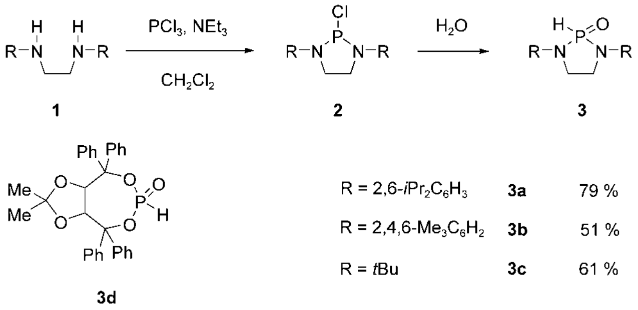
Catalyzed Cross-Couplings

Modular Diamino- and Dioxophosphine Oxides and Chlorides as Ligands for Transition-Metal-Catalyzed C–C and C–N Couplings with Aryl Chlorides**

Lutz Ackermann and Robert Born*

Transition-metal-catalyzed cross-coupling reactions[1] such as the Suzuki coupling[2] and the Buchwald–Hartwig amination[3] provide reliable tools in synthetic organic chemistry. Aryl iodides and activated aryl bromides can be transformed successfully using simple palladium salts. In contrast, analogous reactions of the more readily available aryl chlorides require recently developed stabilizing ligands.[4] While the ligand design focused primarily on electron-rich alkyl-substituted tertiary phosphines,[1,4,5] Li presented an alternative strategy that employs alkyl-substituted secondary phosphine oxides.[6,7] Their synthesis generally relies on the use of the corresponding metalated species,[6,8] thereby limiting the flexibility of this approach. On the other hand, heteroatom-substituted phosphine oxides are easily accessible from diamines, diols, and amino alcohols.[9,10] Hence, we wondered if phosphine oxides derived from diamines or diols could be utilized as ligands for the cross-coupling of aryl chlorides.[11,12] Herein, we present the first use of inexpensive air-stable diaminophosphine oxides in palladium-catalyzed Suzuki-type reactions of aryl chlorides. Furthermore, unprecedented applications of a diaminophosphine chloride[13] to palladium- and nickel-catalyzed C–C and C–N bond-forming reactions are reported.

We synthesized three sterically encumbered, air-stable phosphine oxides **3** directly from PCl_3 and the corresponding diamine in a one-pot procedure (Scheme 1). The reactivity of



Scheme 1. Synthesis of novel diaminophosphine oxides **3**.

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[*] Dr. L. Ackermann, R. Born
Ludwig-Maximilians-Universität München
Department Chemie und Biochemie
Butenandtstrasse 5–13, Haus F, 81377 München (Germany)
Fax: (+49) 89-2180-77425
E-mail: lutz.ackermann@cup.uni-muenchen.de

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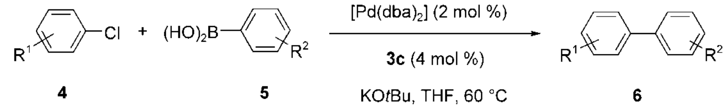
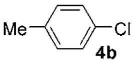
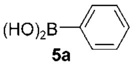
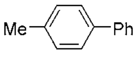
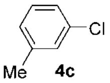
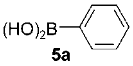
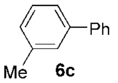
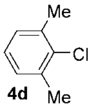
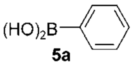
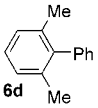
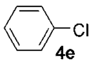
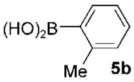
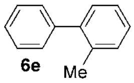
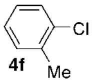
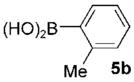
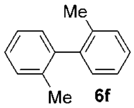
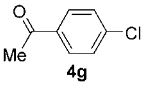
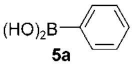
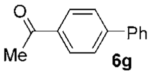
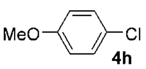
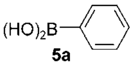
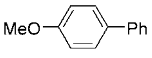
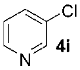
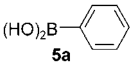
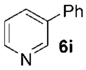
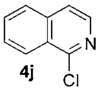
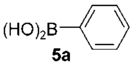
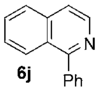
the complexes generated from diaminophosphine oxides **3a**–**c** as well as from taddol derivative **3d** was probed in the palladium-catalyzed Suzuki reaction of 4-chlorobenzotrifluoride (**4a**) with phenylboronic acid (**5a**) (Table 1). Preliminary experiments showed THF and KO*t*Bu to be the best solvent and bases, respectively, when the di(isopropyl)phenyl-substituted ligand **3a** was used. Although the reaction proceeded well at ambient temperature (entry 2), quantitative conversion of aryl chloride **4a** was achieved only with 5 mol% of the palladium catalyst (entries 3 and 4). Changing the substituents on nitrogen to mesityl groups resulted in decreased conversion (entry 5). A significant improvement of catalytic performance was accomplished with the sterically hindered ligand **3c** (entry 6) or the taddol derivative **3d** (entry 7).

