JOC *Note*

pubs.acs.org/joc

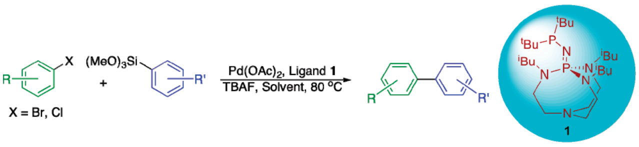
Advantageous Use of $^t\mathrm{Bu_2P{-}N{=}P(^iBuNCH_2CH_2)_3N}$ in the Hiyama Coupling of Aryl Bromides and Chlorides

Steven M. Raders, Jesudoss V. Kingston, and
John G. Verkade*

*Department of Chemistry, Iowa State University,
Ames, Iowa 50011*

jverkade@iastate.edu

Received November 1, 2009



An efficient catalytic route to biaryls by employing (generally) only 0.25 mol % of Pd(OAc)$_2$ and 0.5 mol % of **1** in the Hiyama coupling reaction is reported. High yields for electron-rich, -neutral, and -deficient aryl chlorides are obtained. A variety of phenylsiloxanes undergo coupling with aryl bromides and chlorides with low Pd(OAc)$_2$/**1** loadings.

Palladium-catalyzed C−C bond-forming reactions are exceedingly useful in modern organic synthesis. Biaryls (constituents of aromatic polymers, liquid crystals, natural products, and pharmaceuticals) can be synthesized using, e.g., Pd-catalyzed Suzuki,[1] Negishi,[2] Kumada,[3] Hiyama,[4] and Stille[5] reactions. Despite the toxicity and relatively expensive organotin reagents, the Stille reaction remains a popular approach, especially because of its utility in the stereoselective coupling of vinyl- and alkenylstannanes.[6]

The potentially most attractive of the aforementioned methodologies is Hiyama cross-coupling because organosilicon reagents are commercially available at relatively low cost or can be easily prepared. These reagents are also nontoxic and quite stable to the presence of other functionalities and to a variety of reaction conditions. However, because organosilanes are comparatively unreactive nucleophiles, Hiyama coupling has not yet replaced Stille and Suzuki methodologies.[1,4,5] For example, in contrast to Suzuki, Kumada, and Stille methodologies, there is presently no general method for cross-coupling considerably cheaper, more widely available aryl chlorides with organosilicon compounds.

Hiyama and co-workers showed that aryl(ethyl)dichlorosilanes could be coupled with activated aryl chlorides to give good yields of coupled product after 24−48 h at 120 °C in DMF.[4b] Deshong and Mowery developed a useful protocol for coupling aryl bromides and iodides with siloxane derivatives, which have been touted as the most convenient organosilanes for Hiyama cross-coupling.[4c] However, challenges with aryl chlorides were encountered in that work. Recently, an efficient method for producing biaryls from mesityl-protected aryl alcohols and aryl siloxanes using 2 mol % of Pd(OAc)$_2$ and 8 mol % of CM-phos was reported.[7] Ligands such as PPh$_3$, ^{t}Bu$_3$P, and ^{t}Bu$_2$P-biphenyl were completely ineffective. Even Cy$_2$P-biphenyl/Pd$_2$dba$_3$ (the most effective catalyst utilized by Buchwald for a range of aryl chloride cross-couplings[4c]) produced only a 47% yield of product in the cross-coupling of PhSi(OMe)$_3$ with 4-chloroacetophenone using 10 mol % of Pd$_2$dba$_3$.[4c] It has been reported that an imidazolium chloride/Pd(OAc)$_2$ catalyst was more useful than Cy$_2$P-biphenyl/Pd$_2$dba$_3$ for three activated aryl chlorides, but unactivated substrates such as 4-chloroanisole gave poor yields.[4f] PdCl$_2$(CH$_3$CN)$_2$ in the presence of β-diimine ligands for the coupling of 4-chloroacetophenone with PhSi(OMe)$_3$ afforded only a 62% yield of product.[8]

Recently, we reported the first synthesis of the bulky phosphine **1** (Figure 1) and showed it to be effective in Suzuki−Miyaura cross-coupling reactions, giving high yields of desired biaryls in the presence of 1 mol % of Pd(OAc)$_2$ and 2 mol % of **1**.[9] Ligand **1** features a bulky iminoproazaphosphatrane moiety that provides electron richness to the ^{t}Bu$_2$P group via donation from the "equatorial" ^{i}BuN substituents and via potential transannulation from the basal planar N.[9] Here we show the usefulness of **1** in the Hiyama coupling of a variety of aryl bromides and chlorides to obtain high yields of biaryls with low loadings of Pd (0.25−1.0 mol %) and **1** (0.5−2.0 mol %).

