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Stereoselective formation of boron-stereogenic organoboron derivatives

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Four-coordinate organoboron derivatives present interesting chemical, physical, biological, electronical, and optical properties. Given the increasing demand for the synthesis of smart functional materials based on chiral organoboron compounds, the exploration of stereoselective synthesis of boron-stereogenic organo-derivatives is highly desirable. However, the stereoselective construction of organoboron compounds stereogenic at boron has been far less studied than other elements of the main group due to configurational stability concerns. Nowadays, these species are no longer elusive and configurationally stable compounds have been highlighted. The idea is to show the potential of the stereoselective building of the four-coordinate boron centre and encourage future endeavors and developments in the field.

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1. Introduction

Boron-containing molecules are important from an academic and industrial point of view with widespread applications in organic synthesis, biologically active agents, and functional molecules.[1] Historically, organoboron compounds proved to be strong and reliable key synthons within a diverse range of organic and organometallic transformations. A vacant p-orbital on the group 13 element provides the organoboron derivatives with Lewis acidic properties.[2] In the presence of a Lewis base or a nucleophile, the substrates thus readily interconvert from trivalent to tetravalent and this ability has been used for decades now for the synthesis of optically active molecules; to name only a few examples, asymmetric hydroboration,[3] asymmetric reduction, asymmetric aldol reaction,[4] and asymmetric allyl-and crotylboration.[5] Boron chemistry at that time provided a new perspective for asymmetric synthesis and they all employed chiral organoboron reagents.

As just stated, boron can also form tetravalent compounds.[6] When a Lewis base or a nucleophile coordinates to the trivalent main group element, the resultant tetracoordinate boron adopts a tetrahedral geometry.[7] When the four substituents attached to the boron are different, the boron center becomes

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Clara Aupic

Clara Aupic began her education as an organic chemist in 2010 at the Université Joseph Fournier (Grenoble, France). She obtained her MSc degree in 2015 from Université Claude Bernard, Lyon and then moved to the South of France. She received her PhD degree in organic chemistry in 2019 from Aix-Marseille University under the guidance of Dr J.-L. Parrain and O. Chuzel, working on the design, synthesis, and reactivity of novel chiral boron scaffolds. She is now a Senior Scientist in a contract research organization in Groningen.

stereogenic. However, due to their labile nature and consequently their lower configurational stability, the stereoselective construction of organoboron compounds stereogenic at boron has been far less studied than other elements of the main group, like S,[8] Si,[9] P[10] or N[11] for instance.

Thanks to the recently received boost, these species are no longer elusive and stable compounds have been highlighted. The enantiomerization barrier of the stereogenic center can be correlated to the Lewis acidity of the boron atom. The higher the barrier, the higher the acidity of the boron atom. However, it should be noted that the configurational stability does not only depend on the bond strength of the ligands to the boron atom, but also on different factors, such as the electronegativity and steric effect of the substituents.[12] These parameters directly influence the Lewis acid character of the boron atom, and also the geometry around the boron atom. The latter has been linked to a useful parameter: the tetrahedral character (THC), which is calculated from bond angles at a boron atom. There is a correlation between the Lewis base–Boron bond length and the THC value. The stronger the donor–boron

Corentin Fournet

Corentin Fournet studied chemistry at University of Rennes 1 where he obtained his bachelor's degree in 2019, followed by a Master diploma in organic synthesis in the same university. After his graduation, he moved to Aix-Marseille University where he is currently working towards his PhD under the supervision of Dr Gaëlle Chouraqui, and Dr Olivier Chuzel. His research interests focus on the development of new original FLP-based catalysts designed for hydrogenation reactions.

Jean-Luc Parrain

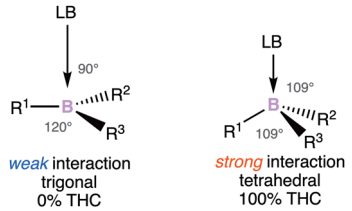
Jean-Luc Parrain obtained his PhD in Chemistry at the University of Nantes (France) under the supervision of Professor Jean-Paul Quintard. After post-doctoral studies in the laboratory of Professor Steve Davies at the University of Oxford (UK), he was appointed a CNRS tenured researcher at the University of Nantes. In 1995, he moved to the University of Marseille and was appointed CNRS "directeur de recherches" in 2001. He was the director of the "Fédération des Sciences Chimiques de Marseille" from 2008 to 2017. He is currently regional delegate for research and innovation for the Provence Alpes Côte d'Azur region. He was awarded, the Clavel Lespiau Distinction (2019) from the French Academy of Sciences. His research interests include new catalytic reactions toward new synthetic methods, development of new organotin, silicon, boron reagents, total synthesis of natural compounds and more recently surface functionalization at nanometric scale.

Gaëlle Chouraqui

Gaëlle Chouraqui obtained her PhD in 2003, from Université Pierre et Marie Curie (Paris – France), where she worked under the guidance of Prof. Max Malacria and Dr Corinne Aubert. After a two year-stay as a Postdoctoral Research Fellow with Prof. James H. Rigby at Wayne State University, she returned to Europe and completed a further year as a Postdoctoral Research Fellow in Prof. Ian Paterson's laboratory at the University of Cambridge. She was appointed CNRS Tenured-Researcher in 2007 at Aix-Marseille University (France) and her research interests are centered on: the development of novel methodologies to reach molecular complexity, the reactivity of donor–acceptor cyclopropanes, and main group catalysis.

