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# 1,2-Boronate Rearrangement: An Efficient Tool for the Opening, Functionalization and Formation of Strained Cycles

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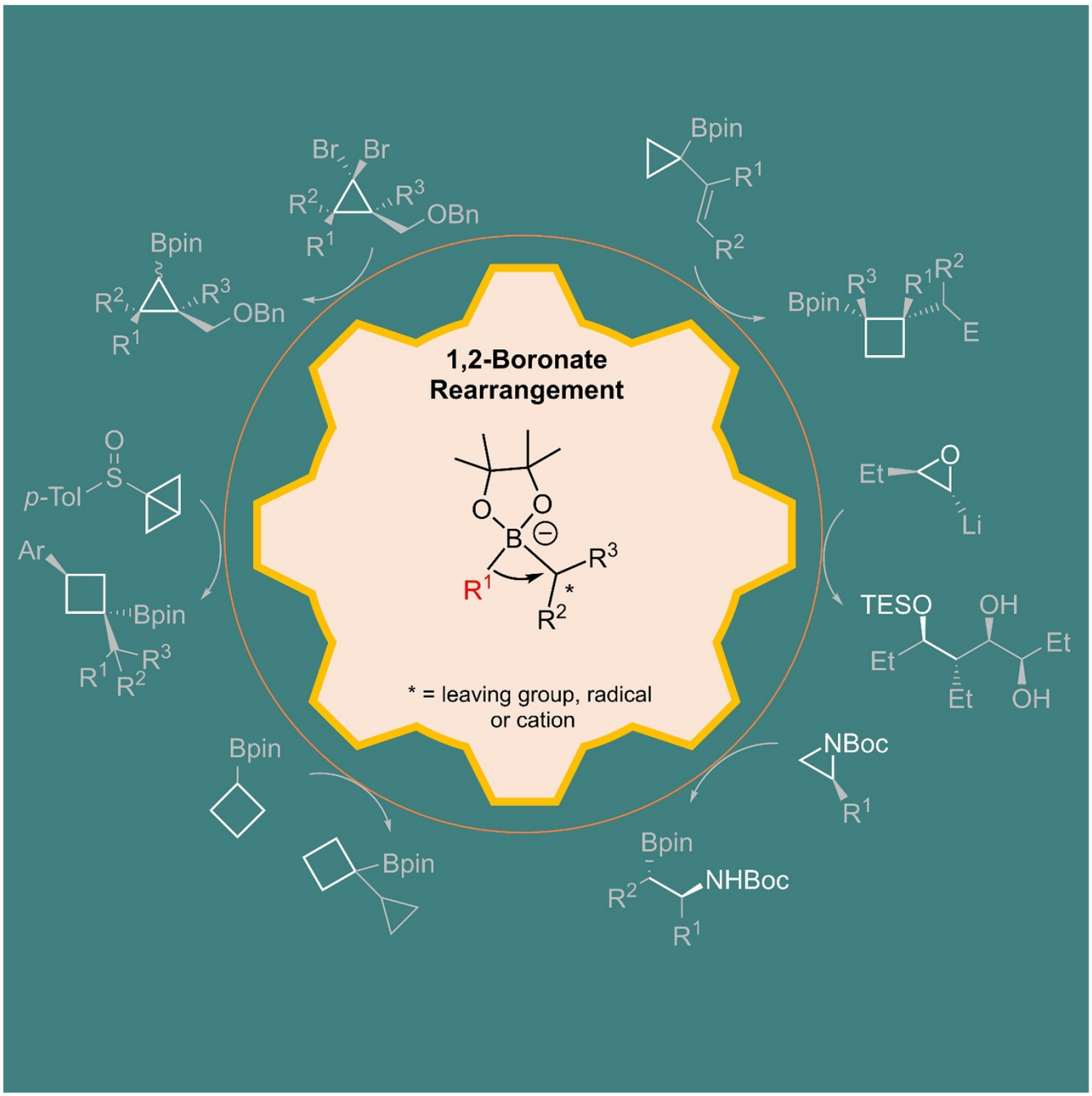
*Rémi Blieck was nominated to be part of this collection by EurJOC Board Member Tatiana Besset.*



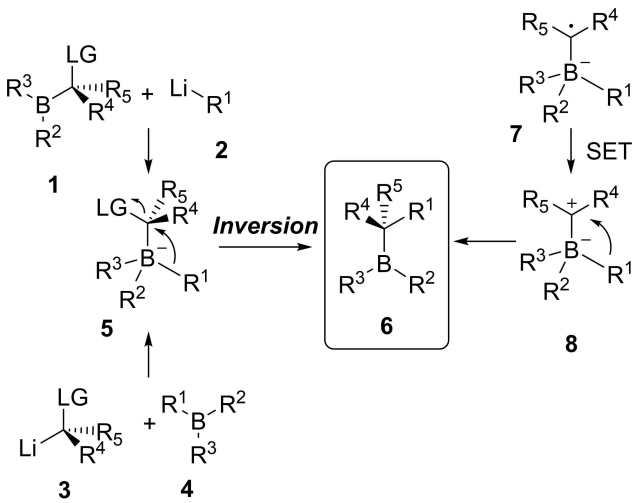
The 1,2-metallate rearrangement occurring with boronate complexes is a strategy of choice for the synthesis of organoboron compounds, giving a direct access to highly functionalized molecules. Lately, significant progress has been made in the use of this reaction for the opening, the functionalization, and the formation of strained cycles. In this review, we will highlight these recent advances, focusing on cycloalkanes and oxygen- or nitrogen-containing strained cycles.

## 1. Introduction

Organoboron reagents are among the most widely used families of compounds in catalysis and organic synthesis.[1] Reactions involving organoboronic compounds usually benefit from a high functional-group tolerance and these reagents generally prove to be non-toxic. Classically, they have been exploited in hydroboration processes[2] and in transition-metal-catalyzed Suzuki-Miyaura couplings.[3] But the synthetic use of organoboron reagents is far from being restricted to these iconic examples.

Among the distinctive transformations allowed by organoboron reagents, the possibility to perform a 1,2-migration of a boron-substituent to an α-carbon, also referred to as Matteson-type rearrangement, has recently received an important attention from the scientific community.[4]

The overall reaction proceeds through the formation of a boronate complex **5**, typically by reaction with an organolithium **2** or an organomagnesium, followed by 1,2-migration with simultaneous departure of a leaving group, sometimes assisted by a Lewis acid activator (Scheme 1). One of the most significant properties of this reaction is the very high stereospecificity of the concerted migration/elimination, because the two groups must align in an *anti*-periplanar manner, making it a very effective tool for asymmetric synthesis.[5] An emblematic example is the possibility to use $LiCHCl_2$, with subsequent reaction with an organometallic species.[6] This reaction allowed the enantioselective homologation of the boronic ester, and could be applied in an iterative manner, giving an excellent control of the formed asymmetric centers.[7] While the original Matteson rearrangement was described with a halide leaving group, over the years many similar reactions were reported featuring various leaving groups. carbamates have been used as efficient leaving group, allowing the formation of the boronate complex by reaction of organoboron with chiral carbanion, and trigger the 1,2-migration without additional electrophile.[8]




**Scheme 1.** 1,2-boronate rearrangement.

Remarkably, flow chemistry proved to have a beneficiary influence on this reaction.[9] Enantioinduction can also be allowed by stereoselective lithiation using chiral diamines such as sparteine.[10] More recently, the catalytic use of a new lithium-isothiourea-boronate complex also allowed enantioselective 1,2-boronate rearrangements.[11] Recent advances in this field also include the development of aza- and oxa-Matteson reactions.[12] Alternatively, radical induction of the 1,2-migration has also been described, with formation of a radical anion **7**.[13] This intermediate could then be further involved in a Single Electron Transfer or an Halogen Atom Transfer, followed by the 1,2-migration.

In the past few years, the strain energy release corresponding to the opening of strained cycle has been efficiently used as driving force for this 1,2-metallate rearrangement, replacing the necessity of an installed leaving group. In this concise review, we intended to highlight these recent developments for the opening, but also for the functionalization and formation of strained cycles, focusing on cycloalkanes and oxygen- or nitrogen-containing 3- and 4-membered rings, by 1,2-boronate rearrangement.

## 2. Strained Cycloalkanes

The synthesis and reactivity of strained cycloalkanes has received a lot of attention for more than 100 years.[14] This scientific interest has been stimulated by the presence of cyclopropanes and cyclobutanes subunits in a large variety of natural products.[15] The attractiveness is notably due to their ability to improve drug's potency, but also to the opportunity to use these compounds as highly reactive intermediates. Cyclopropanes and cyclobutanes have relatively similar ring strain energies (ca. 27.5 and 26.7 $kcal.mol^{-1}$), making them highly prone to ring opening reactions. Lately, this characteristic

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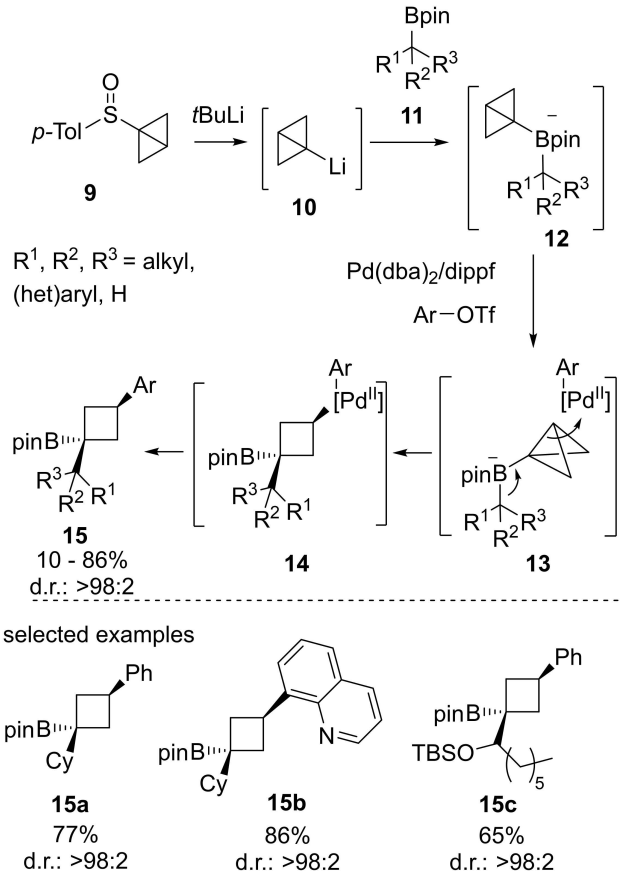
has been exploited for the synthesis of original organoboron reagents by Matteson-type rearrangement.

