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"The Elegance of Epoxidation: Mechanistic Insights, Diverse Applications, and Promising Horizons"

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ABSTARCT

This comprehensive article on epoxidation reactions provides a thorough understanding of the various types of reactions, reagents used, applications, advantages, and disadvantages associated with this important class of reactions. It also highlights recent advances in greener and more sustainable methods and their potential for future applications in various fields of chemistry. By reading this article, researchers and students alike can gain a deeper understanding of the mechanisms and applications of epoxidation reactions and their importance in organic synthesis, polymer chemistry, and medicinal chemistry. The article also highlights the potential for future developments in this area, making it a valuable resource for those interested in exploring new synthetic strategies. In addition, the article provides insights into the advantages and disadvantages of epoxidation reactions, helping researchers and students to carefully consider their selection of synthetic strategies for specific applications. The information on green chemistry and catalysis provides an exciting opportunity for the development of novel and more sustainable methods, promoting the continued use of epoxidation reactions in various fields of chemistry. Overall, this article serves as an essential resource for those interested in epoxidation reactions and their applications, providing a detailed understanding of the mechanisms involved and the potential for future developments in this area. The information provided in this article can be applied to various research projects and industrial processes, making it a valuable resource for both academia and industry.

Keywords: Asymmetric epoxidation, Chiral epoxides, Metal-catalyzed epoxidation, Green chemistry, Bio-based polymers.

INTRODUCTION

Epoxidation is a chemical reaction that involves the formation of an epoxide, a three-membered cyclic ether, from a double bond. It is a significant reaction in organic chemistry due to its synthetic versatility and biological importance. Epoxides are found in a wide range of natural and synthetic compounds, including pharmaceuticals, agrochemicals, and polymers. They also play crucial roles in various industrial applications, such as adhesives, coatings, and composites.[1,2]

The most common method for the epoxidation of alkenes is the reaction with a peracid, such as meta-chloroperbenzoic acid (MCPBA), peracetic acid, and performic acid. Peracids are strong oxidizing agents that can transfer an oxygen atom to a double bond, resulting in the formation of an epoxide. The reaction proceeds through a cyclic intermediate, which is formed by the attack of the peracid on the alkene. The intermediate then collapses to form the epoxide and the corresponding carboxylic acid.[3–6]

Another method for the epoxidation of alkenes is the reaction with an oxone, a triple salt of potassium peroxymonosulfate, which is a powerful oxidizing agent. The reaction proceeds through the formation of an oxirane intermediate, which is subsequently hydrolyzed to form the epoxide. The use of oxone has several advantages over peracids, including its availability, low cost, and environmental friendliness.[5,7,8]

Metal-catalyzed epoxidation is another commonly used method for the epoxidation of alkenes. This method involves the use of metal complexes, such as titanium, molybdenum, and tungsten, as catalysts to activate the peroxide reagent. Metal-catalyzed epoxidation has several advantages over the traditional peracid and oxone methods, including the ability to perform the reaction under milder conditions and the ability to selectively epoxidize certain types of alkenes.[9,10]

Asymmetric epoxidation is a type of epoxidation that involves the formation of a chiral epoxide from an achiral alkene. This reaction is of great importance in the synthesis of enantiopure compounds, which are critical in the pharmaceutical and agrochemical industries. Asymmetric epoxidation can be achieved using a chiral catalyst, such as a chiral metal complex or an organocatalyst.[11–14]

In addition to the epoxidation of alkenes, other types of epoxidation reactions exist. For example, the epoxidation of carbonyl compounds involves the formation of an oxirane intermediate from a carbonyl group, which can then be hydrolyzed to form an epoxide. This reaction is commonly used in the synthesis of epoxide-containing natural products.[15]

In summary, epoxidation is a fundamental organic reaction with wide applications in synthesizing diverse natural and synthetic compounds. Common methods include peracid, oxone, and metal-catalyzed epoxidation for alkenes, while asymmetric epoxidation is crucial for enantiopure compound synthesis. Ongoing research focuses on developing new epoxidation methods and catalysts, reflecting the active pursuit of advancements in organic chemistry.[3,5,16]

Types of Epoxidation

Epoxidation is a chemical reaction that involves the formation of an epoxide, which is a three-membered cyclic ether, from a double bond. Epoxides are important synthetic intermediates and are widely used in the preparation of pharmaceuticals, agrochemicals, and materials. There are several types of epoxidation reactions, which differ in their reagents, catalysts, and reaction mechanisms.

Peroxyacid Epoxidation

The most common method for alkene epoxidation involves reaction with a peroxyacid, such as meta-chloroperbenzoic acid (MCPBA), peracetic acid, or performic acid. Peroxyacids, strong oxidizing agents, transfer an oxygen atom to a double bond, forming an epoxide. The reaction proceeds through a cyclic intermediate formed by the attack of the peroxyacid on the alkene, followed by collapse to yield the epoxide and the corresponding carboxylic acid. Selectivity depends on alkene substitution, peroxyacid structure, and reaction conditions.[3–5,16]

