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Electron-deficient boron-based catalysts for C–H bond functionalisation

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In contrast to transition metal-catalysed C–H functionalisation, highly efficient construction of C–C and C–X (X = N, O, S, B, Si, *etc.*) bonds through metal-free catalytic C–H functionalisation remains one of the most challenging tasks for synthetic chemists. In recent years, electron-deficient boron-based catalyst systems have exhibited great potential for C–H bond transformations. Such emerging systems may greatly enrich the chemistry of C–H functionalisation and main-group element catalysis, and will also provide enormous opportunities in synthetic chemistry, materials chemistry, and chemical biology. This article aims to give a timely comprehensive overview to recognise the current status of electron-deficient boron-based catalysis in C–H functionalisation and stimulate the development of more efficient catalytic systems.

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1. Introduction

Catalytic functionalisation of C–H bonds has been recognised as a powerful and straightforward tool to construct new C–C and C–X (X = N, O, S, B, Si, *etc.*) bonds due to the high step- and atom-economy of this process and the abundance of hydrocarbon compounds. Over the past few decades, tremendous advances have been achieved in this field.[1–26] Furthermore, C–H bond functionalisation reactions also exhibit wide applications in the synthesis of natural products, pharmaceuticals, polymers and various organic functional materials.[27–32] To date, catalyst systems

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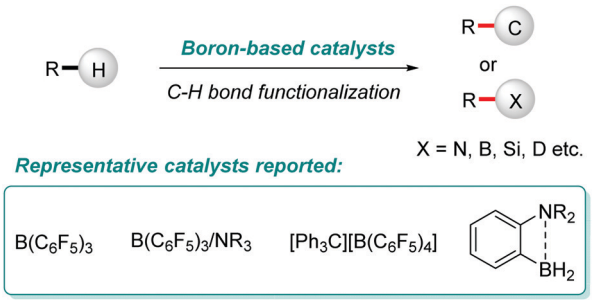

Fig. 1 An overview of C–H bond functionalisation by electron-deficient boron-based catalysts.

reported for C–H functionalisation have overwhelmingly relied on the late and early transition metal complexes, such as Pd, Rh, Ru, Sc, Y, *etc.*[1–24,27–32] Despite numerous advantages of metal catalysis in the field of C–H bond functionalisation, several metal-catalyst-associated issues, such as the trace-metal residue issue, would raise significant concerns in the efficiency of organic electronic materials and the product safety for human consumption. Therefore, the development of metal-free catalytic C–H bond functionalisation is of great interest and significance in synthetic chemistry, materials chemistry, and chemical biology.[33]

Electron-deficient boron-based compounds have exhibited great potential for homogeneous catalysis since the pioneering work developed by Marks's group, Yamamoto's group, Piers's group and Maruoka's group in the 1990s. In their seminal works, Marks and co-workers disclosed that $B(C_6F_5)_3$ could serve as an excellent co-catalyst in metallocene-mediated polymerisation of alkenes.[34–37] Yamamoto and co-workers found that $B(C_6F_5)_3$ could act as an efficient catalyst in Aldol-type reactions.[38–40] Parks and Piers found that $B(C_6F_5)_3$ could activate hydrosilanes in the catalytic hydrosilylation of carbonyl compounds.[41] In 1998, Maruoka and co-workers reported the chemoselective allylation reaction of *ortho*-anisaldehyde using $B(C_6F_5)_3$ as the catalyst.[42] In the last ten years, with the rapid development of the concept of frustrated Lewis pairs (FLPs), electron-deficient boron-based compounds, in particular, $B(C_6F_5)_3$ and the corresponding Lewis pairs, have received substantial attention as a powerful platform for the activation of organic small molecules.[43–60] More significantly, the applications of such electron-deficient boron-based compounds have been extended to the field of catalytic C–H bond transformations, and a series of highly efficient reaction systems for the formation of C–C bonds and C–X bonds including C–N, C–B, C–Si, C–D, *etc.* have been reported successively in recent years (Fig. 1).

Despite the enormous achievements and rapid development of C–H bond functionalisation by electron-deficient boron-based catalysts, there remains a lack of an overview in this field, although a few examples have been previously collected in some reviews.[25,52,53,56,60] In this context, it is highly desirable to provide a timely review to comprehensively recognise the current status and existing challenges of this emerging area, and stimulate further development of new catalytic systems. This review describes all important progress in C–H functionalisation by electron-deficient borane catalysts and the corresponding Lewis pairs. Publications in peer-reviewed journals up to May 2020 have been included. The detailed review is divided into sections based on the nature of C–H bonds, and each subsection is further divided based on the reaction types. The mechanism of some typical reactions and their advantages and limitations are also briefly discussed.

2. Stoichiometric C–H activation by electron-deficient boron-based Lewis pairs

The seminal stoichiometric C–H activation by electron-deficient boron-based Lewis pairs was reported in 2009 by Dureen and Stephan.[61] Over the past few decades, the literature has reported a series of elegant examples that used electron-deficient boron-based Lewis pairs to activate a variety of C(sp)–H bonds of terminal alkynes and C(sp^3)–H bonds, which generally lead to the formation of organoboron compounds or the corresponding ion pairs. These stoichiometric examples are actually the roots for the recent development of catalytic transformations. Some important examples of boron-mediated stoichiometric C–H activation are summarised and highlighted in this section.

Transition metal-mediated C(sp)–H activation of terminal alkynes and the subsequent C–C coupling reactions such as Sonogashira coupling have been well developed.[62] However, the direct C(sp)–H transformation of terminal alkynes with main-group element species remained under-developed. With the emergence of the FLP concept, Stephan and Dureen reported the first C(sp)–H activation of terminal alkynes using frustrated Lewis acid/phosphine pairs in 2009 (Scheme 1).[61] It was found that the frustrated Lewis pair formed by a combination of $B(C_6F_5)_3$ and $^tBu_3P$ smoothly reacted with phenylacetylene in

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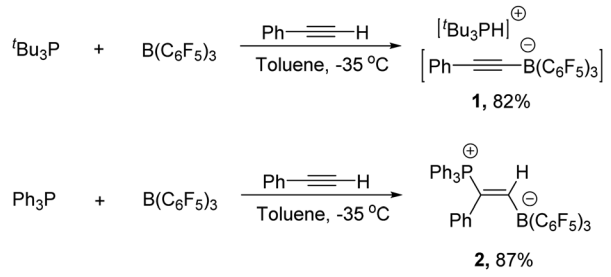
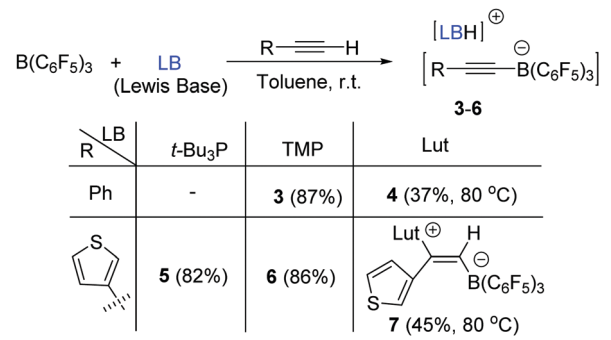


Scheme 1 Reactions of $B(C_6F_5)_3$/phosphine pairs with alkynes.

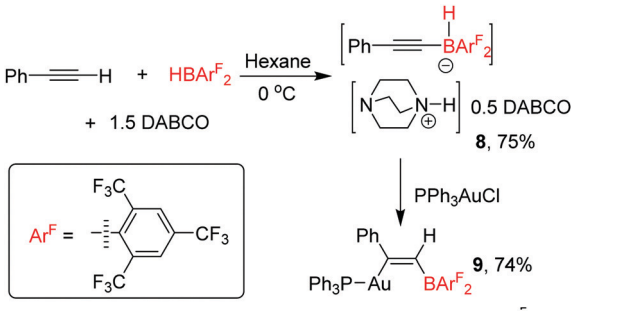
toluene at −35 °C to give ion pair product **1** in 82% yield through C(sp)–H cleavage of the alkynes. In contrast, when $^tBu_3P$ was replaced by Ph_3P, the addition reaction of phenylacetylene with a classical Lewis acid–base adduct $Ph_3P{\cdot}B(C_6F_5)_3$ took place to afford zwitterionic species **2** in 87% yield without the C(sp)–H activation. In 2010, Stephan's group reported a more comprehensive investigation on deprotonation and addition of terminal alkynes with frustrated Lewis pairs by changing the components of diverse frustrated Lewis pairs.[63] Subsequently, the groups of Stephan and Erker also demonstrated that the frustrated Lewis pair of benzyldimethylamine with $B(C_6F_5)_3$ could react with the terminal alkynes RC≡CH (R = ^{n}Bu, Ph, ^{t}Bu, $SiMe_3$) by deprotonation of the alkynes to give the corresponding ammonium alkynylborate salts $[PhCH_2NMe_2H][RC{\equiv}CB(C_6F_5)_3]$.[64]

Berke and co-workers found that the reaction of phenylacetylene or 3-ethynylthiophene with frustrated Lewis pairs derived from $B(C_6F_5)_3$ and bulky Lewis bases 2,2,6,6-tetramethylpiperidine (TMP) and tri-*tert*-butylphosphine also gave the corresponding deprotonation products **3**, **5** and **6** in high yield at room temperature (Scheme 2).[65] Due to the weak Lewis basicity of lutidine (Lut), the reaction of phenylacetylene with the adduct of $B(C_6F_5)_3$ and lutidine produced deprotonation product **4** in 37% yield at 80 °C. However, the corresponding reaction of 3-ethynylthiophene with the FLP of $B(C_6F_5)_3$ and lutidine yielded the 1,2-addition product **7** in 45% yield.

In 2012, Wang and co-workers reported the reaction of terminal alkynes with the FLP comprised of $HBAr^F_2$ (Ar^F = 2,4,6-tris(trifluoromethyl)phenyl) and 1,4-diazabicyclo-[2.2.2]octane (DABCO) in hexane solution at 0 °C. As exemplified in Scheme 3, the ammonium alkynylhydridoborate salt **8**



Scheme 2 Reactions of $B(C_6F_5)_3$/Lewis base pairs with alkynes.

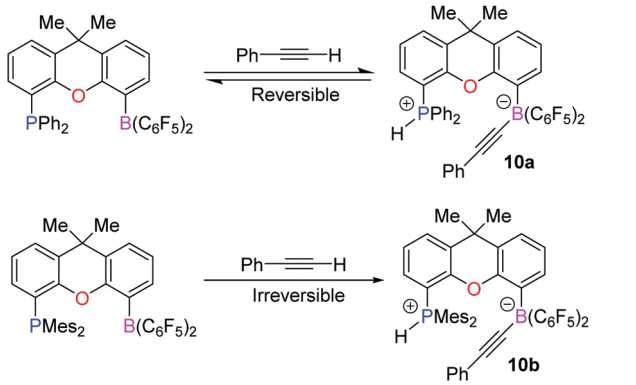


Scheme 3 Activation of phenylacetylene with the $HBAr^F_2$/DABCO pair and its application in the boroauration of phenylacetylene.

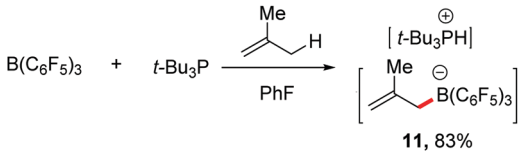
resulting from the deprotonation of phenylacetylene was isolated in 75% yield. Subsequently, the transformation of the ammonium alkynylhydridoborate salt with PPh_3AuCl afforded boroauration product **9** in 74% yield.[66]

In 2018, Aldridge and co-workers developed intramolecular frustrated Lewis pairs derived from dimethylxanthene-based phosphine/borane, which enabled the C–H activation of terminal alkynes to work in a reversible or irreversible fashion depending on the electronic influence of the phosphine moiety. For example, the reaction of phenylacetylene with a diphenylphosphine-substituted Lewis pair proceeded in a reversible way, resulting in a mixture of the FLP, alkyne and phosphonium acetylide **10a** in a solution of dichloromethane or toluene at room temperature. By contrast, when the phenyl groups bound to the phosphine moieties were replaced by a mesityl (Mes = 2,4,6-$Me_3C_6H_2$) group (as a much stronger phosphine donor), the corresponding C–H activation of phenylacetylene proceeded irreversibly to give selectively product **10b** (Scheme 4).[67]

In contrast to the C(sp)–H activation of terminal alkynes, C(sp^3)–H bond activation is much more challenging due to the higher bond dissociation energy.[68] In 2012, Ménard and Stephan reported an allylic C(sp^3)–H activation of isobutylene with $B(C_6F_5)_3$ and $^tBu_3P$ (1 : 1). The reaction was performed in a fluorobenzene solution, which afforded allyl borate product **11** in high yield (83%) (Scheme 5).[69] This reaction is in contrast



Scheme 4 Reactions of dimethylxanthene-based phosphine/borane Lewis pairs with phenylacetylene.



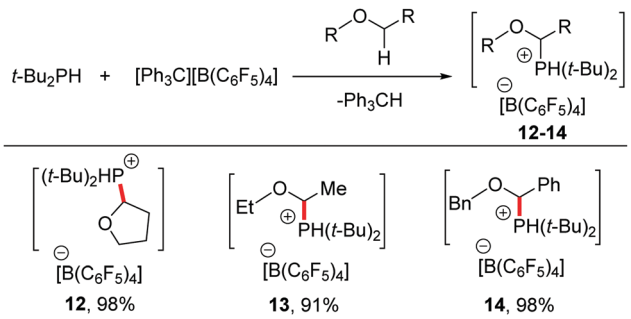
Scheme 5 Stoichiometric C(sp^3)–H activation of isobutylene.

with the previously reported addition reactions of FLPs with ethylene, propene, hexene, and norborene,[70,71] probably due to the steric hindrance of isobutylene which may hamper the analogous addition reaction. This reaction constitutes the first example of C(sp^3)–H activation by FLP.

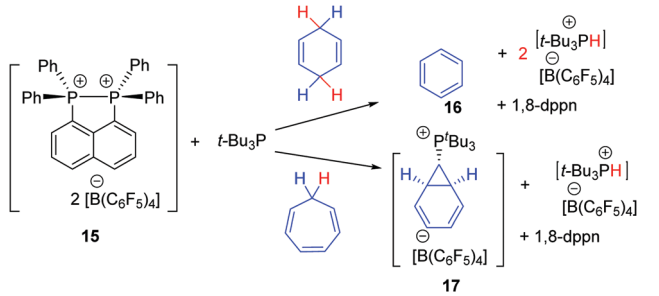
FLP-mediated C–O bond cleavage of ether compounds has been well-studied and even applied to the catalytic deoxygenation of carbohydrates.[72–74] However, a chemoselective C(sp^3)–H bond activation of alkyl-substituted ethers by such Lewis pairs remained rare. In 2014, Stephan and co-workers found that α-C(sp^3)–H functionalisation of various ethers could be realised by a combination of Lewis acid $[Ph_3C][B(C_6F_5)_4]$ and Lewis base $^tBu_2PH$ in FLP (Scheme 6).[75] With this Lewis pair, diverse ethers such as tetrahydrofuran, diethyl ether and dibenzyl ether were converted to the corresponding phosphonium ion salts **12–14** in high isolated yields.

