JOC Article

Aqueous-Phase, Palladium-Catalyzed Cross-Coupling of Aryl Bromides under Mild Conditions, Using Water-Soluble, Sterically Demanding Alkylphosphines

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Sterically demanding, water-soluble alkylphosphines have been used in combination with various palladium salts in Suzuki, Sonogashira, and Heck couplings of aryl bromides under mild conditions in aqueous solvents. The *tert*-butyl-substituted ligands 2-(di-*tert*-butylphosphino)ethyltrimethylammonium chloride (*t*-Bu-Amphos) and 4-(di-*tert*-butylphosphino)-*N*,*N*-dimethylpiperidinium chloride (*t*-Bu-Pip-phos) in combination with palladium(II) salts were found to give catalysts that were significantly more active than catalysts derived from tri(3-sulfonatophenyl)phosphine trisodium (TPPTS). Suzuki couplings of unactivated aryl bromides occurred efficiently at room temperature in water/acetonitrile and water/toluene biphasic mixtures or in neat water. Notably, Suzuki couplings of hydrophilic aryl bromides gave high yields without using organic solvents for the reaction or purification. This methodology has been applied to a highly efficient synthesis of diflunisal. The catalyst derived from *t*-Bu-Amphos was recycled three times in Suzuki couplings in water/toluene before catalyst activity began to significantly drop. The average yield of four cycles was >80% per cycle. Heck and Sonogashira couplings were carried out under mild conditions (50 and 80 °C, respectively) with unactivated aryl bromides to give coupled products in high yield.

Introduction

There is a growing recognition that more environmentally sustainable chemical processes must be developed to replace current methodologies that are both material and energy intensive. In response, industry has begun adopting green chemistry practices, which include the following: waste prevention rather than waste treatment; the use of less toxic reagents and solvents; the use of renewable resources; the minimization of energy demand; and the use of catalysts.[1] The pharmaceutical industry produces significantly higher levels of waste per unit product (25−100+ kg of waste/kg of product) than do the commodity or petrochemical industries (0.1−5 kg of waste/kg of product).[2] In the pharmaceutical industry, approximately 80% of this waste is comprised of solvents.[3] Efforts to reduce or eliminate the use of flammable, toxic, and nonrenewable organic solvents by replacing them with more environmentally acceptable alternatives would be expected to pay significant dividends. Use of alternative solvents as part of a biphasic reaction medium in homogeneous-metal catalyzed reactions has the added benefit of allowing for simplified recovery and potential recycling of the catalytic species.

While a variety of media, such as ionic liquids,[4,5] fluorous solvents,[6] and supercritical carbon dioxide,[7−9] have been promoted as replacements to organic solvents in metal-catalyzed reactions, water represents one of the most economically and environmentally viable options. Water is inexpensive, nontoxic, nonflammable, and readily forms biphasic mixtures with a variety of organic materials. The potential of aqueous-biphasic catalysis with water-soluble catalysts was recognized as early as the 1970s with the development of the Rh/TPPTS (TPPTS = tri(3-sulfonatophenyl)phosphine trisodium, Figure 1) catalyzed hydroformylation of propene at Rhône-Poulenc/Ruhrchemie.[10] Since that time, the utility of a variety of metal-catalyzed reactions in water has been shown.[11−15]

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10.1021/jo048910c CCC: $27.50

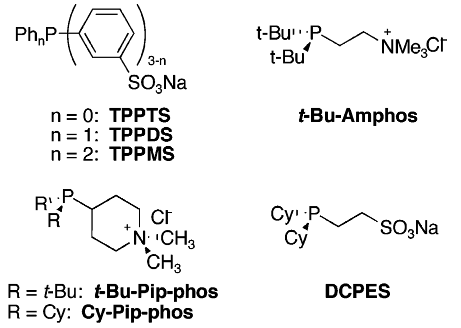

FIGURE 1. Water-soluble phosphine ligands.

Palladium-catalyzed cross-coupling reactions have become a powerful method for the formation of C−C and C−heteroatom bonds. In particular, the Heck,[16,17] Sonogashira,[18] Suzuki,[19−21] and Hartwig−Buchwald[22−25] reactions are widely used synthetic methodologies. Modest catalytic activity and difficulty separating homogeneous palladium catalysts from organic products can present hurdles to large-scale implementation, however. Phosphine ligands are generally required to achieve reasonable levels of activity with unactivated aryl bromide substrates at temperatures below 100 °C. Triphenylphosphine is the most commonly used ligand, but catalysts derived from triarylphosphines typically show little reactivity toward the less reactive aryl chlorides, except at very high temperatures. Recently it has been shown that replacing triarylphosphines with sterically demanding trialkylphosphines,[26−35] sterically demanding *N*-heterocyclic carbenes,[36−41] or ligands that form palladacycles[42] provides catalysts capable of promoting coupling reactions of aryl bromides at room temperature and reactions of aryl chlorides under mild conditions.[43]

Since Casalnuovo's[44] initial report of cross-coupling reactions catalyzed by Pd(TPPMS)$_3$, several examples of Pd-catalyzed cross-coupling reactions have been demonstrated in aqueous solvents.[11,15,45,46] TPPTS and related water-soluble phosphines give synthetically useful yields, but typically require aryl iodide or activated aryl bromide substrates and high temperatures. Although water-soluble phosphines have been developed with a variety of water-solubilizing groups, nearly all of these ligands are based on the triphenylphosphine core. We are interested in applying water-soluble, sterically demanding alkyl- or arylphosphines to aqueous phase cross-coupling reactions in an effort to achieve similar levels of activity with aryl bromides and chlorides that have been achieved in organic solvents.[47,48] We and others have shown that bulky alkylphosphine/Pd catalysts[47,49,50] or palladacyclic catalysts[51,52] efficiently couple aryl bromides under mild conditions and achieve modest activities with aryl chlorides in water. Herein we report that *t*-Bu-Amphos (Figure 1) provides active catalysts for the Suzuki, Sonogashira, and Heck couplings of aryl bromides under mild conditions in aqueous solvents.