Olivier Chuzel

Olivier Chuzel obtained his PhD degree in 2006 from Université Catholique de Louvain (UCL, Belgium) with Professors O. Riant and J.-P. Soumillion, based mainly on photochemistry and metal catalysis. Its PhD was completed by two post-doctoral trainings in E. Schulz's group (ICCMO, Paris-Saclay University) and in V. Vidal's group (Chimie ParisTech – PSL) where he was involved in new methodologies in organometallic enantioselective catalysis. He was then hired as an Assistant Professor in 2008 at Aix Marseille University. His research interests deal with the development of new catalytic and enantioselective processes, with a deep interest in boron chemistry, and growing applications in physical organic chemistry and at the interface activities with physics.



Scheme 1 The tetrahedral character (THC) of the boron atom.

interaction is, the more tetrahedral the boron surrounding is (Scheme 1).

Four-coordinate organoboron derivatives present interesting chemical, physical, biological, and stereoelectronic properties. For instance, from an enantioselective catalysis point of view, the development of alternative to rare, toxic, and costly transition metal is required. In this respect, boron which allows the activation of various chemical bonds offers great potential. Main-group element organo-derivatives have been employed as a useful tool for activation of small molecules in place of transition-metal complexes.[13] In a recent review, Taniguchi stated that "the substituent effects of tetracoordinate boryl groups are unique.[7] They are strong electron-rich groups that greatly influence reactive intermediates such as cations, radicals and π-conjugation systems." On the other hand, given the increasing demand for the synthesis of smart functional-materials based on chiral organoboron compounds,[14] the exploration of stereoselective synthesis of boron-stereogenic organo-derivatives is highly desirable.

Historically, the synthesis of boron-stereogenic organo-compounds relied on the optical and kinetic resolution with chiral auxiliaries.[15] Despite the success of such approaches, they are limited in substrate scope along with low efficiency and poor atom-economy. On the other hand, Vedejs[16] took advantage of the configurational lability of the boron atom and performed Crystallization-Induced Asymmetric Transformation (CIAT).[17] The *in situ* epimerization of the boron centre and diastereoselective crystallization allowed the formation of a single diastereomer in high yield. However, this process requires crystalline products and epimerizable undesired stereoisomers at temperatures below the product melting point. Thus, the development of synthetic methods toward boron-stereogenic derivatives based on asymmetric synthesis has attracted more attention but has proved to be very challenging. In this perspective, we will take a glimpse at the recent progress in the stereoselective construction of boron-stereogenic centers.

Three recently published reviews reported the influence of tetracoordinate boryl groups in organic synthesis.[6,7,18] However, it is worth underlining that only the most recent one[18] mentions, in a non-comprehensive way, the stereoselective formation of boron-stereogenic organoboron derivatives. The intent of this review is to give complementary information on the matter. Namely, we wish to provide insights into the configurational stability of the boron element and to highlight the methods at disposal for its stereogenic construction. This review presents articles collected up until April 2023 and we wish to critically discuss the strategies, scope, applications, and the potential or future development of the stereoselective construction of the tetravalent boron center.

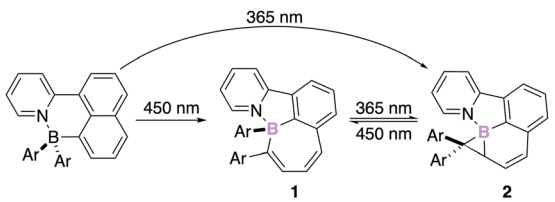
The preparation of original scaffolds in a stereoselective manner offers new perspectives not only in the field of materials science but also in medicinal chemistry. Due to its unique shape and charge distribution, exploration of the chemical space around the stable stereogenic tetravalent boron element could open new avenues in early phase drug discovery[19] and in the development of functional materials. To date and as far as our knowledge goes, only three recent examples reported the enantioselective preparation of such compounds.[20] Otherwise, the common approaches rely on a racemic diastereoselective synthesis or a diastereoselective synthesis starting from an enantiopure compound.

2. Racemic diastereoselective synthesis of boron-stereogenic compounds

2.1. Thermal- or photo-promoted skeletal rearrangements

The development of chiral N,C-chelate organoborate derivatives embedded in rigid π-conjugated structures is of interest for the development of smart materials.[21] The stability of the corresponding stereogenic boron atom offers perspectives in the field of optical materials that exhibit circular dichroism (CD) or circular polarized luminescence (CPL). Those promising properties triggered several groups worldwide and they all showed that irradiation of chelate boron compounds stabilized by a Lewis base (*e.g.* NHC,[22] Py,[23] Pyrazole,[24] phenylazolyl,[25] carbonyl,...[26]), leads to impressive rearrangements of the initial skeleton of the molecule.[27] For instance, Wang has developed a methodology allowing the chemoselective and diastereospecific intramolecular insertion of the boron atom into the π-bond of an aromatic ring. The two-stage photoisomerization and the subsequent reversible photo-rearrangement of the four-coordinate boron derivative 1 deliver a substituted borirane 2 stereogenic at boron (Scheme 2).[28]

Interestingly, the regioselectivity of the transformation was demonstrated thanks to the photoisomerization/C–C bond formation of a chiral organoboron derivative substituted by two different aryl groups.[29] The discrimination between bulky and nonbulky aryl substituents seemed to indicate that steric factors govern the reaction pathway. However, when aryls of similar sizes were employed, Wang clearly demonstrated that the isomerization occurred on the more delocalized substituent



