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Applications of Sharpless asymmetric epoxidation in total synthesis

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ABSTRACT

This report presents the applications of enantioselective epoxidation of prochiral allylic alcohols, so called 'Sharpless asymmetric epoxidation', which is frequently referred as 'kinetic resolution'. This reaction results in the corresponding 2,3-epoxy alcohols in high stereoselectivity as excellent starting materials for the synthesis of complex targets, such as naturally occurring biologically active molecules.

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Contents

1. Introduction

There is a needed command in industry and academia for the efficient and practical synthesis of pure enantiomers. A number of powerful and efficient catalytic asymmetric reactions have been introduced and developed to meet this over mounting demands. Among these processes, the Sharpless strategy for the asymmetric epoxidation of alkenes stands out and is outstandingly distinct due to its wide and exceptional utility and widespread applications.[1]

The Sharpless asymmetric epoxidation triumph and achievements are probably due to five major reasons. First, epoxides are very versatile intermediates and can be easily converted into diols, aminoalcohols, ethers, etc.[2] Hence the formation of enantiomerically pure epoxides is a very important step in the asymmetric synthesis of organic chiral compounds, especially in the total synthesis of natural products. Second, the Sharpless asymmetric epoxidation works perfectly for many primary and secondary allylic alcohols, which are either commercially available or easily accessible. Third, and perhaps most importantly, the products of the Sharpless asymmetric epoxidation often show enantiomeric excesses above 90%. Fourth, the products of the Sharpless asymmetric epoxidation are predictable since the protocol follows a regular trend and gives stereochemically expected models. Finally, the reactants for the Sharpless asymmetric epoxidation are either commercially available and relatively inexpensive or readily accessible.[3]

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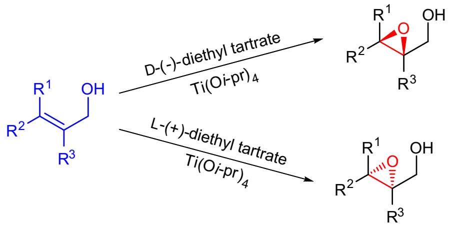
The versatile reactivity of the epoxy alcohol functionality brings about a good opportunity for synthetic organic chemists to take advantage of regio- and stereoselective ring opening; oxidation and reduction, etc. Therefore, the chiral epoxy alcohols are powerful and effective starting materials for the synthesis of complex targets such as biologically active molecules with multiple stereocenters.[4] It should be noted that an overview covering synthetic applications of chiral unsaturated epoxy alcohols prepared via Sharpless asymmetric epoxidation has been published in 2010 by Riera and Moreno.[4]

In 1965, Henbest et al.[5] reported the earliest asymmetric epoxidation of olefins using percamphoric acid but only in low levels of enantioselectivity (8%). However 15 years later, in 1980 the Sharpless asymmetric epoxidation was discovered as a good example of the stereoselective epoxidation of alkenes, using a protocol to achieve full stereochemical control for such an important and key reaction. This protocol stereoselectively converts a prochiral allylic alcohol to an epoxy alcohol using titanium isopropoxide [Ti(O*i*Pr)$_4$], *t*-butyl hydroperoxide (TBHP), and an appropriate chiral diethyl tartrate (DET). Since then Sharpless asymmetric epoxidation has attracted much attention and is used as a tool for the synthesis of optically active epoxides as the known multi-purpose reactive substrate, in laboratories as well as on an industrial scale (Scheme 1).[6]



Scheme 1.

This breakthrough enabled the stereoselective epoxidation of a wide range of alkenes using only 5–10 mol % of the catalyst.[6] Sharpless et al. also discovered that the addition of molecular sieves to the reaction mixture increases the effectiveness of the process.[7] This catalytic system is very resourceful, and can even be used in the epoxidation of highly functionalized molecules. Amides, aldehydes, acetals, silyl ethers, sulfones, and a large number of other groups have been found to be tolerant toward this strategy.[8]

Functional groups that are not compatible are amines, carboxylic acids,[9] phenols,[10] mercaptans, and phosphines (Table 1).[11] Nucleophilic substituents that can lead to an intramolecular ring-opening of the in situ generated epoxide give the undesired cyclized products.[11]

