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Organoboron compounds as mild nucleophiles in Lewis acid- and transition metal-catalyzed C–C bond-forming reactions*

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Abstract: The use of air- and water-stable organoboron compounds for C–C bond-forming reactions are reported. These studies include the Lewis acid-promoted additions of boronic esters to *N*-acyliminium ions and allyl and crotyltrifluoroborate salts to aldehydes. Aryl and alkenyltrifluoroborate salts will add to aldehydes under the influence of rhodium catalysis or in the presence of zinc metal. These salts also participate in palladium-catalyzed Suzuki–Miyaura and other cross-coupling reactions. Finally, a new type of *N*-heterocyclic carbene ligand is reported and used for Pd-catalyzed Suzuki–Miyaura couplings.

One of the most important strategies for the formation of C–C bonds uses organometallic or metalloid compounds as nucleophilic reagents. Organoboron compounds occupy a privileged position among these reagents owing to their ease of synthesis, stability, and increasingly, their commercial availability and synthetic versatility [1]. Our initial interest in using organoboron compounds focused on boron-tethered cycloaddition and free-radical cyclization reactions [2]. The discovery of new reactions utilizing boronic esters or other boron compounds at this oxidation state would allow for the design of novel synthetic strategies. Moreover, the emergence of combinatorial chemistry over the past decade has provided additional impetus for the discovery of new reactions that are operationally simple, use air- and water-stable reagents, and give products that require minimal purification. One of the objectives of our laboratory, therefore, is the development of new practical methods using organoboron compounds as an efficient means for the discovery of novel biologically active molecules. This article summarizes some of the research in this field emanating from our laboratory over the past three years.

REACTION OF ALKENYL AND ARYLBORONATES WITH *N*-ACYLIMINIUM IONS

Nucleophilic additions to *N*-acyliminium ions [3] are widely used as a route to the synthesis of *N*-heterocycles and alkaloid natural products. Several classes of carbon-based nucleophilic partners are commonly employed including allylsilanes, trimethylsilylcyanide (TMSCN), enol derivatives, and electron-rich aromatic compounds. The development of new organometallic derivatives that could serve as nucleophiles would increase the scope of *N*-acyliminium ion reactions. A significant development in amine synthesis, by Petasis and coworkers, is the use of alkenyl and arylboronic acids as nucleophilic partners in Mannich reactions [4]. The boronic acids are relatively air- and water-stable, and the reac-

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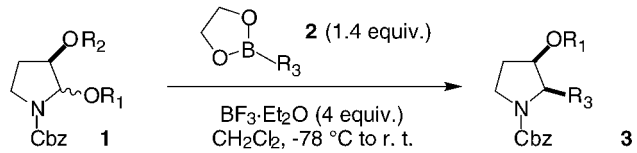
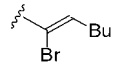
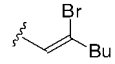
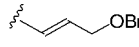
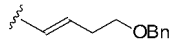
tion has been demonstrated for multicomponent couplings with aldehydes and amines. Since boronic acids should not be intrinsically nucleophilic, an initial activation step must occur prior to reaction with the iminium ions. We envisaged that a similar process would also occur with more electrophilic intermediates, such as *N*-acyliminium ions.

3-Hydroxypyrrolidines were chosen as target structures, since this motif is present in the polyhydroxylated indolizidine and pyrrolizidine alkaloid families, which include many examples of biologically active natural products, such as swainsonine, castanospermine, retronecine, and australine. Pyrrolidine **1** was therefore chosen as a model *N*-acyliminium ion precursor. Reaction of **1** (R^1/R^2 = H) with *E*-hexenylboronic acid in the absence of a Lewis acid did not lead to the desired adducts, but instead resulted in esterification of the boronic acid by **1**. However, addition of the Lewis acid, boron trifluoride etherate, promoted the addition of the *E*-hexenylboronic acid to give **3**. Prior esterification of the boronic acids as the corresponding boronates had a pronounced effect on the efficacy of addition. Ethylene glycol-derived boronates **2** (1.4 equiv) gave excellent yields of the adducts **3** in the presence of $BF_3{\cdot}OEt_2$ (4 equiv) (Table 1) [5]. The reaction is amenable to a range of alkenyl- and arylboronates, producing in all cases the adducts **3** as single diastereomers (>98:2 *cis*:*trans* by ^{1}H NMR). For the additions of alkenyl boronates, the alkene geometry is maintained in the products, as was shown by the exclusive formation of the *Z*-alkenyl-substituted product in the addition of the *Z*-alkenylboronate (Entry 4, Table 1). Use of the methoxy-substituted containing *N*-acyliminium ion precursors did not have a strong effect on the efficacy of the reaction, and again only *cis*-2,3-substituted products **3** were formed (Entries 7–9, Table 1). Functionalized boronates also add successfully, leading to products ready for subsequent synthetic manipulations. Also, whereas most *N*-acyliminium ion precursors require protection of hydroxyl functionality, the addition of boronic ester nucleophiles tolerates free hydroxyl functionality. Interestingly, dialkylalkenylboranes also undergo Lewis acid-promoted addi-