In 2015, Stephan and co-workers presented a highly Lewis acidic diphosphonium dication $[(C_{10}H_6)(Ph_2P)_2]^{2+}$, which was prepared by the reaction of two equivalents of $[Et_3Si][B(C_6F_5)_4]\cdot 2(C_7H_8)$ with difluorophosphorane $(C_{10}H_6)(Ph_2PF_2)(Ph_2P)$ in a C_6H_5F solution and isolated in 95% yield.[76] Diphosphonium salt **15** was relatively stable in coordinating solvents, and the corresponding solid state could also be maintained under air for 24 h without evident decomposition. It was found that the diphosphonium salt-based FLP could be applied in C–H activation reactions. For example, the FLP derived from compound **15** and $^tBu_3P$ transformed 1,4-cyclohexadiene (CHD) into benzene **16** by dehydrogenation of CHD together with the formation of $[^tBu_3PH][B(C_6F_5)_4]$ and 1,8-bis (diphenylphosphanyl)naphthalene (1,8-dppn) (Scheme 7). The analogous reaction of 1,3,5-cycloheptatriene (CHT) gave new phosphonium ion species **17** (Scheme 7).

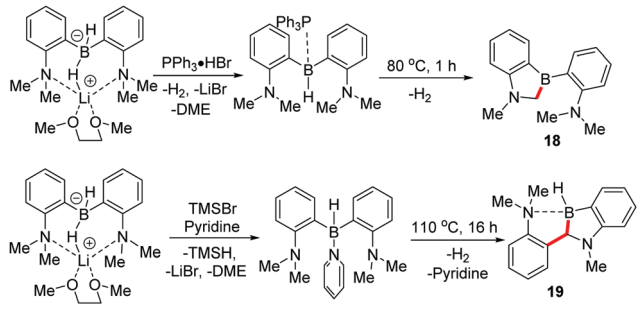
In 2017, Fontaine and co-workers disclosed an elegant example of C(sp^3)–H bond activation by an intramolecular nitrogen/boron FLP. As shown in Scheme 8, upon heating the PPh_3 adduct of $(2\text{-}NMe_2\text{-}C_6H_4)_2BH$ that was prepared from



Scheme 6 Stoichiometric α-C(sp^3)–H activation of ethers.



Scheme 7 C(sp^3)–H activation by 1,2-diphosphonium dication and $^tBu_3P$.



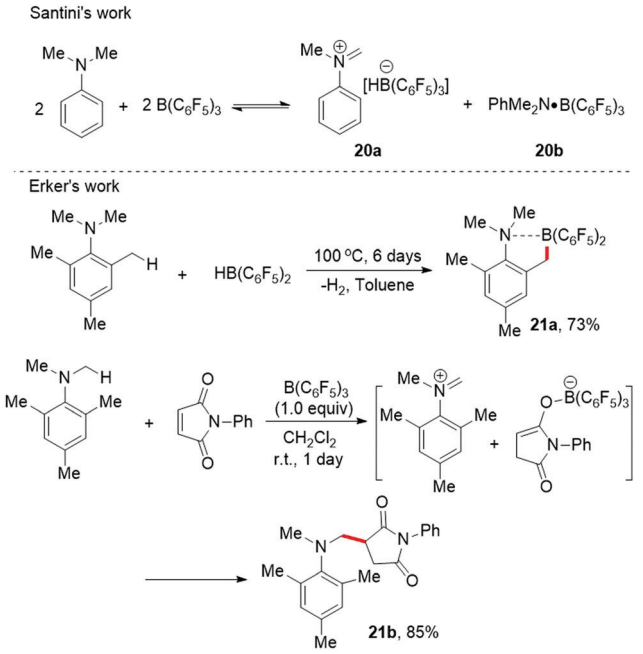
Scheme 8 C(sp^3)–H bond activation by a nitrogen/boron FLP.

$(2\text{-}NMe_2\text{-}C_6H_4)_2BH_2$-LiDME (DME = 1,2-dimethoxyethane), an unprecedented N–B heterocycle **18** was formed by C(sp^3)–H bond cleavage of a methyl group adjacent to a nitrogen atom. Interestingly, in the case of an analogous pyridine adduct of $(2\text{-}NMe_2\text{-}C_6H_4)_2BH$, upon heating at 110 °C, further rearrangement took place to give unprecedented N–B heterocycle **19** *via* a sequential hydride abstraction/1,2-aryl shift process. A series of theoretical calculations were also performed to understand the mechanistic details.[77]

In 2002, Santini and co-workers found that the stoichiometric reaction of $B(C_6F_5)_3$ with *N*,*N*-dimethylaniline could form an iminium salt $[PhCH_3N{=}CH_2]^+[HB(C_6F_5)_3]^-$ (**20a**) *via* hydride abstraction of an aminomethyl group by $B(C_6F_5)_3$, in addition to an adduct product $(C_6F_5)_3B{\cdot}NMe_2Ph$ (**20b**) (Scheme 9, top).[78] In 2017, Erker and co-workers reported an intermolecular redox-neutral C(sp^3)–H functionalisation of amine induced by a boron-based FLP.[79] The reaction of *N*,*N*,2,4,6-pentamethylaniline with Piers' borane $[HB(C_6F_5)_2]$ at 100 °C for 6 days gave benzylic C(sp^3)–H borylated product **21a** in 73% yield (Scheme 9, middle). The reaction of *N*,*N*,2,4,6-pentamethylaniline with $B(C_6F_5)_3$ in the presence of maleimide at room temperature in CH_2Cl_2 solution afforded **21b** in 85% yield (Scheme 9, bottom). In this transformation, the reaction proceeded *via* an intermolecular redox-neutral C–H activation/C–C coupling process with hydride transfer from the N–CH_3 group to the electrophilic maleimide.

3. General mechanistic modes

Inspired by the stoichiometric C–H transformations mentioned above, a series of elegant examples of catalytic C–H functionalisation



Scheme 9 Borane-mediated intermolecular redox-neutral C–H activation/C–C coupling.

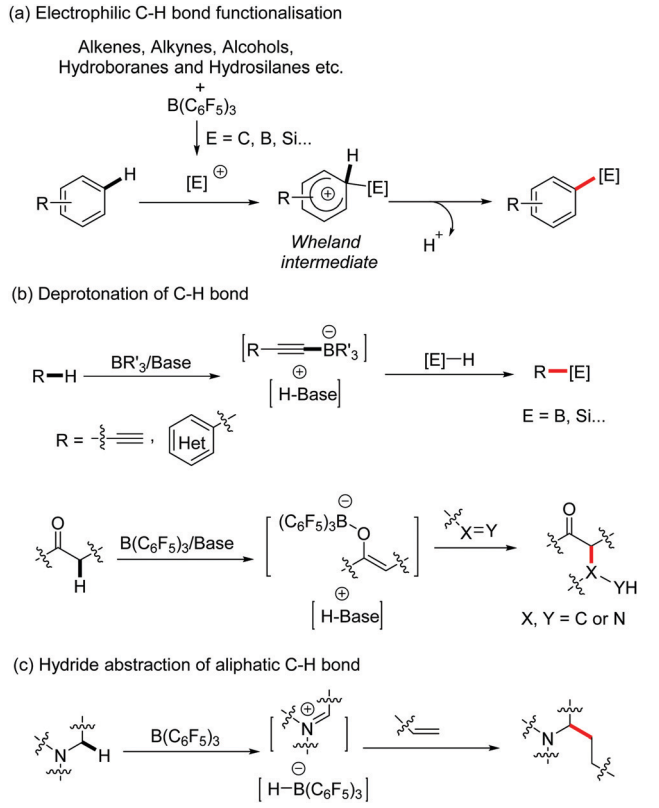


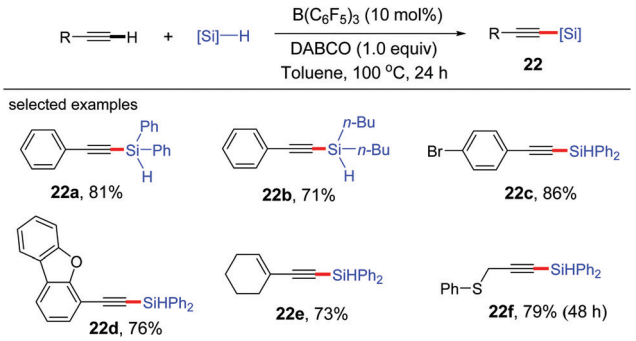
Fig. 2 General mechanistic modes for catalytic C–H bond functionalisation by electron-deficient boron-based catalysts.

have been reported in recent years. In contrast to metal-catalysed C–H functionalisation, the mechanistic processes of C–H functionalisation by electron-deficient boron-based catalysts are evidently different, thus providing significant complementarity to the existing metal-catalysed platforms.[1–24] To help readers to understand better the catalytic transformations of different types of C–H bonds by electron-deficient boron-based catalysts, several general mechanistic modes have been summarised in this section based on the nature of C–H bonds (Fig. 2). (1) First, for electron-rich (hetero)arenes, catalytic C–H functionalisation has been achieved by using single electron-deficient borane, such as $B(C_6F_5)_3$, as a catalyst through an electrophilic C–H functionalisation process (Fig. 2a).[52,53] In this mechanistic scenario, the electron-deficient borane could activate alkenes, alkynes, alcohols, hydroboranes, and hydrosilanes to afford corresponding electrophilic species $[E]^+$, which attack the most electron-rich position of the aryl ring to generate a Wheland intermediate. Then, a followed release of a proton would form a new C–X (C, B, Si *etc.*) bond. (2) For the substrates containing acidic C–H bonds, such as terminal alkynes, some heteroarenes, and carbonyl compounds, a general deprotonation mode is proposed in the presence of an electron-deficient borane and a base to give an ionic pair, which could be trapped by some functional reagents such as hydrosilanes, hydroboranes, alkenes and imines to forge a new C–X (C, Si, B *etc.*) bond (Fig. 2b).[61,63–67,80] (3) Another imporatnt mode of C–H bond cleavage by a single electron-deficient borane is the hydride abstraction. For instance, hydride abstraction of alkyl-substituted amines by a borane catalyst would generate an iminium intermediate, which could react with some terminating reagents such as alkenes to construct a new chemical bond (Fig. 2c).[78,79] Besides these three general modes, more mechanistic details for other specific examples of C–H functionalisation by electron-deficient boron-based catalysts will be presented and discussed in the following sections.

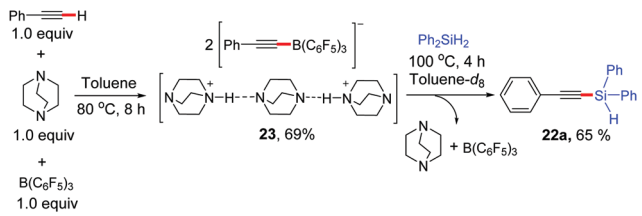
4. Catalytic C(sp)–H functionalisation

Despite extensive studies on the stoichiometric activation and transformation of the C(sp)–H bond of terminal alkynes by electron-deficient boron-based Lewis pairs,[61,63–67] the catalytic C(sp)–H functionalisation of terminal alkynes by an electron-deficient boron-based catalyst system remained unknown until 2018, when Hou and co-workers reported the catalytic C(sp)–H silylation of terminal alkynes with hydrosilanes by a combination of boron Lewis acid $B(C_6F_5)_3$ and an organic base DABCO (Scheme 10).[81] This protocol offers an efficient metal-free route for the synthesis of diverse alkynylsilanes, which are valuable building blocks in the field of synthetic chemistry and materials science.[82–86] This catalytic system showed broad substrate scope, excellent chemoselectivity, excellent functional group tolerance, good scalability, and no requirement for an additional H_2-acceptor.

The stoichiometric reaction of phenylacetylene with DABCO and $B(C_6F_5)_3$ in a 1 : 1 : 1 feed ratio gave ion-pair product **23**, which has been structurally characterised by an X-ray diffraction study (Scheme 11).[81] The reaction of **23** with Ph_2SiH_2



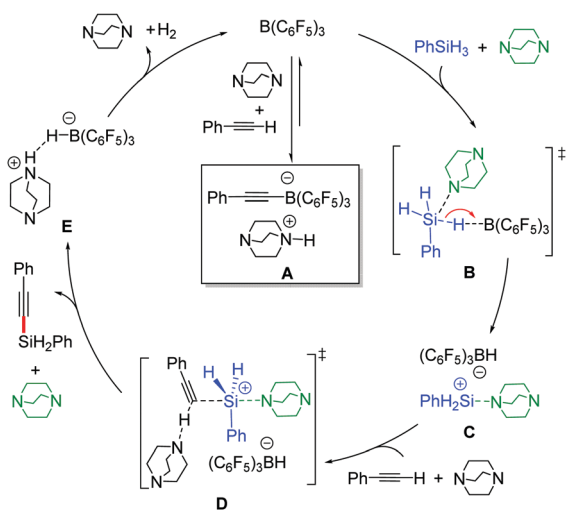
Scheme 10 Catalytic C–H silylation of terminal alkynes with hydrosilanes by a combination of $B(C_6F_5)_3$ and DABCO.



Scheme 11 Stoichiometric reaction of phenylacetylene with DABCO and $B(C_6F_5)_3$.

afforded silylated product **22a** in 65% yield. These results suggest that ion-pair **23** might be involved in the catalytic cycle.

Based on the experimental and density functional theory (DFT) studies, a possible catalytic cycle for the C(sp)–H silylation of phenylacetylene with $PhSiH_3$ was proposed as shown in Scheme 12. The C(sp)–H activation of phenylacetylene by DABCO and $B(C_6F_5)_3$ would reversibly form an ion-pair intermediate like **A**. On the other hand, the activation of $PhSiH_3$ by $B(C_6F_5)_3$ in the presence of DABCO may give ion-pair intermediate **C** *via* **B**. The reaction of **C** with phenylacetylene and DABCO yields the silylated alkyne *via* transition state **D** with the release of DABCO and **E**. Finally, the release of H_2 from **E** regenerates $B(C_6F_5)_3$ and DABCO. It is worth noting that DABCO served as both a Lewis base and a Brønsted base in this catalytic transformation.



