ORGANIC
LETTERS

2003
Vol. 5, No. 17
3033−3035

Ketone Synthesis under Neutral Conditions. Cu(I) Diphenylphosphinate-Mediated, Palladium-Catalyzed Coupling of Thiol Esters and Organostannanes

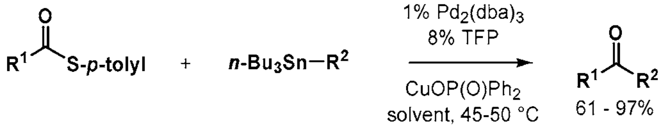
Rüdiger Wittenberg, Jiri Srogl, Masahiro Egi, and Lanny S. Liebeskind*

Emory University, Department of Chemistry, 1515 Pierce Drive,
Atlanta, Georgia 30322

chemLL1@emory.edu

Received May 30, 2003

ABSTRACT



A versatile approach to ketone synthesis is described. The reaction relies on the palladium-catalyzed, copper diphenylphosphinate-mediated coupling of thiol esters with organostannanes under neutral reaction conditions. This reaction complements the previously described coupling of thiol esters with boronic acids that used dual thiophilic–borophilic activation methodology.

Transition-metal-catalyzed cross-coupling reactions represent extremely powerful tools in organic synthesis.[1] As one recent example, thiol esters and boronic acids participate in a palladium-catalyzed, copper-mediated cross-coupling reaction to give ketones under neutral reaction conditions.[2] This new reaction relies upon the unique ability of a Cu(I) carboxylate to effect transmetalation of the intermediate acylpalladium thiolate ($RCOPdL_2SR'$) and a boronic acid through simultaneous thiophilic activation of the palladium thiolate bond and borophilic activation of the boronic acid.[3] To present the synthetic community with additional options for carbon−carbon bond formation through cross-coupling protocols, we now describe an extension of the thiophilic activation methodology to the coupling of thiol esters with organostannanes.[4] This system represents a useful approach to ketone synthesis under neutral reaction conditions from synthetically versatile thiol esters and complements the previously described coupling of thiol esters with boronic acids.[2] Some transformations of thiol esters to ketones are known, but they proceed under basic reaction conditions and are not general.[5] Other acylpalladium-based ketone syntheses are also known.[6]

The coupling reaction of thiol ester **1** with organostannane **2** was examined as a model system (Table 1). No observable reaction occurred between the reaction partners in the presence of various palladium catalysts alone. However, upon addition of Cu(I) 3-methylsalicylate (CuMeSal) or Cu(I)

---

[1] *Metal-Catalyzed Cross-Coupling Reactions*; Diederich, F., Stang, P. J., Eds.; Wiley-VCH: Weinheim, 1998.

[2] Liebeskind, L. S.; Srogl, J. *J. Am. Chem. Soc.* **2000**, *122*, 11260−11261.

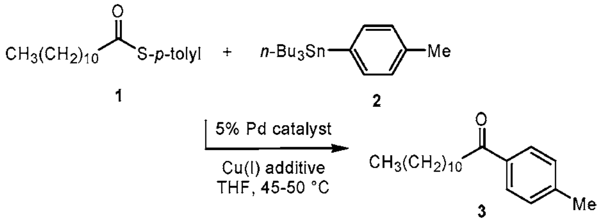
[3] See also: Savarin, C.; Srogl, J.; Liebeskind, L. S. *Org. Lett.* **2001**, *3* (1), 91−93. Savarin, C.; Liebeskind, L. S. *Org. Lett.* **2001**, *3* (14), 2149−2152. Srogl, J.; Liebeskind, L. S. *Org. Lett.* **2002**, *4* (6), 979−981. Kusturin, C. L.; Liebeskind, L. S.; Neumann, W. L. *Org. Lett.* **2002**, *4* (6), 983−985. Liebeskind, L. S.; Srogl, J.; Savarin, C.; Polanco, C. *Pure Appl. Chem.* **2002**, *74* (1), 115−122.

[4] See also: Egi, M.; Liebeskind, L. S. *Org. Lett.* **2003**, *5*, 801−802. Alphonse, F.-A.; Suzenet, F.; Keromnes, A.; Lebret, B.; Guillaumet, G. *Org. Lett.* **2003**, *5*, 803−805.