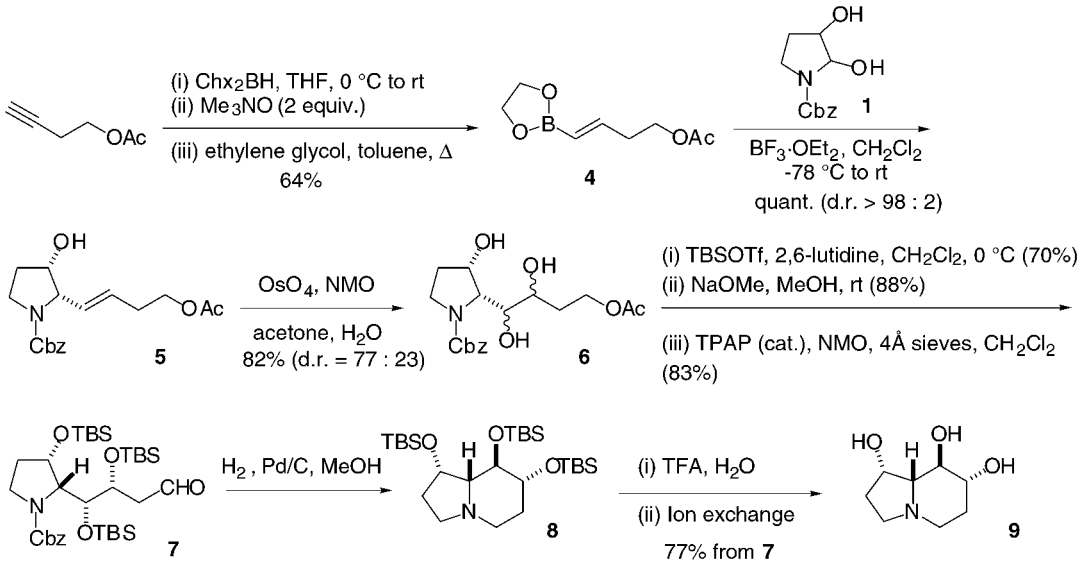
Table 1 Lewis acid-promoted reaction of **1** with aryl and alkenyl boronates **2**.



Entry	R^1	R^2	R^3	Yield [%]
1	H	H	(*E*)-CH=CH^{n}Pr	91
2	H	H	(*E*)-CH=CH^{i}Pr	81
3	H	H	(*E*)-CH=CHPh	64
4	H	H	(*Z*)-CH=CHC$_8$H$_{17}$	80
5	H	H	Ph	70
6	H	H	4-MeOC$_6$H$_4$	83
7	Me	H	(*E*)-CH=CH^{n}Pr	91
8	Me	H	Ph	56
9	Me	Me	(*E*)-CH=CH^{n}Bu	84
10	H	H		98
11	H	H		77
12	H	H		99
13	H	H		81

tion to **1**. For example, hydroboration of 1-hexyne with dicyclohexylborane, followed by reaction of the (*E*)-alkenylborane using the above protocol results in the formation of the pyrrolidines **3**.

The synthetic utility of the reaction has been evaluated through syntheses of both polyhydroxylated indolizidine and pyrrolizidine alkaloids. For example, a short stereoselective synthesis of 6-deoxycastanospermine was achieved from diol **1** and alkenylboronate **4** (Scheme 1) [6]. (*E*)-Alkenylboronate **4** was synthesized by hydroboration of 1-acetoxybut-3-yne with dicyclohexylborane, followed by selective Chx–B bond oxidation and esterification. This is the method of choice for the hydroboration of alkynes that incorporate heteroatom functionality. Addition of alkenylboronate **4** (1.1 equiv) to **1** in the presence of boron trifluoride etherate gave **5** in quantitative yield with excellent diastereoselectivity. Dihydroxylation of the *E*-alkene **5** using 1 mol% OsO_4 and NMO in wet acetone occurred with a facial selectivity of 3.3:1 in favor of the desired diastereomer **6**, as predicted by Vedejs' model. Protection of the triol **6**, ester hydrolysis, and TPAP oxidation of the resultant primary alcohol gave aldehyde **7**. Ring closure to the indolizidine skeleton was achieved by reductive amination using palladium on carbon as a catalyst. Finally, deprotection of **8** followed by cation-exchange chromatography afforded the target compound, 6-deoxycastanospermine **9**.



Scheme 1

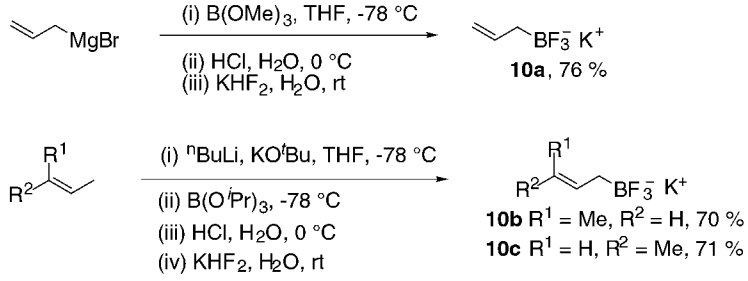
Functionalized pyrrolidines and piperidines are thus accessible by the reaction of alkenyl- and arylboronates with activated *N*-acyliminium ion precursors under Lewis acidic catalysis. The highly stereoselective nature of the addition of organoboronic esters to *N*-acyliminium ions is unusual for the formation of 2,3-disubstituted pyrrolidines. For instance, additions of trimethylallylsilane, trimethylsilyl cyanide, and alkyl copper reagents under Lewis acidic catalysis to the 3-OAc and 3-OTBS analogs of **1** provide mixtures of *trans* and *cis* products [3]. Coordination of either the 3-oxy substituent or the carbonyl oxygen of the Cbz group to the boronates may provide the necessary activation for addition to the intermediate *N*-acyliminium ions, as well as providing a possible rationalization for the exclusive *cis*-selectivity of these reactions.