Results

Suzuki Coupling. In our initial communication[47] we reported that the sterically demanding, water-soluble phosphines *t*-Bu-Amphos and *t*-Bu-Pip-phos (Figure 1) gave highly active catalysts for the Suzuki coupling of aryl bromides in water/acetonitrile solvent mixtures at room temperature. Cyclohexyl-substituted ligands, such as Cy-Pip-phos and DCPES, gave less active catalysts. A 1:1 L:Pd ratio gave the most active catalysts for each of the alkylphosphine ligands, while catalyst activity was significantly diminished at higher L:Pd ratios. Excellent yields were obtained with aryl bromides with a range of steric and electronic properties, using both *t*-Bu-Amphos and *t*-Bu-Pip-phos as ligands (Table 1). Both hydrophilic and hydrophobic aryl bromides gave excellent yields in this system. Highly functionalized substrates, such as a protected amino acid (**1f**, entry 6), were efficiently coupled to give a biphenylalanine derivative (**3f**). Modest activity toward an activated aryl chloride (**1g**) was observed with

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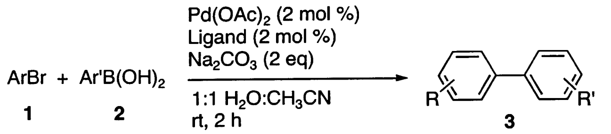
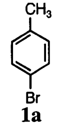
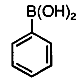
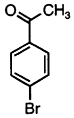
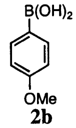
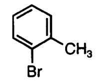
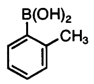
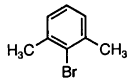
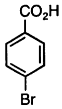
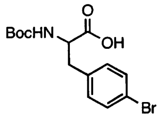
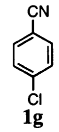
TABLE 1. Scope of Suzuki Coupling in Water/Acetonitrile with *t*-Bu-Amphos or *t*-Bu-Pip-phos



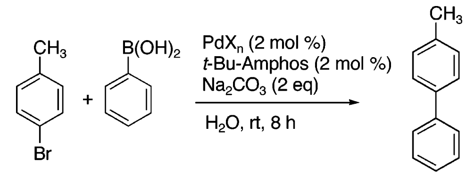
entry	1	2	3	ligand	yield (%)[a]
1	 **1a**	 **2a**	**3a**	*t*-Bu-Amphos *t*-Bu-Pip-phos	94 96
2	 **1b**	 **2b**	**3b**	*t*-Bu-Amphos *t*-Bu-Pip-phos	95 91
3	 **1c**	 **2c**	**3c**	*t*-Bu-Pip-phos	92
4	 **1d**	**2b**	**3d**	*t*-Bu-Amphos *t*-Bu-Pip-phos	90 94
5	 **1e**	**2c**	**3e**	*t*-Bu-Pip-phos	95
6	 **1f**	**2b**	**3f**	*t*-Bu-Pip-phos	94
7	 **1g**	**2a**	**3g**	*t*-Bu-Pip-phos	92[b]

[a] Reaction times were not optimized, but reactions were generally complete in 1−2 h. Average isolated yield from two independent trials. [b] 4 mol % of $Pd(OAc)_2$, 8 mol % of *t*-Bu-Pip-phos, 80 °C, 6 h.

the *t*-Bu-Pip-phos/$Pd(OAc)_2$ system, although a higher catalyst loading of 4 mol % and an increase in temperature to 80 °C was required for complete conversion. At these higher temperatures, a 2:1 L:Pd ratio was found to give higher yields, likely due to improved catalyst stability. Low levels of activity were observed under these conditions with unactivated aryl chlorides, such as 4-chlorotoluene.

One problem with this system was the fact that the active catalyst partitioned primarily into the acetonitrile-rich organic phase of the reaction rather than the aqueous phase. Therefore, we have explored the use of water alone or in combination with toluene as solvent for these catalyst systems. The use of neat water as solvent is attractive because it completely eliminates the use of organic solvents, but low solubility of hydrophobic substrates could be a potential problem. We envisioned that a water/toluene biphasic system may give better activity with hydrophobic substrates. This type of biphasic system would also be well suited for separation of the organic product from the aqueous catalyst solution and possibly recycling of the catalyst.

TABLE 2. Pd Source Screening for Suzuki Coupling in Water



1a **2a** **3a**

entry	Pd source	yield (%)[a]
1	$Pd(OAc)_2$	85
2	$Pd(NO_3)_2$	89
3	$PdSO_4$	86
4	Na_2PdCl_4	89

[a] Determined by GC with use of an internal standard (mesitylene).

