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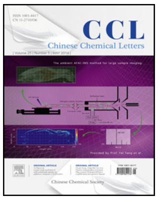

Original article

3-(Diphenylphosphino)propanoic acid: An efficient ligand for the Cu-catalyzed *N*-arylation of imidazoles and 1*H*-pyrazole with aryl halides

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ABSTRACT

3-(Diphenylphosphino)propanoic acid (**L2**) has proved to be an efficient ligand for the copper-catalyzed C–N coupling reactions. *N*-arylation of imidazoles with aryl iodides catalyzed by CuCl/**L2** was smoothly carried out in DMSO at 100 °C with a yield up to 98%. *N*-arylation of 1*H*-pyrazole with aryl iodides and bromides catalyzed by $Cu(OAc)_2$/**L2** in 1,4-dioxane also gave the corresponding products with yields of 40%–98%.

1. Introduction

N-arylheterocycles represent an interesting structural motif frequently utilized by chemical, pharmaceutical, and materials industries [1]. Thus, the development of correspondingly convenient and efficient synthetic methods using these compounds has attracted considerable attention. In the successful C–N coupling methods, palladium [2], nickel [3] and copper [4] catalysts, have been employed in the coupling of nucleophilic aromatic substituents with aryl halides. The lower cost of copper-based catalytic systems makes them particularly attractive for large-scale industrial applications, but requires synthetic chemists to devise milder synthetic methods. The development of new ligand structures for copper-catalyzed, cross-coupling protocols also 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 phosphane ligands [5,6], *N*,*N*-bidentate ligands [7,8], *O*,*O*-bidentate ligands [9–14], and *N*,*O*-bidentate ligands [15–18]. In spite of the significant recent progress, it is still necessary to search for more efficient, air-stable and cheaper ligands, or metal-complexes, to facilitate these coupling reactions under relatively milder conditions.

P,*O*-bidentate derivatives are well-known ligands for organic reactions catalyzed by transition metals. The *P*,*O* chelating ligands can provide additional coordination sites for the catalytic metal center and, thus enhance their efficiency because they not only supply suitable electrons, but also make available steric properties to the phosphorus coordinating atom. Since Keim first reported that nickel(II)/*P*,*O* chelating ligands were highly active in oligomerization and polymerization of ethylene [19], this class of ligands became the focal point and center of interest, and many analogous ligands had been successively synthesized, especially the ligands found in the development of novel homogeneous catalysts [20]. In addition, a notable achievement had been made in the utilization of *P*,*O* chelating ligands. The Pd- and Ni-catalyzed C–C coupling reactions could be achieved under mild conditions [21–23]. However, investigations on the Cu-catalyzed C–N coupling reactions in the presence of *P*,*O* chelating ligands were seldom reported. Based on our previous research [24], herein, we report our recent results on Cu-catalyzed *N*-arylation of nitrogen-containing heterocycles with aryl iodides and bromides under mild conditions by using *P*,*O* bidentate derivatives as ligands.

2. Experimental

2.1. Materials and instruments

All reactions were carried out in air under magnetic stirring conditions unless otherwise noted. ^{1}H NMR spectral data were

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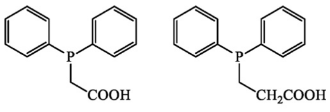


L1 **L2**

Fig. 1. Structures of ligands **1** and **2**.

recorded on a Bruker DPX-400 spectrometers using TMS as internal standard and $CDCl_3$ or DMSO-d_6 as solvent. EI-Mass spectra were measured on a LC/Q-TOF MS (Micromass, England). All other reagents were of analytical grade quality and commercially obtained.

2.2. General procedure for N-arylation of imidazoles and 1H-pyrazole

(2-(Diphenylphosphino)acetic acid) **L1** and (3-(diphenylphosphino)propanoic acid) **L2** (Fig. 1) were synthesized by the literature methods [25].

Procedure for *N*-arylation of imidazoles: CuCl (0.04 mmol), **L2** (0.08 mmol), aryl idione or bromide (0.5 mmol), imidazole or 1*H*-benzo[d]imidazole (0.75 mmol), NaOH (1 mmol), and DMSO (1 mL) was added to a 5 mL tube, then sealed. The mixture was stirred at 100 °C for 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 and filtrated and the solvent was removed under reduced pressure. The residue was purified by flash column chromatography on silica gel with PE/EtOAc (from 2:1 (v/v) to pure EtOAc) as the eluent to afford the desired products.

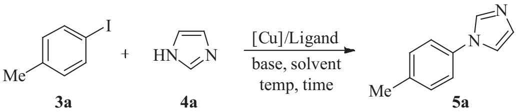
Procedure for *N*-arylation of 1*H*-pyrazole: $Cu(OAc)_2$ (0.03 mmol), **L2** (0.06 mmol), aryl idione or bromide (0.5 mmol), 1*H*-pyrazole (0.75 mmol), NaOH (1 mmol), and 1,4-dioxane (1 mL) was added into a 5 mL tube, then sealed. The mixture was stirred at 100 °C for certain time. After cooling to 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 and filtrated and the solvent was removed under reduced pressure. The residue was purified by flash column chromatography on silica gel with PE/EtOAc, as the eluent, to afford the desired products.

