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Suzuki Cross-Coupling Reactions of Potassium Alkenyltrifluoroborates†

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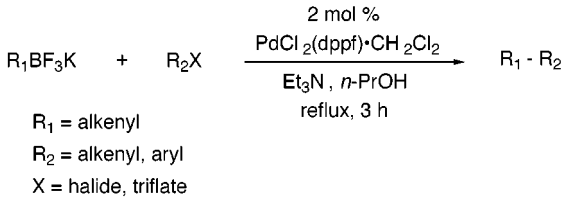
ABSTRACT



The palladium-catalyzed coupling reaction of potassium alkenyltrifluoroborates with aryl or alkenyl halides or triflates proceeds readily with good yields. The trifluoroborates are air- and moisture-stable solids that can be stored indefinitely. The cross-coupling can be effected using $PdCl_2(dppf)\cdot CH_2Cl_2$ as the catalyst in *n*-PrOH in the presence of Et_3N. A variety of functional groups are tolerated.

Palladium-catalyzed cross-coupling reactions of electrophiles with organometallic reagents have become one of the most widely used procedures for carbon−carbon bond formation.[1] Among the possible organometallics, tin (Stille coupling)[2] and boron (Suzuki coupling)[3] derivatives are most frequently used for these cross-coupling reactions because of their tolerance of a broad range of functional groups. The use of organoboron compounds is especially valued for several reasons: they are more easily accessed by a variety of routes, nontransferable groups can be readily incorporated into the organometallic species, and the inorganic byproducts of the reaction are of low toxicity and environmental impact and can be readily removed by simple workup procedures.

However, although the Suzuki coupling reaction is one of the most useful methods yet developed for the synthesis of carbon skeletons, there are still improvements that could be made to render it even more effective. Considerable effort has been made to develop metal/ligand catalyst systems that facilitate the cross-coupling and expand its scope.[4] Surprisingly little work has been performed on the nature of the organoboron coupling partner.

The most commonly utilized organoboron derivatives for Suzuki coupling reactions are boronic acids and boronic esters. Although they are widely employed in such transformations, there are several notorious problems with these derivatives. In particular, the boronic acids are often subject to dimerization and cyclic trimerization with loss of water to form boronic acid anhydrides and boroxines. Because quantitative analysis of these species is often difficult, the determination of precise stoichiometry can be extraordinarily difficult. Boronic esters are often prepared as a means to purify the organoboron species, but some of these are hydrolytically stable and difficult to deal with upon completion of the reaction. Furthermore, the diols utilized to create the boronic esters (e.g., catechol or pinacol) add considerable expense to the overall process and, additionally, must be separated from the desired product after the coupling process.

There are also considerable problems specific to alkenyl boronic acids and esters. For example, vinylboronic acid is

† Dedicated to Professor Herbert C. Brown on the occasion of his 90th birthday.

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readily polymerized and cannot be isolated.[5] Furthermore, vinylboronic esters are not selective in Suzuki-type reactions, yielding mixtures of Suzuki and Heck coupled products.[6]

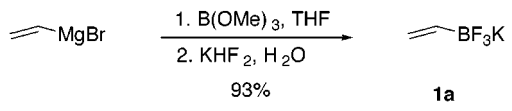
Potassium organotrifluoroborates offer solutions to these problems. These materials are readily prepared by the addition of KHF_2 to a variety of organoboron intermediates.[7] Potassium hydrogen fluoride is an inexpensive source of fluoride. On a molar basis, KHF_2 is one-half the price of catechol and 25 times less expensive than pinacol. The organotrifluoroborates appear to be more nucleophilic[8] than other organoboron reagents and are easily prepared from the corresponding boronic acids or esters (vide infra). The organotrifluoroborates thus generated are monomeric, air-stable, crystalline solids that are readily isolated and indefinitely stable in the air.[7a,9,10]

