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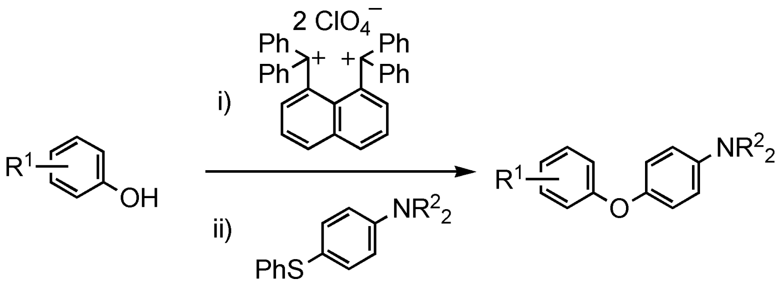

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Bis(triarylmethylium)-Mediated Diaryl Ether Synthesis: Oxidative Arylation of Phenols with *N*,*N*-Dialkyl-4-phenylthioanilines

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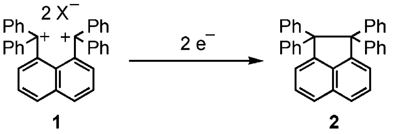
Diaryl ethers constitute an important class of compounds in medicinal and agricultural chemistry, exemplified by the vancomycin family.[1] The classical Ullmann ether synthesis, copper(I)-mediated coupling between phenols and aryl halides, has been extensively used for the preparation of diaryl ethers;[2] however, harsh reaction conditions at high temperatures for long hours have severely limited its utility. Recently, several improved methods have been reported for the Ullmann synthesis that use ionic liquids[3] or catalysts, such as copper−phenanthroline complexes,[4] a 1,3-diketone,[5] or an amino acid.[6] Moreover, palladium-catalyzed coupling reactions using electron-rich bulky phosphine ligands[7] and S$_N$Ar-based reactions of aryl fluorides[2,8] or metal−arene complexes[2] have been employed for diaryl ether formation. Despite the usefulness of these methods, assembling diaryl ethers under mild reaction conditions still remains a challenge.

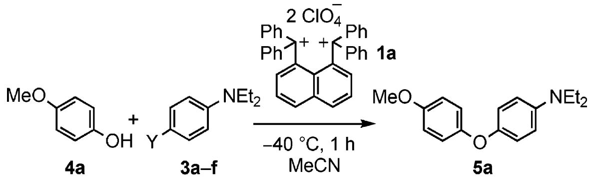
1,8-Bis(diphenylmethylium)naphthalenediyl **1** was first introduced by the group of Gabbaï as the BF$_4^-$ salt,[9] and our group developed an independent synthesis affording the perchlorate salt.[10] These dications undergo reduction with an especially high oxidation potential, compared with those of other dications[11] and monotriarylmethyliums.[12] In this process, a neutral compound, 1,1,2,2-tetraphenylacenaphthene (**2**), is formed via C−C bond formation between the two carbocation centers (Scheme 1).[13]

Scheme 1. Reduction of Dications **1**



Recently, we found that the dications **1** act as an organic two-electron oxidant in the synthesis of benzidines via self-coupling of *N*,*N*-dialkylanilines.[10] Our interest in the oxidizing ability of dications **1** prompted us to apply the oxidative coupling of *N*,*N*-dialkylanilines to the arylation of phenol oxygens. In this communication, we report an oxidative method using dication **1a** for the synthesis of diaryl ethers from phenols and *N*,*N*-dialkyl-4-phenylthioanilines.[14]

Table 1. Effect of the 4-Substituents of Anilines **3**[a]



entry	Y	3	5a (%)
1	Br	**3a**	23
2	Cl	**3b**	33
3	F	**3c**	no reaction
4	Sn^{n}Bu$_3$	**3d**	40
5	SMe	**3e**	7
6	SPh	**3f**	68
7[b]	SPh	**3f**	93[c]

[a] All reactions were performed in the molar ratio of **4a**:**3a**−**f**:**1a** = 2:1:1.2. [b] Molar ratio: **4a**:**3f**:**1a** = 1:2:1.1 (see text). [c] Yield based on **4a**.

