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Highly Stereoselective Chelation Controlled Ene-Reaction of 2-(Alkylthio)allyl Silyl Ethers

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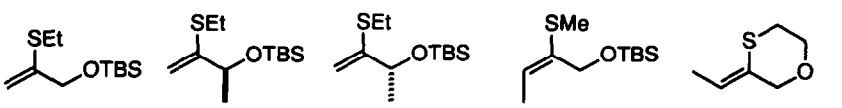
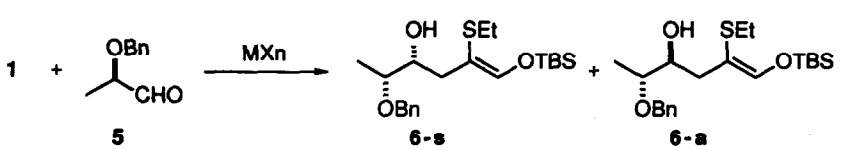
Abstract: Under the chelation conditions the title compounds reacted with α-benzyloxyaldehyde to afford *syn* diol exclusively. Further, three contiguous diastereomeric centers were constructed with high stereoselectivity by using (*E*) or (*Z*)-crotyl silyl ether. This methodology was applied to the stereoselective synthesis of brassinolide side chain.

Ene reactions with carbonyl compounds have constituted a powerful methodology for selective carbon-carbon bond formation.[1] However, there has been few report[2] on the stereoselectivity and mechanism of the ene reactions with α-alkoxy aldehydes under the chelation conditions which have often brought about a high degree of stereocontrol.[3] In the previous paper,[4] we reported highly stereoselective ene reactions of 2-(alkylthio)allyl silyl ethers with a general applicability. This paper describes ene reactions of silyl ethers **1**-**4** with α-alkoxy aldehydes, which have disclosed synthetically useful features to control the stereochemistry of the ene adducts.

In the presence of a Lewis acid the reaction of **1** with α-benzyloxypropanal **5** affords the ene adducts **6**. Among several Lewis acids examined,[5] $SnCl_4$ and $TiCl_2(O\textit{i}\text{-}Pr)_2$ effected almost complete *syn* selection,[6] although the product yield was moderate (eq. 1). The observed *syn* diasterofacial selectivity is reasonably explained by the cyclic chelation model.



1 **2a** **2b** **3** (*E*:*Z*=>99:<1) **4** (*E*:*Z*=3:97)

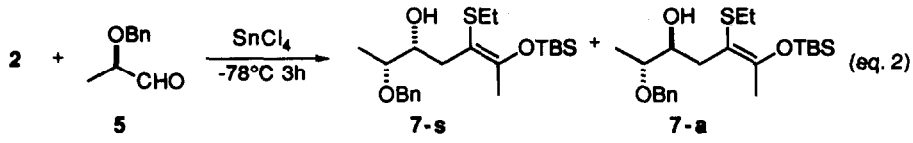


5 **6-s** **6-a** (eq. 1)

$TiCl_2(O\textit{i}\text{-}Pr)_2$	36 %	(**6-s** : **6-a** = >99 : <1)
$SnCl_4$	35 %	(**6-s** : **6-a** = >99 : <1)

Use of an enantiomerically pure α-benzyloxypropanal **5** induced kinetic differentiation in the reaction with optically pure enes[4b]: The (*R*)-**5** reacted smoothly with (*R*)-ene **2a** to give the corresponding adduct **7-s** with

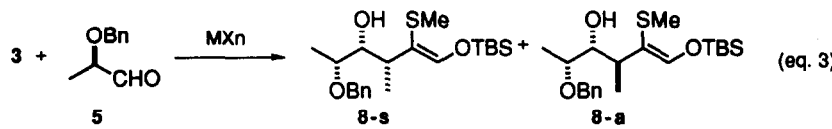
high *syn* selectivity, whereas the reaction with (*S*)-ene **2b** was very sluggish under the similar reaction conditions (eq. 2).



2a 85 % (**7-s** : **7-a** = >98 : <2)
2b 15 % (**7-s** : **7-a** = 60 : 40)

Further, (*E*)-ene **3** exhibited unprecedented behavior in the chelation controlled ene reaction: In every case its diastereofacial selection was complete, but the ratio of **8-s**/**8-a** formed is highly dependent on the Lewis acid used. Especially high *syn* diastereoselection[6] was observed on using $TiCl_2(O\text{-}i\text{-}Pr)_2$ or $SnCl_4$ (Table 1). This has made a good contrast with the *anti* selectivity observed in the ene reaction of **3** with heptanal.[4c] The nature of the ligand as well as acidity of the Lewis acid seems to have a great influence on *syn* selectivity.

