11

ASYMMETRIC OXIDATIONS AND RELATED REACTIONS

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11.1. GENERAL INTRODUCTION

Oxidation is a fundamental technology for converting bulk chemicals into valuable materials and is also a useful tool for sophisticated functionalization of organic molecules. Thus, intensive research efforts have been devoted to the development of selective and practical oxidation methods, and a wide variety of chiral metal-based catalysts and organocatalysts have been developed for catalytic asymmetric oxidation reactions in industry and academia in the last half-century [1]. In contrast to the rapid improvement in stereoselectivity, the enhancement of atom economy [2] falls behind. While atom efficiency (especially active oxygen content in oxygenation reactions) of stoichiometric oxidants is a factor that should be considered, most of the catalytic asymmetric oxidations still use conventional stoichiometric oxidants of low atom-efficiency such as peracids, alkyl hydroperoxides, hypervalent iodine reagents, hypochlorite, and *N*-oxide compounds (Table 11.1). The use of such oxidants causes the formation of large amounts of undesirable waste. From the viewpoint of ecological sustainability, oxidation with a higher atom-efficient, safe, abundant, and preferably inexpensive oxidant is favorable. Considering the requirements, molecular oxygen and hydrogen peroxide are the oxidants of choice [3]. Molecular oxygen offers a large advantage because it is abundant in air and is inexpensive. Aerobic oxidation that directly uses ambient air as an oxidant is similar to respiration in living organisms. Hydrogen peroxide is also recognized as a green oxidant. It is almost as equally atom-efficient as molecular oxygen, and the by-product is safe and clean water. Moreover, its aqueous solution (typically 30–35%) is inexpensive and easy to handle. Consequently, the development of catalytic asymmetric oxidations with molecular oxygen

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TABLE 11.1. Active Oxygen Content

Oxidant	By-product	Active Oxygen Content (%)
O_2	—	100
O_2	H_2O	50
H_2O_2	H_2O	47.0
NaOCl	NaCl	21.6
*t*BuOOH (TBHP)	*t*BuOH	17.8
$KHSO_5$ (Oxone®)	$KHSO_4$	10.5
m$ClC_6H_4CO_3H$ (*m*CPBA)	*m*$ClC_6H_4CO_2H$	9.3
PhIO	PhI	7.3

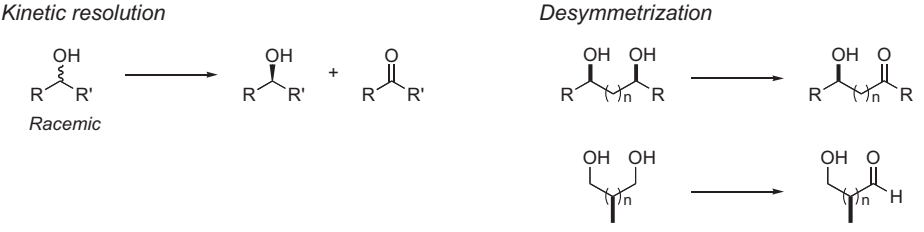
or hydrogen peroxide as oxidants is one of the most important issues to be addressed by organic chemists.

Since the launch of the second edition, remarkable progress has been made in the field of catalytic asymmetric oxidation. This chapter mainly focuses on the recent developments of catalytic asymmetric oxidations using molecular oxygen or hydrogen peroxide as oxidants reported after 2000, and the notable advancements in oxidation using conventional oxidants are also reviewed.

11.2. ASYMMETRIC OXIDATION OF ALCOHOLS

11.2.1. Introduction

Oxidation of alcohols to the corresponding carbonyl compounds is a pivotal process for organic synthesis, and many methods have been developed [4]. Among them, oxidations that employ readily available molecular oxygen, especially ambient air, as the stoichiometric oxidant are the most preferable. Therefore, the development of aerobic alcohol oxidations has attracted increasing interest, and some synthetically valuable protocols using transition-metal complexes and organic molecules as catalyst have been reported [5]. Recently, significant progress has also been made in the development of chiral catalysts. The asymmetric reactions are mainly divided into two classes: kinetic resolution of racemic secondary alcohols and desymmetrization of *meso*- or prochiral diols (Scheme 11.1).

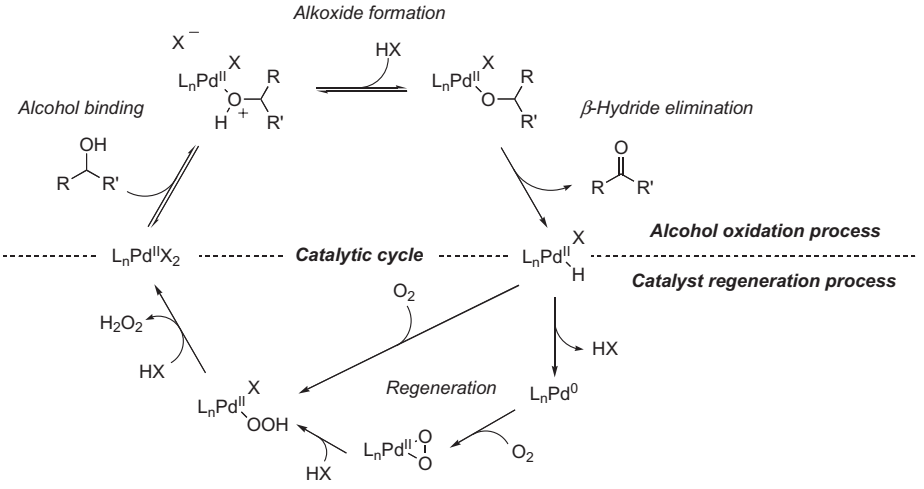


Scheme 11.1.

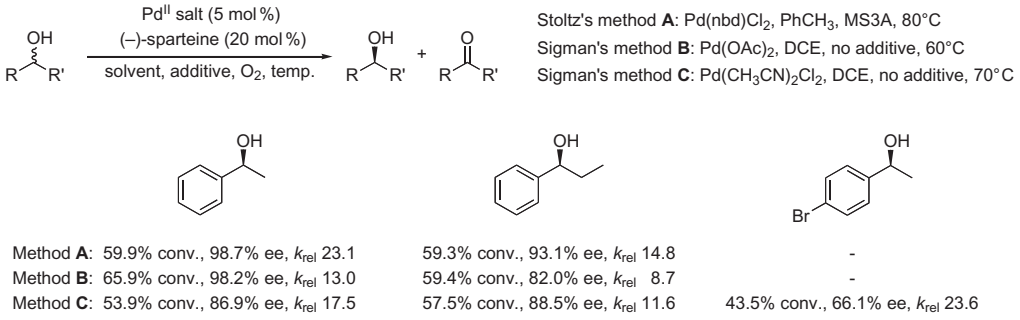
11.2.2. Palladium Catalyst

Among the transition-metal catalysts developed for aerobic oxidation of alcohols, palladium-based complexes, in particular, have been investigated. In 1977, Schwaltz and Blackburn reported the first synthetically valuable, palladium-catalyzed aerobic oxidation of alcohols that uses $PdCl_2$ with NaOAc [6]. Although the following 20 years had seen few developments in this area, the palladium-catalyzed methods have received the most attention over the recent years [7,8]. A generally accepted catalytic cycle is illustrated in Scheme 11.2. The cycle consists of the two separate processes: alcohol oxidation and catalyst regeneration. In the alcohol oxidation process, palladium alkoxide is formed after alcohol coordination, and then β-hydride elimination occurs to give a carbonyl product. The resulting palladium hydride complex is converted to the corresponding palladium hydroperoxo species by the reaction with molecular oxygen, and the subsequent ligand exchange regenerates the initial catalyst. There are two possible pathways to give the Pd^{II} hydroperoxide species: direct insertion of molecular oxygen to Pd^{II}-hydride bond or reductive elimination/peroxo formation/protonolysis sequence. The feasibility of each pathway has been supported by experimental and theoretical studies.

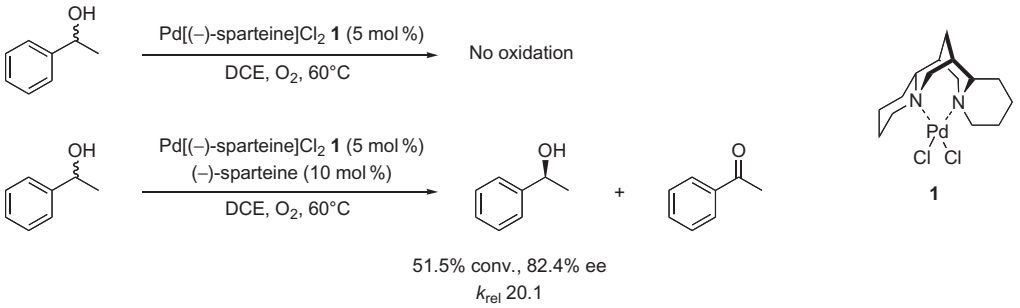
In 1998, Uemura and coworkers reported the palladium-catalyzed aerobic oxidation of alcohols, using a $Pd(OAc)_2$, pyridine, and molecular sieve 3A system [8a,b]. Inspired by the report, Sigman et al. and Stoltz and Ferreira independently disclosed the palladium-catalyzed oxidative kinetic resolution of racemic alcohols, in which a naturally occurring diamine, (–)-sparteine, serves as an effective chiral source (Scheme 11.3) [9,10]. Sigman and coworkers employed the two reaction conditions: $Pd(OAc)_2$ in dichloroethane (DCE) at 60°C and $Pd(CH_3CN)_2Cl_2$ at 70°C. On the other hand, Stoltz's methods utilized $Pd(nbd)Cl_2$ with molecular sieves in toluene at 80°C. While there are slight differences between the reaction conditions of the methods, both systems efficiently resolve a range of benzylic alcohols with good to high k_{rel} values. An allylic alcohol and an aliphatic alcohol also undergo resolution albeit with moderate k_{rel} values.



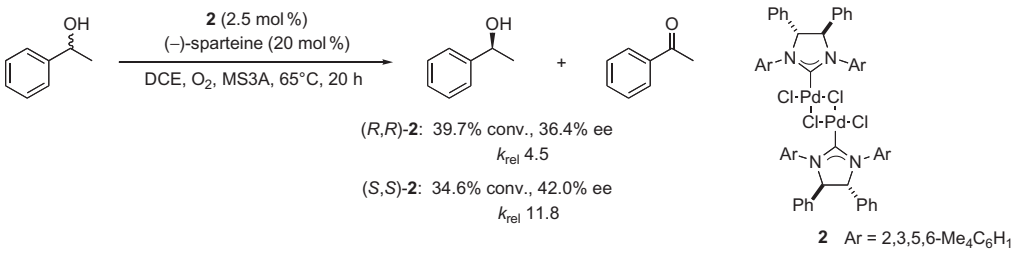
Scheme 11.2.



Scheme 11.3.



Scheme 11.4.



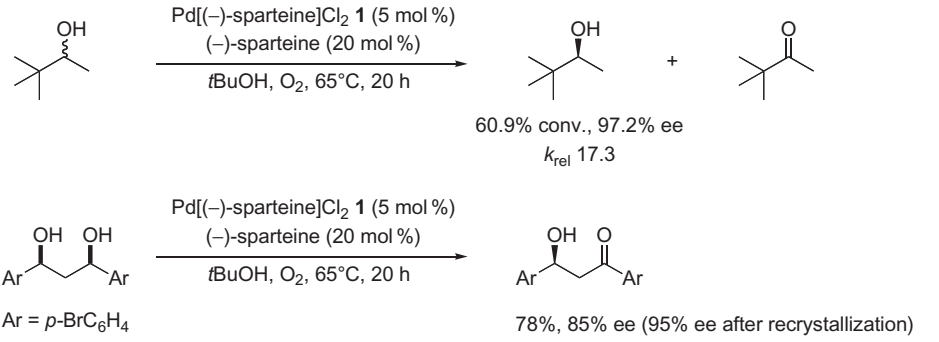
Scheme 11.5.

Moreover, Sigman et al. disclosed that the isolated Pd[(–)-sparteine]Cl_2 complex **1** is incompetent as the catalyst, although catalytic activity is restored by the addition of (–)-sparteine (Scheme 11.4) [9,11]. The additional (–)-sparteine serves as an exogenous base to abstract a proton from a palladium-bound alcohol in the alkoxide formation process. The observation implies that the proton abstraction step might be an enantiomer differentiation process. Indeed, Sigman and Jensen reported that palladium complexes bearing chiral or achiral N-heterocyclic carbene ligands promote the oxidative kinetic resolution in the presence of (–)-sparteine (Scheme 11.5) [12]. (*S*,*S*)-**2** makes a matched pair with (–)-sparteine and exhibits higher selectivity than (*R*,*R*)-**2**.

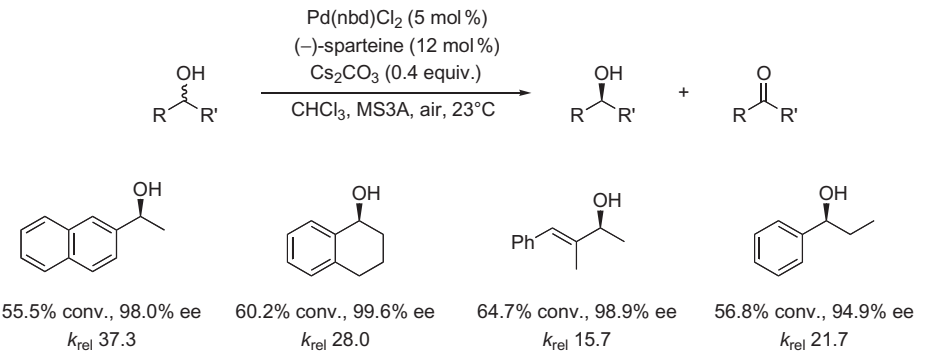
The complex **1**, together with 20 mol % of (–)-sparteine in *t*BuOH, effectively promotes the kinetic resolution of benzylic alcohols with higher selectivity than that observed under the original conditions [13]. Kinetic resolution of nonbenzylic alcohols also proceeds with moderate to high k_{rel} values, and the method could be applied to desymmetrization of 1,3-*meso*-diols to give enantio-enriched β-hydroxyketones with good enantioselectivity (Scheme 11.6).

On the other hand, Stoltz and coworkers reported that the addition of Cs_2CO_3 and *t*BuOH greatly accelerates the reaction, although a long reaction time (typically 4 days) is required to obtain high conversion of alcohols in their original conditions [10,14]. With these additives, the resolutions are achieved in less than 24 h at 60°C with comparable selectivity. Eventually, the group found that the optimal conditions use 5 mol % of $Pd(nbd)Cl_2$ and 12 mol % of (–)-sparteine in chloroform in the presence of 0.4 equivalents of Cs_2CO_3 and molecular sieves at 23°C (Scheme 11.7) [15]. It is worth noting that ambient air is available instead of pure molecular oxygen under these conditions. It has been proposed that chloroform accelerates the reaction rate through hydrogen bonding with some intermediates and/or solvating to the chloride ion.

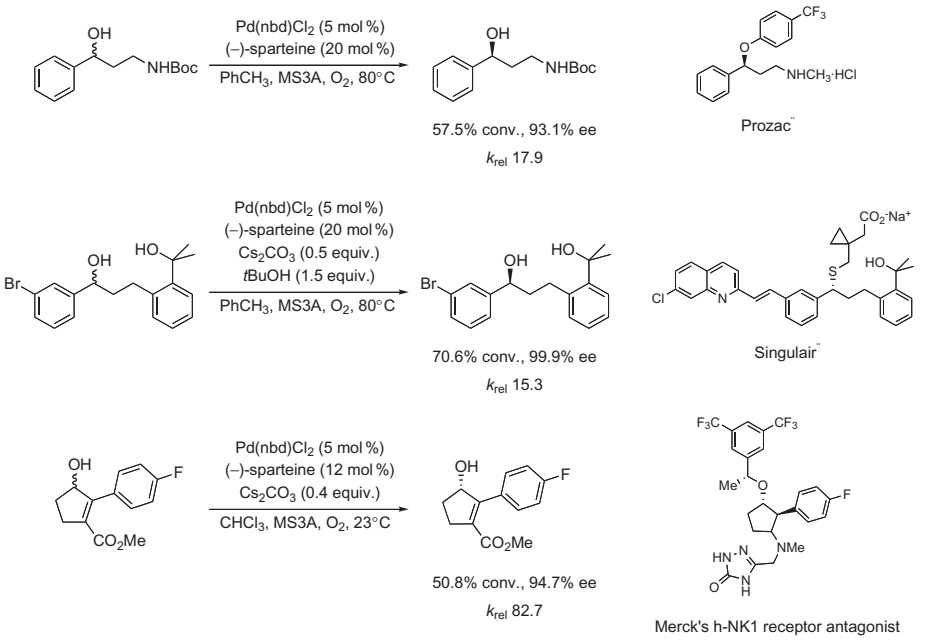
The utility of the Pd/(–)-sparteine-catalyzed aerobic alcohol oxidation can be recognized by its application to the enantioselective preparation of key pharmaceutical



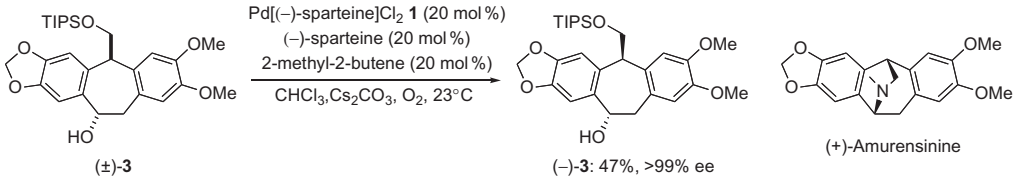
Scheme 11.6.



Scheme 11.7.



Scheme 11.8.



Scheme 11.9.

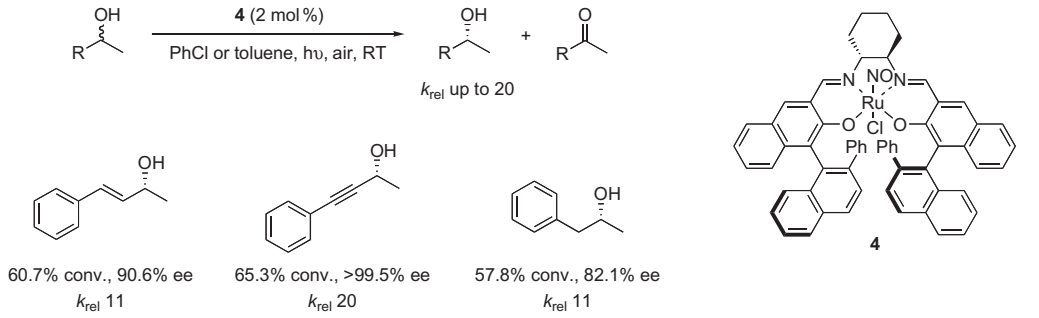
substances including Prozac®, Singulair®, and Merck's h-NK1 receptor antagonist reported by Stoltz and coworkers (Scheme 11.8) [16]. The total synthesis of (+)-amurensinine, a member of the isopavine family that exhibits important biological activities toward Alzheimer's and Parkinson's diseases, was also accomplished by using the palladium catalysis (Scheme 11.9) [17]. The racemic benzylic alcohol (±)-**3** was efficiently resolved to (–)-**3** with >99% ee.

