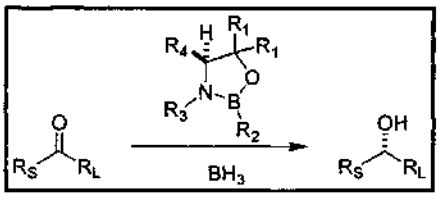
Chapter 1 Asymmetric Synthesis 1

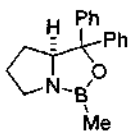
1.1 CBS Reduction

1.1.1 Description

The Corey–Bakshi–Shibata (CBS) reduction[1] employs the use of borane in conjunction with a chiral oxazaborolidine catalyst to conduct enantioselective reductions of ketones.



This reduction method has a number of advantages that include wide scope, predictable absolute stereochemistry, ready availability of the chiral catalyst in both enantiomeric forms, high yields, experimental ease, recovery of the catalyst (as the amino alcohol), and low cost of goods. The most common form of the chiral oxazaborolidine is derived from prolinol and has a methyl substituent on the boron atom (*B*-Me-CBS) **1**. When one conducts a reduction on a novel system for the first time, this catalyst provides a good compromise of cost, enantioselectivity, and experimental ease. If sufficient control is not observed with this reagent, one can then systematically evaluate the numerous variations of this framework.



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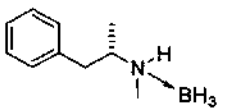
1.1.2 Historical Perspective



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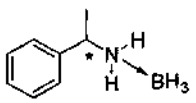

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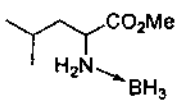


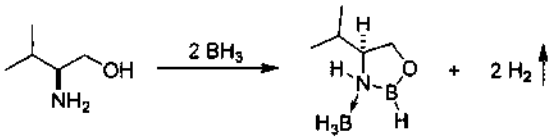
4

The use of optically active borane reagents for asymmetric reductions was first reported by Fiaud and Kagan in 1969.[2] These workers used the desoxyephedrine–boron complex **2** as a

reductant. However, the asymmetric induction was very poor and no greater than 5% *ee* in the reduction of acetophenone was observed. Borch observed similar results employing *R*-(+)- and *S*-(−)-α-phenethylamine–borane complexes **3**[3] as the chiral reagent with a variety of ketones.

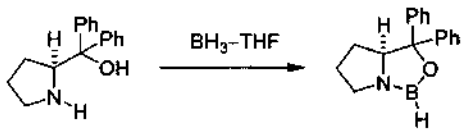
Continuing on this tack, Grundon and co-workers[4] were able to obtain optical purities in the range of 14–22% *ee*. They achieved this improvement by employing 1:1 complexes of leucine methyl ester and diborane **4** in THF. Furthermore, their results were facilitated by the addition of one equivalent of BF_3–etherate. Other chiral auxiliaries used include *L*-valine methyl ester and β-phenylalanine methyl ester.

A major advance in the evolution of chiral boron reagents was reported initially by Itsuno and co-workers in 1981.[5] Stereoselectivities up to 73% *ee* were observed using the 1,3,2-oxazaborolidine derived from β-amino alcohols. Thus (*S*)-valinol **5** in reaction with borane afforded **6**.



5 **6**

This result sat dormant in the literature until a thorough review of B- and Al-based reductants with chiral auxiliaries was conducted by the Corey group. They were intrigued by the work of Itsuno and began detailed studies of the reaction to understand the mechanistic and stereochemical underpinnings of this reduction reaction. Their efforts resulted in the CBS reduction[6] in which improved chiral auxiliaries (**7** → **8**) were developed and a model was formulated to rationalize the stereochemical outcome of this reaction.

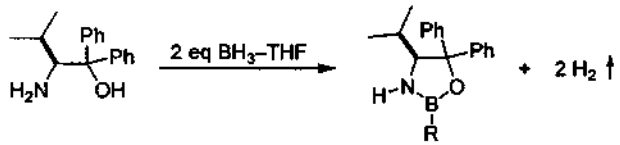


7 **8**

1.1.3 Mechanism

The great utility of this asymmetric reduction system is a result of the detailed and systematic analysis of its mechanism by the Corey group at Harvard and others.[1f, 6, 7] Using the Itsuno conditions as a starting point, the Corey laboratories obtained pure (after sublimation) oxazaborolidine **10** from the reaction of amino alcohol **9** with two equivalents of BH_3–THF

at 35 °C. The structure of this intermediate was confirmed by FT–IR, ^{1}H and ^{11}B NMR, and mass spectroscopy.



9 **10**

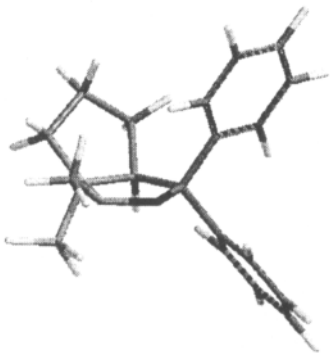
A solution of **10** in THF with acetophenone did not effect reduction even after several hours at 23 °C. Rapid reduction (less than one minute) was only observed after the addition of BH_3–THF (0.6 equivalents) to afford (*R*)-1-phenylethanol in 94.7% *ee*. This stands in contrast to the reduction in the absence of **10** which required much longer reaction times at 23 °C.

Follow-up studies indicated one could reduce the number of equivalents of the oxazaborolidine species to make the process catalytic. With the establishment of this mechanistic foundation, it became possible to rationalize the outcome of this reaction knowing the structure of the catalyst. ^{11}B NMR confirmed the formation of a 1:1 complex between **10** and BH_3–THF for R = H (**11**), while for the species R = Me (**11**) a single crystal X-ray structure was obtained.[8] The *cis*-fused nature of this complex is a result of the concave shape of this bicyclo[3.3.0]octane framework.

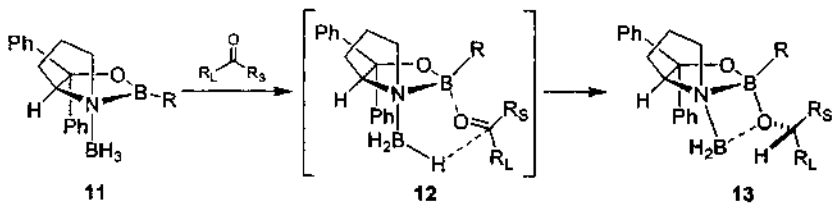
10 **11**

Figure 1 illustrates the 3-dimensional nature of **11**. The oxazaborolidine ring forms the horizontal core to this scaffold with the proline-derived five-membered ring forming the β-face back wall. The *gem*-diphenyl substituents create an additional aspect to the back wall on the β-face and a blocking group on the α-face. The borane moiety complexes to the nitrogen of the heterocyclic ring on the α-face due to the steric interactions it would encounter on the β-face. The only site "open" for a ligand to complex with this catalyst in on the α-face adjacent to the borane group.

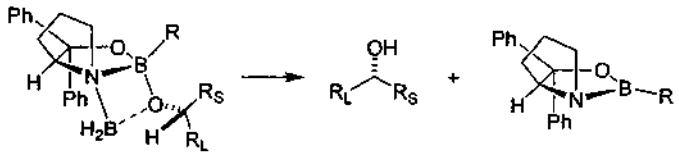
Figure 1



The formation of this complex between the pre-catalyst and borane, sets up this system for interaction with the carbonyl group by activating borane as a hydride donor and increasing the Lewis acidity of the endocyclic boron atom. The later effect serves as the point of coordination to the carbonyl oxygen atom. Once this complexation occurs to form **12**, the chirality of the scaffold restricts the orientation that the substituents on the carbonyl can adopt. In order to minimize steric interactions with the catalyst, the coordination must occur from the α-face (*vide supra*) and the small substituent (R_S) must be oriented in the β-face direction to minimize steric interactions with the substituent on the endocyclic boron atom, compared to the large substituent (R_L). The consequence of these interactions is to place the hydride equivalent in an optimal position for delivery to the carbonyl carbon atom *via* a six-membered transition-state.[9] The result of this hydride transfer is **13**, in which the carbonyl has undergone a net reduction in an enantiocontrolled fashion. This orientation of the reduction can be predicted based on the relative sizes of the carbonyl substituents and the orientation they must adopt in the transition-state **12**. The limited Hammett linear free energy analysis conducted and a measured kinetic isotope effect (k_H/k_D = 1.7) indicate that both the coordination of the carbonyl compound and the transfer of hydride are probably fast and comparably rate-determining.

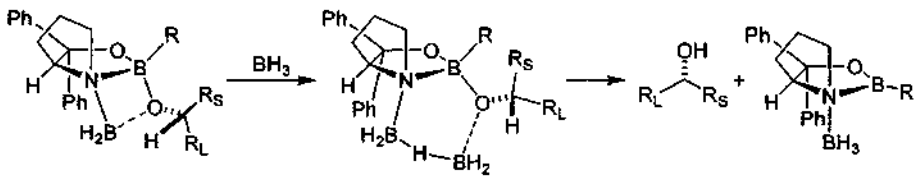


The decomposition of intermediate **13** to the isolated alcohol **14** can occur by one of two possible pathways. The first is a net cyclo-elimination that regenerates the catalyst and forms boronate **10**.



13 **14** **10**

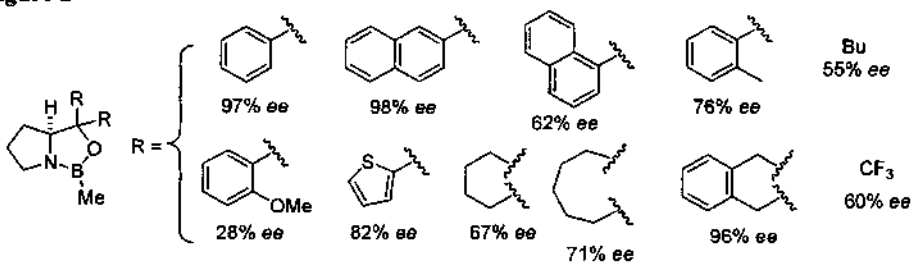
The alternate pathway occurs by the addition of borane to **13** to form the six-membered BH_3-bridged complex **15**. This species then decomposes to regenerate the active catalyst **11**.



13 **15** **14** **11**

1.1.4 Variations and Improvements or Modifications

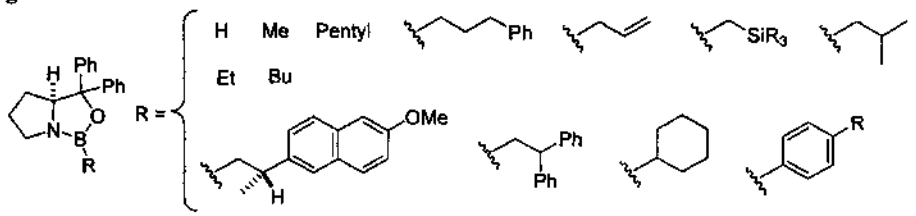
Figure 2



Various laboratories, in an effort to improve reaction yield and stereoselectivity, have made targeted modifications on the core structure of the oxazaborolidine catalyst.[1h] Figure 2 illustrates the level of stereocontrol in the CBS reduction of acetophenone as the R-group was systematically investigated to assess the varying degrees of enantiocontrol. The best

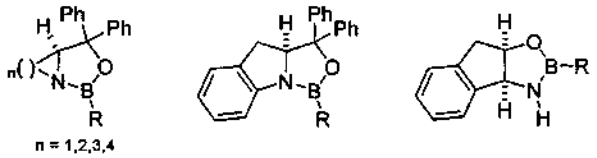
compromise of stereocontrol and synthetic complexity was observed to be the phenyl substituent.

Figure 3

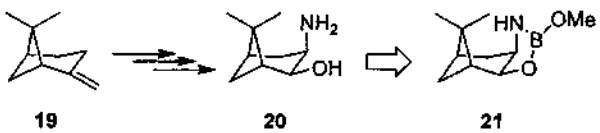


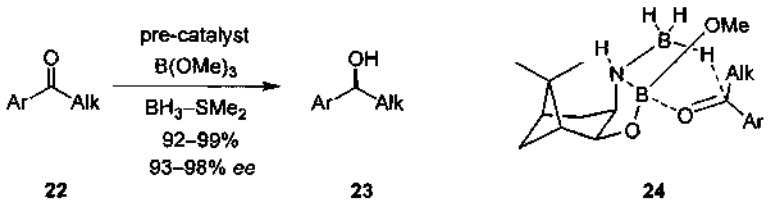
With the heterocyclic substituent optimized, a similar investigation of the B-group was carried out. Examples of the substituents studied are shown in Figure 3.

Additional modifications of the framework have included ring size **16**, ring fusion **17**, and ring substitution **18**.



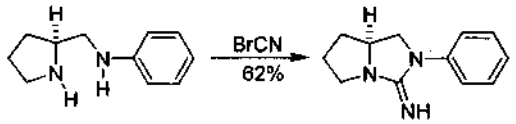
For example, (−)-β-pinene **19** has been used to construct such a modified catalyst.[10] Oxazaborolidine **21** could be prepare in three steps from the monoterpene and was found to be an efficient catalyst for the reduction of ketones. Thus **22** could be reduced with pre-catalyst **20** and trimethoxyboron to alcohol **23**. The chirality of **23** could be rationalized based on the transition-state structure **24**.



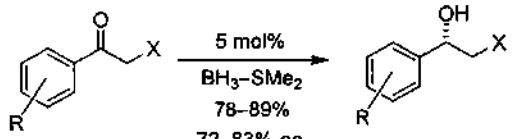


22 23 24

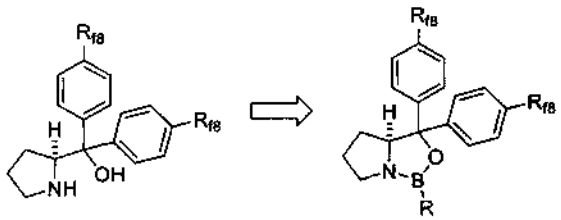
There are reports that extend the nature of the catalyst beyond an oxazaborol*i*dine framework. One such example made use of a chiral guanidine catalyst.[11] Proline-derived **25** was converted to guanidine **26** in good yield. This species was capable of reducing ketones **27** to alcohols **28** by the addition of BH_3–SMe_2.



25 26



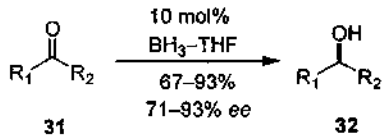
27 28



29 30

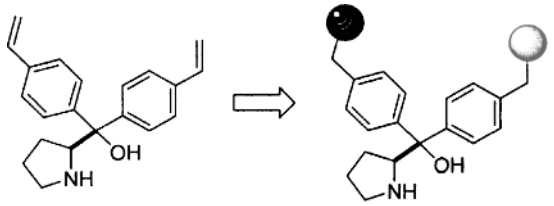
In an attempt to improve the ability to recycle the catalyst, fluorous versions of the oxazaborolidine have been constructed.[12] Pre-catalyst **29** could be prepared in five steps. This species was able to form the requisite chiral catalyst **30** *in situ*. Ketones **31** could be reduced to alcohols **32** in good to excellent chemical and optical yields. It was noted that aryl

ketones were observed to be more efficient in the reduction process. After the reaction was carried out, the catalyst could be recovered in 99% yield.

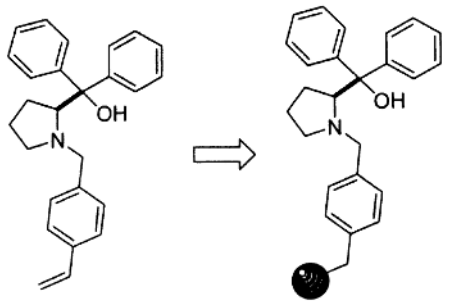


31 **32**

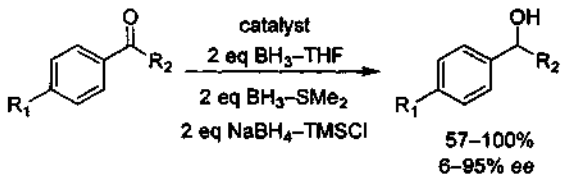
Polymer-bound versions of the oxazaborolidine catalysts have been constructed.[13] The linkage to the polymer has been reported on the phenyls of the heterocycle **34** or through a substituent on the nitrogen **36**. These polymeric catalysts are recyclable and reuseable without significant loss of activity or selectivity. Placing the linker on the nitrogen appears to create steric interactions that weaken complex formation thus giving rise to diminished enantiocontrol in the reduction. Moving the point of attachment for the resin to the phenyl substituent provided a superior reagent. The reduction of aryl ketones **37** proceeded in good to excellent yields with poor to excellent optical purities in the formation of alcohols **38**.



33 **34**

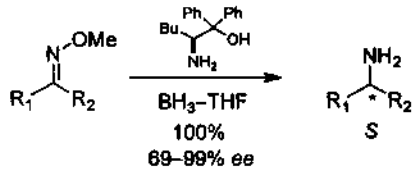


35 **36**



37 38

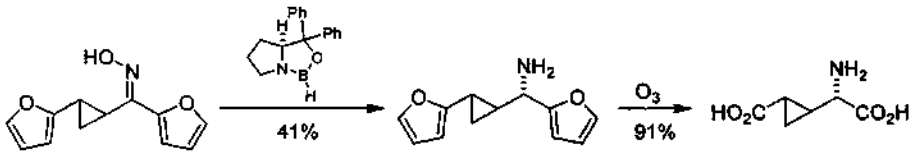
In addition to the reduction of ketones (e.g., aromatic and aliphatic ketones, α-halo ketones, hydroxyketones, enones, and ketoesters), oximes can be reduced to the corresponding amine with this reagent. In general, ketone oxime ethers, such as **39**, can give rise to amines **40** in excellent chemical yield with good to excellent optical purity.[5d]



39 40

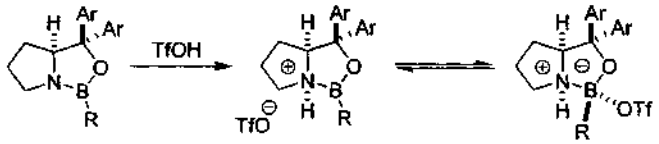
This method was used in the preparation of conformationally constricted analogs of the neurotransmitter glutamate **41**, such as (carboxycyclopropyl)glycines (*L*-CCG I) **42**, that could act as metabatropic glutamate receptor (mGluR) antagonists.[14] Reduction of oxime **43** using the oxazaborolidine derived from prolinol afforded amine **44**. Conversion of the furan rings to carboxylic acids afforded the requisite target **42**.

41 42



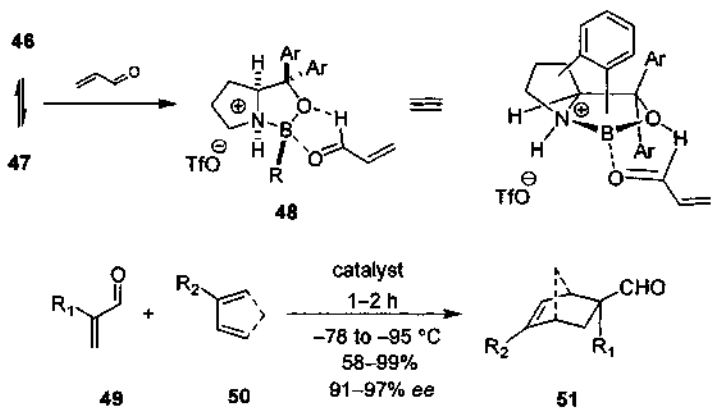
43 44 42

Proline-derived oxazaborolidines **45** have shown to be effective pre-catalysts with triflic acid as an activator to generate cationic Lewis acids.[1g,15] The optimal proportions of **45** and triflic acid was found to be 1.2:1. Protonation of **45** produced a 1.5:1 mixture of **46** and **47** as determined by low temperature ^{1}H NMR. Their interconversion at low temperature (−80 °C) is slow on the NMR timescale. However, this interconversion increases as the temperature rises and at 0 °C this becomes rapid (T_c). Phenyl or *o*-tolyl were determined to be the best substituents for the R group in **45**. For the Ar group of **45**, phenyl and 3,5-dimethylphenyl were determined to be optimal.



