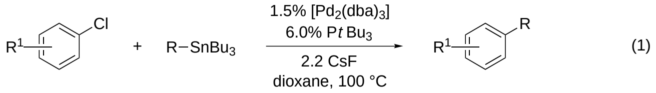
The First General Method for Stille Cross-Couplings of Aryl Chlorides[**]

Adam F. Littke and Gregory C. Fu*

Stille cross-coupling of organotin compounds with aryl iodides, bromides, and triflates (-OSO_2CF_3) is a powerful and widely used method for carbon–carbon bond formation.[1] Although aryl chlorides are both more abundant and less expensive than other coupling partners,[2] to date the only examples of this family of compounds participating in a Stille reaction have involved electron-deficient aryl chlorides.[3–5] Herein we describe a general solution to this long-standing challenge: the use of P*t*Bu_3 as a ligand for palladium and CsF to activate the tin reagent leads to the efficient coupling of an array of aryl chlorides with a broad spectrum of organotin compounds [Eq. (1); R^1 = OMe, NH_2, *o*-Me, etc.; R = vinyl, allyl, Ph, Bu, etc.].

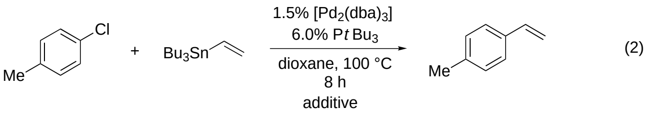


(1)

Very recently, we and others have discovered that with electron-rich and sterically hindered P*t*Bu_3 as a ligand, it is possible to effect palladium-catalyzed couplings of aryl chlorides with amines,[6] arylboronic acids,[7] ketone enolates,[8] and olefins.[9] In our own work, we had found that $[Pd_2(dba)_3]$/P*t*Bu_3 was a particularly effective catalyst system.[7a, 9a] Unfortunately, our attempts to apply this system to the Stille reaction of *p*-chlorotoluene with tributyl(vinyl)tin met with only limited success (Table 1, entry 1).

Given that hypervalent organotin species are typically more reactive (nucleophilic) than their tetravalent precursors and that tin is fluorophilic,[10] we decided to explore the possibility that addition of fluoride might lead to more efficient cross-coupling, perhaps by facilitating transmetalation from tin to palladium.[11, 12] A fluoride-activation strategy has been applied successfully by others to several different cross-coupling processes,[13] but not to Stille reactions of aryl chlorides. In fact, Kosugi et al. have very recently reported that a $[Pd(dba)_2]/PPh_3$/TBAF system does *not* effect Stille couplings of aryl chlorides (TBAF = Bu_4NF).[14] We have found that whereas the presence of tris(dimethylamino)sulfur (trimethylsilyl)difluoride (TAS-F) is detrimental to cross-coupling with the $[Pd_2(dba)_3]$/P*t*Bu_3 system (Table 1, entry 2), the addition of other fluoride sources, including TBAF·3H_2O and KF, is beneficial (entries 3 and 4). The most effective fluoride additive among those that we have surveyed is CsF (entry 5); increasing the quantity of CsF from 1.1 to 2.2 equivalents leads to further improvement in efficiency (entry 5 vs. 6). Finally, we have found that non-fluoride-based additives (e.g., NEt_3, Cs_2CO_3, and NaOH)[15–17] also accelerate the cross-coupling process, but not as effectively as CsF (entries 7–9 vs. entry 5).

Table 1. Effect of additives on the $[Pd_2(dba)_3]$/P*t*Bu_3-catalyzed cross-coupling of 4-chlorotoluene with tributyl(vinyl)tin [Eq. (2)].



