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Asymmetric Organocatalytic Epoxidations: Reactions, Scope, Mechanisms, and Applications

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epoxidation · organocatalysis · reaction mechanisms · small ring systems · synthetic methods

Chiral epoxides serve as versatile building blocks in the synthesis of complex organic frameworks. The high strain imposed by the three-membered ring system makes epoxides prone to a variety of nucleophilic ring-opening reactions. Since the development of the Sharpless epoxidation, there have been many important contributions and advances in this area. With the rapid development of the field of asymmetric organocatalysis, a wide range of organocatalysts is now able to catalyze the epoxidation of broad class of unsaturated carbonyl compounds. In this Minireview, recent progress in the development of organocatalytic asymmetric epoxidation methods, the proposed mechanisms of these reactions and their applications as intermediates is reported.

1. Introduction

Catalytic asymmetric epoxidation is a powerful transformation in organic synthesis because it leads to the generation of optically active epoxides, which are common motifs in biologically active compounds, as well as important biosynthetic intermediates.[1] The epoxide functionality, is for example, featured in the natural products ephothilones A and B, which were isolated from the myxobacterium *Sorangium cellulosum*.[2] These compounds have demonstrated antitumor properties and are currently undergoing clinical trials for cancer treatments.

From the perspective of a synthetic chemist, chiral epoxides are useful and highly versatile building blocks for diversity-oriented synthesis (DOS).[3] The strain of the three-membered ring system makes epoxides prone to a large variety of nucleophilic ring-opening reactions. These favorable processes can be utilized in the formation of a thermodynamically more stable acyclic structure or a larger ring system.[4]

Sharpless pioneered the field of catalytic asymmetric epoxidation with the enantioselective epoxidation of allylic alcohols using titanium tartrates as the catalysts.[5] This was followed by disclosures, from the groups of Jacobsen and Katsuki, on efficient catalytic systems which allowed the enantioselective epoxidation of isolated alkenes based on manganese/salen complexes.[6] In the decades following these discoveries, impressive progress has been made in the development of asymmetric epoxidation reactions.[7]

Asymmetric organocatalysis has recently emerged as a very general synthetic approach for both nucleophilic and electrophilic epoxidation reactions. Highly useful epoxidation protocols have been developed for differently substituted alkenes. Substrates with nearly all possible substitution patterns as well as electronic properties have been targeted. As a result, the toolbox of organocatalytic epoxidation methodologies is now available for a variety of different substrate classes. Organocatalytic epoxidation reactions have now reached a level of maturity, and as such, we felt that it was timely to provide an overview highlighting the different organocatalytic epoxidation concepts developed. In this review, we examine the different organocatalytic epoxidation methods and discuss their mechanisms and applications. It should be noted in advance that we do not intend to provide a comprehensive survey of all published work on this very dynamic area of research. The aim is instead to try to present a—hopefully—clear overview of the various catalyst types available for the asymmetric organocatalytic epoxidation

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reaction. The present review is organized into sections, each of which cover the most representative and significant contributions for each class of epoxidation catalyst.

It is notable that asymmetric organocatalytic epoxidation reactions were developed before the rebirth of organocatalysis in 2000. Some of the organocatalytic asymmetric epoxidation reactions were developed in parallel with the metal-catalyzed asymmetric epoxidation reaction and as such, metal- and organocatalyzed asymmetric epoxidation reactions have walked hand in hand for over 30 years.

2. Enantioselective Epoxidation by Peptide Catalysts

In recent decades, peptides have become attractive catalysts for asymmetric transformations. Their catalytic activity has been successfully demonstrated in oxidation, acylation, and C–C bond-forming reactions.[8] One of the earliest and most thoroughly examined polypeptide-catalyzed reactions is the Juliá–Colonná epoxidation.[9] Since its discovery in 1980, great efforts have been devoted to optimizing the reaction conditions,[10] enhancing the scope,[11] and rationalizing and understanding the mechanism.[12] Recently, new well-designed studies were reported and describe the use of small peptide catalysts to enable highly asymmetric, electrophilic epoxidation of alkenes.[13]

The epoxidation of electron-deficient alkenes, for example, the chalcones, catalyzed by polypeptides, such as poly-L-alanine or poly-L-leucine, is known as the Juliá–Colonná epoxidation.[9a] Several excellent reviews specifically highlight this reaction and its mechanism.[9c–f] Herein, we summarize the main discoveries of this epoxidation reaction leading to improved procedures and creating a context for more recent epoxidation strategies.

2.1. Epoxidation of Electron-Deficient α,β-Unsaturated Ketones

The first successful report of a peptide-catalyzed epoxidation reaction employed a triphasic system consisting of a poly-L-peptide, an organic solvent, and an aqueous layer containing H_2O_2 and NaOH (Scheme 1).[9a] High product yields and enantioselectivities were achieved with this procedure, but the substrate scope was limited and the reaction times were quite long (usually 48 h; Conditions A). Nearly two decades later, an improved protocol was published and involved an insoluble catalyst in a non-aqueous solvent, in combination with a urea/H_2O_2 (UHP) complex as the oxidant and DBU as the base. This improved protocol reduced the reaction times to less than 1 h (Conditions B).[14] The drawbacks of an uncatalyzed background epoxidation were overcome by employing sodium percarbonate as both a base and an oxidant (Conditions C).[15] Finally, the adsorption of the polypeptide onto silica provided a readily recyclable catalyst, which showed high activity and enhanced stereoselectivity (Conditions D).[16]


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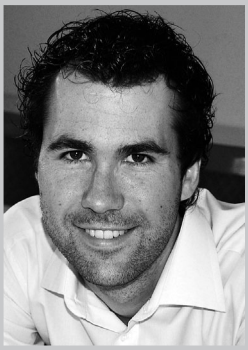
Julian Stiller obtained his Ph.D. in 2011 from TU Dortmund University, Germany with Prof. M. Christmann. Currently he is a postdoctoral fellow at the Center for Catalysis, Aarhus University, Denmark, where he is investigating new applications of asymmetric organocatalysis under the supervision of Prof. K. A. Jørgensen.


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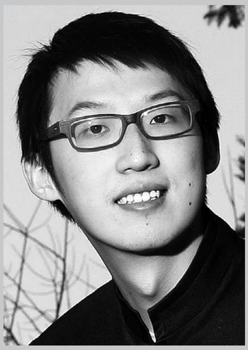
Hao Jiang received his Ph.D. in October 2011 under the supervision of Prof. K. A. Jørgensen. Upon graduation, he continued to work at the Center for Catalysis, Aarhus University as a postdoctoral researcher. His current research involves the development of new useful methodologies in asymmetric catalysis and organic synthesis.


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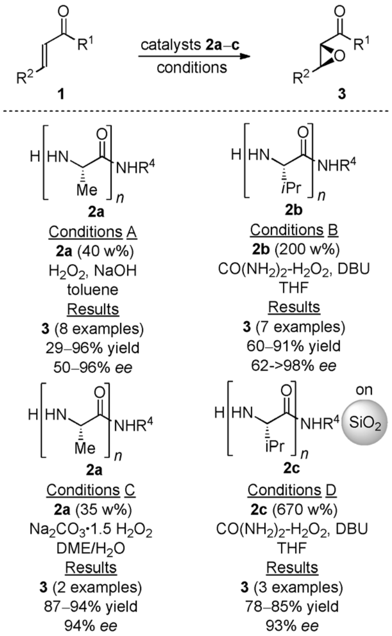
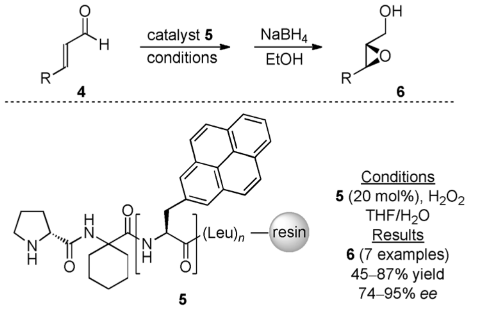


Scheme 1. Enantioselective epoxidation of α,β-unsaturated ketones employing peptide catalysts. DBU = 1,8-diazabicyclo[5-4-0]undec-7-ene, DME = dimethoxyethane.

2.2. Epoxidation of Electron-Deficient α,β-Unsaturated Aldehydes

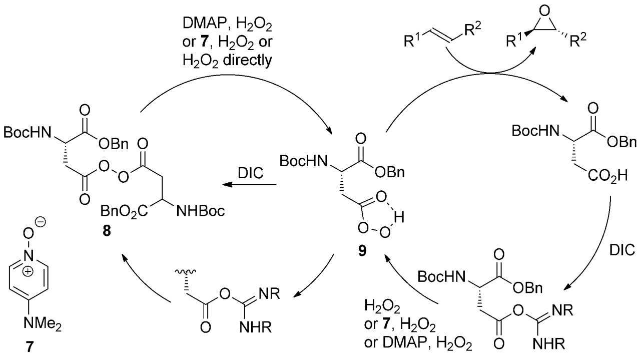
The first highly enantioselective epoxidation of α,β-unsaturated aldehydes (**4**) using resin-supported peptides was realized in 2011 (Scheme 2).[17] It was found that catalyst **5** works efficiently in an aqueous solvent mixture using H_2O_2 as the oxidant. The introduction of three bulky and hydrophobic amino acid units Ala(1-Pyn) to the peptide catalyst was crucial for both reaction rate and stereoselectivity. Interestingly, the addition of L-Pro to the terminal D-Pro led to a complete reversal of the enantioselectivity, while maintaining identical reaction rate and diastereoselectivity.



Scheme 2. Enantioselective epoxidation of α,β-unsaturated aldehydes applying a resin-supported peptide catalyst.

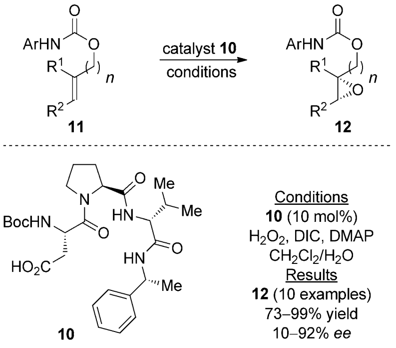
2.3. Electrophilic Epoxidation of Alkenes and Mechanistic Considerations

The epoxidation protocols described in the previous sections were based on a nucleophilic attack of the oxidant onto the alkene. The first highly enantioselective electrophilic epoxidation using a peptide catalyst was reported in 2007.[13] Complementary to the described Juliá–Colonná-based methods for electron-deficient alkenes, a catalytically active peracid is generated in situ by using H_2O_2 or UHP as the terminal oxidant. In the initial studies, a catalyst system based on the readily available amino acid aspartate was optimized to achieve maximum carboxylic acid–peracid interconversions. With DIC activation and DMAP catalysis, the γ-carboxylic acid was transformed into the peracid **9**, which then facilitated the catalytic epoxidation (Scheme 3). Control experiments showed that fast DMAP-mediated perhydrolysis of the diacyl peroxide **8** to the peracid **9** was crucial for good overall reaction rate. Remarkably, 15 catalyst turnovers were achieved within 3.5 h under the optimized reaction conditions, thus affording the corresponding epoxide in 74 % yield. However, no asymmetric induction of the per-aspartate itself was detected.



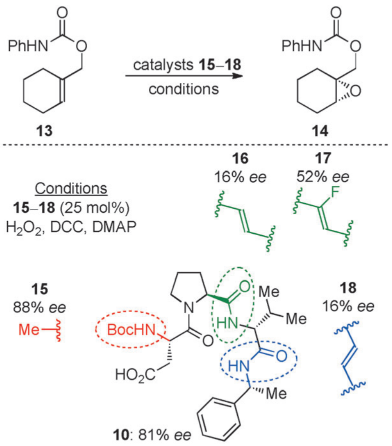
Scheme 3. Mechanism of the Asp-mediated epoxidation. Boc = *tert*-butoxycarbonyl, DMAP = 4-(*N*,*N*-dimethylamino)pyridine, DIC = *N*,*N'*-diisopropylcarbodiimide.

