

# Organotrifluoroborates: Protected Boronic Acids That Expand the Versatility of the Suzuki Coupling Reaction

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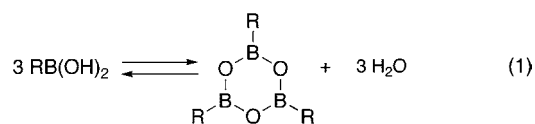
## ABSTRACT

Organotrifluoroborates represent an alternative to boronic acids, boronate esters, and organoboranes for use in Suzuki–Miyaura and other transition-metal-catalyzed cross-coupling reactions. The trifluoroborate moiety is stable toward numerous reagents that are often problematic for other boron species. Consequently, remote functional groups within the organotrifluoroborates can be manipulated, while retaining the valuable carbon–boron bond.

## Introduction

The Suzuki–Miyaura coupling reaction represents one of the most important synthetic transformations developed in the 20th century.<sup>1</sup> Its use is so pervasive that it is difficult to find an issue of any journal in synthetic organic chemistry that does not feature this process in the construction of organic molecules. As might be imagined, innumerable improvements on the original protocol have been recorded. Important contributions include vastly improved catalyst/ligand systems,<sup>2</sup> unique solvents (e.g., ionic liquids<sup>3</sup>), and enhanced experimental conditions (e.g., the use of microwaves<sup>4</sup>). Curiously, until recently little effort has been expended toward further development of the most important component of the process, the organoboron reagent itself.<sup>5</sup>

This is unusual because the organoborons most commonly used for Suzuki–Miyaura coupling are far from ideal. For example, although there are currently over 450 boronic acids available commercially, many of these reagents are difficult to purify because they are waxy solids. The situation is complicated by the equilibrium formation of trimeric cyclic anhydrides (boroxines, eq 1). This equilibrium has no bearing on the coupling process *per se*, but it can influence the reaction stoichiometry. Thus, it is difficult to determine the concentration of



boronic acid versus boroxine in a mixture, and currently no simple assay exists to assess the amount of total boronic acid available. Consequently, many literature protocols for cross-coupling employ excess boronic acid to ensure a complete conversion of the electrophilic component of the reaction, clearly an inefficient use of what might be the most precious component of the reactions.

Boronate esters solve many of these problems, but at some cost. Pinacol or 2-methyl-2,4-pentanediol<sup>6</sup> boronate esters exist as monomeric complexes with defined structures, thereby aiding precise adjustment of stoichiometry. However, the added expense of these diols, combined with a marked decrease in atom economy,<sup>7</sup> makes them less appealing.

Organoboranes utilized in cross-coupling reactions, particularly alkyl-9-borabicyclo[3.1.1] compounds, possess different limitations. These air-sensitive materials are difficult to purify and handle and are always prepared and utilized *in situ* via hydroboration of appropriate alkenes. In addition to the inherent restrictions of the hydroboration reaction itself (especially chemoselectivity limitations), these reagents are not particularly economical.

Most importantly, all trivalent organoboron species are susceptible to reactions with important classes of reagents commonly utilized in organic synthesis (e.g., oxidants, bases, and nucleophiles). Consequently, these organoborons are normally either purchased or prepared and then utilized directly in the Suzuki cross-coupling reaction. Rarely does one find trivalent organoboron reagents carried through synthetic operations wherein remote functional groups are transformed, leaving the carbon–boron bond intact.<sup>8</sup> This has the obvious effect of limiting synthetic approaches to target molecules of interest. By contrast, if more robust organoboron reagents were available, this would tremendously expand the range of retrosynthetic pathways using Suzuki coupling reactions as key transformations in complex molecule synthesis.

## Background: Organotrifluoroborates

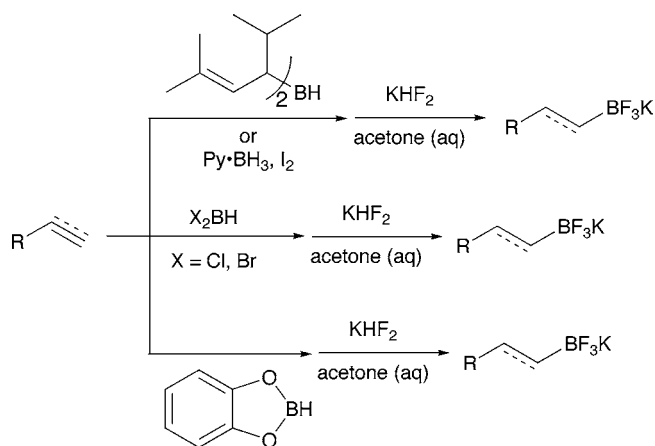
These factors led us to consider organotrifluoroborates as possible nucleophilic partners for the Suzuki coupling reaction. The tetracoordinate nature of the boron in these complexes, fortified by strong boron–fluorine bonds, was anticipated to provide mechanistic inhibition of undesirable reactions typical of trivalent organoborons. This, in turn, would make the organotrifluoroborates essentially a protected organoboron reagent.

Several years before we entered this area of research, Vedejs and co-workers described the facile synthesis of organotrifluoroborates from  $\text{Y}_2\text{BR}$  precursors (Y is a het-

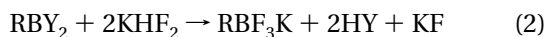
Gary Molander received his B.S. degree in chemistry from Iowa State University. His Ph.D. research was carried out with H. C. Brown at Purdue University, and he then undertook postdoctoral studies with Barry M. Trost at the University of Wisconsin–Madison. He began his academic career at the University of Colorado, Boulder, before joining the Department of Chemistry at the University of Pennsylvania, where he is currently Allan Day Professor of Chemistry.

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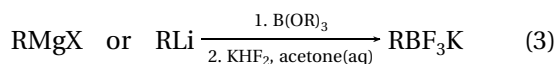
Scheme 1. Hydroboration Routes to Potassium Organotrifluoroborates



eroatomic group) using  $\text{KHF}_2$  as a convenient, inexpensive source of fluoride (eq 2).<sup>9</sup> In principle, a variety of



organotrifluoroborates were thus available in one-pot processes from transmetalation (eq 3) or metalation

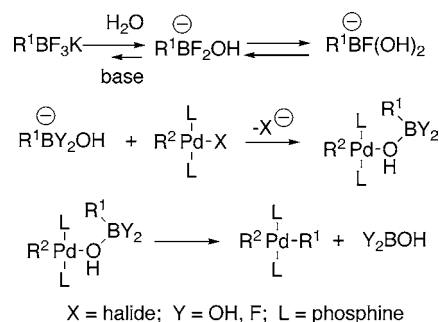


reactions,<sup>10</sup> as well as a variety of hydroborating reagents,<sup>11</sup> each possessing unique characteristics in terms of reactivity and selectivity (Scheme 1).