45 **46** **47**

This *in situ* formed cationic Lewis acid catalyst coordinates enals in a highly organized fashion (**48**) that allows for the execution of asymmetric Diels–Alder reactions. Thus for the initially disclosed acrolein examples, the Diels–Alder adducts **51** produced from enals **49** and dienes **50** could be isolated in good to excellent yields with very high optical purities.

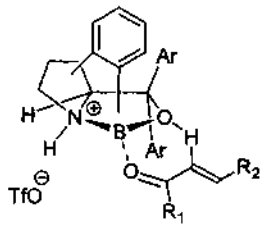


49 **50** **51**

The stereochemical outcome from these reactions could be readily rationalized by examining the interactions present in **48**. The [3.3.0]bicyclic system provided a rigid convex scaffold that only allowed the enal to coordinate from the more exposed face of this

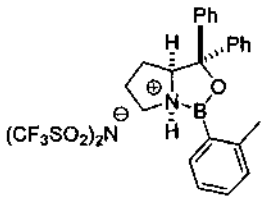
molecule. The carboxaldehyde hydrogen forms an H-bonding interaction with the endocyclic oxygen atom of the heterocyclic scaffold thus only allowing the diene to approach from the periphery of the complex.

An extension to enones has been accomplished but opposite face selectivities were observed. To rationalize this result, an alternate transition-state structure **52** was formulated. Single crystal X-ray structure analysis examining the coordination of BF_3-etherate with enones and enoates was used to provide support for this novel mode of complexation.

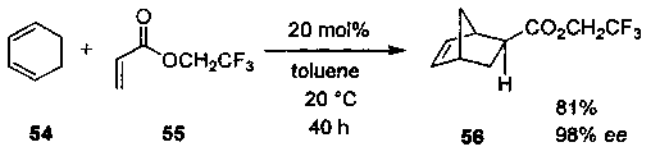


52

Catalysts derived from triflic acid decompose at appreciable rates at or above 0 °C, which limits the utility of these reagents in Diels–Alder reactions. Switching to triflimide as the acid source resulted in protonation of **45** to produce **53**.[16] ^{1}H NMR from −80 to 23 °C showed the formation of three species including **53** and two diastereomeric tetracoordinated boron species in a ratio of 1:1.2. Additionally, **53** was found to have greater thermal stability and superior catalytic efficiency compared to **46**/**47** for less reactive dienes. This was illustrated in the Diels–Alder reaction of **54** with **55** to produce adduct **56**.

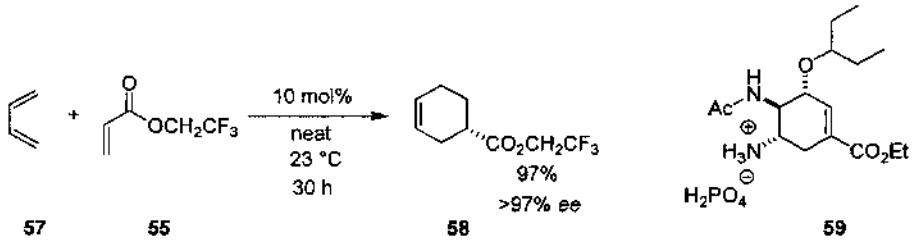


53



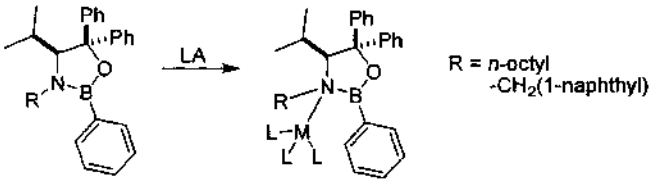
54 **55** **56** 81% 98% *ee*

This last observation was capitalized on by the Corey labs in their efficient synthesis of Tamiflu® (oseltamivir) **59**. The emergence of the virulent strain of influenza, H5N1, coupled with the lack of supply due to the current synthetically challenging route, highlighted the need for such reagents that allow for the rapid and efficient construction of difficult targets. The reaction could be conducted on a multigram scale of **57** and **55** to generate sufficient quantities of the Diels–Alder adduct **58** to complete the target **59**.[17]

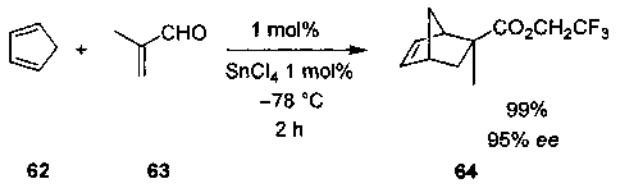


57 **55** **58** **59**

Follow-up work by other groups examined alternate sources of generating Lewis acids from various oxazaborolidines (**60** → **61**).[18] One report scanned the commonly used metal halides and found tin tetrachloride to be the best when coupled to valinol-based oxazaboroline. Thus, cyclopentadiene **61** reacting with methacrolein **63** using such a catalyst afforded the Diels–Alder adduct **64** in excellent yield and excellent optical purity.



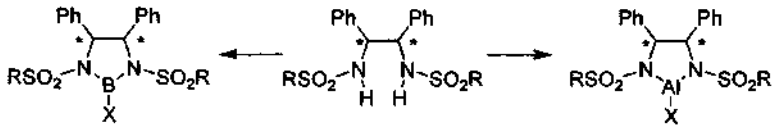
60 **61**



62 **63** **64**

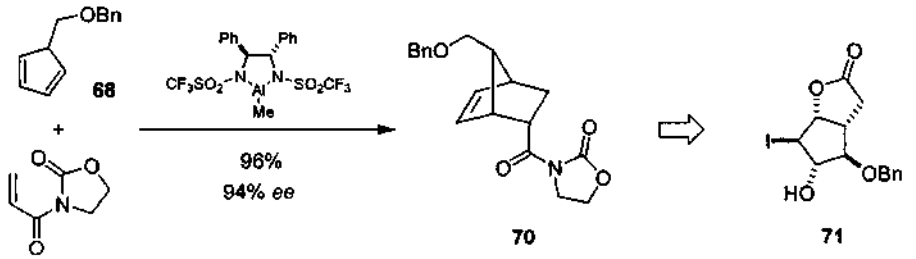
Rather than accessing the chiral pool *via* amino acid precursors for CBS catalysts, the (*R*,*R*)- and the (*S*,*S*)-sulfonamide derivatives of 1,2-diphenyl-1,2-diaminoethane

(stilbenediamine, stien) **66** in complex with boron **65** or aluminum **67** have also been applied to the Diels–Alder reaction.[19]



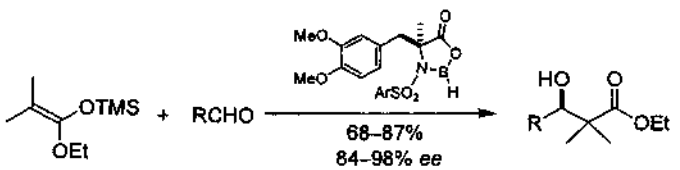
65 **66** **67**

The use of these reagents was exemplified in the preparation of an advanced intermediate in the synthesis of prostaglandins **71**. Diene **68** and dienophile **69** were allowed to undergo the Diels–Alder reaction catalyzed by a derivative of **67** to afford adduct **70**.[19] This intermediate was subsequently transformed into **71**, a well-known precursor in the synthetic preparations of prostaglandins.



68 **69** **70** **71**

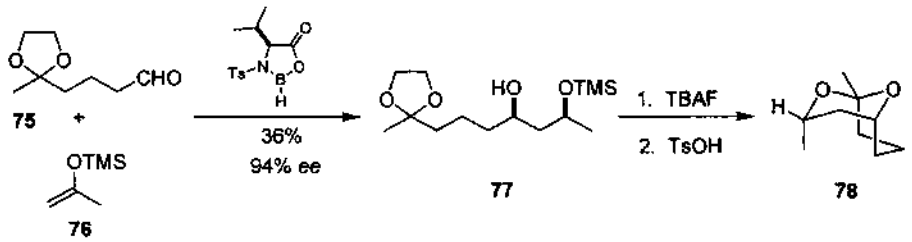
The Lewis acidic nature of these catalysts has permitted their extended use in the Mukaiyama aldol reaction. In this application of CBS reagents, one such example involved the condensation of ketene acetals **72** with aldehydes **73** to produce adducts **74**.[20]



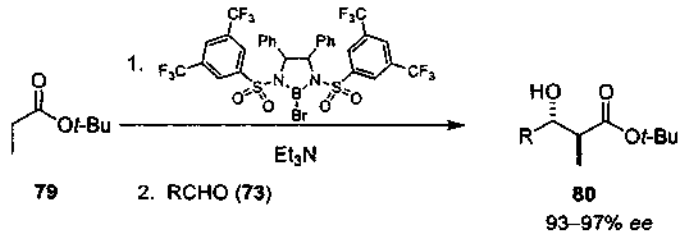
72 **73** **74**

In a similar manner, the insect attractant *endo*-1,3-dimethyl-2,9-dioxabicyclo[3.3.1]nonane **78** could be prepared.[21] To this end, masked keto aldehyde **75**

and silyl enol ether **76** underwent the CBS catalyzed Mukaiyama aldol reaction with a high degree of optical purity to generate **77**. Deprotection and acid-catalyzed spiroketal formation afforded the desired product **78**.



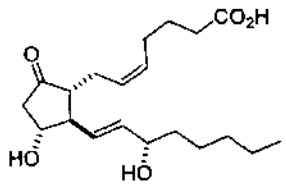
Using the boron complex of the stien system, enantioselective aldol reactions were also possible. Ester **79** could be converted to the corresponding boron enolate using a derivative of **65**, which could then undergo an aldol reaction with aldehydes **73** to afford **80**.[22]



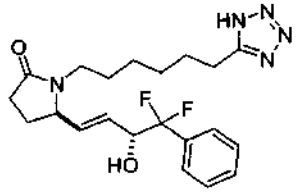
1.1.5 Synthetic Utility

The literature documents a myriad of examples of the synthetic utility of this reduction methodology. The following examples provide a limited glimpse into the scope of substrates that can undergo this type of reduction.

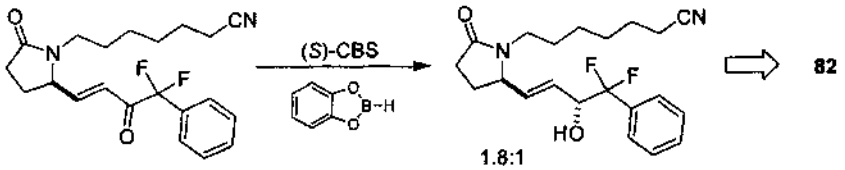
Prostaglandin PGE_2 **81** elicits bone growth, so EP4 receptor antagonists, such as **82**, would have utility in the pharmacological treatment of osteoporosis.[23] Standard reduction conditions investigated (Luche, *L*-selectride, or (*R*)-CBS) for the reduction of **83** to afford **84** gave the wrong stereochemistry. Alcohol **84** with the desired stereochemistry could only be obtained upon use of the reagent (*S*)-CBS.



81

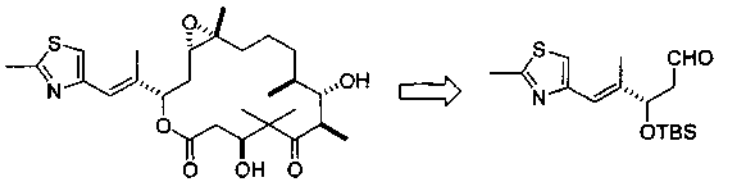


82

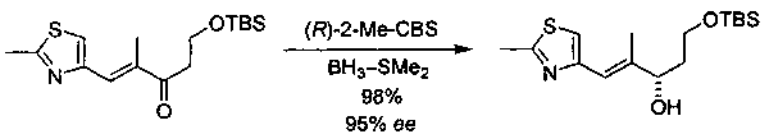


83 84

Epothilone **85** possesses antimitotic properties similar to those of paclitaxel and could therefore have utility in the treatment of cancer. A key intermediate in the synthesis of this natural product is **86**, a C_{12}–C_{21} subunit of **85**.[24] One approach to this compound employed the CBS reduction of ketone **87** to generate **88**, an alcohol related to **86**.



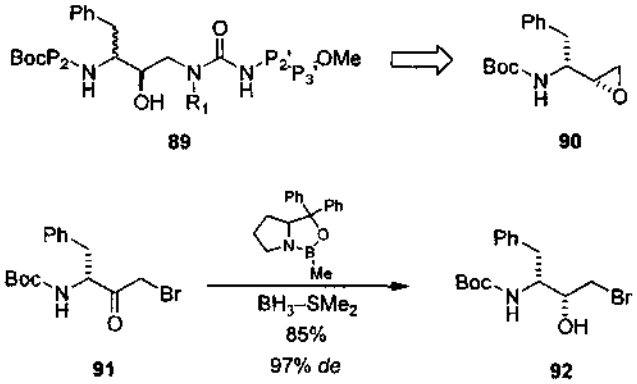
85 86



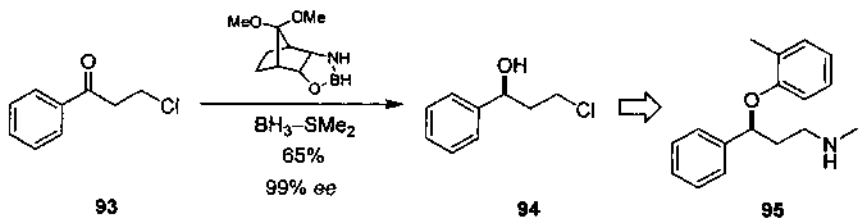
87 88

The mis-processing of amyloid precursor protein (APP) by α-secretase, β-secretase, and γ-secretase is proposed to be one pathway leading to formation of Aβ protein. One theory for the cause of Alzheimer's disease (AD) is based on the idea that Aβ protein

aggregates to form amyloid plaques (a well-known hallmark of AD) that eventually precipitate in the brain. This deposition results in neuronal cell death. Inhibition of any one of these enzymes could be a treatment for AD, thus **89**, a γ-secretase inhibitor, is of pharmacological interest.[25] Epoxy amine **90** is a key synthetic intermediate on the way to **89**. Reduction of ketone **91** using a CBS reagent afforded alcohol **92**. This alcohol is a single transformation away from **90**.

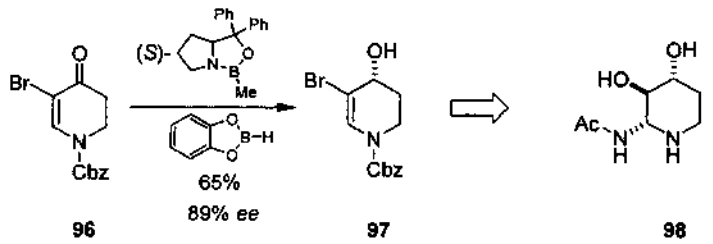


Norepinephrine reuptake antagonists (NETs) have antidepressant activity and have been found to be effective in the treatment of attention deficit hyperactivity disorder (ADHD). (*R*)-tomoxetine (Strattera®) **95** is a marketed drug with a label indication for ADHD. Control of the absolute stereochemistry of these compounds is critical in that the (*S*)-enantiomer is nine times less potent. The CBS reduction could be used to set the desired chirality as demonstrated in the reduction of **93** to produce alcohol **94**.[26] This intermediate could then be readily converted into **95**.



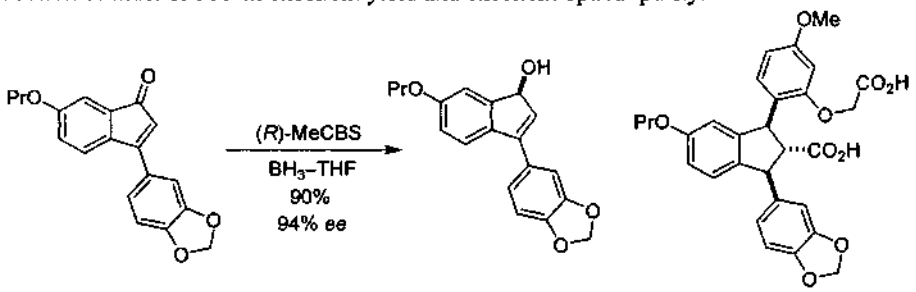
Malfunction of hexosaminidase enzymes can lead to such diseases as Tay-Sachs or Sandhoff. The study of *N*-acetylhexosaminidase inhibitors, such as XylNAc-Isofagomine **98**, could provide greater understanding of the method of malfunction.[27] Enone **96** could be

reduced by a CBS reagent to afford allylic alcohol **97**. The bromine was required to provide differentiation of the faces of ketone to improve % *ee*.



96 **97** **98**

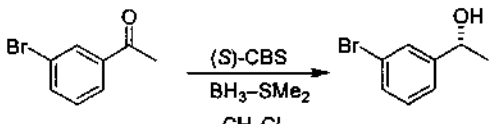
Endothelin and its related peptides play an important role in the biology of vascular smooth muscle. Antagonists of the endothelin receptor would be of great interest in the treatment of cardiovascular and pulmonary disease. One such compound is SB-209670 **101** and could be prepared from alcohol **100**.[28] This alcohol could be accessed *via* the CBS reduction of indenone **99** in excellent yield and excellent optical purity.



99 **100** **101**

1.1.6 Experimental

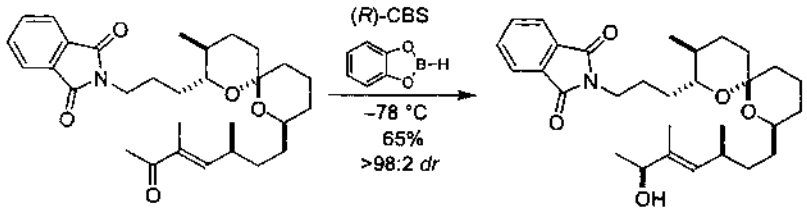
The two examples presented exemplify the utility of this reaction. One can access either enantiomer of the product through the proper choice of chirality contained in the CBS reagent. This reagent possesses great scope in that simple, as well as complex, substrates can be reduced with high efficiency, chemical and optical yields. Additionally, these examples illustrate the relatively simplistic experimental conditions required to conduct these reduction reactions.



102 103

(*R*)-1-(3′-Bromophenyl)-ethanol (103)[29]

Ketone **102** (10.8 g, 64.6 mmol) in 50 mL of CH_2Cl_2 at –20 °C was added dropwise over 2 h to a solution of (*S*)-4,5,6,7-tetrahydro-1-methyl-3,3-diphenyl-1*H*,3*H*-pyrrolo-[1,2-*c*]-[1,3,2]-oxazaborolidine-borane (0.9 g, 3.2 mmol) and BH_3–SMe_2 (5.1 mL, 51 mmol) in 30 mL of CH_2Cl_2. The reaction mixture was stirred for a total 8 h before slowly adding to 50 mL of methanol at –20 °C. Once gas evolution ceased, the solvent was removed *in vacuo* and the residue purified by bulb-to-bulb distillation (94 °C, 0.5 mmHg) to afford **103** as a colorless oil.



104 105

Allylic alcohol (105)[30]

To ketone **104** (196 mg, 0.395 mmol) in 7 mL of toluene was added (*R*)-CBS (0.43 mL, 0.395 mmol, 1.0 M toluene). The mixture was cooled to –78 °C and catecholborane (0.79 mL, 0.79 mmol, 1.0 M THF) was added dropwise. The reaction was stirred for 12 h before quenching with 0.8 mL of methanol and warmed to room temperature. The mixture was diluted with ether and washed with NaOH (1 N), saturated with $NaHCO_3$, until the aqueous washings were colorless. The combined aqueous phases were back extracted 3 times with ether and the combined organic phases were washed with brine, dried (Na_2SO_4), and concentrated *in vacuo*. Purification by chromatography gave **105** (160 mg).

