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Heteroaromatic Thioether–Boronic Acid Cross-Coupling under Neutral Reaction Conditions

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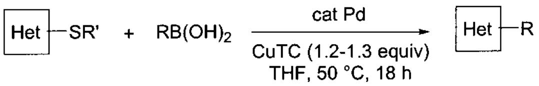
ABSTRACT



π-Deficient heteroaromatic thioethers undergo efficient palladium-catalyzed cross-coupling with boronic acids mediated by copper(I) thiophene-2-carboxylate.

Transition metal-catalyzed cross-coupling procedures have revolutionized the art and practice of organic synthesis in industry and academia.[1] The very mild reaction conditions and broad availability of diverse reaction partners underpin the versatility of the Stille,[2] Suzuki−Miyaura,[3] and Hiyama[4] cross-coupling protocols, in particular. In these important processes, organostannanes, boronic acids, and silanols are most often paired with organic halides or trifluoromethylsulfonates. The introduction of a new class of readily available reaction partner to any of these cross-coupling protocols would significantly extend the impact of these versatile processes.

The cross-coupling of heteroaromatics, although a process of great synthetic potential,[5] has not been used to its full extent due to the limited availability of the corresponding heteroaromatic halides. To fill this void, we disclose herein the palladium-catalyzed, copper(I) thiophene-2-carboxylate (CuTC) mediated, base-free coupling of boronic acids with heteroaromatic thioethers. The latter possess the attributes of excellent reactants: they are easily synthesized, readily accessible, and stable. Related base-free couplings of thiol esters[6] and alkynylthio ethers[7] with boronic acids were recently disclosed.

Table 1 depicts the coupling of a range of thioether substituted heteroaromatics with a variety of boronic acids. In most cases, palladium-catalyzed coupling of the heterocycle-SMe ether proceeded efficiently within 18 h at 50 °C in THF in the presence of at least 1 equiv of CuTC. The best results were obtained with the Pd_2dba_3/tris(2-furyl)phosphine (TFP) catalytic system. Other Pd catalysts also worked, but were less effective.

With refractory substrates, the second valence on the sulfur atom offered the important option of easy modification of the leaving group properties, a feature unusual among most other cross-coupling reactants. Thus, unreactive or less reactive SMe ether substrates were successfully "activated" by replacement of the SMe group with either the SCH_2CONH_2 or SCH_2CONMe_2 pendant ligand. For example, while 2-thiomethyl-*N*-phenyltetrazole did not react with arylboronic acids under the coupling conditions depicted in Table 1, the analogous 2-thioglycolamide derivative shown in entry 12 of Table 1 participated in a facile coupling. The

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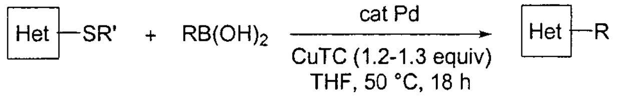
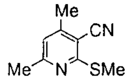
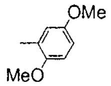
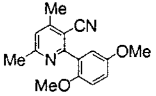
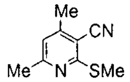
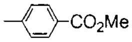
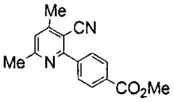
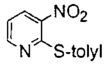
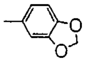
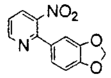
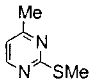
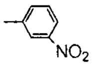
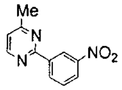
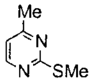
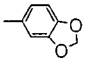
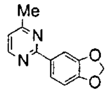
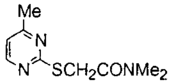
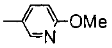
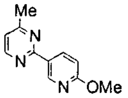
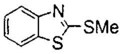
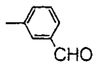
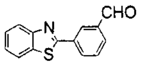
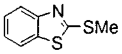
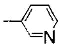
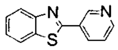
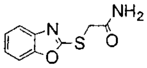
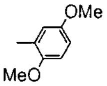
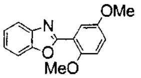
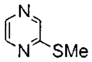
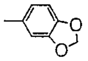
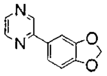
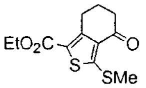
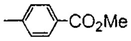
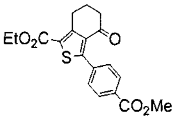
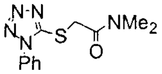
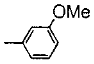
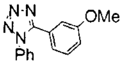
Table 1. Heteroaryl Thioether−Boronic Acid Cross-Coupling[a]



	heteroaryl thioether	boronic acid, R	product	%
1[b]				76
2[b]				72
3[b]				87
4[b]				74
5[b]				86
6[b]				71
7[b]				67
8[c]				53
9[b]				74
10[c]				64
11[b]				82
12[b]				65

