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Published on Web 05/11/2002

Pd/P(t-Bu)$_3$: A Mild and General Catalyst for Stille Reactions of Aryl Chlorides and Aryl Bromides

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Received January 2, 2002

Abstract: Pd/P(t-Bu)$_3$ serves as an unusually reactive catalyst for Stille reactions of aryl chlorides and bromides, providing solutions to a number of long-standing challenges. An unprecedented array of aryl chlorides can be cross-coupled with a range of organotin reagents, including $SnBu_4$. Very hindered biaryls (e.g., tetra-ortho-substituted) can be synthesized, and aryl chlorides can be coupled in the presence of aryl triflates. The method is user-friendly, since a commercially available complex, Pd(P(t-Bu)$_3$)$_2$, is effective. Pd/P(t-Bu)$_3$ also functions as an active catalyst for Stille reactions of aryl bromides, furnishing the first general method for room-temperature cross-couplings.

Introduction

In recent years, tremendous progress has been reported in the development of powerful new methods for carbon−carbon bond formation. Cross-coupling reactions, particularly palladium-catalyzed processes, have been an important component of this progress.[1]

Stille cross-couplings[2,3] have proved to be an especially popular tool for synthetic organic chemists, due in part to the air and moisture stability of organotin reagents, as well as the excellent functional group compatibility of the process.[4] Nevertheless, significant room for improvement remains. For example, increasing the scope of the reaction and developing more versatile catalysts that operate under milder conditions would represent important advances.

With regard to scope, one of the most apparent limitations in the palladium-catalyzed Stille reaction has been the inability to couple unactivated aryl chlorides.[5,6] From a practical viewpoint, because of their lower cost and the wider diversity of available compounds, aryl chlorides are generally more desirable substrates than are bromides or iodides.[7] However, aryl chlorides have proved to be reluctant coupling partners, perhaps due in part to the strength of the C−Cl bond.[8,9]

The development of more versatile catalysts represents a second potential opportunity for enhancing the utility of the Stille reaction. Regarding existing catalysts, Mitchell has noted in a recent review: "A look at the catalyst (or to be exact, precatalyst) and cocatalyst combinations, together with solvent variations, which have been used in the papers cited above will make it clear that there is in fact no 'ideal' system, but that each reaction will basically require optimization. If readers are slightly bewildered by this plethora of possibilities, they are not alone: the author of these lines is, too!"[10,11] The general need for an elevated reaction temperature, which is undesirable from the standpoints of substrate stability and functional group compatibility, is another drawback of previously reported catalysts for Stille cross-couplings.

During the past few years, we have been exploring the application of electron-rich, sterically demanding P(t-Bu)$_3$ in a variety of palladium-catalyzed processes, including Suzuki,[12]

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(1) (a) *Metal-catalyzed Cross-coupling Reactions*; Diederich, F., Stang, P. J., Eds.; Wiley-VCH: New York, 1998. (b) Tsuji, J. *Palladium Reagents and Catalysts, Innovations in Organic Synthesis*; Wiley: New York, 1995.

(2) (a) Kosugi, M.; Sasazawa, K.; Shimizu, Y.; Migita, T. *Chem. Lett.* **1977**, 301−302. (b) Milstein, D.; Stille, J. K. *J. Am. Chem. Soc.* **1978**, *100*, 3636−3638.

(3) For reviews of the Stille reaction, see: (a) Farina, V.; Krishnamurthy, V.; Scott, W. J. *Org. React.* **1997**, *50*, 1−652. (b) Mitchell, T. N. In *Metal-catalyzed Cross-coupling Reactions*; Diederich, F., Stang, P. J., Eds.; Wiley-VCH: New York, 1998; Chapter 4.

(4) (a) For a discussion of applications of the Stille reaction in natural products synthesis (e.g., lepicidin aglycon and rapamycin), see: Nicolaou, K. C.; Sorensen, E. J. *Classics in Total Synthesis*; VCH: New York, 1996; Chapter 31. (b) For some very recent examples, see: Williams, D. R.; Meyer, K. G. *J. Am. Chem. Soc.* **2001**, *123*, 765−766. White, J. D.; Carter, R. G.; Sundermann, K. F.; Wartmann, M. *J. Am. Chem. Soc.* **2001**, *123*, 5407−5413. Liras, S.; Lynch, C. L.; Fryer, A. M.; Vu, B. T.; Martin, S. F. *J. Am. Chem. Soc.* **2001**, *123*, 5918−5924. Hannessian, S.; Ma, J.; Wang, W. *J. Am. Chem. Soc.* **2001**, *123*, 10200−10206. Smith, A. B., III; Minbiole, K. P.; Verhoest, P. R.; Schelhaas, M. *J. Am. Chem. Soc.* **2001**, *123*, 10942−10953.

(5) Only activated aryl chlorides have proved to be suitable substrates. See: (a) Reference 3a, pp 12−16. (b) Reference 3b. (c) Li, J. J.; Gribble, G. W. *Palladium in Heterocyclic Chemistry*; Pergamon: New York, 2000.

(6) Shirakawa and Hiyama have described a nickel catalyst that cross-couples aryl chlorides with organotin compounds. The yields for electron-rich aryl chlorides are moderate (up to 66%). Shirakawa, E.; Yamasaki, K.; Hiyama, T. *J. Chem. Soc., Perkin Trans. 1* **1997**, 2449−2450. Shirakawa, E.; Yamasaki, K.; Hiyama, T. *Synthesis* **1998**, 1544−1549.

