Chiral Oxazaborolidinone-Mediated Enantioselective Ring-Cleavage Reaction of a Mixture of Diastereomeric 1,3-Dioxolane Acetals: Application to Asymmetric Desymmetrization of *meso*-1,2-Diols

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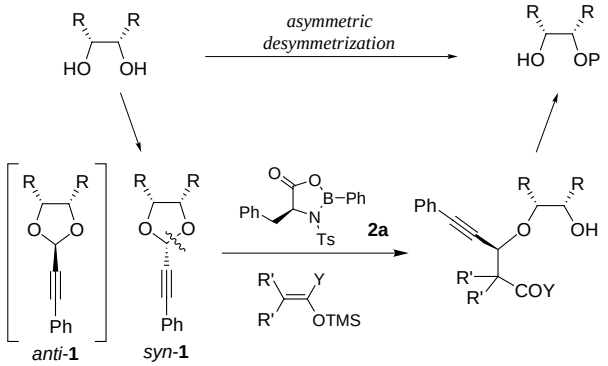
Abstract: Ring-cleavage reaction of a mixture of diastereomeric dioxolane acetals *syn*- and *anti*-**1b-e** proceeds in an enantiodifferentiating manner in the presence of chiral Lewis acid **2**. The reaction is utilized as a key step in asymmetric desymmetrization of *meso*-1,2-diols.

Key words: asymmetric synthesis, acetals, cleavage, diols, Lewis acids

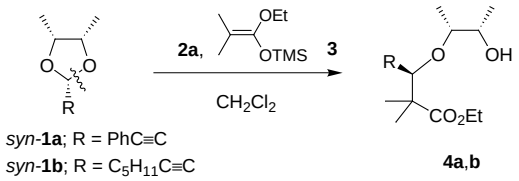
Nonenzymatic approach to the enantiotopic group differentiation, or asymmetric desymmetrization, of prochiral bifunctional compounds has been receiving increasing attention because of its utility in preparing chiral building blocks as well as in constructing multiple stereogenic centers.[1] We recently reported a general method for desymmetrization of *meso*-1,2-diols via oxazaborolidinone-mediated enantioselective ring-cleavage of acetal derivatives (Scheme 1).[2,3] The prochiral diols are first converted to 2-phenylethynyl-1,3-dioxolane acetals *syn*-**1**. Oxazaborolidinone **2a** as a chiral Lewis acid is highly effective in differentiating the enantiotopic C-O bonds of the prochiral acetals *syn*-**1** in subsequent ring-cleavage reaction with silyl ketene acetals. The resulting ring-cleavage products are transformed to desymmetrized derivatives of the *meso*-diols (85-96% ee) in two steps.



Scheme 1

In this desymmetrization process, the stereoselective preparation of *syn*-**1** is indispensable to obtain high overall efficiency because diastereomeric acetals *anti*-**1** are quite less reactive in the ring-cleavage reaction. Acetalization of *meso*-1,2-diols under conventional thermodynamically controlled conditions results in the nonselective formation of *syn*- and *anti*-**1**. Therefore, kinetically controlled conditions ($PhC{\equiv}CCH(OEt)_2$, TsOH (0.1 equiv), molecular sieves 4 A, CH_2Cl_2, r.t.) are employed for *syn* selective acetalization. However, for diols whose rate of acetalization is slow, competitive isomerization of initially produced *syn* acetals to *anti* isomers often makes it difficult to obtain high *syn* selectivity at higher conversion.[2b] We have now found that, by the modification of a substituent at the acetal carbon, both *syn* and *anti* acetals derived from *meso*-1,2-diols undergo ring-cleavage reaction enantioselectively at the same side. Herein, we report an improved method for asymmetric desymmetrization of *meso*-1,2-diols in which a mixture of diastereomeric acetals is used in the ring-cleavage reaction.

