Thiol Ester−Boronic Acid Coupling. A Mechanistically Unprecedented and General Ketone Synthesis

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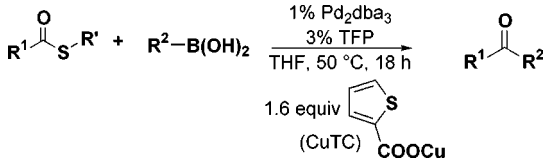
Received September 15, 2000

Highly discriminating activation of a stable carbon−sulfur bond is achieved in the presence of a vast sea of oxygen and nitrogen heteroatoms in various biochemical transformations.[1,2] The Principle of Hard−Soft Acids and Bases,[3] e.g., the selective interaction of a soft substrate with a soft activator in a hard environment and vice versa, helps to rationalize Nature's use of biologically relevant thiophilic metals such as Ni to achieve selective disconnection of the carbon−sulfur bond in water. Implicit in this mode of C−S activation is the capacity of the biological system to prevent the formation of refractory metal thiolates from thiophilic metals.

Given the above considerations, new laboratory-based synthetic processes that involve metal-catalyzed carbon−sulfur bond scission and lead to new carbon−carbon bond formation under very mild conditions should be feasible. It is implicit in the discussion above that metal-catalyzed turnover of organosulfur compounds requires activation of the stable bond that forms between a catalytically active metal and the soft sulfur atom.

We have previously demonstrated the importance of sacrificial Zn^{II} in facilitating the cross-coupling of thioglycolate systems,[4] and more recently described a thiol ester−boronic acid cross-coupling using the principle of "alkylative activation".[5] The latter draws on our earlier disclosures of sulfonium salts as highly effective cross-coupling partners.[6,7] We now report a mechanistically unique and unprecedented Pd-catalyzed coupling of thiol esters[8] with boronic acids to give ketones that proceeds in the presence of Cu^{I} thiophene-2-carboxylate (CuTC)[9] under strictly nonbasic reaction conditions (Table 1, Chart 1). Although many methods for the synthesis of ketones are known,[10−12] none is sufficiently general to allow the coupling of stable and functionally rich reaction partners under *neutral* conditions. Some transformations of thiol esters to ketones are known; they proceed under basic reaction conditions and are not general.[13−18] Aroyl chlorides do participate in couplings with neutral partners such as organostannanes[19,20] and boronic acids,[21,22] but acid chlorides are too reactive to be broadly useful in sensitive, functionally rich systems, and the boronic acid coupling is limited to acid chlorides that can survive the basic conditions inherent in Suzuki−Miyaura couplings.[23]

Table 1. Copper Carboxylate Mediated Thiol Ester−Boronic Acid Cross-Coupling[a]



entry	reactants	ketone (R^1, R^2)	yield, %
1	**1**, **11**	Ph, *o*-MeOPh	88
2	**1**, **12**	Ph, *m*-MeOPh	83
3	**1**, **18**	Ph, 2-naphthyl	79
4	**2**, **16**	*p*-NO_2Ph, 3,4-methylenedioxyphenyl	85
5	**3**, **10**	*p*-HOPh, Ph	81
6	**4**, **17**	2-pyrazyl, (*E*)-*β*-styryl	81
7	**5**, **13**	$C_{11}H_{23}$, *m*-NO_2Ph	79
8	**5**, **15**	$C_{11}H_{23}$, *o*-CHO-*p*-MeOPh	75
9	**6**, **16**	adamantyl, 3,4-methylenedioxyphenyl	52
10	**7**, **18**	$ClCH_2$, 2-naphthyl	57
11	**8**, **14**	$AcOCH_2$, *p*-MeO_2CPh	88
12	**9**, **13**	CF_3, *m*-NO_2Ph	63
13	**9**, **17**	CF_3, (*E*)-*β*-styryl	93

[a] Refer to Chart 1 for structures.

Chart 1. Thiol Ester and Boronic Acid Reactants

1, R^1 = Ph, R' = CH_2CONMe_2	**10**, R^2 = Ph
2, R^1 = *p*-NO_2Ph, R' = Et	**11**, R^2 = *o*-MeOPh
3, R^1 = *p*-HOPh, R' = Et	**12**, R^2 = *m*-MeOPh
4, R^1 = 2-pyrazyl, R' = phenyl	**13**, R^2 = *m*-NO_2Ph
5, R^1 = $C_{11}H_{23}$, R' = *p*-tolyl	**14**, R^2 *p*-MeO_2CPh
6, R^1 = adamantyl, R' = *p*-tolyl	**15**, R^2 = *o*-CHO-*p*-MeOPh
7, R^1 = $ClCH_2$, R' = *p*-tolyl	**16**, R^2 = 3,4-methylenedioxyphenyl
8, R^1 = $AcOCH_2$, R' = *p*-tolyl	**17**, R^2 = (*E*)-β-styryl
9, R^1 = CF_3, R' = *p*-tolyl	**18**, R^2 = 2-naphthyl

The examples in Table 1 demonstrate the generality and efficiency of this new reaction. Although a variety of palladium precatalysts/ligand systems were effective, the reaction was surveyed using $Pd_2(dba)_3$·$CHCl_3$/tris(2-furyl)phosphine. Aromatic and aliphatic *S*-alkyl and *S*-aryl thiol esters coupled efficiently (52−93% yields) with a variety of functionalized boronic acids. Particular attention is drawn to the direct preparation of a chloromethyl ketone from the corresponding thiol ester **7** (Entry

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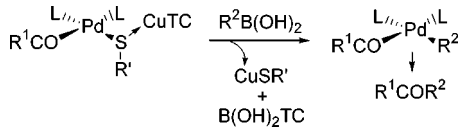
10.1021/ja005613q CCC: $19.00
Published on Web 10/26/2000

Scheme 1



10), the easy generation of trifluoromethyl ketones from trifluoromethyl thiol ester **9** (Entries 12 and 13), and the simple synthesis of a heterocyclic ketone (Entry 6). The special properties of $PhCOSCH_2CONMe_2$ (**1**) are also noted: it undergoes coupling with boronic acids more efficiently and in a greater range of solvents when compared to the simple thiol esters.

