

Highly Stereoselective Chelation-Controlled Allylation and Deuteration of α -Chiral α,α' -Dialkoxy Radicals

Hajime Nagano* and Yukiko Azuma

Department of Chemistry, Faculty of Science, Ochanomizu University, Otsuka, Bunkyo-ku, Tokyo 112

(Received June 20, 1996)

Diastereoselectivity in the radical mediated allylation and deuteration reactions of β -chiral β -alkoxy- α -bromoaldehyde dimethyl acetals and a related alkoxy bromide were remarkably enhanced when the reactions were conducted in the presence of Lewis acid ($\text{MgBr}_2 \cdot \text{OEt}_2$ for allylation; MgI_2 for deuteration).

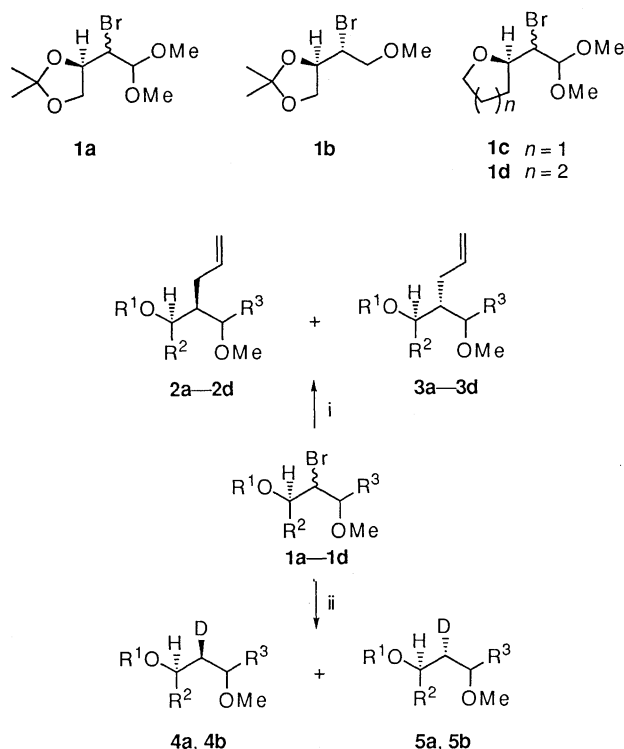
Radical reactions have been shown to proceed with high stereoselectivity, and steric and electronic effects governing the stereoselectivity are fairly well understood.¹ A current interest in radical reactions is the stereochemical control by complexation of radical intermediates with Lewis acids.² However, little is known about 1,2-stereinduction of α -chiral α,α' -dialkoxy radicals by complexation with Lewis acid,³ although esters and sulfoxides showed promise for stereocontrol. We now report that the stereoselectivity in the radical mediated allylation of **1a**–**1d** and deuteration of **1a** and **1b** was remarkably enhanced when the reactions were conducted in the presence of Lewis acid ($\text{MgBr}_2 \cdot \text{OEt}_2$ for allylation; MgI_2 for deuteration) (Scheme 1).

A summary of the allylation and deuteration results is given in Table 1. Allylation of bromides **1a**–**1d**⁴ was conducted with allyltributyltin and azoisobutyronitrile (AIBN) in CH_2Cl_2 under irradiation with a 400 W Xe lamp. Diastereomer ratios of the

products were determined by ^1H NMR. In the absence of Lewis acid, the reaction showed poor stereoselectivity (entries 1, 3, 6, and 8). The stereoselectivity was remarkably enhanced when the reaction was conducted in the presence of $\text{MgBr}_2 \cdot \text{OEt}_2$ (2.5 eq.) (entries 2, 4, 7, and 9). However, the reaction of **1b** gave **2b** in poor yield. The use of less amount of $\text{MgBr}_2 \cdot \text{OEt}_2$ resulted in significantly lower selectivity in the reactions of **1a** and **1b** (entry 5).⁵ Addition of MgI_2 completely suppressed the reaction of **1a**.⁶

The stereochemistry of **2a** and **3a** was determined as follows (Scheme 2). Hydrolysis of **2a** with *p*-toluenesulfonic acid in methanol, followed by benzoylation, gave acetal **6**. Hydrolysis of **6** with HCl in aq. THF gave hemiacetal **7**. The hemiacetal was then reduced with lithium aluminium hydride to give diol **8**, whose ^1H and ^{13}C NMR spectra were identical with those of an authentic sample derived from the previously reported diastereomeric mixture of ester **9**.^{2h} Compounds **2b** and **3b** were prepared from the acetate of **10**^{2h} as follows (i, LiAlH_4 ; ii, acetone, *p*-TsOH; iii, NaH, MeI), and their relative configurations were established.

