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$Pd_2(dba)_3/P(i\text{-}BuNCH_2CH_2)_3N$-Catalyzed Stille Cross-Coupling of Aryl Chlorides

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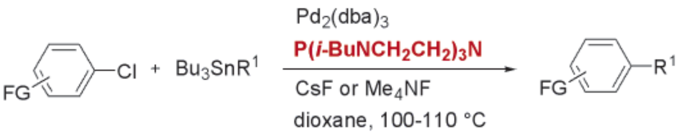
ABSTRACT



The $Pd_2(dba)_3/P(i\text{-}BuNCH_2CH_2)_3N$ (1d) catalyst system is highly effective for the Stille cross-coupling of aryl chlorides with organotin compounds. This method represents only the second general method for the coupling of aryl chlorides. Other proazaphosphatranes possessing benzyl substituents also generate very active catalysts for Stille reactions. Noteworthy features of the method are: (a) commercial availability of ligand 1d, (b) the wide array of aryl chlorides that can be coupled, and (c) applicability to aryl, vinyl, and allyl tin reagents.

The palladium-catalyzed Stille cross-coupling of aryl halides (or halide equivalents) with organotin reagents is an important C−C bond-forming reaction that has found wide application in organic synthesis.[1,2] Until recently, this method was handicapped by the need to use aryl bromides or iodides as the reaction partner. Unlike the case with other Pd-catalyzed processes (e.g., Suzuki[3] and Buchwald−Hartwig amination[4] reactions) where a myriad of catalyst systems allow coupling of economically attractive but notoriously unreactive aryl chlorides, the same is not true with the Stille coupling of aryl chlorides.[5] However, significant progress was achieved recently. For example, Fu,[6] in his pioneering studies, disclosed a palladium-catalyst based on sterically hindered electron-rich $P(t\text{-}Bu)_3$ for the Stille cross-coupling of aryl chlorides. This method, although general, requires a highly air-sensitive and pyrophoric ligand that requires special handling techniques. Although the air-stable $Pd[P(t\text{-}Bu)_3]_2$[7] complex was recommended as an alternative to $Pd_2(dba)_3/P(t\text{-}Bu)_3$ for this process, its high cost is a deterrent to its widespread use. On the other hand, $P(t\text{-}Bu)_3$ has recently become commercially available as the air-stable precursor $[(t\text{-}Bu)_3PH]BF_4$.[8] Nolan[9] reported a Pd/N-heterocyclic carbene system for the Stille reaction of aryl chlorides. However, this protocol provided good yields only for

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(1) For reviews on Stille cross-coupling reaction, see: (a) Stille, J. K. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 508. (b) Farina, V.; Krishnamurthy, V.; Scott, W. J. *Org. React.* **1997**, *50*, 1. (c) Littke, A. F.; Fu, G. C. *Angew Chem., Int. Ed.* **2002**, *41*, 4176.

(2) For applications of the Stille reaction in natural product synthesis, see: (a) Nicolaou, K. C.; Li, Y.; Sugita, K.; Monenschein, H.; Guntupalli, P.; Mitchell, H. J.; Fylaktakidou, K. C.; Vourloumis, D.; Giannakakou, P.; O'Brate, A. *J. Am. Chem. Soc.* **2003**, *125*, 15443. (b) Kadota, I.; Takamura, H.; Sato, K.; Ohno, A.; Matsuda, K.; Yamamoto, Y. *J. Am. Chem. Soc.* **2003**, *125*, 46. (c) Boger, D. L.; Ichikawa, S.; Jiang, H. *J. Am. Chem. Soc.* **2000**, *122*, 12169.

