ORGANIC
REACTIONS

Volume 111

Organic Reactions

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Organic Reactions

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INTRODUCTION TO THE SERIES
BY ROGER ADAMS, 1942

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 Syntheses*, 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*.

INTRODUCTION TO THE SERIES
BY SCOTT E. DENMARK, 2008

In the intervening years since "The Chief" wrote this introduction to the second of his publishing creations, much in the world of chemistry has changed. In particular, the last decade has witnessed a revolution in the generation, dissemination, and availability of the chemical literature with the advent of electronic publication and abstracting services. Although the exponential growth in the chemical literature was one of the motivations for the creation of *Organic Reactions*, Adams could never have anticipated the impact of electronic access to the literature. Yet, as often happens with visionary advances, the value of this critical resource is now even greater than at its inception.

From 1942 to the 1980's the challenge that *Organic Reactions* successfully addressed was the difficulty in compiling an authoritative summary of a preparatively useful organic reaction from the primary literature. Practitioners interested in executing such a reaction (or simply learning about the features, advantages, and limitations of this process) would have a valuable resource to guide their experimentation. As abstracting services, in particular *Chemical Abstracts* and later *Beilstein*, entered the electronic age, the challenge for the practitioner was no longer to locate all of the literature on the subject. However, *Organic Reactions* chapters are much more than a surfeit of primary references; they constitute a distillation of this avalanche of information into the knowledge needed to correctly implement a reaction. It is in this capacity, namely to provide focused, scholarly, and comprehensive overviews of a given transformation, that *Organic Reactions* takes on even greater significance for the practice of chemical experimentation in the 21st century.

Adams' description of the content of the intended chapters is still remarkably relevant today. The development of new chemical reactions over the past decades has greatly accelerated and has embraced more sophisticated reagents derived from elements representing all reaches of the Periodic Table. Accordingly, the successful implementation of these transformations requires more stringent adherence to important experimental details and conditions. The suitability of a given reaction for an unknown application is best judged from the informed vantage point provided by precedent and guidelines offered by a knowledgeable author.

As Adams clearly understood, the ultimate success of the enterprise depends on the willingness of organic chemists to devote their time and efforts to the preparation of chapters. The fact that, at the dawn of the 21st century, the series continues to thrive is fitting testimony to those chemists whose contributions serve as the foundation of this edifice. Chemists who are considering the preparation of a manuscript for submission to *Organic Reactions* are urged to contact the Editor-in-Chief.

PREFACE TO VOLUME 111

> *We will have rings and things and fine array*
>
> William Shakespeare
>
> *The Taming of the Shrew*, 1590–1592

The two chapters in this volume of *Organic Reactions* describe the reductive ring-opening reactions of epoxides with titanium(III) reagents and the reductive cyclization reactions of nitroaryl and nitroalkenyl derivatives. Both chapters feature the generation and synthetic utility of a specific reactive intermediate, a free radical and a nitrene, respectively. Interestingly, despite the wide variety of processes that proceed through reactive intermediates, there are only a limited number of different types of such species, i.e., carbanions, radicals, carbocations, carbenes, carbynes, and nitrenes. These are usually high energy, short-lived, and therefore have significant reactivity to permit an array of transformations. Hence, a critical component in developing a new reaction that deploys a specific type of reactive intermediate is the ability to generate it in a controlled and selective manner, thereby *taming* the inherent reactivity to facilitate the desired bond-forming event in the desired manner. A particularly compelling aspect of *Organic Reactions* chapters is the delineation of so-called *Black-Swan Events* that provides the insight for accessing a specific reactive intermediate with new chemical reactivity. Notably, both chapters feature different types of ring-forming reactions, albeit this is the entire focus of the latter chapter. The first chapter also delineates other *things and fine array* to illustrate the synthetic utility of the reductive opening of epoxides. Another contrasting feature of the chapters is that while the first is almost entirely centered around a specific method to generate a free-radical intermediate, the second compares two different ways to access the same reactive intermediate, both of which constitute named reactions. Hence, this volume of the *Organic Reactions* series represents another stellar contribution that outlines the seminal developments in the generation and productive reactions of reactive intermediates to construct important synthetic motifs embedded in functional molecules.

The first chapter by T. V. (Babu) RajanBabu, William A. Nugent, and Sandipan Halder provides an outstanding treatise on the ring opening of epoxides with titanium(III) reagents. The authors concisely describe the historical events that led to the discovery of the reduction of epoxides by single-electron transfer using titanocene monochloride, which is ascribed to a series of *Black-Swan Events* (vide supra). For instance, Davies and Gibson reported the first example of the conversion of cyclohexene oxide to cyclohexene with titanocene monochloride in 1984; however, this work was preceded by several seemingly unrelated reports. For instance, Linnemann described probably the first epoxide cleavage by an SET process in 1866 using sodium amalgam in water, followed by contributions from Percy Julian in 1954 and mechanistic studies by Kochi in the late 1960s using chromium(II) salts. The culmination of these developments paved the way for the catalytic and stoichiometric titanium(III) reactions with epoxides outlined herein.

The Mechanism and Stereochemistry section describes the critical features associated with the generation of β-titanoxy radicals from epoxides, including the impact of the titanium complex and the mechanistic details for the carbon-oxygen bond cleavage. A particularly valuable feature of this section is the insight into the regeneration of the titanium reagent to facilitate the catalytic version. The authors also delineate the various mechanistic pathways to the β-titanoxy radicals, essential for planning a reaction sequence, including different methods deployed to trap the radicals formed after an initial cyclization. The section then culminates with a discussion of various aspects of regio- and stereocontrol, in which the diastereoselective processes are further subdivided into inter- and intramolecular variations. For example, the cyclization reaction section is organized by the type of Baldwin process, namely, 5-*exo*-trig, 5-*exo*-dig, 6-*endo*-trig, 6-*exo*-trig, and 6-*exo*-dig and includes sections on tandem cyclization reactions and the reactions of β,γ-epoxy alcohols.

