PAPER

Copper(II)-catalyzed C–O coupling of aryl bromides with aliphatic diols: synthesis of ethers, phenols, and benzo-fused cyclic ethers†

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A highly efficient copper-catalyzed C–O cross-coupling reaction between aryl bromides and aliphatic diols has been developed employing a cheaper, more efficient, and easily removable copper(II) catalyst. A broad range of aryl bromides were coupled with aliphatic diols of different lengths using 5 mol% CuCl$_2$ and 3 equivalents of K$_2$CO$_3$ in the absence of any other ligands or solvents to afford the corresponding hydroxyalkyl aryl ethers in good to excellent yields. In this newly developed protocol, aliphatic diols have multilateral functions as coupling reactants, ligands, and solvents. The resulting hydroxyalkyl aryl ethers were further readily converted into the corresponding phenols, presenting a valuable alternative way to phenols from aryl bromides. Furthermore, it was demonstrated that they are useful intermediates for more advanced molecules such as benzofurans and benzo-fused cyclic ethers.

Introduction

The C(aryl)–O bond forming reaction is a valuable process for the preparation of various target compounds.[1] To this end, transition metal-catalyzed C–O coupling of aryl halides with O-nucleophiles is often sought,[2,3] and copper has attracted much attention due to its low cost and less toxicity. While copper-catalyzed diaryl ether synthesis using phenolic nucleophiles is better established,[4] less has been explored on the preparation of aryl alkyl ethers and phenols with aliphatic alcohols and hydroxide as nucleophiles, respectively.

The classical Ullmann reaction for the synthesis of aryl alkyl ethers from aryl halides and alkoxides suffers from drastic reaction conditions.[5] However, significant advancement has been made in this area in the past few decades. In 2002, the Buchwald group reported the first successful copper-catalyzed arylation of aliphatic alcohols with aryl iodides using CuI and 1,10-phenanthroline under mild conditions.[6] Later, other ligands were reported, including *N,N*-dimethylglycin,[7] 8-hydroxyquinoline,[8] and 3,4,7,8-tetramethyl-1,10-phenanthroline.[9] New protocols are also continuously being developed:[10]

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for example, copper-cluster as a catalyst, KF/Al$_2$O$_3$ as a base, or β-amino alcohols as coupling partners. In the case of phenol synthesis, copper-catalyzed methods have been very recently developed.[11] In 2009, the Taillefer group[11a] and the You[11b] group reported independently that metal hydroxide cross-couples directly with aryl iodides in the presence of CuI and either 1,3-diketone or 1,10-phenanthroline in aqueous DMSO. Shortly after these findings, other ligands showing the similar activity were identified.[11c–i]

Despite the remarkable advancements in this regard, there are still several aspects to be addressed for the catalytic C–O cross-coupling reactions toward aryl alkyl ethers and phenols. First, the catalyst is mostly limited to copper(I) salts, especially CuI. Alternative copper salts should be advantageous if they are cheaper, more efficient, and readily removable. Second, these reactions are highly dependent on specific ligands, most of which are expensive and often used in large amounts as much as 50 mol%. Third, most protocols have limited substrate scopes, where aryl iodides are generally required while more available aryl bromides and chlorides are poor in reactivity. Herein, we wish to report an efficient copper(II)-catalyzed C–O cross-coupling reaction between aryl bromides and aliphatic diols. To the best of our knowledge, our work is the first attempt to cross-couple aliphatic diols with aryl halides. To a great extent, this protocol fulfills the above-mentioned requirements, as it has a broad substrate scope for various aryl bromides employing the copper(II) catalyst in the absence of any extra ligands. In addition, the resulting aryl alkyl ethers are further readily converted into phenols and benzo-fused cyclic ethers.

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Results and discussion

In many copper-catalyzed coupling reactions, a variety of bidentate ligands including N,N-, N,O-, and O,O-chelators are often employed.[3a] We were particularly intrigued by the O,O-donor ligands such as ethylene glycol[12a] and 1,1,1-tris(hydroxymethyl)ethane.[12b] We envisioned that they could not only function as ligands, but also couple as O-nucleophiles with aryl halides. Particularly, these polyols could be effective in the coupling with less reactive aryl halides such as aryl bromides. We tested this idea by heating ethylene glycol with 4-iodo- or 4-bromotoluene without N-nucleophiles under the copper-catalyzed C–N coupling conditions published by Buchwald.[13] Indeed, for both 4-iodo- and 4-bromotoluene, the C–O coupling occurred, affording a considerable amount of products at a more elevated temperature.

