

## Palladium-Catalyzed Stille Cross-Couplings of Sulfonyl Chlorides and Organostannanes

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The efficient methods for the construction of carbon–carbon bonds represent an ongoing, central theme of research of organic synthesis.<sup>1</sup> Transition-metal-catalyzed cross-coupling of organometallic reagents with halides or triflates constitutes today one of the most powerful methods to generate carbon–carbon bonds. In the Stille reaction,<sup>2,3</sup> organostannanes are used as reaction partners. They remain attractive because of their availability and air and moisture stability, as well as their compatibility with a variety of functional groups. Arene- and alkanesulfonyl chlorides are readily available compounds but have rarely been used as coupling partners in transition-metal-catalyzed cross-coupling reactions with organometallic species to construct carbon–carbon bonds. Arenesulfonyl chlorides have been engaged in carbon-vinylation,<sup>4</sup> carbon-carbonylation,<sup>5</sup> and homo-couplings.<sup>6</sup> To our knowledge, they have never been used in Stille cross-coupling reactions. We report here that arene and phenylmethanesulfonyl chlorides can be cross-coupled with aryl, heteroaryl, vinyl, and alkenylstannanes with desulfitation in the presence of palladium and copper catalysts.

We examined first the condensation of 1-naphthalenesulfonyl chloride with tributyl(4-fluorophenyl)stannane in the presence of 10 mol % of CuBr·Me<sub>2</sub>S. Four different palladium catalysts were assayed, and, as shown in Table 1, the best conditions were found with 1.5 mol % of Pd<sub>2</sub>dba<sub>3</sub> + 5 mol % tri-2-furylphosphine (TFP).

We then explored the possibility to generalize this new reaction to other arenesulfonyl chlorides and to phenylmethanesulfonyl chloride using organostannanes of different types. The results are summarized in Table 2. With Pd(PPh<sub>3</sub>)<sub>4</sub> as catalyst, the corresponding cross-coupled products were obtained in moderate to poor yields (Table 2). In this case, two major products were obtained: the one arising from the self-coupling of the organostannanes (heteroaryl) and another one, a diarylsulfide, which could be obtained after reduction of the first formed sulfone.<sup>7</sup> However, with 1.5 mol % Pd<sub>2</sub>dba<sub>3</sub>, 5 mol % TFP, and 10 mol % CuBr·Me<sub>2</sub>S, a wide range of electronically and structurally diverse sulfonyl chlorides and organostannanes can be cross-coupled efficiently with desulfitation.<sup>8</sup> Thus, with respect to the electron-rich, electron-neutral, and electron-poor arenesulfonyl chlorides, they react with organostannanes to provide the corresponding biaryl products in good yields in most of the cases. Traces of the byproducts arising from self-coupling of organostannanes were observed in some cases.<sup>9</sup>

When a larger amount of CuBr·Me<sub>2</sub>S (e.g., 1.3 equiv) was used as cocatalyst, the reaction was faster, but the major product was the one arising from the self-coupling of organostannane.<sup>10</sup> Cross-coupling without cocatalyst is somewhat slower than when using 10 mol % of CuBr·Me<sub>2</sub>S. Poorer yield was obtained when performing the same reaction under air atmosphere (entry 22, Table 2).

We have observed that in the reaction of tributyl(thien-2-yl)stannane with toluenesulfonyl chloride (entry 24, Table 2) in DME instead of THF as solvent at 65 °C, the homocoupled product was

**Table 1.** Catalysts Screening

entry	Pd catalysts	yield (%) <sup>a</sup>
1	1.5% Pd <sub>2</sub> dba <sub>3</sub> /5% TFP	90 (92) <sup>b</sup>
2	4% Pd <sub>2</sub> dba <sub>3</sub> /15% TFP	93
3	8% Pd(PPh <sub>3</sub> ) <sub>4</sub>	41
4	8% PdCl <sub>2</sub> (PhCN) <sub>2</sub>	36
5	8% PdCl <sub>2</sub> (PPh <sub>3</sub> ) <sub>2</sub>	35

<sup>a</sup> Yields of cross-coupling products, determined after chromatography.  
<sup>b</sup> In toluene.

obtained in 85% yield. This solvent effect contrasts with what Guillaumet and co-workers found. In their case, DME did not favor homocoupling of organostannanes.<sup>11</sup>

We also examined the palladium-catalyzed carbonylative Stille cross-coupling reaction of arenesulfonyl chlorides and organostannanes in the presence of carbon monoxide (60 bar) at 110 °C in toluene.<sup>12</sup> The carbonylative cross-coupled products were obtained in moderate yields only due to the formation of the carbonylative homocoupled products of stannanes (Scheme 1).

