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Transition-metal-free B-B and B-interelement reactions with organic molecules.

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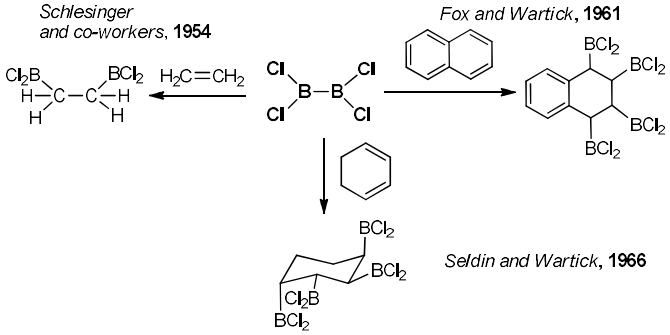
This review is a guided tour along the activation modes and reactivity of B-B, B-Si, B-N, B-S, B-Se and B-P reagents, in the absence of any transition metal complex. Here are disclosed the general concepts related to the homolytic and heterolytic cleavage of the B-B and B-interelement bonds, as well as the generation of the new C-B and C-interelement bonds, in a selective way. The greener consequences of those novel routes facilitate the gram scale preparations of target functionalised organic compounds. Intrinsic data about the suggested mechanisms and spectroscopic evidences that support the innovative theories, are provided along the review. Since this is a stimulating area of work that has emerged within the last decade, this overview serves as the basis to understand the new trends and hopefully to generate inspiration for future discoveries in the field.

1.Introduction

Diboron(4) compounds represent a kind of bifunctional Lewis acids, that interact with Lewis bases to generate Lewis acid-base adducts with or without B-B cleavage. Original studies demonstrated that trimethylamine can easily coordinate to diboron tetrachloride forming a stable tetramer of molecular formula $[B_2Cl_4{\cdot}N(CH_3)_3]_4$.[1a] With the same criteria, one of the non-bonding electron pair of tetramethyldiphosphine was added to diboron tetrachloride to form $[B_2Cl_4{\cdot}P_2(CH_3)_4]$.[1b] The diboron reagents, depending on the nature of the B substituents become avid electron acceptors in B-B reagents and B-interelement systems, although their activation and reactivity has been mainly related to transition-metal assisted reactions.[2] Their reactivity with organic compounds becomes an important source of functionality and the convenient approaches towards transition metal-free selective B-addition reactions, reopen a straightforward synthetic opportunity to generate C-B and C-interelement bonds in a selective and economic way.

2.Transition-metal-free B-B addition to organic molecules

Originally, diboron tetrachloride was added to ethylene in a typical reaction mixture of 6.6 moles of diboron tetrachloride and 10.36 moles of ethylene (both measured as gases) for 4 hours at -80 °C. The product was quantitatively formed and characterised as $Cl_2BC_2H_4BCl_2$, representing the first addition of a borane reagent to an alkene (Scheme 1).[3] A larger range of unsaturated substrates, such as propene, cyclopropene, 2-butene, acetylene, butadiene, allyl halides and 4-chloro-1-butene, were next explored to react with diboron tetrachloride.[4] One mole of acetylene added only one mole of diboron tetrachloride to form $Cl_2BC_2H_2BCl_2$,[5] while one mole of butadiene could, on the other hand, add either one or two moles of diboron tetrachloride. Benzene and ferrocene also reacted with diboron tetrachloride providing the substitution product phenyldichloroborane[6] and ferrocenylichloroborane[7] respectively, while naphthalene promoted the double addition (Scheme 1).[6] An excess of diboron tetrachloride reacted with the conjugated 1,3-cyclohexadiene to simultaneously add the diboron in *cis* addition, giving the first evidences by NMR about the stereoselectivity on the organoboron addition to unsaturated bonds (Scheme 1).[8] The corresponding products were never fully characterised due to the difficulty to be isolated and the authors described them as “adducts”.



Scheme 1 Direct addition of B_2Cl_4 to alkenes and arenes.

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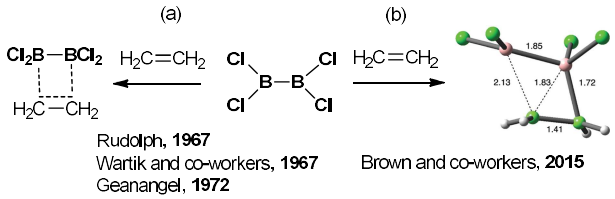
Diboron tetrachloride was initially considered as a π acid system and therefore, the addition of B_2Cl_4 to olefins was thought to proceed through initial "π donation" from the unsaturated linkage to the two vacant p-type orbitals of the adjacent boron atoms forming a π complex (Scheme 2a). [7-11] Subsequent B-B fission would result in the *cis* addition of the two dichloroboryl moieties across the unsaturated bond. The favored orientation in the suggested transition state assumed a near planar configuration for B_2Cl_4, and the driving force for which is the maximum orbital overlap between the vacant p orbitals on the boron atoms and the basic site of the π orbital on the hydrocarbon. Half century later, J. M. Brown and co-workers revisited the field and found *via* DFT analysis that the four atoms involved in bond making and breaking process are close to coplanar geometry in the transition-state. However, there are two different hybridations for the two B involved, one near-tetrahedral B with advanced bonding to both carbons and the less strongly involved B closer to its original trigonal geometry (Scheme 2b).[12] The computational results also demonstrated that the stereospecific addition of B_2Cl_4 to isomeric but-2-enes is a rare concerted $[_2\sigma_s + _2\pi_s]$ process.



Scheme 2 Mechanistic approaches to the straightforward addition of B_2Cl_4 to alkenes.

Comparable reaction between diboron tetrafluoride and ethylene or butadiene only ocurred at higher temperatures.[4] A recent theoretical studies revealed that the main factor to favor the addition to cyclopentadiene of B_2Cl_4 over B_2F_4 might be due to the substantial energy differences involved in the later transition state, that exhibited longer B-B and C=C bonds as well as shorter C-B bonds (Figure 1).[12] Diboron dihalides were considered exceptional reagents for direct addition to unsaturated organic compounds, but their inherent instability became a strong drawback toward the development of the field.[13]

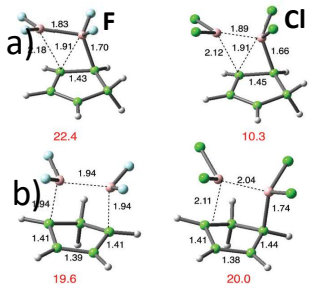


Figure 1 Transition states for a) 1,2 and b) 1,4 addition of B_2F_4 and B_2Cl_4 to cyclopentadiene. Energies in kcal.mol^{-1}

Comparatively to diboron dihalide species, the parent $B_2(NR_2)_4$ and $B_2(OR)_4$ compounds are more stable (and therefore more easy to handle) but less reactive as a consequence of the π donation from the lone pair of N and O substituents to the empty p_z boron orbital.[14,15] Their lowered reactivity laid the foundations for catalytic diboron addition *via* transition metal complexes.[16,17] The initial addition of bis(pinacolato)diboron to alkynes was developed in 1993 by Miyaura and co-workers,[18] while the first diboration of alkenes was exemplified with bis(catecholato)diboron by Marder, Baker and co-workers, in 1995.[19] The area has been growing intensively to our days leaving behind a tremendous gap on straightforward addition of diboron compounds to unsaturated organic compounds in a transition-metal-free context. This void existed until the discovery of the transition metal-free and nucleophilic catalysis of diboryl additions.[20] The first diboration in the absence of transition metal complexes was carried out by Fernández and co-workers,[21] demonstrating that a nucleophilic sp^2 carbene-type boryl moiety, formed upon interaction of tetraalkoxydiboranes and a Lewis base, methoxide, (Figure 2a) can attack non-activated C=C bonds. Computational studies identified the interaction as the overlap between the strongly polarized B-B σ bond (HOMO) and the antibonding π* orbital (LUMO) of the C=C bond (Figure 2). Conceptually, the accepted electrophilic sp^2 boron becomes nucleophilic and forces the olefin to act as an electrophile.

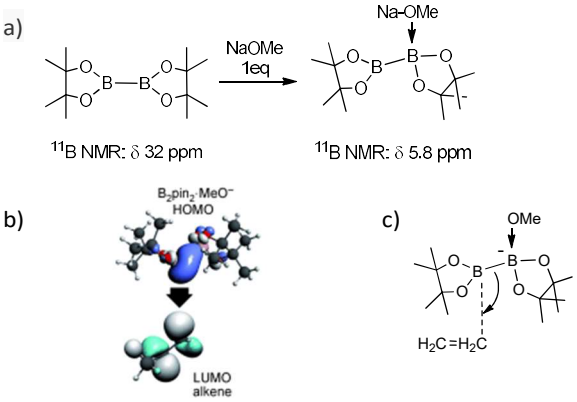
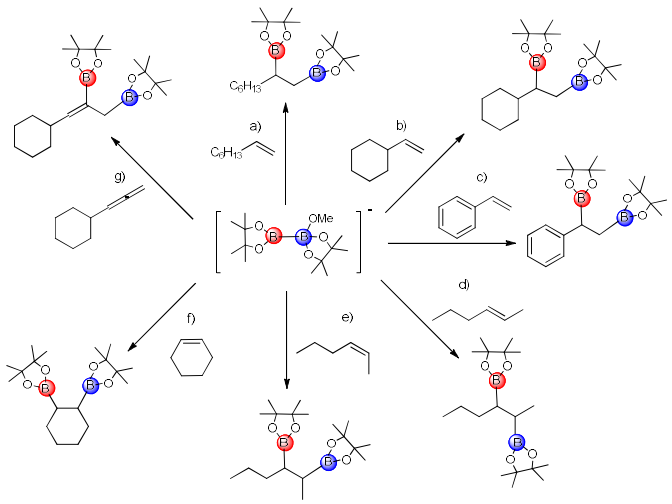


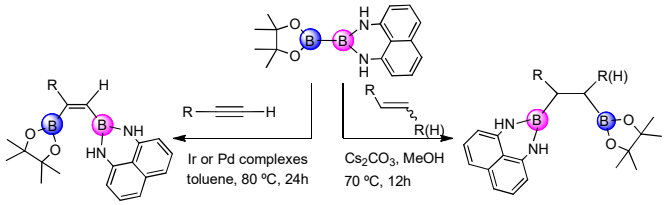
Figure 2 Diboration of alkenes by $[B_2pin_2{\cdot}OMe]^-$.

