

Concerning kinetic resolution by the Sharpless asymmetric dihydroxylation reaction

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The transition state for the product-determining step in the Sharpless asymmetric dihydroxylation reaction is not product-like, and effective kinetic resolution can occur when one face of a chiral alkene is hindered.

Sharpless asymmetric dihydroxylation (AD)¹ and asymmetric epoxidation (AE)² reactions have proved to be very effective means whereby asymmetry can be introduced into molecules starting from prochiral alkenes and allylic alcohols respectively. The AE reaction has also proved useful for effecting kinetic resolution of chiral allylic alcohols. However, with only a few exceptions, the AD reaction has not been effective for carrying out kinetic resolutions and the reasons for this are not well understood.¹

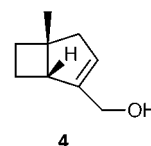
It is known³ that the AD reaction of 1-phenylcyclohexene proceeds with high asymmetric induction. Therefore, reaction of these reagents with 1-phenyl-4-*tert*-butylcyclohexene **1** would also be expected to proceed with high asymmetric induction but two diastereomeric products should result. For instance with AD-mix- β the enantioenriched diastereomers **2** and **3** should form (Scheme 1). If these molecules exist predominantly in the expected chair conformers, the diastereomer **2** has the phenyl group in an equatorial position whereas the phenyl group in the other diastereomer **3** has an axial orientation. The diastereomer **3** will be several kJ mol⁻¹ higher in energy than the diastereomer **2**.⁴ Therefore, if the transition state (TS) for the product-determining step in the AD reaction is product-like, there would be a considerable difference in the rate of formation of these two diastereomers, and an effective kinetic resolution should be possible.

The AD reaction on the alkene **1** was performed following Sharpless's recommended procedure⁵ for tri-substituted alkenes (AD-mix- β , MsNH₂, Bu^tOH-H₂O, 0 °C). Equal quantities of the diols **2** and **3**,⁶ eluting in that order, were obtained, in 84% yield after 'flash' silica gel chromatography. The enantiomeric purity of each diol was determined by the use of NMR chiral shift reagent experiments. The diol **2** from the AD reaction had >99% ee⁷ and the diol **3** had >95% ee.⁸ The racemic diols were obtained using the Sharpless method with quinuclidine as ligand to give the racemic diols in a ratio of ~4.5:1.

The kinetic resolution was also studied under the normal conditions for the AD reaction and the relative rates for the enantiomers (*E*) were determined following a literature procedure⁹ which is related to the relationship derived by Kagan.¹⁰ The percentage conversion of the racemic substrate was followed by NMR spectroscopy. The remaining alkene was separated from the diols **2** and **3**. The ee of the remaining alkene **1** was determined by conversion, using the achiral dihydroxylation reaction, into the same diols **2** and **3**. The enantiopurity of

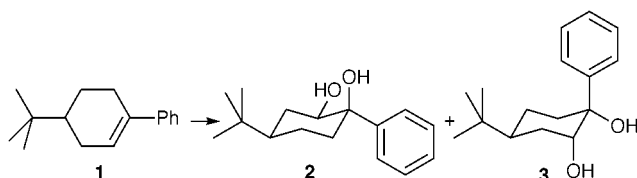
the major diol was then determined as already described. In two separate experiments, conducted at 0 °C, the reactions were stopped at 15 and 94% conversion respectively. The ee for the remaining alkene, for the former reaction, was determined as ~4% and, for the latter, as ~86%. This computes to an *E* of ~2 in each case. This value of *E* is too small for effective kinetic resolution. Clearly the TS of the product-determining step is not product-like.

