Water-Soluble Palladacycles as Precursors to Highly Recyclable Catalysts for the Suzuki Coupling of Aryl Bromides in Aqueous Solvents

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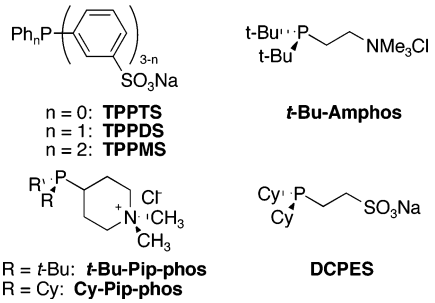
A family of water-soluble palladacycles was prepared from benzylamine or benzaldehyde imine ligands bearing hydrophilic functional groups. The palladacycles derived from *N*,*N*-dimethyl-*p*-hydroxybenzylamine (**7**) and sodium 4-(*N*-benzylideneamino)benzenesulfonate (**10**) gave active catalysts for the Suzuki coupling of aryl bromides and activated aryl chlorides in combination with (2-di-*tert*-butylphosphinoethyl)trimethylammonium chloride (*t*-Bu-Amphos). The catalyst derived from **10**/*t*-Bu-Amphos could be used for 12 reaction cycles in the Suzuki coupling of 4-bromotoluene at 80 °C before a significant loss of catalyst activity was observed.

Introduction

Water has attracted attention as a potential replacement for organic solvents due to its low cost, nonflammability, low toxicity, and the fact that it is a renewable resource.[1] In addition, the use of water in combination with hydrophilic homogeneous metal catalysts offers the potential to easily separate and recycle the metal catalyst from organic product streams. Removal of metal impurities from homogeneous catalysts is a challenging issue, particularly in the manufacturing of pharmaceuticals, where residual metal levels must be in the ppm range.[2] Recyclable catalyst systems allow catalyst loadings that are high enough to provide desirable reaction rates, while lowering the cost of catalyst per unit product. Since Casalnuovo's[3] initial report of palladium-catalyzed cross-coupling reactions in aqueous solvents catalyzed by TPPMS/$Pd(OAc)_2$, there has been a great deal of effort devoted to identifying active, hydrophilic palladium catalysts for a range of cross-coupling reactions.[4−7] Much of this work has focused on the development of water-soluble analogues of phosphines, particularly derivatives of triphenylphosphine.

Since Beller and Herrmann's[8] initial report on the use of a palladacycle precatalyst derived from $(o\text{-tol})_3P$ and $Pd(OAc)_2$, there has been a growing interest in the use of palladacycles as catalyst precursors.[9,10] Mechanistic studies on palladacyclic catalyst systems have shown that palladacycles with a variety of supporting ligands are decomposed under typical palladium-catalyzed cross-coupling conditions.[11−19] In the absence of other supporting ligands, palladium clusters are formed that likely are the true active species. In the presence of phosphine ligands, Pd(0)−phosphine complexes can form. The lability of palladacycle complexes has made identifying recyclable palladacycle catalyst systems challenging. Attempts to attach palladacycles to solid supports have given mixed results, since the supported palladacycle can decompose to give soluble catalyst species that are lost when the solid support is recovered.[12,15] Bergbreiter has reported soluble polymer-supported SCS-pincer complexes that are recyclable catalysts for Heck and Suzuki couplings,[20,21] but recent results show that the pincer complex acts as a slow



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release source of a soluble catalytically active species.[11] In addition to catalyst leaching, most supported palladacyclic systems are limited to reactive aryl iodide substrates, while showing little activity toward aryl bromides or chlorides. An exception is a recent report of a silica-supported oxime palladacycle that was an effective and recyclable catalyst for Suzuki couplings of activated aryl chlorides.[22]

The use of a hydrophilic palladacycle precursor in an aqueous-biphasic solvent system would be an alternate way to obtain a recyclable catalyst system. There are relatively few examples of hydrophilic palladacyclic precatalysts, however. An SCS-pincer complex functionalized with poly(ethylene glycol) arms was shown to be an effective catalyst for the Heck coupling of aryl iodides in an aqueous/organic biphase.[21] Ryabov[23] reported the first example of a water-soluble Schiff base palladacycle, which was applied as a catalyst for ester hydrolysis. Simple oxime-derived palladacycles were shown to be active precatalysts for the Suzuki and Heck couplings of aryl bromides and chlorides.[24−26] High turnover numbers (TONs) were achieved in the Suzuki coupling of activated aryl bromides (10^5) and activated aryl chlorides (10^3), but the recyclability of these catalyst systems was not explored. A hydrophobic palladacycle derived from a sterically demanding Schiff base was shown to give high activity for Suzuki couplings of deactivated aryl bromides in refluxing water.[27] The hydrophobic nature of this palladacycle would presumably not allow the catalyst to be retained in the aqueous phase.

Bedford has shown that simple alkylphosphines, such as tricyclohexylphosphine (Cy_3P), in combination with palladacycles can give highly active catalysts for cross-coupling reactions of aryl bromides and chlorides.[28−31] Our group has been exploring the utility of bulky, hydrophilic alkylphosphines in palladium-catalyzed cross-coupling reactions. We have shown that *t*-Bu-Amphos and *t*-Bu-Pip-phos give catalysts with good activity for the Suzuki, Heck, and Sonogashira coupling of aryl bromides under mild conditions.[32,33] The *t*-Bu-Amphos/Pd-$(OAc)_2$ catalyst system could be completely restrained in the aqueous phase and showed modest recyclability. The catalyst system begins to lose activity after three reaction cycles, presumably due to catalyst deactivation. Therefore, we were interested to see if the combination of a water-soluble alkylphosphine and a palladacycle precursor would show improved activity and stability in aqueous-phase cross-coupling reactions. Herein we report the synthesis of a family of novel water-soluble palladacycles and their ability to act as recyclable precatalysts for the Suzuki coupling of aryl bromides.

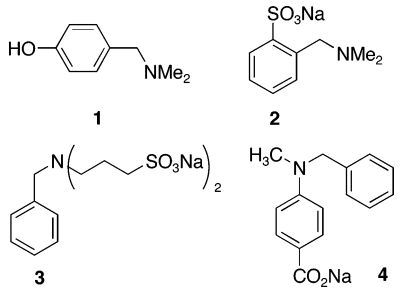


Figure 1. Hydrophilic benzylamine ligands.