Furthermore, Genêt and co-workers reported the palladium-catalyzed cross-coupling of a variety of organotrifluoroborates with aryldiazonium salts.<sup>12</sup> Xia and Chen followed shortly thereafter with a report on the use of diaryliodonium salts as electrophilic partners for the organotrifluoroborates.<sup>13</sup> Curiously, Genêt repeatedly pointed out the enhanced reactivity of aryldiazonium salts over that of aryl bromides, tosylates, and even iodides, and thus no one had attempted to develop conditions under which these latter partners would take part in cross-coupling reactions.<sup>2a</sup>

Nevertheless, the motivation for pursuing this line of research was compelling. The organotrifluoroborates were easily accessed by a variety of one-pot synthetic routes from readily available, inexpensive starting materials. They were monomeric, crystalline compounds that were easily handled and indefinitely stable to moisture and air. They possessed a relatively low molecular weight, and the byproducts from cross-coupling would be relatively benign inorganic materials. Finally, they had the potential to serve as chemically robust surrogates for organoboronic acids, which would allow manipulation of remote functional groups while retaining the carbon–boron bond for later employment. The organotrifluoroborates thus had the capability of increasing convergency and efficiency in the construction of synthetic targets, changing the paradigm for retrosynthetic analysis of complex molecule synthesis involving Suzuki coupling. What remained was the development of cross-coupling protocols for organic

Scheme 2. Hydrolysis To Facilitate Transmetalation



X = halide; Y = OH, F; L = phosphine

halides, a determination of the scope of this process, and some assessment as to whether the promise of their toleration of a variety of reagents could be fulfilled.

## Development of Cross-Coupling Reactions

Suzuki's discovery that base was required for successful cross-coupling of boronic acids, boronate esters, and organoboranes was also key to the development of conditions for cross-coupling of organotrifluoroborates. The role of base in Suzuki cross-coupling reactions is to facilitate the otherwise slow transmetalation step of the catalytic cycle through a bridging hydroxyl group between the catalytic palladium center and the boron reagent (Scheme 2).<sup>14</sup> Prior to our studies, cross-couplings of organotrifluoroborates with aryldiazoniums and diaryliodoniums had been performed under anhydrous conditions, where the opportunity to generate the requisite intermediate was not possible. However, we, and others, determined through NMR studies that fluoride/hydroxyl exchange on the organotrifluoroborates was viable,<sup>15</sup> providing intermediates that were mechanistically capable of promoting transmetalation (Scheme 2). This discovery was incorporated into the development of the cross-coupling protocols, wherein water and a base were viewed as key components of the reactions. In reality, the trifluoroborate is a very useful protected form of a boronic acid, eventually generating intermediates similar to those generated by boronic acid precursors along the palladium-catalyzed reaction pathway.

With a greater understanding of the detailed chemical and physical properties of the organotrifluoroborates in hand, studies to explore the scope of their application began in earnest. Perhaps the single most important cross-coupling process is biaryl synthesis. Enormous efforts had been expended in the development of this transformation, but we sought simple economical conditions to perform the cross-coupling. In fact, we were able to develop extraordinarily straightforward conditions that worked for a variety of standard coupling partners. Thus,  $\leq 0.5$  mol % of  $\text{Pd}(\text{OAc})_2$  as the catalyst in refluxing  $\text{MeOH}$  or  $\text{H}_2\text{O}$  as the solvent using  $\text{K}_2\text{CO}_3$  as the base generally provided high yields of the desired products. In addition to being able to conduct these reactions without the presence of added ligands, quite surprisingly the reactions were not sensitive to the air (Figure 1)!<sup>15a</sup>

As is evident from the few results depicted in Figure 1, the process is extremely general. Electron-rich aryl halides

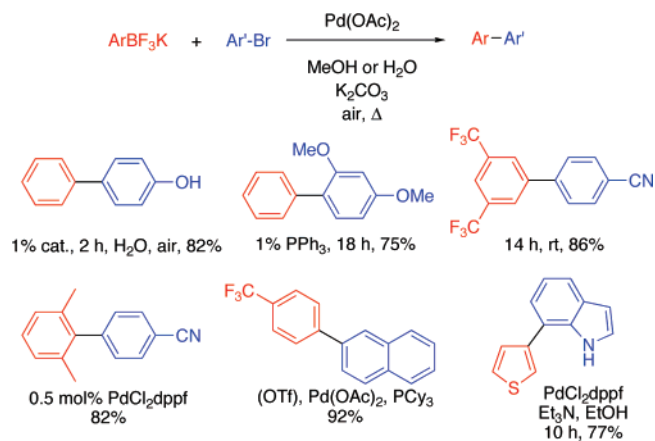
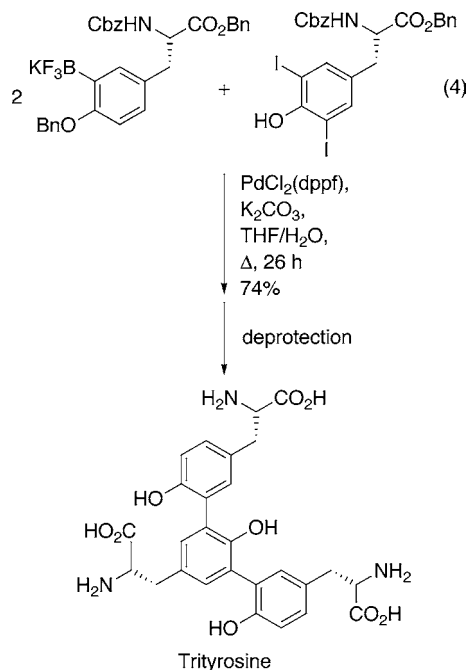


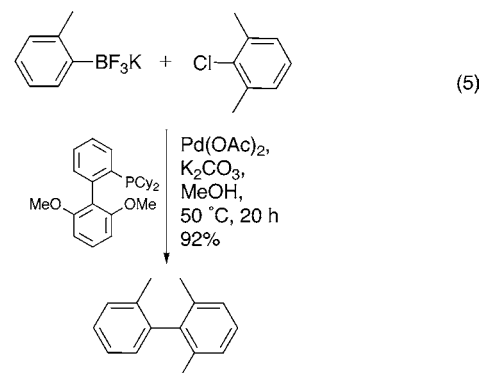
FIGURE 1. Aryl/aryl cross-coupling.

can be employed in the reaction. Electron-poor organotrifluoroborates also work well, in contrast to some protocols involving aryl boronic acids and boronate esters where homocoupling becomes a competing problem.<sup>16</sup> Similarly, sterically hindered aryltrifluoroborates are not inhibited from coupling. Aryl triflates can be utilized as substrates, although they require the addition of  $Cy_3P$  as a ligand.<sup>17</sup> A variety of heteroaromatic systems can also be cross-coupled with equal facility.<sup>18</sup>

A most impressive demonstration of biaryl synthesis was disclosed in the preparation of trityrosine.<sup>19</sup> The analogous pinacol boronate gave none of the double coupling product, while the aryltrifluoroborate afforded the desired product in 74% overall yield (eq 4).



