Organocatalytic Asymmetric Epoxidation and Aziridination of Olefins and Their Synthetic Applications

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1. INTRODUCTION

Epoxides and aziridines are extremely versatile synthetic intermediates and present in a large array of natural products and biologically active molecules (Figure 1). In addition,
epoxides are proposed to be biosynthetic intermediates for the rapid construction of complex polycyclic natural products such as (+)-aurilol and brevetoxin B (Figure 2). The stereochemistry possessed by the epoxides and aziridines in biologically active molecules necessitates their enantioselective synthesis.

Asymmetric catalysis using metals has seen widespread success in the past decades. In recent years, the use of small nonmetal organic molecules as catalysts has witnessed significant development, particularly since the mid-1990s, and established its prominence in synthetic chemistry. To distinguish from metal-catalyzed processes (organometallic catalysis), these nonmetal-catalyzed reactions are often referred to as organocatalysis (Kagan 1999), organocatalysis, or organocatalytic (MacMillan 2000). The organocatalyzed asymmetric epoxidation of olefins is an important part of this field, and some of these systems are very early examples of effective and useful organocatalytic processes. A number of organocatalyzed systems have also been developed for asymmetric aziridination of olefins. This review will highlight various advances in organocatalytic asymmetric epoxidation and aziridination of olefins as well as their synthetic applications.

2. ORGANOCATALYZED ASYMMETRIC EPOXIDATION OF OLEFINS

Asymmetric epoxidation of olefins presents an especially attractive approach to chiral epoxides. Great success has been achieved with metal-catalyzed asymmetric epoxidation of olefins such as epoxidation of allylic alcohols, related heteroatom-containing olefins, and unfunctionalized olefins, as well as nucophileliphobic epoxidation of electron-deficient olefins. Complementary to metal-catalyzed processes, organocatalytic asymmetric epoxidation has also proven to be highly effective for synthesis of chiral epoxides. This section will highlight the progress in this area including phase-transfer catalysts, peptide-type catalysts, chiral ketone and iminium salt catalysts, and chiral amine catalysts, etc.

2.1. Phase-Transfer Catalysts

Use of phase-transfer catalysts (PTCs) was first reported approximately 40 years ago for asymmetric epoxidation of olefins. Chiral epoxides are obtained from electron-deficient olefins (mostly enones) with catalysts such as quaternary ammonium salts and crown ethers in the presence of oxidants (Scheme 1).

2.1.1. Cinchona Alkaloid-Derived Quaternary Ammonium Salts. In 1976, Wynberg and co-workers utilized the cinchona alkaloid-derived quaternary ammonium salt to catalyze epoxidation of α,β-unsaturated ketones with up to 45% ee (Figure 3). Onda reported the epoxidation of an ester-substituted naphthoquinone in 78% ee using catalyst 1 (Figure 3).

In 1998, Taylor and co-workers accomplished the syntheses of three members of the manumycin family, (−)-alisamycin (5), (+)-MT 35214 (6), and (+)-manumycin A (7) (Scheme 2). Key intermediate 4 was synthesized via epoxidation of enone 3 using cinchonidine-derived catalyst in 32% yield and 89% ee and can be obtained in >99% ee after recrystallization. N-Benzylcinnchoninium chloride (8) was employed in the syntheses of palmarumycin and (−)-preussomerin G by Barrett and co-workers in 2002 (Scheme 3). Asymmetric
epoxidation of enone 9 with catalyst 8 in the presence of TBHP gave palmarumycin C2 (10) in 81% yield and >95% ee, which was further converted into (−)-preussomerin G (11).

Quaternary ammonium salt catalysts with various nitrogen substitutions have been investigated (Figure 4). Kawaguchi and co-workers reported catalyst 12 with a N-fluorenyl group in 1986, giving up to 61% ee for epoxidation of cyclic enones.17 In 1998, Arai, Shioiri, and co-workers reported that the substituents on the phenyl ring of the N-benzyl unit in the cinchona alkaloid-derived catalysts played an important role in the asymmetric induction. Up to 92% ee was obtained for epoxidation of chalcones using catalyst 13a (Figure 5).18 However, only 2% ee was obtained when the secondary alcohol of 13a was protected as an allyl ether. In 2001, Adam and co-workers reported that up to 98% ee was obtained for conformationally rigid enones using catalyst 13b and sterically demanding hydroperoxides as the oxidants (Figure 6).19

Epoxidation of enones with catalysts bearing sterically bulky N-substituents (14,20 15,21 and 1622) (Figure 4) has also been investigated. In 1998, Arai, Shioiri, and co-workers reported that 76% ee was obtained for 2-phenyl-1,4-naphthoquinone with catalyst 14 (Figure 7).20a Berkessel and co-workers showed that 2-methyl-1,4-naphthoquinone (vitamin K3) was epoxidized with catalyst 15, bearing a hydroxyl group on the quinoline ring, in 85% ee (Figure 7).21 In 2002, Dehmlow and co-workers reported their studies on analogues of cinchona alkaloids without the quinoline nitrogen atom as phase-transfer catalysts. Up to 84% ee was obtained for epoxidation of 2-isopropyl-1,4-naphthoquinone with catalyst 16 (Figure 7).22

In 2013, Shibata and co-workers reported that β-trifluoromethyl-β,β-disubstituted enones could be epoxidized in high yields and high enantioselectivities with N-3,5-bis(trifluoromethyl)benzyl-substituted catalyst 17 in the presence of methylhydrazine and air (Figure 4 and Table 1).23 It was proposed that H2O2 was likely to be generated in situ from methylhydrazine and air and to act as the oxidant. In their studies, Chen and co-workers found that quinidinium catalyst 18 (Figure 4), bearing a pentafluorobenzyl group, was very effective for epoxidation of β-trifluoromethyl-β,β-disubstituted enones in the presence of H2O2, giving up to 96% yield and 99.7% ee (Table 2).24 The resulting α,β-epoxy ketone 19 could be converted into potentially useful β-trifluoromethyl-β-hydroxy ketone 20 in 91% yield via reduction with Zn and NH4Cl (Scheme 4). The hydrogen-bonding and the π−π stacking interaction of the pentafluorobenzyl unit and the aryl group of the substrate appear to be important contributing factors for the asymmetric induction during this reaction (Figure 8).

The C-9 hydroxyl groups of quaternary ammonium salt catalysts appear to be important for the enantioselectivity in many cases.18,19b,21,24 However, as shown by Lygo25 and Corey,26 respectively, N-antihacencemethyl-substituted amino-
nium salts with the C-9 hydroxyl groups being protected as benzyl ethers are effective catalysts for epoxidation using NaOCl and KOCl as oxidant (Figure 9). Both the nature of O- and N-substituents and the choice of the oxidant are crucial for the enantioselectivity. For example, in 1998, Lygo and co-workers reported that (E)-chalcone was epoxidized in 90% yield and 86% ee with catalyst 21a and NaOCl (Figure 10). The ee’s were further improved by optimizing the reaction conditions (Figure 10).25c Allylic alcohols can be directly converted to α,β-epoxy ketones in 78−87% ee under the epoxidation conditions.27 Epoxidation with catalyst 21b was used in the synthesis of epoxysuccinyl peptide E-64c (a cysteine protease inhibitor) (Scheme 5).28

In 1999, Corey and co-workers demonstrated remarkably high enantioselectivity (91−98.5% ee) for epoxidation of enones with catalyst 21b using KOCl as oxidant (Figure 11).26 The resulting α,β-epoxy ketones can be transformed into other useful synthetic intermediates such as α,β-epoxy esters and α-hydroxy esters (Scheme 6). The epoxidation is proposed to proceed via a transition state described in Figure 12.26 The rigidity of the catalyst allows it to adopt a certain three-dimensional arrangement, which brings the substrate and oxidant into a favorable proximity for the enantioselectivity via electrostatic and van der Waals interactions.

Trichloroisocyanuric acid (TCCA) was also found to be an effective oxidant for epoxidation with catalyst 21b as reported by Liang and co-workers in 2003, with up to 96% ee for epoxidation of chalcones (Figure 13).29 KOCl was believed to be formed in situ from TCCA and KOH and acted as the oxidant in the epoxidation with catalyst 21b (Scheme 7).

### Table 2. Epoxidation of β,β-Disubstituted Enones with Catalyst 18 and H2O2

<table>
<thead>
<tr>
<th>entry</th>
<th>R</th>
<th>Ar</th>
<th>yield (%)</th>
<th>dr</th>
<th>ee (major) (%)</th>
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<td>Et</td>
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<td>100:1</td>
<td>82</td>
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</tbody>
</table>

Scheme 4. Synthesis of β-Hydroxy Ketone 20 via Reduction of α,β-Epoxy Ketone 19

Figure 8. Proposed transition state for epoxidation using catalyst 18.

Figure 9. Quaternary ammonium salt catalysts 21 and 22.
oxidant. Catalyst 21b was also used for epoxidation of \(\alpha,\beta\)-unsaturated sulfones by Dorow and Tymonko in 2006, giving up to 82% ee for (E)-phenyl styrylsulfone with KOCl as oxidant.30

Use of cinchonidine-derived catalyst 23 (Figure 14) for epoxidation was reported by Kim and co-workers in 2003. Up to 78% ee was obtained for epoxidation of 1,3-diarylenones using NaOCl as oxidant.31 In 2010, Park, Jeong, and co-workers showed that high ee’s could be achieved for epoxidation of chalcones with catalyst 24 bearing a N-2,3,4-trifluorobenzyl moiety (Figure 15).32

In 1986, Kawaguchi and co-workers reported the epoxidation of cyclic enones with \(C_2\)-symmetric dimeric catalysts such as cinchonine-derived quaternary ammonium salt 25 (Figure 16), which achieved up to 63% ee in the epoxidation of cyclohexenone.17,33 A number of dimeric quaternary ammonium salts with different linkers were examined for epoxidation of enones by Jew, Park, and co-workers. Up to >99% ee was achieved for diarylenones with 1 mol % catalyst 26 and 1 mol % Span 20 using \(H_2O_2\) as the oxidant (Figure 17).34 The C-9 hydroxyl group of the catalyst was shown to be crucial for high enantioselectivity. Both reactivity and enantioselectivity of the epoxidation are greatly enhanced by addition of the surfactant. In 2006, Wang and co-workers reported the epoxidation of enones with poly(ethylene glycol)-linked cinchona quaternary ammonium salts and TBHP, achieving up to 86% ee for epoxidation of (E)-chalcone.35

2.1.2. Other Quaternary Ammonium Salts. Other quaternary ammonium salt catalysts have been investigated for asymmetric epoxidation of olefins (Figure 18). In 1983, Mazaleyrat reported binaphthyl-based catalyst 27, which epoxidized (E)-chalcone with 37.1% ee in the presence of \(H_2O_2\).36 In 2004, Maruoka and co-workers showed that binaphthyl-based spiro quaternary ammonium salts (28), containing two diaryl methanol groups, were highly effective catalysts for epoxidation of enones (Figure 18).37 A variety of \(\alpha,\beta\)-epoxy ketones were obtained in 80–99% yield and 89–99% ee using catalysts 28 with NaOCl as oxidant (Figure 19). The hydroxyl groups of the catalyst appeared to be important for the reactivity and enantioselectivity of the epoxidation.37 In 1994, Masaki and co-workers reported their studies on the
epoxidation of (E)-chalcone (9.1% ee) with pyrrolidinium salts 29 and 30 as catalysts (Figure 18).38

2.1.3. Guanidinium Salts. In 2003, Murphy and co-workers reported that C_2-symmetric guanidinium salt 31 (Figure 20) was an active and enantioselective epoxidation catalyst, giving chalcone epoxide in 99% yield and 93% ee (Figure 21).39 Epoxidation using cyclic guanidinium salts 32 and 33 was investigated by Nagasawa and co-workers, and up to 60% ee was obtained for 1,3-diaryl enones (Figure 21).40 Several acyclic guanidinium salts such as 34 and 35 were subsequently studied for the epoxidation by the same group (Figure 20).41,42 Bifunctional urea−guanidinium salt 35 was shown to be an effective catalyst, giving the epoxidation products of various 1,3-diaryl enones in 91−99% yield and 85−96% ee (Figure 21).42

2.1.4. Crown Ether-Type Catalysts. Crown ether-type phase-transfer catalysts with attached chiral moieties have also been examined for olefin epoxidation (Figure 22). Bakó and co-workers reported monosaccharide-based crown ether-type catalysts 36 and 37 for the epoxidation,43 affording up to >99% ee for chalcones with TBHP as oxidant (Figure 23).44

2.2. Peptide-Type Catalysts

2.2.1. Polypeptide-Catalyzed Epoxidation under Triphasic Conditions. In 1980, Julia and co-workers reported a polypeptide-catalyzed asymmetric epoxidation45 of (E)-chalcone with H_2O_2−NaOH in toluene−water.46 The reaction system was triphasic due to the insolubility of the polypeptide catalyst in toluene and water. Chalcone epoxide was obtained in 85% yield and 93% ee with poly-L-alanine (41a) at room temperature for 24 h (Scheme 7, Figure 24). The catalyst could be recovered and reused but gave substantially reduced yield and ee for the epoxide. Much lower yields and ee’s were obtained with poly-L-glutamate catalysts 42 and 43 (Scheme 7, Figure 19).
The polypeptide catalysts can be synthesized via polymerization of N-carboxyanhydride (NCA) initiated by a nucleophile such as n-butyamine (Scheme 7). The peptide length is regulated by the ratio of NCA to initiator.

Julia, Colonna, and co-workers subsequently carried out a series of studies on the epoxidation, including catalyst structure, reaction conditions, and substrate scope, etc. The degree of polymerization of the polypeptide catalysts was shown to be important for the enantioselectivity. For example, the ee increased from 11% to 96% for epoxidation of (E)-chalcone as the length of poly-L-alanine increased from \( n = 5 \) to 30. The maximum enantioselectivity was obtained with catalyst 41c (Scheme 7, Figure 24).

A variety of polypeptides derived from different amino acids were also extensively studied. Comparable results (88−95% ee) were achieved for (E)-chalcone with poly-L-leucine and poly-L-isoleucine. These catalysts are more stable than poly-L-alanine under the reaction conditions since they are more sterically hindered and thus less prone to hydrolysis, which is beneficial for the recycle of the catalyst. The copolymer catalyst derived from L-alanine and L-leucine gave 95% ee for (E)-chalcone. Studies showed that polypeptides with carboxyl and ester groups at the C-terminus were also effective catalysts for epoxidation. A cross-linked polystyrene-supported poly-L-alanine gave 82% yield and 84% ee for epoxidation of (E)-chalcone. Reaction conditions were also investigated with (E)-chalcone as substrate and 41a as catalyst, and optimal results were obtained with H\(_2\)O\(_2\)−NaOH in toluene or CCl\(_4\). The epoxidation was further extended to other electron deficient olefins with catalyst 41a, although lower ee’s were obtained as compared to (E)-chalcone (Figure 24).

Ferreira, Bezuidenhoudt, van Rensburg, and co-workers investigated the asymmetric epoxidation of poly-oxygenated chalcones with the triphasic system and the transformations of the resulting chalcone epoxides. For example, chalcone 44 was epoxidized with poly-L-alanine and H\(_2\)O\(_2\)−NaOH in CCl\(_4\) to give epoxide 45 in 74% yield and 84% ee, which was hydrogenated to \( \alpha \)-hydroxydihydrochalcone 46 in 88% yield and 76% ee (Scheme 8). Optically active dihydroflavonol 50 could be synthesized in 83% ee from epoxide 48 via epoxide ring opening with phenylmethanethiol and subsequent cyclization (Scheme 9).

In 1990, Itsuno and co-workers reported the epoxidation of chalcones using poly-L-alanine and poly-L-leucine immobilized on cross-linked aminomethyl polystyrene (CLAMPS) resin.

With CLAMPS-poly-l-leucine catalyst 51, chalcones were effectively epoxidized with up to 99% ee under the triphasic conditions (Figure 25). The polymer-supported catalysts could be recovered and reused several times without substantial loss of catalytic activity. Flisak, Lantos, and co-workers showed that chalcone epoxides could be converted to the corresponding glycidic esters in good yields via Baeyer−Villiger oxidation (Scheme 10).

