

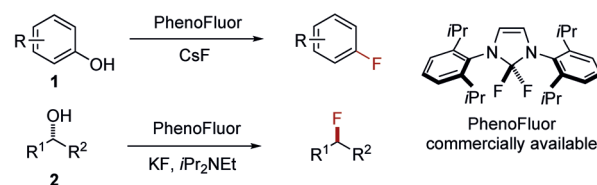
Alkyl Aryl Ether Bond Formation with PhenoFluor**

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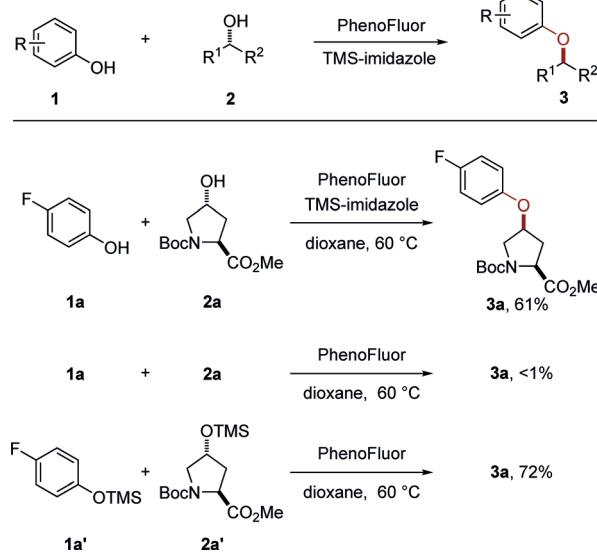
Abstract: An alkyl aryl ether bond formation reaction between phenols and primary and secondary alcohols with PhenoFluor has been developed. The reaction features a broad substrate scope and tolerates many functional groups, and substrates that are challenging for more conventional ether bond forming processes may be coupled. A preliminary mechanistic study indicates reactivity distinct from conventional ether bond formation.

Ethers are common,^[1] yet their synthesis is often challenging. Simple ethers are readily made through the Williamson ether synthesis, which was developed more than 150 years ago,^[2] but even for moderately complex ethers, such as those derived from secondary alcohols, the Williamson synthesis often fails owing to low reactivity and undesired side reactions, such as elimination.^[2] Transition-metal-catalyzed or -mediated cross-coupling reactions, exemplified by Ullmann,^[3] Chan–Lam–Evans,^[4] and Buchwald–Hartwig couplings,^[5] are powerful methods for ether bond formation. Functionally complex secondary alcohols, however, are challenging substrates for these transition-metal-catalyzed reactions as well. The direct coupling between phenols and alcohols for alkyl aryl ether bond formation is appealing and orthogonal to other cross-coupling approaches. The Mitsunobu reaction has been developed for this purpose, and a large substrate scope has been demonstrated.^[6,7] However, several substrate classes, such as salicylaldehydes, are not tolerated, and general alcohol–alcohol cross-couplings are deemed challenging owing to the high pK_a values of typical alcohols.^[8] Likewise, the direct coupling of phenols and 2,2,2-trifluoroethanol in a Mitsunobu reaction has not been reported. Herein, we report a new approach to alkyl aryl ether formation through the use of the reagent PhenoFluor (Scheme 1). The reaction provides a conceptually different, promising reactivity profile, possibly enabled by the tight ion pairing of key intermediates. Our strategy distinguishes itself by operational simplicity—phenols and alcohols can be used directly—and a large substrate scope, which includes salicylaldehydes and 2,2,2-trifluoroethanol. An example of selective glycosylation is also

Previous work: Fluorination with PhenoFluor



This work: Etherification with PhenoFluor



Scheme 1. Fluorination and etherification reactions with PhenoFluor. Boc = *tert*-butoxycarbonyl, TMS = trimethylsilyl.

shown, further demonstrating the potential synthetic applications.

PhenoFluor is a commercially available deoxyfluorination reagent for both alcohols and phenols, with a larger demonstrated substrate scope than any other deoxyfluorination reagent.^[9] We speculated that instead of fluoride, phenolates or alcoholates might act as nucleophiles to provide ethers if the fluoride ions were effectively trapped by silanes.^[10] The reaction of an equimolar mixture of alcohol **2a** and 4-fluorophenol with PhenoFluor and TMS-imidazole (2 equiv) in dioxane at 60 °C for 21 hours afforded ether **3a** in 61 % yield (Scheme 1; for reaction optimization, see the Supporting Information). Without the addition of TMS-imidazole, less than 1 % of ether **3a** was formed, and deoxyfluorination of alcohol **2a** was observed. The yield of the ether bond formation could be increased by using the silyl ethers of phenol **1a** and alcohol **2a**, but for operational simplicity, we opted to develop the ether bond formation directly from phenols and alcohols.