### 2.1. Synthesis of cyclobutanes by opening of bicyclo[1.1.0]butane

In 2019, the possibility to open a strained bicyclo[1.1.0]butane framework by 1,2-boronate rearrangement has been demonstrated by the group of Aggarwal.[16] In this pioneer work, a bicyclo[1.1.0]butyl lithium intermediate **10** was formed from the parent sulfoxide **9** and converted to a boronate complex **12**. In presence of an electrophilic Pd(II) complex, obtained by oxidative addition of an aryl triflate on a Pd(0) precursor, the cleavage of the central C–C σ-bond of the bicyclobutane and formation of a C–Pd bond occurred, simultaneously with the 1,2-migration of the boron substituent. The desired cyclobutanes **15** can then be obtained after reductive elimination (Scheme 2). The high strain energy of the bicyclo[1.1.0]butane unit (ca. 66 kcal.mol$^{-1}$) being released, it provides a crucial driving force, as a less strained cyclopropyl boronate complex remained unconverted under their optimized conditions. This strategy allowed the formation of highly functionalized 1,1,3-trisubtituted cyclobutanes, as single diastereomers, keeping the boronic ester available for further modifications. This reactivity has also been exploited by Bigler, Zhang, Gosselin and co-workers to illustrate the synthetic utility of asymmetric hydrogenation products.[17]

This strategy has been quickly adapted for various functionalizations. In the following years, the group of Aggarwal indeed demonstrated the feasibility to break the central C–C σ-bond of the bicyclo[1.1.0]butane unit in presence of radical, electrophilic or nucleophilic species. Thus, also in 2019, under visible light irradiation, electrophilic radicals generated from alkyl iodides have been used to open the highly strained bicycle and to promote 1,2-migration of the boron substituent, forming cyclobutyl boronic esters.[18] First, the efficiency of this transformation has been demonstrated with a radical trifluoromethylation reaction, in absence of any photocatalyst (Scheme 3). Moderate to high level of diastereoselectivity has been observed, and excellent chirality transfer was obtained in the case of boronic esters bearing chiral structures. Generalization of this approach with various radical precursors has also been studied, and



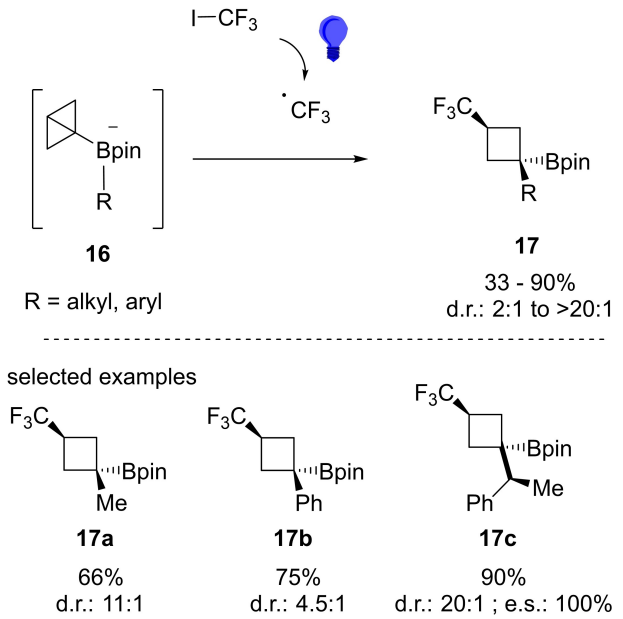

**Scheme 2.** Synthesis of 1,1,3-trisubstituted cyclobutanes by 1,2-boronate rearrangement of strained bicyclo[1.1.0]butyl boronate complexes.

several alkyl halides could be used, if activated by the presence of nitriles, esters, primary amides, or sulfones. This scope highlighted the crucial influence of the steric factor on the stereoselectivity. One important limitation of this approach was the absence of reactivity of nonactivated alkyl iodides, but it was circumvented by the use of sulfones as activating group, which could be eliminated by subsequent reductive cleavage.

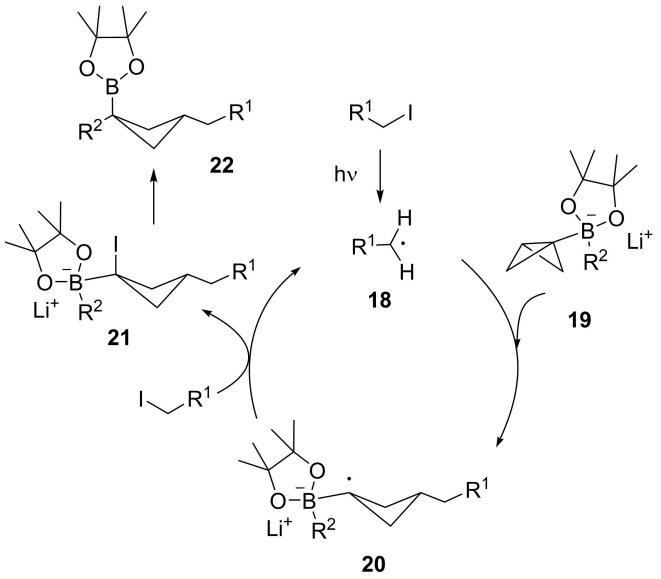
The radical mechanism of this reaction has been deeply investigated in 2021, principally in order to discriminate two different pathways.[19] Indeed, to explain the formation of the

Rémi Blieck obtained his Ph.D. in 2017, working under the supervision of Prof. Florian Monnier and Dr. Marc Taillefer on copper-catalyzed hydrofunctionalizations of allenes. He then joined the team of Dr. Besset in Rouen, focusing on remote C-H activation. In 2019, he joined the team of Prof. Echavarren, working on hydroacenes synthesis. In 2021, he moved to Orsay to work with Dr. de la Torre in the field of total synthesis of natural products. He is interested in the development and application of organometallic catalytic systems, particularly using non-toxic and abundant metals.

Aurélien de la Torre studied chemistry in Montpellier and obtained his PhD in 2014 under the supervision of Dr. Jean-Marie Galano and Dr. Camille Oger. After two post-doctoral positions in the groups of Prof. Nuno Maulide (University of Vienna) and Prof. Ilan Marek (Technion-Israel Institute of Technology), he was appointed in 2018 as Chargé de Recherche CNRS. His research interests include total synthesis, cascade rearrangements and enantioselective cycloaddition reactions.




**Scheme 3.** Radical trifluoromethylation with cleavage of strained bicyclo[1.1.0]butyl boronate complexes with 1,2-metallate rearrangement.

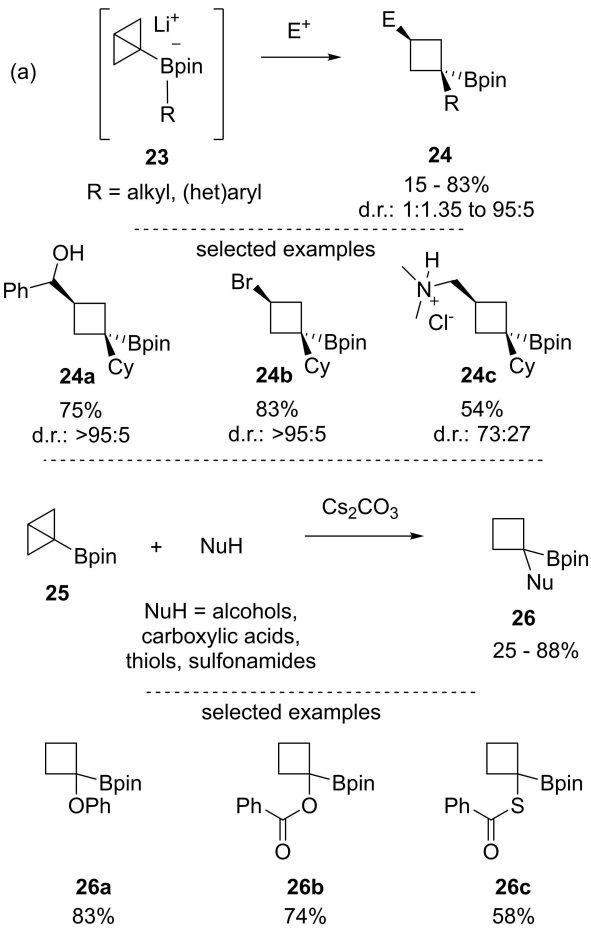



**Scheme 4.** Proposed mechanism of the radical induced 1,2-metallate rearrangement for the formation of 1,1,3-trisubstituted cyclobutanes.

observed product from an α-boryl radical, it is possible to envision an Iodine Atom Transfer (IAT) or a Single Electron Transfer. Using transient absorption spectroscopy, supported by DFT calculations, the authors were able to identify the key α-iodo boronate complex intermediate **21**, specific to the IAT pathway. The proposed mechanism involved photolysis of the C–I bond to generate the corresponding radical **18**, which could then induce cleavage of the central C–C σ-bond of the bicyclo[1.1.0]butane pattern, leading to the formation of the α-boryl radical **20**. The formation of the borylated cyclobutane **22** occurred then by Iodine Atom Transfer followed by 1,2-migration (Scheme 4).

To further extend the applicability of this approach for the synthesis of 1,1,3-trisubstituted cyclobutanes, the same group then studied the use of a wide range of electrophilic reagents (Scheme 5a).[20] The bicyclo[1.1.0]butyl boronate complex **23** was prone to react with aldehydes, but was also reactive among others with dihalodimethylhydantoin, carbon dioxide or tosyl cyanide. This investigation was also the occasion to rationalize the observed diastereoselectivity by DFT calculations and experimental data. The formation of the cis product was favored by a concerted mechanism occurring with large migrating substituent and poorly active electrophiles. On the other hand, smaller migrating substituents and reactive electrophiles lead to the occurrence of both concerted and stepwise mechanism, leading to low diastereoselectivity.

The reactivity of bicyclo[1.1.0]butyl boronic ester with nucleophiles was also established.[21] Adapted with alcohols, carboxylic acids, thiols and sulfonamides, this method gave 1,1-disubstituted borylated cyclobutanes with good yields, in presence of a catalytic amount of $Cs_2CO_3$ (Scheme 5b). In the case where the same reaction was carried out without base,




**Scheme 5.** 1,2-boronate rearrangement with bicyclo[1.1.0]butyl in presence of electrophilic or nucleophilic species.

using sulfonamides, the reaction outcome was significantly altered: formation of borylated cyclopropanes was observed. However, in this case, the plausible mechanism did not rely on 1,2-boronate rearrangement.

