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C–C Coupling Reactions of Aryl Bromides and Arylsiloxanes in Water Catalyzed by Palladium Complexes of Phosphanes Modified with Crown Ethers

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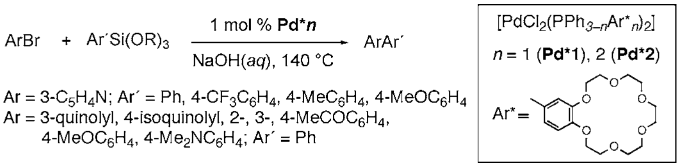
ABSTRACT



The complexes [PdCl$_2$L$_2$], where L is a crown-ether-containing triarylphosphane, catalyze the formation of biaryls from arylsiloxanes and aryl bromides with high yields in water as solvent and under air. The water-insoluble catalysts [PdCl$_2$(PhCN)$_2$] and [PdCl$_2$(PPh$_3$)$_2$] are also efficient, although they decompose more quickly to form black Pd^0.

The palladium-catalyzed aryl−aryl cross-coupling reaction is a simple, efficient, and versatile route to the formation of carbon−carbon bonds that is commonly used in modern organic synthesis[1] to give complex products in a one-step reaction between an aryl halide and an organometallic species, for instance, an organoborane (Suzuki)[2] or organostannane reagent (Stille reaction).[3] Organosilanes are remarkable for their low toxicity, environmental benignity, and high chemical stability, and these advantages can be reinforced by using water as a cheap, nontoxic, and nonflammable solvent.[4] Hiyama showed 20 years ago that transmetalation of organosilanes takes place smoothly after their activation with the fluoride anion.[5] Subsequent developments[6] showed that sodium hydroxide is an effective promoter[7] that is able to activate the coupling of arylsiloxanes[6b,8] in water-containing organic solvents.[9] Recently, Wolf and Lerebours have described a NaOH-promoted coupling method for the

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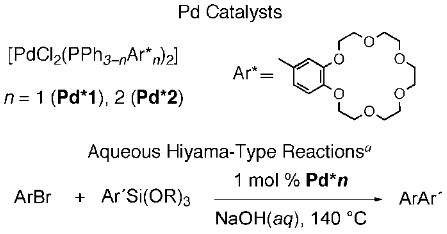
synthesis of biaryls in water using arylsiloxanes and aryl halides with a Pd catalyst of formula $[\{(t\mathrm{Bu})_2\mathrm{P(OH)}(t\mathrm{Bu})_2\mathrm{PO}\}\mathrm{PdCl}]_2$.[10]

We have probed the efficiency of the $[\mathrm{PdCl_2L_2}]$ complexes **Pd*1** and **Pd*2**, where L is a crown-ether-modified triphenylphosphane ligand (Scheme 1), in the Stille cross-coupling of aryl iodides and trichlorostannanes in water.[11] Despite the low water solubility of these Pd complexes, good activities were observed for such reactions under the reported conditions (1 M KOH, 1% Pd, 100 °C). Taking into account these results, we decided to test **Pd*1** and **Pd*2** in aqueous Hiyama-type cross-coupling reactions between trialkoxyarylsilanes and aryl bromides under conditions based on those described by Wolf (Scheme 1).[10] These catalysts were found to be more active than those previously described and allowed the synthesis of biaryls in excellent yields with lower Pd loadings and shorter reaction times.

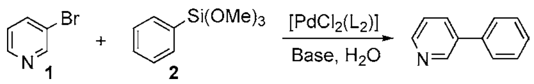
Scheme 1. Pd Catalysts and Aqueous Hiyama-type Cross-Coupling Reactions



[a] In a typical experiment, a mixture of 1.0 mmol of aryl bromide, 1.2 equiv of aryltrimethoxysilane, and 1 mol % of Pd catalyst were stirred under air in 5.0 mL of 0.50 M NaOH at 140 °C for 1.5 h. The products were purified by flash chromatography (silica gel, hexane/ethyl acetate).

