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Expanded Substrate Scope and Improved Reactivity of Ether-forming Cross-Coupling Reactions of Organotrifluoroborates and Acetals

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Abstract

Mixed acetals and organotrifluoroborates undergo $\text{BF}_3 \cdot \text{OEt}_2$ promoted cross-couplings to give dialkyl ethers under simple, mild conditions. A survey of reaction partners identified a hydroxamate leaving group that improves the regioselectivity and product yield in the $\text{BF}_3 \cdot \text{OEt}_2$ -promoted coupling reaction of mixed acetals and potassium alkynyl-, alkenyl-, aryl- and heteroaryltrifluoroborates to access substituted dialkyl ethers. This leaving group enables reaction to proceed rapidly under mild conditions (0 °C, 5–60 min) and permits reactions with electron-deficient potassium aryltrifluoroborates that were less reactive with other acetal substrates. A study of the reaction mechanism and characterization of key intermediates by NMR and X-ray crystallography identified a role for the hydroxamate moiety as a reversible leaving group that serves to stabilize the key oxocarbenium intermediate and the need for a slight excess of organodifluoroborane to serve as a catalyst. A secondary role as an activating ligand for the boron nucleophile is also considered. These studies provide the basis for a general class of reagents that lead to dialkyl ethers by a simple, predictable cross-coupling reaction.

INTRODUCTION

The current practice of synthetic organic chemistry relies heavily on the use of general, predictable coupling reactions of preformed building blocks. This concept provides the framework for chemical peptide synthesis as well as the metal-catalyzed C–C bond-forming cross-coupling reactions that are highly valued in the discovery of new drugs and materials.¹ As just one example, the Suzuki-Miyaura coupling of boronic acids and organohalides has gone from an unknown reaction 30 years ago to one of the most widely used processes in drug discovery today.² To support this and related reactions, more than 4,500 boronic acids and their derivatives are now commercially available,³ along with hundreds of ligands to promote the coupling of ever more challenging and functionalized substrates.

New chemical transformations that offer similar generality and widespread applicability from readily available building blocks are of great interest to the chemical community. This factor makes the development of novel coupling reactions from available starting materials, particularly boronic acid derivatives, one of the most intensely studied areas of organic methodology development.⁴ In addition to constant improvement and more selective

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ASSOCIATED CONTENT

SUPPORTING INFORMATION Experiment procedures and characterization data for all new compounds are available free of charge via internet at <http://pubs.acs.org>.

variants of metal-catalyzed Suzuki-Miyaura couplings,⁵ oxidative Heck reactions,⁶ conjugate additions,⁷ and carbon-heteroatom cross-coupling,⁸ the past year has seen new methods using organoboranes including α -vinylation of aldehydes with potassium vinyltrifluoroborates,⁹ coupling of boronic acids with epoxides and N-acyliminium precursors,¹⁰ C-H arylation and alkylation with boronic acids,¹¹ and other exciting transformations with alkyltrifluoroborates.¹²

Despite the phenomenal success of metal-catalyzed cross-coupling reactions, several important types of chemical connectivities are currently not well served by the existing chemistries. Furthermore, metal-catalyzed cross-coupling reactions are often criticized for their reliance on expensive and toxic metals, particularly palladium.¹³ In seeking to provide alternative chemical methods that maintain the power and predictability of cross-coupling reactions and the use of stable, preformed starting materials, we have targeted the preparation of dialkyl ethers, a widespread moiety that is currently not readily prepared by modern synthetic methods.

Ethers are chemically and metabolically stable functional groups commonly found in bioactive molecules. Over 20 % of the top 200 small molecule pharmaceuticals and 75 % of new chemical entities contain at least one ether group (Chart 1).¹⁴ Despite this, ether-forming reactions are just limited to a few relatively harsh and unsavory methods, exemplified by the Williamson ether synthesis.¹⁵ A particularly challenging task is the preparation of substituted alkyl ethers, such as those formed from two chiral secondary or tertiary alcohols. This deficit in the canon of chemical structures arises from limitations of the known methods for ether synthesis, such as strongly basic Williamson ether synthesis. Tertiary and certain secondary ethers are usually prepared by S_N1-type reactions of unstabilized carbocations that are often plagued by low yields and the formation of side products.¹⁶ Recent research has led to a handful of new approaches, such as metal-catalyzed cross-couplings of alcohols¹⁷, and the coupling of alcohols with diazo-compounds and their precursors;¹⁸ however, these processes require high temperatures and have limited substrate scope. Although above new methods has improved the access to these compounds, general and mild cross-coupling approaches to ethers remain extremely limited.¹⁹

