

# P[N(*i*-Bu)CH<sub>2</sub>CH<sub>2</sub>]<sub>3</sub>N: A Versatile Ligand for the Pd-Catalyzed Amination of Aryl Chlorides

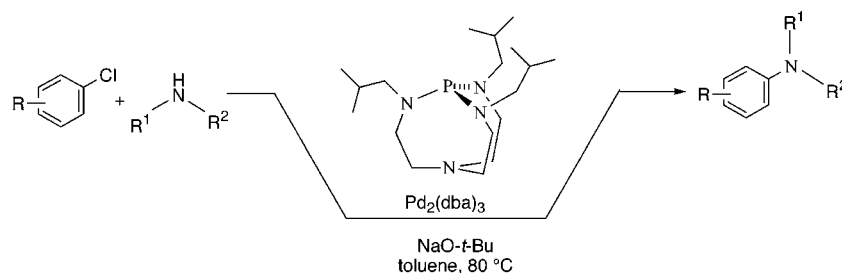
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## ABSTRACT



Palladium-catalyzed amination reactions of aryl chlorides with amines proceeded in the presence of the bicyclic triaminophosphine P[N(*i*-Bu)CH<sub>2</sub>CH<sub>2</sub>]<sub>3</sub>N to afford the corresponding arylamines in good to excellent yields. Electron-poor, electron-neutral, and electron-rich aryl chlorides all participated with equal ease.

The Pd-catalyzed amination of aryl halides (or halide equivalents) has emerged as a powerful tool for the synthesis of substituted anilines in recent years.<sup>1</sup> Though less reactive, aryl chloride substrates are highly desirable compared with their bromide and iodide counterparts in terms of cost and availability. The relatively low reactivity of aryl chlorides has been attributed to their aversion to oxidatively adding to Pd(0) species because of the large dissociation energy (402 kJ/mol at 298 K)<sup>2</sup> of the C–Cl bond. Recently, much progress has been made in the development of catalysts capable of utilizing aryl chlorides as substrates in aryl amination processes.<sup>3</sup> Most of these catalyst systems employ bulky electron-rich alkylphosphines or N-heterocyclic car-

benes as ligands, presumably facilitating the oxidative addition of otherwise unreactive aryl chlorides.

Although triaminophosphines (e.g., P[NMe<sub>2</sub>]<sub>3</sub>) are well-known, they have not been studied (prior to our previous studies<sup>4,5</sup>) in these cross-coupling reactions. This may be partly due to the diminished electron-donating capability of acyclic triaminophosphines (associated with their pseudo C<sub>2</sub> symmetry) compared with trialkylphosphines, as has been rationalized by Woollins recently.<sup>6</sup> We reasoned, however, that triaminophosphines could function as ligands if their framework were made fairly rigid but strain-free in a bicyclic (approximately C<sub>3v</sub>) structure, thus enhancing the lone pair electron density at phosphorus.<sup>7</sup> In accordance with this

(1) For reviews, see: (a) Muci, A. R.; Buchwald, S. L. *Top. Curr. Chem.* **2002**, *219*, 131. (b) Wolfe, J. P.; Wagaw, S.; Marcoux, J.-F.; Buchwald, S. L. *Acc. Chem. Res.* **1998**, *31*, 805. (c) Hartwig, J. F. *Acc. Chem. Res.* **1998**, *31*, 852. (d) Hartwig, J. F. *Angew. Chem., Int. Ed.* **1998**, *37*, 2046.

