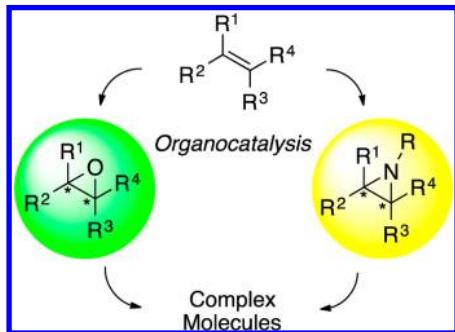


## Organocatalytic Asymmetric Epoxidation and Aziridination of Olefins and Their Synthetic Applications

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### 1. INTRODUCTION

Epoxides and aziridines are extremely versatile synthetic intermediates<sup>1,2</sup> and present in a large array of natural products and biologically active molecules (Figure 1). In addition,

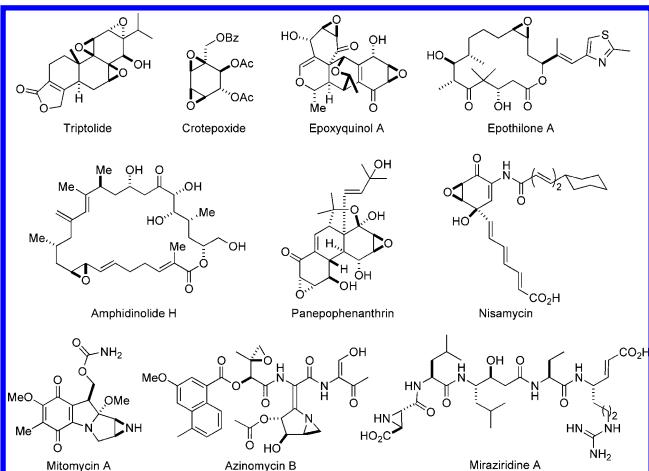


Figure 1. Epoxide or aziridine-containing biologically active molecules.

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epoxides are proposed to be biosynthetic intermediates for the rapid construction of complex polycyclic natural products such as (+)-aurilol and brevetoxin B (Figure 2).<sup>5</sup> The stereochemistry possessed by the epoxides and aziridines in biologically active molecules necessitates their enantioselective synthesis.

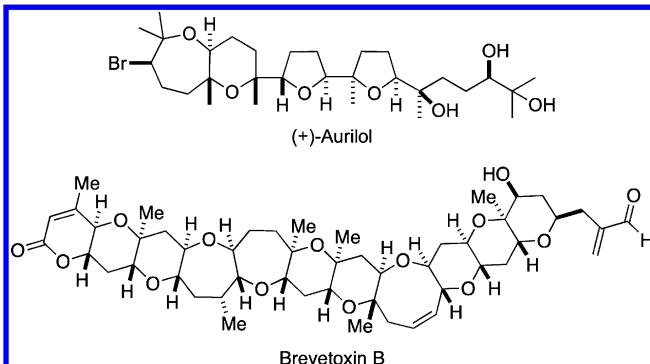


Figure 2. Examples of polycyclic natural products from polyepoxide precursors.

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),<sup>6a</sup> these nonmetal-catalyzed reactions are often referred to as organic catalysis (Kagan 1999),<sup>6a</sup> organocatalysis, or organocatalytic (MacMillan 2000).<sup>6b</sup> 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.

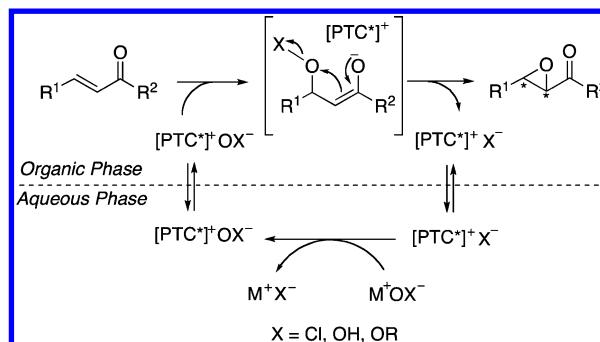
## 2. ORGANOCATALYZED ASYMMETRIC EPOXIDATION OF OLEFINS

Asymmetric epoxidation of olefins presents an especially attractive approach to chiral epoxides.<sup>7</sup> Great success has been achieved with metal-catalyzed asymmetric epoxidation of olefins such as epoxidation of allylic alcohols,<sup>8</sup> related heteroatom-containing olefins,<sup>9</sup> and unfunctionalized olefins,<sup>9b,10</sup> as well as nucleophilic epoxidation of electron-deficient olefins.<sup>11</sup> Complementary to metal-catalyzed processes, organocatalytic asymmetric epoxidation has also proven to be highly effective for synthesis of chiral epoxides.<sup>12</sup> 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).<sup>12</sup>

**Scheme 1. Catalytic Cycle for Asymmetric Epoxidation with Phase-Transfer Catalysts**



**2.1.1. Cinchona Alkaloid-Derived Quaternary Ammonium Salts.** In 1976, Wynberg and co-workers utilized the cinchona alkaloid-derived quaternary ammonium salt **1** to catalyze epoxidation of  $\alpha,\beta$ -unsaturated ketones with up to 45% ee (Figure 3).<sup>13</sup> Onda reported the epoxidation of an ester-substituted naphthoquinone in 78% ee using catalyst **1** (Figure 3).<sup>14</sup>

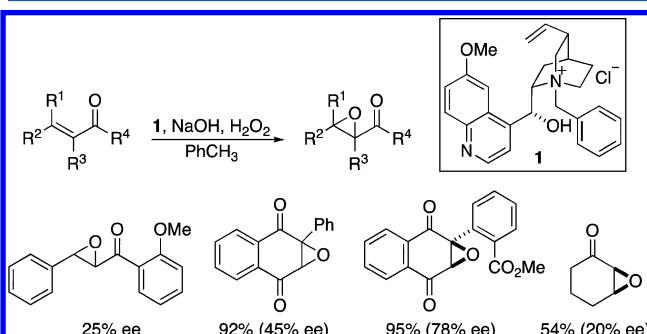
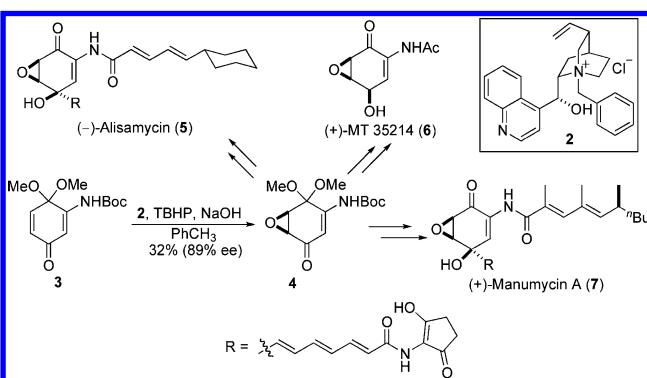


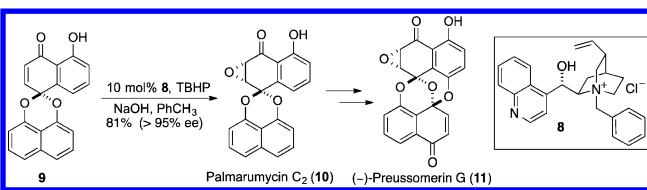
Figure 3. Asymmetric epoxidation using catalyst **1**.

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).<sup>15</sup> Key intermediate **4** was synthesized via epoxidation of enone **3** using cinchonidine-derived catalyst **2** in 32% yield and 89% ee and can be obtained in >99% ee after recrystallization.<sup>15c</sup> N-Benzylcinchoninium chloride (**8**) was employed in the syntheses of palmarumycins and (−)-preussomerin G by Barrett and co-workers in 2002 (Scheme 3).<sup>16</sup> Asymmetric

**Scheme 2. Synthesis of the Members (**5–7**) of the Manumycin Family**

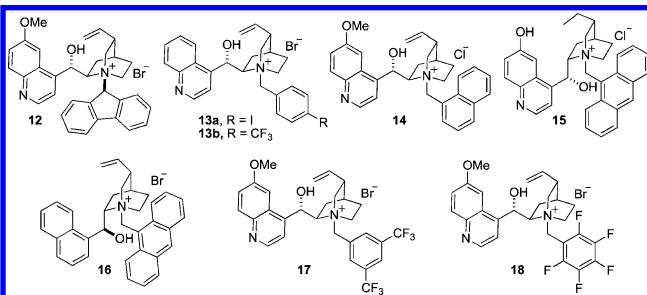


**Scheme 3. Synthesis of Palmarumycin C<sub>2</sub> (10) and (−)-Preussomerin G (11)**



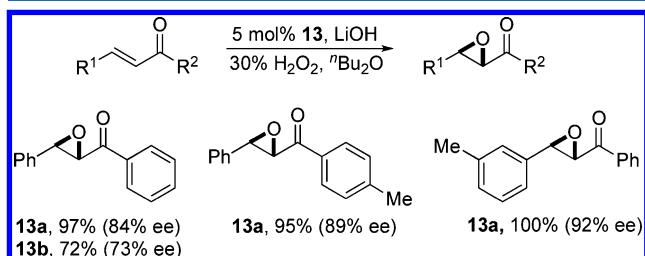
epoxidation of enone **9** with catalyst **8** in the presence of TBHP gave palmarumycin C<sub>2</sub> (**10**) in 81% yield and >95% ee, which was further converted into (−)-preussomerin G (**11**).

Quaternary ammonium salt catalysts with various nitrogen substitutions have been investigated (Figure 4). Kawaguchi and



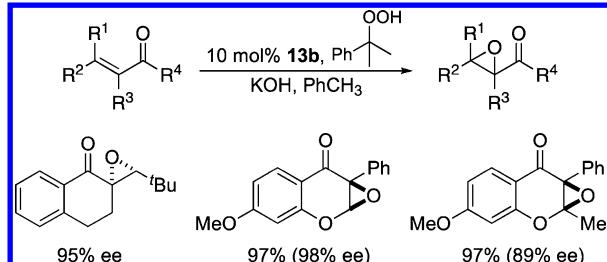
**Figure 4. Quaternary ammonium salt catalysts 12–18.**

co-workers reported catalyst **12** with a *N*-fluorenyl group in 1986, giving up to 61% ee for epoxidation of cyclic enones.<sup>17</sup> 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).<sup>18</sup>

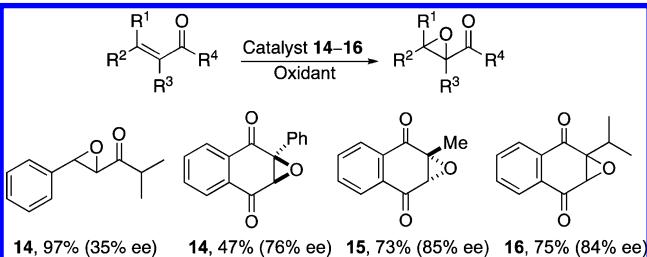


**Figure 5. Epoxidation of enones with catalyst 13.**

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).<sup>19</sup> Epoxidation of enones with catalysts bearing sterically bulky *N*-substituents (**14**,<sup>20</sup> **15**,<sup>21</sup> and **16**<sup>22</sup>) (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).<sup>20a</sup> Berkessel and co-workers showed that 2-methyl-1,4-naphthoquinone (vitamin K<sub>3</sub>) was epoxidized with catalyst **15**, bearing a hydroxyl group on the quinoline ring, in 85% ee (Figure 7).<sup>21</sup> In 2002, Dehmlow and co-workers reported their studies on analogues of cinchona alkaloids without the quinoline nitrogen atom as phase-transfer



**Figure 6. Epoxidation of conformationally fixed enones with catalyst 13b.**



**Figure 7. Epoxidation of enones with catalysts 14–16.**

catalysts. Up to 84% ee was obtained for epoxidation of 2-isopropyl-1,4-naphthoquinone with catalyst **16** (Figure 7).<sup>22</sup>

In 2013, Shibata and co-workers reported that  $\beta$ -trifluoromethyl- $\beta$ , $\beta$ -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).<sup>23</sup> It was

**Table 1. Epoxidation of  $\beta$ , $\beta$ -Disubstituted Enones with Catalyst 17**

entry	Ar <sup>1</sup>	Ar <sup>2</sup>	yield (%)	5 mol% 17, air	ee (major) (%)
				H <sub>2</sub> NNHMe, Cs <sub>2</sub> CO <sub>3</sub>	
1	Ph	Ph	91	95:5	99
2	4-MeOC <sub>6</sub> H <sub>4</sub>	Ph	91	94:6	98
3	Ph	2-MeC <sub>6</sub> H <sub>4</sub>	99	96:4	96
4	Ph	4-O <sub>2</sub> NC <sub>6</sub> H <sub>4</sub>	98	94:6	96
5	Ph	2-naphthyl	99	94:6	98

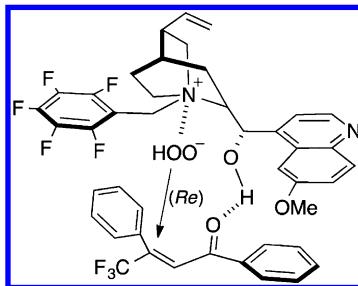
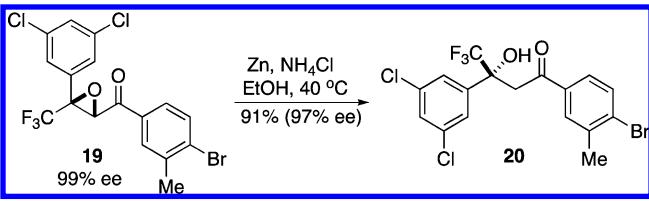
proposed that H<sub>2</sub>O<sub>2</sub> was likely to be generated in situ from methylhydrazine and air and to act as the oxidant. In their studies, Chen and co-workers found that quinidinium catalyst **18** (Figure 4), bearing a pentafluorobenzyl group, was very effective for epoxidation of  $\beta$ -trifluoromethyl- $\beta$ , $\beta$ -disubstituted enones in the presence of H<sub>2</sub>O<sub>2</sub>, giving up to 96% yield and 99.7% ee (Table 2).<sup>24</sup> The resulting  $\alpha$ , $\beta$ -epoxy ketone **19** could be converted into potentially useful  $\beta$ -trifluoromethyl- $\beta$ -hydroxy ketone **20** in 91% yield via reduction with Zn and NH<sub>4</sub>Cl (Scheme 4). The hydrogen-bonding and the  $\pi$ - $\pi$  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.<sup>18,19b,21,24</sup> However, as shown by Lygo<sup>25</sup> and Corey,<sup>26</sup> respectively, *N*-anthracenylmethyl-substituted ammo-

**Table 2. Epoxidation of  $\beta,\beta$ -Disubstituted Enones with Catalyst 18 and  $H_2O_2$**

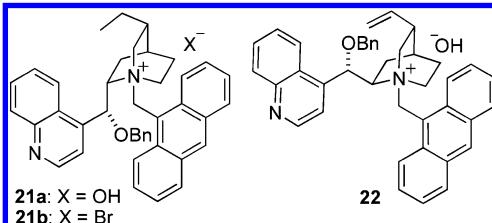
entry	R	Ar	yield (%)	dr	ee (major) (%)
1	Ph	Ph	93	50:1	99
2	Ph	4-ClC <sub>6</sub> H <sub>4</sub>	82	50:1	98
3	Ph	2-MeOC <sub>6</sub> H <sub>4</sub>	94	50:1	99.7
4	Ph	2-naphthyl	87	50:1	98
5	4-BrC <sub>6</sub> H <sub>4</sub>	Ph	96	50:1	97
6	3,5-Cl <sub>2</sub> C <sub>6</sub> H <sub>3</sub>	4-Br-3-MeC <sub>6</sub> H <sub>3</sub>	95	20:1	99
7	Et	Ph	88	100:1	82

**Scheme 4. Synthesis of  $\beta$ -Hydroxy Ketone 20 via Reduction of  $\alpha,\beta$ -Epoxy Ketone 19**



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

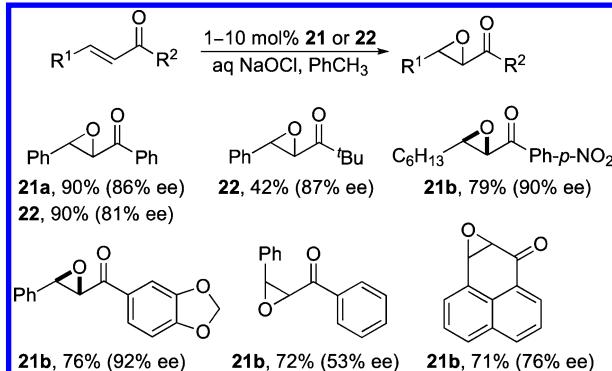
nium salts with the C-9 hydroxyl groups being protected as benzyl ethers are effective catalysts for epoxidation using NaOCl and KOCi as oxidant (Figure 9). Both the nature of O-



**Figure 9. Quaternary ammonium salt catalysts 21 and 22.**

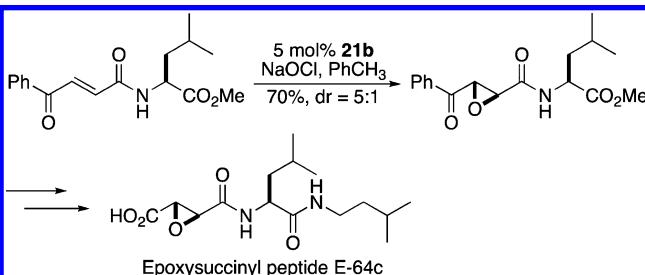
and N-substituents and the choice of the oxidant are crucial for the enantioselectivity. For example, in 1998, Lygo and co-workers reported that (*E*)-chalcone was epoxidized in 90% yield and 86% ee with catalyst 21a and NaOCl (Figure 10).<sup>25a</sup> The ee's were further improved by optimizing the reaction conditions (Figure 10).<sup>25c</sup> Allylic alcohols can be directly converted to  $\alpha,\beta$ -epoxy ketones in 78–87% ee under the epoxidation conditions.<sup>27</sup> Epoxidation with catalyst 21b was used in the synthesis of epoxysuccinyl peptide E-64c (a cysteine protease inhibitor) (Scheme 5).<sup>28</sup>

In 1999, Corey and co-workers demonstrated remarkably high enantioselectivity (91–98.5% ee) for epoxidation of

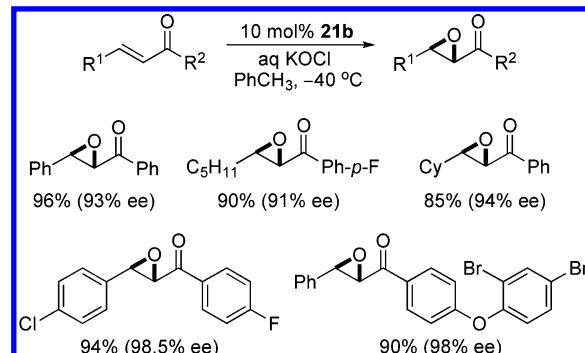


**Figure 10. Epoxidation of enones with catalyst 21 or 22.**

**Scheme 5. Synthesis of Epoxysuccinyl Peptide E-64c**



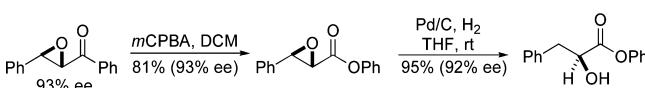
enones with catalyst 21b using KOCi as oxidant (Figure 11).<sup>26</sup> The resulting  $\alpha,\beta$ -epoxy ketones can be transformed into



**Figure 11. Epoxidation of enones with catalyst 21b and KOCi.**

other useful synthetic intermediates such as  $\alpha,\beta$ -epoxy esters and  $\alpha$ -hydroxy esters (Scheme 6). The epoxidation is proposed

**Scheme 6. Transformations of  $\alpha,\beta$ -Epoxy Ketone**



to proceed via a transition state described in Figure 12.<sup>26</sup> 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).<sup>29</sup> KOCi was believed to be formed in situ from TCCA and KOH and acted as the

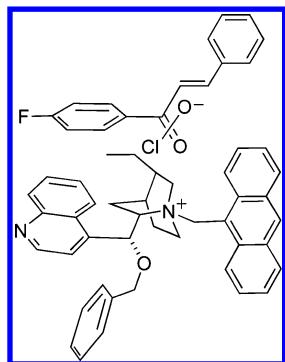


Figure 12. Proposed transition state for epoxidation using catalyst 21b.

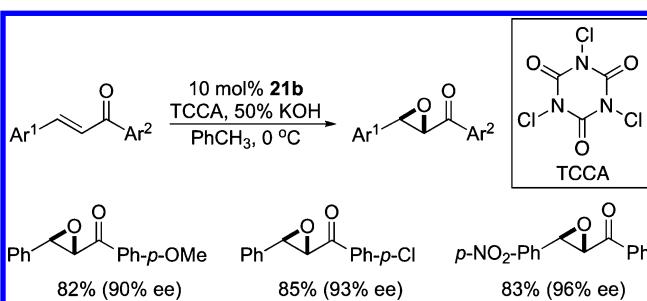


Figure 13. Epoxidation of chalcones with catalyst 21b and TCCA.

oxidant.<sup>29b</sup> 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.<sup>30</sup>

Use of cinchonidine-derived catalyst 23 (Figure 14) for epoxidation was reported by Kim and co-workers in 2003. Up

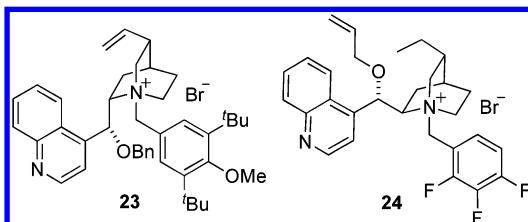


Figure 14. Quaternary ammonium salt catalysts 23 and 24.

to 78% ee was obtained for epoxidation of 1,3-diarylenones using NaOCl as oxidant.<sup>31</sup> 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).<sup>32</sup>

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),

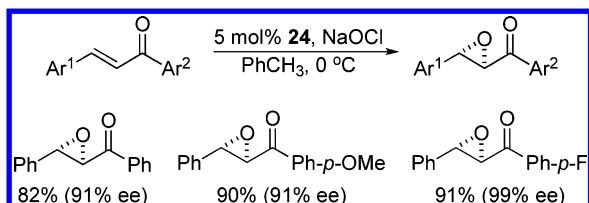


Figure 15. Epoxidation of chalcones with catalyst 24.

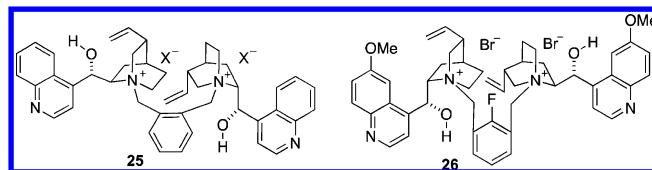


Figure 16. Quaternary ammonium salt catalysts 25 and 26.

which achieved up to 63% ee in the epoxidation of cyclohexenone.<sup>17,33</sup> 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).<sup>34</sup> The C-9

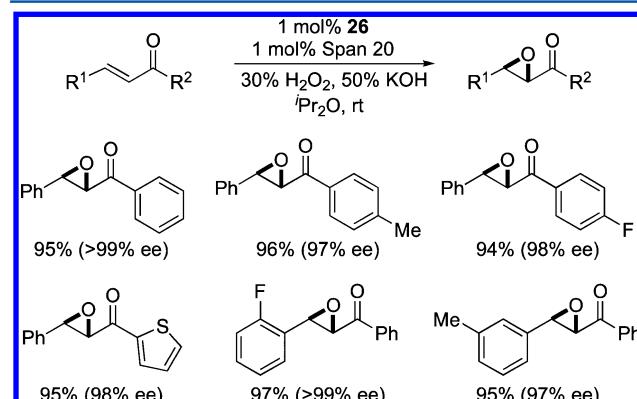


Figure 17. Epoxidation of diarylenones with catalyst 26.

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.<sup>35</sup>

**2.1.2. Other Quaternary Ammonium Salts.** Other quaternary ammonium salt catalysts have been investigated for asymmetric epoxidation of olefins (Figure 18). In 1983,

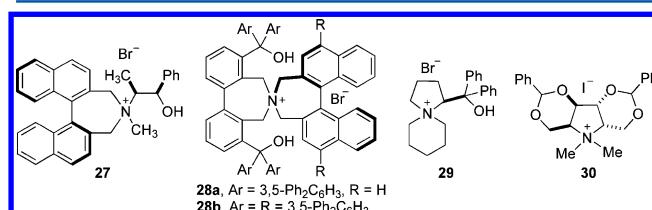
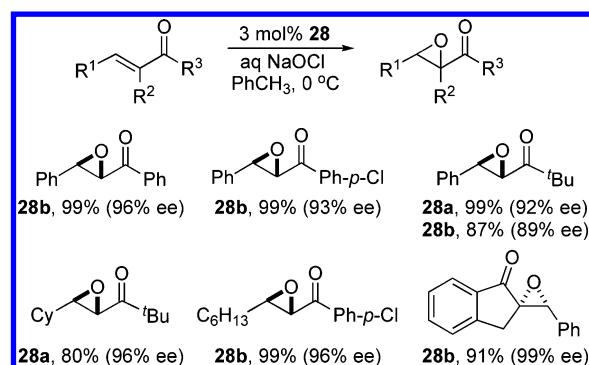


Figure 18. Quaternary ammonium salt catalysts 27–30.

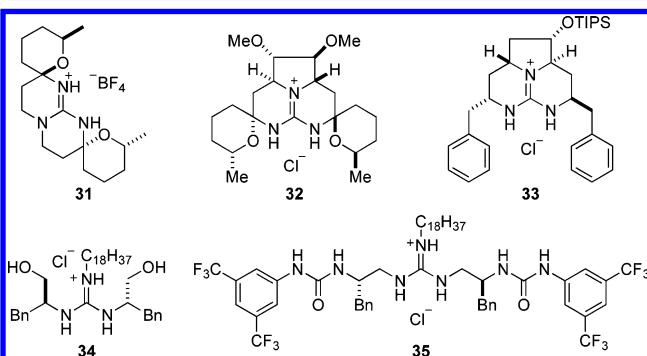
Mazaleyrat reported binaphthyl-based catalyst 27, which epoxidized (E)-chalcone with 37.1% ee in the presence of  $H_2O_2$ .<sup>36</sup> In 2004, Maruoka and co-workers showed that binaphthyl-based spiro quaternary ammonium salts (28), containing two diaryl methanol groups, were highly effective catalysts for epoxidation of enones (Figure 18).<sup>37</sup> 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.<sup>37</sup> In 1994, Masaki and co-workers reported their studies on the



**Figure 19.** Epoxidation of enones with catalyst 28.

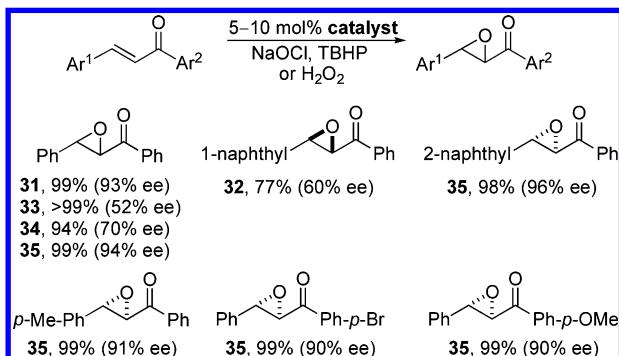
epoxidation of (*E*)-chalcone (9.1% ee) with pyrrolidinium salts **29** and **30** as catalysts (Figure 18).<sup>38</sup>

**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



**Figure 20.** Guanidinium salt catalysts 31–35.

catalyst, giving chalcone epoxide in 99% yield and 93% ee (Figure 21).<sup>39</sup> Epoxidation using cyclic guanidinium salts 32

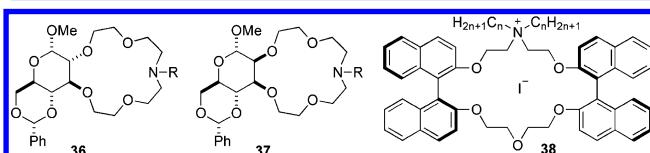


**Figure 21.** Epoxidation of enones with guanidinium salt catalysts.

and 33 was investigated by Nagasawa and co-workers, and up to 60% ee was obtained for 1,3-diaryl enones (Figure 21).<sup>40</sup> Several acyclic guanidinium salts such as 34 and 35 were subsequently studied for the epoxidation by the same group (Figure 20).<sup>41,42</sup> 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).<sup>42</sup>

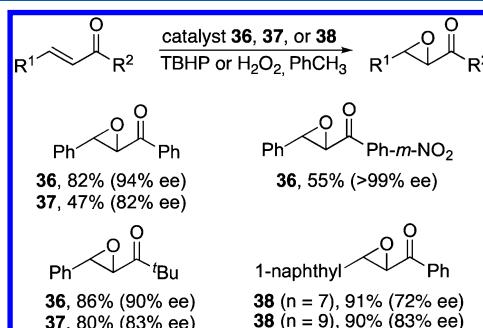
**2.1.4. Crown Ether-Type Catalysts.** Crown ether-type phase-transfer catalysts with attached chiral moieties have also

been examined for olefin epoxidation (Figure 22). Bakó and co-workers reported monosaccharide-based crown ether-type



**Figure 22.** Crown ether-type phase-transfer catalysts 36–38.

catalysts 36 and 37 for the epoxidation,<sup>43</sup> affording up to >99% ee for chalcones with TBHP as oxidant (Figure 23).<sup>43e</sup>



**Figure 23.** Epoxidation of enones with crown ether-type catalysts.

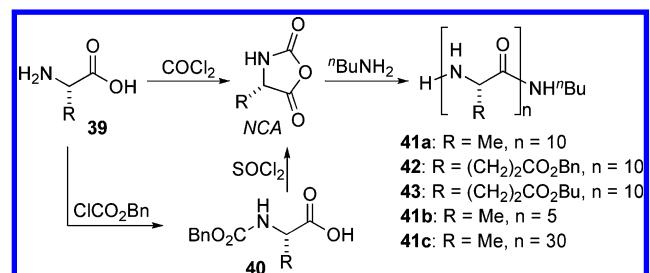
Both the monosaccharide moiety and the nitrogen substituent of the catalyst were important for the reactivity and enantioselectivity of the epoxidation.<sup>43b</sup> Epoxidation with azacrown ether-type catalyst 38 was examined by Hori and co-workers, and up to 83% ee was obtained for 1,3-diaryl enones using  $H_2O_2$  (Figure 23).<sup>44</sup> The alkyl groups on the nitrogen were shown to have a significant effect on the epoxidation. The aliphatic ether oxygen was involved in the complexation with the cation and was also crucial for the epoxidation. Replacement of this oxygen with a methylene group led to a dramatic decrease of the enantioselectivity.<sup>44</sup>

## 2.2. Peptide-Type Catalysts

### 2.2.1. Polypeptide-Catalyzed Epoxidation under Tri-

**phasic Conditions.** In 1980, Juliá and co-workers reported a polypeptide-catalyzed asymmetric epoxidation<sup>45</sup> of (*E*)-chalcone with H<sub>2</sub>O<sub>2</sub>–NaOH in toluene–water.<sup>46</sup> 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,

**Scheme 7.** Synthesis of Polypeptides 41–43



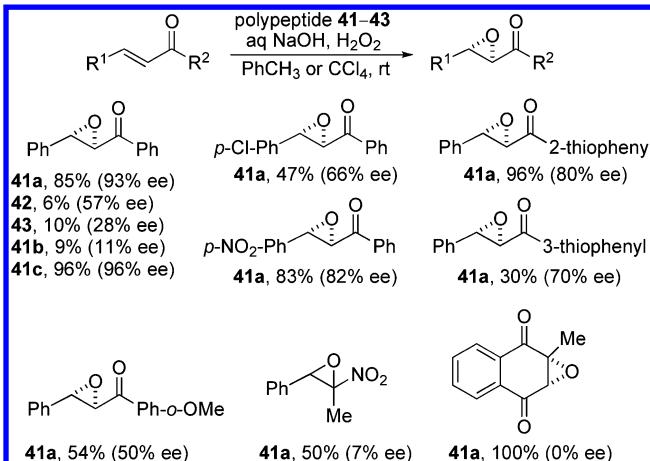


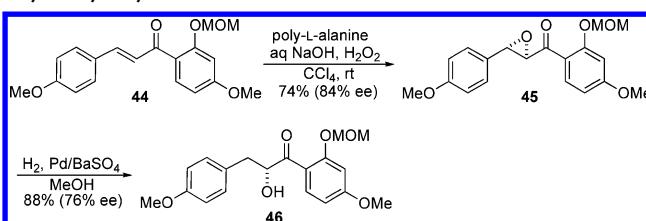
Figure 24. Epoxidation of olefins with polypeptide catalysts 41–43.

Figure 24). The polypeptide catalysts can be synthesized via polymerization of *N*-carboxyanhydride (NCA) initiated by a nucleophile such as *n*-butylamine (Scheme 7). The peptide length is regulated by the ratio of NCA to initiator.

