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Diastereoface-differentiating oxidation of 1-cyclohexenyl ether using a 2,4-pentanediol tether

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Abstract

Diastereoface-differentiating oxidation of the chiral enol ether prepared from cyclohexanone and optically active 2,4-pentanediol gave a diastereomeric mixture of the corresponding 2-hydroxycyclohexanone acetal. The diastereomeric excess of the product reached over 99% by oxidation with *m*-chloroperbenzoic acid at −78°C. Oxidation with *t*-butyl hydroperoxide in the presence of metal catalysts also resulted in high diastereomeric excesses of up to 97%.

Development of facile methods to synthesize optically active products is a key issue in recent organic chemistry, and various reactions have been studied based on different stereocontrol designs: incorporation of a chiral source into a substrate, a reagent, or a catalyst. Although catalytic asymmetric reactions are the best for the production of large amounts of optically active compounds, stoichiometric use of a chiral source is also useful if the product is much more valuable than the chiral source. The requirement for synthetic chemicals with minimum delay, especially in the pharmaceutical field, necessitates not only a low-cost process for the synthesis, but also leaves only a short time to establish the process. Accordingly, a handy and reliable method for asymmetrization of a process resulting in high optical yield is desired. Intending to obtain such a method, we have been developing a stereocontroller applicable to various asymmetric reactions, where a chiral source is not simply incorporated into a substrate and/or a reagent, but acts as a chiral tether between a reagent and a substrate. As a chiral tether, we employed optically active 2,4-pentanediol (PD), a chiral diol commercially available and readily obtainable on a large scale by asymmetric catalytic hydrogenation of 2,4-pentanedione.[1] Because the PD part is flexible, long enough for the intramolecular reaction, inert to most reagents and sterically small, many types of reactions can be applied for this stereocontroller. In addition, the PD tether can be removed from the products by several methods under mild conditions. Based on this reaction design, we have reported several different types of highly diastereodifferentiating asymmetric reactions to produce

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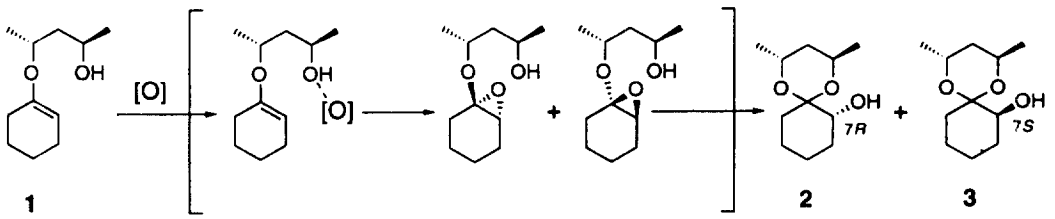
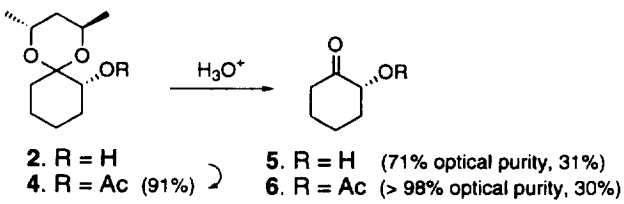
enantiomerically pure compounds after elimination of the PD unit.[2] The connection of a reagent to the PD tether can be a covalent bond of an ether or ester, and also an in situ formed coordination bonding to the hydroxyl group on the PD part. In this report, we would like to present a reaction in the latter category, the oxidation of the olefin in **1** with oxidants having coordination ability to the hydroxyl group as shown in Scheme 1.[3,4]



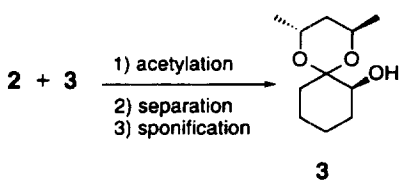
Scheme 1.