As is the case for aryl boronic acids, specialized ligands may be employed to promote coupling in specific systems. Of particular note is the use of Buchwald's S-Phos ligand for the efficient coupling of a variety of aromatic and heteroaromatic chlorides, including electron-rich and sterically hindered substrates (eq 5).<sup>20</sup>



Aryltrifluoroborates can also be coupled under a different set of conditions to alkenyl bromides.<sup>21</sup> The reaction is exceedingly general (Figure 2). Sterically hindered aryltrifluoroborates, electron-deficient arenes, and heteroaromatic systems can be coupled efficiently. A variety of alkenyl bromides can be employed, and the reaction is completely stereospecific with regard to olefin geometry.

The synthesis of biarylmethanes via cross-coupling reactions remains a significant challenge. In some protocols, up to 2 equiv of the arylboron reagent were utilized to achieve acceptable yields of the cross-coupled product. By contrast, conditions have been developed whereby a variety of aryltrifluoroborates can be coupled on an equimolar basis with benzyl bromide, affording the desired product in excellent yields (Figure 3).<sup>22</sup>

In addition to aryltrifluoroborates, alkenyltrifluoroborates are also suitable substrates for cross-coupling processes, providing a complementary route to conjugated, unsaturated arenes.<sup>23</sup> Under the reaction conditions developed, a variety of functional groups are tolerated within both the alkenyl trifluoroborate and the aryl halide (Figure 4). Various substitution patterns about the alkene can also be employed, and the reaction is completely stereospecific with regard to the olefin geometry.

One of the most important reagents developed thus far is potassium vinyltrifluoroborate.<sup>24</sup> Vinylboronic acid and some vinylboronate esters are unstable. Although alternatives to these materials have been developed,<sup>6a,c,25</sup> the physical and chemical properties of vinyltrifluoroborate make it an exceptional vinylating reagent. Easily prepared on 100–200 g scale as a stable, free-flowing, white crystalline powder, vinyltrifluoroborate undergoes coupling with a variety of aryl halides and triflates in good to excellent yields (Figure 5). Under optimized conditions little or no subsequent Heck chemistry can be detected.

Although the parent vinyltrifluoroborate has been utilized less frequently in coupling to alkenyl bromides,<sup>24,26</sup> the resulting conjugated dienes appear in a variety of important materials and are key components for the synthetically important Diels–Alder reaction. In both capacities, stereoselective syntheses are a necessity, and cross-coupling approaches are ideal for this application. The most reliable cross-coupling protocol for alkenylboronic acids and -boronate esters can be traced to the Kishi synthesis of palytoxin,<sup>27</sup> wherein superstoichiometric amounts of toxic thallium bases were found to be most

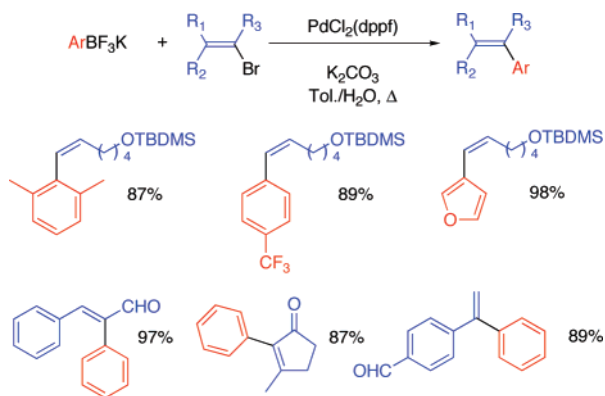


FIGURE 2. Aryl/alkenyl cross-coupling.

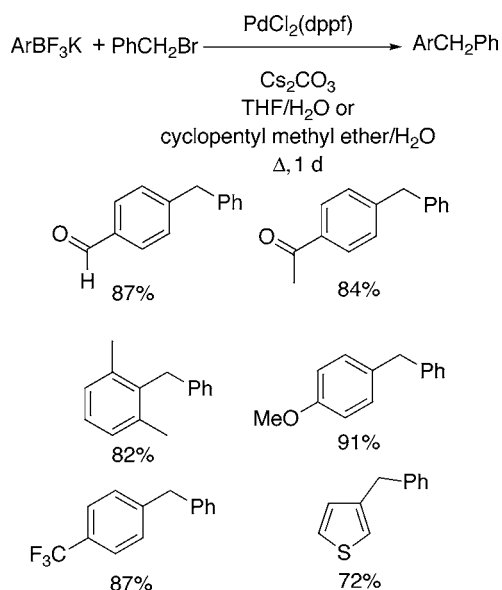


FIGURE 3. Aryl/benzyl cross-coupling.

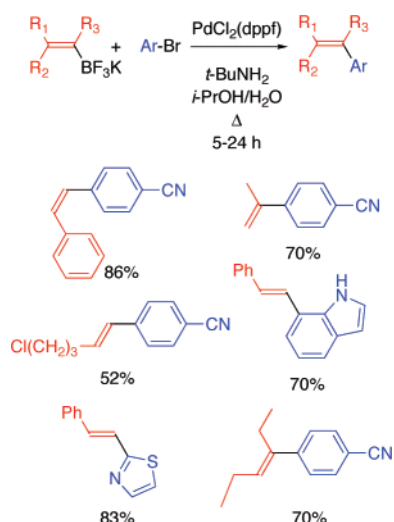


FIGURE 4. Alkenyl/aryl cross-coupling.

effective.<sup>28</sup> By contrast, we determined that a simple and reliable protocol could be employed that was effective for the construction of all geometric isomers of conjugated dienes (Figure 6).<sup>29</sup> The reaction is general for a variety of alkenyl bromide substitution patterns, as well as alkenyl-trifluoroborates (Figure 7).

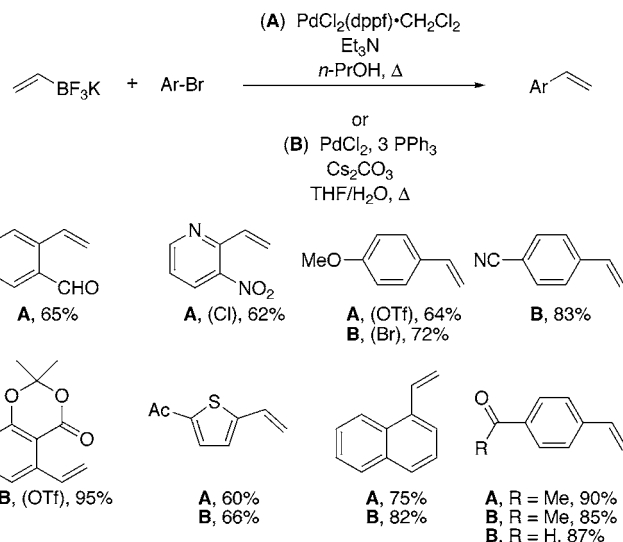


FIGURE 5. Vinyl cross-coupling.