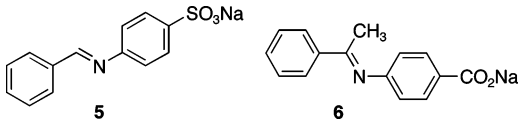
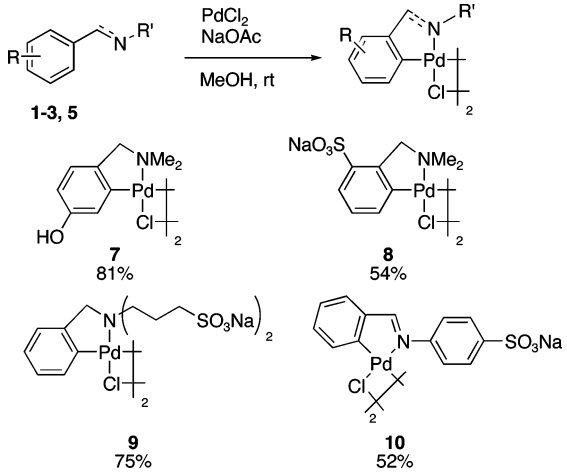


Figure 2. Hydrophilic imine ligands.

Scheme 1. Synthesis of Hydrophilic Palladacycles



Results

Ligand Synthesis. Hydrophilic amine- and imine-based palladacycle precursor ligands were synthesized that incorporated hydroxyl, carboxylate, or sulfonate substituents. *p*-Hydroxybenzylamine **1** (Figure 1) was prepared by reductive amination of *p*-hydroxybenzaldehyde with dimethylamine. A sulfonate-functionalized benzylamine (**2**) was similarly prepared starting from the commercially available 2-formylbenzenesulfonate. A disulfonated benzylamine ligand was prepared by dialkylation of benzylamine with 1,3-propane sultone to give **3**. Sequential reductive amination of *p*-aminobenzoic acid with benzaldehyde and then formaldehyde gave carboxylate-substituted benzylamine **4**.

Schiff base ligands were prepared by the condensation of hydrophilic aniline derivatives with benzaldehyde or acetophenone. Condensation of the sodium salt of sulfanilic acid with benzaldehyde gave the sulfonated Schiff base **6** (Figure 2). Imine ligand **6** could not be prepared directly from the condensation of acetophenone and *p*-benzoic acid. Instead, acetophenone and *p*-aminobenzoic acid were condensed in the presence of cyanide to give an α-cyanobenzylamine that was decomposed to the desired imine with base.

Palladacycle Synthesis. The palladacycles were prepared by stirring a mixture of the appropriate ligand precursor with $PdCl_2$ and sodium acetate in methanol to give the desired chloride-bridged palladacycle dimers (Scheme 1). *p*-Hydroxybenzylamine **1** gave palladacycle **7** in 81% yield as a yellow solid. The neutral form of the palladacycle was insoluble in water, but was soluble

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Table 1. Suzuki Coupling of 4-Bromoanisole Using 7 as a Precatalyst[a]

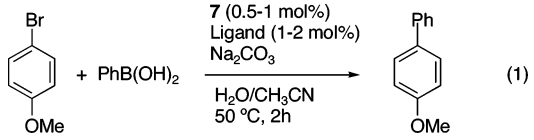
entry	ligand	mol % **7**	yield (%)[b]
1	none	2	23
2	DCPES	2	37
3	*t*-Bu-Pip-phos	2	99
4	*t*-Bu-Pip-phos	1	56
5	*t*-Bu-Amphos	2	>99
6	*t*-Bu-Amphos	1	99
7	*t*-Bu-Amphos	1[c]	99
8	Cy-Pip-phos	2	90
9	Cy-Pip-phos	1	63
10	Cy-Pip-phos	1[c]	63

[a] 4-Bromoanisole (0.2 mmol), $PhB(OH)_2$ (0.3 mmol), Na_2CO_3 (0.4 mmol), **7** (2−4 μmol of Pd), ligand (1:1 L:Pd), 1:1 H_2O/CH_3CN (1.5 mL), 50 °C, 2 h. [b] GC yield determined by comparison to an internal standard (mesitylene) using response factors determined with authentic materials. [c] Water (1.5 mL) used as the solvent.

in basic water, acetonitrile, DMSO, and hot methanol. Sulfonated palladacycles **8**−**10** were prepared from ligands **2**, **3**, and **5** in the same way in 54, 75, and 52% yield, respectively. Complex **8** was soluble in water and methanol, while palladacycles **9** and **10** were soluble in water, but insoluble in methanol.

When carboxylate-functionalized ligands **4** and **6** were reacted with $PdCl_2$, a black precipitate was obtained. This material could not be characterized due to its insolubility in all solvents tested (water, methanol, acetonitrile, methylene chloride, DMSO). Elemental analysis of this material showed that both palladium and the carboxylate ligand were present in approximately equimolar amounts. We believe that ligands **4** and **6** act as bridging ligands through coordination to the imine and the carboxylate group. The resulting network likely also entrains some palladium black, accounting for its color. In contrast, the more weakly coordinating sulfonate anion does not strongly coordinate to palladium, allowing the simple palladacycle dimers to be isolated.