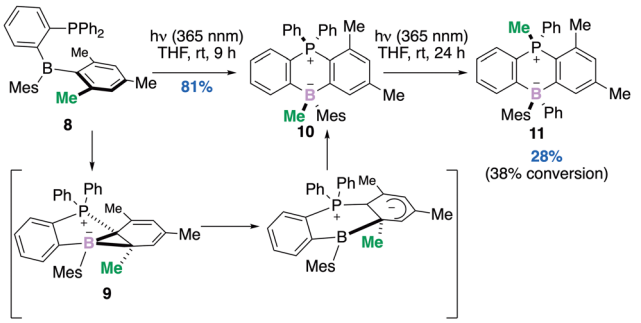
Scheme 2 Photoisomerization from naphthalenylpyridine to borirane *via* borepin.

therefore involving the electronic nature of the substituents.[30] Mechanistic evidence supports an excited-state reactivity of N,C-chelates organoborates,[31] and provides rationalization for the observed regioselectivity.[32]

In 2020, Curran, Liu and Taniguchi reported the thermal rearrangement of an unprecedented diastereomerically pure NHC–ligated borepin **3** into the corresponding NHC–boranorcaradiene **4** at 150 °C for 12 hours, in 67% yield and 97 : 3 diasteromeric ratio.[33] The mechanism and the retention of the diastereoselectivity of this rearrangement has been investigated by means of DFT and supported a 6π-electrocyclic reaction followed by a 1,5-boron shift. Interestingly, the stereoselective construction of the starting material was achieved thanks to a double radical *trans*-hydroboration of cyclic diyne **5** with NHC–borane **6**. The expected adduct was isolated as a single diastereomer in 31% yield together with the product of mono hydroboration **7** in 28% yield (Scheme 3). There are only few examples of isolated boranorcaradiene compared to the more stable borepin. Deepening the knowledge on the synthesis of the boron analogs of norcardiene should give insights into the chemistry of this unusual scaffold.

Another photo-promoted skeletal rearrangement of a phosphine–borane Frustrated Lewis Pair (FLP) **8** this time, occurred *via* a boranorcaradiene **9** followed by migration of the methyl group at the ring junction and provided a stereogenic boron derivative **10**.[34] The authors demonstrated that irradiation for an extended period resulted in an additional Me-migration from boron to phosphorus and provided a single diastereomer of **11** in 28% yield (Scheme 4). From the prospect of developments that are likely to emerge from FLP chemistry in the future, the photoreactivity reported here leading to the diastereoselective formation of the borate species, should open new avenues in synthetic organic chemistry.

It is worth adding that the four-coordinate boron molecules with N,C- or C,C-chelate are often photoresponsive systems.[22] The stereocontrol of the stereogenic boron atom and therefore the construction of 3D defined geometries of this kind of



Scheme 4 Conversion of a Me-substituent on an arene to an anionic Me-borate to a cationic Me-phosphonium.

structure is an appealing topic and could find application in memory molecular devices and switches.

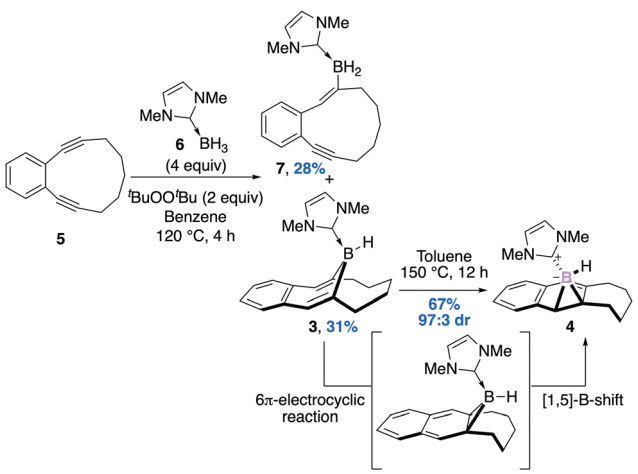
2.2. Reduction of double bonds (B═B or B═C)

Since the first report of a Lewis base stabilized diborene by Robinson,[35] the B═B double bond has attracted considerable attention.[36] Diborenes are both isolobal and isoelectronic with olefins and due to their nucleophilic properties, their role as the ligand of transition metal complexes has been considered. Braunschweig used this nucleophilic feature to perform a hydroboration reaction of diborene **12** with catecholborane (Scheme 5, top).[37]

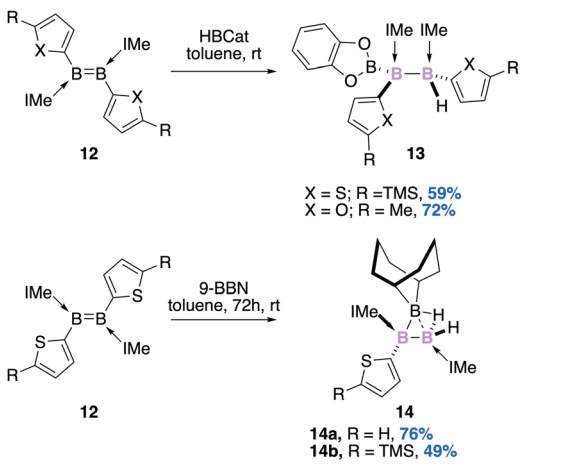
The reaction is diastereospecific (*syn*-addition) and delivers a triborane derivative **13** with two stereogenic boron atoms as a single diastereomer.

In an attempt to perform hydroboration of the same base-stabilized diborene **12** in the presence of the sterically demanding 9-borabicyclo[3.3.1]nonane (9-BBN), Braunschweig also showed that a non-classical B_3 core **14** could instead be diastereoselectively isolated in decent to good yields (Scheme 5, bottom).[38]

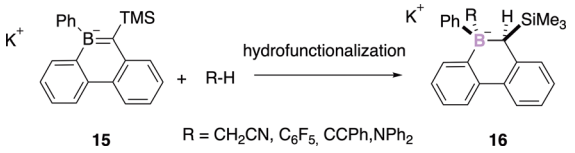
The hydrofunctionalization of B═C bonds is another strategy to perform the diastereoselective construction of the stereogenic boron atom *via* a *syn*-addition. Martin and coworkers



Scheme 3 Stereoselective construction of borepin 3 and its thermal rearrangement.