The optimized catalyst system facilitated the efficient conversion of a representative set of electron-rich aryl chlorides (Table 2). In addition, the catalyst enabled the synthesis of *ortho*-substituted biaryls (entries 3–5) and the functionalization of heteroaromatic aryl chlorides (entries 8 and 9) with good to excellent yields of isolated product.

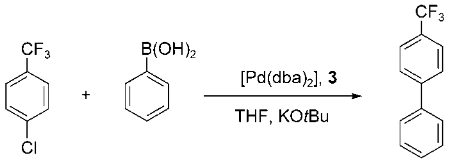
Table 2: Scope of the Suzuki cross-coupling reaction employing phosphine oxide **3c**.[a]



Entry	Aryl chloride	Boronic acid	Product	Yield [%][b]
1	 **4b**	 **5a**	 **6b**	75
2	 **4c**	 **5a**	 **6c**	78
3	 **4d**	 **5a**	 **6d**	70
4	 **4e**	 **5b**	 **6e**	93
5	 **4f**	 **5b**	 **6f**	95
6	 **4g**	 **5a**	 **6g**	81
7	 **4h**	 **5a**	 **6h**	70
8	 **4i**	 **5a**	 **6i**	88
9	 **4j**	 **5a**	 **6j**	94

[a] Reaction conditions: **4** (1.00 mmol), **5** (1.50 mmol), KO*t*Bu (3.00 mmol), [Pd(dba)$_2$] (2 mol%), **3c** (4 mol%), THF (5 mL). [b] Yield of isolated product.

Table 1: Air-stable phosphine oxides **3** in Suzuki cross-coupling reactions.[a]



