be obtained by switching the geometry of the double bond (Scheme 68).[127]



Scheme 68. Copper catalyzed stereospecific synthesis of cyclobutylboronates.

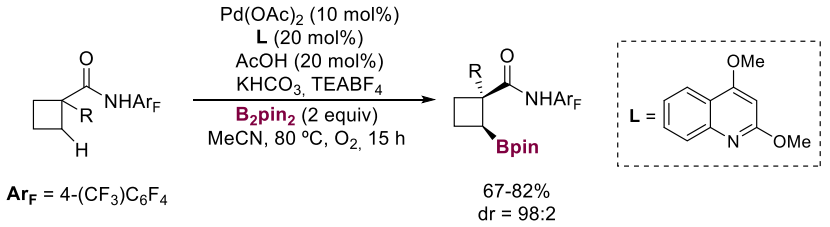
[127] Ito, H.; Toyoda, T.; Sawamura, M. *J. Am. Chem. Soc.* **2010**, *132*, 5990–5992.

In 2014, Sawamura and co-workers reported a diastereoselective method for the C–H borylation of cyclobutanes. One of the limitations of this approach is that nitrogen-containing substituents in the cyclobutane ring are required as directing groups to achieve high levels of diastereoselectivity (**Scheme 69**).[128]



Scheme 69. Stereoselective C–H borylation of cyclobutanes.

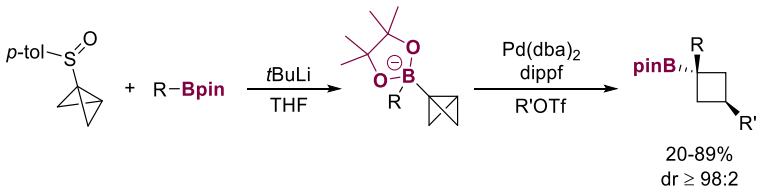
In 2016, Yu and co-workers reported the Pd-catalyzed β-borylation of cyclobutylamides promoted by quinoline-based ligands (**Scheme 70**). Cyclobutylboronates were synthetized with excellent yields as single diastereomers.[129]



Scheme 70. Pd-catalyzed C–H borylation of cyclobutylamides.

[128] Murakami, R.; Tsunoda, K.; Iwai, T.; Sawamura, M. *Chem. Eur. J.* **2014**, *20*, 13127–13131.
[129] He, J.; Jiang, H.; Takise, R.; Zhu, R. Y.; Chen, G.; Dai, H. X.; Dhar, T. G. M.; Shi, J.; Zhang, H.; Cheng, P. T. W.; Yu, J. Q. *Angew. Chem. Int. Ed.* **2016**, *55*, 785–789.

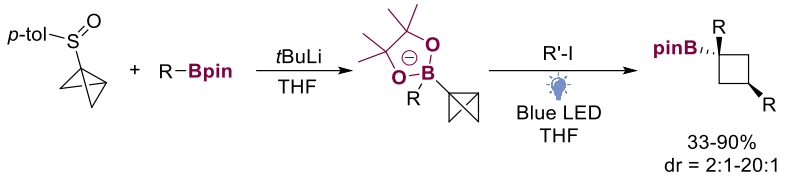
In 2019, Aggarwal developed an unprecedent C–C σ-bond carbopalladation of a strained bicyclo[1.1.0]butyl boronate complex, introducing at the same time an aryl unit and a boronic ester across the mentioned σ-bond. (**Scheme 71**). The pharmaceutically relevant 1,1,3-trisubstituted cyclobutane products were obtained with excellent diastereocontrol.[130]



Scheme 71. Synthesis of cyclobutylboronates by carbopalladation of σ-bonds.

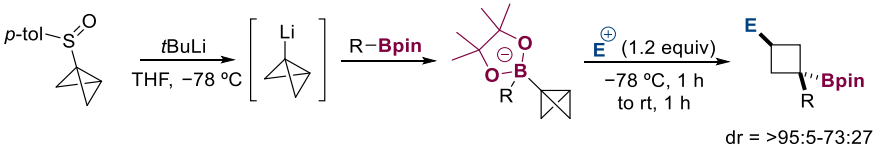
That same year, Aggarwal disclosed the metal free radical addition of alkyl iodines to strained σ-bonds of bicyclo[1.1.0]butyl boronate complexes to afford cyclobutylboronates with moderate to excellent results (**Scheme 72**). They proposed that the radical formed from the alkyl iodine under visible light irradiation added to the central bond of the bicyclo[1.1.0]butyl unit leading to a radical anion. This radical anion underwent a SET process with another molecule of alkyl iodine forming a zwitterionic species, which underwent a 1,2-metalate rearrangement to form the desired cyclobutylboronate.[131]

[130] Fawcett, A.; Biberger, T.; Aggarwal, V. K. *Nat. Chem.* **2019**, *11*, 117–122.
[131] Silvi, M.; Aggarwal, V. K. *J. Am. Chem. Soc.* **2019**, *141*, 9511–9515.



Scheme 72. Radical addition to strained σ-bonds to synthesize cyclobutylboronates.

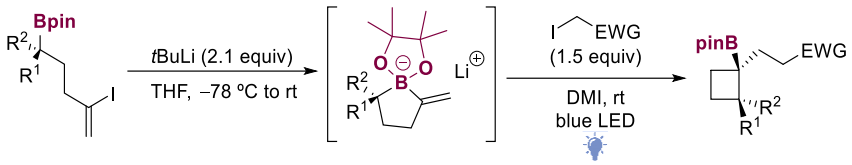
Exploiting the high ring-strain energy of bicyclo[1.1.0]butyl boronate complexes (strain energy ca. 65 kcal/mol), the same group reported the diastereoselective C–C σ-bond difunctionalization of bicyclo[1.1.0]butyl lithium with different electrophiles. The reaction shows broad substrate scope, with a range of different electrophiles and boronic esters. The products are 1,1,3-trisubstituted cyclobutanes (> 50 examples) that were obtained with high diastereoselectivity (**Scheme 73**).



Scheme 73. Synthesis of cyclobutylboronates by C–C σ-bond functionalization.

In an elegant work, Aggarwal reported the photo-induced contraction of five-membered-ring alkenyl boronate complexes into cyclobutanes. The process involves the addition of an electrophilic radical to the electron-rich alkenyl boronate complex, leading the formation of an α-boryl radical. The

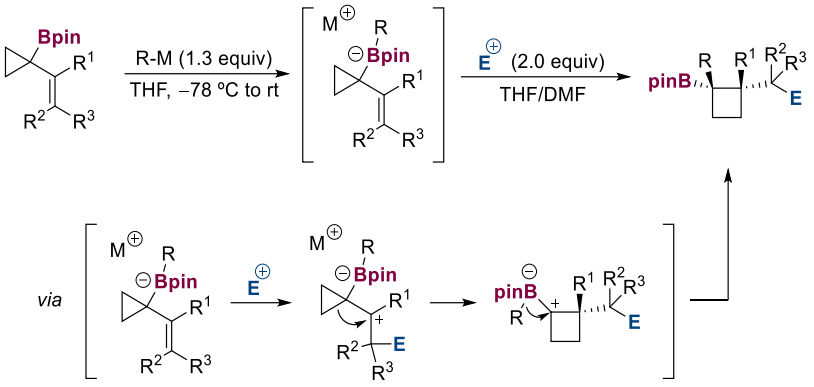
cyclobutyl boronates were formed upon mono electronic oxidation, followed by ring-contractive 1,2-metalate rearrangement (**Scheme 74**).[132]



Scheme 74. Photo-induced contraction of five-membered-ring alkenyl boronate complexes.

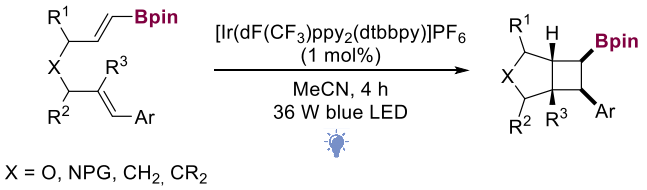
The same group reported the ring-expansion of vinyl-cyclopropyl boronates activated by electrophiles. This reaction occurs *via* a cyclopropane-stabilized carbocation, which triggers ring expansion and concomitant 1,2-metalate rearrangement. A wide number of organometallic reagents, electrophiles and vinyl-cyclopropyl boronic esters can be used following this methodology (**Scheme 75**). This novel approach affords 1,2-substituted cyclobutyl boronic esters with high levels of diastereoselectivity.[133]

[132] Davenport, R.; Silvi, M.; Noble, A.; Hosni, Z.; Fey, N.; Aggarwal, V. K. *Angew. Chem. Int. Ed.* **2020**, *59*, 6525–6528.
[133] Hari, D. P.; Abell, J. C.; Fasano, V.; Aggarwal, V. K. *J. Am. Chem. Soc.* **2020**, *142*, 5515–5520.



Scheme 75. Ring expansion of vinyl-cyclopropyl boronates.

Vinyl boronate esters have been used to synthesize cyclobutylboronates through an intramolecular [2 + 2] cycloaddition reaction. The method provides straightforward access to highly functionalized cyclobutane scaffolds. The authors reported the synthesis of 20 examples with good yield and modest diastereomeric ratios, but they could separate both diastereomer by flash column chromatography (**Scheme 76**).[134]

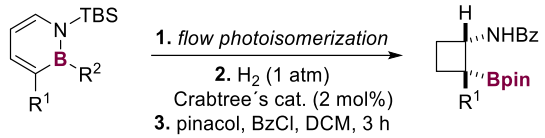


Scheme 76. Photosensitized [2 + 2] cycloaddition of vinyl boronates.

Liu and co-workers reported an elegant work where they access 1,2-aminoborylated cyclobutanes through flow photoisomerization of 1,2-

[134] Scholz, S. O.; Kidd, J. B.; Capaldo, L.; Flikweert, N. E.; Littlefield, R. M.; Yoon, T. P. *Org. Lett.* **2021**, *23*, 3496–3501.

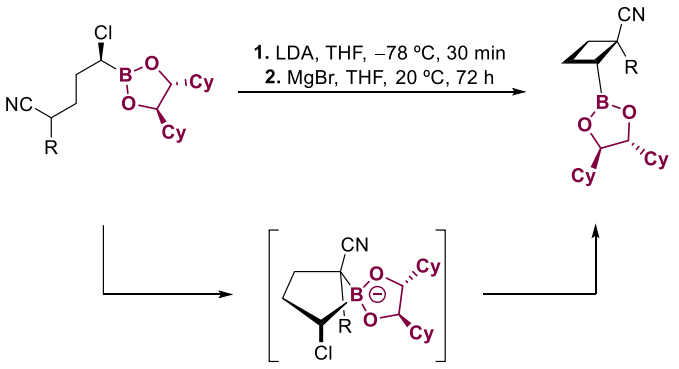
azaborines. The products were obtained in moderate yields from the three-steps sequence, affording the *trans* diastereomer as a major product in all cases. Moreover, they demonstrated the utility of the boronate containing cyclobutanes through the photoredox (hetero)arylation of the corresponding trifluoroborate salt to prepare 2-(hetero)arylated amido-cyclobutanes (Scheme 77).[135]



Scheme 77. Synthesis of 2-amido cyclobutylboronates through 1,2-azaborine flow photoisomerization.

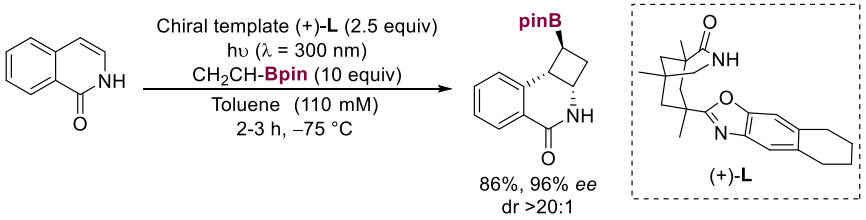
The methods described above allow for the diastereoselective preparation of cyclobutylboronates but do not provide access to enantiomerically pure products. The preparation of enantiomerically enriched cyclobutylboronates represents an additional challenge. The first asymmetric synthesis of cyclobutylboronates was reported in 1999, by Matteson and co-workers. The authors developed a multistep approach based on the stereospecific cyclization of a stabilized carbanion onto a chiral α-chloroalkylboronic ester (Scheme 78).[136]

[135] Giustra, Z. X.; Yang, X.; Chen, M.; Bettinger, H. F.; Liu, S. Y. *Angew. Chem. Int. Ed.* **2019**, *58*, 18918–18922.
[136] Man, H. W.; Hiscox, W. C.; Matteson, D. S. *Org. Lett.* **1999**, *1*, 379–381.



Scheme 78. Synthesis of enantioenriched cyclobutylboronates.

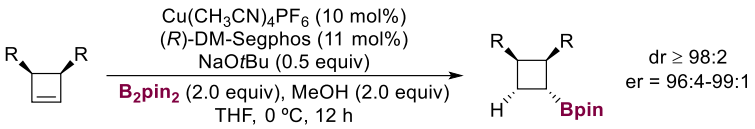
In 2013, Bach and co-workers reported the enantioselective [2 + 2] photochemical cycloaddition between isoquinolone and an alkenyl-boronate promoted by a stoichiometric chiral hydrogen-bonding template, under 300 nm wavelength light. The desired cyclobutylboronate is formed with almost perfect stereocontrol (**Scheme 79**).



Scheme 79. Enantioselective [2 + 2] photochemical synthesis of cyclobutylboronates.

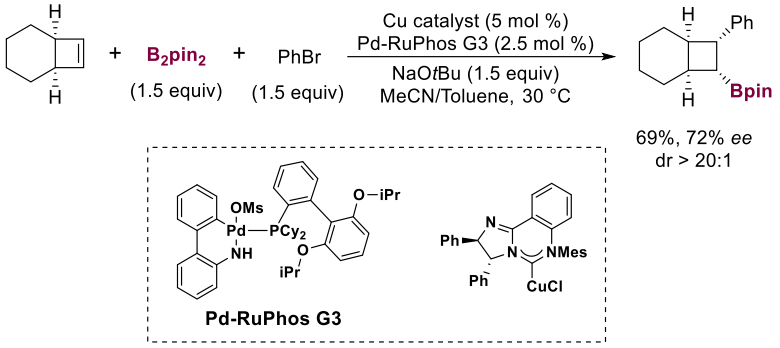
In 2016, our research group reported the first catalytic enantioselective method to prepare enantioenriched cyclobutylboronates. Using an inexpensive copper(I) salt and a commercially available phosphine ligand, a broad variety of borylated cyclobutanes were prepared with high levels of

diastereo- and enantiocontrol. Moreover, this method constitutes the first report of an enantioselective desymmetrization of *meso*-cyclobutenes to prepare chiral cyclobutanes (**Scheme 80**).[137]



Scheme 80. Enantioselective desymmetrization of meso-cyclobutenes.

In 2017, Brown reported the enantioselective arylboration of alkenes using Pd-RuPhos G3 and a copper(I) complex combination. In one example, they reported the formation of a bicyclic cyclobutylboronate with good yield and moderate enantiomeric excess (**Scheme 81**).[138]

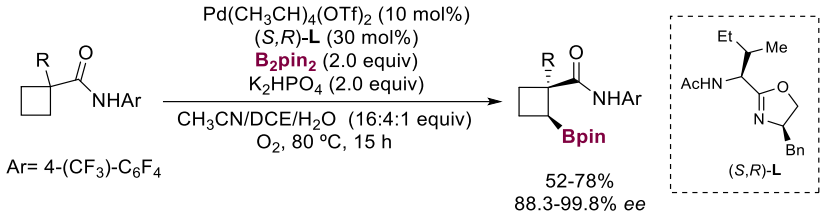


Scheme 81. Enantioselective arylboration of alkenes.

[137] Guisán-Ceinos, M.; Parra, A.; Martín-Heras, V.; Tortosa, M. *Angew. Chem. Int. Ed.* **2016**, *55*, 6969–6972.

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

The same year, Yu and co-workers studied the enantioselective Pd-catalyzed C–H activation of cyclobutylamides. As in their previous report (**Scheme 70**), the amide moiety worked as directing group. In this novel approach, they used a chiral bidentate ligand to obtain *cis* β-borylated-cyclobutylamides with excellent yields and enantioselectivities (**Scheme 82**).[139]

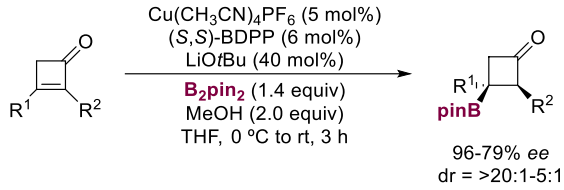


Scheme 82. Enantioselective C-H borylation of cyclobutylamides.

It was in 2019 when Hall and co-workers published the enantioselective conjugate borylation of α-alkyl, β-aryl/alkyl cyclobutenones to access valuable tertiary cyclobutylboronates. By using a high-throughput screening approach (118 chiral ligands), they found that (2*S*,4*S*)-2,4-bis(diphenylphosphino)pentane (BDPP) was the optimal ligand affording the highest enantioselectivity (**Scheme 83**).[140]

[139] He, J.; Shao, Q.; Wu, Q.; Yu, J. Q. *J. Am. Chem. Soc.* **2017**, *139*, 3344–3347.

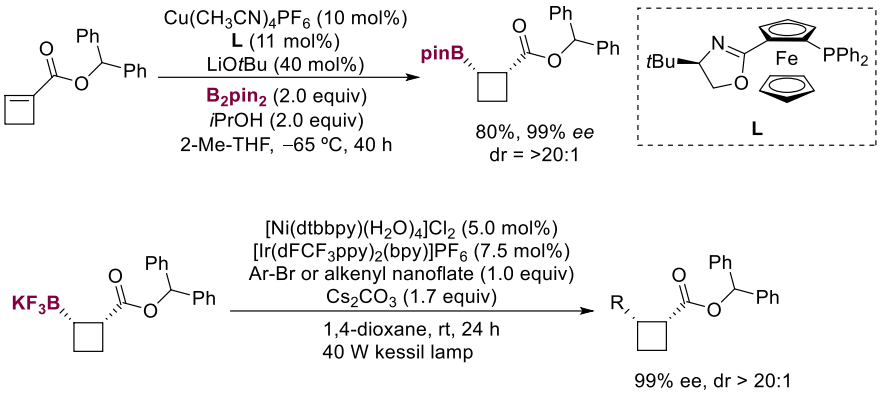
[140] Clement, H. A.; Boghi, M.; McDonald, R. M.; Bernier, L.; Coe, J. W.; Farrell, W.; Helal, C. J.; Reese, M. R.; Sach, N. W.; Lee, J. C.; Hall, D. G. *Angew. Chem. Int. Ed.* **2019**, *58*, 18405–18409.



Scheme 83. Stereoselective conjugate borylation of cyclobutanones.

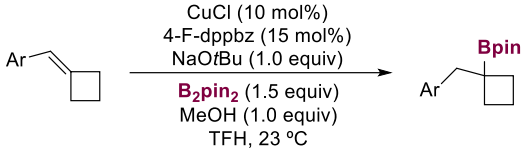
Recently, the same authors, developed the synthesis of a *cis*-β-boronyl cyclobutylcarboxyester by using, again, a high-throughput ligand screening approach.[141] Of the 118 ligands screened, the Naud family of phosphine-oxazoline ligands was found to be the most effective. The *cis* diastereoselectivity could be explained from a sterically controlled, irreversible protonation step. The product was obtained in good yield and with high enantioselectivity (99% *ee*, >20:1 dr). In addition, they developed a diastereoselective nickel/photoredox dual-catalyzed Csp^3–Csp^2 cross-coupling of the corresponding trifluoroborate salt (Scheme 84). The *trans*-β-aryl/heteroaryl and cycloalkenyl cyclobutylcarboxyesters were obtained with excellent diastereoselectivity and high chirality transfer (91–99% *ee*, dr >20:1).

[141] Nguyen, K.; Clement, H. A.; Bernier, L.; Coe, J. W.; Farrell, W.; Helal, C. J.; Reese, M. R.; Sach, N. W.; Lee, J. C.; Hall, D. G. *ACS Catal.* **2021**, *11*, 404–413.



Scheme 84. Enantioselective borylation of cyclobutene 1-carboxyester.

In the last years, other interesting approaches have been developed to obtain symmetric secondary cyclobutylboronates. In 2020, Engle reported the copper-catalyzed hydroboration of benzylidene-cyclobutanes. By the employment of modified ligand 4-F-dppbz, high levels of regiocontrol were achieved. The authors reported a couple of non-symmetric products with modest diastereoselectivities (**Scheme 85**).[142]

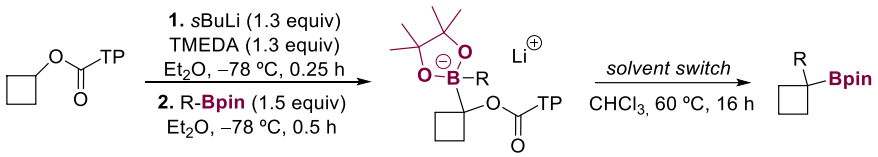


Scheme 85. Regioselective hydroboration of benzylidenecyclobutanes.

In a recent approach, Aggarwal and co-workers used cyclic 2,4,6-triisopropylbenzoates to obtain secondary cyclobutylboronates through a

[142] Kang, T.; Erbay, T. G.; Xu, K. L.; Gallego, G. M.; Burtea, A.; Nair, S. K.; Patman, R. L.; Zhou, R.; Sutton, S. C.; McAlpine, I. J.; Liu, P.; Engle, K. M. *ACS Catal.* **2020**, *10*, 13075−13083.

lithiation-borylation sequence (**Scheme 86**). They demonstrated that the success of the process is governed by a delicate balance of factors involving ease of lithiation, stability of the organolithium, and ease of 1,2-migration. The method shows broad substrate scope, and the versatility of the boron substituted cyclobutanes has been demonstrated by transforming the boronic ester into different functional groups.[143]



Scheme 86. Synthesis of cyclobutylboronates through lithiation, borylation and 1,2-metalate rearrangement.

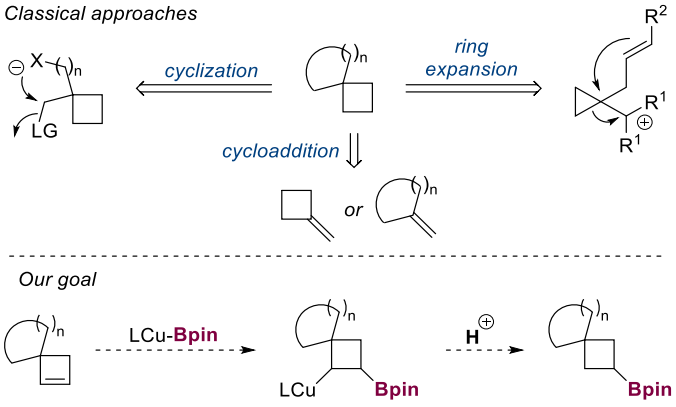
[143] Mykura, R. C.; Songara, P.; Luc, E.; Rogers, J.; Stammers, E.; Aggarwal, V. K. *Angew. Chem. Int. Ed.* **2021**, *60*, 11436–11441.

2. Regioselective Monoborylation of Spirocyclobutenes

2.1 Objectives

As mentioned before, the most common strategies to build spirocycles involve intramolecular S_N2 reactions, [2 + 2] or higher-order cycloadditions and ring expansion approaches (**Scheme 87**). At the beginning of this doctoral thesis the use of spirocyclobutenes to prepare functionalized spirocycles remained unexplored.

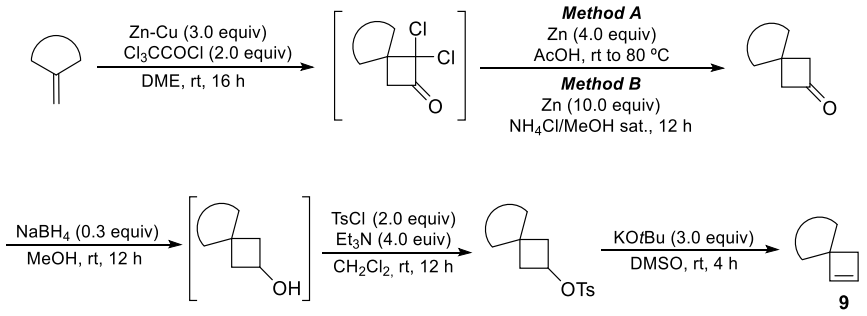
Inspired by our previous work on the enantioselective desymmetrization of meso cyclobutenes, we envisioned that *in situ* generated copper-boryl complexes could react with the strained-alkene of spirocyclobutenes through a migratory insertion/protonation sequence to provide monoborylated spirocycles (**Scheme 87**). The main challenge of our approach was to control the regioselectivity in the insertion step. If successful, our approach could be an interesting strategy to synthesize different spirocycles from a common intermediate.



Scheme 87. Objective of this chapter.

2.2 Synthesis of Starting Materials

To start with our study, we designed a route to obtain spirocyclobutenes. The synthetic strategy to prepare the starting materials starts from an exocyclic alkene that is prepared from the corresponding cyclic ketone, which underwent Wittig olefination after treatment with methyl triphenyl-phosphonium bromide salt in the presence of KO*t*Bu. Cyclobutanones were synthetized trough a [2 + 2] cycloaddition between the exocyclic alkene and the *in situ* generated dichloroketene from trichloro acetyl chloride and zinc dust followed by reduction of the chlorine atoms using Zn dust in acetic acid or a mixture of Zn dust in a saturated solution of ammonium chloride in methanol for more sensitive substrates. The afforded ketone was reduced and the corresponding alcohol tosylated. Finally, the elimination of the tosyl group was carried out in anhydrous DMSO in the presence of 3 equivalents of KO*t*Bu to yield the desired spirocyclobutenes (Scheme 88).



Scheme 88. Designed route for the synthesis of spirocyclobutenes.

Following this synthetic route, we prepare different spirocyclobutenes (**Figure 7**), bearing a wide range of functional groups (**9a**-**9h**) and also different spiro ring systems (**9i**-**9l**). Finally, two asymmetric spirocycles were prepared to test their reactivity (**9m** and **9n**).

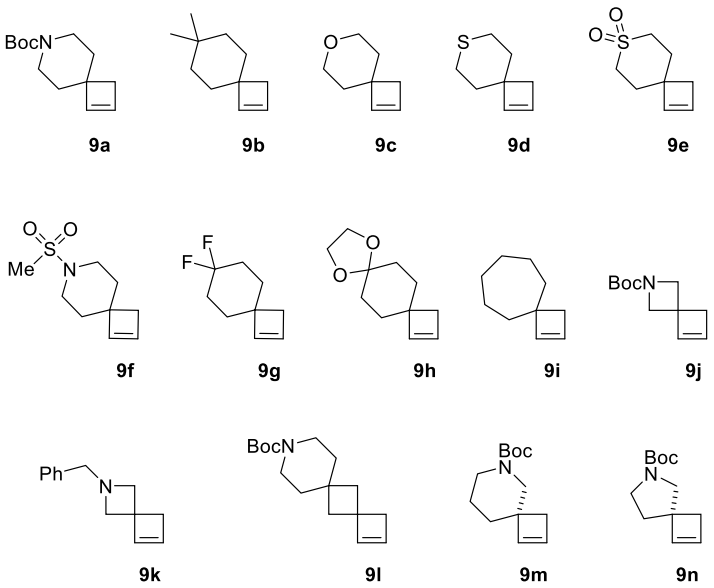


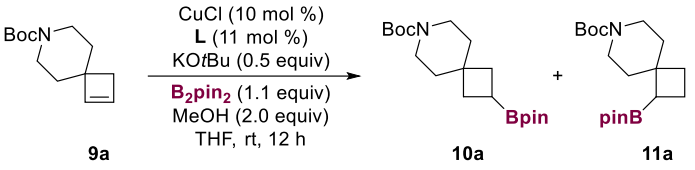
Figure 7. Prepared spirocyclobutenes.

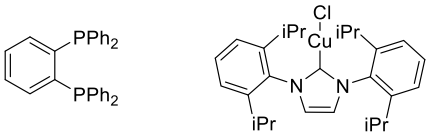
2.3 Screening of Conditions

We chose spirocyclobutene **9a** as model substrate to explore their reactivity under copper(I)-catalyzed borylation conditions using different ligands (**Table 2**). Mixing spirocyclobutene **9a** with CuCl (10 mol%), B_2pin_2 (1.1 equiv), KO*t*Bu (0.5 equiv) and MeOH (2 equiv) with dppbz-**L1** (11 mol%), a bidentate phosphine ligand with a small bite angle (β_n = 83°) we observe complete conversation and excellent yield but both regioisomers

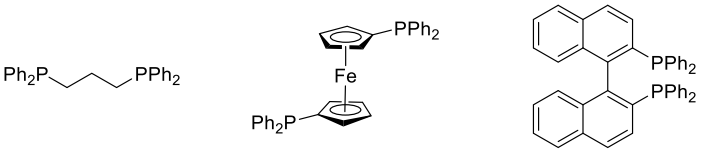
10a and **11a** were obtained in a 1:1 mixture (**Table 2**, **entry 1**). The regioisomeric ratio was determined by oxidation of the boronic ester moiety and comparison of the ^{1}H NMR data of the product with those of the same alcohol prepared through reduction of the corresponding cyclobutanone (see **Scheme 88**). Using NHC-CuCl-**L2** complex (10 mol%), compounds **10a** and **11a** were obtained in good yield but low diastereoselectivity (65:35) (**Table 2**, **entry 2**). Remarkably, xantphos-**L3** (β_n = 108°), afforded borylated spirocycle **10a** in 86% yield as a single regioisomer (**Table 2**, **entry 3**). We observed that using dppp (**L4**, β_n = 91°), dppf (**L5**, β_n = 99°) and BINAP (**L6**, β_n = 93°) as phosphine ligands with a bite angle smaller than xantphos (**L3**) and larger than dppbz (**L2**) moderate regioselectivities were obtained (**Table 2**, **entry 4-6**). We also tried to reduce the amount of the catalyst to 5 mol%, providing only the desired regioisomer albeit in a lower yield (**Table 2**, **entry 7**). Finally, carrying out the reaction without ligand, both regioisomers were obtained in a lower yield indicating that the ligand is necessary to control the reactivity and the regiochemistry of the transformation (**Table 2**, **entry 8**).

Table 2. Effect of the ligand in the copper-catalyzed borylation.





L1 (dppbz) **L2**-CuCl **L3** (xantphos)



L4 (dppp) **L5** (dppf) **L6** (BINAP)

Entry[a]	Ligand	10a:11a[b]	Yield (%)[c]
1	L1	50:50	84
2	L2	65:35	71
3	L3	≥98:2	86
4	L4	83:17	58
5	L5	64:36	79
6	L6	73:27	69
7[d]	L3	≥98:2	69
8	-	60:40	13

[a]Reaction conditions: **9a** (0.1 mmol), B_2pin_2 (0.11 mmol), KO*t*Bu (0.5 equiv), CuCl (10 mol%), **L** (11 mol%), MeOH (0.2 mmol), THF (0.2 M). [b]Determined by ^{1}H NMR. [c]Isolated yield. [d]With 5 mol% of CuCl and 6 mol% of **L3**.

2.4 Scope of the reaction

To study the scope of the reaction, the different synthesized spirocyclobutenes were tested under the optimized copper-catalyzed borylation conditions (Scheme 89).

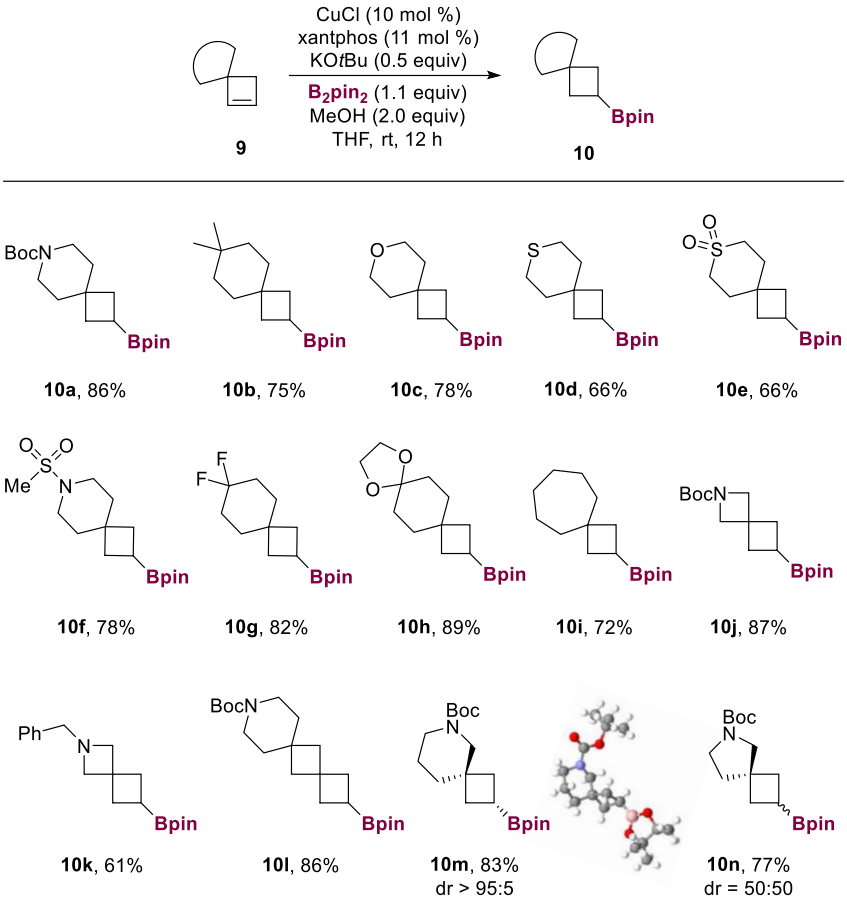
Different monoborylated spiro[3.5]nonanes systems (10a-10h) were successfully synthesized. The reaction works with different functional groups such as carbon chain (10b), ether (10c), thioether (10d), sulfone (10e) or sulfonamide (10f). Moreover, spirocycle with a difluoromethane group, that is frequently used in medicinal chemistry to optimize the properties of bioactive compounds, was successfully prepared (10g).[144] The presence of an acetal was also tolerated under the reaction condition (10h) and offer a handle for further derivatizations.

We were delighted to see that the size of the ring fussed to the cyclobutene could be modified without losing the regiocontrol obtained using xantphos as ligand. Spiro[3.6]decane and different spiro[3.3]-heptanes (10j, 10k) ring systems, were obtained in good yield as single regioisomers. Compound 10k, bearing a tertiary amine in their structure, was isolated using deactivated silica gel with Et_3N to avoid their decomposition during the purification process. Tricyclic compound 10l was compatible with the reaction conditions and only the formation of the desired regioisomer was observed with excellent yield. Finally, we decided to test the scope of the reaction using non-symmetric spirocyclobutenes.

[144] Gillis, E. P.; Eastman, K. J.; Hill, M. D.; Donnelly, D. J.; Meanwell, N. A. *J. Med. Chem.* **2015**, *58*, 8315−8359.

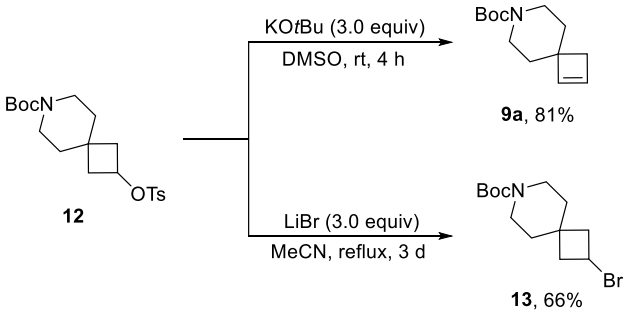
Surprisingly, using identical reaction conditions, asymmetric spiro-cyclobutene **9m**, afford spirocycle **10m** as a single diastereomer in excellent yield. The relative configuration was determined by single X-ray structure analysis which determinates that the -CH_2NBoc group and the boryl moiety are present in a relative *trans* configuration in the final product.

With this great result we decided to synthetize the asymmetric spirocyclobutene **9n** with a pyrrolidine ring attached to the cyclobutene. Unfortunately, using the same reaction conditions, we obtained full conversion but both regioisomers were obtained in almost 1:1 mixture.



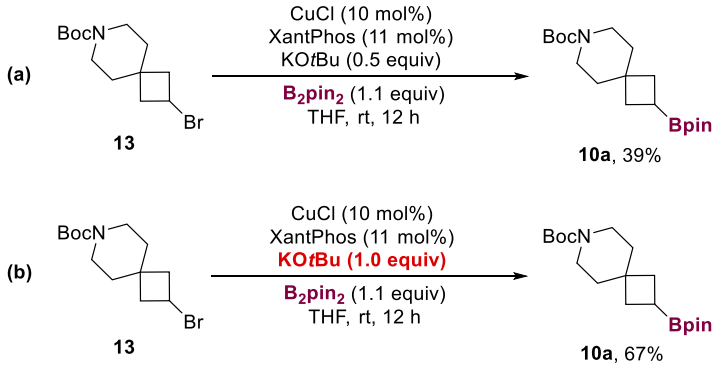
Scheme 89. Scope of the regioselective hydroboration of spirocyclobutenes.

An alternative approach to prepare regioisomer **10a** could be through copper-catalyzed borylation of the corresponding bromide. To compare both approaches we prepared spirocyclobutyl bromide **13**. The preparation of the starting bromide from tosyl-spirocyclobutane **12** compared to the cyclobutene is less convenient as it requires refluxing in CH_3CN for 3 days to obtain the product in only 66% yield (**Scheme 90**).



Scheme 90. Comparison of the synthesis of cyclobutene **9a** and bromide **13**.

Regarding the borylation, when we used the conditions optimized for our cyclobutenes (0.5 equiv of KO*t*Bu) the borylated product **10a** was obtained in only 39% yield (**Scheme 91a**). Increasing the amount of base to 1 equivalent (as Ito published for alkyl bromides)[145] the yield of the borylated product increased to 67% yield (**Scheme 91b**). Although they are both valid approaches, the use of the cyclobutene is more convenient as it doesn't require a stochiometric amount of base and the product was obtained in better yield.

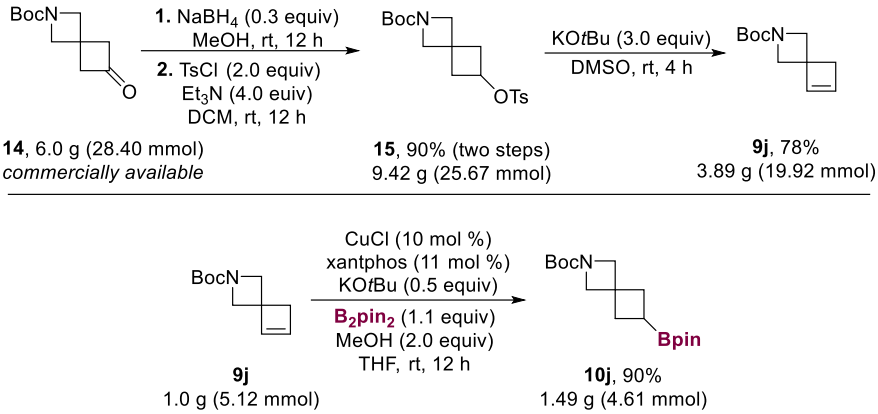


Scheme 91. Borylation of spirocyclobutyl bromide **13**.

[145] Ito, H.; Kubota, K. *Org. Lett.* **2012**, *14*, 890–893.

2.5 Gram Scale Reactions

We also carried out the reactions in gram scale to demonstrate the utility of both, the synthetic approach to obtain spirocyclobutenes and the methodology developed for the regioselective hydroboration (Scheme 92). Starting from 6.0 g of commercially available spirocyclobutanone **14**, we obtained 3.89 g of the corresponding spirocyclobutene **9j** with a 70% overall yield (3 steps). Finally, spirocyclobutyl boronate **10j** was successfully prepared from 1.0 g of spirocyclobutene **9j** with in a 90% yield.



Scheme 92. Gram scale reactions.

2.6 Computational Study

Density Functional Theory (DFT) calculations were carried out at the dispersion-corrected PCM(tetrahydrofuran)/B3LYP-D3/def2-SVP level to understand the complete regioselectivity observed in the transformation when xantphos was used as ligand. This study was carried out in collaboration with Dr. Israel Fernández (UCM).

According to the computed reaction profile involving **9c** and L3Cu-Bpin, the regioselectivity takes place in the initial migratory insertion step, where the associated transition state leading to the observed regioisomer (TS1-L3) lies 4.6 kcal/mol below that leading to the opposite regioisomer (TS1'-L3). This is very likely due to unfavorable steric interactions between the boryl moiety and tetrahydropyran fragments in the latter saddle point which are not present in the favored TS1-L3. With dppbz as ligand (**L1**, **Table 2**), the $\Delta\Delta G^{\neq}$ between the corresponding transition states (TS1-L2 and TS1'-L2) decreased to 2 kcal/mol, which is in qualitative agreement with the lower regioselectivity observed for this ligand (**Figure 8**).

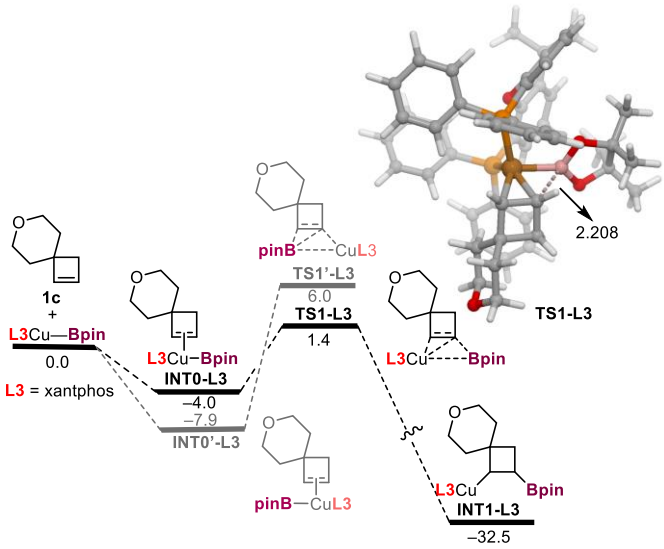


Figure 8. Computed reaction profile for the copper-catalyzed borylation of **9c**. Relative free energies (ΔG, at 298 K) are given in kcal/mol. All data have been computed at the PCM(tetrahydrofuran)-B3LYP-D3/def2-SVP level.

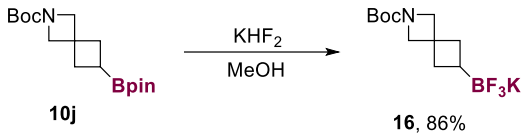
2.7 Functionalization of the C–B bond

Boronic esters are invaluable building blocks for the synthesis of pharmaceuticals and materials.[146] To further demonstrate the versatility of the synthetized spirocyclobutylboronates we explored the possibility to introduce different functional groups in the spirocycle through the C–B bond functionalization.

First, we successfully transformed spirocyclobutylboronate **10j** into the correspondent trifluoroborate salt **16**.[137] These salts are more stable

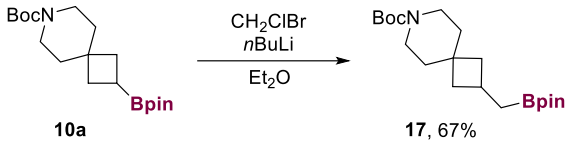
[146] Sandford, C.; Aggarwal, V. K. *Chem. Commun.* **2017**, *53*, 5481–5494.

equivalents of boronic acids and have been widely used in different cross-coupling reactions (**Scheme 93**).[147]



Scheme 93. Synthesis of trifluoroborate salt **16**.

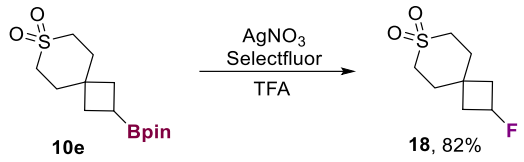
Matteson homologation[148] of the C–B bond to add one carbon atom in spirocycle **10a** was successfully achieved with bromochloromethane in the presence of butyllithium, affording boronic ester derivative **17** (**Scheme 94**).



Scheme 94. Matteson homologation of compound **10a**.

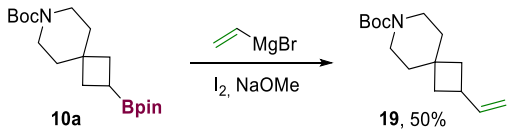
Following the methodology reported by Li,[149] fluorination of cyclobutylboronate **10e** was achieved by treatment with a catalytically amount of $AgNO_3$ in the presence of Selectfluor® and TFA. Fluoro-spirocyclic derivative **18** was obtained with excellent yield (**Scheme 95**).

[147] **(a)** Fang, G. -H.; Yan Z. -J.; Deng, M.-Z. *Org. Lett.* **2004**, *6*, 357–360. **(b)** Molander, G. A.; Ellis, N. *Acc. Chem. Res.* **2007**, *40*, 275–286. **(c)** Darses, S.; Genet, J. P. *Chem. Rev.* **2008**, *108*, 288–325. **(d)** Molander, G. A., Gormisky, P. E. *J. Org. Chem.* **2008**, *73*, 7481–7485.
[148] Silvi, M.; Aggarwal, V. K. *J. Am. Chem. Soc.* **2019**, *141*, 9511–9515.
[149] Li, Z.; Wang, Z.; Zhu, L.; Tan, X.; Li, C. *J. Am. Chem. Soc.* **2014**, *136*, 16439–16443.



Scheme 95. Fluorination of compound **14e**.

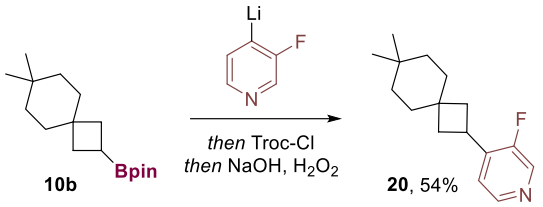
Zweifel olefination[130] of spirocyclobutylboronate **10a** was performed to afford spirocyclic derivative **19** in moderate yield (**Scheme 96**). The presence of the double bond offers a handle for further functionalizations.



Scheme 96. Zweifel olefination of compound **10a**.

Finally, we were interested in the methodology developed by Aggarwal to obtain the cross-coupling reaction between boronic esters and lithiated *N*-heteroaromatics.[150] We were pleased to see that 3-fluoropyridine derivative **20** was obtained following the reported procedure (**Scheme 97**). This functionalization let the introduction of relevant heterocycles in medicinal chemistry into the spirocyclic scaffold.

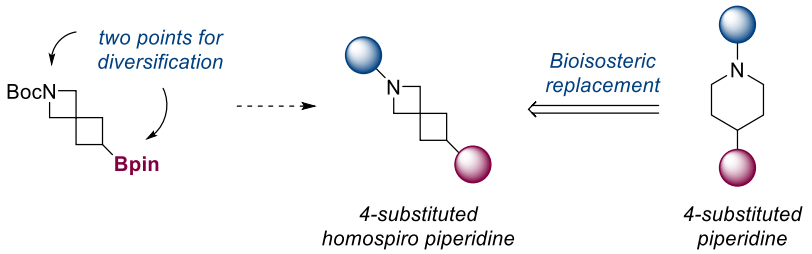
[150] Llaveria, J.; Leonori, D.; Aggarwal, V. K. *J. Am. Chem. Soc.* **2015**, *137*, 10958–10961.



Scheme 97. Aggarwal's cross coupling of **10b**.

2.8 Synthesis of Donepezil Bioisostere

One of the interesting features of small ring spirocycles is their potential use for bioisosteric replacement of commonly used heterocycles. In particular, the 2-azaspiro[3.3]heptane ring system, has been proposed as bioisostere of the piperidine ring with improved water solubility. 4-Substituted piperidines are widely present in commercialized drugs and lead compounds. Spirocycle **10j**, with two handles for diversification, represents an ideal novel building block to substitute the piperidine ring for the homospiro moiety in libraries of compounds (**Scheme 98**).



Scheme 98. Bioisosteric replacement of 4-substituted piperidine.

To highlight the synthetic potential of this approach, we decided to prepare a conformationally restricted analog of the FDA-approved drug Donepezil in which the 4-substituted piperidine would be replaced by the homospiro piperidine framework (**Figure 9**).

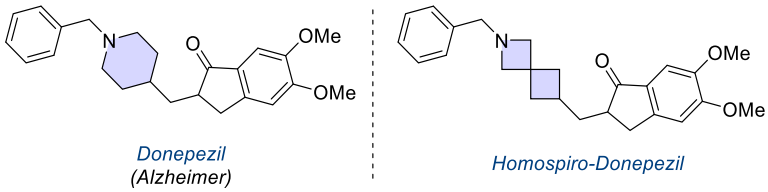
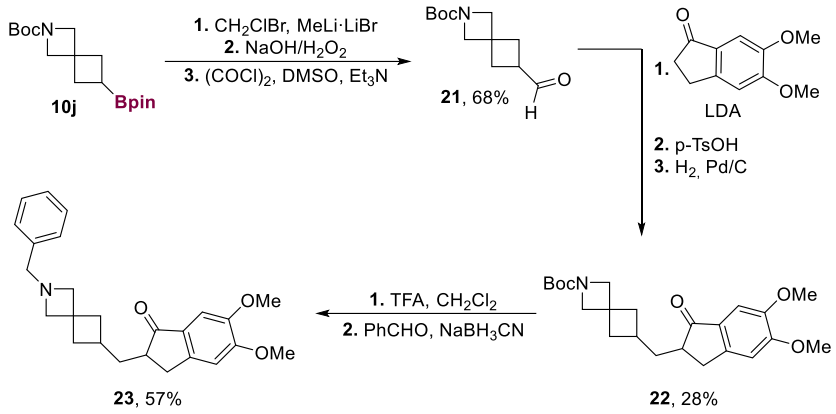


Figure 9. Proposed bioisosteric replacement of Donepezil.

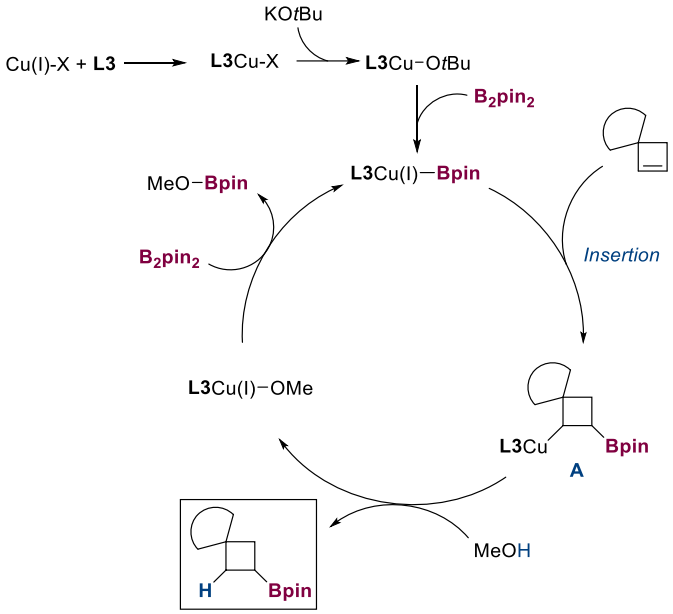
Starting from monoborylated spirocycle **10j**, Matesson homologation followed by double oxidation afforded aldehyde **21** in good yield (3 steps). Then, after some optimization, we found that aldol reaction was successfully achieved using LDA as base. The aldol intermediate was not isolated and subsequently we carried out the dehydration refluxing the mixture in the presence of a catalytic amount of *p*-toluenyl sulfonic acid. The resulting double bond was reduced through hydrogenation over Pd/C providing intermediate **22**. Finally, deprotection of the Boc group followed by reductive amination of the secondary amine afforded Donepezil derivative **23** (**Scheme 99**).



Scheme 99. Synthesis of Donepezil bioisostere.

2.9 Proposed Reaction Mechanism

A plausible mechanism for the copper(I)-catalyzed borylation of cyclobutenes is depicted in Scheme 100. First, a copper-alkoxide is formed by reaction between the ligand, copper(I) salt, and potassium *tert*-butoxide. This alkoxide (L3Cu-O*t*Bu) could undergo a σ-bond metathesis reaction with the boron source to form a copper-boryl complex (L3Cu-Bpin). Then, regioselective insertion of the spirocyclobutene into the copper-boryl complex would afford spirocyclobutyl-copper intermediate A. Finally, reaction with MeOH would provide the hydroboration product and copper-methoxide (L3Cu-OMe) that would regenerate the catalytic cycle.

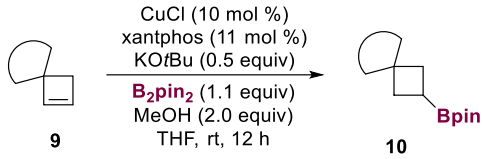


Scheme 100. Proposed mechanism for the regioselective borylation reaction.

2.10 Conclusions/Conclusiones

In this chapter we have described the regioselective hydroboration of spirocyclobutenes (Scheme 101). The combination of a commercially available phosphine ligand (xantphos) with an inexpensive copper(I) salt provided access to different spirocyclobutylboronates as single regioisomers.

Moreover, we have demonstrated the versatility of the products through the functionalization of the C–B bond affording different valuable spirocyclic derivatives from a common intermediate. Additionally, we developed a synthetic route to synthesize a Donepezil bioisostere changing the piperidine ring for the 2-azaspiro[3.3]heptane ring system that has been proposed as bioisostere with improved water solubility.

