3-(Diphenylphosphino)propanoic Acid: An Efficient Ligand for Cu-Catalyzed *N*-Arylations of Indoles and Aryl Amines

Y.S. Liu, N.N Gu, Y. Liu, X.W. Ma, P. Liu[*] and J.W. Xie

School of Chemistry and Chemical Engineering, The Key Laboratory for Green Processing of Chemical Engineering of Xinjiang Bingtuan, Shihezi University, Shihezi City, P.R. China

*Corresponding author: Fax: +86 993 2057270; Tel: +86 993 2057213; E-mail: liuping1979112@aliyun.com

3-(Diphenylphosphino)propanoic acid (**L2**) was found to be an efficient ligand for the copper-catalyzed *N*-arylations of indoles and arylamines with aryl iodides, the C-N coupling reactions catalyzed by CuCl/**L2** were smoothly carried out in DMSO at 120 ºC and give the corresponding products with the yields of 25-98 %.

Keywords: P, O ligands, *N*-arylation, Cu catalyzed, Indoles, Arylamines.

INTRODUCTION

N-Arylheterocycles are prevalent in chemical pharmaceutical and materials industries[1]. So the development of practical methods to synthesize such compounds has attracted considerable attention. Among them, transition metal-catalyzed C-N coupling reactions have proved to be an efficient strategy[2-8]. In particular, the lower cost of copper-based catalytic systems makes them suitable for large-scale industrial applications and has challenged synthetic chemists to devise milder synthetic methods. The design of new ligands structures for copper-catalyzed cross-coupling protocols constitutes an area of considerable interest. Recently, a series of novel mono- and bidentate ligands for Cu-based C-N coupling were discovered, such as organic phosphanes ligands[9-11], *N*,*N*-bidentate ligands[12-21], *O*,*O*-bidentate ligands[22-29], and *N*,*O*-bidentate ligands[30-41]. In spite of the significant progress made, it is still necessary to search more efficient, air stable and low-cost ligands or metal-complexes to facilitate these coupling reactions under relatively milder conditions.

The bidentate derivatives containing phosphorus and oxygen are well-known ligands for organic reactions catalyzed by transition metals, such as the oligomerization and polymerization of ethylene[42], C-C coupling reactions[43-47], *etc*. However, investigations on the copper catalyzed C-N coupling reactions in the presence of phosphorus and oxygen chelating ligands were less reported. As we known, the phosphorus and oxygen chelating ligands can provide additional coordination sites for the catalytic metal center and thus enhance its efficiency, because they not only confer suitable electron, but also

bring about steric properties to the phosphorus coordinating atom[47-49]. So we assumed that they might be a class of efficient ligands for the copper catalyzed C-N coupling reactions. Based on previous research works[50-52], herein we report our results on CuCl-catalyzed *N*-arylation of indoles and arylamines by using 3-(diphenylphosphino)propanoic acid (Fig. 1).

EXPERIMENTAL

All the reactions were carried out under air using magnetic stirring unless otherwise noted. ^{1}H NMR spectral data were recorded on a Bruker DPX-400 spectrometers using TMS as an internal standard and $CDCl_3$ as solvent. EI-Mass spectra were measured on a LC/Q-TOF MS (Micromass, England). All other reagents were of analytical grade quality purchased commercially and used.

^{1}H NMR spectral data were recorded on a Bruker DPX-400 spectrometers using TMS as internal standard and $CDCl_3$ as solvent. Mass spectra were recorded on GC-MS (Agilent 7890A/5975C) instrument under EI model.

General procedure: To a 5 mL of sealed tube was added CuCl (0.04 mmol), 3-(diphenylphosphino)propanoic acid (**L2**) (0.08 mmol), aryl iodide (0.5 mmol), 1*H*-indole (0.75 mmol), NaOH (1 mmol) and DMSO (1 mL). The mixture was stirred at 120 ºC for the certain time. After cooling to room temperature, the mixture was quenched with 10 mL H_2O and extracted with EtOAc (3 × 20 mL). The combined EtOAc extracts were dried with anhydrous Na_2SO_4, filtrated and the solvent was removed under reduced pressure and the residue was purified by flash column chromatography on silica gel with PE/EtOAc
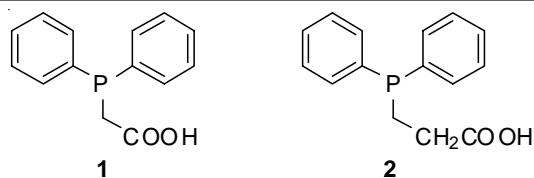
Fig. 1. Structures of ligands **1** and **2**

as the eluent to afford the desired products. All *N*-arylation products reported herein are known compounds and were characterized by ¹H NMR and GC-MS.

Compound 5b: ¹H NMR (400 MHz, CDCl₃): δ 7.70-7.66 (m, 1H), 7.57-7.54 (m, 1H), 7.48 (dd, *J* = 5.6, 2.3 Hz, 4H), 7.35-7.30 (m, 2H), 7.24-7.13 (m, 2H), 6.67 (dd, *J* = 3.3, 0.7 Hz, 1H). GC/MS: *m/z* 193.

