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Suzuki Cross-Coupling Reactions Catalyzed by an Aliphatic Phosphine-Based Pincer Complex of Palladium: Evidence for a Molecular Mechanism

Roman Gerber, Olivier Blacque, and Christian M. Frech*[a]

A new phosphine-based pincer complex with an adamantyl core, [{$C_{10}H_{13}$-1,3-$(CH_2PCy_2)_2$}Pd(Cl)] (**1**), has proved to be an excellent Suzuki catalyst. Catalyst **1** enables the quantitative coupling of a wide variety of electronically activated, deactivated, and/or sterically hindered and highly functionalized aryl bromides with phenylboronic acid in pure water with NaOH as base within very short reaction times and low catalyst loadings and without the need for exclusion of air. Hydrophobic substrates, which lead to inefficient conversions in aqueous solution, are efficiently and quantitatively coupled by **1** in toluene with K_3PO_4 as base. Mechanistic investigations indicate that palladium nanoparticles are probably not the catalytically active form of **1**. Experimental results strongly indicate that the phenyl pincer complex [{$C_{10}H_{13}$-1,3-$(CH_2PCy_2)_2$}Pd(Ph)] (**3**) is a key intermediate in the catalytic cycle of the Suzuki reaction in both toluene and aqueous solution. Treatment of **1** with phenylboronic acid exclusively yields **3** under catalytic reaction conditions. Moreover, stoichiometric reactions of **3** with aryl bromides lead to the exclusive formation of [{$C_{10}H_{13}$-1,3-$(CH_2PCy_2)_2$}Pd(Br)] (**2**) and the corresponding biaryl, thus indicating that biaryl formation occurs either by oxidative addition of aryl bromides to **3**, to form neutral hexacoordinated pincer-type Pd^{IV} intermediates with the general formula of [{$C_{10}H_{13}$-1,3-$(CH_2PCy_2)_2$}Pd(Ar)(Br)(Ph)], followed by reductive elimination of the coupling products or by direct biaryl formation on the Pd^{II} center of **3**, via a four-centered transition state.

Introduction

The Suzuki–Miyaura reaction of aryl halides with arylboronic acids belong nowadays to an indispensable set of palladium-catalyzed cross-coupling reactions and is one of the most important methods for the formation of symmetric and non-symmetric biaryls,[1–3] which are found in polymers,[4] biologically active compounds,[5] ligands,[6] and various other materials.[7] Although recent developments have led to a considerable increase in the activity of Suzuki catalysts, of which some are very efficient, allowing the use of sterically hindered substrates and even aryl chlorides at low catalyst loadings and occasionally at room temperature, a typical reaction protocol still requires prolonged reaction times and relatively high catalyst loadings. Furthermore, many of these catalysts suffer from their poor thermal stability, low functional group tolerance and sensitivity towards both air and moisture and hence require inconvenient inert-atmosphere techniques for their successful use.[8–11] Water is a cheap, readily available, nonflammable, nontoxic solvent and, consequently, one of the most attractive solvent systems, especially for industrial applications.[12] However, few systems have been reported which allow Suzuki reactions to be carried out in air and in aqueous media.[13–16] Moreover, even though some of them efficiently couple aryl halides with arylboronic acids, most of the reported systems are tested with "simple" aryl bromides and additionally exhibit too low activity to be industrially viable. Thus the development of new and stable catalysts with high functional group tolerance, that allow Suzuki reactions to be carried out efficiently in aqueous media without need for the exclusion of air, would be of high general interest. The problem of low substrate solubility in water, which could be the reason for inefficient conversions, can be solved to some extent by the use of phase-transfer catalysts or mixed-aqueous solvent systems.[13]

Pincer complexes of palladium are some of the most active Heck and Suzuki catalysts and continuously attract attention because of their unique balance between stability and reactivity. Seemingly slight electronic and steric modifications of the pincer core and/or the phosphine substituents can dramatically influence their catalytic activities.[17,18]

We report herein the synthesis and catalytic activity of a new phosphine-based pincer complex of palladium with an adamantyl core and the formula of [{$C_{10}H_{13}$-1,3-$(CH_2PCy_2)_2$}Pd(Cl)] (**1**) in Suzuki–Miyaura cross-coupling reactions performed in air and water. An aliphatic pincer core was chosen because of its higher σ-donating properties and its stronger *trans* influence when compared to its phenyl analogue.[19] Whereas the higher electron density on the metal center should facilitate the C–X bond activation of the aryl halides, the stronger *trans* influence should weaken the Pd–C_{aryl} bond and thus, promote aryl migration (C–C bond formation) if aryl pincer complexes are part of the catalytic cycle.[22] Although nowadays pincer-type Heck catalysts are, in most

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cases, considered as depot forms of palladium nanoparticles, the involvement of pincer-type Pd^{IV} intermediates in catalytic cycles in reactions with aryl halides at elevated temperatures cannot be excluded. In contrast, recent experimental observations and computational studies demonstrated that pincer-type Pd^{IV} intermediates of aminophosphine-based systems are thermally accessible and hence, could also be relevant in catalytic transformations, such as the Suzuki reaction.[17d] Our experimental results indicate that palladium nanoparticles are most probably not the catalytically active form of **1**, whereas initial formation of the phenyl pincer complex [{$C_{10}H_{13}$-1,3-$(CH_2PCy_2)_2$}Pd(Ph)] and its involvement in the catalytic cycle were strongly supported by experimental results. Thus, biaryl formation is thought to occur either via neutral hexacoordinated bromo diphenyl pincer-type Pd^{IV} intermediates, with the general formula [{$C_{10}H_{13}$-1,3-$(CH_2PCy_2)_2$}Pd(Ar)(Br)(Ph)], or on the Pd^{II} metal center of the phenyl pincer complex directly, via four-centered transition states.

