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Facile N-Arylation of Amines and Sulfonamides

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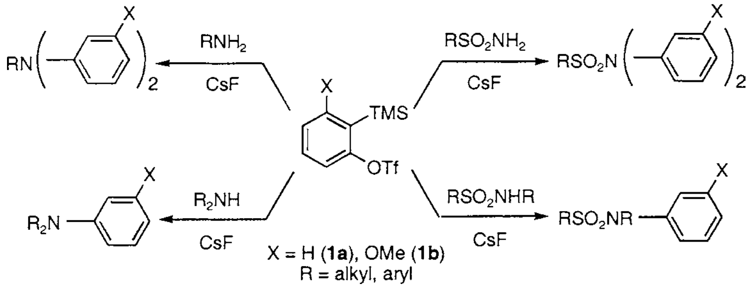
ABSTRACT



A facile, transition-metal-free N-arylation procedure for amines and sulfonamides has been developed, which affords good to excellent yields of arylated products under very mild reaction conditions. A methoxy-substituted aryl triflate affords N-arylated products in high yields with excellent regioselectivity. This chemistry tolerates a variety of functional groups.

Establishing an efficient, reliable methodology for the N-arylation of amines and sulfonamides is currently an active area in organic synthesis. Such subunits are commonly encountered in biologically active compounds,[1] agrochemicals,[2] and compounds of interest in material science.[3] Traditionally, the preparation of arylamines has been carried out under Ullmann-type conditions involving the coupling of amines with aryl halides.[4] Although these copper-promoted reactions are useful, they are usually performed at high temperatures and the yields are not very reproducible.[5] Recently, Buchwald has reported significant improvements in this chemistry.[6] Buchwald[7] and Hartwig[8] have also demonstrated that the palladium-catalyzed N-arylation of a variety of amines by aryl halides is a powerful method for the synthesis of arylamines. Despite these significant recent improvements, there still are limitations in present N-arylation methodology. For example, it is still difficult to prepare N-arylated sulfonamides[9] and present N-arylation methodology may not accommodate certain organic functionality. Of the functional groups that are incompatible with the Cu- or Pd-catalyzed N-arylation methodology, the most important are probably halides and sulfonates,[10] epoxides,[11] and probably carbon−carbon triple bonds. Thus, a simple and general procedure to generate N-arylated products from a variety of

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(2) *CRC Handbook of Pesticides*; Milne, G. W. A., Ed.; CRC Press: Boca Raton, 1994.

(3) (a) Goodson, F. E.; Hartwig, J. F. *Macromolecules* **1998**, *31*, 1700−1703. (b) Goodson, F. E.; Hauck, S. I.; Hartwig, J. F. *J. Am. Chem. Soc.* **1999**, *121*, 7527−7530. (c) Singer, R. A.; Sadighi, J. P.; Buchwald, S. L. *J. Am. Chem. Soc.* **1998**, *120*, 213-214.

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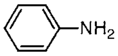
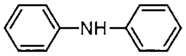
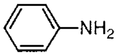
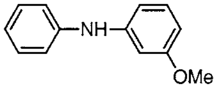
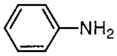
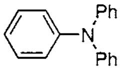
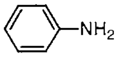
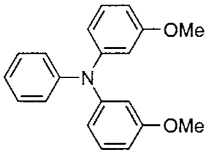
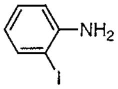
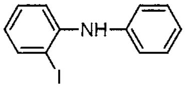
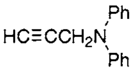
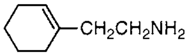
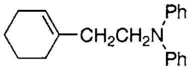
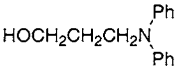
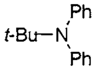
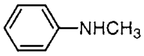
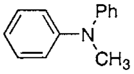
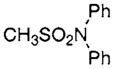
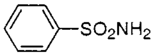
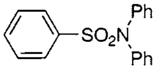
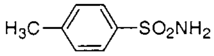
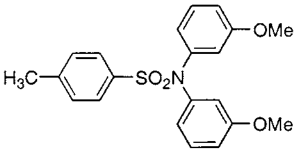
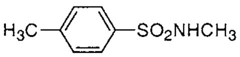
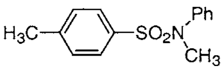
Table 1. Facile N-Arylation of Amines and Sulfonamides[a]

entry	amine/sulfonamide	aryl triflate (equiv)	CsF (equiv)	time (d)	product	% isolated yield
1		**1a** (0.9)	2.0	1		81
2		**1b** (0.9)	2.0	1		84
3		**1a** (2.4)	4.0	3		98
4		**1b** (2.4)	4.0	3		94
5		**1a** (0.9)	2.0	1		83
6	$HC{\equiv}CCH_2NH_2$	**1a** (0.9)	2.0	1	$HC{\equiv}CCH_2NHPh$	62
7	$HC{\equiv}CCH_2NH_2$	**1a** (2.4)	4.0	3	 $HC{\equiv}CCH_2N(Ph)Ph$	78
8		**1a** (2.4)	4.0	3		99
9	$HOCH_2CH_2CH_2NH_2$	**1a** (2.0)	4.0	3	 $HOCH_2CH_2CH_2N(Ph)Ph$	83
10	*t*-$BuNH_2$	**1a** (2.4)	4.0	3	 $t\text{-}Bu{-}N(Ph)Ph$	97
11		**1a** (1.2)	2.0	1		93
12	$CH_3SO_2NH_2$	**1a** (2.4)	4.0	1	 $CH_3SO_2N(Ph)Ph$	80
13		**1a** (2.4)	4.0	1		99
14		**1b** (2.4)	4.0	1		92
15		**1a** (1.2)	2.0	1		87

[a] Reaction conditions: 0.25 mmol of amine or sulfonamide is 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.

amines and sulfonamides, which can tolerate a wide variety of functional groups, remains elusive.