LEWIS ACID-PROMOTED ADDITION OF ALLYL AND CROTYLTRIFLUOROBORATE SALTS TO CARBONYL COMPOUNDS

One of the most widely employed strategies for the formation of synthetically important homoallyic alcohols is the allylation and crotylation reaction of aldehydes and ketones [7]. A number of allylic

organometallic reagents have been employed for this reaction, including the use of *in situ* generated species through Barbier-type reactions. Allyl/crotyl dialkylboranes or boronate esters are particularly useful because of the high yields and excellent levels of diastereocontrol and enantiocontrol they provide [8]. Our interest in this area arose from the need for configurationally stable crotyl and substituted allylmetals that can be stored for extended periods. Vedejs and coworkers have shown that potassium aryltrifluoroborates are readily prepared from boronic acids and aqueous potassium hydrogen fluoride, and that they serve as useful precursors for the formation of Lewis acidic arylboron difluorides ($ArBF_2$) [9]. The salts are more air- and water-stable than the corresponding boronic acids. Moreover, allylboron difluoride was a species theoretically predicted to have higher reactivity in allylation processes [10]. We thus reasoned that the corresponding allyl- and crotyltrifluoroborate salts **10** would similarly be more stable than the corresponding boronic acids or esters, and would act as convenient precursors for the *in situ* formation of the difluorides.

The preparation of the potassium allyl- and crotyltrifluoroborates **10a–c** was achieved via the boronic acids in a manner analogous to that used for the synthesis of other potassium organotrifluoroborate salts (Scheme 2) [11,12]. The addition of either allylmagnesium bromide or crotylpotassium to triisopropyl borate, followed by acidic hydrolysis, was used to prepare the requisite allyl- and crotylboronic acids respectively. Conversion to the potassium allyl- or crotyltrifluoroborate salts **10a–c** was then achieved by treatment with aqueous KHF_2, followed by recrystallization from acetonitrile. The salts are air- and water-stable solids, and can be stored for extended periods of time at room temperature in plastic bottles. Screening a variety of Lewis acids for their effectiveness at promoting the addition of allyltrifluoroborate **10a** to 4-nitrobenzaldehyde, revealed $BF_3{\cdot}OEt_2$ to be the optimal choice. At –78 °C in dichloromethane, allylation by **10a** with 2 equiv of $BF_3{\cdot}OEt_2$, resulted in full conversion to the homoallylic alcohol within 15 min, and with a 93% isolated product yield.

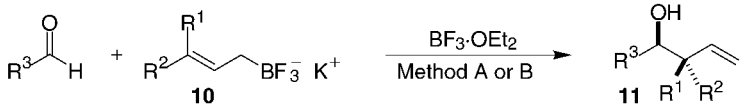


Scheme 2

A variety of substituted and unsubstituted aryl and alkyl aldehydes were then allylated to give the homoallylic alcohols **11** in high isolated yields (Table 2). Two protocols were employed using **10a–c** (2 equiv), with either $BF_3{\cdot}OEt_2$ (2 equiv) at –78 °C in dichloromethane over 15 min (Method A), or with $BF_3{\cdot}OEt_2$ (0.05 equiv) at room temperature over 3–6 h (Method B). While requiring significantly longer reaction times, the use of the catalytic $BF_3{\cdot}OEt_2$ conditions gave comparable yields of **11**. Crotylation using (*Z*)- and (*E*)-potassium crotyltrifluoroborate **10b/c** was found to work equally well using either methods A or B, leading to products **11** with excellent levels of stereocontrol and in uniformly high yields. The general method employing catalytic $BF_3{\cdot}OEt_2$ (Method B) can be applied to the allylation and crotylation of aldehydes with both α- or β-stereocenters. For example, reaction of **10a–c** with aldehyde **12** leads to good yields of products **13**, with varying levels of facial selectivity (Scheme 3) [11].

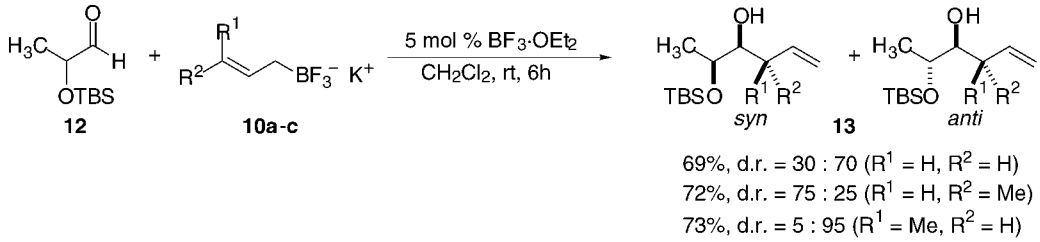
The stereoselectivity of the additions to aldehydes in which the (*Z*)-crotyltrifluoroborate **10b** gives the syn diastereomer of **11**, whereas the (*E*)-crotyltrifluoroborate **10c** gives the anti diastereomer of **11**, is consistent with the addition of a tri-coordinate boron species via a Zimmerman–Traxler-like transition state. The requirement for Lewis acid additives distinguishes the reactivity of **10** from other allylboron compounds, which do not require such activation. Calculations have implied that allylboron

Table 2 Reactions of aldehydes with allyl and (*Z*)- and (*E*)-crotyltrifluoroborates **10a–c**.



