Reformatsky Type Reaction Promoted by Hexabutyldistannane

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$Bu_3SnSnBu_3$ proved to be effective reagent for Reformatsky type reaction. The use of Bu_2SnI_2 as an additive was essential, which proved to be effective for generation of organotin (IV) enolates. From the reaction with aldehydes, aldol type products were obtained in good yields.

Organotin(IV) enolates are used as mild and selective reagents for carbon-carbon bond formation.[1, 2] Though intrinsically more reactive than analogous silyl enolates, organotin(IV) enolates have narrower fields of applications that reflect the difficulty of handling such as moisture sensitive reagents. Hence a convenient procedure to generate organotin(IV) enolates was an important problem that we needed to solve.[3] The direct enolate formation by dehalogenation of α-halo ketones is one of versatile procedures, because which method includes an advantage that regioselective C-C bond formation is performed at the halide group. Although easily available hexabutyldistannane ($Bu_3SnSnBu_3$) is a suitable candidate as an organotin precursor, the heterolytic cleavage of the Sn-Sn bond proved to be difficult in the reaction such as addition to acetylenes.[4] Few example has been reported so far as to the attempts using $Bu_3SnSnBu_3$ in the Reformatsky type reaction, in which the reaction in the presence of palladium complex as a catalyst is included.[5]

$$
\begin{array}{ccc}
\textbf{1} & \textbf{2} & \\
\end{array}
\quad (1)
$$
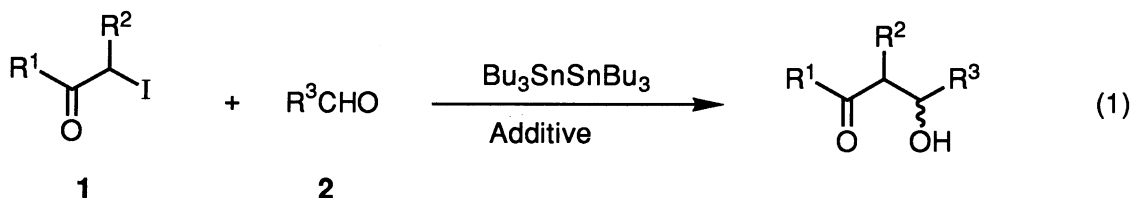
3a: R^1= Ph, R^2= Me, R^3= Ph
3b: R^1= Ph, R^2= Me, R^3= p-CH$_3$C$_6$H$_4$
3c: R^1= Ph, R^2= Me, R^3= p-NO$_2$C$_6$H$_4$
3d: R^1= Ph, R^2= Me, R^3= Et
3e: R^1, R^2= (CH$_2$)$_4$, R^3= Ph
3f: R^1= Me, R^2= H, R^3=Ph
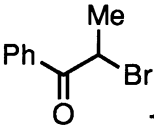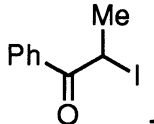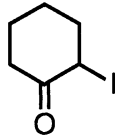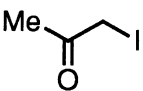
Table 1. Reformatsky Reaction Promoted by $Bu_3SnSnBu_3$ [a]

Entry	α-Halo Ketone (1)	Aldehyde (2)	Additive	Product	Yield/ % (erythro:threo)	
1	Ph─C(Me)(Br)─C(O), **1a**	PhCHO **2a**	-	**3a**	tr.	
2		**2a**	Bu_2SnI_2	**3a**	tr.	
3	Ph─C(Me)(I)─C(O), **1b**	**2a**	-	**3a**	6	
4		**2a**	Bu_2SnI_2	**3a**	77	(51 : 49)
5		**2a**	Bu_2SnI_2-HMPA	**3a**	93	(50 : 50)
6		p-$CH_3C_6H_4CHO$ **2b**	Bu_2SnI_2-HMPA	**3b**	53	(46 : 54)
7		p-$NO_2C_6H_4CHO$ **2c**	Bu_2SnI_2-HMPA	**3c**	99	(54 : 46)
8		EtCHO **2d**	Bu_2SnI_2-HMPA	**3d**	86	(50 : 50)
9	**1c**	**2a**	Bu_2SnI_2-HMPA	**3e**	40	(55 : 45)
10	Me─C(O)─CH₂─I **1d**	**2a**	Bu_2SnI_2-HMPA	**3f**	57	

a) $Bu_3SnSnBu_3$ 2 mmol, α-halo ketone (1) 2 mmol, aldehyde (3) 2 mmol, additive 2 mmol, 60 °C, 3 h.