Scheme 8. Synthesis of Poly-Oxygenated \( \alpha \)-Hydroxydihydrochalcone 46

Scheme 9. Synthesis of Dihydroflavonol 50

Scheme 10. Synthesis of Glycidic Esters via Epoxidation and Baeyer−Villiger Oxidation
synthesized using freshly prepared leucine-NCA in a humidity chamber with 70−75% relative humidity.55

During 1995−1996, Roberts and co-workers reported on their efforts to expand the scope of the poly-L-leucine-catalyzed asymmetric epoxidation under various reaction conditions.56 High ee’s (up to >99%) were achieved for a variety of α,β-unsaturated ketones including heterocyclic enones, alkyl- or alkynyl-substituted enones, dienones, dienediones, and enediones (Figure 26). Along with H2O2, sodium perborate and sodium percarbonate (Na2CO3·1.5H2O2) were also found to be suitable oxidants for the epoxidation.56,57

As shown by Falck and co-workers in 1997, stannyl-substituted enone 56 was an effective substrate for the asymmetric epoxidation, giving stannylepoxide 57 in 90% yield and >99% ee with poly-L-leucine as catalyst (Scheme 12).58 The epoxide was converted into epoxy ketones 58 and 59 by Cu2S-mediated thiocarbonylation and allylation, respectively (Scheme 12).

In 2003, Geller, Militzer, and co-workers reported that addition of phase-transfer catalysts (PTCs), such as tetrabutylammonium bromide (TBAB), as cocatalyst to the triphasic system largely accelerated the polypeptide-catalyzed epoxidation, thus leading to significant reduction of the reaction time and catalyst loading.59 The modified epoxidation process was applied to several enones and an alkanyl sulfone59c,e with one example being carried out on 100 g scale59d,e (Figure 27). In 2004, Roberts and co-workers reported their studies on the epoxidation of enones and arylvinyl sulfones using poly-L-leucine as catalyst and Bu4NHSO4 (Figure 28).60 Epoxidation using poly-L-leucine immobilized on hydrotalcite and TBAB under triphasic conditions was also reported by Segarra and co-workers.61

**2.2.2. Polypeptide-Catalyzed Epoxidation under Biphasic Conditions.** In 1997, Roberts and co-workers developed a highly effective biphasic nonaqueous system for the polypeptide-catalyzed asymmetric epoxidation.62 Aqueous H2O2 and NaOH were replaced with urea−H2O2 (UHP) and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), respectively, which required no aqueous phase. Under biphasic conditions, enones...
were efficiently epoxidized with immobilized poly-L-leucine (CLAMPS-PLL) as catalyst in THF to give the corresponding epoxides with up to >95% ee (Figure 29, Method A). DABCO–1.5H₂O₂ was also found to be an effective oxidant (Figure 29, Method B).⁶² This biphasic system greatly reduced the reaction time. The reaction avoided use of aqueous NaOH, which allowed the epoxidation to be extended to alkali-sensitive substrates and eliminated the degradation of the polypeptide catalyst caused by NaOH.⁶² Roberts and co-workers showed that the epoxidation also proceeded effectively with sodium percarbonate (Na₂CO₃·1.5H₂O₂) in a miscible solvent mixture such as DME/H₂O, giving the epoxides in up to 96% ee (Figure 29, Method C).⁶³ In this case, sodium percarbonate was thought to act as an oxidant as well as a base. The substrate scope for the biphasic system was also investigated by Roberts and co-workers. A variety of α,β-unsaturated ketones including chalcones, alkyl-substituted enones, dienones, trienones, and trisubstituted enones bearing an exocyclic C=C bond were epoxidized with high ee’s (Figure 29).⁶⁴ Wang and co-workers reported the epoxidation of chalcones (up to 96% ee) with polyi-L-leucine using H₂O₂ and NH₄HCO₃.⁶⁵ Roberts and co-workers also extensively studied the epoxidation with the polypeptide catalyst immobilized on a poly(ethylene glycol) (PEG) polystyrene support and absorbed on silica under biphasic conditions (Figure 29, Method E).⁶⁶ They reported that poly-L-leucine could be covalently linked to silica, and the resulting catalyst (60) was highly effective for the epoxidation, giving up to 97% ee for (E)-chalcone (Figure 30).⁶⁶

The synthetic applications of the epoxidation using silica-absorbed and other solid-supported polypeptide catalysts were extensively investigated by Roberts and co-workers. For example, 2′-aminochalcone epoxide (62) was converted to tetrahydroquinolone 63 in 64% yield via an intramolecular nucleophilic ring opening (Scheme 13).⁶⁴d

**Scheme 13. Synthesis of Tetrahydroquinolone 63**

Galactonic acid derivative 79 (Scheme 17)⁷⁰ and naturally occurring styryl lactones such as (+)-goniopyrrole (84) and (+)-goniofurfurone (85) (Scheme 18)⁷¹ were synthesized from nucleophilic addition of Grignard reagents to epoxy ketones 69 and 74 proceeded diastereoselectively to give epoxy tertiary alcohols 70 and 75, respectively. Treatment of 70 with TBSCl and imidazole provided epoxy alcohol 71 in 69% yield via a Payne rearrangement. Epoxide 70 was opened by SnCl₄ to give 1-chloro-2,3-diol 72 in 86% yield with retention of configuration at the benzylic carbon (Scheme 15). SnCl₄ likely coordinated to the epoxide oxygen and delivered the chloride anion to the benzylic carbon intramolecularly.⁶⁹ Epoxide 70 was converted into β-hydroxy ketone 76 with Yb(OTf)₃ via pinacol-type rearrangement (Scheme 16).⁷⁶f
corresponding epoxy ketones 78 and 81 by Roberts and co-workers. The epoxy ketones were also elaborated to several pharmaceuticals, including Taxol side chain 86 (Scheme 19),64a diltiazem hydrochloride (91) (a potent blood-pressure-lowering agent) (Scheme 20),64a (+)-clausenamide (94) (an anti-anmaesic agent with potent hepatoprotective activity) (Scheme 21),66 and anti-inflammatory agents such as (S)-fenoprofen (97)67b,d and (S)-naproxen (100) (Scheme 22).67d

Imidazolium-attached polypeptides have also been investigated for epoxidation. In 2009, Tang, Yang, and co-workers reported that imidazolium-modified poly-L-leucines 101 were highly enantioselective catalysts for epoxidation, providing chalcone epoxides in up to 99% ee (Figure 31).72 A one-pot protocol consisting of Claisen−Schmidt condensation and asymmetric epoxidation with imidazolium-modified poly-L-leucine 101a was also reported by the same group.73 In 2012, Bhagat and co-workers showed that epoxidation of acyclic and cyclic enones could be achieved with imidazolium-based asparagine catalyst 102 using H2O2 as the oxidant in DMF, giving the epoxides in 80−90% ee (Figure 32).74

2.2.3. Polypeptide-Catalyzed Epoxidation under Homogeneous Conditions. Polypeptide catalysts soluble in organic solvents have also been investigated for epoxidation. In 2009, Tang, Yang, and co-workers reported that imidazolium-modified poly-L-leucine 101 were highly enantioselective catalysts for epoxidation, providing chalcone epoxides in up to 99% ee (Figure 31).72 A one-pot protocol consisting of Claisen−Schmidt condensation and asymmetric epoxidation with imidazolium-modified poly-L-leucine 101a was also reported by the same group.73 In 2012, Bhagat and co-workers showed that epoxidation of acyclic and cyclic enones could be achieved with imidazolium-based asparagine catalyst 102 using H2O2 as the oxidant in DMF, giving the epoxides in 80−90% ee (Figure 32).74

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aminoisobutyric acid (Aib) using urea−H₂O₂ and DBU in THF. The epoxide was obtained in 73% yield and 94% ee with catalyst 103 (Scheme 23). The Aib residue likely promoted formation of a helical structure as well as enhanced the solubility of the peptides in organic solvents. In 2001, Roberts and co-workers prepared diaminopoly(ethylene glycol)-bound poly-L-leucine catalysts 104a−d and examined the epoxidation of (E)-chalcone with these catalysts using urea−H₂O₂ and DBU in THF (Figure 33). Under the homogeneous conditions, the chalcone epoxide was obtained with 58−80% conversion and 95−98% ee. Polymer enlarged poly-L-leucine 104e gave higher conversion (>99%) for epoxidation of (E)-chalcone as reported by Tsogoeva and co-workers (Figure 33). They also showed that styrene/aminomethylstyrene-copolymer-linked poly-L-leucine 105 was a highly effective catalyst for epoxidation of (E)-chalcone (Figure 33). The epoxidation was carried out in a membrane reactor. After the epoxide and unreacted chalcone were passed through the nanofiltration membrane, the catalyst was retained on the membrane and reused for epoxidation.

2.2.4. Epoxidation with Peptides Containing Unnatural Amino Acids. Polypeptides containing unnatural amino acids have also been explored for epoxidation. In 2001, Roberts and co-workers showed that poly-β-leucine was a viable epoxidation catalyst, giving the chalcone epoxide in 92% conversion and 70% ee. In 2010, Tanaka and co-workers reported the epoxidation of enones with peptide catalysts containing cyclic α,α-disubstituted amino acids. A variety of enones, including alkyl-substituted enones, were efficiently epoxidized in 96−98% ee with catalyst 106 and urea−H₂O₂ in THF (Figure 34). Introduction of the cyclic α,α-disubstituted amino acid could stabilize the α-helical structure, which was thought to be important for asymmetric induction. Epoxidation with cyclic peptides 107, containing α-aminoisobutyric acid (a helical promoter), was reported by Demizu, Kurihara, and co-workers in 2011 (Figure 35). Catalyst 107b, with a longer side chain at the 3 and 7 positions, gave higher enantioselectivity than 107a for epoxidation of (E)-chalcone. Up to 99% ee was obtained for epoxy ketones with catalyst 107b and urea−H₂O₂. Kudo and Akagawa incorporated 3-(1-pyrenyl)alanine [Ala(1-Pyn)] into resin-supported polypeptide 108 (Figure 36). Various αβ-unsaturated aldehydes were epoxidized with catalyst 108 and H₂O₂, giving epoxy alcohols in up to 95% ee upon reduction with NaBH₄.

Scheme 23. Epoxidation of Chalcone with Soluble Peptide Catalyst

![Scheme 23](image-url)

Figure 33. Epoxidation of chalcone with soluble peptide catalysts.

Figure 34. Epoxidation of enones with peptide catalyst 106.
2.2.5. Mechanistic Insights. In their initial reports, Juliá and Colonna indicated that an α-helical structure of polypeptide catalysts might be important for asymmetric induction.\textsuperscript{57,59} They also suggested that the hydrogen bonding between the peptide and chalcone be involved for stereocontrol as a racemic epoxide was obtained when the epoxidation of chalcone was carried out in methanol, which likely disrupted the hydrogen bonding.\textsuperscript{49} The importance of α-helical structure on the enantioselectivity of the epoxidation has been further demonstrated by Ohkata,\textsuperscript{75,83} Berkessel,\textsuperscript{77} Kelly,\textsuperscript{80} Tanaka,\textsuperscript{81} and others. Studies indicated that the amino acid residues at the N-terminus of the peptide catalysts appeared to be responsible for the stereocchemistry and enantioselectivity of the epoxidation.\textsuperscript{76,84,85} Roberts and co-workers showed that high ee’s (91–92\%) were obtained for epoxidation of chalcone with catalysts 109 containing five or six L-Leu residues at the N-terminus (Scheme 24).\textsuperscript{85c} In their studies, Berkessel and co-workers demonstrated that the enantioselectivity reached the maximum (96–98\%) with a TentaGel S supported catalyst 110 containing only five L-Leu residues (Scheme 24).\textsuperscript{85c} These five residues allowed formation of one helical turn, which provided the basic structural unit required for high enantioselectivity. Molecular modeling studies suggested that chalcone be bound to the α-helix via hydrogen bonding between the carbonyl group and the NH groups of the catalyst. The stereochemical outcome of the epoxidation was proposed to be determined by the helical chirality.\textsuperscript{84a}

A reaction model was also proposed by Kelly and Roberts.\textsuperscript{86a} The α helix binds to H\textsubscript{2}O\textsubscript{2} and chalcone via hydrogen bonding with the N-terminal amide N–H groups. The helical conformation and hydrogen-bonding motif are likely determining factors for the stereocontrol of the epoxidation.\textsuperscript{86} Kelly, Roberts, and co-workers have shown that the conjugate addition of HOO\textsuperscript{•} to olefin, the first step in the epoxidation, is reversible.\textsuperscript{87} In their mechanistic studies, Colonna, Ottolina, and co-workers observed saturation kinetics for both chalcone and HOO\textsuperscript{•} in the epoxidation of chalcone with PEG-bound poly-L-leucine catalyst.\textsuperscript{58,45e} This is consistent with a steady-state random bireactant system, in which both chalcone and HOO\textsuperscript{•} must bind to the catalyst to form the PLL-HOO\textsuperscript{•}-chalcone complex before reaction occurs (Scheme 25).

### 2.3. Chiral Bifunctional Base-Catalyzed Epoxidation

#### 2.3.1. Chiral Guanidines

Various chiral bifunctional bases such as guanidines and amino alcohols have been developed for asymmetric epoxidation of electron-deficient olefins. Taylor and co-workers studied a number of chiral guanidines such as 111–115 (Figure 37) for epoxidation of quinone 124, and up to 60% ee was obtained with 114 and TBHP (Scheme 26).\textsuperscript{90} A series of 5-membered ring (116–120)\textsuperscript{91} and binaphthyl-based guanidines (121–123)\textsuperscript{92} were also investigated by the groups of Ishikawa and Terada, respectively (Figure 37). Up to 70% ee was obtained for epoxidation of (E)-chalcone (Figure 38).\textsuperscript{91b} It is likely that the guanidine acts as a base to deprotonate the oxidant, and the NH group forms the hydrogen bond with the enone and/or the oxidant during the reaction (Figure 39).\textsuperscript{91a}

#### 2.3.2. Chiral β-Amino Alcohols

A class of amino alcohols as outlined in Figure 40 has also been shown to be effective bifunctional catalysts for epoxidation of electron-deficient olefins.\textsuperscript{93} In 2005, Lattanzi reported that readily available α,α-diphenyl-β-prolinol (125a) could act as the catalyst for epoxidation of enones with TBHP, giving up to 80% ee for chalcones (Figure 41).\textsuperscript{94} The reaction mechanism was proposed as outlined in Scheme 27. In this reaction, the amino alcohol acted as a bifunctional catalyst. TBHP was deprotonated by the amine of the catalyst to form a tight ion pair. The hydroxyl group of the catalyst was thought to

![Scheme 24. Epoxidation of Chalcone with Catalyst 109 or 110](image)
coordinate with the enone via hydrogen bonding to activate the double bond and direct addition of the peroxide anion stereoselectively. This noncovalent activation mechanism through hydrogen-bonding interactions was also supported by DFT calculations. An alternative activation mode via formation of an iminium ion between the enone and the prolinol catalyst was believed to be less plausible. Lattanzi and co-workers subsequently showed that the reactivity and enantioselectivity could be further improved with substituted phenyl catalysts, and over 90% ee was obtained with 125b and 125c for some chalcones (Figures 40 and 41). Epoxidation of chalcones using dinaphthyl-L-prolinol catalyst 125e was also reported by Liu and co-workers, and up to 85% ee was obtained (Figures 40 and 41). Zhao, Zhu, and co-workers demonstrated that dendritic and fluffy diaryl-L-prolinol catalysts such as 125f and 125g were effective for epoxidation of enones and could be recycled with little loss of activity and enantioselectivity. In 2007, Zhao and co-workers also reported their studies on the epoxidation with 4-substituted α,α'-diarylprolinols such as 126 (Figure 40). A variety of substituted chalcones were epoxidized in 89–96% ee (Figure 41).
Besides prolinols, various other types of amino alcohols have also been examined. In their further studies, Lattanzi and co-workers showed that four- and six-membered ring catalysts were less effective than corresponding prolinol catalysts (Figures 40 and 41). Amino alcohol with azabicyclo[2.2.1]heptane skeleton was synthesized and investigated for epoxidation by Loh and co-workers (Figure 40). Up to 88% ee was obtained for α,β-unsaturated ketones (Figure 41). Epoxidation using acyclic amino alcohol catalysts such as 129 and 130 was reported by Liu, Zhang, Lattanzi, and co-workers (Figures 40 and 41). Up to 70% ee was obtained for epoxidation of chalcones.

