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α-Borylalkyl radicals: their distinctive reactivity in modern organic synthesis

Nivesh Kumar,† Reddy Rajasekhar Reddy,† Nadim Eghbarieh and Ahmad Masarwa [ID] *

Organoborons are extremely important for synthetic organic chemistry; they can serve as advanced intermediates for a variety of transformations. Such a well-known transformation involves the loss of the boron moiety, creating alkyl radicals. Although these originally developed protocols for alkyl radical generation remain in active use today, in recent years their α-boryl carbon-centred radicals have been joined by a new array of radical generation strategies that offer a unique reactivity to forge a wider diversity of organoborons that often operate under mild and benign conditions. Herein, we will highlight the stability and reactivity of α-borylalkyl radicals and their remarkably recent advances in order to further utilise them for C–C and C–heteroatom bond formation. Their use for this purpose has been reported over the last decade in an attempt to guide the synthetic community. Various transition-metal and metal-free methods for their generation are presented, and more advanced photoredox approaches are discussed, mainly for the period of 2009–2019.

1. Introduction

Organoborons[1] are organometallic equivalents, which are considered to be one of the most valuable reagents in modern organic synthesis, providing rapid access to a wide array of transformations including the construction of C–C and C–heteroatom bonds.[1a,b] These compounds have gained increasing popularity because of the steric and electronic properties of the Lewis acidic boron moiety, which can be easily tuned just by changing the

substitution around it, which allows diverse reactivity, as a stoichiometric reagent and as well as a catalyst.[1c,d]

Nowadays the presence of boron functionality in natural products and synthetic drugs has appeared repeatedly. For example, the antibiotics aplasmomycin, boromycin, and tartolon-B contain boron in the form of borate complex.[2] Drugs such as Tavaborole, Bortezomib and others also contain a boron functional group in them.[3] To synthesise such motifs, metal and metal-free strategies are available;[4] however, radical pathways could provide a unique reactivity to obtain complex structures transformed to a greater extent.

Notably, organoboron[5a–i] derivatives have become a convenient source for alkyl radicals and provide a green alternative to

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a) Previously discussed:
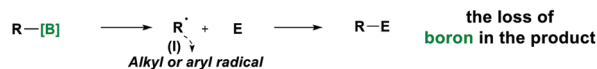
b) This review:
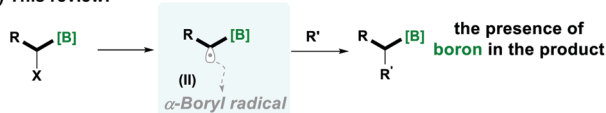
Scheme 1 General schematic representation of α-boryl radicals.

Scheme 2 Stabilisation of the α-boryl radical by an adjacent empty p-orbital.

tin-based radical chemistry.[5j–n] The generation of alkyl radicals (Type-**I**) from organoboron derivatives, through the loss of the boron functionality, is a well-established chemistry, which results in further utilisation of these radicals in various transformations (Scheme 1a).[5i–m]

In comparison, the generation of α-alkyl-radicals from a boron moiety (Type-**II**), without losing boron, is less known and their special reactivity is expected to offer a respectable range of transformations for the synthesis of organic molecules in which the boron functionality is left intact for further utilisation (Scheme 1b).

Before going into the discussion, let us first introduce the characteristics of the α-boryl radical species (which is the equivalent of the α-metalated radical; see **II′**, Scheme 2a) in terms of stability and electronics, based on its substitution pattern. The α-boryl radicals are more stabilised than the secondary alkyl-radicals by 14.5 kcal mol^{-1}. Similarly, the α-boryl radical, obtained by H-abstraction, at the α-position, from Et_3B was found to be more stable than the corresponding methyl radical of toluene.[6] These α-boryl radicals (*e.g.*, **II**) are stabilised by the empty p-orbital of boron through hyperconjugation-like structures, as depicted in Scheme 2A. Upon introduction of oxygen substituents on boron, the stabilisation of the corresponding α-boryl radicals decreases because the empty p-orbital of boron delocalises with nonbonding electrons on oxygen, resulting in decreased availability of the empty p-orbital of boron for radical stabilisation (Scheme 2B).[7] Based on the number of oxygen substitutions on boron, the

radical stabilisation order will be boranes **II-a** > borinates **II-b** > boronates **II-c**. The radical of MIDA-boronate (MIDA: *N*-methyliminodiaceticacid) is the least stable compared with others because the p-orbital is connected to nitrogen (in **II-d**).[7,8]

In this review, we would like to provide information on the reactions that are involved in the generation of α-boryl carbon-centred radical intermediates **II** and their utilisation for the synthesis of various important structural motifs. The key to the success of these reactions largely depends on the good matching philicity of the radical with alkene and other electrophiles. Additionally, this review will provide the various ranges of reactions of α-boryl radicals with electrophiles.

2. Synthetic methods of α-boryl radicals and their applications in synthesis

The α-boryl radical species (*e.g.*, **II**) from different precursors have been generated in several ways for the synthesis of various organic frameworks with boron functionality. In general, for

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understanding the purpose of initiating the α-boryl alkyl radical, the generation has been classified into the following three categories, based on the reaction conditions:

2.1 Using radical initiators

2.2 Visible light-mediated reactions

2.3 Miscellaneous reactions of three-component reactions

2.1 Initiation of the α-boryl radical by a radical initiator

In this category, the formation of α-boryl radicals was mainly promoted by radical initiators such as B(alkyl)$_3$/bromine, azobisisobutyronitrile (AIBN) with stannates or with tris(trimethylsilyl)silane (TTMSS), and lauroyl peroxide (DLP).