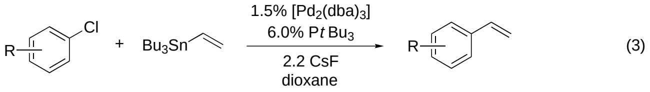
(2)

Entry	Additive (1.1 equiv)	Yield [%][a]
1	none	12
2	TAS-F	4
3	TBAF·3H_2O	24
4	KF	28
5	CsF	50
6	CsF (2.2 equiv)	59
7	NEt_3	16
8	Cs_2CO_3	40
9	NaOH	42

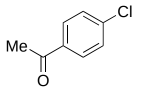
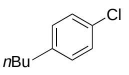
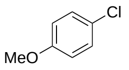
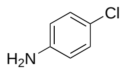
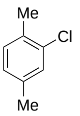
[a] Yield determined after 8 h (GC); average of two runs.

Under our optimized reaction conditions (1.5% $[Pd_2(dba)_3]$/6% P*t*Bu_3/2.2 equiv CsF), we can accomplish Stille cross-couplings of a wide array of aryl chlorides (Table 2).[18, 19] Thus, electron-poor (entry 1), electron-neutral

Table 2. Scope of the $[Pd_2(dba)_3]$/P*t*Bu_3-catalyzed Stille cross-coupling reaction: variation of the aryl chloride [Eq. (3)].



(3)

Entry	Aryl chloride	*T* [°C]	*t* [h]	Yield [%][a]
1		80	12	87
2		100	23	80
3		100	48	82 (90)
4		100	48	61
5		100	36	71 (84)

[a] Yield of isolated product given as an average of two runs. Values in parentheses are yields measured by GC for reaction products that are volatile.

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[**] Support has been provided by the Alfred P. Sloan Foundation, the American Cancer Society, Bristol–Myers Squibb, the Camille and Henry Dreyfus Foundation, the National Science Foundation (Young Investigator Award, with funding from Merck, Pharmacia & Upjohn, Bayer, and Novartis), the Natural Sciences and Engineering Research Council of Canada (predoctoral fellowship to A.F.L.), Pfizer, and Procter & Gamble.

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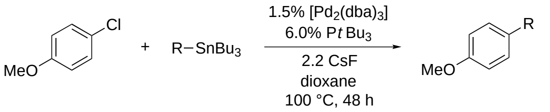
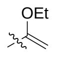
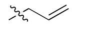
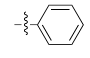
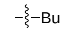
(entry 2), and electron-rich (entry 3) aryl chlorides couple in good yield, with the exception of *p*-chloroaniline, which affords only a fair yield of *p*-aminostyrene (entry 4). Consistent with other cross-coupling processes,[20] the reaction proceeds more rapidly with more electron-poor halides. Sterically hindered aryl chlorides also undergo Stille reaction under our conditions (entry 5).

We have determined that not only a broad spectrum of aryl chlorides, but also a diverse set of organotin reagents, participate in Stille cross-couplings in the presence of $[Pd_2(dba)_3]/PtBu_3/CsF$. For this study, we chose to focus on reactions of *p*-chloroanisole, a relatively challenging test substrate because of its electron-richness. As illustrated in Table 3, we have established that we can couple 1-ethoxyvinyl, allyl, and phenyl groups to *p*-chloroanisole in excellent yield (entries 1–3). Interestingly, even alkyl groups, which are typically very reluctant participants in Stille reactions,[1] can be transferred efficiently under these conditions (entry 4).[21]

Table 3. Scope of the $[Pd_2(dba)_3]/PtBu_3$-catalyzed Stille cross-coupling reaction: variation of the organotin reagent [Eq. (4)].



(4)

Entry	R	Yield [%][a]
1		98
2		87
3		94
4		82

[a] Yield of isolated product given as an average of two runs.

From a purely practical point of view, it is worth noting that many Stille reactions are plagued by difficulties in separating the desired product from the organotin residue.[1b, 22] A number of elegant strategies have been devised to address this issue, such as the use of fluorous tin reagents wherein separation is effected through a fluorous/organic extraction.[23] We have found that purification of the reaction product is not an issue under our conditions, presumably due to in situ generation of insoluble Bu_3SnF.[24]

In summary, we have described a solution to a long-standing challenge in Stille chemistry: the development of a general method for the cross-coupling of aryl chlorides. The catalyst system that we have discovered relies upon the presence of both $PtBu_3$, which we believe enhances the reactivity of the palladium catalyst, and CsF, which we believe enhances the reactivity of the organotin compound. With this new system, which employs commercially available reagents, it is now possible to effect Stille reactions of a wide range of aryl chlorides with a broad array of tin compounds.

