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Review

Recent Developments in Organoboron Chemistry – Old Dogs, New Tricks

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This review covers selected advances in organoboron chemistry in recent years, focusing on both advances in methods for the installation of boron functional groups and the development of novel applications of organoboron reagents.

The Bigger Picture

Organoboron reagents have been synonymous with organic chemistry for over half a century, and continue to see widespread application today, with classic reactions such as hydroboration and Suzuki-Miyaura cross-coupling regularly practiced throughout the chemical community. In particular, applications of organoboron compounds have underpinned pharmaceutical and agrochemical development on both discovery and process scales for decades. While it is noteworthy that these seminal reactions have stood the test of time, continually increasing pressure to improve efficiency in chemical synthesis demands innovation. Over the past few years, through an explosion in the number of new methods for the installation and manipulation of organoboron functional groups, as well as the understanding of their mechanistic operation, organoboron chemistry has risen to this challenge.

INTRODUCTION

Organoboron compounds are one of the most diverse classes of reagent in organic synthesis, providing access to a raft of valuable and indispensable transformations. Since their initial application in organic synthesis over 60 years ago,[1] the continued development of chemistries involving organoboron reagents has increased exponentially. Their popularity stems not only from their diverse reactivity profile, but also from their non-toxic nature and excellent functional group tolerance – characteristics not often shared by other members of the organometallic family, such as organomagnesium or organozinc reagents.[2] This review will offer an overview of recent developments across the broad landscape of organoboron chemistry, covering a range of transformations including: C-B and C-C bond formation, stoichiometric, catalytic, and enantioselective reactions.

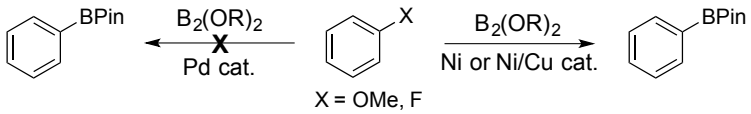
SYNTHESIS OF ORGANOBORON'S

Recent developments in sp^2 borylation

Primarily due to their efficiency as coupling partners in the Suzuki-Miyaura reaction,[3,4] methods for the efficient synthesis of boronic acid pinacol esters (BPins) are highly sought after in organic chemistry. In a seminal report in 1995,[5] Miyaura disclosed the Pd-catalyzed borylation of aryl halides with bis(pinacolato)diboron (B_2Pin_2), which enabled the facile synthesis of aryl BPin units without the need for

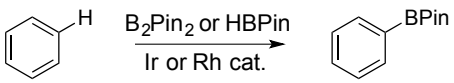
stoichiometric metallation.[6] In a mechanism similar to that of the ground-breaking Suzuki-Miyaura reaction, aryl halides undergo oxidative addition with a Pd(0) catalyst. This complex then undergoes transmetallation with B_2Pin_2, and reductive elimination furnished the desired boronic ester. This important advance greatly increased the range of accessible aryl BPin esters and therefore the scope of further synthetic transformations. Since this initial report by Miyaura, there have been a number of developments in sp^2 borylation of aryl halides. Transition metal-catalyzed borylation of aryl halides is no longer limited to palladium catalysts – a range of inexpensive, abundant, and less toxic transition metals including Cu, Ni, Zn, and Fe can now be utilized as catalysts.[7,8]

This in turn has led to novel and interesting reactivity profiles, allowing the borylation of functional groups previously inactive toward palladium catalysis (Scheme 1). For example, the Martin group have recently disclosed the use of a Ni catalyst to facilitate the borylation of aryl ethers *via* C-OMe cleavage.[9] This enables synthetic chemists to overcome traditional reactivity profiles, carrying a seemingly inert aryl ether through several synthetic transformations before performing a late stage borylation, and thus generating a reactive nucleophile for further functionalization. This type of late stage functionalization strategy is highly desirable in both the pharmaceutical and agrochemical industries, enabling efficient screening of structural activity relationships (SAR) through diversification of active core structures.[10] A complementary protocol was developed by Hosoya and co-workers which enables the borylation of aryl fluorides *via* cooperative Ni/Cu catalysis.[11] This defluoroborylation requires breaking a highly chemically stable C-F bond, and is therefore ideal for late stage functionalization as aryl fluorides can tolerate a number of synthetic transformations prior to borylation. Interestingly, the authors were able to selectively borylate aryl fluorides with a *para*-methoxy substituent under their reaction conditions, demonstrating even greater possibilities for different reactivity pathways.



Scheme 1. Transition metal-catalyzed borylation of previously unreactive functional groups

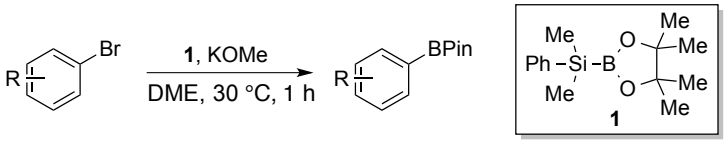
The borylation of aryl halides (and pseudohalides) is not the only area to receive significant attention in recent years. Originally reported shortly after the Miyaura process,[5] the transition metal-catalyzed borylation of seemingly inactive aryl C-H bonds – using either iridium[12,13] or rhodium[14]– represented a significant step forward in aromatic functionalization (Scheme 2).[15] Recent advances have succeeded in tempering reaction conditions, increasing the scope of both functional group tolerance and classes of aromatic and heteroaromatic compounds, as well as vastly increasing the regioselectivity of the process.[16,17]



Scheme 2. Transition metal-catalyzed borylation of arenes via C-H activation

These processes represent noteworthy advances in the field or aryl borylation; however, they all rely on the use of various transition metal catalysts. While metals

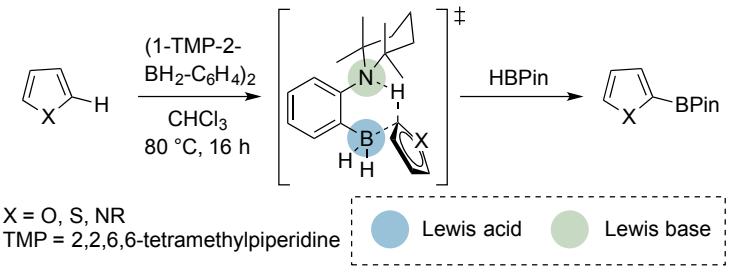
such as copper and iron are significantly less expensive and toxic than their precious metal counterparts (*e.g.*, Pd, Ir, etc.), there remains a strong desire within synthetic chemistry to move away from transition metal-mediated reactions, particularly in the pharmaceutical industry where levels of transition metal contaminants in final products are strictly controlled.[18] As a result of this, processes enabling the borylation of aromatic compounds under transition metal-free conditions are potentially highly valuable. Ito *et al* have disclosed a novel transition metal-free method of borylation of aryl bromides by exploiting the unusual reactivity of a silylborane (Scheme 3).[19] Not only does the reaction proceed under very mild conditions (30 °C for 1 h), it is also tolerant of a wide range of functional groups and sterically demanding substrates, which are known to be difficult to borylate using transition metal catalysis.



Scheme 3. Transition metal-free borylation of aryl halides with silylborane

The unexpected and novel reactivity displayed in the Ito process is fascinating; however, a small drawback is the nature of the silylborane reagent. Although the reagent is commercially available, it remains expensive and synthesis requires the use of stoichiometric organometallics,[20] which may prohibit its use on scale. In attempts to address this issue, the Li group have developed a photochemically promoted, transition metal-free method for the borylation of aryl halides using B_2Pin_2.[21] The Li group were able to develop their process to run in flow, maintaining excellent yields with short residence times (<30 mins). The reaction could also be performed on gram scale with no loss of yield, presenting a viable alternative for the borylation of aryl halides on scale and exemplifying the potential for continuous flow as an efficient means for cost effective synthesis. Shortly after this, Larionov and coworkers reported a similar procedure for the photoinduced borylation of aryl halides with tetrahydroxydiboron, enabling the facile synthesis of aryl boronic acids in the absence of any metal catalysts.[22]

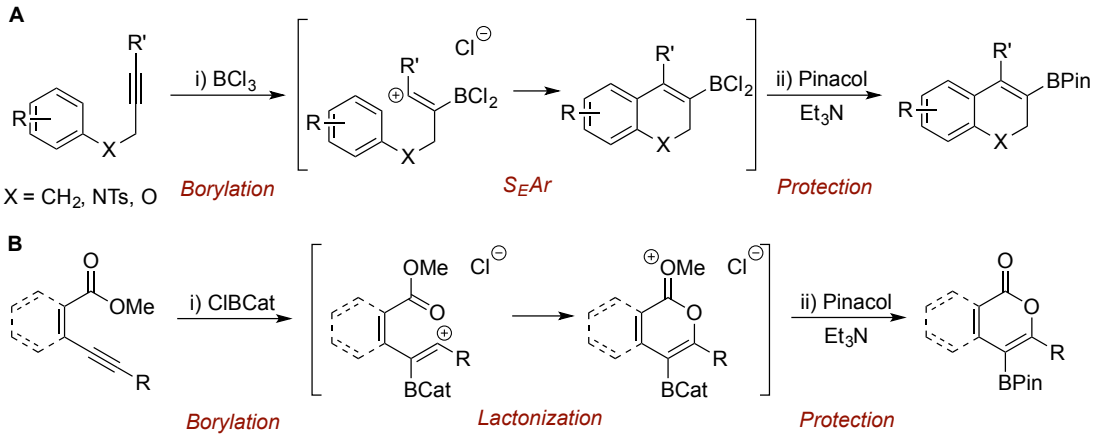
In a further departure from traditional means of aryl borylation, a recent report from Fontaine presents the possible future of C-H functionalization, utilizing intramolecular frustrated Lewis pairs (FLP) as catalysts to effect transition metal-free C-H activation of heteroaryls.[23] This innovative approach utilizes low cost, abundant, and relatively benign organoboranes – such as (1-TMP-2-BH_2-C_6H_4)$_2$ – to activate heteroaryl C-H bonds towards borylation (Scheme 4).



Scheme 4. Frustrated Lewis pair catalyzed C-H borylation

In this process, the Lewis basic amine is prevented from forming a Lewis adduct with the Lewis acidic boron due to conformational constraints. This enables the Lewis basic amine to abstract a proton from the heteroarene, with the electron density from the C-H being transferred to the Lewis acidic borane. This species is then able to react with HBPin, forming the desired heteroaryl BPin and regenerating the FLP catalyst. While the scope of this process is somewhat limited at this time – electron-withdrawing substituents were found to completely inhibit the reaction – the potential for FLP catalysts to facilitate further C-H bond functionalization is an exciting prospect.

