

# Highly Active Palladium Catalysts Supported by Bulky Proazaphosphatrane Ligands for Stille Cross-Coupling: Coupling of Aryl and Vinyl Chlorides, Room Temperature Coupling of Aryl Bromides, Coupling of Aryl Triflates, and Synthesis of Sterically Hindered Biaryls

Weiping Su, Sameer Urgaonkar, Patrick A. McLaughlin, and John G. Verkade\*

Contribution from the Department of Chemistry, Gilman Hall, Iowa State University, Ames, Iowa 50011

Received August 18, 2004; E-mail: jverkade@iastate.edu

**Abstract:** A family of proazaphosphatrane ligands [P(RNCH<sub>2</sub>CH<sub>2</sub>)<sub>2</sub>N(R'NCH<sub>2</sub>CH<sub>2</sub>): R = R' = *i*-Bu, **1**; R = Bz, R' = *i*-Bu, **3**; R = R' = Bz, **4**] for palladium-catalyzed Stille reactions of aryl chlorides is described. Catalysts derived from ligands **1** and **4** efficiently catalyze the coupling of electronically diverse aryl chlorides with an array of organotin reagents. The catalyst system based on the ligand **3** is active for the synthesis of sterically hindered biaryls (di-, tri-, and tetra-*ortho* substituted). The use of ligand **4** allows room-temperature coupling of aryl bromides and it also permits aryl triflates and vinyl chlorides to participate in Stille coupling.

## Introduction

The coupling of two sp<sup>2</sup>-centered carbons remains an important goal as well as a challenge for synthetic organic chemists. Among various strategies, transition-metal-catalyzed processes, especially those catalyzed by palladium, have made significant contributions to this field.<sup>1</sup> The palladium-catalyzed Stille cross-coupling<sup>2</sup> of aryl halides (or halide equivalents) with organotin reagents is an important C–C bond forming reaction that has found wide application in natural product synthesis,<sup>3</sup> carbohydrate chemistry,<sup>4</sup> and biological research,<sup>5</sup> which in part stems from the ready availability of organotin reagents, their air- and moisture-stability and the excellent functional group tolerance of this approach. Until recently, this method was

handicapped by the need to use aryl bromides or iodides as the reaction partner. Surprisingly, unlike the case with other Pd-catalyzed processes (e.g., Suzuki,<sup>6</sup> Heck,<sup>7</sup> and Buchwald-Hartwig amination<sup>8</sup> reactions), wherein a myriad of catalyst systems allow coupling of economically attractive but notoriously unreactive aryl chlorides, the same is not true for the Stille coupling of aryl chlorides.<sup>9</sup> Here, the low reactivity of aryl chlorides has generally been attributed to its reluctance to participate in oxidative addition, the first step of the catalytic cycle. However, significant progress has been achieved recently. For example, Fu,<sup>10</sup> in his pioneering studies, disclosed a palladium-catalyst, based on sterically demanding electron-rich P(*t*-Bu)<sub>3</sub> as the supporting ligand, for the Stille cross-coupling

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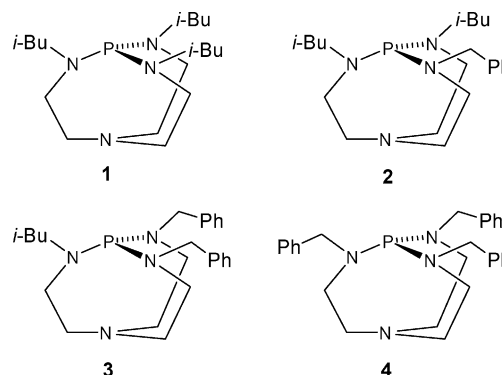
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of aryl chlorides. This method, although general, employs a highly air-sensitive and pyrophoric ligand that requires special handling. Although air-stable  $\text{Pd}[\text{P}(t\text{-Bu})_3]_2$  was recommended as an alternative to  $\text{Pd}_2(\text{dba})_3/\text{P}(t\text{-Bu})_3$  for these reactions, its high cost is a deterrent to its widespread use. On the other hand, the air-stable  $[(t\text{-Bu})_3\text{PH}]\text{BF}_4$ ,<sup>11</sup> which is now commercially available,<sup>12</sup> can serve as a replacement for  $\text{P}(t\text{-Bu})_3$  via its deprotonation by base to release the free ligand in situ. Nolan<sup>13</sup> reported a  $\text{Pd}/\text{N}$ -heterocyclic carbene system for the Stille reaction of aryl chlorides. However, this protocol provided good yields only for activated aryl chlorides. Unactivated and deactivated aryl chlorides afforded only poor to moderate yields. In elegant work, Choudary reported a layered double-hydroxide-supported nanopalladium catalyst for the Stille reaction of aryl chlorides, including electron-rich examples which operate under mild conditions (50 °C).<sup>14</sup> However, the generality of the process remains to be determined. Stille reaction of aryl chlorides in water utilizing palladium-phosphinous acid complexes was described by Wolf.<sup>15</sup> This methodology required quite elevated temperatures (135–140 °C); important functional groups such as esters and aldehydes were not compatible under the conditions employed; and more significantly, no examples involving electron-rich aryl chlorides were reported. More recently, Baldwin found that the  $\text{PdCl}_2/\text{P}(t\text{-Bu})_3$  catalyst system, in combination with  $\text{CuI}$  and  $\text{CsF}$  using DMF as the solvent, facilitates Stille coupling of aryl chlorides at 100 °C.<sup>16</sup> But again, the reaction is effective with electron-deficient aryl chlorides (except for one example reported) and less effective with electron-rich systems (one example reported). Consequently, catalyst systems with a higher degree of stability and activity that can accomplish Stille coupling of electronically diverse aryl chlorides are highly desired.