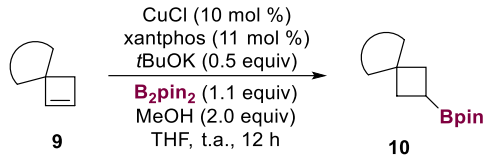


Scheme 101. Regioselective monoborylation of spirocyclobutenes.

Conclusiones

En este capítulo, hemos desarrollado un procedimiento para llevar a cabo la hidroboración regioselectiva de espirociclobutenos (**Esquema 5**). La combinación de una fosfina comercial (xantphos) con una sal de cobre(I) accesible permitió la síntesis de diferentes espirociclobutilboronatos como únicos regioisómeros.

Además, hemos demostrado la versatilidad de los productos obtenidos a través de distintas funcionalizaciones del enlace C–B. Finalmente, diseñamos una ruta sintética para preparar un bioisóstero del fármaco Donepezilo substituyendo el anillo de piperidina por el sistema espirocíclico 2-azaespiro[3.3]heptano, que está considerado como un bioisóstero con mejor solubilidad en agua.



Esquema 5. Monoborilación regioselectiva de espirociclobutenos.

3. Supplementary Data

3.1 General Experimental Details

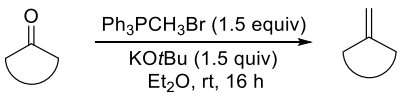
Tetrahydrofuran, toluene, and dichloromethane were purified by passing through a Pure Solv™ column drying system from Innovative Technology, Inc. Diethyl ether was dried using activated 4 Å molecular sieves and stored under argon. DME and MeOH were purchased dry from Acros Organics. Anhydrous DMSO was purchased from VWR. For convenience, borylation reactions were set up in a nitrogen filled glove box Inert PURELAB PL-HE-2GB. However, performing the borylation reactions under argon atmosphere using flame-dried glassware with standard vacuum-line techniques lead to similar results in terms of yields and regioselectivity.

NMR spectra were acquired on a Bruker Avance 300 MHz spectrometer, running at 300, 75, 96 and 282 MHz for ^{1}H, ^{13}C, ^{11}B and ^{19}F, respectively. Chemical shifts (δ) are reported in ppm relative to residual solvent signals ($CDCl_3$, ^{1}H = 7.26 ppm, ^{13}C = 77.16 ppm; Toluene-d_8, ^{1}H = 2.09 ppm, ^{13}C = 20.40 ppm or D_2O, ^{1}H = 4.79 ppm, ^{13}C (MeOH as reference) = 49.5 ppm). For ^{19}F spectra, C_6F_6 is used as internal standard (^{19}F = −164.9 ppm). ^{13}C NMR and ^{19}F 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), quint (quintet), m (multiplet), br (broad). Analytical thin layer chromatography (TLC) was performed using pre-coated aluminum-backed plates (Merck Kieselgel 60 F_{254}) and visualized by ultraviolet irradiation and phosphomolybdic acid dip,

potassium permanganate dip or cerium ammonium molybdate dip. Flash column chromatography (FC) was performed using silica gel Merck-60 or Florisil® 100-200 mesh from Aldrich. 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^+) or Bruker maXis II™ ($APCI^+$). Melting points were determined in a Stuart™ melting point SMP3 apparatus in open capillary tubes.

3.2 Synthesis of Starting Materials

General Procedure for Wittig Olefination of Cyclic Ketones, ***SI-3***



SI-3

A suspension of methyl triphenylphosphonium bromide (1.5 equiv) in anhydrous Et_2O (1.5 mL/mmol), under an argon atmosphere, was cooled to 0 °C and treated with solid potassium *tert*-butoxide (1.5 equiv). The mixture was warmed to room temperature and stirred for 1 h. Cyclic ketone (1.0 equiv) was added and the reaction mixture was stirred at room temperature overnight. Upon complete consumption of the ketone as monitored by TLC, the reaction was quenched with H_2O and extracted with Et_2O. The combined organics were washed with brine and dried over $MgSO_4$. The solvent was removed *in vacuo* (**CAUTION**: in some cases, olefins are volatile). The olefin was purified by flash column chromatography on silica gel to afford the desired product **SI-3**.

Compound **SI-3b**,[151] **SI-3c**,[152] **SI-3d**,[152] **SI-3h**,[153] **SI-3i**[154] and **SI-3m**[155] have been synthesized *via* Wittig olefination described above and the spectral data matched with those previously reported (**Figure 10**).

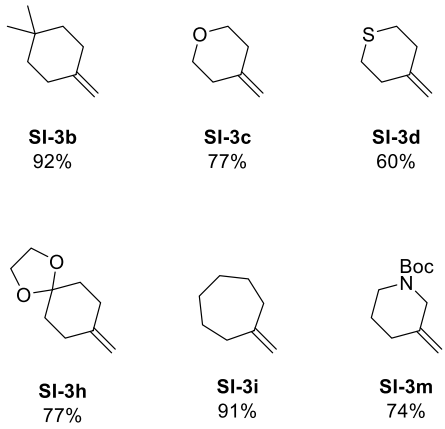
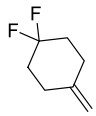


Figure 10. Synthetized exocyclic alkenes.

1,1-Difluoro-4-methylenecyclohexane, SI-3g



SI-3g

From 4,4-difluorocyclohexanone (3.0 g, 22.37 mmol) following the general procedure described above, compound **SI-3g** (1.40 g, 10.59 mmol) was obtained in 47% yield as a colorless oil, after purification by flash column chromatography (SiO_2; pentane).

[151] Romanov-Michailidis, F.; Sedillo, K. F.; Neely, J. M.; Rovis, T. *J. Am. Chem. Soc.* **2015**, *137*, 8892−8895.

[152] Green, S, A.; Vásquez-Céspedes, S.; Shenvi, R. A. *J. Am. Chem. Soc.* **2018**, *140*, 11317−11324.

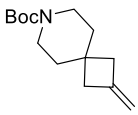
[153] Watson, D. W.; Gill, M.; Kemmitt, P.; Lamont, S. G.; Popescu, M. V.; Simpson, I. *Tetrahedron Lett.* **2018**, *59*, 4479−4482.

[154] Olah, G. A.; Prakash-Reddy, V.; Surya-Prakash, G. K. *Synthesis* **1991**, *1*, 29−30.

[155] Prevost, N.; Shipman, M. *Tetrahedron* **2002**, *58*, 7165−7175.

^{1}H NMR (300 MHz, $CDCl_3$): δ 4.76 (s, 2H), 2.36-2.26 (m, 4H), 1.96 (tt, *J* = 13.5, 6.7 Hz, 4H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 144.8, 123.3 (t, *J* = 240.9 Hz), 110.3, 34.9 (t, *J* = 23.8 Hz), 30.8 (t, *J* = 5.5 Hz). **^{19}F NMR** (282 MHz, $CDCl_3$): δ −100.9. **HRMS (EI$^+$)**: calculated for $C_7H_{10}F_2$ $[M]^+$: 132.0751; found: 132.0756.

tert-Butyl 2-methylene-7-azaspiro[3.5]nonane-7-carboxylate, **SI-3l**

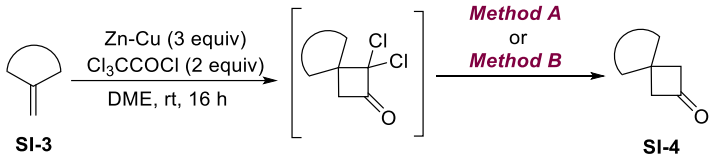


SI-3l

From *tert*-butyl 2-oxo-7-azaspiro[3.5]nonane-7-carboxylate (2.0 g, 8.36 mmol) following the general procedure described above, compound **SI-3l** (1.82 g, 7.67 mmol) was obtained in 92% yield as a colorless oil, after purification by flash column chromatography (SiO_2; cyclohexane/EtOAc 90:10).

^{1}H NMR (300 MHz, $CDCl_3$): δ 4.85-4.79 (m, 2H), 3.38-3.27 (m, 4H), 2.47-2.37 (m, 4H), 1.59-1.51 (m, 4H), 1.45 (s, 9H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 154.3, 143.6, 107.4, 78.6, 41.4, 40.7 (br), 36.3, 33.2, 28.1. **HRMS (ESI$^+$)**: calculated for $C_{14}H_{23}NNaO_2$ $[M+Na]^+$: 260.1626; found: 260.1620.

*General Procedure for the Synthesis of Spirocyclobutanones, **SI-4***



SI-3 **SI-4**

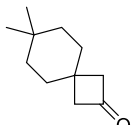
To a suspension of zinc-copper couple (3 equiv) and the corresponding alkene **SI-3** (1 equiv) in 1,2-dimetoxy ethane (2mL/mmol), under an argon atmosphere, was added trichloroacetyl chloride (2 equiv) dropwise at 0 °C under argon atmosphere. The suspension was allowed to warm to room temperature and after stirring for 16 hours the resulting mixture was filtered through a pad of Celite® (Et_2O). The filtrate was washed with H_2O,

a saturated aqueous solution of $NaHCO_3$ and brine, then dried over $MgSO_4$ and the solvent removed *in vacuo*. The residue was used in the next step (method A or method B) without further purification.

Method A: the 2,2-dichlorocyclobutanone was dissolved in AcOH (2 mL/mmol) and Zn dust (10 equiv) was added portionwise at room temperature. The resulting mixture was stirred 4 hours at 80 °C. The resulting mixture was allowed to cool to room temperature, followed by diluting with water and extracted with Et_2O. The organic phase was washed successively with a saturated solution of aqueous $NaHCO_3$, water and brine, then dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by flash column chromatography on silica gel to afford compound **SI-4**.

Method B: the 2,2-dichlorocyclobutanone was dissolved in a saturated solution of NH_4Cl in MeOH (5 mL/mmol). Zinc (10 equiv) was added portionwise at room temperature and stirred for 16 h. After completion, the reaction mixture was filtered through a pad of Celite® (Et_2O) and the solvent was evaporated. The crude residue was purified by flash column chromatography on silica gel or Florisil® to afford compound **SI-4**.

7,7-Dimethylspiro[3.5]nonan-2-one, **SI-4b**

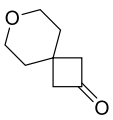


SI-4b

From **SI-3b** (4.50 g, 36.22 mmol) following the general procedure described above, using ***Method A***, compound **SI-4b** (4.10 g, 24.66 mmol) was obtained in 68% yield as a colorless oil, after purification by flash column chromatography (SiO_2; cyclohexane/EtOAc 90:10).

^{1}H NMR (300 MHz, $CDCl_3$): δ 2.71 (s, 4H), 1.68-1.60 (m, 4H), 1.31-1.24 (m, 4H), 0.92 (s, 6H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 208.9, 57.0, 36.9, 33.7, 30.4, 29.6, 28.3 (br). **HRMS (EI$^+$)**: calculated for $C_{11}H_{18}O$ $[M]^+$: 166.1358; found: 166.1356.

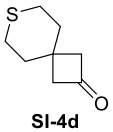
7-Oxaspiro[3.5]nonan-2-one, SI-4c


SI-4c

From **SI-3c** (1.50 g, 15.28 mmol) following the general procedure described above, using ***Method B***, compound **SI-4c** (1.17 g, 8.35 mmol) was obtained in 55% yield as a colorless oil, after purification by flash column chromatography (SiO_2; cyclohexane/EtOAc 85:15).

^{1}H NMR (300 MHz, $CDCl_3$): δ 3.72-3.63 (m, 4H), 2.83 (s, 4H), 1.80-1.72 (m, 4H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 206.6, 65.5, 56.8, 37.2, 28.2. **HRMS (EI$^+$)**: calculated for $C_8H_{12}O_2$ $[M]^+$: 140.0837; found: 140.0837.

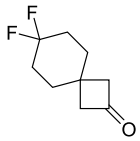
7-Thiaspiro[3.5]nonan-2-one, SI-4d


SI-4d

From **SI-3d** (2.0 g, 17.51 mmol) following the general procedure described above, using ***Method B***, compound **SI-4d** (1.58 g, 10.11 mmol) was obtained in 58% yield as a colorless oil, after purification by flash column chromatography (SiO_2; hexane/Et_2O 80:20).

^{1}H NMR (300 MHz, $CDCl_3$): δ 2.74 (s, 4H), 2.66-2.57 (m, 4H), 2.00-1.92 (m, 4H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 206.1, 56.8, 37.7, 29.5, 25.9. **HRMS (EI$^+$)**: calculated for $C_8H_{12}OS$ $[M]^+$: 156.0609; found: 156.0615.

7,7-Difluorospiro[3.5]nonan-2-one, **SI-4g**

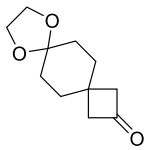


SI-4g

From **SI-3g** (1.40 g, 10.59 mmol) following the general procedure described above, using ***Method A***, compound **SI-4g** (1.13 g, 6.49 mmol) was obtained in 61% yield as a colorless oil, after purification by flash column chromatography (SiO_2; hexane/Et_2O 80:20).

^{1}H NMR (300 MHz, $CDCl_3$): δ 2.82 (s, 4H), 1.99-1.80 (m, 8H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 206.2, 122.7 (t, *J* = 241.3 Hz), 56.3, 33.5 (t, *J* = 5.0 Hz), 31.8 (t, *J* = 24.4 Hz), 29.4. **^{19}F NMR** (282 MHz, $CDCl_3$): δ –101.0. **HRMS (EI$^+$)**: calculated for $C_9H_{12}F_2O$ $[M]^+$: 174.0856; found: 174.0850.

8,11-Dioxadispiro[3.2.4.2]tridecan-2-one, **SI-4h**

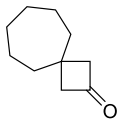


SI-4h

From **SI-3h** (2.28 g, 14.79 mmol) following the general procedure described above, using ***Method B***. The crude product was purified by flash column chromatography (Florisil®, hexane/EtOAc 80:20) to afford **SI-4h** (1.91 g, 9.73 mmol) with 66% yield as a colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ 3.92 (s, 4H), 2.75 (s, 4H), 1.83-1.75 (m, 4H), 1.67-1.57 (m, 4H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 207.6, 108.1, 64.4, 56.5, 34.7, 32.7, 29.6. **HRMS (APCI$^+$)**: calculated for $C_{11}H_{17}O_3$ $[M+H]^+$: 197.1178; found: 197.1172.

Spiro[3.6]decan-2-one, **SI-4i**

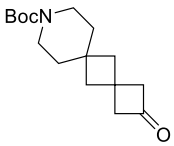


SI-4i

From **SI-3i** (4.26 g, 38.66 mmol) following the general procedure described above, using ***Method A***, compound **SI-4i** (3.41 g, 22.40 mmol) was obtained in 58% yield as a pale yellow oil, after purification by flash column chromatography (SiO_2;

cyclohexane/EtOAc 90:10). The spectral data matched with those previously reported.[156]

tert-Butyl 2-oxo-9-azadispiro[3.1.5^6.1^4]dodecane-9-carboxylate, **SI-4l**

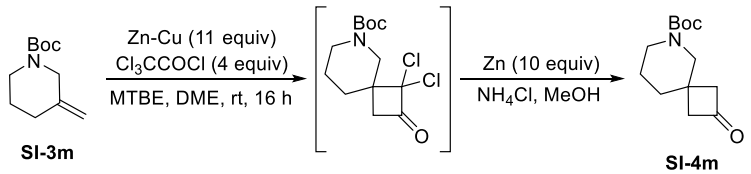


SI-4l

From **SI-3l** (1.0 g, 4.21 mmol) following the general procedure described above, using ***Method B***, compound **SI-4l** (0.68 g, 2.43 mmol) was obtained in 58% yield as a pale yellow oil, after purification by flash column chromatography (SiO_2; cyclohexane/EtOAc 90:10).

^{1}H NMR (300 MHz, $CDCl_3$): δ 3.36-3.29 (m, 4H), 3.10 (s, 4H), 2.09 (s, 4H), 1.58-1.51 (m, 4H), 1.45 (s, 9H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 207.6, 155.1, 79.5, 60.8, 44.3, 40.8 (br), 37.6, 33.2, 28.6, 27.2. **HRMS (EI$^+$)**: calculated for $C_{16}H_{25}NO_3$ $[M]^+$: 279.1834; found: 279.1824.

Synthesis of tert-butyl 2-oxo-7-azaspiro[3.5]nonane-7-carboxylate, ***SI-4m***



SI-3m **SI-4m**

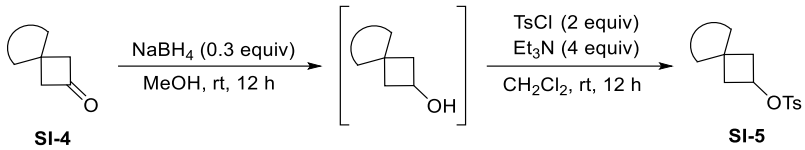
To a suspension of zinc-copper couple (13.5 g, 206 mmol, 11 equiv) and **SI-3m** (3.7 g, 18.76 mmol, 1 equiv) in MTBE (75 mL) was added trichloroacetyl chloride (8.4 mL, 75.0 mmol, 4 equiv) in DME (30 mL) dropwise at 0 °C under argon atmosphere. The suspension was allowed to warm to room temperature and after stirring for 16 hours the resulting mixture was filtered through a pad of Celite (Et_2O). The filtrate was washed

[156] Zhang, E.; Fan, C.-A.; Tu, Y.-Q.; Zhang, F.-M.; Song, Y.-L. *J. Am. Chem. Soc*. **2009**, *131*, 14626–14627.

with H_2O, a saturated aqueous solution of $NaHCO_3$ and brine, then dried over $MgSO_4$ and the solvent removed *in vacuo*. The resulting crude was dissolved in saturated NH_4Cl and MeOH (5 mL/mmol), was added zinc (10 equiv) portionwise at room temperature and stirred for 16 h. After completion of the reaction, the mixture was filtered through a pad of Celite® (Et_2O) and the solvent was evaporated. The crude residue was purified by flash column chromatography (SiO_2; cyclohexane/EtOAc 95:5) to afford compound **SI-4m** (3.0 g, 12.54 mmol) as yellow oil with 67% yield.

^{1}H NMR (300 MHz, $CDCl_3$): δ 3.44-3.32 (m, 4H), 2.88-2.58 (m, 4H), 1.77-1.67 (m, 2H), 1.60-1.49 (m, 2H), 1.41 (s, 9H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 206.3, 154.8, 79.9, 55.3, 52.8 (br), 43.5 (br), 35.7, 30.2, 28.5, 23.3. **HRMS (EI$^+$)**: calculated for $C_{13}H_{21}NO_3$ $[M]^+$: 239.1521; found: 239.1522.

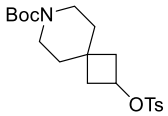
*General Procedure for the Synthesis of Tosylated Spirocyclobutanes, **SI-5***



To a solution of the corresponding cyclobutanone **SI-4** (1.0 equiv) in MeOH (1.7 mL/mmol) at 0 °C, $NaBH_4$ (0.3 equiv) was added portionwise. The resulting mixture was stirred at room temperature for 12 h. Then, the solvent was evaporated and the residue was re-dissolved in EtOAc (3 mL/mmol) and water (3 mL/mmol). The layers were separated and the aqueous phase was extracted with EtOAc (3x). The organic phases were washed with brine, dried over $MgSO_4$ and the solvent evaporated under reduced pressure. The residue was used in the next step without further purification.

To a solution of the corresponding alcohol and triethylamine (4 equiv) in DCM (1.5 mL/mmol), a solution of TsCl (2.0 equiv) in DCM (0.6 mL/mmol) was added dropwise at 0 °C. After being stirred for 12 h at room temperature, water (2.5 mL/mmol of alcohol) and DCM (2.5 mL/mmol of alcohol) were added to the reaction mixture. Then, the layers were separated and the aqueous phase was extracted with DCM (3x). The combined organic phases were dried ($MgSO_4$), filtered, and the solvent evaporated under reduced pressure. The residue was purified by flash column chromatography on silica gel to afford the desired product **SI-5**.

tert-Butyl 2-(tosyloxy)-7-azaspiro[3.5]nonane-7-carboxylate, **12**

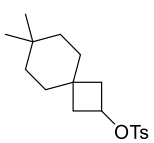


12

From *tert*-butyl 2-oxo-7-azaspiro[3.5]nonane-7-carboxylate (2.0 g, 8.36 mmol) following the general procedure described above, compound **12** (3.20 g, 8.09 mmol) was obtained in 97% yield as a white solid, after purification by flash column chromatography (SiO_2; cyclohexane/EtOAc 90:10). **mp** = 82-84 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.77 (d, *J* = 8.2 Hz, 2H), 7.33 (d, *J* = 8.4 Hz, 2H), 4.83 (quint, *J* = 7.1 Hz, 1H), 3.32-3.20 (m, 4H), 2.45 (s, 3H), 2.26-2.15 (m, 2H), 1.98-187 (m, 2H), 1.52-1.45 (m, 4H), 1.43 (s, 9H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 154.9, 144.9, 134.1, 130.0, 127.9, 79.6, 71.7, 41.0 (br), 40.1, 39.1, 36.1, 32.1, 28.5, 21.8. **HRMS (ESI$^+$)**: calculated for $C_{20}H_{29}NNaO_5S$ $[M+Na]^+$: 418.1664; found: 418.1656.

7,7-Dimethylspiro[3.5]nonan-2-yl 4-methylbenzenesulfonate, **SI-5b**



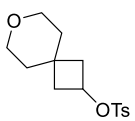
SI-5b

From 7,7-dimethylspiro[3.5]nonan-2-one **SI-4b** (4.10 g, 24.66 mmol) following the general procedure described above, compound **SI-5b** (6.48 g, 20.10 mmol) was obtained

in 82% yield as a white solid, after purification by flash column chromatography (SiO_2; hexane/EtOAc 98:2). **mp** = 93-95 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.77 (d, *J* = 8.3 Hz, 2H), 7.33 (d, *J* = 8.1 Hz, 2H), 4.79 (quint, *J* = 7.3 Hz, 1H), 2.45 (s, 3H), 2.19-2.08 (m, 2H), 1.89-1.77 (m, 2H), 1.47-1.34 (m, 4H), 1.19-1.09 (m, 4H), 0.83 (s, 6H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 144.7, 134.4, 129.9, 127.9, 72.6, 40.7, 36.3, 36.0, 35.7, 33.3, 33.0, 29.5, 28.4 (br), 21.8. **HRMS (ESI$^+$)**: calculated for $C_{18}H_{26}NaO_3S$ $[M+Na]^+$: 345.1500; found: 345.1505.

7,7-Oxaspiro[3.5]nonan-2-yl 4-methylbenzenesulfonate, SI-5c

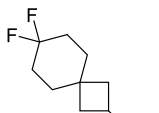


SI-5c

From 7-oxaspiro[3.5]nonan-2-one **SI-4c** (1.14 g, 8.13 mmol) following the general procedure described above, compound **SI-5c** (2.19 g, 7.39 mmol) was obtained in 91% yield as a white solid, after purification by flash column chromatography (SiO_2; cyclohexane/EtOAc 80:20). **mp** = 62-64 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.75 (d, *J* = 8.3 Hz, 2H), 7.32 (d, *J* = 8.1 Hz, 2H), 4.81 (quint, *J* = 7.2 Hz, 1H), 3.57-3.44 (m, 4H), 2.43 (s, 3H), 2.28-2.17 (m, 2H), 1.97-1.88 (m, 2H), 1.57-1.45 (m, 4H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 144.8, 134.1, 129.9, 127.8, 71.7, 64.8, 64.6, 40.6, 39.8, 37.0, 31.2, 21.7. **HRMS (ESI$^+$)**: calculated for $C_{15}H_{20}NaO_4S$ $[M+Na]^+$: 319.0980; found: 319.0973.

7,7-Difluorospiro[3.5]nonan-2-yl 4-methylbenzenesulfonate, SI-5g



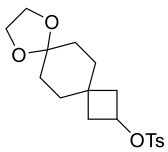
SI-5g

From 7,7-difluorospiro[3.5]nonan-2-one **SI-4g** (453 mg, 2.60 mmol) following the general procedure described above, compound **SI-5g** (738 mg, 2.23 mmol) was obtained

in 86% yield as a white solid, after purification by flash column chromatography (SiO_2; cyclohexane/EtOAc 95:5). **mp** = 78-80 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.77 (d, *J* = 8.3 Hz, 2H), 7.34 (d, *J* = 8.3 Hz, 2H), 4.81 (quint, *J* = 7.2 Hz, 1H), 2.45 (s, 3H), 2.26-2.15 (m, 2H), 2.00-1.90 (m, 2H), 1.84-1.56 (m, 8H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 145.0, 134.1, 130.0, 127.9, 122.8 (t, *J* = 241.1 Hz), 71.4, 39.6, 36.0 (t, *J* = 4.9 Hz), 32.8 (t, *J* = 5.0 Hz), 32.3, 30.9 (t, *J* = 24.3 Hz), 30.7 (t, *J* = 24.2 Hz), 21.8. **^{19}F NMR** (282 MHz, $CDCl_3$): δ –100.7. **HRMS (ESI$^+$)**: calculated for $C_{16}H_{20}F_2NaO_3S$ $[M+Na]^+$: 353.0999; found: 353.0993.

8,11-Dioxadispiro[3.2.4^7.2^4]tridecan-2-yl 4-methylbenzenesulfonate, SI-5h

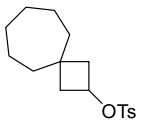


SI-5h

From 8,11-dioxadispiro[3.2.4^7.2^4]tridecan-2-one **SI-4h** (1.82 g, 9.27 mmol) following the general procedure described above, compound **SI-5h** (1.64 g, 4.65 mmol) was obtained in 50% yield as a white solid, after purification by flash column chromatography (Florisil®, cyclohexane/EtOAc 95:5). **mp** = 135-137 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.76 (d, *J* = 8.3 Hz, 2H), 7.32 (d, *J* = 8.4 Hz, 2H), 4.79 (quint, *J* = 7.3 Hz, 1H), 3.89 (s, 4H), 2.44 (s, 3H), 2.21-2.11 (m, 2H), 1.94-1.83 (m, 2H), 1.64-1.45 (m, 8H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 144.8, 134.2, 129.9, 127.9, 108.2, 72.0, 64.3, 40.0, 37.3, 34.0, 32.6, 31.8, 31.5, 21.8. **HRMS (EI$^+$)**: calculated for $C_{18}H_{25}O_5S$ $[M+H]^+$: 353.1423; found: 353.1410.

Spiro[3.6]decan-2-yl 4-methylbenzenesulfonate, SI-5i



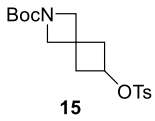
SI-5i

From spiro[3.6]decan-2-one **SI-4i** (3.40 g, 22.33 mmol) following the general procedure described above, compound **SI-5i** (2.38 g, 7.72 mmol) was obtained in 35% yield as a withe

solid, after purification by flash column chromatography (SiO_2; cyclohexane/EtOAc 98:2). **mp** = 72-76 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.77 (d, *J* = 8.3 Hz, 2H), 7.33 (d, *J* = 8.1 Hz, 2H), 4.79 (quint, *J* = 7.3 Hz, 1H), 2.44 (s, 3H), 2.19-2.09 (m, 2H), 1.94-1.83 (m, 2H), 1.62-1.34 (m, 12H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 144.6, 134.2, 129.8, 127.8, 72.3, 43.3, 42.2, 40.4, 36.1, 27.7, 27.6, 23.5, 22.6, 21.6. **HRMS (ESI$^+$)**: calculated for $C_{17}H_{24}NaO_3S$ $[M+Na]^+$: 331.1344; found: 331.1335.

tert-Butyl 6-(tosyloxy)-2-azaspiro[3.3]heptane-2-carboxylate, **15**

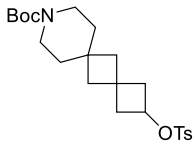


15

From *tert*-butyl 6-oxo-2-azaspiro[3.3]heptane-2-carboxylate (2.0 g, 9.47 mmol) following the general procedure described above, compound **15** (3.35 g, 9.12 mmol) was obtained in 96% yield as a pale yellow solid, after purification by flash column chromatography (SiO_2; hexane/EtOAc 80:20). **mp** = 119-121 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.75 (d, *J* = 8.3 Hz, 2H), 7.33 (d, *J* = 8.0 Hz, 2H), 4.67 (quint, *J* = 7.2 Hz, 1H), 3.83 (s, 4H), 2.52-2.41 (m, 5H), 2.33-2.23 (m, 2H), 1.39 (s, 9H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 156.1, 145.1, 133.9, 130.0, 127.9, 79.7, 69.7, 60.9 (br), 60.1 (br), 41.3, 30.8, 28.4, 21.7. **HRMS (ESI$^+$)**: calculated for $C_{18}H_{25}NNaO_5S$ $[M+Na]^+$: 390.1351; found: 390.1331.

tert-Butyl 2(tosyloxy)-9-azadispiro[3.1.5^6.1^4]dodecane-9-carboxylate, **SI-5l**

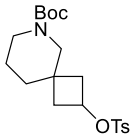


SI-5l

From *tert*-butyl 2-oxo-9-azadispiro[3.1.5^6.1^4] dodecane-9-carboxylate **SI-4l** (630 mg, 2.25 mmol) following the general procedure described above, compound **SI-5l** (920 mg, 2.11 mmol) was obtained in 94% yield as a white solid, after purification by flash column chromatography (SiO_2; cyclohexane/EtOAc 80:20). **mp** = 68-70 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.74 (d, *J* = 8.2 Hz, 2H), 7.32 (d, *J* = 7.5 Hz, 2H), 4.68 (quint, *J* = 7.3 Hz, 1H), 3.29-3.18 (m, 4H), 2.44 (s, 3H), 2.33-2.23 (m, 2H), 2.20-2.09 (m, 2H), 1.80 (s, 4H), 1.42-1.36 (m, 13H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 155.0, 144.7, 134.3, 129.9, 127.9, 79.4, 71.1, 44.6, 44.5, 44.3, 40.6 (br), 37.8, 33.7, 30.0, 28.6, 21.8. **HRMS (ESI$^+$)**: calculated for $C_{23}H_{33}NNaO_5S$ $[M+Na]^+$: 458.1977; found: 458.1955.

tert-Butyl 2-(tosyloxy)-6-azaspiro[3.5]nonane-6-carboxylate, SI-5m

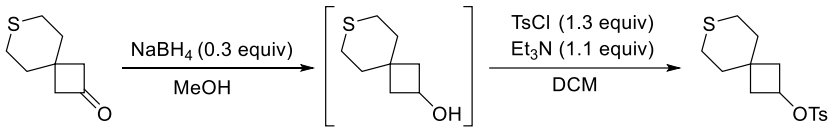


SI-5m

From *tert*-butyl 2-oxo-6-azaspiro[3.5]nonane-6-carboxylate **SI-4m** (1.20 g, 5.01 mmol) following the general procedure described above, compound **SI-5m** (1.31 g, 3.31 mmol) was obtained in 66% yield as a white solid, after purification by flash column chromatography (SiO_2; cyclohexane/EtOAc 90:10). **mp** = 81-83 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.77 (d, *J* = 7.9 Hz, 2H), 7.33 (d, *J* = 7.7 Hz, 2H), 4.92-4.73 (m, 1H), 3.36-3.16 (m, 4H), 2.44 (s, 3H), 2.15-2.00 (m, 2H), 2.00-1.79 (m, 2H), 1.54-1.36 (m, 13H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 155.0, 144.9, 134.2, 130.0, 128.0, 79.7, 71.6, 55.4 (br), 43.5 (br), 38.7, 35.4, 33.0 (br), 28.5, 22.4, 21.8. **HRMS (ESI$^+$)**: calculated for $C_{20}H_{29}NNaO_5S$ $[M+Na]^+$: 418,1664; found: 418.1645.

*Synthesis of 7-thiaspiro[3.5]nonan-2-yl 4-methylbenzenesulfonate, **SI-5d***



SI-4d **SI-5d**

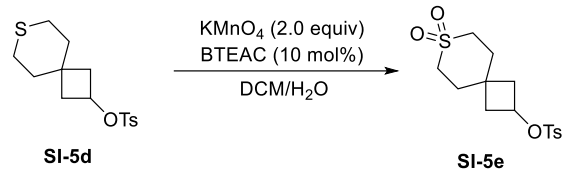
To a solution of 7-thiaspiro[3.5]nonan-2-one **SI-4d** (1.82 g, 11.65 mmol, 1 equiv) in MeOH (1.7 mL/mmol) at 0 °C, $NaBH_4$ (132 mg, 3.50 mmol, 0.3

equiv) was added portionwise. The solution was stirred at room temperature for 12 h. Then, the solvent was evaporated and the residue was dissolved in EtOAc (3 mL/mmol) and water (3 mL/mmol). The layers were separated and the aqueous phase was extracted with EtOAc (3x). The organic extracts were washed with brine, dried over $MgSO_4$ and the solvent evaporated under reduced pressure. The residue was used in the next step without further purification.

The crude was dissolved in DCM (1.5 mL/mmol) and triethylamine (1.79 mL, 12.82 mmol, 1.1 equiv) was added. Then a solution of TsCl (2.89 g, 15.15 mmol, 1.3 equiv) in DCM (0.6 mL/mmol) was added dropwise to the mixture. The solution was stirred at room temperature for 12 h. Then, the crude was diluted with DCM (5 ml/mmol) and washed with brine, dried over $MgSO_4$ and the solvent evaporated under reduced pressure. The residue was purified by flash column chromatography (SiO_2; cyclohexane/EtOAc 90:10) to afford the desired product **SI-5d** (2.65 g, 8.48 mmol) in 73% yield as a yellow solid. **mp** = 93-95 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.75 (d, *J* = 8.1 Hz, 2H), 7.32 (d, *J* = 8.0 Hz, 2H), 4.79 (quint, *J* = 7.4 Hz, 1H), 2.52-2.38 (m, 7H), 2.21-2.10 (m, 2H), 1.89-1.66 (m, 6H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 144.8, 134.1, 129.9, 127.9, 71.7, 40.9, 40.6, 37.7, 32.8, 25.4, 24.9, 21.7. **HRMS (EI$^+$):** calculated for $C_{15}H_{20}O_3S_2$ $[M]^+$: 312.0854; found: 312.0858.

Synthesis of 7,7-dioxido-7-thiaspiro[3.5]nonan-2-yl 4-methylbenzene-sulfonate, ***SI-5e***

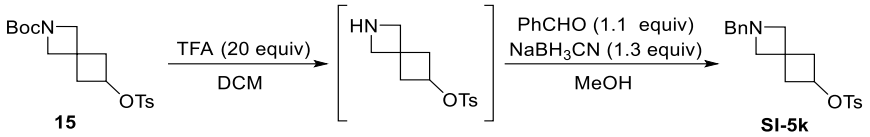


SI-5d **SI-5e**

7-Thiaspiro[3.5]nonan-2-yl 4-methylbenzenesulfonate **SI-5d**, (420 mg, 1.34 mmol, 1 equiv), DCM (2.5 mL/mmol), water (5 mL/mmol), and benzyltriethylammonium chloride (24.9 mg, 0.134 mmol, 10 mol%) were mixed in a round bottomed flask. $KMnO_4$ (423.5 mg, 2.68 mmol, 2 equiv) was added, and the mixture was stirred vigorously at room temperature for 12 h. Then, water (5 mL/mmol) and DCM (5 mL/mmol) were added to the reaction mixture. The layers were separated, and the aqueous phase was extracted with DCM (3x). The organic phase was washed with brine, dried over $MgSO_4$ and the solvent evaporated under reduced pressure. The residue was filtered through a pad of silica gel (DCM) to afford the sulfone **SI-5e** (375 mg, 1.09 mmol) as a white solid in 81% yield. **mp** = 152-154 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.77 (d, *J* = 8.2 Hz, 2H), 7.35 (d, *J* = 8.0 Hz, 2H), 4.84 (quint, *J* = 7.1 Hz, 1H), 2.94-2.83 (m, 4H), 2.46 (s, 3H), 2.36-2.25 (m, 2H), 2.17-2.09 (m, 2H), 2.08-1.98 (m, 4H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 145.2, 133.8, 130.1, 127.9, 70.3, 48.4, 48.2, 39.2, 37.0, 34.0, 31.8, 21.8. **HRMS (ESI$^+$)**: calculated for $C_{15}H_{20}NaO_5S_2$ $[M+Na]^+$: 367.0650; found: 367.0640.

Synthesis of 2-benzyl-2-azaspiro[3.3]heptan-6-yl 4-methylbenzene-sulfonate, ***SI-5k***



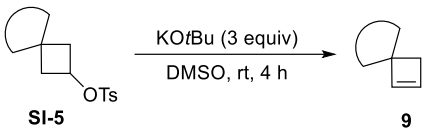
tert-Butyl 6-(tosyloxy)-2-azaspiro[3.3]heptane-2-carboxylate **15** (1.07 g, 2.91 mmol, 1 equiv) was dissolved in DCM (5 mL/mmol) and TFA (4.46 mL, 58.20 mmol, 20 equiv) was added dropwise to the solution. After being stirred at room temperature for 12 h, the reaction mixture was washed with a saturated aqueous solution of Na_2CO_3. The organic phase was washed with brine, dried over $MgSO_4$ and the solvent evaporated under reduced pressure. The crude was used in the next step without further purification.

The crude compound was dissolved in methanol (5 mL/mmol) and PhCHO (325 µL, 3.20 mmol, 1.1 equiv) was added. The solution was cooled to 0 °C and $NaBH_3CN$ (237.7 mg, 3.78 mmol, 1.3 equiv) was added portionwise. Then the mixture was allowed to reach room temperature and stirred for 12 h. After this time, the solvent was removed under reduced pressure. Saturated aqueous $NaHCO_3$ (10 mL/mmol) was added and the mixture was extracted with ethyl acetate (20 mL × 3), condensed and purified by flash column chromatography (SiO_2; DCM to DCM /MeOH 95:5) to afford desired product **SI-5k** (779 mg , 2.18 mmol) as a yellow oil in 75% yield.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.78 (d, *J* = 8.3 Hz, 2H), 7.33 (d, *J* = 8.1 Hz, 2H), 7.31-7.18 (m, 5H), 4.70 (quint, *J* = 7.3 Hz, 1H), 3.53 (s, 2H), 3.16 (s, 4H), 2.50-

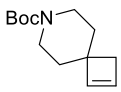
2.39 (m, 5H), 2.29-2.19 (m, 2H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 144.8, 138.0, 134.0, 129.8, 128.4, 128.3, 127.8, 127.0, 70.8, 65.8, 65.2, 63.6, 41.0, 31.9, 21.6. **HRMS (EI$^+$)**: calculated for $C_{20}H_{23}NO_3S$ $[M]^+$: 357.1399; found: 357.1400.

General Procedure for the Synthesis of Spirocyclobutenes



In an oven-dried flask, KO*t*Bu (3.0 equiv) was placed and anhydrous DMSO (2 mL/mmol) was added, under an argon atmosphere, to give a colorless solution. Then, a solution of the corresponding tosylate **SI-5** (1.0 equiv) in DMSO (2 mL/mmol) was added very slowly. After being stirred 4 h at room temperature, the crude was filtered through a pad of silica gel or Florisil®. The solvent was removed under reduced pressure to afford the desired compound **9** (**CAUTION**: some cyclobutenes are volatile).

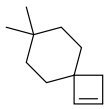
tert-Butyl 7-azaspiro[3.5]non-1-ene-7-carboxylate, **9a**



From **SI-5a** (13.0 g, 32.87 mmol) following the general procedure described above, compound **9a** (5.94 g, 26.60 mmol) was obtained in 81% yield as a colorless oil, after filtration through a pad of silica gel (pentane/Et_2O 80:20).

^{1}H NMR (300 MHz, $CDCl_3$): δ 6.20 (d, *J* = 2.8 Hz, 1H), 6.11-6.08 (m, 1H), 3.58-3.46 (m, 2H), 3.21 (ddd, *J* = 13.4, 7.9, 4.4 Hz, 2H), 2.24 (s, 2H), 1.60-1.52 (m, 4H), 1.44 (s, 9H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 155.1, 143.5, 134.4, 79.3, 47.6, 42.5 (br), 41.6, 35.4, 28.6. **HRMS (ESI$^+$)**: calculated for $C_{13}H_{21}NNaO_2$ $[M+Na]^+$: 246.1470; found: 246.1454.

7,7-Dimethylspiro[3.5]non-1-ene, 9b



9b

From **SI-5b** (4.80 g, 14.89 mmol) following the general procedure described above, compound **9b** (1.71 g, 11.38 mmol) was obtained in 76% yield as a colorless oil, after filtration through a pad of silica gel (pentane). (**CAUTION**: the cyclobutene is volatile).

^{1}H NMR (300 MHz, $CDCl_3$): δ 6.24 (d, *J* = 2.8 Hz, 1H), 6.07 (d, *J* = 2.8 Hz, 1H), 2.17 (s, 2H), 1.61-1.47 (m, 4H), 1.31-1.23 (m, 4H), 0.90 (s, 6H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 145.2, 133.9, 49.5, 42.4, 37.5, 32.4, 29.9 (br), 29.7, 27.6 (br). **HRMS (EI$^+$)**: calculated for $C_{11}H_{18}$ $[M]^+$: 150.1409; found: 150.1405.

7-Oxaspiro[3.5]non-1-ene, 9c

9c

From **SI-5c** (1.03 g, 3.48 mmol) following the general procedure described above, compound **9c** (242 mg, 1.95 mmol) was obtained in 56% yield as a colorless oil, after filtration through a pad of silica gel (pentane/Et_2O 80:20). (**CAUTION**: the cyclobutene is volatile).

^{1}H NMR (300 MHz, $CDCl_3$): δ 6.24 (d, *J* = 2.8 Hz, 1H), 6.15-6.10 (m, 1H), 3.78-3.68 (m, 2H), 3.66-3.55 (m, 2H), 2.29 (s, 2H), 1.78-1.66 (m, 2H), 1.64-1.54 (m, 2H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 143.8, 134.4, 66.3, 46.8, 42.3, 36.4. **HRMS (APCI$^+$)**: calculated for $C_8H_{13}O$ $[M+H]^+$: 125.0966; found: 125.0965.

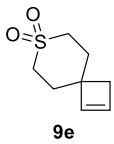
7-Thiaspiro[3.5]non-1-ene, 9d

9d

From **SI-5d** (3.20 g, 10.24 mmol) following the general procedure described above, compound **9d** (1.12 g, 7.99 mmol) was obtained in 78% yield as a pale yellow oil, after filtration through a pad of silica gel (pentane). (**CAUTION**: the cyclobutene is volatile).

^{1}H NMR (300 MHz, $CDCl_3$): δ 6.24 (d, *J* = 2.8 Hz, 1H), 6.08 (d, *J* = 2.8 Hz, 1H), 2.64-2.56 (m, 4H), 2.15 (s, 2H), 1.87-1.79 (m, 4H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 144.2, 134.4, 48.1, 42.2, 37.2, 26.9. **HRMS (EI$^+$)**: calculated for $C_8H_{12}S$ $[M]^+$: 140.0660; found: 140.0657.

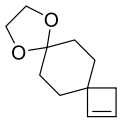
7-Thiaspiro[3.5]non-1-ene 7,7-dioxide, **9e**



9e

From **SI-5e** (940 mg, 2.73 mmol) following the general procedure described above, compound **9e** (343 mg, 1.99 mmol) was obtained in 73% yield as a white solid, after filtration through a pad of silica gel (Et_2O). **mp** = 175-177 °C. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 6.28 (d, *J* = 2.9 Hz, 1H), 6.19-6.16 (m, 1H), 3.04-2.96 (m, 4H), 2.35 (d, *J* = 1.0 Hz, 2H), 2.20-2.12 (m, 4H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 141.8, 135.7, 49.9, 46.3, 40.9, 33.5. **HRMS (ESI$^+$)**: calculated for $C_8H_{12}NaO_2S$ $[M+Na]^+$: 195.0456; found: 195.0444.

8,11-Dioxadispiro[3.2.4^7.2^4]tridecan-2-ene, **9h**



9h

From **SI-5h** (800 mg, 2.27 mmol) following the general procedure described above, compound **9h** (171 mg, 0.95 mmol) was obtained in 42% yield as colorless oil, after purification by flash column chromatography on Florisil® (pentane/Et_2O 95:5).

^{1}H NMR (300 MHz, $CDCl_3$): δ 6.23 (d, *J* = 2.8 Hz, 1H), 6.09-6.06 (m, 1H), 3.92 (s, 4H), 2.22 (s, 2H), 1.71-1.58 (m, 8H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 144.3, 134.2, 108.8, 64.3 (2x), 48.4, 41.7, 33.5, 33.2. **HRMS (APCI$^+$)**: calculated for $C_{11}H_{17}O_2$ $[M+H]^+$: 181.1229; found: 181.1225.

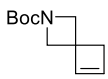
Spiro[3.6]dec-1-ene, **9i**

9i

From **SI-5i** (4.80 g, 15.56 mmol) following the general procedure described above following the general procedure described above, compound **9i** (793 mg, 5.82 mmol) was obtained in 37% yield as colorless oil. **Note**: the product is volatile (this explains the lower yield).

^{1}H NMR (300 MHz, $CDCl_3$): δ 6.27 (d, *J* = 2.8 Hz, 1H), 6.07-6.04 (m, 1H), 2.22 (d, *J* = 1.0 Hz, 2H), 1.72-1.63 (m, 4H), 1.61-1.49 (m, 8H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 145.9, 133.2, 52.4, 44.6, 39.2, 28.0, 24.9. **HRMS (EI$^+$)**: calculated for $C_{10}H_{16}$ $[M]^+$: 136.1252; found: 136.1249.

tert-Butyl 2-azaspiro[3.3]hept-5-ene-2-carboxylate, **9j**

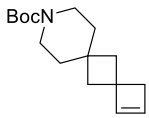


9j

From **SI-5j** (2.0 g, 5.44 mmol) following the general procedure described above following the general procedure described above, compound **9j** (963 mg, 4.93 mmol) was obtained in 91% yield as colorless oil, after filtration through a pad of silica gel (pentane/Et_2O 90:10).

^{1}H NMR (300 MHz, $CDCl_3$): δ 6.13-6.07 (m, 2H), 4.10-4.00 (m, 4H), 2.68 (s, 2H), 1.43 (s, 9H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 156.4, 139.1, 136.9, 79.3, 57.1 (br), 44.9, 43.2, 28.5. **HRMS (ESI$^+$)**: calculated for $C_{11}H_{17}NNaO_2$ $[M+Na]^+$: 218.1157; found: 218.1144.

tert-Butyl 9-azadispiro[3.1.5^6.1^4]dodec-1-ene-9-carboxylate, **9l**

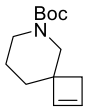


9l

From **SI-5l** (884 mg, 2.03 mmol) following the general procedure described above, compound **9l** (430 mg, 1.63 mmol) was obtained in 80% yield as colorless oil, after filtration through a pad of silica gel (hexane/Et_2O 80:20). **^{1}H NMR** (300 MHz,

$CDCl_3$): δ 6.08-6.01 (m, 2H), 3.36-3.25 (m, 4H), 2.53 (s, 2H), 2.08-1.92 (m, 4H), 1.56-1.46 (m, 4H), 1.44 (s, 9H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 155.0, 143.4, 134.6, 79.2, 46.7, 45.8, 41.1, 40.9 (br), 38.1, 37.5, 33.0, 28.5. **HRMS (EI$^+$)**: calculated for $C_{16}H_{25}NO_2$ $[M]^+$: 263.1885; found: 263.1898.

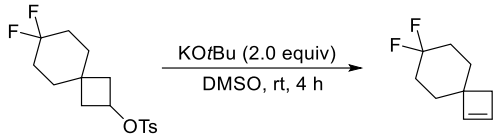
tert-Butyl 6-azaspiro[3.5]non-1-ene-6-carboxylate, **9m**



9m

From **SI-5m** (1.30 g, 3.29 mmol) following the general procedure described above, compound **9m** (318 mg, 1.42 mmol) was obtained in 43% yield as colorless oil, after filtration through a pad of silica gel (pentane/Et_2O 95:5). **^{1}H NMR** (300 MHz, $CDCl_3$): δ 6.13-6.08 (m, 2H), 3.60-3.45 (m, 2H), 3.14 (d, *J* = 13.0 Hz, 1H), 3.10-2.99 (m, 1H), 2.34-2.22 (m, 1H), 2.15-2.05 (m, 1H), 1.64-1.47 (m, 4H), 1.42-1.40 (m, 9H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 155.0, 142.4, 135.4, 79.2, 53.0 (br), 48.4, 43.8 (br), 40.5, 34.4, 28.5, 23.7. **HRMS (ESI$^+$)**: calculated for $C_{13}H_{21}NNaO_2$ $[M+Na]^+$: 246.1470; found: 246.1458.

Synthesis of 7,7-Difluorospiro[3.5]non-1-ene, ***9g***



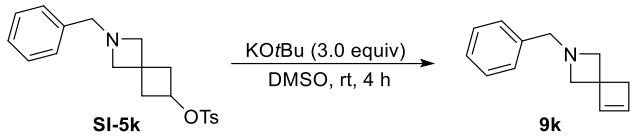
SI-5g **9g**

In an oven-dried flask, KO*t*Bu (734 mg, 6.54 mmol, 2 equiv) was placed and anhydrous DMSO (2 mL/mmol) was added, under an argon atmosphere, to give a colorless solution. Then, a solution of **SI-5g** (1.08 g, 3.27 mmol, 1 equiv) in DMSO (2 mL/mmol) was added very slowly. After being stirred 4 h at room temperature, the crude was filtered through a pad of silica gel (pentane). The solvent was removed under reduced

pressure to afford the desired compound **9g** (211 mg, 1.33 mmol) in a 41% yield as a colorless oil (**CAUTION**: the cyclobutene is volatile).

^{1}H NMR (300 MHz, $CDCl_3$): δ 6.24 (d, *J* = 2.8 Hz, 1H), 6.15-6.11 (m, 1H), 2.27 (d, *J* = 1.0 Hz, 2H) 2.02-1.68 (m, 8H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 143.4, 134.8, 123.6 (t, *J* = 240.7 Hz), 47.7, 41.4, 32.3 (t, *J* = 24.0 Hz), 32.3 (t, *J* = 5.0 Hz). **^{19}F NMR** (282 MHz, $CDCl_3$): δ (–96.70)-(–103.93). **HRMS (EI$^+$)**: calculated for $C_9H_{12}F_2$ $[M]^+$: 158.0907; found: 158.0912.

Synthesis of 2-Benzyl-2-azaspiro[3.3]hept-5-ene, ***9k***

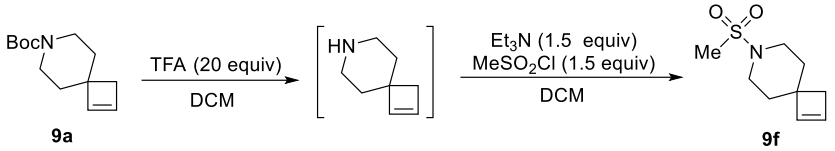


SI-5k **9k**

In an oven-dried flask, KO*t*Bu (380.4 mg, 3.39 mmol, 3.0 equiv) was placed and anhydrous DMSO (2 mL/mmol) was added under argon to give a colorless solution. Then, a solution of **SI-5k** (405 mg, 1.13 mmol, 1.0 equiv) in DMSO (2 mL/mmol) was added very slowly. The reaction mixture was left stirring at room temperature for 4 h. Then, water (10 mL/mmol) and EtOAc (10 mL/mmol) were added to the reaction mixture. The layers were separated, and the aqueous phase was extracted with EtOAc (3x). The organic layer was washed with brine, dried over $MgSO_4$ and the solvent evaporated under reduced pressure. The residue was purified by flash column chromatography (SiO_2, DCM/EtOAc 95:5) to afford the desired product **9k** (143 mg, 0.77 mmol) in 68% yield as a yellow oil. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.25-7.11 (m, 5H), 6.03-5.98 (m, 2H), 3.52 (s, 2H), 3.40-3.34 (m, 2H), 3.24-3.18 (m, 2H), 2.60 (s, 2H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 140.0,

138.4, 136.3, 128.6, 128.4, 127.0, 63.9, 62.9, 46.9, 43.3. **HRMS (EI$^+$)**: calculated for $C_{13}H_{15}N$ $[M]^+$: 185.1204; found: 185.1196.

Synthesis of 7-(methylsulfonyl)-7-azaspiro[3.5]non-1-ene, **1f**



9a **9f**

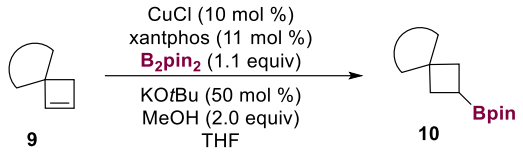
tert-Butyl 7-azaspiro[3.5]non-1-ene-7-carboxylate, **9a** (447 mg, 2.00 mmol, 1.0 equiv) was dissolved in DCM (13 mL/mmol) and TFA (20 equiv) was added dropwise to the solution at 0 °C. After being stirred for 1 h at 0 °C, the reaction was quenched with saturated sodium bicarbonate and extracted with dichloromethane (3 x 20 mL). The organic phase was washed with brine, dried over $MgSO_4$ and the solvent evaporated under reduced pressure. The crude was used in the next step without further purification.

