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Thiol Ester–Boronic Acid Cross-Coupling. Catalysis Using Alkylative Activation of the Palladium Thiolate Intermediate

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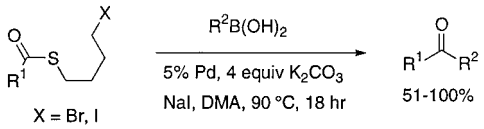
ABSTRACT



Thiol esters and boronic acids do not participate in cross-coupling in the presence of palladium catalysts. However, efficient palladium-catalyzed thiol ester–boronic acid cross-coupling is observed when simple alkylating agents are present. Alkylative conversion of the very stable palladium–thiolate bond to a labile palladium–thioether bond is presumed to be crucial to the catalysis. Of the systems studied, 4-halo-*n*-butyl thiol esters were most effective in this cross-coupling.

New metal-catalyzed synthetic processes that involve carbon−sulfur bond scission and lead to the formation of a new carbon−carbon bond under mild conditions should be feasible if carbon−sulfur oxidative addition is facile and the formation of refractory metal thiolates from thiophilic, redox active metals can be prevented.[1] The oxidative addition of organosulfur compounds to low-valent transition metal species is well-known;[2] therefore the key to catalytic turnover with organosulfur compounds is activation of the very stable bond that forms between the catalytically active metal (such as Ni, Pd, Pt, Rh) and the soft sulfur atom.

From a synthetic perspective, the coupling of stable organosulfur compounds with boronic acids would be a singular boon to the synthetic chemist, since both reaction partners are readily available and stable molecules of low toxicity, and their coupling would provide a uniquely mild method for the synthesis of highly functionalized organics. Given the precedence for oxidative addition of thioorganics to low valent nickel, palladium, and platinum mentioned above, the conceptual key to this proposed coupling reaction is transmetalation of the boronic acid to the metal thiolate intermediate, with concomitant replacement of the thiolate ligand. Unfortunately, the low thiophilicity of boron combined with the low nucleophilic reactivity of organoboron derivatives renders this transmetalation problematic.

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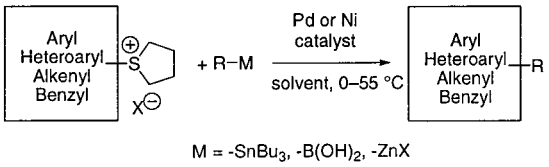
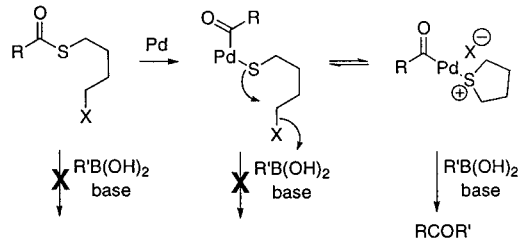
One solution to this problem is found in the unusual efficacy of tetrahydrothiophene-based sulfonium salts as partners in nickel- and palladium-catalyzed cross-coupling with organozinc, -tin, and -boron reagents, where it was convincingly demonstrated that tetrahydrothiophene does not interfere with palladium or nickel catalysis (Scheme 1).[3] This

Scheme 1. Sulfonium Salts in Cross-Coupling



led to the notion of "alkylative activation" of refractory metal thiolate intermediates as a way to weaken the metal−sulfur bond and overcome the low thiophilicity of boron. Application of the principle to thiol ester−boronic acid cross-coupling is depicted in Scheme 2.

Scheme 2. Thiol Ester Cross-Coupling Using Alkylative Activation



To demonstrate the concept of alkylative activation, 4-halo-*n*-butyl and normal thiol esters (Figure 1) were

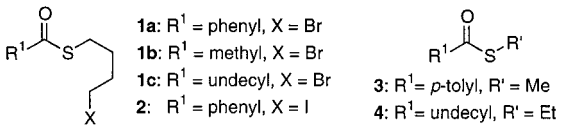
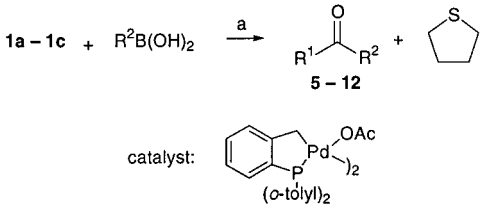


Figure 1. Thiol esters.

prepared and studied as substrates for palladium-catalyzed cross-coupling with boronic acids. In the presence of 5−10% *trans*-di(*μ*-acetato)-bis[*o*-(di-*o*-tolylphosphino)benzyl]dipalladium(II),[4] 20−45% NaI, 4−6 equiv K_2CO_3, in dimethylacetamide (DMA) at 90−95 °C for 12−24 h, various boronic acids underwent cross-coupling with thiol esters **1a**−**c** to give the desired ketones, which were isolated in 50−88% yields.[5] Tetrahydrothiophene was detected by GC/MS, which supports the hypothesis of sulfur scavenging by alkylative displacement. The lower yield entries in Table 1 are

Table 1. Ketone Synthesis Using Thiol Esters and Boronic Acids



	R^1	R^2	product	yield (%)
1	phenyl	phenyl	**5**	88[b]
2	phenyl	3-methoxyphenyl	**6**	57[b]
3	phenyl	2-formyl-4-methoxyphenyl	**7**	78[b]
4	phenyl	2-naphthyl	**8**	76[b]
5	methyl	phenyl	**9**	100[c]
6	methyl	2-naphthyl	**10**	70[b]
7	undecyl	phenyl	**11**	80[b]
8	undecyl	3-methoxyphenyl	**12**	50[b]

