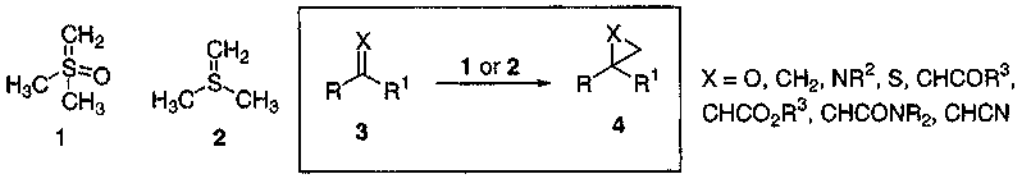
1.1 Corey–Chaykovsky Reaction

1.1.1 Description

The Corey–Chaykovsky reaction entails the reaction of a sulfur ylide, either dimethylsulfoxonium methylide (**1**, Corey's ylide, sometimes known as DMSY) or dimethylsulfonium methylide (**2**), with electrophile **3** such as carbonyl, olefin, imine, or thiocarbonyl, to offer **4** as the corresponding epoxide, cyclopropane, aziridine, or thiirane.[1–7]

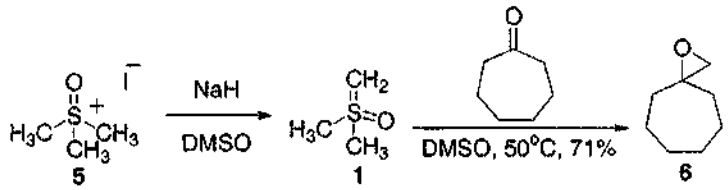


1 **2** **3** **4**

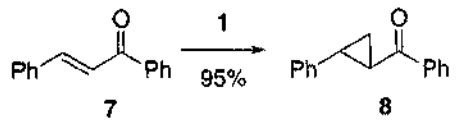
For an α,β-unsaturated carbonyl compound, **1** adds preferentially to the olefin to furnish the cyclopropane derivative, whereas the more reactive **2** generally undergoes the methylene transfer to the carbonyl, leading to the corresponding epoxide. Also due to the difference of reactivities, reactions using **1** require slightly elevated temperature, normally around 50–60°C, whereas reactions using the more reactive **2** can be carried out at colder temperature ranging from −15°C to room temperature. Moreover, while it is preferable to freshly prepare both ylides *in situ*, **2** is not as stable as **1**, which can be stored at room temperature for several days.

1.1.2 Historical Perspective

In 1962, Corey and Chaykovsky described the generation and synthetic utility of dimethylsulfoxonium methylide (**1**) and dimethylsulfonium methylide (**2**).[8–12] Upon treatment of DMSO with NaH, the resulting methylsulfinyl carbanion reacted with trimethylsulfoxonium iodide (**5**) to produce dimethylsulfoxonium methylide (**1**). The subsequent reaction between **1** and cycloheptanone rendered epoxide **6**. Similar results were observed for other ketones and aldehydes as well, with a limitation where treatment of certain ketones (e.g. desoxybenzoin and Δ^4-cholestenone) with **1** failed to deliver the epoxides possibly due to their ease to form the enolate ions by proton transfer to **1**. Interestingly, Michael receptor **7** reacted with **1** to provide access to the "methylene insertion" product, cyclopropane **8**. Meanwhile, thiiranes were isolated in good yields from the reaction of thiocarbonyls and **1**, and methylene transfer from **1** to imines took place to afford aziridines.



5 **1** **6**

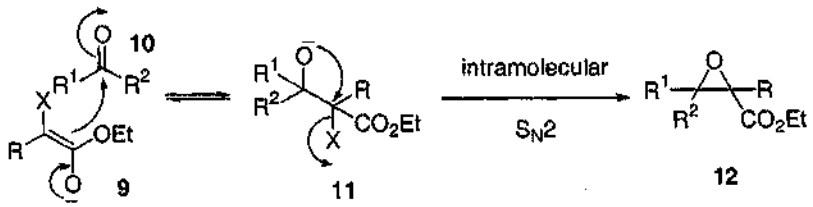


1.1.3 Mechanism

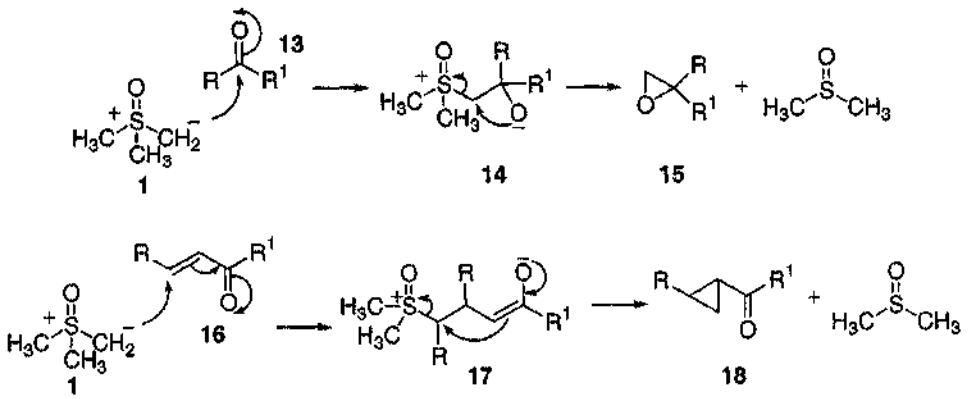
Similar to phosphur ylides, sulfur ylides **1** and **2** possess the nucleophilic site at the carbon atom and the pendant leaving group at the heteroatom (sulfur). Different from the Wittig reaction, the Corey–Chaykovsky reaction does not lead to olefins.

The mechanism of epoxide formation using sulfur ylides[13] is analogous to that of the Darzens condensation. In the Darzens condensation, enolate **9** adds to ketone **10**, forming alkoxide **11**, which undergoes an internal S_N2 to give epoxide **12**. In a parallel fashion, addition of dimethylsulfoxonium methylide (**1**) to ketone **13**, led to betaine **14**, which also undergoes an internal S_N2 to secure epoxide **15**. On the other hand, Michael addition of **1** to enone **16** gives betaine **17**, which subsequently undergoes an internal S_N2 to deliver cyclopropyl ketone **18**.[14]

Darzens condensation:



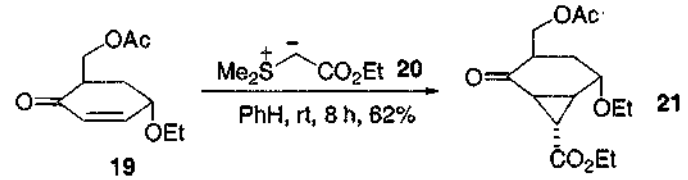
Corey–Chaykovsky reaction:

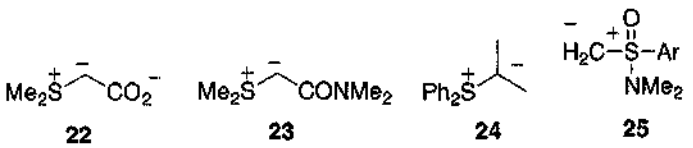


1.1.4 Variations and Improvements

Sulfur ylides **1** and **2** are usually prepared by treatment of either trimethylsulfoxonium iodide (**5**) or trimethylsulfonium iodide, respectively, with NaH or *n*-BuLi.[12] An improvement using KO*t*Bu[13,15] is safer than NaH and *n*-BuLi for large-scale operations.

In addition, NaOMe, and $NaNH_2$, have also been employed. Application of phase-transfer conditions with tetra-*n*-butylammonium iodide showed marked improvement for the epoxide formation.[16] Furthermore, many complex substituted sulfur ylides have been synthesized and utilized. For instance, stabilized ylide **20** was prepared and treated with α-D-*allo*-pyranoside **19** to furnish α-D-cyclopropanyl-pyranoside **21**.[17] Other examples of substituted sulfur ylides include **22–25**, among which aminosulfoxonium ylide **25**, sometimes known as Johnson's ylide, belongs to another category.[18] The aminosulfoxonium ylides possess the configurational stability and thermal stability not enjoyed by the sulfonium and sulfoxonium ylides, thereby are more suitable for asymmetric synthesis.

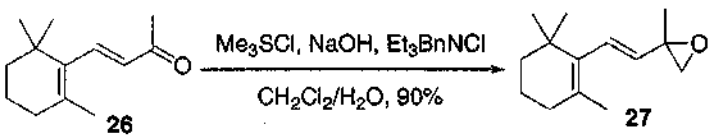




1.1.5 Synthetic Utility

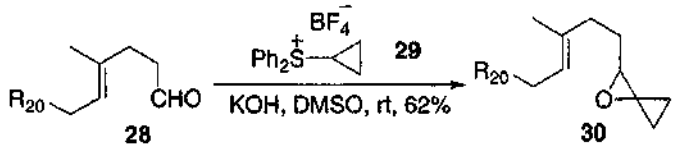
1.1.5.1 Epoxidation

Epoxidation of aldehydes and ketones is the most profound utility of the Corey–Chaykovsky reaction. As noted in section 1.1.1, for an α,β-unsaturated carbonyl compound, **1** adds preferentially to the olefin to provide the cyclopropane derivative. On the other hand, the more reactive **2** generally undergoes the methylene transfer to the carbonyl, giving rise to the corresponding epoxide. For instance, treatment of β-ionone (**26**) with **2**, derived from trimethylsulfonium chloride and NaOH in the presence of a phase-transfer catalyst Et_4BnNCl, gave rise to vinyl epoxide **27** exclusively.[19]

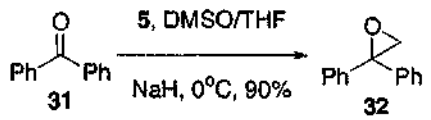


Isolated carbonyls always give epoxides from the Corey–Chaykovsky reaction. Take the aldehyde substrate as an example. Spiro epoxide **30** was produced from the reaction of trisnorsqualene aldehyde **28** (R_{20} represents the polyene side-chain with 20 carbons) with substituted sulfur ylide **29**, prepared *in situ* from cyclopropyldiphenylsulfonium tetrafluoroborate and KOH.[20] For the epoxidation of ketones, the Corey–Chaykovsky reaction works well for diaryl- (**31**),[21] arylalkyl- (**32**),[22]

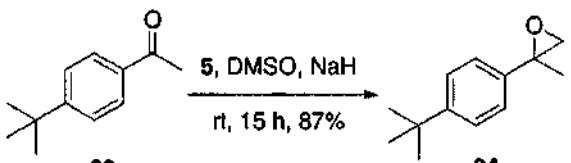
as well as dialkyl (**33**)[23] ketones. When steric bias exists on the substrate, stereoselective epoxidation may be achieved. For example, treatment of dihydrotestosterone (DHT, **35**) with the Corey ylide **1** followed by TPAP oxidation resulted in only one diastereomeric keto-epoxide **36**.[23]



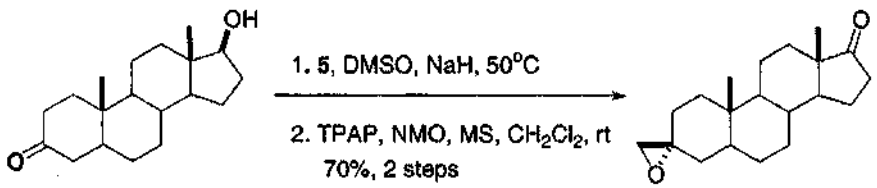
28 **30**



31 **32**

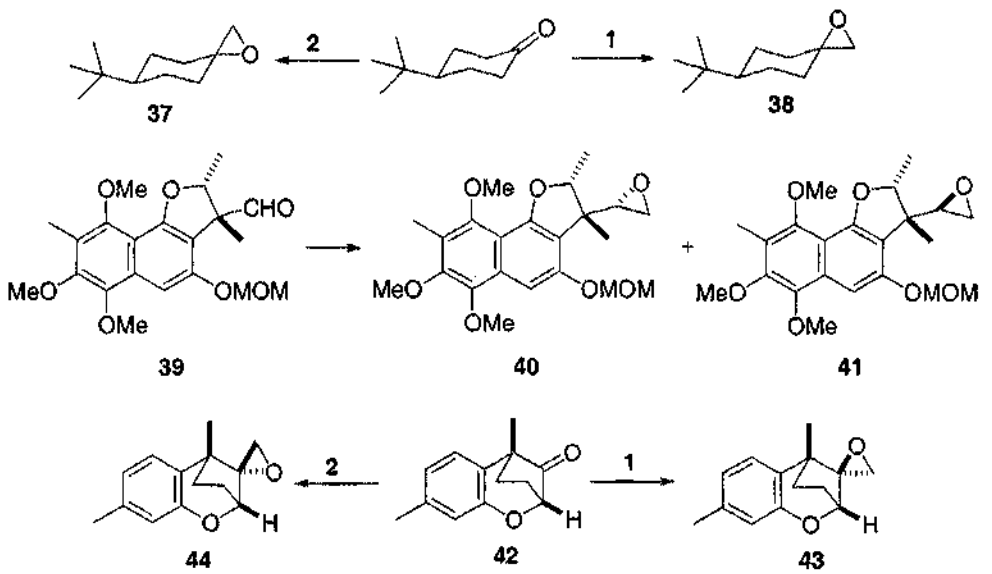


33 **34**

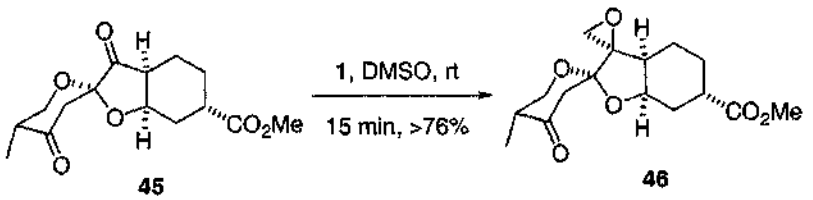


35 **36**

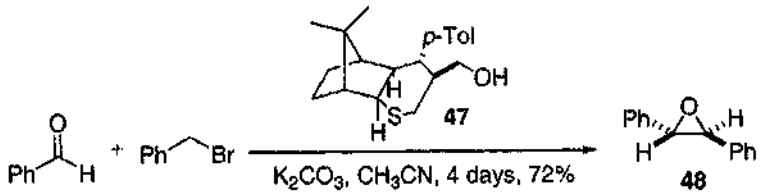
Stereoselective epoxidation can be realized through either substrate-controlled (e.g. **35** → **36**) or reagent-controlled approaches. A classic example is the epoxidation of 4-*t*-butylcyclohexanone.[12] When sulfonium ylide **2** was utilized, the more reactive ylide irreversibly attacked the carbonyl from the axial direction to offer predominantly epoxide **37**. When the less reactive sulfoxonium ylide **1** was used, the nucleophilic addition to the carbonyl was reversible, giving rise to the thermodynamically more stable, equatorially coupled betaine, which subsequently eliminated to deliver epoxide **38**. Thus, stereoselective epoxidation was achieved from different mechanistic pathways taken by different sulfur ylides. In another case, reaction of aldehyde **38** with sulfonium ylide **2** only gave moderate stereoselectivity (**41**:**40** = 1.5/1), whereas employment of sulfoxonium ylide **1** led to a ratio of **41**:**40** = 13/1.[24] The best stereoselectivity was accomplished using aminosulfoxonium ylide **25**, leading to a ratio of **41**:**40** = 30/1. For ketone **42**, a complete reversal of stereochemistry was observed when it was treated with sulfoxonium ylide **1** and sulfonium ylide **2**, respectively.[25]



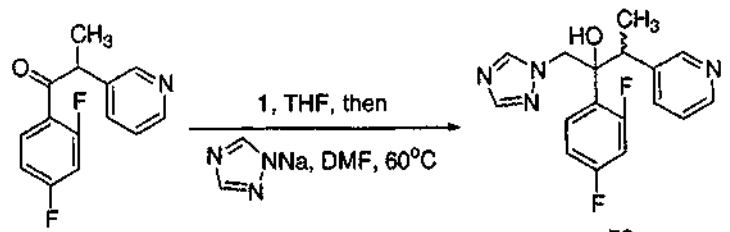
In transforming bis-ketone **45** to keto-epoxide **46**, the elevated stereoselectivity was believed to be a consequence of the molecular shape — the sulfur ylide attacked preferentially from the convex face of the strongly puckered molecule of **45**. Moreover, the pronounced chemoselectivity was attributed to the increased electrophilicity of the furanone versus the pyranone carbonyl, as a result of an inductive effect generated by the pair of spiroacetal oxygen substituents at the furanone α-position.[26]

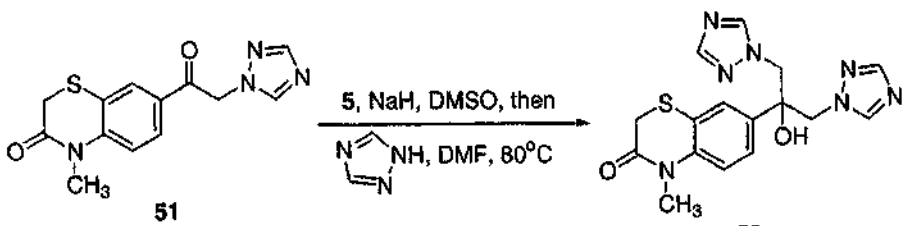


Since chiral sulfur ylides racemize rapidly, they are generally prepared *in situ* from chiral sulfides and halides. The first example of asymmetric epoxidation was reported in 1989, using camphor-derived chiral sulfonium ylides with moderate yields and *ee* (< 47%).[27] Since then, much effort has been made in the asymmetric epoxidation using such a strategy without a significant breakthrough. In one example, the reaction between benzaldehyde and benzyl bromide in the presence of one equivalent of camphor-derived sulfide **47** furnished epoxide **48** in high diastereoselectivity (*trans:cis* = 96:4) with moderate enantioselectivity in the case of the *trans* isomer (56% *ee*).[28]



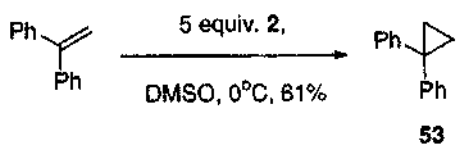
The Corey–Chaykovsky reaction incited some applications in medicinal chemistry. During the synthesis of analogs of fluconazole, an azole antifungal agent, treatment of **49** with **1** led to the corresponding epoxide, which was subsequently converted to **50** as a pair of diastereomers.[29] Analogously, the Corey–Chaykovsky reaction of ketone **51** gave the expected epoxide, which then underwent an S_N2 reaction with 1*H*-1,2,4-triazole in the presence of NaH to deliver **52**, another azole antifungal agent.[30]

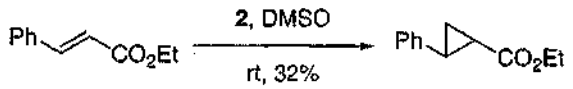




1.1.5.2 Cyclopropanation

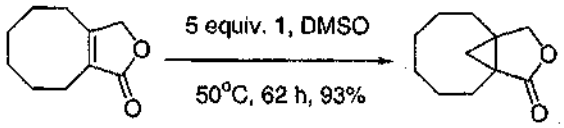
Due to the high reactivity of sulfonium ylide **2** for α,β-unsaturated ketone substrates, it normally undergoes methylene transfer to the carbonyl to give the corresponding epoxides. However, cyclopropanation did take place when 1,1-diphenylethylene[12] and ethyl cinnamate[13] were treated with **2** to furnish cyclopropanes **53** and **54**, respectively.



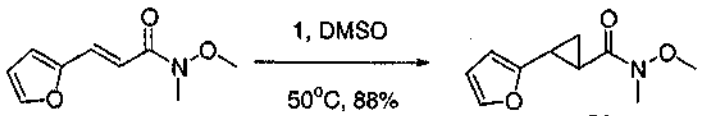


54

Dimethylsulfoxonium methylide (**1**) is the reagent of choice for the cyclopropanation of α,β-unsaturated carbonyl substrates. The reaction is generally carried out at more elevated temperatures in comparison to that of **2**, although exceptions exist. The method works for α,β-unsaturated ketones, esters and amides. Representative examples are found in transformations of 2(5*H*)-furanone **55** to cyclopropane **56**[31] and α,β-unsaturated Weinreb amide **57** to cyclopropane **58**.[32]

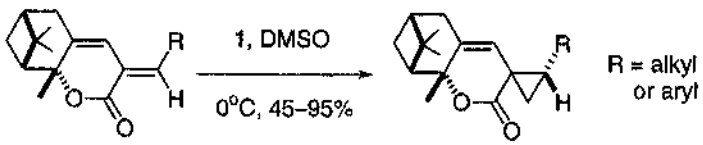


55 **56**

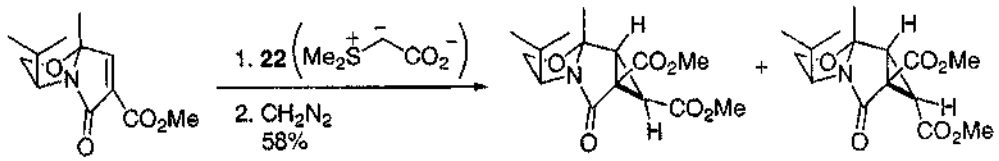


57 **58**

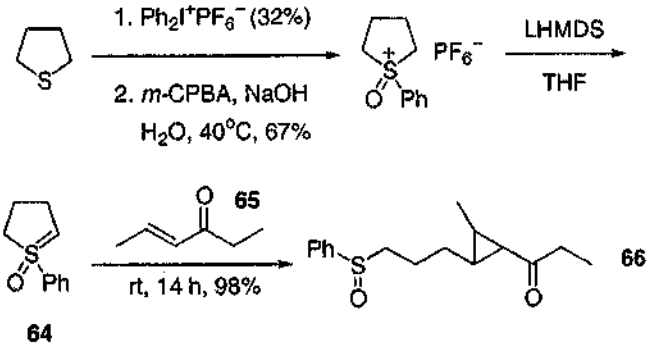
As in the case of epoxidation, asymmetric cyclopropanation can be accomplished through either substrate-controlled or reagent-controlled approaches. The former approach requires an inherent steric bias in the substrates that often exist in the form of chiral auxiliaries. Substrate **59**, derived from 1-hydroxy pinan-3-one, gave only diastereomer **60** when treated with **1**.[33] Ylide **1** attacked the less shielded face opposite to the *gem*-dimethyl group, and DMSO release with formation of the spirocyclic adduct occurred prior to bond rotation. With regard to chiral α,β-unsaturated bicyclic γ-lactam **61**, the cyclopropanation took place in a highly diasteroselective fashion using anion **22** (dimethylsulfuranylidene acetate), resulting in the *anti*-adduct **62** as the predominant product (**62** : **63** = 99:1).[34]



59 **60**

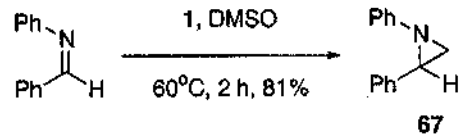


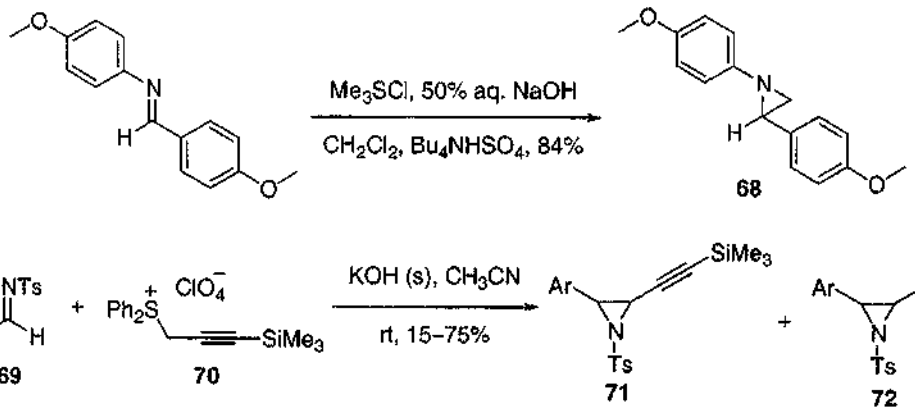
Reagent-controlled asymmetric cyclopropanation is relatively more difficult using sulfur ylides, although it has been done.[35] It is more often accomplished using chiral aminosulfoxonium ylides. Finally, more complex sulfur ylides (e.g. **64**) may result in more elaborate cyclopropane synthesis, as exemplified by the transformation **65** → **66**.[36]



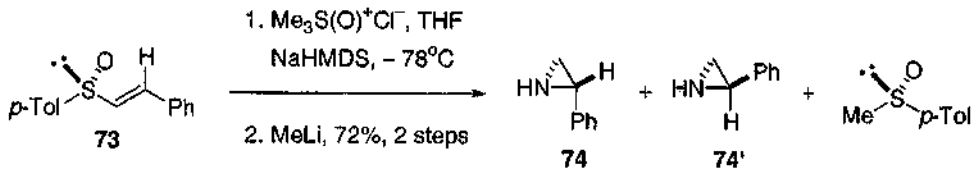
1.1.5.3 Aziridination

In the initial report by Corey and Chaykovsky, dimethylsulfonium methylide (**2**) reacted smoothly with benzalaniline to provide an entry to 1,2-diphenylaziridine **67**.[12] Franzen and Driesen reported the same reaction with 81% yield for **67**.[13] In another example, benzylidene-phenylamine reacted with **2** to produce 1-(*p*-methoxyphenyl)-2-phenylaziridine in 71% yield. The same reaction was also carried out using phase-transfer catalysis conditions.[37] Thus aziridine **68** could be generated consistently in good yield (80–94%). Recently, more complex sulfur ylides have been employed to make more functionalized aziridines, as depicted by the reaction between *N*-sulfonylimine **69** with diphenylsulfonium 3-(trimethylsilyl)propargylide (**70**) to afford aziridine **71**, along with desilylated aziridine **72**.[38]





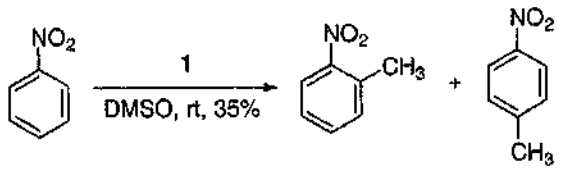
Asymmetric aziridination from imines using the Corey–Chaykovsky reaction is not well studied. The modest asymmetric induction is possibly due to the weak steric bias a chiral auxiliary exerted on the nucleophilic addition. Another possibility is that the bond rotation of the betaine intermediate may be so fast that it is difficult to achieve high stereoselectivity. Nowadays, asymmetric synthesis from imines is most frequently accomplished by addition of transition metal-catalyzed diazo reagents to the imines in the presence of chiral ligands. At any rate, examples of substrate-controlled aziridine formation using the Corey–Chaykovsky reaction can be found in the transformation **73** → **74** and **74′** where *de* was only 20%.[39] However, when the *p*-tolyl group was replaced by a *t*-butyl group, the *de* was as high as 90%.