1.1.7 References

1. (a) [R] Corey, E. J. *Pure Appl. Chem.* **1990**, *62*, 1209–1216. (b) [R] Wallbaum, S.; Martens, J. *Tetrahedron: Asymm.* **1992**, *3*, 1475–1504. (c) [R] Singh, V. K. *Synthesis* **1992**, 605–617. (d) [R] Deloux, L.; Srebnik, M. *Chem. Rev.* **1993**, *93*, 763–784. (e) [R] Taraba, M.; Palecek, J. *Chem. Listy* **1997**, *91*, 9–22. (f) [R] Corey, E. J.; Helal, C. J. *Angew. Chem. Int. Ed.* **1998**, *37*, 1986–2012. g) [R] Corey, E. J. *Angew. Chem. Int. Ed.* **2002**, *41*, 1650–1667. (h) [R] Itsuno, S. *Org. Reac.* **1998**, *52*, 395–576. (i) [R] Cho, B. T. *Aldrichimica Acta* **2002**, *35*, 3–16. (j) [R] Glushkov, V. A.; Tolstikov, A. G. *Russ. Chem. Rev.* **2004**, *73*, 581–608. (k) [R] Cho, B .T. *Tetrahedron* **2006**, *62*, 7621–7643.
2. Fiaud, J.-C.; Kagan, H.-B. *Bull. Soc. Chim. Fr.* **1969**, 2742–2743.
3. Borch, R. F.; Levitan, S. R. *J. Org. Chem.* **1972**, *37*, 2347–2349.
4. Grundon, M. F.; McCleery, D. G.; Wilson, J. W. *Tetrahedron Lett.* **1976**, *17*, 295–296.
5. (a) Hirao, A.; Itsuno, S.; Nakahama, S.; Yamazaki, N. *Chem. Commun.* **1981**, 315–317. (b) Itsuno, S.; Ito, K.; Hirao, A.; Nakahama, S. *Chem. Commun.* **1983**, 469–470. (c) Itsuno, S.; Hirao, A.; Nakahama, S.; Yamazaki, N. *Perkin Trans. I* **1983**, 1673–1676. (d) Itsuno, S.; Nakano, M.; Miyazaki, K.; Masuda, H.; Ito, K.; Hirao, A.; Nakahama, S. *Perkin Trans. I* **1985**, 2039–2044.
6. (a) Corey, E. J.; Bakshi, R. K.; Shibata, S. *J. Am. Chem. Soc.* **1987**, *109*, 5551–5553. (b) Ganem, B. *Chemtracts-Org. Chem.* **1988**, *1*, 40–42.
7. (a) Corey, E. J.; Link, J. O.; Bakshi, R. K. *Tetrahedron Lett.* **1992**, *33*, 7107–7110. (b) Mathre, D. J.; Thompson, A. S.; Douglas, A. W.; Hoogsteen, K.; Carroll, J. D.; Corley, E. G.; Grabowski, E. J. J. *J. Org. Chem.* **1993**, *58*, 2880–2888. (c) Douglas, A. W.; Tschaen, D. M.; Reamer, R. A.; Shi, Y.-J. *Tetrahedron: Asymm.* **1996**, *7*, 1303–1308. For papers related to computational chemistry studies see: (d) Nevalainen, V.; Uggla, R.; Sundberg, M. R. *Tetrahedron: Asymm.* **1995**, *6*, 1431–1440. e) Nevalainen, V. *Tetrahedron: Asymm.* **1994**, *5*, 289–296. (f) Li, M.; Tian, A. *J. Mol. Struct.* **2001**, *544*, 37–47. (g) Harb, W.; Ruiz-Lopez, M. F.; Coutrot, F.; Grison, C.; Coutrot, P. *J. Am. Chem. Soc.* **2004**, *126*, 6996–7008. (h) Alagona, G.; Ghio, C.; Tomasi, S. *Theor. Chem. Acc.* **2004**, *111*, 287–302.
8. Corey, E. J.; Azimioara, M.; Sarhar, S. *Tetrahedron Lett.* **1992**, *33*, 3429–2430.
9. (a) Evans, D. A.; *Science* **1988**, *240*, 420–426. (b) Jones, D. K.; Liotta, D. C.; Shinkai, I.; Mathre, D. J. *J. Org. Chem.* **1993**, *58*, 799–801. (c) Quallich, G. J.; Blake, J. F.; Woodall, T. M. *J. Am. Chem. Soc.* **1994**, *116*, 8516–8525.
10. Krzeminski, M. P.; Wojtczak, A. *Tetrahedron Lett.* **2005**, *46*, 8299-8302.
11. (a) Basavaiah, D.; Rao, K. V.; Reddy, B. S. *Tetrahedron: Asymm.* **2006**, *17*, 1036–1040. b) Basavaiah, D.; Rao, K. V.; Reddy, B. S. *Tetrahedron: Asymm.* **2006**, *17*, 1041–1044.
12. (a) Dlicsek, Z.; Pollreisz, F.; Gomory, A.; Soos, T. *Org. Lett.* **2005**, *7*, 3243–3246. b) Park, J. K.; Lee, H. G.; Bolm, C.; Kim, B. M. *Chem. Eur. J.* **2005**, *11*, 945.
13. Degni, S.; Wilen, C.-E.; Rosling, A. *Tetrahedron: Asymm.* **2004**, *15*, 1495–1499.
14. Demir, A. S.; Tanyeli, C.; Cagir, A.; Tahir, M. N.; Ulku, D. *Tetrahedron: Asymm.* **1998**, *9*, 1035–1042.
15. (a) Corey, E. J.; Shibata, T.; Lee, T. W. *J. Am. Chem. Soc.* **2002**, *124*, 3808–3809. (b) Ryu, D. H.; Lee, T. W.; Corey, E. J. *J. Am. Chem. Soc.* **2002**, *124*, 9992–9993.
16. Ryu, D. H.; Corey, E. J. *J. Am. Chem. Soc.* **2003**, *125*, 6388–6390.
17. Yeung, Y.-Y.; Hong, S.; Corey, E. J. *J. Am. Chem. Soc.* **2006**, *128*, 6310–6311.
18. (a) Futatsugi, K.; Yamamoto, H. *Angew. Chem. Int. Ed.* **2005**, *44*, 1484–1487. (b) Harada, T.; Inui, C. *J. Org. Chem.* **2006**, *71*, 1277–1279.
19. Corey, E. J.; Imwinkelried, R.; Pikul, S.; Xiang, Y. B. *J. Am. Chem. Soc.* **1989**, *111*, 5493–5495.
20. (a) Parmee, E. R.; Tempkin, O.; Masamune, S. *J. Am. Chem. Soc.* **1991**, *113*, 9365-9366. (b) Fujiyama, R.; Goh, K.; Kiyooka, S.-I. *Tetrahedron Lett.* **2005**, *46*, 1211–1215.
21. Kiyooka, S.-I.; Kaneko, Y.; Harada, Y.; Matsuo, T. *Tetrahedron Lett.* **1995**, *36*, 2821–2822.
22. Corey, E. J.; Kim, S. S. *J. Am. Chem. Soc.* **1990**, *112*, 4976–4977.
23. Young, R. N.; Billot, X.; Han, Y.; Slipetz, D. A.; Chauret, N.; Belley, M.; Metters, K.; Mathieu, M.-C.; Greig, G. M.; Denis, D.; Girard, M. *Heterocycles*, **2004**, *64*, 437–446.
24. Reiff, E. A.; Nair, S. K.; Reddy, B. S. N.; Inagaki, J.; Henri, J. T.; Greiner, I. F.; Georg, G. I. *Tetrahedron Lett.* **2004**, *45*, 5845–5847.
25. Bakshi, P.; Wolfe, M. S. *J. Med. Chem.* **2004**, *47*, 6485–6489.

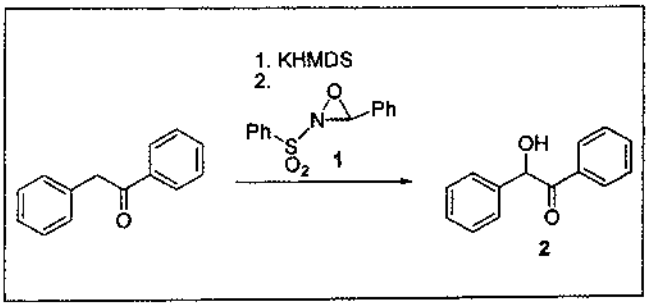
26. Lapis, A. A. M.; de Fatima, A.; Martins, J. E. D.; Costa, V. E. U.; Pilli, R. A. *Tetrahedron Lett.* **2005**, *46*, 495–498.
27. Knapp, S.; Yang, C.; Pabbaraja, S.; Rempel, B.; Reid, S.; Withers, S. G. *J. Org. Chem.* **2005**, *70*, 7715–7720.
28. Clark, W. N.; Tickner-Eldridge, A. M.; Huang, G. K.; Pridgen, L. N.; Olsen, M. A.; Mills, R. J.; Lantos, I.; Baine, N. H. *J. Am. Chem. Soc.* **1998**, *120*, 4550–4551.
29. Powell, M. T.; Porte, A. M.; Reibenspies, J.; Burgess, K. *Tetrahedron* **2001**, *57*, 5027–5038.
30. Crimmins, M. T.; DeBaillie, A. C. *J. Am. Chem. Soc.* **2006**, *128*, 4936–4937.

Paul Galatsis

1.2 Davis Chiral Oxaziridine Reagents

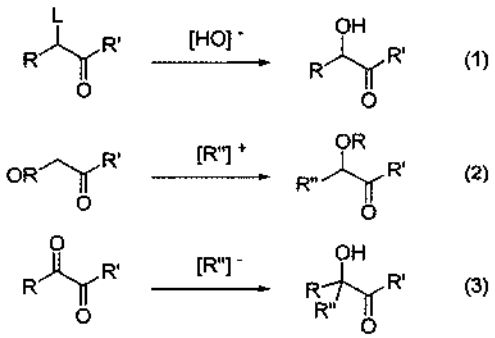
1.2.1 Description

Davis oxaziridine reagents such as **1** have exhibited ample synthetic utility as oxidizing agents for the hydroxylation of enolates to provide α-hydroxy carbonyl compounds, such as **2** with superb yield. When the oxaziridine is chiral and nonracemic, the hydroxylation has been shown to proceed with high stereoselectivity.[1]



1.2.2 Historical Perspective

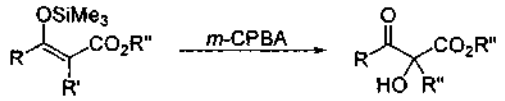
Prior to Davis and co-workers' introduction of *trans*-(±)-2-(phenylsulfonyl)-3-phenyloxaziridine (**1**) for direct enolate oxidation in 1984, there were several nonoxidative procedures for the formation of optically active α-hydroxy carbonyl compounds, but only one actively practiced oxidative method for the synthesis of such compounds.[2]



The most commonly used nonoxidative method used by chemists prior to 1958 is the substitution reaction using either chiral α-amino acids (L = NH_3) or α-halo amides (L = F, Cl,

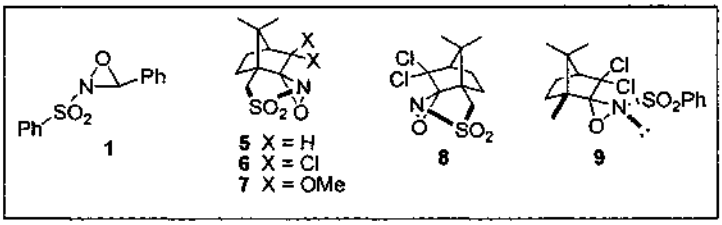
Br, or I) (equation 1). Another method relies on alkylation of α-hydroxy or α-alkoxy carbonyl compounds. The induction of diastereoselectivty, in these cases, is achieved through the use of chiral auxiliaries and other stereodirecting groups (equation 2). The third method frequently utilizes the nucleophilic addition of hydride or other carbanions to α-dicarbonyl compounds (equation 3). In addition to being laborious, nonoxidative methods are limited to the synthesis of acyclic compounds, which greatly reduces the magnitude of their synthetic practicality.

In 1958, Rubottom and co-workers introduced an oxidative methodology, which first requires the conversion of a carbonyl compound to either an enol silane or silyl enol ether. As generated, the enol silane **3**, for example, is then treated with *m*-chloroperbenzoic acid (*m*-CPBA) to form the α-hydroxy carbonyl compound **4** following epoxidation and desilylation.[3]



3 **4**

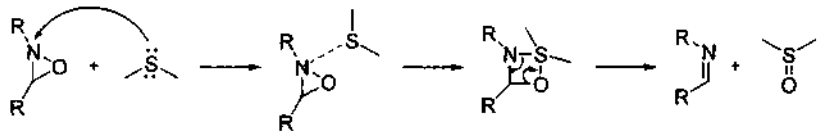
Despite high yield, the Rubottom oxidation is limited by the necessity for synthesis of the requisite silane ethers. The direct oxidation of enolates has thus emerged as the preferred method for the stereoselective formation of α-hydroxy carbonyl compounds because of the method's effectiveness for both acyclic and cyclic substrates. Davis's oxaziridine reagents have proved to be ideally suited for the one-step enolate hydroxylation process. The following chiral oxaziridine reagents have been utilized effectively in this protocol and will be showcased throughout the chapter.



1.2.3 Mechanism

Mechanistic interpretation for this reaction began with comparisons to alkene epoxidations using metal peroxides, dioxiranes, and oxaziridines. In 1982, Mimoun was the first to propose a general mechanism for the oxygen transfer from compounds containing a peroxide moiety (active site oxygen is part of a three-membered ring).[4] Mimoun's mechanistic interpretation can be applied to the oxidation of a sulfide using an oxaziridine reagent. In this

case, coordination between the oxaziridine nitrogen and the substrate would lead to the formation of a four-membered ring as an intermediate.[5] This cyclic intermediate would decompose resulting in the formation of the sulfoxide and imine products.

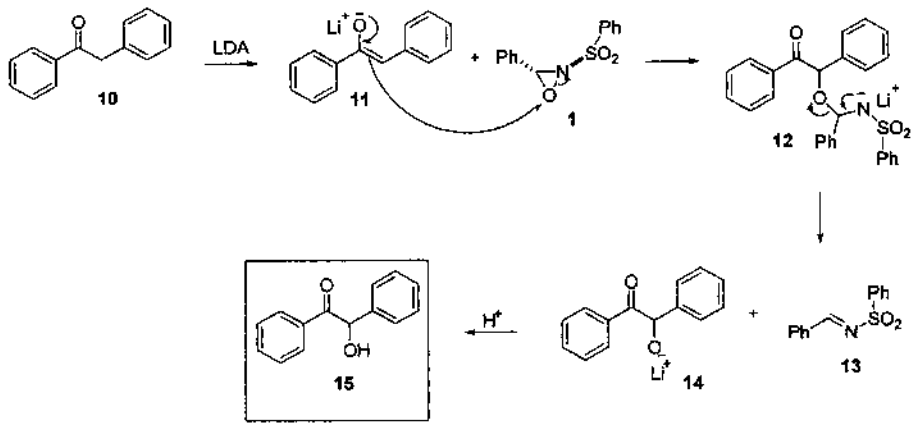


In the following years, studies conducted by Sharpless,[6,7] Bach,[8,9] Curci,[10] and others[11] relied on reaction kinetics to formulate support of a S_N2-type displacement by the nucleophilic substrate on the electrophilic oxygen atom of the three-membered ring. Similarly, the deoxygenation of oxaziridines, such as **1**, is kinetically consistent with the aforementioned S_N2 mechanism.

Davis extensively studied reactions involving **1** and found that all results exhibited properties that suggest the oxygen transfer by oxaziridines is S_N2 in nature.[12] When comparing the mechanism of the nucleophilic ring opening of oxaziridines to those of epoxides, aziridines, and thiiranes, it was found that attack at the nitrogen is favored when the substituent bound to the nitrogen is small and nonobtrusive. When this substituent is large as in **3**, nucleophilic attack at the oxygen is favored, implicating an S_N2 mechanism. Furthermore, when the rate of oxidation was monitored through the use of ^1H NMR, Davis found the reaction to be second-order. Hammett subsituent constants were used to determine the correlation of substituent electronic effects. Additionally, analyses of NMR spectra produced no tendencies that were characteristic of the formation of zwitterion intermediates, which were included in Mimoun's mechanism. NMR spectra suggest that both **A** and **B** are possible transition states for the oxygen transfer; however, transition state **B** is limited to cases when the nucleophile is anionic.

A **B**

These detailed mechanistic studies have led to the following generalized mechanism of enolate oxation by oxaziridine reagents. In the hydroxylation of deoxybenzoin **10** to benzoin **15**, the enolate anion **11** is formed by kinetic deprotonation with LDA. The enolate anion then performs a nucleophilic attack on the oxygen of the oxaziridine **1** in a manner consistent with that proposed in transition state **B**. The hemiaminal **12** intermediate decomposes to form the alkoxide **14** and sulfonimine **13**. The alkoxide is then quenched to provide alcohol **15**.[2]



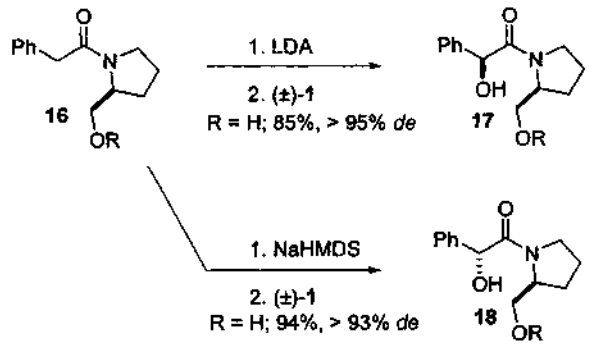
1.2.4 Synthetic Utility

Readers are directed to a thorough review on the chemistry of Davis oxaziridine reagents through 1992. While this work will occasionally be referenced, the primary focus of this section will be on the chemistry from 1992 to the present.

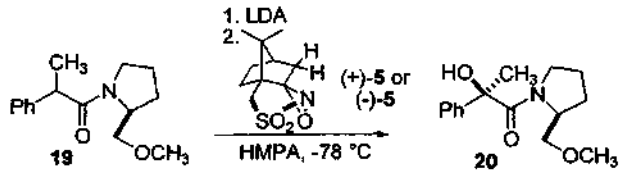
1.2.4.1 Asymmetric oxidation via chiral auxiliaries

Chiral auxiliaries have found abundant use in providing a template for efficient and highly diastereoselective enolate reactions. Concurrent with the development of chiral and nonracemic Davis oxaziridine reagents, the use of chiral auxiliaries to direct the stereoselectivity in these systems has been generalized.

