ORGANIC LETTERS

2003
Vol. 5, No. 21
3799−3802

N,*N*-Dimethyl Glycine-Promoted Ullmann Coupling Reaction of Phenols and Aryl Halides

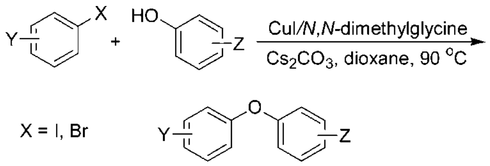
Dawei Ma* and Qian Cai

State Key Laboratory of Bioorganic and Natural Products Chemistry,
Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences,
354 Fenglin Lu, Shanghai 200032, China

madw@pub.sioc.ac.cn

Received June 16, 2003 *(Revised Manuscript Received August 26, 2003)*

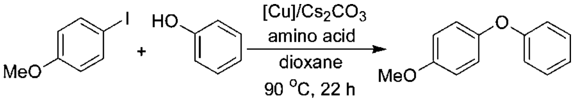
ABSTRACT



Ullmann-type diaryl ether synthesis can be performed at 90 °C using either aryl iodides or aryl bromides as the substrates under the assistance of *N*,*N*-dimethylglycine.

Numerous synthetically challenging and biologically important chemicals contain diaryl ethers as structural elements. Traditionally, copper-catalyzed Ullmann coupling between an aryl iodide or bromide and a phenol has been extensively used for the formation of diaryl ether. However, harsh reaction conditions such as high temperatures (125−220 °C), the usual requirement of stoichiometric quantities of the copper catalyst, and the low to moderate yields have greatly limited the utility of this reaction.[1] Thus, development of new methods for assembling diaryl ethers under relatively mild reaction conditions is receiving increasing interest.[2−4] By using 1-naphthoic acid,[3d] 2,2,6,6-tetramethylheptane-3,5-dione,[3a] or phosphazene P_4-*t*-Bu base[3c] as the additive, Ullmann diaryl ether synthesis at 110−120 °C was achieved. A similar result was observed when soluble copper catalyst was employed.[3b] However, in these cases, less conveniently available catalysts[3b,d] or additives,[3a,c] as well as higher reaction temperatures, are required.

Table 1. Coupling Reaction of 4-Iodoanisole with Phenol under the Catalysis of Copper Salts and Amino Acids[a]



entry	copper salt	amino acid	yield[b] (%)
1	CuI	$MeNHCH_2CO_2H$	37[c]
2	CuI	L-proline	35
3	CuI	$Me_2NCH_2CO_2H{\cdot}HCl$	85
4	CuBr	$Me_2NCH_2CO_2H{\cdot}HCl$	83
5	CuCl	$Me_2NCH_2CO_2H{\cdot}HCl$	71
6	$Cu(OAc)_2$	$Me_2NCH_2CO_2H{\cdot}HCl$	73
7	$CuSO_4$	$Me_2NCH_2CO_2H{\cdot}HCl$	80
8	$CuCl_2{\cdot}2H_2O$	$Me_2NCH_2CO_2H{\cdot}HCl$	74

[a] Reaction conditions: [Cu] (0.04 mmol), amino acid (0.15 mmol), 4-iodoanisole (2 mmol), phenol (3 mmol), Cs_2CO_3 (4 mmol), dioxane (4 mL), 90 °C. [b] Isolated yield. [c] *N*-(4-methoxyphenyl)-*N*-methylglycine was isolated in 2% yield.

---

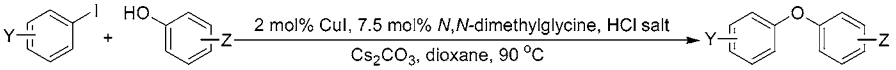
(1) For reviews, see: (a) Lindley, J. *Tetrahedron* **1984**, *40*, 1433−1456. (b) Sawyer, J. S. *Tetrahedron* **2000**, *56*, 5045−5065.