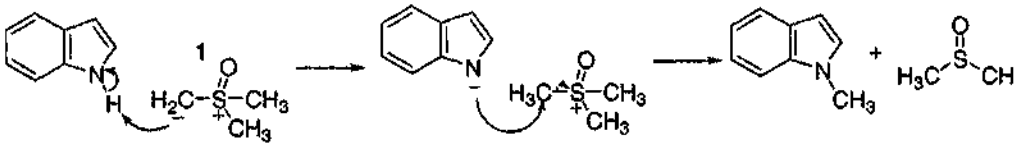
Reagent-controlled aziridination using camphor-derived chiral sulfide **47** has been reported with *ee* values of 84–98% for the *trans* isomer although the *trans : cis* ratio was mediocre.[40]

1.1.5.4 Methylation

C-Methylation products, *o*-nitrotoluene and *p*-nitrotoluene, were obtained when nitrobenzene was treated with dimethylsulfoxonium methylide (**1**).[41] The ratio for the *ortho* and *para*-methylation products was about 10–15 : 1 for the aromatic nucleophilic substitution reaction. The reaction appeared to proceed *via* the single-electron transfer (SET) mechanism according to ESR studies.

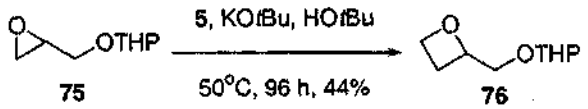


N-Methylation of the NH of heterocycles using **1** is also known as exemplified by the methylation of indole.[42] The interesting mechanism is delineated below. *O*-methylation of weak acids such as phenols, carboxylic acids and oximes as well as *S*-methylation such as *N*-phenylisorhodanine, certain thioketones, and dithiocarboxylic acids have also been reported.[43]

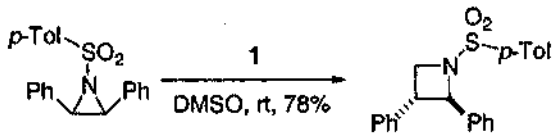


1.1.5.5 Heterocycle and carbocycle formation

Corey's ylide (**1**), as the methylene transfer reagent, has been utilized in ring expansion of epoxide **75** and arizidine **77** to provide the corresponding oxetane **76**[15] and azetidine **78**,[44] respectively.

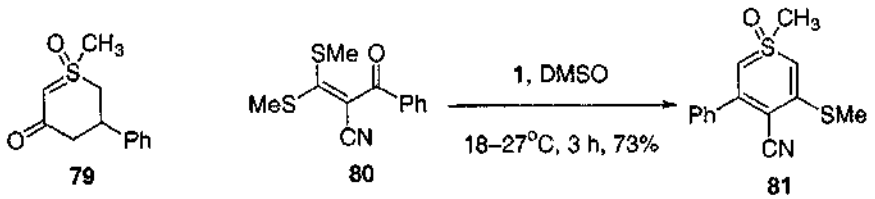


75 **76**

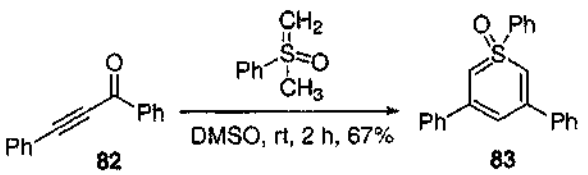


77 **78**

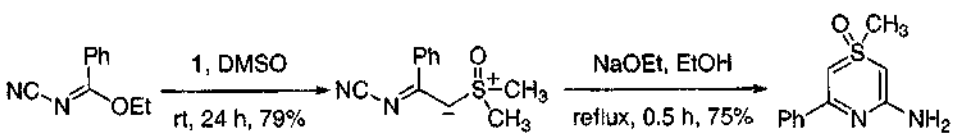
In Corey and Chaykovsky's initial investigation, a cyclic ylide **79** was observed from the reaction of ethyl cinnamate with ylide **1** in addition to 32% of cyclopropane **53**.[10] In a similar fashion, an intermolecular cycloaddition between 2-acyl-3,3-bis(methylthio)acrylnitrile **80** and **1** furnished 1-methylthiabenzene 1-oxide **81**.[45] Similar cases are found in transformations of ynone **82** to 1-arylthiabenzene 1-oxide **83**[46] and *N*-cyanoimidate **84** to adduct ylide **85**, which was subsequently transformed to 1-methyl-1λ^4-4-thiazin-1-oxide **86**.[47]



79 80 81

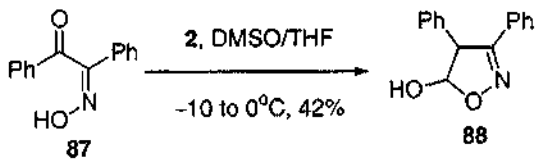


82 83



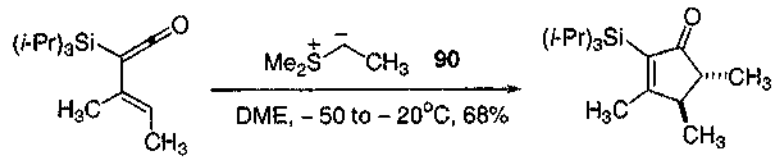
84 85 86

In a unique approach to the synthesis of isoxazole derivatives, α-isonitroso ketone **87** was treated with dimethylsulfonium methylide (**2**) to give 5-hydroxyisoxazoline **88**.[48] It was demonstrated that the reaction proceeded through an epoxyoxime intermediate.



87 88

In addition to the synthesis of heterocycles, the Corey–Chaykovsky reaction bestows an entry to carbocycles as well. The reaction of (trialkylsilyl)vinylketene **89** with substituted ylide **90**[49] led exclusively to *trans*-4,5-dimethyl cyclopentenone **91**.[50] The substituted ylide **90** here serves as a nucleophilic carbenoid reagent in the formal [4 +1] annulation reaction.

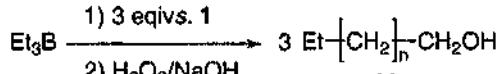


89 91

1.1.5.6 Polyhomologation

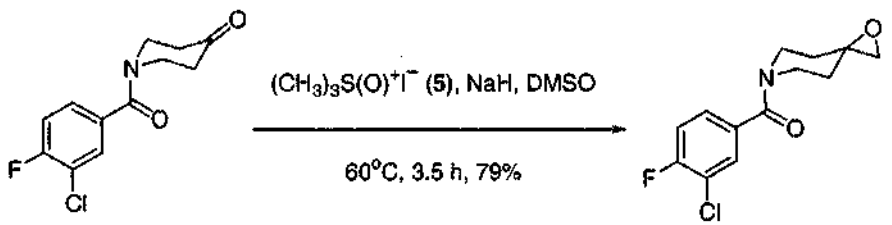
An ingenious application of Corey's ylide (**1**) was discovered by the Shea group in 1997.[51,52] Using trialkylboranes as initiator/catalyst and **1** as the monomer, a living

polymerization led to linear poly*methylene* polymers (as opposed to the common poly*ethylene* polymers). Controlling the initial ratio of ylide **1** and triethylborane leveraged control over molecular weight. Oxidative cleavage of the C–B bond under basic oxidation conditions produced perfectly linear polymethylene **92**. Furthermore, extension of this novel chemistry provided means to build many new polymethylene architectures such as star-shaped polymethylenes, ring expansion of cyclic and polycyclic organoboranes, as well as macrocyclic oligmers and polymers.



92

1.1.6 Experimental



93 **94**

***N*-(3-Chloro-4-fluorobenzoyl)-oxa-6-azaspiro[2,5]-octane** (94):[53]
A solution of dimethylsulfoxonium methylide (**1**) was prepared, under nitrogen, from sodium hydride (1.52 g of 60% despersion in mineral oil, 37.8 mmol) and trimethylsulfoxonium iodide (**5**, 8.32 g, 37.8 mmol) in anhydrous DMSO (20 mL). A solution of *N*-(3-chloro-4-fluorobenzoyl)-piperidine-4-one (**93**, 9.21 g, 36 mmol) in DMSO (20 mL) was added in 30 min and stirring was maintained at 60°C for 3.5 h. The cooled reaction mixture was poured into ice water and extracted with ethyl acetate. The combined organic layers were washed with water and brine and then dried and concentrated. The residue was purified by a short flash chromatography on silica gel, eluting with $CHCl_3$–EtOAc (9:1), to give 7.68 g of **94** (79%) as an oil which crystallized on standing: mp 75–77°C; ^{1}H NMR ($CDCl_3$) δ 1.50 (m, 2H), 1.92 (m, 2H), 2.74 (s, 2H), 3.87 (m, 1H), 4.19 (m, 1H), 7.18 (t, 1H), 7.32 (m, 1H), 7.51 (dd, 1H); IR (KBr, cm^{-1}) 1620.

1.1.7 References

1 [R] Okazaki, R.; Tokitoh, N. In *Encyclopedia of Reagents in Organic Synthesis;* Paquette, L. A., Ed.; Wiley: New York, **1995**, pp 2139–41.
2 [R] Ng, J. S.; Liu, C. In *Encyclopedia of Reagents in Organic Synthesis;* Paquette, L. A., Ed.; Wiley: New York, **1995**, pp 2159–65.
3 [R] Trost, B. M.; Melvin, L. S., Jr. *Sulfur Ylides;* Academic Press: New York, **1975**.
4 [R] Block, E. *Reactions of Organosulfur Compounds* Academic Press: New York, **1978**.
5 [R] Gololobov, Y. G.; Nesmeyanov, A. N. *Tetrahedron* **1987**, *43*, 2609.

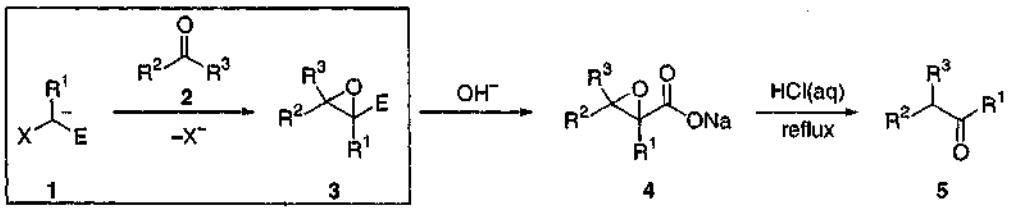
6 [R] Aubé, J. In *Comprehensive Organic Synthesis;* Trost, B. M.; Fleming, I., Ed.; Pergamon: Oxford, **1991**, vol. 1, pp 820–825.
7 [R] Li, A.-H.; Dai, L.-X.; Aggarwal, V. K. *Chem. Rev.* **1997**, *97*, 2341.
8 Corey, E. J.; Chaykovsky, M. *J. Am. Chem. Soc.* **1962**, *84*, 867.
9 Corey, E. J.; Chaykovsky, M. *J. Am. Chem. Soc.* **1962**, *84*, 3782.
10 Corey, E. J.; Chaykovsky, M. *Tetrahedron Lett.* **1963**, 169.
11 Corey, E. J.; Chaykovsky, M. *J. Am. Chem. Soc.* **1964**, *86*, 1640.
12 Corey, E. J.; Chaykovsky, M. *J. Am. Chem. Soc.* **1965**, *87*, 1353.
13 Franzen, V.; Driesen, H. E. *Chem. Ber.* **1963**, *96*, 1881.
14 Mash, E. A.; Gregg, T. M.; Baron, J. A. *J. Org. Chem.* **1997**, *62*, 8513.
15 Wicks, D. A.; Tirrell, D. A. *J. Polym. Sci., Part A: Polym. Chem.* **1990**, *28*, 573.
16 Merz, A.; Märkl, G. *Angew. Chem., Int. Ed. Engl.* **1973**, *12*, 845.
17 Fitzsimmons, B. J.; Fraser-Reid, B. *Tetrahedron* **1982**, *40*, 1279.
18 (a) [R] Johnson, C. R. *Aldrichimica Acta* **1985**, *18*, 3. (b) Johnson, C. R.; Haake, M.; Schroeck, C. *J. Am. Chem. Soc.* **1970**, *92*, 6594. (c) Johnson, C. R.; Janiga, E. R. *J. Am. Chem. Soc.* **1973**, *95*, 7692.
19 Rosenberger, M.; Jackson, W.; Saucy, G. *Helv. Chim. Acta* **1980**, *63*, 1665.
20 Corey, E. J.; Cheng, H.; Baker, C. H.; Matsuda, P. T.; Li, D.; Song, X. *J. Am. Chem. Soc.* **1997**, *119*, 1277.
21 Kulasegaram, S.; Kulawiec, R. J. *J. Org. Chem.* **1997**, *62*, 6547.
22 Cleij, M.; Archelas, A.; Furstoss, R. *J. Org. Chem.* **1999**, *64*, 5029.
23 Maltais, R.; Poirier, D. *Tetrahedron Lett.* **1998**, *39*, 4151.
24 Saito, T.; Suzuki, T.; Takeuchi, K.; Matsumoto, T.; Suzuki, K. *Tetrahedron Lett.* **1997**, *38*, 3755.
25 Mal, J.; Venkateswaran, R. V. *J. Org. Chem.* **1998**, *63*, 3855.
26 Ciufolini, M. A.; Zhu, S.; Deaton, M. V. *J. Org. Chem.* **1997**, *62*, 7806.
27 Furukawa, N.; Sugihara, Y.; Fujihara, H. *J. Org. Chem.* **1989**, *54*, 4222.
28 Saito, T.; Akiba, D.; Sakairi, M.; Kanazawa, S. *Tetrahedron Lett.* **2001**, *42*, 57.
29 Dickinson, R. P.; Bell, A. S.; Hitchcock, C. A.; Narayanawami, S.; Ray, S. J.; Richardson, K.; Troke, P. F. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 2031.
30 Fringuelli, R.; Schiaffella, F.; Bistoni, F.; Pitzurra, L.; Vecchiarelli, A. *Bioorg. Med. Chem.* **1998**, *6*, 103.
31 Janini, T. E.; Sampson, P. *J. Org. Chem.* **1997**, *62*, 5069.
32 Rodriques, K. E. *Tetrahedron Lett.* **1991**, *32*, 1275.
33 Calmes, M.; Daunis, J.; Escale, F. *Tetrahedron: Asymmetry* **1996**, *7*, 395.
34 (a) Groaning, M. D.; Meyers, A. I. *Tetrahedron Lett.* **1999**, *40*, 4639. (b) Romo, D.; Meyers, A. I. *J. Org. Chem.* **1992**, *57*, 6265.
35 Trost, B. M.; Hammen, R. F. *J. Am. Chem. Soc.* **1973**, *95*, 962.
36 (a) Akiyama, H.; Fujimoto, T.; Ohshima, K.; Hoshino, K.; Saito, Y.; Okamoto, A.; Yamamoto, I.; Kakehi, A.; Iriye, R. *Eur. J. Org. Chem.* **2001**, 2265. (b) Chandrasekhar, S.; Narasihmulu, Ch.; Jagadeshwar, V.; Venkatram, Reddy, K. *Tetrahedron Lett.* **2003**, *44*, 3629.
37 Tewari, R. S.; Awatsthi, A. K.; Awasthi, A. *Synthesis* **1983**, 330.
38 Li, A.-H.; Zhou, Y. G.; Dai, L.-X.; Hou, X.-L.; Xia, L.-J.; Lin, L. *J. Org. Chem.* **1998**, *63*, 4338.
39 García Ruano, J. L.; Fernádez, I.; Catalina, M.; Cruz, A. A. *Tetrahedron: Asymmetry* **1996**, *7*, 3407.
40 Saito, T.; Akiba, D.; Sakairi, M. *Tetrahedron Lett.* **2001**, *42*, 5451.
41 Traynelis, V. J.; McSweeney, J. V. *J. Org. Chem.* **1966**, *31*, 243.
42 Kunieda, T.; Witkop, B. *J. Org. Chem.* **1970**, *35*, 3981.
43 [R] Reference 5, pp 2615–2617.
44 Nadir, U. K.; Sharma, R. L.; Koul, V. K. *Tetrahedron* **1989**, *45*, 1851.
45 Rudorf, W.-D. *Synthesis* **1984**, 852.
46 Matsuyama, H.; Takeuchi, T.; Okutsu, Y. *Heterocycles* **1984**, *22*, 1523.
47 Ried, W.; Kuhn, D. *Liebigs Ann. Chem.* **1986**, 1648.
48 Bravo, P.; Ticozzi, C. *Gazz. Chim. Ital.* **1972**, *102*, 395.
49 Corey, E. J.; Jautelat, M. Oppolzer, W. *Tetrahedron Lett.* **1967**, 2325.
50 Loebach, J. L.; Bennett, D. M.; Danheiser, R. L. *J. Am. Chem. Soc.* **1998**, *120*, 9690.
51 Shea, K. J.; Walker, J. W.; Zhu, H.; Paz, M.; Greaves, J. *J. Am. Chem. Soc.* **1997**, *110*, 9049.
52 [R] Shea, K. J. *Chem. Eur. J.* **2000**, *6*, 1113.
53 Vacher, B.; Bonnaud, B. Funes, P.; *et al. J. Med. Chem.* **1999**, *42*, 1648.

Jie Jack Li

1.2 Darzens Glycidic Ester Condensation

1.2.1 Description

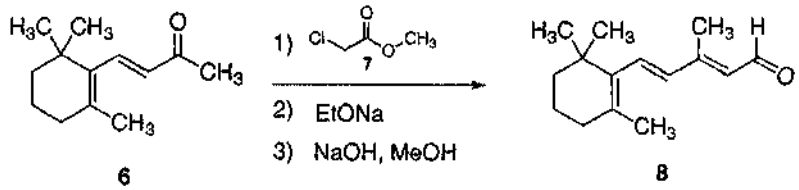
Darzens glycidic ester condensation[1] generally involves the condensation of an aldehyde or ketone **2** with the enolate of an α-halo ester **1** which leads to an α,β-epoxy ester (a glycidic ester) (**3**). Thus the reaction adds two carbons to the electrophile; however, the reaction has been primarily developed as a one-carbon homologation method. That is, subsequent to the condensation, the ester is saponified and decarboxylation ensues to give the corresponding aldehyde or ketone **5**.[2]

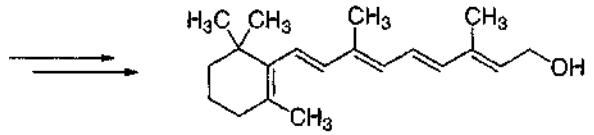


Various stabilized α-halo anions (diazo ketones, imines, nitriles, phosphonates, silicon, sulfones, etc.) have been employed in the reaction. Methods for the preparation of aziridines using the process have been examined, and asymmetric variants have been reported. Although hydroxide can often be used for generating the anion, a non-nucleophilic base (*t*-BuOK, LiHMDS, LDA) is generally used in the reaction to avoid S_N2 displacement of the electrophile. The halide of the nucleophilic component of the reaction is typically chlorine — stronger leaving groups (bromine and especially iodine) lead toward γ-keto esters (after saponification/decarboxylation is carried out), a result of intermolecular S_N2 displacement.[3] The diverse nature of the substrates and conditions that can be employed in the reaction precludes further discussion to the general nature of the reaction.[2]

1.2.2 Historical Perspective

Although glycidic esters were first prepared by Erlenmeyer in 1892, Darzens subsequently studied the reaction and demonstrated its usefulness as a synthetic method.[4] In a significant achievement in synthesis during the 1940s, the titled reaction process was used in the industrial reaction pathway to prepare vitamin A (**9**).[5] Thus methyl chloroacetate (**7**) and β-ionone (**6**) were treated with sodium ethylate to give the corresponding glycidic ester. Upon saponification and decarboxylation, thermodynamically favored trienal **8** is provided, which can be further elaborated to vitamin A.[2,5]

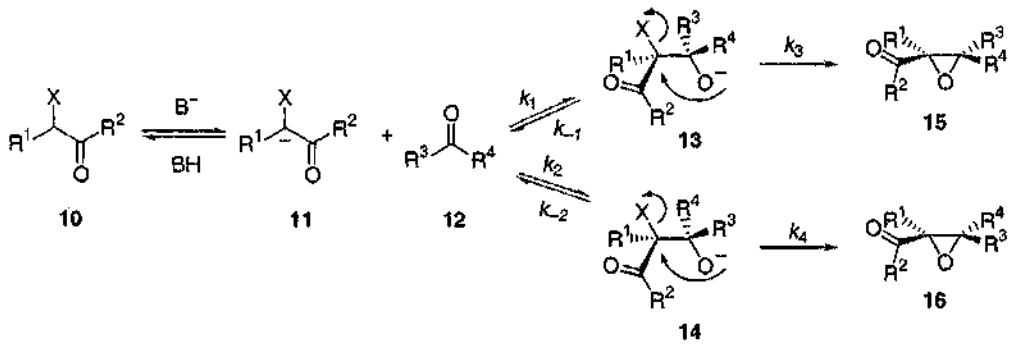




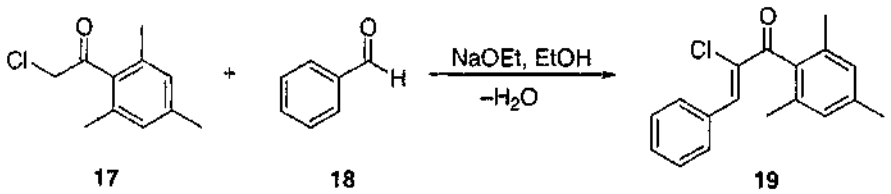
vitamin A (**9**)

1.2.3 Mechanism

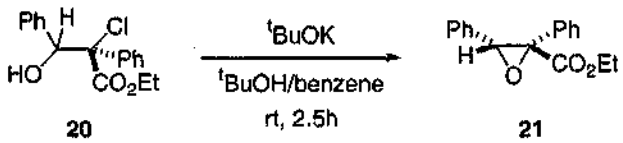
Several years ago, there was much debate concerning the mechanism of the Darzens condensation.[2,3] The debate concerned whether the reaction employed an enolate or a carbene intermediate. In recent years, significant evidence that supports the enolate mechanism has been obtained, wherein the stabilized carbanion (**11**) of the halide (**10**) is condensed with the electrophile (**12**) to give diastereomeric aldolate products (**13**,**14**), which subsequently cyclize via an internal S_N2 reaction to give the corresponding oxirane (**15** or **16**). The intermediate aldolates have been isolated for both α-fluoro- and α-chloroesters **10**.[2,3]



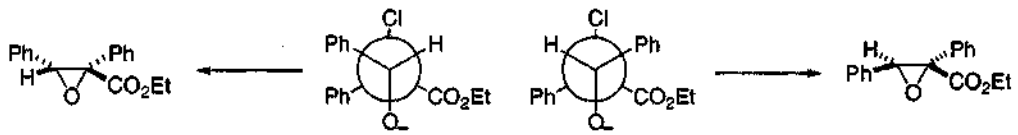
Furthermore, in analogy to the aldol reaction, α-chloro-α,β-unsaturated esters have been observed—likely the result of β-elimination of water from the intermediate halohydrin. For example, when benzaldehyde is condensed with the enolate of **17**, chloride **19** was obtained.[6]



The ratio of products **15** and **16** is dependent on the structures, base, and the solvent. The kinetics of the reaction is likewise dependant on the structures and conditions of the reaction. Thus addition or cyclization can be the rate-determining step. In a particularly noteworthy study by Zimmerman and Ahramjian,[7] it was reported that when both diastereomers of **20** were treated individually with potassium *t*-butoxide only *cis*-epoxy propionate **21** was isolated. It is postulated that the cyclization is the rate-limiting step. Thus, for these substrates, the retro-aldolization/aldolization step is reversible.[7]



20 **21**



21 **22a** **22b** **23**

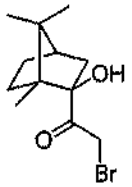
An explanation for the stereoselectivity of the reaction involves optimal overlap of the π-orbital of the carbonyl with the developing electron rich p-orbital on C2 during the S_N2 displacement of the chloride by the alkoxide (**24**). Thus, orbital overlap imposes conformational constraints in the transition state that leads to nonbonding interactions disfavoring transition state **25**.[7]

24 **25**

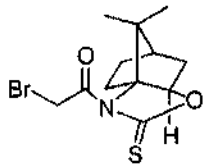
1.2.4 Variations and Improvements

In recent years, several modifications of the Darzens condensation have been reported. Similar to the aldol reaction, the majority of the work reported has been directed toward diastereo- and enantioselective processes. In fact, when the aldol reaction is highly stereoselective, or when the aldol product can be isolated, useful quantities of the required glycidic ester can be obtained. Recent reports have demonstrated that diastereomeric enolate components can provide stereoselectivity in the reaction: examples include the camphor-derived substrate **26**,[8] *in situ* generated α-bromo-*N*-

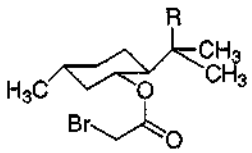
acetyloxazolidinethione **27**,[9] menthol and 8-phenylmenthol esters **28** and **29**.[10] It is noteworthy that Aggarwal recently showed that the camphor derived sulfonium salt **30** could be condensed with various aldehydes in good yields (79–93%), and up to 99% *ee*.[11]



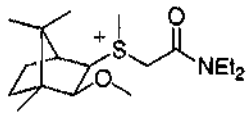
26



27

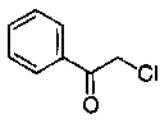


28 R = H
29 R = Ph



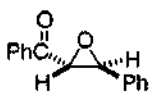
30

Interestingly, phase-transfer catalysts including crown ethers have been used to promote enantioselective variations of Darzens condensation. Tőke and coworkers showed that the novel 15-crown-5 catalyst derived from D-glucose **33** could promote the condensation between acetyl chloride **31** and benzaldehyde to give the epoxide in 49% yield and 71% *ee*.[12] A modified cinchoninium bromide was shown to act as an effective phase transfer catalyst for the transformation as well.[13]

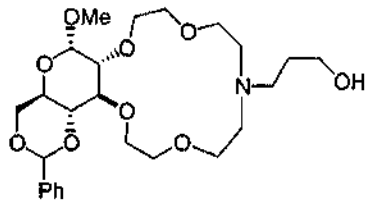


31

33 (5%), PhCHO,
NaOH(aq, 30%),
toluene, –20°C



32
49% yield, 71% ee

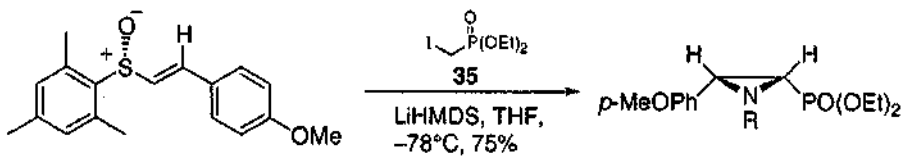


33

In a separate report, preparation of the lithium enolate of **31** in the presence of indium trichloride and benzaldehyde provided a 77% yield of **32** with complete *trans* selectivity; however, sequential addition of indium trichloride and benzaldehyde provided Barbier-type products.[14] Organotin enolates have also been used in a Darzens-type reaction.[15]