Scheme 5 Hydroboration of a base-stabilized diborene (IMe: 1,3-dimethylimidazole-2-ylidene, HBCat: catecholborane).



15 16

Scheme 6 Hydrofunctionalization of borataalkene **16**.

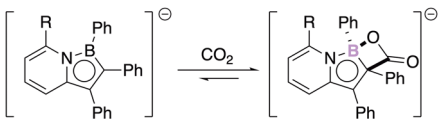
reported the hydroalkylation, hydroarylation, hydroalkynylation, hydroamination, hydroalkoxyalkylation, and hydration of borataalkene **15** and therefore a versatile approach to tetracoordinate stereogenic boron centre **16** (Scheme 6).[39]

The generation of a boron stereogenic centre *via* the addition on B═X systems is quite rare mostly due to the lack of methods to make the aforementioned species.[40,41] It is expected that the growing interest for diborene derivatives would result in an increased number of methods at disposal.

2.3. Miscellaneous

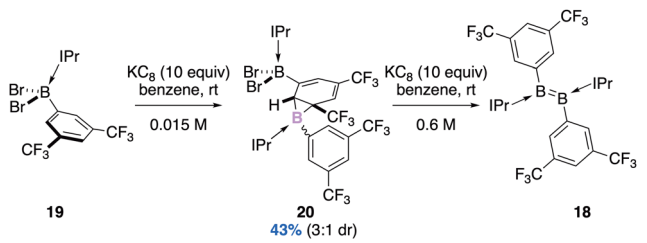
(a) Small molecule activation. Small unreactive molecules activation by main-group compounds, *i.e.* cheap earth elements, is of fundamental but also practical importance. Piers and Rautiainen[42] showed that the 1-bora-7*a*-azaindenide (BN) anions reacted with the electrophile CO_2 (Scheme 7). The Lewis acid/base nature of these BN derivatives allowed the formation of a novel anion **17**. Two stereogenic centers, including the boron atom, were generated in a completely diastereospecific manner, due to the strained four-membered ring.

(b) Borylene *syn*-addition. En route to the formation of diborene **18** from borane **19**, Braunschweig showed that diluted reduction conditions could lead to the diastereoselective formation of a borane/borirane adduct **20** in 43% yield and 3 : 1 diasteromeric ratio (Scheme 8).[43] Three stereogenic centres are generated, the two carbon ones result from the *syn*-addition of borylene onto the aromatic substituent of the starting borane



17
R = H, 80%
R = Me, 73%

Scheme 7 CO_2 activation by a boraazaindenide anion.



19 **20** 43% (3:1 dr) **18**

Scheme 8 A diastereoselective reduction to borirane (IPr: 1,3-diisopropylimidazole-2-ylidene).

(diastereospecific reaction). With an excess of KC_8 (0.6 M in toluene), each diastereomer leads diastereospecifically to the corresponding diborene compounds *E* and *Z* (3 : 1 dr).

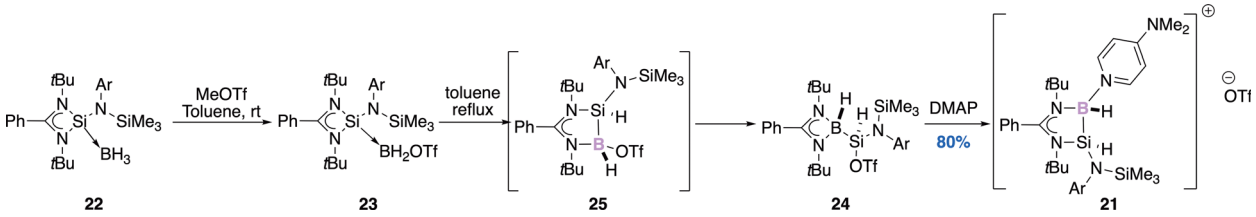
(c) B–H bond activation. In 2018, Su and So[44] reported the diastereoselective formation of an amidosilane–borane adduct **21** thanks to the activation of two B–H bonds (Scheme 9). Treatment of compound **22** with methyl triflate, in toluene at room temperature, forms the corresponding silylene–borane derivative **23**. The latter underwent a B–H bond activation in refluxing toluene to afford the product **24** *via* intermediate **25**. From a mechanistic point of view, the isomerization from **23** to **25** would result from an oxidative 1,1-addition to the silicon atom followed by a 1,2-migration of the OTf group onto the silicon atom. The authors thereafter showed that the coordination center is at the boron atom thanks to the addiction of DMAP. Compound **25** was obtained in 80% yield as a single diastereomer. X-Ray diffraction analysis confirms the relative configurations of the two stereogenic atoms (Si & B). The substituents adopt a *trans* relationship.

(d) Borirane ring opening. A new class of boralactones **26** was synthesized by Curran thanks to the ring opening of stable boriranes **27** (Scheme 10).[45] In the presence of HCl in dichloromethane at 40 °C, the corresponding *cis*- and *trans*-isomers of boralactones **26** are obtained in yields ranging from 40 to 73% and up to 87 : 13 dr (*trans* : *cis*). The 1,3-nucleophilic addition of HCl across the B–C bond leads to a ring-opened enolate intermediate. After tautomerization of the transient species, the diastereoselective ring closure accompanied with chloride displacement gives the expected boralactones.