When a slight excess (1.1 equivalents) of 1,3-bis(dicyclohexylphosphinomethyl)adamantane was added under N_2 to dioxane solutions of [Pd(cod)$(Cl)_2$] (cod = 1,5-cyclooctadiene) and stirred for 3 h at 100 °C in presence of a slight excess (1.2 equivalents relative to palladium) of K_3PO_4, [{$C_{10}H_{13}$-1,3-$(CH_2PCy_2)_2$}Pd(Cl)] (**1**) was formed. Removal of volatiles under reduced pressure and subsequent extraction with pentane/diethyl ether (1:1) gave pure **1** in moderate yields.[20] The $^{31}P\{^1H\}$ NMR spectrum of **1** showed a sharp singlet at $\delta = 52.64$ ppm. The signals attributable to the cyclohexyl and the adamantyl units appeared in the ^1H NMR spectrum as a broad multiplet at $\delta = 1.06$–2.31 ppm. The PdCH hydrogen atom gave rise to a broad singlet at $\delta = 2.76$ ppm. The $^{13}C\{^1H\}$ NMR spectrum displayed, in addition to the peaks for aliphatic carbon atoms, a triplet at $\delta = 72.5$ ppm with a coupling constant of $^2J(P,C) = 2.5$ Hz, which was assigned to the palladium-coordinated carbon atom.[23] The cyclometalation process was confirmed by X-ray crystallography (Figure 1). The solid-state structure of **1** (Figure 1a) exhibits a slightly distorted square-planar geometry around the Pd^{II} center (C3-Pd1-Cl1 = 174.3(2)°, P1-Pd1-P2 = 166.33(6)°). The Pd1–C1 bond measures 2.090(6) Å, and hence is of the expected length.[25] The Pd–Cl bond length is 2.412(2) Å, the Pd–P bond distances are 2.294(2) and 2.290(2) Å, respectively.

Complex **1** is thermally extremely stable and no decomposition was detected within one week when *p*-xylene solutions of **1** were heated at temperatures up to 150 °C under N_2. Similarly, **1** remains intact when mixed aqueous solutions (dioxane/water 1:5) were heated at 100 °C in air for several days.[26] Accordingly, **1** was found to be a highly efficient and extremely reliable Suzuki catalyst. Various electronically activated, deactivated and/or sterically hindered and functionalized aryl bromides were successfully coupled with phenylboronic acid in very high conversion rates and yields within short reaction times and with low catalyst loadings in aqueous media without exclusion of air (Table 1). For example, electronically activated substrates, such as 1-bromo-4-nitrobenzene and 1-(4-bromophenyl)ethanone, were quantitatively coupled with phenylboronic acid at 100 °C in water and NaOH as base with only 0.01 mol% of catalyst **1** within 30 min (Table 1, entries 1 and 2).[27] Slightly retarded conversions were detected for 5-bromo-2-benzofuran-1(3*H*)-one, 3-bromobenzaldehyde, and 4-bromobenzonitrile; 1 h, 2 h, and 2 h, respectively, were required to quantitatively give 5-phenyl-2-benzofuran-1(3*H*)-one, biphenyl-4-carbaldehyde, and biphenyl-4-carbonitrile (Table 1, entries 3–5). An excellent performance was detected for the coupling of phenyl bromide; quantitative C–C coupling required only 15 min (Table 1, entry 6). The activity only slightly decreased with aryl bromide substrates of increasing electron density. For example, when electronically deactivated 1-bromo-4-methoxybenzene was employed, 97% conversion was detected within only 1 hour (Table 1, entry 7). The same product yields but retarded conversions occurred with sterically hindered substrates, such as 1-bromo-2-methylbenzene and 2-bromo-1,3-dimethylbenzene in the presence of 10 mol% (relative to aryl bromide) of tetrabutylammonium bromide (Table 1, entries 8 and 9).[28] Generally excellent conversion rates and yields were observed for reactions performed with phenol derivates. For example, the coupling of 4-bromophenol and 4-bromo-3-

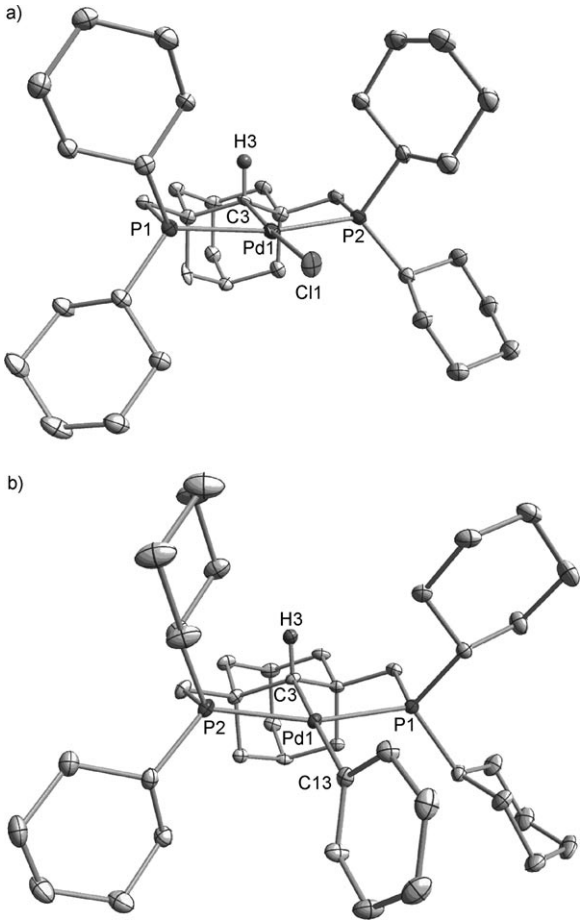


Figure 1. Diamond representations of complexes **1** (a) and **3** (b) in the crystal.[24] Thermal ellipsoids were set at 30% probability. All H atoms except H3 have been omitted for clarity. Selected bond lengths [Å] and angles [°]: a) Complex **1**: Pd1–C3 2.090(6), Pd1–P1 2.294(2), Pd1–P2 2.290(2), Pd1–Cl1 2.412(2); P2-Pd1-P1 166.33(6), C1-Pd1-Cl1 174.3(2). b) Complex **3**: Pd1–C3 2.123(2), Pd1–C13 2.102(3), Pd1–P1 2.2780(8), Pd1–P2 2.2640(7); P2-Pd1-P1 162.75(3), C1-Pd1-C13 176.8(1).