Catalytic Activity of 7−10. The ability of palladacycle **7** to give an active catalyst for the Suzuki coupling of a deactivated aryl bromide was explored alone and in combination with a variety of water-soluble alkylphosphines (eq 1, Table 1). Hydroxybenzylamine palladacycle **7** gave only a modest yield in the Suzuki coupling of 4-bromoanisole at 50 °C. Catalysts derived from a combination of hydrophilic alkylphosphines (1:1 L:Pd) and **7** gave improved yields of the coupling product. *t*-Bu-Pip-phos, *t*-Bu-Amphos, and Cy-Pip-phos all gave effective catalysts (>90% yield) in combination with **7** (2 mol % Pd, entries 3, 5, and 8), while DCPES gave a much less effective catalyst (entry 2). When the catalyst loading was decreased to 1 mol % Pd, the yields dropped significantly for both the *t*-Bu-Pip-phos and Cy-Pip-phos systems, while the *t*-Bu-Amphos/**7** catalyst system again gave a quantitative yield of the coupling product (entries 4, 6, and 9). The *t*-Bu-Amphos/**7** system also gave a quantitative yield of 4-methoxybiphenyl when the reaction was carried out in water. The observed order of reactivity for these ligands was different than that seen when $Pd(OAc)_2$ was used as the precursor. In the case of reactions catalyzed by the alkylphosphine ligands and $Pd(OAc)_2$, the order of activity is *t*-Bu-Amphos ≈ *t*-Bu-Pip-phos > Cy-Pip-phos, which follows the steric demand for these ligands.[34] Using **7** as the catalyst precursor, *t*-Bu-Amphos still gave the most active catalyst, but there was little difference between Cy-Pip-phos and *t*-Bu-Pip-phos.



(1)

The catalyst derived from *t*-Bu-Amphos and palladacycle **7** showed good activity for the cross-coupling of a deactivated aryl bromide (4-bromoanisole) and phenylboronic acid at low catalyst loadings (Figure 3). Yields ≥ 90% were obtained with palladium loadings as low as 0.04 mol % (2300 mol/mol Pd) for coupling reactions carried out in water at 80 °C for 4 h. When the catalyst loading was decreased below 0.02 mol %, the yield dropped slightly to 86% (4300 mol/mol Pd). With 0.01 mol % Pd, a 68% yield (6800 mol/mol Pd) was obtained after 4 h, but only a trace (2%) of product was formed when the catalyst loading was decreased to 0.002 mol % Pd. If this reaction was allowed to proceed for 48 h at 80 °C, the yield was increased to 66% (33 000 mol/mol Pd).

The ability of the other palladacycles to give effective precatalysts with *t*-Bu-Amphos was explored in the coupling of 4-bromotoluene and phenylboronic acid. The catalyst derived from palladacycle **8** and *t*-Bu-Amphos gave a modest yield of the coupled product, while palladacycle **9** in combination with *t*-Bu-Amphos gave an inactive catalyst (Table 2). Longer reaction times did not significantly improve the yield of the product in either case. The sulfonated imine palladacycle **10** gave an efficient catalyst in combination with *t*-Bu-Amphos, however. The coupling reaction using the **10**/*t*-Bu-Amphos system was repeated in the presence of mercury to determine whether the active species was homogeneous or heterogeneous.[35] Mercury had no significant effect (entry 4) on the yield of coupled product, which suggests that the active catalyst is a homogeneous species.

Catalyst Scope. With palladacycles **7** and **10** being identified as effective precatalysts for model Suzuki coupling reactions, the scope of these catalyst systems was explored with a range of aryl halides and arylboronic acids. Palladacycles **7** and **10** both gave excellent yields for electron-deficient, -neutral, and -rich aryl bromide substrates (Table 3). Both hydrophobic and hydrophilic aryl bromides could be coupled in excellent yield using water as the solvent. Catalysts derived from both palladacycle precursors gave lower yields when the aryl bromide contained an *ortho*-methyl substituent. The catalyst derived from palladacycle **10** appeared to be more strongly affected by steric bulk, as it gave lower yields with 2-bromotoluene and 2-bromo-*m*-xylene than **7**. In both cases, the yields were lower than those obtained at room temperature with a catalyst derived from *t*-Bu-Amphos/$Pd(OAc)_2$.[32] Catalysts derived from both **7** and **10** gave modest yields with 4-chlorobenzonitrile. The catalyst derived from **10** required higher temperature (100 °C) to match the yield obtained at 80 °C with precatalyst **7** (higher temperature did not improve the yield with **7**). At 80 °C, the catalyst derived from **7** gave no cross-coupled product with a 4-chlorotoluene. At 120 °C a low yield of the coupling product could be obtained after 4 h.

Precatalysts **7** and **10** both gave good yields in the cross-coupling of 4-bromotoluene and substituted arylboronic acids (Table 4). The presence of electron-donating or -withdrawing groups on the arylboronic acid did not significantly affect the cross-coupling yield. The yields obtained with the two palladacycles were generally the same, with the exception of

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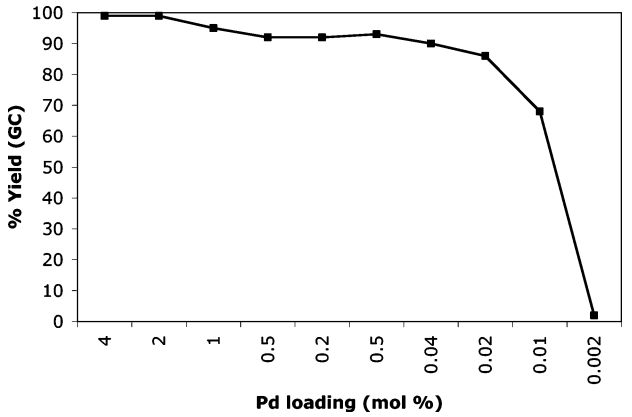


Figure 3. Yield of 4-methoxybiphenyl as a function of catalyst loading (*t*-Bu-Amphos/**7**, 1:1, H_2O, 80 °C, 4 h).

Table 2. Suzuki Coupling Using Palladacycle/*t*-Bu-Amphos Catalyst Systems[a]

entry	palladacycle	yield (%)[b]
1	**8**	60
2	**9**	10
3	**10**	>99[c]
4	**10**	97[d]

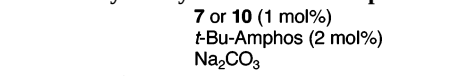
[a] 4-Bromotoluene (0.2 mmol), $PhB(OH)_2$ (0.3 mmol), Na_2CO_3 (0.4 mmol), **8**−**10** (2 μmol Pd), *t*-Bu-Amphos (2 μmol), H_2O (1.5 mL), 80 °C, 4 h. [b] GC yield determined by comparison to an internal standard (mesitylene) using response factors determined with authentic materials. [c] 1 h. [d] Reaction run in the presence of mercury (7 mmol).

