ORGANIC
LETTERS

1999
Vol. 1, No. 13
2137−2140

Improvements in Cross Coupling Reactions of Hypervalent Siloxane Derivatives[†]

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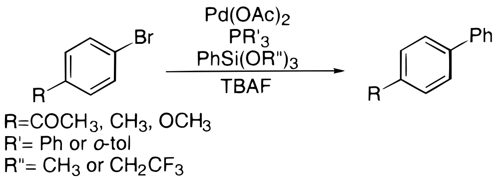
Received October 26, 1999

ABSTRACT



The scope of the palladium-catalyzed cross coupling reaction of aryl halides with phenyltrimethoxysilane has been expanded to include aryl bromides, heteroaryl bromides, and aryl chlorides. A more general Pd(0)-catalyst/ligand system has been developed to activate bromides: palladium(II) acetate ($Pd(OAc)_2$) is activated with triphenylphosphine (PPh_3) or tri-*o*-tolylphosphine ($P(o\text{-tol})_3$) (1:2 molar ratio of Pd:phosphine). Coupling of aryl chloride derivatives required addition of 2-(dicyclohexylphosphino)biphenyl (Buchwald's ligand) to Pd_2dba_3 (tris(dibenzylideneacetone)dipalladium(0)) (1:1.5 molar ratio of Pd:phosphine).

The formation of carbon−carbon bonds by palladium-catalyzed cross coupling reactions is one of the fundamental reactions in the arsenal of synthetic organic chemistry.[1] The traditional methodologies most often used to accomplish these types of transformations are the Stille and Suzuki coupling reactions.[1−3]

Recently, advances have been made to include the use of silicon-derived reagents to effect these types of cross coupling reactions.[4−7] Results from our group[4] as well as Hiyama[7c,e] and others[7a,b,d,f] have found that Pd(0)-catalyzed, fluoride-promoted reactions of silicon derivatives are a viable alternative to the Suzuki and Stille couplings.[8] It has been previously shown that siloxane derivatives cross couple with aryl iodides, electron-deficient aryl bromides, and allylic benzoates in excellent yields.[4]

These initial conditions, which employed bis(dibenzylideneacetone)palladium ($Pd(dba)_2$) or allylpalladium chloride dimer (APC) were not successful when extended to cross

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[†] Dedicated to Professor Wolfgang von Philipsborn on the occasion of his 70th birthday.

(1) (a) Trost, B. M.; Verhoeven, T. R. In *Comprehensive Organometallic Chemistry*; Wilkinson, G., Stone, F. G. A., Abel, E. W., Eds.; Pergamon: Oxford, Vol. 8, 1982; pp 799−938. (b) Tamao, K. *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, Vol. 3, 1991; pp 435−480. (c) Knight, D. W. *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 3, pp 481−578. (d) Tsuji, J. *Palladium Reagents and Catalysts. Innovations in Organic Synthesis*; John Wiley & Sons: New York, 1995; pp 1−985.

(2) For information about recent advances in elucidating the mechanism of the Stille reaction, see: (a) Casado, A. L.; Espinet, P. *J. Am. Chem. Soc.* **1998**, *120*, 8978−8985. (b) Casado, A. L.; Espinet, P. *Organometallics* **1998**, *17*, 954−959. For other articles about the Stille reaction, see: (c) Stille, J. K.; Echavarren, A. M.; Williams, R. M.; Hendrix, J. A. *Org. Synth.* **1992**, *71*, 97−106 and references therein. (d) Farina, V.; Krishnaumurthy, V.; Scott, W. J. *Org. React.* **1997**, *50*, 1−652 and references therein.

(3) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457−2483.

(4) Mowery, M. E.; DeShong, P. *J. Org. Chem.* **1999,** *64*, 1684−1688.

(5) Mowery, M. E.; DeShong, P. *J. Org. Chem.* **1999**, *64*, 3266−3270.

