## ChemComm

Cite this: Chem. Commun., 2011, 47, 6692–6694

### COMMUNICATION

# D-Glucose as green ligand for selective copper-catalyzed phenol synthesis from aryl halides with an easy catalyst removal<sup>†</sup>

Krishna Gopal Thakur and Govindasamy Sekar\*

Received 10th February 2011, Accepted 31st March 2011 DOI: 10.1039/c1cc10782h

With the growing demand of environmentally friendly reagents for organic reactions, for the first time the utility of D-glucose as a ligand in its direct form has been described using a typical example of copper-catalyzed coupling reaction for phenol synthesis with a high degree of selectivity and easy catalyst removal.

Glucose is one of the most naturally abundant organic molecules and it is available in nature mainly as disaccharides and polysaccharides. Chemists utilize carbohydrates for several purposes, namely, synthetic precursors for enantiopure natural products and molecules of high biological, medicinal and material importance.1 An enormous success has been achieved using carbohydrates in asymmetric synthesis by using them as chiral auxiliaries,<sup>2a</sup> chiral starting materials, and as a structural backbone of phosphorus, nitrogen and oxygen based ligands<sup>2b</sup> along with appropriate transition metal salts. Recently Monopoli and Nacci reported the direct usage of a glucose molecule as a stoichiometric reductant for reductive homo coupling of bromo or chloro arenes.<sup>2c</sup> Although having high potential, the direct use of carbohydrate monosaccharides as ligands for organic transformation is hardly visible. In the past few years significant developments have been achieved in the field of cross coupling reactions including developments from our own laboratory.<sup>3</sup> Of particular interest for acquisition of green methods for organic transformations, we recently reported aerobic oxidation of various molecules.<sup>4</sup> The low cost, high environmentally friendly and rich chiral natures of monosaccharides has driven us to explore their capabilities as ligands for the transition metal catalyzed reactions. To the best of our knowledge, no literature is available for the direct use of glucose or any monosaccharide as a ligand for organic reactions.

To develop the applications of monosaccharide molecules as ligands for organic reactions, we initiated our study on Cu-catalyzed synthesis of functionalized phenols from aryl halides and hydroxides through  $C_{(aryl)}$ -O bond forming coupling reactions. Functionalized phenols are very important precursors for the synthesis of many natural products and

Fax: +91 44 2257 4202; Tel: +91 44 2257 4229

molecules having material and medicinal importance. Several attempts have been made including conventional nucleophilic aromatic substitution and oxidation to achieve the most suitable methodology to synthesize simple and functionalized phenols.<sup>5</sup> But most of these methods are infructuous in terms of substrate scope and reaction conditions. Recently, few research groups reported palladium-catalyzed synthetic methodology for phenol through hydroxylation of corresponding aryl halides using coupling reactions.<sup>6</sup> However, the high cost of palladium, oxophilicity associated with the phosphine ligands and formation of appreciable amounts of diaryl ether as byproduct by tiny deviation from the exact reaction conditions<sup>6a</sup> make palladium unpopular.

In recent years, copper as a replacement of palladium catalysts got much attention because of its low cost and high efficiency towards coupling reactions with readily available *O* and *N* donor ligands. Recently, a few copper-catalyzed methods for phenol synthesis has been developed<sup>7</sup> but requirement of very high reaction temperature (300 °C),<sup>7a</sup> high quantity of ligand (50 mol%), limited substrate scope,<sup>7c</sup> and requirement of quaternary ammonium salts,<sup>7d,e</sup> especially fluorides,<sup>7e</sup> demand a more practical, reliable, economic, eco-friendly and general methodology for the synthesis of functionalized phenols.