11.2.3. Ruthenium Catalyst

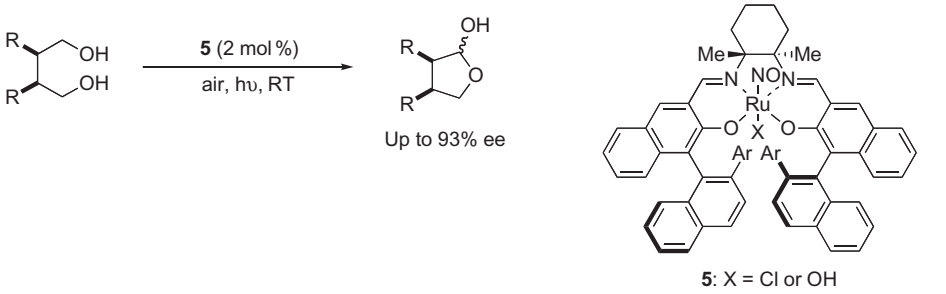
Ruthenium complexes have been known to be effective catalysts for the aerobic oxidation of alcohols [18]. In 2000, Katsuki and coworkers reported the first example of oxidative kinetic resolution of secondary alcohols with ambient air as the oxidant, in which chiral (nitrosyl)ruthenium(salen) complex **4** is employed as precatalyst [19].

The irradiation of visible light promotes dissociation of the nitrosyl ligand to generate a coordinatively unsaturated and catalytically active ruthenium species. Under ambient conditions, kinetic resolution of aryl, alkenyl, alkynyl, and alkyl carbinols efficiently proceeded with k_{rel} values up to 20 (Scheme 11.10). The addition of 1,3-diketones was found to improve the k_{rel} values up to 30 [20]. Katsuki and coworkers also reported that modified ruthenium complexes **5** serve as an efficient catalyst for oxidative desymmetrization of 1,4-*meso*-diols (Scheme 11.11) [21].

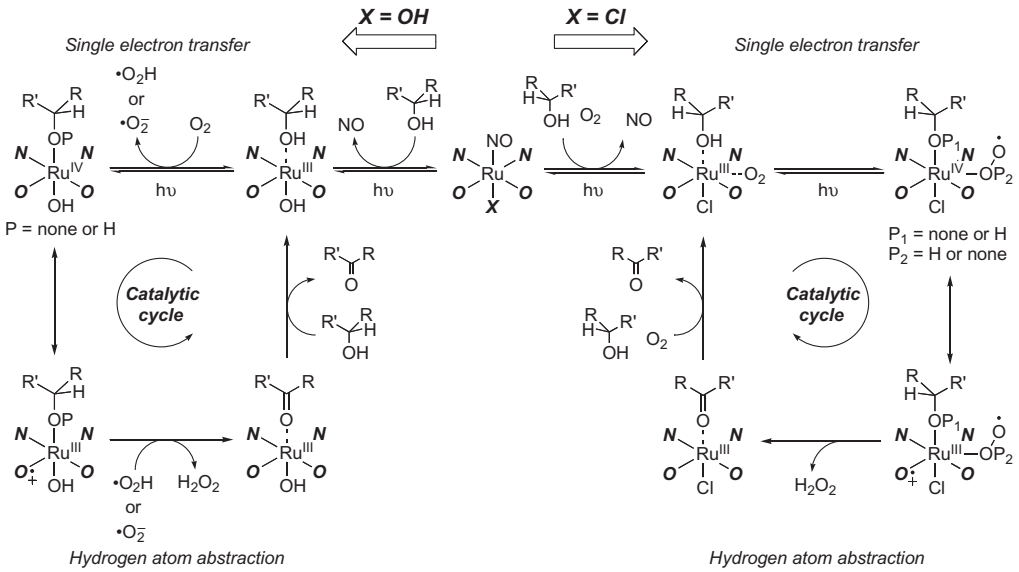
Kinetic studies disclosed that the ruthenium-catalyzed oxidation of alcohols proceeds through the following sequence, although the details differ between the apical ligands used (Scheme 11.12) [22]: A single electron is transferred from the ruthenium ion to dioxygen after dissociation of the nitrosyl group by the irradiation of visible light, and electron delocalization between the ruthenium ion and the donor oxygen atom of the salen ligand gives a cationic phenoxy radical. The following intramolecular hydrogen atom abstraction by the phenoxy radical and the subsequent exchange of the product and alcohol regenerate the alcohol-binding catalyst. It is noteworthy



Scheme 11.10.



Scheme 11.11.

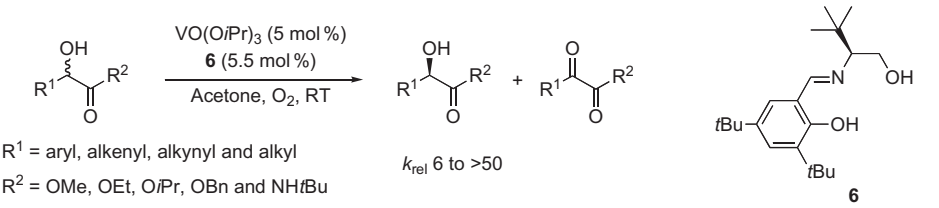


Scheme 11.12.

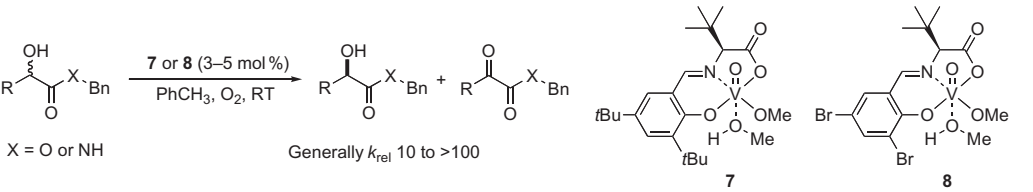
that the ruthenium complex can be regarded as a mimic of galactose oxidase, although each metal ion is not the same [23]. Although desymmetrization of *meso*-diols also traces a similar catalytic cycle, the hydrogen atom is intermolecularly abstracted by a hydroperoxy or superoxide radical as a consequence of the electron delocalization onto the substrate oxygen atom instead of the donor oxygen atom, due to the stabilization of the resultant cation radical by hydrogen bonding with another hydroxy group.

11.2.4. Vanadium Catalyst

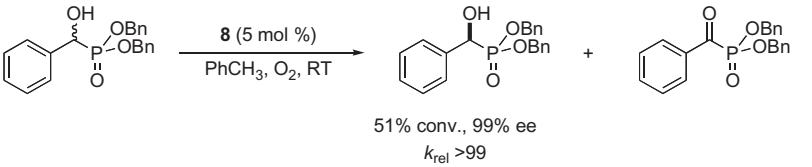
Two elegant reports on vanadium-catalyzed asymmetric aerobic oxidation of α-hydroxy carbonyl compounds were independently published by the groups of authors [24–26]. Toste and coworkers used a vanadium complex *in situ* prepared from $VO(OiPr)_3$ and tridentate Schiff base ligand **6** derived from 3,5-di-*tert*-butylsalicylaldehyde and (*S*)-*tert*-leucinol, and achieved k_{rel} values ranging from 6 to >50 in the kinetic resolution of various α-hydroxy esters (Scheme 11.13). Aliphatic substrates as well as aryl, alkenyl, and alkynyl ones are efficiently resolved, although increased reaction times are required. In addition, α-hydroxy amides are also good substrates for the resolution. The mechanism via a radical species at the carbinol carbon is unlikely for this vanadium-catalyzed oxidation, because the reaction of an α-hydroxy ester having cyclopropyl group at the α-position gives no ring-opening product.



Scheme 11.13.



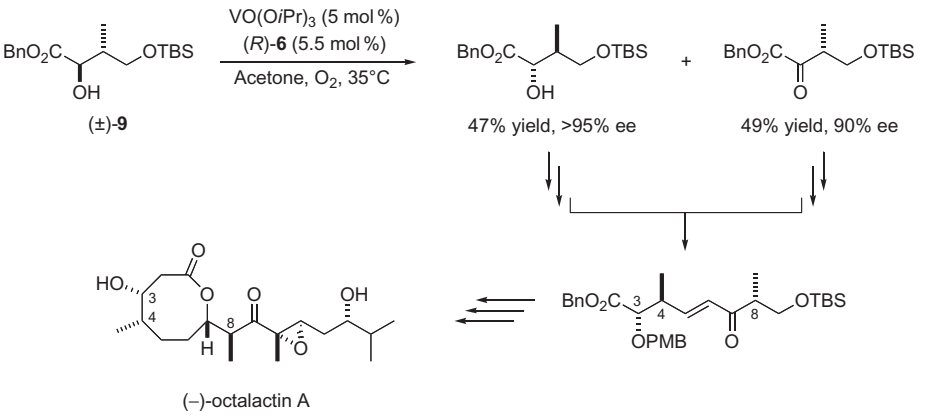
Scheme 11.14.



Scheme 11.15.

On the other hand, Chen and coworkers have shown that α-amino acid–based vanadium(V) complexes **7** and **8** promote kinetic resolution of a wide variety of α-hydroxy esters and amides (Scheme 11.14). In most substrates, high k_{rel} values ranging from 10 to >100 are obtained. Complex **8** can be also applied to asymmetric aerobic oxidation of α-hydroxyphosphonic acid derivatives, which are attractive targets in medicinal chemistry (Scheme 11.15) [27]. Various dibenzyl α-hydroxy phosphonates bearing aryl or vinyl substituent at the α-position are effectively resolved, generally with excellent selectivity (k_{rel} > 99).

Although kinetic resolution is an attractive approach through which to prepare extremely enantio-enriched molecules, the maximum theoretical yield is 50%, and the inherent property limits the synthetic values. However, Toste and coworkers have shown a practical solution to the problem. They applied the vanadium-catalyzed oxidative kinetic resolution to the total synthesis of (–)-octalactin A, possessing cytotoxicity toward B-16-F10 murine melanoma and HCT-116 human colon tumor cell lines (Scheme 11.16) [28]. The key intermediate α-hydroxy ester **9** was effectively resolved into the alcohol and the ketone, with >95% ee and 90% ee, respectively. The two resolution products were combined after several transformations and led to (–)-octalactin A. This

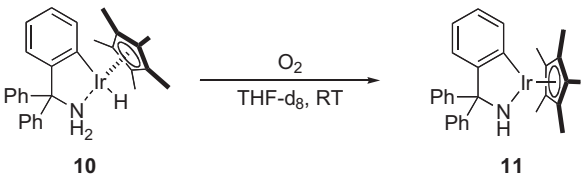


Scheme 11.16.

resolution/recombination approach made it possible to construct the C3, C4, and C8 stereocenters in a single process.

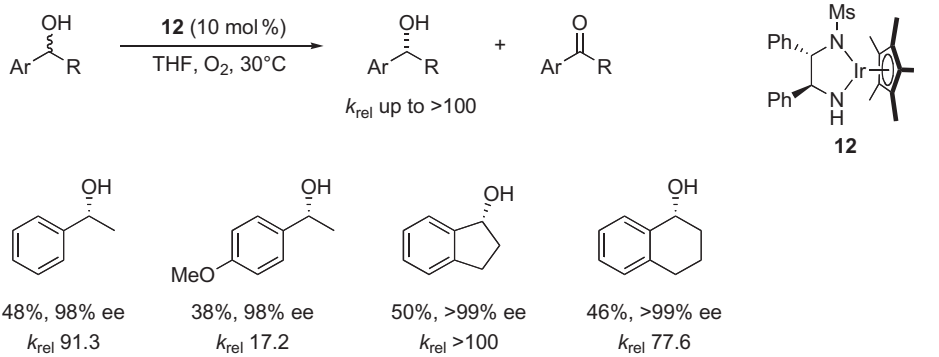
11.2.5. Iridium Catalyst

Chiral iridium amide complexes were identified as a catalyst for oxidative kinetic resolution of racemic secondary alcohols by Ikariya and coworkers [29]. The authors found that the treatment of iridium hydride complex **10** with molecular oxygen or air gave the corresponding amido complex **11** (Scheme 11.17) [29,30]. It is well established that iridium–amido complexes dehydrogenate alcohols to give the amine–hydride complexes and ketones in the asymmetric transfer hydrogenation of ketones [31]. Basing on the finding, they disclosed that chiral iridium complex **12** catalyzed kinetic resolution of benzylic alcohols with high k_{rel} values under air (Scheme 11.18). 1-Indanol underwent resolution efficiently, and the (*R*)-enantiomer was recovered in 50% with >99% ee.

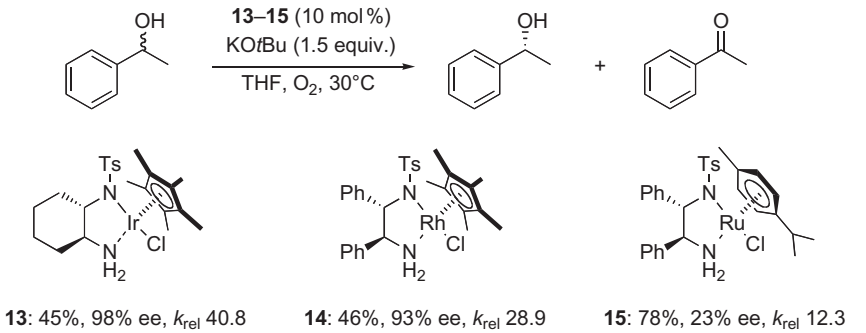


Scheme 11.17.

Moreover, Ikariya and coworkers reported that iridium chloride complex **13**, together with KO*t*Bu, equally promoted the reaction with a k_{rel} value as high as 40.8 (Scheme 11.19) [29]. The rhodium analogue **14** also exhibited high catalytic performance in the presence of the base, but the related ruthenium complex **15** gave a diminished result.



Scheme 11.18.



Scheme 11.19.

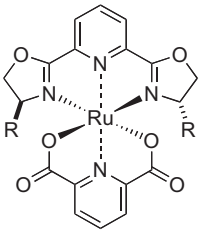
11.3. ASYMMETRIC EPOXIDATION

11.3.1. Introduction

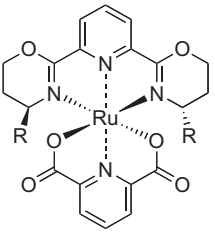
Since the discovery of the Katsuki–Sharpless asymmetric epoxidation [32], a large number of chiral catalysts have been developed [33]. Recently, an increasing social demand for a fundamental solution to environmental problems and pure academic interests has been accelerating the advances of asymmetric epoxidation using greener oxidants, especially aqueous hydrogen peroxide. Remarkable progress has also been made in the development of chiral epoxidation catalysts using alkyl hydroperoxides as oxidant.

11.3.2. Ruthenium Catalyst

Beller and coworkers reported ruthenium-catalyzed asymmetric epoxidation of olefins with aqueous hydrogen peroxide as oxidant [34,35]. On the basis of the

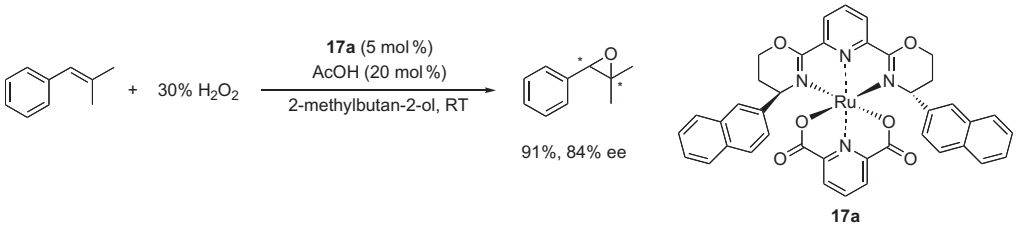


Ru(pybox)(pydic) **16**



Ru(pyboxazine)(pydic) **17**

Figure 11.1.



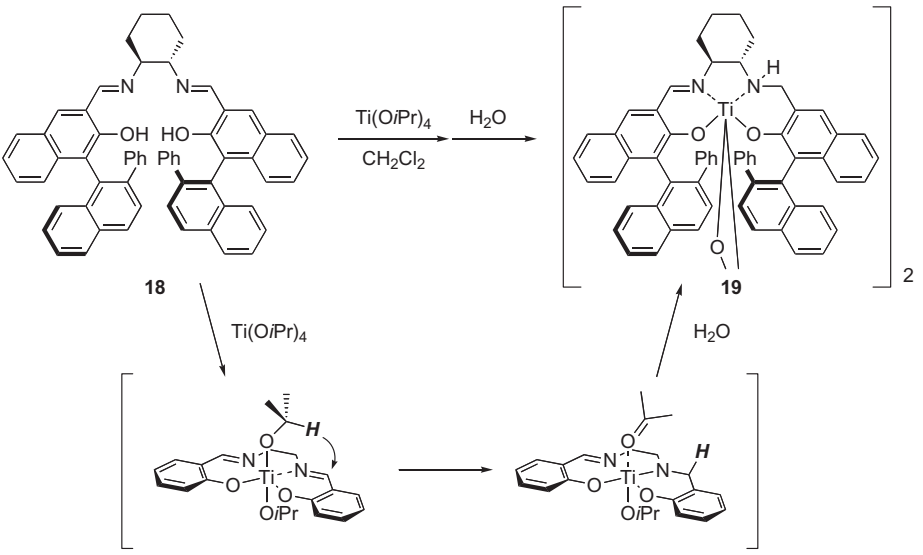
Scheme 11.20.

Nishiyama's report that Ru(pybox)(pydic) complexes **16** (pydic = 2,6-pyridinedicarboxylate) promote epoxidation of *trans*-stilbene with $PhI(OAc)_2$ as oxidant [36], they designed Ru(pyboxazine)(pydic) complexes **17** [pyboxazine = 2,2′-pyridine-2,6-diylbis(5,6-dihydro-4*H*-1,3-oxazine)] for the reaction (Fig. 11.1). The ruthenium complex **17a**–bearing 2-naphthyl groups proved the most effective, and the highest ee value of 84% was achieved in the epoxidation of 2-methyl-1-phenyl-1-propene (Scheme 11.20). The addition of acetic acid improved the catalytic performances, and the authors suggested that the additional acid stabilizes the active intermediate.