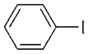
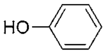
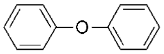
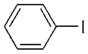
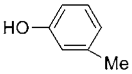
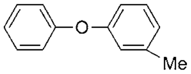
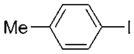
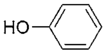
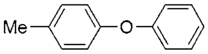
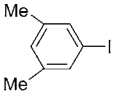
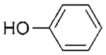
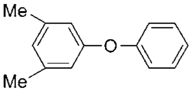
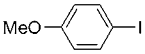
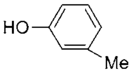
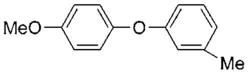
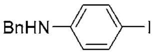
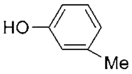
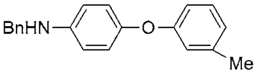
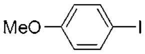
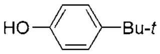
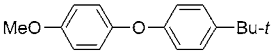
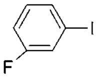
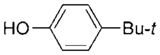
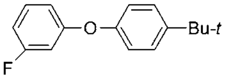
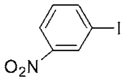
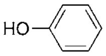
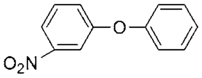
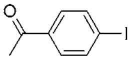
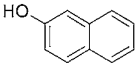
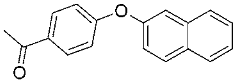
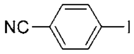
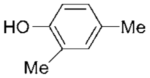
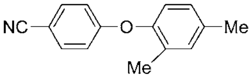
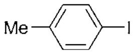
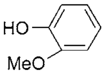
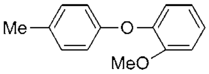
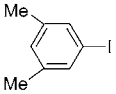
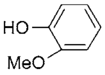
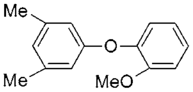
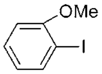
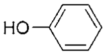
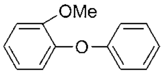
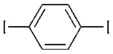
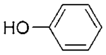
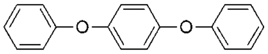
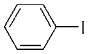
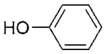
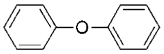
(2) For palladium-catalyzed diaryl ether formation, see: (a) Mann, G.; Hartwig, J. F. *Tetrahedron Lett.* **1997**, *46*, 8005−8008. (b) Aranyos, A.; Old, D. W.; Kiyomori, A.; Wolfe, J. P.; Sadighi, J. P.; Buchwald, S. L. *J. Am. Chem. Soc.* **1999**, *121*, 4369−4378 and references therein.

(3) For recent copper-catalyzed direct coupling reaction of aryl halides and phenols, see: (a) Buck, E.; Song, Z. J.; Tschaen, D.; Dormer, P. G.; Volante, R. P.; Reider, P. J. *Org. Lett.* **2002**, *4*, 1623−1626. (b) Gujadhur, R. K.; Bates, C. G.; Venkataraman, D. *Org. Lett.* **2001**, *3*, 4315−4317. (c) Palomo, C.; Oiarbide, M.; Lopez, R.; Gomez-Bengoa, E. *Chem. Commun.* **1998**, 2091−2092. (d) Marcoux, J.-F.; Doye, S.; Buchwald, S. L. *J. Am. Chem. Soc.* **1997**, *119*, 10539−10540.

10.1021/ol0350947 CCC: $25.00

Table 2. Coupling Reaction of Aryl Iodides with Phenols under the Catalysis of CuI and *N*,*N*-Dimethylglycine[a]



Entry	Aryl iodide		Time (h)	Product	Yield (%)[b]
1			16		86
2			18		93
3			19		91
4			16		95
5			18		89
6			24		73
7			22		82
8			22		83
9			16		96
10			22		78
11			22		94
12			22		71 (74^{c})
13			24		82^{c}
14			24		56^{c} (80^{d})
15			5		77^{c,e}
16			4		96^{c}

[a] Reaction conditions: CuI (0.04 mmol), *N*,*N*-dimethylglycine HCl salt (0.15 mmol), aryl iodide (2 mmol), phenol (3 mmol), Cs_2CO_3 (4 mmol), dioxane (4 mL), 90 °C. [b] Isolated yield. [c] Performed with 0.2 mmol of CuI and 0.6 mmol of *N*,*N*-dimethylglycine HCl salt. [d] Performed with 2 mol of CuI and 2 mmol of *N*,*N*-dimethylglycine HCl salt. [e] Performed with 4 mmol of phenol.

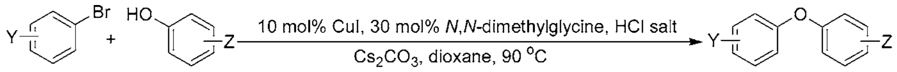
On the basis of our observation that the structures of α- and *β*-amino acids could induce acceleration of Ullmann-type aryl amination of aryl halides and amino acids,[6] we recently reported that CuI/L-proline (or *N*-methylglycine) is an efficient catalytic system to make Ullmann-type aryl

