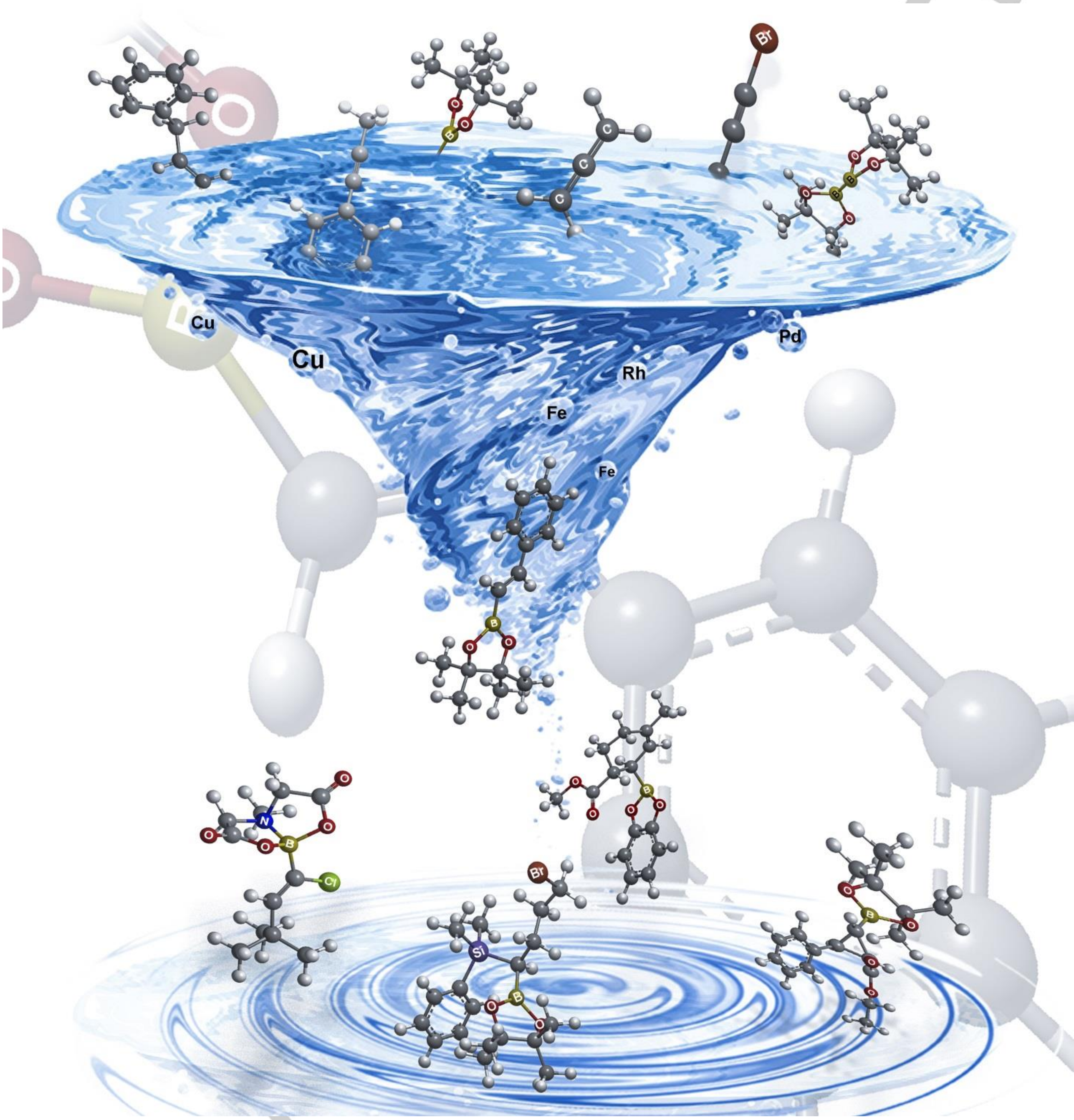
Alkenylboronates: synthesis and applications

Javier Carreras,*[a] Ana Caballero,*[b] and Pedro J. Pérez*[b]



Dedication ((optional))

Abstract: Organoboron compounds have become one of the most versatile building blocks in organic synthesis due to their accesible and efficient conversion into many different functional groups. In particular, alkenylboronates have received much attention as very reactive substrates in Suzuki-Miyaura cross-coupling reactions. Accordingly, efforts towards the development of efficient methods to prepare this type of compounds are constant. In this contribution, the progress in the search for synthetic routes for alkenylboronates and their use in a variety of organic transformations is accounted.

1. Introduction

Boron chemistry has involved two Nobel prizes to Brown (1979, with Wittig) and Suzuki (2010, with Heck and Negishi) for the development of boron compounds in organic synthesis. The versatility of carbon-boron bonds is nowadays exploited for many transformations.[1] The hydroboration of alkenes and alkynes described by Brown in the middle of last century prompted the interest in organoboranes. A second breakthrough in this area was the development of Suzuki-Miyaura cross coupling reactions,[2] which is an essential tool for the construction of new carbon-carbon bonds. Compounds bearing C_{sp2}-B bonds, as aromatic or alkenyl boron derivatives, rapidly became extraordinary popular as partners in this transformation, and their versatility has been widely illustrated in the synthesis of natural products or complex organic molecules. Since then, a plethora of new methodologies for the formation of carbon-boron bonds has been developed, accompanied by a number of protecting groups for boron, affecting both its stability as a strong Lewis acid and the reactivity as well.[3] Albeit boronic acids or catechol boronic esters were initially preferred as reagents due to their high reactivity and atom economy, in the last decades pinacol boronic esters and other boron-based reagents have gained enormous relevance in the field (Figure 1).

In addition to the interest of alkenylboronates as partners in Suzuki-Miyaura coupling, these boron derivatives have also attracted the interest of synthetic organic chemists in the context of different transformations, both creating complex molecules that include the boron group in the final structure and also as a synthetic intermediate for further derivatization. This Focus Review will concentrate on the synthesis and applications of alkenylboronates. Despite this topic having been previously reviewed,[4] we herein aim to provide an update including the most significant and recent developments in the field, with some earlier references to enrich and clarify the comprehensive view.

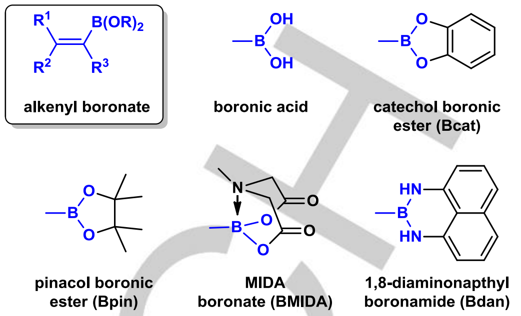


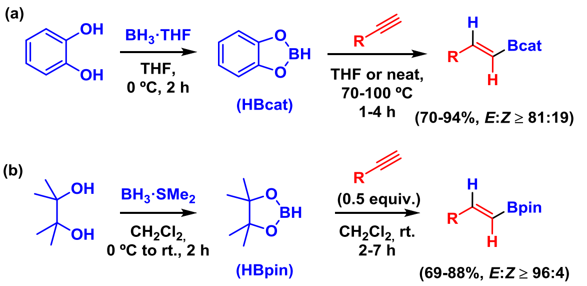
Figure 1. Generic alkenylboronates and some of the most popular boron functional groups. MIDA: *N*-methyliminodiacetic acid