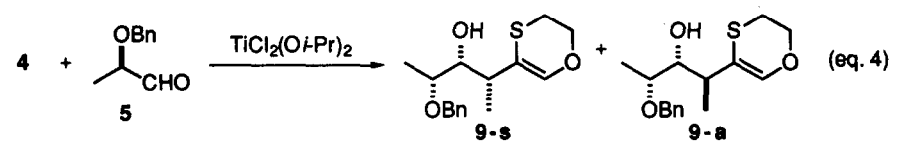
Table 1 Diastereoselectivity of the Ene Reaction of **3** with **5**[a]



entry	MXn	yield(%)	**8-s** : **8-a**[b]
1	$TiCl_4$	70	44 : 56
2	$TiCl_3(O\text{-}i\text{-}Pr)$	69	87 : 13
3	$TiCl_2(O\text{-}i\text{-}Pr)_2$	85	98 : 2
4	$SnCl_4$	66	96 : 4

a) All reactions were carried out at -78°C using 1.1 equiv. of MXn. b) determined by HPLC.

Although, (*Z*) isomer of **3** gave a complex mixture of stereoisomers,[7] *anti* adduct **9-a**[6] was obtained exclusively by the reaction of (*Z*)-ene **4** with **5** (eq. 4).



74 % (**9-s** : **9-a** = 2 : 98)

These results may be explained on the basis of the previously proposed transition state model. As shown in the previous paper,[4c] this ene reaction proceeds through the six membered cyclic transition state, in which the bulky Lewis acid occupies axial position. In the present case such a factor also plays an important role for determining the stereochemical course. In addition, the Lewis acid coordinates *trans* to the aldehyde hydrogen

under the result condition. Consequently, the reaction of **3** or **4** proceeds through TS-E1 or TS-Z1, respectively, to afford the corresponding *syn* or *anti* adduct (Figure 1). The kinetic differentiation observed with **2a** and **2b** is also explained by these transition state models.

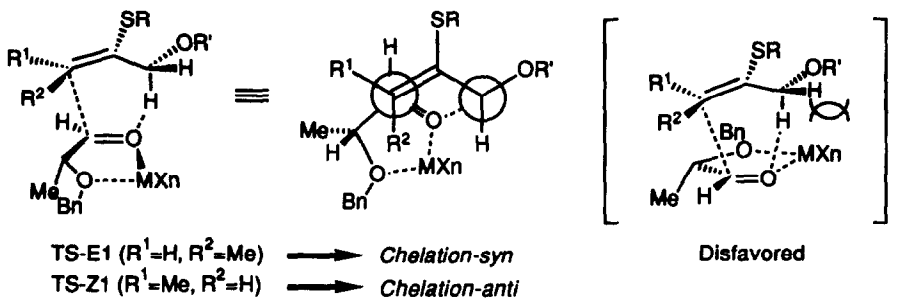
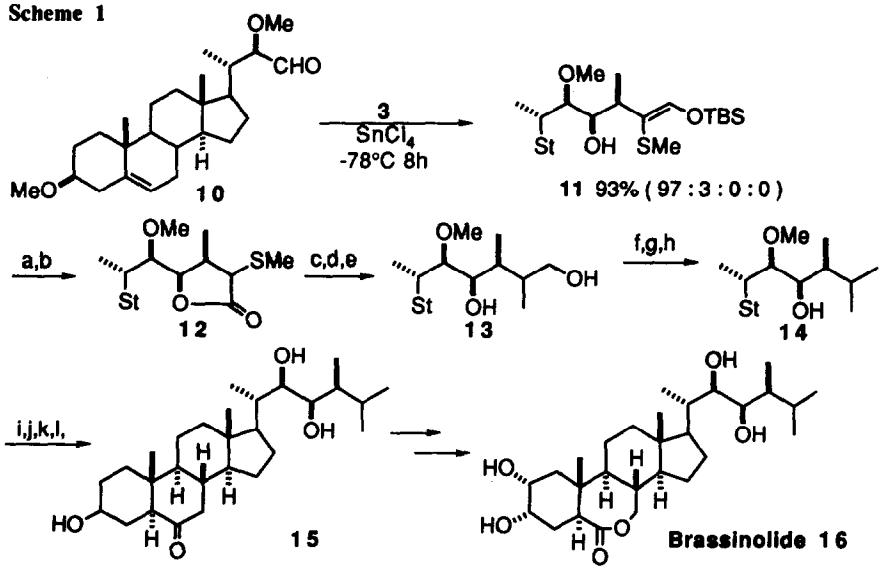