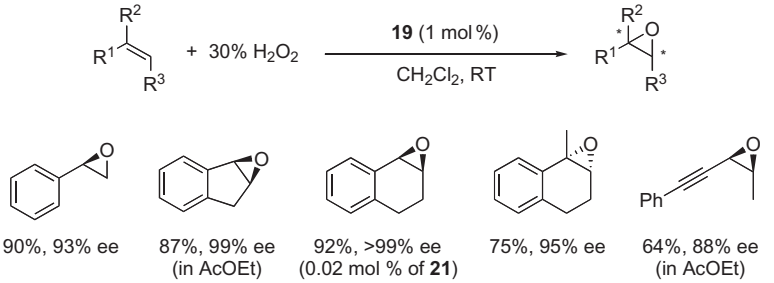
11.3.3. Titanium Catalyst

Katsuki and coworkers identified a chiral titanium complex as a catalyst for asymmetric olefin epoxidation [37]. They found that di-μ-oxo Ti(salalen) complex **18** (salalen = salen/salan hybrid ONNO-type tetradentate ligand), which is readily prepared from $Ti(OiPr)_4$ and the corresponding salen ligand **19** via an intramolecular Meerwein–Ponndorf–Verley reduction, efficiently promotes the epoxidation of unfunctionalized olefins in the presence of one equivalent of 30% hydrogen peroxide as the oxidant (Scheme 11.21).

High yields and high enantioselectivities were obtained with 1 mol % of catalyst in the reaction of conjugated olefins (Scheme 11.22). The epoxidation of styrene, which is still a difficult substrate for asymmetric epoxidation with regard to both enantioselectivity and product selectivity, furnished styrene oxide with the high ee value of 93%, and synthetically important indene oxide was obtained with 99% ee. The reaction of 1,2-



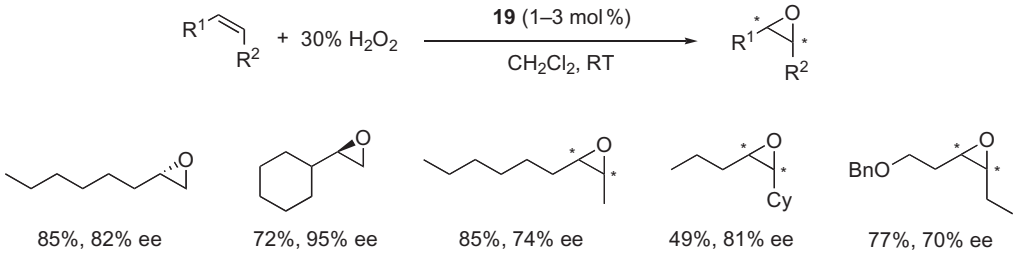
Scheme 11.21. The salen ligand is simplified for clarity.



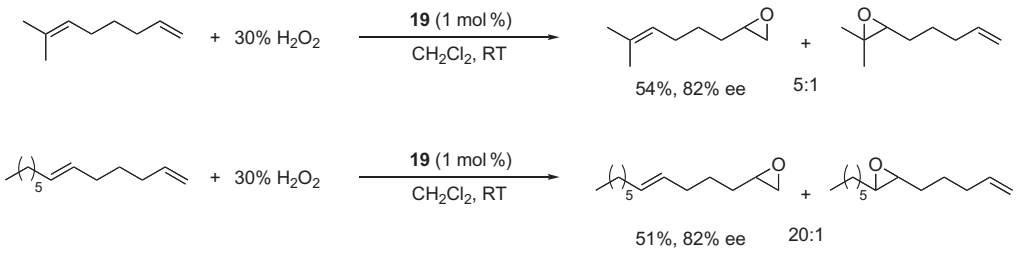
Scheme 11.22.

dihydronaphthalene proceeded smoothly in the presence of only 0.02 mol % of **19** to afford the epoxide in 92% yield with complete enantioselectivity. It is of note that the reaction is stereospecific and that an acyclic *cis*-substituted olefin underwent epoxidation to give the corresponding *cis*-epoxide as a sole product. While dichloromethane is the best solvent, more environmentally friendly ethyl acetate is also available as a solvent without loss of the enantioselectivity.

The remarkable catalysis of complex **19** can be recognized in the results obtained with aliphatic olefins, which are the most challenging substrates for asymmetric olefin epoxidation, due to their inherently low reactivity toward electrophilic oxidant and the difficulty in their enantioface differentiation (Scheme 11.23) [38]. A variety of



Scheme 11.23.



Scheme 11.24.

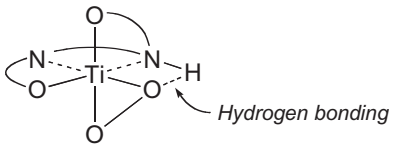


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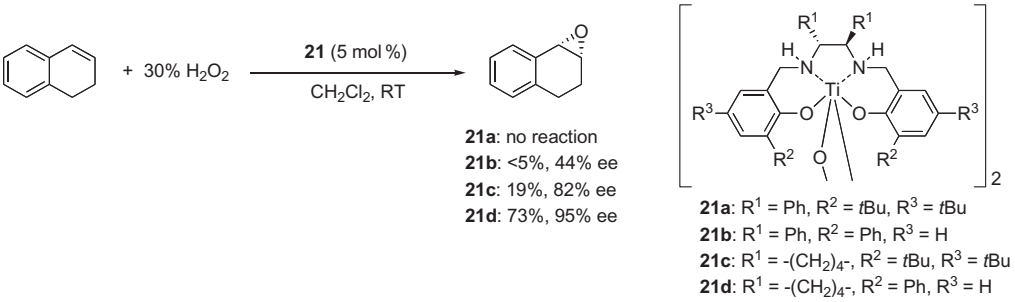
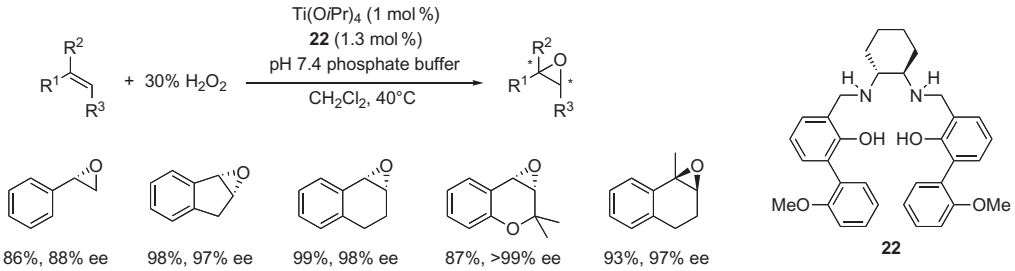
Figure 11.2.

aliphatic olefins such as terminal and *cis*-substituted olefins underwent epoxidation with good to high enantioselectivity. The method was also applied to the regio- and enantioselective epoxidation of substrates containing multiple carbon–carbon double bonds, and good regioselectivity as well as high enantioselectivity was observed (Scheme 11.24).

Although complex **19** is an efficient catalyst for asymmetric epoxidation of olefins, its synthesis requires multiple steps. Moreover, the protocol that uses the intramolecular Meerwein–Ponndorf–Verley reduction is poorly applicable to the preparation of the related Ti(salalen) complexes. On the basis of the hypothesis that a peroxotitanium complex **20** (Fig. 11.2), in which the amino proton of the ligand forms hydrogen bond with the peroxo ligand, is the active species for the reaction, the authors further explored titanium-based epoxidation catalysts and found that titanium (salan) complexes **21**



Scheme 11.25.



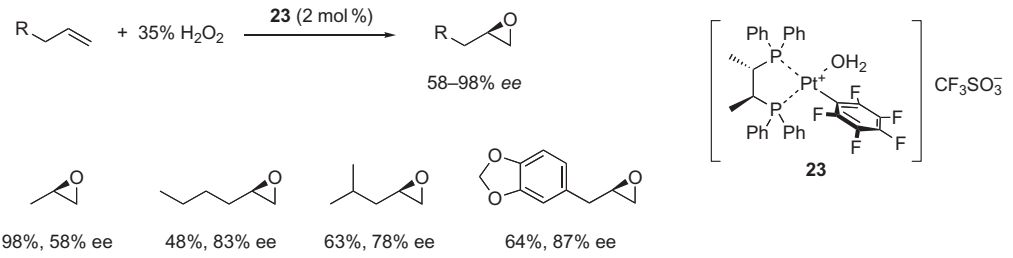
Scheme 11.26.

promote the asymmetric olefin epoxidation (Scheme 11.25) [39]. A brief screening of salan ligands disclosed that complex **21d** bearing cyclohexanediamine moiety and phenyl groups at the C3 and C3′ positions exhibited high asymmetric catalysis. It is worth noting that catalysts *in situ* prepared from $Ti(OiPr)_4$ and the corresponding salan ligands also gave comparable results with the premade catalysts.

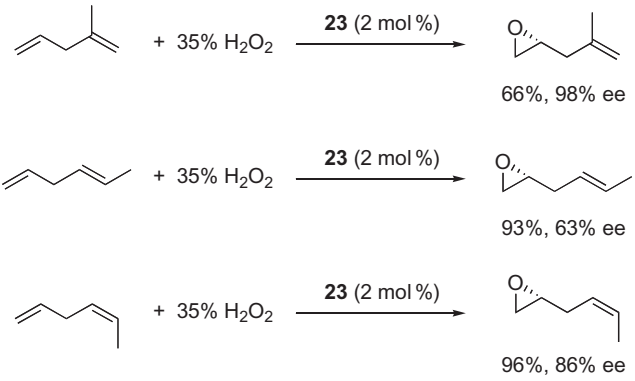
The authors further screened salan ligands with the *in situ* protocol and found that the introduction of *ortho*-substituted aryl groups at the C3 and C3′ positions improved both yield and enantioselectivity [40]. In particular, salan ligand **22**–bearing *ortho*-methoxyphenyl groups, which can be easily prepared from 2,2′-biphenol in short steps, gives the highest enantioselectivity. The addition of a phosphate buffer improved the catalytic performances remarkably, and only 1 mol % of the catalyst loading was sufficient to yield the enantio-enriched epoxides with ee values ranging from 88 to >99% (Scheme 11.26) [41]. The reaction can be performed on a gram scale with catalyst loading of 1–2 mol %.

11.3.4. Platinum Catalyst

Strukul and coworkers have developed cationic Pt^{II}/diphosphine complex **23** with electron-withdrawing pentafluorophenyl ligand and established its utility in enantioselective



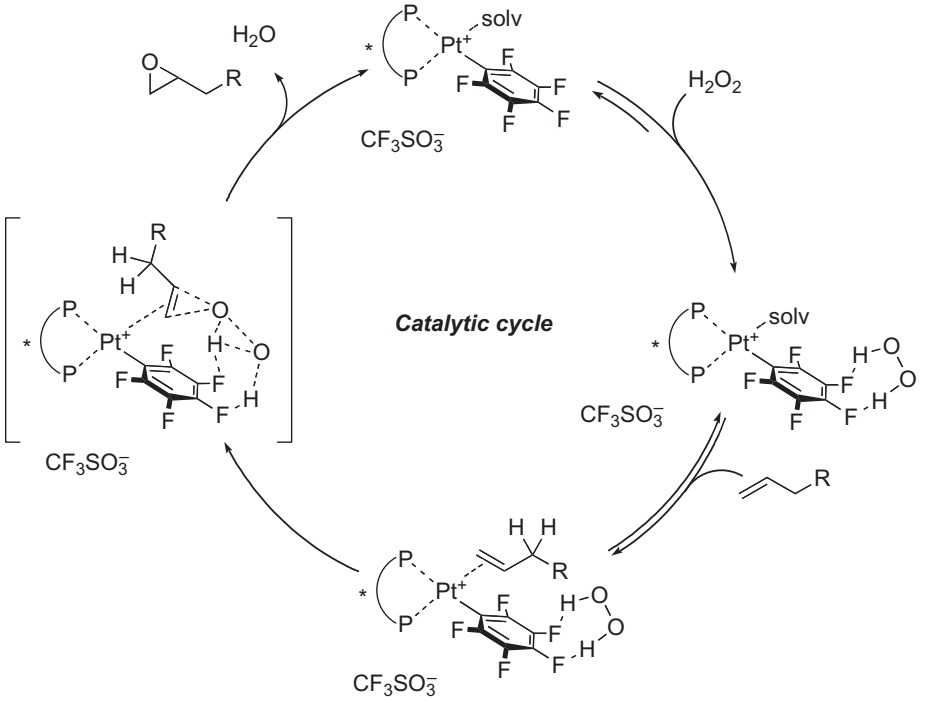
Scheme 11.27.



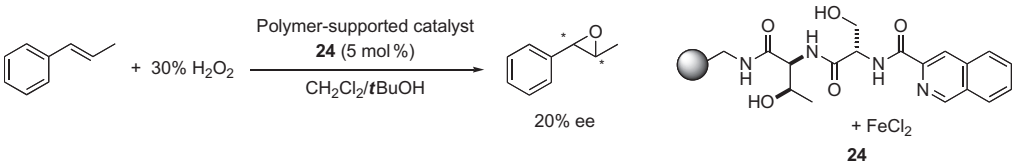
Scheme 11.28.

epoxidation of aliphatic olefins with aqueous hydrogen peroxide (Scheme 11.27) [42]. Various terminal olefins with no substituent at the allylic position are efficiently converted to the corresponding epoxides with moderate to high enantioselectivity. It is worth noting that only one equivalent of 35% hydrogen peroxide is required to obtain an acceptable yield. Another advantage is the high regio- and chemoselectivities. Monosubstituted terminal olefins are selectively oxidized in the presence of internal or geminally disubstituted terminal olefins (Scheme 11.28). Although halogenated solvents are commonly used, the reaction is also performed in water in the presence of surfactants [43].

The researchers proposed that H_2O_2 binds to the *meta*- and *para*-fluorine atoms of the C_6F_5 ligand by hydrogen bonding and that the olefin coordinates to the platinum prior to the oxygen atom transfer [44]. Scheme 11.29 accounts for the limited substrate scope and the extraordinary regioselectivity observed in the epoxidation of dienes.



Scheme 11.29.



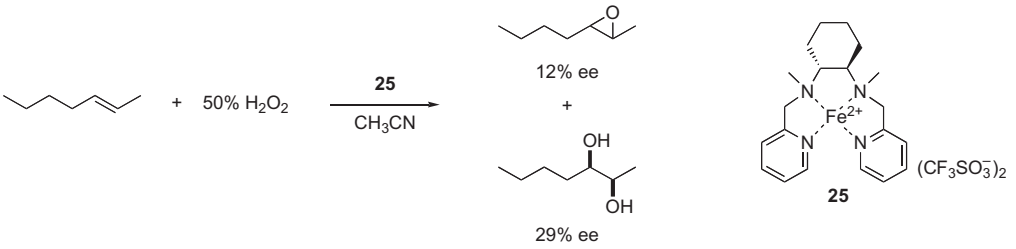
Scheme 11.30.

11.3.5. Iron Catalyst

The development of not only more efficient and selective but also sustainable reactions has emerged as a research frontier in organic synthesis. In the field of metal-catalyzed reaction, iron-based catalysts are the most appealing due to the ubiquity and nontoxicity of iron. Indeed, processes in nature utilize various iron-containing enzymes in biotransformations. Thus, the improvement of asymmetric epoxidation catalysis of iron-based complexes is a topic of current interests [45].

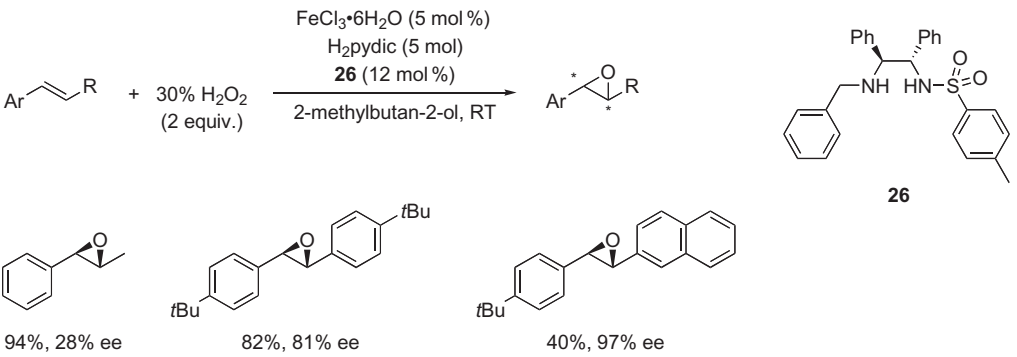
In 1999, Francis and Jacobsen investigated a library of 5760 ligand–metal complexes by high-throughput combinatorial techniques and found that Fe^{II}/peptide complex **24** supported on a polystyrene resin can promote the asymmetric epoxidation of *trans*-β-methylstyrene in the presence of aqueous hydrogen peroxide, albeit with the low ee value of 20% (Scheme 11.30) [46]. On the other hand, in the course of studies on

asymmetric *cis*-dihydroxylation of olefins, Que and coworkers found that Fe^{II} complex **25** together with aqueous hydrogen peroxide as the oxidant can oxidize *trans*-2-heptene to the epoxide (Scheme 11.31) [47]. Accompanying the *cis*-dihydroxylation product with 29% ee, *trans*-2-heptene oxide was obtained with 12% ee. Although the enantiomeric excesses are modest, these results indicated a potential of iron-based complexes as catalysts for asymmetric epoxidation.



Scheme 11.31.

In 2007, Beller and coworkers achieved the first highly enantioselective, iron-catalyzed epoxidation using aqueous hydrogen peroxide as an oxidant (Scheme 11.32) [48]. Chiral amine-based ligands were examined in combination with achiral H_2pydic ligand, and *N*-benzyl-*N*′-toluenesulfonyl-1,2-diphenylethylenediamine **26** was found to exhibit high enantioselectivity in the epoxidation of *trans*-disubstituted aromatic olefins. The authors noted the importance of the sulfonyl group for an intramolecular hydrogen bonding. The method employs an inexpensive iron source, $FeCl_3{\cdot}6H_2O$, and the best ee value of 97% is attained in the reaction of a substituted stilbene. Although the process has a limitation on the substrates, the promising asymmetric epoxidation catalysis of chiral iron-based complexes was proven. Spectroscopic and kinetic studies indicate that the reaction proceeds through benzyl radical intermediates [49]. While a high-valent Fe=O complex is proposed as the active species, further studies are necessary to ensure the mechanism.

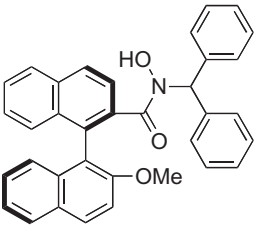


Scheme 11.32.