[a] Thioether (0.50 mmol), boronic acid (0.55 mmol), Pd catalyst, CuTC, and, where indicated, $Zn(OAc)_2$ were placed in reaction vessel. After flushing with argon, THF was added and the reaction mixture was stirred at 50 °C for 18 h. [b] 4% Pd_2dba_3−16% TFP, 1.3 equiv of CuTC. [c] 1% Pd_2dba_3−8% TFP, 1.2 equiv of CuTC, 1.2 equiv of $Zn(OAc)_2$.

examples in entries 6 and 9 also benefited from the use of the thioglycolamide pendant. The modifiable leaving group feature of this system suggests possible applications ranging from solid support-based reagents to pendant-driven substrate recognition.

$Zn(OAc)_2$ was an essential additive in some cases. For example, treatment of 2-(methylthio)benzothiazole with 3-pyridylboronic acid, 1.6 equiv of CuTC, and 5% of Pd catalyst in THF at 50 °C yielded only starting material. Fortunately, the addition of $Zn(OAc)_2$ (1.2 equiv) to the reaction mixture dramatically changed the reaction outcome; the desired cross-coupling product was generated in 53% yield (entry 8). Another example of the beneficial effect of $Zn(OAc)_2$ was observed in the reaction of 2-(methylthio)-pyrazine (entry 10). Under the standard conditions in the presence of 4% of Pd catalyst and 1.2 equiv of copper carboxylate, reaction of 2-(methylthio)pyrazine with 3,4-methylenedioxyphenylboronic acid returned the starting thioether unchanged. However, addition of 1.2 equiv of $Zn(OAc)_2$ to the reaction mixture led to formation of the desired product in 64% yield.

Presumably, the $Zn(OAc)_2$ may function to tie up basic nitrogen atoms that potentially interfere with the reaction system. In the case of 3-pyridylboronic acid, which apparently exists in a zwitterionic form, $Zn(OAc)_2$ could bind to the 3-pyridinyl nitrogen and prevent deprotonation of the boronic acid. The latter is known to interfere with Cu^I carboxylate-mediated thiol ester−boronic acid coupling.[6] $Zn(OAc)_2$ was also effective in the case of the 2-(methylmercapto)pyrazine (entry 10), perhaps by tying up the pyrazine 4-nitrogen and preventing it from interfering with catalysis (by coordination of Cu(I) or by deprotonation of the boronic acid).

In contrast to 2-(methylthio)pyrazine (entry 10, Table 1), 2-bromopyrazine did not react with boronic acids under the current reaction conditions. Similarly, while 2-methylthio-3-nitropyridine easily reacted with 3,4-dimethoxyphenylboronic acid giving the desired coupling product in 87% yield (entry 3, Table 1), the 2-chloro derivative provided only traces of product under the same conditions. Conversely, no reaction was observed (starting material was recovered) when heterocyclic thioethers were subjected to typical Suzuki−Miyaura reaction conditions (2-methylthiobenzothiazole, 2% $Pd(PPh_3)_4$, K_2CO_3, dioxane, 60 °C, 18 h). This comparison underscores the difference between the Suzuki−Miyaura protocol and the base-free CuTC-mediated reaction system described here. In accord with previously reported observations,[6] addition of halides (NaI, LiBr, LiCl, NaCl, Bu_4NBr) to the CuTC-mediated process had a negative impact on the reaction outcome, stopping the reaction even when substoichiometric amounts were used.

Simple aryl thioethers showed limited reactivity in the current cross-coupling system: only those with electron-withdrawing substituents provided cross-coupling products, and only in low yields. Suspecting a sluggish oxidative addition to palladium by the relatively electron-rich aryl thioethers (in contrast to the more electron-deficient heteroaryl thioethers), nickel catalysts were explored. Unfortunately, although a low-valent nickel catalyst is competent at oxidative addition to aromatic thioethers,[8] simply switching from a palladium to a nickel catalyst did not solve the reactivity problem for the boronic acid−aromatic thioether coupling.