Compound 5c: ¹H NMR (400 MHz, CDCl₃): δ 7.68 (ddd, *J* = 7.6, 1.3, 0.8 Hz, 1H), 7.51-7.42 (m, 5H), 7.28 (d, *J* = 3.3 Hz, 1H), 7.23-7.15 (m, 2H), 6.68 (dd, *J* = 3.3, 0.8 Hz, 1H). GC/MS: *m/z* 229.

Compound 5d: ¹H NMR (400 MHz, CDCl₃): δ 7.69-7.66 (m, 1H), 7.63-7.59 (m, 2H), 7.52-7.49 (m, 1H), 7.38-7.35 (m, 2H), 7.27 (t, *J* = 3.2 Hz, 1H), 7.23-7.15 (m, 2H), 6.68 (dd, *J* = 3.3, 0.9 Hz, 1H). GC/MS: *m/z* 271.

Compound 5f: ¹H NMR (400 MHz, CDCl₃): δ 7.67 (ddd, *J* = 7.6, 1.4, 0.8 Hz, 1H), 7.47-7.42 (m, 1H), 7.38-7.34 (m, 2H), 7.24 (dd, *J* = 5.1, 2.2 Hz, 1H), 7.21-7.12 (m, 2H), 7.01-6.96 (m, 2H), 6.65-6.62 (m, 1H), 4.05 (q, *J* = 7.0 Hz, 2H), 1.44 (dd, *J* = 8.2, 5.8 Hz, 3H). GC/MS: *m/z* 237.

Compound 5g: ¹H NMR (400 MHz, CDCl₃): δ 7.71-7.67 (m, 1H), 7.37-7.30 (m, 4H), 7.17-7.14 (m, 3H), 7.05-7.02 (m, 1H), 6.67 (dt, *J* = 2.4, 1.2 Hz, 1H), 2.06 (d, *J* = 2.1 Hz, 3H). GC/MS: *m/z* 207.

Compound 5h: ¹H NMR (400 MHz, CDCl₃): δ 7.69-7.58 (m, 2H), 7.43-7.37 (m, 1H), 7.33 (t, *J* = 2.6 Hz, 1H), 7.24-

7.03 (m, 4H), 6.89 (m, 1H), 6.67 (s, 1H), 3.82 (s, 3H). GC/MS: *m/z* 223.

Compound 5i: ¹H NMR (400 MHz, CDCl₃): δ 7.75-7.69 (m, 3H), 7.66-7.57 (m, 5H), 7.50-7.46 (m, 2H), 7.41-7.36 (m, 2H), 7.25 (s, 1H), 7.21-7.16 (m, 1H), 6.71 (m, 1H). GC/MS: *m/z* 269.

Compound 5j: ¹H NMR (400 MHz, CDCl₃): δ 7.26-7.21 (m, 2H), 7.10-7.06 (m, 2H), 7.04-6.98 (m, 4H), 6.91-6.85 (m, 1H), 2.30 (s, 3H). GC/MS: *m/z* 183.

Compound 5k: ¹H NMR (400 MHz, CDCl₃): δ 7.25-7.18 (m, 4H), 7.13 (t, *J* = 6.9 Hz, 1H), 6.96-6.89 (m, 4H), 2.25 (s, 3H). GC/MS: *m/z* 183.

Compound 5l: ¹H NMR (400 MHz, CDCl₃): δ 7.29-7.27 (m, 1H), 7.24 (td, *J* = 2.0, 1.1 Hz, 2H), 7.09-7.05 (m, 5H), 6.94-6.90 (m, 2H). GC/MS: *m/z* 169.

RESULTS AND DISCUSSION

Ligands **1** and **2** were synthesized by the literature methods[53,54]. To optimize the reaction conditions, a series of reactions between 4-iodotoluene (**3a**) and 1*H*-indole (**4a**) was performed in the presence of base and solvent to evaluate the roles of various ligands and copper sources for the *N*-arylation process. As shown in Table-1, among the explored different ligands and copper sources, **L2** (3-(diphenylphosphino)prop-anoic acid) exhibited the highest catalytic activity with 40 % yield (Table-1, entries 1 and 2). Solvent is another important factor of the catalysis, it was found that DMSO was much better than DMF (Table-1, entry 5). Meanwhile, both toluene and 1,4-dioxane were not suitable to work as reaction solvents (Table-1, entries 3 and 4). The base screening results suggested that NaOH was the best, Na₂CO₃, K₃PO₄, Et₃N gave lower yields (Table-1, entries 6-8). The comparison of different copper sources indicated that CuCl was superior to other

TABLE-1
OPTIMIZATION OF THE REACTION CONDITIONS[a]