(6) (a) Brescia, M.-R.; DeShong, P. *J. Org. Chem.* **1998**, *63*, 3156−3157. (b) Pilcher, A. S.; DeShong, P. *J. Org. Chem.* **1996**, *61*, 6901−6905.

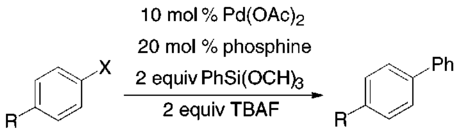
(7) (a) Denmark, S. E.; Wu, Z. *Org. Lett.* **1999**, *1*, 1495−1498. (b) Denmark, S. E.; Choi, J. Y. *J. Am. Chem. Soc.* **1999**, *121*, 5821−5822. (c) Hiyama, T. In *Metal-catalyzed Cross-coupling Reactions*; Diederich, F., Stang, P. J., Eds.; Wiley-VCH: Weinhein, Germany, 1998; pp 421−452 and references therein. (d) Horn, K. A. *Chem. Rev.* **1995**, *95*, 1317−1350. (e) Hiyama, T.; Hatanaka, Y. *Pure Appl. Chem.* **1994**, *66*, 1417−1478 (f) Chuit, C.; Corriu, R. J. P.; Reye, C.; Young, J. C. *Chem. Rev.* **1993**, *93*, 1317−1448.

(8) For an example of a copper(I) salt promoted cross coupling reaction between aryl- or heteroarylsilanes and aryl halides in absence of fluoride, see: Ito, H.; Sensui, H.-o.; Arimoto, K.; Miura, K.; Hosomi, A. *Chem. Lett.* **1997**, 639−640 and references therein.

10.1021/ol991186d CCC: $18.00

coupling of aryl bromides and chlorides.[4] After surveying various Pd(0) catalysts to broaden the scope of the reaction,[9,10] the most suitable catalyst/ligand system was found to be Pd(OAc)$_2$/PPh$_3$ or P(*o*-tol)$_3$ (1:2 molar ratio Pd:P).[11] Using these conditions, excellent yields of cross coupled adducts were obtained irrespective of the substituent attached to the aryl moiety (Table 1).[12] In general, yields are slightly lower using P(*o*-tol)$_3$, but one advantage of using this ligand is that the yield of the homocoupled adduct decreases in the cross coupling of 4-bromotoluene (Table 1, entry 3 (10%) vs entry 4 (3%)).[13]

Table 1. Substrate and Phosphine Studies

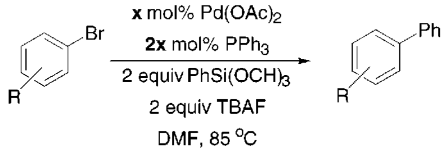


entry	X	R	phosphine	yield[a] (%)
1	Br	COCH$_3$	PPh$_3$	86
2	Br	COCH$_3$	P(*o*-tol)$_3$	78
3	Br	CH$_3$	PPh$_3$	82[b]
4	Br	CH$_3$	P(*o*-tol)$_3$	78[c]
5	Br	OCH$_3$	PPh$_3$	74
6	Br	OCH$_3$	P(*o*-tol)$_3$	70
7	Cl	COCH$_3$	PPh$_3$	29[d]
8	Cl	COCH$_3$	P(*o*-tol)$_3$	30[e]

[a] Reaction times were not optimized, but most reactions were complete within 1−5 h. [b] 10% homocoupled product obtained. [c] 3% homocoupled product obtained. [d] 71% starting material recovered. [e] 70% starting material recovered.

