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Nonbasic, Room Temperature, Palladium-Catalyzed Coupling of Aryl and Alkenyl Iodides with Boronic Acids Mediated by Copper(I) Thiophene-2-carboxylate (CuTC)

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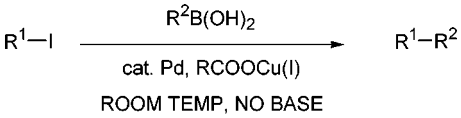
ABSTRACT



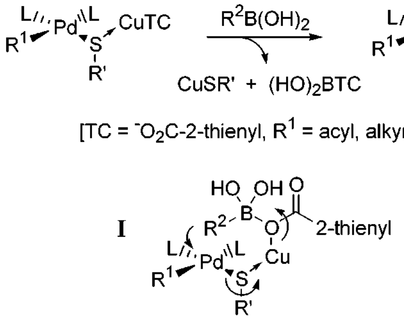
$$R^1{-}I \xrightarrow[\text{cat. Pd, RCOOCu(I)}]{R^2B(OH)_2} R^1{-}R^2$$

ROOM TEMP, NO BASE

A new protocol for the palladium-catalyzed, copper-mediated coupling of aryl and alkenyl iodides with boronic acids is described. As an alternative to the well-known and widely used Suzuki cross-coupling, this reaction occurs in the absence of a base at room temperature and should be particularly useful for the construction of substrates bearing base-sensitive and thermally sensitive moieties.

Suzuki−Miyaura cross-coupling reactions of aryl and alkenyl iodides with boronic acids have been extensively described.[1] Various reaction conditions (catalysts, bases, solvents, temperature) have been used to afford the desired product in good to excellent yields. All of these protocols, however, require the use of a base, and with only a few exceptions due to specific palladium/ligand systems,[2] high temperature is needed for efficient reaction rates. We recently described two Cu^I carboxylate-mediated, Pd-catalyzed cross-coupling reactions of boronic acids with thioorganics: reaction with thiol esters gives ketones[3] and reaction with 1-thioalkynes produces unsymmetrical alkynes.[4,5] These mechanistically novel reactions take place under nonbasic conditions. The key to the reaction is the chemoselective, copper carboxylate-mediated transmetalation from the boronic acid to the organopalladium thiolate intermediate (Scheme 1). Because non-carboxylate Cu^I salts (CuCl, CuBr, CuI, CuCN) were ineffective, it appeared that the Cu^I carboxylate served a dual role in effecting transmetalation from boron to palladium:

Scheme 1. CuTC-Mediated B to Pd Transmetalation



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[1] (a) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457−2483. (b) Suzuki, A. *Pure Appl. Chem.* **1994**, *66*, 2, 213−222. (c) Martin, A. R.; Yang, Y. *Acta Chem. Scand.* **1993**, *47*, 221−230. (d) Li, Y.; Hong, X. M.; Collard, D. M.; El-Sayed, M. A. *Org. Lett.* **2000**, *2* (15), 2385−2388.

[2] (a) Littke, A.; Dai, C.; Fu, G. C. *J. Am. Chem. Soc.* **2000**, *122*, 4020−4028. (b) Bei, X.; Turner, H. W.; Weinberrg, W.; Guram, A. S. *J. Org. Chem.* **1999**, *64*, 6797−6803.

[3] Srogl, J.; Liebeskind, L. S. *J. Am. Chem. Soc.* **2000**, *122* (45), 11260−11261.

[4] Savarin, C.; Srogl, J.; Liebeskind, L. S. *Org. Lett.* **2001**, *3* (1), 91−93.

[5] Related Cu^I carboxylate-mediated couplings of boronic acids with heteroaryl thioethers and thioimidates will be disclosed shortly.

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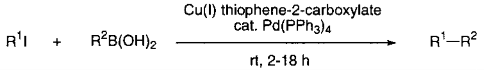
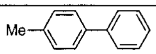
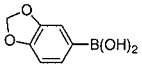
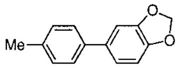
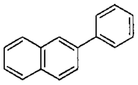
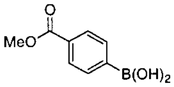
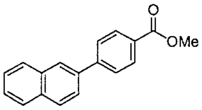
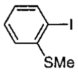
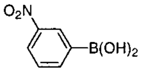
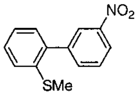
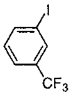
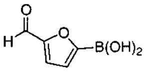
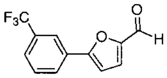
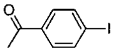
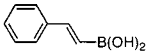
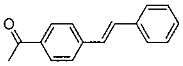
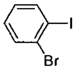
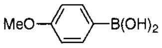
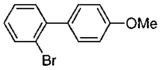
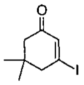
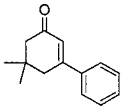
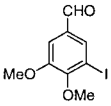
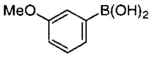
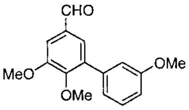
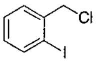
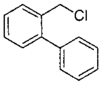
Table 1. Room Temperature, Nonbasic Pd-Catalyzed Cross-Coupling of Boronic Acids Mediated by CuTC