[a] 5−10% *trans*-di(*μ*-acetato)-bis[*o*-(di-*o*-tolylphosphino)benzyl]dipalladium(II),[4] 4−6 equiv of K_2CO_3, 20−45% NaI, DMA, 90−95 °C, 12−24 h. [b] Isolated yield. [c] GC/MS with *n*-decane as internal standard.

associated with electron-rich boron reagents.[6] The acetyl and lauroyl thiol esters also underwent the coupling reaction in good to excellent yields (entries 5−8). For comparison, certain acid chlorides can, under specific conditions, be coupled with organoboron reagents,[7] and Fukuyama[8] and Terfort[9] have reported low yields of ketone from the palladium-catalyzed coupling of a thiol ester with a boronic acid.

Interestingly, in the absence of catalytic NaI the bromobutyl-derived thiol ester **1a** gave only traces of benzophenone when treated with phenylboronic acid in the presence of 8% *trans*-di(*μ*-acetato)-bis[*o*-(di-*o*-tolylphosphino)benzyl]dipalladium(II) in DMA at 95 °C for 22 h. The addition of NaI was undertaken in order to transform the alkyl bromide to the alkyl iodide and facilitate the postulated intramolecular

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(5) **Typical Procedure: 2-Benzoyl-4-methoxybenzaldehyde, 7.** A solution of 6% *trans*-di(*μ*-acetato)-bis[*o*-(di-*o*-tolylphosphino)benzyl]dipalladium(II) (14 mg, 0.03 mmol), K_2CO_3 (313 mg, 2.27 mmol, 4.3 equiv), 33% NaI (26 mg, 0.17 mmol), 2-formyl-4-methoxyphenylboronic acid (113 mg, 0.62 mmol, 1.2 equiv) in dry and degassed dimethylacetamide (2 mL) was treated with 142 mg (0.52 mmol, 1.0 equiv) of thiol ester **1a** for 17 h at 95 °C to give 98 mg (0.41 mmol, 78%) of **7** as white needles. Mp 82−84 °C (Et_2O−hexanes). Complete characterization data are listed in the Supporting Information.

(6) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457−2483.

(7) Haddach, M.; McCarthy, J. R. *Tetrahedron Lett.* **1999**, *40*, 3109−3112. Bumagin, N. A.; Korolev, D. N. *Tetrahedron Lett.* **1999**, *40*, 3057−3060.

(8) Tokuyama, H.; Yokoshima, S.; Yamashita, T.; Fukuyama, T. *Tetrahedron Lett.* **1998**, *39*, 3189−3192.

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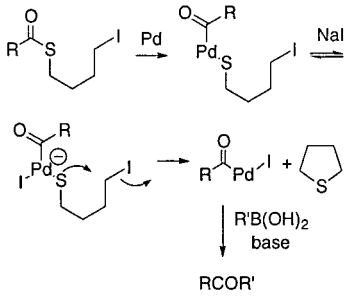
S-alkylative activation. To support this hypothesis, the iodo substrate $PhCOS(CH_2)_3CH_2I$ **2** easily coupled with phenylboronic acid under the same conditions, but in the *absence* of NaI, to give benzophenone in 56% yield. As a suitable control experiment, only a trace of *p*-tolyl phenyl ketone was formed when the simple thiol ester 4-MePhCOSMe, **3**, was treated with phenylboronic acid in the presence of NaI under the standard reaction conditions.

Although less efficient than the intramolecular system, *intermolecular* alkylative activation was also feasible. For example, undecylCOSEt, **4**, was transformed into undecyl phenyl ketone (48%) when treated with $PhB(OH)_2$ and 1,4-dibromobutane in the presence of 6% *trans*-di(μ-acetato)-bis[*o*-(di-*o*-tolylphosphino)benzyl]dipalladium(II), 30% NaI, and 4.1 equiv of K_2CO_3 in DMF at 90 °C for 18 h. While 1,4-dibromobutane was a reasonably effective activator, other alkylating agents were not (1,2-dibromoethane, 1-bromohexane). In all cases employing intermolecular alkylative activation, varying amounts of starting material were recovered. Finally, among $Pd(PPh_3)_4$, $Pd_2(dba)_3$/tris(2-furylphosphine), and *trans*-di(μ-acetato)-bis[*o*-(di-*o*-tolylphosphino)-benzyl]dipalladium(II), the latter was most efficient. In the absence of catalyst, no product was formed.

The mechanism of this cross-coupling is presumed to follow the pathway depicted above in Scheme 2. One role of NaI is therefore to catalytically generate the alkyl iodide from the alkyl bromide; in addition, iodide might ligate the palladium and generate an anionic acylpalladate providing increased electron density for the alkylative activation step (Scheme 3). Although no evidence was obtained for generation of an acyl iodide or a highly reactive acyl sulfonium salt prior to oxidative addition, these intermediates cannot be ruled out.[10]

In conclusion, the possibility of "alkylative activation" of a palladium thiolate intermediate under catalytic carbon−carbon bond-forming conditions was elucidated. Using these conditions, thiol esters participated in Miyaura−Suzuki[6] cross-coupling reactions with boronic acids to give ketones. Intramolecular palladium−sulfur alkylative activation was more efficient than the intermolecular variant.

Scheme 3. Anionic Acylpalladate as an Intermediate



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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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