

ORGANIC SYNTHESIS WITH DIOXIRANES

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Organic Synthesis with Dioxiranes

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FOREWORD

Dioxiranes are three-membered heterocyclic organic peroxides that serve as versatile oxygenation reagents. Their multifaceted applications enhance their utility in various chemical processes. Dioxiranes are primarily accessed by the oxygenation of carbonyl compounds using oxidants like Oxone® and H₂O₂; the latter are inexpensive and offer methods of green oxidation. Since the first dioxirane was synthesized by Talbott and Thompson in 1972, dioxiranes with advanced structures have been developed and explored either stoichiometrically or catalytically (*in situ*) for numerous organic transformations. The book collates all aspects of dioxirane chemistry, including historical developments, characterizations, reaction mechanisms, and different applications of the reagent explored over the last five decades, and will be highly relevant at times, when eco-friendly and environmentally benign green methods of chemical transformations are gaining widespread attention. The book will be highly informative for the scientific community looking for material development using green protocols and green organic transformations, and will provide them with a glimpse of what has already been done using the reagent and what possibilities can be explored in this area. Thus, the book will be useful for a wider scientific community

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PREFACE

Dioxiranes are multitasking agents capable of several types of transformation, both in stoichiometric and catalytic amounts. The dioxiranes are prepared from the reaction of a ketone with caroate (a salt of Caro's acid). While the residue of caroate is considered eco-friendly, acetone and natural carbohydrate-derived-ketones are also environmentally benign. The contemporary use/development of synthetic methodologies is focused on inexpensive, user-friendly and eco-friendly protocols. The United Nations (UN) Sustainable Development Goals (SDGs) are focused on making our environment pollution-free and healthy for all living beings. Organic synthesis has become an important tool to access a myriad of compounds for the material world in application to medicines, food, cosmetics, fertilizers, organic light-emitting diodes, organic solar cells, *etc.*

In this book, our effort is to consolidate and deliver a comprehensive overview of the chemistry of dioxiranes. The research on dioxirane over more than five decades has been collated with more than 400 references. The discovery, characterization, and isolation of dioxiranes are illustrated. The mechanistic aspects are included wherever necessary. The peroxy-linkage present in dioxiranes makes them an excellent oxygen donor, i.e., oxygenation agent. Although these were proposed earlier by Baeyer and Villiger, the first-time synthesis was achieved in 1972. Afterward, different types of efficient dioxiranes have been prepared with higher reactivity and selectivities to tune this peroxy-linkage. In addition, heteroatom dioxirane, where the C-atom of the dioxirane ring is replaced with a heteroatom like N, P, S, Si, *etc.*

The application of dioxirane is very vast, for example, the dioxirane-mediated oxidations have been performed for a variety of functional groups such as amines, anilines, isocyanate, sulfides, thiols, disulfides, thioketones, sulfilimines, selenoesters, alcohols, phenols, boronic acids, boronates, iodo-compounds, phosphines and silane compounds, *etc.*; the products have a myriad of applications. Similarly, epoxidations of various olefins, like alkenes and alkynes, are achieved with dioxiranes. Notably, regioselective, stereoselective, chemoselective, *etc.*, types of epoxidations of alkenes are performed with dioxiranes. The asymmetric Shi epoxidation using catalytic chiral dioxirane precatalysts is included in the book. The epoxidation protocols applicable for the synthesis of biologically-relevant and natural products, like metabolites of Aflatoxin B1, Majucinoids, tetrahydrocannabinol, and pectenotoxins, are discussed. Furthermore, C-H functionalizations of unactivated centers with dioxiranes are covered. C-H oxygenations of primary, secondary and tertiary C-H bonds are successfully performed with dioxiranes. It is noteworthy to mention that the oxygenation of carbohydrates, amino acids, steroids and lipids is achievable with dioxiranes. Supramolecular hosts like α -, β - and γ -cyclodextrins (CDs), were used for site-selective hydroxylation. When a latent ketone chain is present on the substrate, intramolecular hydroxylation, oxygenation-cum-cyclization, and oxygenation-cum-lactonization can give synthetically useful compounds. Biologically relevant compounds like carbohydrates, ent-trachylobane, Eldecalcitol, bryostatin, Taxol[®], thujone, (+)-menthol, eudesmane, Spirochensilide A, Valinomycin, dafachronic acid, *etc.*, were accessed using dioxiranes and are included in the book. The chiral precatalysts are useful for reactions involving asymmetrizations, kinetic resolutions, asymmetric and desymmetrizations.

With this book, we aim to bridge the laboratory research and industrial needs. Therefore, a special emphasis is made on the sustainable chemistry aspect and the synthesis of natural products and drugs. The book will therefore be useful to both beginners and experts in the field of organic chemistry.

We believe this book will serve as an important and useful resource in promoting future applications and innovations in the field of dioxirane chemistry. We thankfully acknowledge all the contributions of those chemists cited for their research in the field.

We are thankful to **Aslam C. Shaikh**, Department of Chemistry, IIT Ropar, for his humble support during book writing. We used ChemDraw 21.0.0 to draw all reactions and several structures in this book, which was very helpful.

We acknowledge the facility and infrastructure of IISER Thiruvananthapuram and CSIR-NIIST, which were very useful for preparing the book.