1.2.5 Synthetic Utility and Applications

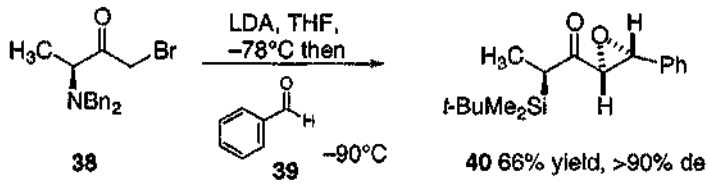
The Darzens condensation reaction has been used with a wide variety of enolate equivalents that have been covered elsewhere.[2] A recent application of this important reaction was applied toward the asymmetric synthesis of aziridine phosphonates by Davis and coworkers.[16] In this application, a THF solution of sulfinimine **34** (0.37 mmol, >98% *ee*) and iodophosphonate **35** (0.74 mmol) was treated with LiHMDS (0.74 mmol) at –78 °C to give aziridine **36** in 75% yield. Treatment of **36** with MeMgBr removed the sulfinyl group to provide aziridine **37** in 72% yield.[16a]



34

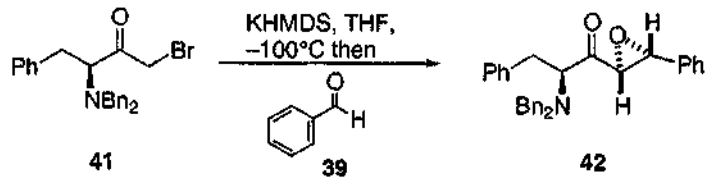
36 R = SOMes
37 R = H

Darzens reaction can be used to efficiently complete the stereoselective synthesis of α′-substituted epoxy ketones. As an example, Enders and Hett reported a technique for the asymmetric synthesis of α′-silylated α,β-epoxy ketones. Thus, optically active α′-silyl α-bromoketone **38** was treated with LDA followed by the addition of benzaldehyde to give α′-silyl epoxyketone **40** in 66% yield with good *de*.[17]



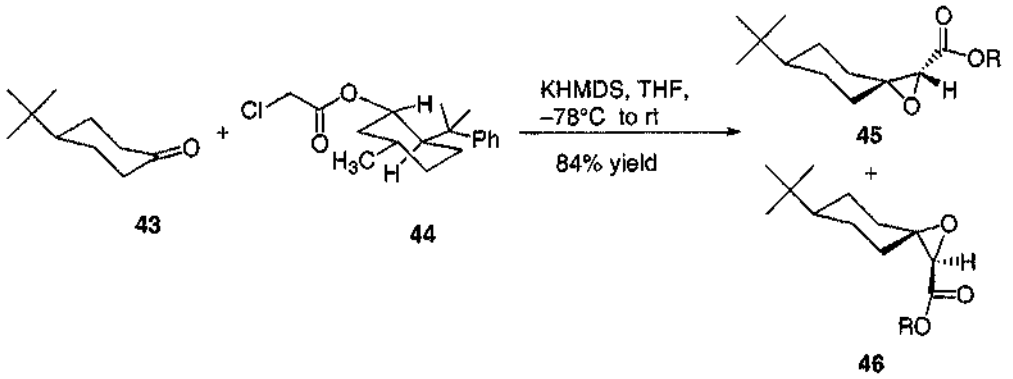
38 39 40 66% yield, >90% de

In a separate report, the Darzens reaction was recently used by Barluenga, Concellón, and coworkers for the preparation of enantiopure α′-amino α,β-epoxy ketones. Accordingly, the Z enolate of α′-amino α-bromo ketone **41** was generated with KHMDS at –100°C. Benzaldehyde was added, and *trans* epoxyketone **42** was isolated in 87% yield and >95% de.[18]

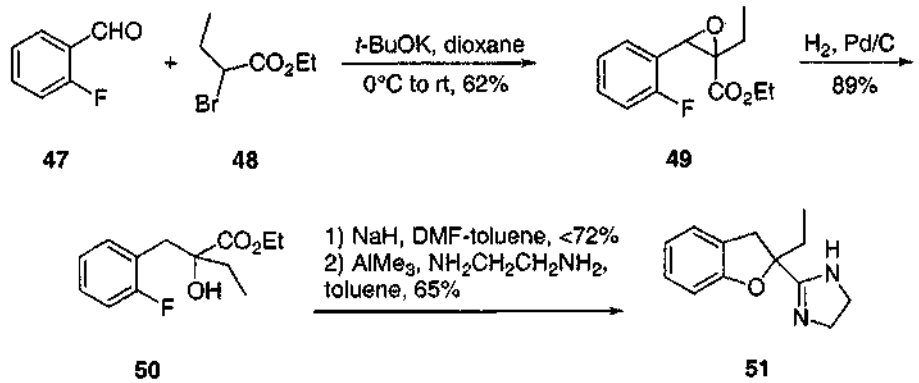


41 39 42

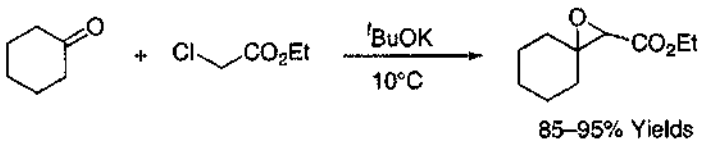
Recently, Darzens reaction was investigated for its synthetic applicability to the condensation of substituted cyclohexanes and optically active α-chloroesters (derived from (–)-phenylmenthol). In this report, it was found that reaction between chloroester **44** and cyclohexanone **43** provided an 84% yield with 78:22 selectivity for the axial glycidic ester **45** over equatorial glycidic ester **46** both having the *R* configuration at the epoxide stereocenter.[19]



Of interest is a recent report of a rapid synthesis of efaroxin (**51**), a potent, selective α_2-adrenoceptor antagonist, using Darzens Reaction. Accordingly, α-bromoester **48** was condensed with aldehyde **47**. The glycidic ester (**49**) was then hydrogenated to reduce the more labile epoxide bond to give alcohol **50**. Subsequent standard transformations subsequently lead to a completed 4-step synthesis of efaroxin.[20]



1.2.6 Experimental[21]



A dry 500-ml round-bottomed three-necked flask fitted with a stirrer, internal thermometer, and a pressure-equalized dropping funnel is placed under nitrogen and the flask is charged with 0.148 mole of freshly distilled cyclohexanone and 0.148 mole of freshly distilled ethyl chloroacetate. A solution of 6.0 g of potassium and 125 mL of dry *tert*-butyl alcohol is introduced into the dropping funnel, and the system is exhausted and

filled with nitrogen. The flask is cooled with an ice bath, stirring is commenced, and the solution of potassium *tert*-butoxide is added from the dropping funnel over a period of about 1.5 hours, the temperature of the reaction mixture being maintained at 10–15°C. After the addition is complete, the mixture is stirred for an additional 1–1.5 h at about 10°C. Most of the *tert*-butyl alcohol is removed by distillation from the reaction flask at reduced pressure (water aspirator). The oily residue is taken up in ether. The ether solution is washed with water, then with saturated aqueous sodium chloride solution, and is finally dried over anhydrous sodium sulfate. The residue obtained on evaporation of the ether is distilled through a 6-in. Vigreux column to give 83–95% yield of colorless glycidic ester.[21a]

1.2.7 References

1. (a) Darzens, G. *Compt. Rend.* **1904**, *139*, 1214. (b) Darzens, G. *Compt. Rend.* **1906**, *141*, 214.
2. [R] Rosen, T. In *Comprehensive Organic Synthesis*; Trost, B. M.; Fleming, I., Ed.; Pergamon: Oxford, **1991**, vol. 2, pp 409–439.
3. [R] Ballester, M. *Chem. Rev.* **1955**, *55*, 283–300.
4. [R] Newman, M. S.; Magerlein, B. J. *Org. React.* **1949**, *5*, 413–441.
5. Isler, O.; Huber, W.; Ronco, A; Kofler, M. *Helv. Chim. Acta*, **1947**, *30*, 1911–1927.
6. Jörlander, H. *Ber.* **1917**, *50*, 1457–65.
7. Zimmerman, H. E.; Ahramjian, L. *J. Amer. Chem. Soc.* **1960**, *82*, 5459–5466.
8. Palomo, C.; oirbide, M; Sharma, A. K; González,-Rego, M. C.; Linden, A; Garcia, J. M.; González, A. *J. Org. Chem.* **2000**, *65*, 9007–12.
9. Wang, Y.-C.; Li, C.-L.; Tseng, H.-L.; Chuang, S.-C.; Yan, T.-H. *Tetrahedron: Asym.* **1999**, *10*, 3249–51.
10. Takagi, R.; Kimura, J.; Shinohara, Y.; Ohba, Y.; Takezono, K.; Hiraga, Y.; Kojimo, S.; Ohkata, K. *J. Chem. Soc., Perkin Trans. 1* **1998**, 689–98.
11. Aggarwal, V. K.; Hynd, G.; Picoul, W.; Vasse, J.-L. *J. Amer. Chem. Soc.* **2002**, *124*, 9964–9965.
12. (a) Bakó, P.; Czinege, E.; Bakó, T.; Czugler, M.; Toke, L. *Tetrahedron: Asym.* **1999**, *10*, 4539–51. (b) Bakó, P.; Vízvárdi, K.; Toppet, S.; Van der Eycken, E.; Hoornaert, G. J.; Tőke, L. *Tetrahedron* **1998**, *54*, 14975–88.
13. Arai, S.; Shirai, Y.; Ishida, T.; Shioiri, T. *Tetrahedron* **1999**, *55*, 6375–86. (b) Arai, S.; Shioiri, T. *Tett. Lett.* **1998**, *39*, 2145–8. (c) Tanaka, K.; Shiraishi, R. *Green Chemistry* **2001**, *3*, 135–6. (d) Arai, S.; Shoiri, T. *Tetrahedron* **2002**, *58*, 1407–13. (e) Arai, S.; Suzuki, Y.; Tokumaru, K.; Shioiri, T.; *Tetrahedron Lett.* **2002**, *43*, 833–6.
14. Hirashita, T.; Kinoshita, K.; Yamamura, H.; Kawal, M.; Arai, S. *J. Chem. Soc., Perkin Trans. 1*, **2000**, 825–828. The authors note that the lithium enolate decomposes in the absence of $InCl_3$.
15. Shimbata, I.; Yamasaki, H.; Baba, A.; Matsuda, H. *J. Org. Chem.* **1992**, *57*, 6909–6914.
16. (a) Davis, F. A.; Ramachandar, T.; Wu, Y. *J. Org. Chem.* **2003**, *68*, 6894–8. (b) Davis, F. A.; Liu, H.; Reddy, G.V. *Tetrahedron Lett.* **1996**, *37*, 5473–76. (c) Davis, F. A.; Liu, H.; Zhou P.; Fang, T.; Reddy, G. V.; Zhang Y. *J. Org. Chem.* **1999**, *64*, 7559–67.
17. Enders, D.; Hett; R. *Synlett* **1998**, 961–2.
18. Barluenga, J.; Baragatña, B.; Concellón, J.M.; Piñera-Nicolás, A.; Díaz, M. R.; García-Granda, S. *J. Org. Chem.* **1999**, *64*, 5048–52.
19. Shinohara, Y.; Ohba, Y.; Takagi, R.; Kojima, S.; Ohkata, K. *Heterocycles* **2001**, *55*, 9–12.
20. Mayer, P.; Brunel, P.; Imbert, T. *Biog. & Med. Chem. Lett*, **1999**, *9*, 3021.
21. Several excellent synthetic procedures have been published: (a) Hunt, R. H.; Chinn, L. J.; Johnson, W. S. *Org. Syn. Coll.* **1963**, *4*, 459. (b) Burness, D. M. *Org. Syn. Coll.* **1963**, *4*, 649–652 (c) (See reference 4) (d) Allen, C. F. H.; VanAllan, J. *Org. Syn. Coll.* **1955**, *3*, 459.

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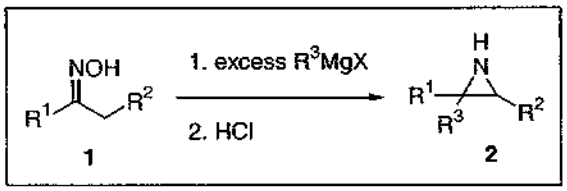
1.3 Hoch–Campbell Aziridine Synthesis

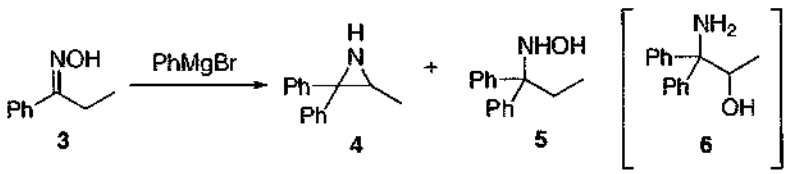
1.3.1 Description

The Hoch–Campbell aziridine synthesis entails treatment of ketoximes with excess Grignard reagents and subsequent hydrolysis of the organometallic complex.[1–11]



1.3.2 Historical Perspective

In 1934, French chemist Hoch reported that the action of phenylmagnesium bromide on the oxime of propiophenone (**3**) at elevated temperature gave two products.[5–7] One was aziridine **4** and the other was erroneously assigned as hydroxylamine **5**. In the subsequent years (1939 onward), Campbell at the University of Notre Dame determined that the purported hydroxylamine **5** was actually β-hydroxylamine **6**.[8–11] The scope of the Grignard reagents was extended to both aryl and aliphatic Grignard reagents.

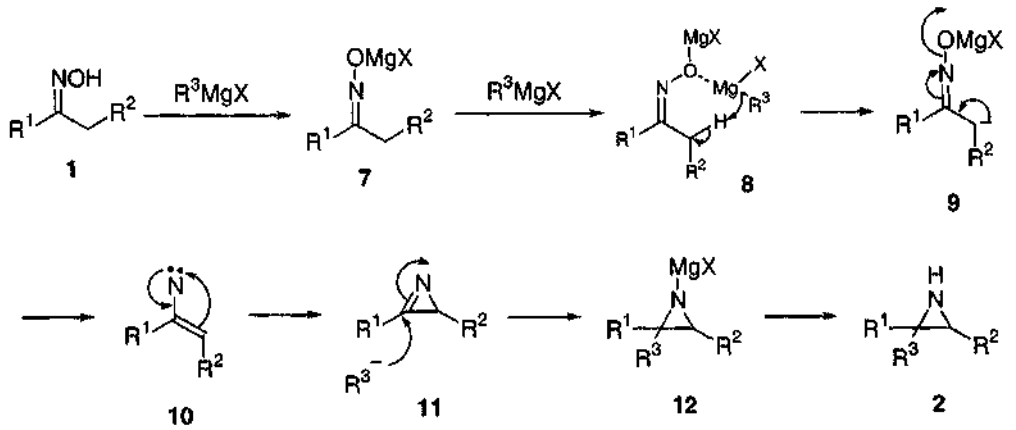


1.3.3 Mechanism

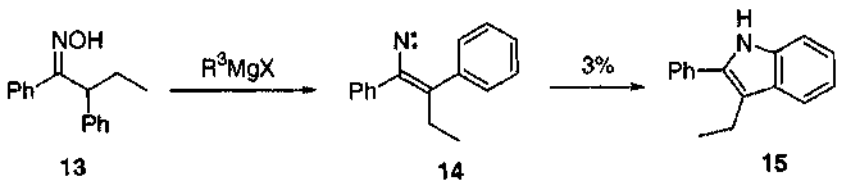
The mechanism of the Hoch–Campbell aziridine synthesis was a contentious issue for quite some time. The incorporation of a double bond into an already highly strained three-membered ring was initially mistakenly thought to preclude the very existence of the 1-azirine system. However, it was established that when ketoximes were treated with Grignard reagents, a rearrangement took place that involved the migration of the nitrogen atom from one carbon to another.[8] At the early stage of the Hoch–Campbell aziridine synthesis, the general mode may be reminiscent of the Neber reaction mechanism.[12] In 1963, Eguchi and Ishii carried out a series of experiments that supported a plausible mechanism that involving an azirine intermediate.[13] In the 1970s, the Laurent group made great strides in deciphering the mechanism of the Hoch–Campbell reaction.[14–17] Their results are summarized herein.

When ketoxime **1** is treated with the Grignard reagent, the first action is abstraction of the oxime proton to give **7**, which complexes with another equivalent of Grignard reagent to form **8**. Intramolecular deprotonation of **8** then gives rise to di-anion **9**, which extrudes OMgX anion to establish vinyl nitrene **10**. Cyclization of vinyl nitrene **10** delivers the key intermediate azirine **11**. Addition of another equivalent of Grignard

reagent to azirine **11** subsequently affords aziridine magnesium halide **9**, which upon acidic workup gives rise to aziridine **2**.

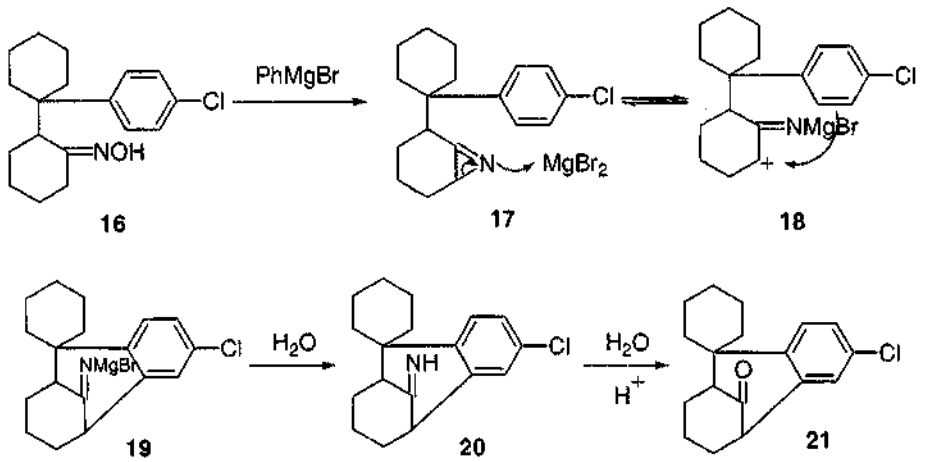


The aforementioned mechanism is supported by the following experimental data. When oxime **13** was treated with Grignard reagent, 3% of the indole **15** was isolated, indicating the possible existence of nitrene intermediate **14**.[16] A 2-phenylazirine intermediate, on the other hand, has been isolated and characterized from the reaction under carefully controlled conditions (adding Grignard reagent to the oxime in toluene).[17]



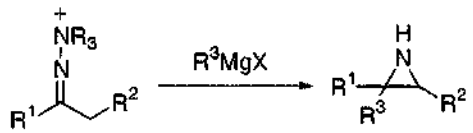
1.3.4 Variations and Improvements

An "intramolecular trapping" variant of the Hoch–Campbell aziridine synthesis was reported by Taguchi *et al.*[18–21] When 2-(1-*p*-chlorophenylcyclohexyl)cyclohexanone (**16**) was treated with phenylmagnesium bromide, the resulting azirine **17** did not undergo the usual intermolecular nucleophilic attack of the second equivalent of phenylmagnesium bromide. Instead, due to the proximity of the benzene ring as a potential nucleophile, the intramolecular ring closure of the intermediate was overwhelmingly favored as compared to the normal Hoch-Campbell reaction, resulting in predominantly the 1-benzobicyclononenone **19**. Hydrolysis of iminylmagnesium bromide **19** then gave imine **20**, which was subsequently hydrolyzed to ketone **21** under acidic conditions.



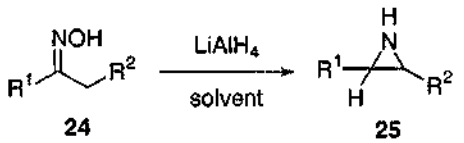
16 17 18 19 20 21

The second variation and improvement involves the use of $N–NR_3^+$ moiety, which in some cases gave better yields than the corresponding ketoxime analogs.[22–24]



22 23

The third variation of the Hoch–Campbell reaction is the replacement of the Grignard reagents with $LiAlH_4$. Evidently, the R^3 would be hydride in this case.[25] The mechanism is strikingly similar to that of the Hoch–Campbell reaction except the azirine is attacked by hydride rather than the Grignard reagent.



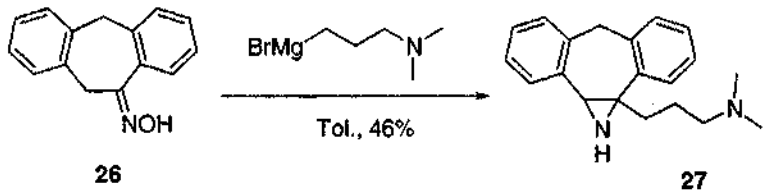
24 25

1.3.5 Synthetic Utility

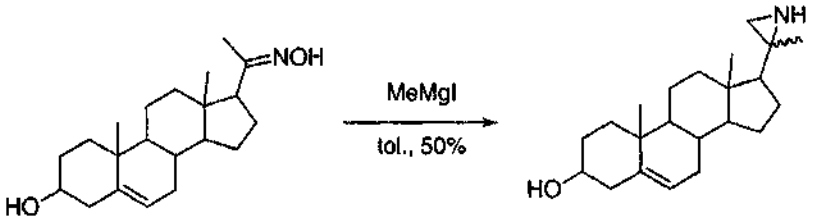
1.3.5.1 Simple ketoximes

Oxime **26** was prepared from 5,11-dihydro-dibenzo[a,d]cyclohepten-10-one. The Hoch–Campbell reaction of **26** with 3-dimethylaminopropylmagnesium bromide produced aziridine **27** in 46% yield after acidic workup.[26] Extension of the Hoch–Campbell reaction to steroids has also been reported.[27] Thus, treatment of 3β-hydroxy-5-pregnen-20-one oxime (**28**) with methylmagnesium iodide furnished a mixture of diastereomers, 20α/20β,21-imino-20-methyl-5-pregnen-3β-ol (**29**) in a 50% combined yield and a 3:1 ratio. On the other hand, homo-adamantan-4-one oxime (**30**) was transformed to homo-adamantano[4,5-b]-2′-ethylaziridine (**31**) in 76% yield upon the action of

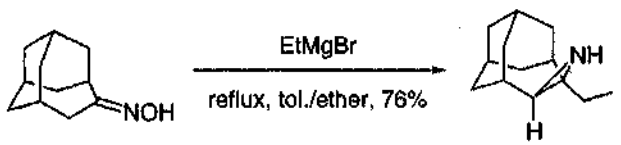
ethylmagnesium bromide.[28] However, the reactions of methylmagnesium iodide and phenylmagnesium bromide gave the corresponding aziridines in only 21% and 22% yield, respectively.



26 27

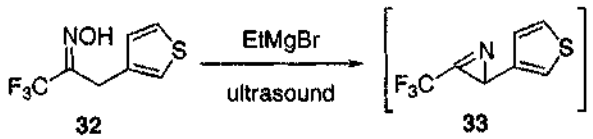


28 29



30 31

Secondary aziridines bearing a trifluoromethyl group were prepared *via* the Hoch–Campbell reaction of Grignard reagents and oximes bearing a trifluoromethyl substituent.[29] One exception was found for the use of allylmagnesium bromide, which gave homoallylic hydroxylamines.[30] Another exception was found for ethylmagnesium bromide where it served exclusively as a reducing agent.[29] Initial reaction of oxime **32** with ethylmagnesium bromide gave azirine **33**. However, the course of reaction was deviated from the normal Hoch–Campbell reaction since single electron transfer (SET) took place and led to radical anion **34**, which was converted to the reduced aziridine **35** upon workup.



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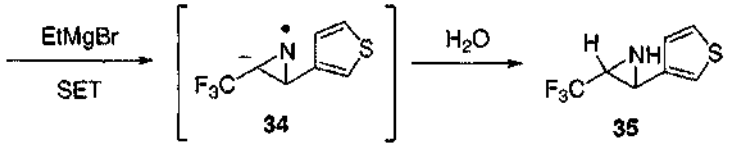
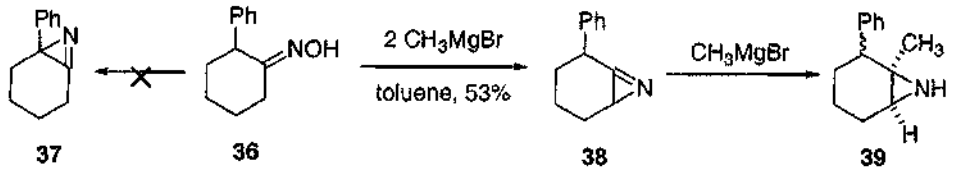
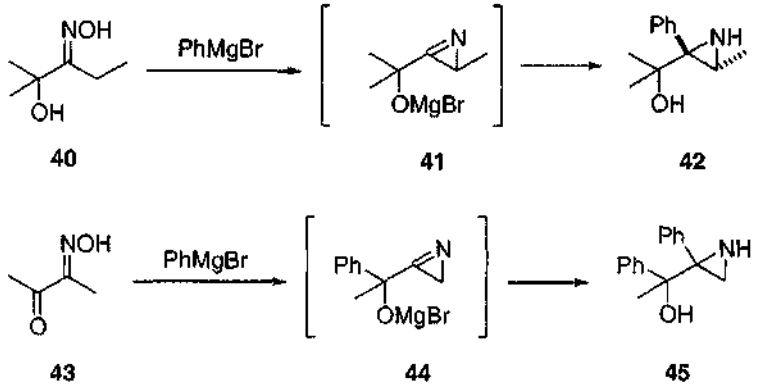


When both α-positions of the oxime possess active hydrogen, the regiochemistry of the Hoch–Campbell reaction prefers the side with more available hydrogens—indicating the process is kinetically controlled.[31] In case of oxime **36**, azirine **37** was not formed.[32] Instead, azirine **38** was obtained exclusively. Addition of the third equivalent of the Grignard reagent delivered aziridine **39** as a mixture of two diastereomers.

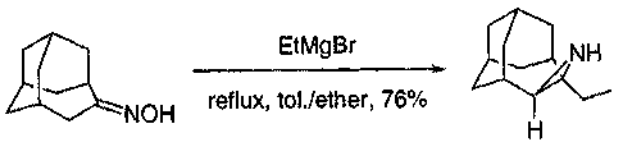


1.3.5.2 α-Hydroxy and α-keto ketoximes

The Hoch–Campbell reaction of α-hydroxy ketoximes do not alter the course of the reaction although deprotonation probably took place concurrently for both the alcohol and the oxime. Treatment of oxime **40** afforded aziridine **42** in 30%, presumably *via* the intermediacy of azirine **41**.[33] α-Keto ketoximes would behave similarly to the α-hydroxy ketoximes in the Hoch–Campbell reaction after addition of the first equivalent of the Grignard reagent to the ketone.[34, 35] Therefore, the reaction between α-keto ketoxime **43** and phenylmagnesium bromide gave aziridine **45** in 41% yield, presumably *via* the intermediacy of azirine **44**.