Table 1. Suzuki cross-coupling reactions of aryl bromides with phenylboronic acid performed in water catalyzed by [{$C_{10}H_{13}$-1,3-$(CH_2PCy_2)_2$}Pd(Cl)] (**1**).[a]

Entry	Aryl halide	Conv. [%][b]	*t* [min]	TOF[c]	TON[d]
1	1-bromo-4-nitrobenzene	100	30	20000	10000
2	1-(4-bromophenyl)ethanone	97	30	19400	9700
3	5-bromo-2-benzofuran-1(3*H*)-one	100	60	10000	10000
4	3-bromobenzaldehyde	97	120	4850	9700
5[e]	4-bromobenzonitrile	100	120	5000	10000
6	phenyl bromide	96	15	38400	9600
7	1-bromo-4-methoxybenzene	97	60	9700	9700
8[f]	1-bromo-2-methylbenzene	97	180	3233	9700
9[f]	2-bromo-1,3-dimethylbenzene	98	180	3267	9800
10	4-bromophenol	100	15	40000	10000
11	4-bromo-3-methylphenol	100	15	40000	10000
12	4-bromo-3,5-dimethylphenol	98	60	9800	9800
13[e]	4-bromoaniline	96	150	3840	9600
14[e]	4-bromo-*N*,*N*-dimethylaniline	94	180	3133	9400
15	2-bromophenol	95	180	3167	9500
16	(4-bromophenyl)methanol	100	60	10000	10000
17	4-bromo-2-(hydroxymethyl)-phenol	100	60	10000	10000
18	5-bromo-2-methoxybenzyl-alcohol	100	60	10000	10000
19	2-bromo-4,5-dimethoxybenzyl-alcohol	100	360	1667	10000
20[e]	2-bromo-4,5-dimethoxybenzyl-alcohol	100	120	5000	10000

[a] Reaction conditions: aryl bromide (2.0 mmol), phenylboronic acid (1.5 equivalents relative to aryl bromide), NaOH (4.0 mmol), water (12 mL), catalyst **1** (0.01 mol%) added in solution (100 μL dioxane), reaction performed at 100 °C without exclusion of air. [b] Determined by GC/MS, based on aryl halide. [c] Defined as moles of product per mole of catalyst per hour. [d] Defined as moles of product per mole of catalyst. [e] 2 mL of dioxane was additionally added to the reaction mixture. [f] 10 mol% of tetrabutylammonium bromide was added to the reaction mixture.

methylphenol with phenylboronic acid, quantitatively yielded biphenyl-4-ol and 2-methylbiphenyl-4-ol, respectively, within only 15 min (Table 1, entries 10 and 11). A slightly slower product formation was observed with sterically hindered 4-bromo-3,5-dimethylphenol; 1 hour was required for its full conversion into 2,6-dimethylbiphenyl-4-ol (Table 1, entry 12). Further retardation was detected with 2-bromophenol, 4-bromoaniline, and 4-bromo-*N*,*N*-dimethylaniline as coupling partners; >95% of biphenyl-2-ol, biphenyl-4-*N*,*N*-dimethylamine and biphenyl-4-amine, respectively, were formed within 3 h (Table 1 entries 13–15). Smooth C–C bond formations also occurred with aromatic alcohols. For example, when reactions were performed with (4-bromophenyl)methanol and 4-bromo-2-(hydroxymethyl)phenol, quantitative conversions were achieved within only 1 hour (Table 1, entries 16 and 17). Similarly, (4-methoxybiphenyl-3-yl)methanol was quantitatively formed within only 1 hour when 5-bromo-(2-methoxyphenyl)methanol was coupled with phenylboronic acid (Table 1, entry 18). Full conversion of electronically deactivated 2-bromo-4,5-dimethoxybenzylalcohol into (4,5-dimethoxybiphenyl-2-yl)methanol was achieved within 2 h in mixed aqueous medium (water/dioxane; 3:1). A reaction time of 6 h was required for its formation in pure water (Table 1, entries 19 and 20).

Highly hydrophobic substrates, such as polyaromatics, which lead to inefficient conversions in water, were successfully coupled within less than 1 h with phenylboronic acid in toluene with K_3PO_4 as base in the presence of 0.01 mol% of **1** (Table 2). Exclusion of air and moisture was not necessary. For example,

Table 2. Suzuki cross-coupling reactions of aryl bromides with phenylboronic acid performed in toluene catalyzed by [{$C_{10}H_{13}$-1,3-$(CH_2PCy_2)_2$}Pd(Cl)] (**1**).[a]

Entry	Aryl halide	Conv. [%][b]	*t* [min]	TOF[c]	TON[d]
1	9-bromoanthracene	100	30	20000	10000
2	4-bromobiphenyl	100	30	20000	10000
3	1,4-dibromobenzene	100	30	10000	10000
4	9,10-dibromoanthracene	100	45	10000	10000
5[e]	1,3-dibromobenzene	100	60	10000	10000
6[e]	1,2-dibromobenzene	100	60	10000	10000
7	1-(4-bromophenyl)ethanone	98	30	19600	9800
8	3-bromobenzaldehyde	82	60	8200	8200
9	1-bromo-4-nitrobenzene	99	30	19800	9900
10	4-bromobenzonitrile	100	30	20000	10000
11	1-bromo-4-*tert*-butylbenzene	91	60	9100	9100
12	1-bromo-4-methoxybenzene	91	30	18200	9100
13	4-bromoaniline	100	30	10000	10000
14	4-bromo-*N*,*N*-dimethylaniline	97	45	12933	9700
15	*N*-(4-bromophenyl)acetamide	100	30	10000	10000
16	1-bromo-2-methylbenzene	79	60	7800	7800
17	1-bromo-2-methylnaphthalene	93	60	9300	9300
18	2-bromo-1,3-dimethylbenzene	83	60	8300	8300

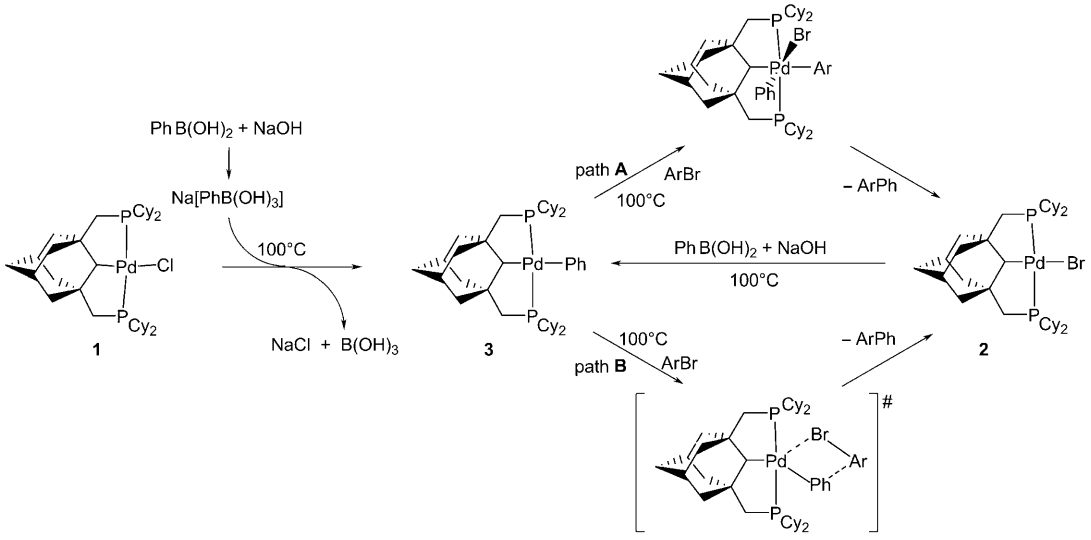
[a] Reaction conditions: aryl bromide (2.0 mmol), phenylboronic acid (1.5 equivalents relative to aryl bromide), K_3PO_4 (4.0 mmol), technical grade (12 mL), catalyst **1** (0.01 mol%) added in solution (100 μL dioxane), reaction performed at 100 °C without exclusion of air. [b] Determined by GC/MS, based on aryl halide. [c] Defined as moles of product per mole of catalyst per hour. [d] Defined as moles of product per mole of catalyst. [e] 2 equivalents (relative to bromide) of phenylboronic acid were used.

