Control of Both Syn and Anti Stereoselectivity in Michael Additions of Organotin Enolates

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Organotin enolates are mild and selective reagents for carbon−carbon bond formation.[1] One of the characteristic applications of these enolates is their stereoselective aldol reactions, where syn/anti diastereoselectivity is facially controlled by substituents on the tin atom.[2] In contrast, little attention has been paid to the Michael addition of organotin enolates,[3] and in particular, effective control of syn/anti selectivity by using tin enolates has not been reported.[4] This fact encouraged us to investigate the control of diastereoselectivity of their Michael reaction by varying the substituents on the tin atom in the enolates.

Tin enolates are available by several methods such as the transeterification of enol acetates,[5] the transmetalation of lithium enolates,[6] and the hydrostannation of unsaturated ketones.[7] We also have recently demonstrated that the treatment of ketones with *N*-stannylcarbamates generates functionalized tin enolates, where effective abstraction of acidic protones in α-halo ketones gave 2-halo enolates.[8] Here we present novel reactivities of two types of tin enolates, tri-*n*-butyltin enolates **I** and dichloro-*n*-butyltin enolate **II**, which are generated by treatment of 2-methoxy ketones **1** with $Bu_3SnN(^iPr)_2$ and $Cl_2BuSnN(^iPr)_2$, respectively. Of interest is that each tin enolate provided opposite diastereoselectivity in Michael additions to unsaturated ketones **2**[9] (Scheme 1).

Initially, we performed the reaction of 2-methoxytri-*n*-butyltin enolate **I** derived from **1a** (Table 1). The enolate underwent 1,4-addition to unsaturated ketone **2a** regioselectively,[10] giving 1,5-diketones **3a** in 64% yield with complete anti selectivity (entry 1). Trimethyl- and triphenyltin enolates also afforded effective Michael additions (entries 2 and 3), where efficient anti selectivities were accomplished. When chloro substituents were introduced on the tin atom of the enolate, conjugate addition of this chlorodi-*n*-butyltin enolate to **2a** led to increase of the syn adduct (entry 4). Of interest is that a significant improvement in the diastereoselectivity was achieved as the number of chlorine substituents was increased. Thus, dichloro-*n*-butyltin (Cl_2BuSn) enolate **II** from **1a** reacted with **2a** to give *syn*-**3a** with 79% diastereoselectivity (entry 5). When 2 equiv of $BuSnCl_3$ was used to prepare $Cl_2BuSnN(^iPr)_2$, syn selectivity was increased up to 91% (entry 6).

Table 2 shows the results of Michael addition starting from 2-methoxy ketones **1** and enones **2**. Similar to **2a**, enones **2b** and **2c** were also reactive with tin enolates of **1a** to give 1,5-diketones **3b** and **3c**, respectively (entries 1−4). In addition, various types of 2-methoxy ketones **1b**−**e** could be used as tin enolate precursors. Thus the tin enolates generated from **1b**−**e** afforded Michael reaction with **2a** to give 1,5-diketones **3d**−**g** (entries 5−12). In all cases, remarkable change of diastereoselectivity was observed by the number of chloro substit-

Scheme 1

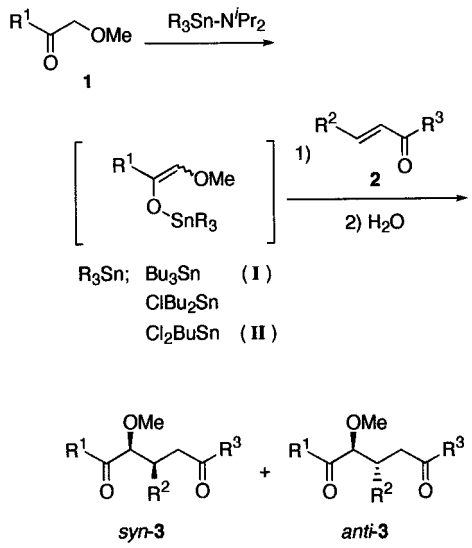
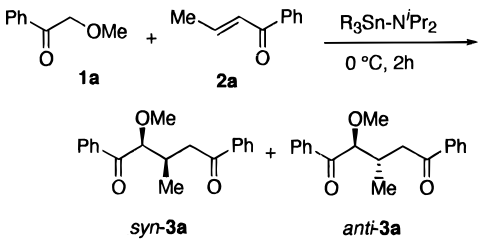