We had previously observed that $Pd(OAc)_2$ gave low activity when used as the precatalyst in the Suzuki coupling of nucleosides in neat water.[53] Therefore, we compared the activity of catalysts derived from $Pd(OAc)_2$ and several more water-soluble palladium sources in combination with *t*-Bu-Amphos (Table 2). The reactions were carried out under conditions previously optimized for the $Pd(OAc)_2$/*t*-Bu-Amphos system (Table 1), but with water alone as solvent. When the coupling of 4-bromotoluene and phenyl boronic acid was run in water alone, longer reaction times were necessary compared to the water/acetonitrile solvent system. Presumably the longer reaction times are necessary due to the low solubility of the aryl bromide in water. The low solubility of $Pd(OAc)_2$ did not significantly affect the overall yield compared with more soluble palladium salts, such as $Pd(NO_3)_2$ and Na_2PdCl_4 (Table 1). Na_2PdCl_4 was chosen as the preferred palladium source for further studies in this system.

With an efficient catalyst system in hand, the scope of the Suzuki coupling in neat water was explored. The hydrophobic aryl bromide 4-bromotoluene (**1a**) gave good yields of coupled products (83−84%) with aryl boronic acids (Table 3, entries 1 and 2). The yields were slightly lower than were obtained with the same substrates in the water/acetonitrile solvent mixture. Reactions in neat water appear to be more sensitive to steric bulk on the aryl bromide than the water/acetonitrile system, as 2-bromotoluene gave only 62% of the cross-coupled product with phenyl boronic acid (entry 3). The hydrophobic biaryl products could be easily separated from the aqueous catalyst mixture with use of ethyl acetate. Since ethyl acetate is a low-toxicity, biodegradable organic solvent derived from renewable resources, this methodology represents an attractive method for large-scale application. Use of neat water as the solvent is particularly well suited for the coupling of hydrophilic aryl bromides (entries 4−7). Biphenyl carboxylic acids could easily be isolated by acidification of the reaction mixture followed by filtration. Recrystallization from water gave excellent yields of spectroscopically pure products. The synthesis of diflunisal (**3k**, entry 6) and ***3l*** (entry 7) are

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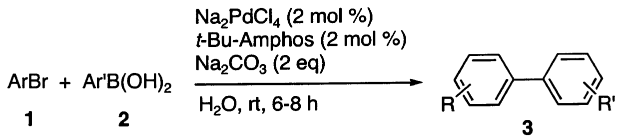
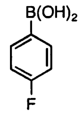
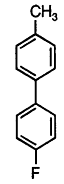
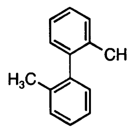
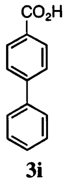
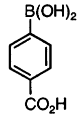
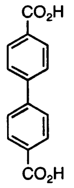
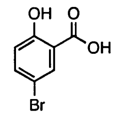
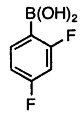
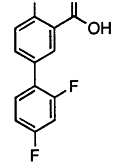
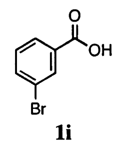
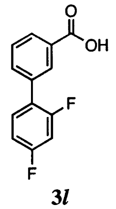
[53] Western, E. C.; Daft, J. R.; Johnson, E. M., II; Gannett, P. M.; Shaughnessy, K. H. *J. Org. Chem.* **2003**, *68*, 6767−6774.

TABLE 3. Scope of Suzuki Coupling with *t*-Bu-Amphos/Na_2PdCl_4 in Water



entry	1	2	product	yield (%)[a]
1	**1a**	**2a**	**3a**	83
2	**1a**	 **2d**	 **3h**	84
3	**1c**	**2c**	 **3c**	62
4	**1e**	**2a**	 **3i**	98
5	**1e**	 **2e**	 **3j**	94
6	 **1h**	 **2f**	 **3k**	95
7	 **1i**	**2f**	 **3*l***	96

[a] Reaction times were not optimized. Average isolated yield from two independent trials.

TABLE 4. Optimization of Suzuki Coupling in 1:1 Water:Toluene

$$\mathbf{1a} + \mathbf{2a} \xrightarrow[\substack{\text{1:1 } H_2O\text{:toluene} \\ \text{rt, 6 h}}]{\substack{Na_2PdCl_4 \text{ (2 mol \%)} \\ t\text{-Bu-Amphos (2 mol \%)} \\ Na_2CO_3 \text{ (2 eq)}}} \mathbf{3a}$$

entry	ligand	PdX_n	yield (%)[a]
1	TPPTS[b]	Na_2PdCl_4	4
2	DCPES	Na_2PdCl_4	36
3	*t*-Bu-Amphos	Na_2PdCl_4	92
4	*t*-Bu-Pip-phos	Na_2PdCl_4	90
5	*t*-Bu-Amphos	$Pd(NO_3)_2$	92
6	*t*-Bu-Amphos	$Pd(SO_4)$	89
7	*t*-Bu-Amphos	$Pd(OAc)_2$	85

[a] GC yields referenced to internal standard (mesitylene). [b] 7.5 mol % of TPPTS, 2.5 mol % of Na_2PdCl_4

particularly noteworthy. Diflunisal is an FDA-approved nonsteroidal antiinflammatory (NSAID).[54] Fluorinated biphenyl carboxylic acids, such as **3k** and **3*l***, have attracted recent attention as potent transthyretin (TTR) amyloid inhibitors.[55] The aqueous-phase methodology gave **3k** and **3*l*** in excellent yields in one step from commercially available precursors without the use of organic solvents in the reaction or purification, while not using protecting groups for the phenolic and carboxylic acid moieties.