Entry	R^1	R^2	R^3	d.r.	Yield [%] (Method A)	Yield [%] (Method B)
1	H	H	4-$O_2NC_6H_4$	–	96	95
2	H	H	*n*-C_7H_{15}	–	82	84
3	H	H	(*E*)-Ph-CH=CH-	–	89	91
4	H	H	4-$MeOC_6H_4$	–	95	89
5	H	H	4-$MeSC_6H_4$	–	90	93
6	H	H	4-NCC_6H_4	–	95	95
7	H	H	3-MeO-4-HOC_6H_3	–	84	85
8	Me	H	*n*-C_7H_{15}	>98:2	74	76
9	H	Me	*n*-C_7H_{15}	>98:2	84	85
10	Me	H	Ph	>98:2	91	92
11	H	Me	Ph	>98:2	94	93
12	Me	H	4-$MeOC_6H_4$	96:4	91	93
13	H	Me	4-$MeOC_6H_4$	97:3	91	95
14	Me	H	4-$O_2NC_6H_4$	>98:2	95	94
15	H	Me	4-$O_2NC_6H_4$	>98:2	96	94

difluoride is a species that should have high reactivity in allylation reactions [10]. However, Guillemin has reported that allylboron difluoride, generated through transmetallation of an allylstannane with boron trifluoride gas in a noncoordinating solvent, does not yield homoallylic alcohol products [13]. Nevertheless, while the identity of the active allylation species has not been definitively established, allylboron difluoride is presumably initially formed *in situ* under our conditions, by the Lewis acid-promoted removal of fluoride from the salts **10**. These reagents offer several advantages over existing allylboron reagents, including stability to air and moisture, rapid and high-yielding additions, and excellent levels of diastereocontrol. We are currently working on extending the scope of these useful reagents and developing milder protocols for their additions.



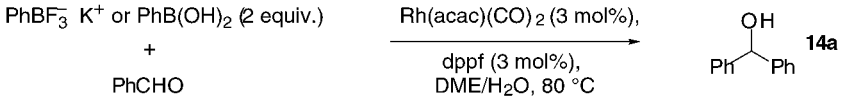
Scheme 3

Rh(I)- AND Zn-CATALYZED ADDITION OF ARYL- AND ALKENYLTRIFLUOROBORATE SALTS TO CARBONYL COMPOUNDS

The palladium-catalyzed cross-coupling reaction between organoboron compounds and organohalides and triflates, commonly referred to as the Suzuki or Suzuki–Miyaura reaction, provides a powerful and general methodology for C–C bond formation [14]. The commercial availability of many boronic acids, the mild reaction conditions required, and the broad functional group tolerance have each contributed

to the versatility of the reaction. It has generally been assumed that a tetracoordinate boron species is required for the transmetallation step in the catalytic cycle of the Suzuki–Miyaura reaction. Coupled with the observations of Vedejs on the enhanced stability of potassium trifluoroborate salts [9], we became interested in whether trifluoroborate salts, which are tetracoordinate, would be more effective than their boronic acid counterparts, in reactions in which transmetallation between boron and a transition-metal complex occurs in the catalytic cycle.

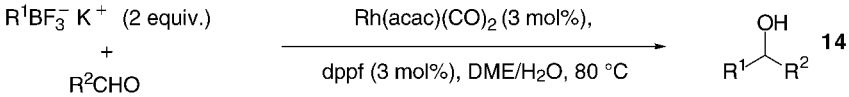
One powerful reaction, which has recently emerged from the laboratory of Miyaura, is the formation of secondary alcohols by the Rh(I)-promoted addition of aryl and alkenylboronic acids to aldehydes [15]. We chose this reaction as our starting point for the investigation of the effectiveness of organotrifluoroborate salts in transmetallations [16]. A direct comparison using the metal source/ligand combination described by Miyaura, $Rh(acac)(CO)_2$ (3 mol%) and 1,1'-bis(diphenylphosphino)ferrocene (dppf) (3 mol%), revealed that the addition of 2 equiv of potassium phenyltrifluoroborate and phenylboronic acid to benzaldehyde both proceeded to full conversion after 16 h in DME/water (1:1) at 80 °C. However, the rate of product **14a** formation from potassium phenyltrifluoroborate was approximately 2 to 3 times that using phenylboronic acid (Scheme 4).



Scheme 4

The use of 2 equiv of the trifluoroborate salt was found to be optimal, with the isolated yields of **14a** dropping to 69% and 28% with 1.5 and 1.1 equiv of potassium phenyltrifluoroborate, respectively. A variety of aldehydes were functionalized using this protocol to give the corresponding allylic and benzylic alcohols **14** (Table 3). The reactions occur more rapidly than with the corresponding boronic acids, and whereas the addition of boronic acids to nitro-substituted aldehydes using Miyaura's conditions did not result in product formation, the addition of trifluoroborate salts was readily accomplished.

