

Desulfitative Carbon–Carbon Cross-Coupling of Thioamide Fragments with Boronic Acids

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Abstract: A novel and general carbon–carbon cross-coupling reaction between cyclic thioamides and boronic acids is described. The reaction is catalytic in palladium(0) and requires stoichiometric amounts of a copper(I) carboxylate as metal cofactor. The mode of cross-coupling in the reaction of cyclic thioamides with boronic acids is easily tunable between carbon–carbon and carbon–sulfur cross-coupling. While the catalytic palladium(0)/copper(I) system provides carbon–carbon bond formation with extrusion of sulfur, stoichiometric quantities of copper(II) under air mediate carbon–sulfur bond formation.

Keywords: copper; cross-coupling; homogeneous catalysis; microwave heating; palladium; thioamides

Transition metal-catalyzed carbon–carbon and carbon–heteroatom cross-coupling reactions belong to the most powerful and flexible transformations known to organic chemists and have revolutionized the art and practice of synthesis in the last two decades.^[1] Among the plethora of cross-coupling procedures known today, protocols involving boronic acids as coupling partners are becoming increasingly popular.^[2] The facts that most boronic acids are air- and moisture-stable, of relatively low toxicity, and are nowadays commercially available, make cross-coupling chemistry utilizing these reagents highly attractive.

One of the most valuable transformations in this context arguably is the Pd-catalyzed Suzuki–Miyaura biaryl cross-coupling involving aryl halides and boronic acids as coupling partners.^[1,3] In addition to aryl halides, the use of organosulfur compounds as electrophilic reaction partners has recently also been report-

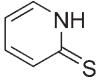
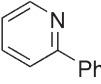
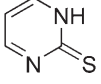
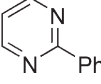
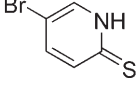
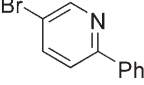
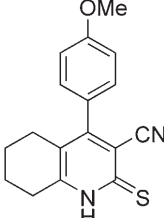
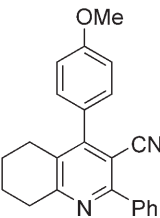
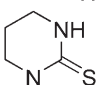
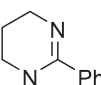
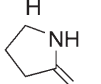
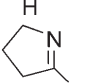
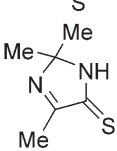
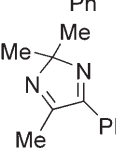
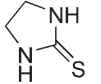
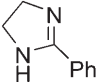
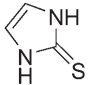
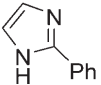
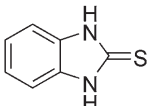
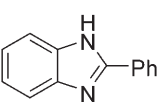
ed.^[4] Notably, sulfonyl chlorides,^[5] sulfones,^[6] sulfonium salts,^[7] thioalkynes,^[8] thiol esters^[9] and thioethers^[10,11] have all been shown to undergo efficient Pd-catalyzed desulfitative cross-couplings with boronic acids leading to the formation of a new carbon–carbon bond with concomitant extrusion of sulfur.^[4–11]

In our laboratories we have recently discovered^[11] an unprecedented direct Pd-catalyzed, Cu(I)-mediated carbon–carbon cross-coupling of a cyclic thiourea with a boronic acid under non-basic Liebeskind–Srogl^[7–10,12] reaction conditions. The observed transition metal-catalyzed desulfitative carbon–carbon coupling of a thiourea containing a latent free thiol functionality can be considered as highly unusual,^[13] since here the competing carbon–sulfur cross-coupling is typically the preferred pathway.^[11,14–17] Because of the potential synthetic utility and interesting mechanistic implications of this novel carbon–carbon cross-coupling reaction we became interested in the scope and limitations of this synthetic transformation and now report the development of a general synthetic method for the coupling of cyclic thioamide fragments with boronic acids under nonbasic reaction conditions.