entry	R^1I	$R^2B(OH)_2$	product	cmpd #	yield (%)
1	4-iodotoluene	$PhB(OH)_2$		**1**	90
2	4-iodotoluene			**2**	73
3	2-iodonaphthalene	$PhB(OH)_2$		**3**	93
4	2-iodonaphthalene			**4**	72
5				**5**	96
6				**6**	81
7				**7**	89
8				**8**	81
9		$PhB(OH)_2$		**9**	85
10				**10**	73
11		$PhB(OH)_2$		**11**	72

it polarized the Pd–S bond through Cu^I coordination to S and it simultaneously activated the trivalent boron through coordination of carboxylate to B (structure **I** in Scheme 1).

This analysis suggests that Cu^I carboxylates should uniquely facilitate boron-based cross-coupling with other "cuprophilic" reaction partners under nonbasic reaction conditions. Supporting that notion, we report herein the efficient, *nonbasic*,[6] *room temperature* coupling of aryl and alkenyl iodides with boronic acids mediated by copper(I) thiophene-2-carboxylate.

Table 1 depicts the room temperature coupling of boronic acids (1.0–1.2 equiv) with aryl and vinyl iodides in the presence of catalytic $Pd(PPh_3)_4$ and Cu^I thiophene-2-carboxylate (CuTC; 1.0–1.2 equiv). The coupling reaction proceeded within 2–18 h at room temperature in good to excellent isolated yields (72–96%) and was compatible with electron-withdrawing and -donating groups on both the iodo substrates and the arylboronic acids. This Cu^I carboxylate-mediated coupling was very selective under the conditions studied—reaction was observed only at the carbon–iodine bond. Bromo, chloro, and triflate derivatives did not couple, even up to 50 °C (neither chlorobenzene, 4-bromoacetophenone, nor 2-naphthyl trifluoromethylsulfonate gave coupling product; see also Table 1, entry 8). Neither did aryl thioethers react (Table 1, entry 5), in contrast to thiol esters[3] and 1-thioalkynyl ethers,[4] which undergo palladium-catalyzed, CuTC-mediated coupling with boronic acids. A refractory oxidative addition of aryl thioethers to palladium is the likely source of nonreactivity.[7]

As one example of the benefit of these new, nonbasic conditions, 2-iodobenzyl chloride was subjected to $Pd(PPh_3)_4$-catalyzed cross-coupling with $PhB(OH)_2$ under three different conditions (Scheme 2). In the presence of 1.1 equiv of CuTC at room temperature in THF, iodo-specific coupling occurred to generate 2-phenylbenzyl chloride in 72% within 12 h. Substituting K_2CO_3 (3.3 equiv) for CuTC under the same

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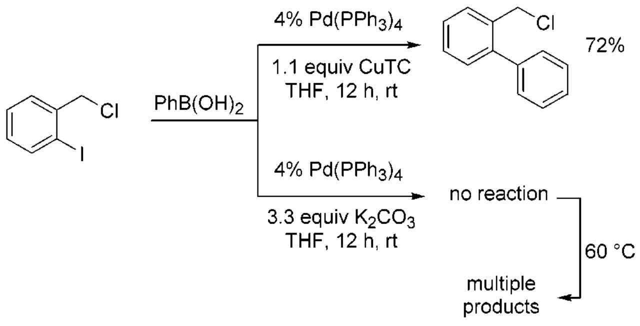
[6] The pH of distilled water is unchanged in the presence of a CuTC slurry.

[7] Mann, G.; Baranano, D.; Hartwig, J. F.; Rheingold, A. L.; Guzei, I. A. *J. Am. Chem. Soc.* **1998**, *120*, 9205–9219.

Scheme 2. A Comparison of the CuTC-Mediated Coupling with Traditional Suzuki Conditions



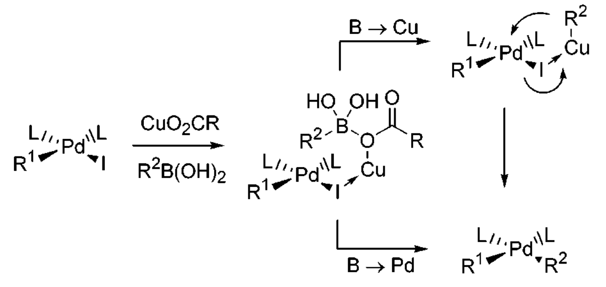
conditions gave no reaction; only starting material was observed by GC/MS analysis. Raising the reaction temperature to 60 °C led to the formation of multiple products (including 2-phenylbenzyl chloride and 2-benzylbiphenyl) and some recovered starting material.