1. Peracid oxidation

Peracid oxidation of some allylic alcohols is known to give predominantly one diastereomer of the corresponding epoxide.[5] Because this diastereodifferentiation originated by coordination of the peracid to the hydroxyl group before the epoxidation, **1** is also expected to react with peracid through intramolecular oxidation with aid from the hydroxyl group of the PD unit, and chirality on the PD tether can control the diastereoface differentiation of the oxidation. The substrate **1** was prepared by the reported method[2b] from (2*R*,4*R*)-PD and cyclohexanone (two steps, 85–95% yield). When *m*-chloroperbenzoic acid (MCPBA, 1.05–1.2 eq.) was added to a solution of **1** in dichloromethane, the oxidation proceeded smoothly at reaction temperatures from 39 to −72°C to give a mixture of one pair of diastereomers. From the following ^{1}H NMR study, the product's structures were determined not to be the primary produced epoxides, but **2** and **3** of the intramolecular acetal exchanged products.[5] By acetylation of the products, the spectrum pattern was almost unchanged, except for one proton on the cyclohexane ring that was shifted downfield. The configuration of the major product **2** was determined to be 7*R* by chemical correlation with (2*R*)-(+)-2-hydroxycyclohexanone **5**[6] and (2*R*)-(+)-2-acetoxycyclohexanone **6** (Scheme 2). The minor isomer **3** was isolated from a mixture of **2** and **3** by acetylation, MPLC separation, and saponification (Scheme 3).



Scheme 2.



Scheme 3.

Table 1
Diastereomeric excess of the MCPBA oxidation product of **1** at varied temperatures[a]

reaction temp. (°C)	39	25	0	−20	−40	−60	−72
dichloromethane	72	75	90	94	97	-	>99
ether	-	44 (45)	28 (26)	15 (21)	7 (12)	−24 (9)	−16 (24)
THF	-	-	−9	−10	−8	0	25

[a] MCPBA was added to a solution of **1** at the indicated temperature. The de obtained by the reverse addition is shown in parentheses.

The isomer ratio was determined by capillary GLC analysis (PEG-20M, 50 m) after a part of the reaction mixture was converted to the trimethylsilyl ethers with trimethylsilyl imidazole. The de {diastereomeric excess=(**2**−**3**)/(**2**+**3**)×100} of the product was 90% when the reaction was performed in dichloromethane at 0°C, but was 28% in ether and −9% in THF at the same temperature. The de in dichloromethane increased with decreasing reaction temperature, and **3** became undetectable (<0.5%) at −72°C; **2** of over 99% de was obtained in an almost quantitative yield (see Table 1). Thus, it appeared that **1** could be oxidized with complete diastereoface differentiation. On the other hand, the poor de using ether or THF as a solvent was not improved by decreasing the reaction temperature. In ether, the de was even decreased with decreasing temperature. The lower des could be explained in that the coordination to the hydroxyl group was not strong enough in ethereal solvents and intermolecular oxidation took place. Supporting this, reverse addition in ether (**1** was added to MCPBA) somewhat affected the de.

The large solvent effect for the diastereoface differentiation of **1** with MCPBA sharply contrasted to that of allylic alcohols. When 2-cyclohexenol, a typical example of allylic alcohols, was treated with MCPBA, diastereodifferentiations in ether and THF were as high as that in dichloromethane to give over 99% de of the product, and the diastereomeric mixture was obtained (*syn*:*anti*=76:23) only in methanol.[7] The difference between **1** and 2-cyclohexenol can be attributed to the length of the tether between a reaction site and the reagent. In the case of 2-cyclohexanol, the coordinated reagent is placed close to the olefin, and thus the intramolecular reaction with favorable entropy is much faster than the intermolecular reaction. On the other hand, the MCPBA coordinated to the hydroxyl group in **1** was placed away from the reaction site, and the acceleration of the intramolecular reaction is not expected.

The temperature effect in dichloromethane, if the coordination was strong enough to proceed with most of the oxidation through the intramolecular path, indicated the stereodifferentiating ability of the PD part as a chiral tether. The Arrhenius-like plot, the natural logarithm of the relative rate constants to give **2** and **3** plotted against the reciprocal reaction temperature, was linear (r=0.996), and the differential enthalpy and entropy were calculated as $\Delta H^{\ddagger}(R)-\Delta H^{\ddagger}(S)=-4.8$ kcal/mol and $\Delta S^{\ddagger}(R)-\Delta S^{\ddagger}(S)=-11.9$ cal/mol K.

