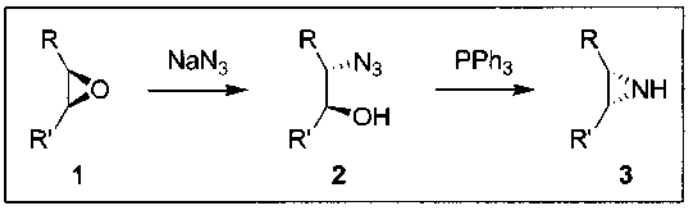
1.1 Blum Aziridine Synthesis

Jeremy M. Richter

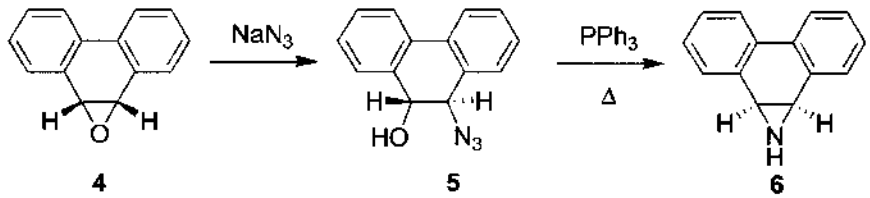
1.1.1 Description



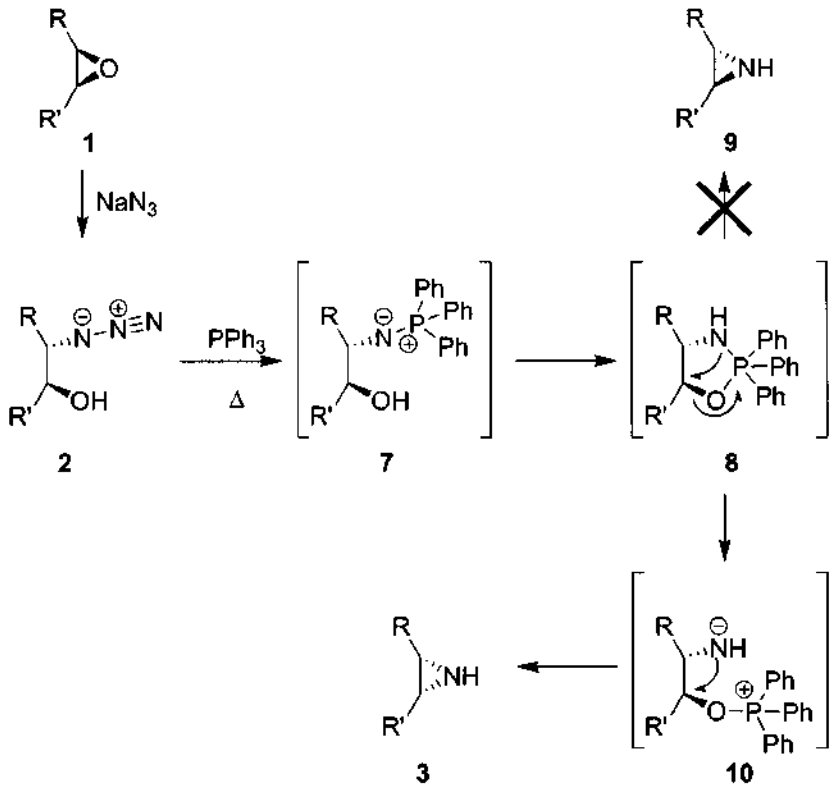
The Blum aziridine isomerization describes the net coversion of epoxides **1** into N–H aziridines **3** *via* an intermediate azido–alcohol **2**. The reaction proceeds by opening of the epoxide with an azide source followed by the Staudinger reduction and cyclization of the intermediate azido–alcohol to give the aziridine.[1] The reaction proceeds with net inversion of stereochemistry around the epoxide.

1.1.2 Historical Perspective

While investigating chemical carcinogens, Jonathan Blum and co-workers[1] hypothesized that arene imines were chemical intermediates in carcinogenesis and therefore sought to prepare several phenanthrene imines to test this hypothesis. However, they found that unsubstituted arene imines could not be prepared by the current methods and required alternate means by which to access these structures. Starting from the stable arene oxides (**4**), Blum and co-workers discovered that these epoxides could be opened by the action of sodium azide, forming the intermediate azido–alcohol **5**. They then found that further heating with triphenylphosphine provided the desired N–H aziridine **6** in good yield.



1.1.3 Mechanism

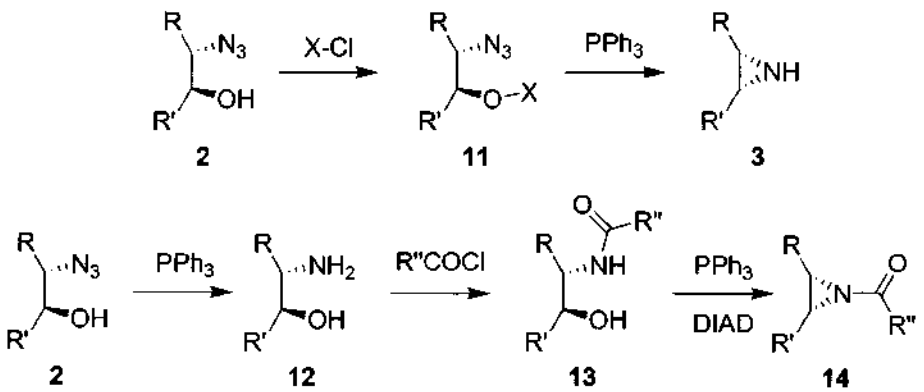


In Blum's original publication on the reaction that bears his name, he postulated a mechanistic interpretation of this process.[1] While investigating sterically flexible systems, he astutely noticed that the *cis/trans* nature of the double bond is conserved during the course of the reaction. That is, the reaction proceeds with complete inversion of stereochemistry but no *cis/trans* isomerisation is observed. In spite of this observation, two mechanistic interpretations could be put forth to explain the overall transformation. Little controversy exists surrounding the initial reaction intermediates and the preparation of the isolable azido–alcohol **2**. Good evidence also exists for the azide reduction proceeding through a standard Staudinger sequence, as the amino-alcohol can be easily isolated if no heat is applied to the system.[2] From this point, the mechanism can be explained by two competing pathways, diverging from the cyclic intermediate **8**. It would certainly seem reasonable to propose that the cyclization occurs in a concerted fashion (*cf.* Wittig Reaction), leading to direct expulsion of triphenylphosphine oxide from intermediate **8** (as shown by the arrows below). However, this reaction would proceed with retention of stereochemistry at the oxygen-containing

carbon, leading to *cis/trans* isomerization. Experimental observations are in contrast to this mechanistic explanation (*vide supra*). Alternatively, the cyclic intermediate **8** could decompose to the linear intermediate **10**. The nitrogen would then be free to participate in an S_N2 displacement of triphenylphosphine oxide, preserving the *cis* configuration of the starting material, albeit with net inversion of stereochemistry. This mechanistic interpretation has been generally accepted and is widely used in the literature.[3]

1.1.4 Variations and Improvements

Few variations or improvements have been reported for the Blum aziridine synthesis. The major modification to the procedure concerns the method of ring closure to form the aziridine from the azido–alcohol. Several groups have reported variations in which the azido–alcohol **2** is activated for displacement (X = Ms, Ts, *etc.*) before reduction of the azide. This alternate sequence then allows for a milder and potentially higher efficiency cyclization to occur.[4,5] Alternatively, the Staudinger can be performed first to generate amino-alcohol **12**, followed by acylation of the nitrogen to give intermediate **13**. The alcohol can then be activated for displacement (*e.g.*, PPh_3/DIAD) to form aziridine **14**.[6,7] This method is especially useful if acylated aziridines are desired, although it does not satisfy the strict definition of a Blum aziridine synthesis.

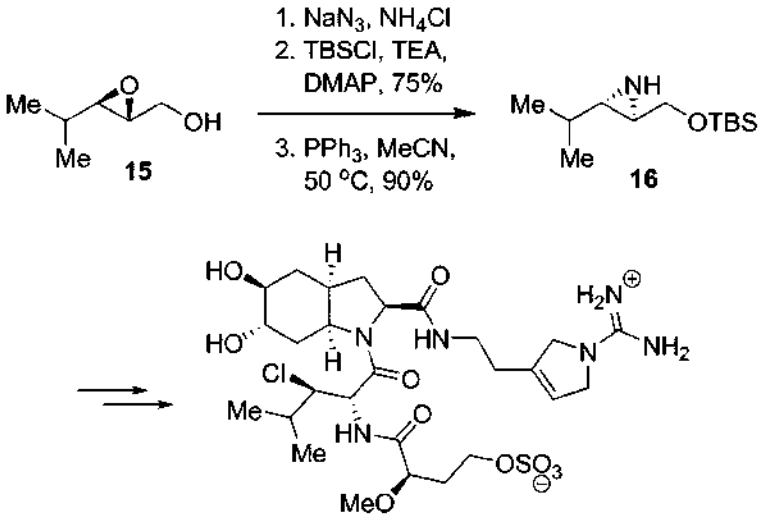


1.1.5 Synthetic Utility

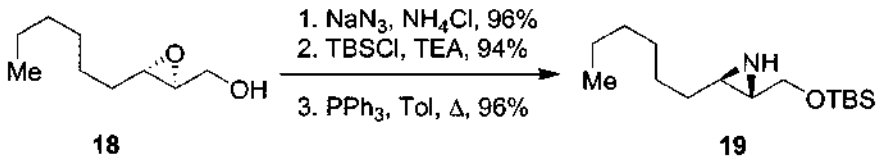
Total Synthesis

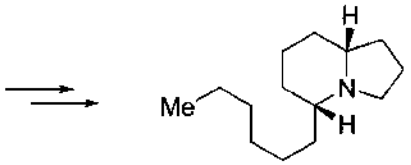
The Blum aziridine synthesis has found widespread utility in the synthetic community. The field of total synthesis has especially benefited from the

power of this transformation. In one example of how this reaction can be applied in complex natural product synthesis, Hanessian and co-workers applied a Blum reaction in the total synthesis of chlorodysinosin A (**17**).[8] In this sequence, epoxide **15** was opened with sodium azide and the primary alcohol protected as the silyl ether. The azide was then treated with triphenylphosphine and heat, resulting in concomitant reduction and aziridine formation to give intermediate **16**. Aziridine **16** was eventually processed to chlorodysinosin A (**17**).



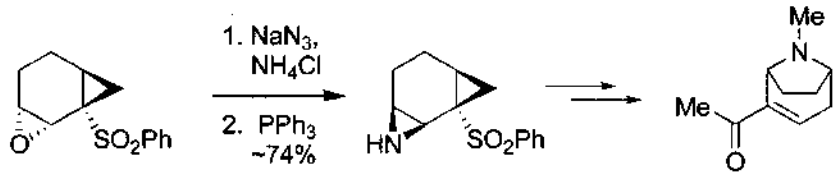
Somfai and Åhman have applied the Blum aziridine synthesis to the total synthesis of indolizidine 209D (**20**).[9,10] Epoxide **18** was opened with sodium azide and the primary alcohol protected as the silyl ether. The azide was then treated with triphenylphosphine and heat, resulting in concomitant reduction and cyclization to give intermediate **19**. Aziridine **19** was eventually processed to indolizidine 209D (**20**).





