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Copper-in-Charcoal (Cu/C) Promoted Diaryl Ether Formation†

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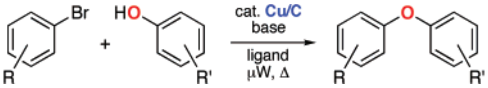
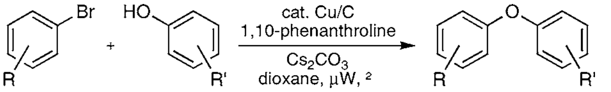
ABSTRACT



Copper impregnated into charcoal efficiently catalyzes cross-couplings between aryl bromides and phenols. The etherifications were conveniently promoted by microwave heating.

For roughly the past decade, synthetic chemists have devoted considerable effort toward developing methodologies for constructing diaryl ethers.[1] Although the increased attention may have arisen, in part, due to the prominence of this functional group in vancomycin and related clinically valued antibiotics,[2] many physiologically active, naturally occurring compounds possess this moiety.[3] While catalytic processes in costly palladium can be especially effective at mediating cross-couplings between aryl halides and phenols,[4] they are oftentimes driven by privileged ligands.[5] Moreover, these approaches are homogeneous in nature, necessitating meticulous product isolation to avoid palladium contamination. As a result, much of the recent literature has focused on the continuing evolution of Ullmann's original copper-based diaryl ether formations.[6] However, with the majority of attention being given to the nature of ligand,[7] base,[8] and copper species[9] in efforts to streamline this transformation, minimal progress has been made employing heterogeneous catalysis to effect etherification. To our knowledge, there are only two reports that offer a heterogeneous source of this inexpensive base metal for such a purpose.[10] We now describe in this communication the application of our recently disclosed, heterogeneous catalyst copper-in-charcoal (Cu/C)[11] to the synthesis of diaryl ethers (Scheme 1).

Scheme 1



The study began with the more challenging, electron-rich case of *para*-bromoanisole, together with *para*-*t*-butylphenol

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† Dedicated to Prof. Madeleine M. Joullié on the occasion of her 80th birthday.

[1] For reviews, see: (a) Frlan, R.; Kikelj, D. *Synthesis* **2006**, 2271. (b) Ley, S. V.; Tomas, A. W. *Angew. Chem., Int. Ed.* **2003**, *42*, 5400. (c) Kunz, K.; Scholz, U.; Ganzer, D. *Synlett* **2003**, 2428. (d) Sawyer, J. S. *Tetrahedron* **2000**, *56*, 5045.

[2] (a) Crowley, B. M.; Mori, Y.; McComas, C. C.; Tang, D.; Boger, D. L. *J. Am. Chem. Soc.* **2004**, *126*, 4310. (b) Evans, D. A.; Katz, J. L.; Peterson, G. S.; Hintermann, T. *J. Am. Chem. Soc.* **2001**, *123*, 12411. (c) Evans, D. A.; Wood, M. R.; Trotter, B. W.; Richardson, T. I.; Barrow, J. C.; Katz, J. L. *Angew. Chem., Int. Ed.* **1998**, *37*, 2700. For reviews, see: (d) Rao, A. V. R.; Gurjar, M. K.; Reddy, G. K. L.; Rao, A. S. *Chem. Rev.* **1995**, *95*, 2135. (e) Zhu, J. *Synlett* **1997**, 133. (f) Nicolaou, K. C.; Boddy, C. N. C.; Brase, S.; Winssinger, N. *Angew. Chem., Int. Ed.* **1999**, *38*, 2096.

[3] (a) Xing, X.; Padmanaban, D.; Yeh, L.; Cuny, G. D. *Tetrahedron* **2002**, *58*, 7903. (b) Boger, D. L.; Patane, M. A.; Zhou, J. *J. Am. Chem. Soc.* **1994**, *116*, 8544. (c) Evans, D. A.; Ellman, J. A. *J. Am. Chem. Soc.* **1989**, *111*, 1063. (d) Nishiyama, S.; Suzuki, Y.; Yamamura, S. *Tetrahedron Lett.* **1988**, *29*, 559.

