Organic Reactions

VOLUME 69

A JOHN WILEY & SONS, INC., PUBLICATION

Published by John Wiley & Sons, Inc., Hoboken, New Jersey

Published simultaneously in Canada.

Wiley Bicentennial Logo: Richard J. Pacifico

Library of Congress Catalog Card Number: 42-20265
ISBN 978-0-470-22397-0

Printed in the United States of America

10 9 8 7 6 5 4 3 2 1

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PREFACE TO THE SERIES

In the course of nearly every program of research in organic chemistry, the investigator finds it necessary to use several of the better-known synthetic reactions. To discover the optimum conditions for the application of even the most familiar one to a compound not previously subjected to the reaction often requires an extensive search of the literature; even then a series of experiments may be necessary. When the results of the investigation are published, the synthesis, which may have required months of work, is usually described without comment. The background of knowledge and experience gained in the literature search and experimentation is thus lost to those who subsequently have occasion to apply the general method. The student of preparative organic chemistry faces similar difficulties. The textbooks and laboratory manuals furnish numerous examples of the application of various syntheses, but only rarely do they convey an accurate conception of the scope and usefulness of the processes.

For many years American organic chemists have discussed these problems. The plan of compiling critical discussions of the more important reactions thus was evolved. The volumes of *Organic Reactions* are collections of chapters each devoted to a single reaction, or a definite phase of a reaction, of wide applicability. The authors have had experience with the processes surveyed. The subjects are presented from the preparative viewpoint, and particular attention is given to limitations, interfering influences, effects of structure, and the selection of experimental techniques. Each chapter includes several detailed procedures illustrating the significant modifications of the method. Most of these procedures have been found satisfactory by the author or one of the editors, but unlike those in *Organic Synthesis*, they have not been subjected to careful testing in two or more laboratories.

Each chapter contains tables that include all the examples of the reaction under consideration that the author has been able to find. It is inevitable, however, that in the search of the literature some examples will be missed, especially when the reaction is used as one step in an extended synthesis. Nevertheless, the investigator will be able to use the tables and their accompanying bibliographies in place of most or all of the literature search so often required.

Because of the systematic arrangement of the material in the chapters and the entries in the tables, users of the books will be able to find information desired by reference to the table of contents of the appropriate chapter. In the interest of economy, the entries in the indices have been kept to a minimum, and, in particular, the compounds listed in the tables are not repeated in the indices.

The success of this publication, which will appear periodically, depends upon the cooperation of organic chemists and their willingness to devote time and effort to the preparation of the chapters. They have manifested their interest already by the almost unanimous acceptance of invitations to contribute to the work. The editors will welcome their continued interest and their suggestions for improvements in *Organic Reactions*.

Chemists who are considering the preparation of a manuscript for submission to *Organic Reactions* are urged to contact the Editor-in-Chief.

CONTENTS

CHAPTER 1

DIOXIRANE OXIDATIONS OF COMPOUNDS OTHER THAN ALKENES

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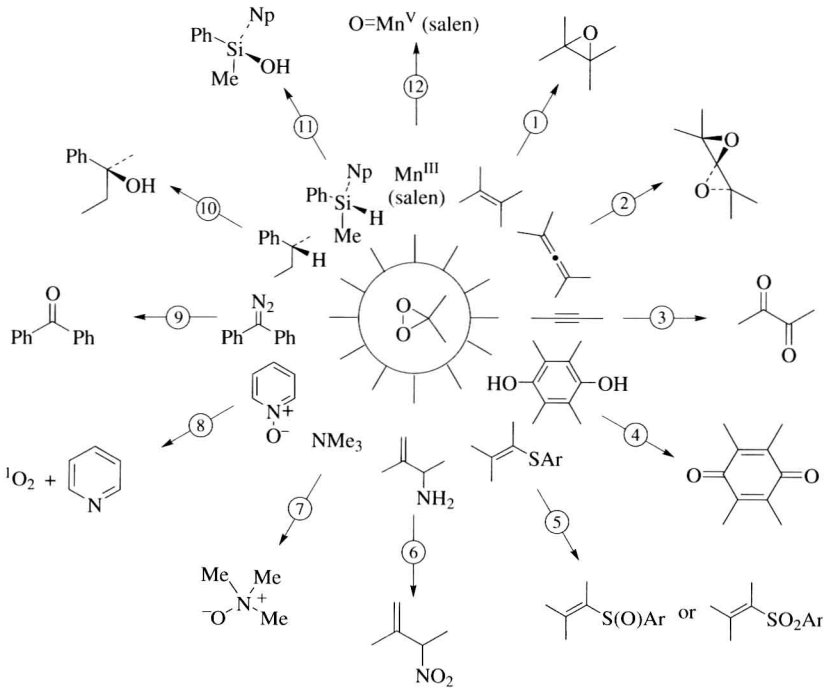
Organic Reactions, Vol. 69, Edited by Larry E. Overman et al.