Various palladium catalysts were assayed. Among Pd$(PPh_3)_4$, Pd_2dba_3 with P(cyclohexyl)$_3$, and Pd_2dba_3 with TFP, $Pd(PPh_3)_4$ was the most efficient; the other palladium catalysts afforded complete reactions but required longer time at room temperature. Both Cu^I thiophene-2-carboxylate and Cu^I 3-methylsalicylate were studied. Although aryl iodides are known to undergo Ullmann reductive coupling in the presence of stoichiometric RCOOCu(I) at or below room temperature,[8] the homocoupling byproduct was not observed with Cu^I thiophene-1-carboxylate (CuTC); only the cross-coupling product of the boronic acid was detected. In contrast, some Ullmann reductive coupling product was detected with Cu^I 3-methylsalicylate. Different solvents (THF, dioxane, *N*,*N*-dimethylacetamide, ethanol, toluene) could be used, although THF and dioxane gave the fastest reaction at room temperature.

The unique ability of CuTC to mediate the room temperature cross-coupling is apparent from comparative and control reactions (and from the reactions depicted in Scheme 2). Palladium-catalyzed reaction of *p*-iodotoluene with phenylboronic acid in the presence of stoichiometric CuTC led to quantitative formation of product (no product was observed if palladium or copper carboxylate was omitted). Reaction with substoichiometric CuTC led to incomplete conversion. Both the copper and the counterion are important; no product was observed when 1 equiv of NaTC was used in place of CuTC, even at 50 °C. No coupling product was observed within 14 h using CuCl, CuI, or CuCN at room temperature.

The mechanism of this process is presumed to begin with room temperature oxidative addition of the carbon−iodine bond to palladium to provide an $ArPdL_2I$ intermediate. This intermediate must undergo a CuTC-mediated, room temperature, base-free transmetalation with $R^1B(OH)_2$. The transmetalation from boron to palladium can occur, either by prior boron to copper transmetalation or directly from the arylpalladium iodide−CuTC complex (Scheme 3). It was previously pointed out that naphthalene-2-boronic acid suffers rapid (2 h) protodeborylation to naphthalene upon treatment with 1 equiv of CuTC in THF at room temperature.[3] This observation provides strong support for direct boron to copper transmetalation; however, the absence of any significant protodeborylation product under the very similar cross-coupling conditions argues against a simple boron to copper transmetalation. Rather, we suggest an intimate interaction of $RPdL_2I$ with both CuTC and the boronic acid as depicted in Scheme 3 (Mori and Hiyama suggested a similar cyclic transmetalation process for the palladium-catalyzed, Ag_2O-mediated coupling of silanols with aryl and vinyl iodides[9]). If prior transmetalation from boron to the Pd−I-bound Cu^I does occur, protodemetalation from this intermediate must be slow relative to a fast internal transfer from copper to palladium. Alternatively, direct transmetalation from boron to palladium is feasible. CuI, which is not an effective cofactor for the coupling (as shown by the previous control experiment), must be generated during this process and subsequently precipitates from solution.

Scheme 3



We note again that no reaction took place when CuTC was substituted with NaTC, even at 50 °C, nor in the presence of excess K_2CO_3 at room temperature, which makes an alternate transmetalation mechanism proceeding by simple RCO_2^--induced nucleophilic activation of the boronic acid unlikely.

In conclusion, a new, base-free protocol for the coupling of aryl and alkenyl iodides with boronic acids is reported. The reaction proceeds within a few hours at room temper-

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(8) Zhang, S.; Zhang, D.; Liebeskind, L. S. *J. Org. Chem.* **1997**, *62*, 2312−2313.

(9) Hirabayashi, K.; Mori, A.; Kawashima, J.; Suguro, M.; Nishihara, Y.; Hiyama, T. *J. Org. Chem.* **2000**, *65*, 5342−5349.

(10) **General experimental procedure.** The boronic acid (1.0−1.2 equiv), Pd catalyst (2−5%), CuTC (1.0−1.2 equiv), and aryl or alkenyl iodide (1.0 equiv) were placed in a 25 mL Schlenk tube. After a vacuum and argon cycle, dry and degassed THF was added (the use of the Schlenk tube with dry, degassed solvents is not critical, although yields are higher with these precautions). When one of the starting materials was an oil, it was added by syringe after the solvent. The reaction mixture was stirred for 2−12 h at room temperature. Following the general procedure, dry and degassed THF (8.0 mL) was added to 4-methyliodobenzene (494 mg, 2.3 mmol, 1.0 equiv), phenylboronic acid (304 mg, 2.5 mmol, 1.1 equiv), Pd$(PPh_3)_4$ (81 mg, 0.7 mmol, 3%), and CuTC (476 mg, 2.5 mmol, 1.1 equiv). The reaction was stirred for 3 h at room temperature. After purification by radial chromatography (hexanes), **1** (348 mg, 2.1 mmol, 90%) was obtained as a white solid.

ature and efficiently generates functionalized molecules in high yields.[10]

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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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