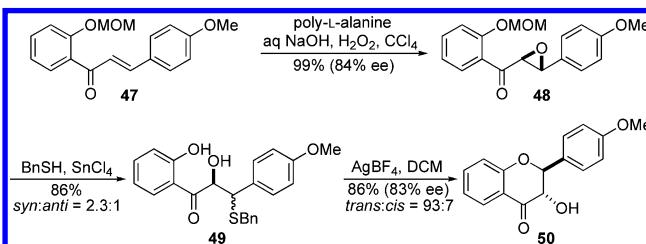
Julia, Colonna, and co-workers subsequently carried out a series of studies on the epoxidation, including catalyst structure, reaction conditions, and substrate scope, etc.<sup>47–50</sup> The degree of polymerization of the polypeptide catalysts was shown to be important for the enantioselectivity. 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).<sup>47</sup> A variety of polypeptides derived from different amino acids were also extensively studied.<sup>49</sup> 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.<sup>49</sup> Studies showed that polypeptides with carboxyl and ester groups at the C-terminus were also effective catalysts for epoxidation.<sup>50</sup> A cross-linked polystyrene-supported poly-L-alanine gave 82% yield and 84% ee for epoxidation of (*E*)-chalcone.<sup>50</sup> Reaction conditions were also investigated with (*E*)-chalcone as substrate and 41a as catalyst, and optimal results were obtained with H2O2–NaOH in toluene or CCl4.<sup>47</sup> 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).<sup>47,48</sup>

Ferreira, Bezuidenhout, 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.<sup>51</sup> For example, chalcone 44 was epoxidized with poly-L-alanine and H2O2–NaOH in CCl4 to give epoxide 45 in 74% yield and 84% ee,<sup>51b</sup> which was hydrogenated to  $\alpha$ -hydroxydihydrochalcone 46 in 88% yield and 76% ee (Scheme 8).<sup>51c,52</sup> Optically active dihydroflavonol 50 could be synthesized in 83% ee from epoxide 48 via epoxide ring opening with phenylmethanethiol and subsequent cyclization (Scheme 9).<sup>51d,e</sup>

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.<sup>53</sup>

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

Scheme 9. Synthesis of Dihydroflavonol 50



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

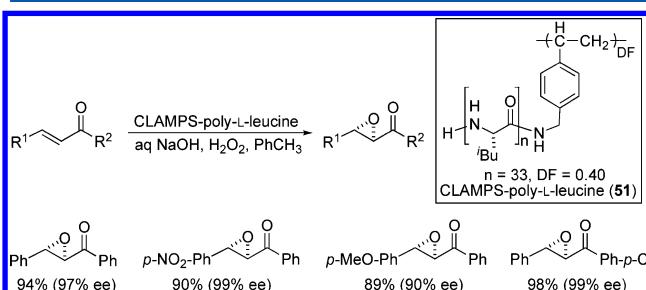
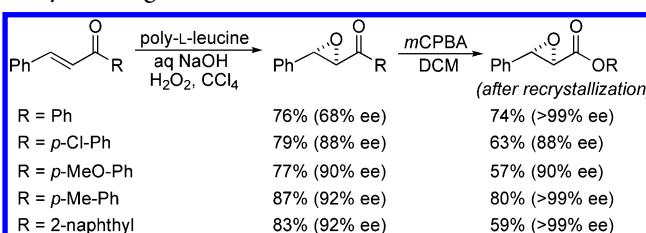


Figure 25. Epoxidation of chalcones with polypeptide catalyst 51.

be recovered and reused several times without substantial loss of catalytic activity.<sup>53</sup> 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).<sup>54</sup> The substituent on the phenyl group was

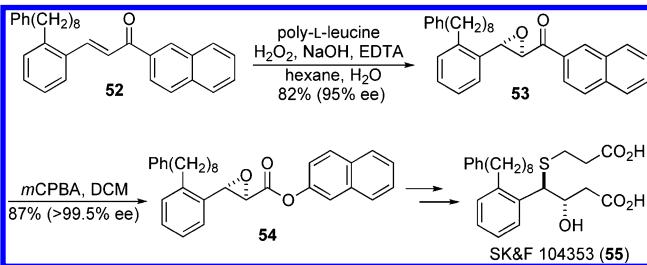
Scheme 10. Synthesis of Glycidic Esters via Epoxidation and Baeyer–Villiger Oxidation



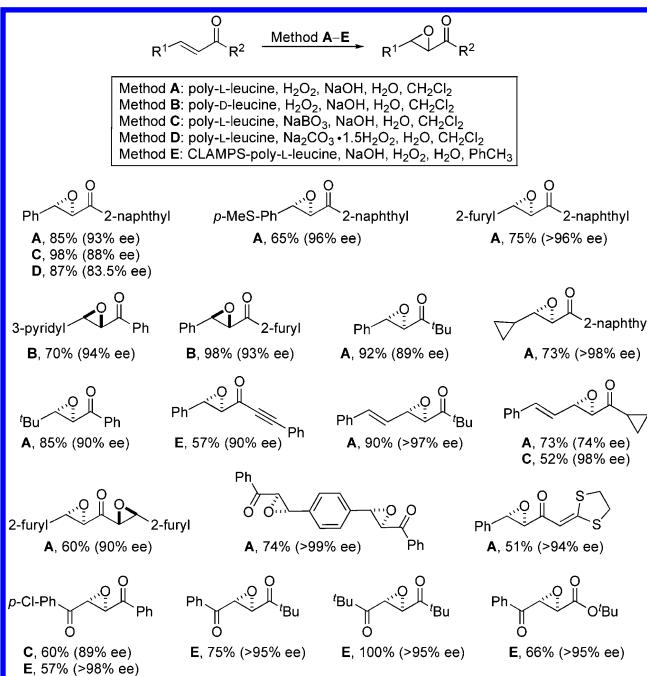
important for the regioselectivity of the Baeyer–Villiger oxidation. Chalcone epoxides and glycidic esters could be made on a multihundred gram scale using this process.<sup>54</sup> Lantos, Novack, and co-workers reported the synthesis of SK&F 104353 (55) (a potent leukotriene antagonist) via asymmetric epoxidation, Baeyer–Villiger oxidation, and further transformations (Scheme 11).<sup>55</sup> The poly-L-leucine catalyst was

synthesized using freshly prepared leucine-NCA in a humidity chamber with 70–75% relative humidity.<sup>55</sup>

**Scheme 11. Synthesis of SK&F 104353 (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.<sup>56</sup> High ee's (up to >99%) were achieved for a variety of  $\alpha,\beta$ -unsaturated ketones including heterocyclic enones, alkyl- or alkynyl-substituted enones, dienones, dienediones, and enediones (Figure 26). Along with H<sub>2</sub>O<sub>2</sub>, sodium perborate and sodium percarbonate (Na<sub>2</sub>CO<sub>3</sub>·1.5H<sub>2</sub>O<sub>2</sub>) were also found to be suitable oxidants for the epoxidation.<sup>56,57</sup>

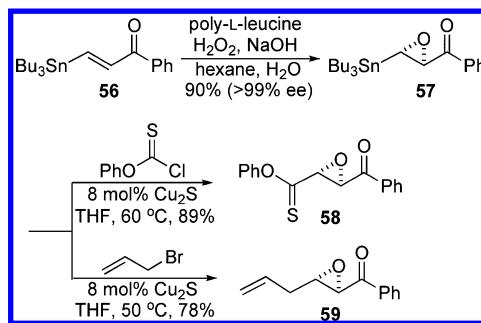


**Figure 26.** Epoxidation of various electron-deficient olefins with polypeptide catalysts.

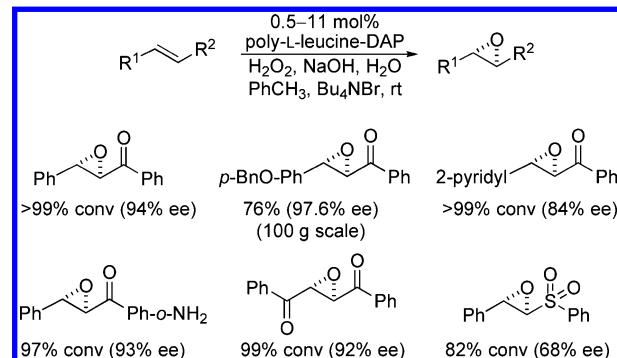
As shown by Falck and co-workers in 1997, stannyl-substituted enone 56 was an effective substrate for the asymmetric epoxidation, giving stannylepoxyde 57 in 90% yield and >99% ee with poly-L-leucine as catalyst (Scheme 12).<sup>58</sup> The epoxide was converted into epoxy ketones 58 and 59 by Cu<sub>2</sub>S-mediated thiocarboxylation 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

**Scheme 12. Epoxidation of Enone 56 and Subsequent Cross Couplings**

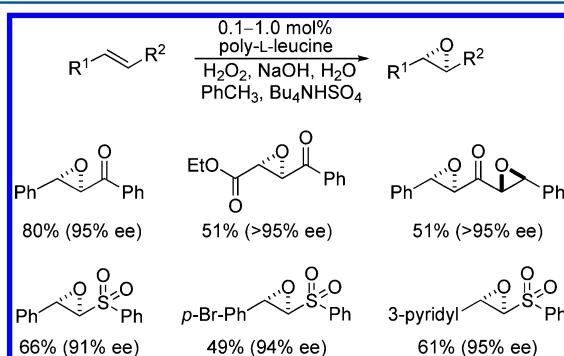


and catalyst loading.<sup>59</sup> The modified epoxidation process was applied to several enones and an arylvinyl sulfone<sup>59c,e</sup> with one example being carried out on 100 g scale<sup>59d,e</sup> (Figure 27). In



**Figure 27.** Epoxidation of olefins with polypeptide catalyst under PTC conditions.

2004, Roberts and co-workers reported their studies on the epoxidation of enones and arylvinyl sulfones using poly-L-leucine as catalyst and Bu<sub>4</sub>NHSO<sub>4</sub> (Figure 28).<sup>60</sup> Epoxidation using poly-L-leucine immobilized on hydrotalcite and TBAB under triphasic conditions was also reported by Segarra and co-workers.<sup>61</sup>



**Figure 28.** Epoxidation of olefins with polypeptide catalyst under PTC conditions.

**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.<sup>62</sup> Aqueous H<sub>2</sub>O<sub>2</sub> and NaOH were replaced with urea–H<sub>2</sub>O<sub>2</sub> (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).

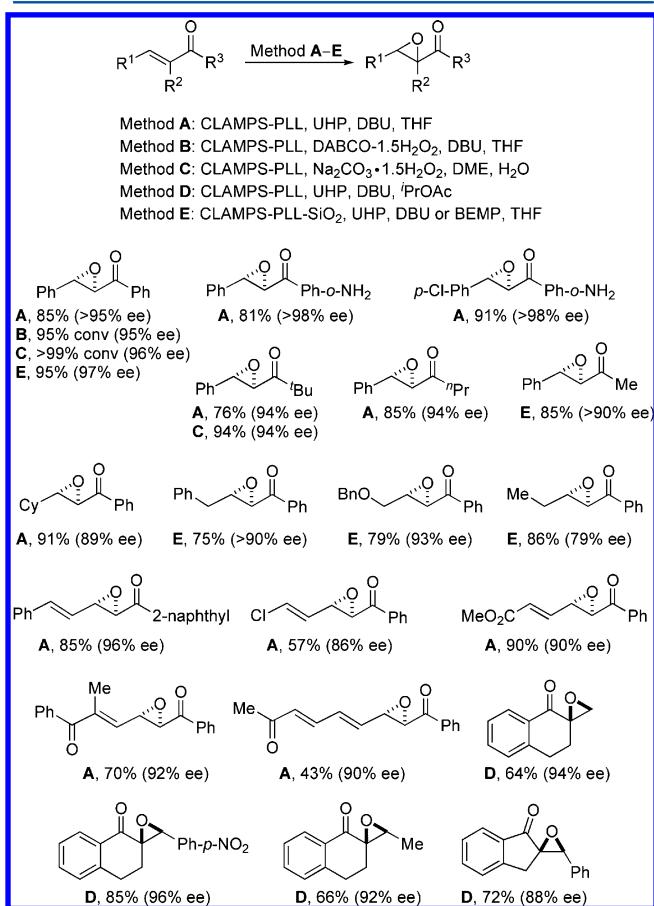


Figure 29. Epoxidation of olefins with polypeptide catalysts under biphasic conditions.

DABCO- $1.5\text{H}_2\text{O}_2$  was also found to be an effective oxidant (Figure 29, Method B).<sup>62</sup> 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.<sup>62</sup> Roberts and co-workers showed that the epoxidation also proceeded effectively with sodium percarbonate ( $\text{Na}_2\text{CO}_3 \cdot 1.5\text{H}_2\text{O}_2$ ) in a miscible solvent mixture such as DME/H<sub>2</sub>O, giving the epoxides in up to 96% ee (Figure 29, Method C).<sup>63</sup> 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  $\alpha,\beta$ -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).<sup>64</sup> Wang and co-workers reported the epoxidation of chalcones (up to 95% ee) with poly-L-leucine using H<sub>2</sub>O<sub>2</sub> and NH<sub>4</sub>HCO<sub>3</sub>.<sup>65</sup>

Roberts and co-workers also extensively studied the epoxidation with the polypeptide catalyst immobilized on a poly(ethylene glycol) (PEG) polystyrene support<sup>66</sup> and absorbed on silica<sup>67</sup> under biphasic conditions (Figure 29, Method E).<sup>67d,e</sup> High ee's were obtained for various enones with these catalysts. The readily prepared silica-absorbed catalyst was highly active, robust, and operationally simple

and could be recycled. Tang and co-workers 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).<sup>68</sup>

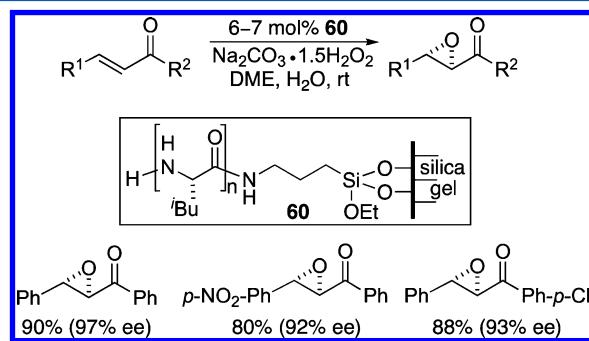
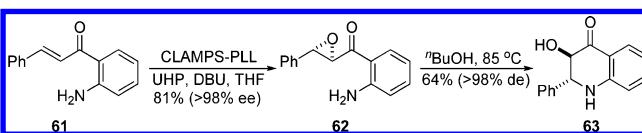


Figure 30. Epoxidation of chalcones with silica-grafted poly-L-leucine.

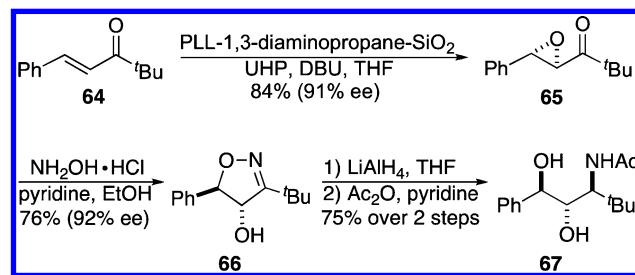
The synthetic applications of the epoxidation using silica-absorbed and other solid-supported polypeptide catalysts were extensively investigated by Roberts and co-workers. For example, 2'-aminochalcone (62) was converted to tetrahydroquinolone 63 in 64% yield via an intramolecular nucleophilic ring opening (Scheme 13).<sup>64d</sup> 3-Acetamido-1,2-

### Scheme 13. Synthesis of Tetrahydroquinolone 63



diol 67 was obtained from epoxy ketone 65 via oxime formation, concomitant epoxide ring opening, reduction, and acetylation (Scheme 14).<sup>67h</sup> As shown in Schemes 15 and 16,

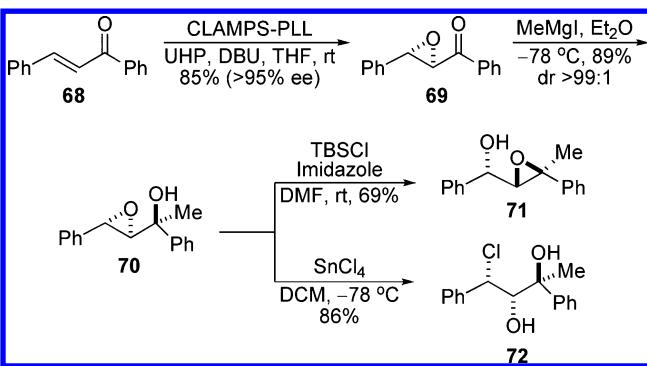
### Scheme 14. Synthesis of 3-Acetamido-1,2-diol 67



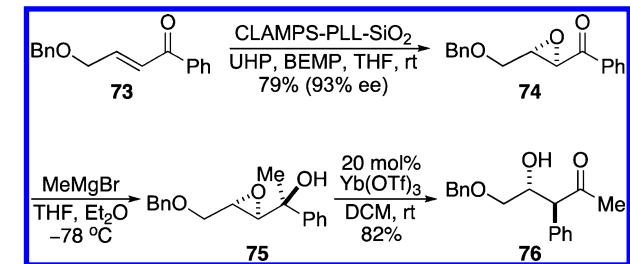
nucleophilic addition of Grignard reagents to epoxy ketones 69 and 74 proceeded diastereoselectively to give epoxy tertiary alcohols 70 and 75, respectively. Treatment of 70 with TBSCl and imidazole provided epoxy alcohol 71 in 69% yield via a Payne rearrangement. Epoxide 70 was opened by SnCl<sub>4</sub> to give 1-chloro-2,3-diol 72 in 86% yield with retention of configuration at the benzylic carbon (Scheme 15). SnCl<sub>4</sub> likely coordinated to the epoxide oxygen and delivered the chloride anion to the benzylic carbon intramolecularly.<sup>69</sup> Epoxy tertiary alcohol 75 was converted into  $\beta$ -hydroxy ketone 76 with Yb(OTf)<sub>3</sub> via pinacol-type rearrangement (Scheme 16).<sup>67e,f</sup>

Galactonic acid derivative 79 (Scheme 17)<sup>70</sup> and naturally occurring styryl lactones such as (+)-goniopypprone (84) and (+)-goniofufurone (85) (Scheme 18)<sup>71</sup> were synthesized from

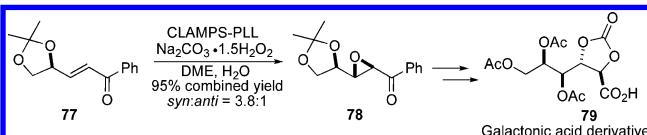
**Scheme 15. Synthesis of  $\alpha,\beta$ -Epoxy Alcohol 71 and Halodiol 72**



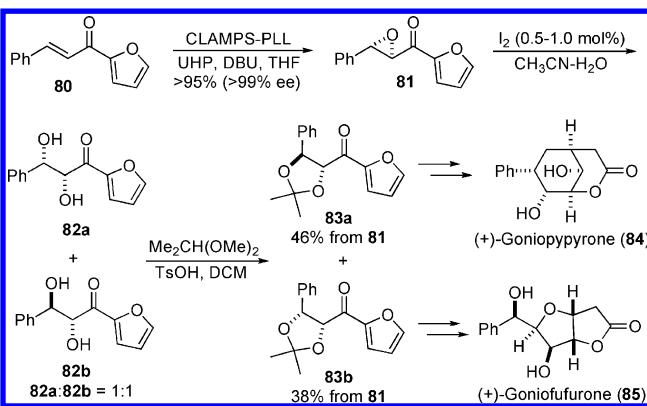
**Scheme 16. Synthesis of  $\beta$ -Hydroxy Ketone 76**



**Scheme 17. Synthesis of Galactonic Acid Derivative 79**

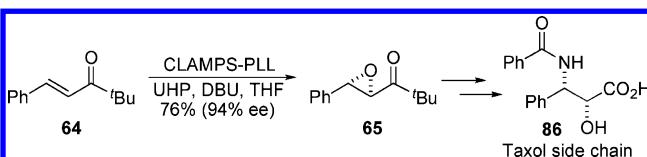


**Scheme 18. Synthesis of (+)-Goniopyprone (84) and (+)-Goniofufurone (85)**



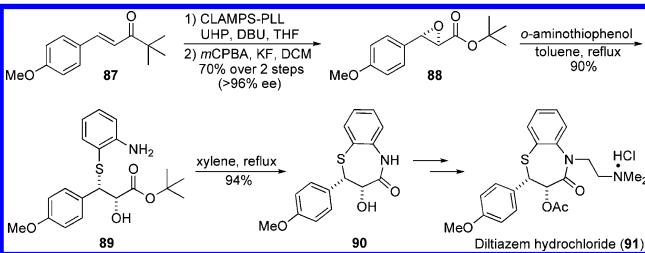
corresponding epoxy ketones 78 and 81 by Roberts and co-workers. The epoxy ketones were also elaborated to several pharmaceuticals, including Taxol side chain 86 (Scheme 19),<sup>64a</sup>

**Scheme 19. Synthesis of Taxol Side Chain 86**



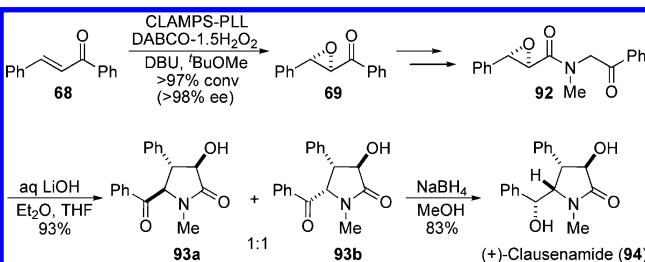
diltiazem hydrochloride (91) (a potent blood-pressure-lowering agent) (Scheme 20),<sup>64a</sup> (+)-clausenamide (94) (an

**Scheme 20. Synthesis of Diltiazem Hydrochloride (91)**

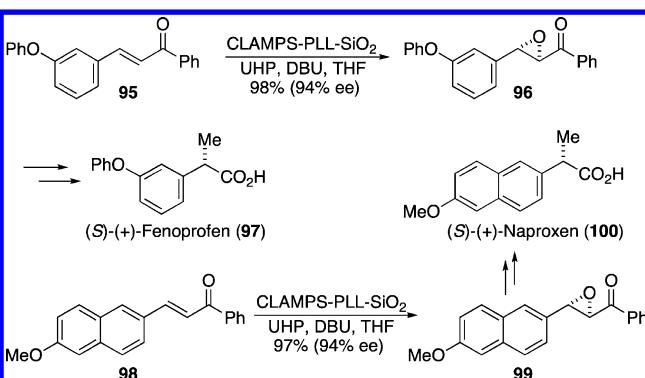


antiamnesic agent with potent hepatoprotective activity) (Scheme 21),<sup>66</sup> and anti-inflammatory agents such as (*S*)-fenoprofen (97)<sup>67b,d</sup> and (*S*)-naproxen (100) (Scheme 22).<sup>67d</sup>

**Scheme 21. Synthesis of (+)-Clausenamide (94)**

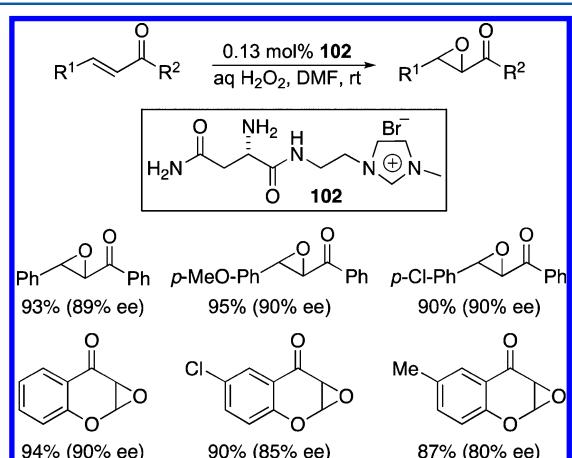
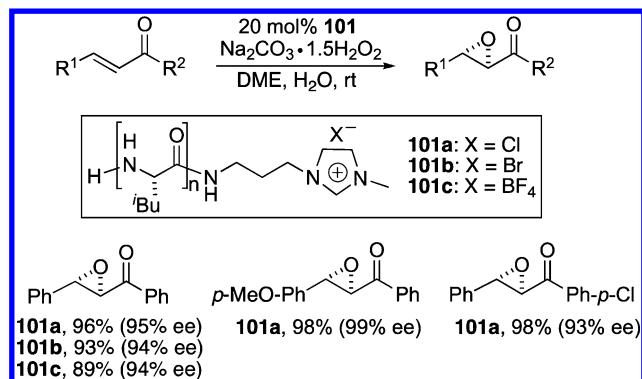


**Scheme 22. Synthesis of (*S*)-Fenoprofen (97) and (*S*)-Naproxen (100)**



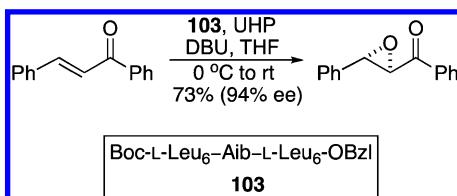
Imidazolium-attached polypeptides have also been investigated for epoxidation. In 2009, Tang, Yang, and co-workers reported that imidazolium-modified poly-L-leucines 101 were highly enantioselective catalysts for epoxidation, providing chalcone epoxides in up to 99% ee (Figure 31).<sup>72</sup> A one-pot protocol consisting of Claisen–Schmidt condensation and asymmetric epoxidation with imidazolium-modified poly-L-leucine 101a was also reported by the same group.<sup>73</sup> 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).<sup>74</sup>

**2.2.3. Polypeptide-Catalyzed Epoxidation under Homogeneous Conditions.** Polypeptide catalysts soluble in organic solvents have also been investigated for epoxidation. In 2000, Ohkata and co-workers reported the epoxidation of (*E*)-chalcone with several soluble oligopeptides containing  $\alpha$ -

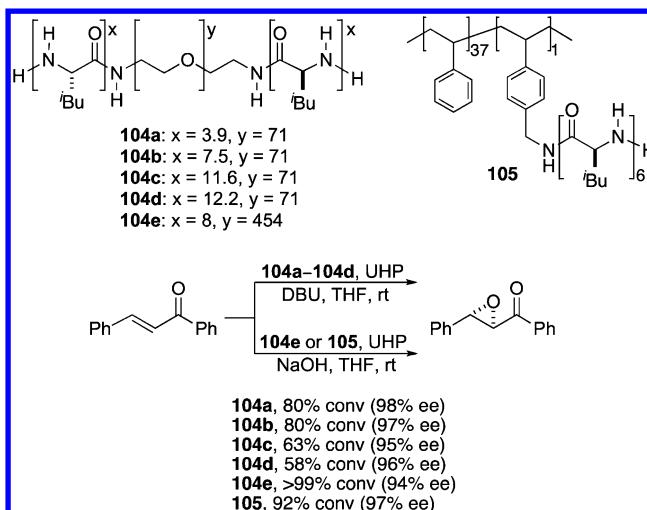


aminoisobutyric acid (Aib) using urea–H<sub>2</sub>O<sub>2</sub> and DBU in THF.<sup>75</sup> The epoxide was obtained in 73% yield and 94% ee with catalyst 103 (Scheme 23). The Aib residue likely

### Scheme 23. Epoxidation of Chalcone with Soluble Peptide Catalyst



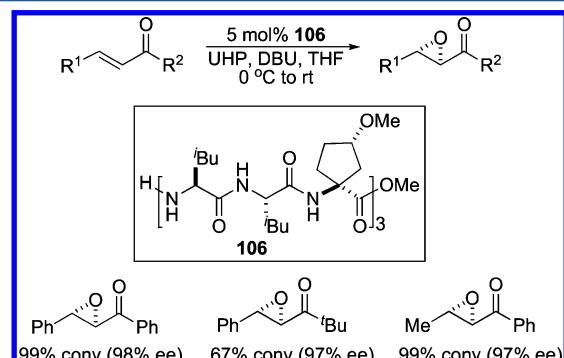
promoted formation of a helical structure as well as enhanced the solubility of the peptides in organic solvents. In 2001, Roberts and co-workers prepared diaminopoly(ethylene glycol)-bound poly-L-leucine catalysts 104a–d and examined the epoxidation of (*E*)-chalcone with these catalysts using urea–H<sub>2</sub>O<sub>2</sub> and DBU in THF (Figure 33).<sup>76,77</sup> 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).<sup>78</sup> They also showed that styrene/aminomethylstyrene-copolymer-linked poly-L-leucine 105 was a highly effective catalyst for epoxidation of (*E*)-chalcone (Figure 33).<sup>78</sup> The epoxidation was carried out in a membrane



**Figure 33.** Epoxidation of chalcone with soluble peptide catalysts.

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.<sup>79</sup> 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–H<sub>2</sub>O<sub>2</sub> in THF (Figure 34).<sup>80</sup> Introduction of the cyclic α,α-disubstituted



**Figure 34.** Epoxidation of enones with peptide catalyst 106.

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).<sup>81</sup> 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–H<sub>2</sub>O<sub>2</sub>. Kudo and Akagawa incorporated 3-(1-pyrenyl)alanine [Ala(1-Pyn)] into resin-supported polypeptide 108 (Figure 36).<sup>82</sup> Various α,β-unsaturated aldehydes were epoxidized with catalyst 108 and H<sub>2</sub>O<sub>2</sub>, giving epoxy alcohols in up to 95% ee upon reduction with NaBH<sub>4</sub>.

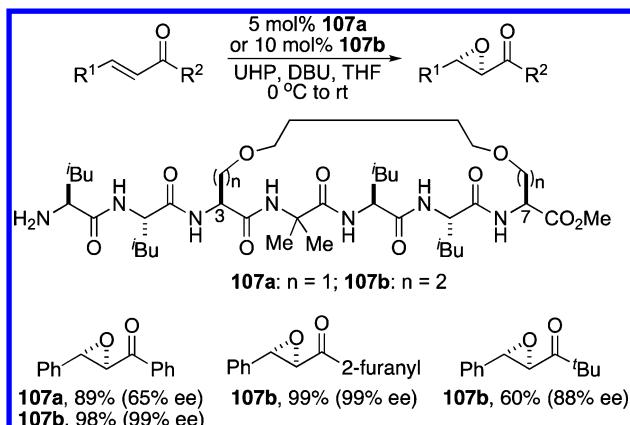


Figure 35. Epoxidation of enones with oligopeptide catalyst 107.

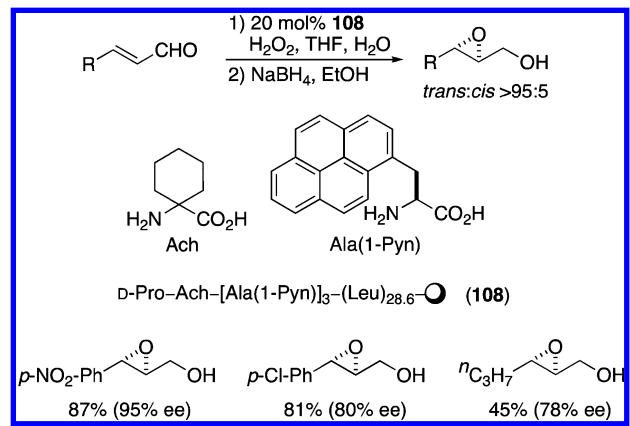
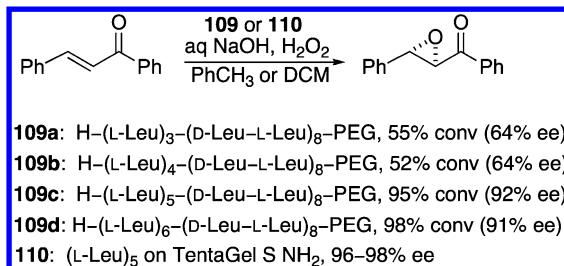


Figure 36. Epoxidation of enals with polypeptide catalyst 108.

**2.2.5. Mechanistic Insights.** In their initial reports, Juliá and Colonna indicated that an  $\alpha$ -helical structure of polypeptide catalysts might be important for asymmetric induction.<sup>47,50</sup> 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.<sup>49</sup> The importance of  $\alpha$ -helical structure on the enantioselectivity of the epoxidation has been further demonstrated by Ohkata,<sup>75,83</sup> Berkessel,<sup>84</sup> Kelly,<sup>77</sup> Tanaka,<sup>80</sup> Demizu, Kurihara,<sup>81</sup> and others. Studies indicated that the amino acid residues at the N-terminus of the peptide catalysts appeared to be responsible for the stereochemistry and enantioselectivity of the epoxidation.<sup>76,84,85</sup> 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).<sup>85c</sup> 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).<sup>84a</sup> 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  $\alpha$ -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.<sup>84a</sup>

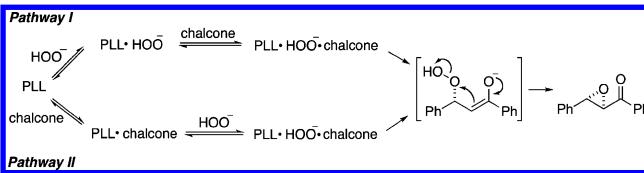
A reaction model was also proposed by Kelly and Roberts.<sup>86a</sup> The  $\alpha$  helix binds to  $H_2O_2$  and chalcone via hydrogen bonding

Scheme 24. Epoxidation of Chalcone with Catalyst 109 or 110



with the N-terminal amidic N–H groups. The helical conformation and hydrogen-bonding motif are likely determining factors for the stereocontrol of the epoxidation.<sup>86</sup> Kelly, Roberts, and co-workers have shown that the conjugate addition of  $HOO^-$  to olefin, the first step in the epoxidation, is reversible.<sup>87</sup> In their mechanistic studies, Colonna, Ottolina, and co-workers observed saturation kinetics for both chalcone and  $HOO^-$  in the epoxidation of chalcone with PEG-bound poly-L-leucine catalyst.<sup>88,45c</sup> This is consistent with a steady-state random bireactant system, in which both chalcone and  $HOO^-$  must bind to the catalyst to form the PLL• $HOO^-$ •chalcone complex before reaction occurs (Scheme 25).

Scheme 25



Pathway I was shown to be kinetically favored over pathway II.<sup>88</sup> Further kinetic studies with calorimetry by Blackmond and co-workers indicated that the epoxidation proceeded via pathway I, with pathway II being kinetically negligible.<sup>89</sup>

### 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).<sup>90</sup> A series of 5-membered ring (116–120)<sup>91</sup> and binaphthyl-based guanidines (121–123)<sup>92</sup> 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).<sup>91b</sup> 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).<sup>91a</sup>

**2.3.2. Chiral  $\beta$ -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.<sup>93</sup> In 2005, Lattanzi reported that readily available  $\alpha,\alpha$ -diphenyl-L-prolinol (125a) could act as the catalyst for epoxidation of enones with TBHP, giving up to 80% ee for chalcones (Figure 41).<sup>94</sup> 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

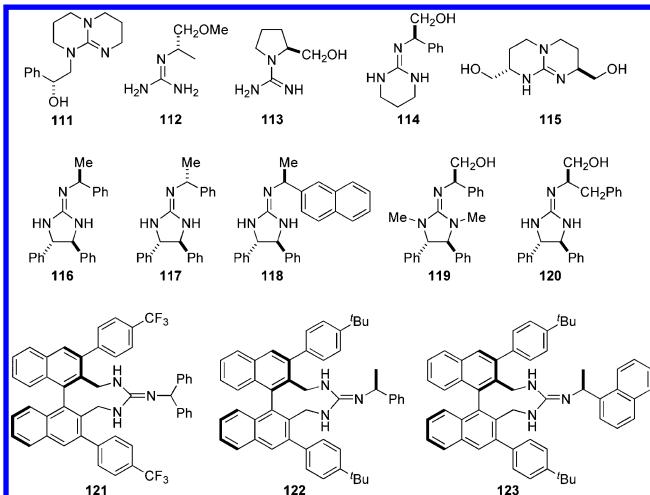


Figure 37. Guanidine catalysts.

**Scheme 26. Epoxidation of Quinone 124 Using Guanidine Catalysts 111–115**

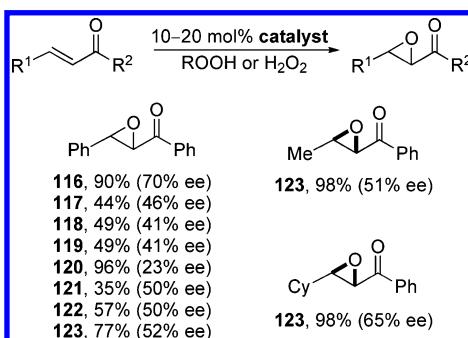
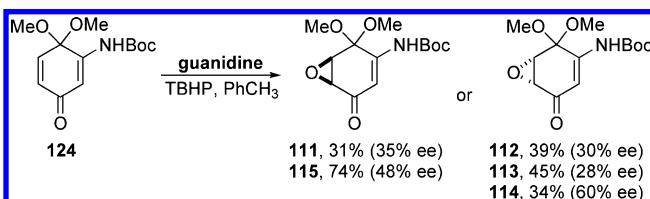


Figure 38. Epoxidation of enones with guanidine catalysts 116–123.

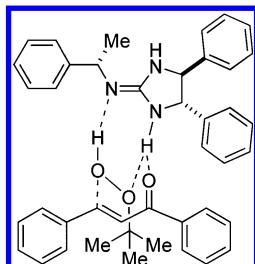


Figure 39. Proposed transition state for guanidine 116-catalyzed epoxidation with TBHP.

coordinate with the enone via hydrogen bonding to activate the double bond and direct addition of the peroxide anion stereoselectively.<sup>93d,94,95</sup> This noncovalent activation mechanism through hydrogen-bonding interactions was also supported by DFT calculations.<sup>95</sup> An alternative activation mode via formation of an iminium ion between the enone and the prolinol catalyst was believed to be less plausible. Lattanzi

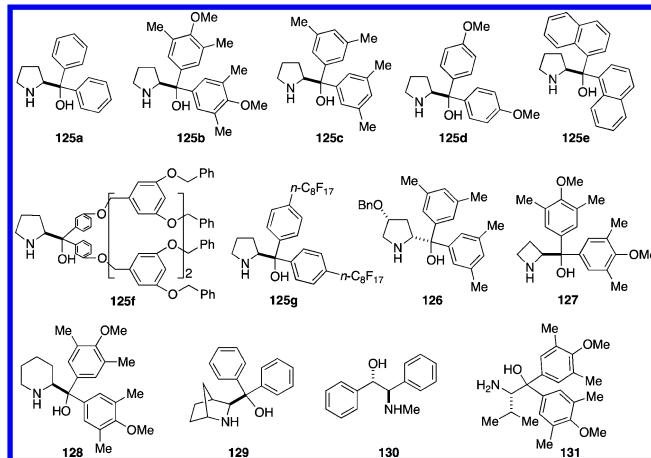
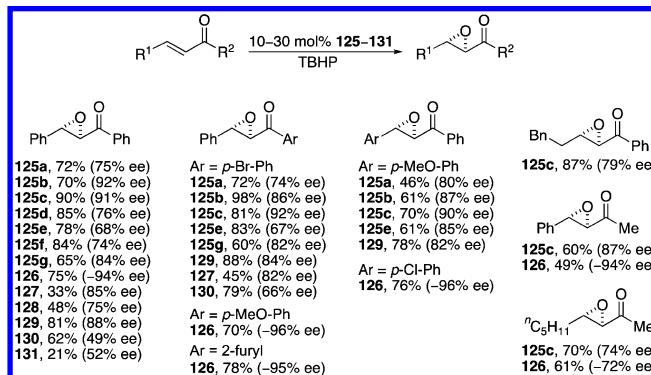
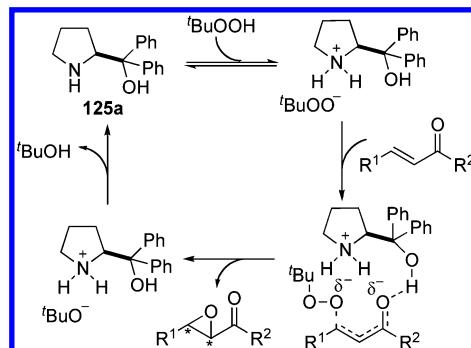
Figure 40.  $\beta$ -Amino alcohol catalysts.