11.3.6. Vanadium Catalyst

A combination of $VO(acac)_2$ and alkyl hydroperoxides is one of the most reliable oxidation systems for hydroxy-directed epoxidation in organic transformation and enables highly diastereoselective synthesis of epoxy alcohols [50,51]. In 1977, Sharpless and coworkers identified chiral hydroxamic acids as effective ligands for the vanadium-catalyzed asymmetric epoxidation of allylic alcohols with TBHP, in which the hydroxamic acid binds to the vanadium as a bidentate ligand, and moderate to good enantioselectivity of up to 80% was observed [52]. Although a singly coordinated species has been proposed as the active catalyst, the formation of inactive doubly or triply coordinated species reduces the efficiency of the vanadium–hydroxamic acid system [53]. Nevertheless, a variety of chiral hydroxamic acid ligands have been introduced by several groups in recent years [54]. For example, Yamamoto and coworkers designed hydroxamic acid **27** bearing axially-chiral binaphthyl group for the vanadium-catalyzed asymmetric epoxidation of allylic alcohols, and demonstrated for the first time that high enantioselectivity of up to 94% ee can be achieved in the vanadium-catalyzed asymmetric epoxidation in the presence of alkyl hydroperoxide as oxidant (Fig. 11.3) [55]. On the basis of this finding, they further screened α-amino acid–based hydroxamic acids and found that *tert*-leucine-derived **28** is an effective ligand for the reaction. The epoxidation proceeded effectively with high enantioselectivity in the presence of $VO(OiPr)_3$ (1 mol %) and **28** (1.5 mol%) [56].

Eventually, Yamamoto and coworkers identified chiral C_2-symmetric bishydroxamic acids **29** as efficient ligands for the vanadium-based method (Scheme 11.33) [57]. The



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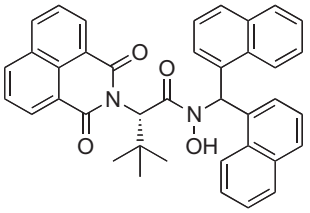

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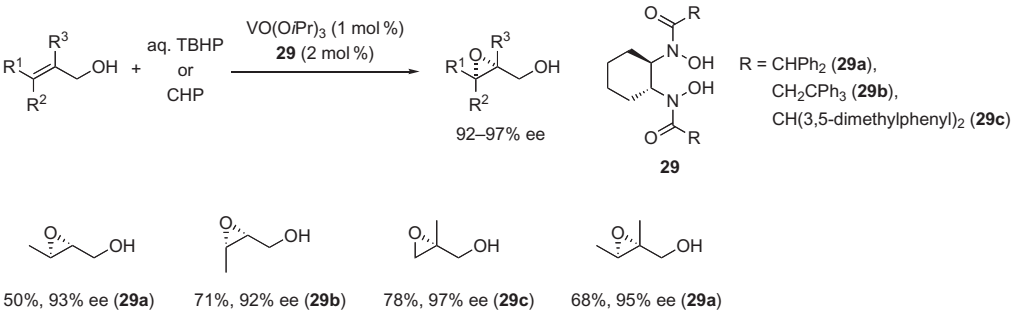
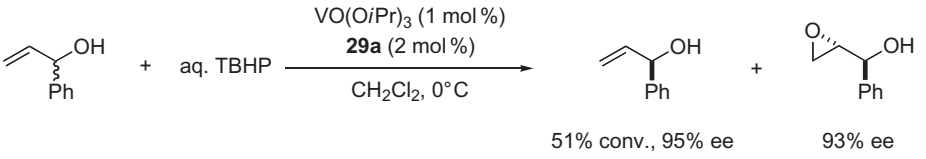
Figure 11.3.



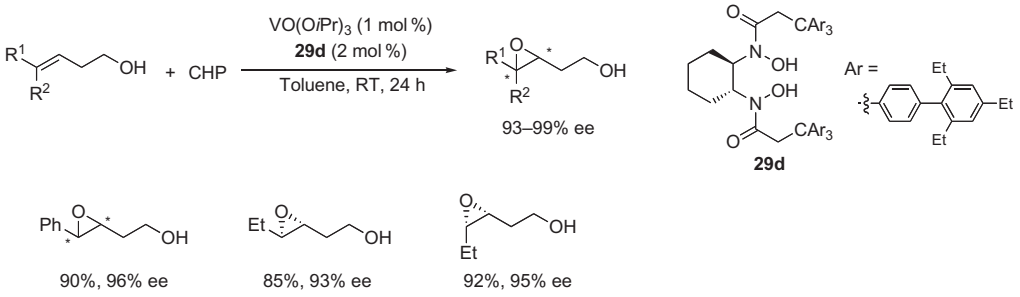
Scheme 11.33.

ligands were designed to selectively generate a 1:1 vanadium/ligand complex in which each hydroxyl group coordinates to the vanadium atom. Indeed, the catalytic activity was kept with more than 1:3 vanadium/ligand ratio. *Trans*-disubstituted and trisubstituted allylic alcohols underwent epoxidation in high enantiomeric excesses, and the reaction of *cis*-substituted allylic alcohols, which are substandard substrates for the Katsuki–Sharpless epoxidation, also proceeded with high enantioselectivity. An intriguing feature of the catalyst system is the availability of aqueous TBHP as a stoichiometric oxidant. It is noteworthy that the method is very effective for the asymmetric epoxidation of small allylic alcohols, which has been unsolved for a long time. With the vanadium catalyst, small epoxy alcohols can be obtained in high yields with high enantioselectivity more than 90% ee by water-extraction technique. The catalytic system was also applied to the kinetic resolution of a racemic secondary alcohol, and both the allylic alcohol and the epoxy alcohol were obtained with high enantiomeric excesses (Scheme 11.34).

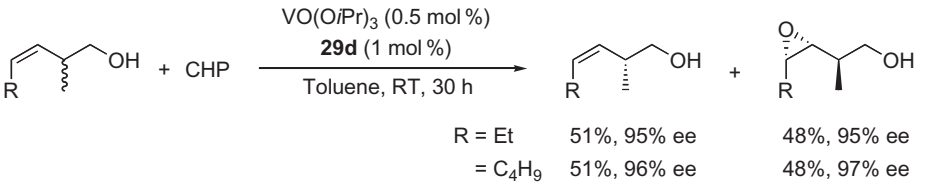
The $VO(OiPr)_3$/bishydroxamic acid system also promotes asymmetric epoxidation of homoallylic alcohols. High yields and enantioselectivities were obtained in the epoxidation of both *cis*- and *trans*-substituted homoallylic alcohols (Scheme 11.35) [58]. Moreover, racemic homoallylic alcohols were effectively resolved, and both the recovered homoallylic alcohols and the epoxides were isolated with high enantiomeric excesses (Scheme 11.36).



Scheme 11.34.



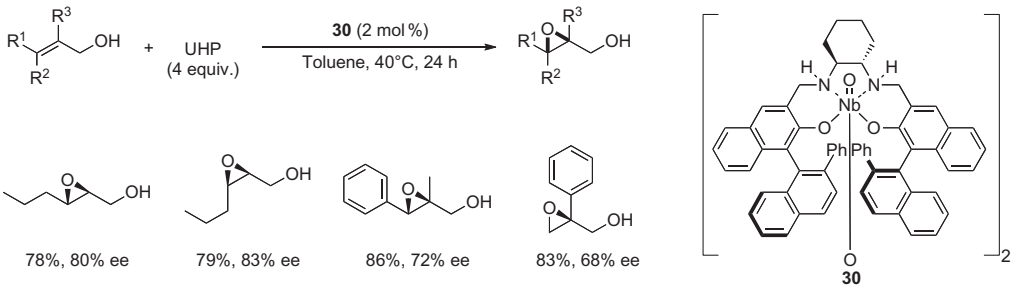
Scheme 11.35.



Scheme 11.36.

11.3.7. Niobium Catalyst

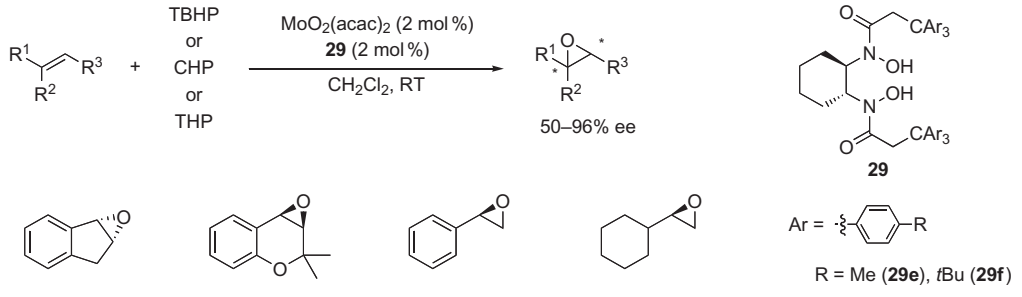
More recently, Egami and Katsuki disclosed that niobium(salan) complexes promote asymmetric epoxidation of allylic alcohols with hydrogen peroxide. The authors initially employed a chiral μ-oxo niobium(salan) complex **30** as catalyst together with urea·hydrogen peroxide (UHP) as oxidant and found that a range of allylic alcohols underwent epoxidation with high enantioselectivity (Scheme 11.37). [59]. While known catalysts for the epoxidation of allylic alcohols need alkyl hydroperoxides as oxidant, the method can utilize hydrogen peroxide. Subsequently to this, protocols using the catalyst *in situ* prepared from $Nb(OiPr)_5$ and the corresponding salan ligand have been developed. More favorable aqueous hydrogen peroxide is available as an oxidant under the conditions (H. Egami and T. Katsuki, unpublished data).



Scheme 11.37.

11.3.8. Molybdenum Catalyst

Chiral C_2-symmetric bishydroxamic acids **29** are effective auxiliaries for molybdenum-catalyzed asymmetric epoxidation of unfunctionalized olefins as well as the vanadium-catalyzed epoxidation of allylic alcohols (Scheme 11.38) [60,61]. The suitable choice of the steric bulkiness of alkyl hydroperoxides leads to achievement of the high enantioselectivity in the asymmetric epoxidation of mono, di-, and tri-substituted olefins. It is worthy to note that the method is stereospecific and that the only *cis*-epoxide

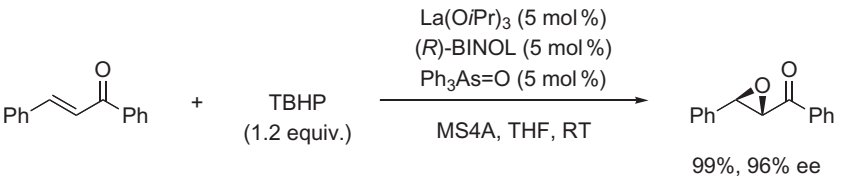


Scheme 11.38.

was obtained in the reaction of *cis*-β-methylstyrene. The molybdenum catalysts with alkyl hydroperoxides have a relatively strong oxidizing property so that less reactive 1-octene could be converted to the epoxide in high yield, albeit with moderate enantioselectivity of 50% ee. The reaction of vinylcyclohexane is more enantioselective, giving the epoxide with 85% ee. The catalyst was also effective for asymmetric oxidation of sulfides and disulfides [62].

11.3.9. Lanthanoid Catalyst

Chiral lanthanoid-based complexes have emerged as versatile catalysts for a wide variety of enantioselective organic transformations, and the Shibasaki group proved that lanthanoid catalysts are remarkably effective for asymmetric epoxidation of α,β-unsaturated carbonyl compounds using alkyl hydroperoxides (Scheme 11.39) [63]. Basically, their catalysts consist of a Lewis acidic lanthanoid atom, BINOL-derived chiral ligand, and triphenylarsine oxide. Inanaga and coworkers also reported that addition of triphenylphosphine oxide enhances the epoxidation catalysis of the lanthanoid complexes [64]. The Shibasaki's method has a broad substrate spectrum, and α,β-unsaturated ketones, esters, amides, and *N*-acyl pyrroles undergo epoxidation with high enantioselectivity. Recently, α,β-unsaturated phosphate was also included in the scope [65]. It is noteworthy that the geometry of *cis*-α,β-unsaturated ketone is considerably retained during epoxidation, although it proceeds stepwise. They successfully utilized the lanthanoid-catalyzed epoxidation in an enantioselective synthesis of (+)-decursin and its related compounds, which exhibit cytotoxicity against various human cancer cell lines [66].

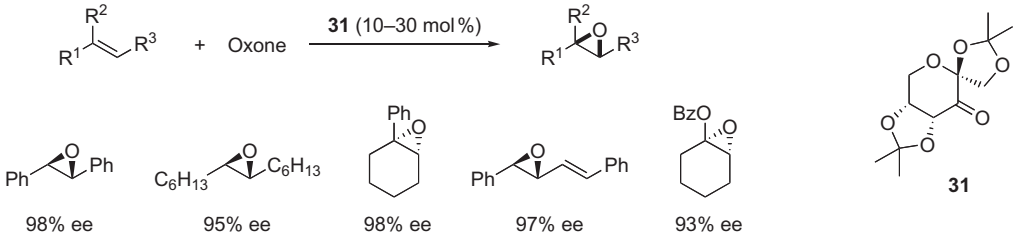


Scheme 11.39.

11.3.10. Organocatalyst

Remarkable progress in the field of asymmetric organocatalysis has been seen in recent years, and it has been successfully applied to catalytic asymmetric epoxidation [67].

Chiral ketones, which were first identified as a catalyst for asymmetric epoxidation by Curci and coworkers in 1984, are some of the most developed epoxidation catalysts [68]. Active dioxirane is generated from ketone and oxone (potassium peroxomonosulfate) under mild reaction conditions. While many valuable chiral ketones have been reported [69], fructose-derived ketone **31** developed by Shi and coworkers is the most reliable catalyst in terms of the high enantioselectivity and broad substrate scope (Scheme 11.40) [70]. In the presence of **31** (typically 20–30 mol %), a variety of *trans*- and trisubstituted olefins including dienes, enynes, and enol ethers are efficiently converted to the epoxides.



Scheme 11.40.

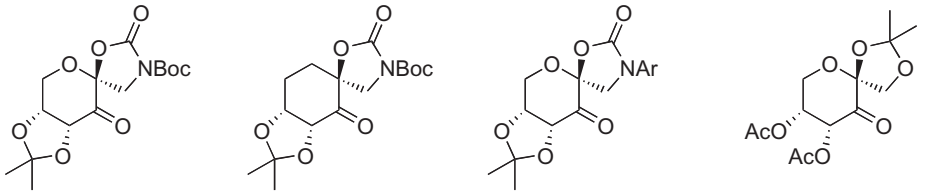
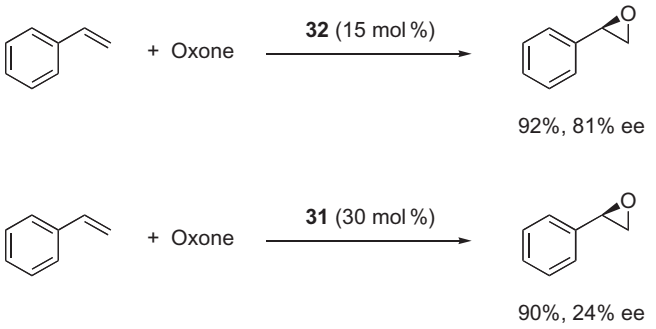


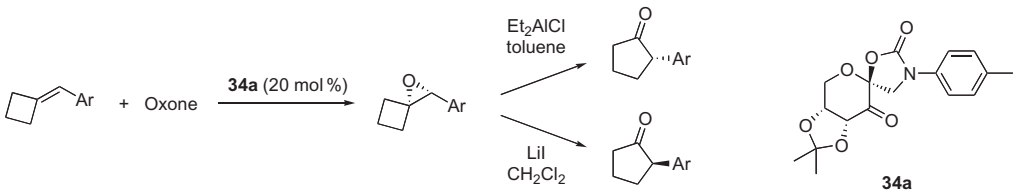
Figure 11.4.



Scheme 11.41.

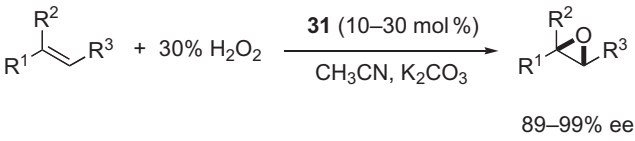
While ketone **31** generally displays high enantioselectivity for these olefins, the method is not effective for *cis*- and terminal olefins. On the basis of the mechanistic understanding, Shi and coworkers introduced a glucose-derived chiral ketone **32** containing an *N*-Boc oxazolidinone that exhibits high enantioselectivity for the epoxidation of *cis*- and terminal olefins (Fig. 11.4) [71]. The reaction of styrene with ketone **32** gave styrene oxide with 81% ee, in contrast to 24% ee with ketone **31** (Scheme 11.41). A carbocyclic analogue **33** and *N*-aryl-substituted variants **34** are also introduced for styrene derivatives and *cis*-disubstituted olefins [72,73]. In addition, chiral ketone **35** bearing electron-withdrawing acetate groups was found to be active enough to promote the epoxidation of α,β-unsaturated esters, and the epoxy esters were obtained in a high yield with high enantioselectivity [74].

Shi and coworkers successfully utilized the ketone-catalyzed method in an enantioselective synthesis of 2-arylcyclopentanones (Scheme 11.42) [75]. In the presence of **34a** and oxone, benzylidenecyclobutanes underwent epoxidation with 86–96% ee, and the subsequent epoxide rearrangement using Lewis acid catalysts such as Et_2AlCl and LiI gave the enantio-enriched 2-arylcyclopentanones [76]. The high enantiomeric excesses of the epoxides were generally maintained in the rearranged products. Choice of the Lewis acids determines the stereochemical course of the reaction, and the rearrangement with Et_2AlCl proceeds via a concerted mechanism with inversion of the configuration. On the other hand, the reactions with LiI go through a stepwise process with double inversion to yield the retention products. Both enantiomers can be synthesized with the single epoxidation catalyst.



Scheme 11.42.

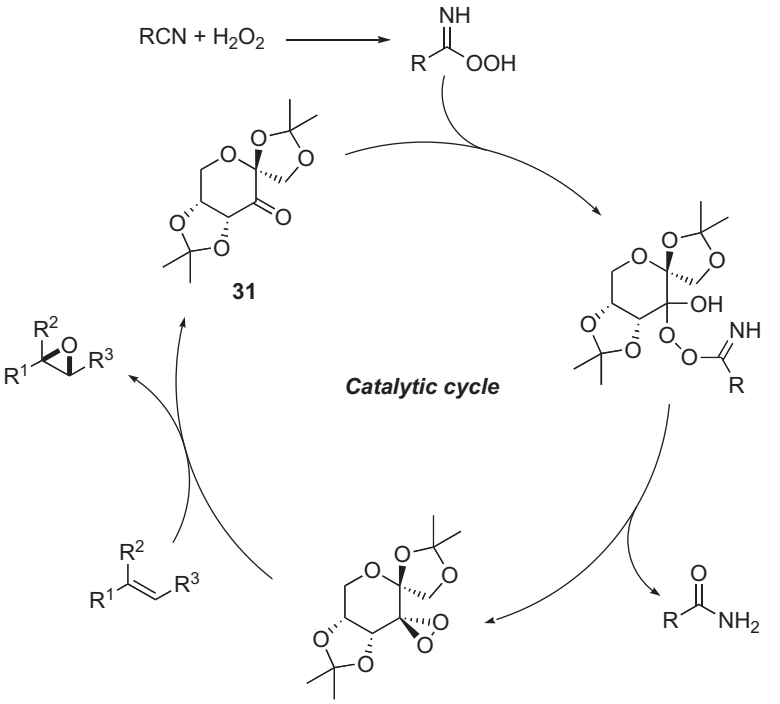
While oxone is the usual oxidant to generate active dioxiranes in the ketone-catalyzed epoxidation, Shi and Shu reported an alternative oxidant, a combination of hydrogen peroxide and acetonitrile (Scheme 11.43) [77]. In the reaction with ketone **31**, a variety of epoxides were obtained in good yields with comparable enantioselectivity. *N*-Aryl-substituted, oxazolidinone-containing ketone **34** was also shown to promote asymmetric epoxidation with high enantioselectivity with hydrogen peroxide.



