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Selective One-Pot Access to Symmetrical or Unsymmetrical Diaryl Ethers by Copper-Catalyzed Double Arylation of a Simple Oxygen Source

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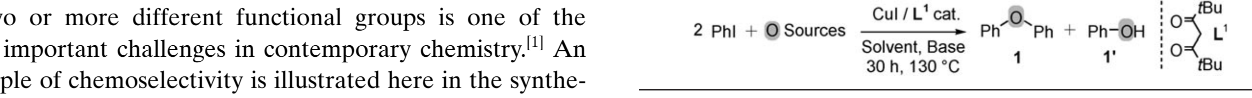
The preferential reaction of a chemical reagent with one of two or more different functional groups is one of the most important challenges in contemporary chemistry.[1] An example of chemoselectivity is illustrated here in the synthesis of symmetrical or unsymmetrical diaryl ethers, which constitute a wide family of active compounds in natural products and polymer science.[2] Their syntheses usually require the presence of copper[3] or palladium[4] catalytic systems that enable the coupling of aryl halides with phenols. Only two examples have been described in which aryl halides are not coupled to oxygen via a phenol but via an inorganic oxygen source (K_3PO_4/H_2O or KOH) to afford diaryl ethers. These methods, which suffer from drawback as a result of the synthesis of only symmetric ethers, use palladium catalytic systems.[5,6] We report herein a novel method that affords selective one-pot access to symmetrical or unsymmetrical diaryl ethers by Cu-catalyzed double arylation of an oxygen source (hydroxide salts or water) by aryl halides.

We recently observed that symmetrical diphenyl ether **1** occurred as a secondary product during the copper-catalyzed synthesis of phenol **1′** from iodobenzene and hydroxide salts.[7] This surprising development encouraged us to carefully adjust reaction parameters for the selective generation of **1** by a double arylation of a simple oxygen source by PhI. A systematic study was undertaken using PhI as the model substrate and 2,2,6,6-tetramethyl-3,5-heptanedione as ligand (**L^1**). As expected, the former was selectively converted to **1′** (Table 1, entries 1 and 2) in the presence of KOH or CsOH in a mixture of DMSO/water (1/1). However, we were pleased to find that, in the presence of Cs_2CO_3 as an additional base, the synthesis of diphenyl ether **1** became fully selective (Table 1, entry 3). The same reaction performed in the presence of one solvent (DMSO or EtOH) also produced a high yield of **1** although the selectivity was lower in the case of ethanol (Table 1, entries 4 and 5, respectively). Finally, the addition of water as a co-solvent with ethanol allowed us to observe the quantitative formation of **1** (Table 1, entry 6). Due to regulatory considerations[8] and the obvious environmental benefits of using $EtOH/H_2O$ as solvent, we optimized this system and first discovered that the original MOH was not necessary to achieve high selectivity (Table 1, entry 7).

Table 1. Conditions for the selective synthesis of diphenyl ether **1**.[a]



Entry	Solvent (2 mL)	MOH (3 equiv)	Base (n equiv)	**1** [%][b]	**1′** [%][b]
1	$DMSO/H_2O$ (1/1)	KOH	–	0	75
2	$DMSO/H_2O$ (1/1)	CsOH	–	0	95
3	$DMSO/H_2O$ (1/1)	CsOH	Cs_2CO_3 (1)	98	0
4	DMSO	CsOH	Cs_2CO_3 (1)	95	0
5	EtOH	CsOH	Cs_2CO_3 (1)	70	10
6	$EtOH/H_2O$ (1/1)	CsOH	Cs_2CO_3 (1)	100	0
7	$EtOH/H_2O$ (1/1)	–	Cs_2CO_3 (4)	90	0
8	$EtOH/H_2O$ (1/1)	–	K_2CO_3 (4)	60	0
9	$EtOH/H_2O$ (1/1)	–	K_3PO_4 (3)	96[c]	0
10	EtOH	–	K_3PO_4 (3)	0	0[d]
11	H_2O	–	K_3PO_4 (3)	0	0

[a] Performed with 10 mol % of CuI, 50 mol % of 2,2,6,6-tetramethyl-3,5-heptanedione **L^1**, 3 equiv of MOH and/or n equiv of base. [b] GC yield determined with 1,3-dimethoxybenzene as standard. [c] 10 mol % of CuI, 30 mol % of **L$_1$** and 3 equiv of K_3PO_4. [d] Formation of PhOEt (97 %).

