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Cyclopropyl and Cyclobutylboronates and Silanes: A Stereoselective Approach

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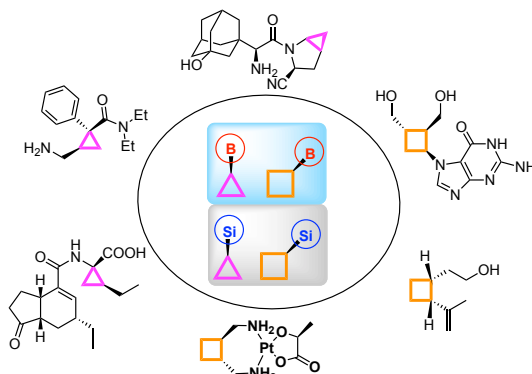
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Abstract Chiral cyclopropyl and cyclobutyl boronic esters and silanes have become attractive intermediates for the preparation of functionalized small rings. This review highlights the stereoselective methods developed for their preparation, including both diastereo- and enantioselective approaches.

1 Introduction

2 Stereoselective Synthesis of Cyclopropyl and Cyclobutylboronates and Silanes.

2.1 Diastereoselective Synthesis of Cyclopropyl and Cyclobutyl boronates and silanes.

2.2 Asymmetric Synthesis of Cyclopropyl and Cyclobutyl boronates and silanes.

3 Conclusions

Key words Stereoselective synthesis, Asymmetric synthesis, Boronates, Silanes, Cyclopropanes, Cyclobutanes, Strained rings

1. Introduction

Cyclopropanes¹ and cyclobutanes² have always fascinated organic chemists due to the challenge involved in their synthesis as well as their unusual reactivity. They are not only extremely useful synthetic intermediates, but are also found in a broad number of natural products,³ pharmaceuticals⁴ and cosmetics⁵ (Figure 1). In particular, stereodefined small rings with multiple stereocenters are gaining increasing attention because they provide rigidity and at the same time three-dimensionality, both valuable attributes in drug discovery. In this context, chiral cyclopropanes and cyclobutanes with silicon and boron containing stereocenters are expected to be promising synthetic intermediates. They present high configurational stability at the C-Si⁶ and C-B⁷ bonds and provide a synthetic handle for further stereospecific transformations. Oxidation, amination, homologation, olefination and cross-coupling reactions offer the

possibility to access structurally diverse cyclopropanes and cyclobutanes from common intermediates (Scheme 1).⁸

Excellent contributions in this field have appeared over the last ten years but have never been compiled before. The aim of this review, is to summarize the existing stereoselective methodologies for the synthesis of cyclopropyl and cyclobutyl boronic esters and silanes.

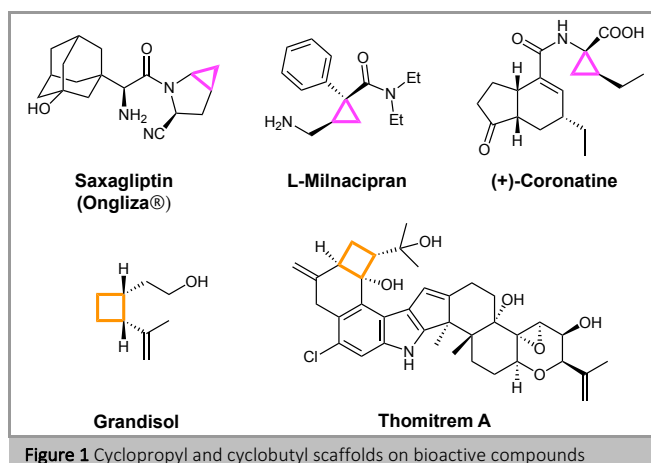
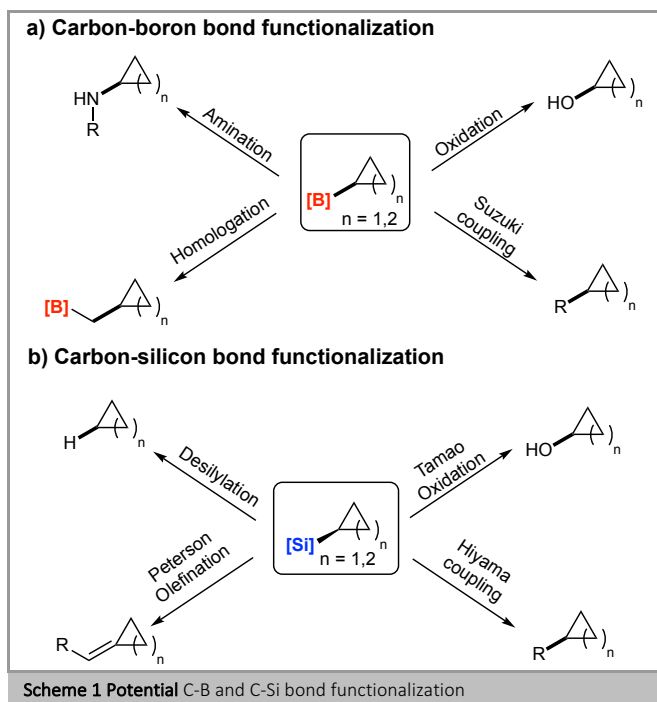
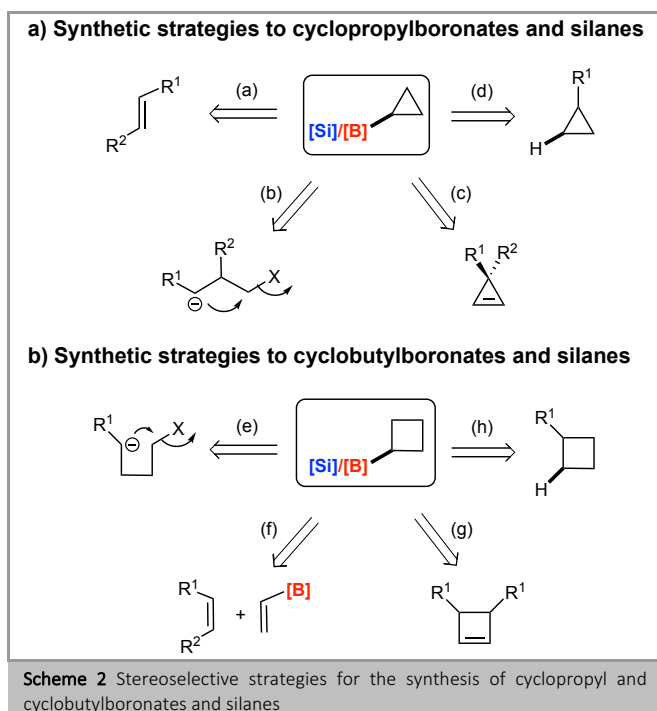


Figure 1 Cyclopropyl and cyclobutyl scaffolds on bioactive compounds



2. Stereoselective Synthesis of Cyclopropyl and Cyclobutyl Boronic Esters and Silanes

Several strategies have been developed for the stereoselective synthesis of cyclopropylboronates and silanes (Scheme 2). The classical approach to prepare these compounds has been for many years the cyclopropanation of functionalized alkenes (a). This outcome is changing rapidly and novel catalytic methods involving ring closing reactions (b), desymmetrization of cyclopropanes (c) and C-H functionalization of cyclopropanes (d), have become attractive alternatives.



The stereoselective synthesis of cyclobutylboronates and silanes has received less attention and in many ways, is still an

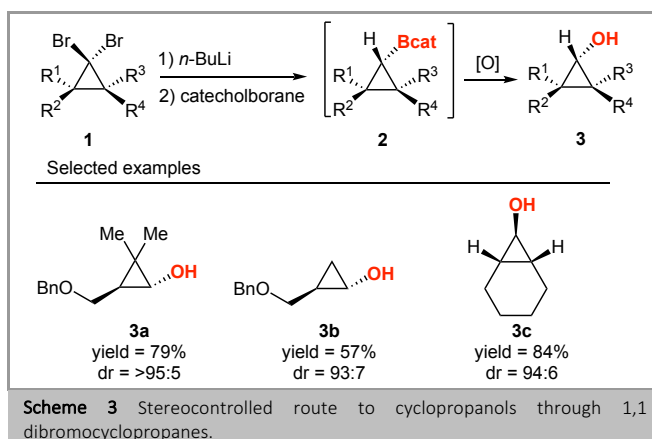
undeveloped field. Reactions involving ring closure (e), [2+2] cycloadditions (f), functionalization of cyclobutenes (g) and C-H activation (h) have been used to prepare these derivatives.

This review is divided into two main sections. The first one describes synthetic methods that are just diastereoselective, that is, those that do not allow for the preparation of enantiomerically enriched compounds. The second section compiles the existing enantioselective methodologies for the preparation of cyclopropyl and cyclobutylboronates and silanes. Both sections are organized considering the type of transformation used to prepare the products.

2.1 Diastereoselective Synthesis of Cyclopropyl and Cyclobutylboronates and Silanes.

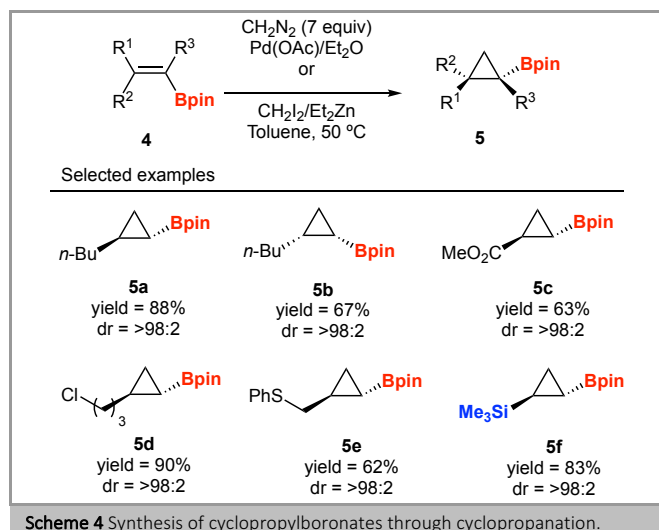
Matteson-Pasto rearrangement

The first general stereoselective method to prepare cyclopropylboronates was published by Danheiser and Savoca in 1985 (Scheme 3).⁹ Starting from dibromocyclopropane **1**, lithium-halogen exchange followed by reaction with catecholborane formed cyclopropylboronate **2** through a Matteson-Pasto rearrangement. Unfortunately, the authors were not able to isolate cyclopropylboronates **2**. Instead, they *in situ* oxidized the C-B bond to isolate cyclopropanols **3** with excellent diastereoselectivity.