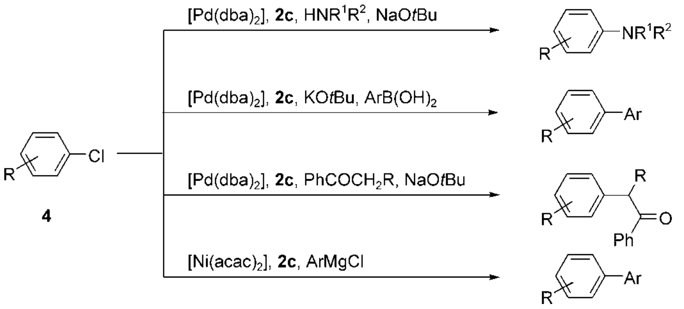
4a **5a** **6a**

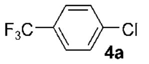
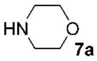
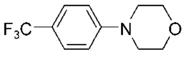
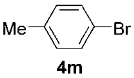
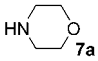
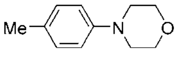
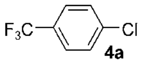
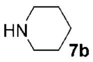
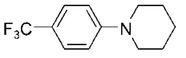
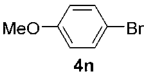
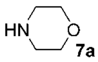
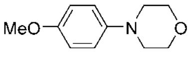
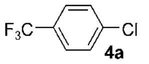
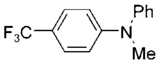
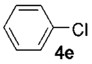
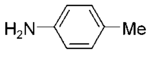
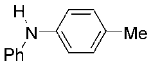
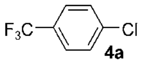
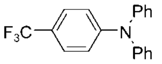
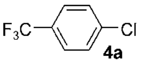
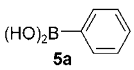
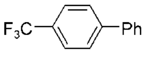
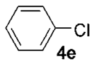
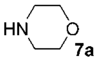
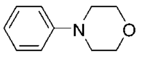
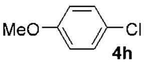
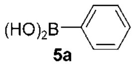
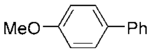
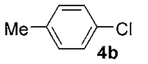
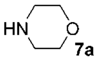
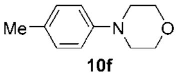
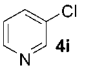
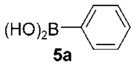
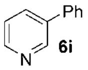
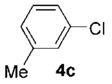
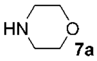
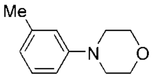
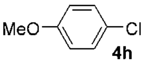
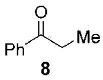
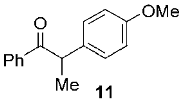
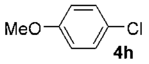
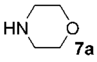
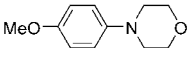
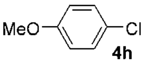
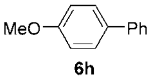
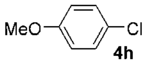
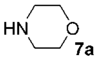
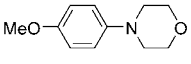
Entry	Ligand	[Pd(dba)]$_2$ [mol%]	*t* [h]	*T* [°C]	Yield [%][b]
1	–	2.0	12	60	<2
2	**3a**	5.0	14	20	83
3	**3a**	5.0	2	60	97
4	**3a**	2.0	18	60	68
5	**3b**	5.0	16	60	(12)[c]
6	**3c**	2.0	3	60	94
7	**3d**	2.0	11	60	92

[a] Reaction conditions: **4a** (1.00 mmol), **5a** (1.50 mmol), KO*t*Bu (3.00 mmol), [Pd(dba)$_2$]/**3** = 1:2, THF (5 mL); dba = dibenzylideneacetone. [b] Yield of isolated product. [c] Determined by GC analysis.

Application of diaminophosphine oxide **3c** to palladium-catalyzed Buchwald–Hartwig amination reactions led to unsatisfactory results, yielding predominantly the corresponding hydrodehalogenated arenes. However, during studies directed towards an in situ preparation of ligands we found that a complex generated from phosphine chloride **2c** and [Pd(dba)$_2$][14] resulted in efficient amination of aryl chlorides (Table 3). The protocol is applicable to various amines **7** (entries 1–4 and 12) and diversely substituted aryl chlorides **4** (entries 1 and 5–8), including deactivated 4-chloroanisole (**4h**) (entry 8). Analogous aryl bromides **4m** and **4n** were converted quantitatively but provided only slightly improved yields of isolated product due to reduction of the aryl halide (entries 10 and 11). It is worth noting that the use of chloride **2c** enabled efficient conversion of deactivated chloroanisole **4h** in a representative set of palladium- and nickel-catalyzed reactions such as Suzuki reaction (entry 14), Buchwald arylation of ketone **8** (entry 16), and nickel-catalyzed Kumada cross-coupling with Grignard reagent **9** (entry 17). While pyridine **6i** was obtained in excellent yield (entry 15), the synthesis of tetra-*ortho*-substituted biaryls was not viable.[5a,15]

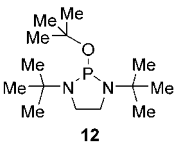
Table 3: Transition-metal-catalyzed coupling reactions of aryl chlorides **4** using phosphine chloride **2c** (see Scheme 1; R = *t*Bu).[a]



Entry	Aryl halide	Pronucleophile	*t* [h]	Product	Yield [%][b]	Entry	Aryl halide	Pronucleophile	*t* [h]	Product	Yield [%][b]
1	 **4a**	 **7a**	3	 **10a**	82	10	 **4m**	 **7a**	1	 **10f**	83
2	 **4a**	 **7b**	3	 **10b**	81	11	 **4n**	 **7a**	1	 **10h**	68
3	 **4a**	PhNHMe **7c**	2	 **10c**	80	12	 **4e**	 **7e**	20	 **10i**	62[d]
4	 **4a**	Ph$_2$NH **7d**	12	 **10d**	59	13	 **4a**	 **5a**	15	 **6a**	89
5	 **4e**	 **7a**	5	 **10e**	81	14	 **4h**	 **5a**	20	 **6h**	62
6	 **4b**	 **7a**	16	 **10f**	75	15	 **4i**	 **5a**	2	 **6i**	91
7	 **4c**	 **7a**	5	 **10g**	81	16	 **4h**	 **8**	24	 **11**	60
8	 **4h**	 **7a**	6	 **10h**	63	17	 **4h**	PhMgCl **9**	24	 **6h**	64
9	 **4h**	 **7a**	8	 **10h**	62[c]						

