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Highly Diastereoselective Reformatsky-Type Reaction Promoted by Tin Iodide Ate Complex

Ikuya Shibata, Toshihiro Suwa, Hideaki Sakakibara, and Akio Baba*

Department of Molecular Chemistry & Frontier Research Center, Graduate School of Engineering, Osaka University, 2-1 Yamadaoka, Suita, Osaka 565-0871, Japan

shibata@ap.chem.eng.osaka-u.ac.jp

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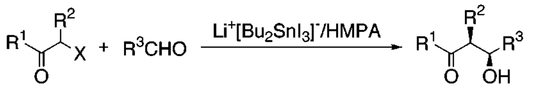
ABSTRACT



An ate type of tin complex, Li$^+$[*n*-Bu$_2$SnI$_3$]$^-$/HMPA, works as a novel type of reagent to accomplish the highly diastereoselective Reformatsky-type reaction by the halogen–metal exchange method.

The Reformatsky reaction is a convenient and useful protocol for carbon−carbon bond formation using α-halocarbonyl compounds.[1] However, the yield and diastereoselectivity of the β-hydroxycarbonyl compounds produced are unsatisfactory. To overcome these problems, many types of modified procedures have been developed so far. Oxidative addition using low-valent metal reagents[2] is a representative method in which diastereoselective reactions have been accomplished in some cases.[2a,b,e] However, in most of them, using low-valent metals causes undesirable side reactions involving dehydration and reduction of unsaturation. As an alternative facile and general route, the halogen−metal exchange method of α-haloketones with ordinal-valent metal reagents can generate various metal enolates.[3] Recently, hypervalent Mn complexes have been focused on as novel reagents for the Reformatsky-type reaction.[4] However, these halogen−metal exchange methods have not attained high diastereoselectivity.[3,4] During our investigation of organotin ate complexes,[5] we found that the tin ate complex Li$^+$[*n*-Bu$_2$SnI$_3$]$^-$/HMPA accomplishes the highest class of *syn*-diastereoselectivity in the Reformatsky-type reaction via halogen−metal exchange method in α-haloketones.

Initially, we performed the reaction of α-iodopropiophenone (**1a**) with benzaldehyde (**2a**) for investigating an effective promotor (Table 1). The equimolar combination of di-*n*-butyltin diiodide (*n*-Bu$_2$SnI$_2$) and lithium iodide (LiI) afforded the desired β-hydroxy ketone **3a** in 67% yield (entry 3). Of particular interest is the high *syn*-selectivity. The sole use of either *n*-Bu$_2$SnI$_2$ or LiI afforded no product at all (entries 1 and 2). The addition of excess amounts of LiI did not change the yield and selectivity (entry 4). Further addition of an equimolar amount of HMPA to the *n*-Bu$_2$SnI$_2$−LiI

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(1) (a) Rathke, M. W.; Weipert, P. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 2, Chapter 1.8, pp 277−299. (b) Rathke, M. W. In *Organic Reactions*; John Wiley & Sons: New York, 1975; Vol. 22, Chapter 2, pp 30−59.

(2) For example, Ge: (a) Kagoshima, H.; Hashimoto, Y.; Oguro, D.; Saigo, K. *J. Org. Chem.* **1998**, *63*, 691. Sn: (b) Harada, T.; Mukaiyama, T. *Chem. Lett.* **1982**, 467. (c) Chan, T. H.; Li, C. J.; Wei, Z. Y. *J. Chem. Soc., Chem. Commun.* **1990**, 505. Co: (d) Orsini, F. *J. Org. Chem.* **1997**, *62*, 1159. In: (e) Chan, T. H.; Li, C. J.; Lee M. C.; Wei, Z. Y. *Can. J. Chem.* **1994**, *72*, 1181. R$_3$Sb: (f) Huang, Y. Z.; Chen. C.; Shen, Y. *J. Chem. Soc., Perkin Trans. 1* **1988**, 2855. TiCl$_4$−Bu$_4$NI: (g) Tsuritani, T.; Ito, S.; Shinokubo, H.; Oshima, K. *J. Org. Chem.* **2000**, *65*, 5066.