---

(1) (a) Miyaura, N.; Yamada, K.; Suzuki, A. *Tetrahedron Lett.* **1979**, 3437. (b) Stanforth, S. P. *Tetrahedron* **1998**, *54*, 263. (c) Suzuki, A. *Pure Appl. Chem.* **1991**, *63*, 419. (d) Wolfe, J. P.; Buchwald, S. P. *Angew. Chem., Int. Ed.* **1999**, *38*, 2413. (e) Zapf, A.; Beller, M. *Chem.—Eur. J.* **2000**, *6*, 1830. (f) Bedford, R. B.; Cazin, C. S. J.; Coles, S. J.; Gelbrich, T.; Horton, P. N.; Hursthouse, M. B.; Light, M. E. *Organometallics* **2003**, *22*, 987.

(2) (a) Baba, S.; Negishi, E. *J. Am. Chem. Soc.* **1976**, *98*, 6729. (b) Dai, C.; Fu, C. *J. Am. Chem. Soc.* **2001**, *123*, 2719.

(3) (a) Tamao, K.; Sumitani, K.; Kumada, M. *J. Am. Chem. Soc.* **1972**, *94*, 4374. (b) Herrmann, W. A.; Bohm, V. P. W.; Reisinger, C. *J. Organomet. Chem.* **1999**, *576*, 23.

(4) (a) Hatanaka, Y.; Hiyama, T. *J. Org. Chem.* **1988**, *53*, 920. (b) Gouda, K.; Hagiwara, E.; Hatanaka, Y.; Hiyama, T. *J. Org. Chem.* **1996**, *61*, 7232. (c) Mowery, M. E.; DeShong, P. *Org. Lett.* **1999**, *1*, 2137. (d) Lee, J.; Fu, G. C. *J. Am. Chem. Soc.* **2003**, *125*, 5616. (e) Riggleman, S.; DeShong, P. *J. Org. Chem.* **2003**, *68*, 8106. (f) Lee, H. M.; Nolan, S. P. *Org. Lett.* **2000**, *2*, 2053.

(5) (a) Stille, J. K. *Pure Appl. Chem.* **1985**, *57*, 1771. (b) Stille, J. K. *Angew. Chem., Int. Ed.* **1986**, *25*, 508. (c) Farina, V.; Krishnamurthy, V.; Scott, W. *J. Org. React.* **1997**, *50*, 1. (d) Hassa, J.; Svignon, M.; Gozzi, C.; Schulz, E.; Lemaire, M. *Chem. Rev.* **2002**, *102*, 1359. (e) Littke, A. F.; Fu, G. C. *Angew. Chem., Int. Ed.* **2002**, *41*, 4176.

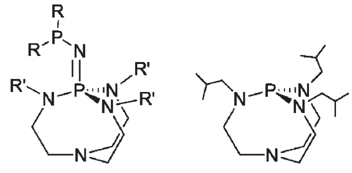
(6) (a) Nakao, N.; Satoh, J.; Shirakawa, E.; Hiyama, T. *Angew. Chem., Int. Ed.* **2006**, *45*, 2271. (b) von Zezschwitz, P.; Petry, F.; de Meijere, A. *Chem.—Eur. J.* **2001**, *7*, 4035. (c) Paley, R. S.; de Dios, A.; Estroff, L. A.; Lafontaine, J. A.; Montero, C.; McCulley, D. J.; Rubio, M. B.; Ventura, M. P.; Weers, H. L.; Fernandez de la Pradilla, R.; Castro, S.; Dorado, R.; Morente, M. *J. Org. Chem.* **1997**, *62*, 6326. (d) Chu, K. H.; Wang, K. K. *J. Org. Chem.* **1986**, *51*, 767.

(7) So, C. M.; Lee, H. W.; Lau, C. P.; Kwong, F. Y. *Org. Lett.* **2009**, *11*, 317.