[5] Anderson, R. J.; Henrick, C. A.; Rosenblum, L. D. *J. Am. Chem. Soc.* **1974**, *96*, 3654−3655. Cardellicchio, C.; Fiandanese, V.; Marchese, G.; Ronzini, L. *Tetrahedron Lett.* **1987**, *28*, 2053−2056. Kawanami, Y.; Katsuki, I.; Yamaguchi, M. *Tetrahedron Lett.* **1983**, *24*, 5131−5132. Tokuyama, H.; Yokoshima, S.; Yamashita, T.; Fukuyama, T. *Tetrahedron Lett.* **1998**, *39*, 3189−3192. Araki, M.; Sakata, S.; Takei, H.; Mukaiyama, T. *Bull. Chem. Soc. Jpn.* **1974**, *47*, 1777−1780. Kim, S.; Lee, J. I. *J. Chem. Soc., Chem. Commun.* **1981**, 1231−1232.

10.1021/ol034962x CCC: $25.00

Table 1. Model System for the Coupling of Thiol Esters with Organostannanes



Pd source	Cu(I) source[a]	yield
$Pd(PPh_3)_4$	CuMeSal	60
$PdCl_2(PPh_3)_2$	CuMeSal	66
$PdCl(PPh_3)_2CH_2Ph$	CuMeSal	69
$PdCl(PPh_3)_2CH_2Ph$	CuTC	71
$Pd(PPh_3)_4$	CuDPP	89 (98)[b]
$PdCl_2(PPh_3)_2$	CuDPP	67 (92)[b]
$PdCl(PPh_3)_2CH_2Ph$	CuDPP	88 (97)[b]
$Pd_2(dba)_3$/TFP[c]	CuDPP	94

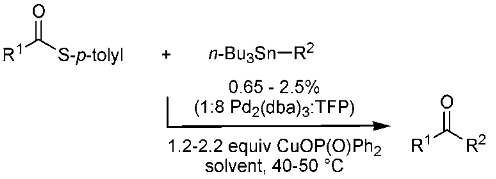
[a] CuTC = Cu(I) thiophene-2-carboxylate; CuMeSal = Cu(I) 3-methylsalicylate; CuDPP = Cu(I) diphenylphosphinate. [b] Yield based on recovered thiol ester. [c] TFP = tri-2-furylphosphine.

thiophene-2-carboxylate (CuTC), copper sources that had earlier proven to be effective for the palladium-catalyzed coupling of boronic acids with thiol esters,[2] heteroaromatic thioethers,[7] or thioalkynes,[8] ketone **3** was generated in moderate to good yields after 24 h in THF at 45−50 °C. Cu(I)Cl was ineffective as an additive, promoting only low conversion to product with various side reactions. No significant difference in efficiency was noted among the palladium catalysts $Pd(PPh_3)_4$, $PdCl_2(PPh_3)_2$, and $PdCl(PPh_3)_2(CH_2Ph)$, all of which produced ketone **3** in isolated yields between 60 and 71%.

The reaction workup was tedious, and removal of the tin residues was not efficient under the conditions mentioned above.[9] In earlier work on Stille cross-coupling reactions mediated only by copper(I) carboxylates,[10] we had noted the effectiveness of the $Ph_2P(O)O^-$ counterion in facilitating the separation of tin residues (as *n*-$Bu_3SnOP(O)Ph_2$) from the reaction mixture. This led in the current study to the consideration of Cu(I) diphenylphosphinate (CuDPP) as a unique mediator for the palladium-catalyzed coupling of thiol esters with organostannanes. In fact, $CuOP(O)Ph_2$ mediated the palladium-catalyzed coupling reaction of **1** with **2** in the presence of 5% $Pd(PPh_3)_4$, $PdCl_2(PPh_3)_2$, or $PdCl(PPh_3)_2(CH_2Ph)$ as catalysts to give ketone **3** in good to excellent isolated yields (Table 1). Notably, after a simple workup and chromatography, the desired product **3** was easily separated from *n*-$Bu_3SnOP(O)Ph_2$ and the copper residues. Additional improvements in yield were obtained using tri-2-furylphosphine (TFP) as a supporting ligand in combination with Pd_2dba_3, a catalyst system for which Farina had noted large rate accelerations in Stille cross-coupling reactions.[11,12]