couplings of phenylboronic acid with 9-bromoanthracene, 4-bromobiphenyl or 1,4-dibromobenzene, 9,10-dibromoanthracene, 1,3-dibromobenzene, and 1,2-dibromobenzene at 100 °C quantitatively yielded 9-phenylanthracene, 1,1′:4′,1″-terphenyl, 9,10-diphenylanthracene, 1,1′:3′,1″-terphenyl, and 1,1′:2′,1″-terphenyl, respectively, generally within 30 min (Table 2, entries 1–6). Remarkably, similar conversion rates and biaryl formations were obtained when functionalized substrates, such as 1-(4-bromophenyl)ethanone, 3-bromobenzaldehyde, 1-bromo-4-nitrobenzene, 4-bromobenzonitrile, 1-bromo-4-*tert*-butylbenzene, 1-bromo-4-methoxybenzene, 4-bromoaniline, 4-bromo-*N*,*N*-dimethylaniline, and *N*-(4-bromophenyl)acetamide, were applied (Table 2, entries 7–15). Slightly slower product formations were detected for sterically hindered substrates, such as 1-bromo-2-methylbenzene, 1-bromo-2-methylnaphthalene, and 2-bromo-1,3-dimethylbenzene (Table 2, entries 16–18).

Overall, complex **1** is a rare example of a highly active Suzuki catalyst that is able to quantitatively couple a large vari-

ety of electronically activated, deactivated, and/or sterically hindered and functionalized aryl bromides with phenylboronic acid in water without the need for exclusion of air.[13–16] Moreover, hydrophobic substrates, which lead to inefficient conversions in water, were quantitatively coupled within less than 1 h in toluene.[29] Thus, whereas **1** is, for most of the reactions examined in nonaqueous media, more efficient than reference systems, such as $[Pd(Cl)(C_6H_3\{NHP(Ph)_2\}_2)]$,[18b] $[Pd_2(Cl)_2(C_6H_2(tBu)_2O)\{P(OR)_2\}_2]$,[10g,31] and $Pd(OAc)_2/PCy_2Ar$,[2i,32] among the majority of catalysts with lower catalytic activities in water, systems with comparable activities have been reported.[16e–h]

The Suzuki cross-coupling is strongly influenced by the reaction temperature; a decrease in temperature leads to a significant drop in activity. For example, whereas 86% conversion into biphenyl was observed after 6 h for the coupling of phenyl bromide and phenylboronic acid in water at 50 °C, only 2% conversion was detected after 6 h for the same reaction at room temperature. The same trend was detected for the reaction in toluene.[33] Importantly, no induction periods were observed, either in aqueous solution or in toluene with **1**, indicating that transformation of **1** into another catalytically active species, such as palladium nanoparticles, is unlikely.[34,35] Indeed, the addition of tetrabutylammonium bromide (ca. 10 mol%)—a salt known to stabilize palladium nanoparticles—to catalytic reactions in toluene improved neither the conversion rates nor the yields. In contrast, its presence led to a significant drop in the conversion rate.[36–38] Conversely, whereas the conversion rate and yield were not influenced by the presence of 0.05 equivalents of PPh_3 (relative to the catalyst) in toluene, the reaction in water gave the same yields but retarded conversions.[35] Similarly, whereas the presence of 0.3 equivalents of thiophene slightly retarded the biphenyl formation in water, a dramatic drop in activity was noticed in toluene.[35] Moreover, the addition of a few drops of metallic mercury to the reaction mixtures of aryl bromides, phenylboronic acid, base, and **1**, led to a dramatic drop in activity in both water and toluene.[35,39–42] The only change to the catalyst at the end of the reaction, both in toluene and in aqueous solution, performed with phenyl bromide, for example, was substitution of the chloride ligand of **1** to give the corresponding palladium bromide complex **2** (Scheme 1).[20] Furthermore, the reaction mixtures remained highly active after the reaction was complete and catalysis was resumed upon addition of more substrates, to afford the coupling products at essentially the same rates, which further supports homogeneous catalysis rather than palladium nanoparticle formation in the catalytic processes.[44] Further experimental observations strongly indicated homogeneous catalysis: When an excess (ca. 10 equivalents relative to **1**) of phenylboronic acid was added to toluene solutions of **1** and NaOH (or K_3PO_4), the neutral phenyl pincer complex $[\{C_{10}H_{13}\text{-}1,3\text{-}(CH_2PCy_2)_2\}Pd(Ph)]$ (**3**; Figure 1b and Scheme 1) was formed at 100 °C.[45] Complex **3** was not formed in the absence of base, giving evidence that hydroxide anions promote the phenyl transfer, possibly by nucleophilic attack on phenylboronic acid.[46] However, the formation of a neutral hydroxide pincer complex as an intermediate in the formation of **3** seems improbable, since no reaction took place when toluene solutions of **1** and NaOH were heated to100 °C, but cannot be completely ruled out. Complex **3** was also formed in mixed aqueous solution (water/dioxane 3:1).[47] Furthermore, **3** proved to be stable towards water and remained unchanged even upon thermal treatment (100 °C) over night. For example, when 1-bromo-4-methoxybenzene (ca. 1.2 equivalents) was added to toluene solutions or dioxane/water (1:3) mixtures of **3**,[48] 4-methoxybiphenyl and **2** were exclusively formed within less than 1 hour at 100 °C,[49] giving strong evidence that **3** is a key intermediate in the catalytic cycle of the Suzuki reaction. The catalytic activities of **3** and **2** are equal to that of **1** both in toluene and in aqueous solution. Overall, following reaction mechanisms are expected to be operative in the Suzuki reaction: The catalytic cycle is initiated by the formation of the phenyl palladium complex **3** from reaction of **1** with phenylboronic acid. Hydroxide anions are thought to activate the boronic acid, which promotes the phenyl transfer to the metal



