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Synthesis of Dialkyl Ethers from Organotrifluoroborates and Acetals

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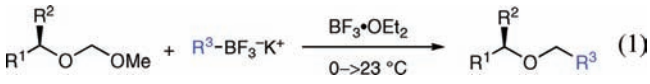
The 1852 report of Williamson on the displacement of alkyl halides with alkoxides established the state of the art for the synthesis of unsymmetrical ethers.[1] Its widespread adoption has entrenched the notion that carbon−heteroatom bonds are generally easier to form than carbon−carbon bonds. In the intervening 150 years, chemists have greatly simplified and expanded the range of C−C bond-forming reactions, leaving the preparation of ethers under classical conditions a relatively harsh and unsavory approach to bond construction. As part of a program aimed at developing modern methods for the synthesis of common functional groups,[2] we now report a strategic alternative to the synthesis of dialkyl ethers that involves the combination of stable, easily prepared acetals and potassium aryl-, alkenyl-, or alkynyltrifluoroborate salts (eq 1):



(1)

The limitations of the Williamson ether synthesis arise from the need for strongly basic nucleophiles and good leaving groups that can lead to side reactions. These reactions are also sensitive to steric hindrance and often cannot be applied to the preparation of more substituted products. In seeking to identify a general approach to ether construction under mild conditions from readily available starting materials, we considered a C−C bond-forming disconnection rather than the traditional C−O bond-forming approach (Scheme 1). Lewis acid-mediated additions of strong organometallic reagents (e.g., alkyllithiums or Grignard reagents) or allylsilanes to acetals are well-known but usually proceed under harsh conditions or with reactants that require prior preparation.[3] Despite the improved availability and operational simplicity offered by boronic acids[4] and potassium organotrifluoroborates,[5] there have been very few reports of ether formation[6] with these reagents. This contrasts with the powerful additions of boron nucleophiles to imines pioneered by Petasis as a mild and attractive synthesis of substituted amines.[7]

In developing this orthogonal approach to ether construction, we first sought to identify a stable functional group that could be easily introduced and would survive multistep synthesis prior to direct conversion to the desired ether. We selected acetals of L-menthol (**1a**−**c**) for our initial studies of the coupling with potassium alkynyltrifluoroborate **2a** in the presence of additives (Table 1). Such starting materials are easily prepared under mildly basic or mildly acid conditions,[8] obviating the need for strong bases at any stage of the ether synthesis. Although we initially believed that electronic differentiation of the acetal would be essential for regiocontrolled coupling (entries 1 and 2), our studies demonstrated that simple methoxymethyl (MOM) protecting groups were excellent, highly regioselective substrates with acetonitrile as the solvent (entry 3).[9] Toluene gave inferior results (entry 6), but dichloromethane was a viable solvent (entry 7). Under these conditions, other fluorophilic Lewis acids gave no reaction (entry 8) or effected

Scheme 1. General Approaches to Alkyl Ether Formation

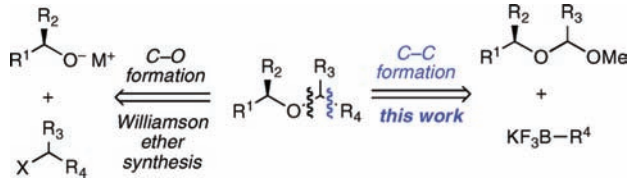
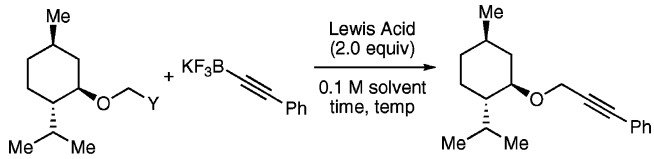


Table 1. Optimization of Lewis Acid-Promoted Ether Formation with (−)-Menthol−OCH_2Y **1** and Potassium Alkynyltrifluoroborate **2a**



