The Directed Ortho Metalation−Ullmann Connection. A New Cu(I)-Catalyzed Variant for the Synthesis of Substituted Diaryl Ethers

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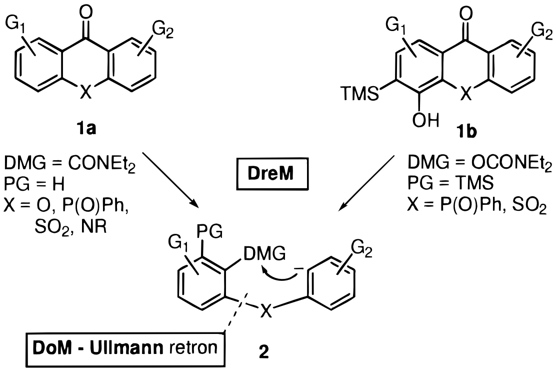
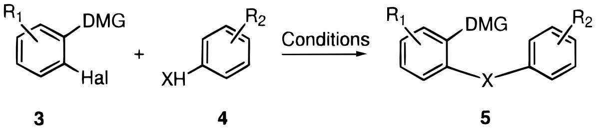
The recent reports by Buchwald, Hartwig, and others have posited valuable new Pd-catalyzed C−N, C−O, and C−S bond coupling methodology for aromatic substrates,[1,2] which is beginning to supplant the classical Ullmann reaction.[3] The utility of diaryl ethers as synthetic intermediates and their structural presence in a variety of bioactive and natural products[4] provides a strong incentive for further method development. In the course of work demonstrating a combined Directed ortho and remote metalation (DoM and DreM) method for the construction of thioxanthones,[5a] xanthones,[5b] acridones,[6] and dibenzo[*b*,*e*]phosphinones,[7] from the corresponding diaryl sulfones, ethers, amines, and phosphine oxides, respectively, **2** → **1a**,**b** (Scheme 1), we have uncovered a new variation of the Buchwald procedure[1a] for systems **2** that augments the synthetic scope and convenience for the construction of substituted diaryl ethers. Herein, we disclose this methodology, which embodies the following features: (a) it employs $CuPF_6(MeCN)_4$ (5 mol %)[8] rather than the air-labile $CuOTf(C_6H_6)_{0.5}$ complex in refluxing toluene or xylenes in the presence of obligatory Cs_2CO_3 (2 equiv) as base;[1a] (b) it is successful for *o*-halo tertiary and secondary benzamides and sulfonamides **3** (Scheme 2), which are reported to be poorly behaved substrates;[1a] the results obtained allow the DoM connection[9,10] and hence regiospecific access to 1,2,3-contiguous aromatic substitution patterns; (c) iodo, bromo, and, in contrast to previous Ullmann generalizations,[1a,3] secondary chloro benzamides serve as coupling partners; (d) thiophenol and benzylamine undergo smooth coupling reactions; and (e) using double Ullmann and Ullmann−Negishi protocols, it may be extended to the assemblage of Ar−O−Ar′-O−Ar″ and Ar−Ar′−O−Ar″ motifs, **7** and **8**, which are structural components of biologically active and natural products.[4]

Scheme 1



DoM / DreM = Directed *ortho* / remote Metalation
DMG = Directed Metalation Group
xanthones (X = O); thioxanthones (X = SO_2);
acridones (X = NH, NR); dibenzo[*b*,*e*]phosphinones (X = P(O)Ph)

Scheme 2[a]



DMG = CONHEt, $CONEt_2$, SO_2NHEt, SO_2NEt_2
Hal = I, Br, Cl
X = O, S

[a] Conditions: 1.2−1.5 equiv of **4**/0.05 equiv of $CuPF_6(MeCN)_4$/2 equiv of Cs_2CO_3/toluene or xylenes/reflux/5−45 h.

Selected results (Table 1) are illustrative of the scope of the methodology. Treatment of *N*-ethyl 2-iodobenzamide with *m*-cresol in the presence of $CuPF_6(MeCN)_4$ complex (5 mol %)[8] and Cs_2CO_3 (2 equiv)[1a] in refluxing toluene for 24 h indicated complete consumption of starting material (GC) and formation of a 97:3 mixture of diaryl ether (**5a**) and deiodinated starting benzamide; normal workup and distillation afforded pure product in 88% yield (entry 1). Cs_2CO_3 appears to be the base of choice, which is attributed to a higher solubility of the formed ArOCs species.[1a] The effect of catalyst solubility on the outcome of the reaction was examined by experiments with the common, notably soluble, Cu(I) sources, CuI and Cu_2O. Both catalysts are as effective as $CuPF_6$ (Table 1, footnote c) but, similar to CuOTf, require longer times compared to $CuPF_6$ for completion of reaction (GC monitoring). 2-Bromo benzamide (entry 2) was equally effective to the iodo derivative; even *N*-ethyl 2-chlorobenzamide (entry 3) led to satisfactory yields of diaryl ether product but required higher reaction temperatures (xylenes,

