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Suzuki-Miyaura Cross-Coupling of Potassium Dioxolanylethyltrifluoroborate and Aryl/Heteroaryl Chlorides

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Abstract

A robust and efficient protocol for the introduction of the dioxolanylethyl moiety onto various aryl and heteroaryl halides has been developed, providing cross-coupling yields up to 93%. Copper-catalyzed borylation of 2-(2-bromoethyl)-1,3-dioxolane with bis(pinacolato)diboron followed by treatment with potassium bifluoride provides the key organotrifluoroborate reagent.

The dioxolanylethyl fragment represents a conveniently protected synthetic equivalent for the propanal substructure.¹ Surprisingly, the installation of such a motif on aryl and heteroaryl systems via cross-coupling has not been extensively studied. Among the principle methods encountered, the Heck reaction between aryl iodides and allyl alcohol leads directly to the aldehyde,² and the Negishi cross-coupling between dioxolanylethylzinc bromide and aryl iodides also provides access to the target structures.³ Finally, the cobalt-catalyzed cross-coupling between aryl Grignard reagents and 2-(2-bromoethyl)-1,3-dioxolane has also been reported (Scheme 1).⁴

These previously reported methods suffer from several non-negligible drawbacks, such as the requisite use of aryl iodides and high boiling solvents in the Heck reaction (Scheme 1, eq 1), and the employment of reactive reagents such as alkylzinc bromide or arylmagnesium bromide for the other two methods (Scheme 1, eqs 2 and 3), thus limiting the substrate scope and versatility. Additionally, these transformations all lack atom economy in that they require the use of a several fold excess of reagents. The combination of these features lowers the general appeal and subsequent application of these methods.

A strategy based on the use of the Suzuki-Miyaura cross-coupling between a dioxolanylethylboron species and aryl electrophiles has, to our knowledge, never been reported, and would provide a mild and versatile alternative pathway.⁵ Moreover, the use of the organotrifluoroborate technology would also be beneficial, allowing the use of stable and

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Supporting Information Available

Experimental procedures, spectral characterization, and copies of ¹H, ¹³C, ¹⁹F and ¹¹B NMR spectra for all compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

robust reagents in near stoichiometric ratios. Organotrifluoroborates have been developed as useful boron-containing reagents for various chemical transformations, and more notably as surrogates for boronic acids in Suzuki-Miyaura coupling reactions.⁶

To our knowledge, the hydroboration of 2-ethenyl-1,3-dioxolane appears in a single report.⁷ In that effort, 9-BBN was utilized to hydroborate the alkene with high regioselectivity for terminal hydroboration, but the resulting air-sensitive organoborane was simply oxidized to the alcohol, and no further chemistry has ever appeared on these or related organoboron intermediates.

We chose another convenient route to access the requisite boron reagents, permitting access to shelf-stable organotrifluoroborates. We recently reported the preparation of potassium β -alkoxyethyltrifluoroborates⁸ using an adaptation of Marder and Liu's conditions,⁹ wherein a Cu(I)-catalyzed borylation of the corresponding primary bromides was followed by treatment with KHF_2 to afford the target structures. The resulting organotrifluoroborates were subsequently used in Suzuki-Miyaura cross-coupling reactions. Based on the success of this approach, we studied an extension of this method to prepare potassium dioxolanylethyltrifluoroborates. Borylation of the commercially available 2-(2-bromoethyl)-1,3-dioxolane with bis(pinacolato)diboron using CuI and polymer-bound triphenylphosphine (PSPPh_3) as the catalytic system afforded the desired product in 69-75% yield (Scheme 2).

Once synthesized, this new trifluoroborate was tested in a Suzuki-Miyaura cross-coupling. Pleasingly, the reaction conditions developed for alkyloxyethyltrifluoroborates translated very well with this new substrate. Indeed, $\text{PdCl}_2\text{A}^{\text{t}}\text{Phos}_2$ ¹⁰ (5 mol %) and Cs_2CO_3 (3 equiv) in a mixture of toluene/ H_2O (4 : 1) at 100 °C in the presence of 1.1 equiv of the trifluoroborate for 14 h allowed the formation of 89% of the desired cross-coupled product **2a** when using 4-bromoanisole as electrophile (Table 1, entry 1). Halving the catalytic loading to 2.5 mol % still provided **2a** in a very acceptable 82% yield.

