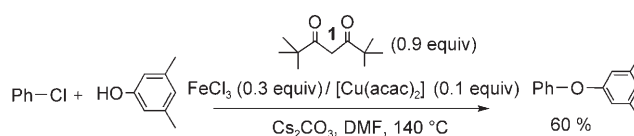


## Copper- or Iron-Catalyzed Arylation of Phenols from respectively Aryl Chlorides and Aryl Iodides

Ning Xia and Marc Taillefer\*<sup>[a]</sup>

The diaryl ether structure is found in numerous important organic compounds in the pharmaceutical and polymer industries.<sup>[1]</sup> The common synthesis of diaryl ethers usually requires the reaction of phenols with aryl halides in the presence of a catalyst containing a transition metal. It has been reported that Pd-catalyzed methods can function in this role, but their high costs and elaborate ligands are drawbacks when compared with copper-mediated reactions.<sup>[2,3]</sup> Indeed, in recent years much work has contributed to improving the traditional Ullmann ether synthesis, which requires stoichiometric quantities of copper and harsh conditions. In spite of great advances in the use of copper catalysts associated with specific ligands,<sup>[4]</sup> the aryl chlorides are still problematic substrates. To our knowledge there are very few examples available involving them in copper-catalyzed arylation with phenols.<sup>[3b,c]</sup> Thus a convenient and general method for arylation from aryl chlorides should be of great interest to industrial production and laboratory research due to their low cost and ready availability.<sup>[5]</sup> Recently we presented an original example of cooperative bimetallic Fe–Cu catalysis affording O-, N-, or C-arylation of nucleophiles from aryl bromides.<sup>[6]</sup> In this work we observed that the efficiency of the catalytic system was dramatically increased by the addition of 2,2,6,6-tetramethyl-3,5-heptanedione (**1**) as ligand, thus allowing, for example, arylation of phenols from non-activated chlorobenzene (Scheme 1).<sup>[6a]</sup>

These initial results encouraged us to carefully investigate this system. We now report the first general method for copper-catalyzed arylation of phenols from aryl chlorides.<sup>[7]</sup> An additional finding of this study, touched upon only brief-

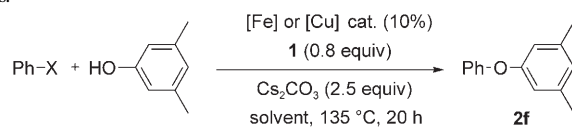


Scheme 1. **1**/Fe/Cu-catalyzed arylation of dimethylphenol with PhCl.<sup>[6a]</sup>

ly here, is the iron-catalyzed arylation of phenols from aryl iodides.<sup>[7]</sup>

A systematic study was first undertaken by choosing 3,5-dimethylphenol as a model substrate (synthesis of **2f**, Table 1). Our first test allowed us to check the result presented in Scheme 1, because we observed that under quite similar conditions the arylation of dimethylphenol from chlorobenzene was indeed possible even in the presence of a lower quantity (10%) of iron catalyst (Table 1, entry 1). The first blank test was undertaken with PhCl and the diketone-**1**/[Cu(acac)<sub>2</sub>] system (Table 1, entry 2). The result was

Table 1. **1**/Cu-catalyzed O-arylation of 3,5-dimethylphenol from aryl halides.



	Fe	Cu	X	Solvent	Yield [%] <sup>[a]</sup>
1	FeCl <sub>3</sub>	[Cu(acac) <sub>2</sub> ]	Cl	DMF	40
2		[Cu(acac) <sub>2</sub> ]	Cl	DMF	60
3		[Cu(acac) <sub>2</sub> ]	Br	DMF	95 <sup>[b]</sup>
4	FeCl <sub>3</sub>		Cl	DMF	0
5	FeCl <sub>3</sub>		Br	DMF	18
6	FeCl <sub>3</sub>		I	DMF	85,97 <sup>[c]</sup>
7		CuBr	Cl	DMSO	18
8		CuBr	Cl	DMF	64
9		CuI	Cl	DMF	57
10		CuBr <sub>2</sub>	Cl	DMF	57
11		CuBr	Cl	DMF	43 <sup>[d]</sup>
12		CuBr	Cl	DMF	91 <sup>[e]</sup>

[a] GC yield yields determined with 1,3-dimethoxybenzene as the internal standard. [b] Reaction temperature: 70 °C. [c] Reaction time: 24 h. [d] 0.4 equiv of ligand. [e] Reaction time: 36 h.