2. Metal-catalyzed oxidation with *t*-butyl hydroperoxide

Other than peracids, several oxidants convert allylic alcohol to the corresponding epoxide with diastereomeric differentiation by the control of the hydroxyl group direction. With the rhenium oxide of such an oxidant, Kennedy et al. have reported that the oxidation of **1** could convert to a single diastereomer quantitatively.[4b] Surprisingly, the diastereodifferentiation was in contrast to the peracid oxidation, and **3** was obtained as the sole product. The opposing diastereoface differentiations with MCPBA and rhenium oxide for the same substrate of **1** prompted us to a further study of the oxidation of **1** with the other hydroxyl group directed oxidant. Allylic alcohols can be converted with diastereodifferentiation to epoxides with *t*-butyl hydroperoxide (TBHP) catalyzed with various metal catalysts.[5] The oxidation of **1**

Table 2
Diastereomeric excess of TBHP oxidation of **1**

run	catalyst	solvent	temp (°C)	yield (%)	de (%)
1	$Ti(OiPr)_4$	CH_2Cl_2	25	43	90
2	$Ti(OiPr)_4$	CH_2Cl_2	0	35	95
3	$Ti(OiPr)_4$	THF	0	40	97
4	$Ti(OiPr)_4$	CH_2Cl_2	−20	10	95
5	$VO(acac)_2$	CH_2Cl_2	0	23	87
6	$MoO_2(acac)_2$	CH_2Cl_2	0	22	75

was carried out by the addition of metal catalysts listed in Table 2 at 0°C to a solution of **1** and TBHP in the presence of molecular sieves 4 Å. The mixture was stirred until no reactant was detected on TLC analysis. The diastereomeric excess of the product after proper workup (21–40% yield) is summarized in Table 2. In all cases, the major isomer was **2**, and the lowest de so far examined was 75% with $MoO_2(acac)_2$ (run 6). In the case of the reaction with $Ti(OiPr)_4$, the de at 25°C was lower than that at 0°C. Differing from MCPBA oxidation, the use of THF as the reaction solvent did not decrease the diastereodifferentiation, but resulted in 97% of the highest de with TBHP, which was higher than that by MCPBA oxidation at the same temperature. The reaction at −20°C with $Ti(OiPr)_4$ became sluggish, and only 10% of the product was yielded.

3. Discussion

Enantiodifferentiating α-hydroxylations of prochiral ketones with chiral oxaziridines[8] or with chiral phase transfer catalysts[9] have been reported, but these processes resulted in a synthetically acceptable ee only from ketones having a particular substituent.[10] The present study succeeded with a simple ketone of cyclohexanone and thus will open a secure way to convert prochiral ketones to optically pure α-hydroxyketones. Because the carbonyl group of the product in the present process is protected as an acetal, the epimerization of the produced hydroxyl bearing carbon is restrained. The use of an alternative chiral auxiliary (3*S*,5*S*)-2,6-dimethyl-3,5-heptanediol instead of (2*R*,4*R*)-PD has been found to be effective for diastereoface differentiating zinc carbenoid addition.[2b] Unfortunately, this bulky analog of **1** was not effective for MCPBA oxidation. The reaction in dichloromethane at 0°C resulted in 89% de and in 95% de at −78°C. The details will be published elsewhere.

The diastereoface of **1** to be oxidized was found to be the *si–re* face in both reactions with MCPBA and TBHP, and the size of the TBHP-catalyst complex did not greatly affect the diastereoface differentiation. Zinc carbenoid addition to **1** occurs predominantly at the same *si–re* face, and the intramolecular cyclopropanation of a diazo ester of **1** also gave the product by the same diastereoface attack.[2] In these respects, the reverse differentiation with rhenium oxide, perfect *re–si* face attack, is exceptional in the diastereodifferentiation using a chiral PD tether. Expected structures of the reaction transition states of *si–re* and *re–si* face-attacks are shown in Fig. 1. Elucidation of the reverse differentiation needs a detailed study of the conformation of the transition state.

4. Conclusions

The asymmetric reaction design using a PD tether, although it needs multi-steps to convert a prochiral substrate to an optically active product, is secure and results in a high optical yield. Concerning the

Fig. 1.

availability of both enantiomers of PD, this method is proved to be effective to obtain optically pure products on a kilogram scale by a simple operation.