2.1.1 B(alkyl)$_3$/Bromine as a radical initiator system. In 1970, Brown and Lane reported two steps in the anti-Markovnikov hydrobromination of alkenes to first form trialkyl borane **1**, which is involved in further reactions with stoichiometric amounts of bromine in the dark, which provides the desired corresponding alkyl bromides **2** (Scheme 3).[9] The bromination reaction mechanism involves the formation of an α-radical to the borane (*i.e.*, **4**) after the reaction of bromine radical with **1**. Furthermore, it will form α-bromoborane **5**, which is involved in another reaction with hydrogen bromide, affording bromo alkane **2**. To the best of our knowledge, this could be the first method that represents the formation of a radical adjacent to borane.[9]
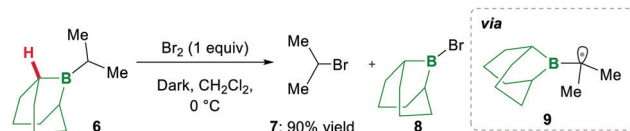
In 1973 the same group extended the above strategy for studying competitive bromination on B-isopropyl-9-borabicyclo-[3.3.1]nonane **6**.[10] Interestingly, they obtained complete selectivity of bromination at an isopropyl group over a bicyclic ring (Scheme 4). This selectivity can result from the interaction between the odd electron and a vacant p-orbital (in **9**), which is much more facile, due to the perfect degree of overlapping, than the C–H bond at the bridgehead position α to boron (highlighted in red in **6**).[10] Moreover, in this bromination study Lane and Brown found that the α-(C–H) position in relation to boron is 5.5 times more reactive than the tertiary hydrogen of cumene, owing to the same reason of the stabilisation of the empty p-orbital of boron.

Scheme 4 Competitive anti-Markovnikov bromination of B-isopropyl-9-borabicyclo[3.3.1]nonane.

2.1.2 AIBN (with stannates or with TTMSS) as a radical initiator. In 1995, Carboni and coworkers[11] generated the α-boryl carbon-centred radical **13** by treating tributyltinhydride with a catalytic amount of AIBN under thermal conditions or photo irradiation for intramolecular cycloaddition to olefin. In this reaction, α-iodoalkenylborane **10** underwent 5-*exo* cyclisation, affording a mixture of the products *syn*- and *anti*-1,2-disubstituted cyclopentane **11**. It also afforded small amount of 6-*endo* cyclisation product **12** (Scheme 5).[11]

Analogously, Batey's[12] research group reported intermolecular additions of α-boryl radicals (see **18**), generated from α-iodoalkylboranes **14**, which are then coupled with electron-rich as well as electron-deficient alkenes. In this reaction, electron-deficient alkene **15** yields less yield because of the telomerisation of radical adducts with electron-deficient alkenes. However, electron-rich alkene **15** afforded good yields and no side reactions were observed (Scheme 6). Interestingly, when they performed a competitive reaction between electron-deficient and electron-rich alkenes, the addition occurred preferentially to the electron-deficient alkene.[12]

Later on, in 1999, the same group[13] described the one-pot intramolecular additions of α-boryl radicals to tethered electron-rich alkenes **20** (or alkynes **21**) *via* **22a** to **23a**, when the organoboron products **23a** were oxidised to 1,3-diols **20a**. When they used the same conditions as above, they observed
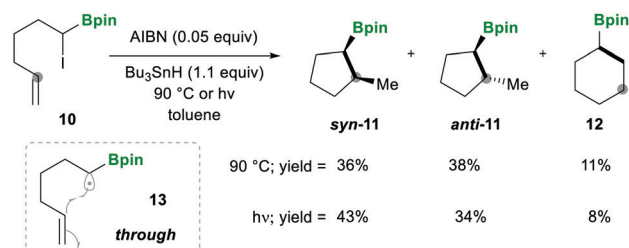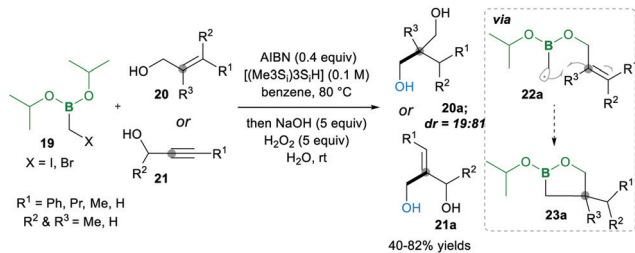
Scheme 5 Intramolecular α-boryl carbon-centred radical cyclisation.

Scheme 3 Anti-Markovnikov hydrobromination of alkenes and its mechanism.
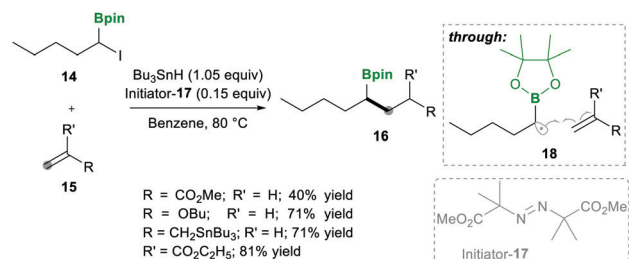
Scheme 6 An intermolecular α-boryl carbon-centred radical coupled with alkenes.
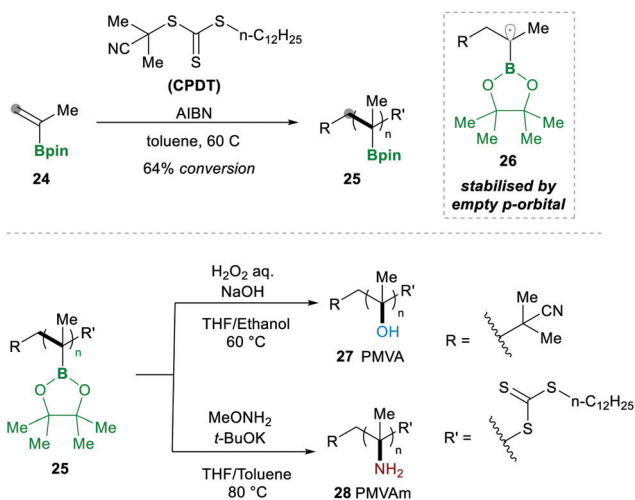
Scheme 7 The α-boryl carbon–centred radical coupled with alkenes and alkynes.