While the use of water alone as solvent provides a particularly effective method for the preparation of hydrophilic biphenyl compounds, yields with hydrophobic substrates were somewhat depressed compared to those of the water/acetonitrile system. Therefore, we explored the use of a hydrophobic cosolvent. Toluene was chosen for our initial studies because it was expected to be a good solvent for the biphenyl products, but a poor one for the hydrophilic catalyst. The quaternary ammonium-substituted trialkylphosphine ligands are structurally similar to ammonium phase-transfer catalysts. To determine whether the activity profile determined for water/acetonitrile might be affected by differences in how the complexes derived from these ligands interacted with the toluene/water biphase, the activity of catalysts derived from these ligands was compared in a model Suzuki coupling (Table 4). Similar to our results in water/acetonitrile, *t*-Bu-Amphos and *t*-Bu-Pip-phos in combination with Na_2PdCl_4 gave the most active catalysts with the smaller DCPES ligand being less active. Again, TPPTS gave an essentially inactive catalyst at room temperature with use of a 3:1 L:Pd ratio.[56-58] Because of its relative ease of synthesis, *t*-Bu-Amphos was chosen as the optimal ligand for further studies. A similar trend in relative activity of the Pd(II) precursors to that seen in water (Table 1) was observed in the water/toluene system (entries 3 and 5−7). Na_2PdCl_4 was chosen as the palladium salt of choice for the preparative scale reactions.

The *t*-Bu-Amphos/Na_2PdCl_4 system proved to give effective catalysts for the Suzuki coupling of hydrophobic aryl bromides at room temperature in a water/toluene biphasic mixture (Table 5). Electron-rich (**1j**, entry 2) and electron-poor (**1b**, entry 3) aryl bromides gave excellent yields of coupled products. A slightly lower yield (80%)

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(54) Hannah, J.; Ruyle, W. V.; Jones, H.; Matzuk, K. W.; Kelly, K. W.; Witzel, B. E.; Holtz, W. J.; Houser, R. A.; Shen, T. Y.; Sarett, L. H.; Lotti, V. J.; Risley, E. A.; Van Arman, C. G.; Winter, C. A. *J. Med. Chem.* **1978**, *21*, 1093−1100.

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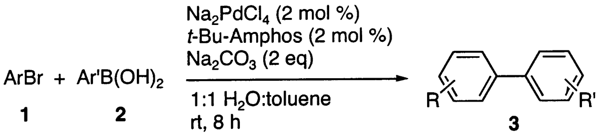
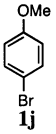
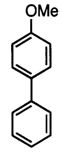
(56) We found no significant difference in activity in TPPTS/Pd catalysts with L:Pd ratios of 2−3:1.

(57) Dupuis, C.; Adiey, K.; Charruault, L.; Michelet, V.; Savignac, M.; Genêt, J.-P. *Tetrahedron Lett.* **2001**, *42*, 6523−6526.

(58) Genêt, J. P.; Linquist, A.; Blard, E.; Mouries, V.; Savignac, M.; Vaultier, M. *Tetrahedron Lett.* **1995**, *36*, 1443−1446.

TABLE 5. Scope of Suzuki Coupling with *t*-Bu-Amphos/Na_2PdCl_4 in 1:1 Water:Toluene



entry	1	2	3	yield (%)[a]
1	**1a**	**2a**	**3a**	92
2	 **1j**	**2a**	 **3m**	95
3	**1b**	**2b**	**3b**	91 95[b]
4	**1a**	**2d**	**3h**	80
5	**1e**	**2a**	**3i**	65
6	**1c**	**2c**	**3c**	74
7	**1d**	**2b**	**3d**	87

[a] Reaction times were not optimized. Average isolated yield from two independent trials. [b] 1:1 ethyl acetate:water as solvent. Determined by GC.

was obtained with an electron-deficient boronic acid (**2d**, entry 4). Coupling with a hydrophilic aryl bromide (**1e**, entry 5) was less effective in the water/toluene system than in water alone. Steric bulk on the aryl bromide was tolerated better in the toluene/water system than in water alone (entry 7), although a slightly depressed yield was obtained in the synthesis of 2,2′-dimethylbiphenyl (**3c**, entry 6) compared to that of the water/acetonitrile system. Comparable yields were obtained in 1:1 ethyl acetate:water (entry 3), which may ultimately prove to be a more environmentally attractive solvent system for these reactions than water/toluene.

One motivation for constraining a homogeneous catalyst to an organic immiscible phase is to allow the catalyst to be easily recovered and recycled. The recyclability of the *t*-Bu-Amphos/Na_2PdCl_4 catalyst was explored in the Suzuki coupling of 4-bromotoluene and phenylboronic acid in a 1:1 water:toluene solvent system. GC analysis of the toluene extract from the initial run showed a 92% yield of **3a** (Table 6). The aqueous layer remaining after toluene extraction was transferred to a new vial containing solid sodium carbonate and phenylboronic acid under nitrogen. A solution of **1a** in toluene was added and the reaction was allowed to stir for 8 h. An 85% yield of **1a** was obtained with the recycled catalyst, although the aryl bromide was not completely consumed. The recycling process was repeated three more times. After one more cycle of high conversion and good yield of cross-coupled product (cycle 3), both conversion and yields began to dramatically decrease in subsequent cycles. After the fourth cycle, it was necessary to separate the aqueous catalyst solution from a large amount of precipitated salts. This extra level of manipulation may have contributed to the significant loss of activity in cycle 5.

