

Cross-Coupling of Mesylated Phenol Derivatives with Potassium Alkoxyethyltrifluoroborates

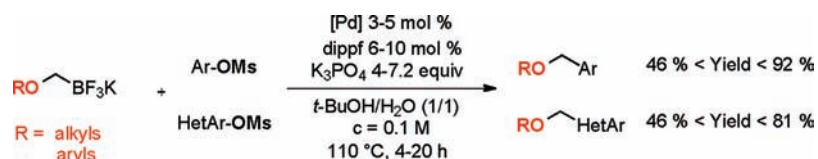
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ABSTRACT



Cross-coupling of mesylated phenol derivatives with various potassium alkoxyethyltrifluoroborates has been achieved. The corresponding aryl and heteroaryl alkoxyethyl compounds have been obtained with equal facility with both electron-rich and electron-poor substituents on the activated alcohol.

Ethers are encountered in a large variety of natural products including lipids, oxiranes, terpenoids, and carbohydrate derivatives.¹ They are known to be of interest in the pharmaceutical, agrochemical, and other industrial sectors. As an example, the quinolylmethoxyphenyl group is recognized as a pharmacophore in leukotriene inhibitors (Figure 1).² Ethers are also important in organic synthesis as protecting groups for alcohols.³

Cross-coupling reactions of alkoxyethylmetallic species, embodying a dissonant reactivity pattern, would represent one of the more straightforward approaches for the synthesis of these alkyl ether compounds. Unfortunately, this approach is somewhat restricted owing to the dearth of readily available reagents and because C_{sp²}-C_{sp³} cross-couplings are known to be quite challenging.⁴

Alkoxyethylstannanes were first reported as nucleophilic partners in the Stille reaction, but their use was limited because of their inherent toxicity and difficulties

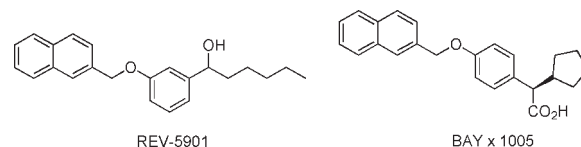


Figure 1. Leukotriene biosynthesis inhibitors.

associated with their purification.⁵ Recently, more environmentally sound alkoxyethylboron species have been employed in the Suzuki–Miyaura reaction to afford the same scaffolds. For example, methoxyethylboronic acid has been used in large excess (2.3 equiv) in the presence of chloro-1,8-naphthyridine to obtain the corresponding cross-coupled compound with a moderate yield of 45%.⁶ Prior to that report, our laboratory had efficiently synthesized and cross-coupled air- and moisture-stable potassium alkoxyethyltrifluoroborates with aryl halides in

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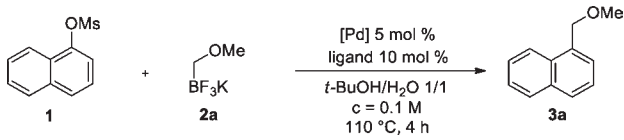
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Table 1. Optimization of the Conditions


| entry | [Pd] | ligand | conversion ^b | yield (%) ^b |
|----------------|--------------------------|---|-------------------------|------------------------|
| 1 ^a | Pd(OAc) ₂ | Cy ₃ PHBF ₄ | 23% | — |
| 2 | Pd(OAc) ₂ | <i>t</i> -Bu ₃ PHBF ₄ | 76% | — |
| 3 | Pd(OAc) ₂ | XPhos I | 43% | — |
| 4 ^a | Pd(OAc) ₂ | RuPhos II | 47% | — |
| 5 ^a | Pd(OAc) ₂ | SPhos III | 37% | — |
| 6 ^a | Pd(OAc) ₂ | DPEPhos IV | 39% | — |
| 7 | Pd(OAc) ₂ | Q-Phos V | 17% | — |
| 8 | Pd(OAc) ₂ | (<i>S</i>)-TolBinap VI | 23% | — |
| 9 | Pd(OAc) ₂ | dppm | 21% | <5 |
| 10 | Pd(OAc) ₂ | dppb | 18% | <5 |
| 11 | Pd(OAc) ₂ | dippf VII | 100% | 61 |
| 12 | PdCl ₂ (dppe) | — | 5% | — |
| 13 | PdCl ₂ (COD) | dippf | 100% | 75 (71) ^c |