Another recently developed method for the metal-free synthesis of sp^2 borylated carbo- and heterocycles is *via* the borylation and subsequent cyclization of alkynes using boron electrophiles. Ingleson reported the use of BCl_3 for the borylation of internal alkynes, followed by intramolecular S_EAr cyclisation at the newly formed vinyl cation, before protecting the resulting sp^2 boron species as the pinacol ester (Scheme 5A).[24] Blum on the other hand utilizes ClBCat as a boron electrophile, with subsequent lactonization and protection giving the desired borylated isocoumarin products (Scheme 5B).[25] The same group have also demonstrated thioboration to deliver borylated benzothiophenes *via* the same reaction manifold.[26]

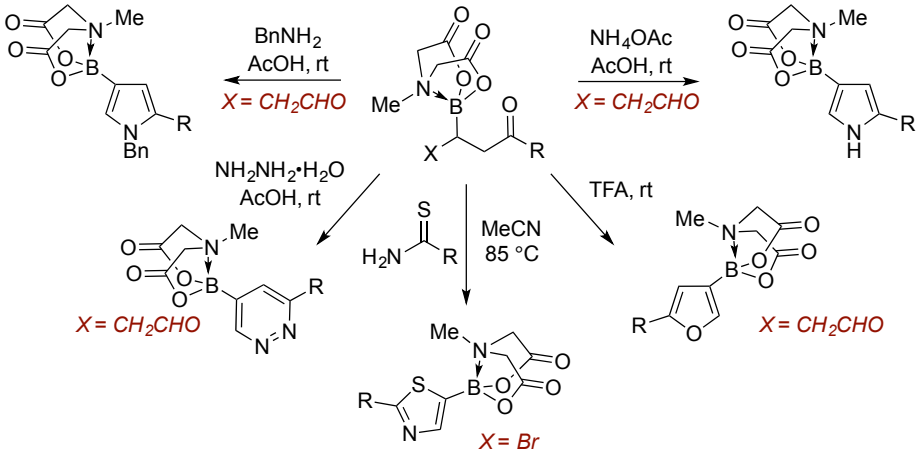


Scheme 5. Metal-free borylation/cyclization strategies

A similar borylation/cyclization process was also reported by Li *et al*, who were able to effect aminoboration of terminal olefins using BCl_3 and trapping with pinacol.[27] These methods offer an array of borylative functionalizations of unsaturated C-C bonds, with carbo-, oxy-, thio-, and aminoboration all achievable under mild conditions using electrophilic boron reagents in the absence of any metal catalysts.

An alternative method for the synthesis of borylated heterocycles has been reported by Yudin and coworkers, who have demonstrated the use of α-boryl aldehydes[28] in the synthesis of a range of borylated heterocycles. Yudin *et al* utilize a boronic acid protected with *N*-methyliminodiacetic acid (MIDA),[29] as the donation of the nitrogen lone pair into the empty p-orbital on boron renders it sp^3 hybridized and as such, inert to a wide range of organic transformations.[30] This methodology is complementary to traditional synthesis (*i.e.*, lithiation/borylation) or even newly developed C-H borylation methods,[23] both of which typically deliver C2 borylated heterocycles. In contrast, through condensation with a variety of reagents, α-boryl aldehydes can deliver borylated heterocycles, which would be difficult – or in some cases even impossible – to access using conventional methodology. Reaction of α-

bromo boryl aldehydes with thioamides enables the facile synthesis of the corresponding 2,5-disubstituted borylated thiazoles (Scheme 6).[31] Alternately, by utilizing 1,4-dicarbonyl boronates, the authors demonstrate the expedient synthesis of substituted pyrroles, furans and pyridazines (Scheme 6).[32] These borylated heterocycles are then amenable to cross-coupling.

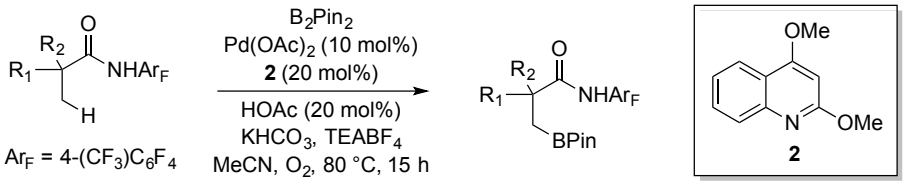


Scheme 6. Synthesis of borylated heterocycles from α-boryl aldehydes

Recent developments in sp³ borylation

While aryl boron species remain a staple in organic chemistry, the continually increasing interest in sp^3 functionalization – especially in the pharmaceutical industry[33] – has led to the increased development of sp^3 boron reagents, particularly those with defined stereochemical character.

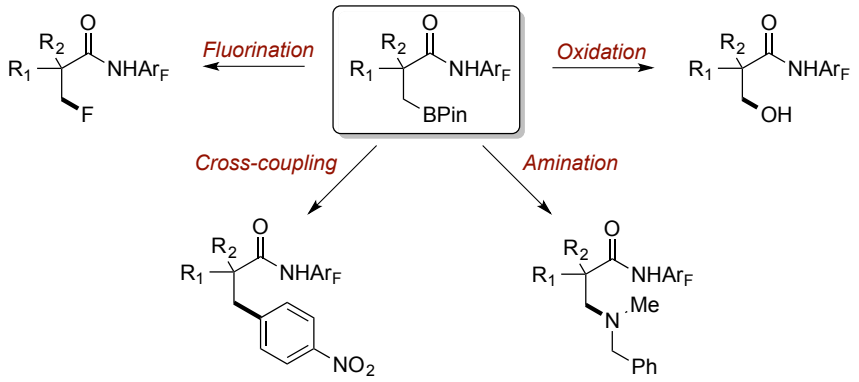
Proceeding in similar fashion to the Miyaura borylation of aryl electrophiles, alkyl halides can now be efficiently borylated under transition metal-catalyzed conditions. Biscoe has reported the Pd-catalyzed borylation of primary alkyl bromides,[34] while Marder and Liu have developed conditions enabling the same process with Cu.[35] More recent research has enabled the selective borylation of unactivated alkyl C-H bonds. Analogous to their work with aryl borylation,[16] and building on work from Shi,[36] Yu and coworkers have reported the Pd catalyzed borylation of sp^3 C-H bonds (Scheme 7).[37]



Scheme 7. Yu's Pd-catalyzed sp³ C-H borylation

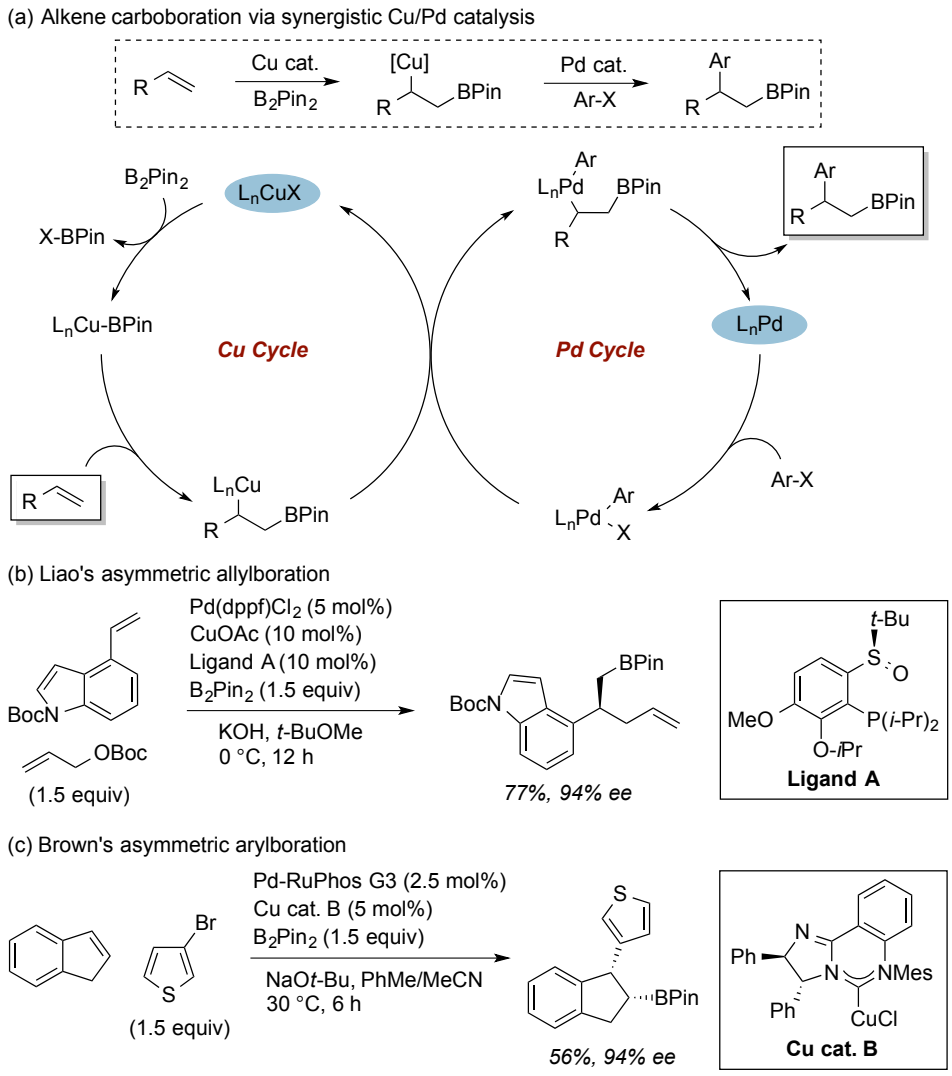
Using an electron deficient polyfluorinated aryl amide in order to direct Pd-insertion, and a quinolone-based ligand, the group were able to generate a range of β-borylated products in good yield, including cyclic carboxylic acid derivatives. The procedure was also reproducible on gram scale with no loss in yield. In order to display the synthetic utility of these sp^3 borylated products, the authors demonstrated a range of synthetic transformations, including cross-coupling,

amination, and fluorination (Scheme 8). While this process does yield useful products, there are some minor drawbacks, such as the directing group requirement in addition to the complex mixture of reagents.