As a model system for our optimization studies we first investigated the potential for Pd-catalyzed, Cu(I)-mediated carbon–carbon cross-coupling between pyridine-2(1*H*)-thione and phenylboronic acid (Table 1, entry 1). Building on our previous experience,^[11] the reaction conditions were refined using controlled microwave heating (MW) in sealed vessels.^[18] One of the best sets of conditions for coupling of the pyridine-2(1*H*)-thione substrate utilized 1.2 equivs. of phenylboronic acid, 4.0 mol % [Pd(PPh₃)₄] as a catalyst, and 3.0 equivs. of Cu(I) thiophene-2-carboxylate (CuTC)^[10] as a metal cofactor in dry THF. An inert atmosphere, preventing oxidation of the Cu(I) cofactor to a Cu(II) species is also advantageous in order to achieve high product yields. The cleanest conversions were achieved by exposing the heterogeneous reaction mixture to microwave heating

Table 1. Pd(0)-catalyzed, Cu(I)-mediated carbon–carbon cross-coupling of cyclic thioamide fragments with phenylboronic acid.^[a]

1. 4 mol % [Pd(PPh₃)₄]
 3.0 equivs. CuTC, THF
 MW, 100 °C, 1 h
 2. + 4 mol % [Pd(PPh₃)₄]
 MW, 100 °C, 1 h

Entry	Substrate	Product	Yield ^[b] [%]
1			90 (71) ^[c]
2			83
3			87
4			97
5			96
6			75
7			52
8			93
9			8
10			67

^[a] For a general procedure, see the Experimental Section.^[b] Isolated yields after column chromatography.^[c] Yield after 1 h.

at 100 °C for 1 h, leading to a 71 % isolated yield of the anticipated 2-phenylpyridine product. Higher reaction temperatures did not improve the efficiency of this transformation, while shorter reaction times led

to incomplete conversions. In order to further improve the product yield in this coupling process an additional quantity of the Pd catalyst (4 mol %) was added to the reaction mixture after the first heating cycle. The vessel was subsequently resubjected to microwave heating at 100 °C for an additional hour. The application of this two-step procedure ultimately led to a 90 % isolated yield of the 2-phenylpyridine coupling product after column chromatography. Careful monitoring of the crude reaction mixture demonstrated that the coupling was completely selective for the carbon–carbon pathway, and that no carbon–sulfur cross-coupling product (see below) was observed.

We were indeed pleased to find that pyridine-2(1*H*)-thione did undergo the anticipated carbon–carbon cross-coupling with phenylboronic acid in high yield, which indicated that these desulfative couplings are not restricted to cyclic thioureas^[11] but are also possible with thioamide fragments embedded into an aromatic heterocycle. In order to investigate the scope of this transformation we selected a small but diverse set of heterocycles containing thioamide fragments and performed cross-couplings with phenylboronic acid applying our optimized set of conditions. As can be seen from the data presented in Table 1, successful cross-coupling was achieved with a variety of aromatic and non-aromatic six-membered and five-membered heterocycles containing thioamide fragments. In general, good to high product yields were obtained using the standard reaction conditions specified above. The only exception proved to be 1,3-dihydroimidazole-2-thione (entry 9) which provided 2-phenyl-1*H*-imidazole in a very modest 8 % yield. The success of the Pd-catalyzed, Cu(I)-mediated carbon–carbon cross-coupling is apparently independent on the ring size, aromaticity/non-aromaticity, the presence of additional heteroatoms or other functional groups (Table 1, entries 1–10).^[19] However, the structural integrity of the thioamide motif needs to be preserved for an efficient carbon–carbon cross-coupling. Thus, attempted cross-coupling of 4-pyridinethiol with phenylboronic acid produced only 15 % of the cross-coupled product, whereas the isomeric 2-pyridinethiol (entry 1) provided a 90 % yield under identical reaction conditions. Attempted coupling of simple aromatic thiols (e.g., *p*-methylthiophenol) with phenylboronic acid using the Pd(0)-catalyzed, Cu(I)-mediated protocol led to no detectable carbon–carbon cross-coupling products.