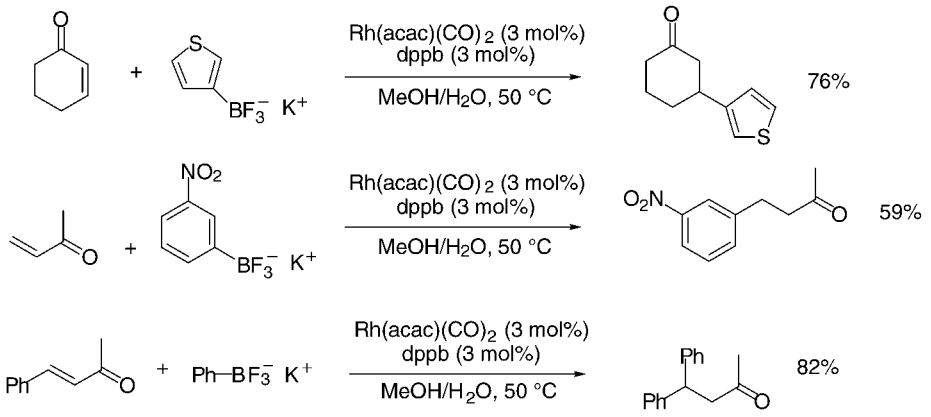
Table 3 Arylation and alkenylation of aldehydes with potassium aryl- and alkenyltrifluoroborates.



Entry	R^1	R^2	Yield [%]
1	Ph	Ph	79
2	Ph	4-$O_2NC_6H_4$	85
3	(*E*)-CH=CHPh	4-$O_2NC_6H_4$	82
4	Ph	3-$O_2NC_6H_4$	88
5	Ph	2-$O_2NC_6H_4$	85
6	(*E*)-CH=CH^{n}Bu	2-$O_2NC_6H_4$	88
7	Ph	4-NCC_6H_4	87
8	(*E*)-CH=CH^{n}Bu	4-NCC_6H_4	85
9		4-NCC_6H_4	80
10	Ph	4-$MeOOCC_6H_4$	71
11	(*E*)-CH=CHPh	4-$MeOOCC_6H_4$	71
12	Ph	C_6H_{11}	86

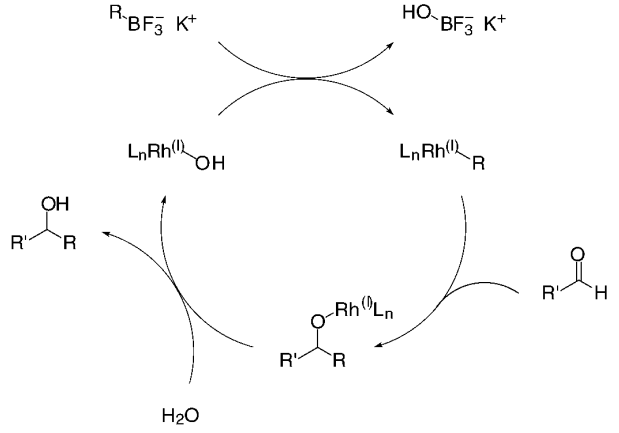
The effect of the ligand upon the reaction of potassium phenyltrifluoroborate with 4-nitrobenzaldehyde was also probed. The ligands dppb (1 equiv) and triphenylphosphine (2 equiv) were also found to be effective in the reaction, with yields dropping from 85% with dppf to 83% with PPh_3 and 76% with 1,4-bis(diphenylphosphino)butane (dppb). This is in sharp contrast to the results obtained in the additions of phenylboronic acid to aldehydes, in which no reaction occurs with PPh_3 as a ligand [15]. This suggests that the P–Rh–P angle does not significantly affect catalyst activity for the addition of aryl and alkenyltrifluoroborate salts. By analogy with room temperature additions of boronic acids to aldehydes with Rh(acac)$(coe)_2$/*t*-Bu_3P [17], aryltrifluoroborate salts will also add to aldehydes using an Rh(acac)$(CO)_2$/*t*-Bu_3P system.

Aryl and alkenyltrifluoroborate salts will also undergo addition to enones under Rh(I) catalysis (Scheme 5). For example, in the presence of Rh(acac)$(CO)_2$ (3 mol%) and dppb (3 mol%) or PPh_3 as the ligand (6 mol%), reaction of enones with 2 equiv of the salts proceeds to full conversion after 16 h in MeOH/water (6:1) at 50 °C. Even the electron-deficient potassium 3-nitrophenyltrifluoroborate will undergo addition to methylvinyl ketone, under conditions where the corresponding 3-nitrophenylboronic acid does not add.



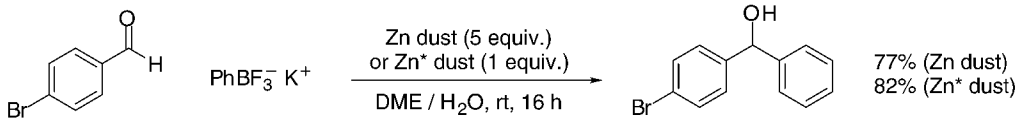
Scheme 5

The greater effectiveness of the organotrifluoroborate salts over boronic acids in the Rh(I)-catalyzed additions to enones and aldehydes presumably reflects more facile transmetallation to form the active Rh–C species. A mechanism has been proposed by Miyaura [15], which also accounts for the requirement of water to achieve catalytic turnover, involving insertion of the C=O bond of the aldehyde with the Rh–C species, followed by hydrolysis of the resultant Rh(I) hydroxide species and give the secondary alcohol products (Scheme 6).



