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Acyclic Stereocontrol Based on Chelation-Controlled Ene Reaction with Chiral α- and β-Alkoxyaldehydes

Koichi Mikami*, Teck-Peng Loh, and Takeshi Nakai*

Department of Chemical Technology, Tokyo Institute of Technology, Meguro-ku, Tokyo 152, Japan

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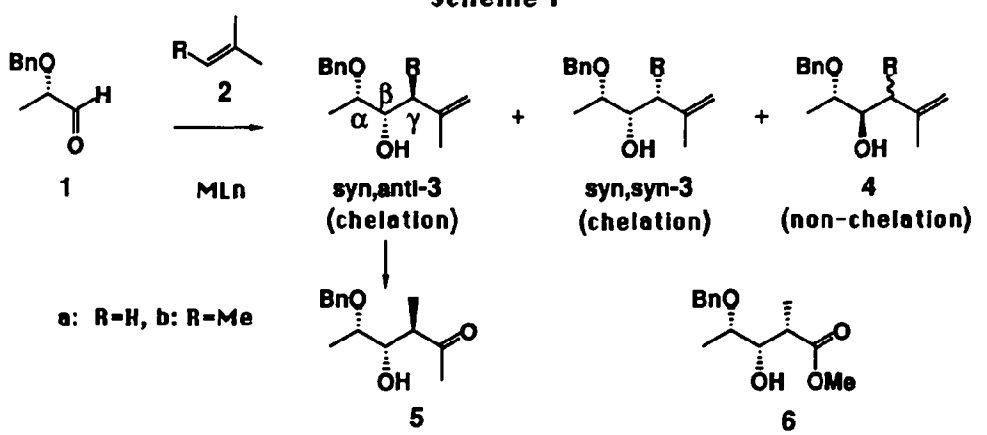
Abstract: The Lewis acid-promoted ene reactions with chiral α- and β-benzyloxyaldehydes have been developed and shown to afford high levels of both diastereofacial (chelation) selection and simple diastereoselection (anti), thus providing an efficient method for stereocontrol over three contiguous chiral centers.

From the synthetic point of view, the ene reaction[1] involving aldehydes as enophiles should constitute an efficient alternative to the carbonyl addition reaction of allylmetals which has now become one of the most useful methods for acyclic stereoselection.[2] However, only limited types of aldehyde enophile have been explored thus far.[1,3] Herein we wish to report the new type of ene reaction using chiral α- and β-alkoxyaldehydes as enophiles (alkoxyaldehyde ene reaction) which proceeds under effective chelation control with a high anti-diastereoselectivity (Scheme I and II).[4,5]

Scheme I



The reaction of chiral α-benzyloxyaldehyde (**1**)[5c] ($[\alpha]_D^{20}$ -64.60 ° (neat)) and isobutylene (**2a**) was found to give indeed the ene products (**3a** and **4a**) in good yield, when carried out using an appropriate Lewis acid (Table 1).[6] Except for entries 1 and 6, all the ene reactions afforded α,β-syn (chelation) product **3a**[5a] with high selectivity and in high yield.[7] Of special value is the $SnCl_4$-promoted reaction (entry 5) which provides **3a** quantitatively with more than 99% selectivity. Thus this new type of ene reaction is proved to proceed under effective chelation control.

Table 1. Ene reaction of isobutylene (**2a**) with **1**.

entry	MLn	%yield	**3a** (syn) : **4a** (anti)[a]
1	$TiCl_4$	<5	---
2	$Cl_3Ti(OPr\text{-}i)$	70	95 : 5
3	Me_2AlCl	80	85 : 15
4	$MeAl(OTf)_2$	82	>99 : <1
5	$SnCl_4$	97	>99 : <1
6	BF_3OEt_2[b]	40	15 : 85

[a] Determined by capillary GLC analysis (XE-50, 50 m, 150 °C).
[b] Two equiv of BF_3OEt_2 to **1** were used.