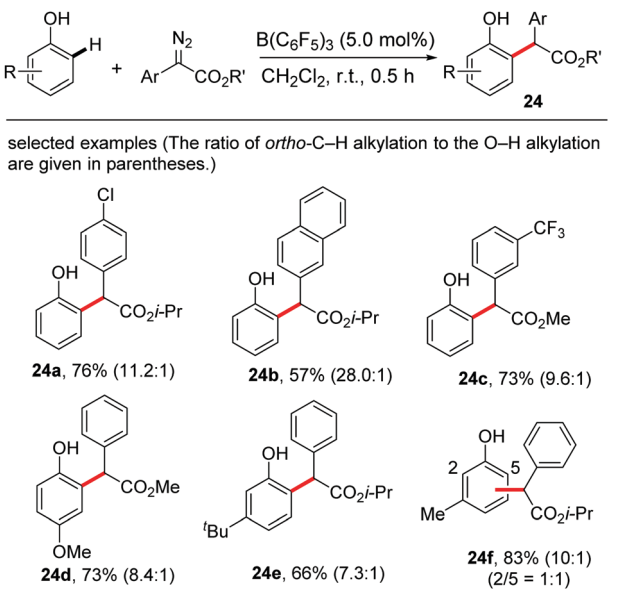
Scheme 12 Proposed mechanism for catalytic C(sp)–H silylation of phenylacetylene with $PhSiH_3$ by a combination of $B(C_6F_5)_3$ and DABCO.

5. Catalytic C(sp^2)–H functionalisation

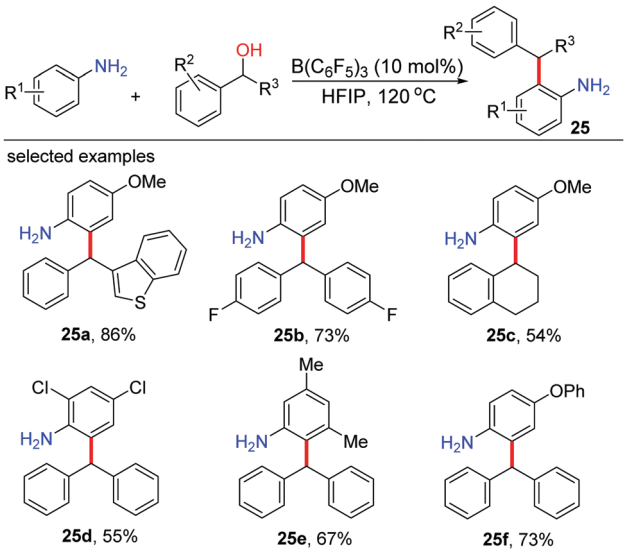
In this section, the catalytic C(sp^2)–H transformations of (hetero)arenes by electron-deficient boron-based catalysts are summarised according to the reaction types.

5.1 C(sp^2)–H alkylation

5.1.1 Coupling with alkylation reagents. Diazo compounds are one of the most important and useful alkylation reagents in the field of synthetic chemistry.[87–89] In 2016, Zhang and co-workers reported an efficient $B(C_6F_5)_3$-catalysed C(sp^2)–H alkylation of unprotected phenols with α-aryl α-diazoesters, affording the *ortho*-alkylated phenols (Scheme 13).[90] The reaction features simple and mild conditions, wide substrate scope, high chemo- and regioselectivity, and gram-scalable synthesis. It should be noted that although highly chemoselective *O*-alkylation and *para*-selective C(sp^2)–H bond alkylation of unprotected phenols with α-aryl α-diazoesters have been achieved under transition-metal catalysis, the *ortho*-selective C(sp^2)–H bond alkylation of phenols is more challenging. In this context, the use of commercially available $B(C_6F_5)_3$ as a catalyst to realise the *ortho*-selective C(sp^2)–H alkylation of phenols is of great significance and interest. Mechanistic studies by NMR analysis and control experiments demonstrated that the selective *ortho*-C–H substitution was governed by hydrogen bonding between the OH group of phenol and the F atom of $B(C_6F_5)_3$.



Scheme 13 *Ortho*-selective C–H alkylation of phenols with α-aryl α-diazoesters.

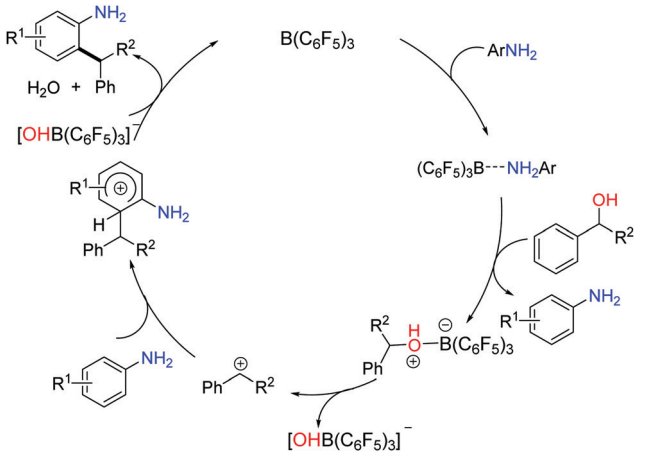


Scheme 14 *Ortho*-C–H alkylation of unprotected arylamines with benzylic alcohols.

Alcohols are a class of stable and readily available organic compounds with low toxicity. In this regard, alcohols have been used as alkylating reagents in transition metal-catalysed *N*-alkylation of anilines and *C*-alkylation of ketones.[91–93] In 2019, Meng, Chan and co-workers developed a highly efficient and chemoselective C(sp^2)–H alkylation of unprotected arylamines using alcohols as alkylating reagents and $B(C_6F_5)_3$ as the catalyst (Scheme 14).[94] Interestingly, the choice of solvents showed a dramatic effect on the chemoselectivity control in this catalytic system. When the reactions were performed in protic HFIP (1,1,1,3,3,3-hexafluoro-2-propanol), C(sp^2)–H alkylation was achieved with negligible *N*-alkylation product formation. In contrast, the use of a polar aprotic solvent CH_3NO_2 mainly gave the *N*-alkylation products. This method showed broad substrate scope, offering convenient access to various functionalised arylamines.

Based on control experiments and DFT calculations, a plausible mechanism for the C–H alkylation of anilines with alcohols was proposed as shown in Scheme 15.[94] The reaction starts with the formation of an adduct of $B(C_6F_5)_3$ and aniline followed by alcohol/amine exchange to generate a $B(C_6F_5)_3$-alcohol complex, which then undergoes dissociation to give a benzylic carbocation. The electrophilic attack of arylamines by carbocation gives a σ-complex intermediate, which produces the final alkylated product and regenerates $B(C_6F_5)_3$ after protolysis.

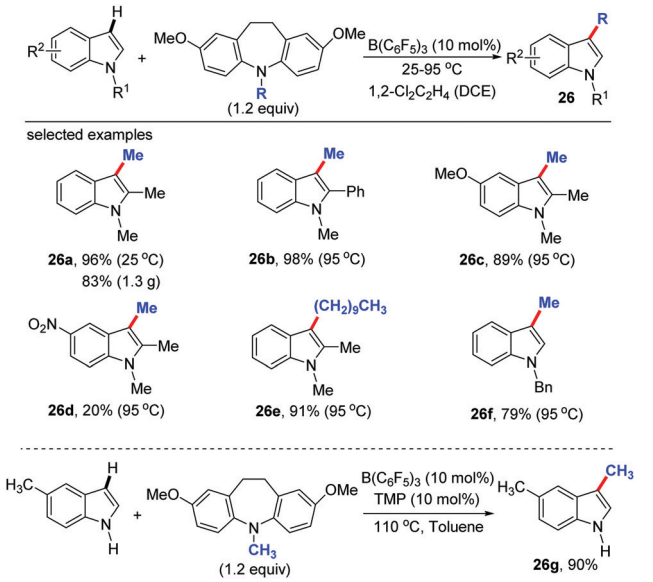
Alkylated indoles, especially methylated indoles, are widely found in biologically active molecules and natural products. The direct C3 methylation of indoles is a challenging transformation since it often suffers from the *N*- and *C*-methylation selectivity problem and low reactivity of some substrates. Very recently, inspired by Santini's seminal work of formation of borohydride ion pair *via* hydride abstraction of *N*-alkyl substituted anilines by $B(C_6F_5)_3$,[78] Melen, Morrill and co-workers developed a $B(C_6F_5)_3$-catalysed direct C3 alkylation of indoles



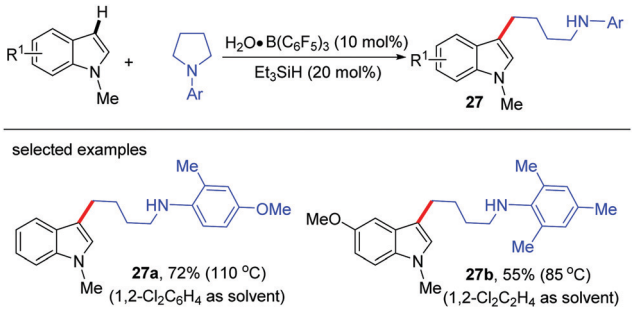
Scheme 15 Plausible mechanism for C(sp^2)–H alkylation of anilines.

using *N*-alkyl substituted anilines as alkylating reagents (Scheme 16).[95] A wide range of indole substrates were alkylated in high yields and high selectivity. A N–H free indole could also be selectively alkylated at the C3–H position in the presence of TMP (10 mol%), affording alkylation product **26g** in high yield. Besides straightforward alkylation, the $B(C_6F_5)_3$-catalysed reaction of indoles with *N*-aryl pyrrolidines in the presence of Et_3SiH afforded the C3–H functionalised indoles *via* an alkylative ring-opening cascade process (Scheme 17).[86] The obtained indoles bearing a 4-(3-indolyl)butylamine unit are found in several drug molecules, such as vilazodone, roxindole, siramesine, and carmoxirole.

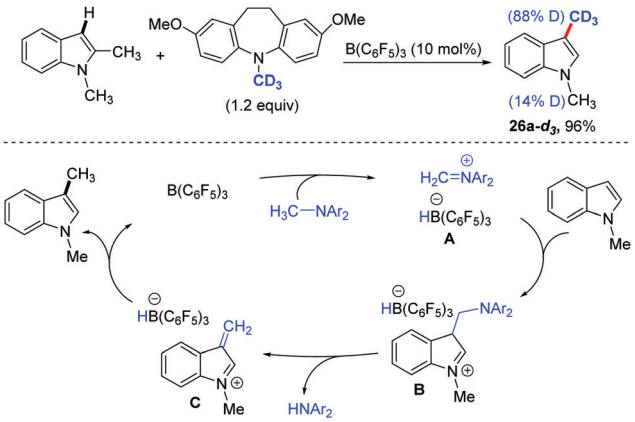
Based on the deuterium-labeled control experiment, a possible catalytic cycle for the $B(C_6F_5)_3$-catalysed methylation of indoles with *N*-methyl substituted anilines was proposed as shown in Scheme 18. At first, $B(C_6F_5)_3$ reacts with an *N*-methyl aniline *via* hydride abstraction to generate iminium-borohydride



Scheme 16 $B(C_6F_5)_3$-Catalysed alkylation of indoles with amine-based alkylating reagents.



Scheme 17 $B(C_6F_5)_3$-Catalysed alkylation-ring opening cascade.

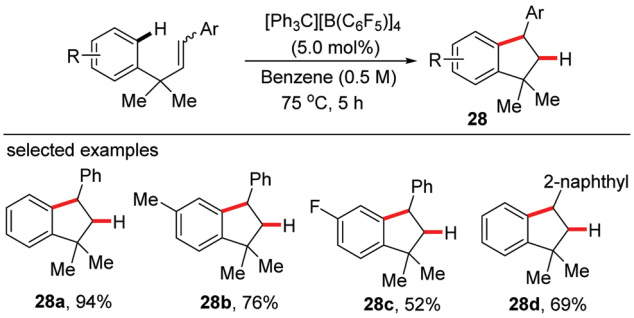


Scheme 18 Proposed mechanism for $B(C_6F_5)_3$-catalysed methylation of indoles.

ion pair **A**, which could be trapped by indole to give **B**. The intramolecular proton transfer of **B** leads to the elimination of aniline *via* an $E1_{CB}$ (CB = conjugate base) process, forming α,β-unsaturated iminium species **C**, which could be reduced by borohydride to give the methylated indole product and regenerate the catalyst $B(C_6F_5)_3$.[95]

5.1.2 Intramolecular hydroarylation of C═C double bonds. The catalytic intramolecular hydroarylation reaction of alkenes is one of the most powerful tools in the synthesis of many types of benzocycloalkanes.[96,97] In 2017, Stokes and co-workers developed an electrophilic intramolecular hydroarylation reaction of β-(α,α-dimethylbenzyl)styrenes using $[Ph_3C][B(C_6F_5)_4]$ as a precatalyst (Scheme 19).[98] Indeed, screening of various catalysts proved that $[Ph_3C][B(C_6F_5)_4]$ exhibited higher efficiency than other Brønsted and Lewis acids such as *p*-TsOH·H_2O (*p*-toluenesulfonic acid monohydrate), HOTf (trifluoromethanesulfonic acid) and TMSOTf (trimethylsilyl triflate). The reaction affords a facile method for the synthesis of diverse indanes bearing a benzylic quaternary center, which is an important structural unit in some functional materials. Regarding the reaction mechanism, the geminal dimethyl-containing quaternary center plays a key role in accelerating the cyclisation of β-(benzyl)styrenes due to the Thorpe–Ingold effect.

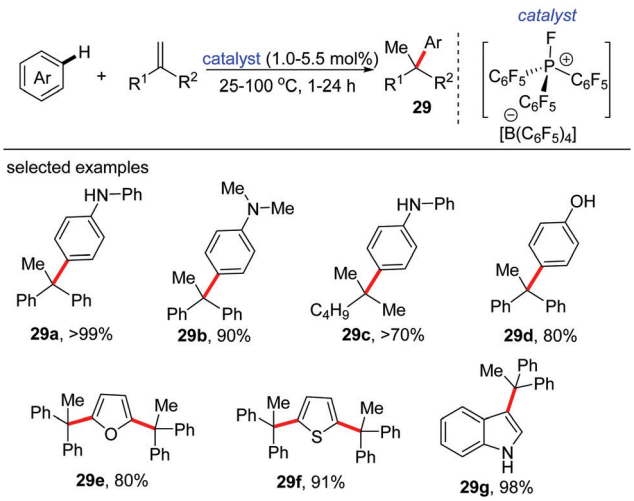
5.1.3 Intermolecular hydroarylation of C═C double bonds. In 2015, Stephan and co-workers reported an efficient main group



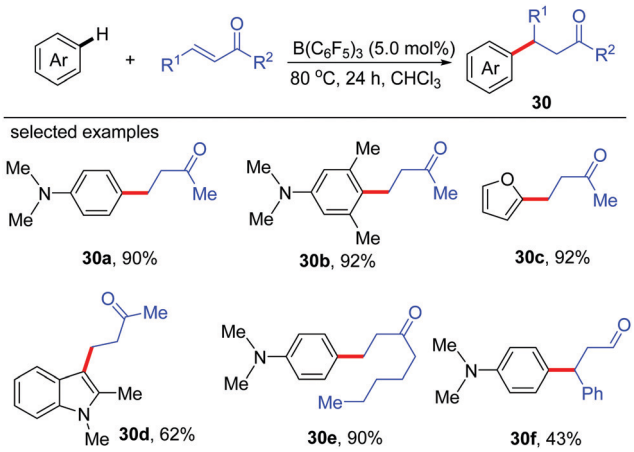
Scheme 19 Intramolecular hydroarylation of β-benzylstyrenes.

catalyst consisting of an electrophilic phosphonium cation and a borate anion, which could promote the intermolecular addition of aromatic $C(sp^2)$–H bonds to 1,1-disubstituted olefins (Scheme 20).[99] Under mild conditions, a series of substituted tertiary aniline, bis-arylamine, phenol, furan, thiophene, and indole derivatives smoothly underwent such transformation to give the desired products in good to excellent yields. This highly chemo- and regioselective C–C bond forming reaction also constitutes the first example of phosphonium-catalysed hydroarylation of olefins.