Scheme 6

We have also begun to investigate the use of other metals that promote the addition of organoboron compounds to carbonyl compounds. For example, we have recently discovered that zinc metal promotes the addition of organotrifluoroborate salts, but not boronic acids, to aldehydes (Scheme 7). The origin of this effect is not clear, and the existence of a surface-mediated effect may be important. Zn(II) salts do not promote the additions. Reaction occurs in DME/H_2O at room temperature with zinc dust (5–10 equiv), but for optimal reaction 1–2 equiv of activated (1,2-dibromoethane/TMSCl) zinc dust (Zn*) can be used. Alternatively, addition of potassium hydrogen fluoride allows the addition of arylboronic acids, via in situ formation and reaction of the aryltrifluoroborate anion. In the absence of water, no reaction occurs for these reactions, even when using Zn*. However, the addition of Lewis acids such as $BF_3{\cdot}OEt_2$ can be used to accomplish the additions to aromatic aldehydes in the absence of water. An organozinc species is presumably involved for each of these reaction conditions, which may allow the possibility of asymmetric additions in the presence of chiral ligands.



Scheme 7

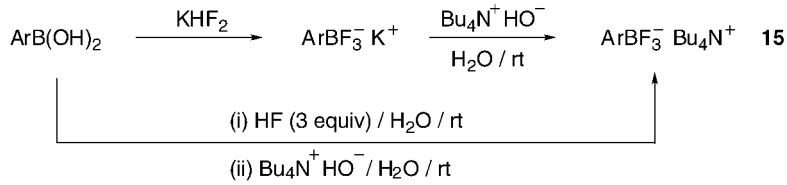
Rhodium(I)-catalyzed additions of organoboron compounds to carbonyl groups is an emerging reaction which is potentially of significant value to both traditional organic synthesis and for combinatorial syntheses. We have demonstrated an important role for the nature of the groups on the boron, which we believe reflects the greater ease with which transmetallation occurs in the catalytic cycle. We are currently pursuing this reaction, as well as investigating alternative catalysts for nucleophilic additions to carbonyl compounds.

CROSS-COUPLING REACTIONS OF TRIFLUOROBORATE SALTS

The success of the Rh(I)-catalyzed addition of trifluoroborate salts to aldehydes and enones, prompted us to study the use of trifluoroborate salts in cross-coupling reactions, such as the Suzuki–Miyaura reaction. At the outset of this investigation it was known from the studies of Wright and coworkers that fluoride ion (CsF) could be used as a base for Suzuki–Miyaura cross-couplings using organoboronic acids [18]. Wright proposed that fluoride ion displacement of the hydroxyls of the boronic acid to form an organotrifluoroborate ion *in situ* could occur, which would then undergo transmetallation. Given this proposal, trifluoroborate salts should be able to participate in the Suzuki–Miyaura reaction. However, Genêt had already established that while the cross-coupling of potassium organotrifluoroborate salts with arenediazonium tetrafluoroborates occurs under mild conditions [19], the salts were not effective in reactions with aryl halides, which are much less reactive coupling partners. Also, during the course of our studies, Molander reported the cross-coupling of potassium alkyltrifluoroborates with alkenyltriflates [20].

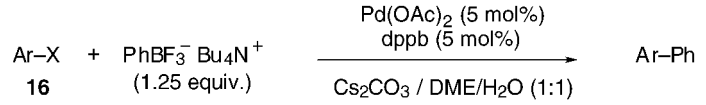
Initially, we have used tetraalkylammonium aryltrifluoroborate salts **15**, rather than the potassium salts, which usually have low solubility in most of the nonpolar organic solvents that are often employed in the Suzuki–Miyaura reaction. The tetrabutylammonium (TBA) salts **15** can either be synthesized by treatment of the corresponding potassium salts with TBA hydroxide, or through the sequential treatment of arylboronic acids with HF and TBA^+OH^- (Scheme 8). The salts **15** are crystalline solids that readily dissolve in nonpolar organic solvents [21].

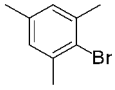
Initial experiments on the choice of palladium source, ligand, and solvent, provided the optimized conditions of $Pd(OAc)_2$ (5 mol%), dppb (5 mol%) and Cs_2CO_3 (1.25 equiv) dissolved in a 1:1 mixture of DME:water at room temperature to 50 °C. A range of aryl iodides and bromides (but not chlorides) underwent reaction with the TBA^+ phenyltrifluoroborate salt (Table 4). We have also successfully used other TBA^+ aryltrifluoroborate salts **15** using these conditions.



Scheme 8

Table 4 Palladium-catalyzed cross-coupling of $PhBF_3^-$ TBA^+ with arylbromides and iodides.