4-Chloroanisole was also reactive and resulted in the formation of the desired 2-(4-methoxyphenethyl)-1,3-dioxolane in 74% isolated yield. To examine the scope of the reaction, aryl chlorides became the focus of the investigation, as they tend to be more challenging than their bromide counterparts. However, when the chlorides failed to react, the corresponding bromides were employed as well. During the course of these studies, both electron-rich (Table 1, entries 1-7) and electron-poor (Table 1, entries 8-14) substrates proved to be efficient partners, providing the diversely substituted dioxolanylethylaryls with yields ranging from 38 to 90%. Substituents at the *ortho*, *meta* and *para*-positions were tolerated, as all 3 different anisole isomers reacted to give the desired products **2a-c** with good to excellent yields (Table 1, entries 1-3). Although the sterically hindered 2,6-dimethyl-4-methoxy-chlorobenzene did not react, the bromo derivative afforded the cross-coupled product **2d** in a promising 48% yield (Table 1, entry 4). A wide array of functional groups proved to be compatible in the process, including free or protected anilines (Table 1, entries 6, 7), nitriles (Table 1, entries 8, 9), aldehydes and ketones (Table 1, entries 11, 12), and fluoro and trifluoromethyl groups (Table 1, entries 13, 14).

Importantly, nitro groups are tolerated as well, providing access to products that were not accessible with the Negishi protocol reported by Cardenas *et al.*² Overall, *meta*-substituted electrophiles (Table 1, entries 3, 5 and 9) provide better yields. Protected amine substrates (entry 7) would appear to be preferred over the free amine counterparts (entry 6). The reaction was also tested on a larger scale (Table 1, entry 14), using a 1:1 trifluoroborate:electrophile ratio and lowering the catalyst loading to 1 mol %. This protocol provided access to the (4-fluorophenethyl)-1,3-dioxolane **2m** in a modest 38% yield.

To explore the scope of the method further, a variety of diverse heteroaryl halides were tested using the same set of conditions. Pyridine, quinoline, furan, thiophene and indole systems reacted well, providing the desired products **3a-f** with modest to excellent yields ranging from 44 to 93% (Table 2, entries 1-6). Although 2-chloropyrimidine did not react, yielding a mixture of the starting electrophile and the hydrolyzed trifluoroborate, the bromo analog afforded the expected dioxolanylethylpyrimidine **3g** in 74% yield (Table 2, entry 7).

In conclusion, a new trifluoroborate has been synthesized and successfully cross-coupled with a wide array of aryl and heteroaryl chlorides or bromides, providing easy and straightforward access to a large variety of dioxolanylethylaryl compounds. The method complements previously reported methods leading to the same substructures. This new sp³-sp² cross-coupling protocol, based on the reliability and versatility of organotrifluoroborates, allows the facile introduction of dioxolanylethyl moieties onto aryl and heteroaryl halides. After hydrolysis of the dioxolanyl moiety to the aldehyde group, further functionalisation is possible, including intramolecular transformations, allowing access to interesting polycyclic structures.¹¹

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Scheme 1.
Synthetic Methods Leading to Arylpropanal and the Corresponding 1,3-Dioxolane Species.

Scheme 2. Synthesis of Potassium Dioxolanylethyltrifluoroborate **1**.

Table 1Suzuki-Miyaura Cross-Coupling of Various Aryl Halides with Dioxolanylethyltrifluoroborate **1**^a

entry	electrophile	product	isolated yield (%)
1			89 (Br) 82 ^b (Br) 74 (Cl)
2			56
3			83
4			48 (Br) 0 ^c (Cl)
5			70
6			62
7			90
8			38 (Br) 82 (Cl)

entry	electrophile	product	isolated yield (%)
9			59
10			71 (Br) 55 (Cl)
11			50 ^d
12			68 ^d
13			69
14			38 ^e

^aReaction conditions: Aryl halide (1.0 equiv), organotrifluoroborate (1.1 equiv), $\text{PdCl}_2\text{A}^t\text{Phos}_2$ (5 mol %), Cs_2CO_3 (3.0 equiv), toluene/ H_2O (4:1, [] = 0.25 M), 100 °C, 14 h.

^bUsing 2.5 mol % catalyst.

^cA mixture of aryl chloride and boronic acid was recovered.

^dProduct contains up to 8 % impurity.

^eReaction performed on a 3 mmol scale using a 1 : 1 trifluoroborate/electrophile ratio and only 1 mol % Pd.

Table 2

Suzuki-Miyaura Cross-Coupling of Various Heteroaryl Halides with Dioxolanylethyltrifluoroborate **1**^a

entry	electrophile	product	isolated yield (%)
1			81
2			93
3			66
4			62
5			44
6			77
7			0 (Cl) 74 (Br)

^aReaction conditions: Heteroaryl halide (1.0 equiv), organotrifluoroborate (1.1 equiv), PdCl₂A^laPhos₂ (5 mol %), Cs₂CO₃ (3.0 equiv), toluene/H₂O (4:1, [] = 0.25 M), 100 °C, 14 h