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# Desymmetrization of *meso*-1,2-Diols via Chiral Lewis Acid-Mediated Ring-Cleavage of 1,3-Dioxolane Derivatives

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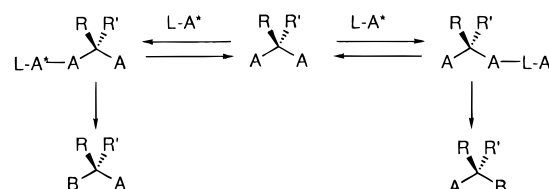*Matsugasaki, Sakyo-ku, Kyoto 606, Japan*

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In transformations leading to enantiomerically pure products, enantiotopic faces or groups of the starting materials have to be differentiated. Chiral Lewis acids have been successfully used in enantioface differentiation, where the enantiotopic faces of a planar substrate are differentiated by conversion to diastereotopic ones through coordination.[1] Although being not intensively studied,[2,3] chiral Lewis acids can also be utilized in enantiotopic group differentiation, or desymmetrization, of nonplanar symmetrical bifunctional compounds (Scheme 1).[4] The role of chiral Lewis acids (L-A*) is completely different in this type of reaction. Diastereomeric complexes are formed through coordination to the enantiotopic functional groups.[5] Selective reaction from a specific diastereomer would lead to the formation of enantiomerically pure product.
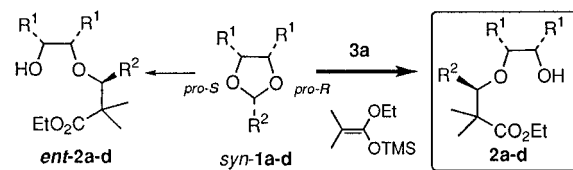
Lewis acid-mediated reaction of *meso*-acetal *syn*-**1** with nucleophiles affords enantiomeric products **2** or ***ent*-2** depending upon whether C−O$_{pro-R}$ or C−O$_{pro-S}$ undergoes bond cleavage (Scheme 2).[6,7] Herein, we wish to report that, in the presence of chiral Lewis acid **3a**, the cleavage reaction proceeds in an enantiodifferentiating manner at the C−O$_{pro-R}$ to give the desymmetrized product **2**.

Condensation of *meso*-2,3-butanediol with benzaldehyde afforded *syn*-**1a** and *anti*-**1a** in a 1.6:1 ratio. Treatment of *syn*-**1a** with Me$_2$C=C(OTMS)OEt in the presence of *N*-tosyl phenylalanine-derived phenylboron complex **3a**[8] (0.3 equiv) in CH$_2$Cl$_2$ at −20 °C for 15 h gave ring-cleavage product **2a** diastereoselectively (>20:1) in 72% yield but with low ee (22%). Under similar conditions, *anti*-**1a** was considerably less reactive
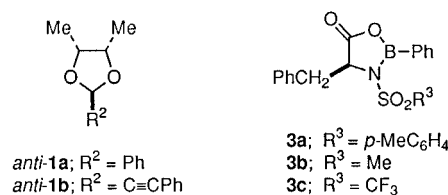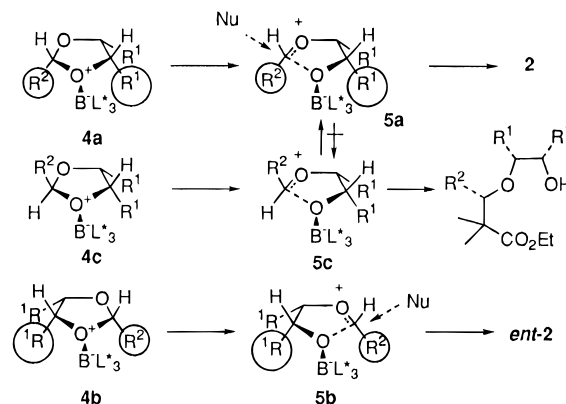
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**Scheme 1**



**Scheme 2**



**a**; R$^1$ = Me, R$^2$ = Ph
**b**; R$^1$ = Me, R$^2$ = PhC≡C
**c**; R$^1$ = Et, R$^2$ = PhC≡C
**d**; R$^1$ = BnOCH$_2$, R$^2$ = PhC≡C

**e**; R$^1$ = Ph, R$^2$ = PhC≡C
**f**; R$^1$-R$^1$ = -(CH$_2$)$_3$-; R$^2$ = PhC≡C
**g**; R$^1$-R$^1$ = -(CH$_2$)$_4$-; R$^2$ = PhC≡C

*anti*-**1a**; R$^2$ = Ph
*anti*-**1b**; R$^2$ = C≡CPh

**3a**; R$^3$ = *p*-MeC$_6$H$_4$
**3b**; R$^3$ = Me
**3c**; R$^3$ = CF$_3$

**Scheme 3**



affording the same product **2a** in 10% yield with the recovery of the starting dioxolane without isomerization to *syn*-**1a**.