5. Experimental

5.1. General

All temperatures are uncorrected. ^{1}H NMR (400 MHz) was recorded on a JEOL GX-400 spectrometer in $CDCl_3$ as a solvent and as an internal standard ($CHCl_3$=7.26 ppm). IR spectra were obtained on a JASCO IR-810 spectrophotometer. Optical rotations were measured on a Perkin–Elmer 243B polarimeter. Analytical GLC was conducted with a Shimadzu GC-17A chromatograph. MPLC was carried out using an FMI pump (10 ml min^{-1}) and a Lobar column (Merck Si-60, type B). All dry solvents were distilled from calcium hydride. All reactions were carried out under a dry nitrogen atmosphere.

5.2. Oxidation of *1* with m-chloroperbenzoic acid

A typical experiment is as follows: A solution of **1** (350 mg, 1.9 mmol) in dry dichloromethane (20 ml) was placed in a two-necked flask (50 ml) equipped with a three-way stopcock and a thermometer. The mixture was cooled to −72°C in a dry ice–ethanol bath, and *m*-chloroperbenzoic acid (purity 82%, 348.1 mg, 1.05 eq.) was added to this at once. After 15 min, a saturated aqueous solution of $NaHCO_3$ was added at the same temperature, and the mixture was allowed to warm up. Extraction of the mixture with dichloromethane (4×), drying ($MgSO_4$) and concentration afforded **2** (352 mg). After MPLC purification, 234.0 mg of colorless oil was obtained (61.6% yield). $[\alpha]_D^{20}$=−22.8 (c 1.1, $CHCl_3$). IR (neat), 3500 cm^{-1} (OH). ^{1}H NMR ($CDCl_3$) δ 4.20 (m, 1H), 4.06 (m, 1H), 3.63 (dd, J=7.3, 3.9 Hz, 1H), 2.15 (brs, 1H, OH), 1.91 (ddd, J=12.2, 7.3, 4.2 Hz, 1H), 1.74 (m, 1H), 1.70–1.41 (m, 7H), 1.27 (m, 1H), 1.23 (d, J=6.3 Hz, 3H), 1.20 (d, J=6.3 Hz, 3H). Anal. calcd for $C_{11}H_{20}O_3$: C, 65.97; H, 10.07. Found: C, 65.66; H, 10.06. MS, *m/z* (M^+) calcd for $C_{11}H_{20}O_3$, 200.1412; found, 200.1413.

5.3. Analysis of diastereomeric excess of a mixture of *2* and *3*

A ratio of **2** and **3** in the reaction mixture was determined by capillary GLC after conversion to trimethylsilyl ethers. A small part of the extract was treated with excess trimethylsilyl imidazole and subjected to GLC on a PEG-20 M capillary column (50 m) at 70°C. The peaks appeared with baseline separation at 70.5 min for the trimethylsilyl ether of **2** and at 72.5 min for that of **3**. The diastereomeric excess was calculated from the integration of these peaks as (**2**−**3**)/(**2**+**3**)×100.

5.4. Oxidation of **1** with t-butyl hydroperoxide in the presence of metal catalyst

A typical experiment is as follows: A solution of **1** (60 mg, 0.36 mmol) and the metal catalyst (0.05 eq.) in anhydrous dichloromethane (1 ml) and molecular sieves (4 Å, powder, 0.1 g) were placed in a 30 ml flask and cooled to 0°C. To this solution, *t*-butyl hydroperoxide (3.6 N dichloromethane solution, 0.15 ml, 1.5 eq.) was added, and the mixture was stirred for 7 h. After the usual work up, a mixture of **2** and **3** was obtained in 21 to 40% yield and subjected to the previous analysis.

5.5. Preparation of (2R)-2-hydroxycyclohexanone (**5**) from **2**

A solution of **2** (98% de, 23 mg, 0.11 mmol) in ether (2 ml) was stirred with *p*-TsOH·H_2O at room temperature for 1.5 h. The mixture after extraction was purified by silica gel column chromatography (elution with 15% ethyl acetate in hexane) to give **5** (4.0 mg) as a colorless oil (31% yield). Optical rotation of **5** depended on the hydrolysis conditions. The maximum optical rotation: $[\alpha]_D^{20}$=10.4 (c 0.6, $CHCl_3$), lit.[6] $[\alpha]_D$=−13.3 (c 0.53, $CHCl_3$) for (2*S*)-(−)-**5** of 91% ee.

