JOC*Note*

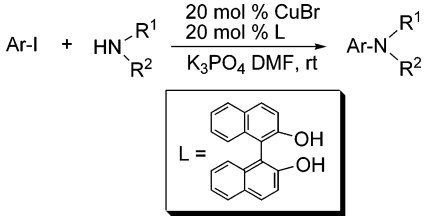
CuBr/*rac*-BINOL-Catalyzed *N*-Arylations of Aliphatic Amines at Room Temperature

Deshou Jiang,[†] Hua Fu,*[,†] Yuyang Jiang,[†,‡] and Yufen Zhao[†]

Key Laboratory of Bioorganic Phosphorus Chemistry and Chemical Biology, Ministry of Education, Department of Chemistry, Tsinghua University, Beijing 100084, P. R. China, and Key Laboratory of Chemical Biology, Guangdong Province, Graduate School of Shenzhen, Tsinghua University, Shenzhen 518057, P. R. China

fuhua@mail.tsinghua.edu.cn

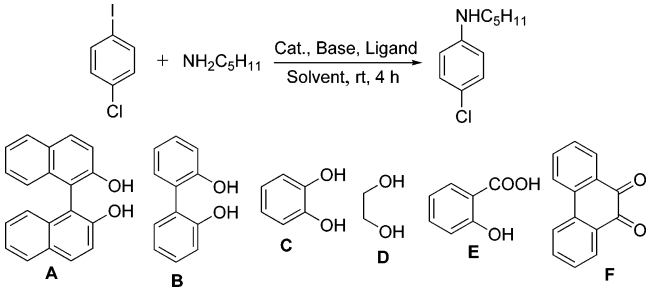
Received October 5, 2006



We have developed an efficient and readily available catalyst system CuBr/racemic BINOL (1,1′-binaphthyl-2,2′-diol) that catalyzes *N*-arylation of aliphatic amines at room temperature, and this inexpensive catalyst system is of high selectivity and tolerance toward various functional groups in the substrates.

Although copper-catalyzed Ullmann reactions were developed more than one hundred years,[1] their applications are limited because of the harsh reaction conditions such as high temperatures, the usual requirement of stoichiometric amounts of copper reagents, long reaction times, and low yields.[2] In the past few years, the copper-catalyzed Ullmann reactions have shown a renaissance because of the correct choice of copper sources, bases, ligands, and other additives,[3] and it is popular to develop highly efficient supporting ligands for copper-catalyzed arylations. Great progress in copper-catalyzed *N*-arylation of amines/amides has been made,[3] but a simple and general procedure for the copper-catalyzed coupling of aliphatic amines with aryl halides under mild conditions has remained elusive.[4] Since 2003, several ligands have been introduced to promote copper-catalyzed *N*-arylation of aliphatic amines, most notably *N*,*N*-diethylsalicylamide,[4] amino acids,[5] amino alcohols,[6] phosphoramidite,[7] and oxime-phosphine oxide.[8] Wan and co-workers very recently reported their research using copper powder/*rac*-BINOL or (copper+CuI)/*rac*-BINOL as the catalyst system; unfortunately, the *N*-arylations were performed at 90−125 °C.[9] To the best of our knowledge, *N*-arylations at room temperature still remain limited. Very recently, Buchwald and co-workers have developed highly selective room temperature copper-catalyzed C−N coupling reactions using CuI/cyclic β-diketone as the catalyst system and Cs_2CO_3 as the base.[10] It is highly desirable to develop more convenient and efficient methods for *N*-arylation at room temperature which are of high tolerance toward functional groups in substrates during the coupling reactions. In this paper, we report an inexpensive and readily available catalyst system using CuBr as the copper

TABLE 1. Copper-Catalyzed C−N Bond Formation of 1-Chloro-4-iodobenzene and Pentylamine: Optimization of the Catalytic Conditions[a]



entry	catalyst[b]	ligand	base	solvent	yield (%)[c]
1	CuI (5%)	A	K_3PO_4	DMF	65
2	CuI (5%)	B	K_3PO_4	DMF	21
3	CuI (5%)	C	K_3PO_4	DMF	42
4	CuI (5%)	D	K_3PO_4	DMF	45
5	CuI (5%)	E	K_3PO_4	DMF	0
6	CuI (5%)	F	K_3PO_4	DMF	47
7	$CuSO_4$ (5%)	A	K_3PO_4	DMF	0
8	CuBr (5%)	A	K_3PO_4	DMF	67
9	CuCl (5%)	A	K_3PO_4	DMF	60
10	CuBr (5%)	A	K_3PO_4	DMSO	65
11	CuBr (5%)	A	K_3PO_4	1,4-dioxane	56
12	CuBr (5%)	A	K_3PO_4	toluene	12
13	CuBr (5%)	A	K_2CO_3	DMF	56
14	CuBr (5%)	A	Cs_2CO_3	DMF	77
15	CuBr (10%)	A	K_3PO_4	DMF	78
16	CuBr (20%)	A	K_3PO_4	DMF	85
17	CuBr (10%)	A	Cs_2CO_3	DMF	82
18	CuBr (20%)	A	Cs_2CO_3	DMF	91