(3) EtMgBr, *n*-BuLi, Et$_2$Zn, Me$_3$Al, Et$_3$B: (a) Aokia, Y.; Oshima, K.; Uchimoto, K. *Chem. Lett.* **1995**, 463. Et$_2$AlCl−Zn: (b) Maruoka, K.; Hashimoto, S.; Kitagawa, Y.; Yamamoto, H.; Nozaki, H. *Bull. Chem. Soc. Jpn.* **1980**, *53*, 3301. Et$_2$AlCl−Bu$_3$SnLi: (c) Matsubara, S.; Tsuboniwa, N.; Morizawa, Y.; Oshima K.; Nozaki, H. *Bull. Chem. Soc. Jpn.* **1984**, *57*, 3242. CeI$_3$: (d) Fukuzawa, S.; Tsuruta, T.; Fujinami, T.; Sakai, S. *J. Chem. Soc., Perkin Trans. 1* **1987**, 1473. AlI$_3$: (e) Borah, H. N.; Boruah, R. C.; Sandhu, J. S. *J. Chem. Soc., Chem. Commun.* **1991**, 154. R$_3$SnSnR$_3$: (f) Kosugi, M.; Koshiba, M.; Sano H.; Migita, T. *Bull. Chem. Soc. Jpn.* **1985**, *58*, 1075. (g) Shibata, I.; Yamaguchi, T.; Baba, A.; Matsuda, H. *Chem. Lett.* **1993**, 97. (h) Shibata, I.; Kawasaki, M.; Yasuda, M.; Baba, A. *Chem. Lett.* **1999**, 689.

(4) Mn complex: Hojo, M.; Harada, H.; Ito, H.; Hosomi, A. *J. Am. Chem. Soc.* **1997**, *119*, 5459.

(5) We have already reported a similar ate complex of tin hydrides, Li$^+$[*n*-Bu$_2$SnI$_2$H]$^-$, which afforded conjugate hydrostannation of enals where high nucleophilicity of apical tin−iodine bond played an important role. Suwa, T.; Shibata, I.; Baba, A. *Organometallics* **1999**, *18*, 3965.

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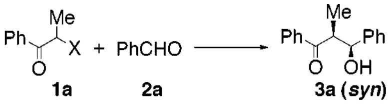
Table 1. Reformatsky-Type Reactions of α-Halo Acetophenone with PhCHO[a]



entry	X	reagent (mmol)	yield (%)[b]	*syn*:*anti*[b]
1	I	Bu_2SnI_2 (2)	tr	
2	I	LiI (2)	tr	
3	I	Bu_2SnI_2 (2), LiI (2)	67	94:6
4	I	Bu_2SnI_2 (2), LiI (4)	66	94:6
5	I	Bu_2SnI_2 (2), LiI (2), HMPA (2)	89	95:5
6	Cl	Bu_2SnI_2 (2), LiI (2), HMPA (2)	89	86:14

[a] **1** (2 mmol), **2a** (1 mmol), THF (1 mL), 6 °C, 12 h. [b] Yields and ratios were determined by ^1H NMR based on **2a**.

system gave the highest yield and *syn*-selectivity examined (entry 5).[6] Instead of α-iodoketones, it is possible to use more easily available α-chloroketones (entry 6) because of easy conversion of α-chloroketones to α-iodoketones with the iodotin reagent. Thus the treatment of n-Bu_2SnI_2−LiI with α-chloro propiophenone under the identical conditions in Table 1 underwent halogen exchange to the corresponding iodoketone quantitatively. The *syn*-selectivity of β-hydroxyketone **3a** is of the highest level in comparison with that of conventional reagents for the Reformatsky-type reaction so far.[2,3]