The mechanism of this desulfative cross-coupling involving cyclic thioamides is related to the traditional Liebeskind–Srogl protocols,^[7–12] in particular to the cross-coupling of *N*-heteroaromatic thioethers with boronic acids.^[10] The reaction requires both the Pd(0) catalyst and the specific Cu(I) carboxylate additive (CuTC) in stoichiometric quantities. Carbon–carbon coupling products were not obtained when CuTC was

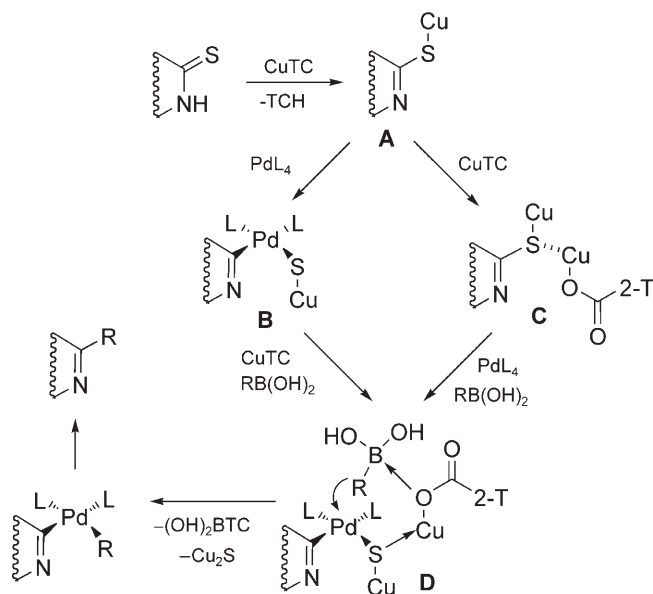


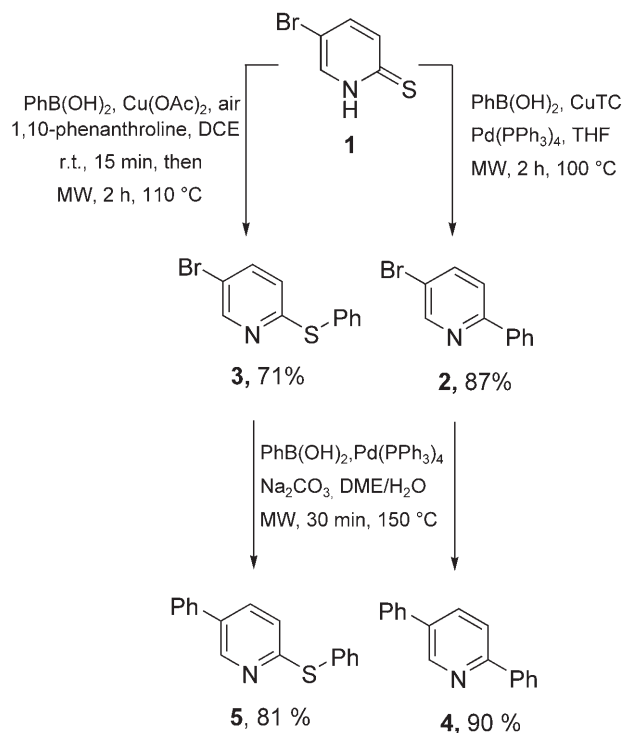
Figure 1. Proposed mechanism for the Pd(0)-catalyzed, Cu(I)-mediated carbon-carbon cross-coupling of thioamides and boronic acids. 2-*T*=2-thienyl. TC=thiophene-2-carboxylate.

replaced with other Cu(I) salts such as CuBr or CuCl. The unique requirement of a Cu(I) carboxylate such as CuTC is accommodated by the intermediate **D** shown in Figure 1: the Cu(I) carboxylate simultaneously polarizes the Pd–S bond through Cu(I) coordination to S while activating the trivalent boron through coordination of the carboxylate to B.^[7–12]