Table 1. Diastereoselectivity in the Michael Addition of 1a with 2a[a]



entry	tin amide[b]	yield (%)	syn:anti
1	$Bu_3SnNPr^i_2$	64	0:100
2	$Me_3SnNPr^i_2$	61	9:91
3	$Ph_3SnNPr^i_2$	59	9:91
4	$ClBu_2SnNPr^i_2$	74	50:50
5	$Cl_2BuSnNPr^i_2$	76	79:21
6	$Cl_2BuSnNPr^i_2$	84[c]	91:9

[a] **1a** 1 mmol, **2a** 1 mmol, tin amide 1 mmol, THF 1 mL. [b] Tin amide was prepared from $R_{4-n}SnX_n$ (X = Cl, Br) (1 mmol) and LDA (11 mmol). [c] 2 equiv of $BuSnCl_3$ was added to LDA.

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(9) As to the Michael addition using α-alkoxy carbonyls, syn-selective reaction was reported by using lithiated α-alkoxyacetamides: Kanemasa, S.; Nomura, M.; Wada, E. *Chem. Lett.* **1991**, 1735.

(10) No products derived from 1,2-addition were detected.

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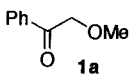
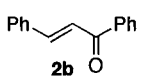
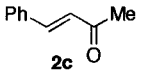
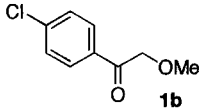
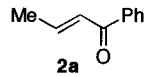
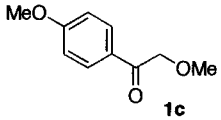
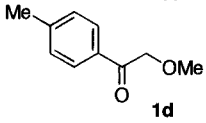
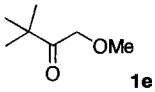
Table 2. Diastereoselective Synthesis of 1,5-Diketones

entry	methoxy ketone	enone	R_3Sn	conditions	product	yield (%)	*syn* : *anti*
1	 **1a**	 **2b**	Bu_3Sn[a] (I)	0°C, 2h	**3b**	66	22 : 78
2			Cl_2BuSn[b] (II)	0°C, 2h	**3b**	99	82 : 18
3	**1a**	 **2c**	(I)	0°C, 2h	**3c**	64	1 : 99
4	**1a**		(II)	0°C, 2h	**3c**	41	82 : 18
5	 **1b**	 **2a**	(I)	rt, 2h	**3d**	60	14 : 86
6			(II)	0°C, 2h	**3d**	53	77 : 23
7	 **1c**	**2a**	(I)	0°C, 2h	**3e**	56	7 : 93
8		**2a**	(II)	0°C, 2h	**3e**	64	80 : 20
9	 **1d**	**2a**	(I)	0°C, 2h	**3f**	60	4 : 96
10		**2a**	(II)	0°C, 2h	**3f**	73	71 : 29
11	 **1e**	**2a**	(I)	rt, 18h	**3g**	36	1 : 99
12		**2a**	(II)	rt, 2h	**3g**	31	82 : 18

1 1 mmol, **2** 1 mmol, THF 1 mL.

