

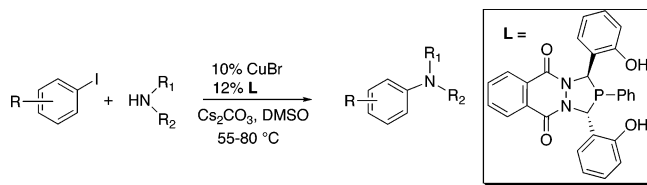
An Ullmann Coupling of Aryl Iodides and Amines Using an Air-Stable Diazaphospholane Ligand

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Received June 12, 2007



A copper-based catalytic system, using an air-stable diazaphospholane as the ligand, was developed for an efficient Ullmann reaction between aryl iodides and alkyl or heterocyclic amines.

The Ullmann-type coupling of aryl halides with amines using copper is recognized as an economic and versatile method for rapidly accessing aryl amines as key synthons (Scheme 1).¹ While ligand-free conditions are known, mono- and bidentate ligands, such as phosphines,² salicylamides,³ diamines,⁴ diols,⁵ amino alcohols,⁶ amino acids,⁷ phosphoramidites,⁸ oxime-phosphine oxides,⁹ and phosphinidenes,¹⁰ have been shown to significantly improve the yield and generality of this reaction. Recently, room-temperature Ullmann reactions have also been

(1) For recent reviews of cross-coupling reactions with copper-based catalysts, see: (a) Ley, S. V.; Thomas, A. W. *Angew. Chem., Int. Ed.* **2003**, *42*, 5400–5449. (b) Kunz, K.; Scholz, U.; Ganzer, D. *Synlett* **2003**, *15*, 2428–2439. (c) Beletskaya, I. P.; Cheprakov, A. V. *Coord. Chem. Rev.* **2004**, *2337–2347*, 721–724.

(2) (a) Gujadhur, R.; Venkataraman, D.; Kintigh, J. T. *Tetrahedron Lett.* **2001**, *42*, 4791–4793. (b) Haider, J.; Kunz, K.; Scholz, U. *Adv. Synth. Catal.* **2004**, *346*, 717–722.

(3) Kwong, F. Y.; Buchwald, S. L. *Org. Lett.* **2003**, *5*, 793–796.

(4) (a) Klapars, A.; Antila, J. C.; Huang, X.; Buchwald, S. L. *J. Am. Chem. Soc.* **2001**, *123*, 7727–7728. (b) Antila, J. C.; Klapars, A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 11684–11688. (c) Antila, J. C.; Baskin, J. M.; Barder, T. E.; Buchwald, S. L. *J. Org. Chem.* **2004**, *69*, 5578–5587.

(5) (a) Kwong, F. Y.; Klapars, A.; Buchwald, S. L. *Org. Lett.* **2002**, *4*, 581–584. (b) Job, G. E.; Buchwald, S. L. *Org. Lett.* **2002**, *4*, 3703–3706.

(6) (a) Lu, Z.; Twieg, R. J.; Huang, S. D. *Tetrahedron Lett.* **2003**, *44*, 6289–6292. (b) Lu, Z.; Twieg, R. J. *Tetrahedron* **2005**, *61*, 903–918.

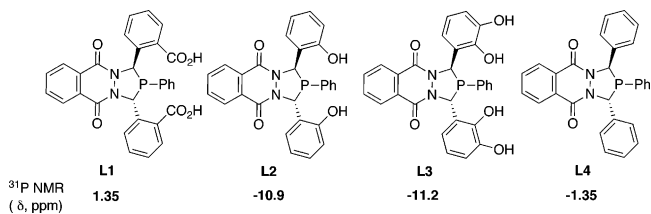
(7) (a) Ma, D.; Zhang, Y.; Yao, J.; Wu, S.; Tao, F. *J. Am. Chem. Soc.* **1998**, *120*, 12459–12467. (b) Cai, Q.; Zhu, W.; Zhang, H.; Zhang, Y.; Ma, D. *Synthesis* **2005**, *5*, 496–499. (c) Zhang, H.; Cai, Q.; Ma, D. *J. Org. Chem.* **2005**, *70*, 5164–5173.