Scheme 1. Possible catalytic cycles of the Suzuki reaction catalyzed by **1**.

center. Subsequent reaction steps either involve the oxidative addition of aryl bromides on **3** and formation of the neutral hexacoordinated pincer-type Pd^{IV} intermediates, of type [{$C_{10}H_{13}$-1,3-$(CH_2PCy_2)_2$}Pd(Ar)(Br)(Ph)],[50] followed by reductive elimination of the coupling products (Scheme 1; path A) or direct biaryl formation on the Pd^{II} center of **3** via a four-centered transition state (Scheme 1; path B).[51–53]

In summary, complex **1** is an efficient and extremely reliable Suzuki catalyst, which enables the quantitative coupling of a variety of electronically activated, deactivated, and/or sterically hindered and functionalized aryl bromides with phenylboronic acid in water with NaOH as base and without the need of exclusion of air (Table 1). Hydrophobic substrates, which lead to inefficient conversions in aqueous solution, were successfully coupled in toluene with K_3PO_4 as base (Table 2). As was the case for the aqueous reaction, exclusion of air was not necessary. Even though the mechanistic investigations performed were not definitive (palladium nanoparticle formation cannot be ruled out) our experimental results strongly indicated that homogeneous reaction mechanisms were operative. The phenyl pincer complex **3** was found to be a possible key intermediate in the catalytic cycle of the Suzuki reaction in both, toluene and aqueous solution. Thus, catalytic mechanisms are expected to either involve oxidative addition of aryl bromides on **3** and formation of the neutral hexacoordinated pincer-type Pd^{IV} intermediates, with the general formula of [{$C_{10}H_{13}$-1,3-$(CH_2PCy_2)_2$}Pd(Ar)(Br)(Ph)], followed by reductive elimination of the coupling products or on the Pd^{II} center of **3** directly, via a four-centered transition state. DFT calculations in order to elucidate whether one of proposed reaction paths is energetically favorable are currently in progress.

Experimental Section

General: All synthetic operations for the complex syntheses were carried out in oven-dried glassware using a combination of glovebox (M. Braun 150B-G-II) and Schlenk techniques under a dinitrogen atmosphere. Solvents were reagent grade or better, freshly distilled under N_2 atmosphere by standard procedures, and degassed by freeze–thaw cycles before use. Deuterated solvents were purchased from Armar, stored in a Schlenk tube (Teflon tap) over CaH_2, distilled, and degassed prior to use. All the chemicals were purchased from Aldrich Chemical Co., Acros Organics, or Fluka and used without further purification.

Analysis: ^1H, $^{13}C\{^1H\}$, and $^{31}P\{^1H\}$ NMR spectroscopic data were recorded at 500.13, 125.76, and 202.46 MHz, respectively, on a Bruker DRX-500 spectrometer. Chemical shifts (δ) are expressed in parts per million (ppm) coupling constants (J) are in Hz. The ^1H and ^{13}C NMR chemical shifts are reported relative to tetramethylsilane; the resonance of the residual protons of the solvent was used as internal standard for ^1H ([D_6]benzene: $\delta = 7.15$ ppm; [D_8]THF: $\delta = 3.58$ and 1.73 ppm; CD_2Cl_2: $\delta = 5.26$ ppm) and *all-d* solvent peaks for ^{13}C ([D_6]benzene: $\delta = 128.0$ ppm; [D_8]THF: $\delta = 67.4$ and 25.2 ppm; CD_2Cl_2: $\delta = 53.5$ ppm). $^{31}P\{^1H\}$ NMR data are reported downfield relative to external 85% H_3PO_4 in D_2O at $\delta = 0.0$ ppm. All measurements were carried out at 298 K. Abbreviations used in the description of NMR data are as follows: s = singlet; d = doublet; t = triplet; m = multiplet; v = virtual. IR spectra were obtained by ATR methods with a Bio-Rad FTS-45 FTIR spectrometer. Elemental analyses were performed on a Leco CHNS-932 analysator at the University of Zurich, Switzerland.

1,3-Bis(dicyclohexylphosphinomethyl)adamantane: Solutions of 1,3-bis(dibromomethyl)adamantane (2.0 g, 6.2 mmol) in THF (20 mL) were treated with $LiPCy_2$ (2 equivalents), freshly prepared by addition of *n*-butyllithium (2.5 M solution in hexanes, 4.96 mL, 12.4 mmol) to solutions of dicyclohexylphosphine (2.5 g, 12.4 mmol) in THF (25 mL) followed by stirring for 2 h. The reaction mixture was heated at 65 °C over night. Removal of the solvent under reduced pressure and addition of diethyl ether (20 mL), followed by filtration through celite afforded the crude product as a white solid. The ligand (2.5 g, 4.4 mmol, 73%) was purified by flash column chromatography on silica gel (THF/pentane 1:5). ^1H NMR (C_6D_6): $\delta = 1.09$–2.24 ppm (m, 62H, H_{Ad} and H_{Cy}); $^{13}C\{^1H\}$ NMR (C_6D_6): $\delta = 50.0$ (m, C_{Ad}), 44.3 (s, C_{Ad}), 43.8 (d, J(P,C) = 8.9 Hz, C_{Ad}), 43.4 (d, J(P,C) = 9.0 Hz, C_{Ad}), 37.0 (d, J(P,C) = 22.1 Hz, CH_2P), 34.0 (d, J(P,C) = 5.7 Hz, C_{Cy}), 33.9 (d, J(P,C) = 5.8 Hz, C_{Cy}), 33.4 (d, J(P,C) = 16.1 Hz, C_{Ad}), 30.7 (d, J(P,C) = 2.8 Hz, C_{Ad}), 30.0 (d, J(P,C) = 9.8 Hz, C_{Ad}), 29.2 (d, ^3J(P,C) = 9.7 Hz, C_{Cy}), 29.1 (d, ^3J(P,C) = 9.7 Hz, C_{Cy}), 27.7–28.1 (m, C_{Cy}), 27.0 ppm (s, C_{Cy}); $^{31}P\{^1H\}$ NMR (C_6D_6): $\delta = -20.18$ ppm (PCy_2).