Methanesulfonyl chloride (232 µL, 3 mmol, 1.5 equiv) was slowly added to a solution of free amine and Et_3N (420 µL, 3 mmol, 1.5 equiv) in DCM (6mL) at 0° C. The reaction mixture was allowed to warm to room temperature and stirred overnight. The solvent was concentrated, and the product was recovered in EtOAc. The resulting mixture was washed with H_2O (3×20 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (SiO_2, DCM/EtOAc 90:10) to afford the desired product **9f** (186 mg, 0.92 mmol) in 46% yield as a yellow pale solid. **mp** = 97-99 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ 6.19 (d, *J* = 2.8 Hz, 1H), 6.12-6.09 (m, 1H), 3.38-3.28 (m, 2H), 3.10-2.99 (m, 2H), 2.75 (s, 3H), 2.25 (s, 2H), 1.80-1.64 (m, 4H).

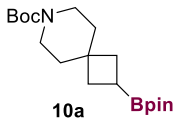
^{13}C NMR (75 MHz, $CDCl_3$): δ 142.8, 134.7, 46.6, 44.5, 41.4, 35.0, 34.8. **HRMS (ESI$^+$)**: calculated for $C_9H_{15}NNaO_2S$ $[M+Na]^+$: 224.0721; found: 224.0709.

3.3 General Procedure for the Copper-Catalyzed Regioselective Monoborylation of Spirocyclobutenes, 10



An oven-dried vial was charged with CuCl (10 mol%), B_2pin_2 (1.1 equiv), KO*t*Bu (0.5 equiv) and xantphos (11 mol%) in the glove box. Anhydrous THF (0.5 mL/0.2 mmol of **9**) was added and the mixture was stirred for 15 min. Then, the corresponding cyclobutene **9** (1.0 equiv) in THF (1 mL/0.2 mmol of **9**) was added dropwise followed by methanol (2.0 equiv). Finally, the reaction mixture was stirred overnight at room temperature. Once the reaction was finished, the resulting solution was filtered through a pad of Celite® (eluted with EtOAc) and concentrated under reduced pressure. The crude product was purified by flash column chromatography on silica gel or Florisil® to afford cyclobutylboronate **10**.

tert-Butyl 2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-7-azaspiro[3.5]-nonane-7 carboxylate, **10a**

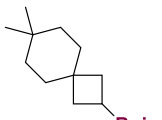


From **9a** (44.7 mg, 0.2 mmol) following the general procedure described above, compound **10a** (60.5 mg, 0.172 mmol) was obtained in 86% yield as a white solid,

after purification by flash column chromatography (SiO_2; hexane/EtOAc 90:10). **mp** = 51-53 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ 3.33-3.20 (m, 4H), 1.91-1.73 (m, 5H), 1.56-1.50 (m, 2H), 1.49-1.40 (m, 11H), 1.25-1.20 (m, 12H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 155.2, 83.2, 79.2, 40.7 (br), 38.1, 37.3, 36.7, 33.1, 28.6, 24.9, 10.1 (br). **^{11}B NMR** (96 MHz, $CDCl_3$): δ 33.5. **HRMS (ESI$^+$)**: calculated for $C_{19}H_{34}BNNaO_4$ $[M+Na]^+$: 374.2479; found: 374.2469.

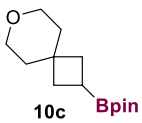
2-(7,7-Dimethylspiro[3.5]nonan-2-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane, **10b**



From **9b** (30.1 mg, 0.2 mmol) following the general procedure described above, compound **10b** (41.9 mg, 0.151 mmol) was obtained in 75% yield as colorless oil, after purification by flash column chromatography (SiO_2; cyclohexane/EtOAc 90:10).

^{1}H NMR (300 MHz, $CDCl_3$): δ 1.86-1.66 (m, 5H), 1.54-1.46 (m, 2H), 1.45-1.37 (m, 2H), 1.23 (s, 12H), 1.20-1.10 (m, 4H), 0.83 (s, 6H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 83.0, 38.8, 35.7, 35.6, 35.2, 33.8, 33.6, 29.7, 28.5 (br), 24.9, 10.4 (br). **^{11}B NMR** (96 MHz, $CDCl_3$): δ 34.0. **HRMS (EI$^+$)**: calculated for $C_{17}H_{31}BO_2$ $[M]^+$: 278.2417; found: 278.2422.

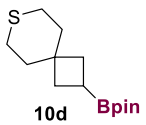
4,4,5,5-Tetramethyl-2(7-oxaspiro[3.5]nonan-2-yl)1,3,2-dioxaborolane, **10c**



From **9c** (24.8 mg, 0.2 mmol) following the general procedure described above, compound **10c** (39.2 mg, 0.155 mmol) was obtained in 78% yield as a pale yellow oil, after purification by flash column chromatography (Florisil®; cyclohexane/EtOAc 90:10).

^{1}H NMR (300 MHz, $CDCl_3$): δ 3.55 (dt, *J* = 13.0, 5.3 Hz, 4H), 1.95-1.76 (m, 5H), 1.65-1.58 (m, 2H), 1.57-1.50 (m, 2H), 1.23 (s, 12H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 83.1, 64.8, 64.6, 39.1, 37.9, 36.4, 33.7, 24.8. [note: *the carbon attached to boron was not observed due to quadrupole broadening caused by the ^{11}B nucleus*]. **^{11}B NMR** (96 MHz, $CDCl_3$): δ 34.4. **HRMS (EI$^+$)**: calculated for $C_{14}H_{25}BO_3$ $[M]^+$: 252.1897; found: 252.1909.

4,4,5,5-Tetramethyl-2-(7-thiaspiro[3.5]nonan-2-yl)-1,3,2-dioxaborolane, **10d**

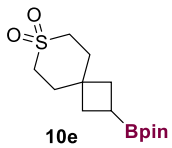


10d

From **9d** (28.0 mg, 0.2 mmol) following the general procedure described above, compound **10d** (35.2 mg, 0.131 mmol) was obtained in 66% yield as yellow oil, after purification by flash column chromatography (SiO_2; cyclohexane/EtOAc 90:10).

^{1}H NMR (300 MHz, $CDCl_3$): δ 2.59-2.43 (m, 4H), 1.89-1.66 (m, 9H) 1.24 (s, 12H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 83.2, 39.8, 38.1, 37.9, 33.7, 25.2, 25.0, 24.9. [note: *the carbon attached to boron was not observed due to quadrupole broadening caused by the ^{11}B nucleus*]. **^{11}B NMR** (96 MHz, $CDCl_3$): δ 33.8. **HRMS (EI$^+$)**: calculated for $C_{14}H_{25}BO_2S$ $[M]^+$: 268.1668; found: 268.1678.

2-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)-7-thiaspiro[3.5]nonane 7,7-dioxide, **10e**

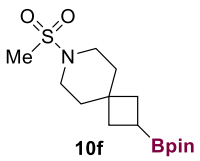


10e

From **9e** (34.4 mg, 0.2 mmol) following the general procedure described above, compound **10e** (39.5 mg, 0.132 mmol) was obtained in 66% yield as a white solid, after purification by flash column chromatography (SiO_2; cyclohexane/EtOAc 70:30). **mp** = 113-115 °C. **^{1}H NMR** (300 MHz, $CDCl_3$): δ

2.99-2.83 (m, 4H), 2.21-2.06 (m, 4H), 1.99-1.82 (m, 5H), 1.24 (s, 12H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 83.5, 48.1, 48.0, 36.6, 35.7, 34.3, 32.0, 24.9. [note: *the carbon attached to boron was not observed due to quadrupole broadening caused by the ^{11}B nucleus*]. **HRMS (EI$^+$)**: calculated for $C_{14}H_{25}BO_4S$ [M]$^+$: 300.1567; found: 300.1573.

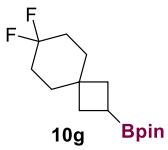
7-(Methylsulfonyl)-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-7-azaspiro[3.5]nonane, 10f



From **9f** (40.3 mg, 0.2 mmol) following the general procedure described above, compound **10f** (51.4 mg, 0.156 mmol) was obtained in 78% yield as a white solid, after purification by flash column chromatography (SiO_2; cyclohexane/EtOAc 70:30). **mp** = 87-89 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ 3.11 (dt, *J* = 11.6, 5.5 Hz, 1H), 2.74 (s, 3H), 1.95-1.76 (m, 5H), 1.75-1.61 (m, 4H), 1.25 (s, 12H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 83.3, 42.9, 42.8, 37.4, 36.5, 36.3, 34.6, 32.8, 24.8. [note: *the carbon attached to boron was not observed due to quadrupole broadening caused by the ^{11}B nucleus*]. **^{11}B NMR** (96 MHz, $CDCl_3$): δ 33.8. **HRMS (EI$^+$)**: calculated for $C_{15}H_{28}BNO_4S$ [M]$^+$: 329.1832; found: 329.1841.

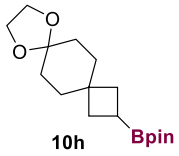
2-(7,7-Difluorospiro[3.5]nonan-2-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane, 10g



From **9g** (31.6 mg, 0.2 mmol) following the general procedure described above, compound **10g** (47.0 mg, 0.164 mmol) was obtained in 82% yield as a white solid, after purification by flash column chromatography (SiO_2; cyclohexane/EtOAc 90:10). **mp** = 52-54 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ 1.92-1.66 (m, 11H), 1.66-1.58 (m, 2H), 1.24 (s, 12H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 123.7 (t, *J* = 240.5 Hz), 83.2, 37.5, 34.8 (t, *J* = 4.8 Hz), 33.4 (t, *J* = 4.9 Hz), 32.6, 30.5 (t, *J* = 23.9 Hz), 30.4 (t, *J* = 23.9 Hz), 24.9, 10.2 (br). **^{19}F NMR** (282 MHz, $CDCl_3$): δ –100.5. **^{11}B NMR** (96 MHz, $CDCl_3$): δ 34.1. **HRMS (EI$^+$)**: calculated for $C_{15}H_{25}BF_2O_2$ $[M]^+$: 286.1916; found: 286.1917.

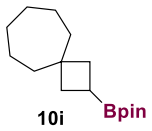
2-(8,11-Dioxadispiro[3.2.4^7.2^4]tridecan-2-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane, 10h



From **9h** (36.1 mg, 0.2 mmol) following the general procedure described above, compound **10h** (55.1 mg, 0.179 mmol) was obtained in 89% yield as a colorless oil, after purification by flash column chromatography (Florisil®; hexane).

^{1}H NMR (300 MHz, $CDCl_3$): δ 3.90 (s, 4H), 1.89-1.73 (m, 5H), 1.71-1.63 (m, 2H), 1.61-1.48 (m, 6H), 1.23 (s, 12H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 109.0, 83.1, 64.3, 38.0, 36.2, 34.5, 33.1, 31.3, 31.2, 24.9. [note: *the carbon attached to boron was not observed due to quadrupole broadening caused by the ^{11}B nucleus*]. **^{11}B NMR** (96 MHz, $CDCl_3$): δ 33.9. **HRMS (EI$^+$)**: calculated for $C_{17}H_{29}BO_4$ $[M]^+$: 308.2159; found: 308.2144.

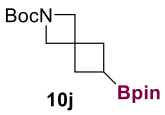
4,4,5,5-Tetramethyl-2-(spiro[3.6]decan-2-yl)-1,3,2-dioxaborolane, 10i



From **9i** (27.2 mg, 0.2 mmol) following the general procedure described above, compound **10i** (38.0 mg, 0.144 mmol) was obtained in 72% yield as a colorless oil, after purification by flash column chromatography (SiO_2; cyclohexane/EtOAc 90:10).

^{1}H NMR (300 MHz, $CDCl_3$): δ 1.89-1.71 (m, 5H), 1.68-1.62 (m, 2H), 1.60-1.54 (m, 2H), 1.52-1.35 (m, 8H), 1.24 (s, 12H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 83.0, 42.1 (x2), 40.9, 35.5, 28.0, 27.9 (x2), 24.9, 23.1, 22.6. [note: *the carbon attached to boron was not observed due to quadrupole broadening caused by the ^{11}B nucleus*]. **HRMS (EI$^+$)**: calculated for $C_{16}H_{29}BO_2$ $[M]^+$: 264.2261; found: 264.2250.

tert-Butyl 6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2-azaspiro[3.3]-heptane-2-carboxylate, **10j**

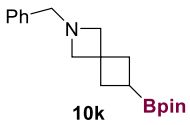


10j

From **9j** (39.1 mg, 0.2 mmol) following the general procedure described above, compound **10j** (56.4 mg, 0.174 mmol) was obtained in 87% yield as a white solid, after purification by flash column chromatography (Florisil®; cyclohexane/EtOAc 90:10). **mp** = 69-71°C.

^{1}H NMR (300 MHz, $CDCl_3$): δ 3.84 (s, 2H), 3.82 (s, 2H), 2.28-2.07 (m, 4H), 1.67 (tt, *J* = 9.6, 7.2 Hz, 1H), 1.40 (s, 9H), 1.21 (s, 12H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 156.4, 83.3, 79.2, 61.9, 61.7, 37.8, 34.5, 28.5, 24.8. [note: *the carbon attached to boron was not observed due to quadrupole broadening caused by the ^{11}B nucleus*]. **HRMS (ESI$^+$)**: calculated for $C_{17}H_{30}BNNaO_4$ $[M+Na]^+$: 346.2166; found: 346.2154.

tert-Butyl 6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2-azaspiro[3.3]-heptane-2-carboxylate, **10k**

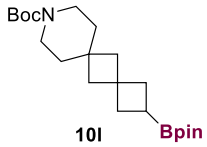


10k

From **9k** (37.1 mg, 0.2 mmol) following the general procedure described above, compound **10k** (38.5 mg, 0.123 mmol) was obtained in 61% yield as a yellow oil, after purification by flash column chromatography (SiO_2 deactivated with Et_3N, DCM/MeOH 95:5).

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.33-7.18 (m, 5H), 3.55 (s, 2H), 3.21 (s, 2H), 3.18 (s, 2H), 2.27-2.08 (m, 4H), 1.77-1.64 (m, 1H), 1.22 (s, 12H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 138.7, 128.6, 128.3, 126.9, 83.1, 67.3, 66.9, 64.1, 39.0, 34.6, 24.9. [note: *the carbon attached to boron was not observed due to quadrupole broadening caused by the ^{11}B nucleus*]. **^{11}B NMR** (96 MHz, $CDCl_3$): δ 33.4. **HRMS (EI$^+$)**: calculated for $C_{19}H_{28}BNO_2$ $[M]^+$: 313.2213; found: 313.2224.

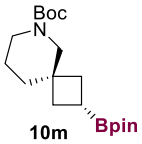
tert-Butyl 2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-9-azadispiro-[3.1.5^6.1^4]dodecane-9-carboxylate, **10l**



From **9l** (52.7 mg, 0.2 mmol) following the general procedure described above, compound **10l** (67.1 mg, 0.171 mmol) was obtained in 86% yield as a white solid, after purification by flash column chromatography (SiO_2; cyclohexane/EtOAc 90:10). **mp** = 62-65 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ 3.30-3.21 (m, 4H), 2.13-1.95 (m, 4H), 1.82 (s, 2H), 1.79-1.68 (m, 3H), 1.45-1.37 (m, 13H), 1.22 (s, 12H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 155.1, 83.1, 79.2, 45.5, 43.3, 40.9 (br), 38.3, 38.1, 37.6, 32.7, 28.6, 24.9. [note: *the carbon attached to boron was not observed due to quadrupole broadening caused by the ^{11}B nucleus*]. **^{11}B NMR** (96 MHz, $CDCl_3$): δ 33.7. **HRMS (EI$^+$)**: calculated for $C_{22}H_{38}BNO_4$ $[M]^+$: 391.2894; found: 391.2901.

tert-Butyl 2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-6-azaspiro[3.5]-nonane-6-carboxylate, **10m**



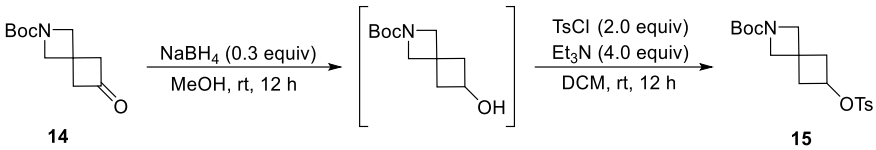
10m

From **9m** (44.7 mg, 0.2 mmol) following the general procedure described above, compound **10m** (58.1 mg, 0.165 mmol) was obtained in 83% yield as a white solid, after purification by flash column chromatography (SiO_2; cyclohexane/EtOAc 90:10). **mp** = 75-77 °C.

^{1}H NMR (300 MHz, Toluene-d_8, 373K): δ 3.33-3.29 (s, 2H), 3.24-3.18 (m, 2H), 1.95-1.87 (m, 2H), 1.82-1.74 (m, 2H), 1.43-1.37 (m, 11H), 1.28-123 (m, 2H), 1.06 (s, 12H). **^{13}C NMR** (75 MHz, Toluene-d_8, 373K): δ 155.2, 83.2, 78.7, 53.8, 44.6, 39.0, 38.1, 32.3, 28.8, 25.0, 22.5. [note: *the carbon attached to boron was not observed due to quadrupole broadening caused by the ^{11}B nucleus*]. **HRMS (EI$^+$)**: calculated for $C_{19}H_{34}BNO_4$ $[M]^+$: 351.2581; found: 351.2587.

3.4 Gram Scale Experiments

Synthesis of tert-butyl 6-(tosyloxy)-2-azaspiro[3.3]heptane-2-carboxylate, ***15***



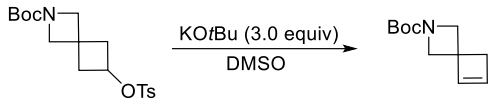
14 **15**

To a solution of *tert*-butyl 2-oxo-7-azaspiro[3.5]nonane-7-carboxylate **14** (6.0 g, 28.4 mmol) in MeOH (1.7 mL/mmol) at 0 °C, $NaBH_4$ (0.3 equiv) was added portionwise. The resulting mixture was stirred at room temperature for 12 h. Then, the solvent was evaporated, and the residue

was re-dissolved in EtOAc (3 mL/mmol) and water (3 mL/mmol). The layers were separated, and the aqueous phase was extracted with EtOAc (3x). The organic phases were washed with brine, dried over $MgSO_4$ and the solvent evaporated under reduced pressure. The residue was used in the next step without further purification.

To a solution of the cyclobutanol and triethylamine (4 equiv) in DCM (1.5 mL/mmol), a solution of TsCl (2.0 equiv) in DCM (0.6 mL/mmol) was added dropwise at 0 °C. After being stirred for 12 h at room temperature, water (2.5 mL/mmol of alcohol) and DCM (2.5 mL/mmol of alcohol) were added to the reaction mixture. Then, the layers were separated, and the aqueous phase was extracted with DCM (3x). The combined organic phases were dried ($MgSO_4$), filtered, and the solvent evaporated under reduced pressure. The residue was purified by flash column chromatography (SiO_2; cyclohexane/EtOAc 80:20) to afford the desired product **15** (9.42 g, 25.6 mmol) in 91% as a white solid.

Synthesis of tert-butyl 2-azaspiro[3.3]hept-5-ene-2-carboxylate, ***9j***

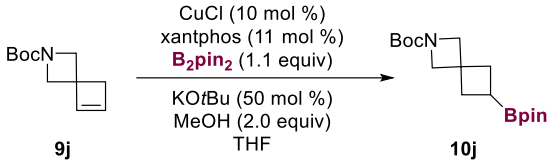


15 **9j**

In an oven-dried flask, KO*t*Bu (3.0 equiv) was placed and anhydrous DMSO (2 mL/mmol) was added, under an argon atmosphere, to give a colorless solution. Then, a solution of tosylate **15** (9.42 g, 25.6 mmol) in DMSO (2 mL/mmol) was added very slowly. After being stirred 4 h at room temperature, the crude was filtered through a pad of silica gel

(pentane/Et_2O 90:10). The solvent was removed under reduced pressure to afford the desired spirocyclobutene **9j** in 78% yield as a colorless oil.

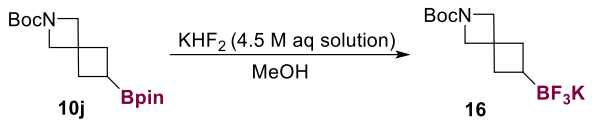
Synthesis of *tert*-butyl 6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2-azaspiro[3.3]heptane-2-carboxylate, **10j**



An oven-dried vial was charged with CuCl (10 mol%), B_2pin_2 (1.1 equiv), KO*t*Bu (0.5 equiv) and xantphos (11 mol%) in the glove box. Anhydrous THF (0.5 mL/0.2 mmol of **9j**) was added and the mixture was stirred for 15 min. Then, cyclobutene **9j** (1.0 g, 5.1 mmol) in THF (1 mL/0.2 mmol of **9j**) was added dropwise followed by methanol (2 equiv). Finally, the reaction mixture was stirred overnight at room temperature. Once the reaction was finished, the resulting solution was filtered through a pad of Celite® (eluted with EtOAc) and concentrated under reduced pressure. The crude product was purified by flash column chromatography (Florisil®; cyclohexane/EtOAc 90:10) to afford cyclobutylboronate **10j** (1.49 g, 4.6 mmol) in a 90% yield as a white solid.

3.5 Functionalization of Monoborylated Spirocycles

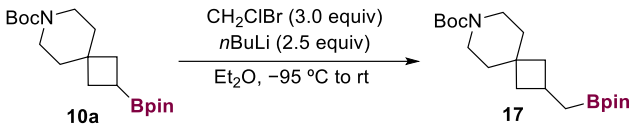
Potassium Trifluoroborate Salt: Synthesis of tert-butyl 6-(trifluoro-λ^4-boraneyl)-2-azaspiro[3.3]heptane-2-carboxylate, **16**



An oven-dried vial was charged with boronic ester **10j** (240 mg, 0.742 mmol, 1.0 equiv) and was dissolved methanol (13 mL). Then, KHF_2 (4.5 M aqueous solution, 0.97 mL) was added dropwise, and the resulting solution was stirred for 30 min at room temperature.[137] After this time, the residue was re-dissolved in methanol (6 mL) and water (4 mL). Again, all volatiles were removed under reduced pressure. This cycle was repeated (x10) to remove all pinacol. The solid that was obtained was triturated with acetone (3 x 5 mL) and filtered through a plug of Celite®. The solvent was evaporated to yield the trifluoroborate salt **16** (192 mg, 0.633 mmol) in 85% yield as a white solid. **mp** = 226-228 °C.

^{1}H NMR (300 MHz, D_2O): δ 4.00-3.76 (m, 4H), 2.23-1.84 (m, 4H), 1.40 (s, 9H), 1.29-1.09 (m, 1H). **^{13}C NMR** (75 MHz, D_2O): δ 158.9, 82.0, 62.9 (br), 62.8 (br), 36.9, 34.5, 33.9, 28.3 [note: the carbon attached to boron was not observed due to quadrupole broadening caused by the ^{11}B nucleus]. **HRMS (ESI$^-$)**: calculated for $C_{11}H_{18}BF_3NO_2$ $[M\text{-}K]^-$: 264.1383; found: 264.1387.

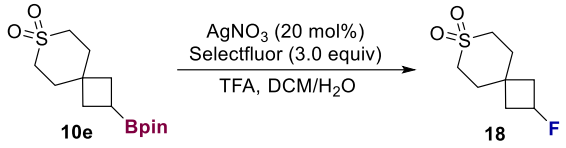
***Matteson Homologation**:* Synthesis of tert-butyl 2-((4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)methyl)-7-azaspiro[3.5]nonane-7-carboxylate, **17**



An oven-dried vial was charged with boronic ester **10a** (70.3 mg, 0.2 mmol, 1 equiv) and was dissolved in anhydrous diethyl ether (2 mL) under an argon atmosphere.[148] Then, bromochloromethane (39.0 µL, 0.6 mmol, 3 equiv) was added and the reaction mixture was cooled to –95 °C (methanol/liquid nitrogen bath). To this mixture, *n*-butyllithium (0.59 mmol, 3 equiv) was added dropwise and the solution was stirred for other 10 minutes at –95 °C, followed by additional 1 h at room temperature. After this time, the whole mixture was filtered through a thin layer of silica and eluted with Et_2O. Once the solvent was evaporated under reduced pressure, the crude mixture was purified by flash column chromatography (SiO_2; hexane/EtOAc 90:10) to afford the homologated product **17** (48.6 mg, 0.133 mmol) in 67% yield as a white solid. **mp** = 56-58 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ 3.31-3.12 (m, 4H), 2.32 (quint, *J* = 8.3 Hz, 1H), 2.01-1.87 (m, 2H), 1.51-1.42 (m, 3H), 1.42-1.28 (m, 12H), 1.15 (s, 12H), 0.88 (d, *J* = 7.7 Hz, 2H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 155.2, 83.0, 79.2, 40.9 (br), 40.4, 39.9 (br), 36.3, 33.9, 28.6, 25.0. [note: the carbon attached to boron was not observed due to quadrupole broadening caused by the ^{11}B nucleus]. **HRMS (ESI$^+$)**: calculated for $C_{20}H_{36}BNNaO_4$ $[M+Na]^+$: 388.2635; found: 388.2630.

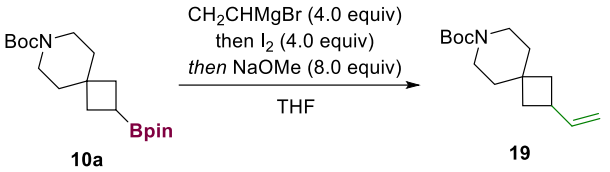
Fluorination: Synthesis of 2-fluoro-7-thiaspiro[3.5]nonane 7,7-dioxide, **18**



According to a literature procedure,[149] in an oven-dried vial was charged with boronic ester **10e** (36.0 mg, 0.12 mmol), $AgNO_3$ (4.1 mg, 0.024 mmol), and Selectfluor (127.5 mg, 0.36 mmol) in the glove box and sealed with a septum. Then, dichloromethane (0.6 mL), H_2O (0.6 mL), and TFA (37 µL, 0.48 mmol) were sequentially added. The reaction mixture was stirred at 50 °C for 6 hours under vigorous stirring. Upon completion, the reaction mixture was cooled to room temperature and extracted with EtOAc (4 × 15 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated under vacuum. The residue was purified by column chromatography (SiO_2; DCM/MeOH 99:1) to afford the desired product **18** (19.0 mg, 0.099 mmol) as a white solid in 82% yield. **mp** = 120-122 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ 5.06 (dtt, *J* = 54.8, 7.0, 5.5 Hz, 1H), 2.99-2.90 (m, 4H), 2.46-2.32 (m, 2H), 2.24-2.17 (m, 2H), 2.17-2.00 (m, 4H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 84.0 (d, *J* = 208.1 Hz), 48.5, 48.3, 39.6 (d, *J* = 21.1 Hz), 37.1, 34.7. **^{19}F NMR** (282 MHz, $CDCl_3$): δ –82.0. **HRMS (ESI$^+$)**: calculated for $C_8H_{13}FNaO_2S$ $[M+Na]^+$: 215.0518; found: 215.0509.

Vinylation: Synthesis of tert-butyl 2-vinyl-7-azaspiro[3.5]nonane-7-carboxylate, **19**

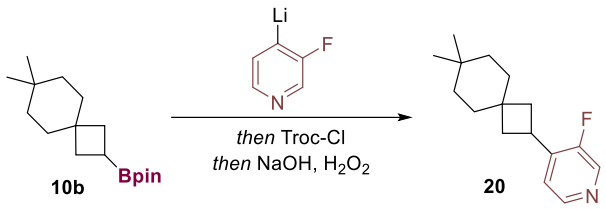


An oven-dried vial was charged with boronic ester **10a** (70.3 mg, 0.2 mmol, 1 equiv) and was dissolved in anhydrous THF (1 mL).[130] Then, vinyl magnesium bromide (0.8 mmol, 1.0 M in THF, 4.0 equiv) was added dropwise at a 0 °C, and the resulting solution was stirred for 30 min at room temperature. After cooling the reaction mixture at –78 °C (dry ice/acetone), a solution of iodine (203.0 mg, 0.8 mmol, 4.0 equiv) in anhydrous THF (1.7 mL) was added dropwise followed by stirring for 20 min. After this time, the solution was warmed at 0 °C, and a suspension of NaOMe (86.4 mg, 1.6 mmol, 8.0 equiv) in methanol (1 mL) was added in a single portion and was stirred for a further 30 min at that temperature. Then, a saturated aqueous solution of $Na_2S_2O_3$ (7 mL) was added, followed by DCM (10 mL). The phases were separated, and the aqueous phase was extracted with DCM (2 × 10 mL). The combined organic phases were dried ($MgSO_4$) and concentrated under reduced pressure. The crude residue was purified by flash column chromatography (SiO_2; cyclohexane/EtOAc 90:10 to 80:20) to afford the desired alkene **19** (25.2 mg, 0.100 mmol) in 50% yield as colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ 5.93 (ddd, *J* = 16.9, 10.2, 6.5 Hz, 1H), 4.99-4.86 (m, 2H), 3.38-3.31 (m, 2H), 3.30-3.22 (m, 2H), 2.98-2.91 (m, 1H), 2.06-1.96 (m, 2H), 1.69-1.55 (m, 4H), 1.44 (s, 11H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 155.1,

143.5, 112.4, 79.3, 40.9 (br), 39.4, 37.6, 36.3, 34.2, 32.2, 28.6. **HRMS (ESI$^+$)**: calculated for $C_{15}H_{25}NNaO_2$ $[M+Na]^+$: 274.1783; found: 274.1774.

Arylation: Synthesis of 4-(7,7-dimethylspiro[3.5]nonan-2-yl)-3-fluoropyridine, **20**



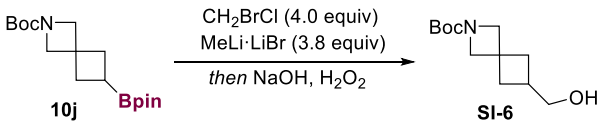
n-Butyllithium (0.6 mmol, 2.0 equiv) was added dropwise, under an argon atmosphere, to a solution of *N*,*N*-diisopropylamine (84 µL, 0.6 mmol, 2.0 equiv) in anhydrous THF (1 mL) at –78 °C and the mixture was allowed to react for 1 h.[150] The solution was warmed to –60 °C and a solution of 3-fluoropyridine (58.3 mg, 0.6 mmol, 2.0 equiv) in THF (0.5 mL) was added and the solution was stirred for 30 min. The mixture was cooled back to –78 °C and a solution of **10b** (83.5 mg, 0.3 mmol) in THF (1 mL) was added dropwise and stirred for 30 min. Then, the solution was warmed to 0 °C and stirred for a further 30 min. The solution was cooled back to –78 °C and 2,2,2-trichloroethyl chloroformate (165 µL, 1.2 mmol, 4.0 equiv) was added dropwise and the resulting mixture was stirred at room temperature overnight. The mixture was transferred to a separating funnel and diluted with Et_2O (10 mL) and saturated aqueous solution of $NaHCO_3$ (10 mL). The layers were separated, and the aqueous phase was extracted with Et_2O (3 × 10 mL). The combined organic phases were dried ($MgSO_4$) and concentrated *in vacuo*. The residue was dissolved in THF (3 mL) and cooled to 0 °C. NaOH (3 M aqueous solution, 1.5 mL) and H_2O_2 (30 % aqueous solution, 1.5 mL) were slowly added. The mixture was warmed to room

temperature and stirred for 14 h. Then, the mixture diluted with Et_2O (5 mL) and then HCl (1 M aqueous solution) was added to acidify the aqueous phase, which was extracted with Et_2O (3 × 5 mL). The aqueous phase was then neutralized with $NaHCO_3$ and extracted with Et_2O (3 × 10 mL). The combined organic phases were dried ($MgSO_4$) and concentrated under reduced pressure. The crude residue was purified by flash column chromatography (SiO_2; hexane/EtOAc 95:5) to afford the desired compound **20** (39.8 mg, 0.161 mmol) in 54% yield as colourless oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ 8.36-8.28 (m, 2H), 7.22-7.14 (m, 1H), 3.63 (quint, *J* = 9.2 Hz, 1H), 2.26 (td, *J* = 9.2, 2.4 Hz, 2H), 1.84 (td, *J* = 9.5, 2.5 Hz, 2H), 1.70-1.62 (m, 2H), 1.48-1.41 (m, 2H), 1.31-1.25 (m, 2H), 1.20-1.14 (m, 2H), 0.89 (s, 6H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 158.4 (d, *J* = 254.1 Hz), 145.8 (d, *J* = 5.0 Hz), 142.0 (d, *J* = 13.3 Hz), 137.6 (d, *J* = 24.7 Hz), 122.6, 38.5, 36.5, 36.2, 36.0, 35.6, 32.6, 29.8, 28.4 (br), 27.6. **^{19}F NMR** (282 MHz, $CDCl_3$): δ –135.3. **HRMS (EI$^+$)**: calculated for $C_{16}H_{22}FN$ $[M]^+$: 247.1736; found: 247.1748.

3.6 Synthesis of Donepezil Bioisostere

Synthesis of tert-butyl 6-(hydroxymethyl)-2-azaspiro[3.3]heptane-2-carboxylate, ***SI-6***

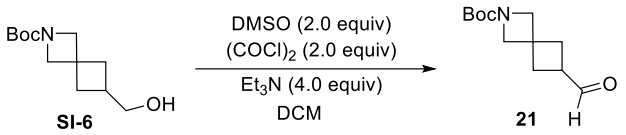


CH_2BrCl (367 µL, 5.64 mmol, 4.0 equiv) was added to a solution of boronate **10j** (458 mg, 1.41 mmol) in anhydrous THF (3 mL/mmol), under an argon atmosphere. The solution was cooled to –78 °C and MeLi·LiBr (3.6 mL of a 1.5 M solution in Et_2O, 5.36 mmol, 3.8 equiv) was added dropwise. The mixture was warmed to room temperature and stirred overnight. Then, the mixture was transferred to a separatory funnel, water was added, and the phases were separated. The aqueous phase was extracted with EtOAc (3x), the combined organic layers dried ($MgSO_4$) and the solvent removed under reduced pressure.

The reaction mixture was redissolved in THF (2 mL/mmol) and cooled to 0 °C. Then, 1M aqueous solution of NaOH (1 mL/mmol) and H_2O_2 (0.2 mL/mmol) were successively added dropwise. The mixture was stirred at room temperature for 1h. After this time, water was added, and the phases were separated. The aqueous phase was extracted with EtOAc (3x), the combined organic layers dried ($MgSO_4$) and the solvent removed *in vacuo*. The residue was purified by flash column chromatography (SiO_2, $CHCl_3$/*i*-PrOH 95:5, flash column chromatography repeated twice to separate from traces of oxidation product of **10j**) to afford alcohol **SI-6** (265 mg, 1.17 mmol) in 83% yield as a colourless oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ 3.87 (s, 2H), 3.77 (s, 2H), 3.48 (d, *J* = 6.2 Hz, 2H), 2.49 (br, 1H), 2.37-2.24 (m, 1H), 2.24-2.13 (m, 2H), 1.95-1.84 (m, 2H), 1.37 (s, 9H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 156.4, 79.4, 66.4, 62.2 (br), 61.5 (br), 35.4, 34.4, 31.4, 28.4. **HRMS (ESI$^+$)**: calculated for $C_{12}H_{21}NNaO_3$ $[M+Na]^+$: 250.1419; found: 250.1411.

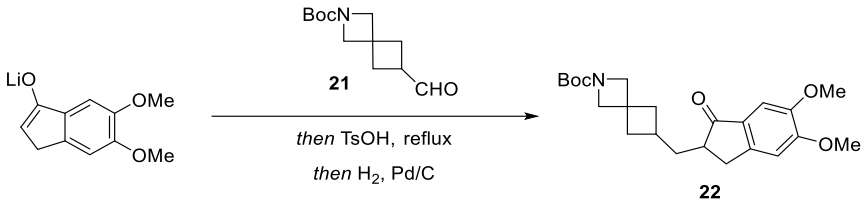
Synthesis of tert-Butyl 6-formyl-2-azaspiro[3.3]heptane-2-carboxylate, ***21***



A solution of DMSO (165 µL, 2.33 mmol, 2 equiv) in DCM (1 mL) was added to a solution of oxalylchloride (200 µL, 2.33 mmol, 2 equiv) in DCM (4 mL) at –78 °C, under an argon atmosphere. The mixture was stirred for 15 min at –78 °C and a solution of alcohol **SI-6** (265 mg, 1.17 mmol) in DCM (1 mL) was added dropwise. After stirring for 30 min, Et_3N (652 µL, 4.68 mmol, 4 equiv) was added to the mixture and then the reaction was allowed to warm to 0 °C. The reaction was stirred for further 45 min. Then, aqueous $NaHCO_3$ was added, and the mixture was extracted with DCM (3x), dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by flash column chromatography (SiO_2; hexane/EtOAc 80:20) to afford the corresponding aldehyde **21** (215 mg, 0.95 mmol) in 82% yield as a colourless oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ 9.71 (s, 1H), 3.93 (s, 2H), 3.81 (s, 2H), 3.15-3.01 (m, 1H), 2.48-2.30 (m, 4H), 1.41 (s, 9H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 201.3, 156.0, 79.3, 61.4 (br), 39.9, 34.6, 32.9, 28.3. **HRMS (EI$^+$)**: calculated for $C_{12}H_{19}NO_3$ $[M]^+$: 225.1365; found: 225.1359.

Synthesis of tert-butyl 6-((5,6-dimethoxy-1-oxo-2,3-dihydro-1H-inden-2-yl)methyl)-2-azaspiro[3.3]heptane-2-carboxylate, ***22***



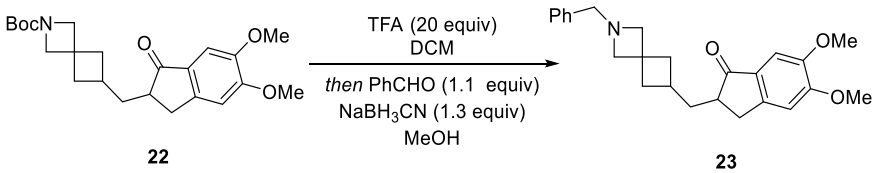
To a solution of *N*,*N*-diisopropylamine (112 µL, 0.80 mmol, 1.1 equiv) of in 3.1 mL of THF at –78 °C, under an argon atmosphere, was added dropwise *n*-butyllithium (0.5 mL, 1.6 M in hexane, 1.1 equiv). The reaction mixture was allowed to stir at 25 °C for 30 minutes. Then, a solution of 5,6-dimethoxy-2,3-dihydro-1*H*-inden-1-one (169 mg, 0.88 mmol, 1.2 equiv) in 1.5 mL of THF at –78 °C was added dropwise to the lithium *N*,*N*-diisopropylamide solution and the mixture was stirred for 1.5 h. After this time, a solution of aldehyde **21** (162.5 mg, 0.72 mmol, 1 equiv) was added to the prepared enolate and the mixture was stirred an additional 1 h. Upon completion by TLC, the reaction mixture was quenched with a saturated solution of NH_4Cl (4 mL), extracted with EtOAc (3x), washed with brine, dried over $MgSO_4$ and the solvent removed under reduced pressure.

In order to carry out the dehydration, the aldol product was dissolved in toluene (0.7 M) and a catalytic amount of *p*-TsOH·H_2O (69.4 mg, 0.365 mmol, 0.5 equiv) was added. The reaction was refluxed (oil bath) for 3 h. Once the reaction was finished, it was diluted with EtOAc (5 mL), washed with a saturated solution of $NaHCO_3$, dried over $MgSO_4$, and the solvent removed under reduced pressure. The crude was used in the next step without further purification.

Pd/C 10% (47 mg, 0.044 mmol, 6 mol%) was added to the crude containing the α,β-unsaturated ketone in THF (15 mL) and H_2 (balloon) was bubbled through the solution. The mixture was stirred under hydrogen atmosphere for 0.5 h at room temperature. Once it was finished by TLC, the reaction mixture was filtered through Celite® and washed with EtOAc (20 mL). The solvent was removed under reduced pressure and the residue purified by flash column chromatography (SiO_2, hexane/EtOAc/Et_3N 50:49:1) to afford product **22** (81.0 mg, 0.202 mmol) in a 28% overall yield (three steps) as pale brown oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.12 (s, 1H), 6.82 (s, 1H), 3.92 (s, 3H), 3.89 (s, 2H), 3.87 (s, 3H), 3.76 (s, 2H), 3.14 (dd, *J* = 16.9, 7.5 Hz, 1H), 2.64 (dd, *J* = 16.9, 3.4 Hz, 1H), 2.56-2.47 (m, 1H), 2.29-2.20 (m, 3H), 1.99-1.91 (m, 1H), 1.86-1.77 (m, 2H), 1.55-1.46 (m, 1H), 1.39 (s, 9H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 207.3, 156.4, 155.6, 149.6, 148.8, 129.4, 107.5, 104.5, 79.2, 62.5, 60.9, 56.3, 56.2, 46.2, 39.6, 39.1, 38.5, 34.4, 32.7, 28.5, 28.4. **HRMS (ESI$^+$)**: calculated for $C_{23}H_{31}NNaO_5$ $[M+Na]^+$: 424.2100; found: 424.2087.

Synthesis of 2-((2-benzyl-2-azaspiro[3.3]heptan-6-yl)methyl)-5,6-dimethoxy-2,3-dihydro-1H-inden-1-one, ***23***



22 **23**

In an oven-dried flask, **22** (81.0 mg, 0.202 mmol, 1 equiv) was dissolved in DCM (5 mL/mmol), under an argon atmosphere, and TFA (309 µL, 4.04 mmol, 20 equiv) was added dropwise to the solution at 0 °C. After being

stirred at room temperature for 1 h, the reaction mixture was washed with a solution of saturated Na_2CO_3. The organic phase was washed with brine, dried over $MgSO_4$ and the solvent evaporated under reduced pressure. The crude was used in the next step without further purification.

The crude mixture was dissolved in methanol (5 mL/mmol) and benzaldehyde (23 µL, 0.222 mmol, 1.1 equiv) was added. The solution was cooled to 0 °C and $NaCNBH_3$ (16.5 mg, 0.263 mmol, 1.3 equiv) was added portionwise. The resulting mixture was stirred at room temperature for 16 h. After this time, the solvent was removed under reduced pressure. Saturated aqueous $NaHCO_3$ (10 mL/mmol) and EtOAc (10 mL/mmol) were added, the phases separated, and the aqueous layer was extracted with EtOAc (20 mL × 3). Finally, the combined organic phases were dried over $MgSO_4$, filtrated, and the solvent was removed under reduced pressure. The reaction crude was purified by flash column chromatography (SiO_2; DCM/Et_3N 99:1 to DCM/MeOH/Et_3N 95:4:1) to afford desired product **23** (44.9 mg, 0.115 mmol) in 57% yield as pale brown oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.30-7.15 (m, 5H), 7.08 (s, 1H), 6.77 (s, 1H), 3.88 (s, 3H), 3.82 (s, 3H), 3.55 (s, 2H), 3.26 (s, 2H), 3.16 (s, 2H), 3.08 (dd, *J* = 16.9, 7.5 Hz, 1H), 2.58 (dd, *J* = 16.9, 3.5 Hz, 1H), 2.52-2.42 (m, 1H), 2.28-2.14 (m, 3H), 1.94-1.85 (m, 1H), 1.83-1.71 (m, 2H), 1.50-1.37 (m, 1H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 207.5, 155.6, 149.6, 149.0, 137.3, 129.5, 128.8, 128.5, 127.4, 107.5, 104.5, 67.2, 66.0, 63.4, 56.3, 56.2, 46.4, 39.6, 38.9, 38.7, 35.6, 32.7, 29.0. **HRMS (EI$^+$)**: calculated for $C_{25}H_{29}NO_3$ $[M]^+$: 391.2147; found: 391.2142.

Chapter III

Stereoselective Diboration of Spirocyclobutenes

Chapter III. Stereoselective Diboration of Spirocyclobutenes

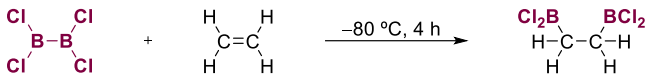
1. Introduction

As mentioned in the previous chapters, organoboron compounds are considered very versatile building blocks used for a wide range of transformations due to their unique reactivity, relative stability and high functional group tolerance.[157] Moreover, they have been used in material chemistry[158] and play an important role in biologically active molecules.[159] Among them, 1,2-diboron compounds which present two vicinal boryl moieties are considered valuable intermediates for concise synthesis of complex molecules through the functionalization of the C–B bonds. The two-boryl moieties can be differentiated and transformed in a selective manner, which allows the preparation of complex molecules and drugs. However, the versatility of the two C–B bonds would be useless without efficient routes to obtain 1,2-organoboron compounds.

Diborations are highly atom-efficient reactions in which two boryl moieties from a diboron reagent are added across an unsaturated bond. In 1954, Schlesinger observed that diboron tetrahalides can react with

[157] Sandford, C.; Aggarwal, V. K. *Chem. Commun*. **2017**, *53*, 5481–5494.
[158] Brooks, W. L. A.; Sumerlin, B. S. *Chem. Rev.* **2016**, *116*, 1375–1397.
[159] Yang, F.; Zhu, M.; Zhang, J.; Zhou, H. *Med. Chem. Commun.* **2018**, *9*, 201–211.

unsaturated hydrocarbons to generate a relative stable liquid compound with formula $Cl_2B–CH_2–CH_2–BCl_2$ (**Scheme 102**). This reaction represents the first addition of a borane reagent to a double bond.[160] After the discovery of this straightforward transformation, the reaction was extended to other unsaturated substrates such as alkynes, dienes or allyl halides among others.[161] Moreover, the diborylated products are difficult to isolate and the authors described them as "*adducts*".



Scheme 102. Addition of diboron tetrachloride to ethylene.

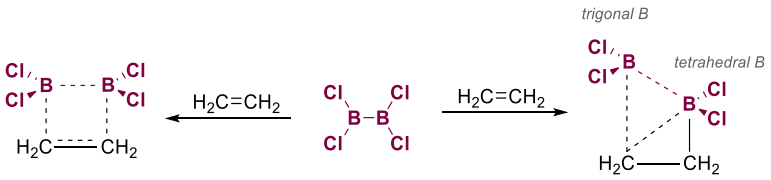
The thermal addition of B_2Cl_4 to ethylene was initially proposed to proceed through a π-donation from the olefin to the empty *p*-orbitals of the boron atoms *via* a four-centered transition state (**Scheme 103**). Subsequent B–B cleavage results in the *cis* addition of the two boron atoms across the double bond. In the suggested mechanism the diboron compound assumed a near planar configuration which justifies the maximum orbital overlap between the empty *p*-orbitals of diborane and the π-orbital of the olefin.[162] Fifty years later, DFT calculations carried out by Brown, Bo and co-workers revisited the mechanism and suggested that

[160] Urry, G.; Wartik, T.; Moore, R. E.; Schlesinger, H. I. *J. Am. Chem. Soc.* **1954**, *76*, 5299–5301.

[161] **(a)** Ceron, P.; Finch, A.; Frey, J.; Kerrigan, J.; Parsons, T.; Urry, G.; Schlesinger, H. I. *J. Am. Chem. Soc.* **1959**, *81*, 6368–6371. **(b)** Feeney, J.; Holliday, A. K.; Marsden, F. J. *J. Chem. Soc.* **1961**, 356–360. **(c)** Chambers, C.; Holliday, A. K. *J. Chem. Soc.* **1965**, 3459–3462. **(d)** Fox, W. B.; Wartik, T. *J. Am. Chem. Soc.* **1961**, *83*, 498–499. **(e)** Kotz, J. C.; Post, E. W. *Inorg. Chem.* **1970**, *9*, 1661–1669.

[162] **(a)** Zeldin, M.; Gatti, A. R.; Wartik, T. *J. Am. Chem. Soc.* **1967**, *89*, 4217–4218. **(b)** Rudolph, R. W. *J. Am. Chem. Soc.* **1967**, *89*, 4216–4217.

the four atoms involved in the transition-state are close to coplanar geometry. However, one of the boron atoms presents near-tetrahedral geometry through bonding to both carbons, with the second boron atom closer to its inherent trigonal geometry (**Scheme 103**).[163]



Scheme 103. Mechanistic approaches for the addition of B_2Cl_4 to alkenes.

Diboron tetrahalides are exceptional reagents for the straightforward addition to unsaturated systems, however their instability represents a drawback for the development of their possible application in organic synthesis.

In contrast with diboron tetrahalides, tetra(dialkylamino)diboron and tetra(alkoxy)diboron reagents are more stable and easier to handle. The cause of this increased stability is the electron donation from the lone pair of the neighboring nitrogen or oxygen atoms to the empty *p* orbital of one of the boron centers that increases the B–B bond energy (104 kcal/mol).[164] Consequently, less *p*-acidic diboron compounds are inert toward diboration of unsaturated substrates. However, different strategies have been developed to take advantage of the utility of tetra(alkoxy)diboron compounds in organic synthesis through the activation of the B–B bond.

[163] Pubill-Ulldemolins, C.; Fernández, E.; Bo, C.; Brown, J. M. *Org. Biomol. Chem.* **2015**, *13*, 9619–9628.
[164] Ishiyama, T.; Miyaura, N. *Chem. Rec.* **2004**, *3*, 271–280.

One of the most well-stablished activation modes consists in the use of low-valent transition metal complexes that undergo oxidative addition and induce the B–B bond cleavage allowing its transfer to unsaturated systems. An alternative and effective approach consists in the mono-quaternization of one of the boron atoms employing neutral or anionic nucleophiles to obtain sp^2–sp^3 diboron adducts. The B(sp^2) moiety gains nucleophilic character and enables the unsaturated substrate to act as electrophile.

In the last twenty years, the number of publications on multi-borylation reactions have exponentially increased.[165] Diboron compounds have been employed to carried out multiple borylation reactions using different transition metal complexes and also through metal-free approaches. A comprehensive review of this literature exceeds the scope of this doctoral thesis. Therefore, only selected examples of 1,2-diboration of alkenes will be included in the next sections.

[165] *For recent reviews see*: **(a)** Takaya, J.; Iwasawa, N. *ACS Catal.* **2012**, *2*, 1993–2006. **(b)** Dewhurst, R. D.; Neeve, E. C.; Braunschweig, H.; Marder, T. B. *Chem. Commun.* **2015**, *51*, 9594–9607 **(c)** Cuenca, A. B.; Shishido, R.; Ito, H.; Fernández, E. *Chem. Soc. Rev.* **2017**, *46*, 415–430 **(d)** Wen, Y.; Deng, C.; Xie, J.; Kang, X. *Molecules* **2019**, *24*, 101. **(e)** Wang, X.; Wang, Y.; Huang, W.; Xia, C.; Wu, L. *ACS Catal*. **2021**, *11*, 1–18. **(e)** Fernández, E.; Cuenca, A.B. *Org. React.* **2021**, *105*, 267–426.

1.1 Transition-Metal-Catalyzed 1,2-Diboration of Alkenes

Transition-metal catalyzed diboration of alkenes with diboron compounds offers a straightforward method to prepare molecules with two carbon–boron bonds. After oxidation of the boryl moieties, 1,2-diols were obtained. This process provides an alternative to the use of highly toxic OsO_4, used for the dihydroxylation of alkenes. Although diboration of alkenes was reported using different catalyst such as palladium,[166] copper,[167] gold,[168] silver,[169] and iron,[170] the most studied transition-metals to undergo this transformation are rhodium and platinum, whose reaction mechanism involves the oxidative addition of the diboron reagent to the metal, insertion of the alkene followed by reductive elimination to afford the 1,2-diboron compound and regenerate the catalytic cycle (**Scheme 104**). The main approaches using these metals will be discussed in this section.

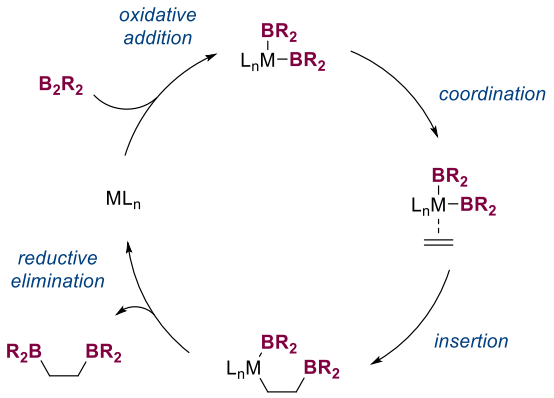
[166] Lillo, V.; Mas-Marzá, E.; Segarra, A. M.; Carbó, J. J.; Bo, C.; Peris, E.; Fernández, E. *Chem. Commun.* **2007**, 3380–3382.

[167] **(a)** Lillo, V.; Fructos, M. R.; Ramírez, J.; Braga, A. A. C.; Maseras, F.; Díaz-Requejo, M. M.; Pérez, P. J.; Fernández, E. *Chem. Eur. J.* **2007**, *13*, 2614–2621. **(b)** Hu, J.; Zhao, Y.; Shi, Z. *Nat. Catal.* **2018**, *1*, 860–869.

[168] **(a)** Corberán, R.; Ramírez, J.; Poyatos, M.; Peris, E.; Fernández, E. *Tetrahedron: Asymmetry* **2006**, 17, 1759–1762. **(b)** Ramírez, J.; Sanaffl, M.; Fernández, E. *Angew. Chem. Int. Ed.* **2008**, *47*, 5194–5197.

[169] Ramírez, J.; Corberán, R.; Sanaú, M.; Peris, E.; Fernández, E. *Chem. Commun.* **2005**, 3056–3058.

[170] Zhou. S.; Pu, Y.; Liu, Z.; Zhang, X.; Zhu, J.; Feng, Z. *Org. Lett.* **2021**, 23, 5565–5570.