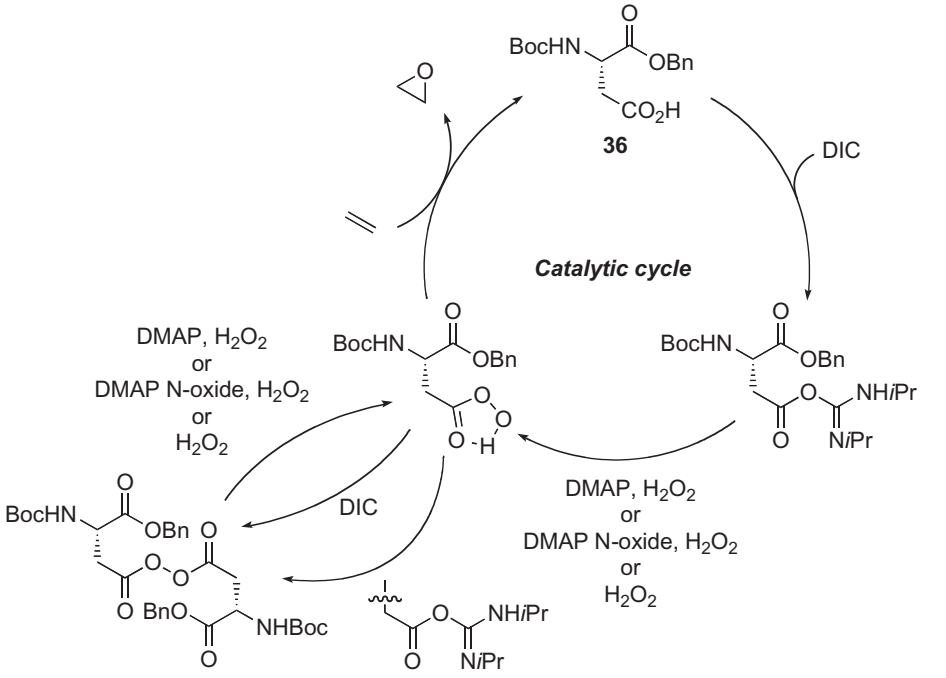
Scheme 11.43.

Acetonitrile, which is usually employed as cosolvent, reacts with hydrogen peroxide to generate peroxyimidic acid and then reacts with the ketone to give the active dioxirane (Scheme 11.44). Under the conditions, a stoichiometric amount of the amide is produced as a by-product.

Percarboxylic acids such as peracetic acid and *m*CPBA are common oxidants for olefin epoxidation in organic transformations. Although the utilization of chiral peracids, even as stoichiometric oxidants, has been studied, methods for achieving high enantioselectivity had not been reported. In 2007, however, Miller and coworkers demonstrated a unique acid/peracid catalytic cycle for asymmetric epoxidation (Scheme 11.45) [78]. At the initial stage of their study, the authors employed benzyl *N*-Boc L-aspartate **36** as catalyst for constructing the hypothesized acid/peracid shuttle system and applied carbodiimide activation technique in peptide synthesis to the purpose. Acid **36** is activated by carbodiimide, and the subsequent reaction with hydrogen peroxide

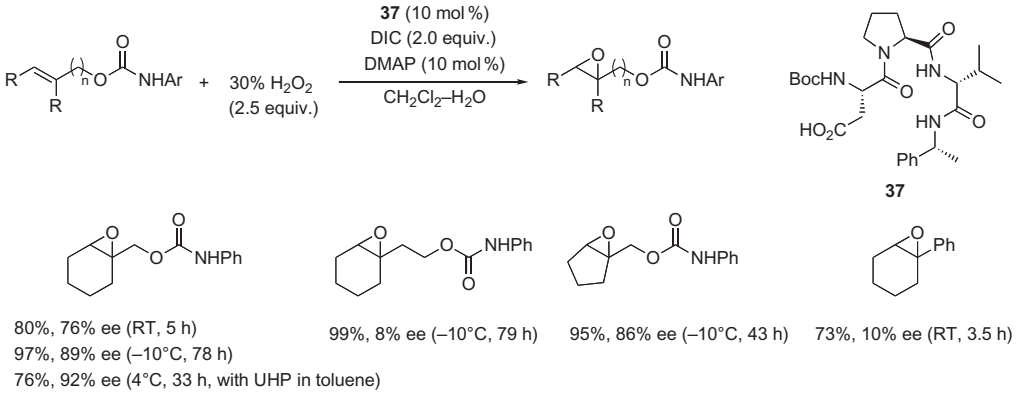


Scheme 11.44.



Scheme 11.45.

affords the active peracid. The peracid oxidizes the olefin to yield the epoxide along with the regeneration of the carboxylic acid catalyst **36**. Although the formation of diacyl peroxide delays the oxygen atom transfer, the addition of DMAP as an acyl transfer catalyst accelerates the entire process and renders the reaction highly catalytic. While DMAP is oxidized to DMAP *N*-oxide under the reaction conditions, *N*-oxide may also serve as acyl transfer catalysts. Indeed, NMO instead of DMAP could promote the epoxidation, albeit with diminished productivity. With an effective acid/peracid shuttle, the authors introduced tripeptide catalyst **37**—the sequence L-Pro-D-Val is well known to induce a β-turn structure that provides an effective asymmetric environment for other asymmetric reactions [79]—and found that trisubstituted olefins bearing carbamate functionality effectively underwent epoxidation with high enantioselectivity (Scheme 11.46). While allylic alcohol-derived substrates showed high enantioselectivity, the elongation of the tether led to the significant loss of the enantioselectivity. The limitation of the substrate scope suggests that hydrogen bonding between the catalyst and the substrate is essential for the enantiocontrol. Three transition state models have been proposed (Fig. 11.5). This study demonstrates that better understanding of peptide-substrate–binding structure including hydrogen-bonding network will offer a potent approach to highly enantioselective epoxidation of other olefins.



Scheme 11.46.

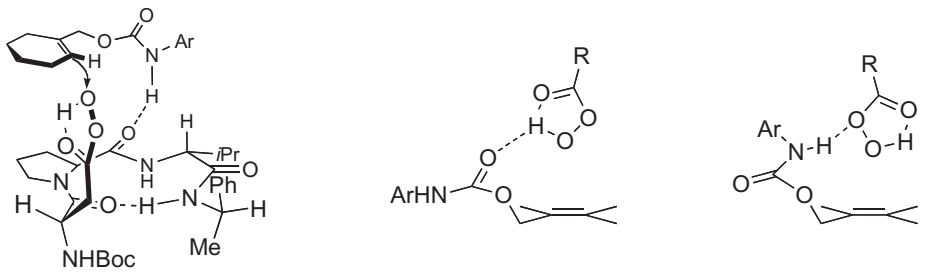
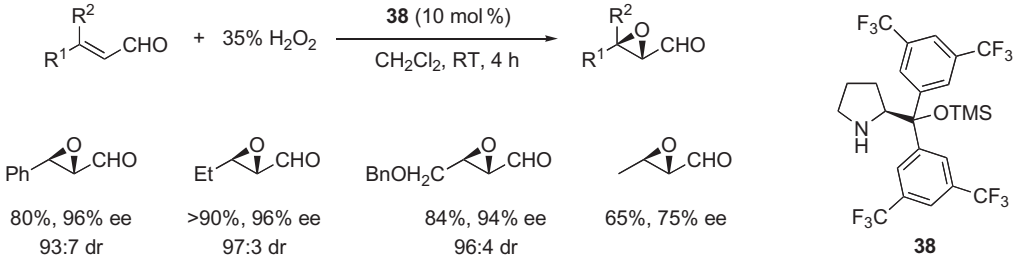
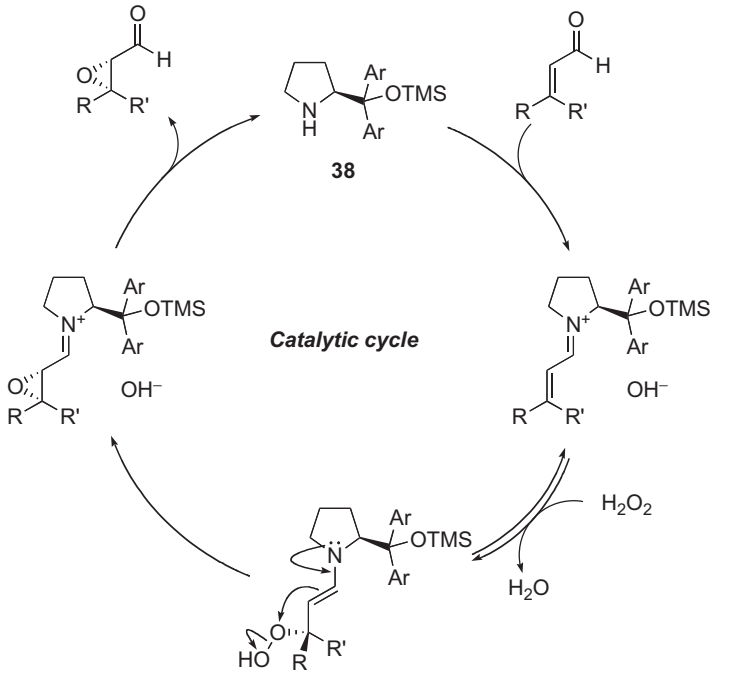


Figure 11.5.

Progress in the field of asymmetric organocatalysis of chiral amines has increased remarkably in recent years. The amine catalysis can be divided into two classes: iminium ion formation, which leads to lowering the LUMO energy, and generation of nucleophilic enamine intermediates [67,80]. The iminium/enamine catalysis has been successfully applied to asymmetric epoxidation. Jørgensen and coworkers identified chiral pyrrolidine **38** as a catalyst for asymmetric epoxidation of α,β-unsaturated aldehydes with aqueous hydrogen peroxide (Scheme 11.47) [81–83]. α,β-Unsaturated aldehydes having an aromatic substituent at the β-position are good substrates for the reaction, and the epoxides were obtained with high diastereo- and enantioselectivity. High stereoselectivity was also observed in the reaction of the alkyl-substituted, α,β-unsaturated aldehydes. While the reaction of β-disubstituted, α,β-unsaturated aldehydes smoothly proceeded, the enantioselectivity was slightly decreased. As described in Scheme 11.48,



Scheme 11.47.



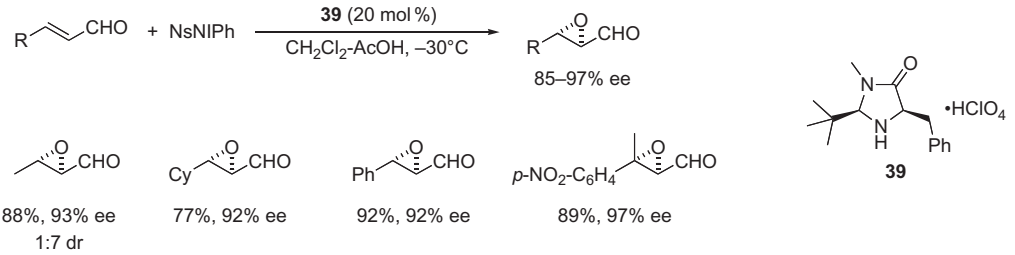
Scheme 11.48.

the reaction proceeds through the well-known Weitz–Scheffer mechanism. The conjugate addition of hydrogen peroxide, which is a good nucleophile and leaving group, to the β-carbon atom of the electrophilic iminium ion is reversible, and the attack on the electrophilic peroxygen atom by the nucleophilic enamine is the step determining the product's stereochemistry.

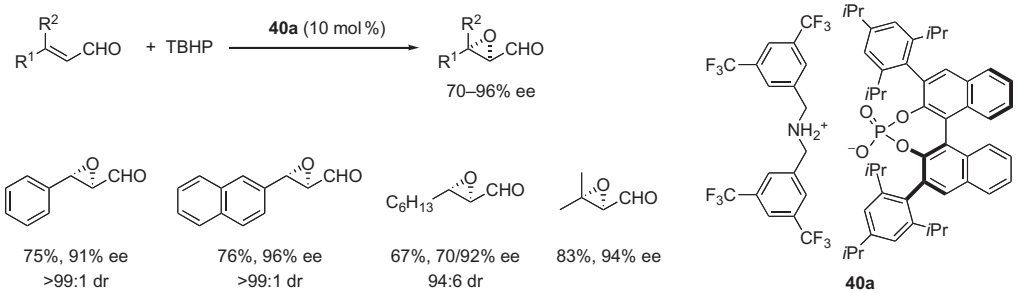
Asymmetric epoxidation of α,β-unsaturated aldehydes by the iminium/enamine catalysis has also been investigated by MacMillan and Lee (Scheme 11.49) [84]. They utilized chiral imidazolidinone salt **39** as a catalyst with not hydrogen peroxide but iodosobenzene as a stoichiometric oxidant. A combination of [(nosylimino)iodo]benzene (NsNIPh) and acetic acid slowly liberates the active iodosobenzene monomer. The reaction of β-substituted, α,β-unsaturated aldehydes furnished the epoxide with high enantioselectivity as single diastereomers, except for crotonaldehyde.

List and coworkers also reported secondary amine-catalyzed asymmetric epoxidation of α,β-unsaturated aldehydes, and their strategy is very attractive, in which the authors utilized a catalyst **40** consist of achiral dibenzylamine and BINOL-derived chiral phosphoric acid (Scheme 11.50) [85]. Together with TBHP as oxidant, the catalyst **40a** promotes the epoxidation of both β-mono- and disubstituted α,β-unsaturated aldehydes to give the epoxides with high diastereo- and enantioselectivities. When the two β-substituents are identical, the enamine intermediate is achiral. However, the substrate underwent epoxidation with high enantioselectivity. Thus, the authors proposed that the chiral phosphoric acid must assist the ring-closing step.

List and coworkers also discovered that chiral ammonium salts pairing chiral diamines and chiral/achiral acids catalyze the asymmetric epoxidation of cyclic enones using

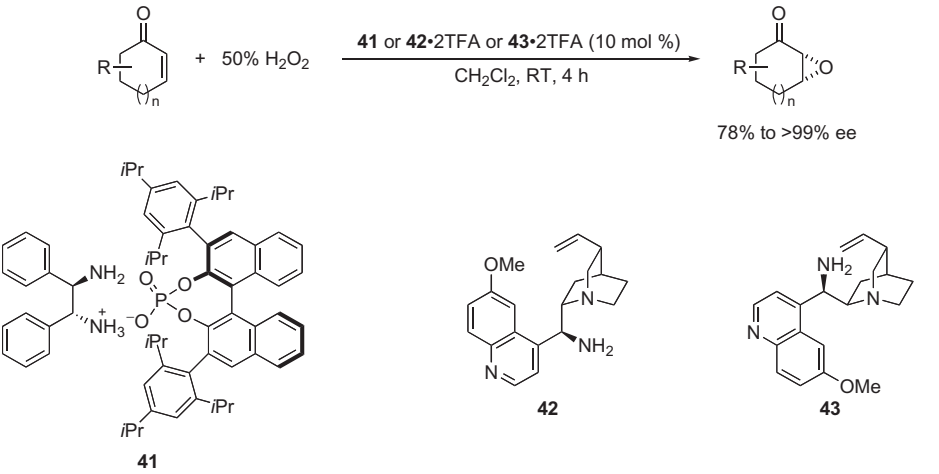


Scheme 11.49.



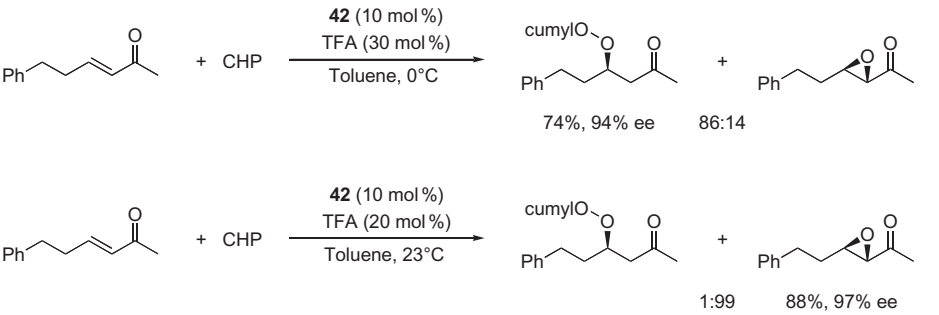
Scheme 11.50.

aqueous hydrogen peroxide as oxidant (Scheme 11.51) [86]. Although there have been enormous numbers of effective epoxidation catalysts for different classes of olefins, no catalyst had been successfully applied to cyclic enones. Ammonium salt **41** derived from 1,2-diphenyldiamine and BINOL-based phosphoric acid induces high enantioselectivity. TFA salts of 9-amino cinchona alkaloids **42** and **43** also proved especially suitable for the epoxidation of β-substituted cyclic enones.



Scheme 11.51.

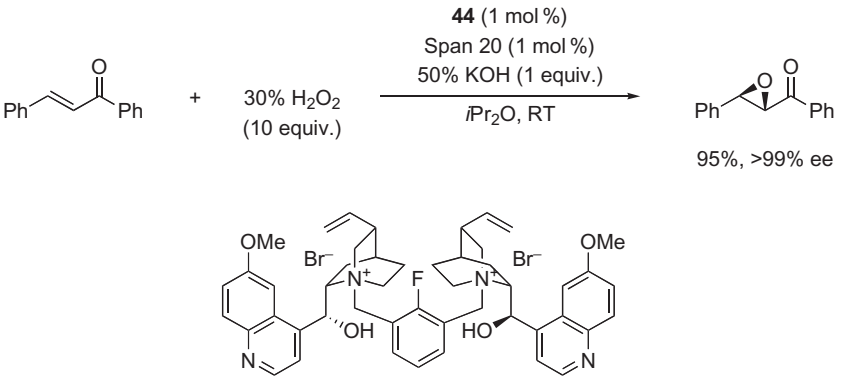
Furthermore, Deng and coworkers recently discovered that cinchona alkaloid–derived chiral diamine **42** also serves as a catalyst for enantioselective peroxidation of α,β-unsaturated ketones [87]. Together with TBHP as nucleophile, optically active peroxides were preferentially obtained in high enantiomeric excesses at 23°C with small formation of epoxides. When using more bulky hydroperoxide such as cumene hydroperoxide, the selective synthesis of the peroxides needs the lower reaction temperature of 0°C (Scheme 11.52). On the other hand, complete inversion of the product selectivity was observed at higher temperature (23 or 55°C), and chiral epoxides were provided



Scheme 11.52.

with high enantioselectivity. While a peroxyenamine intermediate must take a conformation, allowing an interaction between σ^*_{O-O} orbital and enamine π orbial for epoxide ring closure, the diamine unit on the peroxyenamine regulates its conformation to make the epoxide formation difficult but accelerates the protonation. As the result, enantioenriched peroxides were selectively generated. However, the elevated temperature weakens the regulation, and the peroxyenamine undergoes the O–O bond cleavage.