Figure 41. Epoxidation of enones with amino alcohol catalysts 125–131.

**Scheme 27. Proposed Mechanism for Epoxidation of Enones with Catalyst 125a**



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).<sup>96</sup> 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).<sup>97</sup> Zhao, Zhu, and co-workers demonstrated that dendritic and fluorous 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.<sup>98</sup> In 2007, Zhao and co-workers also reported their studies on the epoxidation with 4-substituted  $\alpha,\alpha$ -diarylprolinols such as 126 (Figure 40). A variety of substituted chalcones were epoxidized in 89–96% ee (Figure

41).<sup>99</sup> 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 **127** and **128** were less effective than corresponding prolinol catalyst **125b** (Figures 40 and 41).<sup>100</sup> Amino alcohol **129** with azabicyclo[2.2.1]heptane skeleton was synthesized and investigated for epoxidation by Loh and co-workers (Figure 40).<sup>101</sup> Up to 88% ee was obtained for  $\alpha,\beta$ -unsaturated ketones (Figure 41). Epoxidation using acyclic amino alcohol catalysts such as **130**<sup>102</sup> and **131**<sup>100</sup> was reported by Liu, Zhang, Lattanzi, and co-workers (Figures 40 and 41). Up to 70% ee was obtained for epoxidation of chalcones.<sup>102</sup>

Epoxidation with  $\alpha,\alpha$ -diarylprolinols has been extended to various other electron-deficient olefins. For example, Lattanzi and co-workers showed that 2-arylidene-1,3-diketones<sup>103</sup> and trisubstituted acrylonitriles<sup>104</sup> 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-

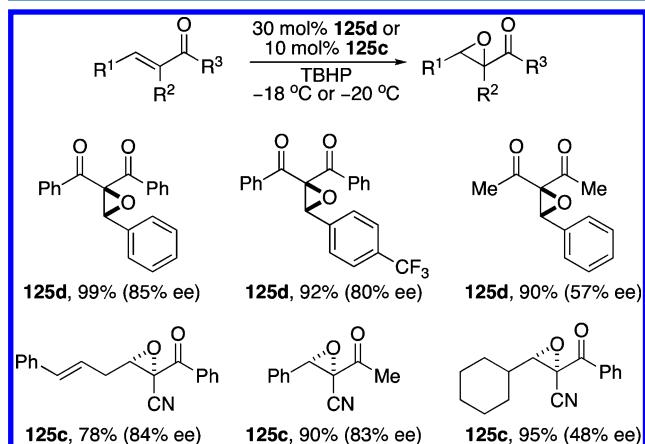


Figure 42. Epoxidation with diarylprolinol catalysts **125c** and **125d**.

workers, a variety of  $\beta,\gamma$ -unsaturated  $\alpha$ -keto esters and  $\alpha,\beta$ -unsaturated trichloromethyl and trifluoromethyl ketones were epoxidized using catalysts **125c** and **126** in up to 99% ee (Figure 43).<sup>105</sup> Chiral epoxide **132** was readily converted to ( $-$ )-norbalasubramide (**135a**) and ( $-$ )-balasubramide (**135b**) (Scheme 28).<sup>105</sup> Gasperi and co-workers also extended the epoxidation to  $\alpha$ -ylideneoxindoles using catalyst **125a** to give the corresponding epoxides with up to 88% ee (Scheme 29).

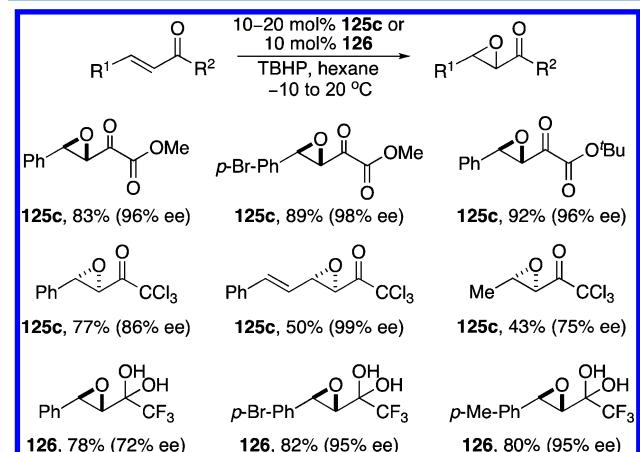
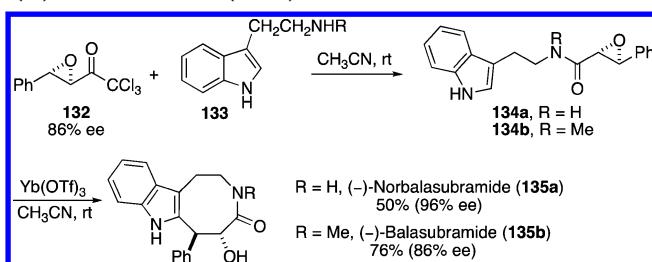
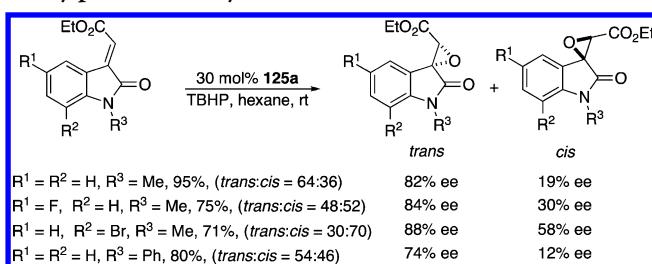


Figure 43. Epoxidation with diarylprolinol catalysts **125c** and **126**.

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



Scheme 29. Epoxidation of  $\alpha$ -Ylideneoxindoles with Diarylprolinol Catalyst **125a**



**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).<sup>107</sup> The epoxide product contains a quaternary stereogenic center and can be opened by nucleophiles such as azide to form chiral alcohols (Scheme 30).

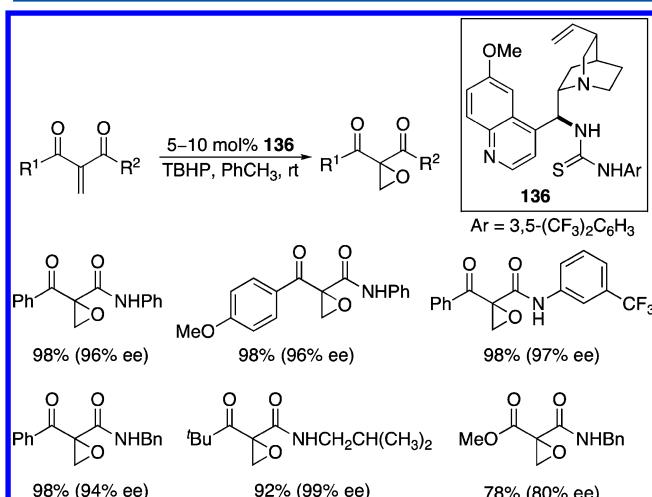
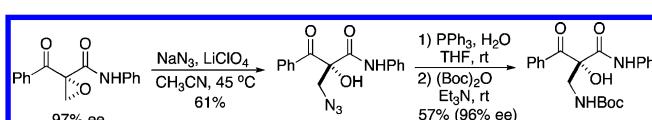


Figure 44. Epoxidation with cinchona thiourea catalyst **136**.

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  $H_2O_2$ , giving the corresponding epoxides in high yields with high dr values ( $\geq 90:10$ ) and ee's (up to 98% ee) (Figure 45).<sup>108</sup> The authors

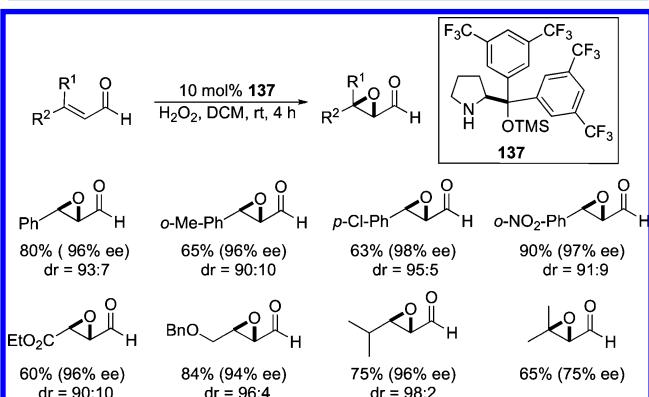
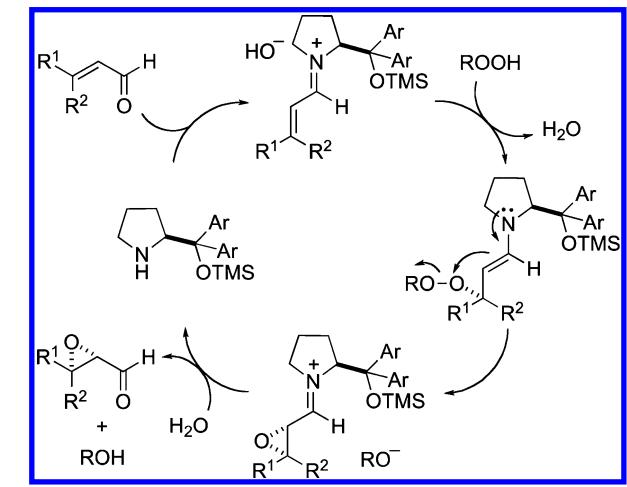


Figure 45. Epoxidation of  $\alpha,\beta$ -unsaturated aldehydes with catalyst **137**.

also showed that the epoxidation could be carried out in a benign solvent such as EtOH–H<sub>2</sub>O (3:1).<sup>109</sup> A mechanistic proposal for the epoxidation is shown in Scheme 31. The chiral

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



amine catalyst initially reacts with the  $\alpha,\beta$ -unsaturated aldehyde to generate an iminium salt intermediate to which  $H_2O_2$  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.<sup>108</sup> In a subsequent computational study,<sup>110</sup> Santos and co-workers indicated that besides being an oxidant,  $H_2O_2$  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).

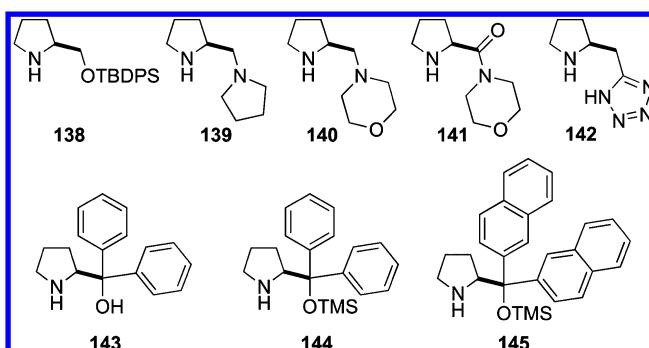


Figure 46. Pyrrolidine-based chiral amine catalysts **138**–**145**.

Various  $\alpha,\beta$ -unsaturated aldehydes were epoxidized using **144** as catalyst (10 mol %) and  $H_2O_2$  or sodium percarbonate as oxidant with up to 98% ee (Figure 47).<sup>111</sup> 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).<sup>112</sup>

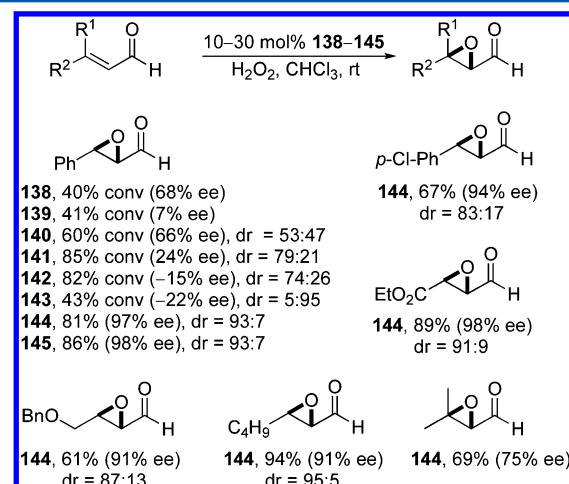


Figure 47. Epoxidation of  $\alpha,\beta$ -unsaturated aldehydes with catalysts **138**–**145**.

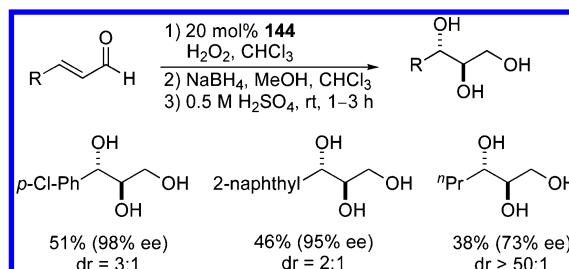
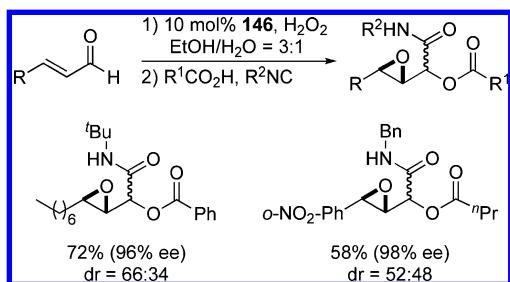
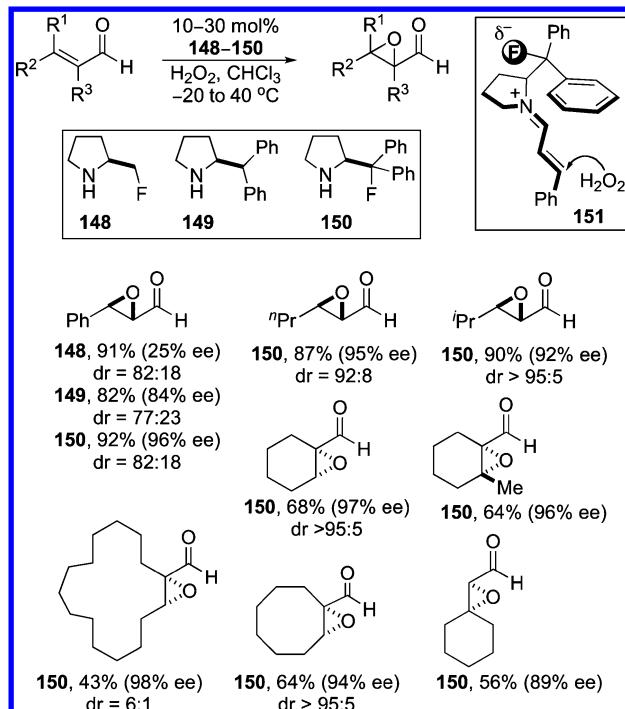
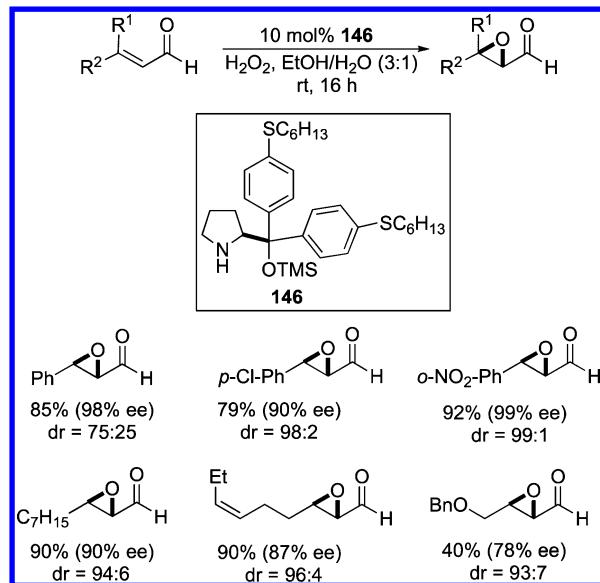


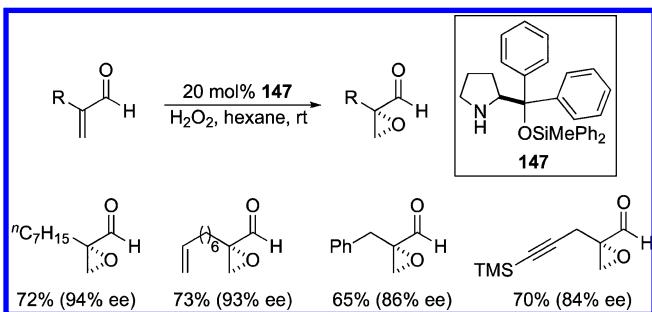
Figure 48. One-pot synthesis of 1,2,3-triols via asymmetric epoxidation.

In 2012, Corrêa, Paixão, and co-workers demonstrated that a modified class of prolinol silyl ethers, such as **146**, efficiently epoxidized  $\alpha,\beta$ -unsaturated aldehydes using  $H_2O_2$  in EtOH–H<sub>2</sub>O (3:1), giving the epoxy aldehydes in up to 99:1 dr and 99% ee (Figure 49).<sup>113</sup> A tandem asymmetric epoxidation/Passerini reaction was also reported with catalyst **146** (Figure 50).<sup>113,114</sup>

$\alpha$ -Substituted acroleins could be epoxidized with diphenylprolinol silyl ether catalyst **147** and  $H_2O_2$  to give the terminal epoxides in up to 94% ee as demonstrated in 2010 by Hayashi



and co-workers (Figure 51).<sup>115</sup> The epoxy aldehyde was readily converted to the corresponding epoxy ester via oxidation with



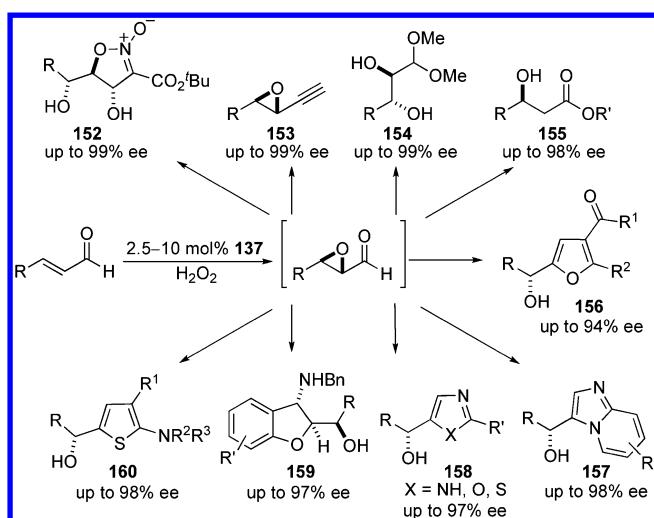
$\text{NaClO}_2$  and esterification with  $\text{TMSCHN}_2$ , as illustrated in the synthesis of (*R*)-methyl palmostirate (a potent oral hypoglycemic and antiketogenic agent).<sup>115</sup>

A series of  $\beta$ -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).<sup>116</sup> 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.<sup>116</sup>

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<sup>108</sup> and other transformations,<sup>117</sup> providing access to a variety of synthetically useful molecules, such as isoxazoline-*N*-oxides (152),<sup>117a</sup> propargylic epoxides (153),<sup>117b</sup> acetal-protected *trans*-2,3-dihydroxyaldehydes (154),<sup>117c</sup>  $\beta$ -hydroxy esters (155),<sup>117d</sup> substituted furans (156),<sup>117e</sup> imidazo[1,2-*a*]pyridines (157),<sup>117f</sup> 1,3-azoles (158),<sup>117g</sup> 2,3-dihydrobenzofurans (159),<sup>117h</sup> and substituted thiophenes (160)<sup>117i</sup> (Scheme 32).

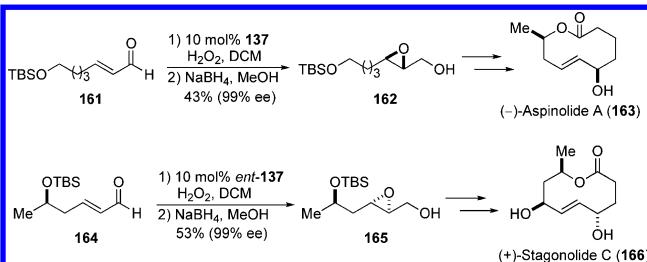
In the syntheses of (−)-aspinolide A (163) and (+)-staganolide C (166) reported by Suryavanshi, Sudalai, and co-

### Scheme 32. One-Pot Syntheses of Various Building Blocks via Asymmetric Epoxidation



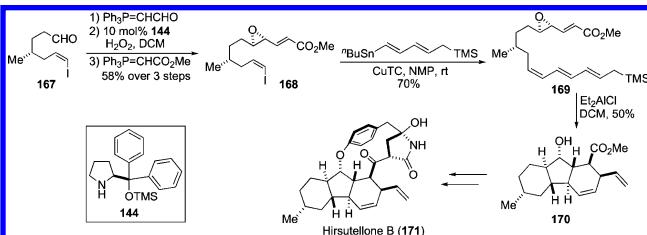
workers, epoxy alcohols **162** and **165** were obtained in 99% ee from the corresponding enals via epoxidation with catalyst **137** and subsequent reduction with NaBH<sub>4</sub> (Scheme 33).<sup>118</sup>

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



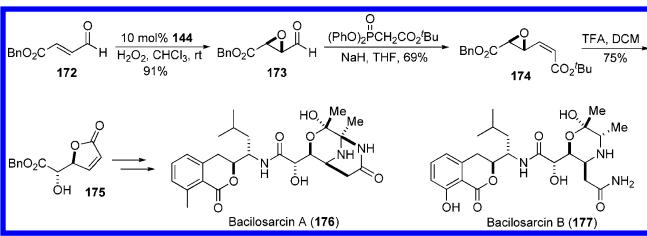
In their total synthesis of hirsutellone B (**171**), Nicolaou and co-workers reported that epoxy ester **168** could be synthesized from aldehyde **167** in 58% overall yield over three steps using **144** as the epoxidation catalyst. Epoxy ester **168** was subsequently transformed into hirsutellone B (**171**) (Scheme 34).<sup>119</sup> Kuwahara and co-workers showed that epoxide **173** was

**Scheme 34. Synthesis of Hirsutellone B (171)**



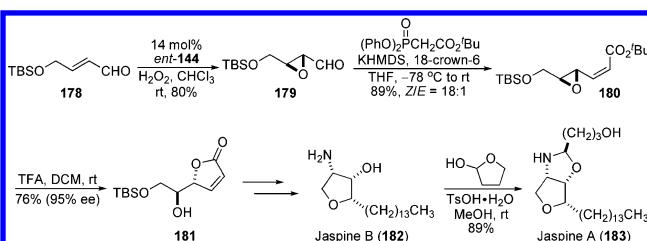
readily converted to lactone **175** via olefination and cyclization (Scheme 35).<sup>120</sup> Lactone **175** was further elaborated to

**Scheme 35. Syntheses of Bacilosarcins A (176) and B (177)**



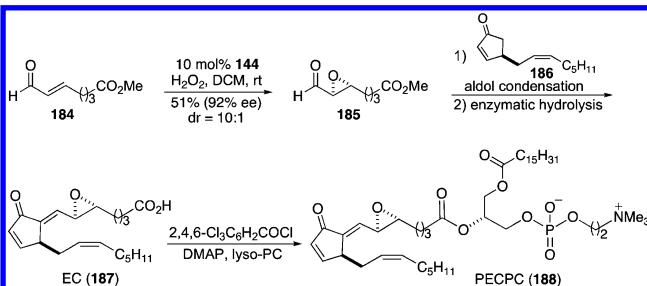
bacilosarcins A (**176**) and B (**177**). This epoxidation/olefination/cyclization sequence was also employed in their total syntheses of jaspines A and B (Scheme 36).<sup>121</sup>

**Scheme 36. Syntheses of Jaspines B (182) and A (183)**



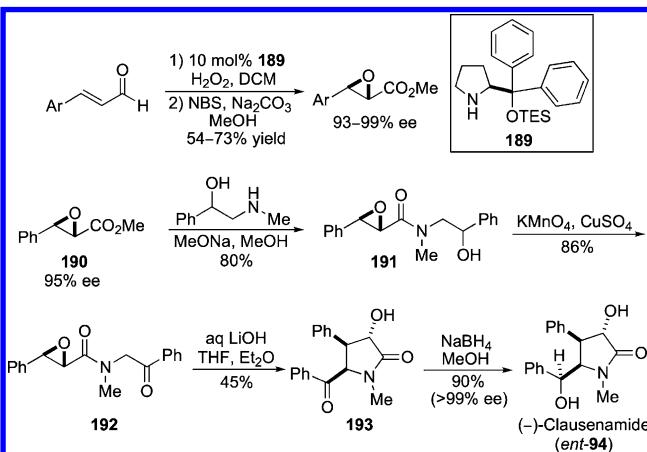
Carreira and co-workers employed catalyst **144** for epoxidation of enal **184** in the synthesis of epoxyisoprostanes such as EC (187) and PECPC (188) (Scheme 37).<sup>122</sup> Epoxy

**Scheme 37. Synthesis of Epoxyisoprostanes**



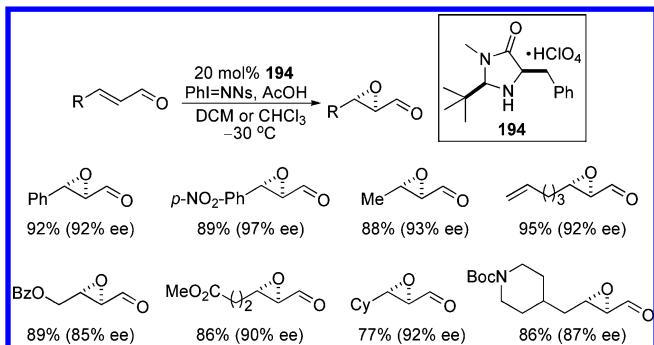
aldehyde **185** was converted to EC by aldol condensation with cyclopentenone **186** and subsequent enzymatic hydrolysis. PECPC was obtained by the coupling of EC with lyso-PC under Yamaguchi's conditions. Xuan, Yan, and co-workers reported a one-pot epoxidation of *trans*-cinnamaldehydes with catalyst **189** and oxidative esterification with NBS in CH<sub>3</sub>OH, giving  $\alpha,\beta$ -epoxy esters in 54–73% yield and 93–99% ee (Scheme 38).<sup>123</sup> Epoxide **190** was utilized to synthesize (−)-clausenamide (*ent*-94) (Scheme 38).<sup>123</sup>

**Scheme 38. Synthesis of (−)-Clausenamide (*ent*-94)**

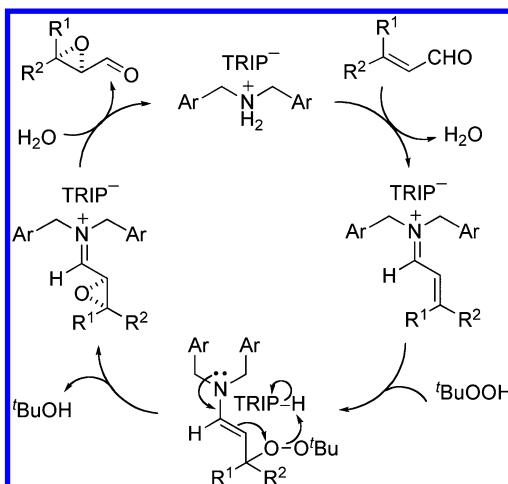


**2.4.2. Chiral Amine Salt Catalysts.** Various chiral amine salt catalysts were investigated for epoxidation of  $\alpha,\beta$ -unsaturated aldehydes and ketones. In 2006, MacMillan and co-workers reported that a variety of enals were effectively epoxidized with imidazolidinone PhI=NNs and AcOH, giving the corresponding epoxides in 72–95% yield and 85–97% ee (Figure 53).<sup>124</sup> 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).

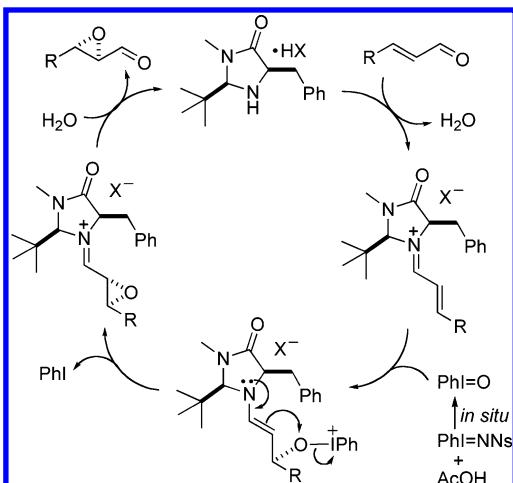
In 2008, List and co-workers reported a counteranion-directed asymmetric epoxidation of enals with amine salts bearing chiral phosphates as catalysts.<sup>125</sup> Among various catalysts examined, amine salt **198** gave the best results for the epoxidation. With this catalyst, a variety of 1,2-disubstituted



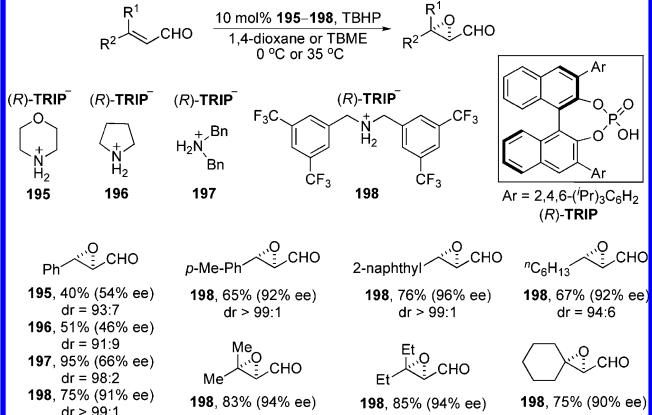
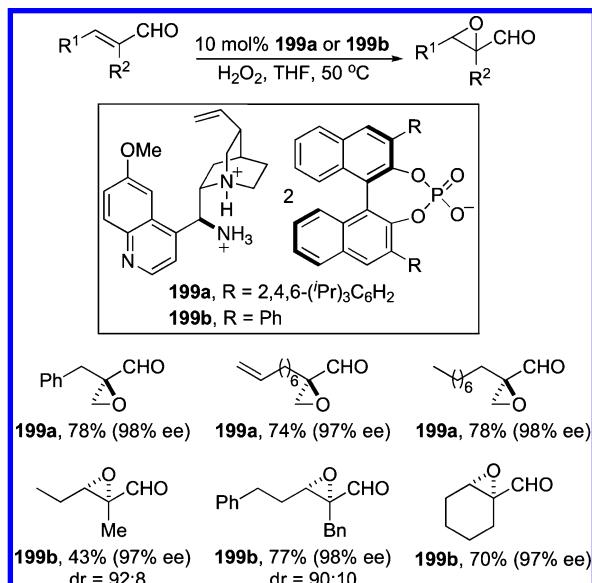
**Scheme 40.** Catalytic Pathway for Epoxidation of Enals with Chiral Amine Salts



**Scheme 39.** Proposed Mechanism for Epoxidation of Enals with Imidazolidinone Salt



and  $\beta,\beta$ -disubstituted enals were efficiently epoxidized in 60–95% yield and up to 96% ee using TBHP as oxidant (Figure 54).<sup>125</sup> In this case, asymmetric induction was controlled by the

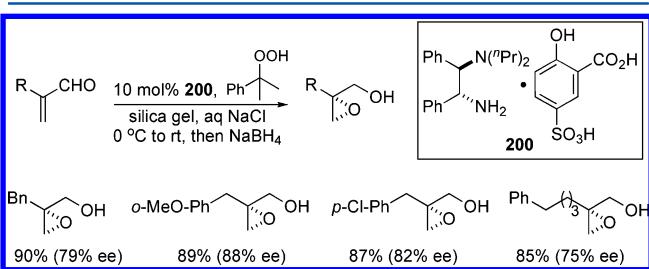


**Figure 54.** Epoxidation of enals with chiral amine salt catalysts **195–198**.

chiral phosphate counteranion (Scheme 40). In their further studies, List and co-workers demonstrated that asymmetric epoxidation of  $\alpha$ -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 H<sub>2</sub>O<sub>2</sub> (Figure 55).<sup>126</sup>

In 2010, Luo, Cheng, and co-workers reported that asymmetric epoxidation of  $\alpha$ -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 NaBH<sub>4</sub> (Figure 56).<sup>127</sup>

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



**Figure 56.** Epoxidation of enals with catalyst **200**.

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).<sup>128,126b</sup> The primary amine

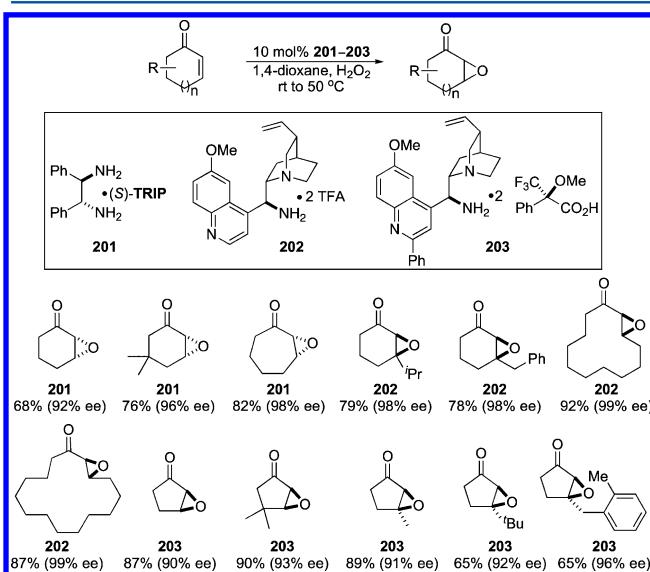
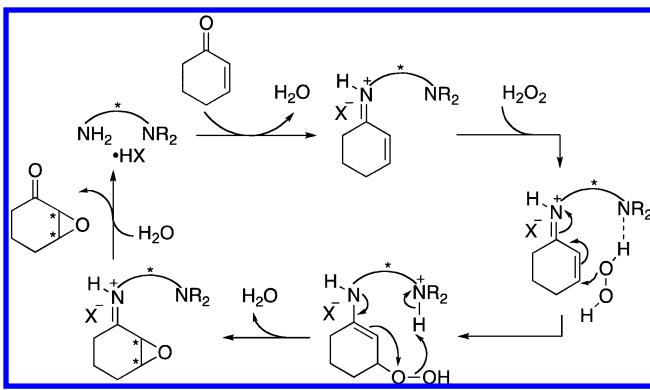


Figure 57. Epoxidation of cyclic enones with catalysts **201–203**.

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  $\text{H}_2\text{O}_2$  to the iminium ion (Scheme 41).<sup>128,126b,129</sup>

#### Scheme 41. Catalytic Pathway for the Amine Salt-Catalyzed Epoxidation of Cyclic Enones



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).<sup>130</sup> However,  $\beta$ -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).<sup>130</sup> In their studies, List and co-workers found that cyclic peroxyhemiketals could be obtained in up to 95% ee from acyclic aliphatic enones with catalyst **205** and  $\text{H}_2\text{O}_2$  (Figure 59).<sup>131,126b</sup> Epoxy ketones could also be obtained in 55–90% yield and 90–99% ee via a one-pot process involving reacting enones with  $\text{H}_2\text{O}_2$  in the presence of catalyst **202** and basic work up with 1 N NaOH (Figure 59).<sup>131,126b</sup>

Zhang and co-workers investigated the structural effect of the catalyst on the epoxidation of chalcones. With amine salt

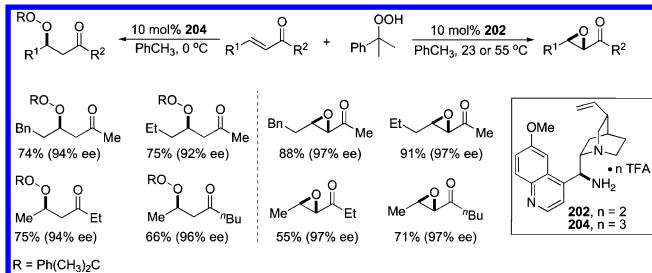


Figure 58. Epoxidation and peroxidation of acyclic enones with catalysts **202** and **204**.