(7) (a) Grushin, V. V.; Alper, H. *Chem. Rev.* **1994**, *94*, 1047−1062. (b) Grushin, V. V.; Alper, H. In *Activation of Unreactive Bonds and Organic Synthesis*; Murai, S., Ed.; Springer-Verlag: Berlin, Germany, 1999; pp 193−226.

(8) Bond dissociation energies for Ph−X: Cl (96 kcal/mol); Br (81 kcal/mol); I (65 kcal/mol). See ref 7a.

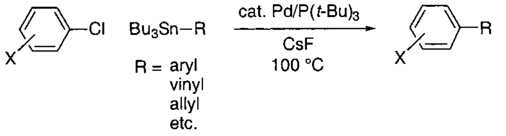
(9) For overviews on coupling reactions of aryl chlorides, see: (a) Stürmer, R. *Angew. Chem., Int. Ed.* **1999**, *38*, 3307−3308. (b) Reference 7.

(10) Mitchell, T. N. *Metal-catalyzed Cross-coupling Reactions*; Diederich, F., Stang, P. J., Eds.; Wiley-VCH: New York, 1998; p 178. Farina and Roth have observed: "...the Stille reaction has been carried out in a variety of solvents using many different catalytic systems, and no general consensus has emerged from the literature as to the rationale for selecting a particular set of conditions..." [Farina, V.; Roth, G. P. In *Advances in Metal-Organic Chemistry*; Liebeskind, L. S., Ed.; JAI: London, UK, 1996; Vol. 5, p 45].

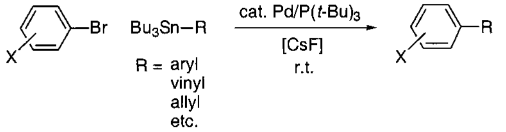
(11) For applications of the Stille reaction in automated parallel synthesis, the need for a truly versatile catalyst system is particularly acute.

10.1021/ja020012f CCC: $22.00 © 2002 American Chemical Society

Heck,[13] Negishi,[14] and Sonogashira[15] couplings.[16,17] In this report, we demonstrate that Pd/P(t-Bu)$_3$ also serves as a versatile catalyst for Stille reactions, providing the first general method for couplings of aryl chlorides (eq 1) and for room-temperature couplings of aryl bromides (eq 2).[18]



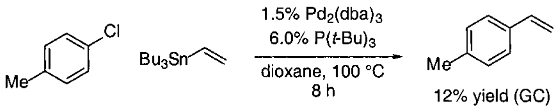
(1)



(2)

Results and Discussion

Aryl and Vinyl Chlorides. To the best of our knowledge, at the time that we began our investigation, there were no examples of palladium-catalyzed Stille reactions in which an unactivated aryl chloride served as a coupling partner.[5,19] Based on our earlier success in accomplishing Suzuki and Heck reactions of a wide array of aryl chlorides using Pd$_2$(dba)$_3$/P(t-Bu)$_3$ as a catalyst,[12a,13a] in initial studies we attempted to apply this system to the cross-coupling of 4-chlorotoluene and vinyltributyltin; unfortunately, we obtained only a small amount of 4-vinyltoluene after 8 h at 100 °C (eq 3).



(3)

In view of the capacity of Pd$_2$(dba)$_3$/P(t-Bu)$_3$ to catalyze Suzuki and Heck reactions of aryl chlorides, we hypothesized that oxidative addition is probably occurring at an acceptable rate under these conditions (eq 3) and that a sluggish subsequent step, perhaps transmetalation,[20] might be impeding effective catalysis (Figure 1). We therefore decided to explore the possibility that enhancing the reactivity of the organotin reagent would facilitate the Stille cross-coupling process.

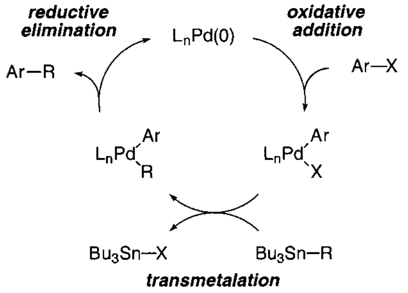
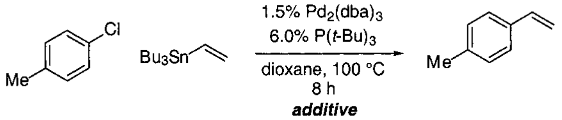


Figure 1. Outline of the catalytic cycle for the Stille cross-coupling reaction.

Table 1. Effect of Additives on the Rate of Pd/P(t-Bu)$_3$-Catalyzed Stille Cross-Coupling of 4-Chlorotoluene with Vinyltributyltin



entry	additive (1.1 equiv)	% yield after 8 h (GC)[a]
1	none	12
2	NEt$_3$	16
3	Cs$_2$CO$_3$	40
4	NaOH	42
5	TBAF•3H$_2$O	24
6	KF	28
7	CsF	50
8	CsF (2.2 equiv)	59

[a] Average of two runs.

