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Heteroaromatic Thioether–Organostannane Cross-Coupling

Masahiro Egi and Lanny S. Liebeskind*

*Emory University, Department of Chemistry, 1515 Pierce Drive,
Atlanta, Georgia 30322*

chemll1@emory.edu

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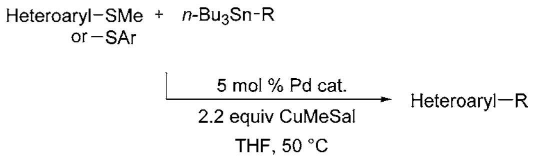
ABSTRACT



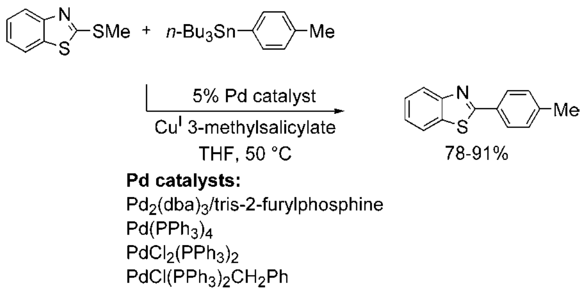
CuMeSal = copper(I) 3-methylsalicylate

Heteroaromatic thioethers and aryl, heteroaryl, and alkenylstannanes participate in a palladium-catalyzed, copper(I)-mediated cross-coupling reaction at 50 °C in THF.

Heteroaromatic compounds are important in the chemical, agricultural, and pharmaceutical industries. Accordingly, the development of new, mild, and general methods to functionalize heteroaromatics is an important synthetic goal. Various nickel- and palladium-catalyzed cross-coupling protocols have been used to achieve that goal,[1−4] with a novel copper-mediated, palladium-catalyzed heteroaromatic thioether−boronic acid coupling being the most recent addition to the repertoire.[5,6] As an extension of our previous studies of thioorganics as versatile reaction partners in cross-coupling reactions,[7] we have explored the palladium-catalyzed, copper-facilitated coupling of heteroaromatic thioethers with organostannanes.[8] Although this system possesses overlap with the analogous boronic acid−heteroaromatic coupling system published earlier,[7b] the tin variant should find use in cases where stannanes are more accessible.

Our studies began with an exploration of the coupling of commercially available (2-methylthio)benzothiazole (**1**) and *p*-tolyltri-*n*-butylstannane (**2**) in the presence of copper(I) 3-methylsalicylate (CuMeSal)[9] using four different palladium catalysts (5% each of $Pd_2(dba)_3$/tris-2-furylphosphine, $Pd(PPh_3)_4$, $PdCl_2(PPh_3)_2$, and $PdCl(PPh_3)_2CH_2Ph$) (Scheme 1). Good yields were obtained in each case (78−91%).

Scheme 1. Catalyst Survey



A study of the cross-coupling of representative heteroaromatic thioethers and organostannanes was undertaken using one of two different reaction systems (Table 1). For the more reactive coupling partners, simple thiomethyl ethers of the heteroaromatic sufficed as substrates using $PdCl(PPh_3)_2(CH_2$-

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(1) Kalinin, V. N. *Synthesis* **1992**, 413−432.
(2) Undheim, K.; Benneche, T. *Acta Chem. Scand.* **1993**, *47*, 102−121.
(3) Angiolelli, M. E.; Casalnuovo, A. L.; Selby, T. P. *Synlett* **2000** (6), 905−907.
(4) Srogl, J.; Liu, W.; Marshall, D.; Liebeskind, L. S. *J. Am. Chem. Soc.* **1999**, *121*, 9449−9450.
(5) Liebeskind, L. S.; Srogl, J. *Org. Lett.* **2002**, *4*, 979−981.

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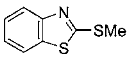
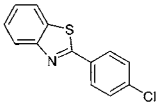
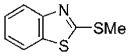
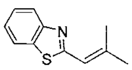
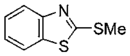
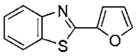
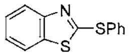
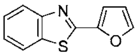
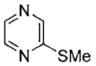
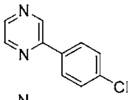
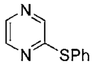
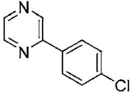
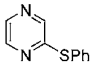
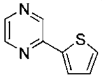
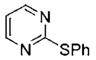
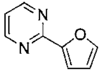
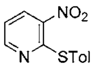
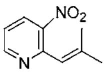
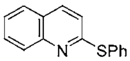
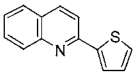
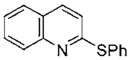
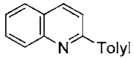
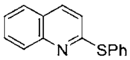
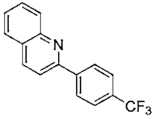
Table 1. Heteroaryl Thioether−Organostannane Coupling

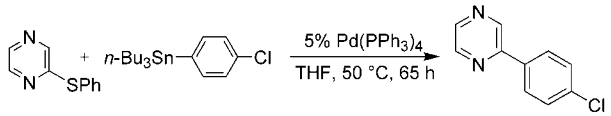
$$\begin{array}{c}\text{Heteroaryl-SMe}\\ \text{-SPh}\end{array} + n\text{-Bu}_3\text{Sn-R} \xrightarrow[\text{THF, 50 °C}]{\begin{array}{c}\text{5 mol \% Pd cat.}\\ \text{2.2 equiv CuMeSal}\end{array}} \text{Heteroaryl-R}$$

	heteroaryl	stannane, R	product	yield (%)
1[a]		4-chlorophenyl		89
2[a]		2-methyl-1-propenyl		81
3[a]		2-furyl		36
4[b]		2-furyl		96
5[a]		4-chlorophenyl		92
6[b]		4-chlorophenyl		93
7[b]		2-thienyl		50
8[b]		2-furyl		79
9[a]		2-methyl-1-propenyl		68
10[b]		2-thienyl		99
11[b]		*p*-tolyl		100
12[b]		4-trifluoro-methylphenyl		94

[a] Catalyst: 5% $PdCl(PPh_3)_2(CH_2Ph)$, 2.2 equiv of CuMeSal. [b] Catalyst: 5% $Pd(PPh_3)_4$, 2.2% equiv of CuMeSal.