To design an asymmetric version of the peracid-catalyzed reaction, the catalytically active aspartate was incorporated into the chiral environment of a tripeptide, thus forming a β turn (Scheme 4).[13] The turn induced by the L-Pro-D-Val sequence in **10** is stabilized by an intramolecular hydrogen bond and provides a short distance between the catalytically active acid group and the chiral C terminus. Several alkenes bearing a carbamate moiety in the allylic position were successfully epoxidized in high yields and excellent enantioselectivities.



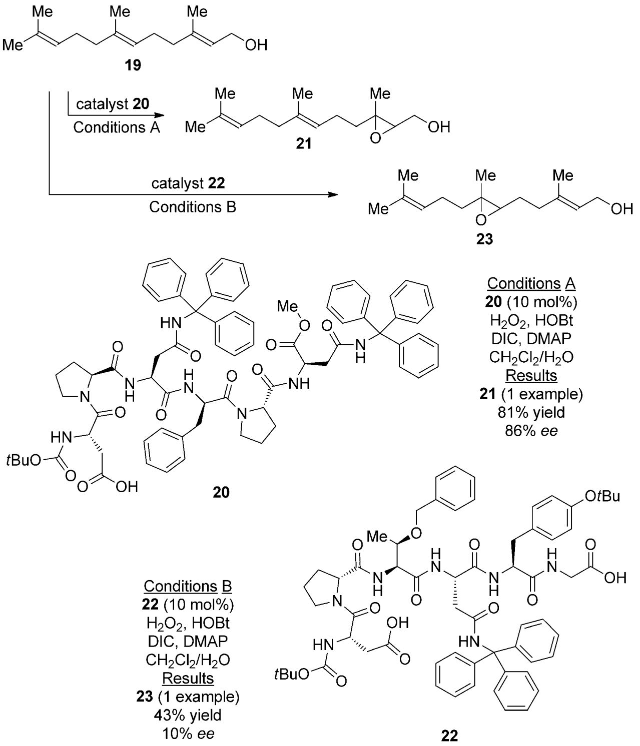
Scheme 4. Tripeptide-mediated asymmetric epoxidation.

The mechanism of the tripeptide-catalyzed asymmetric epoxidation reaction is still under investigation.[18] Hydrogen bonding between the catalyst and alkene is thought to be crucial for a high degree of stereoinduction since substrates lacking obvious hydrogen-bonding capabilities showed nearly no enantioselectivity. To discover the origin of the stereoselectivity induced by the catalyst **10**, a series of modified tripeptides were employed in the reaction (Scheme 5). These experiments systematically examined the role of the various functional groups in the catalysts. It was found that the Boc-protected amine function could be replaced by a simple Me group without affecting the enantioselectivity (compare **10** and **15**). However, lower reaction rates were observed in this case (26% versus 63% after 12 h). When the L-Pro-D-Val amide moiety was exchanged for an isosteric alkene group not capable of hydrogen bonding with the substrate, the enantioselectivity dropped dramatically (compare **10** and **16**). The moderate enantioselectivity induced by **17** could be related to the intermediate effectiveness of the fluoroalkene forming hydrogen bonds to the substrate as compared with the initial peptide **10**. Replacement of the C-terminal amide group by an alkene led to poor selectivity (compare **10** and **18**). This amide is essential for an effective induction of enantioselectivity as the intramolecular hydrogen bond stabilizes the β-turn.



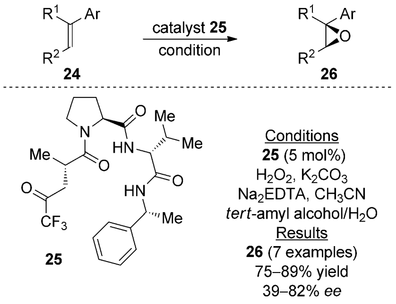
Scheme 5. Modified tripeptides for asymmetric epoxidation. DCC = *N*,*N*′-dicyclohexylcarbodiimide.

To enable the fast identification of potent peptide epoxidation catalysts, a high-throughput screening, based on the one-bead-one-compound library approach, was developed.[19] Later, this procedure was successfully used to tackle the challenging problem of regio- and enantioselective epoxidation of polyenes, such as the sesquiterpene farnesol and related compounds (Scheme 6).[20] Nearly perfect regioselectivity toward the double bond adjacent to the allylic OH group and a high enantioselectivity of 87% *ee* was obtained using the catalyst **20**. Interestingly, catalyst **22** showed a high selectivity for the central double bond. Although the epoxide product was obtained with only 10% *ee*, this is the first example of a peptide catalyst showing selectivity for an internal alkene.



Scheme 6. Site- and enantioselective peptide-catalyzed epoxidation of polyenes. HOBt = 1-hydroxybenzotriazole.

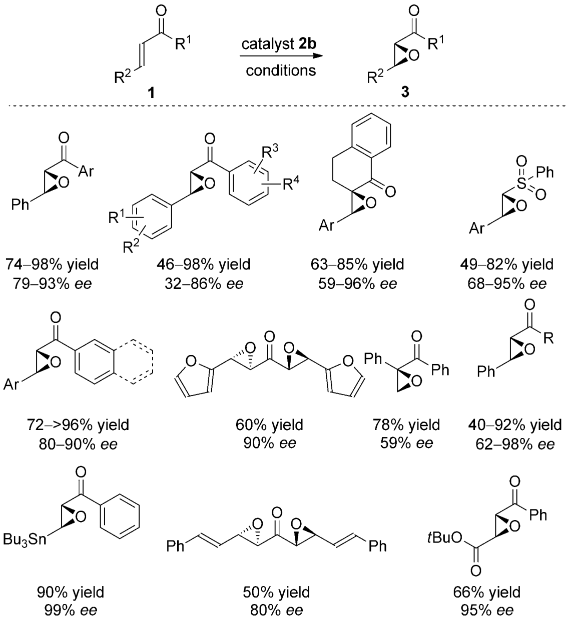
In all the peptide-catalyzed epoxidation reactions described above, an in situ generated per-aspartate moiety was responsible for the catalytic activity. A new type of peptide-based epoxidation catalyst (**25**), which used a transiently generated dioxirane as the catalytically active species, was reported in 2012.[21] Remarkably, high enantioselectivities were achieved for aryl-substituted alkenes lacking a carbamate moiety, substrates which gave poor selectivities in previous reports (Scheme 7).



Scheme 7. Tripeptide mediated asymmetric epoxidation. EDTA = ethylenediamine tetraacetate.

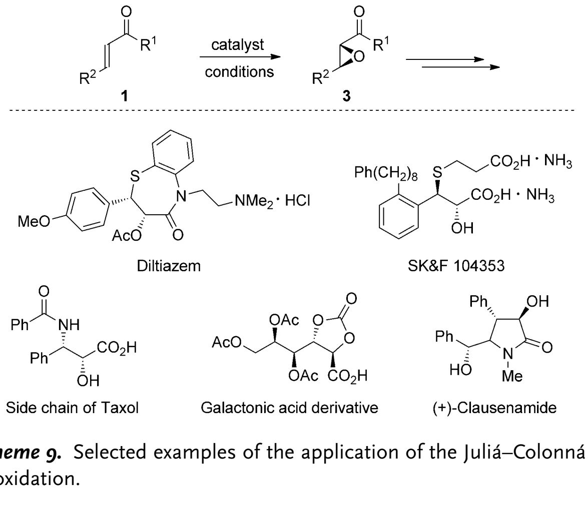
2.4. Applications

Organocatalytic enantioselective epoxidation reactions based on the application of peptide catalysts have found several applications. Selected examples of structural motifs and representative compounds demonstrate the variety of enantioenriched epoxides furnished by the peptide catalyst **2b** (Scheme 8).[22]



Scheme 8. Selected examples of epoxides obtained under peptide catalysis.

Modified Juliá–Colonná conditions have been employed in the target-orientated synthesis of several key intermediates and biologically active compounds (Scheme 9).[11,23] In the selected examples, the stereochemical information stored in the epoxide was used for further asymmetric modifications which usually proceed with a high degree of stereocontrol. The readily scalable epoxidation procedure enabled the synthesis of the epoxide intermediates for the selective leukotriene antagonist SK&F 104353 on multiple 100 gram scale reactions with greater than 99.5% *ee*.[24] The key step in this synthesis was the regioselective opening (35:1 ratio) of the epoxy intermediate with methyl 3-mercaptopropionate.

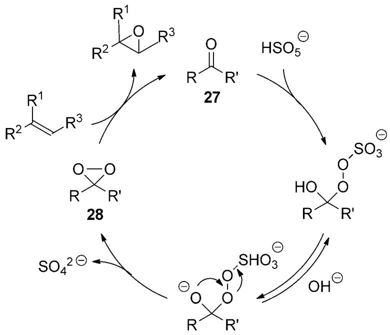


Scheme 9. Selected examples of the application of the Juliá–Colonná epoxidation.

The synthesis of the Taxol side chain and the potent blood pressure lowering agent Diltiazem exemplify the potential of an improved biphasic procedure for the Juliá–Colonná epoxidation.[14b] In both cases, the enantioselective epoxidation/ring-opening sequence is the key step in the synthesis, thus facilitating straightforward access to the desired compound.

3. Enantioselective Epoxidation by Chiral Ketone Catalysts

Asymmetric epoxidation with chiral-ketone-derived catalysts has proven to be one of the most valuable methods for accessing structurally diverse chiral epoxides. The efficiency and ease of this epoxidation method makes it beneficial in synthetic organic chemistry. This enantioselective epoxidation is mediated by dioxiranes, which are derived in situ from a chiral ketone and an oxidant. Oxone (potassium peroxomonosulfate) is the most commonly used oxidant.[25] This strategy has proven to be highly efficient for a broad range of unactivated alkene substrates under mild reaction conditions. The general mechanism of the dioxirane-mediated epoxidation is depicted in Scheme 10. Oxone facilitates the O transfer from the ketone **27** to the alkene via the dioxirane intermediate **28**. The ketone functionality is regenerated upon epoxidation, thus allowing the chiral catalyst to enter another epoxidation cycle.

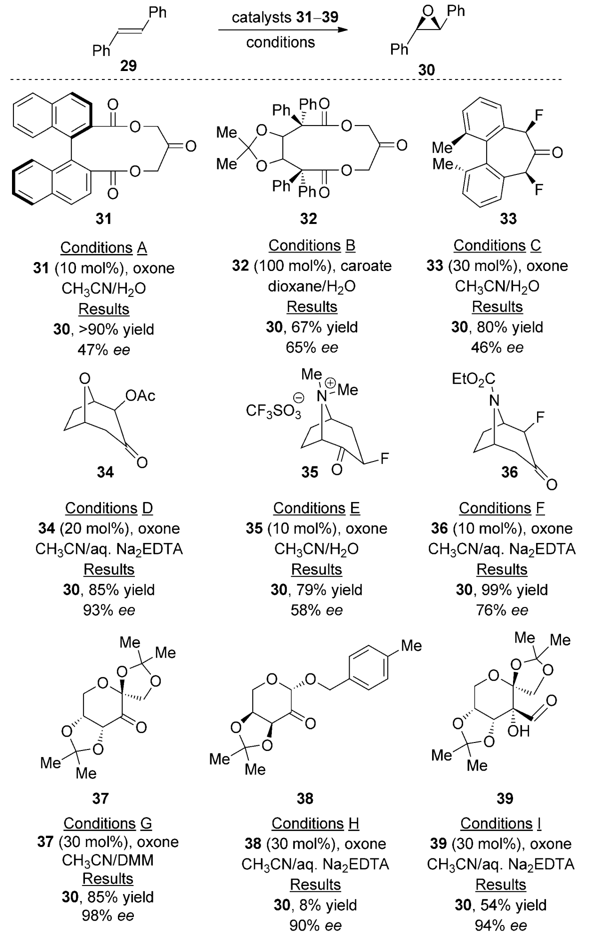


Scheme 10. General mechanism for ketone-catalyzed epoxidation with oxone.

