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

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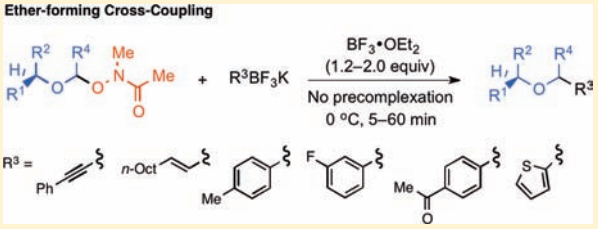
Supporting Information

ABSTRACT: Mixed acetals and organotrifluoroborates undergo $BF_3 \cdot OEt_2$-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 $BF_3 \cdot OEt_2$-promoted coupling reaction of mixed acetals and potassium alkynyl-, alkenyl-, aryl- and heteroaryltrifluoroborates to access substituted dialkyl ethers. This leaving group enables the reaction to proceed rapidly under mild conditions (0 °C, 5−60 min) and permits reactions with electron-deficient potassium aryltrifluoroborates that are less reactive with other acetal substrates. A study of the reaction mechanism and characterization of key intermediates by NMR spectroscopy 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 for the boron nucleophile as an activating ligand was 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 4500 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 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 the introduction of new methods that use 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 connectivies 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 currently cannot be readily prepared using 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 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

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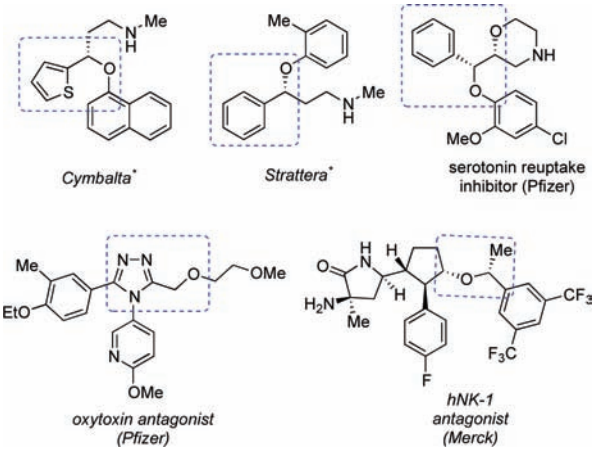
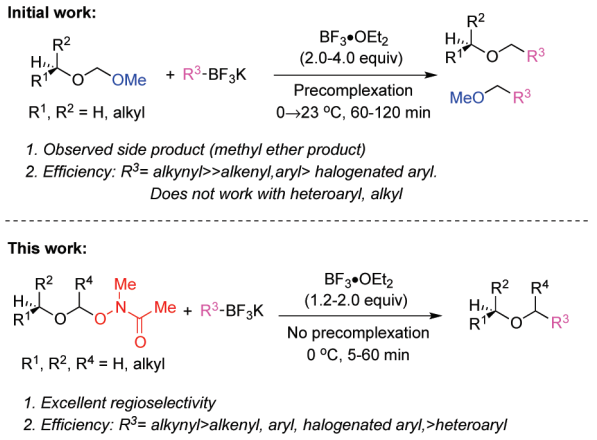
Chart 1. Selected Bioactive Ethers



Scheme 1. Cross-Coupling Reactions of Potassium Organotrifluoroborates and Acetals



as metal-catalyzed cross-couplings of alcohols[17] and the coupling of alcohols with diazo compounds and their precursors;[18] however, these processes require high temperatures and have limited substrate scope. Although the above new methods have improved the access to these compounds, general and mild cross-coupling approaches to ethers remain extremely limited.[19]