Following the pioneering work by Petasis on the 1,2-addition of alkenyl- and arylboronic acids to imines²⁰ and further complemented by outstanding related work including that of Batey,²¹ Langlois,²² and Raeppe,²³ the nucleophilic addition of organoboronic acid derivatives to oxocarbenium ion has gained much interest.²⁴ Furthermore, recent reports have shown that such reactions can be rendered enantioselective. In our own efforts, we recently reported a cross-coupling strategy for the preparation of dialkyl ethers by the BF₃•OEt₂-promoted reaction of potassium organotrifluoroborates and *O*-MOM acetals (Scheme 1).²⁵ Both starting materials are readily available: many potassium organotrifluoroborates are commercially available²⁶ and *O*-MOM acetals are easily prepared from alcohols under mild conditions.²⁷ In the presence of BF₃•OEt₂, an inexpensive and easily handled Lewis acid, these two components undergo a regioselective coupling to give ethers. Alkynyl, aryl, and vinyl boronates were suitable substrates and the chemistry could be extended to substituted acetals that lead to secondary–secondary ethers.

Although pleased with the success and simplicity of this process, we noted several limitations of this first generation approach. First, as the substrates became more substituted the regiochemistry of the reaction eroded, leading to the formation of undesired side products. Second, a relatively large excess of potassium organotrifluoroborate and BF₃•OEt₂ along with a precomplexation step were required. Third, even modestly electron-deficient aryltrifluoroborates were poor substrates and heteroaryltrifluoroborates did not react. In this article, we describe further studies on the substrate scope, mechanism, and reactivity

patterns of this reaction. Most importantly, these studies have led to the identification of a new acetal reaction partner that offers superior reactivity and improved substrate scope using near equimolar ratios of reactants and reagents (Scheme 1).

RESULTS AND DISCUSSION

The primary goals of our continued research were the identification of conditions and reagents that 1) improved the regioselectivity of challenging substrates; 2) allowed for the use of more electron-deficient aryltrifluoroborates, and 3) reduced the requirement for a large excess of potassium organotrifluoroborate and Lewis acid. A brief survey of alternative Lewis acids and reaction conditions did not offer a general solution to our more challenging substrates and the addition of transition metals did not address the regiochemical issues.²⁵ We therefore turned to optimization of the leaving group in the hope of identifying a more robust and operationally-friendly process.

1. Screening of leaving groups

In our initial report, various dialkyl ethers were formed via $\text{BF}_3 \cdot \text{OEt}_2$ promoted coupling of *O*-MOM acetals with potassium aryl-, alkenyl-, or alkynyltrifluoroborates. Reactions proceeded best with alkynyltrifluoroborates, less efficiently with alkenyl- or aryltrifluoroborates and not at all with heteroaryl- and alkyltrifluoroborates. Moderate or low yields were observed with more hindered examples such as secondary-secondary acetals. In some cases, methyl ether side products were observed and the formation of these side products significantly increased when alkenyl- or aryltrifluoroborates or more hindered acetal substrates were used. Likewise, the use of mixed acetals of more acidic alcohols, such as the synthetically important phenol derivatives, led to diminished or completely reversed regioselectivity (eq 1).

(1)

In order to improve the reactivity, selectivity and substrate scope of this ether-forming cross-coupling reaction, we investigated alternative leaving groups (OY in Table 1). The coupling reaction of potassium phenyltrifluoroborate with unsymmetrical acetals of cyclohexanol, which can be easily prepared from commercially available cyclohexyl chloromethyl ether²⁸ or directly from cyclohexanoxyl-MOM via procedure developed by Fujioka et al.,²⁹ was chosen as a model reaction.