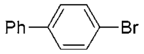
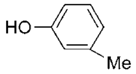
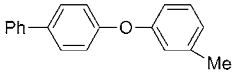
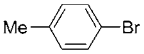
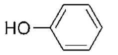
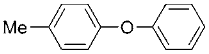
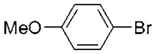
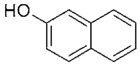
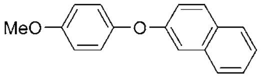
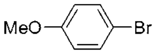
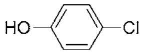
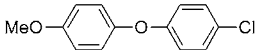
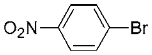
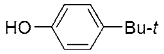
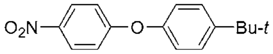
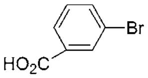
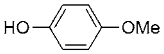
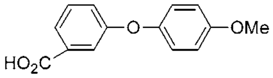
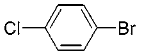
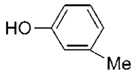
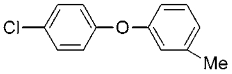
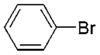
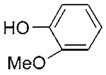
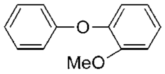
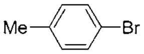
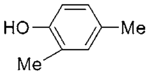
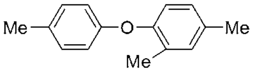
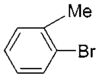
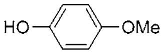
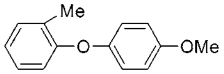
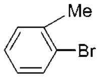
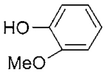
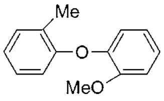
---

(4) For recent copper-catalyzed coupling reaction of arylboronic acids or arylboronates with phenols, see: (a) Evans, D. A.; Katz, J. L.; West, T. R. *Tetrahedron Lett.* **1998**, *39*, 2937−2940. (b) Chen, D. M. T.; Monaco, K. L.; Wang, R.-P.; Winters, M. *Tetrahedron Lett.* **1998**, *39*, 2933−2936. (c) Jung, M. E.; Lazarova, T. I. *J. Org. Chem.* **1999**, *64*, 2976−2977. (d) Dicicco, C. P.; Song, Y.; Evans, D. A. *Org. Lett.* **2001**, *3*, 1029−1032. (e) Petrassi, H. M.; Sharpless, K. B.; Kelly, J. W. *Org. Lett.* **2001**, *3*, 139−142. (f) Chen, D. M. T.; Monaco, K. L.; Li, R.; Bonne, D.; Clark, C. G.; Lam, P. Y. S. *Tetrahedron Lett.* **2003**, *44*, 3863−3865.

(5) For other recent examples, see: (a) Li, F.; Wang, Q.; Ding, Z.; Tao, F. *Org. Lett.* **2003**, *5*, 2169−2171. (b) Wipf, P.; Lynch, S. M. *Org. Lett.* **2003**, *5*, 1155−1158. (c) Krenitsky, P. J.; Boger, D. L. *Tetrahedron Lett.* **2002**, *43*, 407−410. (d) Kalinin, A. V.; Bower, J. F.; Riebel, P.; Snieckus, V. *J. Org. Chem.* **1999**, *64*, 2986−2987. (e) Sawyer, J. S.; Schmittling, E. A.; Palkowitz, J. A.; Smith, W. J. *J. Org. Chem.* **1998**, *63*, 6338−6343. (f) Zhu, J. *Synlett* **1997**, 133−144 and references therein. (g) Nicolaou, K. C.; Boddy, C. N. C.; Natarajan, S.; Yue, T.-Y.; Brase, S.; Ramanjulu, J. M. *J. Am. Chem. Soc.* **1997**, *119*, 3421−3422. (h) Zhu, J. P.; Beugelmans, R.; Bourdet, S.; Chastanet, J.; Roussi, G. *J. Org. Chem.* **1995**, *60*, 6389−6396.

Table 3. Coupling Reaction of Aryl Bromides with Phenols under the Catalysis of CuI and *N*,*N*-Dimethylglycine[a]



Entry	Aryl bromide		Time (h)	Product	Yield (%)[b]
1			24		90
2			24		94
3			24		83
4			24		75
5			20		97
6			24		89
7			24		90
8			24		83
9			24		79
10			24		59 (75[c])
11			24		33 (64[c])

[a] Reaction conditions: CuI (0.2 mmol), *N*,*N*-dimethylglycine HCl salt (0.6 mmol), aryl bromide (2 mmol), phenol (3 mmol), Cs_2CO_3 (4 mmol), dioxane (4 mL), 90 °C. [b] Isolated yield. [c] Reaction was carried out at 105 °C.

amination work at the lowest temperature reported to date.[7] As an extension of this work, we have found that under the action of *N*,*N*-dimethylglycine, CuI-catalyzed coupling reaction of aryl halides and phenols could be carried out at 90 °C to give the corresponding diaryl ethers in good to excellent yields. Herein we wish to detail this result.