(3) For leading references to Suzuki couplings of aryl chlorides, see: (a) Old, D. W.; Wolfe, J. P.; Buchwald, S. L. *J. Am. Chem. Soc.* **1998**, *120*, 9722. (b) Littke, A. F.; Fu, G. C. *Angew Chem., Int. Ed.* **1998**, *37*, 3387. (c) Littke, A. F.; Dai, C.; Fu, G. C. *J. Am. Chem. Soc.* **2000**, *122*, 4020. (d) Bedford, R. B.; Cazin, C. S. J. *Chem. Commun.* **2001**, 1540. (e) Li, G. Y. *Angew. Chem., Int. Ed.* **2001**, *40*, 1513. (f) Herrmann, W. A.; Reisinger, C.-P.; Spiegler, M. *J. Organomet. Chem.* **1998**, *557*, 93. (g) Zhang, C.; Huang, J.; Trudell, M. L.; Nolan, S. P. *J. Org. Chem.* **1999**, *64*, 3804. (h) Urgaonkar, S.; Nagarajan, M. Verkade, J. G. *Tetrahedron Lett.* **2002**, *43*, 8921.

(4) For leading references to Buchwald−Hartwig amination reactions of aryl chlorides, see: (a) Wolfe, J. P.; Tomori, J.; Sadighi, J. P.; Yin, J.; Buchwald, S. L. *J. Org. Chem.* **2000**, *65*, 1158. (b) Hartwig, J. F.; Kawatsura, M.; Hauck, S. I.; Shaughnessy, K. H.; Alcazar-Roman, L. M. *J. Org. Chem.* **1999**, *64*, 5575. (c) Huang, J.; Grasa, G. A.; Nolan, S. P. *Org. Lett.* **1999**, *1*, 1307. (d) Nishiyama, M.; Yamamoto, T.; Koie, Y. *Tetrahedron Lett.* **1998**, *39*, 2367. (e) Bei, X.; Uno, T.; Norris, J.; Turner, H. W.; Weinberg, W. H.; Guram, A. S.; Petersen, J. L. *Organometallics* **1999**, *18*, 1840. (f) Hamann, B. C.; Hartwig, J. F. *J. Am. Chem. Soc.* **1998**, *120*, 7369. (g) Reddy, N. P.; Tanaka, M.; *Tetrahedron Lett.* **1997**, *38*, 4807. (h) Urgaonkar, S.; Nagarajan, M.; Verkade, J. G. *Org. Lett.* **2003**, *5*, 815.

(5) For Pd-catalyzed Stille reactions of activated aryl chlorides, see: Kosugi, M.; Sasazawa, K.; Shimizu, Y.; Migita, T. *Chem. Lett.* **1977**, 301. See also refs 1b and 1c.

(6) (a) Littke, A. F.; Fu, G. C. *Angew Chem., Int. Ed.* **1999**, *38*, 2411. (b) Littke, A. F.; Schwarz, L.; Fu, G. C. *J. Am. Chem. Soc.* **2002**, *124*, 6343.

(7) Available from Strem Chemicals.

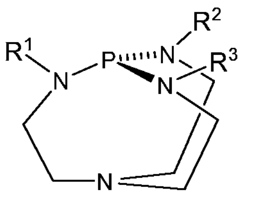
(8) Netherton, M. R.; Fu, G. C. *Org. Lett.* **2001**, *3*, 4295.

(9) Grasa, G. A.; Nolan, S. P. *Org. Lett.* **2001**, *3*, 119.

10.1021/ol0495927 CCC: $27.50

electron-deficient aryl chlorides. For electron−neutral and electron-rich aryl chlorides, only poor to moderate yields were obtained. In an elegant work, Choudary reported a layered double-hydroxide-supported nanopalladium catalyst for the Stille reaction of aryl chlorides, including electron-rich aryl chlorides under mild conditions (50 °C).[10] However, the generality of the process remains to be determined. More recently, the Stille reaction of aryl chlorides in water utilizing palladium−phosphinous acid complexes was described by Wolf.[11] This methodology required very high temperatures (135−140 °C); no examples involving electron-rich aryl chlorides were reported, and important functional groups such as esters and aldehydes were not compatible. Therefore, catalyst systems with both a higher degree of stability and activity (preferably commercially available) that can effect Stille coupling of aryl chlorides are highly desirable.