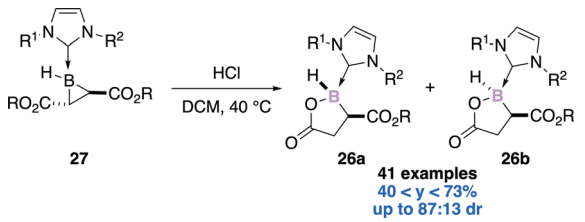
(e) Carbene addition. In an effort to find the best Frustrated Lewis Pair able to enantioselectively perform the hydrogenation of imines, a range of chiral carbene–borenium adducts were synthesized by Melen, Crudden and Stephan.[46] The *meso*-ionic carbene–borane pre-catalyst **28** was synthesized from Soderquist racemic chiral borabicyclodecane **29**.[47] Addition of the meso-ionic carbene (MIC) to the *in situ* generated borane anion leads to the expected adduct **28** as a single diastereomer albeit in low yield (13%) (Scheme 11). The stereogenic carbon atom α to the boron atom might control the approach of the MIC and thus the relative configuration of the boron atom. Unfortunately, this pre-catalyst failed to perform any hydrogenation. The steric hindrance imparted by the borenium FLP precludes any hydride delivery.

(f) DMAP complexation to borane. Jäkle reported the diastereoselective and chemoselective binding of pyridine or 4-DMAP onto a ferrocenyl derivative **30** substituted by two heteronuclear Lewis acids.[48] The vicinal organoboron and organotin were attached to the same Cp ring and the Lewis base reacted preferably onto the boron atom **31** (Scheme 12). A cooperative effect involving a B–Cl···Sn interaction is responsible for the observed total diastereoselectivity.

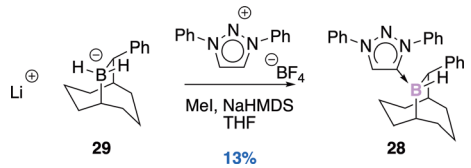
(g) *Via* cycloaddition. A cyclic five-membered P/B Frustrated Lewis Pair **32** has been designed by Erker and featured a bulky mono-bromo octaethylhydrindacenyl (^{Br}Eind) substituent. The authors demonstrated that compound **32** adds to organic π-systems like ethylene, norbornene, chalcone,



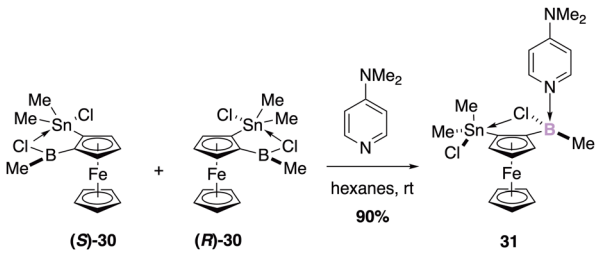
Scheme 9 B–H bond activation.



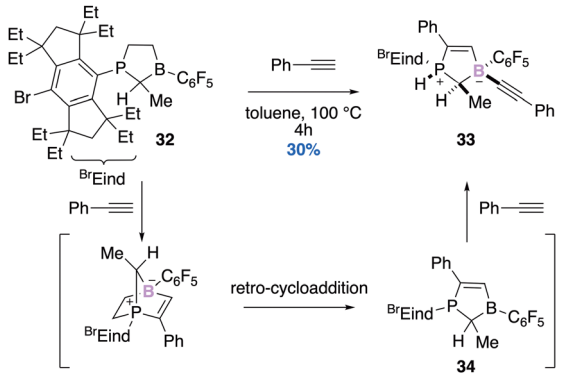
Scheme 10 Borirane ring-opening.



Scheme 11 Carbene addition.



Scheme 12 Chemo- and diastereoselective binding of 4-DMAP to borane.



Scheme 13 Formal Alder–Rickert cycloaddition reaction.

benzaldehyde or even alkynes. The reaction of **32** with an excess of phenylacetylene at 100 °C in toluene for 4 hours, for instance, provided an unsaturated cyclic five-membered P/B derivative **33** (Scheme 13).[49] Mechanistically a formal Alder–Rickert cycloaddition could be at work. A regioselective P/B addition onto the triple bond could be followed by a retro-cycloaddition accompanied with a loss of ethylene. The diastereoselective C–H activation of a second equivalent of phenylacetylene could then occur at the same face of the intermediate FLP **34** and could thus deliver the observed product **33**.

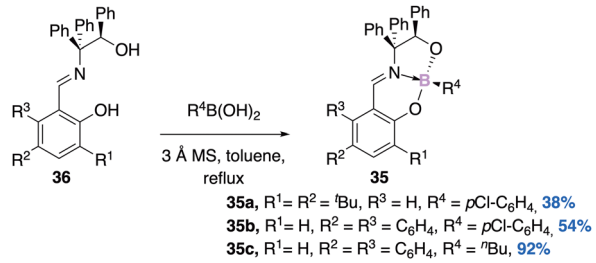
The approach disclosed by Erker and coworkers could be exploited for the design of novel FLPs since this formal Alder–Rickert cycloaddition leads to an intermediate FLP **34**. The surrounding geometry after the split of small molecules like dihydrogen for instance, could play an important role in stereoselective reduction.

It can be concluded that, for the moment, intricate and/or strained structures seems to be required for the diastereoselective control of the stereogenic boron. It is to be expected that the increasing interest for the development of stable tetracoordinate organoboron derivatives and approaches towards elusive species like borylenes or boralkenes would allow considerable progress in this field.