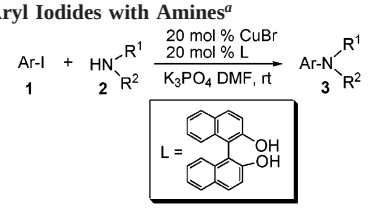
[a] Reaction conditions: 1-chloro-4-iodobenzene (1.0 mmol) and pentylamine (1.5 mmol), ligand (0.2 mmol), base (2 mmol), solvent (1 mL) at room temperature (~25 °C) under N_2. [b] Amount of catalyst relative to 1-chloro-4-iodobenzene. [c] Isolated yield.

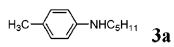
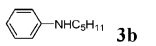
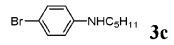
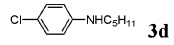
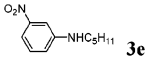
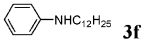
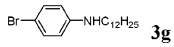
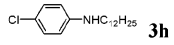
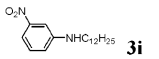
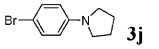
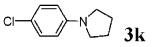
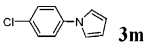
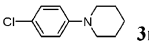
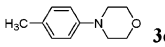
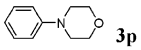
* To whom correspondence should be addressed. Fax: 86-10-62781695.
[†] Key Laboratory of Bioorganic Phosphorus Chemistry and Chemical Biology.
[‡] Key Laboratory of Chemical Biology.

(1) (a) Ullmann, F. *Ber. Dtsch. Chem. Ges.* **1903**, *36*, 2389. (b) Ullmann, F. *Ber. Dtsch. Chem. Ges.* **1904**, *37*, 853.
(2) For a review, see: Lindley, J. *Tetrahedron* **1984**, *40*, 1433.
(3) For recent reviews, see: (a) Ley, S. V.; Thomas, A. W. *Angew. Chem., Int. Ed.* **2003**, *42*, 5400. (b) Kunz, K.; Scholz, U.; Ganzer, D. *Synlett* **2003**, 2428. (c) Beletskaya, I. P.; Cheprakov, A. V. *Coord. Chem. Rev.* **2004**, *248*, 2337. (d) Corbet, J.-P.; Mignani, G. *Chem. Rev.* **2006**, *106*, 2651.
(4) Kwong, F. Y.; Buchwald, S. L. *Org. Lett.* **2003**, *5*, 793.
(5) (a) Ma, D.; Cai, Q.; Zhang, H. *Org. Lett.* **2003**, *5*, 2453. (b) Cai, Q.; Zhu, W.; Zhang, H.; Zhang, Y.; Ma, D. *Synthesis* **2005**, 496. (c) Zhang, H.; Cai, Q.; Ma, D. *J. Org. Chem.* **2005**, *70*, 5164.
(6) (a) Lu, Z.; Twieg, R. J.; Huang, S. D. *Tetrahedron Lett.* **2003**, *44*, 6289. (b) Lu, Z.; Twieg, R. J. *Tetrahedron* **2005**, *61*, 903.
(7) Zhang, Z.; Mao, J.; Zhu, D.; Wu, F.; Chen, H.; Wan, B. *Tetrahedron* **2006**, *62*, 4435.
(8) Xu, L.; Zhu, D.; Wu, F.; Wang, R.; Wan, B. *Tetrahedron* **2005**, *61*, 6553.
(9) Zhu, D.; Wang, R.; Mao, J.; Xu, L.; Wu, F.; Wan, B. *J. Mol. Catal. A: Chem.* **2006**, *256*, 256.
(10) Shafir, A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2006**, *128*, 8742.