A combination of Cs_2CO_3 and MeOH provides a synthetically useful methoxide source to form "*in situ*" the corresponding acid-base Lewis adduct $[B_2pin_2{\cdot}OMe]^-$ when interact with B_2pin_2. Other bases, such as MO^{t}Bu and MOMe (M=Na, K, Li) were also suitable for the adduct formation. The diboration of non-activated olefins, such as terminal and internal alkenes, allenes and vinylarenes can efficiently performed under 70 °C during 6-12h, using THF as solvent (Scheme 3b).

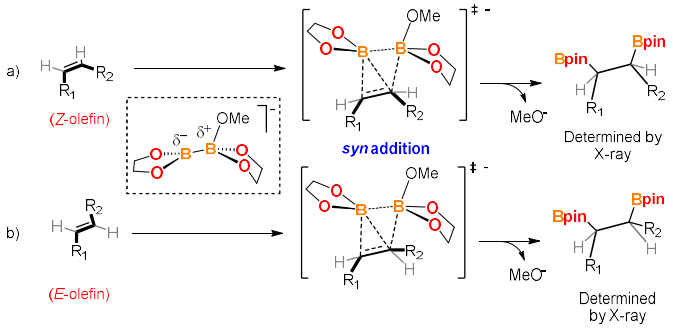


Scheme 3 Diboration of non-activated olefins with $[B_2pin_2{\cdot}OMe]^-$.

The reaction was also carried out with other symmetrical and non-symmetrical diboron reagents. When the diboron reagent was Bpin-Bdan (dan = 1,8-diaminonaphthalene), the methoxide selectively interacts with the most Lewis acidic Bpin moiety and, based on the proposed mechanism, allowed to incorporate the Bdan nucleophilic moiety at the internal C-B bond of the organodiborated product,[22] which is in contrast with the observed trend in the corresponding Pd and Ir- mediated diboration of alkynes with Bpin-Bdan, where the Bdan moiety appears in the terminal position (Scheme 4).[23] Another interesting finding is that the nucleophilic diboration of terminal allene with B_2pin_2 favours the formation of the 1,2-diborated product,[21] in contrast to most transition-metal-catalyzed diborations of allenes, which usually provide the 2,3-diborated isomers as primary products.[24] The unambiguous assignment of the configuration of aliphatic 1,2-diborated esters and the stereospecific *syn*-addition mechanism has been fully addressed from theoretical calculations[21] and empirical data throughout the crystalline sponge method used here to display the crystal structures of the oily diboronic esters formed from internal *E* and *Z* olefins, (Scheme 5).[25]

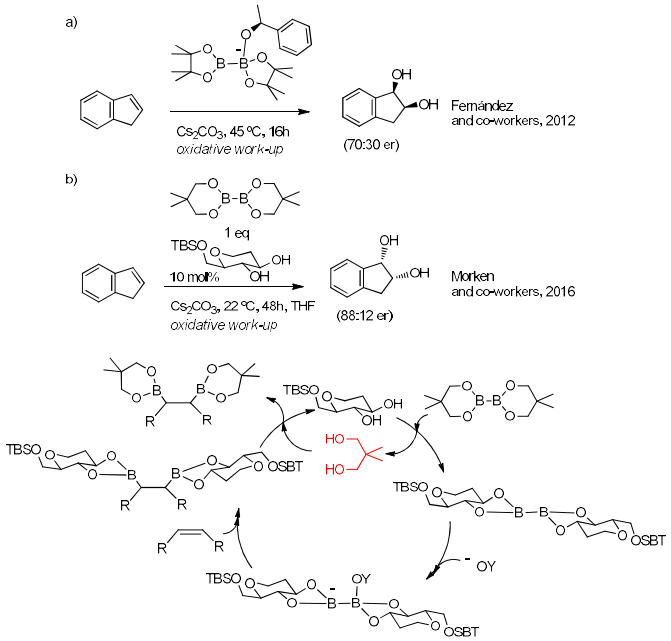


Scheme 4 Complementary regioselective diboration of non-activated olefins with $[Bpin\text{-}Bdan{\cdot}OMe]^-$ (right) *versus* Pd or Ir- mediated diboration (left).



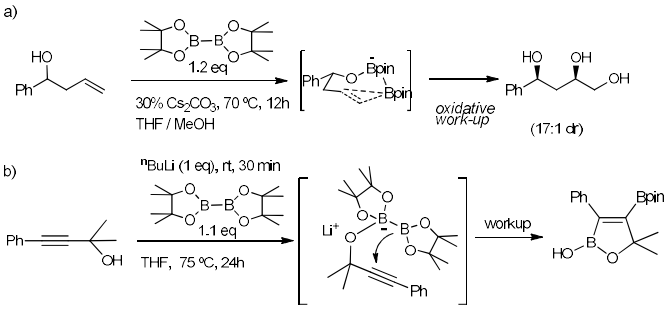
Scheme 5 Stereospecific *syn* diboration of non-activated olefins with $[B_2pin_2{\cdot}OMe]^-$.

The asymmetric 1,2-diboration of olefins has been conducted using economically accessible chiral alcohols to form the chiral Lewis acid–base $[B_2pin_2{\cdot}OR^*]^-$ adduct that is added to cyclic and non-cyclic alkenes providing moderate enantioselectivity (Scheme 6a).[26] Alternatively, the use of cyclic 1,2-diols such as the pseudoenantiomeric glycols 6-tertbutyldimethylsilyl-1,2-dihydrogrlucal (prepared through four steps from D-Glucal triacetate), allowed to efficiently induce asymmetry in the diboration of alkenes by considering that the boronic ester substituents (OR*) might be used catalytically to control the course of the base-promoted reaction. Morken and co-workers,[27] designed the diboration of alkenes with bis(neopentylglycolato)diboron reagent, which in the presence of the chiral carbohydrates favoured the boronate ester exchange (Scheme 6b). Mechanistic experiments suggest the intermediacy of 1,2-bonded diboronates in the diboration reaction.



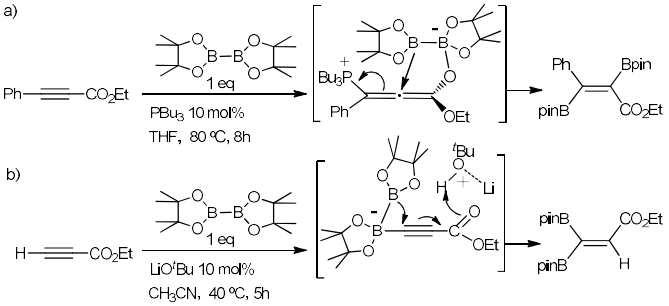
Scheme 6 Enantioselective transition-metal free diboration of olefins with chiral monoalcohols and 1,2-diols.

Directed diboration of alkenyl alcohols has also proved the usefulness of the base-mediated diboron activation in an intramolecular fashion, with the consequent assisted delivery of the boryl units to the unsaturated fragment of the substrate. In that context, the geometry required for the intramolecular activation/addition of the diboron to the alkene could be maintained alongside the adduct association, thus justifying the diastereoselective diboration of homoallylic alcohols (Scheme 7a).[28] An alternative pseudo-intramolecular reaction of diboron reagents and propargyl alcohols, through the alkoxide intramolecular activation and selective delivery of the nucleophilic boryl unit, provides access to the *trans*-diboration of alkynes in a metal-free context.[29a] This approach affords synthetically versatile and densely functionalised *anti*-4-borylated 1,2-oxaborol-2(5H)-oles (Scheme 7b), which are key structural platforms and potent pharmacophores in materials and pharmaceutical sciences. Other diboration of terminal and internal alkynes have recently pointed out the versatility of the method *via* base-catalysed or organosulfide-catalysed protocols.[29b,c]



Scheme 7 Stereoselective intramolecular transition-metal free diboration of homoallylic alcohols and propargylic alcohols.

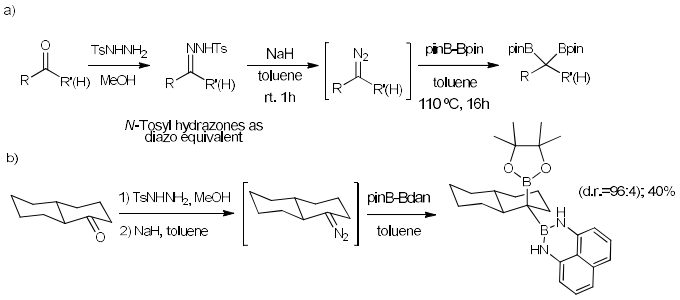
An *anti*-selective diboration of alkynoates can be efficiently performed by means of phosphine-mediated organocatalysis. Through this transformation α,β-diboryl acrylates can be accessed. The two vicinal diboryl moieties installed could be differentiated and transformed in a stepwise manner, allowing for the synthesis of a diverse array of unsymmetrical tetrasubstituted alkenes, such as the synthesis of (*Z*)-tamoxifen analogues, that represent key antiestrogenic anticancer drugs.[30] The phosphine catalysis might be initiated by the conjugate addition of PBu_3 to the alkynoate with assistance of the Lewis acidic activation of the carbonyl group to form a zwitterionic allenoate intermediate (Scheme 8a). The nucleophilic sp^2 boryl group might migrate to the *sp*-hybridised central carbon of the allene moiety to form a phosphorus ylide from where a cyclic boronate can be formed, with concomitant release of the PBu_3 associated with B-O cleavage.[30] When the substrates are terminal alkynes such as propiolates, propiolamides and 2-ethynyazoles the addition of catalytic amounts of Brönsted bases promote the synthesis of functionalised 1,1-diborylalkenes.[31] The 1,1-diboration might be initiated by deprotonation of the terminal alkyne with LiO^{t}Bu to form a lithium acetylide and ^{t}BuOH. When lithium acetylide reacts with B_2pin_2 forms an alkynyl borate intermediate, that suffers the migration of the terminal boryl moiety to the *sp*-hybridised carbon atom of the alkyne along with the protonation of the carbonyl oxygen atom to generate an allenol. The final 1,1-diborated functionalised alkene is recovered after the allenol tautomerization (Scheme 8b).[31] Lithium carbenoids have also been shown to react with B_2pin_2 to afford 1,1-diborylalkenes stereoselectively.[32]