(8) Zhang, Z.; Mao, J.; Zhu, D.; Wu, F.; Chen, H.; Wan, B. *Tetrahedron* **2006**, *62*, 4435–4443.

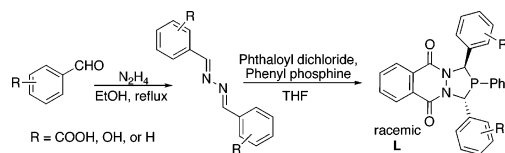
(9) (a) Xu, L.; Mao, J.; Zhu, D.; Wu, F.; Wang, R.; Wan, B. *Tetrahedron* **2006**, *61*, 6553–6560. (b) Zhu, D.; Xu, L.; Wu, F.; Wan, B. *Tetrahedron Lett.* **2006**, *47*, 5781–5784.

(10) Gajare, A. S.; Toyota, K.; Yoshifuji, M.; Ozawa, F. *Chem. Commun.* **2004**, 1994–1995.

SCHEME 1. Synthesis of L1–L4



reported using enolates or diols as ligands.¹¹ In this paper, we report the use of an air-stable diazaphospholane phosphine as a new ligand in the copper-catalyzed coupling of a range of aryl iodides with alkyl or heterocyclic amines for synthesizing a variety of aryl amines. While the diazaphospholane ligand framework has seen success in transition-metal-catalyzed reactions such as allylic alkylation and hydroformylation,¹² its utility in the copper-catalyzed Ullmann reaction has not yet been demonstrated.



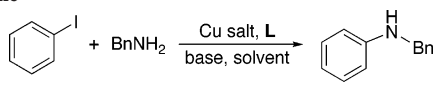
A series of four diazaphospholanes, **L1–L4**, were synthesized using the two-step Landis procedure from readily available starting materials, previously utilized for the synthesis of **L1**^{12b} and **L4**^{12c} (Scheme 1). Aldehydes and hydrazine were first condensed to form functionalized azines, which were then condensed with phthaloyl chloride and phenyl phosphine in one pot to furnish the diazaphospholanes. This facile synthesis was amenable to electron-rich aryl aldehydes, providing two new ligands (**L2** and **L3**) in good yields (57–63% over two steps) as racemic mixtures. These four phosphines, **L1–L4**, exhibited different chemical shifts at the phosphorus center as indicated by ³¹P NMR. Electron-donating substitution on the aromatic rings resulted in an upfield shift of the phosphorus signal by about 12 ppm (**L1** vs **L3**). All phosphines remained stable after exposure to air for months at room temperature.¹³ The convergent and facile synthesis of these stable phosphines may offer future opportunities for rapid access of analogues by changing the substituents of the starting aromatic aldehydes.

All four ligands were investigated in the copper-catalyzed coupling reaction between iodobenzene and benzylamine. Table

(11) For coupling between aryl iodides with primary amines using a β -diketone ligand, see: (a) Shafir, A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2006**, *128*, 8742–8743. For coupling between aryl iodides and aliphatic amines using *rac*-BINOL, see: (b) Jiang, D.; Fu, H.; Ji, J.; Zhang, Y.; Zhao, Y. *J. Org. Chem.* **2007**, *72*, 672–674.

(12) (a) Clark, T. P.; Landis, C. R.; Freed, S. L.; Klosin, J.; Abboud, K. A. *J. Am. Chem. Soc.* **2005**, *127*, 5040–5042. (b) Clark, T. P.; Landis, C. R. *J. Am. Chem. Soc.* **2003**, *125*, 11792–11793. (c) Landis, C. R.; Jin, W.; Owen, J. S.; Clark, T. P. *Angew. Chem., Int. Ed.* **2001**, *40*, 3432–3434. (d) Landis, C. R.; Nelson, R. C.; Jin, W.; Bowman, A. C. *Organometallics* **2006**, *25*, 1377–1391. (e) Landis, C. R.; Jin, W.; Owen, J. S.; Clark, T. P. PCT Int. Appl. WO 2003010174 A1, 2003. (f) Landis, C. R.; Jin, W.; Owen, J. S.; Clark, T. P.; Nelson, R. C. PCT Int. Appl. WO 2005042546 A2, 2005. For a review on phospholane chemistry, see: (g) Clark, T. P.; Landis, C. R. *Tetrahedron: Asymmetry* **2004**, *15*, 2123–2137.