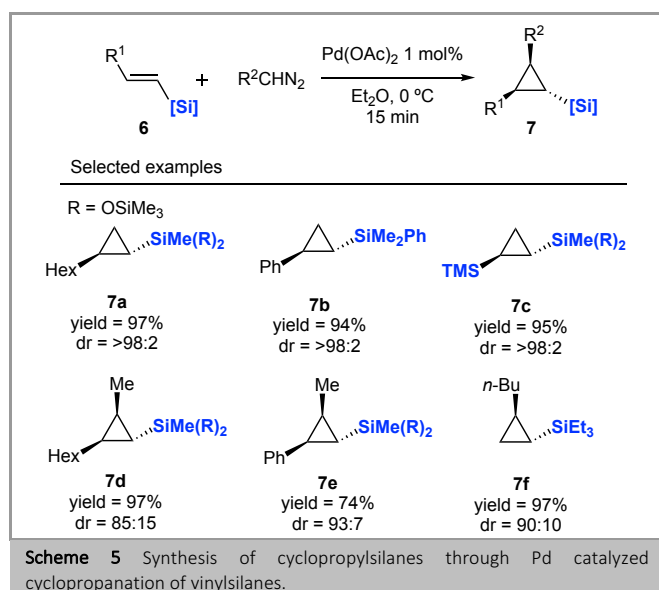


Cyclopropanation reactions

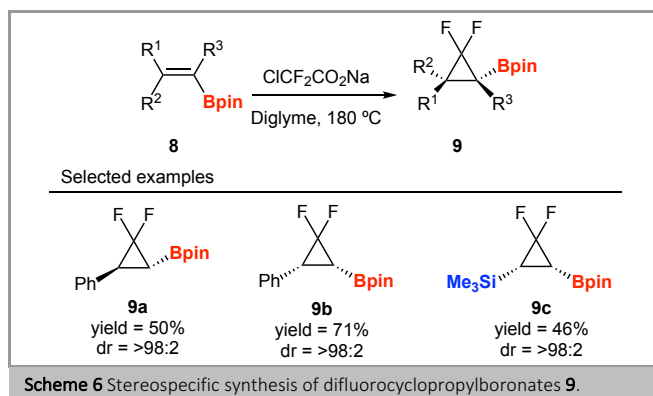
Vinyl boronic esters have been extensively used to prepare stereodefined cyclopropylboronates. In 1989, Carboni and co-workers developed the diastereoselective cyclopropanation of vinyl boronates using diazomethane and a palladium catalyst or the carbenoid generated from diiodomethane/diethylzinc (Scheme 4). Cyclopropylboronates **5** were formed with complete stereospecificity.¹⁰ Interestingly, the methodology was also applied for the synthesis of bifunctionalized cyclopropane **5f**. This example represents the first stereoselective synthesis of a cyclopropane substituted with silyl and boryl substituents. Transfer of acyl carbenes was also studied, but *E/Z* mixtures of cyclopropylboronates were obtained. Several groups have studied the Suzuki-Miyaura cross-coupling reaction of cyclopropylboronates prepared through this methodology.¹¹



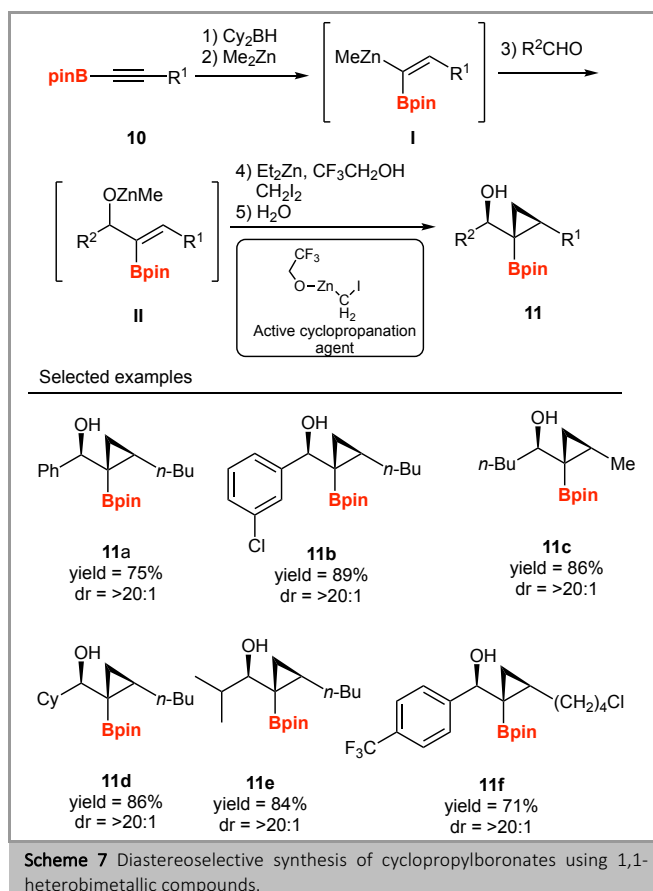
Markó and co-workers applied the Pd catalyzed cyclopropanation of vinyl boronates to more challenging dienes to prepare stereodefined vinyl cyclopropanes.¹² The same group applied this approach to the stereoselective synthesis of cyclopropylsilanes **7**, using vinylsilanes **6** instead of vinyl boronic esters (Scheme 5). This class of compounds showed superior activity allowing to employ only a slight excess of the diazo compound. The cyclopropylsilanes were obtained with high diastereoselectivity even when diazoethane and diazobutane were employed (compounds **7d–7f**, Scheme 5).¹³



For the synthesis of *gem*-difluorocyclopropanes **9**, Amii and co-workers reported the cyclopropanation of vinylboronates with a difluorocarbene generated *in situ* from sodium chlorodifluoroacetate in diglyme at 180 °C (Scheme 6). A series of interesting *gem*-difluorocyclopropanes were prepared with excellent diastereoselectivity.¹⁴ Both, *cis* and *trans* cyclopropanes were prepared by the appropriate choice of the geometry of the starting alkenes.

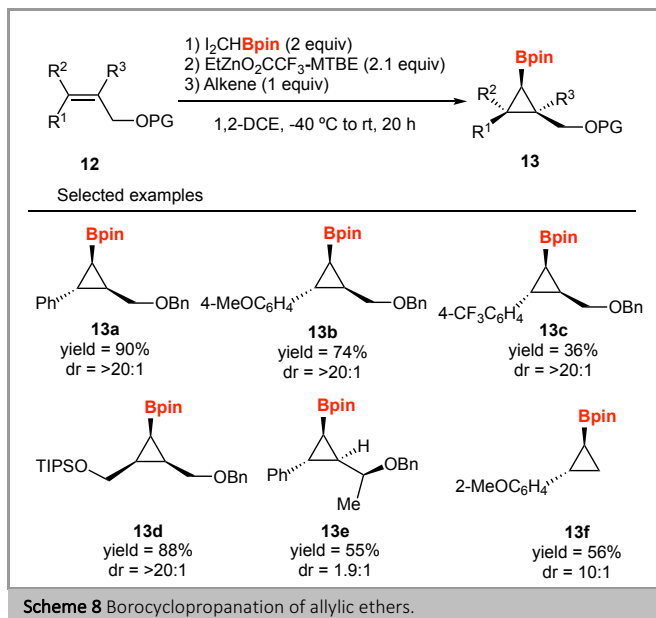


α -Hydroxy vinyl boronic esters have been also used in cyclopropanation reactions (Scheme 7). Walsh and co-workers developed a domino carbonyl addition/alkoxide-directed cyclopropanation. The sequence started by generation of a boron-zinc heterobimetallic compound **I**¹⁵ through regioselective hydroboration of alkynyl boronic ester **10** with dicyclohexylborane followed by selective transmetalation of the $C_{\alpha}B-C$ bond. Reaction of this intermediate with an aldehyde at the Zn-C position, afforded an allylic zinc alkoxide **II** that underwent stereoselective cyclopropanation. The active cyclopropanation reagent was formed by reaction of Et_2Zn , CH_2I_2 and trifluoroethanol. α -Hydroxy cyclopropylboronates **11** were prepared in good yields and high diastereoselectivities.¹⁶



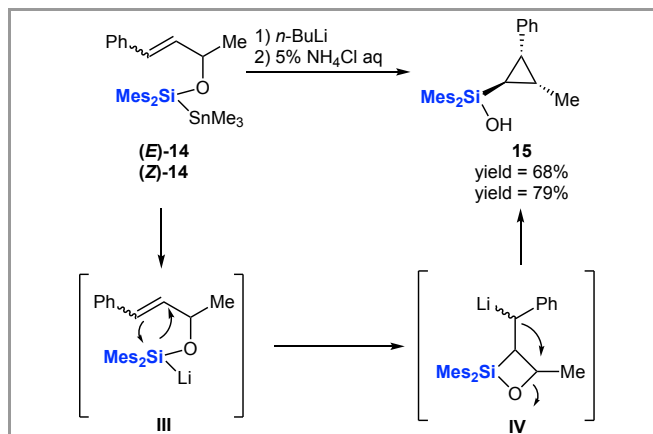
Recently, Charette and co-workers reported a borocyclopropanation of allylic ethers **12** using boromethylzinc

carbenoids via Simmons-Smith reaction (Scheme 8). With this novel approach, they prepared 1,2,3-substituted cyclopropylboronates **13** in good yields and high diastereoselectivities.¹⁷ The starting diiodomethylboronate is prepared from commercially available dichloromethylboronate by double Finkelstein reaction. The reaction worked better with primary allylic ethers than secondary substrates. Simple styrenes are also suitable compounds for the reaction, but the results are not as remarkable as those with allylic ethers.