TABLE 6. Recycling of the *t*-Bu-Amphos/Na_2PdCl_4 Catalyst

$$\mathbf{1a} + \mathbf{2a} \xrightarrow[\text{1:1 } H_2O\text{:toluene, rt, 8 h}]{Na_2PdCl_4 \text{ (2 mol \%)}, \ t\text{-Bu-Amphos (2 mol \%)}, \ Na_2CO_3 \text{ (2 eq)}} \mathbf{3a}$$

cycle	Pd (mol %)	conversion[a]	yield (%)[a]
1	2	100	92
2	0[b]	87	85
3	0[b]	85	84
4	0[b]	65	62
5	0[b]	27	22

[a] Determined by GC relative to an internal standard (mesitylene). [b] The aqueous catalyst solution from the previous cycle was used.

The toluene extract recovered from the first cycle contained <1% of the phosphorus originally charged in the reaction as determined by ^{31}P NMR analysis with trimethyl phosphate as an internal standard. The crude product recovered upon removal of solvent contained no Pd (<1 ppm) as determined by elemental analysis. ^{31}P NMR analysis of the aqueous phase of a reaction run under similar conditions as the recycling experiment above, but with 10 mol % of catalyst, showed (t-Bu-Amphos)$_2$Pd(0) at 61 ppm and two minor, unidentified peaks at 69 and 80 ppm, which together represented approximately 10% of the total area. We expect (t-Bu-Amphos)$_2$Pd(0) to be the resting state of the catalyst system based on similar observations by Fu[59] in the t-Bu$_3$P/Pd system. These results suggest that the loss of catalytic activity was not due to leaching of the catalyst, or its components, into the organic phase. The reasons for the loss of activity are not known, but may include slow catalyst decomposition, mechanical loss during recycling, and a build up of salt byproducts that cannot be removed by extraction.

Sonogashira Coupling. Aqueous-phase Sonogashira couplings have been reported with use of hydrophilic ligands, such as TPPTS,[44,60–62] solid-supported ligands,[63–65] heterogeneous palladium sources,[66] or even microwaves in the absence of palladium.[67] These catalyst systems are limited to the use of aryl iodide substrates or in rare cases aryl bromides at elevated temperatures.[66] Since aryl iodides are expensive substrates on a large scale, a catalyst system that efficiently coupled aryl bromides or chlorides in water would be very attractive. Given the increased activity of the *t*-Bu-Amphos/Pd catalyst for Suzuki couplings of aryl bromides under mild conditions, we have explored the activity of this catalyst toward the Sonogashira coupling.

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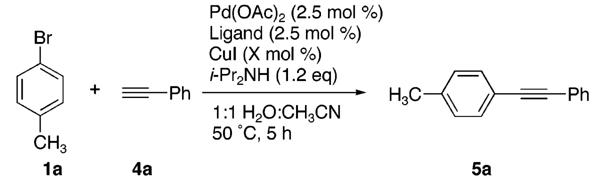
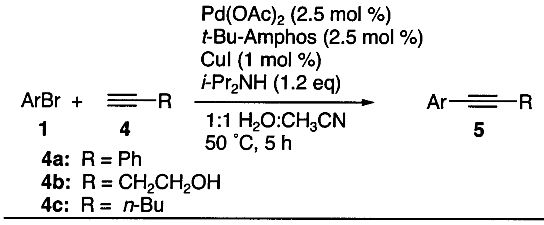
TABLE 7. Ligand Screening in Aqueous-Phase Sonogashira Coupling

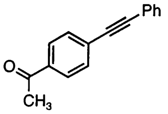
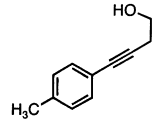
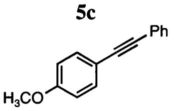
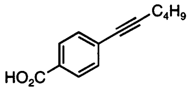
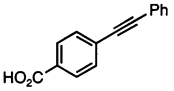
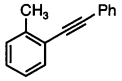
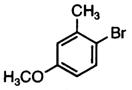
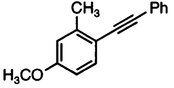
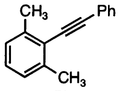
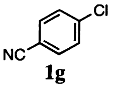
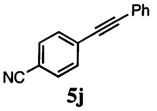


entry	ligand	CuI (mol %)	yield (%)[a]
1	*t*-Bu-Amphos	2	91
2	TPPTS	2	30
3	*t*-Bu-Amphos	1	85
4	TPPTS	1	38
5	*t*-Bu-Amphos	0	58
6	*t*-Bu-Amphos	0[b]	84
7	TPPTS	0	42

[a] GC yield determined relative to internal standard (mesitylene). Remaining peak area primarily due to **1a**. [b] CsOH used in place of diisopropylamine as base.

TABLE 8. Scope of Sonogashira Coupling with *t*-Bu-Amphos/Pd(OAc)$_2$



entry	1	4	product	yield (%)[a]
1	**1b**	**4a**	 **5b**	85 50[b] 76[c]
2	**1a**	**4b**	 **5c**	94
3	**1j**	**4a**	 **5d**	78
4	**1e**	**4c**	 **5e**	84
5	**1e**	**4a**	 **5f**	92
6	**1c**	**4a**	 **5g**	90
7	 **1k**	**4a**	 **5h**	73
8	**1d**	**4a**	 **5i**	30
9	 **1g**	**4a**	 **5j**	36[d]

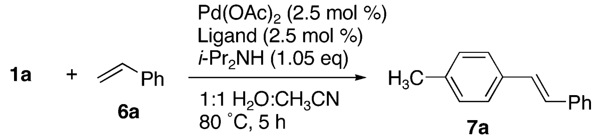
[a] Average isolated yield from two runs. Reaction times were not optimized. [b] 0% CuI. [c] 0% CuI, CsOH in place of *i*-Pr$_2$NH. [d] 5 mol % of Pd(OAc)$_2$, 5 mol % of *t*-Bu-Amphos, 80 °C. Yield determined by GC. 40% conversion of **1g**.