### 2.2. Functionalization of cyclobutanes units

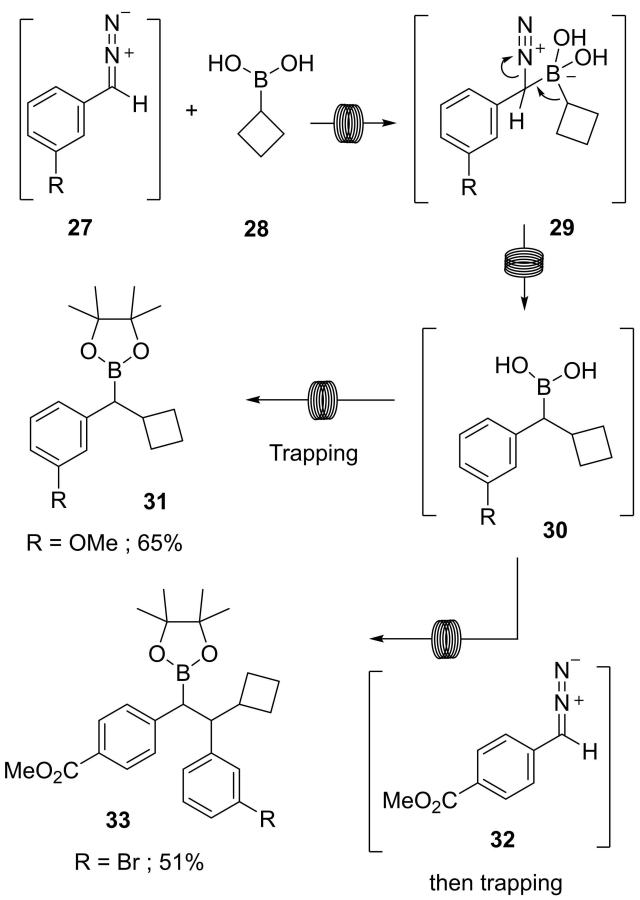
The opening of bicyclo[1.1.0]butyl boronate complexes is not the only available strategy for the synthesis of boron substituted cyclobutanes. The direct functionalization of such strained cycles has also been described in the recent years. Thus, in 2016, the group of Ley reported the use of flow chemistry for the generation of diazo compounds **27**, prone to react with boronic acid **28**.[22] The obtained intermediate **29** underwent loss of nitrogen and 1,2-migration of the boron substituent, then the formed boronic acid **30** has been trapped with pinacol. If low selectivity was observed with small primary boronic acids, giving a large amount of double addition, the reaction was much more selective with secondary boronic acid. It was then possible to form substituted cyclobutane **31** with a good yield of 65% and an acceptable selectivity of 1:0.35 toward the double addition (Scheme 6). Notably, this process being performed in flow, the intermediate before trapping with pinacol could be directly engaged in a second addition with another diazo compounds **32**, in good yield.

In 2017, this versatile strategy has been extended to non-stabilized diazo compounds **35**, obtained from oxadiazolines **34**, again in flow chemistry.[23] This new approach allowed the use of diazo precursors functionalized with strained cycles, leading to the formation of boron-substituted cyclobutane intermediates **37** (Scheme 7). The outcome of the reaction could be controlled by the workup used: treated under air, the boronic acid was easily converted to the corresponding alcohol **39**, while a treatment with tetrabutylammonium fluoride led to an effective protodeboronation. A plausible mechanism is based on the formation of a fluorinated ate complex which, in presence of water, would rearrange, leading to the loss of the boron.[24] This protodeboronation, originally developed on reluctant tertiary boronic esters was here applied to a boronic acid with good 55% yield.

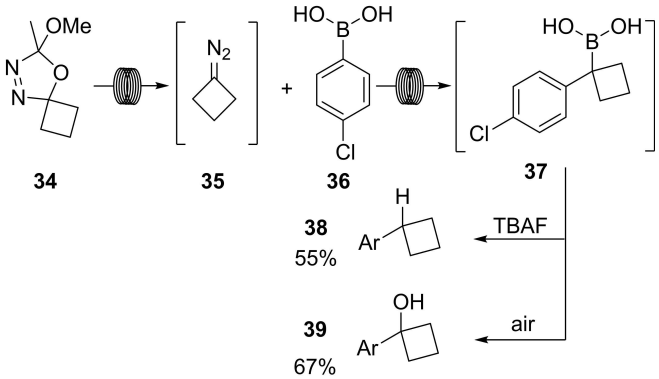
In 2021, the groups of Merchant and Qin demonstrated the possibility to perform a similar reaction using alkyl sulfonylhydrazone **41** as bench-stable starting material.[25] The reaction, derived from the Barluenga Valdés coupling,[26] was efficient with alkyl boronic acid **40** but also with trifluoroborate salts, and successfully applied for the functionalization of cyclobutyl units. In addition, a cyclobutyl-substituted boronic ester was also used efficiently (Scheme 8).

A direct functionalization of a cyclobutane unit was also described in 2019 by the group of Studer, using organolithium reagents **44** and boronic esters **43**.[27] This reaction relies on the formation of a boronate complex **45**, which undergoes H-abstraction at the α-position in presence of an active radical. The obtained radical was prone to react with an oxidant, leading to a zwitterion which, upon 1,2-migration of an aryl- or alkyl-substituent of the boron, led to the formation of an α-substituted boronic ester **46**. Even if the yield remained moderate in these specific cases, the efficiency of this strategy was demonstrated using cyclobutyl-substituted boronic ester with aryl- and alkyl lithium reagents (Scheme 9).

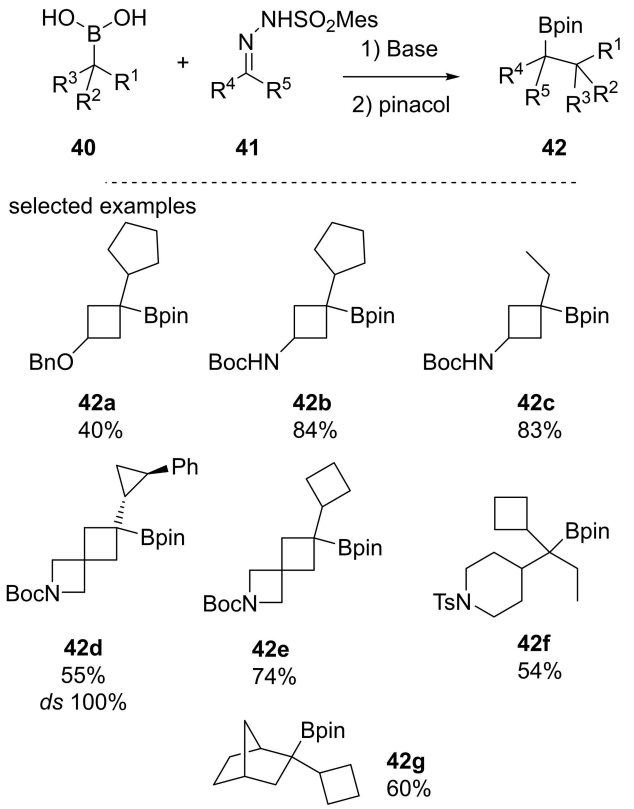
In 2021, the group of Aggarwal studied a lithiation, borylation and 1,2-metallate rearrangement sequence applied on a range of cyclic 2,4,6-triisopropylbenzoate esters, to



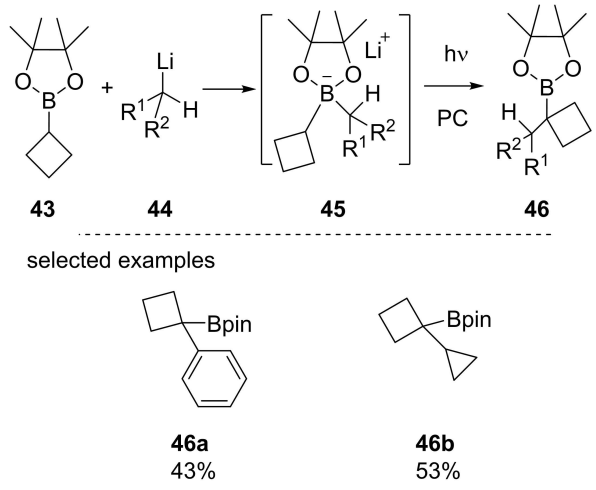

**Scheme 6.** Rearrangement with cyclobutyl-substituted boronic acid and diazo compounds.




**Scheme 7.** Rearrangement with boronic acid and diazo compounds from oxadiazolines.



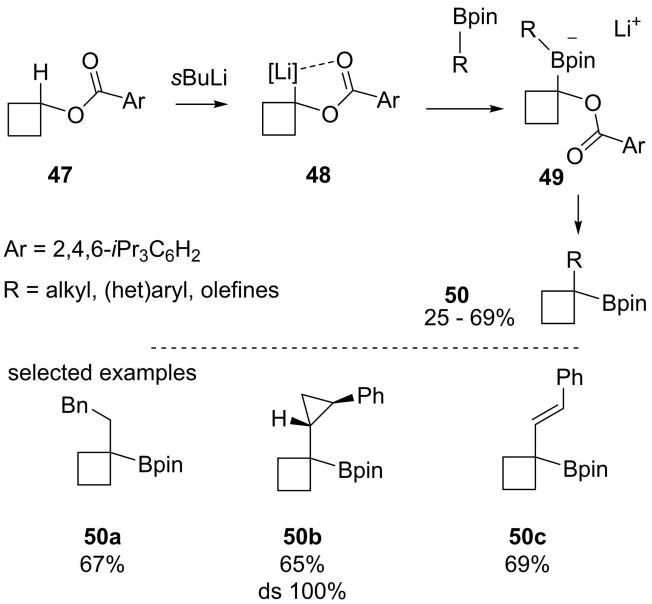

**Scheme 8.** Synthesis of functionalized of cyclobutanes by 1,2-metallate rearrangement with alkyl sulfonylhydrazone.



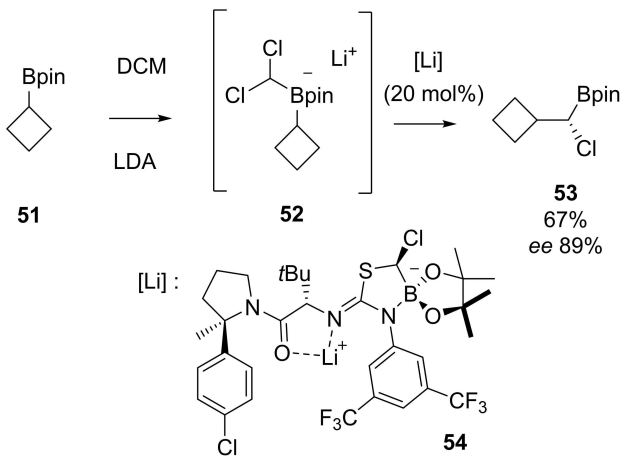

**Scheme 9.** Synthesis of boron-substituted cyclobutanes under irradiation.

determine the effect of the ring size.[28] Both 5- and 6-membered rings were quickly found to be unsuitable, respectively due to a faster competing α-elimination and to a slow deprotonation. In addition, the 3-membered underwent rapid borylation but failed to deliver the rearranged product. Thus, only the cyclobutyl 2,4,6-triisopropylbenzoate ester **47** was successfully engaged in the whole process, the structure having the correct size for an efficient deprotonation and to promote the 1,2-migration. A large scope of boronic esters were suitable for the process, with yields typically around 60% (Scheme 10).

Also in 2021, the group of Jacobsen studied the catalytic enantioselective 1,2-rearrangement of boronic esters with dichloromethane, leading to the synthesis of α-chloro pinacol boronic esters, in presence of a catalytic amount of a lithium-isothiourea-boronate complex **54**.[11] This reaction was found to be highly efficient with a wide scope of primary and secondary boronic esters, including a cyclobutyl-substituted boronic ester **51** (Scheme 11). The obtained α-chloro pinacol boronic esters were then directly engaged in a second coupling in presence of organometallic nucleophiles to give tertiary stereocenters with high enantiocontrol.



