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Enantioselective Ring Cleavage of Dioxane Acetals Mediated by a Chiral Lewis Acid: Application to Asymmetric Desymmetrization of *meso*-1,3-Diols

Toshiro Harada,* Kousuke Sekiguchi, Tomohito Nakamura, Jun Suzuki, and Akira Oku

Department of Chemistry, Kyoto Institute of Technology, Matsugasaki, Sakyo-ku, Kyoto 606-8585, Japan

harada@chem.kit.ac.jp

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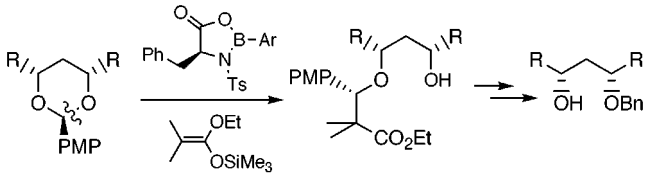
ABSTRACT



Phenylalanine-derived *B*-aryl-*N*-tosyloxazaborolidinones selectively activate one of two enantiotopic oxygen atoms in prochiral *anti* dioxane acetals derived from *meso*-1,3-diols, leading to enantioselective formation of ring-cleavage products. The reaction is utilized as a key step in asymmetric desymmetrization of *meso*-1,3-diols.

Chiral Lewis acids have been successfully used in many face-selective reactions, where the enantiotopic faces of a planar substrate are differentiated by conversion to diastereotopic ones through coordination.[1] Although not yet intensively studied,[2] the use of chiral Lewis acids in enantiotopic group selective reactions involves a completely different mechanism of asymmetric induction and is expected to provide a new approach to nonenzymatic asymmetric desymmetrization of prochiral bifunctional compounds.[3] Diastereomeric complexes are formed through coordination of the enantiotopic functional groups. Selective activation of one of two enantiotopic groups can be achieved through the differentiating complexation by a proper chiral Lewis acid, leading to the formation of desymmetrization product.

Direct evidence for enantiotopic group recognition by a chiral Lewis acid was demonstrated by Reetz et al. in their study on the complexation of a prochiral diamine by a chiral boron compound.[4] We recently disclosed[5] that oxazaborolidinone **2a** as a chiral Lewis acid[6] is effective in enantioselective ring-cleavage reaction of *meso*-1,3-dioxolane acetals *syn*-**1** with silyl ketene acetals (eq 1), and a subsequent study

(1) (a) *Catalytic Asymmetric Synthesis*, 2nd ed; Ojima, I., Ed.; Wiley-VCH: Weinheim, 2000. (b) *Lewis Acids in Organic Synthesis*; Yamamoto, H., Ed.; Wiley-VCH: Weinheim, 2000.

(2) (a) Seebach, D.; Jaeschke, G.; Wang, Y. M. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2395−2396. (b) Ramon, D. J.; Guillena, G.; Seebach, D. *Helv. Chim. Acta* **1996**, *79*, 875−894.

(3) (a) Ward, R. S. *Chem. Soc. Rev.* **1990**, *19*, 1−19. (b) Gais, H. J. In *Methods of Org. Chem. (Houben-Weyl)*; Helmchen, G., Hoffmann, R. W., Mulzer, J., Schumann, E., Eds.; Georg Thieme Verlag: Stuttgart, 1995; Vol. E21a, pp 589−644. (c) Vedejs, E.; Daugulis, O.; Diver, S. T. *J. Org. Chem.* **1996**, *61*, 430−431 and references therein. (d) Willis, M. C. *J. Chem. Soc., Perkin Trans. 1* **1999**, 1765−1784.

(4) Huskens, J.; Goddard, R.; Reetz, M. T. *J. Am. Chem. Soc.* **1998**, *120*, 6617−6618. This paper also dealt with enantioselective conversion of the resulting complex by taking advantage of the deactivation of coordinating functional group.