The use of nucleophiles to increase the reactivity of organotin species, via hypercoordinate intermediates, is a well-established strategy in organic chemistry.[21] In fact, nucleophilic activation of organotin reagents has been exploited by others in palladium-catalyzed Stille cross-couplings. For example, Martinez has reported that tetrabutylammonium difluorotriphenylstannate is a very reactive phenylating agent for couplings of vinyl triflates,[22] and several groups have demonstrated that organotin reagents can be activated through intramolecular coordination by a Lewis base (e.g., an amine).[23]

We therefore surveyed an array of potential activators of the organotin species (Table 1). Although NEt$_3$ furnishes only a small rate enhancement (entry 1 vs entry 2), Cs$_2$CO$_3$ and NaOH[24,25] provide significant acceleration (entries 3 and 4). In view of the well-established fluorophilicity of tin, we felt that fluoride additives might serve as particularly effective activators.[22,26,27] We discovered that fluoride sources can indeed facilitate Stille cross-couplings, with CsF being the most efficient

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(12) (a) Littke, A. F.; Fu, G. C. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 3387−3388. (b) Littke, A. F.; Dai, C.; Fu, G. C. *J. Am. Chem. Soc.* **2000**, *122*, 4020−4028.

(13) (a) Littke, A. F.; Fu, G. C. *J. Org. Chem.* **1999**, *64*, 10−11. (b) Littke, A. F.; Fu, G. C. *J. Am. Chem. Soc.* **2001**, *123*, 6989−7000.

(14) Dai, C.; Fu, G. C. *J. Am. Chem. Soc.* **2001**, *123*, 2719−2724.

(15) Hundertmark, T.; Littke, A. F.; Buchwald, S. L.; Fu, G. C. *Org. Lett.* **2000**, *2*, 1729−1731.

(16) For pioneering studies by Koie of Pd/P(t-Bu)$_3$-catalyzed reactions, see: Nishiyama, M.; Yamamoto, T.; Koie, Y. *Tetrahedron Lett.* **1998**, *39*, 617−620. (b) Yamamoto, T.; Nishiyama, M.; Koie, Y. *Tetrahedron Lett.* **1998**, *39*, 2367−2370. (c) Watanabe, M.; Nishiyama, M.; Koie, Y. *Tetrahedron Lett.* **1999**, *40*, 8837−8840.

(17) For early studies by others of Pd/P(t-Bu)$_3$-catalyzed reactions, see: (a) Hartwig, J. F.; Kawatsura, M.; Hauck, S. I.; Shaughnessy, K. H.; Alcazar-Roman, L. M. *J. Org. Chem.* **1999**, *64*, 5575−5580. (b) Mann, G.; Incarvito, C.; Rheingold, A. L.; Hartwig, J. F. *J. Am. Chem. Soc.* **1999**, *121*, 3224−3225. (c) Kawatsura, M.; Hartwig, J. F. *J. Am. Chem. Soc.* **1999**, *121*, 1473−1478. (d) Kim, J. S.; Sen, A. *J. Mol. Catal. A* **1999**, *143*, 197−201.

(18) Part of our work on Stille reactions of aryl chlorides has been the subject of a preliminary communication: Littke, A. F.; Fu, G. C. *Angew. Chem., Int. Ed. Engl.* **1999**, *38*, 2411−2413.

(19) After our initial report (ref 18), Nolan described a Pd(OAc)$_2$/imidazolium salt/TBAF system that effects Stille reactions of unactivated aryl chlorides in modest yield (15−64%): Grasa, G. A.; Nolan, S. P. *Org. Lett.* **2001**, 3, 119−122.

(20) For mechanistic studies of the Stille reaction, as well as leading references, see: (a) Reference 3. (b) Casado, A. L.; Espinet, P.; Gallego, A. M.; Martinez-Ilarduya, J. M. *Chem. Commun.* **2001**, 339−340. (c) Cotter, W. D.; Barbour, L.; McNamara, K. L.; Hechter, R.; Lachicotte, R. J. *J. Am. Chem. Soc.* **1998**, *120*, 11016−11017.

(21) *Chemistry of Tin*; Smith, P. J., Ed.; Blackie: New York, 1998.

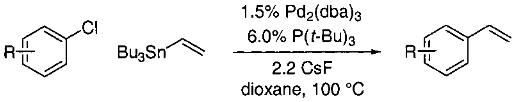
(22) Martinez, A. G.; Barcina, J. O.; Cerezo, A. de F.; Subramanian, L. R. *Synlett* **1994**, 1047−1048. See also: Fouquet, E.; Pereyre, M.; Rodriguez, A. L. *J. Org. Chem.* **1997**, *62*, 5242−5243. Fouquet, E.; Rodriguez, A. L. *Synlett* **1998**, 1323−1324.

(23) For early examples, see: (a) Vedejs, E.; Haight, A. R.; Moss, W. O. *J. Am. Chem. Soc.* **1992**, *114*, 6556−6558. (b) Brown, J. M.; Pearson, M.; Jastrzebski, J. T. B. H.; van Koten, G. *J. Chem. Soc., Chem. Commun.* **1992**, 1440−1441. (c) Farina, V. *Pure Appl. Chem.* **1996**, *68*, 73−78. (d) Fouquet, E.; Pereyre, M.; Rodriguez, A. L. *J. Org. Chem.* **1997**, *62*, 5242−5243.

(24) For Stille cross-couplings of aryl bromides and aryl iodides in the presence of hydroxide, see: Roshchin, A. I.; Bumagin, N. A.; Beletskaya, I. P. *Tetrahedron Lett.* **1995**, *36*, 125−128.