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Dedication

Dedicated to Professor Alex M. Szpilman

CHAPTER 1

Introduction to Dioxirane Chemistry

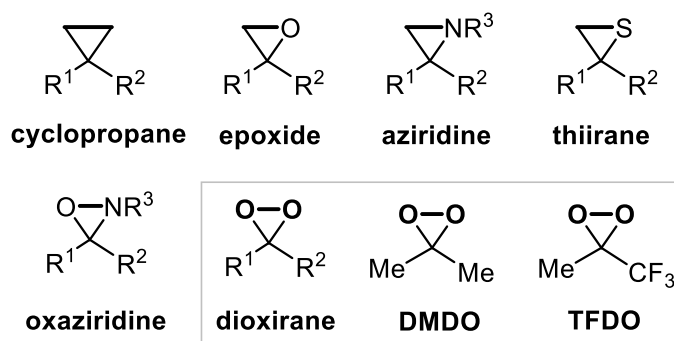
Abstract: The three-membered heterocyclic dioxiranes are organic peroxides bearing two oxygen atoms and a carbon atom. Here, the peroxy group is responsible for the oxygenation attributes. The species was initially proposed as an intermediate in the late 19th century by Baeyer and Villiger, but the establishment of the purported species was experimentally discarded. Nevertheless, a dioxirane derivative was first synthesized in 1972. Afterward, several dioxirane derivatives have been synthesized and explored for a wide range of transformations. These species are either obtained as a reagent solution or catalytically generated *in situ* from the oxidation of a ketone with an inexpensive, environmentally-benign, and user-friendly oxidant like KHSO₅ or H₂O₂. It is worth mentioning that dioxiranes are highly reactive; therefore, the storing the oxidant is difficult. A very low temperature is required for storage. On the other hand, when the dioxirane catalyst is generated *in situ*, the reaction is very pH-sensitive and generally requires a buffer solution. Several dioxiranes are prepared stoichiometrically as a solution or *in situ* generated as catalysts and successfully employed for oxidation. Several chiral ketones are also employed for the *in situ* generation of dioxiranes. Notably, when the scientific community is in search of inexpensive and sustainable synthetic protocols, dioxirane is projected as a suitable candidate.

Keywords: Dioxirane, Dimethyl Dioxirane (DMDO), Oxidation, Organic peroxide, Sustainable chemistry, Trifluoromethyl Dioxirane (TFDO).

INTRODUCTION

Dioxiranes are three-membered heterocyclic compounds bearing two oxygen atoms and a carbon atom [1]. Structurally, dioxiranes are isomeric or have a similar molecular formula to that of carbonyl oxides. Dioxirane (Scheme 1.1), which is an organic peroxide (*vide infra*), is a remarkable oxygen-transfer reagent. This oxidant has attracted the scientific community due to its mild reactivity, high selectivity, ease of access, and eco-friendly attributes. Dioxirane is employed in stoichiometric amounts rather than as a catalyst (*in situ*). Several oxidation reactions are performed to prepare oxygenated compounds; the types of reactions include oxidation of alcohols and sulfides, epoxidations, C–H oxygenation, etc [2]. Oxidation reactions are performed using transition metal-based oxidants/catalysts; as an alternative, dioxirane-mediated oxygen-transfer reactions are preferred, considering their eco-friendly attributes.

Several heterocyclic compounds featuring three-membered rings have been reported. For example, cyclopropane is a carbocyclic derivative, whereas epoxide, aziridine, thiirane, dioxirane, and oxaziridine are heterocyclic analogs [3]. These compounds are planar because any three points determine a plane. These compounds with bent bonds are highly strained due to the smaller internal cyclic bond angles ($\sim 60^\circ$) compared to the tetrahedral bond angle (109.5°) for sp^3 -hybridizations [4]. Therefore, the compounds are reported to be reactive. Except for dioxirane and oxaziridine, which have ring-opening properties, the other three-membered compounds are generally explored as 1,2-synthons in organic synthesis. On the other hand, dioxirane and oxaziridine exhibit oxygen-transfer properties.

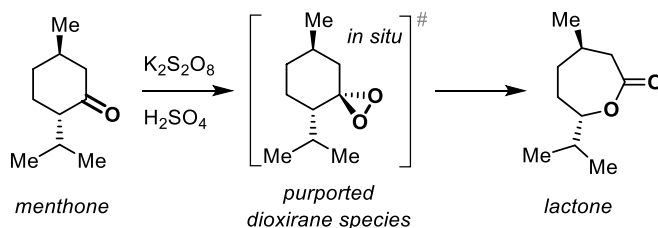


Scheme 1.1. Some examples of three-membered carbocyclic and heterocyclic compounds.

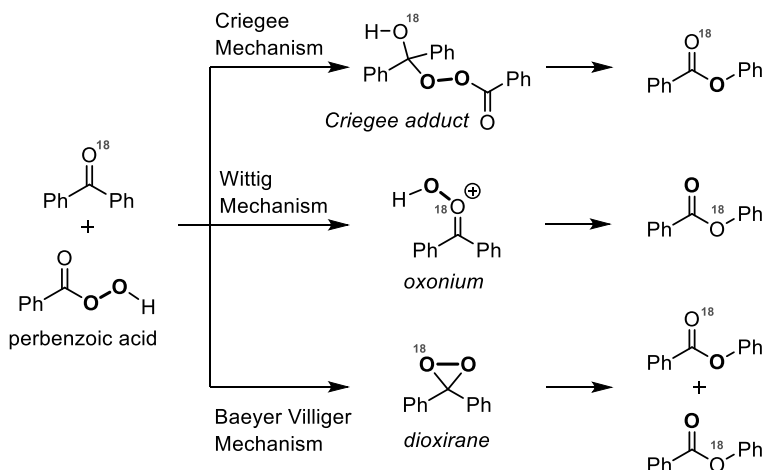
Dimethyl dioxirane (DMDO, *Vide supra*) is the most well-known dioxirane developed by Murray; it is also known as Murray's reagent. DMDO is prepared from acetone and Oxone[®] (a triple salt of Caro's acid, $\text{KHSO}_5 \cdot \text{K}_2\text{SO}_4 \cdot \text{KHSO}_4$) [5, 6]. In syntheses involving DMDO reagent, the by-product is acetone, which is environmentally benign [7]. On the other hand, the catalytic protocol uses Oxone[®], which is considered both inexpensive and eco-friendly. Therefore, the DMDO-mediated protocols are sustainable and inexpensive. Another important dioxirane is methyl(trifluoromethyl)-dioxirane (TFDO) [8]. It is prepared from the reaction of methyl(trifluoromethyl)ketone and Oxone[®]. Among all dioxiranes, TFDO is reported to be the most reactive [9]. Another co-oxidant, *i.e.*, H_2O_2 , is also employed for the generation of dioxirane precatalysts from ketones [10].