3. Diastereoselective synthesis of boron-stereogenic compounds, starting from an enantiopure substrate

As already mentioned, methods for the enantioselective construction of the four-coordinated boron atom are scarce.[21] Racemic resolution or preferred recrystallization methods of a diastereomer is costly from a time and economic perspective. Asymmetric induction, which refers to the control of stereoselectivity exerted by an existing enantiopure starting material, aims at controlling the diastereoselectivity. Accordingly, if the reaction of an enantiopure substrate onto a boron derivative is highly diastereoselective, the absolute configuration of the boron atom will then be perfectly controlled.

To this end, several authors utilized the chiral pool like L-proline, or prolinol,[50] aminoacids,[51] ephedrine,[52] in the presence of boronic acid, to access chiral boron chelates. The tridentate imino-ligand on the boron atom strategy has found several applications.

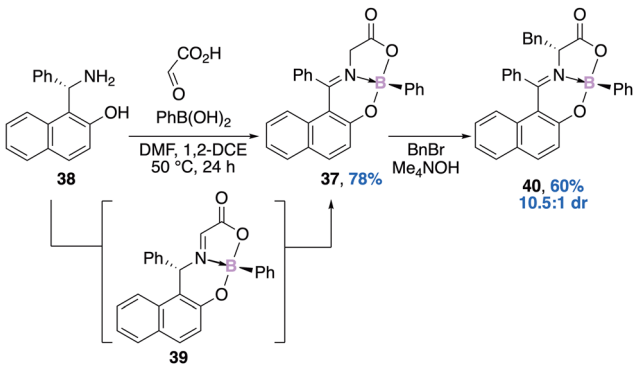


Scheme 14 A stable stereogenic center in imine complexes of aryl- & alkyl-boronates.

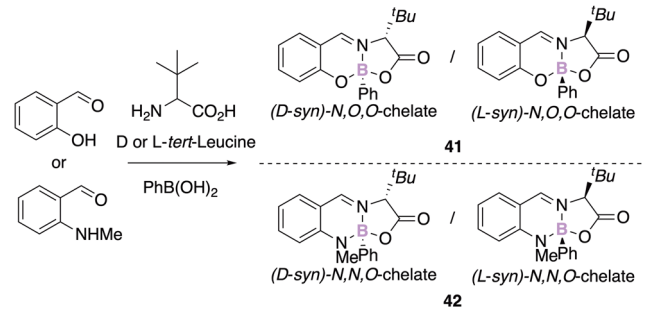
For instance, Braun[53] was able to synthesize a family of boronates **35a–c** in a diastereoselective manner (Scheme 14). Starting from an enantiopure imine **36**, the corresponding boron complex is formed exclusively as a single diastereomer of absolute configuration (*RC*,*RB*)-**35** (determined by DRX). No epimerization product is observed, indicating high thermodynamic stability of these stereoisomers. Next the authors synthesized racemic boron complexes with the boron atom as the only stereogenic center, to answer the question of kinetic stability. The tetrahedral character (THC) of the boron atom calculated is about 69%. The enantiomeric pairs were separated by chiral HPLC and their Circular Dichroism (CD) spectra were obtained.

Finally, the configurational stability of the boron atom was evaluated. The racemization barrier increases slightly with the electron-withdrawing character of the substituents, as the latter increases the B–N bond strength and shortens it. The same authors used the boronate–imine and -amine complexes as chiral dopants for nematic liquid crystals.[54]

In parallel, Hutton's group reported a similar approach for the diastereoselective preparation of a boronate complex **37**.[55] The one-pot, three-component reaction between the chiral base **38** and glyoxylic acid could provide the transient imine which could thereafter react with the phenylboronic acid, thus leading to the boronate complex **39**. A further tautomerization could provide the boron–imine complex **37**, solely stereogenic at boron, in 78% yield with >99% enantiomeric excess (Scheme 15). Three main factors could explain the observed configurational stability



Scheme 15 A chirality transfer process for the preparation of an enantiopure boron–imine complex **37** stereogenic at boron only.



Scheme 16 *tert*-Leucine chiral iminoborates.

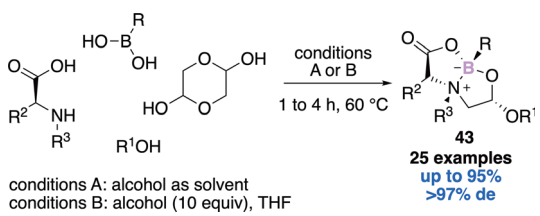
of the boron atom (rate of racemization <0.5% in boiling toluene for 24 h): (i) the tridentate nature of the ligands on the boron atom, (ii) the coordinating acyl group, and (iii) the conformational rigidity of the naphthylphenylimine substituent. Interestingly, benzylation of compound **37** leads to the introduction of an extra stereogenic centre **40** in 60% yield (based on the recovered starting material) with a 10.5 : 1 diastereomeric ratio.

Knight, Herrebout and Harriman recently reported the synthesis of configurationally stable chiral *tert*-leucine iminoborate derivatives obtained thanks to a three-component reaction as single diastereomers (Scheme 16).[56] The enantiopure analogous *N*,*O*,*O*- and *N*,*N*,*O*-boron chelates present dissimilar photophysical properties.