(5) (a) Kinugasa, M.; Harada, T.; Oku, A. *J. Am. Chem. Soc.* **1997**, *119*, 9067−9068. (b) Kinugasa, M.; Harada, T.; Oku, A. *Tetrahedron Lett.* **1998**, *39*, 4523−4526. (c) Harada, T.; Nakamura, T.; Kinugasa, M.; Oku, A. *Tetrahedron Lett.* **1999**, *40*, 503−506. (d) Harada, T.; Yamanaka, H.; Oku, A. *Synlett* **2001**, 61−64.

(6) For the use of relevant oxazaborolidinones in enantioface selective reactions, see: (a) Takasu, M.; Yamamoto, H. *Synlett* **1990**, 194−196. (b) Sartor, D.; Saffrich, J.; Helmchen, G. *Synlett* **1990**, 197−198. (c) For leading references, see: Ishihara, K.; Kondo, S.; Yamamoto, H. *J. Org. Chem.* **2000**, *65*, 9125−9128.

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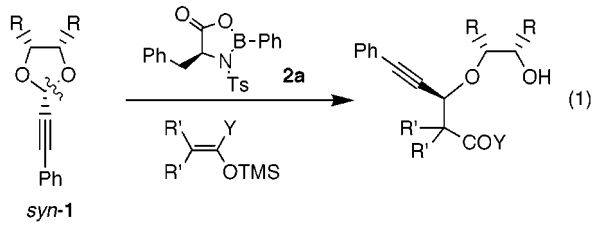
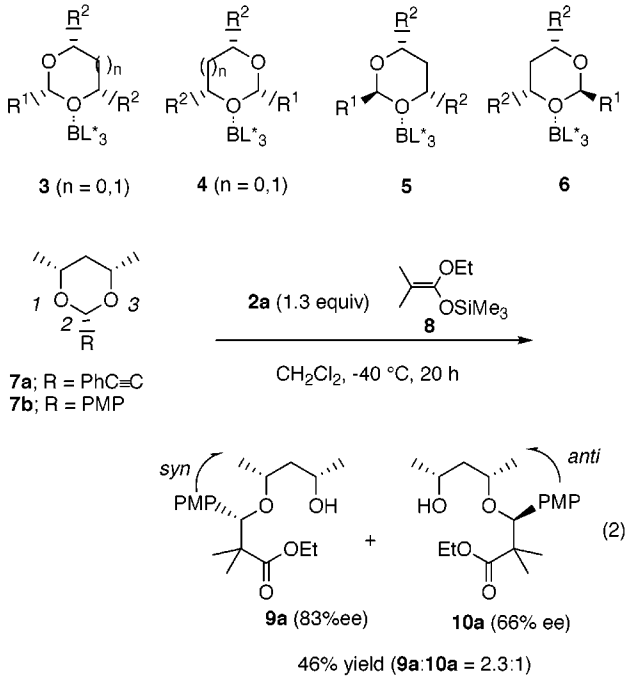
on the mechanism led us to propose that the enantiodifferentiating coordination of an acetal oxygen atom by the chiral Lewis acid is a major factor governing the enantioselectivity.[7]



In this paper, we report oxazaborolidinone-mediated enantioselective ring cleavage of 1,3-dioxane acetals and its application to desymmetrization of *meso*-1,3-diols.[8] The study not only provides a further support for the enantiotopic group selective activation through differentiating complexation by chiral Lewis acids but also gives information on the structure of activated complexes.

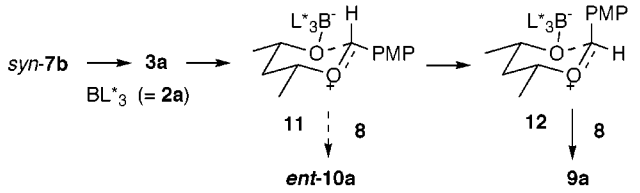
For diastereomeric complexes **3** and **4** derived from *syn* substituted acetals, the substituents R^1 and R^2 around the coordinating oxygen atom are symmetrically disposed with respect to a plane bisecting the acetal ring. Therefore, differentiating complexation by a chiral Lewis acid is anticipated when these two groups are structurally different. Indeed, in the ring-cleavage reaction of *meso*-1,3-dioxolane acetals ($n = 0$), we observed that the sterically less demanding alkynyl group as an R^1 group is essential to obtain high enantioselectivity for various R^2 groups.[5a] We, therefore, initiated the study with analogous 2-phenylethynyl derivative *syn*-**7a** (eq 2). However, treatment of *syn*-**7a** and silyl ketene acetal **8** in the presence of oxazaborolidinone **2a**[9] (1.3 equiv) in CH_2Cl_2 at −40 °C resulted in recovery of the starting material, suggesting that dioxane acetals with three substituents being equatorial are quite less reactive than dioxolane acetals.[10]