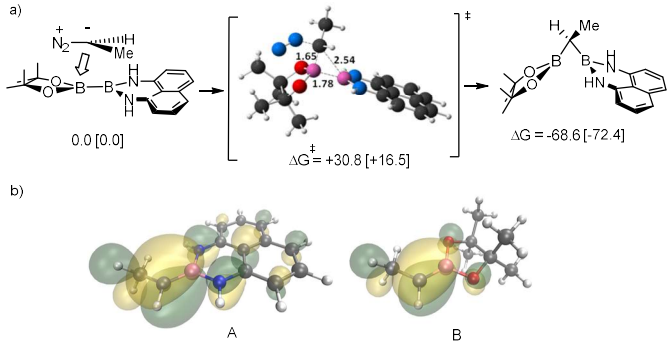
Scheme 8 Stereoselective *anti*-diboration of alkynoates and 1,1-diboration of propiolates, propiolamides and 2-ethynyazoles

Alternative methods to generate 1,1-diborated alkanes have been developed by means of Pt-catalysed diborylation of diazoalkanes with Bpin–Bpin.[33] However, more recently, a metal-free carbon insertion of diazo species, generated from thermal decomposition of *N*-tosylhydrazones, into Bpin–Bpin[34] (Scheme 9a) and Bpin–Bdan (Scheme 9b) have been reported.[35] Employing *N*-tosylhydrazones derived from aldehydes and ketones, a series of *in situ* generated diazo species could be directly diborated. Noteworthy, a marked stereoselection was achieved when employing diazo precursors possessing diastereotopic π faces. A plausible mechanistic pathway has been elucidated by DFT calculations to understand the heterolytic cleavage of Bpin–Bdan and $CH_3(H)CN_2$ as model diazoalkane. Scheme 10 summarizes the outcome of these calculations and the transition state for the formation of the two carbon–boron bonds that indicates the occurrence of a concerted, yet asynchronous mechanism with a free energy barrier of 30.8 kcal mol^{-1}. As the nucleophilic diazo carbon attacks at the electron deficient boron of the Bpin moiety, the 1,2-boron migration of the Bdan moiety occurs to yield the 1,1-diboron intermediate and concomitant release of the dinitrogen (Scheme 10a).[35] In this scenario, significant diastereoselection can be achieved due to a combination of repulsive 1,3-diaxial from substrate and 1,2-*cis* interactions with the diboron reagent. It has also been possible to establish a selective C–Bpin functionalisation from the enriched diastereoselective *gem*-diborated products, *via* alkoxide-assisted selective deborylation of Bpin *versus* Bdan (using 3eq KO^{t}Bu at 0 °C). Computational analysis of the reactivity of 1,1-diborylalkanes with alkoxides using $CH_3(H)C(Bpin)(Bdan)$ and MeO^- as model substrates indicated the formation of a stable Lewis acid–base adduct with preferential interaction of MeO^- and Bpin, followed by deborylation. The stabilization of the carbanion using the α-Bdan moiety is reflected in the HOMO orbital, which shows strong delocalization of the carbanion p-type electron density into the π-channel of the Bdan moiety (Scheme 10, A). According to NBO analysis, the alternative

carbanion using the α-Bpin fragment (Scheme 10, B) supports a less negative charge (−0.14e) than the Bdan fragment (−0.21e). Thus, selective functionalization of the Bpin position is expected.[35]

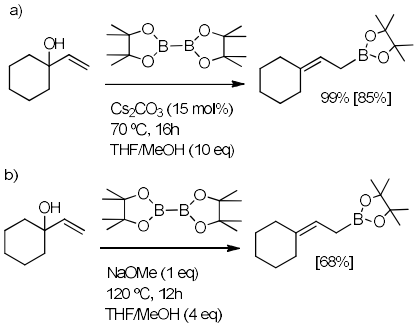


Scheme 9 Metal-free 1,1-diboration of ketones and aldehydes through tosylhydrazones / diazocompounds

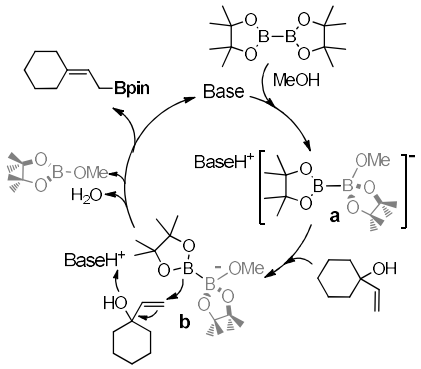


Scheme 10 a) Mechanistic proposal calculated by DFT studies for metal-free 1,1-diboration of diazocompounds with Bpin-Bdan, b) Relative stabilization of the carbanion using the α-Bdan moiety (A) and α-Bpin moiety (B)

The base-catalysed allylic borylation of tertiary allylic alcohols allows for the facile access to 1,1-disubstitued allylboronates. There are two recently reported methodologies that transform 1-vinyl-1-cyclohexanol into the corresponding cyclic allyl boronates with B_2pin_2 in a metal-free comtext. The first method uses catalytic amount of Cs_2CO_3 with MeOH that works at 70 °C, providing quantitative formation of the desired product (Scheme 11a)[36] while the second reported method used 1eq of NaOMe and works at 120 °C for moderate isolated yields (Scheme 11b).[37] The mechanistic approach suggested in both methodologies is also different and for the catalytic procedure in presence of Cs_2CO_3 as base, it has been suggested a S_N2'-type process where the initial step is a base-mediated nucleophilic attack by the methoxy group, formed "in situ" from MeOH and base, to one of the Bpin unit of B_2pin_2 to give the corresponding adduct.[36] The nucleophilic B (sp^2) might attack the terminal position of the allylic alcohol which leads to C-OH bond cleavage (Scheme 12). The addition of MeOH and base is a prerequisite for the formation of adduct, since in their absence no product is observed. The tolerance of other functional groups was also studied and it can be illustrated in Figure 3. The second reported methodology suggests an alkoxide-mediated diborylation of alkenes followed by a boron-Wittig elimination resulting in the formation of allylic boronates (Scheme 13).[37]



Scheme 11 Metal-free borylation of allylic alcohols



Scheme 12 Mechanistic proposal for metal-free borylation of allylic alcohols in reference 35

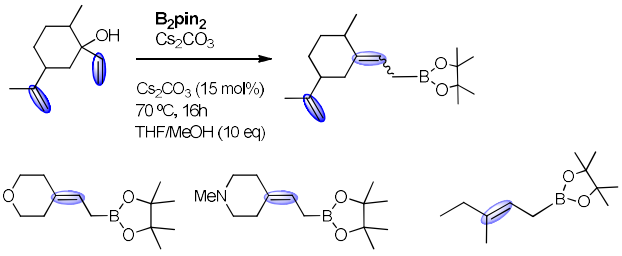
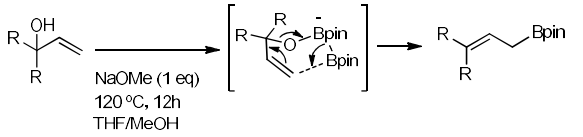


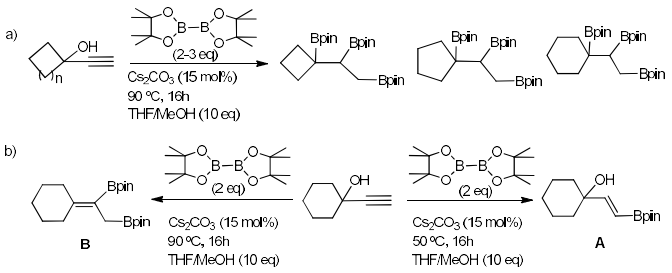
Figure 3 Transition-metal-free borylation of polyfunctional substituted cyclohexyl allylic alcohols



Scheme 13 Mechanistic proposal for metal-free borylation of allylic alcohols in reference 36

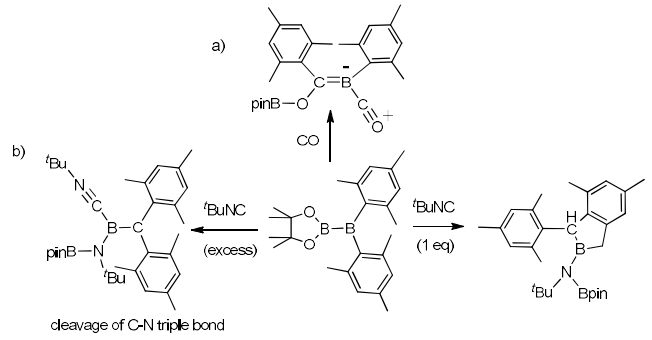
The unexpected tandem performance of the Lewis acid–base adduct, $[HBase]^+[MeOB_2pin_2]^-$, formed from Cs_2CO_3 with MeOH and B_2pin_2, favoured the formation of 1,2,3-triborylated species from the tertiary allylic alcohols, working at 90 °C , with an excess of diboron reagent (Scheme 14a).[36] To complement this

study, it has been carried out the metal-free allylic borylation of 1-propargylic cyclohexanols, to produce the corresponding product with the hydroborated triple bond working at 50 °C (**A**), however, the cyclic alkenyl borane (**B**) is possibly formed as a consequence of the borylation of the intermediate allene (Scheme 14b).



