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Bio-inspired copper catalysts for the formation of diaryl ethers

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Abstract

Aryl bromides and phenols are coupled efficiently to the corresponding diaryl ethers in the presence of a practical Cu(I)/1-butylimidazole catalyst system. The convenient protocol is applied successfully to the synthesis of 16 different diaryl ethers in high yield and selectivity.

Keywords: Diaryl ether; Aryl bromide; Copper; N-Ligands; Imidazole

Diaryl ethers represent a common feature in natural products, pharmaceuticals and agrochemicals as well as in industrial polymers.[1] Selected examples are shown in Figure 1. In addition, macrocyclic diarylethers are of special interest for biologically active compounds, for example, vancomycine, piperazinomycin, RA-I–IV, K13 and others.[2]

In the past, the most general method for the synthesis of diaryl ethers has been the copper-mediated Ullmann coupling of aryl bromides/iodides and phenols with the drawback of harsh reaction conditions and the need of a stoichiometric amount of metal.[3] Due to these problems significant efforts have been undertaken in the last decade to develop more efficient and environmentally benign catalytic coupling processes of phenols. The current status of the methodology is described in detail by Frlan and Kikelj,[4] Beletskaya et al.,[5] and by Kunz et al.[6]

The increased attention in this field over the past years has led to the development of several catalyst systems, which enable aryl ether formation under much milder conditions compared to the classical Ullmann and Goldberg reactions.[4,6,7] So far, mainly copper[8] and palladium[9] complexes evolved as catalysts for this type of reaction. While palladium catalysis has the common disadvantage of high metal and ligand costs (and sometimes the air-sensitivity of special phosphines), copper catalysis is generally

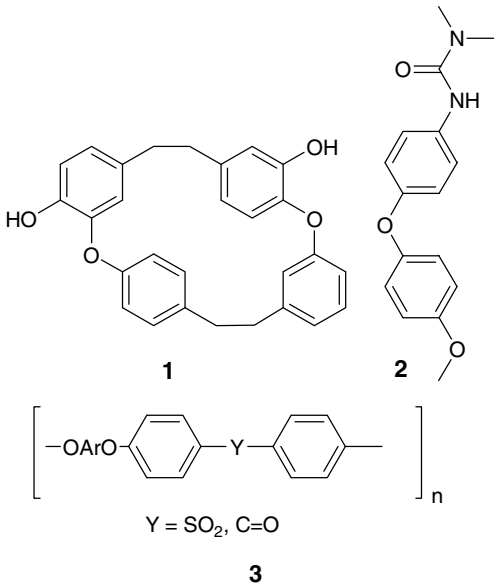

Fig. 1. Riccardine from liverwort (**1**), the herbicide difenoxuron (**2**), poly(aryl ethers) (**3**) used for high-tech plastics.

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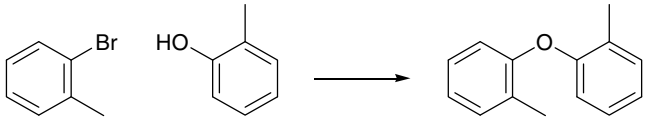
considered to be less expensive. However, this statement is only true for easily available copper pre-catalysts and ligands. In this respect there is still a need for improved and more general catalysts.

Recently, we have developed new catalyst systems for the cyanation of aryl halides based on palladium and copper.[10,11] The combination of copper(I)/1-alkylimidazoles showed unprecedented selectivity and substrate range in that reaction. Inspired by nature, we assumed that imidazoles might be good ligands to control the stability and selectivity of copper catalysts.[12] This idea resulted from the fact that the most abundant metal-binding amino acid in nature is histidine. In fact, in most metalloenzymes the actual binding site contains at least one, in some cases up to three histidine units per metal atom.[13] Consequently, we believed that this and similar systems might be useful for other coupling reactions of aryl halides, too. In this Letter, we report our results on the copper-catalyzed diaryl ether formation from aryl bromides and phenols.