We found here a $Bu_3SnSnBu_3$ promoted Reformatsky reaction could be established effectively by using dibutyltin diiodide (Bu_2SnI_2) as an additive (Eq. 1). With presented method, crossed aldol products 3 were obtained in good yields by the reaction of the generated tin enolates from 1 with aldehydes 2. In particular, expensive catalysts such as palladium complexes are not necessary any more.

Table 1 shows the results of the Reformatsky reactions promoted by $Bu_3SnSnBu_3$. In the case using α-bromo ketone **1a** as an enolate precursor, the reaction with PhCHO did not

proceed at all at 60 °C for 3 h (entry 1), in which starting materials were recovered quantitatively. Using α-iodo ketone **1b** slightly increased the yields of crossed aldol product **3a** (entry 3). On the other hand, under similar conditions, the reaction of **1b** in the presence of an equimolar amount of Bu_2SnI_2 afforded a higher yield (entry 4). Furthermore, the yield of **3a** was increased to 93% in the presence of HMPA (entry 5).

The following procedure is representative. Under nitrogen, to the THF solution of **1b** (2 mmol) was added $Bu_3SnSnBu_3$ (2 mmol), Bu_2SnI_2 (2 mmol) and **2a** (2 mmol). The solution was stirred at 60 °C for 3 h. After quenching with MeOH, product **3a** was obtained by column chromatography with silica gel eluted by hexane/EtOAc (1/1).

Table 1 summarizes the results using various α-iodo ketones. With a more electrophilic aldehyde such as **2c**, product **3c** was obtained in a quantitative yield (entry 7). The reaction of aliphatic aldehyde **2d** also proceeded to afford **3d** in good yield (entry 8). α-Iodo ketones, **1c** and **1d**, which bear enolizable α'-protones also afforded the aldol products **3e** and **3f** effectively (entries 9 and 10). In this way, Bu_2SnI_2-HMPA serves as an effective additive for hexabutyldistannane prompted Reformatsky reactions.

As shown in Scheme 1, it becomes clear that Bu_2SnI_2 plays an important role at the stage of enolates formation. As a tin enolate **A** is easily protonated by ordinary work up,[4] the yields of the enolate were determined as propiophenone **4**. In the case of **1a**, an enolate was not generated at all at 60 °C for 3 h, where the starting material was recovered quantitatively.

| Additive	Yield of 4 (%)
-	6
Bu_2SnI_2	62
Bu_2SnI_2-HMPA	72
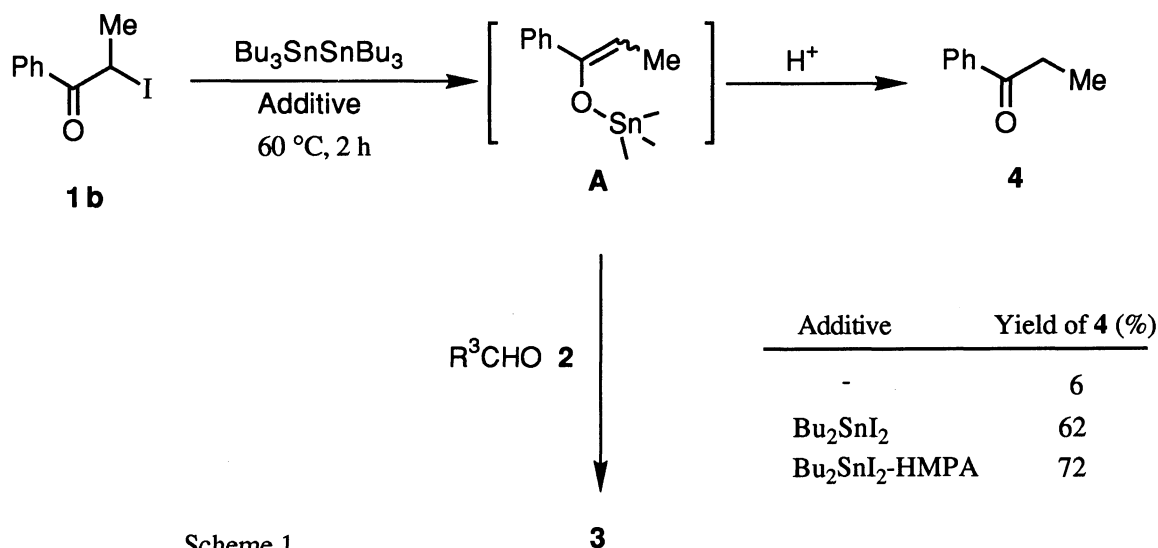
Scheme 1.