[4] (a) Aranyos, A.; Old, D. W.; Kiyomori, A.; Wolfe, J. P.; Sadighi, J. P.; Buchwald, S. L. *J. Am. Chem. Soc.* **1999**, *121*, 4369. (b) Mann, G.; Incarvito, C.; Rheingold, A. L.; Hartwig, J. F. *J. Am Chem. Soc.* **1999**, *121*, 3224.

[5] (a) Burgos, C. H.; Barder, T. E.; Huang, X.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2006**, *45*, 4321. (b) Shelby, Q.; Kataoka, N.; Mann, G.; Hartwig, J. *J. Am. Chem. Soc.* **2000**, *122*, 10718.

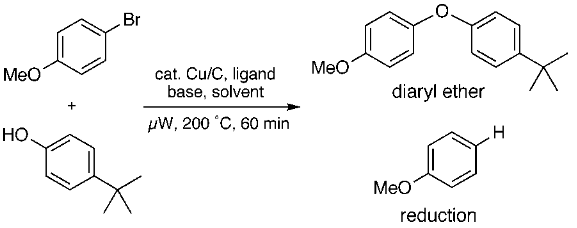
[6] Ullmann, F.; Sponagel, P. *Ber.* **1905**, *38*, 2211.

[7] (a) Chen, Y.; Chen, H. *Org. Lett.* **2006**, *8*, 5609. (b) Ma, D.; Cai, Q. *Org. Lett.* **2003**, *5*, 3799. (c) Buck, E.; Song, Z. J.; Tschaen, D.; Dormer, P. G.; Volante, R. P.; Reider, P. J. *Org. Lett.* **2002**, *4*, 1623. (d) Fagan, P. J.; Hauptman, E.; Shapiro, R.; Casalnuovo, A. *J. Am. Chem. Soc.* **2000**, *122*, 5043.

10.1021/ol0700409 CCC: $37.00

as a reaction partner. It was immediately clear that several parameters: solvent, base, and ligand, all play roles in controlling the degree of conversion even at the high temperatures readily achieved using microwave irradiation (Table 1).[12] Finding conditions that minimize reduction of the aryl bromide was also of paramount concern. Dioxane was determined to be the solvent of choice, whereas alternatives of greater polarity (e.g., $PhCF_3$) led to significantly higher percentages of halide reduction. Cs_2CO_3 appeared to give the best results among bases screened (K_2CO_3, K_3PO_4), as noted by others in related couplings.[13] Most curious was the impact of the ligand. Ultimately, 1,10-phenanthroline (Figure 1) emerged as the only species that both contributed to bromide consumption and discouraged competitive halide reduction. Its rigid, tricyclic structure is apparently key, as neither 2,2′-bipyridyl (bipy) nor (excess) pyridine achieves the 92% isolated yield obtained with ligand **1**.

Table 1. Variations in Reaction Conditions



Cu/C (wt %)	solvent	base	ligand	% yield (ether: reduction)[a]
5	dioxane	Cs_2CO_3	1,10-phenanthroline	85:8
15	**dioxane**	**Cs_2CO_3**	**1,10-phenanthroline**	**94:5**[b]
15	$PhCF_3$	Cs_2CO_3	1,10-phenanthroline	84:7
15	dioxane	K_2CO_3	1,10-phenanthroline	68:5
15	dioxane	Cs_2CO_3	pyridine	79:8
15	dioxane	Cs_2CO_3	2,2′-bipyridine	64:5
15	dioxane	Cs_2CO_3	α-naphthoic acid	67:10

[a] Determined by GC analysis. [b] Most favorable conditions: 1.0 mmol of *para*-bromoanisole, 2.0 mmol of *para-t*-butylphenol, 2.0 mmol of Cs_2CO_3, 0.5 mmol of 1,10-phenanthroline, and 2.0 mL of dioxane; 92% isolated yield.