1.3.6 Experimental



30 **31**

Homo-adamantano[4,5-b]-2′-ethylaziridine (31)[28]

To a stirred solution of ethylmagnesium bromide (6.0 mmol) in ether (5 mL) and toluene (5 mL) was added homo-adamantan-4-one oxime (**30**, 2.0 mmol) in toluene (10 mL) at 100–105°C. The mixture was kept at the same temperature for 3 h. The cooled mixture was poured onto an ice-ammonium chloride mixture and the organic layer was separated and the water layer was extracted with ether (2 × 10 mL). The combined organic layer and extracts were dried (Na_2SO_4). Removal of the solvent under reduced pressure at 40°C gave crude product which was purified on a silica gel column eluting with CH_2Cl_2–MeOH to afford homo-adamantano[4,5-b]-2′-ethylaziridine (**31**) in 76% yield. The aziridine had a foul odor peculiar to aziridines. mp = 74–75°C.

1.3.7 References

1. [R] Freeman, J. P. *Chem. Rev.* **1973**, *73*, 283.
2. [R] Dermer, O. C.; Ham, G. E. *Ethyleneimine and Other Aziridines*, Academic Press: New York, **1969**, pp65–68.
3. [R] Deyrup, J. A. In *Small Ring Heterocycles, Part 1, Aziridines, Azirines, Thiiranes, Thiirenes* Hassner, A., ed.; John Wiley & Sons: New York, **1983**, Chapter 1, pp1–214.
4. (a) [R] Kotera, K.; Kitahonoki, K. *Org. Prep. Proced. Int.* **1952**, *1*, 305. (b) [R] Tanner, D. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 599.
5. Hoch, J. *Compt. Rend. Acad. Sci.* **1934**, *198*, 1865.
6. Hoch, J. *Compt. Rend. Acad. Sci.* **1936**, *203*, 799.
7. Hoch, J. *Compt. Rend. Acad. Sci.* **1937**, *204*, 358.
8. Campbell, K. N.; McKenna, J. F. *J. Org. Chem.* **1939**, *4*, 198.
9. Campbell, K. N.; Campbell, B. K.; Chaput, E. P. *J. Org. Chem.* **1943**, *8*, 99.
10. Campbell, K. N.; Campbell, B. K.; McKenna, J. F.; Chaput, E. P. *J. Org. Chem.* **1943**, *8*, 103.
11. Campbell, K. N.; Campbell, B. K.; Hess, L. G.; Schaffner, I. J. *J. Org. Chem.* **1944**, *9*, 184.
12. [R] O'Brien, C. *Chem. Rev.* **1964**, *64*, 81.
13. (a) Eguchi, S.; Ishii, Y. *Bull. Chem. Soc. Jpn.* **1963**, *36*, 1434. (b) Ishii, Y.; Eguchi, S.; Hironaka, T. *Kogyo Kagaku Zasshi* **1965**, *68*, 293.
14. Alvernhe, G.; Laurent, A. *Bull. Soc. Chim. Fr.* **1970**, 3003.
15. Chaabouni, R.; Laurent, A. *Bull. Soc. Chim. Fr.* **1973**, 2680.
16. Bartnik, R.; Laurent, A. *Bull. Soc. Chim. Fr.* **1975**, 173.
17. Alvernhe, G.; Laurent, A. *J. Chem. Res. (S)* **1978**, 28.
18. Miyano, K.; Taguchi, T. *Chem. Pharm. Bull.* **1970**, *18*, 1806.
19. Imai, K.; Kawazoe, Y.; Taguchi, T. *Yakugaku Zasshi* **1974**, *94*, 452.
20. Imai, K.; Kawazoe, Y.; Taguchi, T. *Chem. Pharm. Bull.* **1976**, *24*, 1083.
21. Takehisa, E. Y.; Kawazoe, Y; Taguchi, T. *Chem. Pharm. Bull.* **1976**, *24*, 1691.
22. Chaabouni, R.; Laurent, A. *Synthesis* **1975**, 464.
23. (a) Diab, Y.; Laurent, A.; Mison, P. *Bull. Soc. Chim. Fr.* **1974**, 2202. (b) Alvernhe, G.; Arsényiadis, S.; Chaabouni, R.; Laurent, A. *Tetrahedron Lett.* **1975**, *18*, 355.
24. Arsényiadis, S.; Laurent, A.; Mison, P. *Bull. Soc. Chim. Fr.* **1980**, II-246.

25. (a) Kotera, K.; Miyazaki, S.; Takahashi, H.; Okada, T.; Kitahonoki, K. *Tetrahedron* **1968**, *24*, 3681. (b) Kotera, K.; Miyazaki, S. *Tetrahedron* **1968**, *24*, 5677.
26. Seidlová, V.; Protiva, M. *Collect. Czech. Chem. Commun.* **1967**, *32*, 1747.
27. Tzikas, A.; Tamm, C.; Boller, A.; Fürst, A. *Helv. Chim. Acta* **1976**, *59*, 1850.
28. Sasaki, T.; Eguchi, S.; Hattori, S. *Heterocycles* **1978**, *11*, 235.
29. Quinze, K.; Laurent, A.; Mison, P. *J. Fluorine Chem.* **1989**, *44*, 211.
30. Felix, C.; Laurent, A.; Lesniak, S.; Mison, P. *J. Chem. Res. (S)* **1991**, 32.
31. Alvernhe, G.; Laurent, A. *Tetrahedron Lett.* **1971**, *22*, 1913.
32. Chaabouni, R.; Laurent, A.; Mison, P. *Tetrahedron Lett.* **1975**, *16*, 1343.
33. Laurent, A.; Marsura, A.; Pierre, J.-L. *J. Heterocycl. Chem.* **1980**, *17*, 1009.
34. Bartnik, R.; Laurent, A. *Tetrahedron Lett.* **1974**, *17*, 3869.
35. Bartnik, R.; Diab, Y.; Laurent, A. *Tetrahedron* **1977**, *32*, 1279.

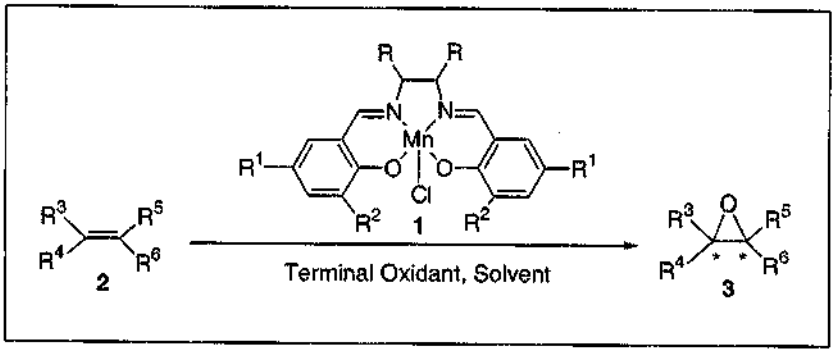
Jie Jack Li

1.4 Jacobsen–Katsuki Epoxidation

1.4.1 Description

The Jacobsen–Katsuki epoxidation reaction is an efficient and highly selective method for the preparation of a wide variety of structurally and electronically diverse chiral epoxides from olefins.[1] The reaction involves the use of a catalytic amount of a chiral Mn(III)salen complex **1** (salen refers to ligands composed of the *N,N'*-ethylenebis(salicylideneaminato) core), a stoichiometric amount of a terminal oxidant, and the substrate olefin **2** in the appropriate solvent (Scheme 1.4.1). The reaction protocol is straightforward and does not require any special handling techniques.

Scheme 1.4.1



To date, a wide variety of structurally different chiral Mn(III)salen complexes have been prepared, of which only a handful have emerged as synthetically useful catalysts. By far the most widely used Mn(III)salen catalyst is the commercially available Jacobsen catalyst wherein R= $-C_4H_8-$ and $R^1 = R^2 = t$-Bu (Scheme 1.4.1).[2] In contrast, a wide variety of terminal oxidants have been successfully employed. Depending on the terminal oxidant, epoxidation reactions can be performed from –78°C to room temperature. A broad range of olefins undergo epoxidation with good enantioselectivity including terminal, *cis*-disubstituted, *trans*-disubstituted, tri-substituted, and tetra-substituted olefins. However, except for a few isolated examples, the olefin must be conjugated to an aromatic group, an alkyne, or an alkene in order to obtain good stereoinduction. Additives such as pyridine *N*-oxides have been shown to exhibit a profound and often beneficial effect on enantioselectivities, *cis/trans* selectivities in the epoxidation of disubstituted olefins, and catalyst lifetime.

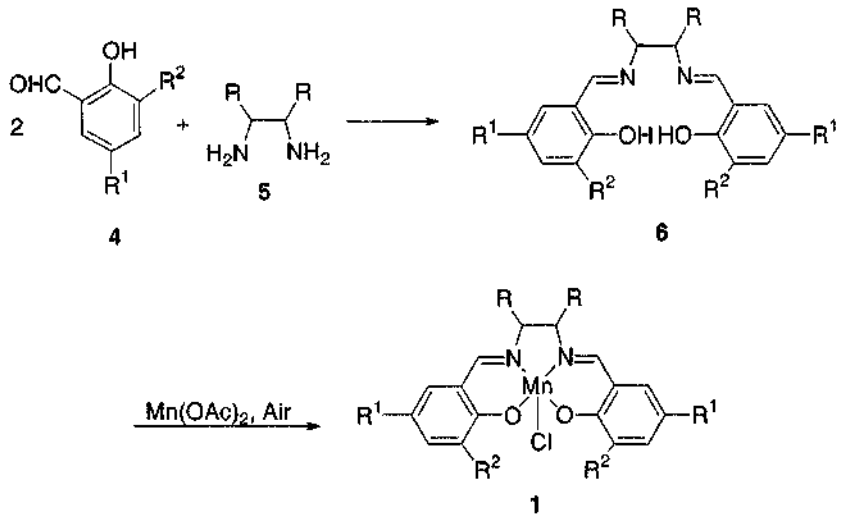
1.4.2 Historical Perspective

In 1990, Jacobsen and subsequently Katsuki independently communicated that chiral Mn(III)salen complexes are effective catalysts for the enantioselective epoxidation of unfunctionalized olefins.[3] For the first time, high enantioselectivities were attainable for the epoxidation of unfunctionalized olefins using a readily available and inexpensive chiral catalyst. In addition, the reaction was one of the first transition metal-catalyzed

tranformations that possessed a broad substrate scope and provided epoxidation products in high *ee* without requiring pre-coordination of the substrate to the active catalyst.

Jacobsen and Katsuki continued independently to develop and improve the epoxidation reaction by expanding the substrate scope, increasing catalyst efficiency, and developing a better understanding of the mechanism of reaction. Catalyst design was an integral part of the development of the epoxidation reaction, and was possible only because the Mn(III)salen catalyst can be readily prepared.[4,5] The synthesis of the catalyst can be accomplished in two steps from a salicylaldehyde **4** and a chiral diamine **5** (Scheme 1.4.2). The short modular synthesis of the catalyst provided the opportunity for systematically studying the effect of steric and electronic properties of the various substituents on the salen ligand **6** on enantioselectivity. This attribute rendered the identification of a highly selective and general catalyst practicable. The most commonly used catalyst, the Jacobsen catalyst, is produced on kilogram scale and has been employed on multi-kilogram scale in the pharmaceutical industry.[6]

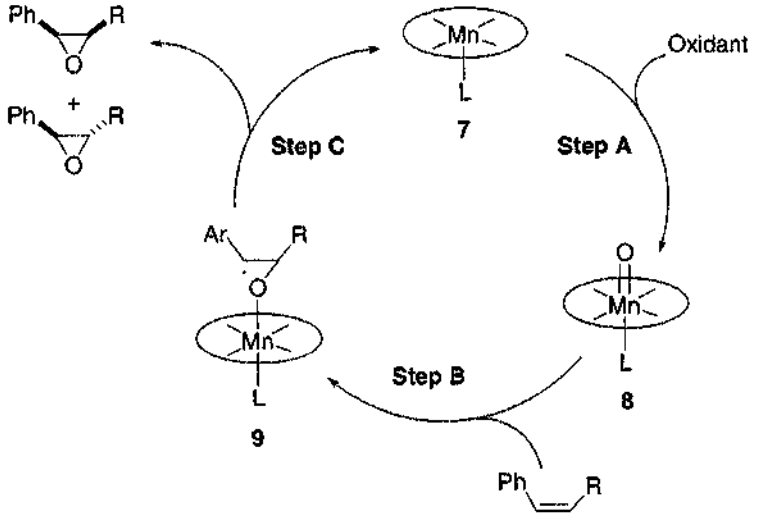
Scheme 1.4.2



1.4.3 Mechanism

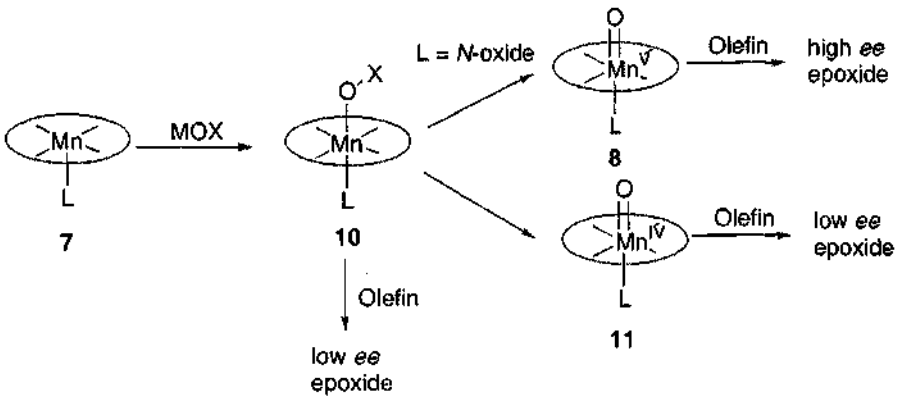
The most widely accepted mechanism of reaction is shown in the catalytic cycle (Scheme 1.4.3). The overall reaction can be broken down into three elementary steps: the oxidation step (Step A), the first C–O bond forming step (Step B), and the second C–O bond forming step (Step C). Step A is the rate-determining step; kinetic studies show that the reaction is first order in both catalyst and oxidant, and zero order in olefin.[7] The rate of reaction is directly affected by choice of oxidant, catalyst loadings, and the presence of additives such as *N*-oxides. Under certain conditions, *N*-oxides have been shown to increase the rate of reaction by acting as phase transfer catalysts.[8]

Scheme 1.4.3



A variety of oxidants have been shown to be effective in generating the putative Mn(V)salen oxo species **8** including sodium hypochlorite, periodates, peracids, peroxides, persulfates, elemental oxygen, and iodosylarenes to name a few. A comparison study of various oxidants in the epoxidation of *cis*-β-methyl styrene in the presence of added *N*-oxide routinely gave the product epoxide with the same sense and degree of enantioselectivity. In contrast, variable enantioselectivities were observed with different oxidants in the absence of *N*-oxides. These results suggest that a common and discrete Mn(V)oxo salen **8** intermediate is preferentially generated in the presence of added *N*-oxide regardless of terminal oxidant.[9] In the absence of added *N*-oxide, a low *ee* pathway perhaps involving either a catalytically active Mn(IV)peroxo-type salen complex **10** or a discrete Mn(IV)oxo salen complex **11** may be operative (Scheme 1.4.4).[10]

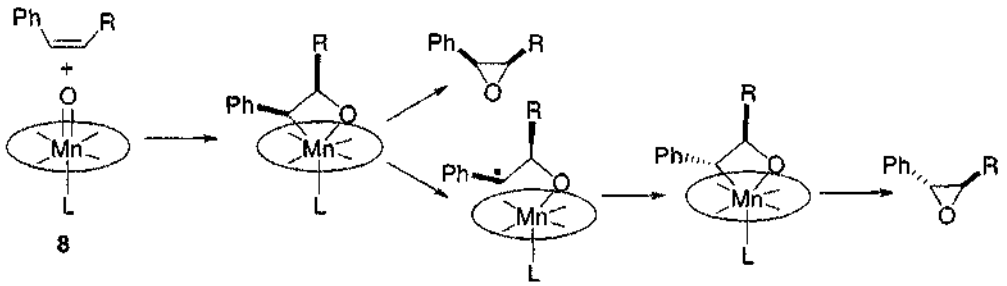
Scheme 1.4.4



While generation of a Mn(V)oxo salen intermediate **8** as the active chiral oxidant is widely accepted, how the subsequent C–C bond forming events occur is the subject of some debate. The observation of *trans*-epoxide products from *cis*-olefins, as well as the observation that conjugated olefins work best support a stepwise intermediate in which a conjugated radical or cation intermediate is generated. The radical intermediate **9** is most favored based on better Hammett correlations obtained with σ vs. σ^+.[11] In addition, it was recently demonstrated that ring opening of vinyl cyclopropane substrates produced products that can only be derived from radical intermediates and not cationic intermediates.[12]

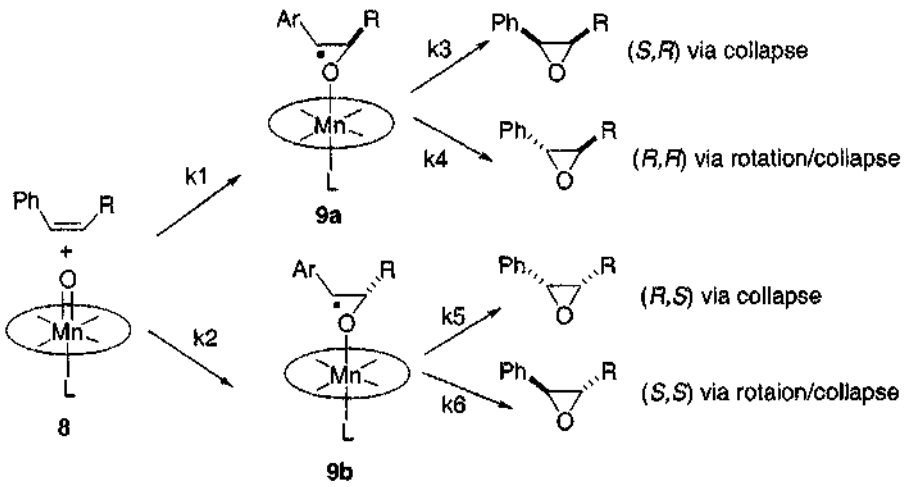
A concerted [2 + 2] cycloaddition pathway in which an oxametallocycle intermediate is generated upon reaction of the substrate olefin with the Mn(V)oxo salen complex **8** has also been proposed (Scheme 1.4.5).[13] Indeed, early computational calculations coupled with initial results from radical clock experiments supported the notion.[14] More recently, however, experimental and computational evidence dismissing the oxametallocycle as a viable intermediate have emerged.[15] In addition, epoxidation of highly substituted olefins in the presence of an axial ligand would require a seven-coordinate Mn(salen) intermediate, which, in turn, would incur severe steric interactions.[16] The presence of an oxametallocycle intermediate would also require an extra bond breaking and bond making step to rationalize the observation of *trans*-epoxides from *cis*-olefins (Scheme 1.4.5).

Scheme 1.4.5



The second C–C bond forming step (step C), while occurring after the first irreversible *ee* determining step (step B), can affect the observed enantioselective outcome of the reaction.[17] If the radical intermediate collapses without rotation ($k_3 >> k_4$, $k_5 >> k_6$), then the observed *ee* would be determined by the first C–C bond forming step (k_1 vs. k_2), that is the facial selectivity (Scheme 1.4.6). However, if rotation is allowed followed by collapse, then the rate of both *trans* pathways (k_4 and k_6) will proportionally effect the observed *ee* of the *cis* epoxide (k_3 vs. k_5). Should bond rotation be permissible, the diastereomeric nature of the radical intermediates **9a** and **9b** renders the distinct possibility of different observed *ee*'s for *trans*-epoxides and *cis*-epoxides.

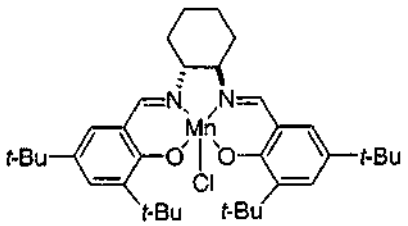
Scheme 1.4.6



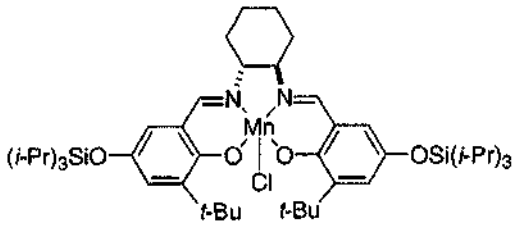
1.4.4 Variations and Improvements

1.4.4.1 Catalyst structure and design

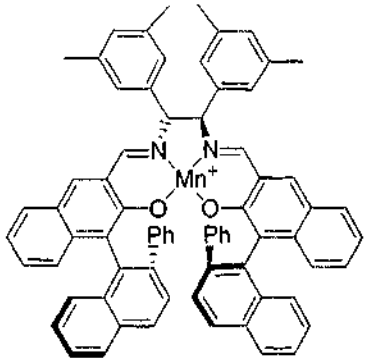
While the Jacobsen catalyst is the most widely used catalyst, a number of other catalysts have been developed through the years that exhibit superior catalyst performance for a given substrate and/or substrate class.[18] The five most prominent catalysts developed to date are shown below, **12–16**. Note that these catalysts all are composed of salen ligands containing electron donating groups. Electron donating groups are thought to stabilize the putative Mn(V)oxo salen complex **8**, thus allowing for a less reactive, more selective catalyst.[19] In addition, the most successful catalysts contain bulky groups at the 3,3′ and 5,5′ position of the salen ring, thus forcing the approach of the olefin near the dissymmetric bridge.



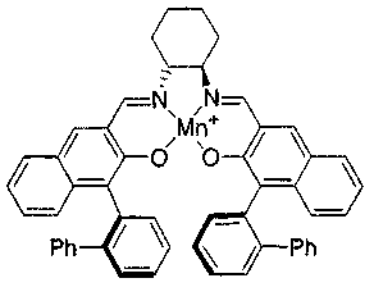
12



13



14



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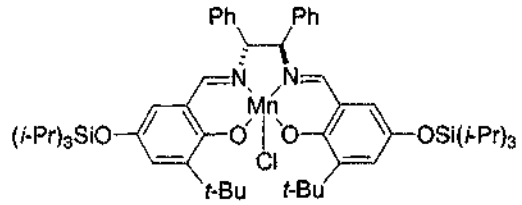


16

1.4.4.2 Additives

One of the most significant developmental advances in the Jacobsen–Katsuki epoxidation reaction was the discovery that certain additives can have a profound and often beneficial effect on the reaction. Katsuki first discovered that *N*-oxides were particularly beneficial additives.[20] Since then it has become clear that the addition of *N*-oxides such as 4-phenylpyridine-*N*-oxide (4-PPNO) often increases catalyst turnovers, improves enantioselectivity, diastereoselectivity, and epoxides yields.[21] Other additives that have been found to be especially beneficial under certain conditions are imidazole and cinchona alkaloid derived salts (*vide infra*).

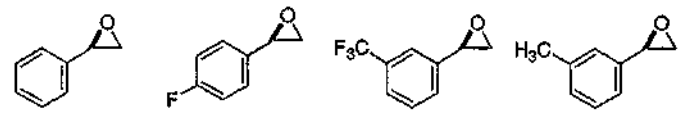
1.4.4.3 Terminal oxidants

Given that the rate determining step is oxidation of the Mn(III)salen complex by the terminal oxidant, it is not surprising that choice of terminal oxidant can have a profound effect on reaction rates and even enantioselectivity. The choice of oxidant can dictate the temperature at which the reaction can be run, which, in turn, can greatly affect selectivity. In addition, the choice of oxidant will determine if the reaction is homogeneous or heterogenous, and whether the reaction is anhydrous or not. A wide variety of terminal oxidants are now available, including sodium hypochlorite, periodates, peracids, peroxides, persulfates, periodates, elemental oxygen, and iodosylbenzenes, to name a few.

1.4.5 Synthetic Utility

1.4.5.1 Epoxidation of terminal olefins

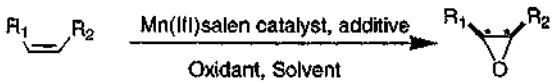
Based on the mechanism of the Jacobsen–Katsuki epoxidation reaction, the *trans*-pathway would reduce the observed *ee*'s in the epoxidation of terminal olefins. Thus, in order to obtain epoxides with good enantioselectivity, high facial selectivity in the first C–O bond-forming event and high *cis/trans* selectivity in the second C–O bond-forming event must be obtained. In 1994, a low-temperature (–78°C) epoxidation protocol was developed by Jacobsen which resulted in increased enantioselectivity for a variety of olefins.[22] The reaction protocol involved using the combination of *m*-CPBA/NMO as terminal oxidant and additive. Most notably, terminal olefins were epoxidized with good enantioselectivities.[23] Deuterium labeling studies showed that the higher enantioselectivities observed in the epoxidation of terminal olefins were a result of a combination of better facial selectivity and higher *cis/trans* selectivity.

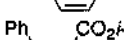
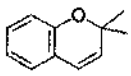
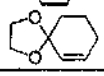


17 86% ee **18** 85% ee **19** 82% ee **20** 80% ee

1.4.5.2 Epoxidation of cis*-disubstituted olefins*

Table 1.4.1. Epoxidation of *cis*-Olefins to give *cis*-Epoxides.



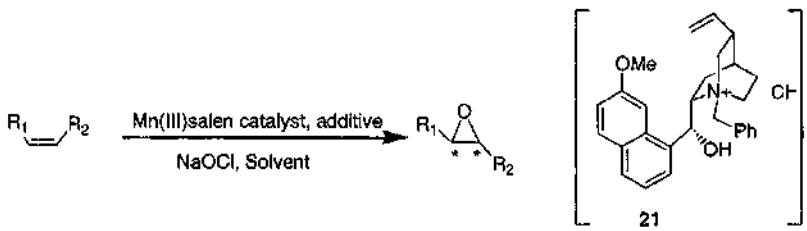
Entry	Substrate	Catalyst	Conditions[a]	ee	*cis/trans*	Reference
1		**13**	a	98	23	15
2		**13**	b	96	10	11
3		**14**	c	98	NA	24b
4		**13**	a	98	NA	19b
5		**12**	c	98	NA	18
6		**13**	b[d]	64	NA	24a
7		**12**	b	94	NA	18

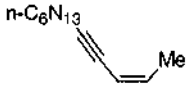
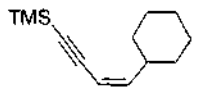
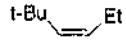
[a]Conditions: (a) 1–5 mol% catalyst, *m*-CPBA/NMO, –78°C, CH_2Cl_2. (b) 1–5 mol% catalyst, NaOCl, 4-phenylpyridine *N*-oxide, 0°C, CH_2Cl_2. (c) 1–5 mol% catalyst, NaOCl, pyridine *N*-oxide, 0°C, CH_2Cl_2. (d) Solvent = diethyl ether

Initial studies on the Jacobsen–Katsuki epoxidation reaction identified conjugated cyclic and acyclic *cis*-disubstituted olefins as the class of olefins best suited for the epoxidation reaction.[24] Indeed a large variety of *cis*-disubstituted olefins have been found to undergo epoxidation with a high degree of enantioselectivity. 2,2′-Dimethylchromene derivatives are especially good substrates for the epoxidation reaction. Table 1.4.1 lists a variety of examples with their corresponding reference.