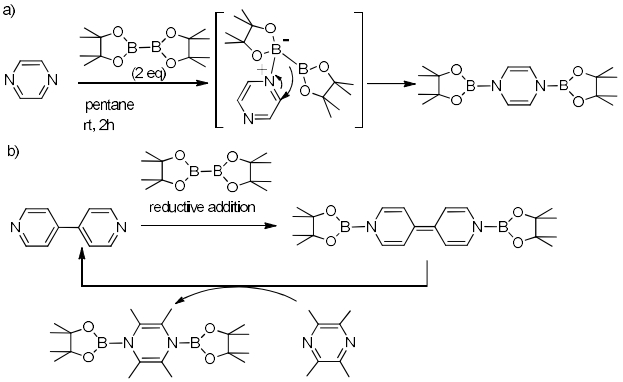
Scheme 14 Metal-free borylation of allylic alcohols toward polyborylated compounds and borylation of propargylic alcohols

Unsymmetrical diborane(4) compounds can react with carbon monoxide and *tert*-butyl isonitrile at room temperature. In fact a benzene solution of Bpin-BMes reacts with CO to incorporate two molecules of CO into the diboron structure (Scheme 15 a) with the corresponding B-B cleavage and the Mes fragment migration.[38] In the case that an excess of the isonitrile reagent is used, two molecules of ^{t}BuNC are incorporated and, in one of them, the carbon–nitrogen triple bond can be completely cleaved in the absence of transition-metal complexes. In the same study it was possible to observe the reactivity of Bpin-BMes with 1 eq of *tert*-butyl isonitrile to provide a cyclic product where a new C-B bond is created (Scheme 15 b).[38] That extraordinary reactivity seems to be related with the high electron afinity of pinB-$BMes_2$ with either CO or isonitriles.[39]



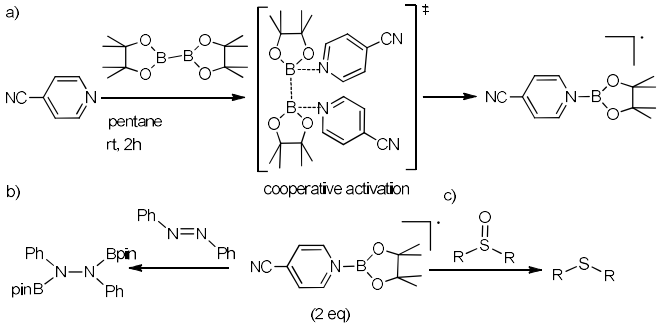
Scheme 15 Metal-free reaction of unsymmetrical diborane(4) compound with carbon monoxide and tert-butyl isonitrile at room temperature.

The reaction of pyrazine type substrates with B_2pin_2, can also promote the B-B cleavage and provide the 1,4-addition of the boryl units on the N atoms. The reaction occurs at room temperature, without the aid of any transition-metal complex.[40] Thus, pyrazine can be easily transformed into *N,N*'-diboryl-1,4-dihydropyrazine (Scheme 16a) and the mechanism suggested is based on the coordination of one of the N atoms of pyrazine to the Bpin to form a four coordinate boron intermediate, making the vicinal B unit more nucleophilic. The concomitant attack of B nucleophile to the C2 carbon of the pyrazine type systems provides a 1,2-addition product that ends up with the 1,4-addition product *via* rearrangement of the α-boryl unit and dearomatization of the substrate.[39] In this line, it has been demonstrated that boron−boron σ-bond activation can also become a formally reductive process where two boryl groups are added to 4,4′-bipyridyl nitrogens (Scheme 16b).[41] This is a conceptually new organocatalytic addition reaction of nonpolar pinB-Bpin bond to unsaturated substrates with formation of pinB−[cat]−Bpin as a key catalyst in the diboration of sterically hindered pyrazines (Scheme 16b).[41]



Scheme 16. 1,4-addition of B_2pin_2 to pyrazine substrates and sterically hindered pyrazines by pinB−[cat]−Bpin organocatalysts

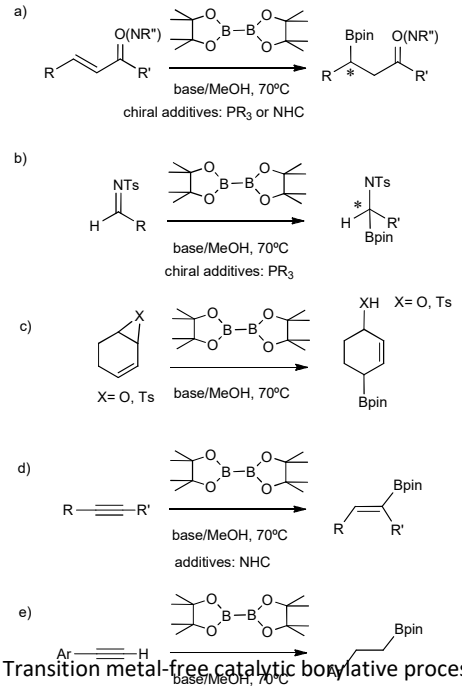
4-Cyanopyridine can promote the homolytic cleavage of B_2pin_2, via the cooperative coordination to the two boron atoms of the diborane to generate pyridine boryl radicals (Scheme 17a).[42] This is a new concept that is based on a cooperative Lewis base mechanism and the captodative effect is responsible for the stability of the generated boryl radical. With this novel activation mode, it is feasible the catalytic reduction of azocompounds and quinones (Scheme 17b), and deoxygenation of sulfoxides to sulphides (Scheme 17c), with 4-cyanopyridine and $B_2(pin)_2$ mild conditions.[42]



Scheme 17 a) Homolytic B-B bond cleavage with 4-cyanopyridine, b) pyridine boryl radicals towards reduction of azo-compounds, c) pyridine boryl radicals towards deoxygenation of sulfoxides to sulfides.

The exploration of metal-free catalytic borylative processes becomes critical to the progress of modern organic synthesis. The activation of B_2pin_2 by forming sp^2-sp^3 hybridised diboron adduct with NHC compounds, was first suggested by Hoveyda and co-workers.[43a,b] They observed that the direct interaction of NHC with B_2pin_2 favour the formation of the adduct [B_2pin_2·NHC] which was fully spectroscopic and structural characterised by Marder and co-workers.[43c] The transition-metal-free NHC-catalysed and [B_2pin_2·OMe^-]-catalysed borylation of α,β-unsaturated carbonyl compounds or imines,[43-45] (Scheme 18a), as well as tosylaldimines[46] (Scheme 18b), are representative examples of this new trend to introduce only one boryl group into the final product, even with asymmetric induction.[44a,43d,45,46] Also the transition-metal-free borylative ring opening of vinyl epoxides and aziridines represents a suitable method towards selective difuntionalisation (Scheme 18c).[47] Those breakthrough discoveries have also been deeply studied from mechanistic perspectives to gain more insight into the power of the selective transition-metal-free versions,[48a,b] in comparison with the original β-borylation with Cu.[48c,d] Monoborylation is also easily afforded by organocatalysed addition of B_2pin_2 to alkynes towards selective β-alkenyl boronates[43e] or alkylboronates[49] (the latter as a tandem borylation/protodeboronation) (Scheme 18 d,e).

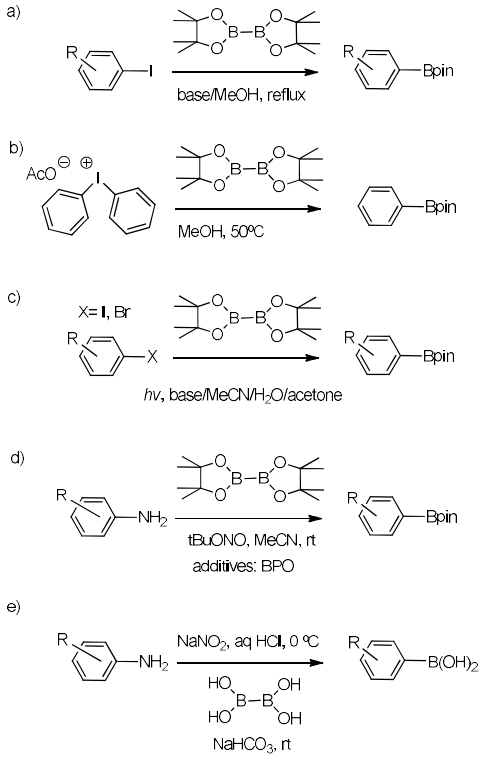
Transition-metal-free borylation of aryl electrophiles has also emerged from the traditional metal-catalysed methodologies, with strength and positive environmental factors. Initially Zhang and co-workers observed that Cs_2CO_3 and MeOH could activate B_2pin_2 and promote the nucleophilic boryl substitution of a wide range of functionalised aryl iodide compounds towards the synthesis of valuable arylboronic esters (Scheme 19a).[50a]



Scheme 18. Transition metal-free catalytic borylative processes of a) α,β–unsaturated carbonyl (imine) compounds, b) tosylaldminies, c) vinyl epoxides and aziridines, d) and e) alkynes.

The authors have not reported a plausible mechanism and they mentioned that cesium cation might be involved in the cleavage of C-I bond.