The reaction between 3-bromopyridine and trimethylphenylsiloxane was studied as a model to determine the standard conditions for the cross-coupling between aryl bromides and arylsiloxanes in water (Table 1). Sodium hydroxide was found to be a better activator than tetrabutylammonium fluoride (TBAF) or potassium carbonate (entries 1−3), giving 3-phenylpyridine as a liquid of high purity without traces of reagents (^{1}H NMR evidence). In contrast, a conversion of only 10 and 50% of 3-bromopyridine was observed when TBAF or $\mathrm{K_2CO_3}$, respectively, was used under the same conditions. Potassium hydroxide gave results similar to those obtained with sodium hydroxide (compare entries 6 and 7). No appreciable differences were found between the activity of **Pd*1** and **Pd*2**, which differ only in the number of crown ether groups per phosphane ligand (entries 3 and 4). Both yellow complexes were completely soluble at the concentration and temperature of the reaction (140 °C), affording yellow−orange solutions that lose their color during the course of the reaction. We found that a 20% excess of arylsiloxane was enough to obtain good yields in most cases (entry 6) instead of the 1:2 ratio of aryl halide to arylsiloxane used previously.[10] However, a greater excess of siloxane enhances the yields with inactivated aryl bromides (see below). Essentially quantitative yields were obtained after 1.5 h at 140 °C (entry 5), although longer reaction times were needed to achieve high yields when the reaction temperature was decreased to 100 °C (entries 8 and 9). Nevertheless, and despite the slower kinetics, conversions of about 90−92% were obtained at 100 °C. The optimal catalyst loading is situated in the range of 0.5 to 1 mol % (compare entries 6, 10, and 11).

Table 1. Screening of Cross-Coupling Reaction Conditions in Water[a]



entry	catalyst	mol % [Pd]	base[b]	temp (°C)	reaction time (h)[c]	ratio **1**:**2**	yield (%)[d]
1	**Pd*1**	1	TBAF	140	18	1:2	10[e]
2	**Pd*1**	1	$\mathrm{K_2CO_3}$	140	18	1:2	51[e]
3	**Pd*1**	1	NaOH	140	18	1:2	96
4	**Pd*2**	1	NaOH	140	18	1:2	96
5	**Pd*2**	1	NaOH	140	1.5	1:2	96
6	**Pd*1**	1	NaOH	140	1.5	1:1.2	96
7	**Pd*1**	1	KOH	140	1.5	1:1.2	96
8	**Pd*2**	1	NaOH	100	1.5	1:1.2	72[e]
9	**Pd*2**	1	NaOH	100	18	1:1.2	90
10	**Pd*1**	0.5	NaOH	140	1.5	1:1.2	92
11	**Pd*1**	0.1	NaOH	140	1.5	1:1.2	6[e]

[a] See footnote to Scheme 1 and Supporting Information for other general conditions. [b] Five milliliters of an aqueous 0.5 M solution. [c] Reagents were mixed at room temperature with vigorous stirring. The reaction time was measured from the moment at which the tabulated temperature was reached. [d] Yields of isolated product. [e] Incomplete conversion.

We also tested the viability of recycling the palladium catalysts. After a first run using **Pd*2** under the standard conditions of entry 6, the reaction products were extracted with pentane at room temperature, and the aqueous solution was reused for a second run, which gave only a 10% yield of product. This is probably due, in part, to the low water solubility of the active catalyst at room temperature. In fact, a pale-grayish solid was observed at the pentane/water interface, which was found to catalyze the reaction with a 65% yield after separation.

