A General Copper-Catalyzed Synthesis of Diaryl Ethers

Jean-François Marcoux, Sven Doye, and
Stephen L. Buchwald*

Department of Chemistry
*Massachusetts Institute of Technology*
Cambridge, Massachusetts 02139

Diaryl ethers are useful intermediates in organic synthesis[1] and are found in a large number of biologically active compounds.[2] The Ullmann ether synthesis[3] has been extensively used for the formation of diaryl ethers.[4,5] However, the harsh reaction conditions (125−220 °C in neat phenol or solvents such as pyridine, collidine, or DMF), the usual requirement for stoichiometric (or greater) quantities of the copper complex, and the fact that unactivated aryl halides usually react in low yields have limited the utility of this reaction.[4] Recent efforts to develop procedures which are applicable to more complex synthetic intermediates have met with only limited success[5a,6] or require the use of an activating group.[7]

We now report a general procedure for the formation of diaryl ethers from the reaction of aryl bromides and iodides with a variety of phenols (Scheme 1). The new procedure is characterized by the following features: (a) its use of a *catalytic* amount of a copper complex (0.25 to 2.5 mol %), (b) its use of cesium carbonate as a base, which eliminates the need to form the phenoxide anion prior to the reaction, (c) its ability to employ a nonpolar solvent (toluene) and lower reaction temperatures than previous reactions, and (d) its use of a stoichiometric amount of a carboxylic acid in the reactions of unactivated aryl halides with less soluble phenols and phenols containing electron-withdrawing groups.

During a study directed toward finding new catalytic methods for the preparation of diaryl ethers, we discovered that cesium carbonate was particularly effective as a base in Ullmann

Scheme 1
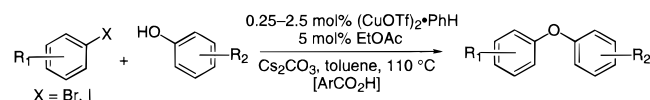
coupling procedures with unactivated aryl bromide substrates in DMF. To the best of our knowledge, the use of cesium carbonate for the Ullmann diaryl ether synthesis has never been reported. These results prompted us to try the reaction in less polar solvents to avoid the problems associated with the use of toxic, high-boiling or water-soluble solvents such as DMF and pyridine. Toluene was found to be the most effective solvent when a catalytic amount of ethyl acetate (5 mol %) was included in the reaction mixture.[8,9] A survey of reactions with a number of other bases (Et$_3$N, DIPEA, DBU, 1,2,2,6,6-pentamethylpiperidine, dicyclohexylmethylamine), including other carbonates, such as K$_2$CO$_3$, Li$_2$CO$_3$, Na$_2$CO$_3$, and BaCO$_3$, confirmed that cesium carbonate is a key element responsible for the improved reaction conditions. The choice of the copper catalyst did not appear to be critical; CuCl, CuBr, CuI, CuBr$_2$, and CuSO$_4$ gave similar results. The use of (CuOTf)$_2$·benzene led to slightly accelerated reaction rates, presumably due to the higher solubility of (CuOTf)$_2$·benzene in toluene, compared to other copper salts, increasing the rate of formation of the reactive copper catalyst. A slight excess of the phenol was employed (0.4−1.0 equiv excess) since the use of 1.0 equiv resulted in very slow conversion as the reaction neared completion.

As shown in Table 1, the procedure employing cesium carbonate as base is extremely effective in coupling phenols with both activated and unactivated aryl bromides and iodides. Consistent with previous studies, aryl iodides react faster than aryl bromides, and aryl chlorides are unreactive.[4,10] The reaction conditions are compatible with a wide range of functionalized substrates, including those containing ethers, ketones, carboxylic acids, esters, dialkylamines, nitriles, nitro groups, and aryl chlorides, whereas those containing primary and secondary amides were found to be poor substrates. This method is particularly suitable for unactivated aryl halides and *ortho*-substituted phenols; e.g., coupling of the sterically demanding 2-isopropylphenol with 2-iodo-*p*-xylene proceeds in high yield (entry 15). Reactions employing 2,6-dimethylphenol were inefficient, and reductive homocoupling of the 5-iodo-*m*-xylene was the major reaction observed (entry 13). Surprisingly, *p*-cresol was less reactive than *o*-cresol or 3,4-dimethylphenol (entries 8−10), and the use of phenol or *p*-chlorophenol produced only small amounts of the desired ethers (entries 18,-20). In these cases, we surmised that the lower solubility of the corresponding cesium phenolate or of the phenoxide−copper complex may account for the lack of reactivity. To circumvent this limitation, we investigated the use of different additives that could help solubilize the key intermediates. We found that stoichiometric quantities of certain carboxylic acids,[11] particularly 1-naphthoic acid, in the presence of molecular sieves[12] promoted the reaction of less reactive phenols. The resulting new procedure allowed for the first time the successful Ullmann coupling of unactivated aryl halides and less reactive phenols,

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(8) The formation of more soluble copper(I) complexes, resulting from the formation of an adduct between the added ester and the alkoxide, has been proposed to be responsible for the rate enhancement. Capdevielle, P.; Maumy, M. *Tetrahedron Lett.* **1993,** *34,* 1007.

(9) Addition of more than 5 mol % of ethyl acetate resulted in lower conversions.

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(11) 2-Thiophenecarboxylic acid has been reported to enhance the reductive homocoupling of aryl iodides: Zhang, S.; Zhang, D.; Liebeskind, L. S. *J. Org. Chem.* **1997,** *62,* 2312.