2. Synthesis of alkenylboronates

The synthesis of alkenylboronates has been described using numerous methodologies. Most of the methods focus on the synthesis of bis-substituted *E*-alkenylboronates, although some significant procedures for the preparation of *Z*-, or α-alkenylboronates are also described in the literature. Similarly, synthetic protocols for tri- and tetrasubstituted alkenylboronates are also known. This is a field in continuous progress that has already led to the availability of some vinylboronates as commercial products. In this section the different methodologies have been organized by substitution pattern of the alkenyl boronate. Since the preparation of polyborylalkenes has been very recently reviewed, it has not been included in this section,[5] neither the synthesis of alkenyl boronates from alkenyl halides, triflates or silanes.[6]

2.1. Synthesis of *E*-Alkenylboronates

Hydroboration of alkynes is the most common and practical method for the synthesis of *E*-alkenylboronates, based on the *syn* addition of the boron-hydrogen bond to the carbon-carbon triple bond. The pioneering work by Brown[7] triggered the development of this area, prompting the design of a number of methodologies, either metal-catalyzed or metal-free, to convert alkynes into alkenylboronates. His seminal work in 1972 promoted the hydroboration of alkynes using catecholborane (prepared by mixing catechol and BH_3·THF) at 70-100 ºC in THF



Scheme 1. Hydroboration of alkynes with catecholborane and pinacolborane

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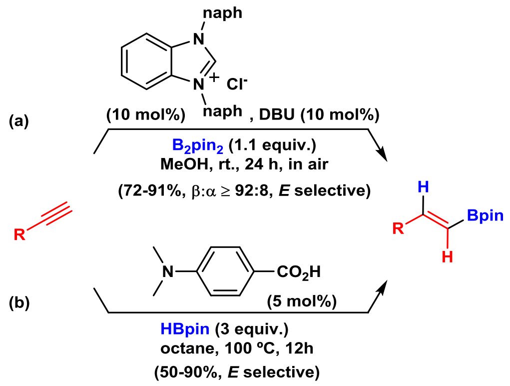
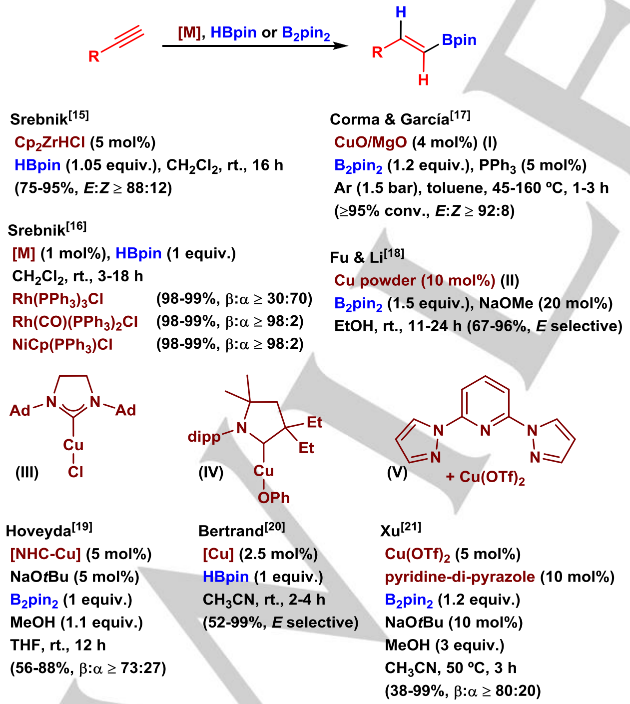
or under neat conditions at the same temperatures, leading to effective conversions and selectivities (Scheme 1a). Later, Knochel reported a similar hydroboration of alkynes at room temperature with 2 equiv. of pinacolborane, which is nowadays the most popular boronate reagent due to its great stability to air or during chromatography purifications (Scheme 1b).[8] Dicyclohexylborane[9] or $HB(C_6F_5)_2$[10] have been reported as catalysts for this reaction.

Other metal-free protocols have been described for this reaction in the past few years. In 2013, Sun achieved this reaction using *N*-heterocyclic carbenes as the catalyst under air (Scheme 2a).[11] A sterically hindered benzimidazole derivative gave excellent results in the β-hydroboration even for non protected propargylic alcohols. Jin established the catalytic activity of carboxylic acids for this reaction, heating the mixture in octane at 100 ºC (Scheme 2b).[12] 4-(Dimethylamino)benzoic acid displayed the highest catalytic activity, although even simple benzoic acid was effective enough. Recently, bases such as Li*Ot*Bu, Na*Ot*Bu (with catalytic amounts of $PhI(OAc)_2$) or NaOH have been applied to reach excellent regioselectivities and high yields, at room temperature (Li*Ot*Bu, $PhI(OAc)_2$-Na*Ot*Bu) or 100 ºC (NaOH) respectively.[13]



Scheme 2. Metal-free hydroboration of terminal alkynes.



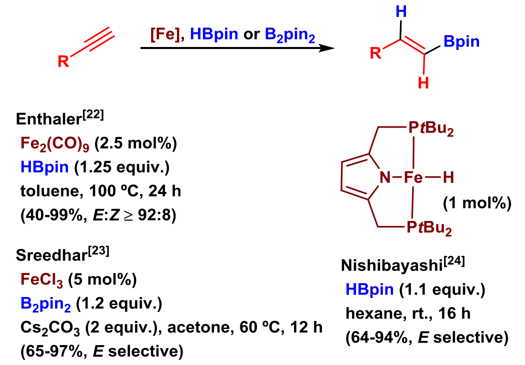
Scheme 3. Metal-catalyzed hydroboration of terminal alkynes. Ad: adamantyl, dipp: 2,6-diisopropylphenyl.

Javier Carreras completed his PhD studies at the Universidad de La Rioja (Spain) in 2010, under the supervision of Profs. Avenoza & Busto studying metathesis reactions in azanorbornene derivatives. After post-doctoral appointments at Max Planck Institut fur Kohlenforschung with Prof. Alcarazo (2011-2013) and ICIQ with Prof. Echavarren on metal-catalyzed transformations and natural product synthesis, he joined Prof. Pérez group as Juan de la Cierva fellow in 2016 working on boron chemistry, copper-catalyzed transformations and C-H functionalization reactions. He is currently assistant professor at Universidad de Alcalá.

Ana Caballero graduated in Chemistry at the Universidad de Sevilla (1999) and obtained her PhD from the Universidad de Huelva under the supervision of Prof. Pedro J. Pérez (2004). Later she moved to the LCC (CNRS, Toulouse) for a postdoctoral stay with Prof. Sylviane Sabo-Etienne. She returned (2007) to the Universidad de Huelva as a ‘‘Ramon y Cajal’’ Postdoctoral Associate, to become first Lecturer and currently Senior Lecturer. In the recent years she has focused on the development of the catalytic functionalization of methane based on the use of supercritical fluids as reaction medium. In 2014 the Royal Spanish Chemical Society awarded her with the Young Investigator Prize.