Thus, we set out investigating copper-catalyzed systems for the C–O coupling between aryl bromides and aliphatic diols. Using 4-bromotoluene and ethylene glycol as model substrates, a variety of copper-catalytic conditions were examined, studying factors such as copper salt, catalyst loading, base, reaction temperature, and time (Table 1). In order to make the reaction protocol simple and practical, we did not incorporate any other solvents than ethylene glycol.[14] When 10 mol% CuI

and 3.0 equiv. of K_2CO_3 were applied at 130 °C for 20 h, only 65% of 4-bromotoluene was converted into the coupled product **2a** in 63% yield (entry 2). Such poor conversions and yields were also observed in cases of most other copper(I) salts tested. Only CuOAc showed conversion over 90% (entry 6) and less than 50% conversion was achieved for the others (entries 3–5). For the reactions with CuBr and CuCl, the low yields are attributed to the formation of the reduced by-product, toluene in 7–20%. Thus, most copper(I) salts seemed not effective enough for the desired coupling reaction. However, by changing the catalyst to copper(II) salts, the reactivity dramatically increased, leading to almost quantitative formation of the product **2a**, showing similar results with all the copper(II) salts tested (entries 8–14). Under the test conditions, we observed that the reaction mixtures with copper(II) salts and CuOAc became homogeneous while those with the other copper(I) salts remained heterogeneous throughout the reaction. The high reactivity with copper(II) salts was sustained even when the catalyst loading was decreased down to 3–5 mol%. The observed reactivity difference between copper(I) and copper(II) salts is interesting. In the coupling reactions, it is generally accepted that copper(I) is the real catalyst species and copper(II) is converted to copper(I) by *in situ* reduction by nucleophiles, which explains the slower reaction and/or lower reactivity with copper(II) salts.[15] However, from what we observed with the reactions, we presume that the apparent higher reactivity of copper(II) salts under our conditions seems to be due to the better stabilization and enhanced solubility of copper complexes. Nonetheless, we think that the reactive catalyst complexes would have copper(I) species reduced from copper(II) sources by plenty of O-nucleophiles, ethylene glycol. Since, in general, copper(II) salts have several advantages over copper(I) salts in respect of cost, air-stability, and water-solubility, employing copper(II) salts could lead to an economical and streamlined process; for instance, the easy removal of catalysts by simple aqueous work-up.[16]

We further screened a series of inorganic bases and reaction temperatures. Both K_2CO_3 and Cs_2CO_3 turned out to be excellent while K_3PO_4 and Na_2CO_3 were less effective (entries 17–19). Stronger bases such as NaOH and KO^{t}Bu produced 7–8% *p*-cresol (entries 15 and 16), because they promoted the cleavage of the ethereal bond of **2a** (*vide infra*), while less than 2% *p*-cresol was detected in the reactions with weaker bases. Meanwhile, no trace of the biarylated product of ethylene glycol was observed. Increasing the amount of ethylene glycol or base did not improve the reaction. Shortening the reaction time (entry 20) and lowering the reaction temperature (entry 22) caused negative effects. After the experiments, we were able to achieve the optimized conditions: 1 M solution of aryl bromide in ethylene glycol, 5 mol% $CuCl_2$ as the catalyst, and 3 equivalents of K_2CO_3 as the base at 130 °C for 20 h. However, we think users can choose any copper(II) salts available as there is little reactivity difference among them.

We then explored the application scopes of our method using a variety of aryl bromides (Table 2). Compared to aryl iodides, aryl bromides are more attractive for industrial appli-

Table 1 Optimization of Cu-catalyzed coupling reactions of 4-bromotoluene with ethylene glycol[a]

Entry	[Cu]	Base	Conv.[b] (%)	Yield[b] (%)
1	—	K_2CO_3	0	0
2	CuI	K_2CO_3	65	63
3	CuBr	K_2CO_3	35	28
4	CuCl	K_2CO_3	42	12
5	Cu_2O	K_2CO_3	50	50
6	CuOAc	K_2CO_3	92	92
7	Cu (powder)	K_2CO_3	0	0
8	$Cu(acac)_2$	K_2CO_3	100	99, 85[c]
9	$CuCl_2$	K_2CO_3	100	99, 99,[c] 88[d]
10	$CuBr_2$	K_2CO_3	99	99, 99[c]
11	$Cu(OAc)_2$	K_2CO_3	97	96, 95[c]
12	$Cu(OH)_2$	K_2CO_3	98	95, 94[c]
13	$CuSO_4$	K_2CO_3	95	95, 95[c]
14	CuO	K_2CO_3	99	99, 97[c]
15	$Cu(acac)_2$	NaOH	93	86
16	$Cu(acac)_2$	KO^{t}Bu	100	92
17	$Cu(acac)_2$	K_3PO_4	93	90
18	$Cu(acac)_2$	Na_2CO_3	70	70
19	$Cu(acac)_2$	Cs_2CO_3	100	98
20[e]	$CuCl_2$	K_2CO_3	91	91
21[f]	$CuCl_2$	K_2CO_3	97	97
22[g]	$CuCl_2$	K_2CO_3	63	63

[a] Reaction conditions: 4-bromotoluene (1.0 mmol), [Cu] (10 mol%), base (3.0 equiv.) in ethylene glycol (1.0 mL) at 130 °C for 20 h. [b] Conversion and yield were determined by GC using *n*-dodecane as an internal standard. [c] 5 mol% [Cu]. [d] 3 mol% [Cu]. [e] 5 mol% $CuCl_2$, 12 h. [f] 120 °C. [g] 100 °C.