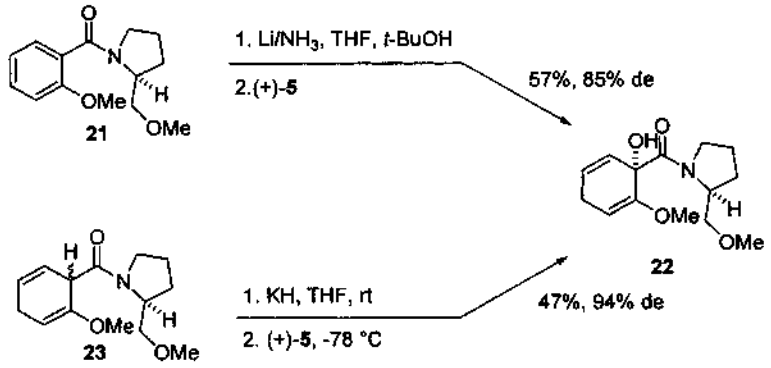
The first example of the use of chiral auxiliaries for diastereoselective α-hydroxylation was published in 1985. Davis and co-workers[13] demonstrated the efficient and highly stereoselective formation of α-hydroxyamides using the (+)-(*S*)-2-pyrrolidinemethanol (R = H) chiral auxiliary. Thus, treatment of **16** with LDA was followed by enolate oxidation with (±)-**1** to provide **17** in high yield and high *de* (> 95%). An interesting reversal was noted when the sodium enolate of **16** was reacted under similar conditions. In this case, production of the (*R*)-product **18** was predominating with only slightly lower diastereoselectivity (93% *de*). In both cases, the chiral auxiliaries could be removed without racemization. The use of the related (+)-(*S*)-2-(methoxymethyl)pyrrolidine auxiliary (R = Me) provided inconsistent results with regard to solvent dependence, selectivity, and yield.[13]



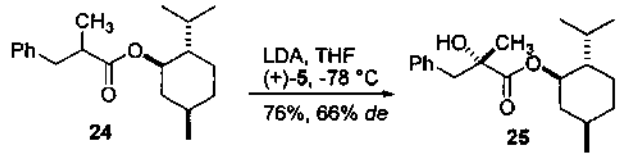
The synthesis of acyclic tertiary α-hydroxy acids poses an additional challenge, in that a specific enolate isomer must be generated prior to reaction with the oxaziridine reagent. As a means of overcoming this challenge, Davis and co-workers utilized a strategy of double stereodifferentiation, wherein the chiral enolate was reacted with an enantiopure oxaziridine. This strategy proved successful for the synthesis of **20** from **19** when either enantiomer of (camphorsulfonyl)oxaziridine **5** was employed as the oxidizing agent in the presence of HMPA.[14] Interestingly, the use of racemic **1** as the oxidizing agent resulted in only modest diastereoselectivity (55% *de*), implicating the necessity for chiral, nonracemic oxaziridines in this system.



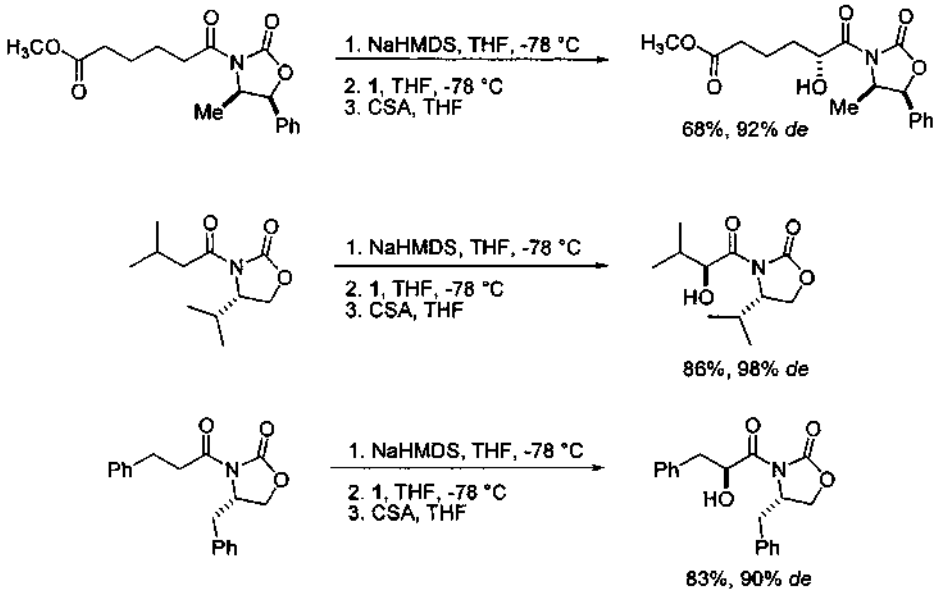
Expanding upon these results, Schultz *et al.* analyzed the oxidation of enolates produced via the Birch reduction of carboxylic acid derivatives.[15] It was found that when **21** was reduced and treated with (+)-**5**, **22** was obtained with only marginal yield and modest enantioselectivity. The enantioselectivity increased when **23** was deprotonated and then treated with (+)-**5**.



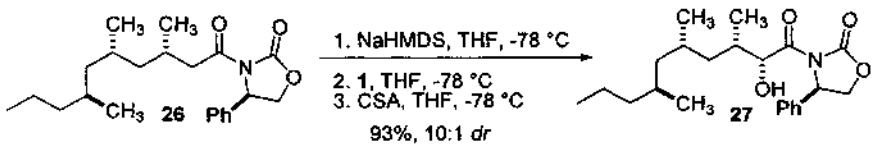
While more plentiful, alcohol-based chiral auxiliaries have been limited in their ability to direct the diastereoselective hydroxylation for the preparation of tertiary α-hydroxy acids. Among these, the best results in this series were obtained when oxidation of the enolate of chiral ester substrate **24** with (+)-**5** yielded (*S*)-**25**.[14b] The use of (−)-**5** as the hydroxylating agent, provided a reversal in stereoselectivity, providing (*R*)-**25**. Interestingly, when substoichiometric amounts (0.5 equiv) of (+)-**5** were used, stereoselectivity improves (94% *de*), a fact attributed to the matching of the enolate geometry to the oxidant. This speculation is credible, as evidenced by the fact that oxidation with 0.50 equivalent of (−)-**5** produces (*S*)-**25** in only 37% *de* in a stereochemically mismatched case.



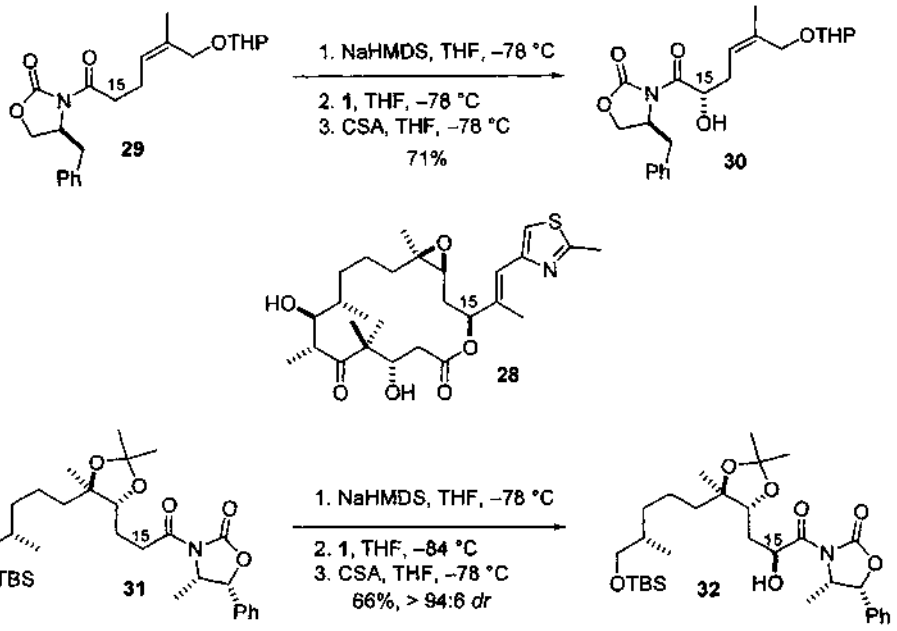
Among chiral enolates, those derived from oxazolidinone carboximides, as developed in the Evans laboratories,[16,17] have shown the most generality in directing the hydroxylation with the racemic Davis oxaziridine **1**. Pioneered in 1985, a variety of carboximide derivatives have been hydroxylated with consistently high levels of diastereoselectivity.[18] The high levels of selectivity are due, in part, to the facile and exclusive formation of the *Z*-enolate under these conditions. Importantly, these reactions are necessarily quenched by the organic soluble camphor sulfonic acid (CSA) to avoid formation of a product arising from intramolecular attack of the alkoxide oxygen at the oxazolidinone carbonyl under standard aqueous acidic workup methods.



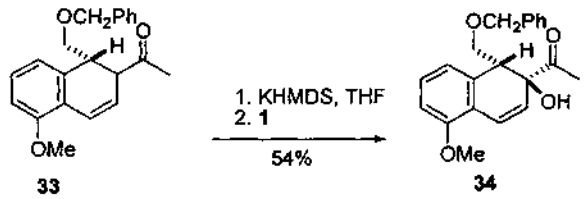
The generality of this method has been demonstrated in a number of total synthesis efforts.[19,20] In their studies aimed at the elucidation of the structure of capensifuranone, the Williams group utilized the 4-phenyl auxiliary for introduction of the hydroxyl substituent in **27**.[21] While the stereocenter was eventually destroyed, this reaction is notable in that high stereoselectivity can be obtained with the 4-phenyl auxiliary, in addition to the auxiliaries used above.



In two separate syntheses of the microtubule stabilizing antitumor agent epothilone B (**28**), the C_{15} stereocenter was prepared using diastereoselective hydroxylation mediated by the carboximide auxiliary. White and co-workers relied upon the 4-benzyl auxiliary to effect the diastereoselectivity in the preparation of **30**.[22a] Meanwhile, the generality of this reaction protocol is showcased by the high functional group tolerance demonstrated in the hydroxylation of **31** to give **32**.[22b]



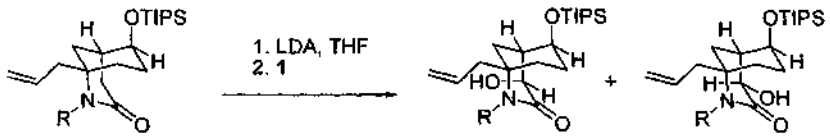
1.2.4.2 Substrate directed diastereoselective hydroxylation



Several examples exist wherein the chirality of the substrate serves to influence the degree of diastereoselectivity obtained on oxidation with racemic and nonracemic oxaziridines. These examples are different from those above, since an auxiliary whose sole purpose is to direct the stereoselectivity is not present. The majority of these examples rely on cyclic stereocontrol to direct the facial selectivity. For example, in Meyers synthesis of the AB-ring of aklavinone, oxidation of the thermodynamic enolate derived from **33** resulted in the production of tertiary α-hydroxy ketone **34** as a single diastereomer in modest yield.[23] The stereoselectivity is rationalized by invoking a transition state wherein pseudo axial addition to

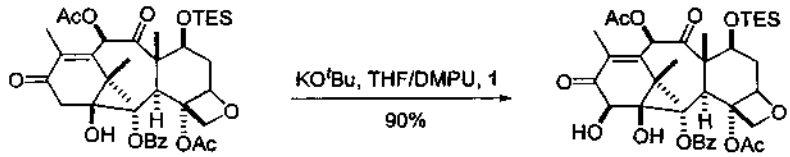
the least hindered top face occurs preferentially, with addition to the bottom face blocked by the neighboring benzyl ether.

Similarly, selectivity was observed in Weinreb's efforts toward the synthesis of the microbial immunosuppressive agent FR901483.[24] In this case, axial addition was favored by reaction of the lithium enolate of amide **35** with racemic **1** to produce **36**. An interesting reversal of stereoselectivity was observed when, on slight alteration of the synthetic sequence, the Boc-protected amide was subjected to similar conditions. For reasons not fully understood, equatorial alcohol **37** was produced in a 53% yield, the structure of which was confirmed by X-ray crystal analysis.



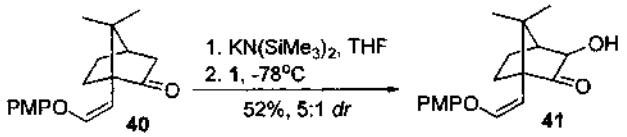
35 **36** R = Bn, 60% **37** R = Boc, 53%

During the synthesis of baccatin III derivatives, Baldelli and co-workers used the diastereoselective 14β-hydroxylation of **38** to form **39** using **1** as the hydroxylating reagent. As part of this study, several solvents, bases, and oxaziridine reagents were tested for this reaction, of which a majority produced high yields.[25] Optimum results were obtained using KO^{t}Bu as the base in a THF/DMPU (83:17) solvent system, though this is likely system dependent. The stereochemistry obtained was rationalized by a folded conformation of the terpene skeleton which precluded attack of the bulky oxaziridine reagents from the α-face. This example illustrates the generality of this approach and demonstrates its potential for use with highly congested and heavily functionalized substrates.

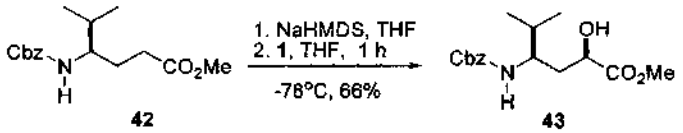


38 **39**

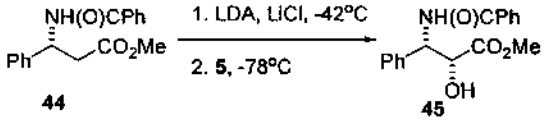
Using a similar strategy, Paquette and co-workers used this method for the α-oxygenation of **40** in the synthesis of precursors of the antitumor agent Taxol.[26] The α-hydroxy ketone **41** was produced by quenching the potassium enolate of **40** with **1**, yielding a 5:1 mixture of the *exo* and *endo* epimers of **41**.



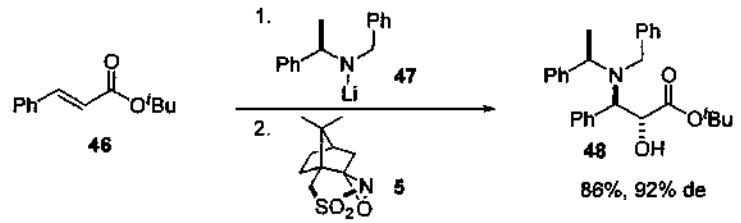
While the majority of examples of substrate control deal with cyclic sterocontrol, there are a few examples where diasteroselectivity is induced in an acylic system.[27] A notable example of this was demonstrated during the synthesis of a fragment of tubulysin, by Wipf and co-workers.[28] Utilizing a Davis reagent in their synthesis of an α-hydroxy-γ-amino acid, the enolate of the γ-amino acid derivative **42** was reacted with **1** to form the α-hydroxy derivative **43** as a single diastereomer in good yield. The stereoselective reaction has precedence in literature and likely involves a highly chelated dianionic species.[29]



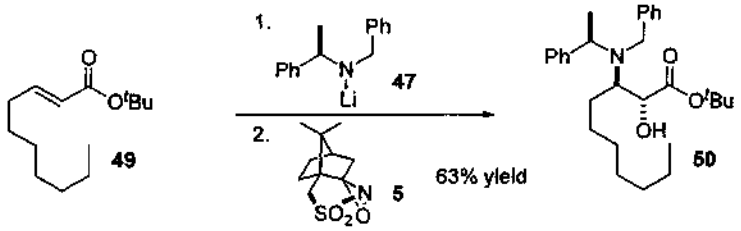
Further examples of acyclic stereocontrol in related amino acid systems make use of chiral and nonracemic oxaziridine reagents to induce high levels of stereocontrol. In 1992, Davis and coworkers synthesized the methyl ester of the Taxol C_{13} side chain using this method.[30] Following enolization, the dianion of **44** was reacted with the Davis reagent **5** to yield the α-hydroxy β-amino acid **45** in 49% yield. While the yield was marginal in this particular example, the 86:14 ratio of stereoisomers produced is impressive in this acyclic system.



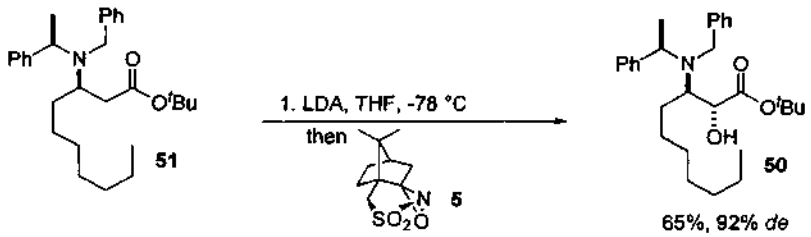
A similar protocol has been generalized in the Davies laboratories, relying on a highly diastereoselective tandem conjugate addition/hydroxylation strategy for synthesis of α-hydroxy-β-amino acid derivatives.[31-37] For example, the enolate produced via diastereoselective conjuagate addition of lithium benzylamide **47** to cinnamate **46** was quenched with (+)-(camphorsulfonyl)oxaziridine (**5**) to give **48** in impressive yield and high diastereoselectivity.



The above protocol was applied during efforts to assign the stereochemistry of the ACE-inhibitor microginin.[38] Following a similar procedure, conjugate addition of **47** to **49** was followed by oxidation with **5** to provide **50** in 63% yield. The (2*S*)-isomer was isolated as a by-product in 4% yield, giving the reaction an overall diastereoselectivity of around 15:1, similar to that obtained above.

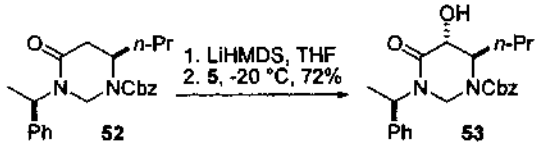


When the above transformation was conducted in a stepwise manner, β-amino acid derivative **51** was deprotonated with LDA and reacted with **5** to produce **50** in 65% yield and ~92% *de*.[38]

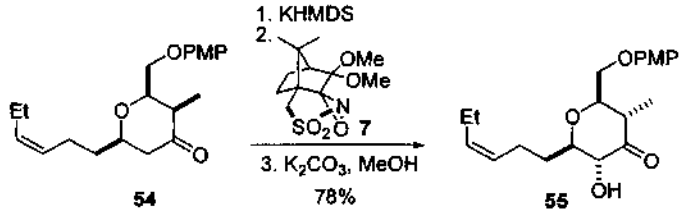


The syntheses of α-hydroxy β-amino acids has also been accomplished using a perhydropyrimidin-4-one template to direct the stereoselectivity of the hydroxylation.[39] For example, the enolate of perhydropyrimidin-4-one **52** was diastereoselectively hydroxylated to obtain **53**.[40] Examination of several oxidizing agents and bases revealed LiHMDS and the

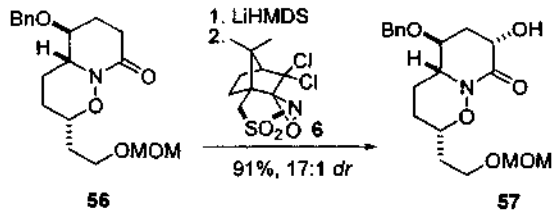
oxaziridine **5** as ideal choices for this transformation. Compound **53** can be hydrolyzed under acidic conditions to produce the enantiomerically pure α-hydroxy β-amino acid.