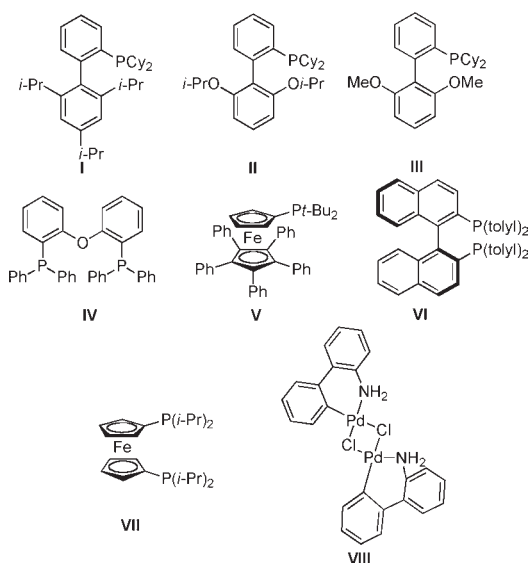
^aTime = 1 h. ^bRelative GC yield using dodecane as the internal standard. ^cIsolated yield.

high yields.⁷ That study was restricted to the use of aryl and heteroaryl chlorides and bromides but afforded the desired target structures in moderate to good yields without employing a large excess of the organoboron reagent.^{7a} Tanaka extended the scope of the reaction to an intramolecular Suzuki–Miyaura cross-coupling with sodium alkoxymethylaryltrifluoroborates bearing an attendant chloride.⁸ However, this method, carried out on a very small scale (0.10 mmol), suffered from a lack of generality, with yields ranging from 4 to 71%.

All of these previous reports employed halides as electrophilic partners, but to develop more environmentally sound processes, more attention is currently given to electrophilic alcohol derivatives.⁹ To our knowledge, no example employing these activating electrophilic partners

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**Figure 2.** Ligands (I–VII) and palladium dimer pre-catalyst VIII.

has been reported in cross-coupling reactions with any alkoxymethylmetallic species. Among all the sulfonated activating groups available, we focused our work on the methanesulfonyl (mesyl) counterpart, which has the advantages of being stable, inexpensive, atom-economical, and easy to handle, even though it is known to be among the least reactive of these nucleofugal species.^{9i,k,m,n,p} We disclose herein the first system for the C_{sp}²–C_{sp}³ Suzuki–Miyaura cross-coupling of aryl and heteroaryl mesylates with various potassium alkoxymethyltrifluoroborates.

Previous reports from our laboratory underscore the fact that the use of potassium trifluoroborates in the cross-coupling of C–O bonded species is facilitated by employing potassium phosphate as a base in a mixture of *t*-BuOH/H₂O (1/1).^{9i,p} Keeping these observations in mind, we screened different palladium and ligand sources with mesylated naphthalene **1** and potassium methoxymethyltrifluoroborate **2a**, a partner known to be difficult,¹⁰ as model substrates (Table 1). Various alkyl or biaryl (Figure 2) monodentate phosphines (including Buchwald ligands) have been tested without success. RuPhos (**II**), which was the best ligand when halides were used as electrophilic partners,^{7a} does not afford the desired compound **3a** (Table 1, entry 4). After extensive screening, only one (bidentate) ferrocenic ligand, dippf (**VII**), led to the formation of **3a** with a 61% GC yield (Table 1, entry 11). Different palladium sources were also tested, and PdCl₂(COD) appeared to be the best catalyst precursor, with **3a** obtained with complete conversion and 71% isolated yield after 4 h (Table 1, entry 13).