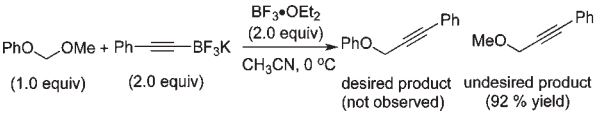
Following the pioneering work by Petasis on the 1,2-addition of alkenyl- and arylboronic acids to imines[20] and further complemented by outstanding related work, including that of Batey,[21] Langlois,[22] and Raeppel,[23] the nucleophilic addition of organoboronic acid derivatives to oxocarbenium ions has gained much interest.[24] Furthermore, recent reports have shown that such reactions can be rendered enantioselective.[25] In our own efforts, we recently reported a cross-coupling strategy for the preparation of dialkyl ethers by the $BF_3 \cdot OEt_2$-promoted reaction of potassium organotrifluoroborates and *O*-methoxymethyl (*O*-MOM) acetals (Scheme 1 top).[26] Both starting materials are readily available: many potassium organotrifluoroborates are commercially available,[27] and *O*-MOM acetals are easily prepared from alcohols under mild conditions.[28] In the presence of $BF_3 \cdot OEt_2$, an inexpensive and easily handled Lewis acid, these two components undergo a regioselective coupling to give ethers. Alkynyl-, aryl-, and alkenylboronates were found to be suitable substrates, and the chemistry could be extended to substituted acetals, leading 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 $BF_3 \cdot OEt_2$ 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 of 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 nearly equimolar ratios of reactants and reagents (Scheme 1 bottom).

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 aryltrifluoborates, 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.[26] 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 $BF_3 \cdot OEt_2$-promoted coupling of *O*-MOM acetals with potassium aryl-, alkenyl-, or alkynyltrifluoroborates. The reaction 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).

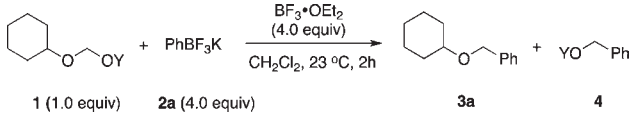


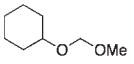
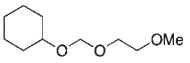
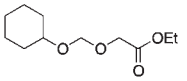
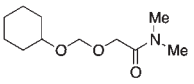
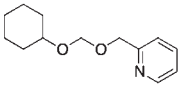
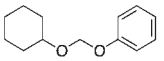
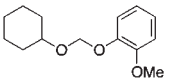
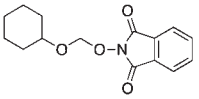
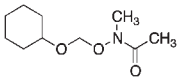
(1)

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 easily be prepared from commercially available cyclohexyl chloromethyl ether[29] or directly from cyclohexanoxyl-MOM via a procedure developed by Fujioka et al.,[30] was chosen as a model reaction.

Our initial report indicated that using a chelating protecting group [i.e., *O*-methoxyethoxymethyl (*O*-MEM)] instead of *O*-MOM was not beneficial, but we reinvestigated this strategy by designing several unsymmetrical acetals capable of chelation (Figure 1

Table 1. Screening of Leaving Groups[a]



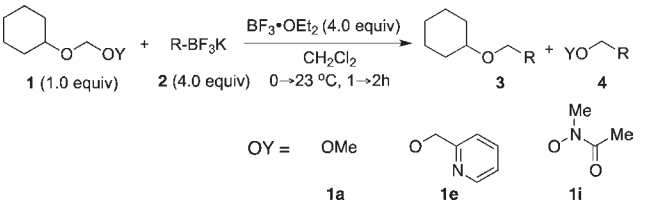
entry	acetal **1**		yield[b] **3a**(%)	ratio **3a**:**4**[c]
1		**1a**	74	6:1
2		**1b**	74	4:1
3		**1c**	79	1:0
4		**1d**	85	1:0
5		**1e**	85	1:0
6		**1f**	61	1:0
7		**1g**	66	1:0
8[d]		**1h**	68	1:0
9		**1i**	90	1:0

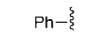
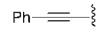
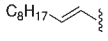
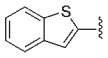
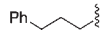
[a] All reactions were performed on a 0.2 mmol scale using premixed $BF_3 \cdot OEt_2$ (0.8 mmol) and $PhBF_3K$ (0.8 mmol), to which the acetal (0.2 mmol) was added. [b] Isolated yields after chromatography. [c] Determined by ^1H NMR integration. [d] The reaction was performed at 40 °C for 90 min.

Figure 1

and Table 1, entries 2−5).[31] As expected, acetal **1b** (Y = methoxyethyl; entry 2) gave results similar to those for **1a** (entry 1). In contrast, acetal derivatives of glycolic acid, **1c** and **1d**, gave higher yields than **1a**, and no side product was observed (entries 3 and 4). Acetal **1e** (Y = 2-pyridinylmethyl) also gave an excellent yield (entry 5). On the basis of the observed reactivity of the *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** (Y = Ph) 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 then turned to N-hydroxylated derivatives (entries 8 and 9), which have similar acidity as phenol but offered improved chelation of the Lewis acid, and we were pleased to observe an excellent yield with hydroxamic acid-derived acetal **1i** (entry 9).