(25) For Hiyama cross-couplings in the presence of hydroxide, see: Hagiwara, E.; Gouda, K.-i.; Hatanaka, Y.; Hiyama, T. *Tetrahedron Lett.* **1997**, *38*, 439−442. See also: Mateo, C.; Fernandez-Rivas, C.; Cardenas, D. J.; Echavarren, A. M. *Organometallics* **1998**, *117*, 3661−3669.

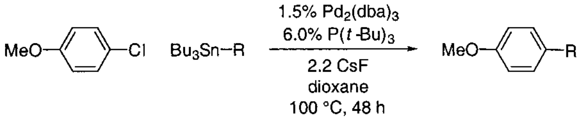
Table 2. Pd/P(t-Bu)$_3$-Catalyzed Stille Cross-Couplings of an Array of Aryl Chlorides with a Vinyltin Reagent

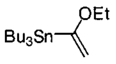


entry	aryl chloride	yield (%)[a]
1	4-acetyl	87[b]
2	4-*n*-Bu	80
3	4-OMe	82 (90)
4	4-NH_2	61
5	2,5-Me_2	71 (84)

[a] All yields are isolated yields (average of two runs). Values in parentheses are yields measured by GC for reaction products that are volatile. [b] Reaction temperature: 80 °C.

Table 3. Pd/P(t-Bu)$_3$-Catalyzed Stille Cross-Couplings of an Array of Organotin Reagents with a Deactivated Aryl Chloride



entry	$Bu_3Sn{-}R$	yield (%)[a]
1	$Bu_3Sn{-}Ph$	94
2		98
3	Bu_3Sn−allyl	87
4	$Bu_3Sn{-}Bu$	82

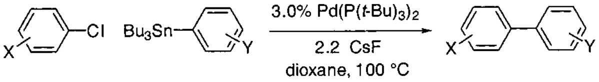
[a] All yields are isolated yields (average of two runs).

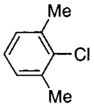
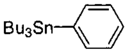
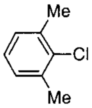
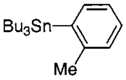
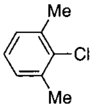
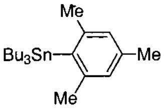
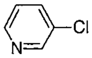
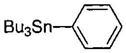
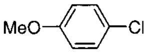
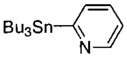
among those that we have examined (entries 5−7). An increase in the quantity of CsF produces a further enhancement in the reaction rate (1.1→2.2 equiv; entry 7 vs entry 8).

Under this set of conditions, vinyltributyltin can be cross-coupled with a broad spectrum of aryl chlorides (Table 2).[28] Thus, electron-poor 4′-chloroacetophenone and electron-neutral 4-(*n*-butyl)chlorobenzene furnish the desired styrene derivatives in good yield (entries 1 and 2). Even deactivated, very electron-rich aryl chlorides can be cross-coupled (entries 3 and 4), although the reaction of *p*-chloroaniline proceeds in more moderate yield. Hindered aryl chlorides also undergo Stille coupling under these conditions (entry 5).

This catalyst system is versatile with respect to not only the aryl chloride but also the organotin reagent (Table 3). With the same experimental procedure, phenyl-, 1-ethoxyvinyl-, and allyltributyltin cross-couple with deactivated *p*-chloroanisole in excellent yield (entries 1−3). Interestingly, Pd/P(t-Bu)$_3$ even effects transfer of simple alkyl groups, which are typically rather reluctant participants in Stille reactions (entry 4).[29,30]

Table 4. Stille Cross-Couplings of Aryl Chlorides Catalyzed by Pd(P(t-Bu)$_3$)$_2$



entry	aryl chloride	$Bu_3Sn{-}R$	yield (%)[a]
1			94
2			96
3			89
4[b]			76
5			47

[a] All yields are isolated yields (average of two runs). [b] Reaction run at 60 °C.

Although the reactivity and the versatility of Pd$_2$(dba)$_3$/P(t-Bu)$_3$ in palladium-catalyzed coupling processes compare very favorably to catalysts based on other ligands, the air sensitivity of P(t-Bu)$_3$ *is* a drawback. To address this issue, we have demonstrated that, for Negishi and Heck couplings of aryl chlorides, use of Pd(P(t-Bu)$_3$)$_2$, a more air-stable, crystalline complex,[31] circumvents the need to handle P(t-Bu)$_3$ itself.[13b,14] Now that Pd(P(t-Bu)$_3$)$_2$ is commercially available,[32] the attractiveness of this approach is even greater.

Clearly, extending this strategy to Pd/P(t-Bu)$_3$-catalyzed Stille couplings of aryl chlorides would enhance the utility of our method. We have recently established that Pd(P(t-Bu)$_3$)$_2$ can indeed be employed as a catalyst for such reactions. In this investigation, we focused our attention on couplings that are particularly challenging, and we were pleased to observe that this easy-to-handle catalyst is remarkably effective (Table 4).

Because the efficiency of other catalysts for Stille reactions is very sensitive to steric effects,[33] we were interested in determining whether Pd(P(t-Bu)$_3$)$_2$ might prove to be useful for

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(26) For early examples of the use of fluoride to accelerate other (non-Stille) cross-coupling reactions, see: (a) Electron-poor aryl chlorides with organosilicon compounds: Gouda, K.-i.; Hagiwara, E.; Hatanaka, Y.; Hiyama, T. *J. Org. Chem.* **1996**, *61*, 7232−7233. (b) Aryl bromides and triflates with organoboron compounds: Wright, S. W.; Hageman, D. L.; McClure, L. D. *J. Org. Chem.* **1994**, *59*, 6095−6097.