Epoxidation with α,α-diarylprolinols has been extended to various other electron-deficient olefins. For example, Lattanzi and co-workers showed that 2-arylidene-1,3-diketones and trisubstituted acrylonitriles could be epoxidized with catalysts 125d and 125c, giving the corresponding epoxides in up to 85% ee (Figure 42). As shown by Zhao and co-workers, a variety of β,γ-unsaturated α-keto esters and α,β-unsaturated trichloromethyl and trifluoromethyl ketones were epoxidized using catalysts 125c and 126 in up to 99% ee (Figure 43). Chiral epoxide 132 was readily converted to (−)-norbalasubramide (135a) and (−)-balasubramide (135b) (Scheme 28). Gaspere and co-workers also extended the epoxidation to α-ylideneoxindoles using catalyst 125a to give the corresponding epoxides with up to 88% ee (Scheme 29).

2.3.3. Cinchona Alkaloid-Derived Thioureas. Cinchona alkaloids and their derivatives have also been investigated for asymmetric epoxidation. Recently, Lattanzi and co-workers reported that 1,1-dicarbonyl terminal olefins were enantioselectively epoxidized with cinchona thiourea catalyst 136 and TBHP to give terminal epoxides in up to 99% ee (Figure 44). The epoxide product contains a quaternary stereogenic center and can be opened by nucleophiles such as azide to form chiral alcohols (Scheme 30).

Figure 42. Epoxidation with diarylprolinol catalysts 125c and 125d.

Figure 43. Epoxidation with diarylprolinol catalysts 125c and 126.

Scheme 28. Synthesis of (−)-Norbalasubramide (135a) and (−)-Balasubramide (135b).

Scheme 29. Epoxidation of α-Ylideneoxindoles with Diarylprolinol Catalyst 125a.

Scheme 30. Transformation of the Terminal Epoxide.
2.4. Epoxidation via Iminium/Enamine Catalysis

2.4.1. Pyrrolidine-Based Catalysts. In contrast to \( \alpha,\beta \)-unsaturated ketones, little had been reported previously for asymmetric epoxidation of \( \alpha,\beta \)-unsaturated aldehydes. In 2005, Jørgensen and co-workers reported a highly enantioselective epoxidation process for \( \alpha,\beta \)-unsaturated aldehydes using diarylprolinol silyl ether catalyst 137 and \( \text{H}_2\text{O}_2 \), giving the corresponding epoxides in high yields with high dr values (≥90:10) and ee’s (up to 98% ee) (Figure 45).\(^1\) The authors also showed that the epoxidation could be carried out in a benign solvent such as \( \text{EtOH} - \text{H}_2\text{O} \) (3:1).\(^2\) A mechanistic proposal for the epoxidation is shown in Scheme 31. The chiral amine catalyst initially reacts with the \( \alpha,\beta \)-unsaturated aldehyde to generate an iminium salt intermediate to which \( \text{H}_2\text{O}_2 \) nucleophilically adds at the \( \beta \)-carbon to form an enamine intermediate. Upon ring closure and subsequent hydrolysis of the epoxy iminium ion, the chiral epoxide is formed with regeneration of the amine catalyst.\(^3\) In a subsequent computational study, Santos and co-workers indicated that besides being an oxidant, \( \text{H}_2\text{O}_2 \) could act as a cocatalyst to promote initial formation of the iminium ion intermediate, and a hydroxyl ion was likely involved in the epoxidation.

In 2006, Córdova and co-workers reported their studies on the epoxidation of \( \alpha,\beta \)-unsaturated aldehydes with a series of pyrrolidine-based catalysts such as 138–145 (Figure 46).

Various \( \alpha,\beta \)-unsaturated aldehydes were epoxidized using 144 as catalyst (10 mol %) and \( \text{H}_2\text{O}_2 \) or sodium percarbonate as oxidant with up to 98% ee (Figure 47).\(^4\) With a one-pot epoxidation/reduction/ring-opening sequence, 1,2,3-triols were synthesized from \( \alpha,\beta \)-unsaturated aldehydes in up to 98% ee (Figure 48).\(^5\) In 2012, Correia, Paixão, and co-workers demonstrated that a modified class of prolinol silyl ethers, such as 146, efficiently epoxidized \( \alpha,\beta \)-unsaturated aldehydes using \( \text{H}_2\text{O}_2 \) in \( \text{EtOH} - \text{H}_2\text{O} \) (3:1), giving the epoxy aldehydes in up to 99:1 dr and 99% ee (Figure 49).\(^6\) A tandem asymmetric epoxidation/Passerini reaction was also reported with catalyst 146 (Figure 50).\(^7\)\(^8\)

\( \alpha \)-Substituted acroleins could be epoxidized with diphenylprolinol silyl ether catalyst 147 and \( \text{H}_2\text{O}_2 \) to give the terminal epoxides in up to 94% ee as demonstrated in 2010 by Hayashi.

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Figure 45. Epoxidation of \( \alpha,\beta \)-unsaturated aldehydes with catalyst 137.

Scheme 31. Proposed Mechanism for Epoxidation of Enals with Pyrrolidine-Based Catalysts

Figure 46. Pyrrolidine-based chiral amine catalysts 138–145.

Figure 47. Epoxidation of \( \alpha,\beta \)-unsaturated aldehydes with catalysts 138–145.

Figure 48. One-pot synthesis of 1,2,3-triols via asymmetric epoxidation.
NaClO₂ and esterification with TMSCHN₂ as illustrated in the synthesis of (R)-methyl palmoxirate (a potent oral hypoglycemic and antiketogenic agent).  

A series of β-fluorinated pyrrolidines was investigated for epoxidation of enals by Gilmour and co-workers. Among them, (S)-2-(fluorodiphenylmethyl)pyrrolidine (150) was found to be a highly effective catalyst, giving epoxides with up to 98% ee (Figure 52).  

The higher ee obtained using 150, as compared to nonfluorinated catalyst 149, could be attributed to the fluorine--iminium ion gauche effect, which allowed the iminium ion (151) to adopt a conformation more favorable for asymmetric induction.

Asymmetric epoxidation of enals with diarylprolinol silyl ether catalysts has been applied to the synthesis of a number of building blocks, natural products, and bioactive molecules. In a series of studies, Jørgensen and co-workers developed various one-pot synthetic processes incorporating their epoxidation method and other transformations, providing access to a variety of synthetically useful molecules, such as isoxazoline-N-oxides (152), propargylic epoxides (153), acetal-protected trans-2,3-dihydroxyaldehydes (154), β-hydroxy esters (155), substituted furans (156), imidazo[1,2-a]pyridines (157), 1,3-azoles (158), 2,3-dihydrobenzofurans (159), and substituted thiophenes (160) (Scheme 32).

In the syntheses of (−)-aspinolide A (163) and (+)-stagonolide C (166) reported by Suryavanshi, Sudalai, and co-workers (Figure 51), the epoxy aldehyde was readily converted to the corresponding epoxy ester via oxidation with NaClO₂ and esterification with TMSCHN₂, as illustrated in the synthesis of (R)-methyl palmoxirate (a potent oral hypoglycemic and antiketogenic agent).  

A series of β-fluorinated pyrrolidines was investigated for epoxidation of enals by Gilmour and co-workers. Among them, (S)-2-(fluorodiphenylmethyl)pyrrolidine (150) was found to be a highly effective catalyst, giving epoxides with up to 98% ee (Figure 52).  

The higher ee obtained using 150, as compared to nonfluorinated catalyst 149, could be attributed to the fluorine--iminium ion gauche effect, which allowed the iminium ion (151) to adopt a conformation more favorable for asymmetric induction.
workers, epoxy alcohols 162 and 165 were obtained in 99% ee from the corresponding enals via epoxidation with catalyst 137 and subsequent reduction with NaBH₄ (Scheme 33). Carreira and co-workers employed catalyst 144 for epoxidation of enal 184 in the synthesis of epoxyisoprostanes such as EC (187) and PECPC (188) (Scheme 37). Epoxy aldehyde 185 was converted to EC by aldol condensation with cyclopentenone 186 and subsequent enzymatic hydrolysis. PECPC was obtained by the coupling of EC with lyso-PC under Yamaguchi’s conditions. Xuan, Yan, and co-workers reported a one-pot epoxidation of trans-cinnamaldehydes with catalyst 189 and oxidative esterification with NBS in CH₃OH, giving α,β-epoxy esters in 54−73% yield and 93−99% ee (Scheme 38). Epoxide 190 was utilized to synthesize (−)-clausenamide (ent-94) (Scheme 38).

### 2.4.2. Chiral Amine Salt Catalysts.

Various chiral amine salt catalysts were investigated for epoxidation of α,β-unsaturated aldehydes and ketones. In 2006, MacMillan and co-workers reported that a variety of enals were effectively epoxidized with imidazolidinone salt catalyst 194 in the presence of iminoiodinane PhI═NNs and AcOH, giving the corresponding epoxides in 72−95% yield and 85−97% ee (Figure 53). The epoxidation was proposed to proceed via an iminium/enamine pathway as shown in Scheme 39. The choice of oxidant was found to be very important for the reaction efficiency and enantioselectivity, and PhI═NNs gave the best results overall. Studies showed that PhI═O was slowly released in situ from PhI═NNs under mild acidic conditions and acted as the actual oxidant (Scheme 39).

In 2008, List and co-workers reported a counteranion-directed asymmetric epoxidation of enals with amine salts bearing chiral phosphates as catalysts. Among various catalysts examined, amine salt 198 gave the best results for the epoxidation. With this catalyst, a variety of 1,2-disubstituted bacilosarins A (176) and B (177). This epoxidation/olefination/cyclization sequence was also employed in their total syntheses of jaspines A and B (Scheme 36).

In their total synthesis of hirsutellone B (171), Nicolaou and co-workers reported that epoxy ester 168 could be synthesized from aldehyde 167 in 58% overall yield over three steps using 144 as the epoxidation catalyst. Epoxy ester 168 was subsequently transformed into hirsutellone B (171) (Scheme 34). Kuwahara and co-workers showed that epoxide 173 was readily converted to lactone 175 via olefination and cyclization (Scheme 35). Lactone 175 was further elaborated to bacilosarins A (176) and B (177). This epoxidation/olefination/cyclization sequence was also employed in their total syntheses of jaspines A and B (Scheme 36).

**Scheme 33. Syntheses of (−)-Aspinolide A (163) and (+)-Stagonolide C (166)**

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\text{Scheme 33. Syntheses of (−)-Aspinolide A (163) and (+)-Stagonolide C (166)}
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**Scheme 34. Synthesis of Hirsutellone B (171)**

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\[
\text{Scheme 34. Synthesis of Hirsutellone B (171)}
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**Scheme 35. Syntheses of Bacilosarins A (176) and B (177)**

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\text{Scheme 35. Syntheses of Bacilosarins A (176) and B (177)}
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**Scheme 36. Syntheses of Jaspines B (182) and A (183)**

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\text{Scheme 36. Syntheses of Jaspines B (182) and A (183)}
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**Scheme 37. Synthesis of Epoxyisoprostanes**

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\text{Scheme 37. Synthesis of Epoxyisoprostanes}
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**Scheme 38. Synthesis of (−)-Clausenamide (ent-94)**

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\[
\text{Scheme 38. Synthesis of (−)-Clausenamide (ent-94)}
\]"
and β,β-disubstituted enals were efficiently epoxidized in 60–95% yield and up to 96% ee using TBHP as oxidant (Figure 54). In this case, asymmetric induction was controlled by the chiral phosphate counteranion (Scheme 40). In their further studies, List and co-workers demonstrated that asymmetric epoxidation of α-branched enals could also be achieved with a catalyst consisting of a quinine-derived amine and a chiral phosphoric acid such as 199a and 199b, giving the epoxides in up to 98% ee with H₂O₂ (Figure 55). In 2010, Luo, Cheng, and co-workers reported that asymmetric epoxidation of α-substituted acroleins could be realized with simple chiral primary−tertiary diamine-based amine salt catalysts bearing achiral counteranions such as 200, giving epoxy alcohols in up to 88% ee upon reduction with NaBH₄ (Figure 56). Cyclic enones had been challenging substrates for previously reported asymmetric epoxidation methods. In 2008, List and co-workers reported that a variety of cyclic enones were
efficiently epoxidized using catalysts containing a chiral diamine and a chiral or achiral acid, such as 201–203, giving the epoxy ketones in up to 99% ee (Figure 57).128,126b The primary amine of the catalyst activates the enone by formation of an iminium ion and the tertiary amine acts as a general base to promote the conjugate addition of H₂O₂ to the iminium ion (Scheme 41).128,126b,129

![Scheme 41. Catalytic Pathway for the Amine Salt-Catalyzed Epoxidation of Cyclic Enones](image)

In 2008, Deng and co-workers reported that epoxy ketones were predominantly formed in up to 97% ee when acyclic aliphatic enones reacted with cumene hydroperoxide in the presence of chiral amine salt catalyst 202 at 23–55 °C (Figure 58).130 However, β-peroxy ketones were obtained as major products in high ee’s when the reaction was carried out with catalyst 204 at lower temperature (0–23 °C) (Figure 58).130 In their studies, List and co-workers found that cyclic peroxymethylketals could be obtained in up to 95% ee from acyclic aliphatic enones with catalyst 205 and H₂O₂ (Figure 59).131,126b Epoxy ketones could also be obtained in 55–90% yield and 90–99% ee via a one-pot process involving reacting enones with H₂O₂ in the presence of catalyst 202 and basic work up with 1 N NaOH (Figure 59).131,126b

Zhang and co-workers investigated the structural effect of the catalyst on the epoxidation of chalcones. With amine salt catalyst 206, epoxy ketones were obtained in up to 84% ee using TBHP (Figure 60).132 In 2011, Zhao, Zou, and co-workers demonstrated that primary−secondary diamine salts were effective catalysts for epoxidation of enones, providing epoxides in 68–87% yield and up to 99% ee with amine salt 207 in the presence of cumene hydroperoxide (Figure 61).133 Presumably, the primary amine moiety activates the enone, and the secondary amine activates the oxidant (Figure 61).

In 2010, Jørgensen and co-workers reported that optically active allylic alcohols could be synthesized from enones via a one-pot epoxidation/Wharton reaction sequence.134 With amine salt catalyst 202 and H₂O₂, various enones were transformed into allylic alcohols in 87–99% ee (Figure 62). In 2011, Tu, Cao, and co-workers demonstrated that spirocycloalkanediones could be synthesized in 93–99% ee from the corresponding cyclic enones by a one-pot epoxidation/semipinacol rearrangement process with amine salt 202 as catalyst and H₂O₂ as oxidant for the epoxidation (Figure 63).135

2.5. Chiral Ketone-Catalyzed Epoxidation

2.5.1. Methodology Development. Dioxiranes are highly effective species for epoxidation of olefins. A chiral dioxirane can be generated in situ from a chiral ketone and an oxidant...
such as oxone (2KHSO₅·KHSO₄·K₂SO₄) or H₂O₂ and can be converted back to the ketone upon epoxidation of an olefin to complete a catalytic cycle (Scheme 42). Significant progress has been made for the ketone-catalyzed asymmetric epoxidation. A variety of structurally diverse ketone catalysts have been investigated and reported by a number of laboratories. A wide range of olefins, particularly unfunctionalized trans-olefins and trisubstituted olefins, have been effectively epoxidized with high enantioselectivity.¹³⁶

In 1984, Curci and co-workers reported the asymmetric epoxidation of olefins with chiral ketones 215 and 216 (Figure 64), with electron-withdrawing trifluoromethyl groups, were shown to be much more active toward epoxidation than 215 and 216. Epoxidation with 218 gave 18% and 20% ee for trans-β-methylstyrene and trans-2-octene, respectively.¹³⁷b Marples and co-workers investigated the epoxidation with α-fluorinated 1-tetralones 219 and 1-indanone 220.¹³⁸ These ketones were found to be active for the epoxidation, although no ee’s were observed for the resulting epoxides.