The possibility of acyclic peroxides, like dioxirane, was first proposed by Baeyer and Villiger for the formation of lactone from the $\text{K}_2\text{S}_2\text{O}_8$ -mediated oxidation of menthone (Scheme 1.2) [11]. This transformation is known as Baeyer-Villiger Oxidation (BVO) [12]. The dioxirane intermediacy was ruled out and a different mechanism involving a Criegee intermediate for the oxidation of benzophenone with perbenzoic acid was proposed (Scheme 1.3) [13]. This mechanism was

supported by ^{18}O -labeled experiments, where the ^{18}O -labeled-carbonyl-derived benzophenone was treated with perbenzoic acid, and phenyl benzoate with ^{18}O -labeled carbonyl was obtained exclusively. Further, the reduction of ^{18}O -phenylbenzoate produced benzyl alcohol enriched with ^{18}O . This observation ruled out the Wittig and dioxirane mechanisms, as these reactions produce phenyl benzoate with ^{18}O -labeled ether in 50% (in 1:1 molar ratio) and 100% (only one product) yields, respectively.



Scheme 1.2. The Baeyer-Villiger oxidation of menthone.



Scheme 1.3. Mechanistic investigation of BVO using ^{18}O -labeling experiments.

Synthesis and Characterizations of Dioxiranes

The first dioxirane species, *i.e.*, fluorous dioxirane, was prepared by treating the dialkoxylithium salt with gaseous fluorine (Scheme 1.4) [14, 15]. The mass spectrometric detection of methylene peroxide from the reaction of ozone (O_3) and ethylene at -190°C was observed; the reaction is reported to be highly unstable. [16] The existence of dioxirane was further supported by *ab initio* calculations and microwave spectroscopy [17 - 21].

Oxidation with Dioxiranes

Abstract: Oxidation reaction is a fundamental method in several natural processes. They are defined as the removal of electrons and hydrogen atoms or the addition of oxygen atoms. In this chapter, ioxiranes are employed as reagents and/or catalysts for the oxidation of several functional groups containing heteroatoms like O, N, S, P, Si, Se, and transition metals. In brief, alcohols and aldehydes are oxidized to carbonyl compounds with higher oxidation states. The nitrogen-containing compounds can be amines, anilines, isocyanates, *etc.*, which are oxidized to give a variety of products like nitro derivatives, diazo compounds, hydroxylamines, nitroxides, lactams, *etc.* The sulfides, thiols, disulfides, thioketones, and sulfilimines give access to sulfoxides, sulfones, sulfoximines, thioketone-S-oxides, thiosulfinates, *etc.* Selenoesters are oxidized to prepare selenic acid and selenonate. Alcohols and phenols are prepared from the reaction of boronic acids and boronates with dioxiranes. Iodo-compounds are being oxidized with dioxiranes to prepare hypervalent iodine compounds, which have several applications in organic synthesis. Phosphines and silane compounds have been oxidized successfully with dioxiranes. Several transition metal atoms in metal complexes can be oxidized using dioxiranes. The detailed study of dioxirane-mediated oxidation is collated in this chapter.

Keywords: Alcohol oxidation, N-containing compounds, Phosphorus oxidation, Sulfide oxidation, Selenide oxidation, Silane oxidation.

INTRODUCTION

Oxidation is defined as the addition of oxygen, loss of electrons, and/or increase in the oxidation state/number. For inorganic reactions, oxidation is defined as the loss of electron(s) and an increase in the oxidation number; here, the oxidation state is assumed to be an integer. However, for organic reactions, although the general concept of oxidation is applicable, visualizing it is not so easy. The oxidation states of atoms in inorganic compounds are well-defined, but the non-integer oxidation states [1] for organic compounds with covalent bonds are quite different. As electrons are generally shared between atoms in organic compounds, direct electron transfer in oxidation reactions is mechanistically not considered for all. For example, the oxidation state of the carbon atom of CH_4 is +4, whereas organic compounds like propane and butane have fractional oxidation numbers, *i.e.*, +2.67 and +2.5, respectively [2]. For such compounds with different types

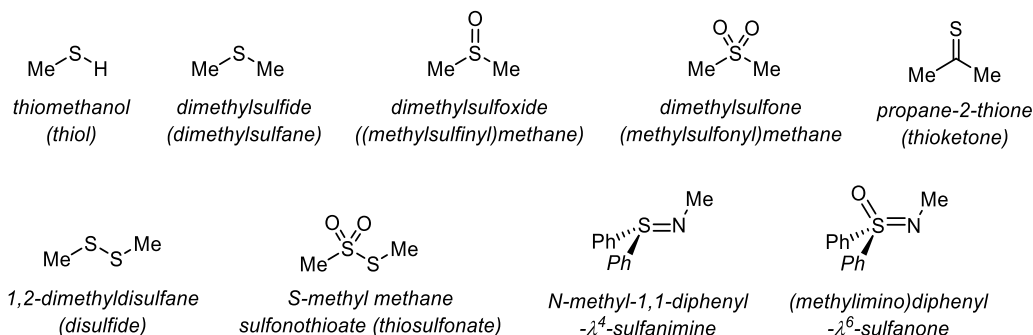
of carbons, atoms are individually assigned on the basis of the neighboring atoms with which they are bonded. Because organic molecules contain different functional groups and carbon atoms in a chain, they can have multiple oxidation states. To simplify the oxidation number, different functional groups are denoted by oxidation levels, from alkane, alcohol, and aldehyde to carboxylic acid level [1, 2]; the opposite corresponds to the reduction level. For example, the reaction involving alcohol to aldehyde is oxidation, and the reverse is reduction. On the other hand, the conversion of any compound to another of the same kind is neither oxidation nor reduction.

