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An efficient intermolecular BINAM–copper(I) catalyzed Ullmann-type coupling of aryl iodides/bromides with aliphatic alcohols

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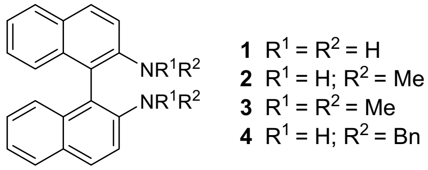
Abstract

A wide range of alkyl aryl ethers are synthesized from the corresponding aryl iodides and aliphatic alcohols through Ullmann-type intermolecular coupling reactions in the presence of a catalytic amount of easily available BINAM–CuI complex. Less reactive aryl bromides have also been shown to react with aliphatic alcohols under identical reaction conditions to give good yields of the alkyl aryl ethers without increasing the reaction temperature and time.

Keywords: Copper catalyst; Coupling reaction; Alkyl aryl ether; Diamine ligands; Ullmann coupling

Alkyl aryl ethers constitute a very important class of organic compounds and solvents, playing a significant role in the production of fragrances, cosmetics, pharmaceuticals and materials.[1] Palladium-catalyzed alkyl aryl ether formation from the corresponding aryl halide and aliphatic alcohols is a recent progress in the area.[2] However, the high costs of palladium salts, high oxophillicity associated with phosphine ligands and tedious multistep processes involved in the synthesis of these ligands have rendered Pd unpopular, particularly for large scale reactions.[3]



The copper-mediated Ullmann-type coupling reaction is an alternative for the palladium-catalyzed reactions for alkyl aryl ether synthesis. However, harsh reaction conditions, requirements of alkoxide bases or sodium hydride, stoichiometric quantities of copper salts and poor reaction conditions limited the scope of this reaction. In fact, only in the last few years have considerable efforts been taken to improve the efficiency of this reaction with the use of copper salts with several ligands such as 1,10-phenanthroline[4] and KF–Al$_2$O$_3$ as base,[5] octanuclear copper clusters,[6] *N*,*N*-dimethylglycine[7] and 3,4,7,8-tetramethyl-1,10-phenanthroline.[8] It is thought that these ligands increase the efficiency of the Ullmann reaction by increasing the solubility of the copper salts by preventing their aggregation.

However, this advance in the field of Ullmann coupling is not sufficient as most of the reactions still require long reaction times (more than 24 h), high reaction temperatures (more than 110 °C) and in some cases, high catalytic loading. In particular, the coupling of aryl bromides with aliphatic alcohol does not provide the alkyl aryl ether at all or only provides poor yields,[4,7] or the catalytic loading or temperature has to be increased to improve the yields.[8] Therefore, a mild, economic and efficient catalytic system is still desirable for this process.

As a part of our ongoing research towards copper-catalyzed oxidation chemistry,[9] very recently we reported 1,1′-binaphthyl-2,2′-diamine (BINAM)–Cu(OTf)$_2$ as an efficient catalyst for the synthesis of diaryl ethers via

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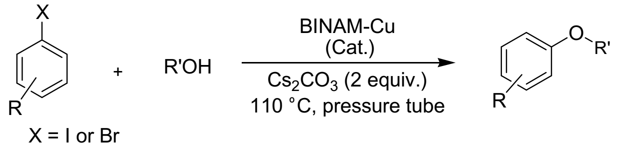
Ullmann coupling.[10] Thus, it was a natural extension for us to investigate the BINAM–copper catalyzed Ullmann-type of coupling of aliphatic alcohols with aryl halides (Scheme 1).

In the preliminary studies, we used 10 mol % of 1,1′-binaphthyl-2,2′-diamine **1** (BINAM) ligand with 5 mol % of CuI for the coupling of *p*-methoxyiodobenzene with ethanol (1.5 mL, also as solvent) at 110 °C and the reaction provided a 37% yield of the corresponding alkyl aryl ether in 30 h (Table 1, entry 1). Increasing the catalytic loading decreased the reaction time, and at the same time the isolated yield was increased gradually. The use of 20 mol % of ligand **1**–CuI complex gave a maximum 96% isolated yield (entry 4) for the coupling reaction. When ligand **1** was replaced with other binaphthyl diamine ligands **2**–**4**, the yields decreased to 66–75%.

The reaction was screened with several copper salts, solvents and bases to optimize the efficiency of the coupling reactions and the results are summarized in Table 2. Although several copper salts catalyzed the reaction, CuI turned out to be the copper salt choice in view of isolated yield (Table 2, entry 1). When the reaction was carried out in other solvents such as dioxane, DMF, DMSO, etc., the reaction did not take place or it gave very poor yields of the alkyl aryl ether. Cs_2CO_3 as base gave the best yields of product in comparison with bases such as Na_2CO_3 and K_2CO_3.