Figure 1 Tansition State Models of the Chelation Controlled Ene Reaction

Thus, the present methodology has allowed us to reflect the geometry of ene to the stereochemical outcome of the ene adduct with high selectivity. By using of this methodology, brassinolide **16**[8] side chain can be constructed stereoselectively. On treating the steroidal aldehyde **10**[9] with **3** the desired chelation-*syn* adduct **11** was obtained with high stereoselectivity. Elaboration of the side chain of **11** to **15**[10] was achieved as shown in Scheme 1. Since conversion of **15** to brassinolide **16** has been reported by several groups[8], synthesis of brassinolide has formally completed.

Scheme 1



a) TBAF 98%; b) PDC 90%; c) KH, MeI 88%; d) Raney Ni ; e) LAH 91% (2steps);
f) MsCl, *i*-Pr_2NEt 88%; g) ehtyl vinyl ether, PPTS; h) LAH then H^+ 80%(2steps);
i) MOMCl, Et_3N 90%; j) BH_3, then H_2O_2,NaOH 80%; k) PDC 91%; l) BBr_3 61%

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References

1. Reviews on Lewis acid promoted ene reactions: (a) Snider, B. B. *Acc. Chem. Res.* **1980**, *13*, 426. (b) Mikami, K.; Terada, M.; Shimizu, T.; Nakai, T. *J. Synth. Org. Chem. Jpn.* **1990**, *48*, 292.
2. Mikami, K.; Loh, T. P.; Nakai, T. *Tetrahedron Asymm.* **1990**, *1*, 13.
3. Review on the chelation control in carbonyl addition reactions: Reetz, M. T. *Angew. Chem. Int. Ed. Engl.* **1984**, *23*, 556.
4. (a) Tanino, K.; Nakamura, T.; Kuwajima, I. *Tetrahedron Lett.* **1990**, *31*, 2165. (b) Tanino, K.; Shouda, H; Nakamura, T.; Kuwajima, I. *ibid.* **1992**, *33*, 1337. (c) Nakamura, T.; Tanino, K.; Kuwajima, I. *Chem. Lett.* **1992**, 1425.
5. $ZnCl_2$ also shows *syn* selectivity(83:17), whereas 2 equiv. of Me_2AlCl shows *anti* selectivity(80:20). $TiCl_4$ and $BF_3{\cdot}OEt_2$ did not provide ene adducts because of decomposition of **1**.
6. The stereochemistry of the ene products was assigned by comparison of the 1,3-diols derived by ozonolysis and LAH reduction with the authentic samples which were prepared from the corresponding aldols: Reetz, M. T.; Kesseler, K.; Jung, A. *Tetrahedron* **1984**, *40*, 4327.
7. (Z) isomer of **3** gave a mixture of stereoisomers including geometrical isomers.
8. (a) Takatsuto, S.; Ikekawa, N. *J. Chem. Soc. Perkin Trans I.* **1983**, 2133. (b) Sakakibara, M.; Mori, K. *Tetrahedron* **1983**, *47*, 663. (c) Takatsuto, S.; Ikekawa, N. *Tetrahedron Lett.* **1983**, *24*, 773. (d) Takatsuto, S.; Yazawa, N.; Ishiguro, M.; Morisaki, M.; Ikekawa, N. *J. Chem. Soc. Perkin Trans. I*, **1984**, 139. (e) Mori, K.; Sakakibara, M.; Okada, K. *Agric. Biol. Chem.* **1984**, *40*, 1767. (f) Kametani, T.; Katoh, T.; Tsubuki, M.; Honda, T. *J. Am. Chem. Soc.* **1986**, *108*, 7055. (g) Kametani, T.; Keino, K.; Kigawa, M.; Tsubuki, M.; Honda, T. *Tetrahedron Lett.* **1989**, *30*, 3141.
9. The aldehyde **10** was prepared from stigmasterol .
10. The spectroscopic data were identical with those reported: Takatsuto, S.; Yazawa,N.; Ishiguro, M.; Morisaki, M.; Ikekawa, N. *J. Chem. Soc. Perkin Trans I.* **1984**, 139.

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