Substrate directed hydroxylation with Davis reagents has also found utility in the synthesis of architecturally complex natural products.[41–44] For example, efforts for the synthesis of (+)-spongistatin 1 by Smith and co-workers relied on hydroxylation of the enolate of **54** with Davis reagent **7**, which was followed by epimerization of the C_5 to produce **55** in high yield.[45]



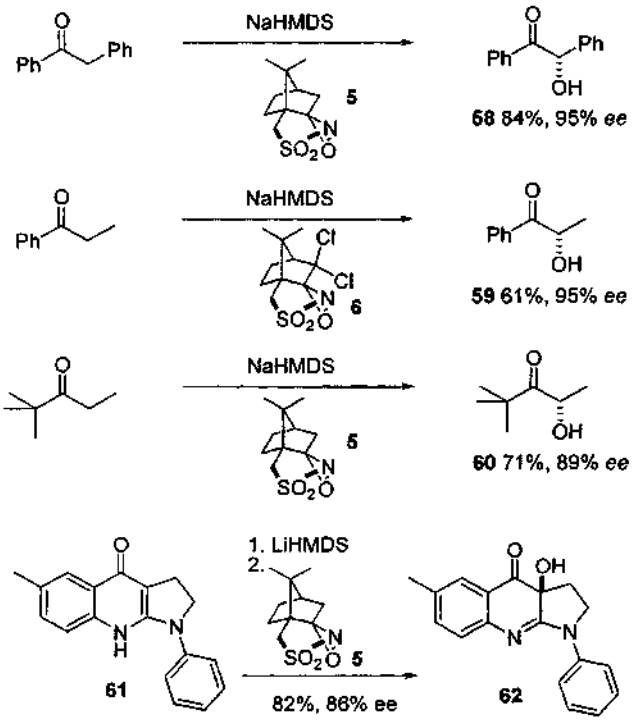
In the syntheses of (−)-lepadins A, B, and C, which exhibit strong cytotoxicity against human cancer cells, enolate oxidation relied on the chiral, nonracemic dichloro oxaziridine **6** to deliver the product **57** in a stereoselective manner.[46] Studies on this reaction demonstrated a higher stereoselectivity for the lithium enolate in comparison to a similarly generated sodium enolate. Their results also indicated that the reaction between **56** and **6** constituted a stereochemically matched case, whereas the use of racemic oxaziridine reagent **1** as well as use of the alternate enantiomer of **6** resulted in greatly reduced diastereoselectivity.



1.2.4.3 Enantioselective oxidation

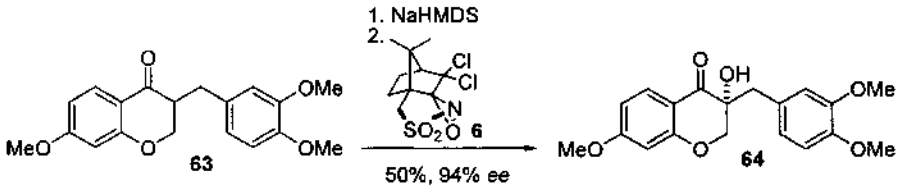
Enantioselective oxidation using Davis chiral oxaziridine reagents is not as well developed as its diastereoselective counterpart. However, a number of simple enolates have been

selectively hydroxylated, primarily in the Davis group.[47] After screening a number of bases and oxaziridines, optimum conditions generally utilize NaHMDS as the base with one of the (camphorsulfonyl)oxaziridine reagents (**5** or **6**). The impressive enantioselectivities for this protocol are demonstrated in the formation of **58**,[48] **59**,[49] and **60**.[50] Extension of this protocol to more complex ketones, or toward the synthesis of tertiary α-hydroxy ketones, is limited by the inability to selectively form a single enolate isomer. While hydroxylation of aromatic ketones has been well-documented,[51,52] the majority of more complicated enantioselective hydroxylations are done on cyclic ketones or lactones.[53]

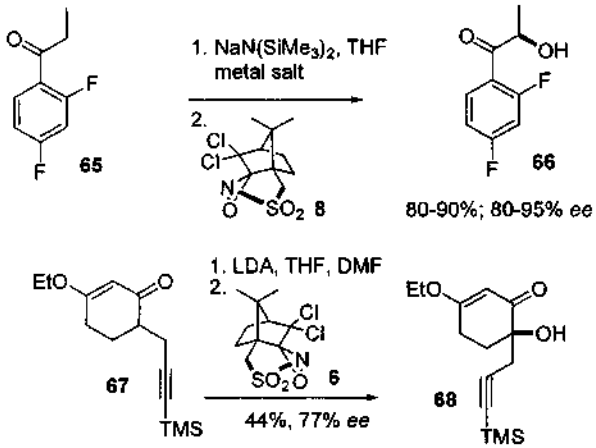


Several examples exist in the literature in which cyclic ketone enolates are enantioselectively hydroxylated by chiral, nonracemic Davis oxaziridine reagents. In contrast to their acyclic counterpart, the enolate geometry is fixed in cyclic systems. During the preparation of enantiomerically pure (–)-blebbistatin, the enolate of the quinolone **61** was reacted with the Davis reagent **5** to afford the optically enriched **62** with 82% yield and 86% *ee*.[54] The related reagent **6** was used in the synthesis of (+)-*o*-trimethylbrazilin, which was

accomplished by converting the enolate of **63** to the enantiomerically pure **64** in 50% yield.[55] Similar procedures were used during the synthesis of the AB ring segment of daunomycin.[56]

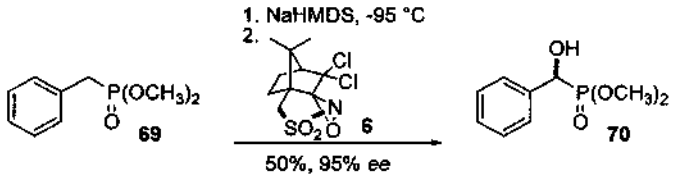


A related procedure was utilized for the syntheses of Sch 42427 and ER-30346, azole antifungals, and (–)-tricycloillicinone; however, slight modifications in the experimental procedures were explored resulting in improved yield and *ee*. During the conversion of the enolate of ketone **65** to the chiral α-hydroxy ketone **66**, Gala and DiBenedetto observed that the metal salts used in the reaction greatly influenced both the yield and the enantioselectivity.[52] Furuya and Terashima were also able to increase both yield and *ee* by carrying out the oxidation of the lithium enolate of **67** using Davis reagent **6** in a mixture of THF and DMF, which increased both the yield and *ee* of **68** by over 30% each.[56]

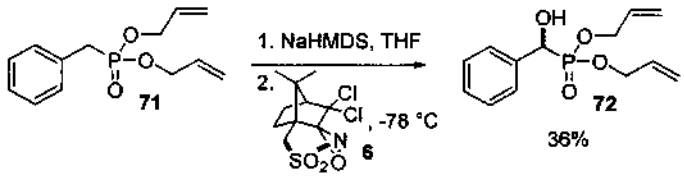


The utility of Davis chiral oxaziridine reagents has been more recently applied to the synthesis of optically active α-hydroxy phosphonates. Two groups have been largely responsible for developments in this area. Principally, Wiemer and co-workers have demonstrated the highly enantioselective hydroxylation of a series of benzyl phosphonates. As shown below for **69**, hydroxylation makes use of oxaziridine **6**, proceeding in moderate

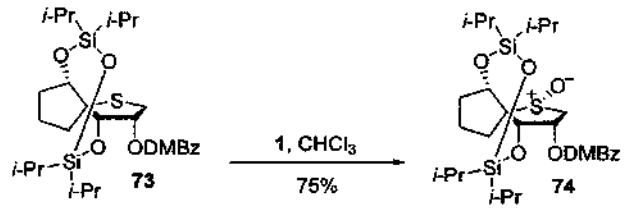
yield to give **70**, with high levels of enantioselectivity. The reaction works equally well with a variety of 4-substituted benzylphosphonates. [57] In an extension of this reaction to a more conformationally flexible molecule, the oxidation of dimethylfarnesylphosphate also proceeded with moderate enantioselectivity.[58]



Finally, Schmidt and coworkers have similarly applied the hydroxylation of phosphonates for synthesis of some sialyltransferase inhibitors. Thus, the stabilized enolate of **71** was selectively oxidized using dichloro(camphorsulphonyl)oxaziridine (**6**) to produce the α-hydroxy diallylphosphonate in low yield but as a single stereoisomer. The reaction was also found to be effective for compounds containing a variety of ring substituents.[59,60]

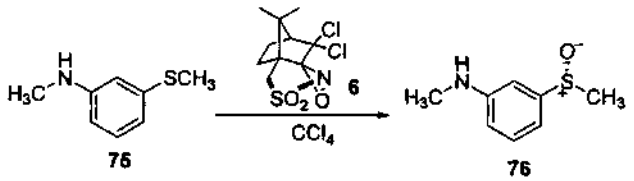


1.2.4.4 Heterocyclic asymmetric oxidation



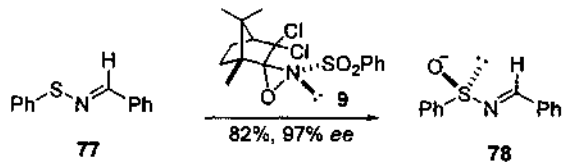
Davis chiral oxaziridine reagents have found ample synthetic utility in the asymmetric oxidation of sulfides to sulfoxides, providing excellent yields and high enantiomeric excess. Sulfoxides have seen growing importance in organic synthesis and the versatility of oxaziridine reagents enables them to be synthesized cleanly and efficiently.[61] The sulfide **73** was oxidized using the Davis reagent **1**, which could easily transfer an oxygen atom to the α-

face of the tetrahydrothiopene ring to form the major product **74** in 75% yield.[62] Similarly, the asymmetric oxidation of **75** using the Davis reagent **6** in carbon tetrachloride produced the sulfoxide intermediate **76** in 95% yield and 75% *ee*.[63]



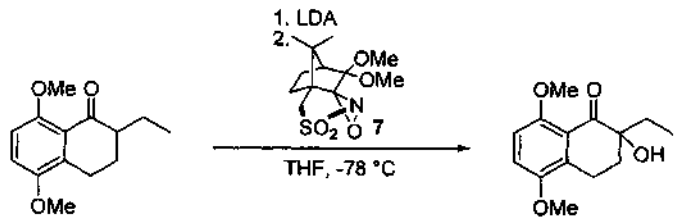
75 **76**

Sulfenimines undergo asymmetric oxidations to form sulfinimines via a reaction with Davis reagents. The sulfenimine **77** was oxidized by **9** to yield the sulfinimine **78** in 82% yield and 97% *ee*. Yields and enantiomeric excess varied based on the oxaziridine reagent used.[64]



77 **78**

1.2.5 Experimental



79 **80**

(–)-(*R*)-2-Ethyl-5,8-dimethoxy-2-hydroxy-1,2,3,4-tetrahydronaphthalen-1-one (80)[65]
A solution of 58.5 mg (0.25 mmol) of tetralone **79** in 2 mL of THF was added dropwise to a stirred and cooled –78 °C solution of 0.3 mL (0.30 mmol) of a 1 M solution of LDA in 2 mL of THF. After the mixture was stirred at –78 °C for 30 min a solution of 116 mg (0.4 mmol) of (+)-**7** in 5 mL of THF was added dropwise. The reaction was monitored by TLC, warmed to 0 °C as required, and quenched by the addition of 3 mL of saturated aqueous NH_4Cl after 0.5–1 h. The reaction mixture was extracted with diethyl ether (3 × 25 mL), and the combined organic extracts were washed with H_2O (20 mL) and brine (20 mL) and dried

($MgSO_4$). The solvent was removed under reduced pressure to give a white solid (170 mg), which was purified by preparative TLC (eluant pentane/ether/CH_2Cl_2, 3:1:1, R_f = 0.3) to give 40.6 mg (66%) of **80**: mp 74–75 °C (lit. colorless oil); IR and NMR spectral data are consistent with reported values. Anal. Calcd for $C_{14}H_{18}O_1$: C, 67.20; H, 7.20. Found: C, 67.09; H, 7.22.

1.2.6 References

1. Davis, F. A.; Vishwakarma, L. C.; Billmers J. M.; Flinn, J. *J. Org. Chem.* **1984**, *49*, 3241–3.
2. [R] Davis, F. A.; Chen, B.-C. *Chem. Rev.* **1992**, *92*, 919–34.
3. Christoffers, J.; Baro, A.; Werner, T. *Adv. Synth. Catal.* **2004**, *346*, 143–51.
4. Mimoun, H. *Angew. Chem. Int. Ed. Engl.* **1982**, *21*, 734–50.
5. Mimoun, H.; Mignard, M.; Brechot, P.; Saussie, L. *J. Am. Chem. Soc.* **1986**, *108*, 3711–8.
6. [R] Sharpless, K. B.; Verhoeven, T. R. *Aldrichimica Acta* **1979**, *12*, 63.
7. [R] Behrens, C. H.; Sharpless, K. B. *Aldrichimica Acta* **1983**, *16*, 67.
8. Lang, T. J.; Wolber, G. J.; Bach, R. D. *J. Am. Chem. Soc.* **1981**, *103*, 3275–82.
9. Bach, R. D.; Wolber, G. J.; Coddens, B. A. *J. Am. Chem. Soc.* **1984**, *106*, 6098–9.
10. Curci, R.; Giannattasio, S.; Sciacovel, O.; Troisi, L. *Tetrahedron* **1984**, *40*, 2763–71.
11. Pitchen, P.; Dunach, E.; Deshmukh, M. N.; Kagan, H. B. *J. Am. Chem. Soc.* **1984**, *106*, 8188–93.
12. Davis, F. A.; Billmers, J. M.; Gosciniak, D. J.; Towson, J. C. *J. Org. Chem.* **1986**, *51*, 4240–45.
13. Davis, F. A.; Vishwakarma, L. C.; *Tetrahedron Lett.* **1985**, *26*, 3539–42.
14. (a) Davis, F. A.; Ultaowski, T. G.; Haque, M. S. *J. Org. Chem.* **1987**, *52*, 5288–90. (b) Davis, F. A.; Reddy, G. V.; Chen, B.-C.; Kumar, A.; Haque, M. S. *J. Org. Chem.* **1995**,*60*, 6148–53.
15. Schultz, A. G.; Harrington, R. E.; Holoboski, M. A. *J. Org. Chem.* **1992**, *57*, 2973–6.
16. Evans, D A. *Aldrichimica Acta* **1982**, *15*, 23.
17. Evans, D. A.; Ennis, M. D.; Mathre, D. J. *J. Am. Chem. Soc.* **1982**, *104*, 1737–9.
18. Evans, D. A.; Morrissey, M. M.; Dorow, R. L. *J. Am. Chem. Soc.* **1985**, *107*, 4346–8.
19. Fürstner, A.; Radkowski, K.; Wirtz, C.; Goddard, R.; Lehmann, C. W.; Mynott, R. *J. Am. Chem. Soc.* **2002**, *124*, 7061–9.
20. Evans, D. A.; Gage, J. R. *J. Org. Chem.* **1992**, *57*, 1958–61.
21. Williams, D. R.; Nold, A. L.; Mullins, R. J. *J. Org. Chem.* **2004**, *69*, 5374–82.
22. (a) White, J. D.; Carter, R. G.; Sundermann, K. F. *J. Org. Chem.* **1999**, *64*, 684–5. (b) Mulzer, J.; Karig, G.; Pojarliev, P. *Tetrahedron Lett.* **2000**, *41*, 7635–38.
23. Meyers, A. I.; Higashiyama, K. *J. Org. Chem.* **1987**, *52*, 4592–7.
24. Kropf, J. E.; Meigh, I. C.; Bebbington, M. W. P.; Weinreb, S. M. *J. Org. Chem.* **2006**, *71*, 2046–55.
25. Baidelli, E.; Battaglia, A.; Bombardelli, E.; Carenzi, G.; Fontana, G.; Gambini, A.; Gelmi, M. L.; Guerini, A.; Pocar, D. *J. Org. Chem.* **2003**, *68*, 9773–9.
26. Elmore, S. W.; Paquette, L. A. *J. Org. Chem.* **1995**, *60*, 889–96.
27. Narasaka, K.; Ukaji, Y.; Watanabe, K. *Bull. Chem. Soc. Jpn.* **1987**, *60*, 1457–64.
28. Wipf, P.; Takada, T.; Rishel, M. J. *Organic Lett.* **2004**, *6*, 4057–60.
29. Hanessian, S.; Schaum, R. *Tetrahedron Lett.* **1997**, *38*, 163–6.
30. Davis, F. A.; Reddy, R. T.; Reddy, R. E. *J. Org. Chem.* **1992**, *57*, 6387–9.
31. Bunnage, M. E.; Davies, S. G.; Goodwin, C. J. *J. Chem. Soc., Perkin Trans. 1* **1993**, 1375–6.
32. Bunnage, M. E.; Chernega, A. N.; Davies, S. G.; Goodwin, C. J. *J. Chem. Soc., Perkin Trans. 1* **1994**, 2373–84.
33. Bunnage, M. E.; Davies, S. G.; Goodwin, C. J. *Synlett* **1993**, 731–2.
34. Bunnage, M. E.; Davies, S. G.; Goodwin, C. J. *Tetrahedron* **1994**, *50*, 3975–86.
35. Bunnage, M. E.; Davies, S. G.; Goodwin, C. J. *J. Chem. Soc., Perkin Trans. 1* **1994**, 2385–91.
36. Davies, S. G.; Epstein, S. W.; Ichihara, O.; Smith, A. D. *Synlett* **2001**, *10*, 1599–601.
37. Davies, S. G.; Epstein, S. W.; Garner, A. C.; Ichihara, O.; Smith, A. D. *Tetrahedron: Asymmetry* **2002**, *13*, 1555–65.
38. Bunnage, M. E.; Burke, A. J.; Davies, S. G.; Goodwin, C. J. *Tetrahedron: Asymmetry* **1995**, *6*, 165–76.
39. Escalante, J.; Juaristi, E. *Tetrahedron Lett.* **1995**, *36*, 4397–400.
40. Cardillo, G.; Tolomelli, A.; Tomasini, C. *Tetrahedron* **1995**, *51*, 11831–40.
41. Dounay, A. B.; Forsyth, C. J. *Org. Lett.* **1999**, *1*, 451–3.

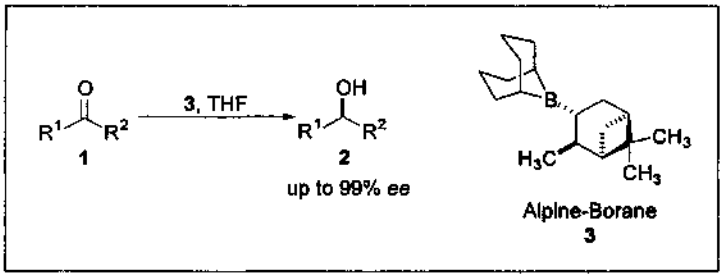
42. Roush, W. R.; Barda, D. A. *Tetrahedron Lett.* **1997**, *38*, 8785–8.
43. Hitotsuyanagi, Y.; Nishimura, K.; Ikuta, H.; Takeya, K.; Itokawa, H. *J. Org. Chem.* **1995**, *60*, 4549–58.
44. Yu,W.; Jin, Z. *J. Am. Chem. Soc.* **2001**, *123*, 3369–70.
45. Smith, A. B., III; Sfouggatakis, C.; Gotchev, D. B.; Shirakami, S.; Bauer, D.; Zhu, W.; Doughty, V. A. *Org. Lett.* **2004**, *6*, 3637–40.
46. Ozawa, T.; Aoyagi, S.; Kibayashi, C. *J. Org. Chem.* **2001**, *66*, 3338–47.
47. Davis, F. A.; Haque, M. S.; Przelawski, R. M. *J. Org. Chem.* **1989**, *54*, 2021–4.
48. Davis, F. A.; Haque, M. S. *J. Org. Chem.* **1986**, *51*, 4083–5.
49. Davis, F. A.; Weismiller, M. *J. Org. Chem.* **1990**, *55*, 3715–7.
50. Davis, F. A.; Sheppard, A. C.; Chen, B.-C.; Haque, M. S. *J. Am. Chem. Soc.* **1990**, *112*, 6679–90.
51. Matsunaga, N.; Kaku, T.; Ojida, A.; Tasaka, A. *Tetrahedron: Asymmetry* **2004**, *15*, 2021–8.
52. Gala, D.; DiBenedetto, D. *J. Tetrahedron: Asymmetry* **1997**, *8*, 3047–50.
53. Davis, F. A.; Haque, M. S.; Ultaowski, T. G.; Towson, J. C. *J. Org. Chem.* **1986**, *51*, 2402–4.
54. Lucas-Lopez, C.; Patterson, S.; Blum, T.; Straight, A. F.; Toth, J.; Slawin, A. M. Z.; Mitchison, T. J.; Sellers, J. R.; Westwood, N. J. *Eur. J. Org. Chem.* **2005**, *9*, 1736–40.
55. Davis, F. A.; Chen, B. C. *J. Org. Chem.* **1993**, *58*, 1751–3.
56. Furuya, S.; Terashima, S. *Tetrahedron Lett.* **2003**, *44*, 6875–8.
57. Pogatchnik, D. M.; Wiemer, D. F. *Tetrahedron Lett.* **1997**, *38*, 3495–8.
58. Cermak, D. M.; Du, Y.; Wiemer, D. F. *J. Org. Chem.* **1999**, *64*, 388–93.
59. Skropeta, D.; Schwörer, R.; Schmidt, R. R. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 3351–4.
60. Skropeta, D.; Schmidt, R. R. *Tetrahedron: Asymmetry* **2003**, *14*, 265–73.
61. Davis, F. A.; Lal, S. G. *J. Org. Chem.* **1988**, *53*, 5004–7.
62. Paquette, L. A.; Dong, S. *J. Org. Chem.* **2005**, *70*, 5655–64.
63. Padmanabhan, S.; Lavin, R. C.; Durant, G. J. *Tetrahedron: Asymmetry* **2000**, *11*, 3455–7.
64. Davis, F. A.; Reddy, R. E.; Szewczyk, J. M.; Reddy, G. V.; Portonovo, P. S.; Zhang, H.; Fanelli, D.; Reddy, R. T.; Zhou, P.; Carroll, P. J. *J. Org. Chem.* **1997**, *62*, 2555–63.
65. Davis, F. A.; Kumar, A.; Chen, B.-C. *J. Org. Chem.* **1991**, *56*, 1143–5.