[a] $Bu_3SnN^iPr_2$ was prepared from Bu_3SnBr (1 mmol) and LDA (1 mmol)
[b] $Cl_2BuSnN^iPr_2$ was prepared from $BuSnCl_3$ (2 mmol) and LDA (1 mmol)

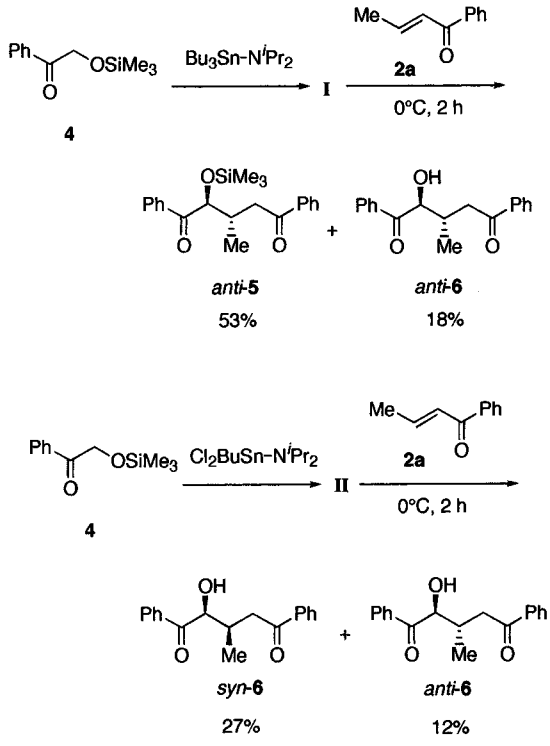
uents on the tin atom. Thus the reaction proceeded with high anti selectivity to give *anti*-**3b**−**g** in the reaction with tri-*n*-butyltin enolates **I** (entries 1, 3, 5, 7, 9, and 11), whereas dichloro-*n*-butyltin enolates **II** induced opposite diastereoselection to form *syn*-**3b**−**g** predominantly (entries 2, 4, 6, 8, 10, and 12).

In place of 2-methoxy ketones **1**, 2-trimethylsiloxy ketone **4** was used as an enolate precursor (Scheme 2). When tri-*n*-butyltin enolate **I** derived from **4** was treated with enone **2a**, 2-trimethylsiloxy 1,5-diketone **5** and 2-hydroxy 1,5-diketone **6** were obtained. Both compounds were revealed as anti isomers. During workup, desilylation of *anti*-**5** took place to form *anti*-**6**. Namely, tri-*n*-butyltin enolate **I** provided an anti-selective reaction. In contrast, in the case of dichloro-*n*-butyltin enolate **II**, only desilylated products **6** were obtained as a syn/anti diastereomeric mixture. Although syn selectivity was not as good as that in the case of 2-methoky ketone **1a**, predominant formation of *syn*-**6** was observed.

In the case of lithium enolates derived from simple ketones, Heathcock et al. demonstrated that syn and anti selectivities of the Michael adducts are dependent on the stereochemistry of lithium enolates.[4] For example, the treatment of propiophenone with LDA at −78 °C provides a *Z*-enolate which affords anti-Michael additions. In contrast, in the case of methoxy ketone **1a**, the control of stereoselectivity was difficult under the same conditions. When the lithium enolate generated from **1a** with LDA at −78 °C was reacted with **2a**, an almost equimolar mixture of both diastereomers, *anti*-**3a** and *syn*-**3a**, was obtained. The 2-methoxy group would prevent the selective formation of *Z*-lithium enolate.

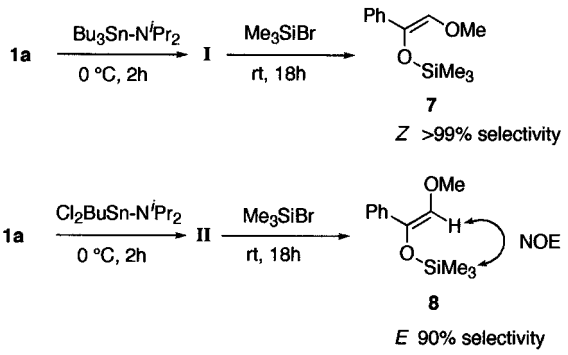
We assume here that *E*/*Z* stereochemistry of the tin enolates of **1** is controlled by the substituents on the tin