In the case of thioamides, however, we experienced that 2–3 equivs. of the CuTC cofactor needed to be employed in order to achieve high conversions. We therefore propose the initial formation of a Cu(I) thiolate species of type **A**^[20] which then can undergo either oxidative addition to the Pd(0) catalyst^[21] (**B**) or further complexation with an additional equivalent of the CuTC cofactor (**C**). Both pathways will ultimately lead to the key intermediate **D** which subsequently undergoes baseless transmetalation with extrusion of Cu₂S followed by reductive elimination in order to provide the carbon-carbon cross-coupled products.

A unique advantage of using thioamides as starting materials for desulfurative carbon-carbon cross-coupling reactions is the fact that the presence of the latent thiol functionality will also allow carbon-sulfur bond formation under suitable reaction conditions. For cyclic thioamides, Cu-mediated carbon-sulfur cross-coupling reactions with boronic acids have been described,^[11,15] although the mechanism for these Cu-mediated transformations is still under debate.^[16]

In order to explore the suitability of cyclic thioamides for carbon-sulfur bond formation we have selected 5-bromopyridine-2(1*H*)-thione (**1**) as a model



Scheme 1. Orthogonal reactivity between carbon-carbon, carbon-sulfur and Suzuki-Miyaura biaryl cross-couplings in 5-bromopyridine-2(1*H*)-thione.

substrate. In addition to a thioamide fragment, this organosulfur compound also contained a Suzuki-active bromide which allowed us to evaluate the anticipated^[22] orthogonality of both the carbon-carbon and carbon-sulfur cross-couplings to the base-catalyzed Suzuki-Miyaura biaryl coupling.^[3]

Using our optimized conditions for Pd-catalyzed desulfurative carbon-carbon cross-coupling (Table 1), 5-bromopyridine-2(1*H*)-thione (**1**) was readily converted into 5-bromo-2-phenylpyridine (**2**) by treatment with phenylboronic acid in 87% yield (Scheme 1). There was no evidence for a competing Suzuki-Miyaura cross-coupling at the bromide position. For the Pd(0)/Cu(I) coupling pathway, this unique selectivity is due to the use of CuTC as a metal cofactor of higher thiophilicity than the Pd catalyst and by the neutral reaction conditions.^[22]

To gain a mechanistic insight into the alternative transition metal-mediated carbon-sulfur cross-coupling pathway we have also performed the cross-coupling of **1** with phenylboronic acid (4.0 equivs.) using stoichiometric quantities of Cu(OAc)₂ in combination with 1,10-phenanthroline as a ligand.^[15] The expected carbon-sulfur cross-coupling product **3** was obtained in 71% yield following a protocol that involved initial *in situ* room temperature oxidation of the thiol to its disulfide promoted by Cu(II) and air, followed by microwave heating to 110 °C for 2 h. Careful HPLC

monitoring of the crude reaction mixture demonstrated that no competing carbon–carbon coupling occurs at the thioamide or bromide positions in these Pd-free transformations. Coupling at the reactive heteroaryl bromide position, however, was achieved by performing base-catalyzed Suzuki–Miyaura cross-couplings with aryl bromides **2** and **3**. The expected biaryl products **4** and **5** were obtained in excellent yields (Scheme 1).

As far as the mechanism for carbon–sulfur cross-coupling is concerned we suggest that for cyclic thioamides a mechanism that involves initial oxidation of the thioamide to a disulfide species promoted by the Cu(II) reagent is in operation.^[16b] The transient formation of a disulfide species in the conversion of thioamide **1** to the cross-coupled product **3** was clearly evident by monitoring the reaction mixture by HPLC and confirmed by an independent synthesis. As recently suggested,^[16b,23] the disulfide may subsequently undergo Cu(I)-catalyzed cross-coupling with the boronic acid to produce the desired sulfide **3** in addition to equal amounts of a catalytically inactive Cu(I) thiolate (**A**, Figure 1), resulting in the observed empirical requirement for stoichiometric amounts of Cu(I). We have confirmed by an independent experiment that the disulfide intermediate undergoes efficient carbon–sulfur cross-coupling with phenylboronic acid in the presence of a stoichiometric amount of a Cu(I) species such as CuTC. Overall product yields higher than 50% however, in this process can only be realized *in the presence of air*, if the Cu(I) thiolate is then presumably oxidized to a Cu(II) species which is able to undergo further coupling with the boronic acid as recently proposed by Taniguchi.^[22]

