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1,2,3,4-Tetrahydro-8-hydroxyquinoline-Promoted Copper-Catalyzed Coupling of Nitrogen Nucleophiles and Aryl Bromides

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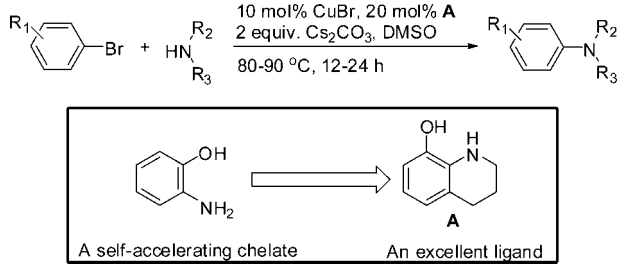
Received July 18, 2008



Based on the dramatic accelerating effect of 2-aminophenol, three ligands derived from 2-aminophenol were developed. Copper-catalyzed coupling reaction of nitrogen-containing nucleophiles with aryl bromides was efficiently carried out under mild conditions using 1,2,3,4-tetrahydro-8-hydroxyquinoline as a novel, simple, and versatile ligand.

N-Arylazoles and *N*-arylamines are important compounds widely employed in the biochemical, pharmaceutical, and material fields.[1] One traditional method for their synthesis is the Ullmann-type coupling reaction of nitrogen nucleophiles with relatively available aryl halides. However, the well-known reaction generally suffers from several shortcomings such as high reaction temperature, the use of stoichiometric amounts of copper reagents, moderate yield, and poor substrate generality, which restrict its industrial applications.[2] Interestingly, copper-catalyzed Ullmann amination reactions can be considerably accelerated by some organic ligands. The original reports based on diamine- and imine-type ligands for arylation of imidazoles by Buchwald and Taillefer generated great interest in exploiting a more effective procedure for copper-catalyzed coupling reactions.[3,4]

Until now, various ligands have been disclosed such as diamine derivatives,[5] amino acids,[6] *N*-hydroxyimides,[7] phosphine oxides,[8] imidazole derivatives,[9] diketones or diphenols,[10] and fluorapatite.[11] Indeed, significant progress was achieved through the use of the ligands mentioned above in the past years. However, most catalyst systems enjoyed only narrow heterocyclic substrates. Moreover, the high cost and availability (some ligands were often prepared by multistep synthesis) limited their applications to laboratory-scale reactions. Thus, it is necessary to design a simple, efficient, and versatile ligand for these coupling reactions.

In 1998, Ma reported an accelerating effect in the amination of aryl halides induced by the structure of α-amino acid and recently demonstrated that amino acids as ligands could promote Ullmann aryl amination.[12] Similarly, Buchwald reported that β-amino ethanol itself could also assist in the arylation reaction with aryl iodides.[13] Soon after that, Twieg described that some amino alcohols could serve as accelerating ligands for copper-catalyzed amination.[14] Recently, we found that 2-aminophenol was a new type of self-accelerating chelate substrate, coupling with iodobenzene to provide triarylamine under mild conditions with 85% yield. However, the *N*-arylation of aniline with iodobenzene hardly occurred under the same conditions (Scheme 1). Obviously, the 2-aminophenol accelerated the *N*-arylation of iodobenzene and showed more reactive than aniline. This is a unique example for the copper catalyzed single-step synthesis of tribenzenamine derivative from amine without ligand addition.[15] The applicability and selectivity between di- and triarylamine for this reaction are being studied in our laboratory. On the other hand, inspired by the accerating effect of 2-aminophenol, we anticipated that it might be a potential ligand for the Ullmann copper-catalyzed reactions.

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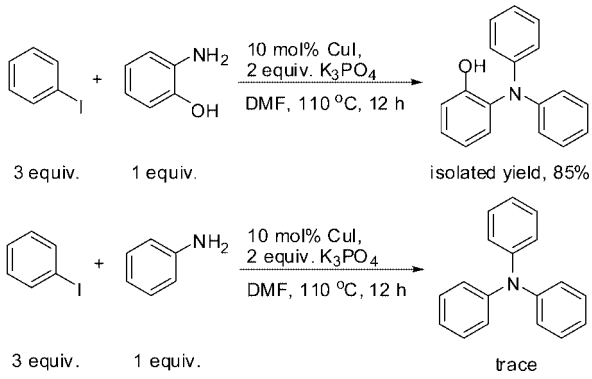
10.1021/jo8015488 CCC: $40.75 © 2008 American Chemical Society
Published on Web 10/09/2008