3.1. Unactivated Alkene Epoxidation Protocols and Mechanistic Considerations

Chiral ketone catalysts for the asymmetric epoxidation reaction can be largely classified into three types (Scheme 11): 1) C_2-symmetric catalysts;[26] 2) bicyclic catalysts,[27] and 3) carbohydrate-derived catalysts.[28] A comprehensive review on the developments of the illustrated catalyst types and their role in enantioselective epoxidation reactions until 2007 has been reported.[29] Since 2007, only carbohydrate-derived ketone catalysts have been explored within the chiral ketone class of epoxidation organocatalysts.

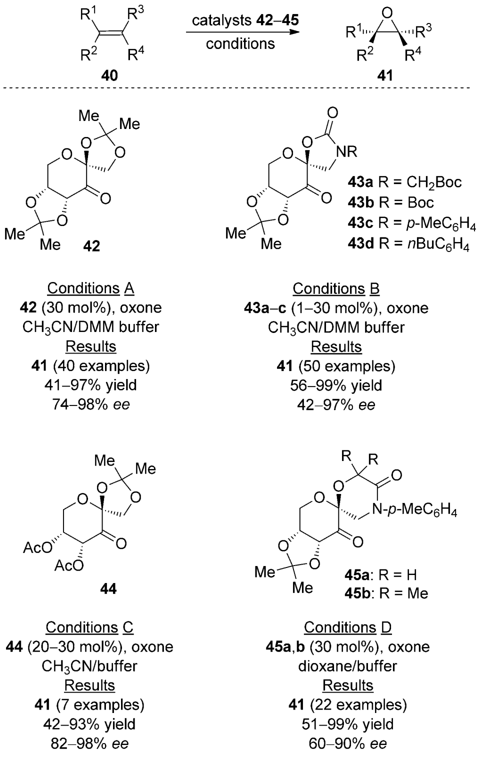
Shi et al. pioneered the use of the sugar-based ketone catalysts, which rank as the most successful for dioxirane



Scheme 11. Selected early examples of chiral ketone catalysts for enantioselective epoxidation reactions on *trans*-stilbene **29**. DMM = dimethoxymethane.

asymmetric epoxidations, thus encompassing the widest variety of substrates with excellent results.[7a,26,29,30]

The fructose-derived catalyst **42** (Scheme 12) was one of the early highly enantioselective epoxidation catalysts.[31] Its design was based on balancing the steric and electronic effects for both the reactivity and selectivity required for the epoxidation reaction: 1) the chiral substituents were placed close to the reacting carbonyl functionality, 2) the quaternary center α to the carbonyl group was used to reduce the possible epimerization of the stereocenters, 3) the approach of the alkene relative to the reacting dioxirane was potentially directed by sterically hindering one face by introduction of a C_2-symmetric element, and 4) the carbonyl was activated by adjacent electron-withdrawing substituents.[32] Although **42** furnished high enantioselectivity, high catalyst loading was required for good conversion because of the rapid decomposition of the ketone. This decomposition was attributed to a competing Baeyer–Villiger oxidation occurring during the reaction when oxone was added to the ketone. A higher pH value was required to suppress this competing reaction. In general, dioxirane epoxidation reactions are carried out at pH 7–8, since oxone tends to decompose at higher pH levels. However, it was demonstrated that an increase in pH to 10.5 allowed lower loading of the catalyst (20–30 mol %) and oxone (1.5 equiv) while providing higher conversions.[33] This result indicated that at a higher pH, the ketone was sufficiently reactive to compete with oxone decomposition as well as to enhance the nucleophilicity of oxone towards the ketone catalysts. Based on this optimization, catalyst **42** has been reported to perform well on a wide range of substrates for epoxidation reactions, including *trans*-di- and trisubstituted alkenes,[34] 2,2-disubstituted vinyl silanes,[35] hydroxyalkenes,[36] conjugated dienes[37] and enynes,[38] as well as silyl enol ethers and esters[39] with excellent results.



Scheme 12. Enantioselective epoxidation with various alkenes and the Shi-derived catalysts.

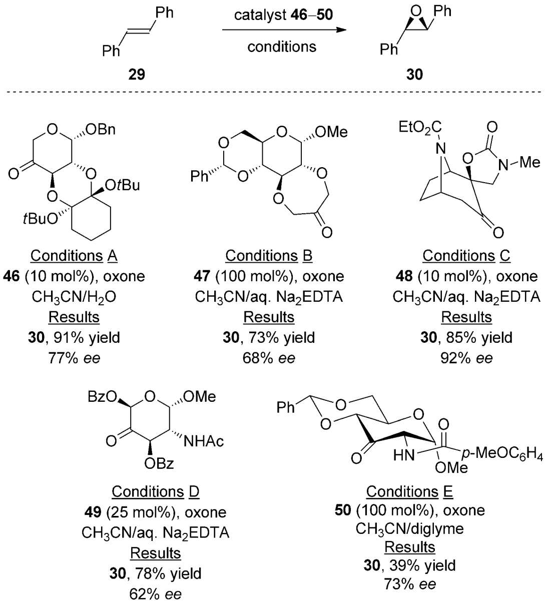
In attempt to further suppress the decomposition process (by the Baeyer–Villiger oxidation), decrease the catalyst loadings, and expand the substrate scope, a series of catalysts **43** (Scheme 12), in which the spirofused ring was replaced with an electron-withdrawing oxazolidinone or diacetate group, were developed. The catalyst **43a** was found to provide comparable results to those of **42** while requiring only 1–5 mol % catalyst loading.[40] The ketone catalysts **43b**,**c** proved to be efficient for alkenes which had not been reactive when **42** was employed. Among these substrate classes were conjugated aromatic *cis* alkenes, conjugated *cis* dienes and enynes, as well as styrenes, and certain trisubstituted and tetrasubstituted alkenes.[41] The enantioselectivity afforded by application of the ketone catalysts **43a–c** was credited to an attractive interaction between the R_π group of the alkene and the spiro-oxazolidinone of the ketone catalyst.

More recently, the scope of the catalysts **43a** and **43d** was extended to nonconjugated *cis* alkenes (Scheme 12). These studies revealed that the relative hydrophobicity of the alkene substituents and/or allylic oxygen functionality possibly allow stereodifferentiation of the prochiral faces of the substrate.[42] In addition, **42** and **43** have also been efficient for the epoxidation of fluoroalkenes.[43] For some substrates, the fluorine atom acted as a directing group through electronic interactions with the catalyst, although in other cases it was detrimental to the selectivity of the reaction. The ketone **44** proved to be more effective than **42** and **43** for electron-deficient alkenes such as α,β-unsaturated esters.[44]

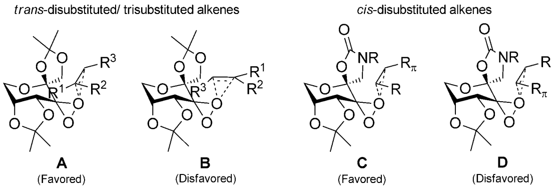
Continued efforts were devoted to combining the steric and electronic features of known chiral ketone catalysts. To broaden the substrate scope further, the lactam ketones **45**, having a morpholine group, were introduced (Scheme 12). Initially, the ketone catalyst **45a** was reported to facilitate the epoxidation of the challenging 1,1-disubstituted terminal alkenes and some *cis* alkenes.[45] Thereafter, the α,α-dimethylmorpholinone-containing chiral ketone catalyst **45b**, which combines features of **42** and **43**, furnished increased enantioselectivity (compared to that of **45a**) for the epoxidation of *trans*- and trisubstitiuted alkenes. This increased selectivity was rationalized by a possible hindering of competing transition state(s) as a result of steric repulsion brought about by the additional dimethyl groups on the morpholine system and the alkene substituent.[46] However, **45a** gives higher enantioselectivity than **45b** in the epoxidation of 1,1-disubstituted terminal alkenes. In this case, the attraction between the aromatic group and the morpholine moiety is hindered by the additional dimethyl substituents, thus resulting in lower enantioselectivity or in some cases, yielding the opposite enantiomer. The use of H_2O_2 as the primary oxidant in combination with CH_3CN as the solvent was also found to be comparable to using oxone with the ketone **42**.[7a,34b,47]

Now commercially available, the Shi catalysts have made a significant impact on organocatalyzed asymmetric epoxidation reactions. Other chiral ketone catalysts that have been developed for epoxidation reactions are depicted in Scheme 13. While several of these catalysts have demonstrated their efficiency in the enantioselective epoxidation of *trans*-stilbene (**29**), none of these new organocatalysts have yet achieved the generality of the Shi-type catalysts.[48]

The rationalization for the enantioselectivity of these reactions is based on a range of synthetic observations and computational studies.[29] The dioxirane-catalyzed epoxidation is predicted to proceed preferentially through a spiro transition state rather than a planar transition state (Scheme 14).[49] Studies on the mechanism of the epoxidation of alkenes catalyzed by **42** have revealed that the six-membered ring in **42** exists in the chair conformation with the alkene approaching from the least-hindered equatorial oxygen atom of the dioxirane.[32] The *trans*-disubstituted or trisubstituted alkene substrates favor the spiro-transition-state structure **A** as they position the substrate to avoid steric interactions with the dioxolane ring of **42**. The planar-transition-state structure **B**, which provides the enantiomer of the product, is believed to be the major competing pathway. As a result of the competition between **A** and **B**, the steric and electronic nature of the substituents on the alkene can greatly influence the enantioselection of the reaction. The ability of conjugated π systems (R = aryl, alkene, or alkyne) to increase the enantioselectivity is thought to result from a lowering of the energy of the π* orbital of the alkene and thus provide favorable secondary orbital interactions. Bulky R^3 substituents and smaller R^1 substituents are provide higher enantioselectivities.



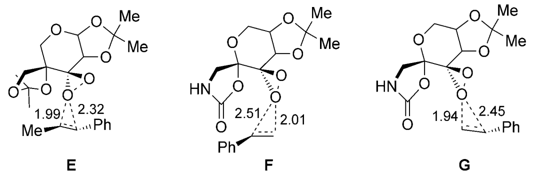
Scheme 13. Most recent chiral ketone organocatalysts for enantioselective epoxidation of *trans*-stilbene **29**.



Scheme 14. Proposed conformations of transition-state structures for dioxirane epoxidation.

In the case of epoxidations *cis*-disubstituted and terminal alkenes, catalyzed by **43b**, the enantioselectivity is thought to originate from the preference for a π-conjugating substituent (R_π) to be oriented in close proximity to the oxazolidinone ring (transition-state structure **C**), compared to having the π-conjugating substituent away from the oxazolidinone ring (transition-state structure **D**; Scheme 14).[50]

Many research groups have undertaken theoretical investigations of the dioxirane epoxidation reaction by focusing on simple model reactions.[51] In perhaps the most thorough mechanistic study to date, multiple transition-state conformations were examined for the epoxidation between the dioxirane derived from the chiral ketone catalyst **42** and *trans*-β-methylstyrene.[52] Using a combination of kinetic isotope effect calculations and experimentally observed results it was found that the transition-state **E** (Scheme 15) is the most



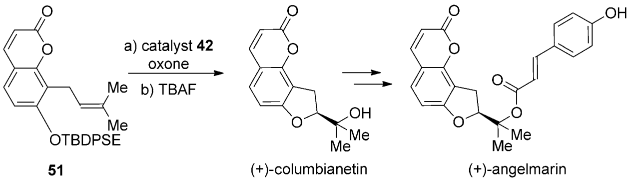
Scheme 15. Transition-state structures for the alkene epoxidation with the catalysts **42** and **43** (bond lengths in Å).

representative conformation. This transition state was not only the most energetically favored, but also showed the most natural asynchronicity when compared to a simple, unhindered dioxirane model with *trans*-β-methylstyrene. The epoxidation of *trans*-disubstituted or trisubstituted alkenes with **42** proceeds via a spiro transition state in which the equatorial oxygen atom is transferred to the product and the six-membered ring of the ketone catalyst exists in the chair conformation.