(13) For an explanation of the air stability for some dialkylaryl phosphines, see: Barder, T. E.; Buchwald, S. L. *J. Am. Chem. Soc.* **2007**, *129*, 5096–5101.

TABLE 1. Effects of the Copper Source, Ligand, Base, and Solvent on the Coupling Reaction between Iodobenzene and Benzylamine


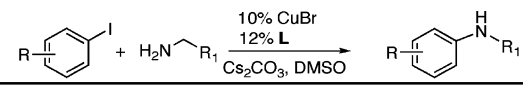
entry	copper salt	ligand	base	solvent	yield ^a (%)
1	Cu ₂ O	L2	K ₂ CO ₃	DMSO	42
2	CuBr	L2	K ₂ CO ₃	DMSO	73
3	CuCl	L2	K ₂ CO ₃	DMSO	67
4	CuI	L2	K ₂ CO ₃	DMSO	36
5	CuBr ₂	L2	K ₂ CO ₃	DMSO	50
6	Cu(CH ₂ COO) ₂ ·H ₂ O	L2	K ₂ CO ₃	DMSO	22
7	CuSO ₄	L2	K ₂ CO ₃	DMSO	10
8	CuCl ₂	L2	K ₂ CO ₃	DMSO	52
9	CuO	L2	K ₂ CO ₃	DMSO	7
10	CuBr	L1	Cs ₂ CO ₃	DMSO	30
11	CuBr	L4	Cs ₂ CO ₃	DMSO	42
12	CuBr	L3	Cs ₂ CO ₃	DMSO	64
13	CuBr	Ph ₃ P	Cs ₂ CO ₃	DMSO	<5
14	CuBr	L2	K ₃ PO ₄ ·H ₂ O	DMSO	62
15	CuBr	L2	Cs ₂ CO ₃	DMSO	87
16	CuBr	L2	Cs ₂ CO ₃	DMF	42
17	CuBr	L2	CsCO ₃	toluene	15
18	CuBr	L2	Cs ₂ CO ₃	DMSO	84^b
19	CuBr	L2	Cs ₂ CO ₃	DMSO	84^c
20	CuBr	L2	Cs ₂ CO ₃	DMSO	57^d

^a Reaction conditions: iodobenzene (0.5 mmol), benzylamine (0.75 mmol), ligand (0.06 mmol), base (1.0 mmol), copper source (0.05 mmol), at 55 °C, 18 h. ^b The ratio of ligand and metal is 2:1. ^c 15 mol % of *rac*-**L2** and CuBr was used. ^d 5 mol % of *rac*-**L2** and CuBr was used.

1 summarizes the results of this reaction by varying the copper source, ligand, base, and solvent. The diazaphospholane without the phenolic substitution, **L4**, was an effective ligand (entry 11, 42% yield), while triphenylphosphine did not result in product formation (entry 13). The best yield was provided by **L2**, a diazaphospholane with two phenolic substitutions on the aromatic rings (entry 15, 87% yield). **L3**, bearing two more phenolic substituents, was less effective compared to **L2** (entry 12, 64% yield). Carboxylate substituents, as seen in **L1**, severely reduced the yield (entry 10, 30%).

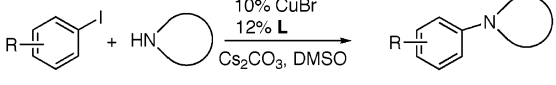
Using **L2** as the ligand, a range of combinations of copper sources, bases, and solvents was examined (Table 1). CuBr and CuCl were significantly better sources than other Cu(I) or Cu(II) salts (entries 1–9), and a very polar aprotic solvent, such as DMSO, was essential to the success of the reaction (entry 15 vs entry 17). The effect of the base on the yield of the reaction was minor (entry 2 vs entry 15). The stoichiometry of **L2** was also varied. A ratio of 1:1 between **L2** and CuBr sufficed, while increasing this ratio to 2:1 did not improve the yield (entry 18). Neither did the yield improve beyond 10 mol % loading of **L2** and CuBr (entry 19), although a reduction of loading to 5 mol % significantly reduced the yield (entry 20). This reaction presumably follows a generally accepted mechanism of the Ullmann reaction based on chelation.¹ The fact that better yields were provided by electron-rich ligands (entries 10–12 and 15) indirectly supports this hypothesis, as the oxidative addition of the aryl halide would be better facilitated by a more electron-rich ligand–Cu(I) complex.

