10.1021/jo062060e CCC: $37.00
Published on Web 12/07/2006

TABLE 2. Copper-Catalyzed Cross-Coupling of Aryl Iodides with Amines[a]



Entry	Aryl iodide	Amine	Product	Time (h)	Yield (%)[b]
1		$NH_2C_5H_{11}$	 **3a**	8	56 (94[c])
2		$NH_2C_5H_{11}$	 **3b**	4	65
3		$NH_2C_5H_{11}$	 **3c**	5	80
4		$NH_2C_5H_{11}$	 **3d**	4	85
5		$NH_2C_5H_{11}$	 **3e**	11	77
6		$NH_2C_{12}H_{25}$	 **3f**	8	83
7		$NH_2C_{12}H_{25}$	 **3g**	10	72
8		$NH_2C_{12}H_{25}$	 **3h**	6	83
9		$NH_2C_{12}H_{25}$	 **3i**	10	72
10			 **3j**	10	67
11			 **3k**	5	71
12			 **3l**	8	52
13			 **3m**	10	51
14			 **3n**	6	67
15			 **3o**	8	54 (91[c])
16			 **3p**	8	73
17			**3q**	8	75
18			**3r**	11	66
19			**3s**	5	71
20			**3t**	4	72
21			**3u**	5	62
22		$NH_2C_5H_{10}OH$	**3v**	3	72
23			**3w**	10	48 (61[c])
24		$NH_2CH_2CHCOOH$	**3x**	10	42 (72[c])
25			**3y**	10	38 (81[c])
26		$NH_2C_5H_{11}$	**3z**	6	55[d]

[a] Reaction conditions: aryl iodide (1.0 mmol), amine (1.5 mmol), ligand (0.2 mmol), K_3PO_4 (2 mmol), solvent (1 mL) at room temperature (~25 °C) under N_2. Amount of catalyst relative to aryl iodide. [b] Isolated yield. [c] At 40 °C. [d] At 50 °C.

catalyst, racemic BINOL (1,1′-binaphthyl-2,2′-diol) as the ligand, and K_3PO_4 as the base to construct C(aryl)−N bonds from aryl iodides at room temperature.

We first chose 1-chloro-4-iodobenzene and pentylamine as the model substrates to optimize the catalytic conditions, including optimization of the copper catalysts, ligands, bases, and solvents in *N*-arylation at room temperature as shown in Table 1. Several ligands including racemic BINOL, 2,2′-biphenol, catechol, ethylene glycol, salicylic acid, and 9,10-phenanthrenequinone were tested in DMF with 5 mol % CuI (relative to 1-chloro-4-iodobenzene) as the catalyst and K_3PO_4 as the base (entries 1−6), and BINOL gave the highest yield (65%, entry 1). Although catechol and 9,10-phenanthrenequinone also displayed certain activity, their efficiency was poor. In addition, no product was observed in the absence of ligand under similar reaction conditions. Other copper salts, $CuSO_4$, CuBr, and CuCl (entries 7−9), were tested in *N*-arylation, using DMF as the solvent and BINOL as the ligand, and the results showed that CuBr was the best catalyst. We also studied the effect of solvents (compare entries 8 and 10−12): DMF and DMSO provided almost the same yields, but the others were bad solvents. Bases also influenced the progress of the reaction, and Cs_2CO_3 gave the highest yield (77% entry 14) with 5 mol % CuBr (relative to 1-chloro-4-iodobenzene) as the catalyst. The yield of the target product was gradually improved with an increase in the amount of CuBr from 5 to 20 mol % (entries 8 and 14−16). K_3PO_4 gave a slightly lower yield than Cs_2CO_3; however, it is cheaper and of practical application in *N*-arylation. The corresponding yield greatly decreased when the reaction was exposed to air, and the presence of a trace amount of water in the reaction system did not affect the reactivity of the substrates, which showed that it was not necessary to perform the *N*-arylation in dry solvent. After the optimization process of solvents, ligands, and catalysts, the following coupling reactions were carried out under our standard conditions: 20 mol % CuBr as the catalyst, 20 mol % racemic BINOL as the ligand relative to aryl iodides, DMF as the solvent, and K_3PO_4 as the base at room temperature.

The scope of the copper-catalyzed *N*-arylation was explored under our standard conditions. As shown in Table 2, the

coupling reactions were performed well for all the substrates examined, and the desired arylamines were obtained in moderate to good yields. The substituted iodobenzenes containing an electron-withdrawing group showed higher reactivity than those containing an electron-donating group. Although the aryl iodides containing an electron-donating group gave slightly lower reaction yields, they could provide high reactivity when the temperature was raised from 25 to 40 °C (see entries 1 and 15). The primary aliphatic amines are slightly better substrates than the cyclic secondary ones, and pyrrole because of its lower basicity showed lower yields than other saturated cyclic secondary amines. Amino acids and amino acid ester showed lower reaction activity relative to the other primary aliphatic amines, and they also displayed high reactivity when temperature was raised from 25 to 40 °C (entries 23−25). Interestingly, *N*-arylation showed high selectivity to a number of reactive functional groups in the presence of our catalyst system. For aryl halides, the coupling of the iodobenzenes containing −Br and −Cl substituents only took place on the C−I bond. We also attempted differently substituted amines, for example, amino alcohol, amino acids and amino acid ester (see entries 22−25), whose coupling reactions exclusively occurred on the amino group, and the other functional groups such as hydroxyl, carboxyl, and ester group remained, which is favorable for construction of the complex molecules. Reaction of tryptophan with iodobenzene produced *N*-monoarylation on the α-amino group rather than on the imino group of the indole ring (see entry 25) at 40 °C. A very electron-rich substrate 4-iodoanisole was also tested by using pentylamine as the partner at room temperature, and only a trace amount of product was observed. However, the *N*-arylation provided a 55% yield product when temperature was raised to 50 °C.