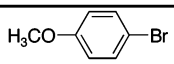
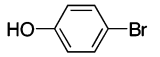
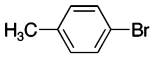
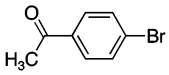
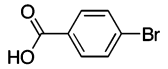
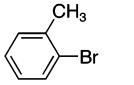
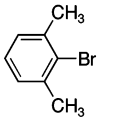
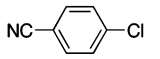
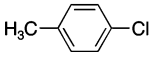
4-methoxyphenylboronic acid, where palladacycle **10** gave a higher yield (90% compared with 79%). The incorporation of an *ortho*-methyl substituent on the aryl boronic acid did not affect the yield of coupled product with either palladacycle. This result is in contrast to the lowered yields seen when an *ortho*-methyl substituent was present on the aryl halide.

Catalyst Recycling. The potential recyclability of the catalysts derived from *t*-Bu-Amphos and palladacycles **7** and **10** was explored in the model cross-coupling of 4-bromotoluene and phenylboronic acid. The reaction was carried out in water at 80 °C for 1 h. After cooling to room temperature, the organic products were extracted with deoxygenated ethyl acetate and the yield was determined by GC. The aqueous phase was then transferred to a new reaction vessel containing fresh reagents. This process was repeated until the yield began to decrease significantly. We have previously reported that $Pd(OAc)_2$/*t*-Bu-Amphos can be used for three reaction cycles in the Suzuki coupling at room temperature before yields begin to decrease.[33] To provide a direct comparison with the palladacycle catalyst precursors, the recycling experiment was repeated at 80 °C. At 80 °C, the $Pd(OAc)_2$/*t*-Bu-Amphos system actually gave slightly poorer results, with catalyst activity degrading significantly in the fourth cycle (Table 5). The catalyst derived from palladacycle **7** was somewhat more efficient than that derived from $Pd(OAc)_2$, giving four cycles of quantitative yield before the efficiency of the catalyst began to degrade. Palladacycle **10** gave a highly recyclable catalyst. This catalyst system gave a quantitative yield of product for 11 catalyst cycles. The yield was 85% in the 12th cycle and then 50% in the 13th. Significantly, the reaction time was kept at 1 h throughout this study; thus there was no apparent loss of catalyst efficiency until the 12th cycle.

As the coupling reaction was repeated using the same aqueous solution, inorganic salts began to precipitate from the reaction mixture. In the recycling study with palladacycle **10**, the aqueous catalyst solution was allowed to stand overnight after the eighth cycle to allow these salts to settle out. The aqueous supernatant was then removed and transferred to a new reaction vial for the subsequent cycles. Significantly, the efficiency of the catalyst solution was not adversely affected by this additional manipulation. An additional three cycles of quantitative yields were achieved after decantation of the catalyst solution from the precipitated salts. The fact that the precipitated solids could be

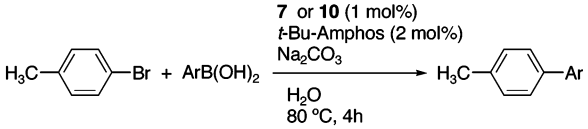
Table 3. Coupling of Aryl Halides with Phenylboronic Acid Catalyzed by 7 or 10/*t*-Bu-Amphos[a]

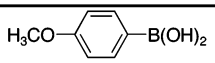
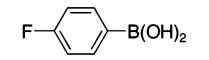
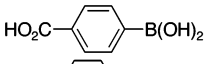
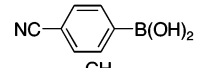
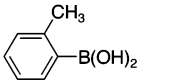


entry	ArX	palladacycle	yield (%)[b]
1		**7**	95
		10	93
2		**7**	90
		10	95
3		**10**	90
4		**7**	86
		10	92
5		**7**	96
		10	90
6		**7**	68
		10	51
7		**7**	64
		10	43
8		**7**	68
		10	57
		10	72[c]
9		**7**	0
		7	22[d]

[a] ArX (1 mmol), $PhB(OH)_2$ (1.5 mmol), Na_2CO_3 (2 mmol), **7** or **10** (0.01 mmol), *t*-Bu-Amphos (0.02 mmol), H_2O (5 mL), 80 °C, 4 h, unless noted otherwise. [b] Average isolated yield of two runs. [c] 100 °C. [d] 120 °C.

Table 4. Coupling of 4-Bromotoleuene with Arylboronic Acids Catalyzed by 7 or 10/*t*-Bu-Amphos[a]



entry	$ArB(OH)_2$	palladacycle	yield (%)[b]
1		**7**	79
		10	90
2		**7**	92
		10	94
3		**10**	80
4		**7**	85
		10	86
5		**7**	86
		10	88

[a] ArX (1 mmol), $PhB(OH)_2$ (1.5 mmol), Na_2CO_3 (2 mmol), **7** or **10** (0.01 mmol), *t*-Bu-Amphos (0.02 mmol), H_2O (5 mL), 80 °C, 4 h, unless noted otherwise. [b] Average isolated yield of two runs.

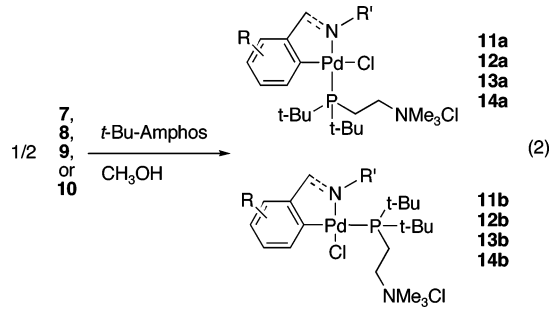
Table 5. Recycling of Catalysts Derived from $Pd(OAc)_2$, 7, or 10/*t*-Bu-Amphos[a]

	reaction yield by cycle[b,c]							
Pd source	1	2	3	4	5	6−11[d]	12	13
$Pd(OAc)_2$	>99%	89%	86%	31%				
7	>99%	>99%	>99%	>99%	66%			
10	>99%	>99%	>99%	>99%	>99%	>99%	85%	50%

[a] 4-Bromotoluene (0.2 mmol), $PhB(OH)_2$ (0.22 mmol), Na_2CO_3 (0.4 mmol), $Pd(OAc)_2$, **7**, or **10** (4 μmol of Pd), *t*-Bu-Amphos (4 μmol), H_2O (1.5 mL), 80 °C, 1 h. [b] GC yield of product extracted with ethyl acetate. [c] Cycles 2−13 used the aqueous solution remaining after the previous cycle. [d] After cycle 8, the reaction was allowed to stand overnight. The catalyst solution was removed from the precipitated salts and used for cycles 9−13.