We confirmed the formation of an ate complex between n-Bu_2SnI_2 and LiI. When equimolar LiI was added to n-Bu_2SnI_2 in THF solvent, ^{119}Sn NMR indicated an upfield shift from −58.0 to −141.4 ppm. The value of coupling constant $^1J(^{119}Sn-^{13}C)$ also increased from 373.2 to 542.9 Hz. These changes indicate the formation of TBP-type complex $Li^+[n\text{-}Bu_2SnI_3]^-$ (**I**),[5,7] as shown in Scheme 1. The presence of equimolar HMPA in the equimolar mixtures of n-Bu_2SnI_2 and LiI afforded a slight change of chemical shift (−158.0 ppm) and coupling constant ($^1J(^{119}Sn-^{13}C) = 548.0$ Hz). It is considered that HMPA interacts with lithium cation to form a complex such as **II**. In this case, the formation of alternative complex Bu_2SnI_2−HMPA by ligand exchange could not be considered, because we confirmed that the obtained values were not consistent with the ones of Bu_2SnI_2−HMPA complex ($\delta(^{119}Sn) = -204.6$, $^1J(^{119}Sn-^{13}C) = 496.1$ Hz). In the Reformatsky-type reaction, the complex **II** gave a superior result in the case of the complex **I** (Table 1, entries 3 and 5). Hence the basicity of **II** would be higher than that of **I**, acting as an effective reagent.

Scheme 1

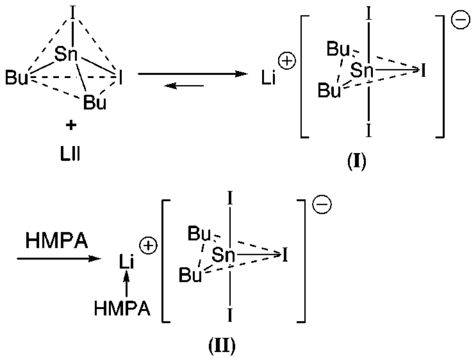
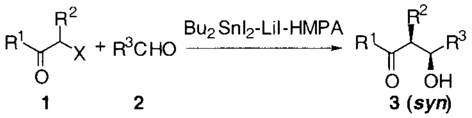


Table 2. *syn*-Selective Reformatsky-Type Reaction[a]



entry	R^1	R^2	X	R^3	product	yield (%)	*syn*:*anti*[b]
1	Ph	Me	I	Ph	**3a**	89	95:5
2	Ph	Me	I	p-MeC_6H_4	**3b**	70	93:7
3	Ph	Me	I	p-ClC_6H_4	**3c**	86	91:9
4	Ph	Me	I	p-$O_2NC_6H_4$	**3d**	89	91:9
5	Ph	Me	I	n-C_5H_{11}	**3e**	53	86:14
6	Ph	Me	I	$PhCH_2CH_2$	**3f**	65	84:16
7	Ph	Me	I	*i*-Pr	**3g**	77	91:9
8	Ph	Me	I	*t*-Bu	**3h**	9	-
9	Ph	Me	I	PhCH=CH	**3i**	65	84:16
10	Ph	Me	I	MeCH=CH	**3j**	45	83:17
11	Ph	H	Cl	Ph	**3k**	93	
12	Me	Me	Cl	Ph	**3l**	50	90:10
13	Et	H	Cl	Ph	**3m**	56	
14	H	*n*-Bu	Cl	Ph	**3n**	37	80:10

[a] Bu_2SnI_2 (2 mmol), LiI (2 mmol), HMPA (2 mmol), **1** (2 mmol), **2** (1 mmol), THF (1 mL). [b] Yields and ratios were determined by ^1H NMR based on **2**.