The Scope and Limitation section starts with a survey of suitable epoxides to provide the reader with a sense of what types of transformations are feasible, followed by an important section on functional-group compatibility and the effects of substrate structure on reactivity. Each section is critical to anyone contemplating utilizing this reaction in complex synthesis. The intramolecular addition reactions and the associated termination strategies comprise a sizable component of this section, including transannular cyclization reactions and the construction of polycyclic products via cascade-type cyclization reactions. The Applications to Synthesis section is organized by the type of transformation, which permits a strategic analysis of these reactions. Hence, each sub-section delineates how this process has been deployed in the synthesis of a target of value to illustrate its impact in useful applications. Notably, this process has been utilized to prepare nearly two hundred natural products and advanced intermediates, making it a “formidable tool” for target-directed synthesis. The Comparison with Other Methods section delineates two critical limitations of the current process that can be mitigated to some degree by using alternative protocols, which thus provides a complementary picture of how to manipulate these types of epoxy alcohols. Additionally, the chapter provides detailed Experimental Conditions, which will be particularly insightful for anyone wishing to understand the nuances of this type of process. The Tabular Survey incorporates reactions reported up to October 2021. The tables mirror the Scope and Limitations section, making identifying examples of a particular process straightforward. Overall, this is an outstanding chapter on a very interesting and powerful synthetic transformation that has been widely deployed in organic synthesis.

The second chapter by Björn C. G. Söderberg and the late William F. Berkowitz outlines the reductive cyclization of 2-nitro- and β-nitrostyrenes, 2-nitrobiphenyls, and 1-nitro-1,3-dienes to prepare indoles, carbazoles, and pyrroles with a particular emphasis on indoles. Notably, the indole core is arguably one of the oldest and most widely studied heterocyclic motifs. For instance, early studies on the synthesis of indigo dye inspired the first chemical synthesis of indole itself by von Baeyer in 1866 by reducing oxindole with zinc dust. The importance of the indole motif in dyes, medicinal chemistry, bioactive natural products, bacterial physiology, and neurotransmitters, such as serotonin and melatonin, make it an important structural array. Thus, methods to prepare this heterocycle have inspired many innovative synthetic approaches. Ironically, the two methods reported herein utilize nitro aromatics as the nitrogen source in the heterocyclic product, which is analogous to the method employed by von Baeyer and Emmerling in 1869 for the conversion of 2-nitrocinnamic acid to indole using iron filings under basic conditions. Interestingly, this approach remained dormant for nearly a century until the development of the Cadogan-Sundberg process and then the related Watanabe-Cenini-Söderberg reaction to convert nitrostyrenes to indoles using trivalent phosphorus reagents and palladium catalysts, respectively.

The Mechanism and Stereochemistry section is organized by the named reaction and the type of product formed. For example, some general mechanistic considerations delineate the importance of forming a nitroso derivative *en route* to the putative nitrene in the Cadogan-Sundberg process. DFT calculations support a concerted [3+1] cycloaddition followed by a retro [2+2] cycloaddition to generate the nitrosoarene, which undergoes a second deoxygenation via an oxazaphosphiridine to afford the nitrene to initiate cyclization. The remainder of the section deals with the caveats that have evolved with this mechanistic proposal in constructing carbazoles, indoles and pyrroles. The format for the Watanabe–Cenini–Söderberg reaction is similar, albeit, in this case, the cyclization is proposed to occur through either the nitroso or the nitrene intermediate. The initiation is thought to involve the formation of a radical anion that reacts with carbon monoxide to form a series of metallacycle intermediates. The recognition that both of these processes undergo cyclization via an equivalent nitroso/nitrene intermediate provides a unifying theme for these reactions.

The Scope and Limitations section commences with the methods used to prepare the substrates for both types of reactions. The remainder of the section is then organized by the type of reaction, namely, 2-nitrostyrenes to form indoles and β-nitrostyrenes to produce indoles in the context of the specific named reaction. Additional sections describe the conversion of 1-nitro-1,3-dienes to pyrroles and the synthesis of heterocyclic analogs of indoles and carbazoles. A particularly useful feature is the direct comparison of the two methods, which gives the reader advice in selecting a specific set of reaction conditions. There is also a section on using other transition-metal catalysts and the applications of elemental sulfur and selenium as reductants. The final component of this section delineates the corresponding reactions of nitro and nitrosobenzenes for comparison. The Applications to Synthesis section provides examples using both methods to target some important compounds, including a few examples of closely related processes. The Comparison with Other Methods section discusses several alternative methods that focus on the N1-C2 cyclization reactions of nitro- and amino-substituted alkenes, alkynes and aryl groups. The organization of the Tabular Survey mirrors the Scope and Limitations, thereby making it easy for the reader to identify a specific transformation. Overall, this is an excellent chapter on two variants of a critical process that will be a valuable resource to a broad cross-section of the synthetic community, given the importance and ubiquity of these types of nitrogen heterocycles.