As summarized in Table 1, we chose the coupling of 4-iodoanisole with phenol mediated with cesium carbonate as a model for exploring the suitable catalytic system. Because of their excellent activity in CuI-catalyzed aryl amination, *N*-methylglycine and L-proline were initially checked as the additives for the present reaction. It was found that the reaction worked at 90 °C in dioxane under the action of 2 mol % CuI and 7.5 mol % *N*-methylglycine to give 4-methoxyphenyl phenyl ether (entry 1). However, the yield was low due to poor conversion and *N*-(4-methoxyphenyl)-*N*-methylglycine was isolated as a side product, which indicated that the activity of this catalytic system was eliminated by the coupling of the additive with the substrate. After L-proline was observed to give the similar result (entry 2), we moved our attention to employing *N*,*N*-dimethylglycine as the additive because this compound is unable to process the *N*-aryl amination. As we expected, when 7.5 mol % commercially available *N*,*N*-dimethylglycine hydrochloride salt was used, the reaction provided 4-methoxyphenyl phenyl ether in 85% yield (entry 3). Under the assistance of *N*,*N*-dimethylglycine hydrochloride salt, other Cu(I) and Cu(II) salts also worked under the above reaction conditions, giving the coupling product in 71−83% yields (entries 4−8). These results demonstrated that the choice of copper salts appeared not to be very critical for the present reaction.

On the basis of the above results, the coupling reaction catalyzed by CuI (2 mol %)/*N*,*N*-dimethylglycine (7.5 mol %) was tested with several different aryl iodides and phenols, and the results are summarized in Table 2. Both electron-rich (entries 3−7) and electron-deficient (entries 8−11) aryl iodides are suitable substrates for this reaction to provide the corresponding diaryl ethers in good to excellent yields. A variety of functional groups of aryl iodides are known to tolerate this reaction condition, which include alkoxyl, amino, fluoro, nitro, carbonyl, and cyano groups. The steric hin-

---

(6) (a) Ma, D.; Zhang, Y.; Yao, J.; Wu, S.; Tao, F. *J. Am. Chem. Soc.* **1998**, *120*, 12459. (b) Ma, D.; Xia, C. *Org. Lett.* **2001**, *3*, 2583−2586.

(7) Ma, D.; Cai, Q.; Zhang, H. *Org. Lett.* **2003**, *5*, 2453−2455.

drance of phenols is slightly disfavored for this reaction. For example, when 2-methoxyphenol was used as the substrate, the reaction gave considerably lower yield in comparison with that of less hindered phenol (compare entries 3 and 12). In this case, increasing the amount of the catalyst and additive gave improved results (entries 12 and 13). However, the steric hindrance of aryl iodides is highly disfavored for this reaction because the coupling reaction of 2-iodoanisole with phenol required 1 equiv of catalyst for completion (entry 14). Under the action of 10 mol % CuI and 30 mol % *N*,*N*-dimethylglycine, the coupling reaction of 1,4-diiodobenzene with phenol gave the double-coupling product. In addition, higher catalyst and additive loading were observed to accelerate the reaction (compare entries 1 and 16).

As shown in Table 3, the present catalytic system is also extremely effective for coupling reaction of aryl bromides and phenols. In all cases, 10 mol % CuI and 30 mol % *N*,*N*-dimethylglycine hydrochloride salt were used to promote the reaction. High yields were obtained even for those aryl bromides with an electron-donating group (entries 2 and 3) and sterically hindered phenols (entries 8 and 9). Noteworthy is the fact that the reaction of 4-methoxyphenyl bromide with 4-chlorophenol, which should be a difficult case for classical Ullmann coupling method,[1,3a] gave the coupling product in 75% yield (entry 4). The excellent yield observed in the reaction of 4-chlorophenyl bromide and 3-methylphenol implies that good selectivity is desirable between aryl bromides and aryl chlorides (entry 7). Additionally, the relatively lower yield for reaction of 2-methylphenyl bromide with 4-methoxyphenol implies that the steric hindrance of aryl bromides is still disfavored for coupling reaction (entry 10). A similar result was observed in the coupling reaction of an ortho-substituted bromide and an ortho-substituted phenol (entry 11). The poor yields resulted from low conversion in both cases because good yields were obtained by raising the reaction temperature to 105 °C (entries 10 and 11).

In summary, we have developed a cheap and simple way to carry out the Ullmann diaryl ether synthesis at the lowest temperature reported to date, which is applicable to a wide variety of substrates with different functional groups. The application of this method to the synthesis of more complex diaryl ethers, as well as mechanism studies, is in progress.

Acknowledgment. The authors are grateful to the Chinese Academy of Sciences, National Natural Science Foundation of China (Grant 20132030), and the Qiu Shi Science & Technologies Foundation for their financial support.

Supporting Information Available: Experimental procedures. This material is available free of charge via the Internet at http://pubs.acs.org.

OL0350947