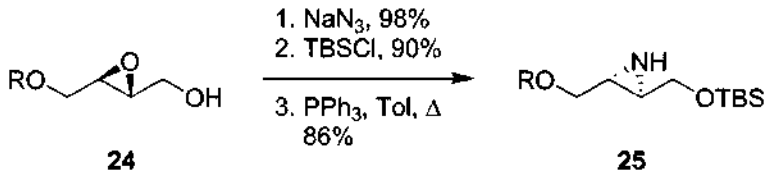
indolizidine 209D (**20**)

Bäckvall and co-workers used the Blum reaction in the total synthesis of ferruginine (**23**).[11] Epoxide **21** was opened with sodium azide and the resultant azido–alcohol was reduced and cyclized with triphenylphosphine in good yield to give aziridine **22**. Intermediate **22** was eventually processed to ferruginine (**23**).

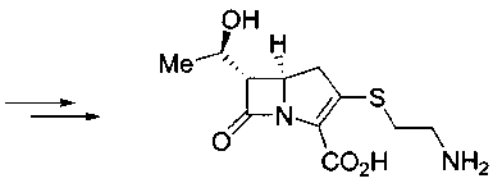


21 **22** ferruginine (**23**)

Finally, Tanner and Somfai completed a formal total synthesis of thienamycin (**26**) using the Blum aziridine synthesis as a key step.[12] As in the previous examples, epoxide **24** was converted to aziridine **25** in good yield using a Blum aziridine synthesis. Intermediate **25** was eventually processed to thienamycin (**26**).



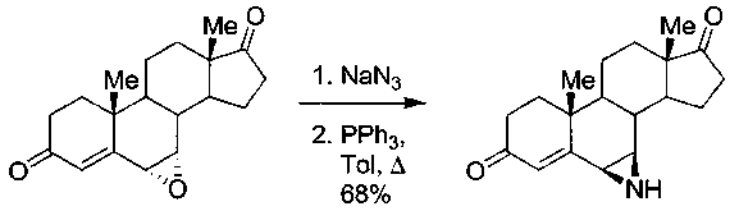
24 **25**



thienamycin (**26**)

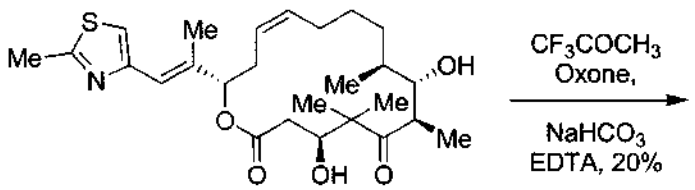
Medicinal and Process Chemistry

Robinson and co-workers reported the preparation of aromatase inhibitors that used the Blum aziridine synthesis as a key step.[13] Epoxy–steroid **27** was opened with sodium azide to form the azido-alcohol, which was then reductively cyclized with triphenylphosphine and heat to provide the desired aziridine **28**. Analog **28** exhibited modest inhibitory activity toward human placental aromatase.

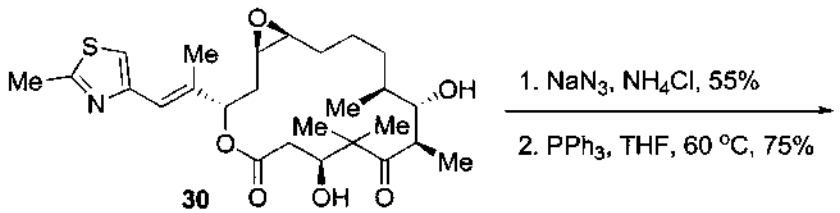


27 **28**

Researchers at Bristol-Myers Squibb reported the preparation of an epothilone analog using the Blum aziridine synthesis as a key step.[14] Epothilone C (**29**) was epoxidized to provide intermediate **30**. Opening of the epoxide with sodium azide followed by reductive cyclization forged the desired N–H aziridine analogue **31** in good yield, especially in light of the complex setting for this transformation.



epothilone C (**29**)



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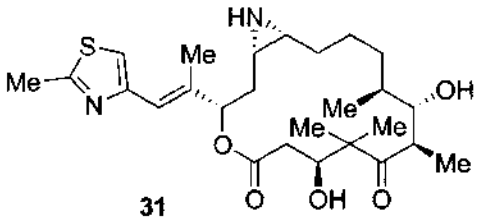
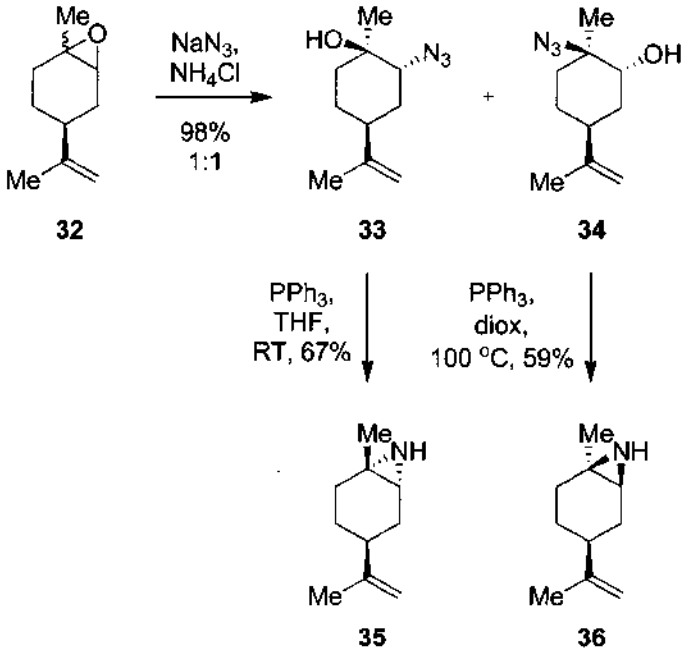


31

Researchers at Lexicon Pharmaceuticals found that limonene aziridines could be efficiently prepared from the corresponding limonene oxides using the Blum aziridine synthesis.[15] Epoxide **32** was opened with sodium azide to produce the regioisomeric azido–alcohols **33** and **34** in an approximate 1 : 1 ratio. The secondary azide was reductively cyclized with triphenylphosphine at ambient temperature, whereas the tertiary azide required heating to effect the same transformation. In this way, the desired aziridines **35** and **36** were prepared in good yield on multigram scale.



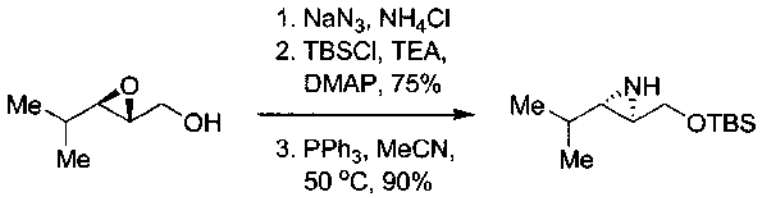
32 **33** **34**

35 **36**

The Blum aziridine synthesis has seen many other uses since its development.[16,17] A common application of the Blum aziridine synthesis is in the preparation of authentic standards while developing novel reactions or synthetic routes.[18–20] The reaction has also found broad utility in the preparation of starting materials or intermediates in novel reaction development.[21–31]

1.1.6 Experimental

Blum aziridine synthesis to prepare a chlorodysinosin A intermediate 16[8]



15 **16**

To a solution of **15** in $CH_3OCH_2CH_2OH$ (0.7 M) was added NaN_3 (10 equiv), NH_4Cl (2 equiv), and water (4 equiv). The mixture was heated to reflux for 24 h, cooled to room temperature, and the solvent removed under vacuum. The residue was then taken up in water, extracted with EtOAc, dried over Na_2SO_4, and concentrated. After drying under reduced pressure for 18 h, the resulting amber oil was taken up in CH_2Cl_2, cooled to 0 °C, and treated sequentially with Et_3N (1.5 equiv), DMAP (cat.), and TBSCl (1.1 equiv). The solution was stirred at 0 °C for 2 h, diluted with CH_2Cl_2, washed with 1 M HCl, dried over Na_2SO_4, and concentrated under vacuum. The crude residue was purified by flash chromatography over silica gel (8% EtOAc/hexanes) to give the azido–alcohol as a 1:1 mixture of regioisomers (75%).

The mixture of azido–alcohols was dissolved in MeCN (0.5 M) and treated with PPh_3 (1.1 equiv). The solution was stirred at RT for 2 h, then heated to 50 °C for 18 h. After removal of MeCN under vacuum, the mixture was taken up in Et_2O, filtered through a pad of Celite, and the filtrate concentrated under vacuum. The crude residue was purified by flash chromatography over silica gel (25% EtOAc/hexanes) to give **16** as a colorless liquid (90% yield).

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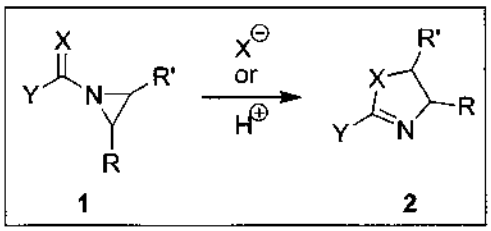
1.2 Gabriel–Heine Aziridine Isomerization

Jeremy M. Richter

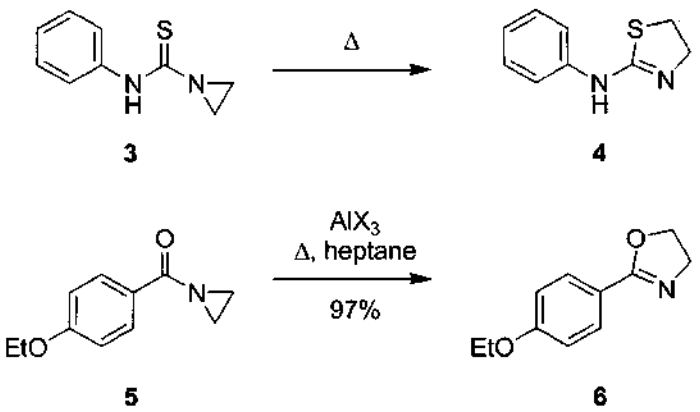
1.2.1 Description



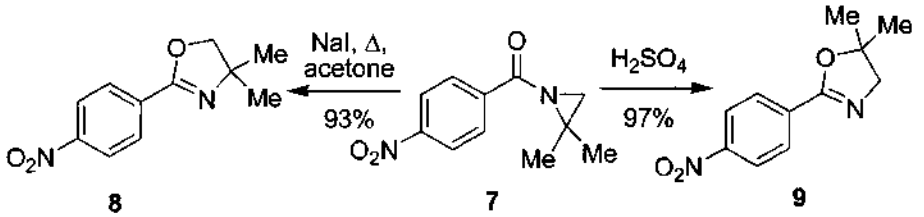
The Gabriel–Heine aziridine isomerization describes the rearrangement of an acylaziridine **1** into an oxazoline **2**.[1–5]

1.2.2 Historical Perspective

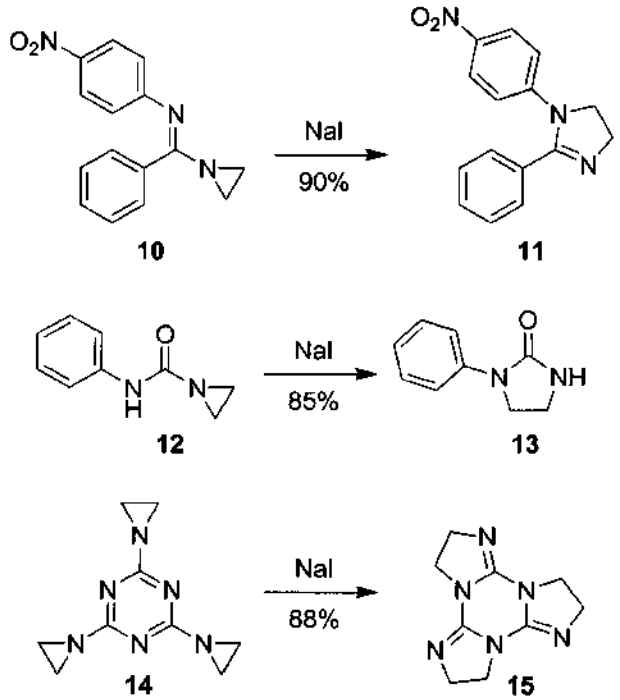
Harold Heine and co-workers were working with ethylenimines, and derivatives thereof, when they became intrigued by the reaction originally reported by Gabriel and coworkers in which thioacyl aziridine **3** was isomerized to thiazoline **4** upon attempted distillation.[1] This report went virtually unnoticed until Heine and co-workers decided to investigate the reaction further.[2] They found that upon exposure of **5** in refluxing heptane to small amounts of aluminum halides, oxazoline **6** was isolated in nearly quantitative yield. They also discovered that the reaction does not occur under purely thermal conditions, but catalysis is required.