Proazaphosphatranes,<sup>17</sup> first synthesized in our laboratories, are unusually electron-rich compounds compared with their acyclic counterparts [e.g.,  $\text{P}(\text{NMe}_2)_3$ ] because: (a) the three  $\text{PN}_3$  nitrogens in these rigid bicyclic triaminophosphines are quite planar,<sup>18</sup> thus contributing their electron-density to phosphorus thereby making it more electron-rich and (b) transannulation from the bridgehead nitrogen's lone pair to phosphorus could also potentially enhance its basicity. Not surprisingly, acyclic triaminophosphines lack both of these electron-richness enhancement features. It should be noted that the catalytic activity of proazaphosphatranes can be further augmented by the introduction of suitable groups on  $\text{PN}_3$  nitrogens.

Previous work in our laboratories has established that a bicyclic proazaphosphatrane<sup>17</sup> bearing *iso*-butyl groups on the  $\text{PN}_3$  nitrogens (**1**) is a highly effective ligand for several  $\text{Pd}$ -catalyzed cross-coupling reactions, including Buchwald-Hartwig

amination,<sup>18</sup> Suzuki,<sup>6h</sup> and  $\alpha$ -arylation<sup>19</sup> reactions. Very recently, we reported in a communication that  $\text{Pd}/\mathbf{1}$  also serves as a general catalyst for the Stille coupling of aryl chlorides.<sup>20</sup> In this paper, we fully describe our studies of Stille coupling of aryl chlorides as well as of room-temperature coupling of aryl bromides.



## Results and Discussion

At the outset, we performed experiments to examine the influence of varying the substituents on  $\text{PN}_3$  nitrogens on catalyst activity. We discovered that palladium catalysts supported by ligands **2–4**, bearing benzyl as well as a combination of *iso*-butyl and benzyl groups on  $\text{PN}_3$  nitrogens, generate more active catalysts for the coupling of 4-chlorotoluene with tributylphenyltin than the one supported by ligand **1**, with ligand **4** functioning as the most effective of all. Activation of the less nucleophilic tin reagent was achieved by the addition of 2.2 equiv of  $\text{CsF}$ .<sup>21</sup>

The scope of the palladium-catalyzed Stille reaction of aryl chlorides was explored by using 1.5 mol % of  $\text{Pd}_2(\text{dba})_3$  and 6 mol % of commercially available ligand **1** (two ligands per palladium) in reactions conducted at 100–110 °C. A selection of pertinent results from our previous communication<sup>20</sup> plus one new example (entry 11) are collected in Table 1. The reaction has a broad scope, tolerating a variety of functional groups ( $\text{NO}_2$ ,  $\text{CN}$ ,  $\text{CO}_2\text{Me}$ ,  $\text{CHO}$ ,  $\text{COPh}$ , and  $\text{OMe}$ ) and substrate steric hindrance. Chloropyridines can also be successfully coupled.

**Stille Cross-Coupling Using the  $\text{Pd}_2(\text{dba})_3/\mathbf{4}$  Catalyst System: Activated Aryl Chlorides.** We were pleased to discover that with **4** as the ligand, the reaction temperature could be decreased to 60 °C without compromising reaction yields in Stille coupling of activated aryl chlorides (Table 2). We also found that the use of a 1:1 (or 1:1.2) ratio of  $\text{Pd}:\mathbf{4}$  generated a more active catalyst than a 1:2 ratio. In the presence of  $\text{CsF}$  as an activator of the organotin reagent, the  $\text{Pd}_2(\text{dba})_3/\mathbf{4}$  catalyst system catalyzed the Stille reactions of a wide array of activated aryl chlorides, encompassing functional groups such as ester (entries 1 and 7), nitro (entry 2), aldehyde (entry 3), ketone (entry 4), cyano (entry 5), and trifluoromethyl (entry 6), with tributylphenyltin at 60 °C in dioxane. All these reactions afforded excellent yields of the corresponding biaryls.