(27) It is worth noting that Kosugi has reported that Pd(dba)$_2$/PPh$_3$/TBAF does *not* effect Stille couplings of aryl chlorides. Fugami, K.; Ohnuma, S.-y.; Kameyama, M.; Saotome, T.; Kosugi, M. *Synlett* **1999**, 63−64.

(28) 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 that has simply been sparged with argon. (b) In the absence of Pd$_2$(dba)$_3$ or of P(t-Bu)$_3$, no reaction ($<$2% conversion) is observed. (c) Cross-coupling is also observed, albeit more slowly, when PCy$_3$ is used instead of P(t-Bu)$_3$. (d) Stille reactions in THF proceed with comparable efficiency as in dioxane; couplings in toluene are somewhat slower. (e) Pd$_2$(dba)$_3$ provides better results than Pd(OAc)$_2$. (f) 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 Table 2.

(29) For the Stille cross-couplings of the other organotin reagents illustrated in Table 3, essentially no butyl transfer is observed ($<$2%).

(30) From a 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 (ref 3a). This is not an issue under our conditions, presumably due to efficient in situ generation of insoluble Bu$_3$SnF.

(31) (a) Otsuka, S.; Yoshida, T.; Matsumoto, M.; Nakatsu, K. *J. Am. Chem. Soc.* **1976**, *98*, 5850−5858. (b) Yoshida, T.; Otsuka, S. *J. Am. Chem. Soc.* **1977**, *99*, 2134−2140. (c) Yoshida, T.; Otsuka, S. *Inorg. Synth.* **1990**, *28*, 113−119. This report states that Pd(P(t-Bu)$_3$)$_2$ is "stable in air in the solid state". Although we have encountered no difficulties *handling* Pd(P(t-Bu)$_3$)$_2$ in air, we recommend that it be *stored* under nitrogen.

(32) Strem Chemicals (Newburyport, MA), catalog no. 46-0252.

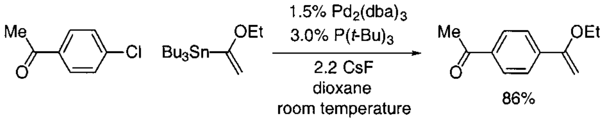
(33) For example, see: (a) Saa, J. M.; Martorell, G.; Garcia-Raso, A. *J. Org. Chem.* **1992**, *57*, 678−685. (b) Farina, V.; Krishnan, B.; Marshall, D. R.; Roth, G. P. *J. Org. Chem.* **1993**, *58*, 5434−5444. (c) Hoye, T. R.; Chen, M. *J. Org. Chem.* **1996**, *61*, 7940−7942. (d) Anderson, J. C.; Namli, H.; Roberts, C. A. *Tetrahedron* **1997**, *53*, 15123−15134.

the synthesis of highly hindered biaryls. Gratifyingly, we discovered that sterically demanding 2-chloro-*m*-xylene couples with phenyltributyltin and even *o*-tolyltributyltin to furnish di- and tri-ortho-substituted biaryls in excellent yield (Table 4, entries 1 and 2).

Most remarkable is the nearly quantitative synthesis of a tetra-ortho-substituted biaryl from two di-ortho-substituted precursors (entry 3). The generation of tetra-ortho-substituted biaryls, particularly unsymmetrical ones, is a challenging task, and there are few examples of successful syntheses of this class of compounds via cross-coupling.[34,35] To the best of our knowledge, the process illustrated in entry 3 represents the first effective synthesis of a tetra-ortho-substituted biaryl through a Stille reaction;[36] typically, products arising from butyl transfer or from homocoupling of the halide or the organotin reagent are observed.

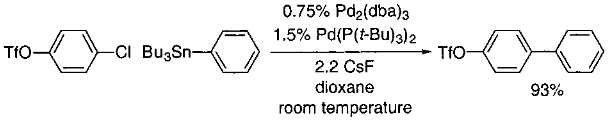
Cross-couplings that involve heteroaromatic substrates are an important family of processes, providing compounds of high value.[5c] We have determined that Pd(P(t-Bu)$_3$)$_2$ catalyzes the coupling of 3-chloropyridine with phenyltributyltin to furnish the desired biaryl in good yield (entry 4). However, Stille reactions of heterocycles are not uniformly efficient: as illustrated in entry 5, a moderate yield of product is obtained in the cross-coupling of a 2-stannylpyridine.[37]

As far as we are aware, there have been no reports of Stille cross-couplings of aryl chlorides that proceed at room temperature.[38] We have discovered that, for activated aryl chlorides, Pd/P(t-Bu)$_3$ can serve as an effective catalyst for this process. For example, 4′-chloroacetophenone undergoes coupling with 1-ethoxyvinyltributyltin at room temperature (eq 4).[39]



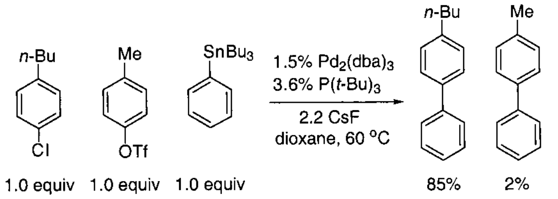
(4)