Attempts to carry out the Sonogashira reaction under conditions similar to those used in the Suzuki coupling—*t*-Bu-Amphos/Pd(OAc)$_2$, CuI, and sodium carbonate in water/acetonitrile—gave modest activity. Amine bases were found to give active catalysts though, with diisopropylamine being the base of choice for these reactions. The activity of catalysts derived from *t*-Bu-Amphos and TPPTS was compared over a range of CuI loadings (Table 7). With CuI loadings of 1−2%, the *t*-Bu-Amphos/Pd(OAc)$_2$ catalyst was significantly more active than the catalyst derived from TPPTS. The yield obtained with the *t*-Bu-Amphos/Pd(OAc)$_2$ decreased slightly (91% to 85%) when the CuI loading was decreased from 2% to 1%. A more significant drop in yield of **5a** was observed in the absence of CuI (entry 6). At higher CuI concentrations, rapid consumption of the alkyne occurred without formation of the cross-coupled product. An 84% yield of **5a** was obtained in the absence of CuI, when CsOH was used as the base in place of diisopropylamine (entry 6). Interestingly, the TPPTS/Pd(OAc)$_2$ gave somewhat higher yields of coupled product as the amount of CuI was decreased with the maximum yield (42%, entry 7) occurring in the absence of copper.

Preparative scale coupling reactions were carried out with 3 mol % of *t*-Bu-Amphos, 3 mol % of Pd(OAc)$_2$, and 1 mol % of CuI in the presence of 1.2 equiv of diisopropylamine. The lower 1% CuI loading was found to give better results in preparative scale couplings. Good to excellent isolated yields of alkyne products were obtained with use of the optimized conditions (Table 8). Introduction of an electron-releasing methoxy group on the aryl bromide resulted in slightly lower yields compared to similar aryl bromides lacking the methoxy group (entries 3 and 7). Introduction of a single *o*-methyl group had no effect on the yield of coupled product (entries 6 and 7). An attempt to couple 2-bromo-*m*-xylene (**1d**) with phenyl acetylene gave a low yield (30%) of **5i** (entry 8), however. A 50% yield of **5b** was obtained when the reaction was carried out in the absence of CuI (entry 1) compared to the 85% yield that was isolated with 1 mol % of CuI. By changing the base from diisopropylamine to cesium hydroxide, a 76% yield was obtained in the absence of copper. Modest activity was observed in the coupling of an activated aryl chloride (**1g**, entry 9). Upon increasing the catalyst loading to 5 mol % and the temperature to 80 °C, a 36% yield of **5h** was obtained as determined by GC. This yield was lower than that obtained under similar conditions for the Suzuki coupling of **1g** with phenylboronic acid (Table 1, entry 7). Attempts to carry out the Sonogashira coupling with *t*-Bu-Amphos/Pd(OAc)$_2$ in other solvent systems, such as neat water, water/toluene, or water/ethyl acetate, were unsuccessful. Low levels of conversion to product were observed in all cases.

Heck Coupling. The Heck reaction typically is one of the most challenging palladium-catalyzed coupling reactions for which to identify highly active catalysts.[16]

TABLE 9. Ligand Optimization in the Aqueous-Phase Heck Coupling



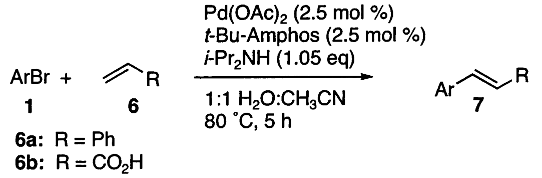
entry	ligand	L:Pd	yield (%)[a]
1	TPPTS	3:1	14
2	*t*-Bu-Amphos	1:1	74
3	*t*-Bu-Amphos	2:1	69
4	*t*-Bu-Amphos	3:1	51

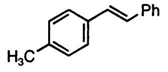
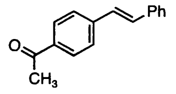
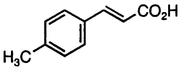
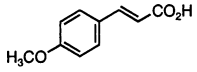
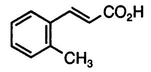
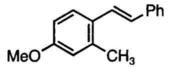
[a] GC yield relative to an internal standard (mesitylene).