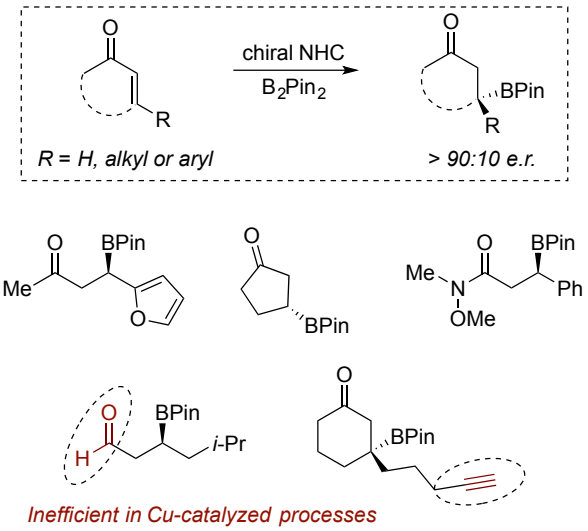
Scheme 8. Derivatization of alkyl BPin products

Since H. C. Brown's seminal report over 50 years ago,[38] the borylation of alkenes to form alkylboranes has been a mainstay in organic synthesis. In keeping with the contemporary focus on reaction efficiency and step economy,[39] steps have been taken to enable the conjunction of the borylation of alkenes with other bond forming processes. For example, Semba and Nakao utilized a dual Cu/Pd catalysis system to affect the arylboration of alkenes.[40] A similar process was reported shortly afterwards by M. K. Brown,[41] who was then able to develop conditions enabling selective *syn*/*anti* arylboration of internal alkenes.[42] As illustrated in Scheme 9a, this chemistry proceeds firstly through the formation of a borylcopper species which then adds across the alkene, yielding a β-borylalkylcopper complex. This can then transmetallate with the ArPdX complex generated after oxidative addition of Pd(0) into the aryl halide. Subsequent investigations of this synergistic catalysis platform have resulted in related asymmetric allyl- and arylboration processes that proceed with high levels of enantioselectivity. Liao demonstrated that asymmetric allylboration could be achieved using a conventional Pd catalyst ($Pd(dppf)Cl_2$) in conjunction with CuOAc and a chiral sulfoxide/phosphine ligand (Scheme 9b)[43] while Brown showcased the utility of a more contemporary Pd catalyst (RuPhos G3) with a chiral NHC-derived Cu catalyst to effect asymmetric arylboration (Scheme 9c).[44] This unification of two catalytic processes into one efficient, multi-bond forming sequence is a perfect example of the progression of modern synthesis, with this methodology not only forming a new C-C bond stereoselectively but also installing a reactive boron species with potential for further functionalization.



Scheme 9. Carboboration of alkenes *via* dual Cu/Pd catalysis

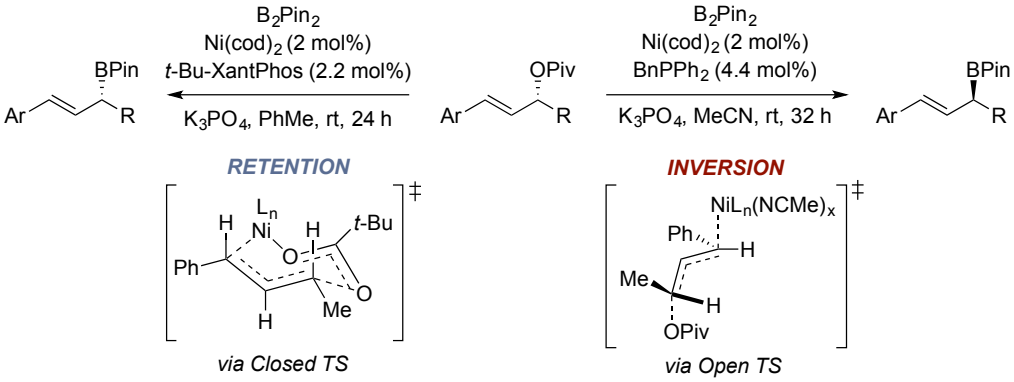
With the increased desire for sp^3 borylated compounds also comes the requirement for methods to effectively synthesize enantioenriched alkylboron species. Hoveyda and coworkers have developed a procedure for the enantioselective boryl conjugate addition (BCA) to α,β-unsaturated carbonyls, utilizing a chiral *N*-heterocyclic carbene (NHC) in the absence of any metal salts (Scheme 10).[45,46] An interaction between the nucleophilic NHC and the Lewis acidic boron reagent promotes nucleophilic attack on the β-position of the α,β-unsaturated carbonyl. The developed conditions promoted BCA on a wide range of substrates, including several containing functional groups traditionally sensitive to Cu-mediated borylation reactions. For example, using the equivalent Cu-catalyzed processes, moieties such as aldehydes and alkynes frequently undergo competitive reaction (*e.g.*, 1,2-additon (aldehyde), cuproboration (alkyne)) with the reactive Cu-BPin species, limiting the scope of the reaction.[45]



Scheme 10. Metal-free enantioselective borylation of alkenes with NHC's

Hoveyda's process is therefore beneficial as it not only represents another metal-free route towards borylated compounds, but also enables the borylation of substrates previously inaccessible using alternative Cu-catalyzed processes.

A highly appealing attribute of a synthetic transformation is the ability to easily generate alternate analogues; for example, procedures in which the regio- or stereoselectivity can be accessed through simply altering the reaction conditions. This enables expedient access to a much wider variety of building blocks for subsequent SAR screening in both pharmaceutical and agrochemical industries. An example of the current state-of-the-art in terms of borylation comes from Watson's group at the University of Delaware. Using Ni catalysis, a method for the borylation of allylic pivalates has been developed.[47] Notably, the authors were able to generate two complementary protocols, providing the ability to tailor the reaction to proceed with either retention or inversion of stereochemistry based simply on the choice of ligand and solvent (Scheme 11).



Scheme 11. Stereospecific borylation of allylic pivalates with either retention or inversion

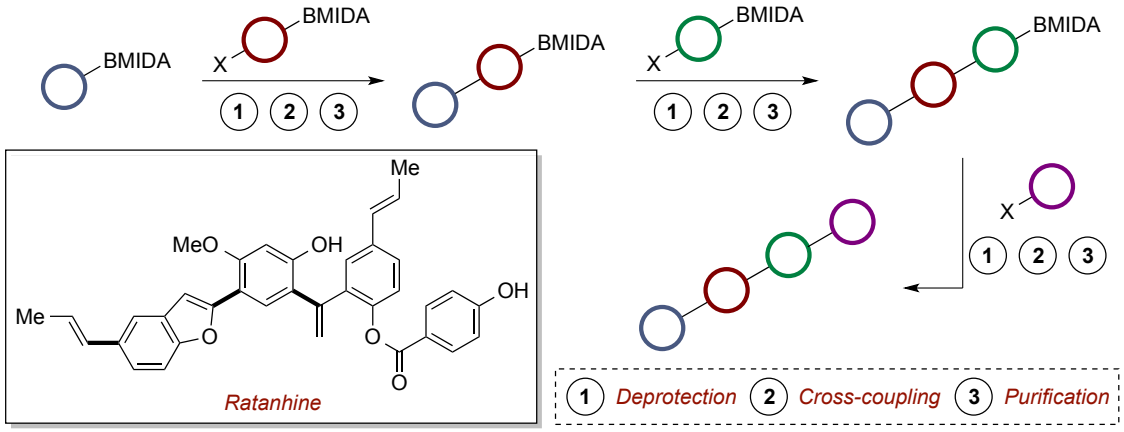
While optimizing the process, the authors noted the stereochemical outcome of the reaction had a high dependency upon the solvent used, with reactions performed in MeCN proceeding with inversion whereas reactions in PhMe

proceeded primarily with retention of stereochemistry. Watson *et al* propose this results from a switch in transition state, with MeCN acting as a ligand for Ni and therefore driving an open transition state. In the absence of more polar solvents, the reaction proceeds through a closed transition state, with the pivalate leaving group directing Ni oxidative addition. This process enables the synthesis of a wide range of enantioenriched allylic boronates in high yield. The mild conditions and excellent functional group tolerance of this chemistry represents a key development in the synthesis of these versatile synthetic building blocks.

APPLICATIONS OF ORGANOBORONS IN SYNTHESIS

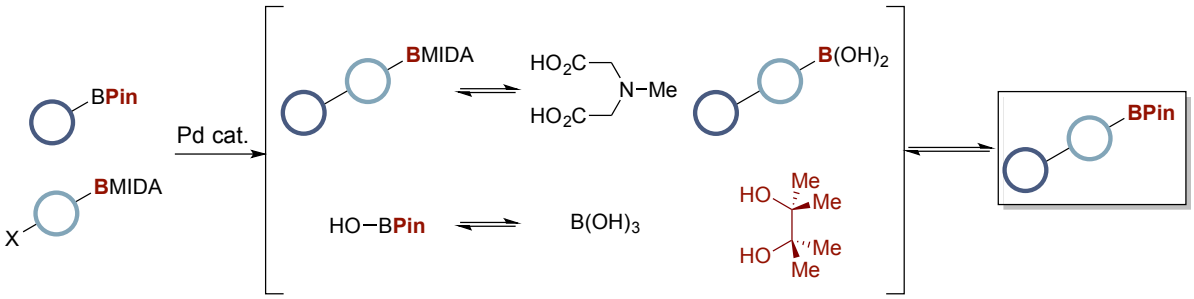
$C(sp^2)$–$C(sp^2)$ bond formation

With Pd-catalyzed Suzuki-Miyaura (SM) cross-coupling representing the most widespread application of organoboron reagents in organic synthesis,[48,49] it is hardly surprising that this reaction receives continued interest from researchers. In addition to the development of new catalysts and ligands to promote cross-coupling of troublesome substrates,[50] there has also been significant development in the past decade of various boron reagents – particularly of protected boronic acids.[4] This protecting group strategy allows the selective cross-coupling of one boron moiety (as either a boronic acid or ester) in the presence of a second organoboron which has been rendered unreactive towards cross-coupling.[51] Utilization of this strategy has been widely applied in iterative synthesis by the groups of Burke[52,53] and Suginome,[54] with the former employing base labile *N*-methyliminodiacetic acid (MIDA) and the latter using an acid labile 1,8-diaminonaphthalene (DAN) protecting group. The most significant development utilizing protected boronic acids in iterative cross-coupling comes from the Burke group, who have developed an automated process, akin to that of peptide synthesis,[55] which enables the synthesis of a range of small molecules *via* sequential SM cross-couplings.[56] Employing a sequential deprotection/cross-coupling, in combination with a "catch and release"-type purification method, Burke *et al* were able to build up complex small molecules in an iterative fashion, without the need for any manual isolation or purification. The catch and release method operates by passing the reaction mixture through a silica plug where a BMIDA product is "caught" allowing the material to be purified by eluting impurities with a specific eluent before eluting or "releasing" the BMIDA product using a different eluent. The authors demonstrated the applicability of this new technology to the pharmaceutical industry by synthesizing a range of derivatives of ratanhine (Scheme 12), a neolignan natural product previously synthesized by the group in a step-wise fashion.[57] The new "synthesis machine" enabled the synthesis of 20 unnatural ratanhine analogues, substituting various aspects of the core structure with pharmaceutically-relevant functional groups and motifs. The use of this technology to quickly and efficiently generate compound libraries from sets of commercially available building blocks marks a significant advance in small molecule synthesis and will no doubt change the way pharmaceutical industries target analogue synthesis going forward.