I would be remiss if I did not acknowledge the entire *Organic Reactions* Editorial Board for their collective efforts in steering this volume through the stages of the editorial process. I thank Dr. Jin K. Cha (Chapter 1) and Dr. Donna M. Huryn (Chapters 1 and 2), who served as the Responsible Editors to marshal the chapters through the various phases of development. I am also deeply indebted to Dr. Danielle Soenen for her continued and heroic efforts as the Editorial Coordinator; her knowledge of *Organic Reactions* is critical to maintaining consistency in the series. Dr. Dena Lindsay (Secretary to the Editorial Board) is thanked for coordinating the authors', editors', and publisher's contributions. In addition, the *Organic Reactions* enterprise could not maintain the quality of production without the efforts of Dr. Steven M. Weinreb (Executive Editor), Dr. Engelbert Ciganek (Editorial Advisor), Dr. Landy Blasdel (Processing Editor), and Dr. Tina Grant (Processing Editor). I would also like to acknowledge Dr. Barry B. Snider (Secretary) for keeping everyone on task and Dr. Jeffery Press (Treasurer) for his fiscal diligence.

I am also indebted to past and present members of the Board of Editors and Board of Directors for ensuring the enduring quality of *Organic Reactions*. The specific format of the chapters, in conjunction with the collated tables of examples, makes this series of reviews both unique and exceptionally valuable to the practicing synthetic organic chemist.

P. Andrew Evans
Kingston
Ontario, Canada

CONTENTS

ORGANIC REACTIONS

CHAPTER 1

RING-OPENING REACTIONS OF EPOXIDES WITH TITANIUM(III) REAGENTS

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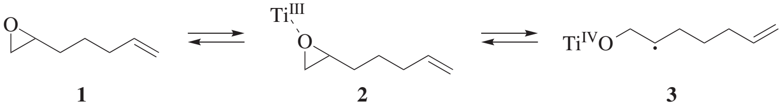
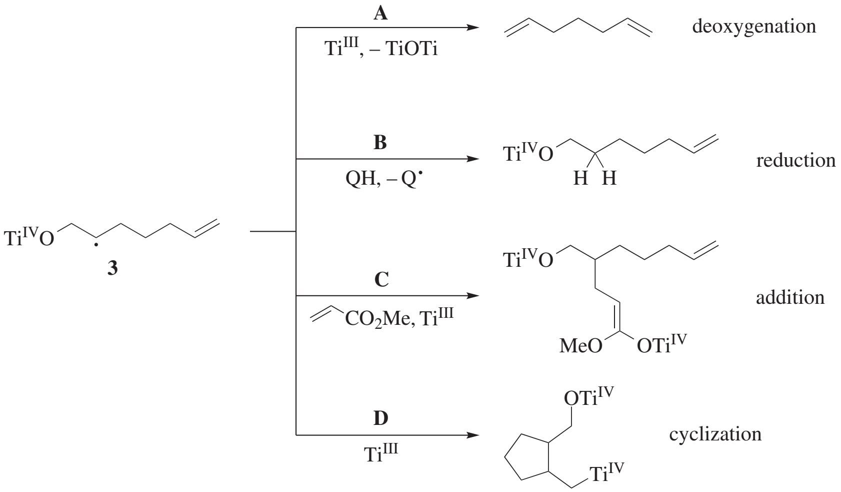
INTRODUCTION

This chapter delineates the ring-opening reactions of epoxides with titanium(III) reagents and catalysts. As shown in Scheme 1, these reactions proceed by a single-electron transfer (SET) mechanism. Using epoxide **1** as an example, this process requires the initial complexation of the epoxide oxygen atom to the titanium atom (structure **2**). Complex **2** then undergoes SET, resulting in the homolysis of one epoxide carbon–oxygen bond to afford a β-titanoxy radical represented by **3**.



Scheme 1

β-Titanoxy radicals, such as **3**, can undergo a variety of subsequent transformations, four of which are depicted as pathways **A**–**D** in Scheme 2. Pathway **A** involves trapping the carbon-centered radical with a second equivalent of titanium(III), which ultimately results in deoxygenation of the epoxide.[1] Pathway **B** is a reduction process, wherein the presence of a suitable donor (QH) enables a hydrogen-atom transfer (HAT) to the radical center; hydrolysis of the resulting alkoxide releases the corresponding alcohol.[1] In pathway **C**, intermolecular addition of radical **3** to an activated vinyl compound (exemplified here by methyl acrylate) leads to the formation of a carbon–carbon bond; trapping the new radical intermediate with a second equivalent of titanium(III) affords a titanium(IV) enolate.[2] Finally, pathway **D** is a cyclization reaction: intramolecular addition of the radical to the pendant alkene is followed by trapping the radical with a second equivalent of titanium(III), to afford the cyclization product as a titanium(IV) organometallic species.[3]



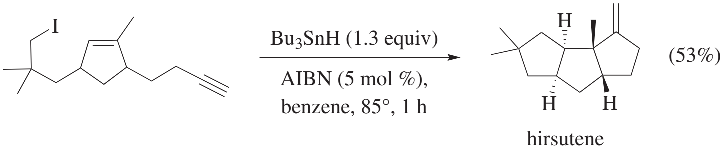
Scheme 2

By far, the most common titanium(III) reagent used for the transformations in Scheme 2 is titanocene monochloride, which is represented herein as Cp_2TiCl.