In 1996, Yang and co-workers reported a number of elegant binaphthyl-based C₂-symmetric ketones 221 for epoxidation of olefins (Figure 65).¹³⁹ The substituents at the 3 and 3’ positions were found to be important for the enantioselectivity. Replacing hydrogens with substituents such as Cl, Br, or an acetal led to higher enantioselectivities (Table 3, entries 1−4). Para-substituted trans-stilbenes were among the most effective substrates. The enantioselectivity generally increased with the size of the substituent on the stilbene.¹³⁹ For example, 91% and 95% ee were achieved for trans-4,4'-diethyl- and trans-4,4'-diter-buty1stilbene, respectively, with 10 mol % ketone 221d.¹³⁹b,c Biphenyl-based catalyst 222 provided moderate selectivity for epoxidation of trans-olefins and trisubstituted olefins (Table 3, entry 5).¹³⁹ Epoxidation of cinnamates with ketones 221 was extensively investigated by Seki and co-workers. Epoxide 236, a key intermediate for diltiazem hydrochloride (91), was obtained in up to 85% ee with catalyst 221b (Scheme 43).¹⁴⁰ Epoxidation with C₂-symmetric ether-linked ketones 223 and 224 was reported by Song and co-
workers in 1997.\textsuperscript{141} Up to 59% ee was obtained for trans-stilbene using ketone 224 (Table 3, entry 8). In their studies, Adam and co-workers showed that up to 81% ee was obtained for epoxidation of trans-olefins and trisubstituted olefins with mannitol-derived ketone 225 and tartaric acid-derived ketone 226 (Table 3, entries 9 and 10).\textsuperscript{142}

In 1999 and 2002, Denmark and co-workers reported a series of ammonium ketones such as 237–242 (Figure 66) for epoxidation (Table 4).\textsuperscript{136a,143,146,147} The electron-withdrawing ammonium ion inductively activates the ketone and functions as a phase-transfer mediator to facilitate the biphasic reaction. Up to 58% ee was obtained for epoxidation of trans-β-methylstyrene with ammonium ketones 237–242 (Table 4, entry 13).\textsuperscript{144} A number of 1,2-diamine- and 1,2-aminoalcohol-based ketone catalysts were investigated for epoxidation by Tomioka and co-workers.\textsuperscript{145} Up to 82% ee was achieved for epoxidation of 1-phenylcyclohexene with ketones 233 and 234 (Table 3, entries 18 and 19).\textsuperscript{145c}

In their studies, Behar and co-workers reported that up to 86% ee was obtained for epoxidation of trans-β-methylstyrene with binaphthyl-based α-fluorinated ketone 229 (Table 3, entry 13).\textsuperscript{144} A number of 1,2-diamine- and 1,2-aminoalcohol-based ketone catalysts were investigated for epoxidation by Tomioka and co-workers.\textsuperscript{145} Up to 82% ee was obtained for epoxidation of 1-phenylcyclohexene with ketones 233 and 234 (Table 3, entries 18 and 19).\textsuperscript{145c}

**Table 3. Epoxidation of Representative Olefins with C\textsubscript{2}-Symmetric Ketone Catalysts**

<table>
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<th>entry</th>
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<th>R\textsubscript{1} (\text{R}_{2})</th>
<th>solvent</th>
<th>R\textsubscript{1} (\text{R}_{2})</th>
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<td>50% ee</td>
<td>Ph - Ph</td>
<td>Ph - Ph</td>
<td>139a,c</td>
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<tr>
<td>2</td>
<td>221b</td>
<td>76% ee</td>
<td>76% ee</td>
<td>Ph - Ph</td>
<td>Ph - Me</td>
<td>139b,c</td>
</tr>
<tr>
<td>3</td>
<td>221c</td>
<td>75% ee</td>
<td>81% ee</td>
<td>Ph - Ph</td>
<td>Ph - Ph</td>
<td>139b,c</td>
</tr>
<tr>
<td>4</td>
<td>221d</td>
<td>71% ee</td>
<td>73% ee</td>
<td>Ph - Ph</td>
<td>Ph - Me</td>
<td>139b,c</td>
</tr>
<tr>
<td>5</td>
<td>222</td>
<td>50% ee</td>
<td>49% ee</td>
<td>Ph - Ph</td>
<td>Ph - Ph</td>
<td>139c</td>
</tr>
<tr>
<td>6</td>
<td>223a</td>
<td>26% ee</td>
<td>29% ee</td>
<td>Ph - Ph</td>
<td>Ph - Me</td>
<td>141a,b</td>
</tr>
<tr>
<td>7</td>
<td>223b</td>
<td>24% ee</td>
<td>-</td>
<td>Ph - Ph</td>
<td>Ph - Me</td>
<td>141b</td>
</tr>
<tr>
<td>8</td>
<td>224</td>
<td>59% ee</td>
<td>20% ee</td>
<td>Ph - Ph</td>
<td>Ph - Ph</td>
<td>141a</td>
</tr>
<tr>
<td>9</td>
<td>225</td>
<td>38.9% ee</td>
<td>-</td>
<td>Ph - Ph</td>
<td>Ph - Ph</td>
<td>142</td>
</tr>
<tr>
<td>10</td>
<td>226</td>
<td>64.8% ee</td>
<td>81% ee</td>
<td>Ph - Ph</td>
<td>Ph - Ph</td>
<td>142</td>
</tr>
<tr>
<td>11</td>
<td>227</td>
<td>94% ee</td>
<td>88% ee</td>
<td>Ph - Ph</td>
<td>Ph - Ph</td>
<td>143</td>
</tr>
<tr>
<td>12</td>
<td>228</td>
<td>-</td>
<td>85% ee</td>
<td>Ph - Ph</td>
<td>Ph - Ph</td>
<td>143</td>
</tr>
<tr>
<td>13</td>
<td>229</td>
<td>-</td>
<td>86% ee</td>
<td>Ph - Ph</td>
<td>Ph - Ph</td>
<td>144</td>
</tr>
<tr>
<td>14</td>
<td>230</td>
<td>-</td>
<td>83% ee</td>
<td>Ph - Ph</td>
<td>Ph - Ph</td>
<td>144</td>
</tr>
<tr>
<td>15</td>
<td>231a</td>
<td>30% ee</td>
<td>-</td>
<td>Ph - Ph</td>
<td>Ph - Ph</td>
<td>145a,b</td>
</tr>
<tr>
<td>16</td>
<td>231b</td>
<td>26% ee</td>
<td>-</td>
<td>Ph - Ph</td>
<td>Ph - Ph</td>
<td>145a</td>
</tr>
<tr>
<td>17</td>
<td>232</td>
<td>18% ee</td>
<td>-</td>
<td>Ph - Ph</td>
<td>Ph - Ph</td>
<td>145b</td>
</tr>
<tr>
<td>18</td>
<td>233</td>
<td>64% ee</td>
<td>62% ee</td>
<td>Ph - Ph</td>
<td>Ph - Ph</td>
<td>145c</td>
</tr>
<tr>
<td>19</td>
<td>234</td>
<td>57% ee</td>
<td>57% ee</td>
<td>Ph - Ph</td>
<td>Ph - Ph</td>
<td>145c</td>
</tr>
</tbody>
</table>

**Table 4. Epoxidation of Representative Olefins with Ammonium Ketone Catalysts**

<table>
<thead>
<tr>
<th>entry</th>
<th>catalyst</th>
<th>R\textsubscript{1} (\text{R}_{2})</th>
<th>R\textsubscript{1} (\text{R}_{2})</th>
<th>solvent</th>
<th>R\textsubscript{1} (\text{R}_{2})</th>
<th>ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>237</td>
<td>58% ee</td>
<td>35% ee</td>
<td>7% ee</td>
<td>Ph - Ph</td>
<td>143,147</td>
</tr>
<tr>
<td>2</td>
<td>238</td>
<td>-</td>
<td>34% ee</td>
<td>58% ee</td>
<td>Ph - Ph</td>
<td>136a</td>
</tr>
<tr>
<td>3</td>
<td>239</td>
<td>-</td>
<td>9% ee</td>
<td>-</td>
<td>Ph - Ph</td>
<td>136a</td>
</tr>
<tr>
<td>4</td>
<td>240</td>
<td>-</td>
<td>40% ee</td>
<td>-</td>
<td>Ph - Ph</td>
<td>136a</td>
</tr>
<tr>
<td>5</td>
<td>241</td>
<td>-</td>
<td>10% ee</td>
<td>-</td>
<td>Ph - Ph</td>
<td>136a</td>
</tr>
<tr>
<td>6</td>
<td>242</td>
<td>-</td>
<td>8% ee</td>
<td>-</td>
<td>Ph - Ph</td>
<td>136a</td>
</tr>
</tbody>
</table>

**Figure 65.** Selected examples of C\textsubscript{2}-symmetric and related ketones.

**Figure 66.** Selected examples of ammonium ketones.
ee was obtained for trans-stilbene using 10 mol % α-fluorinated tropinone-based ketone 237 (Table 4, entry 1). In 1998, Armstrong and co-workers reported that α-fluorinated tropinone-based ketone 243a was an effective catalyst for epoxidation, giving 100% conversion and 83% ee for phenylstilbene with 10 mol % 243a (Figure 67) (Table 5, entry 1).

In 1998, Armstrong and co-workers reported that α-fluorinated tropinone-based ketone 243a was an effective catalyst for epoxidation, giving 100% conversion and 83% ee for phenylstilbene with 10 mol % 243a (Figure 67) (Table 5, entry 1).143,147

Various bicyclo[3.2.1]octan-3-ones and related ketones were subsequently investigated by Armstrong and co-workers.149,150 Ketone 246b was found to be the most enantioselective catalyst, giving 85% conversion and 93% ee max for stilbene, 71% conversion and 91% ee max for phenylstilbene, and 89% conversion and 98% ee max for 1-phenylcyclohexene with 20 mol % catalyst loading (Table 5, entry 8). In their studies, Klein and Roberts showed that 68% ee was achieved for stilbene with α-fluorinated 2,4-dimethyl-8-oxabicyclo[3.2.1]octan-3-one 250 (Table 5, entry 13).151

A variety of six-membered carbocyclic ketones have been investigated for epoxidation. In 1997 and 1999, Shi and co-workers reported a class of quinic acid-derived pseudo-C2-symmetric ketones with two fused ketals such as 251 (Figure 68), which displayed good reactivity and high selectivity for trans-olefins and trisubstituted olefins.152 trans-Stilbene was epoxidized in 91% yield and 96% ee with 10 mol % 251b (Table 6, entry 2).152b Electron-deficient chalcone was also found to be an effective substrate, giving the epoxy ketone in 85% yield and 96% ee.152b Ketone 252, with one ketal away from the α position of the carbonyl, displayed significantly lower reactivity and enantioselectivity as compared to 251, showing that having the chiral control moiety close to the

Figure 67. Selected examples of bicyclo[3.2.1]octan-3-ones and related ketones.

Table 5. Epoxidation of Representative Olefins with Ketone Catalysts 243–250a

<table>
<thead>
<tr>
<th>entry</th>
<th>catalyst</th>
<th>product ee</th>
<th>ketone ee</th>
<th>ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>243a</td>
<td>76% ee</td>
<td>83% ee</td>
<td>148a,b</td>
</tr>
<tr>
<td>2</td>
<td>243b</td>
<td>54% ee</td>
<td>-</td>
<td>148b,149a</td>
</tr>
<tr>
<td>3</td>
<td>243c</td>
<td>86% ee max</td>
<td>-</td>
<td>148b,149a</td>
</tr>
<tr>
<td>4</td>
<td>244a</td>
<td>91.3% ee</td>
<td>73.5% ee</td>
<td>150c</td>
</tr>
<tr>
<td>5</td>
<td>244b</td>
<td>87% ee</td>
<td>-</td>
<td>150c</td>
</tr>
<tr>
<td>6</td>
<td>245</td>
<td>87% ee</td>
<td>-</td>
<td>150c</td>
</tr>
<tr>
<td>7</td>
<td>246a</td>
<td>83% ee max</td>
<td>70% ee max</td>
<td>149a</td>
</tr>
<tr>
<td>8</td>
<td>246b</td>
<td>93% ee max</td>
<td>98% ee max</td>
<td>149a,b</td>
</tr>
<tr>
<td>9</td>
<td>247</td>
<td>64% ee</td>
<td>-</td>
<td>150b</td>
</tr>
<tr>
<td>10</td>
<td>248</td>
<td>77% ee</td>
<td>-</td>
<td>150b</td>
</tr>
<tr>
<td>11</td>
<td>249a</td>
<td>83% ee</td>
<td>82% ee</td>
<td>150a</td>
</tr>
<tr>
<td>12</td>
<td>249b</td>
<td>81% ee</td>
<td>-</td>
<td>150a</td>
</tr>
<tr>
<td>13</td>
<td>250</td>
<td>68% ee</td>
<td>34% ee</td>
<td>151</td>
</tr>
</tbody>
</table>

*aee max = (100 × product ee/ketone ee).*

Figure 68. Selected examples of six-membered carbocyclic ketones.

Table 6. Epoxidation of Representative Olefins with Carbocyclic Ketone Catalysts

<table>
<thead>
<tr>
<th>entry</th>
<th>catalyst</th>
<th>product ee</th>
<th>ketone ee</th>
<th>ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>251a</td>
<td>90% ee</td>
<td>75% ee</td>
<td>152a,b</td>
</tr>
<tr>
<td>2</td>
<td>251b</td>
<td>96% ee</td>
<td>80% ee</td>
<td>152b</td>
</tr>
<tr>
<td>3</td>
<td>252</td>
<td>85% ee</td>
<td>46% ee</td>
<td>154</td>
</tr>
<tr>
<td>4</td>
<td>253a</td>
<td>87.4% ee</td>
<td>-</td>
<td>155</td>
</tr>
<tr>
<td>5</td>
<td>253b</td>
<td>85.4% ee</td>
<td>-</td>
<td>155</td>
</tr>
<tr>
<td>6</td>
<td>253c</td>
<td>80.9% ee</td>
<td>-</td>
<td>155</td>
</tr>
<tr>
<td>7</td>
<td>253d</td>
<td>73.8% ee</td>
<td>-</td>
<td>155</td>
</tr>
<tr>
<td>8</td>
<td>253e</td>
<td>42.0% ee</td>
<td>-</td>
<td>155</td>
</tr>
<tr>
<td>9</td>
<td>255</td>
<td>90% ee</td>
<td>62% ee</td>
<td>156c,f</td>
</tr>
<tr>
<td>10</td>
<td>256</td>
<td>88% ee</td>
<td>-</td>
<td>156c,g</td>
</tr>
<tr>
<td>11</td>
<td>257</td>
<td>86% ee</td>
<td>-</td>
<td>156g</td>
</tr>
<tr>
<td>12</td>
<td>258</td>
<td>86% ee</td>
<td>70% ee</td>
<td>156d</td>
</tr>
<tr>
<td>13</td>
<td>260</td>
<td>43% ee</td>
<td>50% ee</td>
<td>157c</td>
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<tr>
<td>14</td>
<td>261</td>
<td>80% ee</td>
<td>70% ee</td>
<td>157d</td>
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<tr>
<td>15</td>
<td>262</td>
<td>90% ee</td>
<td>70% ee</td>
<td>157d</td>
</tr>
<tr>
<td>16</td>
<td>263</td>
<td>98% ee</td>
<td>66% ee</td>
<td>157d</td>
</tr>
</tbody>
</table>
reacting carbonyl was beneficial for asymmetric induction.\textsuperscript{153}
Zhao and co-workers also reported their studies on the epoxidation with ketone 252 and obtained 85\% ee for stilbene (Table 6, entry 3).\textsuperscript{154}

In 1998, Yang and co-workers reported the epoxidation of various substituted stilbenes with \(\alpha\)-chlorinated cyclohexanones 253 (Figure 68).\textsuperscript{155} The enantioselectivity was found to be significantly influenced by the remote substituent likely due to the electrostatic interaction between the polar C–X bond and the phenyl group of the substrate (Table 6, entries 4–8).\textsuperscript{155} The enantioselectivity also varied (71.5–88.9\% ee) with the substituents on the phenyl groups when various meta- and para-substituted stilbenes were epoxidized with ketone 253b, which could be attributed to the n–π electronic repulsion effect between the Cl atom of the ketone and the phenyl group of the substrate.\textsuperscript{155}

In 2000, Solladié-Cavallo and co-workers reported the epoxidation of \(p\)-methoxyxynamates with \(\alpha\)-halogenated trisubstituted cyclohexanones (Figure 68). Methyl \(p\)-methoxyxynamate was epoxidized in 99\% conversion and 40\% ee with 30 mol \% \(\alpha\)-fluoro ketone 254.\textsuperscript{156d} A series of \(\alpha\)-fluoro ketones including 255–258 was further investigated for epoxidation of olefins (Table 6, entries 9–12),\textsuperscript{156d–f} giving up to 90\% ee for stilbene using ketone 255 (Table 6, entry 9).