The substrate scope of this reaction was then examined using a variety of aryl iodides and primary amines under the optimized condition, which is summarized in Table 2. Aryl iodides were chosen because they are generally accepted as the more reactive aryl halides compared to aryl bromides and chlorides. In general,

TABLE 2. Coupling of Aryl Iodides with Primary Amines^a


entry	Arl	R ₁ NH ₂	yield (%) ^a
1		BnNH ₂	92(85 ^b)
2		BnNH ₂	82
3		BnNH ₂	87
4		BnNH ₂	85 ^c
5		BnNH ₂	80
6		BnNH ₂	83
7			80
8			51(80 ^d)
9			75
10			87
11			82
12			70
13			80
14		hexylamine	87
15		hexylamine	81
16		hexylamine	87 ^e
17		hexylamine	90
18			95
19			86
20		hexylamine	91

^a Reaction conditions: aryl iodides (0.5 mmol), amine (0.75 mmol), *rac*-**L2** (0.06 mmol), Cs₂CO₃ (1.0 mmol), CuBr (0.05 mmol), 55 °C, 24 h. ^b CuBr was replaced with CuCl. ^c The product is 4-iodo-*N*-benzylaniline. ^d At 80 °C, 30 h. ^e The product is 4-iodo-*N*-hexylaniline.

TABLE 3. Coupling of Aryl Iodides with Heterocyclic Amines^a


entry	Arl	R ₁ R ₂ NH	yield (%) ^a
1			98
2			71
3			78
4			95
5			65
6			85
7			93
8			97
9			82 ^b
10			95
11			89
12			85

^a ArI (0.5 mmol), amine (0.75 mol), CuBr (10 mol %), *rac*-L2 (12 mol %), Cs₂CO₃ (2.0 equiv), 80 °C, 24 h. ^b The product is *N*-(4-iodophenyl)imidazole.

this reaction provided good to excellent yields for all of the substrates. Yields did not vary significantly between the reaction of the aryl iodides and alkyl primary amines with varying electronic nature of the substituent on the aryl iodide (entries 1–6 and 14–17). For example, an electron-rich aryl iodide, *p*-methoxyiodobenzene, provided a yield of 80% for this reaction (entry 5), while *m*-nitroiodobenzene, an electron-poor aryl iodide, gave a comparable yield of 83% (entry 6). Sterically more hindered amines such as β -branched amines, however, resulted in significant reduction of yields or prolonged reaction times (entries 8, 9, and 12). The chemospecificity of the reaction was maintained in the presence of another reactive hydroxy group (entries 7 and 19).

In addition to primary amines, we found that this reaction was equally applicable to heterocyclic amines with good to excellent yields (Table 3). Electron-rich and -deficient aryl iodides were reacted with a range of heterocycles such as

indoles, imidazoles, benzoimidazoles, and pyrazoles. The C–N bond formation invariably occurred at the saturated nitrogen center. The substrate scope of this ligand was comparable to that of L-proline^{7c} and diamine^{4d} ligands but required a slightly lower temperature for reaction.

In conclusion, this work illustrates the use of a diazaphospholane as a new ligand for the copper-catalyzed Ullmann reaction using aryl iodides. The reaction conditions are moderate and applicable to both primary and heterocyclic amines in good to excellent yields. Investigations on the nature of this catalytic system are underway and will be reported in due course.