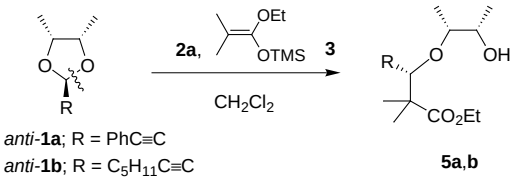
In the presence of oxazaborolidinone **2a** (1.2 equiv), 2-phenylethynyl-1,3-dioxolane acetals *syn*-**1a** reacted with silyl ketene acetal **3** at -78 °C to give ring-cleavage **4a** (96% ee) (eq 1, entry 1 in Table 1). In comparison with *syn*-**1a**, diastereomeric acetal *anti*-**1a** is less reactive and did not undergo ring-cleavage at -78 °C (eq 2, entry 2). At -20 °C, a slow but enantioselective reaction took place for *anti*-**1a** to give ring-cleavage product **5a** in 96% ee and in 59% yield together with the recovery of *anti*-**1a** (41%) (entry 4).[2d] Interestingly, 2-heptynyl derivative *anti*-**1b** exhibited an enhanced reactivity as well as high enantioselectivity. Thus, the reaction of *anti*-**1b** at -40 °C for 15 h gave the corresponding ring-cleavage product **5b** (98% ee) in 89% yield (entry 6). Diastereomeric acetal *syn*-**1b** underwent enantioselective reaction as well at -78 °C to afford ring-cleavage product **4b** (95% ee) in 86% yield (entry 5). Both reactions proceeded in a stereospecific manner (>50:1 diastereoselectivity) with inversion of the stereochemistry at the acetal carbon. Notably, the bond-cleavage of both acetals took place at the same side irrespective of the relative configuration at the acetal carbon, suggesting a successful use of a mixture of *syn* and *anti* acetals for asymmetric desymmetrization.



syn-**1a**; R = PhC≡C
syn-**1b**; R = $C_5H_{11}C{\equiv}C$

4a,**b**

Equation 1



anti-**1a**; R = PhC≡C
anti-**1b**; R = $C_5H_{11}C{\equiv}C$

5a,**b**

Equation 2

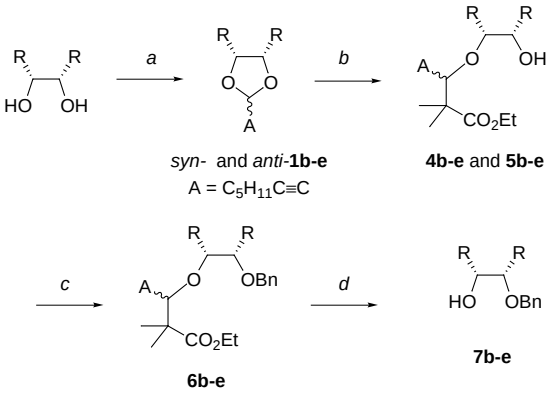
Table 1 Ring-Cleavage of *syn*- and *anti*-**1a** with Oxazaborolidinone **2a**

entry	acetal	temp. (°C)	time (h)	yield (%)	**4:5**[b]	ee[c] (%)
1	*syn*-**1a**	-78	16	72	>50:1	96
2		-20	4	82	>50:1	70
3	*anti*-**1a**	-78	14	0		
4		-20	20	59	1:16	96
5	*syn*-**1b**	-78	14	86	>50:1	95
6	*anti*-**1b**	-40	15	89	1:>50	98

[a]Reactions were carried out by using **2a** (1.2 equiv) and **3** (3 equiv) in CH_2Cl_2 (0.4 M). [b]Determined by 500 MHz ^{1}H NMR analysis. [c]Determined by 500 MHz ^{1}H NMR analysis of the MTPA ester derivative.

We then examined ring-cleavage reaction of a 1:1 mixture of *syn*- and *anti*-**1b**. When the reaction was carried out at -78 °C for 11 h and then at -40 °C for 9 h, a mixture of **4b** and **5b** (1.2:1) was obtained in 92% combined yield. ^{1}H NMR analysis of the MTPA esters derived from the mixture showed that **4b** and **5b** were produced in 83% ee and 97% ee, respectively.[4] Enantioselectivity of **4b** in this reaction was lower than that observed for pure *syn*-**1b** (Table 1, entry 5), suggesting that a part of *syn*-**1b** reacted not at -78 °C but at the higher temperature.