Entry	[Cu] (mol %)	Ligand (mol %)	Base	Solvent	Yield (%)[b]
1	CuCl/4	**1**/8	NaOH	DMSO	29
2	CuCl/4	**2**/8	NaOH	DMSO	40
3	CuCl/4	**2**/8	NaOH	1,4-Dioxane	10
4	CuCl/4	**2**/8	NaOH	Toluene	Trace
5	CuCl/4	**2**/8	NaOH	DMF	20
6	CuCl/4	**2**/8	Na₂CO₃	DMSO	21
7	CuCl/4	**2**/8	K₃PO₄	DMSO	18
8	CuCl/4	**2**/8	Et₃N	DMSO	10
9	Cu(OAc)₂/4	**2**/8	NaOH	DMSO	31
10	CuSO₄/4	**2**/8	NaOH	DMSO	28
11	Cu power/4	**2**/8	NaOH	DMSO	32
12	CuCl/8	**2**/16	NaOH	DMSO	67
13[c]	CuCl/8	**2**/16	NaOH	DMSO	82
14[d]	CuCl/8	**2**/16	NaOH	DMSO	90

[a]Reaction conditions: 4-ioidotoluene (0.5 mmol), 1*H*-indole (1 mmol), base (1 mmol), and solvent (1 mL), reaction time 12 h; [b]Isolated yields;
[c]Temperature 120 ºC. [d]Temperature 120 ºC, reaction time 24 h

TABLE-2
N-ARYLATION OF INDOLES AND ARYL AMINES CATALYZED BY CuCl/**L2**[a]

R—⟨⟩—I + Het-NH →(CuCl/Ligand **2**, DMSO, NaOH, 100°C)→ R—⟨⟩—N-Het

3   **4**   **5**

Entry	R (**3**)	Het-NH	Product	Yield (%)[b]
1	H (**3b**)	1*H*-indole (**4a**)	**5b**	98
2	4-Cl (**3c**)	**4a**	**5c**	85
3	4-Br (**3d**)	**4a**	**5d**	66
4	4-CN (**3e**)	**4a**	**5e**	Trace
5	4-OEt (**3f**)	**4a**	**5f**	90
6	2-CH$_3$ (**3g**)	**4a**	**5g**	25
7	3-OMe (**3h**)	**4a**	**5h**	69
8	4-C$_6$H$_5$ (**3i**)	**4a**	**5i**	96
9	**3a**	Aniline (**4c**)	**5j**	38
10	2-CH$_3$ (**3g**)	**4c**	**5k**	58
11	**3b**	**4c**	**5l**	50

[a]Reaction conditions: aryl halides (0.5 mmol), Het-NH (1 mmol), CuCl (8 mol %), Ligand **2** (16 mol %), NaOH (1 mmol), DMSO (1 mL), 120 °C, reaction time 24 h; [b]Isolated yields

sources, including Cu(OAc)$_2$, CuSO$_4$ and Cu power (Table-1, entries 9-11). The amount of Cu resource/ligand was another important factor of the reaction. When the amount of CuCl/ **L2** was increased from 4 mol %/8 mol % to 8 mol %/16 mol %, the isolated yield of the product (**5a**) was increased to 67 % (Table-1, entry 12). Increasing the reaction temperature from 100 to 120 °C and prolonging reaction time from 12 to 24 h improved the yield from 82 to 90 % (Table-1, entries 13 and 14). So the combination of CuCl (8 mol %)/**L2** (16 mol %), NaOH (2 equiv.) at 120 °C for 24 h in DMSO was chosen as the optimal conditions for *N*-arylation of 1*H*-indoles with 4-iodotoluene.

The role of the CuCl/**L2** system for general *N*-arylation of indoles with various aryl halides was further evaluated and summarized in Table-2. Iodobenzene as a substrate reacted with 1*H*-indole and 98 % yield was obtained (Table-2, entry 1). The electron-poor aryl bromides, such as 1-chloro-4-iodo-benzene and 1-bromo-4-iodobenzene led to the *N*-arylated products in 85 and 66 % yields, respectively (Table-2, entries 2 and 3). However, *N*-arylation product was not observed under the experimental condition, when 4-iodobenzonitrile was used as the substrate (Table-2, entry 4). The electron-rich aryl bromide, such as 1-ethoxy-4-iodobenzene, gave 90 % yield at the same condition (Table-2, entry 5). Notably, sterically demanding *ortho* substituents, such as 1-iodo-2-methyl-benzene, did not hamper the *N*-arylation reaction (25 %, Table-2, entry 6). Both 1-iodo-3-methoxybenzene and 4-iodobiphenyl reacted with the 1*H*-indole and the corresponding products with moderate to excellent yields were obtained (Table-2, entries 7 and 8). In addition, the reactions of aryl iodides such as 1-iodo-4-methylbenzene, 1-iodo-2-methyl-benzene and iodobenzene with aniline were also successful and provided the desired products in moderate yields (Table-2, entries 9-11).

Conclusion

In summary, we have developed a novel and general catalytic method for *N*-arylations of indoles and aryl amines promoted by CuCl/3-(diphenylphosphino)propanoic acid. The system is efficient for the coupling of indoles and aryl amines with aryl iodides to give moderate to excellent yields. The easily availability of the catalyst, mild reaction conditions, experimental simplicity and broad substrate scope are the features of the catalytic method presented in the current paper. The application scope expansion of the catalytic system is currently studied in our laboratory.

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