Table 2. Coupling Reactions of Various Mixed Acetals and Potassium Organotrifluoroborates[a]



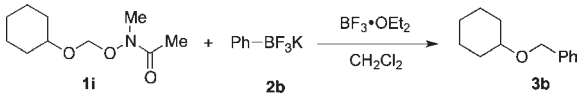
entry	R		**1a** % yield **3**[b] (**3**:**4**)[c]	**1e** % yield **3**[b] (**3**:**4**)[c]	**1i** % yield **3**[b] (**3**:**4**)[c]
1		**2a**	74 (6:1)	85 (1:0)	90 (1:0)
2		**2b**	84 (14:1)	100 (1:0)	100 (1:0)
3		**2c**	58 (6:1)	85 (1:0)	91 (1:0)
4		**2d**	—[d]	28 (1:0)	20 (1:0)
5		**2e**	—[d]	—[d]	—[d]

[a] All reactions were performed on a 0.2 mmol scale with premixed $BF_3 \cdot OEt_2$ (0.8 mmol) and RBF_3K (0.8 mmol), to which the acetal (0.2 mmol) was added. [b] Isolated yields after chromatography. [c] Determined by ^1H NMR integration. [d] Not detected.

We further evaluated the leaving groups with respect to 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 (i.e., acetals **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. On the basis of 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 through changes in the substituents, facilitating further optimization of this reaction for weaker nucleophiles or hindered acetals.

2. Optimization of the Reaction Conditions. In our earlier report, it was necessary to premix an excess amount of potassium organotrifluoroborate (4.0 equiv) with $BF_3 \cdot OEt_2$ (4.0 equiv) in an appropriate solvent prior to the addition of the acetal in the case of sp^2-hybridized nucleophiles. Typically, the cross-coupling required 2 h at 23 °C, while the existence of excess nucleophile 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 and 6). With 2.0 equiv of nucleophile, the reactions were completed within minutes at 0 °C. Using 1.2 equiv each of the nucleophile

Table 3. Optimization of the Coupling Reaction of Acetal 1i and Potassium Phenyltrifluoroborate (2b)[a]



entry	Precomplexation	2b (equiv)	BF_3•OEt_2 (equiv)	temp (°C)	time (min)	yield[b] (%)
1	yes	4.0	4.0	23	120	87
2	no	4.0	4.0	0	5	90
3	no	4.0	4.0	−40	120	nr
4	no	4.0	4.0	−78	120	nr
5	no	2.0	2.0	0	5	97
6	no	1.2	1.2	0	150	97
7	no	1.2	cat.	0	120	nr

[a] All reactions were performed on a 0.2 mmol scale. [b] Isolated yields after chromatography (nr = no reaction).

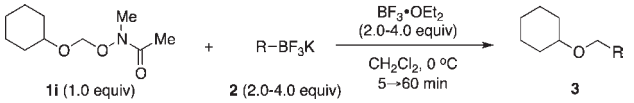
and $BF_3 \cdot OEt_2$ also delivered the desired product in excellent yield with a somewhat longer reaction time.