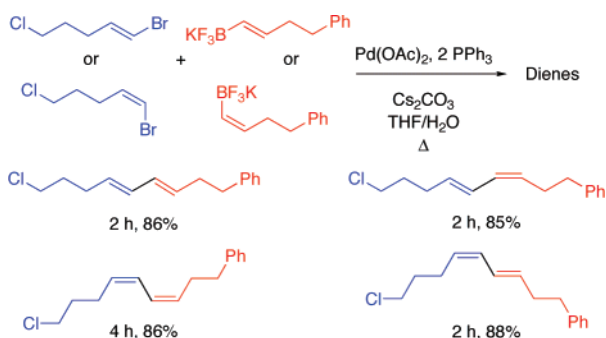


FIGURE 6. Stereospecific alkenyl/alkenyl coupling.

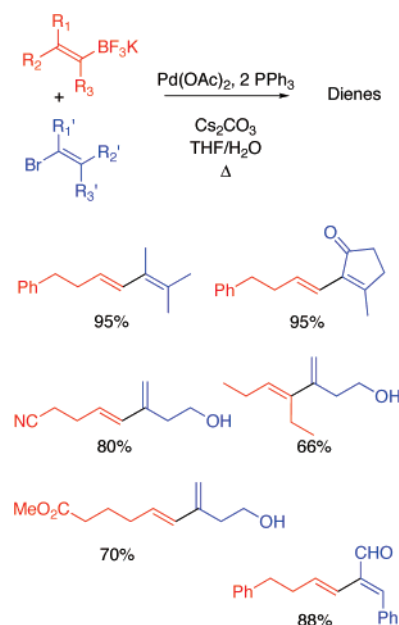
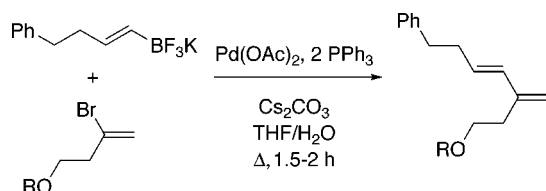


FIGURE 7. Alkenyl/alkenyl cross-coupling.

Inevitably during the course of complex molecule synthesis, vulnerable functional groups must be protected. Arguably the most useful protecting groups for alcohols are silyl ethers, which are easily removed by a variety of fluoride sources. To our surprise and delight, silyl ethers remained intact during the cross-coupling process, despite

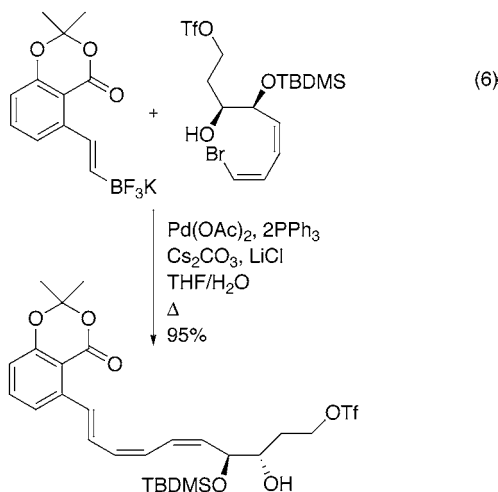


R	% Yield
H	79
TIPS	85
TBDMS	80
TES	80

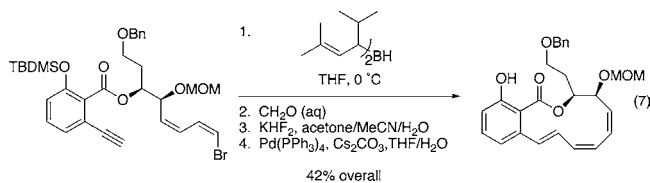
**FIGURE 8.** Tolerance of silyl protecting groups.

the obvious source of fluoride within the reaction mixture (Figure 8).

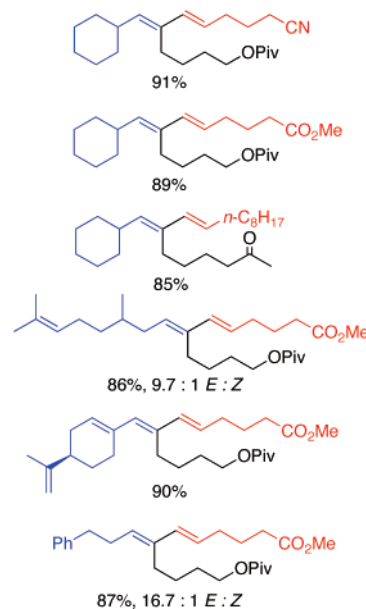
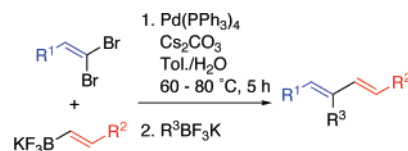
This finding implied that organotrifluoroborate cross-coupling reactions could be employed for the construction of polyfunctional natural products. We took advantage of this for the construction of oximidine II, a salicylate enamide macrolide. In one approach, an alkenyl trifluoroborate reacted with the dienyl bromide to afford the elaborated triene (eq 6). In another approach, an alkyne



was selectively hydroborated with the Snieckus reagent,<sup>11a</sup> and the resulting organoborane was converted *in situ* to the corresponding alkenyl trifluoroborate. The crude material, a free-flowing powder, was subjected to high-dilution macrocyclization, leading to a 42% overall yield of the macrolactone (eq 7).<sup>30</sup> This example highlights



several advantages of the organotrifluoroborates. First, they have an incredibly high propensity to crystallize, even when incorporated within relatively large molecules. Second, they tolerate a diverse array of functional groups and protecting groups. Finally, the synthesis of the mac-



**FIGURE 9.** One-pot synthesis of stereodefined trisubstituted alkenes.

rolactone attests to the robust nature of the coupling reaction itself. Although macrolactones are normally thought of as highly fluxional molecules, the oximidine macrolactone possesses nine contiguous  $sp^2$  centers and thus is highly constrained. That a Suzuki coupling approach could be utilized to prepare such an exceedingly strained system is a testament to the effectiveness and reliability of the coupling process in demanding situations.

Other aspects of conjugated diene synthesis have been explored within the context of organotrifluoroborate chemistry. For example, a synthesis of conjugated, trisubstituted dienes has been developed based upon the Negishi strategy.<sup>31</sup> Thus, 1,1-dibromoalkenes are coupled in a one-pot process first with an alkenyltrifluoroborate and then with an alkyltrifluoroborate, creating the elaborated diene system (Figure 9).<sup>32</sup> The reaction is highly stereoselective when the dibromoalkene possesses substitution at the allylic position and is also tolerant of a diverse array of functional groups. It has advantages over the Negishi protocol in that the organotrifluoroborates can be prepared and stored, facilitating diversity-oriented synthesis. Additionally, the procedure can be carried out in a single reaction flask without isolation of any intermediates.