In the absence of $\text{MgBr}_2 \cdot \text{OEt}_2$ allylation of **1a** proceeds probably through the transition state model A, in which steric and electrostatic repulsions of the oxygen functions are minimized. The allylation reagent would approach equally from the both faces of the radical center in model A to yield **2a** and **3a**. In the

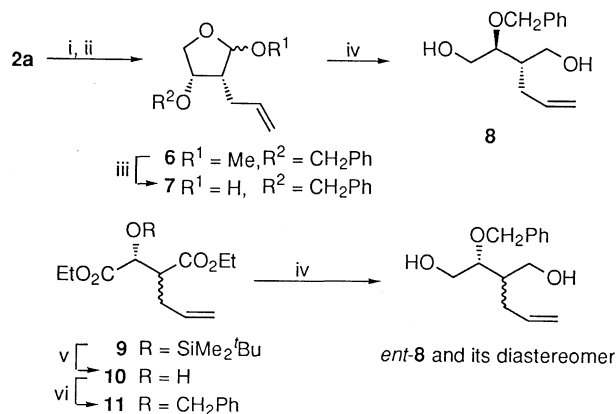


Scheme 1. i, $\text{Bu}_3\text{SnCH}_2\text{CH}=\text{CH}_2$, AIBN, ($\text{MgBr}_2 \cdot \text{OEt}_2$), CH_2Cl_2 , $h\nu$; ii, Bu_3SnD , (AIBN, MgI_2), CH_2Cl_2 , $h\nu$.

Table 1. Diastereoselectivity in allylation and deuteration of bromides **1a**

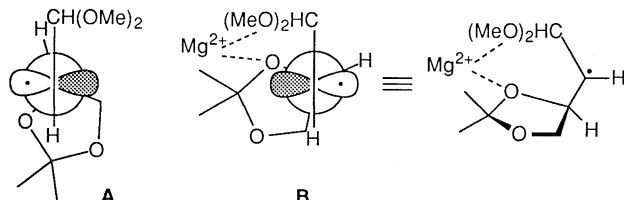
Entry	Bromide	Lewis acid (eq.)	Diastereomer ratio	Yield (%)
1	1a		2a : 3a = 1 : 1.1	52
2	1a	$\text{MgBr}_2 \cdot \text{OEt}_2$ (2.5)	2a : 3a = 52 : 1	70
3	1b		2b : 3b = 1.2 : 1	59
4	1b	$\text{MgBr}_2 \cdot \text{OEt}_2$ (2.5)	2b : 3b = 40 : 1	7
5	1b	$\text{MgBr}_2 \cdot \text{OEt}_2$ (1.0)	2b : 3b = 2.3 : 1	60
6	1c		2c : 3c = 1.2 : 1	50
7	1c	$\text{MgBr}_2 \cdot \text{OEt}_2$ (2.5)	2c : 3c = 36 : 1	58
8	1d		2d : 3d = 1 : 1.5	60
9	1d	$\text{MgBr}_2 \cdot \text{OEt}_2$ (2.5)	2d : 3d = 6.7 : 1	87
10	1a		4a : 5a = 1.3 : 1	51
11	1a	MgI_2 (2.5)	4a : 5a = 11 : 1	61
12	1b		4b : 5b = 1.6 : 1	32 ^b
13	1b	MgI_2 (2.5)	4b : 5b = >9 : 1	37 ^b

^a Allylation and deuteration were carried out as follows. A solution of bromide **1** in dry CH_2Cl_2 (ca. 1.0 mol dm^{-3}) was stirred with the Lewis acid for 10 min. Allyltributyltin (8 eq.) [or tributyltin deuteride (entry 11, 8 eq.; entry 13, 4 eqv.)] and AIBN (0.6–0.9 eq.) were then added and the mixture was irradiated at room temperature under nitrogen. After treatment with $\text{KF} \cdot \text{H}_2\text{O}$, the crude product was chromatographed on silica gel. ^b The low yield is due to the volatility of the products.



Scheme 2. i, *p*-TsOH, MeOH; ii, NaH, DMF, then PhCH₂Br; iii, HCl, aq. THF; iv, LiAlH₄; v, Bu₄NF; vi, PhCH₂Br, Ag₂O.

presence of the Lewis acid allylation of **1a** may proceed through the chelated transition state model **B**. Preferential approach of the reagent to the convex face of **B** gave **2a** with high selectivity.



Entry 4 indicates that the presence of a dimethyl acetal group is required in order to achieve the allylation with high stereoselectivity and in high yield. The highly stereoselective allylation of tetrahydrofuran **1c** (entry 7) shows that the stereochemical control was achieved by the 6-membered chelate ring formation and the participation of the oxygen attached to the carbon β to the radical center (7-membered chelate ring formation), would be negligible.^{2h} Tetrahydropyran **1d** gave, under chelation control, a ratio lower than that observed for tetrahydrofuran **1c** (entry 9).^{7,8}

In the absence of Lewis acid reduction of **1a** and **1b** with tributyltin deuteride (2.5 eq.) showed poor stereoselectivity (entries 10 and 12).^{7,9} The selectivity was highly enhanced when the reduction was conducted with tributyltin deuteride in the presence of MgI₂ (2.5 eq.) and AIBN under irradiation with a 100 W tungsten-filament lamp (entries 11 and 13). Unlike the allylation reactions, reduction of **1a** and **1b** were similar in reactivity and selectivity. The reaction of **1a** performed at 0 °C under chelation control gave a ratio of 4.2 : 1 which was lower than that performed at room temperature. ZnBr₂ was less effective and MgBr₂·OEt₂, Eu(OTf)₃, and Yb(OTf)₃ had no effect.

