

Stereochemistry 2016: Applications of sharpless asymmetric dihydroxylation in total synthesis of natural product

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In continuation of our interest in the field of asymmetric synthesis and total synthesis of natural products, most of them have several stereogenic centers. The aim of this study is to present the applications of sharpless asymmetric dihydroxylation (SAD) (also called the sharpless bishydroxylation). SAD is the chemical reaction of an alkene with osmium tetroxide in the presence of a chiral quinine ligand to form an optically pure vicinal diol. It is common practice to perform this reaction using a catalytic amount of osmium tetroxide, which after reaction is regenerated with either potassium ferricyanide or N-methylmorpholine N-oxide. This dramatically reduces the amount of the highly toxic and very expensive osmium tetroxide needed. These four reagents are commercially available premixed ("AD-mix"). The mixture containing (DHQ)₂-PHAL is called AD-mix- α , and the mixture containing (DHQD)₂-PHAL is called AD-mix- β . Nowadays, SAD is considered as a powerful tool for the preparation of chiral dihydroxy compounds which offers remarkable opportunities for enantioselective synthetic manipulation. In this study, the applications of SAD in total synthesis of naturally occurring compounds will be discussed.

The Asymmetric Dihydroxylation involves the conversion of a substituted alkene to a diol. As a catalyst, Osmium tetroxide is utilized. In order to enantioslectively deliver the oxygens to the olefin, one the various cinchone ligands is utilized.

An example procedure for the dihydroxylation of 1 mmol olefin:

A 25 ml round bottom flask fitted with a magnetic stirrer is loaded with 5 ml of t-butyl alcohol, 5 ml of water and 1.4 g of AD alpha or beta mixture. (95 mg of methane sulfonamide

are also added if the olefin 1,2 is disubstituted, trisubstituted or tetrasubstituted). The mixture is stirred at room temperature until all of the reagents dissolve. The reaction is cooled to 0 C (some of the inorganic salts can precipitate); in the case of slow alkenes, the reaction is left at room temperature.

One mmol of olefin is added at a time and the heterogeneous suspension is stirred until TLC or GC indicates an absence of starting material (about 6-24 hrs). The reaction is stopped by adding sodium sulfite (1.5 g) and then stirred at room temperature for one hour. The reaction mixture is then extracted several times with ethyl acetate or DCM. (When methane sulfonamide is used, the organic layer must be washed with 2N KOH).

The organic layer is then dried and concentrated to give a mixture of crude diol and ligand, which is then purified by flash chromatography (silica gel, EtOAc / Hex; the ligand does not elute under these conditions) to give the pure diol .

By utilizing a catalytic amount of osmium tetroxide, it is common to carry out this reaction, which is after regenerated with reoxidants like potassium ferricyanide or N-methylmorpholine N-oxide. This greatly reduces the amount of highly toxic and very expensive osmium tetroxide required. These four reagents are premix commercially available ("AD-mix").

The reaction mechanism of Sharpless dihydroxylation begins with the formation of the osmium tetroxide - ligand complex. Cycloaddition of [3 + 2] with the alkene gives the cyclic intermediate.

Basic hydrolysis releases the diol and the reduced osmate. For accelerating this stage of catalytic cycle, Methanesulfonamide

(CH₃SO₂NH₂) has been identified as a catalyst. Also, in order to allow non-terminal alkenes substrates, it is frequently utilized as an additive, to react effectively at 0 ° C. Finally, the stoichiometric oxidant regenerates the complex osmium tetroxide - ligand.

The mechanism of Sharpless asymmetric dihydroxylation (SAD) has been extensively studied and a potential secondary catalytic cycle has been identified. Osmium (VIII) – diol complex is formed when the intermediate ester osmylate is oxidized before it dissociates.

The dihydroxylations resulting from this secondary route generally suffer from lower enantioselectivities than those resulting from the primary route. A diagram showing this secondary catalytic pathway is presented below. This secondary pathway can be suppressed by using a higher molar concentration of ligand.

Many catalytic systems and modifications have been developed for SAD.

You will find below a brief overview of the various components of the catalytic system:

Catalytic oxidant: It is still OsO₄, but certain additives can coordinate with osmium (VIII) and modify its electronic properties. From K₂O₂O₂ (OH)₄ (an Os (VI) species), OsO₄ is often generated in situ.

Auxiliary chiral: It is generally a kind of cinchona alkaloid.

Stoichiometric oxidant: Peroxides were among the first stoichiometric oxidants to be used in this catalytic cycle; see Milas' hydroxylation. The disadvantages of peroxides include problems of chemoselectivity. Trialkylammonium N-oxides, such as NMOs - as in the Upjohn reaction - and trimethylamine N-oxide. Potassium ferricyanide (K₃Fe(CN)₆) is the most commonly used stoichiometric oxidant for the reaction, and is the oxidant that comes in commercially available AD mix preparations.

Additive: citric acid: osmium tetroxide is an electrophilic oxidant and with the electron-

deficient olefins, it reacts slowly. It has been found that the rate of oxidation of electron-deficient olefins can be accelerated by keeping the pH of the reaction slightly acidic.

On the other hand, a high pH can increase the oxidation rate of internal olefins, and also increase the enantiomeric excess (for example) for the oxidation of terminal olefins. The dihydroxylation of alkenes by osmium tetroxide is an old and extremely useful method for the functionalization of olefins. As osmium (VIII) reagents like osmium tetroxide (OsO₄) are expensive and extremely toxic, developing catalytic variants of this reaction has become desirable.

Potassium potassium chlorate, hydrogen peroxide (Milas hydroxylation), N-methylmorpholine N-oxide (NMO, Upjohn dihydroxylation), hydroperoxide tert-butyl (tBHP) etc. are some stoichiometric terminal oxidants that have been utilized in these catalytic reactions. Barry Sharpless was the first to develop a general and reliable enantioselective alkene dihydroxylation, called Sharpless Asymmetric Dihydroxylation (SAD).

Low levels of OsO₄ are combined with a stoichiometric ferricyanide oxidant in the presence of chiral nitrogen ligands to create an asymmetric environment around the oxidant.

Limitations:

Cis-olefins belong to the only class of substrates for which no example exceeding 90% ee has been produced.