A catalyst loading study was performed to determine the minimal catalyst required for the coupling reaction (Table 2). Again, the three major electronic subclasses of aryl substituents were investigated (electron-deficient**,** entries 1−4, electron-neutral, entries 5−8, and electron-donating, entries 9−12). A fourth substrate, 2-bromo-*m*-xylene (entries 13−15), was used to determine the effect of steric congestion on catalyst loadings. It was found that in the case of 4-bromoacetophenone (entries 1−4) the reaction gave similar yields independent of the amount of catalyst used. With 4-bromotoluene, the reaction was unsuccessful using 1 mol % of Pd(OAc)$_2$ (entry 5), but increasing the catalyst loading to 3 mol % of Pd(OAc)$_2$ (entry 6) gave only the heterocoupled adduct. A similar trend was observed for 4-bromoanisole; using 1 mol % of Pd(OAc)$_2$ gave mostly recovered starting material (82%, entry 9), but increasing the amount of catalyst to 3 mol % gave only the heterocoupled adduct (80%, entry 10). For relatively unhindered substrates, a catalyst loading of 3 mol % of Pd(OAc)$_2$ is appropriate for aryl bromides. The hindered substrate, 2-bromo-*m*-xylene, underwent successful coupling only with catalyst loadings of 10% (entry 15).

Table 2. Catalyst Loading Studies



entry	R	x (mol % Pd)	yield[a] (%)
1	4-COCH$_3$	1	82
2	4-COCH$_3$	3	83
3	4-COCH$_3$	5	77
4	4-COCH$_3$	10	86
5	4-CH$_3$	1	0[b]
6	4-CH$_3$	3	77
7	4-CH$_3$	5	73
8	4-CH$_3$	10	82[c]
9	4-OCH$_3$	1	15[d]
10	4-OCH$_3$	3	80
11	4-OCH$_3$	5	87
12	4-OCH$_3$	10	74
13	2,6-CH$_3$	3	10[e]
14	2,6-CH$_3$	5	21[f]
15	2,6-CH$_3$	10	85[g]

[a] Reaction times were not optimized. It should also be noted that yields are reproducible and reactions were run on average of three times each. [b] 78% starting material obtained. [c] 10% homocoupled product obtained. [d] 82% starting material obtained. [e] 79% starting material obtained. [f] 62% starting material obtained. [g] 2% starting material obtained.

Since the cross coupling reaction using Pd(OAc)$_2$/PPh$_3$ was accomplished with aryl bromides, the technology was

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(9) In addition to testing Pd(OAc)$_2$, Pd(dba)$_2$, and APC without ligands, some of the catalyst/ligand systems tested were Pd(OAc)$_2$/P(*n*-Bu)$_3$, Pd(dba)$_2$/P(*t*-Bu)$_3$, Pd$_2$dba$_3$/P(*t*-Bu)$_3$, APC/P(*t*-Bu)$_3$. Last, Herrmann's catalyst (Herrmann, W. A.; Resinger, C. P.; Spiegler, M. *J. Organomet. Chem.* **1998**, *557*, 93−96) was synthesized and upon testing failed to give cross coupled adducts.

(10) A report has been published in which alkenyl-monooxydimethylsilanes, dialkoxysilanes, and trialkoxysilanes undergo palladium-catalyzed cross coupling reactions with alkenyl iodides and bromides, as well as aryl iodides. In this case, the catalyst/ligand system used was APC/P(OEt)$_3$. We did not test this particular system using our reaction conditions. For more information, please see: Tamao, K.; Kobayashi, K.; Ito, Y. *Tetrahedron Lett.* **1989**, *30*, 6051−6054.

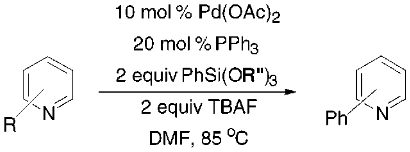
(11) For a detailed discussion of the Pd species formed when 2 equiv or less of phosphine is used with Pd(OAc)$_2$, please see: Amatore, C.; Jutand, A.; M'Barki, M. A. *Organometallics* **1992**, *11*, 3009−3013.