Richard J. Mullins and Michael T. Corbett

1.3 Midland Reduction

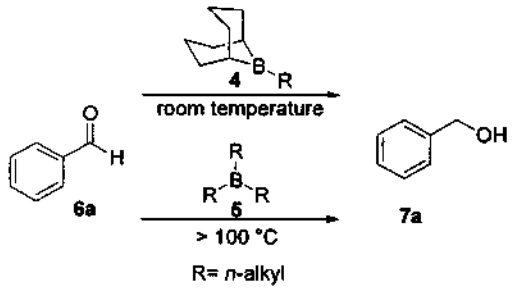
1.3.1 Description

The Midland reduction is the enantioselective reduction of a ketone (**1**) to an optically active alcohol (**2**) using the commercially available reagent alpine borane (**3**).[1]

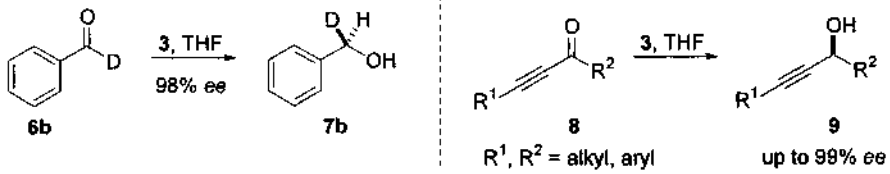


1.3.2 Historical Perspective

In 1977, Midland and co-workers found that *B*-alkyl-9-borabicycle[3.3.1]nonanes (**4**) were unique among trialkyl borane adducts (**5**) in that they rapidly reduced benzaldehyde (**6a**) at room temperature.[2]

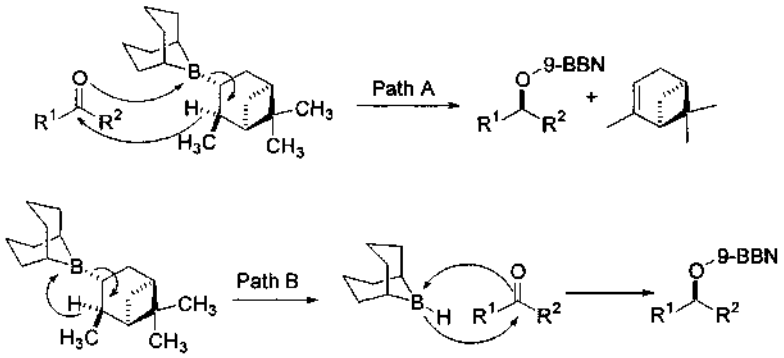


Extension of this methodology to an enantioselective variant soon followed. In 1979 Midland showed that by using the chiral reagent derived from hydroboration of α-pinene by 9-BBN (**3**), deuterium labeled benzaldehyde (**6b**) could be reduced to enantiomerically enriched alcohol **7b** in 98% *ee*.[3] Subsequent studies found that **3** was also useful for the enantioselective reduction of acetylinic ketones (**8**) to propargylic alcohols (**9**).[4]

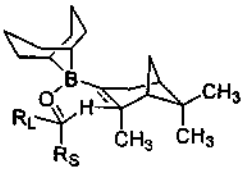


1.3.3 Mechanism and Stereochemical Rationalization

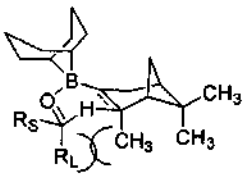
Initial debate over the mechanism of the Midland reduction centered around the idea that this reduction could reasonably proceed *via* either a one-step (Path A) or two-step (Path B) mechanism as shown below. However, mechanistic investigations by Midland showed that the rate of the reaction was dependent on the concentration of the aldehyde, thus lending support to the reaction proceeding *via* Path A[5]. The subsequent development of the enantioselective variant of this reaction using **3** essentially eliminated Path B as a possible mechanism because it is not consistent with the optically active alcohols produced in the reaction. Thus, Path A is widely accepted as the mechanism for this reaction.



The reduction of ketones with **3** affords chiral alcohols with a predictable stereochemical outcome. Transition state **10** is favored over **11** because the smaller group of the ketone (R_S) rather than the large group (R_L) is "axial" and eclipsing the methyl group of the pinene subunit.[6] While there is still some debate over the nuances of the transition state of this reduction, transition state **10** is a reasonable model that accurately predicts the stereochemical outcome of the reduction of ketones with **3**.



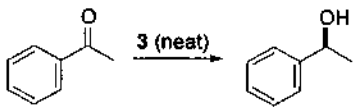
10
Favored Transition State



11
Disfavored Transition State

1.3.4 Variations and Improvements

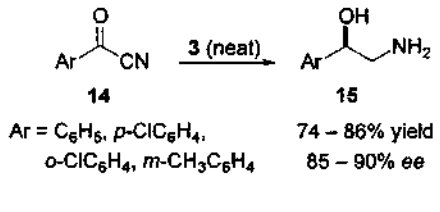
While Midland's initial studies focused on the reduction of aryl aldehydes and alkynyl ketones, expansion of the scope of this methodology was problematic. Attempted reduction of a variety of aldehydes afforded the corresponding alcohols only after long reaction times and in low enantiomeric excess. The moderate increase in the steric bulk of these non-acetylenic ketones is believed to account for the marked decrease in reaction rate. Furthermore, the slow reduction of these ketones is problematic because it allows for the retrohydroboration of **3** into more reactive and achiral 9-BBN. The reduction of the ketone with 9-BBN is then much more facile and leads to optically inactive products (Path B, section 1.3.3). The initial solution to this problem was developed by H. C. Brown and Pai.[7] They found that by carrying out the reaction neat, instead of at 0.5 M in THF,the rate of the bimolecular reduction reaction increased enough so that the unimolecular retrohydroboration reaction was less competitive. Subsequently, Midland found that even better results could be obtained by increasing the pressure in the reaction vessel.[8,9] It was proposed that the reason for the increase in both rate and selectivity was due to the fact that the bimolecular reduction process (Path A, Section 1.3.3) should be favored at high pressure while the dissociative retrohydroboration reaction (Path B) should be suppressed. Indeed, Midland found that by increasing the pressure to 6000 atm the reduction of a variety of ketones, including acetophenone (**12**), was achieved with neat alpine borane (**3**) to the corresponding alcohol (**13**) at noticeably faster rates and with improved enantioselectivity.

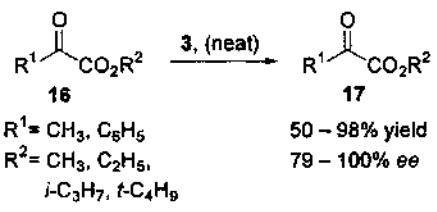


1 atm: 7 days, 78% ee
6000 atm: 1 day, 98.4% *ee*

12 **13**
80% yield

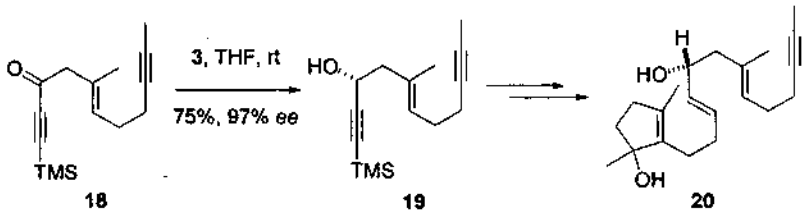
The use of alpine-borane (**3**) has also been extended to include the reduction of acyl cyanides (**14**) to optically active β-amino alcohols (**15**),[10] as well as the reduction of α-keto esters (**16**) into the corresponding α-hydroxy esters (**17**).[11]



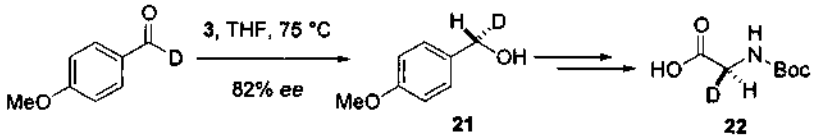


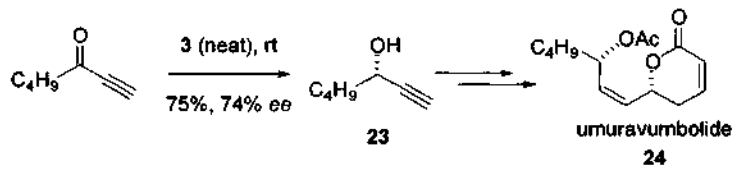
1.3.5 Synthetic Utility

Alpine borane (the Midland reagent, **3**) has found broad use in the synthesis of complex natural products. As early as 1980, only one year after Midland's seminal publication, Johnson and co-workers used **3** for the reduction of ketone **18** to afford alcohol **19** in 75% yield and 97% *ee*.[12] This material was used to complete the synthesis of **20**, a cyclization precursor in Johnson's total synthesis of hydrocortisone acetate.



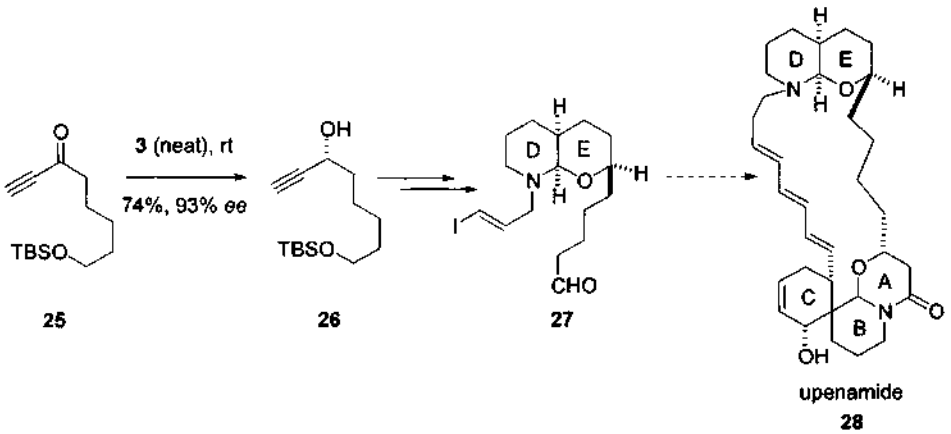
The Midland reduction has also been used in the large-scale synthesis of chiral glycines. Deuterium labeled anisaldehyde was reduced with **3** to provide deuteriated arylmethyl alcohol **21** in 82% *ee*.[13] This alcohol was then converted in 4 steps to *N*-Boc-glycine (**22**).





More recently, alpine-borane (**3**) was used as the first step in the total synthesis of umuravumbolide (**24**). Reduction of 1-heptyn-3-one with **3** produced **23** in 75% yield and 74% *ee*.[14]

The synthesis of the DE ring system of upenamide (**28**) utilized a Midland reduction to set the initial stereocenter in the synthesis. Conversion of **25** to **26** proceeded in 74% yield and 93% *ee*.[15] This material was carried on through a series of transformations to achieve a synthesis of the DE ring system (**27**).



1.3.6 Experimental

Propargylic alcohol (26)[15]

Alkynone **25** (5.09 g, 20.0 mmol) was added to neat (*R*)-alpine-borane (7.23 g, 28 mmol) at 0 °C. The ice bath was removed after 30 min and the red solution was stirred at room temperature for 8 h at which time GC analysis showed complete consumption of starting material. Excess alpine-borane was quenched by the addition of propionaldehyde (1.08 mL, 15 mmol) with external cooling (0 °C) followed by stirring at room temperature for 1 h. The solution was concentrated and subject to high vacuum at 40 °C for 4 h with stirring to remove α-pinene. The residue was diluted with THF (10 mL) and solutions of NaOH (3 M, 7.5 mL) and H_2O_2 (30%, 7.5 mL) (caution: highly exothermic) was added dropwise at 0 °C. The resulting mixture was stirred for 4 h at 40 °C and extracted with ether (3 × 60 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$), filtered, and concentrated. The residue was purified by flash chromatography (hexanes:ethyl acetate, 8:1) to give 3.78 g (74% yield, 93% *ee*) of 14 as a light-yellow oil.

1.3.7 References

1 [R] Midland, M. M. *Chem. Rev.* **1989**, *89*, 1553 (and references therein).
2. Midland, M. M.; Tramontano, A.; Zderic, S. A. *J. Orgmet. Chem.* **1977**, *134*, C17.
3. Midland, M. M.; Tramontano, A.; Zderic, S. A. *J. Orgmet. Chem.* **1978**, *156*, 203.
4. Midland, M. M.; Greer, S.; Tramontano, A.; Zderic, S. A. *J. Am. Chem. Soc.* **1979**, *101*, 2352.
5. Midland, M. M.; McDowell, D. C.; Hatch, R. L.; Tramontano, A. *J. Am. Chem. Soc.* **1980**, 867.
6. Midland, M. M.; Zderic, S. A. *J. Am. Chem. Soc.* **1982**, *104*, 525.
7. Brown, H. C.; Pai, G. G. *J. Org. Chem.* **1982**, *47*, 1606.
8. Midland, M. M.; McLoughlin, J. I. *J. Org. Chem.* **1984**, *49*, 1316.
9. Midland, M. M.; McLoughlin, J. I.; Gabriel, J. *J. Org. Chem.* **1989**, *54*, 159.
10. Midland, M. M.; Lee, P. E. *J. Am. Chem. Soc.* **1985**, *107*, 3237.
11. Brown, J. C.; Pai, G. G.; Jadhav, P. K. *J Am. Chem. Soc.* **1984**, *106*, 1531.
12. Johnson, W. S.; Frei, B.; Gopalan, A. S. *J. Org. Chem.* **1981**, *46*, 1512.
13. Ramalingam, K.; Nanjappan, P.; Kalvin, D. M.; Woodard, R. W. *Tetrahedron*, **1988**, *44*, 5597.
14. Ready, M. V. R.; Rearick J. P.; Hoch, N.; Ramachandran, P V. *Org Lett.* **2001**, *3*, 19.
15. Kiewel, K.; Luo, Z.; Sulikowski, G. A. *Org. Lett.* **2005**, *7*, 5163.

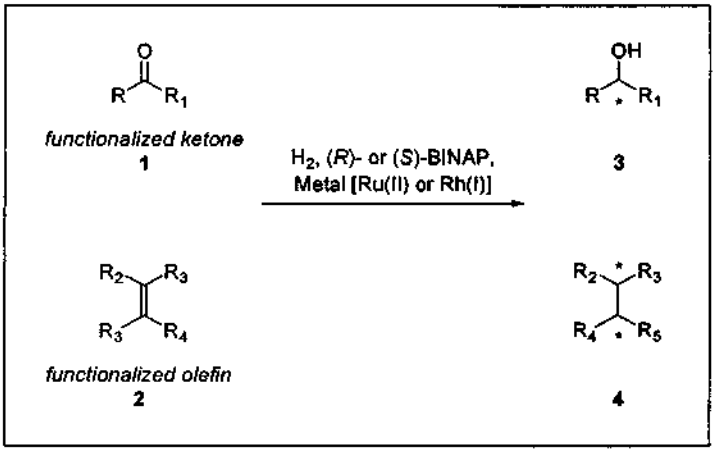
Julia M. Clay

1.4 Noyori Catalytic Asymmetric Hydrogenation

1.4.1 Description

The demand to produce enantiomerically pure pharmaceuticals, agrochemicals, flavors, and other fine chemicals from prochiral precursors has advanced the field of catalytic asymmetric hydrogenation.[1] In 2002 worldwide sales of single enantiomer pharmaceutical products approached $160 billion.[2]

Homogeneous catalytic asymmetric hydrogenation has become one of the most efficient methods for the synthesis of chiral alcohols, amines, α- and β-amino acids, and many other important chiral intermediates. Specifically, catalytic asymmetric hydrogenation methods developed by Professor Ryoji Noyori are highly selective and efficient processes for the preparation of a wide variety of chiral alcohols and chiral α-amino acids.[3] The transformation utilizes molecular hydrogen, BINAP (2,2'-bis(diphenylphosphino)-1,1'-binaphthyl) ligand and ruthenium(II) or rhodium(I) transition metal to reduce prochiral ketones **1** or olefins **2** to their corresponding alcohols **3** or alkanes **4**, respectively.[4]



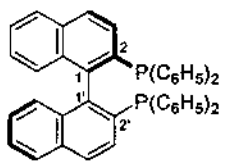
This unique asymmetric transformation has become one of the most efficient, practical, and atom-economical methods for the construction of chiral compounds from simple prochiral starting material.[5] The transformation can offer either (*R*)- or (*S*)-stereoisomer, can have exquisite substrate-to-catalyst (S/C) ratio (100,000:1), and by selecting the appropriate substrate and catalyst, generality can often exceed the merits of a biotransformation. Furthermore, the reaction can proceed with high turnover number (TON), turnover frequency (TOF), and enantiomeric excess (*ee*). The operations of the reaction,

isolation, separation, and purification are simple, easily performed, and well-suited for mass production.[6]

1.4.2 Historical Perspective

In 1968, W. S. Knowles[7] and L. Horner[8] reported independently the first homogeneous catalyzed asymmetric hydrogenation of olefins with chiral monodentate tertiary phosphine Rh-complexes, albeit in low enantiomeric excess (3–15% *ee*).[9] A major breakthrough came in 1971, when H. B. Kagan developed a Rh(I)-complex derived from a C_2 chiral diphosphine ligand of tartaric acid.[10] The Kagan Rh(I)-complex asymmetrically hydrogenated dehydro amino acids leading to phenylalanine in 72% *ee*. Subsequently, the pioneering work of the Knowles group at Monsanto established a method for the industrial synthesis of *L*-DOPA, a drug for treating Parkinson's disease, using DIPAMP-Rh(I) catalyzed asymmetric hydrogenation as a key step.[11] The successful and practical synthesis of *L*-DOPA constitutes a fundamental progression in asymmetric hydrogenation technology, and for his discovery Knowles shared the 2001 Nobel Prize in Chemistry with R. Noyori and K. B. Sharpless.[12a]

In 1980, Professor Noyori and the late H. Takaya consequently designed and synthesized a bidentate phosphine ligand BINAP (2,2'-bis(diphenylphosphino)-1,1'-binaphthyl) **5**, that contained an atropisomeric 1,1'-binaphthyl structure as a chiral element for use in transition metal catalyzed asymmetric hydrogenation reactions (Figure 1).