To judge the generality of this new reaction, the cross-coupling of *S*-*p*-tolyl thiol esters with various tri-*n*-butylorganostannanes was investigated using between 0.65 and 2.5% of a 1:8 Pd_2dba_3/TFP catalyst system and 1.2−2.2 equiv of $CuOP(O)Ph_2$. The results are depicted in Table 2; THF was used as the solvent. The reaction system shows excellent generality and delivers good to excellent isolated yields of ketones from alkyl, aryl, heteroaryl, and functionalized *S*-*p*-tolyl thiol esters and from aryl, heteroaryl, and alkenylstannanes. In general, very good yields are obtained even using 1.2−1.3 equiv of the Cu(I) mediator, although in a few cases higher loadings were used. Some organotin compounds are noticeably sensitive to copper-mediated side reactions such as oxidative homocoupling and protodestannylation, probably

Table 2. Cross-Coupling of Thiol Esters and Organostannanes



entry	thiol ester, R^1	stannane, R^2	R^1COR^2 yield (%)[a]
1[b]	$CH_3(CH_2)_{10}$	*p*-tolyl	91
2[b]	$CH_3(CH_2)_{10}$	2-furyl	78
3[b]	$CH_3(CH_2)_{10}$	2-thienyl	73
4[b]	(*E*)-β-styryl	3-pyridyl	76
5[b]	(*E*)-β-styryl	4-pyridyl	67
6[b]	*p*-$NO_2C_6H_5$	2-pyridyl	70
7[b]	*p*-$NO_2C_6H_5$	1-methyl-2-pyrrolyl	91
8[c]	*p*-$NO_2C_6H_5$	2-pyrimidinyl	61
9[d]	*p*-$NO_2C_6H_5$	2-thiazolyl	69
10[d]	2-benzofuranyl	2-pyrazyl	96
11[d]	1-adamantyl	3-formyl-4-pyridyl	68
12[d]	2-aminophenyl	2-benzofuranyl	93
13[d]	2-acetoxyacetyl	2-benzofuranyl	96
14[e]	$CH_3(CH_2)_{10}$	2-methyl-1-propenyl	92
15[e]	*o*-tolyl	2-methyl-1-propenyl	81
16[e]	*o*-tolyl	2-thienyl	97
17[e]	$CH_3(CH_2)_{10}$	3-propenyl	81

[a] Isolated yields of purified products. [b] Conditions: 1% $Pd_2(dba)_3$, 8% TFP, 1.2 equiv of CuDPP, THF, 50 °C, 7 h. [c] Conditions: 2.5% of $Pd_2(dba)_3$, 20% TFP, 1.2 equiv of CuDPP, THF, 50 °C, 7 h. [d] Conditions: 0.65% $Pd_2(dba)_3$, 5.2% TFP, 1.3 equiv of CuDPP, 1:1 THF/hexanes, 40 °C, 18 h. [e] Conditions: 2.5% of $Pd_2(dba)_3$, 20% TFP, 2.2 equiv of CuDPP, THF, 50 °C, 1−25 h.

---

(6) Farina, V.; Krishnamurthy, V.; Scott, W. J. In *Organic Reactions*; Paquette, L., Ed.; John Wiley & Sons: New York, 1997; Vol. 50, pp 1−652. Mitchell, T. N. *Synthesis* **1992**, 803−815. Haddach, M.; McCarthy, J. R. *Tetrahedron Lett.* **1999**, *40*, 3109−3112. Bumagin, N. A.; Korolev, D. N. *Tetrahedron Lett.* **1999**, *40*, 3057−3060. Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457−2483. Goossen, L. J.; Ghosh, K. *Angew. Chem., Int. Ed.* **2001**, *40*, 3458−3460. Yamamoto, A. *Pure Appl. Chem.* **2002**, *74*, 1−5.

(7) Liebeskind, L. S.; Srogl, J. *Org. Lett.* **2002**, *4*, 979−981.

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

(9) Neither the standard treatment with KF nor washing with an aqueous NaOH solution was effective.

(10) Allred, G. D.; Liebeskind, L. S. *J. Am. Chem. Soc.* **1996**, *118*, 2748−2749.

(11) Farina, V.; Krishnamurthy, V.; Scott, W. J. In *Organic Reactions*; Paquette, L., Ed.; John Wiley & Sons: New York, 1997; Vol. 50, pp 1−652. Mitchell, T. N. *Synthesis* **1992**, 803−815. Stille, J. K. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 508−524.

(12) Farina, V.; Krishnan, B. *J. Am. Chem. Soc.* **1991**, *113*, 9585−9595.