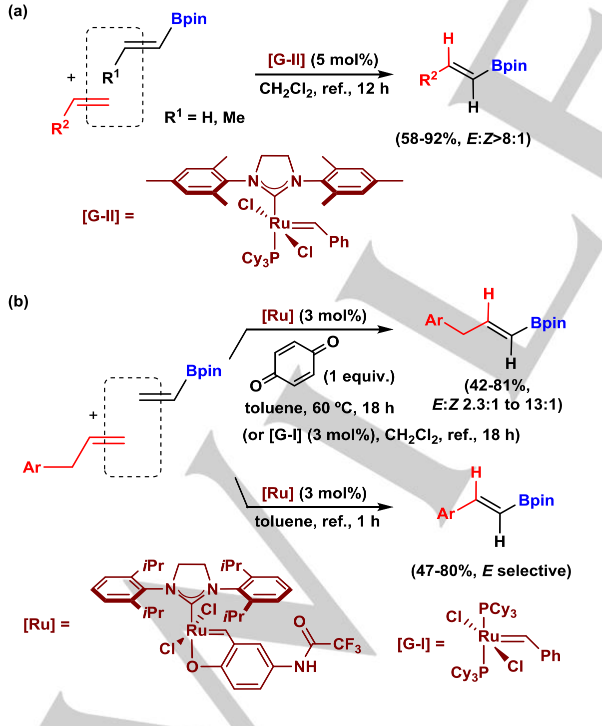
At Universidad de Huelva since 1993, Pedro J. Pérez (FRSC) is currently Professor of Inorganic Chemistry. He received his PhD from Universidad de Sevilla under the supervision of Ernesto Carmona and worked as a Fulbright posdoctoral fellow at the University of North Carolina-Chapel Hill with Maurice Brookhart and Joseph L. Templeton. His research interest is related to the functionalization of hydrocarbons, saturated or unsaturated, by means of metal-catalyzed carbene, nitrene or oxo transfer reactions. He is member of the Academia Europaea (2018) and the Royal Academy of Sciences of Spain (2014), and has been awarded by the Royal Society of Chemistry (Homogeneous Catalysis, 2015), and the Royal Spanish Chemical Society (2016, Gold Medal; 2007, Inorganic Chemistry Award).

Besides the metal-free protocols, an array of various transition metals such as Cu, Rh, Fe or Co have been exploited successfully in the metal-catalyzed hydroboration of alkynes.[14] Earlier work was developed by Srebnik in 1995 with a zirconium complex (Cp_2ZrHCl, Schwartz reagent),[15] followed by the first examples with rhodium or nickel ($Rh(PPh_3)_3Cl$, $Rh(CO)(PPh_3)_2Cl$ and $NiCp(PPh_3)Cl)$)[16] affording the product in quantitative yields, nevertheless with significant differences in regioselectivity (Scheme 3). Copper-based catalysts of different natures have also been extensively used in this transformation over the last decade; heterogeneous catalyst as magnesium oxide-supported copper oxide (I)[17] or copper powder (II),[18] NHC-Cu(I) complexes with adamantyl substituents (III)[19] or (CAAC)CuOPh complexes (IV) [CAAC = cyclic(alkyl)(amino)carbene][20] and air-stable Cu(II)/pyridine-bis-pyrazole system (V) promoted this transformation in moderate to high yield[21] (Scheme 3).



Scheme 4. Iron-catalyzed hydroboration of terminal alkynes.

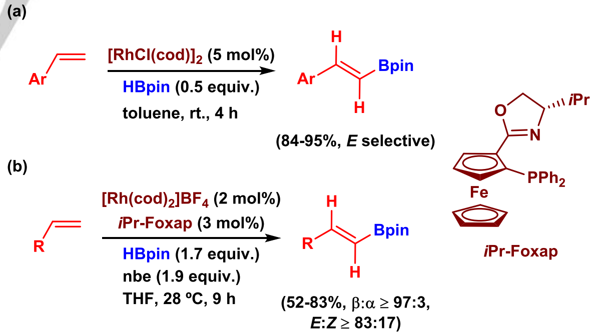
Iron complexes such as $Fe_2(CO)_9$[22] and $FeCl_3$ (or Fe_3O_4 nanoparticles)[23] have emerged in the last years as simple and accessible catalysts. Last year, Nishibayashi presented a well-defined pyrrolide-based PNP pincer iron hydride to form selectively *E*-alkenylboronates (Scheme 4).[24] Other metal complexes have been applied to this transformation, based on gold,[25] silver,[26] palladium[27] or cobalt.[28]



Scheme 5. *E*-Selective olefin metathesis of 1-propenyl pinacolboronate and pinacol vinylboronate.

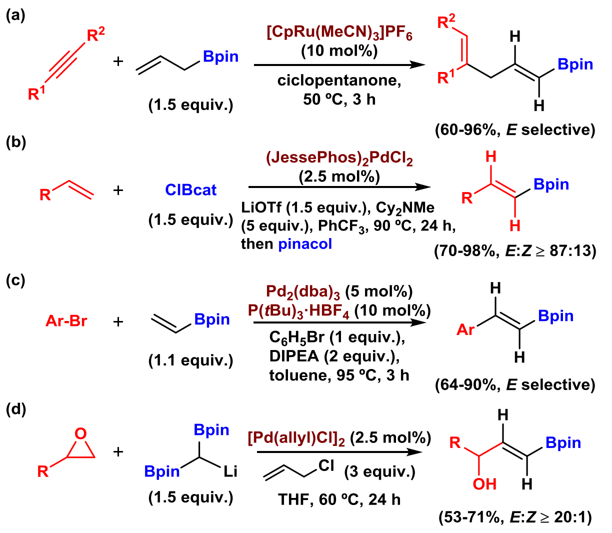
Olefin cross-metathesis (CM), one of the main tools to generate functionalized alkenes, has been applied in the preparation of alkenylboronates. In 2003 Grubbs reported selective CM reactions of 1-propenyl pinacolboronate (or pinacol vinylboronate) with a variety of monosubstituted olefins (Scheme 5a).[29] Satisfactory results were obtained in terms of yields and selectivity. Under similar conditions, Burke presented the reaction using vinyl MIDA boronate, improving the stereoselectivity of the reaction (E:Z > 20:1).[30] Later, Carreaux investigated this reaction with allylbenzene derivatives, which are challenging reagents due to favorable isomerization processes. In the presence or absence of benzoquinone as additive, the reactivity of the same Hoveyda-Grubbs-type catalyst could be directed towards either olefin cross metathesis[31 a] or sequential isomerization/cross-metathesis[31b] respectively (Scheme 5b). Standard olefin cross metathesis was also achieved with Grubbs first generation catalysts.[31a]

Another strategy for the synthesis of *E*-alkenylboronates employing olefins as starting materials is based on the dehydrogenative borylation of alkenes. After initial mechanistic studies and results from Lloyd-Jones[32] and Marder,[33] Masuda screened numerous Rh(I) complexes leading to $[RhCl(cod)]_2$ inducing this reaction with high yields and stereoselectivities when vinylarenes were used (Scheme 6a).[34] In 2015, Miura and Murakami reported a catalytic system formed by $[Rh(cod)_2]BF_4$, a *P*,*N* bidentate ligand (*i*Pr-Foxap) and norbornene as the sacrificial hydrogen acceptor which increased the *E*:*Z* selectivity of aliphatic substituted alkenes to ≥83:17 (Scheme 6b).[35,36] In the last decade, other metal complexes involving rhodium,[37] palladium,[38] iron,[39] cobalt[40] or copper[41] have been effectively employed in this reaction.

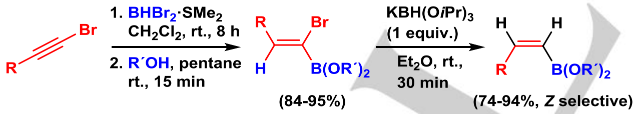


Scheme 6. Rhodium-catalyzed dehydrogenative borylation of alkenes. cod: 1,5-cyclooctadiene. nbe: norbornene.

Additionally, four other methodologies have been applied for the synthesis of *E*-alkenylboronates. Trost described in 2015 a Ru-catalyzed alkene-alkyne coupling reaction using allyl boronates (Scheme 7a).[42] A 1,4-diene motif that includes the *E*-alkenylboronate was formed in a simple manner, and a variety of alkynes could be used, producing polyfunctionalized derivatives. Next year, Watson reported a palladium-catalyzed boryl-Heck reaction using terminal alkenes and catecholchloroborane, in excellent yields and with high stereoselectivity (Scheme 7b).[43] In 2017, the Pd-catalyzed Heck coupling of pinacol vinylboronate and (het)aryl halides was optimized by Wang and Yu (Scheme 7c).[44] Additionally, Meek has reported the coupling/dehydroboration sequence of epoxides with di-Bpin-methane to prepare allylic alcohol-containing alkenylboronates in good yields, high stereoselectivity >20:1 *E*:*Z* and without loss of enantiopurity (Scheme 7c).[45]



Scheme 7. Metal-catalyzed synthesis of *E*-alkenylboronates.