In 2001, Bortolini, Fogagnolo, and co-workers reported that up to 75\% ee could be obtained for epoxidation of \(p\)-methylcinnamic acid with ketone 259 (Figure 68).\textsuperscript{157a} Various keto bile acids and their derivatives were subsequently investigated for epoxidation of olefins.\textsuperscript{157b–d} \(p\)-Methylcinnamic acid epoxide was obtained in 94\% yield and 95\% ee with 1 equiv of 260.\textsuperscript{157a} Up to 98\% ee was achieved for stilbene with ketone 263 (Table 6, entry 16).\textsuperscript{157d}

Noncyclic chiral ketones have also been studied for epoxidation (Figure 69). In 1999, Armstrong and co-workers reported that up to 34\% ee was obtained for epoxidation of 1-phenylcyclohexene with ketone 264 (Table 7, entry 1).\textsuperscript{158} Miller and co-workers prepared a class of peptide-embedded trifluoromethyl ketones such as 265 for epoxidation of olefins.

1-Phenylcyclohexene was epoxidized in 88\% yield and 81\% ee with 10 mol \% ketone 265 (Table 7, entry 2).\textsuperscript{159} In 2003, Wong and co-workers reported the epoxidation with cyclo-dextrin-modified ketone catalyst 266 (Table 7, entry 3).\textsuperscript{160} With this ketone, 4-chlorostyrene could be epoxidized in 40\% ee.\textsuperscript{160} Acetone-bridged cyclohexidines such as 267 (Figure 69) were also synthesized and examined for epoxidation by Blos and co-workers.\textsuperscript{161}

In 1996, Shi and co-workers reported the discovery of fructose-derived ketone 268 (Figure 70) as a very effective chiral inducer for epoxidation of \(trans\)-olefins and trisubstituted olefins.\textsuperscript{162} The ketone was readily prepared from \(d\)-fructose by ketalization and oxidation in two steps.\textsuperscript{163,164} Its enantiomer was easily prepared from l-fructose, which was made from l-sorbose.\textsuperscript{165,166} It was found that the reaction pH had a dramatic effect on the efficiency of the epoxidation, with pH >10 being optimal.\textsuperscript{166,163} The epoxidation process with ketone 268 (typically 10–30 mol \%) has been extended to a wide range of olefins, including aromatic and aliphatic \(trans\)-olefins and trisubstituted olefins,\textsuperscript{166} hydroxyalkenes,\textsuperscript{167} conjugated dienes,\textsuperscript{168} enynes,\textsuperscript{169} silyl enol ethers and enol esters,\textsuperscript{170,171} vinylsilanes,\textsuperscript{172} and fluoroolefins\textsuperscript{173} (Figure 70). The stereochemical outcome of the epoxidation with ketone 268 has been highly predictable. The reaction proceeds mainly via spiro transition state A, with major competition from planar B (Figure 71). This transition state model was further validated and elucidated in the studies on kinetic resolution of substituted cyclohexenes and desymmetrization of substituted 1,4-cyclohexadienes.\textsuperscript{174} Further studies showed that the epoxidation also proceeded efficiently with \(H_2O_2\) as oxidant in the presence of a nitrile such as \(CH_3CN\) (Scheme 44), providing the enantioselectivity comparable to that of using oxone.\textsuperscript{175,176} The peroxyimidic acid resulting from \(H_2O_2\) and \(CH_3CN\) is likely to be the actual oxidant, which reacts with the ketone to generate the dioxirane.

A series of ketones such as 269–274 (Figure 72) was synthesized to investigate the structural requirements of the ketone catalysts for epoxidation.\textsuperscript{153,177,178} Studies showed that the dimethyl spiro five-membered ring and the pyranose oxygen of ketone 268 were important for the reactivity and enantioselectivity of the epoxidation (Table 8).

Replacement of the fused ketal in 268 with a more electron-withdrawing oxazolidinone led to a more robust ketone 275. A variety of olefins were epoxidized in good yields and high ee’s with 1–5 mol \% ketone 275 (Figure 73).\textsuperscript{179} Epoxidation of electron-deficient \(\alpha\beta\)-unsaturated esters was achieved in high ee’s with diacetate ketone 276 (Figure 74). High enantioselectivities were also obtained with this ketone for various \(trans\)-olefins and trisubstituted olefins including less reactive enimide as well as some \textit{cis}-olefins (Figure 74).\textsuperscript{180,173,181}

In addition to \textit{trans}-olefins and trisubstituted olefins, investigations have also been carried out to develop effective ketone catalysts for other types of olefins. During such studies, glucose-derived oxazolidinone ketone 277a (Figure 75) was found to be highly enantioselective for epoxidation of \textit{cis}-olefins.\textsuperscript{182} To further understand the ketone’s structural effect on the epoxidation and develop more practical catalysts, readily prepared \textit{N}-aryl-substituted oxazolidinone ketones such as 277b and 277c (Figure 75) were designed and found to be effective catalysts for the epoxidation.\textsuperscript{183} Epoxidation with ketone 277 can be extended to a wide variety of olefins, including aromatic \textit{cis}-olefins,\textsuperscript{184,182a,b,183a} conjugated \textit{cis}-dienes,\textsuperscript{185} \textit{cis}-enynes,\textsuperscript{186,182a,b} nonconjugated \textit{cis}-olefins.\textsuperscript{187}

| Table 7. Epoxidation of Representative Olefins with Ketone Catalysts 264–266 |
|-----------------|-----------------|-----------------|
| entry | \(R_1\) | \(R_2\) | \(R_3\) | \(R_4\) | \(R_5\) |
| 1 | 264 | 25\% ee | - | - | - |
| 2 | 265 | 42\% ee | - | - | - |
| 3 | 266 | 36\% ee | 26\% ee | - | - |
styrenes, trans-olefins and trisubstituted olefins, as well as tetrasubstituted benzyldicyclobutanes and benzyldicyclopropanes (Figure 75). Epoxidation proceeds in a stereospecific manner. In the case of acyclic cis-olefins, cis-epoxides were exclusively obtained with no isomerization observed during the reaction. For conjugated cis-dienes, the epoxidation generally occurred regioselectively at the cis C=C bond. When nonconjugated cis-dec-4-enoic acid (278) was subjected to the epoxidation conditions, lactone 279 was obtained in 75% yield and 91% ee (Scheme 45). The epoxides obtained from benzyldicyclobutanes can be stereoselectively rearranged to optically active 2-aryl cyclopentanones (Scheme 46). It has also been shown that epoxidation with ketone 277 can be carried out using H₂O₂ as the primary oxidant. Epoxidation of conjugated cis-olefins and terminal olefins with ketones 277 proceeds mainly via spiro transition state C,
with the R_σ substituent of the olefin being in proximity to the oxazolidinone of the ketone catalyst due to the attractive interactions between the two groups (Figure 76). 182a,b,183a,184--188,190,173 van der Waals forces and/or hydrophobic interactions could also have significant influences on the enantioselectivity of the epoxidation. 184b,185--187 In some cases such as nonconjugated cis-dec-4-enoic acid (Scheme 45), the hydrophobic interaction plays a crucial role in stereo-differentiation. 187

Table 8. Epoxidation of Representative Olefins with Ketone Catalysts 268–274

<table>
<thead>
<tr>
<th>entry</th>
<th>catalyst</th>
<th>R&lt;sup&gt;1&lt;/sup&gt;</th>
<th>R&lt;sup&gt;2&lt;/sup&gt;</th>
<th>R&lt;sup&gt;3&lt;/sup&gt;</th>
<th>R&lt;sup&gt;1&lt;/sup&gt;</th>
<th>R&lt;sup&gt;2&lt;/sup&gt;</th>
<th>R&lt;sup&gt;3&lt;/sup&gt;</th>
<th>ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>268</td>
<td>85%* (98% ee)</td>
<td>94%* (95% ee)</td>
<td>94%* (98% ee)</td>
<td>163</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>269</td>
<td>16% (96% ee)</td>
<td>32% (86% ee)</td>
<td>- (82% ee)</td>
<td>177</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>270</td>
<td>76% (96% ee)</td>
<td>100% (97% ee)</td>
<td>178</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>271</td>
<td>91% (76% ee)</td>
<td>96% (38% ee)</td>
<td>178</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>272a</td>
<td>66% (73% ee)</td>
<td>45% (-18% ee)</td>
<td>178</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>272b</td>
<td>76% (83% ee)</td>
<td>89% (88% ee)</td>
<td>178</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>273</td>
<td>34% (90% ee)</td>
<td>44% (61% ee)</td>
<td>177</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>274</td>
<td>10% (88% ee)</td>
<td>61% (87% ee)</td>
<td>153</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Isolated yield.

Figure 73. Asymmetric epoxidation of olefins with ketone 275.

Figure 74. Epoxidation of olefins with ketone 276.

Figure 75. Epoxidation of various olefins with ketones 277.

Scheme 45. Synthesis of Lactone 279 via Epoxidation and Intramolecular Cyclization

Scheme 46. Synthesis of 2-Aryl Cyclopentanones via Epoxidation and Rearrangement
In subsequent studies, morpholinone-containing ketone 283a was found to be a promising catalyst for epoxidation of challenging 1,1-disubstituted terminal olefins, giving up to 88% ee for α-substituted styrenes (Figure 77). Epoxidation with 283a for this class of olefins likely proceeds mainly via planar transition state E as a result of the attractive interaction between the phenyl group of the substrate and the morpholinone of the catalyst (Figure 77). Ketone 283b, bearing two methyl groups on the morpholinone moiety, was designed to incorporate the steric features of ketone 268 (Figure 70) and the electronic properties of 283a into one ketone with the aim to develop a catalyst with a broad substrate scope. Ketone 283b indeed gave generally much higher ee’s for trans-olefins and trisubstituted olefins but lower ee’s for 1,1-disubstituted terminal olefins and cis-olefins as compared to 283a (Figure 77). To search for new ketone catalysts and understand their structural effect on catalytic properties, ketones derived from various carbohydrates such as 284–287 (Figure 78, Table 9, entries 1–4) have also been investigated for epoxidation by Shi and co-workers. Studies showed that effective ketone catalysts required a delicate balance among various factors such as steric and electronic effects. In 2002, Shing and co-workers reported that up to 71% ee was obtained for epoxidation of trans-stilbene with D-glucose-derived ketone 288 (10 mol %) (Table 9, entry 5). Epoxidation with a number of arabinose-derived ketones such as 289–291 was subsequently reported by Shing and co-workers. The enantioselectivity for the epoxidation increased with the size of the R group in ketone 290 (Table 9, entries 7–9). However, the opposite trend was observed for epoxidation of cis-ethyl cinnamate. The epoxide was obtained in up to 68% ee with ketone 290a and could be converted into a protected side chain of Taxol (Scheme 47). In 2003, Zhao and co-workers reported that up to 94% ee was obtained for epoxidation of trans-stilbene with ketone 290a (10 mol %) (Table 9, entry 9).
and aldehydes 292−294 (Table 9, entries 11−13). In 2009, Davis and co-workers reported a series of N-acyl-N-glucosamine-derived ketones such as 295 for the epoxidation (Table 9, entries 14 and 15), providing up to 81% ee for styrene with ketone 295b. In their studies, Jäger and co-workers showed that up to 80% ee could be obtained for ethyl cinnamate with N-acetyl-D-glucosamine-derived ketone 296 (25 mol %). In 2009, Vega-Pérez, Iglesias-Guerra, and co-workers described the epoxidation with glucose-derived seven-membered-ring ketone 297. Up to 74% ee was achieved for phenylstilbene and 1-phenylcyclohexene (Table 9, entry 17). The authors also showed that phenylstilbene was epoxidized in 74% yield and 90% ee with mannose-derived ketone 298 (Table 9, entry 18).

2.5.2. Synthetic Applications. Fructose-derived ketone 268 (Figure 70) and its enantiomer are readily accessible and have proven to be highly effective asymmetric epoxidation catalysts for a wide variety of trans-olefins and trisubstituted olefins. They have been widely used in the synthesis of various complex molecules and biologically active compounds. The synthetic applications are highlighted in this section.

2.5.2.1. Synthesis of Epoxide-Containing Molecules. Ketone 268 has been used for selective installation of the epoxides contained in biologically and medicinally important molecules. In their synthesis of potent tumor inhibitor cryptophycin 52 (302), Moher and co-workers examined various epoxidation methods and employed ketone 268 and oxone to epoxidize compound 299. The resulting epoxide was converted to target molecule 302 in two steps (Scheme 48).

In their synthetic studies toward lituarines A−C, Smith and co-workers showed that triene 314 could be selectively epoxidized at the disubstituted alkene with ketone 268 and oxone, giving epoxide 315 in 57% yield and high diastereoselectivity (>99% de). The resulting epoxide was carried forward in the synthesis of the C1−C19 segments of lituarines A−C (Scheme 52). Site-selective epoxidation was also illustrated by Ready and co-workers in their synthesis of (+)-nigellamine A2 (319). Epoxidation of triene 317 using ketone 268 selectively occurred at the desired alkene with the requisite stereochemistry (Scheme 53).

2.5.2.2. Intermolecular Epoxide Ring Opening. Epoxides are also versatile synthetic intermediates and can be regio- and stereoselectively opened by many kinds of nucleophiles to produce a variety of functionalized molecules. Epoxidation with ketone 268 has been utilized in various synthetic processes. For
example, Ollivier and co-workers reported that asymmetric epoxidation of olefin 320 was relatively challenging but accomplished with ketone 268 to give epoxide 321 in 43% yield and 91% ee. The resulting epoxide was converted to heliannuol L (323) in three steps (Scheme 54).206

Scheme 53. Synthesis of (+)-Nigellamine A2 (319)

In the synthesis of (−)-mesembrine (327), Taber and co-workers showed that olefin 324 could be converted to alcohol 326 in 73% overall yield and 96% ee via epoxidation with ketone 268, followed by epoxide ring opening with allylmagnesium chloride (Scheme 55).207

Scheme 55. Synthesis of (−)-Mesembrine (327)

Myers and co-workers reported that differentiated trans-1,2-diol derivatives such as 330 and 331 were readily prepared from silyl enol ethers in good yields and high ee’s by asymmetric epoxidation with ketone 268 and stereospecific ring opening of the resulting epoxides with BH₃-THF and AlMe₃ via an internal delivery of the nucleophile (Scheme 56).208 As illustrated by Ready and co-workers in the total synthesis of (−)-kibdelone C (335), tetrac 334 was obtained from di 332 in 68% overall yield with >95:5 dr and >90% ee via bis-epoxidation using ketone 268 and subsequent reduction with borane (Scheme 57).209

Scheme 56. Synthesis of trans-1,2-Diol Derivatives 330 and 331

Davies and co-workers showed that optically active epoxide 337 could be converted to syn-fluorohydrin 338 with BF₃·OEt₂ in 81% yield and >99:1 diastereoselectivity via stereoselective Sₘ₁-type epoxide ring opening. The resulting fluorohydrin was further transformed to chiral β-fluorooamphetamine (340) (Scheme 58).210

Scheme 57. Synthesis of (−)-Kibdelone C (335)

In the synthesis of (−)-monanchorin (344), Snider and co-workers reported that olefin 341 was acetalized and subsequently epoxidized with ketone 268 in 84% yield and 90% ee. The resulting epoxide 342 was converted to (−)-monanchorin (344) via guanidine 343 (Scheme 59).211 (+)-Monanchorin (ent-344) could be obtained in an analogous manner via asymmetric epoxidation with ketone ent-268 as catalyst.211 In their synthesis of zincophorin methyl ester (347), Leighton and co-workers showed that olefin 345 could be epoxidized with ketone 268 in 87% yield and 90% ee. Chiral
epoxide 346 was subsequently elaborated to target molecule 347 (Scheme 60).212

In the synthesis of (+)-lysergic acid (351) by Fujii, Ohno, and co-workers, epoxide 349 was used as a key intermediate. However, epoxidation of olefin 348 was found to be nontrivial. When mCPBA was used, the substrate decomposed under the reaction conditions, giving no desired epoxide. cis-Olefins are generally much less enantioselective than trans-olefins and trisubstituted olefins for epoxidation with ketone 268. Nevertheless, epoxide 349 was obtained in 77% yield and 82:18 diastereoselectivity via epoxidation with 268 (Scheme 61).213

The resulting epoxide was transformed into propargyl alcohol 350 via silyl protection and subsequent Zn(II)-mediated epoxide ring opening. Alcohol 350 could be further elaborated to (+)-lysergic acid (351).