In Lewis acid−acetal complex **4a**, the R$^1$ and R$^2$ groups locate respectively at the right- and left-hand sides of a chiral Lewis acid, while the location of the groups is interchanged in diastereomeric complex **4b** (Scheme 3). According to this simplified coordination model, the structural difference between the R$^1$ and R$^2$ groups is an important factor for the differentiation of the enantiotopic oxygen atoms. It was anticipated that the sterically less demanding alkynyl group as R$^2$ would improve the enantioselectivity.

Indeed, higher selectivity was observed for 2-phenylethynyl derivative *syn*-**1b**. Thus, transacetalization of 3,3-diethoxy-1-phenylpropyne with *meso*-2,3-butanediol stereoselectively gave a 86:14 mixture of *syn*- and *anti*-**1b**. Treatment of the mixture with Me$_2$C=C(OTMS)OEt and 0.3 equiv of **3a** at −20 °C afforded ring-cleavage product **2b** (>20:1 diastereoselectivity)

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**Table 1.** Enantioselective Ring-Cleavage of Dioxolanes *syn-***1b**−**g** Mediated by Boron Complexes **3**[a]

| entry | substrate (R[2] = PhC≡C) | 2b-g yield (%) | 2b-g ee (%) [c] | 6a-e[b] | yield (%) | ee [c] (%) |
|---|---|---|---|---|---|---|
| 1 [c,d] | *syn-***1b** | 76 | 71 | **6a** [e] | | |
| 2 [c,f] | | 81 | 89 | | 81 | 89 |
| 3 | | 72 | 94 | | 65 | 93 |
| 4 [c,d,g] | | 73 | 48 | | | |
| 5 [d,h] | | 51 | 58 | | | |
| 6 | *syn-***1c** | 78 | 96 | **6b** [i] | 76 | 96 |
| 7 | *syn-***1d** | 73 | 97 | **6c** [i] | 78 | 96 |
| 8 | *syn-***1e** | 39 | 90 | | | |
| 9 | *syn-***1f** | 68 | 93 | **6d** | 70 | 92 |
| 10 | *syn-***1g** | 78 | 85 | **6e** | 74 | 85 |

*a* Unless otherwise noted, ring-cleavage reactions were carried out in $CH_2Cl_2$ by using boron complex **3a** (1.0 equiv) and $Me_2$-C=C(OTMS)OEt (3 equiv) at −78 °C for 14−16 h. *b* Unless otherwise noted the absolute configuration of **6** was determined by comparing $[\alpha]_D$ with a reported value: (1*R*,2*S*)-**6d** ($[\alpha]^{20}_D$ +17.0 (*c* 1.40, $CHCl_3$), lit. Harada, T.; Ikemura, Y.; Nakajima, H.; Ohnishi, T.; Oku, A. *Chem. Lett.* **1990**, 1441) and (1*R*,2*S*)-**6e** ($[\alpha]^{20}_D$ +13.9 (*c* 1.47, $CHCl_3$), lit. Naemura, K.; Takeuchi, S.; Hirose, K.; Tobe, Y.; Kaneda, T.; Satake, Y. *J. Chem. Soc., Perkin Trans. 1* **1995**, 213). *c* A 86:14 mixture of *syn-* and *anti-***1b** was used. The recovery of the starting material and the *syn:anti* ratio are as follows: entry 1, 18%, 7:93; entry 2, 13%, 12:88; entry 4, 13%, 3:97. *d* The reaction was carried out at −20 °C. *e* See Supporting Information for absolute configuration determination ((2*R*,3*S*)-**6a**; $[\alpha]^{20}_D$ +18.2 (*c* 0.33, $CHCl_3$)). *f* The reaction was carried out at −50 °C. *g* Boron complex **3b** was used. *h* Boron complex **3c** was used. *i* Tentative assignment of the absolute configuration.

