ORGANIC LETTERS

2003
Vol. 5, No. 14
2453−2455

Mild Method for Ullmann Coupling Reaction of Amines and Aryl Halides

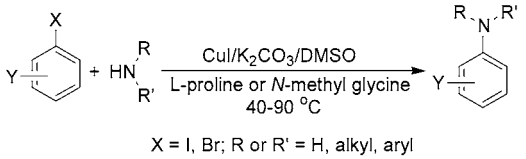
Dawei Ma,*,† Qian Cai,† and Hui Zhang‡

State Key Laboratory of Bioorganic and Natural Products Chemistry, Shanghai Institute of Organic Chemistry, 354 Fenglin Lu, Shanghai 200032, China, and Department of Chemistry, Fudan University, Shanghai 200433, China

madw@pub.sioc.ac.cn

Received April 18, 2003

ABSTRACT



X = I, Br; R or R' = H, alkyl, aryl

Ullmann-type aryl amination of aryl iodides and aryl bromides in DMSO at 40–90 °C gave the corresponding *N*-arylamines or *N*,*N*-diarylamines in good to excellent yields by using either *N*-methylglycine or L-proline as the ligand.

Since it was discovered 100 years ago,[1] Ullmann-type aryl amination has witnessed a number of industrial-scale applications because its products are important in the pharmaceutical and materials world.[2] The synthetic scope of this reaction, however, is greatly limited by its high reaction temperature.[2] This shortcoming stimulated considerable efforts to develop Pd-catalyzed aryl amination methodology.[3] Some exciting achievements have already appeared in this field. For instance, the aryl amination of either aryl iodides or aryl bromides can be carried out at room temperature if certain phosphines are used as the ligands.[4] However, industrial employment of this methodology is limited in many cases due to the air and moisture sensitivity, as well as the higher costs of Pd and the relative ligands.

We have found that the structures of α- and β-amino acids could induce acceleration of Ullmann-type aryl amination, which led to the coupling reaction of aryl halides with α- or β-amino acids at relatively low temperatures.[5] Soon after these reports, Buchwald reported that using ethylene glycol as the ligand afforded the CuI-catalyzed coupling of alkylamines and aryl iodides at 80 °C.[6a] Prior to that, other milder Ullmann-type methodologies for N-arylation of several nitrogen-containing substrates based on employing several specific ligands were disclosed by the same group.[7] Very recently, they also reported that Ullmann-type aryl amination of aryl bromide was carried out at 90 °C using diethylsalicylamide as the ligand.[6a] Stimulated by these results, we realized that the amino acids might be suitable ligands for promoting the typical Ullmann-type aryl amination. Thus, a competitive experiment in which 1 equiv of benzylamine

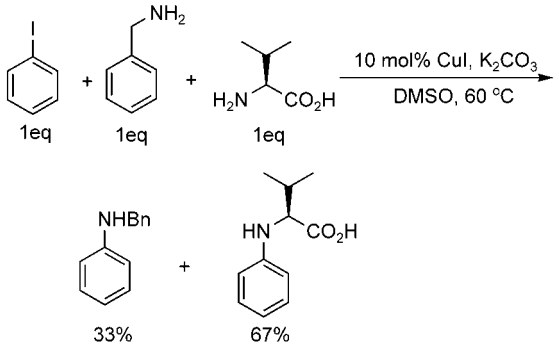
† Shanghai Institute of Organic Chemistry.
‡ Fudan University.