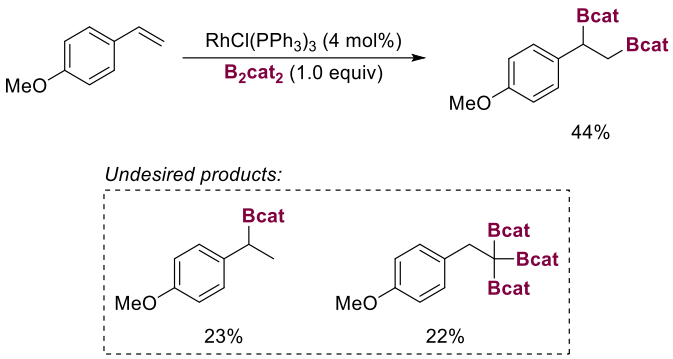


Scheme 104. General catalytic cycle for transition-metal-catalyzed reaction of alkenes with diboron compounds.

1.1.1 Rhodium-Catalyzed 1,2-Diboration of Alkenes

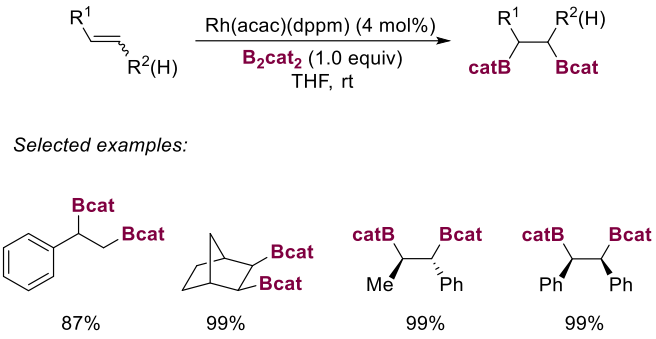
The first efforts of using transition-metal catalyst to achieve the 1,2-diboration of olefins were carried out by Marder and co-workers in 1995 (**Scheme 105**). Using a rhodium(I) complex as catalyst and 4-vinylanisole as starting material the corresponding diboron compound was obtained in 44% yield. The remaining products included 23% of monoborylated product and 22% of the unusual 2,2,2-tris(boronate) ester, both resulting from β-hydride elimination pathways.[171]

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



Scheme 105. Rhodium-catalyzed diboration of 4-vinylanisole.

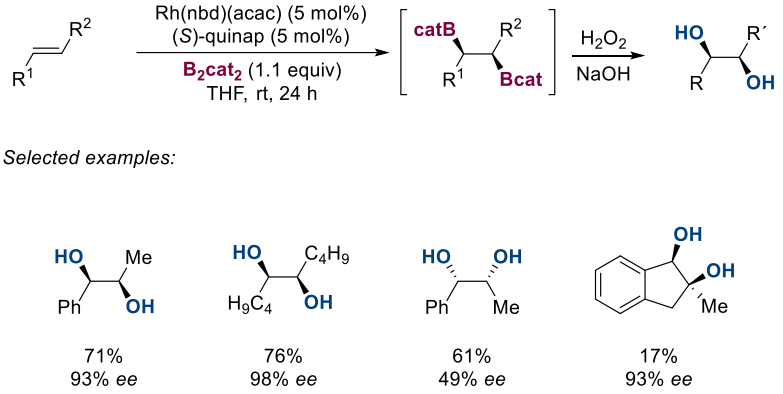
Years later, the same group reported the 1,2-diboration of terminal and unstrained internal alkenes. The improved method used Rh(acac)(dppm) as catalyst affording the diboron compounds in higher yields, avoiding the formation of the undesired products obtained in their previous report (**Scheme 106**).[172]



Scheme 106. Rhodium-catalyzed diboration of alkenes.

[172] Dai, C.; Robins, E. G.; Scott, A. J.; Clegg, W.; Yufit, D. S.; Howard, J. A. K.; Marder, T. B. *Chem. Commun.* **1998**, 1983–1984.

It was in 2003, when Morken and co-workers reported the first enantioselective diboration of internal alkenes using a chiral rhodium(I) complex formed *in situ* by mixing the chiral phosphine ligand (*S*)-quinap and Rh(nbd)(acac) (**Scheme 107**). The reaction appears to be general for *trans* alkenes and does not require the presence of an aromatic group for high reactivity or enantioselectivity.[173] The products were obtained with up to 35:1 *syn*:*anti* diastereoselectivity and enantioselectivities of up to 98%.

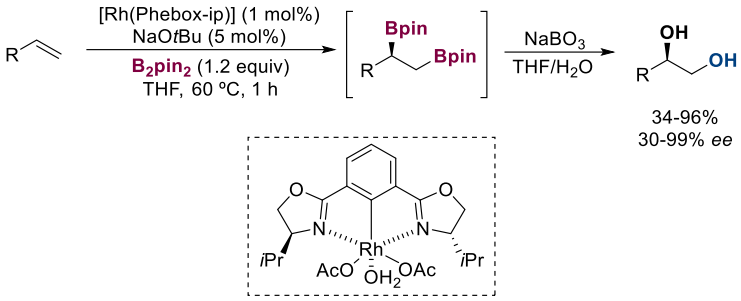


Scheme 107. Rhodium-catalyzed enantioselective diboration of simple alkenes.

More recently, Nishiyama and co-workers, reported the use of chiral rhodium bis(oxazolinyl)phenyl complexes for the asymmetric diboration of terminal alkenes (**Scheme 108**).[174] They found that addition of a Lewis base improved yields and enantioselectivities. Furthermore, they proposed a different catalytic cycle for the reaction, proposing the formation of

[173] **(a)** Morgan, J. B.; Miller, S. P.; Morken, J. P. *J. Am. Chem. Soc.* **2003**, *125*, 8702–8703. **(b)** Trudeau, S.; Morgan, J. B.; Shrestha, M.; Morken, J. P. *J. Org. Chem.* **2005**, *70*, 9538–9544.
[174] Toribatake, K.; Nishiyama, H. *Angew. Chem. Int. Ed.* **2013**, *52*, 11011–11015.

Rh^{III}–Bpin species as key reactive intermediates. As a limitation of this approach, 1,2-disubstituted alkenes could not be diborylated under this reaction conditions. More recently, the same authors, reported the synthesis of optically active 3-amino-1,2-diols from *N*-acyl-protected allylamines using similar conditions.[175]

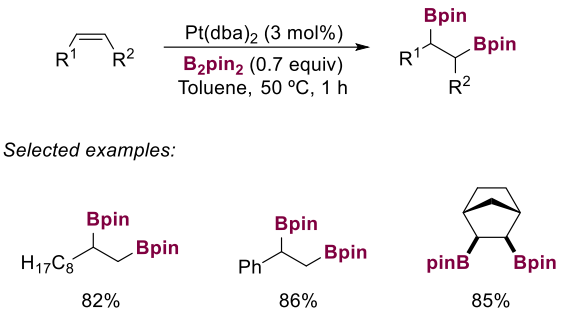


Scheme 108. Asymmetric diboration of terminal alkenes with [Rh(Phebox-ip)].

1.2.2 Platinum-Catalyzed 1,2-Diboration of Alkenes

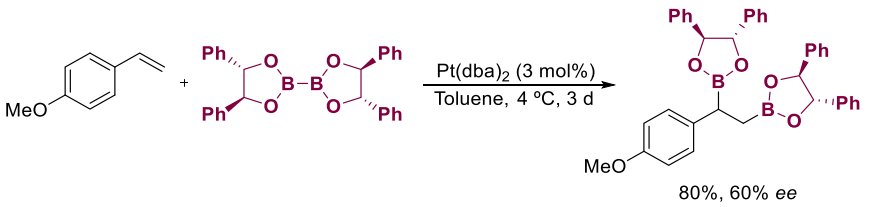
The first platinum-catalyzed alkene diboration was reported by Miyaura and co-workers in 1997. Employing a catalytic amount of $Pt(dba)_2$ in the presence of B_2pin_2, different terminal and strained cyclic alkenes were diborylated in good yields. NMR studies demonstrated that the insertion step occurs in a *syn* fashion (**Scheme 109**).[176] At the same time, Smith and Iverson disclosed a similar approach using $Pt(cod)_2$ as catalyst.[177]

[175] Toribatake, K.; Miyata, S.; Naganawa, Y.; Nishiyama, H. *Tetrahedron* **2015**, *71*, 3203–3208.
[176] Ishiyama, T.; Yamamoto, M.; Miyaura, N. *Chem. Commun.* **1997**, 689–690.
[177] Iverson, C. N. Smith III, M. R. *Organometallics* **1997**, *16*, 2757–2759.



Scheme 109. Pt(dba)$_2$-catalyzed diboration of alkenes.

Marder and co-workers used a chiral diboron reagent in the presence of a catalytic amount of Pt(dba)$_2$ to induce the asymmetric diboration of terminal alkenes. The corresponding enantioenriched 1,2-diborylalkane was obtained with up to 60% *ee* (**Scheme 110**).[178]

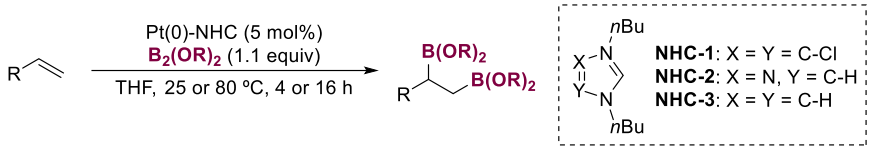


Scheme 110. Pt-catalyzed diboration of alkenes with chiral diboron compounds.

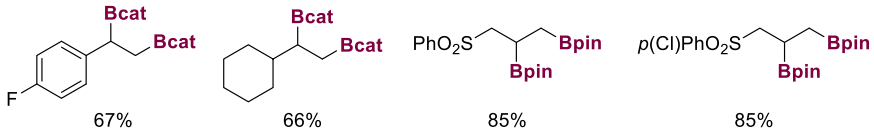
Fernández and co-workers reported in 2006 the use of Pt(0)-NHC complexes to undergo the diboration of different unsaturated systems (**Scheme 111**).[179] This work represents the first diboration of aryl allylic

[178] Marder, T. B.; Norman, N. C.; Rice, C. R. *Tetrahedron Lett.* **1998**, *39*, 155–158.
[179] Lillo, V.; Mata, J.; Ramírez, J.; Peris, E.; Fernández, E. *Organometallics* **2006**, *25*, 5829–5831.

sulfones, that after oxidation of the boryl moieties afford 1,2-dihydroxy sulfones that are valuable synthetic intermediates.



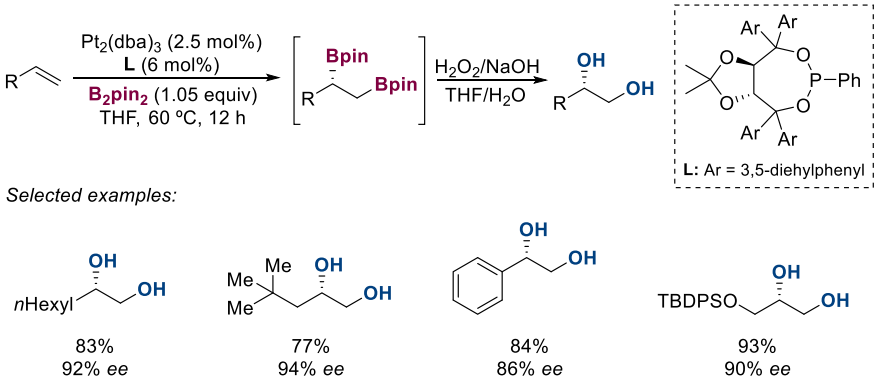
Selected examples:



Scheme 111. Pt(0)-NHC catalyzed diboration of alkenes.

In 2009, Morken and co-workers reported the platinum-catalyzed enantioselective diboration of terminal alkenes with B_2pin_2 and a catalytic amount of dimeric $Pt_2(dba)_3$ in the presence of a chiral taddol-derived phosphonite ligand. The diboration occurs in a highly enantioselective fashion and remarkably, the reaction is insensitive to the nature of the alkyl substituent with large and small groups equally tolerated (**Scheme 112**).[180] Four years later, the same group reported a study with the optimal procedures and expanded substrate scope of this transformation. Reaction progress kinetic analysis and kinetic isotope effects suggests that the stereodefining step is the olefin migratory insertion into a Pt–B bond.[181]

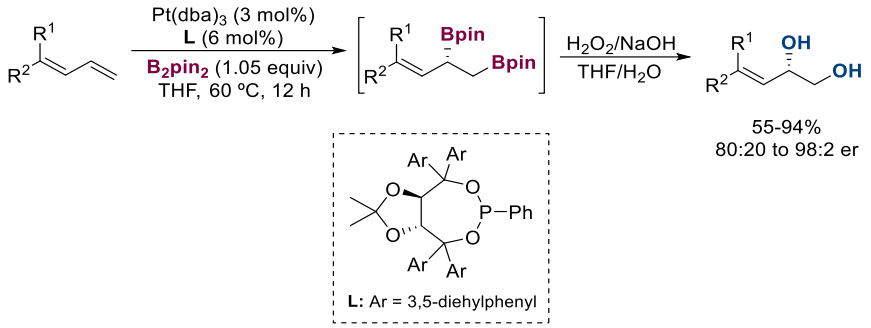
[180] Kliman, L. T.; Mlynarski, S. N.; Morken, J. P. *J. Am. Chem. Soc.* **2009**, *131*, 13210–13211.
[181] Coombs, J. R.; Haeffner, F.; Kliman, L. T.; Morken, J. P. *J. Am. Chem. Soc.* **2013**, *135*, 11222–11231.



Scheme 112. Platinum-catalyzed enantioselective diboration of alkenes.

In 2012, the same research group published the 1,2-diboration of 1,3-dienes.[182] In a previous study, they reported the enantioselective 1,4-diboration of *trans*-1,3-dienes using a platinum catalyst and a phosphonite ligand.[183] They found that replacing the *trans*-diene substrate with *cis*-1,3-dienes, under similar reaction conditions, the 1,2-diboration was favorable, obtaining the products in good yields and excellent enantiomeric ratios (**Scheme 113**). The afforded α-chiral allyl boronates are very versatile reagents for stereoselective allylation reactions.

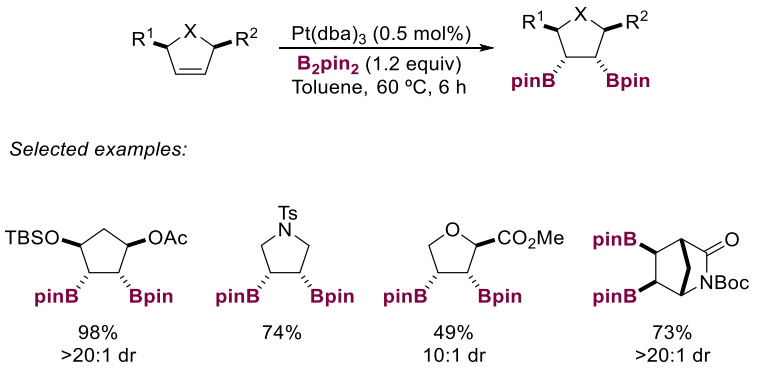
[182] Kliman, L. T.; Mlynarski, S. N.; Ferris, G. E.; Morken, J. P. *Angew. Chem. Int. Ed.* **2012**, *51*, 521–524.
[183] Burks, H. E.; Kliman, L. T.; Morken, J. P. *J. Am. Chem. Soc.* **2009**, *131*, 9134–9135.



Scheme 113. Platinum-catalyzed 1,2-diboration of 1,3-dienes.

Very recently, Morken and co-workers extended the platinum catalyzed diboration of cyclic akenes to mono-unsaturated heterocycles and bicyclic compounds (**Scheme 114**).[184] They proposed that the bis(boryl) platinum intermediate would avoid coordination to the more sterically hindered face of the cyclic alkene, allowing the diastereoselective synthesis of cyclic diboronates. Using a $Pt(dba)_3$ as catalyst and bis(pinacolato) diboron the products were obtained in good yields and good diastereomeric ratios.

[184] Vendola, A. J.; Allais, C.; Dechert-Schmitt, A.-M. R.; Lee, J. T.; Singer, R. A.; Morken, J. P. *Org. Lett.* **2021**, *23*, 2863−2867.

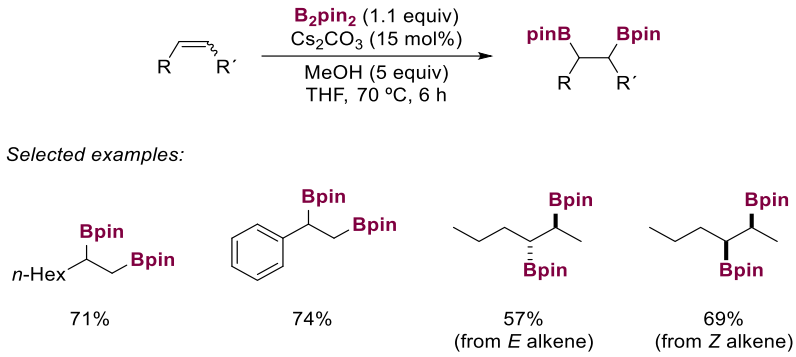


Scheme 114. Pt(dba)$_3$-catalyzed diboration of cyclic alkenes.

1.2 Transition-Metal-Free 1,2-Diboration of Alkenes

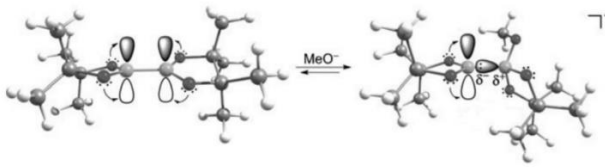
The first transition-metal-free diboration of unactivated alkenes was reported by Fernández and co-workers in 2011.[185] In this pioneering work, the authors described the diboration of double bonds using B_2pin_2 as boron source, a simple base and MeOH as additive to achieve the activation of the diboron reagent. Interestingly the diboration of internal alkenes revealed that it occurs in a *syn* fashion affording the diborylated product with high levels of diastereoselectivity (**Scheme 115**).

[185] Bonet, A.; Pubill-Ulldemolins, C.; Carles Bo, C.; Gulyás, H.; Fernández, E. *Angew. Chem. Int. Ed.* **2011**, *50*, 7158 –7161.



Scheme 115. Transition-metal-free diboration of alkenes.

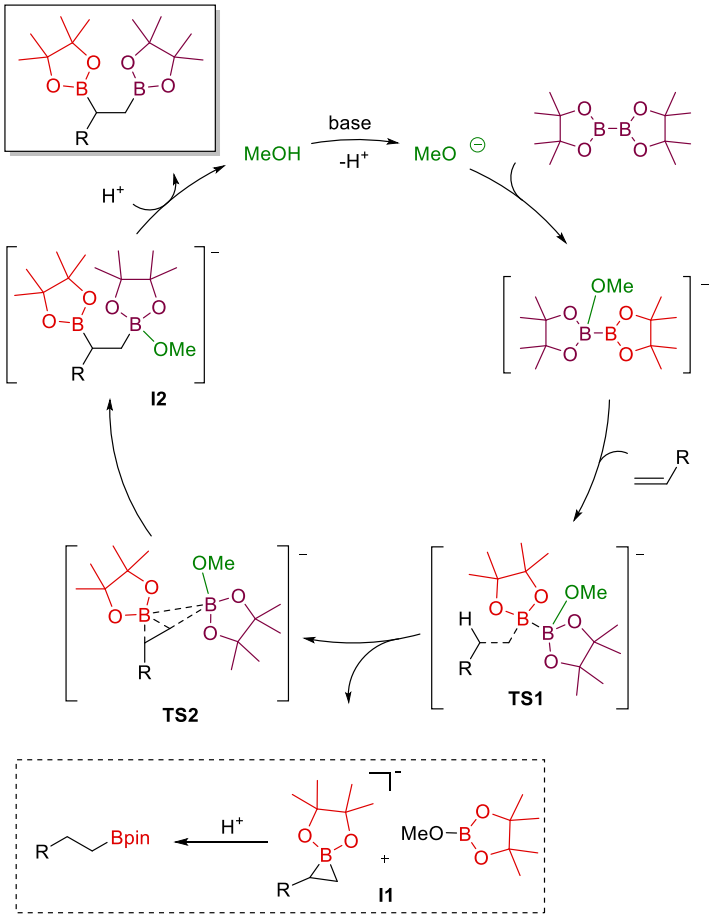
Additionally, DFT calculations revealed that the sp^3 boron atom of the Lewis acid–base adduct loses negative charge density, while the sp^2 gains electron density. Despite the direct charge transfer from the coordinated Lewis base, the loss of negative charge on the sp^3 boron atom can be rationalized by considering that upon rehybridization the boron atom loses the π-symmetric electron donation from the oxygen atoms of the boronic ester moiety inducing the polarization of the B–B bond (**Scheme 116**).



Scheme 116. Loss of the π-symmetric electron donation from the oxygen atoms of the pinacol moiety after Lewis base coordination.

DFT calculations supported the following catalytic cycle. First, methoxide anion, generated *in situ* from MeOH with a catalytic amount of

base, activates the diboron reagent. In **TS1** the sp^2 boron atom of the activated diboron reagent interacts with the unsubstituted carbon atom (C1) of the alkene, while the B–B bond weakens, and the negative charge density on the C2 carbon increases. The interaction leading to **TS1** is the overlap between the B–B σ bond (HOMO) and the antibonding π* orbital (LUMO) of the alkene. The negatively charged C2 atom should be prone to attack the closest electrophilic boron atom, causing the B–B bond cleavage. The distribution of the negative charge density among C1, C2, and the boron atom, might explain the connection between **TS1**, **TS2** and the intermediate **I1** whose protonation affords the hydroborated by-product. The negatively charged C2 in **TS2** should be prone to attack the close electrophilic boron atom causing the B–B bond breakup. Finally, protonation of the methoxide in **I2** affords the desired diborylated product and regenerates the catalytic cycle (**Scheme 117**).

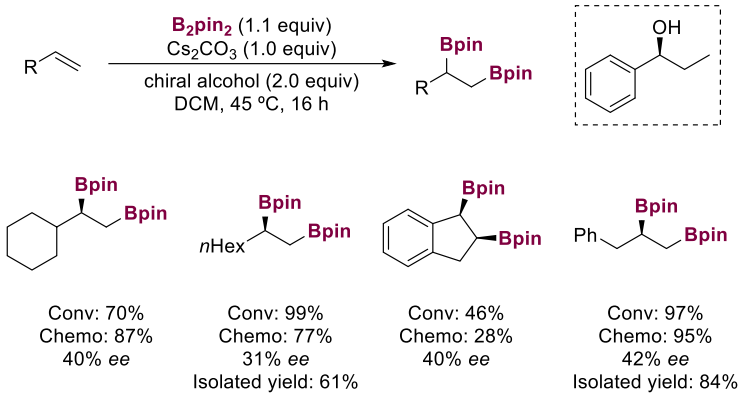


Scheme 117. Proposed catalytic cycle for the diboration of alkenes.

A consecutive study reported by the same research group showed that the use of chiral alcohols to form the Lewis acid-base adduct could induce asymmetry in the diboration process (**Scheme 118**).[186] This report represents the first asymmetric metal-free diboration of alkenes. The

[186] Bonet, A.; Sole, C.; Gulyás, H.; Elena Fernández, E. *Org. Biomol. Chem.* **2012**, *10*, 6621–6623.

combination of bis(pinacolato) diboron with cesium carbonate and economically accessible chiral alcohols represents a straightforward method to prepare enantioenriched diboron compounds albeit in moderate enantiomeric excesses.

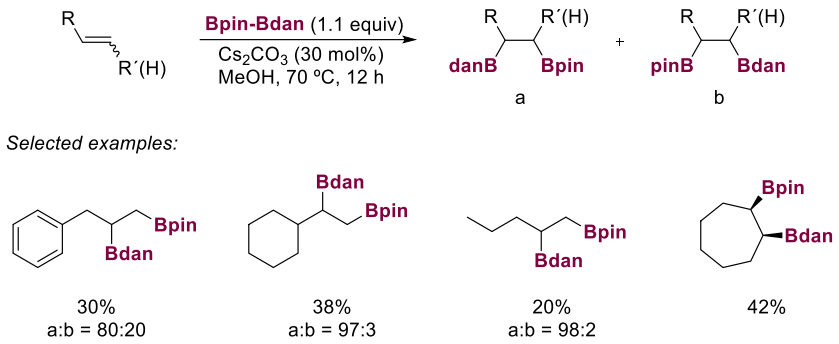


Scheme 118. Asymmetric organocatalytic diboration of alkenes.

In a later report, the same research group reported the diboration of terminal and internal alkenes using the unsymmetrical boron system, Bpin-Bdan (dan = 1,2-diaminonaphthalene) in combination with Cs_2CO_3 and MeOH as solvent (**Scheme 119**).[187] It was observed that the methoxide selectively interacted with the boronic ester moiety due to his stronger Lewis acid character placing the Bdan moiety in the internal position of the olefin. DFT calculations were in good agreement with the experimental observed regioselectivity. Interestingly, this metal-free approach is

[187] Miralles, N.; Cid, J.; Cuenca, A. B.; Carbó, J. J.; Fernández, E. *Chem. Commun.* **2015**, *51*, 1693–1696.

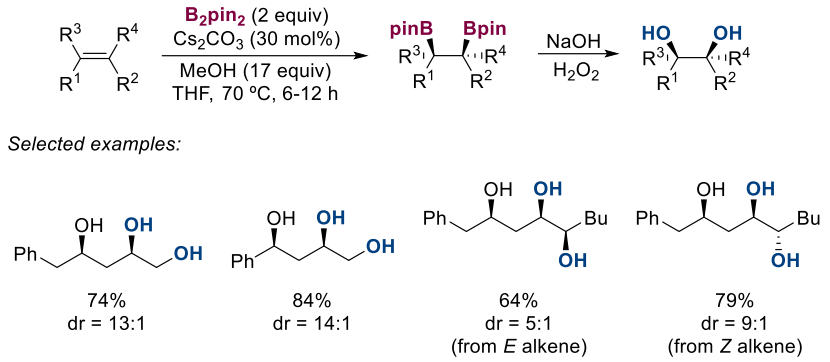
complementary to that described with Ir and Pt complexes where the final products were obtained with the opposite regioselectivity.[188]



Scheme 119. Metal-free diboration of alkenes with Bpin-Bdan.

In 2015 Morken and co-workers reported the hydroxyl-directed stereoselective diboration of cyclic and acyclic allylic alcohol using a base and methanol as additives.[189] After oxidation of the boryl moieties different diols were obtained. That the reaction occurs by stereospecific directed *syn* addition could be proved by the observed selective diboration of both *trans*- and *cis*-olefin substrates (**Scheme 120**).

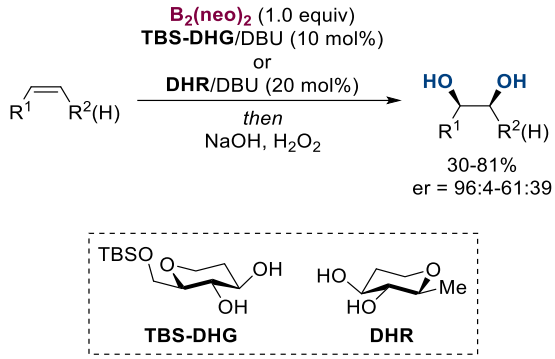
[188] Iwadate, N.; Suginome, M. *J. Am. Chem. Soc.* **2010**, *132*, 2548–2549.
[189] Blaisdell, T. P.; Caya, T. C.; Zhang, L.; Sanz-Marco, A.; Morken, J. P. *J. Am. Chem. Soc.* **2014**, *136*, 9264–9267.



Scheme 120. Directed diboration of alkenyl alcohols.

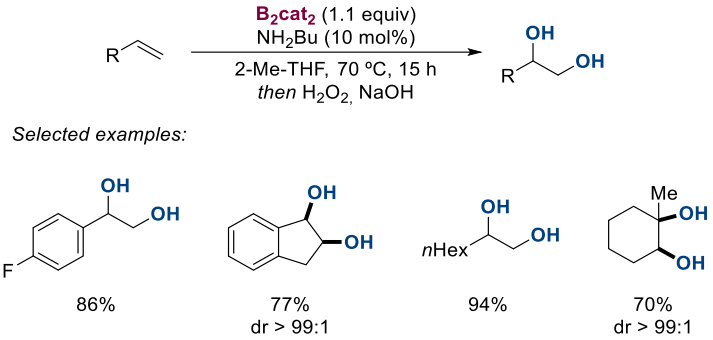
The following year, Morken presented an impressive work describing an operationally simple enantioselective diboration using inexpensive carbohydrate-derived glycols to induce asymmetry (**Scheme 121**). Following this approach, a wide range of alkenes were transformed into the corresponding diborylated products with high yields and excellent enantiomeric excesses. Moreover, the reaction was carried out on large scale (10 g) allowing the formation of the product in good yield and maintaining the asymmetric induction. Mechanistic experiments suggest that $B_2(neo)_2$ undergo a boronate ester exchange in the presence of chiral carbohydrates.[190]

[190] **(a)** Fang, L.; Yan, L.; Haeffner, F.; Morken, J. P. *J. Am. Chem. Soc.* **2016**, *138*, 2508−2511, **(b)** Yan, L.; Meng, Y.; Haeffner, F.; Leon, R. M.; Crockett, M. P.; Morken, J. P. *J. Am. Chem. Soc.* **2018**, *140*, 3663−3673.



Scheme 121. Carbohydrate-catalyzed enantioselective diboration of alkenes.

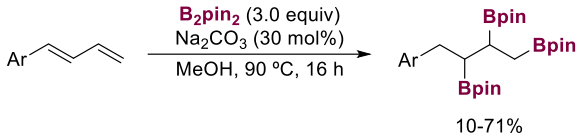
In 2016, Bonet reported the diboration of a wide range of alkenes using simple amine as organocatalysts.[191] The methodology provides a selective transformation with high functional group tolerance (**Scheme 122**). Moreover, NMR and DFT experiments were carried out to understand the reaction mechanism and suggested that the amine activates the diboron reagent in a similar way that described Fernández in the case of methoxide.



Scheme 122. Amine organocatalytic diboration of alkenes.

[191] Farre, A.; Soares, K.; Briggs, R. A.; Balanta, A.; Benoit, D. M.; Bonet, A. *Chem. Eur. J.* **2016**, *22*, 17552–17556

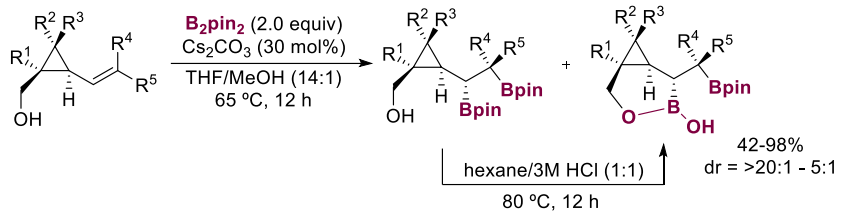
In 2018, Fernández and co-workers reported the transition metal-free triboration of 1,3-dienes using B_2pin_2 in combination with Na_2CO_3 and MeOH as additives (**Scheme 123**). The products are 1,2,3-triborated compounds that have been prepared in moderate to good yields. Moreover, the selective functionalization of the internal C–B bond through a Suzuki-Miyaura cross-coupling reaction offers a powerful tool towards polyfunctionalization.[192]



Scheme 123. Transition-metal-free triboration of 1,3-dienes.

More recently, Marek reported the metal-free diboration of stereodefined alkenyl cyclopropyl methanol derivatives. Performing the reaction in the presence of Cs_2CO_3 and MeOH as additives the desired diborylated products were obtained with good yields and good diastereomeric ratios as a mixture of mono- and diboronic esters.[193] Moreover, they observe that refluxing the mixture of these two diborylated species in a 1:1 mixture of aqueous HCl and hexanes resulted in the full formation of the cyclic boronic acid. It should be highlighted that this transformation could be realized in a one pot sequence directly from the starting alkene (**Scheme 124**).

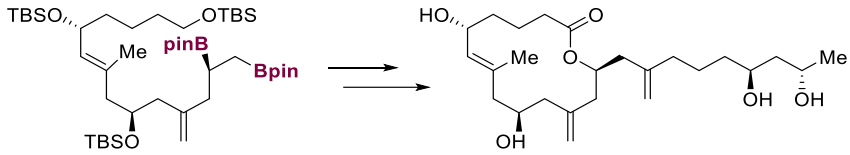
[192] Davenport, E.; Fernández, E. *Chem. Commun.* **2018**, *54*, 10104–10107.
[193] Pierrot, D.; Marek, I. *Angew. Chem. Int. Ed.* **2020**, *59*, 20434–20438.



Scheme 124. Metal-free diboration of alkenyl cyclopropyl methanol derivatives.

1.2 Selective Functionalization of Alkyl 1,2-Diboron Compounds

1,2-Diboron compounds have been attracting increasing interest as versatile building blocks in organic synthesis. However, the most interesting feature of this class of compounds is the possibility to selective functionalize one of the two-boryl moieties. Following this strategy, different compounds could be prepared from a common intermediate and they offer a powerful tool for the synthesis of complex molecules (**Scheme 125**).[194]



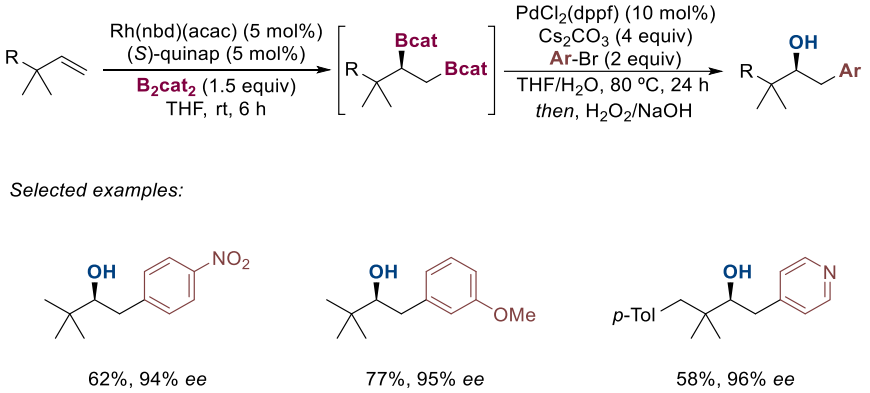
Scheme 125. Total synthesis of Arenolide.

Nowadays, different selective functionalizations of 1,2-diboron compound have been reported, being the selective Suzuki-Miyaura cross-

[194] Liu, X.; Sun, C.; Mlynarski, S.; Morken, J. P. *Org. Lett.* **2018**, *20*, 1898−1901.

coupling the most studied reaction. The high efficiency of the selective cross-coupling is due to the internal chelation between the two boronic esters that enhances the Lewis acidity of one of the boryl moieties.

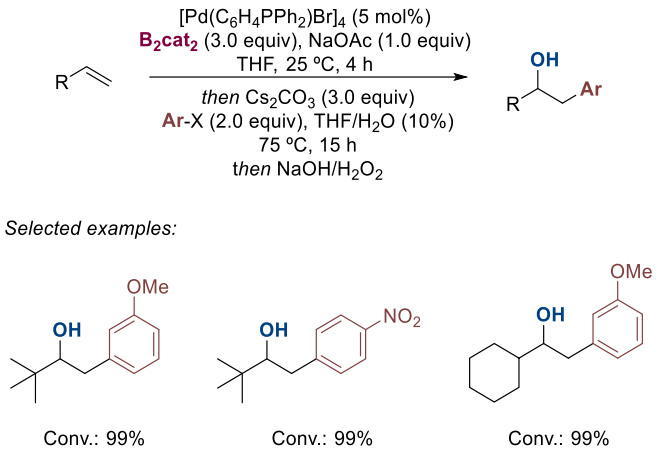
The first selective Suzuki-Miyaura cross coupling of 1,2-diboron compounds was reported by Morken in 2004 (**Scheme 126**). In this study, the authors reported a tandem diboration/Suzuki-cross-coupling reaction of terminal alkenes.[195] The enantioenriched products afforded by the rhodium catalyzed diboration were subjected to *in situ* cross-coupling using $PdCl_2$ as catalyst with different aryl bromides. They proposed that the more accessible C–B bond would react faster leaving the secondary one available for further transformations. After oxidation of the secondary C–B moiety, they observed that the enantiopurity was unaltered during the process. The limitation of this approach is that only good enantioselectivity was obtained for bulky aliphatic alkenes.



Scheme 126. Single-pot asymmetric diboration/Suzuki coupling.

[195] Miller, S. P., Morgan, J. B., Nepveux, F. J. & Morken, J. P. *Org. Lett.* **2004**, *6*, 131–133.

A few years later, Fernández group reported the one-pot diboration/Suzuki cross-coupling of terminal alkenes using a Pd catalyst and B_2cat_2 as boron source (**Scheme 127**).[196] They observed that after completion of the diboration, the addition of aryl halides and aryl triflates provided total monoarylation of the primary alkylboronic ester. Finally, after oxidative work-up led to the formation of the corresponding carbohydroxylated products. Remarkably, only 5 mol% of the palladium catalyst is required to undergo both sequences: the borylation and the cross-coupling reaction.

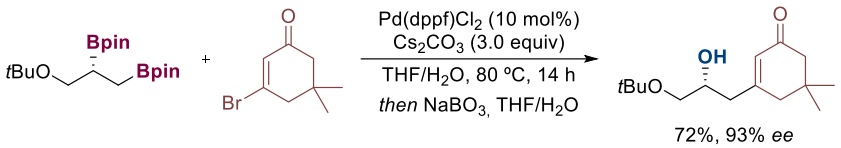


Scheme 127. Pd-catalyzed one-pot diboration/cross-coupling of alkenes.

In 2009, Hoveyda reported the first selective cross-coupling of a 1,2-bis(pinacol) boronate.[197] This isolated example involves the use of two equivalents of a highly activated organic electrophile due to the lower

[196] Penno, D.; Lillo, V.; Koshevoy, I. O.; Sanaffl, M.; Ubeda, M. A.; Lahuerta, P.; Fernández, E. *Chem. Eur. J.* **2008**, *14*, 10648–10655.
[197] Lee, Y., Jang, H. & Hoveyda, A. H. *J. Am. Chem. Soc.* **2009**, *131*, 18234–18235.

reactivity of the pinacol moiety (Scheme 128). The reaction is site-selective for the less-hindered C–B bond and after oxidation they proved that the product was obtained without loss of enantiomeric purity.

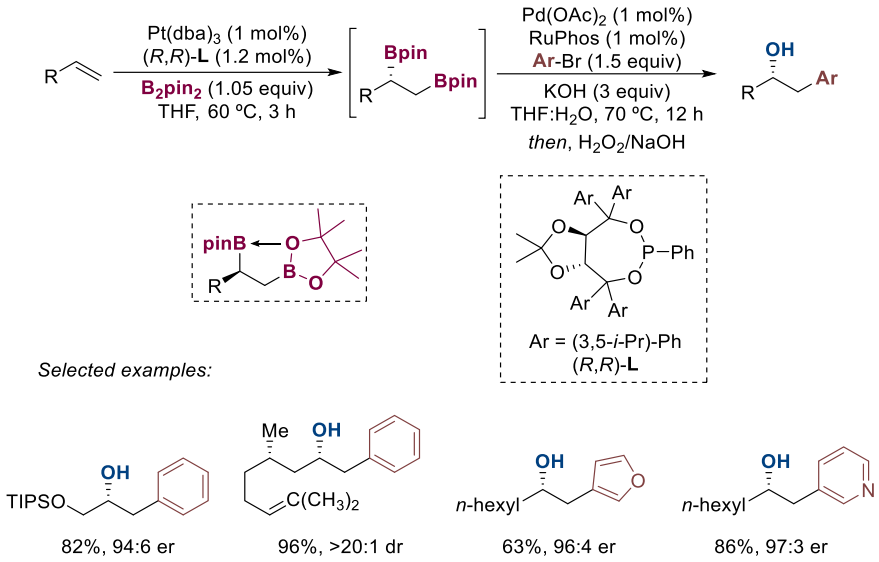


Scheme 128. First selective cross-coupling of a 1,2- bis(pinacol boronate).

In an elegant approach, Morken group, reported in 2014 the asymmetric synthesis of wide array of molecules from terminal alkenes by cascades of diboration and cross-coupling.[198] This methodology provides a powerful strategy for enantioselective carbohydroxylation, carbo-amination and bisalkylation of terminal alkenes. They proposed that the function of the secondary boron atom might be to act as a Lewis acid, coordinating to the pinacolato oxygen of the neighboring boron center, thereby enhancing their Lewis acidity and therefore their reactivity (Scheme 129).

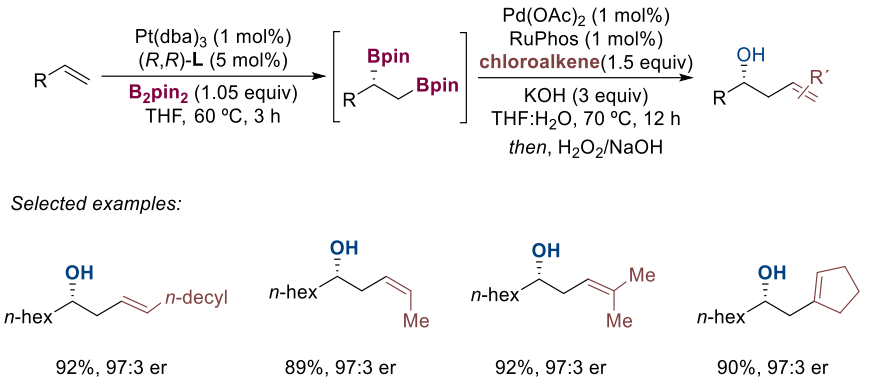
Several olefins were successfully engaged in the tandem transformation affording the products in good yield and with high enantioselectivity. Importantly, substrates containing stereocenters provide the products with excellent diastereomeric ratio (Scheme 129).

[198] Mlynarski, S. N.; Schuster, C. H.; Morken, J. P. *Nature* **2014**, *505*, 386–390.



Scheme 129. Tandem diboration/cross-coupling of terminal alkenes.

Additionally, the cascade reaction occurred efficiently with vinyl chlorides to afford homoallylic alcohols after oxidative work-up.[198] The products were obtained in excellent yields and with high enantiomeric ratios. Moreover, since the olefin stereochemistry is retained during the Suzuki cross-coupling reaction, homoallylic alcohols bearing configurationally defined trisubstituted and *cis*- and *trans*-disubstituted alkenes were prepared (**Scheme 130**).

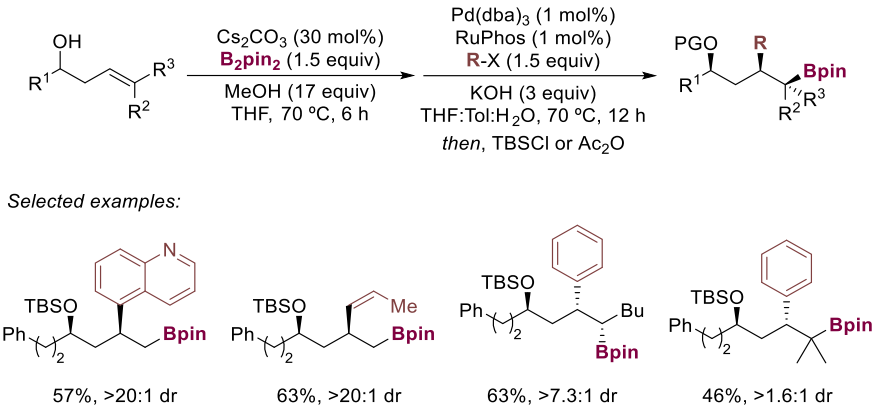


Scheme 130. Tandem diboration/cross-coupling with chloroalkenes.

One year later, the same research group reported a complementary approach to selectively functionalize the secondary boronic ester of vicinal diboron compounds incorporating a hydroxyl moiety as directing group.[199] The hydroxyl-directed transmetalation can merge seamlessly with the previously reported hydroxyl-directed metal-free diboration[189] and allows for stereoselective and site-selective functionalization of homoallylic alcohols. Sequential directed metal-free-diboration/cross-coupling, followed by protection of the directing hydroxy group, furnishes γ-oxygenated boronates from a wide range of substrates. Importantly, the reaction works with terminal alkenes, internal olefins, and trisubstituted alkenes. While the terminal and internal olefins furnish 1,3-*syn* relative stereochemistry, the trisubstituted alkenes furnishes modest 1,3-*anti* induction, these results are in line with the observed in the directed diboration reactions (**Scheme 131**). Finally, they demonstrate the utility of

[199] Blaisdell, T. P.; Morken, J. P. *J. Am. Chem. Soc.* **2015**, *137*, 8712–8715.

the directed cross-coupling by the synthesis of different biologically active compounds.



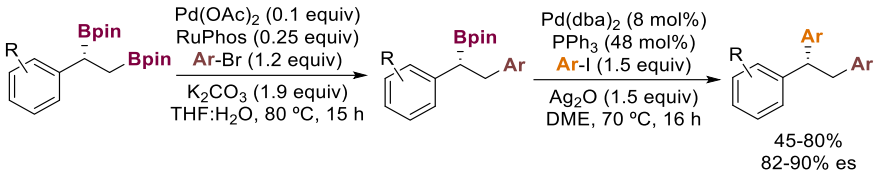
Scheme 131. Tandem directed metal-free-diboration/directed cross-coupling.

In 2016, Crudden reported the orthogonal coupling of benzyl and non-benzylic 1,2-diboronates.[200] The primary C–B bond could be selectively functionalized with different aryl bromides including electron-rich, electron-poor and π-extended substrates. For the next step of the sequence, the benzylic C–B bond was coupled using the previously described silver oxide-promoted conditions reported by the same research group.[201] Again, electron-rich, electron-poor, π-extended and hetero-aromatic aryl iodides were well tolerated as coupling partners for the

[200] Crudden, C. M.; Ziebenhaus, C.; Rygus, J. P. G.; Ghozati, K.; Unsworth, P. J.; Nambo, M.; Voth, S.; Hutchinson, M.; Laberge, V. S.; Maekawa, Y.; Imao, D. *Nat. Commun.* **2016**, *7*, 11065.

[201] Imao, D., Glasspoole, B. W., Laberge, V. S. & Crudden, C. M. *J. Am. Chem. Soc.* **2009**, *131*, 5024–5025.

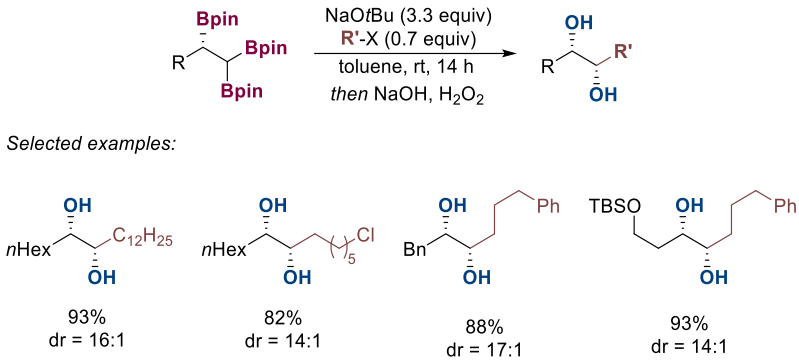
secondary C–B bond. The 1,1´,2-triarylated products were obtained with up to 92% enantiospecificity (Scheme 132).



Scheme 132. Chemoselective cross-coupling reaction of chiral 1,2-diboronic esters.

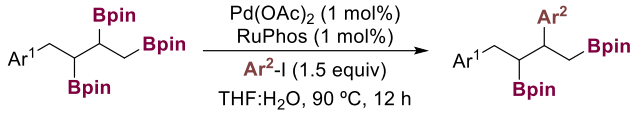
Morken reported in 2014 the enantioselective diboration of vinyl boronates to obtain optically active tris(boronates).[202] Subsequent deborylative alkylation using NaO*t*Bu in toluene provide access to a wide array of 1,2-diols, after oxidative work-up, in a diastereoselective fashion, being the *syn* isomer the predominant product in all cases. The method works efficiently with different primary and secondary electrophiles yielding the products in high yields and diastereomeric ratios (Scheme 133).

[202] Coombs, J. R.; Zhang, L.; Morken, J. P. *J. Am. Chem. Soc.* **2014**, *136*, 16140–16143.



Scheme 133. Deborylative alkylation of chiral 1,1,2-tris(boronates).

Fernández and co-workers reported the straightforward cross-coupling reaction of 1,2,3-vicinal triborated species with aryl iodides (**Scheme 134**). They observed that the internal C–B bond reacted selectively to form a new C–C bond.[203] The authors proposed that the origin of the unexpected chemoselectivity could be due to a plausible double assistance of the two vicinal boryl moieties increasing the Lewis acidity of the internal boronic ester.

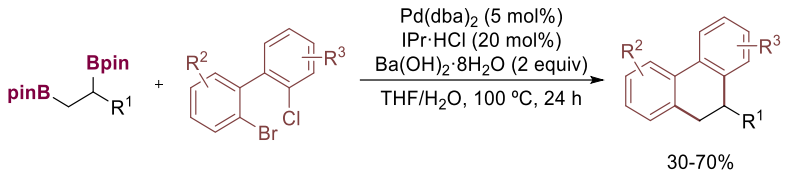


Scheme 134. Selective cross-coupling of 1,2,3-triborated products.

Very recently, Morandi and co-workers reported a cascade Suzuki–Miyaura cross-coupling of 1,2-bisboronic pinacol esters with 2,2´-dihalo

[203] Davenportab, E.; Fernández, E. *Chem. Commun.* **2018**, *54*, 10104–10107.

1,1´-biaryls to afford 9,10-dihydrophenanthrenes.[204] Using biaryls with unsymmetrical substitution-pattern full site-selectivity was observed. Furthermore, this cross-coupling of an alkyl 1,2-bisboronic pinacol ester proceeds through the challenging coupling of a secondary boronate with complete stereoretention (Scheme 135).

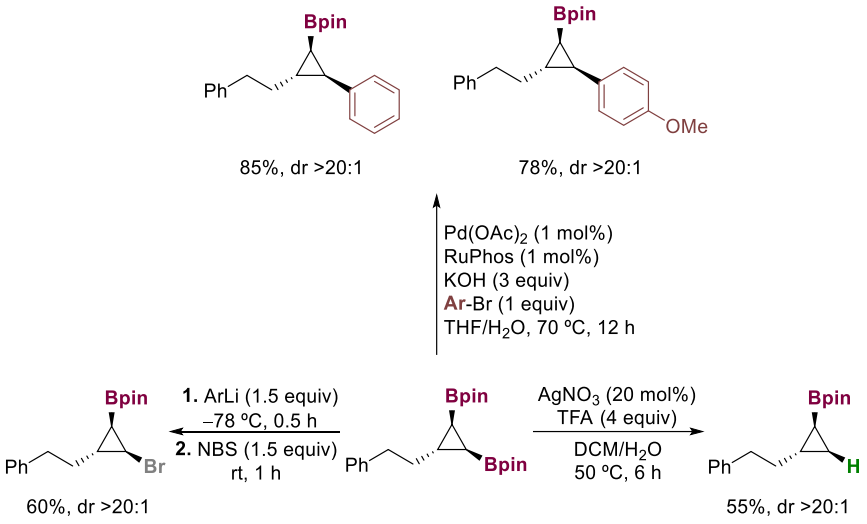


Scheme 135. Double Suzuki-Miyaura cross-coupling of 1,2-diboronic esters.

Recently, after the results presented in this doctoral thesis were reported Wu, Marder and co-workers reported some examples of selective functionalizations of cyclopropyl 1,2-bis(boronates).[205] These examples include selective Suzuki-Miyaura cross-coupling, bromination and protodeboration. The products were obtained in good yields and with exquisite selectivity leaving the other boryl moiety intact (Scheme 136).

[204] Willems, S.; Toupalas, G.; Reisenbauerb, J. C.; Morandi, B. *Chem. Commun.* **2021**, *57*, 3909–3912.

[205] Wu, F.-P.; Luo, X.; Radius, U.; Marder, T. B.; Wu, X.-F. *J. Am. Chem. Soc.* **2020**, *142*, 14074–14079.



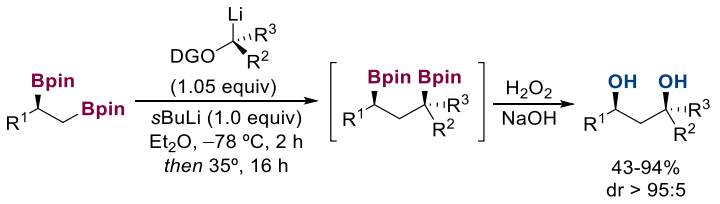
Scheme 136. Selective functionalizations of cyclopropyl bis(boronates).

Along with transition metal-catalyzed transformations, the most common reactions of boronic esters involve the coordination of a Lewis base to the boron atom, followed by a stereospecific 1,2-shift of the boryl moiety. In the literature, we can find a few examples that following this strategy, allow for the selective functionalizations of 1,2-bis(boronic) esters.

In 2016, Aggarwal group reported selective homologation of optically active 1,2-bis(boronic) esters by using enantioenriched primary or secondary lithiated carbamates or benzoates to afford 1,3-bis(boronic esters), which can be oxidized to the corresponding diols with full stereocontrol (**Scheme 137**).[206] They propose that the less hindered

[206] Fawcett, A.; Nitsch, D.; Ali, M.; Bateman, J. M.; Myers, E. L.; Aggarwal, V. K. *Angew. Chem. Int. Ed.* **2016**, *55*, 14663–14667.