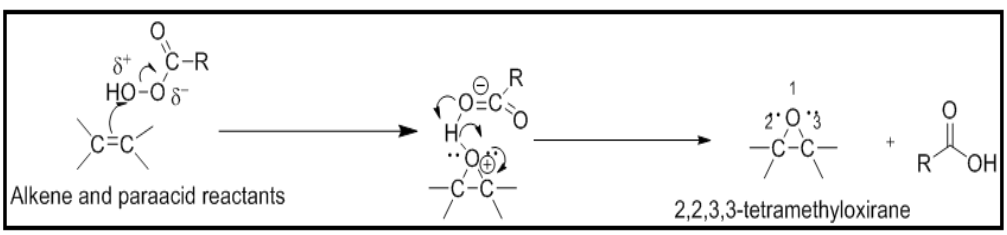

Fig. 1. Epoxidation of alkenes with para-acids

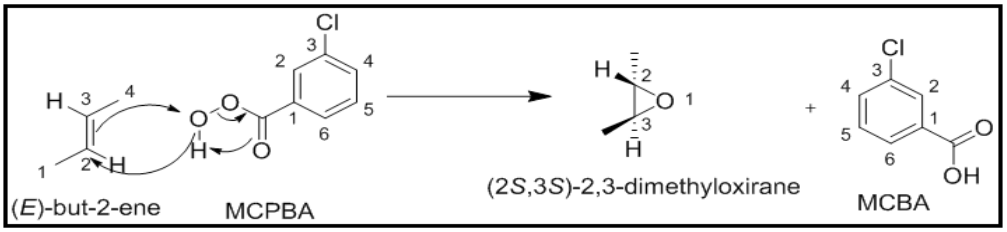

Fig. 2. Epoxidation of alkenes with meta-chloro-perbenzoic acid

Metal-Catalyzed Epoxidation

Metal-catalyzed epoxidation is another commonly used method for the epoxidation of alkenes. This method involves the use of metal complexes, such as titanium, molybdenum, and tungsten, as catalysts to activate the peroxide reagent. Metal-catalyzed epoxidation has several advantages over the traditional peroxyacid method, including the ability to perform the reaction under milder conditions and the ability to selectively epoxidize certain types of alkenes. The mechanism of metal-catalyzed epoxidation involves the coordination of the metal catalyst with the peroxide reagent, followed by the activation of the peroxide and the transfer of an oxygen atom to the alkene. The selectivity of the reaction hinges on factors such as the type of metal catalyst employed, the characteristics of the peroxide reagent, and the reaction conditions. Understanding and optimizing these parameters are crucial for achieving the desired selectivity in catalytic processes.[17,18]

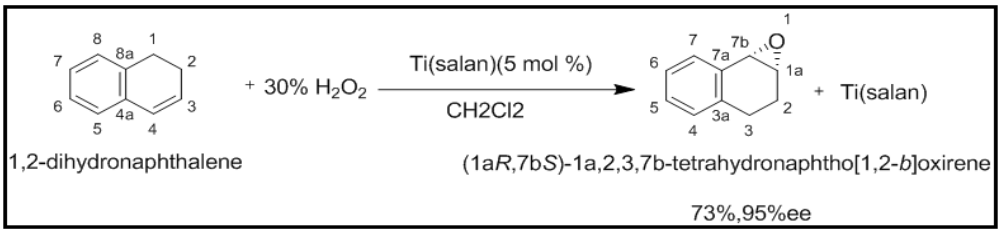

Fig. 3. Metal catalysed(Ti(salan) Epoxidation of 1,2-dihydronapthalene

Oxone Epoxidation

Oxone is a triple salt of potassium peroxymonosulfate, which is a powerful oxidizing agent. The reaction of alkenes with Oxone leads to the formation of an oxirane intermediate through an epoxidation process. This intermediate undergoes hydrolysis to yield the corresponding epoxide. This sequential transformation is a fundamental step in various organic synthesis routes involving epoxide formation.The use of oxone has several advantages over peroxyacids, including its availability, low cost, and environmental friendliness. The selectivity of the reaction depends on the substitution pattern of the alkene and the reaction conditions.[19,20]

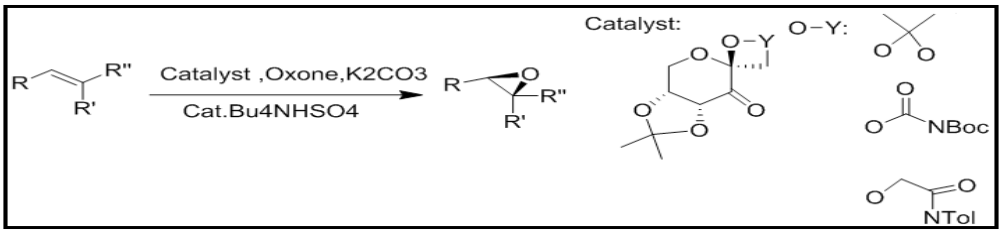

Fig. 4. Oxone catalysed Epoxidation of Alkenes

Asymmetric Epoxidation

Asymmetric epoxidation is a valuable method for synthesizing chiral epoxides, which serve as crucial intermediates in pharmaceutical and natural product synthesis. Additionally, it is employed in producing chiral building blocks essential for drug discovery processes. In this method, a chiral catalyst is used to selectively produce one enantiomer of the epoxide. Some examples of the application of asymmetric epoxidation include the synthesis of epoxides such as limonene oxide, chalcone oxide, and styrene oxide.[21,22]