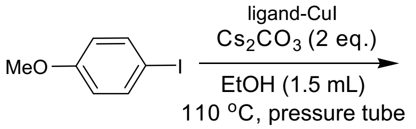
By using the above mentioned optimized conditions, we initiated our investigation into the scope of the BINAM–CuI catalyzed Ullmann-type coupling of aryl halides with aliphatic alcohols and the results are summarized in Table 3. Various aryl iodides reacted with aliphatic primary alcohols, cyclic secondary alcohols and allylic alcohols to give the corresponding alkyl aryl ethers. In the aryl iodide component, the presence of both electron-releasing groups such as methoxy or electron-withdrawing groups such as nitro was tolerated to give the corresponding alkyl aryl ether in moderate to very high yields. In general, the yield increased as the number of carbon in the alcohol decreased except for ethanol, which gave a higher yield than methanol in one case (entry 1 vs 2). In the case of iodobenzene, the presence of an electron-releasing group at the *para* position such as methoxy resulted in the highest yield of alkyl aryl ether (entry 1), whereas the presence of an electron-withdrawing group such as nitro at the *para* position reduced the yield of the corresponding ether to 78% (entry 5).

The presence of an electron-releasing methoxy group in iodobenzene at the *meta* position decreased the yield of the coupling reaction (entries 1 vs 8), whereas the nitro group at the *meta* position increased the yield of the alkyl aryl ether by 10% (entry 6 vs 10). Even in the presence of an *ortho* substituted iodobenzene (which is capable of providing scope for steric bias), the reaction proceeded smoothly to give 73% and 55% isolated yields (entries 11 vs 14).



Scheme 1.

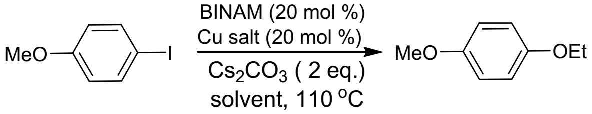
Table 1
The effect of the ratio of ligand and CuI



Entry	Ligand	CuI (mol %)	Time (h)	Yield[a] (%)
1	**1** (10 mol %)	5	30	37
2	**1** (10 mol %)	10	18	64
3	**1** (10 mol %)	20	15	66
4	**1** (20 mol %)	20	12	96
5	**2** (20 mol %)	20	13	66
6	**3** (20 mol %)	20	14	75
7	**4** (20 mol %)	20	11	70

[a] Isolated yield; all the reactions were carried in a pressure tube.

Table 2
The effect of various Cu salts, solvents and bases

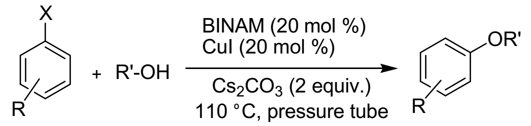


Entry	Cu salt	Solvent	Time (h)	Yield[a] (%)
1	CuI	EtOH	12	96
2	CuBr	EtOH	10	66
3	CuCl	EtOH	24	61
4	$CuCl_2$	EtOH	26	50
5	$Cu(OAc)_2$	EtOH	24	20
6	$CuSO_4$	EtOH	24	25
7	$Cu(OTf)_2$	EtOH	24	0
8	CuI	Dioxane	24	0[b]
9	CuI	DMF	24	22[b]
10	CuI	DMSO	24	40[b]
11	CuI	CH_3CN	36	0[b]
12	CuI	Toluene	24	0[b]
13	CuI	EtOH	26	0[c]
14	CuI	EtOH	26	25[d]

[a] Isolated yield; all the reactions were carried out in a pressure tube.
[b] 1.2 equiv of EtOH was used.
[c] Na_2CO_3 was used as base instead of Cs_2CO_3.
[d] K_2CO_3 was used as base instead of Cs_2CO_3.

We were pleased to note that under our optimized reaction conditions, aryl bromides also reacted with aliphatic alcohols to provide the corresponding alkyl aryl ethers. Both electron-releasing and -withdrawing groups on bromobenzene such as methoxy and nitro reacted with aliphatic alcohols to give the corresponding alkyl aryl ethers in good isolated yields (entries 21–23). It is very important to mention that in general, aryl bromides are less reactive than aryl iodides and require much more drastic reaction

Table 3
The coupling of aryl halides with aliphatic alcohols in the presence of BINAM–CuI catalyst



