#### C–N Coupling

### DOI: 10.1002/anie.200602222

### A Diaminochlorophosphine for Palladium-Catalyzed Arylations of Amines and Ketones\*\*

Lutz Ackermann,\* Julia H. Spatz, Christian J. Gschrei, Robert Born, and Andreas Althammer

Palladium-catalyzed amination reactions of aryl halides are indispensable tools for the synthesis of compounds with N-C(sp<sup>2</sup>) linkages.<sup>[1-4]</sup> Iodides and electronically activated bromides can be successfully transformed by employing simple palladium salts. Aryl chlorides, however, are arguably the most useful single class of substrates because of their lower cost and the wider diversity of available compounds. The conversion of arvl chlorides usually requires recently developed stabilizing ligands.<sup>[5]</sup> The ligand design has been focused predominantly on electron-rich tertiary phosphines.<sup>[6,7]</sup> Owing to their electron-rich nature tertiary phosphines and their transition-metal complexes are often prone to oxidation. An alternative approach makes use of complexes derived from air-stable secondary phosphine oxides.<sup>[8]</sup> However, applications of these catalysts to more challenging substrates, such as ortho-substituted aryl chlorides or acyclic alkyl amines,<sup>[9,10]</sup> have so far not been reported.<sup>[11]</sup>

Recently, we described the diaminooxophosphine (daop) ligand 2, which allowed for palladium-catalyzed amination reactions of electronically deactivated aryl chlorides.<sup>[12,13]</sup> During studies on the insitu generation of daop ligand 2 through salt elimination from the corresponding chlorophosphine 1,<sup>[14]</sup> we observed an initial oxidative addition of chloride 1 to a low-valent palladium species, thereby giving rise to a phosphenium cation.<sup>[12]</sup> Phosphenium cations are isolobal to N-heterocyclic singlet carbenes,<sup>[15,16]</sup> which are frequently employed in transition-metal catalysis.<sup>[7]</sup> Therefore, we wondered if a catalyst with a superior reactivity profile could be developed by preventing salt elimination and daop formation. Herein, we present a sterically hindered diaminochlorophosphine as ligand for efficient arylation reactions of amines and  $\alpha$ -C-H acidic ketones with ample scope.

[\*] Dr. L. Ackermann, Dipl.-Chem. J. H. Spatz, Dipl.-Chem. C. J. Gschrei, Dipl.-Chem. R. Born, Dipl.-Chem. A. Althammer
Department Chemie und Biochemie
Ludwig-Maximilians-Universität München
Butenandtstrasse 5–13, Haus F, 81377 München (Germany)
Fax: (+49) 89-2180-77425
E-mail: lutz.ackermann@cup.uni-muenchen.de
Homepage: http://www.cup.uni-muenchen.de/oc/ackermann/

[\*\*] Support by the DFG (Emmy Noether-Programm), the Fonds der Chemischen Industrie, Professor Paul Knochel, and the Ludwig-Maximilians-Universität is gratefully acknowledged. We thank Saltigo GmbH (Leverkusen) for the generous gift of chemicals.

Supporting information for this article is available on the WWW under http://www.angewandte.org or from the author.

Angew. Chem. Int. Ed. 2006, 45, 7627-7630

© 2006 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

InterScience 7627

Initial experiments were directed at probing the reactivity of various diaminochlorophosphines with respect to salt elimination with NaOtBu (Scheme 1). While diaminochlorophosphine 1 was quantitatively converted to daop 2 within two hours, no reaction occurred when using bulky chloride  $3^{[17]}$  under otherwise identical reaction conditions.



