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Highly regioselective addition of an ester enolate equivalent to α,β-unsaturated ketones: selective formation of both isomers derived from 1,2- and 1,4-additions using α-stannyl ester with additives

Makoto Yasuda, Yozo Matsukawa, Keishi Okamoto, Toshifumi Sako, Noriko Kitahara and Akio Baba*

Department of Applied Chemistry, Faculty of Engineering, Osaka University, 2-1 Yamadaoka, Suita, Osaka 565-0871, Japan. E-mail: baba@ap.chem.eng.osaka-u.ac.jp

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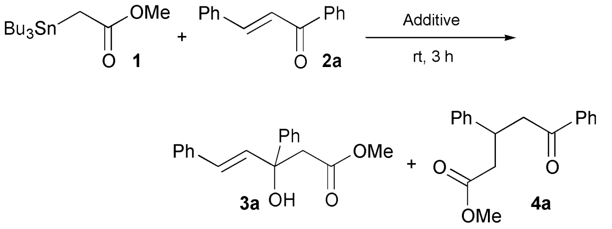
The reaction of α-stannyl ester with α,β-unsaturated ketones in the presence of stannous chloride ($SnCl_2$) and chlorosilanes (Me_3SiCl or Me_2SiCl_2) gave 1,2- and 1,4-addition products, respectively.

The regioselective addition of a nucleophile to α,β-unsaturated carbonyl compounds (1,2- or 1,4-addition) has been focused on in modern organic syntheses. An enolate or its equivalent is often used for the functionalised nucleophile to unsaturated carbonyls. Heathcock reported excellent results using lithium enolate in which either kinetic or thermodynamic conditions effectively control the regioselectivity.[1] The correlation between the character of the metal in the enolate and the regioselectivity was also investigated.[2] We have recently reported the 1,4-addition of organotin ketone enolate using a high coordination method.[3] An organotin ester enolate, however, has significantly different reactivity and character as compared with an organotin ketone enolate and is not suitable for the reaction conditions developed for ketone enolates. For the organotin ester enolates, the equilibrium between *O*-stannylated and *C*-stannylated forms largely lies towards the *C*-stannylated species above 0 °C.[4] The stannylation of lithium ester enolate is reported to give only a *C*-stannylated ester compound (the α-stannyl ester) after distillation,[5] although stannyl ketone enolate generally exists as an equilibrium mixture of both forms.[6] Since enol forms generally show higher reactivity than keto forms, the α-stannyl ester has a lower reactivity than ketone enolates.[7,8] During our study of the activation methodology of α-stannyl ester, we found a novel approach to regiocontrol in the reaction of α,β-unsaturated ketones with α-stannyl ester as an ester enolate equivalent.

First, we examined additives for the reaction of α-stannyl ester **1** with chalcone **2a** and the results are summarized in Table 1. An attempt without additives resulted in no reaction (entry 1). The use of $BF_3{\cdot}OEt_2$ as an additive was not effective at all (entry 2). $TiCl_4$ afforded a low yield of 1,4-addition product **4a** (entry 3). Recently, we have reported a carbonyl allylation system using tributylallylictin(IV) and $SnCl_2$ in which transmetallation occurs to generate an active species.[9,10] This activation methodology was applied to the reaction of **1** in the presence of $SnCl_2$ to give β-hydroxy ester **3a** in 63% yield with excellent selectivity in 1,2-addition manner (entry 4). On the other hand, the addition of chlorotrimethylsilane gave selectively **4a** in practical yields, which were influenced by the solvents used. Nitromethane was the solvent of choice and gave the sole product **4a** in 95% yield (entry 6). These results encouraged us to develop these reaction systems using α-stannyl ester for regioselective addition to α,β-unsaturated ketones.