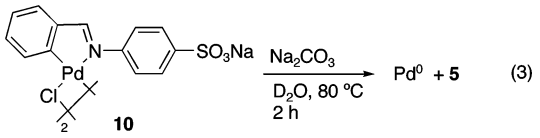
discarded without adversely affecting the catalyst activity indicates that the catalytically active species remains dissolved or suspended in water at room temperature after standing overnight.

Palladacycle Coordination Chemistry and Stability. The palladacycle dimers could be split with *t*-Bu-Amphos to give monomeric phosphine adducts (eq 2). Reaction of palladacycle **7** with *t*-Bu-Amphos in methanol gave two resonances in the ^{31}P NMR spectrum at 53.0 and 50.7 ppm in a ratio of 1:2.5. The presence of two peaks may represent formation of *cis* and *trans* isomers of the phosphine adduct, **11a** and **11b**. Phosphine adduct **11** was isolated in low yield (36%) by precipitation with ether from a concentrated methanol solution as a single isomer as determined by ^{31}P NMR spectroscopy (53 ppm). The palladium-bound carbon of the N−C ligand appeared as a broad singlet, so it was not possible to determine which isomer was isolated. Attempts to grow X-ray-quality crystals of this complex were unsuccessful. ^1H and ^{13}C NMR spectra were consistent with the 1:1 phosphine adduct. *t*-Bu-Amphos adducts of **8**−**10** were prepared and characterized by ^{31}P NMR spectroscopy. Phosphine adduct **14** derived from palladacycle **10** also gave two ^{31}P NMR resonances at 41.6 and 39.9 ppm (4:1 ratio), suggesting the formation of isomers with the phosphine *cis* and *trans* to the imine nitrogen. Benzylamine palladacycles **8** and **9** both gave a single sharp peak in their ^{31}P NMR spectra (52.7 and 52.9 ppm, respectively), indicating that only one isomer (**12a** or **12b** and **13a** or **13b**) was formed in each case.

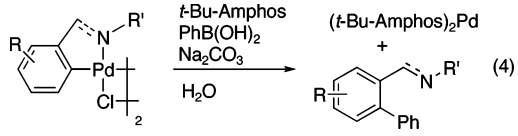


Although palladacycles are often described as thermally stable, there are many examples of palladacycles that decompose under mild conditions.[15,16] In fact, this decomposition is often thought to be the key step in the formation of the catalytically active species in cross-coupling reactions catalyzed by palladacycles.[9,11−14] The stability of the hydrophilic palladacycles was explored by heating them in aqueous base. Hydroxy-functionalized palladacycle **7** was dissolved in aqueous (D_2O) sodium carbonate and heated to 80 °C for 2 h. Some precipitation of palladium black was observed during this time. The ^1H NMR spectrum of the mixture after heating showed that the majority of the palladacycle was intact. Minor peaks corresponding to the free benzylamine ligand were observed. Heating complexes **8** and **9** under similar conditions for 2 h did not result in the precipitation of Pd black. The ^1H NMR spectrum of complex **8** after heating in basic solution showed two broad sets of resonances in an approximately 2:1 ratio. Both sets of peaks were similar to the spectrum of **8** in neutral D_2O. The two peaks may represent *cis* and *trans* isomers of the Pd-cyclic dimer or possibly hydroxide or carbonate analogues of **8**. No evidence of free **2** was observed. A ^1H NMR spectrum of **9** in basic water showed no evidence of decomposition of the palladacycle.

Palladacycle **10** proved to be much more labile. When a basic solution of sulfonated imine palladacycle **10** was heated at 80 °C for 2 h, a large amount of palladium black precipitated from the reaction mixture (eq 3). The ^1H NMR spectrum after heating showed that the palladacycle had been completely decomposed. The major species in solution was the intact imine ligand **5**. Thus under these conditions, the complex appears to have decomposed by clean decomplexation of the palladacycle ligand.



The stability of the palladacycles under the catalytic conditions was also explored. Palladacycles **7**−**10** were stirred in the presence of sodium carbonate (20 equiv), phenylboronic acid (10 equiv), and *t*-Bu-Amphos (2 equiv, L:Pd = 1:1) at room temperature for 6 h and then analyzed by ^1H and ^{31}P NMR spectroscopy. In each case, the ^{31}P NMR spectrum showed a singlet at 53.7 ppm, which we have previously assigned as (*t*-Bu-Amphos)$_2$Pd(0),[34] as the only phosphorus-containing species. The presence of an AXX′ virtual triplet at 1.3 ppm in the ^1H NMR spectrum in each case further confirmed the formation of (*t*-Bu-Amphos)$_2$Pd(0). Due to overlap from phenylboronic acid, it was not possible to determine the fate of the displaced nitrogen ligands. On the basis of results with similar systems by Bedford,[29,36] it is likely that the palladacycle reacted with phenylboronic acid to give the 2-phenyl analogue of the nitrogen ligand (eq 4).



Discussion

Palladacycle complexes **7** and **10** were effective catalyst precursors for Suzuki couplings of aryl bromides in the presence of *t*-Bu-Amphos. The **10**/*t*-Bu-Amphos was a particularly effective and stable catalyst system that can be recycled 11 times before losing activity. Studies in model systems showed that palladacycle **10** was completely decomposed to imine **5** and palladium metal in 2 h at 80 °C. In the presence of the reducing conditions of the catalytic system (*t*-Bu-Amphos, base, and phenylboronic acid), palladacycles **7**−**10** were converted to (*t*-Bu-Amphos)$_2$Pd(0) as the only phosphorus-containing species at room temperature. Displacement of the ligand likely occurs by aryl transfer from boron to palladium followed by reductive elimination to give the 2-aryl analogue of the nitrogen ligand

(36) Bedford, R. B.; Hazelwood, S. L.; Horton, P. N.; Hursthouse, M. B. *Dalton Trans.* **2003**, 4164−4174.

