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Highly stereoselective addition to alkoxy or hydroxy ketones using an α-stannyl ester–stannous chloride system in a chelation-controlled manner

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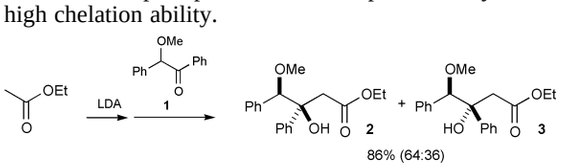
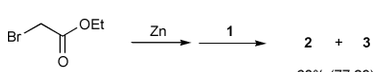
The reaction of an α-stannyl ester with α-alkoxy or hydroxy ketones in the presence of $SnCl_2$ gave aldol-type products with high selectivity in a chelation-controlled manner.

Stereoselective C–C bond formation is undoubtedly important for organic syntheses. Since the transition state of the reaction concerned demands a rigid structure for a selective reaction, chelation of a substrate bearing coordinative sites to a metal center often has a significant effect on the stereoselectivity. A number of selective reactions under chelation-controlled conditions have been reported for carbonyl addition by carbon nucleophiles.[1] Reetz has developed chelation-controlled aldol-type addition to α-alkoxy aldehydes using enol silane in the presence of Lewis acids.[2] However, chelation-controlled addition of a metal enolate or its equivalent to α-alkoxy ketones is scarcely known in spite of the fascinating structure of the products which would be tertiary alcohols bearing a stereocontrolled *O*-substituent. This is probably because the reaction conditions required to achieve the addition to ketones, which are much less reactive than aldehydes, would be too severe to control the selectivity. In this communication, we report a highly diastereoselective addition of an ester enolate equivalent to α-alkoxy or hydroxy ketones using an α-stannyl ester–stannous chloride system in a chelation-controlled manner.

In the initial trials, we obtained moderate selectivities of diastereomers **2** and **3** in the reactions of α-alkoxy ketone **1** with a lithium enolate[3] or zinc enolate equivalent[4] [eqns. (1) and (2)]. These results prompted us to develop a novel system having high chelation ability.



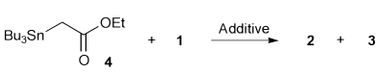
(1)



(2)

A stannyl nucleophile is often used for stereoselective organic synthesis.[5] Keck has reported chelation-controlled addition of allylic stannanes in the presence of $TiCl_4$.[6] We examined the reaction of α-stannyl ester **4** in the presence of metal halides, and the results are summarized in Table 1.

Table 1 Reaction of α-stannyl ester **4** with **1**[a]



Entry	Additive	Solvent	Conditions	Yield (%)	Ratio of **2**:**3**
1	$TiCl_4$	CH_2Cl_2	−78 °C → rt, 3 h	7	—
2	$BF_3{\cdot}OEt_2$	CH_2Cl_2	−78 °C → rt, 3 h	< 5	—
3	$SnCl_2$	CH_2Cl_2	rt, 3 h	40	> 99 : 1
4	$SnCl_2$	MeCN	rt, 3 h	86	> 99 : 1

[a] All reactions were carried out in solvent (1 mL) using **4** (1.2 mmol), alkoxy ketone **1** (1.0 mmol), and additive (1.2 mmol).

However, the use of $TiCl_4$ as an additive gave a complicated mixture with a small amount of the aldol-type product which was confirmed in a crude reaction mixture by NMR (entry 1). In the presence of $BF_3{\cdot}OEt_2$ almost no reaction took place and the starting ketone was recovered (entry 2). Recently, we have reported a carbonyl addition system using α-stannyl ester or tributylallylic stannane with $SnCl_2$ in which transmetallation occurs to generate an active species.[7] This activation methodology successfully attained the stereoselective reaction of **4** with **1** in the presence of $SnCl_2$ to give the product in 40% yield with excellent selectivity (entry 3). Changing the solvent from CH_2Cl_2 to MeCN improved the yield while retaining high selectivity (86% yield, > 99 : 1, entry 4).†

The relative configuration of the stereochemistry of **2** was unambiguously determined by its X-ray analysis and the ORTEP drawing is shown in Fig. 1.‡ It corresponds to the product which is formed by chelation-controlled alkylation.