These results reported herein suggest the possibility that the chelate ring formation with alkoxy groups (weak Lewis base) could be used to enhance the facial selectivity of radical reactions.

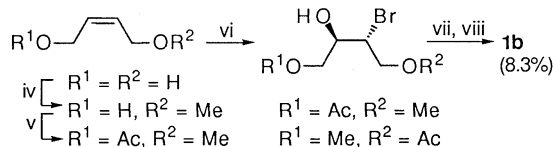
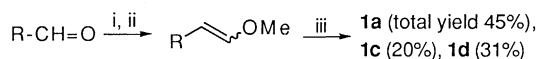
This work was supported by a Grant-in-Aid for Scientific Research from the Ministry of Education, Science and Culture.

References and Notes

1 N. A. Porter, B. Giese, and D. P. Curran, *Acc. Chem. Res.*,

24, 296 (1991); W. Smadja, *Synlett*, **1994**, 1; D. P. Curran, N. A. Porter, and B. Giese, "Stereochemistry of Radical Reactions; Concepts, Guidelines, and Synthetic Applications," VCH, Weinheim (1996).

- 2 a) P. Renaud and M. Gerster, *J. Am. Chem. Soc.*, **117**, 6607 (1995); b) Y. Guindon, B. Guérin, C. Chabot, N. Mackintosh, and W. W. Ogilvie, *Synlett*, **1995**, 449; c) M. P. Sibi, C. P. Jasperse, and J. Ji, *J. Am. Chem. Soc.*, **117**, 10779 (1995); d) N. Moufid and P. Renaud, *Helv. Chim. Acta*, **78**, 1001, 1006 (1995); e) J. H. Wu, R. Radinov, and N. A. Porter, *J. Am. Chem. Soc.*, **117**, 11029 (1995); f) M. Nishida, M. Nobuta, K. Nakaoka, A. Nishida, and N. Kawahara, *Tetrahedron: Asymmetry*, **6**, 2657 (1995); g) M. P. Sibi and J. Ji, *Angew. Chem., Int. Ed. Engl.*, **35**, 190 (1996); h) H. Nagano, Y. Kuno, Y. Omori, and M. Iguchi, *J. Chem. Soc., Perkin Trans. 1*, **1996**, 389; i) M. Nishida, H. Hayashi, A. Nishida, and N. Kawahara, *J. Chem. Soc., Chem. Commun.*, **1996**, 579; j) M. P. Sibi and J. Ji, *J. Am. Chem. Soc.*, **118**, 3063 (1996); k) Y. Guindon, B. Guérin, J. Rancourt, C. Chabot, N. Mackintosh, and W. W. Ogilvie, *Pure Appl. Chem.*, **68**, 89 (1996). See also references cited in Ref. 2e and 2h.
- 3 Renaud has recently reported the chelation controlled stereoselective reactions of 1,2-dioxy-substituted radicals.^{2a}
- 4 Bromides **1a**—**1d** were prepared from (*R*)-2,3-*O*-isopropylidene-glyceraldehyde, (*Z*)-2-butene-1,4-diol, 2-oxolanecarbaldehyde, and 2-oxanecarbaldehyde, respectively.



i, Ph₂P(=O)CH₂OMe, LiN(*i*Pr)₂; ii, NaH; iii, NBS, MeOH; iv, NaH (1.0 eq.), MeI; v, Ac₂O, pyr; vi, NBS, H₂O/THF; vii, *p*-TsOH, H₂O/THF; viii, *p*-TsOH, acetone.

- 5 Guindon has also reported that 3 equivalents of MgBr₂·OEt₂ must be added in order to induce high selectivity in the allylation of α -iodo- β -alkoxy esters.^{2b, 2k}
- 6 Allylation of **1a** using Et₃B in the presence of MgBr₂·OEt₂ (2.5 eq.) at room temperature gave **2a** with lower diastereoselectivity.
- 7 The relative configurations of **2c**, **3c**, **2d**, and **3d** were deduced by correlation of their ¹H NMR spectra with those of **2a** and **3a**.
- 8 It has been reported that in the allylation of α -iodo- β -alkoxy esters the selectivity of tetrahydropyran substrate is higher than that of tetrahydrofuran substrate.^{2b, 2k}
- 9 The stereochemistry of **4a** and **5a** was assigned based on the coupling constants of the hydroxy acetals derived from **4a** and **5a** (*p*-TsOH, MeOH). The relative configurations of **4b** and **5b** were tentatively assigned based on the postulate that **4b** was mainly yielded through the chelated transition state similar to model **B**. Diastereomer ratios of the reduction products were determined by ¹H NMR (400 MHz) integration of CHD. **4a**: δ 1.92 (m), **5a**: δ 1.81 (ddt, *J* = 7.4, 5.6, and 2.0 Hz); **4b**: δ 1.86 (m); **5b**: δ 1.79 (m).