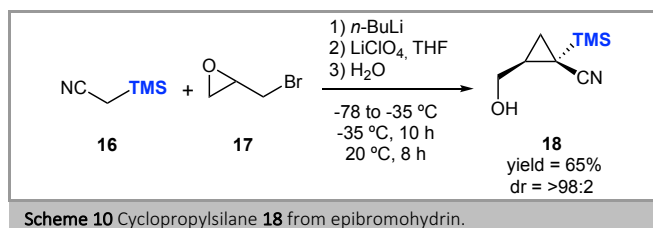


Ring-closing reactions to form three-membered rings

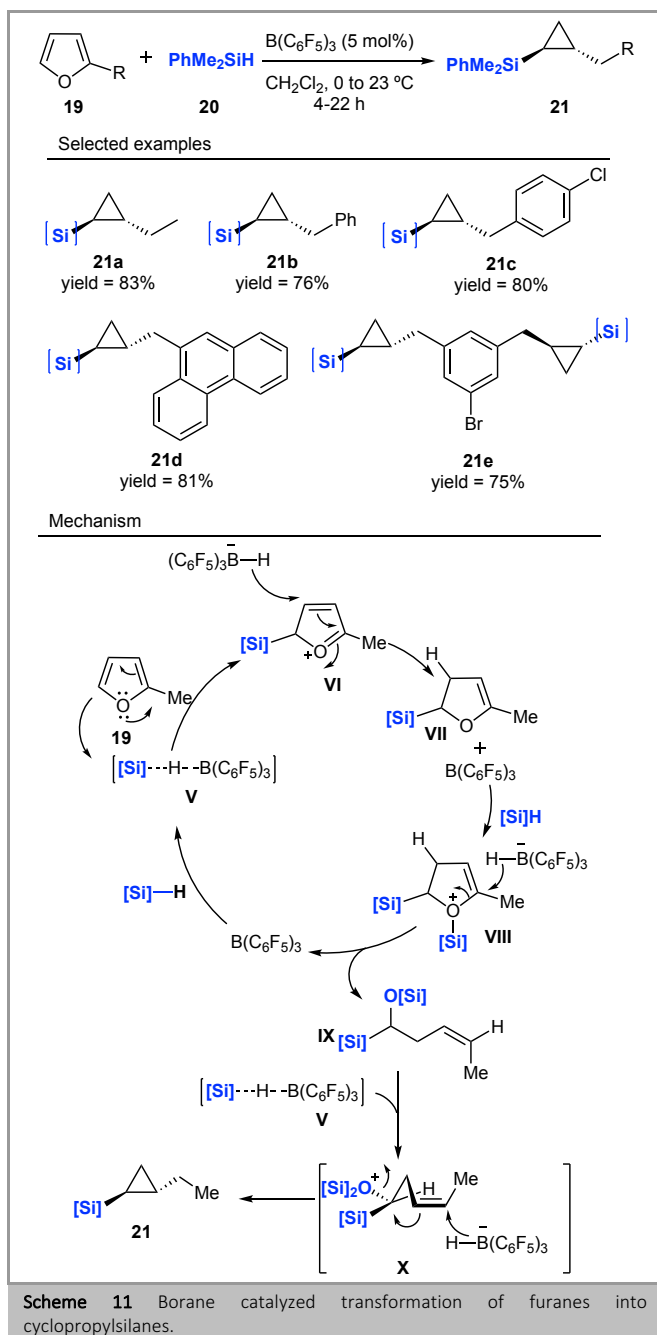
Ring-closing reactions have been also used for the preparation of cyclopropylsilanes and boronates. In 2000, Tamao and co-workers reported the stereoselective synthesis of cyclopropylsilane **15** through a very interesting rearrangement of silylstannane derivative **14** (Scheme 9).¹⁸ It is important to note that the presence of a phenyl group in the olefin was required and both *E* and *Z* isomers gave the same final product. The authors proposed a mechanism in which [(*sec*-allyloxy)dimesitylsilyl]stannane **14** reacts with *n*-BuLi to produce silyl anion **III**. This anion undergoes an intramolecular addition to the double bond (β to the phenyl group) forming an 1-oxa-2-sila-cyclobutane **IV**. Intramolecular $\text{S}_{\text{N}}2$ reaction between the negatively charged benzylic carbon and the sila-oxetane affords cyclopropylsilanol **15**.



In 2001, Langer and co-workers reported a chemo-, regio-, and diastereoselective synthesis of various cyclopropanes from *epi*-bromohydrin **17** and nitriles.¹⁹ Concerning this review, they used α -silyl nitrile **16** to prepare cyclopropylsilane **18** as a single diastereomer (Scheme 10). The stereochemical outcome can be explained by steric interaction of the silyl group and the hydroxymethyl group during the cyclization event.

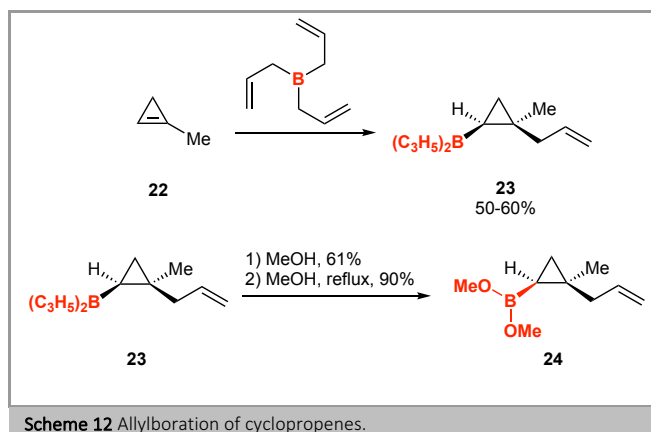


In 2016, Chang and co-workers reported the tris(pentafluorophenyl)borane-catalyzed conversion of furans **19** into *anti* cyclopropylsilanes **21** (Scheme 11). The reaction takes place through a ring-opening and closing cascade, without the use of any transition metal.²⁰ Overall, the transformation is very interesting since furans, readily available from biomass,²¹ are transformed into silicon functionalized intermediates. The proposed mechanism includes attack of 2-methylfuran **19** to activated silylium species **V** to afford **VI**. Oxonium intermediate **VI**, immediately reacts with the borohydride in the media to afford **VII**. Silylation of **VII**, formed intermediate **VIII**, which is attacked by a borohydride, opening the cycle, and forming compound **IX**. A silyl oxonium intermediate **X** is then formed by reaction of **V** and homoallylic silane **IX**. Finally, borohydride nucleophilic attack to **X** formed *trans*-cyclopropylsilane **21**.

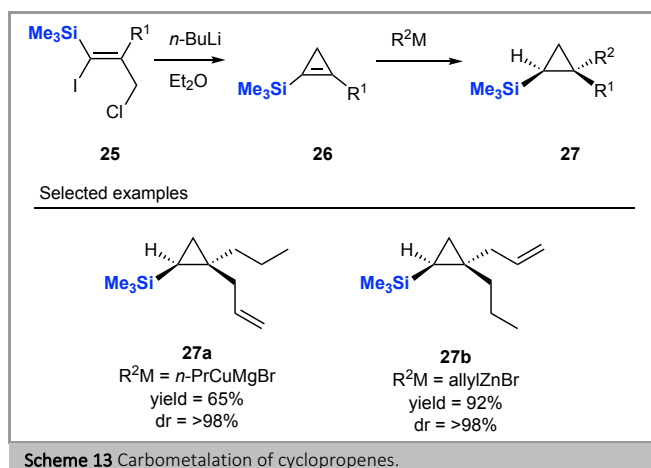


Functionalization of cyclopropenes

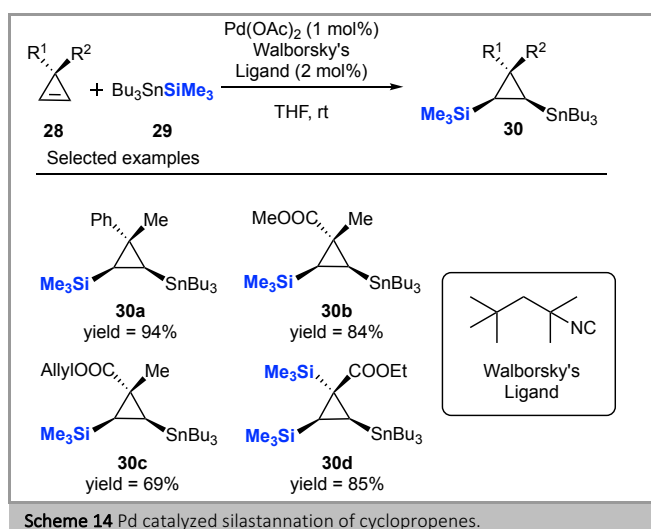
The functionalization of the double bond of cyclopropenes has proven to be a very useful approach for the preparation of cyclopropylsilanes and boronates. In 1971, Bubnov and coworkers published the first diastereoselective synthesis of cyclopropylboranes **23** through a carboboration of cyclopropenes with triallylborane. The cyclopropylborane is obtained along with some ring-opening products. They converted the borane in dimethoxyboronate **24** through a two-step oxidation.²² Although the method is not general for the preparation of a broad variety of cyclopropylboronates, it was the first time in which these synthetic intermediates were prepared stereoselectively.