The addition of a carbon-based nucleophile to an electron-deficient α,β-unsaturated carbonyl compound is one of the most efficient approaches to form C–C bonds. The carbon nucleophiles reported so far are mainly reactive $C(sp^3)$–H units adjacent to an electron-withdrawing group or organometallic reagents. Utilizing (hetero)arenes as a nucleophile is a great challenge in this type of transformation.[100,101] Based on the concept of carbonyl activation through coordination to $B(C_6F_5)_3$, in 2017, Li and Werner reported the first example of $B(C_6F_5)_3$-catalysed intermolecular hydroarylation of C═C double bonds of α,β-unsaturated ketones and aldehyde compounds with aromatic and heteroaromatic hydrocarbon compounds (Scheme 21).[102] This transformation exhibited broad substrate scope, high regioselectivity, and good to excellent isolated yields for desired products.



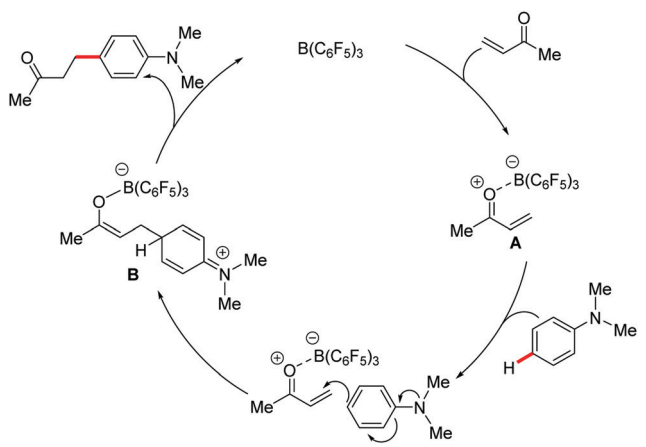
Scheme 20 Hydroarylation of 1,1-disubstituted olefins with (hetero)-arenes.



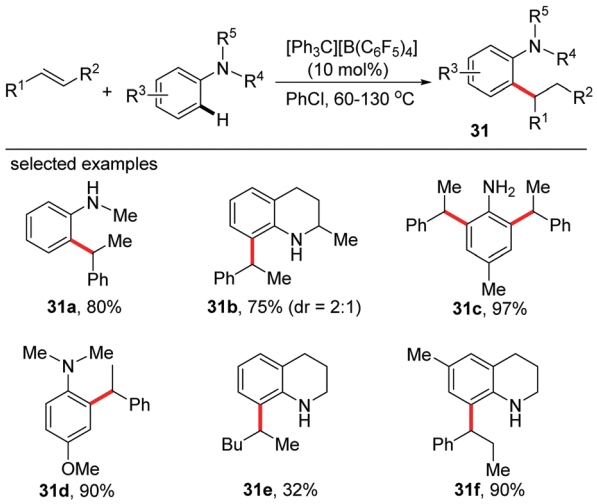
Scheme 21 Hydroarylation of α,β-unsaturated ketone and aldehyde compounds with (hetero)arenes.

A possible mechanism of the $B(C_6F_5)_3$-catalysed hydroarylation of methyl vinyl ketone with *N*,*N*-dimethylaniline as a typical example is shown in Scheme 22.[102] First, carbonyl activation of methyl vinyl ketone by catalyst $B(C_6F_5)_3$ generates electrophilic species **A**. Subsequently, the electrophilic species **A** is attacked by the *para* carbon atom of *N*,*N*-dimethylaniline to form ion pair intermediate **B**, which could be transformed into the desired product and regenerates $B(C_6F_5)_3$ by sequential rearomatisation and protonation of the enolate, and routine keto–enol tautomerisation.

Although the C–H alkylation reactions of protected-anilines with C–C double bonds have been extensively developed, the analogous transformation of N–H free aniline substrates remains rare. In 2018, Yao and co-workers developed selective metal-free hydroarylation of alkenes (including styrenes and unreactive alkenes) with various primary, secondary, and tertiary aromatic amines using commercial available borate $[Ph_3C][B(C_6F_5)_4]$ as the catalyst (Scheme 23).[103] The catalytic reaction proceeded under relatively mild conditions with high chemo- and regioselectivity, affording a series of branch-alkylated aniline derivatives.



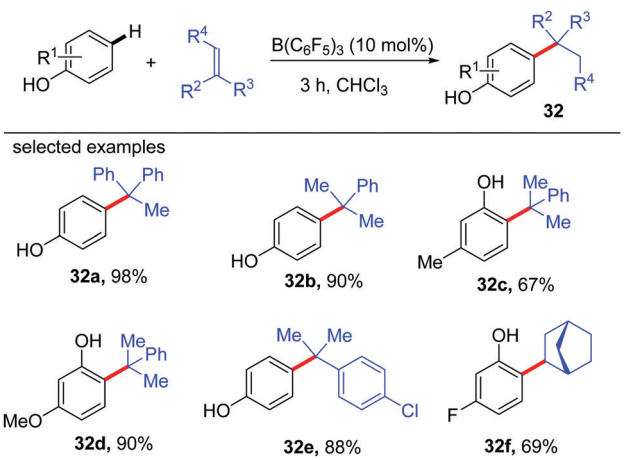
Scheme 22 Possible mechanism of hydroarylation of methyl vinyl ketone with *N*,*N*-dimethylaniline.



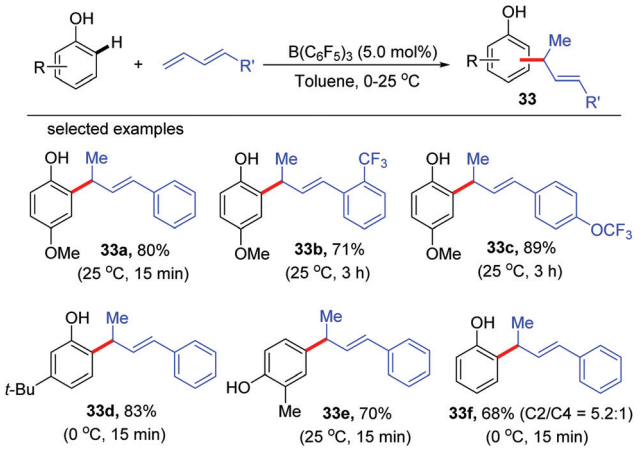
Scheme 23 $[Ph_3C][B(C_6F_5)_4]$-Catalysed hydroarylation of alkenes with anilines.

Besides anilines and electron-rich heterocycles,[102,103] the $C(sp^2)$–H bond addition of phenol substrates to alkenes has also been investigated. In 2018, Bentley and Caputo realised $B(C_6F_5)_3$-catalysed hydroarylation alkenes with phenols (Scheme 24).[104] This transformation took place under mild conditions in good yields, exhibiting excellent chemoselectivity and a wide substrate scope of alkenes and phenols. The regioselectivity in this reaction was dramatically influenced by the steric and electronic effect. Generally, the hydroarylation selectively occurred at the *para* position of phenol. When a *meta*-position of phenol is substituted, the reaction took place selectively at the less hindered *ortho* position. At this stage, the catalytic mechanism is not very clear, and the authors proposed that the activation of either alkene or phenol by $B(C_6F_5)_3$ at the initial step in the catalytic cycle is possible.

Highly 1,2-selective hydroarylation of 1,3-dienes with arenes offers an atom-economical route to allylic arenes. However, such transformations mainly relied on transition-metal catalysts.[105] In 2019, Li and co-workers achieved the 1,2-selective hydroarylation



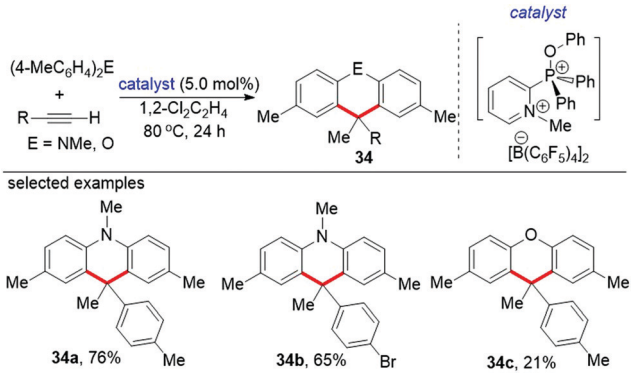
Scheme 24 $B(C_6F_5)_3$-Catalysed hydroarylation of alkenes with phenols.



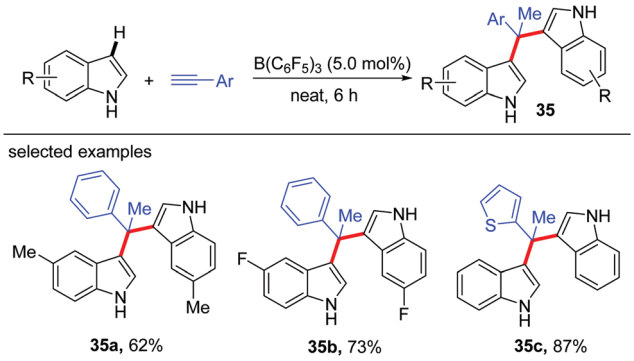
Scheme 25 $B(C_6F_5)_3$-Catalysed 1,2-selective hydroarylation of 1,3-dienes with phenols.

of 1,3-dienes with free phenols under mild conditions using $B(C_6F_5)_3$ as the catalyst (Scheme 25).[106] This method provides efficient access to *ortho*-allyl phenols, which are valuable building blocks for diverse chemical transformations. This protocol exhibits wide substrate scope, good yields, high *ortho*-regioselectivity and excellent chemoselectivity. Moreover, it could also be applied to the late-stage functionalisation of drug molecules. The DFT calculations and control experiments suggest that the formation of an adduct of $B(C_6F_5)_3$ with phenol enables this reaction to work *via* a protonation/Friedel–Crafts-type process.

5.1.4 Intermolecular hydroarylation of C≡C triple bonds. Besides alkenes and 1,3-dienes, the hydroarylation of terminal alkynes with aromatics by boron-based catalysts has also been realised. In 2017, Stephan and co-workers reported a double hydroarylation of alkynes with diarylamines or diarylethers using electrophilic pyridinium-based dicationic salt $[(PhO)P(2\text{-}(N\text{-}Mepy))Ph_2][B(C_6F_5)_4]_2$ as the catalyst, which provides a straightforward method for the synthesis of a series of 9,10-dihydroacridine and 9*H*-xanthene derivatives under mild conditions (Scheme 26).[107] In contrast, the commonly used boron catalyst $B(C_6F_5)_3$ did not work in this transformation.



Scheme 26 Catalytic double hydroarylation of alkynes with diarylamines or diarylethers.



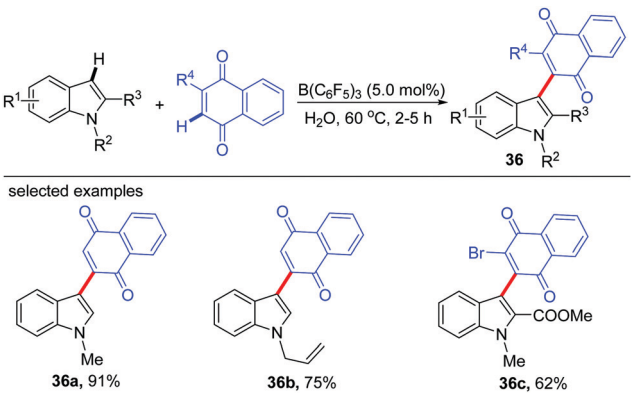
Scheme 27 $B(C_6F_5)_3$-Catalysed bis-hydroindolation of aryl alkynes with indoles.

The hydroamination of alkynes with unprotected diarylamines by $B(C_6F_5)_3$ was reported previously by the group of Stephan.[108]

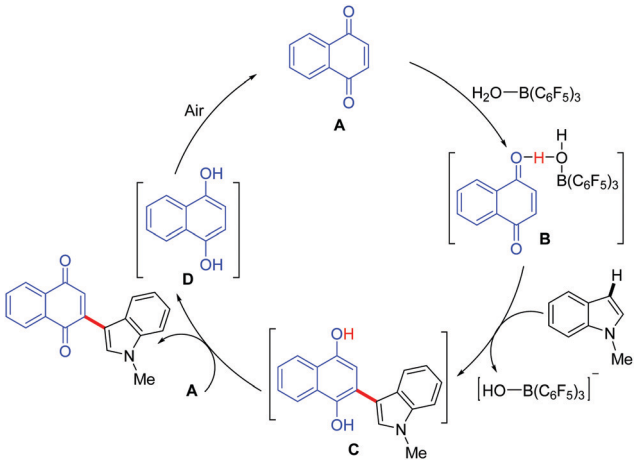
Bis(indolyl)alkane is an important structure framework in many natural products and drugs. From the viewpoint of atom economy, the direct catalytic bis-hydroindolation of alkynes with indoles represents one of the most powerful methods to prepare these compounds with 100% atom efficiency. In 2018, Zhong and co-workers reported the first example of a metal-free double Markovnikov-type C–H addition of indoles to aryl alkynes using $B(C_6F_5)_3$ as the catalyst under solvent-free conditions (Scheme 27).[109] A wide range of N–H free and *N*-protected indoles are well tolerated, affording diverse bis(indolyl)alkanes in moderate to good yields, along with high chemo- and regioselectivities.

5.2 C(sp^2)–H alkenylation

Indolylquinone is an important class of indole derivatives, as well as a building block for the synthesis of valuable biologically active molecules.[110] In 2019, Wang and co-workers reported a $B(C_6F_5)_3$-catalysed formal C(sp^2)–H/C(sp^2)–H cross-coupling of 1,4-naphthoquinones with indoles using water as the solvent (Scheme 28).[111] A wide range of indoles and 1,4-naphthoquinones could undergo the coupling reaction to give the desired products in moderate to good yields. Compared to other known accesses to indole-substituted



Scheme 28 $B(C_6F_5)_3$-Catalysed C(sp^2)–H/C(sp^2)–H cross-coupling.