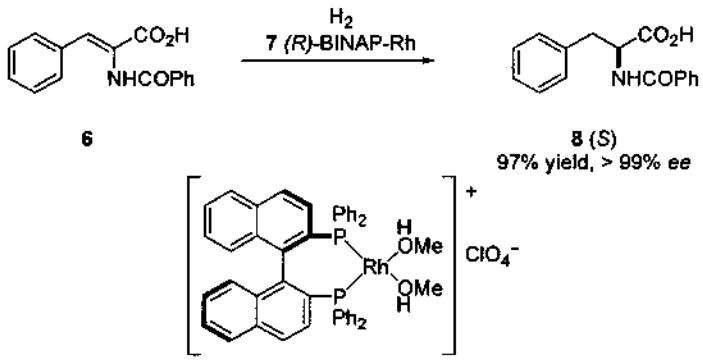
5 *(R)*-BINAP

Figure 1 (*R*)- 2,2'-Bis(diphenylphosphino)-1,1'-binaphthyl **5**

Rhodium(I) complexes of BINAP enantiomers are remarkably effective in various kinds of asymmetric catalytic reactions,[4c] including the enantioselective hydrogenation of α-(acylamino)acrylic acids or esters[4c] to provide amino acid derivatives, and the enantioselective isomerization of allylic amines to enamines.[13] Furthermore, Noyori's discovery of the BINAP-Ru(II) complex was a major advance in stereoselective organic synthesis. The scope and application of the BINAP transition metal catalyst system is far reaching. These chiral Ru complexes serve as catalyst precursors for the highly enantioselective hydrogenation of a range of functionalized ketones and olefins.[4b] For his contribution to asymmetric hydrogenation, Noyori shared the 2001 Nobel Prize in Chemistry with W. S. Knowles and K. B. Sharpless.[12b]

1.4.3 Mechanism

The BINAP ligand **5** (Figure 1) has numerous unique features. The diphosphine is characterized by full aromatic substitution, which exerts steric influence, provides polarizability, and enhances the Lewis acidity of the metal complex. The BINAP molecule is conformationally flexible and can accommodate a wide variety of transition metals by rotation about the binaphthyl C(1)-C(1′) pivot and C(2 or 2′)-P bonds without a serious increase in torsional strain. The framework of the chiral ligand determines enantioselectivity but can also alter the reactivity of the metal complex. In addition, the BINAP binaphthyl groups are axially dissymmetric possessing C_2 symmetry,[14] resulting in the production of an excellent asymmetric environment.[1f]



6 **8** (*S*)
97% yield, > 99% *ee*

7

In 1980, Noyori and co-workers reported cationic BINAP-Rh(I) catalyzing the hydrogenation of α-(acylamino)acrylic acids and esters to give amino acid derivatives in > 90% *ee*.[4c] For instance, catalyst **7** converts (*Z*)-α-(benzamido)cinnamic acid **6** to (*S*)-*N*-benzoylphenylalanine **8** in > 99% *ee* and 97% yield [substrate/catalyst molar ratio (S/C) = 100, 4 atm, room temp., 48 h, EtOH]. This reaction gives excellent enantioselectivity, but proved to be less than ideal because of the *unsaturated dihydride mechanism*, which has been thoroughly investigated by Halpern, Brown, and co-workers.[15] The catalytic asymmetric hydrogenation reaction mechanism of enamide **9** using C_2-chiral diphosphine Rh complex **7** to yield chiral α-amino acids **13** is shown in Figure 2. The Rh complex **7** forms a mixture of two diastereomeric substrate complexes with **9**, which leads to the *S* or *R* hydrogenation product, depending on the *Re/Si* face selection at the α-carbon C(2) in **9**. Hence, the enantioselectivity is determined by the relative equilibrium ratio and reactivity of diastereomer **10**. Under the reaction conditions, the major and more stable diastereomer is consumed much more slowly than the less stable minor isomer because of lower reactivity towards H_2. The thermodynamically favored *Si*-**10** diastereomeric Rh complex, leading to the

R-enantiomer of **13**, is weakly reactive and thus before hydrogenation can occur, it is converted to the highly reactive diastereomer *Re*-**10**. Diastereomer *Re*-**10** ultimately gives the *S*-enantiomer **13** via decoordination and recoordination of substrate **9**. Consequently, the observed enantioselectivity is a result of the delicate balance of the stability and reactivity of diastereomeric **10**. Because of this inherent mechanistic problem, the optimum conditions leading to high enantioselectivity are obtainable only by careful reagent and reaction condition choices. The reaction must be conducted under low substrate concentration and low hydrogen pressure. The BINAP-Rh catalyzed reaction occurs very slowly, because the reactive substrate Rh-complex **10** is present in very low concentration under these hydrogenation conditions. Unfortunately, the scope of the olefinic substrate is narrow. Thus, the BINAP-Rh catalyzed hydrogenation suffers from a mechanistic limitation and therefore remains far from ideal. Respectable enantioselection is obtainable only with Rh complexes of the ligand DuPhos, certain monodentate phosphates, and phosphoamidites.[16,17]

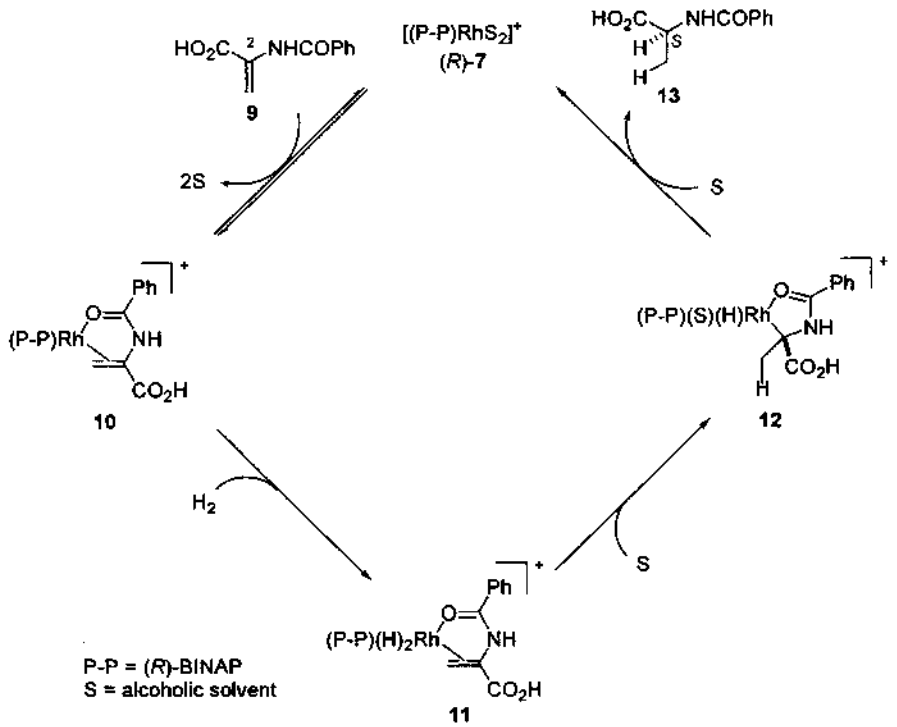
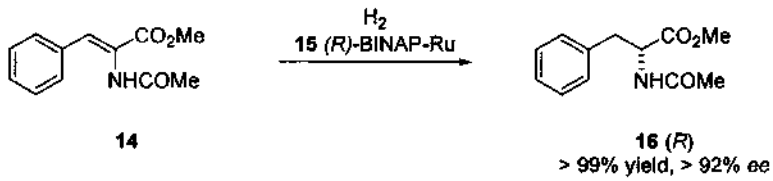
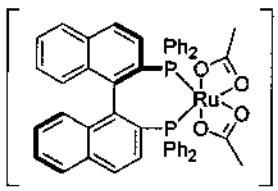


Figure 2 Mechanism of Rh-diphosphine catalyzed hydrogenation of enamide **9**

A breakthrough in catalytic asymmetric hydrogenation came when the Rh(I) metal was replaced by Ru(II). Hydrogenation of methyl (*Z*)-α-(acetamido)-cinnamate **14**, in the presence of $Ru(OCOCH_3)_2$[(*R*)-BINAP] **15**,[4b,18] affords methyl (*R*)-α-(acetamido)cinnamate **16** in 92% *ee* and > 99% yield [substrate/catalyst molar ratio (S/C) = 200, 1 atm, 30 °C, 24 h, MeOH].[19]

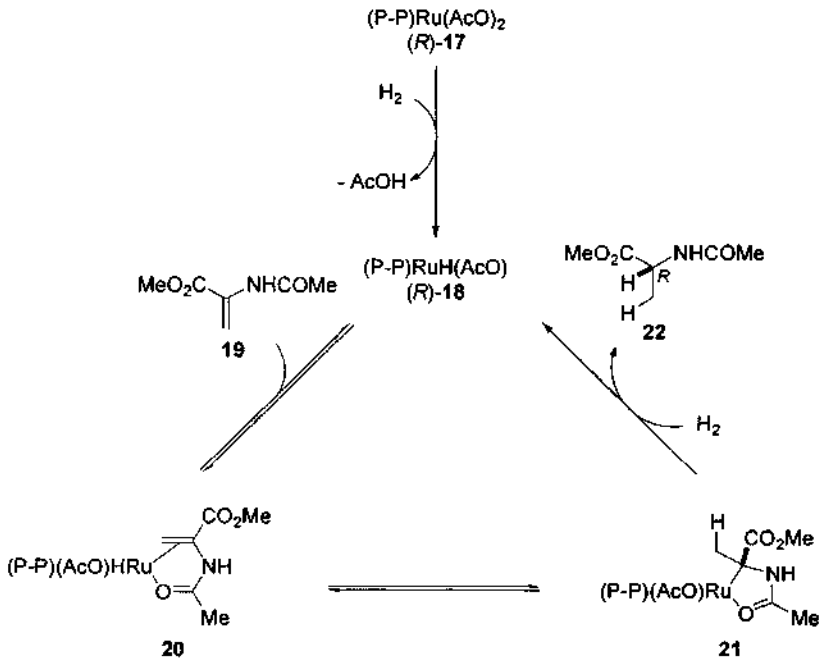


14 **16** (*R*)
> 99% yield, > 92% *ee*



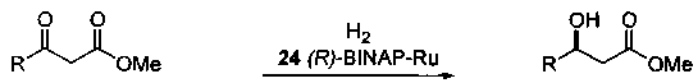
15

The asymmetric induction is opposite of that obtained with the (*R*)-BINAP-Rh **7** catalyst.[19,20] This contrasting behavior was found to be caused by an *unsaturated monohydride mechanism*, which is facilitated by the Ru monohydride catalyst **18** formed by the heterolytic cleavage of H_2 by precatalyst **17** (Figure 3).[19] Importantly, the metal hydride species **18** in this reaction is generated before substrate coordination, unlike the Rh chemistry involving the *unsaturated dihydride mechanism* (Figure 2).[15] The stereochemistry of the product is determined by the cleavage of the Ru–C bond in **21** by H_2. The enantiomeric ratio corresponds well to the relative stability of the diastereomeric substrate RuH complexes *Si*- and *Re*-**20**. The major *Si*-**20** diastereomer is converted to the *R* hydrogenation product by migratory insertion followed by hydrogenolysis. The two hydrogen atoms incorporated in product **22** are from two different H_2 molecules, as confirmed by isotope labeling experiments.[3] This result stands in contrast to the standard Rh-catalyzed reaction, which uses only one H_2 molecule per product.[3]



P-P = (*R*)-BINAP

Figure 3 Mechanism of Ru-complex catalyzed hydrogenation of enamide **19**



23 **25** (*R*)
>99% *ee*

β-Keto esters are effectively reduced by halogen containing chiral precatalysts, including RuX_2(BINAP) **24** (X = Cl, Br, I),[21,22] [RuX(BINAP)(arene)]Y (X = halogen, Y = halogen or BF_4),[23] $[NH_2(C_2H_5)_2][(RuCl(BINAP))_2(\mu\text{-}Cl)_3]$,[24] and other *in situ* formed halogen containing BINAP-Ru complexes.[25] Moreover, various β-keto esters are hydrogenated in alcoholic solvent with an S/C of up to 10,000 to give chiral β-hydroxy esters in high *ee*. Interestingly, the $Ru(OCOCH_3)_2$(BINAP) **15** catalyst, although excellent for the asymmetric

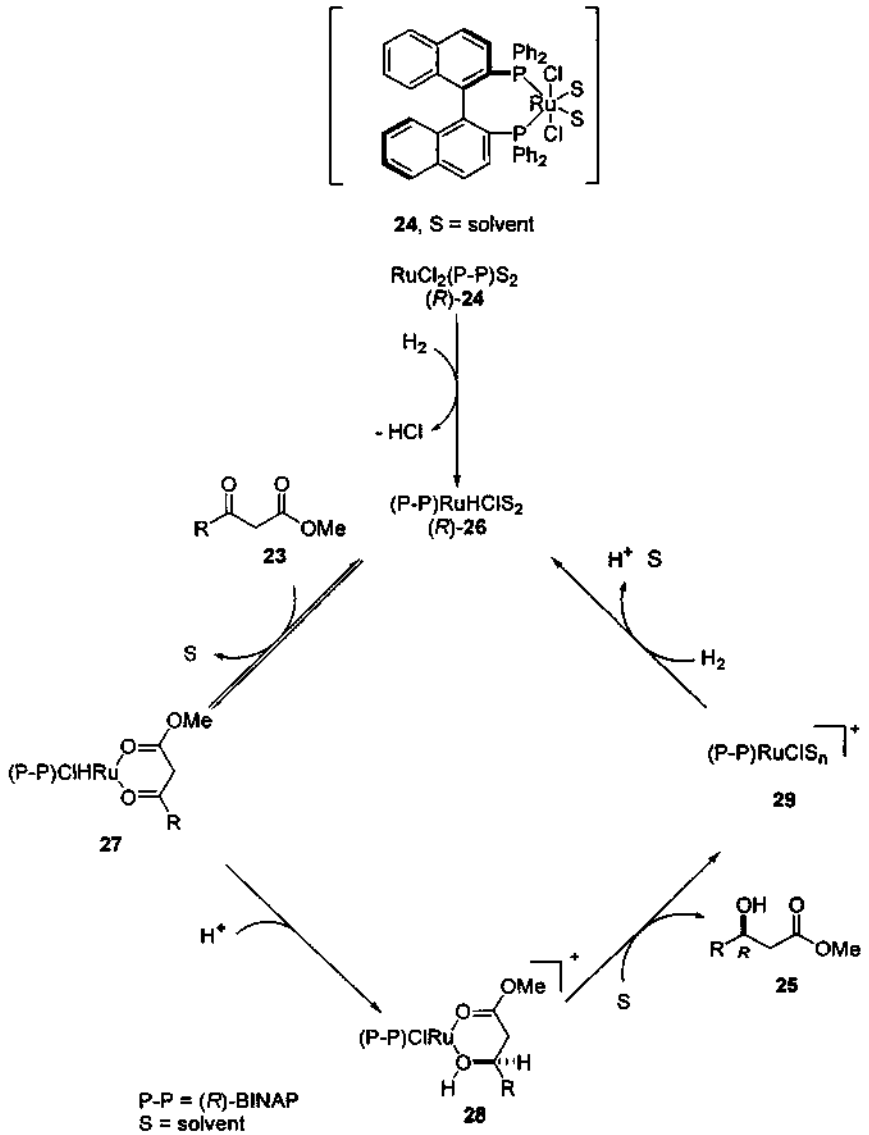
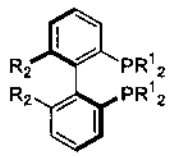


Figure 4 Mechanism of Ru-complex catalyzed hydrogenation of β-keto ester **23**

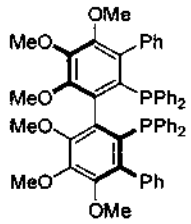
hydrogenation of functionalized olefins, is ineffective in reactions of structurally similar ketones such as β-keto esters.

A mechanistic model for the reduction of β-keto ester **23** is represented in Figure 4, wherein the actual catalyst is RuHCl **26** which is formed by the reaction between **24** and H_2.[26] Initially, **26** interacts reversibly with β-keto ester **23** to form the σ-type chelate complex **27**, in which metal-to-carbonyl hydride transfer is geometrically difficult. However, after protonation at the oxygen, the electrophilicity of the carbon is increased and the geometry is converted from σ to π, which facilitates the hydride migration. The hydroxy ester ligand in the resulting product **28** is liberated by solvent. The cationic Ru complex **29** cleaves H_2 and regenerates **26**. Enantioselectivity of > 99:1 is achieved in the hydride transfer step **27** to **28**. A key step is carbonyl protonation of **27**, caused by HCl generated in the induction step **24** to **26**.[27] The list of potential substrates includes various ketones possessing a directive functional group such as a dialkylamino, hydroxyl, alkoxyl, siloxyl, keto, halogeno, alkoxycarbonyl, alkylthiocarbonyl, dialkylamino-carbonyl, phosphoryl, and sulfoxyl group, among other possibilities.[1c,4a,28]

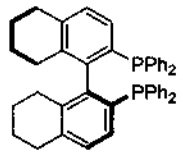
1.4.4 Variations and Improvements



30 *(S)*-BIPHEMP: R^1 = Ph; R_2 = CH_3
31 *(S)*-BIPHEP: R^1 = Ph; R_2 = OCH_3



32 *(S)*-o-Ph-HexaMeO-BIPHEP

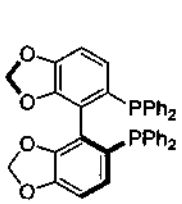


33 *(S)*-H_8-BINAP

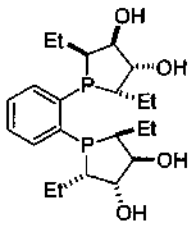
Ever since Professor Noyori demonstrated that BINAP transition metal complexes were highly effective for asymmetric hydrogenation, a vast number of chiral ligands and catalysts have been developed by many researchers in academia and industry.[1d] In particular, many researchers have devoted their efforts to designing and developing new efficient and selective chiral phosphorus ligands. A major feature in the design of the new chiral phosphorus ligands is the ability to tune the steric and electronic properties of ligands within a given scaffold. Modification of the electronic and steric properties of BIPHEMP **30** and MeO-BIPHEP **31** led to the development of new and efficient atropisomeric ligands for ruthenium-catalyzed asymmetric hydrogenation.[1a] In addition, Zhang *et al.* have recently disclosed an *ortho*-substituted BIPHEP ligand, *o*-Ph-HexaMeO-BIPHEP **32**, for the rhodium-catalyzed asymmetric hydrogenation of cyclic enamides.[29] Takaya has found that a modified BINAP

ligand (H_8-BINAP **33**) provides better enantioselectivity than BINAP in Ru-catalyzed hydrogenation of unsaturated carboxylic acids.[30]

The chiral biaryl bisphosphine ligand SEGPHOS **34**, developed by Takasago, possesses a smaller dihedral angle than BINAP. The ligand has provided greater enantioselectivity over BINAP in Ru-catalyzed hydrogenation of a wide variety of carbonyl compounds.[31]



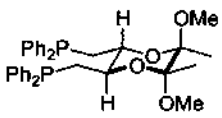
34 *(S)*-SEGPHOS



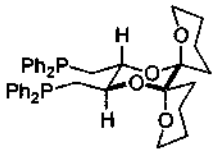
35 KetalPhos

A number of chiral bisphosphane ligands have emerged based on the modification of DuPhos and BPE ligands,[1a] which have proved successful for the rhodium-catalyzed asymmetric hydrogenation of functionalized olefins and ketones. The ligand with four hydroxyl groups, KetalPhos **35**,[32] enables the hydrogenation to be carried out in aqueous solution with high enantioselectivity.