Under similar conditions, *p*-methoxyphenyl (PMP) derivative *syn*-**7b** underwent ring cleavage to some extent (eq 2). In contrast to a high 1,3-*anti* diastereoselectivity observed for dioxolane acetals,[5,7] an inseparable mixture of *syn* isomer **9a** and *anti* isomer **10a** was obtained with a 2.3:1 ratio. The sense of asymmetric induction was opposite between **9a** and **10a**. The major enantiomer of **9a** is the one produced through the cleavage of the C(2)−O(3) bond, while the C(2)−O(1) bond preferentially underwent cleavage to give **10a**.[11] Although both products were obtained with relatively high enantioselectivity, the opposite sense of asymmetric induction resulted in low overall enantioselectivity[12] (39% ee) with respect to desymmetrization of the *meso*-diol.

Formation of **9a** as a major diastereomer can be rationalized by a pathway involving contact ion pairs **11** and **12** as product-determining intermediates (Scheme 1).[7,13] Thus, *syn*

Scheme 1. Proposed Ring-Cleavage Pathway for *syn*-**7b**



ion pair **11**, formed initially via the corresponding acetal−Lewis acid complex **3a** (R^1 = PMP, R^2 = Me, $n = 1$), might be stable and less reactive, undergoing isomerization[13a,b] to the unfavorable but reactive *anti* ion pair **12**, which is then attacked by **8** to give **9a**. It occurred to us that *anti*-dioxane

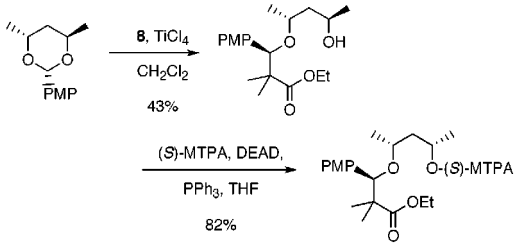
(7) Harada, T.; Nakamura, T.; Kinugasa, M.; Oku, A. *J. Org. Chem.* **1999**, *64*, 7594−7600.

(8) For nonenzymatic desymmetrization of *meso*-1,3-diols, see: (a) Ichikawa, J.; Asami, M.; Mukaiyama, T. *Chem. Lett.* **1984**, 949−952. (b) Harada, T.; Sakamoto, K.; Ikemura,; Y. Oku, A. *Tetrahedron Lett.* **1988**, *29*, 3097−3100. (c) Harada, T.; Ikemura, Y.; Nakajima, H.; Oku, A. *Chem. Lett.* **1990**, 1441−1444. (d) Oriyama T.; Hosoya, T.; Sano, T. *Hetrocycles* **2000**, *52*, 1054−1069.

(9) Kinugasa, M.; Harada, T.; Egusa, T.; Oku, A. *Bull. Chem. Soc. Jpn.* **1996**, *69*, 3639−3650.

(10) Dioxane acetals are less basic than dioxolane acetals. Denmark, S. E.; Willson, T. M.; Almstead, N. G. *J. Am. Chem. Soc.* **1989**, *111*, 9258−9260.

(11) The enantioselectivities of **9a** and **10a** were determined by 500 MHz ^{1}H NMR analysis of the MTPA ester derivatives. The authentic (*S*)-MTPA ester derivative of *ent*-**10a** was prepared from (2*R*,4*R*)-2,4-pentanediol via titanium chloride mediated ring-cleavage reaction of the 2-(*p*−methoxyphenyl)dioxane acetal derivative followed by the Mitsunobu esterification with (*S*)-MTPA. The absolute structure of **9a** was established by its conversion into **18a** (vide infra).