In most cases Cp_2TiCl is generated in situ by the reduction of commercial titanocene dichloride (Cp_2TiCl_2) with zinc or manganese metal powder.[4] Prior to 1999, the reactions depicted in Scheme 2 were invariably carried out utilizing a stoichiometric amount of Cp_2TiCl. A pivotal breakthrough occurred with the invention of catalytic versions of this chemistry. Gansäuer and coworkers developed a catalytic protocol using the Brønsted acid 2,4,6-collidine hydrochloride. Protonolysis of the intermediate titanium alkoxide intermediate regenerates Cp_2TiCl_2, closing the catalytic cycle.[5] In another approach, Oltra and coworkers reported a catalytic process using aprotic conditions that employ a combination of chlorotrimethylsilane and 2,4,6-collidine.[6]

Using these catalytic protocols, the amount of the titanium complex can sometimes be reduced by two or even three orders of magnitude. Workup is greatly simplified and the utilization of Cp_2TiCl chemistry in automated synthesis is now feasible.[7] In some applications, a low steady-state concentration of titanium(III) is actually beneficial in suppressing undesired side-reactions.[8] In addition to these advantages, the enantioselective ring-opening of epoxides using chiral titanium catalysts can now be realized.

Free-radical chemistry dates back to the observation of triphenylmethyl radical by Gomberg in 1900.[9] However, many decades would pass before applications of free-radical chemistry in organic synthesis were pursued. (After all, free-radical processes underlie the chemistry of combustion, the very embodiment of a nonselective organic reaction). However, by the 1980s many of the underlying principles of the kinetic and thermodynamic behavior of radicals had been delineated.[10] Applications of free-radical chemistry in natural-product synthesis, as in the synthesis of hirsutene (Scheme 3), began to emerge.[11]

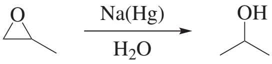


Scheme 3

Radical-based synthetic methods have several advantages, including functional-group compatibility and access to unconventional reaction conditions compared with traditional ionic methods. Radical reactions provide unique reactivity patterns, including a tolerance for steric effects: they are well suited to the formation of highly congested, chiral 4° and vicinal, contiguous stereogenic centers. Cyclic structures can often be assembled with predictable control of the configuration at the newly created stereocenters; however, some limitations remain with this approach. Many early radical-based methods involve termination by HAT from reagents such as tributyltin hydride. When HAT results in the formation of an sp^3 carbon, the subsequent functionalization of this center can be challenging. Moreover, the nature of the radical-chain reaction dictates that there are limited opportunities for reagent control, and selectivity is most often a consequence of substrate control.

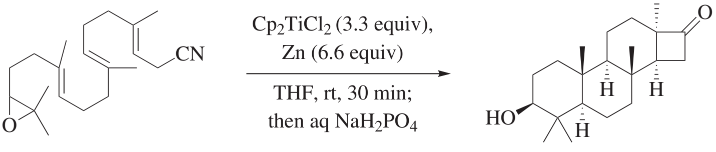
The titanium(III)-mediated ring-opening of epoxides provides a method for addressing the issue of reagent control. The intermediacy of a titanium(III)–epoxide complex such as **2** means that the regio- and stereoselectivity of epoxide opening via SET can be influenced by the ligands on titanium. Moreover, the titanium atom remains bound to the oxygen atom in **3** after carbon–oxygen bond homolysis and can thus influence the course of subsequent chemical events as depicted in Scheme 2.

As is often the case with novel chemistry, the discovery of the reduction of epoxides by SET utilizing titanocene monochloride was anticipated by several "Black Swan Events"[12] in the chemical literature. The reduction of propylene oxide to 2-propanol by sodium amalgam in the presence of water (Scheme 4) was first reported in 1866 when organic chemistry was in its infancy.[13] This may well represent the first report of an epoxide cleavage by SET. The first example of an epoxide ring-opening using a transition-metal reductant involved the use of chromium(II) salts and was reported by the renowned African-American chemist Percy Julian in 1954.[14] Kochi would later provide the key insight that reduction of epoxides by chromium(II) proceeds by discrete one-electron steps.[15] Davies and Gibson reported in 1984 that the treatment of cyclohexene oxide with titanocene monochloride affords cyclohexene in 70% yield along with the titanium oxo complex $[Cp_2TiCl]_2O$.[16] Thus, the stage was set for the following developments.



Scheme 4

The four pathways shown in Scheme 2 represent the state of art in titanium(III) chemistry ca. 1994. Since then, a profusion of novel, alternative reaction pathways for β-titanoxy radicals have been imagined and reduced to practice. These include the loss of a β-hydrogen atom to afford an allylic alcohol,[17] elimination of a suitable leaving group,[18] radical substitution at oxygen,[19] intramolecular arylation,[20] and cross-coupling reactions,[21] to name just a few. The rapid evolution of the field is further illustrated by Scheme 5. This remarkable tandem polycyclization affords the tetracyclic product **4** as a single diastereomer.[22] Neither the final radical cyclization into a nitrile acceptor nor the formation of a strained four-membered ring could have been anticipated based on the understanding of radical reactions in 1994.



4 (50%)

Scheme 5

As a result of such advances, titanium(III)-mediated epoxide opening has emerged as a formidable synthetic tool.[23,24] As of this writing (October 2021) these reactions have been applied in the synthesis of over 170 natural products, drugs, and advanced intermediates. Several review articles have been devoted to these synthetic applications.[25–27] Moreover, it has been suggested that Cp_2TiCl represents a nearly ideal reagent for "green chemistry,"[28] which should further increase interest in using these methods for large-scale synthetic applications.