(eq 4). These results seem to suggest that the palladacycle serves only as a source of palladium and that (*t*-Bu-Amphos)$_2$Pd(0) is the catalytically active species. We have previously identified this species as being the resting state in the Pd(OAc)$_2$/*t*-Bu-Amphos catalyst system.[34]

For some palladacyclic catalyst systems, it has been proposed that the catalytically active species are palladium colloids. Although we observed a *t*-Bu-Amphos complex under catalytically relevant conditions, it is still conceivable that a colloidal species is the true catalyst. Two pieces of evidence point to a homogeneous catalyst. First, removal of the aqueous supernatant from precipitated materials after standing overnight did not result in a loss of catalytic activity during the catalyst recycling study. This result shows that the catalytically active species remains dissolved, or suspended, after the solution is allowed to stand overnight. Second, the addition of mercury did not inhibit the Suzuki coupling reaction. If the active catalyst species were heterogeneous palladium particles, these would be expect to be amalgamated by the mercury, lowering catalyst activity.[35] Therefore, we believe that (*t*-Bu-Amphos)$_2$Pd(0), formed from the palladacycle precursor, acts as a catalyst precursor or resting state for a homogeneous, phosphine-stabilized active species.

Although Pd(OAc)$_2$ and palladacycles **7**−**10** all appeared to give (*t*-Bu-Amphos)$_2$Pd(0) under the reaction conditions, the palladium sources gave very different results in the catalytic reaction. The catalyst derived from Pd(OAc)$_2$ was highly active at room temperature, while catalysts derived from **7** and **10** required temperatures of at least 50 °C to achieve reasonable reaction rates. The higher temperature may represent a slower formation of the (*t*-Bu-Amphos)$_2$Pd(0) species, from the palladacycle precursors. Palladacycle precursors **8** and **9** gave inactive catalysts, although both precursors give (*t*-Bu-Amphos)$_2$Pd(0) under the same conditions as **7** and **10**. Palladacycles **8** and **9** appeared to be more stable when heated in aqueous base, so their low activity may be due to a slower formation of (*t*-Bu-Amphos)$_2$Pd(0). It should be noted that both **8** and **9** in combination with *t*-Bu-Amphos gave complete conversion to (*t*-Bu-Amphos)$_2$Pd(0) on the same time scale as the reactions in Table 2, however.

Among the precursors that gave active catalysts systems—Pd(OAc)$_2$, **7**, and **10**—there were differences in catalytic efficiency, despite the apparent formation of identical catalyst species. The recycling study (Table 5) shows a significant difference in catalyst lifetime for the various precursors. While the catalyst derived from Pd(OAc)$_2$ loses activity after only three cycles, the catalyst derived from **7** remains active for four cycles, while **10** gives a catalyst that retained activity for 11 cycles. One could imagine that this difference was due to the palladacycles acting as slow release sources of active palladium species. Our results show that **10** is more labile than **7** and is completely decomposed in 2 h at 80 °C. Thus it seems unlikely that a significant amount of **10** survives the first 1 h reaction cycle. More subtle effects were seen with different aryl halide substrates. Catalysts derived from Pd(OAc)$_2$ were unaffected by the presence of one, or even two, *ortho*-substituents on the aryl halide.[33] In contrast, catalysts derived from palladacycles **7** and **10** gave lower yields with 2-bromotoluene and 2-bromo-*m*-xylene than with sterically unhindered substrates. Of these, **10** consistently gave lower yields than **7**.

Thus although each of the palladacycle catalyst precursors appear to form the same Pd(0) complex, it is clear that the identity of the palladacycle precursor affects both the activity and lifetime of the catalyst formed in combination with *t*-Bu-Amphos. These results suggest that the displaced palladacycle ligand continues to exert an influence after decomposition of the palladacycle precursor. For example, the increased sensitivity of catalysts derived from **7** and **10** to steric bulk in the aryl halide compared to Pd(OAc)$_2$ suggests that the active species in the palladacycle-derived catalyst systems are more sterically hindered than that derived from Pd(OAc)$_2$. Similarly, the longevity of the catalyst derived from palladacycle **10** suggests that the displaced imine ligand is able to stabilize the catalytically active species. These results seem to suggest that the nitrogen ligands continue to interact with the palladium center after being displaced by the phosphine ligand. The nature of this interaction, if present, is unclear at this time. Additional work to understand the role of these nitrogen ligands on the catalyst system are currently ongoing.

Conclusions

Hydrophilic palladacycles **7** and **10** gave active catalysts for the Suzuki coupling of aryl bromides in combination with *t*-Bu-Amphos. The **7**/*t*-Bu-Amphos systems gave high yields for the coupling of a deactivated aryl bromide (4-bromoanisole) at 80 °C after 4 h with catalyst loadings as low as 0.02 mol % Pd. The catalyst derived from **10**/*t*-Bu-Amphos proved to be highly recyclable. A total of 12 reaction cycles (80 °C, 1 h) with yields >86% were obtained with an average yield of 98% for the 12 reaction cycles. This degree of recyclability is one of the highest that we have been able to find in the literature for a Suzuki coupling of an aryl bromide using a homogeneous, hydrophilic catalyst system. Differences in catalyst stability and efficiency as a function of catalyst precursor suggest that the palladacycle ligands continue to play a role after decomplexation. Further studies will attempt to address how the structure of the palladacycle precursor affects the activity of the resulting catalyst system.

Experimental Section

Nitrogen-Based Palladacycle Ligands. Ligands **1**,[37] **3**,[38] **4**,[39] **5**,[40] and **6**[41,42] were prepared by modifications of literature procedures. Synthetic details for these compounds as well as ligand **2** are included in the Supporting Information.