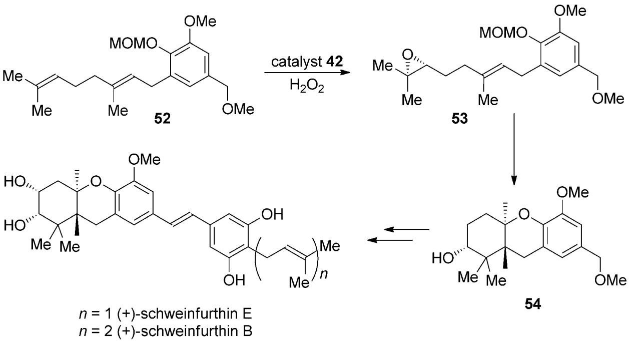
In the same report, the reaction between the dioxirane derived from the chiral ketone catalyst **43** and styrene was also examined.[52] In these studies, the transition-state structure **F**, which leads to the observed major product, was found to be lowest in energy (Scheme 15). In this transition-state structure, the phenyl ring of the styrene is situated on the same side as the oxazolidinone moiety. Again, an asynchronous reaction favoring a longer C–O bond formation adjacent to the phenyl minimizes the phenyl–oxazolidinone interactions. This arrangement is in contrast to increased (repulsive) interactions when a phenyl substituent is on the opposite side of the oxazolidinone ring (transition-state structure **G**).

3.2. Synthetic Applications

As a result of the successful application of the Shi catalysts to access a variety of enantioenriched epoxides, these organocatalysts have been used in key steps for the syntheses of complex optically active molecules. Some recent, selected examples of these syntheses are highlighted (Scheme 16). Recently, **42** was employed in the first total synthesis of (+)-angelmarin, a potent antiausteritic natural product which displayed 100% preferential cytotoxicity against a pancreatic cancer PANC-1 cell line.[53] Epoxidation of the starting material **51**, followed by treatment of the crude reaction mixture with TBAF in THF, provided (+)-columbianetin, which underwent further reactions to give (+)-angelmarin.



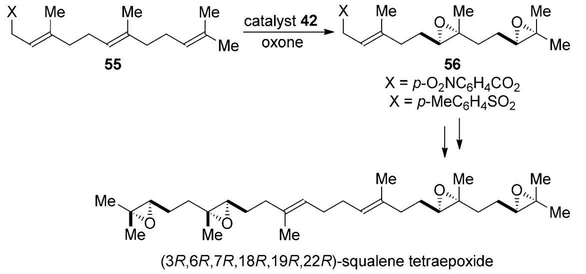
Scheme 16. Synthesis of (+)-angelmarin. TBDPSE = 2-(*tert*-butyldiphenylsilyl)ethyl, TBAF = tetra-*n*-butylammonium fluoride.



Scheme 17. Synthesis of schweinfurthin.

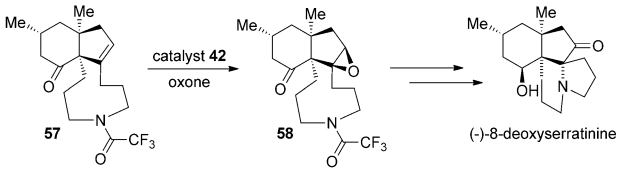
An organocatalytic epoxidation employing **42** was also used for the first total synthesis of schweinfurthin, a potent and differentially active cytotoxic agent based on the NCI 60-cell line assay (Scheme 17).[54] The initial epoxidation reaction proceeded with 91% *ee* and 85% yield, and was followed by a $BF_3{\cdot}OEt_2$-initiated cascade cyclization to furnish the final product.

The organocatalyst **42** was also employed in the regio- and enantioselective synthesis of squalene tetraepoxide, which has been proposed to be a biogenetic precursor to several oxacyclic biologically important triterpenoid derivatives (Scheme 18).[55] The synthetic strategy took advantage of the fact that the epoxidation of the alkene nearest to the heteroatom substituent would be disfavored because of the presence of electron-withdrawing substituents. This feature allowed the anionic coupling of the two farnesol-derived diepoxides to occur, thus resulting in the construction of the 30-carbon chain squalene tetraepoxide in 64% yield.



Scheme 18. Synthesis of squalene tetraepoxide.

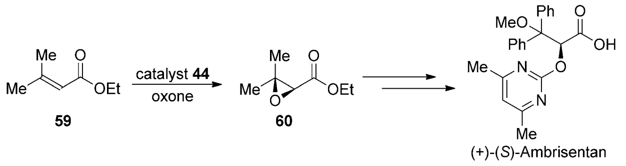
The enantioselective organocatalyzed epoxidation with **42** has also been used as a key step in the first total synthesis of (−)-8-deoxyserratinine (Scheme 19).[56] This alkaloid belongs



Scheme 19. Synthesis of (−)-8-deoxyserratinine.

to the Lycopodium family well known for its unique tetracyclic architecture and potential biological activities. A fully diastereoselective epoxidation of **57** with **42** provided the epoxide **58** in 96 % yield. The epoxide intermediate underwent additional steps to give the desired alkaloid from which an X-ray structure was obtained, thus unambiguously confirming the structure.

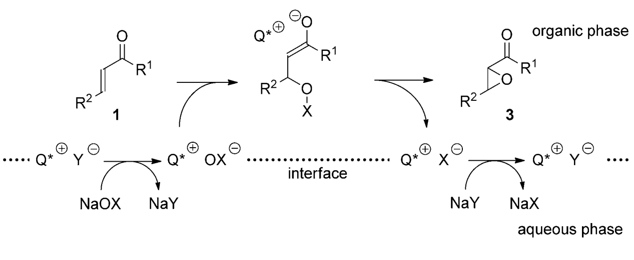
More recently, the synthesis of (+)-ambrisentan, used for the treatment of pulmonary arterial hypertension, was accomplished in only four steps with 53 % overall yield and greater than 99 % *ee* on a greater than 100 gram scale (Scheme 20).[57] The chiral epoxide intermediate was prepared by an enantioselective epoxidation with the ketone catalyst **44**.



Scheme 20. Synthesis of (+)-ambrisentan.

4. Enantioselective Epoxidations by Chiral Phase-Transfer Catalysts

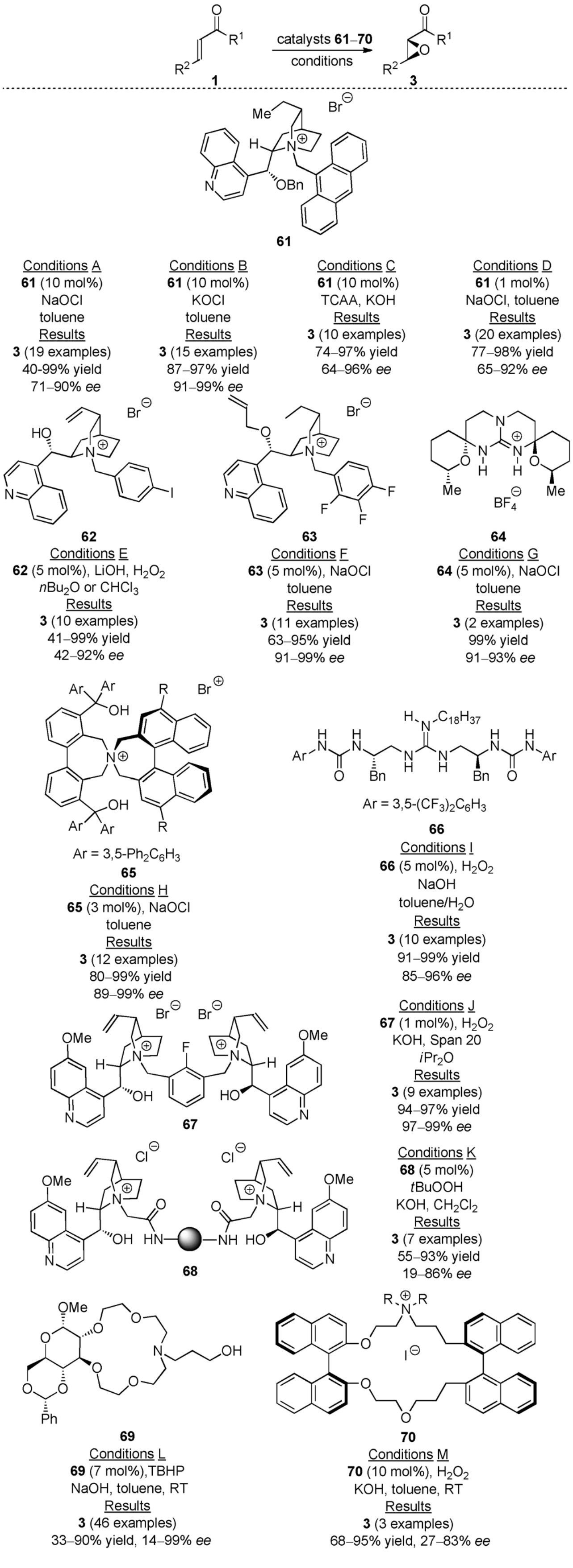
Asymmetric phase-transfer catalysis (PTC) has successfully been applied to a wide range of bond-forming reactions, thus giving access to a variety of enantioenriched organic compounds. One reaction that has had great success with this methodology is the asymmetric epoxidation of electron-deficient alkenes, specifically α,β-unsaturated ketones.[58] This reaction is thought to proceed through a biphasic Weitz–Scheffer-type mechanism in which the quaternary ammonium salt serves to bring the nucleophilic epoxidizing agent across the interface and direct its approach to the alkene (Scheme 21).



Scheme 21. Asymmetric PTC epoxidation mechanism.

4.1. α,β-Unsaturated Ketone Epoxidation Protocols and Mechanistic Considerations

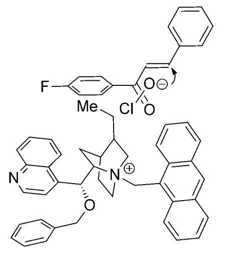
The first example of a methodology which provided good yields and enantioselectivities involved the epoxidation of chalcones using a cinchonium salt **61**.[59] In this report, it was found that the use of NaOCl as an oxidant greatly improved



Scheme 22. Enantioselective epoxidation of *trans*-α,β-unsaturated ketones using various organocatalysts based on PTC. TBHP = *tert*-butylhydrogen peroxide, TCAA = trichloroacetic anhydride.

the enantioselectivity of the reaction (Scheme 22, Conditions A).[60] It was observed that the enantioselectivity changed when H_2O_2 was replaced with NaOCl, and is indicative of two competing reaction pathways. Later studies on this system showed the rate of the reaction to be dependent upon the concentration of NaOCl and catalyst.[61] In this study it was also shown that the polarity of the solvent also influences the enantioselectivity of the reaction, with increased concentrations of EtOAc decreasing the selectivity. Additional studies on **61** showed that by employing 10 mol% of the catalyst, under similar reaction conditions, the asymmetric epoxidation of allylic alcohols can be achieved with high yields and good enantioselectivities.[62]

In 1999, it was demonstrated that the use of **61** with KOCl as the oxidant improved the yields and enantioselectivities for the epoxidation of chalcones (Scheme 22, Conditions B).[63] In this study the authors noted that the phenyl substituent on the carbonyl of **1** is necessary for high enantioselectivity. Substrates containing alkyl and other non-aromatic substituents attached to the carbonyl functionality led to products with lower enantioselectivities. They also found that the enantioselectivity decreased when the aromatic ring (R^1 in **1**) is co-planar with the carbonyl group. This decrease in enantioselectivity led the authors to suggest that the reaction proceeds through a reactive intermediate, shown in Scheme 23, in which the aromatic ring attached to the carbonyl is twisted out of the plane of the carbonyl to allow the carbonyl to be positioned near the ammonium ion of the catalyst. Assuming the hypochlorite forms a contact ion-pair with the ammonium ion, with the chlorine atom closest in proximity, this places the oxygen atom in the correct position to attack a single face of the β-carbon atom of the α,β-unsaturated ketone, thus explaining the observed selectivity.



Scheme 23. Proposed reactive intermediate for the asymmetric PTC epoxidation of chalcones using catalyst **61**.