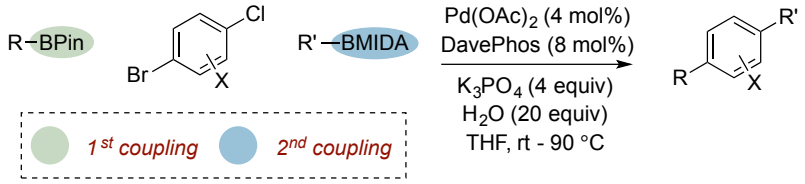
Scheme 12. Automated iterative cross-coupling of protected boronic acids

Burke's process centers around the *in situ* deprotection of the BMIDA to reveal the reactive boronic acid; however, in the absence of automated technology, this requires addition synthetic manipulations, decreasing overall step efficiency. In an attempt to streamline the efficiency of sequential cross-coupling reactions, the Watson group at The University of Strathclyde have developed a protocol which, following an initial cross-coupling of a reactive boronic acid pinacol ester with a haloaryl BMIDA, yields a reactive BPin ester *via* speciation controlled ligand exchange on boron (Scheme 13).[58,59] This process relied upon the use of a suitably hygroscopic inorganic base in combination with a limited quantity of H_2O to facilitate cross-coupling prior to BMIDA hydrolysis.[60] Subsequent deprotection of the protected boronic acid and ligand exchange with the SM byproduct HO-BPin then furnishes a new, formally homologated reactive boronic ester.



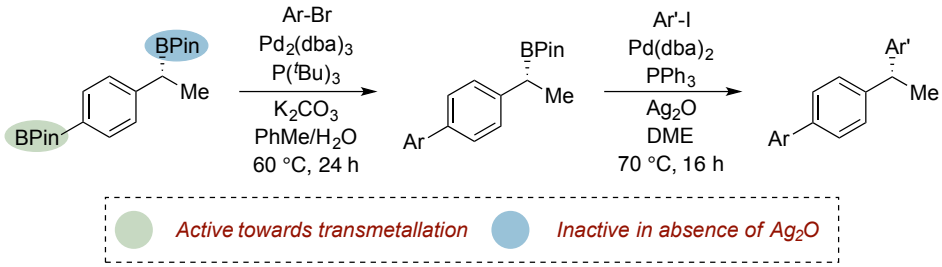
Scheme 13. Speciation controlled formal homologation of boronic esters

The authors were then able to leverage this speciation control to allow the tandem chemoselective cross-coupling of two boron nucleophiles in one-pot.[61] In addition to controlling the speciation events of the boron nucleophiles, simultaneous electrophile control by exploiting the varying rates of oxidative addition of aryl halides[62] enabled the chemoselective formation of two C-C bonds in a single synthetic process (Scheme 14). This methodology enables the facile synthesis of a range of highly substituted compounds from commercial starting materials without the need for any intermediate isolation or purification, increasing the efficiency of this type of multi-bond forming process.



Scheme 14. Tandem chemoselective cross-coupling enabled by speciation control

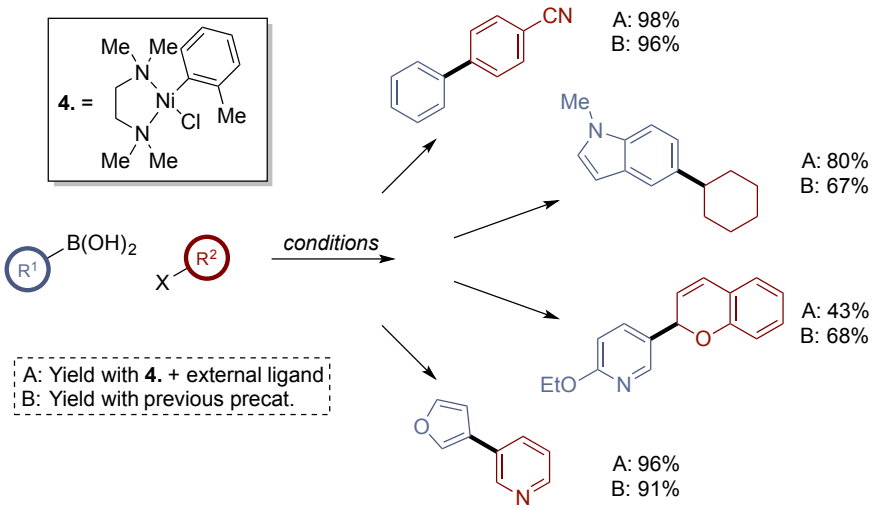
Crudden and coworkers have reported an alternative method for the selective cross-coupling of multiple unprotected boron species. Having previously demonstrated the stereospecific cross-coupling of benzylic BPin esters through use of a Ag_2O additive,[63] the authors recently demonstrated that aryl BPin units could be selectively cross-coupled over their benzylic counterparts in the absence of Ag_2O additives.[64] The benzylic unit can then be activated towards transmetallation by addition of the requisite additive, enabling the synthesis of multi-arylated structures containing a stereogenic centre (Scheme 15). Interestingly, this process could be combined with Morken's neighboring group activation protocol (*vide infra*), enabling three selective sequential cross-coupling reactions through different activation methods.



Scheme 15. Selective cross-coupling of unprotected boronic esters through use of additives

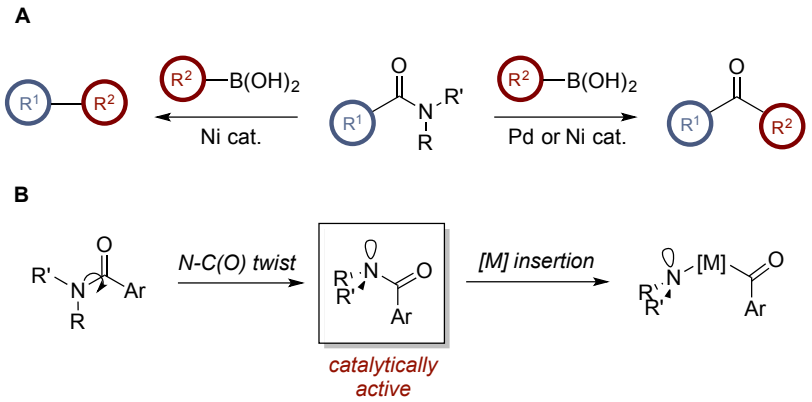
The drive to improve the cost effectiveness of transition metal-catalyzed cross-coupling has led to an abundance of research into Ni-catalyzed SM.[65] Not only do Ni catalysts offer significant financial advantages, they also provide unique and complementary reactivity profiles when compared to traditional Pd(0) catalysis, *vide supra*. However, where uptake in Pd-catalyzed cross-coupling has been widespread, by comparison, Ni catalysis remains underutilized. One of the principle reasons for this lies in the accessibility of stable Ni(0) precursors. For many years the most common source of Ni(0) was $Ni(cod)_2$, which, in contrast to Pd(0), lacked stability unless stored under rigorously dry conditions at low temperature,[65] precluding its use in industrial settings. NiX_2 salts offer a cheaper, air stable alternative to $Ni(cod)_2$; however, these can form inactive polynuclear complexes and also require harsh conditions in order to reduce to the catalytically active Ni(0) species. A range of more stable precatalysts have been developed; however, these have the drawbacks of being tailored to specific transformations, *i.e.*, preformed organometallic complexes containing phosphine ligands explicitly designed for specific bond-forming processes.[65] This renders traditional ligand screening processes more difficult, therefore increasing time and cost of optimizing new reactions. To combat this, Doyle has recently disclosed an air-stable Ni precatalyst with high generality.[66] The use of weakly binding diamine ligand (TMEDA) allows facile ligand exchange with a broad range of common ligands including mono- and bidentate phosphines, NHCs, and even other diamines. The group demonstrated

the generality of their precatalyst by applying it to a range of SM reactions in place of previously reported precatalysts under equivalent conditions (Scheme 16). That yields were generally comparable to those previously reported for such transformations serves to exemplify the potential of this new precatalyst as being both highly modular and general. This should enable the application to a wide range of Ni-catalyzed transformations, providing the grounds for effective ligand screening for reaction optimization and therefore increasing the general uptake of Ni catalysts as a cost effective alternative to Pd for Suzuki-Miyaura cross-coupling.



Scheme 16. Scope of Doyle's air-stable Ni precatalyst vs. previously reported Ni precatalysts

One of the greatest attractions of Ni catalysis, aside from its natural abundance and economic advantages, is the potential to unlock new reactivity pathways. This not only permits the use of readily accessible building blocks for further elaboration, but also facilitates divergent synthesis, carrying seemingly inert functional groups through multiple steps before selective activation. A recent example of this in terms of boron chemistry is the use of amides as electrophiles in Suzuki-Miyaura cross-coupling.

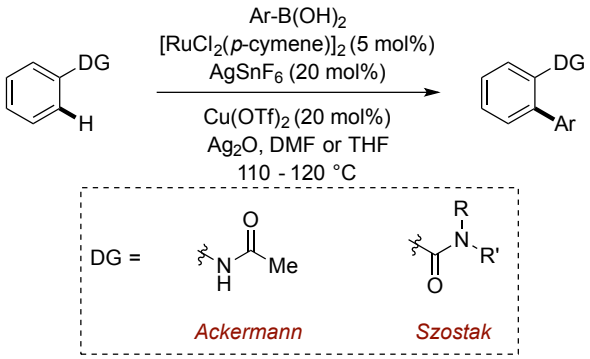


Scheme 17. Suzuki-Miyaura cross-coupling of amides *via* N-C(O) bond cleavage

For example, independent work from the labs of Zou,[67] Garg,[68] and Szostak[69–71] has shown the activation of amide N-C(O) bonds. More interestingly, the authors have

demonstrated complementary reactivity with aromatic amides, allowing the synthesis of either acylated or decarboxylated biaryl products (Scheme 17A). Judicious selection of the substituents on nitrogen results in the disruption of the n_N–π^*_{CO} interaction, which in turn weakens the N-C(O) bond, enabling metal insertion (Scheme 17B). This allows the use of amides, traditionally viewed as inert functional groups in terms of cross-coupling, to be utilized as electrophiles. Through careful tailoring of the reaction conditions, these ubiquitous functional groups can enable the synthesis of either ketones, through retention of the carbonyl, or simple biaryls, *via* decarbonylation. This offers a highly modular process for functionalization, which will likely appeal to the pharmaceutical and agrochemical industries.