For non-P(t-Bu)$_3$-based palladium catalysts, triflates are much more reactive cross-coupling substrates than are chlorides.[1] Equation 5 illustrates that Pd/P(t-Bu)$_3$ activates the C−Cl bond of 4-chlorophenyl triflate, in preference to the C−OTf bond, with excellent selectivity.[40,41]



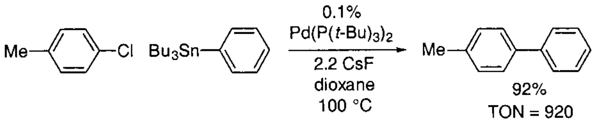
(5)

To establish the generality of this unprecedented selectivity in a Stille cross-coupling for a chloride over a triflate, we performed the intermolecular competition experiment depicted in eq 6. When we allow 4-*n*-butylchlorobenzene and 4-methylphenyl triflate to compete for phenyltributyltin, we obtain almost exclusively the product that arises from coupling of the aryl chloride (85% yield) and only a trace of the biaryl that originates from reaction of the triflate (2% yield).



(6)

Because our goal has been to provide a *general* procedure that will couple even very challenging substrate pairs, until this point we have employed a standard palladium loading of 3% in the Stille cross-couplings of aryl chlorides that we have described (Tables 2−4). Particularly for pharmaceutical/industrial applications, it is desirable to be able to employ low catalyst loadings. For most reactions, this should be straightforward. For example, in the case of the Stille cross-coupling that is illustrated in eq 7, the catalyst loading can simply be decreased to 0.1% Pd(P(t-Bu)$_3$)$_2$, without otherwise modifying the reaction conditions, and the desired biaryl can still be isolated in 92% yield. The turnover number of 920 for this process is the highest that has been observed for a Stille coupling of an aryl chloride.



(7)

Not only aryl halides but also vinyl halides are an important family of substrates for cross-coupling reactions. As far as we are aware, there are no examples of Stille couplings of unactivated vinyl chlorides.[42] We have established that Pd/P(t-Bu)$_3$ serves as an effective catalyst for this process (eq 8). For palladium-catalyzed couplings that employ ligands other than P(t-Bu)$_3$, vinyl halides are generally more reactive than aryl halides. However, as we have previously observed for Pd/P(t-Bu)$_3$-catalyzed Suzuki[12b] and Heck[13b] reactions, for Pd/P(t-Bu)$_3$-

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(34) For examples of difficulties in synthesizing tetra-ortho-substituted biaryls via cross-coupling methodology, see: (a) Watanabe, T.; Miyaura, N.; Suzuki, A. *Synlett* **1992**, 207−210. (b) Johnson, M. G.; Foglesong, R. J. *Tetrahedron Lett.* **1997**, *38*, 7001−7002. (c) Yamada, I.; Yamazaki, N.; Yamaguchi, M.; Yamagishi, T. *J. Mol. Catal. A* **1997**, *120*, L13-L15. (d) Huang, J.; Nolan, S. P. *J. Am. Chem. Soc.* **1999**, *121*, 9889−9890. (e) Bohm, V. P. W.; Weskamp, T.; Gstöttmayr, C. W. K.; Herrmann, W. A. *Angew. Chem., Int. Ed.* **2000**, *39*, 1602−1604. (f) Chaumeil, H.; Signorella, S.; Le Drian, C. *Tetrahedron* **2000**, *56*, 9655−9662. (g) Feuerstein, M.; Doucet, H.; Santelli, M. *Tetrahedron Lett.* **2001**, *42*, 6667−6670.

(35) For examples of successful syntheses of tetra-ortho-substituted biaryls via cross-coupling, see: (a) Suzuki: Cammidge, A. N.; Crepy, K. V. L. *Chem. Commun.* **2000**, 1723−1724. (b) Negishi: Reference 14. (c) Yin, J.; Rainka, M. P.; Zhang, X.-X.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 1162−1163.

(36) Saa has reported the synthesis of tetra-ortho-substituted biaryls from aryl triflates and aryltin reagents in very modest yield (<26%): Saa, J. M.; Martorell, G. *J. Org. Chem.* **1993**, *58*, 1963−1966.

(37) Side reactions, such as hydrodehalogenation and homocoupling of the aryl chloride, are also observed.

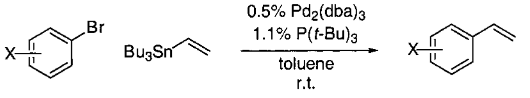
(38) For an example of a coupling of a Cr(CO)$_3$-complexed aryl chloride, see: Prim, D.; Tranchier, J.-P.; Rose-Munch, F.; Rose, E.; Vaissermann, J. *Eur. J. Inorg. Chem.* **2000**, 901−905.