We also observed that K_3PO_4, a base of greater interest to industry,[9] could successfully produce **1** (Table 1, entry 9). Other ligands such as β-diketones (**L^2**, **L^3**), DMEDA **L^4**, or phenanthroline **L^5** were also tested, but in all cases, selectivity was disappointing.[10]

We then investigated the breadth of application of this new method by evaluating a series of aryl iodides under one

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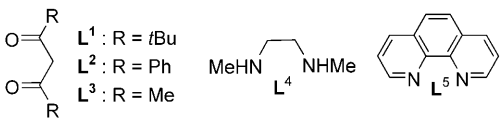
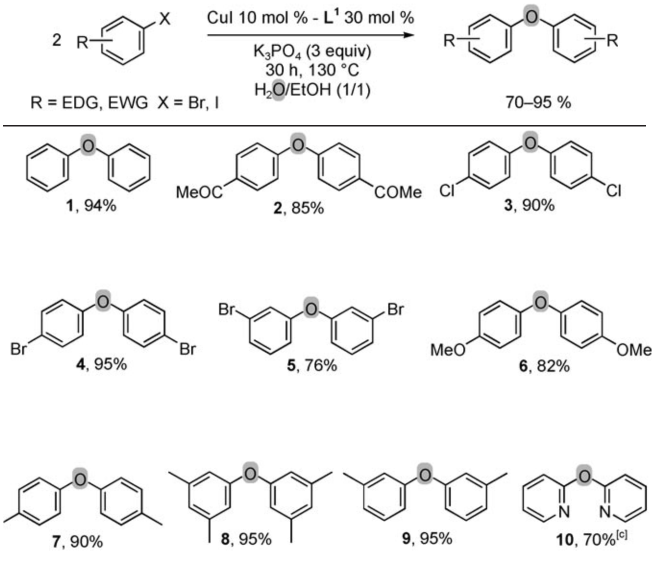


set of optimized conditions (specifically, Table 1, entry 9). Good to excellent yields of symmetrical diaryl ethers **1–9** were obtained with water as the oxygen source (Table 2), with both electron-donating and electron-withdrawing substituents on the aryl ring. The system was also efficient in the presence of 2-bromopyridine, which led to the corresponding diaryl ether **10**.

Table 2. Cu-catalyzed selective synthesis of symmetrical diaryl ethers **1**.[a,b]



[a] Yield of isolated product. [b] Reactions conducted in H_2O/EtOH (2 mL) using ArI except otherwise noted. [c] 2-Bromopyridine was employed as aryl source.

As already observed in related palladium-catalyzed reactions, the selectivity is significantly dependent on the nature of the base.[5] Thus, while the PhOH (in equilibrium with the phenoxide) formed using hydroxide salts (Table 1, entries 1 and 2) does not react with PhI, it is trapped by the latter in the presence of Cs_2CO_3 or K_3PO_4 as bases to produce **1**. Therefore the phenol, the probable intermediate in the reaction, is not observed under our conditions (Table 1, entries 7, 9).

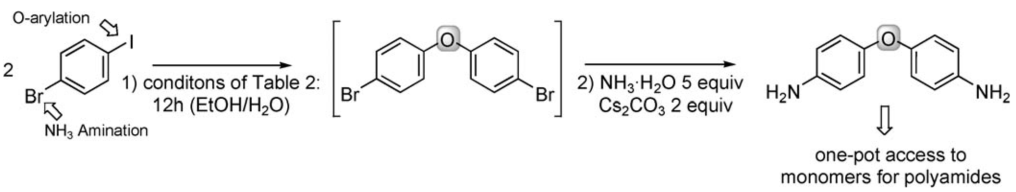
To our knowledge, we have here described the first copper-catalyzed symmetrical diaryl ether synthesis by double arylation of a simple oxygen source (water), whereas the other known procedures employ expensive palladium-based systems.[5,6] Although symmetrical diaryl ethers are very interesting substrates, unsymmetrical examples are of even greater interest. These were examined next.

We first tried to couple together two different aryl iodides but the previously used conditions (with EtOH/H_2O as solvents) lead to mixtures. However, with DMSO as solvent (conditions as in Table 1, entry 4), we were pleased to obtain various unsymmetrical diaryl ethers **11**–**16** selectively in good yields. These were synthesized from aromatic iodides substituted by electron-withdrawing or electron-donating groups and introduced in equimolecular amounts (Table 3, entries 1–6). Under similar conditions, many unsymmetrical diaryl ethers such as **11**–**23** were obtained in good to excellent yields (Table 3, entries 7–18) by cross-coupling of various aryl iodides, with either aryl bromides or even less reactive aryl chlorides, substituted by electron-withdrawing or -donating groups.

In many cases, by-products are mainly unreacted aryl halides (see Table 3, column 3) and symmetrical diaryl ethers formed from the more reactive aryl iodides ($R^1C_6H_4I$, see Table 3, column 2). It is worth noting that when $R^1C_6H_4I$ is introduced in excess (1.8 equiv) over the less reactive $R^2C_6H_4X$ (1 equiv), excellent yields of unsymmetrical ethers are almost always obtained, as illustrated in some selected cases (Table 3, entries 1, 7, 13).