The preparation of bis(*o*-tolyl)ether from 2-bromotoluene and 2-cresol served as a model reaction to study the general influence of different bases, solvents, additives/ligands, temperature and the copper pre-catalyst. Selected experiments are shown in Table 1.[14] As a starting point for our investigations, reaction conditions were chosen similar to those of the Cu/imidazole-catalyzed cyanation reaction. However, a stoichiometric amount of base is added to secure the deprotonation of the phenol for the C–O coupling reaction. In initial experiments K_2CO_3 was used as base. In contrast to the copper-catalyzed cyanation of aryl bromides a reduced amount of 1-butylimidazole led to the best results. Significantly higher or lower concentration of this ligand decreased the yield of the desired bis(*o*-tolyl)-ether (Table 1, entries 1–3).

Obviously, there is a balance between sufficient stabilization of the catalyst metal and access to free coordination sites. Other N-donor ligands, mostly imidazoles, and O-donors were tested and showed no improved performance (Table 1, entries 4–12). Amino acids, like proline[15] and

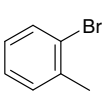
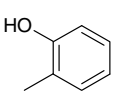
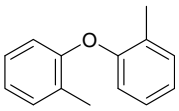
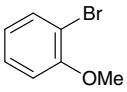
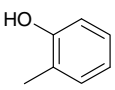
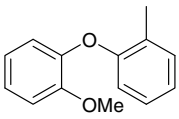
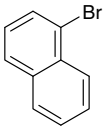
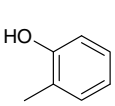
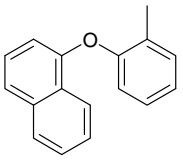
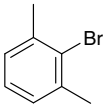
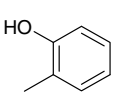
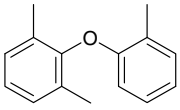
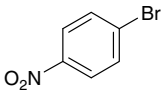
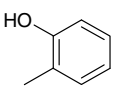
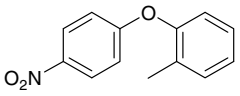
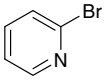
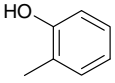
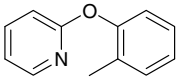
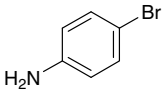
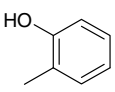
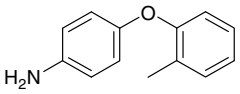
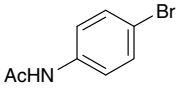
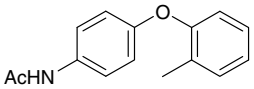
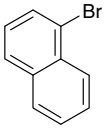
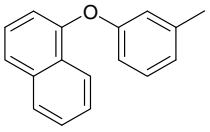
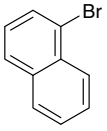
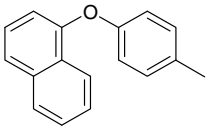
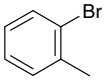
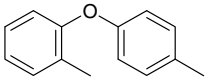
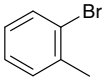
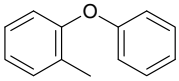
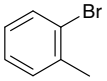
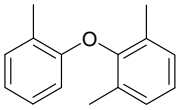
Table 1
Copper-catalyzed reaction of 2-cresol with 2-bromotoluene[a]