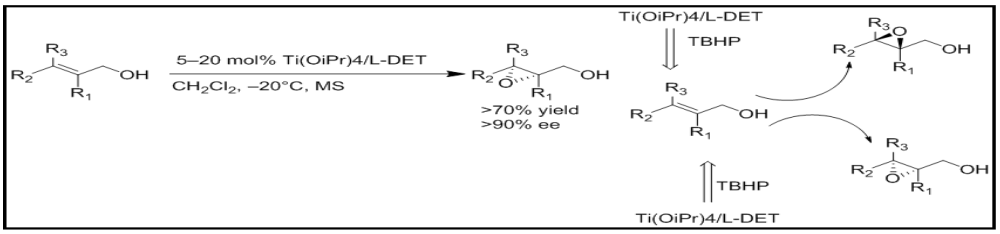

Fig. 5. Katsuki–Sharpless asymmetric epoxidation of allylic alcohols

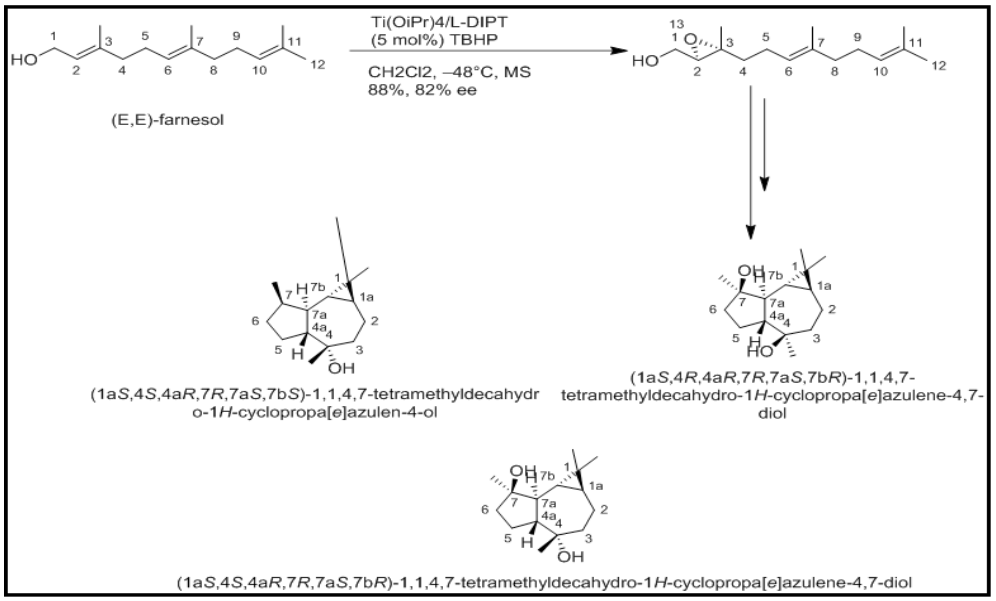

Fig. 6. Katsuki–Sharpless asymmetric epoxidation of (E,E)-farnesol, serving as a pivotal step in the synthesis of sesquiterpene derivatives

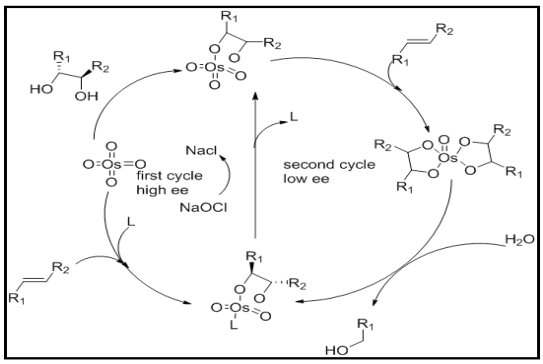

Fig. 7. Mechanism for Sharpless asymmetric dihydroxylation

Base-Catalyzed Epoxidation

Base-catalyzed epoxidation is an important method for the synthesis of epoxides from alkenes. It is used in the preparation of epoxides that are used as intermediates in the synthesis of various chemicals, including surfactants, detergents, and plasticizers. In this method, a base catalyst is used to activate the oxidizing agent, which then reacts with the alkene to produce the epoxide. Some examples of the application of base-catalyzed epoxidation include the synthesis of epoxides such as butadiene oxide, glycidol, and phenyl glycidyl ether.[5,23,24]

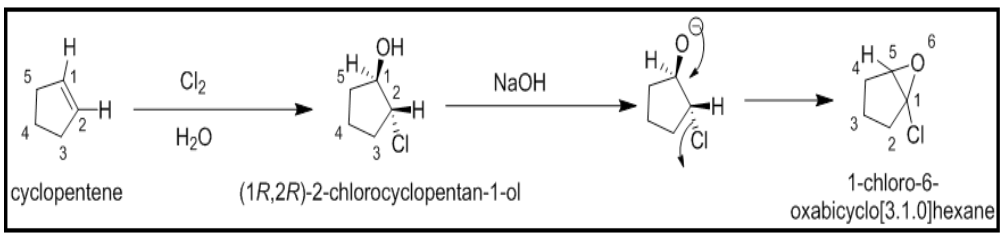

Fig. 8. Base catalysed epoxidation of intramolecular ether synthesis

Enzymatic Epoxidation

Enzymatic epoxidation involves the use of enzymes, such as cytochrome P450 monooxygenases or lipoxygenases, to catalyze the formation of an epoxide from a double bond. Enzymatic epoxidation has several advantages over chemical methods, including the ability to perform the reaction under mild conditions and the ability to selectively epoxidize certain types of alkenes. The selectivity of enzymatic reactions relies on various factors, including the type of enzyme employed, the characteristics of the substrate, and the conditions under which the reaction occurs. Understanding and optimizing these parameters are crucial for achieving the desired selectivity in enzymatic processes.[25]

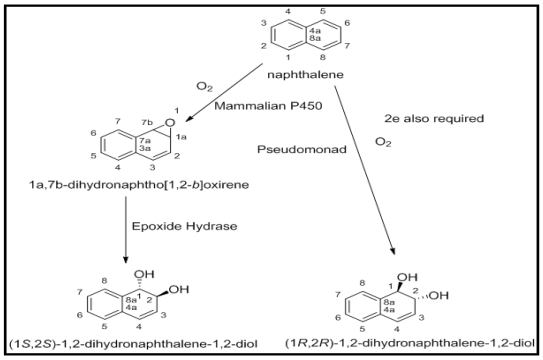

Fig. 9. P-450-catalysed epoxidation

Additionally, chiral epoxides produced through asymmetric epoxidation play a crucial role as intermediates in the synthesis of pharmaceuticals and natural products. They are used as building blocks in the synthesis of drugs such as the antitumor drug taxol and the antiviral drug ganciclovir.[26–28]

Moreover, epoxidation reactions are utilized in the synthesis of fine chemicals, including flavors and fragrances. For example, limonene oxide is used as a flavor and fragrance ingredient, while chalcone oxide is used as a precursor for the synthesis of chalcones, which have various biological activities.[29]

Reagents that uses for the epoxidation

The process of introducing an epoxide functional group into heterocyclic compounds can be accomplished through the utilization of various oxidizing agents. These oxidants encompass peroxy acids, metal-based complexes, and organic peroxide compounds. The selection of the appropriate reagent is contingent upon the specific heterocyclic substrate and the desired regioselectivity of the epoxidation reaction.[22,26]

