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Copper(II)-Catalyzed Ether Synthesis from Aliphatic Alcohols and Potassium Organotrifluoroborate Salts

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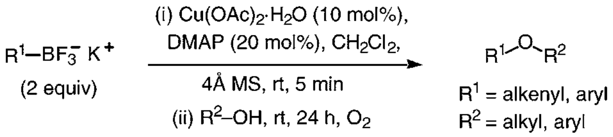
ABSTRACT



A protocol for the copper(II)-catalyzed etherification of aliphatic alcohols under mild and essentially neutral conditions is described. Air- and moisture-stable potassium alkenyl- and aryltrifluoroborate salts undergo cross-coupling with a variety of aliphatic primary and secondary alcohols and phenols, and are tolerant of a range of functional groups. The optimized conditions utilize catalytic copper(II) acetate with 4-(dimethylamino)pyridine as ligand in the presence of 4 Å molecular sieves under an atmosphere of oxygen.

The formation of carbon−heteroatom bonds using metal catalysis is emerging as one of the most significant classes of cross-coupling reactions. In the area of C−O ether bond formation, there has been a resurgence of interest in Cu-mediated reactions beyond that of the classical Ullmann ether synthesis.[1] Buchwald and others have demonstrated that Cu(I) salts effectively promote the cross-coupling of aryl halides with phenoxides, phenols, and aliphatic alcohols.[2] This is an alternative to the analogous Pd-catalyzed reactions developed by Buchwald and Hartwig.[3] Although these Pd- and Cu-catalyzed etherifications occur under milder conditions than the classical protocols, the reactions are still performed under refluxing conditions in the presence of strongly basic alkoxides, and in the case of the Pd-based methods, require expensive catalyst/ligand systems. An alternative approach to ether synthesis is the cross-coupling of alcohols or phenols with organometalloid reagents such as organo-Bi,[4] -Sn,[5] and -B[6−8] compounds. Chan and Evans simultaneously reported the Cu-mediated cross-coupling of arylboronic acids with phenols at *room temperature* to produce diaryl ethers.[6] An obvious limitation of this reaction is that stoichiometric amounts of $Cu(OAc)_2$ and base are required,[7] with substoichiometric quantities of catalyst resulting in poor yields of diaryl ethers.[6b] Moreover, aliphatic alcohols do not participate in cross-coupling even under

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[1] (a) Lindley, J. *Tetrahedron* **1984**, *40*, 1433−1456. (b) Theil, F. *Angew. Chem., Int. Ed.* **1999**, *38*, 2345−2347. (c) Finet, J. P.; Fedorov, A. Y.; Combes, S.; Boyer, G. *Curr. Org. Chem.* **2002**, 6, 597−626. (d) Hassan, J.; Sevignon, M.; Gozzi, C.; Schulz, E.; Lemaire, M. *Chem. Rev.* **2002**, *102*, 1359−1469.

[2] (a) Marcoux, J. F.; Doye, S.; Buchwald, S. L. *J. Am. Chem. Soc.* **1997**, *119*, 10539−10540. (b) Zhu, J.; Price, B. A.; Zhao, S. X.; Skonezny, P. M. *Tetrahedron Lett.* **2000**, *41*, 4011−4014. (c) Wolter, M.; Nordmann, G.; Job, G. E.; Buchwald, S. L. *Org. Lett.* **2002**, *4*, 973−976.

[3] (a) Mann, G.; Hartwig, J. F. *J. Am. Chem. Soc.* **1996**, *118*, 13109−13110. (b) Palucki, M.; Wolfe, J. P.; Buchwald, S. L. *J. Am. Chem. Soc.* **1997**, *119*, 3395−3396. (c) Shelby, Q.; Kataoka, N.; Mann, G.; Hartwig, J. F. *J. Am. Chem. Soc.* **2000**, *122*, 10718−10719. (d) Torraca, K. E.; Huang, X.; Parrish, C. A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2001**, *123*, 10770−10771. (e) Kuwabe, S.; Torraca, K. E.; Buchwald, S. L. *J. Am. Chem. Soc.* **2001**, *123*, 12202−12206. (f) Parrish, C. A.; Buchwald, S. L. *J. Org. Chem.* **2001**, *66*, 2498−2500.

[4] Finet, J. P. *Chem. Rev.* **1989**, *89*, 1487−1501 and references therein.