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Table 2 Copper(II)-catalyzed C–O coupling reactions of various aryl bromides with ethylene glycol[a]

Entry	Product		Yield[b]
1		2a	96%
2		2b	99%
3		2c	99%
4[c]		2d	94%
5		2e	99%
6	Ph	2f	95%
7		2g	96%
8		2h	94%
9	MeO	2i	93%
10	MeO	2j	92%
11	OMe	2k	92%
12	MeO, MeO	2l	94%
13	F	2m	96%
14	Cl	2n	96%
15	Cl	2o	95%

Table 2 *(Contd.)*

Entry	Product		Yield[b]
16[d]		2p	88%
17[e]		2q	90%
18[e]		2r	83%
19	F_3C, F_3C	2s	91%
20	HO	2t	94%
21	HO	2u	94%
22	HO	2v	95%
23		2w	90%
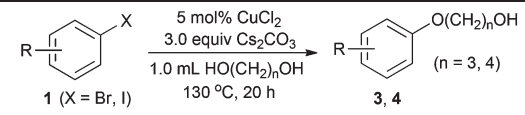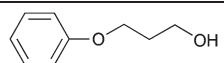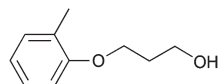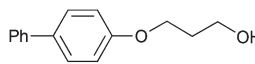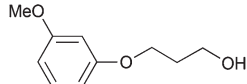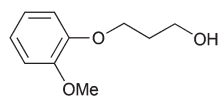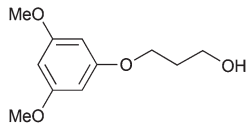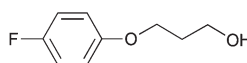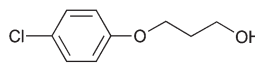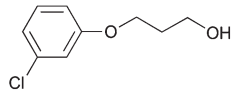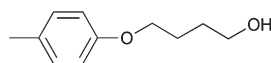
[a] *Reaction conditions*: aryl bromide (1.0 mmol), CuCl$_2$ (5 mol%), K$_2$CO$_3$ 3.0 equiv.) in 1.0 mL ethylene glycol at 130 °C for 20 h. [b] Isolated yield (average of two runs). [c] 140 °C. [d] 110 °C, 36 h. [e] 110 °C.
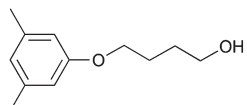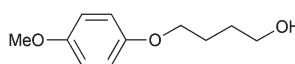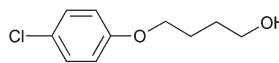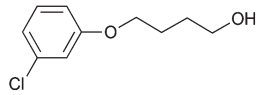
cation, but their usage in the copper-catalyzed C–O coupling reaction with aliphatic alcohols is rather limited due to their low reactivity. Only a few examples have been reported.[8] However, our new catalytic system is found to be readily applicable to various aryl bromides possessing substituents of electron-withdrawing, electronically neutral, and electron-donating groups. Ethylene glycol readily cross-coupled with aryl bromides under the reaction conditions to afford the corresponding arylated products in good to excellent yields. Simple alkyl or phenyl substituted aryl bromides showed almost quantitative reactions (entries 1–6). 1- and 2-Bromonaphthalenes also reacted with ethylene glycol in excellent yields (entries 7 and 8). It is noteworthy that sterically hindered aryl bromides such as 2,6-dimethyl bromobenzene successfully cross-coupled in 94% yield though a little higher temperature was required (entry 4). In fact, in our developed protocol, the reactivity of