Previous work in our laboratories has established that a bicyclic proazaphosphatrane[12] bearing *iso*-butyl (**1d**) groups on the PN$_3$ nitrogens is a highly effective ligand for several Pd-catalyzed cross-coupling reactions of aryl halides, including those of aryl chlorides.[13] We report herein a general and efficient method for the Stille coupling of aryl chlorides with organotin reagents utilizing **1d** as the ancillary ligand. Additionally, we show that proazaphosphatranes possessing groups other than *iso*-butyl on the PN$_3$ nitrogens can also generate a highly active palladium catalyst for the Stille reaction of aryl chlorides.

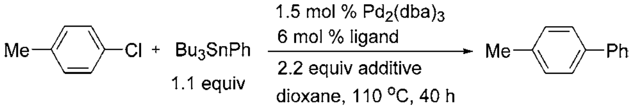


1a: R^1, R^2, R^3 = Me
1b: R^1, R^2, R^3 = *i*-Pr
1c: R^1, R^2 = *i*-Pr, R^3 = Bn
1d: R^1, R^2, R^3 = *i*-Bu
1e: R^1, R^2 = *i*-Bu, R^3 = Bn
1f: R^1, R^2 = Bn, R^3 = *i*-Bu
1g: R^1, R^2, R^3 = Bn
1g: R^1, R^2, R^3 = Bn
1h: R^1, R^2, R^3 = Piv

Figure 1. Proazaphosphatrane Ligands.

For optimization of reaction conditions, Stille coupling of electron−neutral 4-chlorotoluene with phenyltributyltin in dioxane at 110 °C was chosen as a model reaction. Both Fu's[6] and Nolan's[9] studies on the Stille reaction have revealed the importance of a fluoride source in activating organotin compounds for the transmetalation step. Thus, we also tested various fluoride additives. As shown in Table 1, employing CsF as a fluoride source and ligands with either smaller substituents on the PN$_3$ nitrogens (**1a** and **1b**) or a large substituent (**1h**) did not afford the desired coupling product in appreciable amounts (entries 1, 2, and 11). Interestingly, changing one PN$_3$ substituent of **1b** to benzyl led to a dramatic increase in the product yield (**1c**, entry 3). Expectedly, **1d** with *iso*-butyl groups on PN$_3$ nitrogens generated a very active catalyst, providing the desired biphenyl in 84% isolated yield (entry 4). The salutary effect of the benzyl group on catalytic activity was also evident in ligands **1e**−**g**, which also effectively promoted the Stille reaction (entries 7, 9, and 10). Although it is not presently clear what the origin of the beneficial influence of the benzyl group is on the activity of the catalyst, one possibility is that this group stabilizes the active palladium catalyst through the interaction of its aromatic π-orbitals with empty d-orbitals on palladium.[14] Another possibility is that the benzyl group (like *iso*-butyl) possesses the unique balance of stereoelectronic influences required for catalytic activity in this reaction.

Table 1. Screening of Proazaphosphatrane Ligands and Fluoride Additives



entry	ligand	additive	yield (%)[a]
1	**1a**	CsF	<2
2	**1b**	CsF	21
3	**1c**	CsF	42
4	**1d**	CsF	84
5	**1d**	KF	37
6	**1d**	Me$_4$NF	92
7	**1e**	CsF	89
8	**1e**	Me$_4$NF	96
9	**1f**	CsF	91
10	**1g**	CsF	92
11	**1h**	CsF	<2

[a] Isolated yields (average of two runs).

Further optimization of the fluoride additives (entries 4−8) established the efficacy order to be Me$_4$NF > CsF ≫ KF, which probably results from their decreasing solubilities in the solvent used. We chose to use the Pd$_2$(dba)$_3$/**1d**/CsF catalyst system for evaluating the scope of our protocol, due to the commercial availability of **1d**[15] and the lower cost of CsF compared with Me$_4$NF.

As demonstrated in Tables 2 and 3, the Pd$_2$(dba)$_3$/**1d**/CsF catalyst system is remarkably general, high-yielding, and

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(10) Choudary, B. M.; Madhi, S.; Chowdari, N. S.; Kantam, M. L.; Sreedhar, B. *J. Am. Chem. Soc.* **2003**, *124*, 14127.

(11) Wolf, C.; Lerebours, R. *J. Org. Chem.* **2003**, *68*, 7551.

