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Facile *O*-Arylation of Phenols and Carboxylic Acids

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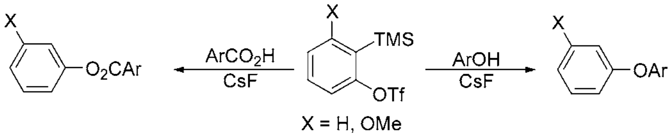
ABSTRACT



A facile, transition-metal-free *O*-arylation procedure for phenols and aromatic carboxylic acids has been developed that affords good to excellent yields of arylated products under very mild reaction conditions. A methoxy-substituted aryl triflate affords *O*-arylated products in high yields with excellent regioselectivity. This chemistry tolerates a variety of functional groups.

Diaryl ethers and aryl esters are commonly found in a variety of biologically active and natural compounds.[1] The classical copper-mediated Ullmann diaryl ether synthesis usually requires rather harsh reaction conditions and stoichiometric amounts of copper.[2] Recently, a number of valuable new methods have been developed for the *O*-arylation of phenols and carboxylic acids.[3] Evans[4] and Chan[5] have independently reported the synthesis of diaryl ethers by the copper(II)-promoted cross-coupling of phenols and arylboronic acids. Buchwald[6] and Hartwig[7] have demonstrated that the Cu- or Pd-catalyzed *O*-arylation of a variety of phenols by aryl halides is also a powerful method for the synthesis of diaryl ethers. Even with these significant improvements in the synthesis of diaryl ethers, there are still some limitations. For example, (1) phenols can smoothly be converted to diaryl ethers only if no strong electron-withdrawing group is present[6a,b] or transition-metal complexes of aryl halides are employed,[8] (2) most reaction conditions are fairly harsh, usually requiring very high temperatures (>110 °C), (3) strong polar and often toxic solvents (toluene) are used, and (4) the yields are often low. Although the microwave-assisted synthesis of diaryl ethers provides some improvements,[9] the reaction conditions are still fairly harsh and not widely applicable in organic synthesis.

The direct esterification of phenols by aliphatic or aromatic carboxylic acids is virtually impossible due to the poor

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(8) (a) Pearson, A. J.; Bruhn, P. R. *J. Org. Chem*. **1991**, *56*, 7092−7097. (b) Pearson, A. J.; Park, J. G.; Zhu, P. Y. *J. Org. Chem*. **1992**, *57*, 3583−3589. (c) Segal, J. A. *J. Chem. Soc., Chem. Commun*. **1985**, 1338−1339. (d) Pearson, A. J.; Bignan, G. *Tetrahedron Lett*. **1996**, *37*, 735−738.

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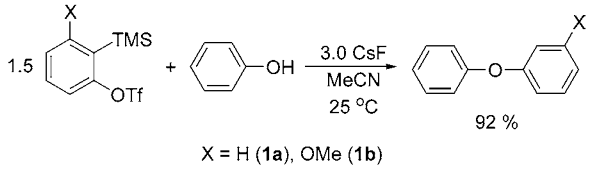
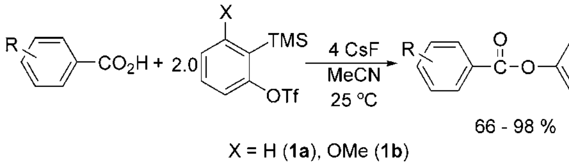
10.1021/ol0361406 CCC: $27.50

Scheme 1



Scheme 2



nucleophilicity of phenols.[10] The direct coupling of aromatic carboxylic acids and aryl halides or the carbonylation of aryl halides using a palladium catalyst to generate the corresponding aryl esters is also difficult.[11] In the classical methods for esterification, a strong acid, such as sulfuric acid, is needed, which is not suitable for acid-sensitive compounds and has the disadvantages of the corrosiveness of the strong acid and accompanying side reactions, such as carbonization, oxidation, etc.[12] Thus, an efficient and reliable procedure to synthesize diaryl ethers from phenols and aryl esters from carboxylic acids under mild reaction conditions, which can tolerate a wide variety of functional groups, would be quite attractive.