Amides have also been used as directing groups for C-H activation processes using organoboron nucleophiles. While there are numerous examples of this,[72] two complementary processes were recently reported using inexpensive ruthenium catalysts for the *ortho* C-H arylation of aromatic amides with boronic acids. Ackermann *et al* utilized an *N*-acyl aniline to direct metal insertion,[72] whereas Szostak and coworkers employed disubstituted benzamides in their process, with the amide carbonyl acting as a weakly coordinating group (Scheme 18).[73] Both methods tolerate wide functional group variation on both coupling components, with high yields and excellent regioselectivity. Szostak's procedure also enables variation of the nitrogen substituents, accommodating both cyclic and dialkyl benzamides.



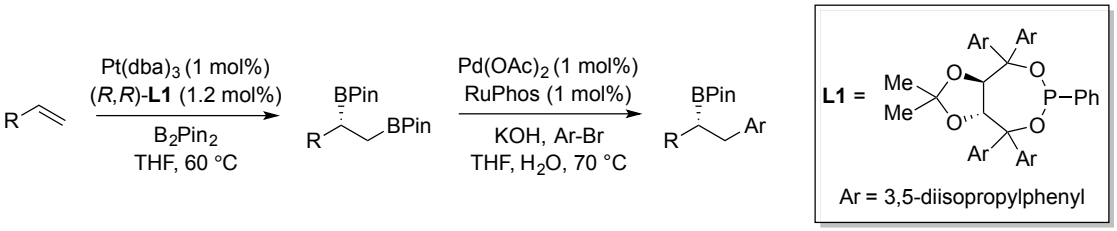
Scheme 18. Amide directed C-H arylation

These recent developments, in conjunction with those previously discussed, further demonstrate of the versatility of organoboron reagents in organic synthesis, and how careful selection of reaction conditions can enable a raft of chemical transformations from simple, readily accessible, starting materials.

C(sp^3)–C(sp^2) bond formation

When considering the ubiquitous nature of organoboron reagents along with the desire for compounds with increased sp^3 character in the pharmaceutical and agrochemical industries,[33] it is perhaps unsurprising that significant effort has recently been devoted to the construction of C(sp^3)–C(sp^2) bonds utilizing organoborons. One such area that has received particular attention is the borylation and subsequent functionalization of alkenes. An example of the current state-of-the-art comes from Morken and coworkers who, building on Miyaura and Suzuki's original process,[74] employed a chiral phosphonite ligand in combination with a Pt catalyst to affect enantioselective diboration of terminal alkenes.[75] The authors were then able to employ these enantioenriched vicinal diboron species in chemoselective SM cross-coupling (Scheme 19).[76] It should be noted that a similar

asymmetric alkene diboration process was developed concurrently by Nishiyama using Rh catalysis.[77]



Scheme 19. Enantioselective diboration and subsequent SM cross-coupling

Morken proposes an intramolecular Lewis acid-Lewis base interaction (Figure 1A) between the empty p-orbital of the proximal BPin unit (**a**) and the oxygen of the terminal BPin unit (**b**).[76,78] This neighboring group activation renders the latter activated towards transmetallation while subsequently deactivating the former, enabling selective cross-coupling. The remaining enantioenriched BPin can then be further functionalized through oxidation, amination, or homologation. The authors demonstrated the power of their methodology *via* the succinct synthesis of a range of biologically relevant molecules. Shortly afterwards, the same group reported a complementary procedure which enabled a selectivity switch in the cross-coupling of these vicinal diboron systems.[79] Here, the Morken team employed a base-mediated diboration of alkenes bearing a β-hydroxyl,[80] which then serves to direct the subsequent coupling, this time *via* hydroxyl-mediated neighboring group activation (Figure 1B), inverting the selectivity of their previously reported process and thus demonstrating the potential of these diboron systems for divergent synthesis.

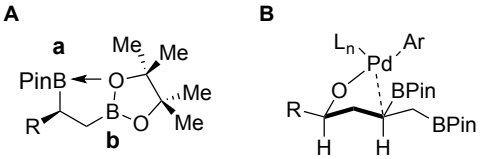
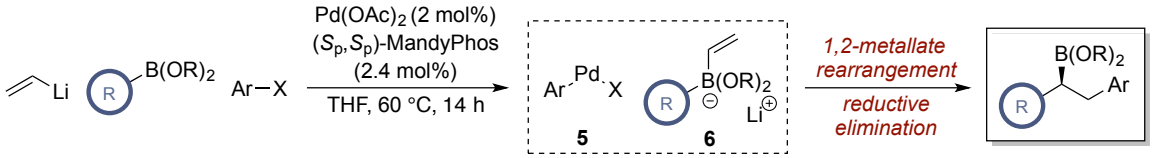


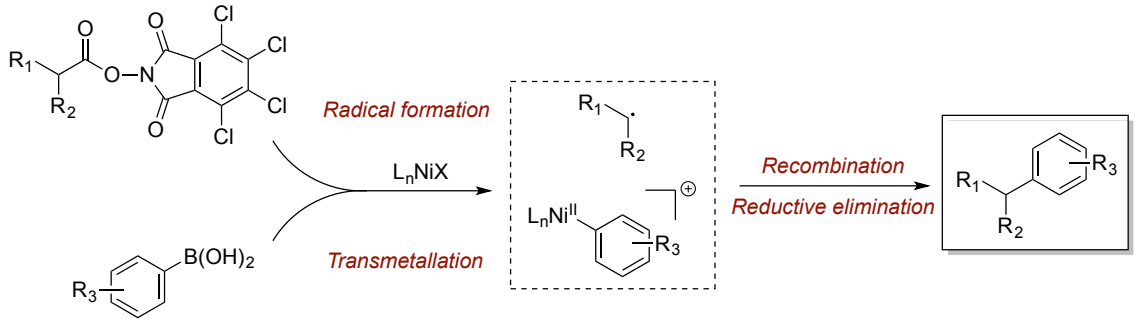
Figure 1. Neighboring group activation of vicinal diboron systems

In a mechanistic departure from traditional Suzuki-Miyaura cross-coupling, Morken and coworkers recently reported the combination of two distinct areas of organoboron chemistry: Pd-catalyzed SM and 1,2-metallate rearrangement of an organoboron with a nucleophilic organometallic reagent.[81,82] This "conjunctive cross-coupling" combines three readily available starting materials to furnish enantioenriched products containing two new C-C bonds and a new chiral C-B center (Scheme 20). Under the developed conditions, an aryl halide undergoes oxidative addition with the Pd(0) catalyst as in a regular SM cycle, forming an electrophilic Pd(II) species (**5**). Concurrently, an organoboron reacts with an organolithium, forming a nucleophilic boronate (**6**). This is then intercepted by the electrophilic Pd(II) intermediate, which promotes a metallate rearrangement, generating a new alkyl Pd(II) species. Reductive elimination then furnishes the desired product while simultaneously regenerating the active Pd(0) catalyst. While the generation of two new C-C bonds, in addition to a chiral C-B center, in a single reaction is indeed commendable, what is perhaps more significant is the potential for this new method of transmetallation to influence catalytic cross-couplings on a much wider scale. The development of this new mechanistic pathway could lead to a raft of new catalytic transformations and increase the portfolio of applications for organoboron reagents.



Scheme 20. Catalytic conjunctive cross-coupling via 1,2-metallate rearrangement

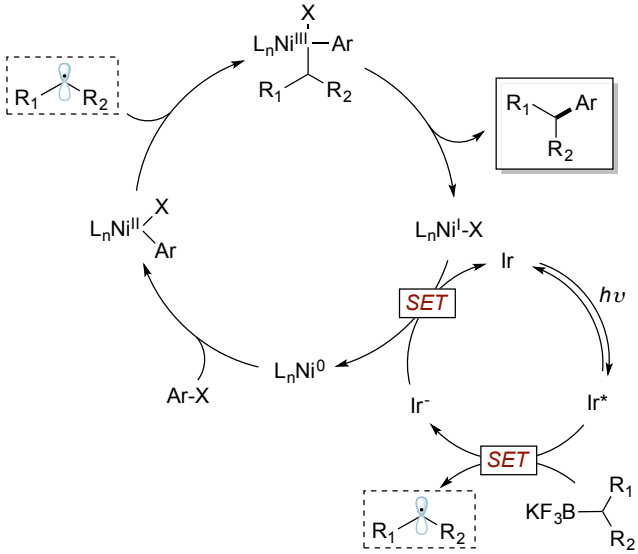
Although the cross-coupling of arylboronic acids with aryl electrophiles has been ubiquitous within Suzuki-Miyaura chemistry for over three decades, the use of corresponding alkyl electrophiles has always presented problems. These species are not only less disposed towards oxidative addition than their aryl counterparts, they can also undergo undesired side-reactions such as β-hydride elimination, limiting their effectiveness in cross-coupling.[83] Efficient methods for the metal-catalyzed cross-coupling of sp^3 coupling partners are therefore highly desirable. The Baran group has disclosed a method which uses redox-active alkyl esters in lieu of traditional halides as coupling partners with boronic acids (Scheme 21).[84] The authors propose a Ni(I)/Ni(III) pathway in which the Ni(I) catalyst undergoes transmetallation with the aryl boronic acid, forming a new Ni(I) complex. This complex then reduces the activated ester which, following fragmentation, forms an alkyl radical. This then combines with the Ni(II) intermediate and, following reductive elimination, reforms the active Ni(I) species.