(12) The overall enantioselectivity is defined by {(C(2)−O(3) cleavage) − (C(2)−O(1) cleavage)}/{(C(2)−O(3) cleavage) + (C(2)−O(1) cleavage)} = {(**9** + *ent*-**10**) − (*ent*-**9** + **10**)}/{(**9** + *ent*-**10**) + (*ent*-**9** + **10**)}.

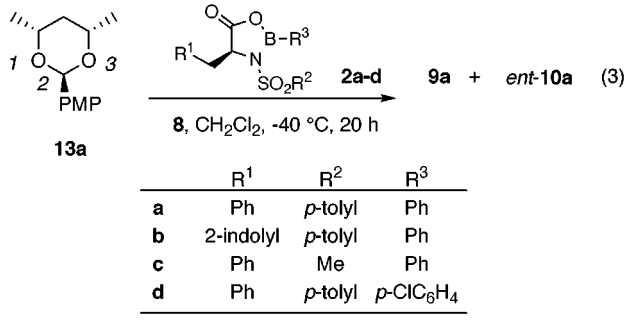
acetals would react smoothly through direct formation of the reactive *syn* ion pairs via activated complexes **5** or **6**. In addition, for diastereomeric complexes **5** and **6**, substituents R^1 and R^2 around the coordinating oxygen atom are oriented pseudo-C_2 symmetrically along the O−B bond axis and a high degree of asymmetric induction was anticipated irrespective of the structures of R^1 and R^2.

Indeed, *anti*-**13a** with axial PMP group underwent facile ring-cleavage reaction at −40 °C to give **9a** as a major diastereomer (9.5:1) with high enantioselectivity (98% ee) (eq 3, entry 1 in Table 1). The selective cleavage of the C(2)−O(1) bond was observed also for a minor diastereomer *ent*-**10a** (65% ee). Therefore, satisfactory overall enantioselectivity (95% ee) could be achieved. Similar results were obtained when related oxazaborolidinones **2b**−**d** were used. Tryptophan-derived **2b** exhibited high enantioselectivity as well (entry 2). Displacement of the tosyl group of **2a** with the mesyl group did not affect the selectivity either (entry 3). Slight decrease in diastereoselectivity was observed for *B*-(*p*-chlorophenyl) derivative **2d** (entry 4).

Table 1. Ring-Cleavage of *anti*-Dioxane Acetal *anti*-**13a**[a]

				ee (%)[c]		
entry	**2**	yield (%)	**9a**:*ent*-**10a**[b]	**9a**	*ent*-**10a**	overall
1	**2a**	90	9.5:1	98	67	95
2	**2b**	60	5.9:1	99	67	93
3	**2c**	70	7.3:1	97	33	92
4	**2d**	70	5.5:1	98	56	91

[a] Reactions were carried out by using **2a** (1.3 equiv) and **8** (3 equiv) in CH_2Cl_2 (0.4 M) at −40 °C for 15−20 h. [b] Determined by 500 MHz ^{1}H NMR analysis. [c] Determined by 500 MHz ^{1}H NMR analysis of the MTPA ester derivatives.



	R^1	R^2	R^3
a	Ph	*p*-tolyl	Ph
b	2-indolyl	*p*-tolyl	Ph
c	Ph	Me	Ph
d	Ph	*p*-tolyl	*p*-ClC$_6$H$_4$

The selective cleavage of the C(2)−O(1) bond was observed also for a minor diastereomer *ent*-**10a** (65% ee). Therefore, satisfactory overall enantioselectivity (95% ee) could be achieved. Similar results were obtained when related oxazaborolidinones **2b**−**d** were used. Tryptophan-derived **2b** exhibited high enantioselectivity as well (entry 2). Displacement of the tosyl group of **2a** with the mesyl group did not affect the selectivity either (entry 3). Slight decrease in diastereoselectivity was observed for *B*-(*p*-chlorophenyl) derivative **2d** (entry 4).

