

Epoxidations and Hydroperoxidations of α,β -Unsaturated Ketones

An Approach through Asymmetric Organocatalysis

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Chapter 2

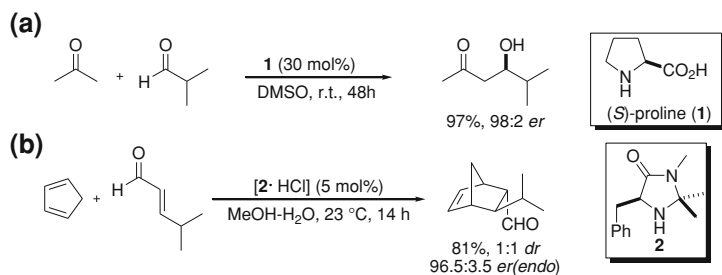
Background

2.1 Asymmetric Organocatalysis

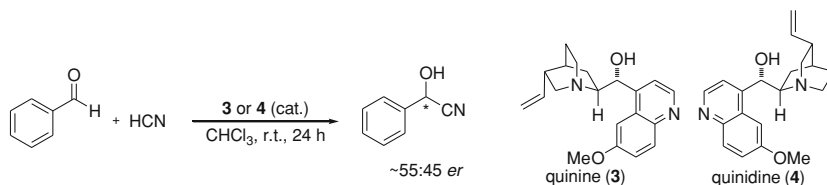
For a long time, the realm of asymmetric catalysis was dominated by metal and biocatalysis. Yet, at the beginning of this century, List's discovery of the (*S*)-proline-catalyzed direct asymmetric intermolecular aldol reaction [1] together with the development of an asymmetric Diels–Alder reaction catalyzed by a chiral imidazolidinone salt by MacMillan et al. [2] have raised awareness of the potential of purely organic molecules as efficient catalysts for a variety of asymmetric transformations and brought to life the term “organocatalysis” to address this research field (Scheme 2.1).

2.1.1 Historical Development

Organocatalysis has a rich background as it is suggested that extraterrestrial, enantiomerically enriched amino acids such as (*S*)-alanine and (*S*)-isovaline played a decisive role in the prebiotic formation of key building blocks such as sugars by promoting the self-aldol reaction of glycolaldehydes in water [3]. In this way, the reactions might have led to the introduction and widespread of homochirality in the living world. The historic roots of organocatalysis date back to the mid of the nineteenth century with von Liebig's accidentally discovery of what is today considered the first organocatalytic reaction, the transformation of dicyan into oxamide in the presence of an aqueous solution of acetaldehyde [4]. In the early 1900s, Bredig's pioneering studies on the use of natural Cinchona alkaloids as enantioselective catalysts were motivated by searching the chemical origin of enzyme activity observed in living organisms [5]. In this context, he developed the first asymmetric organocatalytic reaction by adding hydrogen cyanide to benzaldehyde in the presence of catalytic amounts of either quinine (**3**) or quinidine (**4**) (Scheme 2.2). These studies were conceptually groundbreaking, although the



Scheme 2.1 **a** (*S*)-proline (**1**)-catalyzed direct asymmetric intermolecular aldol reaction. **b** Imidazolidinone (**2**) salt-catalyzed enantioselective Diels–Alder reaction



Scheme 2.2 First enantioselective organocatalytic reaction: asymmetric hydrocyanation of benzaldehyde by Bredig

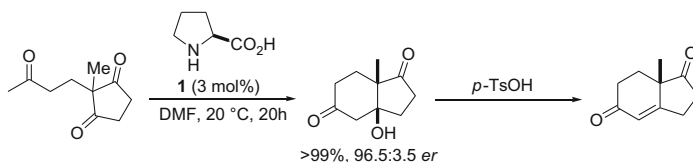
enantiomeric ratio remained rather low (~55:45 *er*), and initiated a line of research which had been continued by Pracejus [6, 7] (~60:40 *er*) and others.

Another key event in the history of organocatalysis was the use of (*S*)-proline as an aldolization catalyst by Hajos and Parrish at Hoffmann-La Roche [8, 9] and Eder et al. [10, 11] at Schering in the early 1970s (Scheme 2.3). Their parallel studies were decisively inspired by the seminal work of Knoevenagel in the late nineteenth century [12].

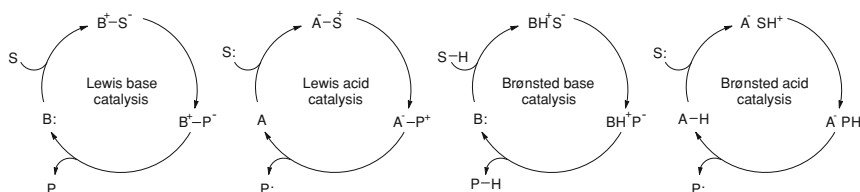
Nonetheless, the real potential of this chemistry was only revealed three decades later by the groups of List and MacMillan who have demonstrated that aminocatalysis, the activation of carbonyl groups via enamine and iminium ion intermediates, is indeed a **general** concept for (asymmetric) catalysis (cf. Scheme 2.1). Evolving from a small collection of chemically unique and unusual, mechanistically poorly understood reactions, organocatalysis has advanced at a truly breathtaking pace since its birth in 2000 and has during the last ten years grown into a thriving area of research, which today represents the third pillar of asymmetric catalysis besides metal and biocatalysis [13–17].

2.1.2 Classification

Organocatalysis can be divided into four areas: Lewis base, Lewis acid, Brønsted base and Brønsted acid catalysis [18]. The corresponding (simplified) catalytic cycles are depicted in Scheme 2.4. Accordingly, Lewis base catalysts (B:) initiate



Scheme 2.3 Hajos–Parrish–Eder–Sauer–Wiechert reaction catalyzed by (*S*)-proline (**1**)



Scheme 2.4 (Simplified) catalytic cycles of Lewis base, Lewis acid, Brønsted base, and Brønsted acid catalysis

the catalytic cycle via nucleophilic addition to the substrate (S). The resulting complex undergoes a reaction and then releases the product (P) and the catalyst for further turnover. Lewis acid catalysts (A) activate nucleophilic substrates (S:) in a similar manner. Brønsted base and acid catalytic cycles are initiated via a (partial) deprotonation or protonation, respectively.

The majority of organocatalysts are N-, C-, O-, P-, and S-based Lewis bases such as amines, carbenes, formamides, phosphoramides, and sulfides. Of those, nitrogen-based systems account for the largest share, partly due to their abundance in the chiral pool. Lewis base organocatalysts operate through diverse mechanisms and convert the substrates into either activated nucleophiles or electrophiles. Typical reactive intermediates are iminium ions, enamines, acyl ammonium ions [19], 1-, 2-, or 3-ammonium enolates [20], among others. The underlying principle of the work discussed within this thesis is the activation of carbonyl compounds as enamine or iminium ion, which represents the basis of what is often called aminocatalysis.

2.1.3 Aminocatalysis

The roots of modern aminocatalysis trace back to the pioneering work of Knoevenagel who, at the turn of the nineteenth century, found that primary and secondary amines, as well as their salts, catalyze the aldol condensation of β -ketoesters or malonates with aldehydes or ketones [21–24]. Remarkably, Knoevenagel himself suggested a possible role of imine formation with the amine catalyst in the course of the reaction [22]. In the first half of the nineteenth century, Kuhn and Fischer and

Marschall discovered that amines and amine salts also catalyze aldol addition and condensation reactions [25–28]. The first iminium-catalyzed conjugate addition reaction to α,β -unsaturated carbonyl compounds was reported in 1937 by Langenbeck using piperidinium acetate as catalyst for the hydration of crotonaldehyde [29]. In the history of iminium catalysis, further important landmarks are: (a) the discovery of iminium-catalyzed transimination by Cordes and Jencks [30], (b) the reports of Baum and Viehe, and more recently Jung et al. [31, 32], on the acceleration of Diels–Alder reactions provided by α,β -unsaturated iminium ions, (c) the proline-catalyzed deracemization of a thianone intermediate in the synthesis of erythromycin by Woodward and co-workers [33], and most importantly (d) the use of alkali metal and ammonium proline salts in the conjugate addition of malonates to α,β -unsaturated aldehydes and ketones in the pioneering work of Yamaguchi and Taguchi between 1991 and 1996 [34–37].

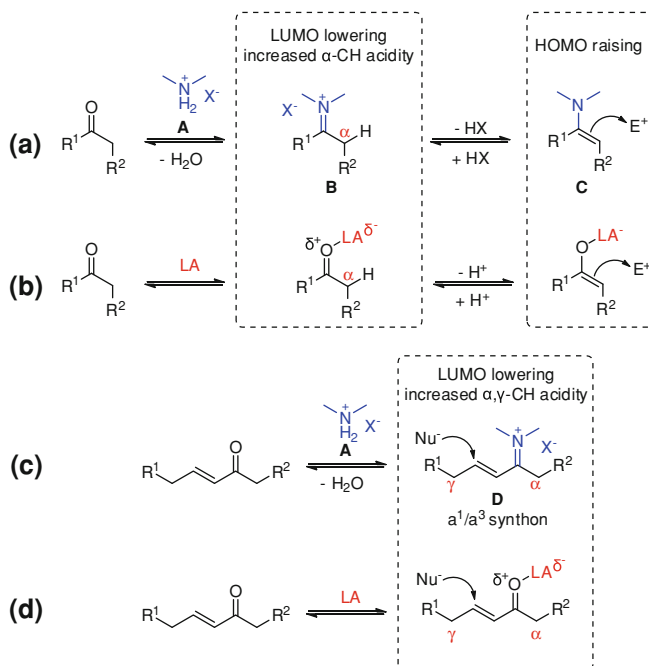
Today's aminocatalytic transformations of carbonyl compounds via iminium ion and enamine intermediates using chiral primary and secondary amines (as well as their salts) as organocatalysts, hinges upon four distinct activation modes and is categorized accordingly in: (a) enamine, (b) iminium ion, (c) dienamine, and (d) SOMO catalysis, which involves the formation of enamine radical cations [38–41].

All distinct activation modes have in common that the initial step constitutes the reversible formation of an iminium ion by condensation of the amine (salt) catalyst (**A**) with the carbonyl compound (Scheme 2.5). The formation of iminium ion **B** effectively lowers the LUMO energy of the system (a)—as does the coordination of a Lewis acid (b). As a result, both nucleophilic additions and α -deprotonation become more facile. α -Deprotonation leads to the generation of enamine **C**, which is more nucleophilic than the enol form of the parent carbonyl compound. The formation of the enamine corresponds to a raise in the HOMO energy of the system and allows for subsequent reaction with a range of electrophiles to obtain α -functionalized carbonyl compounds. For conjugated π -systems, the electronic redistribution induced by the formation of iminium ion **D** facilitates nucleophilic additions (c), including conjugate additions as well as pericyclic reactions. γ -Deprotonation, finally, generates dienamine intermediates (*vide infra*).