In this chapter, we will discuss the oxidation of organic compounds with dioxirane, an oxygenating agent. Thus, the addition of oxygen to different atoms in a molecule is oxidation. Nevertheless, in some cases, such as the oxidation reactions of alcohols and amines to carbonyls and imines, respectively, dehydrogenation is involved. Epoxidation and C-oxygenation will be discussed separately in Chapters 3 and 4.

Oxidation of Sulfur-Containing Compounds

Depending on the bonds around the sulfur atom, the respective functional groups can be named sulfide, thiol, sulfoxide, sulfonic acid, disulfide, sulfone, sulfilimine, thioketone, thiosulfonate, *etc.* (Scheme 2.1) [3, 4]. The sulfur atom can have different oxidation states from -2 to +6 [3, 5]. The λ -notation was introduced by IUPAC to denote the hypervalent atom in a compound with an expanded octet, although the convention of hypervalency is still under debate [6, 7]. The sulfoxides and sulfanimines are λ^4 -sulfanes, whereas the sulfone and sulfanone derivatives are λ^6 -sulfanes. In these two cases, assuming the bonds to be purely covalent, the valence shell electrons for the S-atoms with four and six bonds become 10 and 12 for λ^4 - and λ^6 -sulfanes, respectively. It deviates from the octet rule. Other hypervalent compounds with iodine, phosphorus, and selenides will also be discussed later in this chapter.

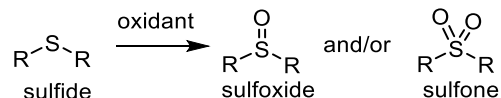
The sulfur-containing compounds have several agricultural [8, 9], pharmaceutical [10 - 14], and synthetic [11] applications, and are also found in natural products [12, 15]. As shown in Scheme 2.1, the sulfur atoms in these derivatives are bonded to different atoms and do not have similar oxidation levels. To raise the oxidation state of the S-atom, oxidation from a lower to a higher state is achieved using dioxirane. The oxidation of different S-containing compounds with dioxiranes has been categorized, and the compounds involved, either as substrates or products of the dioxirane-mediated oxidation chemistry, are discussed below.



Scheme 2.1. Examples of compounds with S-containing functional groups.

Oxidation of Sulfides to Sulfoxides and Sulfones

Oxygenation of sulfides produces sulfoxides and sulfones, which have widespread applications in the preparation of organic functional materials [16 - 18]. The oxidation of sulfide can generate both sulfoxide and sulfone, where sulfone is an over-oxidation product of sulfoxide (Scheme 2.2). Therefore, a protocol that chemoselectively produces either sulfoxide or sulfone is necessary. For sulfoxide preparation, a milder protocol is required to prevent its overoxidation to sulfone.



Scheme 2.2. A schematic diagram illustrating the oxidation of sulfides.

Several protocols have been reported to perform sulphide-to-sulfoxide transformation, *e.g.*, Rh- BuO_2H [19], Ti-hydroperoxide-Zeolite [20], *m*CPBA [21], hypervalent iodine I(III) [22] and I(V) [23 - 26], Oxone[®] [27], H_2O_2 as a terminal oxidant with W-catalyst [28], and 1,3,5-triazo-2,4,6-triphosphor-2,2,4,4,6,6-tetrachloride (TAPC) [29]. The reaction has also been achieved photochemically using O_2 in the presence of dye-sensitized TiO_2 [30], $\text{Bi}_4\text{O}_5\text{Br}_2$ [31] and Uranyl [32], molecular oxygen [33], metal organic-frameworks (MOFs) [34], *etc.* It is noteworthy to mention that contemporary research is focused on sustainable chemistry to develop synthetic protocols that avoid the use/generation of hazardous chemicals/by-products. In this aspect, the dioxirane-mediated protocols, with stoichiometric dioxirane or a ketone precatalyst/co-oxidant Oxone[®], have attracted the attention of the scientific community.

CHAPTER 3

Epoxidation of Olefins and Arenes with Dioxiranes

Abstract: Epoxides are important 1,2-synthons in organic synthesis, and are generally accessed through epoxidation of alkenes. In this case, generally, an unsaturated bond undergoes oxygenation, where a pi-bond with side-overlap of p-orbitals (sp^2 -hybridization) is cleaved, and two new sigma bonds (sp^3 -hybridization) are formed with the O-atom. In this chapter, the epoxidation of various olefins, like alkenes and alkynes, will be discussed. For alkenes, the different types of epoxidation, like regioselective, stereoselective, chemoselective, *etc.*, are discussed. The reactions of special types of alkenes, such as aromatic systems, Buckminsterfullerene, allenes, cumulenes, *etc.*, with dioxiranes are illustrated with suitable examples. Epoxidation can be achieved both stoichiometrically and catalytically. For asymmetric applications, catalytic dioxirane precatalysts are developed. One of the famous examples is Shi epoxidation, where a D-glucose-based precatalyst is employed for the *in situ* generation of a chiral dioxirane catalyst. Many additional chiral catalysts have been reported, and the application of some of them will be covered here. In addition, the non-chiral precatalysts are also explored for the oxygenation of various chiral compounds. The applications are too vast, and the reactions involving dioxiranes for the synthesis of biologically relevant and natural products, like metabolites of Aflatoxin B1, Majucinoids, tetrahydrocannabinol, and pectenotoxins, are emphasized.