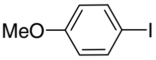
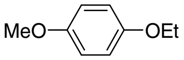
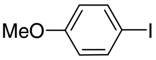
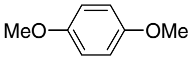
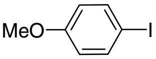
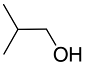
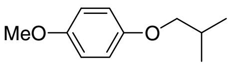
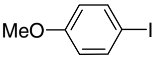
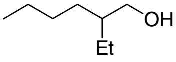
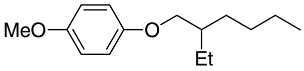
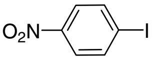
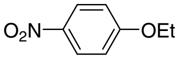
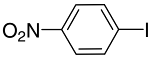
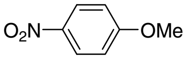
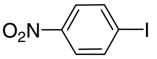
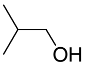
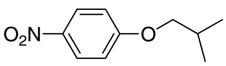
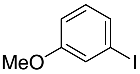
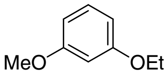
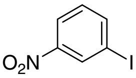
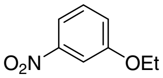
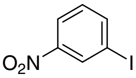
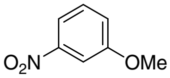
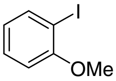
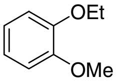
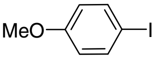
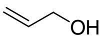
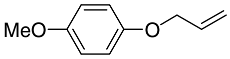
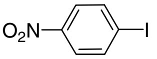
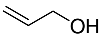
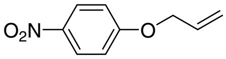
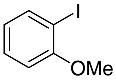
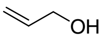
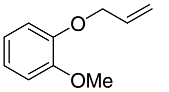
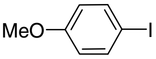
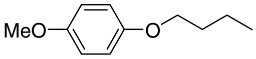
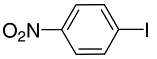
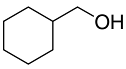
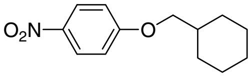
Entry	Aryl halide	Alcohol	Time (h)	Product[a]	Yield[b] (%)
1		EtOH	12		96
2		MeOH	15		80
3			19		74
4			24		72
5		EtOH	10		78
6		MeOH	12		81
7			20		70
8		EtOH	12		79
9		EtOH	11		81
10		MeOH	11		91
11		EtOH	24		73
12			12		79
13			18		64
14			22		55
15		^{n}BuOH	14		78
16			20		60

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Table 3 (*continued*)

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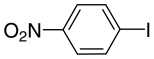
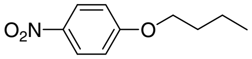
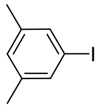
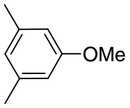
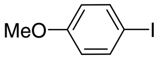
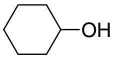
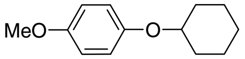
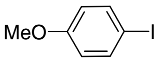
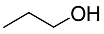
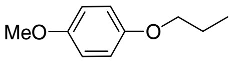
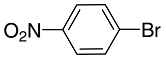
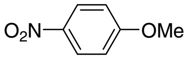
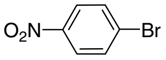
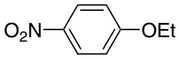
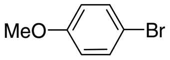
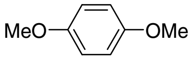
17		^{n}BuOH	24		64
18		MeOH	30		75
19			28		57
20			14		82
21		MeOH	12		88
22		EtOH	11		70
23		MeOH	24		63

[a] All the alkyl aryl ethers gave satisfactory spectral data.

[b] Isolated Yield.[11]

conditions for coupling. However, in the presence of the BINAM–CuI catalyst even aryl bromides reacted with aliphatic alcohols to give good yields of the expected alkyl aryl ethers without increasing the reaction temperature, time or catalytic loading.

In summary, we have developed an efficient, experimentally simple and economically attractive copper-catalyzed O-arylation of aliphatic alcohols with aryl iodides and bromides. Efforts to expand the utility of our new catalytic system to other classes of nucleophiles will be reported in due course.