[{$C_{10}H_{13}$-1,3-$(CH_2PCy_2)_2$}Pd(Cl)] (**1**): $C_{10}H_{13}$-1,3-$(CH_2PCy_2)_2$ (107 mg, 0.19 mmol, 1.1 equivalents) and K_3PO_4 (45 mg, 0.21 mmol, 1.2 equivalents) were added to a yellow suspension of $[Pd(Cl)_2(cod)]$ (cod = 1,5-cyclooctadiene; 50 mg, 0.175 mmol) in dioxane (10 mL), and the resultant mixture was stirred for 3 h at 100 °C. After the reaction was complete, diethyl ether (10 mL) was added. The reaction mixture was filtered through celite and the solvents were removed under reduced pressure. The residue was washed with pentane/diethyl ether (1:1; 3×5 mL). The pure product **1** (64 mg, 0.092 mmol, 53%) was dried in vacuo. ^1H NMR (C_6D_6): $\delta = 2.76$ (br s, 1H, PdCH), 1.06–2.31 ppm (m, 60H, H_{Ad} and H_{Cy}); $^{13}C\{^1H\}$ NMR (C_6D_6): $\delta = 72.5$ (t, ^2J(P,C) = 2.5 Hz, C_{Ad}), 46.0 (vt, J(P,C) = 9.0 Hz, C_{Ad}), 45.4 (s, C_{Ad}), 44.2 (vt, J(P,C) = 11.2 Hz, CH_2P), 37.7 (vt, J(P,C) = 11.3 Hz, CH_2P), 36.3 (s, C_{Ad}), 35.4 (t, J(P,C) = 10.3 Hz, C_{Cy}), 33.9 (t, J(P,C) = 9.3 Hz, C_{Cy}), 30.8 (s, C_{Ad}), 30.4 (s, C_{Ad}), 29.8 (s, C_{Ad}), 29.6 (s, C_{Ad}), 29.4 (s, C_{Ad}), 28.9 (s, C_{Ad}), 27.7 (vt, J(P,C) = 6.4 Hz, C_{Cy}), 27.6–27.2 (m, C_{Cy}), 26.6 (s, C_{Cy}), 26.5 ppm (s, C_{Cy}); $^{31}P\{^1H\}$ NMR (C_6D_6): $\delta = 52.64$ ppm (s, PCy_2). Elemental analysis calcd for $C_{36}H_{61}ClP_2Pd$: C 61.98, H 8.81; found: C 61.78, H 8.65.

[{$C_{10}H_{13}$-1,3-$(CH_2PCy_2)_2$}Pd(CO)][BF_4]: $AgBF_4$ (11 mg, 0.057 mmol) was added to a solution of **1** (40 mg, 0.057 mmol) in dichloromethane (10 mL). The reaction mixture was stirred for 30 min under total exclusion of light. The reaction mixture was filtered through celite. The solvent was removed under reduced pressure. Dissolution of [{$C_{10}H_{13}$-1,3-$(CH_2PCy_2)_2$}Pd][BF_4] in C_6D_6 and subsequent treatment with excess CO gas (ca. 50 equivalents) led exclusively to the formation of [{$C_{10}H_{13}$-1,3-$(CH_2PCy_2)_2$}Pd(CO)][BF_4]. CO release was detected under reduced pressure, precluding accurate elemental analysis. ^1H NMR (C_6D_6): $\delta = 2.68$ (br s, 1H, PdCH), 2.04–1.10 ppm (m, 60H, H_{Ad} and H_{Cy}); $^{13}C\{^1H\}$ NMR (C_6D_6): $\delta = 183.2$ (t, ^2J(P,C) = 15.2 Hz, CO), 87.1 (br s, C_{Ad}), 48.2 (vt, J(P,C) = 6.8 Hz, C_{Ad}), 45.6 (s, C_{Ad}), 43.8 (vt, J(P,C) = 16.9 Hz, CH_2P), 42.9 (vt, J(P,C) = 12.1 Hz, CH_2P), 35.8 (t, J(P,C) = 11.3 Hz, C_{Cy}), 35.6 (t, J(P,C) = 10.5 Hz, C_{Cy}), 35.1 (s, C_{Ad}), 30.6 (s, C_{Ad}), 30.0 (s, C_{Ad}), 29.9 (s, C_{Ad}), 29.7 (s, C_{Ad}), 29.4 (s, C_{Ad}), 29.1 (s, C_{Ad}), 26.7–27.3 (m, C_{Cy}), 26.2 (s, C_{Cy}), 26.5 ppm (s, C_{Cy}); $^{31}P\{^1H\}$ NMR (C_6D_6): $\delta = 74.75$ ppm (s, PCy_2); IR (ATR): $\tilde{\nu} = 2095$ cm^{-1} (s, CO).

[{$C_{10}H_{13}$-1,3-$(CH_2PCy_2)_2$}Pd(Br)] (**2**): To an orange suspension of $[Pd(Br)_2(cod)]$ (cod = cyclooctadiene; 40 mg, 0.107 mmol) in dioxane (10 mL), $C_{10}H_{13}$-1,3-$(CH_2PCy_2)_2$ and 27 mg of K_3PO_4 (0.128 mmol,

1.2 equiv) were added and the mixture was stirred for 3 h at 100 °C. After the reaction was complete, diethyl ether (10 mL) was added. The reaction mixture was filtered through celite. The solvents were removed under reduced pressure. The residue was washed with pentane/diethyl ether (1:1; 3×5 mL) and dried in vacuo to afford **2** (43 mg, 0.058 mmol, 54%). ^{1}H NMR ([D$_8$]THF): δ = 2.83 (br s, 1H, PdCH), 2.48–1.11 ppm (m, 60H, H_{Ad} and H_{Cy}); ^{13}C{^{1}H} NMR ([D$_8$]THF): δ = 76.1 (t, ^2J(P,C) = 3.5 Hz, C_{Ad}), 46.8 (vt, J(P,C) = 8.9 Hz, CH_2P), 46.2 (s, C_{Ad}), 44.6 (vt, J(P,C) = 11.0 Hz, CH_2P), 38.6 (vt, J(P,C) = 8.4 Hz, C_{Ad}), 37.5 (s, C_{Ad}), 35.5 (vt, J(P,C) = 9.5 Hz, C_{Cy}), 34.0 (vt, J(P,C) = 9.7 Hz, C_{Cy}), 31.5 (s, C_{Ad}), 30.6 (s, C_{Ad}), 30.4 (s, C_{Ad}), 29.9 (s, C_{Ad}), 29.3 (s, C_{Ad}), 28.5 (vt, J(P,C) = 6.7 Hz, C_{Cy}), 28.2–27.7 (m, C_{Cy}), 27.2 (s, C_{Cy}), 27.1 ppm (s, C_{Cy}); ^{31}P{^{1}H} NMR ([D$_8$]THF): δ = 53.00 ppm (s, PCy_2). Elemental analysis calcd for $C_{36}H_{61}BrP_2Pd$: C 58.26, H 8.28; found: C 58.08, H 8.19.