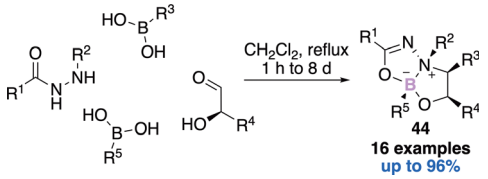
While the *N*,*O*,*O* salicylaldehyde derivative **41** is mainly deactivated by an intramolecular charge transfer process, the corresponding *N*,*N*,*O*-aminobenzaldehyde compound **42** fluoresces in the visible region. Interestingly, the latter is more fluorescent in the solid state, and represents another example of aggregation-induced emission phenomenon.

The multicomponent strategy was also applied to the synthesis of boron analogs of 5-oxofuro[2,3-*b*]furan motifs and led to the assembly of N–B heterocyclic compounds with natural product-like scaffolds, thus expanding the chemical space.

Gois' approach relied on a one-pot four-components reaction to reach the natural product like-bicyclic system **43**.[57] The authors reported 25 examples in yields up to 95% and up to >97% diastereomeric excess (Scheme 17). They further used this strategy to build libraries of potentially bioactive molecules and discovered new HNE inhibitors with IC_{50} up to 1.1 μM[58] or novel modulators of human phenylalanine hydroxylase.[59] Finally, the rapid, reversible, and selective N-terminal cysteine functionalization, under mild aqueous conditions, thanks to this approach was described, therefore highlighting the potential to build well-defined bioconjugates.[60]



Scheme 17 A one-pot four-component reaction.



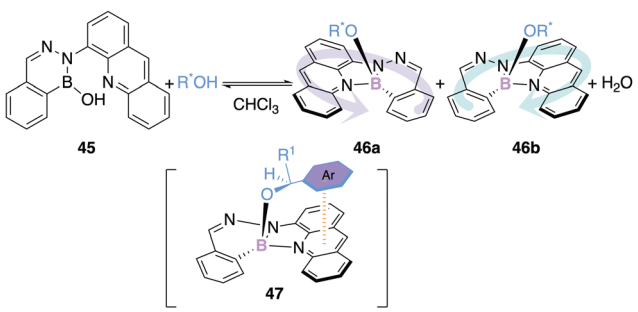
Scheme 18 Construction of dioxadiazaborocines.

Another one-pot four-components reaction reported by Nielsen allowed the construction of dioxadiazaborocines **44** (Scheme 18).[61] First a Petasis three-component reaction occurs in the presence of a readily available hydrazide, an α-hydroxy aldehyde and a first boronic acid. Then the condensation of a second orthogonally reactive boronic acid delivers the expected bicyclic architecture **44** in a diastereo and enantiomerically pure fashion.

The configurational stability of boron(III) chelate was also utilized by Iwasawa and his team as a circular dichroism probe to determine the absolute configuration of chiral alcohols. The addition of a chiral racemic alcohol to a 1,2-dihydro-1-hydroxy-2,3,1-benzo-diazaborine **45** generates a chiral borate **46** containing a stereogenic boron atom (Scheme 19).[62]

The addition of a chiral alcohol containing a π-system allows a secondary π–π interaction due to the presence of the aza-anthracenyl group of the borate (see **47**). Twenty-five examples could be synthesized with diastereomeric excess ranging from 1.8 to 19%.

In 2019, our team reported the diastereoselective preparation of chiral NHC–boranes **48** stereogenic at the boron atom thanks to a chlorination/arylation sequence.[63] The chlorinated NHC borane **49** (1 : 1 dr), with a fixed stereochemistry at the α-carbon center and obtained quantitatively from the enantioenriched NHC–BH_2 **50** undergoes a diastereoselective functionalization at boron, in the presence of a simple Grignard reagent (Scheme 20). The diastereoselectivity has been rationalized through a plausible $S_{RN}1$ mechanism and was supported by EPR observations and DFT calculations. Another interesting finding is the excellent diastereoselective regeneration of the boron stereogenic centre, from a borenium intermediate with a hydride. This represents a promising strategy for metal-free enantioselective reduction catalysis, particularly in FLP-type reduction reactions.



Scheme 19 Circular dichroism probe for the determination of absolute configuration of mono-alcohols.

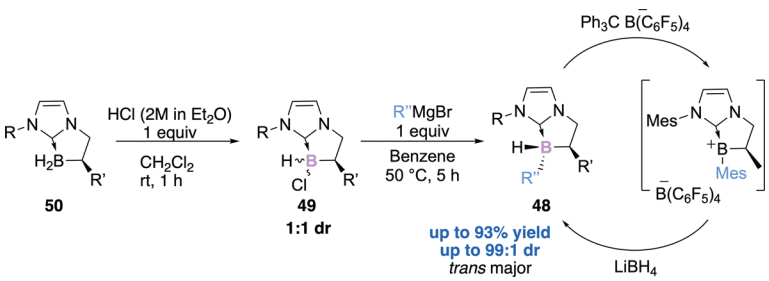
Asymmetric induction for the construction of the additional stereogenic boron is effective. The type of scaffolds is heavily dominated by iminoboronates. Interestingly, heterocyclic natural product-like derivatives are likely to provide access to new bioactive compounds, probes for chemical biology or catalysts for asymmetric synthesis. On the other hand, the diastereoselective construction of NHC–borane compounds offer new perspectives, and applications in the field of main-group elements catalysis. Finally, the photophysical properties imparted by these novel chiral objects could find applications in functional, smart, optical materials.

Going beyond would consist of the construction of tetra-coordinate boron derivatives in an enantioselective fashion.

