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Copper-Mediated, Palladium-Catalyzed Coupling of Thiol Esters with Aliphatic Organoboron Reagents

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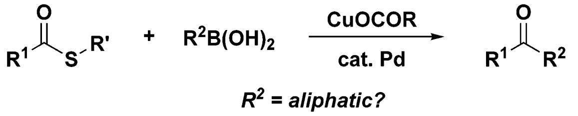
Abstract: Thiol esters and *B*-alkyl-9-BBN derivatives couple in the presence of a copper(I) carboxylate mediator and a palladium catalyst. In contrast to copper-mediated, palladium-catalyzed cross-couplings of thioorganics with boronic acids, the current coupling reaction of 9-BBN derivatives is facilitated by the addition of a base such as Cs_2CO_3. Under optimized conditions, a variety of thiol esters react with different *B*-alkyl-9-BBN derivatives giving ketones in moderate to excellent yields.

Recent publications have demonstrated the efficient, palladium-catalyzed, copper-mediated coupling of various thioorganics (thiol esters, alkynyl thioethers, heteroaromatic thioethers) with both boronic acids[1] and with organotri-*n*-butylstannanes.[2] As a case in point, thiol esters react with boronic acids in a mild, efficient, and general Pd-catalyzed, Cu(I) carboxylate-mediated coupling to give ketones under nonbasic conditions (Scheme 1).[1a,3] In contrast, the synthesis of ketones via noncarbonylative cross-coupling protocols typically requires acyl moieties of greater reactivity than thiol esters (and thus lower functional group compatibility), such as acid halides[4] and anhydrides.[5] These new thioorganic couplings are understood to depend on the ability of the copper(I) carboxylate to activate the catalytic intermediate, R^1-$COPdL_2SR'$, toward transmetalation by both boronic acids and organotri-*n*-butylstannanes. In the case of the boronic acid cross-couplings, the data support a dual activation of both the palladium thiolate and the boronic acid by the copper(I) carboxylate as implied in Figure 1.[1a,b]

SCHEME 1



To date, copper-mediated, palladium-catalyzed couplings of thioorganics have been successfully developed for aromatic, heteroaromatic, and alkenylboronic acids as well as for the analogous organotri-*n*-butylstannanes. Noticeably missing from this new coupling procedure are examples utilizing either aliphatic boron or tin reagents. In fact, alkylboronic acids have been problematic in traditional Suzuki cross-couplings and generally result in low yields of coupling products. Recent studies, however, show promise of improving this situation.[6] In contrast to aliphatic boronic acids, *B*-alkyl 9-BBN reagents, readily prepared by hydroboration of alkenes,[7] can be cross-coupled with various organic halides under mild conditions.[8] In these standard Suzuki−Miyaura couplings, both a base and palladium catalyst are essential for a successful reaction.[9] Other efficient alkylboron cross-coupling partners have also been reported, such as borinate esters (generated from selective monooxidation of *B*-alkyl-9-BBN reagents with anhydrous trimethylamine *N*-oxide),[10,11] trialkylboranes,[12] and potassium alkyltrifluoroborates.[13]

The thiol ester/boronic acid method of ketone synthesis depicted in Scheme 1 is effective with various substituents on the thiol ester (aromatic, heteroaromatic, aliphatic) and with aromatic, heteroaromatic, and alkenylboronic acids. Unfortunately, under standard conditions for the Cu(I) carboxylate-mediated, palladium-catalyzed coupling of thiol esters with boronic acids,[1] the coupling

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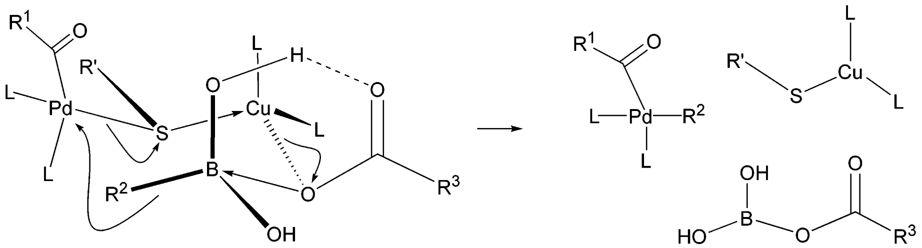
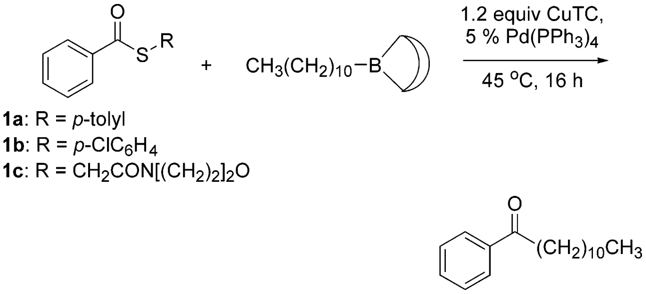


FIGURE 1.