5-*exo* cyclized product **23a** with low yield, but upon the addition of tris(trimethylsilyl)silane, they obtained good yields. This reagent is known to trap the radicals with lower efficiency than tributyltin hydride does; ultimately, it reduces the degree of direct reduction (Scheme 7). Furthermore, the reaction results in good diastereoselectivity up to 19 : 81.[13]

In 2019, Ouchi and Nishikawa[14] carried out the polymerisation of isopropenyl boronate pinacol ester (IPBpin) **24** by taking advantage of the stabilisation of radicals adjacent to the boron through the empty p-orbital **26**. This moderate stabilisation of radicals allows a reaction towards the chain growth of the polymer and suppresses the chain transfer reaction, which leads to a greater chain length of the polymer. Here IPBpin **24** was treated with AIBN and 2-cyano-2-propyl dodecyl trithiocarbonate (**CPDT**) as a chain-transfer agent by reversible addition–fragmentation chain-transfer polymerisation (RAFT), obtaining polymers, *e.g.*, **25**, with high molecular weights (Scheme 8).

Later, to determine the significance of an empty p-orbital (in **26**), they compared IPBpin **24** polymerisation with isopropenyl boronate carrying an *N*-methyliminodiacetic acid ester (IPBmida), which has no such boron p-empty orbital. Predictably, IPBmida was not polymerised, in comparison with IPBpin **24**. Furthermore, they utilised the presence of boron in skeleton **25**, which was transformed to alcohols **27** and amines **28** by

the oxidation of pinacolatoboronate ester for the synthesis of poly(a-methyl vinyl alcohol) (PMVA) and poly(a-methyl vinyl amine) (PMVAm), respectively (Scheme 8).[14]

2.1.3 DLP as a radical initiator. In 2015, Zard[15] and co-workers demonstrated a different reactivity between vinyl pinacolatoboronates (Bpin) and vinyl MIDA-boronates **29** toward radical chemistry. Additionally, they successfully utilised **29** for the synthesis of highly functionalised MIDA boronates **31–41**. The inability to stabilise the radical adjacent to the MIDA-boronates in **32** (the vacant p-orbital is occupied by a lone pair of electrons of nitrogen) allows the formation of highly functionalised organoboron structures from the addition of a wide array of xanthates to vinyl MIDA-boronates **29** *via* xanthate addition and transfer induced by DLP (box D). This method works with a wide range of nucleophiles, which are structurally complex, such as the cyanomethyl radical, which is electrophilic in nature. It was derived from xanthate; the phthalimidomethyl radical has a slight nucleophilic character, which works efficiently with this method and afforded high yields of products **30–31** (Scheme 9A). Importantly, this method can be successfully utilised for the synthesis of complex MIDA boronates **33–34** such as shown in Scheme 9B. Later, the xanthate group was successfully subjected to simple reduction with lauroyl peroxide in isopropanol solvent, yielding the corresponding boronates **35–36**.[15]


Scheme 8 RAFT polymerisation of IPBpin **24**.

Scheme 9 Radical chemistry of vinyl MIDA boronates.

Finally, based on their high reactivity, the products, *e.g.*, **37** and **39**, were successfully utilised for different synthetic transformations (*via* box D) such as ring fusion with the heteroaromatic ring, which afforded the corresponding product **38** in low yields; the xanthates in **39** were replaced with bromine, following base-mediated nucleophilic substitution forms, which substituted cyclopropane **41** with good yields (Scheme 9C).

Consequently, in 2019, they utilised carbon-radical **45**, which is similar to pinacolatoboronate in functionality.[16] It was generated from α-boronylxanthates **42** for the synthesis of the terminal and internal boronates. The α-boronylxanthates **42** were reacted with different substituted alkenes **43** under DLP as a radical initiator and refluxed at 100 °C, yielding products **44** in moderate yields (Scheme 10).[16]

Accordingly, they used vinyl-B(DEA) **46** when they started to diversify the organoboron products through a sequential radical reaction, as described in Scheme 11. In this case, vinyl-B(DEA) **46** forms a non-stabilised radical intermediate **51**, which is similar to the previous case of the B(MIDA) radical intermediates *e.g.*, **42**, this allows the rapid formation of multi-substituted boronylxanthates **46**. Later the B(DEA) functionality of the product was interconverted to pinacolatoborane esters **47**, which were further treated under similar radical reactions and reacted with a wide range of alkenes **48**, affording internal boronylxanthates **49**. Finally, the reduction of the xanthate group in **49** with silyl hydride yielded the internal boranes **50** with good to excellent yields (Scheme 11). This strategy was also expanded for the synthesis of structurally complex internal boranes **50a–50f** with very good yields.
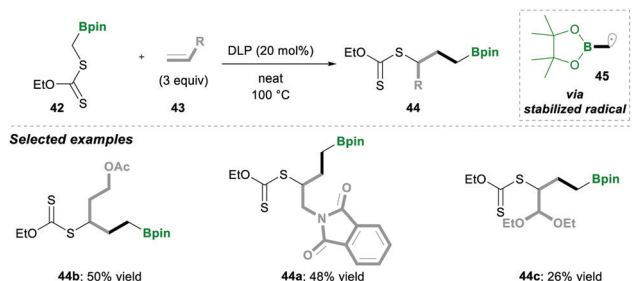
Scheme 10 Synthesis of terminal boranes.

Scheme 11 Synthesis of internal boranes.

Scheme 12 Synthesis of benzopinacolato boranes.

Additionally, they found that increasing the steric hindrance of the substituent in boronates, *e.g.*, the benzopinacolato groups in **52**, results in greater hydrolytic stability, which ultimately reduces the formation of side products.[17] Regarding their hypothesis, they achieved better yields than with their simple pinacolate analogues **42**. Further increasing the substitution at the α-position of boron with methyl, *e.g.*, **52a**, greatly increased the yield of product **54** (Scheme 12A *vs.* Scheme 12B). This clearly means that radical **55** is much more stabilised prior to the addition of alkenes **53** (Scheme 12).[17]

Recently Renaud[18] and co-workers utilised a similar radical initiator, *i.e.*, DLP, as Zard's[15–17] group for the atom transfer radical addition (ATRA) scenario. Here ICH₂Bpin **56** and terminal alkene **57** were reacted in the presence of DLP as a radical initiator, affording 3-iodoalkyl borane **58**. Furthermore, 3-iodoalkyl borane **58** was treated with a nucleophile (TBAF), leading to the cyclopropane product **59** with moderate to good yields (38–77%). In this reaction, various substituted terminal alkenes were tolerated well under these reaction conditions and the corresponding cyclopropanes **59a–59d** were obtained (Scheme 13). Mechanistically, first, radical **60** is generated and then added *via* the ATRA step to alkene **57**, which leads to **58**, followed by the Lewis

Scheme 13 Cyclopropanation *via* ATRA and its mechanism.