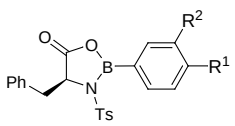
The mixture of **4b** and **5b** was converted to benzyl ether **6b** in 90% yield (Scheme 2). For the removal of the nucleophile-derived moiety, **6b** was then treated in trifluoroacetic acid at r.t. Although the procedure was effective for analogous benzyl ethers derived from 2-phenylethynyl acetals,[2a] undesirable benzylic C-O bond cleavage took place concurrently with propargylic C-O bond cleavage, resulting in low yield of desymmetrization product **7b**. The problem was overcome by the development of an alternative method. We found that benzyl ether **6b** underwent an efficient propargylic C-O bond cleavage by treatment with *tert*-BuOK in DMSO at 100 °C. Desymmetrization product (1*R*,2*S*)-**7b**[2a] of 92% ee was obtained in 99% yield. Under similar conditions, the benzyl ether derivative of **4a**, possessing a 2-phenylethynyl moiety, also gave **7b** in 99% yield. The reaction presumably proceeds through a S_N2' mechanism involving the attack of *tert*-BuOK and/or KCH_2SOCH_3 at the acetylenic carbon γ to the C-O bond cleaved.



a $C_5H_{11}C{\equiv}CCH(OEt)_2$ (1.1 equiv), *p*-TsOH, toluene, reflux. *b* $Me_2C{=}C(OTMS)OEt$ (3 equiv), **2a**,**b** (1.2 equiv), CH_2Cl_2, -78 °C (11 h) and then -40 °C (9 h). *c* $KN(TMS)_2$ (1.5 equiv), BnBr (1.3 equiv), THF, rt, 1.5 h. *d* *tert*-BuOK (1.5 equiv), DMSO, 100 °C, 2 h.

Scheme 2

Asymmetric desymmetrization of representative *meso*-1,2-diols was examined by using oxazaborolidinone-mediated ring-cleavage of a mixture of *syn* and *anti* acetal derivatives (Scheme 2 and Table 2). Transacetalization of the diols with 1,1-dimethoxy-2-octyne under the thermodynamically controlled conditions gave ca. 1:1 mixture of *syn*- and *anti*-**1b**-**e** in high yields. For acetals **1c**-**e**, *B*-(*p*-chlorophenyl)oxazaborolidinone **2b**[5] of higher Lewis acidity was required to achieve the ring-cleavage of the *anti* isomers (entry 4 vs entry 3). *B*-(*m*-Chlorophenyl) derivative **2c**[5] which showed higher conversion of *anti*-**5d** unfortunately resulted in considerable lowering of the enantioselectivity (entry 5). Benzylation and the removal of the nucleophile-derived moiety proceeded efficiently to afford the corresponding desymmetrization product **7b**-**e** of high ee.



2a; R^1, R^2 = H
2b; R^1 = Cl, R^2 = H
2c; R^1 = H, R^2 =Cl

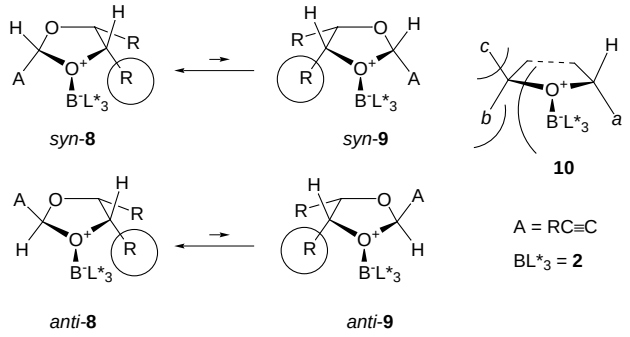
According to our recent study on the mechanism of oxazaborolidine-mediated ring-cleavage reaction, the enantiodifferentiating coordination of an acetal oxygen atom by the chiral Lewis acid is a major factor governing the enantioselectivity.[2d] In the present study, it was shown that the bond-cleavage of *syn*- and *anti*-**1** took place enan-