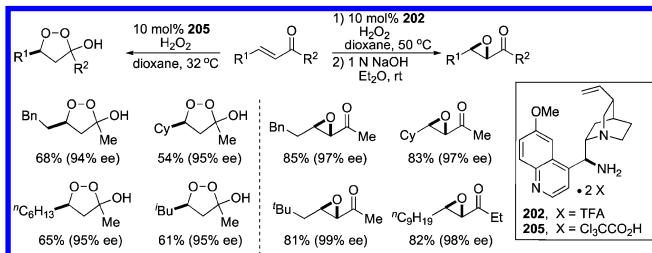


Figure 59. Hydroperoxidation and epoxidation of acyclic enones.

catalyst **206**, epoxy ketones were obtained in up to 84% ee using TBHP (Figure 60).<sup>132</sup> In 2011, Zhao, Zou, and co-

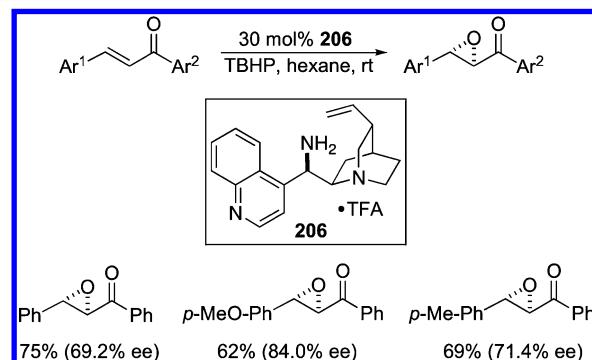


Figure 60. Epoxidation of chalcones with catalyst **206**.

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).<sup>133</sup> 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.<sup>134</sup> With amine salt catalyst **202** and  $\text{H}_2\text{O}_2$ , various enones were transformed into allylic alcohols in 87–99% ee (Figure 62). In 2011, Tu, Cao, and co-workers demonstrated that spirocycloalkanediolines 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  $\text{H}_2\text{O}_2$  as oxidant for the epoxidation (Figure 63).<sup>135</sup>

#### 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

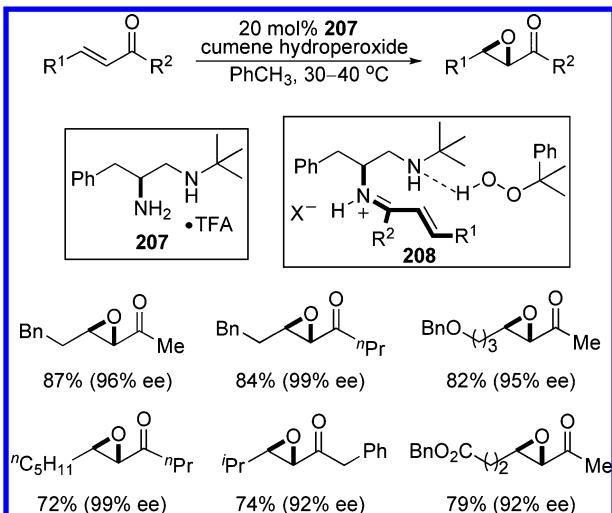


Figure 61. Epoxidation of enones with catalyst 207.

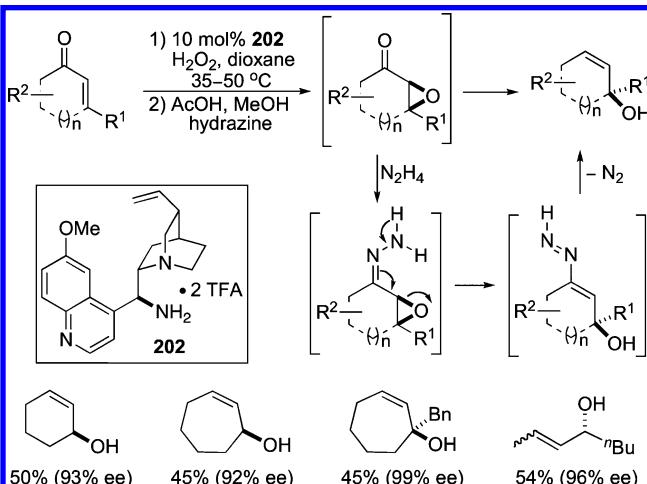


Figure 62. One-pot epoxidation/Wharton reaction sequence.

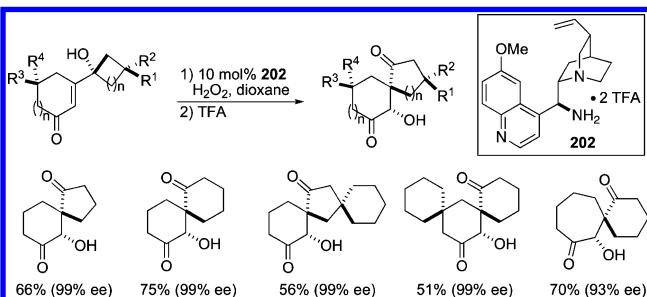
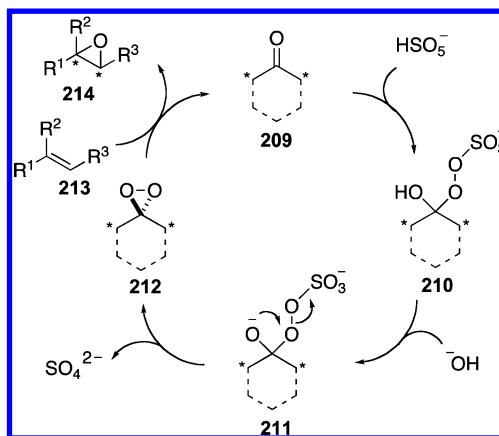


Figure 63. Synthesis of spirocycloalkanediolones with catalyst 202.

such as oxone ( $2\text{KHSO}_5\cdot\text{KHSO}_4\cdot\text{K}_2\text{SO}_4$ ) or  $\text{H}_2\text{O}_2$  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.<sup>136</sup>

In 1984, Curci and co-workers reported the asymmetric epoxidation of olefins with chiral ketones 215 and 216 (Figure

Scheme 42. Catalytic Cycle for the Chiral Ketone-Catalyzed Epoxidation of Olefins



64) and up to 12.5% ee was obtained for *trans*- $\beta$ -methylstyrene.<sup>137a</sup> In their further studies, ketones 217 and

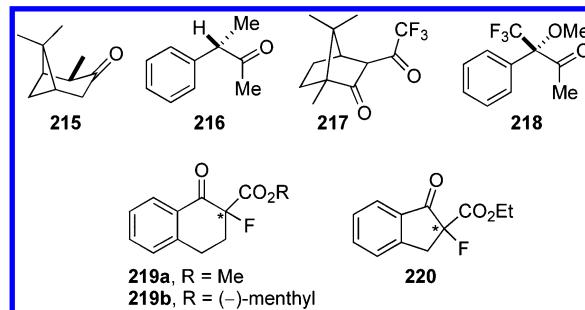
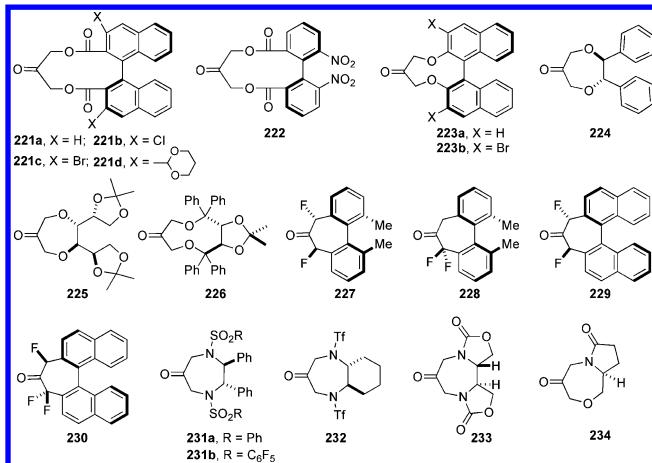


Figure 64. Early examples of chiral ketones for asymmetric epoxidation.

218 (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*- $\beta$ -methylstyrene and *trans*-2-octene, respectively.<sup>137b</sup> Marples and co-workers investigated the epoxidation with  $\alpha$ -fluorinated 1-tetralones 219 and 1-indanone 220.<sup>138</sup> 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  $C_2$ -symmetric ketones 221 for epoxidation of olefins (Figure 65).<sup>139</sup> 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.<sup>139</sup> For example, 91% and 95% ee were achieved for *trans*-4,4'-diethyl- and *trans*-4,4'-*tert*-butylstilbene, respectively, with 10 mol % ketone 221d.<sup>139b,c</sup> Biphenyl-based catalyst 222 provided moderate selectivity for epoxidation of *trans*-olefins and trisubstituted olefins (Table 3, entry 5).<sup>139c</sup> 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).<sup>140</sup> Epoxidation with  $C_2$ -symmetric ether-linked ketones 223 and 224 was reported by Song and co-

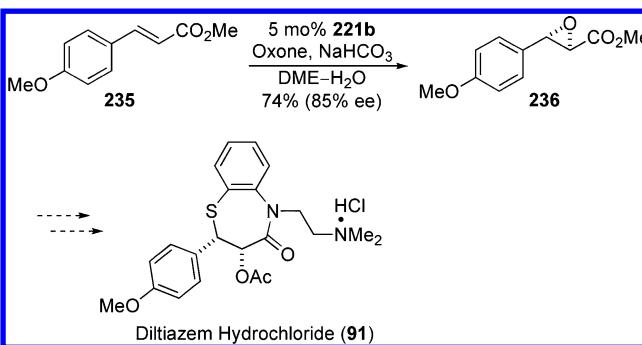
Figure 65. Selected examples of  $C_2$ -symmetric and related ketones.Table 3. Epoxidation of Representative Olefins with  $C_2$ -Symmetric Ketone Catalysts

entry	catalyst	$\text{Ph}-\text{CH=CH-Ph}$	$\text{Ph}-\text{CH=CH-Me}$	$\text{Ph}-\text{CH=CH-Ph}$	$\text{Ph-C}_6\text{H}_4-\text{Ph}$	ref
1	221a	47% ee	-	50% ee	33% ee	139a,c
2	221b	76% ee	-	76% ee	65% ee	139b,c
3	221c	75% ee	-	81% ee	64% ee	139b,c
4	221d	71% ee	-	73% ee	71% ee	139b,c
5	222	50% ee	-	49% ee	-	139c
6	223a	26% ee	29% ee	-	-	141a,b
7	223b	24% ee	-	-	-	141b
8	224	59% ee	20% ee	-	-	141a
9	225	38.9% ee	-	-	-	142
10	226	64.8% ee	-	81% ee	-	142
11	227	94% ee	88% ee	-	59% ee	143
12	228	-	85% ee	-	-	143
13	229	-	86% ee	-	-	144
14	230	-	83% ee	-	-	144
15	231a	30% ee	-	-	-	145a,b
16	231b	26% ee	-	-	-	145a
17	232	18% ee	-	-	-	145b
18	233	64% ee	62% ee	73% ee	82% ee	145c
19	234	57% ee	57% ee	70% ee	78% ee	145c

workers in 1997.<sup>141</sup> 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).<sup>142</sup>

In 1999 and 2002, Denmark and co-workers reported that  $\alpha$ -fluorinated biphenyl-based 7-membered-ring ketones such as 227 (Figure 65) were highly effective epoxidation catalysts, giving 94% and 88% ee for *trans*-stilbene and *trans*- $\beta$ -methylstyrene, respectively (Table 3, entry 11).<sup>136a,143</sup> In

Scheme 43. Synthesis of Diltiazem Key Intermediate 236 Using Ketone 221b



their studies, Behar and co-workers reported that up to 86% ee was obtained for epoxidation of *trans*- $\beta$ -methylstyrene with binaphthyl-based  $\alpha$ -fluorinated ketone 229 (Table 3, entry 13).<sup>144</sup> A number of 1,2-diamine- and 1,2-aminoalcohol-based ketone catalysts were investigated for epoxidation by Tomioka and co-workers.<sup>145</sup> Up to 82% ee was achieved for epoxidation of 1-phenylcyclohexene with ketones 233 and 234 (Table 3, entries 18 and 19).<sup>145c</sup>

Denmark and co-workers reported a series of ammonium ketones such as 237–242 (Figure 66) for epoxidation (Table

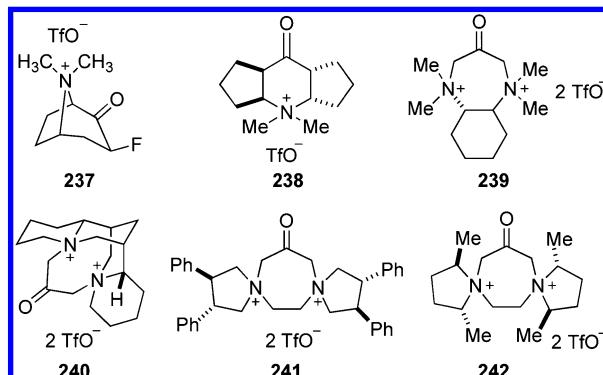
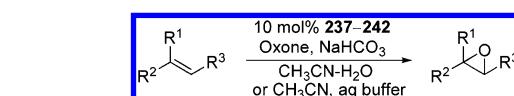


Figure 66. Selected examples of ammonium ketones.

4).<sup>136a,143,146,147</sup> The electron-withdrawing ammonium ion inductively activates the ketone and functions as a phase-transfer mediator to facilitate the biphasic reaction. Up to 58%

Table 4. Epoxidation of Representative Olefins with Ammonium Ketone Catalysts



entry	catalyst	$\text{Ph}-\text{CH=CH-Ph}$	$\text{Ph}-\text{CH=CH-Me}$	$\text{Ph-C}_6\text{H}_4-\text{Ph}$	ref
1	237	58% ee	35% ee	7% ee	143,147
2	238	-	34% ee	58% ee	136a
3	239	-	9% ee	-	136a
4	240	-	40% ee	-	136a
5	241	-	10% ee	-	136a
6	242	-	8% ee	-	136a

ee was obtained for *trans*-stilbene using 10 mol %  $\alpha$ -fluorinated tropinone-based ketone 237 (Table 4, entry 1).<sup>143,147</sup>

In 1998, Armstrong and co-workers reported that  $\alpha$ -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

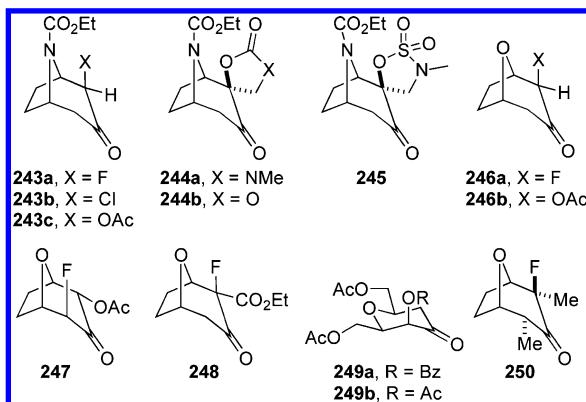
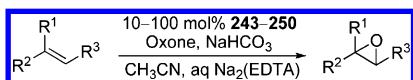


Figure 67. Selected examples of bicyclo[3.2.1]octan-3-ones and related ketones.

Table 5. Epoxidation of Representative Olefins with Ketone Catalysts 243–250<sup>a</sup>



entry	catalyst	Ph- $\text{CH}=\text{Ph}$	Ph- $\text{CH}=\text{Me}$	Ph- $\text{CH}=\text{Ph}$ Ph		ref
1	243a	76% ee	-	83% ee	69% ee	148a,b
2	243b	54% ee	-	-	-	148b,149a
3	243c	86% ee <sub>max</sub>	-	-	-	148b,149a
4	244a	91.5% ee	73.5% ee	-	74% ee	150c
5	244b	87% ee	-	-	-	150c
6	245	87% ee	-	-	69% ee	150c
7	246a	83% ee <sub>max</sub>	-	-	-	149a
8	246b	93% ee <sub>max</sub>	70% ee <sub>max</sub>	98% ee <sub>max</sub>	82% ee <sub>max</sub>	149a,b
9	247	64% ee	-	-	-	150b
10	248	77% ee	-	-	-	150b
11	249a	83% ee	-	82% ee	74% ee	150a
12	249b	81% ee	-	-	-	150a
13	250	68% ee	34% ee	66% ee	-	151

<sup>a</sup>ee<sub>max</sub> = (100 × product ee/ketone ee).

1).<sup>148</sup> Various bicyclo[3.2.1]octan-3-ones and related ketones were subsequently investigated by Armstrong and co-workers.<sup>149,150</sup> Ketone 246b was found to be the most enantioselective catalyst, giving 85% conversion and 93% ee<sub>max</sub> for stilbene, 71% conversion and 98% ee<sub>max</sub> for phenylstilbene, and 89% conversion and 82% ee<sub>max</sub> 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  $\alpha$ -fluorinated 2,4-dimethyl-8-oxabicyclo[3.2.1]octan-3-one 250 (Table 5, entry 13).<sup>151</sup>

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-C<sub>2</sub>-symmetric ketones with two fused ketals such as 251 (Figure 68), which displayed good reactivity and high selectivity for

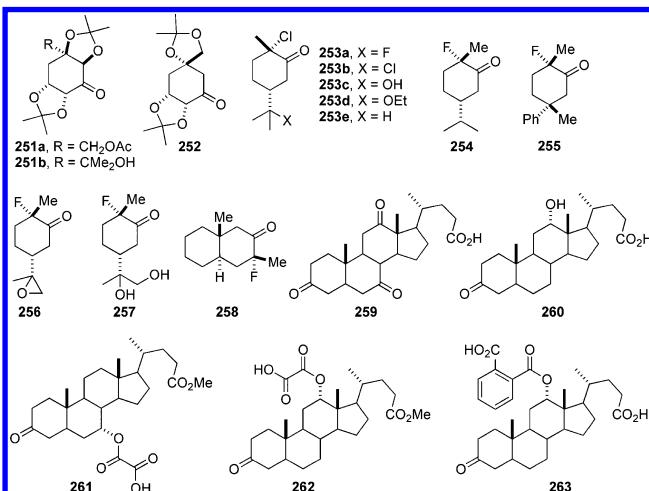


Figure 68. Selected examples of six-membered carbocyclic ketones.

*trans*-olefins and trisubstituted olefins.<sup>152</sup> *trans*-Stilbene was epoxidized in 91% yield and 96% ee with 10 mol % 251b (Table 6, entry 2).<sup>152b</sup> Electron-deficient chalcone was also found to be an effective substrate, giving the epoxy ketone in 85% yield and 96% ee.<sup>152b</sup> Ketone 252, with one ketal away from the  $\alpha$  position of the carbonyl, displayed significantly lower reactivity and enantioselectivity as compared to 251, showing that having the chiral control moiety close to the

Table 6. Epoxidation of Representative Olefins with Carbocyclic Ketone Catalysts

entry	catalyst	Ph- $\text{CH}=\text{Ph}$	Ph- $\text{CH}=\text{Me}$	Ph- $\text{CH}=\text{Ph}$ R		ref
1	251a	90% ee	75% ee	R = Ph, 87% ee	-	152a,b
2	251b	96% ee	80% ee	R = Ph, 92% ee	85% ee	152b
3	252	85% ee	46% ee	R = Ph, 85% ee	-	154
4	253a	87.4% ee	-	-	-	155
5	253b	85.4% ee	-	-	-	155
6	253c	80.9% ee	-	-	-	155
7	253d	73.8% ee	-	-	-	155
8	253e	42.0% ee	-	-	-	155
9	255	90% ee	62% ee	-	-	156c,f
10	256	88% ee	-	-	-	156e,g
11	257	86% ee	-	-	-	156g
12	258	86% ee	70% ee	-	-	156d
13	260	43% ee	50% ee	R = Me, 44% ee	-	157c
14	261	80% ee	70% ee	R = Me, 57% ee	-	157d
15	262	90% ee	70% ee	R = Me, 20% ee	-	157d
16	263	98% ee	66% ee	R = Me, 85% ee	-	157d

reacting carbonyl was beneficial for asymmetric induction.<sup>153</sup> Zhao and co-workers also reported their studies on the epoxidation with ketone **252** and obtained 85% ee for stilbene (Table 6, entry 3).<sup>154</sup>

In 1998, Yang and co-workers reported the epoxidation of various substituted stilbenes with  $\alpha$ -chlorinated cyclohexanones **253** (Figure 68).<sup>155</sup> 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).<sup>155</sup> 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– $\pi$  electronic repulsion effect between the Cl atom of the ketone and the phenyl group of the substrate.<sup>155</sup>

In 2000, Solladié-Cavallo and co-workers reported the epoxidation of *p*-methoxycinnamates with  $\alpha$ -halogenated trisubstituted cyclohexanones (Figure 68). Methyl *p*-methoxycinnamate was epoxidized in 99% conversion and 40% ee with 30 mol %  $\alpha$ -fluoro ketone **254**.<sup>156a</sup> A series of  $\alpha$ -fluoro ketones including **255**–**258** was further investigated for epoxidation of olefins (Table 6, entries 9–12),<sup>156b–h</sup> 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 keto bile acid **259** (Figure 68).<sup>157a</sup> Various keto bile acids and their derivatives were subsequently investigated for epoxidation of olefins.<sup>157b–g</sup> *p*-Methylcinnamic acid epoxide was obtained in 94% yield and 95% ee with 1 equiv of **260**.<sup>157b</sup> Up to 98% ee was achieved for stilbene with ketone **263** (Table 6, entry 16).<sup>157d</sup>

Noncyclic chiral ketones have also been studied for epoxidation (Figure 69). In 1999, Armstrong and co-workers

1-Phenylcyclohexene was epoxidized in 88% yield and 81% ee with 10 mol % ketone **265** (Table 7, entry 2).<sup>159</sup> In 2003, Wong and co-workers reported the epoxidation with cyclodextrin-modified ketone catalyst **266** (Table 7, entry 3).<sup>160</sup> With this ketone, 4-chlorostyrene could be epoxidized in 40% ee.<sup>160</sup> Acetone-bridged cyclodextrins such as **267** (Figure 69) were also synthesized and examined for epoxidation by Bols and co-workers.<sup>161</sup>

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.<sup>162</sup> The ketone was readily prepared from D-fructose by ketalization and oxidation in two steps.<sup>163,164</sup> Its enantiomer was easily prepared from L-fructose, which was made from L-sorbose.<sup>163,165</sup> It was found that the reaction pH had a dramatic effect on the efficiency of the epoxidation, with pH >10 being optimal.<sup>166,163</sup> 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,<sup>163</sup> hydroxyalkenes,<sup>167</sup> conjugated dienes,<sup>168</sup> enynes,<sup>169</sup> silyl enol ethers and enol esters,<sup>170,171</sup> vinylsilanes,<sup>172</sup> and fluoroolefins<sup>173</sup> (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.<sup>174</sup> Further studies showed that the epoxidation also proceeded efficiently with H<sub>2</sub>O<sub>2</sub> as oxidant in the presence of a nitrile such as CH<sub>3</sub>CN (Scheme 44), providing the enantioselectivity comparable to that of using oxone.<sup>175,176</sup> The peroxyimidic acid resulting from H<sub>2</sub>O<sub>2</sub> and CH<sub>3</sub>CN 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.<sup>153,177,178</sup> 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).<sup>179</sup> 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 *cis*-olefins (Figure 74).<sup>180,173,181</sup>

In addition to *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 *cis*-olefins.<sup>182</sup> To further understand the ketone's structural effect on the epoxidation and develop more practical catalysts, readily prepared *N*-aryl-substituted oxazolidinone ketones such as **277b** and **277c** (Figure 75) were designed and found to be effective catalysts for the epoxidation.<sup>183</sup> Epoxidation with ketone **277** can be extended to a wide variety of olefins, including aromatic *cis*-olefins,<sup>184,182a,b,183a</sup> conjugated *cis*-dienes,<sup>185</sup> *cis*-enynes,<sup>186,182a,b</sup> nonconjugated *cis*-olefins,<sup>187</sup>

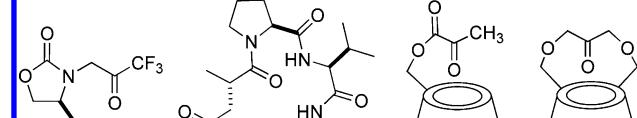
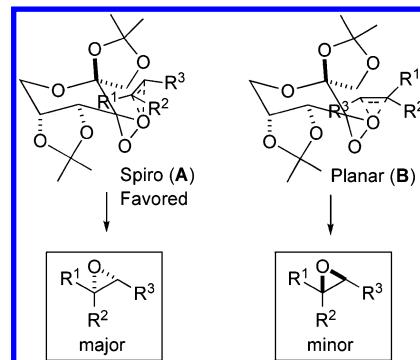
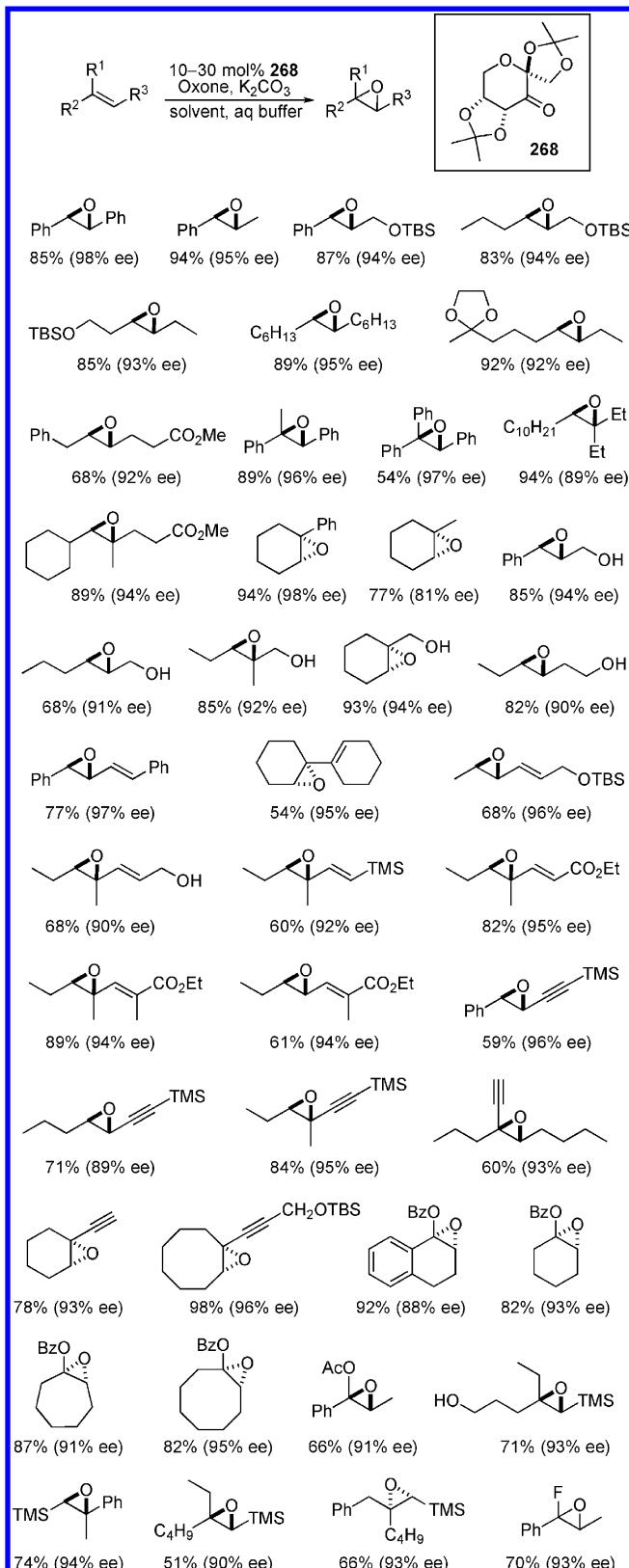


Figure 69. Selected examples of ketones with an attached chiral moiety.

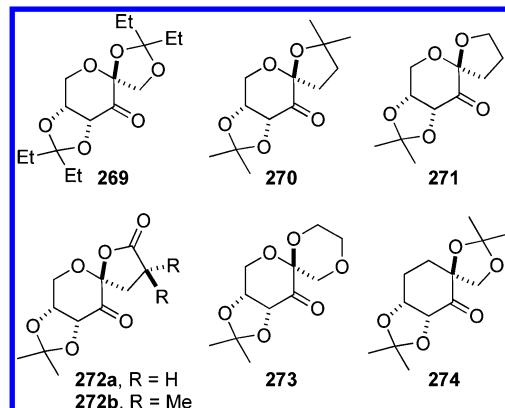
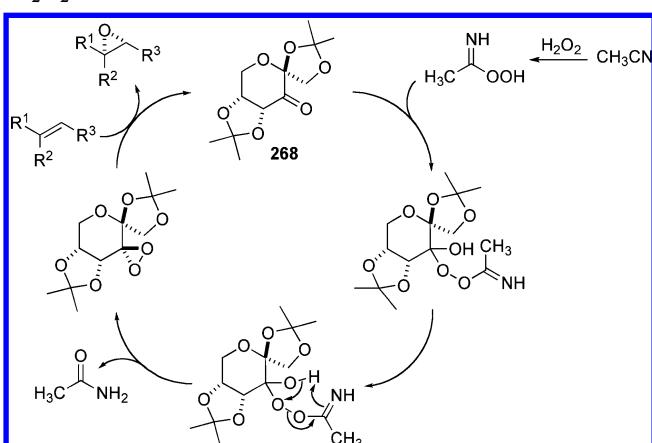
reported that up to 34% ee was obtained for epoxidation of 1-phenylcyclohexene with ketone **264** (Table 7, entry 1).<sup>158</sup> Miller and co-workers prepared a class of peptide-embedded trifluoromethyl ketones such as **265** for epoxidation of olefins.

Table 7. Epoxidation of Representative Olefins with Ketone Catalysts **264**–**266**

entry	catalyst	$R^1$	$R^2$	$R^3$	10–300 mol % <b>264</b> – <b>266</b> oxidant, NaHCO <sub>3</sub> or K <sub>2</sub> CO <sub>3</sub> solvent, aq Na <sub>2</sub> (EDTA)	$R^1$ $R^2$ $R^3$	ref
		Ph	Ph	Me	Ph	Ph	
1	<b>264</b>	25% ee	-		R = Ph, 33% ee	34% ee	158
2	<b>265</b>	-	42% ee	-		81% ee	159
3	<b>266</b>	36% ee	26% ee	R = Me, 35% ee	-		160



**Scheme 44. Catalytic Cycle for Epoxidation of Olefins with  $\text{H}_2\text{O}_2$  as Oxidant**



isomerization observed during the reaction.<sup>182a,b,183a,184a,185–187</sup> For conjugated *cis*-dienes, the epoxidation generally occurred regioselectively at the *cis* C=C bond.<sup>185</sup> 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).<sup>187</sup> The epoxides obtained from benzylideneacyclobutanes can be stereoselectively rearranged to optically active 2-aryl cyclopentanones (Scheme 46).<sup>190a</sup> It has also been shown that epoxidation with ketone 277c can be carried out using  $\text{H}_2\text{O}_2$  as the primary oxidant.<sup>191</sup>

Epoxidation of conjugated *cis*-olefins and terminal olefins with ketones 277 proceeds mainly via spiro transition state C,

styrenes,<sup>188,182b,189</sup> *trans*-olefins and trisubstituted olefins,<sup>182a,b,190a,c</sup> as well as tetrasubstituted benzylideneacyclobutanes<sup>190b</sup> and benzylideneacyclobutanones<sup>190c</sup> (Figure 75). Epoxidation proceeds in a stereospecific manner. In the case of acyclic *cis*-olefins, *cis*-epoxides were exclusively obtained with no

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

entry	catalyst	Ph <sub>2</sub> C=CH <sub>2</sub>	PhCH=CHMe	cyclohexene	ref
1	268	85% <sup>a</sup> (98% ee)	94% <sup>a</sup> (95% ee)	94% <sup>a</sup> (98% ee)	163
2	269	16% (96% ee)	32% (86% ee)	-	177
3	270	-	76% (96% ee)	100% (97% ee)	178
4	271	-	91% (76% ee)	96% (38% ee)	178
5	272a	-	66% (73% ee)	45% (-18% ee)	178
6	272b	-	76% (83% ee)	89% (88% ee)	178
7	273	34% (90% ee)	44% (61% ee)	-	177
8	274	10% (88% ee)	61% (87% ee)	-	153

<sup>a</sup>Isolated yield.

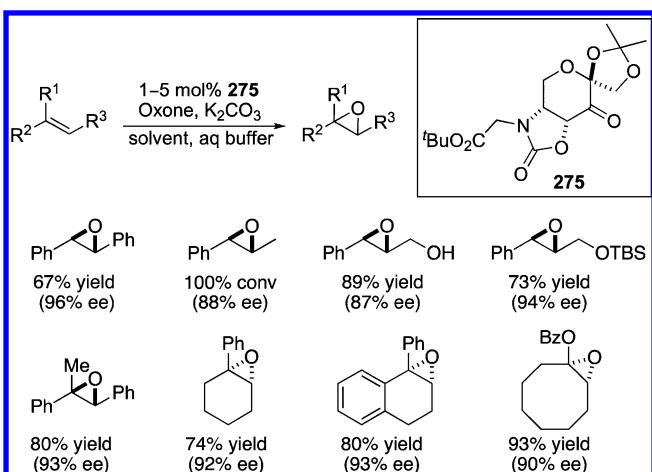


Figure 73. Asymmetric epoxidation of olefins with ketone 275.

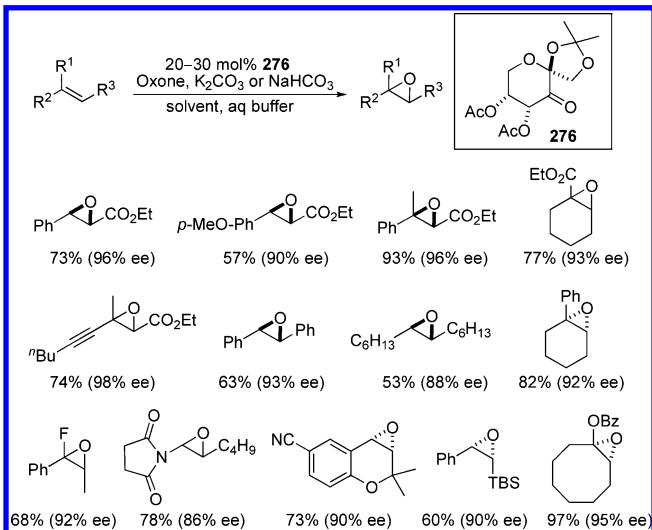


Figure 74. Epoxidation of olefins with ketone 276.

with the R<sub>π</sub> 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).

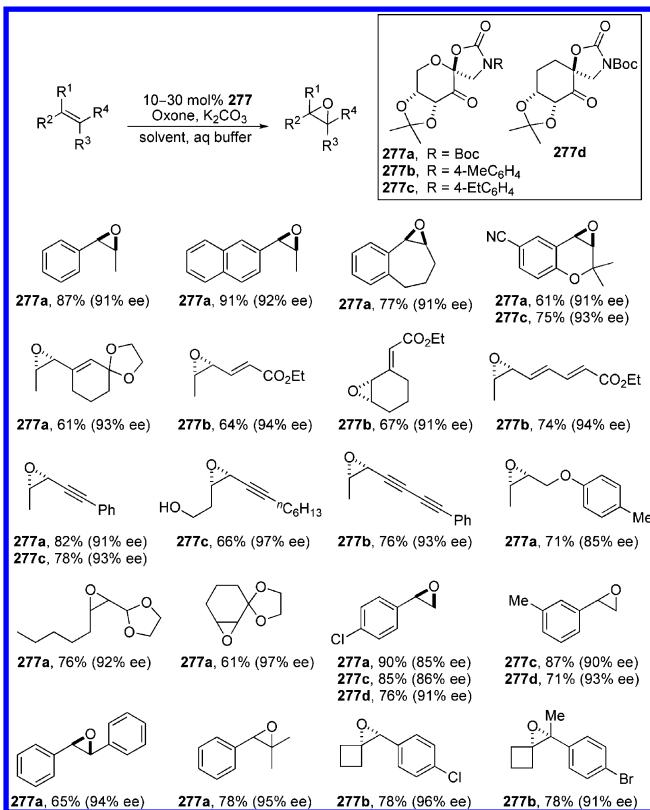
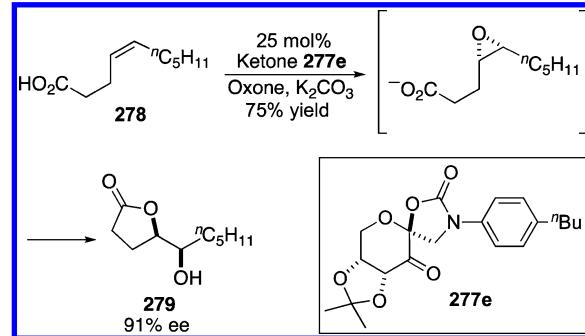
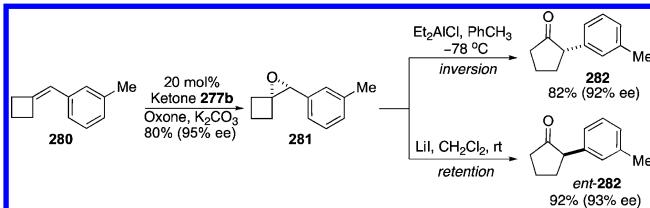


Figure 75. Epoxidation of various olefins with ketones 277.