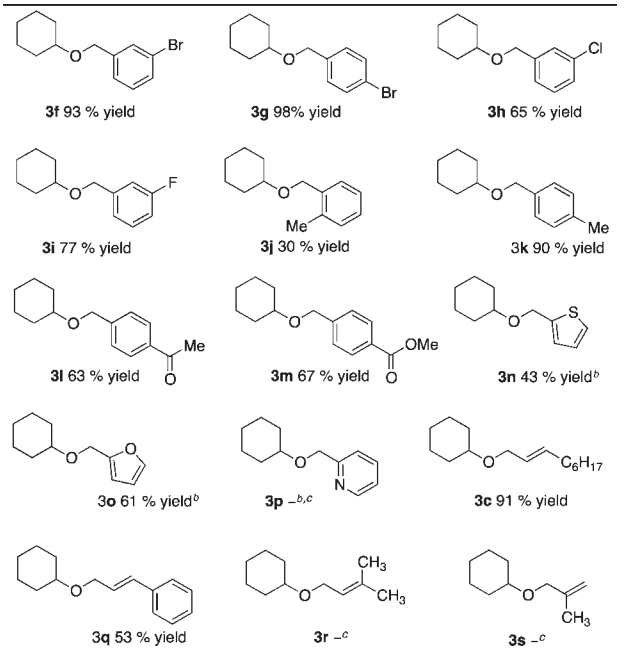
3. Substrate Scope. To examine the scope of the cross-coupling reaction with respect to potassium organotrifluoroborates, we evaluated their reactivities with acetal **1i** (Table 4) under the standard conditions. With the *O*-MOM derivatives, the use of halogenated potassium aryltrifluoroborates proved to be problematic. In contrast, the hydroxymic acid-derived acetal delivered the desired ethers (**3f**−**i**) in good to excellent yields. The reaction was 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** and **3m**). The reaction also gave good yields with oxygen- and sulfur-containing heteroaryltrifluoroborates (**3n**−**p**). Currently, nitrogen-containing heteroaryltrifluoroborates do not afford the desired products, instead giving acetal deprotection as the major product. For maximum efficiency, premixing of the heteroaryltrifluoroborate and $BF_3 \cdot OEt_2$ is recommended. Potassium alkenyltrifluoroborates gave mixed results; reactions worked well with trans-disubstituted alkenes (**3c** and **3q**) but were inefficient with other substitution patterns (**3r** and **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 could be expected following tailoring of the reaction parameters. These results also demonstrate that the reaction is not limited to primary ethers, as the ethers of two secondary alcohols were also formed in good yields.

4. Mechanistic Investigations. 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 why hydroxamic acid-derived acetals give better regioselectivity and better yield and to gain insight into the reaction pathway.

Table 4. Substrate Scope for the Coupling Reaction of Acetal 1i and Potassium Organotrifluoroborates 2[a]





[a] All reactions were performed on a 0.2 mmol scale by adding $BF_3 \cdot OEt_2$ (2.0 equiv) to a suspension of acetal (1.0 equiv) and RBF_3K (2.0 equiv). Isolated yields were calculated after chromatography. [b] The acetal was added to premixed $BF_3 \cdot OEt_2$ (4.0 equiv) and RBF_3K (4.0 equiv). [c] Not detected.

We previously confirmed that the role of $BF_3 \cdot OEt_2$ in the reaction is to abstract a fluoride atom from the organotrifluoroborate (**II** in Scheme 2) to generate organodifluoroborane **III**.[26] The improved regioselectivity of the hydroxamic acid-derived acetals in comparison with the *O*-MOM variants can be attributed to preferential binding of the hydroxamate to the organodifluoroborane. This observation, however, did not fully explain the considerable improvements in substrate scope and reactivity of the potassium organotrifluoroborates.

We hypothesized that the actual nucleophile in the reaction is hydroxamate-complexed organodifluoroborane **VI** and that the hydroxamate ligand plays a role in increasing the nucleophilicity of the organoborane. This could explain both the higher reactivity and the much higher reaction rate. It would also provide a powerful platform for further refinement of the substrate and a novel mode of activating organotrifluoroborates for nucleophilic additions.

To test this hypothesis, we sought to independently prepare the postulated species **VI**. Remarkably, we found that very similar compounds had been previous prepared by Stolowitz and Kliegel;[32] this paved the way for a facile approach to the synthesis. Treatment of preformed phenyldifluoroborane (**6**) with *N*-methyl-*N*-(trimethylsilyloxy)acetamide (**5**) in dichloromethane at 23 °C (eq 2) delivered a colorless crystal whose