TABLE 1. Pd(0)-Catalyzed, CuTC-Mediated Coupling of Benzoyl Thiol Ester with *B*-undecyl-9-BBN



1a: R = *p*-tolyl
1b: R = *p*-ClC$_6$H$_4$
1c: R = CH$_2$CON[(CH$_2$)$_2$]$_2$O

CuTC = Cu^{I} thiophene-2-carboxylate

thiol ester	boron (equiv)	product yield[a] (%)
1a	1.5	30
1b	1.5	48
1c	1.2	29
	1.5	41
	2.0	48

[a] GLC yield using nonadecane as an internal standard.

of *n*-BuB(OH)$_2$ with PhCOS-*p*-tolyl failed to produce any ketone. Nor was 2-*n*-butyl-4,4,5,5-tetramethyl-[1,3,2]dioxaborolane (the corresponding boronate ester prepared from *n*-butyl boronic acid and pinacol) effective as a coupling agent. Suspecting that transmetalation of an aliphatic group from boron to palladium is slower than the corresponding transfer of C-sp^2 and C-sp moieties, an investigation of the more reactive *B*-alkyl-9-BBN reagents was undertaken.

The preparation of *B*-alkyl-9-BBN derivatives was easily achieved by reaction of alkenes with commercially available 0.5 M 9-BBN in THF.[7] Hydroboration proceeded smoothly at room temperature with almost exclusive selectivity for introduction of boron at the less hindered side of the double bond. The resulting *B*-alkyl-9-BBN reagents in THF can be stored under an inert atmosphere at 0 °C for weeks without obvious decomposition. In the first set of experiments, benzoyl thiol esters **1a**−**c** were heated with *B*-undecyl-9-BBN, a stoichiometric amount of Cu(I) thiophene-2-carboxylate (CuTC), and 5% Pd(PPh$_3$)$_4$ at 45 °C in THF. The reaction gave dodecanophenone as the desired product, but only in 25−48% yields (Table 1). Control experiments revealed that both Cu(I) and the Pd(0) catalyst were essential for the couplings. Although not shown in Table 1, various combinations of thiol esters, Cu(I) compounds, Pd catalysts, solvents, and temperature were also screened using *B*-undecyl-9-BBN as the boron reagent, but none of these variations led to promising improvements. In most cases, unreacted thiol esters could be recovered and undecane, the protodeborylation product,[14] was also observed. The latter observation suggested that the *B*-alkyl-9-BBN reagent, although more effective than the corresponding alkylboronic acid, was not sufficiently reactive in transmetalation with the RCOPd(L)$_2$SR′ intermediate. *B*-Styryl-9-BBN gave results similar to those for *B*-undecyl-9-BBN.

Although the presence of an oxygen base is often crucial for the success of traditional Suzuki−Miyaura reactions, such bases were shown to be deleterious to the copper carboxylate-mediated, palladium-catalyzed couplings of *boronic acids* with thioorganics referred to earlier in this paper.[1] In contrast to those boronic acid couplings, the addition of 1 equiv of Cs$_2$CO$_3$ to the couplings of thiol esters and *B*-alkyl-9-BBN reagents greatly improved the product yields. Among the common bases used in the coupling reactions, Cs$_2$CO$_3$ was the best. K$_2$CO$_3$ and K$_3$PO$_4$ were also effective, although quantities greater than 1 equiv were required. A stoichiometric amount of Cu(I) and catalytic amount of Pd(0) were both essential for the couplings. As copper sources both CuTC[1a] and CuMeSal[15] were effective in mediating the couplings, while other Cu(I) species such as CuOAc and CuX (X = Cl, I) resulted in much lower yields. THF, DMA, and 1,4-dioxane were all suitable solvents for the reaction. The couplings even proceeded in EtOH, although ethyl esters were formed as byproducts. As depicted in Table 2, the optimized conditions could be extended to a variety of *B*-alkyl-9-BBN derivatives and thiol esters, which produced the desired aryl−alkyl or alkyl−alkyl ketones in moderate to excellent yields. *B*-Alkyl-9-BBN derivatives prepared from long chain primary alkenes, dienes, and styrene and its derivatives worked well in the coupling reactions. *B*-(2-Hexanonyl)-9-BBN and *B*-(3,3-dimethoxypropyl)-9-BBN were relatively sluggish in the coupling reaction, but still gave the desired ketones in modest yields.