Table 2 Desymmetrization of *meso*-1,2-Diols via Enantioselective Ring-Cleavage Reaction

entry	transacetalization				ring-cleavage					conversion to **7**		
	product	R	yield(%)	*syn*:*anti*	Lewis acid	yield(%)	**4**:**5**[a]	ee (%) of **4**[b]	ee (%) of **5**[b]	product	yield (%)	ee (%)[b]
1	**1b**	Me	88	1:1.1	**2a**	92	1.2:1	83	97	**7b**	89	92
2	**1c**	Et	95	1.1.0	**2b**	70	2.5:1	88	96	**7c**	75	91
3	**1d**	Pr	99	1:1.2	**2a**	46	17:1	87	>98			
4					**2b**	61	2.2:1	86	>98	**7d**	76	91
5					**2c**	78	1.0:1	72	84			
6	**1e**	$BnOCH_2$	95	1:1.0	**2b**	68	2.9:1	84	*c*	**7e**	87	89

[a]Determined by 500 MHz ^{1}H NMR analysis. [b]Determined by 500 MHz ^{1}H NMR analysis of the MTPA ester derivative. [c]Not determined.

tioselectively at the same side irrespective of the relative configuration at the acetal carbon. The result implies that acetal-oxazaborolidinone complexes *syn*- and *anti*-**8** are much more stable than the corresponding diastereomeric complexes *syn*- and *anti*-**9**, respectively (Scheme 3). Although we are not able to elucidate the structure of these complexes at this moment, some information can be deduced from the observed enantioselectivity. In the unstable complexes *syn*- and *anti*-**9**, the sterically demanding R group is located at the position *b* of local structure model **10**, suggesting that the oxazaborolidinone moiety (BL^*_3) causes unfavorable interaction around this position. In the stable complexes *syn*- and *anti*-**8**, on the other hand, sterically less demanding alkynyl group (A) and a hydrogen atom are located at the position *b*, respectively. The observed lower reactivity of *anti*-**1** in comparison with *syn*-**1** can be rationalized if we assume that the oxazaborolidinone moiety also causes unfavorable interaction around the position *c*. Thus, for complex *anti*-**8**, even the sterically less demanding alkynyl group at this position suffers from the steric effect to some extent. The enhanced reactivity of 2-heptynyl derivative (*anti*-**1a**) in comparison with 2-phenylethynyl derivative (*anti*-**1b**) might be steric in origin associated with a remote steric effect across the C-C triple bond.[7]



Scheme 3

In summary, we have shown that a mixture of diastereomeric acetals derived from *meso*-1,2-diols can be successfully used in oxazaborolidinone-mediated enantioselective ring-cleavage reaction. Since these acetals are readily prepared by transacetalization reaction under thermodynamically controlled conditions, their reaction opens an efficient entry into desymmetrization of *meso*-1,2-diols leading to benzyl ether derivatives of high ee.

Acknowledgement

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(4) *Typical experimental procedure*: To a solution of acetal **1a** (71 mg, 0.36 mmol, *syn*:*anti* = 1:1) and 1-ethoxy-2-methyl-1-(trimethylsilyloxy)-1-propene (205 mg, 1.1 mmol) in CH_2Cl_2 (0.27 mL) at -78 °C was added a CH_2Cl_2 solution (0.7 M) of oxazaborolidinone **2a** (0.63 mL, 0.44 mmol).[2d] After being stirred at this temperature for 11 h and then at -40 °C for 9 h, the mixture was quenched by the addition of aqueous $NaHCO_3$ and filtered. The filtrate was extracted twice with ether. The organic layers were dried and concentrated in vacuo. The residue was treated with aqueous acetic acid (70%,

