C–C Coupling

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Copper-Catalyzed C–C Coupling of Thiol Esters and Boronic Acids under Aerobic Conditions

*Hana Prokopcová and C. Oliver Kappe**

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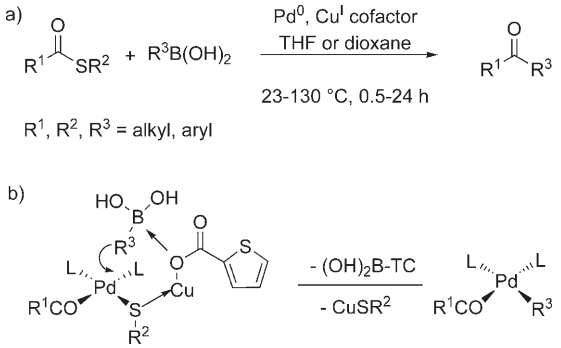
Transition-metal-catalyzed C–C bond forming reactions have revolutionized the art and practice of organic synthesis in the last two decades.[1] The generally mild reaction conditions, high functional group tolerance, and broad availability of starting materials have contributed to the success of these methods. Among the ever increasing number of published transition-metal-catalyzed C–C cross-coupling procedures, protocols involving boronic acids as coupling partners have a prominent role.[2] The fact that most boronic acids are air and moisture stable, are of relatively low toxicity, and are nowadays commercially available, makes cross-coupling chemistry utilizing these reagents highly attractive.[3] Arguably, one of the most valuable transformations in this context is the Pd-catalyzed Suzuki–Miyaura biaryl cross-coupling involving aryl halides and boronic acids as coupling partners under basic reaction conditions.[1,4]

In 2000 a novel and mechanistically unprecedented Pd-catalyzed C–C cross-coupling protocol for the synthesis of ketones from thiol esters and boronic acids under neutral, anaerobic conditions was reported by Liebeskind and Srogl (Scheme 1 a).[5] A key feature of this protocol is the requirement of stoichiometric amounts of a Cu^I-carboxylate species as a metal cofactor (simple Cu^I sources such as Cu^I halides are not effective). The most suitable Cu^I reagents for this purpose have proven to be copper(I) thiophene-2-carboxylate (CuTC) and copper(I) 3-methylsalicylate (CuMeSal), both of which are commercially available. A mechanistic rationalization for the Pd^0-catalyzed, Cu^I-mediated desulfitative cross-coupling is shown in Scheme 1 b.[5,6] After the oxidative addition of the Cu^I-bound thiol ester to the Pd^0 catalyst, the Cu^I-carboxylate serves the dual role of simultaneously polarizing the Pd–S bond through Cu^I coordination to the S center while activating the trivalent boron center through coordination of the carboxylate group to the B atom. Unlike the traditional Suzuki–Miyaura cross-coupling reaction[4]—where the presence of a base is essential—the nonbasic conditions in this unique Pd^0/Cu^I-mediated coupling protocol tolerate the involvement of base-sensitive starting materials and products.[7] Selective desulfitative C–C couplings can be performed even in the presence of Suzuki-active bromides.[8]

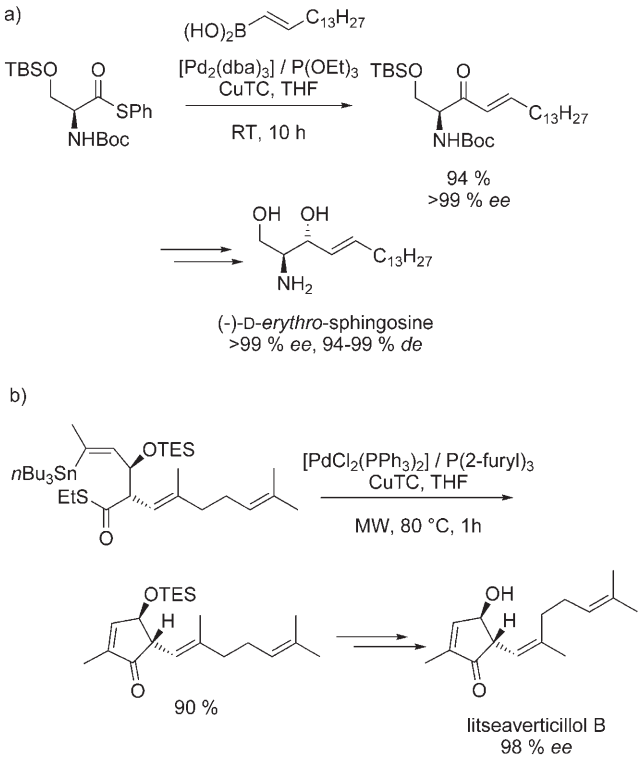


Scheme 1. a) Pd-catalyzed, Cu^I-mediated Liebeskind–Srogl ketone synthesis. b) The proposed mechanism.[6] TC = thiophene-2-carboxylate.