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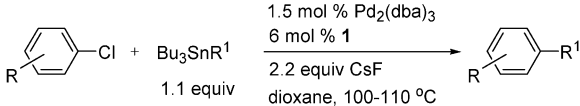
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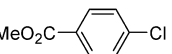
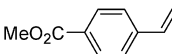
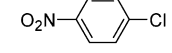
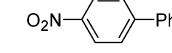
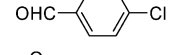
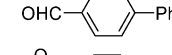
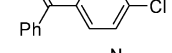
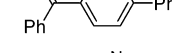
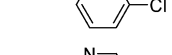
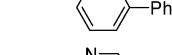
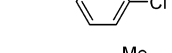
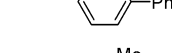
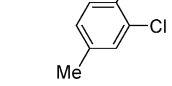
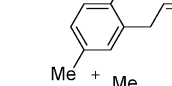
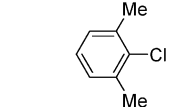
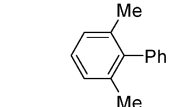
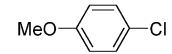
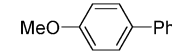

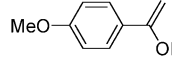
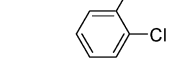
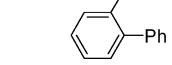
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(21) From the screening of various additives to activate the tin reagent, we found that  $\text{CsF}$  can be replaced by  $\text{Me}_4\text{NF}$ . Other fluoride sources such as  $\text{KF}$  and  $\text{ZnF}_2$  were much less effective. Amines such as  $\text{C}_2\text{NMe}$  (an additive successfully used by Wolf<sup>15</sup>) gave only a moderate yield.

**Table 1.** Stille Cross-Coupling of Aryl Chlorides Catalyzed by Pd<sub>2</sub>(dba)<sub>3</sub>/1



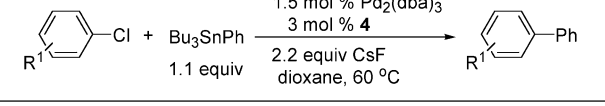
entry	aryl chloride	time (h)	product	yield (%) <sup>a</sup>
1		24		93 <sup>b</sup>
2		30		86 <sup>b</sup>
3		30		89 <sup>b</sup>
4		30		93 <sup>b</sup>
5		36		85 <sup>c</sup>
6		36		99 <sup>c</sup>
7		36	 95 <sup>c</sup> (15:2) <sup>d</sup>	
8		48		95 <sup>c</sup>
9		48		71 <sup>c</sup>
10		48		97 <sup>c</sup>
11		48		91 <sup>c</sup>

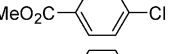
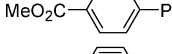
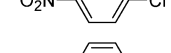
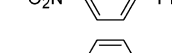
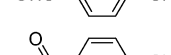
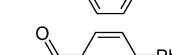
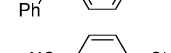
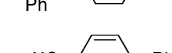
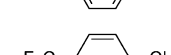
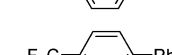
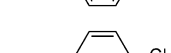
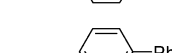
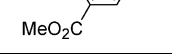
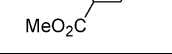
<sup>a</sup> Isolated yields (average of two runs). <sup>b</sup> The reaction temperature was 100 °C. <sup>c</sup> The reaction temperature was 110 °C. <sup>d</sup> The ratio was determined by <sup>1</sup>H NMR spectroscopy.

Encouraged by the results obtained using ligand **4** with 1:1 ratio of L to Pd, we reexamined the activity of a palladium catalyst based on ligand **1** using a 1:1 ratio of L to Pd in the Stille process. For activated aryl chlorides, we found that the use of **1** as the ligand gave results comparable to those obtained when ligand **4** was employed. For example, the reaction of 4-chlorobenzonitrile with phenyltributyltin at 60 °C provided the coupling product in 96% yield using Pd<sub>2</sub>(dba)<sub>3</sub>/1.