In all aspects, the principle of aminocatalytic activation emulates the mechanism of the activation of carbonyl compounds by Lewis acids. In reactions of α,β -unsaturated ketones the steric and electronic similarity of the two carbonyl substituents does not generally permit high levels of discrimination between the free electron lone pairs in the metal-association step, which is essential for attaining high stereocontrol in the following transformation. In aminocatalysis by contrast, iminium ion formation overcomes the necessity of discriminating between the free electron lone pairs.

An overview of the divergent reaction pathways and functionalizations amenable to (a) aldehydes and ketones or (b) enals and enones, respectively, by means of aminocatalysis is provided in Scheme 2.6.

More recently, the formation of dienamines **F** from α,β -unsaturated iminium ions by γ -deprotonation has been synthetically exploited to give rise to γ -functionalized enals upon reaction with electrophiles (Scheme 2.6) [42, 43].

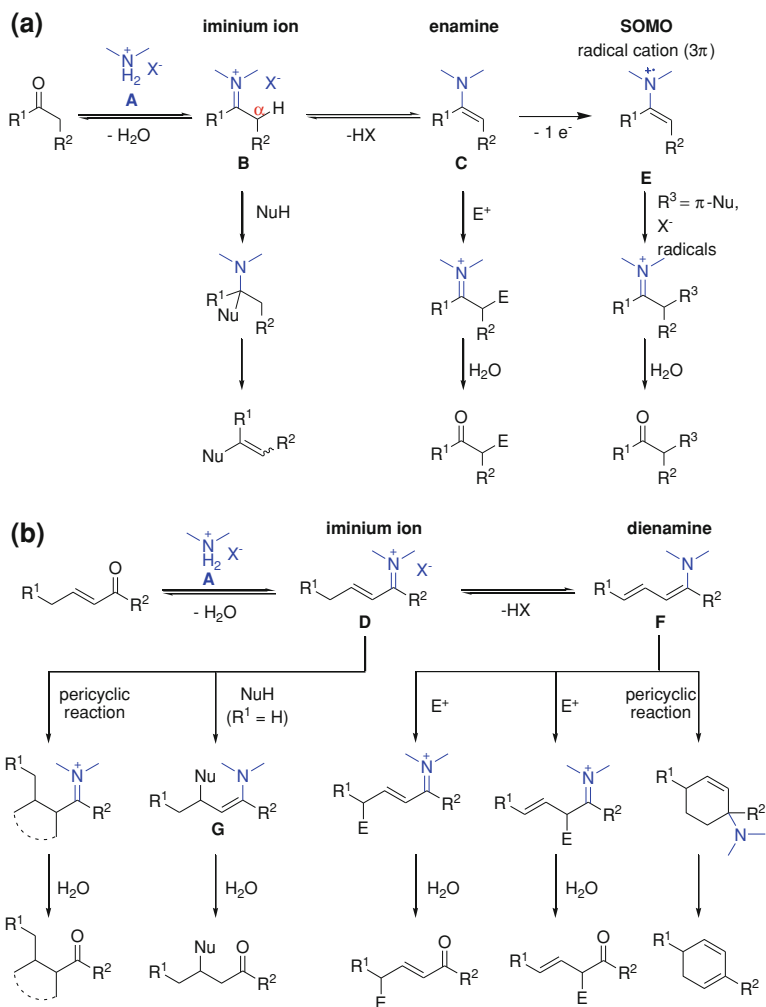


Scheme 2.5 Activation of carbonyl compounds by aminocatalysis (**a**, **c**) versus Lewis acid catalysis (**b**, **d**). (LA Lewis acid, E electrophile, Nu nucleophile)

Their use as electron rich dienes in Diels–Alder reaction has also been reported [44]. A fourth synthetic tool constitutes the SOMO activation of carbonyl compounds. Oxidation of the initially formed enamine **C** affords a radical cation **E** which allows the use of a group of reagents that has previously not been applicable to aminocatalysis such radicals (e.g. TEMPO), π -nucleophiles (e.g. allylsilanes, styrenes), or halides (e.g. LiCl) [45–48].

Enamine and iminium ion catalysis are two divergent reaction modes in organocatalysis, though sharing a common origin. Enamine catalysis proceeds via iminium ion formation and almost always results in iminium ion formation (cf. Scheme 2.6). In a complementary fashion, conjugate addition of a nucleophile to an iminium ion generates an enamine intermediate **G** which can in turn react with another electrophile [49]. The interdependency of those two catalytic intermediates (cf. Scheme 2.7a) combined with the ability of most amine catalysts to promote several types of transformations based on different activation modes side by side makes aminocatalysis the perfect platform for domino and tandem or cascade reactions and a powerful tool in the construction of complex molecular skeletons in a highly stereocontrolled manner as illustrated with numerous elegant examples in the recent literature [50, 51].

One example which presumably operates through the same mechanistic rationale, is the amine-catalyzed asymmetric epoxidation of α,β -unsaturated

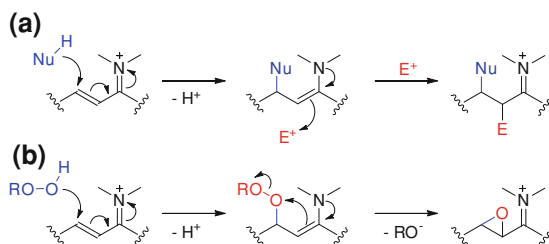


Scheme 2.6 Aminocatalytic activation modes and divergent reaction pathways with **a** aldehydes and ketones, **b** enals and enones

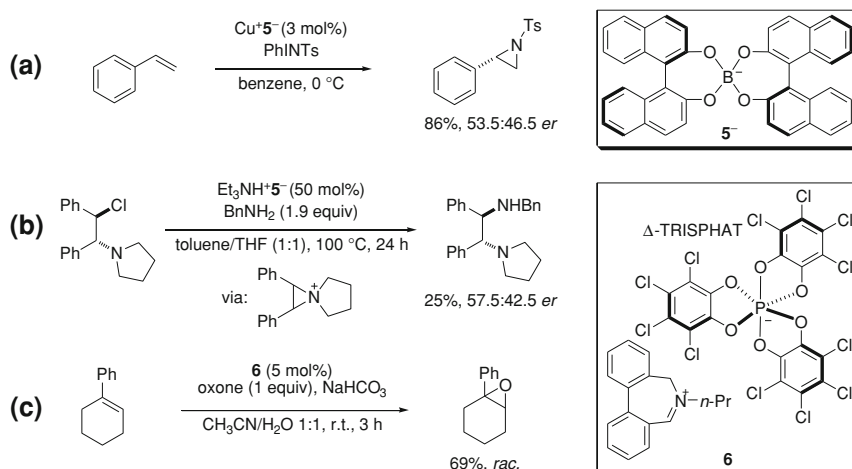
carbonyl compounds with alkyl hydroperoxides or hydrogen peroxide as studied within this thesis. In the course of this reaction, the hydroperoxide serves as both the nucleophile and the electrophile (Scheme 2.7b).

2.1.3.1 Asymmetric Counteranion-Directed Catalysis (ACDC)

Most chemical reactions proceed via charged intermediates or transition states. Such “polar reactions” can be influenced by the counterion, especially if

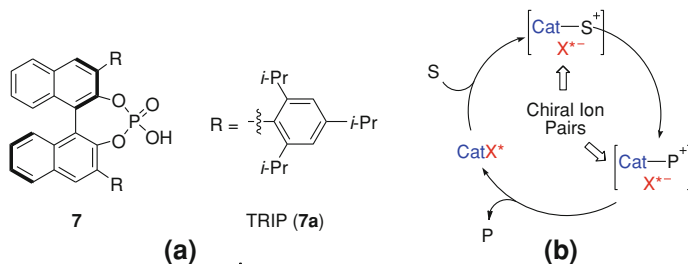


Scheme 2.7 **a** General picture of the iminium ion-enamine interdependency. **b** Iminium ion-enamine interplay in the nucleophilic epoxidation reaction. (*Nu-H* nucleophile, *E* electrophile; R = H, Alk)



Scheme 2.8 Preliminary attempts toward the use of chiral counteranions in asymmetric catalysis

conducted in organic solvents, where ion pairs are ineffectively separated by the solvent. Although efficient asymmetric catalytic transformations involving anionic intermediates with chiral, cationic catalysts have been realized in the context of phase-transfer catalysis [52], analogous versions of inverted polarity attaining reasonable enantioselectivity have been elusive until recently. Attempts toward this end have been undertaken by Arndtsen and Nelson and co-workers (Scheme 2.8, eq. a and b) [53–55]. Both groups applied chiral borate anions such as BINOL-derived borate 5 to several catalytic transformations including copper-catalyzed aziridination and cyclopropanation of olefins and ring opening reactions of *meso*-aziridinium ions, albeit with only moderate success. The highest enantioselectivity observed in all those reactions was 67:33 *er* along with a yield of 3% of the desired product by using a chiral tartrate-derived borate anion [53]. Lacour et al. [56, 57] studied the influence of chiral TRISPHAT anions on enantioselective olefin epoxidation reactions catalyzed by iminium ion 6. However, only racemic product was obtained (eq. c).



Scheme 2.9 **a** Chiral BINOL-derived phosphoric acids [e.g. TRIP (**7a**)]. **b** General concept of asymmetric counteranion-directed catalysis (ACDC) (with Cat = H: special case of Brønsted acid catalysis). (S substrate, P product, CatX catalyst, X^{*-}: chiral anion)

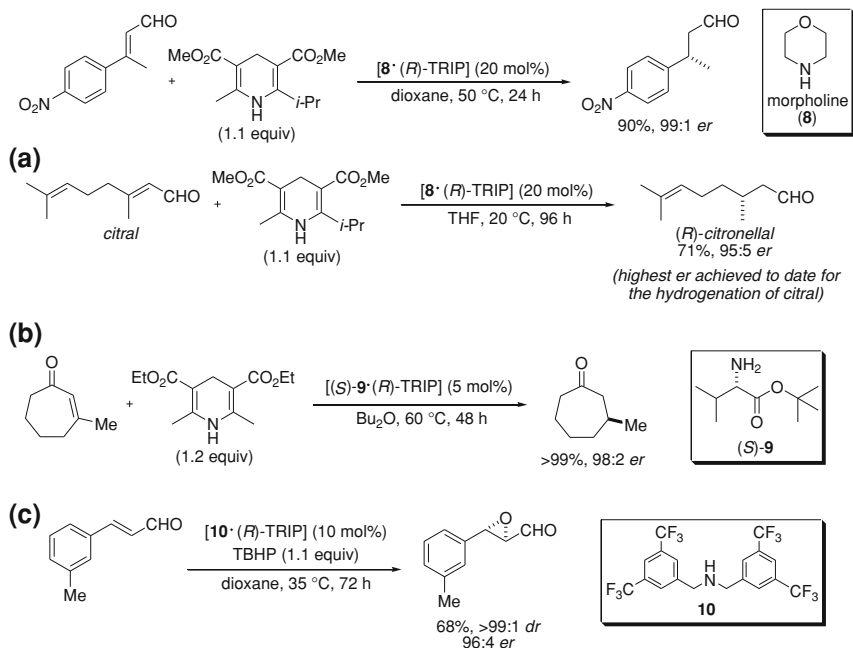
It was not until recently that the use of chiral counteranions in asymmetric catalysis was brought to a useful level of enantioselectivity.