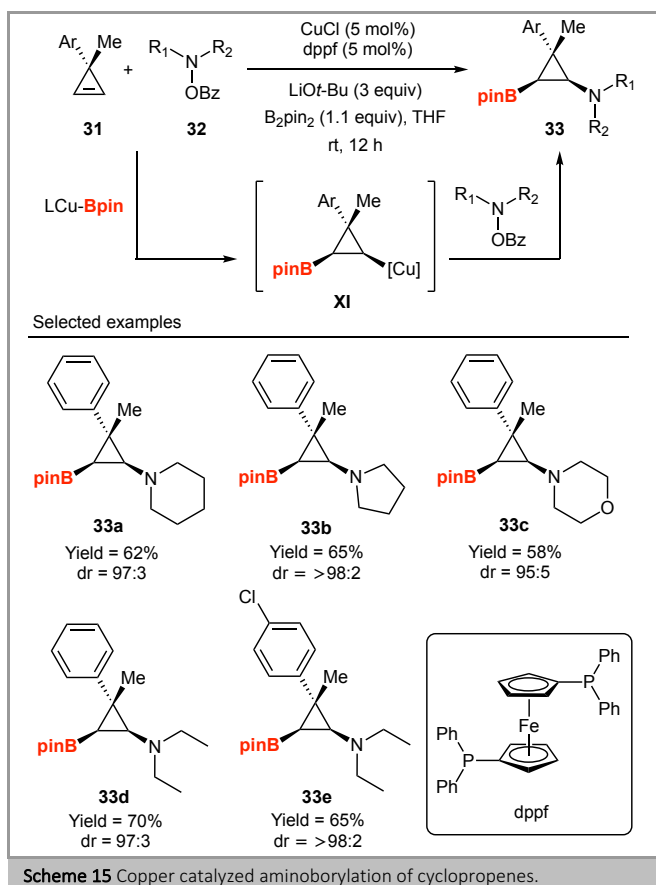
In 1985, Stoll and Negishi synthesized cyclopropenes **26** via cyclization of an alkenyllithium derived from **25**. The carbometallation of **26** with different organometallic reagents afforded cyclopropylsilanes **27** in good yield as single diastereomers.²³



In 2002, Gevorgyan and co-workers published the palladium catalyzed silastannylation of cyclopropenes **28**. The optimal conditions used for this reaction were $\text{Pd}(\text{OAc})_2$ and Walborsky's ligand as catalyst in combination with silyltin reagent **29** (Scheme 14). The desired cyclopropylsilylstannanes **30** were smoothly obtained as single diastereomers.²⁴

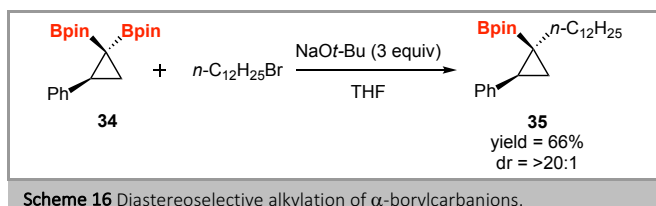


A few years later, Tortosa and co-workers reported the diastereoselective copper-catalyzed aminoborylation of cyclopropenes **31** (Scheme 15).²⁵ High stereocontrol was observed using 5 mol% of CuCl and dpfp as ligand. The use of LiOt-Bu was key, since other bases were not compatible with the electrophilic amine **32**. The reaction proceeded through intermediate **XI**, formed after insertion of the cyclopropene into the Cu-B bond of a copper-boryl complex. Highly functionalized cyclopropylaminoboronates **33** were prepared in good yields and excellent diastereoselectivities.



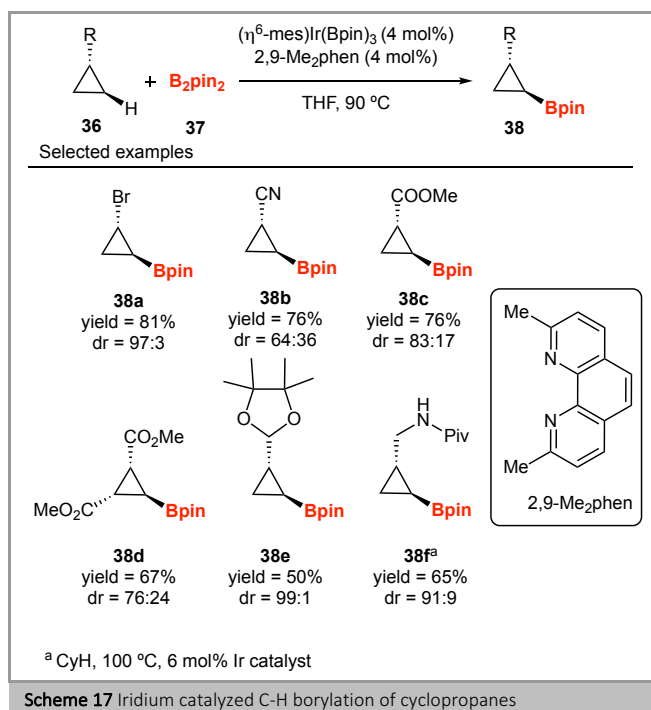
Alkylation of α -boryl carbanions

In an elegant work, Morken and co-workers have used 1,1-bis(pinacolboronate) esters as precursors of α -boryl carbanions, which can react with a variety of alkyl electrophiles (Scheme 16). In one of the examples, the authors used the readily available geminal bis(boryl)cyclopropane **34** for this purpose, obtaining outstanding levels of stereocontrol in the final cyclopropylboronate **35**.²⁶ It is noteworthy the formation of a tertiary sp^3 boron-containing stereocenter.

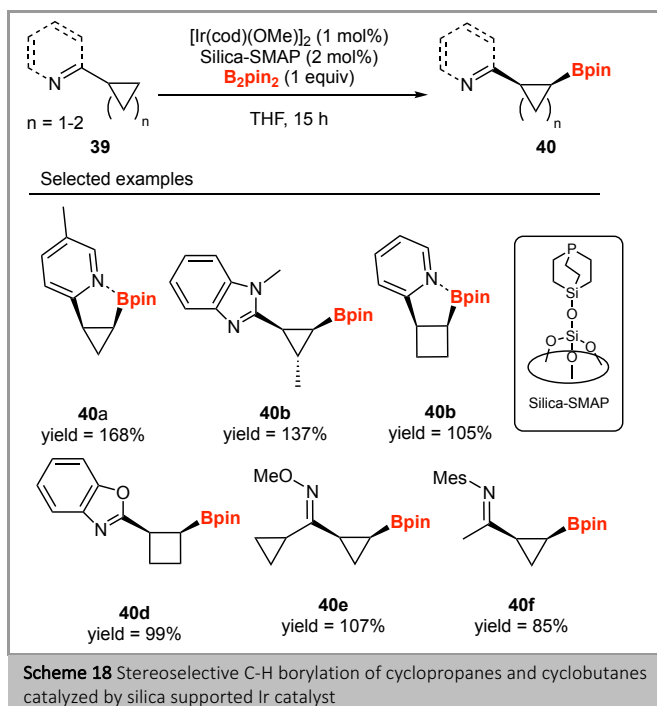


Transition-metal catalyzed C-H activation reactions

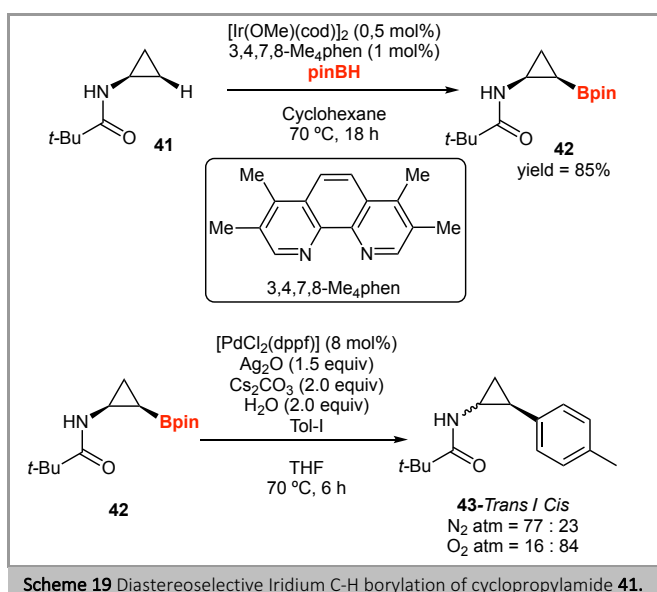
Recently, the C-H activation of functionalized cyclopropanes has become a straightforward method to prepare cyclopropylboronates. In 2013, Hartwig and co-workers reported the iridium catalyzed C-H borylation of mono- and disubstituted cyclopropanes (Scheme 17). The borylation occurs selectively at the methylene C-H bonds of the cyclopropane. *Anti* cyclopropylboronates **38** were prepared with high diastereoselectivities by the combination of iridium and 2,9-Me₂phenanthroline. The diastereoselectivity was sterically controlled and dependent on the size of the substituents on **36**.²⁷



