Communication

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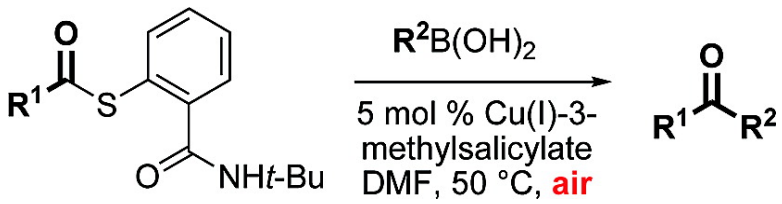

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A New Paradigm for Carbon−Carbon Bond Formation: Aerobic, Copper-Templated Cross-Coupling

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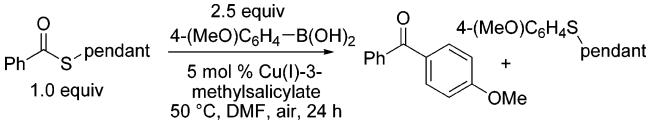
We describe herein a mechanistically unprecedented system for the construction of carbon−carbon bonds: the copper-templated coupling of a thioorganic and a boronic acid that is rendered catalytic under aerobic conditions. This new reaction type evolved from mechanistically distinct earlier transformations discovered in this laboratory[1−3] and subsequently extended in others:[4−9] the anaerobic coupling of a wide range of thioorganics with either boronic acids or organostannanes that require the presence of catalytic quantities of a palladium source and stoichiometric quantities of a Cu^I carboxylate. In this communication, we reveal the unique attributes of the copper-catalyzed, aerobic reaction system applied to the formation of ketones by the coupling of thiol esters with boronic acids at neutral pH.

All published thioorganic−boronic acid cross-couplings have required catalytic quantities of Pd and at least a stoichiometric quantity of a Cu^I carboxylate (or diphenylphosphinate) as a reaction mediator. Simple balancing of the generic reaction equation reveals the reasons for the latter requirement. The Cu^I ion pairs with the thiolate in a thermodynamically strong Cu−SR bond, while a full equivalent of the borophilic carboxylate counterion drives the $-B(OH)_2$ moiety to its thermodynamic sink, $R'C(O)OB(OH)_2$. This implies that the reaction system could be rendered catalytic in Cu if a Cu oxygenate could be regenerated from Cu−SR.[10] We hypothesized that thioorganic−boronic acid cross-couplings carried out under aerobic conditions in the presence of a second sacrificial equivalent of the boronic acid would achieve the desired goal. The strong Cu−SR bond would be broken by forming a thioether (using the second equivalent of boronic acid[11]), and a Cu oxygenate (of undefined oxidation state) would be released to the system.

To test this hypothesis, thiol esters possessing a variety of *S*-pendants were constructed and treated, open to air, with *p*-methoxyphenylboronic acid in DMF in the presence of catalytic Cu^I-3-methylsalicylate and, in the initial studies, with cocatalytic Pd sources. Control experiments revealed that a palladium co-catalyst was not required under the aerobic reaction conditions, making this system mechanistically distinct from our earlier thioorganic−boronic acid couplings. As shown in Table 1, only those thiol esters possessing appropriately positioned ligating *S*-pendant groups participated in efficient aerobic coupling with boronic acids. Key observations included (1) the requirement for a ligating functional group positioned *ortho* but not *para* to the *S*-pendant linkage, (2) the optimum performance of thiol esters derived from bulky −NH*i*-Pr and −NH*t*-Bu thiosalicylamides (contrast entries 5 and 6 with 7 and 8, Table 1), and (3) the formation of the *S*-arylated pendant in a roughly 1:1 ratio with the desired ketonic product.