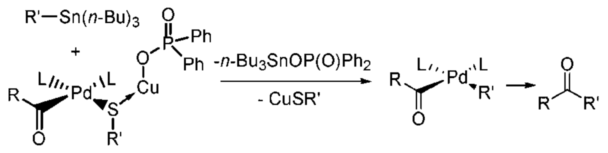
a result of transmetalation from tin to copper.[13] For these cases, it proved to be highly beneficial to reduce the effective concentration of Cu(I) in solution by the use of a 1:1 THF/hexanes solvent mixture in which the copper(I) salts are minimally soluble. For example, no ketonic product was observed in the coupling of 2-(tri-*n*-butylstannyl)thiazole with *p*-nitrobenzoic acid *S*-*p*-tolyl ester in THF alone as a solvent, while with 1:1 THF/hexanes, the product was obtained in 69% isolated yield.

For the most part, the reaction of thiol esters with organostannanes follows the same reactivity pattern as the previously described cross-coupling of thiol esters with boronic acids; however, there are some differences that justify the use of an organotin reaction system. For example, no product was detected in several attempted couplings of boronic acids with 2-amino-thiobenzoic acid *S*-*p*-tolyl ester, while the corresponding organotin version of the reaction furnished the desired product in high yield. Furthermore, while various α-heteroatom heteroarylboronic acids are problematic in cross-couplings (i.e, 2-pyridinylboronic acid), the corresponding organostannanes couple efficiently.

Notably, the cross-coupling of *S*-lauroyl-4-mercaptotoluene with 3-propenyl-tri-*n*-butylstannane at 50 °C for 1 h afforded the desired β,γ-unsaturated ketone in 81% yield, although a significantly diminished yield of the ketone resulted from longer reaction times (37% after 18 h). The easy isolation of the β,γ-unsaturated ketone using the present reaction conditions underscores the utility of this new ketone synthesis.[14]

The requirement in this reaction for a stoichiometric Cu(I) carboxylate or diphenylphosphinate suggests that, at a minimum, thiophilic activation of the acylpalladium(II) thiolate is a necessary prerequisite for transmetalation from tin to palladium (Scheme 1). Since CuCl does promote a low-yield conversion to ketone, it is unclear if concomitant activation of the organostannane by the diphenylphosphinate counterion is responsible for the superior yields in this system.

Scheme 1



In conclusion, a mild synthesis of ketones has been described that takes place under neutral reaction conditions. The reaction system consists of thiol esters and tri-*n*-butylorganostannanes that couple in the presence of low loadings of 1:8 $Pd_2(dba)_3$/TFP as the catalyst system and 1.2−2.2 equiv of Cu(I) diphenylphosphinate.

Acknowledgment. The National Institutes of General Medical Sciences, DHHS, supported this investigation through grant No. GM066153.

Supporting Information Available: Complete description of experimental details and product characterization. This material is available free of charge via the Internet at http://pubs.acs.org.

OL034962X

---

[13] Farina, V.; Kapadia, S.; Krishnan, B.; Wang, C.; Liebeskind, L. S. *J. Org. Chem.* **1994**, *59*, 5905−5911.

[14] **Typical Experimental Procedure for (4-Nitrophenyl)-thiazol-2-yl-methanone.** 2-(Tri-*n*-butylstannyl)thiazole (131 mg, 1.1 equiv, 0.35 mmol), 4-nitrothiobenzoic acid *S*-*p*-tolyl ester (87 mg, 0.32 mmol), CuDPP (120 mg, 1.2 equiv, 0.38 mmol), tri-2-furylphoshine (14 mg, 20 mol %, 64 μmol), and $Pd_2(dba)_3$ (7 mg, 2.5 mol %, 8 μmol) were placed in a Schlenk tube under argon. A 1:1 mixture of dry THF and hexanes (2.5 mL each) sparged with argon was added, and the mixture was heated to 40 °C. After 7 h, the mixture was filtered through a plug of Celite (washed with ether, 15 mL) and then evaporated. The residue was taken up in ethyl acetate (20 mL) and washed with aqueous NH_3 solution (10%) and brine (20 mL each). The organic phase was dried over $MgSO_4$ and concentrated. Purification of the residue by silica gel flash chromatography (hexanes → hexanes/CH_2Cl_2 5:1 → hexanes/CH_2Cl_2 1:1) afforded 52 mg (69%) of the ketone as a pale yellow solid: mp 121 °C; TLC (50% dichloromethane in hexanes, $R_f = 0.42$). Full spectroscopic details are provided in Supporting Information.