Highly Efficient Copper-Catalyzed O-Arylation Using Readily Available (*S*)-*N*-Methylpyrrolidine-2-Carboxamide as the Ligand

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Received 14 September 2007

Abstract: A highly efficient and readily available catalyst system for O-arylation of various phenols using CuI and (*S*)-*N*-methylpyrrolidine-2-carboxamide (Pro-NHMe) was developed. The reaction is widely applicable to the synthesis of diaryl ethers

Key words: Ullmann reaction, O-arylation, cross-coupling, copper-catalyzed, *N*,*N*-ligand

The development of mild synthetic approaches to diaryl ethers has recently attracted much attention.[1] Diaryl ethers, such as the isodityrosine family and its derivatives, the antibiotic vancomycin, and the antitumor drug bouvardin have been reported to show strong biological activity.[2] The cross-coupling of substituted phenols with aryl halides is the most straightforward route to diaryl ethers. Although some significant achievements in the palladium-catalyzed arylation of phenols have been made,[3] the drawbacks of the catalyst systems, such as air sensitivity, high cost, toxicity, noncommercial sophisticated phosphines, limit their applications.[4] Use of copper catalysts as alternatives to palladium catalysts in the Ullmann reaction, will greatly improve the chemical industry in both economic and environmental aspects.[4] Although copper-catalyzed Ullmann reactions have been developed for more than one hundred years,[5] their applications are limited because of the harsh reaction conditions such as high temperatures, the usual requirement of stoichiometric amounts of the copper catalysts, long reaction times and lower yields.[4] In recent few years, interests in copper-catalyzed Ullmann reactions have re-emerged and a large number of highly efficient and inexpensive ligands has been developed for the copper-catalyzed arylations. For examples, 1-naphthoic acid,[6] 2,2,6,6-tetramethylheptane-3,5-dione,[7] phosphazene P_4-*t*-Bu base,[8] *N*,*N*-dimethylglycine,[9] 8-hydroxyquinoline,[10] neocuproine,[11] salicylaldoxime,[12] pyrrolidine-2-phosphonic acid phenyl monoester[13] and dimethylaminomethylphosphonic acid derivatives[14] have all been used for the O-arylation of substituted phenols. Herein, we report (*S*)-*N*-methylpyrrolidine-2-carboxamide (Pro-NHMe), a derivative of natural proline, as the ligand of copper catalyst to construct diary ethers, and some satisfactory results were obtained.

The ligand (*S*)-*N*-methylpyrrolidine-2-carboxamide hydrochloride (Pro-NHMe·HCl) was readily synthesized according to the reported procedure.[15] We optimized the catalysis conditions for O-arylation including the choice of catalysts, bases, solvents and other additives. The experiments showed that the catalyst system containing 10 mol% of CuI and 20 mol% of Pro-NHMe hydrochloride relative to aryl halide in the presence of K_3PO_4 in DMF with 3% H_2O could give the optimal results for O-arylation, and that the addition of a small amount of water in DMF could improve the dissolving power of Pro-NHMe hydrochloride and K_3PO_4 which led to higher reaction yields (Table 1, entries 1 vs. 15). A reported paper showed that L-proline was a poor ligand for O-arylation.[9a] To our surprise, our modified proline (Pro-NHMe) gave excellent results under our standard conditions (Table 1).[16] Coupling reactions of aryl bromides/iodides, even hindered bromides (entries 5–7) with various phenols provided products in excellent yields. Aryl halides containing electron-withdrawing groups gave slightly higher yields than those containing electron-donating groups, while phenols containing electron-rich groups showed higher reactivity than those containing electron-deficient groups. Reaction of aryl dibromide with phenol yielded monoether and diether (entry 9). Aryl halides containing pyridine ring also gave O-arylation products (entries 10 and 11). In addition, the reaction conditions could tolerate other functional groups in the substrates, such as CHO, COMe and NO_2.

