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Organotrifluoroborates: Another Branch of the Mighty Oak

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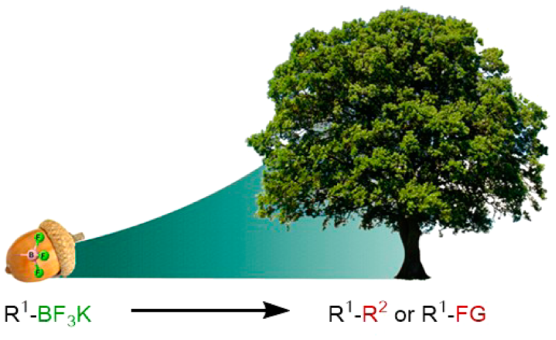
ABSTRACT: Over the past two decades, organotrifluoroborates have evolved from being chemical curiosities to important reagents for the elaboration of organic molecules. Aside from their often-unique reactivity patterns, favorable features of these reagents include their ease of preparation/isolation, reliable crystallinity, enhanced stability, and monomeric structure. Currently >600 structurally diverse reagents of this class are commercially available, and >850 such compounds have been reported from the author's laboratory. The organotrifluoroborates can be utilized as shelf-stable precursors to a variety of end products through simple functional group transformations and have also been employed as partners in cross-coupling reactions between aromatic, alkenyl, alkynyl, and alkyl substrates in library or individual formats. Within the realm of cross-coupling reactions, organotrifluoroborates provide a practical entry to substructural entities not readily accessed using other organometallic reagents, and most recently, the development of a novel mechanistic paradigm for cross-coupling promises to expand the range of accessible cross-coupling partners even further to include both single- and two-electron processes.



INTRODUCTION

Few classes of reagents have altered the chemical synthesis landscape as much as organoborons. The ease of synthesis of these materials by a variety of approaches, combined with their extreme versatility in terms of their transformation to important functional groups as well as their use in C−C bond-forming reactions, has made them indispensible synthetic tools. In particular, the application of boronic acids and their derivatives to transition-metal-catalyzed cross-coupling has transformed entire industries and made a huge impact in academic research as well, allowing rapid and efficient access to chemical entities that were previously challenging to access by any other realistic synthetic strategy.[1]

Organoboron reagents have become the preferred nucleophilic partners in cross-coupling reactions because of their generally low toxicity, their relative stability, their ease of synthesis, and the toleration of sensitive functional groups both in accessing the coupling agents and in the reaction conditions used for cross-coupling. Among the various available organoboron compounds, boronic acids and, to a lesser extent, boronate esters have become the focus of most of the efforts to generalize cross-coupling protocols and have facilitated the use of parallel processes in medicinal chemistry.[2] Employing these reagents, outstanding improvements in synthetic protocols have been made through ligand design[3] and a fundamental understanding of the reaction mechanism,[4] which in particular have led to facilitation of the oxidative addition and reductive elimination steps of the catalytic cycle.

Despite enormous efforts over a period of decades, however, the combination of boronic acids and ligand development has not provided a panacea, and both the physical properties of the boronic acids and their boronate esters as well as their reactivity patterns have left opportunities for both improvements and enhancements. Thus, boronic acids are known to exist as mixtures of the monomeric boronic acids and trimeric, cyclic boroxines,[5] often leading to gummy solids that are difficult to handle. Additionally, the monomer/trimer mixture makes an accurate assessment of stoichiometry challenging. Because of this and a decided propensity of the reagents (particularly heteroarylboronic acids[6]) to protodeboronate[7] under cross-coupling conditions, superstoichiometric quantities of the boron reagents are almost always employed in reactions. Although boronate esters (e.g., pinacolboronates) alleviate some of these issues, these materials are less reactive than boronic acids and furthermore much less atom economical. In addition to the facile protodeboronation mentioned above, other issues arise with individual classes of boronic acids. For example, many alkenylboronic acids readily polymerize.[8] Alkylboronic acids (particularly 2° alkyl systems) are challenging to cross-couple because the high temperatures required to overcome slow transmetalation allow β-hydride elimination of the diorganopalladium intermediate to compete with productive reductive elimination. At present, there is little diversity in terms of substructural coupling units that would expand the range of the overall coupling process; however, there is great interest in enabling new borate monomers for chemical diversification.

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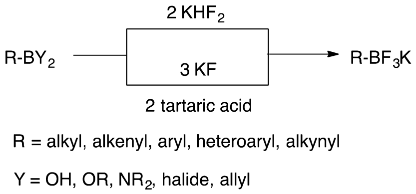
Given this set of circumstances, in retrospect, it is surprising that so much attention was focused on improving conditions for boronic acid cross-coupling and little research was conducted on novel boron-based reagents to expand the scope of Suzuki-type coupling. With a long-standing, but unrequited, interest in the cross-coupling of Csp^3-hybridized organometallics, our interest in developing a new class of organoborons for this purpose was piqued by several reports on the synthesis and cross-coupling of organotrifluoroborates.

In the first seminal contribution,[9] the Vedejs group reported a simple, high-yielding synthesis of potassium organotrifluoroborates that turned out to be effective for virtually all organic moieties (aryl, heteroaryl, alkenyl, alkynyl, alkyl, etc.) and any boronic acid derivative RBY_2 (Y = OH, OR, NR_2, halide, allyl).[10] These reactions take place at room temperature within hours and provide high yields of easily isolated, monomeric products that are either crystalline solids or free-flowing powders. Subsequently, Lennox and Lloyd-Jones published an alternative method for organotrifluoroborate synthesis[11] that involved the use of KF and tartaric acid, which avoided the glassware etching caused by KHF_2 (eq 1).



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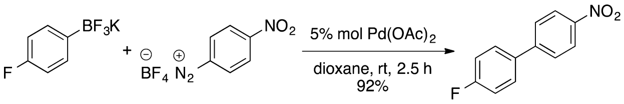
Subsequent to the Vedejs report, the groups of Genêt and Chen reported the palladium-catalyzed cross-coupling of aryltrifluoroborates with activated aryldiazonium[12] and aryliodonium salts,[13] respectively (eqs 2 and 3). Interestingly, these transformations took place very rapidly under *anhydrous* conditions at low temperatures. Given the ease of synthesis of this relatively obscure class of organoboron reagents and their rapid cross-coupling, we envisioned that they might be excellent partners for cross-coupling on a more general platform. In particular, we imagined that the polarization of the carbon−boron bond engendered by the tetracoordinate nature of the trifluoroborate would make them more nucleophilic[14] and, therefore, ideal candidates to explore Csp^3 coupling reactions. Subsequent research would uncover the more latent reactivity of this function, but nevertheless, it got us started on a new and exciting research program that continues to evolve and provide both surprises and valuable new synthetic methods.