An alternative direct transition-metal-free borylation of diaryliodonium acetates with diboron reagents has recently been demonstrated to be a feasible process toward formation of arylboronic esters without any base, additive or catalysts. The reaction involves a direct aryl-boron bond formation through a formal umpolung of the electrophilic B_2pin_2, after activations with AcO^-/MeOH (Scheme 19b).[50b] This transformation opens a new methodological venue for the use of hypervalent diaryliodonium reagents in C-B bond formation. Alternatively, a photolytically generated aryl radical from aryl iodides and aryl bromines could be the key intermediate in a novel transition metal free C-B bond formation in aqueous solution at low temperatures. The adduct [B_2pin_2·OH]$^-$ has been also postulated to be involved in the activation of the diboron reagent.[50c] This reaction is amenable to batch and continuous flow conditions and shows broad substrate scope regarding both the aryl halide and the diboron reagent (Scheme 19c). Similar work has extended the photoinduced borylation of haloarenes, including electron-rich fluoroarenes, to quaternary arylammonium salts.[50d,e]



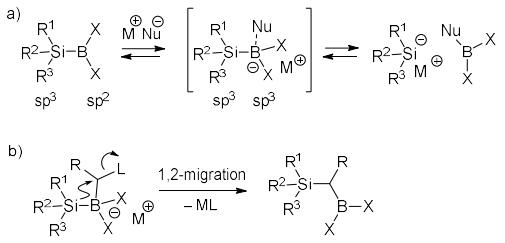
Scheme 19. Transition metal-free catalytic borylation of aryl electrophiles

An entirely new approach to the transition metal-free synthesis of arylboronates is based on the concept to replace an aromatic amino group with a boryl moiety under Sandmeyer reaction conditions. Towards this end, Wang and co-workers used arylamines as convenient substrates, and in the presence of

tert-butyl nitrite (^{t}BuONO, as a suitable diazotization agent) and benozoyl peroxide (BPO) as additive, the corresponding aryl boronate esters were quantitative formed, at room temperature (Scheme 19d).[51a,b] Similarly, the use of tetrahydroxydiboron as diboron reagent directly delivered reactive arylboronic acids by conducting the whole diazotization/borylation sequence in water (Scheme 19e).[51c] Some insights into the reaction mechanism might suggest the concurrence of a radical pathway, thus ruling out the alternative anionic nucleophilic substitution. The uses of aryldiazonoium salts or aryltriazenes as substrates for deaminoborylation, under transition-metal-free conditions, has also been explored.[51d,e]

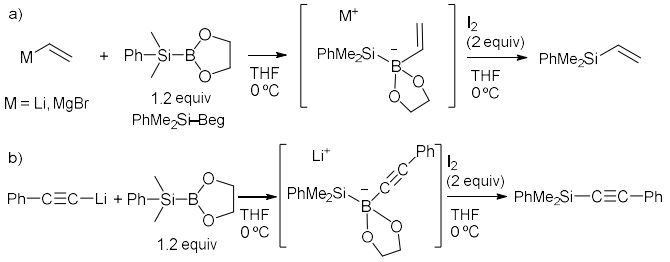
3.Transition-metal-free B-Si addition to organic molecules

Si-B bonds in silylboron compounds are generally inert but can be activated by a nucleophile or a base as well as transition-metal catalysts.[52,53] Because the sp^2-hybridised boron atom in the silylborane compounds has higher Lewis acidity than sp^3-hybridized silicon atom with trialkylsilane moiety, a variety of nucleophiles and bases can coordinate to the boron center to form borate complexes (Scheme 20). This borate formation activates the Si–B bond, where the silyl group is more nucleophilic than that in the non-activated silylborane, Scheme 20a. Depending on the structure of silylboron and reaction conditions (solvent, base, additives), free silyl anion species were also generated from the borate complexes. Nucleophilic reactions of the silyl groups with various electrophiles were reported as a typical reaction. When a leaving group was present at the α-position of the organic ligand on the boron atom, 1,2-migration of the silyl group occurs to afford the 1-boryl-1-silyl substituted compound. (Scheme 20b).



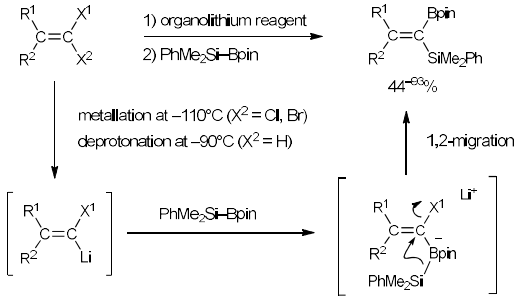
Scheme 20 a) Coordination of a nucleophile to silylborane, b) 1,2-migration reaction

In 1995, Buynak and Geng reported seminal studies on the reaction of silylboranes with alkenyl and alkynyllithium compounds. The borate complexes were converted to the alkenyl- and alkynylsilanes after treatment with iodine (Scheme 21).[54]



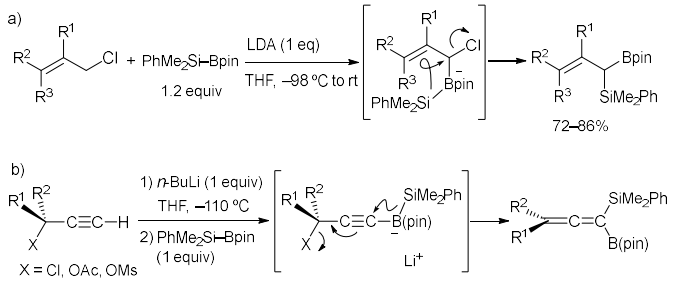
Scheme 21 a) Reaction of a silylborane with alkenyl metals and 1,2-migration of borate complex, b) reaction of a silylborane with an alkynyllithium compound and their 1,2-migration

Hiyama and Shimizu later reported several 1,2-migration reactions of PhMe$_2$SiBpin and in situ-generated carbenoid species (Scheme 22).[32] The 1-halo-1-lithioalkenes that were generated by metalation of 1,1-dihaloalkenes or deprotonation of 1-haloalkenes react with the silylborane to form boronate intermediate. Subsequent 1,2-migration gave the 1-boryl-1-silyl-1-alkenes in a stereospecific manner.



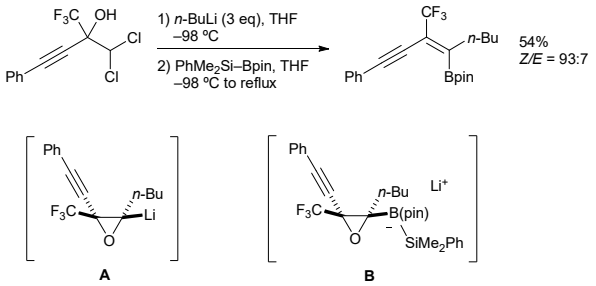
Scheme 22 Synthesis of 1-boryl-1-silyl-1-alkenes from 1,1-dihaloalkenes and PhMe$_2$SiBpin through 1,2-migration

1-Boryl-1-silyl-2-alkenes were synthesized by the reaction of PhMe$_2$SiBpin and in situ-generated α-chloroallyllithiums (Scheme 23a).[55] α-Chloroallyllithiums were prepared by deprotonation of allylic chlorides by lithium diisopropylamide at –98 °C. The reaction went through the boronate intermediate and the 1,2-migration. The 1-boryl-1-silyl-2-alkene products were further utilized in the allylation of aldehydes and acetals to produce homoallyl alcohols and ethers that have (*E*)-alkenylboronate moiety. Treatment of 3-choloro- or 3-alkoxy-1-alkynes with butyllithium at –110 °C generates the corresponding alkynyllithiums, which react with PhMe$_2$SiBpin to produce 1-boryl-1-silylallenes through the 1,2-migration with S_N2' substitution from the borate complex (Scheme 23b).[56] An optically active substrate (R_1 = Me, R_2 = H, X = OMs) with 99% ee gave the chiral allenes with partial racemisation (>74% ee).



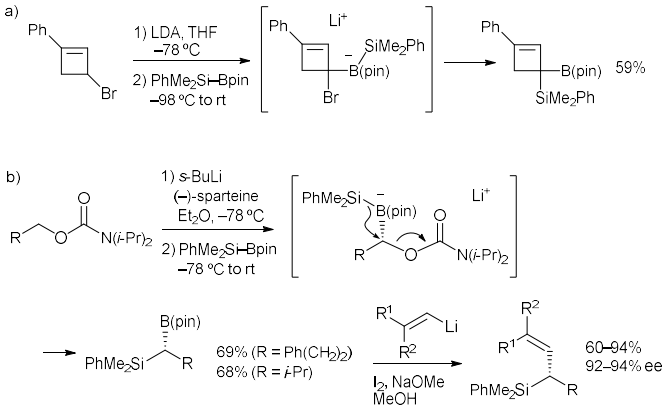
Scheme 23 Synthesis of 1-boryl-1-silyl-2-alkenes from allyl chloride and $PhMe_2SiBpin$ through 1,2-migration

The reaction of CF_3-substituted oxido carbenoids with a silylborane produced CF_3-substituted alkenes with high stereoselectivity (Scheme 24).[57] CF_3-substituted oxido carbenoids **A** were prepared by the reaction of CF_3-substituted dichlorohydrins and butyllithium at –98 °C. After the formation of borate complex **B**, the similar 1,2-migration occurred with opening the oxirane and the subsequent Peterson elimination gave the boryl alkenes with high *Z*-selectivity.



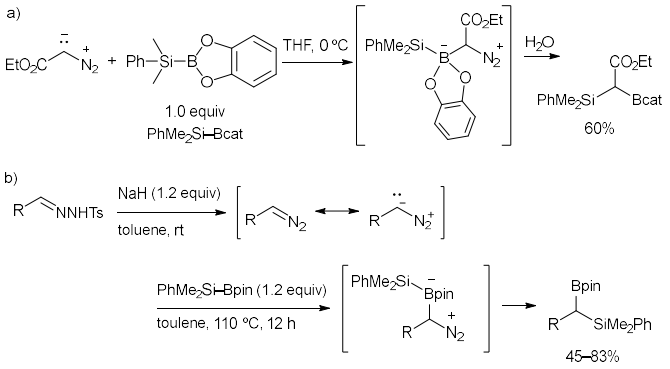
Scheme 24 Stereoselective synthesis of CF_3-containing alkenyl boranes from CF_3-substituted dichlorohydrins.