Curiously, simple alkyltrifluoroborates such as methyl- and ethyltrifluoroborates do not react under the protocol designed for more highly elaborate analogues. However, they do succumb to the reaction by simply recharging the flask with a second catalyst. In this manner, several different conjugated dienes could be prepared (Figure 10).<sup>32</sup>

Historically, cross-couplings with alkylmetallic reagents have proven problematic because of the propensity of the



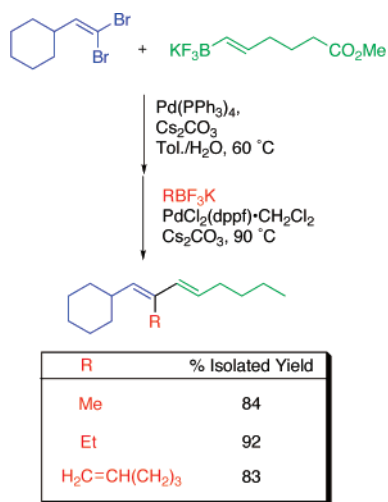


FIGURE 10. Modified synthesis of trisubstituted alkenes.

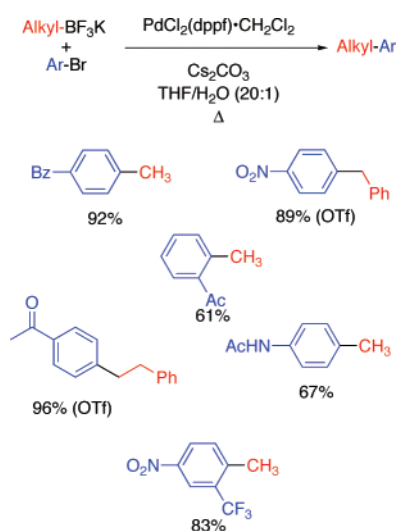


FIGURE 11. Alkyl/aryl cross-coupling.

organopalladium intermediates to undergo  $\beta$ -hydride elimination. With the advent of new more effective ligands, this problem has largely been eliminated. Owing to their ease of preparation and storage and favorable physical properties, organotrifluoroborates provide useful alternatives to organozincs and other organoborons in alkyl coupling reactions. As demonstrated in Figure 11, a number of alkyl/aryl coupling partners can be employed for the synthesis of arenes.<sup>33</sup> For example, MeBF<sub>3</sub>K is an exceptional reagent for cross-coupling, because it can be readily prepared on large scale (> 100 g), stored, and used to incorporate methyl substituents onto a variety of aromatic rings. Long chain alkyltrifluoroborates can also be employed. An advantage of the organotrifluoroborate approach to cross-coupling reveals itself here, in that nitro groups are tolerated, whereas this functional group is sometimes reduced when organoborane cross-coupling reactions are carried out.<sup>34</sup> Finally, diarylmethanes can also be prepared utilizing benzyltrifluoroborates, in a manner complementary to the approach discussed above (Figure 3).

In an analogous manner, alkyltrifluoroborates can be coupled to alkenyl halides and triflates (Figure 12).<sup>35</sup> The

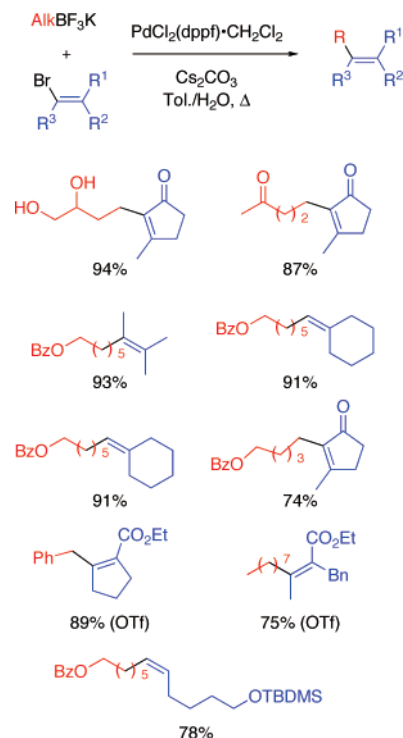
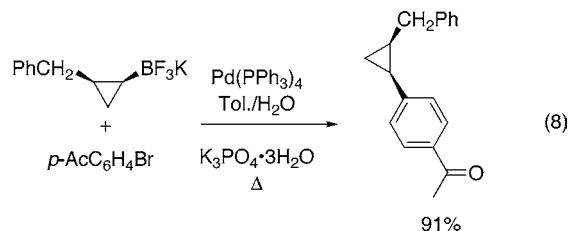


FIGURE 12. Alkyl/alkenyl cross-coupling.

reaction conditions are tolerant of a variety of functional groups, and a diverse array of substitution patterns can be accessed in a completely stereospecific manner.

The only secondary alkyltrifluoroborates that have been coupled thus far are cyclopropyltrifluoroborates (eq 8).<sup>36</sup>

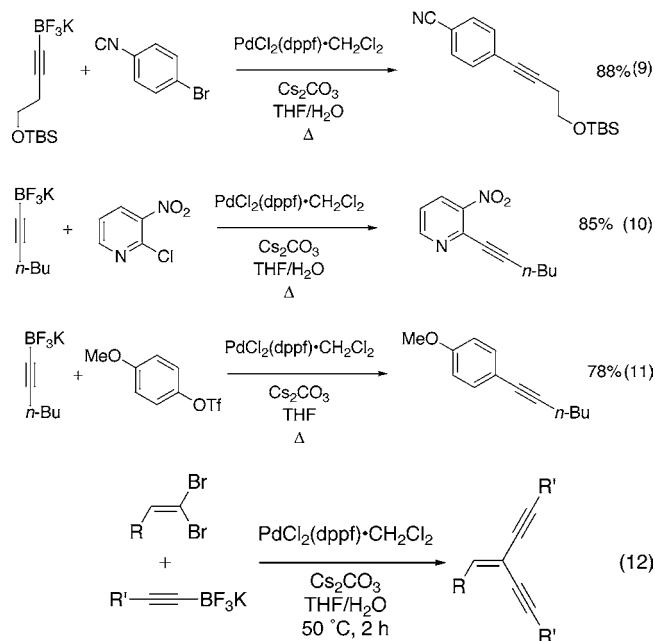


These species undergo high-yielding cross-coupling with aryl bromide electrophiles. The enhanced  $s$  character of the carbon–boron bond is undoubtedly responsible for this success. These cross-coupling reactions are completely stereospecific, occurring with retention of configuration.

Alkynyltrifluoroborates can also be prepared as stable solids and take part in cross-coupling reactions with aryl bromides and triflates, as well as activated aryl chlorides (eqs 9–11).<sup>37</sup> These reactions demonstrate high tolerance of functional groups in the electrophile and can proceed with extremely low catalyst loading (0.05 mol %).

In related chemistry, Kabalka and co-workers revealed that 1,1-dibromoalkenes react with 2 equiv of alkynyltrifluoroborates to provide conjugated enediynes (eq 12).<sup>38</sup> The method provides a useful alternative to the less effective Sonogashira and other protocols for the construction of these compounds.

In addition to these “standard” coupling protocols, a number of innovative and useful variants of the cross-



coupling have been reported. With regard to the nature of the organotrifluoroborate, Batey and Quach have revealed that a cation exchange of potassium organotrifluoroborates with  $\text{Bu}_4\text{NOH}$  leads to the formation of tetrabutylammonium organotrifluoroborates.<sup>15b</sup> These materials are soluble in organic media and also undergo efficient cross-coupling.