Comparison of the cross-coupling of thioorganic substrates using the current palladium-catalyzed, nonnucleophilic, base-free boronic acid system with that using the more potent organomagnesium[9] and -zinc[10] reagents in either a nickel- or palladium-catalyzed protocol is appropriate. The success

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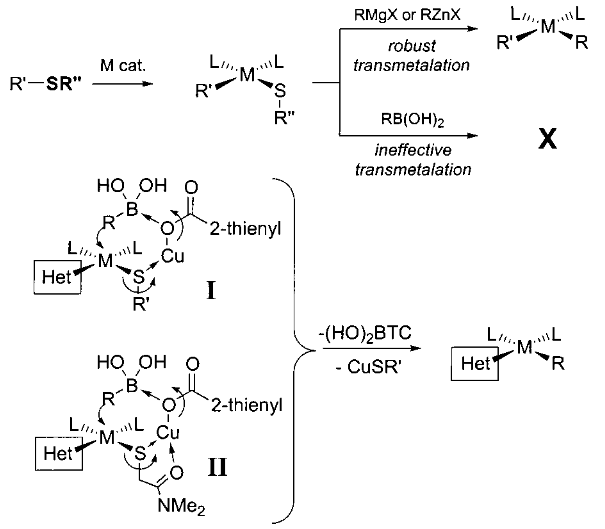
(8) Osakada, K.; Maeda, M.; Nakamura, Y.; Yamamoto, T.; Yamamoto, A. *J. Chem. Soc., Chem. Commun.* **1986**, 442−443.

Scheme 1



of these latter, more nucleophilic reagents can be attributed to an effective transmetalation from RMgX or RZnX to the $R'ML_2SR''$ (M = Pd, Ni) intermediate (Scheme 1). Transmetalation of the more reactive Grignard reagent may be facilitated through formation of an "ate" intermediate, while transmetalation of the organozinc reagent benefits from polarization of the Pd−S bond by the thiophilic Zn(+2).[10b]

In contrast, the mechanism of the current heteroaryl thioether−boronic acid coupling process must take into account the unique ability of the Cu(I) carboxylate, but neither Cu(I) halides nor carboxylates of other metals, to mediate the reaction. Oxidative addition of the heteroaryl−SR′ bond to palladium will provide an intermediate $HetPdL_2$-SR′, which must undergo room temperature, baseless transmetalation with $R^1B(OH)_2$. This process, and the unique requirement of a Cu(I) carboxylate like CuTC, are nicely accommodated by the intermediate **I** depicted in Scheme 1. The Cu(I) carboxylate serves the dual role of simultaneously polarizing the Pd−S bond through Cu(I) coordination to S while activating the trivalent boron through coordination of carboxylate to B. The beneficial effect of the thioglycolamide pendants is attributed to chelation of Cu(I), as shown in intermediate **II** in Scheme 1.

In conclusion, a new method for the cross-coupling of heteroaromatic thioethers with boronic acids has been described. The readily available starting materials and mild and neutral reaction conditions suggest that this procedure could find wide applicability in synthesis and drug design.[11]

Acknowledgment. The National Cancer Institute, DHHS supported this investigation through Grant CA40157. We thank Dr. Paul Reider of Merck Pharmaceutical Co., Dr. Gary Allred of Frontier Scientific, Inc., and Dr. William Neumann of Pharmacia for their interest in and support of this work.

Supporting Information Available: A 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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(9) Fiandanese, V.; Marchese, G.; Naso, F.; Ronzini, L. *J. Chem. Soc., Chem. Commun.* **1982**, 647. Wenkert, E.; Leftin, M.; Michelotti, E. L. *J. Chem. Soc., Chem. Commun.* **1984**, 617. Okamura, H.; Miura, M.; Takei, H. *Tetrahedron Lett.* **1979**, 43. Luh, T. Y. *Acc. Chem. Res.* **1991**, *24*, 257.

(10) (a) Angiolelli, M. E., Casalnuovo, A. L., Selby, T. P. *Synlett* **2000** (6), 905−907. (b) Srogl, J.; Liu, W.; Marshall, D.; Liebeskind, L. S. *J. Am. Chem. Soc.* **1999**, *121*, 9449−9450.

(11) **Typical experimental procedure:** 2-Methylthio-4-methylpyrimidine (0.070 g, 0.50 mmol), 3-nitrophenylboronic acid (0.087 g, 0.55 mmol), Pd_2-dba_3·$CHCl_3$ (0.010 g, 0.01 mmol), TFP (0.019 g, 0.08 mmol), and CuTC (0.125 g, 0.65 mmol) were placed in a reaction vessel, and the vessel was flushed with argon. THF was added, and the reaction mixture was stirred at 50 °C for 18 h. Et_2O (15 mL) was added, and the mixture was extracted with a saturated aqueous solution of NH_4OH (3 × 20 mL). The organic layer was then dried with $MgSO_4$, and solid residues after evaporation were subjected to preparative plate silica gel chromatography (gradient of hexanes: ether:acetone) giving the desired product (0.076 g, 71%) as light yellow crystals. Full details are available in the Supporting Information.