In recent years, chiral BINOL phosphates of the general structure **7** (Scheme 2.9a) have emerged as powerful Brønsted acid catalysts triggered by the seminal works of Akiyama and Terada in 2004 on their use in asymmetric Mannich-type reactions [58–61]. Chiral BINOL-derived phosphoric acids are believed to function as specific Brønsted acid catalysts.¹ The substrate (S) is protonated by the catalyst HX^{*} generating a chiral ion pair [(S – H)⁺ X^{*-}], in which the asymmetry is communicated by the chiral counteranion X^{*-} (Scheme 2.9b; with Cat = H).

Studies undertaken in our laboratory pushed forward the generalization and conceptualization of this approach, namely asymmetric counteranion-directed catalysis (ACDC), by expanding it to catalyst systems with Cat ≠ H (Scheme 2.9b). The efficiency of this concept was initially illustrated with various highly enantioselective catalytic transformations based on iminium ion catalysis (Scheme 2.10) [62–64]. Remarkably, the highest enantioselectivities were consistently observed when using the chiral BINOL-based phosphoric acid **TRIP** (**7a**), bearing sterically demanding 2,4,6-triisopropylphenyl substituents at the 3,3'-positions of the binaphthyl scaffold, as chirality inducing counteranion (Scheme 2.9a) [65]. Later, the ACDC concept was further expanded to Lewis acid and transition-metal catalysis, by our [66, 67] and other research groups [68–70]. The asymmetry transfer from the chiral counteranion X^{*-} to the activated substrate (Cat – S)⁺ within a tight ion pair [(Cat – S)⁺ X^{*-}] (Scheme 2.9b; Cat ≠ H) is most likely the result of a cooperative effect of electrostatic and coordinative interactions conceivably assisted by hydrogen bonding.

The ACDC approach to asymmetric catalysis offers a manifest advantage compared with traditional strategies for catalyst design and optimization. Combinatorial libraries of ACDC catalysts are readily accessible by interchanging the two catalyst components separately. In addition, when using two **chiral** components matched combinations commonly allows further improvement of the asymmetric induction as has been demonstrated in the asymmetric transfer

¹ Specific Brønsted acid catalysis relies on the use of strong Brønsted acids as catalysts.



Scheme 2.10 The ACDC concept in iminium ion catalysis: application to the transfer hydrogenation of **a** enals, and **b** enones as well as, **c** the epoxidation of enals

hydrogenation of ketones catalyzed by the (*S*)-valin-*tert*-butyl ester (**9**) (*R*)-TRIP salt [(*S*)-**9** $\cdot$ (*R*)-TRIP] (Scheme 2.10b). This strategy will also find application in the work described within this thesis.

2.1.3.2 Primary Amine Salt Catalysts

At the outset, the focus of modern aminocatalysis was on the use of chiral secondary amine catalysts, especially substituted pyrrolidines, proline, or imidazolidinone derivatives, for the activation and functionalization of carbonyl compounds. In contrast, chiral primary amine catalysts have been largely neglected, possibly due to unfavorable imine-enamine equilibria [71]. This is surprising in view of the fact that early studies on aminocatalysis have already included the use of primary amino acids, amines and amine salts as catalysts [26, 72–75], and even more so since primary amine catalysis is effectively exploited by natural enzymes such as type I aldolases and decarboxylases, both containing catalytically active lysine residues (Fig. 2.1) [76].

Only recently has primary amine catalysis emerged as a powerful tool for the iminium ion activation of challenging classes of unsaturated carbonyl compounds such as sterically demanding α,β -unsaturated ketones and α -branched enals which are difficult to activate with conventional secondary amine catalysts [77–79]. Owing to reduced steric requirements, the use of primary amines overcomes the inherent difficulties of

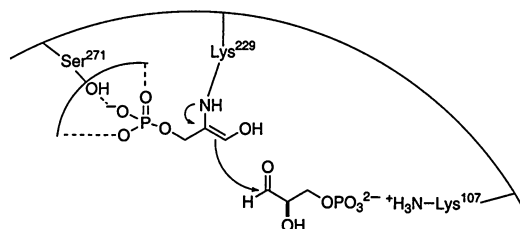
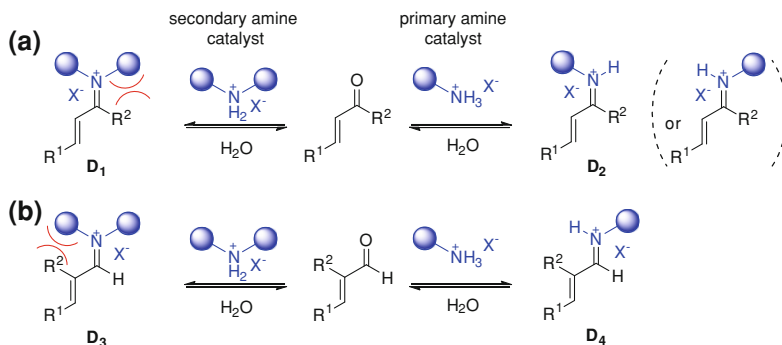


Fig. 2.1 Active site of type I rabbit muscle FDP (fructose-1,6-diphosphate) aldolase [76]

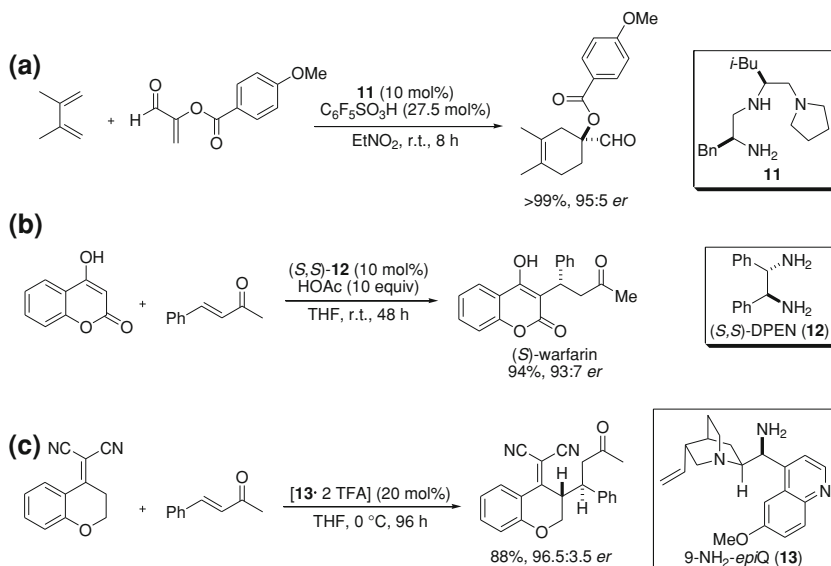


Scheme 2.11 Iminium ion activation of **a** α,β -unsaturated ketones, and **b** α -branched α,β -enals: secondary versus primary amine catalysts

secondary amine catalysts in generating congested covalent iminium ion intermediates, and thus enables transformations of sterically demanding carbonyl compounds which have previously not been realized through secondary amine catalysis (**D₁** and **D₃**, Scheme 2.11). Primary amine catalysts may provide higher equilibrium concentrations of the requisite iminium ion (**D₂** and **D₄**), and thus account for increased reaction rates.

The past years since 2005 have witnessed the rapid development of catalytic asymmetric transformations employing chiral primary amine catalysts [45]. Selected examples are depicted in Scheme 2.12.

Ishihara et al. [80–82] succeeded in activating α -substituted acroleins, in particular α -(acyloxy)acroleins, for Diels–Alder and [2 + 2] cycloaddition reactions by using novel primary amine **11** together with an acid co-catalyst. First evidence of the potential of primary amines as iminium ion activators of α,β -unsaturated ketones was provided by Chin and co-workers in 2006. Their synthesis of warfarin, a widely prescribed anticoagulant, via conjugate addition of 4-hydroxycoumarin to benzylideneacetone was catalyzed by (*S,S*)-DPEN (1,2-diphenylethylenediamine; **12**) in the presence of acetic acid (eq. b) [53–55]. In the same year, List and Martin disclosed the use of (*S*)-valin-*tert*-butyl ester (**9**) (*R*)-TRIP salt [(*S*)-**9** · (*R*)-TRIP] as highly efficient catalyst in the asymmetric transferhydrogenation of cyclic and acyclic α,β -enones (cf. Scheme 2.10b) [64]. Moreover, primary amines derived from naturally abundant Cinchona alkaloids were shown to provide an effective and general catalyst platform for



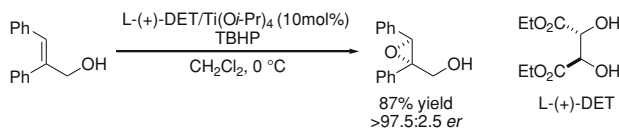
Scheme 2.12 Iminium ion catalysis with primary amine salt catalysts: seminal reports

asymmetric transformations of α,β -unsaturated ketones, including conjugate additions and pericyclic reactions [83]. The seminal report on their use as iminium ion activator of α,β -unsaturated ketones was disclosed by Chen and Deng et al. [84, 85] in 2007. Amino(9-deoxy)*epiquinine* (**13**) as its TFA salt efficiently mediated the enantioselective vinylogous conjugate addition of α,α -dicyanoalkenes to benzylideneacetone and derivatives (Scheme 2.12c). 9-Amino(9-deoxy)*epiquinine* (**13**) and analogues, whose chemistry has been pioneered by Brunner and co-workers [86, 87], have rapidly gained immense popularity and have found widespread application in primary amine catalysis. This is testified by not less than 50 publications since 2007 on their use as chiral organocatalysts from various research groups all around the world including the groups of Melchiorre, Connon, Deng and our group among others [77, 78, 87–91].