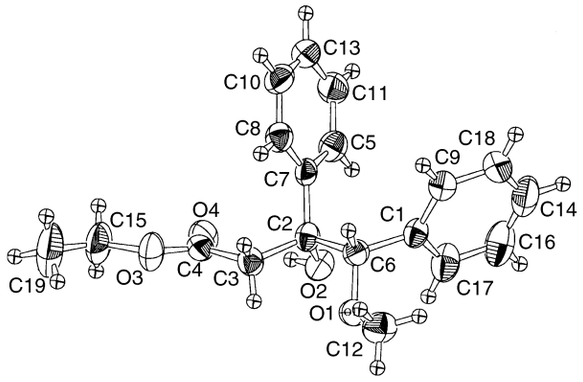
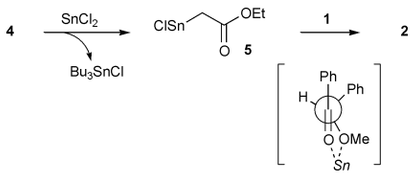


Fig. 1 Molecular structure of **2**.

Although the reaction mechanism is now not clear, we assume that the active species is chlorinated stannous ester **5** which is generated by transmetallation between **4** and $SnCl_2$ (Scheme 1). The metal center has high Lewis acidity and thus high chelation ability to alkoxy ketone. The carbonyl addition proceeds *via* transition states which direct the selective addition by chelation. In fact, a transmetallation was confirmed by the following experiment. A mixture of α-stannyl ester **4** and $SnCl_2$ in MeCN at room temp. gave 71% yield of Bu_3SnCl which was confirmed by ^{119}Sn NMR. A lower yield (16%) of Bu_3SnCl was observed when CH_2Cl_2 was used as a solvent. This significant solvent effect on the transmetallation accounts for the difference in yields in entries 3 and 4 (Table 1). Unfortunately, the signal



Scheme 1 Plausible path of chelation-controlled addition.

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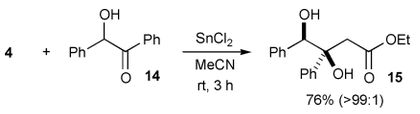
corresponding to the generated nucleophilic tin(II) species was not detected probably because of its broadening in ^{119}Sn NMR.

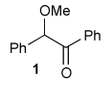
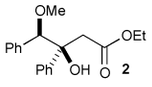
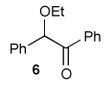
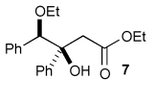
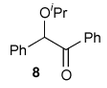
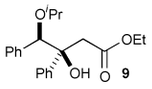
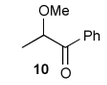
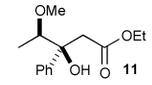
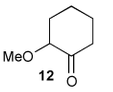
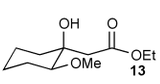
Various alkoxy ketones were investigated and the results are shown in Table 2. The reaction with the α-ethoxy ketone **6** also gave the aldol product **7** in high selectivity and yield (entry 2). Even isopropoxy ketone **8**, which has a bulky substituent, was also subjected to this reaction system to afford **9** exclusively (entry 3). The reaction with 2-methoxypropiophenone **10** provided the selective aldol-reaction in >95:5 selectivity (entry 4). When the cyclic substrate **12** was used, **13** was selectively formed in a 92:8 ratio (entry 5). The relative configuration of the cyclic product **13** was determined by NOE experiment. The increased intensity at the carbonyl methylene protons was observed by irradiating the axial proton bonded to the methoxy-substituted carbon.

The chelation-controlled reaction using hydroxy carbonyl compounds without protection is a challenging problem because organometals for chelates are readily affected or quenched by the protic sites. Actually, the reaction with α-hydroxy ketone **14** performed under Reformatsky reaction conditions or using a lithium enolate according to the procedures employed in eqns. (1) or (2) did not effectively proceed and a significant amount of the starting ketone was recovered. Surprisingly, the stannyl ester–$SnCl_2$ system can provide high yield and high selectivity of **15** even with the use of hydroxy ketones **14** [eqn. (3)].[8] Other additives, $TiCl_4$ and $BF_3{\cdot}OEt_2$ for the reaction of **4** with **14** gave the recovered ketone **14** and low yields (9 and 26%) of **15**, respectively. The reaction with 2-hydroxypropiophenone **16** also gave the product **17** in high selectivity [eqn. (4)].[9] These results show the strong advantage of our system which tolerates protic conditions.

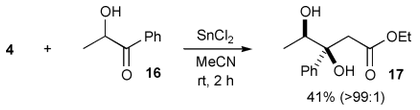


(3)

Table 2 Chelation-controlled reaction of α-stannyl ester **4** with alkoxy ketones in the presence of $SnCl_2$[a]

Entry	Alkoxy ketone	Product	Yield (%)	Dr
1			86	>99:1
2			87	>99:1
3			80	>99:1
4			31	>95:5
5			53	92:8

[a] All reactions were carried out in MeCN (1 mL) using **4** (1.2 mmol), alkoxy ketone (1.0 mmol), and $SnCl_2$ (1.2 mmol) at rt for 3 h.