**Stille Cross-Coupling Using the Pd<sub>2</sub>(dba)<sub>3</sub>/4 Catalyst System: Unactivated, Deactivated, and Hetero Aryl Chlorides.** The Pd<sub>2</sub>(dba)<sub>3</sub>/4 catalyst system was also found to be effective for the cross-coupling of unactivated and deactivated aryl chlorides with tributylphenyltin at 110 °C (Table 3). For example, the reaction of 4-chloroanisole (entry 1), 2-chloro-*p*-xylene (entry 2), and 5-chloro-1,3-benzodioxole (entry 3) with tributylphenyltin all proceeded in high yield at 110 °C using 3 mol % of Pd and 3.5 mol % of **4** (Pd:4 = 1:1.2). Examples in

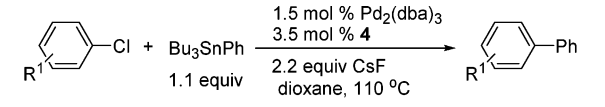
**Table 2.** Stille Cross-Coupling of Activated Aryl Chlorides Catalyzed by Pd<sub>2</sub>(dba)<sub>3</sub>/4

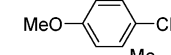
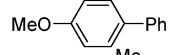
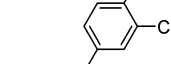
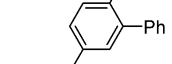
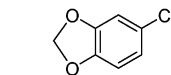
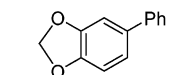
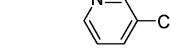
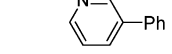
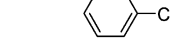
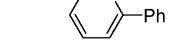
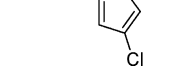
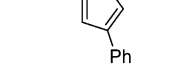


entry	aryl chloride	time (h)	product	yield (%) <sup>a</sup>
1		28		95
2		28		98
3		28		93
4		28		98
5		30		98
6		28		99
7		36		95

<sup>a</sup> Isolated yields (average of two runs).

**Table 3.** Stille Cross-Coupling of Unactivated, Deactivated and Hetero Aryl Chlorides Catalyzed by Pd<sub>2</sub>(dba)<sub>3</sub>/4

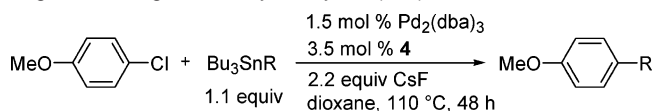


entry	aryl chloride	time (h)	product	yield (%) <sup>a</sup>
1		48		87
2		42		85
3		45		90
4		40		97
5		48		64
6		48		69 <sup>b</sup>

<sup>a</sup> Isolated yields (average of two runs). <sup>b</sup> 6 mol % of **1** was used.

entries 4–6 demonstrate the viability of heteroaryl chlorides in Stille coupling. Interestingly, the reaction of activated 2-chloropyridine provided only a moderate yield (64%) of product compared with deactivated 3-chloropyridine (97%). It should be noted that several research groups have experienced problems in palladium-catalyzed Heck reactions of 2-halopyridines, presumably owing to formation of an unreactive pyridyl-bridged palladium dimer during the course of reaction.<sup>22</sup> Nevertheless,

(22) Nakatsu, K.; Kinoshita, K.; Kanda, H.; Isobe, K.; Nakamura, Y.; Kawaguchi, S. *Chem. Lett.* **1980**, 913. See also: ref 7a.

**Table 4.** Stille Cross-Coupling of 4-Chloroanisole with Various Organotin Reagents Catalyzed by Pd<sub>2</sub>(dba)<sub>3</sub>/4

entry	R <sub>3</sub> SnBu <sub>3</sub>	product (s)	yield (%) <sup>a</sup>
1			57
2			96
3			95 (7:1) <sup>b</sup>
4			67
5			97

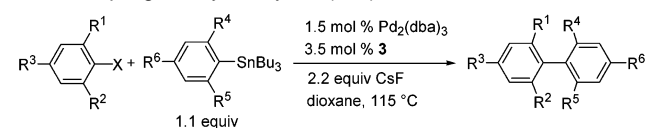
<sup>a</sup> Isolated yields (average of two runs). <sup>b</sup> The ratio was determined by <sup>1</sup>H NMR spectroscopy.

the reaction of 2-chloropyridine occurred in 85% yield with **1** as the ligand when the ratio of Pd to ligand was increased to 1:2 (see Table 1, entry 5). Overall, catalysts based on **1** using a 1:1.2 ratio of L to Pd gave inferior yields for deactivated and unactivated aryl chlorides compared with the catalyst based on **4**.

The coupling of chlorothiophenes is challenging in palladium-based methodologies because of the strong affinity of sulfur for Pd, resulting in catalyst poisoning. Gratifyingly, we found that the Pd<sub>2</sub>(dba)<sub>3</sub>/**1** catalyst system effects Stille coupling of 3-chlorothiophene in respectable yield (Table 3, entry 6). For this substrate, the catalyst based on ligand **4** was less effective. To our knowledge, this represents the first example of Stille coupling of chlorothiophenes.