Historically, the epoxidation of *trans*-olefins typically affords *trans*-epoxides with low enantioselectivity. In 1991, Jacobsen reported that *trans*-epoxides can be obtained from epoxidation of conjugated dienes and enynes containing a *cis*-olefin (Table 1.4.2).[25] Further studies by Jacobsen led to the discovery that addition of cinchona alkaloid-derived salts such as **21** coupled with the use of chlorobenzene as solvent resulted in the formation of the *trans*-diastereomer in high *ee* as the major epoxidation product from the epoxidation of *cis*-olefins.[26] Although it is still unclear as to the exact mechanism by which the cinchona alkaloid-derived salts favor the formation of *trans*-epoxides, clearly, these salts somehow extend the lifetime of the radical intermediate thus allowing for free rotation to occur.

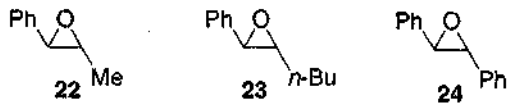
Table 1.4.2. Epoxidation of *cis*-olefins to give *trans*-epoxides



Entry	Substrate	Catalyst	Additive	Solvent	*trans*:*cis*	*ee* (%)	Reference
1		**12**	None	CH_2Cl_2	62:28	90	25a
2		**12**	None	CH_2Cl_2	84:16	98	25a
3		**13**	**21**	C_6H_5Cl	69:31	84	25b
4		**13**	**21**	C_6H_5Cl	> 96:4	90	25b
5		**13**	**12**	C_6H_5Cl	95:5	81	25b

1.4.5.3 Epoxidation of trans*-disubstituted olefins*

Although *trans* epoxides can be obtained *via* epoxidation of acyclic *cis*-conjugated olefins under specified conditions, a direct method based on the epoxidation of *trans*-olefins would be valuable. The Katsuki group recently identified catalyst **15** as an efficient catalyst for the direct epoxidation of *trans*-olefins. Crucial to the success of the catalyst is the inherent adoption of a deeply folded conformation coupled with the use of chlorobenzene as solvent. While only a limited number of substrates have been examined to date using catalyst **15**, the results are very promising. For example, *trans*-β-methyl styrene is epoxidized in 91% *ee*, *trans*-β-*n*-butyl styrene in 95% *ee*, and *trans*-stilbene in 87% *ee*.



91% ee 95% ee 87% ee

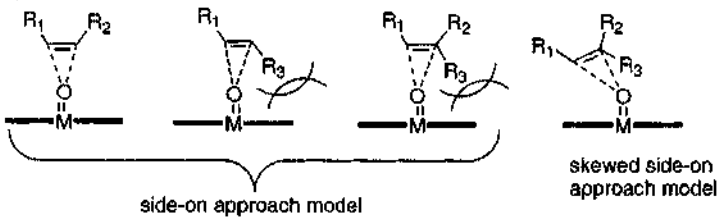
1.4.5.4 Epoxidation of 1,1-disubstituted olefins

To date, no efficient and general Mn(III)salen-catalyst exists that effects epoxidation of 1,1-disubstituted olefins with good enantioselectivity.

1.4.5.5 Epoxidation of tri-substituted and tetra-substituted olefins

During the early development of the Jacobsen–Katsuki epoxidation reaction, it was clear that *trans*-disubstituted olefins were very poor substrates (slow reaction rates, low enantioselectivity) compared to *cis*-disubstituted olefins. The side-on approach model originally proposed by Groves for porphyrin epoxidation systems was used to rationalize the differences observed in the epoxidation of the *cis* and *trans*-disubstituted classes (Scheme 1.4.7).[27]

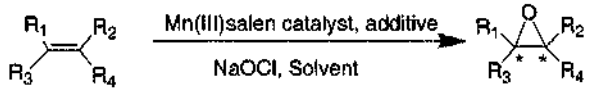
Scheme 1.4.7

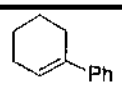
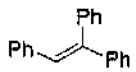
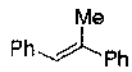
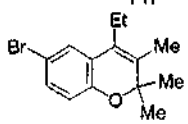
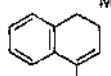
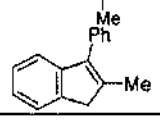


This model predicts that tri-substituted and tetra-substituted olefins would also be poor substrates. Thus it was not until 1994 that a study in the epoxidation of higher substituted olefins appeared. Indeed Jacobsen revealed that tri-substituted olefins,[28] and even tetra-substituted olefins can be excellent substrates.[29,30] A new model was put forth that encompasses a skewed side-on approach of tri-substituted olefins to the Mn-oxo complex. The observation that certain tetrasubstituted olefins undergo epoxidation with good enantioselectivity suggests that further studies are needed in order to fully understand the transition state geometry of the catalyst and substrate.

The Jacobsen–Katsuki epoxidation reaction has found wide synthetic utility in both academia and industrial settings. As described previously, the majority of olefin classes, when conjugated, undergo Mn(salen)-catalyzed epoxidation in good enantioselectivity. In this section, more specific synthetic utilities are presented.

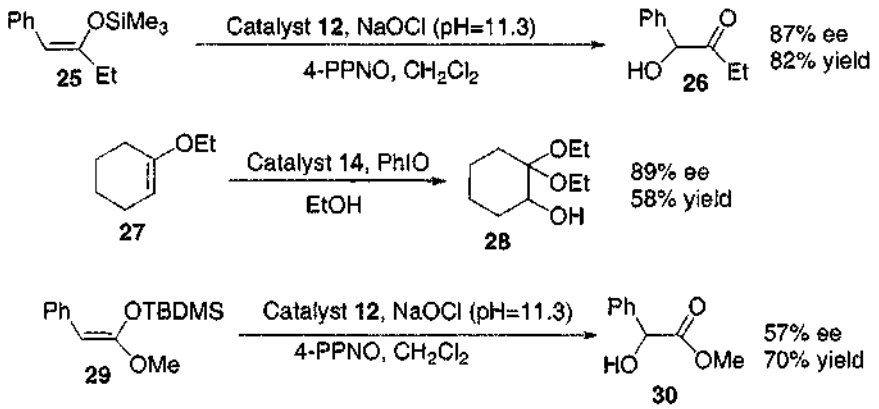
Table 1.4.3. Epoxidation of tri- and tetra-substituted olefins.



Entry	Substrate	Catalyst	Solvent	Yield (%)	Ee (%)	Reference
1		**12**	MTBE	69	93	28
2		**12**	CH_2Cl_2	97	92	28
3		**12**	CH_2Cl_2	91	95	28
4		**16**	CH_2Cl_2	81	97	29
5		**14**	CH_3CN	41	96	30
6		**12**	CH_2Cl_2	90	90	29

1.4.5.6 Preparation of α-hydroxy ketones and esters

Scheme 1.4.8

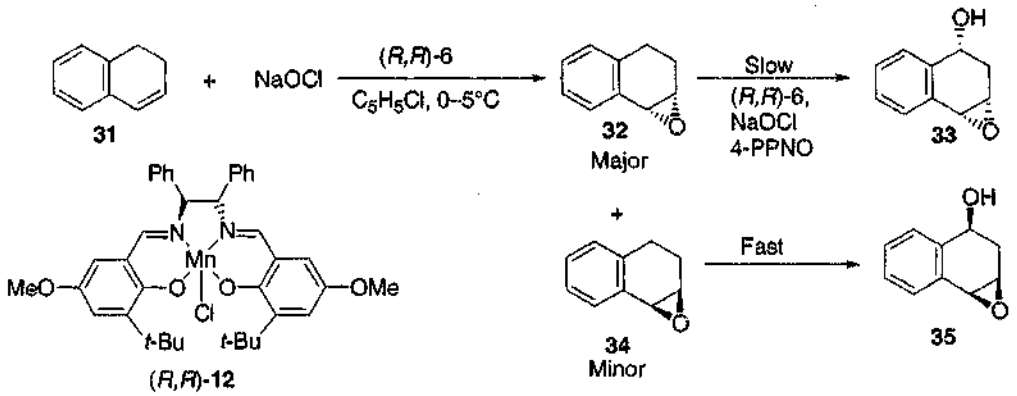


The first asymmetric Mn(salen)-catalyzed epoxidation of silyl enol ethers was carried out by Reddy and Thornton in 1992. Results from the epoxidation of various silyl enol ethers gave the corresponding keto-alcohols in up to 62% *ee*.[31] Subsequently, Adam[32,33] and Katsuki[34] independently optimized the protocol for these substrates yielding products in excellent enantioselectivity.

1.4.5.7 Kinetic resolution

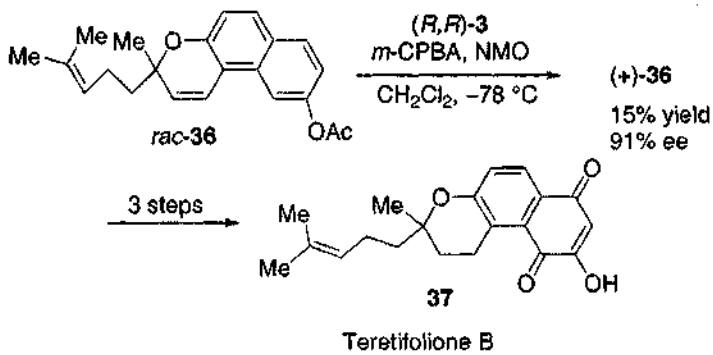
1,2-Dihydronaphthalene is often used as a model olefin in the study of epoxidation catalysts, and very often gives product epoxides in unusually high *ee*'s. In 1994, Jacobsen discovered in his study on the epoxidation of 1,2-dihydronaphthalene that the *ee* of the epoxide increases at the expense of the minor enantiomeric epoxide.[35] Further investigation led to the finding that certain epoxides, especially cyclic aromatically conjugated epoxides, undergo kinetic resolution *via* benzylic hydroxylation up to a k_{rel} of **28** (Scheme 1.4.9).

Scheme 1.4.9



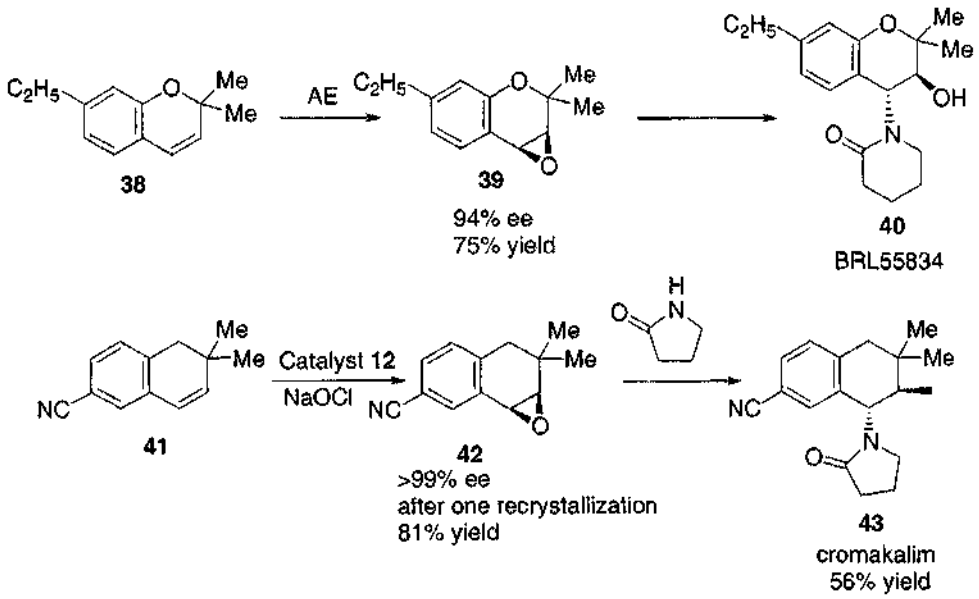
The first application of the Jacobsen–Katsuki epoxidation reaction to kinetic resolution of prochiral olefins was nicely displayed in the total synthesis of (+)-teretifolione B by Jacobsen in 1995.[36]

Scheme 1.4.10



1.4.5.8 Jacobsen–Katsuki epoxidation reaction in total synthesis

Scheme 1.4.11



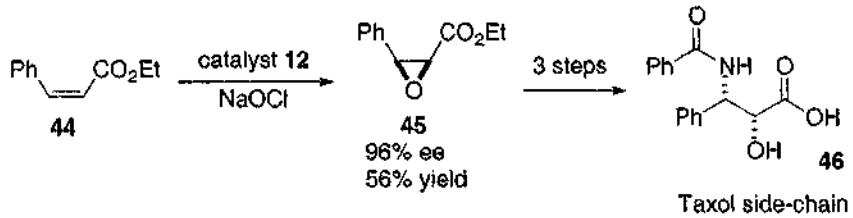
The Jacobsen–Katsuki epoxidation reaction has been widely used for the preparation of a variety of structurally diverse complex molecules by both academia and the pharmaceutical industry. Summarized below are a few examples.

2,2-Dimethylchromene derivatives typically undergo epoxidation with excellent enantioselectivity (Scheme 1.4.11). The ring-opened product epoxides are potent pharmaceutical pharmacophores. BRL55834 (**40**) is a selective potassium channel activator and is comprised of a 2,2-dimethylchromanol-type structure.[37] Epoxidation of the 2,2-dimethylchromene starting material with catalyst **12** in the presence of catalytic amounts of an *N*-oxide additive gave the product epoxide in 94% *ee* and 75% yield. Regioselective ring opening of the chiral epoxide gave BRL55834 (**40**) in 81% yield. The anti-hypertensive agent cromoakalim has also been prepared in a similar fashion.[38]

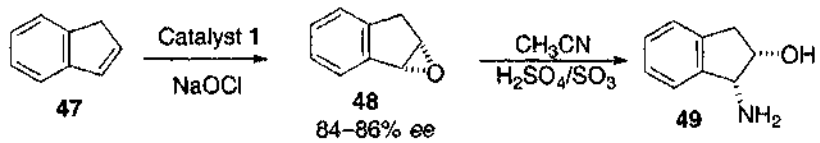
The asymmetric epoxidation of electron-poor cinnamate ester derivatives was highlighted by Jacobsen in the synthesis of the Taxol side-chain. Asymmetric epoxidation of ethyl cinnamate provided the desired epoxide in 96% *ee* and in 56% yield. Epoxide ring opening with ammonia followed by saponification and protection provided the Taxol side-chain **46** (Scheme 1.4.12).

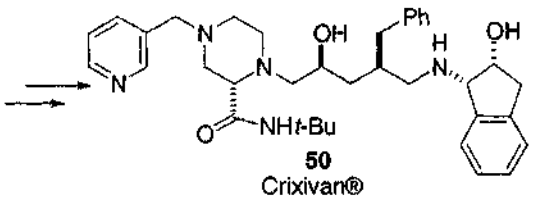
cis-2-Aminoindan-1-ol is a structural motif incorporated in various types of ligands for metal catalysis[6] and also comprises the right-hand portion of the HIV protease inhibitor Crixivan® (**50**).[39] Indene was epoxidized by catalyst **12** in 84–86% *ee*. The product epoxide was then ring-opened *via* Ritter reaction to provide *cis*-2-aminoindan-1-ol, which was then used in the eventual preparation of Crixivan® (**50**).

Scheme 1.4.12



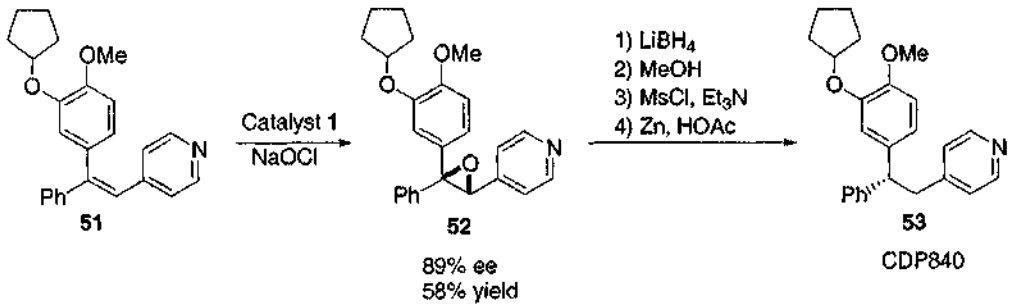
Scheme 1.4.13





CDP840 is a selective inhibitor of the PDE-IV isoenzyme and interest in the compound arises from its potential application as an antiasthmatic agent. Chemists at Merck & Co. used the asymmetric epoxidation reaction to set the stereochemistry of the carbon framework and subsequently removed the newly established C–O bonds.[40] Epoxidation of the trisubstituted olefin **51** provided the desired epoxide in 89% *ee* and in 58% yield. Reduction of both C–O bonds was then accomplished to provide CDP840.

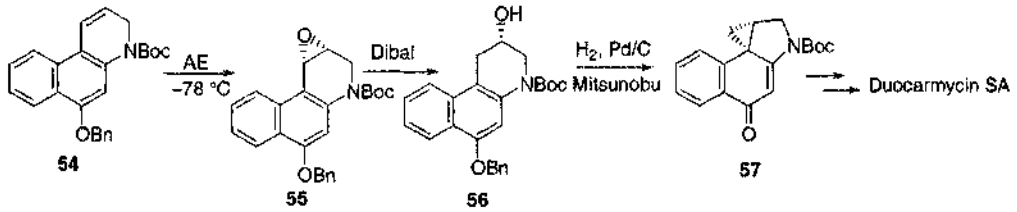
Scheme 1.4.14



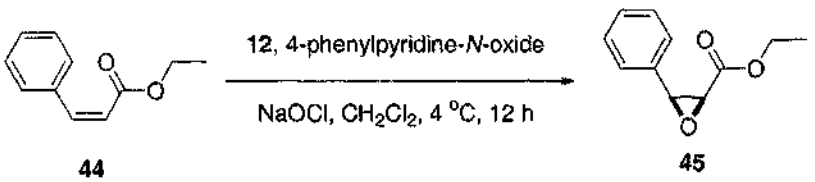
Boger *et al.* prepared Duocarmycin SA *via* asymmetric epoxidation of a cyclic olefin **54**.[41] The stereochemistry set by the epoxidation step was used for subsequent C–C bond forming reactions. Epoxidation of olefin **54** was carried at –78°C to provide

the desired product in 92% *ee* and in 70% yield. Reduction of the benzylic C–O bond followed by partial reduction of the middle phenyl ring and a transannular spirocylization provided the activated cyclopropane which was carried on to Duocarmycin SA.

Scheme 1.4.15



1.4.5 *Experimental*



(2*R*, 3*R*)-Ethyl-3-phenylglycidate (45).

To a solution of *cis*-ethyl cinnamate (**44**, 352 mg, 85% pure, 1.70 mmol) and 4-phenylpyridine-*N*-oxide (85.5 mg, 29 mol%) in 1,2-dichloromethane (4.0 mL) was added catalyst **12** (38.0 mg, 3.5 mol%). The resulting brown solution was cooled to 4°C and then combined with 4.0 mL (8.9 mmol) of pre-cooled bleach solution. The two-phase mixture was stirred for 12 h at 4°C. The reaction mixture was diluted with methyl-*t*-butyl ether (40 mL) and the organic phase separated, washed with water (2 × 40 mL), brine (40 mL), and then dried over Na_2SO_4. The drying agent was removed by filtration the mother liquors concentrated under reduce pressure. The resulting residue was purified by flash chromatography (silica gel, pet ether/ether = 87:13 v/v) to afford a fraction enriched in *cis*-epoxide (**45**, *cis/trans*: 96:4, 215 mg) and a fraction enriched in *trans*-epoxide (*cis/trans*: 13:87, 54 mg). The combined yield of pure epoxides was 83%. *ee* of the *cis*-epoxide was determined to be 92% and the *trans*-epoxide to be 65%.

1.4.7 *References*

1. For reviews see: [R] (a) Jacobsen, E. N.; Wu, M. H. in *Comprehensive Asymmetric Catalysis*, Jacobsen, E. N.; Pfaltz, A.; Yamamoto, H. Eds.; Springer: New York; 1999, Chapter 18.2. [R] (b) Katsuki, T. *Coord. Chem. Rev.* **1995**, *140*, 189–214. [R] (c) E. N. Jacobsen, in *Comprehensive Organometallic Chemistry II*, Eds. G. W. Wilkinsin, G. W.; Stone, F. G. A.; Abel, E. W.; Hegedus, L. S., Pergamon, New York, 1995, vol 12, Chapter 11.1.
2. Jacobsen, E.N.; Zhang, W.; Muci, A. R.; Ecker, J. R.; Deng, L. *J. Am. Chem. Soc.* **1991**, *113*, 7063.
3. (a) Zhang,W.; Loebach, J. L.; Wilson, S. R.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1990**, *112*, 2801. (b) Irie, R.; Noda, K.; Ito, Y.; Matsumoto, N.; Katsuki, T. *Tetrahedron Lett.* **1990**, *31*, 7345.
4. (a) Larrow, J. F.; Jacobsen, E. N.; Gao, Y.; Hong, Y.; Nie, X.; Zepp, C. M. *J. Org. Chem.* **1994**, *59*, 1939. (b) Larrow, J.; Jacobsen, E. N. *Org. Syn.* **1997**, *75*, 1.

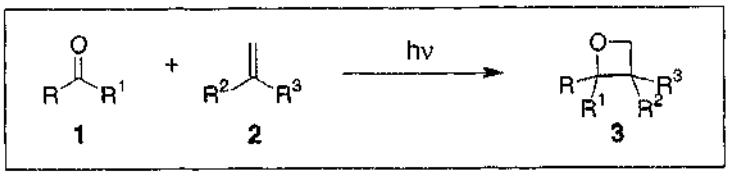
5. Sasaki, H.; Irie, R.; Hamada, T.; Suzuki, K.; Katsuki, T. *Tetrahedron* **1994**, *50*, 11827.
6. [R] Senananyake, C. H. *Aldrichimica Acta* **1998**, *31*, 3.
7. Evidence supporting the Mn(V)oxo salen intermediate: a) Feichtinger, D.; Plattner, D. A. *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 1718. B) Feichtinger, D.; Plattner, D. A. *Chem. Eur. J.* **2001**, *7*, 591.
8. Hughes, D. L.; Smith, G. B.; Liu, J.; Dezeny, G. C.; Senanayake, C. H.; Larsen, R. D.; Verhoeven, T. R.; Reider, P. J. *J. Org. Chem.* **1997**, *62*, 2222.
9. Michael Palucki, Thesis, 1995 Harvard Univeristy.
10. (a) Adam, W.; Mock-Knoblauch, C.; Saha-Möller, C. R.; Herderich, M. *J. Am. Chem. Soc.* **2000**, *122*, 9685. (b) Bryliakov, K. P.; Babushkin, D. E.; Talsi, E. *J. Mol. Catal. A.* **2000**, *158*, 19. c) Paul J. Pospisil, Thesis, 1995 Harvard Univsersity.
11. Jacobsen, E. N.; Deng, L.; Furukawa, Y.; Martinez, L. *Tetrahedron* **1994**, *50*, 4323.
12. Adam, W.; Roschmann, K. R.; Saha-Möller, C. R.; Seebach, D. *J. Am. Chem. Soc.* **2002**, *124*, 5068.
13. (a) Norrby, P.-O.; Linde. C.; Åkermark, B. *J. Am. Chem. Soc.* **1995**, *117*, 11035. (b) Nuguchi, Y.; Irie, R.; Fukuda, T.; Katsuki, T. *Tetrahedron Lett.* **1996**, *37*, 4533.
14. Linde, C.; Arnold, M.; Norrby, P.-O.; Åkermark, B. *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 1723.
15. (a) Cavallo, L.; Jacobsen, H. *Angew. Chem. Int. Ed. Engl.* **2000**, *39*, 589. (b) Adam, W.; Roschmann, K. J.; Saha-Möller, C. R.; Seebach, D. *J. Am. Chem. Soc.* **2002**, *124*, 5068.
16. Finney, N. S.; Pospisil, P. J.; Chang, S.; Palucki, M.; Konsler, R. G.; Hansen, K. B.; Jacobsen, E. N. *Angew. Chem. Int.Ed. Engl.* **1997**, *36*, 1720.
17. Zhang, W.; Lee, N. H.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1994**, *116*, 425.
18. Jacobsen, E. N.; Zhang, W.; Muci, A. R.; Ecker, J. R.; Deng, L. *J. Am. Chem. Soc.* **1991**, *113*, 7063.
19. (a) Jacobsen, E. N.; Guler, M. L.; Zhang, W. *J. Am. Chem. Soc.* **1991**, *113*, 6703. (b) Palucki, M.; Finney, N. S.; Pospisil, P. J.; Guler, M. L.; Ishida, T.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1988**, *120*, 948.
20. Irie, R.; Itoh, Y.; Katsuki, T. *Synlett*, **1991**, 265.
21. Senanayake, C. H.; Smith, G. B.; Ryan, K. M.; Fredenburgh, L. E.; Liu, J.; Roberts, F. E.; Hughes, D. L.; Larsen, R. D.; Verhoeven, T. R.; Reider, P. J *Tetrahedron Lett.* **1996**, *37*, 3271.
22. Palucki, M., Pospisil, P. J.; Zhang, W.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1994**, *116*, 9333.
23. Palucki, M.; McCormick, G. J.; Jacobsen, E. N. *Tetrahedron Lett.* **1995**, *36*, 5457.
24. (a) Chang, S.; Heid, R. M.; Jacobsen, E. N. *Tetrahedron Lett.* **1994**, *35*, 669. (b) Sasaki, H.; Irie, R.; Hamada, T.; Suzuki, K.; Katsuki, T. *Tetrahedron* **1994**, *50*, 11827.
25. (a) Lee, N, H.; Jacobsen, E. N. *Tetrahedron Lett.* **1991**, *32*, 6533. (b) Chang, S.; Lee, N. H.; Jacobsen, E. N. *J. Org. Chem. 1993*, *58*, 6939.
26. Chang, S.; Galvin, J. M.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1994**, *116*, 6937.
27. Groves, J. T.; Myers, R. S. *J. Am Chem. Soc.* **1985**, *108*, 2309.
28. Brandes, B. D.; Jacobsen, E. N. *J. Org. Chem.* **1994**, *59*, 4378.
29. Brandes, B. D.; Jacobsen, E. N. *Tetrahedron Lett.* **1995**, *36*, 5123.
30. Fukuda, T.; Irie, R.; Katsuki, T. *Synlett* **1995**, 197.
31. Reddy, D. R.; Thornton, E. R. *J. Chem. Soc., Chem. Commun.* **1992**, 172.
32. Adam, W.; Fell, R. T.; Mock-Knoblauch, C.; Saha-Möller, C. R. *Tetrahedron Letters* **1996**, *37*, 6531
33. Adam. W.; Fell, R. T.; Stegmann, V. R.; Saha-Möller, C. R. *J. Am. Chem. Soc.* **1998**, *120*, 708.
34. Fukuda, T.; Katsuki, T. *Tetrahedron Letters* **1996**, *37*, 4389.
35. Larrow, J. F.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1994**, *116*, 12129.
36. Vander Velde, S. L.; Jacobsen, E. N. *J. Org. Chem.* **1995**, *60*, 5380.
37. Buckle, D. R.; Eggleston, D. S.; Pinto, I. L.; Smith, D. G.; Tedder, J. M. *Bio. Med. Chem. Lett.* **1992**, 2, 1161.
38. Lee, N. H.; Muci, A. R.; Jacobsen, E. N. *Tetrahedron Lett.* **1991**, *32*, 5055.
39. Vacca, J.; Dorsey, B.; Schlief, W. A.; Levin, R.; Mcdaniel, S.; Darke, P.; Zugay, J.; Quintero, J.; Blahy, O.; Roth, E.; Sardana, V.; Schlabach, A.; Graham, P.; Condra, J.; Gotlib, L.; Holloway, M.; Lin, J.; Chen, I.; Vastag, K.; Ostovic, D.; Anderson, P. S.; Emini, E. A.; Huff, J. R. *Proc. Natl. Acad. Sci. USA* **1994**, *91*, 4096.
40. Lynch, J. E.; Choi, W.-B.; Churchill, H. R. O.; Volante, R. P.; Reamer, R. A.; Ball, R. G. *J. Org. Chem.* **1997**, *62*, 9223.
41. Boger, D. L.; McKie, J. A.; Boyce, C. W. *Synlett* **1997**, 515.