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(3) For representative examples of aryl chloride aminations, see: (a) Ehrentraut, A.; Zapf, A.; Beller, M. *J. Mol. Catal. A: Chem.* **2002**, *3494*, 1. (b) Grasa, G. A.; Viciu, M. S.; Huang, J.; Nolan, S. P. *J. Org. Chem.* **2001**, *66*, 7729. (c) Stauffer, S. R.; Lee, S.; Stambuli, J. P.; Hauck, S. I.; Hartwig, J. F. *Org. Lett.* **2000**, *2*, 1423. (d) Wolfe, J. P.; Tomori, H.; Sadighi, J. P.; Yin, J.; Buchwald, S. L. *J. Org. Chem.* **2000**, *65*, 1158. (e) Wolfe, J. P.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **1999**, *38*, 2413. (f) Bei, X.; Uno, T.; Norris, J.; Turner, H. W.; Weinberg, W. H.; Guram, A. S.

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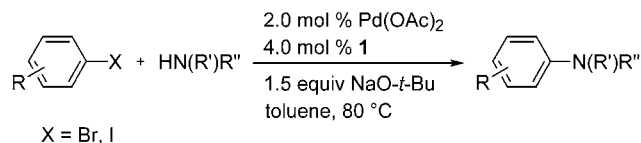
(4) Urgaonkar, S.; Nagarajan, M.; Verkade, J. G. *J. Org. Chem.* **2003**, *68*, 452.

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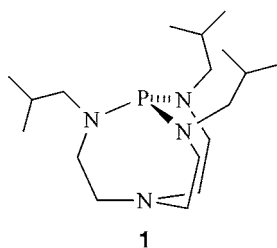
(6) (a) Clarke, M. L.; Cole-Hamilton, D. J.; Slawin, A. M. Z.; Woollins, J. D. *Chem. Commun.* **2000**, 2065. (b) Clarke, M. L.; Cole-Hamilton, D. J.; Woollins, J. D. *J. Chem. Soc., Dalton Trans.* **2001**, 2721.

rationale, we were able to demonstrate that commercially available ligand **1** in combination with Pd(OAc)<sub>2</sub> is a highly efficient catalytic system for the amination of aryl bromides and iodides (Scheme 1).<sup>4</sup> Additionally, we have demonstrated

**Scheme 1.** General Conditions Used for the Amination of Aryl Bromides and Iodides



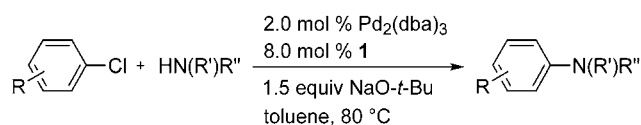
the unusually high activity of ligand **1** in Suzuki cross-couplings of aryl bromides and chlorides with arylboronic acids.<sup>5</sup>



In this contribution, we show that ligand **1** is also effective in the amination of aryl chlorides, thus identifying it as one of the very few ligands that efficiently facilitate amination reactions of aryl chlorides as well as those of aryl iodides and bromides.

The general conditions employed for the amination of aryl chlorides are summarized in Scheme 2. For anilines and

**Scheme 2.** General Conditions Used in the Present Study for the Amination of Aryl Chlorides



cyclic secondary amines, Pd<sub>2</sub>(dba)<sub>3</sub> as a palladium precursor instead of Pd(OAc)<sub>2</sub> in combination with **1** was found to be useful. Also, a slightly higher catalyst loading (4 mol % Pd) was required to obtain good to excellent yields of the arylamine products. However, the Pd(OAc)<sub>2</sub>/**1** catalyst system proved to be advantageous over Pd<sub>2</sub>(dba)<sub>3</sub>/**1**, for primary amines, and an acyclic secondary amine.

(7) For discussions of the electronic structure of tris(alkylamino)-phosphines, see: (a) Cowley, A. H.; Lattman, M.; Stricklen, P. M.; Verkade, J. G. *Inorg. Chem.* **1982**, *21*, 543. (b) Molloy, K. G.; Petersen, J. L. *J. Am. Chem. Soc.* **1995**, *117*, 7696. (c) Xi, S. K.; Schmidt, H.; Lensink, C.; Kim, S.; Wintergrass, D.; Daniels, L. M.; Jacobson, R. A.; Verkade, J. G. *Inorg. Chem.* **1990**, *29*, 2214. (d) Socol, S. M.; Jacobson, R. A.; Verkade, J. G. *Inorg. Chem.* **1984**, *23*, 88. (e) Romming, C.; Songstad, J. *Acta Chem. Scand., Ser. A.* **1980**, *34*, 365. (f) Romming, C.; Songstad, J. *Acta Chem. Scand., Ser. A.* **1979**, *33*, 187.