(8) Domin, D.; Benito-Garagorri, D.; Mereiter, K.; Fröhlich, J.; Kirchner, K. *Organometallics* **2005**, *24*, 3957.

(9) Kingston, J. V.; Verkade, J. G. *J. Org. Chem.* **2007**, *72*, 2816.

DOI: 10.1021/jo902338w

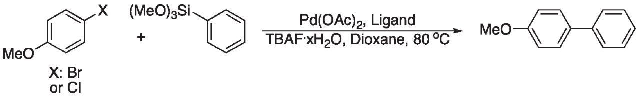


1: R = ^{t}Bu, R' = ^{i}Bu
2: R = Ph, R' = ^{i}Bu
3: R = ^{t}Bu, R' = Me

4

FIGURE 1. Electron-rich phosphines synthesized in our laboratory.

TABLE 1. Optimization Study



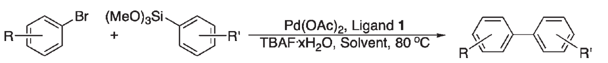
entry	aryl halide	solvent	Pd(OAc)$_2$ (mol %)	ligand (mol %)	yield[a] (%)
1	Cl	dioxane	1.0	**1** (2.0)	86
2	Cl	THF	1.0	**1** (2.0)	64
3	Cl	dioxane	0.5	**1** (1.0)	81
4	Cl	dioxane	0.25	**1** (0.5)	56
5	Cl	dioxane	0.5	**2** (1.0)	6
6	Cl	dioxane	0.5	**3** (1.0)	42
7	Cl	dioxane	0.5	**4** (1.0)	0
8	Cl	dioxane	0.5	**1** (0.5)	70
9	Cl	neat	0.5	**1** (1.0)	81
10	Br	neat	0.5	**1** (1.0)	93
11	Br	neat	0.25	**1** (0.5)	87

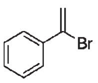
[a] Reaction conditions: 2 mmol of 4-chloroanisole, 4 mmol of trimethoxyphenylsilane, 3.5 mmol of TBAF·xH$_2$O, 5 mL of solvent, 2.5 h.

4-Chloroanisole is the most recalcitrant aryl halide substrate in Hiyama coupling with PhSi(OMe)$_3$. A 40% product yield was obtained using 10 mol % of PdCl$_2$(CH$_3$CN)$_2$ and 20 mol % of P(o-tol)$_3$ in toluene at 80 °C.[10] In the presence of 3 mol % of Pd(OAc)$_2$ and 6 mol % of DABCO, only 20% of the desired product was obtained after 24 h at 80 °C.[11] The highest reported yield (93%) was achieved using microwaves at 120 °C for 10 min in the presence of 1 mol % of an oxime-derived palladacycle.[12] Under the conditions in entry 1 of Table 1, we received an 87% yield of product using ligand **1**. Using Pd$_2$dba$_3$ or Pd(dba)$_2$ decreased the product yield, owing to the formation of Pd black. Increasing the temperature accelerated the formation of Pd black and also decreased product yield. Lower temperatures decreased the amount of Pd black, but decreased product yields were also observed.

Other fluoride sources (e.g., CsF and Bu$_3$SnF) were ineffective in our protocol. Only low product yields were obtained with phosphine analogues **2** and **3** (Table 1, entries 5 and 6), and **4** was completely ineffective (entry 7). Changing the Pd/L ratio from 1:2 to 1:1 gave a moderate product yield of 70% (Table 1, entry 8). When both reactants are liquids, the reaction could be carried out in the absence of solvent to achieve the same yield as in entry 3 (entry 9). When 4-bromoanisole was coupled, an excellent yield of desired biaryl was achieved (entry 10). Decreasing the palladium loading to 0.25 mol % decreased product yield by only 6% (entry 11).