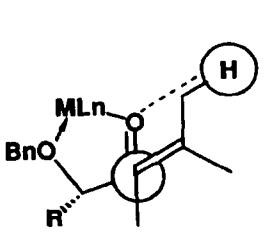
Next, the reaction of 2-methyl-2-butene (**2b**) with **1** was examined, which would present the problem of stereocontrol over three contiguous chiral centers (Table 2).[6] The best result was obtained, as expected, with $SnCl_4$ which showed unprecedented levels (>99%) of both simple diastereoselection (β,γ-anti) and chelation (α,β-syn) diastereofacial selection. Thus, (α,β-syn, β,γ-anti)-**3b** was obtained as a single stereoisomer in good yield (entry 1).[8] The stereochemistry of the major product was assigned, after conversion to β,γ-anti aldol **5**[9]

Table 2. Ene reaction of 2-methyl-2-butene (**2b**) with **1**.

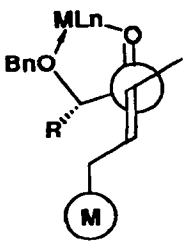
entry	MLn	%yield	syn,anti-**3b** : syn,syn-**3b** : **4b**[a]
1	$SnCl_4$	90	>99 : <1 : 0
2	$MeAl(OTf)_2$	80	80 : 20 : 0
3	$Cl_3Ti(OPr\text{-}i)$	70	95 : 5 : 0
4	$MgBr_2$[b]	85	97 : 3 : 0

[a] Determined by capillary GLC analysis (PEG-20M, 50 m, 200 °C). [b] Run at 20 °C.

which was correlated to the corresponding β,γ-syn isomer derived from the stereochemically-defined ester **6**.[5f] The observed anti-diastereoselectivity[10] is rationalized in terms of the reasonable postulate that the present ene reaction proceeds preferentially through a cyclic (synclinal) transition state (**A**).[3c] The synclinal transition state (**A**) is in direct contrast to the antiperiplanar transition state (**B**) widely-accepted for crotyl-stannane and -silane reactions leading to syn-diastereoselection.[2,4,5b] Thus, the ene and allylmetal methods are complimentary in a stereochemical sense.



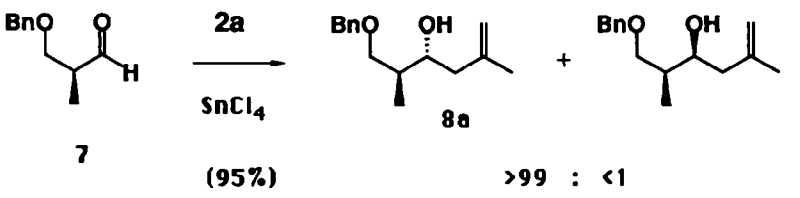
A (synclinal)



B (antiperiplanar)

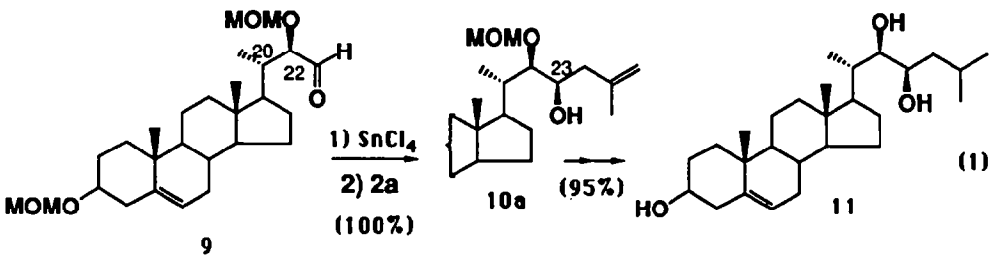
The $SnCl_4$-promoted ene reaction of isobutylene (**2a**) with chiral β-benzyloxyaldehyde (**7**)[5d] ($[\alpha]_D^{27}$ +29 °, c 1.16, $CHCl_3$) was also found to provide a high level of chelation (anti in this case) selection to give **8a**[5a] as a single stereoisomer in 95 % yield (Scheme II).[6]