In conclusion, we have developed a general Pd-catalyzed protocol for the desulfative carbon–carbon cross-coupling of cyclic thioamides with boronic acids. The method is applicable to a range of aromatic and non-aromatic six-membered and five-membered cyclic thioamides. We have also shown that the selectivity of cyclic thioamides in their cross-couplings with boronic acids can be tuned either toward carbon–carbon cross-coupling using non-oxidative Pd(0)/Cu(I) conditions, or toward carbon–sulfur cross-coupling employing Cu(II) in the presence of oxygen.

Experimental Section

General Procedure for the Pd(0)-Catalyzed, Cu(I)-Mediated Carbon–Carbon Cross-Coupling of Thioamides with Phenylboronic Acid (Table 1)

A dry microwave process vial was charged with a stir bar. To the vessel were added the corresponding thioamide (0.18 mmol), PhB(OH)₂ (26.3 mg, 0.22 mmol), Cu(I) thiophene-2-carboxylate (103 mg, 0.54 mmol) and [Pd(PPh₃)₄]

(8.3 mg, 0.007 mmol, 4 mol%). The reaction vessel was flushed with Ar and sealed. Through the septum anhydrous and degassed THF (1.8 mL) was added. The mixture was subsequently heated in a microwave reactor at 100 °C for 1 h. After this period an additional amount of Pd catalyst (8.3 mg, 0.007 mmol, 4 mol%) was added and the reaction mixture was again heated at 100 °C for 1 h. After cooling, the solvent was evaporated and CHCl₃ (90 mL) was added. The crude reaction mixture was subsequently washed with 25% aqueous ammonia (3 × 30 mL). The aqueous ammonium layer was reextracted with CHCl₃ (3 × 30 mL). The combined organic phase was dried with MgSO₄ and the residue after evaporation purified by flash chromatography. Further details can be found in the Supporting Information.

Procedure for Carbon–Sulfur Cross-Coupling of 5-Bromopyridine-(1*H*)-thione (**1**) with Phenylboronic Acid (Scheme 1)

A microwave process vial was charged with a stir bar. To the vessel were added 5-bromopyridine-(1*H*)-thione **1** (30 mg, 0.16 mmol), PhB(OH)₂ (77 mg, 0.63 mmol), Cu(OAc)₂ (28.7 mg, 0.16 mmol), 1,10-phenanthroline (56.9 mg, 0.32 mmol) and 1,2-dichloroethane (1.5 mL). The reaction mixture was stirred under air. After 15 min the reaction vessel was sealed and irradiated at 110 °C for 2 h. After cooling, the mixture was transferred to a round-bottom flask, and was adsorbed on silica gel. The residue was purified by flash chromatography on silica gel (CH₂Cl₂/hexanes 1:1) to provide 5-bromo-2-(phenylthio)pyridine **3**^[11] as a semi-solid; yield: 71%. ¹H NMR ([DMSO-*d*₆, 360 MHz): δ = 8.53 (d, *J* = 2.5 Hz, 1H), 7.88 (dd, *J*₁ = 8.6 Hz, *J*₂ = 2.5 Hz, 1H), 7.60–7.57 (m, 2H), 7.51–7.49 (m, 3H), 6.91 (d, *J* = 8.6 Hz, 1H); MS (pos. APCI): *m/z* = 267.9.

Supporting Information

General experimental details and characterization data (NMR, MS) for all new products.

Acknowledgements

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