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Room Temperature, Metal-Free Synthesis of Diaryl Ethers with Use of Diaryliodonium Salts

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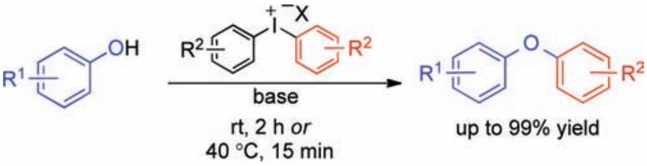
ABSTRACT



A fast, high-yielding synthesis of diaryl ethers with use of mild and metal-free conditions has been developed. The scope includes bulky ortho-substituted diaryl ethers, which are difficult to obtain by metal-catalyzed protocols. Halo-substituents, racemization-prone amino acid derivatives, and heteroaromatics are also tolerated. The methodology is expected to be of high utility in the synthesis of complex molecules and in the pharmaceutical industry.

Diaryl ethers are common structural features in numerous natural products and biologically active compounds.[1] The total synthesis of vancomycin and other glycopeptide antibiotics, as well as anti-HIV agents like chloropeptin, which contain this substructure, has received considerable attention.[2] Despite more than a century of immense focus on finding efficient synthetic routes to this compound class, substituted diaryl ethers remain difficult to obtain for applications in life science and the polymer industry.[3]

The classical Ullmann synthesis from phenols and aryl iodides requires stoichiometric amounts of copper and harsh reaction conditions.[4] The catalytic reaction conditions since developed require high catalyst loadings, excess reagents, elevated temperatures, and long reaction times.[1,3,5] Recent progress includes the copper-catalyzed coupling of phenols and arylboronic acids.[6] This ligand-assisted reaction proceeds at room temperature, but excess amounts of reagents are often needed.[3]

Pd-catalyzed cross-couplings of phenols and aryl halides were reported in 1999,[7] and give high yields of a range of diaryl ethers.[3] Still, they rely on high reaction temperatures and expensive, noncommercial ligands. Furthermore, heteroaromatics and ortho-substituted coupling partners are often challenging in both Cu- and Pd-catalyzed

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Scheme 1. Synthetic Strategies To Form Diaryl Ethers

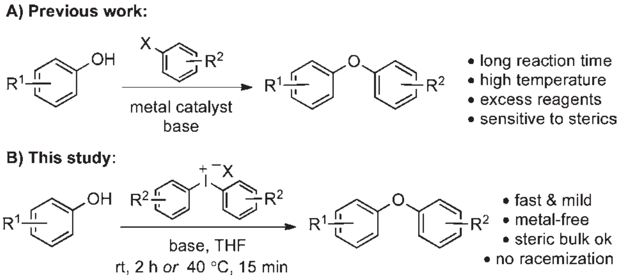
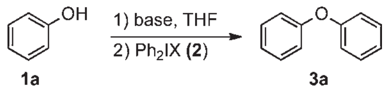


Table 1. Optimization of the Model Reaction[a]



entry	base	**2** (X)	temp (°C)	time	yield (%)[b]
1	NaH	**2a** (OTf)	rt	4 h	93
2	NaOH	**2a** (OTf)	rt	4 h	>99
3	*t*-BuOK	**2a** (OTf)	rt	4 h	97
4	NaOH	**2a** (OTf)	40	1 h	99
5	NaOH	**2b** (BF_4)	40	1 h	>99
6	*t*-BuOK	**2a** (OTf)	40	15 min	>99
7	*t*-BuOK	**2a** (OTf)	rt	2 h	95

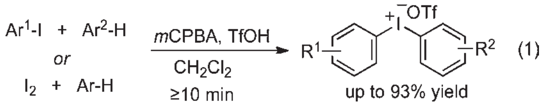
[a] Base (1.1 equiv) and **1a** (1.1 equiv) were stirred at 0 °C for 15 min before addition of salt **2** (1 equiv). [b] Determined by GC with 1,4-dimethoxybenzene as internal standard.