[{$C_{10}H_{13}$-1,3-(CH_2PCy_2)$_2$}Pd(Ph)] (**3**): Cold (−30 °C) solutions of **1** (30 mg, 0.083 mmol) in THF (10 mL) were treated with an equimolar amount of phenyllithium (ca. 0.2 M in dibutyl ether/THF, 0.42 mL) and stirred for 15 min upon warming the reaction mixture to room temperature. Removal of the solvent under reduced pressure and subsequent extraction with pentane (10 mL) afforded **3** (59 mg, 0.081 mmol, 97%). ^{1}H NMR ([D$_8$]THF): δ = 7.9 (d, 2H, ^3J = 5 Hz, C_{Ph}), 6.84 (t, 2H, ^3J = 6.5 Hz, C_{Ph}), 6.74 (t, 1H, ^3J = 7.3 Hz, C_{Ph}), 2.07–1.11 ppm (m, 61H, H_{Ad} and H_{Cy}); ^{13}C{^{1}H} NMR ([D$_8$]THF): δ = 189.8 (br s, Pd-C_{Ph}), 144.2 (s, C_{Ph}), 125.0 (s, C_{Ph}), 122.9 (s, C_{Ph}), 73.9 (br s, C_{Ad}), 51.8 (vt, J(P,C) = 8.8 Hz, C_{Ad}), 46.9 (s, C_{Ad}), 44.9 (vt, J(P,C) = 6.5 Hz, CH_2P), 42.8 (vt, J(P,C) = 8.7 Hz, CH_2P), 37.4 (s, C_{Ad}), 35.04 (2 overlapping triplet signals, C_{Cy}), 31.6 (s, C_{Ad}), 31.3 (s, C_{Ad}), 30.6 (s, C_{Ad}), 30.4 (s, C_{Ad}), 30.0 (s, C_{Ad}), 29.4 (s, C_{Ad}), 27.9–28.6 (m, C_{Cy}), 27.5 (s, C_{Cy}), 27.4 ppm (s, C_{Cy}); ^{31}P{^{1}H} NMR ([D$_8$]THF): δ = 49.81 ppm (s, PCy_2). Elemental analysis calcd for $C_{42}H_{66}P_2Pd$: C, 68.23; H, 9.00. Found: C, 68.04; H, 8.89.

General procedure for Suzuki cross-coupling of aryl bromides with phenylboronic acid: In a round bottom flask in air were placed phenylboronic acid (0.366 g, 3.0 mmol) and the aryl halide (2.0 mmol) with NaOH (6.5 M aqueous solution, 0.6 mL) and water (12.0 mL) or powdered K_3PO_4 (0.848 g, 4.0 mmol) and toluene (12.0 mL). The mixtures were heated to 100 °C and vigorously stirred (see Tables 1 and 2 for reaction times). The catalyst (100 μl of a 2.00 mM solution in dioxane) was added via syringe. Samples, taken from the reaction mixture were diluted with ethyl acetate and analyzed by GC/MS. At the end of catalysis the reaction mixtures were allowed to cool to room temperature, quenched with aqueous HCl (1 M, 10 mL), extracted with ethyl acetate (2×10 mL), the combined extracts were dried ($MgSO_4$) and evaporated to dryness. The crude material was purified by flash column chromatography on silica gel. Yields of the isolated coupling products were generally between 5 and 10%, and sometimes up to 15%, lower than the reported conversions (Tables 1 and 2).

(4,5-Dimethoxybiphenyl-2-yl)methanol: The title compound (Table 1, entry 17) was purified by flash column chromatography on silica gel (CH_2Cl_2/methanol 9:1) as a colorless powder (410 mg, 1.68 mmol, 84%). ^{1}H NMR (CD_2Cl_2): δ = 7.27–7.36 (m, 5H), 6.98 (s, 1H), 6.71 (s, 1H), 4.44 (br s, 2H), 3.81 (s, 3H), 3.75 (s, 3H), 1.47 ppm (br s, 1H, OH); ^{13}C{^{1}H} NMR (CD_2Cl_2): δ = 147.9, 140.1, 132.5, 128.1, 126.5, 125.9, 125.3, 112.6, 111.3, 60.4, 54.2 ppm. Elemental analysis: Calc. for $C_{15}H_{16}O_3$: C, 73.75; H, 6.60. Found: C, 73.67; H, 6.65.

CCDC 724537 and CCDC 724538 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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[23] The assignment of the ^1H and $^{13}C\{1H\}$ NMR signals was confirmed by ^{13}C DEPT, HMQC, HSQC, and COSY experiments.

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[27] Generally retarded conversions but quantitative yields were achieved, when the Suzuki reactions were performed with only 0.001 mol% of catalyst. For example, 97% of biphenyl was obtained after 45 min (instead of 15 min with 0.01 mol% of catalyst) when phenyl bromide was coupled with phenylboronic acid in water at 100 °C.

[28] The coupling of 1-bromo-2-methylbenzene with phenylboronic acid in the absence of tetrabutylammonium bromide gave the same yield but required a prolonged reaction time (6 h).

[29] It is important to mention that even though it is well established that aerobic oxidative arylboronic acid homocoupling can be a substantial side-reaction,[30] homocoupled side-products have never been detected under our reaction conditions.

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[32] Comparisons with the extremely active air- and moisture-stable NHC-bearing $[Pd^{II}(Cl)(R\text{–allyl})]$ (NHC = *N*-heterocyclic carbene) complexes are difficult, since the Suzuki reactions were generally performed at room temperature.[11k]

[33] Only 4% conversion was observed after 6 h at 50 °C when phenyl bromide was coupled with phenylboronic acid. No activity was obtained at 25 °C.

[34] Approximately 75% conversion of phenyl bromide into biphenyl was observed in water after only 5 min and 92% after 10 min in the presence of 0.01 mol% of **1**.