Michael Palucki

1.5 Paterno–Büchi Reaction

1.5.1 Description

The Paterno–Büchi reaction[1–4] is the photo-catalyzed electrocyclization of a carbonyl **1** with an alkene **2** to form polysubstituted oxetane ring systems **3**.

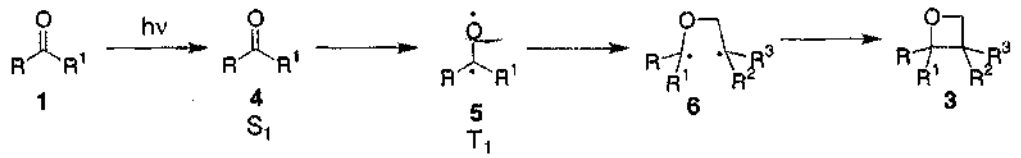


1.5.2 Historical Perspective

In 1909, Paterno and Chieffi[5] noted that mixtures of tri- or tetra-substituted olefins and aldehydes formed trimethylene oxides when exposed to sunlight. Büchi[6] later repeated Paterno's experiments by irradiating 2-methyl-2-butene in the presence of benzaldehyde, butyraldehyde, or acetophenone and rigorously purifying and identifying the resulting products. The reaction thus bears the name of its two primary pioneers and has come to represent any photo-catalyzed [2 + 2] electrocyclization of a carbonyl and an alkene.

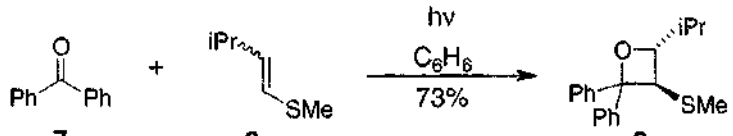
1.5.3 Mechanism

The mechanism of the Paterno–Büchi reaction is not well understood, and while a general pathway has been proposed and widely accepted, it is apparent that it does not represent the full scope of reactions. Büchi originally proposed that the reaction occurred by light catalyzed stimulation of the carbonyl moiety **1** into an excited singlet state **4**. Inter-system crossing then led to a triplet state diradical **5** which could be quenched by olefinic radical acceptors. Intermediate diradical **6** has been quenched or trapped by other radical acceptors and is generally felt to be on the reaction path of the large majority of Paterno–Büchi reactions. Diradical **6** then recombines to form product oxetane **3**.

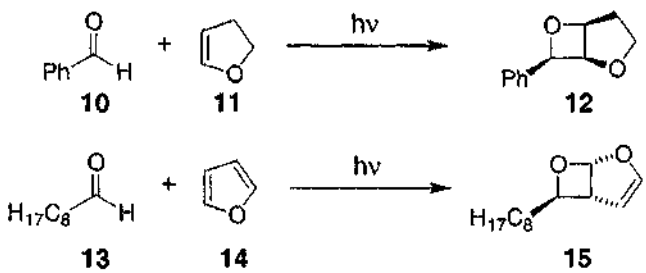


The stability of diradical **6** is often cited as the rationalization for the regiochemistry and relative stereochemistry of the Paterno–Büchi reaction. This "most stable diradical" theory explains the formation of the sterically disfavored 2,3-substituted oxetanes. Quenching of the triplet diradical occurs in such a fashion as to generate the more stable alkyl radical pair and can be predicted using typical rules for radical stabilization. Consideration of the configuration of diradical **6** is the most powerful tool in predicting product distribution and can give a qualitative estimation of products ratios. Generation of 2,3-substituted oxetanes is the major utility of the Paterno–Büchi reaction

and it should be noted that this substitution pattern is opposite that of thermal or acid activated [2 + 2] electrocyclizations.



Relative stereochemistry is also dictated by diradical stability but is highly subject to substituent effects. In the case of open chain alkenes, stereochemical information regarding the E-/Z-substitution is lost. In his work with vinyl sulfides, Smith[7] isolated solely *trans* oxetane **9** regardless of the *E/Z* constitution of sulfide **8**. The conformation of diradical **6** dominates the selectivity and the result is the more stable 3,4-*trans* substituted oxetanes. Five- and six-membered cyclic alkenes react exclusively to generate the *cis* products while larger rings react as the acyclic alkenes do.[8] There are some examples of stereospecific Paterno–Büchi reactions in which the stereochemistry of the acyclic alkenes is retained,[3] particularly if the alkene concentration is very high. These reactions are generally believed to spring from singlet state carbonyls with the high alkene concentration serving to accelerate the coupling rate above that of intersystem crossing. The relative stereochemistry of the 2,3-substituents is controlled by the electronic requirements of radical recombination. Griesbeck[9] has demonstrated and rationalized the preference for endo-selectivity for Paterno–Büchi couplings with 2,3-dihydrofuran **11** with aryl and alkyl aldehydes resulting in the substitution pattern in **12**. He noted that selectivity ranged from 1:1 (non-existent) to greater than 98:2 depending on the cycloalkene used. Other studies[10,11] with acyclic alkenes have demonstrated a preference for the corresponding *cis* geometry. The selectivity is reversed for conjugated alkenes such as 1,3-dienes, styrene, and furan **14** which prefer the thermodynamically more stable 2,3-*trans* (*exo*) oxetanes such as **15**.



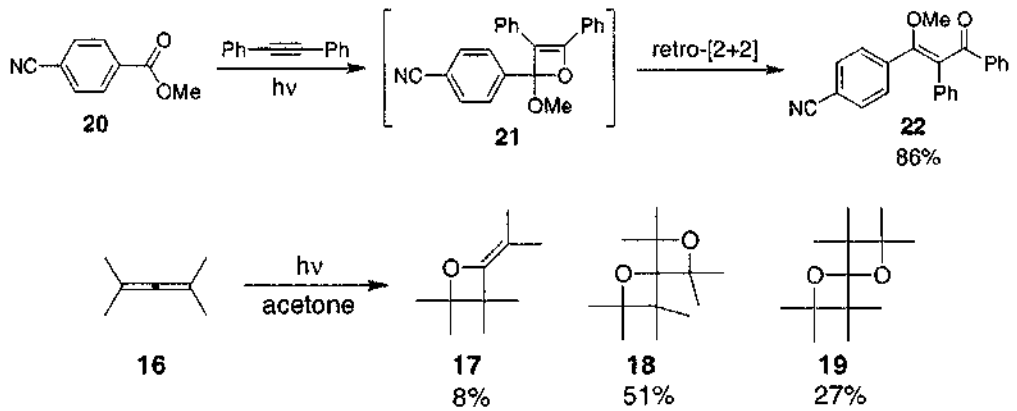
It is evident from the exceptions noted that the mechanism proposed above does not fully capture the pathways open to the Paterno–Büchi reaction. A great deal of effort has been devoted to deconvoluting all of the possible variants of the reaction. Reactions via singlet state carbonyls, charge-transfer paths, pre-singlet exciplexes, and full electron transfer paths have all been proposed.[3] Unfortunately, their influence on product

distribution is not understood and as such represent mechanistic oddities rather than the rule.

1.5.4 Variations and Improvements

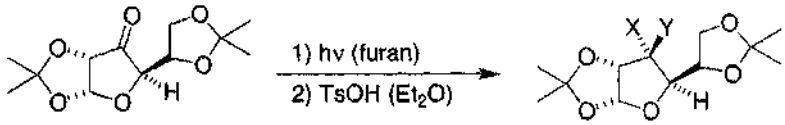
Improvements of the Paterno–Büchi reaction have primarily focused on expanding the scope of substrates and developing asymmetric variants to control stereochemistry. The Paterno–Büchi reaction is extremely permissive of substitution on the carbonyl coupling partner, although radical stabilizing groups are preferred for obvious reasons. Alkyl-, alkynyl-, and aryl-ketones as well as glyoxylates have been used successfully. The majority of Paterno–Büchi reactions use aldehydes or ketones as coupling partners, but the reaction is not limited to just these carbonyls; Cantrell[12] and Miyamoto[13] demonstrated that arene carboxylic acid esters **20** are suitable substrates.

A variety of alkenes can serve as radical quenching partners. Because of the wide scope of acceptable alkene partners, relatively complex alkenes can be used successfully. Mono-, di-, tri-, and even tetra-substituted alkenes will undergo Paterno–Büchi reactions. Heteroatom substituted alkenes include enol ethers, silyl enol ethers, enol acetates, acyl and alkyl enamines, and alkenyl sulfides.[7,14,15] The alkenyl sulfides are particularly interesting as the reactions proceed considerably faster than equivalent enol ethers. Cyclic alkenes are often used, particularly furan because of its synthetically useful *exo* face selectivity (*vide supra*) and the convenient functional handles it provides for subsequent reactions.[16] Araki[17,18] has even used glucals as coupling partners. Allenes such as **16**[19] and dienes[20] will also undergo Paterno–Büchi reactions, albeit with low chemoselectivity. There are also reports of alkynes as radical coupling partners to form oxetenes **21**, although these species are usually unstable and degrade quickly.[21]



The most valuable characteristic of the Paterno–Büchi reaction is the ability to set multiple stereocenters in one reaction and the development of diastereocontrolled reactions has been a major theme of research concerning this reaction. Stereocontrol can be envisioned to spring from either the carbonyl or the alkene and be controlled by either the substrate directly or by a chiral auxiliary. Little success has been achieved in substrate-induced selection by the carbonyl; the most successful results were produced by

Zamojski and Jarosz[22] using cyclic ketone **23** with furan that generated a 75:25 ratio of diastereomers **24** and **25**.



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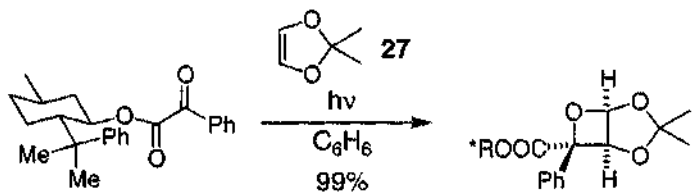
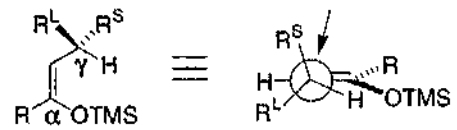
Despite failures in carbonyl substrate-induced selection, auxiliary-induced selection showed good results. Scharf and coworkers[23] performed a systematic study to show that phenylglyoxylates coupled to 8-phenylmenthol **26** gave excellent control of subsequent Paterno–Büchi reactions. With the 8-phenylmenthol moiety blocking the *Si*-face of the glyoxylate and the heterocyclic alkene **27** strongly preferring *endo*-addition, only diastereomer **28** was isolated. The chiral auxiliary could then be recovered in good yield by reduction of the oxetane-substituted ester.



26 **28**

Ironically, auxiliary-induced control via the alkene failed to generate synthetically useful selectivities, but direct substrate-induced control did. In particular, chiral silyl enol ethers with stereocenters in the γ-position allowed the synthesis of enantiomerically pure oxetanes. Bach[24] noted that 1,3-allylic strain in molecules such as **29** locked the conformation as shown and caused approaching diradicals to prefer attack opposite R^L with varying selectivities. Depending on the relative steric bulk of R^S and R^L, diastereoselectivity ranging from 61:39 to 95:5 was achieved. It should be noted that chiral groups appended to the α-carbon failed to impart selectivity.

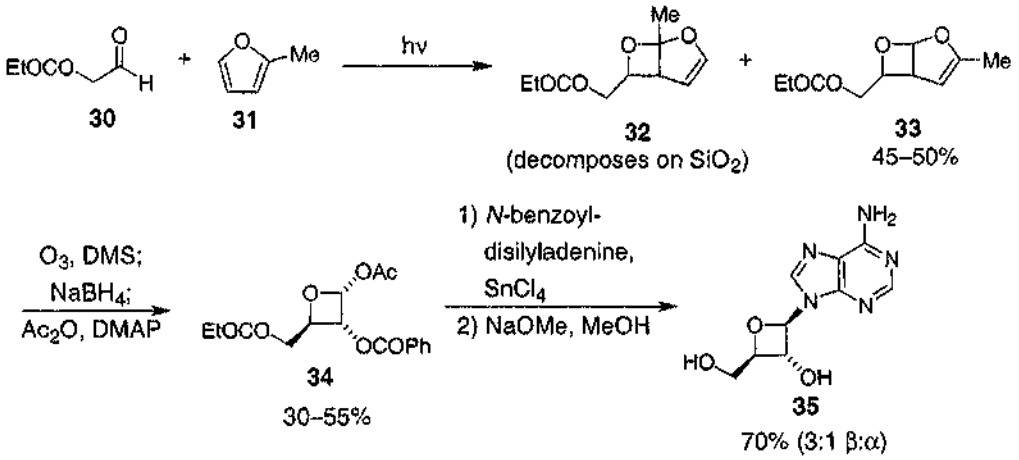


29

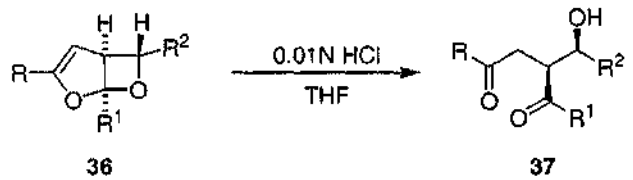
1.5.5 Synthetic Utility

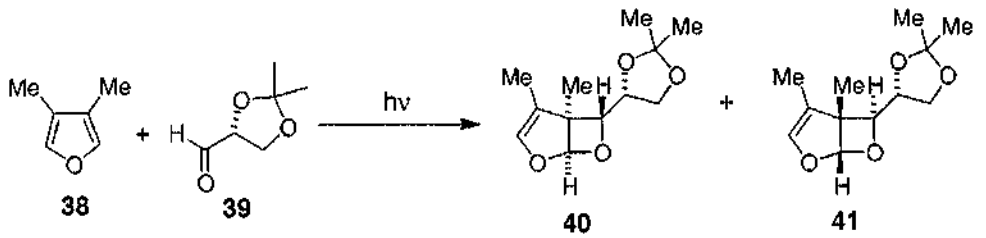
The oxetane functional unit is a rare but occurring group in natural products and appears both as end products as well as synthetic intermediates.[3,4] Paterno–Büchi reactions can be used to insert oxetanes directly into biologically active compounds, as in the example below by Just.[25] The novel nucleotide oxetanocin **35** is synthesized using a

Paterno–Büchi reaction between 2-methylfuran **31** and an α-hydroxyaldehyde **30** to form the core oxetane. Two of the three stereocenters set in the electrocyclization appear in the final product while the third is selectively reversed with anomeric assistance.

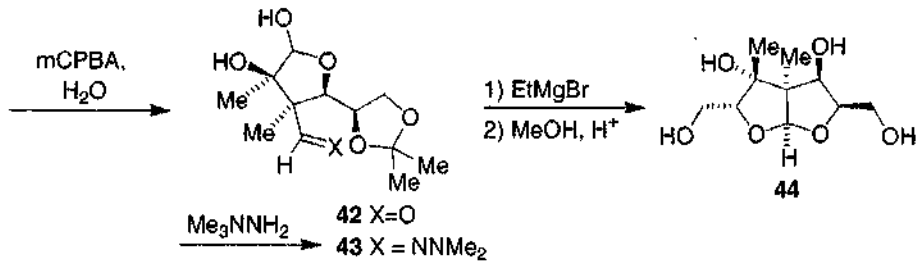


Given the relatively rare appearance of oxetanes in natural products, the more powerful functionality of the Paterno–Büchi reaction is the ability to set the relative stereochemistry of multiple centers by cracking or otherwise derivitizing the oxetane ring. Schreiber noted that Paterno–Büchi reactions of furans with aldehydes followed by acidic hydrolysis generated product **37**, tantamount to a *threo* selective Aldol reaction.[26] This process is referred to as "photochemical Aldolization". Schreiber uses this selectivity to establish the absolute stereochemistry of the fused tetrahydrofuran core **44** of the natural product asteltoxin.[27]





35% (total), 1.2 : 1.0, 54% ee



1.5.6 Experimental

(1(R,S),5(R,S))-6(R,S)-n-Octyl-2,7-dioxabicyclo[3.2.0]hept-3-ene (47).[26]

Nonyl aldehyde (32.66 g, 0.23 mol) and furan (200 mL, 187.2 g, 2.75 mol) were mixed in a 250-mL photolysis flask equipped with a quartz immersion well containing a Vycor filter and a 450-W Hanovia Lamp. The system was kept at –20° C with an isopropyl alcohol bath cooled by a Cryocool Immersion Cooler (CC100). Nitrogen was bubbled throughout the duration of the reaction, and the solution was stirred vigorously. Additional furan (150 mL, 140.4 g, 2.06 mol) was added during the course of the reaction. TLC analysis indicated completion of the reaction after 20 h. After evaporation of excess furan ^{13}C and ^{1}H NMR analysis of the resultant oil (48.70 g, ca. 100%) indicated the desired photoadduct had been formed, without contamination from unreacted nonyl aldehyde.

1.5.7 References

1. [R] Carless, H. A. J. In *Synthetic Organic Photochemistry*; Horspool, W. M., Ed.; Plenum Press: New York, 1984, pp 425.
2. [R] Jones, G. In *Organic Photochemistry*; Padwa, A., Ed.; Dekker: New York, 1981, pp 1.
3. [R] Porco, J. A.; Schreiber, S. L. In *Comprehensive Organic Synthesis*; Trost, B., Ed.; Pergamon Press: Oxford, 1991; Vol. 5, pp 151.
4. Bach, T. *Synthesis* **1998**, *5*, 683.
5. Paterno, E.; Chieffi, G. *Gazz. Chim. Ital.* **1909**, *39*, 341.
6. Buchi, G.; Inman, C. G.; Lipinsky, E. S. *J. Am. Chem. Soc.* **1954**, *76*, 4327.
7. Morris, T. H.; Smith, E. H.; Walsh, R. *J. Chem. Soc., Chem. Commun.* **1987**, 964.
8. Shima, K.; Sakai, Y.; Sakurai, H. *Bull. Chem. Soc. Jpn.* **1971**, *44*, 215.
9. Griesbeck, A. G.; Mauder, H.; Stadtmuller, S. *Acc. Chem. Res.* **1994**, *27*, 70.
10. Bach, T. *Angew. Chem., Int. Ed.* **1996**, *35*, 884.
11. Schroeter, S. H.; Orlando, C. M., Jr. *J. Org. Chem.* **1969**, *34*, 1181.
12. Cantrell, T. S.; Allen, A. C. *J. Org. Chem.* **1989**, *54*, 135.
13. Miyamoto, T.; Shigemitsu, Y.; Odaira, Y. *Chem. Commun.* **1969**, 1410.
14. Bach, T. *Synlett* **2000**, *12*, 1699.
15. Bach, T. *Liebigs Ann./Recueil* **1997**, 1627.
16. D'Auria, M.; Emanuele, L.; Racioppi, R.; Romaniello, G. *Current Organic Chemistry* **2003**, *4*, 1443.
17. Matsuura, K.; Araki, Y.; Ishido, Y.; Kushida, K. *Carbohydr. Res.* **1973**, *29*, 459.
18. Matsuura, K.; Araki, Y.; Ishido, Y. *Bull. Chem. Soc. Jpn.* **1972**, *45*, 3496.
19. Arnold, D. R.; Glick, A. H. *Chem. Commun.* **1966**, 813.
20. Kubota, T.; Shima, K.; Toki, S.; Sakurai, H. *Chem. Commun.* **1969**, 1462.
21. Friedrich, L. E.; Bower, J. D. *J. Am. Chem. Soc.* **1973**, *95*, 6869.
22. Jarosz, S.; Zamojski, A. *Tetrahedron* **1982**, *38*, 1453.
23. Koch, H.; Runsink, J.; Scharf, H.-D. *Tetrahedron Lett.* **1983**, *24*, 3217.
24. Bach, T.; Jodicke, K.; Kather, K.; Frohlich, R. *J. Am. Chem. Soc.* **1997**, *119*, 2437.
25. Hambalek, R.; Just, G. *Tetrahedron Lett.* **1990**, *31*, 5445.
26. Schreiber, S. L.; Hoveyda, A. H.; Wu, H.-J. *J. Am. Chem. Soc.* **1983**, *105*, 660.
27. Schreiber, S. L.; Satake, K. *Tetrahedron Lett.* **1986**, *27*, 2575.

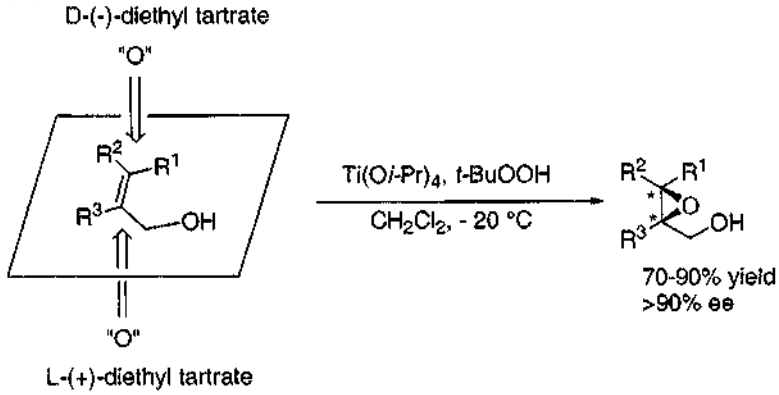
Christopher M. Liu

1.6 Sharpless–Katsuki Epoxidation

1.6.1 Description

The Sharpless–Katsuki asymmetric epoxidation reaction (most commonly referred by the discovering scientists as the AE reaction) is an efficient and highly selective method for the preparation of a wide variety of chiral epoxy alcohols.[1] The AE reaction is comprised of four key components: the substrate allylic alcohol, the titanium isopropoxide pre-catalyst, the chiral ligand diethyl tartrate, and the terminal oxidant *tert*-butyl hydroperoxide. The reaction protocol is straightforward and does not require any special handling techniques. The only requirement is that the reacting olefin contains an allylic alcohol.

Scheme 1.6.1



The AE reaction has emerged as one of the most utilized asymmetric transformations in organic synthesis because of its many appealing attributes. First, the starting allylic alcohols are either commercially available or are easily prepared. Second, the generality of the reaction is substantial given the fact that almost any substitution pattern on the allylic alcohol is permissible, and that a wide variety of functional groups are tolerated. Third, the catalyst, ligand, and oxidant are cheap and readily available. Fourth, the product epoxides are valuable chiral building blocks that can be easily elaborated into more complex molecules. And lastly, the stereochemical outcome of the product epoxide can be predicted with almost complete certainty based on the pneumonic diagram shown in Scheme 1.6.1. These attributes have made the AE reaction one of the most widely utilized asymmetric catalytic transformations to date.

1.6.2 Historical Perspective

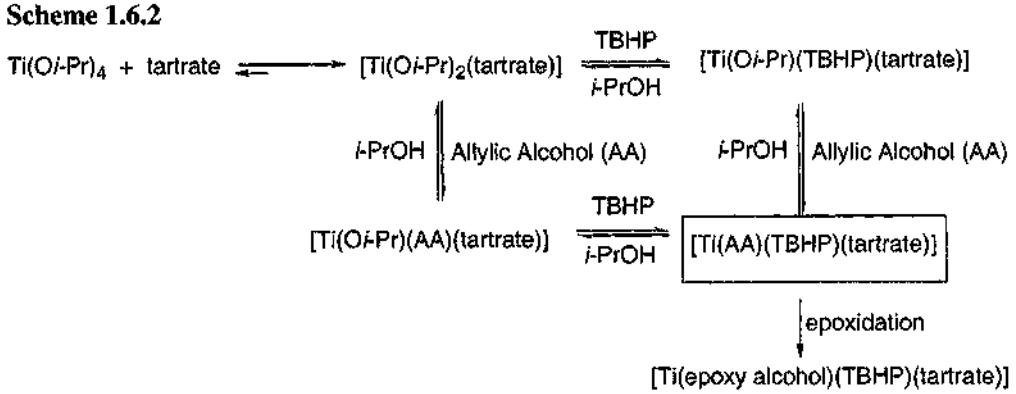
In 1980, Katsuki and Sharpless communicated that the epoxidation of a variety of allylic alcohols was achieved in exceptionally high enantioselectivity with a catalyst derived from titanium(IV) isopropoxide and chiral diethyl tartrate.[2] This seminal contribution described an asymmetric catalytic system that not only provided the product epoxide in remarkable enantioselectivity, but showed the immediate generality of the reaction by examining 5 of the 8 possible substitution patterns of allylic alcohols; all of which were epoxidized in >90% ee. Shortly thereafter, Sharpless and others began to illustrate the

broad scope of the reaction and subsequently demonstrated its wide utility in organic synthesis. Indeed, the AE reaction has emerged as one of the most widely utilized asymmetric transformations. In addition to the asymmetric epoxidation of prochiral allylic alcohols, the reaction protocol has been successfully applied to the kinetic resolution of secondary allylic alcohols[3] and the desymmetrization of meso-bis allylic alcohols.[4] The importance of the discovery and development of this remarkable reaction, along with other asymmetric catalytic reactions, was recognized in part by the presentation of the 2002 Nobel prize in chemistry to K. B. Sharpless, R. Noyori, and J. Knowles.