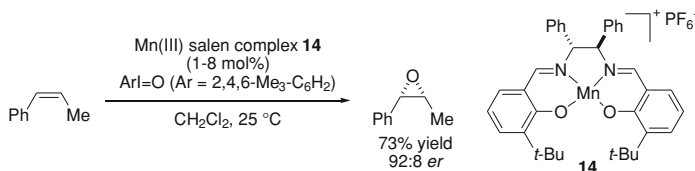
2.2 Catalytic Asymmetric Epoxidation of Electron-Deficient Olefins

2.2.1 Milestones in Catalytic Asymmetric Olefin Epoxidations

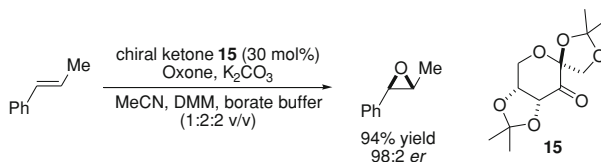
Olefin epoxidation holds a venerable place in the history of catalytic asymmetric synthesis. The pioneering work by Sharpless in the early 1980s on the titanium-tartrate-catalyzed asymmetric epoxidation of allylic alcohols (Scheme 2.13), paved the way for much of today's catalytic asymmetric synthesis [92].



Scheme 2.13 Sharpless' catalytic asymmetric epoxidation of allylic alcohols



Scheme 2.14 Jacobsen-Katsuki epoxidation

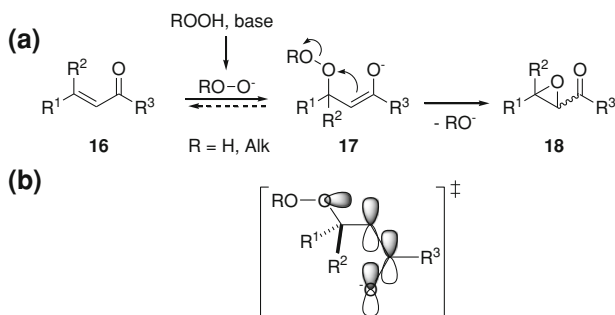


Scheme 2.15 Asymmetric epoxidation catalyzed by chiral ketones

Following this discovery, much progress has been made towards the asymmetric epoxidation of other classes of olefins. Jacobsen and Katsuki introduced manganese-salen complexes as valuable catalysts for the catalytic asymmetric epoxidation of unfunctionalized, and particularly (*Z*)-disubstituted olefins (Scheme 2.14) [93, 94].

More recently, the work of several groups, in particular Shi and co-workers, established dioxiranes, generated *in situ* from chiral ketones and Oxone, as asymmetric epoxidation reagents for a range of alkenes, especially (*E*)-disubstituted olefins (Scheme 2.15) [95].

The advances made in this field have increased greatly the number of enantiomerically enriched epoxides available for use in organic synthesis. Although a few different methods exist for the asymmetric epoxidation of electron-deficient olefins (*vide infra*), no system has gained widespread popularity amongst synthetic organic chemists [96–98]. However, due to the value of the corresponding optically active epoxides as versatile synthetic intermediates, much effort is devoted to the development of a general, highly enantioselective method applicable to a wide range of electron-deficient olefins.



Scheme 2.16 **a** Two-step mechanism of the Weitz–Scheffer epoxidation: conjugate addition of a hydro- or alkyl peroxide followed by epoxide ring closure, **b** putative transition state for epoxide ring closure

2.2.2 Weitz–Scheffer Epoxidation

The general approach for the epoxidation of electron-deficient olefins is their treatment with alkaline hydroperoxides, well-known as the Weitz–Scheffer epoxidation [99, 100]. It is well-established that epoxide formation occurs via a two-step mechanism (Scheme 2.16), which was first proposed by Bunton and Minkoff [101]. Conjugate addition of a peroxyanion generated from hydrogen peroxide or alkyl hydroperoxides under basic conditions at the β -position of an α,β -unsaturated ketone **16** affords β -peroxyenolate **17**. Subsequent intramolecular nucleophilic displacement at the proximal oxygen atom breaks the weak O–O single bond with concomitant ejection of a leaving group—hydroxide or alkoxide—to furnish epoxide **18**.

The non-stereospecificity of these reactions is a strong indication for the formation of an intermediate **17** in the course of the reaction. Unlike for epoxidations with peracids, the alkene geometry is not necessarily retained in the epoxide. For example, the epoxidation of both *trans*- and *cis*-configured α,β -unsaturated ketones with alkaline hydrogen peroxide in methanol furnishes predominantly the corresponding *trans*-epoxide. The non-stereospecificity further implies that hydroperoxide addition is fast, reversible, and causes isomerisation by rotation about the vinylic bond in the peroxyenolate **17** [102].

Electron-deficient olefins exhibit low reactivity toward common electrophilic oxidants such as *meta*-chloroperbenzoic acid (MCPBA). However, under Weitz–Scheffer conditions they are selectively epoxidized in the presence of electron-rich olefins.

Extensive research has been devoted to the development of asymmetric versions of the Weitz–Scheffer epoxidation owing to the synthetic importance of enantiomerically enriched α,β -epoxyketones as chiral building blocks and products of pharmaceutical and biological interest (cf. Fig. 2.2, *vide infra*).

In the mid-1970s, Wynberg et al. [103–105] disclosed the first asymmetric Weitz–Scheffer epoxidation of *trans*-chalcone and derivatives attaining enantioselectivities of up to 77:23 *er* (Scheme 2.17). Cinchona alkaloid-derived quaternary ammonium

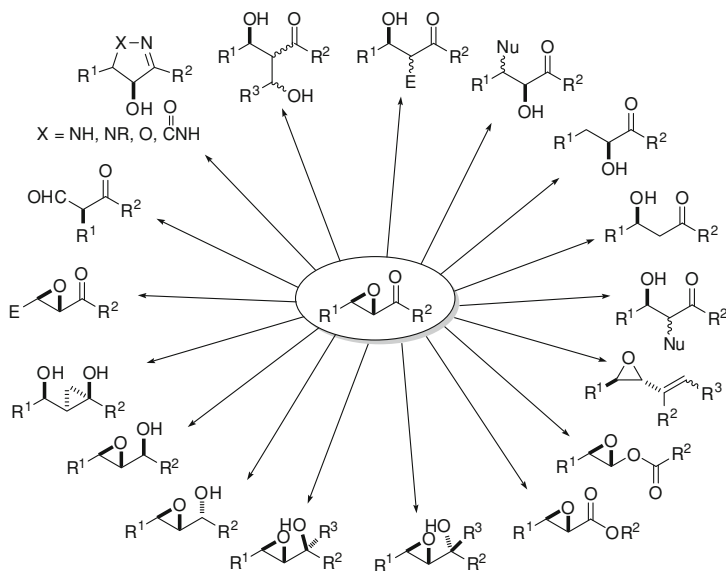
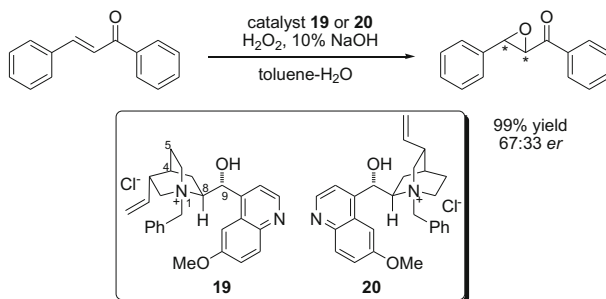


Fig. 2.2 Selected one-step transformations of α,β -epoxy ketones. (*Nu* nucleophile, *E* electrophile)



Scheme 2.17 First asymmetric Weitz–Scheffer epoxidation by Wynberg using *N*-benzylquininium or –quinidinium chloride **19** or **20** as chiral phase-transfer catalyst

salts were applied as chiral phase-transfer catalysts with either hydrogen peroxide, *tert*-butyl hydroperoxide, or sodium hypochlorite as the oxidant under biphasic reaction conditions. Pseudoenantiomeric² [106] catalysts **19** and **20** derived from quinine and quinidine, respectively, produced opposite epoxide enantiomers.

² Pseudoenantiomeric catalysts are diastereomers that afford antipodal products in catalytic asymmetric transformations. The configuration of catalysts **19** and **20** is inverted at C-8 and C-9 whereas it is identical at N-1, C-4, and C-5. Likewise, the starting materials, the naturally abundant cinchona alkaloids quinine and quinidine, are pseudoenantiomers themselves.

The phase-transfer catalyzed nucleophilic asymmetric epoxidation for the first time provided access to enantiomerically enriched chalcone- and naphthoquinone-derived epoxides, and moreover, this approach represents one of the first methods in general for the synthesis of optically active epoxides.

2.2.3 *Synthetic Versatility of α,β -Epoxy Ketones*

Enantiomerically enriched α,β -epoxy ketones are of particular value due to their dense functionalization [107]. Such optically active epoxides may be transformed into numerous products (i.a. pharmaceuticals, agricultural chemicals, and fragrances), where it is distinctly advantageous to use chiral starting materials of high optical purity. Both the epoxide and the adjacent ketone group constitute the starting point for manifold transformations as depicted in Fig. 2.2 [107–110]. Since epoxide can be reliably predicted.

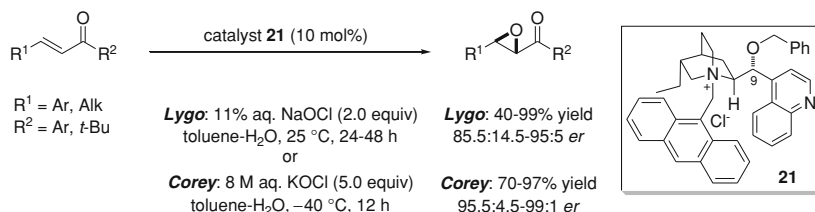
2.2.4 *State of the Art: Catalytic Asymmetric Epoxidation of α,β -Unsaturated Ketones*

Since the pioneering report of Wynberg in 1976, the catalytic asymmetric epoxidation of α,β -unsaturated ketones has been the subject of numerous investigations, and a number of useful methodologies have been developed [96–98, 111]. Moreover, the scope of asymmetric Weitz–Scheffer-type epoxidations was extended to various electron-deficient olefins including nitro olefins [112] and α,β -unsaturated sulfones [113]. In the following section, the state of the art in catalytic asymmetric epoxidation of α,β -unsaturated ketones will be outlined.