Entry	Additive[c] (mol %)	Metal[b]	*T* (°C)	Base[c] (mol %)	Solvent	Conv.[c] (%)	Yield[c] (%)
1	1-Butylimidazole 200	CuI	120	K_2CO_3 130	Toluene	59	47
2	1-Butylimidazole 50	CuI	120	K_2CO_3 130	Toluene	83	75
3	1-Butylimidazole 20	CuI	120	K_2CO_3 130	Toluene	27	20
4	1-Methylimidazole 50	CuI	120	K_2CO_3 130	Toluene	82	75
5	1-Benzylimidazole 50	CuI	120	K_2CO_3 130	Toluene	81	69
6	1,2-Dimethylimidazole 50	CuI	120	K_2CO_3 130	Toluene	43	31
7	2-Methylimidazole 50	CuI	120	K_2CO_3 130	Toluene	5	0
8	4-Methylimidazole 50	CuI	120	K_2CO_3 130	Toluene	5	0
9	2,2′-Bipyridine 50	CuI	120	K_2CO_3 130	Toluene	36	22
10	Acetylacetone 25	CuI	120	K_2CO_3 130	Toluene	0	0
11	1,2-Ethylenediamine 50	CuI	120	K_2CO_3 130	Toluene	64	8
12	TMEDA 50	CuI	120	K_2CO_3 130	Toluene	8	0
13	1-Butylimidazole 50	CuI	120	Cs_2CO_3 130	Toluene	81	70
14	1-Butylimidazole 50	CuI	120	K_3PO_4 130	Toluene	51	46
15	1-Butylimidazole 50	CuI	120	K_3PO_4 130 (dry, Ar-box)	Toluene	85	74
16	1-Butylimidazole 50	CuI	120	Na_2CO_3 130	Toluene	5	4
17	1-Butylimidazole 50	CuI	120	NaO*t*Bu 130	Toluene	2	0
18	1-Butylimidazole 50	CuI	120	K_2CO_3 200	Toluene	89	81
19	1-Butylimidazole 50	CuI	140	K_2CO_3 200	Toluene	100	91
20	1-Butylimidazole 50	CuI	120	K_2CO_3 130	Dioxane	67	56
21	1-Butylimidazole 50	CuI	120	K_2CO_3 130	*o*-Xylene	33	30
22	1-Butylimidazole 50	CuI	120	K_2CO_3 130	NMP	71	63
23	—	CuI	120	K_2CO_3 130	NMP	5	3
24	1-Methylimidazole[d]	CuI	120	K_3PO_4 130	1-Methylimidazole	30	26
25	1-Butylimidazole 50	CuCl	120	K_2CO_3 200	Toluene	95	87
26	1-Butylimidazole 50	CuBr	120	K_2CO_3 200	Toluene	80	72
27	1-Butylimidazole 50	Cu_2O	120	K_2CO_3 200	Toluene	61	56
28	1-Butylimidazole 50	CuI (5)	120	K_2CO_3 200	Toluene	76	67
29	1-Butylimidazole 50	CuI (2.5)	120	K_2CO_3 200	Toluene	45	38

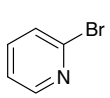
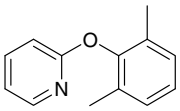
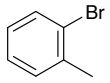
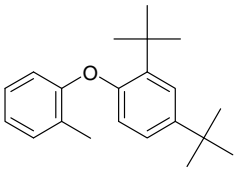
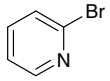
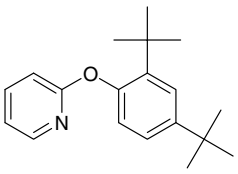
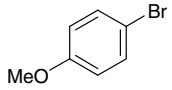
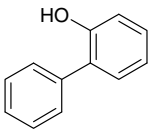
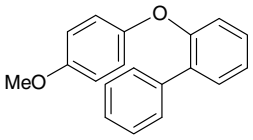
[a] General reaction conditions: 2 mmol 2-bromotoluene, 2.4 mmol 2-cresol, 2 mL solvent, 200 μL tetradecane as internal standard for GC, 16 h.
[b] 10 mol % Cu unless otherwise stated.
[c] GC-conversion and yield.
[d] Large excess (solvent).