Keywords: Chemoselectivity, Epoxidation, Oxirane, Stereoselectivity, Shi epoxidation.

INTRODUCTION

Epoxidation is a fundamental reaction in organic chemistry that converts an olefin to a three-membered oxirane. Depending on the reaction conditions, the oxirane (a 1,2-synthon) can be further converted to different kinds of ring-opened products. In addition, the epoxidation of an alkene can produce up to two stereogenic centers. [1, 2] Epoxidation reactions are therefore very important transformations in organicsynthesis, which can be performed with catalytic or stoichiometric use of the oxi

dant [1, 3, 4]. Several methods have been reported for the epoxidation of olefins, such as Prilezhaev epoxidation with *m*CPBA [5], Julia-Colona epoxidations with NaOH and H₂O₂ [6], Jacobson-Katsuki epoxidation with NaOCl and Mn-salen [7],

Sharpless epoxidation with $\text{Ti}(\text{O}^i\text{Pr})_4$ [8], *etc.* Nevertheless, dioxiranes are extensively employed for epoxidations, both catalytically and stoichiometrically [9]. Several methods have been reported, and Shi epoxidation is one of the famous asymmetric transformations employed for the preparation of chiral epoxides from alkenes. Epoxidation reactions are categorized into different kinds, such as stereoselective, regioselective, enantioselective, diastereoselective, *etc.* In addition, the epoxidation of arenes, alkynes, allenes, and cumulenes will also be discussed briefly.

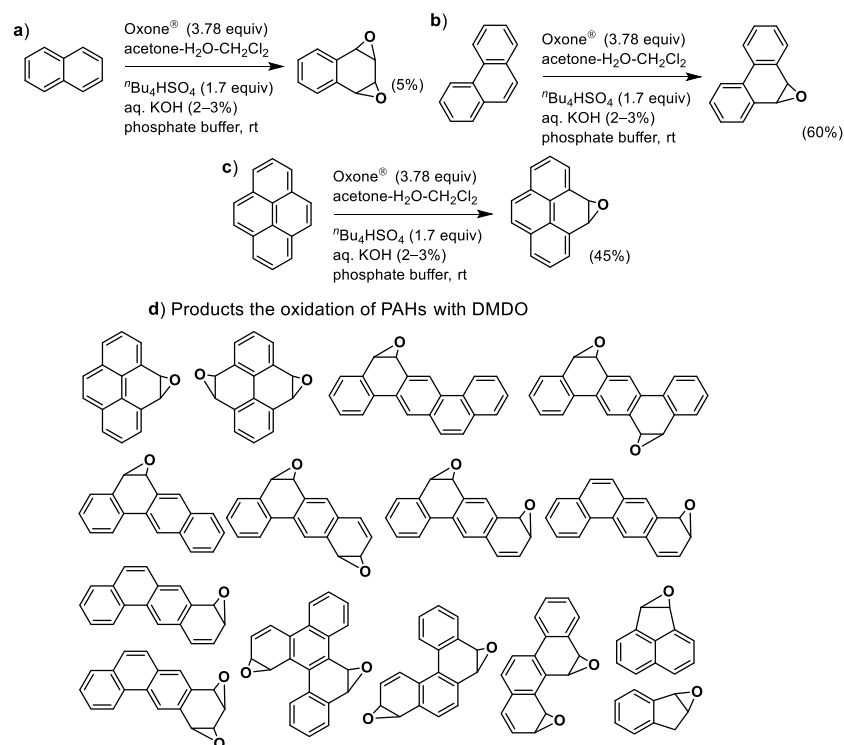
Epoxidation of Arenes

Aromatic compounds have unsaturated bonds with higher stabilities than isolated olefins. These unsaturated bonds undergo epoxidation when treated with dioxiranes. In addition, the fullerenes are also produced as epoxides. The details are discussed below:

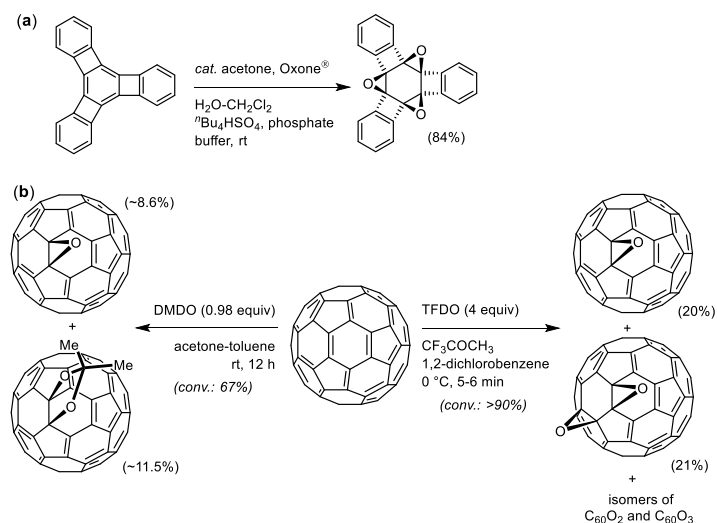
Epoxidation of Aromatic Compounds

The metabolism of polycyclic aromatic hydrocarbons in mammalian systems begins with epoxidation, producing a *monoepoxide* [10]. In organic synthesis, the oxidation of polyaromatic compounds like naphthalene, phenanthrene, pyrene, and anthracene generally produces quinones, lactones, and ring-opened acids [11 - 13]. While the reaction of anthracene with *in situ*-generated DMDO produced 9,10-anthraquinone, epoxides were formed for the oxidation of naphthalene, pyrene, and phenanthrene (Scheme 3.1a–c) [14]. Similarly, the reaction of polyaromatic compounds with the DMDO reagent yielded several epoxides (Scheme 3.1d) [15 - 17]. Similar to the DMDO reagent, TFDO was found to oxidize naphthalene, phenanthrene, and pyrene, and the epoxidation products were obtained in 98, 96, and 10% yields, respectively [18]. Based on NMR and EPR monitoring studies, the mechanism was proposed to proceed through radical pathways [19 - 21].