 $\label{eq:scheme 1. Salt elimination from diaminochlorophosphines with NaOtBu.$ 

The catalytic activity of sterically congested **3** was tested in the amination of electronically deactivated aryl chloride **5a** (Table 1). A palladium complex of **3** (Table 1, entry 3) proved

Table 1: Ligand studies for the amination of aryl chloride 5a.<sup>[a]</sup>

OMe 5a	+ O [Pd N L, N H toluene, 6a	(dba)₂] laOfBu 105 °C, 17h	O 7a	
Entry	[Pd(dba) <sub>2</sub> ] <sup>[b]</sup> (mol %)	L (mol%)	Yield [%] <sup>[c]</sup>	
1	5.0	1 (10.0)	63	
2	5.0	2 (10.0)	62	
3	5.0	3 (10.0)	98	
4	1.0	<b>3</b> (1.0)	32	
5	1.0	3 (2.0)	93	
6	0.5	<b>3</b> (1.0)	86	
7	5.0	4 (10.0)	31	

[a] Reaction conditions: **5a** (1.0 mmol), **6a** (1.2 mmol), NaOtBu (1.3 mmol), toluene (3.0 mL), 105 °C, 17 h. [b] dba = dibenzylideneace-tone. [c] Yield of isolated product.

more active than the ones generated from either chlorophosphine **1** or daop  $2^{[12]}$  (Table 1, entries 1 and 2). The superior catalytic performance allowed for a significant reduction of catalyst loading (Table 1, entries 5 and 6), with an optimal palladium/ligand ratio of 1:2 (Table 1, entries 4 and 5). Importantly, a complex derived from the corresponding daop **4** displayed a considerably reduced efficacy (Table 1, entry 7). These experiments highlight a different working mode for sterically hindered ligand **3**, when compared with the one observed for preligand **1**.<sup>[18]</sup>

Subsequently, the scope of the amination reaction with aryl chlorides was studied, with particular emphasis on more demanding substrate combinations (Table 2). Sterically hindered aniline derivatives were efficiently converted (Table 2, entries 1, 2, 5, 8, 9, and 13). Furthermore, high yields of isolated product were obtained using electron-rich, thereby electronically deactivated, aryl chlorides and bromides, even

# Communications

Table 2: Amination reactions with challenging substrates.<sup>[a]</sup>

			$R^1Cl$ + HNR <sup>2</sup>	[Pd(db	[Pd(dba) <sub>2</sub> ] (5.0 mol %)				
			5 6	<b>3</b> (10.0 tolu	<b>3</b> (10.0 mol %), NaO <i>t</i> Bu toluene, 105 °C		7		
Entry	Chloride	Amine	Product	Yield [%] <sup>[b]</sup>	Entry	Chloride	Amine	Product	Yield [%] <sup>[b]</sup>
1	сі БЪ	Me Me Me <b>6 b</b>	H N <sup>Mes</sup>	97	8	Me Me	Me Me Me <b>6 b</b>	Me Me <b>7</b> i <sup>[c]</sup>	98
2	CI Me 5 c	Me Me Me <b>6 b</b>	H <sub>N</sub> Mes Me <b>7 c</b> <sup>[c]</sup>	97	9	Me Me Me 10a	Me Me Me <b>6 b</b>	Me Me Me 7 j <sup>[c]</sup>	87
3	CI OMe 5 d	MH <sub>2</sub> Me 6 c	H <sub>N</sub> ρTol OMe 7 d	93	10	Me Me	NH2 InOct 6 f	H. N. nOct Me Me 7 k	94
4	CI OMe 5 d	MH <sub>2</sub> Me 6 d	H N OTO OMe 7 e	96	11	Me 5e	NH₂ ⊢ hHex 6g	Me Me 7 I	85
5	Me 5 e	€e	H <sub>N</sub> Ar Me <b>7 f</b> <sup>[d]</sup>	91	12	Me 5e	NH2 Рач <b>6 h</b>	Me Me 7 m	80
6	Me 5 e	MH <sub>2</sub> Me 6c	H. <sub>N</sub> ~ <sup>pTol</sup> Me 7 g	93	13	Ci N 5 f	Me Me <b>6 b</b>	H N <sup>-Mes</sup> N 7 n <sup>[c]</sup>	85
7	Me Kerie Me	MH <sub>2</sub> Me 6d	H N OTOI Me Me 7 h	88	14	сі Сі 5 b	HN <sup>. Me</sup>	Me. <sub>N</sub> .Ph	91

[a] Reaction conditions: **5** (1.0 mmol), **6** (1.2 mmol), NaOtBu (1.3 mmol), [Pd(dba)<sub>2</sub>] (5.0 mol%), **3** (10.0 mol%), toluene (3.0 mL), 105 °C, 2–21 h. [b] Yield of isolated product. [c] Mes = 2,4,6-Me<sub>3</sub>C<sub>6</sub>H<sub>2</sub>. [d] Ar = 2,6-(*i*Pr)<sub>2</sub>C<sub>6</sub>H<sub>3</sub>.