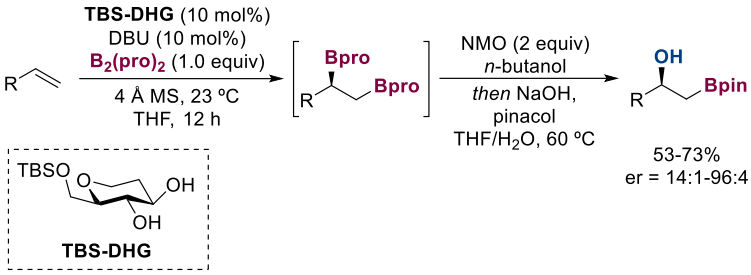
primary boronic ester reacts in preference to the secondary boronic ester, this feature could control the selectivity of the transformation. Moreover, they have found that the selectivity is highly dependent on the nature of the nucleophile.



Scheme 137. Selective homologation of 1,2-bis(boronic) esters.

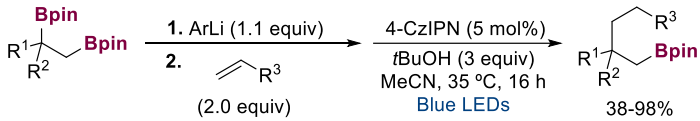
In a recent report Morken and co-workers reported the first site-selective oxidation of 1,2-bis(boronates).[207] They proposed that after coordination of the oxidant, if the 1,2-boronate rearrangement is the rate-limiting step and coordination of the oxidant to boron is reversible, then the more substituted electron-rich carbon may migrate preferentially, providing the selective oxidation at the secondary boryl moiety. A wide number of alkenes were examined in the tandem carbohydrate-catalyzed enantioselective diboration/mono-oxidation sequence providing the products in good yields and enantiomeric ratios (**Scheme 138**).

[207] Yan, L.; Morken, J. P. *Org. Lett.* **2019**, *21*, 3760–3763.



Scheme 138. Selective oxidation of 1,2-bis(boronic) esters.

In 2019, Aggarwal group reported the selective functionalization of the secondary boryl moiety of 1,2-bis(boronic) esters.[208] They found that photoredox catalyzed mono-deboronation generates primary β-boryl radicals that undergo rapid 1,2-boron shift to form thermodynamically favored secondary radicals, allowing for selective functionalization of the more hindered boronic ester. The stereoretentive 1,2-boron shift, enables access to a wide range of functionalized boronic esters with yields up to 98% (**Scheme 139**).



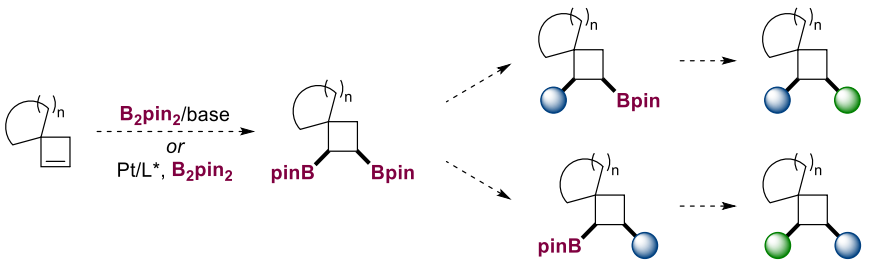
Scheme 139. Selective functionalization of 1,2-bis(boronates) using photoredox catalysis.

[208] Kaiser, D.; Noble, A.; Fasano, V.; Aggarwal, V. K. *J. Am. Chem. Soc.* **2019**, *141*, 14104–14109.

2. Stereoselective Diboration of Spirocyclobutenes

2.1 Objectives

At the beginning of this doctoral thesis there was not any report of diboration of cyclobutenes. We envisioned that spirocyclobutenes could offer a platform to prepare diborylated spirocycles in which the two boryl units could act as orthogonal exit vectors through selective carbon-boron bond functionalization (Scheme 140). To succeed in this approach several difficulties needed to be overcome, such as the control in the diastero- and enantioselectivity of the diboration and chemoselective functionalization of the two boron atoms in the diborylated products. If successful, our approach would provide a unique way to control the directionality of the exit vectors in the spirocyclic framework, allowing access to multiple compounds from a common intermediate.



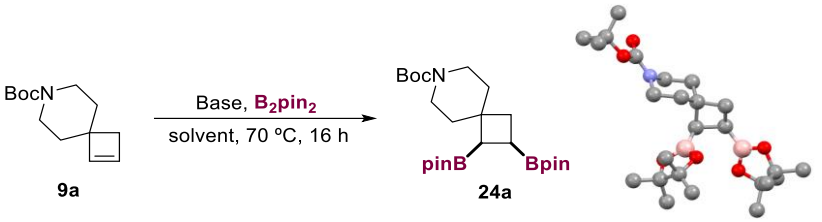
Scheme 140. Objectives of this chapter.

2.2 Transition-Metal-Free Diboration of Spirocyclobutenes

2.2.1 Screening of Conditions

The synthetic route to obtain the starting spirocyclobutenes was described in the previous chapter. Initially, we decided to explore the base-promoted diboration to prepare racemic diborylated spirocycles (**Table 3**). We began our investigation testing the reactivity of spirocyclobutene **9a** under the conditions described for the diboration of cyclohexene (**Table 3**, **entry 1**). Unfortunately, we obtained the diborylated product **24a** in only 29% yield. Switching the solvent to MeOH, the product was obtained in almost the same yield (**Table 3**, **entry 2**). Finally, after some optimization, we found that heating a solution of cyclobutene **9a** with 2 equivalents of B_2pin_2 in MeOH in the presence of 0.6 equivalents of NaOMe, afforded the desired diborylated spirocycle **24a** in 78% isolated yield and as a single *syn* diastereomer (**Table 3**, **entry 3**). The relative stereochemistry was established by single crystal X-ray crystallography.

Table 3. Optimization of the base-promoted diboration of spirocyclobutenes.



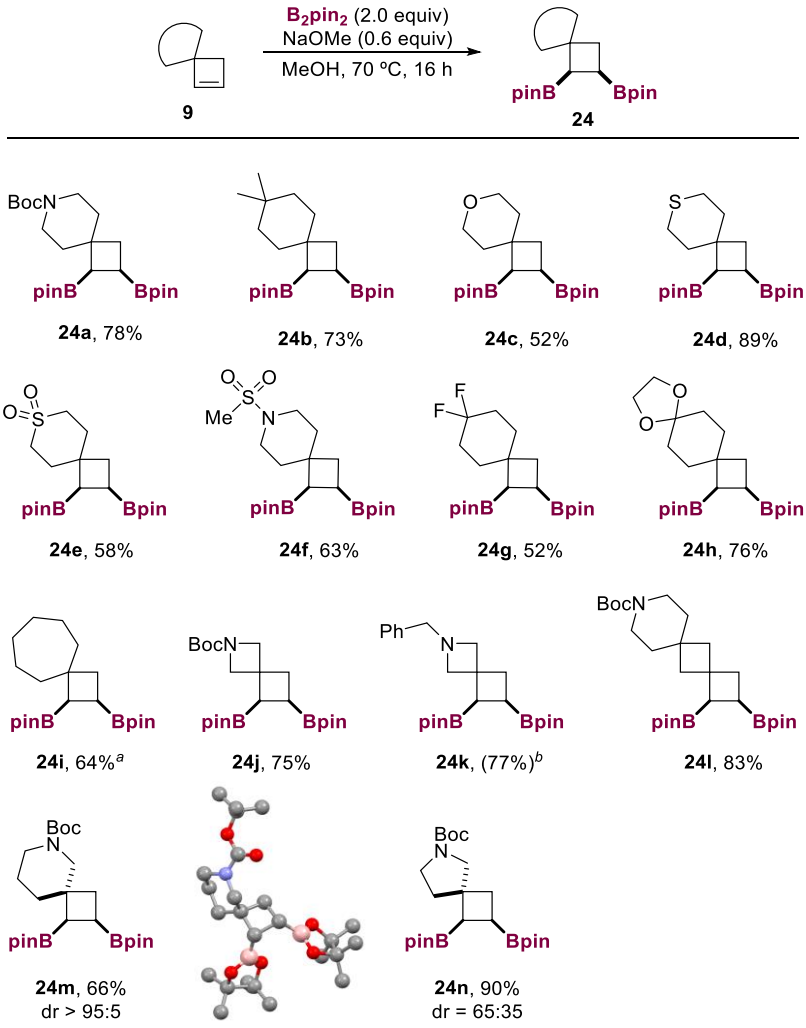
Entry[a]	Solvent	Base	Boron source	Yield[b]
1	THF	NaO*t*Bu (15 mol%)	B_2pin_2 (1.1 equiv)	29%
2	MeOH	NaOMe (0.6 equiv)	B_2pin_2 (1.1 equiv)	31%
3	**MeOH**	**NaOMe (0.6 equiv)**	**B_2pin_2 (2.0 equiv)**	**78%**

[a]Reaction conditions: **9a** (0.2 mmol), solvent (0.2 M). [b]Isolated yield of **24a**.

2.2.2 Reaction Scope

To study the scope of the reaction, we applied the optimized base-promoted diboration conditions to a wide variety of spirocyclobutenes. These conditions allowed us to easily prepare a broad variety of diborylated chiral building blocks in a straightforward manner (**Scheme 141**). We prepared spirocycles containing the spiro[3.5]nonane ring system with different functional groups as connectors: carbon chain (**24b**), ether (**24c**), thioether (**24d**), sulfone (**24e**), sulfonamide (**24f**), difluoromethane (**24g**) and acetal (**24h**). Additionally, the spirocyclobutene with a seven-membered fused ring (**24i**) was obtaining in good yield although was necessary to increase the temperature up to 85 °C to obtain full conversion. Spiro[3.3]heptane ring systems (**24j**, **24k**, **24l**) were successfully synthesized. In the case of compound **24k**, bearing a tertiary amine, we observe decomposition after purification by flash-column chromatography,

therefore, we calculate the yield by ^{1}H NMR using an internal standard. Remarkably, a non-symmetric spirocyclobutene afforded diborylated spirocycle **24m** as a single diastereomer. However, asymmetric spirocycle **9n**, bearing a five membered ring afford the product with excellent yield but as a mixture of diastereomers (**24n**).

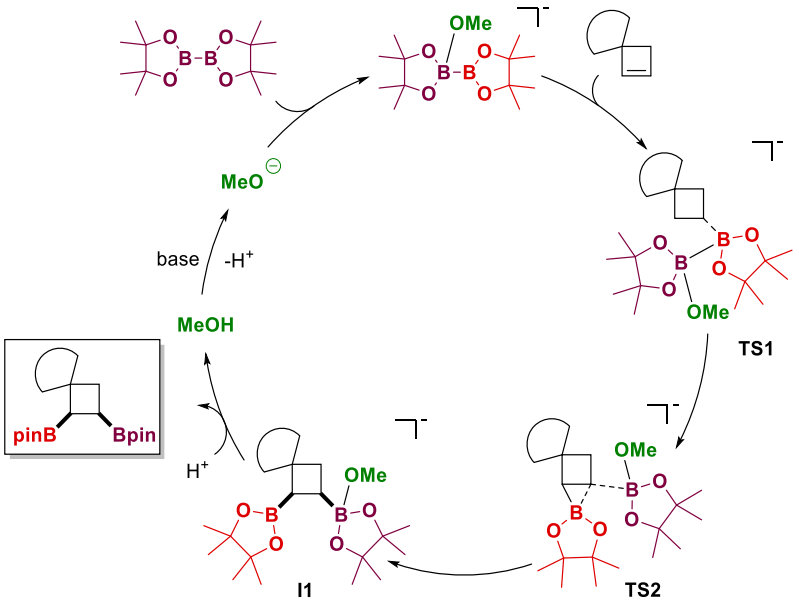


[*a*] T = 85 °C. [*b*] Yield calculated by ^{1}H NMR due to instability of **24k**.

Scheme 141. Scope of the base-promoted diboration of spirocyclobutenes.

2.2.3 Proposed Reaction Mechanism

Based on the calculations carried out by Fernández group we propose the following catalytic cycle. Upon activation of the diboron reagent, the sp^2 boryl moiety interacts with the less hindered carbon atom of the double bond while the B–B bond weakens, and the negative charge density increases on the other carbon of the olefin that is prone to attack the close electrophilic boron atom causing the B–B bond cleavage. Finally, protonation affords the desired product and regenerates the catalytic cycle (Scheme 142). Moreover, additional DFT calculation are needed to understand why in the case of spirocyclobutenes we need two equivalents of the diboron source to obtain full conversion in the diboration process.



Scheme 142. Proposed catalytic cycle for the transition metal-free diboration of spirocyclobutenes.

2.3 Pt-Catalyzed Enantioselective Diboration of Spirocyclobutenes

Then, we turned our efforts to the development of an enantioselective diboration approach of spirocyclobutenes that would provide access to enantioenriched spirocyclic building blocks. To achieve this goal, we turned our attention to the use of platinum complexes. The Pt-catalyzed enantioselective 1,2-diboration of alkenes has been only reported for terminal olefins. It has been shown that disubstituted alkenes prevent the diboration. Additionally, this lack of reactivity has been observed even in strained alkenes such as norbornene.[181]

2.3.1 Screening of Conditions

We chose spirocyclobutene **9a** as a model substrate and taddol-derived phosphoramidites and phosphonites as ligands (**Figure 11**), due to their good reactivity in the previous reported diboration of terminal alkenes.

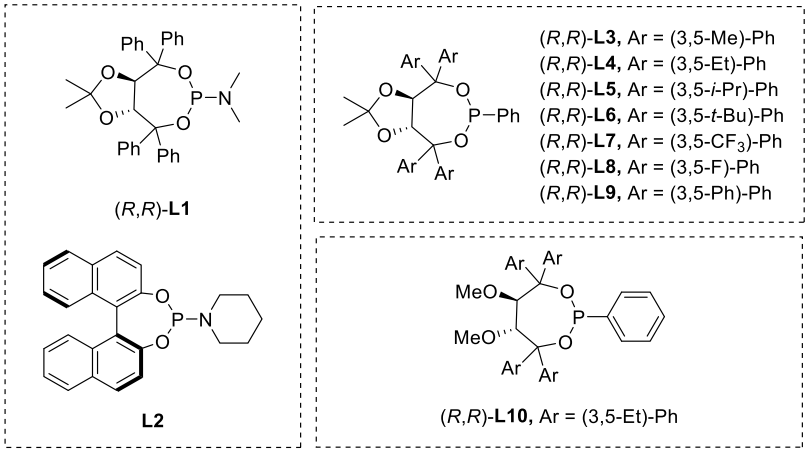
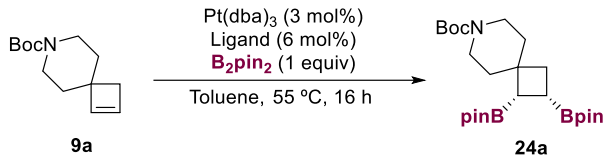


Figure 11. List of tested chiral phosphoramidites and phosphonites ligands.

Phosphoramidite (*R*,*R*)-**L1** provided the desired compound with moderate yield and low enantiomeric ratio. Phosphoramidite **L2**, bearing a cyclic amine, demonstrated to be unreactive in this transformation and only starting material was recovered (**Table 4**, **entries 1 and 2**). Switching to phophonite (*R*,*R*)-**L3** improved the yield and the enantioselectivity (**Table 4**, **entry 3**). With this result we decide to explore the influence of the substituents on the aromatic rings of the chiral phosphonite ligands. Changing the methyl group for ethyl substituents (*R*,*R*)-**L4**, we observed an improvement in the asymmetric induction (**Table 4**, **entry 4**). Phosphonite (*R*,*R*)-**L5**, bearing isopropyl substituents in the aromatic ring (*R*,*R*)-**L5** afforded the diborylated product with the same enantiomeric ratio, although in a lower yield (**Table 4**, **entry 5**). However, a ligand with bulkier substituent (*t*Bu, (*R*,*R*)-**L6**)) decreased the enantiomeric ratio (**Table 4**, **entry 6**). Phosphonite ligand with -CF_3 substituents (*R*,*R*)-**L7** afforded the product as a 1:1 mixture of enantiomers (**Table 4**, **entry 7**) and switching to fluorine atoms (*R*,*R*)-**L8** also resulted in poorer results (**Table 4**, **entry 8**). Finally, the incorporation of phenyl substituents on the ligand yielded the product with a slightly diminished enantioselectivity (**Table 4**, **entry 9**). With the best substituent on the aromatic ring, we decide to change the diol backbone, however, ligand (*R*,*R*)-**L10** showed a lower asymmetric induction (**Table 4**, **entry 9**).

Table 4. Ligand Optimization for the Pt-Catalyzed Enantioselective Diboration.



9a **24a**

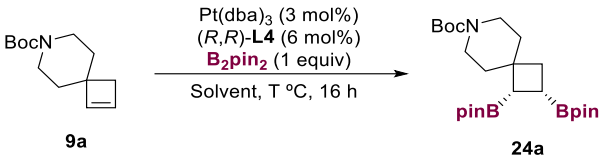
Entry[a]	Ligand	er	Yield[b]
1	(*R*,*R*)-**L1**	60:40	61%
2	(*R*,*R*)-**L2**	-	-
3	(*R*,*R*)-**L3**	74:26	88%
4	(*R*,*R*)-**L4**	**88:12**	**94%**
5	(*R*,*R*)-**L5**	88:12	74%
6	(*R*,*R*)-**L6**	80:20	82%
7	(*R*,*R*)-**L7**	50:50	75%
8	(*R*,*R*)-**L8**	66:34	90%
9	(*R*,*R*)-**L9**	85:15	88%
10	(*R*,*R*)-**L10**	70:30	90%

[a]Reaction conditions: **9a** (0.1 mmol), B_2pin_2 (0.1 mmol), $Pt(dba)_3$ (3 mol%), ligand (6 mol%). [b]Isolated yield.

Once we had the optimal ligand, we decided to study the influence of other reaction parameters. However, we could not improve the result obtained with the previously mentioned reaction conditions. We observe that the yield dropped down at lower or higher temperatures (**Table 5**, **entries 1-2**) or concentrations (**Table 5, entries 3-4**) affording the products with similar enantiomeric ratios. Additionally, other solvents were tested (**Table 5**, **entries 5-8**), but none of them improved the results obtained with toluene. Finally, we also studied the effect of the catalyst loading. Using 1

mol% of the catalytic system Pt/L no product was observed and only starting material was recovered (**Table 5**, **entry 9**). Decreasing the amount of ligand to 3 mol% decreased the product yield and did not improve the asymmetric induction (**Table 5**, **entry 10**).

Table 5. Temperature, concentration, solvent and catalyst loading optimization.



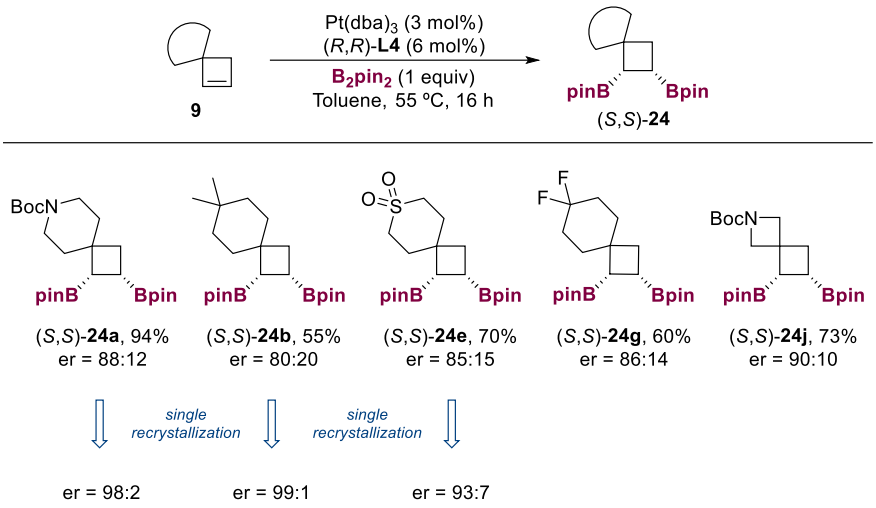
9a **24a**

Entry[a]	Solvent	[Conc]	T (°C)	er	Yield[b]
1	Toluene	0.1 M	25	87:13	31%
2	Toluene	0.1 M	80	86:14	56%
3	Toluene	0.5 M	25	87:13	58%
4	Toluene	1.0 M	25	87:13	51%
5	o-xylene	0.1 M	25	86:14	90%
6	THF	0.1 M	25	82:18	80%
7	1,4-dioxane	0.1 M	25	82:18	75%
8	octane	0.1 M	25	59:41	58%
9[c]	Toluene	0.1 M	25	-	-
10[d]	Toluene	0.1 M	25	86:14	42%

[a]*Reaction conditions*: **9a** (0.1 mmol), B_2pin_2 (0.1 mmol), $Pt(dba)_3$ (3 mol%), ligand (6 mol%). [b]Isolated yield. [c]$Pt(dba)_3$ (1 mol%), **L4** (1 mol%). [d]$Pt(dba)_3$ (3 mol%), **L4** (3 mol%).

2.3.2 Scope of the Enantioselective Pt-Catalyzed Diboration

Compounds (*S*,*S*)-**24b**, (*S*,*S*)-**24e**, (*S*,*S*)-**24g** and (*S*,*S*)-**24j** were prepared as representative examples of spirocycles with different ring sizes and different connectors. The obtained enantiomeric ratios are comparable to those observed for compound (*S*,*S*)-**24a**. Finally, we were pleased to find that a single recrystallization could increase the enantiomeric ratios up to 99:1 (**Scheme 143**).



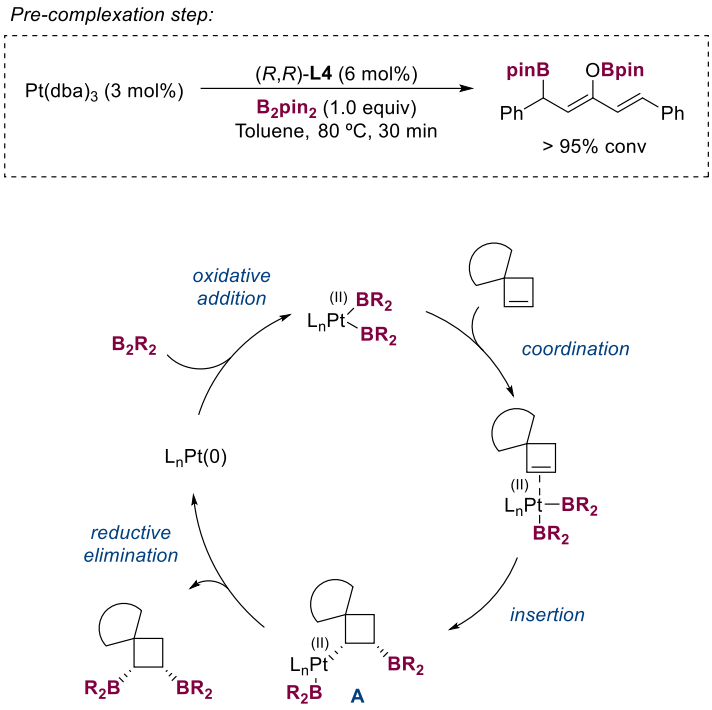
Scheme 143. Enantioselective diboration of spirocyclobutenes.

2.3.2 Plausible Reaction Mechanism

Based on reported studies,[181] a plausible reaction mechanism is depicted in Scheme 144. In the procedure employed for the diboration of spirocyclobutenes, a catalyst "activation step" is needed heating the $Pt(dba)_3$ catalyst with the phosphonite ligand in the presence of B_2pin_2 at 80 °C for 30 min. The pre-complexation at this elevated temperature, is needed to obtain good reactivity and high levels of enantioselectivity. In this step the borylation of the dba occurs and the resulting borylated product would bind less effectively to Pt(0) than dba. The conjugate borylation of dba provides a mechanism for removing the coordinating enone from the platinum and ensures a correct coordination of the metal with the chiral phosphonite ligand (Scheme 144).

After pre-complexation, the catalytic cycle starts with the oxidative addition of the diboron source to Pt(0). Coordination of this complex, followed by insertion of the cyclobutene into the Pt–B bond affords intermediate A. Additional DFT calculations are necessary to understand the regioselectivity in the insertion step, therefore, two possible regioisomers can be formed. Finally, reductive elimination affords the desired product and regenerates the Pt(0) catalyst.

Probably the regioselectivity in the insertion step could be related with the difficulty to improve the enantiomeric ratio in the diborylated products since the enantioselectivity in the insertion step could be different in the two possible regioisomers.



Scheme 144. Proposed reaction mechanism for the Pt-catalyzed diboration of spirocyclobutenes.

2.4 Selective functionalization of the C–B bonds

With an efficient protocol to prepare diborylated spirocycles **24**, we were interested on the possibility of performing chemo- and stereospecific transformations on the two C–B bonds. One of our goals was to use them in selective Suzuki-Miyaura cross-coupling reactions, as it would provide a powerful tool to introduce the spirocyclic scaffold into existing libraries of compounds. However, we had to face the fact that cyclobutylboronates with a pinacol moiety are known to be unreactive compounds in Pd-catalyzed Suzuki-Miyaura cross-coupling reactions. Except for isolated examples, they need to be transformed into trifluoroborates salts or boronic acids[209] to be used as nucleophiles in such processes.[210]

2.4.1 Selective Suzuki-Miyaura Cross-Coupling

Inspired by the pioneering work of Morken with 1,2-terminal diboronic pinacol esters,[198] we envisioned that a second boronic ester in an adjacent carbon of the cyclobutane could act as a Lewis acid coordinating to the oxygen atom of the neighboring pinacolato. This coordination, could

[209] *Selected examples*: **(a)** Burke, M. D.; Wang, P.; Crouch, I. Cross-coupling of unactivated secondary boronic acids. U.S. Patent WO 2015066612, November 3, 2014. **(b)** Li, C.; Xiao, G.; Zhao, Q.; Liu, H.; Wang, T.; Tang, W. *Org. Chem. Front.* **2014**, 1, 225–229.

[210] **(a)** Molander, G. A.; Gorminsky, P. E. *J. Org. Chem.* **2008**, *73*, 7481–7485. **(b)** Li, L.; Zhao, S.; Joshi-Pangu, A.; Diane, M.; Biscoe, M. R. *J. Am. Chem. Soc.* **2014**, *136*, 14027–14030.

increase the Lewis acidity of the "external" boron atom, facilitating the transmetalation step.

It should be noted that all previous examples in the literature describing selective cross-coupling of 1,2-diboronic esters are described with terminal acyclic substrates and distinguish between a primary boronic ester and a secondary boryl unit.[189,195,198,200] Except for examples that require the use of directing groups,[199,203] there are no reports of Suzuki-Miyaura cross-coupling reactions discriminating between two secondary boronic esters.

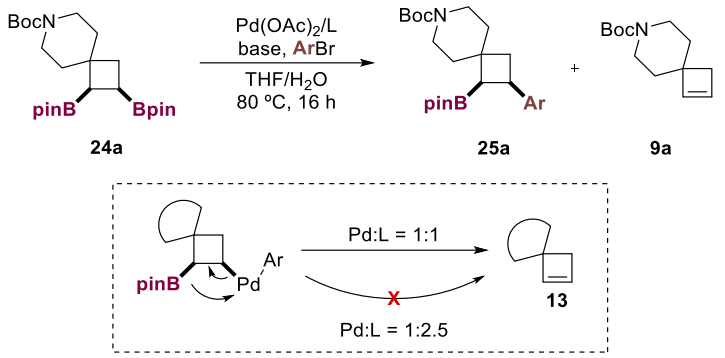
Screening of Conditions

To test this hypothesis, we chose spirocycle **24a** as a model substrate and PhBr as electrophile, in the presence of $Pd(OAc)_2$ and an electron-rich monodentate phosphine (**Table 6**). Disappointingly, using a 1 mol% of $Pd(OAc)_2$ and RuPhos as ligand in a 1:1 ratio, 9% of cyclobutene **9a** was obtained along with unreacted starting material (**entry 1**). Increasing the amount of palladium and ligand to 5 mol% only increased the yield of cyclobutene **9a** (**entry 2**). We reasoned that **9a** could be formed through an unusual β-boryl elimination process,[211] favored by the rigid *syn* disposition of the palladium and the adjacent boron atom after transmetalation. After some experimentation, we found that increasing the ligand:palladium ratio from 1:1 to 2.5:1 was key to suppress the β-boryl elimination affording the monoarylated product **25** in good yield as a single regio- and stereoisomer

[211] **(a)** Miyaura, N.; Suzuki, A. *J. Organomet. Chem.* **1981**, *213*, C53–C56. **(b)** Lam, K. C.; Lin, Z.; Marder, T. B. *Organometallics* **2007**, *26*, 3149–3156.

(**entry 4**). Other electron-rich monodentate phosphines (**entries 5-7**) or a different base (**entry 8**) provided inferior results. Notably, the amount of aryl bromide could be reduced to 1.2 equivalents (**entry 9**).

Table 6. Optimization of the selective Suzuki-Miyaura cross-coupling.



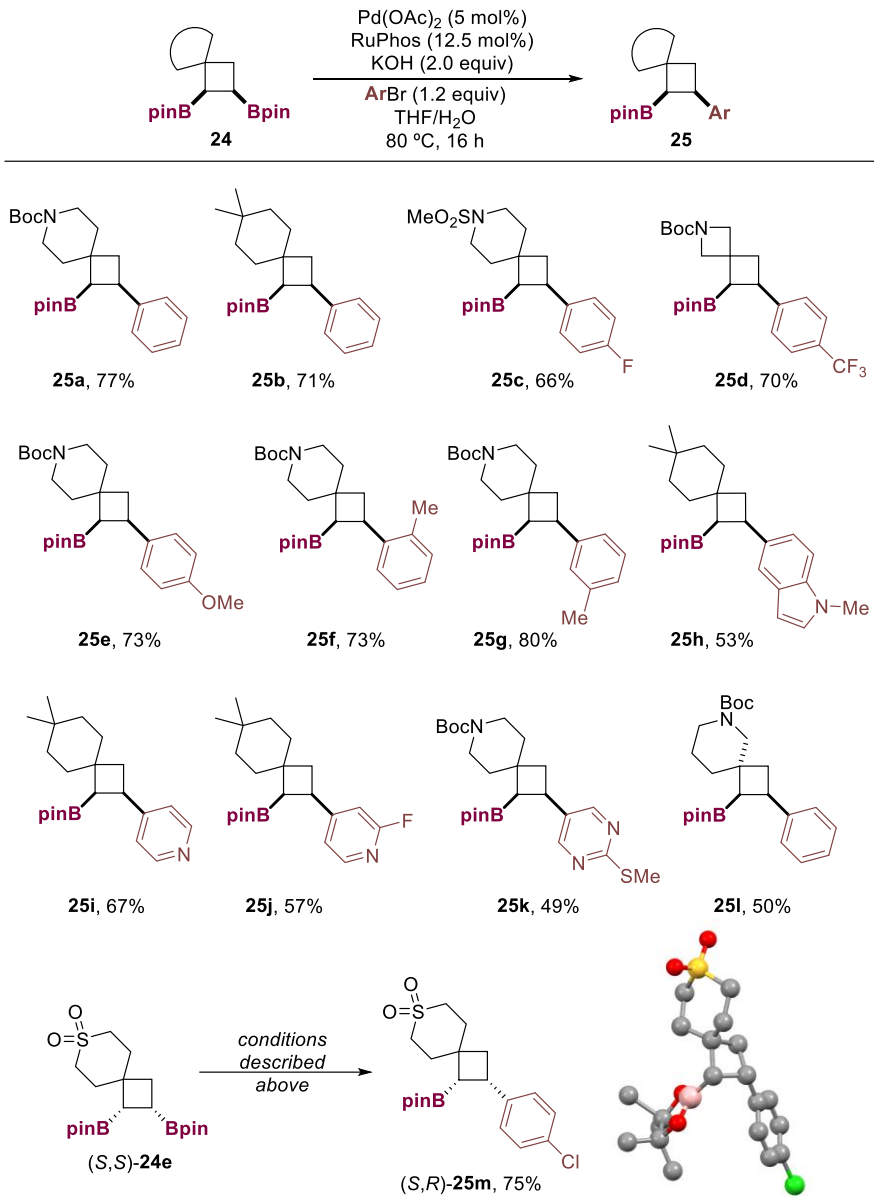
Entry	$Pd(OAc)_2$	L (mol%)	Base	Yield 24a[c]	Yield 9a
1[a]	1 mol%	RuPhos 1%	KOH	-	9%[c]
2[a]	5 mol%	RuPhos 5%	KOH	-	45%[c]
3[a]	5 mol%	RuPhos 10%	KOH	59%	4%[d]
4[a]	**5 mol%**	**RuPhos 12.5%**	**KOH**	**66%**	**-**
5[a]	5 mol%	SPhos 12.5%	KOH	65%	6%[d]
6[a]	5mol%	cataCXium 12.5%	KOH	30%	1%[d]
7[a]	5 mol%	XPhos 12.5%	KOH	52%	7%[d]
8[b]	5 mol%	RuPhos 12.5%	K_2CO_3	32%	-
9[b]	5 mol%	RuPhos 12.5%	KOH	77 [e]	-

[a]*Reaction conditions*: **24a** (0.1 mmol), $Pd(OAc)_2$, Ligand, KOH (2.0 equiv), ArBr (1.5 equiv), THF:H_2O (10:1, 0.1 M), 80 °C, 16 h. [b]ArBr (1.2 equiv). [c]Isolated yields. [d]Yield calculated by ^1H NMR. [e]Reaction scale: 1 mmol of **24a**.

Scope of the Selective Suzuki-Miyaura Cross-Coupling

With the optimal conditions in hand, we next explored the scope of the cross-coupling reaction. We observed that our approach worked with exquisite chemoselectivity with different spiro ring systems (**Scheme 145**). Additionally, the scope in the aryl electrophile was very broad including aryl rings with electron withdrawing (**25c, 25d, 25m**) and electron donating groups (**25e**), ortho- (**25f**) and meta-substituted rings (**25g**). Additionally, challenging nitrogen-containing heterocycles afford the desired coupling in moderate to good yields (**25h-25k**). Asymmetric diboryl-spirocycle **24l** afford the desired coupling **25l** without losing the regioselectivity.

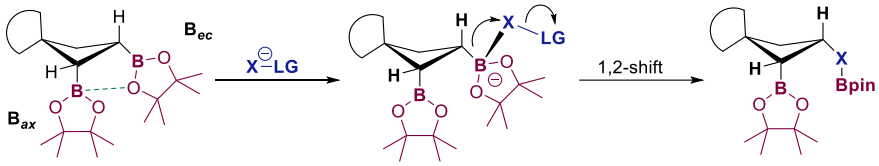
The *syn* relative stereochemistry between the aryl ring and the boryl moiety in the products suggests that the transmetalation step takes place with retention of the configuration. The relative *syn* stereochemistry of the coupling products was assigned by single X-ray crystallography of compound (*S*,*R*)-**25m** (**Scheme 145**). Moreover, with this example we determined the absolute configuration of the diborylated products obtained with the platinum catalyzed approach.



Scheme 145. Selective cross-coupling of spirocyclobutyl-diboronates.

2.4.2 Selective Oxidation of Diboryl-Spirocyclobutanes

Along with transition-metal-catalyzed transformations, the most common reactions of boronic esters involve the coordination of a Lewis base to the boron atom, followed by a stereospecific 1,2-shift of the boryl moiety. The favoured conformer in **24** should place the external boron atom in a pseudo-equatorial position (B_{ec}) in a puckered conformation to avoid 1,3-diaxial interactions with the substituents of the spiro carbon (Scheme 146). We hypothesized that if the coordination of the Lewis base to the boron atoms was rate-limiting, steric effects could favour coordination of B_{ec} over the axial (B_{ax}). Additionally, coordination of the oxygen of the pinacolato in B_{ec} with B_{ax}, could increase the Lewis acidity of B_{ec}.

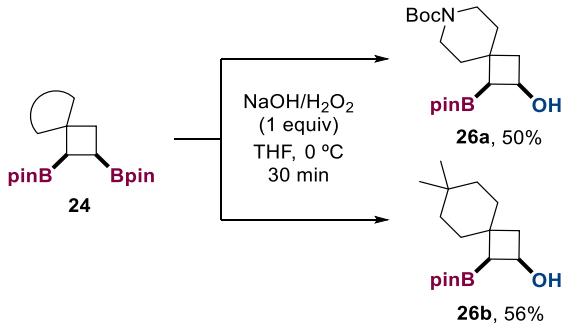


Scheme 146. Selective functionalization of the external boron atom.

Following this hypothesis and using 1 equivalent of the oxidant at room temperature for 1 hour a complex mixture of products was obtained including remaining starting material.

Finally, after some optimization, we found that it is possible to oxidize selectively the boronic ester that is in equatorial position controlling the amount of oxidant (H_2O_2, 1 equiv), the temperature (0 °C) and the reaction

time (only 30 min). Alcohols **26a** and **26b** were obtained in moderate yields (**Scheme 147**).



Scheme 147. Selective oxidation of diboryl-spirocyclobutanes.

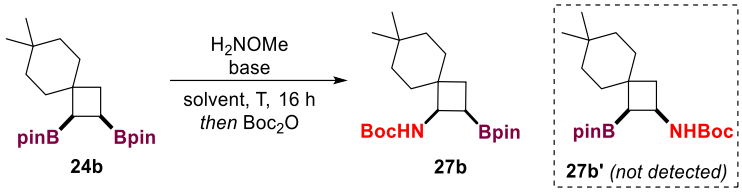
2.4.3 Selective Amination of Diboryl-Spirocyclobutanes

Following the same strategy, we wondered if it would be possible to develop a selective amination of the diboryl spirocyclobutanes.

First, we examined the optimal conditions described in the pioneering work of Morken,[212] using *n*BuLi as base in the presence of methoxyamine. Disappointingly, a complex mixture of products was obtained (**Table 7**, **entry 1**). Surprisingly, switching to KO*t*Bu as base,[213] we observe that selective amination was achieved at B_{ax} instead at B_{ec} (**Table 7**, **entry 2**). We tried to increase the yield increasing the amount of the electrophilic amine (**Table 7**, **entry 3**) or the temperature (**Table 7**, **entry 4**), however, the yield of the selective amination dropped down in both cases.

[212] Mlynarski, S. N.; Karns, A. S.; Morken, J. P. *J. Am. Chem. Soc.* **2012**, *134*, 16449−16451
[213] Edelstein, E. K.; Grote, A. C.; Palkowitz, M. D.; Morken, J. P. *Synlett* **2018**, *29*, 1749−1752.

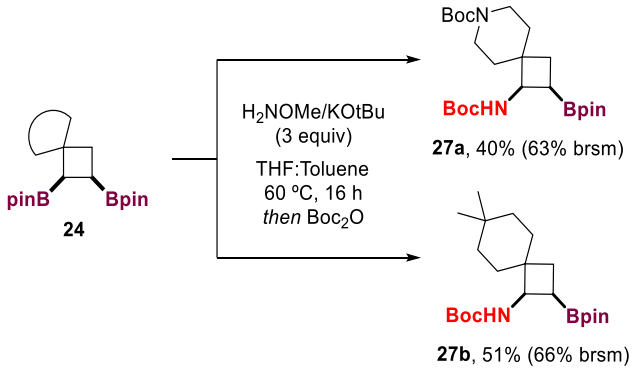
Table 7. Optimization of the selective amination.



Entry[a]	Base	Amine	Solvent	T	Yield 27b[b]
1	*n*BuLi (3 equiv)	$MeONH_2$ (3 equiv)	THF	60 °C	-
2	**KO*t*Bu (3 equiv)**	**$MeONH_2$ (3 equiv)**	**Tol:THF**	**60 °C**	**51**
3	KO*t*Bu (4 equiv)	$MeONH_2$ (4 equiv)	Tol:THF	60 °C	41
4	KO*t*Bu (3 equiv)	$MeONH_2$ (3 equiv)	Tol:THF	80 °C	25

[a]Reaction conditions: **24b** (0.2 mmol), solvent (0.2 M). [b]Isolated yields of **27b**.

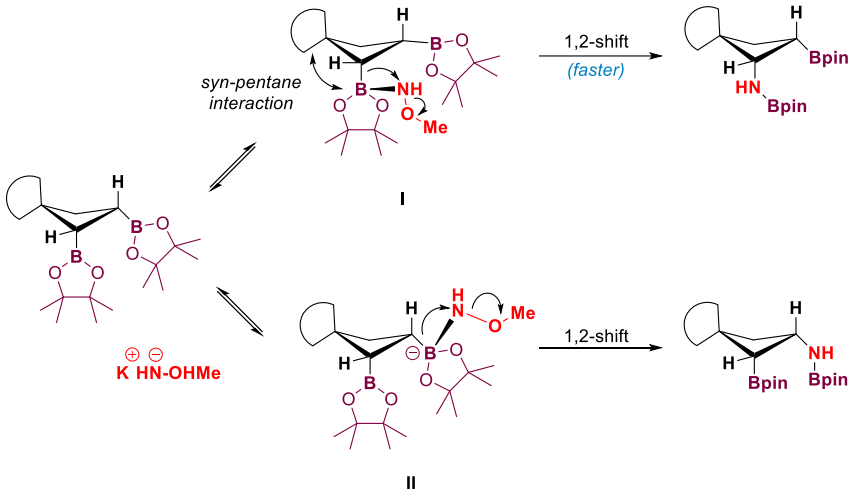
With the optimal conditions in hand, compounds **27a** and **27b** were obtained as single regioisomers (**Scheme 148**) in a moderate yield. The structure of the obtained regioisomer was assigned using 2D-NMR experiments (COSY and HMBC). These experiments are more detailed in the supplementary section of this chapter. To the best of our knowledge this is the first example of selective mono-amination of a diboronic ester.



Scheme 148. Selective amination of diboryl spirocyclobutanes.

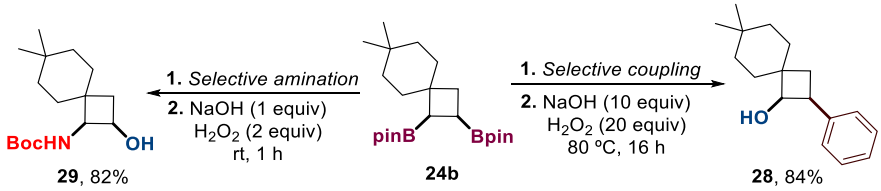
A plausible explanation for the selective amination could imply a reversible coordination of the nucleophilic nitrogen to the boron atoms in **24** under the reaction conditions to form boronate complexes **I** and **II** (**Scheme 149**). Boronate complex **I** presents a destabilizing interaction between the equatorial substituent of the spiro carbon and the pinacol moiety after sp^3-hybridation of the boron (*syn* pentane type interaction). This interaction is not present in boronate complex **II**. The relief of steric strain[214] in **I** could explain a faster 1,2-shift than in **II**, leading to the selective amination of $\mathbf{B}_{ax}$.

[214] Aggarwal, V. K.; Fang, G. Y.; Ginesta, X.; Howells, D. M.; Zaja, M. *Pure Appl. Chem.* **2006**, *78*, 215–229.



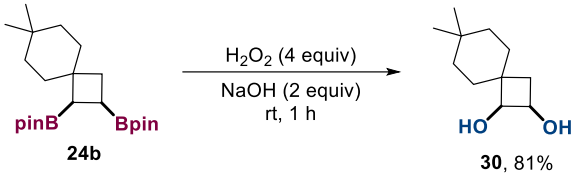
Scheme 149. Possible explanation of the selective amination.

Once we controlled the selective mono-functionalization of diboronates **24**, we designed different difunctionalizations to demonstrate the versatility of the diboryl spirocyclobutanes. Starting from spirocycle **24b**, sequential cross-coupling/oxidation provided spirocyclobutanol **28** as single product in good overall yield. Moreover, amination followed by oxidation of **24b** afforded spirocyclic amino-alcohol **29**. These transformations represent formal diastereoselective hydroxy-arylation and amino-hydroxylation reactions of the cyclobutene (**Scheme 150**).



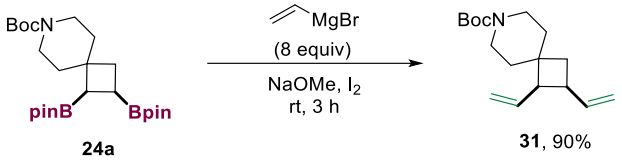
Scheme 150. Difunctionalization of **24b**.

Finally, we also studied the straightforward homo-difunctionalization of diboryl spirocyclobutanes. Double oxidation[130] of **24b** afford spirocyclobutane diol **30** in good after 1 hour (**Scheme 151**).



Scheme 151. Double oxidation of **24b**.

Moreover, double Zweifel olefination, afford compound **31** in high yield, the double bond offers a handle for further derivatization (**Scheme 152**).[215]



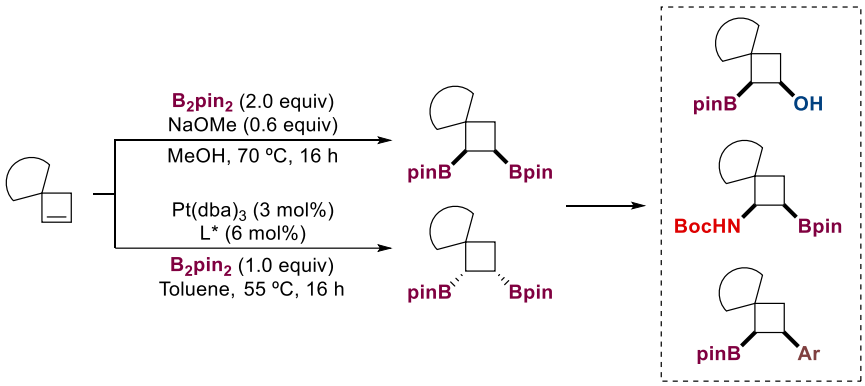
Scheme 152. Double Zweifel olefination of **24a**.

[215] Armstrong, R. J.; Aggarwal, V. K. *Synthesis* **2017**, *49*, 3323–3336.

3.5 Conclusions/Conclusiones

In this chapter, we have studied two approaches for the preparation of chiral spirocycles through the diboration of spirocyclobutenes. First, we have developed a transition-metal-free diboration to prepare spirocycles in a diastereoselective fashion. Later, we developed an asymmetric version to synthetize optically active spirocycles. Using a platinum catalyst and a chiral phosphonite ligand, different spirocycles have been prepared with high levels of enantioselectivity. Moreover, we found that a simple recrystallization could increase the enantiomeric ratio up to 99:1.

Moreover, selective functionalization of the boryl moieties in the products (Suzuki-Miyaura cross-coupling, oxidation, and amination) allows unique control on the directionality and nature of the substituents on the spirocycle framework and provides facile access to a wide variety of novel building blocks from a common intermediate (Scheme 153).

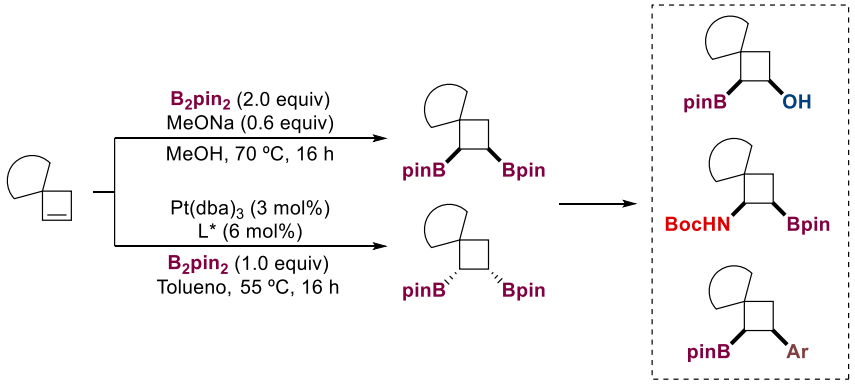


Scheme 153. Diboration and selective functionalization of spirocyclobutenes.

Conclusiones

En este capítulo hemos estudiado dos aproximaciones para la preparación de espirociclos quirales mediante la diborilación de espirociclobutenos. En primer lugar, desarrollamos un procedimiento sin metales (catalizado por una base de Lewis) para preparar los productos de manera diastereoselectiva. Después, nos centramos en el desarrollo de un procedimiento para obtener los productos enantioenriquecidos. Para ello usamos un catalizador de platino y un fosfonito quiral. Además, conseguimos incrementar el exceso enantiomérico a través de una simple recristalización (Esquema 6).

Finalmente, la funcionalización selectiva de los productos nos permitió controlar la naturaleza y la direccionalidad de los sustituyentes del espirociclo, pudiendo sintetizar una gran variedad de compuestos a partir de un mismo intermedio.

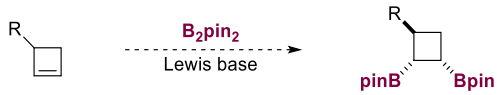


Esquema 6. Diborilación de espirociclobutenos y funcionalización selectiva.

3. Diboration of Monosubstituted Cyclobutenes

3.1 Objectives

With a well-established approach for the transition-metal-free diboration of spirocyclobutenes we decided to explore the reactivity and the stereoselectivity of mono-substituted cyclobutenes. We wondered if the presence of the substituent could provide some steric differentiation to induce stereoselectivity in the products (Scheme 154).

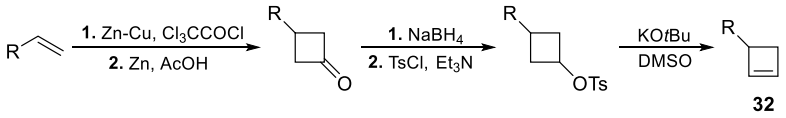


Scheme 154. Objective of this section.

3.2 Synthesis of Monosubstituted Cyclobutenes

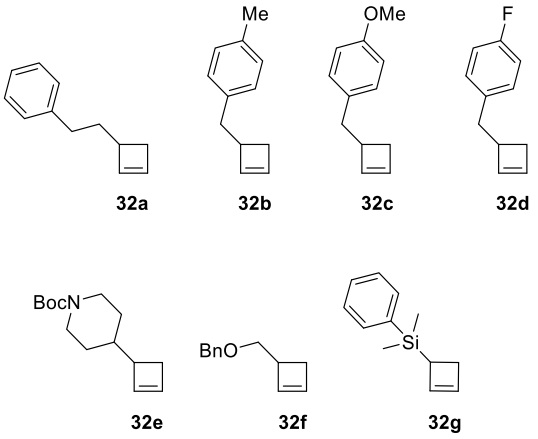
Mono-substituted cyclobutenes can be prepared starting from the corresponding terminal alkene and following the same synthetic route that have been developed for the synthesis of spirocyclobutenes. First, [2 + 2] cycloaddition between the alkene and the *in situ* generated dichloroketene from trichloro acetyl chloride and zinc dust followed by reduction of the chlorine atoms using Zn dust in acetic acid afford the corresponding cyclobutanone. The obtained ketone was reduced and the cyclobutanol was tosylated. Finally, the elimination of the tosyl group was carried out in

anhydrous DMSO in the presence of 3 equivalents of KO*t*Bu to yield the desired cyclobutenes **32** (Scheme 155).



Scheme 155. Synthesis of mono-substituted cyclobutenes.

Following the previously described synthetic sequence different mono-substituted cyclobutenes were prepared (Scheme 156). It should be noted that, in all cases, the starting alkene was commercially available.

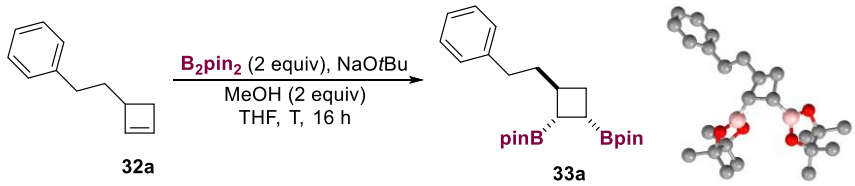


Scheme 156. Synthetized mono-substituted cyclobutenes.

3.3 Screening of Conditions

We began our investigation using cyclobutene **32a** as model substrate. We were disappointed to find that stirring a solution of **32a** with 1 equivalent of NaO*t*Bu, with 2 equivalents of B_2pin_2 in the presence of MeOH for 16 hours, only starting material was recovered (**Table 8**, **entry 1**). Moreover, heating the same solution al 50 °C yield the desired product in 70% yield (**Table 8**, **entry 2**). Finally, we observe that the amount of base can be reduced to 0.6 equivalents affording the product in high yield (**Table 8**, **entry 3**) and a single diastereomer as we can verify by X ray structure analysis of **33a**. The *anti-syn* relative configuration was determined by single X-ray structure analysis which showed that the insertion of the boryl moieties occurs in the opposite face of the substituent present in the cyclobutene.

Table 8. Optimization of the metal-free diboration of cyclobutenes.

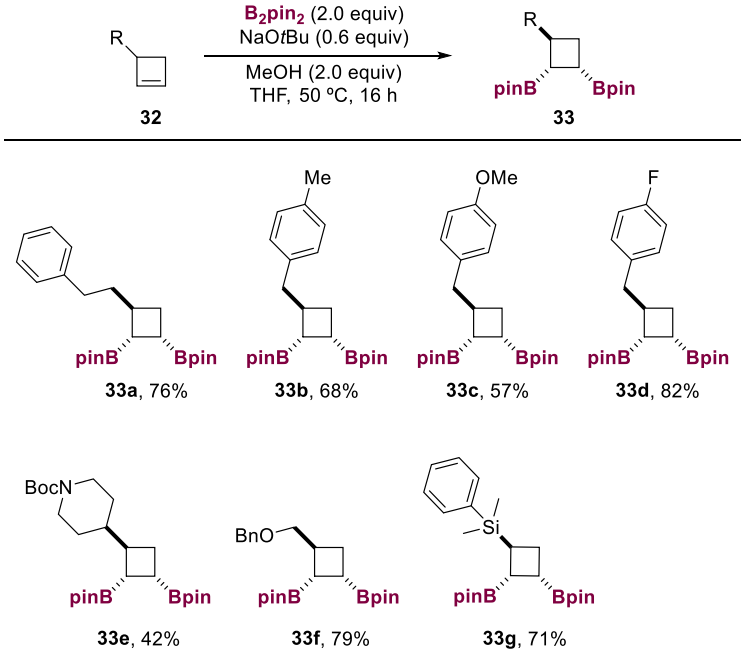


Entry[a]	Base	T	Yield[b]
1	NaO*t*Bu (1 equiv)	rt	-
2	NaO*t*Bu (1 equiv)	50 °C	70%
3	NaO*t*Bu (0.6 equiv)	50 °C	76%

[a]Reaction conditions: **32a** (0.2 mmol), solvent (0.2 M). [b]Isolated yields of **33a**.