Table 2
Scope and limitations of the copper/1-alkylimidazole-catalyzed diarylether synthesis[a]

Entry	Aryl bromide	Hydroxybenzene	Product	T (°C)	Metal	Conversion[b] (%)	Yield[b] (%)
1				120	CuCl	95	87
2				120	CuCl	78	54
3				120	CuCl	>99	89
4				140	CuI	88	75
5				120	CuCl	>99	>99
6				120	CuCl	>99	>99
7				120	CuCl	>99	93
8				120	CuCl	>99	85
9				120	CuCl	84	84
10				120	CuCl	89	85
11				120	CuCl	86	84
12				140	CuI	99	96
13				140	CuI	51	49

(*continued on next page*)

Table 2 (*continued*)

Entry	Aryl bromide	Hydroxybenzene	Product	*T* (°C)	Metal	Conversion[b] (%)	Yield[b] (%)
14				120	CuCl	100	95
15				140	CuI	93	87
16				120	CuCl	>99	>99
17				120	CuCl	79	78

[a] General reaction conditions: 2 mmol aryl bromide, 2.4 mmol phenol, 10 mol % metal precursor, 4 mmol K_2CO_3, 1 mmol 1-butylimidazole, 2 mL toluene, 200 μL tetradecane as internal standard for GC, 16 h.
[b] GC-conversion and yield.

pipecolinic acid,[16] which have been successfully used as ligands in aryl halide aminations, were also tested in the model reaction, but gave no diaryl ether coupling product.

Variation of bases revealed that Cs_2CO_3 also led to good results (Table 1, entry 13), comparable to dry K_3PO_4, which must be handled under strict exclusion of moisture (Table 1, entries 14 and 15). Other typical bases such as NaO*t*Bu and Na_2CO_3 are not suited for the aryl ether coupling under these conditions (Table 1, entries 16 and 17). Increasing the amount of K_2CO_3 from 1.3 to 2 equiv showed a slight positive effect on the yield (Table 1, entry 18). At higher temperature (140 °C instead of 120 °C) the yield increased to 91% (Table 1, entry 19).

Other solvents like dioxane, *o*-xylene or NMP resulted in lower yield of the product (up to 63%) (Table 1, entries 20–22). Even in polar NMP, which is known to stabilize metals, the presence of 1-butylimidazole is essential (Table 1, entry 23). Notably, applying 1-alkylimidazoles (e.g., 1-methylimidazole) in large excess as solvent for the reaction resulted in low yield (Table 1, entry 24).

Experiments with different copper sources showed that copper(I) chloride gave slightly better results than copper(I) iodide, while copper(I) bromide and copper(I) oxide are worse catalyst precursors (Table 1, entries 25–27). In agreement with other known copper-catalyzed coupling reactions lower concentrations of the active metal (Table 1, entries 28 and 29) are not sufficient for high conversion and good yields.

With the optimized results in hand, we set out to evaluate the scope of our novel protocol for the coupling of aryl bromides with various phenols (Table 2). Most electron-poor and electron-rich aryl bromides react with 2-cresol in good to excellent yield and selectivity. Only for the sterically more hindered 2-bromo-*m*-xylene a higher temperature of 140 °C is required to obtain 75% of the product. In general, there is no significant difference in reactivity between electron-rich and electron-poor bromobenzenes. For example, both 4-bromonitrobenzene and 4-bromoaniline are coupled with 2-cresol in 99% and 93% yield, respectively (Table 2, entries 5 and 7). At this point it is also interesting to note that 4-bromoaniline showed no sign of self-coupling, indicating an excellent selectivity of the catalytic system towards the reaction at the oxygen atom.

Despite the basic conditions and the reaction temperature of 120 °C, the acetyl group of 4-bromoacetanilide is not cleaved, resulting in a good yield of 85% of the product (Table 2, entry 8). In addition to bromobenzenes, also 2-bromopyridine gave the corresponding ether in excellent yield (Table 2, entries 6, 14 and 16). Here, without copper catalyst only ca. 10% of the desired product is formed at this temperature. All other cresols and phenols themselves react similarly well.

