

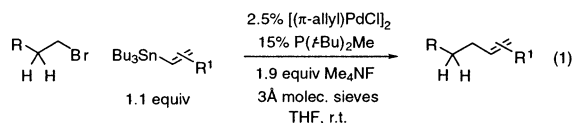
## Room-Temperature Stille Cross-Couplings of Alkenyltin Reagents and Functionalized Alkyl Bromides that Possess $\beta$ Hydrogens

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The Stille cross-coupling reaction<sup>1,2</sup> is a powerful method for generating carbon–carbon bonds under conditions that are compatible with a broad range of functional groups. As a consequence of these attractive attributes, it has been applied in a wide array of disciplines, spanning areas such as materials science<sup>3</sup> and natural products synthesis.<sup>4</sup> Although innumerable reports have described Stille reactions of  $C_{sp^2}$ –X electrophiles, there are few examples of cross-couplings of  $C_{sp^3}$ –X electrophiles, particularly those that bear  $\beta$  hydrogens;<sup>5</sup> indeed, we are aware of only four successes:  $\alpha$ -bromoketones (Migita),<sup>6</sup> 1-bromo-1-phenylethane (Sustmann),<sup>7</sup> an  $\alpha$ -chloroether (Mioskowski),<sup>8</sup> and fluorinated alkyl iodides (Fuchikami).<sup>9,10</sup> In this communication, we significantly expand the scope of Stille reactions of  $C_{sp^3}$ –X electrophiles, demonstrating that Pd/P(*t*-Bu)<sub>2</sub>Me catalyzes the room-temperature cross-coupling of a variety of functionalized, unactivated,  $\beta$ -hydrogen-containing alkyl bromides with an array of alkenyltin reagents (eq 1).



We have recently reported that bulky, electron-rich phosphines furnish unusually effective catalysts for Suzuki reactions of  $C_{sp^3}$ –X electrophiles with a range of organoboron reagents.<sup>11</sup> Thus, PdL<sub>n</sub> complexes (L = P(*t*-Bu)<sub>2</sub>Me or PCy<sub>3</sub>) appear to possess desirable reactivity profiles with respect to two of the impediments to efficient cross-coupling of  $C_{sp^3}$ –X electrophiles: relatively slow oxidative addition and rapid  $\beta$ -hydride elimination (Figure 1; note that the alkyl halides of Migita/Sustmann/Mioskowski/Fuchikami are all either activated toward oxidative addition or stabilized against  $\beta$ -hydride elimination).

Unfortunately, when we applied Pd/PCy<sub>3</sub> (or Pd/P(*t*-Bu)<sub>2</sub>Me) to the Stille coupling of *n*-decyl bromide with vinyl-SnBu<sub>3</sub>, we obtained essentially none of the desired product (Table 1, entry 1). Given that Pd/PCy<sub>3</sub> catalyzes Suzuki reactions of *n*-decyl bromide,<sup>11a,d</sup> we postulated that our inability to achieve Stille cross-coupling was probably due to slow transmetalation. Because Lewis-basic additives have been shown to facilitate certain Stille reactions, presumably by generating hypervalent stannate complexes that are more reactive toward transmetalation,<sup>12</sup> we explored the utility of a variety of potential activators, illustrative examples of which are provided in Table 1. Although N(*i*-Pr)<sub>2</sub>Et, CsOH·H<sub>2</sub>O, NaOMe, KF, and CsF were largely ineffective (entries 2–6), the addition of Bu<sub>4</sub>NF·3H<sub>2</sub>O led to the formation of an appreciable quantity of the cross-coupling product (entry 7).<sup>13</sup> Additional optimization revealed that Me<sub>4</sub>NF/3 Å molecular sieves serve as a particularly effective activator, furnishing a 73% yield of 1-dodecene (entry 8).

We have determined that, as for Suzuki reactions of alkyl electrophiles,<sup>11</sup> the structure of the ligand has a remarkable influence on Stille reactions of alkyl bromides. Decreasing or increasing the

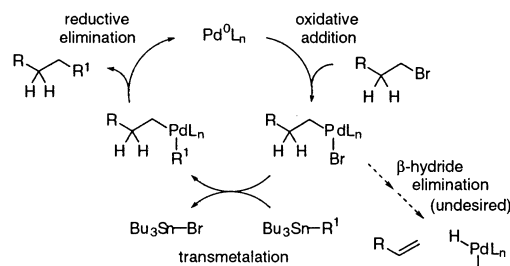


Figure 1. Mechanism for the Stille cross-coupling reaction.

Table 1. Effect of Lewis-Basic Additives on the Stille Coupling of an Alkyl Bromide

entry	additive	yield (%) <sup>a</sup>
1	none	<2
2	N( <i>i</i> -Pr) <sub>2</sub> Et	<2
3	CsOH·H <sub>2</sub> O	7
4	NaOMe	4
5	KF	<2
6	CsF	<2
7	Bu <sub>4</sub> NF·3H <sub>2</sub> O	32
8	Me <sub>4</sub> NF (1.9 equiv), 3 Å molec. sieves	73

<sup>a</sup> Determined by GC versus a calibrated internal standard (average of two runs).

size of just one of the cyclohexyl groups of PCy<sub>3</sub> leads to a markedly less efficient coupling catalyst (Table 2, entry 1 vs entries 2–4). P(*t*-Bu)<sub>3</sub>, which is a useful ligand for a wide array of palladium-catalyzed couplings of  $C_{sp^2}$ –X electrophiles,<sup>14</sup> is not effective for Stille reactions of alkyl bromides (entry 5). Whereas replacing one of the *t*-Bu groups of P(*t*-Bu)<sub>3</sub> with an ethyl group does not lead to an appreciable enhancement in reactivity (entry 6), substitution with a methyl group furnishes an active catalyst (entry 7). Under these conditions, other families of ligands, such as phosphites (entry 8), triarylphosphines (entries 9–11), arsines (entry 12), and carbenes (entry 13), afford ineffective catalysts.