(12) **General procedure for cross coupling reactions:** phenyltrimethoxysilane (2.178 g, 10.983 mmol) was added to 2-bromo-*m*-xylene (1.004 g, 5.425 mmol), Pd(OAc)$_2$ (0.119 g, 0.530 mmol), and PPh$_3$ (0.283 g, 1.079 mmol) in 40 mL of DMF (under Ar). TBAF (10.80 mL, 10.80 mmol) was added via syringe. The reaction mixture was degassed (one freeze−pump−thaw cycle). The reaction was heated at 83 °C (23.5 h). The reaction was quenched (50 mL H$_2$O) and extracted (4 × 50 mL Et$_2$O). The organic layers were dried over MgSO$_4$ and concentrated in vacuo. Purification by flash chromatography (55 mm, 15 cm, pentane) gave 2,6-dimethylbiphenyl (825 mg, 85% yield) as a colorless oil: TLC $R_f = 0.43$ (pentane); IR (CCl$_4$) 3062 (w), 3022 (w), 2962 (w), 2924 (w), 1558 (vs), 1541 (vs), 1463 (m), 1443 (w), 1251 (m), 1216 (m), 1111 (m), 1072 (m), 1072 (m), 1009 (s), 973 (m), 829 (s), 808 (m); ^{1}H NMR (CDCl$_3$) δ 2.03 (s, 3H), 7.07−7.18 (m, 5H), 7.31−7.35 (m, 1H), 7.40−7.44 (m, 2H); ^{13}C NMR (CDCl$_3$) 20.8, 126.6, 127.0, 127.3, 128.4, 129.0, 136.1, 141.1, 141.9; GCMS 183 ((M + 1), 13), 182 ((M$^+$), 88), 181 (30), 168 (15), 167 (100), 166 (30), 165 (56), 152 (22), 83 (25).

(13) This has not been a general trend observed in the literature, and it is a new finding for this particular substrate. At this point in time, we do not have a specific rationalization for this observation. Mechanistic studies with assorted phosphines are underway to elucidate the electronic and steric roles played by phosphines in the catalytic cycle.

extended to heteroaryl bromides. Both 2-bromopyridine (72%, Table 3, entry 1) and 3-bromopyridine (62%, entry 3) gave excellent yields of cross-coupled adducts, 2- and 3-phenylpyridine, respectively, when phenyltrimethoxysilane was employed. Previously, it had been shown that electron-withdrawing substituents on the siloxane often improved the yield of the coupling reaction. However, attempts to increase the yield by changing the siloxane to phenyltris(trifluoroethoxy)silane were unsuccessful. In the case of 2-bromopyridine (entry 2), the reaction gave only starting material. With 3-bromopyridine (62%, entry 4), the reaction gave an identical yield to that when phenyltrimethoxysilane was used. This was contrary to the results seen with aryl iodides, where yields could be increased by replacing phenyltrimethoxysilane with phenyltris(trifluoroethoxy)silane.[4]

Table 3. Cross Coupling Reactions with Bromopyridines

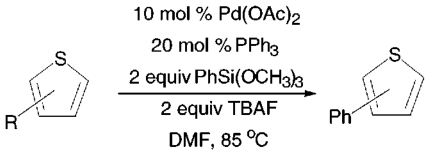


entry	R	R"	yield[a] (%)
1	2-Br	CH_3	76
2	2-Br	CH_2CF_3	0[b]
3	3-Br	CH_3	62
4	3-Br	CH_2CF_3	62[c]

[a] Reaction times were not optimized, but most reactions were complete within 1−5 h. [b] 90% starting material recovered. [c] 3% starting material recovered.

The siloxane cross coupling reaction is also applicable to bromothiophene derivatives. Coupling of 2-bromothiophene (Table 4, entry 1) gave a 64% yield of the heterocoupled adduct 2-phenylthiophene as well as 30% of the homocoupled adduct 2,2′-bithiophene. Results for the cross coupling of 3-bromothiophene were better; the yield of the heterocoupled adduct 3-phenylthiophene was 70% (entry 2), and only 6% of the homocoupled adduct 3,3′-bithiophene was obtained.