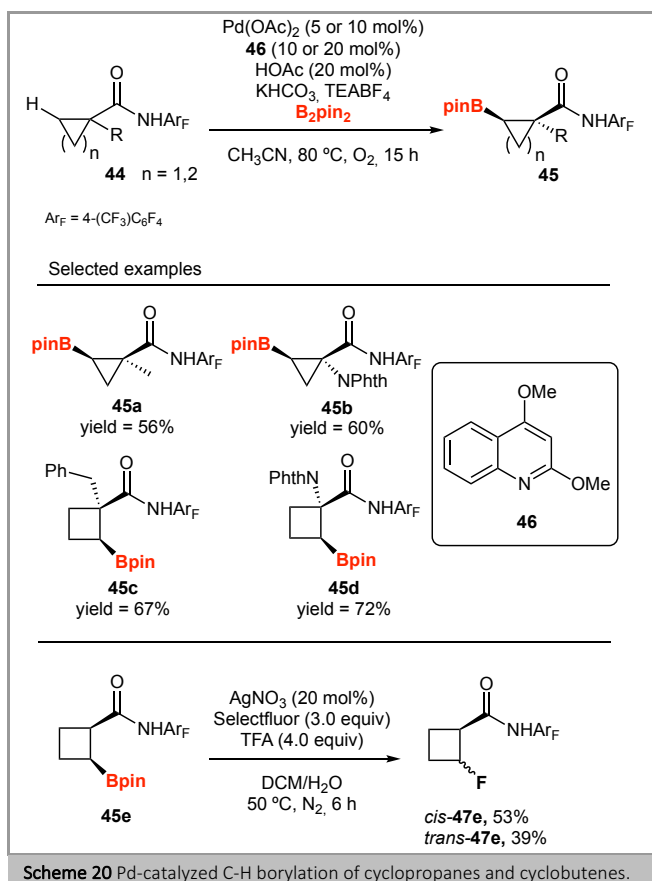
Sawamura and co-workers studied the C-H activation of cyclopropanes and cyclobutanes carrying nitrogen-containing substituents. Using a silica-supported monophosphane-Ir catalyst, *cis* cyclopropyl and cyclobutylboronates **40** were prepared with excellent diastereocontrol (Scheme 18). Pyridines, oxazoles and imines served as directing groups in this transformation. Both the bis(pinacolato)diboron and the pinacolborane produced in situ can act as borylating agents. Consequently, the yields shown in scheme 16 are higher than 100% (maximum yield 200%).²⁸



A method for the synthesis of 2-arylcyclopropylamines (ACPAs) was developed by Itami and co-workers through sequential C-H borylation and Suzuki-Miyaura coupling (Scheme 19). Starting from readily available *N*-cyclopropylpivalamide **41**, they obtained the *cis* C-H borylation product **42** in high yield using an iridium catalyst and a phenanthroline type ligand. The observed *syn* diastereoselectivity is complementary to that observed by Hartwig *et al* under steric control (Scheme 17).²⁷ Using an enantiomerically enriched compound, they demonstrated that the Suzuki-Miyaura cross-coupling of the products took place with retention of the configuration at the boron-containing stereocenter but with epimerization at the nitrogen-bound carbon. Interestingly, this epimerization was partially suppressed in the presence of O₂.²⁹ In a later work, the same authors applied this methodology to quickly assemble a library of LSD1 inhibitors.³⁰

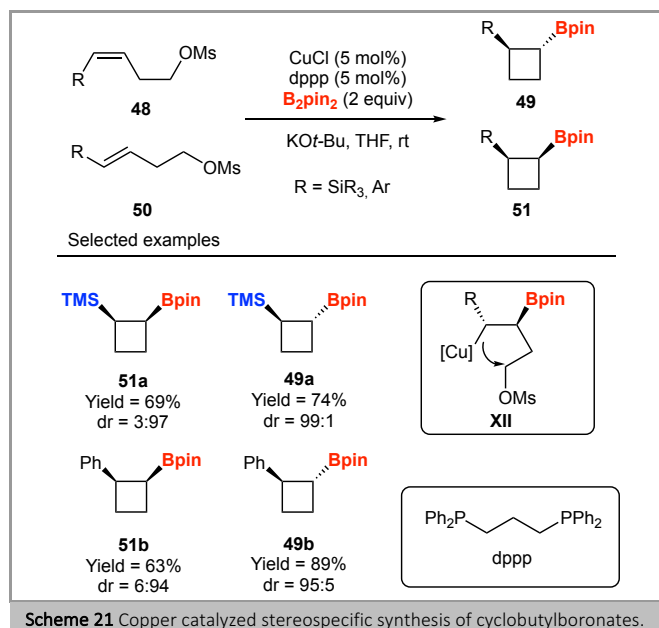


In 2016, Yu and co-workers reported a Pd catalyzed β -borylation of amides promoted by quinoline-based ligands (Scheme 20). This methodology is compatible with both α -methyl C-H bonds and α -methylenes in a wide range of cyclic and non-cyclic amides. Among these substrates, cyclopropyl and cyclobutylamides **44** gave excellent results, affording cyclopropyl and cyclobutylboronates **45** with good yields as single diastereomers.³¹ They successfully transform the C-B bond into C-C bond via Suzuki coupling and into a C-F bond, although the last transformation was not diastereoselective.



Ring closing reactions to form four-membered rings

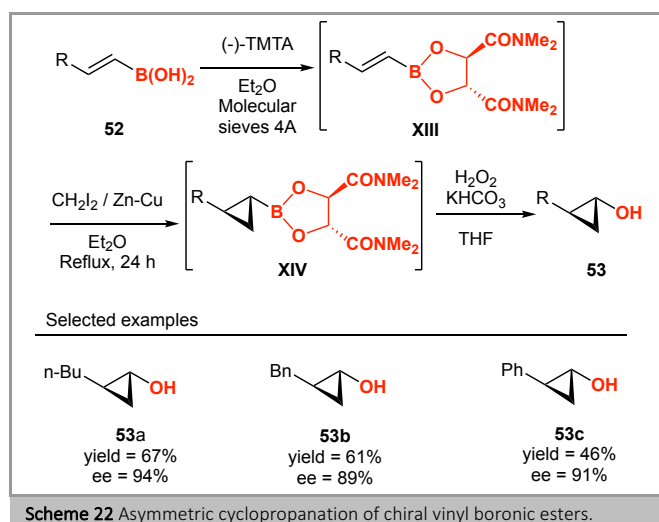
The diastereoselective synthesis of cyclobutylboronates has received considerably less attention than the preparation of cyclopropyl derivatives. Schemes 18 and 20 show some of the few examples reported in the literature to prepare these compounds. Ito and co-workers reported the stereospecific synthesis of cyclobutylboronates **49** and **51** through the copper-catalyzed borylation of homoallylic sulfonates **48** and **50** (Scheme 21).³² Both *syn* and *anti* cyclobutylboronates were prepared just by switching the geometry of the double bond in the starting materials. The reaction involved an initial insertion of the double bond into the Cu-B bond of a copper-boryl complex to form alkyl copper intermediate **XII**. Then, the cyclobutylboronate is formed through an intramolecular S_N2 reaction. The reaction required a silyl or an aryl group on the alkene to control the regiochemistry in the insertion step. They could oxidize both the C-Si and C-B bond. Additionally, they successfully carried out the Matteson homologation of the C-B bond.



2.2 Asymmetric Synthesis of Cyclopropyl and Cyclobutyl boronates and silanes.

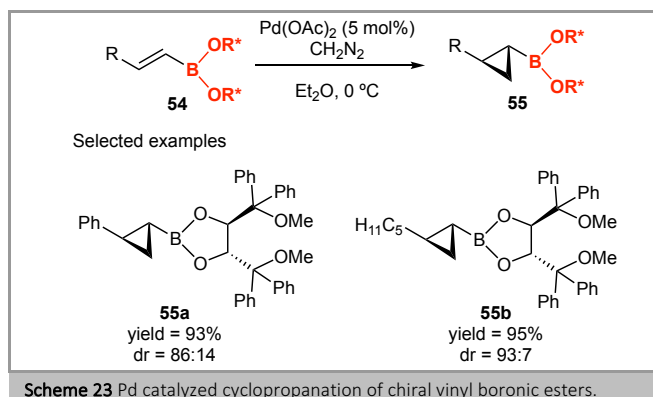
Cyclopropanation reactions

The first asymmetric synthesis of cyclopropylboronates was published by Imai and co-workers in 1990. Using a Simmons-Smith type reaction on optically pure 1-alkenylboronic esters **XIII**, they prepared cyclopropylboronates **XIV** with good stereocontrol. They carried out the *in situ* C-B bond oxidation to obtain cyclopropyl alcohols **53**, since cyclopropylboronates **XIV** were not stable enough to be isolated (Scheme 22).³³



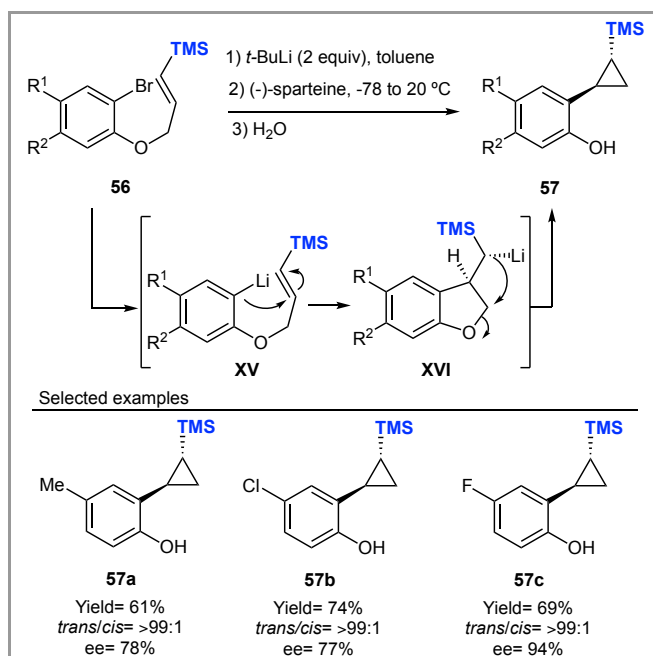
Between 1997 and 2009, Pietruszka and co-workers reported a series of publications to optimize this approach, using a variety of chiral alkenylboronic esters **54**, Pd(OAc)₂ and diazomethane or Simmons-Smith-type protocols.³⁴ Importantly, they were able to isolate cyclopropyl boronic esters **55**. The best results were obtained using a dimethyl tartrate derivative as chiral auxiliary on the boron (Scheme 23). Using a similar approach, Deng et al reported the Pd catalyzed cyclopropanation of vinyl boronates

XIII, previously used by Imai. After hydrolysis of the boronic ester, Deng was able to isolate the cyclopropyl boronic acids and use them in Suzuki-Miyaura cross-couplings.³⁵