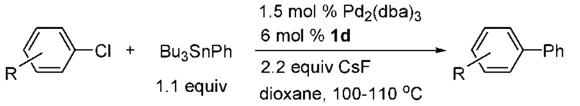
(12) For recent reviews, see: (a) Verkade, J. G. *Top. Curr. Chem.* **2002**, *233*, 1. (b) Kisanga, P. B.; Verkade, J. G. *Tetrahedron* **2003**, *59*, 7819. (c) Verkade, J. G.; Kisanga, P. B. *Aldrichimica Acta*, in press.

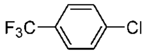
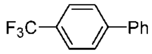
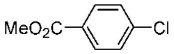
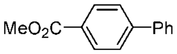
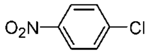
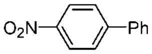
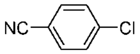
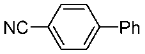
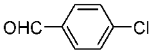
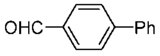
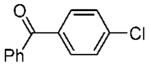
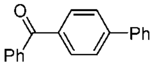
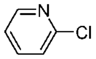
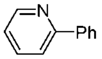
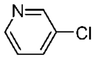
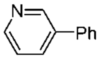
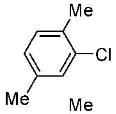
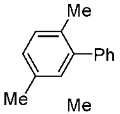
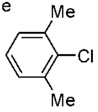
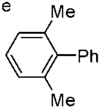
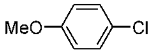
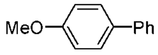
(13) (a) Urgaonkar, S. Nagarajan, M.; Verkade, J. G. *J. Org. Chem.* **2003**, *68*, 452. (b) You, J.; Verkade, J. G. *Angew. Chem., Int. Ed.* **2003**, *42*, 5051. (c) You, J.; Verkade, J. G. *J. Org. Chem.* **2003**, *68*, 8003. Also see refs 3h and 4h.

(14) For Pd−arene interactions in palladium complexes, see: (a) Reid, S. M.; Boyle, R. C.; Mague, J. T.; Fink, M. J. *J. Am. Chem. Soc.* **2003**, *125*, 7816. (b) Catellani, M.; Mealli, C.; Motti, E.; Paoli, P.; Perez-Carreno, E.; Pregosin, P. S. *J. Am. Chem. Soc.* **2002**, *124*, 4336. (c) Yin, J.; Rainka, M. P.; Zhang, X.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 1162.

(15) Ligand **1d** is commercially available from Aldrich and Strem Chemicals.

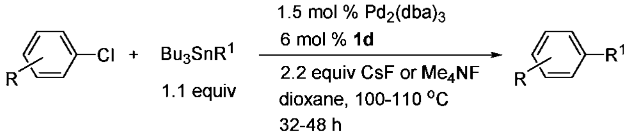
Table 2. Stille Cross-Coupling of Aryl Chlorides with Phenyltributyl Tin

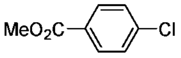
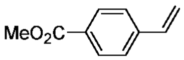
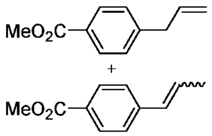
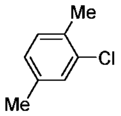
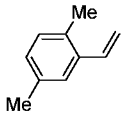
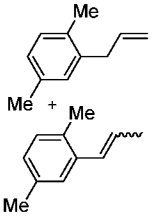
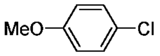
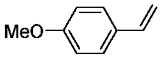
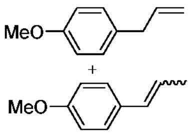
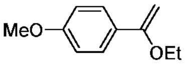


entry	aryl chloride	time (h)	product	yield (%)[a]
1		30		96[b]
2		24		95[b]
3		30		86[b]
4		24		96[b]
5		30		89[b]
6		30		93[b]
7		36		85
8		36		99
9		36		90
10		48		95
11		48		98[c]
12		48		71
13		48		90[c]

[a] Isolated yields (average of two runs). [b] Reaction was carried out at 100 °C. [c] Me_4NF was used in place of CsF.