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surprising, because in absence of iron salt, diaryl ether **2f** was obtained in a very acceptable yield (60%). Another indication of the efficiency of this system was that the reaction using bromobenzene allowed us to obtain ether **2f** quantitatively at a remarkably low temperature (70 °C, Table 1, entry 3). The second blank test was performed without copper and showed as expected that the arylation from PhCl did not proceed at all with a catalytic system only based on iron (Table 1, entry 4). However, when we tested the bromobenzene under the same conditions as previously, we were intrigued by the formation of a modest but significant amount of ether **2f** (18%; Table 1, entry 5). Finally, we selected iodobenzene, which is a more powerful electrophile, with which we obtained the coupling product in 85% yield (see below). We then continued our study and by a systematic variation of parameters we were able to establish a protocol permitting the arylation of 3,5-dimethylphenol with chlorobenzene in excellent yield (entry 12). Among the solvents, bases, and copper sources tested (Table 1, entries 7–12), DMF, caesium carbonate, and copper bromide were found to be the best combination.

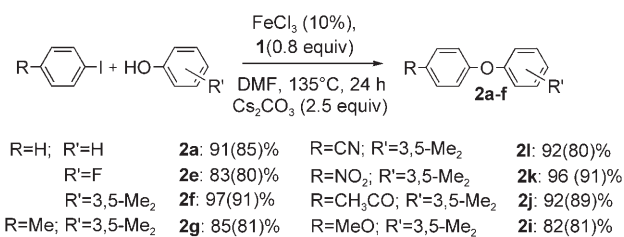
Next we explored the breadth of application of this new method. Thus the system diketone-**1**/[Cu(acac)<sub>2</sub>] efficiently promotes cross-coupling reactions between phenols and chlorobenzene or aryl chlorides, which are deactivated by electron-donating substituents. We have thus isolated several different diaryl ethers **2a–i** using unreactive substrates such as chlorobenzene, 4-chlorotoluene, and even 4-chloroanisole (Table 2, entries 1–10). That the O-nucleophile can also be varied considerably is attested to by the following examples that all undergo efficient coupling under our conditions: *p*-toluene, *p*-methoxyphenol, *p*-fluorophenol, *p*-tertbutylphenol, 3,5 dimethylphenol, and phenol itself. In most cases when the reactions were carried out with Cs<sub>2</sub>CO<sub>3</sub> as the base, excellent isolated yields were obtained at 135 °C, a remarkably low temperature relative to those required in the classic stoichiometric Ullmann arylation of phenol with aryl chlorides. In the presence of more reactive aryl chlorides substituted by electron-withdrawing groups (CH<sub>3</sub>CO, CN or NO<sub>2</sub>) our catalytic system also gave excellent yields of biaryl ethers (Table 2, entries 11–13). However here, particularly for NO<sub>2</sub>, the catalyst proved unnecessary and cross-coupling proceeds in high yield by nucleophilic aromatic substitution.<sup>[8]</sup>

We believe that these results indicate that we have discovered an efficient global method for arylation of phenols from aromatic chlorides. The stronger donor character of β-diketone **1** compared to acac probably facilitates oxidative addition of the chlorobenzene to copper.<sup>[9]</sup> This may also be the key to the successful arylation of dimethylphenol from phenyl iodide catalyzed by iron (Table 1, entry 6). We confirmed the efficiency of the ligand **1**/iron combination as a catalyst by conducting screening tests with phenyl iodide or with iodobenzenes bearing electron-donating substituents (Scheme 2). Thus very good isolated yields of diaryl ethers were obtained from un- or deactivated aryl iodides, (iodobenzene, 4-iodotoluene, or 4-iodoanisole) with phenol, 4-flu-

Table 2. Ligand **1**/Cu-catalyzed O-arylation of phenols from aryl chlorides.