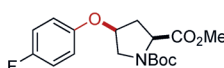
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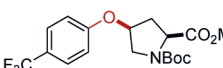
Supporting information for this article is available on the WWW under <http://dx.doi.org/10.1002/anie.201500902>.

Table 1: Cross-coupling of phenols and alcohols.

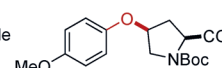
$$\begin{array}{ccc}
 \text{Ar-OH} & + & \text{HO-CH(R}^1\text{)-R}^2 \\
 \text{1} & & \text{2}
 \end{array}
 \xrightarrow[\text{dioxane, } T]{\text{PhenoFluor TMS-imidazole}}
 \begin{array}{c}
 \text{Ar-O-CH(R}^1\text{)-R}^2 \\
 \text{3}
 \end{array}$$



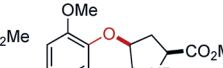
3a, 23 °C, 63%^[a]
60 °C, 71%^[b]
120 °C, 87%^[a]



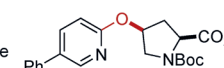
3b, 80 °C, 92%^[a]



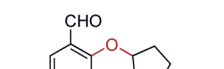
3c, 80 °C, 75%^[b]



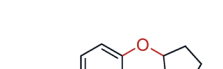
3d, 100 °C, 67%^[b]



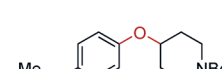
3e, 100 °C, 79%^[a]



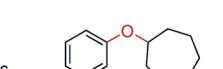
(±)-**3f**, 100 °C, 60%^[b]



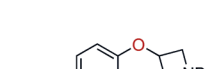
(±)-**3g**, 80 °C, 68%^[b]



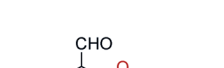
3h, 100 °C, 97%^[c]



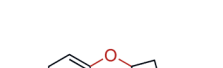
(±)-**3i**, 80 °C, 57%^[b]



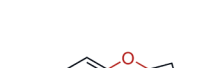
3j, 80 °C, 93%^[b]



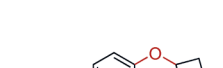
3k, 80 °C, 81%^[b]



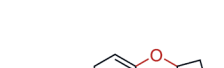
3l, 80 °C, 82%^[b]



3m, 80 °C, 66%^[b]



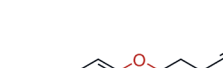
3n, 80 °C, 52%^[b]



3o, 80 °C, 88%^[b]



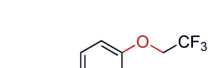
3p, 80 °C, 50%^[b]



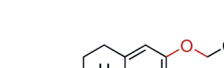
3q, 23 °C, 71%^[a,d]



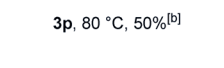
3r, 23 °C, 70%^[a,d]



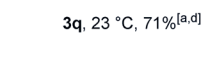
3s, 23 °C, 85%^[a,d]



3t, 23 °C, 84%^[a,d]



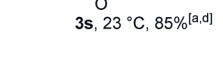
3u, 23 °C, 69%^[a,d,e]



3v, 100 °C, 71%^[b]



3w, 100 °C, 63%^[a]



3x, 23 °C, 50%, α/β = 99:1^[b,d,f]

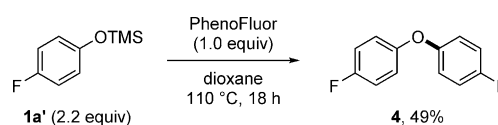
[a] 1/2/PhenoFluor/TMS-imidazole = 1.0:2.0:2.0:4.0. [b] 1/2/PhenoFluor/TMS-imidazole = 1.5:1.0:1.5:3.0. [c] 1/2/PhenoFluor/TMS-imidazole = 1.0:3.0:3.0:6.0. [d] TMSNEt₃ was used instead of TMS-imidazole. [e] A yield of 85% was obtained when the reaction was carried out at 80 °C. [f] Toluene was used as the solvent instead of dioxane. Bn = benzyl, Bz = benzoyl.