protocols (Scheme 1A).[3] Thallium(III)-mediated oxidative couplings have been employed in natural product synthesis, although the demand for excess toxic thallium reagent makes this approach unsuitable for large-scale reactions.[8]

Metal-free methods with limited scope include reactions with benzyne intermediates[9] and S_NAr additions to electron-poor aryl halides under mild conditions.[10] The synthesis of diaryl ethers from phenols and diaryliodonium salts was reported already in the 1950s.[11] The reaction employed diaryliodonium halides and inorganic bases in protic solvents, and required prolonged reaction times and high temperature to give diaryl ethers in moderate to good yields.[12−14]

The use of diaryliodonium salts has recently gained considerable attention in organic synthesis.[15] Their properties allow for both metal-catalyzed[16] and metal-free reactions,[17] avoiding the drawbacks of organometallic chemistry, such as cost, toxicity, and threshold values in pharmaceutical products.

We and others have developed efficient one-pot routes to diaryliodonium salts, and these compounds are now inexpensive and easily available (eq 1).[18] We are presently investigating these selective and nontoxic reagents as electrophilic arylating agents,[19] and herein we present our preliminary results on the arylation of phenols under mild and racemization-free conditions (Scheme 1B).



The previous use of base in refluxing protic solvents is detrimental to racemization-prone substrates, such as α-amino acid-substituted phenols that are common in natural products. We envisioned that a mild arylation procedure could be developed by using aprotic solvents and diaryliodonium triflates or tetrafluoroborates, as salts with those anions are soluble also in less polar solvents.[20]

Phenol (**1a**) and diphenyliodonium triflate (**2a**) were chosen as model substrates in the optimization of reaction conditions yielding diphenyl ether (**3a**). An initial solvent screening with NaH as base revealed that DMF, toluene, THF, and dichloromethane all gave >90% conversion within 4 h at room temperature, while acetonitrile was less efficient. Further optimization was performed in THF,

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(12) Recent reports: (a) Crimmin, M. J.; Brown, A. G. *Tetrahedron Lett.* **1990**, *31*, 2017 (MeOH or DMF, 95 °C). (b) Huang, X.; Zhu, Q.; Xu, Y. *Synth. Commun.* **2001**, *31*, 2823 (DMF, 100 °C, 10 h). In synthesis of polybrominated ethers:(c) Teclechiel, D.; Sundström, M.; Marsh, G. *Chemosphere* **2009**, *74*, 421 (water/dioxane, 80 °C, 3 h). (d) Liu, H.; Bernhardsen, M.; Fiksdahl, A. *Tetrahedron* **2006**, *62*, 3564 (H_2O, reflux, 2 h). (e) Marsh, G.; Stenutz, R.; Bergman, A. *Eur. J. Org. Chem.* **2003**, 2566 (H_2O/dioxane, 80 °C, 1−8 h). (f) Couladouros, E. A.; Moutsos, V. I.; Pitsinos, E. N. *ARKIVOC* **2003**, 92 (DMF, 90 °C, 3 h).

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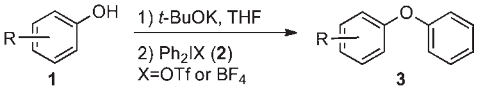
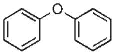
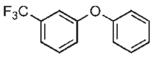
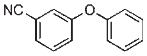
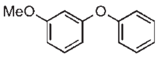
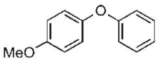
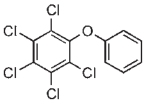
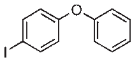
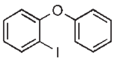
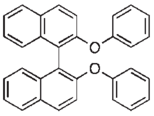
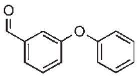
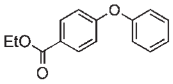
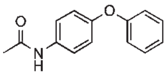
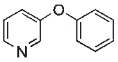
(20) The nucleophilicity of the phenoxide was expected to increase in an aprotic solvent. The previous use of protic solvents is likely due to insolubility of diaryliodonium halides in aprotic media.