Scheme 21. Ni-catalyzed cross-coupling of redox-active esters and boronic acids

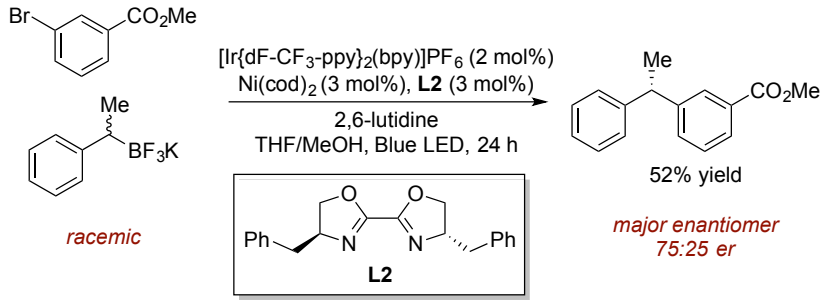
The redox-active esters can be synthesized either beforehand or *in situ* from the corresponding carboxylic acids which, along with boronic acids, are some of the most widely available building blocks in organic synthesis.[48,49] This provides a large and varied potential scope of this coupling, which will likely be attractive to synthetic chemists. In addition, the reaction is highly scalable, with the authors demonstrating the process on gram scale with no loss in yield, and widely functional group tolerant. Halide-bearing arylboronic acids were effectively cross-coupled with complete selectivity for the alkyl ester, retaining the halide functionality for potential elaboration.

In a similar fashion to alkyl electrophiles, the use of sp^3 boron species as nucleophiles in cross-coupling has traditionally been challenging, with problems such as protodeboronation, sluggish transmetallation and β-hydride elimination all being contributing factors.[1] To combat this, and building on extensive work with organotrifluoroborates,[86] in 2014 Molander and coworkers moved away from conventional two-electron processes and employed a cooperative Ni/Ir-catalyzed single-electron transmetallation strategy to enable the cross-coupling of potassium alkyltrifluoroborates with aryl halide electrophiles.[87]



Scheme 22. Photoredox/Ni-catalyzed cross coupling *via* single-electron transmetallation

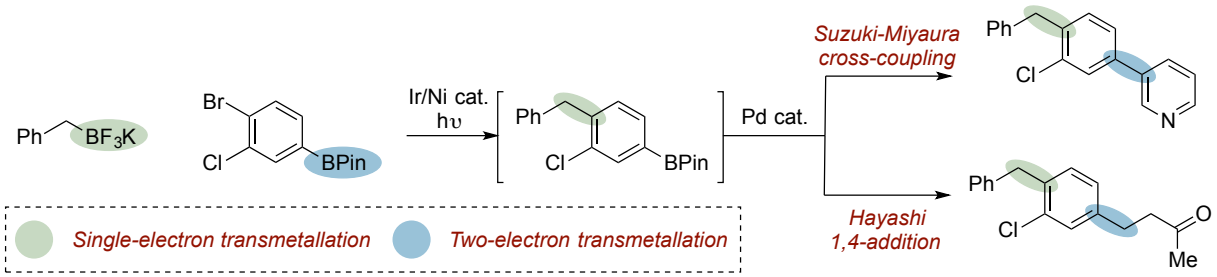
Here, visible light excitation of the iridium photocatalyst forms a highly oxidizing photoexcited Ir* which can undergo single-electron-transfer (SET) with the organotrifluoroborate (Scheme 22). Subsequent fragmentation forms an alkyl radical, which can then add to the Ni(II) intermediate generated from oxidative additive of the aryl halide to the active Ni(0). Reductive elimination from the high valent Ni(III) furnishes the desired product, along with a Ni(I) species. SET then regenerates Ni(0) along with the reduced Ir species, closing both catalytic cycles. The Molander group have been able to apply this methodology to a range of aryl and heteroaryl halides, along with a variety of alkyltrifluoroborates, including α-alkoxymethyl, α-aminomethyl, and α-trifluoromethylbenzyl species.[88] It was also shown that a chiral ligand could promote stereoconvergent cross-coupling (Scheme 23).[87]



Scheme 23. Stereoconvergent cross-coupling via single-electron transmetallation

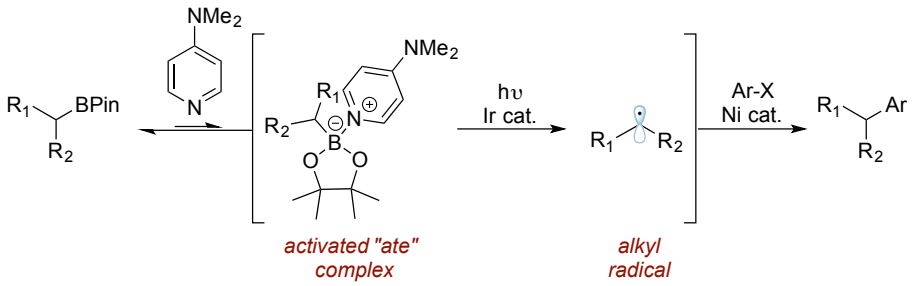
In a further demonstration of the utility of this methodology, the authors showcased the orthogonal reactivity of multiple boron species under their photoredox cross-coupling in combination with traditional two-electron processes.[89] This enables the selective cross-coupling of an alkyltrifluoroborates under the single-electron transmetallation manifold while maintaining a second reactive boron species, such as a BPin moiety, intact for further functionalization (Scheme 24). This offers an alternative to conventional protecting group strategies for sequential cross-coupling, enabling efficient elaboration of functionalized

building blocks without the need for intermediate purification or modification through deprotection. The development of a new mechanism for transmetallation of potassium organotrifluoroborates demonstrates the continued diversity and importance of organoboron reagents in synthesis.



Scheme 24. Orthogonal reactivity of multiple boron species using photoredox cross-coupling

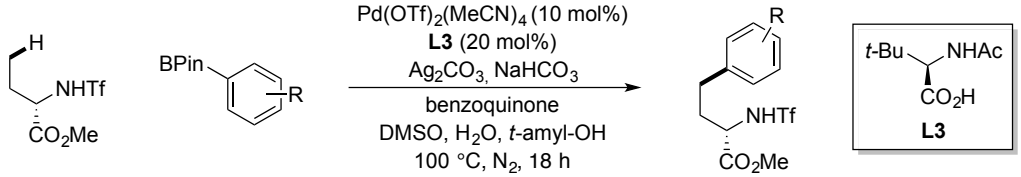
In an interesting evolution of this photoredox-mediated single electron transmetallation, Ley and coworkers have recently adapted the process to enable its use in flow (Scheme 25).[90] Their initial attempts to utilize organotrifluoroborates in flow were frustrated by the limited solubility of potassium trifluoroborate salts. However, switching to a boronic ester with a suitable basic additive furnished a homogeneous solution ideal for use in a flow reactor. Here, the basic DMAP additive forms an adduct with the Lewis acidic boron of the BPin ester, and this activated "ate" complex can then be fragmented by the Ir photocatalyst to yield an alkyl radical in similar fashion to Molander's system. The reaction offered comparable yields in flow to the batch process however with greatly reduced reaction times (50 min in flow *vs.* 24 h in batch with BF_3K), demonstrating its utility in high throughput production.



Scheme 25. Photoredox single-electron transmetallation in flow

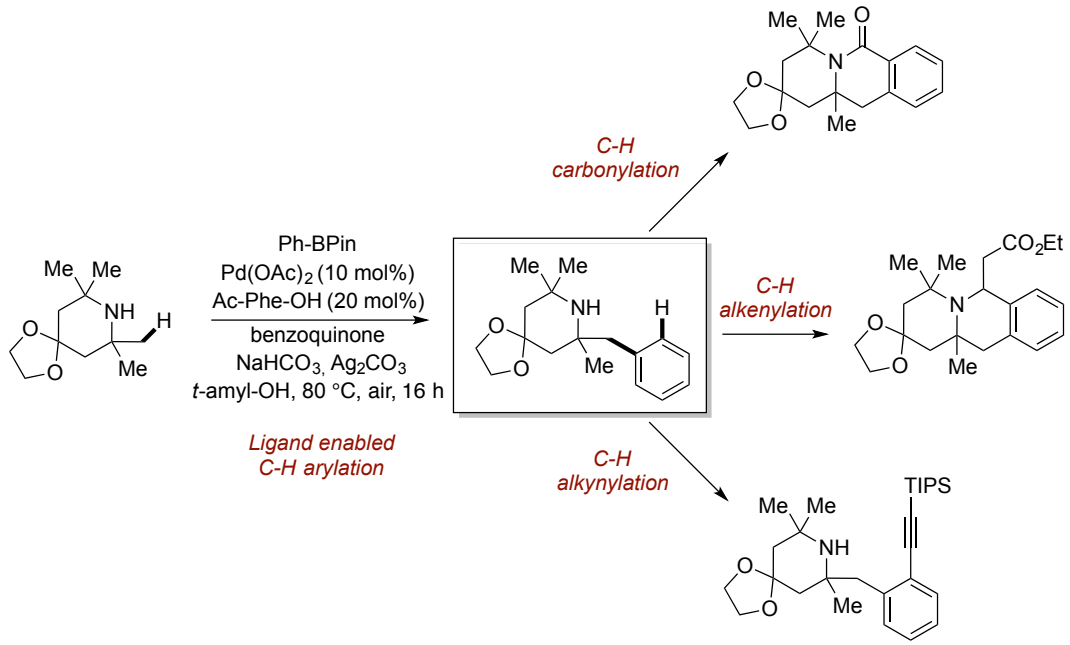
The development of the Suzuki-Miyaura cross-coupling paved the way in industry and academia for the facile construction of sp^2 C-C bonds and, as a result of this, the presence of biaryl motifs became ubiquitous in pharmaceuticals.[46] With drug discovery research now looking to move away from these types of planar skeletons,[33] C(sp^3)-H activation has come to the forefront in recent years as a means to build biologically relevant carbon frameworks. While much of the research in this area has focused around the use of different directing groups,[91] Yu and coworkers recently reported a novel ligand-enabled sp^3 C-H arylation *via* Pd catalysis.[92] This allows the use of much more weakly coordinating directing groups, such as secondary amines, and therefore enables the synthesis of increasingly synthetically useful, biologically relevant compounds without the need for directing group removal, something which often requires harsh conditions to facilitate. Yu *et al*

utilize a mono-*N*-protected amino acid (MPAA) ligand to facilitate C-H activation and subsequent cross-coupling with arylboronic esters (Scheme 26).