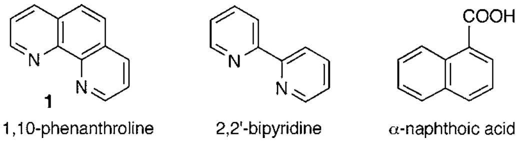
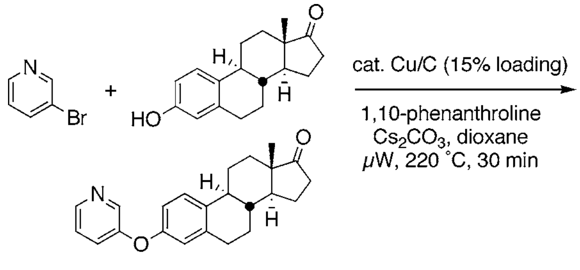


Figure 1. Selected ligands used with Cu/C in this study.

Cu/C is easily prepared in water,[11] and the extent of loading using $Cu(NO_3)_2$ had been arbitrarily chosen within the 3−5% range. During the course of this study, impregnation with greater amounts of copper was examined and the higher loading catalysts proved to be superior. Copper levels up to 15% showed both greater activity and greater selectivity toward diaryl ether formation. By contrast, such high loadings with nickel-in-charcoal were previously found to decrease catalyst (Ni/C) activity due to pore blockage.[14] Additional assistance by microwave (μW) irradiation was expected to significantly enhance reaction rates.[12] Indeed, this combination of 10−15% Cu loaded into charcoal and microwave heating was found to effectively form most desired diaryl ethers in less than an hour.[15] Table 2 shows several representative examples, from which the following features emerge: (1) both electronically activated and deactivated bromides, as well as phenols, can be used; (2) sensitive functionalities, such as an aldehyde (entry 2) and a nitro group (entry 3), are unaffected; (3) a thioether presented no obstacles to coupling (entry 6); (4) a naphthyl case (entry 8) readily participates; (5) heteroaromatic bromides smoothly react (entries 9 and 10). A noteworthy example is illustrated in Scheme 2, where a pyridyl ether of estrone (**2**) was cleanly formed.

Scheme 2



2 (86% isolated)

As has been the case with related Pd-catalyzed Suzuki, Heck, and Sonogashira cross-couplings involving aryl halides,[16] considerable effort is being devoted to making aryl chlorides viable reaction partners. Preliminary studies suggest that while Cu/C can catalyze a net displacement of chloride

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(8) Hosseinzadeh, R.; Tajbakhsh, M.; Mohadjerani, M.; Alikarami, M. *Synlett* **2005**, 1101.

(9) (a) Ghosh, R.; Samuelson, A. G. *New J. Chem.* **2004**, *28*, 1390. (b) Kalinin, A. V.; Bower, J. F.; Riebel, P.; Snieckus, V. *J. Org. Chem.* **1999**, *64*, 2986.

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(12) (a) Desai, B.; Kappe, C. O. *Top. Curr. Chem.* **2004**, *242*, 177. (b) Lipshutz, B. H.; Frieman, B. A.; Lee, C.; Lower, A.; Nihan, D. M.; Taft, B. R. *Chem. Asian J.* **2006**, *1*, 417.

(13) (a) Marcoux, J.; Doye, S.; Buchwald, S. L. *J. Am. Chem. Soc.* **1997**, *119*, 10539. (b) Cristau, H.; Cellier, P. P.; Hamada, S.; Spindler, J.; Taillefer, M. *Org. Lett.* **2004**, *6*, 913.

(14) Lipshutz, B. H.; Tasler, S.; Chrisman, W.; Spliethoff, B.; Tesche, B. *J. Org. Chem.* **2003**, *68*, 1177.

(15) Ether formation can also be effected by conventional heating; microwave irradiation was used mainly for convenience.

(16) (a) Yi, C.; Hua, R. *Tetrahedron Lett.* **2006**, *47*, 2573. (b) Anderson, K. W.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2005**, *44*, 6173. (c) Feuerstein, M.; Doucet, H.; Santelli, M. *Tetrahedron Lett.* **2004**, *45*, 8443. (d) Li, G. Y.; Zheng, G.; Noonan, A. F. *J. Org. Chem.* **2001**, *66*, 8677.