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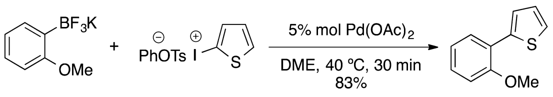

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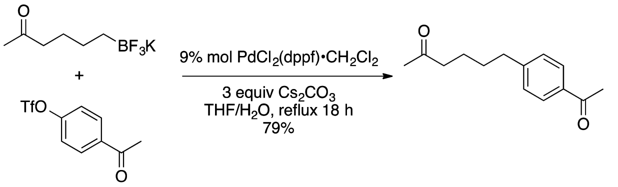
PALLADIUM-CATALYZED CROSS-COUPLING REACTIONS

Our own efforts in using organotrifluoroborates as cross-coupling partners began in 2000, when we sought to develop a method for the cross-coupling of alkyltrifluoroborates with organic triflates.[15] The initial goal was to find conditions for the challenging Csp3 coupling of secondary alkyls, but the realization of this particular objective was to require more than a decade. Nevertheless, important information was derived from this early study. First, in their initial efforts Genêt and coworkers had indicated that organotrifluoroborates were reluctant to cross-couple with aryl halides, which implied that only the highly activated diazonium and iodonium electrophiles were suitable partners. Importantly, as pointed out above, these studies were conducted under *anhydrous* conditions. Our work demonstrated that a general protocol required *aqueous* media, under which conditions a variety of 1° alkyltrifluoroborates coupled effectively with both aryl and enol triflates (eqs 4 and 5). Of note in this seminal study was the very high catalyst loading required, as well as the relatively harsh reaction conditions.



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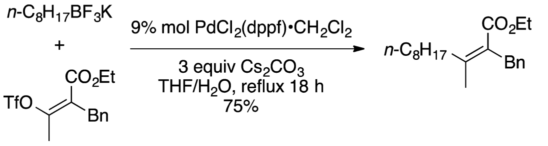

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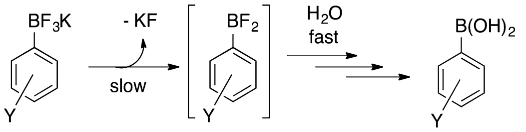
The requirement for aqueous base prompted a preliminary study on the stability of alkyltrifluoroborates to these reaction conditions, wherein it was revealed that hydrolysis to boronic acids (or fluorinated derivatives thereof) was relatively facile. In fact, the analogous boronic acids were demonstrated to couple under the same conditions as the trifluoroborate. Studies using aryltrifluoroborate starting materials revealed the same phenomenon,[16] providing the first indications that the organotrifluoroborates did not remain intact under basic, protic conditions but rather served as a stable reservoir for boronic acid derivatives that were intermediates in the key transmetalation step.

Our early mechanistic studies were followed by rigorous and elegant studies from other groups that not only quantified the hydrolysis rates of various organotrifluoroborates but also provided amazing insight into the mechanistic details of the cross-coupling reactions. In studies on the hydrolysis of *aryltrifluoroborates*,[17] the Perrin group established that the electronic effects of arene substituents play a defining role in the rate of hydrolysis of the trifluoroborato group, with electron-donating groups enhancing the rate and electron-withdrawing groups inhibiting the process. Under the conditions employed, hydrolysis appeared to occur in a manner that was virtually pH independent, where loss of the first fluoride was rate limiting and no fluoroborate intermediates were detected (eq 6). The hydrolysis rates were thus reflective of the ability of substituents on the arene to stabilize the boron center upon conversion from a tetracoordinate to a tricoordinate moiety, the latter of which is isoelectronic with a benzylic carbocation.



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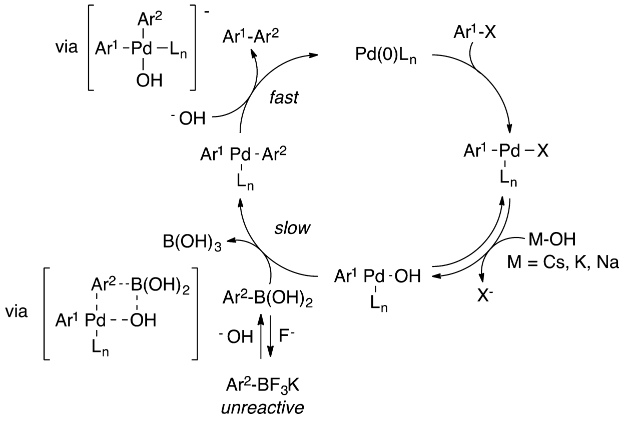
In an examination of a diverse array of *nonaromatic* organotrifluoroborates under a prescribed set of conditions (phosphate buffer, pH 7.5), the Perrin group subsequently found that hydrolysis rates varied by over 5 orders of magnitude depending on the structure of the organotrifluoroborate, correlating well with the pK_a of the corresponding carboxylic acid (Figure 1).[18]

Between the publication of these two studies, an exhaustive and highly detailed examination of organotrifluoroborate hydrolysis was carried out by Lennox and Lloyd-Jones, largely under conditions reminiscent of those used in Suzuki coupling reactions (THF/H_2O, Cs_2CO_3, 55 °C).[19] This study revealed that although some organotrifluoroborate reagents (e.g., isopropyl, β-styryl, anisyl) hydrolyzed directly and rapidly to generate the corresponding boronic acid derivatives, others (e.g., alkynyl, *p*-nitrophenyl) hydrolyze extremely slowly, in line with the observations of Perrin. Most interesting were those organotrifluoroborates that exhibited complex hydrolytic behavior, requiring acid catalysis for efficient hydrolysis (e.g., 4-FC_6H_4, naphthyl, furyl, and benzyl). This behavior was found to be created by phase-splitting of the THF/H_2O mixture caused by the base and various inorganics present in the mixture. The contradiction of requiring acid to facilitate hydrolysis under basic pH conditions has the effect of ensuring a slow release of boronic acids under typical Suzuki conditions, and it also introduces a variety of ancillary factors that affect the hydrolysis rate, including the nature of the vessel in which the reaction is carried out (e.g., glass versus Teflon-lined), the shape of the vessel, stirring rate, and so forth. This important study not only confirmed that organotrifluoroborates can indeed serve as stable reservoirs for boronic acids, providing a slow release of the latter to effect cross-coupling, but also provided a prescription for tuning the release to match the rate of the key transmetalation rate, thereby minimizing protodeboronation. This study revealed another correlation to hydrolysis rate, i.e., the DFT-derived B−F bond length of the intermediate difluoroborane [r(B−F)]. Additionally, the Swain−Lupton resonance value in combination with a weighted Charton steric parameter was also found to be predictive of hydrolysis rates, providing tools for predicting the ease of hydrolysis of diverse classes of organotrifluoroborates.

The combination of these studies provided irrefutable evidence for the role that organotrifluoroborates play as precursors to boronic acids in Suzuki−Miyaura coupling reactions. This knowledge, combined with the elegant studies of Amatore and Jutand on the critical part played by base and fluoride on the transmetalation and reductive elimination aspects of these cross-coupling reactions,[4a,c,e] paint a detailed picture of the overall process (Scheme 1).

Scheme 1. Detailed Mechanism of Aryltrifluoroborate Cross-Coupling



More subtle advantages for the use of organotrifluoroborates in cross-coupling were derived from further mechanistic studies,[20] which revealed that the inherent nature of these reagents inhibited side reactions (protodeboronation, oxidation, homocoupling) that often plague boronic acid cross-couplings. Some of the significant findings of the study revealed the following: (1) Low water concentrations could be utilized to reduce the concentration of $RB(OH)_3$ species, which inhibits transmetalation and increases protodeboronation.[4a,c] (2) Fluoride can serve as a reductant for the palladium(II) precatalysts, minimizing the amount of homocoupling derived from an organoboron species that would normally serve as the reductant through double transmetalation on a PdX_2 species followed by reductive elimination. (3) In reactions performed in THF, the trifluoroborate promotes the decomposition of THF hydroperoxide, thereby reducing the amount of alcohol byproducts in the reaction mixtures derived from oxidized organoborons. (4) The amount of aerobic homocoupling derived from the aryl halide in organotrifluoroborate cross-couplings is reduced by the presence of high concentrations of aryl halide and low concentrations of boronic acid, the latter of which is assured by the slow hydrolysis rate of the organotrifluoroborates relative to catalytic turnover.