The ability of KOCl to effectively epoxidize a range of chalcones using **61** led to the development of other methodologies which allow the in situ generation of this oxidant. The first method, involving in situ generation of KOCl, utilized trichloroisocyanuric acid and KOH (Scheme 22, Conditions C).[64] This procedure provided good yields and moderate to high enantioselectivities for a range of chalcone derivatives. In another report, a variety of oxidants were explored, however, only those that formed the hypochlorite ion were observed to provide good results. Interestingly, 15 mol% NaOCl was found to work well for both the epoxidation of α,β-unsaturated ketones and allylic alcohols, and also allows a decreased catalyst loading (Conditions D).[65]

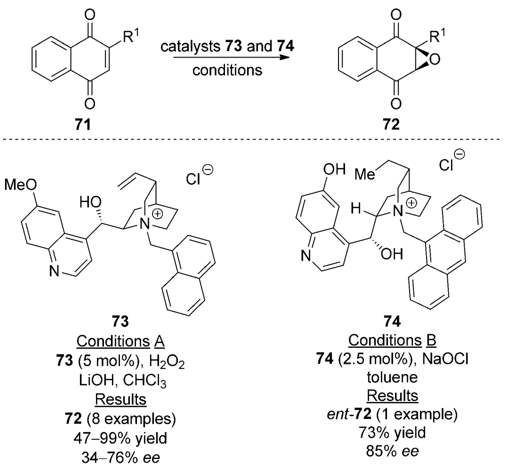
It has also been shown that quaternary salts derived from cinchonine are effective catalysts for the enantioselective epoxidation of 1,3-diarylenones. Expanding upon the original report on PTC epoxidations, which employed a cinchonine derivative and only provided low enantioselectivity, it was found that the presence of an electron-withdrawing group in the *para* position of the N-benzyl ring of the catalyst was necessary to obtain good enantioselectivities.[66] Of the electron-withdrawing groups examined, the 4-iodobenzyl derivative **62** gave the best results (Scheme 22, Conditions E).[67] Additional screening also showed that the free hydroxy group on the catalyst was necessary to achieve enantioselectivity.[66b] In another example of a cinchonine-derived catalyst containing an electron-withdrawing benzyl group, the trifluorobenzyl-cinchona catalyst **63** was found to give moderate to high yields and enantioselectivities for 1,3-diarylenones (Conditions F).[68]

Further expansion of the asymmetric epoxidation of α,β-unsaturated ketones, using PTCs, has been achieved through the development of several other ammonium salt catalysts. The C_2-symmetric, tetracyclic guanidinium salt **64** provided high enantioselectivities for two chalcones, although yields were not reported (Scheme 22, Conditions G).[69] The use of the chiral quaternary ammonium bromide **65** turned out to be effective in the epoxidation of chalcone derivatives, thus providing high yields and enantioselectivities (Conditions H).[70] The key feature of this catalyst is that it gives high enantioselectivity for the epoxidation of **1** with alkyl substituents (R^1), and also for the substrates **1** in which the carbonyl group and phenyl ring (R^1) are coplanar. The guanidine-urea bifunctional catalyst **66** was also shown to give high yields and good enantioselectivities for the epoxidation of 1,3-diarylenones (Conditions I).[71]

In addition to the monomeric catalysts described above, dimeric and polymeric catalysts have also been developed for the asymmetric epoxidation of α,β-unsaturated ketones under PTC. The dimeric catalyst **67** was found to work well with 1,3-diarylenones but again, not with alkyl-substituted substrates (Scheme 22, Conditions J).[72] Based on the crystal structure of the catalyst, the authors propose a transition-state structure in which the carbonyl interacts with one of the iminium ions, while the other iminium ion interacts with the peroxide, thus allowing attack to occur from only one face. The polymeric catalyst **68** was shown to epoxidize 1,3-diarylenones in poor to high yields and moderate enantioselectivities (Conditions K).[73]

Chiral crown ethers have also been employed in the asymmetric epoxidation of α,β-unsaturated ketones. The α-D-glucose-derived crown ether **69** has been shown to epoxidize a wide range of aryl-substituted chalcones and aliphatic analogues, thus providing moderate yields and good enantioselectivities (Scheme 22, Conditions L).[74] This catalyst was also used in the epoxidation of N-methylproline-substituted α,β-unsaturated ketones.[75] In many of these contributions an α-D-mannose-derived crown ether was also demonstrated to provide similar results. The aza-crown ether **70** (where R is a straight chain alkyl group) was found to provide high yields and similar enantioselectivties for several chalcone derivatives (Conditions M).[76]

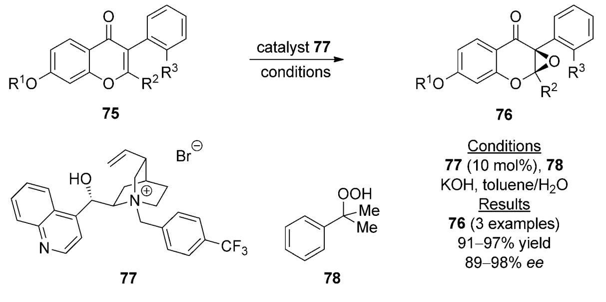
While there has been a great deal of work on the PTC epoxidation of trans-α,β-unsaturated ketones, methods for epoxidizing *cis*-α,β-unsaturated ketones remain scarce. The first example of a methodology, for the epoxidation of naphthoquinones, which provided good yields and moderate



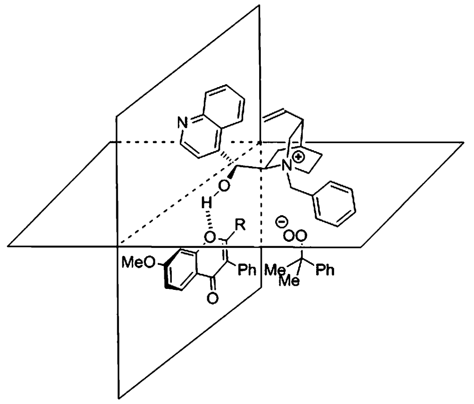
Scheme 24. Enantioselective epoxidation of *cis*-α,β-unsaturated ketones.

enantioselectivities involved the use of the catalyst **73** (Scheme 24, Conditions A).[77] In this study, it was found that bulky R^1 substituents of the naphthoquinone were needed to obtain high enantioselectivites. When 2-methyl-1,4-naphthoquinone (vitamin K_3) was employed as a substrate the enantioselectivity was limited to 34% *ee*. In an attempt to improve the enantioselectivity, a second study was performed in which modifications were made at various positions in both the quinine and quinidine catalyst.[78] Based on a screening of a number of catalysts the authors found that the best results were achieved when the catalyst **74** was employed (Conditions B).

Quaternary ammonium salts have also been shown to be effective for the asymmetric epoxidation of isoflavones. The catalyst **77** was shown to provide full conversion and high enantioselectivities in the epoxidation of the isoflavones **75** (Scheme 25).[79] Based on the selectivity trends observed with different catalysts it was proposed that the configuration of the hydroxy group of the catalyst was the major factor in determining the favored enantiomer of the epoxide product. These experimental results, as well as additional computational studies led the authors to suggest that the reaction proceeds through the aggregate shown in Scheme 26.



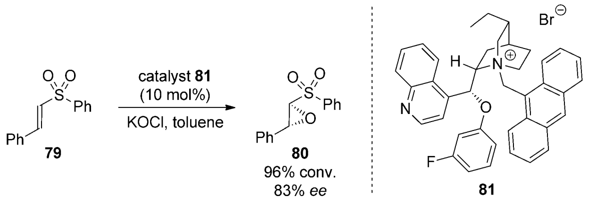
Scheme 25. Asymmetric PTC epoxidation of isoflavones.



Scheme 26. Mechanism of asymmetric PTC epoxidation of isoflavones.

4.2. Other Alkene Epoxidation Protocols and Mechanistic Considerations

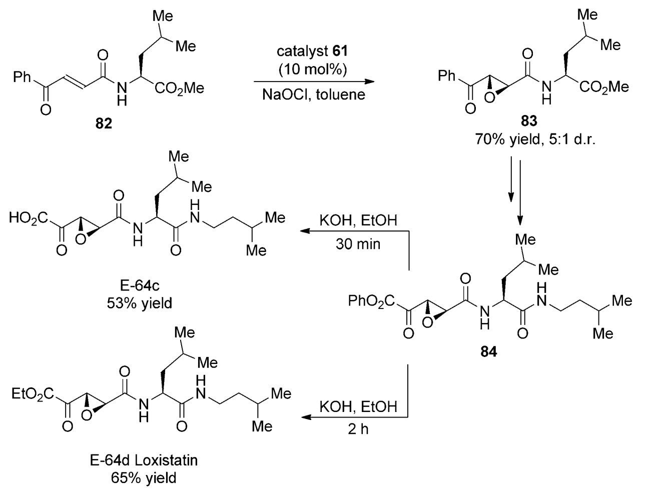
To our knowledge, there is only one example of the PTC asymmetric epoxidation of an alkene which is not in conjugation with a carbonyl functionality. The epoxidation of phenyl vinyl sulfone was carried out with the catalyst **81**, thus giving the desired product in high yield and good enantioselectivity (Scheme 27).[80] During the catalyst screening process for this reaction, it was found that the *meta*-fluorobenzyl substituent on the 9-hydroxy group of the catalyst led to better results than unsubstituted, *ortho*-substituted, disubstituted benzyl ethers, and alkyl ethers. The authors propose that the addition of a *meta*-fluoro substituent on the benzyl ether in the catalyst increases the rigidity of the catalyst by intramolecular π-stacking interactions.



Scheme 27. Asymmetric PTC epoxidation of phenyl vinyl sulfone.

4.3. Synthetic Applications

Because of the limited scope of substrates that are currently able to undergo asymmetric epoxidation using chiral quaternary ammonium PTC, this class of reaction is rarely employed in synthesis. However, the potential of these catalytic reactions has been demonstrated in the total synthesis of the epoxysuccinyl peptide E-64c and its analogue E-64d (Loxistatin; Scheme 28).[81] The authors show that epoxidation of the α,β-unsaturated ketone **82** can be achieved



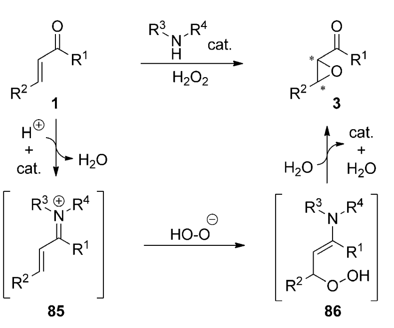
Scheme 28. Synthesis of E-64c and E-64d (Loxistatin) by organocatalytic epoxidation.

in good yield and moderate diastereoselectivity. From the epoxide **83**, the intermediate **84** can be generated in three steps and is readily transformed into the desired products.

5. Enantioselective Epoxidation by Secondary and Primary Amine Catalysts

Since its renaissance, aminocatalysis has rapidly become one of the most reliable strategies for the asymmetric functionalization of carbonyl compounds.[82] Aminocatalysts are excellent promoters for the sequential and stereoselective addition of a nucleophilic and an electrophilic species across the electron-deficient alkene in α,β-unsaturated aldehydes and ketones. This ability makes aminocatalysis a highly suitable strategy for asymmetric Weitz–Scheffer-type epoxidations[83] of this class of molecules. It is noteworthy that the substrates of the aminocatalytic epoxidation reaction and those of the previously discussed PTC reactions are, in general, complementary. The mechanism of the aminocatalytic epoxidation reaction is depicted in Scheme 29.