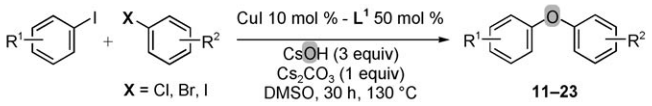
The catalytic system presented here is also known to promote C−O or C−N bond formation from aryl halides,[11] as we showed for example with the Cu-catalyzed arylation of ammonia.[12] The potential range of applications of this method is thus very large. As an example, the combination of diaryl ether synthesis and amination methods affords simple access to one of the most popular monomers with a flexible linkage, namely 4,4′-oxydianiline (Scheme 1). This useful building block and cross-linking agent for polymers,[13] was easily obtained (70 % isolated yield) by a chemoselective one-pot procedure. Many other combinations could be envisioned with applications in both polymer chemistry and the life sciences.

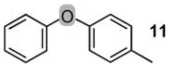
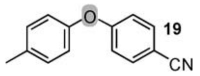
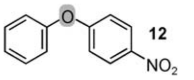
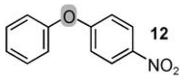
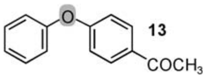
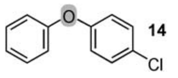
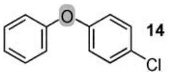
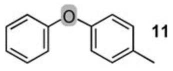
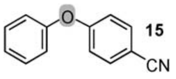
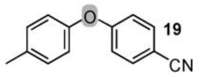
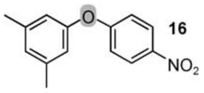
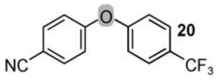
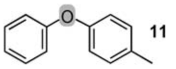
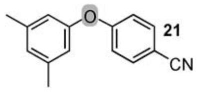
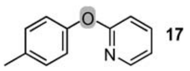
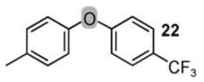
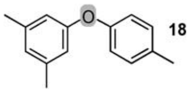
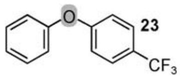
In summary, we have presented here an original and versatile method that allows the one-pot synthesis of various symmetrical or unsymmetrical diaryl ethers from aryl halides and very simple oxygen sources, namely H_2O or hydroxide salts. This controlled and highly selective process, very competitive to existing protocols based on palladium,



Scheme 1. One-pot access to monomers for polyamides.

Table 3. Cu-catalyzed selective synthesis of unsymmetrical diaryl ethers **11**–**23**.[a]



Entry	R^1	R^2, X	Ar–O–Ar'	Yield [%][b,c]	Entry	R^1	R^2, X	Ar–O–Ar'	Yield [%][b,c]
1	H	*p*-CH_3, **I**	 **11**	72, 96[d]	10	*p*-CH_3	*p*-CN, **Br**	 **19**	82
2	H	*p*-NO_2, **I**	 **12**	71	11	H	*p*-NO_2, **Br**	 **12**	83
3	H	*p*-$COCH_3$, **I**	 **13**	65	12	H	*p*-CN, **Cl**	 **14**	72
4	H	*p*-Cl, **I**	 **14**	85	13	H	*p*-CH_3, **Cl**	 **11**	40, 95[d]
5	H	*p*-CN, **I**	 **15**	78	14	*p*-CH_3	*p*-CN, **Cl**	 **19**	75
6	*m*,*m*'-$(CH_3)_2$	*p*-NO_2, **I**	 **16**	93	15	*p*-CN	*p*-CF_3, **Cl**	 **20**	61
7	H	*p*-CH_3, **Br**	 **11**	59, 97[d]	16	*m*,*m*'-$(CH_3)_2$	*p*-CN, **Cl**	 **21**	73
8	*p*-CH_3	2-Py, **Br**	 **17**	92	17	*p*-CH_3	*p*-CF_3, **Cl**	 **22**	80
9	*m*,*m*'-$(CH_3)_2$	*p*-CH_3, **Br**	 **18**	50	18	H	*p*-CF_3, **Cl**	 **23**	77

[a] Reactions conducted with 1 equiv of each aryl halide, 3 equiv of CsOH, 1 equiv of Cs_2CO_3 in 2 mL of DMSO. [b] Yield of isolated product. [c] For $R^2C_6H_4X$ (column 3) by-products are mainly unreacted aryl halides (e.g., 20% of the *p*-$CF_3C_6H_4Cl$ remains at the end of the reaction for entry 17). For $R^1C_6H_4I$ (column 2) by-products are mainly the corresponding symmetrical diaryl ethers (between 2 and 15% when $R^1 = H$ and only traces when $R^1 \neq H$). [d] 1.8 equiv of $R^1C_6H_4I$ and 1 equiv $R^2C_6H_4X$: yield based on $R^2C_6H_4X$.

employs a copper catalyst system. Extensive applications are expected very soon.[7a,14]

Experimental Section

General procedures for isolation and full characterization of all the phenols are reported in the Supporting Information.

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Keywords: arylation · catalysis · copper · diaryl ethers · selectivity

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