Using an *in situ*-generated DMDO catalyst, triepoxidation of *tris*(benzocyclobutadieno)cyclo-hexatriene was performed [14], and the reaction yielded triepoxide in 84% yield (Scheme 3.2a) [22].



Scheme 3.1. DMDO-mediated epoxidation of PAHs under (a–c) catalytic conditions and (d) examples of epoxides isolated under stoichiometric conditions.



Scheme 3.2. (a) Synthesis of cyclohexatriene-triepoxy using DMDO catalyst and (b) epoxidations of fullerene using DMDO and TFDO.

CHAPTER 4

C–H Oxygenation with Dioxiranes

Abstract: C–H oxygenation is an important transformation for the functionalization of unactivated centers. Using dioxirane precatalysts and reagents, C–H bond hydroxylation/oxygenation is successfully achieved. For example, methanol is prepared from methane, which is a very important transformation. The primary, secondary, and tertiary C–H bonds are successfully oxygenated with dioxiranes. Here, the tertiary C–H bonds are found to be more reactive towards oxygenation using dioxirane species. Further, the oxygenation of carbohydrates, amino acids, steroids, and lipids is easily done with dioxiranes. Notably, primary and secondary alcohols formed from the C–H bond oxygenation of primary and secondary alkenes, respectively, can be further oxidized to carbonyl compounds. However, the reactions can be successfully stopped at the *mono*-oxygenation stage using triflic anhydrides, which produce protected alcohols with triflic groups. Furthermore, in the presence of supramolecular hosts like α -, β -, and γ -cyclodextrins (CDs), site-selective hydroxylation can be done. For example, site-selective hydroxylation is achieved with dioxirane in a regio-selective manner for cyclohexanes and *cis*- and *trans*-decalin derivatives. With a latent ketone group present on the substrate, under oxidation conditions, intramolecular hydroxylation, oxygenation-*cum*-cyclization, and oxygenation-*cum*-lactonization can be performed. In some cases, oxygenation is preferred for secondary C–H bonds over tertiary cases, where the δ -position of the C–H bond to the carbonyl group plays a crucial role. The C–H bond hydroxylation/oxygenation with dioxirane is applicable for the synthesis/functionalization of biologically relevant compounds like carbohydrates, *ent*-trachylobane, Eldecalcitol, bryostatin, Taxol[®], thujone, (+)-menthol, eudesmane, Spirochensilide A, Valinomycin, dafachronic acid, *etc.*

Keywords: C–H activation, C–H oxygenation, C–H hydroxylation, Chemoselectivity, Lactonization.

INTRODUCTION

Recent years have observed steady progress in the development of synthetic protocols *via* C–H activation [1, 2]. These advances have enabled the formation of diverse bonds, such as C–C, C–O, C–N, and C–S, making this approach highly valuable for the synthesis of new compounds. The reactions are quite applicable, as the methodologies are applied largely in a catalytic fashion using transition metals like Cu, Pd, Ru, Ni, Fe, Ir, *etc.* [3 - 5]. It is worth mentioning that the

protocol generally requires a directing group that allows C–H activation by metal stabilization. One of the very common and classical examples of C–H activation is the *ortho*-lithiation procedure. Here, on an anisole ring, the *ortho*-H to the methoxy group is abstracted by lithium, and the lithium-ion is stabilized by coordinating with the O-atom of the methoxy group. Then, this nucleophilic center can be used for coupling with an electrophile. In this chapter, dioxirane-mediated C-oxygenation will be covered briefly. It includes a variety of C–H activations and/or C-oxygenations for aliphatic, benzyl, and aromatic systems [6, 7]. At large, the installation of new C–O is very important, because many medicines contain O, S, and N heteroatoms. For example, around 75% of the chiral heterocyclic drugs approved by the Food and Drug Administration (FDA) contain at least one O-atom [8]. This chapter discusses the application of dioxiranes in C-oxygenation for the synthesis of several natural product derivatives. In addition, in the presence of a latent ketone chain on the substrate, it can be converted *in situ* into a dioxirane species, which then produces an intramolecular C-oxygenation product.