By comparing the reaction of 2-bromo-*m*-xylene and 2-cresol (Table 2, entry 4) with the reaction of 2-bromotoluene and 2,6-dimethylphenol (Table 2, entry 13), in which the same product is formed, it became clear that steric

hindrance is better tolerated on the side of the aryl bromide than on the phenol substrate (75% vs 49% yield).

In conclusion, we have shown that Cu(I)/1-alkylimidazole allows for a general diaryl ether synthesis from aryl bromides and phenols. Good to excellent yields are obtained with this bio-inspired catalyst system. Due to the low cost of the metal and ligands and no expensive base or solvents the reaction is very convenient and can be easily upscaled.

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References and notes

1. Theil, F. *Angew. Chem.* **1999**, *111*, 2493–2495; . *Angew. Chem., Int. Ed.* **1999**, *38*, 2345–2347.
2. Ley, S. V.; Thomas, A. W. *Angew. Chem.* **2003**, *115*, 5558–5607; *Angew. Chem., Int. Ed.* **2003**, *42*, 5400–5449.
3. (a) Ullmann, F. *Chem. Ber.* **1904**, *37*, 853–854; (b) Lindley, J. *Tetrahedron* **1984**, *40*, 1433–1456.
4. Frlan, R.; Kikelj, D. *Synthesis* **2006**, 2271–2285.
5. Beletskaya, I. P.; Cheprakov, A. V. *Coord. Chem. Rev.* **2004**, *248*, 2337–2364.
6. Kunz, K.; Scholz, U.; Ganzer, D. *Synlett* **2003**, 2428–2439.
7. Ouali, A.; Spindler, J.-F.; Jutand, A.; Taillefer, M. *Adv. Synth. Catal.* **2007**, *349*, 1906–1916.
8. Ullmann reactions with the use of stoichiometric amounts of copper: (a) Buck, E.; Song, Z. J.; Tschaen, D.; Dormer, P. G.; Volante, R. P.; Reider, P. J. *Org. Lett.* **2002**, *4*, 1623–1626; (b) Wipf, P.; Jung, J. K. *J. Org. Chem.* **2000**, *65*, 6319–6337; With catalytic use of copper: (c) Miao, T.; Wang, L. *Tetrahedron Lett.* **2007**, *48*, 95–99; (d) Lipshutz, B. H.; Unger, J. B.; Taft, B. R. *Org. Lett.* **2007**, *9*, 1089–1092; (e) Cai, Q.; Zou, B. L.; Ma, D. W. *Angew. Chem.* **2006**, *118*, 1298–1301; *Angew. Chem., Int. Ed.* **2006**, *45*, 1276–1279; (f) Cristau, H.-J.; Cellier, P. P.; Hamada, S.; Spindler, J.-F.; Taillefer, M. *Org. Lett.* **2004**, *6*, 913–916; (g) Xu, L.-W.; Xia, C.-G.; Li, J.-W.; Hu, X.-X. *Synlett* **2003**, 2071–2073; (h) Luo, Y. T.; Wu, J. X.; Ren, R. X. *Synlett* **2003**, 1734–1736; (i) Gujadhur, R.; Venkataraman, D. *Synth. Commun.* **2001**, *31*, 2865–2879; (j) Gujadhur, R. K.; Bates, C. G.; Venkataraman, D. *Org. Lett.* **2001**, *3*, 4315–4317; (k) Marcoux, J. F.; Doye, S.; Buchwald, S. L. *J. Am. Chem. Soc.* **1997**, *119*, 10539–10540; (l) Kalinin, A. V.; Bower, J. F.; Riebel, P.; Snieckus, V. *J. Org. Chem.* **1999**, *64*, 2986–2987; (m) Pellón, R. F.; Docampo, M. L. *Synth. Commun.* **2003**, *33*, 921–926; (n) Paine, A. J. *J. Am. Chem. Soc.* **1987**, *109*, 1496–1502.