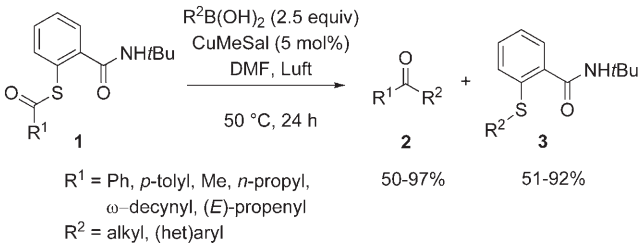
In the past few years the usefulness of this Pd-catalyzed, Cu^I-mediated C–C cross-coupling method in the absence of a base (generally referred to as Liebeskind–Srogl reaction)[9] has been explored. Successful C–C bond formation with either boronic acids or organostannanes has been achieved for a wide variety of thioorganic starting materials such as peptidylthiol esters,[10] heteroaromatic thioethers,[11] benzylthiocyanates,[12] thioalkynes,[13] bis(arylthiobutenediones),[14] methyl thiopseudourea derivatives,[15] and cyclic thioamides.[16] Two recent applications of the Liebeskind–Srogl ketone synthesis for the preparation of the natural products (−)-D-*erythro*-sphingosine[17] and litseaverticillol B[18] are highlighted in Scheme 2. In the case of litseaverticillol B, an intramolecular version of the protocol employing an organostannane precursor was applied.[18]

A surprising twist to the theme of Pd-catalyzed, Cu^I-mediated C–C couplings has been the recent disclosure of a formally related, but mechanistically unique ketone synthesis involving thiol esters and boronic acids as starting materials under neutral conditions. The publication by Villalobos, Srogl, and Liebeskind[19] describes a Cu-catalyzed thiol ester/boronic acid coupling under aerobic conditions in the absence of a Pd source (Scheme 3). Remarkably, all the published thioorganic/boronic acid couplings to date required catalytic quantities of Pd, a stoichiometric amount of Cu^I carboxylate, and were performed under strictly anaerobic

[*] H. Prokopcová, Prof. Dr. C. O. Kappe
Institute of Chemistry
Karl-Franzens University Graz
Heinrichstrasse 28, 8010 Graz (Austria)
Fax: (+43) 316-380-9840
E-mail: oliver.kappe@uni-graz.at
Homepage: http://www.maos.net



Scheme 2. Application of the Liebeskind–Srogl reaction to natural product synthesis. a) Synthesis of (−)-D-erythro-sphingosine. b) Synthesis of litseaverticillol B. TBS = *tert*-butyldimethylsilyl; dba = dibenzilideneacetone; CuTC = copper(I) thiophene-2-carboxylate; Boc = *tert*-butoxycarbonyl; TES = triethylsilyl; MW = microwave.

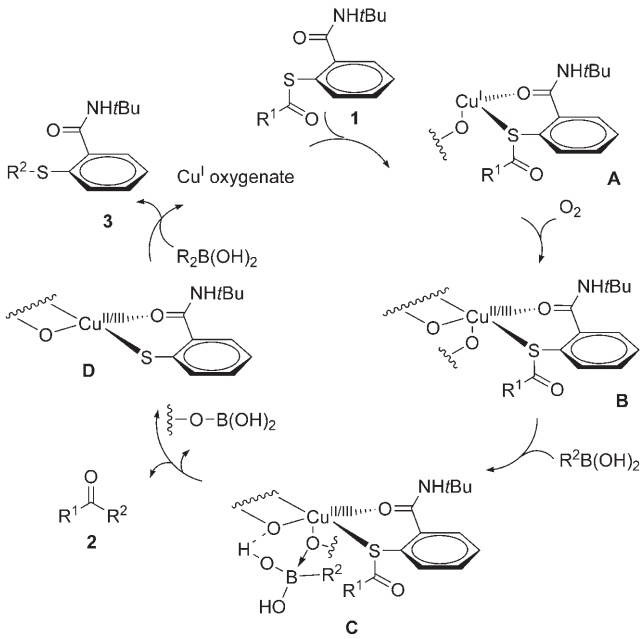


Scheme 3. Cu-catalyzed aerobic cross-coupling of thiol esters with boronic acids.

reaction conditions.[5–18] In contrast, the novel Cu-catalyzed protocol depends solely on an active Cu species without the need for a Pd source. Both the absence of Pd in the catalytic sequence and the lack of any precedent for oxidative addition of the thiol ester to Cu^{I} point to a mechanistically unparalleled system for the construction of C–C bonds.