In this communication, we report our initial finding of the study of D-glucose as a green ligand for copper-catalyzed synthesis of functionalized phenols (Scheme 1). The initial reaction of iodobenzene with KOH in the presence of 40 mol% of D-glucose L1 and 20 mol% of CuI in H<sub>2</sub>O/DMSO (1:1) at 120 °C provided quantitative yield of the phenol. Replacement of D-glucose L1 by monosaccharide based ligands such as D-mannose L2 and gluconolactone L4 reduced the yield to 96% and 78% respectively (Fig. 1). Then the reaction was screened with several other conventional oxygen and nitrogen based ligands and most of the ligands provided very poor results compared to D-glucose L1.

The investigation was further carried out on the effect of various copper salts, solvent mixtures, catalyst loading, bases



Scheme 1 Copper/D-glucose-catalyzed synthesis of functionalized phenol.

Department of Chemistry, Indian Institute of Technology Madras, Chennai, 600 036, India. E-mail: gsekar@iitm.ac.in;

<sup>&</sup>lt;sup>†</sup> Electronic supplementary information (ESI) available: Experimental procedures and characterization data, full spectroscopic data for all compounds, <sup>1</sup>H NMR & <sup>13</sup>C NMR spectra for all the compounds. See DOI: 10.1039/c1cc10782h





Entry	Aryl halide	t/h	Product	Yield (%) <sup>l</sup>
1		24	Срон	99/94 <sup>c</sup>
2	MeO	30	MeO-OH	93
3	MeO	24	MeO	99
4	OMe	35	ОМе	52
5		24	HO	84
6		28	>-он	67
7		24	OH	82
8	0 <sub>2</sub> N-	16	O <sub>2</sub> N-OH	99
9	O <sub>2</sub> N	16	O <sub>2</sub> N OH	83
10		20	)-ОН	84
11		24	но-СУ-С	93
12	Ph	24	Ph OH	87
13	HO	24	ОН	83
14	Br	24	HOHO	70
15	) O Br	34	<b>)</b> ————————————————————————————————————	69
16	NC - Br	28	NC — ОН	99
17	O <sub>2</sub> N-Br	24/66 <sup>d</sup>	O <sub>2</sub> N-OH	99/99 <sup>d</sup>
18	Br	16	но	83



Fig. 1 Optimization and a comparison of reactivity between monosaccharide ligands and conventional ligands.

and temperature to find out the best reaction conditions for D-glucose/Cu-catalyzed phenol synthesis.<sup>8a</sup> CuI and Cu(OAc)<sub>2</sub>. H<sub>2</sub>O have shown similar activity towards phenol formation reactions. Since Cu(OAc)<sub>2</sub> is water soluble and cheaper than CuI, we decided to proceed with Cu(OAc)<sub>2</sub>. The coupling reaction did not produce even trace amounts of phenol in the absence of ligand D-glucose L1, which shows the Cu(OAc)<sub>2</sub> alone without ligand D-glucose is not a catalyst for the phenol forming coupling reaction. Further optimization to reduce the catalyst loading showed that only 5 mol% of Cu(OAc)<sub>2</sub> and 5 mol% of L1 are sufficient for the quantitative yield of the product phenol. KOH was found to be the best among the hydroxyl bases screened and a DMSO/H<sub>2</sub>O (1:1) solvent ratio is found to be the most effective solvent for this reaction.

Surprisingly, most of the reactions with higher catalyst loading provided lesser yields of the phenol product except when we used Cu(OAc)<sub>2</sub>-L1 in 5:10 and 20:40 ratios.<sup>8a</sup>

To study the preference of iodobenzene towards nucleophile KOH in the presence of competitive nucleophiles, the reaction was performed in the presence of styrene, morpholine, phenol and ethanol. Surprisingly, the new catalyst L1-Cu(OAc)<sub>2</sub> provided very high selectivity towards phenol as a product and other coupling products were not obtained.<sup>8b</sup> When ethanol or phenol was added as a competitive nucleophile with KOH, even after 24 h there was no sign of corresponding alkyl aryl<sup>3</sup> or diaryl ether formation. Notably, diaryl ether formation is a problem with the progress of the phenol formation reaction since the generated phenol will always behave as a competitive nucleophile to produce diaryl ether as a byproduct.<sup>3</sup> In the presence of styrene, iodobenzene reacted only with KOH to yield the phenol selectively in 95% and no Heck reaction was observed.<sup>9</sup> Similarly, when morpholine was used as the competitive nucleophile with KOH, only phenol was obtained in quantitative yield through C(aryl)-O bond formation whereas C(aryl)-N bond formation did not take place.10