1.6.3 Mechanism

Elucidating the mechanism of the AE reaction has been the focus of much effort given the importance of the AE reaction in synthetic organic chemistry.[5] Fundamental questions that need to be addressed include the following: what is the rate law/rate determining step, what is the structure of the active catalyst complex, and what are the underlying factors that impart such high enantioselectivity? Answers to all of these questions have been largely addressed through careful experimental[6] and computational studies.[7]

Scheme 1.6.2



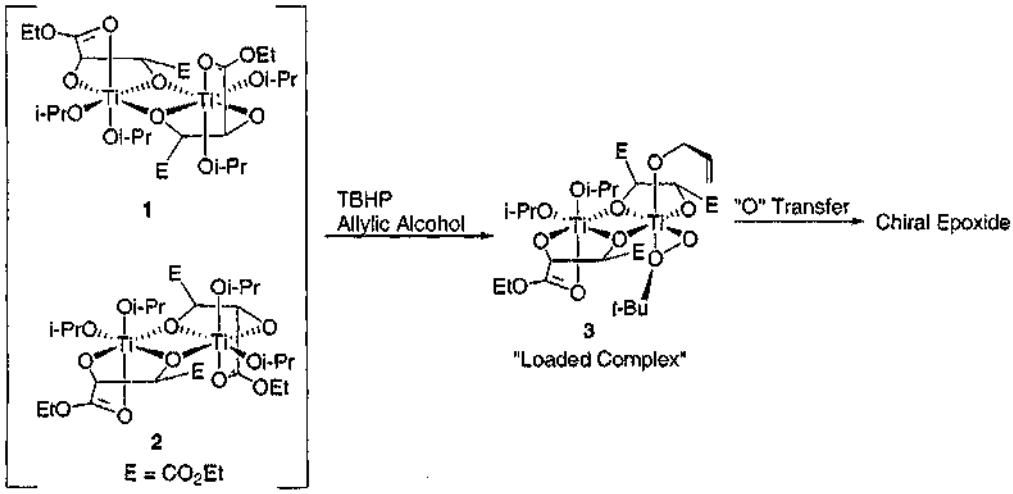
Sharpless *et al.* have shown that a dynamic process exists between various relevant titanium species during the AE reaction via rapid alkoxide exchange.[8] First, complexation of the bidentate tartrate ligand occurs rapidly with Ti(i-OPr)$_4$ with concomitant release of 2 equivalents of iPrOH. Subsequent ligand substitution of another i-OPr alkoxide with TBHP produces the Ti(O-iPr)(TBHP)(tartrate) complex. Likewise, ligand substitution of an O-*i*-Pr alkoxide with the allylic alcohol (AA) produces the Ti(O-*i*-Pr)(AA)(tartrate). Final substitution of either complex with AA or TBHP respectively produces the "loaded" complex Ti(TBHP)(AA)(tartrate). Rate determining intramolecular transfer of the peroxide oxygen to the coordinated allylic alcohol provides Ti(O-*t*-Bu)(EA)(tartrate) where EA is the product epoxy alcohol. Ligand displacement of the product epoxy alcohol and tBuOH with another allylic alcohol and TBHP regenerates the loaded complex. The ability of alkoxides to rapidly ligand exchange on the titanium center allows for the titanium catalyst to effectively catalyze the desired reaction with good efficiency.

$$\text{rate} = k\,\frac{[\text{allylic alcohol}][\text{Ti(O-iPr)}_2\text{tartrate}][\text{TBHP}]}{[\text{inhibitor alcohol}]^2}$$

A great deal of kinetic information on the AE reaction has been obtained. The rate of reaction is first order in allylic alcohol, $Ti(O\text{-}iPr)_2$(tartrate), and TBHP. In addition, the rate is inversely-square dependent on isopropoxide. This reflects the required replacement of two isopropoxide ligands on $Ti(O\text{-}iPr)_2$(tartrate) with TBHP and the allylic alcohol. The rate-determining step is oxygen transfer from the peroxide to the olefin.

Studies in varying the amount of tartrate per titanium have shown that exactly 1 equivalent of tartrate per titanium is required for good catalytic activity and selectivity.[6a] The active catalyst is proposed to be the dimeric complex Ti_2(tartrate)$_2$(O-*i*-Pr)$_4$. Sharpless has shown that a protocol using a ratio 1:1.2 equivalents of $Ti(O\text{-}i\text{-}Pr)_4$ to tartrate ligand is optimal for the AE reaction. This ratio maximizes the concentration of the more highly active and enantioselective catalyst Ti_2(tartrate)$_2$(O-*i*-Pr)$_4$, while suppressing the concentration of the less selective and less catalytically active Ti_2(tartrate)(O-*i*-Pr)$_6$/$Ti(O\text{-}i\text{-}Pr)_4$ complexes as well as the catalytically inactive Ti_2(tartrate)$_2$ complex.

Scheme 1.6.3



Determining the placement and orientation of tartrate ligand, allylic alcohol, and TBHP about the Ti-catalyst during the critical oxygen transfer step is crucial to understanding why such high enantioselectivities are achieved with a large variety of allylic alcohols. Any proposed model must take into effect the absolute stereochemistry of the product as predicted by the pneumonic diagram in Scheme 1.6.1, since virtually all AE reactions abide by this diagram. Structural evidence supports a dimeric titanium tartrate species as the predominant species in solution.[9] NMR shows the tartrate carbonyls are equivalent thus suggesting fast equilibrium of the two structurally degenerate complexes **1** and **2** (Scheme 1.6.4). Loading of the catalyst with TBHP and

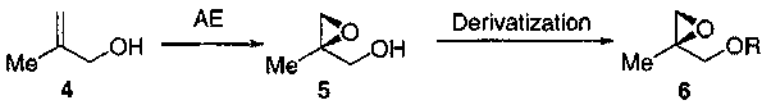
allylic alcohol gives the "loaded complex" **3**. The structure of the proposed loaded complex is based on minimization of stereoelectronic interaction of the TBHP and allylic alcohol with the adjacent tartrate ligand and the trajectory required for oxygen transfer of the distal oxygen to the olefin.[10] Relative rate studies of electronically diverse olefins reveals that the olefin acts as the nucleophile. This model also agrees with the predictive outcome as shown by pneumonic diagram in Scheme 1.6.10. It can not be unequivocally ruled out that both titanium species are participating in the epoxidation step. A mechanism involving zwitterionic titanium species has also been proposed.[11]

1.6.4 Variations and Improvements

The AE reaction is general and efficient, thus few substantial improvements have been reported. The most significant improvement to the original conditions is the addition of activated molecular sieves.[12] The addition of activated molecular sieves allows for almost all AE reaction to be performed under catalytic conditions (5–10 mol%). The role of the molecular sieves is thought to sequester any adventitious water or water that may be generated during the course of the reaction via side reactions.

The ability to perform the AE reaction under catalytic conditions via the addition of molecular sieves has greatly enhanced the synthetic utility of the reaction. For water-soluble epoxy alcohols, the catalytic conditions are beneficial for both enantioselectivity and isolated yield. In addition, epoxy alcohols that are susceptible to ring opening via nucleophilic substitution at the C-3 position also greatly benefit from catalytic conditions, since the substitution reaction is known to be promoted by Ti(IV) species.[13]

Table 1.6.1. Epoxidation of 2-methyl-2-propene-1-ol; beneficial effects of catalytic reactions and derivatization.[14]



4 **5** **6**

Entry	Catalyst (%)	Ligand (%)	R =[a]	% yield	% ee[b]
1	Ti(O-*t*-Bu)$_4$ (100)	DET (100)	H	-	85
2	Ti(O-*i*-Pr)$_4$ (27)	DET (27)	H	32	94
3	Ti(O-*t*-Bu)$_4$ (7.6)	DET (10)	H	47	>95
4	Ti(O-*i*-Pr)$_4$ (5)	DIPT (6)	PNB	78	92(98)
5	Ti(O-*i*-Pr)$_4$ (5)	DIPT (6)	Tos	69	95
6	Ti(O-*i*-Pr)$_4$ (5)	DIPT (6)	Nps	60	92

[a] PNB is p-nitrobenzoate, Tos is tosylate, and Nps is 2-naphthylenesulfonyl.
[b] number in parenthesis is the ee after recrystallization.

In conjunction with the addition of molecular sieves, Sharpless *et al.* as also developed an *in situ* derivatization of product epoxy alcohols that were previously difficult to isolate.[15] The derivatization of the product has been accomplished via esterification or sulfonylation of the alcohol functionality. The derivatization is possible only under catalytic conditions given the overwhelming presence of isopropoxide from stoichiometric amounts of Ti(O-i-Pr)$_4$ and the presence of the diol ligand diethyl tartrate.

Advantages of the *in situ* generation include ease of isolation and ee upgrades of crystalline products.[16] Table 1.6.1 shows the beneficial effect of performing the AE reaction under catalytic conditions as well as *in situ* derivatization.

A number of reaction variables or parameters have been examined. Catalyst solutions should not be prepared and stored since the resting catalyst is not stable to long term storage. However, the catalyst solution must be aged prior to the addition of allylic alcohol or TBHP. Diethyl tartrate and diisopropyl tartrate are the ligands of choice for most allylic alcohols. TBHP and cumene hydroperoxide are the most commonly used terminal oxidant and are both extremely effective. Methylene chloride is the solvent of choice and $Ti(i\text{-}OPr)_4$ is the titanium precatalyst of choice. Titanium (IV) *t*-butoxide is recommended for those reactions in which the product epoxide is particularly sensitive to ring opening from alkoxide nucleophiles.[13]

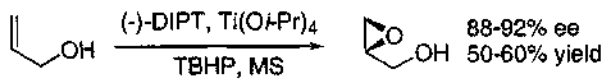
1.6.5 Synthetic Utility

The AE reaction has been applied to a large number of diverse allylic alcohols. Illustration of the synthetic utility of substrates with a primary alcohol is presented by substitution pattern on the olefin and will follow the format used in previous reviews by Sharpless but with more current examples. Epoxidation of substrates bearing a chiral secondary alcohol is presented in the context of a kinetic resolution or a match versus mismatch with the chiral ligand. Epoxidation of substrates bearing a tertiary alcohol is not presented, as this class of substrate reacts extremely slowly.

1.6.5.1 Allyl alcohol

Epoxidation of the simplest allylic alcohol, allyl alcohol **7**, is achieved in 88–92% ee with yields of 50–60% using diisopropyl tartrate as ligand.[12] *In situ* derivatization of the product glycidol **8** via esterification, sulfonylation, or ring opening with nucleophile is an attractive alternative to isolating glycidol.

Scheme 1.6.4

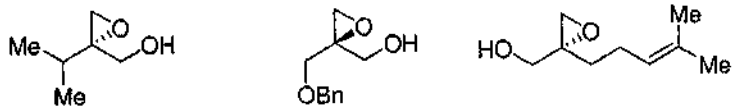


7 **8**

1.6.5.2 2-Substituted allyl alcohols

In general, 2-substituted allylic alcohols are epoxidized in good enantioselectivity. Like glycidol, however, the product epoxides are susceptible to ring opening via nucleophilic attack at the C-3 position. Results of the AE reaction on 2-methyl-2-propene-1-ol followed by derivatization of the resulting epoxy alcohol are shown in Table 1.6.1. Other examples are shown below.

Scheme 1.6.5



9[17] 95% ee, 85% yield

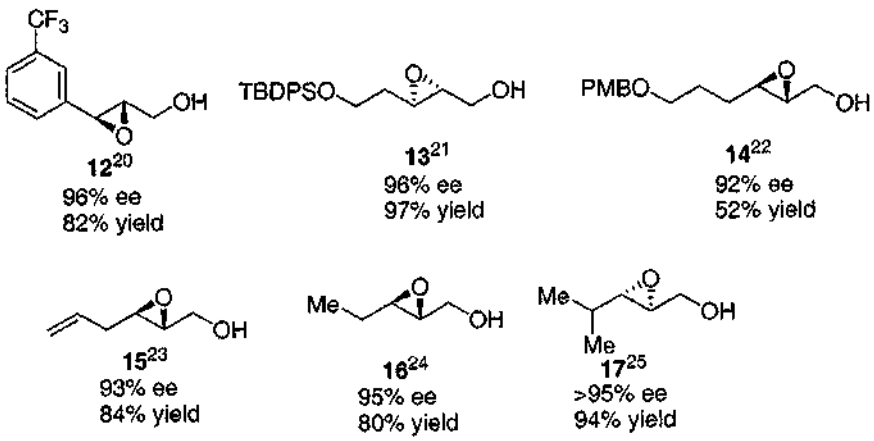
10[18] >95% ee, 74% yield

11[19] 88% ee, 77% yield

1.6.5.3 3E-Substituted allyl alcohols

This class of substrate is one of the most widely used class of substrates for the AE reaction. The starting allylic alcohols are readily prepared and are generally epoxidized in high enantioselectivity. Epoxide **12** was obtained in high enantioselectivity and utilized in the rapid preparation of (*S*)-Fenfluramine. Epoxide **13** was prepared under the standard AE conditions and then oxidized with DDQ to provide the corresponding 4-hydroxy-2,3-unsaturated carbonyl. These type of structures are found in numerous polyketides, including macrosphelide A. Epoxide **14** was prepared via the AE reaction and utilized in the synthesis of (−)-swainsonine. Epoxides **15** and **16** were utilized in the synthesis of baikiain and the acyl side chain segment of polyoxypeptin A respectively. Finally, epoxide **17** was prepared and subsequently incorporated in the formal synthesis of the proteasome inhibitor (+)-lactacystin.

Scheme 1.6.6



12[20] 96% ee, 82% yield

13[21] 96% ee, 97% yield

14[22] 92% ee, 52% yield

15[23] 93% ee, 84% yield

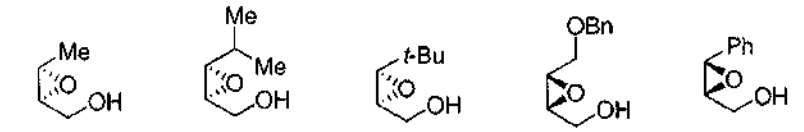
16[24] 95% ee, 80% yield

17[25] >95% ee, 94% yield

1.6.5.4 3Z-Substituted allyl alcohols

This class of substrate is the only real problematic substrate for the AE reaction. The enantioselectivity of the AE reaction with this class of substrate is often variable. In addition, rates of the catalytic reactions are often sluggish, thus requiring stoichiometric loadings of Ti/tartrate. Some representative product epoxides from AE reaction of 3Z-substituted allyl alcohols are shown below.

Scheme 1.6.7



18[17] 92% ee 68% yield

19[26] 66% ee 54% yield

20[27] 25% ee 75% yield

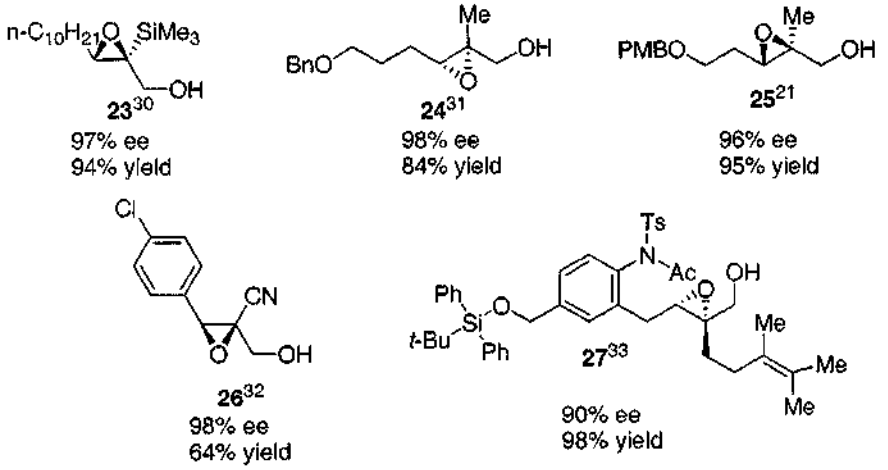
21[28] 92% ee 84% yield

22[29] 78% ee 61% yield

1.6.5.5 2,3E-Disubstituted allyl alcohols

As with *3E*-substituted allyl alcohols, *2,3E*-substituted allyl alcohols are epoxidized in excellent enantioselectivity. Examples of AE reactions of this class of substrate are shown below. Epoxide **23** was utilized to prepare chiral allene oxides, which were ring opened with TBAF to provide chiral α-fluoroketones. Epoxide **24** was used to prepare 5,8-disubstituted indolizidines and epoxide **25** was utilized in the formal synthesis of macrosphelide A. Epoxide **26** represents an AE reaction on the very electron deficient 2-cyanoallylic alcohols and epoxide **27** was an intermediate in the total synthesis of (+)-varantmycin.

Scheme 1.6.8



23[30] 97% ee 94% yield

24[31] 98% ee 84% yield

25[21] 96% ee 95% yield

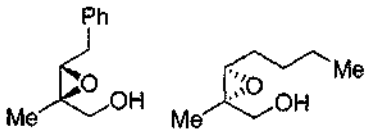
26[32] 98% ee 64% yield

27[33] 90% ee 98% yield

1.6.5.6 2,3Z-Disubstituted allyl alcohols

There are only limited examples of AE reactions on 2,3Z-substituted allyl alcohols. This may be due in part to the difficulty involved in selectively preparing the starting allylic alcohol.

Scheme 1.6.9

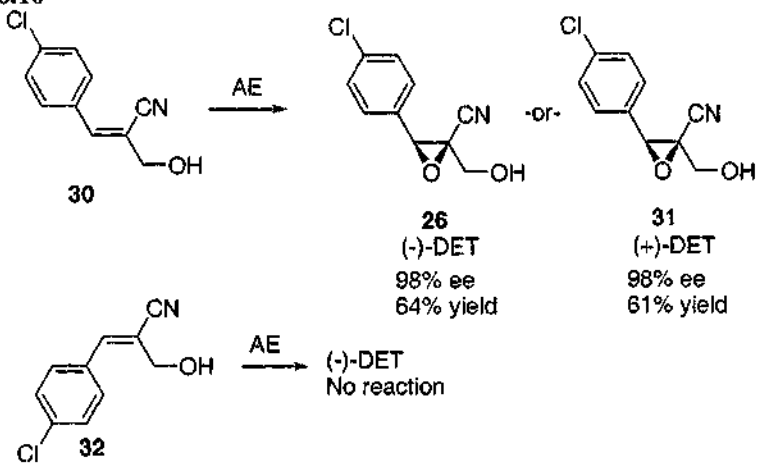


28[34] 91% ee 90% yield

29[2] 89% ee 80% yield

Although the limited examples of AE reactions on 2,3Z-substituted allyl alcohols appear to give product epoxides in good enantioselectivity, the highly substituted nature of these olefins can have a deleterious effect on the reactivity. For example, Aiai has shown that the 2,3E-substituted allyl alcohol **30** can be epoxidized with either (−)-DET or (+)-DET in good yields and enantioselectivity. However, the configurational isomer **32** is completely unreactive using (−)-DET, even after a 34 h reaction time.

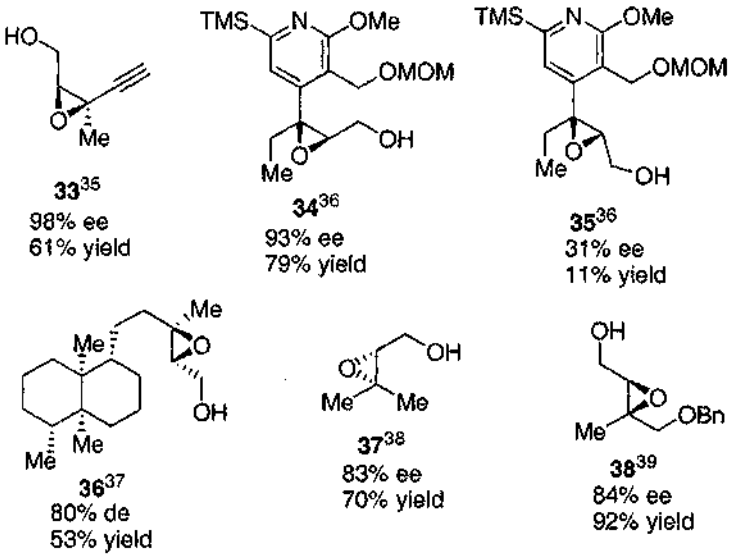
Scheme 1.6.10



1.6.5.7 3,3-Disubstituted allyl alcohols

The 3,3-disubstituted allyl alcohols generally undergo the AE reaction with good enantioselectivity. Epoxide **33** was prepared by the AE reaction on an enyne and subsequently elaborated to the core unit of the non-nucleoside reverse transcriptase inhibitor taurospongin A. The highly functionalized epoxide **34** was prepared in good enantioselectivity and yield using (+)-DET as ligand. Interestingly, epoxidation of the isomeric substrate in which the methyl group is E to the alcohol with (−)-DET gave the diastereomeric product **35** in only 31% ee and in 11% yield. Not surprisingly, the reaction was relatively sluggish. Epoxide **36** was obtained in a 9:1 diastereomeric ratio under standard AE conditions and was utilized in the synthesis of *ent*-nakamural A. Epoxide **37** was prepared and trapped *in situ* as the trityl ether. Crystallization of the trityl ether increased the ee to >99%. Epoxide **38** was prepared and utilized in the synthesis of the tricyclic core of Phomactin A.

Scheme 1.6.11



33[35]
98% ee
61% yield

34[36]
93% ee
79% yield

35[36]
31% ee
11% yield

36[37]
80% de
53% yield

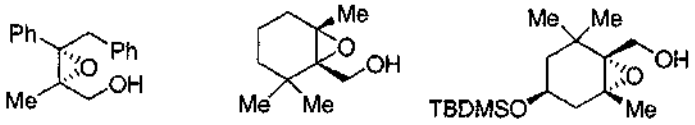
37[38]
83% ee
70% yield

38[39]
84% ee
92% yield

1.6.5.8 2,3,3-Trisubstituted allyl alcohols

The AE reactions on *2,3,3*-trisubstituted allyl alcohols have received little attention, due in part the limited utility of the product epoxides. Selective ring opening of tetrasubstituted epoxides are difficult to achieve. Epoxide **39** was prepared using stoichiometric AE conditions and were subsequently elaborated to Darvon alcohol. Epoxides **40** and **41** were both prepared in good selectivity and subsequently utilized in the preparation of (-)-cuparene and the polyfunctoinal carotenoid peridinin, respectively.

Scheme 1.6.12



39[40]
94% ee
90% yield

40[41]
98% ee
89% yield

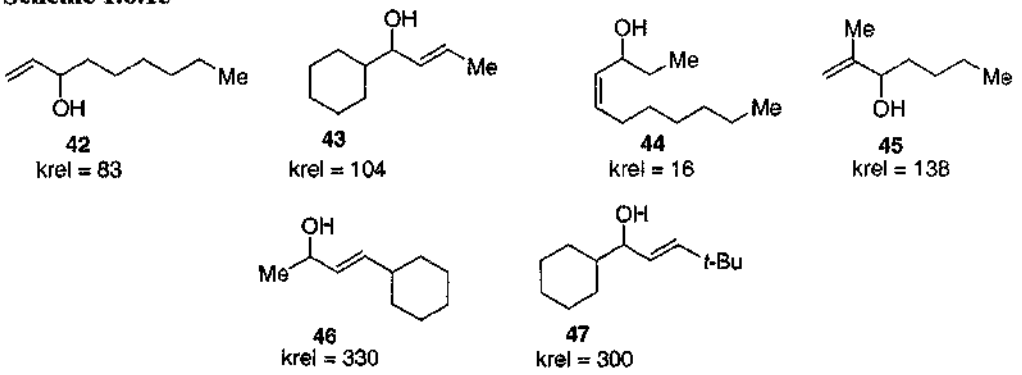
41[42]
92% de
99% yield

1.6.5.9 Kinetic resolution of chiral allylic alcohols

Given the universal predictive value of the pneumonic diagram in Scheme 1.6.1 coupled with the high enantioselectivity observed with a wide variety of allylic alcohols, it is not surprising that the AE reaction is sensitive to preexisting chirality on the allylic alcohol substrate. Indeed, allylic secondary alcohols can undergo effective kinetic resolution to provide enantiomerically enriched allylic secondary alcohols and diastereomerically enriched product epoxides.[43] The relative rates (k_{rel}) of each enantiomer of the starting allylic alcohol with a given enantiomer of tartrate ligand can be significantly different. Thus using 0.6 equiv of TBHP, and carrying out the reaction to 55 ± 5% conversion, chiral secondary allylic alcohols can be obtained in excellent enantioselectivity and in moderate yield.[44] If the epoxy alcohol is desired, then 0.45 equivalents of TBHP is often

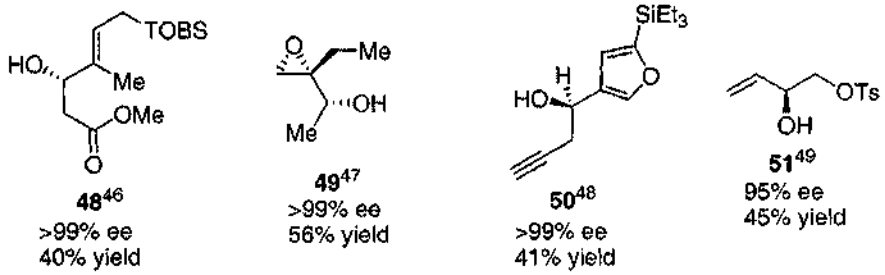
used. Shown below are a number of racemic allylic alcohols with their relative rates of each enantiomer.[45]

Scheme 1.6.13



The application of the AE reaction to kinetic resolution of racemic allylic alcohols has been extensively used for the preparation of enantiomerically enriched alcohols and allyl epoxides. Allylic alcohol **48** was obtained via kinetic resolution of the racemic secondary alcohol and utilized in the synthesis of rhozoxin D. Epoxy alcohol **49** was obtained via kinetic resolution of the enantioenriched secondary allylic alcohol (93% ee). The product epoxy alcohol was a key intermediate in the synthesis of (−)-mitralactonine. Allylic alcohol **50** was prepared via kinetic resolution of the secondary alcohol and the product utilized in the synthesis of (+)-manoalide. The mono-tosylated 3-butene-1,2-diol is a useful C_4 building block and was obtained in 45% yield and in 95% ee via kinetic resolution of the racemic starting material.