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substrates seems to be less influenced by *ortho*-substituents in terms of steric and electronic factors; 1-bromo-2-methoxybenzene, which has an electron-donating group, and 1-acetyl-2-bromobenzene, which has an electron-withdrawing group, underwent the reactions at comparable efficiencies (entries 11 and 18). In the case of acetyl bromobenzenes, they all behaved similarly regardless of their substitution positions, except for the need for adjusting each reaction temperature and time for the completion (entries 16–18). It was observed that acetyl bromobenzenes were reduced to acetophenones and the coupled products were further cleaved to the phenolic by-products, acetyl phenols at 130 °C. Lowering the reaction temperature to 110 °C was helpful in minimizing such side reactions. Yet, the moderate yields were attributed to the formation of acetyl phenols up to 8%. Excellent yields were observed in the reactions with 4-fluoro- and 3-, 4-chlorobromobenzene and the coupling reaction occurred only at the carbon bearing bromine (entries 13–15). Meanwhile, our catalytic system showed a good tolerance toward a variety of functional groups. Besides those described above, functional groups such as trifluoromethyl, phenolic hydroxyl, aliphatic hydroxyl, and carboxylic acid were compatible under the reaction conditions (entries 19–22). Particularly, it is noteworthy that the phenolic hydroxyl group did not participate in the C–O coupling reaction to give diaryl ether (entry 20). Heterocyclic compounds such as 3-bromopyridine also afforded the corresponding product in 90% yield (entry 23). For those reactions showing excellent yields in Table 2, almost pure products were obtained simply by aqueous work-up, because all the reagents including copper(II) chloride, bases, and diols were water-soluble and easily removed from the organic phase.

We then turned our attention to longer diols for arylation (Table 3). We assume that the coupling reaction is mediated *via* the chelation of diols to the copper catalyst, thus the C–O bond formation would proceed when the aliphatic diols could effectively form cyclic bidentate ligands. Therefore, diols which can form a 5- or 6-membered ring in the copper complexes would be preferred in this reaction, as most reported bidentate ligands are often 1,2- or 1,3-N,N-, N,O- and O,O-donors. Not too surprisingly, 1,3-propanediol cross-coupled with aryl bromides in good yields (entries 1–9), whereas 1,4-butanediol reacted in lower yields when the same aryl bromides were used (entries 10–14). For both 1,3-propanediol and 1,4-butanediol, Cs_2CO_3 was a more effective base than K_2CO_3, presumably because of the better solubility and basicity of Cs_2CO_3. In the case of arylation with 1,4-butanediol, aryl iodides showed significantly better reaction conversions than aryl bromides. For both 1,3-propanediol and 1,4-butanediol, the effects of various substituents of aryl halides were similar to those observed for ethylene glycol. Diols longer than 1,4-butanediol such as 1,5-pentanediol and 1,6-hexanediols were essentially ineffective in this coupling reaction with aryl bromides, showing poor conversions less than 30%. However, their reactions with aryl iodides showed good conversions up to 90%. Some branched aliphatic diols were briefly tested. 1,2-Propanediol and 1,3-butanediol were effectively coupled with

Table 3 Copper(II)-catalyzed C–O coupling reactions of aryl bromides with aliphatic diols of different lengths[a]

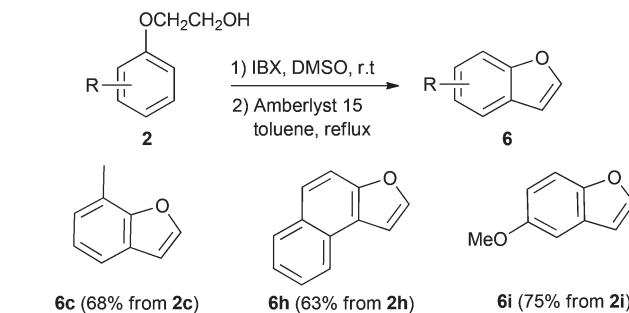| Entry	Product		Yield[b]	
			X = Br	X = I
1		**3b**	96%, 90%[c]	—[d]
2		**3c**	86%, 77%[c]	—[d]
3		**3f**	84%, 82%[c]	—[d]
4		**3j**	95%, 93%[c]	—[d]
5		**3k**	90%, 82%[c]	—[d]
6		**3l**	92%, 86%[c]	—[d]
7		**3m**	93%, 81%[c]	—[d]
8		**3n**	87%, 79%[c]	—[d]
9		**3o**	86%, 82%[c]	—[d]
10		**4a**	80%	91%
11		**4e**	62%	78%
12		**4i**	78%	86%
13		**4n**	62%	80%
14		**4o**	72%	91%