when bearing *ortho* substituents (Table 2, entries 3–12). Thus, tetra-*ortho*-substituted diaryl amines were prepared in high yields (Table 2, entries 5, 8, and 9). Acyclic alkyl amines are difficult substrates, as the palladium amide complexes derived thereof easily undergo  $\beta$ -hydride elimination.<sup>[3]</sup> Nonetheless, the catalyst formed from bulky **3** performed well in arylation reactions of alkyl amines (Table 2, entries 10–12). Also the synthesis of a heteroaromatic species or of a tertiary amine proceeded well (Table 2, entries 13, and 14, respectively).

Among representative secondary chlorophosphines, sterically hindered diaminochlorophosphine **3** exhibited superior catalytic performance in the  $\alpha$ -arylation<sup>[19]</sup> of ketone **8a** with aryl chloride **5a** (Table 3, entry 1, and the Supporting Information).

A palladium complex that was generated from ligand **3** proved applicable to the  $\alpha$ -arylation employing iodides, bromides, and chlorides (Table 3, entries 1–3). With respect to aryl chlorides, electronically deactivated electrophiles were efficiently converted, thus giving rise to the corresponding ketones with high yields of isolated product (Table 3, entries 4–11).

**Table 3:** Scope of the  $\alpha$ -arylation using electron-rich chlorides.<sup>[a]</sup>



[a] Reaction conditions: 8 (1.2 mmol), 5 (1.0 mmol), NaOtBu (1.3 mmol), [Pd(dba)<sub>2</sub>] (2.0 mol%), 3 (4.0 mol%), toluene (2.5 mL), 105 °C, 24 h. [b] Yield of isolated product.

In summary, we have demonstrated that sterically hindered substituents on the nitrogen atoms of secondary chlorophosphines prevent formation of diaminooxophosphines and thereby facilitate efficient palladium-catalyzed arylation reactions of amines and  $\alpha$ -C–H acidic ketones with ample scope. toluene (3.0 mL) was stirred for 10 min at room temperature under N<sub>2</sub>. NaOtBu (125 mg, 1.30 mmol), **6a** (103 mg, 1.18 mmol), and **5a** (147 mg, 1.03 mmol) were added, and the resulting mixture was stirred at 105 °C for 17 h. Et<sub>2</sub>O (50 mL) and brine (50 mL) were added to the cooled reaction mixture. The separated aqueous phase was extracted with Et<sub>2</sub>O ( $3 \times 50$  mL). The combined organic layers were dried over MgSO<sub>4</sub> and concentrated in vacuo. The remaining residue was purified by column chromatography on silica gel (*n*-pentane/ Et<sub>2</sub>O, 5:1 $\rightarrow$ 4:1) to yield **7a** as an orange solid (199 mg, 98%).

### **Experimental Section**

Representative procedure for the palladium-catalyzed amination of aryl chlorides (Table 1, entry 3): A solution of [Pd(dba)<sub>2</sub>] (29 mg, 0.05 mmol, 5.0 mol%) and **3** (44 mg, 0.10 mmol, 10.0 mol%) in