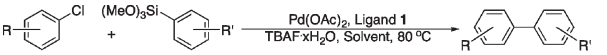
TABLE 2. Scope of Aryl Bromides

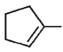


entry	R	R^1	time	yield (%)[a,b]
1	3-OMe	4-Me	3 h	91[c] (Lit: 80)
2	4-NMe$_2$	4-Me	5 h	71[d]
3	4-CF$_3$	H	2 h	93[e] (Lit: 87-99)
4	4-NO$_2$	H	2 h	91[e] (Lit: 51-93)
5	4-COMe	H	2 h	91[e] (Lit: 55-99)
6	4-CN	H	2 h	84[e] (Lit: 85)
7	3-CO$_2$Me	4-OMe	1.5 h	87[f]
8	2,6-Me	4-OMe	2 h	89[g]
9	2-F	4-OMe	0.5 h	83[c]
10	4-^{t}Bu	4-OMe	0.5 h	85[c]
11	 Br	4-Me	1 h	78[c]

[a] Average of two runs. Yields are isolated yields. [b] Reaction conditions: 2 mmol of aryl bromide, 4 mmol of siloxane, 3 mmol of TBAF·xH$_2$O. [c] 0.5 mol % of Pd(OAc)$_2$, 1 mol % of **1**, neat. [d] 1 mol % of Pd(OAc)$_2$, 2 mol % of **1**, 5 mL of dioxane. [e] 0.5 mol % of Pd(OAc)$_2$, 1 mol % of **1**, 5 mL of dioxane. [f] 0.25 mol % of Pd(OAc)$_2$, 0.5 mol % of **1**, 5 mL of dioxane. [g] 1 mol % of Pd(OAc)$_2$, 2 mol % of **1**, neat.

TABLE 3. Scope of Aryl Chlorides



entry	R	R^1	time	yield (%)[a,b]
1	3-OMe	H	1.5 h	87[c] (Lit: 25)
2	2-CF$_3$	H	3 h	82[d]
3	4-CN	H	2 h	93[e]
4	4-CO$_2$Me	H	2 h	95[e]
5	4-COMe	H	1.5 h	95[e] (Lit: 62-99)
6	3,4-OCH$_2$O-	H	2 h	90[c]
7	2-Me	H	2 h	87[d]
8	1-naphthyl	H	1 h	83[d]
9	 Cl	H	0.5 h	91[c]

[a] Average of two runs. Yields correspond to isolated yields. [b] Reaction conditions: 2 mmol of aryl chloride, 4 mmol of siloxane, 3 mmol of TBAF·3H$_2$O, neat, time: 0.5−2 h. [c] 0.5 mol % of Pd(OAc)$_2$, 1 mol % of **1**, neat. [d] 1 mol % of Pd(OAc)$_2$, 2 mol % of **1**, neat. [e] 0.5 mol % of Pd(OAc)$_2$, 1.0 mol % of **1**, 5 mL of dioxane.

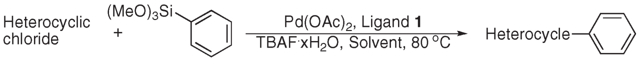
With the low catalyst loading in Table 1, entry 11, we investigated a variety of aryl bromides (Table 2). All the products in Table 2 have been reported previously using other coupling approaches, although the products in Table 2, entries 1 and 3−6, those in Table 3, entries 1 and 5, and the product in Table 4, entry 2, have also been reported earlier via Hiyama coupling (see the corresponding references in the last column of these tables). Pleasingly, a wide range of aryl bromides can be coupled with a variety of siloxanes. For example, electron-donating aryl bromides bearing OMe or NMe$_2$ substituents are coupled with p-tolyltrimethoxysilane in moderate to excellent product yields (Table 2, entries 1 and 2). Electron-withdrawing aryl bromides containing CF$_3$, NO$_2$, COMe, or CN substituents are also easily coupled with PhSi(OMe)$_3$ in good to excellent yields (Table 2, entries 3−6). Surprisingly, methyl 3-bromobenzoate was coupled to p-methoxyphenyltrimethoxysilane in 87% yield in the presence of only 0.25 mol % of Pd(OAc)$_2$ and 0.50 mol % of **1** (Table 2, entry 7).

With some Hiyama catalyst systems, aryl bromides bearing an ortho methyl or phenyl group have provided only low to

---

(10) Li, J.; Deng, C.; Xie, Y. *Synthesis* **2006**, 969.
(11) Li, J.; Deng, C.; Liu, W.; Xie, Y. *Synthesis* **2005**, 3039.
(12) Alacid, E.; Nájera, C. *Adv. Synth. Catal.* **2006**, *348*, 945.