The electrophilic partner in the cross-coupling has also been the subject of significant investigation. Stefani and co-workers explored the use of aryl and alkenyl tellurides as partners for the organotrifluoroborates.<sup>39</sup> Enol tosylates have proven to be viable electrophilic partners as well.<sup>40</sup> Finally, diverse methods have been utilized to enhance the reactivity of organotrifluoroborates in cross-coupling transformations. In addition to Buchwald's S-Phos ligand discussed above,<sup>20</sup> bis(thiourea) ligands utilized under aerobic conditions have been touted as possessing high activity when coupled with activated aryl bromides,<sup>41</sup> and palladium on activated carbon has been employed in biaryl synthesis using water as the solvent.<sup>42</sup> Additionally, microwave<sup>4,43</sup> and ultrasound<sup>44</sup> technologies have enhanced the organotrifluoroborate cross-coupling process with great success.

In a relatively brief time frame, the organotrifluoroborates have proven to be extremely versatile in their ability to partake in cross-coupling transformations. In the fullness of time, it would appear that they will be at least as competent as, and in some instances superior to, other organoboron reagents in terms of their ability to undergo cross-coupling with a variety of suitable electrophilic partners. They have already seen application in areas as diverse as nonlinear optical materials<sup>45</sup> and porphyrin synthesis.<sup>46</sup> As stated earlier, factors that set them apart include their desirable physical and chemical properties that make them easy to prepare, isolate, store, and utilize. What makes the organotrifluoroborates unique, however, is their ability to serve as protected boronic acids. This

feature has the possibility to make them transformational in terms of their use in multistep organic synthesis.

## Organotrifluoroborates: Protected Boronic Acid Equivalents

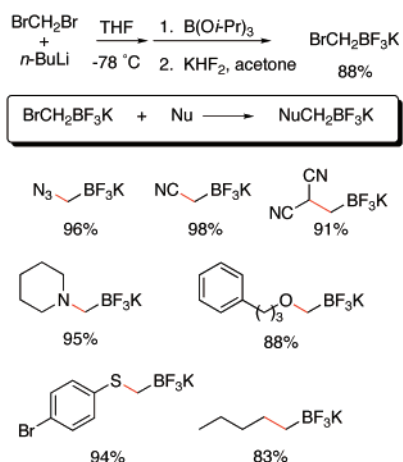
In multistep syntheses of complex molecules, vulnerable functional groups must often be protected to prevent them from undergoing undesired transformations while synthetic operations are conducted elsewhere in the molecule. Alcohols, amines, and all types of carbonyl compounds can claim a bevy of protecting groups, each with unique characteristics and sensitivities that can be installed easily and removed under specified conditions.

For reactive organometallics, the concept of protecting groups is much less well developed and in most cases inconceivable. In the cross-coupling arena, only organosilanes and organostannanes have been routinely carried through multiple synthetic steps prior to cross-coupling. Although organosilanes provide extraordinary possibilities as cross-coupling reagents,<sup>47</sup> to date they have proven to be much less versatile than other organometallics. Organostannanes (Stille couplings<sup>48</sup>) are losing favor because of their perceived toxicity, combined with the difficulty of removing tin-containing byproducts from the cross-coupled product. Consequently, the opportunity to develop protected organoborons that are able to be installed into an organic molecule and carried through a variety of synthetic operations is quite compelling.

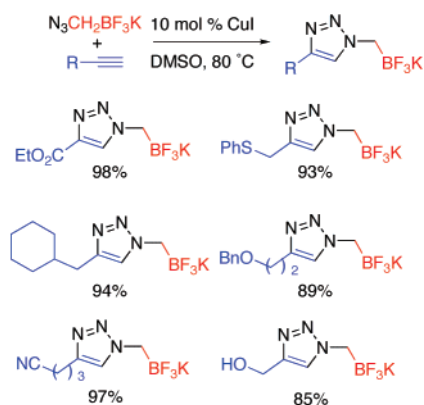
As Brønsted acids, boronic acids react readily with a variety of bases and nucleophiles. The Lewis acidic boronate esters are less susceptible in this regard but still have vulnerabilities. Both sets of reagents are electron deficient and relatively easily oxidized. Because many organic functional group transformations involve bases, nucleophiles, and oxidants, our initial efforts have been focused in this area to demonstrate that organotrifluoroborates can be subjected with impunity to such treatment, remaining intact for further manipulations.

An interesting line of research within this manifold has led to the construction of more highly functionalized organotrifluoroborates with many potential subsequent applications. Thus, metal-halogen exchange of dibromo- or diiodomethane with butyllithium in the presence of  $\text{B}(\text{O}i\text{-Pr})_3$  and then  $\text{KHF}_2$  leads, in high yields, to the corresponding halomethyltrifluoroborates (Figure 13).<sup>49</sup> These stable, free-flowing solids can be treated with a number of nucleophiles, providing more highly elaborated organotrifluoroborates that in many cases cannot be made readily by either hydroboration or transmetalation approaches.

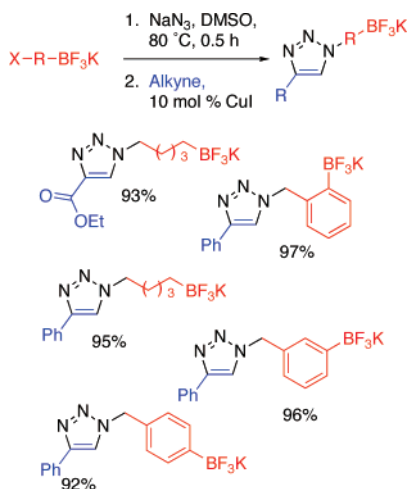
Many of these new materials possess novel reactivities, but we chose first to examine the chemistry of azidomethyltrifluoroborate ( $\text{N}_3\text{CH}_2\text{BF}_3\text{K}$ ). This material undergoes copper-catalyzed 1,3-dipolar cycloaddition with alkynes to afford the corresponding triazolomethyltrifluoroborates (Figure 14).<sup>50</sup> Any number of functionalized terminal alkynes can take part in this reaction, with exceptional outcomes.



**FIGURE 13.** Synthesis and typical reactions of potassium bromomethyltrifluoroborate.



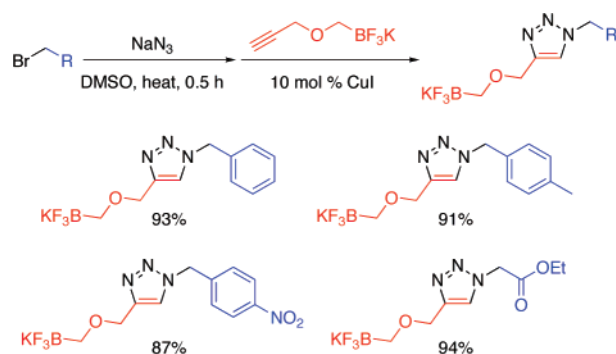
**FIGURE 14.** “Click” chemistry of potassium azidomethyltrifluoroborate.