Table 4. Cross Coupling Reactions with Bromothiophenes



		yield (%)	
entry	R	heterocoupled	homocoupled
1	2-Br	64	30
2	3-Br	70	6

Extension of this catalyst/ligand system to the coupling of aryl chlorides was not generally successful. Attempts to couple 4-chloroacetophenone (Table 1, entry 7) with PPh_3 gave 29% of the heterocoupled adduct 4-acetylbiphenyl, and the remaining 71% was recovered starting material. Using P(*o*-tol)$_3$ gave similar results (Table 1, entry 8); the yield of heterocoupled adduct was 30%, and the amount of recovered starting material was 70%. Attempts to couple 4-chlorobiphenyl gave none of the heterocoupled adduct, *p*-terphenyl, and only starting material was recovered.

Since the Pd(OAc)$_2$/PPh_3 catalyst system was unable to activate aryl chlorides, the inclusion of alternative phosphine ligands was surveyed.[14] Recently, Fu and co-workers reported that tri-*tert*-butylphosphine (P(*t*-Bu)$_3$) was an excellent ligand for Pd(0)-catalyzed Suzuki couplings of aryl chlorides at ambient temperature.[15] Attempts to employ this catalyst/ligand system (Pd$_2$(dba)$_3$:P(*t*-Bu)$_3$) in the siloxane cross coupling reaction with aryl chlorides, even after heating at high temperature for 48 h, failed to provide biaryl products.[16] In all cases, only starting material was recovered.

Buchwald and co-workers have developed a series of phosphine ligands for activation of aryl chlorides in catalytic aminations[17] as well as for activation of aryl chlorides in the preparation of diaryl ethers.[18] Of the Buchwald ligands tested, one ligand was found to be effective in siloxane couplings and is depicted in Figure 1.[19,20]

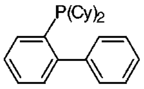


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Figure 1. 2-(Dicyclohexylphosphino)biphenyl (Buchwald's ligand **1**) employed in siloxane cross couplings.[20]

The results of siloxane cross couplings of aryl chlorides with ligand **1** are summarized in Table 5. Using 4-chloroacetophenone (Table 5, entry 1) or 4-chlorotoluene (Table 5, entry 2) as substrates gave moderate to good yields of the

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(14) There is a report that describes the cross coupling of organochlorosilanes with aryl chlorides. The Pd complex used in this case is [(*i*-Pr$_3$P)$_2$-PdCl$_2$], and unfortunately this Pd species only cross-coupled aryl chlorides that were electron-deficient. In the case of electron-neutral or electron-rich aryl chlorides, the reactions were much slower and failed to give satisfactory yields of coupled products. This catalyst system was never tested using our reaction conditions. For more information, please see: Gouda, K.-i.; Hagiwara, E.; Hatanaka, Y.; Hiyama, T. *J. Org. Chem.* **1996**, *61*, 7232−7233.

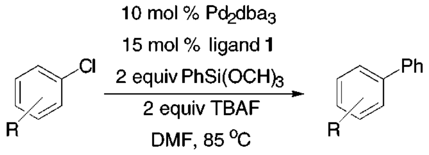
(15) (a) Littke, A. F.; Fu, G. C. *J. Org. Chem.* **1999**, *64*, 10−11. (b) Littke, A. F.; Fu, G. C. *Angew. Chem., Int. Ed.* **1998**, *37*, 3387−3388.

(16) Amount Pd:P was a 1:2 ratio. The reaction conditions described in ref 10 normally use 1.5 mol % of Pd$_2$(dba)$_3$ and 6 mol % of P(*t*-Bu)$_3$. Experiments we conducted used either the same amount or twice as many equivalents of Pd$_2$(dba)$_3$ and P(*t*-Bu)$_3$. In all experiments conducted, the ratios of Pd:P were kept identical to that in ref 15.

