JOC *Article*

Copper-Catalyzed Arylation of Amines Using Diphenyl Pyrrolidine-2-phosphonate as the New Ligand

Honghua Rao,[†] 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

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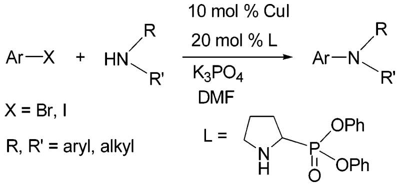

We have developed a general, efficient, and inexpensive catalyst system for arylation of amines by using 10 mol % of CuI as the copper source, 20 mol % of diphenyl pyrrolidine-2-phosphonate (DPP) as the ligand, K_3PO_4 as the base, and DMF containing 2% water (v/v) as the solvent.

Introduction

Arylamines have been shown to be effective targets for pharmaceuticals and other biologically active molecules, and their preparation has attracted much attention.[1] In recent years, transition-metal-catalyzed arylation of amines has been extensively utilized in medicinal chemistry and process development groups of pharmaceutical companies as well as in academic laboratories.[2−4] Although some significant achievements in the palladium-catalyzed arylation of amines have been made,[5−9] the drawbacks of the catalyst systems, such as air sensitivity, high cost, and toxicity, limit their applications. Use of copper catalysts,[10] as alternatives of palladium catalysts in the Ullmann reaction,[11] will greatly improve the chemical industry in both economic and environmental aspects. Therefore, the search for milder and more efficient catalyst systems for performing the classic copper-catalyzed arylation of amines and amides has been the subject of recent focus.[12] For example, copper-catalyzed arylations of anilines,[13] amides,[14] indoles,[15] imidazole,[16] and hydrazides[17] have been reported. Although the ligand-free copper-catalyzed Ullmann cross-coupling reaction was described,[18] research showed that use of the proper ligands could greatly improve the reaction activity,[13−17] and so chemists have already changed their interest to the cheaper and more practical ligand-promoted copper-catalyzed chemistry, which could modulate the reactivity of catalysts and provide more effective and more versatile catalyst systems. Some efficient ligands have been developed for the copper-catalyzed arylation of amines, including bidentate ligands such as aliphatic diamines,[19] 1,10-phenanthroline and its

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[†] Tsinghua University, Beijing.

[‡] Tsinghua University, Shenzhen.

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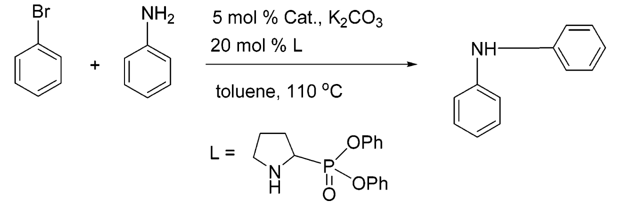
10.1021/jo051221w CCC: $30.25

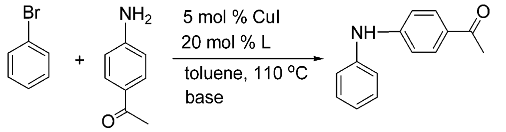
TABLE 1. Copper-Catalyzed Arylation of Aniline: Effect of Copper Catalyst[a]



entry	catalyst	time, h	yield,[b] %
1	$CuSO_4{\cdot}5H_2O$	48	25
2	$CuSO_4$	48	30
3	CuBr	48	40
4	$CuCl_2$	48	35
5	CuI	36	45

[a] Reaction conditions: bromobenzene (1.5 mmol), aniline (1.0 mmol), catalyst (0.05 mmol), ligand (0.2 mmol), K_2CO_3 (2.0 mmol) in toluene (2.0 mL) under N_2. [b] Isolated yield.

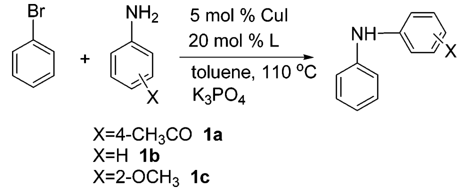
TABLE 2. Copper-Catalyzed Arylation of 4′-Aminoacetophenone: Effect of Base[a]



entry	base	time, h	yield,[b] %
1	K_2CO_3	36	51
2	Na_2CO_3	36	38
3	Cs_2CO_3	36	57
4	$K_3PO_4{\cdot}7H_2O$	36	35
5	$K_3PO_4{\cdot}7H_2O$	48	50
6	K_3PO_4	36	63

[a] Reaction conditions: bromobenzene (1.5 mmol), 4′-aminoacetophenone (1.0 mmol), CuI (0.05 mmol), ligand (0.2 mmol), base (2.0 mmol) in toluene (2.0 mL) under N_2. [b] Isolated yield.