	R <sup>1</sup>	R <sup>2</sup>	Product	Yield [%] <sup>[a]</sup>
1	H	H		<b>2a</b> 81
2	H	4-Me		<b>2b</b> 80
3	H	4-OMe		<b>2c</b> 91
4	H	4- <i>t</i> Bu		<b>2d</b> 87
5	H	F		<b>2e</b> 40
6	H	3,5-Me <sub>2</sub>		<b>2f</b> 82
7	4-Me	3,5-Me <sub>2</sub>		<b>2g</b> 91
8	4-Me	4-MeO		<b>2h</b> 99
9	4-MeO	4-Me		<b>2h</b> 53
10	4-MeO	3,5-Me <sub>2</sub>		<b>2i</b> 81
11	4-MeCO	3,5-Me <sub>2</sub>		<b>2j</b> 95
12	4-NO <sub>2</sub>	3,5-Me <sub>2</sub>		<b>2k</b> 88
13	4-CN	3,5-Me <sub>2</sub>		<b>2l</b> 90

[a] Yield of isolated product.

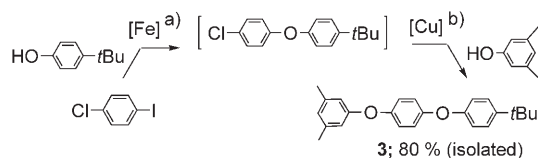


Scheme 2. Ligand **1**/Fe-catalyzed arylation of phenols from aryl iodides (isolated yields in brackets).<sup>[7]</sup>

orophenol, or 3,5-dimethylphenol. The reaction also takes place quantitatively with electron-withdrawing groups on the aryl iodides (R=NO<sub>2</sub>, CN, or CH<sub>3</sub>CO), but here good yields with the same substrates are obtained under S<sub>N</sub>Ar conditions. Although the aryl iodides are much less challenging than the chlorides, this catalytic system is very interesting because it constitutes the first report of C–O coupling catalyzed by iron.<sup>[7,10]</sup>

A final example shows the advantage of complementary use of copper and iron in this catalytic system: using both

metals with ligand **1** enables a chemoselective one-pot synthesis of an unsymmetrical polyether as demonstrated by the preparation of oligomer **3** in 80% isolated yield (Scheme 3). Such compounds, which are otherwise difficult



Scheme 3. In situ chemoselective **1**/Fe- and **1**/Cu-catalyzed synthesis of a polyarylether. a) Conditions as in Scheme 2; b) in situ addition of CuBr and of the 3,5-dimethylphenol; conditions as in Table 2.

to synthesize selectively, are important target molecules for the life sciences.<sup>[11]</sup>

In summary, we have checked the utility of diketone **1**, which was first introduced for bimetallic Fe–Cu catalysts,<sup>[6a]</sup> in copper-catalyzed arylation of phenols from aryl chlorides. This reaction—of considerable economic importance—provides a challenge to which we supply the first satisfying solution. Commercial availability, low cost, and low toxicity of the copper system makes it very competitive to existing Pd-based protocols. Moreover, our method is easily adaptable to an industrial scale for which financial and environmental factors are of greater importance.<sup>[6a,7]</sup> Finally, we have also shown the efficiency of catalysts employing diketone **1** using iron alone as the metal and its use with both metals to afford a clean entry into the regioselective synthesis of unsymmetrical aromatic polyethers.

## Experimental Section

For synthesis and characterization data of **2** and **3** and a general procedure for the catalytic reactions, see the Supporting Information.

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**Keywords:** aryl chlorides • aryl iodides • copper • coupling reactions • iron