[5] Blouin, M.; Frenette, R. *J. Org. Chem.* **2001**, *66*, 9043−9045.

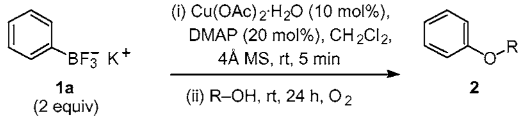
[6] (a) Chan, D. M. T.; Monaco, K. L.; Wang, R. P. *Tetrahedron Lett.* **1998**, *39*, 2933−2936. (b) Evans, D. A.; Katz, J. L.; West, T. R. *Tetrahedron Lett.* **1998**, *39*, 2937−2940.

[7] A catalytic variant of the protocol utilizing a stoichiometric chemical oxidant to regenerate the Cu catalyst has been reported, but, the optimal oxidant used in the reaction varied as the nucleophilic component was changed; furthermore, competitive oxidation of the boronic acids was problematic. See: Lam, P. Y. S.; Vincent, G.; Clark, C. G.; Deudon, S.; Jadhav, P. K. *Tetrahedron Lett.* **2001**, *42*, 3415−3418.

[8] (a) Jung, M. E.; Lazarova, T. I. *J. Org. Chem.* **1999**, *64*, 2976−2977. (b) Petrassi, H. M.; Sharpless, K. B.; Kelly, J. W. *Org. Lett.* **2001**, *3*, 139−142. (c) Decicco, C. P.; Song, Y.; Evans, D. A. *Org. Lett.* **2001**, *3*, 1029−1032.

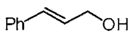
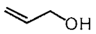
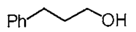
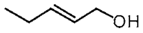
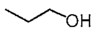
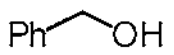
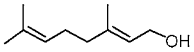
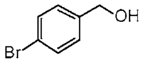
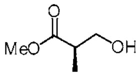
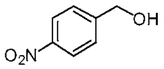
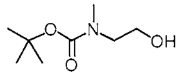
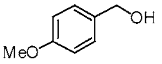
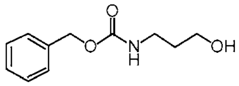
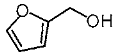
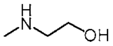
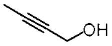
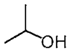
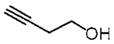
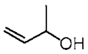
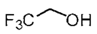
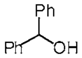
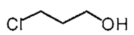
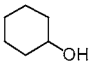
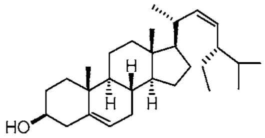
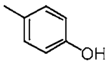
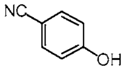
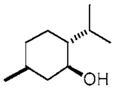
10.1021/ol034454n CCC: $25.00

Table 1. Copper(II)-Catalyzed *O*-Phenylation of Alcohols[a]



1a
(2 equiv)

2

entry	R-OH	product	% yield[b]	entry	R-OH	product	% yield[b]
1		**2a**	89 (65)[c]	16		**2p**	93
2		**2b**	95	17		**2q**	74
3		**2c**	78	18		**2r**	83
4		**2d**	71	19		**2s**	87
5		**2e**	94	20		**2t**	90
6		**2f**	75	21		**2u**	93
7		**2g**	80	22		**2v**	85
8		**2h**	90 (60)[c]	23		**2w**	– (30)[e]
9		**2i**	92	24		**2x**	71
10		**2j**	– (61)[d]	25		**2y**	69
11		**2k**	82	26		**2z**	75
12		**2l**	95	27		**2aa**	67
13		**2m**	93	28		**2bb**	48
14		**2n**	82				
15		**2o**	77	29		–	–[f]

[a] Reaction times are not optimized for individual substrates. [b] Isolated yields. [c] Yields in parentheses are obtained using $PhB(OH)_2$ under the same conditions. [d] Yield of the homocoupled diaryldiyne product. [e] Yield of the diphenylated product. [f] Unreacted starting material was isolated.

stoichiometric conditions,[6a] and the process has thus far been limited to the coupling of phenol derivatives[6−8a,c] and *N*-hydroxyphthalimides.[8b] These problems have clearly limited the scope of the reaction. As part of our interest in the chemistry of organoboron compounds,[9] we now report the first catalytic coupling of organoboron compounds with primary and secondary aliphatic alcohols under essentially neutral conditions at room temperature.