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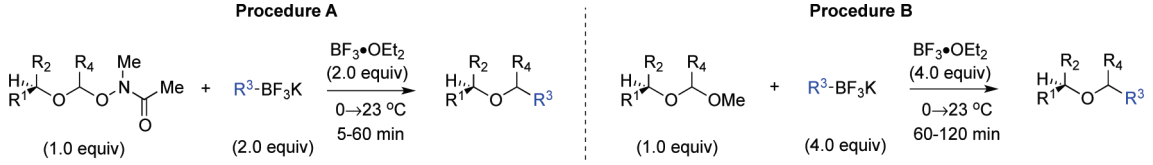
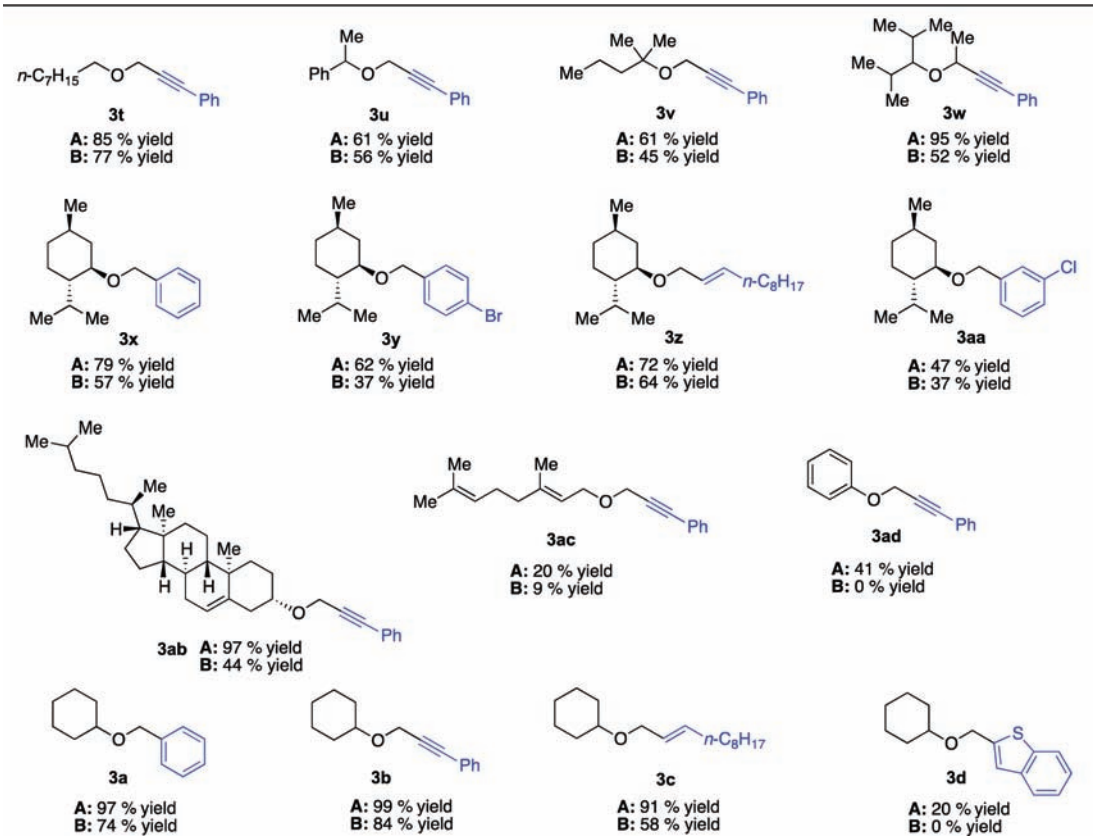
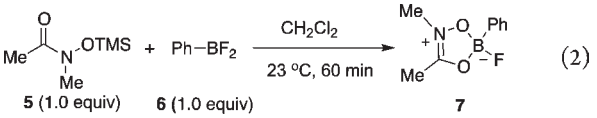
Table 5. Direct Comparison of Hydroxamic Acid-Derived and MOM-derived Acetals[a]





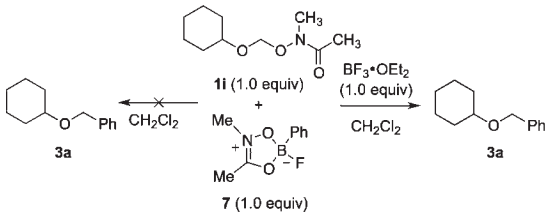
[a] Procedure A: $BF_3 \cdot OEt_2$ (0.4 mmol) was added to a suspension of acetal (0.2 mmol) and R^3BF_3K (0.4 mmol) in solvent at 0 °C. The isolated yield was calculated after chromatography. Procedure B: the solution of acetal (0.5 mmol) was added to a premixed suspension of $BF_3 \cdot OEt_2$ (2.0 mmol) and R^3BF_3K (2.0 mmol) in solvent. The isolated yield was calculated after chromatography.

structure was confirmed by X-ray crystallography (Figure 2). Complex (±)-**7** was found to be an air-stable and readily handled compound, although it was susceptible to gradual hydrolysis.