ACKNOWLEDGMENTS

Generous financial support from the *Deutsche Forschungsgemeinschaft (Schwerpunktprogramm "Peroxidchemie: Mechanistische und Präparative Aspekte des Sauerstofftransfers"* and *Sonderforschungsbereich SFB 347 "Selektive Reaktionen Metall-aktivierter Moleküle")*, the *Fonds der Chemischen Industrie*, the *NIH-MBRS Program* (Grant S06 GM 08194), the Welch Foundation (Grant AX-1593), and the DAAD *(Deutscher Akademischer Austauschdienst)* is gratefully appreciated. The authors also thank Dr. Chantu R. Saha-Möller and Mrs. Ana-Maria Krause for their help in preparing the tabular and graphical material.

INTRODUCTION

Epoxidations, heteroatom oxidations, and Y–H insertions constitute the best investigated oxidations by dioxiranes. An overview of these transformations is displayed in the rosette of Scheme 1. These preparatively useful oxidations have been extensively reviewed during the last decade.[1–14] In a previous chapter,[15] we presented the epoxidation of double bonds [π bonds in simple alkenes and those functionalized with electron donors (ED), electron acceptors (EA), and with both ED and EA substituents; case 1 in the rosette] with either isolated or in situ generated dioxiranes. The recent developments in the dioxirane-mediated asymmetric epoxidation have also been extensively covered there.[15] The present chapter concerns the remaining oxidations in the rosette of Scheme 1, that is, epoxidation of the double bonds in the cumulenes, such as allenes (transformation 2), acetylenes (transformation 3), and arenes (transformation 4); the oxidation of heteroatom functionalities, mainly lone pairs on sulfur (transformation 5), on nitrogen (transformations 6 and 7), and on oxygen as the deoxygenation of *N*-oxides (transformation 8); the oxidation of C=Y functionalities (e.g., transformation 9), Y–H insertions (σ bonds) such as C–H in alkanes (transformation 10) and Si–H in silanes (transformation 11); and the oxidation of organometallic substrates including metal (transformation 12) and ligand-sphere oxidation.

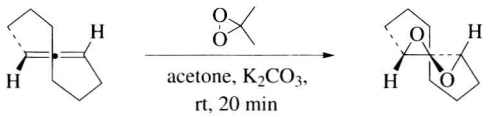


Scheme 1. An overview of dioxirane oxidations (Np = 1-naphthyl).

MECHANISM

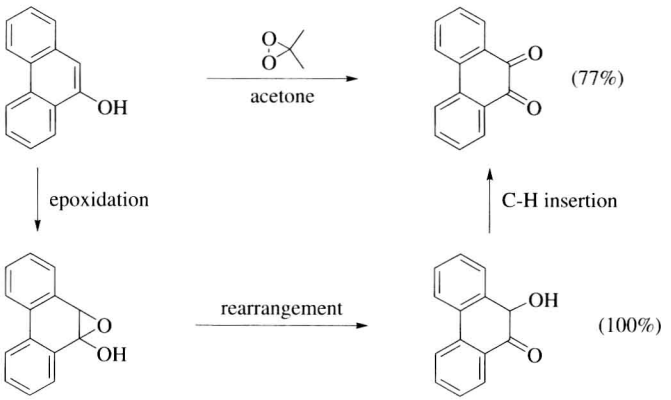
Allenes, Alkynes, and Arenes

Although the products of the dioxirane oxidation of allenes, alkynes, and arenes are usually more complex than those of the epoxidation of simple C=C double bonds, the initial step of the oxidation is usually epoxidation. Therefore, the same mechanism that has been extensively discussed in the previous chapter[15] also applies in these reactions. The oxygen transfer proceeds with complete retention of the initial olefin configuration through the concerted spiro transition state.[15] An example is shown in Eq. 1, in which the oxidation of the chiral allene proceeds in nearly quantitative yield (95%) with preservation of the starting allene configuration in the spiro-bisepoxide.[16]



(95%) (Eq. 1)