The electron-rich ligands that give highly active catalysts for Suzuki, Stille, and Sonogashira couplings at room temperature generally require much higher temperatures for Heck couplings.[32,34] While electron-rich ligands promote oxidative addition of less reactive aryl bromides and chlorides, they would be expected to inhibit migratory insertion. Aqueous-phase Heck couplings utilizing TPPTS or related hydrophilic ligands give modest activity for aryl iodides and activated aryl bromides at 80 °C[44,68–71] and in some cases can be applied to unactivated aryl bromides at higher temperatures.[72] Recently, aqueous-phase Heck couplings of aryl bromides under relatively mild conditions (80 °C) have been reported with use of tri(4,6-dimethyl-3-sulfonatophenyl)phosphine (TXPTS)[48] or palladium nanoparticles.[73]

The activity of the *t*-Bu-Amphos/Pd(OAc)$_2$ catalyst system was compared with that of TPPTS for the Heck coupling of 4-bromotoluene and styrene at 80 °C. Similar to the Sonogashira reaction, initial trials showed that diisopropylamine was the base of choice for the *t*-Bu-Amphos/Pd(OAc)$_2$. A temperature of 80 °C was necessary for complete conversion. Since catalyst stability can become a problem at this temperature, we compared the activity of the *t*-Bu-Amphos/Pd(OAc)$_2$ over *t*-Bu-Amphos:Pd(OAc)$_2$ ratios of 1:1 to 3:1 (Table 9). The highest yields of *E*-stilbene (**7a**) were obtained when the *t*-Bu-Amphos:Pd(OAc)$_2$ ratio was ≤2:1 (entries 2 and 3), while the yield of **7a** was lower with a 3:1 ratio (entry 4). In all cases, only the *E*-stilbene isomer was observed by GC. Under the same conditions with 3:1 TPPTS:Pd(OAc)$_2$, which is optimal for this ligand,[56–58] only a 14% yield of **7a** was obtained. It should be noted that a 28% yield of **7a** can be obtained with the TPPTS/Pd(OAc)$_2$ system under the same conditions when sodium carbonate is used as base.[48] Similar yields are obtained with both the *t*-Bu-Amphos and TXPTS systems, although longer reaction times are needed with the *t*-Bu-Amphos system (5 h vs 2 h).

TABLE 10. Scope of Heck Coupling with *t*-Bu-Amphos/Pd(OAc)$_2$



entry	1	6	product	yield (%)[a]
1	**1a**	**6a**	 **7a**	84
2	**1b**	**6a**	 **7b**	92
3	**1a**	**6b**	 **7c**	78
4	**1j**	**6b**	 **7d**	75
5	**1c**	**6b**	 **7e**	55
6	**1k**	**6a**	 **7f**	73

[a] Average isolated yield from two trials. Reaction times were not optimized.

The scope of the 1:1 *t*-Bu-Amphos:Pd(OAc)$_2$ system was explored by using styrene and sodium acrylate as alkene substrates (Table 10). Coupling reactions of sterically unhindered aryl bromides with styrene gave excellent yields of *E*-stilbene products (entries 1 and 2). The yields of *E*-cinnamic acids obtained with sodium acrylate were slightly lower than those obtained with styrene. NMR analysis of the isolated products confirmed that the *E*-alkenes were formed exclusively. The system appears to be unaffected by either electron-deficient or electron-rich aryl bromide substrates (entries 2 and 4, respectively). The *t*-Bu-Amphos system showed more sensitivity to steric bulk on the aryl bromide in the Heck reaction than in either the Sonogashira or Suzuki reactions. Incorporation of a single *o*-methyl group resulted in a 15–20% decrease in yield (entries 5 and 6). Attempts to couple an activated aryl chloride (**1g**) were unsuccessful, even with high catalyst loadings. Similar to the Sonogashira coupling, attempts to use other solvents, such as water or water/toluene, were unsuccessful. As a result, attempts to recycle the catalyst were unsuccessful.

Conclusion

The *t*-Bu-Amphos/PdX$_n$ system provides a general and high-yielding methodology for carrying out Suzuki, Sonogashira, and Heck couplings in aqueous solvents. Suzuki coupling reactions of a diverse range of both aryl bromides and aryl boronic acids can be accomplished at room temperature in water/acetonitrile, water/toluene,

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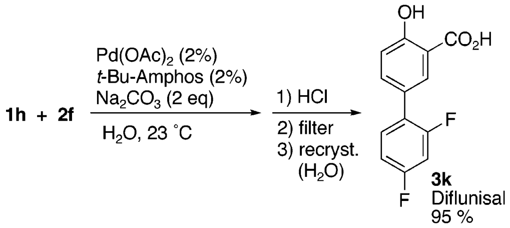
or water alone. To our knowledge, *t*-Bu-Amphos/PdX$_n$ represents one of two catalyst systems capable of carrying out Suzuki couplings of unactivated aryl bromides at room temperature in aqueous solvents.[74] Particularly noteworthy are the highly efficient coupling of hydrophilic aryl bromides with water as the only solvent. Using acid to precipitate the product allows isolation without the use of any organic solvents. The synthesis of diflunisal shows the potential utility of this methodology. With use of the procedure outlined in Table 2, diflunisal[54,55] was synthesized in 95% yield in a single step from commercially available precursors with water as the only solvent for preparation and purification (eq 1). Synthetic procedures for diflunisal from the patent literature with Pd-catalyzed coupling involve a variety of organic solvents, including 1,1,2-trichloroethane, [75] while a classical organic synthetic approach requires five steps.[76] The use of water in combination with renewable and low-toxicity solvents such as ethyl acetate represents an environmentally sustainable approach to the coupling of hydrophobic aryl bromides.