Peroxy acids

Peroxy acids are among the most commonly used oxidizing agents for epoxidation reactions. Examples include meta-chloroperbenzoic acid (MCPBA), peracetic acid (PAA), and perbenzoic acid (PBA). These reagents are often preferred due to their high reactivity and the ease of handling and storage. MCPBA, in particular, is widely used due to its high selectivity and mild reaction conditions.[30]

Metal complexes

Metal complexes, such as molybdenum and tungsten catalysts, have also been used for the epoxidation of heterocycles. These reagents offer the advantage of high selectivity and mild reaction conditions. For example, the Jacobsen catalyst, which consists of a chiral salen ligand and a titanium center, has been used for the enantioselective epoxidation of pyrroles.[31–33]

Organic peroxides

Organic peroxides, such as tert-butyl hydroperoxide (TBHP) and hydrogen peroxide (H_2O_2), can also be used for the epoxidation of heterocycles. These reagents offer the advantage of being relatively cheap and safe to handle. However, their use often requires higher reaction temperatures and longer reaction times compared to peroxy acids.[34,35]

Other reagents

Other reagents that have been used for the epoxidation of heterocycles include oxone, an inorganic oxidizing agent, and dimethyldioxirane (DMDO), an organic peroxide. Oxone offers the advantage of being a solid reagent that can be easily handled and stored, while DMDO is a highly reactive and selective reagent that is often used for the epoxidation of electron-rich heterocycles. Oxone offers the advantage of being a solid reagent that can be easily handled and stored, while DMDO is a highly reactive and selective reagent that is often used for the epoxidation of electron-rich heterocycles.[36,37]

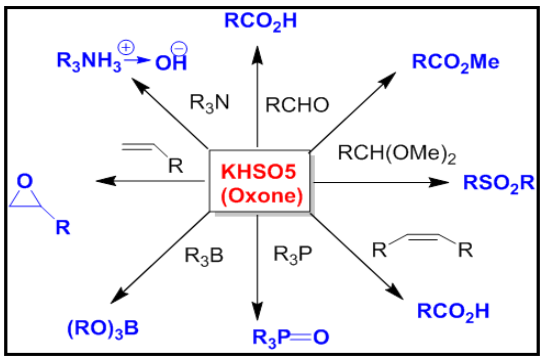

Fig. 10. Oxone as an Oxidizing agent and reactions

In addition to these reagents, green chemistry approaches have been developed for the epoxidation of heterocycles. For example, some studies have investigated the use of molecular oxygen and visible light as green oxidizing agents for the epoxidation of pyrroles and other heterocycles. These methods offer the advantage of being environmentally friendlier and potentially more cost-effective compared to traditional oxidizing agents.[38]

Epoxidation is an important reaction in organic synthesis and has found wide-ranging applications in various fields, including pharmaceuticals. Many pharmaceutical products use epoxidation methods in their synthesis to introduce epoxide functional groups into the molecule, which can confer a range of biological activities. In this context, we will discuss some examples of pharmaceutical products that use epoxidation methods in their synthesis.

Epothilones

Epothilones are a class of natural products that have shown promising anticancer activity. They are structurally similar to taxanes, but their mechanism of action is different. Epothilones contain a macrocyclic lactone ring and a tetraene chain with an epoxide functional group. The synthesis of epothilones involves the selective epoxidation of the tetraene chain. Various oxidizing agents, such as dimethyldioxirane, m-chloroperbenzoic acid, and peracids, have been used for this purpose.[39]

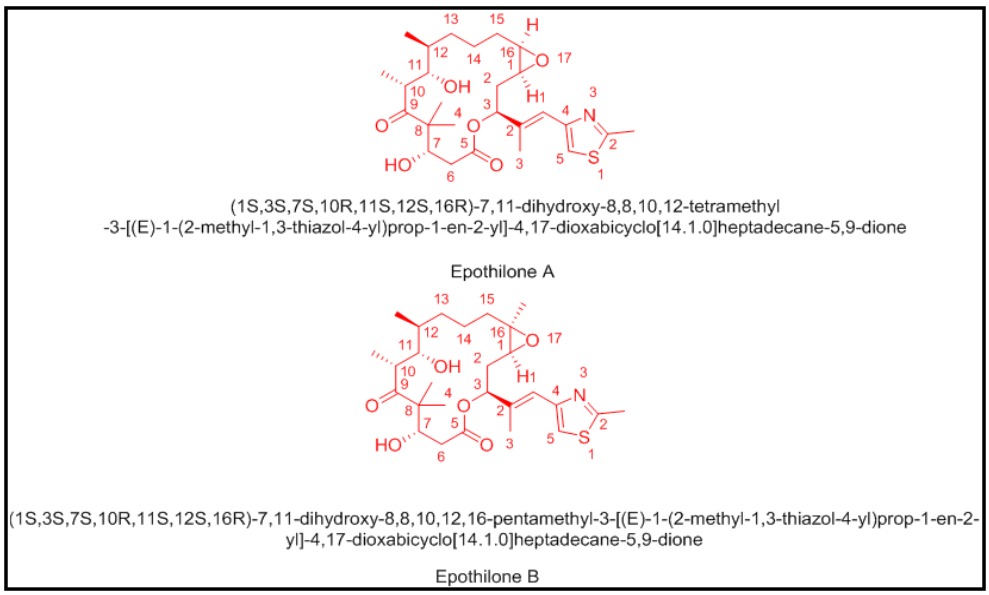

Fig. 11. Structure of Epothilone A and B

Taxol

Taxol is a widely used chemotherapy drug that is derived from the Pacific yew tree. It works by stabilizing microtubules and preventing cell division. Taxol contains a complex tetracyclic skeleton with an epoxide functional group. The synthesis of Taxol involves the epoxidation of the C13-C14 double bond, which is often carried out using peroxy acids or m-chloroperbenzoic acid.[40,41]

Artemisinin

Artemisinin is a natural product that is derived from the Artemisia annua plant. It is used in the treatment of malaria and has shown promising activity against cancer. Artemisinin contains a peroxide functional group, which is generated by the epoxidation of the C12-C13 double bond using peroxy acids or m-chloroperbenzoic acid.[42,43]