Scheme 26. Yu's ligand-enabled sp³ C-H arylation

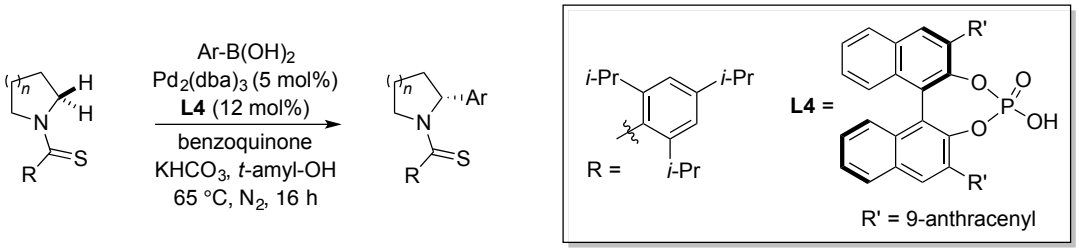
Notably the reaction did not proceed to any degree in the absence of the MPAA ligand, highlighting its crucial role in accelerating C-H activation. A wide range of arylboronic esters were tolerated under the reaction conditions, in addition to a variety of alkyl amines including amino alcohols and amino acid derivatives. Gaunt and He were able to further develop this idea of using an amino acid ligand to promote C-H activation, enabling cyclic amines to be used as weakly coordinating substrates.[93] Here the authors use arylboronic esters in combination with a palladium catalyst under similar conditions to those developed by Yu, but in this case proceeding through a proposed 4-membered palladacycle. In a further demonstration of the power of C-H activation methodology, the group performed a range of further derivitizations via C-H functionalization on their arylamine products (Scheme 27).



Scheme 27. Gaunt's ligand-enabled sp³ C-H arylation and subsequent C-H functionalization

As is frequently the case with the development of important new methodology, an asymmetric variant soon followed. Yu and coworkers recently reported the Pd-catalyzed enantioselective α-arylation of thioamides utilizing a chiral phosphoric acid ligand (Scheme 28).[94] This enabled the enantioselective functionalization of a range of thioamides, both cyclic and acyclic, including motifs unable to undergo α-arylation using traditional lithiation techniques, such as azetidine. A wide variety of arylboronic acids were tolerated in the procedure, and the reaction could be

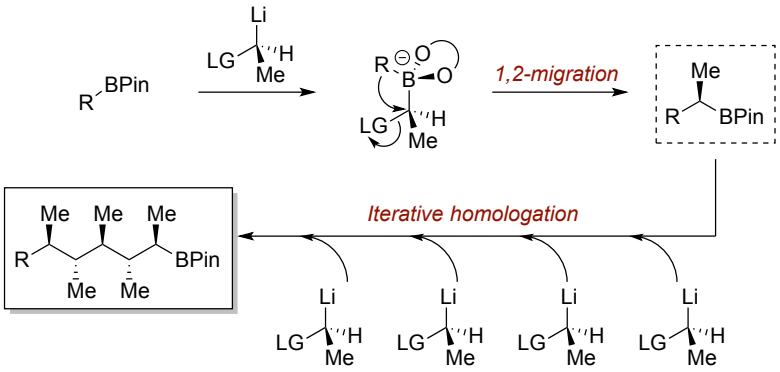
performed on gram scale with no loss of yield or enantioselectivity, making it highly attractive for drug discovery, as many active pharmaceutical agents contain an α-aryl amine. The thioamide directing group could also be removed under conditions sufficiently mild to avoid any erosion of stereochemistry.



Scheme 28. Enantioselective α-arylation of thioamides with chiral phosphoric acid ligand

C(sp³)–C(sp³) bond formation

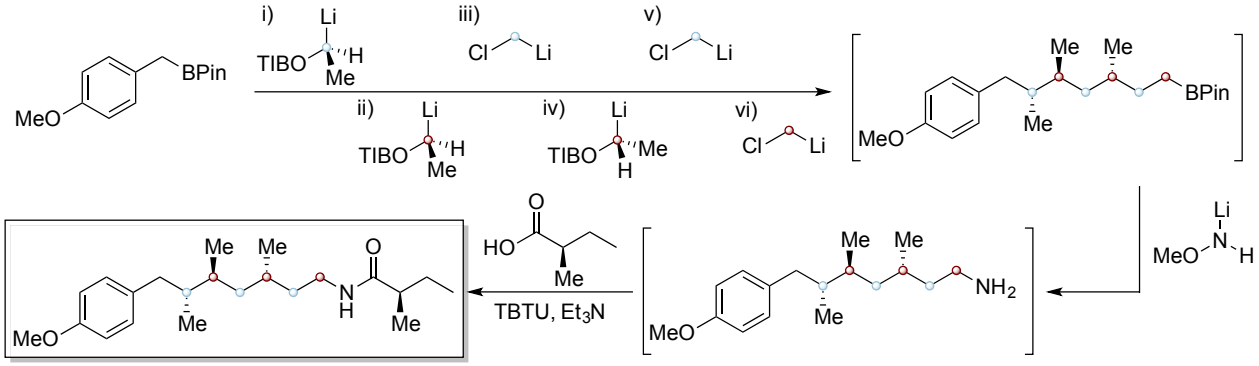
In addition to their broad utility in aromatic chemistry, organoboron reagents have also found use in the synthesis of more complex molecular structures. One example of this comes from the Aggarwal group, who have developed methodology for the stereochemically defined homologation of boronic esters, enabling the synthesis of molecules with not only pre-determined chain length but also defined shape.[95] This method of "assembly-line synthesis" proceeds *via* the reaction of a boronic acid pinacol ester with a chiral organolithium complex, forming a boronate complex which, upon warming to room temperature, undergoes a Matteson type 1,2-migration[96] to form the homologated boronic ester. This homologated ester can then re-enter the iterative cycle for further homologation (Scheme 29). Through careful control of the stoichiometry of reagents and the reaction conditions, the Aggarwal group was able to utilize this iterative homologation in order to furnish molecules with ten contiguous stereocentres with excellent control of both chain length and stereoselectivity.



Scheme 29. Iterative homologation of boronic esters *via* assembly-line synthesis

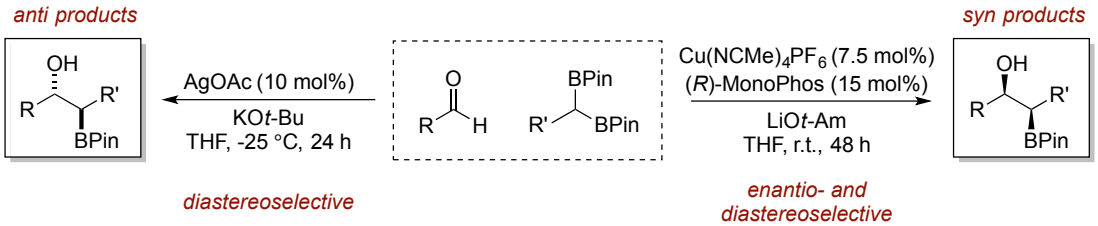
The authors capitalized on their methodology by demonstrating the streamlined synthesis of a range of natural products, including the highly potent neurotoxin (+)-Kalkitoxin.[97] Using their assembly-line synthesis, Aggarwal *et al* synthesized the linear core of (+)-Kalkitoxin from a commercially available boronic ester in one iterative sequence requiring only a single purification (Scheme 30). This core could then be converted into the desired natural product in five simple steps, furnishing

(+)-Kalkitoxin in just seven steps (longest linear sequence), a significant improvement in efficiency when compared to previous syntheses.[98]



Scheme 30. Assembly-line synthesis of (+)-Kalkitoxin core

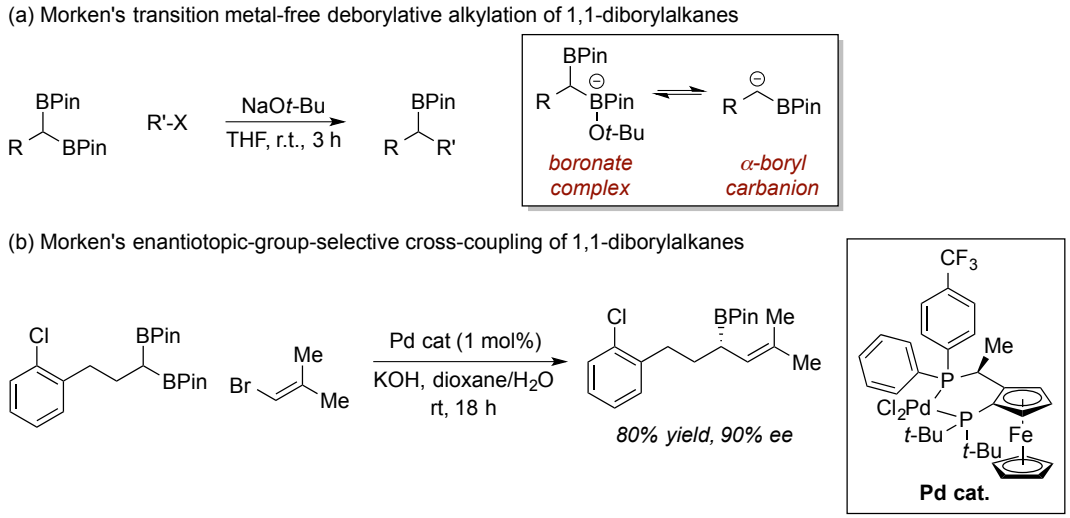
1,1-Diborylalkanes, specifically geminal boronic acid pinacol esters have also become highly prevalent in recent years. In addition to cross-coupling, as demonstrated by Shibata[99] and later rendered enantioselective by Morken,[100] these species can undergo a wide variety of transformations. Meek and coworkers have demonstrated the use of geminal BPins in the enantio- and diastereoselective addition to aldehydes to form 1,2-hydroxyboronates – valuable building blocks in organic synthesis (Scheme 31). Under Cu-catalyzed conditions in the presence of a chiral phosphoramidite ligand along with a suitable basic promoter, racemic 1,1-diborylalkanes could form a chiral α-borylalkyl-Cu species which could then undergo enantiospecific 1,2-addition, affording the desired 1,2-hydroxyboronates in high enantiomeric ratio with good *syn*-selectivity.[101] The authors were also able to develop a complementary Ag-catalyzed protocol in order to deliver the *anti*-diastereomer in high selectivity, although this process did not furnish enantiopure products as a result of a different activation process and absence of chiral ligand.[102] Further development of their Cu-catalyzed enantioselective protocol enabled α-ketoesters to be used as electrophiles in place of aldehydes, furnishing β-boryl tertiary alcohols in excellent enantio- and diasteroselectivity.[103]