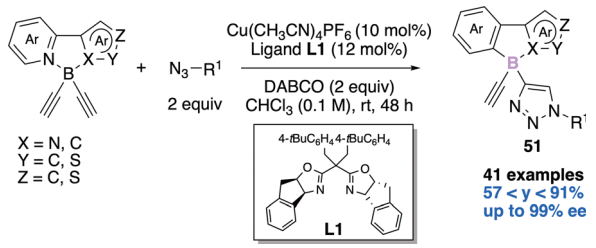
However, given the labile nature of ligands attached to the boron atom, this approach is a challenge to synthetic organic chemists. As the following section will show, this is a challenge recently and successfully addressed by two different groups.[21]

4. Enantioselective synthesis of boron-stereogenic compounds

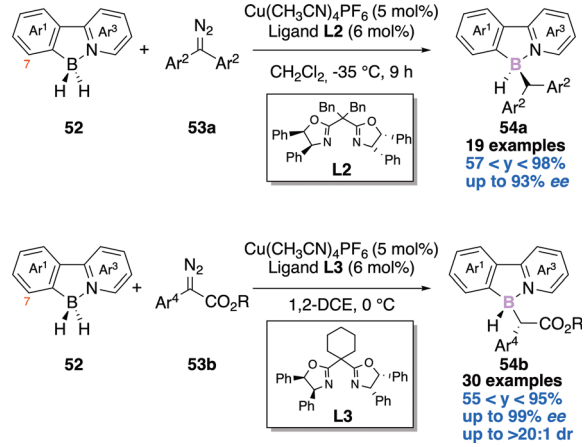
In 2021, He and coworkers elegantly tackled the challenge of creating a tetrahedral boron-stereogenic center in an enantioselective manner,[21a] thanks to a copper-catalyzed azide–alkyne cycloaddition (CuAAC) desymmetrization reaction (Scheme 21). In the presence of two equivalents of azide, two equivalents of DABCO, 10 mol% of copper catalyst [$Cu(CH_3CN)_4PF_6$] and 12 mol% of the indane-fused BOX chiral ligand L1, the authors were able to obtain the desired *N*,*N*-π conjugated scaffolds **51** in yields ranging from 57 to 91% and up to 99% enantiomeric excess (ee). The scope of this desymmetrization is large (41 examples) and the novel chiral building blocks exhibit bright fluorescence and CPL (Circularly Polarized Luminescence)



Scheme 20 A two-step sequence for the diastereoselective preparation of NHC–boranes stereogenic at the boron atom.



Scheme 21 First enantioselective construction of a boron-stereogenic center.

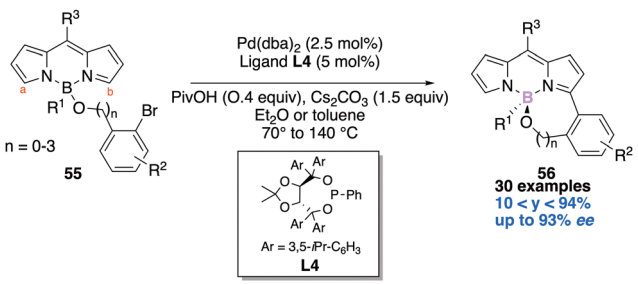


Scheme 22 Second enantioselective construction of a boron-stereogenic centre.

signals. These chiral compounds have therefore potential applications as chiral fluorescent probes.

The second example reports an enantioselective copper-catalyzed desymmetric B–H bond insertion reaction of 2-arylpyridine-boranes **52** with diazo derivatives **53a–b** to access boron-stereogenic centres **54a–b** (Scheme 22).[21b] Computational investigations were reported and explain the excellent enantioselectivity and diastereoselectivity observed.

Mechanistically, the borane could transfer its hydride to the carbene centre leading to a transient borenium. A subsequent S_E2 process could deliver the observed product **54a–b**. Notably, introduction of a substituent at the C7-position of the 2-arylpyridyl improves the stereocontrol (Scheme 22).



Scheme 23 Third enantioselective construction of a boron-stereogenic centre.

The third and last example disclosed the desymmetrisation of the equivalent hydrogens H^a and H^b on the pyrrole units of the BODIPY core **55**.[21c] The Pd-mediated desymmetric intramolecular C–H arylation reaction using a TADDOL-based phosphonite ligand **L4** delivered a large scope of 6- to 9-membered ring BODIPY scaffolds **56** and the enantiomeric excesses reported are good to excellent (Scheme 23). The authors next studied the photophysical properties of their molecules and found out that they display yellow to bright fluorescence and the quantum yields range from 0.7 to 48.4%. Very interestingly they further functionalized these valuable molecules and demonstrated their use as chiral fluorescent probes.

Due to configurational stability concerns, examples reporting the enantioselective construction of the tetravalent stereogenic boron element are scarce and limited. Accordingly, the approaches (i) rely on a desymmetrization strategy and (ii) utilize similar π-conjugated starting scaffolds. These three examples are clearly important breakthroughs in this field and elegantly expand the diversity of chiroptical objects at disposal. A step forward would consist in enlarging the scope of methods at disposal to access a broader range of different chiral building blocks.

5. Conclusions

Four-coordinate organoboron derivatives cover a broad spectrum of scientific applications and thanks to the development of more stable species, significant progress has been made in recent years for the stereoselective construction of the boron atom. This review intended to give an overview of the state of the art. Obviously, there is a lack of a general method for the enantioselective approach, and we believe that the full potential of the stereoselective building of the four-coordinate boron center is yet to come. To conclude, this highlight clearly illustrates that tetracoordinate organoboron species stereogenic at boron has become a mainstay and is very likely to play a greater role in the future.

Author contributions

Writing – original draft: AAM, GC and OC. Writing – review & editing: AA, CA, CF, JLP, GC and OC. Funding acquisition: JLP, GC and OC. The final manuscript has been read and approved by all authors.

Conflicts of interest

There are no conflicts to declare.

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