(8) 2,8,9-Triisobutyl-2,5,8,9-tetraaza-1-phosphabicyclo[3.3.3]undecane, Aldrich cat. no. 56,588-1.

As shown in Tables 1 and 2, electronically diverse aryl chlorides can be coupled to a variety of amines in the

**Table 1.** Amination of Aryl Chlorides with Anilines<sup>a</sup>

entry	chloride	amine	product	yield (%) <sup>b</sup>
1				88
2				90
3				94 <sup>c</sup>
4				87
5				99
6				88 <sup>c</sup>
7				87
8				98
9				95
10				91 <sup>c</sup>

<sup>a</sup> Conditions: 1.0 equiv of aryl chloride, 1.2 equiv of amine, 1.5 equiv of NaO-*t*-Bu, 2.0 mol % Pd<sub>2</sub>(dba)<sub>3</sub>, 8.0 mol % ligand **1**, 5 mL of toluene, 80 °C. <sup>b</sup> Isolated yields (average of at least two runs). <sup>c</sup> Performed with 4.0 mol % Pd<sub>2</sub>(dba)<sub>3</sub>.

presence of **1** and Pd<sub>2</sub>(dba)<sub>3</sub>. Both primary and secondary anilines were efficiently coupled with electron-poor, electron-neutral, and electron-rich aryl chlorides (Table 1). *ortho*-Substitution of the aryl chloride had a rather minor effect in cross-coupling efficiency. For example, while the reaction of 4-chlorotoluene with *p*-anisidine proceeded in 99% yield (entry 5, Table 1), the analogous reaction with 2-chlorotoluene gave an 87% yield (entry 7, Table 1) of the corresponding product. The reactions of sterically hindered and less nucleophilic diphenylamine, required a higher catalyst loading (8 mol % Pd). Secondary cyclic amines were also readily coupled, and the amination products were obtained in high

yields (entries 1–6, Table 2). In most cases, hydrodehalogenated arenes, resulting from competitive  $\beta$ -hydride elimination,<sup>9</sup> were the side products (<3%).

**Table 2.** Amination of Aryl Chlorides with Cyclic Secondary Amines<sup>a</sup>

entry	chloride	amine	product	yield (%) <sup>b</sup>
1				90
2				94
3				86
4				95
5				89
6				87

<sup>a</sup> Conditions are identical to those used in Table 1. <sup>b</sup> Isolated yields (average of at least two runs).

Notably, the reactions of chloropyridines also proceeded without difficulty with the Pd<sub>2</sub>(dba)<sub>3</sub>/1 catalyst system, giving rise to the desired products in good yields (Table 3).

**Table 3.** Amination of Chloropyridines<sup>a</sup>

entry	chloride	amine	product	yield (%) <sup>b</sup>
1				53
2				89
3				88
4				90
5				87
6				83

<sup>a</sup> Conditions are identical to those used in Table 1. <sup>b</sup> Isolated yields (average of at least two runs).

Generally, monodentate ligands [e.g., (*o*-tol)<sub>3</sub>P] are considered to be unsuitable for this class of substrates because they can compete with the pyridine substrates for palladium to form catalytically inactive *trans*-bis(pyridyl)palladium species.<sup>10</sup> However, the electron-richness of ligand 1 inhibits such side reactions.