2.2.4.1 Asymmetric Phase-Transfer Catalysis

Asymmetric phase-transfer catalysis (PTC) is a powerful strategy applicable to a wide range of transformations that proceed through anionic intermediates.

The most commonly used phase-transfer catalysts for the catalytic asymmetric epoxidation of α,β -unsaturated ketones are alkylated Cinchona alkaloids. Based on the seminal studies of Wynberg et al. (cf. Sect. 2.2.2), contributions from several research groups during the late 1990s led to dramatic improvements in terms of scope and level of enantioselection of the enone epoxidation. The groups of Lygo [114, 115] and Corey [116] achieved significant improvements by structural modification of the original Wynberg-type phase-transfer catalysts **19** and **20**



Scheme 2.18 Asymmetric PTC: enone epoxidation according to Lygo and Corey with *N*-9-anthracenylmethyl-*O*-benzyl-modified dihydroquinine-derived phase-transfer catalysts **21**

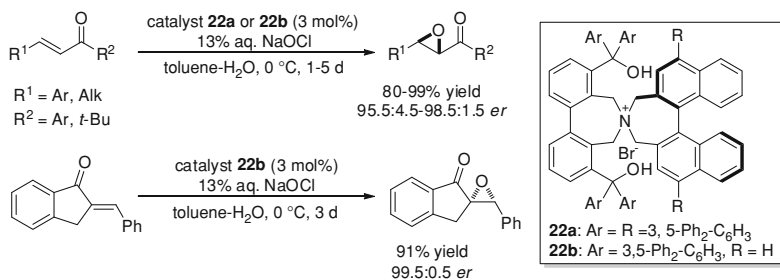
(Scheme 2.17) [114–117]. In particular, the introduction of a large 9-anthracenylmethyl group in place of the benzyl group at the quinuclidine nitrogen and a benzyl group on the secondary alcohol at C-9 in phase-transfer catalyst **21** was found to have a profound effect on the enantioselectivity of the epoxidation reaction (up to 99:1 *er*) (Scheme 2.18) [114]. Aqueous solutions of hypochlorites emerged as the oxidizing agents of choice giving superior results when compared to hydrogen peroxide, whenever *O*-alkylated Cinchona alkaloid-derived phase-transfer catalysts such as **21** were employed. Corey found that the use of freshly prepared 65% potassium hypochlorite at lower temperature instead of sodium hypochlorite led to further improvement in enantioselectivities [116].

Whereas the epoxidation reaction turned out to be general for a broad range of *trans*-chalcone derivatives, α,β -enones bearing alkyl substituents at the β -position furnished epoxides with reduced enantioselectivity. Moreover, substrates with enolizable alkyl groups adjacent to the ketone (substituent R²) gave only low conversions under the standard reaction conditions (<10%), and the starting material was recovered in high yield. Competing enolization is the most likely explanation for this observation [118].

Recently, C₂-symmetric axially chiral quaternary *N*-spiroammonium salts such as catalysts **22a** or **b** were introduced by the Maruoka group as powerful chiral phase-transfer catalysts [119]. By means of these catalysts, the high enantioselectivities achieved for chalcone-type substrates were also retained for α,β -enones bearing alkyl substituents at the β -position, and moreover, for β -benzylidene- α -indanone and its tetralone analogue (Scheme 2.19).

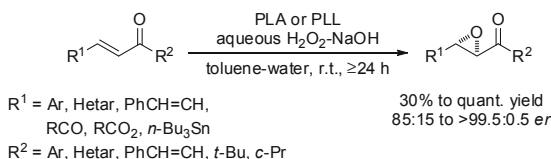
2.2.4.2 Polyamino Acid-Mediated Epoxidation (Juliá-Colonna Epoxidation)

The polyamino acid-catalyzed asymmetric epoxidation of α,β -unsaturated ketones was first reported by Juliá and Colonna and co-workers in the early 1980s [120, 121]. The original reaction conditions were triphasic, consisting of the insoluble polyamino acid catalyst [poly-L-alanine (PLA) or poly-L-leucine (PLL)], an aqueous solution of sodium hydroxide, aqueous hydrogen peroxide as the oxidant, and a solution of chalcone in an organic solvent (Scheme 2.20). A range of



Scheme 2.19 Catalytic asymmetric epoxidation of α,β -unsaturated ketones (including β -benzylidene- α -indanone) with PTCs **22a** or **b** by Maruoka et al

Scheme 2.20 Scope of the Juliá-Colonna epoxidation under triphasic reaction conditions

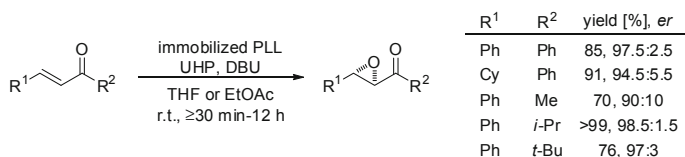


α,β -enones, in particular chalcone and simple analogues, were epoxidized with high enantioselectivities (generally $\geq 95:5$ *er*). It was found that the level of enantiocontrol of the epoxidation was dependent on the chain length of the polyamino acid and increased as the average chain length increased from 10 to 30 residues. Somewhat surprisingly, poly-L-valine emerged to be completely ineffective as epoxidation catalyst [122].

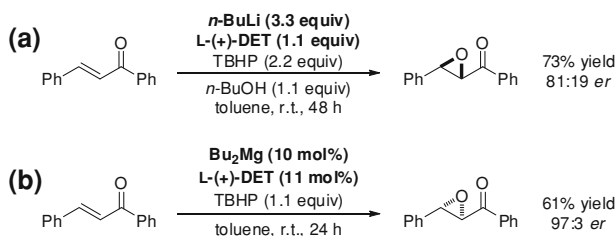
Despite the excellent enantioselectivity, a number of problems limited the applicability of this methodology, namely the long reaction times even for relatively reactive substrates such as chalcone and the narrow substrate scope. In particular, enolizable substrates such as benzylidene acetone are found to be epoxidized very slowly or not at all.

Extensive studies by Roberts and co-workers resulted in significant improvements to overcome these limitations. The modified reaction conditions comprised the use of a non-aqueous solvent, an organic base (e. g. 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU)), water-free oxidants such as urea-hydrogen peroxide (UHP) or percarbonate, along with **immobilized** poly-L-leucine as catalyst [123–127]. These non-aqueous, biphasic reaction conditions allowed for greatly enhanced reaction rates (from ca. 24 h to 30 min in the case of chalcone) and lower catalyst loadings (5 instead of 20 mol%). Moreover, substantial expansion of the range of α,β -enones was achieved and previously unreactive enolizable substrates such as benzylidene acetone as well as those bearing alkyl groups at the β -position readily underwent the epoxidation reaction (Scheme 2.21) [125].

The mechanism of the polyleucine-catalyzed epoxidation is still under investigation [102, 128–131]. Kinetic studies indicate that the reaction proceeds via the reversible addition of polyleucine-bound hydroperoxide to the enone [132].



Scheme 2.21 Expanded substrate scope under Robert's biphasic reaction conditions [125]



Scheme 2.22 Jackson's asymmetric chalcone epoxidation using either the **a** stoichiometric lithium *tert*-butyl peroxide (+)-DET or the **b** catalytic magnesium *tert*-butyl peroxide (+)-DET system

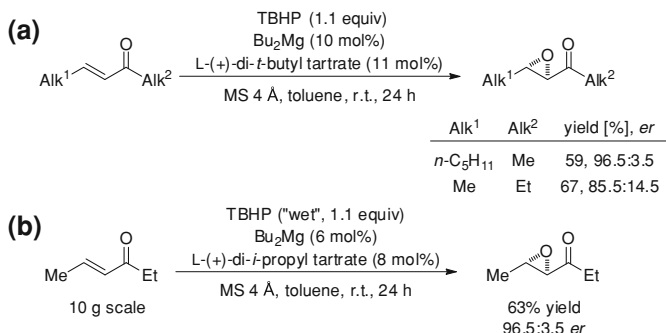
2.2.4.3 Metal Peroxides in Combination with Chiral Ligands

Several methods for the catalytic asymmetric epoxidation of α,β -unsaturated ketones rely on the use of a chiral ligand coordinated to the metal atom of a metal peroxide, which then effects a Weitz–Scheffer epoxidation. A number of metals and chiral ligands have been used for this purpose and the most successful approaches are discussed below.

Jackson et al. had previously established the use of lithium *tert*-butylperoxide generated *in situ* from *n*-butyl lithium and *tert*-butyl hydroperoxide (TBHP) together with stoichiometric amounts of diethyl tartrate (DET) for the epoxidation of *trans*-chalcone resulting in moderate yield and enantioselectivity (81:19 *er*) of the chalcone epoxide (Scheme 2.22a). However, upon replacement of *n*-butyllithium by dibutylmagnesium, catalytic amounts of the chiral ligand DET and the base were sufficient to provide high levels of asymmetric induction on a range of chalcone-type substrates (Scheme 2.22b) [133].

Intriguingly, the catalytic magnesium system provided epoxides antipodal to those obtained using stoichiometric lithium peroxides, despite employing the identical enantiomer of the chiral ligand (+)-DET. The Jackson group further optimized the magnesium-based catalyst system and identified conditions which not only tolerated chalcone-type substrates but were applicable to a variety of enolizable aliphatic enones without loss of catalyst efficiency (Scheme 2.23) [134, 135].

The addition of 4 Å molecular sieves was crucial to retain as high conversions for aliphatic enones as for chalcone-type substrates. Moreover, the use of tartrate esters derived from secondary or tertiary alcohols instead of DET led to improved



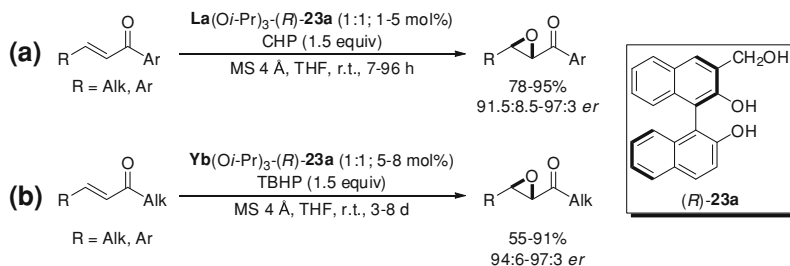
Scheme 2.23 Catalytic asymmetric epoxidation of aliphatic enones with **a** magnesium di-*tert*-butyl tartrate under anhydrous and with **b** magnesium diisopropyl tartrate under "wet" reaction conditions

enantioselectivities with the optimal ligand being di-*tert*-butyl tartrate (Scheme 2.23a) [134]. The use of "wet" *tert*-butyl hydroperoxide in combination with 4 Å molecular sieves at lower catalyst loadings of both dibutylmagnesium and diisopropyl tartrate further enhanced the operational simplicity and practicality of the process which was illustrated by a large scale synthesis of 4,5-epoxy-3-hexanone in good yields along with improved enantioselectivity of 96.5:3.5 *er* (Scheme 2.23b) compared to 85.5:14.5 *er* previously attained (Scheme 2.23a) [135]. Jackson's catalytic asymmetric epoxidation of aliphatic α,β -enones proceeds with the highest enantioselectivities obtained prior to this work for this substrate class.