(2)

Attempts to employ (±)-**7** as a nucleophile without additional reagents failed with several electrophiles. Mixed acetals gave no product when (±)-**7** was added alone, although full conversion was observed in the presence of $BF_3 \cdot OEt_2$ (eq 3). We believe that in this case the $BF_3 \cdot OEt_2$ serves to activate the hydroxamate to generate the oxocarbenium ion, which is trapped by phenyl transfer from (±)-**7**. Attempts to add (±)-**7** to more reactive electrophiles (including benzaldehyde, acetylchloride, and Meerwein salt) gave no products.



(3)

Crossover Experiments with Boron Complexes. An alternative (or possibly complementary) 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 means of three experiments. First, a reaction of *O*-MOM cyclohexanol **1a** in the presence of both the phenylboron hydroxamate complex (±)-**7** and phenyldifluoroborane **6** was performed to look for the formation of acetal **1i**, which would be indicative of the reversibility of oxocarbenium ion generation. Indeed, when

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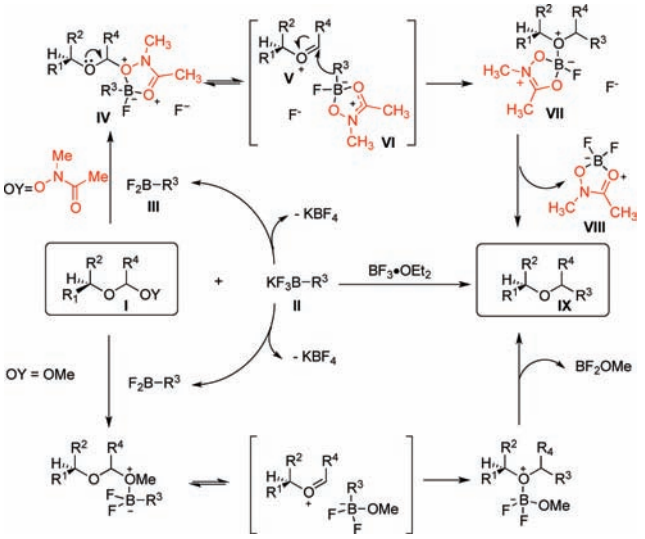
Scheme 2. Proposed Mechanism



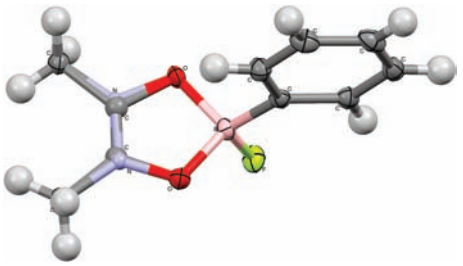
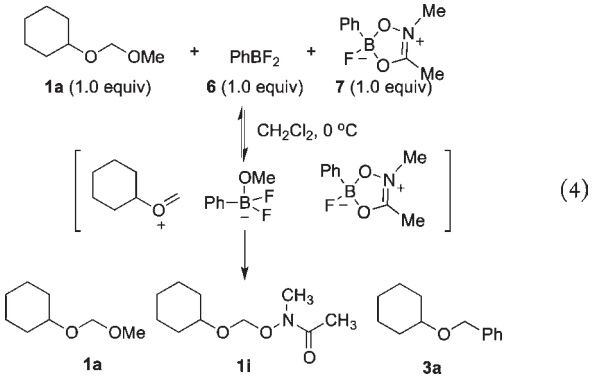


Figure 2. Crystal structure of (±)-7. Ellipsoids include 50% of the electron density. Two enantiomers occupy the same position in the crystal in a 0.53:0.47 ratio, leading to the disordered positions of C7 and N13 in the five-membered ring.