9. (a) Mann, G.; Incarvito, C.; Rheingold, A. L.; Hartwig, J. F. *J. Am. Chem. Soc.* **1999**, *121*, 3224–3225; (b) Aranyos, A.; Old, D. W.; Kiyomori, A.; Wolfe, J. P.; Sadighi, J. P.; Buchwald, S. L. *J. Am. Chem. Soc.* **1999**, *121*, 4369–4378; (c) Harkal, S.; Kumar, K.; Michalik, D.; Zapf, A.; Jackstell, R.; Rataboul, F.; Riermeier, T.; Monsees, A.; Beller, M. *Tetrahedron Lett.* **2005**, *46*, 3237–3240.
10. (a) Schareina, T.; Zapf, A.; Mägerlein, W.; Müller, N.; Beller, M. *Synlett* **2007**, 555–558; (b) Schareina, T.; Zapf, A.; Mägerlein, W.; Müller, N.; Beller, M. *Chem. Eur. J.* **2007**, *13*, 6249–6254.
11. (a) Schareina, T.; Zapf, A.; Mägerlein, W.; Müller, N.; Beller, M. *Tetrahedron Lett.* **2007**, *48*, 1087–1090; (b) Schareina, T.; Zapf, A.; Beller, M. *Tetrahedron Lett.* **2005**, *46*, 2585–2588; (c) Schareina, T.; Zapf, A.; Beller, M. *J. Organomet. Chem.* **2004**, *689*, 4576–4583; (d) Schareina, T.; Zapf, A.; Beller, M. *Chem. Commun.* **2004**, 1388–1389; (e) Sundermeier, M.; Zapf, A.; Beller, M. *Angew. Chem.* **2003**, *115*, 1700–1703; *Angew. Chem., Int. Ed.* **2003**, *42*, 1661–1664; (f) Sundermeier, M.; Mutyala, S.; Zapf, A.; Spannenberg, A.; Beller, M. *J. Organomet. Chem.* **2003**, *684*, 50–55; (g) Sundermeier, M.; Zapf, A.; Beller, M.; Sans, J. *Tetrahedron Lett.* **2001**, *42*, 6707–6710.
12. For recent work on Fe catalysts with imidazole ligands see: Schröder, K.; Tong, X.; Bitterlich, B.; Tse, M. K.; Gelacha, F. G.; Brückner, A.; Beller, M. *Tetrahedron Lett.* **2007**, *48*, 6339–6342.
13. (a) Sendra, V.; Cannella, D.; Bersch, B.; Fieschi, F.; Menage, S.; Lascoux, D.; Coves, J. *Biochemistry* **2006**, *45*, 5557–5566; (b) Hernandez-Romero, D.; Sanchez-Amat, A.; Solano, F. *FEBS J.* **2006**, *273*, 257–270; (c) Klabunde, T.; Eicken, C.; Sacchettini, J. C.; Krebs, B. *Nat. Struct. Biol.* **1998**, *5*, 1084–1090.
14. Standard reaction procedure: 2 mmol aryl bromide, base, metal precursor, ligand and 2.4 mmol of the phenol are put in a pressure tube under argon. Then 2 mL solvent and 200 μL tetradecane as internal standard for GC are added and the mixture is stirred for 16 h at the temperature given. After cooling to room temperature 5 mL water and 3 mL *tert*-butyl methyl ether are added, thoroughly mixed and the organic phase is analyzed by GC. Conversion and yield are calculated as average of two parallel runs. On small scale the products can be isolated by column chromatography (SiO_2, ethyl acetate/hexane) after washing the organic phase with water, drying over sodium sulfate and distilling off the solvents. On a larger scale crystallization or distillation (depending on the product) can be used. Identification of the compounds was performed by GC/MS and NMR spectroscopy, all analyses gave satisfactory data.
15. Yeh, V. S. C.; Wiedeman, P. E. *Tetrahedron Lett.* **2006**, *47*, 6011–6016.
16. Guo, X.; Rao, H.; Fu, H.; Jiang, Y.; Zhao, Y. *Adv. Synth. Catal.* **2006**, *348*, 2197–2202.