In the reaction of **1b**, 6% yield of **4** was obtained. Furthermore, the addition of Bu_2SnI_2 effectively increased the yield of **4**.[6] In particular, Bu_2SnI_2-HMPA afforded 72% yield of **4**.

In this way, the use of α-iodo ketone as a substrate and Bu_2SnI_2-HMPA as an additive affords an effective method for generation of organotin(IV) enolates by $Bu_3SnSnBu_3$. The formed enolate **A** reacts with electrophiles to afford product **3**.

References
1) M. Pereyre, P. J. Quintard, and A. Rahm, "Tin in Organic Synthesis," Butterworth, London (1987) p. 286; I. Omae, "Organotin Chemistry; J. Organomet. Chem. Lib. 21," Elsevier, New York (1989).
2) S. Shenvi and J. K. Stille, *Tetrahedron Lett.*, **23**, 627 (1982); A. Baba, M. Yasuda, I. Shibata, and H. Matsuda, *J. Chem. Soc., Perkin Trans. 1*, **1990**, 3205.
3) For generation of organotin(IV) enolates, transmetalation of lithium enolates,[3a] hydrostannation of α,β-unsaturated ketones,[3b] and transesterification of enol acetates[3c] are known as general procedures.   a) Y. Yamamoto, H. Yatagai, and K. Maruyama, *J. Chem. Soc., Chem. Commun.*, **1981**, 162;   b) M. Pereyre, and J. Valade, *Bull. Soc. Chim. Fr.*, **1967**, 1928;   c) M. Pereyre, B. Bellegarde, J. Mendelsohn, and J. Valade, *J. Organomet. Chem.*, **11**, 97 (1968).
4) For example, although $Me_3SnSnMe_3$ is reactive in the addition of distananne to acetylene compounds, $Bu_3SnSnBu_3$ is not reported at all.   T. N. Mitchel, K. Kwetkat, D. Rutschow, and U. Schneider, *Tetrahedron*, **45**, 969 (1989).
5) M. Kosugi, M. Koshiba, H. Sano, and T. Migita, *Bull. Chem. Soc. Jpn.*, **58**, 1075 (1985).
6) We consider redistribution of $Bu_3SnSnBu_3$ took place by Bu_2SnX_2 to form $Bu_3SnSnBu_2X$ (Eq. 2), which would be effective for the formation of the enolate.

$$Bu_3SnSnBu_3 \; + \; Bu_2SnX_2 \; \longrightarrow \; Bu_3SnSnBu_2X \; + \; Bu_3SnX \quad (2)$$
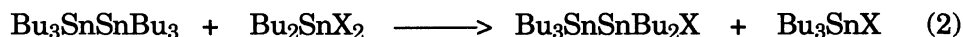
In the case of X=I, although the novel type of distannane was not detected by ^{119}Sn NMR, the signal for Bu_3SnI was observed at 72 ppm at room temperature.   Meantime, in the case of X=Br, a signal for Bu_3SnBr (129 ppm) and a new one at -135 ppm were detected.