[35] For the kinetics of an exemplary Suzuki reaction, see graphs S1 and S2 in the Supporting Information.

[36] Tetrabutylammonium bromide is known to stabilize palladium nanoparticles. See, for example: a) T. Jeffery in *Advances in Metal-Organic Chemistry, Vol. 5* (Ed.: L. S. Liebeskind), JAI Press, Greenwich, **1996**, p. 153; b) M. T. Reetz, E. Westermann, *Angew. Chem.* **2000**, *112*, 170; *Angew. Chem. Int. Ed.* **2000**, *39*, 165; c) A. Zapf, M. Beller, *Chem. Eur. J.* **2001**, *7*, 2908.

[37] The addition of tetrabutylammonium bromide to Suzuki reactions performed in water is not appropriate, since this additive influences the substrate solubility, thereby influencing the conversion rates and yields.

[38] The presence of tetrabutylammonium bromide is expected to retard the conversion rates if (initial)aryl bromide coordination on pincer-type Pd^{II} centers is involved in the catalytic cycle, as the bromide anions suppress their coordination at the metal center.

[39] For a comprehensive review article about the problem of distinguishing true homogeneous catalysis from soluble or other metal-particle heterogeneous catalysis under reducing conditions see: J. A. Widegren, R. G. Finke, *J. Mol. Catal. A Chem* **2003**, *198*, 317.

[40] Quantitative poisoning experiments are usually performed at temperatures below 50 °C, whereas our experiments were conducted at 100 °C. High temperatures may lead to dissociation of thiophene or PPh_3 from heterogeneous systems, thereby regenerating the catalyst. However, examples of Heck reactions performed at 180 °C with resorcinol-derived pincer complexes of palladium for example, were effectively stopped after addition of the corresponding amounts of CS_2, thiophene, or PPh_3.[41]

[41] D. Morales-Morales, R. E. Cramer, C. M. Jensen, *J. Organomet. Chem.* **2002**, *654*, 44.

[42] Overall, the standard tests performed to distinguish homogeneous from heterogeneous catalysis were not conclusive and thus, palladium nanoparticles as the catalytically active forms of **1** cannot be excluded completely. Nevertheless, their involvement seems to be less likely, as indicated by following observation. Palladium nanoparticle formation and their relevance in catalytic cycles of cross-coupling reactions are generally to be considered at reaction temperatures above 120 °C,[43] whereas the Suzuki reactions are performed at 100 °C. Even though palladium nanoparticles are known to readily activate aryl bromides, C_{aryl}–Cl bond activations require significantly higher reaction temperatures (> 160 °C). Exemplary Suzuki cross-coupling reactions performed at 100 °C in the presence of 0.01 mol% of **1** with chlorobenzene and 4-chloroanisole as coupling partners led to 47% biphenyl and 33% 4-methoxybiphenyl within 3 h in water and 40% conversion of 4-chloroanisole into 4-methoxybiphenyl within only 2 h in toluene. Such conversions would be unlikely if palladium nanoparticles were the catalytically active form of **1**. However, further investigations were carried out (see below).

[43] a) W. J. Sommer, K. Yu, J. S. Seras, Y. Ji, X. Zheng, R. J. Davis, C. D. Sherril, C. W. Jones, M. Weck, *Organometallics* **2005**, *24*, 4351; b) K. Yu, W.

Sommer, J. M. Richardson, M. Weck, C. W. Jones, *Adv. Synth. Catal.* **2005**, *347*, 161; c) J. G. de Vries, *Dalton Trans.* **2006**, 421.

[44] Although halide exchange reactions of pincer complexes with aryl bromides have shown to be possible via Pd^{IV} intermediates (in highly polar solvents),[17d] the involvement of palladium nanoparticles cannot be ruled out completely: Decomposition of a minor amount of **1** to form the anionic complex $[ArPdBr_2]^-$ or its dimer via Pd^0 intermediates may occur to promote the halide exchange with the pincer complex. Alternatively, a bromide ligand could dissociate from $[ArPdBr_2]^-$ or its dimer and exchange with the pincer complexes directly.

[45] The identity of **3** was confirmed by its independent synthesis upon treatment of THF solutions of **1** with an equimolar amount of phenyl lithium (see the experimental part and the X-ray structure in Figure 1).

[46] Hydroxide anions are expected to promote the phenyl transfer in toluene with K_3PO_4 as base as well, since phenylboronic acid contains water. Indeed, reactions performed in anhydrous toluene with dry phenylboronic acid lead to significantly reduced conversion rates and yields. On the other hand, when few drops of water were added to these reaction mixtures a dramatic increase of the conversion rate and yield was noticed. The generally higher conversion rates observed with K_3PO_4 as base in toluene (when compared to the use of NaOH) was attributed to its lower nucleophilicity and solubility.

[47] It should be noted that (in contrast to the reaction performed in toluene) the slow formation of **3** was observed in aqueous solution also without the presence of base, which indicates that hydroxide anions indeed promote the phenyl transfer of phenylboronic acid to the metal center.

[48] 1-bromo-4-methoxybenzene (instead of phenyl bromide) was used as coupling partner in order to exclude biphenyl formation via binuclear decomposition of **3**.

[49] A mixed aqueous solvent system was used to increase the substrate and catalyst solubility, in order to monitor the conversion of **3** into **2** by $^{31}P\{^1H\}$ NMR spectroscopy.

[50] *Cis* arrangement of the aryl and phenyl units is required for biaryl formation, unless halide dissociation occurs, which might be possible in aqueous solution but certainly is not when using toluene as solvent.[17d]

[51] a) A. R. Dick, J. W. Kampf, M. S. Sanford, *J. Am. Chem. Soc.* **2009**, *131*, 12790; b) K. L. Hull, E. L. Lanni, M. S. Sanford, *J. Am. Chem. Soc.* **2006**, *128*, 14047.

[52] Even though strong experimental evidence for homogeneous catalysis was obtained, the outcome of standard tests to distinguish true homogeneous catalysis from soluble or other metal-particle heterogeneous catalysis was not conclusive and some of them would indeed suggest heterogeneous catalysis. Hence the latter cannot be ruled out. Even though we clearly favor homogeneous catalytic reaction mechanisms, the possibility that two parallel catalytic cycles could be operative might provide another explanation for the experimental results obtained.

[53] A molecular reaction mechanism with a strongly related pincer system was independently suggested: D. Olsson, O. F. Wendt, *J. Organomet. Chem* **2009**, *694*, 3112.

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