As an arylation reagent of phenol oxygens, 4-substituted *N*,*N*-diethylanilines **3** were adopted to suppress the self-coupling reaction at the *para* position. 4-Methoxyphenol (**4a**) was chosen as a model substrate and was treated with **3a**−**f** in the presence of dication **1a** at −40 °C in CH$_3$CN. The results are summarized in Table 1. Aryl bromide **3a**, chloride **3b**, and arylstannane **3d** gave the desired diaryl ether **5a** along with *N*,*N*,*N′*,*N′*-tetraethylbenzidine (entries 1, 2, and 4). Although diaryl ether **5a** was obtained only in 7% yield in the reaction with 4-methylthioaniline **3e** (entry 5), the yield of **5a** was dramatically improved by using 4-phenylthioaniline **3f** up to 68% yield (entry 6).[15] Moreover, when 2.0 molar amounts of **3f** were used and the addition order was changed (conditions A, vide infra), ether **5a** was produced in 93% yield. For comparison, the arylation of phenol **4a** with **3f** was examined by employing DDQ,[16] a triarylaminium radical cation,[17] or cerium ammonium nitrate (CAN),[18] which are widely used as oxidants. While DDQ gave ether **5a** in 48% yield, (4-BrC$_6$H$_4$)$_3$N$^{+\bullet}$SbCl$_6^-$ and CAN resulted in undesirable side reactions without forming **5a**. Thus, dication **1a** is a superior oxidizing agent in the arylation.

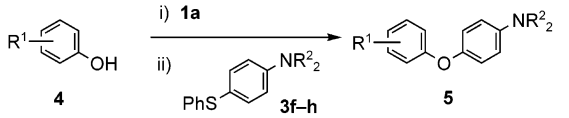
To explore the scope of the oxidative diaryl ether formation, the reactions of several other phenols with **3f** were examined. As shown in Table 2, 4-substituted phenols (4-methoxy- and 2,4-dimethylphenols) and sterically hindered phenols (2,6-dimethyl- and 2,4,6-trimethylphenols) underwent the arylation to afford the corresponding diaryl ethers **5a**−**d** in good yield when treated with **1a** and then **3f** in MeCN at −40 °C (conditions A) (entries 1 and 4−6). The reaction of halogen-substituted phenols with **3f** gave better yields of **5e**−**h** in CH$_2$Cl$_2$ at −78 °C (conditions B, entries 7−10), compared with conditions A. Even a highly hindered 2,6-dichlorophenol was transformed to the corresponding ether **5h** in 82% yield (entry 10). However, 1- and 2-naphthols gave no arylation products, probably due to the ease of oxidative self-coupling.[19]

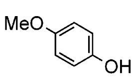
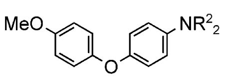
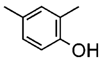
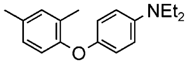
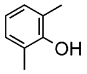
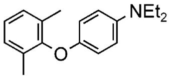
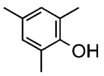
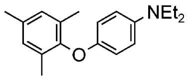
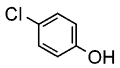
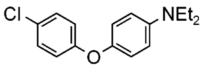
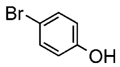
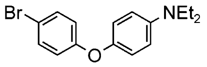
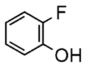
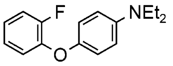
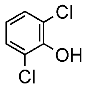
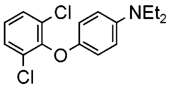
N,*N*-Dibenzyl- and *N*,*N*-diallylanilines **3g**,**h** could also be employed as arylation reagents. The corresponding diaryl ethers **5i**,**j** with 4-dibenzylamino and 4-diallylamino groups were obtained in 69 and 86% yield under conditions B and A, respectively. Deprotection of the groups on the nitrogen provides an amino group, which acts as a surrogate for a wide range of functional groups.[20]