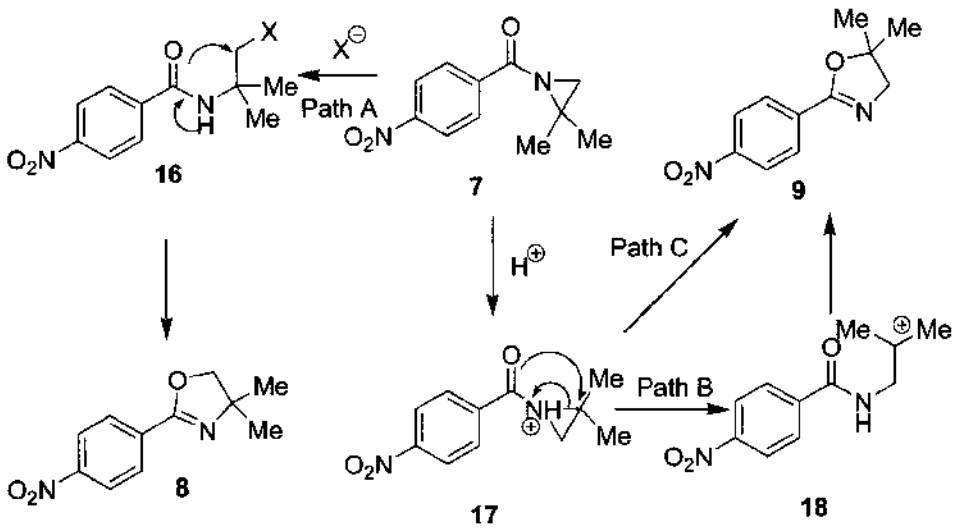
Further work from the Heine group revealed that the reaction could be accomplished under milder conditions and that the choice of catalyst determined the regiochemical outcome of the reaction.[3] For example, in the presence of iodide, **7** rearranges to **8**, wherein the least substituted carbon atom migrates. Alternatively, upon exposure to acid, **7** rearranges to **9**, wherein the most substituted carbon atom migrates. These results suggest that alternate mechanisms may be operable in these two transformations, a point that will be discussed below.



Heine also demonstrated that the rearrangement can occur on differentially acylated aziridines to give rise to different heterocycles such as imidazolines (**11**), imidazolones (**13**), and complex heterocycles such as **15**.[4,5] Futhermore, this reaction has been the subject of reviews by Heine and others.[6,7]



1.2.3 Mechanism



In Heine's seminal publications, he astutely noticed that different products are observed under acidic and nucleophilic catalysis.[3] Heine put forth a mechanistic explanation for the formation of both of these products.[6] He proposed that the rearrangement of **7** under nucleophilic catalysis proceeds through aziridine ring opening with the halide followed by displacement with oxygen to form **8** (two sequential S_N2 reactions, Path A). Alternatively, he proposed that the acid-catalyzed rearrangement of **7** to **9** proceeds through protonation of the aziridine nitrogen, formation of a tertiary carbocation, and subsequent attack by the oxygen on this carbocation (Path B). This mechanistic explanation of the nucleophilic catalysis (*i.e.*, **7** to **8**) is still generally accepted and has received further support as more examples have been presented in the literature.[8] His explanation for the acid-catalyzed rearrangement has come under scrutiny, though, and has been modified through further studies. Shortly after Heine put forth his mechanistic interpretation, Nishiguchi and co-workers proposed that the acid catalyzed rearrangement could potentially proceed through an S_Ni reaction (*i.e.*, Path C).[9] Convincing clarity in terms of both nucleophilic and acidic catalysis was not gained until the computational and experimental studies of Hori and co-workers, who concluded that two sequential S_N2 reactions (Path A) were likely operable for nucleophilic catalysis and an S_Ni pathway (Path C) accounted for the observed product under acidic catalysis.[10]

Further evidence exists to support these mechanistic interpretations, in that retention of configuration is observed if the aziridine is chiral in

nature.[11] The mechanism is thus limited to either a double inversion or front-side attack to account for this retention of stereochemistry.

Any mechanistic discussion of reactions of this nature also inherently requires comments on the regioselectivity of the migration. Regioselectivity in the Gabriel–Heine aziridine isomerization is observed under a variety of conditions.[12,13] As mentioned previously (*vide supra*), the most substituted carbon migrates under acidic catalysis and the least substituted carbon migrates under nucleophilic catalysis. This trend holds for acyl shifts, but thioacyl shifts are less regioselective, with more scrambling observed.[14] Finally, Eastwood and co-workers showed that aziridines substituted with electron-donating groups form 2,4-substituted oxazolines upon rearrangement, while those substituted with electron-withdrawing groups form 2,5-substituted oxazolines selectively.[15]

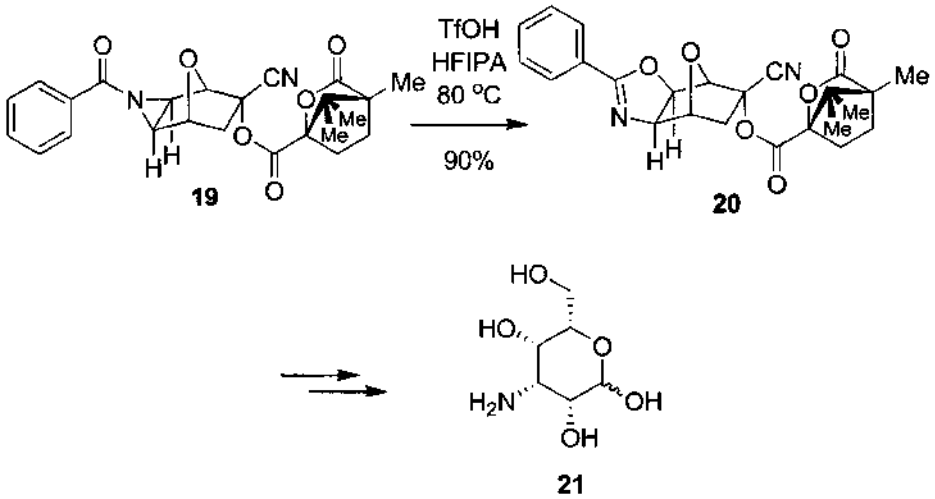
1.2.4 Variations and Improvements

Several variations and improvements of the Gabriel–Heine aziridine isomerization have been reported, primarily surrounding the catalyst selection and/or reaction conditions. An electrochemical rearrangement has been reported, which gave the desired oxazolines in moderate yield.[16] In addition to the catalysts initially reported, several other catalysts have been used in this reaction, including TfOH,[17] Yb(biphenol)OTf, $Ti(O\textit{i}\text{-}Pr)_4$, $Zr(Cp)_2(SbF_6)_2$,[18] $Cu(OTf)_2$, $Zn(OTf)_2$, $BF_3{\cdot}OEt_2$, $MgBr_2{\cdot}OEt_2$,[19] $Sn(OTf)_2$,[20,21] Mn(salen),[22] P_2S_5,[23] and TBAI.[24] The reaction has also been performed in the microwave in good yields and rapid reaction times.[25,26] Finally, one major variation of the Gabriel–Heine aziridine isomerization is the use of similar reaction conditions to convert acyl–aziridines into oxazolidinones using $BF_3{\cdot}OEt_2$.[4,27,28]

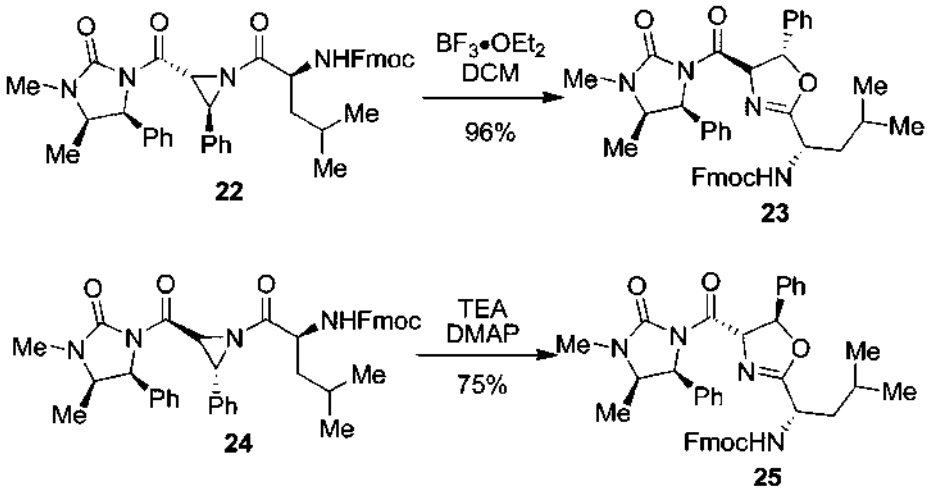
1.2.5 Synthetic Utility

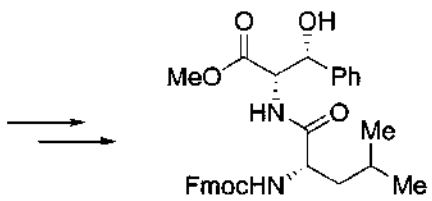
Total Synthesis

The Gabriel–Heine aziridine isomerization has been used only twice in the context of total synthesis, despite finding widespread utility in alternate contexts. The Vogel group has prepared 3-amino-3-deoxy-L-talose (**21**) using the Gabriel–Heine reaction as a key step.[29–31] The synthesis commences with readily available aziridine **19**, which undergoes a Gabriel–Heine rearrangement under triflic acid catalysis at 80 °C in hexafluoroisopropanol to generate oxazoline **20**. This intermediate was further transformed into 3-amino-3-deoxy-L-talose (**21**).



Cardillo and co-workers used the Gabriel–Heine aziridine isomerization during the preparation of a dipeptide fragment of lysobactin.[32–36] Both enantiomers of the fragment were prepared using this reaction. The group first prepared the incorrect diastereomer of the target fragment by ring expansion of aziridine **22** to oxazoline **23** using $BF_3{\cdot}OEt_2$ in nearly quantitative yield. It is surprising that the diastereomer (**24**) corresponding to the natural product was rearranged solely by the action of triethyl amine and dimethylaminopyridine to give **25** in 75% yield. This compound was further processed to the desired intermediate for lysobactin (**26**).