- [1] a) A. V. Rama Rao, M. K. Gurjar, L. Reddy, A. S. Rao, *Chem. Rev.* **1995**, *95*, 2135; b) *The Pesticide Manual*, 10th ed. (Ed.: C. Tomlin), British Crop Protection Council, Farnham, **1994**.
- [2] a) C. H. Burgos, T. E. Barder, X. Huang, S. L. Buchwald, *Angew. Chem.* **2006**, *118*, 4427; *Angew. Chem. Int. Ed.* **2006**, *45*, 4321; b) G. Mann, C. Incarvito, A. L. Rheigold, J. F. Hartwig, *J. Am. Chem. Soc.* **1999**, *121*, 3224; c) S. Harkal, K. Kumar, D. Michalik, A. Zapf, R. Jackstell, F. Rataboul, T. Riemeier, A. Monsees, M. Beller, *Tetrahedron Lett.* **2005**, *46*, 3227.
- [3] a) K. Kunz, U. Scholz, D. Ganzer, *Synlett* **2003**, *15*, 2428; b) I. P. Beletskaya, A. V. Cheprakov, *Coord. Chem. Rev.* **2004**, *248*, 2337; c) F. Monnier, M. Taillefer, *Angew. Chem.* **2008**, *120*, 3140; *Angew. Chem. Int. Ed.* **2008**, *47*, 3096.
- [4] a) B. H. Lipshutz, J. B. Unger, B. R. Taft, *Org. Lett.* **2007**, *9*, 1089; b) A. Ouali, J.-F. Spindler, A. Jutand, M. Taillefer, *Adv. Synth. Cat.* **2007**, *349*, 1906; c) A. Ouali, J.-F. Spindler, H.-J. Cristau, M. Taillefer, *Adv. Synth. Cat.* **2006**, *348*, 499; d) A. Ouali, R. Laurent, A.-M. Caminade, J.-P. Majoral, M. Taillefer, *J. Am. Chem. Soc.* **2006**, *128*, 15990; e) Y. Jin, J. Liu, Y. Yin, H. Fu, Y. Jiang, Y. Zhao, *Synlett* **2006**, 1564; f) Q. Cai, B. Zou, D. Ma, *Angew. Chem.* **2006**, *118*, 1298; *Angew. Chem. Int. Ed.* **2006**, *45*, 1276; g) H.-J. Cristau, P. P. Cellier, S. Hamada, J.-F. Spindler, M. Taillefer, *Org. Lett.* **2004**, *6*, 913; h) D. Ma, Q. Cai, *Org. Lett.* **2003**, *5*, 3799; i) E. Buck, Z. J. Song, D. Tschäen, P. G. Dormer, R. P. Volante, P. J. Reider, *Org. Lett.* **2002**, *4*, 1623; j) J. Hassan, M. Sévignon, C. Gozzi, E. Schultz, M. Lemaire, *Chem. Rev.* **2002**, *102*, 1359; k) R. K. Gujadhur, C. G. Bates, D. Venkataraman, *Org. Lett.* **2001**, *3*, 4315; l) A. V. Kalinin, J. F. Bower, P. Riebel, V. Snieckus, *J. Org. Chem.* **1999**, *64*, 2986; m) J.-F. Marcoux, S. Doye, S. L. Buchwald, *J. Am. Chem. Soc.* **1997**, *119*, 10539.
- [5] a) K. Weissmermel, H. J. Arpe, *Industry Organic Chemistry*, Wiley-VCH, Weinheim (Germany), **1997**, p. 349.
- [6] a) M. Taillefer, N. Xia, A. Ouali, *US* **2006** 60/818,334 and *PCT* **2007/001836**; b) M. Taillefer, N. Xia, A. Ouali, *Angew. Chem.* **2007**, *119*, 952; *Angew. Chem. Int. Ed.* **2007**, *46*, 934.
- [7] Patented results: N. Xia, M. Taillefer, **2007 US** patent 60996830.
- [8] a) Under similar conditions 4-fluoronitrobenzene reacts more quickly than 4-chloronitrobenzene; b) Related results are known although often following from the use of more activated substrates or metal (Pd)-catalyzed systems: B. Smith, J. March, *March's Advanced Organic Chemistry: Reactions, Mechanisms, and Structure*, 6th ed., Wiley, New York, **2007**, p. 853, and references therein.
- [9] M. Fabre, J. Jaud, M. Hliwa, J.-P. Launay, J. Bonvoisin, *Inorg. Chem.* **2006**, *45*, 9332.
- [10] Very recently the group of Prof. Carsten Bolm obtained similar results in the case of phenyl iodide or of aryl iodides deactivated by electron-donating substituents (O. Bistri, A. Correa, C. Bolm, *Angew. Chem.* **2008**, *120*, 596; *Angew. Chem. Int. Ed.* **2008**, *47*, 586). In the case of aromatic iodides activated by electron-withdrawing substituents we found under our conditions that the presence of the catalytic system Fe/diketone **1** was not necessary to obtain excellent isolated yields of **2j**, **2k**, and **2l**.
- [11] L. L. J. Winneroski, Y. Xu, J. S. York, patent **2005** WO 05/037763 A1.

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