With 4 mol % Pd<sub>2</sub>(dba)<sub>3</sub>, coupling of more recalcitrant amines (e.g., primary and acyclic secondary amines) was facilitated and the corresponding substituted anilines were obtained in moderate to good yields. For the aforementioned amines, 5 mol % Pd(OAc)<sub>2</sub> was found to give results comparable to those with Pd<sub>2</sub>(dba)<sub>3</sub> (8 mol % Pd), and therefore the former palladium compound was employed (Table 4) for the remainder of the study. The reaction of

**Table 4.** Amination of Aryl Chlorides with Primary Amines and an Acyclic Secondary Amine<sup>a</sup>

entry	chloride	amine	product	yield (%) <sup>b</sup>
1				90
2				91
3				63
4		<i>n</i> -HexNH <sub>2</sub>		49
5		<i>n</i> -HexNH <sub>2</sub>		43
6		Et <sub>2</sub> NH		56

<sup>a</sup> Conditions: 1.0 equiv of aryl chloride, 1.4 equiv of amine, 1.5 equiv of NaO-*t*-Bu, 5.0 mol % Pd(OAc)<sub>2</sub>, 10.0 mol % ligand 1, 5 mL of toluene, 80 °C. <sup>b</sup> Isolated yields (average of at least two runs).

cyclohexylamine, a cyclic primary amine, was especially efficient under these conditions, allowing a diverse group of aryl chlorides to be successfully employed (entries 1–3, Table 4). While reasonable yields were obtained for the coupling of 4-chlorobenzotrile and 3-chloroanisole with a long-chain primary aliphatic amine (*n*-hexylamine, entries 4 and 5, Table 4), the reaction of the acyclic secondary amine, diethylamine, proceeded only with an electron-poor aryl chloride (entry 6, Table 4).

For the reactions discussed in Table 4, we also observed the formation of hydrodehalogenated side products.

Although, in all cases, some of the reaction components were assembled inside a glovebox (i.e., NaO-*t*-Bu, a suitable Pd precursor and solid aryl chloride), we have found that its use is not an absolute requirement. Yields were very similar when all the reaction components were assembled outside a glovebox using standard Schlenk techniques. However, we recommend storing moisture-sensitive NaO-*t*-Bu in a desiccator if a glovebox is not available. Although ligand **1** is unusually stable to oxidation, it was stored in a closed container under an inert atmosphere.

Triaminophosphine **1** is the first member of a new class of phosphines shown to be an effective ligand in palladium-assisted C–N bond-forming reactions. Although the use of **1** requires higher loading than trialkylphosphines and also the use of a strong base (NaO-*t*-Bu), its low cost compared with other well-known ligands and its considerable ability to effect aminations of a broad spectrum of substrates favors it as a ligand of choice. Further, the effectiveness of **1** in promoting palladium-catalyzed coupling of amines with aryl chlorides as well as bromides and iodides broadens the utility

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(9) Based on TLC. For a proposed reaction mechanism, see (a) Alcazar-Roman, L. M.; Hartwig, J. F. *J. Am. Chem. Soc.* **2001**, *123*, 12950. (b) Mann, G.; Hartwig, J. F. *J. Am. Chem. Soc.* **1996**, *118*, 13109. (c) Also see refs 1a–d.

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of this compound beyond its well established use as a strong nonionic base in stoichiometric and base-catalyzed reactions.<sup>11</sup>

Although we presently do not have a clear understanding of the origin of the exceptional reactivity of our Pd/**1** catalyst system, our working hypothesis is that the effectiveness of ligand **1** arises from two factors: (a) phosphorus electron richness stemming from pseudo  $C_{3v}$  symmetry and possible N→P transannulation, thus enhancing the oxidative addition step, and (b) steric bulk provided by the *iso*-butyl groups, thus promoting the reductive elimination step. Studies underway are aimed at further optimization of the stereo-electronic properties of triaminophosphine ligands in metal-assisted reactions.

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**Supporting Information Available:** Experimental procedures and references for known compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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