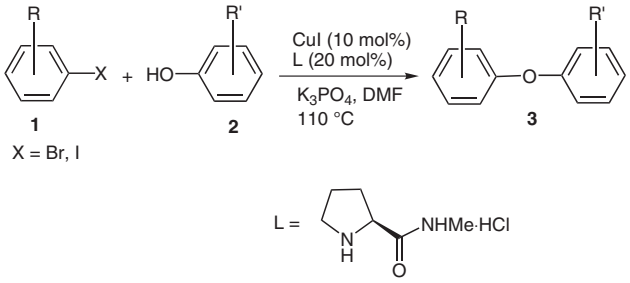
In summary, we have developed a highly efficient and readily available ligand (*S*)-*N*-methylpyrrolidine-2-carboxamide that could promote the copper-catalyzed O-arylation of aryl bromides or aryl iodides.

Acknowledgment

This work was supported by the National Natural Science Foundation of China (Grant No. 20472042 and 20672065), Programs for New Century Excellent Talents in University (NCET-05-0062), Changjiang Scholars and Innovative Research Team in University (PCSIRT) (No. IRT0404) in China and the Key Subject Foundation from Beijing Department of Education (XK100030514).

SYNLETT 2008, No. 2, pp 0221–0224
Advanced online publication: 21.12.2007
DOI: 10.1055/s-2007-1000878; Art ID: W17007ST

Table 1 Copper-Catalyzed Cross-Coupling of Aryl Halides with Substituted Phenols[a]



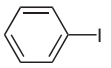
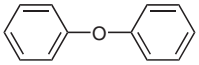
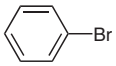
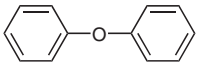
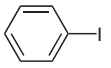
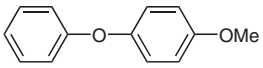
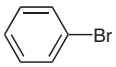
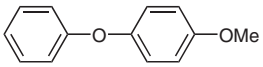
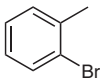
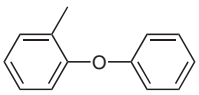
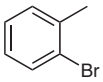
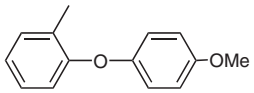
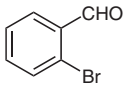
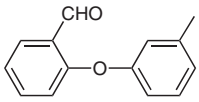
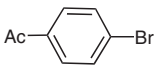
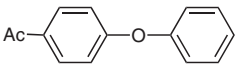
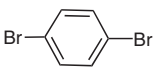
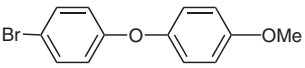
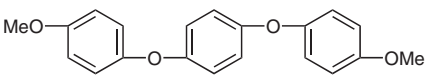
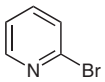
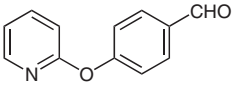
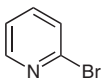
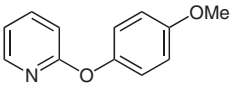
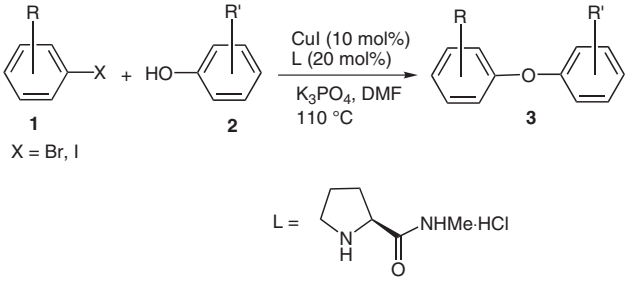
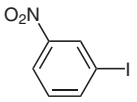
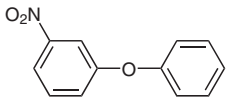
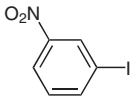
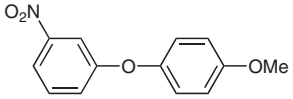
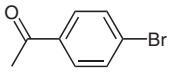
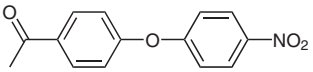
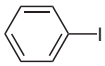
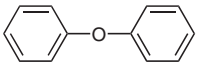
Entry	Aryl halide	Product	Time (h)	Yield (%)[b]
1		 **3a**	36	94
2		 **3a**	36	92
3		 **3b**	30	95
4		 **3b**	30	91
5		 **3c**	30	96
6		 **3d**	30	97
7		 **3e**	36	90
8		 **3f**	30	94
9		 **3g**  **3h**	36	65 30
10		 **3i**	20	93
11		 **3j**	30	92