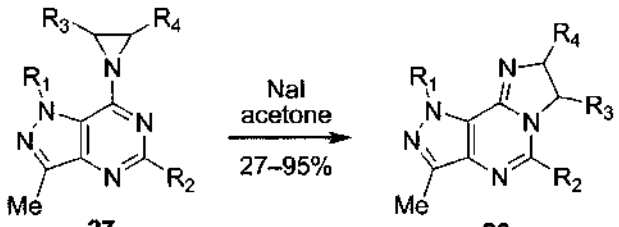




26

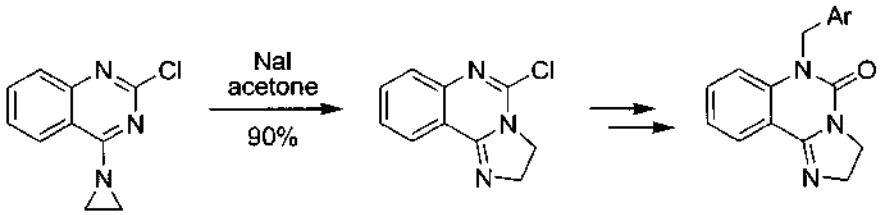
Medicinal and Process Chemistry

Much like with total synthesis, the Gabriel–Heine aziridine isomerization has not found widespread application within the medicinal chemistry community, despite its ability to efficiently generate a variety of azoles. DeWald and co-workers at Parke–Davis used the Gabriel–Heine reaction in the preparation of potential antipsychotics.[37] Compound **27** was rearranged upon exposure to sodium iodide in acetone to provide compounds of type **28** in moderate to good yield, which were evaluated as nondopamine-binding antipsychotics.



27 **28**

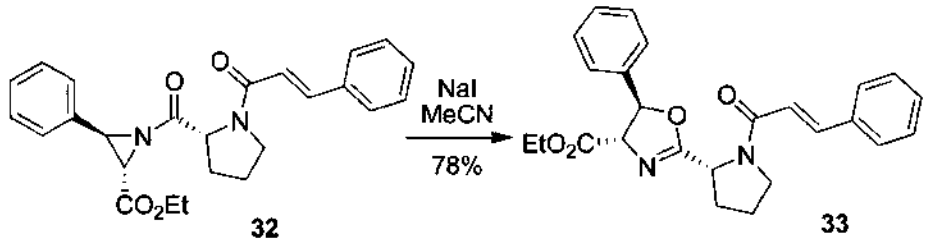
Researchers at Sandoz prepared a series of bronchodilators using the Gabriel–Heine aziridine isomerization as a key step.[38,39] Aziridine **29** was reacted with sodium iodide and acetone to prepare the ring-expanded product **30** in 90% yield. Further manipulations furnished the title compounds **31** in good yield, which were evaluated as bronchodilators.



29 **30** **31**

Iqbal and co-workers used the Gabriel–Heine aziridine isomerization to confirm the stereochemistry of an intermediate for preparation of an HIV

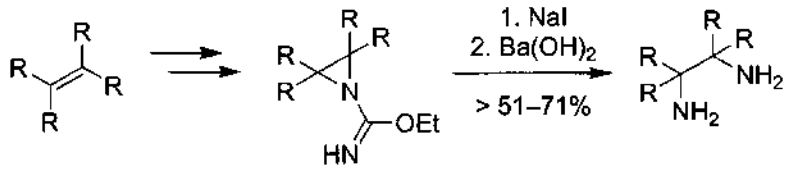
protease inhibitors.[40] Aziridine **32** was rearranged with sodium iodide in acetonitrile to give the desired oxazoline **33**, which enabled verification of the stereochemistry in the previous step.



32 **33**

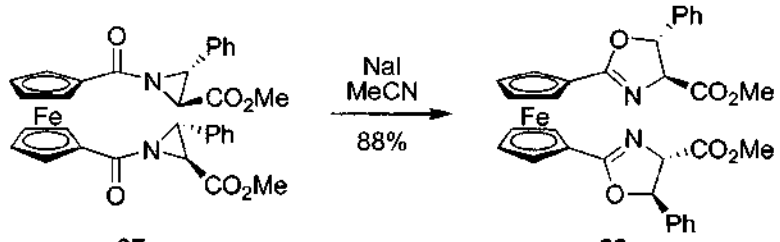
Miscellaneous Examples

Kohn and Jung reported the conversion of alkenes into vicinal diamines using the Gabriel–Heine aziridine isomerization as a key step during this sequence.[41] Alkene **34** was converted into the aziridine **35** using standard chemistry. Rearrangment under the action of sodium iodide provided the desired imidazolone, which was hydrolyzed with barium hydroxide to give the vicinal diamine **36**.



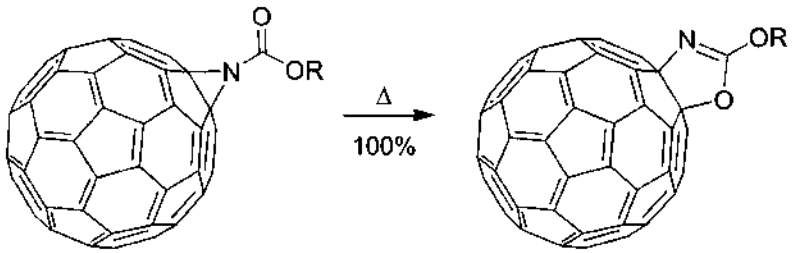
34 **35** **36**

Bonini and co-workers reported the use of the Gabriel–Heine aziridine isomerization to prepare ferrocenyl-oxazolines.[42] Bis-aziridine **37** was rearranged with sodium iodide in acetonitrile to provide the desired bisoxazoline **38** in excellent yield.



37 **38**

The Banks and Mattay groups independently reported the use of the Gabriel–Heine aziridine isomerization in the context of fullerenes.[43,44] Acylaziridinofullerine **39** was rearranged simply by heating to provide the oxazininofullerine **40** in quantitative yield.

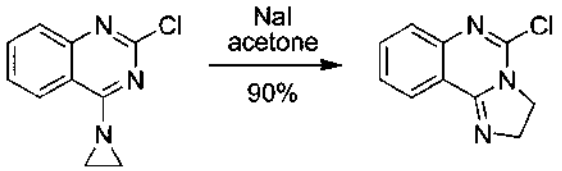


39 **40**

The Gabriel–Heine aziridine isomerization has seen many other uses since its development, whether in the preparation of starting materials or for studies of fundamental reactivities.[45–54]

1.2.6 Experimental

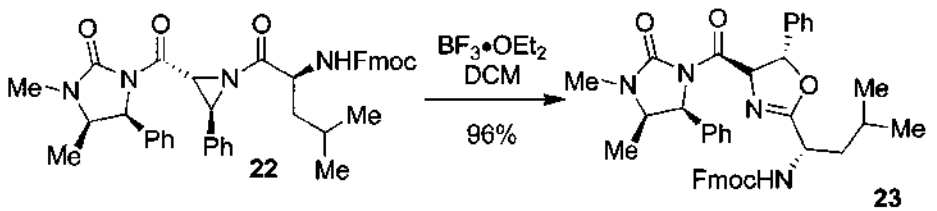
Gabriel–Heine Aziridine Isomerization to Prepare Bronchodilators[39]



29 **30**

Compound **29** (32 g, 0.16 mol) was dissolved in anhydrous acetone (500 mL) and stirred with 3.2 g (0.021 mol) of NaI for 90 min. The solvent was evaporated *in vacuo* and the residue treated with methylene chloride. Insoluble material was filtered off, and the filtrate extracted with saturated sodium chloride solution, dried (sodium sulfate), and evaporated. The crystalline material that was formed on addition of acetone was filtered off and dried at 50 °C in vacuo, yielding 28.7 g of **30** (90%).

Gabriel–Heine Aziridine Isomerization to Prepare the Lysobactin Fragment[32]



A solution of **22** (0.24 g, 0.36 mmol) in CH_2Cl_2 (5 mL) was treated with $BF_3{\cdot}Et_2O$ (0.045 mL, 0.36 mmol) at room temperature for 6 h. The reaction was quenched with sat. $NaHCO_3$ (3 mL), extracted three times with CH_2Cl_2, and dried over Na_2SO_4. The solvent was evaporated at reduced pressure to afford **23** (0.23 g, 96%), which required no further purification.

1.2.7 References

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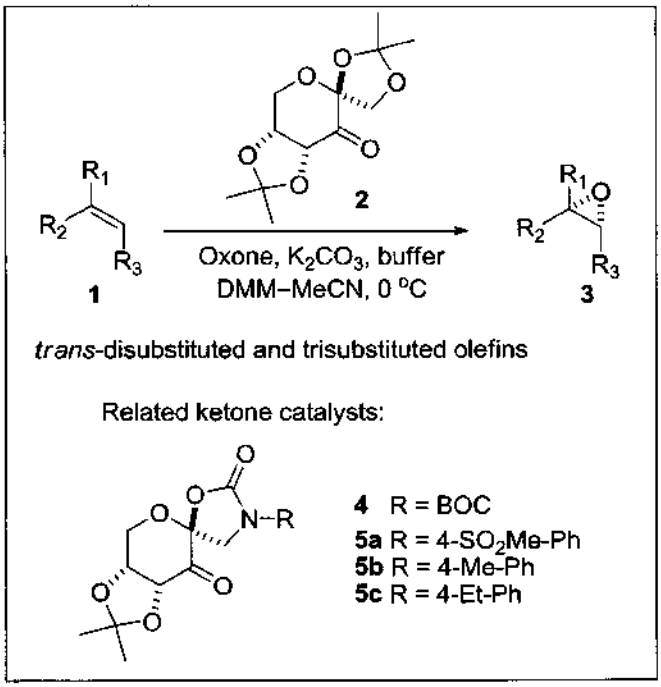
1.3 Shi Epoxidation

Bingwei Vera Yang

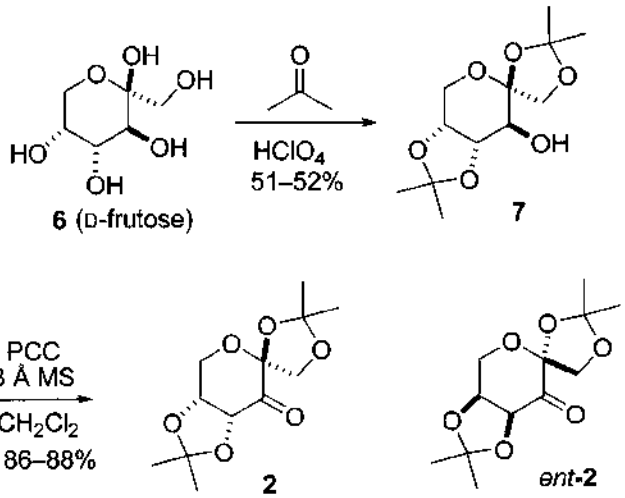
1.3.1 Description



The Shi epoxidation refers to the asymmetric epoxidation of alkenes **1** using Oxone (potassium peroxymonosulfate, $2KHSO_5 \cdot KHSO_4 \cdot K_2SO_4$) as the primary oxidant and a fructose-derived chiral ketone catalyst **2**.[1,2] This procedure generates epoxides **3** with high enantiomeric excesses from *trans*-disubstituted and trisubstituted olefins. *cis*-Disubstituted olefins and styrenes are asymmetrically expoxidized under similar conditions using glucose-derived catalysts **4**[3–6] or **5**.[7,8]

1.3.2 Historical Perspective

Professor Yian Shi at the Colorado State University first reported the use of a fructose-derived chiral ketone **2** for the asymmetric epoxidation in 1996.[1] This ketone is conveniently synthesized from an inexpensive chiral starting material D-fructose *via* ketalization and oxidation.[9–11] The enantiomer of ketone **2**, *ent*-**2**, can be prepared by the same methods from L-fructose, which is derived from L-sorbose.[12,13]

