ORGANIC
LETTERS

2001
Vol. 3, No. 17
2757−2759

Sterically Demanding, Water-Soluble Alkylphosphines as Ligands for High Activity Suzuki Coupling of Aryl Bromides in Aqueous Solvents

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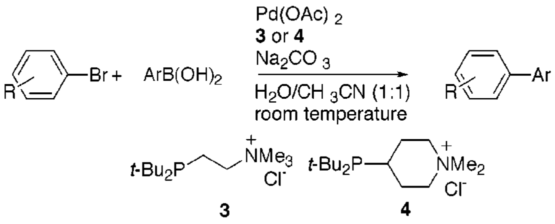
Received June 28, 2001

ABSTRACT



Sterically demanding, water-soluble alkylphosphines have been found to give highly active catalysts for Suzuki coupling of aryl bromides in aqueous solvents. A variety of aryl bromides and boronic acids were coupled in excellent yield. Turnover numbers up to 734 000 mmol/mmol Pd have been achieved under mild conditions.

Aqueous-phase, palladium-catalyzed coupling reactions are of interest as environmentally benign synthetic methods that would decrease the use of volatile organic solvents and simplify catalyst recovery.[1] Water-soluble phosphines, such as tris(3-sulfanotophenyl)phosphine (TPPTS, **1**, Figure 1), have been applied to aqueous-phase Heck,[2] Sonogashira,[3] Suzuki,[2c,4] and Buchwald−Hartwig[5] coupling reactions of aryl bromides, but the activity of these systems remains too low to be industrially viable. Water-soluble catalysts with increased activity toward aryl bromides and chlorides are necessary for wider application of aqueous-phase catalyst systems. It has recently been shown that sterically demanding alkylphosphines, such as tri-*tert*-butylphosphine (**2**), provide high activity catalysts for a range of palladium-catalyzed coupling reactions in organic solvents. Catalysts derived from these ligands have allowed the first general couplings of aryl bromides at room temperature and of unactivated aryl

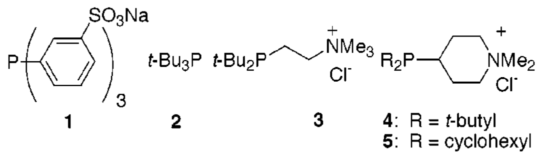


Figure 1.

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[1] Genet, J. P.; Savignac, M. *J. Organomet. Chem.* **1999**, *576*, 305−317.

[2] (a) Genet, J. P.; Blart, E.; Savignac, M. *Synlett* **1992**, 715−717. (b) Bumagin, N. A.; Bykov, V. V.; Beletskaya, I. P. *Zh. Org. Khim.* **1995**, *31*, 481−487. (c) Gelpke, A. E. S.; Veerman, J. J. N.; Goedheijt, M. S.; Kamer, P. C. J.; van Leeuwen, P. W. N. M.; Hiemstra, H. *Tetrahedron* **1999**, *55*, 6657−6670.

[3] Hessler, A.; Stelzer, O.; Dibowski, H.; Worm, K.; Schmidtchen, F. P. *J. Org. Chem.* **1997**, *62*, 2362−2369.

[4] (a) Casalnuovo, A. L.; Calabrese, J. C. *J. Am. Chem. Soc.* **1990**, *112*, 4324−4330. (b) Badone, D.; Baroni, M.; Cardamone, R.; Ielmini, A.; Guzzi, U. *J. Org. Chem.* **1997**, *62*, 7170−7173. (c) Uozumi, Y.; Danjo, H.; Hayashi, T. *J. Org. Chem.* **1999**, *64*, 3384−3388. (d) Paetzold, E.; Oehme, G. *J. Mol. Catal. A: Chem.* **2000**, *152*, 69−76.