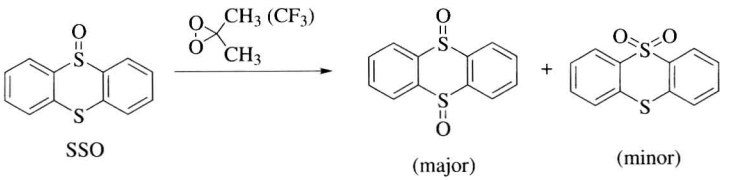
Since the initial epoxidation products of the allenes, alkynes, and arenes are usually labile substances, they may undergo subsequent reactions, which include further oxidation by dioxirane other than epoxidation. For example, in the dimethyldioxirane (DMD) oxidation of the phenanthrene derivative in Scheme 2,[17] the second oxidation by DMD involves C–H insertion instead of epoxidation.



Scheme 2. DMD oxidation of 9-hydroxyphenanthrene.

Heteroatom Substrates

Through a detailed study of the competitive oxidation of the sulfide versus sulfoxide functionalities in thianthrene 5-oxide (SSO),[18] a pronounced electrophilic character has been demonstrated for DMD and methyl(trifluoromethyl)dioxirane (TFD).[19,20] Thus, dioxiranes prefer to oxidize the sulfide over the sulfoxide functionality, a typical behavior of an electrophilic oxidant (Scheme 3). Also, the

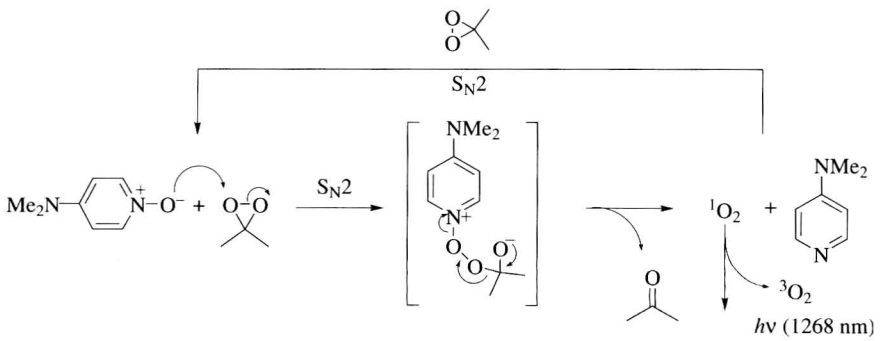


Scheme 3. Competitive oxidation of the sulfide vs. sulfoxide functionalities in thianthrene-5-oxide (SSO) by the dioxiranes DMD and TFD.

kinetic data[6] for the oxidation of sulfides and sulfoxides have revealed the electrophilic character of dioxiranes. Thus, the heteroatom oxidations by dioxirane are generally explained in terms of a S_N2-type attack of the heteroatom lone pair on the dioxirane peroxide σ^*-orbital.[21,22]

A possible single-electron-transfer (SET) mechanism in N-oxidations[23,24] has been discounted[21] on the basis of kinetic experiments by comparing the relative rates of oxygen transfer by DMD with those of alkylation by methyl iodide. For the latter, an S_N2 mechanism unequivocally applies. Similar reactivities (linear correlation of rates) for N-oxidation also establish the S_N2 pathway for dioxirane oxidations. This conclusion is supported by a kinetic study of the DMD oxidation of substituted *N*,*N*-dimethylanilines.[25]

The heterolytic mechanism is presumably also valid for a variety of oxygen-type nucleophiles, e.g., amine *N*-oxides, ClO^-, HO^-, HOO^-, RO^-, ROO^-, $RC(O)OO^-$, and $^-OS(O)_2OO^-$, which all catalyze the decomposition of dioxiranes with the evolution of molecular oxygen.[26,27] A typical case is illustrated with 4-dimethylaminopyridine *N*-oxide in Scheme 4.[26] The chemiluminescence emitted by the generated singlet oxygen confirms the heterolytic nature of the dioxirane decomposition.[26] Further support for this mechanism has been provided by theoretical work, from which it was concluded that the oxidation of primary amines by DMD does not proceed by a radical process.[28]