Next, we explored the generality of this regiocontrolled system using either $SnCl_2$–MeCN or Me_3SiCl–$MeNO_2$ with various types of enones **2a–e**, and showed the results in Table 2.† Excellent regiocontrol was observed in the reaction with phenyl ketone **2b**, which has an alkyl substituent on the terminal olefinic carbon (entries 3 and 4). In the reaction with alkyl ketone **2c** using $SnCl_2$, the low yield of **3c** in entry 5 was ascribed to the polymerization of the starting enone, although regioselectivity was high (entry 5). Chlorotrimethylsilane gave 83% yield of products with high selectivity (entry 6). The cyclic substrate **2d** was also applied to these systems. When

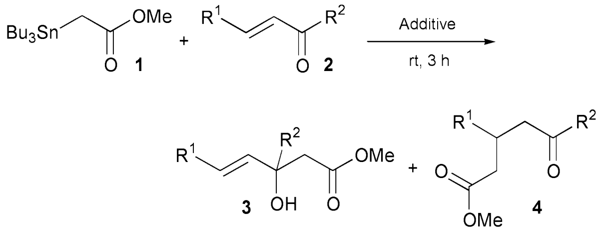
Table 1 Effect of additives on regioselective addition of **1** to enone **2a**[a]

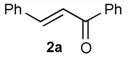
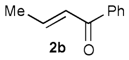
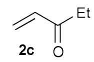
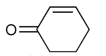
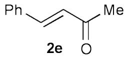


Entry	Additive	Solvent	Yield (%)	Ratio of **3a**/**4a**
1	None	MeCN	0	—
2[b]	$BF_3{\cdot}OEt_2$	CH_2Cl_2	0	—
3[b]	$TiCl_4$	CH_2Cl_2	19	< 1/99
4	$SnCl_2$	MeCN	63	> 99/1
5[c]	Me_3SiCl	MeCN	47	< 1/99
6[c]	Me_3SiCl	$MeNO_2$	95	< 1/99

[a] All reactions were carried out in solvent (1 mL) using **1** (1.2 mmol), unsaturated ketone **2a** (1.0 mmol), and additive (1.2 mmol). [b] Reaction temperature −78 °C to rt. [c] Additive (2.0 mmol) was used.

Table 2 Control of regioselectivity in addition of **1** to various enones **2**[a]



Entry	Enone	Additive	Solvent	Yield (%)	Ratio of **3**/**4**
1	 **2a**	$SnCl_2$	MeCN	63	> 99/1 (**3a**/**4a**)
2		Me_3SiCl	$MeNO_2$	95	< 1/99
3	 **2b**	$SnCl_2$	MeCN	91	> 99/1 (**3b**/**4b**)
4		Me_3SiCl	$MeNO_2$	92	< 1/99
5	 **2c**	$SnCl_2$	MeCN	23	> 99/1 (**3c**/**4c**)
6		Me_3SiCl	$MeNO_2$	83	5/95
7	 **2d**	$SnCl_2$	MeCN	50	> 99/1 (**3d**/**4d**)
8		Me_3SiCl	$MeNO_2$	90	< 1/99
9	 **2e**	$SnCl_2$	MeCN	80	> 99/1 (**3e**/**4e**)
10		Me_3SiCl	$MeNO_2$	59	46/54
11		Me_2SiCl_2	$MeNO_2$	63	5/95

[a] All reactions were carried out in solvent (1 mL) using **1** (1.2 mmol), unsaturated ketone **2** (1.0 mmol). Either $SnCl_2$ (1.2 mmol) or chlorosilanes (2.0 mmol) were used as additives.

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acetonitrile was used as a solvent in the reactions with **2a–d** in the presence of chlorotrimethylsilane, the same or lower yields were observed but selectivity was not significantly affected. In the reaction with 4-phenylbut-3-en-2-one **2e**, the 1,2-adduct **3e** was obtained in good yield with perfect selectivity (entry 9). However, the reaction using chlorotrimethylsilane did not give selective 1,4-addition (**3e**/**4e** = 46/54, entry 10). The low selectivity is ascribed to the conjugation of the phenyl group with the olefinic moiety which could be kept by 1,2-addition and broken by 1,4-addition.[11] Unexpectedly, Michael adduct **4e** was favored (**3e**/**4e** = 5/95) when dichlorodimethylsilane was used as an additive instead of chlorotrimethylsilane (entry 11).