[a] *Reaction conditions*: aryl halide (1.0 mmol), CuCl$_2$ (5 mol%), Cs$_2$CO$_3$ (3.0 equiv.) in 1.0 mL aliphatic diol at 130 °C for 20 h. [b] Isolated yield (average of two runs). [c] K$_2$CO$_3$ was used as the base. [d] The reaction was not tested.
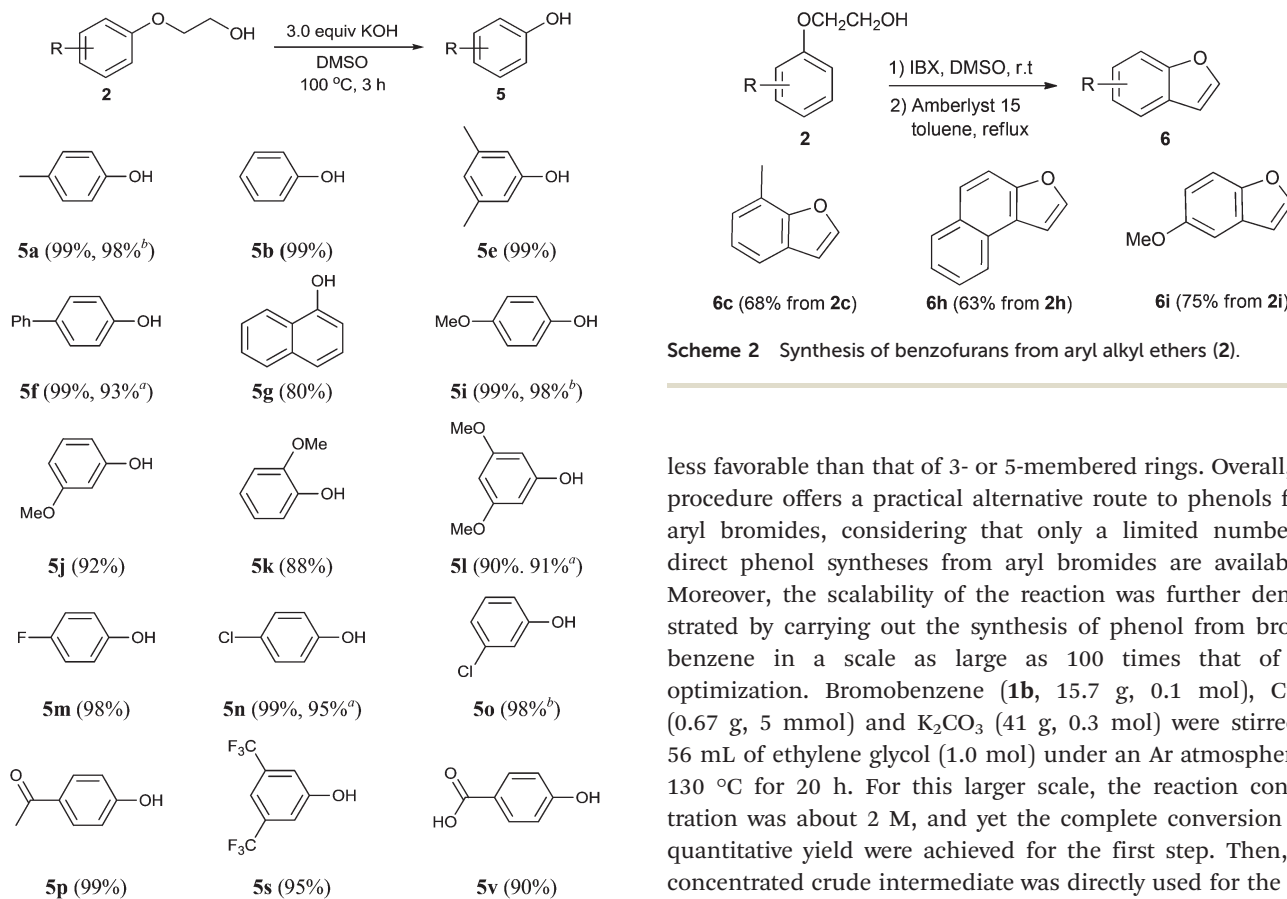
Scheme 1 Synthesis of phenols from aryl alkyl ethers. *Reaction conditions*: aryl alkyl ether (2) (1.0 mmol) and KOH (3.0 equiv.) in DMSO (3.0 mL) at 100 °C for 3 h. [a]Yield from 3, 120 °C, 5 h. [b]Yield from 4.

5a (99%, 98%[b]) 5b (99%) 5e (99%)
5f (99%, 93%[a]) 5g (80%) 5i (99%, 98%[b])
5j (92%) 5k (88%) 5l (90%. 91%[a])
5m (98%) 5n (99%, 95%[a]) 5o (98%[b])
5p (99%) 5s (95%) 5v (90%)

Scheme 2 Synthesis of benzofurans from aryl alkyl ethers (2).