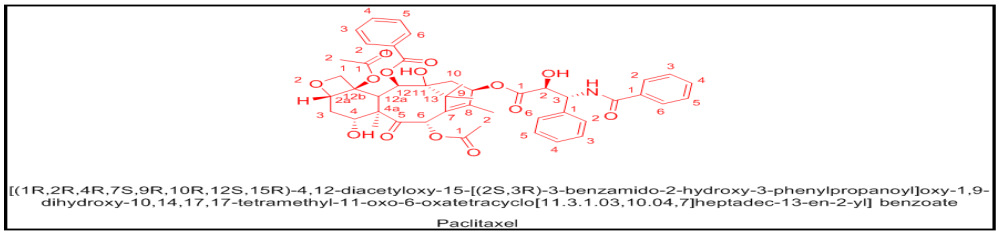

Fig. 12. Structure of Taxol(Paclitaxel)

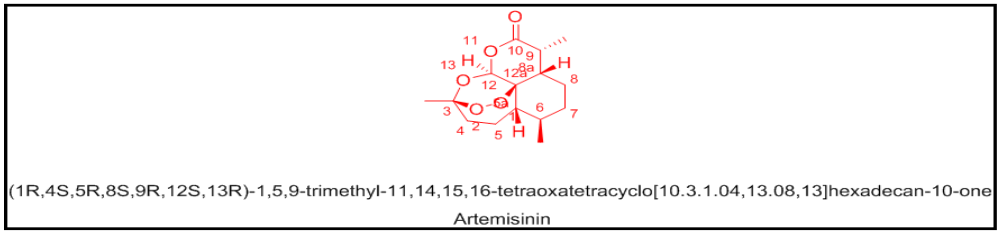

Fig. 13. Structure of Artemisinin

Camptothecin

Camptothecin is a natural product that has shown promising anticancer activity. It works by inhibiting topoisomerase I and preventing DNA replication. Camptothecin contains a lactone ring and a pentacyclic skeleton with an epoxide functional group. The synthesis of Camptothecin involves the epoxidation of the C9-C10 double bond using peroxy acids or m-chloroperbenzoic acid.[44,45]

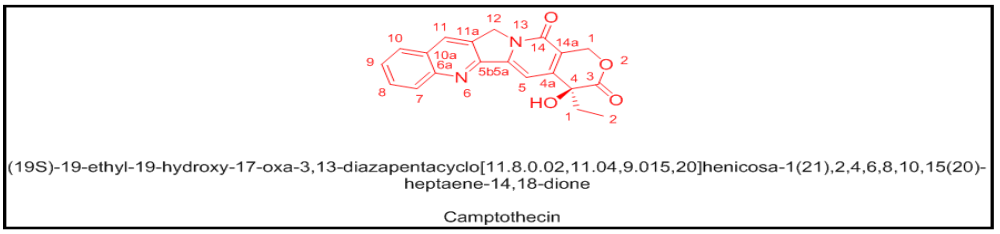

Fig. 14. Structure of Camptothecin

Ivermectin

Ivermectin is an antiparasitic medication extensively utilized for treating diverse parasitic infections, such as river blindness and scabies. It contains a macrocyclic lactone ring with an epoxide functional group. The synthesis of Ivermectin involves the epoxidation of the C22-C23 double bond using peroxy acids or m-chloroperbenzoic acid.[46,47]

Epoxidation in various heterocycles

Pyrroles

Pyrroles are a class of heterocycles that are widely used in the synthesis of natural products and pharmaceuticals. The epoxidation of pyrroles is usually regioselective and occurs at the C2-C3 double bond, and the resulting epoxides can be further functionalized to yield a range of derivatives with different biological activities. The epoxidation of pyrroles has been achieved using various oxidizing agents, such as dimethyldioxirane and peracids. There are several methods for achieving regioselective epoxidation of pyrroles, including catalytic ring-opening reactions[48], solvent-free catalytic methods[49] and reactions catalyzed by InBr3[50] The axial ligand of cytochrome P450 biomimetics can also influence the regioselectivity of epoxidation versus dehydrogenation[51], Additionally, pyrroles can be used in regioselective alkylation reactions.[52]

Thiophenes

They are a class of heterocycles that are widely used in the synthesis of pharmaceuticals and agrochemicals. The epoxidation of thiophenes has been achieved using various oxidizing agents, such as peroxy acids and m-chloroperbenzoic acid. The epoxidation of thiophenes is usually regioselective and occurs at the C2-C3 double bond. The resulting

epoxides can be further functionalized to yield a range of derivatives with different biological activities[53]. There are also various methods for synthesizing thiophenes, including modular synthetic routes that enable the functionalization of individual positions of thiophene sequentially via regioselective halogenations and cross-coupling reactions.[54–56] The regio- and chemoselectivity of reactions involving thiophenes can be predicted using density functional theory-based reactivity indices.[57]

Imidazoles

Imidazoles are a class of heterocycles that are widely used in the synthesis of pharmaceuticals and agrochemicals. The epoxidation of imidazoles is usually regioselective and occurs at the C2-C3 double bond, and the resulting epoxides can be further functionalized to yield a range of derivatives with different biological activities. Various oxidizing agents, such as dimethyldioxirane and peracids, have been used for the epoxidation of imidazoles.[58] Additionally, imidazoles have been used in the synthesis of spirocyclic compounds, such as spiro-[imidazole-indene] derivatives, through Rh(III)-catalyzed [3+2] spirocyclization and ruthenium(II)-catalyzed [3+2] spiroannulation reactions.[59,60]

Oxazoles

They are a class of heterocycles that are commonly used in the synthesis of natural products and pharmaceuticals. The epoxidation of oxazoles is typically regioselective and occurs at the C2-C3 double bond, and the resulting epoxides can be further functionalized to yield a range of derivatives with different biological activities. Various oxidizing agents, such as peracids and m-chloroperbenzoic acid, have been used for the epoxidation of oxazoles[61]. The synthesis of oxazoles can also be achieved through different methods, such as Lewis acid-promoted three-component cyclization[62] and gold(I)-catalyzed oxidative annulation[63] Additionally, fungal peroxygenases have been investigated for their ability to selectively epoxidize n-3 and n-6 fatty acids.[64]