[a] General reaction conditions: Amination: **4** (1.00 mmol), **7** (1.20 mmol), NaO*t*Bu (1.30 mmol), [Pd(dba)$_2$] (5 mol%), **2c** (10 mol%), toluene (2.5 mL), 105 °C. Ketone arylation: **4** (1.00 mmol), **8** (1.20 mmol), NaO*t*Bu (1.30 mmol), [Pd(dba)$_2$] (2 mol%), **2c** (4 mol%), toluene (2.5 mL), 105 °C. Kumada reaction: **4** (1.00 mmol), **9** (1.50 mmol), [Ni(acac)$_2$] (3 mol%), **2c** (3 mol%) in THF (5 mL), 20 °C. Suzuki reaction: **4** (1.00 mmol), **5** (1.50 mmol), KO*t*Bu (3.00 mmol), [Pd(dba)$_2$] (5 mol%), **2c** (10 mol%), THF (5 mL), 60 °C. [b] Yield of isolated product. [c] Using **12** (10 mol%) instead of **2c**. [d] Conversion, determined by GC analysis.

NMR studies directed towards elucidating the catalyst's mode of action in amination reactions were performed. Addition of phosphine chloride **2c** to a solution of [Pd(dba)$_2$] in toluene gave rise to a compound displaying a singlet low-field resonance at $\delta = 308.7$ ppm in the ^{31}P NMR spectrum, suggesting the formation of a phosphenium species.[14] Upon addition of an excess NaO*t*Bu to this mixture, phosphine **12** ($\delta = 110.3$ ppm) was formed along with a compound exhibiting a resonance at $\delta = 115.2$ ppm, which was also selectively generated by reaction of phosphine **12** with [Pd(dba)$_2$].



12

In the amination reaction of aryl chloride **4h** the system **12**/[Pd(dba)$_2$] exhibited catalytic activity comparable to that observed with **2c**/[Pd(dba)$_2$] (Table 3, entries 8 and 9). To the best of our knowledge, this is an unprecedented example for the use of a highly modular, diaminooxophosphine (daop) ligand in palladium-catalyzed amination reactions of deactivated aryl chlorides.[11]

In summary, we have presented the use of air-stable diamino- and dioxophosphine oxides as ligands in palladium-catalyzed Suzuki reactions of aryl chlorides. The unprecedented use of a diaminophosphine chloride as a ligand precursor in palladium- and nickel-catalyzed C–C and C–N bond-forming reactions of aryl chlorides has also been demonstrated. Further studies are directed towards an improvement of the present systems.

Experimental Section

Representative procedure for palladium-catalyzed amination using phosphine chloride **2c** (Table 3, entry 8): A solution of [Pd(dba)$_2$] (29 mg, 0.05 mmol, 5 mol%) and phosphine chloride **2c** (23 mg, 0.10 mmol, 10 mol%) in toluene (2.5 mL) was stirred for 10 min at ambient temperature under N$_2$. NaO*t*Bu (125 mg, 1.3 mmol), morpholine (**7a**) (105 mg, 1.2 mmol), and 4-chloroanisole (**4h**) (142 mg, 1.00 mmol) were added, and the resulting mixture was stirred at 105 °C for 6 h. Et$_2$O (50 mL) and brine (50 mL) were added to the cold reaction mixture. The separated aqueous phase was extracted with Et$_2$O (2 × 50 mL). The combined organic layers were dried over MgSO$_4$ and concentrated in vacuo. The remaining residue was purified by column chromatography on silica gel (*n*-pentane/Et$_2$O, 4:1→2:1) to yield **10h** as a white solid (121 mg, 63%).

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