The sum total of these investigations revealed that, although our initial hypothesis concerning the nature of the trifluoroborate reactivity in the cross-coupling reaction was incorrect, our empirical investigation led us to a system that serendipitously exhibited many features that were advantageous to the overall process. In the ensuing years, we strived to build upon the mechanistic foundations discussed above to uncover practical applications of both single- and two-electron organotrifluoroborate coupling. Along the way, we were able to find methods that take advantage of the characteristics of the organotrifluoroborates to control the stereochemistry of these processes as well as prevent metal hydride elimination that extended the utility of these transformations.[21]

Aryl/Heteroaryltrifluoroborate Cross-Coupling. For the vast majority of routine biaryl coupling reactions, organotrifluoroborates can be used in effective cross-coupling schemes under extremely mild conditions. As an example, in aryl bromide coupling reactions, stoichiometric quantities of the trifluoroborates can be used, low loadings (0.2−2 mol %) of

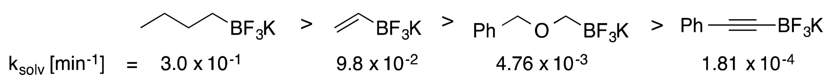


Figure 1. Rates of hydrolysis.

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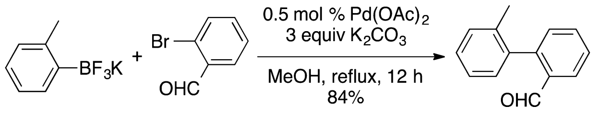
$Pd(OAc)_2$ as a catalyst without added ligands are effective, and protic solvents such as MeOH or EtOH either at room temperature or heating for several hours with 3 equiv of added base (K_2CO_3, Et_3N, or *t*-$BuNH_2$) are sufficient to achieve high yields of the desired products. Most remarkably, these reactions can be carried out in the air (eq 7). Some extremely electron-deficient aryltrifluoroborates can be induced to couple, wherein the corresponding boronic acids fail because of extensive protodeboronation (eq 8).[22]



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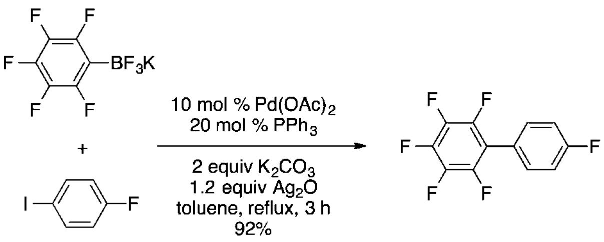

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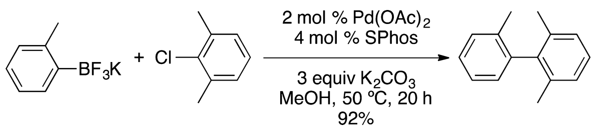
For the more demanding cross-coupling of aryl chlorides and, in particular, electron-rich and sterically encumbered electrophiles, $Pd(OAc)_2$ in the presence of the SPhos supporting ligand proved effective with a variety of aryltrifluoroborates (eq 9).[23]



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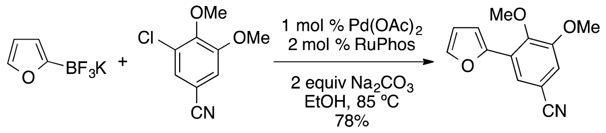
Heteroaryl cross-couplings bring their own set of demands, most particularly in terms of their inherent instability with regard to protodeboronation,[6] which manifests itself not only in an inability to store such reagents for long periods of time but also in the cross-coupling itself. Using boronic acid coupling partners, it is not uncommon to encounter protocols that require up to 250% excess reagent to achieve satisfactory yields. To address this challenge, numerous heteroaryltrifluoroborates were prepared and found to be stable upon storage for months with no sign of protodeboronation.[24] In an extensive study, a single set of conditions allowed the cross-coupling of over 20 structurally diverse heteroaryltrifluoroborates, including five-membered ring heterocycles, six-membered ring heterocycles, and heterobiaryls with a variety of aryl- and heteroaryl chlorides and bromides (eq 10). Most impressively, normally challenging 2-trifluoroboratopyridines could also be cross-coupled with aryl and heteroaryl bromides as well (eq 11).[25]



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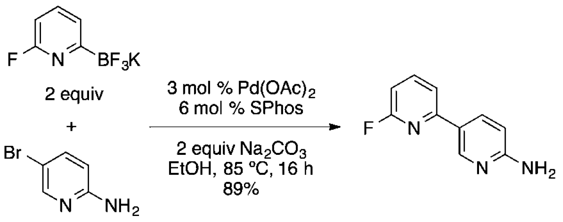

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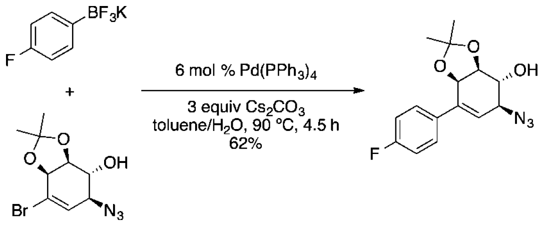

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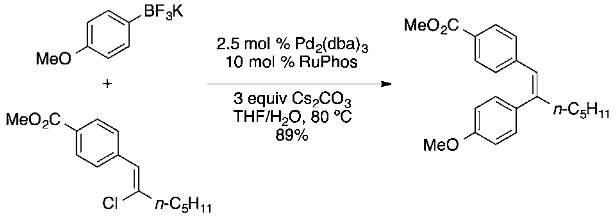

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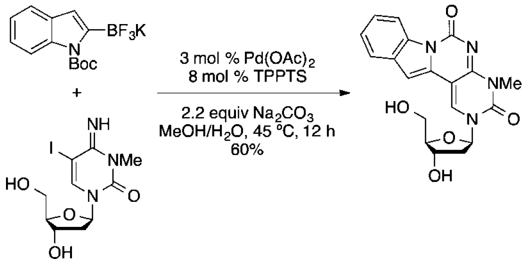

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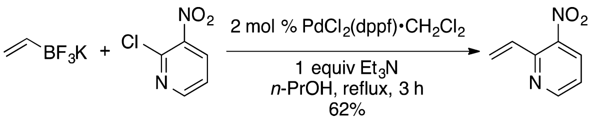
Both aryl and heteroaryltrifluoroborates can be coupled effectively with a variety of alkenyl electrophiles in palladium-catalyzed cross-coupling reactions (eqs 12–14).[26] The reactions are stereospecific and tolerant of a variety of sensitive functional groups (e.g., aldehydes, ketones, esters, azides, and alcohols). Bromides are the most common nucleofuges,[27] but chlorides, iodides, triflates, phosphates, tosylates, and telluryl groups have also been employed.[21]

Alkenyltrifluoroborate Cross-Coupling. Owing to the inherent instability of many alkenylboron reagents, alkenyltrifluoroborates serve a highly useful role in the installation of C–C double bond units into organic molecules. This role is magnified because of the sensitivity of alkenylmagnesium and alkenylzinc reagents to air and water, as well as the perceived toxicity of alkenylstannanes and the lack of atom economy of the latter. One of the most useful (and highly exploited) alkenyltrifluoroborates is actually the simplest, i.e., the parent compound, vinyltrifluoroborate (eq 15).[28] As an air- and moisture-stable solid that can be stored for months with no special precautions, this material serves as an excellent vinylating agent in cross-coupling reactions with aryl and heteroaryl iodides, bromides, chlorides, diazonium salts, and triflates.[21]