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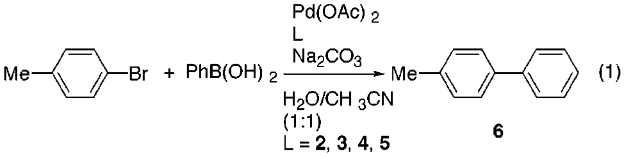
10.1021/ol0163629 CCC: $20.00

Table 1. Ligand Optimization in Aqueous-Phase Suzuki Coupling[a]



entry	ligand	L:Pd	yield[b] of **6** (%)
1	**2**	2:1[c]	2
2	**3**	1:1	98
3	**3**	2:1	73
4	**4**	1:1	99
5	**4**	2:1	32
6	**5**	1:1	46
7	**5**	2:1	2

[a] Reactions run on 0.2 mmol scale with 0.5 mol % Pd at room temperature. [b] GC yield after 1 h. Mass balance was within 5%. [c] 2.5 mol % Pd, 4 h.

chlorides under moderate conditions.[6] To date, there have been no examples of the application of sterically demanding, water-soluble alkylphosphines to aqueous-phase coupling reactions. Therefore, we have prepared a series of water-soluble phosphines modeled on the steric and electronic properties of *t*-Bu_3P (**3**−**5**, Figure 1). Ligands **3** and **4** provided highly active catalysts for the Suzuki coupling of aryl bromides at room temperature in aqueous solvents.

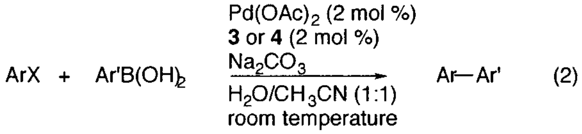
Table 2. Low Catalyst Loading Coupling Reactions[a]

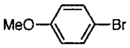
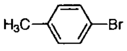
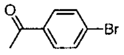
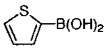
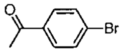
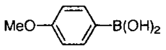
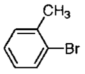
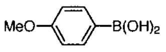
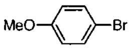
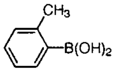
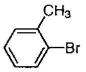
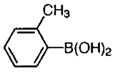
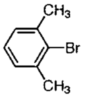
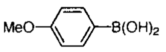
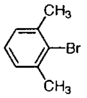
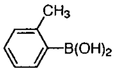
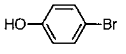
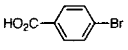
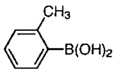
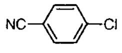
entry	ligand	mol % Pd	*T* (°C)	time (h)	yield[b] of **6** (%)	TON[c]
1	**3**	9.92×10^{-3}	23	24	99	9 980
2	**4**	9.80×10^{-3}	23	24	>99	10 100
3	**3**	1.03×10^{-3}	80	4	>99	95 600
4	**4**	1.01×10^{-3}	80	4	>99	97 800
5	**4**	9.95×10^{-5}	80	4	73	734 000

[a] See Supporting Information for the experimental procedure. [b] Average GC yield (≥2 runs) by comparison to mesitylene using response factors from authentic samples. Mass balances were within 5%. [c] As mmol product/mmol Pd.

Ligands **3** and **4** were prepared in analogy to the previously reported synthesis of **5**[7] and were isolated as water-soluble, modestly air-sensitive solids. With ligands **3**−**5** in hand, their ability to promote aqueous-phase Suzuki couplings was compared to that of TPPTS under previously reported conditions (Table 1, eq 1).[4a] At room temperature, TPPTS/$Pd(OAc)_2$ gave low conversion in the coupling of 4-bromotoluene and phenylboronic acid (entry 1). In contrast, ligands **3** and **4** gave nearly quantitative yields of 4-methylbiphenyl at room temperature with 0.5 mol % Pd after 1 h (entries 2 and 4). Ligand **5** gave a less active catalyst than ligands **3** or **4** (entry 6). For each of the ligands prepared in this study, a 1:1 ratio of ligand:Pd gave higher activity than a 2:1 ratio. These results are consistent with those recently reported for the *t*-Bu_3P/Pd catalyst system.[6c,g] Catalysts derived from **3**, **4**, or **5**/$Pd(OAc)_2$ partitioned predominately in the organic