Scheme 14 Iron catalysed radical-based Markovnikov alkene hydro-functionalisation.

base-mediated intramolecular 1,3-elimination of **62** to finally afford the cyclopropanation product **59**.[18]

2.1.4 Boryl radicals generated by involving metal-mediated reactions. In 2017, Baran[19] and co-workers developed an attractive radical-based Markovnikov olefin hydrofunctionalisation (Scheme 14). In this method, the boron-based alkene (**63**), under the conditions of Fe(acac)$_3$ and PhSiH$_3$ as the hydrogen source, reacts with electron-deficient olefins **63′** (Michael acceptors), affording the desired additional product **64** with good yields *via* an α-boryl radical intermediate **65**. Here 1,1-disubstituted boroalkenes successfully reacted with α,β-unsaturated esters and Weinreb amides, yielding the products **64a–c** with good yields. Olefins containing a boron-based functionality such as pinacol boronic esters **63**, 1,8-diaminonaphthalene boronamides (MIDA), and *N*-methyliminodiacetic acid esters were tolerated well as competent coupling partners (Scheme 14).[19]

Based on mechanistic investigations, they proposed the mechanism as depicted in Scheme 15. The first step of the reaction mechanism involves the formation of a bridged dimeric Fe complex **66** on the solvolysis of Fe(acac)$_3$ with ethanol. This bridged complex reacts with PhSi(OEt)H$_2$, which was generated from PhSiH$_3$ upon reaction with Fe(II) species, yielding a hydride-bridged iron complex **67**. This hydride-bridged complex forms an active species L$_2$Fe(III)H. L$_2$Fe(III)H then reacts with olefin **63**, which forms tertiary radical **65** *via* hydrofunctionalisation. Furthermore, the radical species **65** was added to the Michael acceptor, followed by reduction with Fe(II) and finally, upon protonation, yielded the desired product **64**.[19]

In 2019, the Yorimitsu group[20] reported the transition-metal-free diborylation of alkynes as an efficient approach for preparing 1,2-diborylated alkanes **71** or alkenes **72**. The reaction was proposed to proceed *via* the 1,2-diboryl-1,2-dimetalloalkane
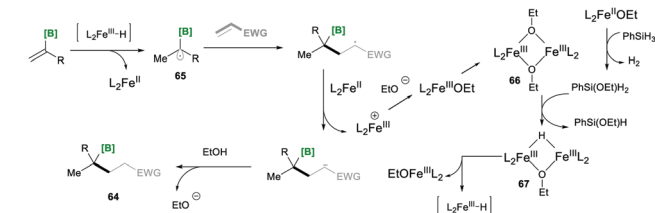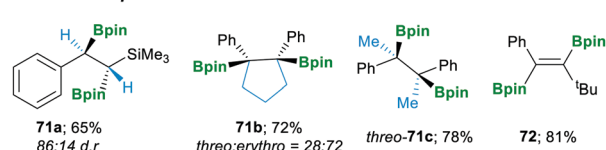

Scheme 15 Proposed mechanism for the iron-catalysed radical-based Markovnikov alkene hydrofunctionalisation.

Scheme 16 Transition-metal-free diborative reduction of alkynes' direct access to vicinal-bisboronate esters.

intermediates **69–70**. First, a single-electron reduction of the alkyne **68** generated radical anion **73**, which readily attacked B$_2$pin$_2$, affording a borate intermediate. This borate intermediate followed an inter-metallate rearrangement (a cross-over experiment suggested that this step yielded a mixture of inter- and intra-products if there is a B$_2$nep$_2$ and B$_2$pin$_2$ mixture); an attack took place on the sterically less hindered carbon, which furnished the intermediate **69**. This again takes a single electron, finally forming dianion **70**, which in the presence of an electrophile afforded 1,2-diborylated alkanes **71**. Alternatively, treatment with oxidant lithium iodide yielded 1,2-diborylated alkene **72** with *E*-isomer as the major product. Consequently, using the aforementioned method, they prepared a variety of 1,2-diborylated alkanes **71a–c** in good yield and with moderate diastereoselectivity (Scheme 16).[20]

2.2 Visible light-mediated reactions for the formation of α-boryl radicals

These visible light-mediated reactions, in general, include two types: radical-induced 1,2-migrations and radical addition to vinyl boronic esters, vinyl boronate esters, and boronate complexes.

2.2.1 Radical-induced 1,2-migrations. In 2017, Aggarwal[21] and co-workers reported an elegant tactic for photochemical alkylation of vinyl boronate ester complexes **74**. The last fifty years has been witness to the 1,2-metalate rearrangement, which has been well documented in the literature. However, this would be the first report in which the photoredox reaction was combined with 1,2-metalate rearrangement (Scheme 17). The proposed reaction mechanism involves the irradiation of

Scheme 17 Visible light-mediated alkylation of vinyl-boronates *via* the 1,2-migratory rearrangement.

Scheme 18 Radical-induced enantiospecific three-component alkylation reactions on indoles and furans.

iodoacetophenone **75** with visible light, leading to the homolytic dissociation of the carbon–iodine bond, which further attacks the vinyl boronate **74**, generating the α-boronate radical **77** intermediate. Furthermore, single-electron transfer to alkyl iodide by an electron-rich α-boronate radical continues the catalytic cycle and furnishes the α-boronate carbocation **79**, which then spontaneously follows the 1,2-metalate rearrangement to afford the desired product **78** (Scheme 17). This method offers a wide substrate scope, with high atom economy, and three-component coupling, affording two new C–C bond-forming events in a single step.[21]

Similarly, in 2018, the same group developed an enantiospecific three-component alkylation reaction on indoles **80** and furan **81′** following the boronate complex photoredox strategy.[22] This method was found to be highly efficient; it allowed introducing a diverse class of functional groups in the final products **86–86′**. The mechanism pathway is followed by the reaction described in Scheme 18; first, the photocatalyst Ru(II) undergoes irradiation with visible light to generate an excited Ru(II)-catalyst, which becomes reduced by electron-rich sacrificial boronate complex **87** (this was observed in the reaction mixture **85**) *via* a single electron transfer (SET) step.