Potassium organotrifluoroborates have seen only minimal use in palladium-catalyzed cross-coupling reactions. For example, potassium aryl- and 1-alkenyltrifluoroborates have been demonstrated to couple with arenediazonium tetrafluoroborates or diaryliodonium salts.[9,11] Vinyl pyrimidines have been synthesized by cross-coupling of potassium vinyltrifluoroborates with halopyrimidines.[12] More recently we reported the cross-coupling of potassium alkyltrifluoroborates with different aryl- and alkenyltriflates.[13]

As part of an ongoing project on the use of organotrifluoroborates in Suzuki coupling reactions, we initiated a study on the behavior of alkenyltrifluoroborates in this reaction. In this letter we report our preliminary results, which expands the cross-coupling of alkenyltrifluoroborates from arenediazonium salts and diaryliodonium salts to more useful aryl halides, aryl triflates, and alkenyl halides.

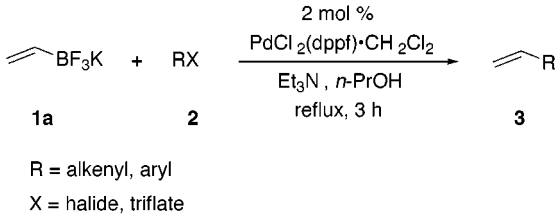
We initially focused our attention on the use of potassium vinyltrifluoroborate (**1a**)[9a,b,14] as a potentially useful alkenylating agent. Potassium vinyltrifluoroborate was efficiently prepared in one step using a modification of known procedures[7–9,15] through addition of vinylmagnesium bromide to trimethyl borate and in situ treatment of the resulting boronic ester with KHF_2 (Scheme 1).

Scheme 1



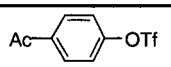
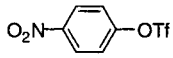
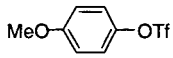
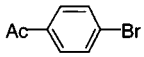
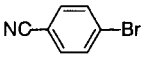
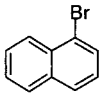
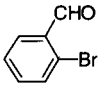
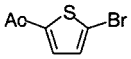
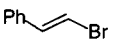
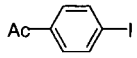
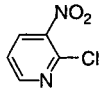
Reaction conditions for the vinylation were explored using 4-acetylphenyl triflate as the coupling partner. The best yields of 4-acetylstyrene were obtained with $PdCl_2$(dppf) (2 mol %) using Et_3N (1 equiv) as a base in *n*-PrOH at reflux (Scheme 2). These conditions and those optimized for the alkyl derivatives[13] were applied to the rest of the substrates in the study.[16]

Scheme 2



The results of this study are shown in Table 1. Potassium vinyltrifluoroborate reacted with a wide variety of organic halides and triflates, affording the corresponding functionalized styrenes **3** in good yields. Interestingly, the reaction

Table 1. Cross-Coupling of Organic Halides and Triflates with Potassium Vinyltrifluoroborate

entry	R-X	reaction conditions[a]	isolated yield (%)
1		A	95
2		B	84
3		A	82
4		B	72
5		A	64
6		A[b]	90
7		A	68
8		B	69
9		A	75
10		B	68
11		A	65
12		A	60[c]
13		A	74
14		B	72
15		A	73
16		A	62
17		B	64

[a] Conditions A: $PdCl_2$(dppf)•CH_2Cl_2 (2 mol %), Et_3N (1 equiv) in *n*-PrOH heated at reflux for 3 h. Conditions B: $PdCl_2$(dppf)•CH_2Cl_2 (9 mol %), Cs_2CO_3 (3 equiv) in THF−H_2O (10:1) heated at reflux for 6 h. [b] MeOH was used as solvent. [c] With a 76% conversion (calculated by ^1H NMR analysis) after 12 h.