Synthesis of Palladacycle 7. The palladacycles were prepared by a modification of the procedure reported by Cope.[43] $PdCl_2$ (0.1773 g, 1.0 mmol) was added to the solution of **1** (150 mg, 1.0 mmol) and sodium acetate (82 mg, 1.0 mmol) in methanol (5 mL). The resulting heterogeneous mixture was stirred at room temperature overnight. All of the palladium chloride was dissolved and replaced with a yellow precipitate. The precipitate was filtered off, washed with methanol (2 × 10 mL), and dried in vacuo to give **7** as a yellow solid (246 mg, 84%). Recrystallization from methanol gave an analytically pure sample of **7**. ^{1}H NMR (CD_3CN, 360 MHz): δ 6.99−6.31 (m, 8H), 3.85 (brs, 4H), 2.76 (brs, 12H). ^{13}C NMR (DMSO-d_6, 90.6 MHz): δ 154.0, 150.7, 138.3, 122.3, 119.7, 111.7, 72.1, 51.0. Anal. Calcd for $C_{18}H_{24}Cl_2N_2O_2Pd_2$: C, 37.01; H, 4.14; N, 4.80. Found: C, 36.56; H, 3.99; N, 4.53.

(37) Bhattacharyya, S. *Synth. Comm.* **2000**, *30*, 2001−2008.
(38) Mizoguchi, M., U.S. Patent, 5,792,619, 1998; *Chem. Abstr.* **129**: 92568.
(39) Gribble, G. W.; Nutaitis, C. F. *Synthesis* **1987**, 709−711.
(40) Reinehr, D.; Metzger, G.; Guesta, F.; Planchenault, D.; Signoret, E., European Patent, EP 957,085, 1999; *Chem. Abstr.* **131**:352569.
(41) Shukla, H. K.; Astik, R. R.; Thaker, K. A. *J. Indian Chem. Soc.* **1981**, *58*, 1182.
(42) Landor, S. R.; Sonola, O. O.; Tatchell, A. R. *Bull. Chem. Soc. Jpn.* **1984**, *57*, 1658−1661.
(43) Cope, A. C.; Friedrich, E. C. *J. Am. Chem. Soc.* **1968**, *90*, 909−913.

Palladacycle 8. To the solution of **2** (237 mg, 1.00 mmol) and sodium acetate (82 mg, 1.0 mmol) in methanol (20 mL) was added palladium chloride (177.3 mg, 1.00 mmol). The resulting mixture was stirred overnight at room temperature until the palladium chloride dissolved to give a wine-colored solution. The solvent was removed under reduced pressure. The residue was taken up in a hot methanol and water mixture (10 mL of methanol and 2 mL of water). Acetone (5 mL) was added, and the flask was placed in a freezer overnight. The mixture was filtered and the precipitate was dried in vacuo to give a yellow powder (186 mg, 53%). ^{1}H NMR (D_2O, 360 MHz): δ 7.55 (d, J = 8.09 Hz, 2H), 7.46 (d, J = 7.35 Hz, 2H), 7.08 (vt, J = 8.09 Hz, 2H), 4.35 (s, 4H), 2.82 (s, 12H). ^{13}C NMR (D_2O, 90.6 MHz): δ 145.3, 143.8, 138.2, 126.1, 123.9, 72.3, 52.9. One of the aromatic peaks was not observed. Anal. Calcd for $C_{18}H_{22}Cl_2N_2Na_2O_6Pd_2S_2$: C, 28.59; H, 2.93; N, 3.70. Found: C, 28.74; H, 2.82; N, 3.93.

Palladacycle 9. $PdCl_2$ (124 mg, 0.70 mmol) was added to a solution of **3** (280 mg, 0.70 mmol) and sodium acetate (57.4 mg, 0.70 mmol) in methanol (12 mL). The mixture was stirred at room temperature overnight. The resulting mixture was then filtered and washed with methanol (2 × 10 mL). The product was dried in vacuo to give a yellow powder (281 mg, 75%). ^{1}H NMR (D_2O, 360 MHz): δ 7.20−6.85 (m, 8H), 4.15 (s, 4H), 3.13−2.96 (m, 12H), 2.92−2.75 (m, 4H), 2.75−2.76 (m, 8H). ^{13}C NMR (D_2O, 90.6 MHz): δ 150.1, 141.3, 134.0, 126.8, 126.4, 123.2, 67.8, 61.1, 49.2, 23.9. Anal. Calcd for $C_{26}H_{36}Cl_2N_2Na_4O_{12}Pd_2S_4 \cdot 2H_2O$: C, 28.17; H, 3.64; N, 2.53. Found: C, 28.23; H, 3.54; N, 2.46.

Palladacycle 10. $PdCl_2$ (0.1773 g, 1.0 mmol) was added to the solution of Schiff base **5** (0.28 g, 1.00 mmol) and sodium acetate (0.08 g, 1.00 mmol) in methanol (25 mL). The resulting heterogeneous mixture was stirred at room temperature for 24 h. The reaction was filtered to give a black solid, which was taken up in DMSO (5 mL) and filtered through Celite to remove precipitated Pd(0). Diethyl ether (60 mL) was added slowly to the filtrate to form two layers. After standing for 24 h, the mixture was filtered. The product was recovered as a yellow solid (0.2205 g, 52%). ^{1}H NMR (D_2O, 360 MHz): δ 9.06 (d, J = 7.40 Hz, 4H), 8.36 (s, 2H), 8.05 (d, J = 8.01 Hz, 4H), 7.89−7.70 (m, 5H), 7.69−7.50 (m, 3H). ^{13}C NMR (DMSO-d_6, 90.6 MHz): δ 172.8, 150.6, 147.9, 133.9, 132.1, 131.6, 128.6, 126.6, 126.3, 123.4, 112.2. Anal. Calcd for $C_{26}H_{18}Cl_2N_2Na_2O_6Pd_2S_2$: C, 36.81; H, 2.14; N, 3.30. Found: C, 37.44; H, 2.64; N, 3.51.

Stability of Palladacycle (10). Palladacycle **10** (5.8 mg) and sodium carbonate (21 mg) were added to an NMR tube in a drybox. The NMR tube was sealed and moved from the drybox. After D_2O was added (0.5 mL), the NMR tube was placed in an 80 °C oil bath. ^{1}H NMR data were obtained at regular intervals. The ^{1}H NMR spectrum showed that palladacycle **10** decomposed to **5** in 2 h under basic conditions. ^{1}H NMR (D_2O, 360 MHz): δ 9.97(s, 1H), 7.99-(d, J = 8.02 Hz, 2H), 7.79−7.68 (m, 1H), 7.67−7.50 (m, 4H), 6.88 (d, J = 8.62 Hz, 2H).