A plausible reaction mechanism for the above-mentioned diaryl ether synthesis is shown in Scheme 2. Treatment of phenols **4** with dication **1a** generates aryloxyl radicals **6**.[21] Subsequently added 4-phenylthioaniline **3f** is also oxidized by the remaining dication **1a**, leading to a stable radical cation **7**,[22] which traps **6** on the sulfur atom to afford sulfonium salts **8**.[23] Successive 1,2-migration of the

10.1021/ja051839n CCC: $30.25

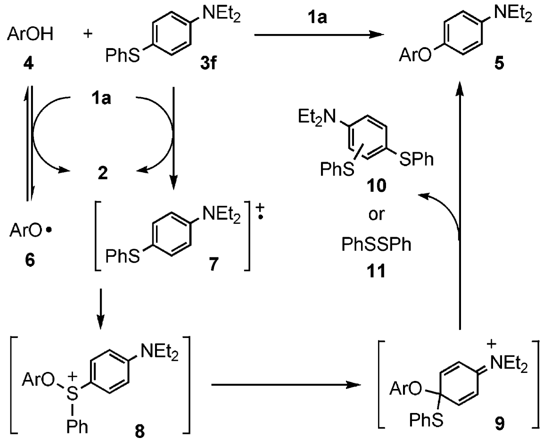
Table 2. 4-Dialkylaminophenylations of Various Phenols[a]



Entry	4	Conditions[b]	5		Yield/%
1		A		5a	93 (86)[c]
2[d]		B		5i	69
3[e]		A		5j	86
4		A		5b	86
5		A		5c	62
6		A		5d	73
7		B		5e	66
8		B		5f	67
9		B		5g	69
10		B		5h	82

[a] All reactions were carried out in the molar ratio of **4**:**1a**:**3f−h** = 1:1.1:2. [b] Conditions A: (i) MeCN, −40 °C, 0.5 h; (ii) −40 °C, 0.5 h. Conditions B: (i) CH_2Cl_2, −78 °C, 0.5 h; (ii) −40 °C, 0.5 h. [c] Conducted in 1.0 mmol scale. [d] $R^2 = CH_2Ph$. [e] R^2 = allyl.

Scheme 2. A Plausible Reaction Mechanism



aryloxy groups proceeds from the sulfur atom to the neighboring carbon atom, the *ipso*-position of the phenylthio group, affording iminium salts **9**. There are two probable pathways from **9** to diaryl ethers **5**. One path involves elimination of a phenylsulfenyl cation, which yields **5** along with phenylsulfenyl adduct **10** of **3f**. In the other path, iminium salts **9** undergo homolytic cleavage of the C−S bond to give a thiyl radical, which leads to diphenyl disulfide (**11**) and the radical cations. Thus, the formed radical cations are reduced with the remaining thioaniline **3f** to afford **5**, due to the high stability of radical cation **7**. Bis(phenylthio)aniline **10** (32% yield) and **11** (62% yield) were isolated as coproducts in the arylation of **4a** (Table 2, entry 1), which supports the two pathways from **9** to **5**.

In conclusion, various aryl 4-dialkylaminophenyl ethers were readily synthesized without heating in good yield from phenols and *N*,*N*-dialkyl-4-phenylthioanilines. This oxidative arylation of phenols was successfully promoted by dication **1a** via *ipso*-substitution of the phenylthio group in the anilines through a radical process.

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Supporting Information Available: Spectroscopic data and experimental details. This material is available free of charge via the Internet at http://pubs.acs.org.

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(22) The color of the reaction mixture changed from red to blue upon addition of **3f**. The ESR spectra of the mixture of **3f** and **1a** in CH_2Cl_2 at 5 K suggested the existence of a radical species.
(23) An ab initio calculation on radical cation **7** was performed at the Hartree−Fock level using the 3-21G* basis set. The SOMO has the largest coefficient on the sulfur atom. Furthermore, on treatment of radical cation **7** with BEt_3, which acts as an ethyl radical donor in the presence of oxygen,[24] ethylation of **7** was effected on the sulfur atom to yield the corresponding sulfonium salt in 13% yield.
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