Our initial report indicated that a chelating leaving group (i.e., *O*-methoxyethoxymethyl – *O*-MEM) was not beneficial compared to the *O*-MOM, but we reinvestigated this strategy by designing several unsymmetrical acetals capable of chelation (Figure 1 and Table 1, entries 2–5).³⁰ As expected, acetal **1b** (Y = methoxyethyl) gave similar results compared to **1a** (entry 2). In contrast, acetal derivatives of glycolic acid **1c** and **1d** gave a higher yield than **1a** with no side product observed (entries 3, 4). Acetal **1e** (Y = 2-pyridinylmethyl) also gave an excellent yield (entry 5). Based on our observed reactivity of *O*-MOM acetal of phenol (eq 1), we anticipated that phenolic leaving groups would also provide improved regioselectivity in simple cases. Indeed, the reaction of acetal **1f** (OPh) gave no side product (entry 6) but did not improve the reaction yield. In an attempt to maintain the electronic properties of the phenol while offering a site of chelation, we tested acetal **1g**; no side

product was observed, but the yield was not improved (entry 7). We turned to *N*-hydroxylated derivatives (entries 8, 9), which have similar acidity as phenol while offering improved chelation of the Lewis acid, and were pleased to observe excellent yield with hydroxamic acid-derived acetal **1i** (entry 9).

We further evaluated the leaving groups for improving the outcome of the reactions with various potassium organotrifluoroborates using a screen of selected potassium alkynyl-, alkenyl-, heteroaryl-, and alkyltrifluoroborates (Table 2). Both the 2-hydroxymethylpyridine and *N*-hydroxy-*N*-methylacetamide leaving groups (**1e** and **1i**, respectively) gave superior results in terms of reactivity, chemical yield, and regioselectivity. In both cases, no side product was detected. A heteroaryltrifluoroborate salt yielded the desired product, albeit in lower yield. An alkyl derivative gave only recovered starting materials or deprotected alcohol. Based on these results, we chose to further optimize the hydroxamic acid-derived acetals. These acetals not only provided the best yields with different nucleophiles, but also should be electronically and sterically tunable by changing the substituents, facilitating further optimization of this reaction involving weaker nucleophiles or hindered acetals.

2. Optimization of reaction conditions

In our earlier report, it was necessary to premix an excess amount of potassium organotrifluoroborates (4.0 equiv) with $\text{BF}_3 \cdot \text{OEt}_2$ (4.0 equiv) in an appropriate solvent prior to the addition of acetals with sp^2 -hybridized nucleophiles. Typically, the cross-coupling required 2 h at 23 °C, while the existence of excess nucleophiles for a relatively long time at this temperature could affect the functional group tolerance of this method. With the hydroxamate leaving group, reactions occurred without the requirement of precomplexation or excess nucleophile (Table 3, entries 5, 6). With 2.0 equiv of nucleophile, the reactions were completed within minutes at 0 °C. Using 1.2 equiv each of the nucleophile and $\text{BF}_3 \cdot \text{OEt}_2$ also delivered the desired product in excellent yield with somewhat longer reaction times.

3. Substrate scope

To examine the scope of the cross-coupling reaction of potassium organotrifluoroborates, we evaluated their reactivity with *N*-(cyclohexyloxymethoxy)-*N*-methylacetamide (acetal **1i**) (Table 4) under the standard conditions. With the *O*-MOM derivatives, the use of halogenated potassium aryltrifluoroborates proved problematic. In contrast, the hydroxamic acid-derived acetals delivered the desired ethers in good to excellent yields (**3f–3i**). Reactions were less efficient with *ortho* substituted aryl nucleophiles (**3j**). Despite the Lewis acid used in the reaction, carbonyl functional groups such as ketones and esters were tolerated (**3l**, **3m**). Reactions also occurred in good yields with oxygen- and sulfur-containing heteroaryltrifluoroborates (**3n–3p**). Currently, nitrogen-containing heteroaryltrifluoroborates do not afford the desired products and give acetal deprotection as the major product. For maximum efficiency, premixing of the heteroaryltrifluoroborates and $\text{BF}_3 \cdot \text{OEt}_2$ is recommended. Potassium alkenyltrifluoroborates gave mixed results; reactions worked well with *trans* disubstituted alkene (**3c**, **3q**) but were inefficient with other substitution patterns (**3r**, **3s**).