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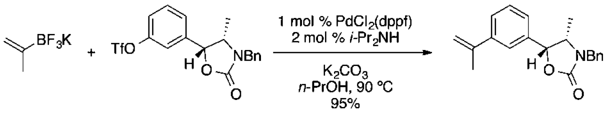
More highly elaborated alkenyltrifluoroborates of all kinds have been used in coupling reactions with both aryl and heteroaryl electrophiles (eqs 16 and 17).[29] Numerous functional groups have been embedded within the alkenyltrifluoroborates, including halides, ketones, and esters, and the reactions are stereospecific with regard to the olefin geometry of the alkenyltrifluoroborate.[21]



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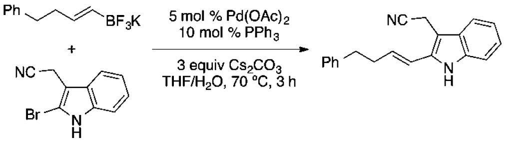

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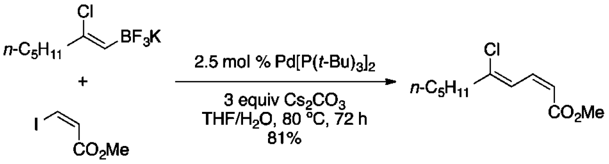
Importantly, conjugated dienes can also be prepared readily by the cross-coupling of alkenyltrifluoroborates with alkenyl electrophiles.[29b] These coupling reactions are stereospecific with regard to both coupling partners, allowing access to all possible stereoisomeric conjugated dienes (eqs 18 and 19).[21,26b,29b]



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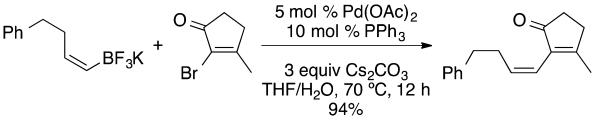

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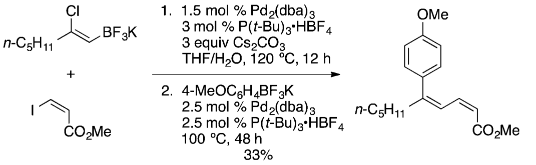
Advantage can be taken of various chemoselectivities to sequence cross-coupling reactions, permitting access to stereodefined, trisubstituted, conjugated alkene systems that are challenging to access by other means (eqs 20 and 21).[26b,30]



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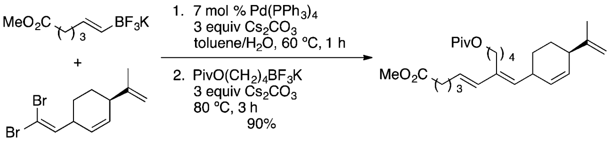

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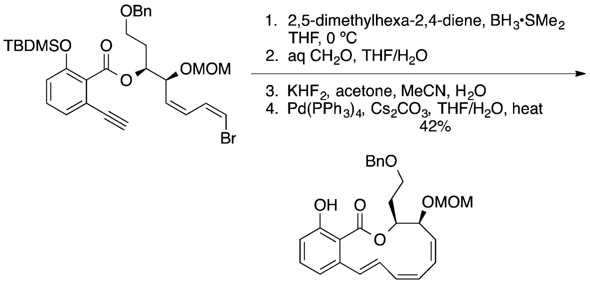
An intramolecular cross-coupling leading to a key conjugated diene en route to oximidine II was carried out in a "telescoped" sequence.[31] Thus, the alkyne starting material was hydroborated with an elaborated diallylborane (generated in situ) and converted directly to the corresponding alkenyltrifluoroborate. This material was cross-coupled after a crude workup, leading to the desired macrolactone in 42% overall yield (eq 22). The process is quite efficient given the nature of the cyclization, which requires formation of a 12-membered ring that is highly strained owing to the presence of nine contiguous sp^2 centers in the molecule.



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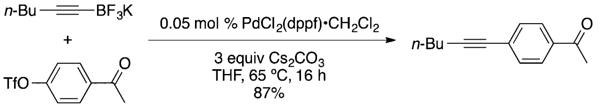
Alkynyltrifluoroborate Cross-Coupling. Alkynyltrifluoroborates provide an alternative to Sonogashira cross-couplings, and the reagents provide the same types of advantages in terms of stability and storability as other organotrifluoroborate salts. Interestingly, among all of the organotrifluoroborates, the alkynyl derivatives appear to be the only ones that react without hydrolysis, with the $B_{sp3}-C_{sp}$ bond being sufficiently polarized to make them nucleophilic enough to transmetalate directly. In the most favorable cases, no H_2O is required for these reactions, and extraordinarily low catalyst loadings (<0.05 mol %) are sufficient to induce coupling (eqs 23 and 24).[32] Aryl bromides, triflates, and more highly activated aryl chlorides serve as suitable electrophiles. Interestingly, diazonium salts are not effective partners because electron transfer from the trifluoroborates with loss of nitrogen affords reduced aromatic products. Alkenyl bromides have also served as valuable electrophiles in alkynyltrifluoroborate cross-coupling (eq 25).[33]



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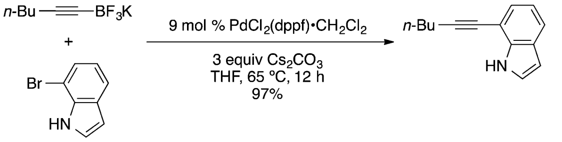

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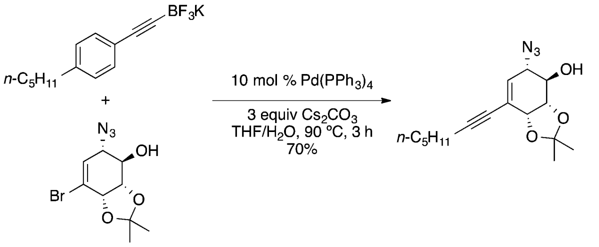

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Alkyltrifluoroborate Cross-Coupling. As mentioned at the outset, the initial motivation for beginning an exploration of the chemistry of the organotrifluoroborates was to develop general conditions for coupling of 2° alkyl systems. As also pointed out, the entire premise for our initial optimism that we might be able to bring about this transformation was somewhat

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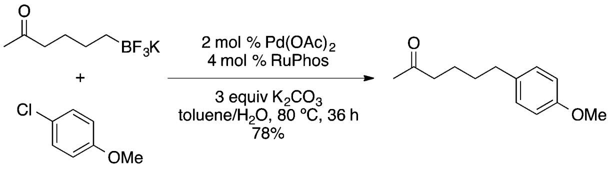
naïve. However, in 2001, we were able to develop a reasonably effective protocol for coupling of 1° alkyltrifluoroborates with highly activated aryl electrophiles (eqs 4 and 5).[15]

Over the next few years, ligand development in cross-coupling reactions reigned supreme,[3] and with a detailed understanding of the factors leading to successful oxidative addition and reductive elimination came the capability to engage even the least reactive aryl chloride electrophiles and to explore previously recalcitrant coupling partners. It was at this juncture in 2008 that I received a phone call from Dr. Spencer Dreher in the Process Research and Catalytic Reactions Discovery and Development Laboratory at Merck, who was interested in developing the cross-coupling of alkyltrifluoroborates with aryl chlorides. The convergence of having access to novel ligands capable of facilitating the cross-coupling cycle with previously unreactive electrophiles and the availability of tremendously powerful high-throughput experimentation techniques developed at Merck[34] provided the seeds for what became a wonderful collaboration and the establishment of the UPenn/Merck High Throughput Experimentation Laboratory in the Department of Chemistry at Penn,[35] which has enabled much of the research in our laboratories that has followed.