Isoxazoles

Isoxazoles are a class of heterocycles that are widely used in the synthesis of natural products and pharmaceuticals. The epoxidation of isoxazoles is usually regioselective and occurs at the C2-C3 double bond, and the resulting epoxides can be further functionalized to yield a range of derivatives with different biological activities. There are several methods for synthesizing isoxazoles, including copper-catalyzed [4+2]-cycloadditions[65] sequential 1,3-dipole cycloaddition reactions[66] and intermolecular [5+1]-cycloadditions[67] Additionally, the regioselectivity of the reaction can be reversed using a ruthenium catalyst[68]. The regioselectivity of the reaction strongly depends on the substrate substituents, and the resulting products can be carboxylic acids or delta bicyclic lactones.[69]

Pyrazoles are a class of heterocycles that are commonly used in the synthesis of natural products and pharmaceuticals. The epoxidation of pyrazoles is usually regioselective and occurs at the C2-C3 double bond, and the resulting epoxides can be further functionalized to yield a range of derivatives with different biological activities. Various oxidizing agents, such as dimethyldioxirane and peracids, have been used to achieve the epoxidation of pyrazoles.[70–73]

Recent advances and future prospects

Epoxidation reactions have been widely studied and utilized in various fields of chemistry, including organic synthesis, polymer chemistry, and medicinal chemistry.[74–78] Recent advances and developments in the field of epoxidation have led to several potential applications and future prospects. As an example, the integration of green chemistry principles into certain oxidative transformations of steroids has led to significant advancements in synthetic chemistry related to these compounds.[75] Insect pheromones are attractive targets for the development of synthetic procedures, and recent research has focused on synthesizing these intraspecific chemical messengers using methodologies such as asymmetric epoxidations and dihydroxylations.[76] Synthetic routes to glycosidase inhibitors, such as indolizidine iminosugars, have also been developed using asymmetric epoxidation and other synthetic strategies.[78]

One recent advance is the development of new reagents and catalysts, such as a new copper(I) catalyst and a new silver-based reagent, which offer high selectivity, mild reaction conditions, high reactivity, and selectivity. developments include the use of chiral pyrrolidines as organocatalysts, the direct photo-epoxidation of propylene using

molecular oxygen, and the use of heterogeneous nanocatalysts for alcohol oxidation, epoxidation of alkenes, and allylic oxidation of alkenes.[75,79,80]

Recent developments in the field of epoxidation include the use of alternative and greener oxidizing agents, such as molecular oxygen and photocatalysts, for the selective epoxidation of alkenes.[81] These methods offer environmentally friendly and cost-effective alternatives to traditional oxidizing agents. Additionally, the application of epoxidation reactions in various fields has expanded in recent years. For example, the use of epoxides as building blocks in the synthesis of green polymers, such as epoxy resins, polycarbonates, and nonisocyanate polyurethanes, has been widely explored.[81–83] Enzymatic epoxidation using fungal peroxygenases has also been investigated as a potential green synthesis technology for epoxides.[84] The development of green synthesis technology for propylene oxide by propylene epoxidation with hydrogen peroxide as the oxidizing agent has also been reviewed.[85]

In recent years, the utilization of epoxidation reactions has broadened, encompassing the incorporation of epoxides as fundamental units in polymer synthesis. Additionally, research has explored the epoxidation of bio-based feedstocks like vegetable oils and fatty acids as a viable pathway for producing bio-based polymers and materials.[86] Significant research has been dedicated to developing stable heterogeneous catalysts for epoxidation by immobilizing catalytically active metal species onto organic or inorganic materials. These materials include polymers, ion-exchange resins, alumina, zeolite, and silica.[87] Epoxidation reactions have been utilized in the synthesis of various pharmaceuticals and natural products. For example, the epoxidation of terpenoids has been used as a key step in the synthesis of several natural products with potential medicinal properties, including taxol and artemisinin. The epoxidation of amino acids and their derivatives has also been studied for the synthesis of biologically active compounds and pharmaceutical intermediates.[88,89] The enzymatic synthesis of epoxides has become increasingly popular due to its environmentally friendly nature, offering high regioselectivity and minimal by-product formation. Moreover, the use of hydrogen peroxide (H_2O_2) as a green oxidant and the requirement for mild operating temperatures result in lower energy consumption, making this enzymatic process advantageous.[90] Olefin epoxides are widely used in organic chemistry and can act as intermediates of organic synthesis reactions, as well as organic ingredients in organic synthesis, petrochemical, pharmaceutical, perfume, electronics industry, fine chemical, polymer synthesis materials, and other fields.[91]

Epoxidation reactions offer opportunities for creating novel materials and bioactive compounds. One area of interest is the development of new catalytic systems for selective epoxidation reactions. Selective epoxidation of alkenes and other unsaturated compounds is challenging due to the possibility of over-oxidation or side reactions. However, recent research has shown promising results in the development of new catalytic systems that offer high selectivity and efficiency. As an illustration, novel catalytic systems comprising heterogeneous Ag-TiO_2-SiO_2 composite materials have been synthesized. These materials were employed for the selective epoxidation of cyclohexene using hydrogen peroxide (H_2O_2) as the oxidant. The incorporation of silver (Ag) into the TiO_2-SiO_2 matrix enhances catalytic activity, enabling efficient conversion of cyclohexene to cyclohexene oxide with high selectivity.[92] Additionally, chloro and triflate manganese(II) complexes have been found to have catalytic activity in epoxidation reactions and can be reused as catalytic systems for alkene epoxidation.[93] Recent research has placed emphasis on employing gold (Au) nanoparticles as catalysts for propylene epoxidation using a combination of hydrogen (H_2) and oxygen (O_2). These studies have highlighted the critical roles played by various factors such as catalyst synthesis methods, material support, nanoparticle sizes, and dispersion amounts. Understanding these factors is essential for optimizing the catalytic performance of Au nanoparticles in propylene epoxidation reactions.[94] Recent research has concentrated on developing greener and more energy-efficient processes for alkene epoxidation, aiming to minimize waste generation and energy consumption. These efforts include exploring alternative reaction conditions, such as catalytic systems and environmentally friendly oxidants, to enhance efficiency and sustainability. By reducing waste and energy usage, these advancements contribute to the development of more environmentally friendly chemical processes