5.6. Preparation of (2R)-2-acetoxycyclohexanone (**6**) from **2**

To a solution of **2** (1.00 g, 5.42 mmol) in dry pyridine (5 ml), acetic anhydride (1.5 ml, 3.03 eq.) was added at room temperature. After 24 h, the mixture was extracted with ether (×3) and washed with a saturated aqueous solution of $CuSO_4$ and then water. Drying over $MgSO_4$, concentration, and column chromatography (silica gel, elution with 20% ethyl acetate in hexane) afforded 0.948 g of **4** as a colorless oil. $[\alpha]_D^{20}$=−40.3 (c 0.7, methanol), IR (neat) 1750 cm^{-1} (C=O), ^1H NMR ($CDCl_3$) δ 4.90 (m, 1H), 4.18 (m, 1H), 4.02 (m, 1H), 1.82 (m, 1H), 1.65–1.73 (m, 2H), 1.45–1.65 (m, 7H), 1.25 (d, J=6.3 Hz, 3H), 1.11 (d, J=6.3 Hz, 3H). MS, *m/z* (M^+) calcd for $C_{13}H_{22}O_4$, 242.1518; found, 242.1498. A solution of **4** (300 mg, 1.24 mmol) in ether (20 ml) was stirred with 2 N hydrochloric acid (2 ml) at room temperature for 24 h. Extraction and purification by column chromatography (silica gel, elution with 30% ethyl acetate in hexane) afforded **6** (58.5 mg, 30.3%) as a colorless oil. $[\alpha]_D^{20}$=89.3 (c 1.0, methanol). Authentic (*R*)-**6** was prepared by oxidation of (1*R*,2*R*)-2-acetoxycyclohexanol with pyridinium chlorochromate (80% yield). $[\alpha]_D^{20}$=89.5 (c 1.0, methanol).

5.7. Isolation of diastereomerically pure **3**

Diastereomerically pure **3** was isolated through the following method: A mixture of **2** and **3** in a 1:1 ratio was acetylated and separated by MPLC on silica gel (elution with 15% ethyl acetate in hexane). Acetate of **3** (35% yield from a mixture): $[\alpha]_D^{20}$=−6.4 (c 0.6, methanol), IR (neat) 1740 cm^{-1} (C=O), ^1H NMR ($CDCl_3$) δ 5.15 (s, 1H), 4.05 (m, 1H), 3.92 (m, 1H), 1.81–1.66 (m, 2H), 1.65–1.35 (m, 9H), 1.17 (d, J=6.3 Hz, 3H), 1.08 (d, J=6.3 Hz, 3H). MS, *m/z* (M^+) calcd for $C_{13}H_{22}O_4$, 242.1518; found, 242.1517. The obtained diastereomerically pure acetate (280 mg) was dissolved in a mixture of methanol (10 ml) and 1 N NaOH aqueous solution (0.5 ml) and allowed to stand for 24 h. The mixture was extracted with dichloromethane (3×10 ml), dried over sodium sulfate, and purified on a short column (silica gel, elution with 20% ethyl acetate in hexane) to give 175.5 mg of **3** as a colorless oil (75.9% yield). The diastereomeric purity of this sample was over 99% by GLC analysis. $[\alpha]_D^{20}$=−10.5 (c 1.7, $CHCl_3$), IR (neat) 3500 cm^{-1} (OH), ^1H NMR ($CDCl_3$) δ 4.10 (m, 1H), 4.02 (m, 1H), 3.73 (m, 1H), 2.21 (m, 1H), 1.80 (m, 1H), 1.72–1.65 (m, 2H), 1.65–1.56 (m, 2H), 1.54–1.38 (m, 2H), 1.33 (m, 1H), 1.18 (d, J=6.1 Hz, 3H), 1.02 (d, J=6.1 Hz, 3H). MS, *m/z* (M^+) calcd for $C_{11}H_{20}O_3$, 200.1412; found, 200.1413.

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