In one of the initial efforts in the collaboration, a single, universal set of conditions was developed for the cross-coupling of 1° alkyltrifluoroborates with aryl- and heteroaryl chlorides (eqs 26 and 27).[36] A wide range of functional groups within both the trifluoroborate and the aryl chloride were tolerated, including aldehydes, ketones, esters, nitriles, silyl ethers, and nitro groups, and aryl bromides, iodides, and triflates were also demonstrated to cross-couple effectively. Stoichiometric quantities of the reagents were used, demonstrating that protodeboronation and other deleterious side reactions were kept to an absolute minimum.



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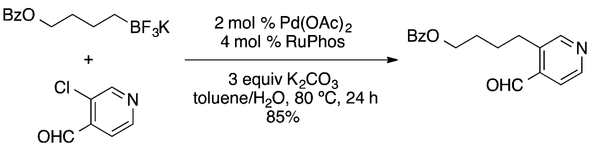

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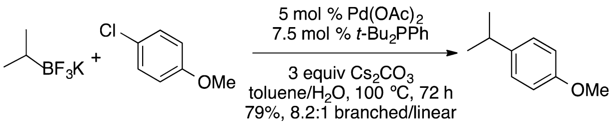
The more challenging cross-coupling of 2° alkyltrifluoroborates also succumbed to high-throughput experimentation, and a set of reaction conditions that allowed good yields of products and reasonably high regioselectivities (avoiding isomerization from β-hydride elimination, olefin reinsertion, and reductive elimination) was found (eq 28).[37] Although this was a major advance, the limitations were obvious. More highly hindered aryl chlorides (such as 2-chloroanisole) gave lower yields of product with extensive isomerization, the catalyst loading was high, and the reaction conditions were relatively harsh. With even further precatalyst development, Biscoe and co-workers employed a modification of this protocol that avoided isomerization in most cases, providing 2° alkyl coupling products with >50:1 regioisomeric fidelity (eq 29).[38] Importantly, the Biscoe group also established that the reactions transpired with high enantiospecificity, displaying inversion of configuration in the transformation (eq 30). Even with all of the improvements, challenges remained in cross-coupling of 2° alkyltrifluoroborates. In particular, more highly hindered systems such as *trans*-2-methylcyclohexyltrifluoroborate still could not be coupled without significant isomerization, presumably as a consequence of the rigorous conditions required for the reaction resulting from slow transmetalation.



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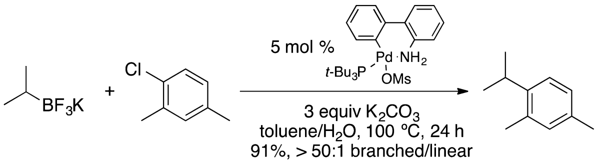

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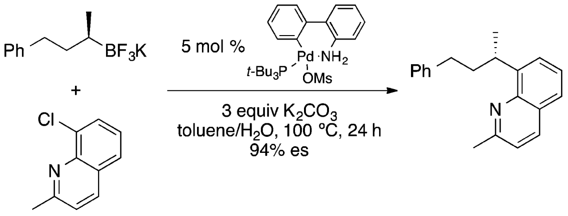

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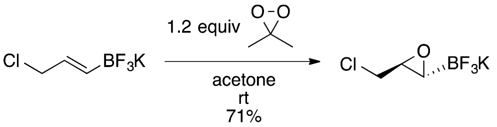
Novel Platforms. The success achieved in the cross-coupling of 1° and 2° alkyltrifluoroborates allowed utilization of alkyltrifluoroborate platforms that introduced important and useful subunits outside of what was considered the norm for cross-coupling. Our efforts in this area received a huge boost on the basis of two key observations. The first was when Dr. Maria Ribagorda discovered that, under anhydrous conditions, the organotrifluoroborates were more robust than we had imagined at the outset of our studies. Boron forms extraordinarily strong bonds with fluorine, and when the trifluoroborates are generated, occupation of the boron empty p orbital by one of the fluorides inhibits many reactions that would mechanistically require initial interaction at the boron center. Maria took advantage of this in her synthesis of oxiranyltrifluoroborates. Thus, although tricoordinate organoborons are readily oxidized with boron—carbon bond cleavage, Maria was able to retain the valuable boron—carbon bond and selectively oxidize the carbon—carbon double bond in reaction of alkenyltrifluoroborates with dimethyl dioxirane (eq 31).[39]



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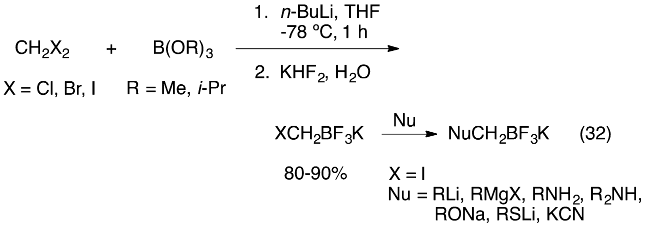
Based on the newly recognized level of enhanced stability that was characteristic of the trifluoroborate unit in nonaqueous solvents, Dr. Jungyeob Ham created a family of highly useful cross-coupling platforms. He first developed a convenient synthesis of novel alkylating agents, the halomethyltrifluoroborates.[40] (Subsequent development of this chemistry led to an industrial-scale process by which >100 kg of $BrCH_2BF_3K$ could be produced in less than one month using flow chemistry techniques.[41]) One of these small building blocks, ICH_2BF_3K, proved to be a useful electrophile for generating a variety of



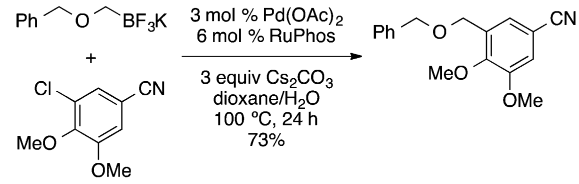
$$\mathrm{CH_2X_2} + \mathrm{B(OR)_3} \xrightarrow[\text{2. KHF}_2\text{, H}_2\text{O}]{\text{1. }n\text{-BuLi, THF, -78 °C, 1 h}} \underset{80\text{-}90\%}{\mathrm{XCH_2BF_3K}} \xrightarrow{\mathrm{Nu}} \mathrm{NuCH_2BF_3K} \quad (32)$$

X = Cl, Br, I; R = Me, *i*-Pr; X = I; Nu = RLi, RMgX, RNH_2, R_2NH, RONa, RSLi, KCN

novel organotrifluoroborates (eq 32) that could be used as partners for subsequent cross-coupling efforts. In reactions with various carbon-based and heteroatom-based nucleophiles, the trifluoroborate unit again remained intact.