with potential applications in various industrial sectors.[95] Organic catalysis for epoxidation using hydrogen peroxide has been investigated, exploring the potential of different organic species to catalyze ethene epoxidation.[96] These developments in catalytic systems for selective epoxidation reactions offer exciting prospects for the synthesis of new materials and bioactive compounds in the future. Epoxidation reactions have potential applications in the field of renewable energy. Epoxidation of vegetable oils and bio-based feedstocks is investigated for synthesizing sustainable polymers. By introducing epoxide groups, functionalized molecules are formed, enabling polymerization into biodegradable materials. This research offers potential for green chemistry advancements and the creation of eco-friendly materials.[97,98] The epoxidation of unsaturated fatty acids can produce epoxy fatty acid methyl esters, which have potential as biofuels.[99] There is an increasing interest in using renewable resources as substitutes for petroleum-based polymers. Much effort has been directed towards developing polymeric materials from vegetable oils as a sustainable alternative. Research has focused on finding a straightforward, cost-effective method of epoxidation suitable for industrial applications.[97]

Advantages and disadvantages of epoxidation

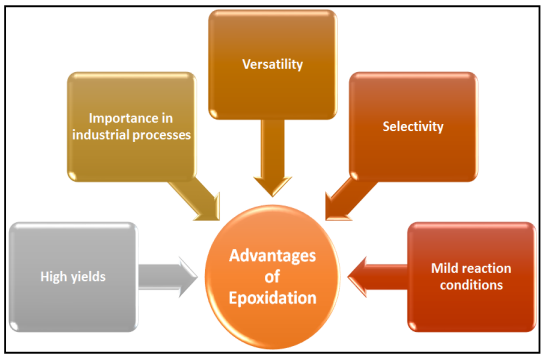

Fig. 15. Advantages of Epoxidation Reaction

Epoxidation is a widely utilized reaction in various fields of chemistry, including organic synthesis, polymer chemistry, and medicinal chemistry. Like any other chemical reaction, there are both advantages and disadvantages associated with the use of epoxidation reactions.

Advantages

Versatality

Epoxidation reactions are versatile and can be used to synthesize a wide range of epoxides, which have numerous applications in various fields of chemistry.[100–103] For example, epoxidation reactions can be used in green-chemical aqueous phase synthesis and environmental remediation.[100] Vanadium complexes can be used as catalysts in epoxidation reactions, and non-conventional solvents can be used as reaction media.[101] Cytochrome P450 enzymes can catalyze both hydroxylation and epoxidation reactions, and protein engineering can enhance catalysis.[102] Epoxidation reactions can also be used in electrocatalysis, such as in the selective electrocatalytic cyclooctene epoxidation.[104] Mesoporous phenolic resins can be used as catalysts in asymmetric epoxidation and aldol reactions.[103]

Selectivity

Epoxidation reactions can be highly selective, meaning that it is possible to selectively epoxidize one or more double bonds in a molecule. This selectivity can be achieved through careful choice of the oxidizing agent and reaction conditions. For example, Nb-EISA catalysts with relatively low Nb loadings have been shown to exhibit exceptional propylene epoxidation performance with H_2O_2 as oxidant, with nearly total propylene oxide selectivity (>99%) and high productivity.[105] Similarly, manganese(III) tetraphenylporphyrin encapsulated by ion-modified hexagonal mesoporous silica has been shown to exhibit enhanced epoxidation selectivity.[106] In the context of ethylene epoxidation, studies have demonstrated that Ag-Cu alloy catalysts exhibit higher selectivity towards ethylene oxide in comparison to pure Ag catalysts. The selectivity is primarily governed by the relative strength of the metal-carbon versus metal-oxygen bonds, indicating the crucial role of alloy composition in dictating catalytic performance. These findings underscore the importance of understanding the intricate interplay between catalyst structure and activity in ethylene epoxidation reactions.[107]

Mild reaction conditions

Epoxidation reactions are applicable to a broad spectrum of substrates due to their ability to occur under relatively mild conditions.[108–112] For example, intercalated catalysts have been developed for the epoxidation of allylic alcohols under mild and solvent-free conditions.[109] Oxido-molybdenum(V) complexes have been employed as catalysts for the selective epoxidation of a variety

of olefins. These complexes have demonstrated high turnover frequencies (TOF values) in a solvent mixture of CH_3CN/H_2O, where hydrogen peroxide serves as a green oxidant and $NaHCO_3$ acts as a promoter. [108] Mesoporous niobium oxyhydroxide catalysts have been synthesized for the epoxidation of cyclohexene under mild reaction conditions.[110] Acidic three-liquid-phase microemulsion systems have also been designed for epoxidation reactions under mild conditions.[112]

High yields

Epoxidation reactions can yield high amounts of the desired product when performed under optimized conditions, making them a cost-effective synthetic strategy. As an illustration, a designed peroxygenase enzyme successfully attained high conversions (up to 98%), excellent enantioselectivity (up to 98% ee), and satisfactory product yields (ranging from 50% to 80%) in enantiocomplementary epoxidations of different α,β-unsaturated aldehydes.[113] Oxido-molybdenum corroles were employed as reliable catalysts for the selective epoxidation of diverse olefins, achieving high turnover frequencies (TOF values of 2066-3287 h^{-1}) and good yields.[108] Carbonyl-stabilized ammonium ylide-mediated epoxidation reactions were also found to achieve high enantioselectivities and high yields.[114] Further investigations have documented remarkable activity in the epoxidation of olefins utilizing nanocrystalline zirconosilicate catalysts.[115] Additionally, high yields (up to 100%) and exceptional enantioselectivities (up to 99% ee) were achieved using bis-amino-bis-pyridine manganese complexes.[116]