Experimental Section

General Procedure for the Synthesis of L2 and L3. The corresponding azine (8 mmol) in THF (65 mL) was treated with phenyl phosphine, and the reaction mixture was stirred for 5 min at 0 °C. Phthaloyl dichloride was slowly added to the resulting yellow slurry, and the solution was stirred at room temperature overnight. About 50 mL of THF was removed in vacuo, and the residual THF was then filtered off to obtain a white solid. The crude product was further washed with THF (3 mL) and Et₂O (3 × 5 mL) and dried in vacuo to obtain a white solid.

L2: Yield 63%, white powder, mp 272–274 °C; ¹H NMR (DMSO-*d*) δ 10.24 (br s, 2H), 8.27 (d, *J* = 8.8 Hz, 1H), 8.16 (d, *J* = 8.8 Hz, 1H), 7.93–7.99 (m, 2H), 7.26 (t, *J* = 8.8 Hz, 1H), 7.10–7.18 (m, 5H), 6.88 (d, *J* = 8.0 Hz, 1H), 6.63–6.80 (m, 5H), 6.39 (d, *J*_{P–H} = 17.2 Hz, 1H), 6.14–6.15 (m, 1H), 5.97 (d, *J* = 6.8 Hz, 1H); ¹³C NMR (DMSO-*d*) δ 155.7 (s, CO), 155.5 (s, CO), 154.8 (s, COH), 152.7 (s, COH), 134.0, 133.8, 133.1, 132.9, 132.7, 132.4, 130.1, 130.0, 129.9, 129.3, 128.7, 128.3, 127.9, 127.4, 127.2, 126.9, 125.4, 124.8, 120.5, 118.9, 117.9, 115.6, 114.6, 59.3 (d, *J*_{C–P} = 31.4 Hz), 57.6 (d, *J*_{C–P} = 18.9 Hz), 124–140 ppm have not been assigned due to the complexity; ³¹P NMR (DMSO-*d*) δ –10.92; IR (KBr, cm^{–1}) 3272.6, 1621.2; HRMS (EI) calcd for C₂₈H₂₀N₂O₄P [M – H⁺] 479.1161, found 479.1155.

L3·THF: ¹H NMR indicated that THF was bound with the ligand and was difficult to remove; yield 57%, white powder, mp 272–274 °C; ¹H NMR (DMSO-*d*) δ 9.61 (s, 1H), 9.24 (s, 1H), 9.06 (s, 1H), 8.70 (s, 1H), 8.25 (d, *J* = 7.2 Hz, 1H), 8.14 (d, *J* = 7.6 Hz, 1H), 7.93–7.99 (m, 2H), 7.27 (t, *J* = 7.2 Hz, 1H), 7.10–7.20 (m, 4H), 6.75 (d, *J* = 8.6 Hz, 1H), 6.67 (s, 1H), 6.57 (t, *J* = 8.0 Hz, 1H), 6.33–6.39 (m, 2H), 6.16 (d, *J* = 7.6 Hz, 1H), 5.96 (t, *J* = 8.0 Hz, 1H), 5.43 (d, *J* = 7.6 Hz, 1H); ¹³C NMR (DMSO-*d*) δ 155.6 (s, CO), 155.6 (s, CO), 145.4 (s, COH), 144.5 (s, COH), 142.1 (s, COH), 140.9 (s, COH), 134.0, 133.8, 133.0, 132.7, 132.5, 132.2, 130.1, 130.0, 128.2, 127.4, 127.2, 126.9, 125.9, 125.8, 121.3, 119.5, 117.8, 115.9, 114.8, 114.0, 113.1, 59.0 (d, *J*_{C–P} = 31.5 Hz), 56.7 (d, *J*_{C–P} = 19.1 Hz), 113–134 ppm have not been assigned due to the complexity; ³¹P NMR (DMSO-*d*) δ –11.21; IR (KBr, cm^{–1}) 3278.46, 1621.3; HRMS (EI) calcd for C₂₈H₂₀N₂O₆P [M – H⁺] 511.1059, found 511.1054.

Acknowledgment. This work is supported by an Australian Research Council Discovery Project Grant to F.L. (ARC-DP055068).

Supporting Information Available: Experimental procedures, characterization data for ligands, and spectra for coupling products. This material is available free of charge via the Internet at <http://pubs.acs.org>.

JO0712291