SCHEME 1. Inducing Acceleration Effect of 2-Aminophenol



Thus, three 2-aminophenol derivatives **A**, **B**, **C**, and the similar ligand **D** of 8-hydroxyquinoline were tested to seek the optimal ligand. As shown in Figure 1, all 2-aminophenol derivatives promoted the coupling reaction under the indicated conditions and ligand **A** gave the highest GC yield (66%) relative to lignads **B** (60%) and **C** (52%). However, the ligand **D**, once reported as a good ligand was not efficient under the reaction conditions.[16] The synergistic electron-donating groups and flexible tetrahedral steric structure of the ligand **A**, **B**, and **C** facilitated the oxidative addition and reductive elimination reaction, while the electron-withdrawing "N" atom and planar structure of 8-hydroxyquinoline **D** make the formation of radical [Cu^{III}] intermediate unfavorable and more sterically encumbered. Finally, the blank test indicated that trace product was observed in the absence of any ligand. Thus the study proved that the ligand **A** was the most effective ligand for the copper-catalyzed C−N bond-forming reaction, and further experiments were focused on it.

Since the reaction conditions are crucial to the reaction outcome, a brief survey of influencing factors using the reaction of bromobenzene and cyclohexylamine as a model was carried out. As shown in Table 1, polar-donor solvents DMSO, DMF, and CH_3CN were more efficient solvents compared with proton solvent ethanol and weakly polar solvent dioxane. Both Cu(I) and Cu(II) were effective; however, CuBr was the best choice. After screening a variety of bases such as Cs_2CO_3, K_3PO_4, and K_2CO_3, we found that Cs_2CO_3 gave the best result. It was pointed out that the ratio of copper and ligand played an important role in the reaction. The ratio of 1:2 was much better than 1:1 (entries 9 and 11) even at lower catalyst loading. Perhaps the molecular structure of four-coordinate complex makes the copper ion more stable in reaction system relative to two coordinate complex. Finally, doubling the amount of catalyst and ligand, the reaction showed 82% GC yield (Table 1, entry 12). The reaction condition in entry 12 is the optimal one.

Encouraged by the above results, we further investigated other amines. As shown in Table 2, this catalyst system was capable of the coupling of aryl bromides and primary amines as well as the coupling of cyclic secondary amines. The coupling reaction of benzylamine with bromobenzene and benzylamine with inactive 1-bromo-4-methylbenzene underwent reaction smoothly at 80 °C within 12 h in 92% and 82% yield, respectively (Table 2, entries 2 and 3). Increasing the hindrance of amines (e.g., cyclohexylamine and morpholine) led to a decrease in amination yields even at elevated temperatures (Table 2, entries 1 and 4). Monitoring these reactions by GC−MS showed that approximately 10% byproduct (benzene) was observed. In addition, our reaction system was also suitable for the coupling of nitrogen heterocyclic compounds. Imidazole (Table 2, entry 5), benzimidazole (Table 2, entry 6), pyrrole (Table 2, entry 7), and indole (Table 2, entry 8) were transformed smoothly under the indicated conditions. Even hindered 2-methylimidazole (Table 2, entry 9) was coupled in 73% yield, and no significant byproduct was observed.

To explore the scope of the coupling reaction of aryl bromides with imidazole, a variety of the substituted aryl bromides were tested under the optimal reaction conditions. In general, the catalyst system tolerates various aryl halides containing −CN, −Ac, −F, and $-NH_2$ functional groups. Aryl bromides with electron-withdrawing and electronically neutral groups showed greater reactivity compared with those with electron-donating groups. For example, the reaction of 4-bromobenzonitrile and imidazole proceeded in 94% isolated yield at 80 °C in 12 h (Table 2, entry 10), while the inactive