Probably the most general method for the catalytic asymmetric epoxidation of α,β -unsaturated carbonyl compounds was developed by Shibasaki and co-workers and uses a combination of lanthanoid alkoxides and BINOL or its derivatives with alkyl hydroperoxides as the oxygen source [136, 137]. Two types of catalyst systems exist: (a) one of them is represented by the general structure $\text{LnM}_3[(R)\text{-BINOL}]$ (Ln = lanthanoid, M = alkali metal) and comprises alkali metals whereas (b) the other one is alkali metal-free. In both cases oligomeric complexes between the lanthanoid metal and BINOL are formed.

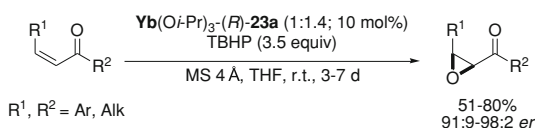
Alkali metal-free catalyst systems gave superior results in the catalytic asymmetric epoxidation of α,β -unsaturated ketones. The choice of the optimal lanthanoid metal depended on the nature of the enone substrate. The lanthanum-(*R*)-3-hydroxymethyl-BINOL complex (La-(*R*)-**23a**) in combination with cumyl hydroperoxide (CHP) was the ideal choice for the epoxidation of aromatic chalcone-type substrates (Scheme 2.24a), whereas the catalytic activity for aliphatic α,β -unsaturated ketones could be improved by the use of ytterbium complexes along with TBHP as the oxidant (Scheme 2.24b) [138–140].

Remarkably, the alkali metal-free complex ytterbium-(*R*)-3-hydroxymethyl-BINOL (Yb-(*R*)-**23a**) converted *cis*-enones to the corresponding *cis*-epoxides in good yields and with high levels of asymmetric induction when using TBHP as the



Scheme 2.24 Catalytic asymmetric epoxidation of α,β -unsaturated ketones with lanthanoid-BINOL complexes according to Shibasaki et al. [138]

Scheme 2.25 Catalytic asymmetric formation of *cis*-epoxides from *cis*-enones by Shibasaki et al. [141]



oxygen source (Scheme 2.25) [141]. Only for aromatic *cis*-enones ($\text{R}_2 = \text{Ar}$) minor amounts (up to 32%) of the corresponding *trans*-epoxy ketones were formed at the same time. This report is remarkable since it constitutes one of the rare examples of the selective formation of *cis*-epoxides through nucleophilic epoxidation of *cis*-olefins [118].

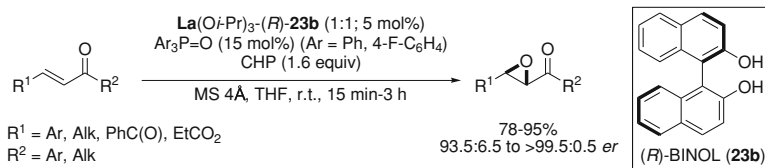
Later on, Inanaga et al. [140, 142–144] found that the use of additives such as triphenylphosphine oxide or *tris*(4-fluorophenyl)phosphine oxide led to enhanced reaction rates which allowed for significantly shortened reaction times (Scheme 2.26). The optimized conditions applied best to chalcone-type substrates (up to >99.5:0.5 *er*) whereas simple aliphatic enones lagged behind in terms of the level of enantiocontrol (93.5:6.5 *er* with $\text{R}^1 = \text{PhCH}_2\text{CH}_2$, $\text{R}^2 = \text{Me}$).

According to the authors, the increased catalyst activity resulted from the deoligomerization of the lanthanoid-BINOL complexes through coordinative saturation of the lanthanoid metal with additional ligands [144].

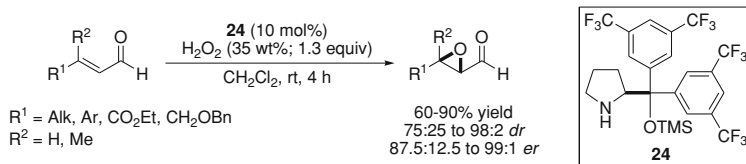
Shibasaki's lanthanoid-BINOL and related catalyst systems proved to be very general [136], and found widespread application in the catalytic asymmetric epoxidation of α,β -unsaturated esters [145], amides [146, 147], and several ester surrogates such as *N*-acylpyrroles [148–150] or imidazoles [151, 152].

2.2.5 Recent Advances: The Organocatalytic Approach

This chapter focuses on catalytic asymmetric epoxidations of α,β -unsaturated carbonyl compounds mediated by small molecule organocatalysts such as (*S*)-proline and its derivatives. Recent advances within the realm of phase-transfer



Scheme 2.26 Catalytic asymmetric epoxidation of α,β -unsaturated ketones with a lanthanum-BINOL complex and triarylphosphine oxide as additive according to Inanaga et al. [143]



Scheme 2.27 First catalytic asymmetric epoxidation of α,β -unsaturated aldehydes by Jørgensen et al. [153]

catalysis, the Julia-Colonna, and the Shi epoxidation, which can be considered borderline organocatalytic, were covered in the previous chapter (Sect. 2.2.4).

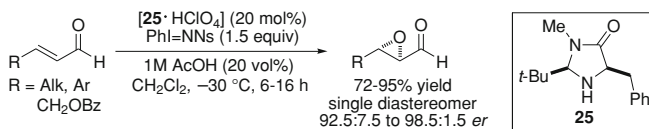
2.2.5.1 Organocatalytic Asymmetric Epoxidation of α,β -Unsaturated Aldehydes

The development of new organocatalytic methods—in particular of those based on iminium ion catalysis—for the asymmetric epoxidation of α,β -unsaturated carbonyl compounds has advanced this research field decisively by extending the substrate scope beyond ester, amide, and chalcone derivatives.

In 2005, Jørgensen and co-workers presented the first direct catalytic asymmetric epoxidation of α,β -unsaturated aldehydes, a reaction that had remained a challenge to chemists [153]. Indeed direct approaches to enantiomerically enriched α,β -epoxy aldehydes were hitherto not available. In the presence of catalytic amounts of the chiral secondary amine α,α -[3,5-bis(trifluoromethyl)phenyl]prolinol trimethylsilyl ether (**24**) and with aqueous hydrogen peroxide as the oxidant, a range of α,β -epoxy aldehydes could be obtained in high yields along with high enantioselectivities from both aromatic and aliphatic enals in a single step (Scheme 2.27).

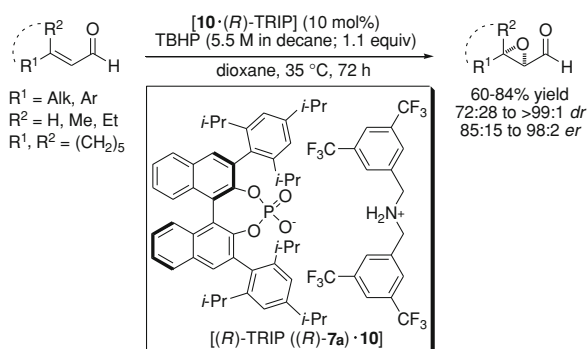
This seminal work also revealed the compatibility of amine catalysts with various oxidants and dispelled scepticism, which predicted severe difficulties from catalyst degradation via competing catalyst *N*-oxidation.

Alternative protocols for the catalytic asymmetric epoxidation of α,β -unsaturated aldehydes based on iminium ion activation were developed by the MacMillan and List groups.



Scheme 2.28 Catalytic asymmetric epoxidation of α,β -unsaturated aldehydes by MacMillan et al.

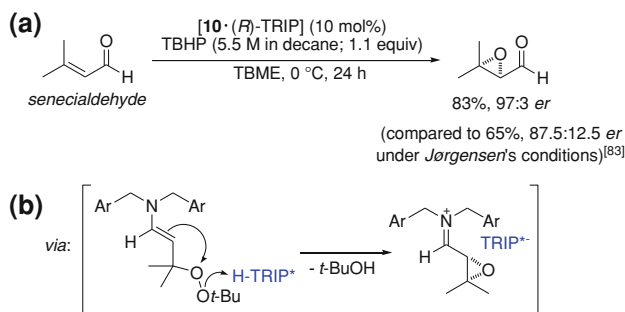
Scheme 2.29 Catalytic asymmetric epoxidation of α,β -unsaturated aldehydes by List and Wang



MacMillan and co-workers identified chiral imidazolidinone **25** as its perchlorate salt to effectively mediate the epoxidation reaction with hypervalent iodine reagents as oxidants (which are rarely used in nucleophilic epoxidation reactions) (Scheme 2.28) [154]. A mechanistic study with ^{15}N labelled imidazolidinone catalyst **25** revealed that iodosobenzene indeed brought about slow catalyst degradation by oxidation. Thus, key to achieving high levels of both reaction efficiency and enantioselectivity was the use of $[(N\text{-Nosylimino})\text{iodo}]\text{benzene}$ ($\text{PhI} = \text{NNs}$) as an iodosobenzene surrogate which, in the presence of acetic acid, provided a slow release of iodosobenzene over time ('internal syringe pump').

List and Wang successfully applied the ACDC concept to the catalytic asymmetric epoxidation of α,β -unsaturated aldehydes [62]. Among all combinations tested, catalyst salt $[10 \cdot (R)\text{-TRIP}]$ comprising an achiral dibenzylamine derivative **10** together with the BINOL phosphate TRIP (**7a**) as the chiral counteranion and only source of chirality, turned out to be the catalyst of choice furnishing the desired α,β -epoxy aldehydes in high yields and enantioselectivities (Scheme 2.29).

Remarkably, symmetrically β,β -disubstituted enals such as senecialdehyde (3-methylbutenal) gave the desired epoxides with excellent enantioselectivities up to 97:3 *er* in the presence of the ACDC catalyst $[10 \cdot (R)\text{-TRIP}]$ (Scheme 2.30a). This represents a great advancement compared to the results obtained with the catalyst system described by Jørgensen and co-workers, where this substrate class was converted into the corresponding epoxides with significantly lower enantioselectivities (87.5:12.5 *er*; cf. Scheme 2.30a). Moreover, this observation raises interesting mechanistic questions. Since the initial conjugate addition product is achiral, the stereogenic center is created during the epoxide ring closure.