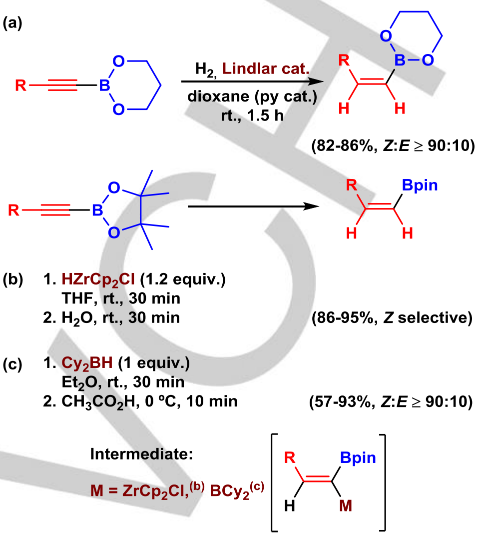


Scheme 8. Hydroboration of bromo alkynes for the synthesis of *Z*-alkenylboronates.

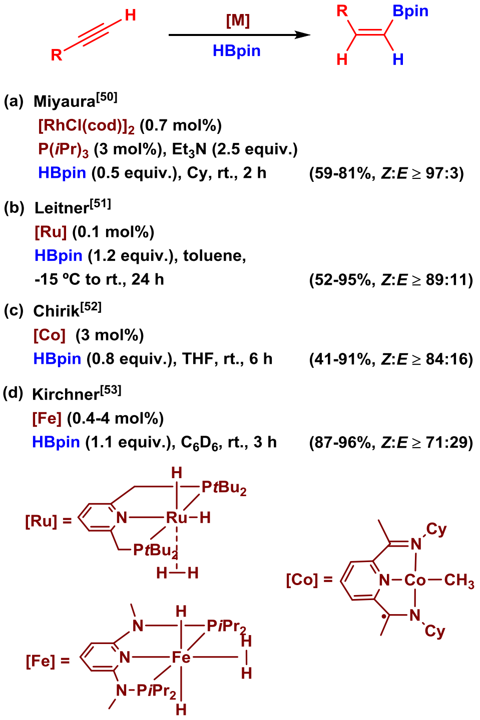
2.2. Synthesis of *Z*-Alkenylboronates

The first examples described for the synthesis of *Z*-alkenylboronates consisted of two-step protocols and required the pre-functionalization of the alkyne to obtain this regioisomer. Work in this area was initiated by Brown in 1984, using bromo alkynes as starting materials (Scheme 8). Hydroboration with dibromoborane and further reaction with sterically hindered hydrides, such as KBH(O*i*Pr)$_3$, proceeded efficiently toward *Z*-alkenyl boronic esters.[46]

Later, alkynylboronates became accessible and popular for the synthesis of *Z*-alkenylboronates. Brown first described the *cis*-hydrogenation using Lindlar catalyst (Scheme 9a),[47] and subsequently two other methodologies were reported for the same type of substrates. Srebnik studied the hydrozirconation of alkynylboronates and further hydrolysis to yield isomerically pure products in a one-pot procedure (Scheme 9b).[48] Molander later described a hydroboration/protonation sequential process using Cy$_2$BH as the hydroboration reagent for alkynylboronates (protodeboronation was performed in the more reactive boron



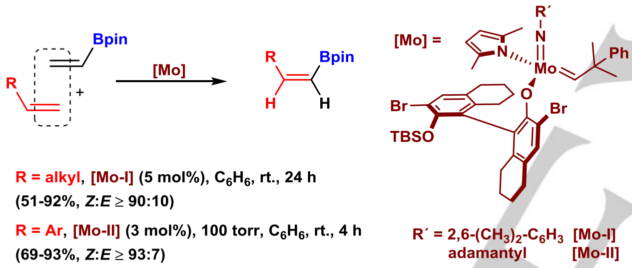
Scheme 9. Alkynyl boronates as precursors of *Z*-alkenylboronates.



Scheme 10. Metal-catalyzed *cis* hydroboration of terminal alkynes. Cy: cyclohexane.

functionality, -BCy_2, to afford the *Z*-alkenylboronate, see Scheme 9c).[49] A one-pot methodology was also presented starting from terminal alkynes and the functional group tolerance was significantly expanded in this work when compared with the previous reports.

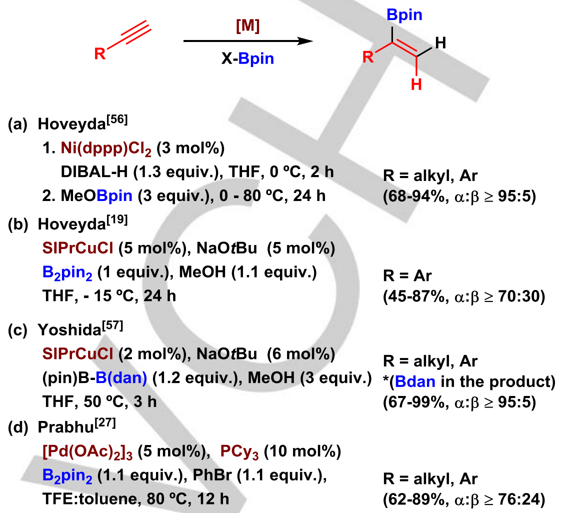
In this century, several metal-catalyzed selective *cis*-hydroboration reactions have appeared in the literature using terminal alkynes. Initial work was developed by the group of Miyaura using rhodium and iridium complexes (Scheme 10a). Rhodium, in combination with bulky phosphines such as P*i*Pr_3 or PCy_3, led selectively to *cis* alkenylboronates (*Z*:*E*, ≥97:3) using catechol- or pinacolborane.[50] Later, three different pincer complexes, with diverse metals, were reported for this transformation. Leitner described a hydride pincer complex [Ru(PNP)$(H)_2(H_2)$] for the selective hydroboration of alkynes.[51] Oxygen and nitrogen based functional groups were well tolerated (Scheme 10b). Chirik reported a bis(imino)pyridine cobalt complex previously employed in alkene hydrogenation or dehydrogenative silylation that readily performed this reactivity (Scheme 10c).[52] More recently, Kirchner has developed iron(II) polyhydride complexes containing PNP pincer ligands, which presented high reactivity toward terminal alkynes (Scheme 10d). Related with hydroboration, good to excellent stereoselectivity was obtained to *Z*-vinyl boronates (*Z*:*E*, ≥90:10 except in the case of Bn as the substituent).[53] A copper-catalyzed *Z*-stereoselective hydroboration of alkynes with 1,8-naphthalenediaminatoborane (HB(dan)) has been described by Lee and Yun.[54] They found copper(I)−thiophene-2-carboxylate together with DPEphos was a competent catalytic system and several arylacetylenes were transformed in good yields and stereoselectivities (*Z*:*E* ≥78:22).



Olefin metathesis has also been applied for the synthesis of *Z*-alkenylboronates. Hoveyda reported the reaction of monosubstituted olefins with pinacol vinylboronate catalyzed by a Mo-based monoaryloxide pyrrolide complex with excellent *Z*-selectivity.[55] In the case of styrene derivatives, reduced pressure (100 Torr) was employed to increase the selectivity in the more challenging aryl olefins in cross metathesis (Scheme 11).

