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Kinetic resolution of epoxy alcohols with the Sharpless Ti-isopropoxide/tartaric ester complex

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ABSTRACT

When investigating the Sharpless epoxidation of enol-protected 4-hydroxy-1,2-cyclopentanediones, the ability of the asymmetric Ti(O*i*Pr)$_4$/tartaric ester complex to discriminate between enantiomeric epoxides formed in situ was discovered, leading to the epoxide opening reaction of only one enantiomer. This observation was used in the kinetic resolution of racemic substituted 2,3-epoxy-4-hydroxy-cyclopentanol, to afford enantiomerically enriched epoxyalcohols in good yields and with *ees* up to 96%.

1. Introduction

The kinetic resolution of allylic alcohols via Sharpless asymmetric epoxidation is a widely used reaction in the synthesis of various enantiomerically pure compounds[1] and in the total synthesis of several natural products.[2,3]

It has previously been found that cyclic secondary allylic alcohols are poor substrates for Sharpless kinetic resolutions.[4] In this respect, cyclohexenol has been found to be the worst compound, while substituted cyclohexenols[5] and cyclopentenols[6] afford slightly better results in the oxidations. Because of this knowledge, Sharpless asymmetric epoxidation is not usually used for the synthesis of enantiomerically pure cyclic secondary epoxy alcohols. However, there is a need for these compounds because they are important intermediates in the various regio- and stereoselective ring-opening reactions[2,7] that afford chiral building blocks and intermediates.[8]

Usually, the in situ ring opening of the epoxy alcohols formed during Sharpless kinetic resolutions is the reaction that has to be avoided,[9] thus making the synthesis of certain epoxy alcohols difficult using standard asymmetric epoxidation processes. 2-Alkyl-allylic alcohols often suffer from this limitation.[10]

Although the kinetic resolution of substituted 2,3-epoxy alcohols has been extensively studied, only a few efficient cases have been found: the resolution of *meso*-epoxy alcohols[11] (the opening of *meso*-epoxy alcohols with amines leads to chiral beta-amino alcohol units[12]) and terminal epoxy alcohols.[13]

We have previously found that the asymmetric oxidation of 3-alkyl-1,2-cyclopentanediones with the Sharpless complex results in lactone carboxylic acids in good yield and with high *ee* values (Scheme 1, A, example a).[14] We have also reported that a hydroxyl group in the allylic or homoallylic[15,16] position plays an important role in determining the selectivity of the reaction. Thus, 3-benzyl-1,2-cyclopentanedione **5** with 4-silylprotected OH group gave lactone carboxylic acids as a mixture of two diastereomers in a 1:1 ratio with excellent enantioselectivities for both diastereomers **8** and **9** (*ee* values 97% and 95%), while the corresponding unprotected 4-hydroxy-3-benzyl-1,2-cyclopentanedione **6** afforded reduced enantiopurities of 70% *ee* and 80% *ee* for lactone acids **10** and **11**, but improved diastereoselectivity 3:1 (Scheme 1, A, example b). In the first case, only the highly stereoselective cascade oxidation[17] may occur, while in the second case the highly stereoselectivity cascade oxidation and low stereoselectivity allylic oxidation of cyclic allylic alcohol compete, reducing the enantiopurity of the resulting product.

When the enol OH in 4-hydroxy-1,2-cyclopentanedione substrate is protected, only the epoxidation of the allyl alcohol moiety may occur. The Baeyer–Villiger-type oxidation does not proceed; instead, the ring opening reaction of the resulting epoxide may occur (Scheme 1, B).[18]

Herein, the oxidation of allylic systems with the subsequent epoxide opening is investigated. First, the obtained data on the oxidation of 4-hydroxy-1,2-cyclopentanedione enol ether **1** led us to the understanding that the enantiomers of the formed epoxide behave differently in the presence of the Sharpless complex: the epoxide openings proceed at different rates. This opens up the possibility of the kinetic resolution of these epoxides. Thus,

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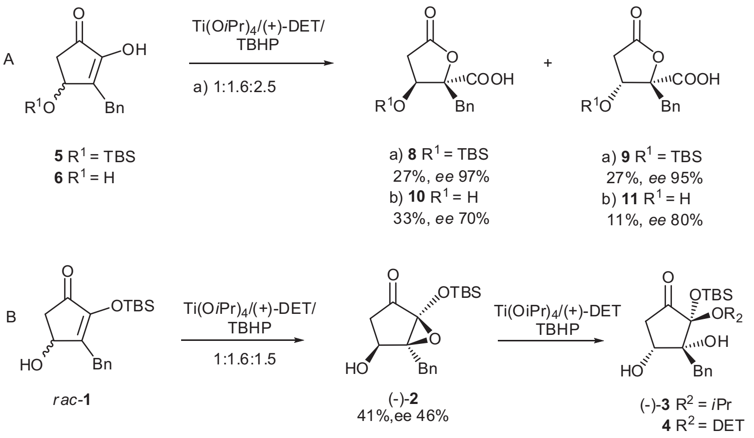


Scheme 1. Reactions of 4-hydroxy-1,2-cyclopentanediones.