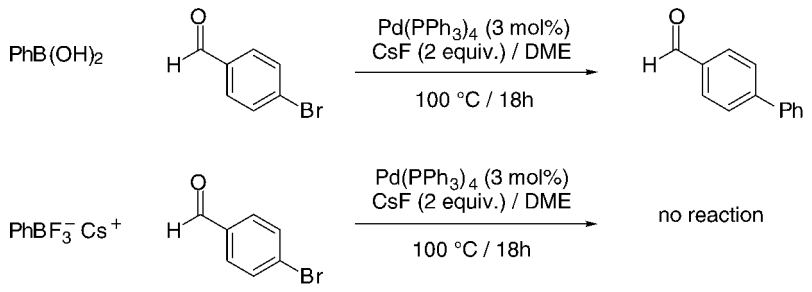


Entry	Halide 16	Temp (°C)	Time (h)	Yield (%)
1	PhI	rt	12	quant.
2	4-MeC(O)C_6H_4I	rt	12	92
3	4-MeC(O)C_6H_4Br	rt	12	90
4	4-MeOC_6H_4I	50	24	82
5	4-MeOC_6H_4Br	50	24	79
6	4-$O_2NC_6H_4$Br	50	24	79
7	4-ClC_6H_4Br	50	12	96
8	4-NCC_6H_4Br	rt	12	93
9		50	24	93
10		rt	12	97
11		50	24	85

Interestingly, water cosolvent was found to be essential for the reaction to proceed, since reactions performed in the absence of water showed low conversion in the case of the TBA^+ salts, and no reaction in the case of the K^+ salts. The TBA^+ salts afforded significantly higher yields then their K^+ counterparts in the presence of DME or other nonpolar organic solvents. However, the addition of 10 mol% of a phase-transfer catalyst, such as tetra-*n*-butylammonium iodide (TBAI), did result in comparable yields using the K^+ salts. This is consistent with a phase-transfer effect, since the potassium salts are more soluble in the aqueous phase than the organic phase.

The requirement for added cesium carbonate and water as the cosolvent in the reaction is not consistent with the aryl trifluoroborate anion being the boron species that undergoes transmetallation in the catalytic cycle. Furthermore, while reaction of 4-bromobenzaldehyde under Wright's conditions (2 equiv of CsF / DME / 100 °C) [18] with $PhB(OH)_2$ occurred as reported, reaction of $Cs^+PhBF_{3^-}$ did not afford any of the cross-coupled product (Scheme 9).

These results are consistent with Matos and Soderquist's mechanistic study that describes a hydroxyborate species participating in a four-centered hydroxo-μ_2-bridged transition state in the transmetallation event [22]. Thus, at least one oxygen atom must be attached to the boron for transmetallation to occur, and under our conditions partial hydrolysis of the aryl trifluoroborate anion is necessary for catalysis to take place. This mechanistic observation presumably is general for the conditions of



Scheme 9

Wright and coworkers as well as other fluoride ion-promoted Suzuki–Miyaura and other cross-coupling reactions. Further investigations using trifluoroborate salts in such reactions are currently underway in our laboratories.

NEW PALLADIUM *N*-HETEROCYCLIC CARBENE COMPLEXES FOR CROSS-COUPLING REACTIONS

A significant development in the area of transition metal catalysis is the growing use of nucleophilic *N*-heterocyclic carbenes, especially imidazol-2-ylidenes, as alternatives for the widely used phosphine ligands in homogenous catalysis [23]. Most of the *N*-heterocyclic carbene based complexes **17** reported are either *N*-alkyl- or *N*-aryl-substituted (Fig. 1). We have recently demonstrated the utility of carbamoyl imidazolium salts **18** as *N*,*N*-disubstituted carbamoyl cation equivalents for the formation of tri- and tetrasubstituted ureas, carbamates, and thiocarbamates [24]. We envisaged that these salts could serve as precursors for *N*-heterocyclic carbene-based complexes **19**, and were interested in whether the introduction of the electron-withdrawing carbamoyl substituent would effect the catalytic potential of the complexes for C–C bond forming and other reactions. The Suzuki–Miyaura cross-coupling reaction was considered to be an effective test case to probe this question.

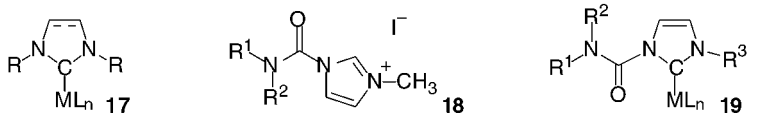
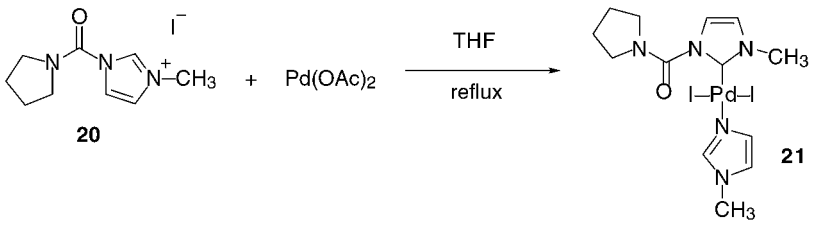


Fig. 1

The complex **21** was formed by treatment of the carbamoyl imidazolium salt **20** with palladium(II) acetate in refluxing THF (Scheme 10). The complex **21** exists as orange-red crystals and is very stable to both air and moisture. X-ray crystal structure analysis clearly shows that the complex exists in the *trans* configuration, and the Pd–C bond length (1.970 Å) lies in the range of known carbene complexes (1.948–2.074 Å) [25].