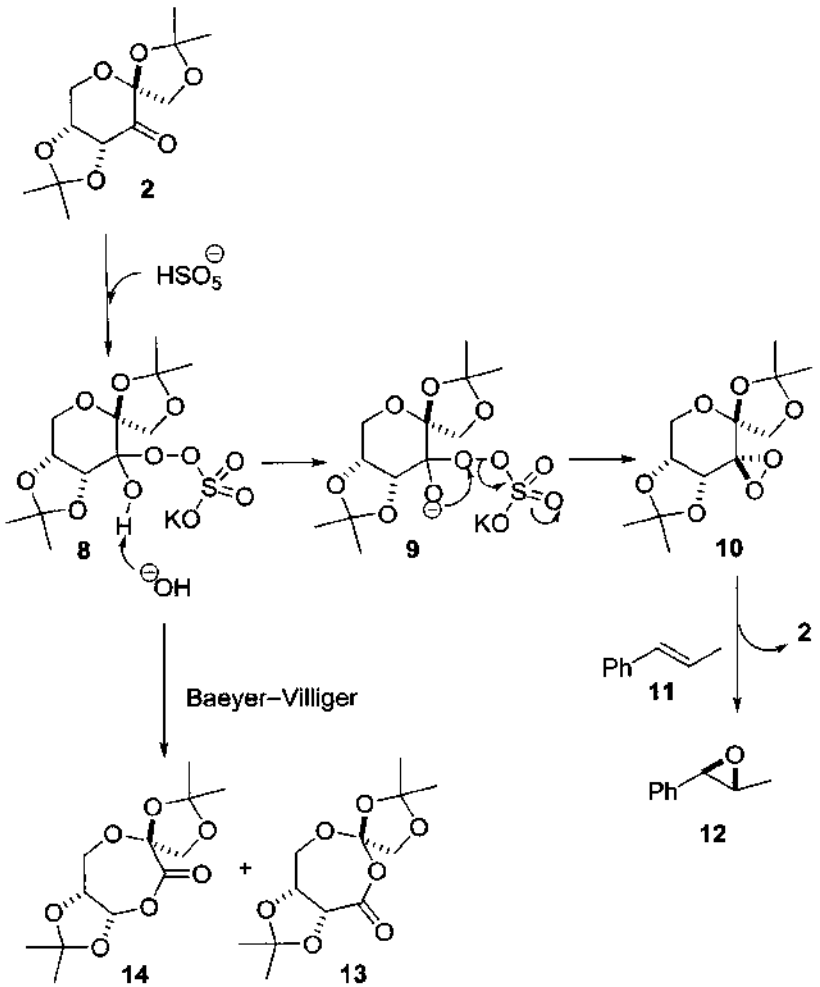


The epoxidation of olefins using dioxiranes generated *in situ* from Oxone and ketones is an established transformation. This reaction can be performed with catalytic amount of ketone, which is regenerated after the reactive intermediate dioxirane delivers oxygen to the double bond. Furthermore, a chiral ketone catalyst could be used for an asymmetric epoxidation if the chiral control elements are close to the reacting carbonyl. In 1984, Curci reported the first asymmetric epoxidation using chiral ketone (+)-isopinocamphone or (*S*)-(+)-3-phenylbutan-2-one (maximum *ee* = 12.5%).[14] However, it was only until the discovery of Shi's fructose-derived chiral ketone **2** that the organocatalytic asymmetric epoxidation received extensive attention, particularly notable for its high enantioselectivity, broad generality and green chemistry advantages. The wide scope of olefin substrates, especially the unactivated alkenes, makes Shi epoxidation one of the most powerful methods for converting olefins to chiral epoxides.

1.3.3 Mechanism

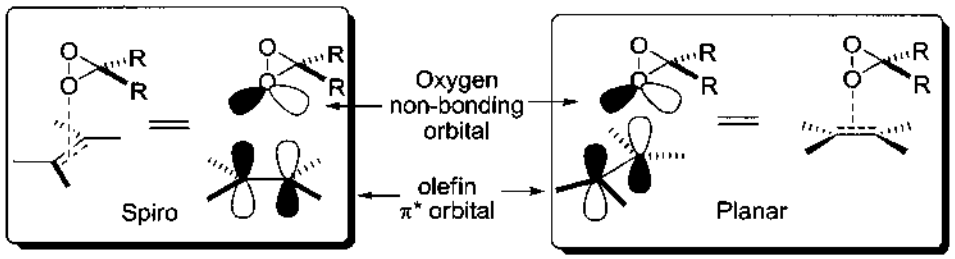
The epoxidation with *in situ* generated dioxiranes often requires careful control of the reaction pH. Since Oxone rapidly autodecomposes at high pH, early epoxidations were usually carried out at pH 7–8. In contrast, higher pH was found to be beneficial to epoxidation with ketone **2**.[9,15] For example, conversion of *trans*-β-methylstyrene **11** to its epoxide **12** increased from ~ 5% at pH 7–8 to > 80% at pH > 10 while a high enantioselectivity (90–92% *ee*) was retained. Analysis of the reaction cycle implied that a Baeyer–Villiger oxidation from intermediate **8** could be one of the possible decomposition pathways for ketone **2**. A higher pH would facilitate the formation of anion **9** and subsequent formation of dioxirane **10**, thus

suppressing the competing Baeyer–Villiger oxidation. The catalytic procedure at pH 10 requires substantially less Oxone, < 30% of the amount at pH 7 8, suggesting that ketone **2** can react with Oxone fast enough to avoid the autodecomposition of Oxone. The epoxidation is typically carried out around pH 10.5 by adding either K_2CO_3 or KOH as the reaction proceeds. Performing the reaction at higher pH greatly reduces the required amount of ketone catalyst, 30 mol% in most cases, leading to a catalytic process of epoxidation.

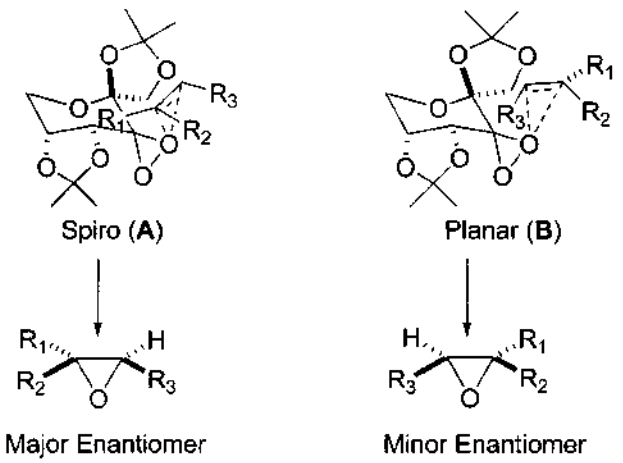


The stereochemical outcome of the epoxidation can be rationalized by a spiro transition state model. Two extreme epoxidation modes, spiro and planar, are known for epoxidation with dimethyldioxirane, and the spiro transition state is the optimal transition state for oxygen atom transfer from

dimethyldioxirane to alkene, presumably due to the stabilizing interactions between the oxygen nonbonding orbital and the alkene π* orbital in the spiro transition state.[16]



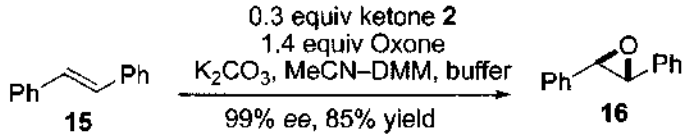
Studies have shown that the epoxidation of *trans*-di and tri-substituted olefins with ketone **2** mainly goes through the spiro transition state (spiro **A**). Planar transition state **B** competes with spiro **A** to give the opposite enantiomer.[1,9] Spiro **A** is favored by conjugation of the alkene that lowers the energy of the π* orbital of the alkene and enhances the stabilizing interaction between the dioxirane and the olefin. Decreasing the size of R_1 (further favoring spiro **A**) and/or increasing the size of R_3 (disfavoring planar **B**) can also result in higher *ee*'s of the epoxidation. The transition state modes for ketone **2** were further supported by results obtained from kinetic resolution of 1,6- and 1,3-disubstituted cyclohexenes[17] and de-symmetrization of cyclohexadiene derivatives.[18]



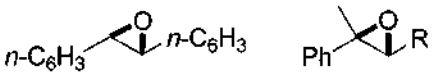
1.3.4 Variations and Improvements

Variation of Chiral Ketones

The asymmetric epoxidation with chiral ketone **2** has achieved high enantionselectivity with a wide range of unfunctionalized *trans*-disubstituted and trisubstituted olefins (selected examples are listed below).[9] 2,2-Disubstituted vinyl silanes are epoxidized in high *ee*'s and enantiomerically enriched 1,1-disubstituted epoxides can be obtained *via* the desilylation of these epoxides (*e.g.*, **18**).[19] Allylic alcohols and conjugated dienes and enynes are effective substrates (e.g. **19** and **20**).[20–23] The epoxidations of enol ethers and enol esters were also studied.[24] The resulting epoxides (*e.g.*, **21**) from enol esters can undergo stereoselective rearrangement to give optically active α-acyloxy ketones, (*S*)-**22** or (*R*)-**23**, under different acidic conditions.[25–27]

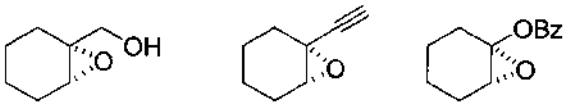


Additional examples, *ee* (yield%):

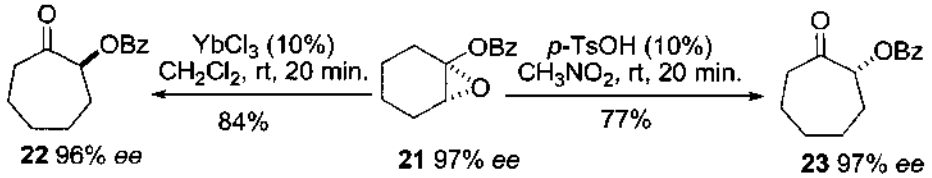


17 95% *ee* (89)

18a R = TMS, 94% *ee* (74)
18b R = H



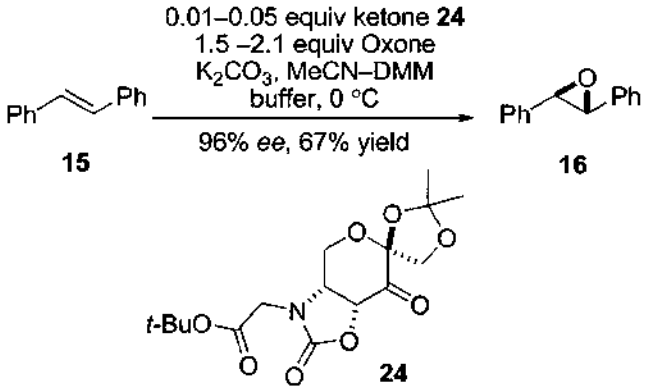
19 94% *ee* (93) **20** 93% *ee* (78) **21** 93% *ee* (82)



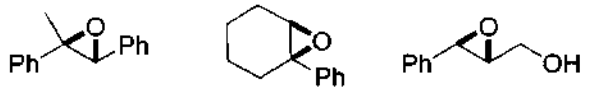
22 96% *ee* **21** 97% *ee* **23** 97% *ee*

