Amplified Asymmetric Dihydroxylation of a Racemic Cyclopentene

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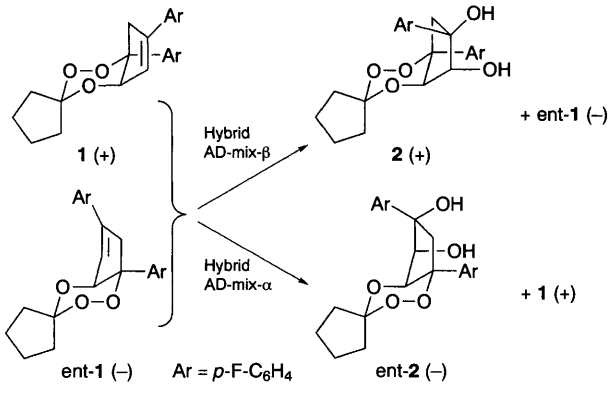
Racemic cyclopenteno-1,2,4-trioxane **1**/ent-**1** by iterative dihydroxylation with *N*-methylmorpholine *N*-oxide in the presence of catalytic amounts of K_2OsO_4 and $(DHQD)_2PHAL$ in aqueous Me_2CO at 25 °C gives essentially enantiomerically pure diols **2** (96% e.e.) and ent-**2** (98% e.e.) in yields of 31.5 and 43%, respectively.

Catalytic asymmetric dihydroxylation (AD) is of great potential in organic synthesis.[1] However, notwithstanding an abundant literature, few applications to cycloalkenes have been reported.[2] In principle, a racemic cyclic olefin can undergo AD to furnish either enantiomerically pure olefin or 1,2-diol, but not both at the same time. We now describe a new procedure, which lifts this restriction. The reagents chosen are the hybrid AD-mixes-β and α which employ *N*-methylmorpholine *N*-oxide (NMO) as oxidant in the presence of catalytic amounts of potassium osmate, and 1,4-bis(dihydroquinidine)phthalazine, [$(DHQD)_2PHAL$], and 1,4-bis(dihydroquinine)phthalazine, [$(DHQ)_2PHAL$], respectively, in aqueous acetone as solvent.[3,4] The reaction of hybrid AD-mix-β with racemic cyclopentene **1**/ent-**1** is typical[5] (Scheme 1). As dihydroxylation proceeded, the remaining olefin became increasingly enriched in ent-**1**, a satisfactory enantiomeric excess (e.e.) of 95% being achieved at 62% conversion (Table 1, entry 5). On the other hand, although the e.e. of the diols was biased towards **2** at the start (81%) (entry 1), it declined as ent-**2** was competitively produced from accumulating ent-**1** reaching 61% at 62% completion (entry 5).



Scheme 1

Thus, the problem is to salvage the incompletely enriched diols and make the reaction fully efficient. A solution would be to convert the diol to olefin and repeat AD. Ideally, olefin of 70% e.e. should furnish enantiomerically pure diol in 85% yield.[6]

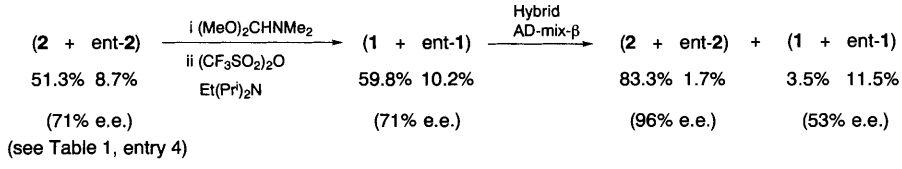
Of the methods available for conversion,[7] the mildest[8] was used in order to minimize dehydration. Exposure of a mixture of diols **2** and ent-**2** of 71% e.e. (Table 1, entry 4) to an excess of *N*,*N*-dimethylformamide dimethyl acetal at room temp. afforded the corresponding 1,3-dioxolanes, which on direct treatment with trifluoromethanesulfonic anhydride and ethyldiisopropylamine underwent elimination to **1** and ent-**1** in 70% yield without alteration of the enantiomeric ratio† (Scheme 2). Next, submission of the regenerated olefin to hybrid AD-mix-β gave, after 85% conversion, diol **2** (>96% e.e.) together with a minor amount of racemized olefin (53% e.e.). Thus, by using the same chiral reagent, ent-**1** and **2** were both obtained in high optical purity (>95% e.e.) in yields of 40 and 36%, respectively, from the same sample of racemic olefin.‡

This iterative procedure worked equally well for repairing an incompletely resolved mixture of olefins. For example, at 50% conversion, enrichment in ent-**1** and **2** was preparatively