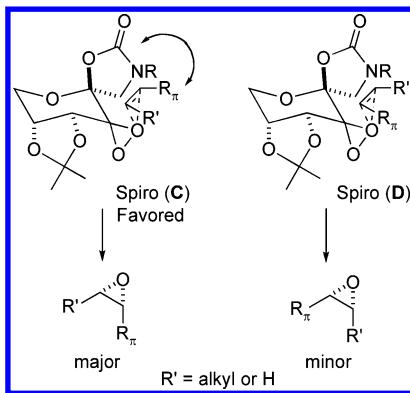
Scheme 45. Synthesis of Lactone 279 via Epoxidation and Intramolecular Cyclization



Scheme 46. Synthesis of 2-Aryl Cyclopentanones via Epoxidation and Rearrangement

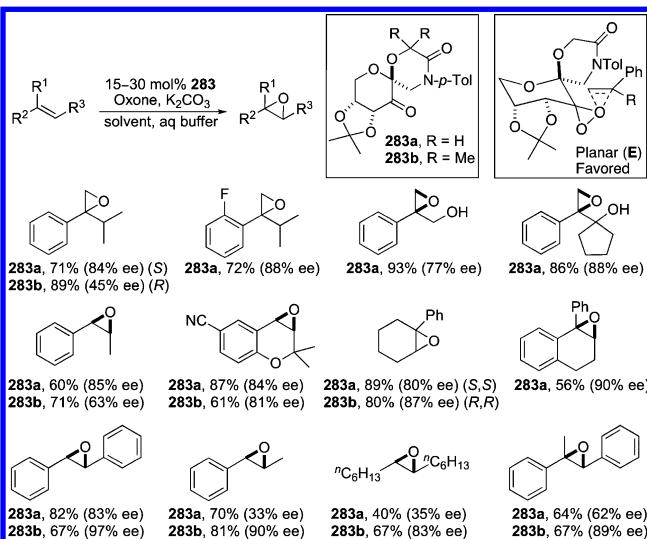


76).<sup>182a,b,183a,184–188,190,173</sup> van der Waals forces and/or hydrophobic interactions could also have significant influences on the enantioselectivity of the epoxidation.<sup>184b,185–187</sup> In some cases such as nonconjugated *cis*-dec-4-enoic acid (Scheme 45), the hydrophobic interaction plays a crucial role in stereo-differentiation.<sup>187</sup>



**Figure 76.** Proposed transition states for epoxidation with ketones 277.

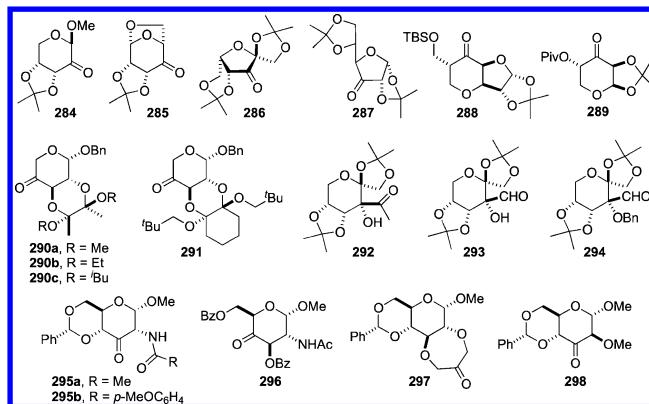
In subsequent studies, morpholinone-containing ketone 283a was found to be a promising catalyst for epoxidation of challenging 1,1-disubstituted terminal olefins, giving up to 88% ee for  $\alpha$ -substituted styrenes (Figure 77).<sup>192a</sup> Epoxidation with



**Figure 77.** Epoxidation of olefins with ketone catalysts 283.

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 283a also gave good ee's for certain *cis*-olefins and trisubstituted olefins (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).<sup>192b</sup>

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 Shing and co-workers.<sup>177</sup> 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



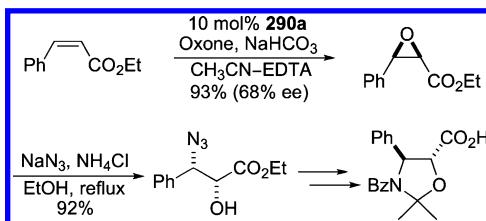
**Figure 78.** Selected examples of carbohydrate-derived aldehydes and ketones.

**Table 9.** Epoxidation of Representative Olefins with Ketone and Aldehyde Catalysts 284–298

entry	catalyst	$\text{Ph}=\text{Ph}$	$\text{Ph}=\text{Me}$	$\text{Ph}=\text{Ph}-\text{R}$	$\text{R}^1-\text{CH}(\text{O})-\text{R}^3$		ref
					$\text{R}^1-\text{CH}(\text{O})-\text{R}^3$	$\text{R}^1-\text{CH}(\text{O})-\text{R}^3$	
1	284	88% ee	59% ee	-	-	-	177
2	285	74% ee	41% ee	-	-	-	177
3	286	75% ee	62% ee	-	-	-	177
4	287	-	23% ee	-	-	-	177
5	288	71% ee	28% ee	$\text{R}=\text{Me}$ , 45% ee	-	-	193
6	289	67% ee	40% ee	$\text{R}=\text{Ph}$ , 68% ee	-	-	194a
7	290a	42% ee	43% ee	$\text{R}=\text{Ph}$ , 68% ee	-	-	194b
8	290b	54% ee	60% ee	$\text{R}=\text{Ph}$ , 78% ee	-	-	194b
9	290c	76% ee	79% ee	$\text{R}=\text{Ph}$ , 90% ee	85% ee	194b,c	
				$\text{R}=\text{Me}$ , 87% ee			
10	291	77% ee	-	$\text{R}=\text{Me}$ , 89% ee	-	-	194e
11	292	39% ee	-	$\text{R}=\text{Ph}$ , 36% ee	-	-	195
12	293	94% ee	-	$\text{R}=\text{Ph}$ , 92% ee	67% ee	195	
13	294	63.5% ee	-	$\text{R}=\text{Ph}$ , 81% ee	48% ee	195	
14	295a	61% ee	-	-	-	-	196
15	295b	69% ee	-	-	-	-	196
16	296	62% ee	50% ee	$\text{R}=\text{Ph}$ , 56% ee	-	-	197
17	297	68% ee	57% ee	$\text{R}=\text{Ph}$ , 74% ee	74% ee	198a,b	
18	298	80% ee	-	$\text{R}=\text{Ph}$ , 90% ee	60% ee	198c	

epoxidation of *trans*-stilbene with D-glucose-derived ketone 288 (10 mol %) (Table 9, entry 5).<sup>193</sup> Epoxidation with a number of arabinose-derived ketones such as 289–291 was subsequently reported by Shing and co-workers.<sup>194</sup> The enantioselectivity for the epoxidation increased with the size of the R group in ketone 290 (Table 9, entries 7–9),<sup>194b,c</sup> with up to 90% ee being obtained for phenylstilbene using 10 mol % 290c (Table 9, entry 9).<sup>194b,c</sup> 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).<sup>194d</sup> In 2003, Zhao and co-workers reported that up to 94% ee was obtained for epoxidation of *trans*-stilbene with ketone

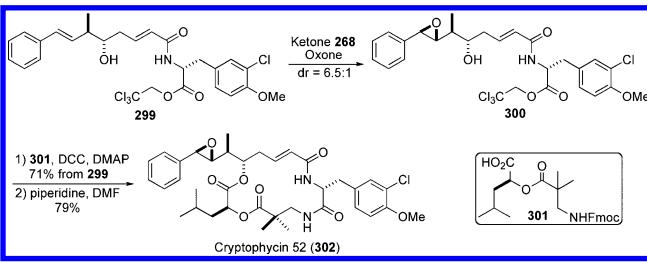
Scheme 47. Synthesis of Protected Side Chain of Taxol



and aldehydes **292–294** (Table 9, entries 11–13).<sup>195</sup> In 2009, Davis and co-workers reported a series of *N*-acyl-D-glucosamine-derived ketones such as **295** for the epoxidation (Table 9, entries 14 and 15),<sup>196</sup> 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 %).<sup>197</sup> 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).<sup>198a,b</sup> The authors also showed that phenylstilbene was epoxidized in 74% yield and 90% ee with mannose-derived ketone **298** (Table 9, entry 18).<sup>198c</sup>

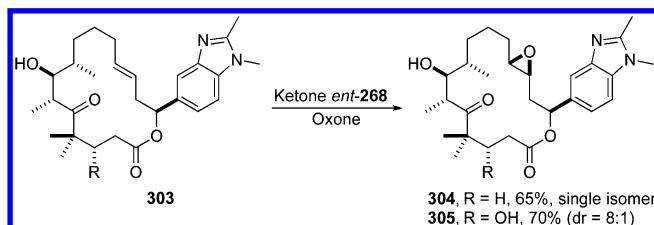
**2.5.2. Synthetic Applications.** Fructose-derived ketone **268** (Figure 70) and its enantiomer are readily accessible and have proven to be highly effective asymmetric epoxidation catalysts for a wide variety of *trans*-olefins and trisubstituted olefins. They have been widely used in the synthesis 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).<sup>199</sup>

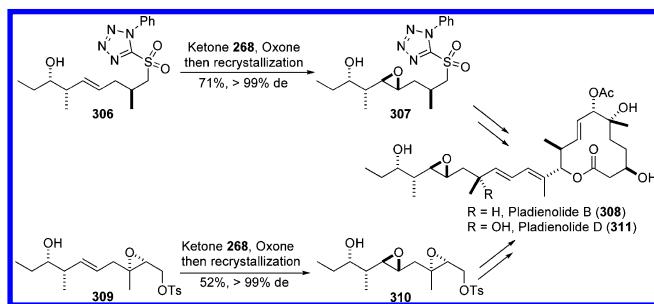
Scheme 48. Synthesis of Cryptophycin **52** (**302**)

In their synthesis of highly potent anticancer agent epothilone and its analogues,<sup>200</sup> Altmann and co-workers showed that epoxides **304**<sup>200b</sup> and **305**<sup>200c</sup> could be stereoselectively obtained from macrocyclic olefin **303** in good yields with ketone *ent*-**268** and oxone (Scheme 49). Functional groups such as benzimidazole appear to be tolerated under the epoxidation conditions. It seems that the macrocyclic ketone did not interfere with the epoxidation.

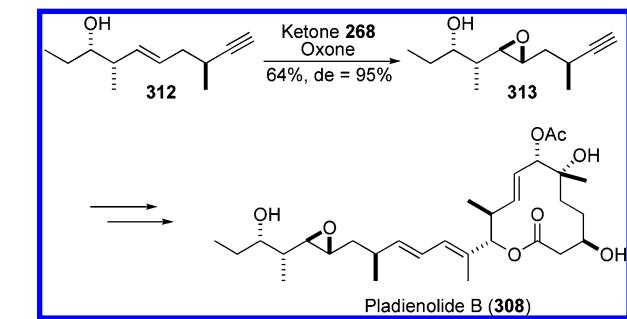
Pladienolides **B** (**308**) and **D** (**311**) are potent antitumor agents. Epoxidation with ketone **268** was employed in the total synthesis of these two molecules by Kotake and co-workers. Epoxides **307** and **310** were obtained in good yield and high

Scheme 49. Synthesis of Epothilone Analogues **304** and **305**

diastereoselectivity (>99% de) and elaborated to pladienolides **B** and **D**, respectively (Scheme 50).<sup>201</sup> In their synthesis of

Scheme 50. Synthesis of Pladienolides **B** (**308**) and **D** (**311**)

pladienolide **B** (**308**), Ghosh and co-workers also utilized the epoxidation with ketone **268** to prepare key intermediate **307** from olefin **306** (Scheme 50).<sup>202</sup> In Chandrasekhar's synthesis of pladienolide **B**, key intermediate **313** was obtained in 64% yield and 95% de via epoxidation of olefin **312** with ketone **268** and oxone (Scheme 51).<sup>203</sup>

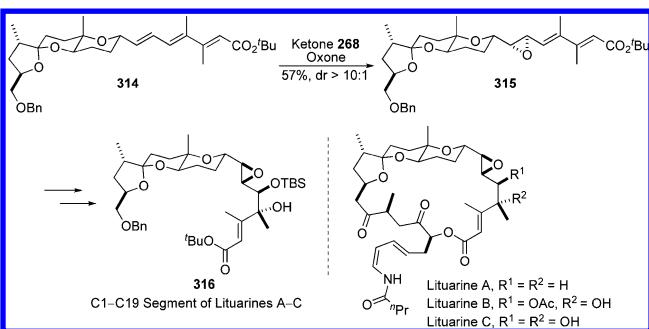
Scheme 51. Synthesis of Pladienolide **B** (**308**)

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 (>10:1). The resulting epoxide was carried forward in the synthesis of the C1–C19 segments of lituarines A–C (Scheme 52).<sup>204</sup>

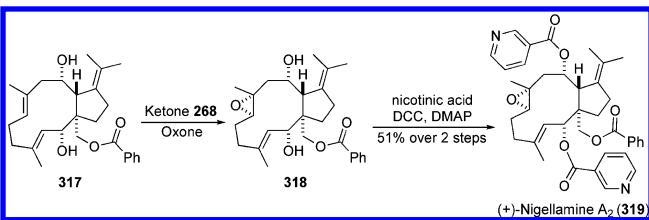
Site-selective epoxidation was also illustrated by Ready and co-workers in their synthesis of (+)-nigellamine A<sub>2</sub> (**319**). Epoxidation of triene **317** using ketone **268** selectively occurred at the desired alkene with the requisite stereochemistry (Scheme 53).<sup>205</sup>

**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

**Scheme 52. Synthesis of the Segment (316) of Lituarines A–C**

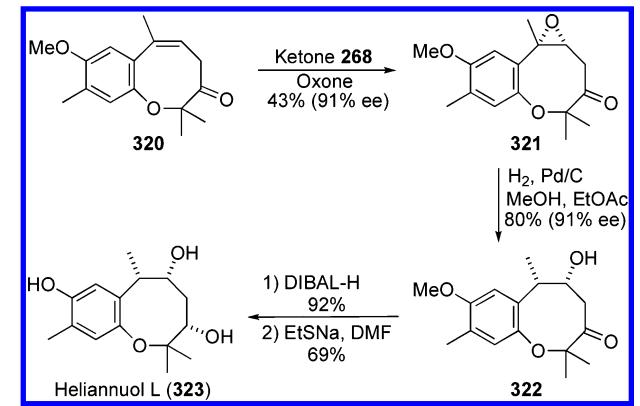


**Scheme 53. Synthesis of (+)-Nigellamine A<sub>2</sub> (319)**



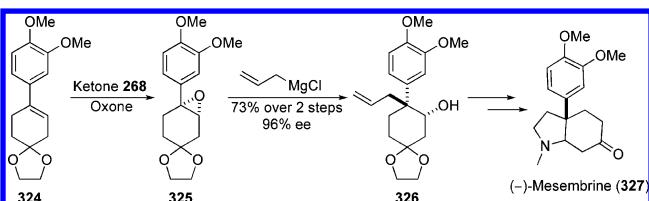
example, Ollivier and co-workers reported that asymmetric epoxidation of olefin 320 was relatively challenging but accomplished with ketone 268 to give epoxide 321 in 43% yield and 91% ee. The resulting epoxide was converted to heliannuol L (323) in three steps (Scheme 54).<sup>206</sup>

**Scheme 54. Synthesis of Heliannuol L (323)**



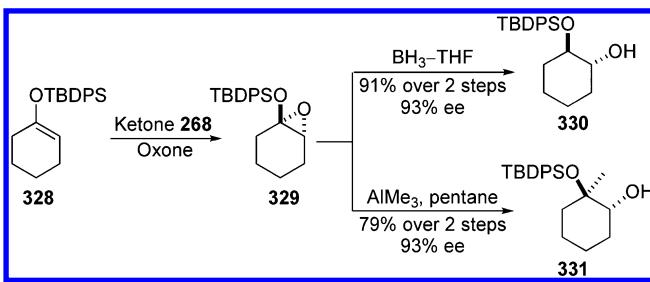
In the synthesis of (−)-mesembrine (327), Taber and co-workers showed that olefin 324 could be converted to alcohol 326 in 73% overall yield and 96% ee via epoxidation with ketone 268, followed by epoxide ring opening with allylmagnesium chloride (Scheme 55).<sup>207</sup>

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



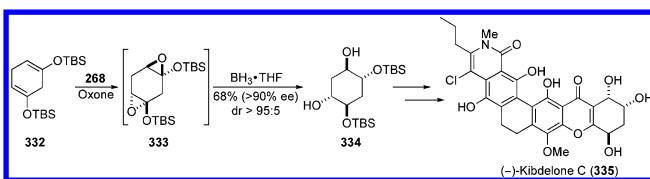
Myers and co-workers reported that differentiated *trans*-1,2-diol derivatives such as 330 and 331 were readily prepared from silyl enol ethers in good yields and high ee's by asymmetric epoxidation with ketone 268 and stereospecific ring opening of the resulting epoxides with BH<sub>3</sub>–THF and AlMe<sub>3</sub> via an internal delivery of the nucleophile (Scheme 56).<sup>208</sup> As

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



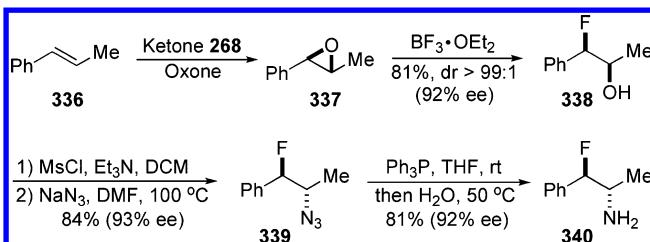
illustrated by Ready and co-workers in the total synthesis of (−)-kibdelone C (335), tetraol 334 was obtained from diene 332 in 68% overall yield with >95:5 dr and >90% ee via bis-epoxidation using ketone 268 and subsequent reduction with borane (Scheme 57).<sup>209</sup>

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



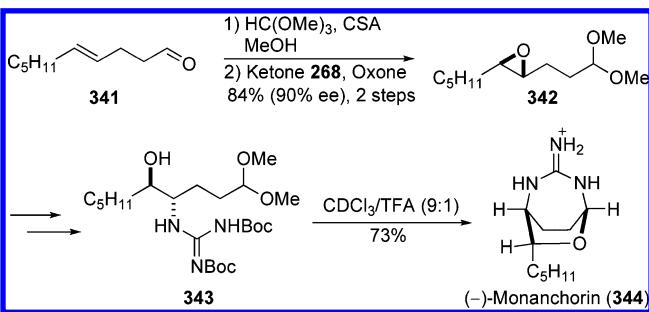
Davies and co-workers showed that optically active epoxide 337 could be converted to *syn*-fluorohydrin 338 with BF<sub>3</sub>·OEt<sub>2</sub> in 81% yield and >99:1 diastereoselectivity via stereoselective S<sub>N</sub>1-type epoxide ring opening. The resulting fluorohydrin was further transformed to chiral β-fluoroamphetamine (340) (Scheme 58).<sup>210</sup>

**Scheme 58. Synthesis of β-Fluoroamphetamine (340)**



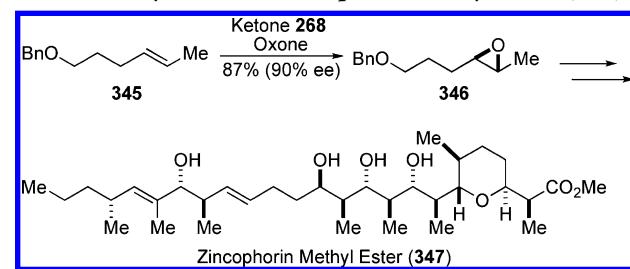
In the synthesis of (−)-monanchorin (344), Snider and co-workers reported that olefin 341 was acetalized and subsequently epoxidized with ketone 268 in 84% yield and 90% ee. The resulting epoxide 342 was converted to (−)-monanchorin (344) via guanidine 343 (Scheme 59).<sup>211</sup> (+)-Monanchorin (*ent*-344) could be obtained in an analogous manner via asymmetric epoxidation with ketone *ent*-268 as catalyst.<sup>211</sup> 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

Scheme 59. Synthesis of (−)-Monanchorin (344)



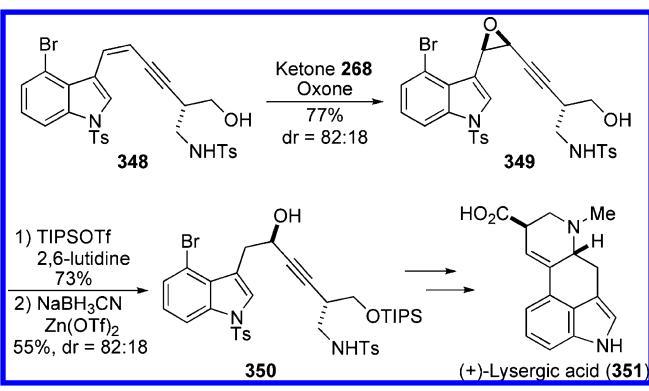
epoxide 346 was subsequently elaborated to target molecule 347 (Scheme 60).<sup>212</sup>

Scheme 60. Synthesis of Zincophorin Methyl Ester (347)



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 *m*CPBA 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).<sup>213</sup>

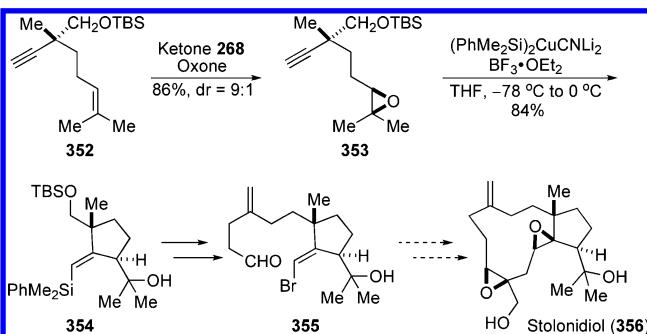
Scheme 61. Synthesis of (+)-Lysergic Acid (351)



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).

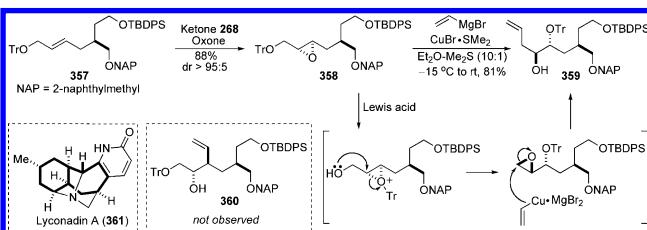
In the synthetic studies toward stolonidiol (356), Siegel and co-workers showed that trisubstituted olefin 352 was epoxidized with ketone 268 to give epoxide 353 in 86% yield and 9:1 diastereoselectivity. Epoxide 353 was cyclized to vinylsilane 354 in 84% yield with dilithium bis[dimethyl(phenyl)silyl]-cyanocuprate (Scheme 62).<sup>214</sup>

Scheme 62. Synthetic Studies toward Stolonidiol (356)



In their synthetic studies toward lyconadin A (361), Castle and co-workers employed ketone 268 for epoxidation of olefin 357 to give epoxide 358 in 88% yield and >95:5 dr (Scheme 63).<sup>215</sup> Interestingly, treatment of epoxide 358 with vinyl-

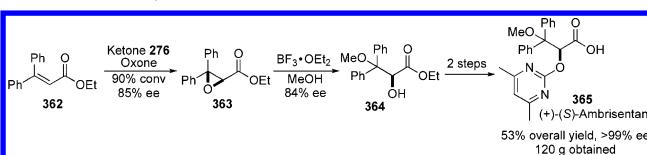
Scheme 63. Synthetic Studies toward Lyconadin A (361)



magnesium bromide and CuBr-SMe<sub>2</sub> led to an unexpected Payne rearrangement product 359 in 81% yield, and desired homoallylic alcohol 360 was not obtained.

Synthesis of (+)-(S)-ambrisentan (365) (a drug for treatment of pulmonary arterial hypertension) via asymmetric epoxidation of ethyl 3,3-diphenyl acrylate with ketone 276 was reported by Shi and co-workers (Scheme 64).<sup>216</sup> The

Scheme 64. Synthesis of (+)-(S)-Ambrisentan (365)

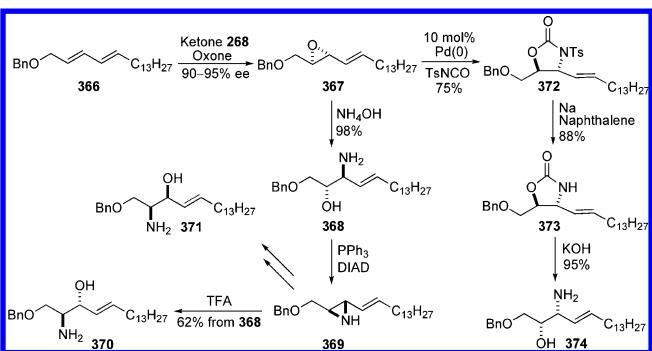


compound was obtained in four steps with 53% overall yield and >99% ee on 120 g scale. The optical purity was readily enhanced by simple filtration to remove the much less soluble racemic form.

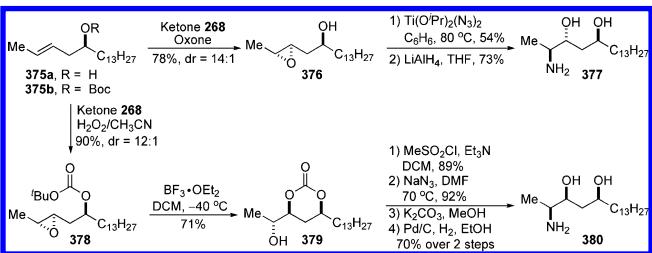
Somfai and co-workers reported a divergent synthesis of four sphingosine isomers using optically active vinyl epoxide 367 as a common key intermediate (Scheme 65).<sup>217</sup> Vinyl epoxide 367, obtained from epoxidation of diene 366 with ketone 268, was regio- and stereoselectively converted to amino alcohols 368, 370, 371, 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).<sup>218–220</sup>

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.<sup>168</sup> The

**Scheme 65.** Divergent Synthesis of *D*-*erythro*-Sphingosine and Its Isomers

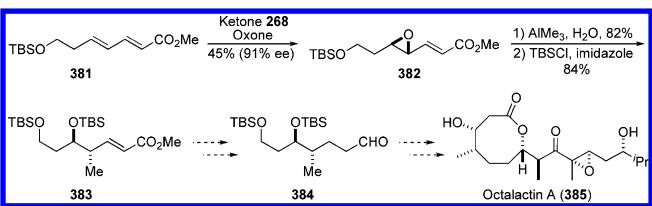


**Scheme 66.** Synthesis of 2-Amino-3,5-diols 377 and 380

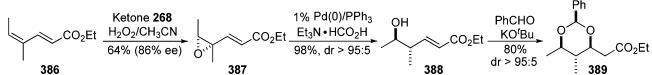


resulting vinyl epoxides have proven to be valuable synthetic intermediates as illustrated in Campagne's synthetic studies toward octalactin A (385) (Scheme 67),<sup>221</sup> O'Doherty's

**Scheme 67.** Synthesis of Subunit of Octalactin A (385)

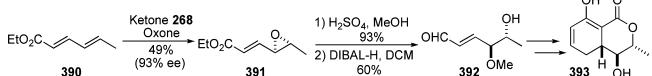


**Scheme 68.** Synthesis of *syn*-3,5-Dihydroxy Ester 389



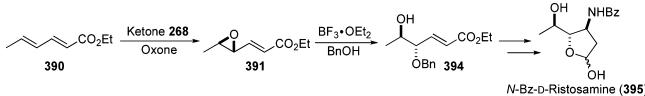
synthesis of protected 1,3-diol 389 (Scheme 68),<sup>222</sup> Kitahara's synthesis of insecticidal tetrahydroisocoumarin 393 (Scheme 69),<sup>223</sup> Matsushima's synthesis of *N*-Bz-*d*-ristosamine (395) (Scheme 70),<sup>224</sup> and Smith's synthesis of (+)-irciniastatin A (399) (Scheme 71).<sup>225</sup>

**Scheme 69.** Synthesis of Tetrahydroisocoumarin 393

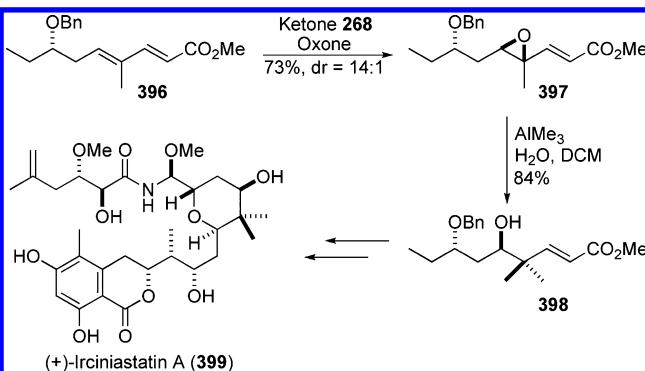


As reported by Pagenkopf and co-workers in their synthetic studies toward amphidinolide C (404), nonconjugated diene 400 could also be preferentially epoxidized at the trisubstituted double bond with ketone *ent*-268 (Scheme 72).<sup>226</sup>

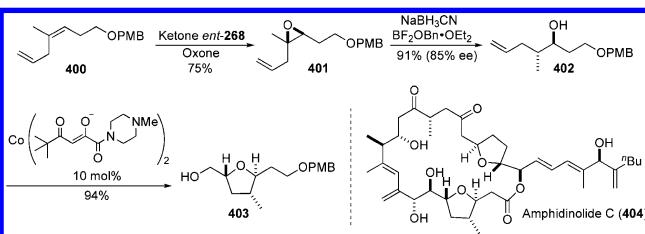
**Scheme 70.** Synthesis of *N*-Bz-*d*-Ristosamine (395)



**Scheme 71.** Synthesis of (+)-Irciniastatin A (399)

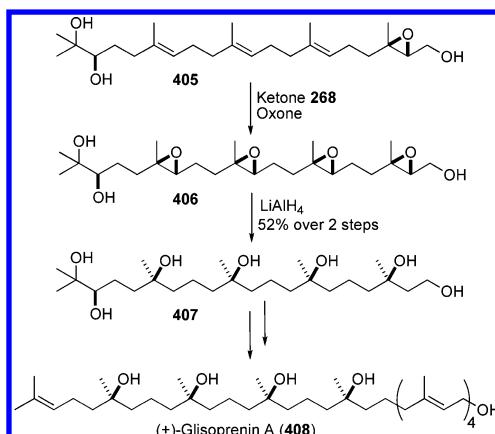


**Scheme 72.** Synthesis of the Substructure of Amphidinolide C (404)



As shown by Kishi and co-workers in the total synthesis of (+)-glisoprenin A (408), three of four chiral tertiary alcohols in compound 407 were installed via tris-epoxidation of triene 405 with ketone 268 and subsequent epoxide ring opening with LiAlH4 (Scheme 73).<sup>227</sup>

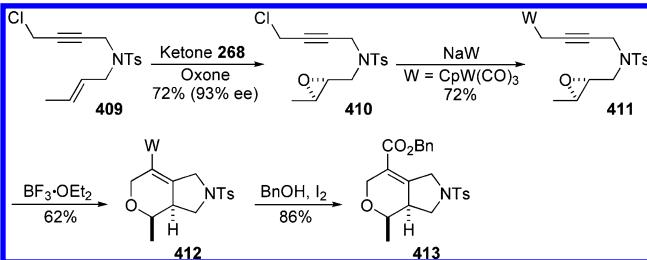
**Scheme 73.** Synthesis of (+)-Glisoprenin A (408)



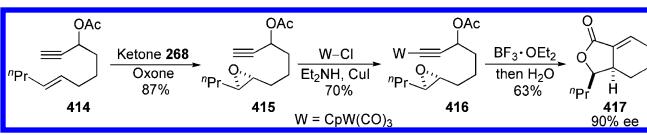
**2.5.2.3. Intramolecular Epoxide Ring Opening.** Epoxides can undergo regio- and stereoselective intramolecular ring opening. Asymmetric epoxidation with ketone 268 has been employed to construct various optically active cyclic molecules. For example, Liu and co-workers reported that alkynyl epoxides, obtained from the asymmetric epoxidation using ketone 268, could undergo tungsten-mediated [3 + 3]<sup>228a</sup> and

[3 + 2]<sup>228b</sup> 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

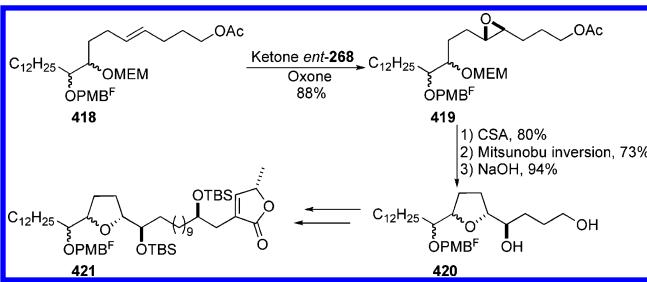


#### Scheme 75. Tungsten-Mediated [3 + 2] Cycloaddition of Alkynyl Epoxide



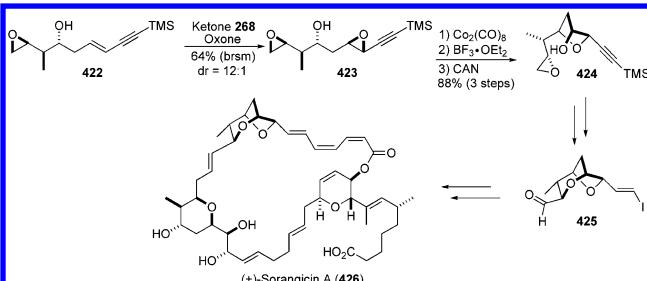
In their synthesis of (+)-murisolin stereoisomer libraries, Curran and co-workers employed the epoxidation with ketone *ent*-268 to stereoselectively install the epoxide onto the double bond of compound 418. Tetrahydrofuran 420 was synthesized from epoxide 419 via acid-promoted epoxide opening, Mitsunobu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

#### Scheme 76. Synthesis of (+)-Murisolin 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).<sup>230,231</sup>

#### 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),<sup>232,233</sup> Williams (Scheme 79),<sup>234</sup> and Micalizio (Scheme 80).<sup>235</sup>

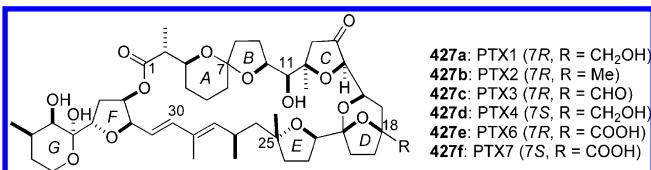
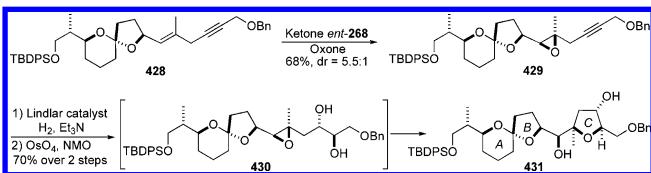
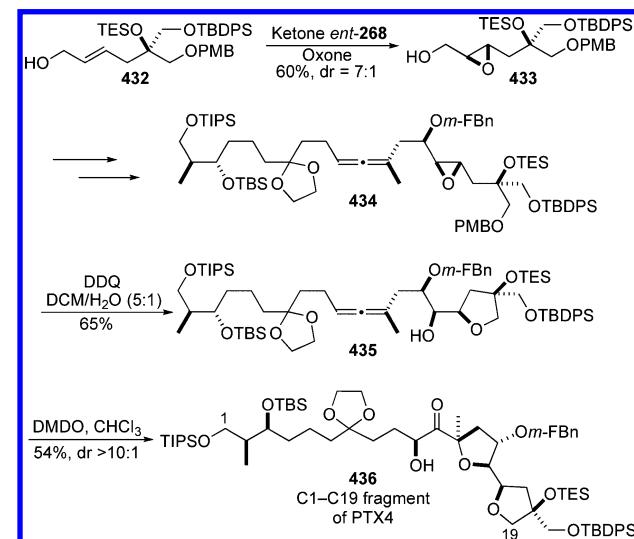


Figure 79. Structure of members of the pectenotoxin family.