in 33% yield with 63% ee. A separate experiment using pure *anti-***1b** showed that it was unreactive under these conditions. For the reaction of the phenylethynyl derivative, a stoichiometric amount of **3a** was required to achieve higher yields. Under stoichiometric conditions at −20 °C, the reaction of a 6.3:1 mixture of *syn-* and *anti-***1b** afforded **2b** of 71% ee in 76% yield together with the recovery of the unreactive *anti* isomer (Table 1, entry 1). The degree of enantioselectivity was enhanced by carrying out the reaction at the lower temperatures: **2b** of 94% ee was obtained at −78 °C (entry 3). Although we have not fully surveyed the related amino acid-derived boron complexes, preliminary results suggest that the structure of the *N*-sulfonyl moiety influences the enantioselectivity (entries 4 and 5).

Boron complex **3a** was also effective in ring-cleavage of other dioxolanes that could be prepared stereoselectively (*syn*:*anti* >20:1) from the diols under the kinetically controlled conditions.[9] Not only the reaction of *syn-***1c**−**e** derived from acyclic diols (entries 6−8) but also *syn-***1f,g** derived from cyclic diols proceeded with high enantioselectivity (85−97% ee).

Ring-cleavage products **2** were readily converted to desymmetrized *meso*-1,2-diol derivatives **6** without the loss of stereogenic integrity (Table 1). Thus, benzylation (KN(TMS)$_2$, BnBr, THF) of the hydroxy group of **2** followed by treatment of the resulting benzyl ethers in trifluoroacetic acid at room temperature furnished **6a**−**e** of high enantiomeric purities in good yields. The enantiomeric purities were determined by ^{1}H-NMR (300 and/or 500 MHz) analysis of the (*S*)-MTPA ester derivatives.

The absolute configurations of the three stereogenic centers in ring-cleavage products **2a,b** were determined by correlation experiments.[10] The stereochemical outcome demonstrates that, in the presence of chiral boron complex **3a**, the C−O$_{pro-R}$ of *syn-***1** underwent selective bond-cleavage with inversion of the configuration at the acetal carbon. By recent mechanistic studies on the Lewis acid-mediated ring-cleavage of acetals, the possibility of a direct $S_N2$-type limiting mechanism involving a Lewis acid−acetal complex was ruled out, and a wide mechanistic spectrum for a dissociative $S_N1$-type mechanism was revealed.[6f,11] Denmark et al. have proposed an intimate ion pair as a reactive intermediate for the reaction with selective inversion of the configuration.[6f] The major ring-cleavage product **2** is therefore suggested to be produced through a mechanism involving an initial formation of Lewis acid−dioxolane complex **4a**, dissociation to intimate ion pair **5a**, and the attack of the nucleophile in an invertive manner (Scheme 3). Assuming diastereomeric ion pairs **5a** and **5b** are intercepted by the nucleophile in similar rates, the observed enantioselectivity can be interpreted in terms of the preferential formation of complex **4a** and structurally related ion pair **5a** over **4b** and **5b**, respectively.

High diastereoselectivity observed in the present ring-cleavage reaction suggests that ion pair **5a** did not isomerize to the diastereomer **5c** (Scheme 3).[12] The ion pair **5c** would also be formed by dissociation of the complex **4c** derived from *anti-***1**. The observed nonreactivity of *anti-***1b** indicates that the formation of the complex **4c** using **3a** is not feasible and therefore suggests that the structurally related ion pair **5c** might be highly unstable relative to **5a**.[13]

In summary, desymmetrization of *meso*-1,2-diols was realized by a chiral Lewis acid-mediated enantioselective ring-cleavage of the dioxolane derivatives. The study demonstrates the potential use of chiral Lewis acid in enantiotopic group-selective reactions. Works are in progress to reduce the amount of Lewis acids and to clarify the origin of the enantioselection.

**Supporting Information Available:** A typical experimental procedure, characterization data for new compounds, and structural determination of **2a,b** (8 pages). See any current masthead page for ordering and Internet access instructions.

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(12) Isomerization of ion pair intermediates has been proposed for the low diastereoselectivity in the titanium complex-promoted ring-cleavage of 1,3-dioxanes.[6f,11d]

(13) The reaction of *anti-***1a** was sluggish but gave **2a**, the same diastereomer obtained from *syn-***1a**. The result supports for the possible isomerization of ion pair **5c** to **5a**.