2.3. Synthesis of α-Vinylboronate

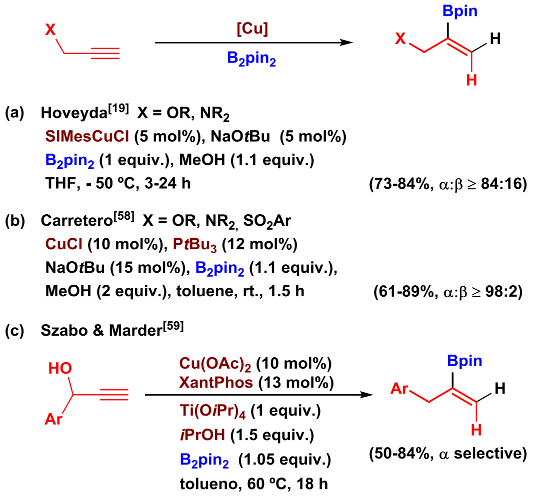
The selective preparation of α-vinylboronates has been achieved starting from diverse starting materials, such as alkynes, allenes, methylenecyclopropanes or aldehydes. From terminal alkynes, Hoveyda developed a hydroalumination reaction catalyzed by Ni(dppp)Cl_2 followed by addition of methoxy(pinacolato)borane to give such substitution pattern.[56]



Scheme 12. α-Hydroboration of terminal alkynes.

Selectivities toward the α position were higher than 95% with good yields for aromatic and aliphatic substituents (Scheme 12a). Shortly after, the same group achieved the direct hydroboration by using SIPrCuCl.[19] Tuning the steric and electronic properties of the NHC-copper complex, the α site selectivity can be improved up to 96:4 (α:β) for aromatic substituents (Scheme 12b). Under similar conditions, but using a mixed diboron compound ((pin)B–B(dan)), Yoshida reported excellent results with 1,8-diaminonaphthalene (dan) as protecting group for boron, independent of the alkyne substituent (Scheme 12c).[57] The mixture of readily available palladium acetate with PCy_3 has also been reported for this reactivity by Prabhu,[27] with good to excellent selectivities but with high dependence of the substrate employed (Scheme 12d).

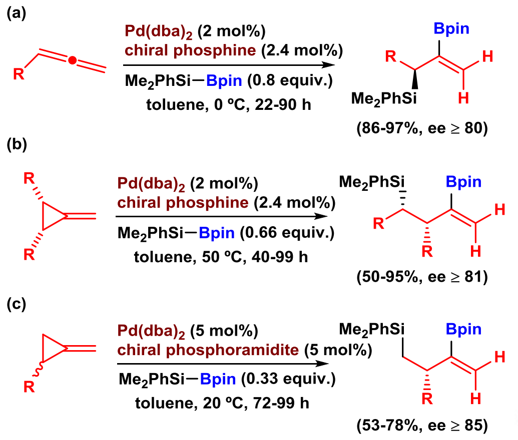
Furthermore, Hoveyda reported the α-selective copper-catalyzed hydroboration of propargylic alcohols and amines (Scheme 13a).[19] Again, a fine tuning was performed leading to



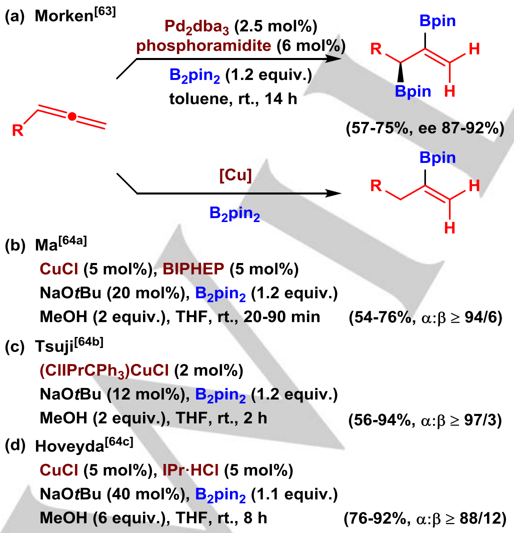
Scheme 13. α-Hydroboration of propargylic alkynes.

SIMes as the suitable NHC ligand for these substrates. Better results were found using protected reagents (ethers, carbamate, tosylamide or phtalamide). Carretero extended this reactivity to propargylic substituted alkynes with copper chloride in the presence of P*t*Bu$_3$, especially with 2-pyridylsulfone derivatives, as this functional group can be further transformed by Cu-catalyzed allylic substitution with Grignard reagents.[58] Szabó and Marder have applied a similar methodology for unprotected propargylic alcohols, with the Cu(II)-XantPhos system and Ti(O*i*Pr)$_4$ as an additive (Scheme 13c).[59] 1-Aromatic substituted propargylic alcohols gave good yields and perfect selectivities *via* proposed allenes intermediates, affording α-vinylboronates.

Allenes constitute a key entrance to the preparation of α-vinylboronates. Suginome opened this route with the asymmetric silaboration of allenes, first by using silylboranes bearing diol-derived chiral auxiliaries,[60a] and later in a reaction catalyzed by palladium(0) and binaphthyl derived phosphines (Scheme 14a).[60b,c] Versatile alkenylboronates were obtained as silyl- or boronate groups can be further transformed. The same group has investigated the silaborative cleavage of methylenecyclopropanes, to give functionalized α-vinylboronates in good yields and high enantioselectivities (Scheme 14b,c).[61] Furthermore, platinum(0) complexes have improved the regioselectivity in the opening of 1-alkyl-2-methylenecyclopropanes in the racemic version.[62]



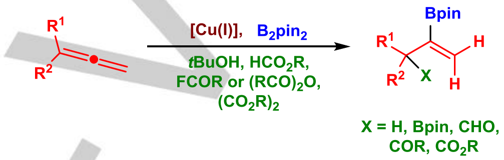
Scheme 14. Silaboration of allenes and silaborative cleavage of methylenecyclopropanes.



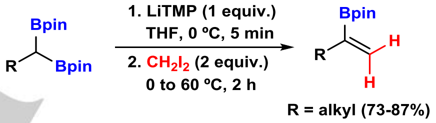
Scheme 15. Synthesis of α-vinylboronates from monosubstituted allenes

Morken also used monosubstituted allenes, affording enantioselective diboration with excellent enantiomeric excess catalyzed by Pd$_2$dba$_3$ and TADDOL-derived phosphoramidites (Scheme 15a).[63] The same substrates have been hydroborated by several groups with different copper catalytic systems (NHC or phosphines) and gave high to excellent regioselectivities (Scheme 14b-d).[64] Cyclic substituents can be obtained with similar methodologies and intramolecular cyclizations.[65]

1,1-Disubstituted allenes have been suitable precursors to obtain α-vinylboronates with an adjacent quaternary center (Scheme 16). Hoveyda described the asymmetric protoboration of these substrates catalyzed by chiral NHC-copper complexes.[66] With the appropriate choice of the reagents, boraformylation,[67] boroacylation[68,69] boraalkoxyoxalylation[69] or asymmetric diboration[70] have been described with different copper(I)-phosphine catalytic systems.