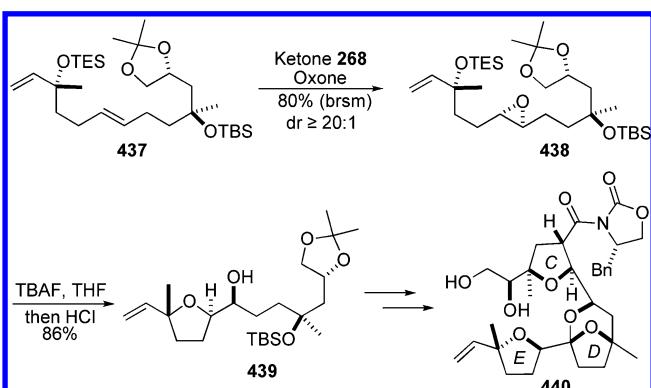
#### Scheme 78. Synthesis of the ABC-Ring Fragment (431) of Pectenotoxins



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

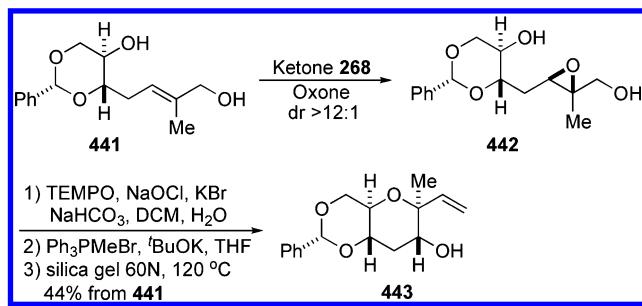


#### Scheme 80. Synthesis of CDE-Ring Fragment (440) of Pectenotoxin 2



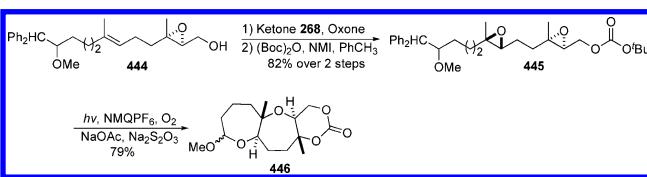
In the synthesis of 2-methyltetrahydropyran **443**, a key intermediate toward ladder-shaped polyethers, Torikai and co-workers showed that allylic alcohol **441** could be effectively epoxidized with ketone **268** in high stereoselectivity (>12:1 dr). Compound **443** was readily prepared from **441** in 44% overall yield (Scheme 81).<sup>236</sup>

**Scheme 81. Synthesis of 2-Methyltetrahydropyran **443****



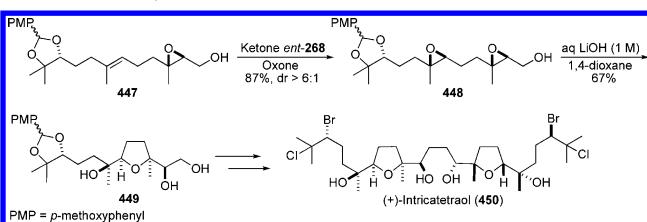
Floreancig and co-workers reported that tricyclic compound **446** could be obtained in good overall yield via sequential epoxidation of **444** with ketone **268**, formation of the carbonate, and electron-transfer-initiated cascade cyclization (Scheme 82).<sup>237</sup>

**Scheme 82. Synthesis of **446** via Electron-Transfer-Initiated Cascade Cyclization**



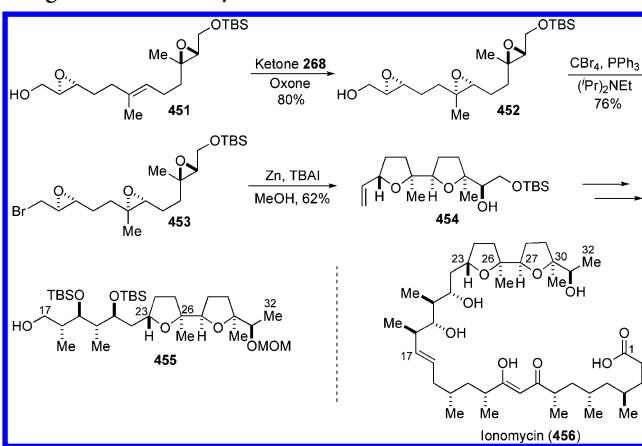
In the total synthesis and determination of stereochemistry of (+)-intricate tetraol (**450**), Morimoto and co-workers reported that olefin **447** could be epoxidized with ketone *ent*-**268** in 87% yield and >6:1 dr. The epoxide-opening cyclization of compound **448** gave tetrahydrofuran **449**, which was subsequently transformed to (+)-intricate tetraol (**450**) (Scheme 83).<sup>238</sup>

**Scheme 83. Synthesis of (+)-Intricate Tetraol (**450**)**



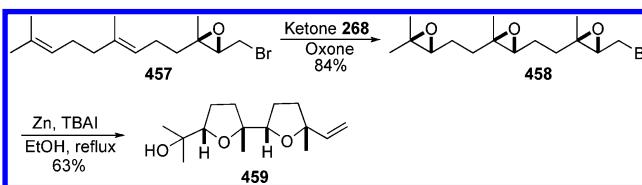
In the synthesis of bis-tetrahydrofuran C17–C32 segment (**455**) of antibiotic ionomycin (**456**), Marshall and co-workers utilized ketone **268** to epoxidize olefin **451** to give compound **452**, which was converted to bromide **453**. Treating **453** with Zn and TBAI led to formation of vinyl 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).<sup>239</sup> Marshall and co-workers also employed this asymmetric epoxidation/Zn-initiated epoxide cascade cyclization to synthesize bis-

**Scheme 84. Synthesis of the Bis-Tetrahydrofuran C17–C32 Fragment of Ionomycin**

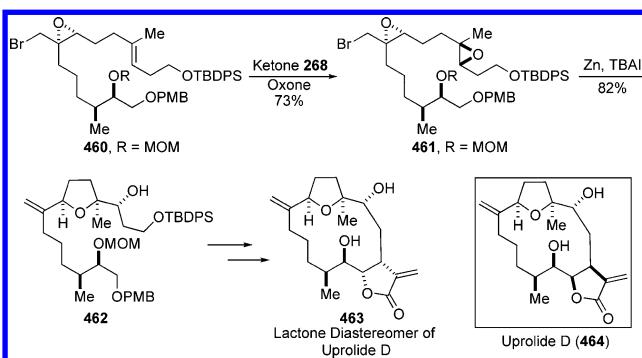


tetrahydrofuran **459** (Scheme 85)<sup>240</sup> and the lactone diastereomer (**463**) of the cembranolide uprolide D (**464**) (Scheme 86).<sup>241</sup>

**Scheme 85. Synthesis of Bis-THF via Zn-initiated Epoxide Cascade Cyclization**



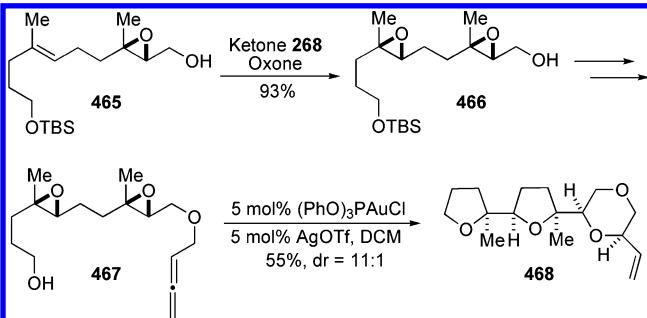
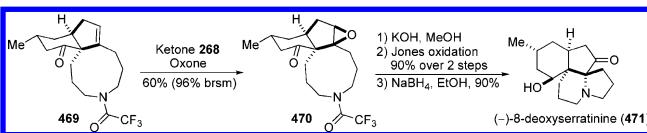
**Scheme 86. Synthesis of the Lactone Diastereomer of the Cembranolide Uprolide D**



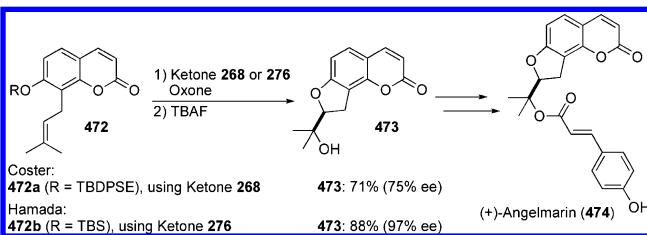
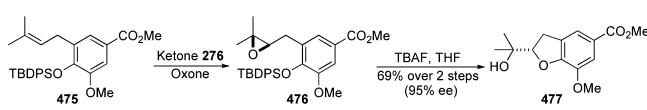
Lee, Gagné, and co-workers reported a Au(I)-catalyzed cyclization of allenyl epoxides. For example, bis-tetrahydrofuran **468** was obtained with 55% yield and 11:1 dr when allenyl epoxide **467** was treated with (PhO)<sub>3</sub>PAuCl catalyst (Scheme 87).<sup>242</sup>

In the synthesis of *Lycopodium* alkaloid (−)-8-deoxyserratinine (**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).<sup>243</sup> However, the undesired diastereomer was predominantly formed when *m*CPBA was used.

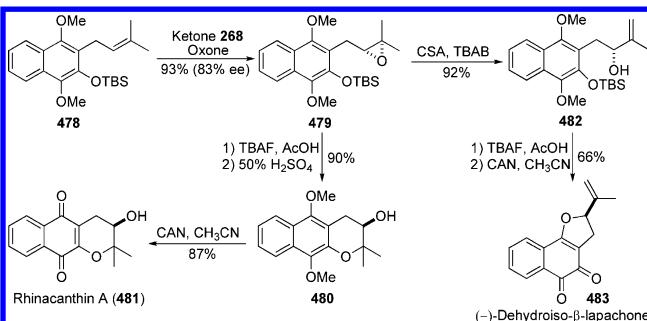
Prenylphenol derivatives have been shown to be effective substrates for epoxidation with ketone **268** or **276**. Higher ee's were obtained with ketone **276** than **268** in some cases. The resulting chiral epoxides were elaborated to various biologically

**Scheme 87. Au(I)-Catalyzed Cyclization of Allenyl Epoxide****Scheme 88. Synthesis of (−)-8-Deoxyserratinine (471)**

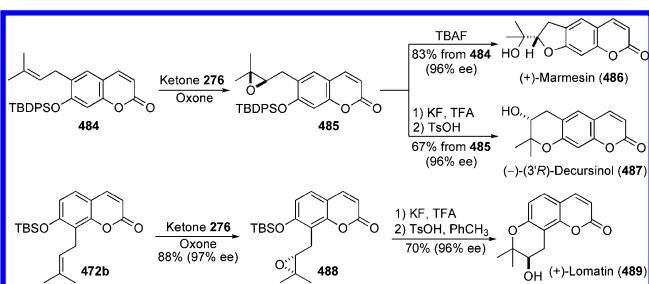
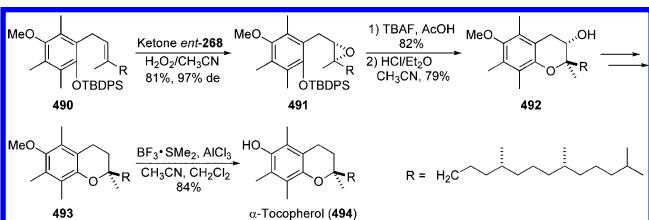
active dihydrobenzofurans and dihydrobenzopyrans as illustrated in Coster's synthesis of (+)-angelmarin (474) (Scheme 89)<sup>244</sup> and methyl (+)-7-methoxyanodendroate (477) (Scheme 89).

**Scheme 89. Synthesis of (+)-Angelmarin (474)****Scheme 90. Synthesis of Methyl (+)-7-Methoxyanodendroate (477)**

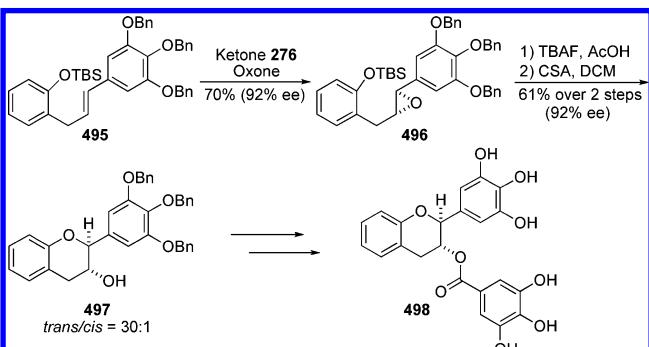
90),<sup>245</sup> Kimachi's synthesis of rhinacanthin A (481)<sup>246a</sup> and (−)-dehydroiso-β-lapachone (483)<sup>246b</sup> (Scheme 91), Hamada's synthesis of (+)-angelmarin (474) (Scheme 89),<sup>247</sup> (+)-marmesin (486), (−)-(3'R)-decursinol (487), and (+)-lomatian

**Scheme 91. Synthesis of Rhinacanthin A (481) and (−)-Dehydroiso-β-lapachone (483)**

(489) (Scheme 92),<sup>247</sup> and Woggon's synthesis of α-tocopherol (494) (Scheme 93).<sup>248</sup>

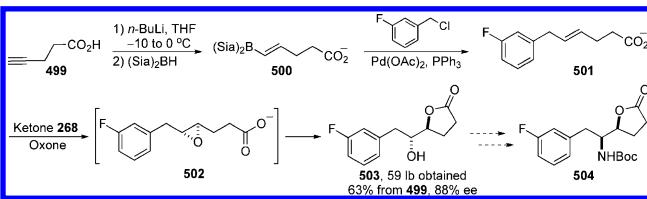
**Scheme 92. Synthesis of (+)-Marmesin, (−)-(3'R)-Decursinol, and (+)-Lomatian****Scheme 93. Synthesis of α-Tocopherol (494)**

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).<sup>249</sup>

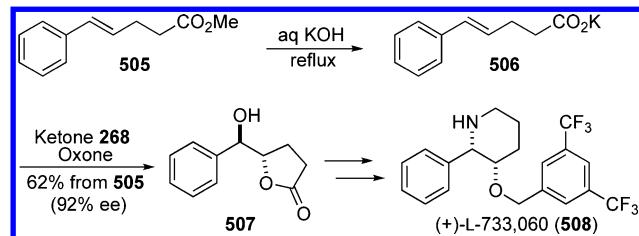
**Scheme 94. Synthesis of (−)-5,7-Dideoxy-Gallocatechin Gallate (498)**

Synthesis of chiral hydroxy lactones via asymmetric epoxidation of alkenyl carboxylic acids has been reported. In their synthesis of hydroxy lactone 503, 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 501. Epoxidation of 501 with ketone 268 and in-situ lactonization yielded 59 lb of lactone 503 in 63% overall yield and 88% ee (Scheme 95).<sup>250</sup> 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).<sup>251,252</sup> Seward

Scheme 95. Pilot-Plant-Scale Synthesis of Lactone 503

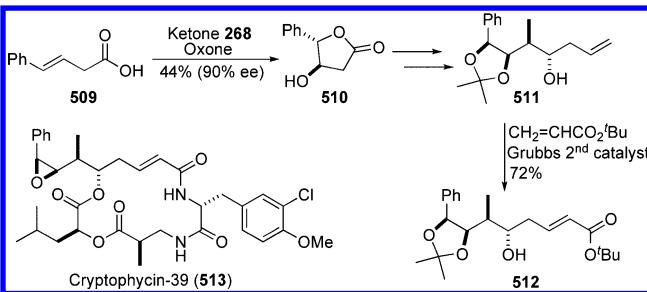


Scheme 96. Synthesis of NK1 Receptor Antagonist (+)-L-733,060 (508)



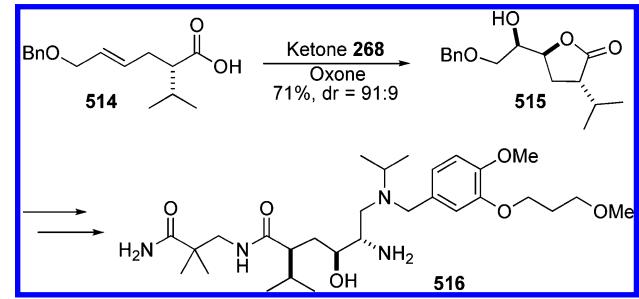
and co-workers utilized the epoxidation to form lactone 510, which was converted to cryptophycin-39 unit A precursor (512) (Scheme 97).<sup>253</sup> Asymmetric epoxidation with ketone 268

Scheme 97. Synthesis of Cryptophycin-39 Unit A Precursor (512)



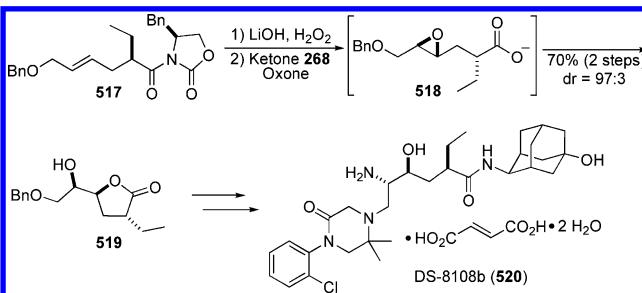
268 and in-situ lactonization process was also effectively employed by Nakamura and co-workers in their synthesis of renin inhibitors 516 (Scheme 98)<sup>254</sup> and DS-8108b (520) (Scheme 99).<sup>255</sup>

Scheme 98. Synthesis of Renin Inhibitor 516



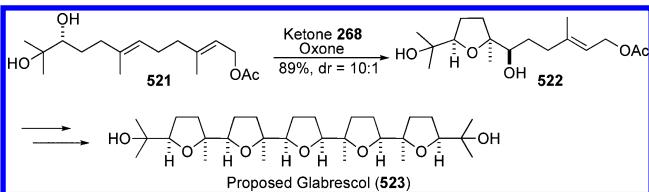
When two or more alkenes are present in a molecule, steric and electronic differences around the double bonds allow the epoxidation to proceed site selectively as illustrated in various cases. For example, in the synthesis of initially assigned glabrescol (523) reported by Kodama and co-workers, diene 521 was regio- and stereoselectively epoxidized using ketone 268 to give monotetrahydrofuran 522 in 89% yield and 10:1 dr after the concomitant ring closure. Further elaboration gave

Scheme 99. Synthesis of Renin Inhibitor DS-8108b

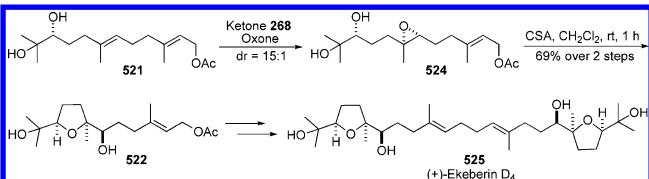


$C_s$ -symmetric penta-THF 523 (Scheme 100).<sup>256</sup> Morimoto and co-workers reported that monotetrahydrofuran 522 was

Scheme 100. Synthesis of Initially Assigned Glabrescol (523)

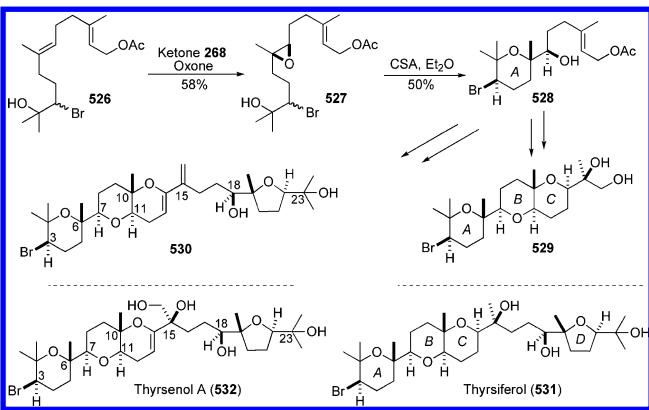


obtained from diene 521 in 69% overall yield and 15:1 dr via epoxidation and subsequent CSA-promoted cyclization and elaborated to antiplasmodial  $C_2$ -symmetric (+)-ekeberin D<sub>4</sub> (525) (Scheme 101).<sup>257</sup>

Scheme 101. Synthesis of (+)-Ekeberin D<sub>4</sub> (525)

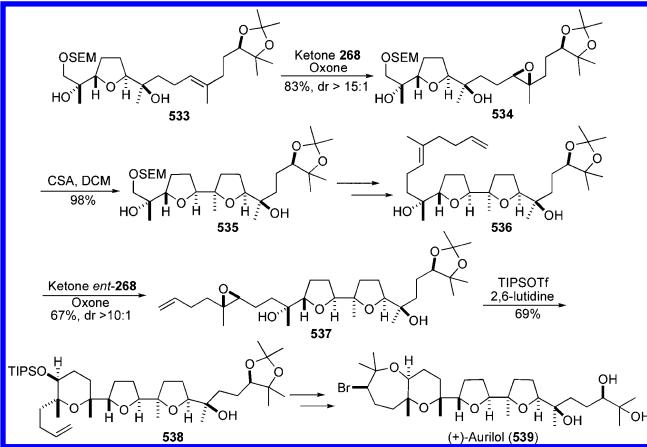
In their synthetic studies toward thrysiferol (531)<sup>258</sup> and thyrsenol A (532)<sup>259</sup> (Scheme 102), McDonald and co-workers showed that the internal double bond of compound 526 was site and stereoselectively epoxidized with ketone 268 to give epoxide 527. Under carefully controlled reaction conditions, one of the bromohydrin epoxide diastereomers preferentially cyclized to give bromotetrahydropyran 528 in 50% yield.

Scheme 102. Synthesis of Substructure 529 and Dideoxydidehydrothyrsenol (530)



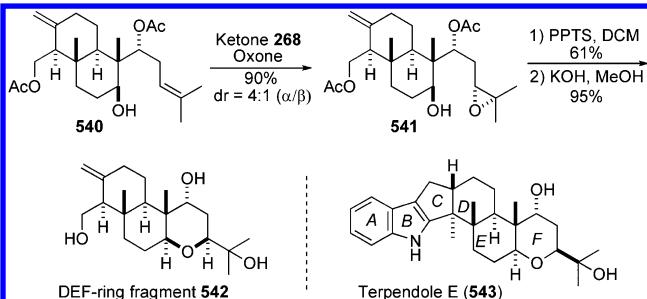
In the total synthesis of bromotriterpene polyether (+)-aurilol (**539**) reported by Morimoto and co-workers, compounds **533** and **536** were epoxidized with ketone **268** and its enantiomer to give epoxides **534** and **537** in high diastereoselectivities (Scheme 103).<sup>260</sup> Epoxidation of **536** occurred site selectively at the trisubstituted alkene.

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



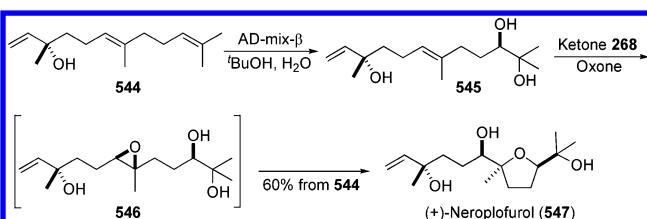
In their synthetic studies toward terpendole E (**543**), Oikawa and co-workers reported that asymmetric epoxidation of diene **540** with ketone **268** occurred selectively at the trisubstituted double bond, giving epoxide **541** in 90% yield and 4:1 dr. Upon cyclization and deprotection, epoxide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

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



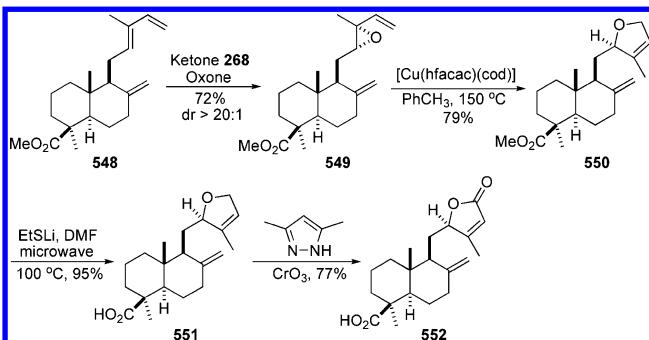
Huo and co-workers reported the synthesis of (+)-neroplofurofuran (**547**) via asymmetric dihydroxylation of (+)-nerolidol (**544**), site- and stereoselective epoxidation of the trisubstituted alkene of compound **545** with ketone **268**, and subsequent in-situ cyclization (60% overall yield) (Scheme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

**Scheme 105. Synthesis of (+)-Neroplofurofuran (**547**)**



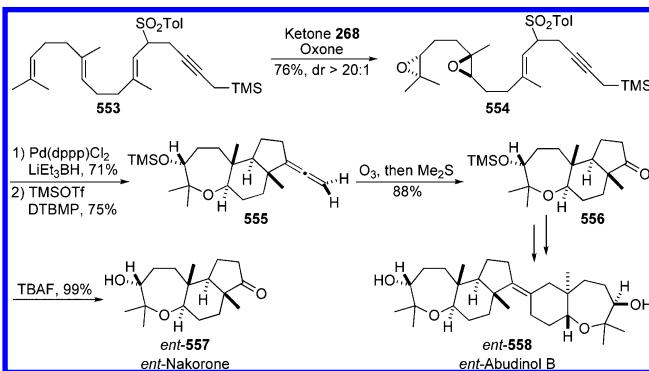
Njardarson and co-workers reported that epoxidation of triene **548** with ketone **268** occurred selectively at the trisubstituted alkene, giving vinyl epoxide **549** in 72% yield and >20:1 dr. The epoxide was subsequently elaborated to several heterocycle-containing labdane natural products such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

**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).<sup>264</sup> In

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

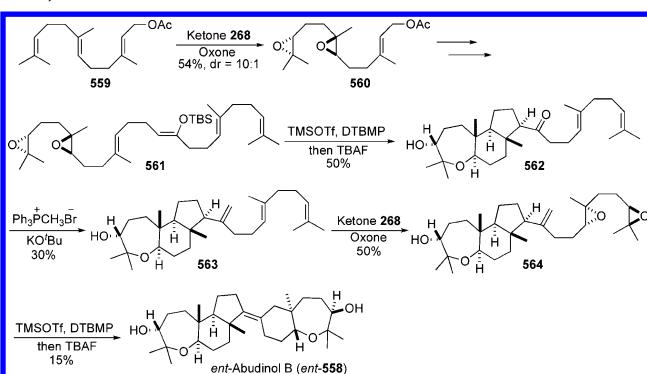


another synthetic route to *ent*-abudinol B (*ent*-**558**), McDonald and co-workers showed that the two trisubstituted alkenes in **563** were selectively epoxidized with ketone **268**. The unreacted terminal alkene subsequently participated in TMSOTf-promoted cyclization to form *ent*-abudinol B (*ent*-**558**) in 15% yield (Scheme 108).<sup>265</sup>

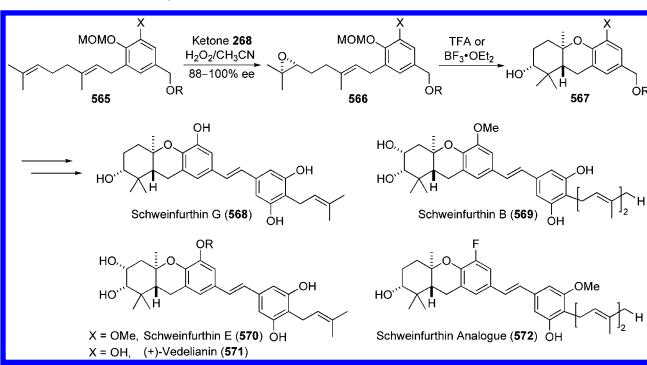
Wiemer and co-workers reported that monoepoxides **566** could be obtained with high ee's via site- and stereoselective epoxidation of the terminal trisubstituted alkene of dienes **565**. Acid-promoted cyclization of epoxides **566** led to hexahydroxanthenes **567**, which were subsequently elaborated to schweinfurthins G (**568**),<sup>266</sup> B (**569**), and E (**570**)<sup>267</sup> as well as related compound (+)-vedelianin (**571**)<sup>268</sup> and schweinfurthin analogue **572**<sup>269</sup> (Scheme 109).

Siegel and co-workers reported that epoxidation of commercially available (-)-caryophyllene (**573**) with ketone *ent*-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

**Scheme 108. Biomimetic Synthesis of *ent*-Abudinol B (*ent*-558)**

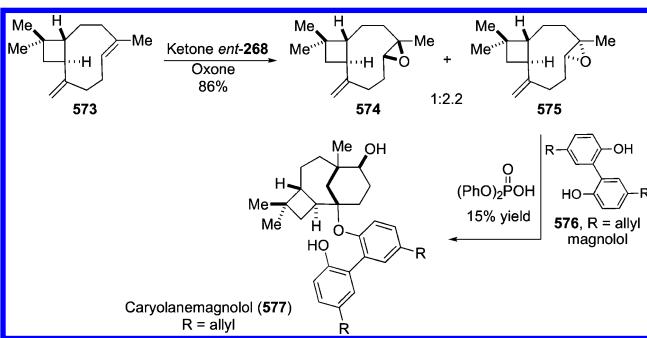


**Scheme 109. Synthesis of Schweinfurthins and Vedelianin**



574 when *m*CPBA 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).<sup>270</sup>

**Scheme 110. Synthesis of Caryolanemagnolol (577)**

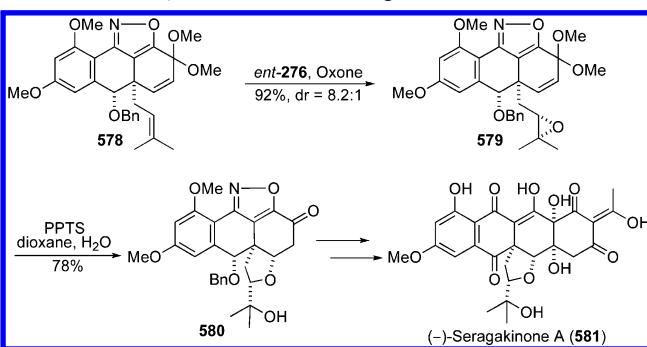


Suzuki and co-workers reported that the trisubstituted alkene of 578 was site- and stereoselectively epoxidized with ketone *ent*-276, giving epoxide 579 in 92% yield and 8.2:1 dr. Epoxide-opening cyclization of 579 and further elaboration led to (−)-seragakinone A (581) (Scheme 111).<sup>271</sup>

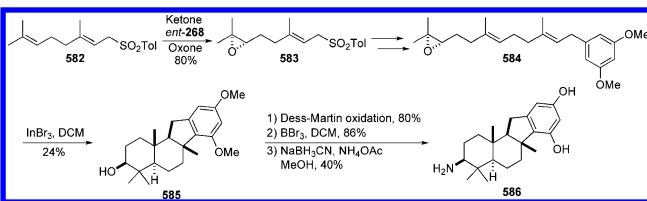
Sponge meroterpenoid pelorol analogues such as 586 were synthesized by Andersen and co-workers. The epoxide in 583 was installed via site- and enantioselective epoxidation of diene 582 with ketone *ent*-268. InBr<sub>3</sub>-promoted cyclization of epoxide 584 led to construction of polycyclic structure 585, which was converted to compound 586 (Scheme 112).<sup>272</sup>

In the synthesis of lactodehydrothrysiferol (590), Floreancig and co-workers showed that bis-epoxide 588 could be obtained in 82% yield via one-pot sequential epoxidations of diene 587.

**Scheme 111. Synthesis of (−)-Seragakinone A (581)**

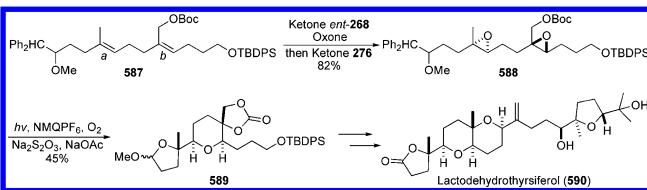


**Scheme 112. Synthesis of Sponge Meroterpenoid Pelorol Analogue (586)**



The more reactive alkene **a** was selectively epoxidized with ketone *ent*-268, followed by addition of ketone 276 to complete the epoxidation of the less reactive alkene **b** (Scheme 113).<sup>273</sup>

**Scheme 113. Synthesis of Lactodehydrothrysiferol (590)**

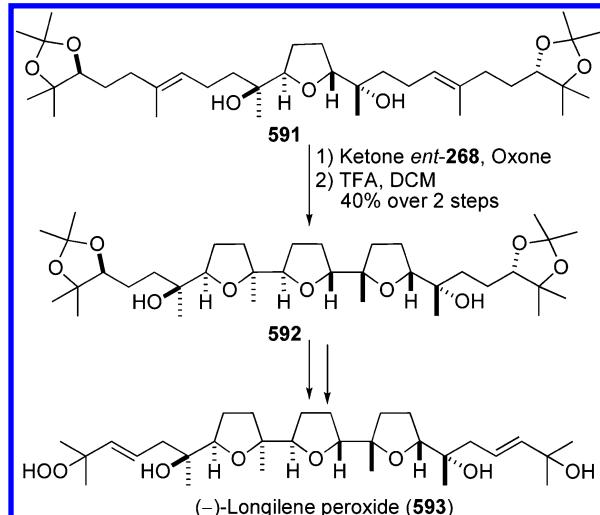


When a substrate contains multiple alkenes, all double bonds can be simultaneously epoxidized with ketone 268 or its enantiomer, allowing the rapid increase of molecular complexity via epoxide-ring-opening cyclization.<sup>274</sup> For example, in the synthesis of (−)-longilene peroxide (593) reported 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).<sup>275</sup> 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 diepoxyde 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).<sup>276</sup>

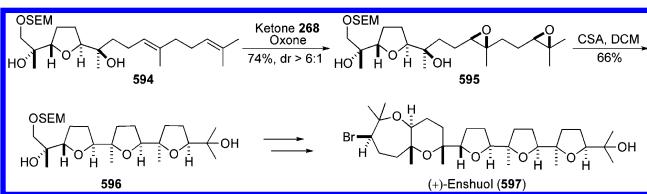
In their studies on electron-transfer-initiated cascade cyclizations, Floreancig and co-workers utilized ketone catalyst 268 for epoxidation of diene 598, giving bis-epoxide 599 in 85% yield. Bis-epoxide 599 was converted to bis-tetrahydrofuran 600 in 66% yield upon photoirradiation (Scheme 116).<sup>277</sup>

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).<sup>278</sup>

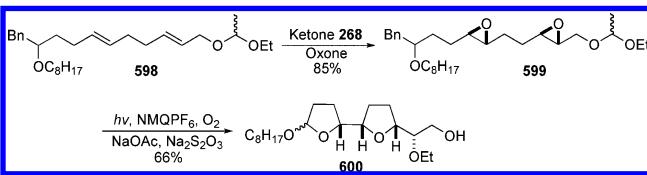
Scheme 114. Synthesis of (−)-Longilene Peroxide (593)



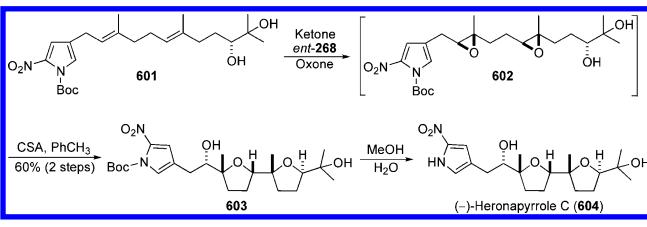
Scheme 115. Synthesis of (+)-Enshuol (597)



Scheme 116. Synthesis of Bis-THF via Electron-Transfer-Initiated Cascade Cyclizations



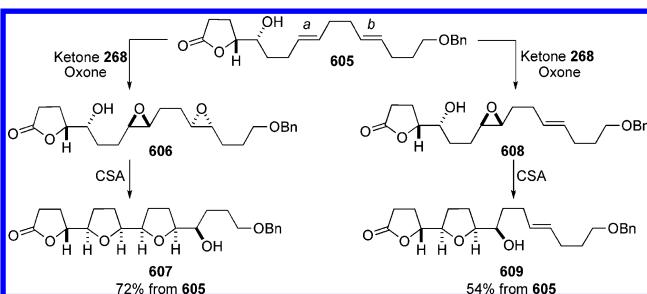
Scheme 117. Synthesis of (−)-Heronapyrrole C (604)



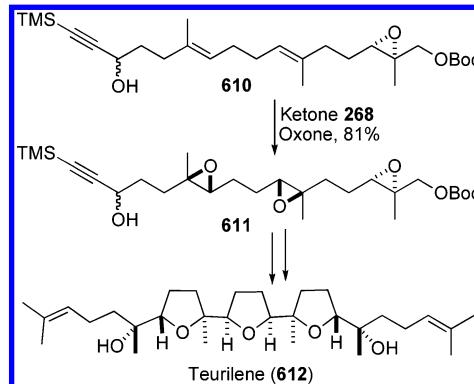
Sinha and co-workers employed the epoxidation with ketone 268 and *ent*-268 in the synthesis of a library of bis-THF annonaceous acetogenins. For example, bis-THF lactone 607 was obtained from 605 via bis-epoxidation and subsequent CSA-mediated cyclization in 72% overall yield. Interestingly, alkene *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).<sup>279</sup>