**Stille Cross-Coupling Using the Pd<sub>2</sub>(dba)<sub>3</sub>/4 Catalyst System: Variation of Organotin Reagents.** The scope of the Pd<sub>2</sub>(dba)<sub>3</sub>/4/CsF catalyst system was further expanded to include a diverse set of organotin reagents, in which deactivated 4-chloroanisole was chosen as the coupling partner (Table 4). Functionalities on organotin reagents that were successfully coupled using this methodology included vinyl (entries 1 and 2), allyl (entry 3), aryl (Table 3, entry 1), and heteroaryl groups (entries 4 and 5 in Table 4). The results obtained in the latter entries are particularly significant, since very few examples of Stille reactions of aryl chlorides with heteroaryl tin reagents are known. To the best of our knowledge, this is the first time that cross-coupling of an aryl chloride with organotin reagents possessing thiophene and furan moieties has been successfully carried out.

**Synthesis of Sterically Hindered Biaryls Using the Pd<sub>2</sub>(dba)<sub>3</sub>/3 Catalyst System.** An important criterion used to judge the performance of a catalyst system in Pd-catalyzed cross-coupling processes is its ability to generate sterically hindered biaryls. Although great progress has been achieved in closely

**Table 5.** Synthesis of Sterically Hindered Biaryls via Stille Cross-Coupling Catalyzed by Pd<sub>2</sub>(dba)<sub>3</sub>/3

entry	aryl halide	stannane	product	yield (%) <sup>a</sup>
1				99
2				88
3				97
4				81
5				98
6				97
7				86
8				77
9				88 <sup>b</sup>

<sup>a</sup> Isolated yields (average of two runs). <sup>b</sup> 3 mol % of Pd<sub>2</sub>(dba)<sub>3</sub> and 7 mol % of **3** were used.

related Suzuki-Miyaura cross-coupling reactions for synthesizing tri- and tetra-*ortho* substituted biaryls,<sup>23</sup> their efficient production via the Stille reaction has not been rewarding so far except for the catalyst system [Pd(P(*t*-Bu)<sub>3</sub>)<sub>2</sub>] reported by Fu.<sup>10b</sup> As a logical extension of our efforts, the synthesis of sterically hindered biaryls via Stille coupling was then examined using proazaphosphatranes as ligands. Disappointingly, the reaction of 2-chloro-*m*-xylene with 2,4,6-trimethylphenyl(tributyl)tin provided only a trace amount of tetra-*ortho* substituted biaryl when **1** was employed as the ligand. However, ligands **2** and **4** afforded a 27% and 61% yield of the desired biaryl, respectively. Subsequently, much to our delight, we found that the introduction of ligand **3** allowed such cross-coupling to occur in high yield (81%, Table 5, entry 4). The ability of the catalyst system Pd<sub>2</sub>(dba)<sub>3</sub>/**3** to produce sterically hindered biaryls was then explored (Table 5). As seen from this table, the reaction tolerates not only one or two *ortho*-substituents on the aryl halide, but it also tolerates the same steric hindrance on the aryl tin reagent.

(23) (a) Navarro, O.; Kelly, R. A.; Nolan, S. P. *J. Am. Chem. Soc.* **2003**, *125*, 16194. (b) Altenhoff, G.; Goddard, R.; Lehmann, C. W.; Glorius, F. *Angew. Chem., Int. Ed.* **2003**, *42*, 3690. (c) Yin, J.; Rainka, M. P.; Zhang, X.-X.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 1162. (d) Walker, S. D.; Barder, T. E.; Martinelli, J. R.; Bulchwald, S. L. *Angew. Chem., Int. Ed.* **2004**, *43*, 1871.

**Table 6.** Room Temperature Stille Cross-Coupling of Aryl Bromides Catalyzed by Pd<sub>2</sub>(dba)<sub>3</sub>/4

entry	aryl or heteroaryl bromide	stannane	product	yield (%) <sup>a</sup>
1				99
2				87
3				97
4				98
5				97
6				97
7				98
8				99 <sup>b</sup>
9				97
10				93
11				99 <sup>b</sup>
12				98 <sup>b</sup>
13				91 <sup>b</sup>

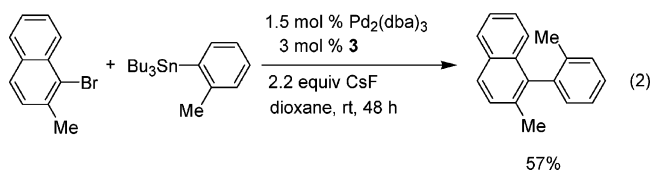
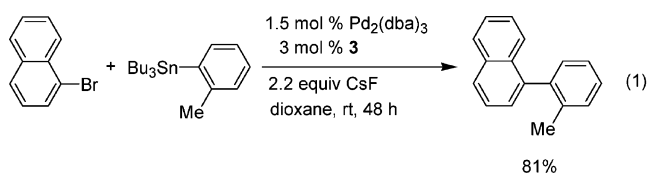
<sup>a</sup> Isolated yields (average of two runs). <sup>b</sup> The reaction temperature was 50 °C.