TABLE 4. Scope of Heterocyclic Chlorides



entry	heterocyclic chloride	time (h)	yield[a],[b] (%)
1	2-pyridyl	2	81[c]
2	3-pyridyl	1.5	82[d] (lit: 63−92)
3	2-thiopheneyl	1	95[c]

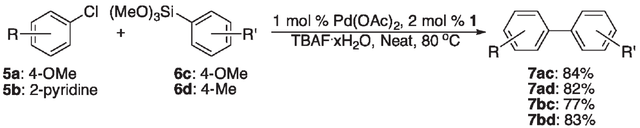
[a] Average of two runs. Yields are isolated yields. [b] Reaction conditions: 2 mmol of aryl chloride, 4 mmol of siloxane, 0.5 mol % of $Pd(OAc)_2$, 1 mol % of **1**, 3 mmol of TBAF, time 0.5−2 h. [c] Neat conditions. [d] 5 mL of dioxane.

moderate yields of products.[7,8,10,11,13] Here, sterically hindered 2-bromo-*m*-xylene coupled with *p*-methoxyphenyltrimethoxysilane to give an 89% product yield (Table 2, entry 8). α-Bromostyrene coupled well with *p*-tolyltrimethoxysilane in the absence of solvent to produce a 78% product yield (Table 2, entry 11).

We next focused on aryl chloride substrates (Table 3). Such chlorides are generally quite refractory in palladium-assisted coupling reactions owing to their reluctance to oxidatively add to Pd(0).[14] Hence, only aryl chlorides with highly electron-withdrawing substituents tend to undergo coupling with aryl siloxanes.[8,10,11,13,15] Electron-donating groups on aryl chlorides generally lead to low to moderate yields.[10,11,13,15a,b] Here, ligand **1** effectively facilitates coupling of not only electron-withdrawing aryl chlorides under low catalyst loadings but also electron-donating and sterically hindered aryl chlorides. Aryl chlorides with electron-withdrawing groups such as CF_3, CN, CO_2Me, and COMe are efficiently coupled to $PhSi(OMe)_3$ in excellent yields in the presence of only 0.5 mol % of $Pd(OAc)_2$ and 1 mol % of **1** (Table 3, entries 3−5). The coupling of 2-chlorotrifluorotoluene with $PhSi(OMe)_3$ proceeded smoothly with 1 mol % of $Pd(OAc)_2$ and 2 mol % of **1** to provide 82% of the desired product (entry 2). This is the first time that the products in entries 2−4 have been made from an aryl chloride via Hiyama coupling.

Electron-donating aryl chlorides were coupled with $PhSi(OMe)_3$ with surprising efficiency. Thus, 3-chloroanisole underwent coupling to give 87% of the biaryl product in 1.5 h (Table 3, entry 1). This biaryl was made only once previously in a Hiyama coupling in which only 25% of the desired product was obtained via the reaction of 3-chloroanisole with $PhSi(OMe)_3$ in the presence of 5 mol % of $Pd(acac)_2$ and 5 mol % of the phosphite $[3\text{-Me-}2,6\text{-}t\text{-}Bu_2C_6H_2OP(OCH_2)_2]_2C$ in *p*-xylene at 120 °C.[13a] The electron-rich aryl chloride 5-chloro-1,3-benzodioxole underwent coupling in 90% isolated yield (Table 3, entry 6).

SCHEME 1. Reaction of Aryl Chlorides with Aryl Siloxanes



Reaction conditions: 2 mmol aryl chloride, 4 mmol siloxane, 3 mmol $TBAF{\cdot}xH_2O$, time: 2 h.

Sterically demanding aryl bromides are difficult substrates in some catalytic Hiyama approaches, leading to only moderate yields of the corresponding coupled products.[7,8,10,11,13] Thus, sterically encumbered aryl chlorides might be predicted to be even more problematic in this respect. However, using only 1 mol % of $Pd(OAc)_2$/2 mol % of **1**, 2-chlorotoluene and 1-chloronaphthalene were coupled with $PhSi(OMe)_3$ in good yields (87% and 83%, respectively, Table 3, entries 7 and 8). Even 1-chlorocyclopentene was coupled with $PhSi(OMe)_3$ using only 0.5 mol % of $Pd(OAc)_2$/1 mol % of **1**, producing a 91% product yield (entry 9). To the best of our knowledge, this is the first time 1-chlorocyclopentene has been used for Hiyama coupling.