1 (1.0 equiv) **2a** (2.0 equiv) **3a**

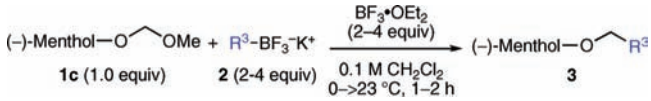
entry	Y	Lewis acid	solvent	temp (°C)	time (h)	yield (%)[a]
1	SMe (**1a**)	$BF_3{\cdot}OEt_2$	CH_3CN	0	1	45
2	OCH_2CH_2OMe (**1b**)	$BF_3{\cdot}OEt_2$	CH_3CN	0	1	84
3	OMe (**1c**)	$BF_3{\cdot}OEt_2$	CH_3CN	0	1	91
4	OMe (**1c**)	$BF_3{\cdot}OEt_2$	CH_3CN	−78	2	NR[c]
5	OMe (**1c**)	$BF_3{\cdot}OEt_2$	CH_3CN	−40	6	69
6	OMe (**1c**)	$BF_3{\cdot}OEt_2$	toluene	0	1	18[b]
7	OMe (**1c**)	$BF_3{\cdot}OEt_2$	CH_2Cl_2	0	2	85
8	OMe (**1c**)	TMSCl	CH_2Cl_2	40	6	NR[c]
9	OMe (**1c**)	$SiCl_4$	THF	0	2	−[d]
10	OMe (**1c**)	$SiCl_4$	CH_3CN	0	2	87

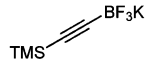
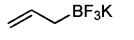
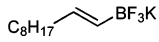
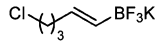
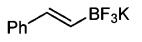
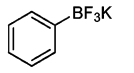
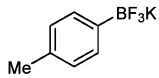
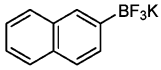
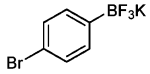
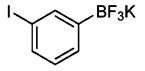
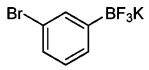
[a] Isolated yield after chromatography. [b] Percent conversion including a significant quantity of L-menthol detected by ^{1}H NMR analysis (500 MHz). [c] No reaction. [d] MOM deprotection was observed; no desired product was detected by ^{1}H NMR analysis (500 MHz) of the unpurified reaction mixture.

deprotection (entry 9); however, $SiCl_4$ in acetonitrile provided the desired product in 87% yield (entry 10). The major side product in these reactions was L-menthol, which arose from competing removal of the acetal and constituted the mass balance.

(−)-Menthol−MOM **1c** was treated with a variety of potassium organotrifluoroborates **2** to provide the desired ethers **3** in moderate to good yields (Table 2). Potassium alkynyltrifluoroborate (**2b**) proceeded in good yield under the optimized conditions (entry 1). Because of the reduced reactivity of sp^2-hybridized potassium organotrifluoroborates, we found it necessary to premix excess potassium organotrifluoroborate and $BF_3{\cdot}OEt_2$ in dichloromethane prior to addition of the acetal.[10] Potassium allyl- (**2c**) and alkenyltrifluoroborates (**2d**−**f**) proceeded in good yield under these modified conditions (entries 2−5). Simple potassium aryltrifluoroborates delivered the desired ethers in good yield (entries 6−8), but less reactive halogenated potassium aryltrifluoroborates gave lower yields and regioselectivities (entries 9−11).[11] Preliminary

Table 2. Variation of Potassium Organotrifluoroborate **2** in the Lewis Acid-Promoted Dialkyl Ether Formation with Acetal **1c**[a]



entry	R^3–BF_3K	**2** (equiv)	BF_3•OEt_2 (equiv)	% yield (**3**)[b]
1[c]		**2b** (2.0)	2.0	71 (**3b**)
2		**2c** (4.0)	4.0	77 (**3c**)
3		**2d** (4.0)	4.0	64 (**3d**)
4		**2e** (4.0)	4.0	65 (**3e**)
5		**2f** (4.0)	4.0	53 (**3f**)
6		**2g** (4.0)	4.0	57 (**3g**)
7		**2h** (4.0)	4.0	76 (**3h**)
8		**2i** (4.0)	4.0	74 (**3i**)
9		**2j** (4.0)	3.0	37 (**3j**)
10		**2k** (4.0)	3.0	40 (**3k**)
11		**2l** (4.0)	3.0	45 (**3l**)

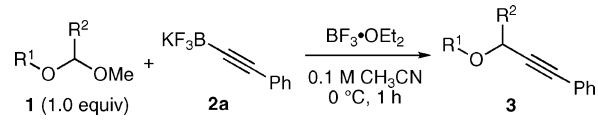
[a] Premixing of BF_3•OEt_2 and R^3–BF_3K **2** in CH_2Cl_2 followed by addition of **1c** (0.5 mmol) in CH_2Cl_2 provided superior results. [b] Isolated yield after chromatography. [c] Reaction performed at 0 °C in CH_3CN (cf. Table 1).