6c (68% from 2c) 6h (63% from 2h) 6i (75% from 2i)

aryl bromides predominantly at the primary hydroxyl group, whereas 2,3-butanediol turned out to be less effective under our reaction conditions, though detailed studies have not been carried out in this regard.
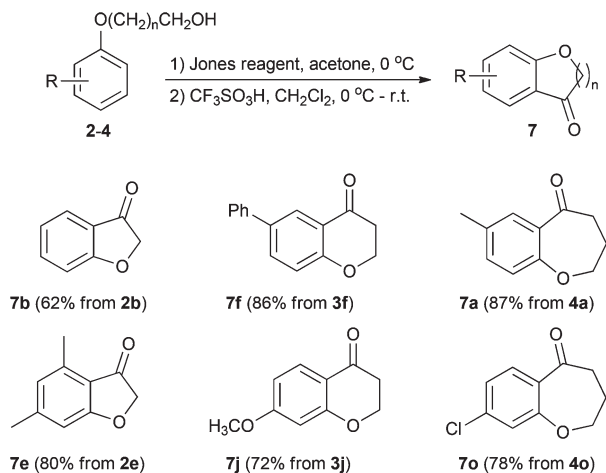
The hydroxyalkyl aryl ethers resulting from the reactions can serve as useful intermediates. For instance, the terminal primary alcohol can be transformed into various functional groups such as leaving groups for substitution, aldehydes, carboxylic acids, and so forth. Moreover, phenols can be liberated from the ethers by base-mediated intramolecular S_N2 reaction in an analogy to the Payne rearrangement pathway. We believe that the driving forces of this cleavage reaction are intramolecular cyclic ether formation and innate character of phenolate as a good leaving group. The hydroxyethyl aryl ethers (2) were treated with 3 equivalents of KOH in DMSO at 100 °C and the corresponding phenols (5) were obtained in good to excellent yields (Scheme 1). Most of them were cleaved with great easiness regardless of the substituents on the aryl ring. Similarly, the ethers derived from 1,4-butanediols (4) were smoothly transformed to the phenols (5a, 5i and 5o). The ethers (3) derived from 1,3-propanediols required slightly more heat and longer reaction time for full conversion (5f, 5l and 5n). One can assume that formation of a 4-membered ring would be

less favorable than that of 3- or 5-membered rings. Overall, the procedure offers a practical alternative route to phenols from aryl bromides, considering that only a limited number of direct phenol syntheses from aryl bromides are available.[11] Moreover, the scalability of the reaction was further demonstrated by carrying out the synthesis of phenol from bromobenzene in a scale as large as 100 times that of the optimization. Bromobenzene (1b, 15.7 g, 0.1 mol), CuCl$_2$ (0.67 g, 5 mmol) and K$_2$CO$_3$ (41 g, 0.3 mol) were stirred in 56 mL of ethylene glycol (1.0 mol) under an Ar atmosphere at 130 °C for 20 h. For this larger scale, the reaction concentration was about 2 M, and yet the complete conversion and quantitative yield were achieved for the first step. Then, the concentrated crude intermediate was directly used for the next reaction. Dealkylation of 2b proceeded smoothly in the presence of KOH (16.8 g, 0.3 mol) in 200 mL of DMSO under a N$_2$ atmosphere. Aqueous work-up followed by distillation of the concentrated crude product under reduced pressure afforded 8.75 g of phenol 5b as a colorless liquid (93% over 2 steps).

Another example showing the utility of the hydroxyalkyl aryl ethers is demonstrated by the synthesis of benzo-fused compounds. Benzo-fused cyclic ethers including benzofuran, benzofuranone, and benzopyranone are widely present in nature and they often appear as biologically active molecules and important synthetic intermediates.[17] It is conceivable that these cyclic ethers can be readily prepared from our coupled products by means of conventional synthetic methods. Indeed, we were able to synthesize several compounds of those classes uneventfully. For the synthesis of benzofurans, the terminal alcohols of hydroxyethyl aryl ethers (2) were oxidized to the corresponding aldehydes, which underwent intramolecular cyclization to afford the products (6) (Scheme 2).[18] When the terminal hydroxyl groups of arylated diols, 2, 3, and 4, were further oxidized to the carboxylic acids and the subsequent cyclizations were carried out, benzofuranone, benzopyranone, and benzooxepinone were obtained respectively (Scheme 3).[19] As our C–O coupling protocol provides one-step synthesis for hydroxyalkyl aryl ethers with various functional groups on the aryl ring, the synthetic route becomes much simplified and a library of these series can be rapidly generated. Thus, our method is readily applicable in the research areas where high-throughput synthesis is necessary.

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Scheme 3 Synthesis of benzo-fused cyclic ethers from aryl alkyl ethers (2–4).