The scope of this new aerobic cross-coupling was briefly probed through the reaction of a variety of *S*-acyl-NH*t*-Bu thiosalicylamides

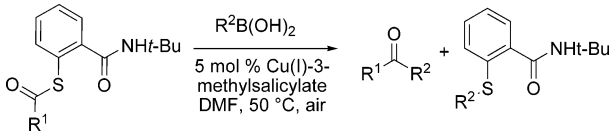
Table 1. *S*-Pendant Effects in Cu-Catalyzed Aerobic Coupling



entry	pendant	ketone (%)	thioether (%)	biaryl[a] (%)
1	$-C_6H_5$	trace	trace	57
2	$-(2\text{-}C_6H_4NHCOPh)$	6	trace	37
3	$-(CH_2)_2CONHt\text{-}Bu$	trace	trace	31
4	$-(2\text{-}C_6H_4CONHPh)$	34	28[b]	trace
5	$-(2\text{-}C_6H_4CONmorpholinyl)$	30	25[b]	54
6	$-(2\text{-}C_6H_4CONHMe)$	32	33[b]	trace
7	$-(2\text{-}C_6H_4CONHi\text{-}Pr)$	77	84	7
8	$-(2\text{-}C_6H_4CONHt\text{-}Bu)$	81	75	4

[a] Biaryl = 4,4′-dimethoxybiphenyl, boronic acid homocoupling. [b] Isolated as a mixture with coeluting starting material; yield estimated from ^{1}H NMR using 4,4′-di-*tert*-butylbiphenyl as an internal standard.

Table 2. Aerobic Coupling of Thiol Esters and Boronic Acids



entry	R^1	R^2	ketone (%)	thioether (%)
1	phenyl	*p*-$(MeO)C_6H_4$	81	75
2	phenyl	furan-2-carbaldehyde-5-yl	91	78
3	*p*-tolyl	2-BrC_6H_4	86	83
4	*p*-tolyl	2-naphthyl	83	92
5	*p*-tolyl	(*E*)-*β*-styryl	87	83
6[a−c]	*p*-tolyl	(*E*)-1-pentadecenyl	97	74
7	methyl	3,4-methylenedioxyphenyl	75	71
8	*n*-propyl	6-methoxypyridin-3-yl	68	61
9	*ω*-decynyl	2-thienyl	50	51
10[c]	(*E*)-propenyl	2-furyl	74	81

[a] Propylene oxide was added as a mild acid scavenger to minimize protodeborylation. [b] Cu^I-2,6-dihydroxycarboxylate was used, giving slightly better yields than Cu^I-3-methylsalicylate. [c] Yield is based on recovered starting material.

with 2.5 equiv of a boronic acid and 5 mol% Cu^I-3-methylsalicylate in DMF at 50 °C open to air. This study, depicted in Table 2, demonstrates that aromatic, heteroaromatic, and alkenyl boronic acids are suitable reaction partners for aromatic, aliphatic, and α,*β*-unsaturated thiol esters. Aldehydic and acetylenic functional groups are tolerated (entries 2 and 9) as is modest steric hindrance in the boronic acid (entry 3). Cyclohexylboronic acid, the only aliphatic boronic acid explored in this study, was unreactive.

Control experiments with stoichiometric copper sources under argon suggest the importance of Cu oxidation states >1 in the specific carbon−carbon bond forming step of the overall process: under identical conditions, Cu^I-3-methylsalicylate produced less than

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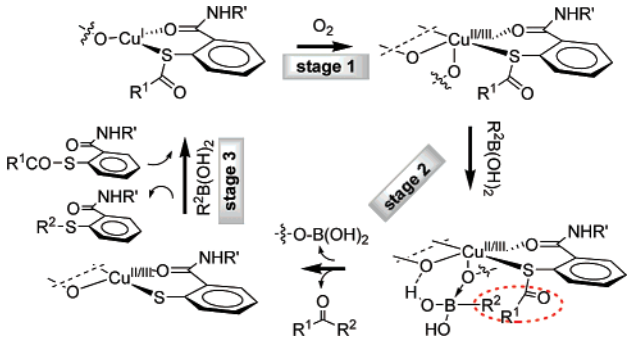
Scheme 1. Proposed Mechanism