3.4 Scope of the Reaction

Next, we applied the optimized metal-free borylation conditions to the previously synthesized cyclobutenes (**Scheme 157**). Compounds bearing different substituents were tolerated under the reaction conditions (**33a-33g**). Aromatic rings with different electron-donating and electron-withdrawing groups (**33b-33d**) afforded the desired diborylated cyclobutanes in good yields. Moreover, piperidine substituted cyclobutene afford the corresponding product (**33e**) in a moderate yield. Other functionalities like an ether (**33f**) or a silyl group (**33g**) were also tolerated under the reaction condition. In all cases, the products were obtained as single diastereomers.



Scheme 157. Scope of the stereoselective diboration of cyclobutenes.

3. Supplementary Data

3.1 General Experimental Details

Tetrahydrofuran, toluene and dichloromethane were purified by passing through a Pure Solv™ column drying system from Innovative Technology, Inc. Diethyl ether was dried using activated 4 Å molecular sieves and stored under argon. DME and MeOH were purchased dry from Acros Organics. For convenience, borylation reactions were set up in a nitrogen filled glove box Inert PURELAB PL-HE-2GB. However, performing the borylation reactions under argon atmosphere using flame-dried glassware with standard vacuum-line techniques lead to similar results in terms of yields, diastereoselectivity and enantioselectivity.

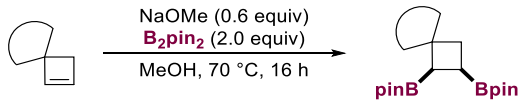
NMR spectra were acquired on a Bruker Avance 300 MHz spectrometer, running at 300, 75, 96, and 282 MHz for ^{1}H, ^{13}C, ^{11}B and, ^{19}F, respectively. Chemical shifts (δ) are reported in ppm relative to residual solvent signals ($CDCl_3$, ^{1}H = 7.26 ppm, ^{13}C = 77.16 ppm or Toluene-d_8, ^{1}H = 2.09 ppm, ^{13}C = 20.40 ppm). For ^{19}F spectra, C_6F_6 is used as internal standard (^{19}F = –164.9 ppm). ^{13}C NMR and ^{19}F 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 F_{254}) and visualized by ultraviolet irradiation and phosphomolybdic acid dip, potassium permanganate dip or cerium ammonium molybdate dip. Flash column chromatography (FC) was

performed 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 HPLC using chiral columns. 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^+) or Bruker maXis IITM ($APCI^+$). Melting points were determined in a StuartTM melting point SMP3 apparatus in open capillary tubes.

$Pt(dba)_3$, **L1**, **L2**, and **L3** were purchased from Strem Chemicals. **L4**,[216] **L5**,[217] **L6**,[218] **L7**,[218] **L8**,[218] **L9**,[219] and **L10**[218] have been synthesized following the reported procedures. Freshly Zn-Cu couple was prepared using the reported procedure and stored under argon atmosphere.[220]

[216] Kliman, L.T.; Mlynarski, S. N.; Morken, J. P. *J. Am. Chem. Soc.* **2009**, *131*, 13210–13211.
[217] Coombs, J.R.; Haeffner, F.; Kliman, L. T.; Morken, J.P. *J. Am. Chem. Soc.* **2013**, *135*, 11222–11231.
[218] Dailler, D.; Rocaboy, R.; Baudoin, O. *Angew. Chem. Int. Ed.* **2017**, *56*, 7218–7222.
[219] Seebach, D.; Hayakawa, M.; Sakaki, J.; Schweizer, W. B. *Tetrahedron* **1993**, *49*, 1711–1724.
[220] Danheiser, R, L.; Savariar, S.; Cha, D.- D. *Organic Synthesis* **1990**, *68*, 32–40.

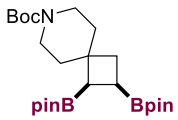
3.2 General Procedure for the Transition-Metal-Free Diboration of Spirocyclobutenes, 24



9 24

An oven-dried vial was charged with sodium methoxide (0.6 equiv) and bis(pinacolato)diboron (2.0 equiv) was sealed with a septum inside a glove box. Then, the vial was placed outside the glove box and connected to an argon-vacuum line, evacuated and backfilled with argon (x3). Anhydrous MeOH (0.5 mL/0.2 mmol) was added to dissolve the mixture. Then, a solution of **9** (1 equiv) in MeOH (0.5 mL/0.2 mmol) was added and the resulting mixture was stirred at 70 °C for 16 h. After cooling to room temperature, the solvent was removed under reduced pressure and H_2O (5 mL/0.2 mmol) and EtOAc were added. The aqueous phase was extracted with EtOAc (3 × 10 mL). The organic layers were combined, dried ($MgSO_4$) and concentrated under reduced pressure. The crude product was purified by flash column chromatography on silica gel or Florisil® to afford **24**.

(1*R**,2*R**)-tert-Butyl 1,2-bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-7-azaspiro[3.5]nonane-7-carboxylate, **24a**

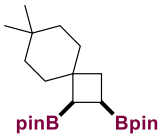


24a

From **9a** (44.7 mg, 0.2 mmol) following the general procedure described above, compound **24a** (74.5 mg, 0.156 mmol) was obtained in 78% yield as a white solid, after purification by flash column chromatography (SiO_2; hexane/EtOAc 95:5 to 90:10). **mp** = 112-114 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ 3.61-3.45 (m, 2H), 3.12 (dt, *J* = 13.2, 6.4 Hz, 1H), 2.99 (ddd, *J* = 13.0, 8.5, 4.1 Hz, 1H), 2.03-1.85 (m, 3H), 1.75-1.52 (m, 5H), 1.43 (s, 9H), 1.25 (s, 24H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 155.1, 83.3, 83.2, 79.1, 40.8 (br), 39.6, 37.8, 36.3, 32.6, 28.6, 25.6, 25.5, 24.8, 24.6. [note: *the carbons attached to boron were not observed due to quadrupole broadening caused by the ^{11}B nucleus*]. **^{11}B NMR** (96 MHz, $CDCl_3$): δ 33.6. **HRMS (ESI$^+$)**: calculated for $C_{25}H_{45}B_2NNaO_6$ $[M+Na]^+$: 500.3331; found: 500.3319.

2,2'-{7,7-(1*R**,2*R**)-Dimethylspiro[3.5]nonane-1,2-diyl}bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolane), **24b**

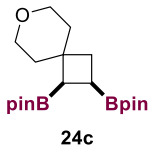


24b

From **9b** (30.1 mg, 0.2 mmol) following the general procedure described above, compound **24b** (59.2 mg, 0.146 mmol) was obtained in 73% yield as white solid, after purification by flash column chromatography (SiO_2; cyclohexane/EtOAc 95:5). **mp** = 82-84 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ 1.96-1.77 (m, 3H), 1.68-1.54 (m, 3H), 1.51-1.43 (m, 2H), 1.29-1.16 (26H), 1.13-1.05 (m, 2H), 0.83 (s, 3H), 0.81 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 83.1, 83.0, 41.2, 36.0, 35.6, 34.7, 33.2, 30.4 (br), 29.7, 26.7 (br), 25.6, 25.5, 24.8, 24.6. [note: *the carbons attached to boron were not observed due to quadrupole broadening caused by the ^{11}B nucleus*]. **^{11}B NMR** (96 MHz, $CDCl_3$): δ 33.0. **HRMS (ESI$^+$)**: calculated for $C_{23}H_{42}B_2NaO_4$ $[M+Na]^+$: 427.3167; found: 427.3156.

2,2'-{(1*R**,2*R**)-7-Oxaspiro[3.5]nonane-1,2-diyl}bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolane), **24c**

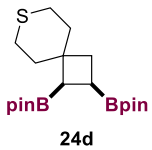


24c

From **9c** (24.8 mg, 0.2 mmol) following the general procedure described above, compound **24c** (39.0 mg, 0.103 mmol) was obtained in 52% yield as a white solid, after purification by flash column chromatography on (Florisil®; hexane/EtOAc 98:2 to 90:10). **mp** = 80-82 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ 3.74-3.59 (m, 2H), 3.59-3.48 (m, 1H), 3.47-3.36 (m, 1H), 2.03-1.90 (m, 3H), 1.80-1.62 (m, 5H), 1.33-1.18 (m, 24H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 83.3, 83.1, 65.0, 64.7, 39.1, 38.7, 37.4, 33.2, 25.6, 25.5, 24.8, 24.6. [note: *the carbons attached to boron were not observed due to quadrupole broadening caused by the ^{11}B nucleus*]. **^{11}B NMR** (96 MHz, $CDCl_3$): δ 34.2. **HRMS (ESI$^+$)**: calculated for $C_{20}H_{36}B_2NaO_5$ $[M+Na]^+$: 401.2647; found: 401.2634.

2,2'-{(1*R**,2*R**)-(7-thiaspiro[3.5]nonane-1,2-diyl}bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolane), **24d**



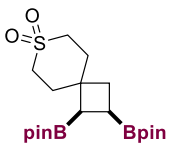
24d

From **9d** (28.0 mg, 0.2 mmol) following the general procedure described above, compound **24d** (70.4 mg, 0.179 mmol) was obtained in 89% yield as a white solid, after purification by flash column chromatography (SiO_2; cyclohexane/EtOAc 95:5). **mp** = 72-75 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ 2.68-2.58 (m, 1H), 2.56-2.41 (m, 3H), 1.98-1.76 (m, 7H), 1.71-1.63 (m, 1H), 1.25 (s, 24H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 83.3, 83.2, 40.3, 39.5, 38.0, 32.9, 25.6, 25.5, 25.0, 24.8, 24.6. [note: *the carbons attached to boron were not observed due to quadrupole broadening caused*

by the ^{11}B nucleus]. **HRMS (ESI$^+$)**: calculated for $C_{20}H_{36}B_2NaO_4S$ $[M+Na]^+$: 417.2418; found: 417.2409.

(1*R**,2*R**)-(1,2-bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-7-thiaspiro[3.5]nonane 7,7-dioxide, **24e**

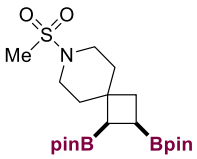


24e

From **9e** (34.4 mg, 0.2 mmol) following the general procedure described above, compound **24e** (49.2 mg, 0.115 mmol) was obtained in 58% yield as a white solid, after purification by flash column chromatography (SiO_2; DCM/EtOAc 70:30).

^{1}H NMR (300 MHz, $CDCl_3$): δ 3.10-2.99 (m, 1H), 2.98-2.91 (m, 2H), 2.89-2.78 (m, 1H), 2.36-2.24 (m 1H), 2.22-2.08 (m, 3H), 2.06-1.88 (m, 3H), 1.85-1.76 (m, 1H), 1.34-1.19 (m, 24H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 83.7, 83.4, 48.4, 48.1, 38.9, 36.0, 33.7, 32.2, 25.4, 25.3, 24.8, 24.7. [note: *the carbons attached to boron were not observed due to quadrupole broadening caused by the ^{11}B nucleus*]. **^{11}B NMR** (96 MHz, $CDCl_3$): δ 34.1. **HRMS (ESI$^+$)**: calculated for $C_{20}H_{36}B_2NaO_6S$ $[M+Na]^+$: 449.2316; found: 449.2313. **mp** = 192-194 °C.

(1*R**,2*R**)-(7-(methylsulfonyl)-1,2-bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-7 azaspiro[3.5]nonane, **24f**

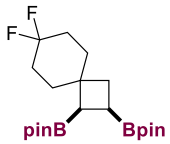


24f

From **9f** (40.3 mg, 0.2 mmol) following the general procedure described above, compound **24f** (57.0 mg, 0.125 mmol) was obtained in 63% yield as white solid, after purification by flash column chromatography (SiO_2; DCM/EtOAc 90:10). **mp** = 158-160 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ 3.40-3.24 (m, 2H), 3.06-2.82 (m, 2H), 2.72 (s, 3H), 1.99-1.86 (m, 3H), 1.84-1.69 (m, 5H), 1.33-1.22 (m, 24H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 83.5, 83.3, 43.1, 42.8, 38.8, 37.7, 35.5, 34.7, 32.6, 25.5, 25.4, 24.8, 24.7. [note: *the carbons attached to boron were not observed due to quadrupole broadening caused by the ^{11}B nucleus*]. **HRMS (ESI$^+$)**: calculated for $C_{21}H_{40}B_2NO_6S$ $[M+H]^+$: 456.2762; found: 456.2756.

2,2'-{(1*R**,2*R**)-7,7-difluorospiro[3.5]nonane-1,2-diyl}bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolane), **24g**

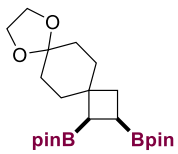


24g

From **9g** (31.6 mg, 0.2 mmol) following the general procedure described above, compound **24g** (43.1 mg, 0.105 mmol) was obtained in 52% yield as a white solid, after purification by flash column chromatography (SiO_2; cyclohexane/EtOAc 95:5). **mp** = 124-126 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ 1.99-1.61 (m, 12H), 1.25 (s, 24H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 123.8 (t, *J* = 240.6 Hz), 83.4, 83.2, 39.8, 34.7 (t, *J* = 4.8 Hz), 32.8 (t, *J* = 4.8 Hz), 32.5, 30.7 (t, *J* = 24.2 Hz), 30.5 (t, *J* = 24.2 Hz), 25.6, 25.5, 24.8, 24.7. [note: *the carbons attached to boron were not observed due to quadrupole broadening caused by the ^{11}B nucleus*]. **^{19}F NMR** (282 MHz, $CDCl_3$): δ –98.9, –95.3. **^{11}B NMR** (96 MHz, $CDCl_3$): δ 34.0, 30.5. **HRMS (ESI$^+$)**: calculated for $C_{21}H_{36}B_2F_2NaO_4$ $[M+Na]^+$: 435.2665; found: 435.2660.

2,2'-{(1*R**,2*R**)-8,11-dioxadispiro[3.2.4^7.2^4]tridecane-1,2-diyl}bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolane), **24h**



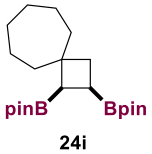
24h

From **9h** (36.1 mg, 0.2 mmol) following the general procedure described above, compound **24h** (65.6 mg, 0.151 mmol) was obtained in 76% yield as a white solid,

after purification by flash column chromatography (Florisil®; cyclohexane/EtOAc 95:5). **mp** = 98-100 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ 3.88 (s, 4H), 1.95-1.40 (m, 12H), 1.26-1.19 (m, 24H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 109.1, 83.2, 83.0, 64.2, 64.1, 40.3, 35.7, 34.2, 32.7, 31.6, 31.3, 25.6, 25.5, 24.7, 24.6. [note: *the carbons attached to boron were not observed due to quadrupole broadening caused by the ^{11}B nucleus*]. **HRMS (ESI$^+$)**: calculated for $C_{23}H_{40}B_2NaO_6$ $[M+Na]^+$: 457.2909; found: 457.2894.

2,2'-{(1*R**,2*R**)-spiro[3.6]decane-1,2-diyl}bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolane), **24i**

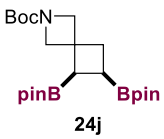


24i

From **9i** (27.2 mg, 0.2 mmol) following the general procedure described above (the reaction was performed at 85 °C), compound **24i** (50.1 mg, 0.128 mmol) was obtained in 64% yield as white solid, after purification by flash column chromatography (SiO_2; cyclohexane/EtOAc 95:5). **mp** = 61-63 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ 1.94-1.34 (m 16H), 1.29-1.13 (m, 24H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 83.1, 83.0, 44.4, 42.3, 40.1, 34.8, 28.2, 25.6, 25.5, 24.8, 24.6, 23.0, 22.7. [note: *the carbons attached to boron were not observed due to quadrupole broadening caused by the ^{11}B nucleus*]. **HRMS (ESI$^+$)**: calculated for $C_{22}H_{40}B_2NaO_4$ $[M+Na]^+$: 413.3010; found: 413.2997.

(5*R**,6*R**)-*tert*-Butyl 5,6-bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2-azaspiro[3.3]heptane-2-carboxylate, **24j**



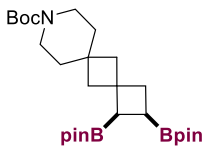
24j

From **9j** (39.1 mg, 0.2 mmol) following the general procedure described above, compound **24j** (67.4 mg, 0.150 mmol) was obtained in 75% yield as a white solid, after

purification by flash column chromatography (SiO_2; cyclohexane/EtOAc 90:10). **mp** = 89-92 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ 4.03 (d, *J* = 9.1 Hz, 1H), 3.95-3.85 (m, 2H), 3.70 (d, *J* = 9.2 Hz, 1H), 2.24 (d, *J* = 8.7 Hz, 2H), 2.03-1.94 (m, 1H), 1.88-1.75 (m, 1H), 1.42 (s, 9H), 1.29-1.20 (m, 24H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 156.5, 83.4, 83.3, 79.0, 63.4 (br), 59.6 (br), 39.8, 36.0, 28.5, 25.2, 25.1, 25.0 (x2), 24.9. [note: *the carbons attached to boron were not observed due to quadrupole broadening caused by the ^{11}B nucleus*]. **^{11}B NMR** (96 MHz, $CDCl_3$): δ 33.2. **HRMS (ESI$^+$)**: calculated for $C_{23}H_{42}B_2NO_6$ $[M+H]^+$: 450.3198; found: 450.3193.

(1*R**,2*R**)-*tert*-Butyl 1,2-bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-9-azadispiro[3.1.5^6.1^4]dodecane-9-carboxylate, **24l**

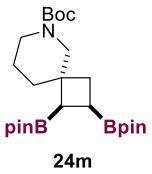


24l

From **9l** (52.7 mg, 0.2 mmol) following the general procedure described above, compound **24l** (85.4 mg, 0.165 mmol) was obtained in 83% yield as a yellow pale oil, after purification by flash column chromatography (SiO_2; cyclohexane/EtOAc 95:5 to 90:10).

^{1}H NMR (300 MHz, $CDCl_3$): δ 3.30-3.20 (m, 4H), 2.23 (t, *J* = 9.6 Hz, 1H), 2.09-1.76 (m, 6H), 1.69-1.62 (m, 1H), 1.48-1.37 (m, 13H), 1.27-1.21 (m, 24H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 155.2, 83.2, 83.0, 79.1, 47.2, 43.0, 40.9 (br), 39.5, 39.4, 38.3, 37.5, 32.8, 28.6, 25.6, 25.3, 24.8, 24.7. [note: *the carbons attached to boron were not observed due to quadrupole broadening caused by the ^{11}B nucleus*]. **HRMS (ESI$^+$)**: calculated for $C_{28}H_{49}B_2NNaO_6$ $[M+Na]^+$: 540.3644; found: 540.3639.

(1*R**,2*R**)-*tert*-butyl 1,2-bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-6-azaspiro[3.5]nonane-6-carboxylate, **24m**

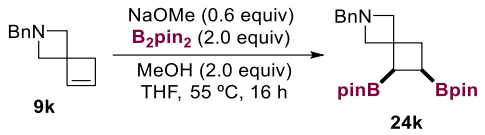


24m

From **9m** (89.3 mg, 0.4 mmol) following the general procedure described above, compound **24m** (126.0 mg, 0.264 mmol) was obtained in 66% yield as a white solid, after purification by flash column chromatography on silica gel (SiO_2; cyclohexane/EtOAc 95:5 to 90:10). **mp** = 111-113 °C.

^{1}H NMR (300 MHz, $CDCl_3$, mixture of rotamers): δ 4.06-3.52 (m, 2H), 3.16-2.72 (m, 2H), 2.08-1.76 (m, 3H), 1.70-1.53 (m, 2H), 1.49-1.35 (m, 11H), 1.22 (s, 24H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 155.3, 83.4, 83.1, 79.1, 54,1 (br), 44.1 (br), 40.5, 35.6, 31.2, 28.6, 25.6, 25.5, 24.7, 24.6, 21.9. [note: *the carbons attached to boron were not observed due to quadrupole broadening caused by the ^{11}B nucleus*]. **HRMS (ESI$^+$)**: calculated for $C_{25}H_{46}B_2NO_6$ $[M+H]^+$: 478.3511; found: 478.3512.

Synthesis of (5R,6R*)-2-benzyl-5,6-bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2-azaspiro[3.3]heptane,* ***24k***



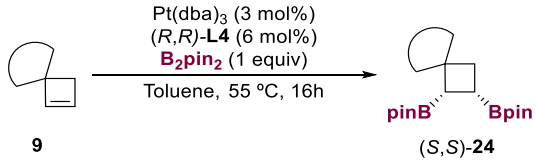
9k **24k**

An oven-dried vial was charged with sodium methoxide (9.7 mg, 0.18 mmol, 0.6 equiv) and bis(pinacolato)diboron (152.4 mg, 0.6 mmol, 2.0 equiv)) and was sealed with a septum inside a glove box. Then, the vial was placed outside the glove box and connected to an argon-vacuum line, evacuated and backfilled with argon (x3). Anhydrous THF (0.75 mL) was added to dissolve the mixture. Then, a solution of **9k** (55.6 mg, 0.3 mmol,

1.0 equiv) in THF (0.75) and MeOH (24 µL, 0.6 mmol, 2.0 equiv) were added and the resulting mixture was stirred at 55 °C for 16 h. After cooling to room temperature, H_2O (5 mL) and EtOAc were added. The aqueous phase was extracted with EtOAc (3 × 10 mL). The organic layers were combined, dried ($MgSO_4$) and concentrated under reduced pressure. Compound **24k** was obtained in 77% yield. We observed that the product decomposed during the purification process. Therefore, the yield was calculated by ^{1}H NMR using toluene as internal standard.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.29-7.05 (m, 5H), 3.58 (m, 2H), 3.45 (d, *J* = 7.4 Hz, 1H), 3.35-3.18 (m, 2H), 3.06 (d, *J* = 7.6 Hz, 1H), 2.32-2.20 (m, 2H), 1.90-1.69 (m, 2H), 1.19 (s, 24H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 137.5, 128.6, 128.1, 126.9, 83.1, 82.9, 67.1, 64.5, 62.8, 40.3, 35.8, 25.1, 24.9, 24.8, 24.7. [note: *the carbons attached to boron were not observed due to quadrupole broadening caused by the ^{11}B nucleus*]. **HRMS (ESI$^+$)**: calculated for $C_{25}H_{40}B_2NO_4$ $[M+H]^+$: 440.3143; found: 440.3139.

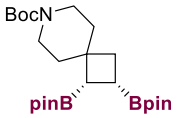
3.3 General Procedure for the Platinum-Catalyzed Diboration of Spirocyclobutenes, 24



An oven-dried vial was charged with $Pt(dba)_3$ (3 mol%), (*R*,*R*)-3,5-diethylphenyl-TADDOL-PPh (**L4**) (6 mol%), B_2pin_2 (1.0 equiv) and anhydrous toluene (1 mL/mmol) inside a glove box. The vial was sealed with a butyl/PTFE septum cap, removed from the glove box, and heated to 80 °C

(oil bath) for 30 minutes.[216] The vial was cooled to room temperature, returned to the glove box and charged with spirocyclobutene **9** (1.0 equiv), sealed and the resulting mixture was stirred at 55 °C for 16 h. The reaction mixture was diluted with ethyl acetate and passed through a pad of silica. The crude product was purified by flash column chromatography on silica gel to afford enantioenriched **24**.

(1*S*,2*S*)-*tert*-Butyl 1,2-bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-7-azaspiro[3.5]nonane-7-carboxylate, (*S,S*)-**24a**

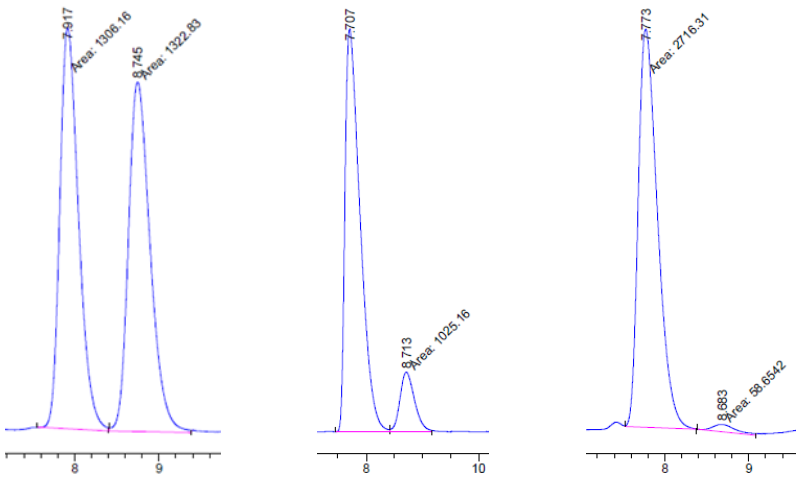


(*S*,*S*)-**24a**

From **9a** (89.3 mg, 0.4 mmol) following the general procedure described above, compound (*S,S*)-**24a** (180.0 mg, 0.377 mmol) was obtained in 94% yield as a white solid, after purification by flash column chromatography on silica gel (SiO_2; cyclohexane/EtOAc 95:5 to 90:10). $[\alpha]_D^{20}$ = +22.8 (*c* = 1.0, $CHCl_3$). **mp** = 106-108 °C.

Compound (*S,S*)-**24a** was obtained with 88:12 enantiomeric ratio determined by chiral HPLC using Chiralpak-IC column [hexane/*i*PrOH (99.3:0.7)], 1.0 mL/min: τ_{major} = 7.77 min, τ_{minor} = 8.68 min. The enantiomeric ratio of (*S,S*)-**24a** was improved through enantiomeric enrichment through the following procedure. Enantiomerically enriched (*S,S*)-**24a** (180.0 mg, er = 88:12) was dissolved in hexane (0.5 mL) at 25 °C. The resulting supersaturated solution was allowed to stand for 2 days at –20 °C. The deposited crystals were separated from the mother liquor. The mother liquors were concentrated under reduced pressure obtaining (*S,S*)-**24a** in 67% yield with er = 98:2.

HPLC chromatograms



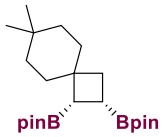
Racemic | er = 88:12 | er = 98:2

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	7.917	MM	0.2574	1306.16394	84.57737	49.6830
2	8.745	MM	0.2990	1322.83240	73.74866	50.3170

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	7.707	BV	0.2826	7293.11719	390.19189	87.6758
2	8.713	MM	0.2981	1025.15796	57.32458	12.3242

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	7.773	MM	0.2658	2716.30542	170.33740	97.8863
2	8.683	MM	0.3122	58.65423	3.13161	2.1137

2,2'-((1*S*,2*S*)-7,7-Dimethylspiro[3.5]nonane-1,2-diyl)bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolane), (*S*,*S*)-**24b**



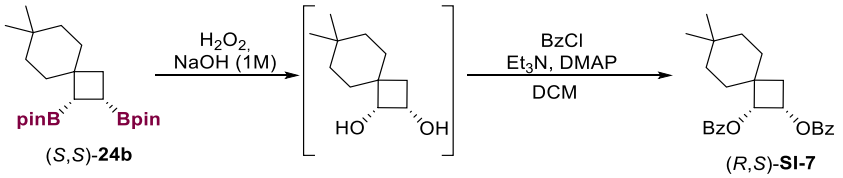
(*S*,*S*)-**2b**

From **9b** (45.1 mg, 0.3 mmol) following the general procedure described above, compound (*S*,*S*)-**24b** (67.0 mg, 0.166 mmol) was obtained was obtained in 55% yield as a white solid, after purification by flash column chromatography (SiO_2; cyclohexane/EtOAc 95:5). $[\alpha]_D^{20}$ = +12.3 (*c* = 1.0, $CHCl_3$). **mp** =76-79 °C.

(*S*,*S*)-**24b** (67.0 mg, er = 80:20) was dissolved in EtOH (0.25 mL) at 25 °C. The resulting supersaturated solution was allowed to stand for 2 days at 0 °C. The deposited crystals were filtered and washed with cold EtOH to give

(+)-**24b** (26.7 mg) in 40% yield with er = 99:1. Compound (*S*,*S*)-**24b** was transformed into **SI-7** through oxidation followed by benzoylation to determine the enantiomeric ratio.

Synthesis of (1*R*,2*S*)-7,7-dimethylspiro[3.5]nonane-1,2-diyl dibenzoate, (*R*,*S*)-**SI-7**

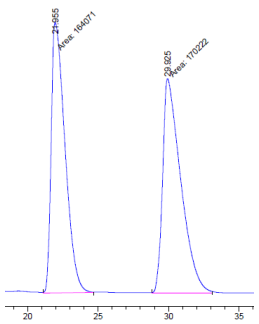


To boronic ester (*S*,*S*)-**24b** (26.7 mg, 0.066 mmol, 1.0 equiv) in THF (0.2 mL), an aqueous solution of 1M NaOH (0.13 mL, 0.13 mmol) was added, and the reaction mixture was cooled to 0 °C. Then, a solution of H_2O_2 (26 µL, 30% (w/w), 4.0 equiv) was added dropwise. A white precipitate was formed within 10 min. After 1 hour at room temperature, water was added, and the mixture was extracted with EtOAc (x3). The combined organic layers were washed with brine, dried with $MgSO_4$, filtered, and concentrated under reduced pressured. The diol was used in the next step without further purification. To a solution of diol in DCM (0.7 mL), 4-dimethyl-aminopyridine (DMAP) (2.2 mg, 0.018 mmol, 27 mol%), triethylamine (20 µL, 0.198 mmol, 3 equiv) and benzyl chloride (15 µL, 0.132 mmol, 2.0 equiv) were added. The reaction mixture was stirred for 16 hours 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

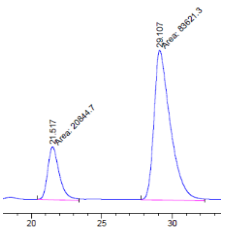
chromatography (SiO_2, hexane/EtOAc 95:5) to afford compound (*R*,*S*)-**SI-7** (11.0 mg, 0.028 mmol) in 43% yield (two steps) as colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.98 (d, *J* = 7.1 Hz, 2H), 7.92 (d, *J* = 7.1 Hz, 2H), 7.56-7.46 (m, 2H), 7.40-7.29 (m, 4H), 5.58-5.51 (m, 1H), 5.33-5.28 (m, 1H), 2.30 (ddd, *J* = 12.7, 7.2, 2.4 Hz, 1H), 2.14 (dd, *J* = 12.7, 5.2 Hz, 1H), 1.88-1.73 (m, 3H), 1.66-1.58 (m, 1H), 1.39-1.18 (m, 4H), 0.91 (s, 3H), 0.88 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 166.0, 165.8, 133.1, 133.0, 130.2, 129.8, 129.7, 128.5, 128.4, 76.1, 67.6, 41.8, 37.0, 35.8, 35.3, 33.1, 30.2 (br), 29.8, 28.1, 26.8 (br). **HRMS (ESI$^+$)**: calculated for $C_{25}H_{28}NaO_4$ $[M+Na]^+$: 415.1885; found: 415.1871. **$[\alpha]_D^{20}$** = +10.9 (*c* = 1.0, $CHCl_3$). The enantiomeric ratio was determined by chiral HPLC using Chiralpak-IA column [hexane/*i*PrOH (99.5:0.5)], 0.5 mL/min: τ_{minor} = 22.6 min, τ_{major} = 30.1 min.

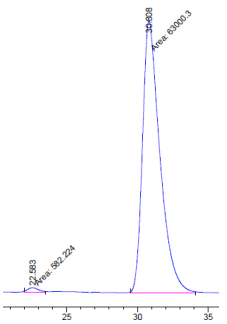
HPLC chromatograms



Racemic



er = 80:20



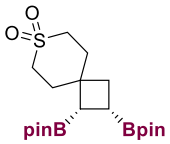
er = 99:1

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	21.955	MM	1.1337	1.64071e5	2412.10864	49.0800
2	29.925	MM	1.4867	1.70222e5	1908.27856	50.9200

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	21.517	MM	0.9541	2.08447e4	364.11969	19.9536
2	29.107	MM	1.3509	8.36213e4	1031.70398	80.0464

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	22.583	MM	0.8465	582.22406	11.46336	0.9157
2	30.808	MM	1.4263	6.30003e4	736.16376	99.0843

(1*S*,2*S*)-1,2-Bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-7-thiaspiro[3.5]nonane 7,7-dioxide, (*S,S*)-**24e**

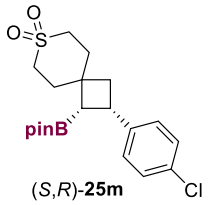


(*S*,*S*)-**24e**

From **9e** (17.2 mg, 0.1 mmol) following the general procedure described above with slightly modification [(Pt(dba)$_3$ (0.05 equiv), (*R*,*R*)-**L4** (0.1 equiv)], compound (*S,S*)-**24e** was obtained. Purification by flash column chromatography (SiO_2; DCM/EtOAc 90:10) afforded (*S,S*)-**2e** (29.8 mg, 0.07 mmol) in 70% yield as white solid. $[\alpha]_D^{20}$ = +19.3 (*c* = 1.0, $CHCl_3$). **mp** = 187-188 °C.

The enantioenriched (*S,S*)-**24e** (82.0 mg, er = 85:15) was dissolved in hexane (0.35 mL) and DCM (0.1 mL) at 25 °C until crystallization began (within 16 h) and then allowed to stand for 2 days at 0 °C. The deposited crystals were filtered and washed with cold hexane to give (*S,S*)-**2e** in 62% yield with er = 93:7. Compound (*S,S*)-**24e** was transformed into (*S,R*)-**25m**

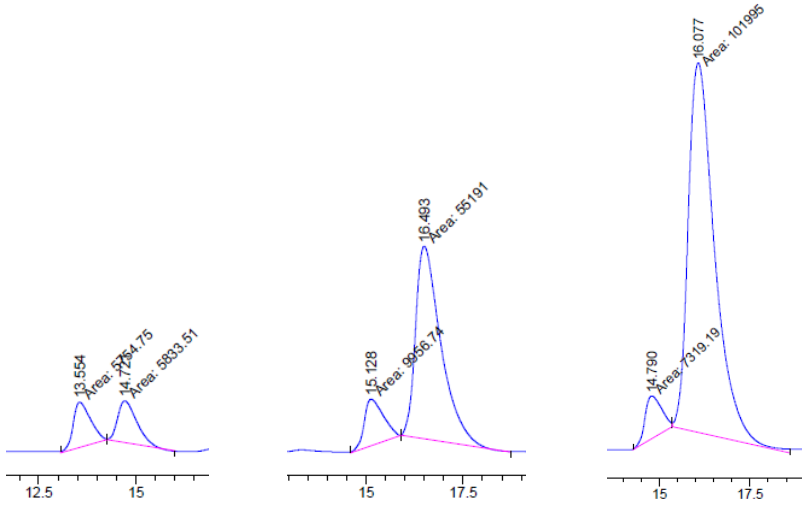
through selective Suzuki-Miyaura cross-coupling to determine the enantiomeric ratio.



(*S*,*R*)-**25m**

$[\alpha]_D^{20}$ = −20.2 (*c* = 1.0, $CHCl_3$). **mp** = 182-184 °C. The enantiomeric ratio was determined by chiral HPLC using Chiralpak-IA column [hexane/*i*PrOH (97:3)], 1.0 mL/min: τ_{minor} = 14.8 min, τ_{major} = 16.1 min.

HPLC chromatograms



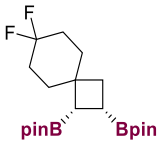
Racemic | er = 85:15 | er = 93:7

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	13.554	MM	0.5162	5754.75342	185.82297	49.6602
2	14.721	MM	0.5689	5833.50928	170.88828	50.3398

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	15.128	MM	0.4024	9956.74219	293.92462	15.2833
2	16.493	MM	0.7587	5.51910e4	1212.43713	84.7167

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	14.790	MM	0.3711	7319.18994	231.66411	6.6955
2	16.077	MM	0.8475	1.01995e5	2005.69348	93.3045

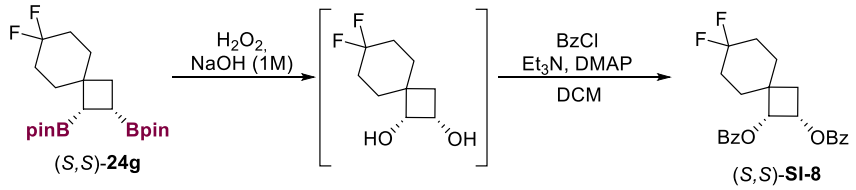
2,2'-((1*S*,2*S*)-7,7-Difluorospiro[3.5]nonane-1,2-diyl)bis(4,4,5,5-etramethyl-1,3,2-dioxaborolane), (*S,S*)-**24g**



(*S*,*S*)-**24g**

From **9g** (32.0 mg, 0.2 mmol) following the general procedure described above, compound (*S,S*)-**24g** was obtained. Purification by flash column chromatography (SiO_2; cyclohexane/EtOAc 90:10) afforded (*S,S*)-**24g** (49.4 mg, 0.119 mmol) in 60% yield as white solid with er = 86:14. $[\alpha]_D^{20}$ = +14.7 (*c* = 1.0, $CHCl_3$). **mp** = 116-118 °C. Compound (*S,S*)-**24g** was transformed into **SI-8** through oxidation followed by benzoylation to determine the enantiomeric ratio.

Synthesis of (1*S*,2*S*)-7,7-dimethylspiro[3.5]nonane-1,2-diyl dibenzoate, (*S,S*)-**SI-8**

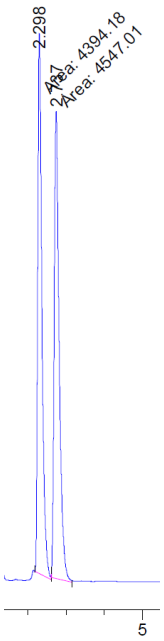


To boronic ester (*S,S*)-**24g** (86.0 mg, 0.21 mmol, 1.0 equiv) in THF (0.45 mL), an aqueous solution of NaOH (0.21 mL, 0.21 mmol, 1M) was added, and the reaction mixture was cooled to 0 °C. Then, a solution of H_2O_2 (42 µL, 30% (w/w), 4.0 equiv) was added dropwise. A white precipitate was formed within 10 min. After 1 h at room temperature, water was added, and the mixture was extracted with EtOAc (x3). The combined organic layers were washed with brine, dried with $MgSO_4$, filtered, and concentrated under reduced pressured. The diol was used in the next step without further purification. To a solution of diol in DCM (2.2 mL), 4-dimethylaminopyridine (6.9 mg, 0.042 mmol, 27 mol%), triethylamine (176

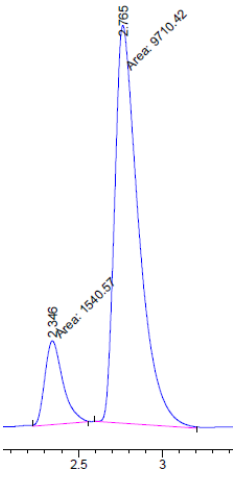
µL, 1.26 mmol, 6 equiv) and benzyl chloride (98 µL, 0.84 mmol, 4.0 equiv) were added. The reaction mixture was stirred for 16 hours at room temperature and then quenched with H_2O. The aqueous layer was extracted with Et_2O (x3) and the combined organic phases were washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (SiO_2, hexane/EtOAc 98:2) to afford compound (*S,S*)-**SI-8** (58.3 mg, 0.146 mmol) in 69% yield (two steps) as colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ 8.06-7.90 (m, 4H), 7.60-7.49 (m, 2H), 7.45-7.31 (m, 4H), 5.68-5.56 (m, 1H), 5.46-5.36 (m, 1H), 2.43-2.30 (m, 1H), 2.28-2.16 (m, 1H), 2.14-1.78 (m, 8H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 165.7, 133.4, 133.2, 129.8, 129.7, 128.6, 128.5, 122.92 (t, *J* = 241.0 Hz), 74.6, 67.6, 41.0, 35.8, 33.05 (t, *J* = 5.0 Hz), 30.8 (t, *J* = 24.6 Hz), 30.5 (t, *J* = 24.4 Hz), 28.39 (t, *J* = 4.9 Hz). **^{19}F NMR** (282 MHz, $CDCl_3$): δ –98.4, –102.1. **HRMS (ESI$^+$)**: calculated for $C_{23}H_{23}F_2O_4$ $[M+H]^+$: 401.1564; found: 401.1569. **$[\alpha]_D^{20}$** = +12.3 (*c* = 1.0, $CHCl_3$). The enantiomeric ratio was determined by chiral HPLC using Chiralpak-IA column [hexane/*i*PrOH (99.5:0.5)], 0.5 mL/min: τ_{minor} = 22.6 min, τ_{major} = 30.1 min.

HPLC chromatograms



Racemic

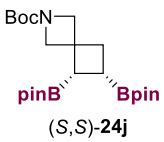


er = 86:14

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	2.298	MM	0.1269	4394.18213	576.95483	49.1454
2	2.737	MM	0.1519	4547.01025	498.88205	50.8546

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	2.346	MM	0.1245	1540.56543	206.18318	13.6927
2	2.765	MM	0.1655	9710.41699	977.66803	86.3073

(5*S*,6*S*)-*tert*-butyl 5,6-bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2-azaspiro[3.3]heptane-2-carboxylate, (*S,S*)-**24j**

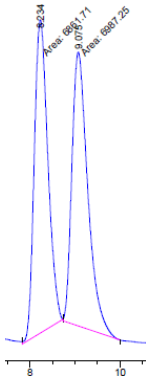


(*S,S*)-**24j**

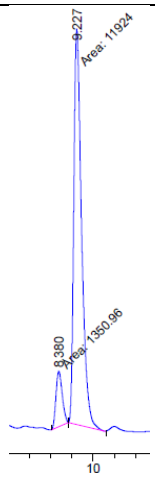
From **9j** (58.6 mg, 0.3 mmol) following the general procedure described above, compound (*S,S*)-**24j** was obtained. Purification by flash column chromatography (SiO_2; cyclohexane/EtOAc 90:10) afforded (*S,S*)-**24j** (99.0 mg, 0.220 mmol) in 73% yield as white solid with er = 90:10. $[\alpha]_D^{20}$ = +33.2 (*c* = 2.0, $CHCl_3$). **mp** = 80-82 °C. The enantiomeric ratio was determined by chiral HPLC using

Chiralpak-IA column [hexane/*i*PrOH (99.5:0.5)], 0.5 mL/min: τ_{minor} = 8.4 min, τ_{major} = 9.2 min.

HPLC chromatograms



Racemic

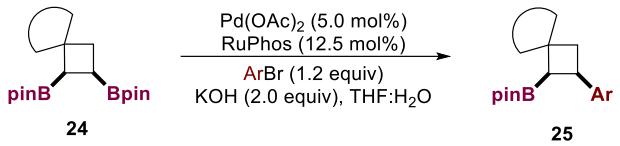


er = 90:10

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	8.234	MM	0.3491	6861.70752	327.61548	49.5467
2	9.075	MM	0.4065	6987.25391	286.48633	50.4533

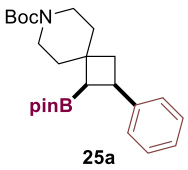
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	8.380	MM	0.3464	1356.96655	65.29091	10.0542
2	9.227	MM	0.4312	1.21395e4	469.19995	89.9458

3.4 General Procedure for the Selective Suzuki-Miyaura Cross-Coupling of Diborylated Spirocycles, 25



An oven-dried vial was charged with $Pd(OAc)_2$ (5.0 mol%), RuPhos (12.5 mol%), the corresponding aryl bromide (1.2 equiv), KOH (2.0 equiv) and diboronic ester **24** and sealed with a septum. The vial was connected to an argon-vacuum line, evacuated and backfilled with argon (3x). Then, THF and deoxygenated water ([substrate] = 0.1 M; 95:5 v:v THF:H_2O) were added through the teflon septum cap and the resulting mixture was sonicated for 2 minutes. The reaction mixture was stirred for 16 h at 80 °C. Then, the reaction mixture was cooled to room temperature and H_2O (5 mL) was added. The layers were separated, and the aqueous phase was extracted with dichloromethane (3 x 10 mL). The combined organic layers were washed with a saturated NaCl solution, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was purified by flash column chromatography on silica gel to afford **25**.

(1*R**,2*S**)-*tert*-Butyl 2-phenyl-1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-7-azaspiro[3.5]nonane-7-carboxylate, **25a**

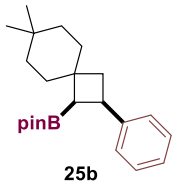


From **24a** (47.7 mg, 0.1 mmol) following the general procedure described above using bromobenzene as aryl electrophile, compound **25a** (32.7 mg, 0.077 mmol) was obtained in 77% yield as a white solid, after purification

by flash column chromatography (SiO_2; cyclohexane/EtOAc 95:5). **mp** = 180-182 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.28-7.06 (m, 5H), 3.78 (q, *J* = 9.9 Hz, 1H), 3.55-3.26 (m, 3H), 3.25-3.12 (m, 1H), 2.45-2.34 (m, 1H), 2.14-2.03 (m, 2H), 1.84-1.58 (m, 4H), 1.46 (s, 9H), 0.93 (s, 6H), 0.88 (s, 6H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 155.1, 144.4, 127.9, 127.0, 125.6, 83.0, 79.3, 41.3 (br), 37.6, 36.4, 35.6, 35.1, 34.4, 28.6, 24.9, 24.7 [note: *the carbon attached to boron was not observed due to quadrupole broadening caused by the ^{11}B nucleus*]. **HRMS (ESI$^+$)**: calculated for $C_{25}H_{38}BNNaO_4$ $[M+Na]^+$: 450.2792; found: 450.2784.

2-{(1*R**,2*S**)-7,7-Dimethyl-2-phenylspiro[3.5]nonan-1-yl}-4,4,5,5-tetramethyl-1,3,2-dioxaborolane, 25b

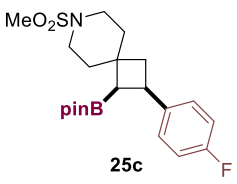


25b

From **24b** (40.4 mg, 0.1 mmol) following the general procedure described above using bromobenzene as aryl electrophile, compound **25b** (25.1 mg, 0.071 mmol) was obtained in 71% yield as a white solid, after purification by flash column chromatography (SiO_2; hexane/EtOAc 95:5). **mp** = 98-100 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.26-7.14 (m, 4H), 7.12-7.06 (m, 1H), 3.72 (q, *J* = 9.9 Hz, 1H), 2.30 (t, *J* = 10.7 Hz, 1H), 2.09-1.98 (m, 2H), 1.78-1.66 (m, 2H), 1.61-1.54 (m, 2H), 1.31 (t, *J* = 6.1 Hz, 2H), 1.20-1.04 (m, 2H), 0.95 (s, 6H), 0.89 (s, 3H), 0.88 (9H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 145.3, 127.8, 127.1, 125.3, 82.7, 37.2, 36.4, 36.2, 35.3, 35.0 (br), 34.6, 33.1, 29.8, 28.7 (br), 24.9, 24.7 [note: *the carbon attached to boron was not observed due to quadrupole broadening caused by the ^{11}B nucleus*]. **^{11}B NMR** (96 MHz, $CDCl_3$): δ 32.9. **HRMS (ESI$^+$)**: calculated for $C_{23}H_{35}BNaO_2$ $[M+Na]^+$: 377.2628; found: 377.2616.

(1*R**,2*S**)-2-(4-Fluorophenyl)-7-(methylsulfonyl)-1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-7-azaspiro[3.5]nonane, **25c**

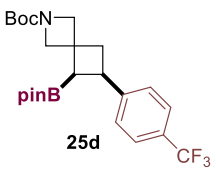


25c

From **24f** (45.5 mg, 0.1 mmol) following the general procedure described above using 1-bromo-4-fluorobenzene as aryl electrophile, compound **25c** (28.0 mg, 0.066 mmol) was obtained in 66% yield as a white solid, after purification by flash column chromatography (SiO_2; DCM/EtOAc 95:5). **mp** = 148-150 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.16-7.09 (m, 2H), 6.99-6.87 (m, 2H), 3.74 (q, *J* = 9.8 Hz, 1H), 3.36-3.20 (m, 2H), 3.14 (dt, *J* = 11.3, 5.4 Hz, 1H), 3.00 (dt, *J* = 11.7, 5.7 Hz, 1H), 2.76 (s, 3H), 2.43-2.32 (m, 1H), 2.15-2.05 (m, 2H), 1.97-1.88 (m, 2H), 1.83 (t, *J* = 5.6 Hz, 2H), 0.95 (s, 6H), 0.91 (s, 6H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 161.4 (d, *J* = 243.4 Hz), 139.6 (d, *J* = 3.1 Hz), 128.5 (d, *J* = 7.9 Hz), 114.7 (d, *J* = 21.0 Hz), 83.2, 43.4, 43.2, 37.0, 35.9, 34.9, 34.5, 34.4, 24.9, 24.7 [note: *the carbon attached to boron was not observed due to quadrupole broadening caused by the ^{11}B nucleus*]. **^{19}F NMR** (282 MHz, $CDCl_3$): δ –121.1. **HRMS (EI$^+$)**: calculated for $C_{21}H_{31}BFNO_4S$ $[M]^+$: 423.2051; found: 423.2047.

(5*R**,6*S**)-*tert*-Butyl 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-6-(4-(trifluoromethyl)phenyl)-2-azaspiro[3.3]heptane-2-carboxylate, **25d**



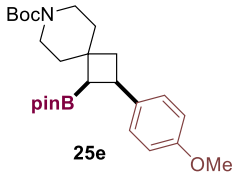
25d

From **24j** (44.9 mg, 0.1 mmol) following the general procedure with slightly modification (1.2 equivalents of KOH was used instead of 2.0 equivalent) using 1-bromo-4-(trifluoromethyl)benzene as aryl electrophile, compound **25d** (32.7 mg, 0.07 mmol) was obtained in 70% yield as a

white solid, after purification by flash column chromatography (SiO_2; cyclohexane/EtOAc 95:5). **mp** = 138-140 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.50 (d, *J* = 8.1 Hz, 2H), 7.25 (d, *J* = 6.4 Hz, 2H), 4.15-4.04 (m, 2H), 3.88-3.77 (m, 2H), 3.69 (q, *J* = 9.5 Hz, 1H), 2.93-2.76 (m, 1H), 2.54-2.37 (m, 2H), 1.44 (s, 9H), 0.92 (s, 6H), 0.89 (s, 6H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 156.4, 147.6, 128.4 (q, *J* = 32.5 Hz), 127.3, 125.0 (q, *J* = 3.6 Hz), 127.7, 83.5, 79.4, 59.9 (br), 36.8, 35.5, 35.2, 28.6, 25.0, 24.6. [note: *the carbon attached to boron was not observed due to quadrupole broadening caused by the ^{11}B nucleus*]. **^{19}F NMR** (282 MHz, $CDCl_3$): δ –65.5. **HRMS (ESI$^+$)**: calculated for $C_{24}H_{33}BF_3NNaO_4$ $[M+Na]^+$: 490.2352; found: 490.2340.

(1*R**,2*S**)-*tert*-butyl 2-(4-methoxyphenyl)-1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-7-azaspiro[3.5]nonane-7-carboxylate, **25e**

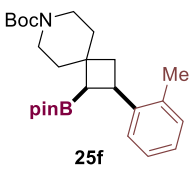


25e

From **24a** (47.7 mg, 0.1 mmol) following the general procedure described above using 4-bromoanisole as aryl electrophile, compound **25e** (33.5 mg, 0.073 mmol) was obtained in 73% yield as a yellow pale solid, after purification by flash column chromatography (SiO_2; cyclohexane/EtOAc 95:5 to 80:20). **mp** = 152-154 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.10 (d, *J* = 8.1 Hz, 2H), 6.79 (d, *J* = 8.7 Hz, 2H), 3.82-3.65 (m, 4H), 3.53-3.25 (m, 3H), 3.23-3.10 (m, 1H), 2.35 (t, *J* = 11.4 Hz, 1H), 2.12-2.02 (m, 2H), 1.81-1.60 (m, 4H), 1.45 (s, 9H), 0.99-0.89 (m, 12H). **^{13}C NMR** (75 MHz, $CDCl_3$): 157.9, 155.1, 136.5, 128.1, 113.4, 83.0, 79.3, 55.5, 41.2, 37.6, 36.4, 35.4, 34.7, 34.4, 34.2 (br), 28.6, 25.0, 24.7. **HRMS (ESI$^+$)**: calculated for $C_{26}H_{40}BNNaO_5$ $[M+Na]^+$: 480.2897; found: 480.2885.