Facile and diastereoselective ring-cleavage reaction of *anti*-**13a** implies that *anti* ion pair **12**, once formed, undergoes a rapid attack by **8**, as observed for dioxolane acetal *syn*-**1**,[7] before isomerizing to the more stable *syn* ion pair **11**. It is most probable that the enantiodifferentiating coordination of the O(3) oxygen atom of *anti*-**13a** by oxazaborolidinone **2,** followed by a rate-determining dissociation of the resulting activated complex to the contact ion pair, is a major factor governing the enantioselectivity.[7] Our working model for the activated complexes is shown in Scheme 2. In this model, the acetal oxygen atom coordinates to the face of the oxazaborolidinone *trans* to the benzyl group and *cis* to the tosyl group. A coordination to the opposite face might be sterically less feasible because the benzyl group takes the conformation in which the phenyl group is placed over the oxazaborolidinone ring.[14] Of three staggered conformers around the O−B bond of a complex derived from the O(3)

Scheme 2. Proposed Model of the Activated Complexes

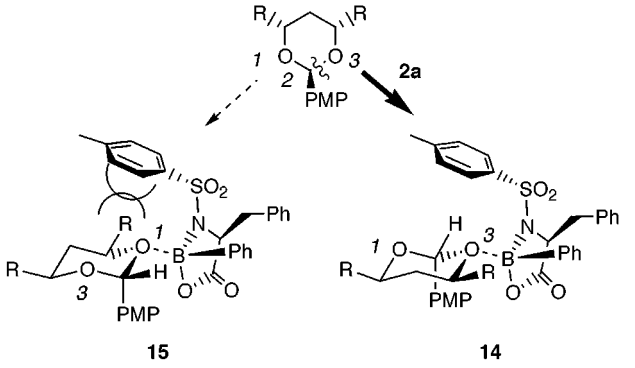
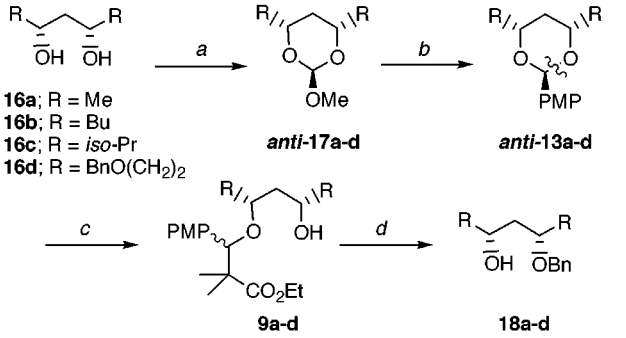


Table 2. Asymmetric Desymmetrization of *meso*-1,3-Diols



		yield (%)				ee (%)[g] [α]$_D$ (CHCl$_3$)	
entry	diols	**17**	**13**	**9**	**18**	**18**	
1	**16a**	97[h]	53[i]	83	62	93	+57.4 (*c* 0.70)
2	**16b**	67	77	94[j]	79	86	+49.6 (*c* 1.00)
3	**16c**	52	94	94[j]	79[k]	94	+58.6 (*c* 1.00)
4	**16d**	57	82	89	67	92	+13.1 (*c* 1.01)

[a] HC(OMe)$_3$ (1.5 equiv), TsOH, cyclohexane, 70 °C, 1 h. [b] *p*-MeOC$_6$H$_4$MgBr (1.5 equiv), Et$_2$O, room temperature, 24 h. [c] Unless otherwise noted, **2a** (1.3 equiv), **8** (3 equiv), CH_2Cl_2, −40 °C, 15−20 h. [d] BnBr (1.3 equiv), NaN(TMS)$_2$ (1.5 equiv), THF, room temperature, 1.5 h, and then CF_3CO_2H, 0 °C, 3 h. [e] Unless otherwise noted, isolated yields of *anti* isomer. [f] The absolute structure of **18a** was determined by the measurement of specific rotation.[8c] For **18b**−**d**, the structures were established by the modified Mosher's method.[17] [g] Determined by 500 MHz ^{1}H NMR analysis of the MTPA ester derivative. [h] Combined yield of *anti*- and *syn*-**17a** (1.6:1). [i] A mixture of *anti*- and *syn*-**17a** was used. [j] **2d** (1.3 equiv) was used. [k] Ring-cleavage product **9c** was treated with LiAlH$_4$ (2.0 equiv) in THF, and the resulting diol was used in transformation to **18c**.