This electron-rich, reduced Ru(I)-catalyst breaks the C–I bond by the SET pathway, resulting in an electrophilic radical **83**, and recycles the Ru(II) photocatalyst back to complete the catalytic cycle. Radical **83** attacks electron-rich furyl boronate **87**, leading to an α-boronate radical **84**. This α-boronate radical **84** undergoes SET reaction which yields the zwitterionic species **83**, which undergoes a 1,2-metallate rearrangement to furnish a boronic ester **82**. Oxidative re-aromatisation in the presence of molecular iodine and K_2CO_3 finally affords the desired 2,5-disubstituted furans **86** (Scheme 18). The reaction was found to be highly efficient and affords the product in good yield and with a high enantiomeric ratio (in **86b–86′b**).[22]

Very recently, Shi[23] and co-workers reported an unprecedented approach for synthesising *gem*-Bis(boryl)alkanes[5b–f] **90**. In this protocol they generated an alkenyl diboronate intermediate **89**, starting from alkenyl Grignard reagents **88**, which are added to bis(pinacolato)diboron (B_2pin_2), which then under visible-light photoredox catalytic conditions reacts with a wide range of alkyl halide **91**, resulting in a wide range of highly substituted *gem*-diboryl alkanes **90** in moderate to good yield (Scheme 19).

Under the aforementioned reaction conditions, even a complex structure was attractively tolerated (**90a–d**, **90g**); the reaction condition was found to be very mild and tolerated a wide range of functional groups (**90e–f**) (Scheme 19). After a detailed mechanistic study and more than one quantum yield (experimentally found to be $\Phi = 49.8$), it was found that the reaction followed a radical chain pathway. Vinyl Grignard **88** was added in the first step to electrophilic bis(pinacolato)-diboron (B_2pin_2), leading to intermediate **89**. This electron-rich sacrificial bis-boronate intermediate **89** transferred a single-electron to excited Ru(II)-catalyst (Ru*(bpy)$_2^{2+}$), generating a reduced Ru(I)-complex. Then the reduced Ru(I)-complex followed a single electron transfer with alkyl halide **91**, generating a carbonyl stabilised electrophilic-radical **93** and regenerated the active Ru(bpy)$_2^{2+}$ catalyst. The highly reactive radical **93** attacked the electron-rich boronate complex **89**, leading to an electron-rich α-bisboryl radical **92**. This α-bisboryl radical **92** afforded a single electron to the alkyl halide, leading to α-bisboryl carbocation **94**, which then followed a spontaneous 1,2-boryl migration, furnishing the desired *gem*-bis(boryl)alkane product **90**. The alkyl radical that formed in the previous catalytic step propagated a chain reaction, leading to very high quantum yield ($\Phi = 49.8$) from the reaction (Scheme 19).[23]
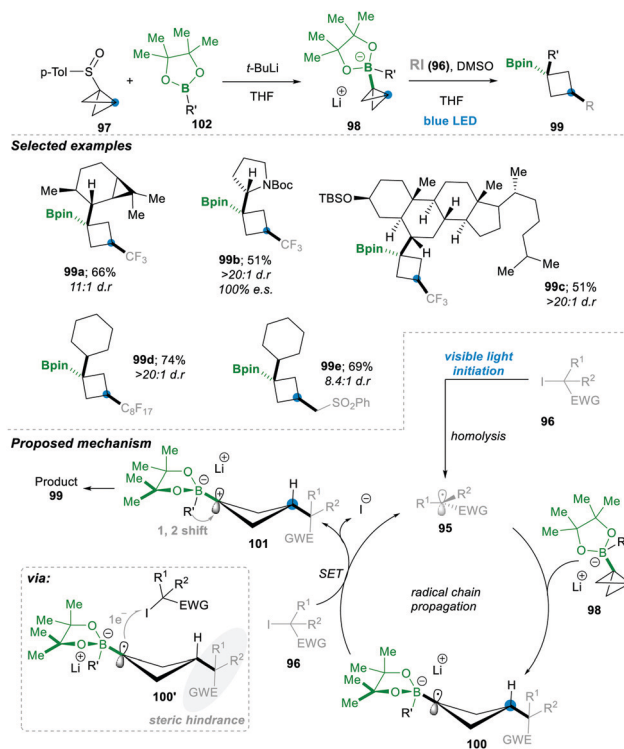
Aggarwal's[24] research group has continued to open up a new avenue by adding radical **95** to the σ-bonds of highly strained bicyclobutyl-boronate **98**, leading to a highly substituted boronic

Scheme 19 Radical-triggered 1,2-boryl-migration approach for gem-diboryl alkanes.

Scheme 20 Radical-triggered stereocontrolled approach for cyclobutyl boronic ester synthesis.

ester containing cyclobutyl motif **99** in a very efficient manner (Scheme 20). *In situ*, compound **97**, along with **102**, generates the bicyclobutyl-boronate complex **98**, upon addition of the electrophilic radical **95** (generated from alkyl halides **96**), leading to 1,3-alkylated cyclobutyl boronic esters **99** in a very good yield and with complete stereospecificity. Since boronate esters are electron rich, nucleophilic radicals (generated from electronically rich alkyl halides), they were ineffective as expected. The mechanism includes as a first step an electrophilic radical **95** generated photochemically from alkyl iodides **96**. This attacked the σ-bond of a highly strained bicyclobutane-boronate complex **98**, which yielded an electron-rich cyclobutane boronate radical **100**. The thus formed cyclobutane radical **100** followed SET with alkyl iodide **96**, leading to cyclobutane-boronate carbocation **101**. This zwitterionic intermediate prefers to undergo an energetically favoured 1,2-metalate alkyl migration, affording the desired 1,3-disubstituted cyclobutyl boronic esters **99** with excellent stereoselectivity. The reaction condition was mild, with a wide substrate and functional group range; even natural compounds with complex structures worked smoothly and afforded the desired product **99c** in a moderate yield of 51% and with very high dr > 20 : 1. The stereoselectivity is thought to come from the