Reaction of Palladacycles with *t*-Bu-Amphos. Palladacycle dimer (0.01 mmol, 0.02 mmol in Pd) and *t*-Bu-Amphos (5.4 mg, 0.02 mmol) were taken up in an NMR tube in a drybox. The NMR tube was then sealed and charged with deoxygenated water (0.5 mL). In the case of palladacycle **7**, the mixture was heated at 80 °C for several minutes to give a clear yellow solution. The formation of palladacycle phosphine adducts was monitored by ^{31}P NMR spectroscopy: **11**, 53.0 and 50.7 ppm (1:2.5); **12**, 52.7 ppm; **13**, 52.9 ppm; **14**, 41.6 and 39.9 ppm (4:1).

Palladacycle Phosphine Adduct (11). Palladacycle **7** (29.2 mg, 0.05 mmol) and *t*-Bu-Amphos (26.7 mg, 0.10 mmol) were taken up in deoxygenated methanol (3 mL). The mixture was refluxed 20 min. Methanol was evaporated in vacuo. The residue was dissolved in a minimum amount of methanol and precipitated with ether (10 mL) to give a pale yellow solid (20 mg, 36%). ^{1}H NMR (D_2O, 360 MHz): δ 7.10 (d, J = 8.32 Hz, 1H), 6.90 (s, 1H), 6.62 (d, J = 7.77 Hz, 1H), 4.01 (s, 2H), 3.26−3.06 (m, 2H), 2.86 (s, 9H), 2.53 (s, 6H), 2.48−2.36 (m, 2H), 1.52 (d, J_{P-H} = 13.87, 18H). ^{13}C NMR (D_2O, 90.6 MHz): δ 155.8, 141.4, 140.1, 125.5, 124.3 (br), 112.2, 73.8 (brs), 65.2 (brs), 53.4 (brs), 38.1 (d, J_{C-P} = 16.79 Hz), 31.04 (d, J_{C-P} = 4.58 Hz), 30.96 (d, J_{C-P} = 4.58 Hz). ^{31}P NMR (D_2O, 202.5 MHz): δ 53.6 (s).

General Procedure for Ligand Screening Trials. Under nitrogen, a vial was charged with an appropriate amount of palladacycle, ligand, sodium carbonate (42.4 mg, 0.4 mmol), and phenylboronic acid (36.6 mg, 0.3 mmol). To this was added deoxygenated 1:1 H_2O/CH_3CN (1.5 mL). 4-Bromoanisole (25 μL, 0.2 mmol) and an internal standard, mesitylene (22 μL), were added via syringe. The reactions were run at the desired temperature. Aliquots were removed at a regular interval from the organic layer and analyzed by GC. In the case of water (1.5 mL) as the solvent, the reaction was run at the desired time and was then allowed to cool to room temperature. Ethyl acetate (1 mL) and mesitylene were added to the reaction mixture. Yields were calculated using response factors determined with authentic samples of 4-bromoanisole and 4-methoxybiphenyl.

General Procedure for Low Catalyst Loading Trials. Stock solutions were prepared by dissolving the appropriate amount of palladacycle **7** in deoxygenated acetonitrile to give solutions that were 3.5×10^{-2} to 3.5×10^{-4} M in Pd. An appropriate amount of *t*-Bu-Amphos was dissolved in deoxygenated water to give solutions that were 7.5×10^{-2} to 7.5×10^{-4} M in P. Under nitrogen, a vial was charged with sodium carbonate (42.4 mg, 0.4 mmol) and phenylboronic acid (36.6 mg, 0.3 mmol). To this were added deoxygenated water (1.5 mL) and 4-bromoanisole (25 μL, 0.2 mmol). The catalyst and ligand solutions were added via syringe. The reaction was allowed to stand for 4 h at 80 °C. The reaction then was allowed to cool to room temperature, and ethyl acetate (1 mL) was added. Aliquots were removed from the organic layer and analyzed by GC. Yields were calculated using response factors determined with authentic samples of 4-bromoanisole and 4-methoxybiphenyl.

General Procedure for Catalyst Recycling Trials. Under nitrogen, a vial was charged with $Pd(OAc)_2$, **7**, or **10** (1 mol%), *t*-Bu-Amphos (5.4 mg, 2 mmol %), sodium carbonate (42.4 mg, 0.4 mmol), and phenylboronic acid (27 mg, 0.22 mmol). To this mixture was added deoxygenated water (1.5 mL). 4-Bromotoluene was added via syringe (25 μL, 0.2 mmol). The reactions were run at 80 °C for 1 h. After the reaction mixture was cooled to room temperature, deoxygenated ethyl acetate (1 mL) was added and stirred for 1 min. The upper layer was separated via cannula, and mesitylene (15 μL) as internal standard was added to this layer. Aliquots were removed from the organic layer and analyzed by GC. The aqueous layer was transferred via cannula to a vial that was charged with phenylboronic acid (27 mg, 0.22 mmol) and sodium carbonate (21 mg, 0.2 mmol). 4-Bromotoluene (25 μL, 0.2 mmol) was added via syringe for the subsequent cycle.

General Procedure for the Preparatory Scale Suzuki Coupling Reaction of Water-Insoluble Aryl Halides and Arylboronic Acids. In a drybox, a round-bottom flask was charged with palladacycle dimer (0.01 mmol), *t*-Bu-Amphos (5.4 mg, 0.02 mmol), sodium carbonate (212 mg, 2.00 mmol), and arylboronic acid (1.5 mmol). The flask was sealed and removed from the drybox. Deoxygenated water (5 mL) and aryl halide (1.0 mmol) were added via syringe, and the reaction was stirred at 80 °C for 4 h unless noted. After the reaction was allowed to cool to room temperature, saturated sodium bicarbonate (20 mL) was added to the reaction mixture. The resulting mixture was extracted with ether (3 × 30 mL). The combined ether extracts were dried ($MgSO_4$), and the solvent was removed under reduced pressure. The crude material was flash chromatographed on a short silica gel column.

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Supporting Information Available: Syntheses for ligands **1**−**6** and palladacycles **7**−**14** and characterization of the ligands, palladacycle complexes, and cross-coupled products. This information is available via the Web at http://pubs.acs.org.

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