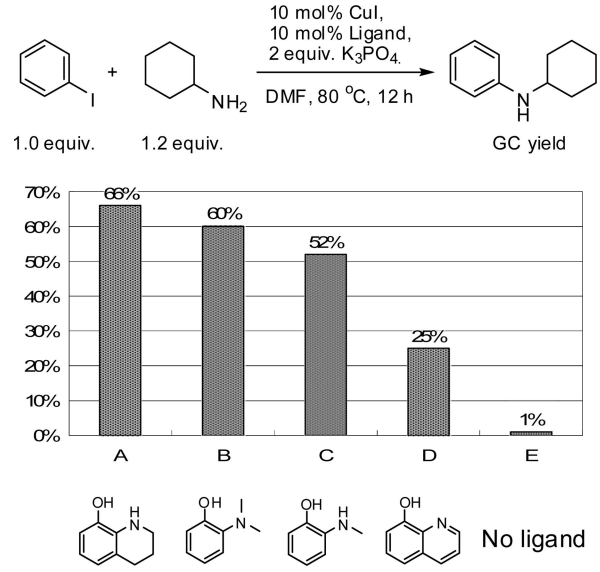
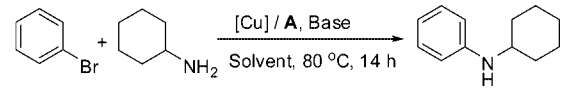


FIGURE 1. Screening of ligands for the *N*-arylation of cyclohexylamine.

TABLE 1. Optimization of the Reaction Conditions[a]



entry	Cu/L	solvent	[Cu]	base	yield (%)
1	10:10	CH_3CN	CuI	K_3PO_4	28
2	10:10	DMF	CuI	K_3PO_4	30
3	10:10	DMSO	CuI	K_3PO_4	33
4	10:10	ethanol	CuI	K_3PO_4	17
5	10:10	dioxane	CuI	K_3PO_4	7
6	10:10	DMSO	CuBr	K_3PO_4	48
7	10:10	DMSO	CuCl	K_3PO_4	35
8	10:10	DMSO	$CuCl_2$	K_3PO_4	40
9	10:10	DMSO	CuBr	Cs_2CO_3	53
10	10:10	DMSO	CuBr	K_2CO_3	41
11	5:10	DMSO	CuBr	Cs_2CO_3	67
12	10:20	DMSO	CuBr	Cs_2CO_3	82

[a] Reaction conditions: [Cu] (0.1 mmol), base (2 mmol), solvent (1 mL), bromobenzene (1 mmol), cyclohexylamine (1.2 mmol), N_2. Yield (GC) was calibrated with decane as a standard.

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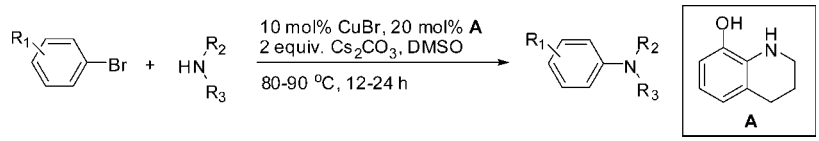
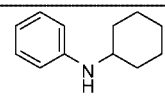
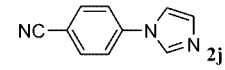
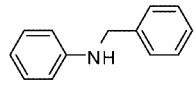
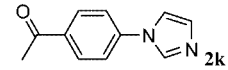
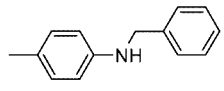
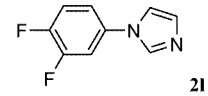
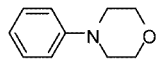
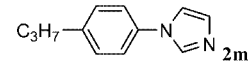
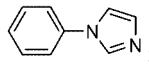
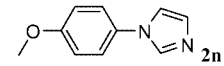
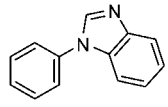
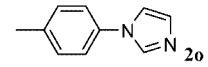
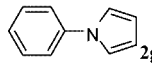
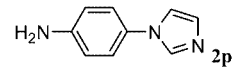
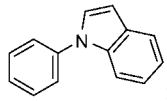
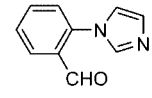
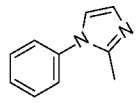
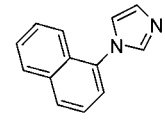
TABLE 2. N-Arylation of Amines and 1*H*-Azoles with Aryl Bromides[a]



entry	(°C/h)	products	yield (%)	entry	(°C/h)	products	yield (%)
1	90 °C 24 h	 **2a**	82	10	80 °C 12 h	 **2j**	94
2	80 °C 12 h	 **2b**	92	11	80 °C 12 h	 **2k**	95
3	80 °C 12 h	 **2c**	82	12	80 °C 12 h	 **2l**	82
4	90 °C 24 h	 **2d**	75	13	80 °C 12 h	 **2m**	84
5	80 °C 12 h	 **2e**	92	14	80 °C 12 h	 **2n**	85
6	90 °C 24 h	 **2f**	87	15	90 °C 24 h	 **2o**	80
7	90 °C 24 h	 **2g**	77	16	90 °C 24 h	 **2p**	78
8	90 °C 24 h	 **2h**	84	17	90 °C 24 h	 **2q**	77
9	90 °C 24 h	 **2i**	73	18	90 °C 24 h	 **2r**	68