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(4) See, *inter alia*: Evans, D. A.; Dinsmore, C. J.; Watson, P. S.; Wood, M. R.; Richardson, T. I.; Trotter, B. W.; Katz, J. L. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 2704−2708. Nicolaou, K. C.; Takayanagi, M.; Jain, N. F.; Natarajan, S.; Koumbis, A. E.; Bando, T.; Ramanjulu, J. M. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 2717−2719. Sawyer, J. S.; Schmittling, E. A.; Palkowitz, J. A.; Smith, W. J., III. *J. Org. Chem.* **1998**, *63*, 6338−6343 and references therein. Boger, D. L.; Miyazaki, O. L.; Beresis, R. T.; Castle, S. L.; Wu, J. H.; Jin, Q. *J. Am. Chem. Soc.* **1998**, *120*, 8920−8926.

(5) (a) Beaulieu, F.; Snieckus, V. *J. Org. Chem.* **1994**, *59*, 9, 6508−6509. (b) Familoni, O. B.; Ionica, I.; Bower, J. F.; Snieckus, V. *Synlett* **1997**, 1081−1083.

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(7) Gray, M.; Chapell, B. J.; Taylor, N. J.; Snieckus, V. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1558−1560.

(8) Kubas, G. J. *Inorg. Synth.* **1979**, *19*, 90−92.

(9) Snieckus, V. *Chem. Rev.* **1990**, *90*, 879−933.

(10) Maillet, M.; Snieckus, V. Unpublished results.

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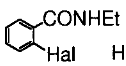
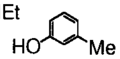
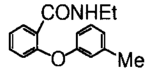
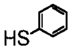
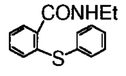
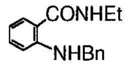
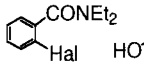
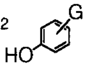
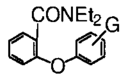
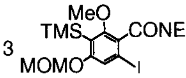
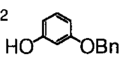
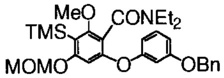
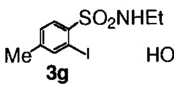
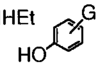
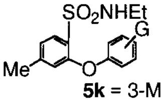
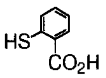
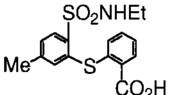
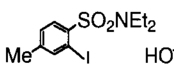
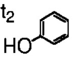
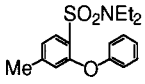
Table 1. Cu(I)-Catalyzed Ullmann Synthesis of 5[a]

Entry	Arylhalide 3	Phenol/Thiophenol 4	Diaryl ether/sulfide 5	yld, %[b]
				
1	**3a** Hal = I		**5a**	88
2[c]	**3b** = Br			92
3	**3c** = Cl			58
4	**3a**		 **5b**	97
5	**3a**	H_2N-Bn	 **5c**	85
				
6	**3d** Hal = I		**5d** = 2-Me	74
7			**5e** = 3-Me	71
8			**5f** = 4-F	77
9			**5g** = 4-OMe	77
10			**5h** = 3,4-diOMe	78
11	**3e** = Br		**5i** = H	88
12[c]			**5e**	74
13	 **3f**		 **5j**	47
				
14	**3g**		**5k** = 3-Me	60
15			**5l** = 2-CONEt$_2$	49
16[d]	**3g**		 **5m**	65
17	 **3h**		 **5n**	76

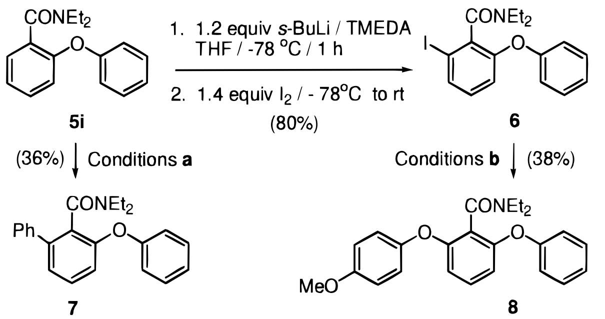
[a] Unless otherwise noted, CuPF$_6$(MeCN)$_4$ was used as catalyst. [b] Yields are of purified materials. Solvent: xylenes (entries 3, 6–12, and 17) and toluene (entries 1, 2, 4, 5, and 14–16) at 0.5 M. For entry 13, the reaction was performed in a sealed tube at 140 °C using toluene as solvent. GC analysis of crude reaction mixture inducated 1–5% formation of dehalogenated starting material for entries 1, 2, 4, and 5 and 7–17% for entries 3 and 6–12. [c] Using **3b**, yields of **5a** with CuI (84%) and Cu$_2$O (83%), respectively. Using **3e**, yields of **5e** with CuI (71%) and Cu$_2$O (75%), respectively. [d] 1.1 equiv of **4** and 3 equiv of Cs$_2$CO$_3$ were used.