Conclusions

In conclusion, we have developed a highly efficient and practical C–O coupling reaction between aryl bromides and aliphatic diols using copper(ii) catalysts. When compared to previously reported C–O(alkyl) coupling reactions, the developed protocol has the following advantages: (1) CuCl$_2$, the catalyst of choice, is not only readily available but also very effective in the C–O coupling. The good solubility of CuCl$_2$ in both reactant diols and water greatly enhances the reactivity of the catalytic system by rendering homogeneous reactions and makes it easy to remove the catalyst by simple aqueous work-up. (2) Our catalytic system is reactive enough so that it is applicable to a broad range of aryl bromides, which are more economically viable than aryl iodides. (3) The reaction conditions are very straightforward, consisting of the coupling components (aryl bromide and diol), copper catalyst, and base. It is essentially ligand-free and no additional solvents or additives are required. Unlike the coupled product from simple alcohols, the products, hydroxyalkyl aryl ethers, can be readily converted into more advanced molecules, for example, benzo-fused cyclic ethers, by transforming the terminal hydroxyl group. In addition, we developed a highly effective method to synthesize phenols from the hydroxyalkyl aryl ethers, presenting a valuable alternative way to phenols from aryl bromides. Overall, we believe that our protocol can find wide use both in academia and industry.

Acknowledgements

Notes and references

1 (a) J. H. P. Tyman, Synthetic and Natural Phenols, in Studies in Organic Chemistry, Elsevier, New York, 1996, vol. 52; (b) F. Theil, Angew. Chem., Int. Ed., 1999, 38, 2345.

2 For reviews on Pd-catalyzed C–O bond formation, see: (a) A. de Meijere and F. Diederich, Metal-Catalyzed Cross-Coupling Reactions, Wiley-VCH, Weinheim, 2004; (b) S. Enthaler and A. Company, Chem. Soc. Rev., 2011, 40, 4912; (c) J. Tsuji, Palladium Reagents and Catalysts Innovations in Organic Synthesis, John Wiley & Sons, Chichester, 1995; (d) A. K. Yudin, Catalyzed Carbon-Heteroatom Bond Formation, Wiley-VCH, Weinheim, 2011, pp. 35–68; (e) M. Catellani, E. Motti and N. D. Ca', Acc. Chem. Res., 2008, 41, 1512.

3 For reviews on Cu-catalyzed C–O bond formation, see: (a) G. Evano, N. Blanchard and M. Toumi, Chem. Rev., 2008, 108, 3054; (b) F. Monnier and M. Taillefer, Angew. Chem., Int. Ed., 2009, 48, 6954; (c) B. C. Ranu, R. Dey, T. Chatterjee and S. Ahammed, ChemSusChem, 2012, 5, 22; (d) Q. Cai, H. Zhang, B. Zou, X. Xie, W. Zhu, G. He, J. Wang, X. Pan, Y. Chen, Q. Yuan, F. Liu, B. Lu and D. Ma, Pure Appl. Chem., 2009, 81, 227; (e) P. Das, D. Sharma, M. Kumar and B. Singh, Curr. Org. Chem., 2010, 14, 754; (f) A. W. Thomas and S. V. Ley, Angew. Chem., Int. Ed., 2003, 42, 5400.

4 Selected examples for Cu-catalyzed synthesis of diaryl ethers: (a) J. F. arcoux, S. Doye and S. L. Buchwald, J. Am. Chem. Soc., 1997, 119, 10539; (b) Q. Cai, B. Zou and D. Ma, Angew. Chem., Int. Ed., 2006, 45, 1276; (c) A. Ouali, R. Laurent, A.-M. Caminade, J.-P. Majoral and M. Taillefer, J. Am. Chem. Soc., 2006, 128, 15990; (d) C. Palomo, M. Oiarbide, R. López and E. Gómez-Bengoa, Chem. Commun., 1998, 2091; (e) R. K. Gujadhur, C. G. Bates and D. Venkataraman, Org. Lett., 2001, 3, 4315; (f) R. A. Altman and S. L. Buchwald, Org. Lett., 2007, 9, 643; (g) N. Xia and M. Taillefer, Chem. – Eur. J., 2008, 14, 6037; (h) H.-J. Cristau, P. P. Cellier, S. Hamada, J.-F. Spindler and M. Taillefer, Org. Lett., 2004, 6, 913; (i) A. Ouali, J.-F. Spindler, H.-J. Cristau and M. Taillefer, Adv. Synth. Catal., 2006, 348, 499; (j) H. Rao, Y. Jin, H. Fu, Y. Jiang and Y. Zhao, Chem. – Eur. J., 2006, 12, 3636; (k) P. J. Fagan, E. Hauptman, R. Shapiro and A. Casalnuovo, J. Am. Chem. Soc., 2000, 122, 5043.

5 (a) F. Ullmann, Ber. Dtsch. Chem. Ges., 1904, 37, 853; (b) F. Ullmann, Ber. Dtsch. Chem. Ges., 1905, 38, 2211.

6 M. Wolter, G. Nordmann, G. E. Job and S. L. Buchwald, Org. Lett., 2002, 4, 973.

7 (a) H. Zhang, D. Ma and W. Cao, Synlett, 2007, 243; (b) Q. Cai, G. He and D. Ma, J. Org. Chem., 2006, 71, 5268; (c) D. Ma and Q. Cai, Org. Lett., 2003, 5, 3799.