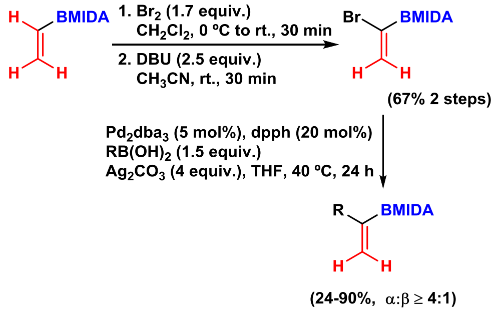
Scheme 16. Boro-functionalization of 1,1-disubstituted allenes



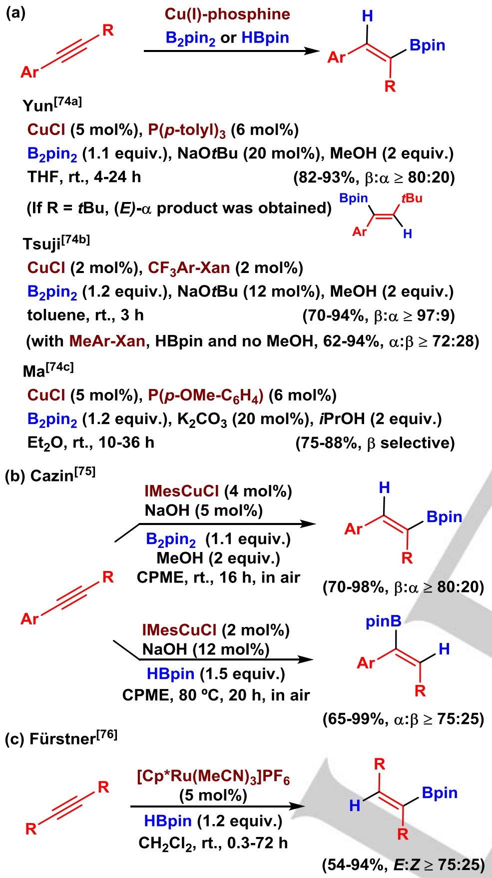
Scheme 17. Synthesis of α-vinylboronates from geminal bis(boronate) substrates

Morken has investigated the reaction of substituted geminal bis(boronate) with diiodomethane, in the presence of a strong base (LiTMP), to form α-vinylboronates.[71] This transition-metal free protocol yielded the products in a simple and efficient method (Scheme 17). Using aldehydes instead of CH$_2$I$_2$, *trans* alkenylboronates or trisubstituted derivatives were obtained.

In 2013, Burke reported the synthesis of 1,1-disubstituted olefin-containing MIDA boronates by a bromination-elimination process to vinyl MIDA boronate. This building block ((1-bromovinyl)-MIDA boronate) can be further functionalized to access a wide range of α-vinyl MIDA boronates in moderate to high yields and stereoselectivity by palladium cross-coupling reactions (Scheme 18).[72]



Scheme 18. Synthesis of α-vinyl MIDA boronates.

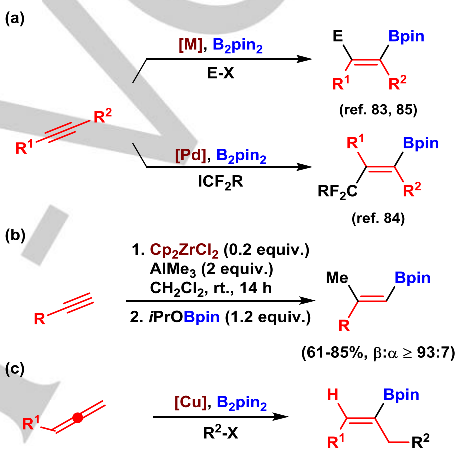


Scheme 19. Hydroboration of internal alkynes. CPME: Cyclopentyl methyl ether. Xan: XantPhos derivative.

2.4. Synthesis of tri- and tetrasubstituted alkenyl boronate

Several methodologies commented in the previous sections have been successfully applied for the synthesis of more substituted alkenylboronates.[73] Hydroboration of internal alkynes, for example, has been broadly studied with copper as the catalyst. Copper(I) compounds along with different phosphines led to trisubstituted Z-alkenylboronates (β selectivity, Scheme 19a).[74] Nevertheless, first Tsuji, by changing the XantPhos ligand,[74b] and later Cazin[75] by modulating the reaction conditions with NHC-copper complexes, showed that the selectivity can be tuned from β to α position (Scheme 19a,b). Noteworthy, Fürstner described the first *trans* selective hydroboration of internal alkynes using [Cp*Ru(MeCN)$_3$]PF$_6$ with high to exceptional *trans* selectivity obtained with the symmetrical substrates (Scheme 19c).[76] Later, Liu disclosed the Pd-catalyzed *trans* hydroboration of terminal and internal 1,3-enynes with high selectivity and stereoselectivity assisted by 1,4-azaborine-based phosphine ligands.[77]

In the case of functionalized alkynes, such as alkynoate esters or amides,[78] propargylic alcohols and ethers,[79] thioacetylenes[80] or ynamides,[81] different copper catalysts (or metal-free phosphine catalysis in the prior case) have been employed inducing α or β selectivity, being both regioisomers available in all cases. The hydroboration of allenes has also been exploited for the synthesis of trisubstituted alkenes, the catalyst and the substituents both influencing the regioselectivity of the process to the internal or distal double bond.[64b,82]



Scheme 20. Carboboration of alkynes and allenes.

Another strategy for the synthesis of tri- and tetrasubstituted alkenylboronates is the carboboration of alkynes or allenes, generating new C-B and C-C bonds (Scheme 20a). Initial work was developed by Suginome with palladium and nickel[83] and recently Bai & Zhu and Zhang have described the Pd-catalyzed *trans* carboboration with fluoroalkyl halides.[84] Nevertheless copper complexes are the most successful catalysts described for this transformation, generating the new C-C bond from an electrophile (R-X).[85] Selectivity can be tuned by ligand control. Other metals such as iron or zirconium have also been used in this transformation.[86] It is worth highlighting the Zr-catalyzed carboalumination/transmetalation methodology of terminal alkynes described by Aggarwal that uses available materials, and is scalable to gram amounts, providing trisubstituted alkenylboronates in excellent regioselectivities (Scheme 20b).[86b] Allenes are also suitable substrates for this synthetic tool under similar reaction conditions (Scheme 20c).[87]

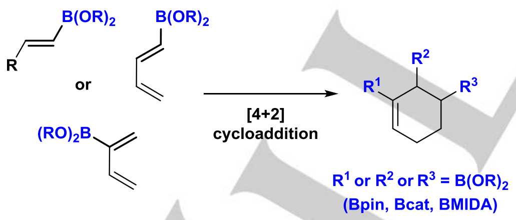
Other strategies for the synthesis of polysubstituted alkenylboronates are the dehydrogenative borylation of 1,1-disubstituted alkenes (Scheme 21a),[88] dehaloborylation of gem-dihaloalkenes to produce *Z*-1-halo-1-alkenyl boronate esters (Scheme 21b),[89] the bromoboration of alkynes[90] (Scheme 21c) and the reaction of ketones with 1,1-organodiboronates or by diboration/elimination sequence leading to different substitution patterns (Scheme 21d).[71,91]

Propargylic alcohols[92] recently found application for the synthesis of polysubstituted alkenylboronates and, additionally, these substrates have been prepared in a variety of transformations involving hydroboration/cyclization of 1,6-enynes and related substrates,[93] and olefin metathesis or enyne metathesis.[94] In recent times, the Heck coupling between arylvinyl MIDA boronates and aryl iodides was disclosed by the Cossy group.[95]

3. Applications of alkenylboronates

The most significant application of alkenylboronates in organic synthesis consists of their use as partners in Suzuki-Miyaura cross-coupling reactions, mainly due to the development of new boron protecting groups that has increased their versatility toward that end.[96] Besides this role, the simple transformation of C-B bonds in a variety of functional groups[1] has boosted the use of these molecules in reactions that implied olefins, for further derivatization once a more elaborated building block has been obtained.