(1) Ullmann, F. *Ber. Dtsch. Chem. Ges.* **1903**, *36*, 2382−2384.
(2) For a review, see: Lindley, J. *Tetrahedron* **1984**, *40*, 1433−1456.
(3) For reviews, see: (a) Hartwig, J. F. *Angew. Chem., Int. Ed.* **1998**, *37*, 2046−2067. (b) Wolfe, J. P.; Wagaw, S.; Marcoux, J.-F.; Buchwald, S. L. *Acc. Chem. Res.* **1998**, *31*, 805−818. (c) Yang, B. H.; Buchwald, S. L. *J. Organomet. Chem.* **1999**, *576*, 125−146.
(4) (a) Hamann, B. C.; Hartwig, J. F. *J. Am. Chem. Soc.* **1998**, *120*, 7369−7370. (b) Old, D. W.; Wolfe, J. P.; Buchwald, S. L. *J. Am. Chem. Soc.* **1998**, *120*, 9722−9723. (c) Wolfe, J. P.; Buchwald, S. L. *J. Org. Chem.* **1997**, *62*, 6066−6068.
(5) (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.
(6) (a) Kwong, F. Y.; Klapars, A.; Buchwald, S. L. *Org. Lett.* **2002**, *4*, 581−584. (b) Kwong, F. Y.; Buchwald, S. L. *Org. Lett.* **2003**, *5*, 793−796.
(7) (a) Kiyomori, A.; Marcoux, J.-F.; Buchwald, S. L. *Tetrahedron Lett.* **1999**, *40*, 2657−2640. (b) Klapars, A.; Antilla, J.; Huang, X.; Buchwald, S. L. *J. Am. Chem. Soc.* **2001**, *123*, 7727−7729. (c) Wolter, M.; Klapars, A.; Buchwald, S. L. *Org. Lett.* **2001**, *3*, 3803−3805.

10.1021/ol0346584 CCC: $25.00
Published on Web 06/07/2003

and 1 equiv of L-valine were reacted with 1 equiv of iodobenzene (Scheme 1) was undertaken and it was found

Scheme 1



that, in this case, not only *N*-phenyl valine (67% yield) but also *N*-benzyl aniline (33% yield) were isolated. This result clearly indicated that the α-amino acid had an accelerating effect on the coupling of iodobenzene and benzylamine.

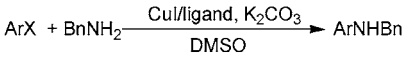
Encouraged by this result, we examined several amino acids as the ligands using the coupling reaction of iodobenzene and benzylamine as a model. It is obvious that some amino acids could couple with iodobenzene during the reaction, thereby reducing the activity of the catalytic system. We decided to solve this problem by choosing some less reactive N-substituted or N,N-disubstituted amino acids as our ligands. To compare the efficacy of each ligand, the reaction was carried out at 40 °C and quenched after 12 h.

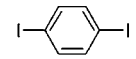
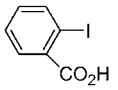
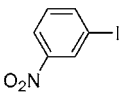
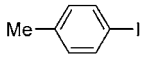
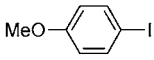
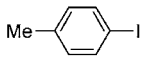
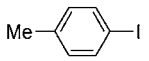
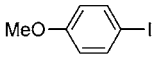
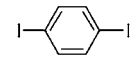
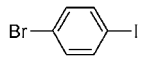
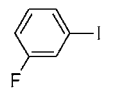
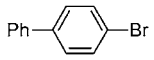
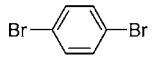
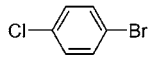
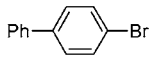
Table 1. Coupling Reaction of Iodobenzene with Benzylamine under the Catalysis of CuI and Amino Acids[a]

Entry	Amino acid	Yield of *N*-benzyl aniline (%)[b]
1	MeHN, CO_2H	72[f]
2	Me_2N, CO_2H	68
3	BnHN, CO_2H	62
4	Bn_2N, CO_2H	52
5	MeHN, CO_2H	63
6	Me_2N, CO_2H	55
7	BnHN, CO_2H	57
8	N H, CO_2H	46
9[c]	MeHN, CO_2H	56[f]
10[d]	MeHN, CO_2H	72[f]
11[e]	MeHN, CO_2H	87[g]

