[17] The reaction with NaOH as the additive was somewhat less clean than the reaction with CsF.

[18] General experimental: Under an atmosphere of argon or N_2, a solution of aryl chloride (1.0 mmol; in dioxane (0.5 – 0.6 mL)) and a solution of P*t*Bu$_3$ (0.060 mmol; in dioxane (0.5 – 0.4 mL)) were added in turn to a Schlenk tube charged with [$Pd_2(dba)_3$] (0.015 mmol) and CsF (2.2 mmol). The organostannane (1.05 mmol) was then added by syringe, and the Schlenk tube was sealed, placed in an 80 – 100 °C oil bath, and stirred for 12 – 48 h. The reaction mixture was then cooled to room temperature, diluted with Et_2O, and filtered through a pad of silica gel. The silica gel was washed thoroughly with Et_2O, and the combined Et_2O washings were concentrated by rotary evaporation. The product was then purified by flash chromatography.

[19] Notes: a) These cross-coupling reactions do not appear to be highly air- or moisture-sensitive. For example, they can be conducted in reagent-grade dioxane through which argon has been bubbled. b) In the absence of [$Pd_2(dba)_3$] or of P*t*Bu$_3$, no reaction (<2 % conversion) is observed. c) The reactions proceed to completion with only 1.1 equiv of CsF and with only 3.6 % P*t*Bu$_3$, but more slowly than under the conditions described in reference [18]. d) The reaction is slower with PCy_3 than with P*t*Bu$_3$, and it does not proceed in the presence of electron-rich and sterically hindered tris(2,4,6-trimethoxyphenyl)phosphane. e) Cross-couplings in THF proceed with comparable efficiency as in dioxane; reactions in toluene are somewhat slower. f) [$Pd(OAc)_2$] is inferior to [$Pd_2(dba)_3$] as a catalyst precursor. g) Lower catalyst loadings may be used in these Stille couplings, at the expense of slightly lower yields. For example, cross-coupling of 4-*n*-butyl-1-chlorobenzene with tributyl(vinyl)tin in the presence of 0.25 % [$Pd_2(dba)_3$] and 1.0 % P*t*Bu$_3$ affords 4-*n*-butylstyrene in 67 % yield.

[20] *Metal-catalyzed Cross-coupling Reactions* (Eds.: F. Diederich, P. J. Stang), WILEY-VCH, New York, **1998**.

[21] In the Stille cross-couplings of the other organostannanes illustrated in Table 3, essentially no butyl transfer is observed (<2 %).

[22] For a general discussion of the problem of separating reaction products from organotin residues, see: D. Crich, S. Sun, *J. Org. Chem.* **1996**, *61*, 7200 – 7201.

[23] M. Hoshino, P. Degenkolb, D. P. Curran, *J. Org. Chem.* **1997**, *62*, 8341 – 8349; D. P. Curran, *Angew. Chem.* **1998**, *110*, 1230 – 1255; *Angew. Chem. Int. Ed.* **1998**, *37*, 1174 – 1196.

[24] a) Addition of fluoride (e.g., KF) after a reaction is complete is a common method for removing organotin halide impurities: D. Milstein, J. K. Stille, *J. Am. Chem. Soc.* **1978**, *100*, 3636 – 3638; J. E. Liebner, J. Jacobus, *J. Org. Chem.* **1979**, *44*, 449 – 450. b) Stille and Scott have reported that the addition of CsF to cross-coupling reactions of vinyl triflates with organotin compounds leads to ~80 % removal of tin: W. J. Scott, J. K. Stille, *J. Am. Chem. Soc.* **1986**, *108*, 3033 – 3040. c) Under our conditions, we do not detect any Bu_3SnCl at the end of the reaction.

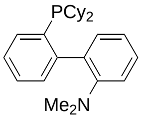
A Highly Active Catalyst for the Room-Temperature Amination and Suzuki Coupling of Aryl Chlorides[**]

John P. Wolfe and Stephen L. Buchwald*

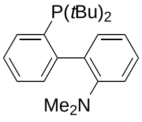
Palladium-catalyzed amination[1] and Suzuki coupling[2] reactions have found widespread use in many areas of organic synthesis. These methods permit the construction of C_{sp^2}–C_{sp^2} bonds or C_{aryl}–N bonds which cannot be easily or efficiently formed using classical transformations. Most procedures commonly used for these processes employ triarylphosphane-based catalyst systems.[1, 2] While these catalysts are readily available, they usually require elevated reaction temperatures (usually 50 – 100 °C) to function efficiently, and tend to be unreactive towards aryl chloride substrates.[3–5]

We recently reported that 2-dicyclohexylphosphanyl-2′-dimethylaminobiphenyl (**1**, Cy = cyclohexyl) was an excellent ligand for palladium-catalyzed cross-coupling reactions of aryl chlorides.[6] Although the Pd/**1** catalyst system was effective for the room-temperature Suzuki coupling of both electron-rich and electron-deficient aryl chloride substrates,[7] room-temperature catalytic aminations of aryl chlorides were inefficient; only the highly activated 4-chlorobenzonitrile was effectively transformed.