Very recently, we have found that silylaryl triflate **1a** in the presence of CsF can react with a variety of amines and sulfonamides to generate *N*-arylated amines and sulfonamides in excellent yields under very mild reaction conditions.[13] Thus, it was a natural extension for us to investigate the *O*-arylation of phenols and carboxylic acids using this silylaryl triflate and CsF. Herein, we report a facile, high-yielding, transition-metal-free method for the *O*-arylation of phenols and carboxylic acids by reacting silylaryl triflates with a variety of phenols and carboxylic acids under very mild reaction conditions.

We first examined the reaction of phenol with 1.2 equiv of 2-(trimethylsilyl)phenyl triflate (**1a)** and 2 equiv of CsF in acetonitrile at room temperature, which are our standard reaction conditions for the *N*-arylation of amines and sulfonamides.[13] We obtained only a 66% yield of the desired diphenyl ether in 20 h. After optimizing this reaction system using phenol and 1.5 equiv of silylaryl triflate **1a**, plus 3.0 equiv of CsF in acetonitrile for 1 d at room temperature, we were able to obtain diphenyl ether in a 92% isolated yield (Scheme 1).

Using these optimal reaction conditions, this method has been applied to the *O*-arylation of a wide variety of phenols (Table 1, entries 1−10). Phenol itself and phenol with an electron-donating *p*-methoxy group react well with silylaryl triflate **1a**[14] to give the corresponding diaryl ethers in high yields (entries 1 and 2). If 4,5-dimethyl-2-(trimethylsilyl)phenyl trifluoromethanesulfonate (**1c**)[15] is allowed to react with *p*-methoxyphenol, we can obtain the corresponding diaryl ether in a 96% yield (entry 3). It should be noted that phenols bearing an electron-withdrawing substituent generally behave poorly or are completely inert toward diaryl ether formation when using aryl halides.[6] However, under our reaction conditions, phenols with an electron-withdrawing group, such as a nitro or aldehyde group, work quite well to generate the corresponding diaryl ethers in high yields (entries 4 and 5). When using the methoxy-substituted silylaryl triflate **1b**,[16] *p*-nitrophenol affords the corresponding diaryl ether as a single isomer in a 96% yield (entry 6). Note that we only obtain the product of nucleophilic attack at the position meta to the methoxy group of the aryne, which is consistent with our earlier results[13] and the work of others with this aryne.[15,17] It is noteworthy that 4-iodophenol reacts well with silylaryl triflates **1a** and **1b** to generate the desired iodo-substituted diaryl ethers in excellent yields (entries 7 and 8). Thus, halides are readily accommodated by our reaction conditions. We believe that this is the first method for diaryl ether formation that readily tolerates halides other than the use of ruthenium-complexed aryl halides.[8d] Interestingly, if we use 1,2-benzenediol, we can obtain a 72% yield of the double *O*-arylation product (entry 9). The sterically hindered phenol 2,4,6-trimethylphenol also reacts smoothly with silylaryl triflate **1a** to afford a 68% yield of the desired product (entry 10). Thus, this chemistry provides a very convenient method to prepare a variety of diaryl ethers that tolerates a number of functional groups and produces very high yields under very mild reaction conditions.

We have also investigated the *O*-arylation of carboxylic acids to generate aryl esters (Scheme 2). As shown in Table 1, entries 11−16, benzoic acid and a number of functionally substituted benzoic acids react smoothly with silylaryl triflates **1a** and **1b** to generate the corresponding aryl esters in high yields. Benzoic acids with an electron-donating group, like a methoxy group (entries 13 and 14), generally afford better yields than benzoic acids with an electron-withdrawing group, like a nitro group (entry 12). Once again, the methoxy-substituted silylaryl triflate **1b** affords only one product in which nucleophilic attack has occurred at the position meta