The standard conditions selected above were applied to synthesize a series of biaryls in water using **Pd*2** as catalyst (Table 2). Thus, 3-bromopyridine was efficiently coupled to *para*-substituted phenylsiloxanes, independently of the electronic nature of the substituent in the *para* position (electron-withdrawing, electron-neutral, or electron-donating, entries 1−4). However, the reaction of 2-bromopyridine with trimethoxyphenylsilane gave lower yields of the desired biaryl product (entry 5), probably due to the sensitivity of the 2-position of the pyridine ring to a nucleophilic attack in the basic medium. Fused heterocycles, such as 3-bromo-

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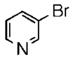
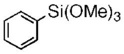
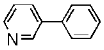
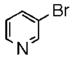
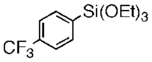
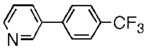
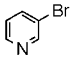
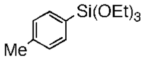
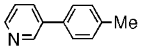
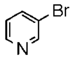
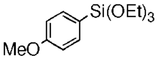
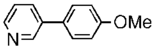
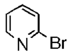
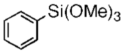
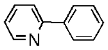
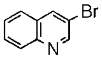
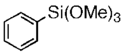
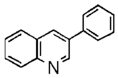
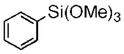
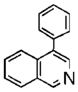
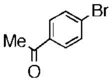
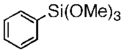
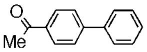
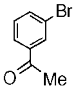
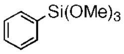
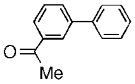
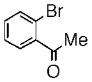
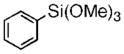
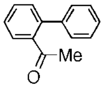
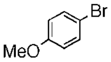
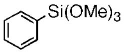
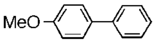
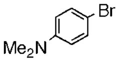
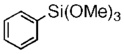
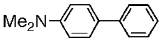
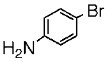
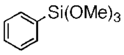
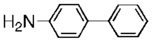
Table 2. Cross-Coupling Reactions of Arylsiloxanes with Aryl Bromides Catalyzed by **Pd*2** in Water[a]

entry	aryl bromide	arylsiloxane	product	yield (%)[b]
1				96
2				98
3				98
4				98
5				75
6				95
7				90
8				90
9				95
10				85
11				90[c]
12				92[c]
13				25[d]

[a] See footnote to Scheme 1 and Supporting Information for other general conditions. [b] Yields of isolated product. [c] Traces of products resulting from the homocoupling of the aryl bromide were also found. [d] Two equivalents of arylsiloxane and 5 h of reaction time were used; incomplete conversion (75% of *p*-bromoaniline).

quinoline or 4-bromoisoquinoline, were also coupled with trimethoxyphenylsilane in excellent yields (entries 6 and 7).

The electronic influence of the substituent on the aryl bromide was also studied. Both electron-withdrawing (entries 8−10) and electron-donating substituents (entries 11 and 12) gave excellent yields. The steric influence of the *ortho* substitution in 2-bromoacetophenone is low (compare entries 9 and 10), and the conversion was complete without the need for the high Pd loadings required in other cases.[8d] The yields obtained for 4-bromoaniline under the standard conditions were negligible, but they increased to a modest 25% with longer reaction times and higher arylsiloxane to aryl bromide ratios (entry 13 and footnote d). It is worth mentioning that all the preparations were carried out under air because, under anaerobic conditions, the yields of cross-coupling products often decreased and the formation of homocoupled products was favored. This is especially relevant with inactivated aryl bromides containing electron-donating substituents (entries 11 and 12), whose yields decrease considerably when the reactions are carried out under an inert atmosphere. For instance, 4-bromo-*N*,*N*-dimethylaniline produced about 80% of the heterocoupled and 15−20% of the homocoupled products after 5 h of reaction in the presence of 2 equiv of arylsiloxane under argon. In contrast, essentially quantitative yields of only *N*,*N*-dimethylbiphenyl-4-amine were achieved under the same conditions in air. The disminution of homocoupled products in aerobic conditions is unexpected. Oxygen is known to induce homocoupling in Suzuki reactions, for instance.[12] The presumed catalytic cycle involves double organoboron transmetalation, reductive elimination of the biaryl, and reoxidation of the Pd^0 center with oxygen. Symmetrical biaryls can be synthesized by Pd-catalyzed oxidative homocoupling of organostannanes or organoboron derivatives using oxygen as oxidant.[13] It is interesting to highlight that the presence of oxygen in the hydrosilylation of olefins catalyzed by Pt enhances the conversion and prevents olefin bond isomerization. It has been proposed that oxygen breaks up the multinuclear Pt species that are responsible for the isomerization and supplies monometallic compounds, which are the active species in the hydrosilylation.[14]