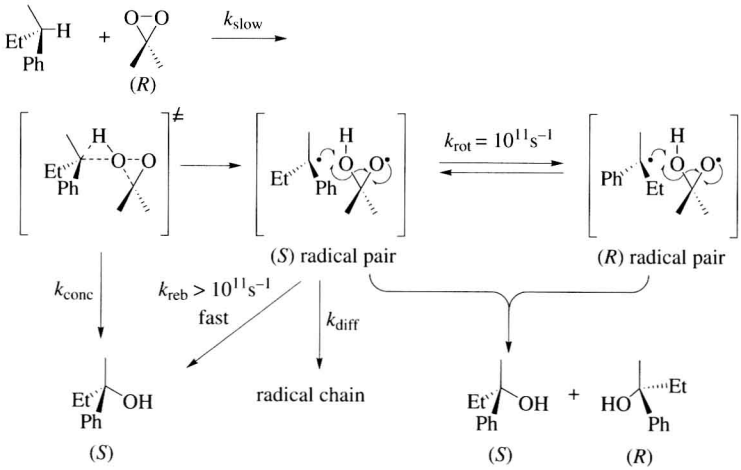
Scheme 4. S_N2 Mechanism for the *N*-oxide-induced decomposition of DMD.

Alkanes and Silanes

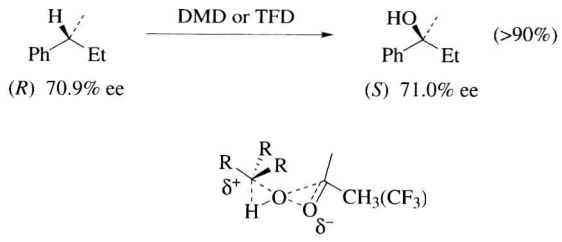
Two mechanisms have been suggested for the insertion of an oxygen atom into the Y–H bond of alkanes and silanes. Abundant evidence, which includes kinetics,[29] kinetic isotope effects,[30] and stereoselectivity,[31] all unequivocally support a concerted oxenoid-type mechanism (Figure 1).

Nonetheless, radical reactivity has been observed recently and interpreted in terms of the dioxirane diradical as the active oxidant, in particular, the so-called "molecule-induced homolysis."[32–35] It has also been proposed[36] that alkane hydroxylation may proceed by a rate-determining oxygen insertion into the alkane C–H bond to generate a caged radical pair, followed by very fast collapse (oxygen rebound) to hydroxylated products (Scheme 5).

That hydroxylation of (*R*)-2-phenylbutane proceeds with 100% retention to furnish (*S*)-2-phenylbutan-2-ol for both DMD[37] and TFD[31] sheds serious doubt on the involvement of out-of-cage radical intermediates in such C–H oxidations (Eq. 2).



Scheme 5. Concerted oxenoid-type (k_{conc}) vs. oxygen-rebound (k_{reb}) mechanisms for C–H insertion by DMD.

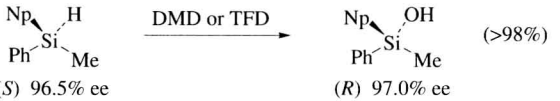


(Eq. 2)

Figure 1. Concerted oxenoid-type transition state for C–H insertion.

The tertiary benzyl radical derived from this optically active substrate is one of the fastest radical clocks (the configurational persistence of this radical is estimated to be about 10^{-11} seconds)[38] and serves as a definitive probe for the intervention of radical intermediates. Thus, as shown in Scheme 5,[37] if a caged radical pair is formed, collapse with configurational conservation by oxygen rebound (k_{reb}) must be faster than diffusion out of the cage (k_{diff}), as well as in-cage isomerization (k_{rot}), since such competitive processes would lead to racemization.

As in the C–H oxidation of (*R*)-2-phenylbutane (Eq. 2), the hydroxylation of the (+)-(*S*)-(α-Np)PhMeSiH silane enantiomer by both dioxiranes DMD and TFD proceeds with complete retention of configuration to afford (+)-(*R*)-(α-Np)PhMeSiOH (Eq. 3).[39,40] Therefore, a similar mechanism would appear to apply for the oxidation of C–H and Si–H bonds.



(*S*) 96.5% ee (*R*) 97.0% ee (Eq. 3)

Most recent theoretical work on oxygen transfer for C–H insertion supports the concerted spiro oxenoid-type mechanism, in which the transition structure has considerable dipolar and also some diradical character.[41–43] Under typical preparative conditions, for example, in the presence of molecular oxygen, it was concluded that a concerted mechanism applies for the C–H insertion.