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References and notes

1. (a) Yamazaki, N.; Washio, I.; Shibasaki, Y.; Mitsuru Ueda, M. *Org. Lett.* **2006**, *8*, 2321–2324; (b) Asano, M.; Inoue, M.; Katoh, T. *Synlett* **2005**, 2599–2602; (c) Jiang, H.; Leger, J.-M.; Huc, I. *J. Am. Chem. Soc.* **2003**, *125*, 3448–3449; (d) Bolm, C.; Hildebrand, J. P.; Muñiz, K.; Hermanns, N. *Angew. Chem., Int. Ed.* **2001**, *40*, 3284–3308; (e) Gu, W. X.; Jing, X. B.; Pan, X. F.; Chan, A. S. C.; Yang, T. K. *Tetrahedron Lett.* **2000**, *41*, 6079–6082; (f) Matsumoto, Y.; Uchida, W.; Nakahara, H.; Yanagisawa, I.; Shibanuma, T.; Nohira, H. *Chem. Pharm. Bull.* **2000**, *48*, 428; (g) Cao, B.; Park, H.; Joullie, M. M. *J. Am. Chem. Soc.* **2002**, *124*, 520–521; (h) Temal-Laïb, T.; Chastanet, J.; Zhu, J. *J. Am. Chem. Soc.* **2002**, *124*, 583–590; (i) Kawata, S.; Hirama, M. *Tetrahedron Lett.* **1998**, *39*, 8707–8710.
2. For some recent reports on palladium-catalyzed aryl ether synthesis, see (a) Vorogushin, A. V.; Huang, X.; Buchwald, S. L. *J. Am. Chem. Soc.* **2005**, *127*, 8146–8149; (b) Kataoka, N.; Shelby, Q.; Stambuli, J.; Hartwig, J. *J. Org. Chem.* **2002**, *67*, 5553–5566; (c) Kuwabe, S.; Torraca, K. E.; Buchwald, S. L. *J. Am. Chem. Soc.* **2001**, *123*, 12202–12206; (d) Prim, D.; Campagne, J.-M.; Joseph, D.; Andrioletti, B. *Tetrahedron* **2002**, *58*, 2041–2075; (e) Hartwig, J. F. *Angew. Chem., Int. Ed.* **1998**, *37*, 2046–2067; (f) Palucki, M.; Wolfe, J. P.; Buchwald, S. L. *J. Am. Chem. Soc.* **1997**, *119*, 3395–3396; (g) Torraca, K. E.; Huang, X.; Parrish, C.; Buchwald, S. *J. Am. Chem. Soc.* **2001**, *123*, 10770–10771.
3. Shelby, Q.; Kataoka, N.; Mann, G.; Hartwig, J. *J. Am. Chem. Soc.* **2000**, *122*, 10718–10719.
4. Wolter, M.; Nordmann, G.; Job, G. E.; Buchwald, S. L. *Org. Lett.* **2002**, *4*, 973–976.
5. Hosseinzadeh, R.; Tajbakhsh, M.; Mohajerani, M.; Alikarami, M. *Synlett* **2005**, 1101–1104.
6. (a) Manback, G. F.; Lipman, A. J.; Stockland, R. A., Jr.; Freidl, A. L.; Hasler, A. F.; Stone, J. J.; Guzei, I. A. *J. Org. Chem.* **2005**, *70*, 244–250; (b) Xiao, X. Y.; Li, R.; Hurst, D.; Zhuang, H.; Shi, S.; Czarnik, A. W.; Robichaud, A. J.; Wacker, D. A.; Robertson, D. W. *J. Comb. Chem.* **2002**, *4*, 536–539.
7. Zhang, H.; Ma, D.; Cao, W. *Synlett* **2007**, 243–246.
8. Altman, R. A.; Shafir, A. S.; Choi, A.; Lichtor, P. A.; Buchwald, S. L. *J. Org. Chem.* **2008**, *73*, 284–286.
9. (a) Mannam, S.; Kumar, S. A.; Sekar, G. *Adv. Synth. Catal.* **2007**, *349*, 2253–2258; (b) Mannam, S.; Sekar, G. *Tetrahedron Lett.* **2008**, *49*, 1083–1086; (c) Mannam, S.; Sekar, G. *Tetrahedron Lett.* **2008**, *49*, 2457–2460.
10. Naidu, A. B.; Ragunath, O. R.; Prasad, D. J. C.; Sekar, G. *Tetrahedron Lett.* **2008**, *49*, 1057–1061.

11. *Typical representative experimental procedure*: An oven-dried screw-cap pressure tube fitted with a septum was charged with Cs_2CO_3 (325 mg, 1 mmol), CuI (19 mg, 0.1 mmol), BINAM (28.4 mg, 0.1 mmol), *p*-methoxyiodobenzene (117 mg, 0.5 mmol) and a magnetic stir bar. The pressure tube was evacuated and back-filled with anhydrous nitrogen. Ethanol (1.5 mL) was added and the reaction mixture was stirred at 110 °C for 12 h. (The progress of the reaction was followed by TLC), After the complete disappearance of *p*-methoxyiodobenzene (by TLC), the reaction mixture was allowed to cool to room temperature and the crude product was purified by column chromatography on a silica gel using ethyl acetate/hexane solvent mixture to give 4-ethoxyanisole[12] (73 mg, 96%) as a white solid; R_f 0.46 (in hexanes); FTIR (neat) 1229, 2929, 2980 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.38 (t, $J = 6.8$ Hz, 3H), δ 3.75 (s, 3H), 3.97 (q, $J = 6.8$ Hz, 2H), δ 6.82 (s, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.92, 55.7, 64.06, 114.6, 115.5, 153.1, 153.7.
12. Siegman, J. R.; Houser, J. J. *J. Org. Chem.* **1982**, *47*, 2773–2779.