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Molecular Recognition by Artificial Chiral Catalysts Utilizing a Metal Chelate. A Remarkable Difference in Reactivity Between Geometrical Isomers of Silyl Enolates in Asymmetric Aldol Reactions Using Chiral Tin(II) Catalysts

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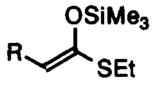
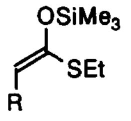
Abstract: A remarkable difference in reactivity between (E)- and (Z)-enolates in the asymmetric aldol reactions of silyl enolates with aldehydes using chiral tin(II) Lewis acids was found. This difference can be interpreted to mean that the chiral catalyst coordinated by aldehydes via a metal chelate recognizes the geometry of the silyl enolates.

It is well-known in the aldol reactions of enolate components with aldehydes that the geometry of the enolates strongly influences the stereoselectivity.1) However, there have been few reports about differences in reactivity between (E)- and (Z)-enolates. It is generally believed that (E)- and (Z)-enolates react almost equally. Actually, in our studies on aldol reactions such as boron, titanium, tin(II), and tin(IV) mediated- and Lewis acid- or trityl salt-catalyzed reactions,2) significant differences in reactivity were not observed.

Recently, we have reported asymmetric aldol reactions of silyl enolates with aldehydes using chiral tin(II) Lewis acids.3) While the reactions attained very high diastereo- and enantioselectivities, we found a remarkable difference in reactivity between the (E)- and (Z)-enolates (**1-3**). Herein we report some preliminary results on this interesting phenomena, leading to molecular recognition by a chiral catalyst.

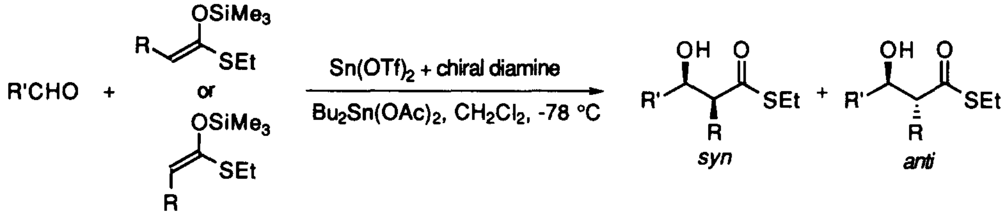


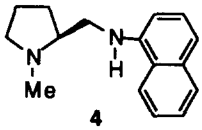
1E : R = Me
2E : R = $\mathrm{OSi^tBuMe_2}$
3E : R = OBn



1Z : R = Me
2Z : R = $\mathrm{OSi^tBuMe_2}$
3Z : R = OBn

First, we carried out the reaction of (Z)-1-ethylthio-1-trimethylsiloxypropane (**1Z**, Z/E = 95/5) with benzaldehyde in the presence of a chiral tin(II) Lewis acid consisting of tin(II) triflate, (S)-1-methyl-2-[(N-1-naphthylamino)methyl]pyrrolidine (**4**), and dibutyltin diacetate ($Bu_2Sn(OAc)_2$) at -78 °C for 0.5 h in dichloromethane. The desired aldol adduct was obtained in an 83.5% yield (*syn/anti* = >99/1, *syn* = >98% ee). On the other hand, in the reaction of (E)-1-ethylthio-1-trimethylsiloxypropane (**1E**, Z/E = 5/95) with benzaldehyde, the aldol adduct was obtained in a 15.2% yield (*syn/anti* = 84/16, *syn* = 84% ee). The yield of the reaction using the (Z)-enolate was, after correction, 7.7 times higher than that using the (E)-enolate (Y(Z/E) = 7.7). We tested other aldehydes under the same reaction conditions, and almost the same ratio level was obtained (Y(Z/E): octylaldehyde, 6.1; cyclohexylcarboxaldehyde, 8.3). The effect of the chiral source (the chiral diamine) was also examined (benzaldehyde; Y(Z/E): (S)-1-methyl-2-[(1-piperidin-1-yl)methyl]pyrrolidine (**5**), 6.7; (S)-1-pentyl-2-[(1-piperidin-1-yl)methyl]pyrrolidine (**9**), 5.8). It is noted that these results can be interpreted to mean that the chiral complex consisting of tin(II) triflate, a chiral diamine, $Bu_2Sn(OAc)_2$, and an aldehyde recognized the geometry of the silyl enolates.





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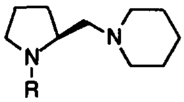
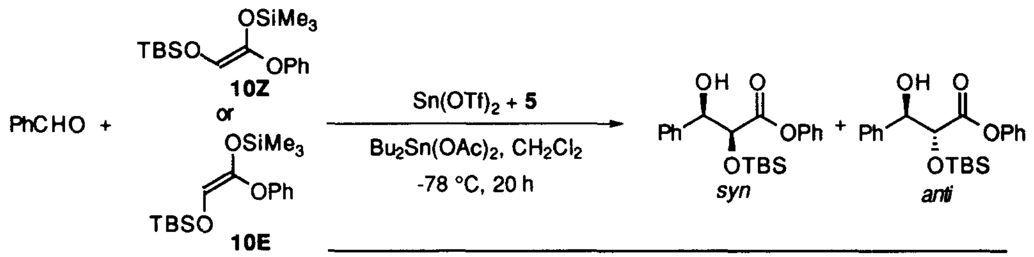


5: R = Me
6: R = Et
7: R = Pr
8: R = Bu
9: R = C_5H_{11}

We then tested the reaction of 2-*t*-butyldimethylsiloxy-1-ethylthio-1-trimethylsiloxyethane (**2**). In this case also, the Z-isomer (**2Z**) was much more reactive than the E-isomer (**2E**). The reactions of (E)- and (Z)-2-*t*-butyldimethylsiloxy-1-ethylthio-1-trimethylsiloxyethane with benzaldehyde were carried out in the presence of tin(II) triflate, chiral diamine **5**, and dibutyltin diacetate at -78 °C for 1 h in dichloromethane, and **2Z** was found to be 18 times more reactive than **2E**.4) The 1-alkyl group of the chiral diamine influenced the reactivity and when chiral diamine **9** was used, the yield using **2Z** was 130 times higher than that using **2E**.