It is also surprising that the reaction of *para*-iodotoluene with trimethoxyphenylsilane afforded yields as low as 20% after 22 h at 140 °C. *para*-Iodoaniline did not react at all under the same conditions. The same Pd complex catalyzes the Stille reaction between these iodoaryls and $PhSnCl_3$ in water with nearly quantitative yields.[11] On the other hand, the reaction of 3-chloropyridine with trimethoxyphenylsilane was unsuccessful. After addition of the chloride and the catalyst at room temperature, the color of the aqueous solution immediately turned intense orange and a copious precipitate of Pd black was observed after warming.

In our previous work on the Stille reaction,[11] we observed that complexes without water-solubilizing groups, such as $[PdCl_2(PPh_3)_2]$, produced remarkable conversions, although lower than those obtained with the crown ether phosphane complexes. Interestingly, the yields obtained at 140 °C for the Hiyama model reaction using $[PdCl_2(PPh_3)_2]$, $[PdCl_2(PhCN)_2]$, or mixtures of $[PdCl_2(PhCN)_2]$ and PPh_3 as the catalysts were nearly quantitative and comparable to those produced by **Pd*1** or **Pd*2** (Table 3, entries 2−5). In contrast, the yield obtained at 100 °C with $[PdCl_2(PPh_3)_2]$ was appreciably lower than that obtained with **Pd*2** (45−50% versus 72%; entry 1 of Table 3 and entry 8 of Table 1). An important difference between both series of catalysts is that the insoluble catalysts decompose appreciably to give a copious and fine dispersion of Pd black even before reaching the reaction temperature (140 °C), whereas no apparent formation of metallic Pd^0 is observed with crown ether phosphane complexes at 100 or 140 °C. The presence

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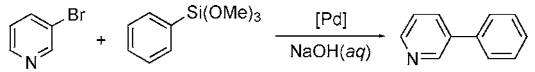
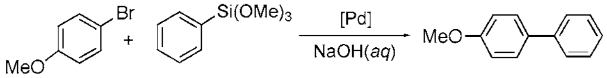
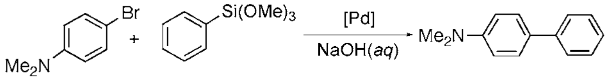
(12) Miyaura, N. In *Metal-Catalyzed Cross-Coupling Reactions*, 2nd ed.; de Meijere, A., Diederich, F., Eds.; Wiley-VCH: Weinheim, Germany, 2004; Chapter 2.

(13) See, for example: (a) Yoshida, H.; Yamaryo, Y.; Ohshita, J.; Kunai, A. *Tetrahedron Lett.* **2003**, *44*, 1541. (b) Shirakawa E.; Nakao, Y.; Murota, Y.; Hiyama, T. *J. Organomet. Chem.* **2003**, *670*, 132 and references therein.

(14) See, for instance: Stein, J.; Lewis, L. N.; Gao, Y.; Scott, R. A. *J. Am. Chem.* Soc. **1999**, *121*, 3693−3703 and references therein.