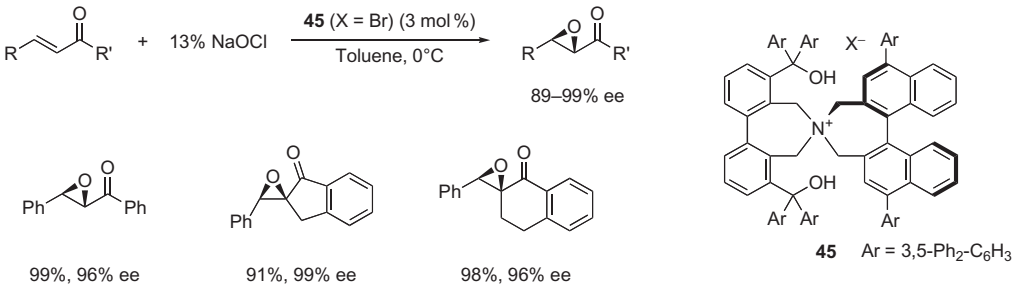
Phase transfer catalysis is a powerful methodology for organic synthesis under aqueous conditions and has been applied to asymmetric epoxidation of α,β-unsaturated carbonyl compounds [88]. Cinchona alkaloid–derived quaternary ammonium salts have been developed for the asymmetric epoxidation of α,β-unsaturated ketones by several research groups [89]. Dimeric cinchona phase transfer catalyst **44** was also identified by Jew and Park (Scheme 11.53) [90]. With aqueous hydrogen peroxide as oxidant, chalcone derivatives underwent epoxidation in high enantiomeric excesses. The addition of surfactants led to significant improvements not only in yield but also in enantioselectivity, and Span 20 (sorbitan monolaurate) was found to be most effective. The catalyst with naphthyl group as the spacer between the cinchona units and the corresponding monomeric catalysts bearing an arylmethyl group on nitrogen atom displayed no asymmetric induction, indicating the synergistic operation of the two cinchona units in the epoxidation event.



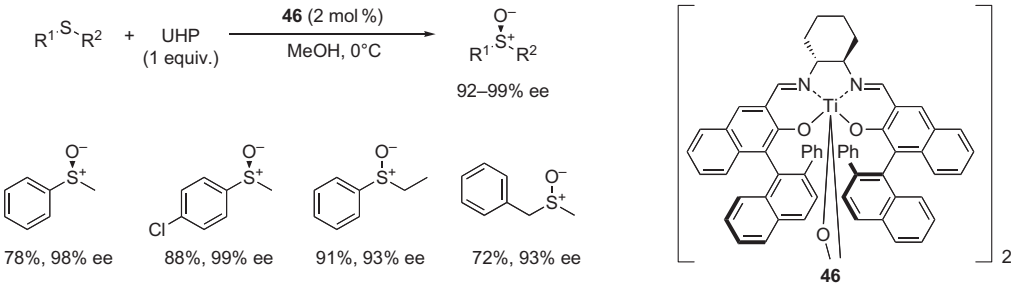
44

Scheme 11.53.

Maruoka and coworkers have identified chiral spiro ammonium salts bearing an axially chiral binaphthyl unit as the phase transfer catalyst for a wide variety of organic synthesis [88] They designed a new phase transfer catalyst **45** (X = Br) with dual function for asymmetric epoxidation of enones using aqueous sodium hypochlorite as oxidant (Scheme 11.54) [91]. The hydroxyl groups are appropriately placed to recognize and activate the enone substrate through hydrogen bonding. Indeed, the removal of the hydroxyl groups considerably retarded the reaction's progress and the enantioselectivity was diminished. X-ray crystallographic analysis of **45** (X = PF_6) revealed that the diarylhydroxymethyl groups form chiral pockets close to the nitrogen cation and that the hexafluorophosphate anion, which is hypothetically regarded as hypochlorite anion in the epoxidation, is located in the chiral pocket.



Scheme 11.54.



Scheme 11.55.

11.4. ASYMMETRIC SULFIDE OXIDATION

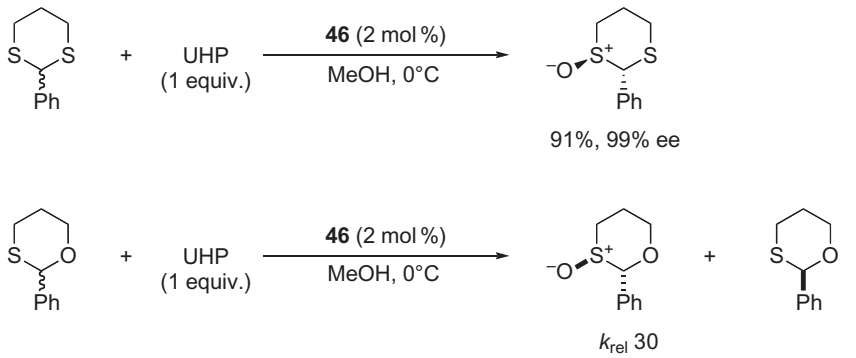
11.4.1. Introduction

Since the development of the titanium/tartrate-catalyzed asymmetric oxidation of sulfides that was independently reported by the Kagan and Modena groups in the early 1980s, significant efforts have been made to expand the scope of asymmetric sulfide oxidation [92–94]. There are a number of powerful catalysts for specific sulfides today. Current interests are directed toward the development of more sustainable methods using greener hydrogen peroxide as the oxidant and more enantioselective catalysts for challenging substrates such as dialkyl sulfides.

11.4.2. Titanium Catalyst

While a number of asymmetric sulfide oxidations using titanium-based catalysts have been developed, there were few reports that used hydrogen peroxide as oxidant and achieved both high enantioselectivity and a wide substrate scope [95]. In 2001, Saito and Katsuki demonstrated that di-μ-oxo titanium(salen) complex **46** catalyzed asymmetric oxidation of sulfides with high enantioselectivity in the presence of UHP as the oxidant (Scheme 11.55) [96]. Not only aryl methyl sulfides but also ethyl phenyl sulfide and benzyl methyl sulfide gave high enantioselectivity. Ti(salen) complex **46** was also

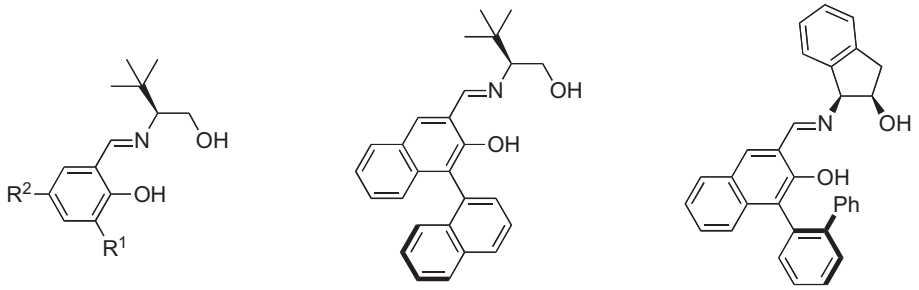
successfully applied to desymmetrization of thioacetals and oxidative kinetic resolution of racemic 2-substituted-1,3-oxathianes (Scheme 11.56) [97]. NMR study indicates that the Ti(salen)$(OMe)_2$ complex generated from complex **46** in methanol is further transformed into the active peroxo species upon treatment with hydrogen peroxide. Different from the corresponding Ti(salalen) complex **19**, Ti(salen) complex **46** is incompetent to epoxidation. The employment of aqueous hydrogen peroxide instead of anhydrous UHP resulted in the loss of the enantioselectivity due to a partial participation of low-enantioselective titanium η^1-hydroperoxo species.



Scheme 11.56.

11.4.3. Vanadium Catalyst

Vanadium complexes *in situ* prepared from $VO(acac)_2$ and chiral aminoalcohol-derived tridentate Schiff bases **6** and **47a** were first identified by Bolm and Bienewald as highly enantioselective catalysts for the sulfide oxidation in 1995 [98]. After the initial report, several groups reported modified Schiff base ligands (Fig. 11.6) [54]. Vetter



6: $R^1 = R^2 = t$Bu
47a: $R^1 = t$Bu, $R^2 = NO_2$
47b: $R^1 = R^2 = I$

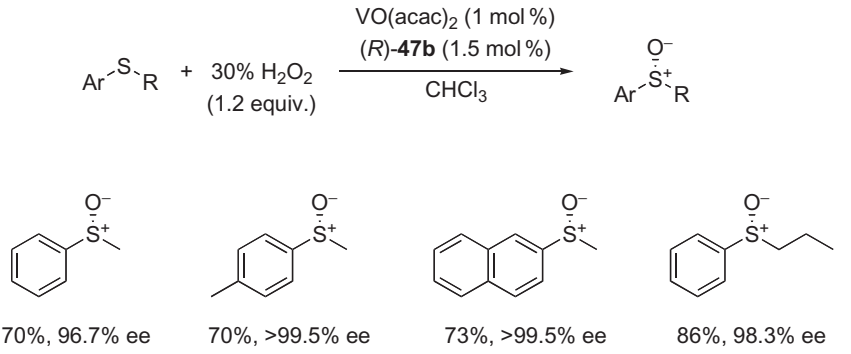
48

49

Figure 11.6.

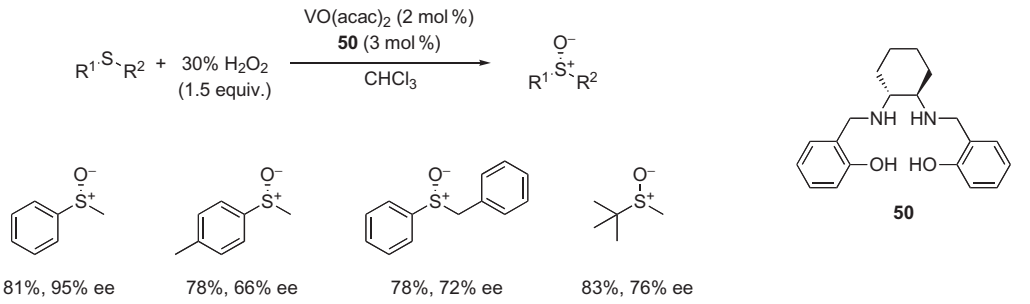
and Berkessel examined several Schiff base ligands derived from chiral salicylaldehydes in combination with (*S*)-*tert*-leucinol, and the best enantioselectivity was observed with **48** bearing an axially chiral binaphthyl framework [99]. Katsuki and coworkers reported that (1*S*,2*R*)-1-amino-2-indanol and an axially chiral salicylaldehyde gave an effective ligand **49** for the reaction [100]. Simple diiodo ligand **47b** was also introduced by Anson and coworkers [101].

Jackson and coworkers achieved the highly enantioselective synthesis of alkyl aryl sulfoxides by combining the vanadium-catalyzed sulfide oxidation and subsequent oxidative kinetic resolution of sulfoxides (Scheme 11.57) [102,103]. With diiodo ligand **47b**, thioanisole is oxidized to methyl phenyl sulfoxide in the (*R*)-enriched form. The following kinetic resolution event slowly occurs, and the minor (*S*)-enantiomer is preferentially converted into the sulfone. Thus, the sulfoxide is obtained with extremely high enantiopurity. The k_{rel} value in the kinetic resolution has been measured to be as high as 7.7.



Scheme 11.57.

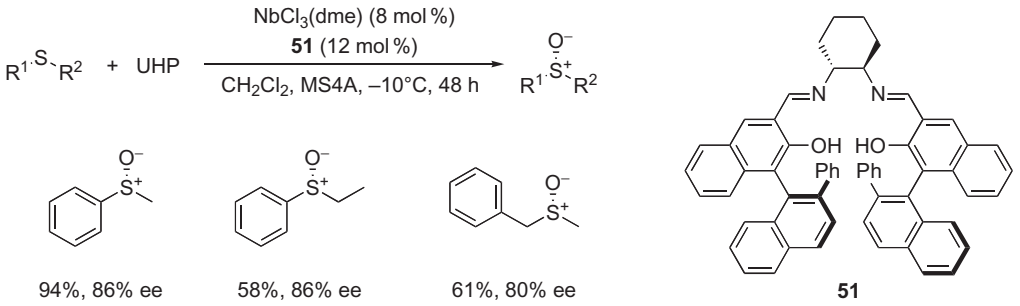
On the other hand, Zhu and coworkers examined ONNO-type tetradentate ligands for the vanadium-catalyzed asymmetric sulfide oxidation (Scheme 11.58) [104]. Interestingly, the most simplified ligand **50** that has no substituents on the benzene ring exhibited the highest enantioselectivity. The catalyst also applied to oxidative kinetic resolution of racemic sulfoxides, and the enantio-enriched sulfoxides were recovered in high enantiomeric excesses.



Scheme 11.58.

11.4.4. Niobium Catalyst

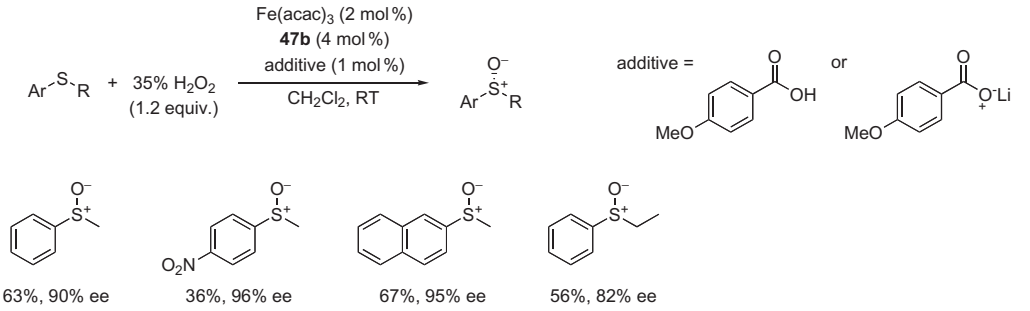
Asymmetric oxidation catalysis of niobium-based complexes was first disclosed by Miyazaki and Katsuki and applied to asymmetric oxidation of sulfides (Scheme 11.59) [105]. A niobium complex *in situ* prepared from $NbCl_3$(dme) and salen ligand **51** serves as an efficient catalyst for several sulfides including benzyl methyl sulfide in the presence of UHP as oxidant. High enantioselectivities of more than 80% ee were observed.



Scheme 11.59.

11.4.5. Iron Catalyst

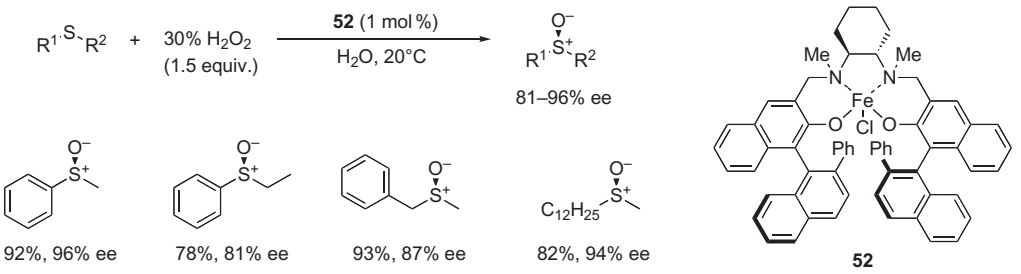
Legros and Bolm reported iron-catalyzed asymmetric sulfide oxidation that uses $Fe(acac)_3$ and tridentate Schiff base ligand **47b** with aqueous hydrogen peroxide [106]. The introduction of an iodine atom at C3 and C5 positions gave higher enantioselectivity than that of bulky alkyl substituents such as a *tert*-butyl group. However, only moderate yields and enantioselectivities were obtained under the original conditions. Thus, Bolm and coworker further explored the iron-catalyzed oxidations. On the basis of the Jacobsen's observation that the addition of acetic acid led to significant improvements on the reaction efficiency in iron-catalyzed epoxidation using aqueous hydrogen peroxide [107], the authors examined the influence of carboxylic acids and found that addition of 0.5 equivalent of benzoic acid relative to $Fe(acac)_3$ remarkably improved both the yield and enantioselectivity in the oxidation of methyl phenyl sulfide. Eventually, *p*-methoxybenzoic acid and its lithium salt were chosen as the additives (Scheme 11.60) [108]. In the



Scheme 11.60.

all cases, remarkable improvements were observed, and enantioselectivity higher than 80% ee was obtained in the oxidation of aryl methyl sulfides. From the observed positive nonlinear effect and the necessity of a half equivalent of the carboxylic acid/carboxylate additive with respect to iron, a monocarboxylate-bridged diiron(III) complex has been proposed as a key intermediate in the catalytic cycle.

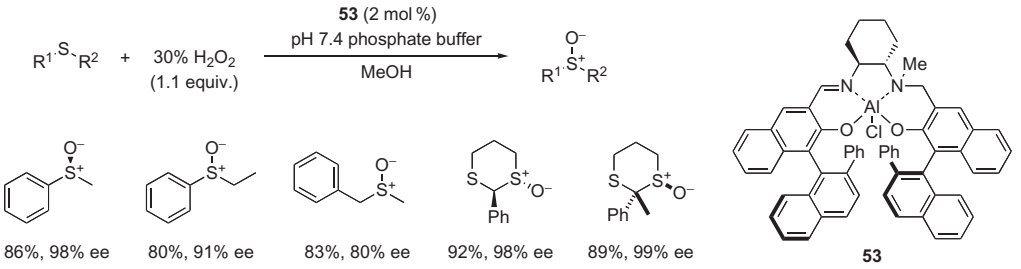
Egami and Katsuki also reported an iron-based catalyst for the reaction (Scheme 11.61) [109]. Fe(salan) complex **52** serves as an effective catalyst, with aqueous hydrogen peroxide as oxidant. The method employs the most favorable solvent, water, and can be performed even in the absence of a surfactant. It is noteworthy that not only alkyl aryl sulfides but also dialkyl sulfides underwent oxidation with high enantioselectivity. Scarso and Strukul also reported the platinum-catalyzed asymmetric sulfide oxidation in water, but their system requires the addition of a surfactant [110].



Scheme 11.61.