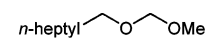
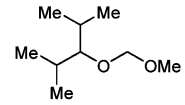
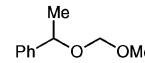
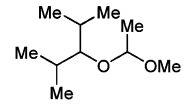
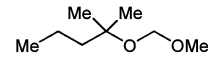
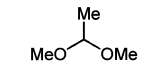
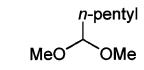
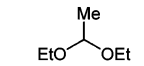
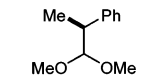
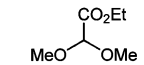
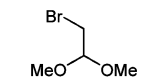
attempts to employ potassium alkyl- and heteroaryltrifluoroborates gave primarily acetal deprotection.[12]

Primary, secondary, and tertiary MOM-protected alcohols all gave the desired products under these conditions (Table 3, entries 1−6). More substituted acetals were excellent substrates and afforded the expected ethers in good to excellent yield (entries 7−12). These experiments demonstrated that this process tolerates functional groups, including esters and alkyl halides (entries 11 and 12). Several of these products, such as the sterically demanding products prepared in entries 3−6 and the bromo-substituted compound in entry 12, would be particularly challenging to prepare by Williamson ether synthesis. With the more reactive potassium alkynyltrifluoroborates (cf. Table 3 vs Table 2), fewer equivalents of the nucleophile were required; in many cases, only 1.2 equiv was sufficient (i.e., Table 3, entries 7−10).

In accord with prior studies,[13] ^{11}B NMR spectroscopy revealed the activation of potassium phenyltrifluoroborate **2g** by BF_3•OEt_2 to provide phenyldifluoroborane (21.88 ppm)[14] and its corresponding etherate with consumption of BF_3•OEt_2.[10] In addition, benzyl ether **3g** was observed by ^1H NMR spectroscopy upon addition of

Table 3. Variation of Acetal **1** in the Lewis Acid-Promoted Dialkyl Ether Formation with Potassium Alkynyltrifluoroborate **2a**[a]



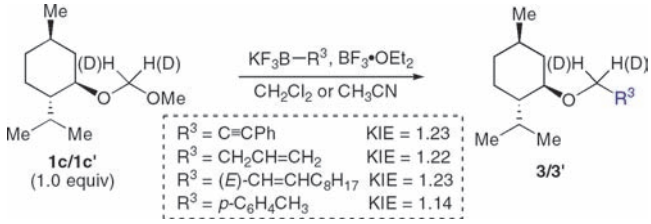
entry	acetal	**1**	**2a** (equiv)	BF_3·OEt_2 (equiv)	% yield (**3**)[b]
1		**1d**	1.2	1.2	84 (**3m**)
2		**1e**	2.0	2.0	77 (**3n**)
3		**1f**	2.0	2.0	80 (**3o**)
4		**1g**	2.0	2.0	56 (**3p**)
5		**1h**	2.0	2.0	52 (**3q**)
6		**1i**	2.0	2.0	45 (**3r**)
7		**1j**	1.2	1.2	88 (**3s**)
8		**1k**	1.2	1.2	86 (**3t**)
9		**1l**	1.2	1.2	84 (**3u**)
10		**1m**	1.2	1.2	90 (**3v**)[c]
11		**1n**	2.0	2.0	67 (**3w**)[d]
12		**1o**	2.0	2.0	98 (**3x**)[d]

[a] All reactions were carried out on a 0.5 mmol scale. [b] Isolated yield after chromatography. [c] dr = 1.5:1.0, as determined by ^1H NMR analysis (500 MHz) of the unpurified product. [d] Reaction allowed to warm to 23 °C over 4 h.