In conclusion, we have developed an efficient and readily available catalyst system CuBr/*rac*-BINOL that could catalyze *N*-arylation of aliphatic amines at room temperature, and the inexpensive catalyst system is of high selectivity and tolerance toward various functional groups in the substrates, so it can widely be used in the synthesis of the compounds containing the C−N bond.

Experimental Section

General Procedure A: Room Temperature Coupling of Aryl Iodides with Amines. A flask was charged with CuBr (28 mg, 0.2 mmol), 1,1′-binaphthyl-2.2′-diol (57 mg, 0.2 mmol), K_3PO_4 (424 mg, 2 mmol), and any remaining solids (amine and/or aryl halide). The flask was evacuated and backfilled with nitrogen (this procedure was repeated three times). Aryl halide (1 mmol, if liquid), amine (1.5 mmol, if liquid), and DMF (1 mL) were added to the flask under nitrogen atmosphere. The flask was sealed and the mixture was allowed to stir under nitrogen atmosphere at the shown temperature for the indicated period of time (see Table 2). After completion of the reaction, the mixture was diluted with ethyl acetate, the solution was filtered, and the inorganic salts were removed. The solvent of the filtrate was removed with the aid of a rotary evaporator, and the residue was purified by column chromatography on silica gel, using petroleum ether/ethyl acetate (60:1 to 4:1) as eluent to provide the desired product.

5-(4-Chlorophenylamino)pentan-1-ol (3v). Yellow oil, yield 71%. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.07−7.12 (m, 2H), 6.47−6.53 (m, 2H), 3.62 (t, J = 6.18 Hz, 2H), 3.06 (t, J = 6.87 Hz, 2H), 2.74 (s, br, 1H), 1.54−1.61 (m, 4H), 1.41−1.49 (m, 2H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 146.8, 129.0, 121.6, 113.7, 62.5, 43.9, 32.3, 29.0, 23.2. HR-EI-MS $[M + H]^+$ m/z calcd for $C_{11}H_{17}ClNO$ 214.0999, found 214.1003.

General Procedure B: Coupling of Aryl Iodides with Amino Acids. The procedure is similar to general procedure A, except 3.0 mmol of K_3PO_4 was used as the base, and the reaction temperature was maintained at 40 °C for 10 h. After the coupling the solution was cooled to 25 °C, and water (5 mL) and Et_2O (5 mL) were added to the solution. The resulting solution was partitioned into two phases, the aqueous phase was separated, and the organic fraction was extracted with additional 10% NaOH (3 × 3 mL). The combined aqueous phase was neutralized to pH 4 with 20% HCl and extracted with Et_2O (3 × 20 mL). The resulting organic fraction was dried over $MgSO_4$. After removal of the solvent, the residue was purified by column chromatography on silica gel to provide the target product.

***N*-Phenyl-L-tryptophan (3y).** Eluent: ethyl acetate/methanol (10:1). Yellow oil, yield 81%. ^{1}H NMR (DMSO-d_6, 300 MHz) δ 7.52 (d, 2H, J = 7.81 Hz), 7.31 (d, 1H, J = 7.82 Hz), 7.16 (s, 1H), 6.92−7.05 (m, 4H), 6.48−6.55 (m, 3H), 4.11 (t, J = 6.87 Hz, 1H), 3.51 (s br, 2H), 3.04−3.23 (m, 2H). ^{13}C NMR (DMSO-d_6, 75 MHz) δ 175.6, 148.2, 136.5, 129.4, 127.7, 124.2, 121.5, 118.9, 118.7, 116.9, 112.9, 111.9, 110.5, 57.4, 28.5. HR-EI-MS $[M + H]^+$ m/z calcd for $C_{17}H_{17}N_2O_2$ 281.1290, found 281.1300.

Acknowledgment. This work was supported by the Excellent Dissertation Foundation of the Chinese Ministry of Education (No. 200222), Program for New Century Excellent Talents in University (NCET) in China, the Excellent Young Teacher Program of MOE, P. R. China, the National Natural Science Foundation of China (Grant Nos. 20472042 and 20672065), and the Key Subject Foundation from Beijing Department of Education (XK100030514).

Supporting Information Available: Synthetic procedures, characterization data, and ^{1}H, ^{13}C NMR spectra of these synthesized compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

JO062060E