The usefulness of our catalytic system also applies to the coupling of 4-chloroanisole and 2-chloropyridine which were coupled with *p*-methoxyphenyltrimethoxysilane and *p*-tolyltrimethoxysilane in the presence of 1 mol % of $Pd(OAc)_2$ and 2 mol % of **2** to give moderate to good product yields (Scheme 1).

Next, we turned our focus to heterocyclic aryl chlorides (Table 4). Only a few literature reports on the use of heterocyclic aryl chlorides in Hiyama coupling have appeared.[12,15c] Here, we show that such substrates couple well with $PhSi(OMe)_3$, in the presence of 0.5 mol % of $Pd(OAc)_2$/1 mol % of **1**. Thus, 2-chloropyridine and 2-chlorothiophene underwent coupling to give an 81 and 95% isolated product yield, respectively, in the absence of solvent (Table 3, entries 1 and 3). When dioxane was used as solvent, GC revealed very low conversion to product. To the best of our knowledge, this is the first time these products have been made from a heterocyclic aryl chloride via Hiyama coupling. When 3-chloropyridine was coupled with $PhSi(OMe)_3$, dioxane was required to suppress the rate of Pd black production until the starting material was consumed. After 1.5 h, an 82% yield of the desired biaryl was isolated (Table 3, entry 2). The highest reported literature yield for this reaction was 92%, which was obtained using 1 mol % of an oxime-derived palladcycle under microwave conditions at 120 °C.[12]

Herein we have demonstrated the wide utility of low loadings of $Pd(OAc)_2$/**1** (generally 0.25 mol % of $Pd(OAc)_2$ and 0.5 mol % of **1**) and relatively mild conditions (generally 80 °C for 0.5−3 h) for coupling a wide range of aryl bromides and chlorides with phenylsiloxanes. These reactions are characterized by generally good to excellent product yields. Further work directed at further expanding the substrate scope is currently underway.

Experimental Section

General Procedure for the Hiyama Coupling of Aryl Bromides and Chlorides. A 10 mL vial was charged with 3 mmol of $TBAF{\cdot}xH_2O$ (794 mg), 0.5 mol % of $Pd(OAc)_2$ (2.24 mg), and 1.0 mol % of ligand **1** (10.03 mg) in a glovebox. The vial was

---

(13) (a) Ju, J.; Nam, H.; Jung, H.; Lee, S. *Tetrahedron Lett.* **2006**, *47*, 8673. (b) Shi, S.; Zhang, Y. *J. Org. Chem.* **2007**, *72*, 5927. (c) Murata, M.; Yoshida, S.; Nirei, S.; Watanabe, S.; Masuda, Y. *Synlett* **2006**, 118.

(14) (a) Grushin, V. V.; Alper, H. *Chem. Rev.* **1994**, *94*, 1047. (b) Grushin, V. V.; Alper, H. In *Activation of Unreactive Bonds and Organic Synthesis*; Murai, S., Ed.; Springer: Berlin, 1999; p 193. (c) Herrmann, W. A. In *Applied Homogenous Catalysis With Organometallic Compounds, A Comprehensive Handbook*; Cornils, B., Herrmann, W. A., Eds.; VCH: Weinheim, 1996; Vol. 1, p 722.

(15) (a) Wu, Z.; Yang, M.; Li, H.; Qi, Y. *Synthesis* **2008**, 1415. (b) Pan, C.; Liu, M.; Zhao, L.; Wu, H.; Ding, J.; Cheng, J. *Catal. Commun.* **2008**, *9*, 1685. (c) Ackermann, L.; Gschrei, C. J.; Althammer, A.; Reiderer, M. *Chem. Commun.* **2006**, 1419.

capped and brought outside the glovebox where 4 mmol of arylsiloxane and 2 mmol of aryl halide were added under an argon flow. The reaction vessel was heated to 80 °C for the specified times given in the tables. The mixtures were then purified by column chromatography (0−5% EtOAc) to obtain pure biaryls.

Acknowledgment. We thank the National Science Foundation for a grant (07500463) in support of this work.

Supporting Information Available: ^{1}H and ^{13}C NMR for all compounds as well as experimental prodedures. This material is available free of charge via the Internet at http://pubs.acs.org.