Organotrifluoroborate salts have recently been utilized in various metal-catalyzed reactions, including Pd-catalyzed Suzuki−Miyaura cross-couplings[9,10] and Rh(I)-catalyzed additions to aldehydes[11a] and enones.[11] These salts offer an air- and moisture-stable alternative to other organoboron compounds. They can be stored under normal atmospheric

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(9) Batey, R. A.; Quach, T. D.; Shen, M.; Thadani, A. N.; Smil, D. V.; Li, S. W.; MacKay, D. B. *Pure Appl. Chem.* **2002**, *74*, 43−55.

(10) (a) Darses, S.; Michaud, G.; Genêt, J. P. *Eur. J. Org. Chem.* **1999**, *1875*, 5−1883. (b) Littke, A. F.; Dai, C.; Fu, G. C. *J. Am. Chem. Soc.* **2000**, *122*, 4020−4028. (c) Batey, R. A.; Quach, T. D. *Tetrahedron Lett.* **2001**, *42*, 9099−9103. (d) Molander, G. A.; Katona, B. W.; Machrouhi, F. *J. Org. Chem.* **2002**, *67*, 8416−8423. (e) Molander, G. A.; Bernardi, C. R. *J. Org. Chem.* **2002**, *67*, 8424−8429. (f) Frohn, H. J.; Adonin, N. Y.; Bardin, V. V.; Starichenko, V. F. *Tetrahedron Lett.* **2002**, *43*, 8111−8114.

(11) (a) Batey, R. A.; Thadani, A. N.; Smil, D. V. *Org. Lett.* **1999**, *1*, 1683−1686. (b) Pucheault, M.; Darses, S.; Genêt, J. P. *Eur. J. Org. Chem.* **2002**, *21*, 3552−3557.

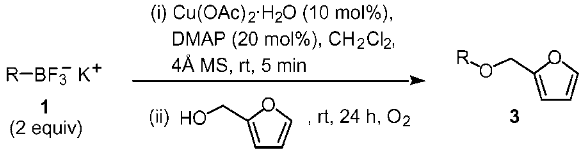
conditions for extended periods; are readily synthesized from the corresponding boronic acids by treatment with KHF_2,[12] and several are now commercially available. The initial goal of our study was the development of conditions suitable for the formation of aryl alkyl ethers, since these products were reported to be inaccessible using the original Chan and Evans protocol. $PhBF_3^-K^+$ and cinnamyl alcohol were chosen as model coupling partners. Optimization experiments for the formation of cinnamyl phenyl ether included the effect of the copper catalyst, ligand, solvent, atmosphere, and the presence of molecular sieves. The optimal copper source is $Cu(OAc)_2{\cdot}H_2O$, based on reaction yield, cost, and ease of handling. Of the nitrogen-based ligands examined, the secondary diamine, DMEDA, gave none of the desired product, while the tertiary aliphatic amines (DIPEA, TMEDA, Et_3N) and 1,10-phenanthroline afforded only moderate yields. The *N*-heterocyclic ligands (pyridine, imidazole, DMAP) gave the highest yields under an atmosphere of air. Under an inert atmosphere (N_2) the reaction yields were significantly lowered, often resulting in only one turnover of catalyst. Performing the reaction under an atmosphere of O_2 generally increased the yields by ~10% over those obtained in air. These observations are consistent with those made by Evans.[6b] Finally, the presence of 4 Å MS was required, as reaction in their absence gave only trace amounts of the cross-coupled ether.