(4)

In conclusion, we have shown a highly diastereoselective addition of an alkoxycarbonylmethyl group to α-alkoxy or hydroxy ketones, controlled by the chelation effect, using an α-stannyl ester–$SnCl_2$ system. The transmetallation between the α-stannyl ester and $SnCl_2$ generates an active species which has high Lewis acidity to form a chelate. Further investigation of the scope and limitations of the methodology, and the reaction mechanism is now under way.

This work was supported by a Grant-in-Aid for Scientific Research from the Ministry of Education, Science, Sports, and Culture, of the Japanese Government.

Notes and references

† *Representative experimental procedure* for the synthesis of **2**: to a mixture of $SnCl_2$ (1.2 mmol) and α-alkoxy ketones **1** (1.0 mmol) in MeCN (1 mL) was added an α-stannyl ester **4** (1.2 mmol) under nitrogen. The solution was stirred for 3 h at ambient temperature. The reaction mixture was poured into the mixed solvent of Et_2O (30 mL) and aq. NH_4F (15%; 15 mL) with vigorous stirring for 10 min. The precipitating Bu_3SnF was filtered off. The filtrate was extracted with Et_2O (30 mL × 2), dried ($MgSO_4$) and evaporated. Recrystallisation (hexane–benzene, 9:1) of the resultant residue gave the pure product **2**.

‡ *Crystal data* for **2**: $C_{19}H_{22}O_4$, M = 314.38, monoclinic, a = 12.14(10), b = 5.9(1), c = 23.99(8) Å, V = 3741.0(9) Å^3, T = 300 K, space group $P2_1/n$ (no. 14), Z = 4, μ(Mo-Kα) = 0.9 cm^{-1}, 4075 reflections measured, 3894 unique (R_{int} = 0.032) which were used in all calculations. The final agreement factors were R = 0.051, R_w = 0.090. CCDC 182/1866.

1 M. T. Reetz, *Acc. Chem. Res.*, 1993, **26**, 462; M. T. Reetz, *Angew. Chem., Int. Ed. Engl.*, 1994, **23**, 556; X. Chen, E. R. Hortelano, E. L. Eliel and S. V. Frye, *J. Am. Chem. Soc.*, 1992, **114**, 1778.

2 M. T. Reetz, K. Kesseler and A. Jung, *Tetrahedron*, 1984, **40**, 4327; M. T. Reetz, B. Raguse, C. F. Marth, H. M. Hugel, T. Bach and D. N. A. Fox, *Tetrahedron*, 1992, **48**, 5731; M. T. Reetz and D. N. A. Fox, *Tetrahedron Lett.*, 1993, **34**, 1119.

3 A flask was charged with $MeCO_2Et$ (1.25 mmol) and dried THF (1 mL) under nitrogen and was cooled to −78 °C. A 2.0 M solution of lithium diisopropylamide (from Aldrich) in THF–heptane–EtPh (0.63 mL) was added and the mixture was stirred for 20 min keeping it at −78 °C. To the mixture was added **1** (1.0 mmol). After 3 h of stirring at −78 °C, the reaction mixture was quenched with 10 mL of aq. NH_4Cl, and extracted with Et_2O.

4 A flask was charged with Zn powder (6.0 mmol) and dried benzene–Et_2O (5:1, 2 mL) under nitrogen. A solution of ethyl 2-bromoacetate (5.5 mmol), **1** (5.0 mmol) in benzene–Et_2O (5:1, 5 mL) was slowly added over a period of 30 min to the mixture at 80 °C. Additional solvent (5 mL) was introduced and the reaction mixture was stirred for 2 h at 80 °C.

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8 The stereochemistry of the product **15** was determined by the following transformation: the methoxy-hydroxy ester **2** was converted by Fujita's method using $AlBr_3$–EtSH–CH_2Cl_2 at rt for 3 h to a dihydroxy ester whose NMR spectrum shows excellent agreement with the product **15** (yield of **15**, 26%, recovery of **2**, 68%). M. Node, K. Nishide, M. Sai, K. Ichikawa, K. Fuji and E. Fujita, *Chem. Lett.*, 1979, 97; M. Node, K. Nishide, M. Sai and E. Fujita, *Tetrahedron Lett.*, 1978, **52**, 5211.

9 The reaction was carried out using **4** (3.6 mmol), **16** (1.0 mmol), and $SnCl_2$ (3.0 mmol).