single-electron transferring step (**100** to **101**), since the cyclobutane boronate radical **100** has a rigid four-membered ring and alkyl iodide needs to approach it from the less hindered side; the hindrance is caused by the 3-position group of cyclobutane (see **100′** in the shaded portion of the box of Scheme 20). For the same reason, the following step of 1,2-metalate alkyl migration goes from the opposite lobe of the p-orbital (see **101**). This 1,2-metalate rearrangement step is much faster than the C–B bond rotation in cyclobutane boronate carbocation **101**; consequently, only the *cis*-cyclobutane product was formed during the course of the reaction (Scheme 20).[24]

Very recently, Studer[25a] and co-workers reported smart initiation by a visible light mediated reaction leading to the α-C–H bond functionalisation of boronate complex **105**, which is obtained from the addition of alkyl lithium **104** to boronic esters **103**, followed by 1,2-migration, yielding the α-functionalised boron compounds **106** (Scheme 21).[25a]

In this reaction, in the presence of iridium as a photocatalyst, trifluoromethyl radical **109** forms, which then undergoes the regeoselective abstraction of an α-C–H proton of boronate complex **105**, forming α-radical anion **107**. This α-radical anion **107** in the presence of oxidant CF₃I results in the zwitter-ion **108**, followed by 1,2-migration, yielding α-aryl/alkylated functionalised boron compounds **106**. This method works well with various aryl and alky boronic esters, with acceptable yields. Of note, this method forms products **106c–d** with retention of enantioselectivity and high diastereoselectivity *via* stereospecific migration (Scheme 21).[25b]

2.2.2 Photoredox catalysis for radical addition to vinyl boronate esters. Visible light-mediated radical addition to vinyl

Scheme 21 H-atom transfer induced the α-functionalisation of borates and its mechanism.
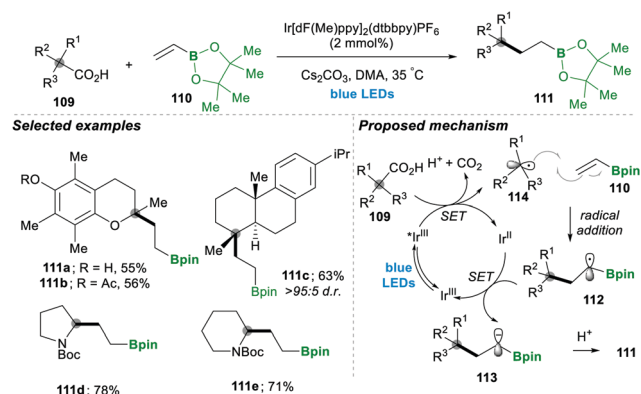
Scheme 22 Visible light-mediated decarboxylative strategy: direct access to alkyl boronic esters.

Scheme 23 Visible light-mediated decarboxylative strategy: radical addition and polar cyclisation cascade.

boronic esters was elegantly demonstrated by Aggarwal *et al.*[26] In their report, they started with readily commercially available carboxylic acid **109**, which upon decarboxylation and followed by single-electron transfer generated a carbon-centred radical **114**, which was then added to vinyl boronic esters **110**. The proposed mechanism, is described in Scheme 22, involving in its first step the photoexcited Ir(III)-catalyst, takes a single electron from a carboxyl radical and a reduced Ir(II)-catalyst, which decarboxylates, leading to an alkyl radical **114**. The conjugate addition of alkyl radical **114** to vinyl boronic ester **110** resulted in a stabilised intermediate α-boryl ester radical (**112**), which then follows a single electron transfer with reduced photocatalyst Ir(II) to afford α-boryl ester anion **113**, regenerating the active Ir(III)-catalyst to continue the catalytic cycle. In the final step, the protonation of α-boryl ester anion **113** affords the desired product **111** in moderate to good yield. The aforementioned strategy worked perfectly on a variety of carboxylic acid-containing natural products, *e.g.*, **111a–b** starting from Trolox, and **111c** from dehydroabietic acid. This method provides a general approach to produce γ-amino boronic esters **111d–e** (Scheme 22).[26]

Analogously, the same research group reported on a decarboxylative radical addition and a polar cyclisation cascade for

constructing a C–C bond to obtain the functionalised cyclopropanes by photoredox catalysis (Scheme 23), in which primarily used proline **115**-based nucleophiles, which reacted with chloroalkylalkenes **116/117** in the presence of photoredox catalyst (4CzIPN) and caesium carbonate as a base, yielded the highly functionalised cyclopropanes **118/119** with good yields (Scheme 3A).[27] Furthermore, they tested different carboxylic acids under the same reaction conditions, which provided a wide range of functionalised cyclopropanes **119a–d** (Scheme 23C). Even more complex carboxylic acids also reacted well under this condition, *e.g.*, **119c**. The generality of the ring cyclisation can also be extended to five-membered rings.[27] The mechanistic studies of this transformation primarily show a photocatalyst under visible light irradiation that generates the excited state catalyst, which further oxidises the carboxylic acid to a radical upon the extrusion of carbon dioxide. Later this alkyl radical **120** is added to chloroalkylalkene, which forms the boron-stabilised radical intermediate **121**, which is then reduced by the oxidized photocatalyst forming stabilised carbanion **122**. Finally, 3-*exo*-*tert* cyclisation provides highly functionalised cyclopropanes **119** (Scheme 23B).[27]

2.3 Miscellaneous reactions of the three-component strategy

Reactions that did not fit into the above categories have been discussed here and are listed below.

Scheme 24 Radical-induced three-component alkylation reactions of alkenylboronates.

Scheme 25 Radical-induced multi-component coupling of boronic esters and furans.

