Shi Asymmetric Epoxidation Reaction

Reviews:


General Transformation:

It is proposed that the Shi epoxidation proceeds through a dioxirane intermediate and a spiro transition state and that a so-called planar transition state is a main competing pathway. The spiro transition state is believed to be electronically favored as a result of a stabilizing interaction between an oxygen lone pair of the dioxirane with the \(^*\) orbital of the olefin.

Catalyst Conditions:

- Ketone 1 can be readily prepared from D-fructose ($\frac{15}{kg}$) by ketalization (acetone, HClO\(_4\), 0 °C, 53%) and oxidation (PCC, 23 °C, 93%). L-Fructose can be prepared in 3 steps from readily available L-sorbose.
- Ketone 1 can be used catalytically (20–30 mol %).
- Oxone (a commercial mixture of 2:1:1 KHSO\(_5\):KHSO\(_4\):K\(_2\)SO\(_4\)) is used as the stoichiometric oxidant but \(\text{H}_2\text{O}_2/\text{CH}_3\text{CN}\) can also be used (peroxyimidic acid is the proposed oxidant).
- Generally, the optimum pH for dioxirane epoxidation is 7–8. At higher pH, Oxone tends to decompose. However, at pH 7–8 the Shi catalyst decomposes due to competing Baeyer-Villiger reaction. By increasing the pH to 10.5 (by addition of K\(_2\)CO\(_3\)), the amount of ketone used can be reduced to a catalytic amount (30 mol %) and the amount of Oxone can be reduced to a stoichiometric amount (1.5 equiv), suggesting that at this pH the ketone is sufficiently reactive to compete with Oxone decomposition.
- Dimethoxymethane (DMM) and CH\(_3\)CN (2:1 v/v) solvent mixtures generally provide higher ee's.
- Reaction temperatures range from –10 to 20 °C.
- It is proposed that the Shi epoxidation proceeds through a dioxirane intermediate and a spiro transition state and that a so-called planar transition state is a main competing pathway. The spiro transition state is believed to be electronically favored as a result of a stabilizing interaction between an oxygen lone pair of the dioxirane with the \(^*\) orbital of the olefin.

Examples:

1. Effect of smaller R\(_1\) (also known as "T-branch"); phenyl groups can be considered smaller than methyl.

\[
\begin{align*}
{\text{H}_3\text{C}} & \text{O} \text{H}_3\text{C} \quad \text{H}_3\text{C} \\
{\text{H}_3\text{C}} & \text{O} \text{H}_3\text{C} \quad \text{H}_3\text{C} \\
{\text{H}_3\text{C}} & \text{O} \text{H}_3\text{C} \quad \text{H}_3\text{C}
\end{align*}
\]

<table>
<thead>
<tr>
<th>R(_1)</th>
<th>R(_2)</th>
<th>R(_3)</th>
<th>ee</th>
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<tbody>
<tr>
<td>26% ee</td>
<td>79% ee</td>
<td>81% ee</td>
<td>98% ee</td>
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2. Effect of larger R\(_3\) (also: "L-branch").

\[
\begin{align*}
{\text{H}_3\text{C}} & \text{O} \text{H}_3\text{C} \quad \text{H}_3\text{C} \\
{\text{H}_3\text{C}} & \text{O} \text{H}_3\text{C} \quad \text{H}_3\text{C} \\
{\text{H}_3\text{C}} & \text{O} \text{H}_3\text{C} \quad \text{H}_3\text{C}
\end{align*}
\]

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<td>76% ee</td>
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</tr>
<tr>
<td>76% ee</td>
<td>97% ee</td>
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3. Comparing the size of R\(_1\) and R\(_3\).

\[
\begin{align*}
{\text{H}_3\text{C}} & \text{O} \text{H}_3\text{C} \quad \text{H}_3\text{C} \\
{\text{H}_3\text{C}} & \text{O} \text{H}_3\text{C} \quad \text{H}_3\text{C} \\
{\text{H}_3\text{C}} & \text{O} \text{H}_3\text{C} \quad \text{H}_3\text{C}
\end{align*}
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Proposed Catalytic Cycle:

Higher ee's are observed with smaller R\(_1\) and larger R\(_3\) substituents.

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Monooxidation of conjugated dienes favors the more electron-rich or less sterically hindered olefin. The amount of catalyst used must be properly controlled (0.2–0.3 equiv) to prevent bis-epoxidation. Vinyl silanes and allylic silyl ethers are deactivated towards epoxidation (attributed to steric and inductive deactivation, respectively).

Epoxidation of enynes occurs selectively at the C–C double bond.