[a] Reaction conditions: CuI (0.5 mmol), amino acid (0.5 mmol), iodobenzene (5 mmol), benzylamine (5 mmol), DMSO (3 mL), 40 °C, 12 h. [b] Isolated yield. [c] CuI (0.25 mmol), amino acid (0.25 mmol). [d] CuI (0.25 mmol), amino acid (0.5 mmol). [e] CuI (0.5 mmol), amino acid (1 mmol). [f] Less than 3% *N*-phenyl-*N*-methylglycine was observed. [g] Less than 5% *N*-phenyl-*N*-methylglycine was observed.

Table 2. Coupling Reaction of Aryl Halides with Benzylamine under the Catalysis of CuI and Amino Acids[a]

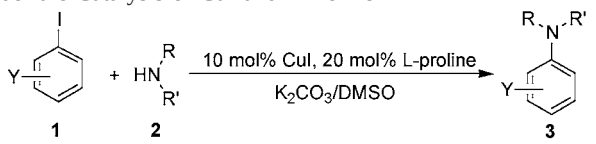


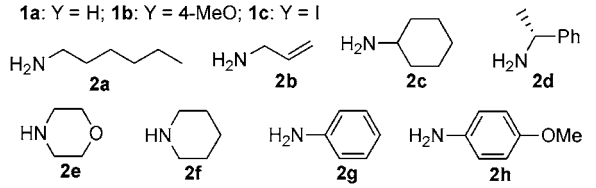
entry	ArX	ligand[b]	temp. (°C)	time (h)	yield (%)[c]
1		A	40	13	82
2		A	40	12	91
3		A	40	23	80
4		A	40	13	64[d]
5		A	40	13	64
6		A	60	20	66
7		B	60	16	85
8		B	60	13	84
9		B	60	14	89
10		B	60	12	81
11		B	60	14	80
12		A	40	11	53
13		B	70	20	82
14		B	70	20	76
15		B	70	28	68

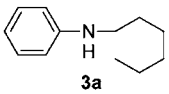
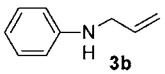
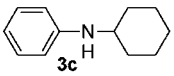
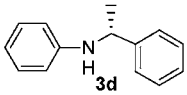
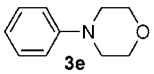
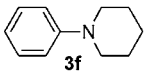
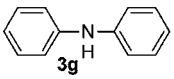
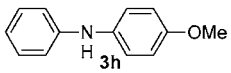
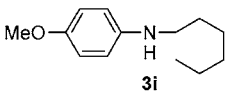
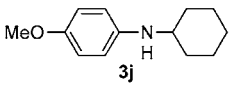
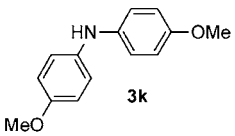
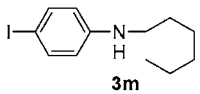
[a] Reaction conditions: CuI (0.5 mmol), amino acid (1 mmol), aryl iodide (5 mmol), benzylamine (7.5 mmol), DMSO (3 mL). [b] A: *N*-methylglycine. B: L-proline. [c] Isolated yield. [d] *N*-(4-Methylphenyl)-*N*-methylglycine was isolated in about 5% yield.

The conversion for each reaction was examined through its isolated yield of the corresponding arylamine. As shown in Table 1, it was found that all amino acids we chose could prompt the coupling reaction at this condition. The α-amino acids gave better conversion in comparison with the *β*-amino acids (compare entries 1 and 5, as well as entries 2 and 6), while the N-substituted amino acids were superior to the N,N-disubstituted amino acids (compare entries 1 and 2, as well as entries 5 and 6). Using *N*-methylglycine as the ligand, we found that the best ratio between CuI and the ligand was 1:2 (compare entries 1 and 11, as well as entries 9 and 10). In the case of using 10 mmol % CuI and 20 mol % *N*-methylglycine, the reaction was near completion and gave *N*-benzyl aniline in excellent yield (entry 11). Although