Synthesis of a 3-boryl-3-silylcyclobutene compound from the corresponding 3-bromocyclobutene was reported.[58] The reaction of 3-bromocyclobutene proceeded with $PhMe_2SiBpin$ and LDA (Scheme 25a). The 3-boryl-3-silylcyclobutene was obtained in a moderate yield. A useful method for synthesis of optically active 1-boryl-1-silyl alkanes from carbamates was reported by Aggarwal's group (Scheme 25b).[59] Asymmetric deprotonation of the carbonyl α-proton of carbamates was first conducted in the presence of a stoichiometric amount of (–)-sparteine, giving chiral organolithiums. The complex with a $PhMe_2SiBpin$ underwent stereospecific 1,2-migration to afford optically active 1-boryl-1-silylalkanes. The subsequent Zweifel olefination gave the optically active allylsilanes in high enantiomeric excess (92–94% ee).



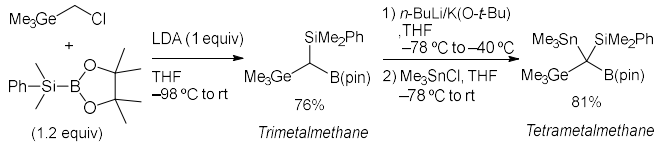
Scheme 25 a) Synthesis of 3-boryl-3-silylcyclobutene, b) stereospecific *gem*-silylborylation of lithiated carbamate and asymmetric synthesis of tertiary allylsilanes

In 1995, Buynak and Geng reported the reaction of a silylborane with an α-diazo ester (Scheme 26a).[52] The 1,2-migration of the borate intermediate, which generated from the diazo ester, gave a 1-boryl-1-silyl ester. As mentioned in the previous part Wang and co-workers recently broaden the scope of this type of the reaction (Scheme 26b).[33] The *in situ*-generated diazo alkanes by reaction of hydrazones and NaH base reacted with $PhMe_2SiBpin$, giving the 1-boryl-1-silyl alkanes after heating at 110 °C in toluene.



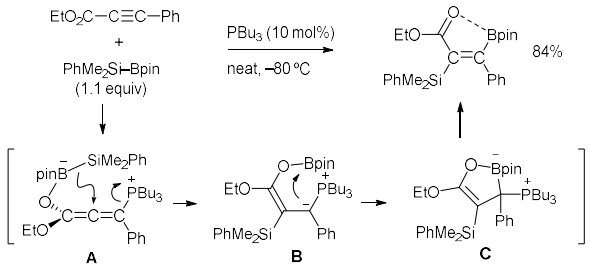
Scheme 26 Reaction of diazo compounds with silylboranes

Shimizu and co-workers beautifully synthesized interesting poly-metallated compounds, 1-boryl-1-germyl-1-silylmethane and 1-boryl-1-germyl-1-silyl-1-stannylmethane by utilizing the deprotonation of chlorogermylmethane, 1,2-migration of their borate complexes, and metalation/stannylation procedure (Scheme 27).[60]



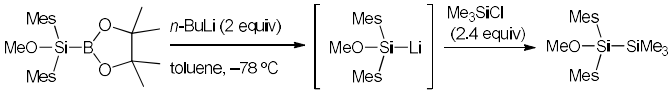
Scheme 27 Synthesis of trimetalmethane and tetrametalmethane *via gem*-silylboration of chlorogermylmethane

Similar to the reaction of B_2pin_2 shown in Scheme 8, the PBu_3-catalysed reaction of alkynoate with $PhMe_2SiBpin$ was also developed (Scheme 28).[30] This reaction produced (*Z*)-3-boryl-2-silylalknenoate in high yield with excellent stereoselectivity. The catalytic reaction starts from the formation of zwitterionic allenoate through the conjugate addition of PBu_3 to alkynoate. 1,2-Migration of the silyl group in the borate intermediate and subsequent trapping of the boron group by the ylide carbon gave the cyclic intermediate. Finally, the elimination of PBu_3 produced the β-boryl-α-silyl products.



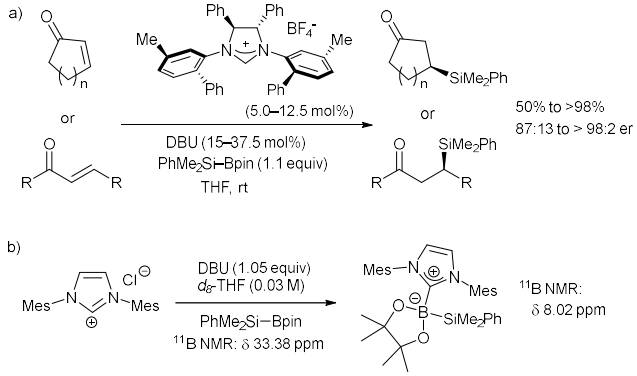
Scheme 28 PBu_3-catalyzed reaction of $PhMe_2SiBpin$ and alkynoate.

In 2001, Kawachi and Tamao reported the first example of the generation of free silyl anion species from silylboranes by the Si-B bond cleavage with ^{n}BuLi to (Scheme 29), which was checked by Si NMR.[61] They also found that the KO^{t}Bu can activate the silylborane but did not show the clear evidence of the free silyl anion generation. Kleeberg later characterised the free silyl anion species generated in reaction of the silylboane and [K$^+$(18-C-6)(O^{t}Bu)] in toluene by X-ray crystallography.[62,63]



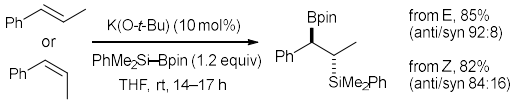
Scheme 29 Generation of silylanion by reaction between silylborane and butyllithium.

Silylboranes are also activated by *N*-heterocyclic carbenes (NHC) (Scheme 30a).[64] Hoveyda and co-workers developed an asymmetric silyl conjugated addition of α,β-unsaturated carbonyl compounds, with silylborane using a chiral NHC catalyst. The reaction gave the corresponding β-silyl ketones in high yields with high enantioselectivities. An NHC-B-Si complex, which is the plausible reaction intermediate, was observed by ^{11}B NMR (Scheme 30b).



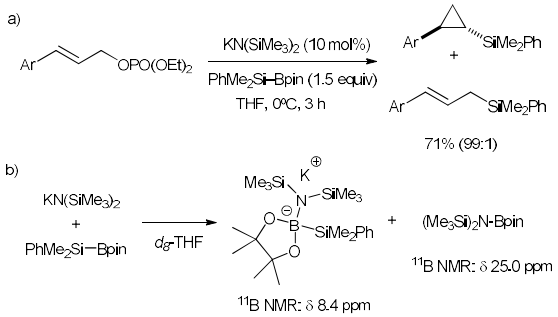
Scheme 30 a) Chiral NHC-catalyzed asymmetric conjugate silylation of α,β-unsaturated carbonyl compounds, b) ^{11}B NMR observation of NHC-coordinated silylborane.

Ito and co-workers reported the alkoxy base-catalysed silaboration of aromatic alkenes with silylboranes (Scheme 31).[65] The reaction of both (*E*)- and (*Z*)-1,2-disubstituted alkenes provided the same *anti*-product as the major product, suggesting an anionic character of the intermediate. This stereoselective preference contrasts with those found in transition metal-catalyzed silaboration reactions.[52,53]



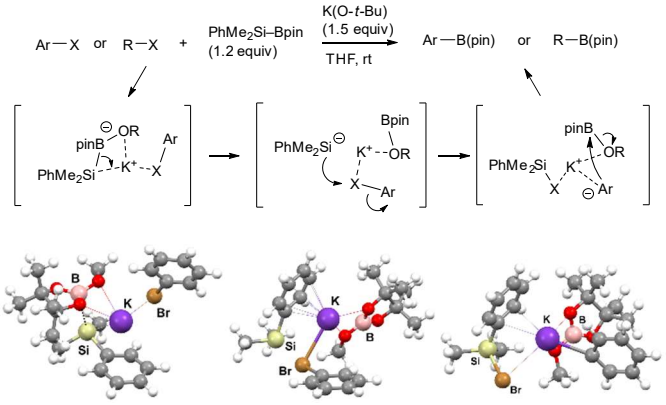
Scheme 31 Alkoxy base-catalysed silaboration of aromatic alkenes

Shintani, Nozaki, and co-workers reported a silylative cyclopropanation of allyl phosphates with $PhMe_2SiBpin$ in the presence of stoichiometric amount of $KN(SiMe_3)_2$ as a base (Scheme 32a).[66] They supposed that the in situ formation of borate complex with bis(trimethylsilyl)amide is the key for this reaction (Scheme 32b). Similar to the above case, the dimethylphenylsilyl group would first attack to the aromatic alkenes at the β-position, and the subsequent intramolecular cyclization affords the cyclopropanation product.



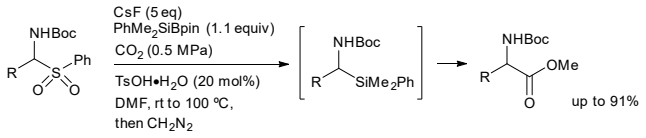
Scheme 32 a) Silylative cyclopropanation of allylic phosphates, b) complex between $PhMe_2SiBpin$ and $KN(SiMe_3)_2$

Boryl substitution reaction of aromatic and alkyl halides were proceeded in the presence of silylboranes and alkoxide base (Scheme 33).[67-69] This reaction seems to be curious because the reaction of silylborane and alkoxide base usually produces silyl nucleophiles. The reaction mechanism of the anomalous reactivity was investigated by the experiments and DFT calculations.[69] After the Si–B bond cleavage, the halogen atom in the substrate is attacked by the anionic silyl group and eliminated by silicon atom with a formation of hydrocarbon nucleophile, which then attack to the boron atom to produce the borylation product. The reaction possesses high reactivity toward various aromatic halides (X = Cl, Br, I) including sterically hindered ones and moderate functional group compatibility.