TABLE 3. Copper-Catalyzed Arylation of Arylamines: Effect of Solvent[a]



entry	arylamine	solvent	time, h	yield,[b] %
1	**1a**	toluene	36	45
2		1,4-dioxane	36	55
3		DMF	36	63
4		DMF^w	36	67
5	**1b**	toluene	36	47
6		1,4-dioxane	36	50
7		DMF	36	52
8		DMF^w	36	55
9	**1c**	toluene	36	48
10		1,4-dioxane	36	50
11		DMF	36	54
12		DMF^w	36	59

[a] Reaction conditions: bromobenzene (1.5 mmol), substituted aniline (1.0 mmol), CuI (0.05 mmol), ligand (0.2 mmol), K_3PO_4 (2.0 mmol) in 2.0 mL of solvent under N_2. DMF^w: DMF with 2% water (v/v). [b] Isolated yield.

derivatives,[20] 2,2′-bipyridine,[21] 8-hydroxyquinoline,[12,21,22] bidentate phosphines,[12,21,22] diphosphinidenecyclobutene[23] and ethylene glycol,[13a] amino acids with secondary amino groups such as *N*-methylglycine and proline,[24] and monodentate phosphines such as tri-*o*-tolylphosphine and tri-*n*-butylphosphine.[25] Herein, we would like to report a new and efficient ligand of copper-catalyzed arylation of amines, diphenyl pyrrolidine-2-phosphonate (DPP).

Results and Discussion

DPP could easily be synthesized according to the reported procedure.[26] We attempted various reaction conditions including optimization of the copper sources, bases, solvents, amount of catalysts, and the ligand (DPP) in order to achieve the best results in the Ullmann coupling reactions.

Copper Source. Several readily available copper compounds, $CuSO_4$, CuBr, $CuCl_2$, and CuI, were screened for the Ullmann coupling reaction of bromobenzene with aniline in toluene at 110 °C using 5 mol % of copper salt as the catalyst, 20 mol % of DPP as the ligand, and 2 equiv of K_2CO_3 as the base (Table 1). The experiments showed that air-stable and inexpensive CuI gave the best result.

Choice of Base. We also investigated the coupling of bromobenzene and 4′-aminoacetophenone in different bases (Table 2). Among the bases we selected, potassium phosphate gave the best result, and the other bases, K_2CO_3, Na_2CO_3, Cs_2CO_3, are less efficient. Interestingly, potassium phosphate with heptahydrate ($K_3PO_4{\cdot}7H_2O$) was the least efficient for the amination reaction. However, as the reaction time was increased, a higher yield was afforded, and this result showed that the amination rate was influenced by the amount of water in the catalyst system.

Choice of Solvent. Solvents also played important roles in the catalytic amination reactions, and the coupling reactions of bromobenzene with different arylamines, including neutral, electron-rich, and electron-deficient arylamines, were investigated to find an optimal solvent. As shown in Table 3, the reaction efficiency is the highest in DMF, compared to toluene or 1,4-dioxane. We also found that the addition of a trace amount of water (2% relative to DMF (v/v)) could improve the reaction efficiency, which is in good agreement with the reported results.[27]

Amount of CuI and the Ligand. In the process of optimization, the effect of the amount of CuI and the ligand was also investigated. No desired amination products were obtained in the absence of the ligand

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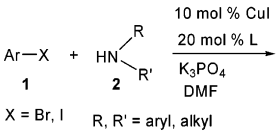
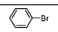
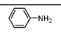
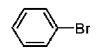
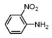
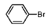
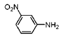
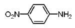
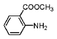
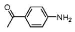
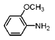
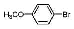
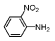
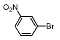
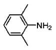
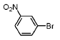
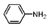
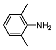
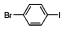
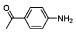
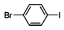
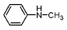
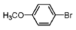
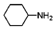
TABLE 4. Coupling of Aryl Halides with Various Amines[a]



Entry	Aryl halide	Amine	Product	Temp. (°C)	Time, h	Yield[b] (%)
1			**3a**	110	36	57
2			**3b**	110	30	75
3			**3c**	110	30	73
4			**3d**	110	30	71
5			**3e**	110	30	70
6			**3f**	110	30	65
7			**3g**	110	36	60
8			**3h**	110	36	70
9			**3i**	100	30	62
10			**3c**	100	30	80
11			**3j**	110	28	66
12			**3k**	100	24	73
13			**3l**	110	36	60
14			**3m**	90	30	78
15			**3n**	90	30	75
16		$CH_3(CH_2)_{11}NH_2$	**3o**	90	24	73
17			**3p**	90	16	84

[a] Reaction conditions: CuI (0.2 mmol), ligand (0.4 mmol), K_3PO_4 (4 mmol) in DMF (3 mL, with 2% water (v/v)) under N_2; (1) aryl halide (2 mmol), amine (3 mmol) for entries 1−11 and 14−17; (2) aryl halide (3 mmol), amine (2 mmol) for entries 12−13. [b] Isolated yield.