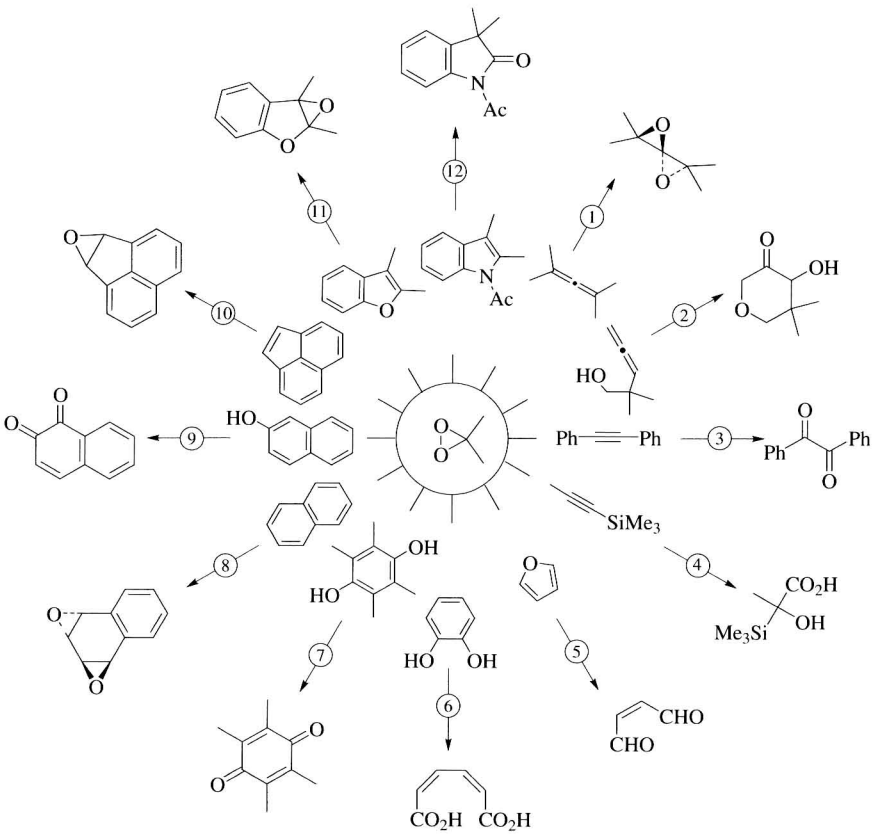
SCOPE AND LIMITATIONS

The oxidation of double bonds (π bonds) in cumulenes (allenes, acetylenes) and arenes, of heteroatom functionalities (lone-pair electrons), of transition-metal complexes, and Y–H insertions (σ bonds) has been successfully performed, either with isolated or with in situ generated dioxiranes. Thus, a broad spectrum of substrates has been oxidized by dioxiranes. The pertinent examples are listed in Tables 1–7 (see Tabular Survey). An isolated (distilled) acetone solution [DMD (isol.)] is the most often used dioxirane owing to its convenient preparation and relatively low cost. Although methyl(trifluoromethyl)dioxirane (TFD) is considerably more reactive than DMD, its application is limited because of its high cost and the high volatility of trifluoroacetone. With DMD (isol.), the scale of the reaction is usually limited to 100 mmol because DMD (isol.) is quite dilute (ca. 0.08 M). In the case of TFD (ca. 0.6 M), the prohibitive cost of trifluoroacetone obliges small-scale (ca. 10 mmol) applications. When a large-scale preparation is desired, the in situ mode [DMD (in situ)] is recommended, for which both biphasic[44–47] and homogeneous[48,49] media are available. It should be kept in mind that when one operates in aqueous solution, both the substrate and the oxidized products should resist hydrolysis and persist at temperatures above 0°. An advantage of the in situ mode is that it may be carried out with less than stoichiometric amounts (<0.5 equiv.) of ketone, which is important for enantioselective oxidations.[50–54]

Allenes, Alkynes, and Arenes

Representative examples of oxidations of allenes, alkynes, and arenes are collected in the rosette of Scheme 6.

The products of dioxirane oxidation of allenes depend on the reaction conditions and the substrate structure. Unfunctionalized allenes give the corresponding spiro-bisepoxides usually in good yields[16,54] at subambient temperatures when dry dioxirane solution is employed (Eq. 1).[16] If the allene is unsymmetrically substituted, a mixture of regioisomers is obtained, and the selectivity is highly dependent on the allene structure.[16,55] Since these spiro-bisepoxides are labile toward hydrolysis, the in situ oxidation mode is not recommended. If the allene substrate contains a hydroxy functionality, the latter will react with the spiro-bisepoxide intermediate to form ring-opened and/or rearranged products.[56–58] The final products may be cyclic or acyclic, depending on the reaction conditions, the chain-length of the substituent that contains the hydroxy functionality, and the other substituents on the allene. For example, when the hydroxyallene



Scheme 6. An overview of dioxirane oxidations of allenes, alkynes, and arenes.