Scheme 1.6.14

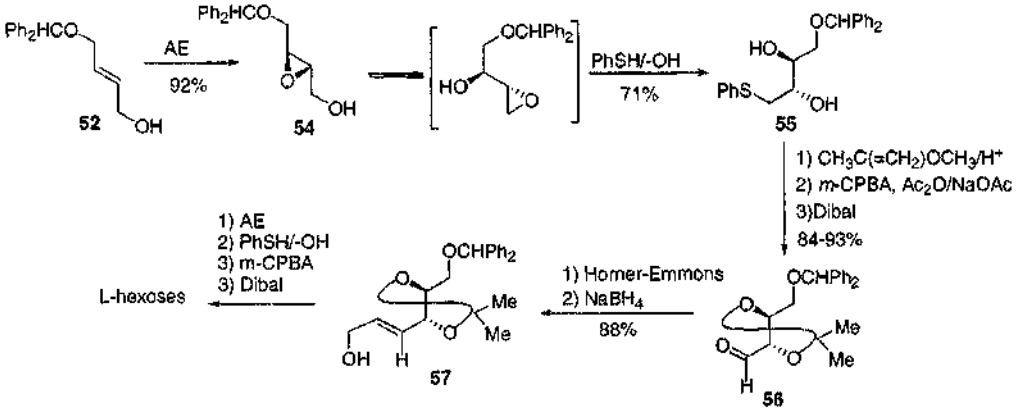


1.6.5.10: Unique synthetic applications

Sharpless and Masumune have applied the AE reaction on chiral allylic alcohols to prepare all 8 of the L-hexoses.[50] AE reaction on allylic alcohol **52** provides the epoxy alcohol **53** in 92% yield and in >95% ee. Base catalyze Payne rearrangement followed by ring opening with phenyl thiolate provides diol **54.** Protection of the diol is followed by oxidation of the sulfide to the sulfoxide via *m*-CPBA, Pummerer rearrangement to give the *gem*-acetoxy sulfide intermediate and finally reduction using Dibal to yield the desired aldehyde **56**. Horner-Emmons olefination followed by reduction sets up the second substrate for the AE reaction. The AE reaction on optically active **57** is reagent

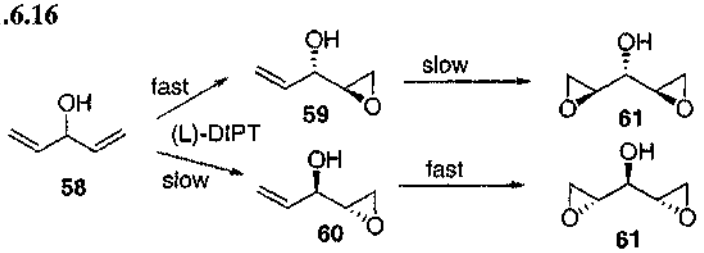
controlled. This four-step reiterative two-carbon extension cycle was used to prepare all 8 L-hexoses.

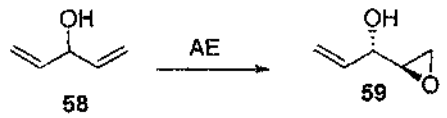
Scheme 1.6.15



Desymmetrization of meso-bis-allylic alcohols is an effective method for the preparation of chiral functionalized intermediates from meso-substrates. Schreiber *et al* has shown that divinyl carbonyl **58** is epoxidized in good enantioselectivity.[51] However, because the product epoxy alcohols **59** and **60** also contain a reactive allylic alcohol that are diastereomeric in nature, a second epoxidation would occur at different rates and thus affect the observed ee for the first AE reaction and the overall de. Indeed, the major diastereomeric product epoxide **59** resulting from the first AE is less reactive in the second epoxidation. Thus, high de is easily obtainable since the second epoxidation removes the minor diastereomer.

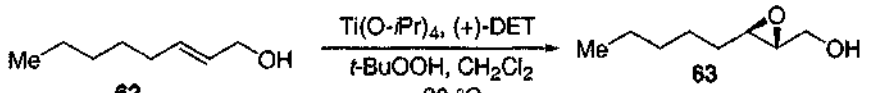
Scheme 1.6.16





Time (h)	%ee	% de
3	84	92
24	93	99.7
140	>97	>99.7

1.6.6 Experimental[12]



crude: 88% yield, 92.3 % ee
recrystallization: 73% yield, > 98% ee

An oven dried 1-L three-necked round-bottomed flask equipped with a magnetic stir bar, pressure equalizing addition funnel, thermometer, nitrogen inlet and bubbler was charged with 3.0 g of 4A powdered, activated molecular sieves and 350 mL of dry CH_2Cl_2. The flask was cooled to –20°C. L-(+)-Diethyl tartrate (1.24 g, 6.0 mmol) and Ti(O-i-Pr)$_4$ (1.49 mL, 1.42 g, 5.00 mmol, via syringe) were added sequentially with stirring. The reaction mixture was stirred at –20°C as TBHP (39 mL, 200 mmol, 5.17 M in isooctane) was added through the addition funnel at a moderate rate (over 5 min). The resulting mixture was stirred at –20°C for 30 min. (E)-2-octenol (**62**, 12.82 g, 100 mmol) dissolved in 50 mL of CH_2Cl_2 was then added drop wise through the same addition funnel over a period of 20 min while maintaining the temperature at –15 to –20°C. The mixture was stirred for an additional 3.5 h at –15 to –20°C. The reaction was allowed to warm to room temperature and poured into a beaker containing ferrous sulfate heptahydrate (33 g, 120 mmol), citric acid monohydrate (11 g, 60 mmol) and 100 mL of deionized water. The two-phase mixture was stirred for 10 min and separated. The aqueous phase was extracted with two 30 mL portions of ether. The combined organic layers were treated with 10 mL of precooled (0°C) solution of 30% NaOH (w/v) in saturate brine and stirred for 1 h at 0°C. To this was added 50 mL of water and the aqueous phase extracted with 2 × 50 mL of ether. The combined organic layers were dried over sodium sulfate, filtered and concentrated. Crude product yield was 88% with a 92.3% ee. Two crystallizations in petroleum ether affords the product **63** in > 98% ee and in 73% isolated yield.

1.6.7 References

1. For excellent reviews see: [R] (a) Johnson, R. A.; Sharpless, K. B. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed,; Pergamon Press: New York, 1991; Vol. 7, Chapter 3.2. [R] (b) Johson, R. A.; Sharpless, K. B. In *Catalytic Asymmetric Synthesis*; Ojima, I., Ed,; VCH: New York, 1993; Chapter 4.1, pp 103-158.
2. Katsuki, T.; Sharpless, K.B. *J. Am. Chem. Soc.* **1980**, *102*, 5974.
3. Martin, V. S.; Woodard, S. S.; Katsuki, T.; Yamada, Y.; Ikeda, M.; Sharpless, K. B. *J. Am. Chem. Soc.* **1981**, *103*, 6237.
4. (a) Hatakeyama, S.; Sakurai, K.; Takano, S.; *J. Chem.. Soc., Chem. Commun.* **1985**, 1759. (b) Hafele, B.; Schroter, d.; Jager, V. *Angew Chem., Int. Ed. Engl.* **1986**, *25*, 87. c) Schreiber, S. L.; Schreiber, T. S; Smith, D. B. *J. Am. Chem. Soc.* **1987**, *109*, 1525.
5. [R] (Finn, M. G.; Sharpless, B. M. In Asymmetric Synthesis; Morrison, J. D., Ed.; Academic Press: New York,Vol 5, Chapter 8.
6. (a) Woodard, S. S.; Finn, M. G.; Sharpless, B. M. *J. Am. Chem. Soc.* **1991**, *113*, 106. (b) Finn, M. G.; Sharpless, K. B. *J. Am. Chem. Soc.* **1991**, *113*, 113-126. c) Potvin, P. G.; Bianchet, S. *J. Org. Chem.* **1992**, *57*, 6629.
7. Wu, Y.-D.; Lai, D. K. W. *J. Am. Chem. Soc.* **1995**, *117*, 11327.
8. Sharpless, K. B.; Woodard, S. S.; Finn, M. G. *Pure & Appl. Chem.*. **1983**, *55*, 1823.
9. X-Ray crystallographic structure of a Ti_2(dibenzyltartamide)$_2$(OiPr)$_4$ species has been obtained.
10. Potvin, P. G.; Bianchet, S. *J. Org. Chem.* **1992**, *57*, 6629.
11. Corey, E. J. *J. Org. Chem.* **1990**, *55*, 1693.

12. Gao, Y.; Hanson, R. M.; Klunder, J. M.; Ko, S. Y.; Masamune, H.; Sharpless, K. B. *J. Am. Chem. Soc.* **1987**, *109*, 5765.
13. Lu, L. D.-L.; Johnson, R. A.; Finn, M. G.; Sharpless, K. B. *J. Org. Chem.* **1984**, *49*, 728.
14. (a) Meister, C.; Scharf, H. D. *Justus Liebigs Ann. Chem.*. **1983**, 913. (b) Tanner, D.; Somfai, P. *Tetrahedron* **1986**, *42*, 5985. c) Giese, B.; Rupaner, R.; *Justus Liebigs Ann. Chem.*. **1987**, 231.
15. Klunder, J. M.; Ko, S. Y.; Sharpless, B. M. *J. Org. Chem.* **1986**, *51*, 3710.
16. For examples of *in situ* derivatization see: (a) Berger, D.; Overman, L. E.; Renhowe, R. A. *J. Am. Chem. Soc.* **1993**, *115*, 9305. (b) Uemura, I.; Yamada, K.; Sugiura, K.; Miyagawa, H.; Ueno, T. *Tetrahedron Asymm.* **2001**, *12*, 942. (c) DeGoey, D. A.; Chen, H.-J.; Flost, W. J.; Grampovnik, D. J.; Yeung, C. M.; Klein, L. L.; Kempf, D. J. *J. Org. Chem.* **2002**, *67*, 5445.
17. Gao, Y.; Hanson, R. M.; Klunder, J. M.; Ko, S. Y.; Masamune, H.; Sharpless, K. B. *J. Am. Chem. Soc.* **1987**, *109*, 5765.
18. Tanner, D.; Somfai, P. *Tetrahedron* **1986**, 42, 5985.
19. McDonald, F. E.; Bravo, F.; Wang, X.; Wei, X.; Toganoh, M.; Rodriguez, J. R.; Do, B.; Neiwert, W. A.; Hardcastle, K. I. *J. Org. Chem.* **2002**, *67*, 2523.
20. Goument, B.; Duhamel, L.; Mauge, R. *Tetrahedron* **1994**, *50*, 171.
21. Chakraborty, R. K.; Purkait, S.; Das, S. *Tetrahedron* **2003**, *59*, 9127.
22. Lindsay, K. B.; Pyne, S. G. *J. Org. Chem.* **2002**, *67*, 7774.
23. Ginesta, X.; Pericas, M. A.; Riera, A. *Tetrahedron Lett.* **2002**, *43*, 779.
24. Makino, K.; Suzuki, T.; Awane, S.; Hara, O.; Hamada, Y. *Tetrahedron Lett.* **2002**, *43*, 9391.
25. Green, M. P.; Prodger, J. C.; Hayes, C. J. *Tetrahedron Lett.* **2002**, *43*, 6609.
26. Wood, R. D.; Ganem, B.; *Tetrahedron Lett.* **1982**, *23*, 707.
27. Adam, W.; Braun, M.; Griesbeck, A.; Lucchinni, V.; Staab, E.; Will, B.; *J. Am. Chem. Soc.* **1989**, *111*, 203.
28. Katsuki, T.; Lee, A. W.; Ma, P.; Martin, V. S.; Masamune, S.; Sharpless, K. B. *J. Org. Chem.* **1982**, *47*, 1373.
29. Denis, J.-N.; Greene, A. E.; Serra, A. A.; Luche, M.-J. *J. Org. Chem.* **1986**, *51*, 46.
30. Kabat, M. M. *Tetrahedron Asymm.* **1993**, *4*, 1417.
31. Satake, A.; Shimizu, I. *Tetrahedron Asymm.* **1993**, *4*, 1405.
32. Aiai, M.; Robert, A.; Baudy-Floc'h, M.; Le Grel, P. *Tetrahedron Asymm.* **1995**, *6*, 2249.
33. Morimoto, Y.; Oda, K.; Shirahama, H.; Matsumoto, T.; Omura, S. *Chemistry Lett.* **1998**, 909.
34. Sharpless, K. B.; Behrens, C. H.; Katsuki, T.; Lee, A. W.; Martin, V. S.; Takatani, M.; Viti, S. M.; Walker, F. J.; Woodard, S. S. *Pure Appl. Chem.* **1983**, *55*, 589.
35. Ghosh, A. K.; Lei, H. *Tetrahedron Asymm.* **2003**, *14*, 629.
36. Gabarda, A. E.; Du, W.; Isarno, T.; Tangirala, R. S.; Curran, D. P. *Tetrahedron* **2002**, *58*, 6329.
37. Diaz, S.; Cuesta, J.; Gonzalez, A.; Bonjoch, J. *J. Org. Chem. Soc.* **2003**, *68*, 7400.
38. Uemura, I.; Yamada, K.; Sugiura, K.; Miyagawa, H.; Ueno, T. *Tetrahedron Asymm.* **2001**, *12*, 943.
39. Mohr, P. J.; Halcomb, R. L. *Org. Lett.* **2002**, *4*, 2413.
40. Erickson, T. J. *J. Org. Chem.* **1986**, *51*, 934.
41. Abad, A.; Agullo, c.; Arno, M.; Cunat, A. C.; Garcia, M. T.; Zaragoza, R. *J. Org. Chem.* **1996**, *61*, 5916.
42. Furuichi, N.; Hara, H.; Osaki, T.; Mori, H.; Katsumura, S. *Angew. Chem. Int. Ed.* **2002**, *41*, 1023.
43. Martin, V. S.; Woodard, S. S.; Katsuki, T.; Yamada, Y.; Ikeda, M.; Sharpless, K. B. *J. Am. Chem. Soc. 1981*, *103*, 6237.
44. Note that the maximum yield for a kinetic resolution is 50%.
45. (a) See reference 43. (b) Carlier, P. R.; Mungall, W. S.; Schroder, G.; Sharpless, K. B. *J. Am. Chem. Soc.* **1988**, *110*, 2978.
46. Lafontaine, J. A.; Provencal, D. P.; Gardelli, C.; Leahy, J. W. *J. Org. Chem.* **2003**, *68*, 4215.
47. Takayama, H.; Kurihara, M.; Kitajima, M.; Said, I. M.; Aimi, N. *J. Org. Chem. Soc.* **1999**, *64*, 1772.
48. Pommier, A.; Stepanenko, V.; Jarowicki, K.; Kocienski, P. J. *J. Org. Chem.* **2003**, *68*, 4008.
49. Neagu, C.; Hase, T. *Tetrahedron Lett.* **1993**, *34*, 1629.
50. Ko, S. Y.; Lee, A. W. M.; Masamune, S.; Reed, L. A. III; Sharpless, K. B; Walker, F. J. *Science*, **1983**, *220*, 949.
51. (a) Schreiber, S. L.; Schrieber, T. S.; Smith, D. B. *J. Am. Chem. Soc.* **1987**, *109*, 1525-1529. (b) Poss, C. S.; Shreiber, S. L. *Acc. Chem. Res.* **1994**, *27*, 9.

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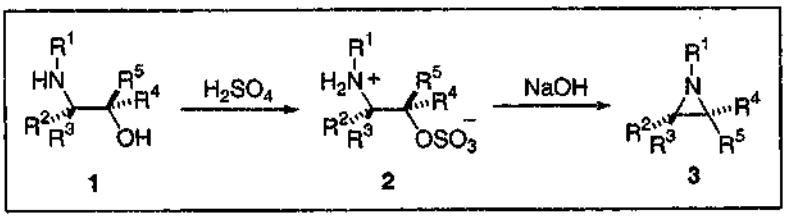
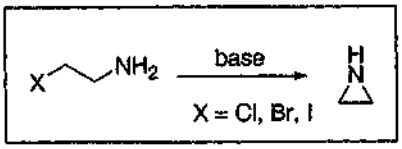
1.7 Wenker Aziridine Synthesis

1.7.1 Description

The Wenker aziridine synthesis entails the treatment of a β-amino alcohol **1** with sulfuric acid to give β-aminoethyl sulfate ester **2** which is subsequently treated with base to afford aziridine **3**.[1] Before the discovery of the Mitsunobu reaction, which transforms an amino alcohol into an aziridine in one step under very mild conditions, the Wenker reaction was one of the most convenient methods for aziridine synthesis. However, due to the involvement of strong acid and then strong base, its utility has been limited to substrates without labile functionalities.

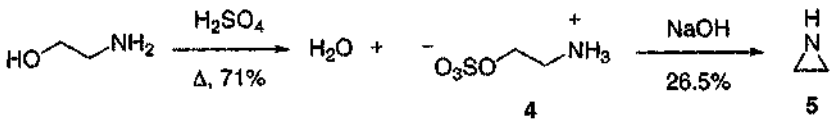


A related aziridine synthesis is the Gabriel reaction (a.k.a. Gabriel–Cromwell reaction),[2,3] which involves an intramolecular S_N2 reaction of a β-amino halide. However, the reaction has become so common that the name Gabriel is not tightly related to the transformation.



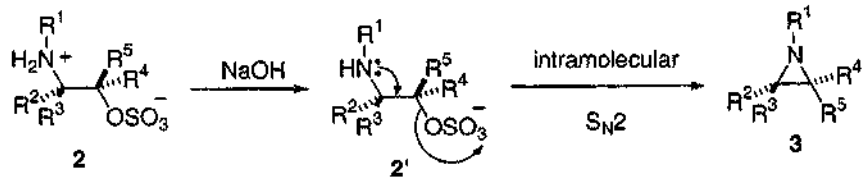
1.7.2 Historical Perspective

In 1935, Wenker[4] first prepared β-aminoethyl sulfate ester (**4**, a solid) from thermal dehydration of monoethanolamine acid sulfate at 250°C according to Gabriel's procedure.[4] Subsequently, the mixture of **4** and 40% NaOH aqueous solution was distilled. Further fractional distillation of the distillate in the presence of KOH and then Na at 55–56°C led to pure aziridine in 26.5% yield.



1.7.3 Mechanism

The mechanism for the Wenker aziridine synthesis is very straightforward. As depicted by conversion **2**→**3**, the transformation is a simple case of intramolecular S_N2 displacement process, in which the sulfate ester is the leaving group.



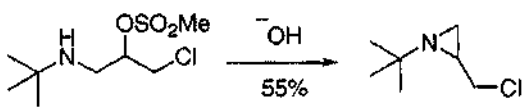
2 **2'** **3**

1.7.4 Variations and Improvements

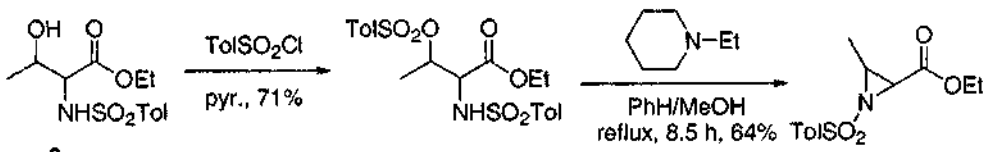
Due to the convenience of the Wenker aziridine formation from β-aminoethyl sulfate ester (**4**) and base, many improvements ensued. Leighton *et al.* improved the yield of the first step for the formation of sulfate ester **4**.[5] First of all, both ethanolamine and 95% sulfuric acid were diluted with half of their weight of water and then slowly mixed together at 0°C. Finally, by keeping the temperature below 145°C, sulfate ester **4** was obtained in 90–95% yield.

Another improvement of the Wenker reaction was utilization of flash distillation, which boosted the yield of **5** to 83% based on **4**.[6] In addition, a procedure involving the use of an aqueous reaction medium and the generation of the aziridine in solution was developed, which obviates the isolation and handling of anhydrous aziridine.[7]

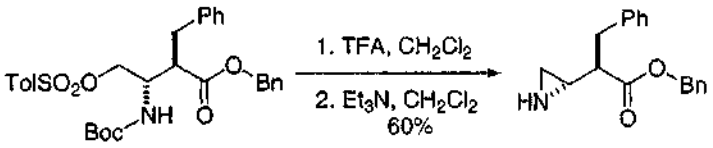
Mesylates and tosylates may be used as variants of the *O*-sulfate ester. For instance, 55% of aziridine **7** was obtained from base-mediated cyclization of amino mesylate **6**.[8] In comparison, the classic Wenker protocol only gave 3% of **7**. In another instance,[9] *N*-tosyl amino alcohol **8** was tosylated to give **9**, which was transformed to aziridine **10** in 64% yield, along with 29% of the β-elimination product due to the presence of the ester moiety. Likewise, aziridine **12** was assembled from tosylate **11** in two steps and 60% yield.[10]



6 **7**



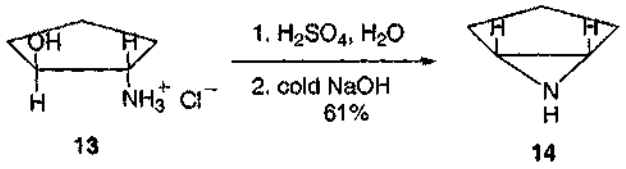
8 **9** **10**



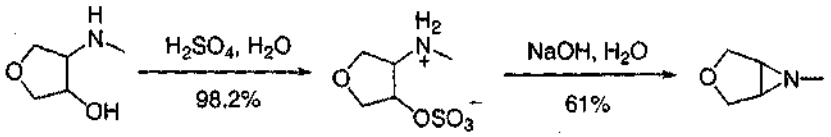
11 12

1.7.5 Synthetic Utility

As described in Section 1.7.1, the utility of the Wenker reaction is limited to substrates without labile functionalities because of the involvement of strong acid and then strong base. The Fanta group prepared a variety of aziridines by taking advantage of the Wenker reaction.[11–14] For example, 6-aza-bicyclo[3.1.0]hexane (**14**) was produced from the ring-closure of (±)-*trans*-2-aminocyclopentanol hydrochloride (**13**).[11] In a similar fashion, sulfate ester **16** was prepared from *N*-methyl *dl-trans*-3-amino-4-hydroxytetrahydrofuran (**15**). Subsequent treatment of sulfate ester **16** with NaOH then delivered aziridine **17**.[14] Additional examples of Wenker aziridine synthesis may also be found in references 15–17.

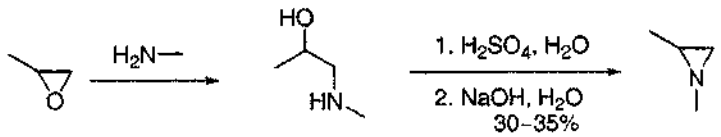


13 14

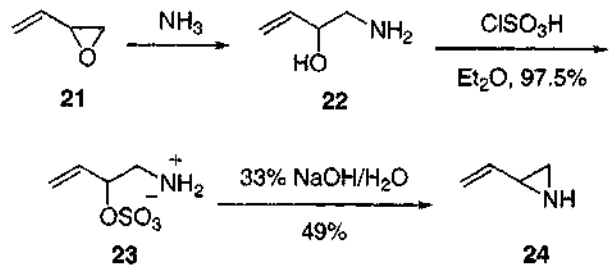


15 16 17

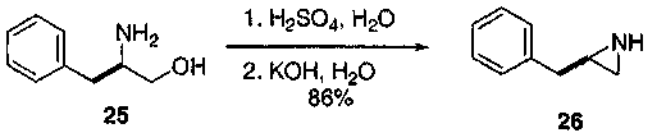
Due to the abundance of epoxides, they are ideal precursors for the preparation of β-amino alcohols. In one case, ring-opening of 2-methyl-oxirane (**18**) with methylamine resulted in 1-methylamino-propan-2-ol (**19**), which was transformed to 1,2-dimethyl-aziridine (**20**) in 30–35% yield using the Wenker protocol.[18] Interestingly, 1-amino-3-buten-2-ol sulfate ester (**23**) was prepared from 1-amino-3-buten-2-ol (**22**, a product of ammonia ring-opening of vinyl epoxide **21**) and *chlorosulfonic acid*. Treatment of sulfate ester **23** with NaOH then led to aziridine **24**.[19]



18 19 20



1.7.6 *Experimental*



(*S*)-2-Benzyl-aziridine (26)[17]

A cold mixture of sulfuric acid (98%, 4 g), and water (4 mL) was added to an amino-alcohol **25** (40 mmol) in water (2.4 mL) at 0–5°C. The mixture was heated to 120°C and then water was carefully distilled off *in vacuo*. The solid sulfate residue was treated with 6.2 M potassium hydroxide, and steam-distilled. The distillate was saturated with potassium hydroxide pellets and the upper organic layer, which separated, was fractionally distilled from potassium hydroxide through a short column to give a colorless oil aziridine **26** in 96% yield.

In addition, an *Organic Synthesis* procedure of preparing aziridine from β-amino alcohol exists.[20]

1.7.7 *References*

1. (a) [R] Deyrup, J. A. In *Small Ring Heterocycles*, Part 1, Hassner, A., ed.; Wiley-Interscience: New York, **1983**, 1–214. (b) [R] Dermer, O. C.; Ham, G. E. *Ethyleneimine and Other Aziridines*, Academic Press: New York, 1969.
2. (a) Filigheddu, S. N.; Masala, S.; Taddei, M. *Tetrahedron Lett.* **1999**, *40*, 6503. (b) Shustov, G. V.; Krutius, O.; Voznesenskii, V. N.; Chervin, I. I.; Eremeev, A. V.; Kostyanovskii, R. G.; Polyak, F. D. *Tetrahedron* **1990**, *46*, 6741. (c) Okada, I.; Ichimura, K.; Sudo, R. *Bull. Chem. Soc. Jpn.* **1970**, *43*, 1185. (d) Gabriel, S. *Ber.* **1895**, *28*, 2929.
3. Gabriel, S. *Ber.* **1888**, *21*, 1049, 2667.
4. Wenker, H. *J. Am. Chem. Soc.* **1935**, *57*, 2328.
5. Leighton, P. A.; Perkins, W. A.; Renquist, M. I. *J. Am. Chem. Soc.* **1947**, *69*, 1540.
6. Reeves, W. A.; Drake, G. L., Jr.; Hoffpauir, C. L. *J. Am. Chem. Soc.* **1951**, *73*, 3522.
7. Wystrach, V. P.; Kaiser, D. W.; Schaefer, F. C. *J. Am. Chem. Soc.* **1955**, *77*, 5915.
8. Gaertner, V. R. *J. Org. Chem.* **1970**, *35*, 3952.
9. (a) Nakagawa, Y.; Tsuno, T.; Nakajima, K.; Iwai, M.; Kawai, H.; Okawa, K. *Bull. Chem. Soc. Jpn.* **1972**, *45*, 1162. (b) Okawa, K.; Kinutani, T.; Sakai, K. *Bull. Chem. Soc. Jpn.* **1968**, *41*, 1353.
10. Park, J.-i.; Tian, G.; Kim, D. H. *J. Org. Chem.* **2001**, *66*, 3696.
11. Fanta, P. E. *J. Chem. Soc.* **1957**, 1441.
12. Fanta, P. E.; Walsh, E. N. *J. Org. Chem.* **1966**, *31*, 59.
13. Kaschelikar, D. V.; Fanta, P. E. *J. Am. Chem. Soc.* **1960**, *82*, 4927.
14. Kaschelikar, D. V.; Fanta, P. E. *J. Am. Chem. Soc.* **1960**, *82*, 4930.
15. Brois, S. J. *J. Org. Chem.* **1962**, *27*, 3532.

16. Brewster, K; Pinder, R. M. *J. Med. Chem.* **1972**, *15*, 1078.
17. Xu, *J. Tetrahedron: Asymmetry* **2002**, *13*, 1129.
18. Minoura, Y.; Takebayashi, M.; Price, C. C. *J. Am. Chem. Soc.* **1959**, *81*, 4689.
19. Stogryn, E. L.; Brois, S. J. *J. Am. Chem. Soc.* **1967**, *89*, 605.
20. Allen, C. F. H.; Spangler, F. W.; Webster, E. R. *Org. Synth., Coll. Vol. IV*, **1963**, 433.

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