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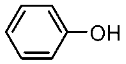
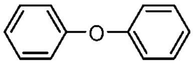
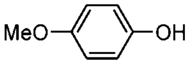
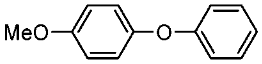
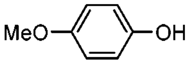
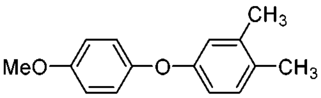
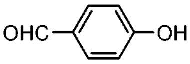
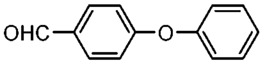
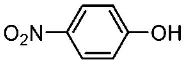
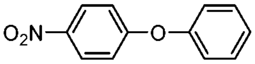
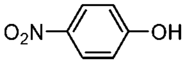
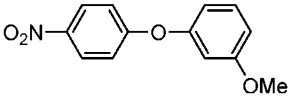
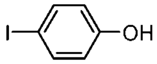
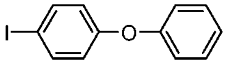
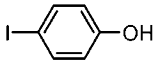
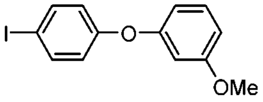
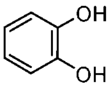
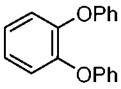
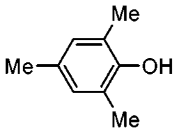
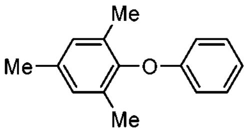
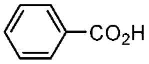
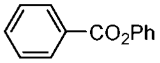
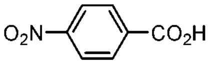
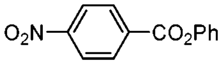
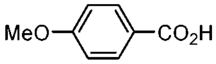
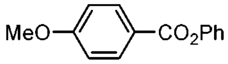
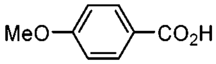
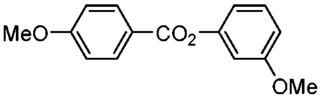
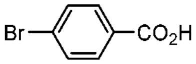
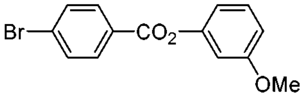
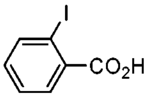
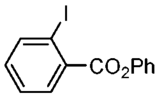
Table 1. Facile *O*-Arylation of Phenols and Carboxylic Acids[a]

entry	phenol or carboxylic acid	aryl triflate (equivs)	CsF (equivs)	product	% isolated yield
1		**1a** (1.5)	3.0		92
2		**1a** (1.5)	3.0		98
3		**1c** (1.5)	3.0		96
4		**1a** (1.5)	3.0		91
5		**1a** (1.5)	3.0		96
6		**1b** (1.5)	3.0		96
7		**1a** (1.5)	3.0		95
8		**1b** (1.5)	3.0		94
9[b]		**1a** (3.0)	6.0		72
10		**1a** (1.5)	3.0		68
11		**1a** (2.0)	4.0		81
12		**1a** (2.0)	4.0		66
13		**1a** (2.0)	4.0		96
14		**1b** (2.0)	4.0		98
15		**1b** (2.0)	4.0		89
16		**1a** (2.0)	4.0		78

[a] Reaction conditions: 0.25 mmol of phenol or carboxylic acid are allowed to react with the number of equivalents of aryl triflate and CsF shown in the table and 4.0 mL of MeCN as solvent at room temperature for 1 d. [b] The reaction time is 2.5 d.

to the methoxy group (entries 14 and 15). Halogen-substituted benzoic acids also work well, generating the desired halogen-substituted aryl esters in good yields (entries 15 and 16). Unfortunately, for reasons we do not presently understand, we have been unable to get acceptable yields of aryl esters from simple aliphatic carboxylic acids.

In summary, we have developed an efficient, mild, transition-metal-free method for the *O*-arylation of phenols and aromatic carboxylic acids. A variety of functional groups are compatible with the reaction conditions. The regioselectivity of the methoxy-substituted aryl triflate **1b** is excellent. Further studies into the scope of different heteroatom-containing substrates and additional silylaryl triflates are currently under way in our laboratories.

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Supporting Information Available: Detailed experimental procedures and characterization data for all previously unknown products. This material is available free of charge via the Internet at http://pubs.acs.org.

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