Table 2. Representative Cu/C-Catalyzed Diaryl Ether Formations Assisted by Microwave Heating

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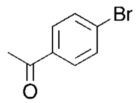
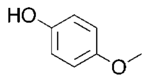
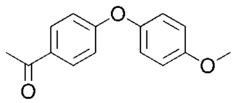
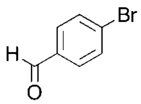
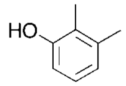
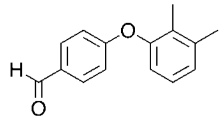
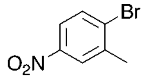
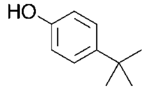
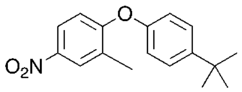
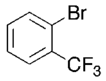
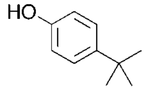
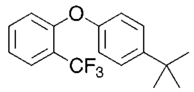
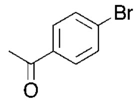
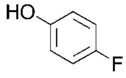
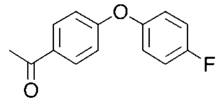
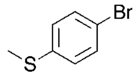
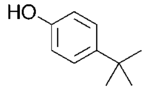
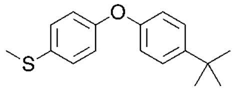
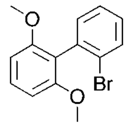
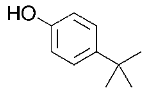
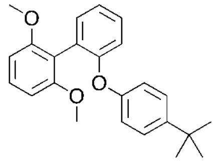
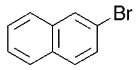
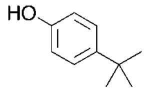
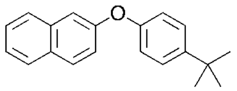
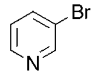
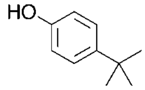
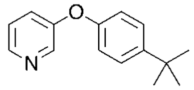
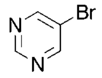
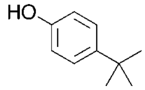
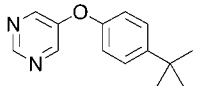
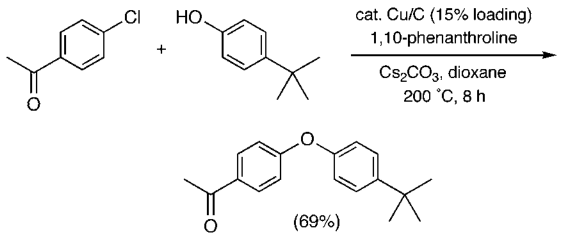
1			30 min, 180 °C		86
2			25 min, 200 °C		87
3			25 min, 190 °C		79 [b]
4			90 min, 200 °C		79
5			30 min, 220 °C		85
6			60 min, 200 °C		89
7			180 min, 220 °C		82
8			30 min, 200 °C		80
9			30 min, 200 °C		86
10			45 min, 200 °C		82

[a] Standard reaction conditions (unless otherwise noted): 1.0 mmol of aryl bromide, 30 mg of Cu/C, 0.5 equiv of 1,10-phenanthroline, 2.0 equiv of phenol, 2.1 equiv of Cs_2C0_3, 0.5 M (2.0 mL) dioxane. [b] K_3PO_4 (2.1 equiv) was used instead of CS_2CO_3.

leading to the corresponding diaryl ether, to date, only activated cases can be used and the reaction times are too long to be practical (Scheme 3). This is likely to be a ligand effect, and alternatives to phenanthroline are being investigated.

Scheme 3



Several control experiments were conducted to assess the extent of heterogeneity, in particular, given the high temperatures employed. As expected, no reaction occurred in the absence of Cu/C, even under extended reaction times with heating to 200 °C. Further studies suggested that an effective amount of copper was being released from charcoal into solution during etherification, *unlike* other chemistry of this catalyst.[11] Thus, after filtering a partially converted reaction mixture to remove the heterogeneous catalyst, further etherification within the filtered solution resubmitted to the reaction conditions was observed (Scheme 4).