Importance in industrial processes

Epoxides have numerous industrial applications, including their use as solvents, adhesives, and plastics. Epoxidation reactions are therefore important for the synthesis of these compounds.[117–119] For example, epoxides can be used to create carboxylic acid-modified epoxides from natural oils, which can be used as food preservatives, coating materials, and anti-corrosion coatings.[119] Epoxides can also be used to create cyclic carbonates, which have several industrial applications, including as ink binders and for imparting water repellency.[120,121] The synthesis of cyclic carbonates using MCM-41 supported dual imidazolium ionic liquids catalysts is a promising method for industrial applications.[120]

Disadvantages

Toxicity of oxidizing agents

Oxidizing agents used in epoxidation reactions, such as m-chloroperbenzoic acid (m-CPBA) and peracids, can be toxic and hazardous to handle[122,123] Oxidative stress is a frequently observed mechanism in the toxicology of environmental agents, uniting the effects of various classes of toxic substances with diverse physicochemical properties.[124] Most oxidizing agents are toxic by ingestion, and the degree of toxicity varies widely[122] Chromium(VI) compounds and the residual chromium after the reaction are highly toxic, requiring careful handling or disposal due to their toxicity.[123] Chromium in all oxidation states has been identified as carcinogenic.[125,126]

Potential for over-oxidation

Epoxidation reactions have the potential for over-oxidation, which can lead to the formation of unwanted byproducts. For example, the over-oxidation of epoxides to diols or the formation of sulfones instead of sulfoxides can occur.[127–130] However, recent advances in epoxidation methods have been developed to minimize waste generation and energy consumption, which could provide sustainability in terms of environmental impact and energy consumption.[95]

Side reactions

Epoxidation reactions are susceptible to side reactions, including the generation of diols or other oxygen-containing functional groups. In the epoxidation of soybean oil, a significant side reaction is the epoxide ring opening reaction (ROR), which consistently diminishes the selectivity to epoxidized soybean oil (ESBO). This reaction is crucial for the production of polyols and lubricants.[131] Nevertheless, research into the epoxidation of soybean oil in toluene using peroxoacetic and peroxoformic acids revealed minimal occurrence of side reactions. This was evidenced by the absence of an OH band in the IR spectra, the formation of less than 2% of higher molecular weight products observed in gel permeation chromatography, and selectivity values ranging between 0.9 and 1.[132] Recent developments in greener and energy-efficient alkene epoxidation processes aim to minimize waste generation and energy consumption, which could significantly reduce both operational costs and greenhouse gas

emissions. These advancements focus on improving the efficiency of epoxide synthesis through various methods, as discussed in a recent review paper.[95]

Limitations for certain substrates

Epoxidation reactions may not be suitable for certain substrates, such as highly sterically hindered or functionalized alkenes, which may not undergo epoxidation selectively or efficiently.[133,134] However, recent advances in epoxidation methods have been developed to minimize waste generation and energy consumption, which could provide sustainability in terms of environmental impact and energy consumption.[95] For example, $He+O_2$ plasma can drive the epoxidation of alkenes in solution, generating epoxides without oxidant waste-streams, running at room temperature and atmospheric pressure, and requiring no catalyst.[135]

Environmental concerns

The use of traditional oxidizing agents in epoxidation reactions can be environmentally damaging due to potential hazardous waste disposal and pollution. There are several alternative methods that have been developed to minimize waste generation and energy consumption, including the use of eco-friendly oxidants such as molecular oxygen and hydrogen peroxide, which produce water as the only by-product.[95,136,137] Furthermore, recent advancements in energy-efficient methods for epoxidation have emerged, including continuous flow chemistry, reactive distillation, microwave-assisted synthesis, microreactors, and sonochemical techniques.[95]

In conclusion, epoxidation reactions have many advantages, including their versatility and ability to produce highly useful bulk and fine chemicals. However, there are also some drawbacks to consider when selecting a synthetic strategy. These include toxicity, side reactions, and environmental concerns. For instance, one main drawback of fatty acid epoxidation is the potential formation of peroxy fatty acids when carboxyl groups react with hydrogen peroxide.[138] Developing greener and more sustainable epoxidation methods, such as alternative oxidizing agents and catalytic systems, can address some of these drawbacks and promote the continued use of epoxidation reactions in chemistry. For instance, the use of titanisilicate epoxidation catalysts has been proposed as a way to overcome some of the challenges associated with traditional epoxidation methods.[139] Additionally, continuous flow epoxidation of alkenes using a heterogeneous catalyst has been developed as a more efficient and sustainable method.[140] Thermochemical studies have also been conducted to better understand the reactivity of epoxides and related compounds.[141] Overall, it's important to weigh the advantages and disadvantages of epoxidation reactions and consider developing more sustainable methods to address the drawbacks.

CONCLUSION

In conclusion, this article provides a comprehensive overview of epoxidation reactions, covering the various types of reactions, reagents used, applications, advantages, and disadvantages associated with this important class of reactions. It also highlights recent advances in greener and more sustainable methods and their potential for future applications in various fields of chemistry.

The article offers valuable insights into the mechanisms involved in epoxidation reactions and their importance in organic synthesis, polymer chemistry, and medicinal chemistry. The examples of pharmaceutical compounds and natural products synthesized using epoxidation reactions demonstrate the significant impact of this class of reactions on drug discovery and development.

The information on green chemistry and catalysis provides an exciting opportunity for the development of novel and more sustainable methods, promoting the continued use of epoxidation reactions in various fields of chemistry. The potential for further research and application in this area is significant, making this article a valuable resource for researchers and students interested in exploring new synthetic strategies.

In summary, this article offers a comprehensive understanding of epoxidation reactions and their applications, highlighting their importance and potential for future development. It is an essential resource for both academia and industry, providing valuable insights for researchers and students interested in this important area of chemistry.

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Conflicts of interest

The research and its findings are driven solely by scientific merit and unwavering integrity, with no competing interests influencing the work.

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