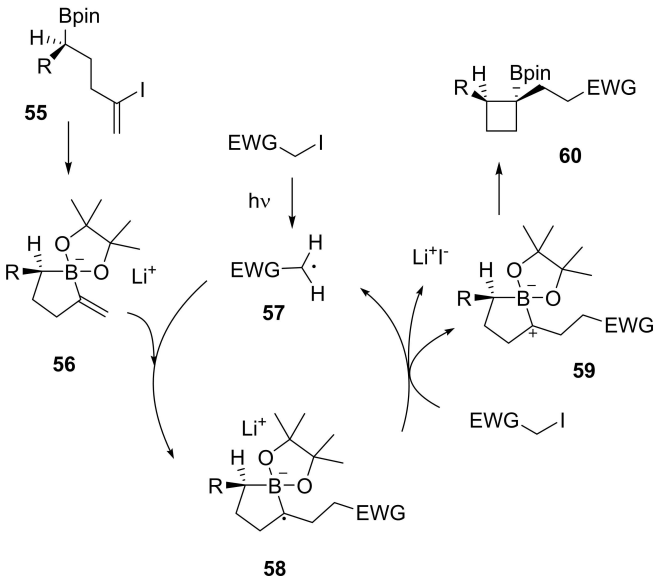

**Scheme 10.** 1,2-metallate rearrangement with cyclobutyl-2,4,6-triisopropyl-benzoate esters.




**Scheme 11.** Catalytic asymmetric homologation of cyclobutyl-substituted boronic ester with lithium-isothiourea-boronate complex.

### 2.3. Ring contraction from 5-membered rings

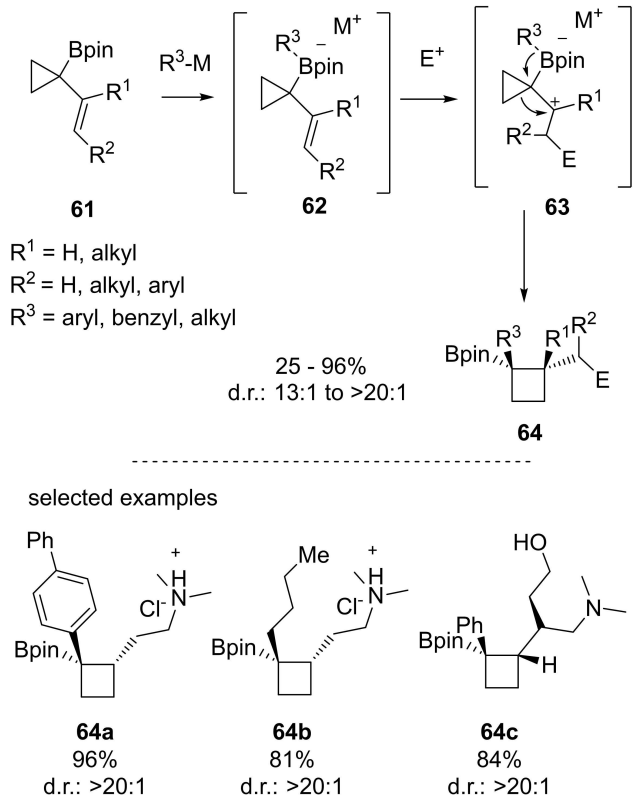
Commonly, 1,2-metallate rearrangements are used to release strain in a structure, but this reaction also demonstrated its efficiency in ring contraction reaction, leading to an increase in strain energy. In 2020, the group of Aggarwal used cyclic 5-membered ring alkenyl boronates **56** as starting material for the visible-light promoted ring contraction by 1,2-migration, leading to the synthesis of cyclobutyl boronic esters **60**.[29] The required cyclic 5-membered ring **56**, quantitatively formed from accessible alkenyl iodide **55**, reacted with photogenerated electrophilic radicals **57**. The obtained radical **58** underwent single electron transfer, leading to the formation of a zwitterion intermediate **59**, which allowed the desired 1,2-migration (Scheme 12).




**Scheme 12.** Proposed mechanism for the ring contraction.

### 2.4. Ring expansion from 3-membered rings

The 1,2-metallate shift can also be a useful tool for ring expansion reaction. In 2020, the formation of 4-membered rings from cyclopropyl moieties, induced by a Matteson-type rearrangement, has been depicted by Aggarwal and co-workers.[30] They used vinylcyclopropyl boronic esters **61** as starting material, which could react first with an organometallic then with an electrophile, giving a carbocation in α position to the strained ring. This intermediate **63** would trigger 1,2-metallate migration of the substituent originating from the organometallic species, leading to the formation of substituted cyclobutanes **64** (Scheme 13). The reaction was efficient with aryl- or alkyl-lithium and Grignard reagents as organometallic species, and diverse electrophiles, including iminium salts, benzodithiolydium salt, benzaldehyde dimethyl acetal, Selectfluor, dimethyl(methylthio)sulfonium salt as -SMe source and $HBF_4$ as H source.




**Scheme 13.** Ring-expansion from vinylcyclopropyl boronic esters.

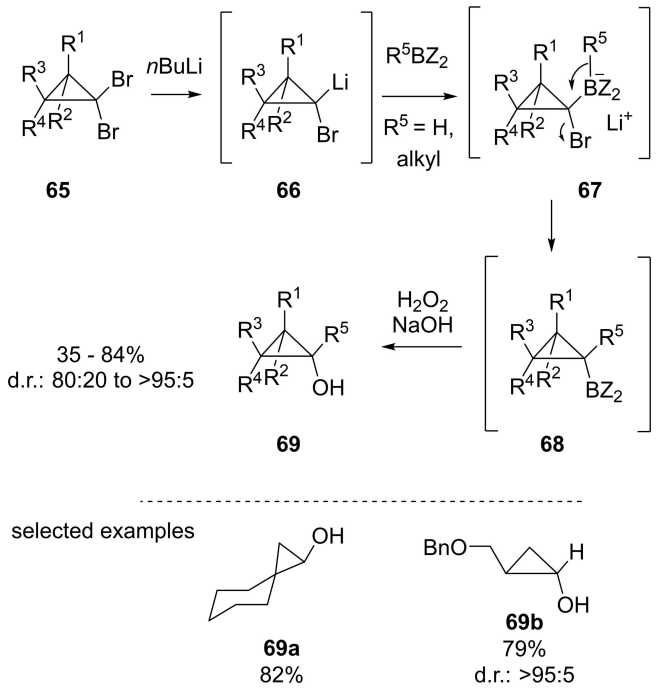
### 2.5. Functionalization of cyclopropanes units

In addition to methods leading to the formation of borylated cyclobutanes, cyclopropanes were also studied in the context of synthetic application of 1,2-boronate rearrangement.

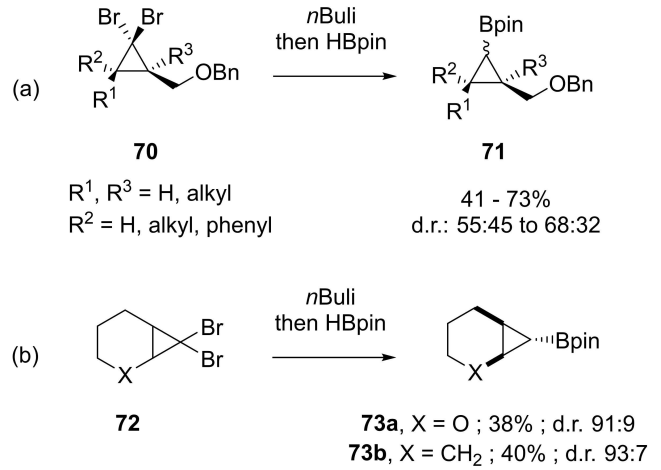
In 1985, the group of Danheiser reported the possibility to use 1,1-dibromocyclopropane **65** as starting material for the synthesis of cyclopropanol derivatives **69** via the formation of cyclopropylboranes **68** by 1,2-metallate rearrangement.[31] After lithiation of one of the two halogens and formation of the boronate complex **67**, the 1,2-migration lead to the formation of the desired cyclopropylboranes **68** which was then submitted to Brown oxidation (Scheme 14). The reaction was efficient for the synthesis of secondary cyclopropanols using catecholborane, and tertiary cyclopropanols using trialkylboranes. In addition, the diastereoselectivity was controlled at the halogen-metal exchange step, either by using a chelating group on the starting material or by steric control.

This approach has been recently revisited by the group of Neouchy, who published in 2022 the synthesis of stable cyclopropyl pinacol boronic esters **71**.[32] They demonstrated that the chelation of the lithium with an ether oxygen had unfortunately a limited effect on the reaction stereoselectivity (Scheme 15a), while the use of a fused 6-membered ring **72** led to high level of diastereoselectivity (Scheme 15b).

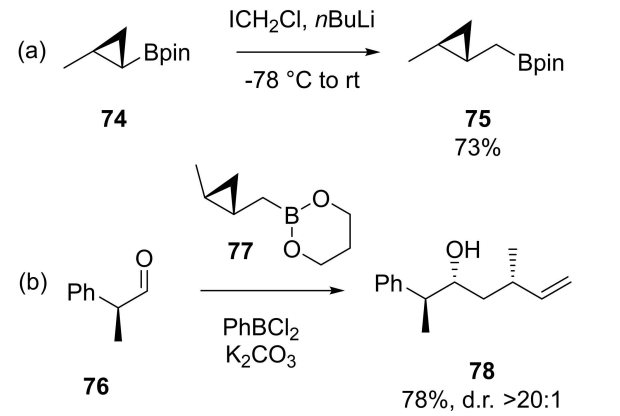
Another reaction that emerged in the 1980s was the homologation reaction using halomethyllithium, known as Matteson homologation, which was rapidly applied to a wide



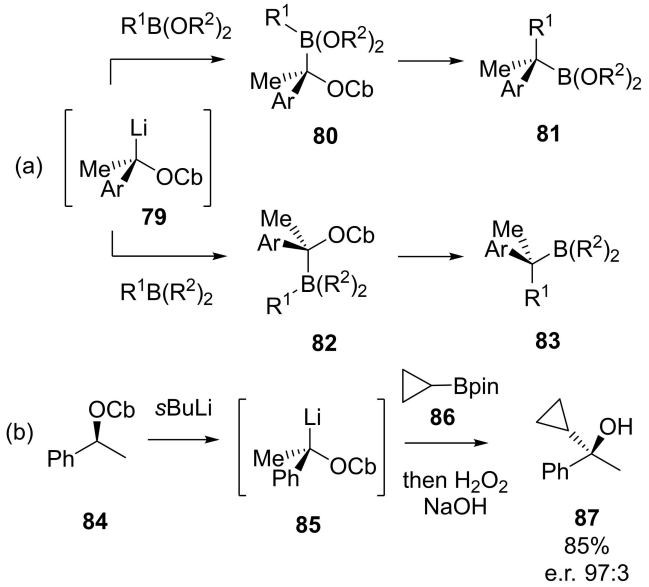

**Scheme 14.** Synthesis of cyclopropanols by 1,2-metallate rearrangement.




**Scheme 15.** Synthesis of cyclopropyl pinacol boronic esters.




**Scheme 16.** Matteson homologation applied on cyclopropyl-substituted boronic ester and application to homocrotylation



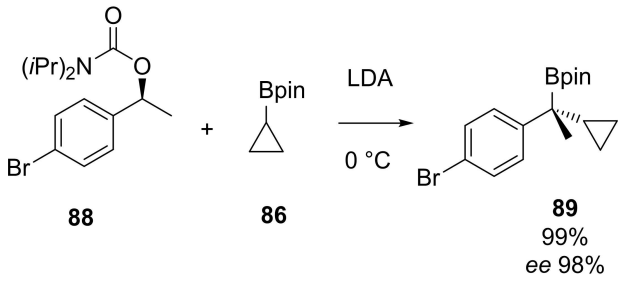

**Scheme 17.** 1,2-boronate rearrangement with cyclopropyl-substituted boronic esters and lithiated carbamates.

scope of organoboron reagents.[5,6,33] Originally not directly applied to strained cycloalkanes, this efficient strategy became a classical method of derivatization for boron-substituted strained cycles **74** (Scheme 16a).[34] This method has also been used by the team of Krauss to report the synthesis of a highly selective homocrotylation reagent **77** (Scheme 16b).[35]

In 2008, the group of Aggarwal reported the used of chiral secondary carbamates **84**, prone to undergo lithiation, as suitable reagent for borylation, 1,2-migration and oxidation sequence.[36] Notably, the reaction was described to be enantiodivergent, as the use of boronic ester led to retention of stereochemistry while using boranes leads to an inversion of configuration (Scheme 17a). During the course of their study, a cyclopropyl-substituted boronic ester **86** was found to be a suitable reagent for this reaction (Scheme 17b).