Subsequent studies demonstrated that the bulky phosphane **2** was a more effective ligand than **1** in palladium-catalyzed C–O bond forming reactions, presumably due to its ability to increase the rate of reductive elimination in these processes.[5g, 8] Furthermore, experiments designed to determine whether the amino group on **2** was necessary for effective catalysis revealed that for some substrate combinations the desamino ligand **4** was as effective as **2**, prompting us to examine the use of **4** in amination processes.[9]



1



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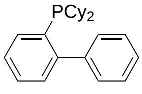
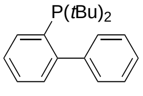


3



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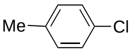
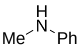
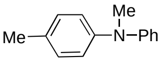
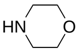
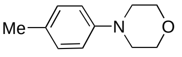
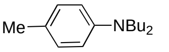
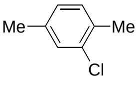
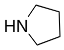
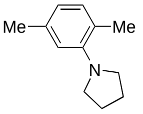
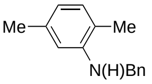
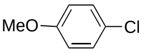
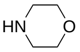
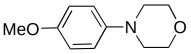
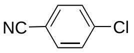
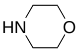
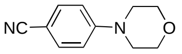
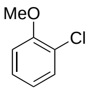
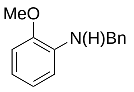
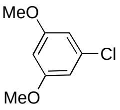
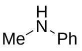
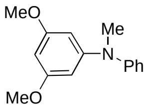
Supporting information for this article is available on the WWW under http://www.wiley-vch.de/home/angewandte/ or from the author.

As shown in Table 1, mixtures of palladium acetate and **4** effectively catalyzed the room-temperature amination of a variety of aryl chloride substrates, including substrates which are electron-rich and/or *ortho*-substituted. Secondary amines were found to be effective coupling partners, and primary amines were successfully arylated with *ortho*-substituted aryl halides. Reactions of primary amines with aryl halides that lack *ortho* substituents failed to proceed to completion under these conditions,[10] and substrates containing base-sensitive functional groups could not be transformed due to the inefficiency of the room-temperature reactions in the presence of bases weaker than NaO*t*Bu (e.g. K_3PO_4).[10] In a few cases the amination reactions of aryl chlorides were effected using low catalyst loadings (0.05 mol% Pd) with **3** or **4** as ligand at 100 °C (Table 1, entries 1, 2). However, this protocol of low catalyst amount is not yet general.[10]

Catalysts based on ligand **4** were also effective for the room-temperature Suzuki coupling of aryl chlorides using 1.0–1.5 mol% Pd in the presence of a stoichiometric amount of KF. These conditions tolerate the presence of a wide variety of functional groups, and provide the desired products in excellent yields (Table 2).[11]

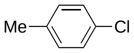
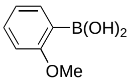
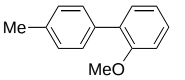
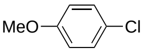
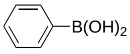
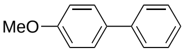
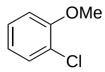
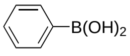
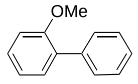
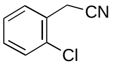
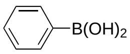
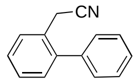
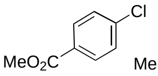
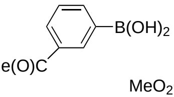
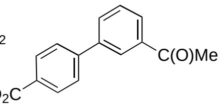
Use of catalysts based on **3** or **4** at 100 °C allowed for effective Suzuki coupling at low catalyst loadings; higher turnover numbers were usually obtained with **3** (Table 3).[12] The coupling of 4-bromoacetophenone with phenylboronic acid (entry 3) was achieved with 10^{-6} mol% Pd (10^8 turnovers),[13] although a control reaction conducted in the absence of phosphane ligands proceeded to completion with 10^{-3} mol% $Pd(OAc)_2$, suggesting that reactions of this substrate combination are particularly facile.[14] Aryl chlorides were effectively coupled with 0.02–0.05 mol% Pd, the lowest catalyst loadings reported thus far for the Suzuki coupling of aryl chlorides.[13a]

Table 1. Room-temperature catalytic amination of aryl chlorides.[a]