(13) (a) Denmark, S. E.; Almstead, N. G. *J. Am. Chem. Soc.* **1991**, *113*, 8089−8110. (b) Denmark, S. E,; Almstead, N. G. *J. Org. Chem.* **1991**, *56*, 6458−6467. (c) Mori, I.; Ishihara, K.; Flippin, L. A.; Nozaki, K.; Yamamoto, H.; Bartlett, P. A.; Heathcock, C. H. *J. Org. Chem.* **1990**, *55*, 6107−6115. (d) Sammakia, T.; Smith, R. S. *J. Am. Chem. Soc.* **1992**, *114*, 10998−10999.

coordination, only **14** does not experience significant nonbonded interaction. On the other hand, unfavorable interactions exist in all three staggered conformers of an alternative complex derived from the O(1) coordination as shown, for example, in **15** of a local conformation similar to that of **14** around the O−B bond. This working model also explains the high enantioselectivity as well as the absolute configuration of the products in the ring-cleavage reaction of dioxolane acetal *syn*-**1** with the sterically less demanding alkynyl group.[15,16]

Desymmetrization of representative *meso*-1,3-diols **16a**−**d** was examined by using the ring cleavage of *anti* acetal derivatives (Table 2). The diols were converted into cyclic ortho esters *anti*-**17a**−**d** (*anti*:*syn* = 1.6−2.0:1) by treatment with trimethyl orthoformate.[18,19] A subsequent Grignard reaction of pure *anti* ortho esters gave *anti*-**13a**−**d** exclusively.[18] The crucial ring-cleavage reaction using oxazaborolidinone **2a** or **2d** afforded **9a**−**d** in high yield. Benzylation of **9a**−**d**, containing a minor diastereomer, followed by treatment with trifluoroacetic acid, furnished desymmetrized derivatives **18a,b,d** of high ee. Transformation to **18c** was accomplished after $LiAlH_4$ reduction to the corresponding diol owing to the difficulty in direct benzylation of **9c** with the sterically demanding isopropyl group.

In summary, we have developed a highly enantioselective method for asymmetric desymmetrization of *meso*-1,3-diols. The method relies on oxazaborolidinone-mediated ring-cleavage reaction of *anti*-dioxane acetals where chiral Lewis acids **2** selectively activates one of the enantiotopic acetal C−O bonds through enantiodifferentiating complexation.

Acknowledgment. This work was supported partially by Grant-in-Aid for Scientific Research from Ministry of Education, Culture, Sports, Science and Technology, Japan (Priority Areas, no. 706: Dynamic Control of Stereochemistry) and by the Nagase Science and Technology Foundation.

Supporting Information Available: Experimental procedures and absolute structure determination of desymmetrized products **18a**−**d** and ring-cleavage products **9a** and **10a** by modified Mosher's method. This material is available free of charge via the Internet at http://pubs.acs.org.

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(14) A relatively small vicinal coupling constant observed for the benzyl protons of **2b** (J = 2.7 and 5.4 Hz) supports this conformation. Other rotamers might be less stable owing to unfavorable interaction with the sulfonyl or carbonyl oxygen atom.

(15) Enantioselectivities observed in ring-cleavage reaction of *anti*-dioxolane acetals[5d] as well as ethylene glycol derived dioxolane acetals[16] are also consistent with the present model.

(16) Kinugasa, M.; Harada, T.; Oku, A. *J. Org. Chem.* **1996**, *61*, 6772−6773.

(17) Ohtani I.: Kusumi. T.; Kashman. Y.; Kakisawa, H. *J. Am. Chem. Soc.* **1991**, *113*, 4092−4096.

(18) Eliel, E. L.; Knoeber, M. C. *J. Am. Chem. Soc.* **1968**, *90*, 3444−3458.

(19) Ortho ester *syn*-**17c** could be isomerized by treatment with BF_3·Et_2O (0.2 equiv) in Et_2O at −78 °C to give a 4.7: 1 mixture of *anti*- and *syn*-**17c** (80% yield). Under similar conditions, *syn*-**17d** was converted almost completely into *anti*-**17d** (25:1, 78% yield), which was precipitated from the reaction mixture.