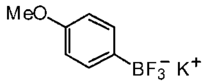
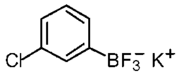
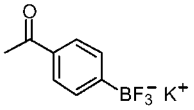
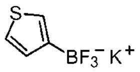
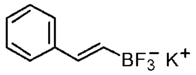
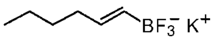
Optimized conditions employed reaction of 2 equivalents of potassium organotrifluoroborate salt **1** with 1 equivalent of an unactivated aliphatic alcohol in the presence of 10 mol % $Cu(OAc)_2{\cdot}H_2O$, 20 mol % DMAP, and 4 Å MS in CH_2Cl_2 at room temperature under an atmosphere of O_2 for 24 h. The scope and limitations of this protocol were explored using a series of alcohols with $PhBF_3^-K^+$ (Table 1). Phenols, aliphatic, allylic, internal propargylic alcohols undergo cross-coupling without complication. A variety of functionalities are tolerated including arylhalides which do not participate in cross-coupling (Table 1, entry 5), and alkylhalides which do not undergo nucleophilic displacement under these reaction conditions (Table 1, entries 11−13). Alkene isomerization did not occur under these conditions (Table 1, entries 1, 17−19, 28), nor did epimerization of an α-stereocenter in an enantiomerically pure ester (Table 1, entry 20). Terminal alkyne and N−H amine functionality are not compatible with the reaction as catalytic, oxidative homocoupling (Eglinton reaction)[13] and competitive *N*-arylation occurs respectively (Table 1, entries 10 and 23). Secondary aliphatic alcohols also undergo cross-coupling, although in lower yields than primary alcohols (Table 1, entries 24−29). The reaction appears to be quite sensitive to steric effects around the hydroxyl group. Thus, arylation of cyclohexanol, stigmasterol, and menthol occurred in 67%, 48% and 0% yields (Table 1, entries 27−29). Unsurprisingly, all attempts at reaction with tertiary alcohols also did not furnish cross-coupled ethers.

Boronic acids also undergo cross-coupling under the optimized conditions, although yields are appreciably lower. For example, cross-coupling of cinnamyl alcohol with $PhBF_3^-K^+$ and $PhB(OH)_2$ occurred in 89% and 65% yields, respectively. Similarly, furfuryl alcohol underwent coupling in 90% and 60% yields, respectively. The poorer reactivity profile exhibited by boronic acids appears to be linked to their greater propensity toward Cu promoted oxidation.[6b] GC analysis revealed a greater rate of biaryl ether formation using boronic acids rather than trifluoroborate salts, resulting in greater isolated yields of the undesired phenol and homocoupled biphenyl ether byproducts. From an experimental standpoint it should be noted that these oxidation side products are not only produced with trifluoroborates, but also occur under Evans' conditions for diaryl ether formation. Lowering the amount of organoboron reagent, below 2 equiv, results in a steady decrease in the yield of both product and side products.

Finally, the nature of the organotrifluoroborate was examined, using 2-furfuryl alcohol as a model primary alcohol cross-coupling partner (Table 2). Electron-rich aryl trifluoroborates such as 4-methoxyphenyltrifluoroborate (Table 2, entry 1) give the best results, whereas electron-deficient salts such as 4-acetylphenyltrifluoroborate did not couple

Table 2. Copper(II)-Catalyzed *O*-Arylation/Alkenylation of 2-Furfuryl Alcohol with Various $RBF_3{-}K^+$ Salts



entry	trifluoroborate	product	% yield[a]
1		**3a**	quant.
2		**3b**	71[b]
3		–	–
4		**3c**	76
5		**3d**	61
6		**3e**	55

[a] Isolated yield. [b] 48 h reaction time.

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(12) Vedejs, E.; Fields, S. C.; Schrimpf, M. R. *J. Am. Chem. Soc.* **1993**, *115*, 11612−11613.

(13) (a) Eglinton, G.; Galbraith, A. R. *Chem. Ind. (London)* **1956**, 737−738. (b) Behr, O. M.; Eglinton, G.; Galbraith, A. R.; Raphael, R. A. *J. Chem. Soc.* **1960**, 3614−3625. (c) Hay, A. S. *J. Org. Chem.* **1962**, *27*, 3320−3321.

(Table 2, entry 3). Heterocyclic and alkenyl trifluoroborate salts are effective partners in the reaction. However, alkyltrifluoroborate derivatives do not act as effective reagents under these conditions, presumably because of their lower reactivity toward transmetalation with Cu salts.

In conclusion, we have developed a mild and essentially neutral protocol for the synthesis of alkyl−aryl and alkyl−vinyl ethers via the Cu(II)-catalyzed cross-coupling of potassium organotrifluoroborate salts with unactivated primary and secondary aliphatic alcohols. Arylboronic acids also participate in the reaction, although product yields are lower. This reaction further extends the scope of aryl and alkenyl boron cross-coupling chemistry, and we anticipate its use in both complex molecule synthesis and parallel synthesis applications. Further investigations on this and related chemistry is currently under way in our laboratory.

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Supporting Information Available: Experimental procedures and characterization data for all compounds isolated. ^{1}H and ^{13}C spectra of all novel compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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