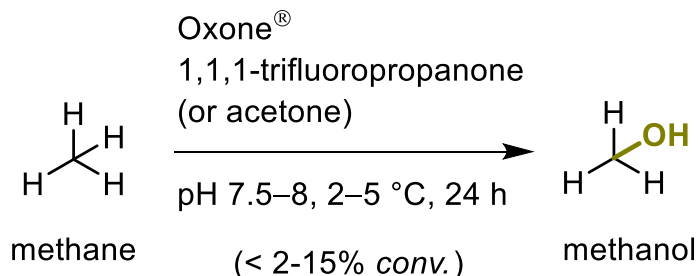
C–H Hydroxylations

Alkanes are quite stable, and their functionalization often requires harsh conditions. Although difficult, the C–H oxygen insertion of an alkane is known to be achieved with TFDO [9]. The reactivities of various types of C–H bonds towards this dioxirane-mediated oxygenation were different, and the reactivity order noted was tertiary $\approx$ benzhydrylic $>$ R-cyclopropyl $>$ benzylic $\approx$ secondary $>$ primary [10]. It implies that tertiary C–H is very reactive compared to the primary analog. As discussed in Chapter 2, Section 2.2, the C–H hydroxylation of norbornane with TFDO unexpectedly produced both the corresponding alcohol and ketone [9, 11]. It indicated that alcohol can be oxidized to a ketone by TFDO. It opened a new way to access carbonyl compounds from alcohol using dioxirane oxidant. Alcohols were treated with TFDO; primary alcohols produced aldehydes, while secondary alcohols yielded ketones [12]. To prevent *in situ* oxidation of alcohols to carbonyl compounds, the alcohols were trapped *via* one-pot functionalization. [13] Notably, this dioxirane-mediated protocol was applicable to the oxidation of chiral alkanes, and the products retained configuration [11].

Hydroxylation of Primary C–H Bonds

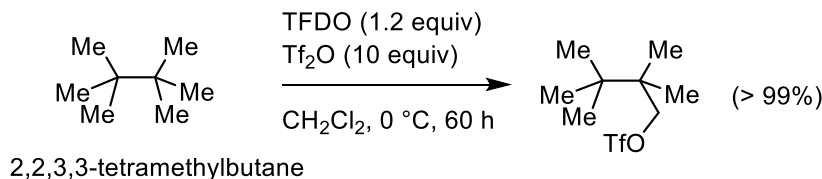
Methane is the smallest hydrocarbon/organic compound. In organic synthesis, it has significant importance because several compounds can be synthesized by the derivatization of methane. Such a derivative of methane is methanol, which has many applications in organic synthesis. Therefore, the conversion of methane to methanol is very important, and the process involves a C–H activation.

Methane, when reacted with *in situ*-generated TFDO/DMDO catalyst under standard pressure and temperature below 5°C, produced methanol [14]. Although the reaction had only <2% conversion (15% methanol selectivity), the selectivity to generate methanol was more than 95% (Scheme 4.1). The reaction with the TFDO-catalyst displayed faster reactivity than the DMDO-mediated reaction, with 15% conversion compared to 2% for the latter. For DMDO, the reaction with a stoichiometric amount of oxidation gave a 5% conversion. It is worth noting that the stoichiometric reaction with TFDO also displayed higher conversion than DMDO.



Scheme 4.1. Preparation of methanol from methane.

Experiments suggested that the oxygenation of tertiary C–H bonds was easier than that of primary and secondary C–H bonds. Here, the amount of dioxirane and time needed were the least for the tertiary C–H bonds. The oxidation products of primary and secondary C–H bonds, *i.e.*, alcohols, are prone to further oxidation to produce carbonyl compounds like ketones [12] and carboxylic acids [15]. To prevent the over-oxidation of alcohols, oxidation was performed with excess trifluoroacetic anhydride (Tf_2O) [13]. The corresponding alcohol was protected *in situ* to give a *mono*-triflated product. For instance, when 2,2,3,3-tetramethylbutane was reacted with TFDO in the presence of excess Tf_2O , the *mono*-triflated product was isolated in >99% yield (Scheme 4.2).



Scheme 4.2. Oxidation of 2,2,3,3-tetramethylbutane with TFDO in the presence of Tf_2O .

CHAPTER 5

Asymmetric Synthesis with Dioxiranes

Abstract: Chiral compounds have a myriad of applications in the fields of food, cosmetics, medicines, agrochemicals, *etc.* It is noteworthy to mention that around 40% of global drugs are chiral. Therefore, dioxirane-mediated oxygenation to prepare chiral molecules is very important. The achiral dioxirane-mediated oxidation of chiral compounds produces a series of chiral derivatives; these oxygenations are covered here. The reactions include diastereoselective epoxidation of *oxidosqualenes* to diepoxides, oxidation of chiral *vic*-diols to α -hydroxyketones, oxidation of sulfides to sulfoxides, *etc.* However, the preparation of chiral molecules from an achiral scaffold/substrate requires a chiral environment. In this aspect, this chapter also compiles oxygenation reactions with chiral dioxiranes or in the presence of chiral additives, drawn from the vast literature. Notably, the chiral dioxirane-based fructose-precatalysts are explored significantly, famous for their use in the Shi epoxidation. The precatalysts are employed for asymmetrization of *meso* and *racemic vic*-diols, kinetic resolution of allyl-substituted cyclohexene, asymmetric desymmetrization of 1,3,5-trisubstituted 1,4-cyclohexadiene, *etc.*

Keywords: Asymmetric synthesis, Asymmetric desymmetrization, Asymmetric oxidation, Chiral compounds, Kinetic resolution.

INTRODUCTION

Asymmetric synthesis offers access to chiral molecules. The applications of chiral molecules are too vast, including food, cosmetics, medicines, agrochemicals, *etc.* The importance of chiral molecules can be drawn from the data that out of fifteen global drugs, six have a chiral core (40%) [1, 2]. Several important medicines contain O, N, and S-heteroatoms [3, 4]. Therefore, the installation of a C–O bond is very important [5, 6]. For asymmetric oxygenation, a chiral environment is required. Such environments can be created either by treating a chiral reagent/catalyst/additive host (Chapter 1, Schemes **1.15–1.18**) with achiral substrates, or by reacting a chiral substrate with an achiral reagent/catalyst. Another way is to implement chiral hosts or additives that provide a chiral environment for asymmetric induction.