In the synthetic studies toward stolonidiol (356), Siegel and co-workers showed that trisubstituted olefin 352 was epoxidized with ketone 268 to give epoxide 353 in 86% yield and >95:5 dr (Scheme 63).215 Interestingly, treatment of epoxide 358 with vinylmagnesium bromide and CuBr·SMe2 led to an unexpected Payne rearrangement product 359 in 81% yield, and desired homoallylic alcohol 360 was not obtained.

Somfai and co-workers reported a divergent synthesis of four sphingosine isomers using optically active vinyl epoxide 367 as a common key intermediate (Scheme 65).217 Vinyl epoxide 367, obtained from epoxidation of diene 366 with ketone 268, was regio- and stereoselectively converted to amino alcohols 368, 369, 370, and 374. McDonald and co-workers showed that 2-amino-3,5-diols 377 and 380 could be readily synthesized via asymmetric epoxidation of olefin 375, regioselective intermolecular or intramolecular epoxide ring opening, and subsequent stereoselective installation of the amino groups (Scheme 66).218

While relatively electron-deficient conjugated diene esters are less reactive, epoxidation with ketone 268 usually occurs at the distal double bonds in high regio- and stereoselectivity.168 The compound was obtained in four steps with 53% overall yield and >99% ee on 120 g scale. The optical purity was readily enhanced by simple filtration to remove the much less soluble racemic form.

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resulting vinyl epoxides have proven to be valuable synthetic intermediates as illustrated in Campagne’s synthetic studies toward octalactin A (385) (Scheme 67). O’Doherty’s synthesis of protected 1,3-diol 389 (Scheme 68). Kitahara’s synthesis of insecticidal tetrahydroisocoumarin 393 (Scheme 69). Matsushima’s synthesis of N-Bz-D-ristosamine (395) (Scheme 70).

As reported by Pagenkopf and co-workers in their synthetic studies toward amphidinolide C (404), nonconjugated diene 400 could also be preferentially epoxidized at the trisubstituted double bond with ketone ent-268 (Scheme 72).

2.5.2.3. Intramolecular Epoxide Ring Opening. Epoxides can undergo regio- and stereoselective intramolecular ring opening. Asymmetric epoxidation with ketone 268 has been employed to construct various optically active cyclic molecules. For example, Liu and co-workers reported that alkynyl epoxides, obtained from the asymmetric epoxidation using ketone 268, could undergo tungsten-mediated \( [3 + 3] \) reaction (Scheme 73).
[3 + 2] cycloadditions to form optically active bicyclic pyrans and lactones such as 413 and 417 (Schemes 74 and 75).

Scheme 74. Tungsten-Mediated [3 + 3] Cycloaddition of Alkynyl Epoxide

Scheme 75. Tungsten-Mediated [3 + 2] Cycloaddition of Alkynyl Epoxide

In their synthesis of (+)-murusolin stereoisomer libraries, Curran and co-workers employed the epoxidation with ketone 268 to stereoselectively install the epoxide onto the double bond of compound 418. Tetrahydrofuran 420 was synthesized from epoxide 419 via acid-promoted epoxide opening, Mitsunobu inversion, and subsequent hydrolysis (Scheme 76).229a

Scheme 76. Synthesis of (+)-Murusolin and Its Diastereoisomers

In the synthesis of (+)-sorangicin A (426) (a potent antibiotic), Smith and co-workers showed that enyne 422 could be epoxidized with ketone 268 in high diastereoselectivity. The resulting epoxide was converted to the dioxabicyclo[3.2.1]octane fragment (425) of (+)-sorangicin A (Scheme 77).230,231

Scheme 77. Synthesis of (+)-Sorangicin A

Asymmetric epoxidation with ketone 268 and its enantiomer was applied to the synthesis of subunits of pectenotoxins (a family of macrolides possessing potent anticancer activities) (Figure 79) by Brimble (Scheme 78),232,233 Williams (Scheme 79),234 and Micalizio (Scheme 80).235

Figure 79. Structure of members of pectenotoxin family.

Scheme 78. Synthesis of the ABC-Ring Fragment (431) of Pectenotoxins

Scheme 79. Synthesis of C1–C19 Fragment (436) of Pectenotoxin 4

Scheme 80. Synthesis of CDE-Ring Fragment (440) of Pectenotoxin 2
In the synthesis of 2-methyltetrahydropyran 443, a key intermediate toward ladder-shaped polyethers, Torikai and co-workers showed that allylic alcohol 441 could be effectively epoxidized with ketone 268 in high stereoselectivity (>12:1 dr). Compound 443 was readily prepared from 441 in 44% overall yield (Scheme 81).

Floreancig and co-workers reported that tricyclic compound 446 could be obtained in good overall yield via sequential epoxidation of 444 with ketone 268, formation of the carbonate, and electron-transfer-initiated cascade cyclization (Scheme 82).

In the total synthesis and determination of stereochemistry of (+)-intricatetraol (450), Morimoto and co-workers reported that olefin 447 could be epoxidized with ketone ent-268 in 87% yield and >6:1 dr. The epoxide-opening cyclization of compound 448 gave tetrahydrofuran 449, which was subsequently transformed to (+)-intricatetraol (450) (Scheme 83).

In the synthesis of bis-tetrahydrofuran C17–C32 segment (455) of antibiotic ionomycin (456), Marshall and co-workers utilized ketone 268 to epoxidize olefin 451 to give compound 452, which was converted to bromide 453. Treating 453 with Zn and TBAI led to formation of vinyl bis-tetrahydrofuran 454 via Zn-initiated reduction—elimination and in-situ cyclization. Compound 454 was further elaborated to bis-tetrahydrofuran C17–C32 segment 455 (Scheme 84). Marshall and co-workers also employed this asymmetric epoxidation/Zn-initiated epoxide cascade cyclization to synthesize bis-tetrahydrofuran 459 (Scheme 85) and the lactone diastereomer (463) of the cembranolide uprolide D (464) (Scheme 86).

Lee, Gagné, and co-workers reported a Au(I)-catalyzed cyclization of alleny1 epoxides. For example, bis-tetrahydrofuran 468 was obtained with 55% yield and 11:1 dr when alleny1 epoxide 467 was treated with (PhO)3PAuCl catalyst (Scheme 87). In the synthesis of Lycopodium alkaloid (−)-8-deoxyxeratine (471), Yang and co-workers showed that the desired epoxide was obtained as the sole product in 60% yield via epoxidation of olefin 469 with ketone 268 (Scheme 88). However, the undesired diastereomer was predominantly formed when mCPBA was used.

Prenylphenol derivatives have been shown to be effective substrates for epoxidation with ketone 268 or 276. Higher ee’s were obtained with ketone 276 than 268 in some cases. The resulting chiral epoxides were elaborated to various biologically...
active dihydrobenzofurans and dihydrobenzopyrans as illustrated in Coster’s synthesis of (−)-angelmarin (474) (Scheme 89)\(^{244}\) and methyl (+)-7-methoxyanodendroate (477) (Scheme 90).\(^{245}\) Kimachi’s synthesis of rhinacanthin A (481)\(^{246a}\) and (−)-dehydroiso-β-lapachone (483) (Scheme 91), Hamada’s synthesis of (+)-angelmarin (474) (Scheme 89)\(^{247}\), (+)-marmesin (486), (−)-(3′R)-decursinol (487), and (+)-lomatin (489) (Scheme 92)\(^{247}\) and Woggon’s synthesis of α-tocopherol (494) (Scheme 93)\(^{248}\).

Kan and co-workers employed the ketone 276-catalyzed epoxidation in the synthesis of (−)-5,7-dideoxy-gallocatechin gallate (498). Epoxidation of olefin 495 with ketone 276 and subsequent intramolecular acid-promoted cyclization provided dihydrobenzopyran 497, which was further transformed to target compound 498 (Scheme 94).\(^{249}\)

Synthesis of chiral hydroxy lactones via asymmetric epoxidation of alkenyl carboxylic acids has been reported. In their synthesis of hydroxy lactone 503, a key pharmaceutical intermediate, a team at DSM Pharma Chemicals showed that the asymmetric epoxidation process could be carried out on an industrial level. Hydroboration of 4-pentynoic acid lithium salt and subsequent Suzuki coupling with 3-fluorobenzyl chloride gave alkene 497. Epoxidation of alkene 495 with ketone 276 and subsequent intramolecular acid-promoted cyclization provided dihydrobenzopyran 497, which was further transformed to target compound 498 (Scheme 94).\(^{249}\)

Sudalai and co-workers reported that lactone 507 was obtained in 62% yield and 92% ee via epoxidation of alkene 506 with ketone 268 and in-situ lactonization. Lactone 507 was elaborated to (+)-L-733,060 (508), a NK1 receptor antagonist (Scheme 96).\(^{251,252}\)

Sewald
and co-workers utilized the epoxidation to form lactone 510, which was converted to cryptophycin-39 unit A precursor (512) (Scheme 97). Asymmetric epoxidation with ketone 268 and in-situ lactonization process was also effectively employed by Nakamura and co-workers in their synthesis of renin inhibitors 516 (Scheme 98) and DS-8108b (520) (Scheme 99).

When two or more alkenes are present in a molecule, steric and electronic differences around the double bonds allow the epoxidation to proceed site selectively as illustrated in various cases. For example, in the synthesis of initially assigned glabrescol (523) reported by Kodama and co-workers, diene 521 was regio- and stereoselectively epoxidized using ketone 268 to afford monotetrahydrofuran 522 in 89% yield and 10:1 dr after the concomitant ring closure. Further elaboration gave C$_2$-symmetric penta-THF 523 (Scheme 100). Morimoto and co-workers reported that monotetrahydrofuran 522 was obtained from diene 521 in 69% overall yield and 15:1 dr via epoxidation and subsequent CSA-promoted cyclization and elaborated to antiplasmodial C$_2$-symmetric (+)-ekeberin D$_4$ (525) (Scheme 101).

In their synthetic studies toward thyrsiferol (531) and thyrsenol A (532) (Scheme 102), McDonald and co-workers showed that the internal double bond of compound 526 was site and stereoselectively epoxidized with ketone 268 to give epoxide 527. Under carefully controlled reaction conditions, one of the bromohydrin epoxide diastereomers preferentially cyclized to give bromotetrahydropyran 528 in 50% yield.
In the total synthesis of bromotriterpene polyether (+)-aurilol (539) reported by Morimoto and co-workers, compounds 533 and 536 were epoxidized with ketone 268 and its enantiomer to give epoxides 534 and 537 in high diastereoselectivities (Scheme 103).260 Epoxidation of 536 occurred site selectively at the trisubstituted alkene.

Scheme 103. Synthesis of (+)-Aurilol (539)

In their synthetic studies toward terpendole E (543), Oikawa and co-workers reported that asymmetric epoxidation of diene 540 with ketone 268 occurred selectively at the trisubstituted double bond, giving epoxide 541 in 90% yield and 4:1 dr. Upon cyclization and deprotection, epoxide 541 was converted to the DEF-ring terpenoid fragment of terpendole E (Scheme 104).261

Scheme 104. Synthesis of the DEF-Ring Terpenoid Fragment (542) of Terpendole E

Huo and co-workers reported the synthesis of (+)-neroplofurol (547) via asymmetric dihydroxylation of (+)-nerolidol (544), site- and stereoselective epoxidation of the trisubstituted alkene of compound 545 with ketone 268, and subsequent in-situ cyclization (60% overall yield) (Scheme 105).262

Scheme 105. Synthesis of (+)-Neroplofurol (547)

Njardarson and co-workers reported that epoxidation of triene 548 with ketone 268 occurred selectively at the trisubstituted alkene, giving vinyl epoxide 549 in 72% yield and >20:1 dr. The epoxide was subsequently elaborated to several heterocycle-containing labdane natural products such as 551 and 552 (Scheme 106).263

Scheme 106. Synthesis of Labdane Natural Products 551 and 552

McDonald and co-workers reported that triene 553 was site- and stereoselectively epoxidized with ketone 268, giving bis-epoxide 554 in 76% yield and >20:1 dr. The bis-epoxide was further transformed to ent-nakorone (ent-557) and ent-abudinol B (ent-558) in a biomimetic fashion (Scheme 107).264

Scheme 107. Biomimetic Synthesis of ent-Nakorone and ent-Abudinol B

Wiemer and co-workers reported that monoepoxides 566 could be obtained with high ee’s via site- and stereoselective epoxidation of the terminal trisubstituted alkene of dienes 565. Acid-promoted cyclization of epoxides 566 led to hexahydroxyanthanes 567, which were subsequently elaborated to Schweinfurthins G (568),266 B (569), and E (570) as well as related compound (+)-vedelianin (571)268 and Schweinfurthin analogue 572 (Scheme 109).

Siegel and co-workers reported that epoxidation of commercially available (−)-caryophyllene (573) with ketone 268 site selectively occurred at the trisubstituted alkene, giving diastereomeric epoxides 575 and 574 in a ratio of 2.2:1, while these two epoxides were formed in a ratio of 1:5 favoring another synthetic route to ent-abudinol B (ent-558), McDonald and co-workers showed that the two trisubstituted alkenes in 563 were selectively epoxidized with ketone 268. The unreacted terminal alkene subsequently participated in TMSOTf-promoted cyclization to form ent-abudinol B (ent-558) in 15% yield (Scheme 108).265

Wiemer and co-workers reported that monoepoxides 566 and 567 were obtained with high ee’s via site- and stereoselective epoxidation of the terminal trisubstituted alkene of dienes 565. Acid-promoted cyclization of epoxides 566 led to hexahydroxyanthanes 567, which were subsequently elaborated to Schweinfurthins G (568), B (569), and E (570) as well as related compound (+)-vedelianin (571) and Schweinfurthin analogue 572 (Scheme 109).

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574 when mCPBA was used. Treating epoxide 575 with diphenyl phosphate and magnolol (576) led to a single-step formation of caryolanemagnolol (577) in 15% yield (Scheme 110).270 Suzuki and co-workers reported that the trisubstituted alkene of 578 was site- and stereoselectively epoxidized with ketone ent-268, giving epoxide 579 in 92% yield and 8:2:1 dr. Epoxide-opening cyclization of 579 and further elaboration led to (−)-seragakinone A (581) (Scheme 111).271 Sponge meroterpenoid pelorol analogues such as 586 were synthesized by Andersen and co-workers. The epoxide in 583 was installed via site- and enantioselective epoxidation of diene 582 with ketone ent-268. InBr3-promoted cyclization of epoxide 584 led to construction of polycyclic structure 585, which was converted to compound 586 (Scheme 112).272

When a substrate contains multiple alkenes, all double bonds can be simultaneously epoxidized with ketone 268 or its enantiomer, allowing the rapid increase of molecular complexity via epoxide-ring-opening cyclization.274 For example, in the synthesis of (−)-longiline peroxide (593) reported by Morimoto and co-workers, two tetrahydrofuran rings were made via asymmetric bis-epoxidation of diene 591 with ketone ent-268 and subsequent TFA-promoted epoxide-opening cyclization (Scheme 114).275 Morimoto and co-workers also employed the bis-epoxidation to synthesize (+)-enshuol (597) and determine its absolute configuration. Diene 594 was epoxidized with ketone 268 to give diepoxide 595 in 74% yield and >6:1 dr. Acid-promoted epoxide-opening cascade cyclization of 595 yielded compound 596, which was elaborated to (+)-enshuol (597) (Scheme 115).276 In their studies on electron-transfer-initiated cascade cyclizations, Floreancig and co-workers utilized ketone catalyst 268 for epoxidation of diene 598, giving bis-epoxide 599 in 85% yield. Bis-epoxide 599 was converted to bis-tetrahydrofuran 600 in 66% yield upon photolysis (Scheme 116).277 Synthesis of (−)-heronapyrrole C (604) via a cascade cyclization was reported by Stark and co-workers. Bis-epoxide 602 was generated by asymmetric epoxidation of diene 601 using ketone ent-268 and converted to bis-tetrahydrofuran 603 in 60% overall yield (Scheme 117).278
Sinha and co-workers employed the epoxidation with ketone 268 and ent-268 in the synthesis of a library of bis-THF annonaceous acetogenins. For example, bis-THF lactone 607 was obtained from 605 via bis-epoxidation and subsequent CSA-mediated cyclization in 72% overall yield. Interestingly, alkene a in substrate 605 could be selectively epoxidized by controlling the reaction conditions, giving mono-THF lactone 609 in 54% overall yield upon cyclization with CSA (Scheme 118).