To effectively suppress the decomposition of ketone catalyst *via* Bayer–Villiger oxidation (see the mechanism scheme), Shi replaced the fused ketal

moiety in ketone **2** by a more electron-withdrawing oxazolidinone (**24**) and acetates (**25**).[28,29] Only 5 mol% (1 mol% in some cases) of ketone **24** was needed to get comparable reactivity and enantioselectivity for 20–30 mol% of ketone **2**.[28]

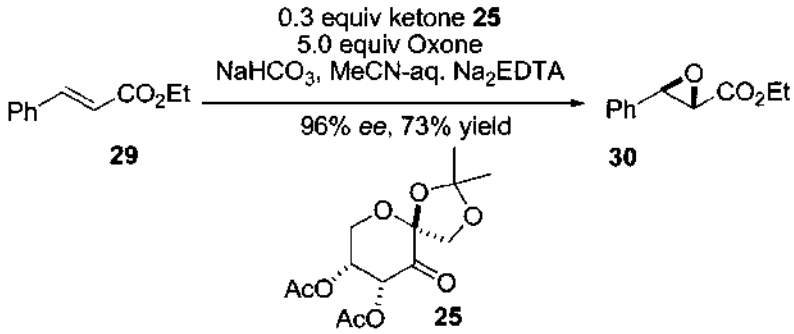


Additional examples
ee (yield%):

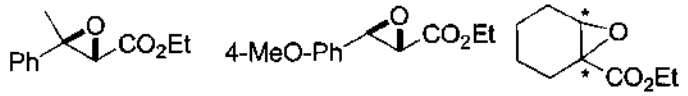


26 93% *ee* (80) **27** 92% *ee* (74) **28** 87% *ee* (89)

Ketone **25** has shown to provide high *ee*'s and good yields for epoxidation of a number of electron-deficient α,β-unsaturated esters,[29] whereas ketone **2** epoxidizes α,β-unsaturated esters sluggishly due to the low reactivity of its dioxirane as an electrophilic reagent toward electron-deficient olefins.

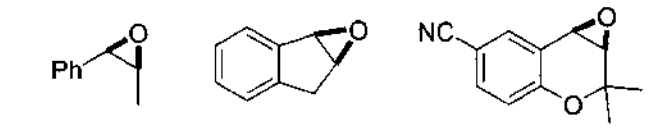


Additional examples
ee (yield%):

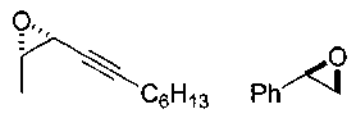


31 96% *ee* (93) **32** 90% *ee* (57) **33** 93% *ee* (77)

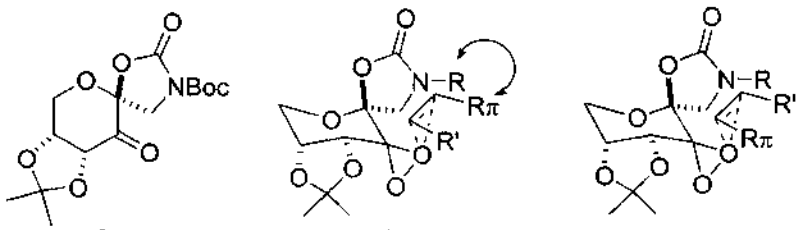
The substrate scope was expanded to *cis*-olefins and certain terminal olefins when a new series of glucose-derived ketones **4** and **5** were developed. In 2000, Shi reported an *N*-Boc oxazolidinone-bearing ketone **4** to be a highly enantioselective catalyst for the epoxidation of various *cis*-olefins conjugated with an aromatic or alkyne group.[3] The stereopreference of the olefin appears to be directed by an attraction from the oxazolidinone moiety of ketone **4**. In the transition state, Rπ substituent on the substrate prefers to be proximal to the oxazolidinone of ketone **4** (spiro **C** favored over spiro **D**).[3–6]



34 91% *ee* (87) **35** 83% *ee* (88) **36** 91% *ee* (61)



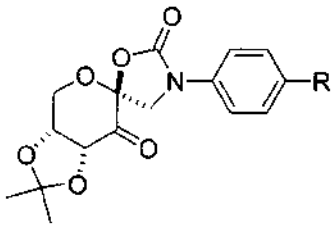
37 87% *ee* (77) **38** 81% *ee* (92)



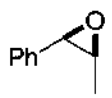
4 Spiro (**C**) Favored Spiro (**D**)

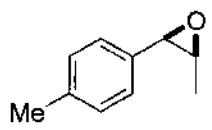
The *N*-aryl oxazolidinone-bearing ketone catalysts **5** are readily prepared in large quantities from glucose and inexpensive anilines in four steps.[30] Phenyl groups substituted with methylsulfonyl (**5a**) or alkyls (**5b**, **5c**) consistently provide high enantioselectivity for a variety of *cis*-olefins and certain terminal olefins.[7,8] *cis*-β-Methylstyrenes can be epoxidized with

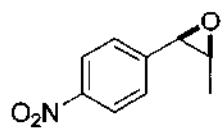
ketones **5a** and **5b** in high conversions and *ee*'s.[31] Substituents on the phenyl group of the olefins further enhance its (Rπ) interaction with the *N*-aryl group of the ketone catalyst, favoring spiro transition state **F** over spiro transition state **G** and consequently increasing the enantioselectivity (**39** and **40** *vs.* **34**).



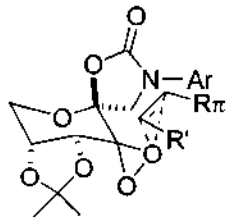
Epoxidation with ketones **5a** or **5b**, *ee* (yield %):

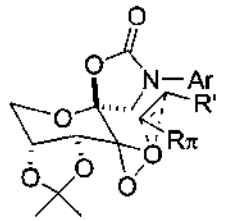






5a R = SO_2Me **5b** R = Me **5c** R = Et	**34** 90% *ee* (100)/**5a** 84% *ee* (99)/**5b**	**39** 92% *ee* (96)/**5a** 88% *ee* (100)/**5b**	**40** 97% *ee* (91)/**5a** 98% *ee* (86)/**5b**





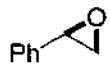
Spiro (**F**)
Favored

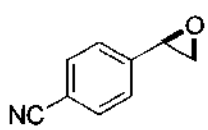
Spiro (**G**)

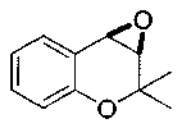
Ar = 4-alkyl-Ph, 4-SO_2Me-Ph;
Rπ = alkene, alkyne, Ph, substituted Ph; R' = H, alkyl.

Ketone **5c** is one of the most effective catalysts for the epoxidation of various styrenes (R′ = H)[8] and *cis*-enynes (Rπ = alkyne).[32]

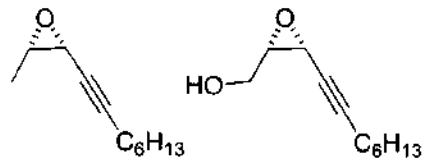
Epoxidation with ketone **5c**, *ee* (yield%):





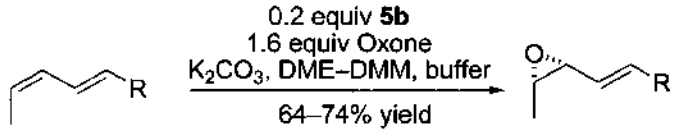


38 86% *ee* (72) **41** 90% *ee* (86) **42** 84% *ee* (100)

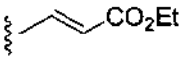


37 90% *ee* (84) **43** 97% *ee* (68)

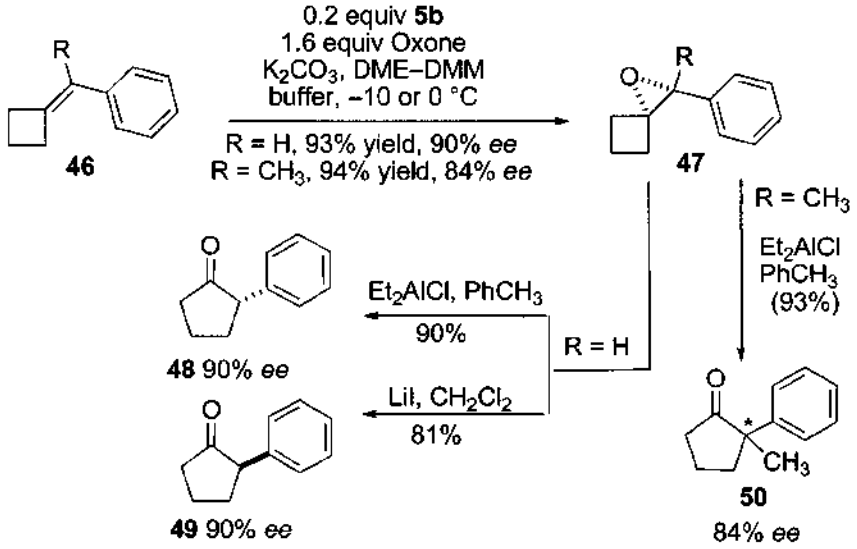
Ketone **5b** demonstrates a broader substrate scope than that displayed by any other *N*-aryl-oxazolidinone-containing catalyst. Conjugated *cis*-dienes **44** can be epoxidized with **5b** in high *ee*'s with no *cis–trans* isomerization.[33]



44 **45**

R = Ph (85% *ee*), CO_2Et (94% *ee*),  (94% *ee*)

Trisubstituted and tetrasubstituted benzylidenecyclobutanes **46** undergo highly enantioselective epoxidation with ketone **5b** followed by epoxide rearrangement upon treatment with Et_2AlCl or LiI to afford optically active 2-aryl cyclopentanones (**48**, **49** or **50**).[34,35]



46 **47**

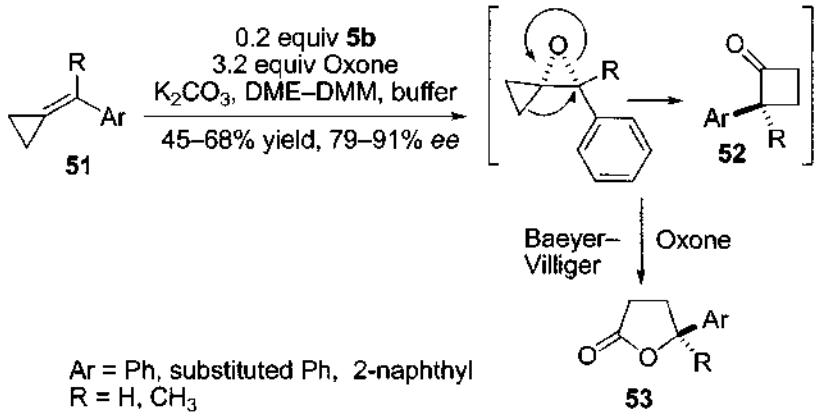
48 90% *ee*

49 90% *ee*

50
84% *ee*

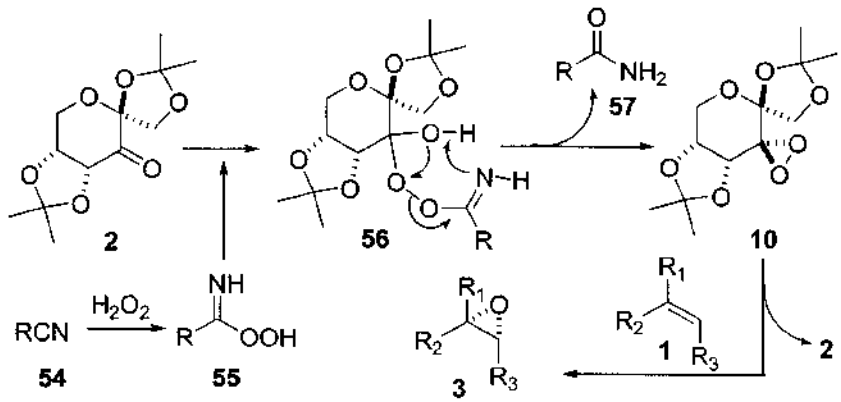
When benzyliden-cyclopropanes **51** are subjected to epoxidation with **5b**, optically active γ-aryl-γ-butyrolactones **53** can be obtained in moderate yield

and good enantioselectivity *via* an *in situ* epoxide rearrangement and a Baeyer–Villiger oxidation.[36]

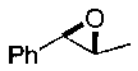


Variations of Oxidant: Hydrogen Peroxide as Primary Oxidant

While Oxone has been commonly used to generate dioxiranes from ketones, Shi's studies have shown that epoxidation with ketone **2** or **5c** can be carried out with a nitrile and H_2O_2 as the primary oxidant, giving high enantioselectivity for a variety of olefins.[37–39] Peroxyimidic acid **55** is likely to be the active oxidant that reacts with the ketone to form dioxirane **10**. Mixed solvents, such as CH_3CN–EtOH–CH_2Cl_2, improve the conversions for substrates with poor solubilities. This epoxidation system is mild and provides conversion and enantioselectivity similar to that using Oxone as oxidant.