Although the exact reaction mechanism for either course using stannous chloride or chlorosilanes is not clear, the regiocontrol can be explained by the following assumption at the present stage. In the $SnCl_2$ system, the active tin(II) species generated by transmetallation has high Lewis acidity.[9,10] The strong interaction between carbonyl oxygen and the tin center in the nucleophile effectively accelerates the carbostannylation. The resulting Sn–O bond is strong enough for irreversible reaction. In order to examine the chlorosilane system, an NMR study was performed. The mixture of **1** and chlorotrimethylsilane in acetonitrile underwent transmetallation to give tributylchlorostannane and silylketene acetal, as determined by NMR.[12,13] After standing for 48 h at rt, the silylketene acetal completely disappeared and α-silyl ester was observed by NMR.[14,15] This resulting solution including silyl ester and tributylchlorostannane was inert to chalcone **2a**. These results suggest that tributylchlorostannane would act as a Lewis acid for Mukaiyama-type Michael addition of silylketene acetal.[16] Another possibility, namely, that further transmetallation to give stannylketene acetal from chlorostannane and silylketene acetal, which would have high reactivity and a short life time under the conditions employed in this procedure, is not completely ruled out at this stage.[4] The difference in active species generated in each system causes the highly regiocontrolled reactions.

The solvent effect of acetonitrile or nitromethane on yields probably relates to their coordination ability to the concerned active species. The additive effect of chlorosilanes on selectivity of **3e**/**4e** is still not clear.

In conclusion, regioselective addition of α-stannyl ester to α,β-unsaturated ketones was achieved in 1,2- and 1,4-addition manner by using stannous chloride and chlorosilanes as additives, respectively. The transmetallation of stannyl ester with these additives generates the key reactive intermediates with proper selectivities. α-Stannyl esters will be attractive functionalized nucleophiles with these activation methodologies because they are easy to prepare and handle and can be stored for months owing to their moderate stability. The detailed reaction mechanism is now under investigation and will be reported in a full account.

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Notes and references

† *Experimental procedure* for the synthesis of **3**: see the representative experimental procedure in our previous paper[9] (use an α-stannyl ester instead of allylstannane). *General procedure* for the synthesis of **4**: to a mixture of chlorosilane (Me_3SiCl or Me_2SiCl_2, 2.0 mmol) and an α-stannyl ester **1** (1.2 mmol) in nitromethane (1 mL) was added α,β-unsaturated ketones **2** (1.0 mmol) under nitrogen. The mixture was stirred for 3 h at ambient temperature. The reaction mixture was poured into the mixed solvent of Et_2O (30 mL) and aqueous NH_4F (15%; 15 mL) with vigorous stirring for 10 min. The resulting Bu_3SnF was filtered off. The filtrate was extracted with Et_2O (30 mL × 2) and washed by aq.HCl (1 M, 20 mL × 2) and $NaHCO_3$ (20 mL × 1) and dried ($MgSO_4$) and evaporated. The crude reaction mixture was purified by column chromatography and recrystallisation or distillation gave pure products **4**.

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11 In the case of 1,4-addition to **2a**, a new conjugation with another phenyl group could appear in the resultant enolate which is first generated in this reaction course before quenching.

12 A mixed solution of **1** (1.0 mmol) and chlorotrimethylsilane (2.0 mmol) in CD_3CN (0.5 mL) in a sealed tube at rt for 10 min showed a signal corresponding to tributylchlorostannane at 122 ppm in ^{119}Sn NMR. The silylketene acetal was also observed in ^{29}Si NMR (21 ppm) and in ^{1}H NMR (3.16 and 3.12 ppm, each signal has a doublet with $J = 2.7$ Hz).

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