Entry	Halide	Amine	Product	Mol% Pd	*t* [h]	Yield [%]
1				1.0 0.005	19 19	98 95[b]
2				1.0 0.05/**3**	20 26	94 89[b]
3		HNBu$_2$		2.0	18	81
4				1.0	21	98
5		H$_2$NBn		2.0	18	99
6				2.0	20	90
7				1.0	15	86
8		H$_2$NBn		1.0	14	99
9				1.0	16	97

[a] Reaction conditions: 1.0 equiv of aryl chloride, 1.2 equiv of amine, 1.4 equiv of NaO*t*Bu, 1–2 mol% $Pd(OAc)_2$, 2–4 mol% **4**, toluene (1 mL per mmol of halide), room temperature. Reaction times *t* have not been minimized. The yields given represent yields of isolated product (average of two or more experiments) estimated to be ≥95% pure by ^1H NMR spectroscopy and GC analysis (known compounds) or combustion analysis (new compounds). [b] The reaction was run at 100 °C using $[Pd_2(dba)_3]$ in place of $Pd(OAc)_2$. Bn = benzyl; dba = *trans*,*trans*-dibenzylideneacetone.

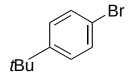
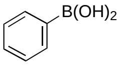
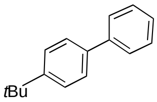
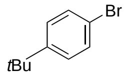
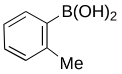
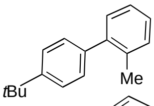
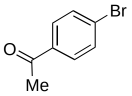
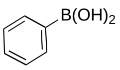
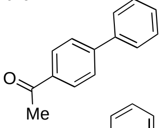
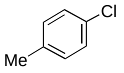
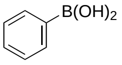
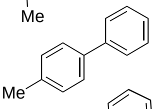
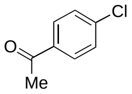
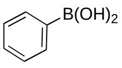
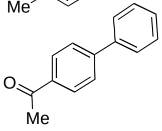
Table 2. Room-temperature Suzuki coupling of aryl chlorides.[a]

Entry	Halide	Boronic acid	Product	Mol% Pd	*t* [h]	Yield [%]
1				1	24	95
2				1.5	21	92
3				1	24	96
4				1	20	91
5				1	2	91

[a] Reaction conditions: 1.0 equiv of aryl chloride, 1.5 equiv of boronic acid, 3.0 equiv of KF, cat. $Pd(OAc)_2$, cat. **4** (two ligands per Pd center), THF (1 mL per mmol of aryl chloride), room temperature. Reaction times *t* have not been minimized.

Although the reasons for the high activity of catalysts supported by **3** and **4** are not well understood at this time, we believe that several structural features of the ligands are of importance. The electron-rich phosphane facilitates oxidative addition of the aryl chloride[15] and binds tightly to the metal to prevent precipitation of the catalyst. The steric encumbrance of the ligands promotes reductive elimination,[8] and examination of models reveals that the *o*-phenyl moiety may be oriented such that a favorable interaction between the aromatic π system and the metal orbitals occurs.[16] This interaction may also orient the arene ring of the substrate perpendicular to the N–Pd bond, placing it in the stereoelectronically optimum arrange-

Table 3. Suzuki coupling at low catalyst loading.[a]

Entry	Halide	Boronic acid	Product	Mol % Pd	Ligand	t [h]	Yield [%]
1				2×10^{-2} 5×10^{-3}	4 3	26 16	92 93
2				5×10^{-3}	3	20	96
3				1×10^{-3} 1×10^{-3} 1×10^{-6}	4 – 4	19 19 24	96[e] 100[b] 91[c]
4				1×10^{-1} 5×10^{-2}	4 3	25 25	95 94[d]
5				2×10^{-2}	4	23	92

[a] Reaction conditions: 1.0 equiv of aryl halide, 1.5 equiv of boronic acid, 2.0 equiv of K_3PO_4, cat. $Pd(OAc)_2$, cat. ligand (two ligands per Pd center), toluene (3 mL per mmol of halide), 100 °C. Reaction times t have not been minimized. All reactions proceeded to completion unless otherwise noted. [b] Yield according to GC. [c] Result of two experiments, one proceeded to only 99% conversion. [d] The reaction proceeded to 99% conversion. [e] $Pd_2(dba)_3$ used in place of $Pd(OAc)_2$.

ment for reductive elimination to take place.[17] The combination of these effects serve to accelerate oxidative addition without inhibition of transmetalation or reductive elimination.