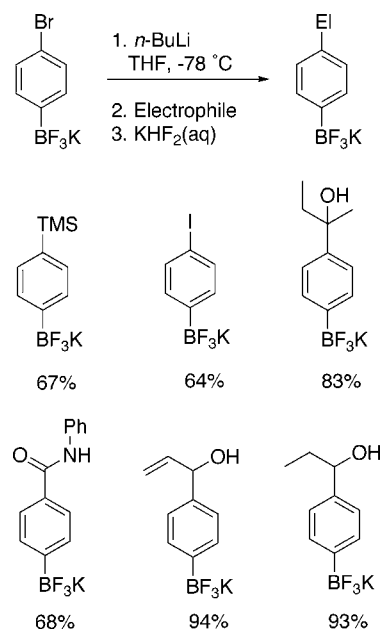
**FIGURE 15.** 1,3-Dipolar cycloadditions.

One is not restricted to  $\text{N}_3\text{CH}_2\text{BF}_3\text{K}$  as a “click chemistry” precursor. It seems that any  $\text{S}_{\text{N}}2$ -reactive, halide-containing organotrifluoroborate can take part in a related one-pot, three-component reaction, leading to a different family of triazolotrifluoroborates in which the boron substituent remains intact (Figure 15).

Finally, another substitution pattern of triazolotrifluoroborates can be obtained by incorporating the trifluoroborate into the alkyne instead of the azide compo-



**FIGURE 16.** One-pot, three-component couplings.



**FIGURE 17.** Metal–halogen exchange of *p*-bromophenyltrifluoroborate.

nent of the reaction (Figure 16). In this manner, small libraries of compounds can be created rapidly and efficiently, with further diversification possible upon cross-coupling of the organotrifluoroborate.

Metal–halogen exchange reactions can also be carried out while leaving the trifluoroborate intact.<sup>51</sup> In doing so, a reactive nucleophile is generated in the presence of the boron moiety and reacted with a variety of electrophiles (Figure 17). This reactivity is distinct from the chemistry developed by Knochel on the corresponding pinacol boronates using dialkylmagnesium reagents.<sup>52</sup>

One of the most glaring limitations of organoborons is their susceptibility to oxidation. This, combined with the intolerance of most carbonyl functionalities to transmetalation protocols and hydroboration reactions, makes aldehydes and ketones difficult to introduce into organoborons without some type of protection scheme. By contrast, organotrifluoroborates are exceptionally resistant to a number of oxidants, allowing facile conversion of alcohols to aldehydes and ketones (Figure 18).<sup>53</sup> Batey’s ion exchange was used in these oxidations to generate tetrabutylammonium trifluoroborates,<sup>15b</sup> permitting the reactions to be conducted homogeneously in  $\text{CH}_2\text{Cl}_2$ .



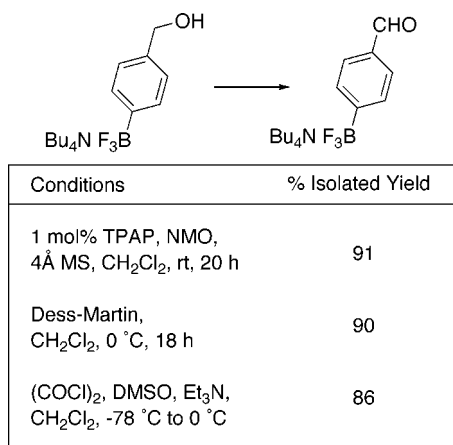


FIGURE 18. Oxidation of hydroxy organotrifluoroborates.

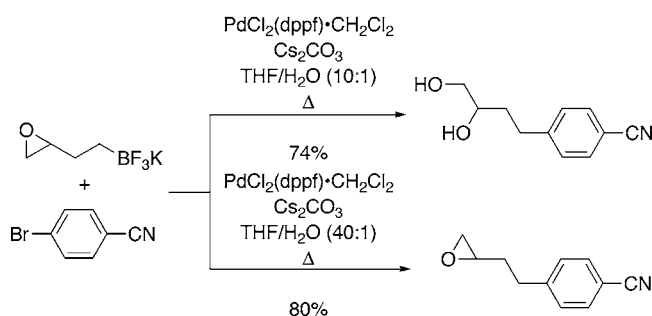
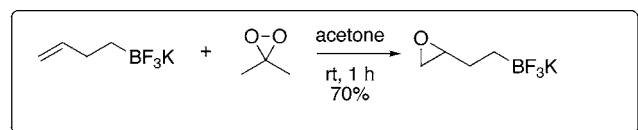


FIGURE 19. Epoxidation of unsaturated potassium organotrifluoroborates.

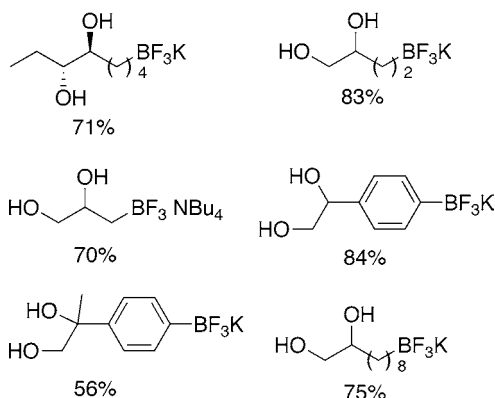
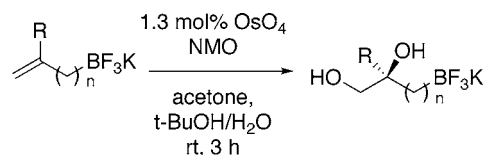
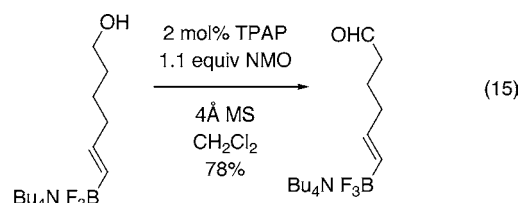
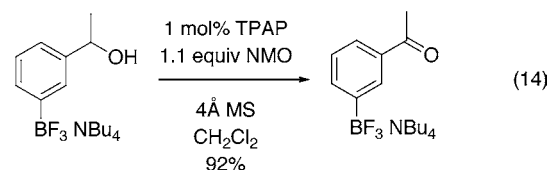
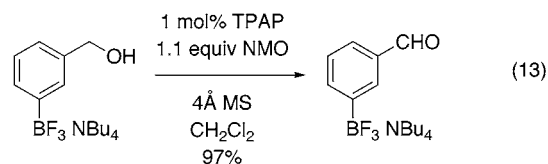
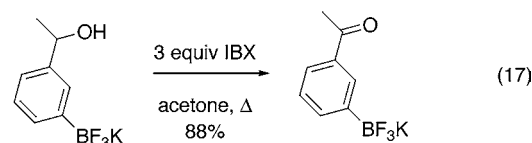
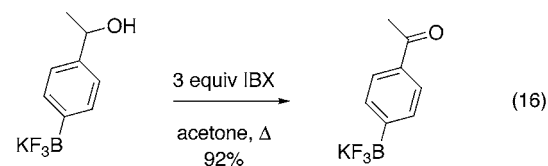


FIGURE 20. Dihydroxylation reactions.