This chapter focuses on epoxide-opening reactions involving well-defined titanium(III) reagents, especially titanocene monochloride and its congeners. Both stoichiometric and catalytic reactions are considered. Additionally, there exist a number of ill-defined (and in some cases unstable) formulations obtained by reduction of Cp_2TiCl_2 with alternative metals such as sodium amalgam,[29] magnesium,[30] or indium powder.[31] These will be mentioned principally as a point of comparison with the chemistry of titanium(III). As noted in the "Comparison with Other Methods" section, the observed products from such reactions often are significantly different from those obtained using Cp_2TiCl, and consequently, such examples are not included in the Tabular Survey.

In addition to epoxides, titanocene monochloride reacts with a variety of other functional groups. Although several of these reactions (such as those with aromatic aldehydes and organic halides) are useful, a detailed discussion of such chemistry is outside the scope of the current chapter. Such reactions will be addressed to some extent in the context of functional-group compatibility in the "Scope and Limitations" section with the aim to familiarize the reader with these alternative reactions to avoid potential side reactions.

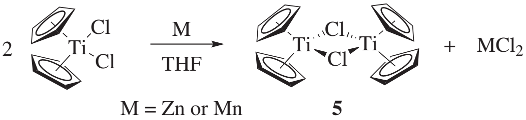
Several conventions are used throughout the chapter in the interest of consistency and clarity. Throughout our discussion, "normal addition" will refer to the addition of a solution of titanium(III) to a solution of an epoxide; conversely "inverse addition" implies addition of an epoxide to a titanium(III) solution. 2,4,6-Collidine (2,4,6-trimethylpyridine) is frequently used as a co-reagent in reactions of Cp_2TiCl. In all cases where collidine or its hydrochloride salt (abbreviated coll•HCl) appears in schemes, it specifically refers to the 2,4,6-isomer. Finally, all the reactions described in this chapter are followed by an aqueous hydrolysis step. In the interest of clarity, the hydrolysis step is indicated in schemes only when an unusual protocol is employed or there is a didactic purpose for its inclusion. In all schemes, the symbol "R" is used exclusively to represent hydrocarbyl substituents, whereas the symbol "Q" is used where substituents may additionally contain heteroatoms (NO_2, CO_2Me, etc.). All available diastereomeric and enantiomeric ratios are reported in the schemes. The literature up to October 2021 is covered. Insights gleaned while writing the current chapter are described in a recent essay, which provides solutions to several longstanding "mechanistic mysteries" in titanium(III) chemistry.[8]

MECHANISM AND STEREOCHEMISTRY

Generation of β-Titanoxy Radicals from Epoxides

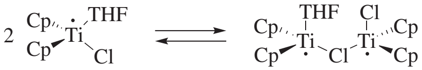
Nature of the Reagent. Titanocene monochloride is typically prepared by reduction of commercial bis(cyclopentadienyl)titanium(IV) dichloride in THF (Scheme 6).

In the solid state, this titanium(III) reagent forms a bis-chloride-bridged dimer, **5**, as confirmed by X-ray crystallographic analysis.[32,33]



Scheme 6

In contrast to the solid-state dimer **5**, when dissolved in the donor solvent tetrahydrofuran, the reagent exists in an equilibrium between the monomer **6** and the "open" dimer **7**. The dimerization equilibrium constant for the reaction shown in Scheme 7 is 3×10^3 M^{-1}.[34] Each titanium atom in **6** and **7** possesses a singly occupied $d^1_{z^2}$ orbital[35,36] and, consistent with the availability of this unpaired electron, both **6** and **7** function as reducing agents. Dimer **7** is a slightly stronger reductant than **6**, as revealed by cyclic voltametric studies.[33,34]

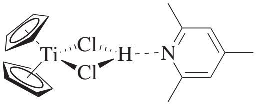


6 **7**

Scheme 7

Because titanocene monochloride is usually generated by in situ reduction of Cp_2TiCl_2 with either zinc or manganese metal (Scheme 6), other metal salts ($ZnCl_2$ or $MnCl_2$) are generated and will be present in solution. These salts have no effect upon the redox potential of **6** and **7** or upon the dimerization equilibrium constant.[34] It is significant that, unlike in **5**, both structures **6** and **7** possess a potentially vacant coordination site. In the absence of a reactant, this site is generally occupied by a molecule of THF as shown in Scheme 7. The presence of $ZnCl_2$ or $MnCl_2$ may actually serve a protective function, especially for $(C_5H_4R)_2TiCl$ analogues bearing an electron-withdrawing substituent on the Cp ring. For instance, when these species are generated under electrochemical conditions the loss of the cyclopentadienyl ligand is the major pathway, but not when zinc or manganese is used as reductant. This is attributed to efficient chloride abstraction from $[(C_5H_4R)_2TiCl_2]^-$ by Zn^{2+} or Mn^{2+}.[37]

When reactions with Cp_2TiCl are carried out under catalytic conditions, 2,4,6-collidine hydrochloride is often added as a mild acid, thus providing a stoichiometric source of chloride for MCl_2. Although primarily intended to promote protonolysis of titanium alkoxide species,[38] two additional roles have been identified for this reactant. Kinetic studies indicate that collidine hydrochloride can activate the manganese powder that is used as the stoichiometric reductant. This effect significantly reduces the induction period for some catalytic reactions.[39] The presence of collidine hydrochloride also protects the catalyst from decomposition by forming the titanium(III) ate complex **8** (Figure 1). It has been proposed that the presence of collidine hydrochloride disrupts the usual monomer–dimer equilibrium by the formation of an equilibrium mixture of monomeric Cp_2TiCl and **8**.[40]



8

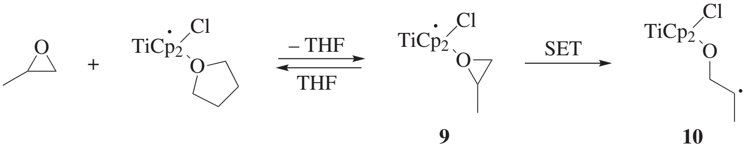
Figure 1. The original structure proposed for the adduct of Cp_2TiCl with collidine hydrochloride.