Table 2 shows the results using complex **II**. Besides benzaldehyde **2a**, other aromatic aldehydes **2** reacted effectively to give **3b**−**d** in good yields with high *syn*-selectivities beyond 91% (entries 2−5). In the case of aliphatic aldehydes, primary and secondary ones reacted well to give **3e**−**g** (entries 5−7). Tertiary substituted aliphatic aldehyde, however, scarcely produced the desired **3h** because of its steric hidrance (entry 8). The reaction using α,β-unsaturated aldehydes gave only 1,2-adducts **3i** and **3j** in moderate yields with high *syn*-selectivities (entries 9 and 10). Primary α-chloroketone reacted well to give a high yield of

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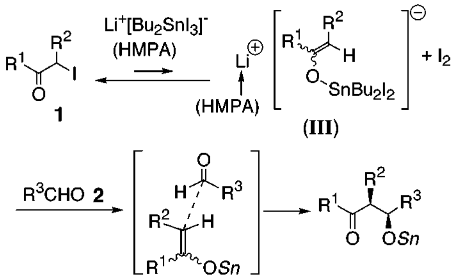
(6) **General Experimental Procedure.** To a THF (1 mL) solution of n-Bu_2SnI_2 (0.95 g, 2 mmol) and LiI (0.266 g, 2 mmol) was added HMPA (0.360 g 2 mmol) at 6 °C (bath temp), and the solution was stirred for 5 min. To the solution was added α-iodopropiophenone (**1a**) (0.520 g, 2 mmol) and benzaldehyde (**2a**) (0.106 g, 1 mmol). The solution was stirred at 6 °C (bath temp) for 12 h. MeOH (3 mL) was added to quench the reaction, and volatiles were removed under reduced pressure. The residue was subjected to column chromatography, eluting with hexanes−EtOAc (1:1) to give a *syn*-rich mixture of β-hydroxy ketones **3a**. Further purification was performed by TLC, eluting with hexane−diethyl ether (1:1). The stereochemistry of **3a** was assigned by ^1H NMR in comparison with the stereochemically defined authentic samples.

(7) For example, see: (a) Davis, A. G. *Organotin Chemistry*; VCH: New York, **1997**; pp 18. (b) Harrison, P. G. *Chemistry of Tin*; Blackie; London, 1989; p 71. (c) Holecek, J.; Nádvorník, M.; Handlír, K.; Lycka, A. *J. Organomet. Chem.* **1983**, *241*, 177. (d) Nádvorník, M.; Holecek, J.; Handlír, K.; Lycka, A. *J. Organomet. Chem.* **1984**, *275*, 43.

3k (entry 11). The regiospecificity of the reaction was obtained by the reaction of halogenated 2-butanone derivatives such as 3-chloro-2-butanone and 1-chloro-2-butanone (entries 12 and 13). Each isomer afforded the corresponding β-hydroxy ketone **3l**, **3m** without any isomerization of the enolate. Although the yield was not good, α-chloroaldehyde gave an acceptable *syn*-selectivity of β-hydroxy aldehyde **3n** (entry 14).

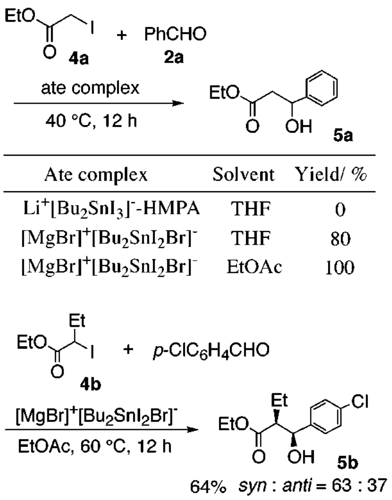
As to the reaction path, the tin ate complex reacts with α-iodoketone to form highly coordinated tin enolate (**III**), accompanying iodine (Scheme 2).[8,9] Unfortunately, when the mixture of **1a** and complex **II** was monitored by ^{1}H NMR at room temperature, no peaks other than **1a** were detected.[10] We consider that the small amount of enolates (**III**) in the equilibrium is immediately trapped by an aldehyde to form a β-stannyloxyketone. The high *syn*-selectivity could be explained by the noncyclic antiperiplaner transition state[11] because the hypervalent tin center cannot coordinate to the oxygen of an aldehyde any more.