This use of carbamate was then exploited for the synthesis of functionalized organoboron, in order to get model substrate to explore their reactivity.[37] In 2014, an alternative protocol has been described by the group of Fandrick, successfully reporting a similar 1,2-migration of a cyclopropyl unit on lithiated secondary benzylic carbamates without needing cryogenic conditions (Scheme 18).[38] This reaction, efficient up to multi-kilogram scale, was also used as key step for the asymmetric synthesis of a FLAP inhibitor.[39]

In 2017, the group of Aggarwal investigated the possibility to use ortho-lithiated benzamine **90** as reagent, involved in a sequence composed of activation of the amine by an electrophile, 1,2-metallate rearrangement followed by 1,3-borotropic shift.[40] This method demonstrated a high level of specificity



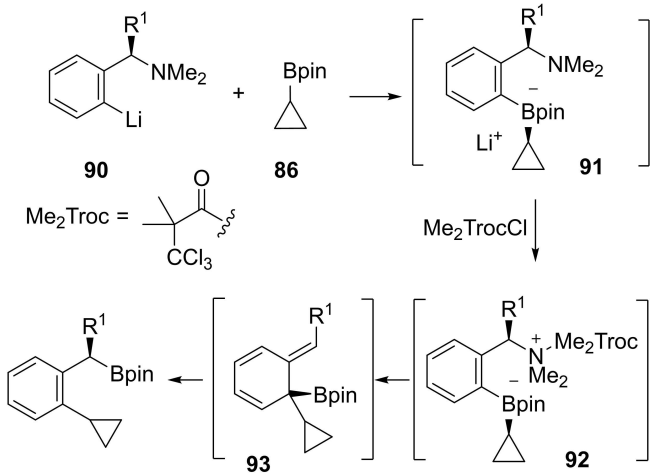

**Scheme 18.** 1,2-migration of cyclopropyl unit under non-cryogenic conditions.

using secondary boronic esters and was found to be efficient with cyclopropyl-substituted boronic ester **86**, giving yields around 50% in these cases (Scheme 19).

In addition to these examples, most of the methods developed for the functionalization of cyclobutane units have also proven to be effective in functionalizing cyclopropane derivatives. First, the example developed by the group of Ley using cycloalkane substituted boronic acids **96**, reacting in flow with in-situ generated diazo compounds **95**, included some examples with 3-membered rings (Scheme 20).[22]

The functionalization of cyclobutanes using alkyl sulfonylhydrazone **99**, described by the groups of Merchant and Qin was also efficient using cyclopropyl-substituted boronic acid.[25] Notably, using disubstituted cyclopropane, an excellent level of diastereospecificity was observed (Scheme 21).

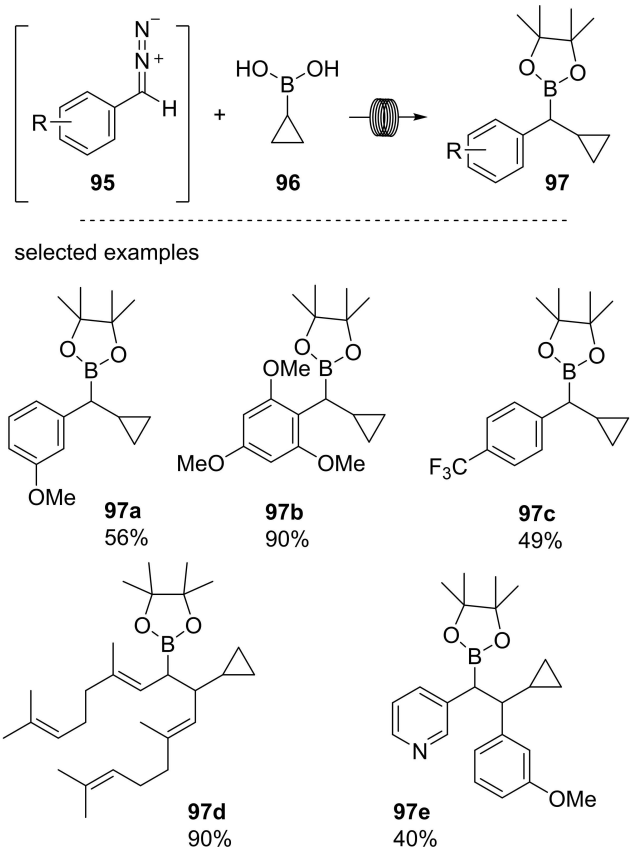
Also, the synthesis of organoboron by visible light promoted hydrogen atom transfer and 1,2-migration of boron substituent, developed by Studer and co-workers, was efficient for the functionalization of cyclopropanes.[27] These examples



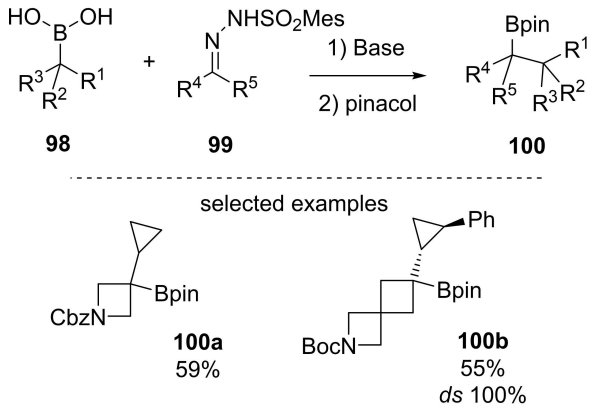

**94a**, $R^1$ = H, 54%

**94b**, $R^1$ = Me, 53%
*ee* 92%

**Scheme 19.** 1,2-metallate rearrangement followed by 1,3-borotropic shift on lithiated benzamides.



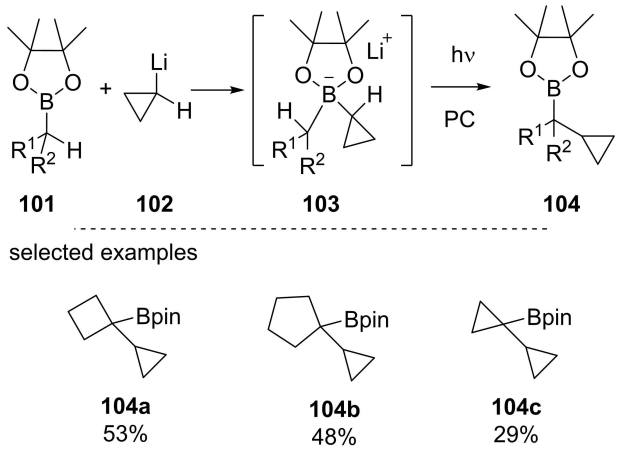

**Scheme 20.** 1,2-migration of cyclopropane units using boronic acid with diazo compounds.



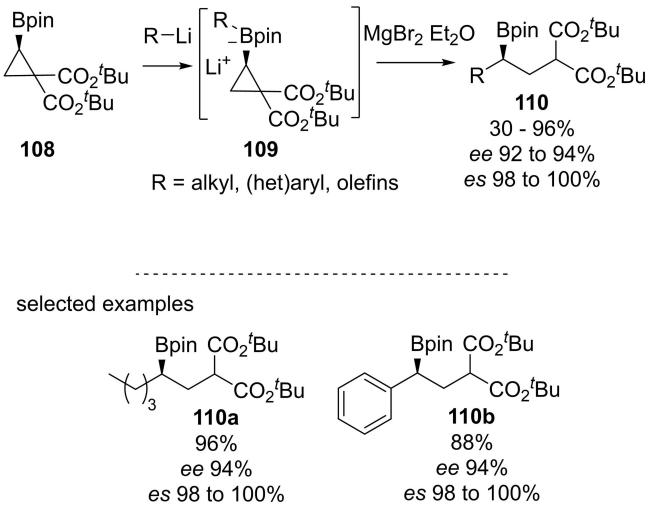

**Scheme 21.** Use of cyclopropane units in the functionalization of cyclobutanes by 1,2-metallate rearrangement with alkyl sulfonylhydrazone.

demonstrated a high level of regioselectivity, with the three-membered ring acting as migrating group (Scheme 22). This trend could be explained by the strength of C–H bond of cyclopropane, compared to other alkanes. Good to modest yields were obtained using 5-, 4- and 3-membered ring substituted boronic esters.

During their study on the reactivity of cyclic 2,4,6-triisopropylbenzoate esters in a lithiation, borylation and 1,2-




**Scheme 22.** Coupling of boronic ester and lithiated cyclopropyl, under irradiation.




**Scheme 24.** Opening of activated cyclopropane by 1,2-boronate rearrangement.

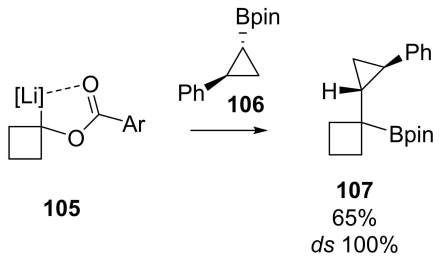
metallate rearrangement sequence, the group of Aggarwal observed that, if cyclopropyl 2,4,6-triisopropylbenzoate esters did not afford the desired product, a cyclopropyl substituted boronic ester **106** was a suitable reagent for the reaction.[28] In this instance, the starting material stereochemistry was efficiently transferred to the product (Scheme 23).

### 2.7. Opening of cyclopropanes by 1,2-boronate rearrangement

Contrary to cyclopropyl 2,4,6-triisopropylbenzoate esters,[28] some 3-membered cycloalkanes were found to be suitable reagents for opening reaction by Matteson-type rearrangement. In 2019, cyclopropyl boronic ester di-activated by the presence of two esters groups **108**, have been successfully converted to γ-carbonyl boronic ester **110** by 1,2-metallate rearrangement, in presence of a Lewis acid.[41] A broad scope of migrating group, including alkyl-, aryl- and heteroaryl- groups was employed efficiently, with an excellent enantiospecificity, the starting material being obtained with high enantioselectivity by asymmetric hydroboration of cyclopropane (Scheme 24).