Finally, the reactions of 2-benzyloxy-1-ethylthio-1-trimethylsiloxyethane (**3**) were investigated, and we found a very big difference in reactivity between the E- and Z-isomers. When the reaction was carried out in the presence of tin(II) triflate, chiral diamine **5**, and $Bu_2Sn(OAc)_2$ at -78 °C for 1 h in dichloromethane, the yield of the reaction using the Z-isomer (**3Z**) was 115 times higher than that using the E-isomer (**3E**).5) 1-Alkyl groups influenced the reactivity strongly, and when 1-ethyl-, 1-propyl-, 1-butyl, and 1-pentyl-2-[(1-piperidin-1-yl)methyl]pyrrolidines (**6-9**) were employed, only the Z-isomer reacted to give the adduct (>80% yield, *syn/anti* = <5/>95, *anti* = >95% ee) and no adduct was obtained from the E-isomer. We tested aldehydes other than benzaldehyde such as octylaldehyde, cyclohexylcarboxaldehyde, and crotonaldehyde under the same conditions using 1-ethyl-2-[(1-piperidin-1-yl)methyl]pyrrolidine (**6**), and found that in all cases the Z-isomer reacted smoothly, while the E-isomer did not react at all. Thus, in the reactions of 2-benzyloxy-1-ethylthio-1-trimethylsiloxyethane (**3**) with several aldehydes, the reaction proceeded only when the Z-isomer was used.

In summary, we found a remarkable difference in reactivity between (E)- and (Z)-enolates in the asymmetric aldol reactions of silyl enolates with aldehydes using chiral tin(II) catalysts. Particularly, in the reactions of **3**, only the Z-enolate reacted under the specified conditions. High selectivities of **3** compared to **1** or **2** could be explained by the different transition states between the asymmetric aldol reactions of **3** with aldehydes (*anti*-selectivities)3d) and the reaction of **1** or **2** with aldehydes (*syn*-selectivities).3a,d) Moreover, although the precise reaction mechanism is not yet clear, the ethylthio group of the enolates could have the most important role in the unique selectivities, because almost the same reactivity was observed in the reactions of (Z)- and (E)-2-*t*-butyldimethylsiloxy-1-phenoxy-1-trimethylsiloxyethane (**10Z** and **10E**) with benzaldehyde under the same reaction conditions (Scheme 1).6)



	Yield (%)	*syn*/*anti*	ee (%, *syn*,*anti*)
10Z (Z/E = >95/5)	80	73/27	72, 89
10E (Z/E = <5/>95)	87	6/94	nd, 90

Scheme 1

The remarkable differences reported here can be interpreted to mean that the chiral catalyst coordinated by aldehydes via a metal chelate recognizes the geometry of the silyl enolates.7) It should be noted that an artificial chiral catalyst with a much lower molecular weight compared to enzymes realized almost perfect molecular recognition by utilizing a metal chelate.

Further studies to clarify the precise mechanism of the recognition and gain a better understanding of chiral recognition are now in progress.

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2) For example, (a) Kobayashi, S.; Murakami, M.; Mukaiyama, T. *Chem. Lett.* **1985**, 1535. (b) Kobayashi, S.; Matsui, S.; Mukaiyama, T. *Chem. Lett.* **1988**, 1491. (c) Kobayashi, S.; Hachiya, I. *J. Org. Chem.* **1992**, *57*, 1324. (d) Kobayashi, S.; Hachiya, I. *Tetrahedron Lett.* **1992**, *33*, 1625. (e) Kobayashi, S.; Hachiya, I.; Ishitani, H.; Araki, M. *Synlett* **1993**, 472.
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4) **2Z**: Z/E = 100/0. **2E**: Z/E = 0/100.
5) **3Z**: Z/E = 90/10. **3E**: Z/E = 0/100.
6) In these reactions, it should be noted that the geometry of the silyl enolates (**10Z** and **10E**) corresponds to the stereochemistry of the products (*syn*/*anti* ratio). In the asymmetric reactions of **1**, **2**, or **3** with aldehydes using the same chiral tin(II) Lewis acid, *syn* or *anti* adducts were obtained preferentially in all cases (regardless of the geometry of the enolates). While **10Z** gave the *syn* adduct, the *anti* adduct was obtained from **10E**,[3f)] and this may be explained by the traditional cyclic transition states. On the other hand, it was confirmed by ^{1}H NMR that no metal exchange from Si to Sn took place in the enolates, **10Z** and **10E**.
7) When enantiomeric **4** (derived from D-proline) was employed in the reactions of benzaldehyde with **1E** and **1Z**, the yield of the reaction using **1Z** was 7.2 times higher than that using **1E** (Y(Z/E) = 7.2). Although the difference in the two results using enantiomeric diamines can be regarded as significant, the influence of the chirality on the recognition of the geometry of the silyl enolates is still not yet clear at this stage.

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