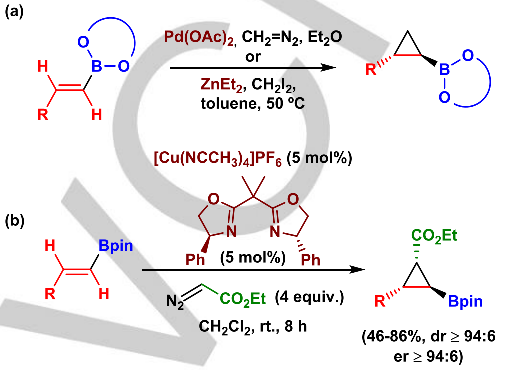
Since the first applications by Matteson in the 60s in radical and organometallics additions,[97] numerous reactions containing alkenylboronates have been developed. Some of the earlier examples included halodeboration, Michael addition or radical chemistry.[98] One of the most studied reactions of alkenylboronates involves a cycloaddition step.[4b,99d] In particular, they have been included in Diels-Alder cycloadditions as diene or dienophiles to obtain flexible cyclohexenes and related molecules (Scheme 22).[99] Although alkenylboronates and 1,3-dienyl boronates display low reactivity, good results have been obtained at high temperatures, either introducing electron withdrawing groups or favoring intramolecular interactions.[100] The asymmetric version has also been studied by using diols as chiral inductors, with titanium and chromium complexes or oxazaborolidinium cations.[101]



Scheme 22. General scheme for Diels-Alder cycloadditions with alkenylboronates.

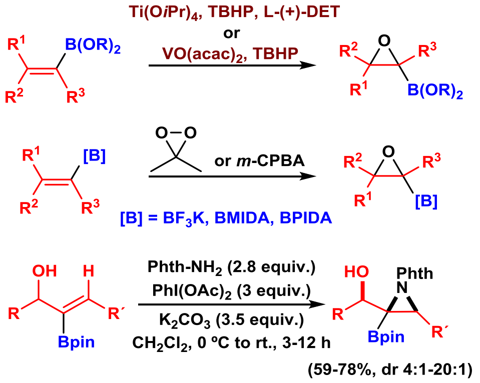
On the other hand, in 1,3-dipolar cycloaddition reactions alkenylboronates have shown good reactivity towards diazo compounds, nitrile oxides, nitrones or azomethyne ylides to obtain different heterocycles as pyrazolines, isoxazolines, isoxazolidines or pyrrolidines.[102]

The preparation of versatile three-member rings from alkenylboronates has also attracted the interest of synthetic chemists. Cyclopropanation reactions were described in the last century by carbene addition or Simmons-Smith reactions (Scheme 23a).[103] The use of chiral diols in the boronates, strategy initiated by Imai and particularly exploited by Pietruszka and other authors, promoted good diastereoselectivities in the borocyclopropane products.[104] Moreover, we have recently described the first highly enantio- and diastereoselective cyclopropanation of 1-alkenylboronates with ethyl diazoacetate, using Cu(I)-BOX complex as catalyst (Scheme 23b).[105]

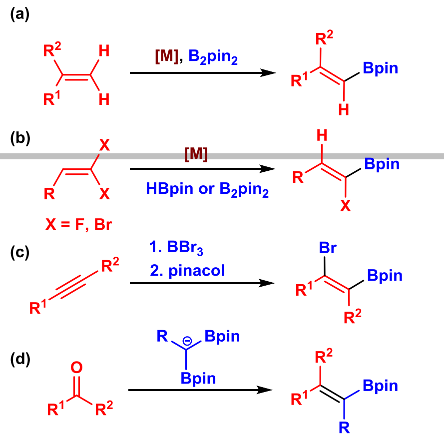


Scheme 23. Synthesis of cyclopropylboronates

The epoxidation reactions have been studied under Sharpless conditions or using vanadium oxides for alkenylboronates,[106] or with four-coordinated boron derivatives (-BF$_3$K, -BMIDA, -BPIDA) in the presence of other common epoxidation reagents such as *m*-CPBA or DMDO (Scheme 24).[107] In both cases satisfying diastereoisomeric ratios have been obtained, using chiral auxiliaries (chiral diols in the boronate or –BPIDA, a pinene derivative of –BMIDA)[106a,107b] or

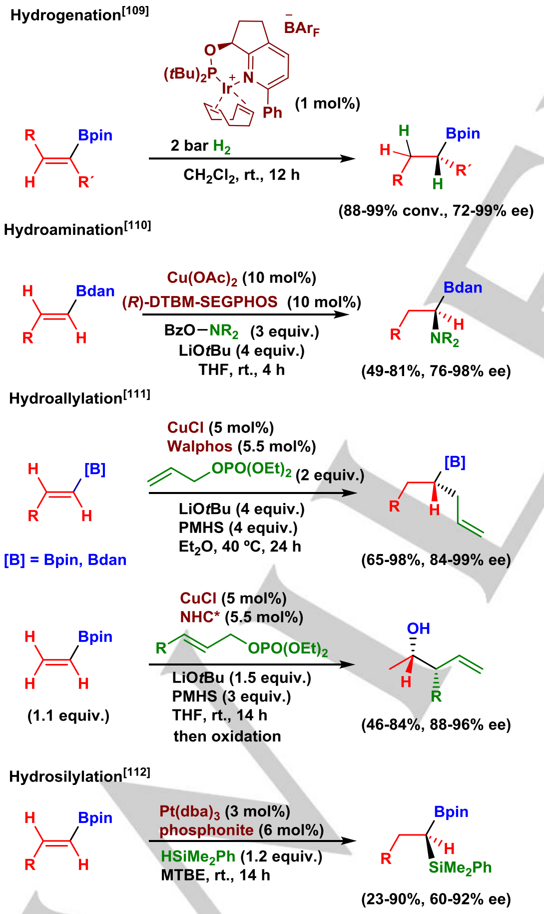


Scheme 24. Synthesis of boronate substituted epoxides and aziridines. PIDA: pinene-derived iminodiacetic acid.



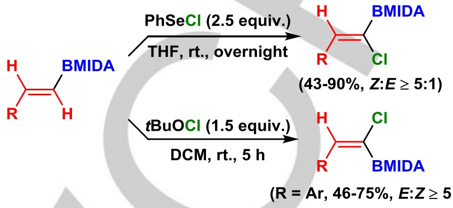
allylic alcohol as epoxidation director.[106b,c] The only example of aziridination was described by Walsh for 2-Bpin-substituted allylic alcohols in the presence of $PhI(OAc)_2$ and *N*-aminophthalimide in a metal free protocol, with good yields and excellent diastereoselectivity (Scheme 24).[108] For both epoxides and aziridine rings, no enantioselective procedures have been yet described.

Hydrofunctionalization reactions of alkenylboronates, especially on the challenging asymmetric versions have been broadly expanded in the last years providing chiral building blocks that include the versatile boronate groups. Pfaltz described the enantioselective hydrogenation of alkenylboronates using iridium complexes bearing *N*,*P*-ligands as catalysts (Scheme 25).[109] α-Aminoboronic acids can be prepared in moderate yields from alkenylboronates by a hydroamination protocol developed by Hirano and Miura with Cu(II)-diphosphine catalysts.[110] Hydroallylation was also developed independently by Yun and Hoveyda for these substrates using allylic phosphates as reagents under copper catalysis.[111] Recently, the Pt-catalyzed enantioselective hydrosilylation has been described by Morken group.[112] In all those cases excellent enantiomeric excesses were obtained (Scheme 25).