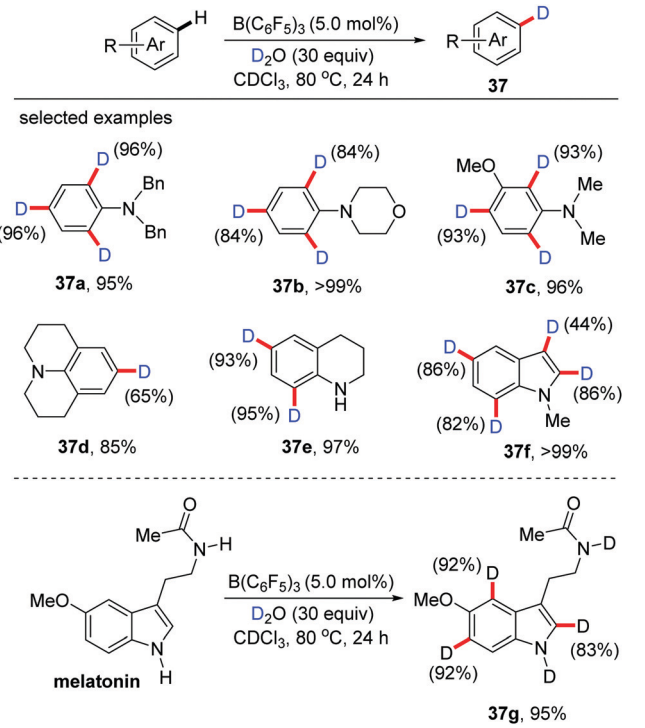
Scheme 29 Possible mechanism of $B(C_6F_5)_3$-catalysed $C(sp^2)$–H/$C(sp^2)$–H bond cross-coupling.

1,4-naphthoquinones, this method is more practical, convenient and efficient because the reaction can be performed under open-air, mild and metal-free conditions. In addition, the solvent and a part of the catalyst $B(C_6F_5)_3$ could be recycled by a simple filtration process. Therefore, the reaction provides an atom-economical and green approach for the synthesis of indole-substituted 1,4-naphthoquinones.

A possible reaction mechanism for such $B(C_6F_5)_3$-catalysed $C(sp^2)$–H/$C(sp^2)$–H cross-coupling is shown in Scheme 29.[111] First, the interaction between catalyst $B(C_6F_5)_3$ and H_2O could form a corresponding adduct.[112] Then, 1,4-naphthoquinone may be activated by the $B(C_6F_5)_3$–H_2O adduct *via* a Brønsted acid activation mode to generate electrophilic species **B**. A nucleophilic attack to **B** by the C3-position of 1-methylindole would yield intermediate **C** and release an anionic hydroxyboron species $[B(C_6F_5)_3–OH]^-$. The oxidation of the 1,4-hydroquinone unit in **C** by 1,4-naphthoquinone **A** gives the final product *N*-methylindole-substituted 1,4-naphthoquinone together with the formation of 1,4-hydroquinone **D**. The oxidation of **D** by air regenerates 1,4-naphthoquinone **A**.

5.3 $C(sp^2)$–H deuteration

Deuterium labeled arenes are of great importance and interest in drug molecules and are also widely used as a powerful tool for reaction mechanism investigations. Hydrogen–deuterium exchange reactions constitute a facile approach for the synthesis of deuterium-labeled arenes. In 2017, Werner and co-workers developed the $B(C_6F_5)_3$-catalysed regioselective C–H deuteration of electron-rich (hetero)arenes, *e.g.* anilines and indoles, using D_2O as the deuterium source and $CDCl_3$ as the solvent (Scheme 30).[113] The reaction efficiently proceeded under mild conditions with high deuterium incorporation. This protocol is also suitable for the deuterium incorporation of complex molecules of natural products and pharmaceuticals, such as melatonin (Scheme 30, bottom). The mechanistic studies suggest that the coordination of D_2O to $B(C_6F_5)_3$ weakens the O–D bond and subsequently results in the formation of



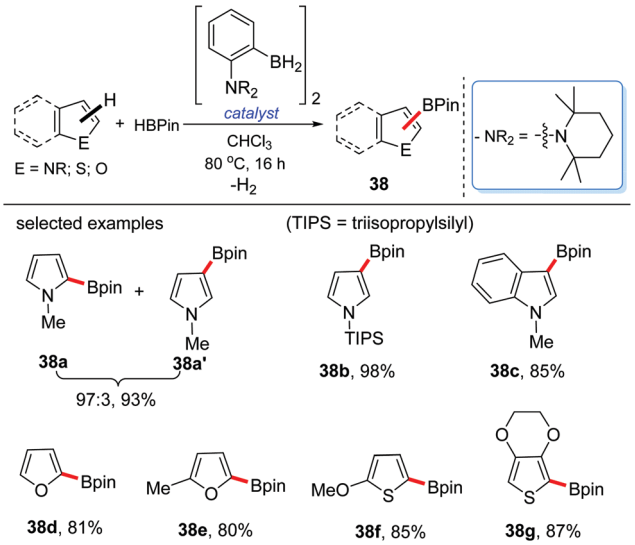
Scheme 30 $B(C_6F_5)_3$-Catalysed regioselective deuteration of electron-rich aromatic compounds.

an electrophilic D^+ species, which should be active species in the catalytic cycle.

5.4 $C(sp^2)$–H borylation

Organoboron compounds are widely found in pharmaceuticals and functional materials, and are also versatile building blocks in organic synthesis.[114] Consequently, the development of efficient methods for the construction of C–B bond continues to be a hot topic in the field of synthetic chemistry. Compared with traditional multistep synthesis, the direct borylation of an aryl C–H bond with boron sources constitutes an atom- and step-economical approach since it obviates the prefunctionalisation of substrates. It has been recently found that electron-deficient boron-based catalysts exhibit great performance in the $C(sp^2)$–H borylation of diverse (hetero)arenes.

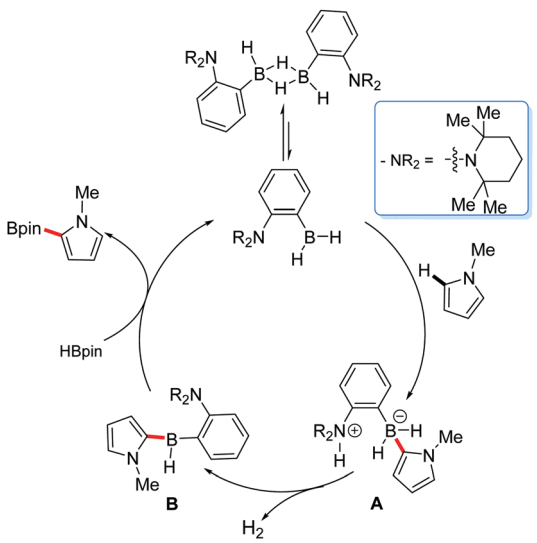
In 2015, Fontaine and co-workers reported an elegant metal-free, catalytic $C(sp^2)$–H borylation of various heteroarenes using a boron-containing intramolecular frustrated Lewis pair as the catalyst, which represents a substantial breakthrough in the field of frustrated Lewis pairs catalysis (Scheme 31).[115] Electron-rich arenes such as pyrroles, indoles, thiophene, and furan derivatives worked well in this transformation, giving the corresponding borylated products in good yields. The mechanistic studies indicate that the borylation reaction starts from the C–H bond activation of heteroarenes by a borane-containing frustrated Lewis pair, which gives zwitterionic species like **A** (Scheme 32).[115] The release of H_2 from **A** generates intermediate **B**, which subsequently undergoes σ-bond metathesis with HBpin to give the final borylation product. The DFT



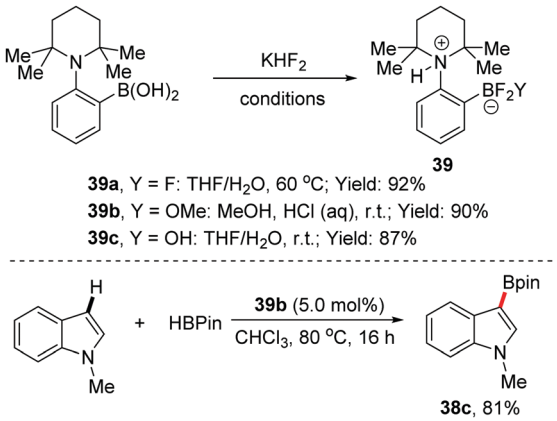
Scheme 31 FLP-catalysed C–H borylation of heteroarenes.

calculations and the kinetic isotope effect experiments suggest that C–H cleavage is involved in the rate-determining step of the catalytic cycle.

Although the metal-free C–H borylation of heteroarenes has been established by using the intramolecular N/B frustrated Lewis pair as the catalyst (Scheme 32),[115] the Lewis acidic moiety of such a catalyst is usually sensitive to moisture and air, which limits its further application in the field of synthetic chemistry to some extent. In this context, Fontaine and co-workers developed a series of air and moisture stable intramolecular trifluoro- and difluoro-borate derivatives of bulky (tetramethylpiperidino)benzene (Scheme 33).[116] Such intramolecular FLPs were demonstrated to be robust precatalysts for the efficient C–H borylation of diverse heteroarenes, *e.g.* pyrrole, indole, thiophene and furan derivatives. For example,



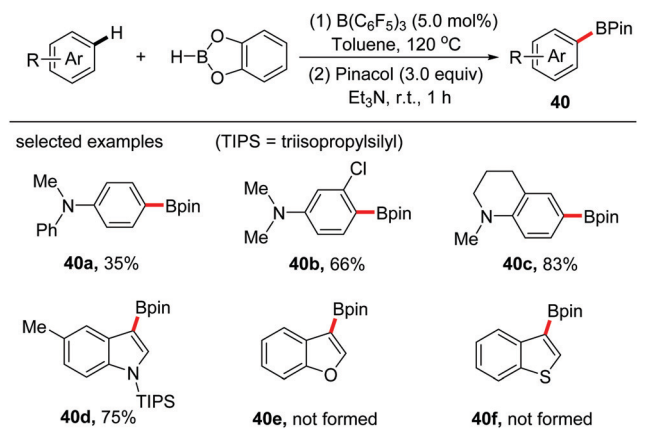
Scheme 32 Proposed mechanism for FLP-catalysed C–H borylation of heteroarenes.



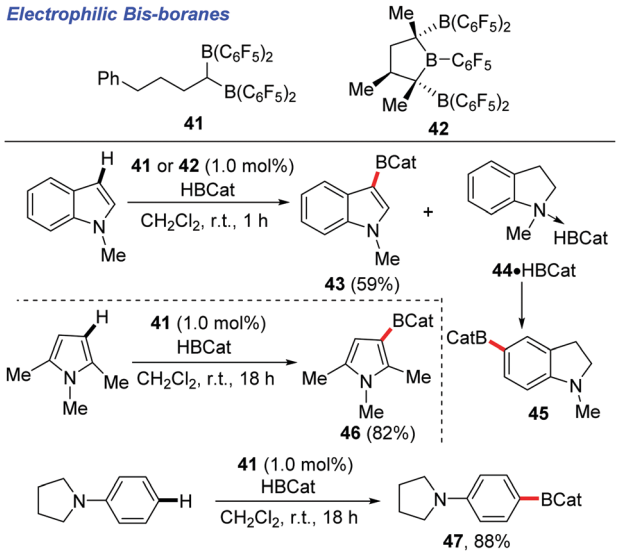
Scheme 33 Synthesis of bench-stable fluoroborate precatalysts for C–H borylation of heteroarenes.

the C–H borylation of 1-methylindole with HBpin took place smoothly to give product **38c** in 81% yield in the presence of a catalytic amount of **39b** (5 mol%).

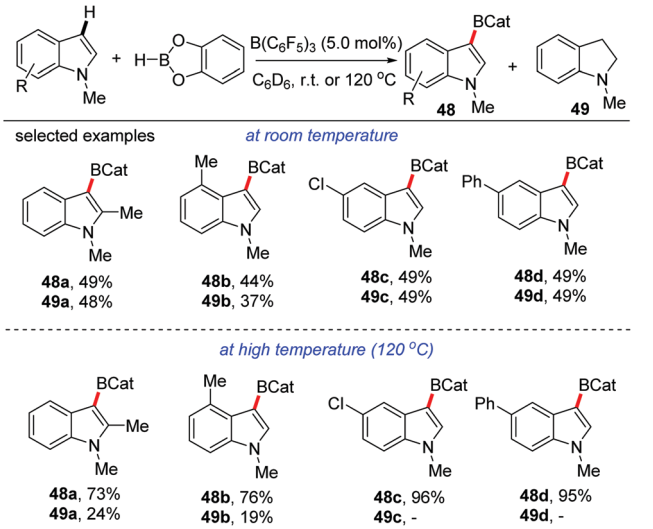
In 2017, Oestreich, Klare and co-workers reported C–H borylation of electron-rich arenes with catecholborane using $B(C_6F_5)_3$ as the catalyst (Scheme 34).[117] The catalytic borylation worked very well for aniline and indole derivatives at 120 °C, affording the desired products in moderate to high yields. When an appropriate alkene such as norbornene or norbornadiene was used as a dihydrogen acceptor, the $B(C_6F_5)_3$-catalysed C–H borylation of *N*,*N*-dimethylanilines efficiently proceeded even at room temperature. The mechanistic studies suggest that the B–H bond of catecholborane is first activated by the boron Lewis acid to form a boronium ion species, which then accepts nucleophilic attack by the electron-rich position of (hetero)arenes to generate an ion pair intermediate. Finally, the borylated product is produced by the release of dihydrogen. Almost at the same time, Takita, Uchiyama, and co-workers also achieved a similar electrophilic C–H borylation of various (hetero)arenes such as pyrrole, thiophene, and indole derivatives by a combination of a catalytic amount of $B(C_6F_5)_3$ and a sulfur Lewis base.[118]



Scheme 34 $B(C_6F_5)_3$-Catalysed C–H borylation of electron-rich arenes.



Scheme 35 C(sp^2)–H borylation catalysed by electrophilic bis-boranes.



Scheme 36 $B(C_6F_5)_3$-Catalysed C–H borylation of *N*-methylindoles and convergent disproportionation reaction of indoles.

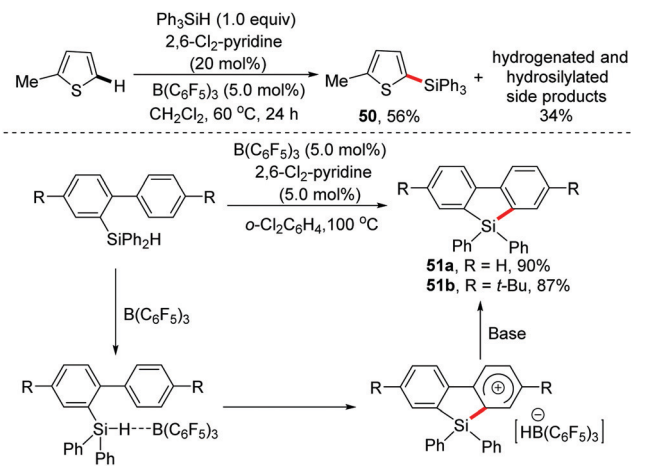
In 2017, Erker and co-workers also realised a similar metal-free catalytic C–H borylation of electron-rich arenes and heteroarenes with catecholborane (Scheme 35).[119] In this transformation, the electrophilic geminal chelate bis-boranes bearing strongly Lewis acidic $B(C_6F_5)_2$ and $B(C_6F_5)$ groups were used as catalysts. Compared with the $B(C_6F_5)_3$-catalysed system reported by Oestreich,[117] the electrophilic bis-borane catalyst system enabled the borylation reactions to work at room temperature even in the absence of a dihydrogen acceptor. However, it showed a relatively limited substrate scope compared to Oestreich's catalytic system.