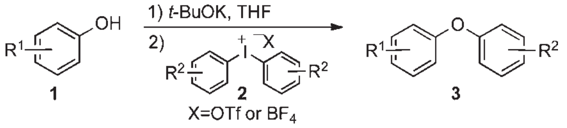
Table 2. Phenylation of Functionalized Phenols **1**[a]

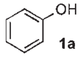
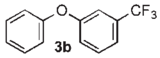
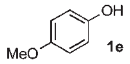
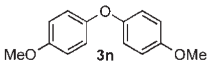
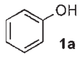
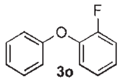
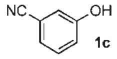
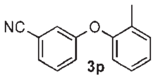
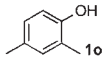
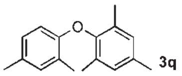
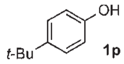
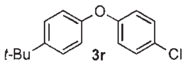
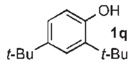
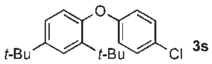
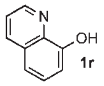
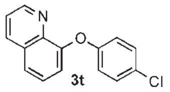


entry	1	2	temp (°C)	diaryl ether 3		yield (%)
1	**1a**	**2a**	40		**3a**	93
2	**1a**	**2b**	40		**3a**	98
3[b]	**1a**	**2b**	40		**3a**	95
4	**1a**	**2b**	rt		**3a**	99
5	**1b**	**2a**	40		**3b**	82
6	**1c**	**2a**	40		**3c**	72
7	**1d**	**2b**	40		**3d**	85
8	**1d**	**2b**	rt		**3d**	99
9	**1e**	**2a**	40		**3e**	79
10	**1f**	**2a**	40		**3f**	99
11	**1g**	**2a**	40		**3g**	87
12	**1h**	**2a**	40		**3h**	89
13[c]	**1i**	**2a**	40		**3i**	99
14	**1j**	**2a**	40		**3j**	75
15	**1j**	**2b**	rt		**3j**	80
16	**1k**	**2b**	40		**3k**	97
17	**1k**	**2b**	rt		**3k**	91
18	**1l**	**2a**	40		**3l**	67
19	**1m**	**2a**	40		**3m**	87

[a] **1** (1.0−1.1 equiv), *t*-BuOK (1.1 equiv), and **2** (1.0−1.2 equiv) were used. [b] NaOH as base. [c] 2 equiv of **2a**.

Table 3. Arylation of Functionalized Phenols **1** with Salts **2**[a]



entry	phenol 1	salt 2	diaryl ether 3	yield (%)
1		**2c**		90
2		**2d**		86
3		**2e**		72
4		**2f**		90
5		**2g**		99
6		**2h**		99
7		**2h**		81
8		**2h**		98

[a] **1** (1.0−1.1 equiv), *t*-BuOK (1.1 equiv), and **2** (1.0−1.2 equiv) were used at 40 °C.

and both NaOH and *t*-BuOK proved more efficient than NaH (Table 1, entries 1−3).

At 40 °C, the reaction went to completion within 1 h, and tetrafluoroborate **2b** worked equally well as triflate **2a** (entries 4 and 5). The reaction time was finally investigated, and **3a** was obtained in excellent yield already within 15 min at 40 °C or 2 h at room temperature (entries 6 and 7).

The reaction scope was subsequently explored by using substituted phenols **1** and diphenyliodonium triflate **2a** or tetrafluoroborate **2b**. Excellent isolated yields of diphenyl ether **3a** were obtained with both salts at 40 °C (Table 2, entries 1 and 2). Reactions employing NaOH or room temperature provided equally good results (entries 3 and 4). Phenols with electron-withdrawing substituents worked equally well as those with electron-donating substituents, giving diaryl ethers **3b**−**e** in high yields (entries 5−9).