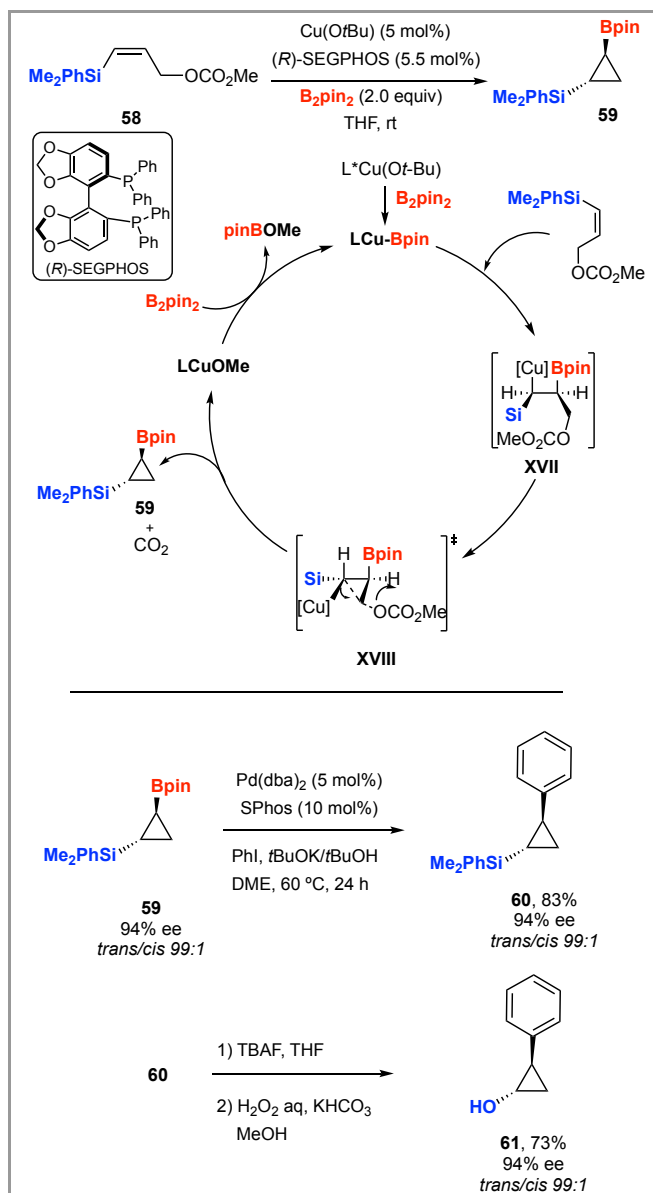
Ring-closing reactions to form three-membered rings

In 2002, Barluenga and co-workers³⁶ reported the asymmetric synthesis of silylcyclopropanes **57** via tandem carbolithiation/ γ -elimination of aryl bromides **56** (Scheme 24). Organolithium **XV**, formed by bromine-lithium exchange, underwent an intramolecular 5-exo carbolithiation to afford intermediate **XVI**, probably favored by the silyl group. Then, an intramolecular cyclization provided silylcyclopropanes **57**. Using a stoichiometric amount of (-)-sparteine, the authors achieved moderated to good enantioselectivities and excellent diastereoselectivities. The method represents one of the first examples for the preparation of enantiomerically enriched cyclopropylsilanes.



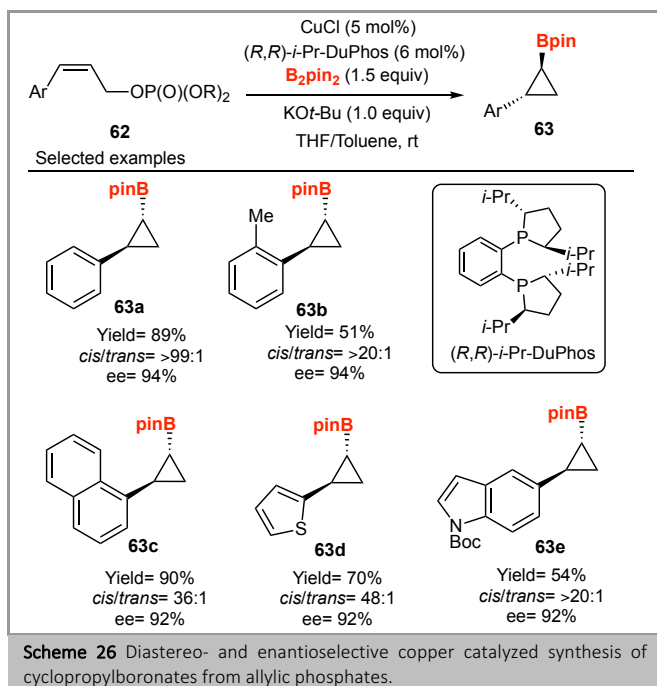
A different example involving ring closure was reported by Sawamura, Ito and co-workers in 2008.³⁷ In this case, the asymmetric synthesis of boron-silicon cyclopropane **59** was

achieved through an enantioselective Cu(I) catalyzed borylation of allylic carbonates **58** (Scheme 25). Using 5 mol% of Cu(*Ot*-Bu) and (*R*)-SEGPHOS as chiral ligand, bifunctional *trans* cyclopropane **59** was prepared in high yield with excellent diastereo- and enantioselectivity. The *Z* configuration on the double bond was critical to achieve this excellent result, affecting the reaction rate, the *cis/trans* selectivity and the chemoselectivity. Indeed, when the *E* carbonate was used a mixture of compounds was obtained. Interestingly, both silane and boronate moieties were selectively transformed into an enantiomerically enriched cyclopropanol, through Suzuki-Miyaura cross-coupling followed by Tamao-Fleming oxidation. The proposed mechanism starts with in situ formation of a chiral copper-boryl complex. Insertion of the double bond into the Cu-B bond provides an alkyl copper intermediate **XVII**. The regiochemistry in the insertion step is controlled by the silyl group while the chiral copper-boryl complex controls the stereoselectivity on the newly created C-B bond. Through transition state **XVIII**, a diastereoselective intramolecular S_N2 type transformation affords *trans* cyclopropane **59** (scheme 25). From **59**, they successfully obtained the Suzuki coupling product **60**. Subsequent oxidation of the C-Si group afforded cyclopropanol **61**.



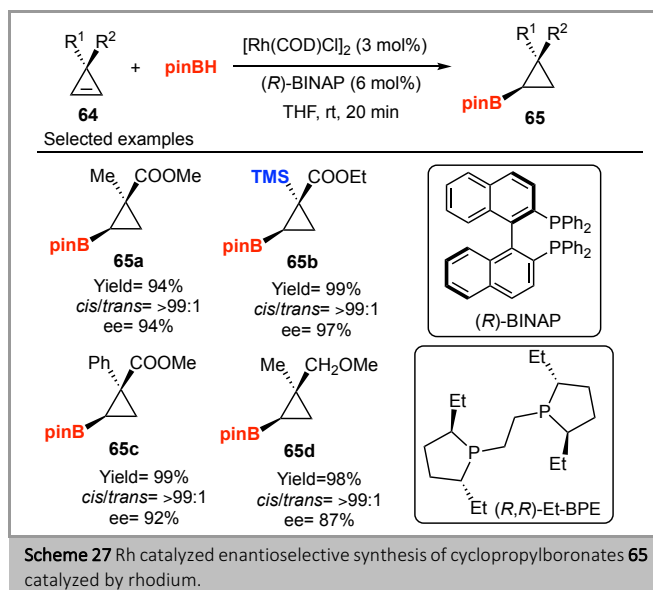
Scheme 25 Enantioselective synthesis of silicon-boron cyclopropyl derivatives.

Later, in 2010, the same research group³⁸ extended this methodology to aryl substituted (*Z*)-allylic phosphates **62**. A different chiral ligand, (*R,R*)-*i*-Pr-DuPhos, was used to achieve stereocontrol. The catalytic system was successfully applied to a wide range of aryl and heteroaryl substrates (Scheme 26). Cyclopropylboronates **63** were obtained in moderate to high yields with excellent *trans*-diastereoselectivity and high ee's. Interestingly, the authors could perform the transformation with (*E*)-allylic phosphates, providing access to enantiomerically enriched *cis* cyclopropylboronates, with good diastereoselectivities but moderate ee's.

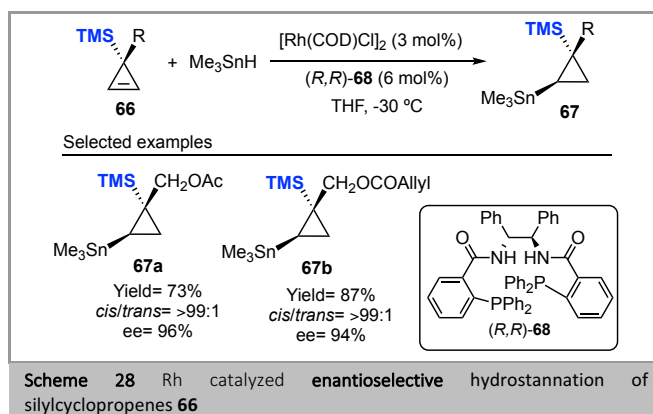


Desymmetrization of cyclopropenes

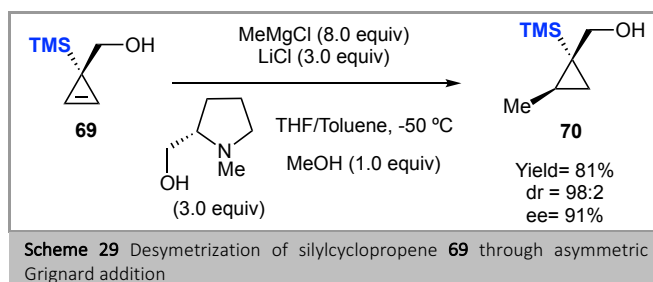
Several authors have developed asymmetric desymmetrizations of cyclopropenes to prepare enantiomerically enriched cyclopropylsilanes and boronates. Following their previous work on Pd catalyzed diastereoselective silastannylation of cyclopropenes (Scheme 14),²⁴ Gevorgyan and co-workers³⁹ reported the enantioselective hydroboration of cyclopropenes **64** (Scheme 27). A series of *cis* cyclopropylboronates **65** were prepared in excellent yields and high degree of diastereo- and enantiocontrol using the combination of [Rh(COD)Cl]₂ (3 mol%) and the chiral ligand (*R*)-BINAP (6 mol%). A remarkable directing effect of the ester group was observed compared to the sterically controlled Pd catalyzed hydrostannylation of the same substrates.³⁷ For that reason, the *cis* isomer was exclusively formed. This interaction between catalyst and substrate resulted key not only to provide high diastereoselectivity but also to control the enantioselectivity. Indeed, when a phenyl-methyl substituted cyclopropene was used, the desired product was obtained with only 58% ee. The cyclopropene **64d** with a methoxymethyl group at 3-position underwent the hydroboration in very good yield and high ee, but in this case ligand (*R,R*)-Et-BPE (Scheme 27) was used. The methodology provides access to bifunctional cyclopropane **65b**, containing boron and silicon moieties. Subsequent Suzuki-Miyaura cross-coupling of the products, allowed for the preparation of trisubstituted cyclopropanes in good yields.