The advantages of the hydroxamate leaving group are most clearly seen by a direct comparison to reactions performed using the *O*-MOM group. In all cases, superior results were obtained (Table 5). It should be noted that all of these examples were performed under the same reaction conditions without individual optimization; higher yields for some of these results can be expected following tailoring of the reaction parameters. These results also demonstrate that the reaction is not limited to primary ethers; the ethers of two secondary alcohols can also be formed in good yields.

In an effort to understand the success of this reaction, as well as to support our continued development of this transformation and related reactions, mechanistic investigations were undertaken. In particular, we aimed to explain the reason for hydroxamic acid-derived acetals giving better regioselectivity and better yield, and gain insight into the reaction pathway.

We hypothesized that the actual nucleophile in the reaction cleophilicity of the organoborane. This could explain both the was the hydroxymate complexed organodifluoroborane **VI** and higher reactivity as well as the much faster reaction times. It that the hydroxymate ligand played a role in increasing the nu- would also provide a powerful platform for further refinement of the substrates and a novel mode of activating organotrifluoroborates for nucleophilic additions.

Attempts to employ ($\pm$) **7** as a nucleophile without additional reagents failed with several electrophiles. Mixed acetals gave no product when ($\pm$) **7** was added alone, although full conversion was observed in the presence of $\text{BF}_3 \cdot \text{OEt}_2$ (eq 3). We believe

that in this case the $\text{BF}_3 \cdot \text{OEt}_2$ serves to activate the hydroxamate to generate the oxocarbenium ion, which is trapped by phenyl transfer from ($\pm$) **7**. Attempts to add ($\pm$) **7** to more reactive electrophiles including benzaldehyde, acetylchloride, and Meerwein salt gave no products.

Crossover experiments with boron complex—An alternative, or possibly complimentary, explanation for the improvements offered by the hydroxamate leaving group is the improved stabilization of the oxocarbenium ion intermediate, which we postulated could be achieved by its reversible formation. This hypothesis was examined by three experiments. First, a reaction of *O*-MOM cyclohexanol **1a** in the presence of both the phenylboron hydroxamate complex ($\pm$) **7** and phenyldifluoroborane **6** was performed to look for incorporation for formation of acetal **1i**, which would be indicative of the reversibility of oxocarbenium ion generation. Indeed, by quenching the reaction prior to completion (5 min at 0 °C), we observed significant amounts of **1i** (eq 4).

This postulate was confirmed by an experiment in which two structurally different hydroxamic acid-derived acetals with similar reactivity were used as starting materials. By quenching the reaction prior to completion (5 min at 0 °C), we observed acetals **1j** and **8'** as crossover products (eq 5). This experiment again demonstrated that oxocarbenium ion formation is reversible. As a control reaction, we also confirmed that the product ethers were stable to the reaction conditions and that crossover products were not being formed by fragmentation of the ether products (eq 6).

^1H NMR study on the reaction mechanism—Further studies on the reaction mechanism were performed by ^1H NMR analysis of the reaction mixtures using different ratios of acetal **1i** and organodifluoroborane **6**. If the reaction proceeded via the proposed mechanism (Scheme 2), maximum yield should be observed in case A, B, and C; 50 % and 10 % of maximum yield should be observed in case D and E, respectively. However, the maximum yield was not observed without the excess phenyldifluoroborane (case C); only 12 % product yield was formed

(4)

(5)

(6)

in case D; and no product formation was observed in case E. The reaction was also faster when excess phenyldifluoroborane was used.

The results indicated that an excess amount of phenyldifluoroborane **6** was necessary for the reaction to go to completion and achieve the maximum yield.³² It is possible that the excess phenyldifluoroborane is involved in promoting oxocarbenium ion and complex **7** formation via fluoride abstraction. To test this hypothesis, additional ^1H NMR experiments were performed. A catalytic amount of alkyl difluoroborane **10**, which was known not to transfer the alkyl group, was added (Scheme 4, **G**). This “unreactive” alkyl difluoroborane would serve to abstract the fluoride. Identical results were obtained with either 1.2 equiv **6** or 1.0 equiv **6** and 0.2 equiv **10** confirming that the role of excess organodifluoroborane is to serve as a catalyst.