Received: April 23, 1999 [Z13310IE]
German version: *Angew. Chem.* **1999**, *111*, 2568–2570

Keywords: cross-coupling · homogeneous catalysis · palladium · Stille reactions

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[1] a) J. K. Stille, *Angew. Chem.* **1986**, *98*, 504–519; *Angew. Chem. Int. Ed. Engl.* **1986**, *25*, 508–524; b) V. Farina, V. Krishnamurthy, W. J. Scott, *Org. React.* **1997**, *50*, 1–652; c) T. N. Mitchell in *Metal-catalyzed Cross-coupling Reactions* (Eds.: F. Diederich, P. J. Stang), WILEY-VCH, New York, **1998**, chap. 4; d) for recent mechanistic work, see: A. L. Casado, P. Espinet, *J. Am. Chem. Soc.* **1998**, *120*, 8978–8985.

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[10] *Chemistry of Tin* (Ed.: P. J. Smith), Blackie, New York, **1998**.

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[12] For examples of enhanced reactivity in Stille reactions due to intramolecular coordination of a nucleophile to an organotin reagent, see: a) E. Vedejs, A. R. Haight, W. O. Moss, *J. Am. Chem. Soc.* **1992**, *114*, 6556–6558; b) J. M. Brown, M. Pearson, J. T. B. H. Jastrzebski, G. van Koten, *J. Chem. Soc. Chem. Commun.* **1992**, 1440–1441; c) V. Farina, *Pure Appl. Chem.* **1996**, *68*, 73–78; d) E. Fouquet, M. Pereyre, A. L. Rodriguez, *J. Org. Chem.* **1997**, *62*, 5242–5243.

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[15] For Stille cross-couplings of aryl bromides and aryl iodides in the presence of hydroxide, see: A. I. Roshchin, N. A. Bumagin, I. P. Beletskaya, *Tetrahedron Lett.* **1995**, *36*, 125–128.

[16] For Hiyama cross-couplings in the presence of hydroxide, see: E. Hagiwara, K.-i. Gouda, Y. Hatanaka, T. Hiyama, *Tetrahedron Lett.* **1997**, *38*, 439–442. See also: C. Mateo, C. Fernandez-Rivas, D. J. Cardenas, A. M. Echavarren, *Organometallics* **1998**, *17*, 3661–3669.

[17] The reaction with NaOH as the additive was somewhat less clean than the reaction with CsF.

[18] General experimental: Under an atmosphere of argon or N_2, a solution of aryl chloride (1.0 mmol; in dioxane (0.5 – 0.6 mL)) and a solution of P*t*Bu$_3$ (0.060 mmol; in dioxane (0.5 – 0.4 mL)) were added in turn to a Schlenk tube charged with [Pd$_2$(dba)$_3$] (0.015 mmol) and CsF (2.2 mmol). The organostannane (1.05 mmol) was then added by syringe, and the Schlenk tube was sealed, placed in an 80 – 100 °C oil bath, and stirred for 12 – 48 h. The reaction mixture was then cooled to room temperature, diluted with Et$_2$O, and filtered through a pad of silica gel. The silica gel was washed thoroughly with Et$_2$O, and the combined Et$_2$O washings were concentrated by rotary evaporation. The product was then purified by flash chromatography.