Using a chiral host, an asymmetric environment can be imposed. In Chapter 2, the oxidation of prochiral sulfides with *in situ* generated dioxiranes in the presence of chiral bovine serum albumin (BSA) produced chiral sulfoxides with enantioselectivities of up to 89% *ee* (Chapter 2, Scheme 2.7) [7, 8]. β -CD-derived ketone precatalyst was employed for stereoselective epoxidation of (*S*)-terpenes and *S*-limonene for the preparation of *cis*- and *trans*-epoxides (Chapter 3, Scheme 3.27) [9]. The β -CD-core provides a chiral environment for this asymmetric induction.

In Chapter 1, the list of chiral dioxirane reagents and precatalysts designed and synthesized is discussed (Chapter 1, Scheme 1.15–1.18). The precatalysts are useful for various asymmetric transformations, and are categorized in Chapter 3 based on their scaffolds, such as carbohydrate-derived dioxirane precatalysts, peptide-derived dioxirane precatalysts, bile acid-based dioxirane precatalysts, C2-symmetric scaffold-based precatalysts, halogenated precatalysts, *etc.* (Section 3.2.3.2). Chiral ketone precatalyst 1,2:4,5-di-*O*-isopropylidene-D-erythro-hexo-2,3-diulo-2,6-pyranose was employed for the asymmetric oxidation of prochiral sulfides; the sulfoxides obtained had enantioselectivities of 6–25% *ee* (Chapter 2, Scheme 2.8) [10]. The catalytic protocol is similar to the Shi-organocatalytic system [11]. This protocol was also applied to the enantioselective oxidation of disulfides; the thiosulfinates were isolated in yields up to 97% with enantioselectivities up to 96% *ee* (Scheme 2.17) [12]. Enantioselective epoxidation with chiral dioxirane precursor was achieved for olefins, conjugated olefins, and conjugated *cis*-enynes (Schemes 3.22 and 3.24) [13 - 17]. The Shi epoxidation protocol was employed as a key step during the synthesis of monoterpenoids [18].

In Chapter 3, the enantioselective epoxidation of allylic alcohol was discussed (Schemes 3.16 and 3.18–3.20) [19 - 24]. In Chapter 4, a substrate with a ketone chain and a chiral tertiary δ C–H bond, *i.e.*, an undecanoate ketone, was subjected to oxidation conditions [25]. Corresponding oxygenation-*cum*-cyclization-*cum*-dehydration product, *i.e.*, chiral 3,4-dihydropyran, was obtained in 78% yield with 73% *ee* (Scheme 4.29). Further, for chiral amino acids, C–H and N–H hydroxylations were studied (Schemes 4.31–4.34) [26 - 28].

A chiral substrate like Penicillin contains a sulfide group. In the chiral environment of the substrate, the reaction with DMDO led to the formation of chiral sulfide, and a single diastereomer was obtained in quantitative yield (Chapter 2, Scheme 2.9) [29]. Similarly, in a chiral Ru-complex, sulfides were diastereoselectively oxidized with DMDO, and d.r. was obtained up to 1:99 (Chapter 2, Scheme 2.10) [30]. Chiral (*R*)-sulfilimine (80% *ee*) upon reaction with DMDO yielded the (*R*)-oxygenated product in 90% yield and 80% *ee*; retention of

configuration was observed (Chapter 2, Scheme 2.11) [31]. Chiral hypervalent iodine compounds were prepared from chiral iodo-substrates upon oxidation with DMDO (Chapter 2, Schemes 2.43 and 2.44) [2, 32 - 40]. The oxidation of chiral silane with DMDO and TFDO yielded chiral silanol in >98% yield and 80% *ee* (Chapter 2, Scheme 2.48b) [41].

Using dioxirane chemistry, synthesis/functionalization of biologically-relevant compounds and natural products, like metabolites of Aflatoxin B1, majucinoids, tetrahydrocannabinol, pectenotoxins, *ent*-trachylobane, eldecalcitol, bryostatin, Taxol®, thujone, (+)-menthol, eudesmane, spirochensilide A, Valinomycin, dafachronic acid, *etc.*, was successfully achieved (Chapters 3 and 4).

In this chapter, the application of dioxirane in asymmetrizations and kinetic resolutions will be discussed.

Asymmetrizations and Kinetic Resolutions of *Vicinal* Diols

By employing stereoselective and stereospecific reactions, chirality can be introduced into an achiral molecule. In mixtures of *dl*- and *meso*-isomers, the *dl*-mixture contains two isomers in an equimolar ratio with opposite specific rotations; therefore, the overall specific rotation is nullified, and the solution is called racemic. On the other hand, for *meso*-isomers, each molecule has chiral centres with similar specific rotation. Thus, each center cancels the other in a molecule, and the molecules with chiral centers become optically inactive. For achiral/*meso*-compounds, the asymmetrization/desymmetrization technique is used to convert them into chiral compounds. For example, between two chiral centres, only one chiral centre is predominantly converted to an achiral centre, leaving behind the other untouched; thus, the molecule gains optical activity. In such a case, chirality is obtained by intramolecular transformation.

The case for racemic *dl*-mixture is quite similar to the asymmetrization/desymmetrization technique. While asymmetrization/desymmetrization involves differential selectivity of reaction centres present on the same molecule, the transformation here is compared between two isomers/molecules. In a mixture of two chiral isomers, one isomer (*e.g.*, *dl* isomers) is chemically converted to another species, leaving behind a sample enriched with the other isomer. This process is termed kinetic resolution and is based on the different reactivities of two enantiomers in a chiral environment.

The oxidation of a chiral molecule to another chiral molecule is so simple that it may not need any additional chiral reagent/catalyst/host additive. For example, (1*R*,2*R*)-cyclohexane-1,2-diol with 95% *ee*, when oxidized with DMDO, yielded

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