With Pd/P(*t*-Bu)<sub>2</sub>Me as the catalyst, we can cross-couple an array of functionalized alkyl bromides with a range of alkenyltin reagents at room temperature (Table 3). Thus, the reaction conditions are compatible with groups such as olefins, acetals, ethers, nitriles, esters, and amides. With respect to the tin reagent, not only is vinyl-SnBu<sub>3</sub> a suitable reactant, but a variety of compounds, including progressively more challenging trans- (entries 1–5) and cis-disubstituted (entries 6–8), as well as trisubstituted (entry 9), olefins, can be cross-coupled.<sup>15</sup>

Unfortunately, the susceptibility of P(*t*-Bu)<sub>2</sub>Me to oxidation can make its handling inconvenient. As illustrated in Table 3, air- and

**Table 2.** Effect of Ligand Structure on the Stille Coupling of an Alkyl Bromide

$n\text{-Dec-Br} + \text{Bu}_3\text{Sn-CH=CH}_2 \xrightarrow[\text{THF, 24 h, r.t.}]{\substack{2.5\% [(\pi\text{-allyl})\text{PdCl}]_2 \\ 15\% \text{ ligand} \\ 1.9 \text{ equiv Me}_4\text{NF} \\ 3\text{Å molec. sieves}}}$ 
 $n\text{-Dec-CH=CH}_2$

entry	ligand	yield (%) <sup>a</sup>
1	PCy <sub>3</sub>	73
2	PCy <sub>2</sub> Et	17
3	PCy <sub>2</sub> Me	<2
4	PCy <sub>2</sub> ( <i>t</i> -Bu)	9
5	P( <i>t</i> -Bu) <sub>3</sub>	<2
6	P( <i>t</i> -Bu) <sub>2</sub> Et	<2
7	<b>P(<i>t</i>-Bu)<sub>2</sub>Me</b>	<b>86</b> ←
8	P(OPh) <sub>3</sub>	<2
9	PPh <sub>3</sub>	<2
10	P( <i>o</i> -tol) <sub>3</sub>	<2
11	P(2-furyl) <sub>3</sub>	<2
12	AsPh <sub>3</sub>	<2
13	IMesHCl <sup>b</sup>	<2

<sup>a</sup> Determined by GC versus a calibrated internal standard (average of two runs). <sup>b</sup> 1,3-Bis(2,4,6-trimethylphenyl)imidazolium chloride.

**Table 3.** Room-Temperature Stille Cross-Couplings of Alkyl Bromides that Contain  $\beta$  Hydrogens

$\text{R-Br} + \text{Bu}_3\text{Sn-CH=CH-R}^1 \xrightarrow[\text{THF, r.t.}]{\substack{2.5\% [(\pi\text{-allyl})\text{PdCl}]_2 \\ 15\% \text{ P}(\textit{t}\text{-Bu})_2\text{Me or [HP}(\textit{t}\text{-Bu})_2\text{Me]BF}_4 \\ 1.9 \text{ equiv Me}_4\text{NF} \\ 3\text{Å molec. sieves}}}$ 
 $\text{R-CH=CH-R}^1$

entry	R-Br	tin reagent	yield (%) <sup>a</sup>	
			P( <i>t</i> -Bu) <sub>2</sub> Me	[HP( <i>t</i> -Bu) <sub>2</sub> Me]BF <sub>4</sub>
1		Bu <sub>3</sub> Sn-CH=CH- <i>n</i> -Hept	96	92
2		Bu <sub>3</sub> Sn-CH=CH-OTHP	71	70
3		Bu <sub>3</sub> Sn-CH=CH-OTHP	62	64
4		Bu <sub>3</sub> Sn-CH=CH-OTHP	60	66
5		Bu <sub>3</sub> Sn-CH=CH- <i>n</i> -Hept	59	59
6		Bu <sub>3</sub> Sn-CH=CH-Ph	74	77
7		Bu <sub>3</sub> Sn-CH=CH-Ph	58	65
8		Bu <sub>3</sub> Sn-CH=CH-Ph	55	53
9		Bu <sub>3</sub> Sn-CH=CH-OTHP	55	53

<sup>a</sup> Isolated yield, average of two runs.

moisture-stable [HP(*t*-Bu)<sub>2</sub>Me]BF<sub>4</sub>, which is also commercially available,<sup>16</sup> furnishes yields that are comparable to the phosphine itself.<sup>17</sup>

In conclusion, we have established that a Pd/P(*t*-Bu)<sub>2</sub>Me-based catalyst can achieve room-temperature Stille cross-couplings of a variety of alkenyltin reagents with a range of functionalized alkyl

bromides that contain  $\beta$  hydrogens. In view of the limited prior success in this area, we believe that this report reveals a significant new dimension to the Stille reaction. Our current efforts are focused on developing catalysts that expand the scope of this and related coupling processes, as well as on gaining a better understanding of the origin of the unusual reactivity of Pd/trialkylphosphine-based catalysts.

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**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>.

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