1,1-Disubstituted epoxides can be synthesized enantioselectively by Shi epoxidation of trisubstituted vinyl silanes followed by TBAF-mediated desilylation.
A modified catalyst is useful for epoxidation of cis-disubstituted olefins and styrenes.

\[
\text{Ph} \stackrel{\text{Oxone, K}_2\text{CO}_3, \text{DME, DMM}}{\longrightarrow} \text{Ph}
\]

82%, 91% ee

The enantiomeric excess is generally high for cyclic olefins and for acyclic olefins conjugated with an alkynyl or aromatic group.


In both cases, it is proposed that the \( \alpha \)-substituent of the substrate prefers to be proximal to the spiro oxazolidinone.

Enol esters can be used as substrates for the preparation of \( \alpha \)-hydroxyketones in either enantiomeric form.

\[
\text{Ph} = \text{CH}_3 \quad \text{Oxone, K}_2\text{CO}_3, \text{DME, DMM} \quad \rightarrow \quad \text{Ph} = \text{CH}_3
\]

66%, 91% ee

91% ee

94% ee

195 °C, 0.5 h

92%

98% ee


Kinetic resolution of racemic 1,3- and 1,6-disubstituted cyclohexenes can provide optically enriched allylic silyl ethers.

\[
\text{OTMS} \quad \xrightarrow{35 \text{ mol} \% 1} \quad \text{OTMS}
\]

49% conversion

96% ee

trans:cis >20:1

95% ee trans

\[
\text{OTBS} \quad \xrightarrow{35 \text{ mol} \% 1} \quad \text{OTBS}
\]

70% conversion

99% ee

trans:cis 4:1

81% ee trans

The original Shi catalyst decomposes (via the Baeyer-Villiger pathway) faster than it reacts with electron-deficient \( \alpha,\beta \)-unsaturated esters. A second-generation catalyst, incorporating electron-withdrawing acetate groups, slows the Baeyer-Villiger decomposition.

\[
\text{Ph CO}_2\text{Et} \xrightarrow{\text{73\%, 96\% ee}} \text{Ph CO}_2\text{Et}
\]


**Applications in Synthesis:**

**Glabrescol:**

\[
\text{squalene} \xrightarrow{\text{asymmetric dihydroxylation}} \text{Glabrescol} \quad 73\%
\]

\[
\text{H}_3\text{C} - \text{CH}_3 - \text{CH}_3 - \text{CH}_3 - \text{CH}_3 - \text{CH}_3 - \text{CH}_3 - \text{CH}_3 - \text{CH}_3
\]

\[
\text{HO} - \text{CH}_3 - \text{CH}_3 - \text{CH}_3 - \text{CH}_3 - \text{CH}_3 - \text{CH}_3 - \text{CH}_3 - \text{CH}_3
\]

\[
\text{88\% ee}
\]

1. Oxone, DMM, \( \text{CH}_3\text{CN}, \text{H}_2\text{O}, \text{pH} \, 10.5, \, 0 \, ^\circ \text{C}, \, 1.5 \, \text{h}
\]

\[
\text{CSA, toluene, 0 \, ^\circ \text{C}, 1 \, \text{h}} \quad 31\% \, (2 \, \text{steps})
\]

originally proposed structure of Glabrescol


**Cryptophycin 52:**

The Shi epoxidation system provided the desired epoxide in a 6:1 diastereomeric ratio, while other epoxidation methods never exceeded a 2:1 ratio.

\[
\text{H}_3\text{C} - \text{CH}_3 - \text{CH}_3 - \text{CH}_3 - \text{CH}_3 - \text{CH}_3 - \text{CH}_3 - \text{CH}_3 - \text{CH}_3
\]

\[
\text{HO} - \text{CH}_3 - \text{CH}_3 - \text{CH}_3 - \text{CH}_3 - \text{CH}_3 - \text{CH}_3 - \text{CH}_3 - \text{CH}_3
\]

\[
\text{88\% ee}
\]

\[
\text{H}_3\text{C} - \text{CH}_3 - \text{CH}_3 - \text{CH}_3 - \text{CH}_3 - \text{CH}_3 - \text{CH}_3 - \text{CH}_3 - \text{CH}_3
\]

\[
\text{HO} - \text{CH}_3 - \text{CH}_3 - \text{CH}_3 - \text{CH}_3 - \text{CH}_3 - \text{CH}_3 - \text{CH}_3 - \text{CH}_3
\]

\[
\text{79\%}
\]


Soojin Kwon
**Octalactin A:**

Bluet, G.; Campagne, J.-M. *Synlett* **2000**, *1*, 221–222.

**Thrysiferol:**

Post epoxidation, only one bromohydrin diastereomer cyclized to the bromotetrahydropyran. The unreactive diastereomer was separated from the cyclization product and isolated in 30% yield.

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