Unlike the traditional Suzuki−Miyaura cross-coupling of boronic acids and organic halides, where the presence of a base is essential,[23] base was deleterious in the current chemistry. Addition of 1 equiv of KOAc to the reaction of $PhCOSCH_2CONMe_2$ with $PhB(OH)_2$ in the presence of 1% $Pd_2(dba)_3 \cdot CHCl_3$/TFP (tris-2-furylphosphine) and CuTC significantly suppressed the yield of ketone. In a dramatic demonstration, 2-naphthyl phenyl ketone was formed in 60% yield from naphthalene-2-boronic acid and thiol ester $PhCOSCH_2CONMe_2$ *in acetic acid as solvent*! These "baseless" conditions should open new possibilities for the synthesis of base-sensitive compounds. In addition to THF (the solvent of choice), ethanol and 2-propanol are acceptable, although some competitive alcoholysis of the thiol ester takes place in these solvents. Coordinating solvents (DMA, NMP, acetonitrile) and coordinating ligands (NaI, LiCl, alkyl sulfide) negatively affect the reaction outcome, completely preventing the reaction in many cases.

The mechanistic key to this new reaction is the selective activation of a catalytically generated acylpalladium−thiolate in a way that facilitates transmetalation from boron to palladium, while retaining compatibility with all other components of the reaction system. Although a detailed understanding of this cross-coupling is not currently in hand, the process requires transmetalation from boron to palladium mediated by CuTC (Scheme 1). A number of observations are significant: Although naphthalene-2-boronic acid (**18**) suffers rapid (2 h) protodeborylation to naphthalene upon treatment with 1 equiv of CuTC in THF at room temperature, the protodeborylation is suppressed with high efficiency in the presence of 1 equiv of thiol ester **1**, $PhCOSCH_2CONMe_2$. Therefore, a thiol ester−CuTC complex is deemed important in the cross-coupling. Presumably then, cross-coupling of the thiol ester with the boronic acid is initiated by oxidative addition of the CuTC-bound thiol ester to the Pd(0) catalyst. (Efficient chelation of CuTC to $PhCOSCH_2CONMe_2$ helps rationalize the special reactivity of this thiol ester in the cross-coupling chemistry. The coordinating solvent DMA inhibited the cross-coupling of *S*-alkyl and *S*-aryl thiol esters, but not $PhCOSCH_2CONMe_2$.) Transmetalation from boron to palladium must occur next, either preceded by boron to copper transmetalation or directly from the acylpalladium thiolate−CuTc complex. If prior transmetalation from boron to the *S*-bound Cu^I does occur, protodemetalation from this intermediate must be slow relative to a fast internal transfer from copper to palladium. Mixed anhydrides are not intermediates in the process: $PhCOSCH_2CONMe_2$, **1**, does not react with CuTC to give a mixed anhydride, either alone or catalyzed by palladium.

Both the copper cation and the carboxylate anion are critical to the reaction. Cu^I halides and CuCN were ineffective. Coupling to ketone was not observed when $PhCOSCH_2CONMe_2$ and $PhB(OH)_2$ were exposed to 1% $Pd_2(dba)_3$ and K_2CO_3 or KOAc in the absence of a thiolate scavenger. Nor was ketone efficiently formed in the presence of added Zn^{II} carboxylates (low yields of the desired ketonic product were observed in some reaction mixtures), even though Zn^{II} salts functioned as metal−thiolate activator/scavengers in nickel-catalyzed cross-coupling reactions of thio-organics with organozinc reagents.[4]

Since Cu^I halides and CuCN are ineffective, the carboxylate counterion is clearly important in facilitating transmetalation from boron, possibly through direct coordination to trivalent boron. If this mechanistic speculation is correct, then any solvent or added ligand that binds to copper and blocks formation of the requisite thiol ester Cu^I complex will interfere with Cu-mediated transmetalation. Furthermore, any added base may bind to boron and retard reaction by blocking coordination of the Cu^I carboxylate to the trivalent boron.

In conclusion, a mild and general method for the palladium-catalyzed, copper-mediated coupling of thiol esters and boronic acids under "baseless" conditions has been developed. The general availability of both reaction partners and the nonbasic reaction condition suggest new possibilities for the synthesis of highly functionalized and base-sensitive compounds under these cross-coupling conditions. Additional investigation of the scope and limitation of this chemistry (heteroaromatic and alkylboron reagent couplings; amino acid thiol esters as reactants), as well as of the origin of carbon−boron bond activation, is in progress in our laboratory. Extension of this new reaction to polymer-supported reactions is obvious and also under study.

Acknowledgment. The National Cancer Institute, DHHS supported this investigation through grant No. CA40157. We are most grateful to Dr. Paul Reider of Merck Pharmaceutical Co. for his interest in and generous support of this work and to Dr. Gary Allred of Frontier Scientific, Inc. of Logan, Utah for facilitating this study with a generous supply of boronic acids. We thank Ms. Heather Petralia for her experimental assistance with this project, and Ms. Cecile Savarin for her expert proofreading of the manuscript.

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

JA005613Q