Table 3. Scope of Suzuki Couplings with **3** or **4**/$Pd(OAc)_2$[a]



Entry	Aryl Halide	Boronic Acid	Ligand	Yield[b] Ar-Ar'
1		$PhB(OH)_2$	3 4	94 % 96 %
2		$PhB(OH)_2$	4	93 %
3			4	88 %
4			3 4	95 % 91 %
5			3 4	95 % 93 %
6			4	94 %
7			4	92 %
8			3 4	90 % 94 %
9			4	67 %[c]
10		$PhB(OH)_2$	4	87 %
11			4	95 %
12		$PhB(OH)_2$	3 4	64 %[d,e] 92 %[d]

[a] 2 mol % Pd, 1:1 L:Pd, at room temperature. See Supporting Information for complete reaction conditions. Reactions were complete in 1−2 h in all cases. [b] Average yield of two runs that agreed within 5%. [c] Determined by ^1H NMR of isolated material. Product was contaminated by 2,2′-dimethylbiphenyl (30% yield based on *o*-tolylboronic acid). [d] 4 mol % Pd, 2:1 L:Pd, 80 °C. [e] GC yield after 6 h.

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(6) (a) Littke, A. F.; Fu, G. C. *J. Org. Chem.* **1999**, *64*, 10−11. (b) Bei, X.; Turner, H. W.; Weinberg, W. H.; Guram, A. S. *J. Org. Chem.* **1999**, *64*, 6797−6803. (c) Littke, A. F.; Dai, C.; Fu, G. C. *J. Am. Chem. Soc.* **2000**, *122*, 4020−4028. (d) Zapf, A.; Ehrentraut, A.; Beller, M. *Angew. Chem., Int. Ed.* **2000**, *39*, 4153−4155. (e) Littke, A. F.; Fu, G. C. *Angew. Chem., Int. Ed.* **1999**, *38*, 2411−2413. (f) Wolfe, J. P.; Tomori, H.; Sadighi, J. P.; Yin, J.; Buchwald, S. L. *J. Org. Chem.* **2000**, *65*, 1158−1174. (g) Hartwig, J. F.; Kawatsura, M.; Hauck, S. I.; Shaughnessy, K. H.; Alcazar-Roman, L. M. *J. Org. Chem.* **1999**, *64*, 5575−5580. (h) Kawatsura, M.; Hartwig, J. F. *J. Am. Chem. Soc.* **1999**, *121*, 1473−1478. (i) Mann, G.; Incarvito, C.; Rheingold, A. L.; Hartwig, J. F. *J. Am. Chem. Soc.* **1999**, *121*, 3224−3225. (j) Watanabe, M.; Nishiyama, M.; Koie, Y. *Tetrahedron Lett.* **1999**, *40*, 8837−8840. (k) Böhm, V. P. W.; Herrmann, W. A. *Eur. J. Org. Chem.* **2000**, 3679−3681. (l) Baudoin, O.; Guénard, D.; Guérite, F. *J. Org. Chem.* **2000**, *65*, 9268−9271. (m) Dai, C.; Fu, G. C. *J. Am. Chem. Soc.* **2001**, *123*, 2719−2724.

phase of the reaction mixture, although addition of ether drove the catalyst into the aqueous phase. Water-miscible cosolvents that give homogeneous reaction mixtures, such as methanol and DMF, could be used in place of acetonitrile with no change in reaction yield or rate. Reactions carried out in water alone occurred more slowly than when a cosolvent was used, however.