Martín and co-workers synthesized teurilene (612) via epoxide-opening cascades (Scheme 119).<sup>280</sup> 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

Scheme 118. Synthesis of Tetrahydrofuran Lactones 607 and 609

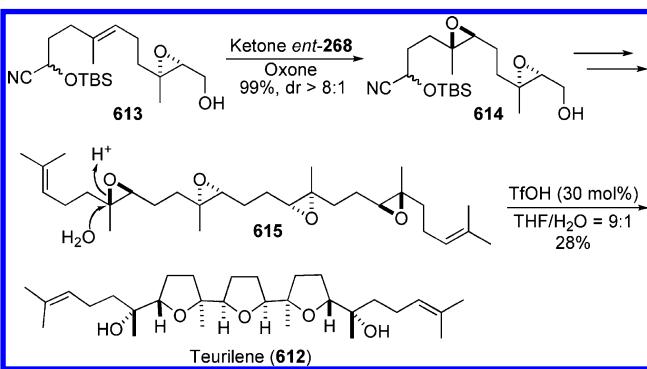


Scheme 119. Synthesis of Teurilene (612) by Martín



with ketone *ent*-268 and subsequently transformed to tetraepoxide 615. Treating 615 with TfOH led to direct formation of teurilene (612) via an epoxide-opening cascade triggered by hydrolysis of the terminal epoxide (Scheme 120).<sup>281</sup>

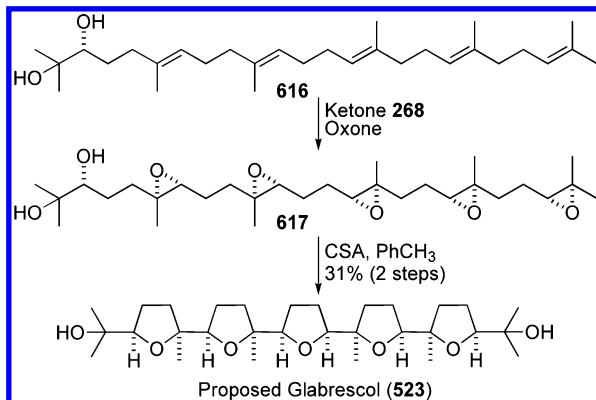
Scheme 120. Synthesis of Teurilene (612) by Morimoto



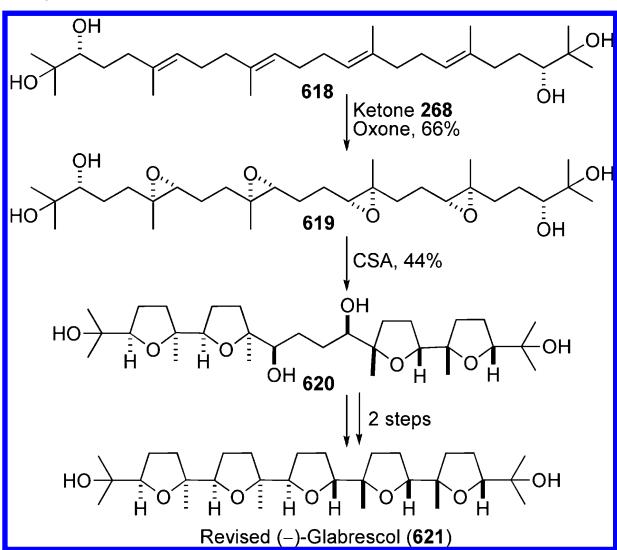
Corey and co-workers reported that polyene 616 was stereoselectively and simultaneously epoxidized with ketone 268 to give pentaepoxide 617, which was converted to initially assigned *C*<sub>5</sub>-symmetric glabrescol (523) in 31% overall yield (Scheme 121).<sup>282</sup> In their studies on the determination of the correct structure of glabrescol, *C*<sub>2</sub>-symmetric pentacyclic oxasqualenoid 621, prepared via tetraepoxidation of polyene 618 and subsequent cyclization, matched the reported isolated natural product glabrescol (621).<sup>283,284</sup>

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

Scheme 121. Synthesis of Initially Assigned Glabrescol (523)



Scheme 122. Synthesis of Revised (−)-Glabrescol (621) by Corey



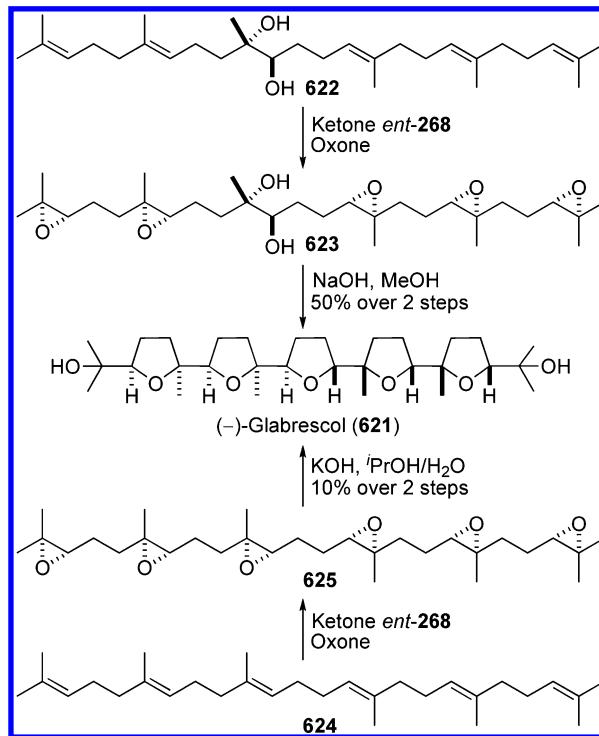
(Scheme 123).<sup>285</sup> The results suggested two alternative biogenetic approaches to (−)-glabrescol.

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).<sup>281</sup>

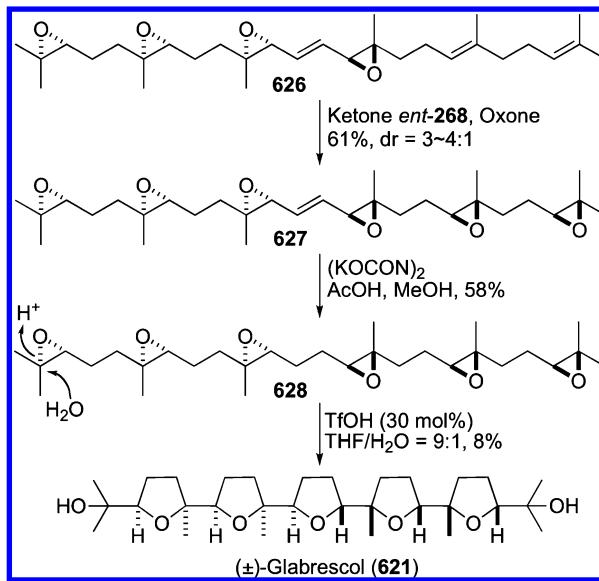
In the initial synthesis of (+)-omaezakianol (another member of the oxasqualenoid family) reported by Morimoto and co-workers, diepoxyde 630 and triepoxide 634 were prepared via epoxidation with ketone *ent*-268 and ketone 268, respectively. Monotetrahydrofuran 632, derived from 630, was coupled with 634 via cross metathesis to give triepoxide 635, which was elaborated to (+)-omaezakianol (637) (Scheme 125).<sup>286</sup> 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).<sup>281</sup>

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-

Scheme 123. Synthesis of (−)-Glabrescol (621) by Qu



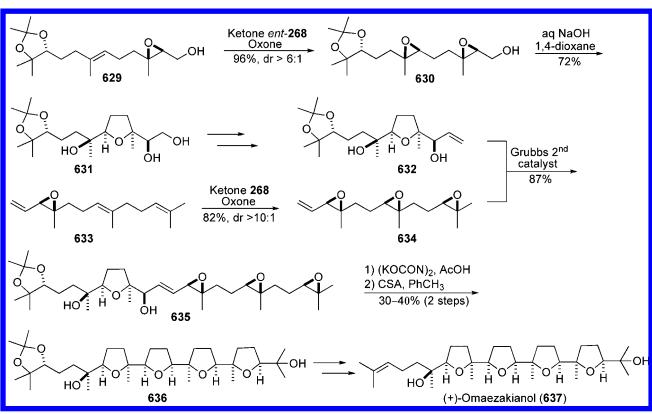
Scheme 124. Synthesis of (±)-Glabrescol (621) by Morimoto



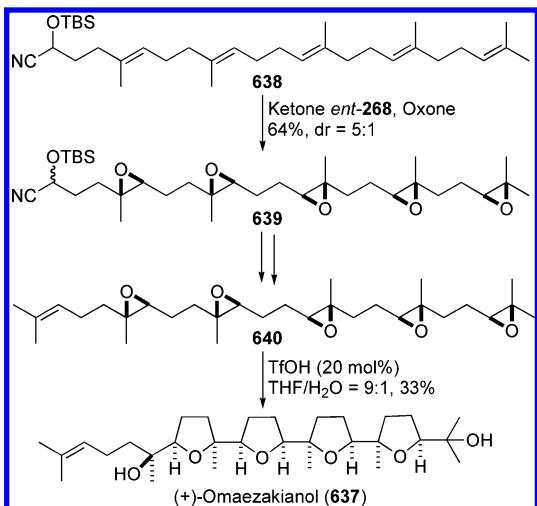
opening cascade cyclization, and reduction with Na (Scheme 127).<sup>287</sup>

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).<sup>288</sup> These studies provide useful insights into polyether biosynthesis.

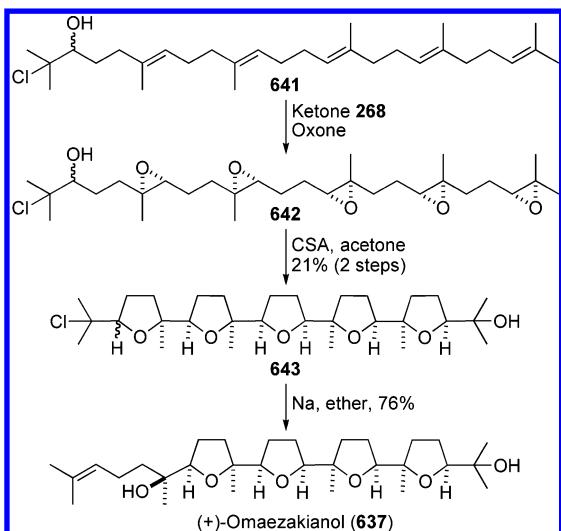
**Scheme 125. Synthesis of (+)-Omaezakianol (637) by Morimoto**



**Scheme 126. Synthesis of (+)-Omaezakianol (637) by Morimoto**

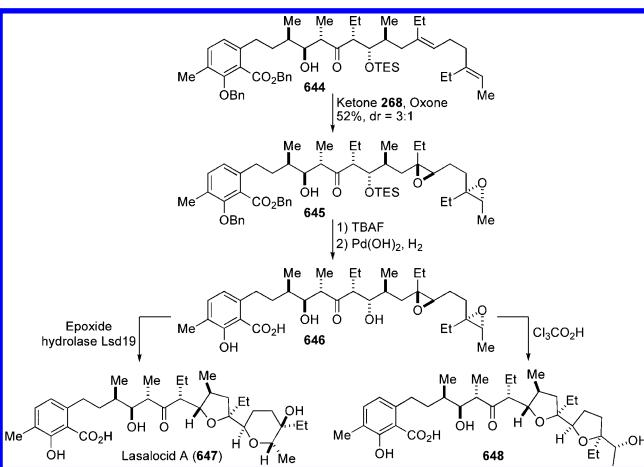


**Scheme 127. Synthesis of (+)-Omaezakianol (637) by Xiong and Corey**

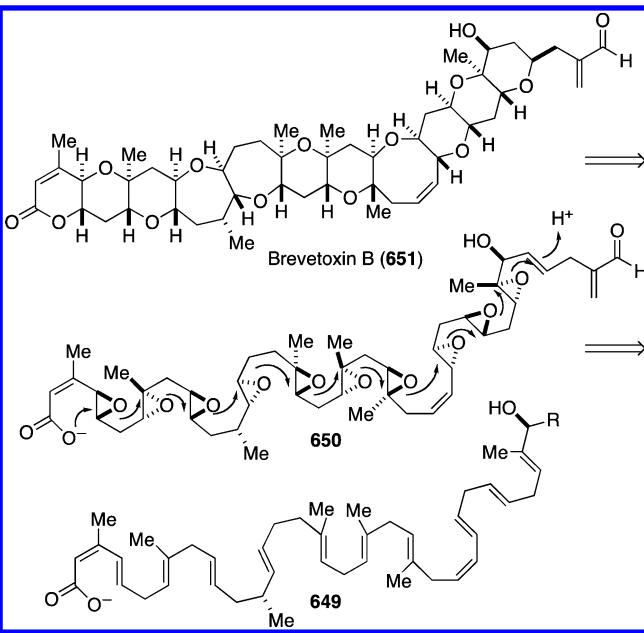


Fused polycyclic ethers such as brevetoxin B (**651**) are a class of biologically important molecules and may biosynthetically derive from polyenes via polyepoxidation and epoxide-opening cascade cyclization (Scheme 129).<sup>289,290</sup> The biomimetic

**Scheme 128. Biosynthesis of Lasalocid A (647)**



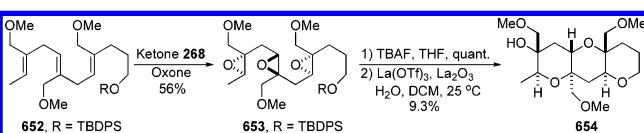
**Scheme 129. Proposed Biosynthetic Pathway for Brevetoxin B (651)**



polyene–polyepoxide–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.

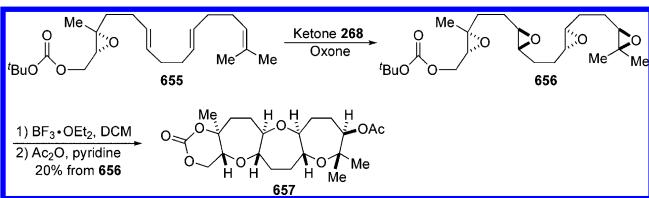
Murai and co-workers reported that triepoxide **653** was obtained in 56% yield via tris-epoxidation of **652** with ketone **268**. Tricyclic ether **654** was formed in 9.3% yield from the triepoxide via  $\text{La}(\text{OTf})_3$ -catalyzed cascade cyclization upon desilylation (Scheme 130).<sup>291</sup>

**Scheme 130. Synthesis of Fused Tricyclic Ether **654****



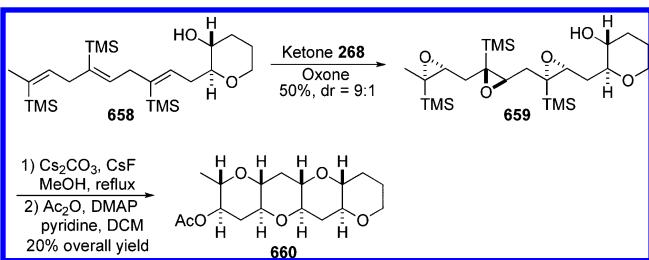
McDonald and co-workers reported various studies on biomimetic synthesis of fused polycyclic ethers.<sup>292</sup> For example, triene **655** was epoxidized with ketone **268** to introduce three epoxides. Tetracyclic ether **657** was obtained in 20% overall yield from tetraepoxide **656** via Lewis acid-promoted cascade endo cyclization and subsequent acetylation (Scheme 131).<sup>292e</sup>

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



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**. Tetrahydropyran **660** was formed in 20% overall yield via an epoxide-opening cascade cyclization of triepoxide **659** promoted by  $\text{Cs}_2\text{CO}_3/\text{CsF}$  and acetylation (Scheme 132).<sup>293</sup> The trimethylsilyl groups directed 6-endo cyclization

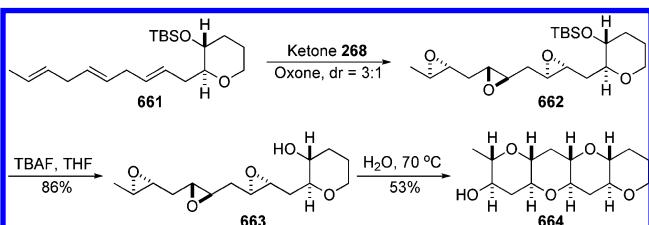
**Scheme 132.** Synthesis of Tetrahydropyran **660** via TMS-Directed Cyclization



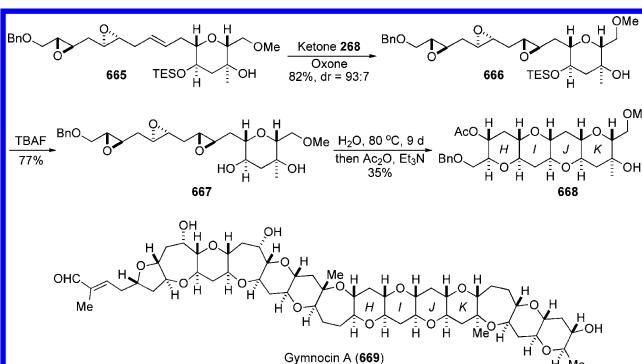
cyclizations and “disappeared” after each cyclization.<sup>294,295</sup> Their subsequent studies showed that triepoxide **663**, obtained from tris-epoxidation of triene **661** with ketone **268** and deprotection, underwent 6-endo cyclizations to form tetracyclic tetrahydropyran **664** without the need for directing groups when the reaction was carried out in water (Scheme 133).<sup>296</sup> This methodology was applied to the synthesis of the HIJK-ring fragment (**668**) of gymnocin A (Scheme 134).<sup>297</sup>

Jamison and co-workers reported the total synthesis of *ent*-dioxepandehydrothrysiferol (**676**) via bromonium-initiated cascade cyclization. Diepoxyde **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

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

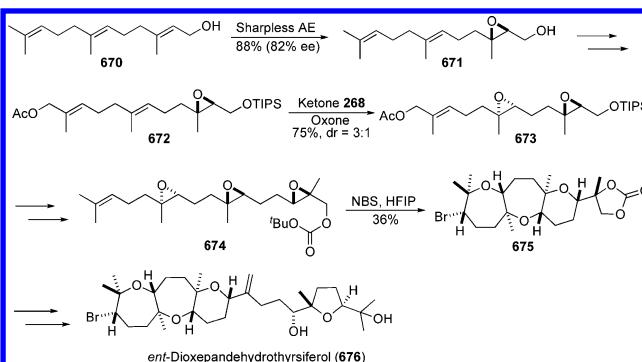


**Scheme 134.** Synthesis of HIJK-Ring Fragment (**668**) of Gymnocin A



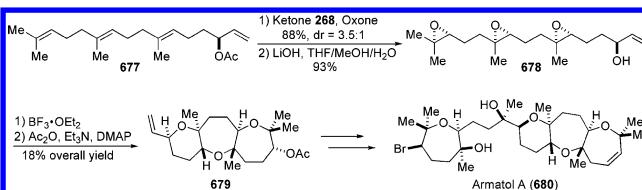
transformed to target molecule **676** (Scheme 135).<sup>298</sup> They also accomplished the total synthesis of armatol A (**680**) and

**Scheme 135.** Synthesis of *ent*-Dioxepandehydrothrysiferol (**676**)



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  $\text{BF}_3 \cdot \text{OEt}_2$ -promoted cyclization of triepoxide **678**, followed by acetylation, and further elaborated to armatol A (**680**) (Scheme 136).<sup>298b</sup>

**Scheme 136.** Synthesis of Armatol A (**680**)



## 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).<sup>299</sup>

In 1976, Lusinchi and co-workers reported that an oxaziridinium salt (**683**) (Figure 80) could be prepared via methylation of the corresponding oxaziridine with  $\text{FSO}_2\text{Me}$  or

**Scheme 137.** Chiral Iminium Salt-Catalyzed Asymmetric Epoxidation

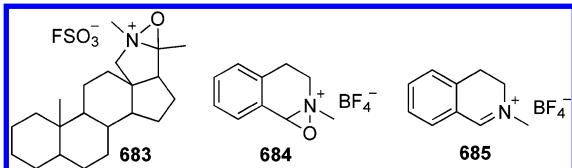
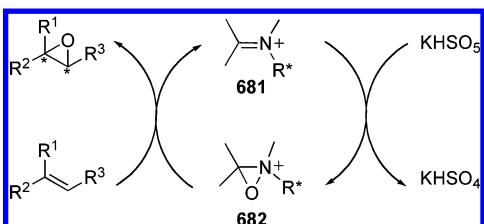


Figure 80. Oxaziridinium and iminium salts.

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

**2.6.1. Dihydroisoquinoline-Based Iminium Salts.** An early example employing an oxaziridinium salt for asymmetric epoxidation of olefins was reported by Bohé and co-workers in 1993.<sup>305</sup> Several unfunctionalized olefins were epoxidized with 1.1 equiv of recrystallized oxaziridinium salt **686** (Figure 81),

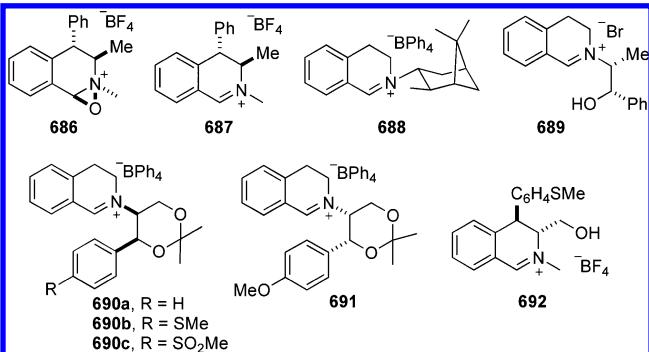


Figure 81. Dihydroisoquinoline-based oxaziridinium and iminium salts.

giving up to 42% ee for *trans*-stilbene.<sup>305b</sup> Stilbene oxide was obtained in 79% yield and 35% ee when the epoxidation was run with 5 mol % iminium salt **687**, oxone (1.3 equiv), and NaHCO<sub>3</sub> (4 equiv) in CH<sub>3</sub>CN–H<sub>2</sub>O (Table 10, entry 1).<sup>305b</sup>

Page and co-workers reported a number of dihydroisoquinoline-based iminium salts, such as **688**–**691**, with chiral moieties attached on the iminium nitrogen (Figure 81).<sup>306,307</sup> 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). *trans*-Stilbene

**Table 10. Epoxidation of Representative Olefins with Iminium Salt Catalysts 687–692<sup>a</sup>**

entry	catalyst	Ph–CH=Ph	Ph–CH=Me	Ph–CH=Ph R	cyclohexene	ref
1 <sup>b</sup>	<b>687</b>	35% ee	22% ee	–	–	305b
2	<b>688</b>	73% ee	–	R = Me, 15% ee	40% ee	306a
3	<b>689</b>	12% ee	–	R = Me, 20% ee	30% ee	307a
4	<b>690a</b>	15% ee	–	R = Ph, 59% ee	41% ee	307a,b
5 <sup>c</sup>	<b>690a</b>	–	9% ee	–	49% ee	307e
6	<b>690b</b>	<5% ee	–	R = Ph, 51% ee	31% ee	307c
7	<b>690c</b>	<5% ee	–	R = Ph, 50% ee	39% ee	307c
8 <sup>d</sup>	<b>690c</b>	67% ee	–	R = Ph, 63% ee	48% ee	307d
9	<b>691</b>	35% ee	–	R = Ph, 71% ee	45% ee	307c
10 <sup>e</sup>	<b>692</b>	45% ee	–	–	–	308

<sup>a</sup>Reactions were carried out with olefin, iminium salt (5–10 mol %), oxone, and inorganic base (NaHCO<sub>3</sub> or Na<sub>2</sub>CO<sub>3</sub>) in CH<sub>3</sub>CN–H<sub>2</sub>O at 0 °C unless otherwise stated. <sup>b</sup>Reactions were carried out at rt.

<sup>c</sup>Reactions were carried out with NaOCl in the presence of 25 mol % K<sub>2</sub>CO<sub>3</sub> in CH<sub>2</sub>Cl<sub>2</sub>. <sup>d</sup>Reactions were carried out with TPPP in CHCl<sub>3</sub> at –40 °C. <sup>e</sup>The reaction was carried out with *m*CPBA in CH<sub>2</sub>Cl<sub>2</sub>.

was epoxidized in 78% yield and 73% ee with 10 mol % iminium salt **688** in the presence of oxone and Na<sub>2</sub>CO<sub>3</sub> in CH<sub>3</sub>CN–H<sub>2</sub>O (Table 10, entry 2).<sup>306a</sup> Rozwadowska and co-workers reported that stilbene oxide could be obtained in 70% yield and 45% ee with 10 mol % (+)-thiomicamine-derived iminium salt **692** and *m*CPBA (Figure 81) (Table 10, entry 10).<sup>308</sup>

Iminium salt **690c** was found to be an effective catalyst for epoxidation of some *cis*-olefins, giving up to 97% ee for 2,2-dimethyl-6-cyanochromene by running the reaction under nonaqueous conditions (in CHCl<sub>3</sub>) at –40 °C with tetraphenylphosphonium monoperoxyxulfate (TPPP) as the oxidant (Figure 82).<sup>309,307d</sup> The resulting epoxide (**693**) was

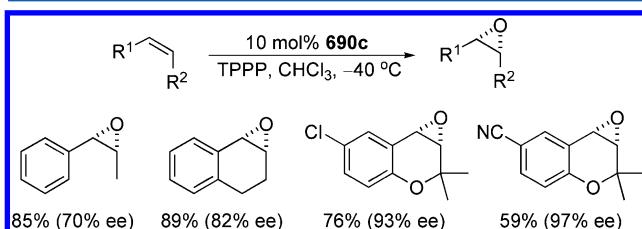
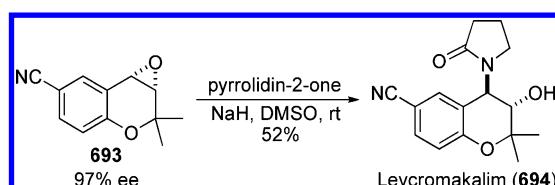


Figure 82. Epoxidation of *cis*-olefins with iminium salt catalyst **690c**.

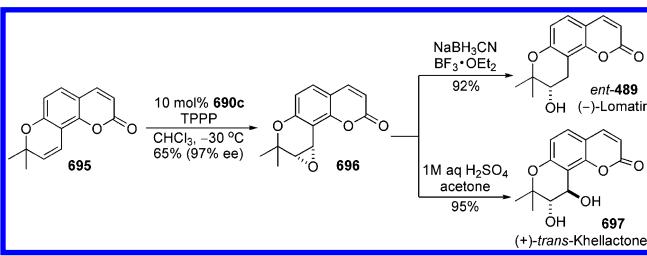
converted to levcromakalim (**694**) (an antihypertensive agent) with pyrrolidin-2-one and NaH in 52% yield (Scheme 138).<sup>309</sup> Total synthesis of (–)-lomatatin (*ent*-**489**) and (+)-(3'S,4'R)-*trans*-khellactone (**697**) was also achieved using iminium salt

**Scheme 138. Synthesis of Levcromakalim (694)**



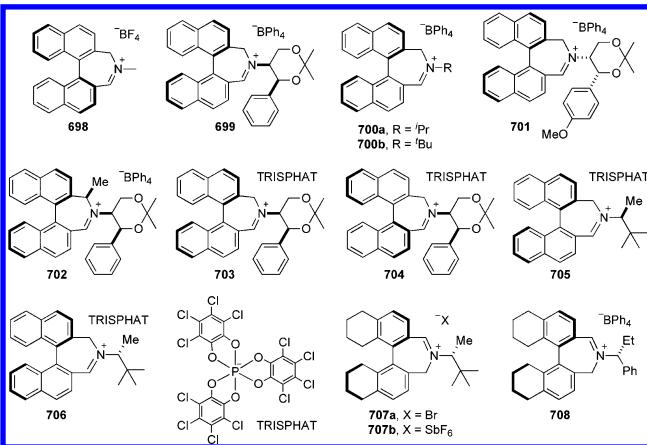
690c-catalyzed epoxidation as the key step (Scheme 139).<sup>310</sup> Epoxide **696** was obtained in 65% yield and 97% ee from

**Scheme 139. Synthesis of (−)-Lomatin and (+)-trans-Khellactone**



seselin **695** with TPPP as oxidant under nonaqueous conditions. Reductive cleavage of the epoxide with  $\text{NaBH}_3\text{CN}$  afforded (−)-lomatin (*ent*-**489**) in 92% yield. (+)-Khellactone (**697**) was obtained in 95% yield by epoxide opening with  $\text{H}_2\text{SO}_4$ . Epoxidation with catalyst **690c** was also applied to the kinetic resolution of racemic 2-substituted chromenes, giving up to 99% ee for the epoxide.<sup>311</sup>

**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-



**Figure 83. Binaphthylazepinium-based iminium salts.**

workers reported the preparation and use of binaphthyl-based iminium salt catalyst **698** for asymmetric epoxidation.<sup>312</sup> For example, 1-phenylcyclohexene was epoxidized with 5 mol % **698** in the presence of oxone and  $\text{NaHCO}_3$  in  $\text{CH}_3\text{CN}-\text{H}_2\text{O}$  to give the epoxide in 80% yield and 71% ee (Table 11, entry 1).

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-phenyl-3,4-dihydronaphthalene (Table 11, entry 2).<sup>313</sup> This catalyst was shown to be very active as demonstrated by the low catalyst loading (0.1 mol %) and the short reaction time for epoxidation of 1-phenylcyclohexene.<sup>313a</sup> Page and co-workers also reported a range of binaphthyl-based iminium salts achiral at the nitrogen atom.<sup>314</sup> Among them, catalysts **700a** and **700b** were found to be most enantioselective, giving 82% and 84% ee for epoxidation of 1-phenylcyclohexene, respectively (Table 11, entries 4 and 5).<sup>314</sup> Recently, Page and co-workers reported that introducing a

**Table 11. Epoxidation of Representative Olefins with Iminium Salt Catalysts 698–708<sup>a</sup>**

entry	catalyst	$\text{Ph}=\text{Ph}$	$\text{Ph}=\text{Ph}$	$\text{Ph}-\text{Ph}$	$\text{Ph}-\text{Ph}$	ref
1	<b>698</b>	31% ee	45% ee	71% ee	-	312
2	<b>699</b>	20% ee	49% ee	91% ee	95% ee	313a,b
3 <sup>b</sup>	<b>699</b>	-	61% ee	89% ee	89% ee	313c
4	<b>700a</b>	22% ee	64% ee	82% ee	83% ee	314
5	<b>700b</b>	-	67% ee	84% ee	-	314
6	<b>701</b>	18% ee	56% ee	-	81% ee	313d
7	<b>702</b>	-	64% ee	94% ee	94% ee	315
8	<b>703</b>	-	47% ee	79% ee	71% ee	316a
9	<b>704</b>	-	52% ee	81% ee	83% ee	316a
10 <sup>c</sup>	<b>705</b>	30% ee	61% ee	84% ee	86% ee	316b
11 <sup>c</sup>	<b>706</b>	30% ee	61% ee	86% ee	87% ee	316b
12 <sup>c,d</sup>	<b>707a</b>	-	67% ee	83% ee	92% ee	317a
13 <sup>c,d</sup>	<b>707b</b>	-	65% ee	92% ee	91% ee	317b
14 <sup>c</sup>	<b>708</b>	-	68% ee	68% ee	94% ee	317a

<sup>a</sup>Reactions were carried out with olefin, iminium salt (5 mol %), oxone, and inorganic base ( $\text{NaHCO}_3$  or  $\text{Na}_2\text{CO}_3$ ) in  $\text{CH}_3\text{CN}-\text{H}_2\text{O}$  at 0 °C unless otherwise stated.

<sup>b</sup>Reactions were carried out with TPPP in  $\text{CH}_3\text{CN}$  at −40 °C. <sup>c</sup>2.5 mol % 18-crown-6 was added, and  $\text{CH}_2\text{Cl}_2-\text{H}_2\text{O}$  (3:2, v/v) was used as solvent. <sup>d</sup>2.5 mol % iminium salt was used.

pseudoaxial substituent at a carbon atom adjacent to the nitrogen in the binaphthylazepinium-based iminium salt could improve enantioselectivity for epoxidation of some olefins.<sup>315</sup> For example, 94% ee was achieved for epoxidation of 1-phenylcyclohexene with iminium salt **702** (Table 11, entry 7).<sup>315</sup>

In 2006, Lacour and co-workers reported a number of binaphthyl-based iminium salts with TRISPHAT as counterions such as **703–706** (Figure 83),<sup>316</sup> and up to 87% ee was obtained for epoxidation of 1-phenyl-3,4-dihydronaphthalene (Table 11, entry 11).<sup>316b</sup> 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  $\text{H}_8$ -binaphthyl-based iminium salts **707** and **708** with a larger dihedral angle around the biaryl twist gave high enantioselectivity for the epoxidation (Table 11, entries 12–14).<sup>317</sup> It was shown that the counteranion was important for the catalyst's reactivity and selectivity, with  $\text{SbF}_6^-$  being optimal.<sup>317</sup> Iminium salt **707b** proved to be very effective in the epoxidation of a variety of trisubstituted olefins, giving up to 98% ee (Figure 84).<sup>317b,c</sup>

**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).<sup>307b,c,e,313c,315,318,319</sup> Various oxidants were examined for the reaction with iminium salt **710** (Table 12, entries 2–7),<sup>307b,e,318,313c</sup> giving up to 70% ee for 1-phenylcyclohexene with TPPP in  $\text{CH}_2\text{Cl}_2-\text{CH}_3\text{CN}$  at −78 °C (Table 12, entry

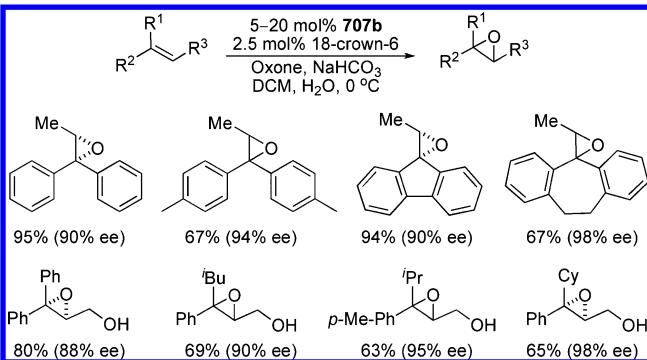


Figure 84. Epoxidation of trisubstituted olefins using iminium salt 707b.

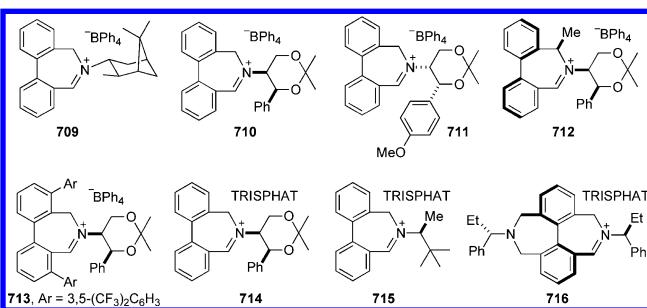


Figure 85. Biphenylazepinium-based iminium salts.