Moreover, this process has been implicated in a three-component mechanism with an electrophile. Also, the need of the double activation has been demonstrated, as the use of a mono-activated cyclopropyl boronic ester did not lead to ring-opening. Without sufficient activation, the Lewis acid interacted with the pinacol group, giving a borinic ester resulting from a cleavage of one of the oxygen-boron bonds.

In 2022, Marek's group disclosed the successful use of a 1,2-metallate rearrangement applied for the opening of cyclopropyl boronic esters **112**.[42] The reaction led to the formation of two vicinal tertiary or quaternary stereocenters with an excellent diastereoselectivity. Readily accessible cyclopropenyl esters **111** were used as starting materials and submitted to a copper-catalyzed hydro- or carboborylation followed by conversion of the esters to the corresponding phosphates **113**. In presence of various lithiated intermediates, the cyclopropyl boronic esters underwent a stereospecific ring-opening 1,2-metallate rearrangement with excellent yields (Scheme 25). Mainly developed on tetrasubstituted cyclopropyl boronic esters, this process has also been shown to be effective on pentasubstituted cyclopropyl boronic ester.



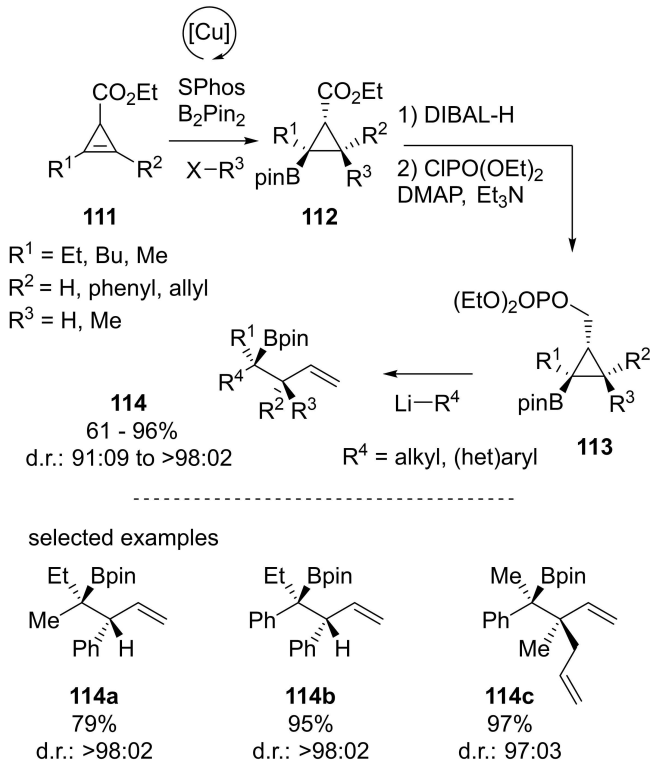

**Scheme 23.** 1,2-metallate rearrangement with cyclobutyl-2,4,6-triisopropylbenzoate esters and cyclopropyl-substituted boronic ester.

## 3. Strained Oxygen-Containing Cycles

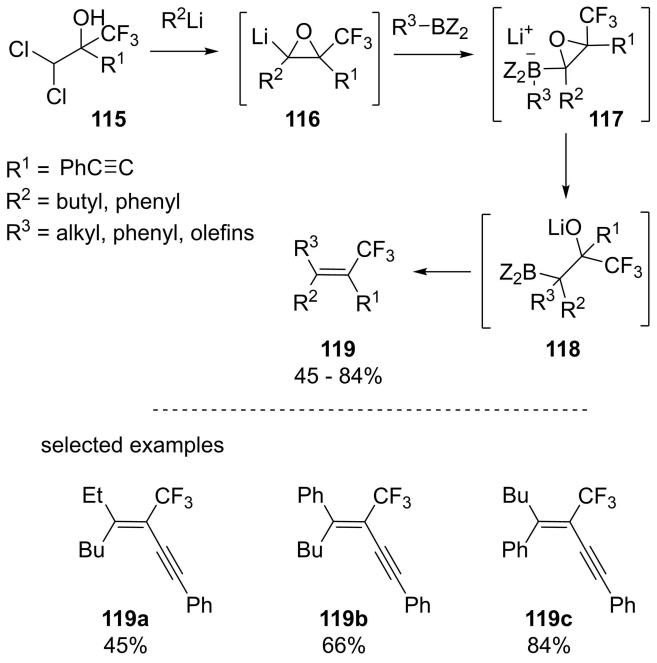
The formation or the opening of oxygen-containing strained cycles are very common steps in the synthesis of compounds of interest.[43] In particular, lithiated oxiranes have emerged as highly important reactive intermediates.[44] More recently, oxetanes were also increasingly used in organic synthesis.[45] In this context, their use as suitable reagent for the Matteson-type rearrangement has been extensively studied recently.

### 3.1. Opening of oxiranes with subsequent elimination

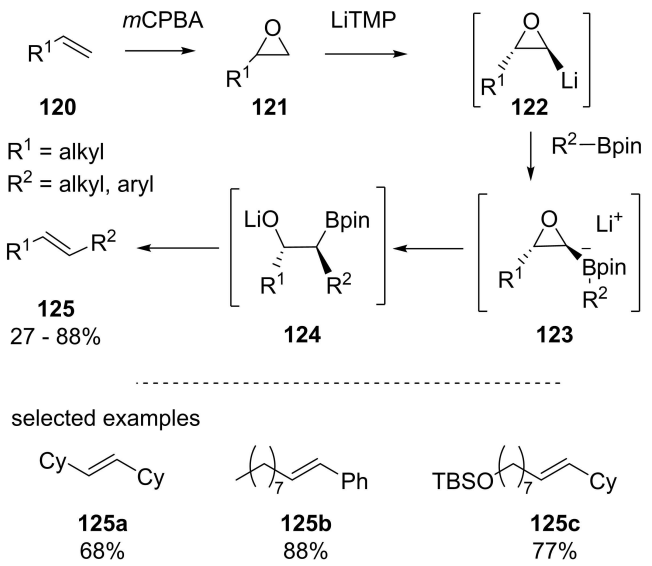
In 2001, studying reactivity of a lithiated intermediate of $CF_3$-containing poly-substituted oxiranes, the group of Shimizu observed the formation of tetrasubstituted alkenes in presence




**Scheme 25.** Opening of borylated cyclopropanes.




**Scheme 26.** Opening of transient oxirane by 1,2-boronate rearrangement with LiOBpin elimination.



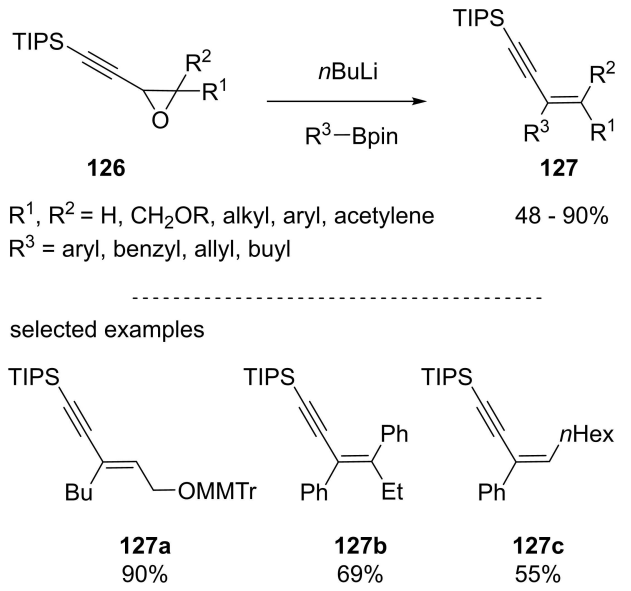

**Scheme 27.** Synthesis of di-substituted alkene by 1,2-boronate rearrangement with subsequent elimination.

of organoboron.[46] Few years later, in an extension of this investigation, a mechanism has been suggested by the same authors.[47] The lithiated oxirane **116**, obtained from acyclic $CF_3$-substituted dichlorohydrins **115** with organolithium, reacted with the organoboron. This intermediate **117** is suitable for 1,2-migration of the boron-substituent, causing the opening of the strained cycle. After rotation, a *syn*-elimination of LiOBpin lead to the formation of the tetra-substituted alkene **119** (Scheme 26). Worth noting, using a silylborane, the elimination of LiOSi allowed to keep the boron group on the resulting alkene. The same approach was used in 2004 with bis(pinacolato)diboron, giving a direct synthesis of Panomifene.[48]

This strategy for the synthesis of substituted alkenes has been extended in 2019 by the group of Hirschhäuser.[49] Starting from simple mono-substituted alkenes **120**, a sequence involving a stereospecific epoxidation, trans-lithiation, borylation, stereospecific 1,2-migration and syn-elimination efficiently afforded *E*-olefins **125** (Scheme 27). In addition, the process could be repeated on the obtained disubstituted olefin to form tri- and tetra-substituted olefins with high diastereomeric excesses.

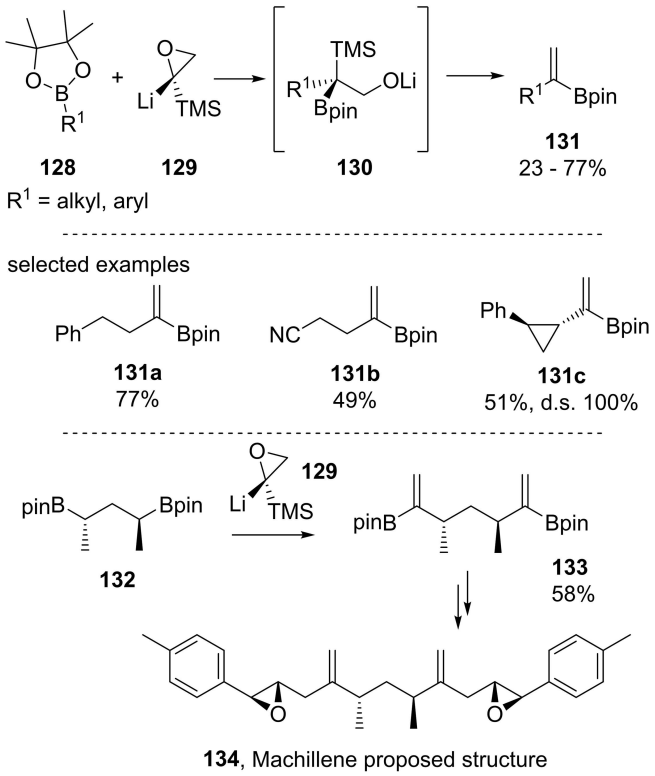
The same year, Mamane, Pale and co-workers exploited a similar reactivity on alkynyl-substituted oxiranes **126**, leading to 1,3-enynes **127**.[50] The method was efficient with aryl-, benzyl-, allyl- and alkyl-substituted boronic esters and an excellent stereocontrol of the reaction outcome was achieved, with the formation of the *E* or *Z*-enynes being completely dependent of the initial oxirane configuration (Scheme 28).