### Table 1 (continued)

Entry	Aryl halide	t/h	Product	Yield (%)
19		24	HO	80
20		20	ОН	54
21	Ph CI	24	о Рh — Он	30 <sup>c</sup>
22		$24/80^{d}$	02NОН	$99/80^{d}$

<sup>a</sup> ArX (0.5 mmol), Cu(Oac)<sub>2</sub>·H<sub>2</sub>O (0.025 mmol), D-glucose (0.025 mmol) and KOH (2–4 mmol) were reacted in 2 mL DMSO/H<sub>2</sub>O.
<sup>b</sup> Isolated yield. <sup>c</sup> Reaction performed in 10 mmol scale. <sup>d</sup> Reaction performed without catalyst.

Then the investigation was initiated to know the efficiency of the L1-Cu(OAc)<sub>2</sub> catalyzed phenol formation reaction towards several aryl halides and the results are summarized in Table 1. Various aryl iodides and bromides were converted to corresponding phenols under the optimized reaction conditions. Aryl iodides containing both electron-donating (entries 2-6, and 13) and electron-withdrawing groups (entries 8-12) provided good to excellent yields. Performances of aryl bromides with an electron-donating group in the ortho position are quite satisfactory (entries 14 and 18) and many aryl bromides with electron-withdrawing groups provided excellent yields of the corresponding phenol (entries 15-17). In the presence of an electron-withdrawing nitro group, chloro benzenes also provided excellent yields for the phenol formation (entry 22) but with a weak electron-withdrawing benzoyl group, chlorobenzene provided less yield (entry 21).

The conventional nucleophilic substitution reactions were performed with bromo- and chlorobenzenes containing electron-withdrawing nitro groups without a copper catalyst and these reactions took much more time than the coppercatalyzed reactions (entries 17 and 22). Many dihalobenzenes were also converted to corresponding dihydroxybenzenes with moderate to excellent yields (entries 18-20). It was found that 1-bromo-2-iodobenzene provided a very good yield of the corresponding dihydroxy product but when 1,2-diiodobenzene was the substrate the yield reduced drastically (entries 18 and 20), which may be because of higher steric bulk with the iodo group compared to the bromo group. When two iodo groups are apart in 1,3-diiodobenzene, an excellent yield of corresponding dihydroxy product is obtained (entry 19). The other sterically hindered ortho-substituted aryl halides also yielded the corresponding phenols in moderate to good yields (entries 4 and 5). Even nucleophilic and base sensitive groups like hydroxy, ketone and acid sensitive cyano groups containing aryl halides survived well during the course of the reaction. The phenol formation reactions of simple iodobenzene and p-chlorobenzophenone were carried out in large scale (10 mmol) and they provided similar yields compared to small scale reactions (entries 1 and 21). Catalyst removal and reuse

nowadays is an important issue in research.<sup>11</sup> Importantly, in all our reactions, the catalyst removal is a much easier task as both the copper salt and ligand come out from organic phase to water along with all other inorganic components during water work-up. In general, a fairly pure product is obtained just by water work-up of the reaction mixture. In summary, we have developed an efficient and environmentally friendly catalyst system (D-glucose/Cu(OAc)<sub>2</sub>) for the conversion of aryl halides to corresponding phenols with an easy way of catalyst removal. This new catalytic system provides high selectivity towards phenol formation in the presence of many competitive nucleophiles. This is the first report of direct usage of readily available D-glucose as a ligand in transition metalcatalyzed organic reactions. The D-glucose is one of the cheapest ligands among reports available in literature and contains multiple chiral centers. This could open up a new scope for enantiopure synthesis of various important optically active phenols, as well as kinetic resolution of optically active aryl halides in one of the cheapest and environmentally friendly ways. The application of this water soluble D-glucose as a ligand for other organic reactions, detailed mechanistic study and kinetic resolution of racemic aryl halides for synthesis of enantiopure phenols are under progress.