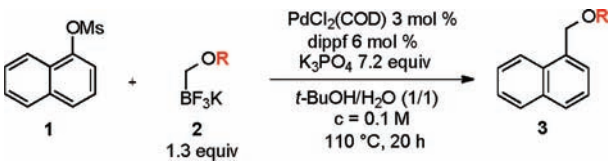
We then investigated the scope of this reaction by varying the nature of the potassium alkoxymethyltrifluoroborates

(10) The Suzuki–Miyaura cross-couplings between 4-chlorobenzonitrile or 4-chloroanisole and **2a** resulted in low yields of 34% and 41%, respectively.

2 in the presence of the mesylated naphthalene **1** (Table 2). All these nucleophiles **2** have first been prepared starting from the potassium chloromethyltrifluoroborate, instead of its corresponding bromo counterpart as earlier reported,^{7a} to avoid any KBr salt contamination.^{9p,11} It is important to note that, among them, some of the potassium alkoxymethyltrifluoroborates (**2b**, **2c**, **2f**, and **2i**) bear alcohol protecting groups (Table 2, entries 2, 3, 6 and 9) known to be stable under Suzuki–Miyaura reaction conditions but which can be easily removed to generate the corresponding hydroxymethyl group.

We applied the previously optimized conditions (Table 1, entry 13) to a broad spectrum of potassium alkoxymethyltrifluoroborates **2** (Table 2).

Table 2. Scope of Potassium Alkoxymethyltrifluoroborates



| entry | R | | | yield (%) |
|-------|--|-----------|-----------|----------------------|
| 1 | Me | 2a | 3a | 71 ^a |
| 2 | Bn | 2b | 3b | 82 (79) ^b |
| 3 | <i>t</i> -Bu | 2c | 3c | 87 |
| 4 | Cyclopentyl | 2d | 3d | 76 |
| 5 | Cyclopropyl-CH ₂ | 2e | 3e | 90 |
| 6 | TMS-CH ₂ -CH ₂ | 2f | 3f | 91 |
| 7 | CH ₃ (CH ₂) ₃ CH(CH ₃) | 2g | 3g | 79 |
| 8 | Menthyl | 2h | 3h | 72 ^c |
| 9 | PMB | 2i | 3i | 82 |

^a 5 mol % PdCl₂(COD), 10 mol % dippf, 110 °C, 4 h. ^b Reaction run on a 4 mmol scale using 2 mol % of PdCl₂(COD) and 4 mol % of dippf. ^c 5 mol % palladium precatalyst **VIII**, 10 mol % dippf, 4 equiv of K₃PO₄, 110 °C, 4 h.

The cross-coupling reaction is very tolerant of both acyclic and cyclic substituents on the alkoxymethyl counterpart: the desired compounds **3a–i** were obtained with yields ranging from 71% to 91%. The catalyst loading could be reduced significantly by scaling the reaction (Table 2, entry 2). Moreover, even on a small scale the catalyst and ligand loadings can be reduced to 3 and 6 mol %, respectively, for almost all the substrates by increasing the reaction time to 20 h. The potassium methoxymethyltrifluoroborate **2a** does not follow this trend, affording a lower yield of desired compound **3a**, perhaps because of decomposition

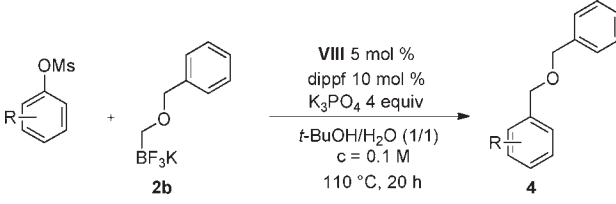
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under the reaction conditions. Of particular note, potassium phenoxymethyltrifluoroborate does not react well in the cross-coupling, as a complex mixture of compounds was formed in the reaction with naphthyl mesylate (**1**).