Received: June 2, 2006 Revised: July 25, 2006 Published online: October 17, 2006

## Communications

**Keywords:** arylation  $\cdot$  C–N coupling  $\cdot$  cross-coupling  $\cdot$  palladium  $\cdot$  phosphane ligands

- [1] B. Schlummer, U. Scholz, Adv. Synth. Catal. 2004, 346, 1599– 1626.
- [2] J. F. Hartwig in *Modern Arene Chemistry* (Ed.: D. Astruc), Wiley-VCH, Weinheim, 2002, pp. 107–168.
- [3] L. Jiang, S. L. Buchwald in *Metal-Catalyzed Cross-Coupling Reactions*, 2nd ed. (Eds.: A. de Meijere, F. Diederich), Wiley-VCH, Weinheim, 2004, pp. 699–760.
- [4] A. Zapf, M. Beller, T. Riermeier in *Transition Metals for Organic Synthesis*, 2nd ed. (Eds.: M. Beller, C. Bolm), Wiley-VCH, Weinheim, **2004**, pp. 231–256.
- [5] A. F. Littke, G. C. Fu, Angew. Chem. 2002, 114, 4350-4386; Angew. Chem. Int. Ed. 2002, 41, 4176-4211.
- [6] Selected recent examples: a) E. R. Strieter, S. L. Buchwald, Angew. Chem. 2006, 118, 939-942; Angew. Chem. Int. Ed. 2006, 45, 925-928; b) Q. Shen, S. Shekhar, J. P. Stambuli, J. F. Hartwig, Angew. Chem. 2005, 117, 1395-1399; Angew. Chem. Int. Ed. 2005, 44, 1371-1375; c) F. Rataboul, A. Zapf, R. Jackstell, S. Harkal, T. Riermeier, A. Monsees, U. Dingerdissen, M. Beller, Chem. Eur. J. 2004, 10, 2983-2990; d) M. Nishiyama, T. Yamamoto, Y. Koie, Tetrahedron Lett. 1998, 39, 617-620.
- [7] For the use of N-heterocyclic carbenes in catalysis, see: W. A. Herrmann, Angew. Chem. 2002, 114, 1342-1363; Angew. Chem. Int. Ed. 2002, 41, 1290-1309.
- [8] G. Y. Li, Angew. Chem. 2001, 113, 1561–1564; Angew. Chem. Int. Ed. 2001, 40, 1513–1516.
- [9] G. Y. Li, G. Zheng, A. F. Noonan, J. Org. Chem. 2001, 66, 8677 8681.
- [10] G. Burton, P. Cao, G. Li, R. Rivero, Org. Lett. 2003, 5, 4373-4376.
- [11] L. Ackermann, Synthesis 2006, 1557-1571.
- [12] L. Ackermann, R. Born, Angew. Chem. 2005, 117, 2497–2500; Angew. Chem. Int. Ed. 2005, 44, 2444–2447.
- [13] For the use of a triaminophosphine ligand, see: S. Urgaonkar, J.-H. Xu, J. G. Verkade, J. Org. Chem. 2003, 68, 8416–8423.
- [14] Examples for transition-metal-catalyzed coupling reactions employing air-stable heteroatom-substituted secondary phosphine oxides: a) L. Ackermann, R. Born, J. H. Spatz, D. Meyer, *Angew. Chem.* 2005, 117, 7382–7386; *Angew. Chem. Int. Ed.* 2005, 44, 7216–7219; b) L. Ackermann, *Org. Lett.* 2005, 7, 3123–3125; c) L. Ackermann, C. J. Gschrei, A. Althammer, M. Riederer, *Chem. Commun.* 2006, 1419–1421; d) L. Ackermann, A. Althammer, R. Born, *Angew. Chem.* 2006, 118, 2681–2685; *Angew. Chem. Int. Ed.* 2006, 45, 2619–2622; e) L. Ackermann, A. Althammer, *Org. Lett.* 2006, 8, 3457–3460.
- [15] D. Gudat, Coord. Chem. Rev. 1997, 163, 71-106.
- [16] H. Nakazawa, Adv. Organomet. Chem. 2004, 50, 107-143.
- [17] M. B. Abrams, B. L. Scott, R. T. Baker, Organometallics 2000, 19, 4944-4956.
- [18] Studies directed towards elucidating the catalyst's working mode were performed by employing either [Pd(dba)<sub>2</sub>] or [PdCl<sub>2</sub>-(PhCN)<sub>2</sub>]. Accordingly, addition of chlorophosphine 3 to a solution of [PdCl<sub>2</sub>(PhCN)<sub>2</sub>] in toluene yielded the catalytically active homobimetallic chlorophosphine complex [{LPdCl<sub>2</sub>}<sub>2</sub>] (L=3). For relevant coordination chemistry, see, for example: a) D. E. Berry, K. A. Beveridge, G. W. Bushnell, K. R. Dixon, *Can. J. Chem.* 1985, *63*, 2949–2957; b) reference [11].
- [19] D. C. Culkin, J. F. Hartwig, Acc. Chem. Res. 2003, 36, 234-245.