Recent DFT studies have demonstrated that the energy of complex **8** is 18.4 kcal/mol lower than that of the two separate species.[41] However, in the minimized structure, the second chlorine atom is not coordinated to the titanium atom. Thus, the titanium atom is accessible for epoxide binding and subsequent inner-sphere electron transfer, so that the rate of this process is essentially unchanged from that involving uncomplexed Cp_2TiCl.[41]

Assigning a redox potential to Cp_2TiCl in THF is complicated by issues of solution speciation.[34,42] The most readily oxidizable component of such solutions is $Cp_2TiCl_2^-$ ($E° = -1.27$ V versus Fc^+/Fc), but this anion does not react with epoxides because it lacks an open coordination site for inner-sphere electron-transfer.[34,43] Moreover, such solutions contain both monomeric Cp_2TiCl and dimeric $(Cp_2TiCl)_2$, and these species have slightly different redox potentials. The effective redox potential for this mixture is typically given as $E° = -0.8$ V versus Fc^+/Fc,[28] which corresponds to a broad oxidation wave in the cyclic voltammogram.[34] This value may be compared to more potent one-electron reductants such as SmI_2 ($E° = -1.41$ V versus Fc^+/Fc).

Electrochemical and DFT studies have been used to probe the reduction of $Cp_2Ti(IV)Cl_2$ to $[Cp_2Ti(III)Cl_2]^-$ and its subsequent loss of chloride ion in the presence of various ligands. The goal of these studies was to screen for catalytic reaction conditions without actually running any catalytic reactions.[44]

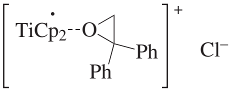
Mechanism of Epoxide Carbon–Oxygen Bond Cleavage. The titanium(III)-mediated carbon–oxygen bond homolysis of epoxides proceeds by an inner-sphere electron-transfer mechanism. This process requires prior coordination of the epoxide to the titanium atom,[43] as depicted in Scheme 8 for the case of propylene oxide and monomeric Cp_2TiCl.



Scheme 8

DFT calculations indicate that replacement of the metal-bound THF by an epoxide is approximately thermoneutral. In the case of propylene oxide in Scheme 8, the formation of complex **9** is exothermic by 2.2 kcal/mol.[43] The more sterically encumbered isobutylene oxide is forced to adopt a less favorable geometry: the bound epoxide is turned 90° relative to the position adopted by propylene oxide in complex **9**, so that replacement of THF by isobutylene oxide is actually disfavored (difference in binding enthalpy = +2.2 kcal/mol).[43] This difference is of little practical importance, because exchange is rapid, and the subsequent carbon–oxygen bond homolysis is typically rate-limiting. Nevertheless, synthetic chemists should be aware of the need for epoxide coordination to titanium(III); in some cases, highly encumbered epoxides fail to undergo carbon–oxygen bond cleavage apparently due to the inability of the epoxide to coordinate to titanium.[45,46] Another practical implication is that strongly metal-binding solvents should be avoided.[47]

In one case, it is possible to observe the complex formed by reaction of Cp_2TiCl with an epoxide using EPR techniques at 243 K. The epoxide, 1,1-diphenylethylene oxide, is a sterically demanding substrate, and both DFT calculations and the spectroscopic results indicate that it is not possible for this epoxide to bind to the titanium atom without loss of the chloride ligand. Consequently, the complex is best represented by structure **11** (Figure 2). Complex **11** persists for only a short period (<5 min) even at 243 K and decomposes by the expected carbon–oxygen bond homolysis.[36]



11

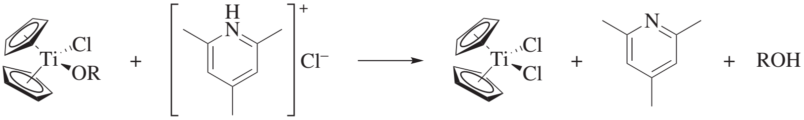
Figure 2. The structure of the titanium(III)-epoxide complex.

Once the epoxide is coordinated to the titanium atom, the carbon–oxygen bond cleavage in Scheme 8 proceeds rapidly to afford the β-titanoxy radical (represented as the major constitutional isomer **10**). The activation energy for this step for typical epoxides is calculated to be in the range of 7.0 to 10.3 kcal/mol,[43] and the carbon–oxygen bond cleavage is mildly exothermic. Calculated reaction energies for typical epoxides are between −1.8 and −8.5 kcal/mol. This reaction energy may seem surprisingly low given the release of epoxide ring strain and the formation of a strong titanium–oxygen bond, but these factors are counterbalanced by the energetic costs of not only the carbon–oxygen bond cleavage, but the replacement of a stable titanium-centered radical by a high-energy carbon-centered radical.[43] The reaction enthalpy for the carbon–oxygen bond homolysis in complex **11** is somewhat higher (−22.5 kcal/mol), reflecting the higher stability of the product radical.[36]

Regarding β-titanoxy radicals **10**, computational studies show that the inductive effect of the alkoxide is negligible. Essentially no significant stabilization or destabilization of the radical center is exerted by the $ClCp_2TiO$ group.[48] The rate constant for titanium-mediated epoxide opening has been determined to be in the range $k = 0.5–2\ M^{-1}s^{-1}$.[43] The issue of whether the SET step in Scheme 8 might itself be reversible is addressed below in the discussion of the regioselectivity of carbon–oxygen bond cleavage.