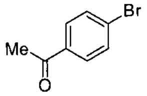
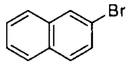
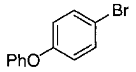
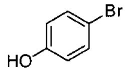
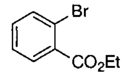
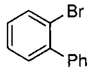
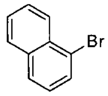
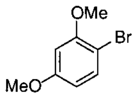
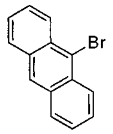
(39) Notes: (a) As with other processes catalyzed by Pd/P(t-Bu)$_3$ that are conducted at room temperature (refs 12b and 13b), use of a Pd:phosphine ratio of 1:1, rather than 1:2, leads to a faster reaction. (b) Use of 0.75% Pd$_2$(dba)$_3$/1.5% Pd(P(t-Bu)$_3$)$_2$ (same amounts of Pd and P(t-Bu)$_3$ as in eq 4; both Pd$_2$(dba)$_3$ and Pd(P(t-Bu)$_3$)$_2$ are easy-to-handle solids) provides a similar result. (c) Pd/P(t-Bu)$_3$ can also catalyze room-temperature Stille reactions of electron-neutral aryl chlorides, but the processes are very slow; for example, after 14 days, 4-chlorotoluene cross-couples with phenyltributyltin to furnish 4-methylbiphenyl in 78% isolated yield (0.75% Pd$_2$(dba)$_3$/1.5% Pd(P(t-Bu)$_3$)$_2$).

(40) For analogous results with Pd/P(t-Bu)$_3$-catalyzed Suzuki reactions, see Reference 12b.

(41) Use of 0.75% Pd$_2$(dba)$_3$/1.5% Pd(P(t-Bu)$_3$)$_2$ furnishes a convenient alternative to 1.5% Pd$_2$(dba)$_3$/3.0% P(t-Bu)$_3$, since Pd$_2$(dba)$_3$ and Pd(P(t-Bu)$_3$)$_2$ are easy-to-handle solids.

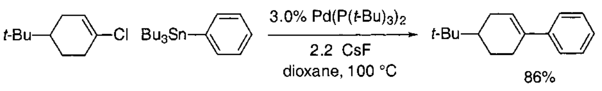
Table 5. Room-Temperature Stille Cross-Couplings of an Array of Aryl Bromides with a Vinyltin Reagent



entry	aryl bromide	yield (%)[a]
1		88
2		88
3		85
4		85[b]
5		92
6		76
7		91
8		89
9		66

[a] All yields are isolated yields (average of two runs). [b] Solvent: Et_2O.

catalyzed Stille processes, aryl chlorides couple in preference to vinyl chlorides (eq 9).

 (8)

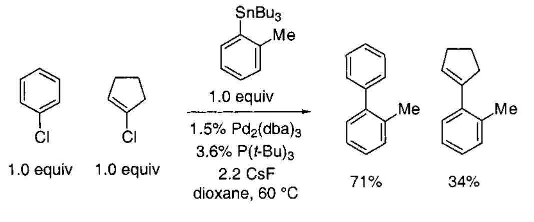
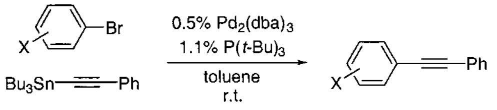
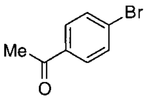
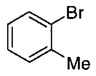
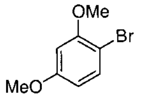
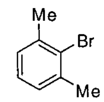
 (9)

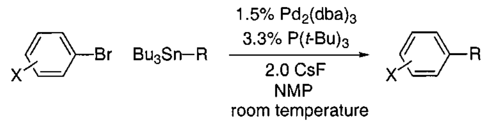
Table 6. Room-Temperature Stille Cross-Couplings of an Array of Aryl Bromides with an Alkynyltin Reagent

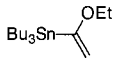
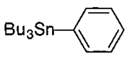
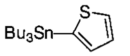
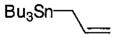
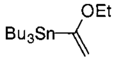
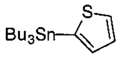
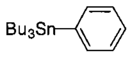
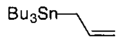


entry	aryl bromide	yield (%)[a]
1		97
2		97
3		83
4		95

[a] All yields are isolated yields (average of two runs).

Table 7. Room-Temperature Stille Cross-Couplings of Aryl Bromides



entry	aryl bromide	Bu_3Sn–R	yield (%)[a]
1	2-bromotoluene		97
2	2-bromotoluene		94
3	2-bromotoluene		97
4	2-bromotoluene		81
5	1-bromo-2,4-dimethoxybenzene		97
6	1-bromo-2,4-dimethoxybenzene		97
7	1-bromo-2,4-dimethoxybenzene		97
8	1-bromo-2,4-dimethoxybenzene		95[b]

[a] All yields are isolated yields (average of two runs). [b] Solvent: Et_2O.

Aryl Bromides. Although the palladium-catalyzed Stille reaction of aryl bromides is a well-established process,[3] there nevertheless remains room for improvement. For example, as noted in the Introduction, previously reported catalyst systems are not entirely general, and they require elevated temperatures.[43]

We have determined that Pd/P(t-Bu)$_3$ effects the room-temperature cross-coupling of a wide variety of aryl bromides with a broad range of organotin reagents. As illustrated in Table 5, in the presence of 1% Pd, Stille couplings of vinyltin reagents proceed in very good yield.[44] Activated (entry 1), electron-

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(42) For some examples of Stille couplings of activated vinyl chlorides, see: (a) Peet, W. G.; Tam, W. *J. Chem. Soc., Chem. Commun.* **1983**, 853–854. (b) Kobayashi, Y.; Kato, N.; Shimazaki, T.; Sato, F. *Tetrahedron Lett.* **1988**, *29*, 6297–6300. (c) Liebeskind, L. S.; Wang, J. *Tetrahedron Lett.* **1990**, *31*, 4293–4296. (d) Rubin, Y.; Knobler, C. B.; Diederich, F. *J. Am. Chem. Soc.* **1990**, *112*, 1607–1617. (e) Farina, V.; Hauck, S. I. *J. Org. Chem.* **1991**, *56*, 4317–4319. (f) Liebeskind, L. S.; Yu, M. S.; Yu, R. H.; Wang, J.; Hagen, K. S. *J. Am. Chem. Soc.* **1993**, *115*, 9048–9055. (g) May, P. D.; Larsen, S. D. *Synlett* **1997**, 895–896.