Based on the above data, we propose a revised mechanism for this transformation (Scheme 5). The interaction of potassium organotrifluoroborate and $\text{BF}_3\cdot\text{OEt}_2$ produces organodifluoroborane **B** and potassium tetrafluoroborate. This organodifluoroborane **B** serves as a Lewis acid and binds to the hydroxamate moiety. Abstraction of a second fluoride by the excess organodifluoroborane **D** opens a coordination site on the boron atom that is quickly occupied by oxygen lone pair to form the 5-membered ring complex **G**. This complex dissociates reversibly to form oxocarbenium ion **H** and boron complex **I**. Either complex **I** or organotrifluoroborate ion **F** could serve as the reactive nucleophile to transfer the R^3 to **H** and deliver irreversibly dialkyl ether **K**. Both possible nucleophiles are ate-complexes and further studies to evaluate their relative nucleophilicities are ongoing.

CONCLUSION

In summary, we have developed an improved approach to ether-forming cross-coupling reactions in which hydroxamic acid-derived acetals couple with available organotrifluoroborates to form dialkyl ethers with excellent regioselectivity in good to excellent yields and functional group tolerance. Isolation of a likely key intermediate, combined with crossover and control experiments provided insight into the mechanism, also providing an explanation for the superiority of the hydroxamate leaving group compared to our first generation approach.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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32. See Supporting Information for detailed results on percentage of conversion and product yield of experiments.

Figure 1.

Figure 2.

Crystal structure of ($\pm$)7. Ellipsoids include 50 % of the electron density. Two enantiomers occupy the same position in the crystal with the ratio 0.53:0.47 leading to the disordered positions of C7 and N13 in the 5-membered ring.

Initial work:

1. Observed side product (methyl ether product)
2. Efficiency: $\text{R}^3 = \text{alkynyl} > \text{alkenyl, aryl} > \text{halogenated aryl}$.
Does not work with heteroaryl, alkyl

This work:

1. Excellent regioselectivity
2. Efficiency: $\text{R}^3 = \text{alkynyl} > \text{alkenyl, aryl, halogenated aryl} > \text{heteroaryl}$

Scheme 1.

Cross-coupling reactions of potassium organotrifluoroborates and acetals

Scheme 3.¹H NMR experiment

All experiments were performed on 0.07 mmol scale in 1.0 mL CD₂Cl₂. Product yield was measured using ¹H NMR integration against internal standard peak.

Scheme 4.

Coupling reactions with catalytic organodifluoroborane.

All experiments were performed on 0.07 mmol scale in 1.0 mL CD₂Cl₂. Product yield was measured using ¹H NMR integration against internal standard peak.

Scheme 5.
Revised mechanism for ether-forming cross coupling reactions.

Chart 1.
Selected bioactive ethers

Table 1

Screening of leaving group

$\text{1 (1.0 equiv)} + \text{2a (4.0 equiv)} \xrightarrow[\text{CH}_2\text{Cl}_2, 23\text{ }^\circ\text{C}, 2\text{h}]{\text{BF}_3 \cdot \text{OEt}_2 (4.0\text{ equiv})} \text{3a} + \text{4}$

entry	acetal 1	yield ^a 3a(%)	ratio 3a:4 ^b
1	 1a	74	6:1
2	 1b	74	4:1
3	 1c	79	1:0
4	 1d	85	1:0
5	 1e	85	1:0
6	 1f	61	1:0
7	 1g	66	1:0
8 ^c	 1h	68	1:0
9	 1i	90	1:0

All reactions were performed on a 0.2 mmol scale with pre-mixed $\text{BF}_3 \cdot \text{OEt}_2$ (0.8 mmol) and PhBF_3K (0.8 mmol) followed by the addition of the acetal (0.2 mmol).

^a Isolated yield after chromatography.

^b determined by ^1H NMR integration

^c The reaction was performed at 40 °C for 90 min.