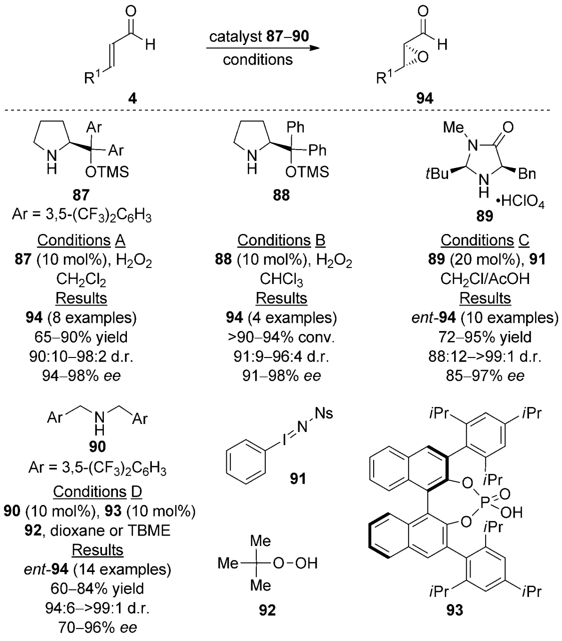
The condensation of an aminocatalyst and an α,β-unsaturated carbonyl compound generate an iminium-ion species, thus activating the Michael acceptor for conjugate addition of a peroxy nucleophile. The resulting catalyst-bound enamine species completes the formation of the oxirane ring by an S_N2-type reaction on the oxygen atom. Upon catalyst hydrolysis, enantioenriched epoxy aldehyde or ketone products are afforded and the liberated chiral amine may enter another cycle of catalysis.



Scheme 29. General mechanism of the aminocatalytic epoxidation reaction.

5.1. Epoxidation of α,β-Unsaturated Aldehydes Protocols and Mechanistic Considerations

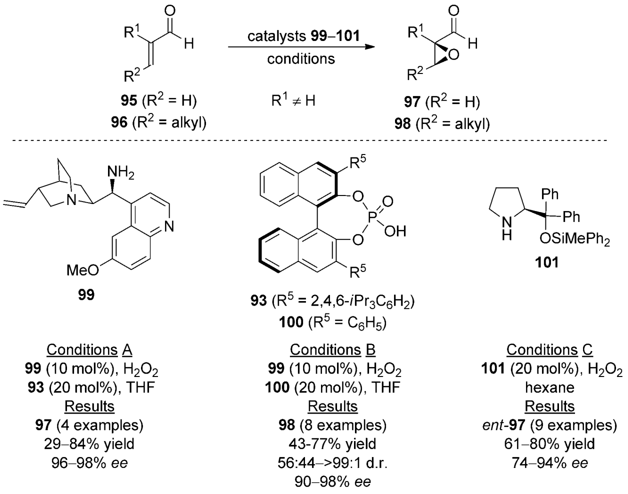
Several different protocols have been reported for enantioselective aminocatalytic epoxidation of α,β-unsaturated aldehydes (Scheme 30). The first successful report appeared in 2005, where the silyl-protected diarylprolinol catalyst **87**[84] was shown to be a highly potent catalyst for this reaction. In combination with aqueous H_2O_2 as the oxidant, this bulky secondary amine promoted the epoxidation of α,β-unsaturated aldehydes **4** with high diastereoselectivities and excellent enantioselectivites (Conditions A).[85] Several months later, a similar methodology employing a diphenyl variant of the silyl-protected prolinol catalyst **88** was disclosed (Conditions B).[86] As an alternative, a homogenous oxidant, the hypervalent iodine compound **91**, was also found to facilitate the desired epoxidation reaction in the presence of the imidazolidinone-based catalyst **89** (Conditions C).[87] The authors demonstrated that the compound **91** slowly released the monomeric iodosobenzene, which was the actual oxidant in the epoxidation reaction. This internal syringe pump effect was crucial for minimizing catalyst oxidation by iodosobenzene. In addition to the aforementioned protocols, which all relied on the use of a chiral amine to induce chirality, the salt



Scheme 30. Enantioselective epoxidation of α,β-unsaturated aldehydes. TBME = *tert*-butylmethylether, TMS = trimethylsilyl.

of an achiral amine and a chiral phosphoric acid was also be applied (Conditions D).[88] In such a catalytic system, the amine **90** acts as the rate enhancer, whereas the chiral phosphoric acid **93** governs the approach of the oxidant **92**, thus resulting in the formation of the epoxy aldehydes *ent*-**94** in 60–84 % yield, 94:6 to greater than 99:1 d.r., and 70–96 % *ee*.

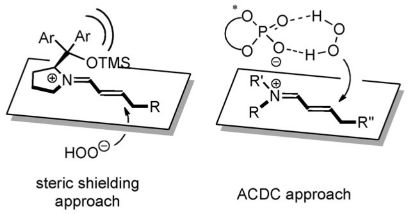
While secondary amines readily engage with the α-unbrached α,β-unsaturated aldehyde **4** to form the activated iminium-ion species, the corresponding condensation with the α-branched substrates **95** and **96** is more demanding. To tackle this challenge, primary-amine-based catalysts, such as the quinine-derived amine **99**, can be employed (Scheme 31).[89]



Scheme 31. Enantioselective epoxidation of α-branched α,β-unsaturated aldehydes.

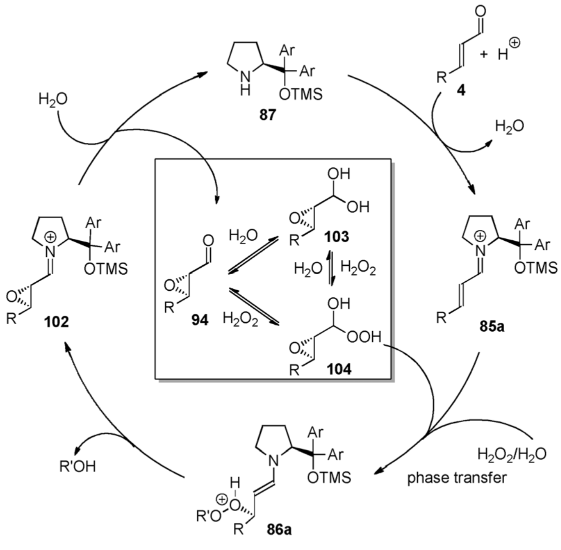
When applied as its bis(phosphoric acid) salt (with **100**), the trisubstituted epoxide products **98** are formed in good yields, moderate to excellent diastereoselectivities, and excellent enantioselectivities (Conditions B). A slightly modified protocol employing **93** as the chiral acid was optimized for the α-substituted acroleins **95**. It is noteworthy that secondary amine catalysts such as **101** are compatible with this specific class of α-branched substrates (i.e. with no β-branching, **95**) and the corresponding α,α-disubstituted epoxides *ent*-**97** are formed in 61–80 % yield and 74–94 % *ee* (Conditions C).[90]

In terms of reaction mechanisms, all of the reviewed aminocatalytic α,β-unsaturated aldehyde epoxidations follow the general catalytic cycle depicted in Scheme 29. Nevertheless, the achieved stereoselectivity in these reactions can have different origins (Scheme 32). The stereochemical information to be transferred to the substrate is either stored in the aminocatalyst, or in a chiral acid cocatalyst, or in the combination of both. In cases where the aminocatalyst is the sole source of chirality, such as the epoxidation protocols employing silyl-protected diarylprolinol-type catalysts, a steric shielding principle for the stereodifferentiation applies in most cases (Scheme 32, left).[84] In the catalyst-bound iminium-ion species, the bulky group of the amine shields one of the two faces of the conjugated system, thereby forcing the oxidant to approach from the sterically least-hindered side. Alternatively, the origin of chirality can be solely, or in part, stored in a chiral acid cocatalyst, such as the binol-derived phosphoric acids **93** and **100**. Such an approach is called the asymmetric counterion directed catalysis (ACDC; Scheme 32, right).[91] The corresponding anion of the phosphoric acid is ion paired to the iminium ion as a chiral counterion. The Brønsted basic oxo groups of this counterion then coordinate the approaching peroxide, thereby directing the delivery of the nucleophile. The use of a combination of a chiral amine and a chiral acid allows fine-tuning of a given catalytic system to achieve the desired selectivities.



Scheme 32. The origin of stereoselectivity in the epoxidation of α,β-unsaturated aldehydes.

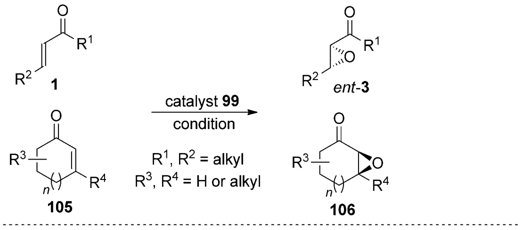
A recent study on the mechanism of the epoxidation of α,β-unsaturated aldehydes using the silyl-protected diarylprolinol catalyst **87** disclosed an interesting autoinductive behavior (Scheme 33).[92] A substantial increase of reaction rate was detected over the course of the reaction, thus indicating a product-induced rate increase. It was rationalized that the epoxy aldehyde **94**, unlike its parent α,β-unsaturated aldehyde **4**, readily reacted with H_2O_2 at the interface of the organic and aqueous layers. This reversible formation of the peroxy adduct **104** increased the levels of peroxides in the organic phase, hence, rendering the product a phase-transfer catalyst. The possibility of **104** being the actual nucleophile in the oxo-Michael reaction could not be ruled out.



Scheme 33. Mechanistic proposal for the organocatalytic asymmetric epoxidation of α,β-unsaturated aldehydes with the silyl-protected diarylprolinol catalyst **87**.

5.2. Epoxidation of α,β-Unsaturated Ketone Protocols and Mechanistic Considerations

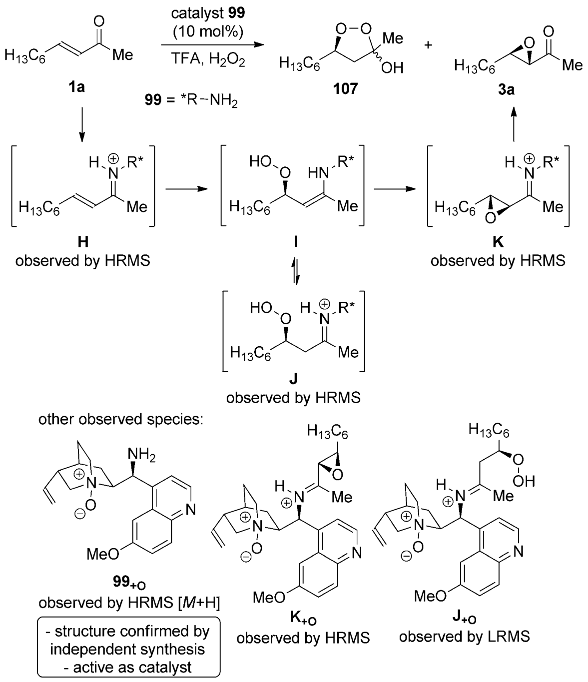
The asymmetric aminocatalytic epoxidation of α,β-unsaturated ketones has also been achieved, thus providing facile access to the highly enantioentiched epoxy ketones *ent*-**3** from the acyclic α,β-unsaturated ketones **1** in synthetically useful yields (Scheme 34).[93] While bulky secondary amine catalysts fail to condense with **1**, the requisite chiral iminium-ion species is readily formed between the primary amine **99** and **1** in the presence of an acidic additive. Two successful protocols have been independently developed by employing **99** as the catalyst in combination with either H_2O_2 (Conditions A)[93a] or (2-hydroperoxypropan-2-yl)benzene (Conditions B)[93b] as the oxidant. The H_2O_2-based strategy could be further extended to include the cyclic α,β-unsaturated ketones **105** as the substrates, thus furnishing the diastereomerically pure epoxides **106** in moderate to good yields and excellent enantioselectivities (Conditions C).[89b,94]



Conditions A	Conditions B	Conditions C
99 (10 mol%), TFA **1**, H_2O_2, dioxane NaOH	**99** (10 mol%) TFA, **1** $PhMe_2C\text{-}OOH$ toluene	**99** (10 mol%) TFA, **105**, H_2O_2 dioxane
Results	Results	Results
ent-**3** (20 examples) 40–88% yield >99:1 d.r. 90–99% *ee*	*ent*-**3** (6 examples) 54–91% yield >99:1 d.r. 96–97% *ee*	**106** (19 examples) 23–92% yield >99:1 d.r. 91–99% *ee*

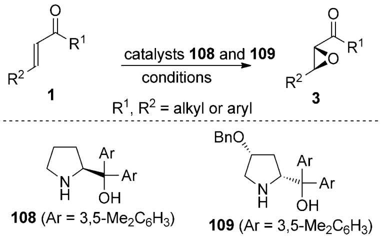
Scheme 34. Enantioselective epoxidation of α,β-unsaturated ketones employing a quinine-derived primary amine catalyst. TFA = trifluoroacetic acid.