Scheme 2

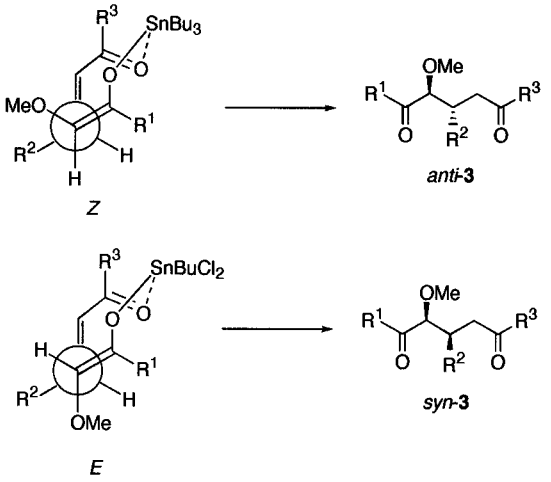


atom. Namely, tri-*n*-butyltin enolates **I** would exist as *Z*-forms, whereas dichloro-*n*-butyltin enolates **II** as *E*-isomers. The treatment of tin enolate **I** of **1a** with Me_3-SiBr at rt gave TMS enolate **7** selectively (Scheme 3). ^1H NMR spectra of **7** indicated the vinyl proton at 6.26 ppm. In contrast, enolate **II** afforded a stereoisomeric TMS

Scheme 3



Scheme 4



enolate **8** in 90% selectivity where the vinyl proton was detected at 5.34 ppm. The silylation of lithium enolate derived from **1a** gave a mixture of **7** and **8**. An NOE experiment suggested that TMS enolate **7** exists as the *Z*-isomer and enolate **8** as the *E*-isomer because a greater enhancement was observed at the vinyl proton of **8** than that in the case of **7** by the irradiation of methyl protons of TMS groups. Although the exact reason Cl_2BuSn group prefers *E*-enolate is not clear, dipole repulsion between chloro groups and alkoxy group would be responsible for the stereochemistry. As a result, the difference of stereochemistry of the enolate induces the opposite diastereoselectivity in the Michael reaction. The reactions proceeded via eight-membered chelated transition state in consideration with adverse R^1-R^3 interaction as proposed previously (Scheme 4).[4]

This reaction is very convenient because all treatments were able to be performed in a one-pot procedure from the formation of the starting tin amides. Moreover, the present method provided both stereoisomers (syn and anti). Further applications to other tin enolates are now in progress.

Experimental Section

Analysis. ^1H and ^{13}C NMR spectra were recorded at 400 and 100 MHz, respectively. Samples for ^1H and ^{13}C NMR spectra of product were examined in $CDCl_3$ containing 0.03% (w/v) of tetramethylsilane. Column chromatography was performed by using Wakogel C-200 mesh silica gel. Preparative TLC was carried out on Wakogel B-5F silica gel. Yields were determined by ^1H NMR or GLC using internal standards.

Materials. Bu_3SnCl, Bu_3SnBr, Bu_2SnCl_2, and $BuSnCl_3$ were commercially available. LDA was used as commercially available (Aldrich Co. Ltd. 1M hexane solution). Alkoxy ketones **1a** were commercially available. Compounds **1b**−**e** were prepared by the oxidation of the corresponding silyl enolates with iodosobenzene in the presence of BF_3 etherate.[11] Unsaturated ketone **2a** was prepared by the dehydration of 3-hydroxybutyrophenone which was provided from the aldol reaction of acetophenone and acetaldehyde. Unsaturated ketones **2b** and **2c** were commercially available. THF was freshly distilled over sodium benzophenone ketyl. All reactions were carried out under dry nitrogen.