The various synthons generated by Ham and others could subsequently be used as tools for the synthesis of functionalized arenes and heteroarenes via cross-coupling. As a class, the value of cross-coupling reactions in many respects resides in the ready availability of a vast number of structurally diverse and relatively inexpensive aryl- and heteroaryl halide coupling partners. The number of such commercially available halides dwarfs that of analogous benzylic or pseudobenzylic halides and alcohols, as well as aryl esters or aldehydes that might be used as starting materials for elaboration toward the same target. Consequently, complementary approaches to desired products using aryl halide partners through a different retrosynthetic bond disconnection are highly valued on several levels. It is in this vein that the alkoxymethyl- and aminomethyltrifluoroborates first generated by Dr. Ham have found traction in the late-stage synthesis of benzylic and pseudobenzylic alcohols and amines.

Cross-coupling using alkoxymethyltrifluoroborates allows a highly effective synthesis of benzylic ethers or benzylic alcohols, the latter being derived from protected benzylic alcohol precursors (eqs 33 and 34).[42] This approach to benzylic ethers and alcohols through carbon−carbon bond formation with haloarene and −heteroarene partners nicely complements that of approaches based on less readily available benzylic alcohols, or halides, as well as those involving aryl aldehydes or esters.



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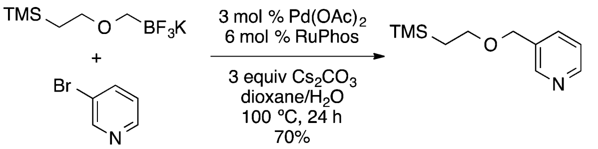
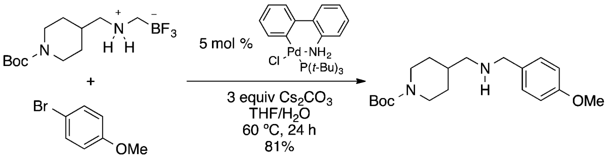


(34)

The chemistry was extended from *α*-alkoxymethyltrifluoroborates to *α*-alkoxyalkyltrifluoroborates (Scheme 2).[43] These materials could be prepared in high enantiomeric purity, and in contrast to 2° alkyl systems (eq 30), the cross-coupling transpired with retention of configuration with extremely high stereochemical fidelity. A rationale for both the stereochemistry of the transmetalation and the lack of *β*-hydride elimination/isomerization that often accompanies 2° alkyl cross-coupling was proposed. The latter invokes complexation of the benzylic ether arene with the Pd center, inhibiting agostic interactions of the metal center with the *β*-C−H bonds that lead to eventual elimination.

More opportunities for introduction of diversity are possible within the realm of aminomethylation reactions. The most prevalent methods for preparing aminomethylated arenes or -heteroarenes are reductive amination of aromatic aldehydes, reduction of aromatic nitriles, alkylation of aminomethylated arenes, or amination of benzylic or pseudobenzylic halides. Preparation of these useful products by a complementary carbon−carbon bond-forming reaction from structurally diverse aryl- and heteroaryl halides provides a unique protocol to access these materials. Aminomethyltrifluoroborates derived from 1° amines (eq 35),[44] 2° amines (eq 36),[45] and even heteroarylamines (eq 37)[46] have been prepared and induced to cross-couple with aromatic halides.



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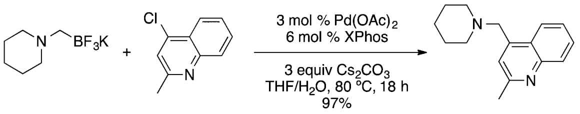

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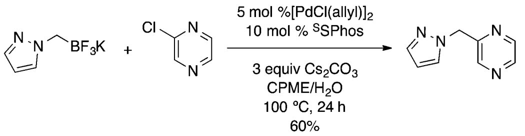

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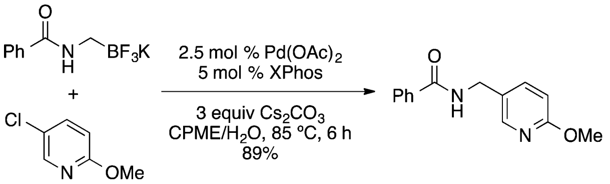
Amine derivatives have also been prepared directly in this manner, introducing added efficiency into the overall process because the entire functional unit can be incorporated directly rather than initially introducing the amine with subsequent amine functionalization in a separate step. Thus, amidomethyltrifluoroborates (eq 38),[47] Boc-protected (1° and 2°) aminomethyltrifluoroborates (eqs 39 and 40),[48] sulfonamidomethyltrifluoroborates (eq 41),[49] *N*-trifluoroboratomethylisoindolin-1-ones (eq 42),[50] and imidomethyltrifluoroborates[51] have all been prepared and cross-coupled effectively with a variety of aryl electrophiles, including halides, various sulfonates,[47,48a,49,50,52] and sulfamates (eq 43).[53]



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β-Heteroatomically substituted organometallic synthons present a different set of challenges centered about their inherent stability. Lewis acidic organometallics (such as tricoordinate organoborons) typically undergo *syn* elimination with *β*-heterosubstituents, whereas more ionic organometallics (such as organolithiums or organomagnesiums) rapidly decompose by an *anti* elimination process. As it transpires, organotrifluoroborates find a happy medium, and both

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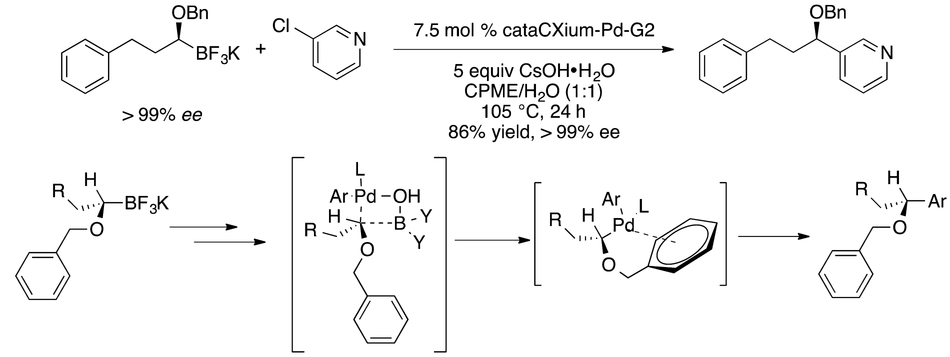
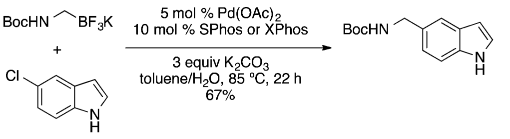
Scheme 2. Cross-Coupling of α-Alkoxyalkyltrifluoroborates





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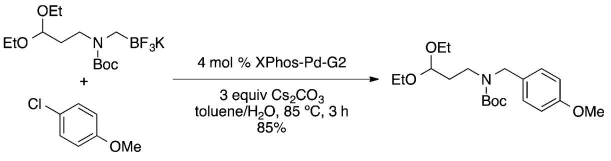

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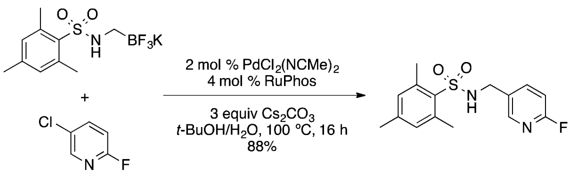

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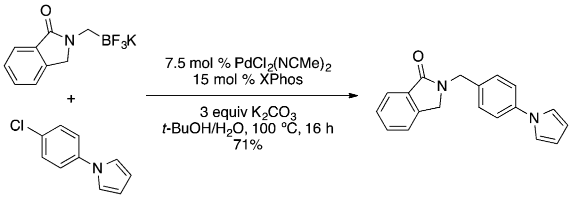

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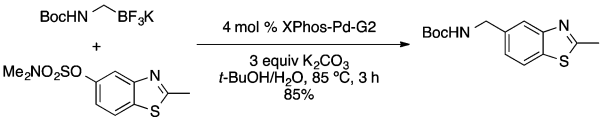
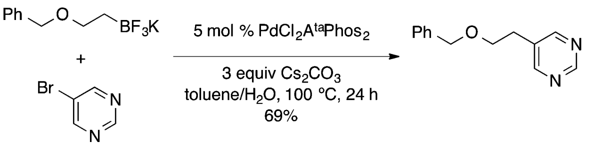


(43)

β-alkoxyethyltrifluoroborates[54] and β-aminoethyltrifluoroborate derivatives (Cbz- and Boc-protected amines, as well as amides)[55] can be prepared, isolated, and stored for long periods of time with no observable decomposition. Their cross-coupling with a variety of aryl- and heteroaryl halides and triflates provides a facile entry to phenethylamine products through a process that is complementary to other approaches to the same substructures (eqs 44–46).