Despite great advances in metal-free catalytic C(sp^2)–H borylation of heteroarenes, attempts to achieve the analogous transformation of *N*-methylindoles often suffered from the regioselectivity and side reaction (such as reduction) problems. In 2017, Zhang and co-workers reported a highly regioselective $B(C_6F_5)_3$-catalysed C–H borylation of *N*-methylindoles with wide substrate scope (Scheme 36).[120] At room temperature, the reaction of *N*-methylindole with catecholborane in the presence of 5.0 mol% $B(C_6F_5)_3$ usually produced a mixture of borylated indoles and indolines in an almost 1 : 1 ratio. By taking advantage of $B(C_6F_5)_3$-catalysed dehydrogenation of heterocycles at high temperature, the convergent disproportionation reaction of indoles could be achieved by heating the reaction mixture at 120 °C, which transformed the indoline products back to indoles. The continuous consumption of undesired indolines enabled the formal formation of C3–H borylated indoles in high yields and good selectivity.

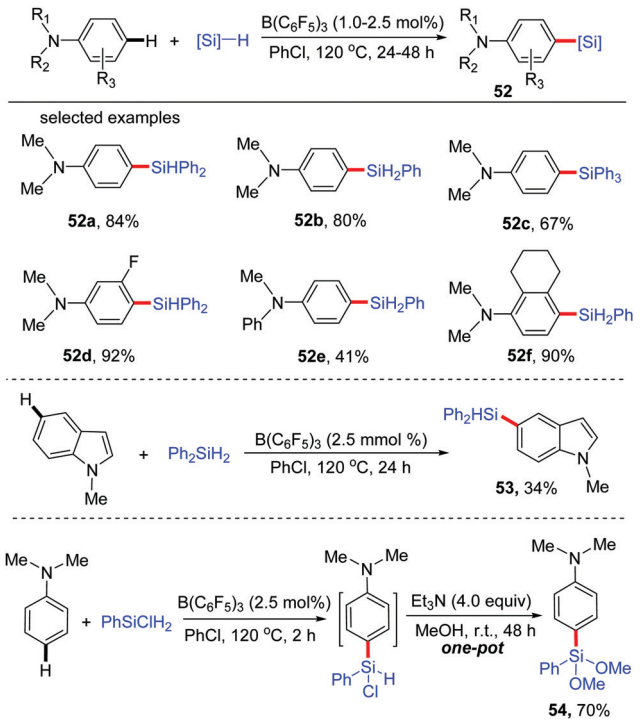
5.5 C(sp^2)–H silylation

Silyl-substituted (hetero)arenes play an important role in the field of organic electronics and photonics, pharmaceuticals, and synthetic chemistry.[121] Therefore, the development of an efficient method for the formation of C–Si bonds is highly desirable. In 2013, Ingleson and co-workers reported a $B(C_6F_5)_3$-mediated C–H dehydrogenative silylation of heteroarenes with hydrosilanes.[122] The only catalytic example in this work was the C–H silylation of 2-methylthiophene in the presence of 5 mol% of $B(C_6F_5)_3$, which afforded the silylated product in 56% yield, along with hydrogenated and hydrosilylated side products in a combined 34% yield (Scheme 37, top). In 2014, the Ingleson group achieved a catalytic intramolecular dehydrogenative silylation reaction of hydrosilyl-substituted biphenyls by using a combination of $B(C_6F_5)_3$ and 2,6-dichloropyridine as the catalyst (Scheme 37, bottom).[123] In the catalytic cycle, the Si–H bond of the hydrosilane unit is activated by Lewis acid $B(C_6F_5)_3$ followed by the electrophilic silylation of the aryl ring to generate a Wheland intermediate. Finally, the deprotonation of the silylated arenium cation by a base such as 2,6-dichloropyridine affords the benzofused silole product.

In 2016, Hou and co-workers disclosed a $B(C_6F_5)_3$-catalysed intermolecular C(sp^2)–H dehydrosilylation of electron-rich arenes with hydrosilanes (Scheme 38).[124] The reaction features



Scheme 37 $B(C_6F_5)_3$-Mediated and -catalysed C(sp^2)–H silylation.

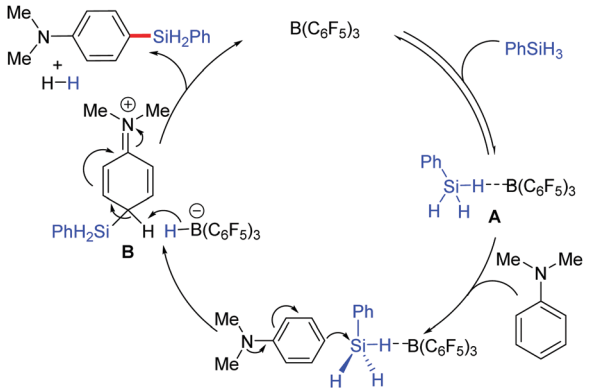


Scheme 38 $B(C_6F_5)_3$-Catalysed aromatic C–H silylation with hydrosilanes.

broad substrates, good compatibility of functional groups, and no need for any Lewis base and hydrogen acceptor. A series of *N*,*N*-disubstituted anilines could be silylated at the *para* position in moderate to high yields by the release of H_2 (Scheme 38, top). In the case of *N*-methylindole, an extraordinary C5-selective C–H silylation was observed albeit with low 34% yield (Scheme 38, middle). More significantly, highly sensitive chlorohydrosilanes such as $PhSiH_2Cl$ and Ph_2SiHCl could also be used as silicon sources, thus offering opportunities for further transformation of the Si–Cl bond (Scheme 38, bottom). Almost at the same time, Oestreich and co-workers independently found that Lewis acid $B(C_6F_5)_3$ could serve as an efficient catalyst for electrophilic $C(sp^2)$–H silylation of *N*,*N*-dimethylaniline with $PhMe_2SiH$.[125]

A possible catalytic cycle for the intermolecular C–H silylation of *N*,*N*-dimethylaniline with phenylsilane is shown in Scheme 39.[124] The activation of the hydrosilane by $B(C_6F_5)_3$ through a B–H interaction forms weak adduct **A**. The nucleophilic attack of the *para*-position carbon of electron-rich *N*,*N*-dimethylaniline to the electrophilic silicon center in **A** could generate ion-pair intermediate **B**. Finally, the release of dihydrogen from **B** gives the silylated product and regenerates $B(C_6F_5)_3$.

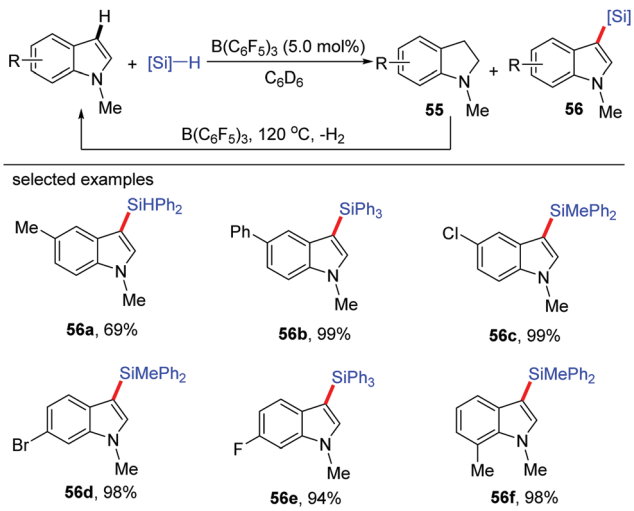
In 2017, Zhang and co-workers achieved $B(C_6F_5)_3$-catalysed highly selective C3–H silylation of various indoles with hydrosilanes at high temperature (Scheme 40).[126] Usually, the C–H silylation of indoles with hydrosilanes at room temperature often gave a mixture of C3-silylated indoles and the transfer hydrogenated product indolines in about a 1 : 1 ratio. In 2016, the groups of Paradies and Kanai reported the $B(C_6F_5)_3$-catalysed dehydrogenative oxidation of various *N*-protected indolines into



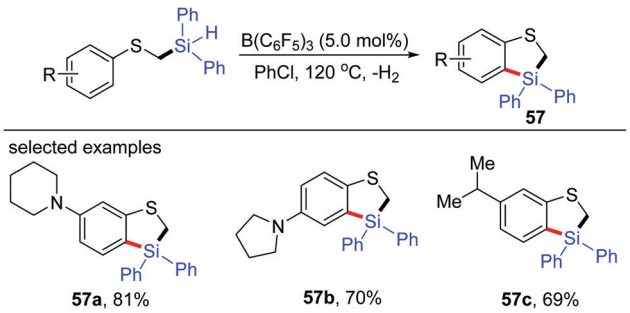
Scheme 39 Proposed mechanism for $B(C_6F_5)_3$-catalysed C–H silylation of *N*,*N*-dimethylaniline with phenylsilane.

indoles at high temperatures (120–150 °C).[127,128] These findings provided a possible chance for suppressing the formation of indolines in the process of $B(C_6F_5)_3$-catalysed C–H silylation of indoles. Indeed, when the $B(C_6F_5)_3$-catalysed silylation reaction of indoles with hydrosilanes was performed at 120 °C, the highly selective C3–H silylation of indoles proceeded smoothly, affording the desired products in high yields (up to 99% yield) (Scheme 40).[126] Similar to the analogous C–H borylation of indoles (Scheme 36),[120] the continuous oxidation of indoline to indole enabled this convergent disproportionation reaction to be a highly selective, atom-economical and practical approach to silylated indoles.

In 2018, Hou and co-workers reported the regioselective α-$C(sp^3)$–H silylation of methyl sulfides with hydrosilanes by a yttrium metallocene catalyst.[129] Inspired by the electrophilic intermolecular C–H silylation developed previously by the same group,[124] they successfully transformed the silylated aromatic sulfide products into the corresponding heterocyclic [1,3]-thiasilolane products through intramolecular C–H silylation catalysed by $B(C_6F_5)_3$ (Scheme 41).[129] Besides dialkylamino-substituted arenes (products **57a**,**b**), alkyl-substituted arenes

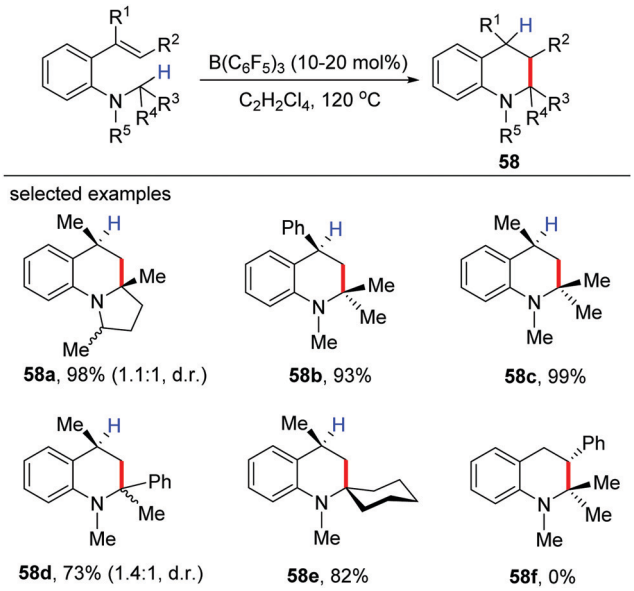


Scheme 40 Silylation and convergent disproportionation of indoles.



Scheme 41 Intramolecular C–H silylation of aryl methyl sulfides.

which did not undergo the intermolecular C–H silylation reaction under similar conditions were also suitable substrates for this intramolecular C–H silylation giving the desired annulation product (*e.g.*, **57c**) in good yield. In this work, the combination of a yttrium catalyst and boron catalyst offered an atom-efficient route for the synthesis of heterocyclic [1,3]-thiasilolanes, which was generally difficult to achieve by traditional methods.[130]



Scheme 42 $B(C_6F_5)_3$-Catalysed intramolecular C–H alkylation of vinyl anilines.

6. Catalytic C(sp^3)–H functionalisation

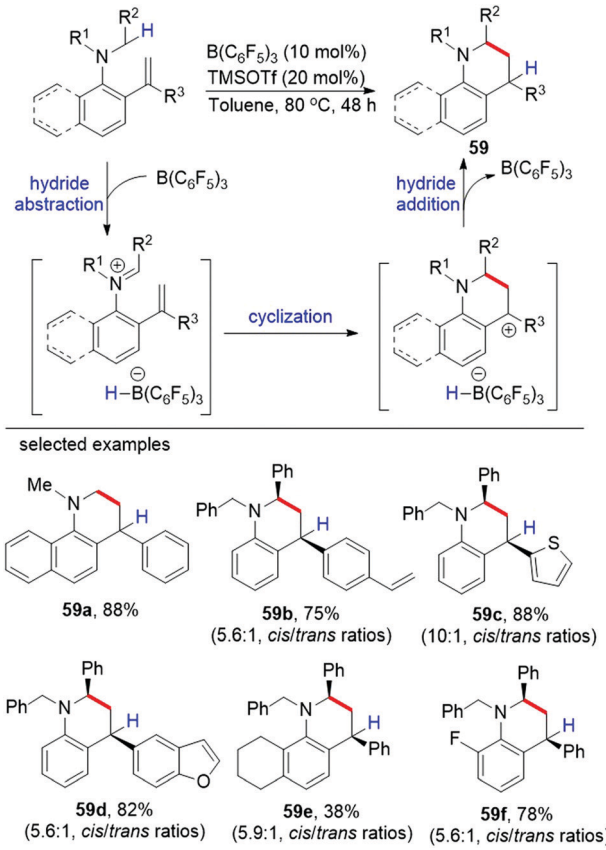
Recently, the application of electron-deficient boron-based catalysts has been also extended to C(sp^3)–H bond functionalisations, such as alkylation, amination, deuteration and silylation. Actually, examples discussed in this section mainly cover α- and β-C(sp^3)–H functionalization of alkyl-substituted amines and α-C(sp^3)–H functionalization of carbonyl derivatives. Generally, the C(sp^3)–H functionalization of alkyl-substituted amines typically proceeds *via* a hydride abstraction process catalysed by a single electron-deficient borane catalyst, while the C(sp^3)–H bond functionalization of carbonyl derivatives is initialed from a deprotonation process in the presence of an electron-deficient borane and a base. Details are described below.