In conclusion, we have developed a new, highly active catalyst system based on ligand **4** for the palladium-catalyzed amination and Suzuki coupling of aryl chlorides at room temperature and at low catalyst loading. Although **4** provides better results for room-temperature reactions, **3** is frequently more effective for reactions with low levels of the palladium catalyst and for Suzuki coupling reactions of very hindered substrates.[12] The mild reaction conditions employed for these transformations provide further evidence that the oxidative addition of aryl chlorides to complexes of Pd^0 can be induced to occur at low temperatures when catalysts which possess suitable steric and electronic properties are used.

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[9] Ligands **3** and **4** are air-stable, crystalline solids which are prepared in one step. These ligands are now commercially available from Strem Chemical Co.

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[11] The scope and limitations of Suzuki couplings which employ **3** or **4** will be the subject of a full paper.

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[14] Under these conditions, Suzuki coupling reactions of other substrates give little or no products in the absence of phosphane ligands.

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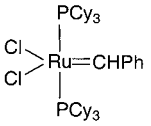
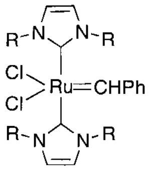
Highly Active Ruthenium Catalysts for Olefin Metathesis: The Synergy of N-Heterocyclic Carbenes and Coordinatively Labile Ligands[**]

Thomas Weskamp, Florian J. Kohl,
Wolfgang Hieringer, Dieter Gleich, and
Wolfgang A. Herrmann*

N-Heterocyclic carbenes (NHCs) have been established in homogeneous catalysis to complement and extend the capabilities of the ubiquitous phosphanes.[1, 2] In olefin metathesis[3] ruthenium alkylidene compounds **2**[4] bearing two NHC ligands exhibit a catalytic activity comparable to that of the phosphane system **1**.[5] Herein, we show that it is the combination of NHCs with coordinatively more labile ligands on the ruthenium center that allows NHCs to develop their full potential in this class of catalysts.



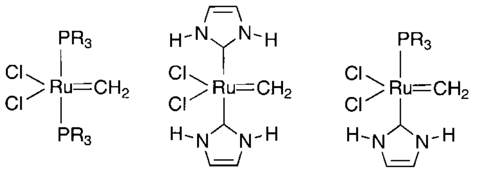
1



2

2a: R = Isopropyl
2b: R = Cyclohexyl (Cy)

In the catalytic cycle of olefin metathesis the mechanistic scheme for **1** postulates the dissociation of a phosphane ligand as the key step in the dominant reaction pathway.[6] Theoretical investigations of Group 11 transition metal NHC complexes, which suggest a strong metal–NHC bond,[7] raise the question as to whether this mechanism can be transferred to metathesis catalysts of type **2**. To address this problem we calculated the dissociation energies of NHC and phosphanes for ruthenium–alkylidene model compounds (Figure 1) according to Equation (1) by density functional (DFT) methods.[8, 9] The results compiled in Table 1 demonstrate that the ligand dissociation energies ascend in the series $PH_3 < PMe_3 < NHC$.[10a] As a consequence of the higher coordination energy the dicarbene complexes **2** should disfavor a dissociative pathway similar to that of **1**.[6] A mixed NHC/phosphane complex of type **3**, however, reveals a phosphane dissociation energy in the same order of magnitude as **1**. Therefore, **3** should be able to populate the dissociative pathway[6] just as readily as **1**. In contrast to **1**, however, a phosphane-free species **A** is considered as the key intermediate in the catalytic cycle.

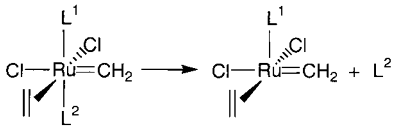


1m: R = H
1n: R = Methyl

2m

3m: R = H
3n: R = Methyl

Figure 1. Model compounds for the calculation of ligand dissociation energies.



(1)

Table 1. Calculated ligand dissociation energies ΔE [kcal mol^{-1}] for the model compounds as depicted in Equation (1).[a]

Model compound	ΔE for PH_3	ΔE for PMe_3	ΔE for NHC
1m ($L^1 = L^2 = PH_3$)	18.2 (19.4)	–	–
1n ($L^1 = L^2 = PMe_3$)	–	27.0 (25.8)	–
2m ($L^1 = L^2 = NHC$)	–	–	45.0 (42.2)
3m ($L^1 = PH_3$; $L^2 = NHC$)	18.7 (15.8)	–	46.9 (49.7)
3n ($L^1 = PMe_3$; $L^2 = NHC$)	–	26.0 (24.9)	42.0 (43.4)

[a] Ligand dissociation energies without ethylene coordination are given in brackets.

The air-stable NHC/phosphane complexes **3a–c** are accessible in excellent yields by adding 1.2 equivalents of the appropriate NHC to a solution of **1** in THF.[11] Low temperature is crucial for the selectivity of the phosphane/NHC substitution reaction. At room temperature the selectivity is

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