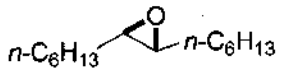


Epoxidation with ketones **2** or **5c**, *ee* (yield %):

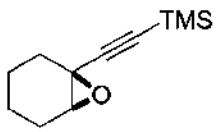


11 92% *ee* (93)/2

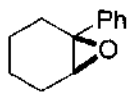
15 98% *ee* (90) /2



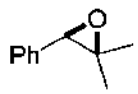
17 92% *ee* (97) /2



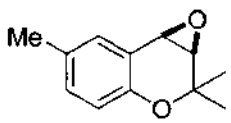
58 95% *ee* (93)/2



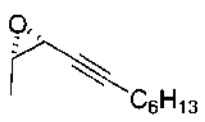
59 96% *ee* (90)/2



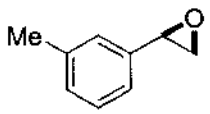
60 92% *ee* (82)/**5c**



61 91% *ee* (89)/**5c**



17 90% *ee* (65)/**5c**

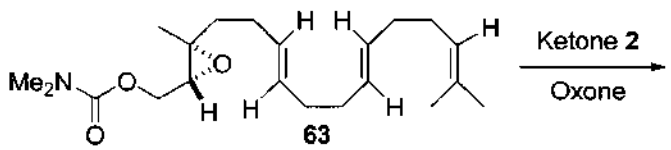


62 83% *ee* (93)/**5c**

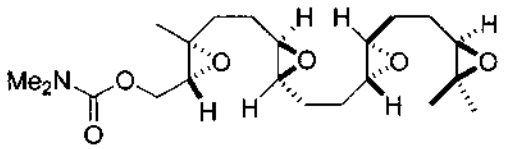
1.3.5 Synthetic Utility

The availability of ketone **2** and its effectiveness toward a wide variety of *trans*-disubstituted and trisubstituted olefins make Shi epoxidation a widely applicable method in many syntheses published over the past decade. Selected examples are highlighted in this section.

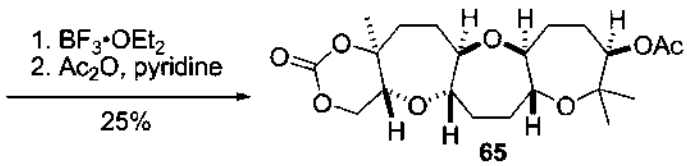
A group of polycyclic polyether natural products are of special interest owing to their fascinating structure and biological activities. One of the proposed biosynthetic origins of these molecules features an epoxide-opening cascade pathway. Shi asymmetric epoxidation of un-activated alkenes has been frequently employed in the preparation of polyepoxide intermediates. McDonald and co-workers studied a series of tandem *endo*-selective and stereospecific oxacyclization of polyepoxides mediated by Lewis acid. Polyepoxides, such as **64**, can be obtained from the epoxidation of triene **63** with ketone **2**.[40] Furthermore, a cascade cyclization, initiated by a Lewis acid-promoted epoxide opening of **64**, furnished the desired polyether **65**.



63

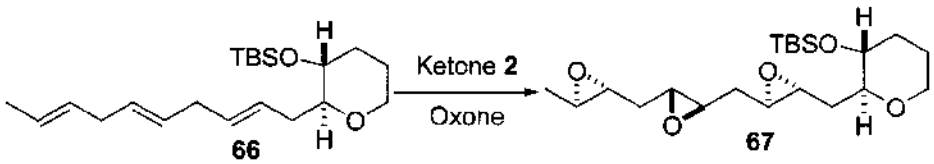


64

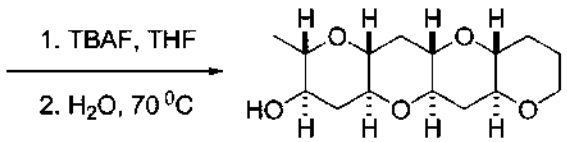


65

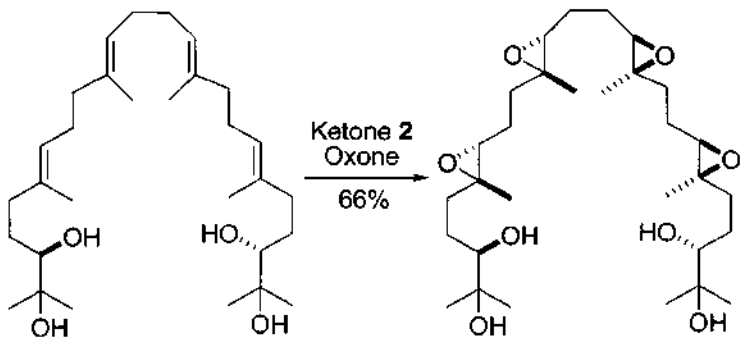
In recent studies, Jamison and co-workers reported the formation of tetrahydropyran **68** *via* selective epoxide-opening reactions in water.[41] The polytetrahydropyran precursor **67** was prepared from the epoxidation of polyalkene **66** with ketone **2**.



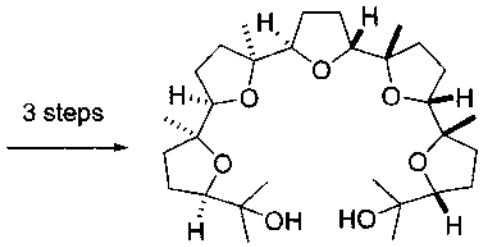
66 67



68



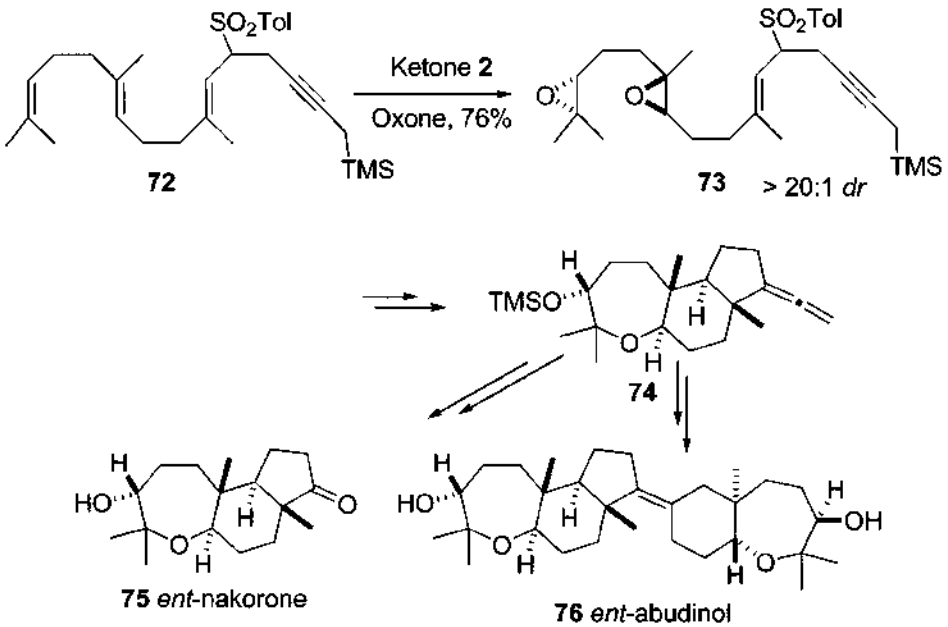
69 70



71, glabrescol

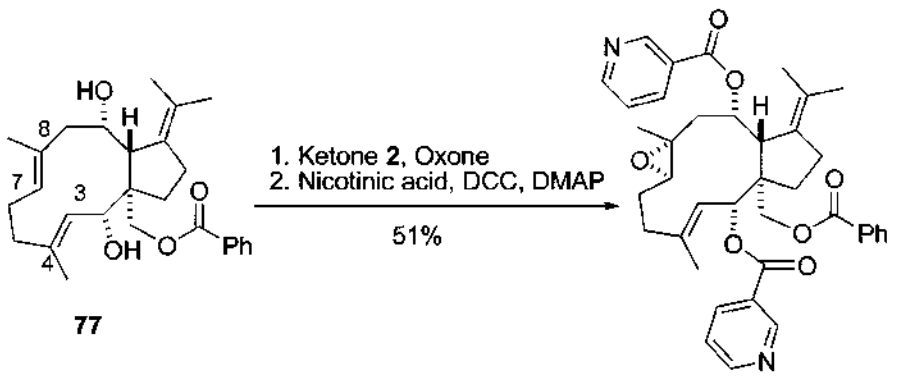
In 2000, in an effort to verify the structure of a polycyclic oxasqualenoid, glabrescol **71**, Corey and co-workers applied the Shi epoxidation in the conversion of tetraene **69** to tetra-epoxide **70**, which was subsequently transformed to glabrescol **71** in three steps.[42,43]

The high specificity of the Shi epoxidation permits the regioselective epoxidation in some polyene compounds. McDonald and co-workers employed ketone **2** in the total synthesis of nakorone and abudinol.[44] Triene-yne **72** was selectively epoxidized on the two more electron-rich double bonds, leaving the olefin next to the electron-withdrawing sulfone group intact. Bis-epoxide **73** was transformed into both *ent*-nakorone **75** and *ent*-abudinol B **76**.