Table 3. Coupling Reaction of Aryl Halides with Amines under the Catalysis of CuI and L-Proline[a]





entry	2	product	temp. (°C)	time (h)	yield (%)[b]
1	**2a**	 **3a**	60	14	87
2	**2b**	 **3b**	60	14	80
3	**2c**	 **3c**	60	14	70
4	**2d**	 **3d**	60	18	75
5	**2e**	 **3e**	80	26	73
6	**2f**	 **3f**	80	26	61
7	**2g**	 **3g**	90	27	66
8	**2h**	 **3h**	90	36	82
9	**2a**	 **3i**	60	24	79
10	**2c**	 **3j**	80	26	80
11	**2h**	 **3k**	90	27	81
12	**2a**	 **3m**	60	9	86

[a] Reaction conditions: CuI (0.5 mmol), L-proline(1 mmol), aryl iodide (5 mmol), amine (7.5 mmol), DMSO (3 mL). Amine: **1a** for entries 1−8, **1b** for entries 9−11, and **1c** for entry 12. [b] Isolated yield.

L-proline appeared to be less effective than *N*-methylglycine (compare entries 1 and 8), we selected it as the ligand in many cases described later because it was found to be less reactive toward coupling with aryl halides than *N*-methylglycine.

For aryl iodides bearing an electron-withdrawing group, *N*-methylglycine was also a good ligand that led to complete the reaction even at 40 °C (Table 2, entries 1−3). However, for aryl iodides carrying an electron-donating group, the conversion was not satisfactory even at 60 °C using *N*-methylglycine (entries 4−6). We reasoned that this problem might result from the coupling of *N*-methylglycine with aryl iodides that consumed the ligand (entry 4). Indeed, when proline (less reactive) was used as the ligand, good yields were observed for both electron-rich and electron-deficient aryl iodides at 60 °C (entries 7−11). Similarly, aryl bromide gave only moderate yields under the action of CuI and *N*-methylglycine at 40 °C (entry 12), while good yields were obtained by switching the ligand to proline and carrying out the reaction at higher temperature (entries 13−15).

Using L-proline as the ligand, we tested the coupling reaction using a number of aryl iodides and amines. The results are summarized in Table 3. It was found that all primary amines worked well, affording the corresponding coupling product in good yields (entries 1−4, 9, 10, and 12), while secondary amines gave slightly lower yields (entries 5 and 6). Furthermore, the present catalytic system also worked well for the coupling of arylamines with aryl iodides even at 90 °C, leading to diarylamines (entries 7, 8, and 11).

In conclusion, we have discovered a new catalytic system to make Ullmann-type aryl amination work at the lowest temperature reported to date. The key was using a suitable amino acid as the ligand. Although in some cases the complete conversion was restricted by coupling of the ligands with aryl halides, the lower reaction temperature used here and the convenient availability of the ligands are still attractive for arylamine preparation in many cases.[8]

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.

OL0346584

(8) For other recent efforts on the development of more efficient catalytic systems for Ullmann-type aryl amination, see: (a) Gujadhur, R. K.; Bates, C. G.; Venkataraman, D. *Org. Lett*. **2001**, *3*, 4315−4317. (b) Gujadhur, R. K.; Venkataraman, D.; Kintigh, J. T. *Tetrahedron Lett*. **2001**, *42*, 4791−4793. (c) Goodbrand, H. B.; Hu, N.-X. *J. Org. Chem*. **1999**, *64*, 670−674. (d) Kang, S.-K.; Kim, D.-H.; Park, J.-N. *Synlett* **2002**, 427−430. (e) Kelkar, A. A.; Patil, N. M.; Chaudhari, R. V. *Tetrahedron Lett*. **2002**, *43*, 7143−7146.