This work was supported by the DST (Project No.: SR/S1/ OC-06/2008) New Delhi, India. K. G. T. thanks CSIR India for the research fellowship.

#### Notes and references

- (a) P. P. Deshpande and S. J. Danlshefsky, *Nature*, 1997, **387**, 164;
   (b) K. Tatsuta and S. Hosokawa, *Sci. Technol. Adv. Mater.*, 2006,
   **7**, 397; (c) A. David, *Isr. J. Chem.*, 2010, **50**, 204; (d) Y. Huang,
   S. Hu, S. Zuo, Z. Xu and C. Han, *J. Mater. Chem.*, 2009, **19**, 7759.
- M. Arisawa, S. Utsumi, M. Nakajima, N. G. Ramesh, H. Tohma and Y. Kita, *Chem. Commun.*, 1999, 469;
   (b) M. Dieguez, C. Claver and O. Pamies, *Eur. J. Org. Chem.*, 2007, 4621; (c) A. Monopoli, V. Calo, F. Ciminale, P. Cotugno, C. Angelici, N. Cioffi and A. Nacci, *J. Org. Chem.*, 2010, **75**, 3908.
- 3 A. B. Naidu, E. A. Jaseer and G. Sekar, J. Org. Chem., 2009, 74, 3675.
- 4 (a) P. Muthupandi, S. K. Alamsetti and G. Sekar, *Chem. Commun.*, 2009, 3288; (b) S. K. Alamsetti and G. Sekar, *Chem. Comm.*, 2010, 7235.
- 5 (a) T. George, R. Mabon, G. Sweeny, J. B. Sweeney and A. J. Tavassoli, J. Chem. Soc., Perkin Trans. 1, 2000, 2529, references therein; (b) R. Bal, M. Tada, T. Sasaki and Y. Iwasawa, Angew. Chem., Int. Ed., 2006, 45, 448.
- 6 (a) K. W. Anderson, T. Ikawa, R. E. Tundel and S. L. Buchwald, J. Am. Chem. Soc., 2006, 128, 10694; (b) T. Schulz, C. Torborg, B. Schäffner, J. Huang, A. Zapf, R. Kadyrov, A. Börner and M. Beller, Angew. Chem., Int. Ed., 2009, 48, 918.
- 7 (a) C. M. Kormos and N. E. Leadbeater, *Tetrahedron*, 2006, 62, 4728; (b) A. Tilli, N. Xia, F. Monnier and M. Taillefer, *Angew. Chem., Int. Ed.*, 2009, 48, 8725; (c) D. Zhao, N. Wu, S. Zhang, P. Xi, X. Su, J. Lan and J. You, *Angew. Chem., Int. Ed.*, 2009, 48, 8729; (d) D. Yang and H. Fu, *Chem.–Eur. J.*, 2010, 16, 2366; (e) L. Jing, J. Wei, L. Zhou, Z. Huang, Z. Li and X. Zhou, *Chem. Commun.*, 2010, 46, 4767.
- 8 (a) The optimization table for various copper salts, solvent mixtures, catalyst loading, bases and temperature is available in electronic supplementary information (Table 1†); (b) The results are summarized in Table 2† of the electronic supplementary information.
- 9 V. Declerck and J. Martinez, F. Lamaty Synlett, 2006, 3029.
- 10 (a) J. Xie, X. Zhu, M. Huang, F. Meng, W. Chen and Y. Wan, Eur. J. Org. Chem., 2010, 3219.
- 11 (a) S. Munirasu, A. Deshpande and D. Baskaran, *Macromol. Rapid Commun.*, 2008, **29**, 1538; (b) continuous removal of the catalyst from polyphenylene ethers, L. M. Phynes, *US Patent* 4654418, 1987.