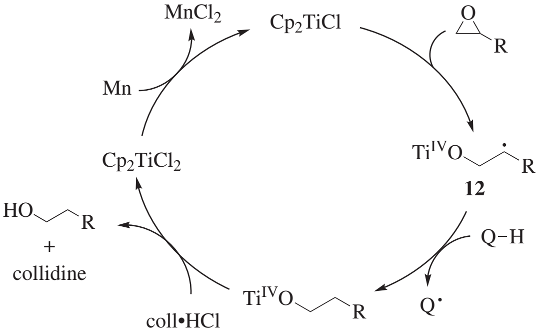
Regeneration of Cp_2TiCl During Catalysis. Reduction of an epoxide as in Scheme 8 results in concomitant oxidation of the titanium atom from the +3 to the +4 oxidation state. Consequently, a stoichiometric reductant is required (typically manganese or zinc powder) in addition to the substoichiometric titanium catalyst. However, after reduction of the epoxide, the titanium is generally present as a titanium(IV) alkoxide, which cannot be directly converted to Cp_2TiCl. Therefore, the titanium-containing product must first be converted back to the Cp_2TiCl_2 precatalyst, and this process may be accomplished under either protic or aprotic conditions.

Protic recycling of the catalyst involves the use of a Brønsted acid to regenerate Cp_2TiCl_2 from titanium(IV) intermediates. It has been proposed[5] that for efficient protonolysis of the titanium alkoxide intermediate, the pK_a difference between the proton donor and a typical alcohol (e.g., MeOH, pK_a = 15.5) should be at least 3. On the other hand, the acid should not have a pK_a lower than that of pyridine hydrochloride, which promotes the opening of epoxides to chlorohydrins in chloroform. This suggests a pK_a window in the range of 5.25–12.5. At the same time, the conjugate base of the acid should not coordinate to and deactivate the titanium catalyst. A Brønsted acid that satisfies these requirements is 2,4,6-collidine hydrochloride (coll•HCl), which has been widely utilized for this purpose (Scheme 9).[5]



Scheme 9

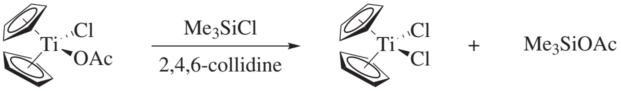
The use of coll•HCl in a hypothetical titanium(III)-catalyzed epoxide reduction is illustrated in Scheme 10. A hydrogen atom donor Q–H has been included to trap the intermediate β-titanoxy radical **12**. (The mechanism of hydrogen-atom transfer to



Scheme 10

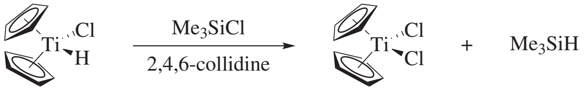
β-titanoxy radicals is discussed below.) The resultant titanium alkoxide **13** is released as the corresponding alcohol upon reaction with coll•HCl.

Aprotic catalysis involves the use of chlorotrimethylsilane rather than a protic acid to convert titanium(IV) intermediates back to Cp_2TiCl_2 prior to re-reduction to Cp_2TiCl with manganese (the stoichiometric reductant). Aprotic catalysis has been recommended for reactions that produce titanium products other than simple alkoxides, for example $Cp_2Ti(H)Cl$ or $Cp_2Ti(Cl)OAc$.[49] Regeneration of Cp_2TiCl_2 from $Cp_2Ti(Cl)OAc$ is illustrated in Scheme 11. In such reactions, chlorotrimethylsilane cannot be used alone because of its tendency to promote carbocation reactivity; the combination of 2,4,6-collidine and chlorotrimethylsilane is proposed to afford a silylated pyridinium ion that does not promote such undesired side reactions.[6]



Scheme 11

Aprotic catalysis has also been suggested to regenerate Cp_2TiCl_2 from $Cp_2Ti(H)Cl$, which is another potential intermediate generated in the reaction of Cp_2TiCl with epoxides.[49,50] In this case, chlorotrimethylsilane purportedly reacts with the titanium hydride by σ-bond metathesis, affording trimethylsilane as coproduct (Scheme 12). However, the premise that $Cp_2Ti(Cl)H$ is an unusually robust intermediate appears to be incorrect:[51] as discussed below (Scheme 19), $Cp_2Ti(H)Cl$ rapidly decomposes to Cp_2TiCl and molecular hydrogen.



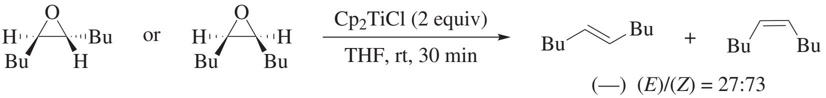
Scheme 12

A modified protic catalyst system has also been proposed to promote recycling of $Cp_2Ti(Cl)H$ to Cp_2TiCl.[52] In this protocol, triethylborane (1.5 equivalents) is employed as an additive, and lutidine hydrochloride serves as the Brønsted acid; yields using this catalyst are slightly higher than when using lutidine hydrochloride alone. The proposed mechanism requires that triethylborane undergo spontaneous homolysis to produce ethyl radicals at room temperature under argon. The resulting ethyl radicals purportedly abstract hydrogen from $Cp_2Ti(H)Cl$, forming Cp_2TiCl and ethane.[52] However, there is no evidence to support this claim.