Scheme 31. Transition metal-catalyzed 1,2-addition of 1,1-diborylalkanes

In terms of cross-coupling, previous examples of C(sp^3)-C(sp^3) bond formation using alkyl boron reagents have typically relied upon the use of highly activated alkyl 9-BBN reagents with metal catalysts such as Pd[104] or Ni.[105] The reactivity of these species thereby limits their use in organic synthesis, with both functional group tolerance and purification presenting potential issues. Recent developments have enabled the use of much less reactive 1,1-diborylalkanes in conjunction with unactivated alkyl electrophiles in a deborylative alkylation process to construct saturated C-C bonds. Morken and coworkers have reported a base-promoted deborylative alkylation procedure which enables the facile synthesis of alkylboronic

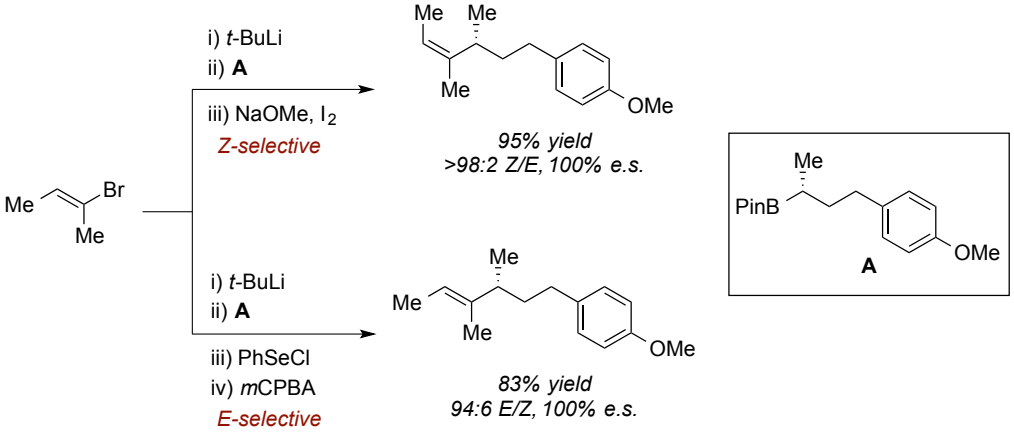
esters under mild conditions (Scheme 32a).[106] This valuable transformation not only precludes the use of any reactive boron species and metal catalysts, it also provides chemists access to highly versatile building blocks, forging a new C(sp^3)-C(sp^3) bond while also retaining a reactive BPin moiety for further functionalization. The authors propose the formation of a boronate complex using an alkoxide base, which then forms an α-boryl carbanion *via* deborylation. This intermediate then reacts rapidly with alkyl electrophiles to form the desired alkylboronic ester. Morken subsequently capitalized on this activation mode by coupling with a Pd catalyst with chiral ligand to allow an enantiotopic-group-selective cross-coupling reaction (Scheme 32b).[107,108]



Scheme 32. C-C bond formation using 1,1-diborylalkanes

Shortly afterwards, and building upon Morken's initial report,[106] Xiao and Fu reported a Cu-promoted deborylative alkylation protocol.[109] Although, unlike Morken's process, this C(sp^3)-C(sp^3) cross-coupling is not metal-free, the authors found that the addition of a catalytic amount of Cu was sufficient in promoting the reaction and enabled the synthesis of a wide array of alkylboronic esters, including a variety of functional groups absent from the original report, such as acetals, halides, esters, and heterocyclic motifs.

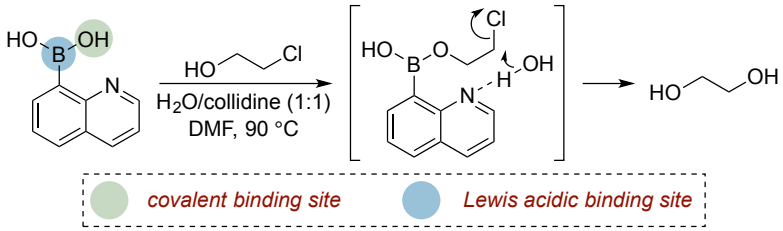
The utility of boronate activation within stereoselective cross-coupling has also been shown in a modern twist to the Zweifel olefination recently described by Aggarwal (Scheme 33).[110] Lithiation of a vinyl bromide and addition to an enantioenriched sp^3-organoboron compound results in the expected boronate species. Treatment with either I_2 or PhSeCl/*m*CPBA then delivers the *Z*- or *E*-olefin product, respectively, with high stereospecificity.



Scheme 33. Stereodivergent olefination using vinyl organoborons

Boron reagents as additives

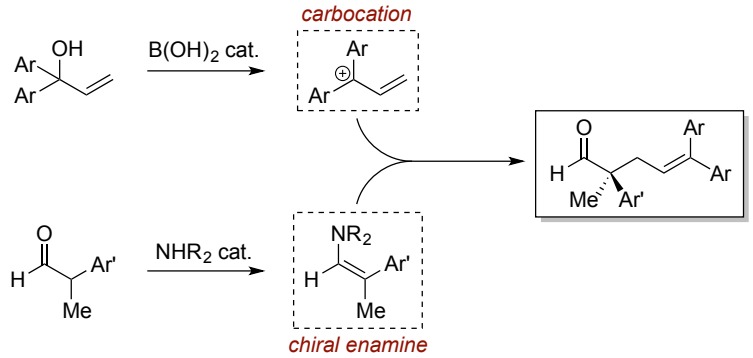
Since its inception over 40 years ago, modern transition metal-catalysis has fundamentally changed the landscape of synthetic chemistry. The same could be said for the advent of modern organocatalysis within the last two decades. Organocatalysts have several advantages over their transition metal-based counterparts, including stability, facile synthesis, and low cost, along with avoiding the use of transition metals with potential downstream toxicity complications for drug and agrochemical development.[111] In addition to their role as reagents in transition metal-catalyzed cross-coupling, and as a further testament to their flexibility in synthesis, boronic acids have also been utilized as catalysts in the activation of hydroxyl containing compounds. When considering classes of compounds as potential catalysts, boronic acids appear ideally suited. Their Lewis acidic nature, in addition to the two hydroxyl groups on boron, provide the potential for a range of binding interactions with substrates. The majority of arylboronic acids are air stable, crystalline solids, making them easy to handle. The first example of the use of boronic acids as catalysts in organic synthesis dates back to 1963, when Letsinger and coworkers utilized a quinolone derived boronic acid for the hydrolysis of chloro-alcohols to diols (Scheme 34).[112]



Scheme 34. Boronic acid catalyzed hydrolysis of chloro-alcohols

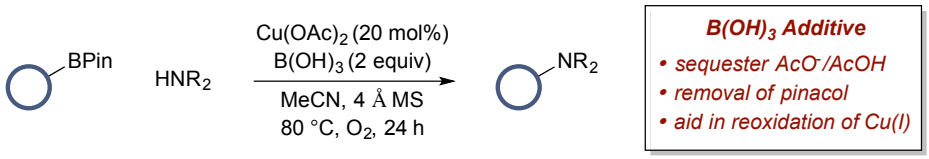
Since then the field has expanded considerably, with boronic acids being used as catalysts in amidation, esterification, alkylation, and cycloaddition reactions among others.[113] Recent developments have targeted merging boronic acid catalysis with other methods of catalytic activation, such as chiral amine organocatalysis. This type of dual catalysis, in which both substrates are individually activated through catalysis, presents a number of challenges, such as interplay between the Lewis basic amine and the Lewis acidic boronic acid, leading to unproductive reaction

pathways. Hall and coworkers have recently reported the successful realization of cooperative boronic acid and chiral amine catalysis to furnish stereogenic quaternary carbon centers *via* enantioselective alkylation (Scheme 35).[114] Here, an allylic alcohol is activated by boronic acid catalysis, forming a reactive carbocation. This is then intercepted by a chiral enamine, generated from the aldehyde substrate and chiral amine catalyst. The use of HFIP as a solvent was found to be key in both solubilizing the ferrocenium boronic acid catalyst as well as stabilizing the carbocation intermediate. This example of boronic acid catalysis demonstrates the power of boron reagents beyond transition-metal-catalysis, and its combination with other organocatalyzed processes, particularly those of an asymmetric nature, could form the basis for a new catalysis platform.



Scheme 35. Dual boronic acid and chiral amine catalyzed asymmetric alkylation

Another recent example of utilizing boron reagents outside of their traditional role in transition-metal-catalysis come Watson *et al*, who used a boric acid additive to enable the Cu-catalyzed Chan-Lam amination of aryl boronic esters (Scheme 36).[115] Having previously addressed the general lack of reactivity of aryl BPins in the Chan-Lam amination using stoichiometric Cu,[116] the authors sought to delve deeper into the reaction mechanism in an attempt to unearth the nature of the reactivity issue. A series of spectroscopic and computational experiments, along with crystallographic identification of key intermediates, allowed the Watson team to develop a full mechanistic picture of the Chan-Lam amination. Importantly, this also enabled the identification of several counterproductive processes: slow reoxidation of the Cu(I) catalyst leads to increased side reactions, such as oxidation and protodeboronation; pinacol liberated from the reaction of BPin esters can inhibit the Cu catalyst, thus limiting catalyst turnover; AcO^-/AcOH generated from the $Cu(OAc)_2$ catalyst can also inhibit the reaction. These three key issues could be solved through the addition of a boric acid additive, which serves to sequester both AcO^-/AcOH and pinacol, as well as promote Cu(I) oxidation, enabling general catalytic conditions for the amination of BPin esters. This is a valuable step forward as these boronic esters have become ubiquitous in organic synthesis, due to their increased stability and ease of preparation over their acid counterparts.



Scheme 36. Use of boric acid additive to enable catalytic Chan-Lam amination of BPin esters

Conclusions

Organoboron reagents are integral to some of the most robust methods in the organic chemistry toolbox. However, the selected recent advances described above demonstrate how these eponymous organic reagents remain at the cutting edge of contemporary organic chemistry research today. Modern twists on classic reactions enable a more diverse range of bond formations under increasingly mild conditions, while recent studies have documented the genesis of a series of new transformations involving organoborons: enantioselective bond formations, photoredox processes, and boronic acid-catalyzed reactions are at the vanguard of the field of catalysis. As such, the development of novel and exciting applications of organoboron reagents is sure to continue and the tricks of this old dog of organic chemistry continue to surprise.

AUTHOR CONTRIBUTIONS

Conceptualization, J.W.B.F., A.J.B.W.; Writing – Original Draft, J.W.B.F.; Writing – Review & Editing, J.W.B.F., A.J.B.W.; Funding Acquisition, A.J.B.W.

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