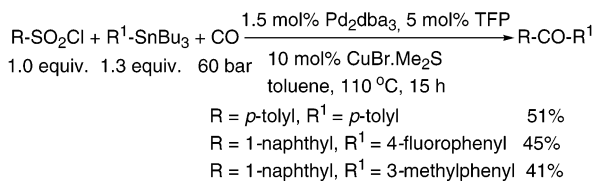
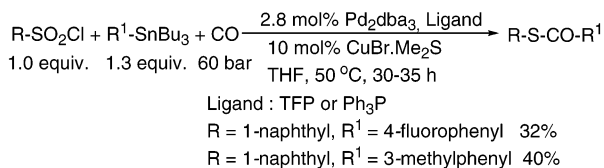
When we used THF instead of toluene as solvent in the carbonylative Stille reaction, the Ar–S–CO–Ar<sup>1</sup> product was obtained as traces. The amount of thioester increased with the amount of TFP added to the reaction mixture. The formation of the thioethers arises from the reduction of the sulfonyl chloride by the phosphine into the corresponding sulfenyl chloride,<sup>13</sup> which then undergoes the arylcarbonylation (Scheme 2). This process is analogous to the known Co<sub>2</sub>(CO)<sub>8</sub>-catalyzed carbonylation of thiols<sup>14</sup> and to the thiocarbonylation of acetylenes with thiols and carbon monoxide catalyzed by palladium<sup>15</sup> or platinum complexes.<sup>16</sup>

When TsCl was mixed with 1 equiv of PdCl<sub>2</sub>(PhCN)<sub>2</sub> in THF-d<sub>8</sub>, a signal (δ<sub>c</sub> 145.2 ppm) typical of the C–Pd bond<sup>17</sup> appeared in the <sup>13</sup>C NMR spectrum after 10 min at 45 °C. The metal may insert into the SO<sub>2</sub>–Cl bond first with rapid subsequent elimination of SO<sub>2</sub> or first onto the C–S bond with subsequent elimination of SO<sub>2</sub>. Both mechanisms convert the arenesulfonyl chloride into an arylpalladium species, which then undergoes the cross-coupling reaction with the organostannane, in a similar way as aryl halides or triflates would undergo the Stille condensations.<sup>2</sup> In those reactions and under our conditions,<sup>8</sup> the sulfonyl chloride group is more reactive (entries 9–11, Table 2) than the corresponding chloride<sup>18</sup> and bromide.<sup>19</sup> For example, in the reaction of 4-bromobenzenesulfonyl chloride with tributyl(4-fluorophenyl)stannane, the cross-coupled product (38%) (entry 11, Table 2) and the bis cross-coupled product (traces) are obtained together with 4-bromobenzenesulfonic acid (32%) and 4'-fluoro-1,1'-biphenyl-4-sulfonic acid (2.5%).<sup>20</sup> However, sulfonyl chlorides proved to be less

**Table 2.** Palladium-Catalyzed Stille Cross-Couplings of Sulfonyl Chlorides and Organostannanes

R-SO <sub>2</sub> Cl + R <sup>1</sup> -SnBu <sub>3</sub>		1.5 mol% Pd <sub>2</sub> dba <sub>3</sub> , 5 mol% TFP 10 mol% CuBr·Me <sub>2</sub> S Solvent, reflux, 2-4 h		R-R <sup>1</sup>
entry	R	R <sup>1</sup>	yield <sup>a</sup>	
1 <sup>b</sup>	1-naphthyl	4-fluorophenyl	90 (92) <sup>c</sup>	
2 <sup>d</sup>	1-naphthyl	4-fluorophenyl	93	
3 <sup>e</sup>	1-naphthyl	4-fluorophenyl	41	
4 <sup>b</sup>	1-naphthyl	4-methylphenyl	81	
5 <sup>b</sup>	1-naphthyl	3-methylphenyl	81	
6 <sup>e</sup>	1-naphthyl	3-methylphenyl	39	
7 <sup>b</sup>	1-naphthyl	3-nitrophenyl	82	
8 <sup>b</sup>	phenyl	phenyl	84	
9 <sup>b</sup>	4-chlorophenyl	4-methylphenyl	66 <sup>f</sup>	
10 <sup>b</sup>	4-chlorophenyl	4-fluorophenyl	51 <sup>f</sup>	
11 <sup>b</sup>	4-bromophenyl	4-fluorophenyl	38 <sup>g</sup>	
12 <sup>b</sup>	4-iodophenyl	4-fluorophenyl	traces <sup>g</sup>	
13 <sup>b</sup>	4-nitrophenyl	4-fluorophenyl	89	
14 <sup>b</sup>	4-nitrophenyl	4-methylphenyl	89	
15 <sup>b</sup>	4-methylphenyl	4-methylphenyl	78	
16 <sup>b</sup>	4-methylphenyl	3-nitrophenyl	80	
17 <sup>b</sup>	4-methylphenyl	3-methylphenyl	73	
18 <sup>e</sup>	4-methylphenyl	3-methylphenyl	35	
19 <sup>b</sup>	4-methylphenyl	4-fluorophenyl	70	
20 <sup>e</sup>	4-methylphenyl	4-fluorophenyl	38	
21 <sup>b</sup>	4-methylphenyl	phenyl	68	
22 <sup>e</sup>	4-methylphenyl	phenyl	35 (22) <sup>h</sup>	
23 <sup>b</sup>	4-methylphenyl	2-thienyl	38	
24 <sup>i</sup>	4-methylphenyl	2-thienyl	8 <sup>j</sup>	
25 <sup>b</sup>	4-methylphenyl	3-[(E)-2-phenylethenyl]	41	
26 <sup>b</sup>	4-methylphenyl	vinyl	25	
27 <sup>b</sup>	4-methylphenyl	3-pyridinyl	55	
28 <sup>b</sup>	benzyl	4-fluorophenyl	19 (41) <sup>c</sup>	
29 <sup>c</sup>	benzyl	3-methylphenyl	38	
30 <sup>c</sup>	benzyl	4-methylphenyl	38	