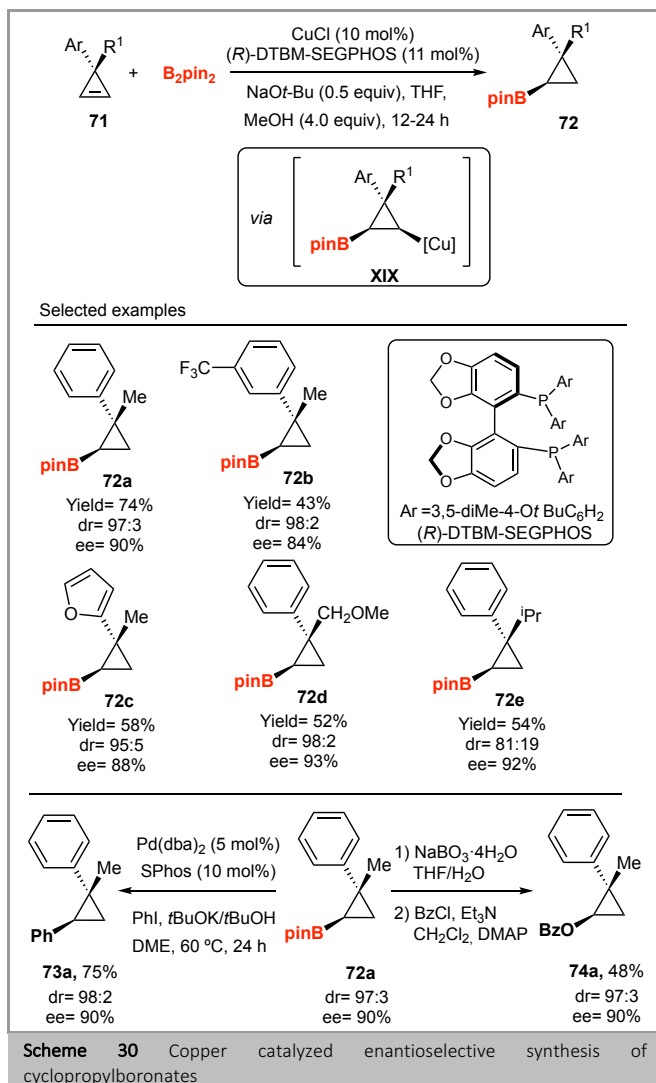
The same group reported the related enantioselective hydrostannylation of cyclopropenes.⁴⁰ The same rhodium salt was used in combination with the chiral ligand (*R,R*)-**68** (Scheme 28). This time, the reaction was not restrictive to the use of coordinating substrates and, therefore, was more general than the hydroboration (Scheme 27). Concerning this review, silylcyclopropenes **66** provided stannyl cyclopropylsilanes **67** in high yields and excellent stereocontrol (Scheme 28).



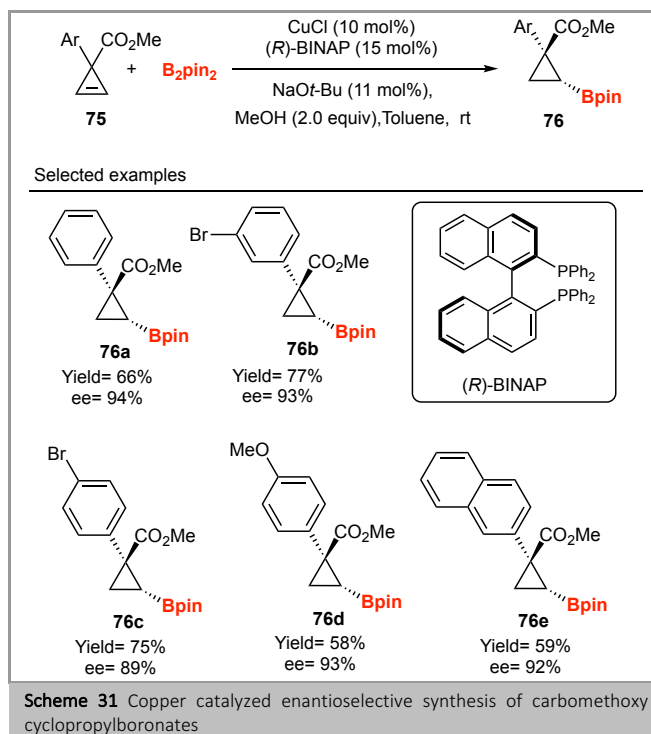
In the same context of desymmetrization of cyclopropenes, Fox and co-workers,⁴¹ published the synthesis of the enantioenriched silylcyclopropane **70** (Scheme 29). This example is part of a broader study on the enantioselective carbomagnesation of cyclopropenes using *N*-methylprolinol as chiral ligand. Notable, the silyl group was compatible with the reaction conditions, and **70** was obtained in high yield and excellent diastereo- and enantioselectivity.



More, recently, Tortosa and co-workers²⁵ reported the copper-catalyzed borylation of cyclopropenes using (*R*)-DTBM-SEGPHOS as ligand (Scheme 30). This approach nicely complements that reported by Gevorgyan since a directing group on the cyclopropane was not needed to provide stereocontrol. A wide range of cyclopropylboronates **72** were prepared in good yield and high enantiocontrol. They only observed the formation of a single diastereomer. Oxidation to cyclopropanols **74a** and Suzuki-Miyaura coupling on the products to obtain **73a** were also successfully applied. The reaction starts with the formation of a chiral copper-boryl complex followed by insertion of the cyclopropene to form cyclopropylcopper intermediate **XIX**. The methanol serves as a proton source to provide the hydroboration product and to regenerate the catalytic cycle. Notably, the authors trapped the proposed cyclopropylcopper intermediate with electrophilic amines, instead of methanol, to generate cyclopropylaminoboronates (Scheme 15). Unfortunately, only the diastereoselective approach was developed as the use of chiral ligands did not provide good levels of stereocontrol. These results were highlighted above, in the diastereoselective section of this review (Scheme 15).



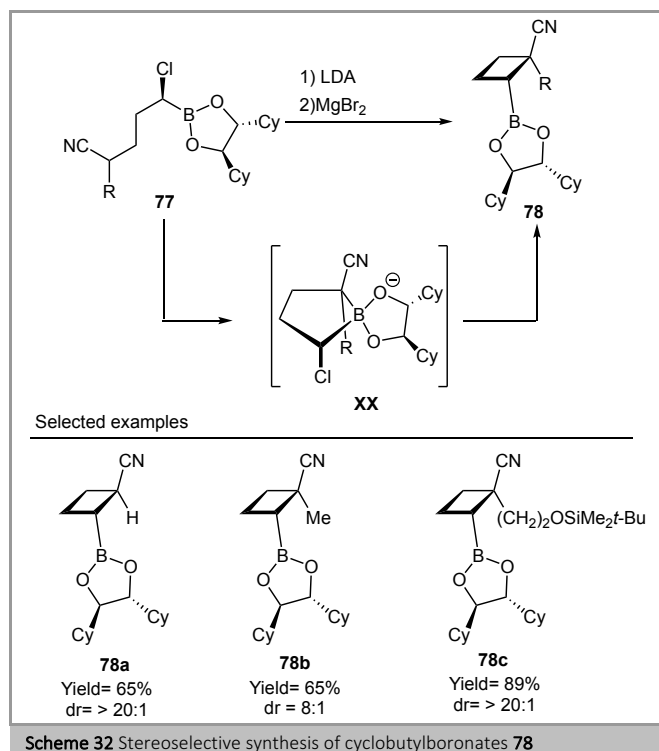
ligand instead of (*R*)-DTBM-SEGPHOS used by Tortosa. Surprisingly, with their catalytic system the ester group was necessary to observe high stereocontrol.