Scheme 2.30 **a** Catalytic asymmetric epoxidation of senecialdehyde according to List and Wang. **b** Proposed reaction pathway

Consequently, the chiral BINOL phosphate (*R*)-TRIP (**7a**) must be involved in this C–O bond-forming event and presumably assists the enantioselective cyclization of the achiral peroxyenamine intermediate (Scheme 2.30b).

2.2.5.2 Organocatalytic Asymmetric Epoxidation of α,β -Unsaturated Ketones

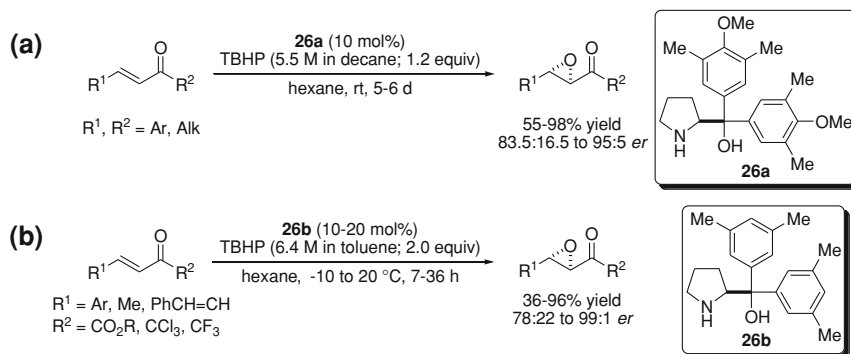
Unfortunately, secondary amine catalysts such as trimethylsilyl diarylprolinol ether **24** and related compounds which efficiently mediated the catalytic asymmetric epoxidation of α,β -unsaturated aldehydes turned out to be less active to completely inactive for the epoxidation of α,β -unsaturated ketones.

Lattanzi and later Zhao and co-workers identified unprotected α,α -diarylprolinol derivatives such as **26a** or **b** and other structurally diverse β -amino alcohols to provide an effective platform for the epoxidation of an array of electron deficient olefins including α,β -unsaturated ketones with *tert*-butylhydroperoxide as the oxidant (Scheme 2.31a and b) [154–164].

Within these reports it was proposed by the authors that α,α -diarylprolinol catalysts may be operating through hydrogen bonding interactions. TBHP may be activated via general base catalysis by the prolinol derivative (Fig. 2.3).

The formation of iminium ions between α,β -unsaturated ketones and catalysts **26a–b** as an alternative activation pathway was ruled out by the authors given the known unreactive nature of enone carbonyls and the detrimental effect of an acid co-catalyst on the outcome of those reactions.³ Moreover, a strong solvent effect could be detected further supporting the involvement of non-covalent hydrogen bonding interactions. However, whereas this method is well developed for chalcone and derivatives, it was scarcely applied to simple aliphatic enones, and when so, giving inferior results and enantioselectivities of 87.5:12.5 *er* at the most. In addition, the present epoxidation protocol requires the use of TBHP as the

³ Although smaller in number, reports exist which denote the activation of enone systems as iminium ion in the presence of secondary amine (salt) catalysts.



Scheme 2.31 Catalytic asymmetric epoxidation of electron deficient olefins including α,β -unsaturated ketones by **a** Lattanzi [157], and **b** Zhao et al. [164]

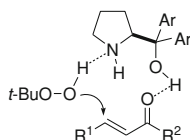


Fig. 2.3 Proposed mode of activation of electron deficient olefins by diarylprolinol derivatives via hydrogen bonding interaction. ($R^1 = \text{Ar, Alk}$; $R^2 = \text{Ar, Alk, CO}_2\text{R, CCl}_3, \text{CF}_3$)

oxidant. Aqueous hydrogen peroxide which is an inexpensive and environmentally benign alternative cannot be employed [160].

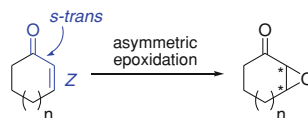
Furthermore, chiral guanidines have been explored as base catalysts in the nucleophilic epoxidation of different types of α,β -enones. Promising, but not yet fully satisfactory levels of stereocontrol have been achieved to date by means of this approach [165–168]. In contrast, chiral guanidinium salts as well as bifunctional guanidinium-urea and guanidinium-hydroxyl organocatalysts delivered α,β -epoxy ketones mostly derived from chalcone-type substrates in high yields and with good to high enantioselectivities with either hydrogen peroxide or TBHP as the oxidant [169–171].

A catalytic asymmetric epoxidation of α,β -unsaturated ketones truly relying on iminium ion activation of the enone carbonyls and a method giving highly enantioenriched α,β -epoxy ketones from simple aliphatic enones had not been put into practice prior to this work.

2.2.6 Asymmetric Epoxidation of Cyclic α,β -Unsaturated Ketones

Cyclic enones constitute a special class of α,β -unsaturated ketones. Up to a ring size with $n \leq 4$, they feature a (*Z*)-configured double bond as well as a rigid *s-trans* conformation of the enone moiety in their thermodynamically stable form (Scheme 2.32).

Scheme 2.32 Asymmetric epoxidation of simple cyclic enones



Strained (*E*)-2-cycloheptenone ($n = 2$), -octenone ($n = 3$), and—nonenone ($n = 4$) can only be generated via photoisomerization [172–175]. As the ring size increases, the amount of strain decreases and (*E*)-configured cycloalkenones ($n \geq 5$) are the stable isomers.

Cyclic systems ($n \leq 4$) are restricted to the *s-trans* conformation, which avoids problems arising from *s-cis/s-trans* interconversion. By contrast, in open-chain systems the equilibrium between the *s-cis* and *s-trans* conformer has to be taken into account. Based on this, one might suspect that the minimal conformational flexibility inherent in cyclic enones would facilitate their asymmetric epoxidation. Yet, the asymmetric epoxidation of *s-trans*-fixed cyclic enones under Weitz–Scheffer conditions has been little studied to date. Indeed, some asymmetric Weitz–Scheffer-epoxidations rigorously require *s-cis* conformation of acceptors, and are thus not applicable to cyclic enones [176, 177]. Successful implementations of cyclic enones in asymmetric nucleophilic epoxidations had been limited to particular substrate classes such as benzoquinone [178, 179], naphthoquinones [180–184], the respective monoketals [185–188], isoflavones [189], and perinaphthenone prior to this work [118].

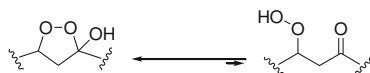
Until 2008, to the best of our knowledge, there was not a single general method available which would allow for the highly enantioselective (catalytic) epoxidation of simple cyclic enones [190]. The literature precedence for the (catalytic) asymmetric epoxidation of 2-cyclohexenone is compiled in Table 2.1.

The highest enantioselectivity of 81.5:18.5 *er* was attained by Baba and co-workers in 1986 by using a quinine-derived bis(phase-transfer catalyst) **27** together with 9-methylfluorenyl hydroperoxide (**28**) as the oxidant (Table 2.1) [190, 191]. All other attempts gave inferior results [120, 156, 192–196]. In many cases, 2,3-epoxycyclohexanone was obtained in almost racemic form although the respective catalyst systems efficiently mediated the epoxidation of other types of α,β -unsaturated ketones such as chalcone and derivatives with good to high enantioselectivities. The use of a TADDOL-derived stoichiometric hydroperoxide **29** has recently been studied by Seebach et al. [194]. Whereas an enantiomeric ratio of 91:9 *er* was achieved in the epoxidation of **3-methyl-2-cyclohexenone**, 2,3-epoxycyclohexanone derived from unsubstituted 2-cyclohexenone was obtained in only 55:45 *er*. In contrast, the phase-transfer conditions applied by Wynberg and Marsman were suitable for the asymmetric epoxidation of 2-cyclohexenone, but not so for 3-methyl-2-cyclohexenone since this olefin may be too sterically crowded to be epoxidized with *tert*-butylhydroperoxide [192].

The development of a highly enantioselective and **general** catalytic epoxidation of cyclic enones was desirable in light of the synthetic value of enantiomerically

Table 2.1 Comprehensive data for the (catalytic) asymmetric epoxidation of 2-cyclohexenone

	chiral catalyst	oxidant	er		chiral catalyst	oxidant	er
Baba et al.			81.5:18.5	Julia, Colonna et al.		H ₂ O ₂	<52.5:47.5
Strukul et al.		H ₂ O ₂	74.5:25.5	Armstrong et al.		Oxone®	51.5:48.5
Wynberg and Marsman		<i>t</i> -BuOOH	60:40	Laschat et al.			59.5:40.5
Lattanzi		<i>t</i> -BuOOH	53:47	Seebach and Aoki			55:45

Scheme 2.33 Equilibrium between cyclic peroxyhemiketals and β -hydroperoxy carbonyl compounds

pure cyclic α,β -epoxy ketones [197–202], and even more so due to the absence of such a method prior to this work.⁴

2.3 Synthesis and Relevance of 3-Hydroxy-1,2-dioxolanes and 1,2-Dioxolanes

3-Hydroxy-1,2-dioxolanes (Scheme 2.33) and 1,2-dioxolanes are organic peroxides. Both contain an O–O bond embedded in a five-membered ring. 3-Hydroxy-1,2-dioxolanes are cyclic peroxyhemiketals of β -hydroperoxy carbonyl

⁴ The asymmetric epoxidation of higher homologues has indeed not been studied at all and for the asymmetric epoxidation of cyclopentenone only one literature report is known to date [190].

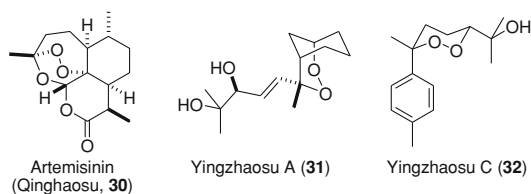


Fig. 2.4 Peroxidic natural products with antimalarial activity

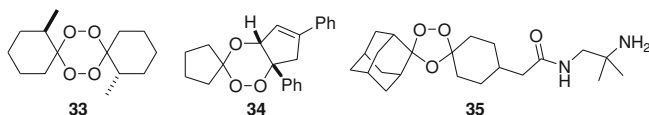


Fig. 2.5 Potent antimalarial drug candidates: tetroxane **33**, trioxane **34**, and trioxolane **35**

compounds with the equilibrium distribution being dependent on the precise structure and substitution pattern of those compounds. However, monocyclic peroxyhemiketals are of remarkable stability and the content of the ring-opened form in the equilibrium mixture is low as detected by ^{13}C NMR (no carbonyl resonances) (*vide infra*).