<sup>a</sup> Yields of cross-coupling products, determined after flash chromatography. <sup>b</sup> In THF. <sup>c</sup> In toluene for 6 h. <sup>d</sup> 4 mol % Pd<sub>2</sub>dba<sub>3</sub>, 15 mol % of TFP in THF. <sup>e</sup> 8 mol % Pd(PPh<sub>3</sub>)<sub>4</sub> in THF. <sup>f</sup> Traces of the homocoupling of arenesulfonyl chloride were isolated. <sup>g</sup> See text for byproducts. <sup>h</sup> 8 mol % Pd(PPh<sub>3</sub>)<sub>4</sub> under air atmosphere. <sup>i</sup> 1.5 mol % Pd<sub>2</sub>dba<sub>3</sub>, 5 mol % of TFP/AsPh<sub>3</sub> in DME. <sup>j</sup> 85% of the homocoupled product of stannane was isolated, based on the organostannane.

**Scheme 1.** Carbonylative Stille Cross-Coupling**Scheme 2.** Preparation of Thioesters

reactive<sup>20</sup> than the corresponding iodides. Thus, reactivity order is ArI > ArSO<sub>2</sub>Cl > ArBr ≫ ArCl.

In summary, palladium-catalyzed, copper-mediated couplings of readily available arene-, phenylmethanesulfonyl chlorides, and aryl,

heteroaryl, vinyl, and alkenylstannanes are presented. This opens new possibilities for medicinal chemistry and material sciences.

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**Supporting Information Available:** Experimental procedures, unknown compound characterization and references to known compounds(PDF). This material is available free of charge via the Internet at <http://pubs.acs.org>.

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- (8) Typical experimental procedure: In a round-bottom flask dried under vacuum were placed CuBr·Me<sub>2</sub>S (0.10 mmol), the corresponding sulfonyl chloride (1.00 mmol), Pd<sub>2</sub>dba<sub>3</sub> (0.015 mmol), and tri-2-furylphosphine (0.05 mmol). Then the solvent (5 mL) and the organostannane (1.3 mmol) were added under an argon atmosphere. The reaction was stirred at reflux for 2–4 h, and then 5 mL of aqueous KF (1 M) solution was added and stirred for 10 min. The solution was filtered through a pad of Celite, rinsed with ether, and washed with brine (3 times). The aqueous layer was extracted again twice with ether. The combined organic phases were dried (MgSO<sub>4</sub>), filtered, concentrated under reduced pressure (solvents were removed under reflux on cooling to –20 °C in the cases of low boiling point or low molecular mass compounds), and purified by flash chromatography.
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- (18) Aryl chlorides react only when using electron-rich or sterically hindered ligands. See, for example: (a) Litke, A. F.; Fu, G. C. *Angew. Chem., Int. Ed.* **1999**, *38*, 2411–2413. (b) Wolfe, J. P.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **1999**, *38*, 2413–2416.
- (19) Aryl bromides are reactive under these conditions. See, for example: Farina, V.; Krishnan, B. *J. Am. Chem. Soc.* **1991**, *113*, 9585–9595.
- (20) For reaction work up, see Supporting Information.

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