(12) The reaction between 1-naphthoic acid and cesium carbonate leads to the formation of some water. The addition of 5 Å molecular sieves increases the rate of the reaction by removing the water thus formed.

Table 1. Copper(I) Triflate-Catalyzed Formation of Diaryl Ethers in Toluene in the Presence of Cesium Carbonate[h]

Entry	Halide	Phenol	Aryl ether	Equiv of phenol	Isolated yield without additive (%)[a]	Isolated yield with additive (%)[b]
	(R-C6H4-X)	(HO-C6H3(Me)Me)	(R-C6H4-O-C6H3(Me)Me)			
1	X = I, R = Cl			1.4	89 (87)[c]	
2	Br	COOEt		1.4	80[d]	
3	I	Me		1.4	87 (86)[c] (72)[e]	
4	Br	t-Bu		1.4	85	
5	I	t-Bu		1.4	91	
6	I	OMe		1.4	77	
7	Br	NMe₂		1.4	83	
8				1.4	90	
9				1.4	87	
10				1.4	29	80
11				2.0	85	
12				2.0	84	
13				2.0	20-30[f]	
14				1.4	76	
15				1.4	83	
16				2.0	5[g]	79
17				2.0		88
18				1.4	0[g]	81
19				2.0		93
20				2.0	34[g]	79 (69)[c]

[a] All reactions were conducted in toluene at 110 °C in the presence of 1.4 or 2.0 equiv of Cs₂CO₃, 2.5 mol % of (CuOTf)₂·PhH (5 mol % Cu) and 5 mol % of EtOAc for 12–26 h. [b] An equimolar amount of 1-naphthoic acid (compared to the cesium carbonate) and 250 mg/mmol of activated 5 Å molecular sieves were added to the mixture. [c] 0.25 mol % of (CuOTf)₂·PhH was used. [d] The partial hydrolysis of the ester could be avoided by adding 250 mg/mmol of activated 5 Å molecular sieves to the mixture. [e] 0.05 mol % of (CuOTf)₂·PhH was used. [f] Approximate yield because the product was contaminated with ~25% of a byproduct resulting from the reductive homocoupling of the aryl iodide. [g] GC yields. [h] Unless otherwise noted, the yields refer to the average of at least two isolated yields of >95% purity as determined by GC, ¹H NMR, and/or elemental analysis.

such as phenol and chlorophenol (entries 18 and 20).[13] The good yield obtained for the coupling of *p*-cresol and 2-bromoanisole (entry 16) is also noteworthy compared with the 44% reported by Boger for the same product using the more reactive iodide in the presence of an excess of sodium hydride and of CuBr (2.0 equiv).[6b] Furthermore, the fact that the use of a catalyst level as low as 0.05 to 0.25 mol % of (CuOTf)₂·benzene resulted in only a slight decrease in yield (entries 1, 3, and 20)

(13) To the best of our knowledge no general study of the reactions of unactivated aryl halides has appeared in the literature.

Scheme 2
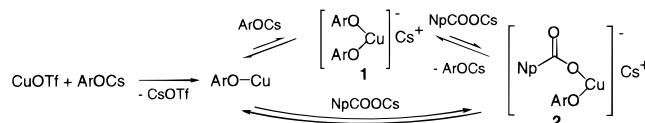
suggests that the reaction conditions are sufficiently mild to prevent the undesired reduction of copper(I) species to copper-(0).[14a,15]

It has been proposed that copper-catalyzed nucleophilic substitution proceeds *via* the formation of a complex between the aryl halide and the copper.[4] As previously reported,[4,16] we observed that the rate of the reaction was not greatly influenced by the presence of electron-donating or electron-withdrawing groups on the aryl halide or phenol substrates (in the latter case, this refers to reactions in the presence of 1-naphthoic acid). This observation, combined with the fact that aryl triflates and unactivated aryl chlorides failed to react, does not support a mechanism in which a negative charge develops on the aromatic ring resulting from the direct attack of the phenolate.[4b] It has recently been proposed that the methoxylation of aryl bromides involves the formation of an active cuprate-like intermediate of the general structure [(RO)₂Cu]⁻M⁺.[14b] We believe that the nature of the cation plays an important role during the formation or the solubilization of such an intermediate. Cesium phenoxides and carboxylates are relatively soluble in organic solvents.[17] Their use could enhance the solubility of the possible key reaction intermediates **1** and **2** (Scheme 2), as compared to their potassium and sodium counterparts. Based on a recent report,[11] we suggest that in the presence of less nucleophilic phenols, the cesium naphthoate participates in the formation of the reactive intermediate **2**, thereby increasing its solubility and the rate of its subsequent reaction.

In summary, we have developed a general procedure for the copper-catalyzed coupling of a wide range of activated and unactivated aryl bromides and iodides with phenols, using cesium carbonate as a base. In addition, the use of 1-naphthoic acid as an additive for the efficient coupling of less soluble phenoxides is important in that it extends the generality of the reaction, rendering it more useful in organic synthesis.

Supporting Information Available: Detailed experimental procedures including analytical and spectroscopic data for all compounds (9 pages). See any current masthead page for ordering and Internet access instructions.

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(15) Under the conditions described, no diaryl ethers were observed for unactivated aryl bromides (entries 2–4, 11, and 18) in the absence of copper catalyst, whereas 23% and 1% GC yields of the corresponding diaryl ethers were obtained for entries 1 and 17, respectively.
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