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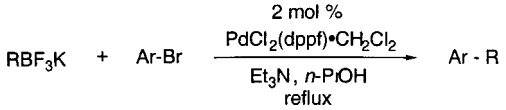
proceeded with satisfactory yields for aryl derivatives bearing electron-donating groups (entry 5), as well as for activated chlorides (entries 16 and 17). At this point in time, unactivated aryl chlorides remain problematic. *ortho*-Substituted substrates (entries 11, 16, and 17) also afforded good yields of the coupling products. Moreover, many functional groups (ketone, nitro, ether, nitrile, aldehyde) were tolerated in the reaction. In certain cases (entries 5, 13, 14, 16, and 17), yields of the products were modest because the products were relatively easily oligomerized.

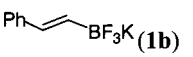
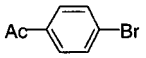
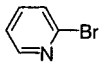
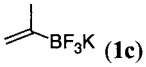
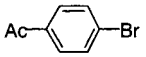
These coupling conditions have been found to be of general use. Consequently, it is possible to couple an alkenyl group not only onto aryl or heteroaryl halides, but also onto alkenyl derivatives (entries 13 and 14) affording the conjugated diene in good yield.

Having demonstrated that **1a** can act as an efficient vinylating agent of organic halides and triflates, we briefly investigated the scope of the coupling reaction using more highly substituted potassium alkenyltrifluoroborates.

Thus, as outlined in Table 2, potassium styryltrifluoroborate[15] (**1b**) reacted with 4-bromoacetophenone (entry 1)

Table 2. Cross-Coupling of Aryl Bromides with Potassium Alkenyltrifluoroborates **1b**−**c**



entry	RBF_3K	ArBr	t (h)	isolated yield (%)
1	 **(1b)**		8	91
2	**1 b**		8	83
3	 **(1c)**		5	81

and also with 2-bromopyridine (entry 2) leading to the corresponding stilbene derivatives in high yields.

Finally, the presence of α-substitution in the organoboron partner (entry 3) was studied. In this manner, potassium isopropenyltrifluoroborate (**1c**) proved to be a very efficient reagent for the introduction of an isopropenyl group.

A key question remains as to whether the trifluoroborates remain intact during the coupling, or whether they react with the alcohol or water during the course of the reactions forming boronic acids or esters that subsequently couple. Mechanistic studies are underway to resolve this issue.

In summary, palladium-catalyzed cross-coupling reactions of potassium alkenyltrifluoroborates with aryl and alkenyl halides and triflates have been achieved with good yields. The reaction proceeded with *ortho*-substituted substrates and also with electron-rich derivatives. A variety of functional groups were tolerated in the coupling reaction. The organoboron derivatives can be prepared by different routes, including transmetalation and both catalyzed and noncatalyzed hydroboration. The trifluoroborates are monomeric solids that possess several advantages over the corresponding boronic acids and esters. The ease of isolation, purification, storage, and handling makes them highly attractive intermediates for laboratory scale and industrial processes and especially for combinatorial chemistry. A variety of functionalized and structurally diverse organotrifluoroborates can be synthesized and stored for coupling when needed. The full scope of this method is currently under further investigation in our laboratories.

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Supporting Information Available: Full experimental details. This material is available free of charge via the Internet at http://pubs.acs.org.

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(16) **Representative Procedure for the Cross-Coupling Reaction of Potassium Alkenyltrifluoroborates. 4-Acetylstyrene.** A solution of potassium vinyltrifluoroborate (**1a**) (60 mg, 0.448 mmol), $PdCl_2(dppf)\cdot CH_2Cl_2$ (6 mg, 0.007 mmol), 4-acetylphenyltriflate (100 mg, 0.373 mmol), and Et_3N (37.7 mg, 0.373 mmol) in *n*-PrOH (6 mL) was heated at reflux under an N_2 atmosphere. The reaction mixture was stirred at reflux for 3 h, then cooled to room temperature, and diluted with water (10 mL) followed by extraction with ether (10 mL × 3). The ethereal solution was washed with brine (20 mL) and dried over $MgSO_4$. The solvent was removed in vacuo, and the crude product was purified by silica gel chromatography (eluting with hexane/ethyl acetate 10:1) to yield 4-acetylstyrene (52 mg, 0.356 mmol, 95%).