β-Trifluoroborato carbonyls represent another special class of cross-coupling synthons. In the case of ketone homoenolates, these materials can be prepared by copper-catalyzed borylation of α,β-unsaturated ketones with B_2Pin_2 or by alkylation of enolates by ICH_2BPin, followed in each case by quenching with KHF_2. Subsequent cross-coupling with a variety of aryl and heteroaryl chlorides is generally highly effective (eq 47).[56]



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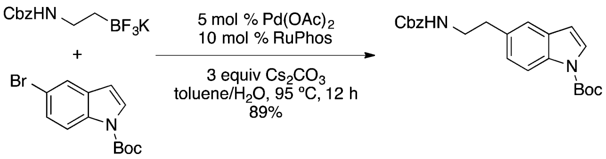

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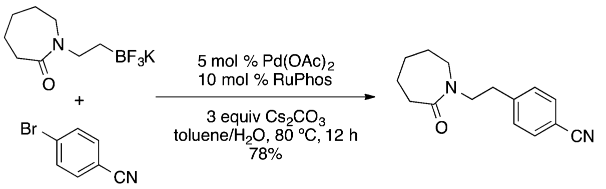

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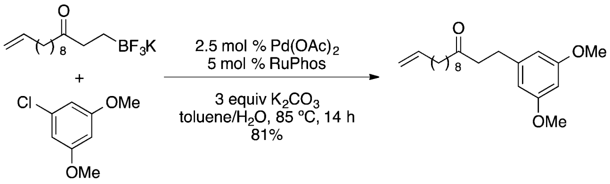
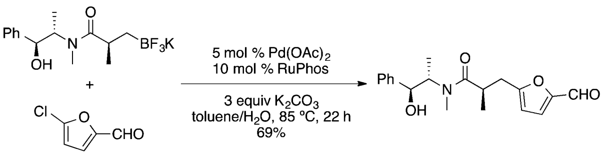


(47)

The utilization of boron homoenoates of amides in cross-coupling protocols[57] allowed the development of enantioselective entries to the desired products. In the first such approach to be explored, a reaction was developed wherein chiral, nonracemic enolates were alkylated with ICH_2BPin in a diastereoselective manner and converted to the trifluoroborates. Cross-coupling of the resulting enantioenriched partners transpired with virtually complete stereochemical fidelity, providing the desired targets with >95:5 dr (eq 48).[58]



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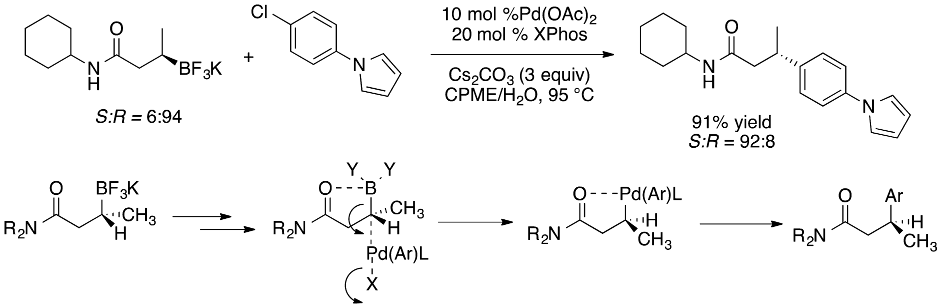
Scheme 3. Cross-coupling of Enantioenriched β-Trifluoroboratoamides



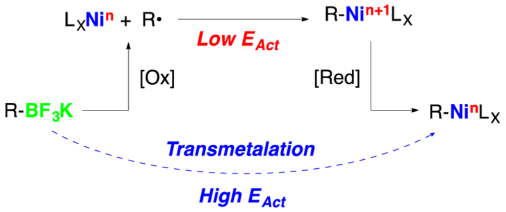
A complementary variation of the reaction involved an enantioselective copper-catalyzed borylation of α,β-unsaturated amides with B_2Pin_2 in the presence of a Josiphos ligand and conversion to the trifluoroborate with KHF_2. Cross-coupling of the organotrifluoroborate afforded the cross-coupled product with inversion of configuration (Scheme 3).[59] It was postulated that the boronate species generated upon hydrolysis of the trifluoroborate transmetalates via an open transition state, S_E2 mechanism with inversion of configuration. Reductive elimination with retention of configuration provided the observed product. The starting materials can be accessed in high ee, and the cross-coupling also transpired with near complete stereochemical fidelity, affording the products in a manner exhibiting an umpolung of reactivity.

SINGLE-ELECTRON TRANSMETALATION IN DUAL-CATALYZED PHOTOREDOX/CROSS-COUPLING

As noted previously, our initial goal in exploring organotrifluoroborate chemistry was to find a means to carry out 2° alkyl cross-coupling reactions in a general and highly effective manner. Although progress was made along these lines in specific product classes (Schemes 2 and 3) and even in generic systems (eqs 28–30), it appeared to us that perhaps we were pushing up against the limit of capabilities of Pd-catalyzed cross-coupling under the traditional mechanistic scenario. Successful reactions typically required high catalyst loadings, strongly basic conditions, and high temperatures for extended periods of time that were not conducive to the incorporation of sensitive functional groups. Furthermore, the reactions could not be conducted on more sterically challenging substrates without substantial isomerization.