Peroxide-containing natural products, including several examples of 3-hydroxy-1,2-dioxolanes and related ring systems, occur widely in nature and often possess desirable pharmacological properties as pointed out in the following section [203].

2.3.1 Peroxidic Natural Products

The most prominent example among all peroxide natural products is the active antimalarial agent sesquiterpene 1,2,4-trioxane artemisinin (qinghaosu, **30**) isolated from the common shrub *Artemisia annua* (sweet wormwood) (Fig. 2.4) [204]. Similar antimalarial activities were found for the naturally occurring peroxides yingzhaosu A (**31**) and yingzhaosu C (**32**) containing a 1,2-dioxane core structure [205].

However, the most aggressive parasite, *Plasmodium falciparum*, is showing first resistance effects to artemisinin and its semisynthetic derivatives [206, 207]. Consequently, there is an urgent need for the development of new effective antimalarial remedies. Synthetic cyclic peroxides command increasing attention. They offer a structurally simpler, synthetically readily accessible alternative to artemisinin (**30**) and its analogues. Therefore, much effort is devoted to the development of new strategies for the synthesis of novel cyclic peroxidic compounds of diverse structures to identify a promising new lead in search of efficient antimalarials [208].

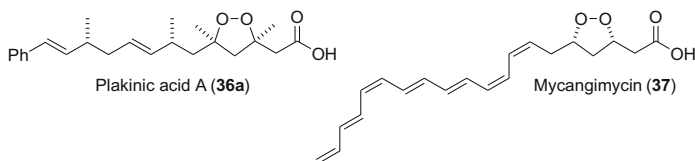
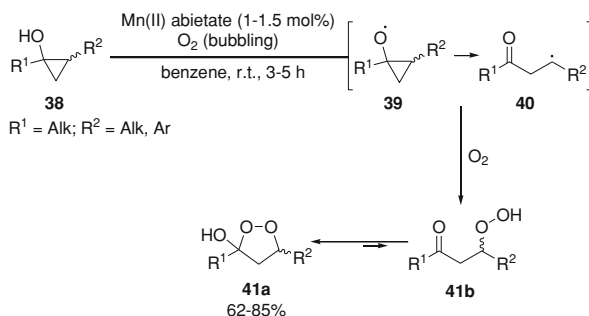


Fig. 2.6 Naturally occurring plakinic acid A (**36a**) and mycangimycin (**37**)

Scheme 2.34 Aerobic oxidation of cyclopropanols **38** to cyclic peroxyhemiketals **41a** [221]



Strikingly, tetroxane **33**, trioxane **34**, or trioxolane **35** show artemisinin-like antimalarial activity although their carbocyclic skeletons bear no resemblance to that of artemisinin (Fig. 2.5) [208, 209].

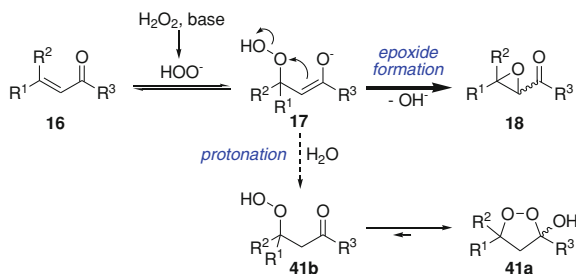
Accordingly, it is not necessary to simulate the artemisinin framework to secure superior antimalarial potency. The indispensable feature for antimalarial efficacy appears to be the peroxide unit [210].

Naturally occurring five-membered cyclic peroxides containing a 1,2-dioxolane unit such as plakinic acid A **36a** (a member of the plakinic acid natural products family characterized by a common 1,2-dioxolane-3-acetic acid “head” and different aliphatic “tails”) [211], or mycangimycin **37**, but also synthetic 1,2-dioxolane-based analogues display anticancer, antifungal, and antiplasmodial activity (Fig. 2.6) [212–214].

2.3.2 General Methods for the Synthesis of 3-Hydroxy-1,2-dioxolanes

The methods to introduce a peroxide functionality into organic compounds are limited. In the synthesis of most peroxides, irrespective of their structural complexity, the peroxide moiety is pre-formed and introduced as either (a) molecular oxygen (through a reaction with singlet oxygen or radical trapping with triplet oxygen), (b) by nucleophilic addition of hydrogen or alkyl peroxides, or (c) by reaction with ozone [215].

Scheme 2.35 Competing reaction pathways under Weitz–Scheffer reaction conditions: epoxide formation versus protonation of β -peroxyenolate intermediate **17**. (Base = *i.a.* NaOH, LiOH, *t*-BuNH₂)



Syntheses of 3-hydroxy-1,2-dioxolanes (cf. Scheme 2.33) have been achieved by various methods [216, 217]. Currently available methodologies mainly rely on the reaction of hydrogen peroxide or singlet oxygen with α,β -unsaturated carbonyl compounds or exploit the aerobic oxidation of cyclopropanols. These methods will be briefly introduced in the following sections. A direct enantioselective approach to 3-hydroxy-1,2-dioxolanes from simple, readily available starting materials had not been described prior to this work.

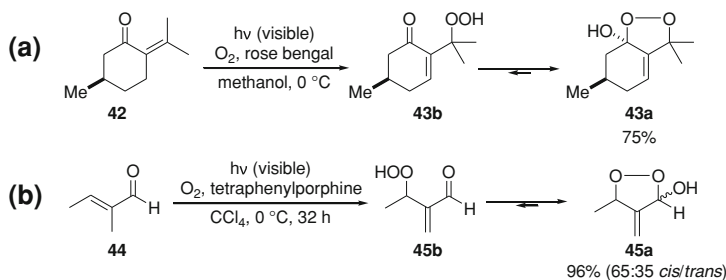
2.3.2.1 Aerobic Oxidation of Cyclopropanol Derivatives

Cyclopropanols undergo ring-opening under metal-catalyzed aerobic oxidation; when subjected to single-electron oxidants $\text{Fe}(\text{acac})_3$, $\text{Cu}(\text{acac})_2$, $\text{VO}(\text{acac})_2$, or $\text{Mn}(\text{II})$ abietate under an atmosphere of oxygen, they are converted to β -hydroperoxy ketones which exist in equilibrium predominantly as the cyclic peroxyhemiketals (*vide infra*, Scheme 2.34) [218–221]. Among the metal salts listed above, $\text{Mn}(\text{II})$ abietate and $\text{Mn}(\text{II})$ acetylacetonate did not only mediate the aerobic oxidation of bicyclic cyclopropanols but also of simple, readily available cyclopropanols of the general structure **38** [221]. The reaction proceeds via the successive formation of an alkoxy radical **39** and a β -carbonyl radical **40**. The oxidation of cyclopropanol derivatives provides expedient access to cyclic peroxyhemiketals **41a**; yet, this transformation holds little promise for the development of an asymmetric version since it proceeds through a radical pathway involving the ablation of preexisting stereocenters.

2.3.2.2 Nucleophilic Addition of Peroxides to α,β -Unsaturated Ketones

Nucleophilic conjugate addition of alkaline hydrogen peroxide to α,β -unsaturated ketones **16** generates β -peroxyenolate intermediates **17** which undergo ring closure to form α,β -epoxyketones **18** (cf. Scheme 2.16). Alternatively, intermediates **17** can be intercepted by protonation to afford cyclic peroxyhemiketals **41a** (Scheme 2.35).

Although β -peroxyenolates **17** show an overwhelming preference for epoxide formation, cyclic peroxyhemiketals of type **41a** have occasionally been observed as by-products of Weitz–Scheffer-type epoxidations of α,β -unsaturated ketones **16**.



Scheme 2.36 Photooxygenation of α,β -unsaturated carbonyl compounds with singlet oxygen [228, 229]

Their formation was first noticed in 1950 by Nazarov and Akhrem who studied the epoxidation of mesityl oxide [222]. They were the first ones to separate, purify, and characterize a slightly higher boiling by-product, before in 1958, Payne unambiguously elucidated its structure as 3-hydroxy-3,5,5-trimethyl-1,2-dioxolane (**41a** with $\text{R}^1 = \text{R}^2 = \text{R}^3 = \text{Me}$) [113].

3-Hydroxy-1,2-dioxolanes are formed in varying amounts along with the corresponding epoxides depending on the enone structure and the precise reaction conditions [222–226]. Although this method provides in most cases low yields (<20%) of 3-hydroxy-1,2-dioxolanes, it is highly valuable and still used on a preparative scale due to the limited number of operationally simple alternative approaches to this substrate class [227]. Extension of this approach to an asymmetric route to 3-hydroxy-1,2-dioxolanes seems feasible since it has previously been demonstrated in the context of asymmetric Weitz–Scheffer-type epoxidations, that it is possible to render the conjugate addition of hydrogen peroxide to α,β -unsaturated carbonyl compounds enantioselective in the presence of a chiral catalyst.

2.3.2.3 Singlet Photooxygenation

Akin to the reaction with alkaline hydrogen peroxide (*vide supra*), photooxygenation with singlet oxygen ($^1\text{O}_2$) provides direct access to 3-hydroxy-1,2-dioxolanes from α,β -unsaturated carbonyl compounds in a single step. As shown in Scheme 2.36a, pulegone (**42**) readily reacts with singlet oxygen to give ene adduct **43b**, which spontaneously cyclizes to the corresponding peroxyhemiketal **43a** [228]. Analogous results were obtained with α,β -unsaturated aldehydes: tiglic aldehyde (**44**) gave peroxyhemiacetal **45** in 96% yield (Scheme 2.36b) [229]. α,β -Unsaturated carbonyl compounds with fixed *s-cis* conformation are more rapidly oxidized by singlet oxygen than conformationally flexible substrates whereas those substrates which are constrained to the *s-trans* conformation did not participate at all in the reaction.

The oxidative thermolysis of cyclic α -azo hydroperoxides developed by Baumstark et al. [230] demonstrates an alternative method for the direct synthesis of 3-hydroxy-1,2-dioxolanes.

Dussault and co-workers have disclosed stereoselective routes to 3-alkoxy-substituted-1,2-dioxolanes. Methoxymethyl (MOM)-protected 3-hydroxy-1,2-dioxolanes were obtained via regio- and diastereoselective photooxygenations of chiral, racemic (*Z*)-allylstannanes by singlet oxygen [231]. Stereospecific cyclization of hydroperoxy acetals onto chiral, enantiomerically enriched oxetanes furnished optically active 3-methoxy-1,2-dioxolanes [232], a strategy which was later exploited in the context of the synthesis of plakinic acid A (**36a**) [211].

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