Table 3. Catalysis with Water-Insoluble Pd Precursors[a]

entry	[Pd]	mol% [Pd]/PPh$_3$	temp (°C)	yield (%)[b]
				
1	[PdCl$_2$(PPh$_3$)$_2$]	1	100 °C	45–50[c]
2	[PdCl$_2$(PPh$_3$)$_2$]	1	140 °C	95[d,e]
3	[PdCl$_2$(PhCN)$_2$]	1	140 °C	95[e]
4	[PdCl$_2$(PhCN)$_2$]/PPh$_3$	1/1	140 °C	95[e]
5	[PdCl$_2$(PhCN)$_2$]/PPh$_3$	1/4	140 °C	95[e]
6	[PdCl$_2$(PhCN)$_2$]/PPh$_3$	1/100	140 °C	0
				
7	[PdCl$_2$(PhCN)$_2$]	1	140 °C	76[d,e]
				
8	[PdCl$_2$(PhCN)$_2$]	1	140 °C	71[d,e]

[a] Conditions: 1 mmol of aryl bromide, 1.2 mmol of arylsiloxane, 5 mL of 0.5 M NaOH, 1.5 h. See footnote to Scheme 1 and Supporting Information for other general conditions. [b] Yields of isolated product. [c] Incomplete conversion. [d] Complete conversion, homocoupled product was also found. [e] Formation of Pd black was observed.

of progressively higher concentrations of the PPh$_3$ ligand retards the precipitation of Pd (entries 3–5), but the yields were only modified when a large excess of triphenylphosphane was used, which hampered the reaction (entry 6). Crown ether catalysts are, however, significantly more efficient in the coupling of electron-donating aryl bromides (compare, respectively, entries 7 and 8 in Table 3 with entries 11 and 12 in Table 2).

These results raise the question of the nature of the catalysis, that is, heterogeneous (bulk Pd or metal nanoparticles) or homogeneous (molecular). It is well-established that palladium(II) complexes, such as [PdCl$_2$(PR$_3$)$_2$], are reduced to Pd^0 complexes under conditions similar to those employed here.[15] The comparable activity of soluble and insoluble complexes might be due to the generation of the same common active species, either metallic or molecular, independently of the Pd precatalyst used. Deposition of Pd^0 was not usually observed in the reactions with **Pd****n*, and the Pd black formed from the insoluble complexes was found to be inactive as a catalyst. Nevertheless, the process can appear to be homogeneous if the catalyst consists of soluble metal nanoparticles.[16] Pd nanoclusters are able to catalyze the formation of C–C bonds,[17] although it has been postulated that metal colloids could, on occasion, be acting as the source of Pd^0 molecular catalysts.[18] Kinetic studies have shown an induction period of about 30 min for the reaction catalyzed by PPh$_3$ and **Pd****n* complexes under the standard conditions. Furthermore, the activity of these complexes drops drastically in the presence of metallic mercury (Hg drop test). However, neither of these experiments provides irrefutable evidence of a heterogeneous process. In addition, the isolation of a pale-grayish solid after the first run with **Pd*2** (see above) that is able to catalyze a second run could be indicative of molecular catalysis.

In summary, the complexes **Pd*1** and **Pd*2** catalyze the formation of biaryls from arylsiloxanes and aryl bromides in only water as solvent. Yields generally in the range of 90–98% are obtained for both activated and inactivated aryl bromides using Pd loadings of 1 mol % and reaction times of 1.5 h, both of which are better than those described previously.[10] The reactions are compatible with air, and in addition, yields are significantly increased by its presence. The viability of catalyst recycling has been shown for **Pd*2**, but practical problems arise from its poor solubility in water at room temperature. The water-insoluble catalysts [PdCl$_2$(PhCN)$_2$] and [PdCl$_2$(PPh$_3$)$_2$] are also notably efficient, but they produce lower yields in cross-coupling products with inactivated aryl bromides. Moreover, they decompose more quickly to form inactive Pd black, thus precluding catalyst reuse. In our opinion, the water solubility of the crown ether phosphanes is responsible for the enhanced stability of **Pd*1** and **Pd*2** under these reaction conditions. Our current efforts are directed at further expanding the reaction scope to other substrates and elucidating the nature of the catalyst.

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Supporting Information Available: Experimental procedures and spectroscopic data for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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