It can be reasoned that, if the product-determining step in the AD reaction is reactant-like and if the alkene is highly enantiofacially directing, then a kinetic resolution should be effective when there is considerable difference in the ease of approach to the two faces of a chiral alkene.¹¹ Such an effect has been demonstrated¹² recently for one molecule, which displays axial chirality. Recently we completed¹³ an asymmetric synthesis of grandisol in which the key step is the kinetic resolution of the primary allylic alcohol **4** by a Sharpless AE reaction. The

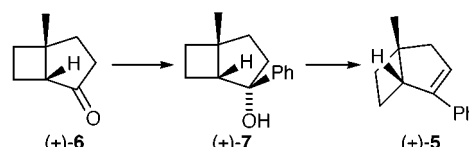


key feature in that resolution is that the molecule presents both an open convex face and a more-hindered, concave face to the reagents. The reaction proceeds to give products of attack on one face only, the convex face. This system appeared suitable to pursue the study of the kinetic resolution by the AD reaction. Indeed, the alkene **5** appears ideal for this study. Control of product formation in the Sharpless AD reaction should be determined mainly by the enantiofacial selectivity of the styrene moiety. The concave face of this molecule is hindered, so there should be a considerable difference in the rate of reaction of the enantiomers of this molecule and kinetic resolution should be effective.

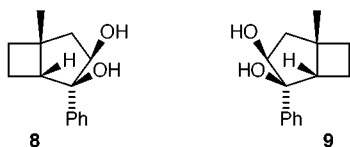
Reaction of the bicyclic ketone **6**¹⁴ with PhMgBr and Et₂O at 0 °C gave, in 88% yield, a single racemic alcohol, mp 56–58 °C, presumed to be the diastereomer **7** (Scheme 2). Dehydration of this alcohol (CH₂Cl₂, Et₃N, MsCl, 0 °C) gave as an oil the alkene **5** (81%).¹⁵ A kinetic resolution of this substrate was examined in two separate experiments with 26 and 50% oxidant respectively. However, because the alkene **5** is somewhat unstable, in each case the ees for both the diol (presumed to be enantiomer **8**, based on the application of Sharpless' mnemonic) and the recovered alkene **5** were determined, after separation, in the following way. The diol **8** was converted to the mono Mosher ester derivative [(+)-MTPA, CH₂Cl₂, DCC, DMAP] and the ee determined.¹⁶ The alkene was converted to the same diol (presumed to be mainly **9**) by the achiral dihydroxylation



Scheme 1



Scheme 2



reaction (quinuclidine ligand) and this diol was converted to the mono Mosher ester derivative from which the ee was obtained. The ees for the diols in the two reactions were 88 and 80%, and for the alkenes they were 52 and 80%, respectively. The enantiomeric ratios for these two reactions calculate to $E = 26$ and 21, respectively (the same within experimental error), which translates to an effective kinetic resolution ($>95\%$ ee at 60% conversion).

In conclusion, we find that the reaction of 1-phenyl-4-*tert*-butylcyclohexene with AD-mix- β gives the two diastereomers **2** and **3** in very high enantiopurity. However, the rate difference between formation of the two enantiomers is only small ($E \sim 2$) and kinetic resolution is ineffective. We also find that the reaction of the alkene **5** with AD-mix- β gives an effective kinetic resolution ($E > 20$) and only one diastereomeric diol is formed. These results are consistent with an early, rather than a late, transition state for the product-determining step in the Sharpless AD reaction.

Notes and references

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- 7 Chiral shift reagent $[\text{Eu}(\text{hfc})_3]$ in 15% $\text{C}_6\text{D}_6\text{-CCl}_4$. The Bu^t protons' resonance due to the minor enantiomer was not visible by proton NMR, but the ^{13}C satellite of the Bu^t protons' resonance of the major isomer was. Addition of 1% of the racemate gave a discernible peak for the minor enantiomer.
- 8 Chiral shift reagent $[\text{Eu}(\text{tfc})_3]$ in 15% $\text{C}_6\text{D}_6\text{-CCl}_4$. Addition of 5% of the racemate was required before a discernible peak for the Bu^t protons' resonance of the minor enantiomer could be detected.
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- 16 In the ^1H NMR spectrum, methoxy resonances at $\delta 3.37$ and 3.53 for the diastereomers produced from the racemic diol showed separation at the base-line.

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