(1)

Initial recycling experiments show that the *t*-Bu-Amphos/Na_2PdCl_4 can be recycled several times in a water/toluene solvent system. While degradation of catalyst activity was observed after three cycles, the average yield after four cycles was >80% per cycle. Attachment of a structurally similar ligand to a solid support might improve the recyclability of the catalyst system, and will be explored in future work. Also noteworthy is that no leaching of phosphorus (<1% of phosphine in the reaction) or palladium (<0.02% of palladium charged, <1 ppm in organic product) was observed. Therefore, the *t*-Bu-Amphos/Na_2PdCl_4 in a water/toluene biphasic solvent provides a highly efficient method to separate the organic product from the catalyst system without the need to use distillation, recrystallization, or palladium sequestration agents.[77]

Sonogashira and Heck reactions catalyzed by the *t*-Bu-Amphos/$Pd(OAc)_2$ can be achieved efficiently with aryl bromides under significantly milder conditions than are possible with the commonly used TPPTS ligand. The *t*-Bu-Amphos ligand allows coupling reactions of both activated and deactivated aryl bromides under mild conditions and is tolerant of some degree of steric bulk on the aryl bromide. Given the lower cost and wider availability of aryl bromides compared to aryl iodides, the *t*-Bu-Amphos system should prove more widely applicable than TPPTS or similar ligands. Hydrophobic reaction products from the Heck and Sonogashira reactions can be easily isolated by using ethyl acetate.

On the basis of the observed dependence of catalytic activity on the L:Pd ratio observed with the *t*-Bu-Amphos system, we believe that the active catalyst is a monophosphine complex, but that the resting state is (*t*-Bu-Amphos)$_2$Pd(0) based on our observation of this species in catalytic systems. These results are similar to observations made by Fu in the *t*-Bu_3P/Pd system.[59] Characterization of the complexes formed under catalytic conditions between the alkylphosphines described in this paper and Pd(II) sources, including the effect of ligand structure on reduction chemistry, are currently ongoing and will be reported soon. Other current efforts include application of the *t*-Bu-Amphos/Pd(II) system to other aqueous-phase coupling reactions and the development of next generation ligands capable of promoting the coupling aryl chlorides.

Experimental Section

Representative Procedure for the Suzuki Coupling in Water. In a drybox, a round-bottom flask was charged with Na_2PdCl_4 (0.02 mmol), *t*-Bu-Amphos (0.02 mmol), sodium carbonate (2.0 mmol), aryl halide (1.0 mmol), and aryl boronic acid (1.2 mmol). The flask was sealed with a septum and removed from the drybox. Degassed water (5 mL) was added and the reaction was stirred at room temperature for 6−8 h. Hydrophobic products were isolated by ethyl acetate extraction of the reaction mixture followed by column chromatography of the crude product. Hydrophilic products were isolated by acidifying the reaction mixture and filtering off the solid product followed by recrystallization from water.

Representative Procedure for the Suzuki Coupling in Water/Toluene. In a drybox, a round-bottom flask was charged with Na_2PdCl_4 (0.02 mmol), *t*-Bu-Amphos (0.02 mmol), sodium carbonate (2 mmol), aryl halide (1.0 mmol), and arylboronic acid (1.2 mmol). The flask was sealed with a septum and removed from the drybox. Degassed toluene (2.5 mL) and water (2.5 mL) were added and the reaction was stirred at room temperature until GC analysis showed no residual aryl bromide (6−8 h). The reaction was taken up in water and the product extracted with ethyl acetate. The crude material was flash chromatographed on a short silica gel column eluting with a mixture of ethyl acetate and hexanes.

Representative Procedure for the Sonogashira Coupling. $Pd(OAc)_2$ (8.8 mg, 0.03 mmol), *t*-Bu-Amphos (8.0 mg, 0.03 mmol), and copper iodide (1.9 mg, 0.01 mmol) were added to a round-bottom flask equipped with a stir bar and rubber septum while in the drybox. Upon removing the flask from the drybox, the aryl bromide (1.00 mmol), diisopropylamine (121.7 mg, 1.2 mmol), alkyne (1.20 mmol), and degassed 1:1 CH_3CN:H_2O (10 mL) were added via syringe. For the best yields the alkyne should be added last to prevent homocoupling of the alkyne. The reaction was placed in a preheated oil bath and allowed to stir until determined to be complete by GC (4−6 h). The reaction was poured into saturated sodium carbonate (50 mL), extracted with ethyl acetate, and dried with $MgSO_4$. Products were purified by flash chromatography (SiO_2).

Representative Procedure for the Heck Coupling Reactions. $Pd(OAc)_2$ (5.6 mg, 0.025 mmol), *t*-Bu-Amphos (6.7 mg, 0.025 mmol), and alkene (1.50 mmol) were added to a round-bottom flask equipped with a stir bar and rubber septum while in the drybox. Upon removing the flask from the drybox, the aryl bromide (1.00 mmol), diisopropylamine

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(107.4 mg, 1.05 mmol), and degassed 1:1 CH_3CN:H_2O (10 mL) were added via syringe. The round-bottom flask was placed in an oil bath at 80 °C and allowed to stir for several hours. The reaction mixture was added to saturated sodium carbonate (50 mL). Coupled products derived from styrene were extracted with ethyl acetate. The solvent was removed and the crude product purified by column chromatography. When sodium acrylate was used, the crude reaction was extracted with ethyl acetate and the extracts discarded. The pH of the aqueous phase was then brought to ca. 1 with concentrated H_2SO_4. The cinnamic acid product was extracted with CH_2Cl_2 and the combined organic extracts were dried over $MgSO_4$. Removal of solvent under reduced pressure gave the crude product, which was recrystallized from H_2O/ethanol.

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Supporting Information Available: Experimental details, characterization data, and the NMR spectra of newly reported compounds **1f** and **5h**. This material is available free of charge via the Internet at http://pubs.acs.org.

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