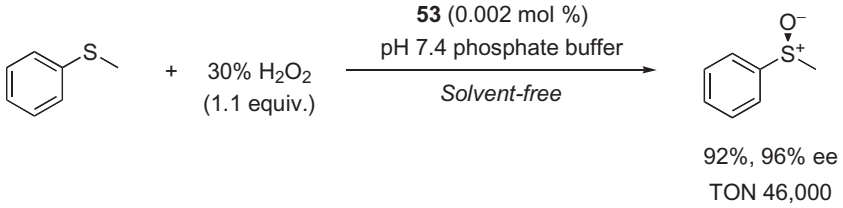
11.4.6. Aluminum Catalyst

Recently, Katsuki and coworkers identified aluminum(salalen) complexes as efficient catalysts for asymmetric sulfide oxidation using aqueous hydrogen peroxide (Scheme 11.62) [111]. Al(salalen) complex **53** promotes the oxidation of a wide variety of sulfides with high enantioselectivity even under aqueous conditions. Aryl methyl sulfides undergo highly enantioselective oxidation, and ethyl phenyl sulfoxide and benzyl methyl sulfoxide are also obtained with high enantioselectivity. Other sulfur-containing compounds such as cyclic sulfides and thioacetals are also good substrates for the oxidation system



Scheme 11.62.

[112]. The author proposed a η^2-hydroperoxide as the active species. It is noteworthy that the catalyst promotes the reaction under solvent-free conditions, and the exceptionally high turnover number of the catalyst is observed without erosion of the high enantioselectivity (Scheme 11.63) [113].

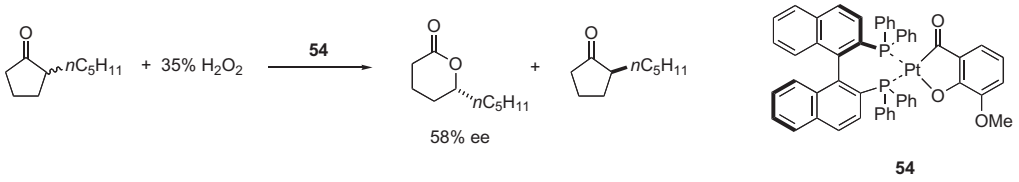


Scheme 11.63.

11.5. ASYMMETRIC BAEYER-VILLIGER OXIDATION

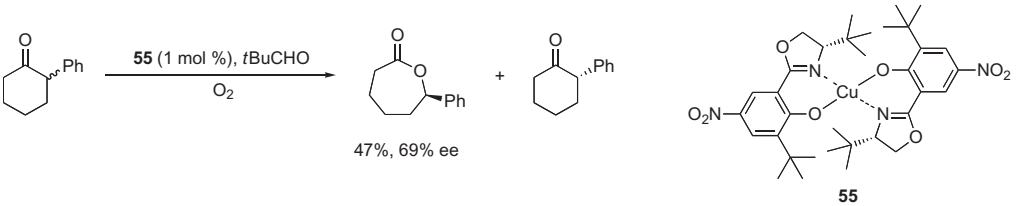
The Baeyer–Villiger oxidation is a powerful method for obtaining esters from the carbonyl compounds [114,115]. The configuration of the migrating group is retained through the process, and the reaction is stereospecific at the migrating carbon. The predictable order of migrating groups and the broad tolerance of functionalities also offer a great advantage. In 1994, the Strukul and Bolm groups independently reported the first examples of the asymmetric Baeyer–Villiger oxidation using metal complexes as catalyst [116,117]. Strukul and coworkers discovered that chiral platinum catalyst **54** promotes the oxidative kinetic resolution of racemic mixture of cyclic ketones with aqueous hydrogen peroxide as oxidant and achieved ee values of up to 58% (Scheme 11.64). On the other hand, the Bolm's group identified chiral copper catalyst **55** for the reaction of racemic 2-aryl cycloalkanones and obtained the lactones with up to 69% ee (Scheme 11.65). The method employs molecular oxygen as oxidizing agent in the presence of pivalaldehyde as a sacrificial reductant (the Mukaiyama condition) [118].

Since the initial reports on the metal-catalyzed asymmetric Baeyer–Villiger oxidations, significant advances have been seen in the field of the reaction. Especially, Bolm and coworkers have dedicated their research efforts to this area and found several useful catalysts. For example, an aluminum/BINOL complex was found to be an effective catalyst for the reaction [119]. Although a substoichiometric amount of the catalyst was required, 3-substituted cyclobutanones underwent in good enantiomeric excesses of up to 73% ee (Scheme 11.66). The parallel kinetic resolution of the racemic bicyclooctane

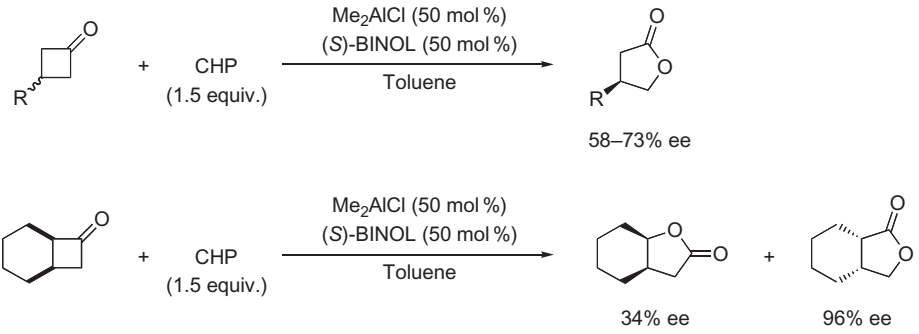


54

Scheme 11.64.



Scheme 11.65.



Scheme 11.66.

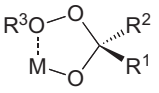
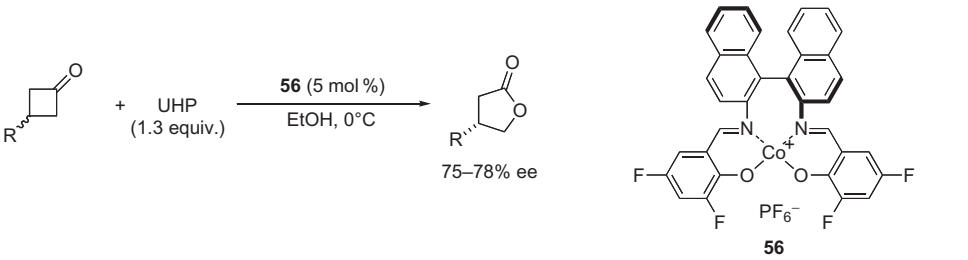


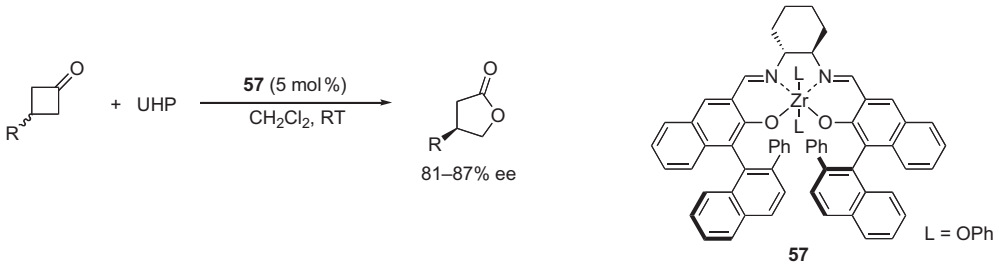
Figure 11.7.

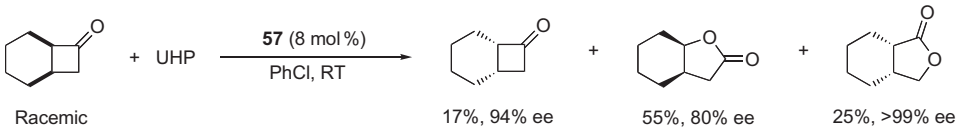
furnished the two lactones [120]. One is the lactone normally obtained in common Baeyer–Villiger reactions, and the enantiomeric excess is as high as 34%. The other is the constitutional isomer of the normal one and obtained with high enantioselectivity of 96% ee. The subsequent studies employing substituted BINOL derivatives provided a more efficient method that needs less catalyst, and the high ee value of up to 84% ee was achieved in the reaction of 3-phenylcyclobutanone [121]. The aluminum/BINOL system was proposed to proceed via a cyclic Criegee intermediate involving a pentacoordinated aluminum complex (Fig. 11.7).

The conformational regulation of metal-bound Criegee intermediates by chelate formation was first proven as an efficient strategy by Uchida and Katsuki (Scheme 11.67) [122]. They reported that chiral *cis*-β cobalt^{III} complex **56** bearing axially chiral binaphthyldiamine catalyzes the Baeyer–Villiger oxidation of 3-substituted cyclobutanones in the presence of UHP. Interestingly, the corresponding cobalt(salen) complexes in a *trans*-configuration show no asymmetric induction. Aoki and Seebach have also reported that the regulation of Criegee intermediate is essential for chiral alkyl hydroperoxide-mediated Baeyer–Villiger oxidation [123].



Scheme 11.67.

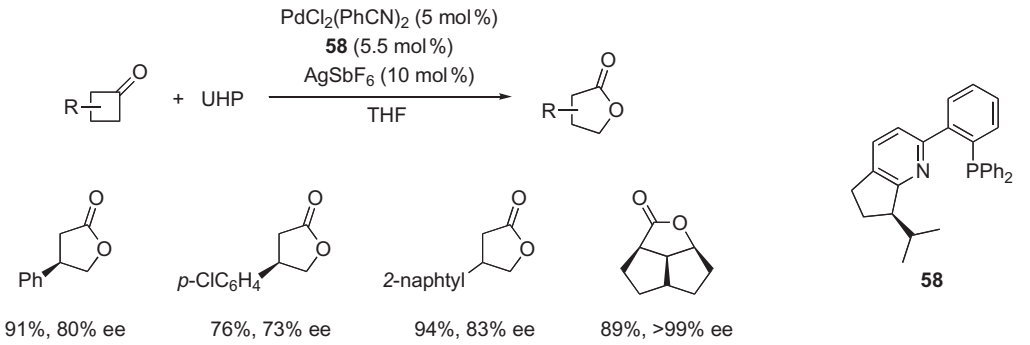




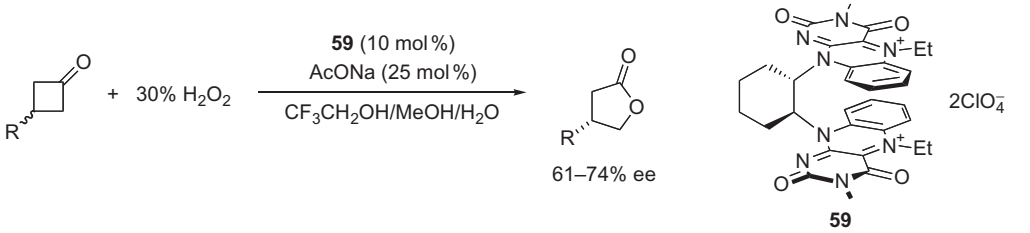
Scheme 11.68.

Subsequently, Katsuki and coworkers reported the zirconium-catalyzed Baeyer–Villiger reaction using UHP as oxidant (Scheme 11.68) [124]. In the presence of Zr(salen) complex **57**, a range of 3-substituted cyclobutanone derivatives efficiently underwent oxidation to give the enantio-enriched lactones with high enantioselectivity. Zr(salen) complex **57** also promoted parallel kinetic resolution of racemic cyclobutanones, and the lactones and the recovered ketone were obtained in high enantiomeric excesses. The authors proposed that the salen ligand of **57** adopts a *trans*-topology in the resting state but that *cis*-β one in the transition state. The related hafnium(salen) complex also catalyzed the reaction with the comparable enantioselectivity [125].

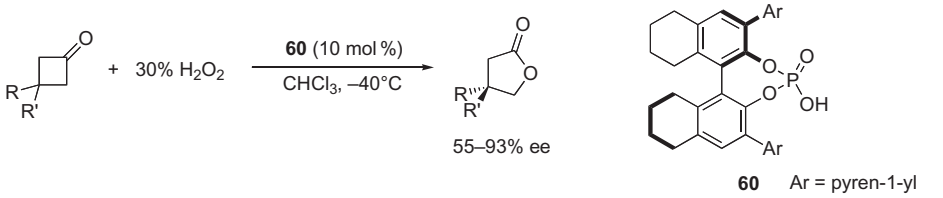
A palladium complex has been identified by Ito and coworkers as a Baeyer–Villiger oxidation catalyst. A cationic palladium^{II} complex bearing *P*,*N*-ligand **58** promoted the reaction of cyclobutanones with good enantioselectivity (Scheme 11.69) [126]. The complete enantioselectivity was achieved in the reaction of a tricyclic ketone. Recently, Malkov and Kočovský also reported chiral terpene-derived *P*,*N*-ligands for the palladium-catalyzed reaction, and a good enantioselectivity of up to 81% ee was observed in the reaction of 3-substituted cyclobutanones [127].



Scheme 11.69.



Scheme 11.70.



Scheme 11.71.

Metal-free, enzyme-catalyzed reactions are also effective methods for the Baeyer–Villiger reactions, and many developments have been reported [128]. Although high enantioselectivities have been realized for some substrates, the scope of enzymatic methods is inherently narrow. A bio-inspired organocatalyst based on flavin has been developed by Murahashi and Imada (Scheme 11.70) [129,130]. Planer-chiral bisflavin perchlorate **59** catalyzes the reaction of cyclobutanones with aqueous hydrogen peroxide as oxidant to give the corresponding γ-butyrolactones with 61–74% ee.

Recently, chiral phosphoric acids were identified by Ding and coworkers as catalyst for the asymmetric Baeyer–Villiger oxidation of cyclobutanones with aqueous hydrogen peroxide as oxidant (Scheme 11.71) [131]. A phosphoric acid catalyst **60** that

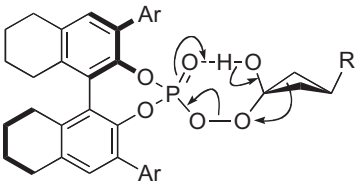
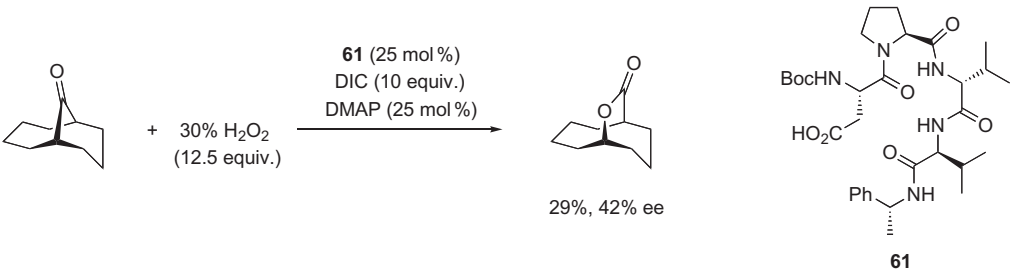


Figure 11.8.



Scheme 11.72.

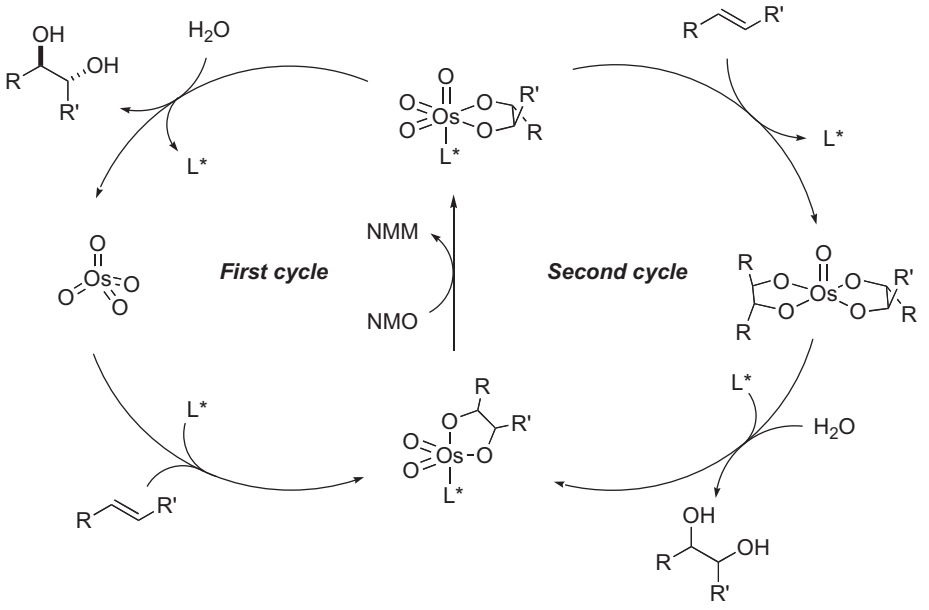
has the H_8-BINOL backbone (H_8-BINOL = 5,5′,6,6′,7,7′,8,8′-octahydro-,1′-bi-2-naphtyl) exhibited higher enantioselectivity than the BINOL derivatives. Aromatic substituents at the C3 and C3′ positions also significantly affected the enantioselectivity, and the introduction of pyren-1-ly groups afforded the highest enantioselectivity in the reaction of 3-phenylcyclobutanone. On the basis of a mechanism proposed for the peracid-mediated Baeyer–Villiger oxidation, the authors suggested that the reaction proceeds via a cyclic Criegee intermediate and that the formation of the intermediate allows the highly enantioselective migration (Fig. 11.8).

Today, a useful level of enantioselectivity has been achieved by several metal- and organo-catalyzed methods, but good substrates are quite limited to cyclobutanone derivatives. Unfortunately, most of the known catalysts cannot be applied to cycloalkanones with larger ring sizes, regarding reactivity and stereoselectivity. The development of more effective methods based on novel activation mechanisms will cross the bounds and open a new horizon in the field of asymmetric Baeyer–Villiger oxidation. Recently, Miller and coworkers demonstrated a simple method, the chiral peracid-mediated asymmetric oxidation. Peracid is a standard reagent for the nonasymmetric Baeyer–Villiger reaction and it is utilized for a wide range of ketones irrespective of the ring size. The authors applied the peracid/carboxylic acid shuttle, which has been previously applied to asymmetric epoxidation of olefins [78], and achieved to render the reaction catalytic (Scheme 11.72) [132]. Aspartate-derived oligopeptide **61** catalytically promotes the oxidation of ketones to yield lactones with moderate but promising enantioselectivity.