3. Results and discussion

3.1. Copper-catalyzed N-arylation reactions of imidazoles

To optimize the reaction conditions, a series of reactions between 4-iodotoluene (**3a**) and imidazole (**4a**) were 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** exhibited the highest catalytic activity with 41% yield (Table 1, entries 1 and 2). The comparison of different copper sources indicated that CuCl was superior to other sources, including $Cu(OAc)_2$, Cu_2O, and CuI (Table 1, entries 3–5). The screening results of bases suggested that NaOH was the best (Table 1, entries 6–9) and that 66% yield was achieved. The amount of Cu resource/**L2** was another important factor of the reaction investigated. When the amount of Cu resource/**L2** was increased from 2 mol%/8 mol% to 4 mol%/16 mol%, the isolated yield of the product (**5a**) increased to 97% (Table 1, entries 10 and 11). Solvent was another important factor in the catalysis. It was confirmed that DMSO was much better than DMF. Meanwhile, and both toluene and 1,4-dioxane were not suitable for use as reaction solvents (Table 1, entries 12–14). The combination of CuCl (8 mol%)/**L2** (16 mol%), NaOH (2 equiv.) at 100 °C for 12 h in DMSO was chosen as the optimal conditions for *N*-arylation of imidazole with 4-iodotoluene.

Table 1
Optimization of the reaction conditions.[a]



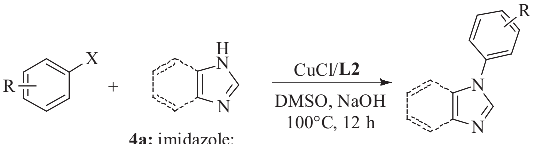
3a **4a** **5a**

Entry	[Cu] (mol%)	Ligand (mol%)	Base	Solvent	Yield (%)[b]
1	$Cu(OAc)_2$/2	**1**/4	NaOH	DMSO	20
2	$Cu(OAc)_2$/2	**2**/4	NaOH	DMSO	41
3	CuCl/2	**2**/4	NaOH	DMSO	66
4	Cu_2O/2	**2**/4	NaOH	DMSO	52
5	CuI/2	**2**/4	NaOH	DMSO	33
6	CuCl/2	**2**/4	Na_2CO_3	DMSO	0
7	CuCl/2	**2**/4	Cs_2CO_3	DMSO	38
8	CuCl/2	**2**/4	K_3PO_4	DMSO	15
9	CuCl/2	**2**/4	NEt_3	DMSO	0
10	CuCl/6	**2**/12	NaOH	DMSO	87
11	CuCl/8	**2**/16	NaOH	DMSO	97
12	CuCl/8	**2**/16	NaOH	Toluene	0
13	CuCl/8	**2**/16	NaOH	DMF	13
14	CuCl/8	**2**/16	NaOH	1,4-dioxane	0

[a] Reaction conditions: 4-ioidotoluene (0.5 mmol), imidazole (1.0 mmol), base (1.0 mmol), and solvent (1 mL), 12 h, 100 °C.
[b] Isolated yields.

The role of the CuCl/**L2** system for general *N*-arylation of imidazoles with various aryl halides was further evaluated and summarized in Table 2. In general, most of aryl iodides reacted with imidazole smoothly and the desired products were obtained with moderate to excellent yields. Iodobenzene, as a substrate, reacted with imidazole with only 62% yield (Table 2, entry 1), but 1-chloro-4-iodobenzene, 1-fluoro-4-iodobenzene and 4-iodo-1,1′-biphenyl led to the *N*-arylated products with yields of 90–98% (Table 2, entries 5–7). Furthermore, the catalytic system could tolerate a variety of functional groups, including the nitro, and ether groups (Table 2, entries 2, 4, and 8). When

Table 2
N-arylation of imidazoles with aryl halides catalyzed by CuCl/**L2**.[a]



3 **5**

4a: imidazole;
4b: 1*H*-benzo[d]imidazole

Entry	R, X (**3**)	Het-NH	Product	Yield (%)[b]
1	H, I (**3b**)	**4a**	**5b**	62
2	4-OEt, I (**3c**)	**4a**	**5c**	94
3	4-COMe, I (**3d**)	**4a**	**5d**	20
4	4-NO_2, I (**3e**)	**4a**	**5e**	77
5	4-Ph, I (**3f**)	**4a**	**5f**	93
6	4-Cl, I (**3g**)	**4a**	**5g**	98
7	4-F, I (**3h**)	**4a**	**5h**	90
8	3-OMe, I (**3i**)	**4a**	**5i**	77
9	2-Me, I (**3j**)	**4a**	**5j**	78
10	2-OMe, I (**3k**)	**4a**	**5k**	92
11	2-NH_2, I (**3l**)	**4a**	**5l**	61
12	4-NO_2, I (**3e**)	**4b**	**5m**	94
13	4-Ph, I (**3f**)	**4b**	**5n**	70
14	4-Cl, I (**3g**)	**4b**	**5o**	87

[a] Reaction conditions: aryl halides (0.5 mmol), imidazoles (1.0 mmol), CuCl (8 mol%), **L2** (16 mol%), NaOH (1.0 mmol), DMSO (1 mL), 100 °C, reaction time 24 h.
[b] Isolated yields.