Typical Procedure for the Michael Reaction between 1a and Enone 2a. Tri-*n*-butyltin chloride (Bu_3SnCl) or bromide (Bu_3SnBr) (1 mmol) was dissolved to a THF solution of LDA (1 mmol) at 0 °C. The reaction mixture was stirred for 15 min to form tri-*n*-butyltin diisopropylamide ($Bu_3SnN^iPr_2$), and **1a** (1 mmol) was added. After the solution was stirred at 0 °C for 30 min, enone **2a** was (1 mmol) added and stirring was continuied for 2 h. The mixture was quenched with MeOH (3 mL) and chromatographed on silica gel to give anti 1,5-diketone **3a** (hexane/EtOAc = 3/1). The ratio of the syn/anti diastereomers was determined by ^1H NMR.

(2*SR*,3*SR*)-1,5-Diphenyl-2-methoxy-3-methyl-1,5-pentanedione (*anti*-3a): colorless wax, IR 1660 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.06 (d, 3H, J = 6.4 Hz), 2.83−3.51 (m, 3H,), 3.36 (s, 3H), 4.34 (d, 1H, J = 5.9 Hz), 7.41−8.22 (m, 10H); ^{13}C NMR ($CDCl_3$) δ 17.20, 32.80, 40.67, 58.21, 88.99, 127.93, 128.38, 128.60(d), 132.80, 133.43, 135.29, 137.09, 199.10, 200.14; HRMS-(CI) calcd for $C_{19}H_{20}O_3$ 297.1412, found 297.1485 (m + 1)$^+$.

(2*SR*,3*RS*)-1,5-Diphenyl-2-methoxy-3-methyl-1,5-pentanedione (*syn*-3a): colorless wax; IR 1680 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.92 (d, 3H, J = 6.4 Hz), 2.83−3.51 (m, 2H), 2.83−2.88 (m, 1H), 3.33 (s, 3H), 4.84 (d, 1H, J = 5.9 Hz), 7.41−8.22 (m, 10H); ^{13}C NMR ($CDCl_3$) δ 14.29, 32.22, 41.89, 58.50, 84.78, 128.03, 128.64, 128.72 (d), 133.28, 133.43, 135.41, 137.05, 199.48, 199.89; HRMS(CI) calcd for $C_{19}H_{20}O_3$ 297.1412, found 297.1494 (m + 1)$^+$.

Determination of Stereochemistry of Enolates. Tri-*n*-butyltin bromide (Bu_3SnBr) (1 mmol) was dissolved in a THF solution of LDA (1 mmol) at 0 °C to form tri-*n*-butyltin diisopropylamide. The reaction mixture was stirred for 15 min, and **1a** (1 mmol) was added. After the solution was stirred at 0 °C for 2 h, trimethylsilyl bromide (1 mmol) was added and stirring was continuied at rt for 18 h. The mixture was chlomatographed on silica gel eluted by hexane to give silyl enolate **7**. Compounds **7** and **8** were easily decomposed after several days. The ratio of the *E*/Z-diastereomers was determined by ^1H NMR (>99% *Z*-selectivity). ^1H NMR ($CDCl_3$) δ 0.21 (s, 9H), 3.46 (s, 3H), 6.26 (s, 1H) 7.1 5−8.20 (m, 5H).

Silyl enolate **8** was obtained similarly starting from dichlorobutyltin amide (*Z*/*E* = 10/90): ^1H NMR ($CDCl_3$) δ 0.19 (s, 9H), 3.51 (s, 3H), 5.34 (s, 1H), 7.15−8.20 (m, 5H).

The silylation of lithium enolate derived from **1a** with LDA gave a 6:4 mixture of **7** and **8**. Irradiation of methyl proton of TMS group indicated 8.5% enhancement at the vinyl proton of **8**, whereas only 1.3% enhancement was observed at the vinyl proton of **7**. This NOE experiment suggested that TMS enolate **7** exsist as the *Z*-isomer and enolate **8** as the *E*-isomer.

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Supporting Information Available: ^1H, ^{13}C, and HRMS spectral data of compounds **3b**−**g**, **5**, and **6** (4 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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