(17) (a) Wolfe, J. P.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **1999**, *38*, 2413−2416. (b) Yang, B. H.; Buchwald, S. L. *J. Organomet. Chem.* **1999**, *576*, 125−146. (b) Old, D. W.; Wolfe, J. P.; Buchwald, S. L. *J. Am. Chem. Soc.* **1998**, *120*, 9722−9723.

(18) Aranyos, A.; Old, D. W.; Kiyomori, A.; Wolfe, J. P.; Sadighi, J. P.; Buchwald, S. L. *J. Am. Chem. Soc.* **1999**, *121*, 4369−4378.

Table 5. Activation of Aryl Chlorides



entry	R	yield (%)
1	4-$COCH_3$	47
2	4-CH_3	63
3	4-OCH_3	71

heterocoupled adducts. The cross coupling of 4-chloroanisole (Table 5, entry 3) gave a 71% yield of the heterocoupled adduct. This yield is comparable to the yields obtained with bromides by using $Pd(OAc)_2$/(PPh_3 or P(*o*-tol)$_3$) (Table 1, entries 5 and 6).

The last series of substrates examined in the siloxane coupling reaction was aryl triflates. Previous studies from our group had found that aryl triflates did not undergo the coupling reaction using hypervalent siloxanes formed in situ.[4] Attempts to couple either 4-nitrophenyl triflate or 4-carbomethoxyphenyl triflate with siloxanes in the presence of $Pd(OAc)_2/PPh_3$ gave none of the expected heterocoupled adducts, although starting material was consumed in both cases. The current state of the siloxane coupling technology does not extend to include aryl triflates as substrates.[21]

In conclusion, the siloxane cross coupling technology has been expanded to efficiently couple aryl and heteroaryl bromides in excellent yields using $Pd(OAc)_2$ and either PPh_3 or P(*o*-tol)$_3$. Catalyst loadings for relatively unhindered substrates can be as low as 3 mol % of $Pd(OAc)_2$, while hindered arenes required 10 mol % of catalyst. Aryl chlorides have been coupled in moderate to good yields by employing Buchwald's ligand. Future goals include development of a general and reliable method for the synthesis of various aryl- and alkenyl-substituted siloxanes as well as application of the cross coupling technology to the synthesis of natural products. Cross coupling reactions using these aryl-substituted siloxanes will be reported in due course.

Acknowledgment. We thank Dr. Yiu-Fai Lam and Ms. Caroline Ladd for their assistance in obtaining NMR and mass spectral data, respectively. We also thank Professor Steve Buchwald and Dr. John Wolfe for helpful discussions. This work was partially supported by a research grant from the National Cancer Institute (CA82169-01). M.M. thanks the Organic Division of the American Chemical Society for a Graduate Fellowship (sponsored by Pfizer, Inc.).

Supporting Information Available: Detailed experimental procedures as well as full characterization of novel compounds synthesized. IR, ^{1}H and ^{13}C NMR, and GCMS spectra for 2,6-dimethylbiphenyl. This material is available free of charge via the Internet at http://pubs.acs.org.

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(19) One ligand, 1-(*N*,*N*-dimethylamino)-1′-(dicyclohexylphopshino)-biphenyl, gave poor yields when used with electron-deficient substrates, and with electron-neutral substrates, it was unreactive. A second ligand, 2-(di-*tert*-butylphosphino)biphenyl, was found to be completely unreactive using 4-chlorotoluene as a substrate.

(20) Ligand **1** is commercially available from Strem Chemical Co. and was recrystallized from absolute EtOH prior to use.

(21) A report in which alkenyl, alkynyl, aryl, and alkyl silanes are cross-coupled to enol and aryl triflates in the presence of Pd(0) and fluoride ion is available. For more information, please see: Hatanaka, Y.; Hiyama, T. *Tetrahedron Lett.* **1990**, *31*, 2719−2722.