Using a lithiated epoxysilane **129** as starting material, the group of Aggarwal published, also in 2019, the synthesis of 1,1-disubstituted vinyl boronic esters **131**, through 1,2-migration.[51] The reaction was efficient with a large scope of aliphatic boronic esters, and electron-rich aromatic boronic esters, giving modest to good yield. However, using electron deficient substituted boronic esters, a mixture of vinyl boronic ester and vinyl silane was obtained. Taking advantage of the excellent stereospecificity of the process, the use of chiral starting




**Scheme 28.** Synthesis of 1,3-enynes by 1,2-boronate rearrangement followed by elimination.

material allowed a complete transfer of the chiral information (Scheme 29). The usefulness of this methodology has been illustrated with a short total synthesis of a proposed structure **134** for Machillene, with a double 1,2-boronate rearrangement as second step. This sample displayed several differences compared to the reference NMR data, raising concern about the proposed structure.

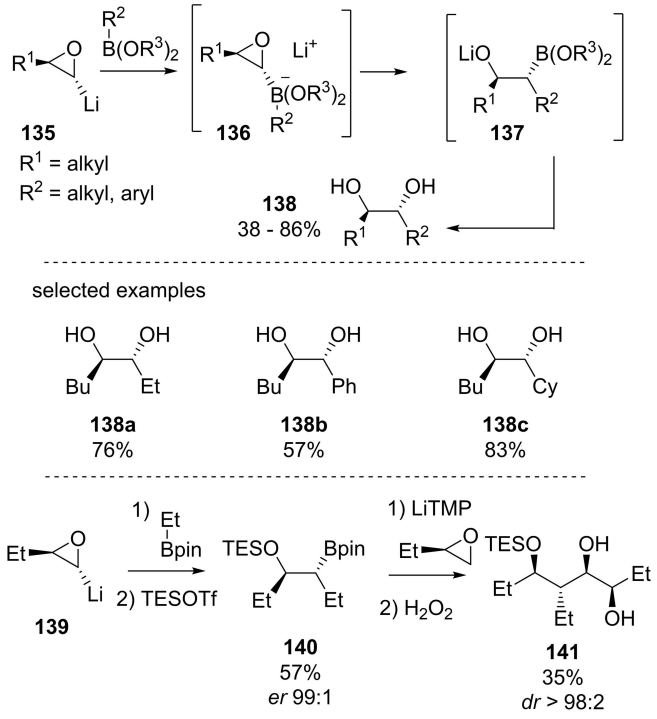



**Scheme 29.** Synthesis of 1,1-disubstituted vinyl boronic esters and total synthesis of a proposed Machillene structure.

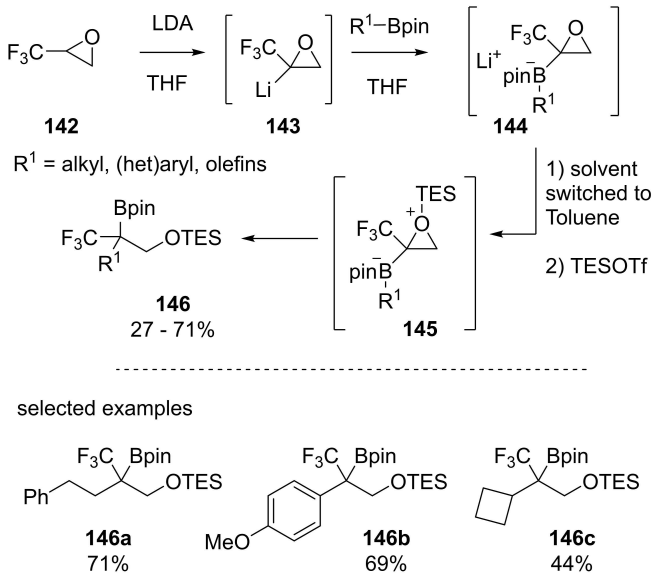
### 3.2. Opening of oxiranes without elimination

Parallel to these examples with subsequent elimination, the possibility to open a lithiated oxirane **135** by 1,2-metallate rearrangement of boronate complexes **136** has been demonstrated in 2009 by the group of Aggarwal.[52] The reaction proved to be effective with alkyl-substituted oxiranes and alkyl- and phenyl-substituted boronic esters, giving good yields. Styrene oxide also was a suitable starting material, with the need to change the lithiation conditions from LiTMP to *s*BuLi. The obtained organoboron **137** was then either oxidized, giving a diol **138**, or successfully engaged in a second stereospecific lithiation/borylation/migration process, allowing the control of numerous stereogenic centres (Scheme 30).

In 2020, the same team expanded this methodology to trifluoromethylated oxiranes **142**, giving a direct access to tertiary trifluoromethyl boronic esters **146**.[53] The presence of the trifluoromethyl group had an important impact on the reactivity and in presence of TESOTf, in THF, it seems to promote a 1,2-migration of an oxygen atom from the pinacol, leading to the obtention of a borinic ester. This undesired reactivity could be circumvented by a solvent exchange, the lithiation and borylation being performed in THF and the Lewis-acid promoted 1,2-migration being realised in toluene (Scheme 31). The reaction was efficient with a large scope of aliphatic, aromatic, heteroaromatic or vinylic boronic esters, and the high stereospecificity of the mechanism was once again




**Scheme 30.** Opening of lithiated oxiranes by 1,2-metallate rearrangement.



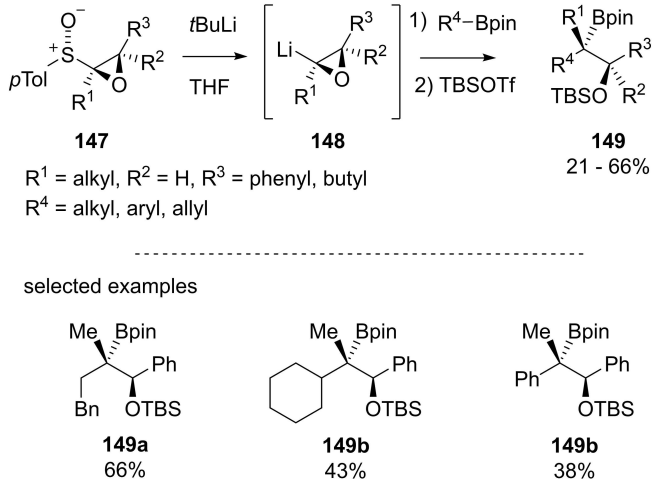

**Scheme 31.** Opening of 2-trifluoromethyl oxirane by 1,2-boronate rearrangement.

demonstrated using chiral 2-trifluoromethyloxirane, with excellent chirality transfer.

In 2014, the group of Blakemore also studied the opening of lithiated oxirane by 1,2-rearrangement of a boronate intermediate and demonstrated the possibility to use sulfinyl epoxides **147** as starting material.[54] In presence of LDA, an efficient sulfoxide-metal exchange took place, even in the case of highly substituted sulfinyl epoxides (Scheme 32).

### 3.3. Functionalization of oxetane

Almost all of the studies on the reactivity of strained oxygenated rings towards Matteson-type rearrangements focused on oxiranes. However, the four-membered derivatives, oxetanes, have quite similar ring strain energy (ca. 25.3 kcal.mol$^{-1}$ for oxetane, ca 26.8 kcal.mol$^{-1}$ for oxiranes).[45] Despite this similarity, to the best of our knowledge, only one article includes an oxetane as substrate of choice in a 1,2-boronate rearrangement. In 2016, a collaboration between the teams of Harvey, Leonori and Aggarwal studied the functionalization of aromatic compounds with boronic esters.[55] Among the scope, one example using an oxetane-substituted boronic ester **150** and a furan **151** has been published (Scheme 33).




**Scheme 32.** Opening of lithiated oxirane derived from sulfinyl epoxides.

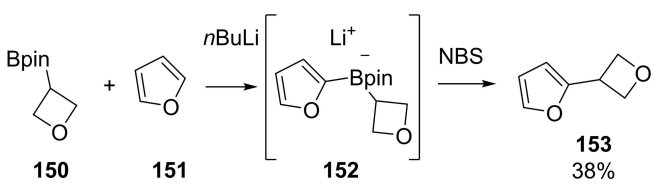
## 4. Strained Nitrogen-Containing Cycles

Nitrogen-containing heterocycles are key patterns in natural products and drugs.[56] Moreover, aziridines and azetidines are important synthetic intermediates, which can be ring-opened to generate linear amines.[57] In recent years, the 1,2-boronate rearrangement has been exploited in various methods for the functionalization and ring-opening of these strained heterocycles.

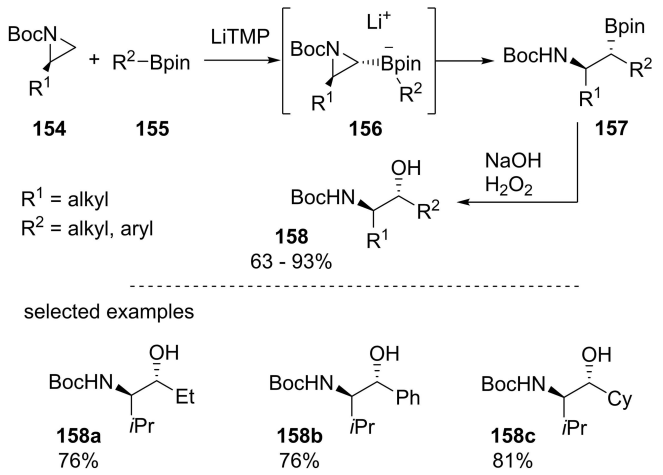
### 4.1. Ring-opening of nitrogen-containing heterocycles

The first example of 1,2-boronate-rearrangement-induced ring-opening of nitrogen heterocycles was described by Aggarwal and co-workers in 2009,[58] concurrently with their report on the ring-opening of epoxides.[52] The authors exploited the known diastereoselective lithiation of N-protected aziridines, to generate a metallated aziridine which can be trapped by an electrophile.[59] In this case, the lithiated aziridine reacts with a boronic ester **155**, forming a boronate intermediate **156** which undergoes a 1,2-boronate rearrangement (Scheme 34). After Brown oxidation, β-amino alcohols **158** are obtained in good to excellent yield.