Ph) as the palladium source. In some cases, however, the reactions were quite sluggish and significant quantities of starting materials were recovered from the attempted couplings. In these cases, the thiomethyl ethers were replaced with the heteroaromatic thiophenyl (or thio-*p*-tolyl) ethers and $PdCl(PPh_3)_2(CH_2Ph)$ was replaced with $Pd(PPh_3)_4$, which is a more stable palladium source over prolonged reaction times. The switch from heteroaryl−SMe ethers to heteroaryl−SAr ethers was predicated on the presumption that a sluggish copper-mediated transmetalation from tin to the heteroaryl−PdL_2−SMe intermediate was the cause of the low yields. In both systems a variety of heteroaromatic sulfides and organostannanes were cross-coupled when CuMeSal was present as an activator (Table 1). No coupling reactions were observed with either allyltri-*n*-butylstannane or tetra-*n*-butylstannane.

Scheme 2. Control Experiment



equiv CuMeSal	yield
0 equiv	0%
2.2 equiv	93%

Copper(I) 3-methylsalicylate was superior to copper(I) thiophene-2-carboxylate,[7f] the only other Cu^I source investigated in this study. A control experiment demonstrated the crucial importance of copper to a successful reaction. No coupling occurred between 2-thiophenylpiperazine and 4-chlorophenyltri-*n*-butylstannane in the presence of 5% $Pd(PPh_3)_4$ in THF after 65 h, but a 93% yield of the coupling product was obtained within 21 h when 2.2 equiv of CuMeSal was present in the reaction mixture (Scheme 2).

In summary, a palladium-catalyzed, copper-mediated coupling of heteroaromatic thioethers with aryl, heteroaryl, and alkenylstannanes has been described.[10] The reaction provides a useful complement to the recently described and related coupling of heteroaromatic thioethers with boronic acids. A related study of the coupling of thiol esters with organostannanes to give ketones has been completed and will be published shortly.

Acknowledgment. The National Cancer Institute, DHHS, supported this investigation through Grant CA40157. We thank Dr. Jiri Srogl for his insight and for his preparation of some of the heteroaromatic thioethers used in this study.

Supporting Information Available: Complete description of experimental details and product characterization. This material is available free of charge via the Internet at http://pubs.acs.org.

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(6) Alphonse, F. A.; Suzenet, F.; Keromnes, A.; Lebret, B.; Guillaumet, G. *Synlett* **2002** (3), 447−450.

(7) (a) Liebeskind, L. S.; Srogl, J.; Savarin, C.; Polanco, C. *Pure Appl. Chem.* **2002**, *74*, 115−122. (b) Liebeskind, L. S.; Srogl, J. *Org. Lett.* **2002**, *4*, 979−981. (c) Kusturin, C. L.; Liebeskind, L. S.; Neumann, W. L. *Org. Lett.* **2002**, *4*, 983−985. (d) Savarin, C.; Srogl, J.; Liebeskind, L. S. *Org. Lett.* **2001**, *3*, 91−93. (e) Savarin, C.; Srogl, J.; Liebeskind, L. S. *Org. Lett.* **2000**, *2*, 3229−3231. (f) Liebeskind, L. S.; Srogl, J. *J. Am. Chem. Soc.* **2000**, *122*, 11260−11261. (g) Zhang, S.; Marshall, D.; Liebeskind, L. S. *J. Org. Chem.* **1999**, *64*, 2796−2804. (h) Srogl, J.; Liu, W.; Marshall, D.; Liebeskind, L. S. *J. Am. Chem. Soc.* **1999**, *121*, 9449−9450.

(8) We thank Professor G. Guillaumet for informing us of his related study of copper-mediated heteroaromatic thioether−organostannane cross-coupling. See the following Letter in this issue.

(9) See Supporting Information for: Savarin, C.; Srogl, J.; Liebeskind, L. S. *Org. Lett.* **2001**, *3* (1), 91−93.

(10). **Typical Experimental Procedure.** CuMeSal (100 mg, 0.466 mmol, 2.2 equiv) and $Pd(PPh_3)_4$ (12.3 mg, 0.011 mmol, 0.05 equiv) were added to a solution of 2-(phenylthio)pyrimidine (40.0 mg, 0.212 mmol, 1.0 equiv) and 2-(tri-*n*-butylstannyl)furan (83.5 mg, 0.234 mmol, 1.1 equiv) in THF (2.6 mL). The reaction mixture was stirred under nitrogen at 50 °C for 18 h, and then 5% aqueous NH_4OH (10 mL) was added and the mixture was stirred for an additional 10 min. The reaction mixture was filtered through a plug of Celite, and the filtrate was extracted with Et_2O. The organic layer was washed with brine (5 mL), dried over $MgSO_4$, and evaporated. Purification by SiO_2 column chromatography with CH_2Cl_2 gave 2-(furan-2-yl)pyrimidine (24.6 mg, 79%) as white crystals. Full details are available in Supporting Information.