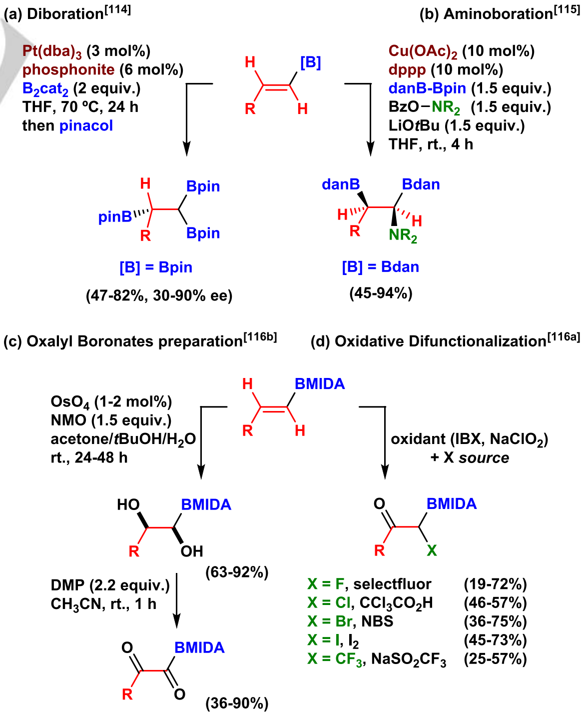
Scheme 25. Asymmetric hydrofunctionalization reactions of alkenylboronates. PMHS: poly(methylhydrosiloxane).

Very recently, the stereodivergent synthesis of *E* and *Z* α-chloroalkenylboronates through chlorination of *trans* alkenyl MIDA boronates was optimized by Wang using different chlorination reagents in an efficient metal-free protocol (Scheme 26),[113] producing a versatile building block that can be further transformed *via* the olefin, halogen or boronate.



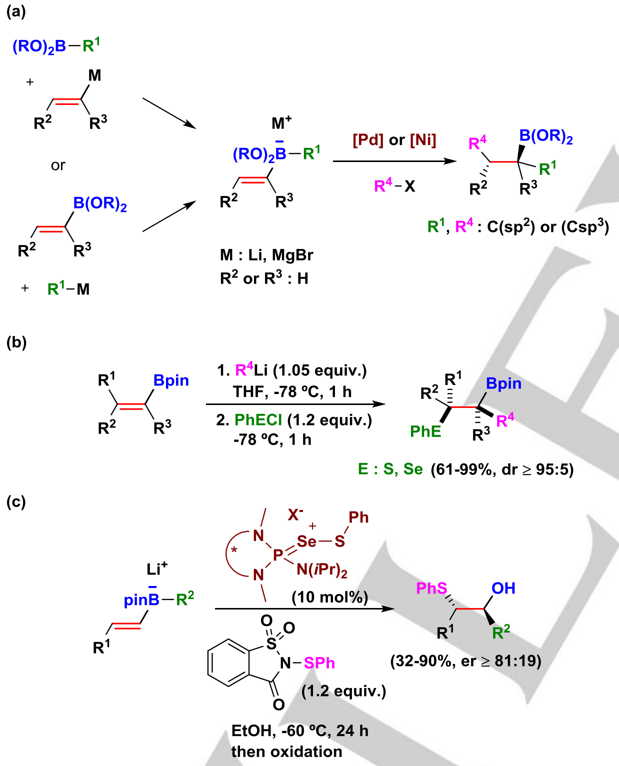
Scheme 26. Stereodivergent chlorination of alkenyl MIDA boronates.

Interestingly, difunctionalization reactions have been also described for alkenylboronates. Morken first presented the platinum catalyzed enantioselective diboration of vinylboronates (Scheme 27a).[114] Two years later Hirano and Miura reported the regio- and stereoselective aminoboration of alkenylboronates, although the enantioselectivy obtained for two examples was yet moderate (70-76% ee).[115] The oxidation of these olefins toward oxalyl MIDA boronates or halogenated and trifluoromethylated α-boryl ketones has been recently described (Scheme 27b,c).[116] The ozonolysis of alkenyl MIDA boronates has also been achieved by Bode and Ito affording acylboronates, which are intermediates in the synthesis of α-amino acylborons.[117]



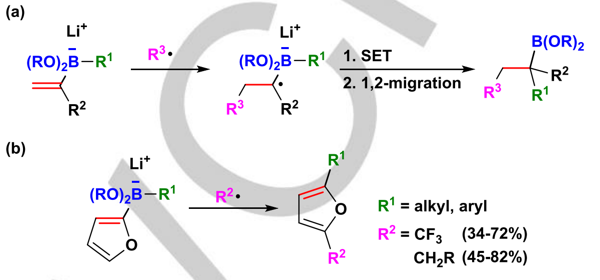
Scheme 27. Difunctionalization reactions of alkenylboronates. NMO: *N*-methylmorpholine *N*-oxide. DMP: Dess–Martin periodinane. IBX: 2-Iodoxybenzoic acid.

Very recently, the reactivity of tetracoordinate alkenylboronate complexes by 1,2-migration rearrangement has been exploited by several authors (Scheme 28). Morken presented in 2016 a palladium-catalyzed *conjunctive* cross-coupling methodology to obtain secondary alcohols (after oxidation) in high enantiomeric excess using three components: an organolithium, an organoboronic ester, and an organotriflate.[118] The same group has developed this method to obtain secondary and tertiary alkylboronates with $C(sp^2)$ or $C(sp^3)$ substituents in excellent ee's by palladium or nickel catalysis (Scheme 28a).[119] Aggarwal has investigated the reactivity of the same complexes with different electrophiles, achieving high diastereoselectivities by using PhSeCl or PhSCl (Scheme 28b).[120] Denmark has lately published the transition-metal free enantioselective carbosulfenylation of alkenylboronates, affording β-sulfur secondary or tertiary alcohols, after oxidation (Scheme 28c).[121]



Scheme 28. Construction of non-racemic alkylboronates (or alcohols) bearing two vicinal stereogenic centers.

The mentioned substrates, tetracoordinated alkenylboronate complexes, have also been employed in radical chemistry. Studer[122] and Aggarwal,[123] independently, and later Renaud[124] have shown that the vinylboronate complexes are efficient radical acceptors, and the radical anion adducts undergo 1,2-alkyl/aryl shift from boron to carbon, leading to a variety of synthetically useful products (Scheme 29a). This method has been applied by Aggarwal in heterocycles such as furan or indole to give 2,5-disubstituted furans or 2,3-disubstituted indoles (Scheme 29b).The 1,2-metalate rearrangements and photoredox catalysis has merged on this topic with several contributions also from Aggarwal group.[123b,c] Simple vinyl-BMIDA and vinyl-Bpin are also suitable substrates for radical chemistry.[125]



Scheme 29. General mechanism of radical reactions in tetracoordinated alkenylboronate complexes and furan application**.** SET: single-electron transfer.

4. Conclusions

This review provides an insight into the increasing development of synthetic protocols for the preparation of alkenylboronates and their further use in organic reactions, where the versatility of the products is significantly increased with the incorporation of the boronate group. A number of transformations have been described. Further progress seems to focus in the use of alkenylboronates in processes related with asymmetric applications of these flexible substrates, employing pinacol boronate or the more robust protecting groups Bdan or BMIDA.

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Keywords: boron chemistry • alkenylboronates • borylation • boron catalysis • boronate compounds

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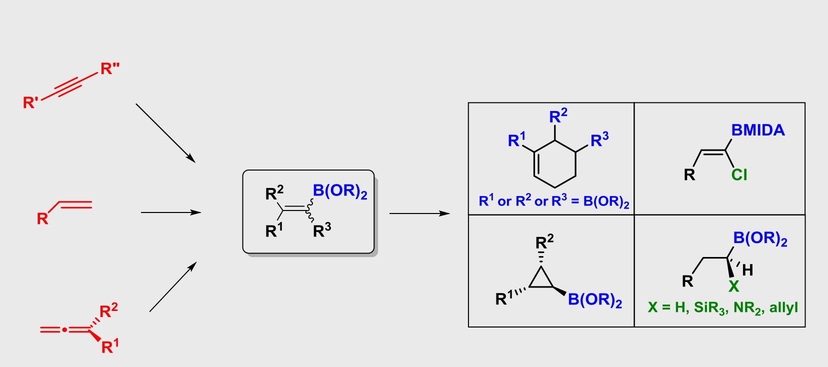
FOCUS REVIEW



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