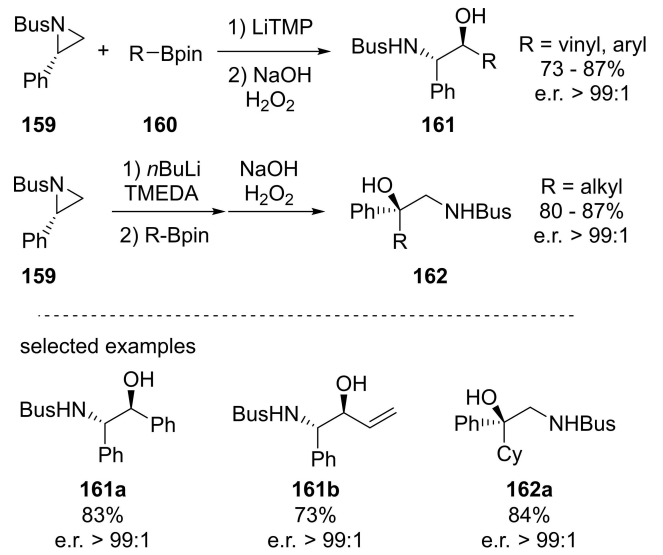
In the case of aryl-substituted aziridines, the Boc protecting group had to be replaced by a less labile tert-butylsulfonyl (Bus) group, to avoid undesired migration of the protecting group from nitrogen to carbon.[60] Moreover, when alkyl boronic esters were employed, the reaction lead to a mixture of regiosomers. Kinetic studies showed that using LiTMP as a base, lithiation occurred preferentially at the least hindered terminal position, but slowly equilibrated to the most favoured benzylic position. The regioselectivity could be reversed by switching to a less hindered base (*n*BuLi, TMEDA), in which case the lithiation had to be performed before introducing the boronic ester (Scheme 35). Remarkably, in both cases the reaction was



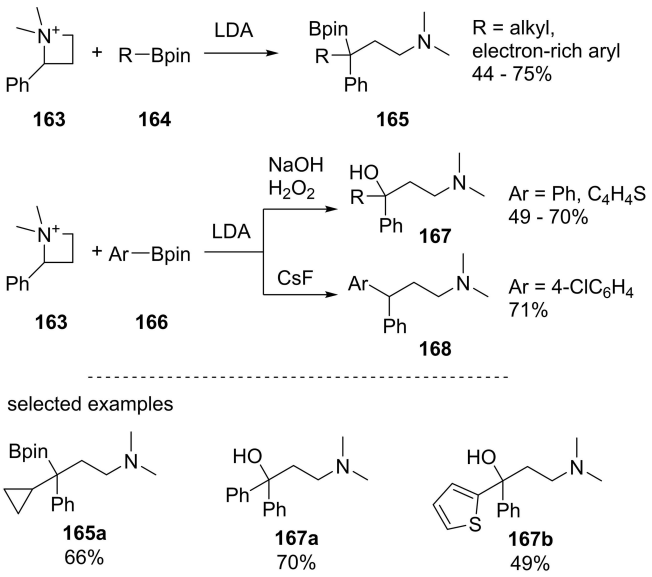

**Scheme 33.** Functionalization of oxetane by 1,2-boronate rearrangement.




**Scheme 34.** Opening of aziridines by 1,2-metallate rearrangement.




**Scheme 35.** Opening of Bus-protected aziridines.




**Scheme 36.** Opening of azetidinium by 1,2-boronate rearrangement.

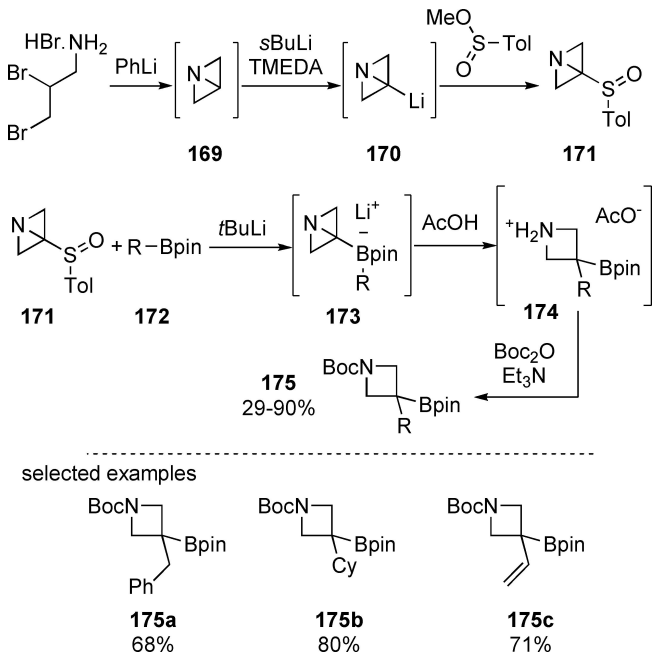
completely stereospecific, and enantioenriched amino alcohols were obtained from the corresponding enantioenriched aziridines without erosion of enantiomeric excess.

Following this work, the same group studied the 1,2-boronate-rearrangement-induced ring-opening of 4-membered aza-heterocycles. However, simply transposing the reaction conditions to Boc-protected azetidines led to no reaction, probably due to the higher energy barrier for azetidine ring-opening. Nevertheless, the authors could observe the desired reactivity when using azetidinium as substrates.[61] It should be noted that the tendency of azetidinium to smoothly undergo ring-opening had been previously observed by Couty and co-workers.[62] Aggarwal and co-workers could adapt this reactivity to 2-phenyl azetidinium **163**, using LDA to generate the azetidinium ylide intermediate, directly trapped by a boronic ester to undergo the key 1,2-boronate rearrangement (Scheme 36). The resulting γ-amino boronic esters **165** were isolated in moderate to good yields. When non-electron-rich aryl boronic esters were used, the products underwent protodeboronation, preventing their isolation. However, the boronic ester could be directly converted to the corresponding alcohol **167** by subjecting the reaction mixture to Brown oxidation conditions *in situ*. The protodeboronation could also be performed efficiently by adding CsF at the end of the reaction. Unlike for aziridines, the reaction using enantioenriched azetidinium led to the formation of a racemic product, due to isomerization of the azetidinium ylide by a ring-opening / ring-closing mechanism.

Recently, the same group reported the ring opening of azabicyclo[1.1.0]butane derivatives through Matteson-type rearrangement. The main challenge of this reactivity is the generation and stability of the azabicyclo[1.1.0]butyl lithium intermediate **170**. Azabicyclo[1.1.0]butane **169** was prepared by treatment of 2,3-dibromopropanamine with phenyl lithium. An unprecedented *in-situ* lithiation was developed using *s*BuLi and TMEDA, and the azabicyclo[1.1.0]butyl lithium intermediate **170** was trapped as a sulfone **171** to facilitate its handling (Scheme 37).[63] The lithiated intermediate could be easily regenerated from the sulfone **171** by treatment with *t*BuLi, and react with a boronic ester to make a boronate complex **173**. Upon acidic treatment, the 1,2-boronate rearrangement can occur, providing azetidines with a boronic ester substituent **174**. The reaction proceeded well in the presence of primary, secondary, tertiary, aryl and vinyl boronic esters. For purification, the products were immobilized on silica to remove all byproducts, and released upon Boc protection.

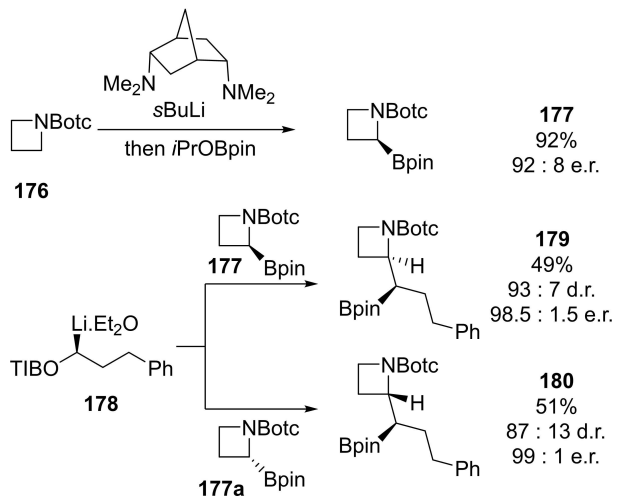
### 4.2. Functionalization of nitrogen-containing heterocycles

In 2019, the group of Hodgson exploited their expertise in the field of metalation of small heterocycles[59,60,64] to develop a




**Scheme 37.** Opening of azabicyclo[1.1.0]butane by 1,2-boronate rearrangement leading to formation of azetidines.

synthesis of azetidine-containing boronic esters using a Matteson-type rearrangement.[65] The synthesis started with the preparation of an azetidin-2-yl boronic ester **177** by lithiation of a tert-butoxythiocarbonyl (Botc) protected azetidine **176** and trapping with iPrOBpin (Scheme 38). Remarkably, this reaction could be performed enantioselectively using the DIANANE diamine as an additive.[66] The resulting boronic ester **177** could be homologated through 1,2-boronate rearrangement by reaction with an α-triisopropylbenzoyloxy (TIBO) organolithium. The authors developed two sets of conditions: one using an excess of boronic ester and one using an excess of organolithium. In the latter case the organolithium was generated from the corresponding stanyl derivative by tin-lithium exchange. The homologation proceeds in moderate to good yield. Starting from racemic partners, poor diastereoselectivities were observed, which is indicative of weak match/mismatch effect. On the other hand, the reaction could be performed from enantioenriched boronic ester with enantioenriched lithiobenzoate. In both cases the products were obtained in moderate yield and with high enantio- and diastereoselectivities.




**Scheme 38.** Functionalization of azetidine by 1,2-boronate rearrangement.

## 5. Summary and Outlook

In conclusion, the 1,2-metallate rearrangement of boronate complexes has recently emerged as an important tool to exploit the reactivity of strained cycles (Table 1). The high stereospecificity of the process, resulting from the required *anti*-periplanar configuration between the migrating and the leaving group, makes it a particularly effective method for enantioselective synthesis.

In the case of strained cycloalkanes, numerous methods have been to functionalize cyclobutanes and cyclopropanes, but the strategy has also demonstrated its efficiency for the opening of cyclopropanes. Boron-substituted cyclobutanes moieties have also been synthesized via Matteson-type rearrangement, either by opening of highly strained bicyclo[1.1.0]butane or by ring contraction. Oxygen- and nitrogen-containing strained cycles also proved to be efficiently involved in functionalization or opening through a 1,2-boronate rearrangement, giving a highly selective access to a wide variety of organoboron reagents. However, the number of examples using these heterocycles remains quite low, and the considerable dynamism observed in this field in recent years, coupled with the importance of heterocycles in organic synthesis, suggest that many new developments are to be expected. In particular, the boronate rearrangement-induced ring-opening of 4 membered hetero- and carbocycles will provide a useful method for the synthesis of diversely substituted acyclic structures.

In addition, several challenges remain to be addressed. Thus, the possibility to achieve asymmetric induction using a catalytic amount of chiral lithium complex has been recently demonstrated. It is certain that this pioneer work paves the way for many more developments in this field. Another great challenge would be to describe more practical conditions, as the need of cryogenic reactive conditions could limit the implementation of the 1,2-boronate rearrangement. For these

**Table 1.** Synthetic table of known reaction of strained cycles by 1,2-boronate rearrangement.

| Structure | Functionalization | Formation | Opening |
|---|---|---|---|
| Cyclopropanes | Known | Unknown | Known |
| Cyclobutanes | Known | Known | Unknown |
| Oxiranes | Unknown | Unknown | Known |
| Oxetanes | Known | Unknown | Unknown |
| Aziridines | Unknown | Unknown | Known |
| Azetidines | Known | Known | Known |

reasons, it is clear that the use of 1,2-metallate rearrangement of boronate complexes, particularly with strained cycles, is a research domain that will continue to be highly dynamic.

## Acknowledgements

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## Conflict of Interest

The authors declare no conflict of interest.

**Keywords:** Organoboron chemistry · Strained cycles · Matteson rearrangement · Boronate complexes · Synthetic methods

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