Marti and co-workers synthesized teurilene (612) via epoxide-opening cascades (Scheme 119). Epoxidation of olefin 610 with ketone 268 gave epoxide 611 (81% yield), which could be elaborated to teurilene (612). Morimoto and co-workers reported a biomimetic synthesis of teurilene. Epoxide 614 was prepared via asymmetric epoxidation of 613 with ketone ent-268 and subsequently transformed to tetraepoxide 615. Treating 615 with TIOH led to direct formation of teurilene (612) via an epoxide-opening cascade triggered by hydrolysis of the terminal epoxide (Scheme 120).

Corey and co-workers reported that polyene 616 was stereoselectively and simultaneously epoxidized with ketone 268 to give pentaepoxide 617, which was converted to initially assigned Cs-symmetric glabrescol (523) in 31% overall yield (Scheme 121). In their studies on the determination of the correct structure of glabrescol, Cs-symmetric pentacyclic oxasqualenoid 621, prepared via tetraepoxidation of polyene 618 and subsequent cyclization, matched the reported isolated natural product glabrescol (Scheme 122).

Qu and co-workers reported that glabrescol (621) was synthesized in two steps from polyene 622 or squalene (624) via polyepoxidation with ketone ent-268 and base-promoted middle-to-terminal double epoxide-opening cascade cyclization...
The results suggested two alternative biogenetic approaches to (−)-glabrescol.

Morimoto and co-workers showed that meso-hexaepoxide 628, prepared via site- and stereoselective epoxidation of compound 626 with ketone ent-268 and subsequent reduction, underwent an acid-promoted biomimetic epoxide-opening cascade cyclization to give (±)-glabrescol (621) in 8% yield (Scheme 124).281

In the initial synthesis of (+)-omaezakianol (another member of the oxasqualenoid family) reported by Morimoto and co-workers, diepoxide 630 and triepoxide 634 were prepared via epoxidation with ketone ent-268 and ketone 268, respectively. Monotetrahydrofuran 632, derived from 630, was coupled with 634 via cross metathesis to give triepoxide 635, which was elaborated to (+)-omaezakianol (637) (Scheme 125).286 In their second-generation synthesis of (+)-omaezakianol, Morimoto and co-workers showed that pentaepoxide 640, prepared via epoxidation of polyene 638 with ketone ent-268 and subsequent transformations, was directly converted to (+)-omaezakianol (637) in 33% yield via aforementioned acid-promoted biomimetic epoxide-opening cascade cyclization (Scheme 126).281

Xiong, Corey, and co-workers reported a three-step synthesis of (+)-omaezakianol (637) from racemic chlorohydrin 641 via pentaepoxidation with ketone 268, CSA-promoted epoxide-opening cascade cyclization, and reduction with Na (Scheme 127).287

In studies on the biosynthesis of lasalocid A (647) by Oguri, Oikawa, and co-workers, bis-epoxide 646, a proposed substrate for epoxide hydrolase Lsd19, was prepared via epoxidation of diene 644 with ketone 268 and subsequent deprotection. Lasalocid A (647) was indeed formed via 5-exo-6-endo cyclization when 646 was incubated with Lsd19. On the other hand, 5-exo-5-exo cyclization product 648 was obtained when 646 was treated with trichloroacetic acid (Scheme 128).288 These studies provide useful insights into polyether biosynthesis.
Fused polycyclic ethers such as brevetoxin B (651) are a class of biologically important molecules and may biosynthetically derive from polyenes via polyepoxidation and epoxide-opening cascade endo cyclization (Scheme 129). The biomimetic polyene–polypeptide–polycyclization process could rapidly construct stereochemically complex molecules from simple polyene precursors and would present a synthetically attractive and powerful strategy for synthesis of polyethers. Epoxidation with ketone 268 has proven to be a valuable method for such studies.

Murai and co-workers reported that triepoxide 653 was obtained in 56% yield via tris-epoxidation of 652 with ketone 268. Tricyclic ether 654 was formed in 9.3% yield from the triepoxide via La(OTf)₃-catalyzed cascade cyclization upon desilylation (Scheme 130).
McDonald and co-workers reported various studies on biomimetic synthesis of fused polycyclic ethers. For example, triene 655 was epoxidized with ketone 268 to introduce three epoxides. Tetracyclic ether 657 was obtained in 20% overall yield from tetraepoxide 656 via Lewis acid-promoted cascade endo cyclization and subsequent acetylation (Scheme 131).

Jamison and co-workers reported Si-directed formation of fused polycyclic ethers. Triepoxide 659 was obtained from vinylsilane 658 in 50% yield and 9:1 dr via tris-epoxidation with ketone 268. Tetracyclic tetrahydropyran 660 was formed in 20% overall yield via an epoxide-opening cascade cyclization of triepoxide 659 promoted by Cs2CO3/CsF and acetylation (Scheme 132). The trimethylsilyl groups directed 6-endo cyclizations and “disappeared” after each cyclization. Their subsequent studies showed that triepoxide 663, obtained from tris-epoxidation of triene 661 with ketone 268 and deprotection, underwent 6-endo cyclizations to form tetracyclic tetrahydropyran 664 without the need for directing groups when the reaction was carried out in water (Scheme 133). This methodology was applied to the synthesis of the HIJK-ring fragment (668) of gymnocin A (Scheme 134).

Jamison and co-workers reported the total synthesis of ent-dioxepandehydrothyrsiferol (676) via bromonium-initiated cascade cyclization. Diepoxide 673 was prepared via epoxidation of 672 with ketone 268 in 75% yield and was further elaborated to triepoxide 674. Polycyclic compound 675 was obtained in 36% yield by treating 674 with NBS and transformed to target molecule 676 (Scheme 135). They also accomplished the total synthesis of armatol A (680) and determined its absolute configuration. Three trisubstituted alkenes of tetraene 677 were stereoselectively epoxidized using ketone 268, with the terminal alkene being untouched. Tricyclic ether 679 was obtained in 18% overall yield via BF3·OEt2-promoted cyclization of triepoxide 678, followed by acetylation, and further elaborated to armatol A (680) (Scheme 136).

2.6. Chiral Iminium Salt-Catalyzed Epoxidation

Like dioxiranes, oxaziridinium salts are a class of effective agents for epoxidation of olefins, and they can be generated in situ from the corresponding iminium salts and oxidants, typically Oxone. Upon epoxidation of the olefin, the iminium salt is regenerated. A catalytic asymmetric epoxidation could be realized when a chiral iminium salt catalyst is used (Scheme 137).

In 1976, Lusinchi and co-workers reported that an oxaziridinium salt (683) (Figure 80) could be prepared via methylation of the corresponding oxaziridine with FSO3Me or

Scheme 131. Synthesis of Fused Polycyclic Ether 657 via Polyepoxide Cyclization

Scheme 132. Synthesis of Tetrahydropyran 660 via TMS-Directed Cyclization

Scheme 133. Synthesis of Tetrahydropyran 664 via Water-Promoted Cyclization

Scheme 134. Synthesis of HIJK-Ring Fragment (668) of Gymnocin A

Scheme 135. Synthesis of ent-Dioxepandehydrothyrsiferol (676)

Scheme 136. Synthesis of Armatol A (680)
by oxidation of the corresponding iminium salt with a peracid.\textsuperscript{300} Subsequently, Hanquet and co-workers reported that oxaziridinium salt \textit{684} could be similarly prepared by methylation or oxidation method,\textsuperscript{301} and it was found to be highly reactive for epoxidation of olefins.\textsuperscript{302} They further showed that the epoxidation could be run with a catalytic amount of the corresponding iminium salt (\textit{685}) (Figure 80) using oxone\textsuperscript{−}NaHCO\textsubscript{3} in CH\textsubscript{3}CN−H\textsubscript{2}O or \textit{m}CPBA−NaHCO\textsubscript{3} in CH\textsubscript{2}Cl\textsubscript{2}.\textsuperscript{303,304} A wide variety of chiral iminium salts, such as dihydroisoquinoline-, binaphthylazepinium-, biphenylazepinium-based iminium salts, have been investigated for the epoxidation.

\textbf{2.6.1. Dihydroisoquinoline-Based Iminium Salts.} An early example employing an oxaziridinium salt for asymmetric epoxidation of olefins was reported by Bohe and co-workers in 1993.\textsuperscript{305} Several unfunctionalized olefins were epoxidized with 1.1 equiv of recrystallized oxaziridinium salt \textit{686} (Figure 81), giving up to 42% ee for \textit{trans}-stilbene.\textsuperscript{305b} Stilbene oxide was obtained in 79% yield and 35% ee when the epoxidation was run with 5 mol % iminium salt \textit{687}, oxone (1.3 equiv), and NaHCO\textsubscript{3} (4 equiv) in CH\textsubscript{3}CN−H\textsubscript{2}O (Table 10, entry 1).\textsuperscript{305b}

Page and co-workers reported a number of dihydroisoquinoline-based iminium salts, such as \textit{688}−\textit{691}, with chiral moieties attached on the iminium nitrogen (Figure 81).\textsuperscript{306,307} This type of iminium salt catalyst was readily prepared from various chiral primary amines, and they were extensively investigated for epoxidation of olefins (Table 10, entries 2−9). \textit{trans}-Stilbene was epoxidized in 78% yield and 73% ee with 10 mol % iminium salt \textit{688} in the presence of oxone and Na\textsubscript{2}CO\textsubscript{3} in CH\textsubscript{3}CN−H\textsubscript{2}O (Table 10, entry 2).\textsuperscript{306a} Rozwadowska and co-workers reported that stilbene oxide could be obtained in 70% yield and 45% ee with 10 mol % (+)-thiomicamine-derived iminium salt \textit{692} and \textit{m}CPBA (Figure 81) (Table 10, entry 10).\textsuperscript{308} Iminium salt \textit{690c} was found to be an effective catalyst for epoxidation of some \textit{cis}-olefins, giving up to 97% ee for 2,2-dimethyl-6-cyanochromene by running the reaction under nonaqueous conditions (in CHCl\textsubscript{3}) at −40 °C with tetraphenylphosphonium monoperoxysulfate (TPPP) as the oxidant (Figure 82).\textsuperscript{309,307d} The resulting epoxide (\textit{693}) was converted to levocromakalim (\textit{694}) (an antihypertensive agent) with pyrrolidin-2-one and NaH in 52% yield (Scheme 138).\textsuperscript{309} Total synthesis of (−)-lomatrin (\textit{ent}-489) and (+)-(3'S,4'R)-trans-khellactone (\textit{697}) was also achieved using iminium salt...
690c-catalyzed epoxidation as the key step (Scheme 139). Epoxide 696 was obtained in 65% yield and 97% ee from seselin 695 with TPPP as oxidant under nonaqueous conditions. Reductive cleavage of the epoxide with NaHCO₃ afforded (−)-lomatin (ent-489) in 92% yield. (+)-Khellactone (697) was obtained in 95% yield by epoxide opening with H₂SO₄. Epoxidation with catalyst 690c was also applied to the kinetic resolution of racemic 2-substituted chromenes, giving up to 99% ee for the epoxide.

2.6.2. Binaphthylazepinium-Based Iminium Salts. A series of binaphthylazepinium-based chiral iminium salt catalysts such as 698−708 have been studied for epoxidation of olefins (Figure 83, Table 11). In 1996, Aggarwal and co-workers reported the preparation and use of binaphthyl-based iminium salt catalyst 698 for asymmetric epoxidation. For example, 1-phenylcyclohexene was epoxidized with 5 mol % 698 in the presence of oxone and NaHCO₃ in CH₃CN−H₂O at 0 °C unless otherwise stated. Reactions were carried out with TPPP in CH₃CN at −40 °C. 2.5 mol % 18-crown-6 was added, and CH₂Cl₂−H₂O (3:2, v/v) was used as solvent. 2.5 mol % iminium salt was used.

In 2004, Page and co-workers reported a highly enantioselective iminium salt catalyst (699) (Figure 83), achieving up to 95% ee for epoxidation of 1-phenylcyclohexene with iminium salt 702 (Table 11, entry 7).

In 2006, Lacour and co-workers reported a number of binaphthyl-based iminium salts with TRISPHAT as counterions such as 703−706 (Figure 83), and up to 87% ee was obtained for epoxidation of 1-phenyl-3,4-dihydronaphthalene (Table 11, entry 11). The studies showed that the epoxide’s stereochemistry was determined by the configuration of the binaphthyl group of the iminium salt catalyst but not by the configuration of the N-substituent. In their efforts to elucidate the structural parameters needed for high asymmetric induction in epoxidation, Lacour and co-workers showed that H₈-binaphthyl-based iminium salts 707 with a larger dihedral angle around the biaryl twist gave high enantioselectivity for the epoxidation (Table 11, entries 12−14). It was shown that the counteranion was important for the catalyst’s reactivity and selectivity, with SbF₆⁻ being optimal.

Recently, Page and co-workers reported that introducing a pseudoaxial substituent at a carbon atom adjacent to the nitrogen in the binaphthylazepinium-based iminium salt could improve enantioselectivity for epoxidation of some olefins. For example, 94% ee was achieved for epoxidation of 1-phenylcyclohexene with iminium salt 707b (Table 11, entry 7).

2.6.3. Biphenylazepinium-Based Iminium Salts. Page and co-workers investigated a number of biphenylazepinium salt catalysts such as 709−713 for epoxidation (Figure 85). Various oxidants were examined for the reaction with iminium salt 710 (Table 12, entries 2−7), giving up to 70% ee for 1-phenylcyclohexene with TPPP in CH₂Cl₂−CH₃CN at −78 °C (Table 12, entry 7).
4. Biphenyl-based iminium salt 710 with a pseudoaxial methyl group gave 82% ee for epoxidation of 1-phenyl-cyclohexene (Table 12, entry 9). 2,2-Dimethyl-6-cyanochromene was epoxidized in 100% conversion and 98% ee with 712 (10 mol %) and TPPP (2 equiv) in CHCl₃ at 0 °C. Epoxidation with iminium salt 710 was applied to the total synthesis of (+)-scuteflorin A (721) (Scheme 140).

Scheme 140. Synthesis of (+)-Scuteflorin A (721)

Xanthyletin 717 was efficiently epoxidized with catalyst 710 and TPPP to give epoxide 718 in 97% yield and >99% ee. The epoxide was converted to target molecule 721 via acid-promoted epoxide ring opening, selective oxidation, and esterification with 3,3-dimethyl acryloyl chloride.

Lacour and co-workers reported their studies on the epoxidation with biphenylazepinium salts bearing TRISPHAT as counterions such as 714−716. Up to 85% ee was obtained for 1-phenyl-3,4-dihydronaphthalene with doubly bridged biphenylazepinium salt catalyst 716 (Table 12, entry 13).