Table 12. Epoxidation of Representative Olefins with Iminium Salt Catalysts 709–716<sup>a</sup>

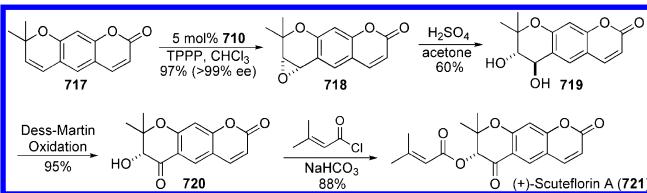
entry	catalyst	Ph $\text{CH=}$ Ph	Ph $\text{CH=}$ R	cyclohexene	1-phenylcyclohexene	ref
1	709	0% ee	R = Ph, 17% ee	29% ee	38% ee	307b
2	710	15% ee	R = Ph, 59% ee	60% ee	41% ee	307b, 318a
3 <sup>b</sup>	710	14% ee	R = Ph, 60% ee	67% ee	22% ee	318a
4 <sup>c</sup>	710	33% ee	R = Me, 50% ee	70% ee	65% ee	313c
5 <sup>d</sup>	710	-	-	64% ee	-	318b
6 <sup>e</sup>	710	-	-	56% ee	-	318c
7 <sup>f</sup>	710	-	-	68% ee	-	307e
8	711	-	R = Me, 50% ee	63% ee	-	307c
9	712	-	R = Ph, 35% ee	82% ee	78% ee	315
10	713	6% ee	R = Me, 26% ee	44% ee	-	319
11 <sup>g</sup>	714	17% ee	R = Me, 42% ee	69% ee	76% ee	321a
12 <sup>g</sup>	715	17% ee	R = Me, 46% ee	66% ee	80% ee	321b, 316b
13 <sup>g</sup>	716	-	R = Me, 55% ee	71% ee	85% ee	322

<sup>a</sup>Reactions were carried out with olefin, iminium salt (5 mol %), oxone, and inorganic base (NaHCO<sub>3</sub> or Na<sub>2</sub>CO<sub>3</sub>) in CH<sub>3</sub>CN–H<sub>2</sub>O at 0 °C unless otherwise stated. <sup>b</sup>Reactions were carried out with catalyst (10 mol %) and TPPP in CH<sub>3</sub>CN at –40 °C. <sup>c</sup>Reactions were carried out with catalyst (10 mol %) and TPPP in CH<sub>2</sub>Cl<sub>2</sub>–CH<sub>3</sub>CN at –40 or –78 °C. <sup>d</sup>20 mol % of catalyst and electrochemically generated persulfate was used as the oxidant. <sup>e</sup>10 mol % of catalyst and H<sub>2</sub>O<sub>2</sub> was used as the oxidant. <sup>f</sup>10 mol % of catalyst and NaOCl was used as the oxidant. <sup>g</sup>2.5 mol % 18-crown-6 was added, and CH<sub>2</sub>Cl<sub>2</sub>–H<sub>2</sub>O (3:2, v/v) was used as solvent.

<sup>4</sup>).<sup>313c</sup> Biphenyl-based iminium salt 712 with a pseudoaxial methyl group gave 82% ee for epoxidation of 1-phenyl-

cyclohexene (Table 12, entry 9).<sup>315</sup> 2,2-Dimethyl-6-cyanochromene was epoxidized in 100% conversion and 98% ee with 712 (10 mol %) and TPPP (2 equiv) in CHCl<sub>3</sub> at 0 °C.<sup>315</sup> Epoxidation with iminium salt 710 was applied to the total synthesis of (+)-scutellorin A (721) (Scheme 140).<sup>320</sup>

Scheme 140. Synthesis of (+)-Scutellorin 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 (Figure 85).<sup>321,316b,322</sup> Up to 85% ee was obtained for 1-phenyl-3,4-dihydronaphthalene with doubly bridged biphenylazepinium salt catalyst 716 (Table 12, entry 13).<sup>322</sup>

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

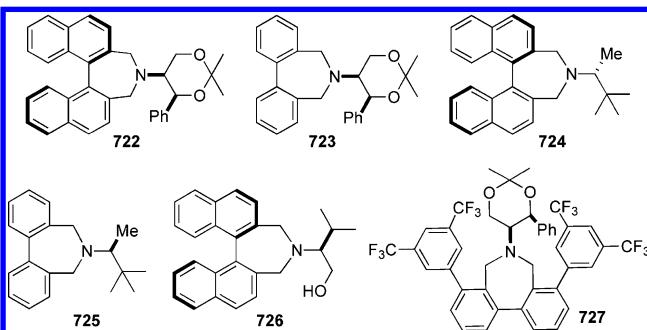


Figure 86. Binaphthyl and biphenyl azepines 722–727.

Table 13. Epoxidation of Representative Olefins with Biaryl Azepine Catalysts 722–727<sup>a</sup>

entry	catalyst	Ph $\text{CH=}$ Ph	Ph $\text{CH=}$ R	cyclohexene	1-phenylcyclohexene	ref
1	722	-	R = Me, 48% ee	78% ee	80% ee	316a
2	723	-	R = Me, 36% ee	53% ee	51% ee	316a
3 <sup>b</sup>	724	14% ee	R = Me, 59% ee	86% ee	86% ee	316b
4 <sup>b</sup>	725	22% ee	R = Me, 22% ee	39% ee	70% ee	316b
5	726	17% ee	R = Me, 45% ee	81% ee	80% ee	323
6	727	7% ee	R = Ph, 13% ee	47% ee	-	319

<sup>a</sup>Reactions were carried out with olefin, catalyst (5–10 mol %), oxone, and NaHCO<sub>3</sub> in CH<sub>3</sub>CN–H<sub>2</sub>O at 0 °C unless otherwise stated. <sup>b</sup>2.5 mol % 18-crown-6 was added, and CH<sub>2</sub>Cl<sub>2</sub>–H<sub>2</sub>O (3:2, v/v) was used as solvent.

used as catalysts for epoxidation of olefins (Table 13, entries 1–4).<sup>316</sup> Up to 86% ee was obtained for 1-phenylcyclohexene using catalyst **724** and oxone (Table 13, entry 3).<sup>316b</sup> 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).<sup>323</sup> It was postulated that the amine was oxidized *in situ* to the corresponding iminium salt, which catalyzed the epoxidation.<sup>323</sup>

**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).<sup>324</sup> Epoxidation with ketiminium salt

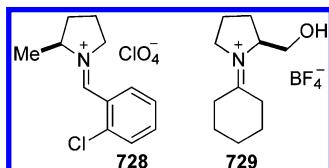


Figure 87. Exocyclic iminium salts.

Table 14. Epoxidation of Olefins Using Isolated or in-Situ-Generated Exocyclic Iminium Salts

entry	catalyst	Ph=Ph	Ph=R	Ph=Ph Me	cyclohexene	ref
1	<b>728</b>	15% ee	-	-	22% ee	324
2	<b>729</b>	-	R = CH <sub>2</sub> OH, 39% ee	-	-	325
3	<b>730 + 732</b>	46% ee	R = Me, 25% ee	59% ee	46% ee	326
4	<b>731 + 732</b>	65% ee	-	-	-	326

catalyst **729** was described by Komatsu and co-workers in 2000.<sup>325</sup> 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).<sup>326</sup> Up to 65% ee was obtained for *trans*-stilbene with amine **731** and aldehyde **732** (Table 14, entry 4).

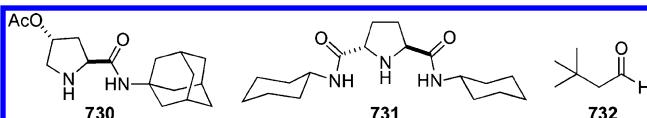


Figure 88. Iminium salt precursors.

## 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.<sup>327</sup> 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).<sup>327</sup> 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).<sup>328</sup> Up to 66% ee

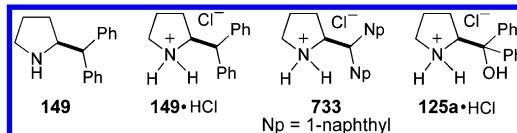


Figure 89. Pyrrolidine-based amine and amine HCl salt catalysts.

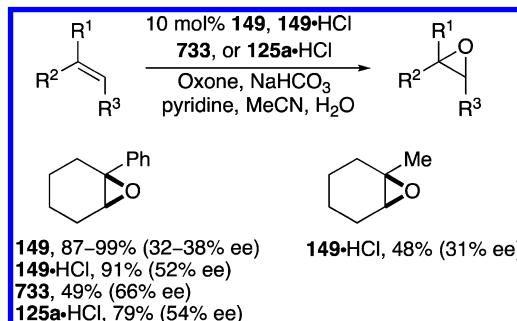


Figure 90. Epoxidation of olefins with amine or amine salt catalyst.

was obtained for epoxidation of 1-phenylcyclohexene with 10 mol % **733** (Figure 90).<sup>328</sup> 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).<sup>328,329</sup>

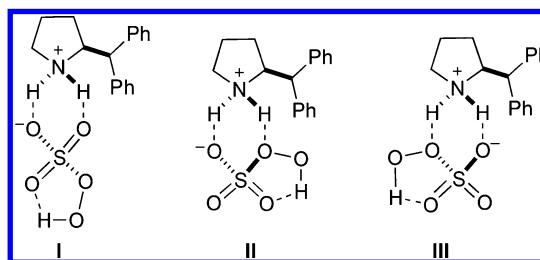


Figure 91. Possible forms of pyrrolidinium peroxyomonosulfate.

In 2005, Yang and co-workers investigated a number of pyrrolidine-based chiral amine catalysts such as **150** and **734** for epoxidation of unfunctionalized olefins (Figure 92).<sup>330</sup> With

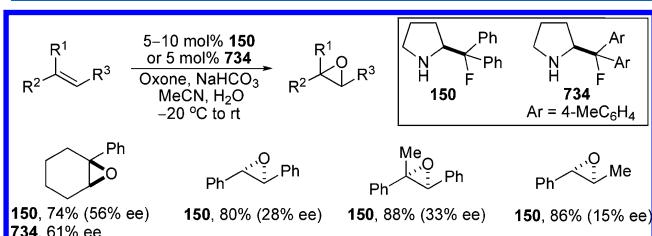


Figure 92. Epoxidation of olefins with catalysts **150** and **734**.

fluorinated catalyst **150** or **734**, up to 61% ee was achieved for epoxidation of 1-phenylcyclohexene using oxone buffered with NaHCO<sub>3</sub>. It was believed that the electronegative fluorine atom may stabilize ammonium salts through hydrogen bonding and charge–dipole interactions (Figure 93), which was beneficial for the catalytic efficiency.<sup>330</sup> Shi and co-workers showed that *cis*-1-propenylphosphoric acid potassium salt (**735**) could be epoxidized in 100% conversion and 74% ee using amine catalyst **737** and H<sub>2</sub>O<sub>2</sub>–CH<sub>3</sub>CN (Scheme 141).<sup>331,332</sup>

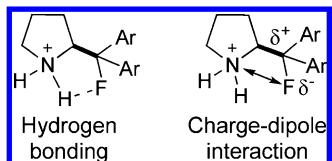
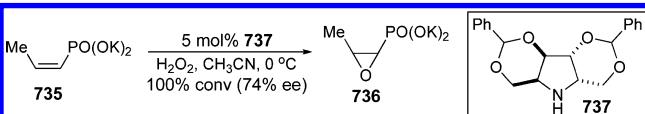


Figure 93. Stabilization of the ammonium salts.

**Scheme 141. Epoxidation of *cis*-1-Propenylphosphoric Acid Salt with Amine 737****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

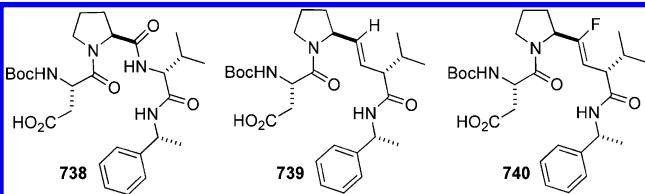


Figure 94. Aspartic acid-based peptide catalysts 738–740.

epoxidized with peptide 738 as catalyst and  $\text{H}_2\text{O}_2$  or urea– $\text{H}_2\text{O}_2$  (UHP) as oxidant, giving the corresponding epoxides in 73–99% yield and up to 92% ee (Figure 95).<sup>333,334</sup> Epoxidation

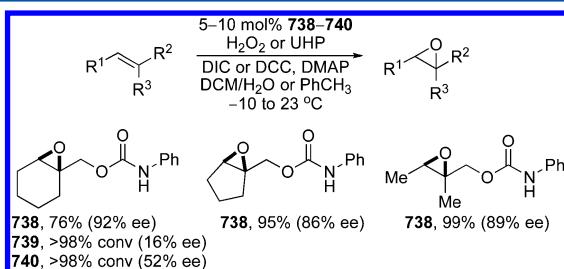


Figure 95. Epoxidation of olefins with aspartic acid-based catalysts 738–740.

likely proceeds via a chiral carboxylic acid/peracid cycle. The carboxyl group of the catalyst is first activated by diisopropylcarbodiimide (DIC) to form intermediate 742, which reacts with  $\text{H}_2\text{O}_2$  to form the transient peracid 743. Upon epoxidation of the olefin, the carboxylic acid is regenerated (Scheme 142).<sup>333</sup> 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).<sup>333b</sup> Miller and co-workers subsequently showed that aspartic acid-based peptides 744 and 745 were effective catalysts for the site-selective epoxidation of polyenes.<sup>335</sup> 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

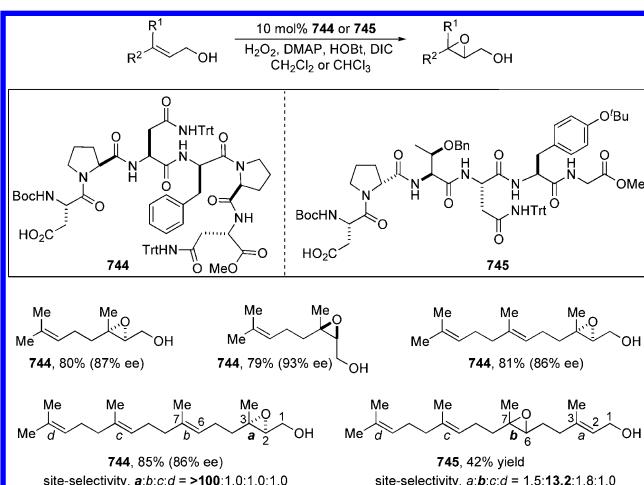
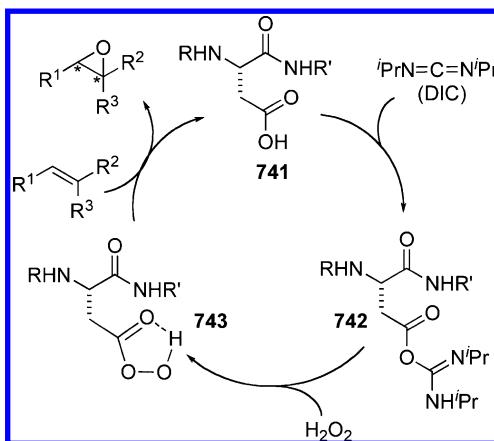
**Scheme 142. Proposed Mechanism for Epoxidation with Aspartic Acid-Based Catalysts**

Figure 96. Epoxidation of polyenes with aspartic acid-based catalysts 744 and 745.

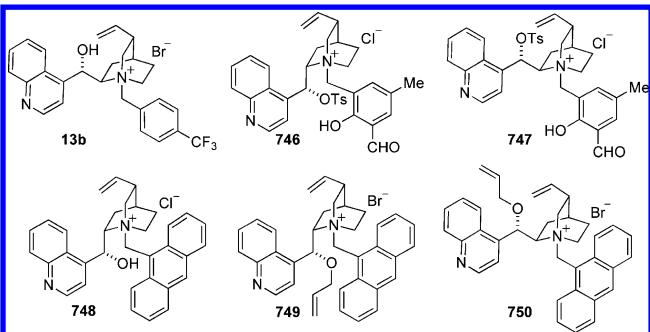
geranylgeraniol, the 6,7-olefin was site-selectively epoxidized with catalyst 745, affording the corresponding epoxide in 42% yield.

**3. ORGANOCATALYZED ASYMMETRIC AZIRIDINATION OF OLEFINS**

Asymmetric aziridination of olefins provides a useful strategy for preparation of optically active aziridines,<sup>336</sup> 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,<sup>336f</sup> which will be discussed in this section.

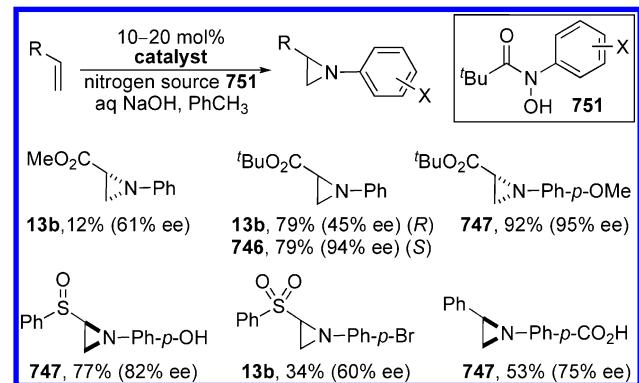
**3.1. Chiral Quaternary Ammonium Salt-Catalyzed Aziridination**

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).<sup>337</sup> In 2005, Murugan and co-workers showed that up to 95% ee could be achieved for aziridination of



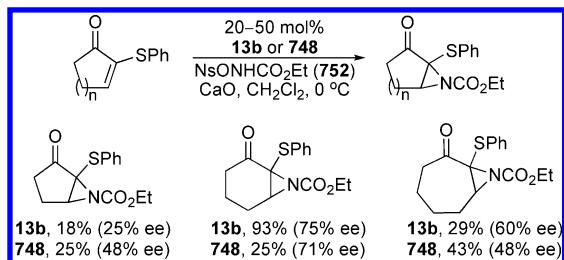
**Figure 97.** Quaternary ammonium salt catalysts **13b** and **746–750**.

*tert*-butyl acrylate with ammonium salt catalysts **746** and **747** (Figures 97 and 98).<sup>338</sup>



**Figure 98.** Aziridination of olefins with quaternary ammonium salt catalysts.

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 *NsONHCO<sub>2</sub>Et* (**752**) as the nitrogen source (Figure 99).<sup>339</sup> Minakata and co-workers

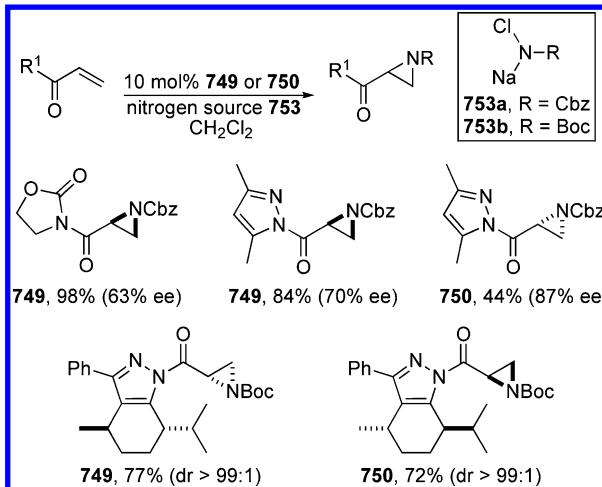


**Figure 99.** Aziridination of cyclic enones with catalyst **13b** or **748**.

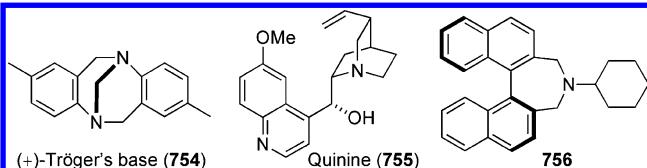
employed *N*-chloro-*N*-sodiocarbamates **753** as nitrogen sources for asymmetric aziridination of  $\alpha,\beta$ -unsaturated amides, giving up to 87% ee with ammonium salt catalysts **749** and **750** (Figures 97 and 100).<sup>340</sup> High diastereoselectivities (up to >99:1 dr) were achieved for substrates bearing chiral auxiliaries (Figure 100).<sup>341</sup>

### 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*·H<sub>2</sub>O.<sup>342</sup> NH aziridines were obtained in up to 67% ee with (+)-Tröger's base (**754**) (Figures 101 and

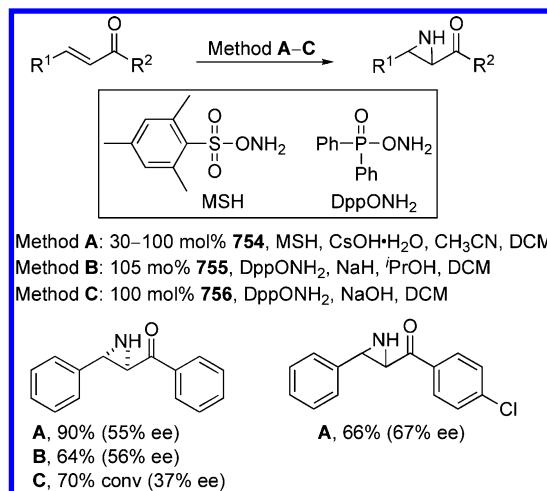


**Figure 100.** Aziridination of olefins with catalyst **749** or **750**.



**Figure 101.** Chiral amines **754–756**.

102). The amine promoter could be used in a catalytic amount. In their studies, Armstrong and co-workers showed that up to

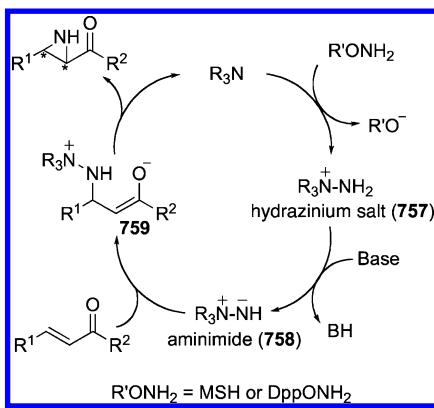


**Figure 102.** Asymmetric aziridination of chalcones using chiral amines **754–756**.

56% ee could be obtained for aziridination using quinine (**755**) and *O*-(diphenylphosphinyl)hydroxylamine (DppONH<sub>2</sub>) (Figures 101 and 102).<sup>343</sup> Page and co-workers investigated the asymmetric aziridination of chalcone with binaphthalene-based chiral amines and MSH or DppONH<sub>2</sub> as *N*-transfer agent, achieving 37% ee with amine **756** (Figures 101 and 102).<sup>344</sup>

A possible catalytic cycle for the amine-promoted aziridination is shown in Scheme 143. The tertiary amine R<sub>3</sub>N first reacts with O-substituted hydroxylamine R'ONH<sub>2</sub> 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

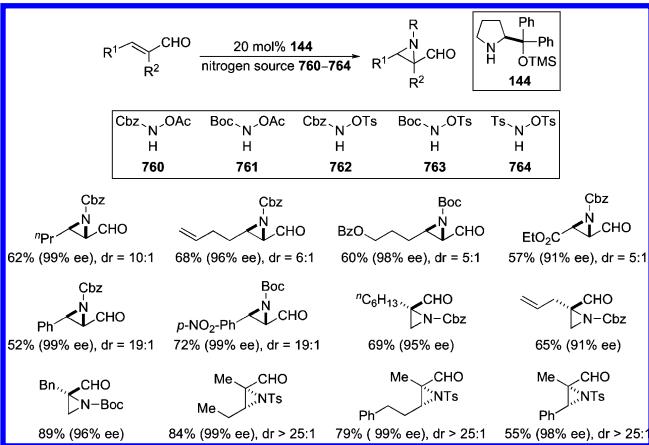
**Scheme 143. Proposed Mechanism for the Amine-Promoted Aziridination of Olefins**



olefin followed by ring closure to give the aziridine and regenerate the tertiary amine.<sup>342,343</sup>

### 3.3. Aziridination via Iminium/Enamine Catalysis

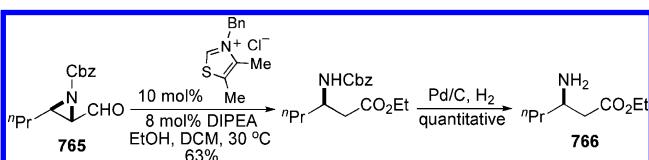
**3.3.1. Pyrrolidine-Based Catalysts.** Asymmetric aziridination of  $\alpha,\beta$ -unsaturated aldehydes has been achieved with chiral secondary amine catalysts. In 2007, Córdova and co-workers reported that a variety of  $\alpha,\beta$ -unsaturated aldehydes were effectively aziridinated with diphenylprolinol 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).<sup>345</sup> The resulting aziridine



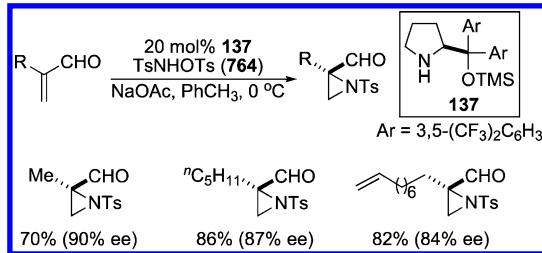
**Figure 103.** Aziridination of  $\alpha,\beta$ -unsaturated aldehydes with chiral amine 144.

(765) was converted into  $\beta$ -amino acid ester 766 by ring opening and concomitant esterification, followed by removal of the Cbz group (Scheme 144).<sup>345a</sup> In their studies, Greck, de Figueiredo, and co-workers showed that  $\alpha$ -branched enals were

**Scheme 144. Synthesis of  $\beta$ -Amino Acid Ester 766 from Aziridine 765**



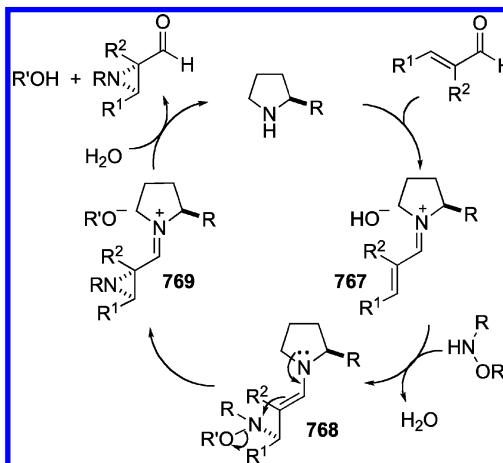
aziridinated in 69–86% yield and up to 90% ee with amine catalyst 137 and TsNHOTs (764) (Figure 104).<sup>346</sup>



**Figure 104.** Aziridination of  $\alpha$ -branched enals catalyzed by 137.

The proposed mechanism for the asymmetric aziridination is shown in Scheme 145. The amine catalyst first reacts with the

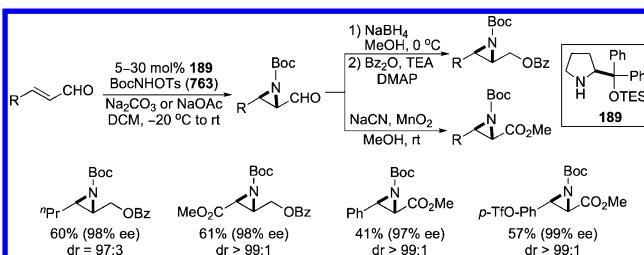
**Scheme 145. Proposed Mechanism for the Chiral Amine-Catalyzed Aziridination of Enals**



enal to form iminium salt intermediate 767, which is then attacked by the acylated hydroxycarbamate throughaza-conjugate 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.<sup>345</sup>

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).<sup>347</sup>

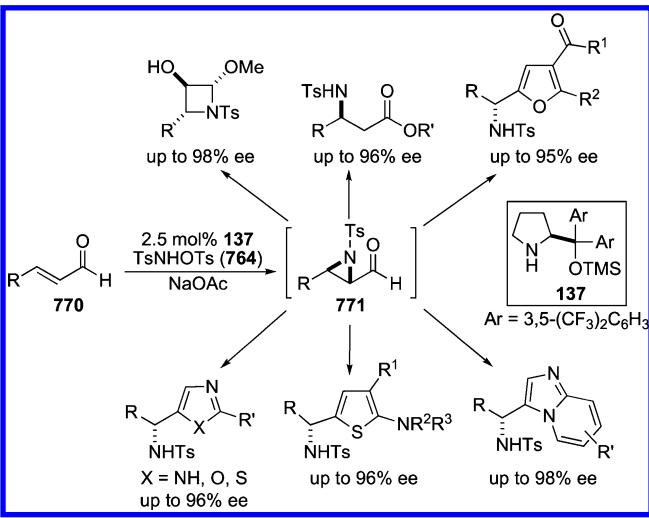
Jørgensen and co-workers showed that various optically active building blocks could be readily prepared via a one-pot process using chiral amine 137-catalyzed asymmetric aziridina-



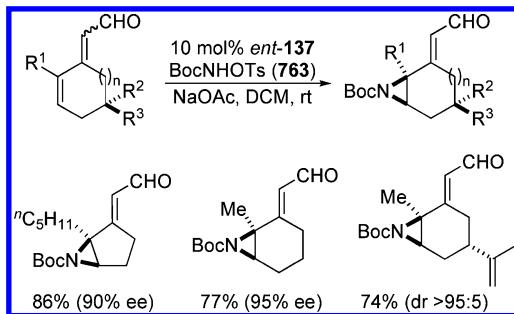
**Figure 105.** Aziridination of  $\alpha,\beta$ -unsaturated aldehydes with chiral amine 189.

tion of enals 770 as the key step (Scheme 146).<sup>117c–g,i</sup> They also studied the remote aziridination of cyclic 2,4-dienals with

**Scheme 146.** One-Pot Synthesis of Various Building Blocks via Asymmetric Aziridination



catalyst *ent*-137 and nitrogen source BocNHOtS (763) (Figure 106).<sup>348</sup> Aziridination occurred regioselectively at the endocyclic

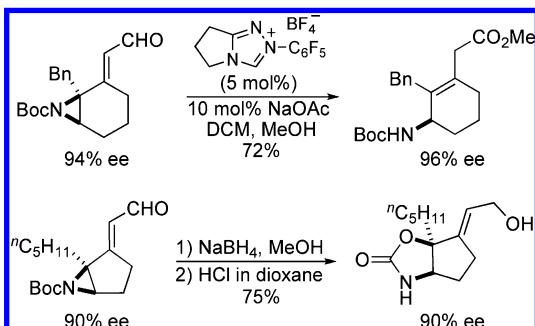


**Figure 106.** Aziridination of 2,4-dienals catalyzed by *ent*-137.

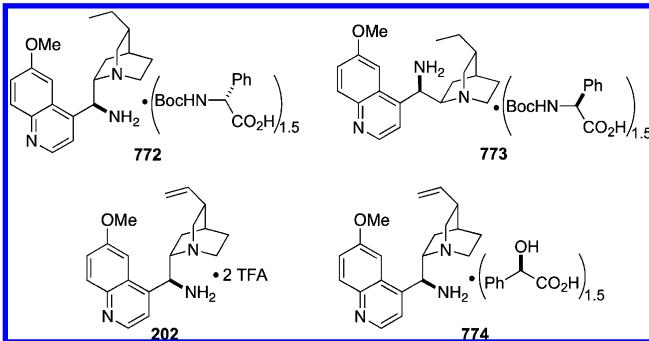
clic double bond, giving the aziridines in up to 95% ee. The aziridine products could be transformed into allylic  $\delta$ -amino esters and oxazolidinones (Scheme 147).

**3.3.2. Chiral Amine Salt Catalysts.** The asymmetric aziridination has been extended to  $\alpha,\beta$ -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

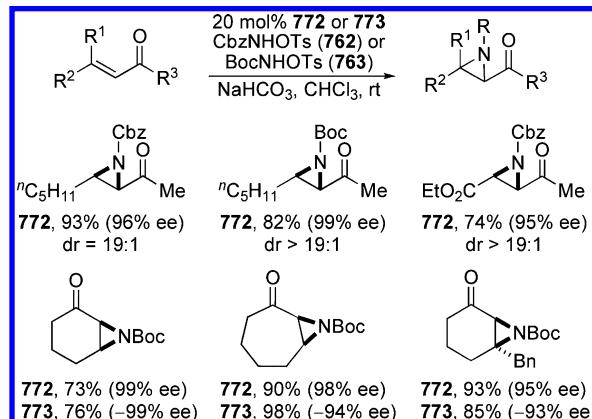
**Scheme 147.** Further Transformations of Aziridines



and 773 as catalysts, giving the corresponding aziridines in up to 99% ee (Figures 107 and 108).<sup>349</sup>

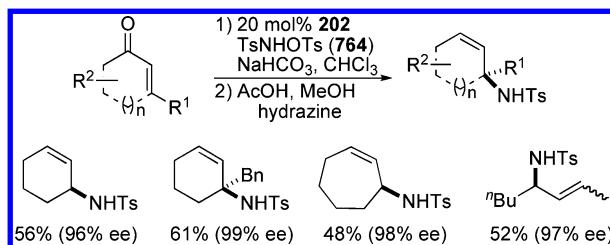


**Figure 107.** Chiral amine salt catalysts.



**Figure 108.** Aziridination of enones using chiral amine salt 772 or 773.

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).<sup>134</sup> They also showed that oxazolidi-



**Figure 109.** One-pot aziridination/Wharton reaction sequence.

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  $S_N2$  reaction using NaI in the same pot (Figures 107 and 110).<sup>350</sup>

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).<sup>351</sup> The resulting chiral aziridine (776) was elaborated to the key intermediate (780) toward (–)-agelastatin A (781) (Scheme 148).<sup>351</sup>

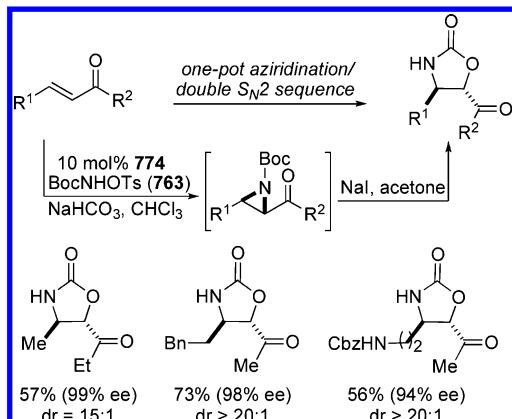
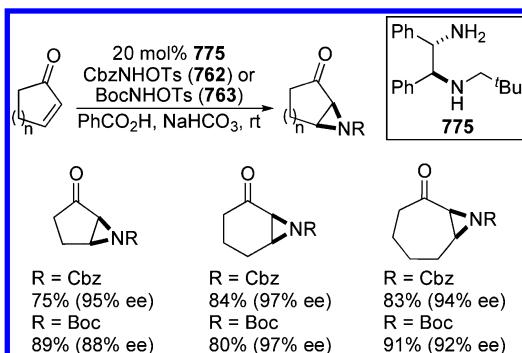
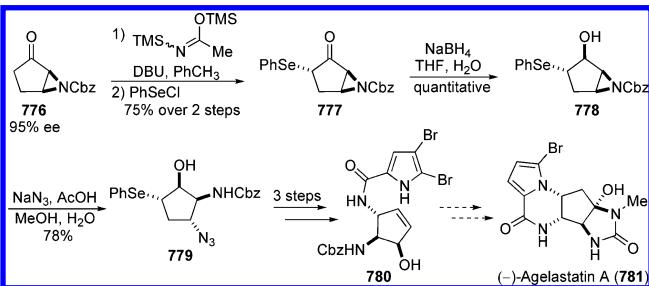
Figure 110. One-pot aziridination/double S<sub>N</sub>2 reaction sequence.

Figure 111. Aziridination of cyclic enones with diamine catalyst 775.

**Scheme 148. Synthesis of the Key Intermediate (780) toward (−)-Agelastatin A (781)**



### 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  $\alpha$ -acyl acrylates were aziridinated in up to 82% ee with catalyst 782 and BocNHOTs (763) (Figure 112).<sup>352</sup> 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  $\alpha,\alpha$ -disubstituted- $\alpha$ -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

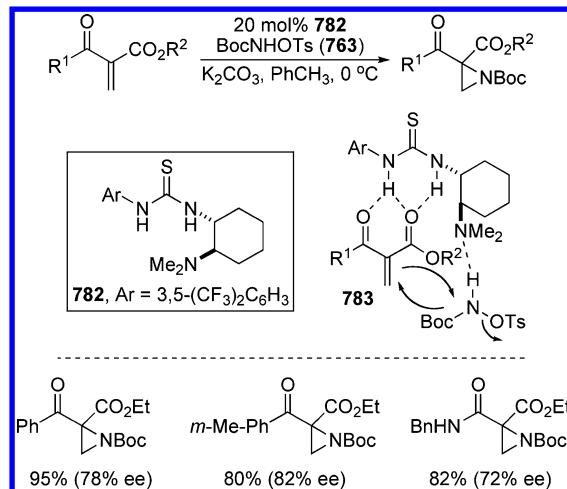
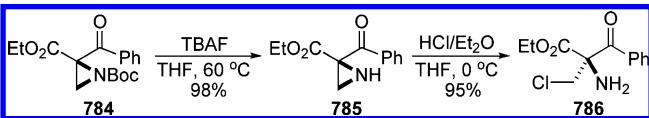


Figure 112. Aziridination of olefins with chiral amino thiourea catalyst 782.

**Scheme 149. Synthesis of  $\alpha,\alpha$ -Disubstituted- $\alpha$ -amino Acid Ester 786**



catalysts such as chiral guanidines and chiral  $\beta$ -amino alcohols have proven very effective for electron-deficient  $\alpha,\beta$ -unsaturated carbonyl substrates (mostly  $\alpha,\beta$ -unsaturated ketones), obtaining high selectivities. Chiral amine-catalyzed epoxidation via iminium ion/enamine pathway has expanded the nucleophilic epoxidation to  $\alpha,\beta$ -unsaturated aldehydes in addition to  $\alpha,\beta$ -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<sub>2</sub>-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 sterics and/or electronics. Epoxidation with ketone 268 displayed unprecedented generality and practicality for non-metal 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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### Notes

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development of new synthetic methods, asymmetric catalysis, and synthesis of natural products.

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