Arylation of pentachloro phenol **1f** resulted in quantitative yield of product **3f** (entry 10). Likewise, iodo-substituted substrates **1g**,**h** delivered the corresponding diaryl ethers **3g**,**h** that can easily be used in cross-coupling reactions (entries 11 and 12). These products would be difficult to obtain with Pd-catalyzed reactions due to chemoselectivity problems, which nicely illustrates the potential of the developed methodology.

Ortho-substituted phenols are problematic substrates in metal-mediated arylations.[1b,3a] Gratefully, steric bulk posed no problem in this reaction, as exemplified by *o*-iodo product **3h** (entry 12). The sterically hindered 1,1′-bi-2-naphthol (**1i**) was an excellent substrate, delivering the diarylated product as a precipitate without need for further purification (entry 13).

Carbonyl-substituted phenols **1j**−***l***, including paracetamol, were also arylated in good yields (entries 14−18). Furthermore 3-hydroxypyridine, which is a privileged scaffold, was smoothly phenylated to give **3m** in high yield (entry 19).

All reactions were run without precautions to avoid air or moisture. The temperature was selected to 40 °C for conveniently short reaction times. It should be stressed that room temperature works equally well, as demonstrated in entries 4, 8, 15, and 17. Likewise, *t*-BuOK was chosen as base for practical reasons, but NaOH can also be used (entry 3). Oxidative dearomatization of the phenol was not observed.[14]

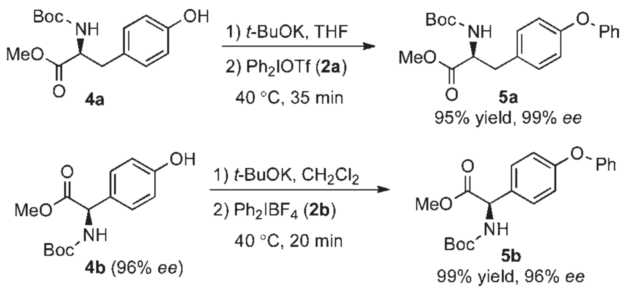
Various symmetrical diaryliodonium salts **2** were subsequently employed. Electron-deficient salt **2c** efficiently arylated **1a** to give CF_3-substituted product **3b** (Table 3, entry 1, cf. Table 2, entry 5). The electron-rich salt **2d** delivered dimethoxy ether **3n** without difficulties (entry 2). Steric hindrance in the diaryliodonium salt posed no problem, as bis(ortho-substituted) salts **2e**,**f** arylated phenols **1a**,**c** to give **3o**,**p** (entries 3 and 4).

Even highly substituted diaryl ether **3q**, with three ortho substituents, was obtained in quantitative yield (entry 5). *p*-Chloro salt **2h** was employed to arylate a range of phenols. Notably, 2,4-di(*tert*-butyl) phenol **1q** delivered **3s** in high yield, despite the severe steric hindrance from the ortho substituent (entry 7). Quinolin-8-ol (**1r**) was also arylated with **2h** to give heteroaryl ether **3t** in excellent yield (entry 8).

The mild conditions of this protocol were demonstrated by arylation of the racemization-prone tyrosine derivative **4a** and aryl glycine derivative **4b** (Scheme 2). Both α-amino acid derivatives were arylated in excellent yields without loss of enantiomeric excess.[21]

To conclude, we have developed a fast, high-yielding synthesis of diaryl ethers. The reaction conditions are mild, metal-free, and avoid the use of halogenated solvents, additives, or excess reagents. Precautions to avoid air or moisture are not needed. The scope includes ortho- and halo-substituted diaryl ethers, which are difficult to obtain by metal-catalyzed protocols.

Scheme 2. Arylation of α-Amino Acid Derivatives **4a** and **4b**



The potential of the developed methodology has been demonstrated by arylation of two α-amino acid derivatives without racemization. With the recent advancements in efficient synthetic procedures for diaryliodonium salts, the reagents are now inexpensive and easily available. The application to aliphatic alcohols is underway, and will be reported in due time.

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Supporting Information Available. Experimental procedures, analytical data, and ^1H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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[21] Phenol **4b** was arylated in dichloromethane, as a byproduct lowered the yield in THF.