In 2006, Ready and co-workers reported that compound **77**, which contains three double bonds, was regio- and stereo-selectively epoxidized at

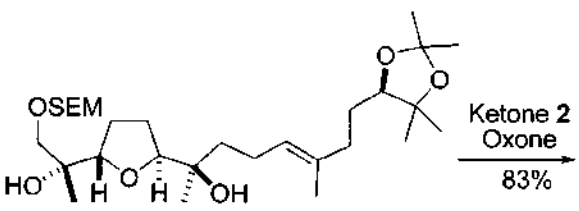
the desired C7–C8 double bond. The resulting epoxide was converted into (+)-nigellamine A_2 **78**.[45]



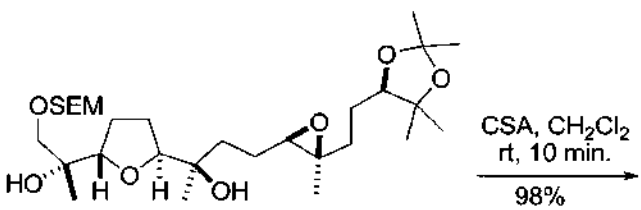
77

(+)-nigellamine A_2 **78**

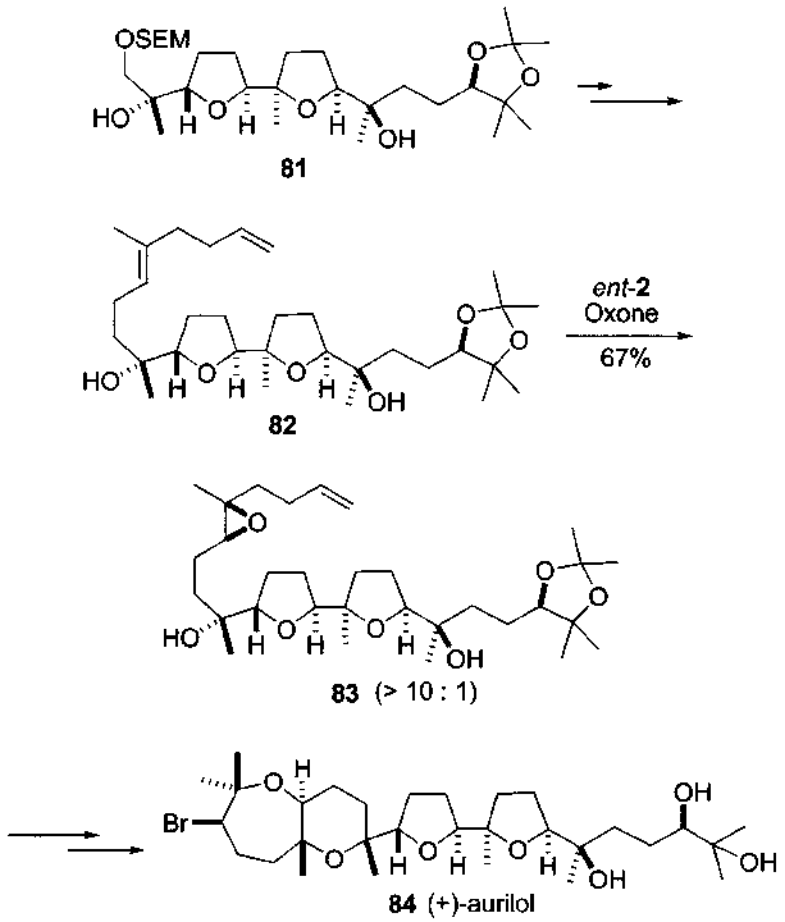
Selective epoxidation of polyene compound has also achieved with *ent*-**2**, the enantiomer of ketone **2**. In Morimoto's total synthesis of polyether (+)-aurilol, Shi epoxidation was utilized twice, with ketone **2** and *ent*-**2**, respectively.[46] Epoxidation of **79** with ketone **2** gave epoxide **80** with high diastereoselectivity. Epoxide **80** underwent acid catalyzed 5-*exo*-*tet* cyclization to produce tetrahydrofuran **81** with the desired stereochemistry. Subsequently, diene **82** was selectively epoxidized with *ent*-**2** only at the trisubstituted olefin to give epoxide **83**. Epoxides **80** and **83** played important roles in setting stereocenters in the final product.



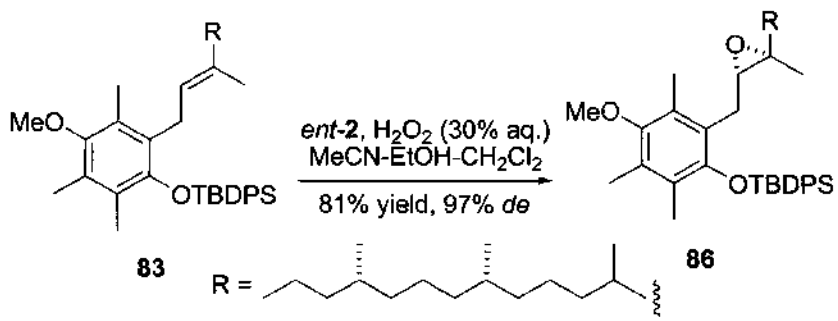
79

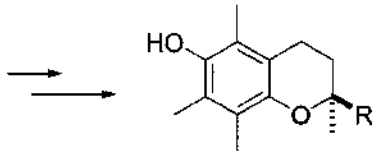


80 (> 15 : 1)



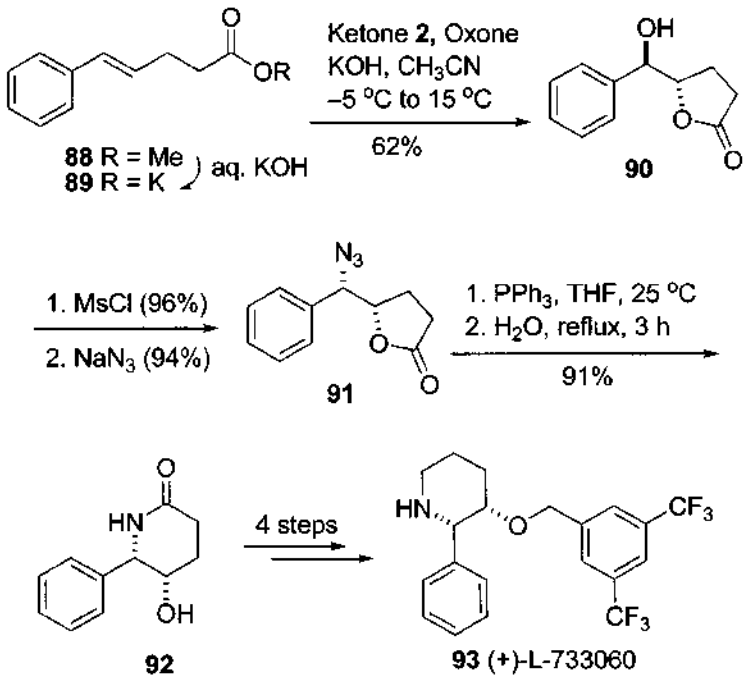
A diastereoselective synthesis of α-tocopherol **87** features a Shi epoxidation with *ent*-**2** and a carefully controlled intramolecular epoxide opening cyclization for the formation of the chromanol ring. Good conversion and high enantioselectivity have been achieved in the epoxidation step.[47]





87 α-tocopherol

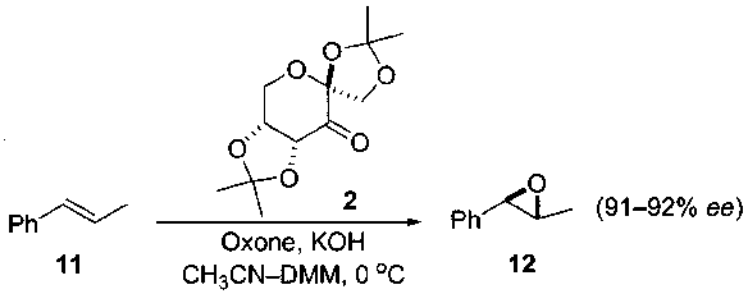
A recent publication described a short enantioselective synthesis of (+)-L-733,060, a selective and potent nonpeptide neurokinin substance P receptor antagonist.[48] The key chirality-inducing step involved a Shi epoxidation of homoallylic carboxylate **89**. Subsequent intramolecular reductive cyclization of azidolactone constructed the piperidine ring.



In summary, the broad application of the Shi epoxidation in the total synthesis of natural products and in drug discovery is a good indication that the reaction will receive more attention and find extended use in the future. Together with the Sharpless epoxidation and the Jacobsen epoxidation, Shi epoxidation has been considered one of the three major catalytic enantioselective epoxidations useful for the synthesis of chiral epoxides.

1.3.6 Experimental

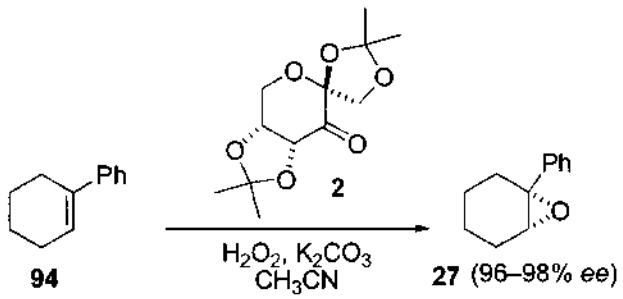
Standard Conditions



***(R,R)-trans*-β-Methylstyrene oxide (12).**[38]

A 2-L, three-necked, round-bottomed flask equipped with a 5-cm, egg-shaped, Teflon-coated stir bar and two addition funnels is cooled in an ice bath. The flask is charged with *trans*-β-methylstyrene **11** (5.91 g, 50.0 mmol), 500 mL of a 2 : 1 mixture of dimethoxymethane (DMM) and acetonitrile (CH_3CN), 300 mL of potassium carbonate–acetic acid buffer solution, tetrabutylammonium hydrogen sulfate (0.375 g, 1.1 mmol), and the chiral ketone **2**[11] (4.52 g, 17.5 mmol, 35 mol%). One addition funnel is charged with a solution of Oxone (46.1 g, 75.0 mmol) in 170 mL of aqueous 4×10^{-4} M disodium ethylenediaminetetraacetate (Na_2EDTA) solution, and the other addition funnel is charged with 170 mL of 1.47 M aqueous potassium hydroxide (KOH) solution. The two solutions in the addition funnels are added dropwise at the same rate over 2.5 h to the cooled reaction mixture, which is stirred vigorously at 0 °C. The resulting suspension is stirred at 0 °C for an additional hour, and then 250 mL of pentane is added. The aqueous phase is separated and extracted with two 250-mL portions of pentane, and the combined organic phases are dried over Na_2SO_4, filtered, and concentrated by rotary evaporation at 0 °C. The resulting oil is loaded onto 50 g of Whatman 60 Å (230–400 mesh) silica gel packed in a 5-cm-diameter column. The silica gel is first washed with 200 mL of hexane to remove trace amounts of unreacted olefin, then the product is eluted with 200 mL of 10 : 1 hexane:ether to afford 6.02–6.31 g (90–94%) of *trans*-β-methylstyrene oxide **12**.

Asymmetric Epoxidation Using Ketone 2 and H_2O_2 as Primary Oxidant



(*R,R*)-1-Phenylcyclohexene oxide (27).[38]

A 250-mL, round-bottomed flask equipped with a 4.5-cm, egg-shaped Teflon-coated magnetic stirbar is charged with 1-phenylcyclohexene **94** (7.91 g, 50.0 mmol) and the chiral ketone **2**[11] (1.29 g, 5.00 mmol, 10 mol%). The flask is cooled in an ice bath, and 75 mL of CH_3CN and 75 mL of a solution of 2.0 M potassium carbonate and 4×10^{-4} M EDTA are added. The reaction mixture is cooled to 0 °C, and 20 mL (200 mmol) of 30% hydrogen peroxide (H_2O_2) is added. The resulting mixture is vigorously stirred at 0 °C for 6 h, then diluted with 50 mL of hexane. The aqueous phase is separated and extracted with three 200-mL portions of hexane, and the combined organic phases are washed with two 50-mL portions of 1 M aqueous sodium thiosulfate solution and 100 mL of brine, dried over Na_2SO_4, filtered, and concentrated by rotary evaporation at 0 °C. The resulting oil is applied to 180 g of Whatman 60 Å (230–400 mesh) silica gel packed in a 5-cm-diameter column; then the product is eluted with 600 mL of hexane and finally 1 L of 20 : 1 hexane/Et_2O to afford 6.88–8.01 g (79–92%) of (*R,R*)-1-phenylcyclohexene oxide (**27**) as a colorless oil.

1.3.7 References

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