Scheme 2



When iodomethyl ethylester **4a** was treated with benzaldehyde **2a**, no reaction occurred and starting substrates were recovered. This limitation could be solved by the use of $MgBr_2 \cdot OEt_2$ instead of LiI, and desired β-hydroxy ester **5a** was obtained in 80% yield (Scheme 3). Moreover, the use of EtOAc as a solvent afforded a quantitative yield. In the reaction of secondary iodoester **4b**, although high *syn*-selectivity could not be attained (63% selectivity), the reaction proceeded in moderate yield (64%). In this case, we also confirmed the ate tin complex,[12] by the fact that ^{119}Sn NMR indicated an upfield shift from −58.0 to −114.6 ppm when equimolar $MgBr_2 \cdot OEt_2$ was added to n-Bu_2SnI_2 in ethyl acetate-d_8. Namely, the ate complex $MgBr^+[n\text{-}Bu_2SnBrI_2]^-$ also works in the Reformatsky reactions.

Scheme 3



Ate complex	Solvent	Yield/ %
$Li^+[Bu_2SnI_3]^-$-HMPA	THF	0
$[MgBr]^+[Bu_2SnI_2Br]^-$	THF	80
$[MgBr]^+[Bu_2SnI_2Br]^-$	EtOAc	100

In conclusion, we developed ate-type tin complexes to perfom Reformatsky-type reaction with high *syn*-selectivities. It is not necessary to isolate the tin complex, which was generated in situ by simply mixing easily available n-Bu_2SnI_2 with LiI or $MgBr_2 \cdot OEt_2$. The further investigation of mechanistic studies is now in progress.

Acknowledgment. This work was supported financially by a Grant-in Aid for Scientific Research from Ministry Education, Science and Culture. Thanks are due to the Analytical Center, Osaka University, for assistance in obtaining HRMS spectra.

Supporting Information Available: Experimental procedures and IR, ^{1}H NMR, ^{13}C NMR, and HRMS spectrum for **3a**−**g**, **3i**−**n**, **5a** and **5b**, and ^{13}C- and ^{119}Sn NMR data for the tin ate complex **I** and **II**. This material is available free of charge via the Internet at http://pubs.acs.org.

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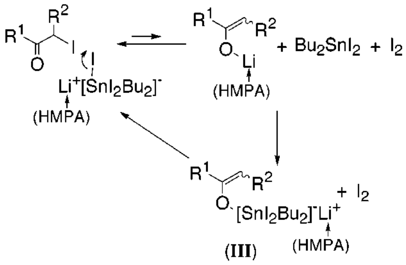
(8) For the generation of tin enolate (**III**), we tentatively consider that the reaction of **1** with tin complex (**I**) affords a lithium enolate initially, which reacts with Bu_2SnI_2.



Although the possibility of the contribution of the lithium enolates to react with aldehydes cannot be excluded, we consider that the tin enolates react with aldehydes, because lower diastereoselectivities have been obtained in the case of lithium enolates.[3a]

(9) The enolate formation via attack of iodine anion has been reported for AlI_3[3e] and TiI_4 systems.[9a] (a)Hayakawa, R.; Shimizu, M. *Org. Lett.* **2000**, *2*, 4079.

(10) There is also another possibility that the reaction may proceed through a SET mechanism, which is already suggested in the indium-mediated reaction,[2e] although no homocoupling products of haloketones or aldehydes have been obtained.

(11) Yamamoto, Y. *Acc. Chem. Res.* **1987**, *20*, 243.

(12) We have already revealed the structure of a similar ate complex of tin hydrides $MrBr^+[n\text{-}Bu_2SnBrIH]^-$, which afforded hydrostannation of alkynes. Suwa, T.; Shibata, I.; Ryu, K.; Baba, A. *J. Am. Chem. Soc.* **2001**, *123*, 4101.