The method is ideal for synthesizing alkyl−alkyl ketones and aryl−alkyl ketones with various functional groups that can withstand basic reaction conditions. Other alkylboron coupling partners, such as BEt$_3$, 2-*n*-butyl-4,4,5,5-tetramethyl-[1,3,2]dioxaborolane, *B*-undecyl-9-oxa-10-borabicyclo[3,3,2]decane, and potassium *n*-butyltrifluoroborate were also investigated in the coupling reaction with thiol esters, but the desired ketone product was not formed.

Unfortunately, not all thiol esters could be successfully coupled with aliphatic boron reagents. The basic reaction

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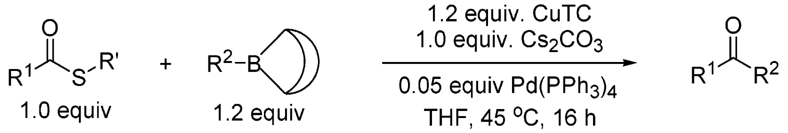
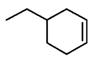
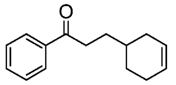
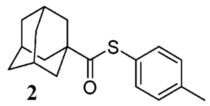
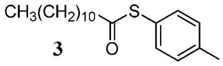
(14) Control experiments showed that heating *B*-undecyl-9-BBN with 1 equiv of CuTC in THF for 3 h produced undecane as the protodeborylation product in more than 90% yield.

(15) See the Supporting Information for: Savarin, C.; Srogl, J.; Liebeskind, L. S. *Org. Lett.* **2001**, *3* (1), 91−93.

TABLE 2. ***B*-Alkyl-9-BBN Derivatives: Thiol Esters Coupling under Basic Conditions**

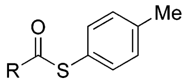


thiol ester	R^2	ketone	yield (%)[a]
1c	-$(CH_2)_{10}CH_3$	$PhCO(CH_2)_{10}CH_3$ **4a**	83
	-$(CH_2)_2Ph$	$PhCO(CH_2)_2Ph$ **4b**	82
	-$(CH_2)_2$-4-ClC_6H_4	$PhCO(CH_2)_2$-4-ClC_6H_4 **4c**	76
	-$(CH_2)_2$-4-$MeOC_6H_4$	$PhCO(CH_2)_2$-4-$MeOC_6H_4$ **4d**	78
		 **4e**	64
	-$(CH_2)_2CH{=}C(Me)_2$	$PhCO(CH_2)_2CH{=}C(Me)_2$ **4f**	52
	-$CH_2)_3C{\equiv}C$-n-C_4H_9	$PhCO(CH_2)_3C{\equiv}C$-n-C_4H_9 **4g**	85
	-$(CH_2)_3COMe$	$PhCO(CH_2)_3COMe$ **4h**	47[b]
	-$(CH_2)_2CH(OMe)_2$	$PhCO(CH_2)_2CH(OMe)_2$ **4i**	48
	-$(CH_2)_3Cl$	$PhCO(CH_2)_3Cl$ **4j**	21
	-CH(Me)Ph	$PhCOCH_2CH(Me)Ph$ **4k**	56
 **2**	-$(CH_2)_{10}CH_3$	adamantyl$CO(CH_2)_{10}CH_3$ **4l**	52
	-$(CH_2)_2$-4-$MeOC_6H_4$	adamantyl$CO(CH_2)_2$-4-$MeOC_6H_4$ **4m**	63
 **3**	-$(CH_2)_{10}CH_3$	$CH_3(CH_2)_{10}CO(CH_2)_{10}CH_3$ **4n**	90
	-$(CH_2)_2$-4-$MeOC_6H_4$	$CH_3(CH_2)_{10}CO(CH_2)_2$-4-$MeOC_6H_4$, **4o**	55

[a] Isolated yields. [b] Intramolecular aldol-dehydration product (43%) was formed under the basic conditions.

conditions required to induce the coupling of the *B*-alkyl-9-BBN reactants led to decomposition of some thiol esters, such as those shown in Figure 2. Neither did *B*-sec-alkyl-9-BBN reagents (i.e., prepared from cyclohexene) react with thiol esters to give the desired ketones. For example, neither *B*-cyclohexyl-9-BBN nor *R*-Alpine Borane returned any ketonic product upon reaction with thiol ester **1c**.