(DPP), which showed that the addition of the ligand could promote the Ullmann arylation of amines, and further experiments showed that the catalyst system containing 10 mol % of CuI and 20 mol % of ligand, relative to substrates, was the optimal choice.

Comparison of DPP with Other Ligands. The cross-coupling of aniline and aryl bromide in DMF containing 2% water (v/v) using 20 mol % of other standard ligands, such as *N,N′*-tetramethylethyldiamine[19] and proline,[24] were tested in the presence of 10 mol % of CuI and 2 equiv of K_3PO_4, respectively, and we found that the corresponding conversion ratios were lower than 60%, which was equal to the result using DPP as the ligand.

Scope of Substrates. The scope of the copper-catalyzed aryl amination reaction was explored by using 10 mol % of CuI as the copper source, 20 mol % of DPP as the ligand, 2 equiv of K_3PO_4 as the base, and DMF containing 2% water (v/v) as the solvent. The coupling reaction of aryl halides with various amines was carried out using the catalyst system, and the desired amination products were obtained in moderate to good yields. As shown in Table 4, we found that the ligand could promote the conversion of all of the substrates to the corresponding arylamines, and aryl bromides containing an electron-withdrawing group on the benzene ring afforded better results (entries 1, 8, and 10 in Table 4). However, the coupling of 1-bromo-3-nitrobenzene with 2,6-dimethylaniline (entry 9 in Table 4) did not give satisfactory results because of steric effects. Aryl iodides showed higher reactivity than aryl bromides in the coupling reaction. For example, the coupling of 1-bromo-4-iodobenzene with 4′-aminoacetophenone or *N*-methylaniline (entries 12 and 13 in Table 4) yielded the target product **3k** or **3l** containing bromine on the benzene ring.

Conclusions

A general and efficient protocol for amination of aryl halides with aromatic amines or aliphatic amines has been developed by using diphenyl pyrrolidine-2-phosphonate as the new ligand of CuI in the Ullmann reaction. In comparison to other transition-metal catalyst systems, such as palladium-catalyzed arylamination, this protocol is simple and avoids the use of air-sensitive and expensive catalysts or additives.

Experimental Section

General Procedure for the Preparation of Compounds 3a−p. A flask was charged with CuI (40 mg, 0.2 mmol), diphenyl pyrrolidine-2-phosphonate hydrochloride (136 mg, 0.4 mmol), and potassium phosphate (552 mg, 4 mmol), evacuated, and backfilled with nitrogen at low temperature. Aryl halide (2 mmol for entries 1−11 and 14−17 in Table 4, 3 mmol for entries 12 and 13) and amine (3 mmol), DMF (3 mL, containing 2% H_2O (v/v)) were added to the flask under nitrogen. The flask was immersed in an oil bath, and the reaction mixture was stirred at the indicated temperature for the corresponding reaction time shown in the tables. The reaction mixture was cooled to room temperature, 10 mL of ethyl acetate was added, the resulting suspension was filtered, the filtrate was concentrated, and the residue was purified by column chromatography on silica gel (hexanes−EtOAc = 20:1−8:1) to provide the desired product. Characterization data of two representative compounds are shown as follows:

Diphenylamine (3a):[28] white solid; yield 57%; mp 52−53 °C (lit.[28b] mp 54 °C); ^1H NMR ($CDCl_3$, 300 MHz) δ 7.24−7.29 (m, 4H), 7.08 (d, 4H, $J = 7.57$ Hz), 6.93 (t, 2H, $J = 7.22$ Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 143.1, 129.4, 121.2, 118.0; HR-EI-MS M^+ *m/z* calcd for $C_{12}H_{11}N$ 169.0891, found 169.0885.

***N*-Dodecylbenzenamine (3o):**[29] milk-white oil; yield 73%; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.18 (t, 2H, $J = 7.54$ Hz), 6.70 (t, 1H, $J = 7.20$ Hz), 6.62 (d, 2H, $J = 7.89$ Hz), 3.11 (t, 2H, $J = 7.03$ Hz), 1.67−1.65 (m, 2H), 1.29 (m, 18H), 0.91 (t, 3H, $J = 6.00$ Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 148.7, 129.3, 117.2, 112.8, 44.1, 32.1, 29.71, 29.6, 29.5, 27.3, 22.8, 14.2; HR-EI-MS M^+ *m/z* calcd for $C_{18}H_{31}N$ 261.2457, found 261.2452.

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Supporting Information Available: General experimental methods, preparation of the ligand, characterization data, and ^1H and ^{13}C NMR spectra of the ligand and compounds **3a−p**. This material is available free of charge via the Internet at http://pubs.acs.org.

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