(1*R**,2*S**)-*tert*-Butyl 1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2-(*o*-tolyl)-7-azaspiro[3.5]nonane-7-carboxylate, **25f**

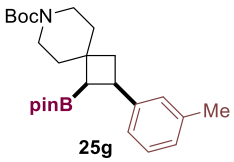


25f

From **24a** (47.7 mg, 0.1 mmol) following the general procedure described above using 1-bromo-2-methylbenzene as aryl electrophile, compound **25f** (32.4 mg, 0.073 mmol) was obtained in 73% yield as a yellow pale solid, after purification by flash column chromatography (SiO_2; cyclohexane/EtOAc 95:5). **mp** =173-175 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.24-7.02 (m, 4H), 3.76 (q, *J* = 10.1, 9.5 Hz, 1H), 3.59-3.28 (m, 3H), 3.25-3.12 (m, 1H), 2.51 (t, *J* = 10.8 Hz, 1H), 2.23 (s, 3H), 2.20-2.12 (m, 1H), 2.11-2.00 (m, 1H), 1.87-1.75 (m, 2H), 1.72-1.63 (m, 2H), 1.46 (s, 9H), 0.87 (s, 6H), 0.83 (s, 6H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 155.2, 141.8, 136.5, 129.8, 126.7, 125.8, 125.3, 82.9, 79.3, 41.2 (br), 37.6, 36.5, 35.5, 34.1, 33.6, 28.6, 24.8, 24.4, 19.7. [note: *the carbon attached to boron was not observed due to quadrupole broadening caused by the ^{11}B nucleus*]. **HRMS (ESI$^+$)**: calculated for $C_{26}H_{40}BNNaO_4$ $[M+Na]^+$: 464.2948; found: 464.2937.

(1*R**,2*S**)-*tert*-Butyl 1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2-(*m*-tolyl)-7-azaspiro[3.5]nonane-7-carboxylate, **25g**

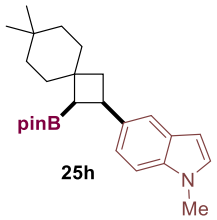


25g

From **24a** (47.7 mg, 0.1 mmol) following the general procedure described above using 1-bromo-3-methylbenzene as aryl electrophile, compound **25g** (35.2 mg, 0.080 mmol) was obtained in 80% yield as a yellow pale solid, after purification by flash column chromatography (SiO_2; cyclohexane/EtOAc 95:5 to 90:10). **mp** = 169-171 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.12 (t, *J* = 7.5 Hz, 1H), 7.01-6.88 (m, 3H), 3.74 (q, *J* = 9.8 Hz, 1H), 3.54-3.26 (m, 3H), 3.24-3.12 (m, 1H), 2.38 (t, *J* = 11.3 Hz, 1H), 2.29 (s, 3H), 2.13-2.02 (m, 2H), 1.81-1.64 (m, 4H), 1.46 (s, 9H), 0.94 (s, 6H), 0.89 (s, 6H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 155.1, 144.3, 137.2, 127.9, 127.8, 126.3, 124.1, 82.9, 79.3, 41.0 (br), 37.6, 36.4, 35.6, 35.0, 34.4, 34.0 (br), 28.6, 24.9, 24.6, 21.5. **HRMS (ESI$^+$)**: calculated for $C_{26}H_{40}BNNaO_4$ $[M+Na]^+$: 464.2948; found: 464.2934.

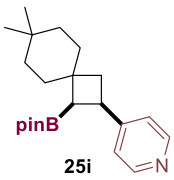
5-{(1*R**,2*S**)-7,7-Dimethyl-1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)spiro[3.5]nonan-2-yl}-1-methyl-1*H*-indole, **25h**



From **24b** (40.4 mg, 0.1 mmol) following the general procedure described above using 5-bromo-1-methyl-1*H*-indole as aryl electrophile, compound **25h** (21.5 mg, 0.053 mmol) was obtained in 53% yield as a white solid, after purification by flash column chromatography (SiO_2; cyclohexane/EtOAc 85:15).

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.46-7.43 (m, 1H), 7.16 (d, *J* = 8.5 Hz, 1H), 7.05 (dd, *J* = 8.4, 1.5 Hz, 1H), 6.97 (d, *J* = 3.0 Hz, 1H), 6.38 (dd, *J* = 3.1, 0.8 Hz, 1H), 3.84 (q, *J* = 9.9 Hz, 1H), 3.74 (s, 3H), 2.37 (t, *J* = 11.1 Hz, 1H), 2.15-2.04 (m, 2H), 1.75 (q, *J* = 5.7 Hz, 2H), 1.66-1.59 (m, 2H), 1.34 (t, *J* = 6.1 Hz, 2H), 1.19-1.05 (m, 2H), 0.91 (s, 3H), 0.89 (s, 3H), 0.88 (s, 6H), 0.81 (s, 6H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 136.0, 135.5, 128.6, 128.5, 121.6, 118.7, 108.3, 100.7, 82.6, 37.0, 36.4, 36.3, 35.8 (br), 35.5, 34.7, 33.1, 32.9, 29.9, 28.8 (br), 24.9, 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 $C_{26}H_{38}BNO_2$ $[M]^+$: 407.2996; found: 407.2985.

4-{(1*R**,2*S**)-7,7-Dimethyl-1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)spiro[3.5]nonan-2-yl}pyridine, **25i**

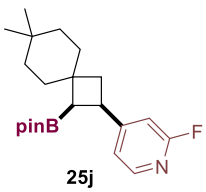


25i

From **24b** (40.4 mg, 0.1 mmol) following the general procedure described above using 4-bromopyridine as aryl electrophile (freshly prepared from 4-bromopyridine hydrochloride), compound **25i** (23.8 mg, 0.067 mmol) was obtained in 67% yield as a white solid, after purification by flash column chromatography (SiO_2; hexane/EtOAc 90:10 to 80:20). **mp** = 115-117 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ 8.43 (d, *J* = 4.1 Hz, 2H), 7.08 (d, *J* = 5.3 Hz, 2H), 3.65 (q, *J* = 10.3 Hz, 1H), 2.27 (t, *J* = 10.5 Hz, 1H), 2.12-2.00 (m, 2H), 1.78-1.66 (m, 2H), 1.55 (t, *J* = 6.2 Hz, 1H), 1.31 (t, *J* = 6.1 Hz, 1H), 1.17-1.06 (m, 2H), 0.99 (s, 6H), 0.91-0.86 (m, 12H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 154.6, 149.2, 122.6, 83.1, 37.8, 36.3, 36.1, 34.7, 34.4, 33.1, 29.8, 28.5 (br), 24.9, 24.8 [note: *the carbon attached to boron was not observed due to quadrupole broadening caused by the ^{11}B nucleus*]. **^{11}B NMR** (96 MHz, $CDCl_3$): δ 31.6. **HRMS (ESI$^+$)**: calculated for $C_{22}H_{35}BNO_2$ $[M+H]^+$: 356.2761; found: 356.2758.

4-{(1*R**,2*S**)-7,7-Dimethyl-1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl}spiro[3.5]nonan-2-yl)-2-fluoropyridine, **25j**

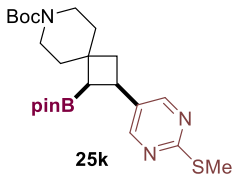


25j

From **24b** (40.4 mg, 0.1 mmol) following the general procedure described above using 4-bromo-2-fluoropyridine as aryl electrophile, compound **25j** (21.2 mg, 0.057 mmol) was obtained in 57% yield as a pale yellow solid, after purification by flash column chromatography (SiO_2; cyclohexane/EtOAc 90:10). **mp** = 130-132 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ 8.03 (d, *J* = 5.2 Hz, 1H), 6.93 (d, *J* = 5.2 Hz, 1H), 6.72 (s, 1H), 3.66 (q, *J* = 9.7 Hz, 1H), 2.24 (t, *J* = 11.0 Hz, 1H), 2.08 (d, *J* = 9.1 Hz, 2H), 1.71 (q, *J* = 5.6 Hz, 2H), 1.54 (t, *J* = 5.9 Hz, 2H), 1.31 (t, *J* = 6.1 Hz, 2H), 1.17-1.09 (m, 2H), 1.03 (s, 6H), 0.92 (s, 6H), 0.89 (s, 3H), 0.88 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 164.1 (d, *J* = 237.6 Hz), 161.1 (d, *J* = 7.7 Hz), 146.7 (d, *J* = 15.3 Hz), 120.4 (d, *J* = 3.8 Hz), 107.80 (d, *J* = 36.8 Hz), 83.2, 37.9, 36.3, 36.0, 34.8, 34.7, 34.4, 33.2, 29.8, 28.6 (br), 24.9, 24.8. [note: *the carbon attached to boron was not observed due to quadrupole broadening caused by the ^{11}B nucleus*]. **^{19}F NMR** (282 MHz, $CDCl_3$): δ –73.1.

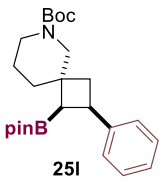
(1*R**,2*S**)-*tert*-butyl 2-(2-(methylthio)pyrimidin-5-yl)-1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-7-azaspiro[3.5]nonane-7-carboxylate, **25k**



From **24a** (47.7 mg, 0.1 mmol) following the general procedure described above using 5-bromo-2-(methylthio)pyrimidine as aryl electrophile, compound **25k** (23.3 mg, 0.049 mmol) was obtained in 49% yield as a yellow pale solid, after purification by flash column chromatography (SiO_2; DCM/EtOAc 90:10). **mp** = 145-148 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ 8.36 (s, 2H), 3.66 (q, *J* = 9.9 Hz, 1H), 3.51-3.38 (m, 2H), 3.34-3.17 (m, 2H), 2.53 (s, 3H), 2.37 (t, *J* = 10.7 Hz, 1H), 2.18-2.07 (m, 2H), 1.80-1.72 (m, 2H), 1.67-1.59 (m, 2H), 1.45 (s, 9H), 1.02 (s, 6H), 0.96 (s, 6H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 169.7, 156.4, 155.0, 131.7, 83.5, 79.5, 41.0 (br), 37.4, 36.6, 36.5, 34.0, 30.3, 28.6, 24.9, 24.8, 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 $C_{24}H_{39}BN_3O_4S$ $[M+H]^+$: 476.2754; found: 476.2739.

(1*R**,2*S**)-*tert*-butyl 2-phenyl-1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-6-azaspiro[3.5]nonane-6-carboxylate, **25l**

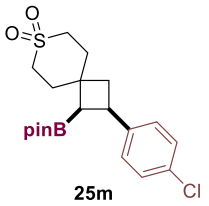


25l

From **24m** (23.9 mg, 0.05 mmol) following the general procedure described above using bromobenzene as aryl electrophile, compound **25l** (10.7 mg, 0.025 mmol) was obtained in 50% yield as a yellow pale solid, after purification by flash column chromatography (SiO_2; cyclohexane/EtOAc 95:5). **mp** = 175-177 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.26-7.16 (m, 4H), 7.15-7.07 (m, 1H), 4.43 (br, 1H), 4.08 (br, 1H), 3.81-3.39 (m, 2H), 2.70-2.41 (m, 2H), 2.12-1.91 (m, 3H), 1.60-1.43 (m, 12H), 0.94 (s, 6H), 0.88 (s, 6H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 155.5, 144.3, 127.9, 127.3, 125.7, 83.1, 79.1, 53.5 (br), 44.2 (br), 36.8, 36.1, 35.3, 32.3 (br), 28.7, 25.0, 24.8, 22.8 [note: *the carbon attached to boron was not observed due to quadrupole broadening caused by the ^{11}B nucleus*]. **HRMS (ESI$^+$)**: calculated for $C_{25}H_{38}BNNaO_4$ $[M+Na]^+$: 450.2792; found: 450.2782.

(1*R**,2*S**)-2-(4-Chlorophenyl)-1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-7-thiaspiro[3.5]nonane 7,7-dioxide, **25m**



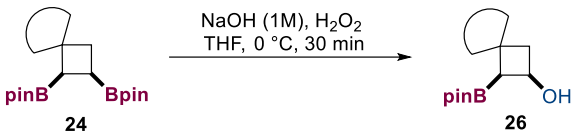
25m

From **24e** (51.0 mg, 0.12 mmol) following the general procedure described above using 1-bromo-4-chlorobenzene as aryl electrophile, compound **25m** (37.0 mg, 0.090 mmol) was obtained in 75% yield as a white solid, after purification by flash column chromatography (SiO_2; DCM/EtOAc 98:2). **mp** = 192-194 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.26-7.19 (m, 2H), 7.12-7.06 (m, 2H), 3.75 (q, *J* = 10.0 Hz, 1H), 3.12-2.99 (m, 2H), 2.92-2.80 (m, 2H), 2.49-2.24 (m, 5H),

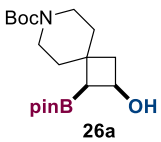
2.20-2.09 (m, 2H), 096-0.89 (m, 12H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 141.6, 131.8, 128.5, 128.1, 83.5, 48.8, 48.5, 35.2, 35.0, 34.4, 34.0, 33.9, 24.9, 24.7. [note: *the carbon attached to boron was not observed due to quadrupole broadening caused by the ^{11}B nucleus*]. **^{11}B NMR** (96 MHz, $CDCl_3$): δ 31.6. **HRMS (EI$^+$)**: calculated for $C_{20}H_{28}BClO_4S$ $[M]^+$: 410.1490; found: 410.1478.

3.5 General Procedure for the Chemoselective Oxidation of Diborylated Spirocycles, 26



An oven-dried vial was charged with diboronic ester **24** (1.0 equiv), THF (0.2 mL) and an aqueous solution of NaOH (1M, 1.0 equiv). Then, the reaction mixture was cooled to 0 °C, followed by the addition of a solution of H_2O_2 (30% (w/w), 1.0 equiv). The resulting mixture was stirred for 30 min at 0 °C. Once the reaction was finished, the aqueous layer was extracted with ethyl acetate (3 x 10 mL) and the combined organics were dried over $MgSO_4$, filtered, and concentrated under reduced pressured. The combined organic layers were washed with saturated NaCl solution, dried over $MgSO_4$, and finally concentrated under reduced pressure. The crude product was purified by flash column chromatography on silica gel to afford alcohol **26**.

(1*S**,2*R**)-*tert*-butyl 2-hydroxy-1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-7-azaspiro[3.5]nonane-7-carboxylate, **26a**

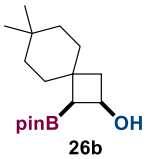


26a

From **24a** (143.2 mg, 0.3 mmol) following the general procedure described above, compound **26a** (55.0 mg, 0.150 mmol) was obtained in 50% yield as a white solid, after purification by flash column chromatography (SiO_2; cyclohexane/EtOAc 90:10 to 85:15). **mp** = 97-99 °C.

^{1}H NMR (300 MHz, $CDCl_3$): 4.27 (dq, *J* = 9.6, 7.6 Hz, 1H), 3.45-3.10 (m, 5H), 2.28 (ddd, *J* = 11.3, 7.5, 3.6 Hz, 1H), 2.04 (dd, *J* = 8.2, 3.6 Hz, 1H), 1.74 (dd, *J* = 11.6, 7.7 Hz, 1H), 1.55-1.46 (m, 4H), 1.40 (s, 9H), 1.30-1.23 (m, 12H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 155.0, 83.8, 79.3, 64.4, 43.4, 41.0 (br), 38.3, 37.5, 37.0 (br), 32.3, 28.5, 25.3, 24.9. **^{11}B NMR** (96 MHz, $CDCl_3$): δ 31.9. **HRMS (ESI$^+$)**: calculated for $C_{19}H_{34}BNNaO_5$ $[M+Na]^+$: 390.2428; found: 390.2415.

(1*S**,2*R**)-7,7-dimethyl-1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)spiro[3.5]nonan-2-ol, **26b**



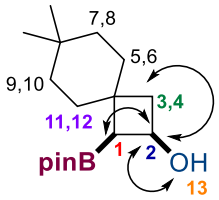
26b

From **24b** (121.3 mg, 0.3 mmol) following the general procedure described above, compound **26b** (49.0 mg, 0.167 mmol) was obtained in 56% yield as a white solid, after purification by flash column chromatography (SiO_2; cyclohexane/EtOAc 90:10). **mp** = 67-69 °C.

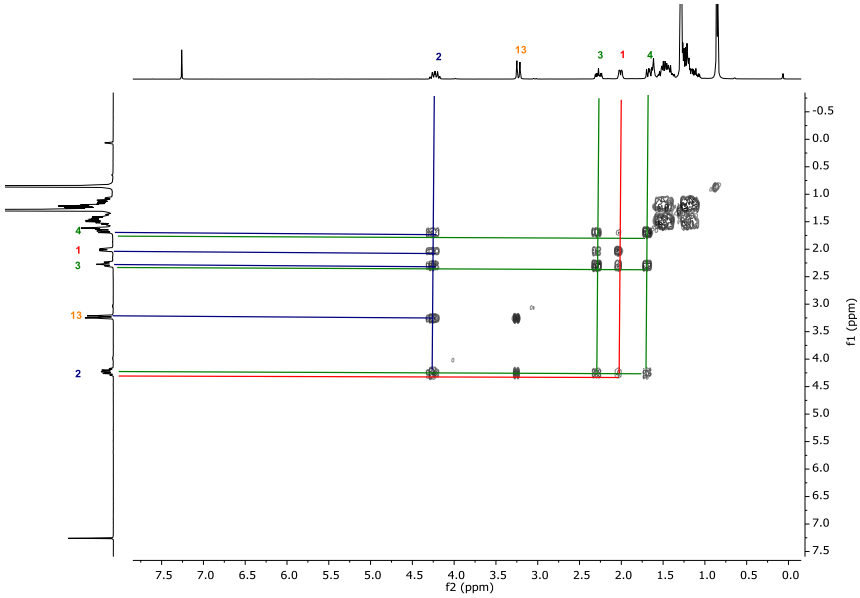
^{1}H NMR (300 MHz, $CDCl_3$): 4.22 (dq, *J* = 11.1, 7.9 Hz, 1H), 3.23 (d, *J* = 11.1 Hz, 1H), 2.32-2.20 (m, 1H), 2.00 (dd, *J* = 8.4, 3.6 Hz, 1H), 1.66 (dd, *J* = 11.4, 7.9 Hz, 1H), 1.56-1.35 (m, 4H), 1.30-1.24 (m, 12H), 1.22-1.04 (m, 4H), 0.85 (s, 3H), 0.84 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 83.7, 64.8, 44.0, 37.5 (br), 36.3, 36.0, 35.3, 34.6, 33.6, 29.6, 29.3 (br), 27.6 (br), 25.4, 25.0. **^{11}B NMR** (96 MHz, $CDCl_3$): δ 33.4. **HRMS (ESI$^+$)**: calculated for $C_{17}H_{31}BNaO_3$ $[M]^+$: 317.2264; found: 317.2249.

2D-NMR spectroscopy (COSY and HMBC) was used to elucidate the structure

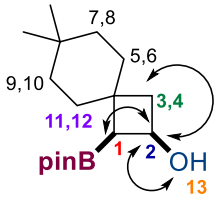
Vicinal COSY Correlations of **26b**



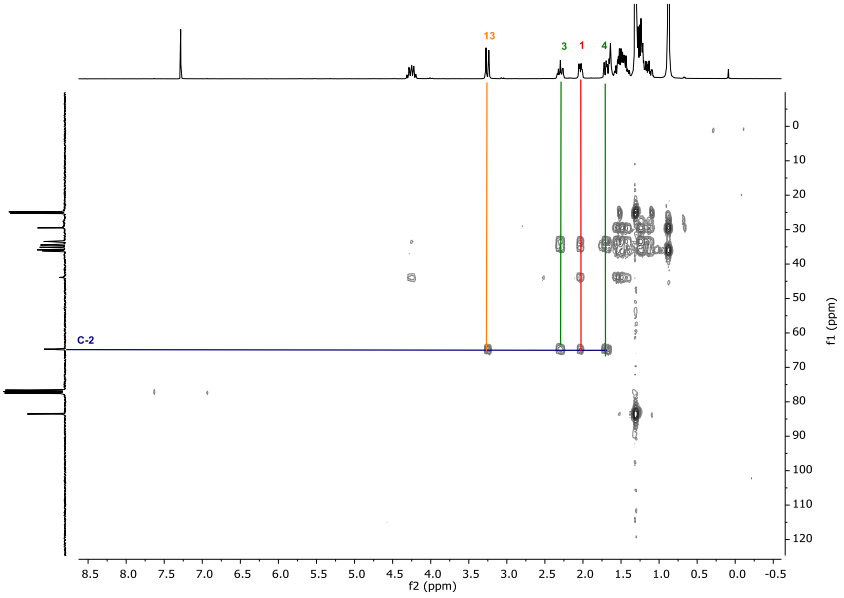
Key evidence
CH(1): COSY to CH(2)
CH(2): COSY to methylene group CH_2(3,4), CH(1) and OH(13)
CH_2(3,4): COSY to CH(2)
Numbers denote proton identifiers



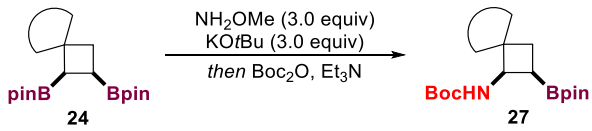
HMBC Correlations of **26b**



Key evidence
CH(2): HMBC to CH(13), CH_2(3,4)and CH(1)
No HMBC correlation with CH_2(11,12)
Numbers denote proton and carbon identifiers



3.6 General Procedure for the Chemoselective Amination of Diborylated Spirocycles, 27



Preparation of methoxyamine solution: to a round bottom flask was added *O*-methylhydroxylamine hydrochloride (15.0 g, 0.18 mol) and sodium hydroxide (7.2 g, 0.18 mol). The flask was purged with N_2, anhydrous THF (30.0 mL) and one drop of water were added. The mixture was vigorously stirred for 12 h. The supernatant was then transferred to another flame-dried round bottom flask containing DRIERITE® (49.0 g). The solution was stirring for 16 hours. The supernatant was filtered under an atmosphere of N_2 with THF washes (2 x 10 mL). The concentration of the methoxyamine THF solution was determined by ^{1}H NMR spectroscopy using toluene as an internal standard (solution concentration typically around 1.8 M).

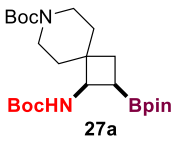
In a nitrogen-filled glove box an oven-dried vial was charged with potassium *tert*-butoxide (3.0 equiv) and anhydrous toluene (0.4 mL/0.1 mmol). To this mixture, a solution of *O*-methylhydroxylamine (3 equiv) in THF was added followed by a solution of diboronic ester **24** (1.0 equiv) in anhydrous THF (0.35 mL/0.1 mmol). The vial was sealed with a septum and placed outside the glove box.[221] The reaction mixture was stirred for 14 h at 60 °C (oil bath). After this time, the reaction was cooled to room temperature, NaOH (3 M aqueous solution, 1.7 mL/0.1 mmol) was added

[221] Edelstein, E. K.; Grote, A. C.; Palkowitz, M. D.; Morken, J. P. *Synlett*. **2018**, *29*, 1749–1752.

and the resulting mixture stirred for 5 min. There upon, the resulted mixture was extracted with DCM (3× 10 mL) and the combined organic layers were washed with saturated NaCl solution, dried over $MgSO_4$ and finally concentrated under reduced pressure.

Then, the crude residue was again dissolved in DCM (1.5 mL), and triethylamine was dropwise added (2 equiv) followed by di-*tert*-butyl dicarbonate (4 equiv). The solution was stirred for 16 h at room temperature. After this time, H_2O (10 mL) was added, and the resulted mixture was extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with saturated NaCl solution, dried over $MgSO_4$, and finally concentrated under reduced pressure. The crude product was purified by flash column chromatography on silica gel to afford **27**.

(1*R**,2*R**)-*tert*-Butyl 1-((*tert*-butoxycarbonyl)amino)-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-7-azaspiro[3.5]nonane-7-carboxylate, **27a**



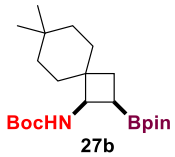
27a

From **24a** (143.2 mg, 0.3 mmol) following the general procedure described above, compound **27a** (55.3 mg, 0.119 mmol) was obtained in 40% yield as a white solid, after purification by flash column chromatography (SiO_2; cyclohexane/EtOAc 95:5). The yield based on recovered starting material is 63%. **mp** = 114-116 °C.

^{1}H NMR (300 MHz, $CDCl_3$, mixture of rotamers): δ 5.82-5.54 (m, 1H), 4.05-3.93 (m, 1H), 3.81-3.57 (m, 2H), 3.06-2.64 (m, 2H), 2.22-2.10 (m, 1H), 1.74-1.59 (m, 3H), 1.50-1.35 (m, 21H), 1.24 (s, 12H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 155.5, 155.0, 83.7, 79.2, 78.8, 53.5, 43.4, 40.9 (br), 39.9 (br), 37.7, 30.6,

28.6, 28.5, 24.9, 24.8, 17.2 (br). **HRMS (ESI$^+$)**: calculated for $C_{24}H_{43}BN_2NaO_6$ $[M+Na]^+$: 489.3112; found: 489.3103.

(1*R**,2*R**)-*tert*-Butyl 7,7-dimethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)spiro[3.5]nonan-1-yl)carbamate, **27b**



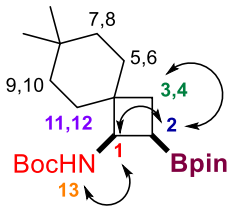
27b

From **24b** (80.8 mg, 0.2 mmol) following the general procedure described above, compound **27b** (40.1 mg, 0.102 mmol) was obtained in 51% yield as a white solid, after purification by flash column chromatography (SiO_2; cyclohexane/EtOAc 98:2). The yield based on recovered starting material is 66%. **mp** = 89-91 °C.

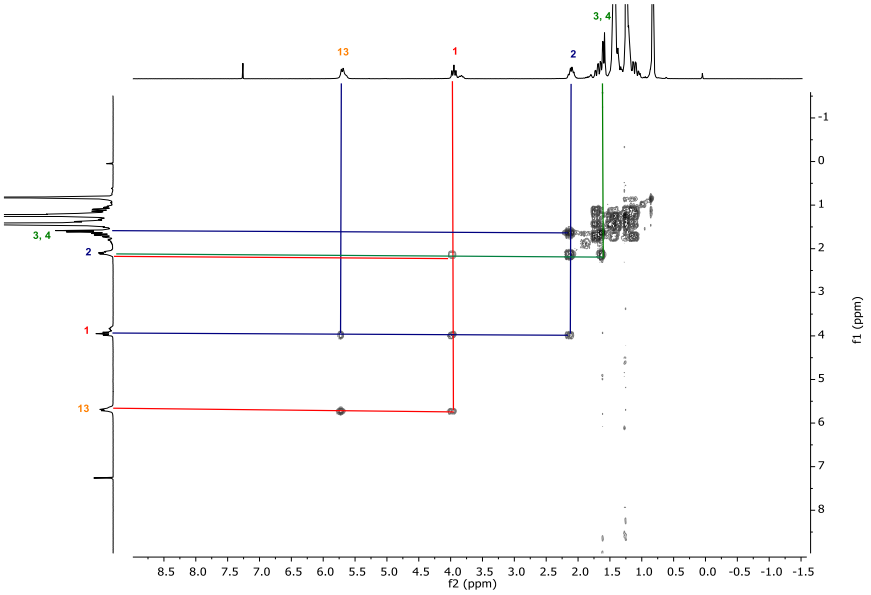
^{1}H NMR (300 MHz, $CDCl_3$, mixture of rotamers): δ 5.77-5.61 (m, 1H), 3.96 (t, *J* = 9.7 Hz, 1H), 3.85 (t, *J* = 9.4 Hz, rotamer), 2.17-2.02 (m, 1H), 1.77-1.58 (m, 3H), 1.48-1.38 (m, 12H), 1.31-1.03 (m, 16H), 0.83 (s, 6H). **^{13}C NMR** (75 MHz, $CDCl_3$, mixture of rotamers): δ 155.6 (155.8), 83.4 (83.6), 78.5 (79.3), 54.0 (54.9), 44.8 (45.2), 35.6, 34.9, 34.6, 31.0 (31.9), 29.8, 29.2 (29.0), 28.6, 27.1 (26.8), 24.9, 24.8, 17.3 (br). **^{11}B NMR** (96 MHz, $CDCl_3$): δ 33.8. **HRMS (ESI$^+$)**: calculated for $C_{22}H_{40}BNNaO_4$ $[M+Na]^+$: 416.2948; found: 416.2942.

2D-NMR spectroscopy (COSY and HMBC) was used to elucidate the structure

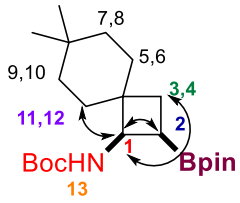
Vicinal COSY Correlations of **27b**



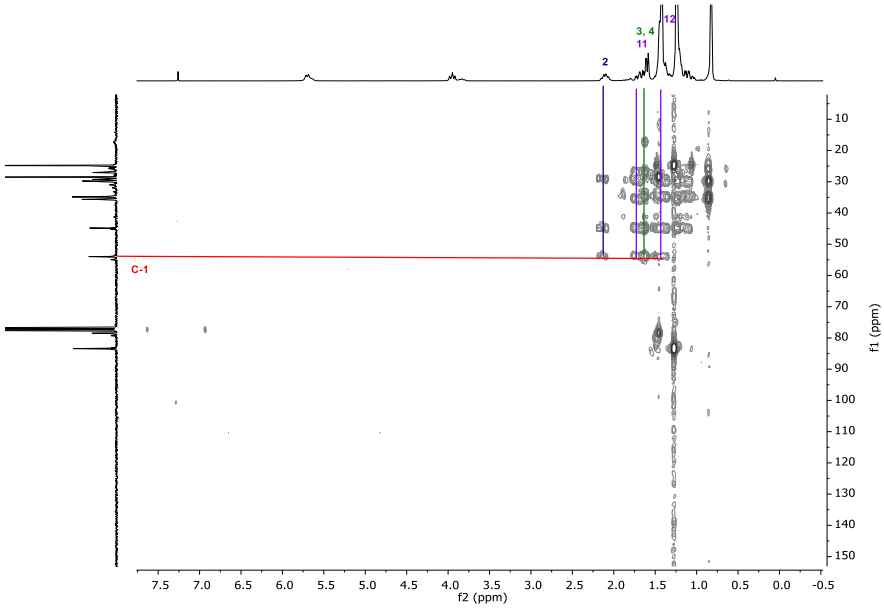
Key evidence
CH(1): COSY to NH(13) and CH(2)
CH(2): COSY to methylene group CH_2(3,4)
CH_2(3,4): COSY to CH(2)
No COSY correlation between CH(1) and CH_2(3,4)
Numbers denote proton identifiers



HMBC Correlations of **27b**

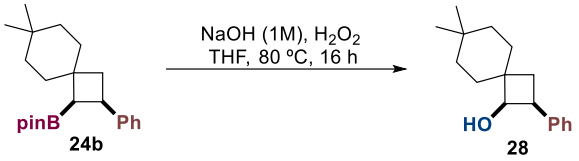


Key evidence
CH(1): HMBC to CH(2), CH_2(3,4) and CH_2(11,12)
Numbers denote proton and carbon identifiers



3.6 Difunctionalization of C–B bonds

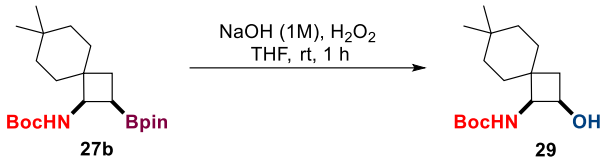
Cross-coupling/Oxidation**: Synthesis of (1R*,2S*)-7,7-dimethyl-2-phenylspiro[3.5]nonan-1-ol, **28



To boronic ester **24b** (35.4 mg, 0.10 mmol, 1.0 equiv) in THF (0.2 mL), an aqueous solution of NaOH (1.0 mL, 1.0 mmol, 1M) was added. Then, a solution of H_2O_2 (0.2 mL, 30% (w/w), 20 equiv) was added dropwise. The resulting reaction mixture was stirred for 14 h at 80 °C (oil bath). After this time, the aqueous layer was extracted with ethyl acetate (3 x 10 mL) and the combined organics were dried over $MgSO_4$, filtered, and concentrated under reduced pressured. The crude product was purified by flash column chromatography on silica gel (SiO_2; cyclohexane/EtOAc 90:10). Compound **28** (20.5 mg, 0.084 mmol) was obtained in 84% yield as a white solid. **mp** = 70-72 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.39-7.32 (m, 2H), 7.28-7.21 (m, 3H), 4.16 (dd, *J* = 6.9, 2.7 Hz, 1H), 3.75 (td, *J* = 9.0, 6.8 Hz, 1H), 2.17 (dd, *J* = 11.2, 8.9 Hz, 1H), 2.00 (ddd, *J* = 11.5, 8.8, 2.7 Hz, 1H), 1.69-1.56 (m, 3H), 1.50-1.40 (m, 1H), 1.36-1.18 (m, 5H), 0.93 (s, 3H), 0.91 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 138.8, 128.7, 128.6, 126.6, 75.9, 41.2, 40.3, 36.0, 35.7, 33.4, 32.7, 29.9, 29.3 (br), 27.8 (br), 27.7. **HRMS (ESI$^+$)**: calculated for $C_{17}H_{24}NaO$ $[M+Na]^+$: 267.1725; found: 267.1711.

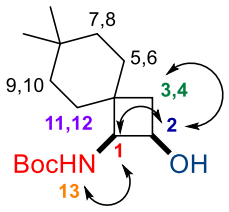
General Procedure for the Chemoselective Amination/Oxidation**: Synthesis of (1S*,2R*)-tert-butyl (2-hydroxy-7,7-dimethylspiro[3.5]nonan-1-yl) carbamate, **29



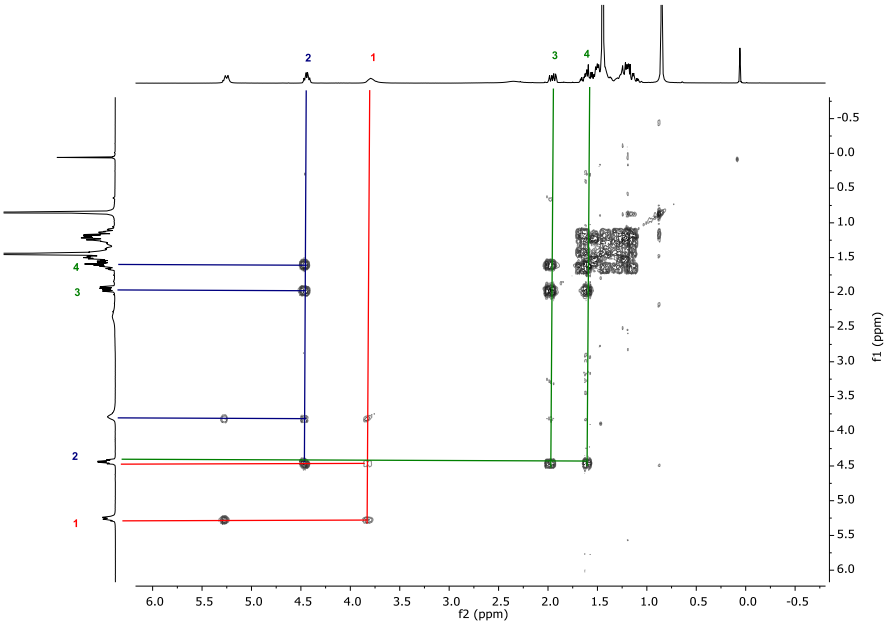
To boronic ester **27b** (39.3 mg, 0.10 mmol, 1.0 equiv) in THF (0.2 mL), an aqueous solution of NaOH (0.10 mL, 0.10 mmol, 1M) was added, and the reaction mixture was cooled to 0 °C. Then, a solution of H_2O_2 (20 µL, 30% (w/w), 2.0 equiv) was added dropwise. A white precipitate was formed within 10 min. After 1h at room temperature, water was added, and the mixture was extracted with EtOAc (3x). The combined organic layers were washed with brine, dried with $MgSO_4$, filtered, and concentrated under reduced pressured. The crude product was purified by flash column chromatography on silica gel (SiO_2; cyclohexane/EtOAc 70:30). Compound **29** (23.2 mg, 0.082 mmol) was obtained in 82% yield as colourless oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ 5.24 (d, *J* = 8.3 Hz, 1H), 4.45 (td, *J* = 6.7, 3.9 Hz, 1H), 3.80 (br, 1H), 2.17 (br, 1H), 1.96 (ddd, *J* = 12.7, 6.9, 1.8 Hz, 1H), 1.68-1.38 (m, 14H), 1.29-1.09 (m, 4H), 0.86 (s, 6H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 156.2, 79.5, 65.8, 56.5, 41.6, 39.0, 36.0, 35.0, 34.5, 30.4 (br), 29.7, 28.7, 28.5, 26.6 (br). **HRMS (ESI$^+$)**: calculated for $C_{16}H_{29}NO_2$ [M-OH]$^+$: 267.2198; found: 267.1710.

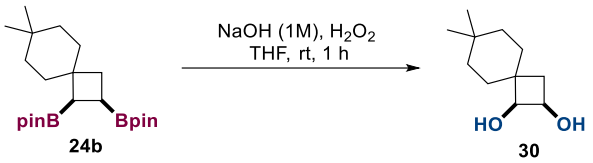
2D-NMR spectroscopy (COSY) was used to elucidate the structure of 29



Key evidence
CH(2): COSY to CH_2(3,4) and CH(1).
CH(1): COSY to NH(13) and CH(2)
CH_2(3,4): COSY to CH(2)
No COSY correlation between CH(1) and CH_2(3,4)
Numbers denote proton identifiers



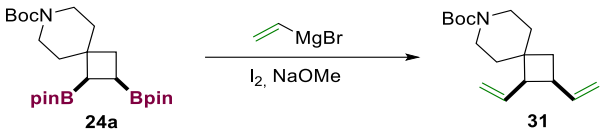
Double Oxidation**: Synthesis of (1S*,2R*)-7,7-dimethylspiro[3.5]nonane-1,2-diol, **30



To boronic ester **24b** (40.4 mg, 0.10 mmol, 1.0 equiv) in THF (0.2 mL), an aqueous solution of NaOH (0.20 mL, 0.20 mmol, 1M) was added, and the reaction mixture was cooled to 0 °C. Then, a solution of H_2O_2 (40 µL, 30% (w/w), 4.0 equiv) was added dropwise. A white precipitate was formed within 10 min. After 1h at room temperature, water was added, and the mixture was extracted with EtOAc (3x). The combined organic layers were washed with brine, dried with $MgSO_4$, filtered, and concentrated under reduced pressured. The crude product was purified by flash column chromatography on silica gel (SiO_2; hexane/EtOAc 70:30). Diol **30** (15.0 mg, 0.081 mmol) was obtained in 81% yield as white solid. **mp** = 110-112 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ 4.27 (dt, *J* = 6.9, 5.5 Hz, 1H), 3.90 (dd, *J* = 5.6, 2.6 Hz, 1H), 2.45 (br, 1H), 1.98 (ddd, *J* = 12.3, 7.0, 2.6 Hz, 1H), 1.69-1.58 (m, 2H), 1.56-1.32 (m, 3H), 1.31-1.14 (m, 5H), 0.87 (s, 6H).**^{13}C NMR** (75 MHz, $CDCl_3$): δ 74.8, 65.2, 40.8, 39.7, 35.9, 35.6, 33.2, 29.8, 29.4 (br), 27.6. **HRMS (ESI$^+$)**: calculated for $C_{11}H_{20}NaO_2$ $[M+Na]^+$: 207.1361; found: 207.1350.

Double Vinylation**: Synthesis of (1R*,2S*)-tert-butyl 1,2-divinyl-7-azaspiro [3.5]nonane-7-carboxylate, **31



24a 31

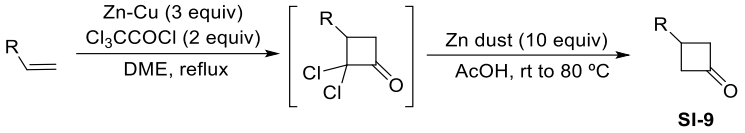
A stirred solution of boronic ester **24a** (47.7 mg, 0.10 mmol, 1.0 equiv) in THF (0.5 mL) and DMSO (0.5 mL), under an argon atmosphere, was cooled to 0 °C and a solution of vinyl magnesium bromide (842 µL, 0.8 mmol, 8.0 equiv, 0.95 M), was added dropwise. The resulting mixture was stirred at room temperature for 30 min. Then, the solution was cooled again to 0 °C and a suspension of NaOMe (54 mg, 1.0 mmol, 10 equiv) in MeOH (3M) was added, followed by addition (dropwise) of a solution of iodine (0.5 M in MeOH, 1.6 mL, 0.8 mmol, 8.0 equiv). The resulting mixture was stirred at room temperature for 3 h. After this time, $MgSO_4$ (saturated aqueous solution, 5 mL) was added, followed by DCM. The phases were separated, and the aqueous phase was extracted with DCM (3x). The combined organic layers were dried with $MgSO_4$, filtered, and concentrated under reduced pressured. The crude product was purified by flash column chromatography on silica gel (SiO_2; cyclohexane/EtOAc 95:5). The desired compound **31** (25.0 mg, 0.090 mmol) was obtained in 90% yield as pale-yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ 6.01-5.80 (m, 2H), 5.12-4.90 (m, 4H), 3.55-3.43 (m, 1H), 3.42-3.23 (m, 2H), 3.19-3.05 (m, 2H), 2.73 (t, *J* = 10.3 Hz, 1H), 2.05-1.80 (m 2H), 1.71-1.58 (m, 2H), 1.48-1.38 (m, 11H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 155.1, 139.9, 136.1, 116.8, 114.4, 79.3, 51.7, 40.9, 40.5, 38.1,

37.8, 36.4, 34.4, 34.2, 28.6. **HRMS (ESI$^+$)**: calculated for $C_{17}H_{27}NNaO_2$ $[M+Na]^+$: 300.1939; found: 300.1926.

3.7 General Procedure for the Synthesis of Monosubstituted Cyclobutenes

*General Procedure for the Synthesis of Cyclobutanones, **SI-9***



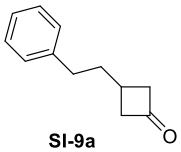
SI-9

To a suspension of zinc-copper couple (3.0 equiv) and the corresponding alkene (1.0 equiv) in 1,2-dimetoxy ethane (2mL/mmol) was added trichloroacetyl chloride (2 equiv) dropwise at 0 °C under argon atmosphere. The suspension was allowed to warm to room temperature and after stirring for 16 hours, the resulting mixture was filtered through a pad of Celite® (Et_2O). The filtrate was washed with H_2O, a saturated aqueous solution of $NaHCO_3$ and brine, then dried over $MgSO_4$ and the solvent removed *in vacuo*. The residue was used in the next step without further purification.

Then, the 2,2-dichlorocyclobutanone was dissolved in AcOH (2 mL/mmol) and Zn dust (10 equiv) was added portionwise at room temperature. The resulting mixture was stirred 4 hours at 80 °C. The resulting mixture was allowed to cool to room temperature, followed by diluting with water and extracted with Et_2O. The organic phase was washed

successively with a saturated solution of aqueous $NaHCO_3$, water and brine, then dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by flash column chromatography on silica gel to afford compound **SI-9**.

3-Phenethylcyclobutanone, SI-9a

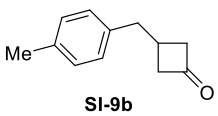


SI-9a

From 4-phenyl-1-butene (3.76 mL, 25.0 mmol) following the general procedure described above, compound **SI-9a** (2.65 g, 15.21 mmol) was obtained in 61% yield as a colorless oil, after purification by flash column chromatography (SiO_2; hexane/EtOAc 90:10).

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.37-7.16 (m, 5H), 3.25-3.08 (m, 2H), 2.78-2.63 (m, 4H), 2.49-2-32 (m, 1H), 2.01-1.88 (m, 2H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 208.1, 141.5, 128.6, 128.5, 126.1, 52.6, 38.1, 34.7, 23.6. **HRMS (EI$^+$)**: calculated for $C_{12}H_{14}O$ $[M]^+$: 174.1045; found: 174.1046.

3-(4-Methylbenzyl)cyclobutanone, SI-9b

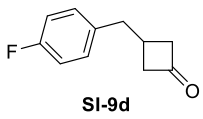


SI-9b

From 4-allyltoluene (1.0 mL, 6.54 mmol) following the general procedure described above, compound **SI-9b** (808 mg, 4.64 mmol) was obtained in 71% yield as a colorless oil, after purification by flash column chromatography (SiO_2; cyclohexane/EtOAc 90:10).

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.15-7.08 (m, 4H), 3.17-3.06 (m, 2H), 2.87 (d, *J* = 7.3 Hz, 2H), 2.83-2.65 (m, 3H), 2.34 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 207.9, 137.0, 136.0, 129.3, 128.5, 52.3, 41.5, 25.2, 21.1. **HRMS (EI$^+$)**: calculated for $C_{12}H_{14}O$ $[M]^+$: 174.1045; found: 174.1047.

3-(4-Fluorobenzyl)cyclobutanone, SI-9d

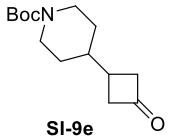


SI-9d

From 1-allyl-4-fluorobenzene (2.70 mL, 20.0 mmol) following the general procedure described above, compound **SI-9d** (1.98 g, 11.1 mmol) was obtained in 56% yield as a colorless oil, after purification by flash column chromatography (SiO_2; cyclohexane/EtOAc 95:5).

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.17-7.11 (m, 2H), 7.03-6.95 (m, 2H), 3.17-3.07 (m, 2H), 2.89-2.86 (m, 2H), 2.82-2.62 (m, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 207.5, 161.7 (d, $J_{C\text{-}F}$ = 244.4 Hz), 135.8 (d, $J_{C\text{-}F}$ = 3.3 Hz), 130.0 (d, $J_{C\text{-}F}$ = 7.9 Hz), 115.5 (d, $J_{C\text{-}F}$ = 21.4 Hz), 52.3, 41.2, 25.2. **^{19}F NMR** (282 MHz, $CDCl_3$): δ -166.7. **HRMS (EI$^+$)**: calculated for $C_{11}H_{11}FO$ $[M]^+$: 178.0794; found: 178.0799.

tert-Butyl 4-(3-oxocyclobutyl)piperidine-1-carboxylate, SI-9e

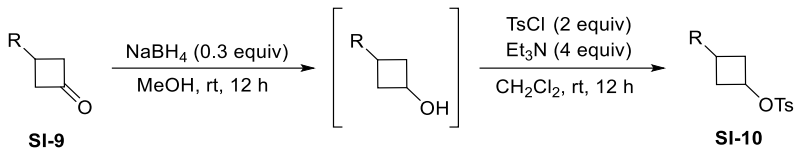


SI-9e

From *tert*-butyl 4-vinylpiperidine-1-carboxylate (1.9 g, 9.0 mmol) following the general procedure described above, compound **SI-9e** (790 mg, 3.1 mmol) was obtained in 35% yield as a colorless oil, after purification by flash column chromatography (SiO_2; cyclohexane/EtOAc 80:20).

^{1}H NMR (300 MHz, $CDCl_3$): δ 4.20-4.02 (m, 2H) 3.15-2.98 (m, 2H), 2.83-2.60 (m, 4H), 2.17-2.03 (m, 1H), 1.77-1.64 (m, 2H), 1.44 (s, 9H), 1.41-1.34 (m, 1H), 1.24-1.04 (m, 2H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 207.2, 154.9, 79.5, 50.7, 43.8 (br), 42.0, 30.0, 29.4, 28.5. **HRMS (EI$^+$)**: calculated for $C_{14}H_{23}NO_3$ $[M]^+$: 253.1678; found: 253.1687.

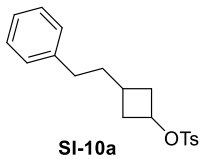
*General Procedure for the Synthesis of Tosyl-Cyclobutanes, **SI-10***



To a solution of the corresponding cyclobutanone **SI-9** (1 equiv) in MeOH (1.7 mL/mmol) at 0 °C, $NaBH_4$ (0.3 equiv) was added portionwise. The resulting mixture was stirred at room temperature for 12 h. Then, the solvent was evaporated, and the residue was re-dissolved in EtOAc (3 mL/mmol) and water (3 mL/mmol). The layers were separated, and the aqueous phase was extracted with EtOAc (3x). The organic phases were washed with brine, dried over $MgSO_4$ and the solvent evaporated under reduced pressure. The residue was used in the next step without further purification.

To a solution of the corresponding alcohol and triethylamine (4 equiv) in DCM (1.5 mL/mmol), a solution of TsCl (2.0 equiv) in DCM (0.6 mL/mmol) was added dropwise at 0 °C. After being stirred for 12 h at room temperature, water (2.5 mL/mmol of alcohol) and DCM (2.5 mL/mmol of alcohol) were added to the reaction mixture. Then, the layers were separated, and the aqueous phase was extracted with DCM (3x). The combined organic phases were dried ($MgSO_4$), filtered, and the solvent evaporated under reduced pressure. The residue was purified by flash column chromatography on silica gel to afford the desired product **SI-10**.

3-Phenethylcyclobutyl 4-methylbenzenesulfonate, SI-10a

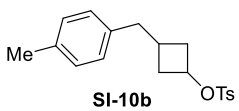


SI-10a

From cyclobutanone **SI-9a** (1.86 g, 10.67 mmol) following the general procedure described above, compound **SI-10a** (3.34 g, 10.11 mmol) was obtained in 95% yield as a pale yellow oil, after purification by flash column chromatography (SiO_2; cyclohexane/EtOAc 98:2 to 90:10).

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.79 (d, *J* = 7.6 Hz, 2H), 7.35 (d, *J* = 7.9 Hz, 2H), 7.30-7.08 (m, 5H), 4.99-4.87 (m, 1H, *minor isomer*), 4,70-4.57 (m, 1H, *major isomer*), 2.56-2.45 (m, 5H), 2.41-2.25 (m, 2H), 2.08-1.94 (m, 1H), 1.83-1.69 (m, 4H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 144.7, 141.8, 134.2, 129.9, 128.4 (3x), 127.9, (127.1), 125.9, (75.1), 71.3, (42.1), 38.4, (37.3), 37.0, 35.0, (34.0), 33.5, (28.0), 26.3, 21.7, (14.2). **HRMS (ESI$^+$)**: calculated for $C_{19}H_{22}NaO_3S$ $[M+Na]^+$: 353.1187; found: 353.1180.

3-(4-Methylbenzyl)cyclobutyl 4-methylbenzenesulfonate, SI-10b

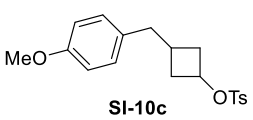


SI-10b

From cyclobutanone **SI-9b** (773 mg, 4.44 mmol) following the general procedure described above, compound **SI-10b** (1.13 g, 3.42 mmol) was obtained in 77% yield as a colorless oil, after purification by flash column chromatography (SiO_2; cyclohexane/EtOAc 98:2 to 90:10).

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.78 (d, *J* = 8.3 Hz, 2H), 7.33 (d, *J* = 8.1 Hz, 2H), 7.07 (d, *J* = 7.7 Hz, 2H), 6.96 (d, *J* = 7.8 Hz, 2H), 4.92 (quint, 6.7 Hz, 1H, *minor isomer*), 4.65 (quint, *J* = 7.4 Hz, 1H, *major isomer*), 2.65 (d, *J* = 7.1 Hz, 2H), 2.45 (s, 3H), 2.39-2.27 (m, 2H), 2.31 (s, 3H), 2.12-1.80 (m, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 144.7, 136.8, 135.7, 134.2, 129.9, 129.2, (128.6), 128.4, 127.9, (74.8), 71.5, 42.2, (40.9), 36.9, (34.7), (29.6), 28.2, 21.8, 21.1. **HRMS (ESI$^+$)**: calculated for $C_{19}H_{22}NaO_3S$ $[M+Na]^+$: 353.1187; found: 353.1186.

3-(4-Methoxybenzyl)cyclobutyl 4-methylbenzenesulfonate, SI-10c

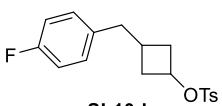


SI-10c

From cyclobutanone **SI-9c**[222] (937 mg, 4.93 mmol) following the general procedure described above, compound **SI-10c** (1.47 g, 4.24 mmol) was obtained in 86% yield as a colorless oil, after purification by flash column chromatography (SiO_2; cyclohexane/EtOAc 95:5 to 90:10).

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.77 (d, *J* = 8.3 Hz, 2H), 7.32 (d, *J* = 8.5 Hz, 2H), 6.98 (d, *J* = 8.4 Hz, 2H), 6.79 (d, *J* = 8.6, 2H), 4.90 (quint, *J* = 7.3 Hz, 1H, *minor isomer*), 4.63 (quint, *J* = 7.5 Hz, 1H, *major isomer*), 3.77 (s, 3H), 2.62 (d, *J* = 7.1 Hz, 2H), 2.44 (s, 3H), 2.38-2.28 (m, 2H), 2.10-1.78 (m, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 158.2, 144.7, 134.3, 132.0, 129.9, (129.6), 129.4, 128.0, 114.0, (74.8), 71.5, 55.4, 41.8, (40.4), 36.8, (34.7), (29.7), 28.4, 21.8. **HRMS (ESI$^+$)**: calculated for $C_{19}H_{22}NaO_4S$ $[M+Na]^+$: 369.1136; found: 369.1124.

3-(4-Fluorobenzyl)cyclobutyl 4-methylbenzenesulfonate, SI-10d



SI-10d

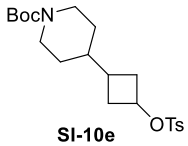
From cyclobutanone **SI-9d** (1.95 g, 10.94 mmol) following the general procedure described above, compound **SI-10d** (2.65 g, 7.92 mmol) was obtained in 72% yield as a colorless oil, after purification by flash column chromatography (SiO_2; cyclohexane/EtOAc 95:5 to 90:10).