6.1 C(sp^3)–H alkylation

6.1.1 Intramolecular C(sp^3)–H addition to C=C double bonds. It was known that $B(C_6F_5)_3$ could abstract hydrides from C–H bonds adjacent to a nitrogen atom of an *N*-alkylamine, affording an iminium ion and a borohydride.[78,79,131,132] However, this important transformation was rarely explored in a catalytic fashion.[127,128,133] In 2018, Paradies, Grimme and co-workers reported the first $B(C_6F_5)_3$-catalysed intramolecular C–H alkylation of vinyl anilines to give tetrahydroquinoline derivatives (Scheme 42).[134] In particular, various quinolines bearing tetrasubstituted stereocenters could be prepared by this novel method in moderate to high yields. However, in some cases, the diastereoselectivity of the products (such as **58a**, **d**) was low. Stilbene-type substrates showed no reactivity in such intramolecular cyclisation (*cf.*, **58f**), probably due to the low stability of the corresponding carbon cation species formed in the catalytic process. Based on kinetic experiments and quantum-mechanical analysis, it was proposed that the catalytic reaction proceeded *via* the hydride abstraction from the α-C(sp^3)–H bond of amines by $B(C_6F_5)_3$. This transformation represents a new application of electron-deficient borane catalysis in C–C bond formation reactions, providing an efficient access to polycyclic tetrahydroquinoline derivatives.

In 2018, Wang and co-workers also realised a similar $B(C_6F_5)_3$-catalysed intramolecular α-C(sp^3)–H bond addition to the C=C double bond of vinyl-substituted *N*,*N*-dialkyl anilines *via* a hydride-transfer process, offering a facile access to a series of synthetically useful nitrogen-containing heterocycles (Scheme 43).[135] In most cases, the desired products could be obtained in high yields by using Lewis acidic TMSOTf as an additive in the catalytic system. Control experiments indicated that the catalytic reaction started with the abstraction of an α-hydride from an *N*-alkyl substituent by $B(C_6F_5)_3$, followed by intramolecular cyclisation and hydride transfer from the resulting borohydride to the carbon cationic intermediate to give the desired product. The dual roles of $B(C_6F_5)_3$ (oxidant and hydride-transfer reductant) enabled such redox-neutral cyclisation reactions to proceed in the absence of a transition metal catalyst or an external oxidant.

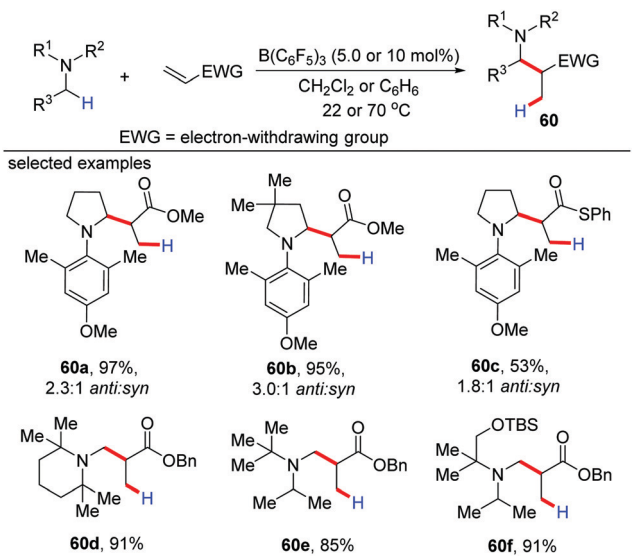
6.1.2 Intermolecular C(sp^3)–H addition to C=C double bonds. The catalytic α-C(sp^3)–H bond functionalisation of amino-compounds is one of the most powerful tools for the preparation of diverse valuable α-substituted amines, which are widely prevalent in bioactive molecules, natural products and pharmaceuticals. Examples reported previously for this kind of transformation typically required oxidative conditions and metal-based catalysts.[136,137] In 2018, Wasa and co-workers achieved a metal-free catalytic intermolecular C(sp^3)–H alkylation of *N*-alkylamines with α,β-unsaturated compounds by using $B(C_6F_5)_3$ as the catalyst, which afforded the corresponding α-substituted amines in moderate to high yields (Scheme 44).[133] The reaction proceeded under redox-neutral and mild conditions and showed broad substrate



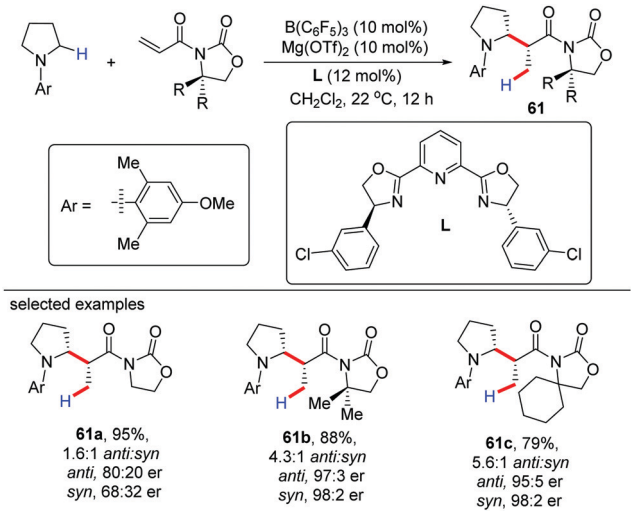
Scheme 43 $B(C_6F_5)_3$-Catalysed intramolecular C–H alkylation of vinyl-substituted *N*,*N*-dialkyl arylamines.

scope. In this transformation, $B(C_6F_5)_3$ played dual roles (hydride acceptor and activator of α,β-unsaturated carbonyl compounds).

Enantioselective α-C(sp^3)–H alkylation of *N*-alkylamines with α,β-unsaturated compounds could also be realised under



Scheme 44 C(sp^3)–H alkylation of *N*-alkylamines with α,β-unsaturated carbonyl compounds.

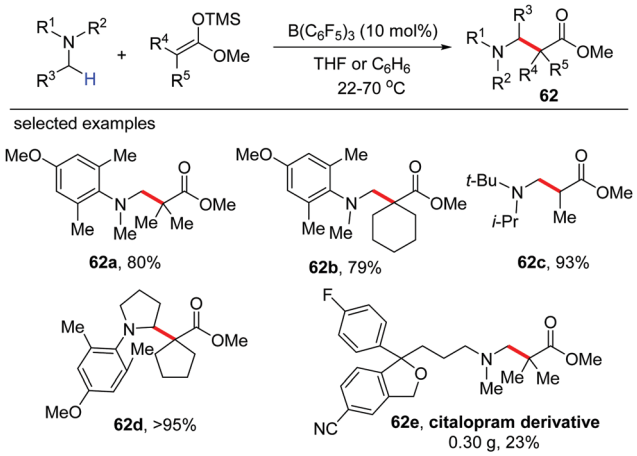


Scheme 45 Synthesis of chiral α-substituted amines.

redox-neutral conditions through concerted action of $B(C_6F_5)_3$ with an additional Lewis acid bearing a chiral ligand. After screening various potential Lewis acids and chiral ligands, a combination of $B(C_6F_5)_3$, $Mg(OTf)_2$ and chiral PyBOX ligand [(*S*,*S*)-2,2′-(2,6-pyridinediyl)bis(4-(3-Cl-phenyl)-2-oxazoline)] was found to show high performance.[133] Under the optimal conditions, a series of α-substituted chiral amines were obtained in moderate to high enantioselectivity and diastereoselectivity (Scheme 45). This work represents an important progress in chiral frustrated Lewis pair catalysis, and also provides knowledge for designing more efficient Lewis acid/base cooperative catalysis systems.

Oxidative cross-coupling of α-C(sp^3)–H bonds of amine compounds with ketone or the corresponding enolate nucleophiles provides an atom-economical access to β-amino carbonyl compounds *via* the formation of a new C(sp^3)–C(sp^3) bond.[138] However, such transformations usually require transition metal catalysts and stoichiometric oxidants, which may limit their application scope. In 2019, Wasa and co-workers developed an alternative strategy using $B(C_6F_5)_3$ as the catalyst, which enabled the coupling of *N*-alkylamines with silicon enolates under redox-neutral and metal-free conditions, efficiently affording various β-amino esters (Scheme 46).[139] This protocol obviates the use of an external oxidant, releasing hydrosilane as the only byproduct. It is also suitable for late-stage functionalisation of some bioactive molecules, such as citalopram.

In contrast to recent advances in the direct α-C(sp^3)–H functionalisation of tertiary amines,[140] the β-C(sp^3)–H functionalisation of tertiary amines is underdeveloped due to the relatively low reactivity of C–H bonds at the β-position.[141,142] In 2019, Ma, Zhao and co-workers reported the first metal-free catalytic redox-neutral β-C(sp^3)–H alkylation of acyclic tertiary amines with *para*-quinone methides using $B(C_6F_5)_3$ as the catalyst (Scheme 47).[143] The reaction system is compatible with many important functional groups, affording various β-functionalised tertiary amines in moderate to high yields. In regards to the reaction mechanism, it is proposed that

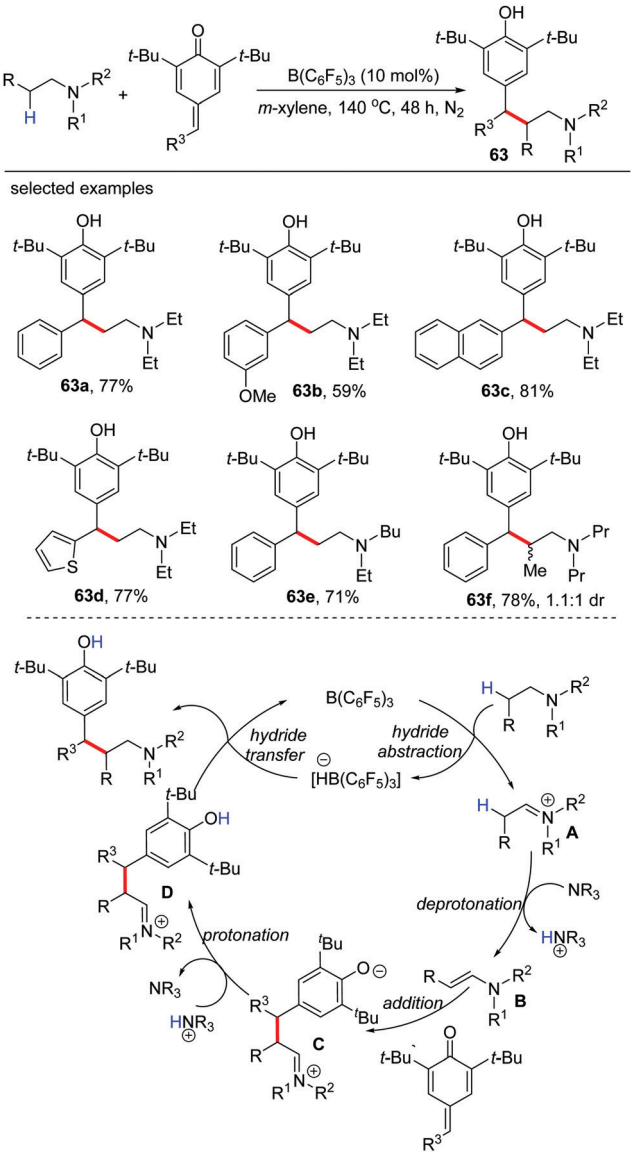


Scheme 46 $B(C_6F_5)_3$-Catalysed C–H alkylation of *N*-alkylamines with silicon enolates.

tertiary amine undergoes hydride abstraction by $B(C_6F_5)_3$ to form an iminium ion like **A**, which subsequently undergoes deprotonation to give enamine intermediate **B** (Scheme 47). The reaction of **B** with *para*-quinone methide *via* the conjugate addition of enamine generates iminium **C**, which could be protonated to form intermediate **D**. Finally, the alkylated product is formed *via* hydride transfer from $[HB(C_6F_5)_3]$ to **D** and the catalyst $B(C_6F_5)_3$ is regenerated. The amine substrate also plays an important role in this catalytic cycle, serving as a Brønsted base to achieve the proton shuttle.

6.1.3 Intermolecular C(sp³)–H addition to C=N double bonds. α-C(sp³)–H bond addition of carbonyl compounds to aldimines or ketoimines, known as Mannich-type reactions, provides an important approach to the synthesis of α-amino-substituted carbonyl compounds.[144,145] Despite enormous advances so far, carbonyl compounds reported previously in such transformations were mainly limited to those bearing highly acidic α-C–H bonds, such as 1,3-dicarbonyl compounds.[146] In 2016, Wasa and co-workers developed a frustrated Lewis acid/Brønsted base pair catalyst system consisting of $B(C_6F_5)_3$ and alkylamine, which could promote the direct Mannich-type reaction of unactivated ketones, esters, amides, and thioesters with imines (Scheme 48).[147] The catalytic reaction took place at room temperature, giving a series of β-amino ketones or carboxylic derivatives with moderate to high diastereoselectivity. A possible reaction mechanism is shown in Scheme 48 (bottom). Lewis basic PMP could deprotonate an acidic α-C–H bond of the $B(C_6F_5)_3$-activated ketone *via* intermediate **A**, generating ion pair **B** that contains a boron enolate and an ammonium ion. Subsequently, the nucleophilic attack of the boron enolate to an activated imine *via* intermediate **C** yields the desired Mannich-type product and regenerates the catalyst.

In 2017, Wasa's group achieved further advances in the field of FLP-catalysed direct Mannich-type reactions. Based on racemic results described in Scheme 48, the analogous catalytic enantioselective α-C–H bond addition of mono-carbonyl compounds to various imines was realised by cooperative catalysis

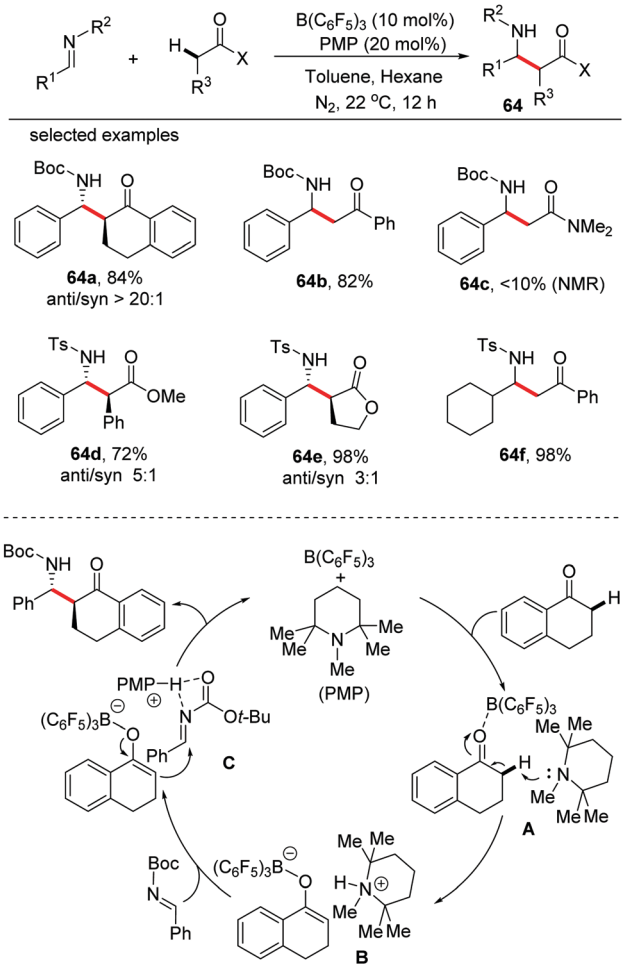


Scheme 47 β-C(sp³)–H functionalisation of tertiary amines.