To investigate the mechanism of the primary-amine-catalyzed epoxidation of α,β-unsaturated ketones, the epoxidation of the model substrate **1a** was studied by NMR spectroscopy and high resolution mass spectroscopy (HRMS; Scheme 35).[89b,95] Upon treating **1a** with the bistrifluoroacetic acid salt of **99** and H_2O_2, a mixture of two products, the peroxy hemiacetal **107** and the epoxy ketone **3a**, were formed. Therefore, a procedure involving a basic workup was implemented to convert **107** into the desired epoxide product. Moreover, three cationic intermediates (**H**–**J**) along the path of the proposed catalytic cycle were successfully identified by HRMS, hence confirming a Weitz–Scheffer-type mechanism of the developed primary-amine-catalyzed epoxidation of α,β-unsaturated ketones. Interestingly, this HRMS study also revealed the presence of an oxidized aminocatalyst ($\mathbf{99}_{+O}$) and its condensation products $\mathbf{K}_{+O}$ and $\mathbf{J}_{+O}$ in the reaction mixture. The N-oxide species $\mathbf{99}_{+O}$, prepared by an independent synthesis, was found to catalyze the epoxidation of **1a** with similar efficiency and stereoselectivity as its parent amine **99**.



Scheme 35. Mechanism of the epoxidation of α,β-unsaturated ketones: identification of intermediates by HRMS.

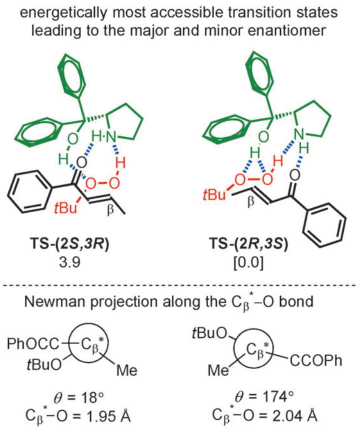
In addition to the primary amine catalysts, a series of secondary amines bearing a free hydroxy group can also promote the enantioselective epoxidation of the α,β-unsaturated ketones **1** (Scheme 36).[96] Among the evaluated candidates, the diarylprolinols **108** and **109** proved to be the most potent catalysts for the desired epoxidation reaction. Because of the lack of condensation between these secondary amines and the α,β-unsaturated ketone substrates, a different mode of action was proposed for these catalysts. The authors suggested that the diarylprolinols, such as **108** and **109**, formed an effective network of hydrogen-bonding interactions with the α,β-unsaturated ketone and the peroxide nucleophile (TBHP).[97]



Conditions A	Conditions B
108 (20 mol%), TBHP hexane	**109** (30 mol%), TBHP hexane
Results	Results
3 (15 examples) 16–98% yield >99:1 d.r. 6–92% *ee*	*ent*-**3** (13 examples) 49–90% yield >99:1 d.r. 72–96% *ee*

Scheme 36. Enantioselective epoxidation of α,β-unsaturated ketones employing a secondary amine-derived catalyst.

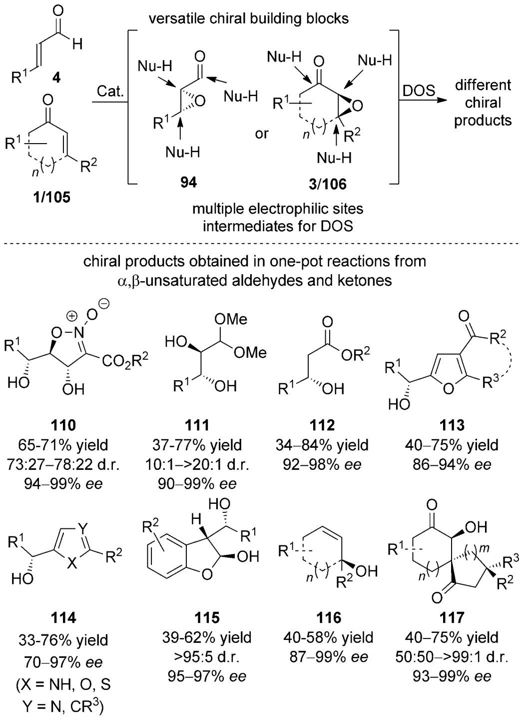
This hypothesized noncovalent mode of activation was supported by the available experimental data as well as a computational study. Furthermore, the origin of enantioselectivity was explained based on the computed energy of the most accessible transition-state structures of a model system consisting of the diphenylprolinol, (*E*)-1-phenylbut-2-en-1-one, and TBHP (Scheme 37). This investigation indicated a preference, by 3.9 kcal mol^{-1}, for the epoxide product having a 2*R*,3*S* configuration, and matched the experimentally observed result. This difference in activation barrier was rationalized by the achievement of a more stable staggered conformation as well as a more effective hydrogen-bonding network in TS-(2*R*,3*S*).



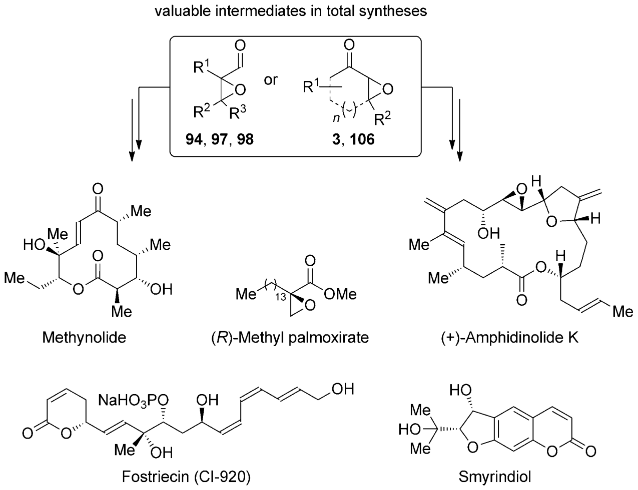
Scheme 37. Origin of enantioselectivity of the diphenylprolinol catalyzed α,β-unsaturated ketone epoxidation. Energies are in kcal mol^{-1}, including solvent polarization and zero-point vibrational corrections.

5.3. Synthetic Application of Chiral Epoxy Aldehydes and Ketones

The epoxy aldehydes and ketones are reactive molecules with multiple electrophilic sites, and thus offer rich possibilities for synthetic modifications and transformations. The addition of a suitable dinucleophilic species to these electrophiles may lead to many interesting ring-opening and annulation strategies.[98] Some of the enantioenriched building blocks, for example, **110**–**117**, generated by such strategies are depicted in Scheme 38. For example, by the in situ addition of a nitroacetate and a base to the crude reaction mixture of the aminocatalyzed epoxidation of α,β-unsaturated aldehydes, the chiral isoxazoline-*N*-oxides **110** can be obtained in high yields and stereoselectivities.[98a]



Scheme 38. Diversity-oriented asymmetric synthesis: one-pot strategies incorporating aminocatalytic epoxidation reactions.

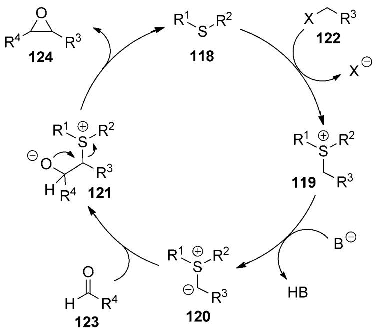


Scheme 39. Epoxy aldehydes and ketones in target-directed synthesis: representative targets.

In addition to their application in DOS, chiral epoxy aldehydes and ketones are also frequently used as synthetic intermediates in target-directed synthesis.[99] Some representative examples of target molecules, which incorporated the use of these building blocks along their synthetic path, are illustrated in Scheme 39. The multiple electrophilic sites present in chiral epoxy carbonyls are excellent handles for the crosslinking of fragments of the end product. Moreover, the chirality stored in the molecule can often direct the approach of an incoming reactant. In the course of assembling the final structure, the electrophilic epoxide functionality is usually ring opened, for example, as in the synthesis of the natural product smyrindiol.[99c] However, for other targets, for example, (*R*)-methyl palmoxirate,[90] the three-membered oxirane ring is required. This α-branched epoxy ester is easily synthesized in two steps from a corresponding epoxy aldehyde.

6. Enantioselective Epoxidation by Chiral Sulfur Ylide Catalysts

Sulfur ylides provide a unique path to generating epoxides by alkylation of aldehydes. Originally developed as the Corey–Chaykovsky reaction, developments in this area have made access to a wide range of disubstituted epoxides possible.[100] Several reviews on sulfide-mediated/catalyzed epoxidation reactions have been published, therefore, this review will summarize important aspects of catalytic methods prior to the most recent review in 2007 and will focus on areas that have shown progress since then.[101] It should also be noted that this review is limited to chiral-sulfide-catalyzed epoxidations and will not cover chiral-sulfide-mediated reactions. In the catalytic cycle, the ylide **120** is formed by alkylation of the sulfide **118** and subsequent deprotonation of the sulfonium salt **119** (Scheme 40). The ylide then attacks the carbonyl compound **123** to form the betaine intermediate **121** which collapses to produce the epoxide product **124** and sulfide **118** which can re-enter the catalytic cycle.

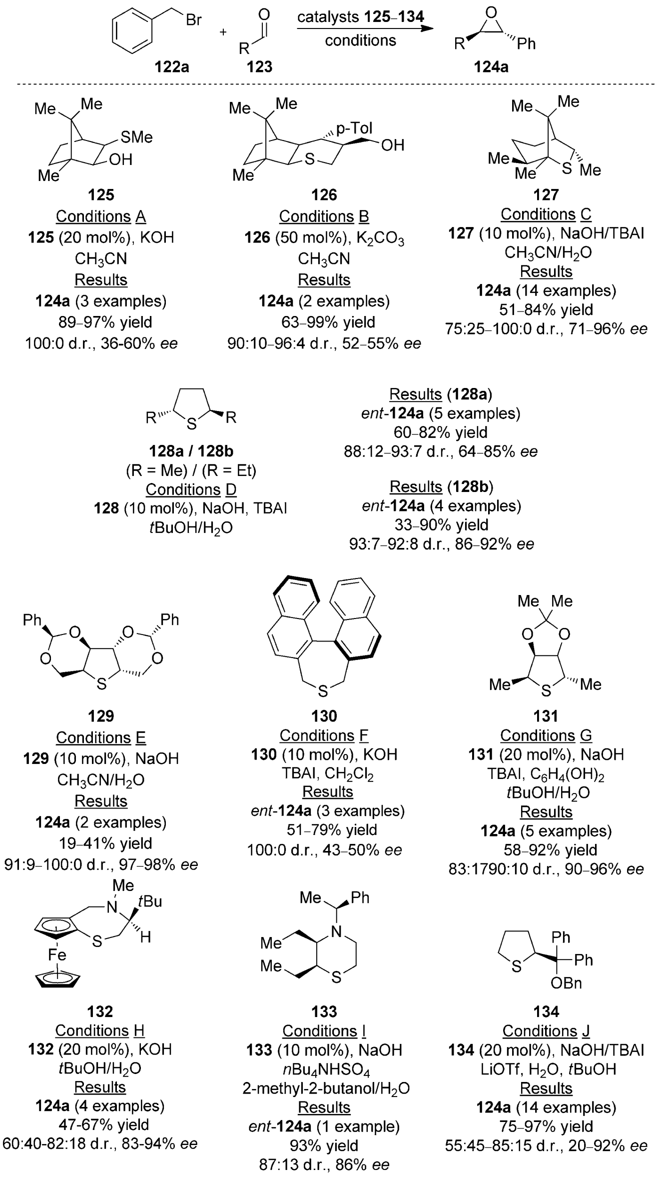


Scheme 40. General mechanism for the sulfide-catalyzed epoxidation reaction.