2.3.1 Transition-metal free three-component reaction. In 2017, the Studer group exploited the radical acceptor properties of boron-substituted alkene **123**.[28] First, the electronically rich in nature vinylboronate complex **124** was generated *in situ*, followed by the addition of an electrophilic carbon-centred radical **126**, which led to a radical anion intermediate **125**. The thus generated intermediate followed a 1,2-alkyl/aryl metallate-rearrangement, resulting in 2° and 3° alkyl boronic esters **129** (Scheme 24).

This can take place by two possible pathways: the radical anion intermediate **125** can further undergo either outer sphere electron transfer (electron-catalysis, pathway 1) or inner sphere electron transfer (atom transfer addition, pathway 2). In the case of electron-catalysis, a single electron transfer from the radical anion intermediate **125** to an alkyl halide takes place, which yielded zwitterionic species **127** and regenerated perfluroralkyl radical **126**. The previously formed zwitterionic intermediate **127** followed a spontaneous 1,2-metallate rearrangement and afforded the desired boronic esters **129**. The second path, atom transfer addition, follows an iodide abstraction by a vinylboronate radical anion intermediate **125**, leading to an α-haloboronate intermediate **128**, which further follows a 1,2-alkyl migration (assisted by counter cation Li$^+$) and yields the expected product **129**. To understand the proposed mechanism, Togni's reagent (CF$_3$ source, it cannot follow the iodine transfer pathway) was also tested and the reaction worked perfectly; this result supported the likelihood of pathway 1. However, an electron-poor alkyl halide afforded the product; therefore, pathway 2 is also possible. Accordingly, the reaction mechanism could depend on the kinetic ability of an alkyl radical, depending on whether reduction or iodine atom transfer is faster (Scheme 24).[28]

In the same year, Aggarwal[29] and co-workers reported on the trifluoromethyl radical-induced multi-component approach for 2,5-disubstituted furans **134** with good yields and excellent enantiospecificity (Scheme 25). This reaction worked *via* generating the boronate complex **135** from furan-2-yllithium **131**, which initiates single-electron transfer, leading to electrophilic

trifluoromethyl-radical **138** (initiation step). This highly reactive, electrophilic CF$_3$-radical **138** adds to an electron-rich boronate complex **135**, which leads to intermediate **136** *via* a radical addition step. Intermediate α-boryl radical **136** then undergoes oxidation with Umemoto's reagent A, affording a highly reactive oxonium intermediate **137**, which then follows the 1,2-metallate rearrangement to furnish boronic ester **134**. Iodine and K$_2$CO$_3$ facilitate oxidative re-aromatisation, finally affording the desired 2,5-disubstituted furans **134** in good yield (Scheme 25).[29]

Similarly to the previous case of Studer, in 2018 Renaud and co-workers showed the three-component alkylation reaction of alkenylboronic esters **140**, α-halocarbonyl and organolithium (Scheme 26). The reaction was found to be highly efficient and worked on a wide range of halides and organolithium reagents.[25a] This operationally simple method offered two C–C bond formations, along with the generation of a quaternary-carbon centre (α- to boronic esters, **146**) in a single step. Three possible competing reaction pathways were proposed: in pathway 1, radical-**142** reacts with R–X *via* atom transfer, leading to α-haloboronate **143**, which further follows a 1,2-metalate-rearrangement to

Scheme 26 Radical-induced three-component alkylation reactions of alkenylboronates.

forge **146**. In pathway 2, single-electron-transfer by intermediate **142** provides an inverse-boron ylide **144** and a reduced halide, the former of which undergoes a fast intramolecular 1,2-migration, leading to **146**. In the last possible pathway 3, **142** undergoes a radical 1,2-migration, resulting in boron-centred radical anion **145**, which in fact is an initial step for a chain reaction.

However, investigations and a controlled study of the mechanism and additional literature supported by Studer and Aggarwal (see Schemes 20 and 24 for details) revealed that pathway 2 (the inverse ylide mechanism) was most likely to explain the three-component alkylation reactions of alkenyl-boronates better than the two others shown in Scheme 26.[25a]

2.3.2 Ni-catalysed cross-coupling of three-component reaction. A work by Lovinger and Morken,[30] in 2017, resulted in the catalytic enantioselective, electrophilic coupling of vinyl boronate **147** (Scheme 27). Using the Ni-Pybox complex, they explored substrate-controlled stereoselectivity; the reaction was observed to work on both primary and secondary electrophiles. The reaction is thought to result in three mechanistic scenarios: first, in the presence of Ni-catalyst, the C–Br bond of **149** dissociates, leading to carbon-centred radical **155** and nickel complex **151**. Path b, suggested by Studer and Aggarwal independently, coupled with vinyl boronate complex **147** affords an α-boronate radical **153**. This electronically rich radical undergoes a single-electron transfer with an organic-halide, regenerating a carbon-centred radical **155** and α-boronate carbocation **154**. This α-boronate carbocation **154**, as described in Scheme 27, undergoes 1,2-metalate rearrangement to afford the racemic product **148**. However, in order to explain the enantioselectivity of the reaction, carbon-centred radical **155** is generated from the C–Br bond, combined with nickel complex **151**. This leads to intermediate

152, which consequently follows a stereoselective metal-induced migration to forge intermediate **150**, and finally **150** undergoes reductive elimination to yield **148**. Another path suggested by Fu and co-workers is Path a; here the carbon-centred radical **155** engages with vinyl boronate complex **147**, leading to α-boronate radical **153**, which recombines with nickel complex **151**, affording intermediate α-boronate Ni-complex **156**. Of note, using a chiral ligand in the reaction, intermediate **156** undergoes a facile reductive elimination, which leads to a non-racemic product **148**.[30]

To better understand the exact path followed by the reaction, which depends on the nature of the radical formed during the first step, the substrate is completely controlled. The electrophilic radical followed the Studer–Aggarwal cycle. It attacks the electron-rich vinyl boronate complex in a much faster step, following a radical chain reaction. In the case of a non-stabilised carbon radical, formed in the first step, it follows the Fu-type cycle. A detailed mechanistic investigation suggested that it follows the conjunctive coupling path, affording the β-boronate Ni-complex, which follows a two-electron reductive elimination pathway to afford a stereospecific product (Scheme 27).[30]