Excellent yields were obtained in all cases. Even very sterically hindered 2,4,6-triisopropyl bromobenzene can be coupled. For example, the reaction of 2,4,6-triisopropyl bromobenzene with *o*-tolyltributyltin gave an 88% isolated product yield (Table 5, entry 9). To our knowledge, this represents the first example of the synthesis via a Stille reaction of a tri-*ortho*-substituted biaryl bearing *ortho* groups larger than a methyl group.

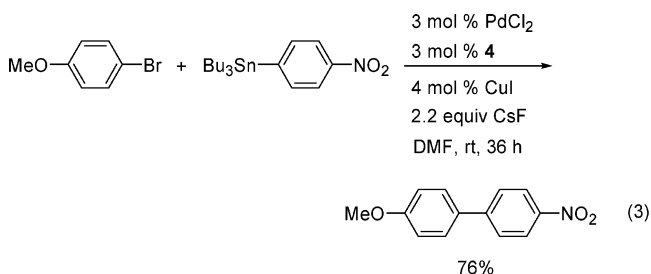
**Stille Cross-Coupling of Aryl Bromides at Room Temperature Using the Pd<sub>2</sub>(dba)<sub>3</sub>/4 Catalyst System.** We next turned our attention to Stille reactions of aryl bromides. There are numerous reports on Stille reactions of aryl bromides at elevated temperatures,<sup>24</sup> but only one general catalyst system [Pd<sub>2</sub>(dba)<sub>3</sub>/P(*t*-Bu)<sub>3</sub>] has been described for room-temperature reactions.<sup>10b</sup> Initially, we performed room-temperature Stille experiments were using **1** as the ligand. We found that although Pd<sub>2</sub>(dba)<sub>3</sub>/1/CsF catalyzes the room-temperature coupling of 4-*tert*-butylbromobenzene and 4-bromo-3-methylanisole with vinyl(tributyl)tin in 91% and 82% yields, respectively, reactions did not proceed to completion in THF even after 21 h. We were pleased to observe, however, that the use of **4** as the ligand leads to a significantly more active catalyst, allowing the reaction to proceed to completion in 10–16 h. For room-temperature

Stille couplings, THF was found to be the most effective solvent. The results described in Table 6 demonstrate that Pd<sub>2</sub>(dba)<sub>3</sub>/4/CsF enables coupling of electronically and sterically diverse aryl bromides with a broad spectrum of tin reagents at room temperature. Thus, electron-neutral 4-*tert*-butylbromobenzene (Table 6, entries 1–4), *ortho*-substituted and electron-rich 4-bromo-3-methylanisole (entries 5–7), and even very electron-rich 4-*N,N*-dimethylaminobromobenzene coupled in excellent yields (entries 9 and 10) at room temperature. However, Stille reactions of substrates containing the thiophene moiety were very slow at room temperature, and mild heating (50 °C) was required for the reactions to proceed to completion (entries 8, 11, 12, and 13). This result may be ascribed to a tendency of the thiophenic sulfur to bind to palladium, thus reducing its activity and/or retarding transmetalation.

Even sterically hindered biaryls could be synthesized at room temperature using ligand **3** (eqs 1 and 2). Equation 2, which depicts the first successful synthesis of a tri-*ortho*-substituted biaryl through a Stille reaction of an aryl bromide at room-temperature, is particularly interesting.