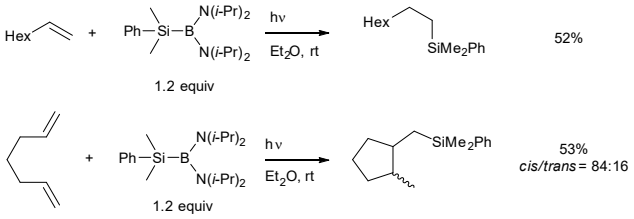
Scheme 33 Boryl substitution of aromatic and alkyl halides by $PhMe_2SiBpin$ and alkoxy base. Molecular models of transition states are illustrated based on the DFT calculations.

α-Amide sulfones, an *N*-Boc imine precursor, were converted to the corresponding α-amino acids in the presence of a silylborane, CsF, and CO_2 (Scheme 34).[70] The silyl group undergoes nucleophilic reaction with the in-situ generated *N*-Boc imine to produce the α-amide silanes, which were further activated by CsF to react with carbon dioxide to produce α-amino acid products.



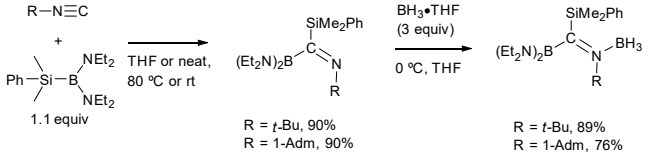
Scheme 34 α-Amino acid synthesis from CO_2 using silylborane reagent.

Examples of photo-induced reactions of silylborane were still very rare. Ito and co-workers reported the several photoreactions in 2000 (Scheme 35).[71] UV irradiation to a silylborane could cause the homolytic cleavage of the Si–B bond. A silyl adduct was obtained in moderate yield in the presence of a terminal alkene and [bis(dimethylamino)boryl]dimethylphenylsilane after irradiation of UV light with a high-pressure mercury lamp. The reaction of the silylborane with 1,6-diene afforded a cyclization product in a moderate yield.



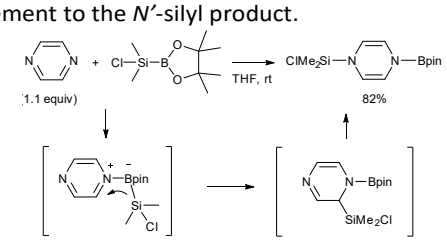
Scheme 35 Photo-induced reactions of silylborane.

Reaction between silylboranes and isocyanides was reported by Suginome and Ito in 2000 (Scheme 36).[72] The reaction proceeds without a catalyst in THF at 80 °C or in neat conditions at room temperature The α-carbon of the isocyanide was inserted between the Si–B bond. The products were isolated as the BH_3 adducts.



Scheme 36 Reaction of silylborane and isocyanide

Suginome also reported dearomatization reaction of pyrazine with a silylborane (Scheme 37).[40] Similar to the reaction of diboron (Scheme 16), the *N*-boryl-*N'*-silyl-1,4-dihydropyrazine was obtained in high yield after the reaction in THF for 24 h. They propose a reaction mechanism including the nucleophilic reaction of the silyl group on to the C2 carbon and rearrangement to the *N'*-silyl product.

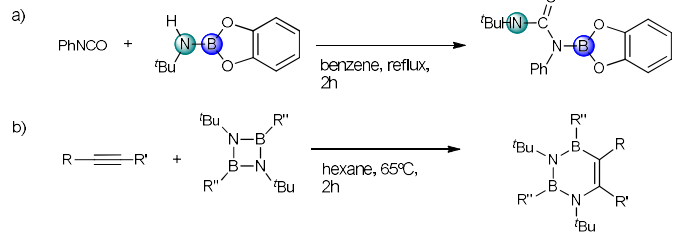


Scheme 37 Reaction between silylborane and pyrazine

4.Transition-metal-free B-N addition to organic molecules

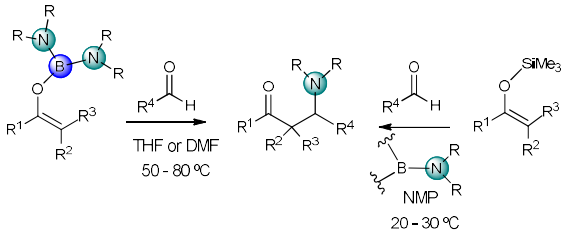
Aminoboranes become useful reagents to be added to organic molecules in order to contribute efficiently towards heterofunctionalisation protocols. The synthesis of aminoboranes has nowadays been simplified by the effective method described by Bertrand and co-workers[73] based on a catalyst-free dehydrocoupling of amines and pinacolborane to

generate corresponding aminoboranes. Initial attempts to add straightforward B-N reagents to organic molecules were originally limited to interact with isocyanates (Scheme 38a), isothiocyanates and carbodiimides.[74] But in 1988 the direct aminoboration of a C-C triple bond was described as a [4+2] cycloaddition to produce simultaneously C-B and C-N bonds in the formation of a heterocycle (Scheme 38b).[75]



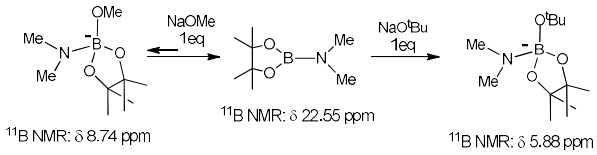
Scheme 38 Initial attempts to aminoboration of organic substrates

Aminoboranes can also be used to aminate organic substrates taking advantages of the Lewis acidic properties of B atom. In that context, Suginome and co-workers have demonstrated the benefits of aminoborane derivatives in amination reactions such as Strecker-type aminative cyanation, reductive amination, and a Mannich-type reaction, by considering the aminoboranes as "compatible" iminium ion generators in aminative C-C bond formations (Scheme 39).[76]

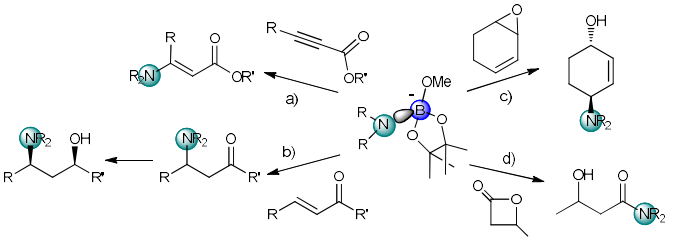


Scheme 39 Aminoboranes in amination reactions through iminium ion formation

In 2013, Fernández and co-workers established a transition metal-free activation of pinB-NMe_2 and pinB-NEt_2, *via* alkoxy ions, for selective addition of the amine group into unsaturated substrates.[77] The formation of the Lewis acid-base adduct [RO^-→Bpin-NMe_2] was established by spectroscopic evidences. Thus, after addition of 1 eq of NaO*t*Bu or 1 eq of NaOMe, a shift in the ^{11}B NMR spectra was observed. The initial 22.55 ppm (due to a sp^2 Bpin moiety bonded to an amino group) moved to 5.88 ppm or 8.74 ppm (corresponding to the sp^3 Bpin moiety of the adduct [RO^-→Bpin-NMe_2]) (Scheme 40). This type of activation seems to be the platform to enhance the nucleophilic attack of amino moieties towards electron deficient olefins such as α,β-unsaturated carbonyl compounds, (Scheme 41a,b) cyclic vinyl epoxides (Scheme 41c), as well as the ring opening of β-butyrolactone, forming exclusively the β-hydroxy *N,N*-dimethylbutyramide (Scheme 41d). A transition-metal-free aminoboration of non-activated unsaturated hydrocarbons has not been yet described.



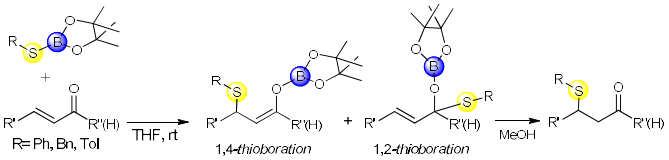
Scheme 40 ^{11}B NMR data of the suggested [MeO^-→Bpin-NMe_2] and [$^tBuO^-$→Bpin-NMe_2] adducts



Scheme 41 Alkoxy activation of aminoboranes towards transition-metal-free amination protocols

5.Transition-metal-free B-S addition to organic molecules

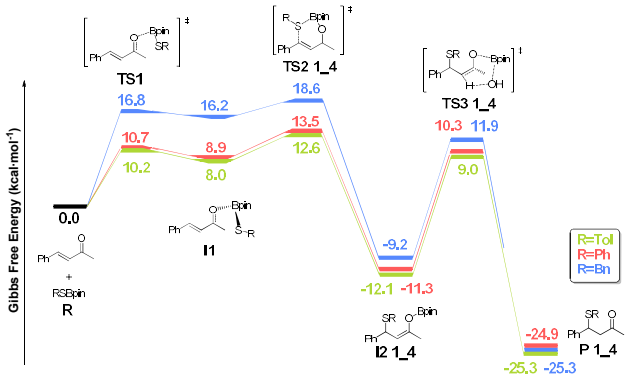
The original idea to prepare alkenyl 1,2-thioboranes from thioboranes came from the pioneer work of Miyaura and co-workers in 1993. They used palladium complexes to activate 9-(alkylthio)-9-borabicyclo[3.3.1]nonane to be added to terminal alkynes. The reaction takes place with high degree of regioselectivity locating the SR group at the internal position of the 1-boryl-2-thio-1-alkenes.[78] The next attempt to add the thiodioxaborolane, pinB-SR (R=Ph, Tol and Bn), was developed in a transition-metal-free context and notably, the easy activation of the thioborane reagents with α,β-unsaturated ketones and aldehydes took place at room temperature without other additives.[79] The key point of this reactivity is based on the Lewis acidic properties of the boryl unit of the pinB-SR reagent that interacts with the basic oxygen of the carbonyl moiety. Consequently, the SR fragment becomes more nucleophilic and promotes the 1,4- versus the 1,2-addition, as a function of the involved substrate. The thioborated products can be further transformed into β-sulfido carbonyl compounds by addition of MeOH (Scheme 42).