The tetra-*n*-propylammonium perruthenate (TPAP) protocol has been used to oxidize primary and secondary alcohols of aryltrifluoroborates (eqs 13 and 14), and hydroxyalkyl alkenyltrifluoroborates can be converted to the corresponding aldehydes as well (eq 15).



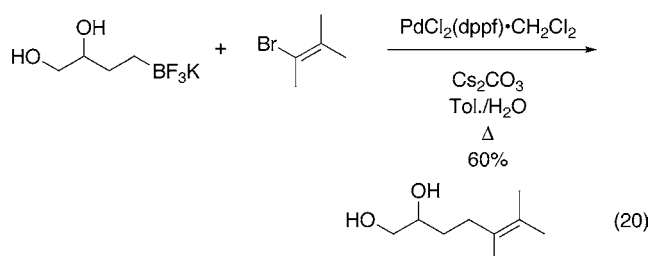
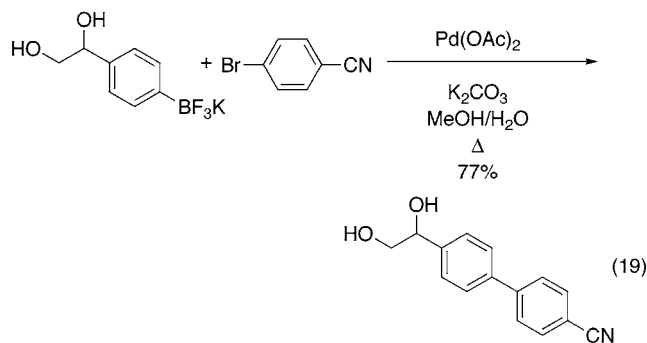
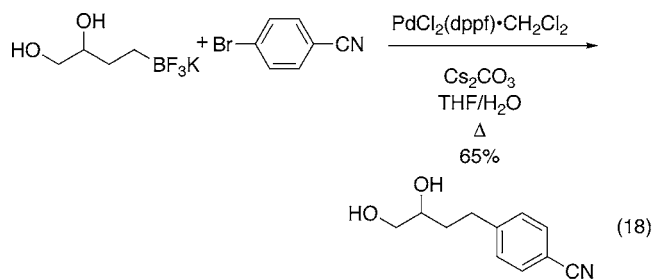
In addition to TPAP, Dess–Martin, and Swern protocols for carbonyl synthesis, *o*-iodoxybenzoic acid (IBX) can also be employed for the oxidation of alcohols in the presence of the trifluoroborate moiety. The procedure appears to be reasonably general for diverse substitution patterns (eqs 16 and 17).



Epoxides are useful as synthetic intermediates, but methods for their introduction into organic molecules are nearly mutually exclusive to reaction conditions tolerated by trivalent organoborons. Epoxides can be introduced readily into unsaturated organotrifluoroborates employing dimethyl dioxirane as the oxidant (Figure 19).<sup>54</sup> The epoxyalkyltrifluoroborates created can undergo cross-coupling with aromatic halides. When 10:1 THF/H<sub>2</sub>O is utilized as the solvent, the coupling occurs concurrently with epoxide ring opening. When 40:1 THF/H<sub>2</sub>O is employed, the coupling can be achieved while retaining the epoxide moiety.

Similarly, alkenyltrifluoroborates can be oxidized using the “Upjohn process”, affording a variety of dihydroxy organotrifluoroborates (Figure 20).<sup>55</sup> These more highly elaborated organotrifluoroborates are also excellent substrates for cross-coupling reactions with aryl and alkenyl halides (eqs 18–20).

It was recently disclosed that organotrifluoroborates bearing aldehyde and ketone functional groups can undergo alkenation reactions employing several different protocols. Simple Wittig alkenation takes place efficiently,



generating predominantly (*Z*)-alkenylated trifluoroborates (Figure 21).<sup>56</sup>

Stabilized ylides work equally efficiently, affording functionalized (*E*) unsaturated aryltrifluoroborates (Figure 22).

Horner–Wadsworth–Emmons (HWE) conditions can be applied to appropriately functionalized organotrifluoroborates, adding molecular complexity stereoselectively to readily available starting materials (Figure 23). The Batey ion exchange protocol was employed as a workup procedure to facilitate purification and isolation of the desired products.

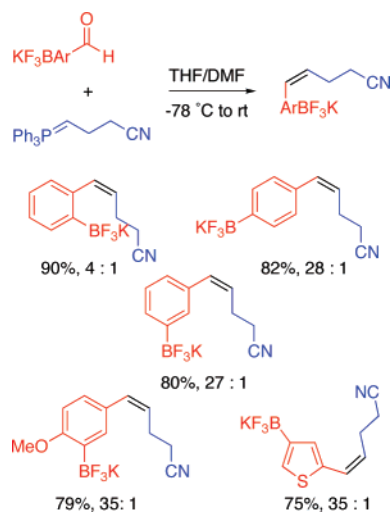


FIGURE 21. Wittig reactions of organotrifluoroborates.

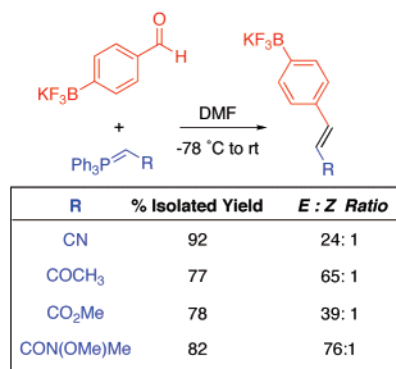


FIGURE 22. Alkenation with stabilized ylides.

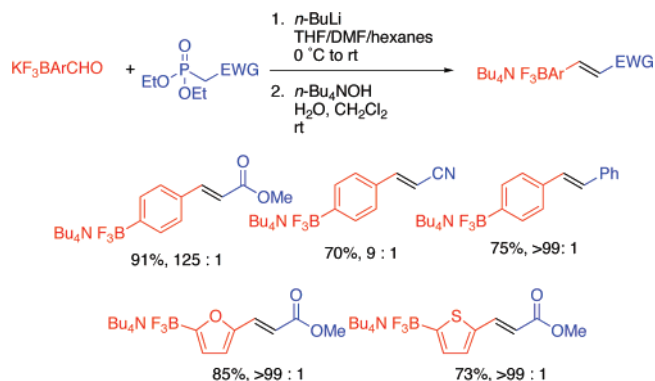


FIGURE 23. HWE reactions of organotrifluoroborates.

Research continues in this arena, which promises to provide new opportunities for the elaboration of diverse functional groups in the presence of the organotrifluoroborate moiety. Unique strategies for the construction of organic molecules will be developed, and organotrifluoroborates will assume a useful niche among the stable of organometallics capable of undergoing cross-coupling reactions.

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