Mechanistic Pathways of β-Titanoxy Radicals

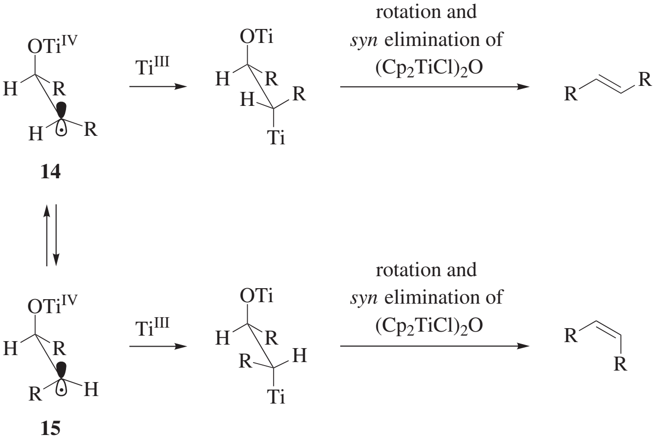
Epoxide Deoxygenation. In the absence of other radical acceptors, the β-titanoxy radical **10** generated in Scheme 8 will react with a second equivalent of Cp_2TiCl.

In the case of 1° and 2° radicals, this will generally result in cleavage of the carbon–oxygen bond of the titanoxy moiety, affording the corresponding alkene. There have been no formal mechanistic studies on this pathway, but several observations provide mechanistic insight. In particular, deoxygenation proceeds with loss of configurational identity, as is illustrated in Scheme 13 for the case of (*E*)- and (*Z*)-5-decene oxide.[4] In each case a 27:73 mixture of (*E*)- and (*Z*)-alkenes is observed by GLC analysis.



Scheme 13

The titanium-containing product from this deoxygenation is the oxo-bridged dimer $Cp_2ClTi–O–TiClCp_2$, which has previously been isolated as a crystalline solid after reduction of cyclohexene oxide with Cp_2TiCl.[16] The predominant formation of the (*Z*)-alkene in Scheme 13 is contra-thermodynamic, because the (*E*)-alkene is slightly lower in energy. Given the need for *two equivalents* of Cp_2TiCl, one way to rationalize this stereochemical outcome is shown in Scheme 14. After initial carbon–oxygen bond homolysis, rotation about the carbon–carbon bond allows interconversion of radicals **14** and **15**; conformation **15** is expected to be more stable than **14** for steric reasons. Trapping of the radicals by titanium(III) is then proposed to occur on the side opposite the bulky titanoxy substituent. Rotation and *syn* elimination would result in predominant formation of the (*Z*)-alkene. An attractive feature of this mechanism is that it minimizes charge separation in the transition state, which means that elimination proceeds without the relatively high-energy formation of a Cp_2TiCl^+ cation and a Cp_2ClTiO^- anion. Nevertheless, Curtin–Hammett kinetics may instead be applicable, and some caution is required in

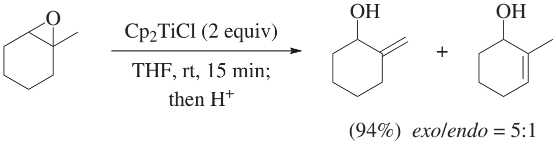


Scheme 14

generalizing the process outlined in Scheme 14. Furthermore, calculations showing the viability of a *syn* elimination involving two bulky titanocene moieties has not been reported. Moreover, cycloalkene oxides where *syn* elimination is precluded readily undergo deoxygenation, wherein a *trans*-periplanar transition state would need to be invoked. The resulting ionic species, Cp_2TiCl^+ and Cp_2ClTiO^-, would then recombine to form the oxo-bridged dimer.

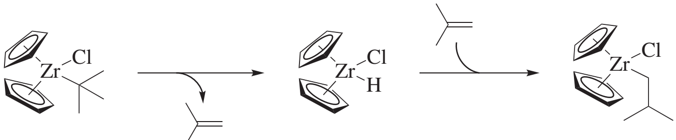
Because of the requirement for a second equivalent of titanium(III) in Scheme 14, deoxygenation is kinetically favored by a high concentration of titanium(III). Consequently, these reactions are best accomplished by the addition of a solution of the epoxide to pre-generated Cp_2TiCl.[4] Epoxide deoxygenation is generally not observed even as a side reaction under protic catalytic conditions.[38] In contrast, catalytic deoxygenation has been achieved under aprotic conditions (20 mol % titanium, 2,4,6-collidine, chlorotrimethylsilane), but yields are somewhat lower than those obtained with stoichiometric deoxygenation.[17]

Elimination of β-Hydrogen. In contrast to mono- and disubstituted epoxides, treatment of trisubstituted epoxides with Cp_2TiCl generally does not result in deoxygenation. Instead, the process results in the loss of a hydrogen atom to afford an allylic alcohol as exemplified by Scheme 15.[51,53]



Scheme 15

One proposed mechanism involves the combination of the 3° β-titanoxy radical with Cp_2TiCl to afford a 3° titanium(IV) organometallic that then undergoes β-hydride elimination. For instance, an analogy can be drawn with the well-known instability of 3° zirconium(IV) organometallic species (Scheme 16).[53−55] *tert*-Butyl zirconocene complex **16** is prepared by treatment of Cp_2ZrCl_2 with *t*-BuLi or *t*-BuMgCl at low temperature. When this solution is allowed to warm to room temperature, β-hydride elimination of isobutylene generates Schwartz's reagent (**17**), which upon re-addition of isobutylene delivers **18**.[56,57]



16 **17** **18**

Scheme 16