140 °C). High yields were achieved in coupling with thiophenol (entry 4) and benzylamine (entry 5); on the other hand, *p*-anisidine showed incomplete reaction.[11,12]

In contrast to secondary amides, tertiary 2-iodo and 2-bromo benzamides were less reactive, requiring refluxing xylenes (140 °C) conditions (entries 6–12). Reaction of **3d** with 2,6-dimethylphenol produced primarily deiodinated product, undoubtedly reflecting a steric effect. Even a multifunctional benzamide provided a highly substituted diaryl ether in preparatively useful yield (entry 13). *N*,*N*-Diethyl 2-chlorobenzamide failed to produce synthetically meaningful amounts of diaryl ether. The higher reactivity of secondary compared to tertiary benzamides may be due to formation of soluble and therefore more reactive Cu–amide complexes of the former under the slightly basic reaction conditions.[13]

The CuPF$_6$/Cs$_2$CO$_3$ conditions were also successful for the Ullmann reaction of *o*-iodo-*p*-toluenesulfonamides, available by regioselective metalation/iodination,[10] with representative phenol partners (entries 14–17, Table 1). As observed for benzamides, coupling was incomplete with *p*-anisidine.[11]

Scheme 3[a]



[a] Conditions: (a) 1.1 equiv of *s*-BuLi/THF/–78 °C/1 h/then ZnCl$_2$/1.4 equiv of PhI/0.1 equiv of PdCl$_2$(PPh$_3$)$_2$/0.2 equiv of DIBALH/rt/16 h; (b) 1.2 equiv of 4-(MeO)C$_6$H$_4$OH/0.05 equiv of CuPF$_6$(MeCN)$_4$/2 equiv of Cs$_2$CO$_3$/xylenes/reflux/24 h.

To provide additional synthetic scope, sequential DoM–Ullmann coupling and DoM–transition metal catalyzed cross coupling reactions were investigated (Scheme 3). Thus, diaryl ether **5i** (Table 1, entry 11) was selectively transformed into the corresponding 2-iodo derivative **6** in high yield using the standard DoM protocol for the powerful amide DMG.[9] CuPF$_6$-catalyzed coupling of **6** with *p*-methoxyphenol provided the bis-diaryl ether **8** in 38% yield (isolated).[14] On the other hand, one-pot lithiation of **5i**, transmetalation with ZnCl$_2$, and cross coupling with iodobenzene under Negishi conditions[15] led to the triaryl diether **7** in 36% yield. Despite the modest yields, these results illustrate new routes to regiospecifically designed products of mixed aryl–aryl and aryl–*O*–aryl structural motifs.[16]

In summary, we have established a new variant of the Buchwald catalytic Ullmann diaryl ether synthesis,[1a] **3** + **4** → **5**, using CuPF$_6$ as a more convenient, air insensitive copper source compared to the CuOTf–benzene complex. Synthetic scope has been established in coupling of *o*-iodo and -bromo benzamides and the corresponding sulfonamides with phenols, thiophenols, and benzylamine.[16] In contrast to the previous study,[1a] secondary and tertiary benzamides have been shown to be well tolerated in the coupling process. Connections between DoM and Negishi cross coupling and the Ullmann process, **5i** → **7**, **8**, indicate further reaction links from which diverse synthetic application may be anticipated.

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Supporting Information Available: Experimental procedures with spectral data (NMR, IR, MS) for all new compounds.

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[11] Reactions of **3a** and **3g** with *p*-anisidine resulted in low conversions into the corresponding diarylamines (<40% yields). Polymerization of anilines in the presence of CuPF$_6$ has been reported: Suzuki, T.; Hasegawa, K.; Ando, O. JP 63243130 1988; *Chem. Abstr.* **1988**, *110*, 86797q.

[12] In the reaction of *N*-(2-bromophenyl)pivaloylamide with *m*-cresol and 2,6-dimethylphenol 2-*t*-butylbenzoxazole was obtained as the major product. Se also: Perry, R. J.; Wilson, B. D. *J. Org. Chem.* **1992**, *57*, 6351–6354 (for details, see the Supporting Information).

[13] For studies of CuI-benzamide complex formation and thermal reactions, see: Broadbelt, L. J.; Klein, M. T.; Dean, B. D.; Andrewa, S. M. *J. Polymer. Sci. A: Polymer Chem.* **1997**, *35*, 3305–3322.

[14] Formation of a 75:23:5 mixture of **8**:**5i**:**6** was observed (GC analysis).

[15] Negishi, E.-I.; Bagheri, V.; Chatterjee, S.; Luo, F.-T.; Miller, J. A.; Stoll, A. T. *Tetrahedron Lett.* **1983**, *24*, 5181–5184.

[16] Phenolic diaryl ethers are of current interest in polymer synthesis; see: Higashimura, H.; Fujisawa, K.; Moro-oka, Y.; Kubota, M.; Shiga, A.; Terahara, A.; Uyama, H.; Kobayashi, S. *J. Am. Chem. Soc.* **1998**, *120*, 8529–8530.