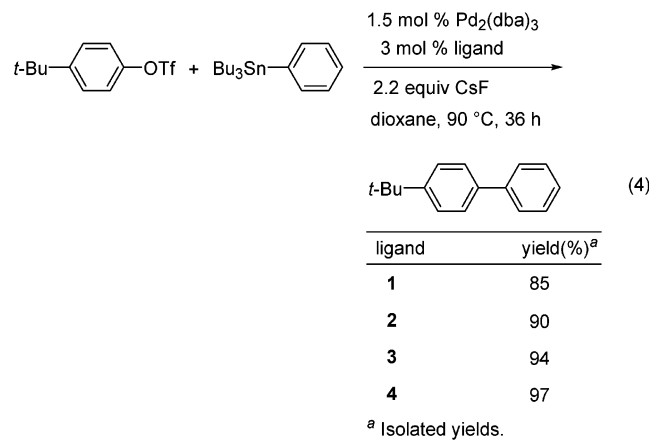
Another challenging coupling of electron-rich 4-bromoanisole with electron-deficient 4-(tributylstannyl)nitrobenzene was also accomplished at room-temperature in good yield (eq 3). Interestingly, the reaction proceeded quite sluggishly using our standard conditions [Pd<sub>2</sub>(dba)<sub>3</sub>/4/THF or Pd<sub>2</sub>(dba)<sub>3</sub>/4/dioxane]. However, by employing the conditions developed by Baldwin<sup>16</sup> [except that in the present study ligand **4** was employed whereas Baldwin used P(*t*-Bu)<sub>3</sub>], the desired coupling product was obtained in 76% isolated yield. It should also be noted that in this case, the addition of CuI to the reaction mixture significantly improved the yield because in its absence, only a trace amount of the desired coupled product was obtained. Similar enhancement of a Stille process using a combination of CuI and CsF was observed by Baldwin.<sup>16</sup>



We also briefly examined the efficacy of aryl triflates as substrates in Stille reactions catalyzed by proazaphosphatrane ligands. We found that aryl triflates are also viable substrates

(24) For recent examples, see: Alonso, D. A.; Njera, C.; Pacheco, M. C. *Org. Lett.* **2000**, *2*, 1823. See also: refs 13 and 15.

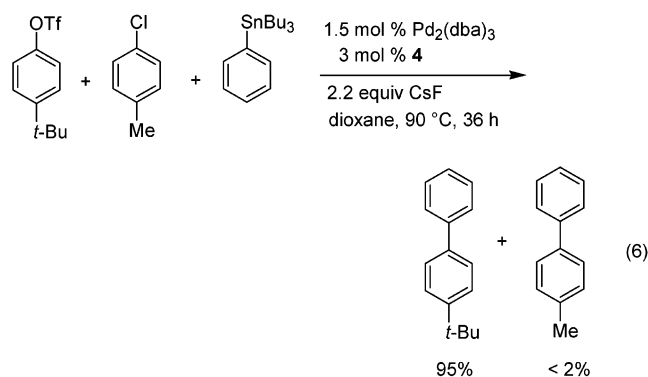
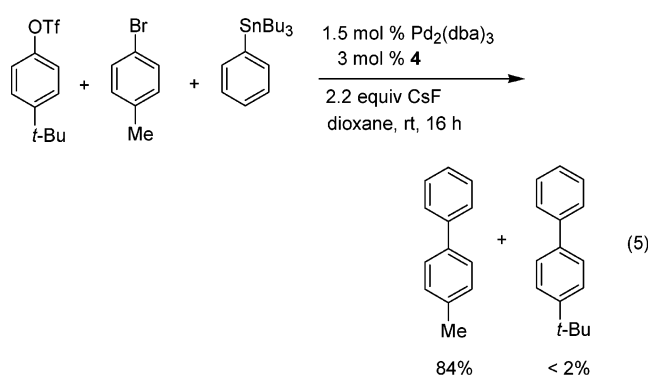
and again the use of ligand **4** provided the best results (eq 4). The reaction did not proceed to completion with the use of ligand **1** even after 36 h, whereas the use of ligands **2**, **3**, and **4** led to completion within that time.



**Competition Experiments for the Order of Reactivity.** To determine the order of reactivity of aryl halides and triflates in Stille cross-couplings catalyzed by Pd<sub>2</sub>(dba)<sub>3</sub>/**4**, two competition experiments were conducted as shown in eqs 5 and 6. Not surprisingly, it was established that the product obtained was derived almost exclusively from the aryl bromide (eq 5), whereas the competition experiment between aryl chloride and triflate performed at 90 °C revealed that the aryl triflate reacted in preference to the aryl chloride (eq 6). From these two experiments, it can be concluded that the order of reactivity under our conditions follows the traditional order: aryl bromide > aryl triflate > aryl chloride.<sup>2</sup> It is worthy of note that this observed reactivity is quite different from the one reported by Fu's group for Stille coupling using P(*t*-Bu)<sub>3</sub> as a ligand, which follows the unexpected order: aryl bromide > aryl chloride > aryl triflate.<sup>10b</sup>

**Stille Cross-Coupling of Vinyl Chlorides Using the Pd<sub>2</sub>(dba)<sub>3</sub>/**4** Catalyst System.** Another challenging Stille reaction involves the use of unactivated vinyl chlorides and not unexpectedly, only one catalyst system (Pd/P(*t*-Bu)<sub>3</sub>)<sup>10b,25</sup> has thus far been reported for the Stille coupling of such substrates. In that report, 3 mol % of Pd(P(*t*-Bu)<sub>3</sub>)<sub>2</sub> was employed as the catalyst, and the reaction temperature was 100 °C. We observed that the Pd<sub>2</sub>(dba)<sub>3</sub>/**4** catalyst system was also effective for cross-coupling a vinyl chloride with various tin reagents at 100 °C, affording the corresponding coupled products in excellent yields (Table 7).