Table 2

Coupling reactions of various mixed acetals and potassium organotrifluoroborates

$\text{1 (1.0 equiv)} + \text{2 (4.0 equiv)} \xrightarrow[\text{CH}_2\text{Cl}_2, 0 \rightarrow 23^\circ\text{C}, 1 \rightarrow 2\text{h}]{\text{BF}_3 \cdot \text{OEt}_2 (4.0 \text{ equiv})} \text{3} + \text{4}$

$\text{OY} = \text{OMe (1a)}, \text{OCH}_2\text{N (1e)}, \text{O-N(Me)C(=O)Me (1i)}$

entry	R	1a % yield 3^a (3:4) ^b	1e % yield 3^a (3:4) ^b	1i % yield 3^a (3:4) ^b
1		74 (6:1)	85 (1:0)	90 (1:0)
2		84 (14:1)	100 (1:0)	100 (1:0)
3		58 (6:1)	85 (1:0)	91 (1:0)
4		— ^c	28 (1:0)	20 (1:0)
5		— ^c	— ^c	— ^c

All reactions were performed on a 0.2 mmol scale with pre-mixed $\text{BF}_3 \cdot \text{OEt}_2$ (0.8 mmol) and RBF_3K (0.8 mmol) followed by the addition of acetal (0.2 mmol).

^a Isolated yield after chromatography.

^b ratio determined by ^1H NMR integration.

^c not detected.

Table 3

Optimization of acetal (1i) and potassium phenyltrifluoroborate (2b) coupling reaction

Reaction scheme: Acetal 1i (a cyclohexane ring with a -CH2OCH2C(=O)NMe group) reacts with potassium phenyltrifluoroborate 2b (Ph-BF₃K) in the presence of BF₃·OEt₂ and CH₂Cl₂ to form product 3b (a cyclohexane ring with a -CH2OCH2Ph group).

entry	Precomplexation	2b (equiv)	BF ₃ ·OEt ₂ (equiv)	temp (°C)	time (min)	yield ^a (%)
1	!!	4.0	4.0	23	120	87
2	+	4.0	4.0	0	5	90
3	+	4.0	4.0	-40	120	nr
4	+	4.0	4.0	-78	120	nr
5	+	2.0	2.0	0	5	97
6	+	1.2	1.2	0	150	97
7	+	1.2	cat.	0	120	nr

All reactions were performed on a 0.2 mmol scale.

^a Isolated yield after chromatography. nr: no reaction.

Table 4

Substrate scope for acetal (1i) and potassium organotrifluoroborates (2) coupling reaction

All reactions were performed on a 0.2 mmol scale by adding $\text{BF}_3 \cdot \text{OEt}_2$ (2.0 equiv) into a suspension of acetal (1.0 equiv) and RBF_3K (2.0 equiv). Isolated yield were calculated after chromatography.

^a premixed $\text{BF}_3 \cdot \text{OEt}_2$ (4.0 equiv) and RBF_3K (4.0 equiv) followed by addition of acetal.

^c not detected.

Table 5

Direct comparison of hydroxamic acid-derived acetals and MOM derived acetals

Procedure A		Procedure B	
 A: 85 % yield B: 77 % yield	 A: 61 % yield B: 56 % yield	 A: 61 % yield B: 45 % yield	 A: 95 % yield B: 52 % yield
 A: 79 % yield B: 57 % yield	 A: 62 % yield B: 37 % yield	 A: 72 % yield B: 64 % yield	 A: 47 % yield B: 37 % yield
 A: 97 % yield B: 44 % yield	 A: 20 % yield B: 9 % yield	 A: 41 % yield B: 0 % yield	
 A: 97 % yield B: 74 % yield	 A: 99 % yield B: 84 % yield	 A: 91 % yield B: 58 % yield	 A: 20 % yield B: 0 % yield

Procedure A: $\text{BF}_3 \cdot \text{OEt}_2$ (0.4 mmol) was added into suspension of acetal (0.2 mmol) and $\text{R}^3\text{BF}_3\text{K}$ (0.4 mmol) in solvent at 0 °C. Isolated yield was calculated after chromatography. **Procedure B:** solution of acetal (0.5 mmol) was added into a premixed suspension of $\text{BF}_3 \cdot \text{OEt}_2$ (2.0 mmol) and $\text{R}^3\text{BF}_3\text{K}$ (2.0 mmol) in solvent. Isolated yield was calculated after chromatography.