Extensive exploratory investigations into the scope and limitations of this synthetic protocol have revealed that only thiol esters of type **1**, possessing appropriately positioned ligating S-pendant groups, participated in efficient Cu-catalyzed couplings (Scheme 3). S-aryl-NH*t*Bu thiosalicylamides **1** proved to have the optimum reactivity to form desired ketones **2** because of the steric bulk and favorable spatial orientation of the S-pendant group. The scope of this new aerobic coupling was probed by the reaction of different *S*-aryl-NH*t*Bu thiosalicylamides **1** and 2.5 equivalents of a boronic acid in the presence of 5 mol% CuMeSal in DMF at 50 °C while open to the air. Successful C–C coupling was achieved for aromatic, aliphatic, and α,β-unsaturated thiol esters (**1**) with aromatic, heteroaromatic, and alkenylboronic acids. In all instances it was observed that both the S-arylated byproduct (**3**) and the desired ketone (**2**) were formed in approximately a 1:1 ratio.

Notably, all Cu^{I} sources were used in catalytic amounts while open to the air, and all were effective for initiating the reaction regardless of the counterion. In contrast, only those Cu^{II} sources bearing an oxygenate counterion (carboxylate or diphenylphosphinate) were able to initiate and support the aerobic reaction. The authors suggested that Cu^{I} must be accessible for effective catalysis and that this requires in situ reduction of Cu^{II} to the active Cu^{I} by the boronic acid; this reduction is apparently facile in the presence of an oxygenate counterion, but not in the presence of a halide counterion such as chloride.[19] For the purpose of regenerating Cu^{I} in the reaction mixture, a second, sacrificial equivalent of boronic acid must be employed to break the strong Cu–S bond in the initially formed Cu–thiolate species, and to regenerate the key Cu–oxygenate species and an equimolar amount of thioether byproduct **3**. The proposed reaction mechanism for the aerobic Cu-catalyzed thiol ester/boronic acid coupling is summarized in Scheme 4. On the basis of the extensive knowledge of Cu^{I} dioxygen reactions,[20] the authors propose an initial aerobic activation of the Cu^{I}-coordinated thiol ester **A** to a higher oxidation state $Cu^{II/III}$ intermediate **B**. Simultaneous Lewis acid activation of the thiol ester by coordination to Cu and trivalent boron activation by coordination of the oxygenate species to the boron center (**C**), direct the nucleophilic R^2 moiety towards the thiol ester, producing desired ketone **2** and higher oxidation $Cu^{II/III}$-thiolate **D**. The



Scheme 4. Proposed mechanism for the Cu-catalyzed thiol ester/boronic acid cross-coupling.

catalytic cycle concludes with the reaction of $Cu^{II/III}$-thiolate **D** and a second equivalent of the boronic acid to produce weakly coordinating thioether **3** as a byproduct, and to regenerate the key Cu^{I}–oxygenate species for re-entry into the catalytic cycle.[21]

The Cu-catalyzed aerobic cross-coupling system described by Liebeskind and co-workers is of key interest to the synthetic community for several reasons. First of all, the presented Cu-mediated C–C bond forming methodology is mechanistically unprecedented. In contrast to the well-known oxidative addition/transmetallation/reductive elimination pathway in transition-metal catalysis,[1] this reaction apparently proceeds through a novel coupling reaction that is templated by a higher oxidation state Cu species. This transformation differs from the more traditional Liebeskind–Srogl C–C couplings (Scheme 1) because it does not require an expensive Pd catalyst and it requires catalytic, instead of stoichiometric, amounts of Cu.

Even though the success of this process stems from the use of specifically functionalized thiol esters and a sacrificial equivalent of a boronic acid, the aerobic coupling of thiol esters to boronic acids under base-free conditions will be a useful synthetic alternative for those cases where highly selective functionalizations of complex molecules are required, and where the need of a second equivalent of boronic acid is not critical. It should be further emphasized that the presence of the ligating S-pendant group provides an extraordinary level of chemoselectivity to the process as simple thiol esters appear untouched under the aerobic conditions and those bearing the ligating S-pendant group react at room temperature. It will be interesting to see if the reaction and mechanistic concept outlined in Scheme 4 can be adapted to other thioorganic C–C coupling pathways. Clearly, additional mechanistic studies and experimentation is needed to expand the scope of this transformation, and to perhaps find conditions that would allow C–C bond formation without having to incorporate the appropriate ligating S-pendant groups.

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