8 J. Niu, P. Guo, J. Kang, Z. Li, J. Xu and S. Hu, J. Org. Chem., 2009, 74, 5075.

9 (a) A. Shafir, P. A. Lichtor and S. L. Buchwald, J. Am. Chem. Soc., 2007, 129, 3490; (b) R. A. Altman, A. Shafir, A. Choi, P. A. Lichtor and S. L. Buchwald, J. Org. Chem., 2008, 73, 284.

10 (a) G. F. Manbeck, A. J. Lipman, R. A. Stockland, A. L. Freidl, A. F. Hasler, J. J. Stone and I. A. Guzei, J. Org.

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This journal is © The Royal Society of Chemistry 2014

Chem., 2005, **70**, 244; (*b*) R. Hosseinzadeh, M. Tajbkhsh, M. Mohadjerani and M. Alikarami, *Synlett*, 2005, 1101; (*c*) G. E. Job and S. L. Buchwald, *Org. Lett.*, 2002, **4**, 3703.

11 (*a*) A. Tlili, N. Xia, F. Monnier and M. Taillefer, *Angew. Chem., Int. Ed.*, 2009, **48**, 8725; (*b*) D. Zhao, N. Wu, S. Zhang, P. Xi, X. Su, J. Lan and J. You, *Angew. Chem., Int. Ed.*, 2009, **48**, 8729; (*c*) K. G. Thakur and G. Sekar, *Chem. Commun.*, 2011, **47**, 6692; (*d*) L. Jing, J. Wei, L. Zhou, Z. Huang, Z. Li and X. Zhou, *Chem. Commun.*, 2010, **46**, 4767; (*e*) K. Yang, Z. Li, Z. Wang, Z. Yao and S. Jiang, *Org. Lett.*, 2011, **13**, 4340; (*f*) S. Maurer, W. Liu, X. Zhang, Y. Jiang and D. Ma, *Synlett*, 2010, 976; (*g*) J. Jia, C. Jiang, X. Zhang, Y. Jiang and D. Ma, *Tetrahedron Lett.*, 2011, **43**, 5593; (*h*) Y. Xiao, Y. Yu, H.-S. Cheon and J. Chae, *J. Org. Chem.*, 2013, **78**, 5804; (*i*) D. Wang, D. Kuang, F. Zhang, S. Tang and W. Jiang, *Eur. J. Org. Chem.*, 2014, 315.

12 (*a*) F. Y. Kwong, A. Klapars and S. L. Buchwald, *Org. Lett.*, 2002, **4**, 581; (*b*) Y. J. Chen and H. H. Chen, *Org. Lett.*, 2006, **8**, 5609.

13 They observed about 9% of *O*-arylated ethylene glycol as the by-product during C–N coupling reaction between aryl iodides and alkylamines using CuI as the catalyst, ethylene glycol as the ligand, and Cs_2CO_3 as the base. See: ref. 12*a*.

14 The coupling reaction of ethylene glycol and 4-iodo or 4-bromotoluene was briefly tested in DMSO. 86% and 25% GC yields were obtained for 4-iodotoluene and 4-bromotoluene, respectively. The study on the solvent effect was not further pursued as we wanted to keep the reaction conditions as simple as possible.

15 (*a*) G. Lefevre, G. Franc, A. Tlili, C. Adamo, M. Taillefer, I. Ciofini and A. Jutand, *Organometallics*, 2012, **31**, 7694; (*b*) E. Sperotto, G. P. M. van Klink, G. van Koton and J. G. de Vries, *Dalton Trans.*, 2010, **39**, 10338.

16 The crude product after aqueous work-up (Table 2, entry 1) was subjected to ICP analysis to determine the remaining amount of copper and copper was not detected with the detection limit of 0.1 ppm.

17 (*a*) M. Kamal, A. K. Shakya and T. Jawaid, *Int. J. Med. Pharm. Sci.*, 2011, **1**, 1; (*b*) G. P. Ellis, Chromenes, Chromanones, and Chromones, in *Chemistry of Heterocyclic Compounds*, John Wiley & Sons, Inc., 1977, vol. 31.

18 (*a*) Z. Liu, Z.-C. Chen and Q.-G. Zheng, *Org. Lett.*, 2003, **5**, 3321; (*b*) M. Witczak and H. Kwiecien, *Synth. Commun.*, 2005, **35**, 2223.

19 G. K. Surya Prakash, P. Yan, B. Torok and G. A. Olah, *Catal. Lett.*, 2003, **87**, 3.

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Org. Biomol. Chem., 2014, **12**, 4747–4753 | **4753**