Table 3. Stille Cross-Coupling of Aryl Chlorides with Vinyl and Allyl Tin Reagents



entry	aryl chloride	product (s)	yield (%)[a]
1			93[b]
2			98 (1:4)[b,c]
3			34
4			72[d]
5			95 (15:2)[c]
6			23
7			53[d,e]
8			89[d,e,f]
9			94 (7:1)[c]
10			97

[a] Isolated yields (average of two runs). [b] Reaction was carried out at 100 °C. [c] Ratio represents that of the desired allylation product to its conjugated regioisomer. The ratio was determined by NMR spectroscopy. Isolated yields are for the mixtures of regioisomers. [d] Me_4NF was used in place of CsF. [e] Performed with 1.5 equiv of tin reagent. [f] Ligand **1e** was employed.

tolerant of a range of functionalities.[16] Thus, reactions of activated or deactivated aryl chlorides with phenyltributyltin provided excellent yields, as did reactions of chloropyridines. The method is compatible with a trifluoromethyl (Table 2, entry 1), ester (Table 2, entry 2), nitro (Table 2, entry 3), cyano (Table 2, entry 4), aldehyde (Table 2, entry 5), or ketone (Table 2, entry 6) functional group. Even reactions of ortho-substituted aryl chlorides occurred in high yields (Table 2, entries 9−11). As seen in entries 12 and 13 of this table, the use of the more soluble fluoride additive Me_4NF provided a higher yield of the desired product than did CsF.

The scope of the $Pd_2(dba)_3$/**1d**/CsF catalyst system was further extended to reactions of aryl chlorides with vinyltin and allyltin reagents (Table 3). Electron-poor (Table 3, entries 1 and 2), sterically hindered (Table 3, entries 3−5), and electron-rich (Table 3, entries 6−10) aryl chlorides can be efficiently coupled, although for the reaction of electron-rich 4-chloroanisole with tributyl(vinyl)tin, the $Pd_2(dba)_3$/**1e**/Me_4NF catalyst system resulted in a higher yield of the desired product (compare entries 6−8). Interestingly, reactions of aryl chloride with allyltributyltin afforded the desired allylation product along with its regioisomer. For example, for electron-deficient aryl chlorides, the desired allylation product was obtained as a minor isomer (Table 3, entry 2), whereas electron-neutral and electron-rich aryl chlorides gave the desired Stille product as the major isomer (Table 3, entries 5 and 9).

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(16) **General Procedure.** An oven-dried Schlenk flask equipped with a magnetic stirring bar was charged with $Pd_2(dba)_3$ (1.5 mol %) and CsF or Me_4NF (2.2 mmol) inside a glovebox. If the aryl chloride (1.0 mmol) was a solid, it was also added at this time. The flask was capped with a rubber septum and removed from the glovebox. Ligand **1** (6.0 mol %) was then added via syringe from a stock solution (2 mM in dioxane). Aryl chloride (if a liquid, 1.0 mmol), tin reagent (1.1 mmol), and dioxane (2 mL) were then successively added via syringe. Under a positive pressure of argon, the flask was sealed with a Teflon screw-cap, and then the reaction mixture was heated at the temperature indicated (see Tables 1−3) until the starting material had been completely consumed as judged by TLC. The mixture was then cooled to room temperature, diluted with ether or acetone, filtered, and concentrated in vacuo. The crude product was purified by column chromatography on silica gel.

In summary, we have discovered that members of a family of proazaphosphatrane ligands in combination with $Pd_2(dba)_3$ generate very active palladium catalysts for the Stille cross-coupling of aryl chlorides with organotin compounds,[17] furnishing desired products in high yields. The methodology is compatible with functional groups such as an ester, nitro, trifluoromethyl, keto, cyano, and aldehyde. We believe that the range of Pd-catalyzed cross-couplings that can be accomplished with triaminophosphine **1d** renders this ligand a suitable alternative to alkylphosphines, giving additional impetus to our exploration of this class of compounds in metal-catalyzed reactions.

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Supporting Information Available: Experimental details and ^1H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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(17) Further studies on the Stille reaction of aryl chlorides with various substituted aryl tin reagents are ongoing and will be reported in due course.