Table 1

Compatible functional groups				Incompatible groups
Acetals, ketals	Azides	Ketones	Silyl ethers	Amines (most)
Acetylenes	Carboxylic esters	Nitriles	Sulfones	Carboxylic acids
Alcohols	Epoxides	Nitro	Sulfoxides	Mercaptanes
Aldehydes	Ethers	Olefins	Tetrazoles	Phenols (most)
Amides	Hydrazines	Pyridines	Ureas	Phosphines

The advantages of the catalytic method over the stoichiometric reactions, include easier isolation of the products, requirement of conditions, possible in situ derivatization of the product, and enhanced yields of the sensitive epoxy alcohols. In the latter case, some epoxy alcohols are unstable under the stoichiometric reaction conditions, probably due to the mild Lewis acidity of titanium alkoxides, which could stimulate unwanted ring-opening of the oxirane.[12]

In continuation of our interest in the recent applications of named reactions[13] and particularly with those leading to asymmetric and total synthesis,[14] herein we highlight the applications of Sharpless asymmetric epoxidation as a powerful tool, in the key step (steps) for the total synthesis of various classes of natural products with biological activities.

1.1. Mechanism of the Sharpless asymmetric epoxidation

An important and significant feature of this catalytic asymmetric process is based on the fact that the allylic alcohol is coordinated to the metal during epoxidation and in this way the molecule is attached to the chiral complex during the reaction. In fact in the absence of an allylic hydroxyl moiety, no reaction takes place. The allylic hydroxyl group activates the oxidant and controls the delivery of oxygen to the substrate, preferentially to one of the two possible enantiotopic faces of the alkene. In this way, the hydroxyl moiety provides selective epoxidation of the allylic alkenes even in the presence of other C–C double bonds in a same molecule.[15]

The creation of several Ti–tartrate complexes is possible in the reaction system. Sharpless himself suggested that epoxidation is catalyzed by a single Ti center in a diametric complex with a C2 symmetric axis. IR, ^{1}H, ^{13}C, ^{17}O NMR spectroscopy, and mass spectrometry all suggest that such a dinuclear structure is dominant and abundant in the solution phase. It elevates the reaction much faster than Ti(IV) tetraalkoxide alone and shows selective ligand-accelerated reaction (Scheme 2).[16]

The allylic hydroxyl moiety is coordinated and pre-orientated through its O-atom to the catalyst. The catalyst creates a Sharpless-type transition state via the h2-coordinated TBHP molecule. Three coordination sites are available via exchange of two isopropoxides and dissociation of the coordinated ester carbonyl group. The hydroperoxide should engage the equatorial position and one of the two available axial coordination sites. The allylic alcohol hydroxyl group should occupy the other axial site. To reach the necessary proximity for the delivery of oxygen to the olefin, the diacetal oxygen occupies the equatorial position, and the proximal oxygen is placed in the axial site. The axial site on the lower face of the system is selected for the peroxide due to the larger steric demands, which the alkyl group needs. The allylic alcohol hydroxyl group binds to the remaining axial coordination site, where stereochemical and stereoelectronic effects force the most stable conformation of the system (Scheme 3).[7b]

The optimal ratio for Ti/tartrate was found to be 2:2. Less than 1 equiv of tartrate decreases the ee because of the non-asymmetric epoxidation. Excess tartrate inhibits the reactivity by forming the inert complex (Ti-tartrate)$_2$. Dimethyl, diethyl, and di-iso-propyl tartrate (DMT, DET, DIPT) all induce high asymmetry. (*E*)-Allylic alcohol-DET affords greater ee than DIPT. The efficiency of the kinetic resolution is increased with steric bulk of the tartrate alkyl ester, hydroperoxide, alkyl moiety, and using the *trans*-olefin substituent. Free and excess alcohol inhibits catalyst reactivity. The use of molecular sieves is required to remove any moisture.[16] Added alcohols had no effect on the relative rates of kinetic resolutions; free ROH is not associated with the active complex for oxygen transfer.[16]

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