Scheme II



cf. Me_2AlCl (76%) 66 : 34

In view of the high level of chelation selectivity, this alkoxyaldehyde ene methodology was applied to the steroid side chain synthesis. Thus, (20*S*, 22*R*)-22-alkoxy-23-aldehyde (**9**),[11] easily obtainable via the glyoxylate ene reaction,[3c] was reacted with **2a** in the presence of $SnCl_4$ (eq 1). The desired chelation product **10a** was obtained as a single stereoisomer in quantitative yield after column chromatography.[12] Selective hydrogenation (H_2/PtO_2) of the 25,26-olefin followed by deprotection of the MOM group (6*N* HCl) of **10a** gave norbrassinolide-type side chain **11** in 95% overall yield.[13]



In conclusion, the alkoxyaldehyde ene methodology thus developed is more advantageous than the allylmetal methodology for acyclic stereocontrol in terms of the easy availability of the olefin (ene) and the operational simplicity, along with the high level of both diastereofacial (chelation) selection and anti-diastereoselection.

References and Notes

(1) Review on Lewis acid-promoted ene reactions: B. B. Snider, Acc. Chem. Res., **13**, 426 (1980).

(2) Reviews: Y. Yamamoto, Acc. Chem. Res., **20**, 243 (1987); R. W. Hoffmann, Angew. Chem. Int. Ed. Engl., **23**, 932 (1984).

(3) Glyoxylate ene reactions: (a) B. B. Snider and J. W. van Straten, J. Org. Chem., **49**, 2443 (1979); (b) J. K. Whitesell, Acc. Chem. Res., **18**, 280 (1987); (c) K. Mikami, T.-P. Loh, and T. Nakai, Tetrahedron Lett., **29**, 6305 (1988); (d) K. Mikami, M. Terada, and T. Nakai, J. Am. Chem. Soc., **111**, 1940 (1989). Chloral ene reactions: (e) J. B. Benner, G. B. Gill, S. J. Parrott, B. Wallace, and M. J. Begley, J. Chem. Soc., Perkin 1, 315 (1984); (f) K. Maruoka, Y. Hoshino, T. Shirasaka, and H. Yamamoto, Terahedron Lett., **29**, 3967 (1987).

(4) Review on the issue of the chelation vs. non-chelation control in carbonyl addition reactions: M. T. Reetz, Angew. Chem. Int. Ed. Engl., **23**, 556 (1984). However, the issue of the chelation/non-chelation control in the ene reactions remains largely unexplored.

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(6) The following procedure is illustrative for the present asymmetric ene reaction. To a dichloromethane solution of aldehyde was added a Lewis acid (1.0 equiv) at -78 °C. The mixture was stirred at that temperature for 10 min and then an olefin was added into the mixture. The resulting mixture was stirred at that temperature for 3-5 h. Usual work-up followed by silica gel chromatography afforded a stereoisomeric mixture of the ene product.

(7) It is noted that aluminum reagents provide the chelation product (entries 3 and 4), whereas BF_3OEt_2 leads to the formation of the non-chelation product (entry 6).[5a]

(8) In order to obtain the non-chelation isomers (**4b**) useful as references, the addition reaction of β-methy crotylsilane was carried out in the presence of BF_3OEt_2 to give β,γ–syn- and anti-**4b** in a ratio of 89 : 11.[4]

(9) This type of anti-aldols is otherwise difficult to obtain.

(10) A comparably high level of anti diastereoselection was also obtained in a similar reaction of **2b** with achiral α-benzyloxyacetaldehyde.

(11) S. Takatsuto and N. Ikekawa, J. Chem. Soc., Perkin 1, 2133 (1983).

(12) It should be noted here that the inverse addition of the Lewis acid resulted in a decrease in stereoselectivity (6 : 1).

(13) S. Takatsuto, B. Ying, M. Morisaki, and N. Ikekawa, Chem. Pharm. Bull., **29**, 903 (1981). The authors thank Prof. N. Ikekawa and Dr. Y. Fujimoto for providing the authentic sample of **11**.