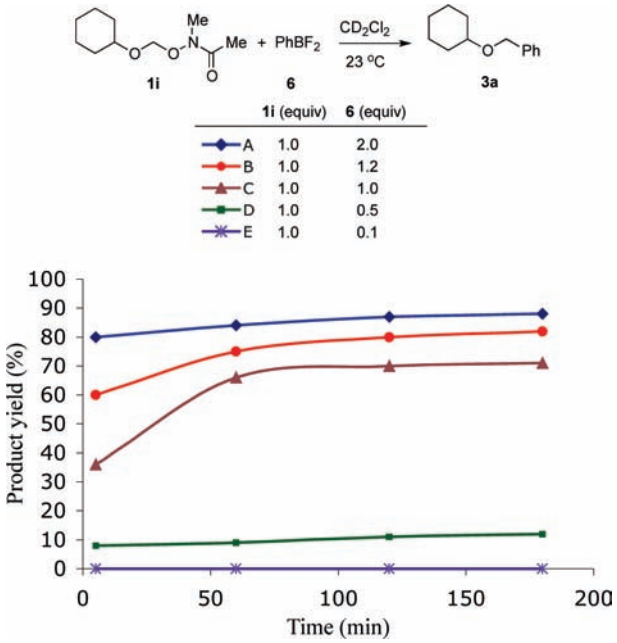
the reaction was quenched prior to completion (5 min at 0 °C), we observed significant amounts of **1i** (eq 4).



(4)

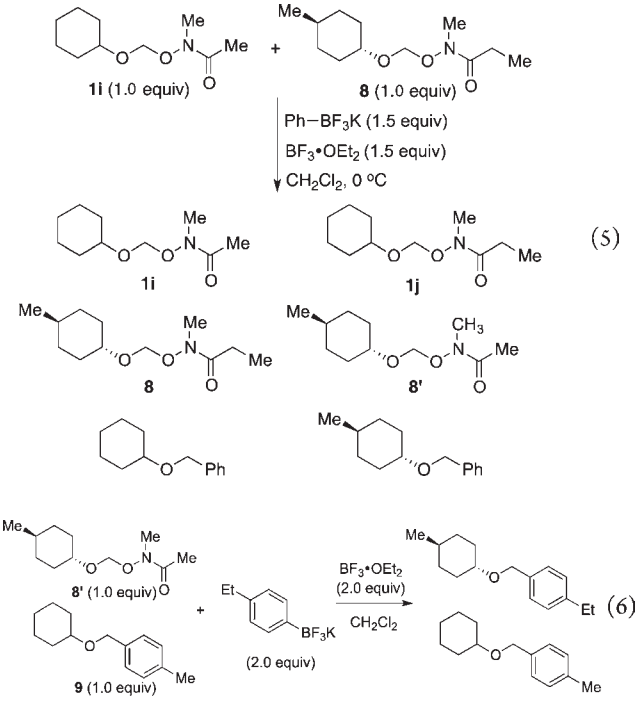
This postulate was confirmed by an experiment in which two structurally different hydroxamic acid-derived acetals with similar reactivities were used as starting materials. When the reaction was quenched prior to completion (5 min at 0 °C), we observed acetals **1j** and **8′** as crossover products (eq 5). This experiment again demonstrated that formation of the oxocarbenium ion is reversible. As a control reaction, we also confirmed that the product ethers were stable under the reaction conditions and that

Scheme 3. ^{1}H NMR Experiments[a]



[a] All of the experiments were performed on a 0.07 mmol scale in 1.0 mL of CD_2Cl_2. Product yields were measured using ^{1}H NMR integration against an internal standard peak.

the crossover products were not formed by fragmentation of the ether products (eq 6).



(5)

(6)

^{1}H NMR Study of the Reaction Mechanism. Further studies of the reaction mechanism were performed by ^{1}H NMR analysis of reaction mixtures using different ratios of acetal **1i** and organodifluoroborane **6** (Scheme 3). If the reaction proceeds via the proposed mechanism shown in Scheme 2, the maximum yield should be observed in cases A, B, and C, and 50% and 10% of maximum yield should be observed in cases D and E,