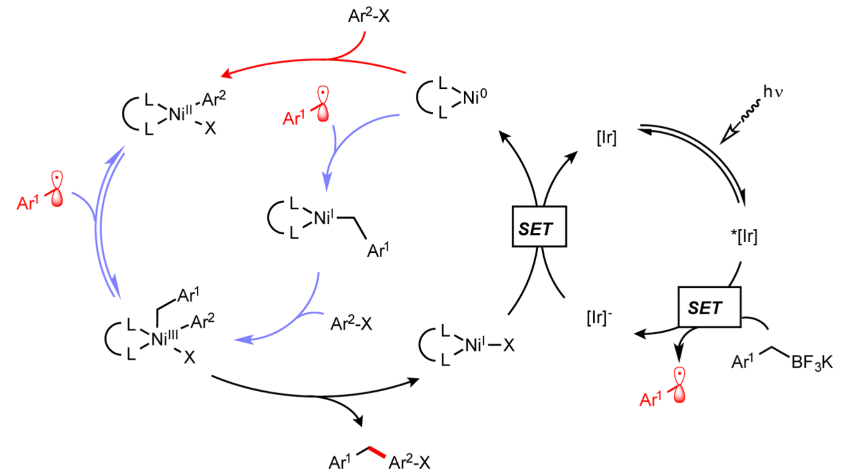
At this point, a graduate student in the group, John Tellis, came up with an alternative mechanistic paradigm for cross-coupling (Scheme 4) that promises to have major implications for many types of related conversions going forward. The transformation that John devised was designed to circumvent the limitations imposed by the two-electron nature of all of the steps involved in traditional cross-coupling reactions, but in particular to avoid the high energy of activation associated with transmetalation when using relatively non-nucleophilic organoboron reagents. The scheme devised would be initiated by oxidation of the alkyltrifluoroborate to generate a radical, a process we knew to be viable.[60] The resultant radical would react with a transition-metal-based cross-coupling catalyst to generate an intermediate complex in which the transition metal center was formally oxidized by a single electron. Subsequent single-electron reduction of this complex would then return the transition metal to its original oxidation state. In the stated order, this series of elementary steps is formally equivalent to a transmetalation, that is, the transfer of an alkyl group from an organometallic reagent to a transition-metal catalyst in which the oxidation state of the transition metal remains unchanged. Importantly, and in stark contrast to the conventional transmetalation pathway, the characteristically small kinetic barriers[61] of single-electron transmetalation would allow these reactions to occur readily under mild conditions and at room temperature, providing facile entry to cross-couplings that were challenging or impossible under the traditional two-electron paradigm. This mechanistically novel process would have the effect of transferring the rate-limiting step in the cross-coupling from that of transmetalation to the oxidation of an organometallic nucleophile or reduction of the formed organometallic intermediate complex via low-barrier single-electron transfer (SET) processes facilitated by suitable redox agents, the reactivity of which are easily predicted by measurement of electrochemical potentials. The exploitation of odd-electron reaction pathways would provide an opportunity to uncover unique and complementary reactivity patterns that are wholly inaccessible to the more traditional two-electron pathways. For example, because of the stability of the radicals derived by their oxidation, more highly substituted C_{sp3} nucleophiles are ideally primed for successful implementation in cross-coupling reactions.

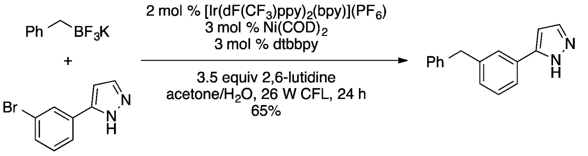
Scheme 4. Novel Mechanistic Paradigm for Cross-Coupling



Initial studies were conducted on benzylic organotrifluoroborates. Importantly, suitable photoredox catalysts were to be utilized in the SET redox reactions. Thus, an iridium (photoredox)/nickel (cross-coupling) dual catalytic cycle was envisioned (Scheme 5). Visible light excitation of a photoredox catalyst {such as $Ir[dFCF_3ppy]_2(bpy)PF_6$} was expected to generate an excited-state complex sufficiently oxidizing to effect the oxidative fragmentation of an organotrifluoroborate. Potassium organotrifluoroborates are clearly suitable organometallic partners in this new class of cross-couplings because previous reports had documented their ability to function as carbon radical sources upon photoredox catalysis.[62] At the outset, we had proposed that capture of the resulting radical at Ni^{II} would yield a diorganonickel(III) intermediate,[63] reductive

Scheme 5. Dual Catalytic, Single-Electron-Transfer Cross-Coupling





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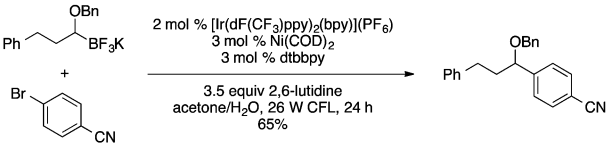

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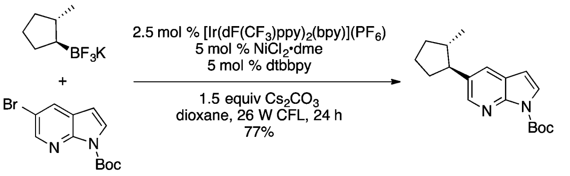

(51)

elimination from which would generate the coupled product and Ni^{I} complex, which was reported to be unreactive toward aryl halides.[64] Subsequent calculations performed by my colleague, Professor Marisa Kozlowski, and her talented postdoctoral research associate, Dr. Osvaldo Gutierrez, revealed another, more favorable, reaction pathway.[65] Thus, their computational studies revealed that a more likely scenario involves reaction of the radical generated with a Ni^{0} complex, producing an organonickel(I) complex. This intermediate would undergo oxidative addition with an aryl halide to generate a diorganonickel(III) complex, thus converging with the Ni^{0}/Ni^{II} catalytic cycle. The photoredox cycle and the cross-coupling cycles are mutually closed when the Ni^{I} complex is reduced, concurrently oxidizing the reduced iridium photocatalyst. An extremely important piece of information that derived from this study was the calculated reversibility of the radical addition to the Ni^{II} complex, which has major implications for stereoconvergent processes of all types based on enantioenriched nickel catalysts.

Investigations that began with benzyltrifluoroborates revealed that the process worked as planned, and a variety of substituted benzylic trifluoroborates (including 2° benzylic) could be cross-coupled effectively with aryl- and heteroaryl halides (eq 49).[66] In contrast to the Pd-catalyzed reactions we had developed, the reactions took place at room temperature under near-neutral reaction conditions. Initial studies indicated that the reactions were far more tolerant of heteroaryl halides than any of our previous Pd-catalyzed systems, and thus, pyridines, pyrazoles, pyrimidines, indoles, oxadiazoles, and quinolines were all tolerated, along with functional groups such as nitriles, phenols, aldehydes, esters, sulfonamides, and protected amino acids. Because of a favorable redox potential, alkoxyalkyltrifluoroborates could also be employed in the reaction (eq 50), and 2° alkyltrifluoroborates (even sterically hindered substrates, eq 51) were subsequently found to be suitable partners as well,[67] thereby fulfilling the initial goal of our program initiated 15 years before.

■ CONCLUSIONS

Although this Perspective has focused on our interest in cross-coupling reactions, organotrifluoroborates also serve as useful synthons in a variety of other carbon−carbon bond-forming reactions (both catalyzed and noncatalyzed) as well as functional group conversions through stoichiometric transformations.[68] Their unique properties complement those of related organoborons and, indeed, those of other organometallic reagents as well. Consequently, what began as a naïve and in fact deeply flawed hypothesis concerning the reactivity of these reagents has spawned an exciting and fruitful research program that continues to branch out in new and indeed unexpected realms. My graduate mentor, Professor H. C. Brown, was very fond of the quote "Tall oaks from little acorns grow"[69] to describe the growth of organoboron chemistry from its humble beginnings with the chemistry of $NaBH_4$ and the subsequent discovery of the hydroboration reaction. With the continued exploration of organotrifluoroborate chemistry and certainly other areas of related organoboron research, more and more boughs continue to grow on this magnificent tree.

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Notes

The authors declare no competing financial interest.

Biography

Gary Molander completed his undergraduate studies at Iowa State University under the tutelage of Professor Richard C. Larock. He earned his Ph.D. at Purdue University under the direction of Professor Herbert C. Brown and undertook postdoctoral training with Professor Barry M. Trost at the University of Wisconsin, Madison. He began his academic career at the University of Colorado, Boulder, moving to the University of Pennsylvania in 1999, where he is currently the Hirschmann−Makineni Professor of Chemistry.

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