In a subsequent work of 2019, a neutral boron-based enantioselective three-component approach was reported by the same research group.[31] In this report, 10 mol% of Ni(II)-catalyst and 13 mol% of chiral diamine ligand (L) mixed with organozinc reagent **157**, alkyl halide **158** and neutral organoboron **159** afforded the desired product **160** in moderate yield and with high enantio and diastereoselectivity. A series of mechanistic experiments suggested that a reaction following a radical pathway experiment, e.g., in the presence of a TEMPO reaction did not afford product **160**. The proposed catalytic pathway includes in the first step the homolytic cleavage of the C–I bond (in **158**), which takes place in the presence of the Ni(I)–R complex **163**, leading to carbon-centred radical **161** and Ni(II)-complex (**164**). The formed carbon-centred radical **161**, when added to alkenyl-pinacole boron ester **159**, yields a more stable α-boryl radical **162**, which when combined with Ni(II)-complex **164** by single-electron oxidation, affords intermediate
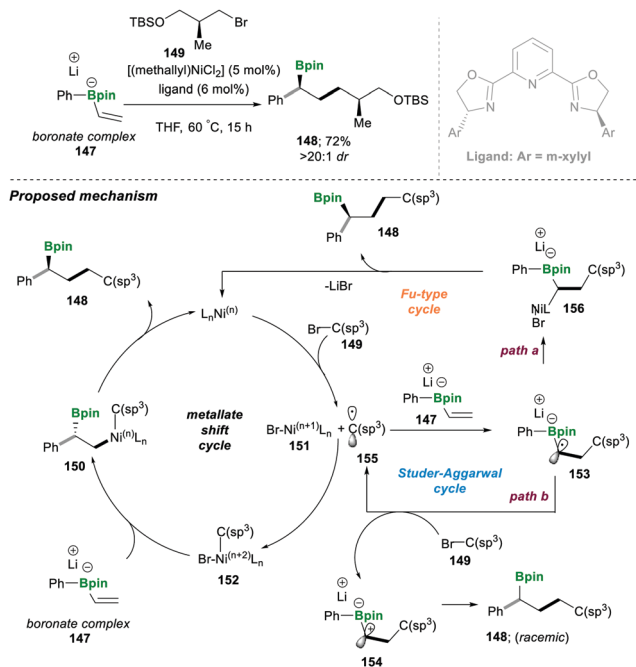
Scheme 27 Ni-catalysed radical-induced enantioselective conjunctive cross-coupling.
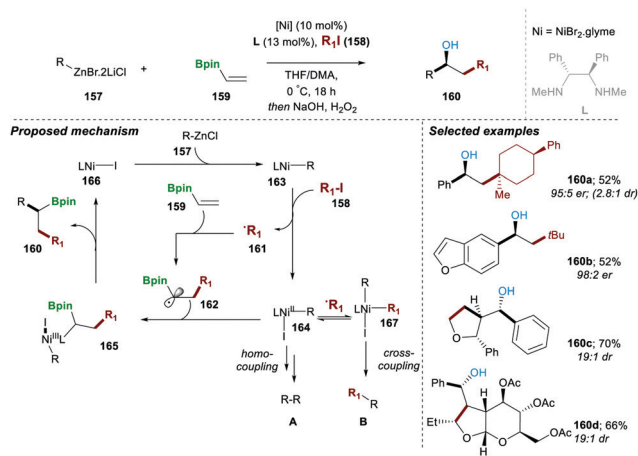
Scheme 28 Ni-catalysed radical-induced enantioselective multi-component cross-coupling.

Ni(III) **165**. This advanced intermediate **165** undergoes a facile reductive elimination step, regenerating active Ni(I)-iodide **166** catalyst, along with the desired product **160**. It worth mentioning that in the absence of vinylBpin **159** the homo and cross-coupling products A and B were also observed, following a similar mechanism. This method was found to be highly general and worked with a wide range of substrate scopes with functional group tolerance. In all the cases, desired products were obtained in good yield and with very high er and dr (Scheme 28).[31]

3. Conclusions and outlook

For more than a century, organoboron chemistry has offered novel routes towards fabricating synthetically highly valuable compounds. For example, organoborons are widely used in constructing C–C/C–heteroatom bonds by activating the C–B bond. Additionally, they can be involved in radical chemistry. Their radical strategies complement the existing approaches for the formation of new bonds. This radical approach generally relies on the cleavage of the C–B bond to create alkyl/aryl radicals. Thanks to this radical approach, new bond formation can be achieved; however, the product will lose the boron moiety. By overcoming this main limitation, of losing the boron group by radical transformation, a new reactivity in the field of organoboron chemistry can be designed. In recent years, organoboron radical chemistry has elegantly opened up new pathways without losing the valuable boron moiety; this includes the growing field of α-boryl carbon-centred radical intermediates, *e.g.*, **II**, which were developed by many research groups.

In this review, we wish to emphasise the importance of radical **II** generation from organoborons, leading to (a stable and) synthetically useful α-boron carbon-centred radical intermediate **II**, which is further followed by forged new connections. For its generation we chiefly focused on a few main strategies: (1) using radical initiators: in this strategy, the formation of α-boryl radicals was mainly promoted by radical initiators such as the B(alkyl)₃/bromine system, AIBN (with stannates or TTMSS), and DLP, (2) visible-light mediated reactions including the photoredox catalysis *via* SET reactions, (3) three-component coupling reactions, (4) metal and metal-free mediated reactions, and (5) radical addition to vinyl boronic esters, vinyl boronate esters, and boron ate complexes.

As highlighted in this review, **II**'s unique stability and reactivity have been discussed in depth, many challenging transformations have been accomplished, and a good mechanistic understanding of these processes has been acquired over the last ten years.

Owing to the potential for the synthesis of α-boron carbon-centred radical species **II**, this field will continue to grow rapidly, and more appealing transformations are expected to appear in the years to come.

Future approaches to expand the synthetic utility of these α-boryl carbon-centred radical intermediates can be through

the generation of more stabilized radical analogues, such as 1,1-diboryl-radical and the 1,1-borylsilyl-radical. Such studies are already ongoing in our research group.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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