[a] Reaction conditions: CuBr (0.1 mmol), A (0.2 mmol), Cs_2CO_3 (2 mmol), ArBr (1.2 mmol), amines or 1*H*-azoles (1.0 mmol) in DMSO (1 mL) under N_2 at 80 °C for 12 h or 90 °C for 24 h. Isolated yield.

aryl bromides such as 1-bromo-4-methylbenzene (Table 2, entry 15) required higher temperatures and longer time to afford the corresponding *N*-arylimidazole. Because of the steric hindrance, the *ortho*-substituted aryl bromides required the use of longer reaction time or of higher reaction temperature (Table 2, entries 17 and 18). Fortunately, our catalyst system performed well at the elevated temperatures. The steric hindrance effect is more significant than the electronic effect. Even 2-bromobenzaldehyde, containing an electron-withdrawing group resulted in lower yield than bromobenzene (Table 2, entries 5 and 17). Since the oxidative addition process increases the steric hindrance around the [Cu^I] complex, substance with bulk group hardly form the radical [Cu^{III}] intermediate.

In conclusion, a dramatic accelerating effect existing in the *N*-arylation of 2-aminophenol with iodobenzene was found. Following that, an effective and versatile 2-aminophenol derivative ligand for the copper-catalyzed *N*-arylation reaction of nitrogen nucleophiles was developed under relatively mild conditions. It is noted that the ligand of 1,2,3,4-tetrahydro-8-hydroxyquinoline is very simple, economical, and even commercially available. We believe that it is of great importance to academic research and industrial application.

Experimental Section

General Procedure for the Copper-Catalyzed Coupling of Nitrogen Heterocycles or Amines with Aryl Bromides. A flame-dried Schlenk test tube with a magnetic stirring bar was charged with CuBr (14 mg, 0.1 mmol), ligand (30 mg, 0.2 mmol), Cs_2CO_3 (652 mg, 2.0 mmol), amine or nitrogen-containing heterocycle (1.0 mmol), aryl halide (1.2 mmol), and DMSO (1 mL) under N_2. After the reaction mixture was heated at 80 °C for 12 h or 90 °C for 24 h, the reaction mixture was cooled to ambient temperature, diluted with 2−3 mL of ethyl acetate, filtered through a plug of silica gel, and washed with 10 mL of ethyl acetate. The filtrate was concentrated, and the resulting residue was purified by column chromatography on silica gel (ethyl acetate/petroleum ether) to provide the desired product.

***N*-Cyclohexylaniline (2a).** According the general procedure, cyclohexylamine (108 μL, 1.0 mmol) was coupled with bromobenzene (126 μL, 1.2 mmol) under the indicated conditions. The crude product was purified over a silica gel column using ethyl acetate/petroleum ether (1/30) to give a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.14 (t, J = 8.0 Hz, 2H), 6.64 (t, J = 7.6 Hz, 1H), 6.57 (d, J = 8.0 Hz, 2H), 3.49 (bs, 1H), 3.20−3.28 (m, 1H), 2.06 (m, 2H), 1.78 (m, 2H), 1.7 (m, 1H), 1.17−1.40 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.5, 129.4, 117.0, 113.3, 51.8, 33.6, 26.1, 25.2; GC−MS (EI, *m*/*z*) 175 [M^+].

1-Phenyl-1*H*-imidazole (2e). According the general procedure, imidazole (68 mg, 1.0 mmol) was coupled with bromobenzene (126 μL, 1.2 mmol) under the indicated conditions. The crude product was purified over a silica gel column using ethyl acetate/petroleum ether (1:2−2:1, v/v) to give a yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 (s, 1H), 7.46−7.50 (m, 2H), 7.34−7.40 (m, 3H), 7.29 (s, 1H), 7.21 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.1, 135.5, 130.2, 129.6, 127.4, 121.2, 118.1; GC−MS (EI, *m*/*z*) 144 [M^+].

Acknowledgment. This work was supported by the National Natural Science Fund of China (Project No. 20876021) and the Program for Changjiang Scholars and Innovative Research Team in University (IRT0711). We appreciate the financial support. We appreciate the financial support.

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

JO8015488