20% of the ketone, while $Cu^{II}(OAc)_2$ generated the ketone in 60% yield. In contrast to $Cu^{II}(OAc)_2$, stoichiometric $Cu^{II}Cl_2$ was completely ineffective in promoting the ketone synthesis under argon, further attesting to the importance of partnering an oxygenate counterion with the $-B(OH)_2$ moiety in this coupling. Significantly, using catalytic quantities of Cu open to air, all $Cu^{I}X$ sources explored were effective, regardless of the nature of the counterion (X = halide, carboxylate, diphenylphosphinate), but only those $Cu^{II}X_2$ sources bearing an oxygenate counterion (X = carboxylate or diphenylphosphinate, but not halide) were able to initiate and support the aerobic reaction. We propose that Cu^{I} must be accessible for effective catalysis. This requires *in situ* reduction of a Cu^{II} pre-catalyst to Cu^{I} by the boronic acid, an apparently facile process with an oxygenate but not with a chloride counterion on Cu^{II}. This is reminiscent of the requirement for an oxygenate counterion to facilitate boron to palladium transmetalation in Miyaura−Suzuki cross-couplings.[12]

The mechanism of this aerobic cross-coupling must take into account (1) active catalysis without Pd, using sources of Cu only, (2) catalytic turnover under aerobic but not anaerobic conditions, (3) the apparent requirement for accessing Cu^{I} during the catalytic cycle, (4) the requirement for a thiol ester bearing a chelating *S*-pendant, and finally (5) the production in a roughly 1:1 ratio of both the desired ketone and the thioether derived from the *S*-pendant and the boronic acid. The absence of palladium in the catalytic sequence and the lack of any precedent for oxidative addition of thiol esters to Cu^{I} make a traditional oxidative addition−transmetalation−reductive elimination pathway for this new reaction unlikely. Rather, on the basis of the control experiments, we suggest that the thiol ester−boronic acid aerobic cross-coupling occurs through a novel, higher oxidation state, Cu-templated coupling reaction (Scheme 1).

Closely paralleling extensively documented studies of Cu^{I}-dioxygen reactions,[13−17] we suggest that the process is initiated by aerobic activation of Cu^{I} coordinated to the thiol ester (stage 1), which generates a higher oxidation state $Cu^{II/III}$ intermediate (both Cu^{II} and Cu^{III} are accessible through the low-energy interconversion of $[Cu_2(\mu\text{-}\eta^2\text{:}\eta^2\text{-}O_2)]^{2+}$ and $[Cu_2(\mu\text{-}O_2)]^{2+}$).[13−17] Metal templating by $Cu^{II/III}$ provides simultaneous Lewis acid activation of the thiol ester along with templated delivery of an adjacent nucleophilic organometallic moiety (R^2 in Scheme 1, delivered directly either from boron or through the intermediacy of Cu) producing the ketone and a higher oxidation Cu-thiolate. The catalytic cycle is completed by reaction of the $Cu^{II/III}$ thiolate with the second (sacrificial) equivalent of the boronic acid.[11,18] This would regenerate the requisite Cu^{I} for reentry into the catalytic cycle and remove thiolate ligand from the reaction system by producing the weakly coordinating *S*-arylation product. Apparently, binding of the chelating thiol ester to the Cu catalyst significantly modulates its ability to induce undesired side reactions such as Cu-catalyzed aerobic homocoupling of the boronic acid[19] and Castro−Stevens-like oxidative dimerization of the terminal alkyne shown in entry 9 of Table 2.

In its current manifestation, this new aerobic coupling of thiol esters and boronic acids should find utility in applications where highly selective functionalizations of complex molecules are required and where the need for a second equivalent of boronic acid and formation of the thioether side product are both unimportant. This will be demonstrated in the near future through disclosure of the selective carbon−carbon bond functionalization of small peptides with boronic acids using catalytic Cu under ambient, aerobic conditions.[20]

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Supporting Information Available: Experimental procedures, synthesis and characterization of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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