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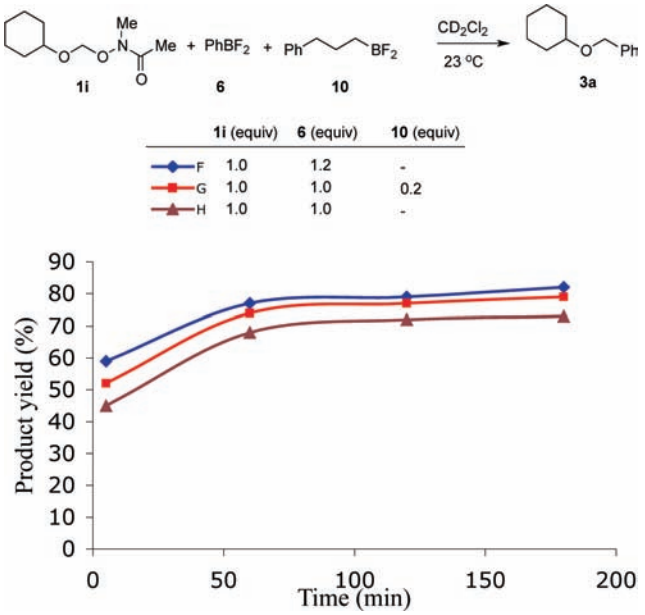
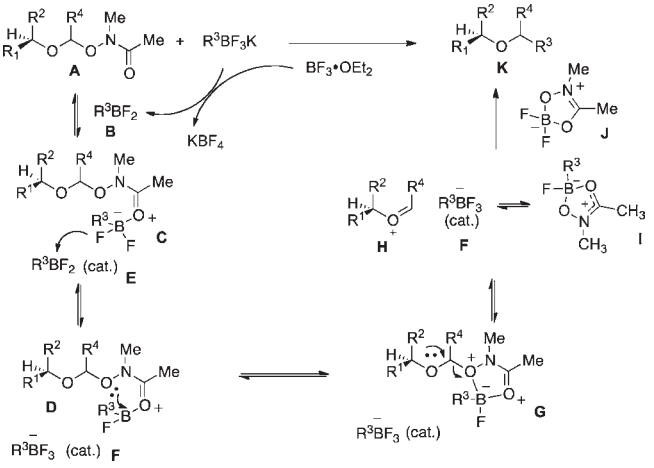
Scheme 4. Coupling Reactions with Catalytic Organodifluoroborane[a]



[a] All of the experiments were performed on a 0.07 mmol scale in 1.0 mL of CD_2Cl_2. Product yields were measured using ^1H NMR integration against an internal standard peak.

Scheme 5. Revised Mechanism for Ether-Forming Cross-Coupling Reactions



respectively. However, the maximum yield was not observed without excess phenyldifluoroborane (case C); only 12% product yield was formed in case D, and no product formation was observed in case E. The reaction was also faster when excess phenyldifluoroborane was used.

These results indicated that an excess amount of phenyldifluoroborane **6** was necessary for the reaction to go to completion and achieve the maximum yield.[33] It is possible that the excess phenyldifluoroborane is involved in promoting the formation of oxocarbenium ion and complex **7** via fluoride abstraction. To test this hypothesis, additional ^1H NMR experiments were performed. A catalytic amount of alkyldifluoroborane **10**, which is known not to transfer the alkyl group, was added (G in Scheme 4). This "unreactive" alkyldifluoroborane would serve to abstract the fluoride. Identical results were obtained with either 1.2 equiv of **6** or 1.0 equiv of **6** and 0.2 equiv of **10**, confirming that the role of the excess organodifluoroborane is to serve as a catalyst.

On the basis of the above data, we propose a revised mechanism for this transformation (Scheme 5). The interaction of potassium organotrifluoroborate and $BF_3 \cdot OEt_2$ produces organodifluoroborane **B** and potassium tetrafluoroborate. **B** serves as a Lewis acid and binds to the hydroxamate moiety. Abstraction of a second fluoride by the excess organodifluoroborane **E** opens a coordination site on the boron atom that is quickly occupied by an oxygen lone pair, forming the five-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 R^3 to **H**, irreversibly delivering 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. The isolation of a likely key intermediate, combined with crossover and control experiments, has provided insight into the mechanism as well as an explanation for the superiority of the hydroxamate leaving group in comparison with our first-generation approach.

ASSOCIATED CONTENT

Supporting Information. Experimental procedures, characterization data for all new compounds, and crystallographic data for (±)-**7** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(33) See the Supporting Information for detailed results on the percentages of conversion and product yields in the experiments.