Table 1 Copper-Catalyzed Cross-Coupling of Aryl Halides with Substituted Phenols[a] (continued)



Entry	Aryl halide	Product	Time (h)	Yield (%)[b]
12		 **3k**	16	90
13		 **3l**	16	94
14		 **3m**	36	79
15		 **3a**	36	86[c]

[a] Reaction conditions: aryl halide (1 mmol for entry 9; 2 mmol for others), substituted phenol (3 mmol), ligand (0.4 mmol), CuI (0.2 mmol), K_3PO_4 (4.4 mmol), DMF (3 mL with 3% H_2O) at 110 °C under N_2.
[b] Isolated yield.
[c] The reaction was conducted in the absence of H_2O.

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(16) **General Procedure for the Preparation of Compounds 3a–m**: Aryl halide (2 mmol for entries 1–8 and 10–14, 1 mmol for entry 9 in Table 1), substituted phenol (3 mmol) and (*S*)-*N*-methylpyrrolidine-2-carboxamide hydrochloride (66 mg, 0.4 mmol) were added to a flask with potassium phosphate (607 mg, 4.4 mmol) and DMF containing 3% H_2O (3 mL), and the mixture was stirred for 30 min at r.t. Under a nitrogen atmosphere CuI (40 mg, 0.2 mmol) was added to the flask. The flask was immersed in an oil bath, and the reaction mixture was stirred at 110 °C for the reaction time shown in Table 1. The reaction mixture was then allowed to cool to r.t., diluted with EtOAc (10 mL) and filtered, and the filtrate was concentrated under vacuum to give the crude product. Purification by column chromatography on silica gel (hexane–EtOAc, 15:1 → 50:1) afforded the desired pure product.
1-Methoxy-4-*o*-tolyloxybenzene (3d):[17] colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.18 (m, 1 H), 7.07 (m, 1 H), 6.97 (m, 1 H), 6.79 (m, 5 H), 3.73 (s, 3 H), 2.26 (s, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 156.03, 155.51, 151.26, 131.49, 129.21, 127.18, 123.28, 119.53, 118.18, 114.98, 55.76, 16.42. HRMS (EI): *m*/*z* [M^+] calcd for $C_{14}H_{14}O_2$: 214.0994; found: 214.0986.
1-Bromo-4-(4-methoxyphenoxy)benzene (3g): white solid; mp 84–86 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.36 (d, *J* = 8.25 Hz, 2 H), 6.86–6.97 (dd, *J* = 8.94, 25.08 Hz, 4 H), 6.80 (d, *J* = 8.91 Hz, 2 H), 3.79 (s, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 157.9, 156.3, 149.7, 132.6, 121.0, 119.3, 115.1, 114.8, 55.7. HRMS (EI): *m*/*z* [M^+] calcd for $C_{13}H_{11}BrO_2$: 277.9942; found: 277.9948.
(17) Aranyos, A.; Old, D. W.; Kiyomori, A.; Wolfe, J. P.; Sadighi, J. P.; Buchwald, S. L. *J. Am. Chem. Soc.* **1999**, *121*, 4369.