[19] Notes: a) These cross-coupling reactions do not appear to be highly air- or moisture-sensitive. For example, they can be conducted in reagent-grade dioxane through which argon has been bubbled. b) In the absence of [Pd$_2$(dba)$_3$] or of P*t*Bu$_3$, no reaction (<2 % conversion) is observed. c) The reactions proceed to completion with only 1.1 equiv of CsF and with only 3.6 % P*t*Bu$_3$, but more slowly than under the conditions described in reference [18]. d) The reaction is slower with PCy$_3$ than with P*t*Bu$_3$, and it does not proceed in the presence of electron-rich and sterically hindered tris(2,4,6-trimethoxyphenyl)phosphane. e) Cross-couplings in THF proceed with comparable efficiency as in dioxane; reactions in toluene are somewhat slower. f) [Pd(OAc)$_2$] is inferior to [Pd$_2$(dba)$_3$] as a catalyst precursor. g) Lower catalyst loadings may be used in these Stille couplings, at the expense of slightly lower yields. For example, cross-coupling of 4-*n*-butyl-1-chlorobenzene with tributyl(vinyl)tin in the presence of 0.25 % [Pd$_2$(dba)$_3$] and 1.0 % P*t*Bu$_3$ affords 4-*n*-butylstyrene in 67 % yield.

[20] *Metal-catalyzed Cross-coupling Reactions* (Eds.: F. Diederich, P. J. Stang), WILEY-VCH, New York, **1998**.

[21] In the Stille cross-couplings of the other organostannanes illustrated in Table 3, essentially no butyl transfer is observed (<2 %).

[22] For a general discussion of the problem of separating reaction products from organotin residues, see: D. Crich, S. Sun, *J. Org. Chem.* **1996**, *61*, 7200 – 7201.

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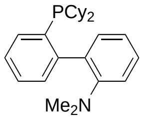
A Highly Active Catalyst for the Room-Temperature Amination and Suzuki Coupling of Aryl Chlorides**

John P. Wolfe and Stephen L. Buchwald*

Palladium-catalyzed amination[1] and Suzuki coupling[2] reactions have found widespread use in many areas of organic synthesis. These methods permit the construction of $C_{sp^2}-C_{sp^2}$ bonds or $C_{aryl}-N$ bonds which cannot be easily or efficiently formed using classical transformations. Most procedures commonly used for these processes employ triarylphosphane-based catalyst systems.[1, 2] While these catalysts are readily available, they usually require elevated reaction temperatures (usually 50 – 100 °C) to function efficiently, and tend to be unreactive towards aryl chloride substrates.[3–5]

We recently reported that 2-dicyclohexylphosphanyl-2′-dimethylaminobiphenyl (**1**, Cy = cyclohexyl) was an excellent ligand for palladium-catalyzed cross-coupling reactions of aryl chlorides.[6] Although the Pd/**1** catalyst system was effective for the room-temperature Suzuki coupling of both electron-rich and electron-deficient aryl chloride substrates,[7] room-temperature catalytic aminations of aryl chlorides were inefficient; only the highly activated 4-chlorobenzonitrile was effectively transformed.

Subsequent studies demonstrated that the bulky phosphane **2** was a more effective ligand than **1** in palladium-catalyzed C–O bond forming reactions, presumably due to its ability to increase the rate of reductive elimination in these processes.[5g, 8] Furthermore, experiments designed to determine whether the amino group on **2** was necessary for effective catalysis revealed that for some substrate combinations the desamino ligand **4** was as effective as **2**, prompting us to examine the use of **4** in amination processes.[9]



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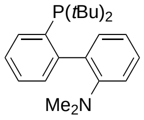

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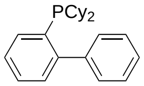

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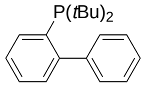

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[**] We gratefully acknowledge the National Institutes of Health (GM 58160 and GM 34917) and the National Cancer Institute (Training grant NCI no. CIT32CA09112), who provided financial support for this work. We also thank Pfizer, Merck, and Novartis for additional unrestricted support. J.P.W. is a recipient of a fellowship from the Organic Division of the American Chemical Society sponsored by Schering-Plough, for which he is grateful. We thank Dr. Ken Kamikawa for performing preliminary experiments on the room-temperature catalytic amination of aryl chlorides, Dr. Bryant Yang for performing the experiments depicted as entries 1 and 2 of Table 2, and Dr. Robert Singer for performing the experiment depicted in entry 3 of Table 2.

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