Ring closing reactions to form four-membered rings

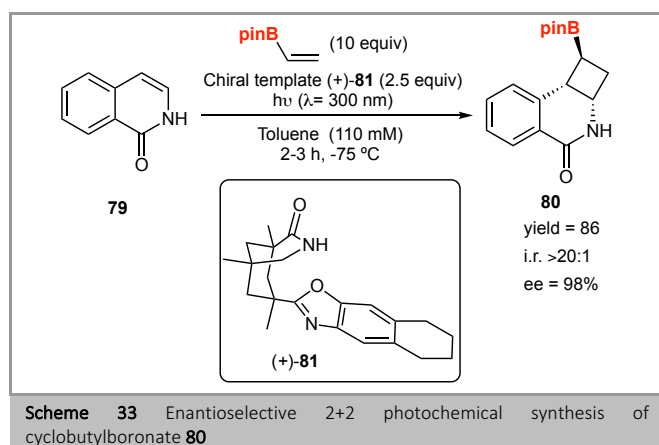
The synthesis of enantiomerically enriched cyclobutylboronates and silanes has been much less studied than the three membered ring derivatives. In this context, Matteson and co-workers published the first synthesis of enantiomerically enriched cyclobutylboronates **78** (Scheme 32). Deprotonation of enantiopure **77** using LDA, led to intermediate **XX**, which upon treatment with MgBr_2 produced the desired products **78** in good yield and high diastereoselectivities.⁴³

At the same time as Tortosa, Lin, Tian and co-workers⁴² reported the copper-catalyzed asymmetric hydroboration of cyclopropenes (Scheme 31). The authors employed (*R*)-BINAP as



[2+2] Cycloadditions

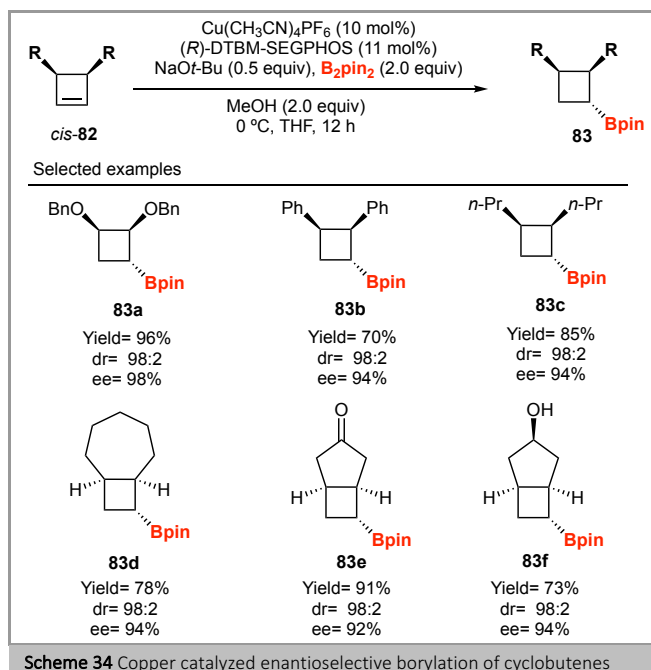
In 2013, Bach and co-workers⁴⁴ developed a very elegant synthesis of the cyclobutylboronate **80** through an enantioselective intermolecular [2+2] photocycloaddition (Scheme 33). Despite that the structural scope is limited to the isoquinolone bicyclic skeleton **80**, the strategy is very efficient and innovative. Using the chiral template (+)-**81** and under the effect of light, a [2+2] cycloaddition proceeded in high yield, excellent isomeric ratio and almost perfect stereocontrol.



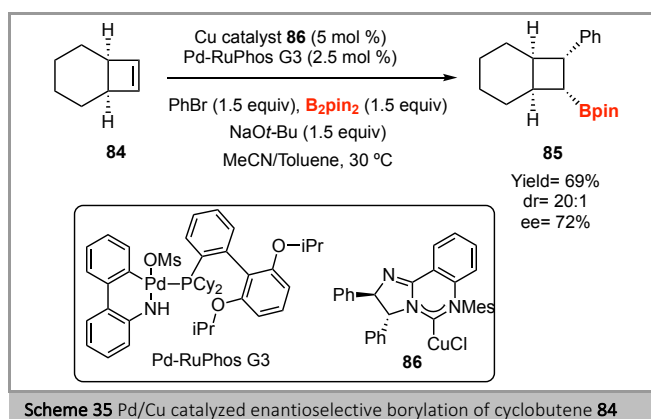
Desymmetrization of cyclobutenes

In 2016, Tortosa and co-workers⁴⁵ applied for the first time the desymmetrization strategy to prepare enantiomerically enriched cyclobutylboronates (Scheme 34). Using $\text{Cu}(\text{CH}_3\text{CN})_4\text{PF}_6$ (10 mol%) and (*R*)-DTBM-SEGPHOS (Scheme 30) as chiral ligand, *meso*-cyclobutenes **82** were desymmetrized to provide cyclobutylboronates **83** in high yields and excellent diastereo- and enantioselectivities. The catalytic system worked well for a broad variety of substrates, with alkyl and aryl substituents, and was compatible with functional groups such as ketones or free

alcohols. Different bicyclic cyclobutylboronates were also prepared with this method. Subsequent C-B functionalization, provided interesting synthetic intermediates. This method represents the first catalytic enantioselective approach for the preparation of enantiomerically enriched cyclobutylboronates.



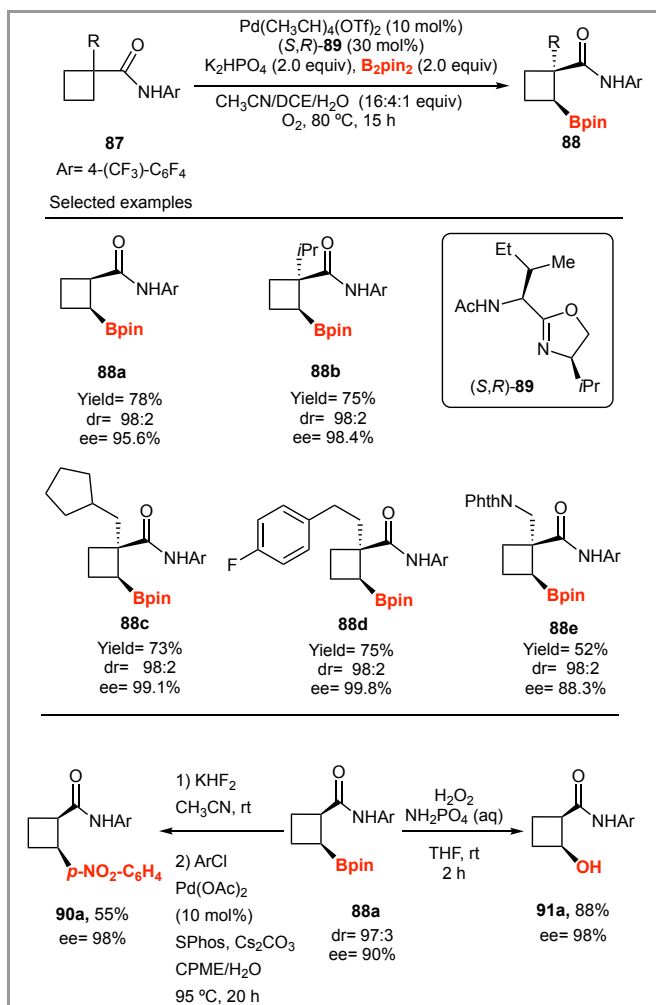
Recently, Logan and Brown reported the enantioselective arylboration of alkenes by combination of Pd-RuPhos G3 and Cu(I) catalyst **86** (Scheme 35). Concerning this review, they applied the optimized conditions to cyclobutene **84** to prepare cyclobutylboronate **85** with excellent diastereoselectivity and good enantiomeric excess.⁴⁶



Transition-metal catalyzed C-H activation reactions

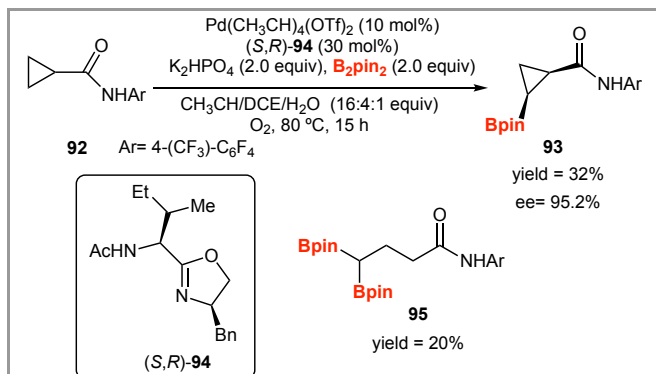
In the context of C-H activation, Yu and co-workers⁴⁷ recently reported the asymmetric synthesis of cyclobutylboronates **88** (Scheme 36) through the Pd(II) catalyzed borylation reaction of cyclobutylamides **87**. The amide moiety served as a directing group in this C-H activation. Excellent chemoselectivity, good yields and high ee's were observed using the chiral bidentate APAO ligand (*S,R*)-**89**. A wide range of substituents were compatible with the optimized conditions. Functionalization of

the C-B bond provided access to valuable enantiomerically enriched cyclobutanes.



Scheme 36 Enantioselective C-H borylation of cyclobutylamides

In the same report, Yu applied this approach to cyclopropylamide **92** to prepare cyclopropylboronate **93** (Scheme 37). Although excellent enantioselectivity was observed with (S,R)-**94**, the transformation was less efficient since diborylated product **95** was obtained as a by-product in an appreciable 20% yield.



Scheme 37 Enantioselective C-H borylation of cyclopropylamides

3 Conclusions

Since the innovative diastereoselective synthesis of cyclopropylboronate by Danheiser and Savoca in 1985, a number of stereoselective methods for the synthesis of cyclopropyl and cyclobutylboronates and silanes has been developed, enabling different ways to prepare these useful building blocks.

The development of asymmetric methods in recent years, have made possible the preparation of enantiomerically enriched compounds, amplifying the utility of these class of reagents, especially in drug discovery. Despite the effort made in this field, the structural scope is still limited. For example, the preparation of enantiomerically enriched cyclobutylsilanes is still uncharted territory. In this context, it would be especially interesting the development of enantioselective C-H activation methodologies that do not require a directing group and enantioselective [2+2] cycloadditions. Additionally, efforts on the functionalization of the C-B and C-Si bonds on the products are necessary to increase their synthetic utility. There is no doubt that the interest on these building blocks will increase in the years to come. Hopefully, this review will inspire synthetic chemists to bring novel methodologies for their synthesis and further synthetic applications.

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Biosketches



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