Ether bond formation proceeds at 23 °C, but higher yields are obtained at elevated temperature. The reaction tolerates a variety of functional groups, including aldehydes, alkenes, alkynes, amines, amides, esters, halides, and ketones (Table 1). Both electron-poor and -rich phenols are suitable substrates. Substituted salicylaldehydes cannot be used to access ethers with alcohols in Mitsunobu reactions owing to the condensation of the aldehyde with Huisgen zwitterions, the key intermediates in Mitsunobu reactions.^[8] However, under our current cross-coupling reaction conditions, products (±)-**3f** and **3k** were obtained in 60% and 81% yield, respectively. Furthermore, pyridinols and quinolinols are also suitable substrates (see **3e**, **3l**, **3m**, **3r**, and **3u**).

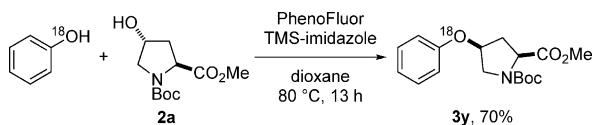
Primary and secondary alcohols, including β,β-branched alcohols, can be employed. Alkyl trifluoroethyl ethers can be made through Mitsunobu reactions,^[11] but the synthesis of aryl trifluoroethyl ethers in Mitsunobu reactions has not been reported.^[12–14] As shown in Table 1, ether bond formation of phenols and 2,2,2-trifluoroethanol proceeded with PhenoFluor at 23 °C (**3r–3u**). Moreover, lactols also undergo

PhenoFluor-mediated C–O bond formation: 2,3,4,6-Tetra-*O*-benzyl-D-galactose, for example, undergoes glycosylation with 99:1 α/β selectivity (**3x**);^[15] glycosylation under Mitsunobu conditions afforded **3x** in 30:70 α/β selectivity (see the Supporting Information).

Mechanistically, we believe that the ether bond formation reported here is distinct from conventional ether bond forming reactions. For example, diaryl ether bond formation was found to occur when 1 equivalent of PhenoFluor was treated with 2.2 equivalents of the aryl silyl ether **1a'** (Scheme 2); diaryl ethers cannot be accessed through conventional Mitsunobu reactions by an S_N2 pathway. An ¹⁸O labeling experiment established that the oxygen atom con-

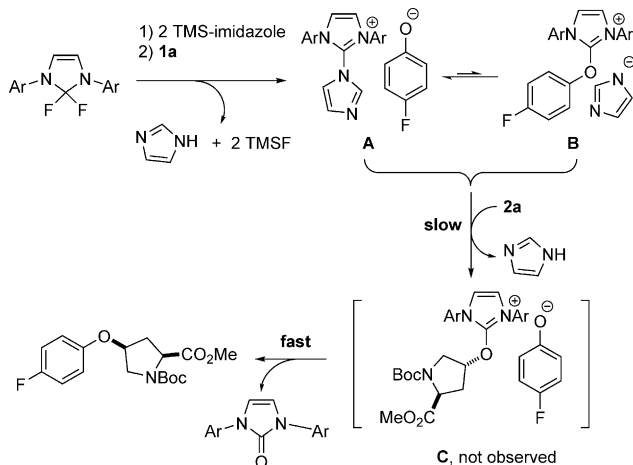

Scheme 2. Diaryl ether formation.

tained in the ether product originates from the phenol (Scheme 3). Moreover, we established that ether bond formation proceeds with inversion at the carbinol center (see the Supporting Information). In situ ^{19}F NMR and



Scheme 3. The ^{18}O label originates from phenol.

HRMS monitoring of the reaction revealed the presence of ion pairs **A** and **B**, but not **C**, which leads us to propose a slow formation of ion pair **C**, followed by fast nucleophilic displacement to form the desired product (Scheme 4).



Scheme 4. Proposed mechanism. Ar = 2,6-diisopropylphenyl.

Given the similarities between the PhenoFluor-mediated deoxyfluorination^[9a,b] and the ether bond formation reported here, we believe that the formation of tight ion pairs is of particular relevance for PhenoFluor-mediated reactivity, and may be, at least in part, responsible for the efficient C–O bond formation and the large substrate scope.

In conclusion, we have developed a novel alkyl aryl ether synthesis from alcohols and phenols with PhenoFluor. The presented ether bond formation has a large substrate scope and can provide ethers that are challenging to obtain with conventional Mitsunobu reactions. We believe that the distinct PhenoFluor-based reactivity shown here may contribute to the development of more general ether bond formation reactions.

Keywords: alkyl aryl ethers · C–O bond formation · fluorine · Mitsunobu reaction · PhenoFluor

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