6.1. Sulfide-Catalyzed Asymmetric Epoxidation Protocols and Mechanistic Considerations

The first enantioselective sulfide-catalyzed epoxidation reaction was developed in 1989.[102] Using a catalyst derived from camphorsulfonic acid the authors prepared an optically active oxirane in 23% yield and 31% *ee*. Since this report, a variety of chiral-sulfide-catalyzed epoxidation reactions have emerged. Scheme 41 depicts the chiral sulfides that have provided the highest yields and enantioselectivity for a range of aldehydes.

After the first report of an enantioselective sulfide-catalyzed epoxidation, several other camphor-derived sulfide catalysts have been developed. The catalysts **125** and **126** were both shown to provide high diastereoselectivity and low enantioselectivity for benzaldehyde and *para*-substituted benzaldehydes (Scheme 41, Conditions A and B).[103] The camphor-derived sulfide catalyst **127** was recently found to function well for both aromatic and aliphatic aldehydes (Conditions C).[104]



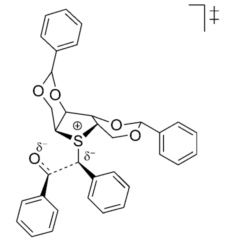
Scheme 41. Selected examples of chiral sulfide catalysts for formation of epoxides from aldehydes. TBAI = tetra-*n*-butylammoniumiodide.

C_2-symmetric sulfide catalysts have been shown to be successful promoters of the asymmetric epoxidation reaction. The catalysts **128a** and **128b** were found to work for a range of aromatic and heteroaromatic aldehydes, as well as cinnamaldehyde (Scheme 41, Conditions D).[105] During the development of this catalytic methodology, the authors suggested that the sulfonium salt formation and the attack of the ylide on the carbonyl were both slow reaction steps in the catalytic cycle.[106] To accelerate the reaction without affecting the selectivity the authors introduced an iodide salt into the reaction mixture to convert the benzyl bromide into a benzyl iodide in situ. By using TBAI, the reactions could be carried out with 10 mol% catalyst over a four to six day period.

Shortly after the development of the catalysts **128**, the C_2-symmetric sulfides **129** and **130** were reported to catalyze the conversion of aromatic aldehydes into *trans*-diarylepoxides (Scheme 41).[107] The use of **129** gave low yields, but high diastereo- and enantioselectivities. The catalyst **130** was found to work best with benzyl iodide as a reagent and provided moderate yields, high diastereoselectivity, and low enantioselectivity.[108]

The design of **128a** was improved upon with the development of catalyst **131** (Scheme 41).[109] This catalyst gave moderate to high yields, good diastereoselectivities, and high enantioselectivities for several aromatic aldehydes. The increased selectivities observed with **131** are thought to result from the introduction of the acetal bridge, thus creating a rigid bicyclic ring system which forces the methyl groups at the 2- and 5-positions into a pseudoaxial position.

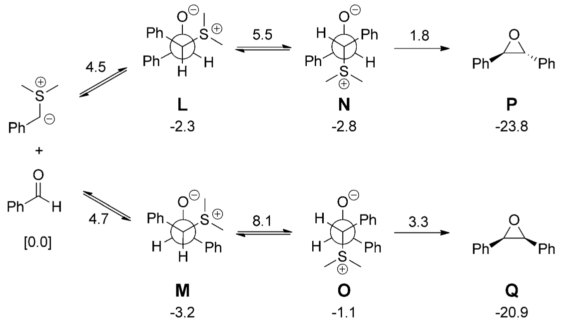
To understand the origin of the enantioselectivity in the epoxidation reaction catalyzed by **128a** and **129**, a series of DFT calculations were performed.[107a,110] Conformational studies on both **128a** and **129** showed that the conformer with the phenyl positioned away from the sulfide ring was favored by less than 1 kcal mol^{-1}. Calculations were performed on both conformers of the ylide and with both approaches of the aldehyde, thus leading to four possible transition-state structures. In all the transition-state structures calculated, the aldehyde preferred to approach the sulfonium ylide from the less-hindered face, with the sulfonium and carbonyl oxygen atom on the same side. For **129**, the approach shown in Scheme 42, which leads to the observed product, was found to be the favored transition-state structure. For **128a** an approach leading to a *cis* epoxide was favored by 1–2 kcal mol^{-1} over the other transition-state structures, and the authors argue that the observed selectivity represents a Boltzmann distribution of the products.



Scheme 42. Transition-state structure for the favored addition conformation of benzaldehyde to the yilde intermediates of **129**.

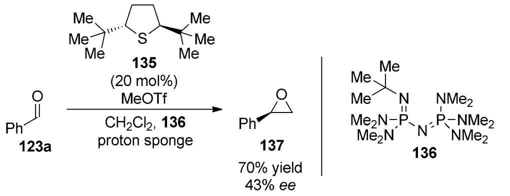
In addition to camphor-derived and C_2-symmetric sulfide catalysts, several other additions have been developed. The catalyst **132** was found to give low to moderate yields and diastereoselectivities, but high enantioselectivities for several aldehydes containing aromatic, heteroaromatic, and unsaturated substituents (Scheme 41).[111] However, in all cases long reaction times (7–14 days) were required. The sulfide **133** was demonstrated to work catalytically with benzaldehyde, thus generating the *trans*-diphenyl epoxide in high yield and good diastereo- and enantioselectivity.[112] The most recently reported sulfide catalyst, **134**, was shown to deliver the epoxide for a range of aromatic aldehydes as well as cinnamaldehyde.[113]

In an attempt to explain the origin of the high diastereoselectivity provided by the chiral sulfur catalysts, DFT calculations exploring the reaction between phenyl-stabilized ylide (PhCH=SMe$_2$) and benzaldehyde were employed.[114] Consistent with previous studies on the Corey–Chaykovsky epoxidation, the reaction was found to occur in a stepwise manner.[115] Addition of the ylide to benzaldehyde occurs with the oxygen atom of the carbonyl and the sulfonium group in a cisoid configuration. Two different betaine intermediates, **L** and **M**, can be formed depending on the positioning of the phenyl ring during the approach (Scheme 43). For elimination to occur the betaine intermediate must undergo a C–C bond rotation to position the sulfur atom antiperiplanar to the oxygen atom. The favorability of the formation of *trans* epoxides is attributed to the fact that the C–C bond in betaine **L** has a lower barrier than reversion. The authors suggest that the difference in rotational barriers is responsible for the observed diastereoselectivity.



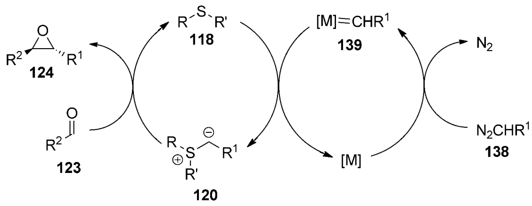
Scheme 43. Proposed pathway of the chiral sulfide catalytic cycle. Numbers reported are electronic energies (kcal mol^{-1}).

Although many catalytic methods have been developed for the formation of *trans*-disubstituted epoxides, the catalytic asymmetric synthesis of terminal epoxides has proven to be a challenging task. Only a single methodology involving sulfide catalysts currently exists in the literature.[116] By using the catalyst **135** and the phosphazene base **136**, the terminal epoxide **137** was furnished in 70% yield and 43% *ee* (Scheme 44).[117]



Scheme 44. Chiral-sulfide-catalyzed asymmetric methylene transfer for the formation of epoxides. Tf = trifluoromethanesulfonyl.

While sulfide-catalyzed epoxidation reactions, proceeding through the alkylation/deprotonation pathway, have proven to be a simple and efficient route to obtain the *trans*-epoxides **124**, the scope of these reactions is rather limited. To improve the utility of sulfide catalysts, a new method was introduced which involves reacting the carbene intermediate **139** with sulfide **118** to generate the ylide **120** (Scheme 45). The preliminary work in this area employed the diazo compound **138** which decomposed in the presence of a metal catalyst to produce the metal carbene intermediate **139**, which reacted with the chiral sulfide catalyst to form the ylide **120**.[101b]

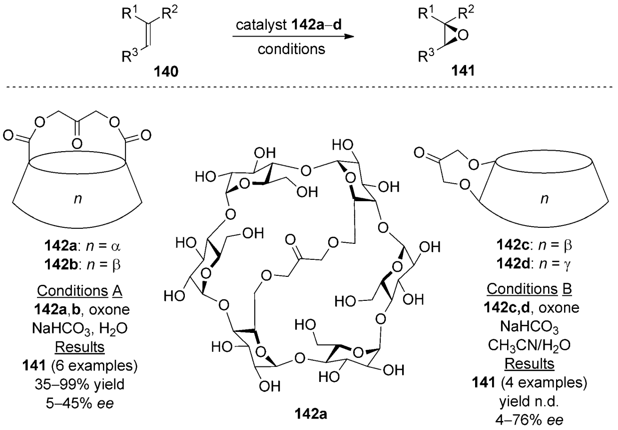


Scheme 45. In situ generation of diazo compound and the resulting catalytic epoxidation cycle.

This was the first method to expand the scope of substrates used in the asymmetric catalytic sulfur-ylide-mediated epoxidation reactions. The method provided several advantages over previous methods, including: 1) the neutral operating conditions for this method allowed use of base-sensitive substrates, 2) the carbene intermediates are much more reactive than alkyl halides and ylide formation with less-reactive sulfides was possible, and 3) it allowed access to ylides which could not be formed from direct addition of a diazo compound and sulfide. A variety of sulfide catalysts have been developed for this cooperative catalytic method, however, as no new work has been published in this area since the last, very through, review on this method in 2007 we refer the reader to the previous review for further information on this area.[101c] The synthetic utility of the catalytic sulfur-ylide-mediated epoxidation remains scarce in asymmetric syntheses.[118] However, there are many reports in which chiral sulfur ylides are used as auxiliaries to access essential optically pure complex molecules.[119–121]

7. Enantioselective Epoxidation by Cyclodextrin Catalysis

Beside peptides, cyclodextrins are a second class of macromolecules useful in asymmetric catalysis.[122] These bucketlike complexing agents perform Michaelis–Menten catalysis under enzymatic conditions by mimicking the active site of an enzyme. After recognition and complexation of the substrate within the lipophilic cyclodextrin cavity, the reaction takes place and finally the product is released recovering the free cyclodextrin. Based on this principle, in 2004 the first cyclodextrin-catalyzed asymmetric epoxidation was reported, and used oxone as the oxidation agent in water in the presence of $NaHCO_3$.[123] The epoxidation was carried out by a dioxirane group formed in situ from a ketone placed in the bottom of the cyclodextrin bucket. However, the enantioselectivity was quite low (0–12% *ee*). One year later the modified catalysts **142a** and **142b** were presented and gave low to moderate enantioselectivities and moderate to excellent yields in the epoxidation of mono-, di-, and trisubstituted alkenes (Scheme 46).[124] Sterically demanding substrates such as stilbenes were successfully epoxidized by **142c** and **142d**, in which the catalytic active ketone moiety was attached on the side of the cyclodextrin. By using these new catalysts, products with up to 76% *ee* were obtained.[125]



Scheme 46. Enantioselective epoxidation by cyclodextrin catalysis.

8. Concluding Remarks

Because of the inherent strain of the three-membered ring system, chiral epoxides are privileged building blocks in asymmetric synthesis as well as in biosynthetic pathways. In synthetic chemistry, new and useful methods for enantioselective epoxidations have been under continuous development. In recent times, the advances in enantioselective organocatalytic epoxidation reactions have been particularly evident. In this review article, we attempted to unveil the most significant progress in this dynamic area of research. The state-of-the-art asymmetric epoxidation methodologies, using many different types of organocatalysts, have been summarized. The underlying mechanisms as well as the synthetic applications of the assembled epoxide products have also been discussed. We hope to have provided a representative overview of asymmetric organocatalytic epoxidation reactions and their applications.

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