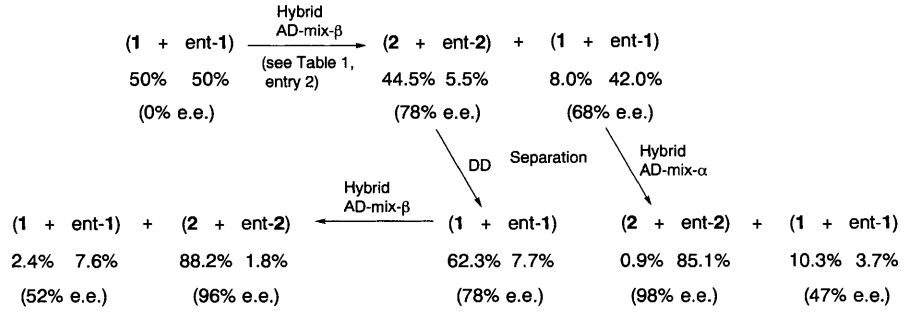
Table 1 Asymmetric dihydroxylation of racemic **1** and ent-**1** by using hybrid AD-mix-β[a]

Entry	K_2OsO_4 (mol %)[b]	Reaction time/min	Ligand[c] (mol %)	Completion of reaction (%)	Olefin[d] e.e. (%)	Diol[e] e.e. (%)
1	1	13	5	25	18	81
2	1	22	5	50	68	78
3	1	25	10	57	93	78
4	3.5	35	10	60	95	71
5	1.4	45	5	62	95	61

[a] Experiments performed at 25 °C. [b] Olefin (1 mmol) in acetone: H_2O (5 : 1, 2 ml); NMO (1.2 mmol). [c] The ligand is $(DHQD)_2PHAL$. [d] Enriched in ent-**1**. [e] Enriched in **2**.



Scheme 2



Scheme 3

insufficient (Table 1, entry 2). However, separation and dedihydroxylation (DD) of the diol component furnished olefin of the same e.e. (78%) (Scheme 3). Once again, the action of hybrid AD-mix-β on the recovered olefin was entirely effective in producing nearly pure diol **2** (96% e.e.). In complementary fashion, subjection of the olefin component (68% e.e.) to the reagent containing the ligand of the opposite chirality, namely hybrid AD-mix-α, delivered, at 86% conversion, ent-**2** in high optical purity (>98% e.e.). In both cases, the residual olefin suffered further racemization (52 and 47% e.e.). By these expedients, both enantiomers **2** and ent-**2** were obtained in yields of 31.5 and 43% from the same sample of starting olefin.

The present procedure demonstrates how poor asymmetric induction on dihydroxylation can be turned to synthetic advantage by exploiting the efficient kinetic resolution of olefins through recycling.[9] Such amplified asymmetric dihydroxylation should be applicable to other racemic cyclic olefins.

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Footnotes

† General procedure for the dedihydroxylation (deoxygenation) of trioxanediols to olefins. Diol (1 mmol) was treated with neat *N,N*-dimethylformamide dimethyl acetal (3 ml) for 48 h at room temp. The crude dimethylaminodioxolanes, obtained as a mixture of stereoisomers (1 : 1) after evaporating the reagent under reduced pressure, were dissolved in dry toluene (30 ml). To the resulting solution was added $Et(Pr^i)_2N$ (4 equiv.) and then a solution of trifluoromethanesulfonic anhydride (2 equiv.) in toluene (90 ml) with stirring at room temp. After 60 min, the reaction mixture was diluted with Et_2O, washed (aq. $NaHCO_3$) and dried. The Et_2O solution was evaporated and the olefin isolated (70% yield) from the residue by chromatography over SiO_2.

‡ The e.e. for **1** and ent-**1** was determined by HPLC analysis (Chiracel-OG column, 25 cm × 2 cm, Daicel Chemical Industries, Ltd, Tokyo 100, Japan, 2.5% isopropyl alcohol in hexane, 25 °C). Optical purities of **2** and ent-**2** were established by conversion to Mosher's monoesters, the diastereoisomeric ratio of which was estimated by ^1H NMR spectroscopy at 400 MHz. $[\alpha]_D^{20}$ values (*c* 1, $CHCl_3$) were: +115 **1**, −113.3 ent-**1**, +76.5 **2**, −78.5 ent-**2**; ^1H NMR ($CDCl_3$): δ 1.52–1.90 (m, 7H), 2.50 (d, *J* 16 Hz, 1H), 2.58–2.63 (m, 1H), 2.65 (d, *J* 16 Hz, 1H), 2.41 (d, *J* 0.8 Hz, 1H), 3.08 (s, 1H), 4.65 (d, *J* 8 Hz, 1H), 4.85 (dd, *J* 8, 0.8 Hz, 1H), 7.05–7.62 (m, 8H), ^{13}C NMR ($CDCl_3$) δ 163.5, 161.0, 139.5, 137.7, 128.5, 128.0, 127.7, 126.8, 126.5, 115.5, 115.3, 115.2, 115.0, 112.9, 80.6, 79.6, 50.9, 37.5, 37.1, 24.9, 22.3.

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