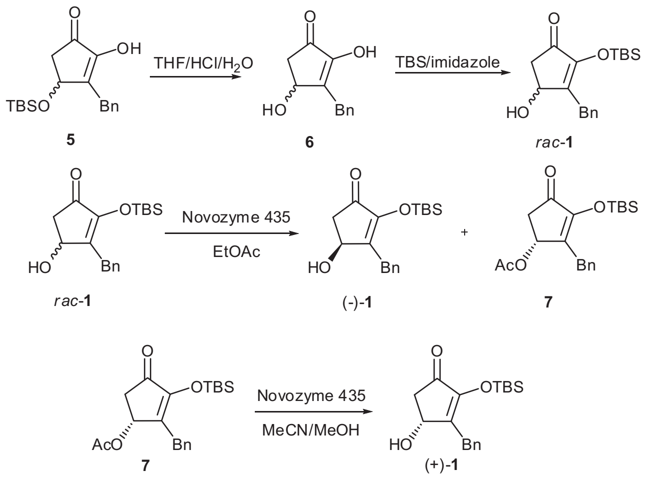
the epoxide opening of *rac*-**2**, cyclohexane epoxyalcohol *rac*-**15** and aliphatic epoxyalcohol *rac*-**13** were investigated.

Herein we have demonstrate the possibility of the kinetic resolution of racemic epoxides from 4-hydroxy-1,2-cyclopentanedione by using the Sharpless titanium isopropoxide/tartaric ester complex. We also found that with other common epoxy alcohols, the resolution is not efficient enough for preparative purposes.

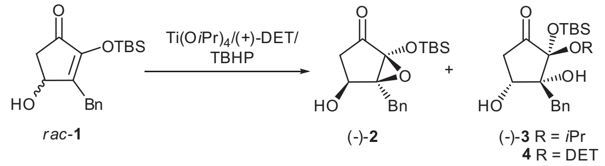
2. Results and discussion

2.1. Synthesis of substrates

The 4-silyloxy substituted 3-benzyl-1,2-cyclopentanedione **5** was prepared according to a procedure recently described by us.[14] The protecting silyl group was removed with 3 M HCl in THF to afford **6** in 70% yield. The enol hydroxyl group of **6** was selectively protected to afford *rac*-**1** (yield 66%). For the synthesis of enantiomeric alcohols, the allylic alcohol was subjected to enzymatic acylation to afford (−)-**1** (yield 60%, *ee* 88%) and enriched acetate **7** in 30% yield. The other enantiomer was obtained by enzymatic deacetalization of enriched acetate **7** with Novozyme 435, resulting in (+)-**1** (yield 79%, *ee* 99%) (see Scheme 2).



Scheme 2. Synthesis of substrates.



Scheme 3. Sharpless kinetic resolution of substrate *rac*-**1**.

2.2. Allylic oxidation of cyclopentenols

The preliminary results of the oxidation of *rac*-**1** with (+)-DET (Scheme 3) showed that the substrate with an enol-protecting silyl group reacts, as expected, as an allylic alcohol to give epoxide (−)-**2** as a single diastereomer, with modest *ee* values. Additionally, the ring opening of the resulting epoxide also occurs to a certain extent, to give isopropyl acetal **3** and tartaric ester acetal **4** (as single diastereomers) (Fig. 1). This result suggests stereodifferentiation in the epoxide opening (Table 1, No. 1).

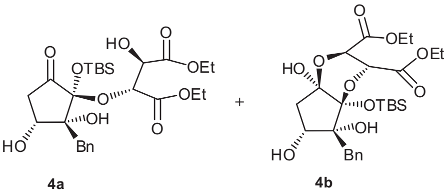


Figure 1. Tartaric ester acetals.

The epoxidation of highly enantioenriched (−)-**1** (*ee* = 96%) with Ti(O*i*Pr)$_4$/(−)-DET/TBHP complex gave epoxide (−)-**2** in 18% yield (*ee* 90%), isopropyl acetal (−)-**3** in 2% isolated yield (*ee* 98%) and DET acetal **4** in 24% isolated yield. There was 17% of unreacted substrate left, with *ee* 96%.

At the same time, the epoxidation of (−)-**1** (88% *ee*) with the Ti(O*i*Pr)$_4$/(+)-DET/TBHP complex gave epoxide (−)-**2** in 31% isolated yield and with 88% *ee*, as expected. The unreacted (−)-**1** retained its initial stereoisomeric state (88% *ee*). It is notable that in this case, no isolatable amounts of acetals **3** and/or **4** were formed.

We looked at this interesting phenomenon in more detail. When oxidizing substrates **1** with different enantiopurities with (+)-DET/TBHP complex, we observed that the product profile (ratio of acetals **3** + **4**/epoxide **2**) depended on the enantiomeric purity of the initial substrate (Fig. 2). The lower the excess of one enantiomer of the substrate, the higher the amount of formed acetals (Fig. 2).