Lacour and co-workers reported that binaphthyl and biphenyl azepines 722−725 (Figure 86) could be directly

Table 12. Epoxidation of Representative Olefins with Iminium Salt Catalysts 709−716⁴

<table>
<thead>
<tr>
<th>entry</th>
<th>catalyst</th>
<th>Ph</th>
<th>Ph</th>
<th>Ph</th>
<th>R</th>
<th>ref</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>709</td>
<td></td>
<td></td>
<td></td>
<td>R = Ph, 17% ee</td>
<td>29% ee</td>
</tr>
<tr>
<td>2</td>
<td>710</td>
<td>15% ee</td>
<td>R = Ph, 59% ee</td>
<td>60% ee</td>
<td>41% ee</td>
<td>307b,318a</td>
</tr>
<tr>
<td>3⁴</td>
<td>710</td>
<td>14% ee</td>
<td>R = Ph, 60% ee</td>
<td>67% ee</td>
<td>22% ee</td>
<td>318a</td>
</tr>
<tr>
<td>4⁴</td>
<td>710</td>
<td>33% ee</td>
<td>R = Me, 50% ee</td>
<td>70% ee</td>
<td>65% ee</td>
<td>313c</td>
</tr>
<tr>
<td>5⁴</td>
<td>710</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>64% ee</td>
<td>318b</td>
</tr>
<tr>
<td>6⁴</td>
<td>710</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>56% ee</td>
<td>318c</td>
</tr>
<tr>
<td>7⁴</td>
<td>710</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>68% ee</td>
<td>307e</td>
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<tr>
<td>8</td>
<td>711</td>
<td>-</td>
<td>R = Me, 50% ee</td>
<td>63% ee</td>
<td>-</td>
<td>307c</td>
</tr>
<tr>
<td>9</td>
<td>712</td>
<td>-</td>
<td>R = Ph, 35% ee</td>
<td>82% ee</td>
<td>78% ee</td>
<td>315</td>
</tr>
<tr>
<td>10</td>
<td>713</td>
<td>6% ee</td>
<td>R = Me, 26% ee</td>
<td>44% ee</td>
<td>-</td>
<td>319</td>
</tr>
<tr>
<td>11⁴</td>
<td>714</td>
<td>17% ee</td>
<td>R = Me, 42% ee</td>
<td>69% ee</td>
<td>76% ee</td>
<td>321a</td>
</tr>
<tr>
<td>12⁴</td>
<td>715</td>
<td>17% ee</td>
<td>R = Me, 46% ee</td>
<td>66% ee</td>
<td>80% ee</td>
<td>321b,316b</td>
</tr>
<tr>
<td>13⁴</td>
<td>716</td>
<td>-</td>
<td>R = Me, 55% ee</td>
<td>71% ee</td>
<td>85% ee</td>
<td>322</td>
</tr>
</tbody>
</table>

⁴Reactions were carried out with olefin, iminium salt (5 mol %), oxone, and inorganic base (NaHCO₃ or Na₂CO₃) in CH₃CN−H₂O at 0 °C unless otherwise stated. ⁵Reactions were carried out with catalyst (10 mol %) and TPPP in CH₃CN at −40 °C. ⁶Reactions were carried out with catalyst (10 mol %) and TPPP in CH₂Cl₂−CH₃CN at −40 or −78 °C. ⁷20 mol % of catalyst and electrochemically generated persulfate was used as the oxidant. ⁸10 mol % of catalyst and H₂O₂ was used as the oxidant. ⁹10 mol % of catalyst and NaOCl was used as the oxidant. ¹₀2.5 mol % 18-crown-6 was added, and CH₂Cl₂−H₂O (3:2, v/v) was used as solvent.

4.313c Biphenyl-based iminium salt 712 with a pseudoaxial methyl group gave 82% ee for epoxidation of 1-phenyl-cyclohexene (Table 12, entry 9). 2,2-Dimethyl-6-cyanochromene was epoxidized in 100% conversion and 98% ee with 712 (10 mol %) and TPPP (2 equiv) in CHCl₃ at 0 °C. Epoxidation with iminium salt 710 was applied to the total synthesis of (+)-scuteflorin A (721) (Scheme 140).

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Lacour and co-workers reported their studies on the epoxidation with biphenylazepinium salts bearing TRISPHAT as counterions such as 714−716. Up to 85% ee was obtained for 1-phenyl-3,4-dihydronaphthalene with doubly bridged biphenylazepinium salt catalyst 716 (Table 12, entry 13).

Lacour and co-workers reported that binaphthyl and biphenyl azepines 722−725 (Figure 86) could be directly

Figure 86. Binaphthyl and biphenyl azepines 722−727.
used as catalysts for epoxidation of olefins (Table 13, entries 1–4). Up to 86% ee was obtained for 1-phenylcyclohexene using catalyst 724 and oxone (Table 13, entry 3). In their studies, Page and co-workers showed that up to 81% ee was achieved in the epoxidation of unfunctionalized olefins with binaphthyl azepine 726 as catalyst (Table 13, entry 5). It was postulated that the amine was oxidized in situ to the corresponding iminium salt, which catalyzed the epoxidation.

2.6.4. Exocyclic Iminium Salts. Chiral exocyclic iminium salts have also been investigated for asymmetric epoxidation of olefins. In 1999, Armstrong and co-workers reported that 1-phenylcyclohexene was epoxidized in 100% conversion and 22% ee with stoichiometric iminium salt 728 and oxone (Figure 87) (Table 14, entry 1). Epoxidation with ketiminium salt catalyst 729 was described by Komatsu and co-workers in 2000. Cinnamyl alcohol was epoxidized in 70% yield and 39% ee with 10 mol % 729 (Table 14, entry 2). In 2001, Wong, Yang, and co-workers reported an epoxidation process involving in-situ generation of iminium salts from chiral amines and aldehydes (Figure 88). Up to 65% ee was obtained for trans-stilbene with amine 731 and aldehyde 732 (Table 14, entry 4).

2.7. Chiral Amine or Chiral Amine Salt-Catalyzed Epoxidation

During their studies on iminium salt-catalyzed epoxidations of olefins, Aggarwal and co-workers discovered that test substrate 1-phenylcyclohexene could be epoxidized by simple amines with oxone as oxidant. Both secondary and tertiary amines were effective promoters. Among the amines examined, pyrrolidine gave the highest conversion for 1-phenylcyclohexene. Asymmetric induction was also observed with chiral amine catalyst 149 (Figure 89). In their subsequent studies, Aggarwal and co-workers found that the HCl salt of amine 149 gave more consistent and reproducible results as well as a higher ee value than 149 itself (Figure 90). Up to 66% ee was obtained for epoxidation of 1-phenylcyclohexene with 10 mol % 733 (Figure 90). Studies indicated that the protonated ammonium salt likely acted as a phase-transfer catalyst to bring the oxidant into the organic phase and as an activator of the oxidant via hydrogen bonding (Figure 91).

Figure 87. Exocyclic iminium salts.

Figure 88. Iminium salt precursors.

Figure 89. Pyrrolidine-based amine and amine HCl salt catalysts.

Figure 90. Epoxidation of olefins with amine or amine salt catalyst.

Figure 91. Possible forms of pyrrolidinium peroxymonosulfate.

Figure 92. Epoxidation of olefins with catalysts 150 and 734.
2.8. Aspartic Acid-Based Peptide-Catalyzed Epoxidation

Miller and co-workers reported the electrophilic epoxidation of olefins using aspartic acid-based peptide catalysts such as 738−740 (Figure 94). Various carbamate-containing olefins were epoxidized with peptide 738 as catalyst and H$_2$O$_2$ or urea−H$_2$O$_2$ (UHP) as oxidant, giving the corresponding epoxides in 73−99% yield and up to 92% ee (Figure 95). It was thought that the hydrogen bonding between the substrate and the peptide catalyst played a crucial role in the enantioselectivity. Only 16% ee was obtained when the proline peptide bond of 738 was replaced by an olefin isostere (739) (Figures 94 and 95). The ee increased to 52% by introducing a fluorine atom to the alkene (740) (Figure 95). Miller and co-workers subsequently showed that aspartic acid-based peptides 744 and 745 were effective catalysts for the site-selective epoxidation of polyenes. As shown in Figure 96, the 2,3-olefin was regio- and enantioselectively epoxidized with catalyst 744 to give the epoxide in up to 93% ee. Notably, in the case of geranylgeraniol, the 6,7-olefin was site-selectively epoxidized with catalyst 745, affording the corresponding epoxide in 42% yield.

3. ORGANOCATALYZED ASYMMETRIC AZIRIDINATION OF OLEFINS

Asymmetric aziridination of olefins provides a useful strategy for preparation of optically active aziridines, which are important building blocks in organic synthesis and can be regio- and stereoselectively transformed to various nitrogen-containing molecules. During the past few years, significant progress has been made in the field of the organocatalyzed/promoted aziridination of olefins, particularly electron-deficient ones, which will be discussed in this section.

3.1. Chiral Quaternary Ammonium Salt-Catalyzed Aziridination

Cinchona alkaloid-derived quaternary ammonium salts have been used as phase-transfer catalysts for the asymmetric aziridination of electron-deficient olefins. In 1996, Prabhakar and co-workers reported that up to 61% ee was obtained for aziridination of methyl acrylate with ammonium salt 13b as catalyst and N-aryl hydroxamic acids 751 as nitrogen sources (Figures 97 and 98). In 2005, Murugan and co-workers showed that up to 95% ee could be achieved for aziridination of...
tert-butylic acrylate with ammonium salt catalysts 746 and 747 (Figures 97 and 98).338

In 2004, Fioravanti, Pellacani, Tardella, and co-workers showed that up to 75% ee could be obtained for aziridination of 2-phenylsulfanyl-substituted cyclic enones with ammonium salts 13b and 748 (Figure 97) using NsONHCO2Et (752) as the nitrogen source (Figure 99).339 Minakata and co-workers employed N-chloro-N-sodiocarbamates 753 as nitrogen sources for asymmetric aziridination of α,β-unsubstituted amides, giving up to 87% ee with ammonium salt catalysts 749 and 750 (Figures 97 and 100).340 High diastereoselectivities (up to >99:1 dr) were achieved for substrates bearing chiral auxiliaries (Figure 100).341

3.2. Amine-Promoted Aziridination via Aminimide

In 2006, Shi and co-workers reported a chiral amine-promoted asymmetric aziridination of chalcones with O-mesitylenesulfonylhydroxylamine (MSH) as the NH source in the presence of a base such as CsOH·H2O.342 NH aziridines were obtained in up to 67% ee with (+)-Tröger’s base (754) (Figures 101 and 102). The amine promoter could be used in a catalytic amount. In their studies, Armstrong and co-workers showed that up to 56% ee could be obtained for aziridination using quinine (755) and O-(diphenylphosphinyl)hydroxylamine (DppONH2) (Figures 101 and 102).343 Page and co-workers investigated the asymmetric aziridination of chalcone with binaphthalene-based chiral amines and MSH or DppONH2 as N-transfer agent, achieving 37% ee with amine 756 (Figures 101 and 102).344

A possible catalytic cycle for the amine-promoted aziridination is shown in Scheme 143. The tertiary amine R3N first reacts with O-substituted hydroxylamine R’ONH2 to form the hydrazinium salt (757), which is deprotonated by a base to generate the aminimide intermediate (758). The aminimide then undergoes conjugate addition to the electron-deficient...
olefin followed by ring closure to give the aziridine and regenerate the tertiary amine.342,343

3.3. Aziridination via Iminium/Enamine Catalysis

3.3.1. Pyrrolidine-Based Catalysts. Asymmetric aziridination of \( \alpha,\beta \)-unsaturated aldehydes has been achieved with chiral secondary amine catalysts. In 2007, Córdova and co-workers reported that a variety of \( \alpha,\beta \)-unsaturated aldehydes were effectively aziridinated with diphenylprolinol silyl ether 144 as catalyst and acylated hydroxycarbamates 760–764 as nitrogen sources, giving the aziridines in high enantioselectivities (up to 99% ee) (Figure 103).345 The resulting aziridine (765) was converted into \( \beta \)-amino acid ester 766 by ring opening and concomitant esterification, followed by removal of the Cbz group (Scheme 144).345 In their studies, Greck, de Figueiredo, and co-workers showed that \( \alpha \)-branched enals were aziridinated in 69–86% yield and up to 90% ee with amine catalyst 137 and TsNHOTs (764) (Figure 104).346

The proposed mechanism for the asymmetric aziridination is shown in Scheme 145. The amine catalyst first reacts with the enal to form iminium salt intermediate 767, which is then attacked by the acylated hydroxycarbamate through azaconjugate addition to generate enamine intermediate 768. Upon ring closure, 768 is converted to iminium ion 769, which is hydrolyzed to give the aziridine and regenerate the amine catalyst.345

In 2009, Hamada and co-workers reported the asymmetric aziridination of \( \alpha,\beta \)-unsaturated aldehydes with chiral amine 189 and BocNHOTs (763). The resulting products were converted to other aziridine derivatives with up to 99% optical purity via reduction and oxidation (Figure 105).347

Jørgensen and co-workers showed that various optically active building blocks could be readily prepared via a one-pot process using chiral amine 137-catalyzed asymmetric aziridinat-
tion of enals 770 as the key step (Scheme 146). They also studied the remote aziridination of cyclic 2,4-dienals with

catalyst ent-137 and nitrogen source BocNHOTs (763) (Figure 106). Aziridination occurred regioselectively at the endocy-
clic double bond, giving the aziridines in up to 95% ee. The aziridine products could be transformed into allylic δ-amino esters and oxazolidinones (Scheme 147).

3.3.2. Chiral Amine Salt Catalysts. The asymmetric aziridination has been extended to α,β-unsaturated ketones with chiral amine salt catalysts. Melchiorre and co-workers reported that acyclic and cyclic enones were effectively aziridinated with cinchona alkaloid-derived amine salts 772 and 773 as catalysts, giving the corresponding aziridines in up to 99% ee (Figures 107 and 108).

Jørgensen and co-workers reported that optically active allylic amines were readily obtained with 94−99% ee via asymmetric aziridination of enones using amine salt catalyst 202 and TsNHOTs (764), followed by one-pot Wharton reaction (Figures 107 and 109). They also showed that oxazolidi-
nones could be obtained with up to 99% ee from enones through asymmetric aziridination with chiral amine salt 774 and BocNHOTs (763), followed by double S,2 reaction using NaI in the same pot (Figures 107 and 110).

In 2011, Hamada and co-workers showed that chiral diamine catalyst 775 was effective for asymmetric aziridination of cyclic enones, giving the corresponding aziridines in 75−91% yield and 88−97% ee using CbzNHOTs (762) or BocNHOTs (763) as nitrogen source (Figure 111). The resulting chiral aziridine (776) was elaborated to the key intermediate (780) toward (-)-agelastatin A (781) (Scheme 148).
3.4. Chiral Amino Thiourea-Catalyzed Aziridination

Chiral bifunctional amino thioureas can also be used as catalysts for aziridination of electron-deficient olefins. In 2012, Lattanzi and co-workers reported that α-acyl acrylates were aziridinated in up to 82% ee with catalyst 782 and BocNHTs (763) (Figure 112). It was suggested that the thiourea and amino groups of the catalyst activate the substrate and nucleophile, respectively. As shown in Scheme 149, the resulting aziridine (784) could be readily converted to α,α-disubstituted-α-amino acid ester 786 in high yield.

4. CONCLUSION

Organocatalytic asymmetric epoxidation of olefins has witnessed exponential growth during the last few decades. As shown in this review, significant contributions from various research groups have obtained remarkable results for asymmetric epoxidation of olefins. Systems including phase-transfer catalysts, peptide catalysts, and bifunctional base catalysts such as chiral guanidines and chiral β-amino alcohols have proven very effective for electron-deficient α,β-unsaturated carbonyl substrates (mostly α,β-unsaturated ketones), obtaining high selectivities. Chiral amine-catalyzed epoxidation via iminium ion/enamine pathway has expanded the nucleophilic epoxidation to α,β-unsaturated aldehydes in addition to α,β-unsaturated ketones. A major advancement in electrophilic asymmetric epoxidation has been achieved with chiral ketone catalysts. Researchers from a number of laboratories have investigated a wide variety of structurally diverse ketone catalysts including C_2-symmetric-, ammonium-, bicyclic-, carbocyclic-, and carbohydrate-derived ketone catalysts and obtained impressive results. Chiral iminium salts have also shown to be effective epoxidation catalysts, achieving high enantioselectivities for certain olefin classes and requiring very low catalyst loading. Chiral amine salts provide interesting potential systems for asymmetric epoxidation. Additionally, aspartic acid-based peptide catalysts have demonstrated highly promising results for asymmetric epoxidation of olefins. Among these systems, readily available fructose-derived ketone 268 (Figure 70) has been shown to be highly enantioselective, general, predictable, practical, and scalable. Flexibility in the catalyst design has allowed variations to be synthesized in order to address various steric and electronic needs of substrates, further broadening the generality of this class of catalyst. The ease of use and effectiveness of catalyst 268 has been documented in its synthetic applications. Its versatility has also been shown in the epoxidation of polyunsaturated systems, being able to indiscriminately provide polyepoxides rapidly or discriminately by selectively epoxidizing a certain olefin class via steric and/or electronic effects. Epoxidation with ketone 268 displayed unprecedented generality and practicality for nonmetal systems at the time, which opened up new perspectives for practical asymmetric reactions using simple chiral, organic molecules as catalysts and contributed greatly to the revital-
ization of the yet-to-be termed field of “organic catalysis” or “organocatalysis”.

Significant progress has also been made for organocatalyzed asymmetric aziridination of electron-deficient olefins using catalysts such as cinchona alkaloid-derived quaternary ammonium salts, chiral amines, and amine salts as well as amino thioureas. High enantioselectivities have been obtained in various cases, which provides promising results for future development and application in this field.

Despite the extensive research presented herein, there continues to be a need for more selective and robust catalysts to accomplish the challenging incorporation of oxygen and nitrogen into organic frameworks. As asymmetric organic synthesis continues to mature and evolve, catalytic enantioselective epoxidation and aziridination of olefins is sure to be at the forefront.

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