2 mL) and THF (2 mL) at r.t. for 1 h. The mixture was diluted with water, extracted twice with ether, and washed with aqueous $NaHCO_3$. The organic layers were dried and concentrated in vacuo. Purification of the residue by flash column chromatography (SiO_2, 5-20% ethyl acetate in hexane) gave a 1.2:1 mixture of **4b** and **5b** (104 mg, 92% yield). **4b**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.92 (3H, t, *J* = 7.1 Hz), 1.04 (3H, d, *J* = 6.3 Hz), 1.11 (3H, d, *J* = 6.6 Hz), 1.23 (3H, s), 1,27 (3H, s), 1.27 (3H, t, *J* = 7.0 Hz), 1.3-1.4 (4H, m), 1.5-1.55 (2H, m), 2.18 (1H, br), 2.23 (2H, dt, *J* = 1.9 and 7.0 Hz), 3.71 (1H, dq, *J* = 3.3 and 6.3 Hz), 3.87 (1H, m), 4.1-4.2 (2H, m), 4.44 (1H, t, *J* = 1.9 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.08, 13.94, 14.15, 17.26, 18.54, 18.99, 22.98, 22.50, 28.30, 30.95, 47.51, 60.55, 69.59, 73.06, 76.62, 76.88, 87.76, 175.80; IR (liquid film) 3470 (br), 2220, 1725 cm^{-1}. (*S*)-MTPA ester of **4b**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.90 (3H, t, *J* = 7.1 Hz), 1.10 (3H, d, *J* = 6.3 Hz), 1.23 (3H, s), 1.2-1.25 (6H, m), 1.26 (3H, s), 1.3-1.4 (4H, m), 1.45-1.5 (2H, m), 2.17 (2H, br t, *J* = ca. 7 Hz), 3.59 (3H, br s), 3.84 (1H, dq, *J* = 3.9 and 6.3 Hz), 4.1-4.15 (2H, m), 4.47 (1H, t, *J* = 1.8 Hz), 5.25 (1H, dq, *J* = 3.9 and 6.3 Hz), 7.42 (3H, m), 7.59 (2H, m) [a minor diastereomer resonated at δ 1.01 (3H, d, *J* = 6.3 Hz), 1.20 (3H, s), 3.57 (3H, br s), 4.44 (1H, t, *J* = 1.9 Hz) and 5.11 (1H, m)]. **5b**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.92 (3H, t, *J* = 7.2 Hz), 1.08 (3H, d, *J* = 6.5 Hz), 1.12 (3H, d, *J* = 6.4 Hz), 1.21 (3H, s), 1.28 (3H, t, *J* = 7.0 Hz), 1.30 (3H, s), 1.3-1.45 (4H, m), 1.5-1.6 (2H, m), 2.24 (2H, dt, *J* = 1.9 and 7.0 Hz), 2.60 (1H, br), 3.71 (1H, dq, *J* = 2.8 and 6.4 Hz), 3.89 (1H, m), 4.1-4.2 (2H, m), 4.55 (1H, t, *J* = 1.9 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.95, 14.07, 14.80, 16.96, 18.23, 18.59, 22.09, 23.38, 28.30, 30.95, 47.35, 60.97, 67.82, 73,64, 76.65, 77.55, 87.37, 177.00; IR (liquid film) 3500 (br), 2230, 1720 cm^{-1}. (*S*)-MTPA ester of **5b**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.91 (3H, t, *J* = 7.1 Hz), 1.2-1.25 (15H, m, including s (3H) at 1.20 and s (3H) at 1.23, 1.3-1.4 (4H, m), 1.45-1.55 (2H, m), 2.17 (2H, dt, *J* = 1.9 and 7.1 Hz), 3.58 (3H, br s), 3.81 (1H, dq, *J* = 2.9 and 6.5 Hz), 4.0-4.15 (2H, m), 4.50 (1H, t, *J* = 1.9 Hz), 5.21 (1H, dq, *J* = 2.9 and 6.5 Hz), 7.42 (3H, m), 7.59 (2H, m) [a minor diastereomer resonated at δ 4.36 (1H, t, *J* = 1.9 Hz)].

(5) Oxazaborolidinones **2b** and **2c** were prepared by the reaction of *N*-tosyl-L-phenylalanine with *p*-$ClC_6H_4BBr_2$ and *m*-$ClC_6H_4BBr_2$,[6] respectively.
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