Catalysts derived from **3** and **4**/$Pd(OAc)_2$ are highly active catalysts for Suzuki couplings of aryl bromides (Table 2). The coupling of 4-bromotoluene and phenylboronic acid in a 2:1 mixture of water and acetonitrile was used as a model reaction. An increased ratio of water was used to avoid precipitation of salts, which appeared to limit activity at higher reaction concentrations. At room temperature, quantitative yields were obtained with as little as 0.01 mol % **3** or **4**/$Pd(OAc)_2$ after 24 h (entries 1 and 2), which is comparable to the best turnover numbers reported for room-temperature Suzuki couplings of aryl bromides in organic solvents[6c] and is unprecedented for aqueous-phase systems.[4d] At 80 °C, quantitative yields were obtained after 4 h using 1×10^{-3} mol % **3** or **4**/$Pd(OAc)_2$. No significant difference was observed in the turnover number or frequency of catalysts derived from **3** or **4**. At ppm catalyst loadings of **4**/$Pd(OAc)_2$, 734 000 turnovers were achieved after 4 h at 80 °C (entry 5), but longer reaction times did not give further conversion. *The average turnover frequency (TOF) was 184 000* h^{-1}. This level of productivity is 2 orders of magnitude higher than the most active aqueous-phase catalyst system previously reported for the Suzuki coupling of aryl bromides (TON = 9 000 mmol/mmol Pd; TOF = 5 400 mmol/h).[8]

Catalysts derived from **3** and **4** were used to couple a range of aryl halides and boronic acids (eq 2, Table 3). Upon completion of the reactions, extraction with ether gave the biaryl products in >95% purity as determined by GC. Excellent yields (>88%) were obtained with electron-rich, -neutral, and -poor aryl bromides and boronic acids (entries 1−4). The catalyst system also tolerated sterically demanding aryl bromides and boronic acids (entries 5−8) to give mono- and di-*ortho*-substituted biphenyl products in excellent yield with no change in the reaction time. Preparation of 2,2′,6-trimethylbiphenyl occurred in modest yield (67%), however, along with a significant amount of aryl halide reduction to *m*-xylene and boronic acid homocoupling to 2,2′-dimethylbiphenyl (entry 9). Water-soluble aryl bromides also gave high yields of biphenyl products (entries 10 and 11) with this system. Coupling of activated aryl chlorides with ligand **4** required high catalyst loading (4 mol %) and temperature (80 °C) to achieve high yield (92%), while **3**/$Pd(OAc)_2$ gave only 64% yield (66% conversion) under the same conditions (entry 10). Both **3** and **4** gave low conversions (<30%) with 4-chlorotoluene and 4-chloroanisole under these conditions.

In conclusion, we have shown that sterically demanding, water-soluble alkylphosphines give highly active catalysts for Suzuki couplings of aryl bromides in aqueous solvents. Ligands **3** and **4** have provided the first room-temperature aqueous-phase Suzuki couplings. Catalysts derived from **3** and **4** both showed high activity toward aryl bromides, while the more sterically demanding ligand **4** gave catalysts with activity toward aryl chlorides higher than that of **3**. The more facile synthesis of **3** makes it the preferred ligand for aryl bromide couplings, however. These aqueous-phase catalysts may prove useful in applications such as solution-phase combinatorial library synthesis and modification of water-soluble biomolecules, as well as in environmentally benign synthesis. Preparation of ligands with improved water solubility and activity, particularly toward aryl chlorides, are currently being pursued.

Acknowledgment. The authors acknowledge The University of Alabama and a DuPont Co. Aid to Education Grant for support of this work.

Supporting Information Available: Experimental procedures and NMR spectra for ligands **3** and **4** and the products in Table 3. This material is available free of charge via the Internet at http://pubs.acs.org.

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(7) (a) Mohr, B.; Lynn, D. M.; Grubbs, R. H. *Organometallics* **1996**, *15*, 4317−4325. (b) See Supporting Information for experimental procedures.

(8) Beller, M.; Krauter, J. G. E.; Zapf, A. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 772−774.