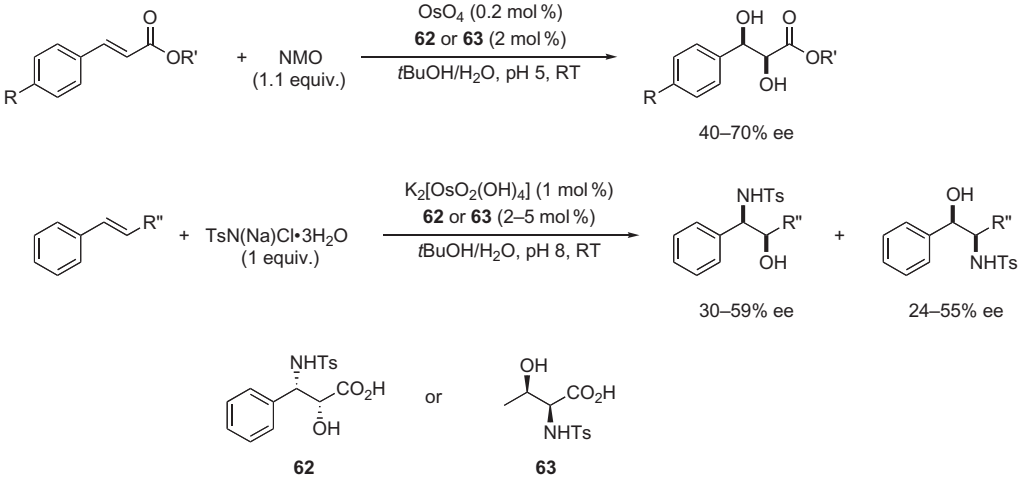
11.6. ASYMMETRIC DIHYDROXYLATION

The Sharpless asymmetric dihydroxylation of olefins is an important chemical process, providing access to synthetically valuable 1,2-diols with two contiguous stereogenic centers [133]. Osmium tetroxide, together with cinchona alkaloid–derived ligands, is employed as a catalyst, and NMO and potassium ferricyanide/potassium carbonate are common oxidants for the reaction. Several types of chiral cinchona alkaloid–derived ligands have been introduced in accordance with the substitution pattern of olefins, and high enantioselectivity is obtained in most cases. There are two potential catalytic cycles for the osmium-catalyzed dihydroxylation of olefins using NMO as oxidant (Scheme 11.73). The left cycle, in which the chiral alkaloid ligand binds to the osmium, is called the first cycle, and the reaction proceeds with high enantioselectivity. On the other hand, the second cycle does not involve the chiral ligand but 1,2-diol ligand. In general, the participation of the second cycle leads to reduced enantioselectivity. Thus, rapid hydrolysis of Os(VIII) trioxoglycolate is essential for achieving high enantioselectivity.

Recently, however, Fokin and Sharpless discovered a unique utilization of the second cycle for enantioselective dihydroxylation and aminohydroxylation [134], which is the aza-analogue of the dihydroxylation and a powerful approach to amino alcohols. In the course of further investigations of the osmium-catalyzed oxidations, the authors discovered that certain classes of olefins undergo rapid dihydroxylation or aminohydroxylation in the absence of the alkaloid ligand, even with very low catalyst loadings [135]. On the basis of the observation, the authors set out the research to account for the exceptional phenomenon and found that chiral *N*-sulfonyl-1,2-hydroxyamines serve as effective ligands for the asymmetric reactions via the second cycle (Scheme 11.74) [136].

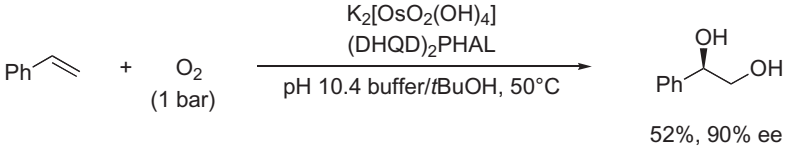


Scheme 11.73.



Scheme 11.74.

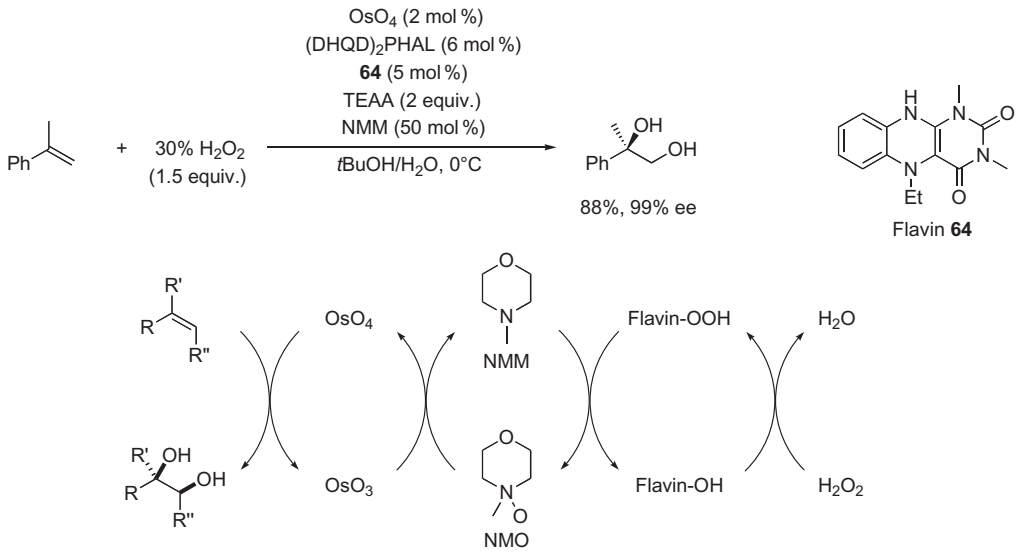
In the common procedures of the Sharpless asymmetric dihydroxylation, NMO or potassium ferricyanide/potassium carbonate is used as an oxidant to give the active osmium tetroxide. However, the cogeneration of stoichiometric amount of NMM or ferrocyanide is problematic from the viewpoint of atom economy. Thus, alternative methods for the catalytic regeneration of osmium tetroxide from an osmate[VI] species have been studied. Beller and coworkers achieved the asymmetric dihydroxylation using molecular oxygen without the addition of mediators (Scheme 11.75) [137]. While the elevated reaction temperature led to somewhat decreased enantioselectivity, optically active 1,2-diols could be obtained with reasonable enantioselectivity. Bäckvall and coworkers also disclosed that flavin **64** can mediate the osmium-catalyzed dihydroxylation in the presence of aqueous hydrogen peroxide as the terminal oxidant (Scheme 11.76) [138]. The reaction proceeded efficiently under the mild conditions, and high enantioselectivity was observed.



Scheme 11.75.

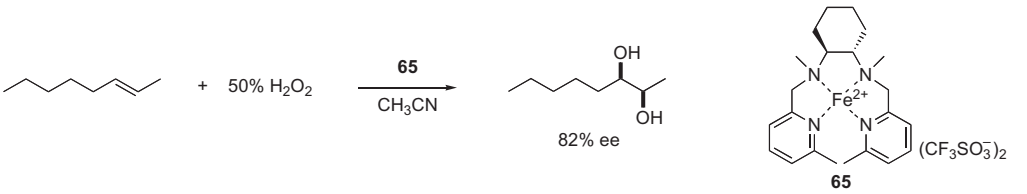
The Sharpless asymmetric dihydroxylation displays excellent enantioselectivity for a wide range of olefins and is frequently utilized in organic synthesis. However, a major drawback of the Sharpless method is the toxicity of the osmium reagent and waste materials derived from it. Thus, the development of an alternative method using more environmentally benign metals has been urged.

Que and coworkers for the first time discovered an iron-based catalyst for enantioselective *cis*-dihydroxylation of olefins. In the presence of aqueous hydrogen peroxide as



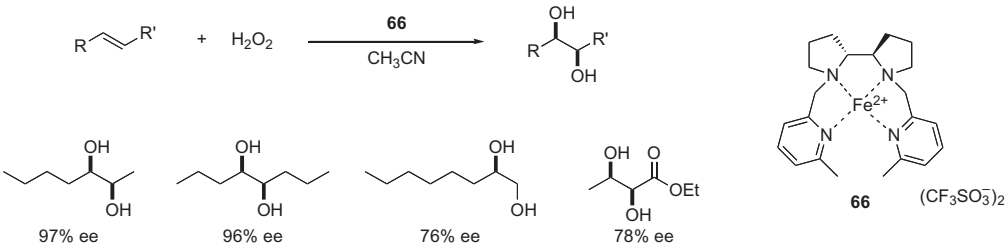
Scheme 11.76.

the oxidant, iron^{II} complex **65** bearing a tetraaza ligand promotes oxidations of olefins to yield diols and epoxides [47]. Terminal and *trans*-disubstituted olefins underwent epoxidation in an enantioselective manner, and good enantioselectivity of 82% ee is obtained in the dihydroxylation of *trans*-2-octene, while a small amount of the epoxidation product is produced (Scheme 11.77). The methyl group on the pyridine ring of **65** dramatically affects the product selectivity, and the related iron complex **25** without methyl groups preferentially yielded epoxides. X-ray analysis revealed that the tetraaza ligand in **65** adopts a *cis*-β topology, in which the two pyridine nitrogen atoms coordinate *cis* to each other, whereas **25** has a *cis*-α one.



Scheme 11.77.

Quite recently, Que and coworkers extended the iron catalysis for the reaction [139]. Replacing the *trans*-1,2-diaminocyclohexane backbone of **65** with rigid bipyrrolidine led to a significant improvement of both the product- and enantioselectivity. The iron catalyst derived from **66**, which adopts a *cis*-α topology in the solid state, promoted the dihydroxylation of *trans*-disubstituted olefins in high enantiomeric excesses up to 97% ee (Scheme 11.78). The ee values are comparable to the Sharpless osmium-catalyzed system. Terminal olefins also underwent dihydroxylation with good enantioselectivity.



Scheme 11.78.

While the process has not yet reached a level for practical use in terms of the requirement for limiting oxidant, future work will provide improvements that overcome this drawback. Recently, Chen and White disclosed the remarkable oxidation catalysis of the related iron catalyst for predictable stereoselective hydroxylation of unactivated C–H bonds [140].[141]

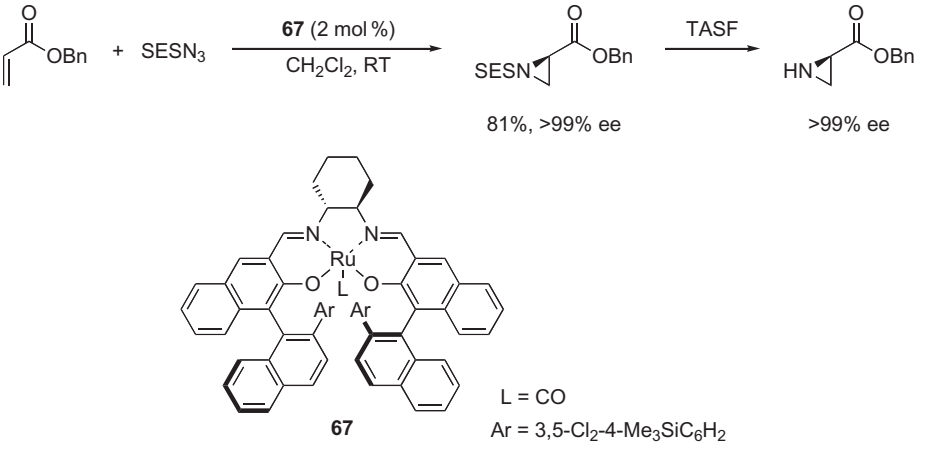
As described above, the toxicity of osmium reagents is a serious problem for the Sharpless asymmetric dihydroxylation, and the development of alternative methods using nontoxic, environmentally benign catalysts is desirable. Que's iron catalysts still fail to stand up to practical use, but further improvements will lead to truly powerful asymmetric dihydroxylation methods.

11.7. ASYMMETRIC AZIRIDINATION

Aziridines, the nitrogen counterpart of epoxides, are versatile building blocks in organic synthesis and an important class of biologically active compounds. Significant progress has been made in the field of catalytic asymmetric aziridination of olefins [141]. Evans and coworkers first identified chiral copper/bisoxazoline complexes as catalysts for nitrene-transfer aziridination and enabled the highly enantioselective synthesis of chiral aziridines [142]. Simultaneously, Jacobsen and coworkers demonstrated the utility of chiral diimine ligands for copper-catalyzed aziridination [143]. Subsequent to the publications, a large number of copper-based variants have been reported, and manganese(porphyrin) and -(salen) complexes were also found to be effective catalysts for the reaction [144,145]. These reactions were proposed to proceed via active nitrenoid species and most of the known methods employ a hypervalent iodine reagent such as PhI=NTs as nitrenoid precursor. While chiral aziridines were yielded as the *N*-sulfonyl protected forms, the deprotection of *N*-sulfonyl groups usually requires harsh conditions. Thus, the development of catalytic asymmetric synthesis of optically active aziridines without a protecting group or with a readily removable group has attracted much attention in recent years. On the other hand, with respect to atom economy, the use of PhI=NTs as nitrene precursor is not favorable due to the generation of a copious amount of iodobenzene as a by-product. Azide compounds are an ideal nitrene precursor in terms of atom efficiency since they liberate only nitrogen gas along with the nitrene formation. *p*-Toluenesulfonyl azide (TsN_3) is known to decompose, giving a free nitrene intermediate under ultraviolet irradiation or heating [146]. Jacobsen and coworkers employed TsN_3 in their copper/diimine-catalyzed asymmetric aziridination under irradiation [147]. Mueller and coworkers also reported asymmetric aziridination using $p$$NsN_3$ in the

presence of a rhodium catalyst [148]. However, the enantioselectivities were only moderate.

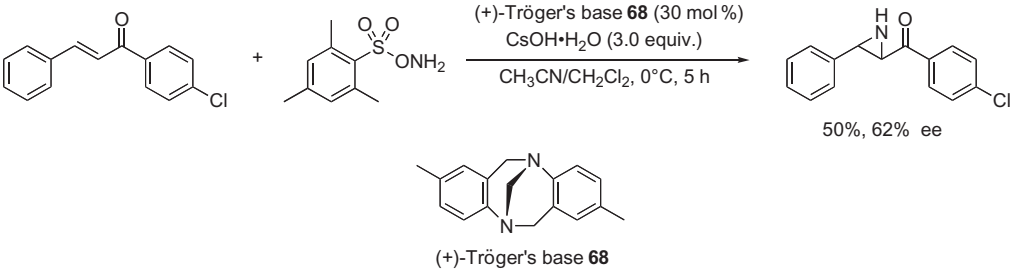
Katsuki and coworkers reported that chiral ruthenium(salen) complex **67** promotes the aziridination of olefins with TsN_3 without irradiation at room temperature, and optically active aziridines were yielded in high enantiomeric excesses [149,150]. The authors further investigated azide compounds as nitrene precursors and found that *p*- and *o*-nitrobenzenesulfonyl azide (*p*- and *o*-NsN_3) and 2-(trimethylsilyl)ethanesulfonyl azide ($SESN_3$) also underwent aziridination enantioselectively [151]. Especially, the reaction with $SESN_3$ efficiently proceeded to give aziridines with high enantioselectivity. It is noteworthy that less nucleophilic, α,β-unsaturated esters also underwent aziridination with complete enantioselectivity and that the SES-protecting group was readily removed by tris(dimethylamino)sulfonium difluorotrimethylsilicate (TASF) without the loss of the enantioselectivity (Scheme 11.79) [152].



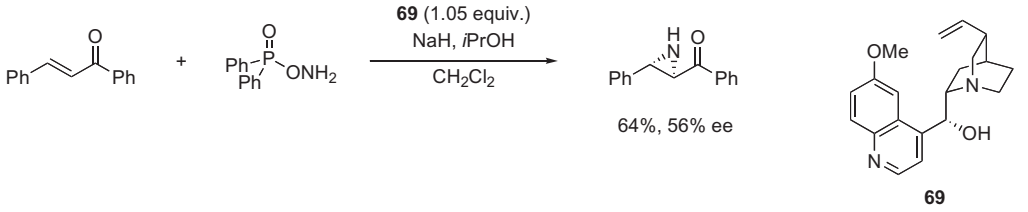
Scheme 11.79.

An aminimide that is produced by deprotonation of the corresponding aminimine has been reported to undergo aziridination of chalcone by the following sequence: conjugate addition and ring closure via N-N bond cleavage [153]. Shi and coworkers discovered that *N*-methylmorpholine-derived aminimide could be catalytically generated in the presence of *O*-mesitylenesulfonylhydroxylamine and $CsOH{\cdot}H_2O$. The reaction also works with a catalytic amount of a chiral tertiary amine, (+)-Tröger's base **68**, giving enantio-enriched aziridines (Scheme 11.80) [154]. Although the reaction is substoichiometric and the enantioselectivity is moderate, this method could produce nonprotected aziridines in a nonracemic form. Subsequent to this publication, Armstrong and coworkers also reported aminimide-mediated asymmetric aziridination of chalcone using quiniclidine and *O*-(diphenylphosphinyl)hydroxylamine (Scheme 11.81) [155]. Although the method needs a stoichiometric amount of quiniclidine **69**, the enantio-enriched α-keto aziridine was yielded with 56% ee.

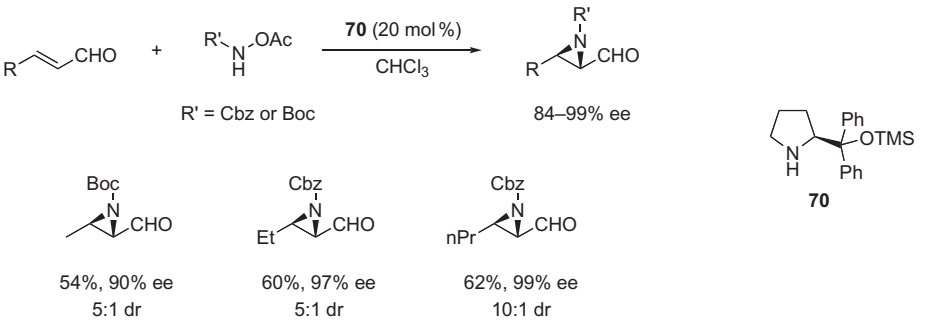
The iminium/enamine catalysis, which has been successfully demonstrated in the secondary amine-catalyzed asymmetric epoxidation of α,β-unsaturated aldehydes, was also applied to asymmetric aziridination by using acetyl hydroxylcarbamate as nitrene equivalent by Córdova and coworkers. The reaction proceeds through a quite similar



Scheme 11.80.



Scheme 11.81.



Scheme 11.82.

pathway to that of the epoxidation [156]: iminium ion formation, conjugate addition of hydroxylamine to the iminium ion, enamine attack on the electrophilic nitrogen atom and hydrolysis of the iminium ion. Chiral pyrrolidine **70** promotes the reaction of enals bearing β-alkyl substituents to give the *N*-Boc- or *N*-Cbz-protected 2-formylaziridines with good diastereo- and high enantioselectivity (Scheme 11.82). The product 2-formylaziridines are rather unstable under the reaction conditions due to the high reactivity. Thus, short reaction time at elevated temperature is recommended for obtaining 2-formylaziridines in higher yield.

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