Additional experiments indicated that the combination of three components: cesium phenoxide, 1,10-phenanthroline, and high temperature, appears to be crucial for leaching to occur, suggesting solubilization of a ligand-stabilized copper

Table 3. Cross-Couplings with a Phenol as the Limiting Reagent

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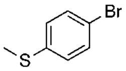
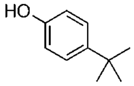
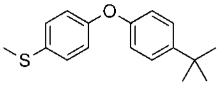
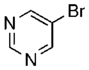
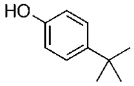
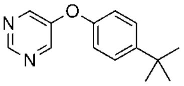
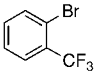
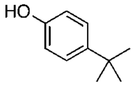
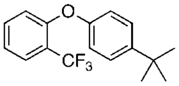
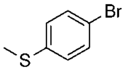
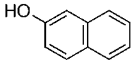
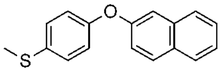
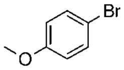
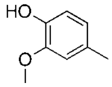
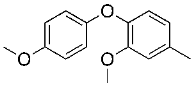
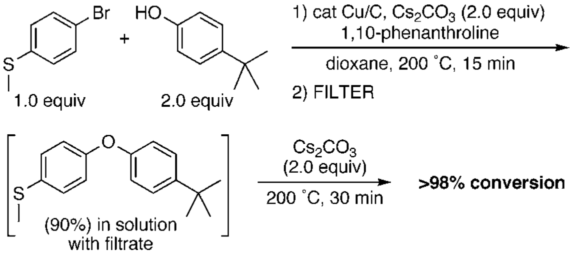
1			60 min, 200 °C		87
2			60 min, 200 °C		83
3			120 min, 200 °C		80
4			80 min, 200 °C		85
5			30 min, 200 °C		82

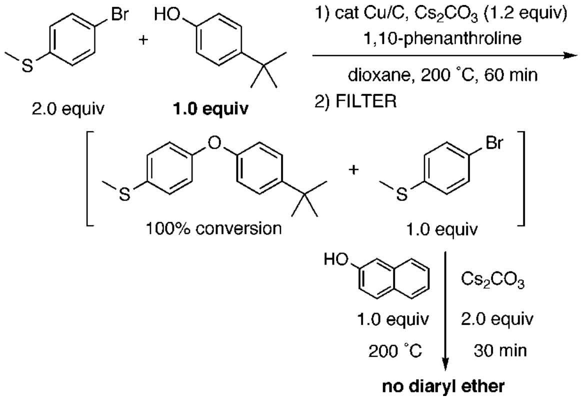
[a] Standard reaction conditions: 2.0 mmol of phenol, 60 mg of Cu/C, 1.0 mmol of 1,10-phenanthroline, 3.0 mmol of aryl bromide, 2.4 mmol of Cs_2CO_3, 0.67 M (in 3.0 mL of 1,4-dioxane). [b] Isolated and chromatographically purified.

phenoxide. When used as the limiting reagent, phenoxide is consumed en route to the diaryl ether. Therefore, copper, as the (presumed) counterion, may no longer remain in solution. Indeed, filtration of the heterogeneous reaction mixture followed by addition of a different phenol to the filtrate led to no etherification (Scheme 5). Thus, by simply adjusting the stoichiometry, active copper does not remain in solution. It is unknown at this point whether copper has been reabsorbed by the charcoal or precipitated from the solution. Nonetheless, filtration of the catalyst (from the reaction in Table 3, entry 1) and reuse with fresh coupling partners led to full conversion to the desired diaryl ether, suggesting that Cu/C can be recycled. The generality of this alternative stoichiometry (i.e., with phenol as the limiting reagent) was tested using several substrate combinations (Table 3). Although slightly more time was required to complete each reaction, the yields are comparable to those seen earlier (cf., Table 2). Moreover, less cesium base is needed, which allows for use of less solvent.

Scheme 4



Scheme 5



In summary, diaryl ethers can be constructed from aryl bromides and phenols using an easily prepared, inexpensive, and effective heterogeneous catalyst, Cu/C, under the influence of microwave irradiation. Although active copper has been found in solution during ether formation, with consumption of phenoxide it is no longer present in the medium. Prospects for extending this technology to aryl chlorides are encouraging and will be reported in due course.

Acknowledgment. We warmly thank the NSF (CHE 05-50232) for supporting our program in organocopper chemistry and Boehringer-Ingelheim for graduate student support.

Supporting Information Available: Detailed experimental procedures and complete characterization data for new diaryl ethers. This material is available free of charge via the Internet at http://pubs.acs.org.

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