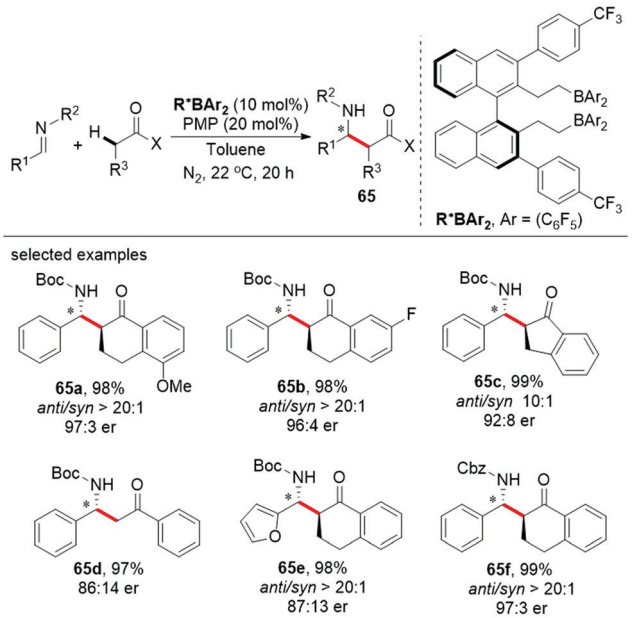
of chiral organoborane and PMP (1,2,2,6,6-pentamethylpiperidine) at room temperature (Boc = *t*-butyloxy carbonyl; Cbz = benzyloxycarbonyl, Scheme 49).[148] In this transformation, the organoborane bearing chiral binaphthyl framework plays a crucial role in controlling the enantioselectivity. A wide range of imines and carbonyl compounds could smoothly undergo the catalytic reaction, giving the desired products in moderate to high enantiomeric purity and diastereoselectivity.

6.2 C(sp³)–H alkenylation

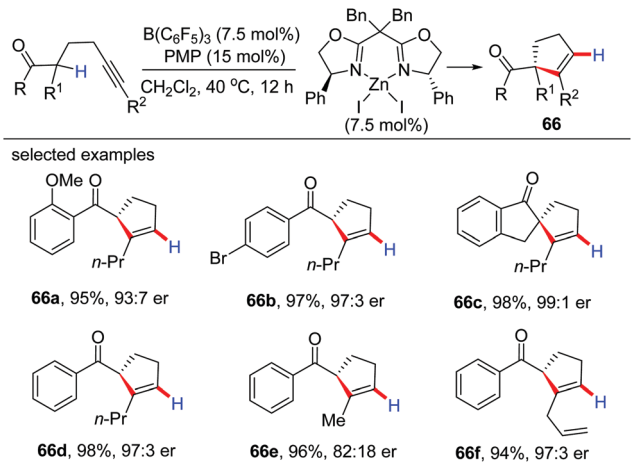
The enantioselective Conia-Ene reaction refers to the intramolecular 1,5-hydrogen shift reaction of carbonyl compounds bearing an alkene or alkyne moiety to generate enantioenriched cyclic products, and this process is generally achieved by cooperative Lewis acid/Lewis acid catalysis or Lewis base/Lewis acid catalysis.[149–152] Examples reported to date have been mainly



Scheme 48 α-C(sp^3)–H alkylation of carbonyl compounds *via* Mannich-type reactions catalysed by FLPs.



Scheme 49 Enantioselective α-C(sp^3)–H alkylation of carbonyl compounds *via* Mannich-type reactions catalysed by FLPs.

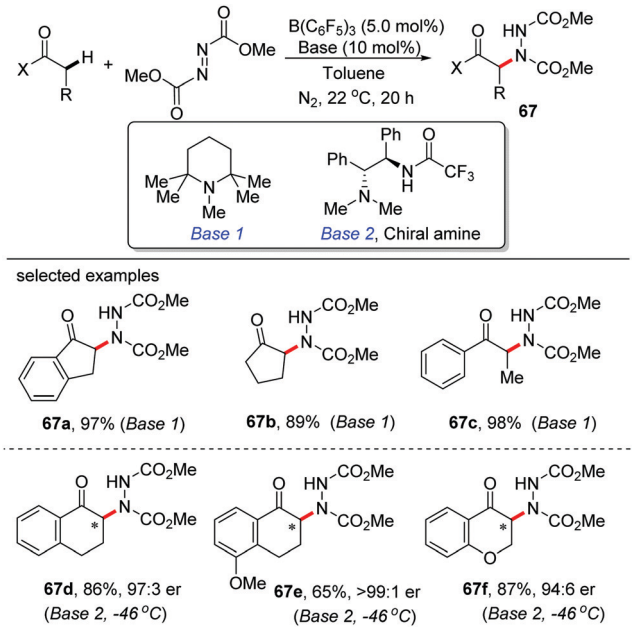


Scheme 50 Enantioselective Conia-Ene-type cyclisations of alkynyl ketones.

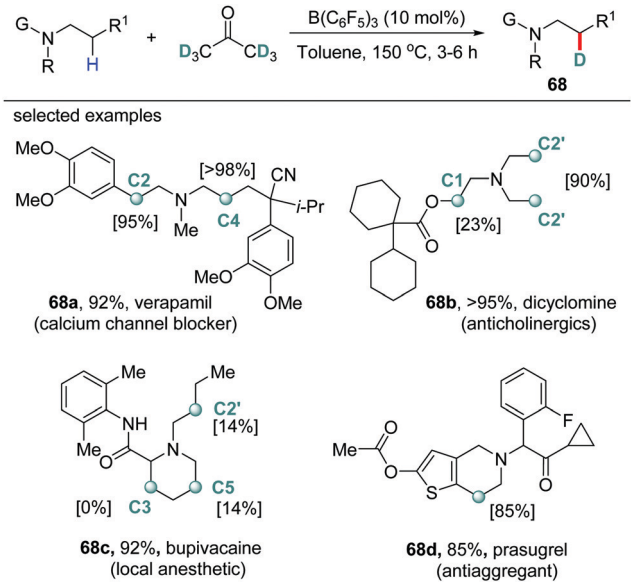
confined to activated carbonyl compounds such as 1,3-dicarbonyl compounds,[149–152] while the direct enantioselective Conia-Ene-type reaction of mono-carbonyl compounds remains a challenge. In 2019, Wasa and co-workers realised a highly enantioselective Conia-Ene-type reaction of ketones bearing an alkyne moiety by the cooperative three-component catalyst system consisting of $B(C_6F_5)_3$, an *N*-alkylamine PMP and a chiral bis-oxazoline ligated zinc complex (Scheme 50).[153] The reaction proceeded under mild conditions to give the corresponding formal intramolecular C(sp^3)–H alkenylation (cyclisation) products in moderate to high enantioselectivity. It is proposed that $B(C_6F_5)_3$ functions as an activator for the carbonyl group and *N*-alkylamine acts as a Brønsted base to deprotonate the $B(C_6F_5)_3$-activated ketone, generating an enolate and an ammonium ion. In this catalytic system, the chiral Lewis acid worked as a cocatalyst to activate the alkyne moiety and control the enantioselectivity.

6.3 C(sp^3)–H amination

Stereoselective α-C(sp^3)–H amination of carbonyl compounds with electrophilic amine sources, *e.g.* dialkyl azodicarboxylates, is one of the most important methods for the construction of *N*-substituted stereogenic centers, which are widely found in biologically active molecules and pharmaceuticals.[154] In 2017, Wasa and co-workers reported direct α-amination of unactivated carbonyl compounds, such as ketones, esters, amides, thioesters and thioamides, with dialkyl azodicarboxylates by using frustrated Lewis pair catalyst systems (Scheme 51).[155] After optimisation, the combination of Lewis acidic $B(C_6F_5)_3$ and hindered PMP showed high performance for the formation of desired amination products. Furthermore, the corresponding enantioselective α-amination of unactivated carbonyl compounds has also been achieved by a catalyst system consisting of $B(C_6F_5)_3$ and a chiral amine. The asymmetric reaction proceeded at −46 °C, affording α-aminocarbonyl compounds in moderate to high enantioselectivity. This method broadened



Scheme 51 α-Amination of carbonyl compounds.



Scheme 52 Catalytic β-amino C–H bond deuteration of *N*-alkylamine-based drug molecules.

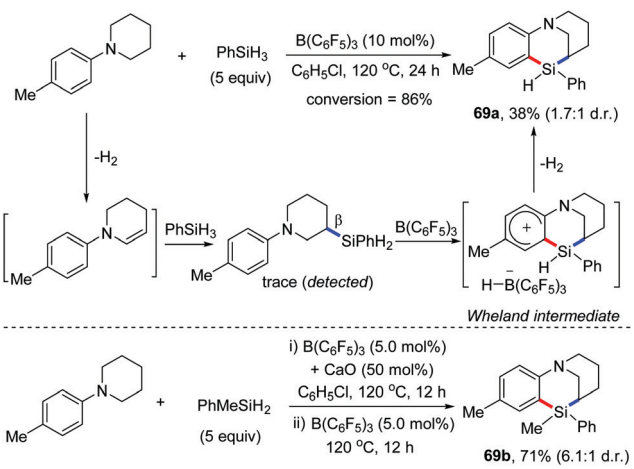
the application perspective of chiral frustrated Lewis pair catalyst systems in the enantioselective construction of carbon–heteroatom bonds.

6.4 C(sp^3)–H deuteration

Deuterium-labeled molecules are widely used as a pivotal tool for mechanism studies, quantitative analysis and drug discoveries.[156–159] In particular, the introduction of deuterium into pharmaceuticals may dramatically change the properties of their pharmacokinetic and pharmacodynamics. To this regard, catalytic C–H deuteration has been evolved to be one of the most important and efficient methods for the introduction of deuterium into drugs *via* hydrogen isotope exchange. Previously, it has been reported that $B(C_6F_5)_3$ could serve as an efficient catalyst for the C(sp^2)–H deuteration of electron-rich arenes.[113] In 2019, Wasa and co-workers further developed a regioselective $B(C_6F_5)_3$-catalysed β-amino C(sp^3)–H bond deuteration of an assortment of *N*-alkylamine-based drug molecules using acetone-d_6 as a deuterium source (Scheme 52).[160] It was demonstrated that the deuteration reaction started with the cooperation of Lewis acidic $B(C_6F_5)_3$ and Brønsted basic *N*-alkylamine, resulting in the conversion of a drug molecule into the corresponding enamine intermediate, which could react with acetone-d_6 to give a β-deuterated amine-based drug in high yields with up to 99% deuterium incorporation.

6.5 Cascade sp^3 and sp^2 C–H silylation

Silicon-containing N-heterocycles are of great interest in medicinal chemistry due to the unique physicochemical properties of silicon.[161–163] In this context, it is of significant importance to develop new catalytic systems for the efficient construction of sila-N-heterocycles from readily available starting materials. In 2018, Chang, Park and co-workers developed an unprecedented approach towards the synthesis of bridged sila-N-heterocycles *via* $B(C_6F_5)_3$-catalysed cascade sp^3 and sp^2 C–H silylation of *N*-aryl piperidines with hydrosilanes (Scheme 53).[164] The catalytic reaction was initiated by the dehydrogenation of the piperidine ring in the presence of $B(C_6F_5)_3$ to generate an enamine intermediate, which could undergo a β-selective hydrosilylation to form a new C(sp^3)–Si bond. Finally, an intramolecular dehydrogenative C(sp^2)–H silylation of the resulting β-silylated *N*-aryl piperidine yielded the bridged sila-N-heterocycle. The reaction conditions and experimental procedures were especially crucial for the success of this reaction. As exemplified in Scheme 53, the reaction of 1-tolylpiperidine with 5.0 equiv. of phenylsilane using $B(C_6F_5)_3$ as the catalyst at 120 °C afforded the silylated product in a low yield and poor diastereoselectivity (1.7 : 1). However, if $B(C_6F_5)_3$ was added to the reaction system in two portions and a basic CaO compound was used as the additive, the target product was obtained in 71% yield with an elevated diastereoselectivity (6.1 : 1).



Scheme 53 Cascade silylation of *N*-aryl piperidines.

7. Conclusions and outlook

In the past decade, metal-free catalytic C–H bond functionalisation by electron-deficient boron-based catalysts has received increasing attention and achieved great advances. A series of elegant examples of the construction of C–C and C–X (such as C–B, C–Si, C–D and C–N) bonds from diverse C–H bonds have been developed based on these catalytic methods. This emerging field has exhibited considerable potential for highly selective and efficient synthesis of functionalised alkynes, (hetero)arenes, amines and ketones under metal-free conditions. More significantly, some of the methods such as $B(C_6F_5)_3$-catalysed C–H deuteration have been applied to the modification of bioactive molecules and pharmaceuticals. Catalytic enantioselective C–H functionalisations such as α-C(sp^3)–H amination of ketones and α-C(sp^3)–H alkylation of *N*-alkylamines have also been achieved by using chiral boron Lewis acids, chiral Brønsted bases or a combination with additional chiral ligands.

Despite rapid advances in this field, there are still many limitations and challenges. For example, these types of C–H bonds that are suitable for electron-deficient boron catalysts are mainly confined to relatively reactive C–H bonds, such as the acidic C(sp)–H bond of terminal alkynes, the C(sp^2)–H bond of electron-rich (hetero)arenes, and the α-C–H bond of amines or ketones. In this regard, the design and development of new boron-based catalyst systems that can promote the activation of inert C–H bonds is highly desired, and remains an important and challenging research topic. Furthermore, enantioselective C–H functionalisation is still under-developed, often suffering from limited substrate scope and low enantioselectivity. Therefore, the development of highly enantioselective C–H functionalisation with broad types of substrates would be of special significance and interest given the importance of asymmetric catalysis in drug design and synthesis. At this stage, many mechanistic details are still not clear, and therefore, the determination of true catalytic species and establishment of more reasonable catalytic cycles by means of kinetic methods, NMR techniques and DFT calculations should be helpful for designing more efficient, selective catalysts and further advancing this field. Finally, the application of metal-free catalytic C–H functionalisation by electron-deficient boron-based catalysts in the late stage functionalisation of bioactive molecules and drugs is still in its infancy, and further investigations along this line are highly expected.

Conflicts of interest

There are no conflicts of interests to declare.

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