Scheme 42 Transition-metal-free 1,2- and 1,4-thioboration

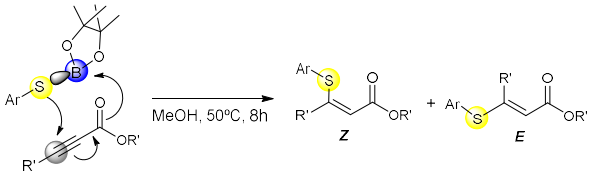
From the thiodioxaborolanes studied, the BnS−Bpin resulted less activated presumably because of the lack of electron delocalization

from sulfur, making the boron atom less Lewis acidic. DFT-based studies provided a suitable mechanism for the reaction and are useful tools to analyze the change in the nucleophilicity of the reagents by the modification of the substituent on the RS moieties (Scheme 43).[79] It has been postulated that the reaction occurs in three main steps, the first being the interaction of the carbonyl oxygen with the empty p orbital of the boron atom through a first transition state TS1 and forming the corresponding intermediate I1 (Scheme 43). The sulfido group attacks the C_β position passing through the transition state TS2 1_4 (Scheme 43). This transition state gives rise to the intermediate I2-1_4, which finally undergo the protonation to give the corresponding β-sulfido carbonyl compounds and the byproduct HOBpin (Scheme 43).



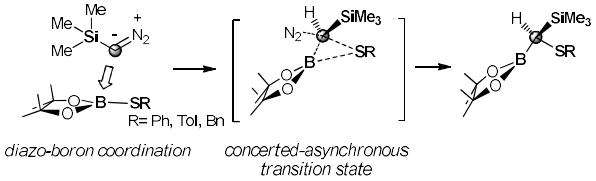
Scheme 43 Relative Gibbs free energies for the reaction pathway of the 1,4-addition of the RS–Bpin reagents to the substrate 4-phenyl-3-buten-2-one. All energies are in kcal mol^{-1}

The feasible reactivity of ynones with pinB-SPh and pinB-SBn, to promote the synthesis of vinyl sulphides, in the absence of transition metal complexes or additives, has also been successfully achieved.[0] The addition of ArS groups to the α,β-acetylenic ketones takes place regioselectively in the C_β position with a stereoselectivity *Z*/*E* of ca. 3/1, independent of the nature of the Ar group in the thiodioxaborolane reagent (Scheme 44).



Scheme 44 Transition-metal-free addition of pinB-SAr (Ar=Ph, Bn) to ynones.

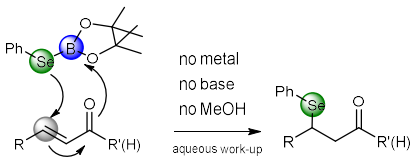
The insertion of the diazo derivative Me_3SiCHN_2 into pinB–SR σ bonds (R = Ph, Tol, Bn) also allows for a direct synthesis of multisubstituted H–C(SR)(Bpin)($SiMe_3$) compounds (Scheme 45).[81] The mechanism of the insertion of the diazo reagent into the interelement B-S σ bond, might be understood as an initial interaction of the nucleophilic diazo carbon to the electron deficient boron of the Bpin moiety, followed by the 1,2-migration of the adjacent SR moiety to yield the α,α–substituted product and the concomitant release of dinitrogen. The interest of these multisubstituted H–C(SR)(Bpin)($SiMe_3$) compounds is illustrated by their consecutive base-assisted transformations to lead deborylative alkylations, Sommelet–Haüser rearrangements, and deprotoalkylations. Intramolecular cyclizations can also be selectively performed either *via* desilylative or deborylative manifolds by fine-tuning the base employed.[81]



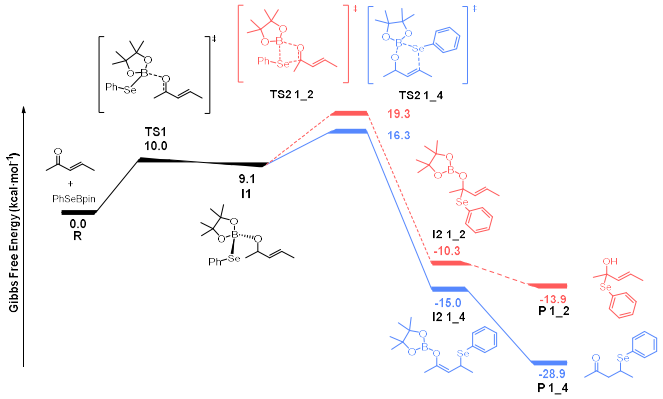
Scheme 45 Suggested mechanism for the insertion of Me_3SiCHN_2 into RS-Bpin

6.Transition-metal-free B-Se addition to organic molecules

The working hypothesis based on the "pull–push" effect of Bpin moieties, which easily form Lewis acid–base adducts and enhance the nucleophilic character of the interelement, was also explored for phenylselenoborane systems, which can be synthetised by the room temperature Rh catalysed dehydrogenative borylation of the selenol (PhSeH) and one equivalent of the borane (HBpin).[82] Activated olefins, such as α,β-unsaturated ketones and aldehydes, directly react with a phenylselenium borane, at room temperature, without any metal or organocatalytic assistance, to form β-(phenylseleno) substituted ketones and aldehydes.[83] This is the first example of selenoboration of organic compounds with pinB-SeR systems (Scheme 46). DFT studies propose a plausible mechanism for the reaction and explain the high selectivity towards the 1,4-addition product, versus 1,2-adduct (Scheme 47). Alternatively, but also in a metal-free context, the reaction of organoselenoboranes $B(SeR)_3$ with acetylenes, ketones and α,β–unsaturated carbonyl compounds has been described to afford organoselenium compounds, probably *via* a radical mechanism.[84]

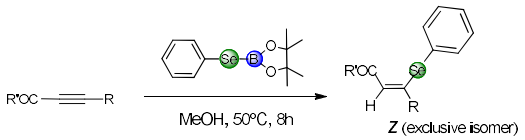


Scheme 46 Transition-metal-free 1,2- and 1,4-thioboration



Scheme 47 Proposed reaction pathway for the reaction of PhSeBpin with 3-penten-2-one. All energies are in kcal mol^{-1}

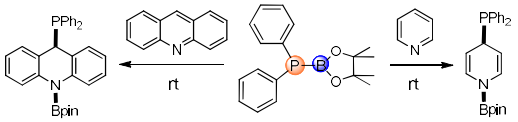
The selective β-SePh addition to α,β-acetylenic ketones has also been demonstrated to offer a flexible and reliable route to stereodefined (*Z*)-alkenyl selenides through the powerful "pull–push" properties of Bpin units in the reactions of the pinB-SePh with ynones, in a metal-free context without any additive except MeOH as solvent (Scheme 48).[80] This straightforward method between ynones and pinB-SePh simplifies the previous method to obtain (*Z*)-β-(arylseleno)-α,β-unsaturated ketones *via* addition of selenoesters to alkynes catalyzed by copper.[85]



Scheme 48 Transition-metal-free addition of pinB-SePh to ynones.

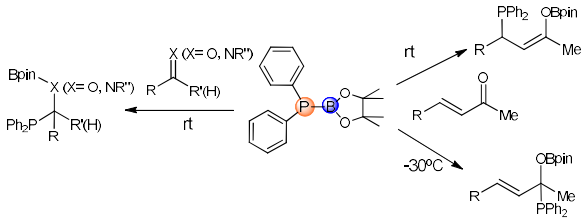
7.Transition-metal-free B-P addition to organic molecules

The phosphinoboronate esters, pinB-PR_2, can be prepared by reaction of pinBO^{i}Pr with Li[PR_2] in a straightforward manner. Interestingly, the π-dative interaction between the phosphorous lone pair and the empty orbital of the boron atom, can be mitigated in basis to the Lewis-acidity and Lewis-basicity at the B and P atoms by tuning their specific substituents.[86] For phosphinoboronate esters of formula pinB-PR_2, the interaction of the lone pair in oxygen and the p vacant orbital at boron, favours the single bond nature of the P-B bond and therefore its reactivity. The addition of pinB-PPh_2 to acridine takes place at room temperature to afford the 1,4-addition product as the *syn* isomer. Similar addition was also observed to pyridine to form the 1,4-dihydropyridine (Scheme 49).[87] However, the phosphinoboration of allenes and terminal alkynes required the presence of Rh complexes.



Scheme 49 Transition-metal-free addition of pinB-PPh_2 to acridine and pyridine.

As it was observed for B-B reagents,[46] pinB-PPh_2 could be added to aldehydes, ketones and aldimines at room temperature to afford the corresponding 1,2-adduct (Scheme 50). But also as it was observed for B-S reagents, the addition of pinB-PPh_2 to α,β-unsaturated ketones generated the 1,2- and 1,4-addition product, depending on the reaction conditions, (solvent and temperature) (Scheme 50).[87] Interestingly, all that reactivity shows the potential of this transition-metal-free addition of B-P reagents to organic molecules toward strategic synthesis of phosphines.



Scheme 50 Transition-metal-free addition of pinB-PPh_2 to ketones, imines and α,β-unsaturated ketones .

Conclusions

This tutorial discloses an important and emergent topic in chemical science that aims to functionalise organic molecules with B-B or B-interelement reagents. For both, familiar chemists on organoboron chemistry, but also for general research chemists we have provided a guided tour along the activation and reactivity of B-B, B-Si, B-N, B-S, B-Se and B-P systems, in the absence of any transition metal complex. The greener consequences of those novel routes facilitate the gram scale preparations of functionalised organic compounds which in addition can be efficiently synthetised in a selective way. The main achievements on this field appear in the primary literature from the last decade, and the discovery of the transition-metal-free B-B and B-interelement addition to organic molecules becomes a stimulating area of work and researchers are invited to generate knowledge around these initial observations to create unknown protocols in organic synthesis.

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