The introduction of the menthyl group (Table 2, entry 8) required the use of 5 mol % of catalyst for the reaction to go to completion and afforded **3h** with 65% yield. By switching the palladium source from PdCl₂(COD) to a palladium dimer precatalyst **VIII** developed by Buchwald (Figure 2) and reducing the amount of base to 4 equiv, we were able to increase the yield of **3h** to 72%.¹² This air-stable precatalyst is known to form the catalytically active species by cleavage of the dimer in favor of the ligand insertion under conditions where protodeboronation is slowed.¹³

We next pursued an examination of electron-rich and -poor aryl mesylates as electrophilic partners (Table 3). Encouraged by the previous result with the menthyl species

Table 3. Scope of Functionalized Aryl Mesylates



| entry | Ar-OMs | | yield (%) |
|-------|--------|-----------|-----------|
| 1 | | 4a | 92 |
| 2 | | 4b | 60 |
| 3 | | 4c | 78 |
| 4 | | 4d | 64 |
| 5 | | 4e | 77 |
| 6 | | 4f | 55 |
| 7 | | 4g | 67 |
| 8 | | 4h | 71 |
| 9 | | 4i | 69 |
| 10 | | 4j | 46 |

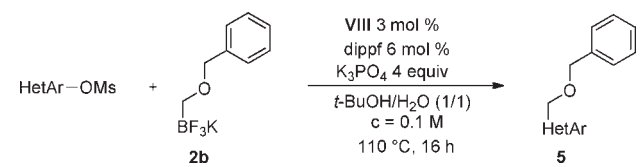
(Table 2, entry 8), we tested the two optimized conditions [PdCl₂(COD) versus palladium precatalyst **VIII** with 7.2 or 4 equiv of K₃PO₄, respectively], and it has been observed that almost all the yields increased by 10–15% by using the latter set of conditions. The reaction seems to proceed well without being influenced by the electronic density on the aryl ring, and the desired compounds **4a–j** can be obtained with yields up to 92%. Moreover, the reaction is compatible with a large variety of substituents such as ethers (**4b–d**), ketones (**4f–h**), and trifluoromethyl (**4i**) and nitrile (**4j**) groups (Table 3, entries 2–4, 6–10). It has also been noticed that purifying the compounds under basic alumina instead of silica gel increases almost all the yields by 10% (Table 3, entries 1, 3, 5–8, 10).

We further extended the scope of the reaction to more difficult heteroaryl mesylate partners (Table 4). It has already

been demonstrated that cross-couplings of heteroaryl halides with potassium alkoxymethyltrifluoroborates remains very challenging because of their lack of reactivity.^{7a} Using the least reactive electrophilic species, we were pleased to be able to couple several heteroaryl mesylates with moderate to good yields. Mesylated quinoline, dibenzothiophene, and isoquinoline provided the alkoxymethyl compounds **5a, d, e** with yields ranging from 57% to 81% (Table 4, entries 1, 4, and 5). To favor the completion of the reaction for the dibenzofuran and the benzothiazole, 5 mol % of precatalyst were used to afford **5b** and **5c** with 69% and 46% yields, respectively (Table 4, entries 2 and 3).

In summary, we have developed an efficient method that enables the cross-coupling of various potassium alkoxymethyltrifluoroborates with mesylated partners through C–O activation in very high yields. When desired, hydroxymethyl compounds should be easily accessed by following this procedure utilizing alkoxymethyl derivatives that are easily cleaved to the corresponding alcohol. A large array of functionalized aryl electrophilic partners has been successfully engaged in the cross-coupling to obtain the desired compounds with good yields. Moreover, several heteroaryl mesylates have also proven to be suitable electrophilic partners in this reaction even though the scope of the reaction is more limited. This method represents a complementary way to generate an alkoxymethyl linkage, which is known to be encountered in compounds of biological interest.

Table 4. Scope of Heteroaryl Mesylates



| entry | HetAr-OMs | | yield (%) |
|-------|-----------|-----------|-----------------|
| 1 | | 5a | 81 |
| 2 | | 5b | 69 ^a |
| 3 | | 5c | 46 ^a |
| 4 | | 5d | 68 |
| 5 | | 5e | 57 |

^a 5 mol % palladium precatalyst **VIII**, 10 mol % dippf.

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Supporting Information Available. Experimental procedures and spectral data. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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