During earlier studies of the copper carboxylate-mediated, palladium-catalyzed coupling of thioorganics with boronic acids, it was noted that boronic acids were much superior to boronate esters as reactants. This and



R = $ClCH_2$, CF_3, $CH_3CO_2CH_2$, Me_2N, *E*-β-styryl

FIGURE 2.

other observations led to the proposal that the copper(I) carboxylate functioned as a unique dual activator, acting through the soft Cu(I) ion as a thiophilic agent to help polarize the palladium thiolate bond while simultaneously providing borophilic activation through the hard carboxylate counterion. The much greater reactivity of boronic acids over boronate esters and the deleterious effect of added oxygen bases on the coupling reaction led to the proposal of the hydrogen bonded, ternary complex depicted in Figure 1, above, as the reactive intermediate. A low energy reaction path proceeding through this ternary complex would most likely be sensitive to steric effects and depend on the presence of hydrogen bonds from the boronic acid to the carboxylate counterion. The inability to form hydrogen bonds to the copper carboxylate may account for the poor reactivity of boronate esters in the palladium-catalyzed, copper-mediated coupling of thioorganics.

Like boronate esters, the greater steric demand of the *B*-alkyl-9-BBN reagents should render reaction through the dual activation, ternary complex pathway quite difficult, and as confirmed above, *B*-alkyl-9-BBN reactants participate only sluggishly under the nonbasic cross-coupling conditions. Nevertheless, stepwise, separate activation of the palladium thiolate by Cu(I) and of the *B*-alkyl-9-BBN by Cs_2CO_3 is still feasible; hence, the 9-BBN system is susceptible to base-induced activation.

In summary, through the use of *B*-alkyl-9-BBN derivatives the Pd(0)-catalyzed, Cu(I) carboxylate-mediated cross-coupling of thiol esters has been broadened to include aliphatic boron reagents. In contrast to the palladium-catalyzed, copper carboxylate-mediated coupling of thioorganics with boronic acids, the presence of a base (Cs_2CO_3) was required in the current reagent system in order to provide activation of the boron reagents. Aryl−alkyl and alkyl−alkyl ketones with a variety of functional groups have been synthesized in moderate to excellent yields.

Experimental Section

General Procedure for Preparing *B*-Alkyl-9-BBN Reagents. To a round-bottomed flask was added alkene (5.0 mmol), and then the mixture was cooled to 0 °C under the protection of argon. 9-BBN (10 mL, 0.5 M) in THF (5.0 mmol) was added slowly via syringe. The reaction solution was stirred at 0 °C for 1 h and then room temperature for another 2 h. The resulting *B*-alkyl-9-BBN reagent solution (0.5 mmol/mL) was stored below 0 °C before using.

General Procedure for Cross-Coupling Reaction. Thiol ester (0.40 mmol), CuTC (91 mg, 0.48 mmol), Cs_2CO_3 (130 mg, 0.40 mmol), and $Pd(PPh_3)_4$ (23 mg, 0.02 mmol) were added into a Schlenk tube and then degassed with argon. The *B*-Alkyl-9-BBN reagent (0.96 mL, 0.5 mmol/mL, 0.48 mmol) in THF was added via syringe. Then dry and degassed THF (4 mL) was added. The dark brown suspension was stirred under the protection of argon at 45 °C for 16 h. Then Et_2O (10 mL) was added, and the reaction was quenched with 2 M HCl followed by 1 M $NH_3{\cdot}H_2O$ and then brine. After evaporation of the solvent, the residue was purified by silica gel chromatography or preparative plate silica chromatography (SiO_2, 500 μm, gradient of hexanes/Et_2O) to give the desired product.

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Supporting Information Available: A complete description of the synthesis and characterization data of all compounds prepared in this study. This material is available free of charge via the Internet at http://pubs.acs.org.

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