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.78-7.72 (m, 2H), 7.36-7.28 (m, 2H), 7.04-6.87 (m, 4H), 4.94-4.82 (m, 1H, *minor isomer*), 4.70-4.57 (m, 1H, *major isomer*), 2.65 (d, *J* = 6.8 Hz, 2H), 2.44 (s, 3H), 2.39-2.25 (m, 2H), 2.10-1.78 (m, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 161.6 (d, $J_{C\text{-}F}$ = 243.9 Hz), 144.8, 135.5 (d, *J* =

[222] Malkov, A. V.; Friscourt, F.; Bell, M.; Swarbrick, M. E.; Kočovský, P. *J. Org. Chem.* **2008**, *73*, 3996–4003.

3.3 Hz), 134.2, 129.9), 129.8, 127.9, 115.3 (d, $J_{C\text{-}F}$ = 21.1 Hz), (74.6), 71.2, 41.7, (40.4), 36.8, (34.6), (29.6), 28.2, 21.7. **HRMS (ESI$^+$)**: calculated for $C_{18}H_{19}FNaO_3S$ $[M+Na]^+$: 357.0937; found: 357.0928.

tert-Butyl 4-(3-(tosyloxy)cyclobutyl)piperidine-1-carboxylate, **SI-10e**

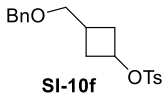


SI-10e

From cyclobutanone **SI-9e** (704 mg, 2.78 mmol) following the general procedure described above, compound **SI-10e** (820 mg, 2.00 mmol) was obtained in 72% yield as a white solid, after purification by flash column chromatography (SiO_2; cyclohexane/EtOAc 90:10 to 80:20). **mp** = 62-64 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.75 (d, *J* = 8.4 Hz, 2H), 7.31 (d, *J* = 8.0 Hz, 2H), 4.89-4.76 (m, 1H, *minor isomer*), 4.66-4.55 (m, 1H, *major isomer*), 4.15-3.94 (m, 2H), 2.66-2.52 (m, 2H), 2.42 (s, 3H), 2.37-2.24 (m, 2H), 1.84-1.67 (m, 2H), 1.58-1.45 (m, 3H), 1.41 (s, 9H), 1.32-1.18 (m, 1H), 0.96-0.82 (m, 2H). **^{13}C RMN** (75 MHz, $CDCl_3$): δ 154.9, 144.8, 134.2, 129.9, 127.9, 79.4, 71.0, 42.8, 35.1, 31.9, 29.2, 28.6, 21.7. **HRMS (ESI$^+$)**: calculated for $C_{21}H_{31}NNaO_5S$ $[M+Na]^+$: 432.1821; found: 432.1809.

3-((Benzyloxy)methyl)cyclobutyl 4-methylbenzenesulfonate, **SI-10f**



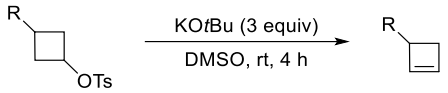
SI-10f

From cyclobutanone **SI-9f**[223] (3.61 g, 18.98 mmol) following the general procedure described above, compound **SI-10f** (5.93 g, 17.12 mmol) was obtained in 90% yield as a colorless oil, after purification by flash column chromatography (SiO_2; cyclohexane/EtOAc 90:10 to 80:20).

[223] Kabalka, G. W.; Yao, M.-L. *J. Org. Chem.* **2004**, *69*, 8280–8286.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.71 (d, *J* = 8.3 Hz, 2H), 7.30-7.18 (m, 7H), 6.64 (quint, J = 6.7 Hz, 1H), 4.40 (s, 2H), 3.32 (d, *J* = 5.6 Hz, 2H), 2.37 (s, 3H), 2.31-2.21 (m, 2H), 2.08-1.83 (m, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 144.6, 138.3, 134.0, 129.8, 128.3, 127.7, 127.5, 127.4, 73.3, 72.9, 71.3, 33.8, 26.5, 21.5. **HRMS (ESI$^+$)**: calculated for $C_{19}H_{22}NaO_4S$ $[M+Na]^+$: 369.1136; found: 369.1129.

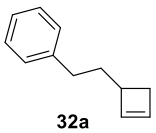
General Procedure for the Synthesis of Cyclobutenes, ***32***



SI-10 **32**

In an oven-dried flask, KO*t*Bu (3 equiv) was placed and anhydrous DMSO (2 mL/mmol) was added, under an argon atmosphere, to give a colorless solution. Then, a solution of the corresponding tosylate **SI-10** (1 equiv) in DMSO (2 mL/mmol) was added very slowly. After being stirred 4 h at room temperature, the crude was filtered through a pad of silica gel. The solvent was removed under reduced pressure to afford the desired compound **32** (**CAUTION**: some cyclobutenes are volatile).

(2-(Cyclobut-2-en-1-yl)ethyl)benzene, **32a**



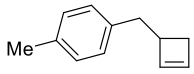
32a

From tosylate **SI-10a** (1.25 g, 3.78 mmol) following the general procedure described above, compound **32a** (435 mg, 2.75 mmol) was obtained in 73% yield as a colorless oil, after filtration through a pad of silica gel (pentane).

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.37-7.31 (m, 2H), 7.27-7.21 (m, 3H), 6.17-6.15 (m, 1H), 6.13-6.11 (m, 1H), 2.95-2.86 (m, 1H), 2.77-2.67 (m, 3H), 2.19-2.12

(m, 1H), 1.92-1.80 (m, 2H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 142.8, 140.8, 135.5, 128.6, 128.4, 125.8, 43.9, 36.9, 36.6, 34.6. **HRMS (EI$^+$)**: calculated for $C_{12}H_{14}$ $[M]^+$: 158.1096; found: 158.1088.

1-(Cyclobut-2-en-1-ylmethyl)-4-methylbenzene, **32b**

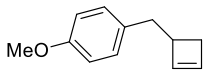


32b

From tosylate **SI-10b** (1.10 g, 3.33 mmol) following the general procedure described above, compound **32b** (232 mg, 1.47 mmol) was obtained in 44% yield as a colorless oil, after filtration through a pad of silica gel (pentane).

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.22-7.16 (m, 4H), 6.25-6.21 (m, 1H), 6.18-6.16 (m, 1H) 3.22-3.13 (m, 1H), 2.88-2.80 (m, 2H), 2.81-2.72 (m, 1H), 2.43 (s, 3H), 2.34-2.25 (m, 1H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 140.8, 138.4, 135.4, 135.3, 129.1, 128.6, 45.3, 40.6, 36.7, 21.1.

1-(Cyclobut-2-en-1-ylmethyl)-4-methoxybenzene, **32c**

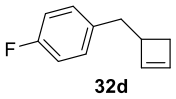


32c

From tosylate **SI-10c** (1.43 g, 4.13 mmol) following the general procedure described above, compound **32c** (485 mg, 2.78 mmol) was obtained in 67% yield as a pale-yellow oil, after filtration through a pad of silica gel (hexane/EtOAc 90:10).

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.11 (d, *J* = 8.4 Hz, 2H), 6.83 (d, *J* = 8.5 Hz, 2H), 6.14-6.09 (m, 1H), 6.08-6.04 (m, 1H), 3.79 (s, 3H), 3.09-2.99 (m, 1H), 2.75-2.69 (m, 2H), 2.69-2.60 (m, 1H), 2.22-2.12 (m, 1H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 158.0, 140.8, 135.5, 133.6, 129.6, 113.8, 55.4, 45.4, 40.1, 36.7. **HRMS (EI$^+$)**: calculated for $C_{12}H_{14}O$ $[M]^+$: 174.1045; found: 174.1041.

1-(Cyclobut-2-en-1-ylmethyl)-4-fluorobenzene, 32d

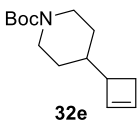


32d

From tosylate **SI-10d** (0.5 g, 1.50 mmol) following the general procedure described above, compound **32d** (211 mg, 1.30 mmol) was obtained in 87% yield as a colorless oil, after filtration through a pad of silica gel (pentane).

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.17-7.11 (m, 2H), 7.01-6.93 (m, 2H), 6.11-6.10 (m, 1H), 6.09-6.08 (m, 1H), 3.09-3.02 (m, 1H), 2.76 (d, *J* = 7.7 Hz, 2H), 2.66 (dd, *J* = 13.5 Hz, 4.1, 1H), 2.22-2.13 (m, 1H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 161.5 (d, *J* = 243.1 Hz), 140.5, 137.0 (d, *J* = 3.2 Hz), 135.7, 130.0 (d, *J* = 7.7 Hz), 115.1 (d, *J* = 21.0 Hz), 45.1, 40.2, 36.6. **HRMS (EI$^+$)**: calculated for $C_{11}H_{11}F$ $[M-F]^+$: 143.0861; found: 143.0875.

tert-Butyl 4-(cyclobut-2-en-1-yl)piperidine-1-carboxylate, 32e

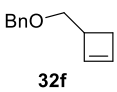


32e

From tosylate **SI-10e** (712 mg, 1.74 mmol) following the general procedure described above, compound **32e** (206 mg, 0.87 mmol) was obtained in 50% yield as a colorless oil, after filtration through a pad of silica gel (pentane/Et_2O 90:10).

^{1}H NMR (300 MHz, $CDCl_3$): δ 6.15-6.06 (m, 2H), 4.17-4.01 (m, 2H), 2.76-2.53 (m, 2H), 2.22-2.11 (m, 1H), 1.75-1.63 (m, 2H), 1.45 (s, 9H), 1.42-1.33 (m, 1H), 1.20-1.03 (m, 2H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 154.9, 138.9, 136.1, 79.1, 49.0, 44.0 (br), 40.5, 34.7, 29.6, 28.7. **HRMS (ESI$^+$)**: calculated for $C_{14}H_{23}NO_2$ $[M+Na]^+$: 260.1626; found: 260.1623.

((Cyclobut-2-en-1-ylmethoxy)methyl)benzene, 32f



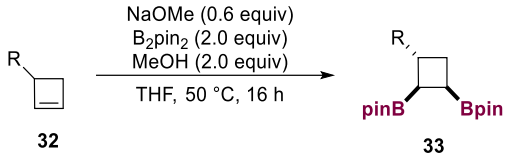
32f

From tosylate **SI-10f** (2.21 g, 6.38 mmol) following the general procedure described above, compound **32f** (823 mg, 4.72

mmol) was obtained in 74% yield as a colorless oil, after filtration through a pad of silica gel (pentane/Et_2O 90:10).

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.30-7.15 (m, 5H), 6.02 (s, 2H), 4.46 (s, 2H), 3.50-3.40 (m, 2H), 3.09-3.01 (m, 1H), 2.65-2.56 (m, 1H), 2.17-2.09 (m, 1H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 138.8, 138.5, 137.0, 128.5, 127.8, 127.6, 74.0, 73.2, 43.7, 34.6. **HRMS (EI$^+$)**: calculated for $C_{12}H_{14}O$ $[M]^+$: 174.1045; found: 174.1031.

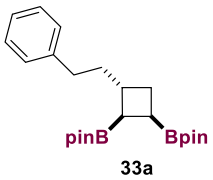
3.8 General Procedure for Metal-Free Diboration of Cyclobutenes, 33



32 **33**

An oven-dried vial was charged with sodium methoxide (0.6 equiv) and bis(pinacolato)diboron (2.0 equiv) was sealed with a septum inside a glove box. Then, the vial was placed outside the glove box and connected to an argon-vacuum line, evacuated and backfilled with argon (x3). Anhydrous THF (0.5 mL/0.2 mmol) was added to dissolve the mixture. Then, a solution of **32** (1 equiv) in THF (0.5 mL/0.2 mmol) was added followed by dry MeOH (2.0 equiv). The resulting mixture was stirred at 50 °C for 16 h. After cooling to room temperature, H_2O and EtOAc were added. The aqueous phase was extracted with EtOAc (3 × 10 mL). The organic layers were combined, dried ($MgSO_4$) and concentrated under reduced pressure. The crude product was purified by flash column chromatography on silica gel to afford **33**.

2,2'-(3-Phenethylcyclobutane-1,2-diyl)bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolane), **33a**

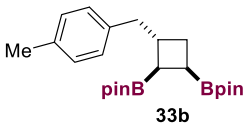


33a

From cyclobutene **32a** (31.6 mg, 0.2 mmol) following the general procedure described above, compound **33a** (62.7 mg, 0.15 mmol) was obtained in 76% yield as a white solid, after purification by flash column chromatography (SiO_2; cyclohexane/EtOAc 95:5).

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.29-7.10 (m, 5H), 2.59-2.33 (m, 3H), 2.17-2.04 (m, 1H), 1.98-1.80 (m, 2H), 1.77-1.61 (m, 3H), 1.31-1.19 (m, 24H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 143.4, 128.5, 128.3, 125.5, 83.2, 83.1, 39.9, 37.5, 33.5, 30.3, 25.2, 25.0, 24.8. [note: *the carbons attached to boron were not observed due to quadrupole broadening caused by the ^{11}B nucleus*]. **HRMS (ESI$^+$)**: calculated for $C_{24}H_{38}B_2NaO_4$ $[M+Na]^+$: 435.2854; found: 435.2868. **mp** = 89-91 °C.

2,2'-(3-(4-Methylbenzyl)cyclobutane-1,2-diyl)bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolane), **33b**



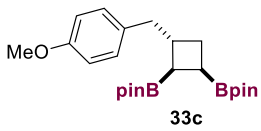
33b

From cyclobutene **32b** (31.6 mg, 0.2 mmol) following the general procedure described above, compound **33b** (56.0 mg, 0.14 mmol) was obtained in 68% yield as a white solid, after filtration through a pad of silica gel (cyclohexane/EtOAc 95:5).

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.07-7.01 (m,4H), 2.70-2.57 (m,3H), 2.29 (s, 3H), 2.11-2.02 (m, 1H), 1.97-1.85 (m, 2H), 1.77-1.71 (m, 1H), 1.24 (s, 12H), 1.19 (s, 6H), 1.15 (s, 6H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 138.0, 134.9, 128.9, 128.8, 83.1, 82.9, 43.4, 38.6, 30.1, 25.1, 24.9, 24.8, 21.1. [note: *the carbons attached to boron were not observed due to quadrupole broadening caused*

by the ^{11}B nucleus]. **HRMS (ESI$^+$)**: calculated for $C_{24}H_{38}B_2NaO_4$ $[M+Na]^+$: 435.2854; found: 435.2863. **mp** = 82-84 °C.

2,2'-(3-(4-Methoxybenzyl)cyclobutane-1,2-diyl)bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolane), **33c**

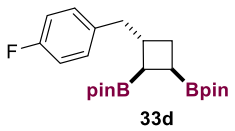


33c

From cyclobutene **32c** (34.8 mg, 0.2 mmol) following the general procedure described above, compound **33c** (48.8 mg, 0.11 mmol) was obtained in 57% yield as a pale yellow oil, after purification by flash column chromatography (SiO_2; cyclohexane/EtOAc 95:5).

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.06 (d, *J* = 8.5 Hz, 2H), 6.78 (d, *J* = 8.5 Hz, 2H), 3.76 (s, 3H), 2.68-2.54 (m, 3H), 2.10-2.00 (m, 1H), 197-1.83 (m, 2H), 1.79-1.68 (m, 1H), 1.24 (s, 12H), 1.18 (s, 6H), 1.13 (s, 6H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 157.8, 133.3, 129.9, 113.6, 83.1, 82.9, 55.4, 42.9, 38.7, 30.1, 25.1, 25.0, 24.9, 24.8. [note: *the carbons attached to boron were not observed due to quadrupole broadening caused by the ^{11}B nucleus*]. **HRMS (ESI$^+$)**: calculated for $C_{24}H_{38}B_2NaO_5$ $[M+Na]^+$: 451.2803; found: 451.2799.

2,2'-(3-(4-Fluorobenzyl)cyclobutane-1,2-diyl)bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolane), **33d**



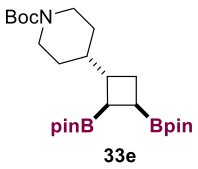
33d

From cyclobutene **32d** (32.4 mg, 0.2 mmol) following the general procedure described above, compound **33d** (68.0 mg, 0.16 mmol) was obtained in 82% yield as a white solid, after purification by flash column chromatography (SiO_2; cyclohexane/EtOAc 95:5). **mp** = 72-74 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.13-7.05 (m, 2H), 6.95-6.86 (m, 2H), 2.72-2.55 (m, 3H), 2.09-2.00 (m, 1H), 1.96-1.82 (m, 2H), 1.78-1.68 (m, 1H), 1.18 (s,

12H), 1.18 (s, 6H), 1.13 (s, 12H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 161.4 (J_{C-F} = 242.5 Hz), 136.7 (J_{C-F} = 3.1 Hz), 130.3 (J_{C-F} = 7.7 Hz), 114.8 (J_{C-F} = 20.9 Hz), 83.2, 82.9, 43.0, 38.6, 30.1, 25.1, 25.0, 24.9, 24.7. [note: *the carbons attached to boron were not observed due to quadrupole broadening caused by the ^{11}B nucleus*]. **HRMS (ESI$^+$)**: calculated for $C_{23}H_{35}B_2FNaO_4$ $[M+Na]^+$: 439.2603; found: 439.2594.

tert-Butyl 4-(2,3-bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl) cyclobutyl)piperidine-1-carboxylate, **33e**

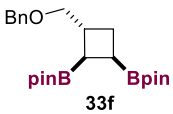


33e

From cyclobutene **32e** (47.5 mg, 0.2 mmol) following the general procedure described above, compound **33e** (41.2 mg, 0.08 mmol) was obtained in 42% yield as a colorless oil, after purification by flash column chromatography (SiO_2; cyclohexane/EtOAc 90:10). **mp** = 135-137 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ 4.12-3.85 (m, 2H), 2.70-2.50 (m, 2H), 2.19-1.93 (m, 2H), 1.90-1.62 (m, 3H), 1.60-1.50 (m, 2H), 1.42 (s, 9H), 1.24 (s, 24H), 1.02-0.83 (m, 3H). **^{13}C MNR** (75 MHz, $CDCl_3$): δ 155.0, 83.2, 83.1, 79.1, 43.9, 41.9, 29.0, 28.7, 28.6, 25.3, 25.1, 24.9, 24.7. [note: *the carbons attached to boron were not observed due to quadrupole broadening caused by the ^{11}B nucleus*]. **HRMS (ESI$^+$)**: calculated for $C_{26}H_{47}B_2NNaO_6$ $[M+Na]^+$: 514.3487; found: 514.3490.

2,2'-(3-((Benzyloxy)methyl)cyclobutane-1,2-diyl)bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolane), **33f**



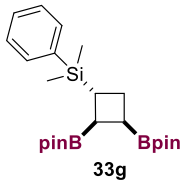
33f

From cyclobutene **32f** (34.8 mg, 0.2 mmol) following the general procedure described above, compound **33f** (67.7 mg, 0.16 mmol) was obtained in 79% yield as a white solid,

after purification by flash column chromatography (SiO_2; cyclohexane/EtOAc 90:10). **mp** = 48-50 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.30-7.13 (m, 5H), 4.43 (s, 2H), 3.42-3.34 (m, 2H), 2.71-2.53 (m, 1H), 2.08-1.79 (m, 3H), 1.76-1.64 (m, 1H), 1.22-1.11 (m, 24H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 139.2, 128.3, 127.6, 127.4, 83.6, 83.2, 83.1, 75.2, 72.9, 36.7, 27.5, 25.2, 25.1, 25.0, 24.9. [note: *the carbons attached to boron were not observed due to quadrupole broadening caused by the ^{11}B nucleus*]. **HRMS (ESI$^+$)**: calculated for $C_{24}H_{38}B_2NaO_5$ $[M+Na]^+$: 451.2803; found: 451.2797.

(2,3-Bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)cyclobutyl)dimethyl (phenyl)silane, **33g**



33g

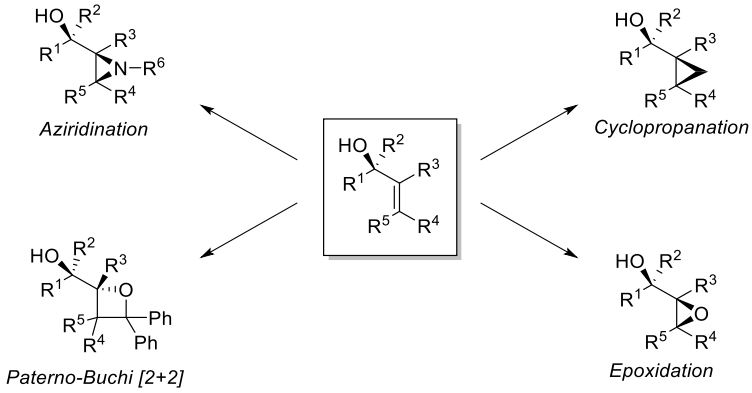
From cyclobutene **32g**[224] (37.7 mg, 0.2 mmol) following the general procedure described above, compound **33g** (63.0 mg, 0.14 mmol) was obtained in 71% yield as a colorless oil, after filtration through a pad of silica gel (cyclohexane/EtOAc 90:10). **mp** = 68-70 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.32-7.24 (m, 2H), 7.13-7.05 (m, 3H), 2.00-1.69 (m, 5H), 1.02 (s, 12H), 1.00 (s, 6H), 0.98 (s, 12H), 0.04 (s, 3H), 0.02 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 139.2, 134.1, 128.8, 127.7, 83.2, 83.0, 27.1, 25.3, 25.1, 24.9, 24.8, 23.1, -4.7, -5.0. [note: *the carbons attached to boron were not observed due to quadrupole broadening caused by the ^{11}B nucleus*]. **HRMS (ESI$^+$)**: calculated for $C_{24}H_{40}B_2NaO_4Si$ $[M+Na]^+$: 465.2780; found: 465.2787

[224] Murakami, M.; Usui, I.; Hasegawa, M.; Matsuda, T. *J. Am. Chem. Soc.* **2005**, *127*, 1366–1367.

Annex: Synthesis of Allylic Alcohols from Vinyl Epoxides

Enantioenriched allylic alcohols are versatile building blocks in organic synthesis.[225] They are employed in a wide variety of diastereoselective transformations to afford molecules with up to three contiguous stereocenters. In many of these transformations the alcohol serves as a directing group and ensures a high level of selectivity.[226] Examples of these transformations include epoxidation, aziridination, Simmons-Smith type cyclopropanation or Paterno-Buchi reaction among others (**Scheme 158**).

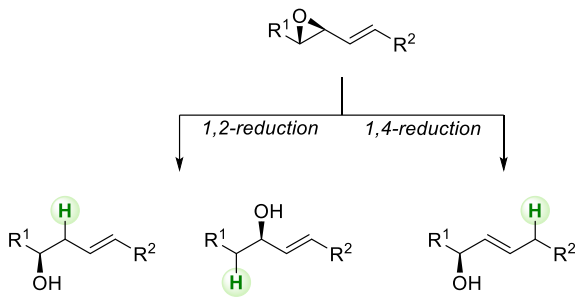


Scheme 158. Diastereoselective transformation of allylic alcohols.

[225] Lumbroso, A.; Cooke, M. L.; Breit, B. *Angew. Chem. Int. Ed.* **2013**, *52*, 1890–1932.
[226] Hoveyda, A. H.; Evans, D. A.; Fu, G. C. *Chem. Rev.* **1993**, *93*, 1307–1370.

1. Classical Approaches for the Reduction of Allylic Epoxides

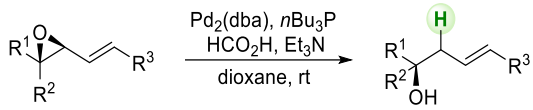
As mentioned before, the availability of chiral vinyl epoxides makes them ideal substrates to prepare enantiomerically enriched compounds through reactions that enable chirality transfer. It is surprising, however, to find that one of the most intuitive transformations with these substrates, a simple reduction, remains unsolved. The reduction of vinyl epoxides can produce three different products, resulting from a 1,2-reduction (at either position of the epoxide) or a 1,4 pathway (**Scheme 159**).



Scheme 159. Possible products obtained through the reduction of allylic epoxides.

The palladium catalyzed hydrogenolysis of vinyl epoxides was first reported by Tsuji in 1989. This approach affords selectively the 1,2-reduction at the allylic position providing a robust method to obtain homoallylic alcohols (**Scheme 160**).[227]

[227] **(a)** Oshima, M.; Yamazaki, H.; Shimizu, I.; Nisar, M.; Tsuji, J. *J. Am. Chem. Soc. 111*, **1989**, 6280–6287. **(b)** Kakei, H.; Nemoto, T.; Ohshima, T.; Shibasaki, M. *Angew. Chem. Int. Ed.* **2004**, *43*, 317–320.



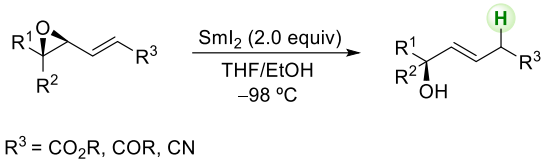
Scheme 160. Palladium catalyzed hydrogenolysis of vinyl epoxides.

Other possibility is the use of aluminum and boron-based hydrides as reducing agents. In these cases, the observed regioselectivity is highly substrate dependent. All three possible modes of oxirane opening have been observed, with most examples providing 1,2-reducted products.[228]

On the other hand, the 1,4-reduction was carried out using different superstoichiometric amount of a metal and in some cases difficult to handle reaction conditions. The 1,4-reduction of vinyl oxiranes was reported using two equivalents of freshly prepared SmI_2, working at the unpractical temperature of −98 °C.[229] Furthermore, the substitution in the double bonds is limited to strong electro-withdrawing groups in the alkene (Scheme 161).

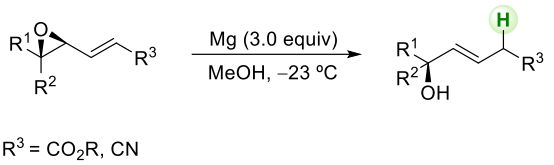
[228] *Selected examples:* **(a)** Lenox, R. S.; Katzenellenbogen, J. A. *J. Am. Chem. Soc.* **1973**, *95*, 957–959. **(b)** Zaidlewicz, M.; Uzarewicz, A.; Sarnowski, R. *Synthesis* **1979**, 62–64. **(c)** Nicolaou, K. C.; Daines, R. A.; Uenishi, J.; Li, W. S.; Papahatjis, D. P.; Chakraborty, T. K. *J. Am. Chem. Soc.* **1988**, *110*, 4672–4685. **(d)** Gupta, A.; Vankar, Y. D. *Tetrahedron Lett.* **1999**, *40*, 1369–1372. **(e)** Nagumo, S.; Nakano, T.; Hata, K.; Mizukami, M.; Miyashita, M. *Org. Lett.* **2010**, *12*, 908–911. **(f)** Takamura, H.; Wada, H.; Lu, N.; Kadota, I. *Org. Lett.* **2011**, *13*, 3644–3647. **(g)** Krishna, P. R.; Kadiyala, R. R. *Tetrahedron Lett.* **2010**, *51*, 4981–4983.

[229] **(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.



Scheme 161. 1,4-Reduction of vinyl epoxides using SmI_2.

Other approach consists in the use of three equivalents of activated magnesium in dry methanol.[230] In this case, the substrate scope is even more limited and only esters or cyano groups attached to the double bond are suitable substituents to afford the desired product (**Scheme 162**).



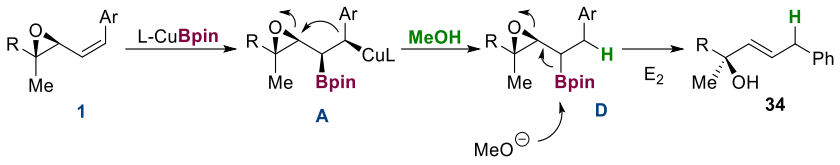
Scheme 162. 1,4-Reduction of vinyl epoxides with magnesium in methanol.

Moreover, functional groups such as ketones or alkyl or aryl halides are incompatible with both strong reductants mentioned before.

[230] Pak, C. S.; Lee, E.; Lee, G. H. *J. Org. Chem.* **1993**, *58*, 1523–1530.

2. Previous Work in Our Research Group

Based on the reported literature, at the beginning of this project, the development of a catalytic and mild method to reduce vinyl epoxides in an 1,4-manner it was still a challenge. Looking at the previous results obtained using vinyl epoxides under copper-boron catalysis, we hypothesized that if we could intercept intermediate **A** after cyclization adding a proton source, epoxy boronate **D** could be afforded. In the presence of a base, this intermediate could undergo a β-oxygen elimination to give the formal 1,4-reduction product (**Scheme 163**). The base-promoted elimination of α-epoxy alkyl-boronates has not been reported before, however, our research group reported a related elimination with α-epoxy vinyl-boronic esters.[231]

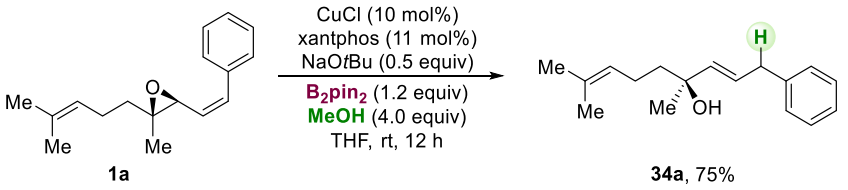


Scheme 163. Possible 1,4-reduction of vinyl epoxides (our hypothesis).

To test this hypothesis, vinyl epoxide **1a** was selected as model substrate. Surprisingly, using copper chloride in combination with xantphos, NaO*t*Bu and B_2pin_2 in the presence of four equivalents of MeOH as proton source, allylic alcohol **34a** was obtained as a single *E*-isomer in

[231] Jarava-Barrera, C.; Parra, A.; Amenós, L.; Arroyo, A.; Tortosa, M. *Chem. Eur. J.* **2017**, *23*, 17478–17481.

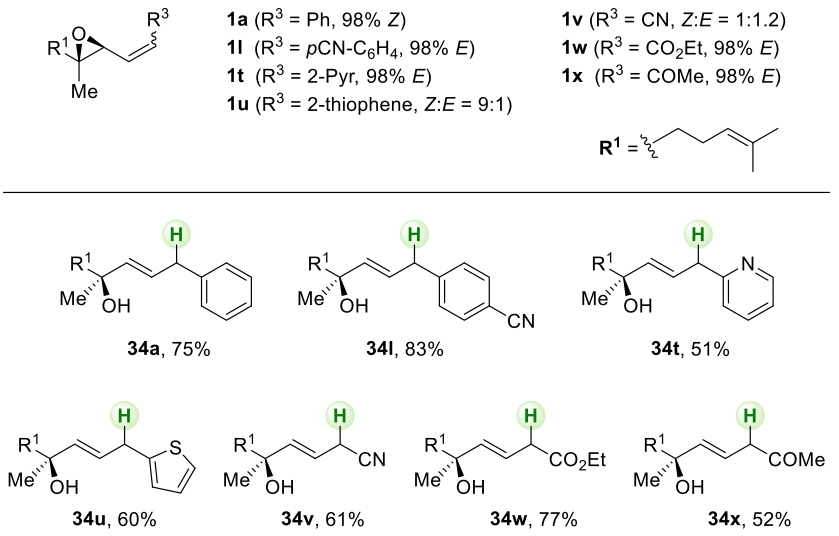
75% yield (**Scheme 164**). This result indicated that the elimination promoted by the base occurs spontaneously with stereocontrol. It is noteworthy that the 1,4- reduction of vinyl epoxides with a simple aryl group in the double bond is virtually unknown in the literature.[232]



Scheme 164. Copper-catalyzed 1,4-reduction of vinyl epoxides.

The reaction scope was studied with different vinyl epoxides. The reaction worked smoothly for vinyl epoxides bearing different aromatic ring on the alkene (**Scheme 165**) including heteroaromatic rings such a pyridine (**34t**) and thiophene (**34u**). The method is also effective with strong electron withdrawing groups on the alkene. Nitriles (**34v**), esters (**34w**) or ketones (**34x**) are suitable substrates for this transformation. These compounds were synthetized with efficiencies comparable to those observed with SmI_2 or Mg/MeOH.

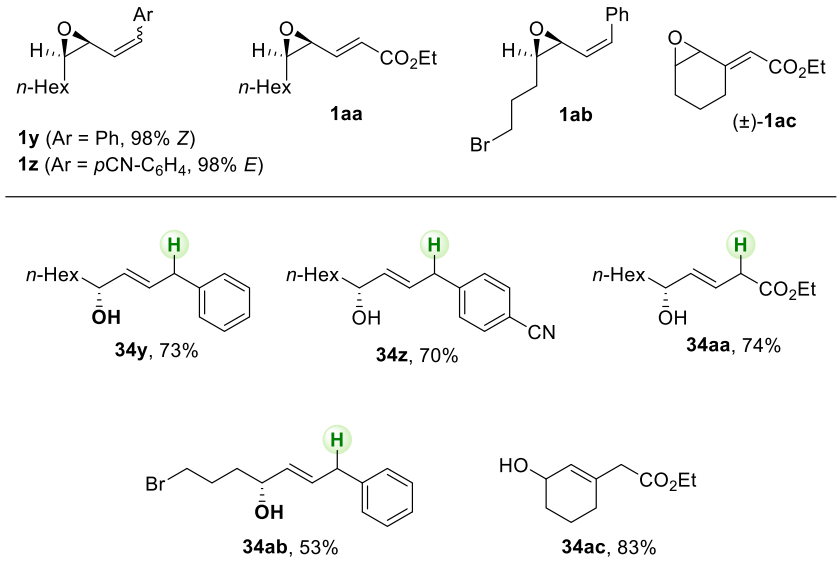
[232] *For an isolated example*: Fronza, G.; Fuganti, C.; Högberg, H.-E.; Pedrocchi-Fantoni, G.; Servi, S. *Chem. Lett.* **1988**, *17*, 385–388.



Scheme 165. Reaction scope with modifications on the alkene.

The reaction scope includes modifications on the epoxide (**Scheme 166**). Disubstituted epoxides (**1y-1ab**) afforded the corresponding allylic alcohols (**34y**-**34ab**) in good yield and as single *E*-isomers. The chemoselectivity observed for example **34ab** is remarkable since alkyl bromides are known to undergo borylation at the C–Br bond under similar reaction conditions.[233]

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



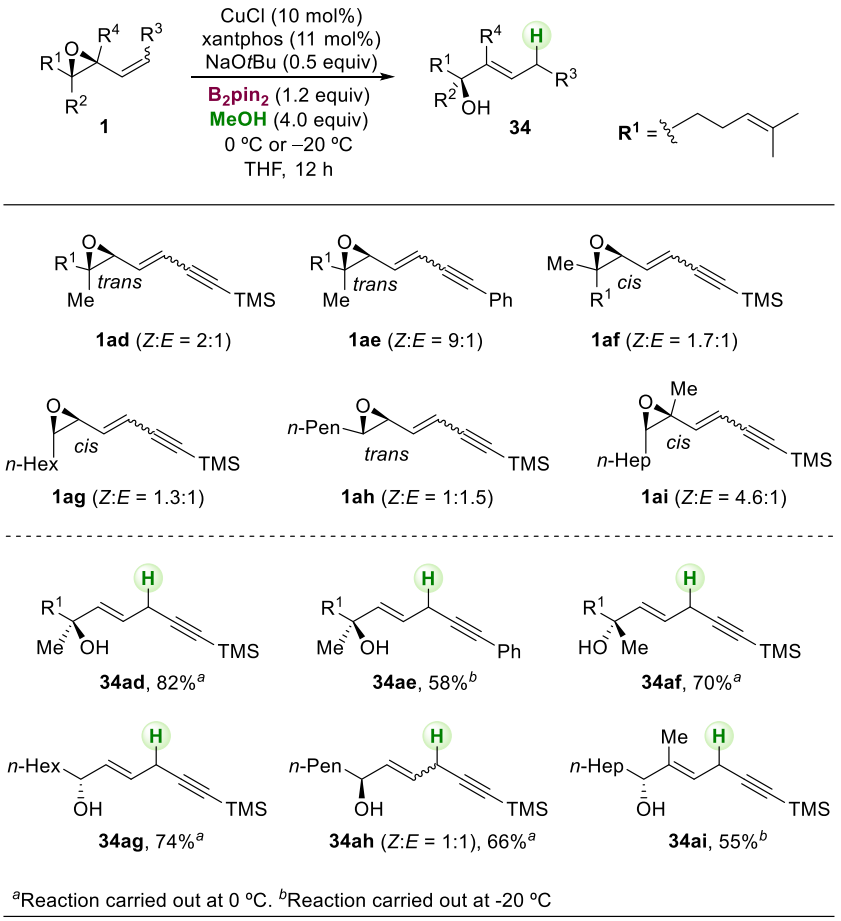
Scheme 166. Reaction scope with modifications on the epoxide.

Finally, the reaction scope includes the selective 1,4-reduction of epoxyenynes, a class of vinyl epoxides bearing a versatile alkyne attached to the double bond (Scheme 167). These compounds have never been selectively reduced in a 1,4-manner and the products would be enantioenriched skipped enynes, interesting building blocks that can be further functionalized through different stereoselective transformations.[234]

When we applied the optimized conditions to *trans*-epoxyenyne **1ad**, at 0 °C, only 1,4-reduction of the vinyl epoxide was observed, without borylation of the alkyne (Scheme 167). Skipped enyne **34ae**, with a phenyl

[234] **(a)** Makida, Y.; Takayama, Y.; Ohmiya, H.; Sawamura, M. *Angew. Chem. Int. Ed.* **2013**, *52*, 5350–5354. **(b)** Wei, X.-F.; Xie, X.-W.; Shimizu, Y.; Kanai, M. *J. Am. Chem. Soc.* **2017**, *139*, 4647–4650. **(c)** Wei, X.-F.; Wakaki, T.; Itoh, T.; Li, H.-L.; Yoshimura, T.; Miyazaki, A.; Oisaki, K.; Hatanaka, M.; Shimizu, Y.; Kanai, M. *Chem* **2019**, *5*, 585–599.

group in the alkyne, was also synthetized with high chemo- and stereocontrol. The corresponding *cis*-epoxide **1af** provided allylic alcohol **34af** as a single *E*-isomer, with similar efficiency. Both *cis* and *trans* disubstituted epoxyenynes **1ag** and **1ah** were also tested. Although both compounds provided the 1,4-reduction product in high yield, we observed that the substitution at R^2 of the epoxide ($R^2 \neq H$) was necessary to control the *E/Z* geometry of the newly formed double bond in the products. Finally, challenging epoxide **1ai** afforded skipped enyne **34ai**, with a challenging trisubstituted *E*-olefin.

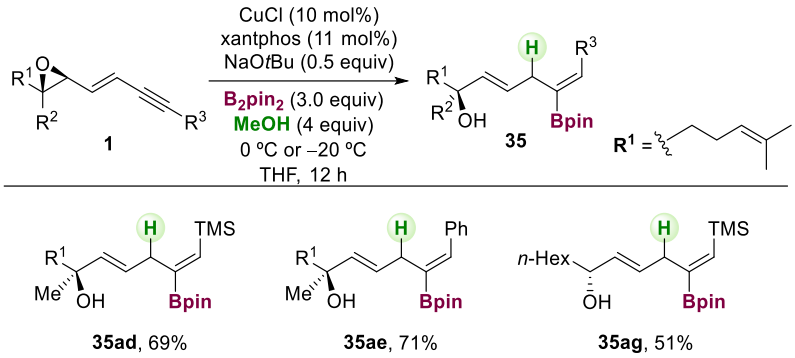


Scheme 167. 1,4-Reduction of epoxyenynes.

Remarkably, the starting epoxyenynes were prepared and used as mixtures of *E/Z* isomers, without affecting the outcome of the transformation.

When the 1,4-reduction of epoxyenynes was carried out at room temperature, the product derived from the borylation of the alkyne was detected. Gratifyingly, when the reaction was carried out with three

equivalents of the diboron reagent at room temperature, under otherwise identical conditions, skipped dienes **35ad**, **35ae** and **35ag** were obtained in good yields as single regio- and stereoisomers. This reduction-borylation sequence afford functionalized skipped dienes (**Scheme 168**), that would be difficult to prepare using other methods. These results indicated that the 1,4-reduction of the vinyl epoxide moiety takes place first, followed by a regioselective hydroboration of the alkyne. This order is a crucial factor to control the regioselectivity in the borylation of the alkyne. Skipped dienes **35ae** and **35ag** are particularly attractive molecules because they have a bifunctional boron-silicon alkene, that could be selectively functionalized through orthogonal cross-coupling reactions.[235]



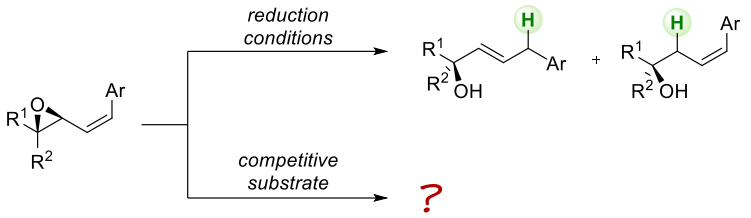
Scheme 168. Synthetized skipped dienes.

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

3. Objectives

Based on the previous results obtained by Dr. Laura Amenós during her PhD thesis, we proposed the following objectives for this project (Scheme 169).

- To explore the reactivity of vinyl epoxides under different reduction conditions to demonstrate the advantages of our methodology.
- To make competing experiments to demonstrate the functional group compatibility under our mild conditions.
- Try to functionalize the boryl moiety in the skipped dienes to demonstrate the synthetic utility of the products.



Scheme 169. Objectives of this project.

4. Reduction of Vinyl Epoxides under Different Conditions

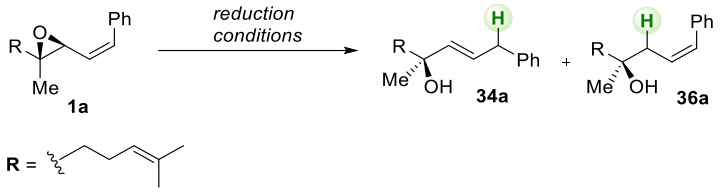
We decided to compare our mild reduction conditions with other reducing agents typically used with vinyl epoxides to demonstrate the advantages of our methodology.

As expected, $LiAlH_4$ (2 equiv) cleanly provided homoallylic alcohol **36a** (**Table 9**, **entry 2**) through a 1,2-reduction of the oxirane at the allylic position.[236] The use of SmI_2 (2 equiv), under the same reaction conditions described in the literature,[237] provided a complex mixture of products (**Table 9**, **entry 3**) from which we could not identify the 1,4-reduction product. Moreover, activated Mg (3 equiv) in MeOH[238] gave a mixture of the reduced 1,2- and 1,4-products with poor regioselectivity (**Table 9**, **entry 4**). Remarkably, epoxide **1a** did not react upon addition of BH_3 (**Table 9**, **entry 5**) and only starting material was recovered.[239] Finally, we tried conditions to generate copper hydride species that have been shown to be effective for the 1,4-reduction of propargylic epoxides.[240] We tried different reaction conditions, using IPrCuCl as copper catalyst with a NMC ligand (**Table 9**, **entry 6**) or $Cu(OAc)_2$ with 1,2-bis- (diphenylphosphino)-benzene (dppbz) as ligand (**Table 9**, **entry 7**). In both cases the reaction was carried out in the presence of PMHS as hydride source, although, we did

[236] Mandal, A. K.; Schneekloth, J. S. Jr.; Kuramochi, K.; Crews, C. M.; *Org. Lett.* **2006**, *8*, 427–430.
[237] Molander, G. A.; La Belle, B. E.; Hahn, G. *J. Org. Chem.* **1986**, *51*, 5259–5264.
[238] Pak, C. S.; Lee, E.; Lee, G. H. *J. Org. Chem.* **1993**, *58*, 1523–1530.
[239] Zaidlewicz, M.; Uzarewicz, A.; Sarnowski, R. *Synthesis* **1979**, 62–64.
[240] **(a)** Lipshutz, B. H.; Lower, A.; Noson, K. *Org. Lett.* **2002**, *4*, 4045–4048. **(b)** Deutsch, C.; Lipshutz, B. H.; Krause, N. *Angew. Chem. Int. Ed.* **2007**, *46*, 1650–1653.

not obtain the desired reduction product and only unreacted vinyl epoxide was observed.

Table 9. Reduction of vinyl epoxides under different conditions.



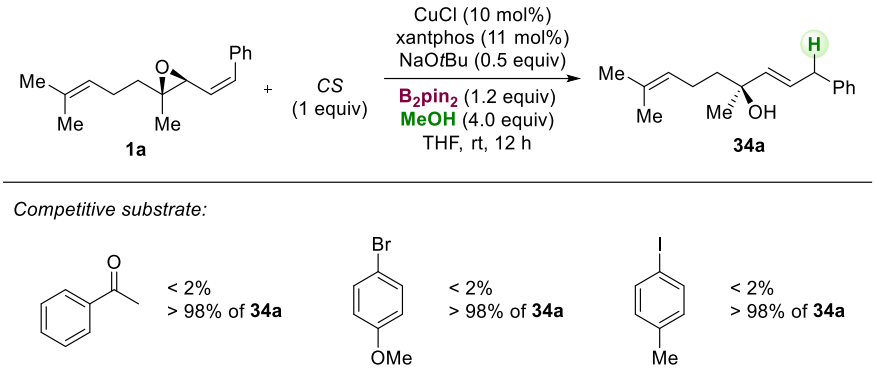
Entry	Conditions	34a:36a	Yield (%)[a]
1	**A:** Our conditions	100:0	75
2	**B:** LiAlH4, THF, 0 °C, 1.5 h	0:100	61
3	**C:** SmI_2 (2 equiv), THF/MeOH, -90 °C, 1 h	-	-[b]
4	**D:** Mg (3 equiv), MeOH, −20 °C, 2 h	75:25	72
5	**E:** BH_3·THF (2 equiv), THF, 12 h	-	-[c]
6	**F:** IPrCuCl (10 mol %), NaO*t*Bu (30 mol %), PMHS (2 equiv), tol, 12 h	-	-[c]
7	**G:** $Cu(OAc)_2$ (10 mol %), NaOtBu (30 mol %), dppbz, PMHS (2 equiv), tol, 12 h	-	-[c]

[a]Isolated yield. [b]Complex mixture. [c]Unreacted starting material.

5. Competing Experiments

To further compare our method with the classical approaches based in the use of SmI_2 or Mg/MeOH or aluminum hydride-based reagents, we tested our conditions in the presence of three functional groups that are incompatible with these reductants (**Scheme 170**). We set up the reaction of **1a** under the optimal reaction conditions, in the presence of 1 equivalent

of a ketone, an aryl bromide, or an aryl iodide. It should be noted that the borylation of these substrates are reported under similar copper-catalyzed conditions.[241] Gratifyingly, in all cases we observed clean conversion of epoxide **1a** to desired allylic alcohol **34a**, without detecting significant borylation of the competitive substrate (<2% of borylation).

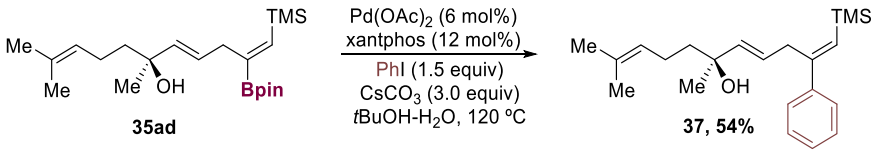


Scheme 170. Competitive experiments.

6. Suzuky-Miyaura Cross-Coupling Reaction

Finally, to demonstrate the synthetic utility of bifunctional boron-silicon skipped dienes, substrate **35ad** was transformed into functionalized skipped diene **37** through a selective Suzuki–Miyaura reaction in moderate yield (**Scheme 171**).

[241] **(a)** McIntosh, M. L.; Moore, C. M.; Clark, T. B. *Org. Lett.* **2010**, *12*, 1996–1999. **(b)** Kleeberg, C.; Dang, L.; Lin, Z.; Marder, T. B. *Angew. Chem. Int. Ed.* **2009**, *48*, 5350–5354.

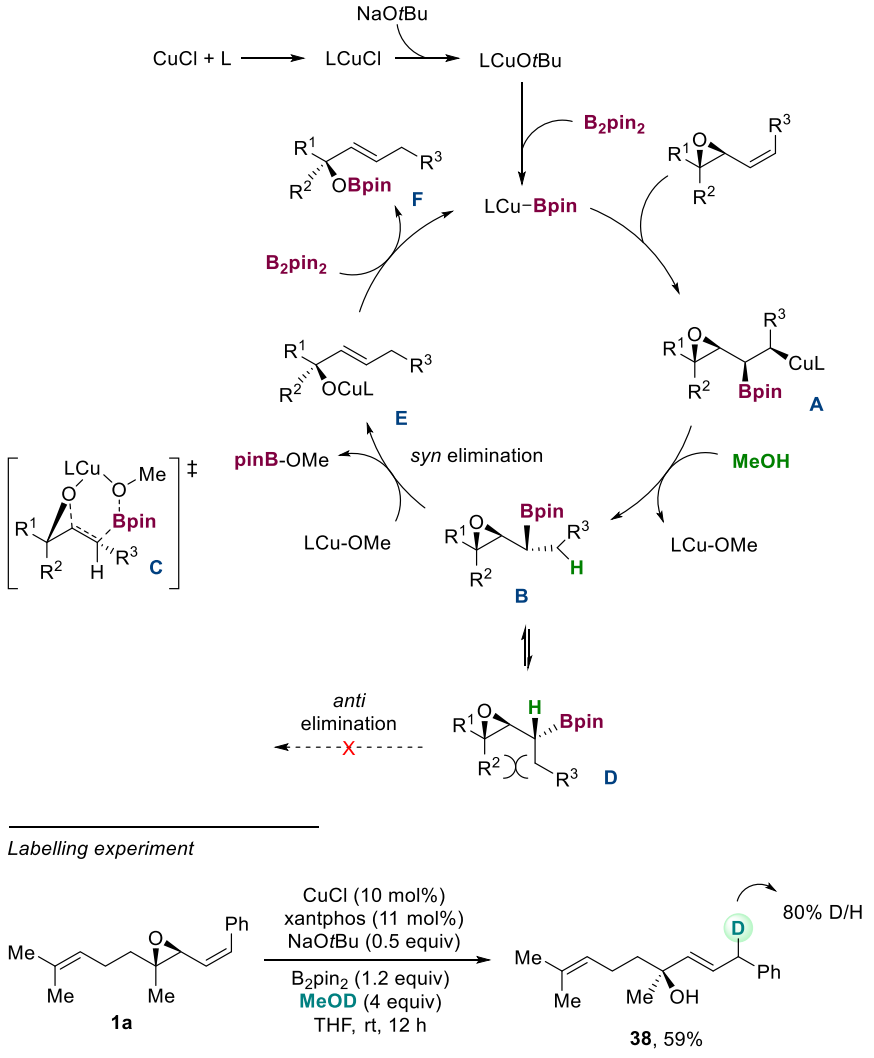


Scheme 171. Suzuki-Miyaura cross-coupling reaction of skipped dienes.

7. Proposed Mechanism

A plausible mechanistic pathway for the 1,4-reduction of vinyl epoxides is depicted in **Scheme 172**. First, copper(I) chloride is coordinated to the ligand and in the presence of NaO*t*Bu, generates the copper alkoxide. Then, reaction with B_2pin_2 through a σ-bond metathesis affords the active copper(I)-boryl complex, followed by insertion of the alkene into the Cu–B bond, to form intermediate **A**. According to our previous observations in the cyclopropane formation, we assumed a *syn* approach of the copper-boryl complex to the vinyl epoxide in an s-*trans* conformation. Protonation of intermediate **A** provides epoxy boronate **B** and prevents the formation of the cyclopropyl ring. From intermediate **B**, a *syn*-elimination process would justify the *E* geometry of the new formed double bond. We believe this *syn*-elimination could be promoted by the copper methoxide present in the media through transition state **C**. When $R^2 \neq H$, the conformer leading to the *anti*-elimination product (conformer **D**) would present a non-favorable 1,5-*syn* pentane-type interaction. When $R^2 = H$, this interaction is reduced and both elimination pathways are favored. After ring opening, copper-alkoxide **E** is formed. This intermediate would react with a molecule of B_2pin_2 and restart the catalytic cycle. To support this mechanism, the

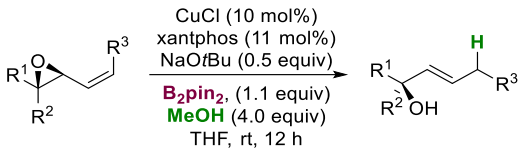
reduction of **1a** was carried out in the presence of deuterated methanol (MeOD), affording compound **38** with 80% deuterium incorporation at the allylic-benzylic position.



Scheme 172. Proposed mechanism for copper-catalyzed 1,4-reduction of vinyl epoxides.

8. Conclusions

In summary, we have explored the reactivity of vinyl epoxides under copper(I) catalyzed borylation conditions. In the presence of methanol, under the same reaction conditions developed for the synthesis of cyclopropylboronates (*Chapter I*), allylic alcohols were obtained with complete chirality transfer. Compared with other methods, our conditions are mild, easy to handle, and show high functional group tolerance. With these conditions, challenging epoxyenynes have been 1,4-reduced to selectively produce skipped enynes or bifunctional skipped dienes, that can be used for orthogonal cross-coupling transformations.



Scheme 173. Reactivity of allylic epoxides under copper catalysis.

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