Recently, aryl triflate **1a**[12] has been employed to generate benzyne, which can easily undergo a variety of electrophilic,[13] nucleophilic,[13] and cycloaddition reactions.[14] Nitrogen-containing compounds, such as azirines,[15] oxazoles,[16] pyrroles,[17] and imidazoles,[18] are known to react with arynes to afford N-arylation products. However, the N-arylation of amines[19] and sulfonamides by arynes has not been widely

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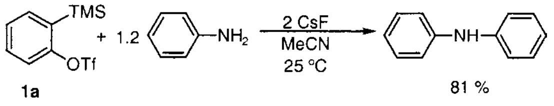
studied due to the difficulty in generating arynes under convenient reaction conditions.

Herein we report the facile, transition-metal-free N-arylation of amines and sulfonamides by the reaction of silylaryl triflates with a variety of amines and sulfonamides. The new procedure is characterized by the following features: (1) The mild base CsF is employed. (2) The reaction is run at room temperature. (3) The procedure works well with a variety of amines and sulfonamides, affording good to excellent yields.

We first allowed 2-(trimethylsilyl)phenyl triflate (**1a)** to react with CsF and 1.2 equiv of aniline in acetonitrile at room temperature for 20 h. Diphenylamine was obtained in an 81% yield (Scheme 1), and only a trace of triphenylamine was isolated (Table 1, entry 1).

Scheme 1



This methodology can be applied to the N-arylation of a variety of primary amines (Table 1**,** entries 1−10). Excess aniline reacts smoothly with aryl triflate **1a** and CsF to give the corresponding secondary amine in an 81% yield (entry 1). It is noteworthy that *o*-iodoaniline also reacts with aryl triflate **1a** to generate the desired iodo-substituted product in an 83% isolated yield (entry 5). Thus, halides are readily accommodated by our reaction conditions. The methoxy-substituted silylaryl triflate **1b** also reacts cleanly with aniline to generate a single isomer in good yield with excellent regioselectivity (entry 2). This regioselectivity can be readily explained by steric and electronic effects, both of which favor nucleophilic attack at the position meta to the methoxy group of the aryne.[18,20] Silylaryl triflate **1a** also reacts with an excess of propargylamine to afford a 62% yield of the secondary N-arylated amine and 15% of the diarylated amine was also isolated (entry 6).

Diarylation products are also readily obtained in excellent yields when an excess of the silylaryl triflate is employed with primary amines (entries 3, 4, and 7−10). A wide variety of alkyl- and arylamines undergo efficient coupling. It should be pointed out that a variety of functional groups, including halides, hydroxyl groups, and carbon−carbon double and triple bonds, survive under our reaction conditions (entries 5−9). A hydroxyl-substituted amine (entry 9) has been observed to react selectively with the NH$_2$ group, instead of the OH group, to afford the corresponding diarylation product in a good yield, although an 8% yield of the O-arylation product was isolated as a side product. Furthermore, we can selectively prepare secondary or tertiary arylamines by simply changing the ratio of the reactants (compare entries 1 and 3, and 2 and 4). As expected, a secondary amine can also be arylated in an excellent yield (entry 11).

Although some effort has been devoted recently to the N-arylation of sulfonamides, the scope of this chemistry with respect to either the sulfonamide or the aryl halide is still very limited.[9,21] As shown in Table 1, entries 12−15, alkane- and arenesulfonamides both efficiently undergo N-arylation under our reaction conditions. Using primary sulfonamides and an excess of triflate, one obtains the corresponding diarylation products in high yield. Unfortunately, we have been unable to effect simple monoarylation of sulfonamides such as RSO$_2$NH$_2$. The methoxy-substituted silylaryl triflate **1b** also reacts cleanly with *p*-toluenesulfonamides to afford a high yield and excellent regioselectivity (entry 14). One can also start with secondary sulfonamides and produce the corresponding tertiary sulfonamides in excellent yield (entry 15).

We have also investigated the use of carboxamides to generate *N*-arylamides, employing the silylaryl triflate **1a** and CsF at room temperature. Unfortunately, only low yields of the corresponding *N*-arylamides could be obtained.

In summary, we have developed an efficient, mild, transition-metal-free method for the N-arylation of amines and sulfonamides. 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 silylaryl triflates are currently underway in our laboratories.

Acknowledgment. We are grateful to the Petroleum Research Fund, administered by the American Chemical Society, for their generous financial support.

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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