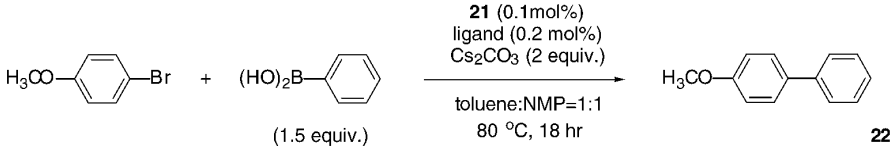


Scheme 10

Initial optimization studies were conducted upon the cross-coupling of 4-bromoacetophenone with phenylboronic acid. Quantitative yields of products were obtained with 0.1 mol% of the precatalyst **21** in toluene at 80 °C, using cesium carbonate as a base. This protocol does not work well with more electron-rich aryl halides. Addition of a phase-transfer catalyst such as benzyltriethylammonium bromide or the use of toluene/NMP as the solvent led to a substantial increase in the rate of product formation. The addition of external ligands also affected the overall yields of the cross-coupling product **22** (Table 5). Optimized yields of **22** were obtained using 0.2 mol% of triphenylphosphine and 0.1 mol% of the complex **21**.

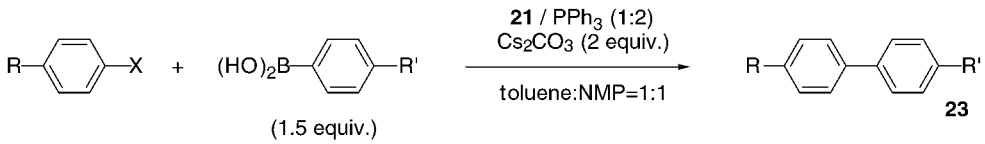
Using a 1:2 ratio of the complex **21** to PPh_3 with 2 equiv of Cs_2CO_3 in toluene:NMP the Suzuki–Miyaura reaction of 4-substituted aryl halides with arylboronic acids can be effected in good yields and with relatively low catalyst loadings (Table 6). The reaction temperature for the reactions of

Table 5 Effect of external ligand on the cross-coupling of phenylboronic acid with 4-bromoanisole using complex **21**.



Entry	Ligand	Yield [%]
1	—	66
2	PPh_3	92
3	dppb	64
4	$P(OEt)_3$	63
5	(*o*-biphenyl)P(*t*-Bu)$_2$	17

Table 6 Complex 21/PPh_3 promoted Suzuki–Miyaura cross-coupling of 4-aryl halides with arylboronic acids.



Entry	R	X	R'	mol% (21)	Temp. [°C]	T [h]	Yield [%]
1	$COCH_3$	I	H	0.5	50	5	95
2	$COCH_3$	I	H	5×10^{-4}	130[a]	18	99
3	$COCH_3$	I	H	1×10^{-4}	130[a]	18	58
4	OCH_3	I	H	0.5	80	18	91
5	$COCH_3$	Br	H	0.5	50	5	94
6	$COCH_3$	Br	H	1×10^{-3}	130[a]	18	75
7	$COCH_3$	Br	H	1×10^{-4}	130[a]	18	48
8	OCH_3	Br	$COCH_3$	0.5	80	48	86
9	OCH_3	Br	Cl	0.5	80	48	91
10	OCH_3	Br	OCH_3	0.5	80	48	91
11	CHO	Br	H	0.5	50	18	96
12	Cl	Br	H	1	50	18	90
13	CN	Cl	H	2	80	48	64
14	CN	Cl	$COCH_3$	2	80	48	68

[a]Xylene was used as solvent in these reactions.

electron-deficient aryl halides can be reduced from 80 °C to 50 °C (Entries 1, 5, 11, and 12, Table 6). Turnover numbers as high as 580 000 were achieved with 4-iodoacetophenone and 4-bromoacetophenone, at elevated temperatures (Entries 2, 3, 6, and 7, Table 6). However, higher catalyst loadings were necessary for the reactions of an activated aryl chloride with arylboronic acids (Entries 13 and 14, Table 6) in high yields.

N-acyl-substituted heterocyclic carbene complexes have been demonstrated to act as efficient catalysts for the Suzuki–Miyaura coupling. The electron-withdrawing character of the carbamoyl substituent does not prevent catalysis from occurring. Complexes **19** are efficiently synthesized from carbamoyl imidazolium salts **18**. Electronic and steric tuning of the groups R^1, R^2, and R^3 in **19** should allow modification of catalytic behavior. Preliminary investigations have revealed that complexes such as **21**, including polymer-bound species, will also promote a variety of other cross-coupling reactions.

CONCLUSIONS

C–C bond-forming reactions are the foundations of most organic syntheses. The studies outlined in this paper further underline the preeminence of organoboron compounds as mildly nucleophilic reagents for C–C bond formation. This includes their use in modifications of the well-known Suzuki–Miyaura reaction, as well as their additions to aldehydes, enones, and *N*-acyliminium ions promoted both by Lewis acids and transition-metal catalysts.

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