(43) For examples of room-temperature Stille reactions of activated aryl bromides, see: (a) Bumagin, N. A.; Gulevich, Yu. V.; Beletskaya, I. P. *Bull. Acad. Sci. USSR., Div. Chem. Sci.* **1984**, 1044–1049. (b) Barchin, B. M.; Valenciano, J.; Cuadro, A. M.; Alvarez-Builla, J.; Vaquero, J. J. *Org. Lett.* **1999**, *1*, 545–547.

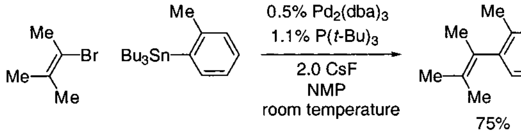
(44) Stille reactions in Et_2O proceed with comparable efficiency as in toluene; couplings in dioxane are somewhat slower.

neutral (entry 2), and deactivated (entries 3 and 4) aryl bromides react cleanly under these conditions. Ortho substituents are well-tolerated (entries 5−7), even for a very electron-rich aryl bromide (entry 8), although with an extremely challenging di-ortho-substituted aryl bromide, a somewhat lower yield is obtained (entry 9).

Under the same conditions, Pd/P(*t*-Bu)$_3$ also catalyzes room-temperature cross-couplings of aryl bromides with alkynyltin reagents (Table 6). Thus, reactions of activated (entry 1), ortho-substituted (entry 2), ortho-substituted and deactivated (entry 3), and di-ortho-substituted (entry 4) bromides furnish arylacetylenes in excellent yield.

For certain organotin reagents, Pd/P(*t*-Bu)$_3$-catalyzed Stille cross-couplings under the conditions described in Tables 5 and 6 are not efficient. For these substrates, a fluoride-activation strategy has proved to be effective (CsF; Table 7). Thus, 1-ethoxyvinyl-, phenyl-, 2-thienyl-, and allyltributyltin couple with bulky 2-bromotoluene (entries 1−4), as well as hindered and deactivated 1-bromo-2,4-dimethoxybenzene (entries 5−8), in very good yield at room temperature.

Finally, we have briefly examined the applicability of Pd/P(*t*-Bu)$_3$ to the Stille cross-coupling of vinyl bromides. Equation 10 illustrates that this catalyst system can couple even very sterically demanding substrates in good yield at room temperature.



(10)

Conclusions

We have established that Pd/P(*t*-Bu)$_3$ serves as an unusually versatile catalyst for Stille reactions of aryl chlorides and bromides, providing solutions to a number of long-standing challenges. Noteworthy aspects of this study include the following:

(a) The development of a general method for Stille reactions of aryl chlorides. We have described the only examples to date of effective Stille couplings of unactivated aryl and vinyl chlorides. We have demonstrated the transfer of a wide array of groups (including alkyl) from the organotin reagent, the synthesis of very hindered biaryls (e.g., tetra-ortho-substituted), the unprecedented reaction of an aryl chloride in preference to an aryl triflate, and coupling with a low catalyst loading. The method is user-friendly, since a commercially available complex, Pd(P(*t*-Bu)$_3$)$_2$, can serve as the catalyst.

(b) The development of a general method for Stille reactions of aryl bromides at room temperature. We have reported very versatile procedures for cross-coupling a broad spectrum of aryl bromides with a diverse range of organotin reagents, all at room temperature. These are the first examples of room-temperature Stille couplings of unactivated aryl bromides.

Thus, relative to previously reported catalysts for Stille cross-coupling reactions, Pd/P(*t*-Bu)$_3$ exhibits unique reactivity. We anticipate that this catalyst system will find use in an extensive array of applications.[45]

Acknowledgment. Support has been provided by the Alexander von Humboldt-Stiftung (postdoctoral fellowship to L.S.), Boehringer-Ingelheim, Bristol-Myers Squibb, the National Institutes of Health (National Institute of General Medical Sciences, R01-GM62871), the Natural Sciences and Engineering Research Council of Canada (predoctoral fellowship to A.F.L.), Novartis, and Pharmacia. We thank Michael J. Smith for the preparation of *o*-tolyltributylstannane. Funding for the MIT Department of Chemistry Instrumentation Facility has been provided in part by NSF CHE-9808061 and NSF DBI-9729592.

Supporting Information Available: Experimental procedures and compound characterization data (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

JA020012F

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(45) Since our original report (ref 18), several groups have already described applications of our method for Stille cross-coupling: (a) Kraxner, J.; Arlt, M.; Gmeiner, P. *Synlett* **2000**, 125−127. (b) Zhu, J.; Price, B. A.; Zhao, S. X.; Skonezny, P. M. *Tetrahedron Lett.* **2000**, *41*, 4011−4014. (c) Zhang, N.; Thomas, L.; Wu, B. *J. Org. Chem.* **2001**, *66*, 1500−1502. (d) Pereira, R.; Iglesias, B.; de Lera, A. R. *Tetrahedron* **2001**, *57*, 7871−7881.