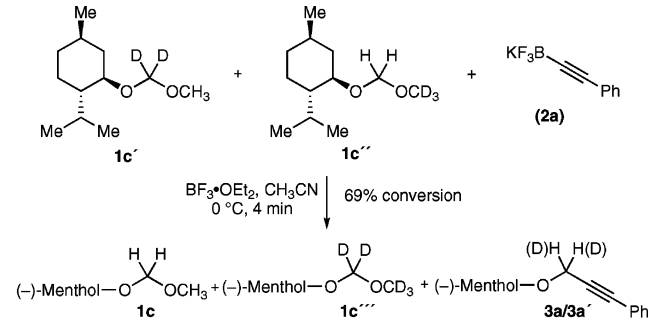
(−)-menthol−MOM **1c**, demonstrating the intermediacy of phenyldifluoroborane. Secondary kinetic isotope effects indicative of sp^3-to-sp^2 hybridization (i.e., oxocarbenium formation) as the rate-determining step were observed between **1c** and isotopically labeled **1c′** regardless of the potassium organotrifluoroborate employed (Scheme 2).[15] Crossover studies utilizing isotopically labeled derivatives of **1c** gave the expected ethers **3a/3a′** and all possible isotopically labeled isomers of **1c**, as observed by electrospray ionization mass spectrometry, suggesting that the rate-limiting formation of the oxocarbenium intermediate was reversible (Scheme 3).

On the basis of these experiments, a plausible reaction pathway is proposed (Scheme 4). Upon interaction of the potassium organotrifluoroborate **II** with BF_3•OEt_2, organodifluoroborane **IV** and its corresponding etherate (not shown) are produced and presumably serve as the active Lewis acids. The less encumbered

Scheme 2. Normal Secondary Kinetic Isotope Effects Demonstrate That the Proposed Oxocarbenium Intermediate Is Formed in the Rate-Determining Step

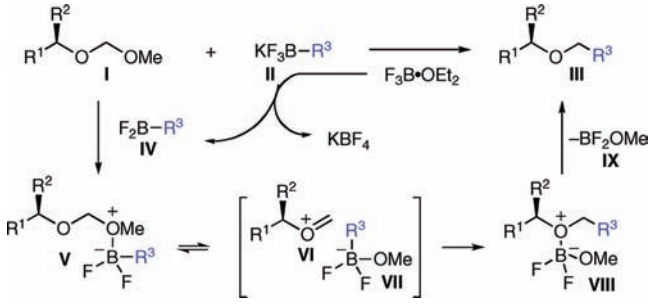


Scheme 3. Crossover Experiments Demonstrate the Reversibility of the Formation of the Proposed Oxocarbenium Intermediate



crossover products (starting materials **1c´** and **1c´´** also observed)

Scheme 4. Postulated Reaction Pathway for Ether Formation



oxygen of acetal **I** binds to organodifluoroborane **IV** to form zwitterion **V**, which reversibly collapses to form oxocarbenium **VI** and nucleophilic organodifluoroalkoxyborate **VII**. We postulate that the rate-determining nature of the oxocarbenium formation (cf. Scheme 2) is due to this equilibrium and that nucleophilic capture of a *discrete* oxocarbenium intermediate **VI** by organodifluoroalkoxyborate **VII** is relatively facile, ultimately delivering dialkyl ether **III**. The superior performance of potassium alkynyltrifluoroborates relative to other potassium organotrifluoroborates is attributed to the greater migratory ability of sp-hybridized alkynyldifluoroalkoxyborates **VII** (R^3 = alkynyl).

In summary, we have identified a versatile synthesis of dialkyl ethers via cross-coupling of potassium organotrifluoroborates and acetals. This work provides a strategic alternative to the synthesis of ethers from distinct reaction partners without the need for deprotection or redox chemistry.[16] It interfaces with the growing interest in stable, commercially available organoboron reagents for the modular synthesis of complex molecules.[17] Furthermore, it offers an avenue to the synthesis of highly hindered ethers, such as those derived from chiral secondary and tertiary alcohols. The known ability of transition-metal catalysts to accelerate similar processes[18] offers a pathway for future developments to enhance the chemical yield, substrate scope, and stereochemical outcome.

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Supporting Information Available: Experimental procedures and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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