**<sup>31</sup>P NMR Studies.** To gain some insights into the mechanism,<sup>26</sup> we investigated the fate of ligand **4** in Stille reactions by <sup>31</sup>P NMR spectroscopy. A mixture of **4** (δ 127.9) and Pd<sub>2</sub>(dba)<sub>3</sub> in a 1:1 ratio at room temperature shows a phosphorus resonance at δ 132.4. We tentatively assigned this peak to a Pd-**4** complex. We then monitored the reaction of 1-bromo-4-*tert*-butylbenzene with tributylphenyltin in THF at room temperature as well as the reaction of 4-chlorotoluene with



**Table 7.** Stille Cross-Coupling of Vinyl Chlorides Catalyzed by Pd<sub>2</sub>(dba)<sub>3</sub>/**4**

entry	tin reagent	product	yield (%) <sup>a</sup>
1	Bu <sub>3</sub> Sn-Ph	Vinyl-Ph	91
2	Bu <sub>3</sub> Sn-S	Vinyl-S	83
3	Bu <sub>3</sub> Sn-O	Vinyl-O	93

<sup>a</sup> Isolated yields (average of two runs).

tributylphenyltin in dioxane at 110 °C in the presence of ligand **4**. In both cases, the same <sup>31</sup>P chemical shift at 132.4 ppm was observed as the only major phosphorus-containing species (>90%). These observations suggest that perhaps the Pd-**4** complex (δ 132.4) is the resting state species in the catalytic cycle. Further work in our laboratory is underway to delineate the palladium-species involved in these reactions.

## Conclusions

Proazaphosphatranes (**1**, **3**, and **4**) provide general and effective palladium catalysts for Stille transformations. Catalysts utilizing **1** and **4** as the supporting ligand efficiently allow coupling of electronically diverse aryl chlorides with a wide array of organotin reagents. Reactions of sterically hindered substrates are most effectively catalyzed with **3** as the supporting ligand and Stille couplings of aryl bromides are more easily

(25) Stille couplings of activated vinyl chlorides are known. See: (a) Rubin, Y.; Knobler, C. B.; Diederich, F. *J. Am. Chem. Soc.* **1990**, *112*, 1607. (b) Liebeskind, L. S.; Yu, M. S.; Yu, R. H.; Wang, J.; Hagen, K. S. *J. Am. Chem. Soc.* **1993**, *115*, 9048. (c) May, P. D.; Larsen, S. D. *Synlett* **1997**, 895.

(26) For an excellent review of the mechanisms of the Stille reaction, see: Espinet, P.; Echavarren, A. M. *Angew. Chem., Int. Ed.* **2004**, *43*, 4704.

facilitated at room-temperature with ligand **4**. Vinyl chlorides and aryl triflates are also suitable substrates.

We believe that a unique balance of unusual electron-richness and steric hindrance is a salient feature of these ligands. The exceptional activity shown by the palladium catalyst supported by ligand **4** may also stem from the possibility that a benzyl group stabilizes the active palladium catalyst through the interaction of its aromatic  $\pi$ -orbitals with empty  $d$ -orbitals on palladium.<sup>27</sup> Another possibility is that subtle stereoelectronic effects presently unclear may operate to ligate **4** more tightly to the Pd center compared with **1**, thereby maintaining a higher

electron density at palladium favoring oxidative addition, while simultaneously inhibiting decomposition of the complex.

**Acknowledgment.** We thank the Aldrich Chemical Co. for their generous support of this study by supplying research samples. The National Science Foundation is gratefully acknowledged for financial support of this work in the form of a grant.

**Supporting Information Available:** Experimental details, references for known compounds, complete characterization of unknown compounds, and copies of <sup>1</sup>H and <sup>13</sup>C for all compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

(27) Pd-arene interactions in palladium complexes have been proposed to contribute to their catalytic activity. See (a) Reid, S. M.; Boyle, R. C.; Mague, J. T.; Fink, M. J. *J. Am. Chem. Soc.* **2003**, *125*, 7856. (b) Catellani, M.; Mealli, C.; Motti, E.; Paoli, P.; Perez-Carreno, E.; Pregosin, P. S. *J. Am. Chem. Soc.* **2002**, *124*, 4336. See also: refs 8a, 22c, and 22d.

JA0450096