Zhang has developed a series of 1,4-diphosphane ligands with a conformationally rigid 1,4-dioxane backbone, as exemplified by T-Phos **36** and SK-Phos **37**. These ligands have proved highly efficient and selective (> 99% *ee*) for the asymmetric hydrogenation of arylenamides and MOM-protected β-hydroxyl enamides.[33]



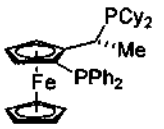
36 *(R,R,R,R)*-T-Phos



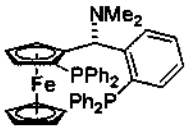
37 *(R,R,R,R)*-SK-Phos

Many chiral ferrocene-based bisphosphane ligands with great structural variations have been developed recently. Togni and Spindler introduced non-C_2-symmetric ferrocene-based Josiphos type ligands.[34] Josiphos **38** has been found to be effective for Rh-catalyzed hydrogenation of α-acetamidocinnamate, dimethyl itaconate, and β-keto esters. A class of non-C_2-symmetrical ferrocene-based 1,5-diphosphane ligands (TaniaPhos **39**) has also been

developed by Knochel.[35] These ligands have been effectively used in Rh- and Ru-catalyzed asymmetric hydrogenation of functionalized α-(acylamino)acrylic acids and esters, β-keto esters, and imines. The TaniaPhos type ligands (**39**), which have a MeO group at the stereogenic carbon, have shown excellent applications in hydrogenation of several ketone and olefin substrates.[36]

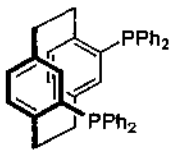


38 (*R*)-(*S*)-Josiphos

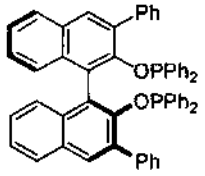


39 TaniaPhos

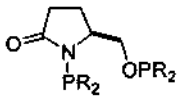
Although the first P-chiral bisphosphane (DIPAMP) was developed by Knowles over 30 years ago, the discovery of new efficient P-chiral bisphosphanes has been slow partly because of the difficulties in ligand synthesis. Pye and Rossen have developed a planar chiral bisphosphine ligand, [2.2]-PHANEPHOS **40**, based on a paracyclophane backbone.[37] The ligand has shown excellent enantioselectivity in Rh- and Ru-catalyzed hydrogenations.



40 (*S*)-[2,2]PHANEPHOS



41 (*S*)-Ph-*o*-BINAPO



42 (*S*)-Cy,Cy-oxoProNOP: R = Cy
43 (*S*)-Cp,Cp-oxoProNOP: R = Cp

The discovery of highly efficient bisphosphinites, bisphosphonites, and bisphosphites for asymmetric hydrogenation has been relatively slow compared to chiral bisphosphane ligands, due to their greater conformational flexibility and instability. Zhang has recently reported on a series of *o*-BINAPO ligands with substituents at the 3 and 3′ positions of the binaphthyl group. The ligand Ph-*o*-BINAPO **41** is an efficient ligand for hydrogenation of α-dehydroamino acid derivatives.[38] The *o*-BINAPO ligands have also been applied in Ru-catalyzed hydrogenation of β-aryl-β-(acylamino)acrylates and up to 99% *ee*'s have been obtained.[39]

Several efficient amidophosphine- and aminophosphine-phosphinite ligands have been reported by Agbossou and Carpentier.[40] Amidophosphine-phosphinite ligands (*S*)-Cy,Cy-oxoProNOP **42** and (*S*)-Cp,Cp-oxoProNOP **43** are efficient ligands for Rh-catalyzed

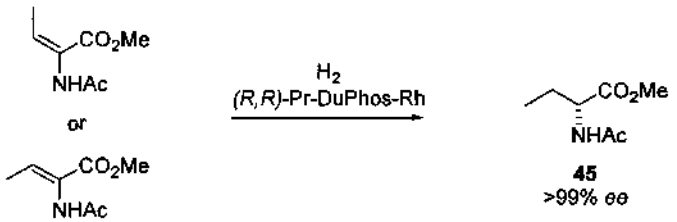
hydrogenation of dihydro-4,4-dimethyl-2,3-furandione, and up to 98% *ee*'s have been obtained.

1.4.5 Synthetic Utility

Professor Ryoji Noyori developed and utilized the BINAP molecule as a chiral ligand to effect stereoselectivity in transition metal catalyzed asymmetric hydrogenation. The catalytic asymmetric hydrogenation reaction has been applied to a number of diverse functionalized ketones and olefins. The following illustrations represent the synthetic utility of the asymmetric hydrogenation reaction using the BINAP ligand, as well as new chiral phosphorus ligands.

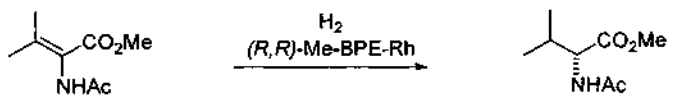
1.4.5.1 Hydrogenation of dehydroamino acid derivatives

A number of natural and unnatural amino acids are now available in >90% *ee* due to catalytic asymmetric hydrogenation of (*Z*)- or (*E*)-α-(acylamino)acrylic acids or esters, and this methodology is gaining practical significance in industry and academics.[1f] In general, high enantioselectivity is achieved for *Z*-isomeric substrates of α-dehydroamino acids, where as hydrogenation of the *E*-isomeric substrates usually proceeds with slow rates and poor enantioselectivity.[11b,41] Interestingly, the DuPhos-Rh system provides excellent enantioselectivity for both *Z*- and *E*-isomeric substrate **44** and gives a single hydrogenation product **45** regardless of starting *Z*- and *E*-isomeric substrate.[41b]



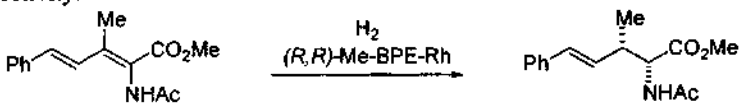
44 **45**
>99% *ee*

Hydrogenation of β,β-disubstituted α-dehydroamino acids **46** remains a challenging problem. The less bulky Me-DuPhos- or Me-BPE-type ligands provide excellent enantioselectivity to give a variety of β,β-disubstituted products **47**.[42]



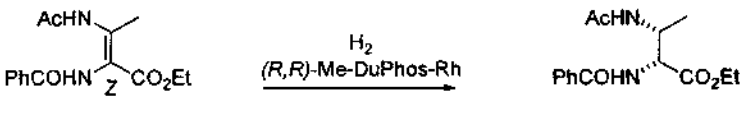
46 **47**
98.2% *ee*

The asymmetric hydrogenation of β,β-disubstituted α-dehydroamino acid **48**, in which the β-substituents are nonequivalent, provides the opportunity to selectively construct two contiguous stereogenic centers as seen in **49**. The Me-DuPhos and Me-BPE ligands facilitate the rhodium catalyzed hydrogenation of the *E*- and *Z*-isomers with excellent enantioselectivity.[42]

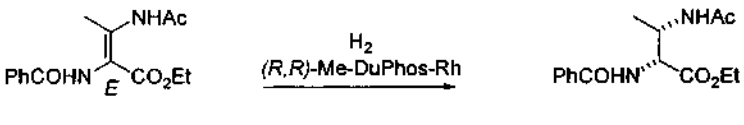


48 **49**
90.6% *ee*

Furthermore, the asymmetric hydrogenation of the *E*- or *Z*-isomer of β-(acetylamino)-β-methyl-α-dehydroamino acids (**50** and **51**, respectively) with the Me-DuPhos-Rh catalyst provides either diastereomer of *N*,*N*-protected 2,3-diaminobutanoic acid derivatives (**52** and **53**) with excellent enantioselectivity.[43]



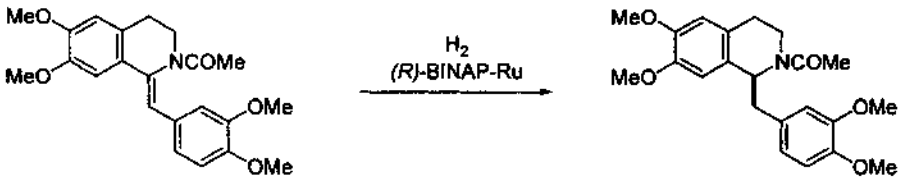
50 **52**
96% *ee*



51 **53**
> 98% *ee*

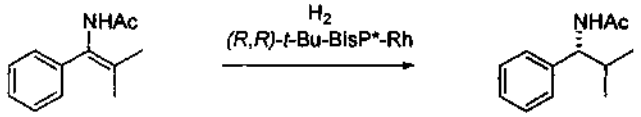
1.4.5.2 Hydrogenation of enamides

The Ru-BINAP system has shown excellent enantioselectivity in hydrogenation of (*Z*)-*N*-acyl-1-alkylidenetetrahydroisoquinolines **54**. Thus, a series of chiral isoquinoline products **55** can be efficiently synthesized.[44]



54 **55**
99.5% *ee*

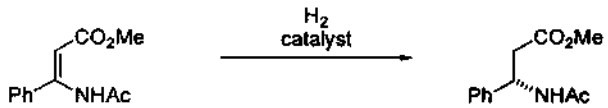
Rhodium catalyzed hydrogenation of enamides has attracted much attention recently. With the development of more efficient chiral phosphorus ligands, extremely high *ee*'s can be obtained. Hydrogenation of tetra-substituted enamides, such as β,β-dimethyl-α-phenyl enamide derivative **56**, has been reported with *t*-Bu-BisP* and *t*-Bu-MiniPhos providing amide **57** with excellent *ee*.[45]



56 **57**
99% *ee*

1.4.5.3 Hydrogenation of (β-acylamino) acrylates

Asymmetric hydrogenation of (β-acylamino) acrylates provides β-amino acids, an important constituent in many chiral drugs.[46] Many Rh and Ru complexes with chiral phosphorus ligands such as BINAP,[47] DuPhos,[48] BICP,[49] BDPMI,[50] and MalPHOS[51] are effective for the hydrogenation of (*E*)-β-alkyl (β-acylamino)acrylates. However, only a few chiral ligands, such as BDPMI[39,50] or TangPhos,[52] can hydrogenate (*Z*)-β-alkyl (β-acylamino)acrylate **58** in over 93% *ee*.

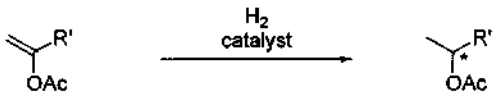


58 **59**

catalyst: (*S*)-Xylyl-*o*-BINAPO-Ru, **59** (99% *ee*)[39]
catalyst: (*S,S,R,R*)-TangPhos-Rh, **59** (93.8% *ee*)[52b]

1.4.5.4 Hydrogenation of enol esters

In contrast to many examples of highly enantioselective hydrogenations of enamides, only a few successful demonstrations exist for the asymmetric hydrogenation of enol esters. One possible reason is the acyl group of an enol ester has weaker coordinating ability to the metal catalyst than the corresponding enamide substrate. Both Rh and Ru complexes associated with chiral phosphorus ligands such as DuPhos[53] and C_2-TunaPhos,[54] respectively, are effective for the asymmetric hydrogenation of α-(acyloxy)acrylate **60**.

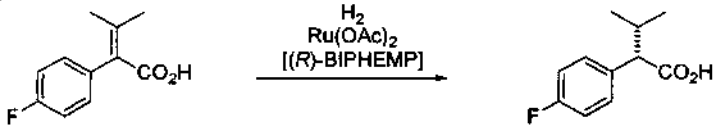


60 **61**

catalyst: (*R*,*R*)-Et-DuPhos-Rh, **61** (>99% ee, *R*-confign., R' = CO_2Et)
catalyst: (*S*)-C_2-TunaPhos-Ru, **61** (97.7% ee, *S*-confign., R' = 1-Np)

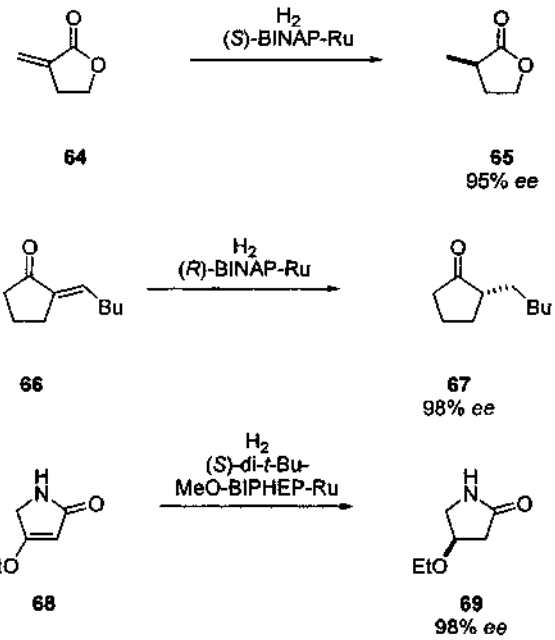
1.4.5.5 Hydrogenation of α-β-unsaturated carbonyls

Significant progress has been achieved in the asymmetric hydrogenation of α,β-unsaturated carboxylic acids with chiral Ru catalysts. In the case of hydrogenation of **62**, high hydrogenation pressure and low temperature are required to achieve good enantioselectivity of (*S*)-2-(4-fluorophenyl)-3-methylbutanoic acid **63**, a key intermediate in the synthesis of the calcium antagonist Mibefradil.[55]



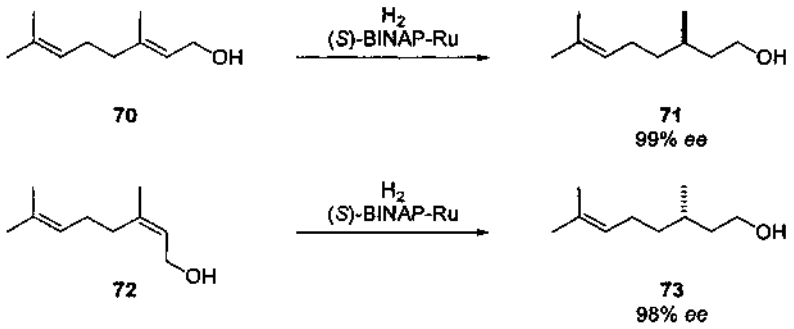
62 **63**
94% ee

Many chiral phosphorus ligands with Ru complexes have achieved excellent enantioselectivity in the hydrogenation of α,β-unsaturated esters, amides, lactones, and ketones. The Ru-BINAP system is efficient for hydrogenation of 2-methylene-γ-butyrolactone **64** and 2-methylene-cyclopentanone **66**.[56,57] With a dicationic (*S*)-di-*t*-Bu-MeOBIPHEP-Ru complex under high hydrogen pressure, 3-ethoxy pyrrolidinone **68** is hydrogenated to give (*R*)-4-ethoxy-γ-lactam **69** in 98% *ee*.[58]



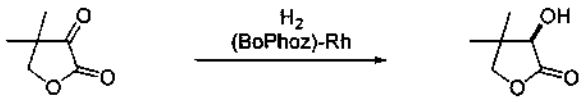
1.4.5.6 Hydrogenation of unsaturated alcohols

Asymmetric hydrogenation of allylic and homoallylic unsaturated alcohols was not very efficient until the discovery of the BINAP-Ru catalyst. With $Ru(BINAP)(OAc)_2$ as catalyst, geraniol **70** and nerol **72** are successfully hydrogenated to give (*S*)- or (*R*)-citronellol (**71** and **73**, respectively) in high overall yield with good enantioselectivity of 98 and 99% *ee*.[59]



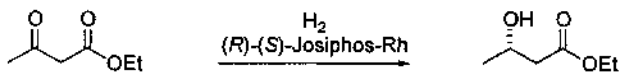
1.4.5.7 Hydrogenation of ketones

Hydrogenation of α-keto esters and amides has been studied with Rh and Ru catalysts. Several neutral Rh catalysts with chiral ligands such as MCCPM[60] and Cy,Cy-oxoProNOP[61] have demonstrated excellent reactivity and enantioselectivity in the hydrogenation of α-keto esters and amides. A cationic (BoPhoz)-Rh complex efficiently hydrogenates the cyclic α-keto ester, dihydro-4,4-dimethyl-2,3-furandione **74**, with a high turnover number to afford α-hydroxy ketone **75**.[62]



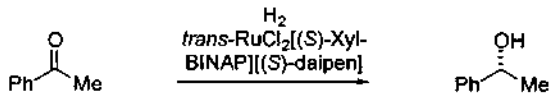
74 **75**
97.2% *ee*

Asymmetric hydrogenation of β-keto esters has been very successful using chiral Ru catalysts and a detailed review on this subject is available.[1c] The BINAP-Ru catalyst gives high enantioselectivity on a variety of β-keto esters.[22a] Furthermore, a Josiphos-Rh complex is found to be effective for hydrogenation of ethyl 3-oxobutanoate **76** to afford β-hydroxy ketone **77** with good enantioselectivity.[34]

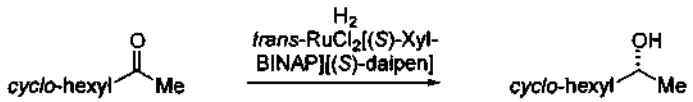


76 **77**
97% *ee*

The asymmetric hydrogenation of unfunctionalized ketones is a more challenging task, due to the lack of secondary coordination to the metal.[26,63] Enantioselective hydrogenation of simple aromatic and aliphatic ketones, **78** and **80**, respectively, has been achieved with a XylBINAP-Ru complex in the presence of a chiral diamine such as daipen.[64]



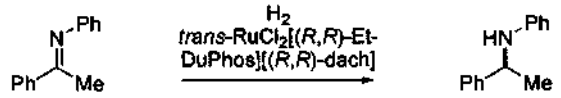
78 **79**
99% *ee*



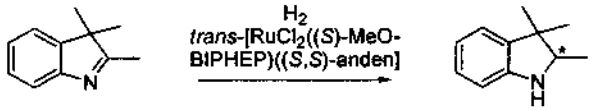
80 **81**
85% *ee*

1.4.5.8 Hydrogenation of imines

Currently, only a few efficient chiral catalytic systems are available for hydrogenation of imines. The recent development of *trans*-[$RuCl_2$(bisphosphine)(1,2-diamine)] complexes has provided promise in this area.[65] High enantioselectivity has been reported in hydrogenation of acetophenone *N*-arylimine derivatives **82** using a *trans*-[$RuCl_2$(Et-DuPhos)][dach] system and up to 94% *ee* has been obtained under basic conditions.[65] A *trans*-[$RuCl_2$(MeO-BIPHEP)][anden] complex has also shown promise in the asymmetric hydrogenation of cyclic imines **84** with moderate enantioselectivity (88% *ee*).[65]



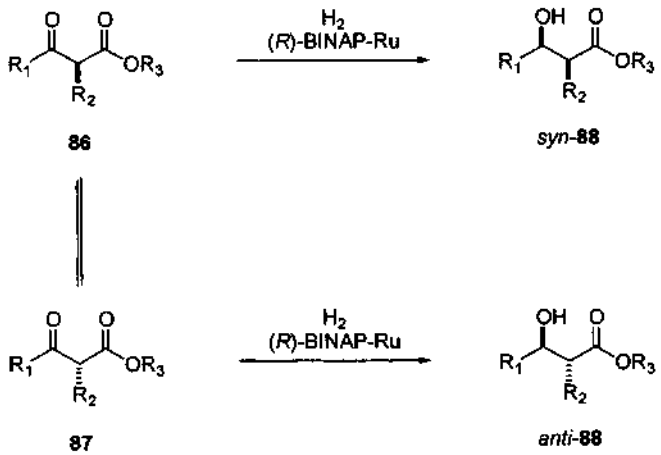
82 **83**
94% *ee*



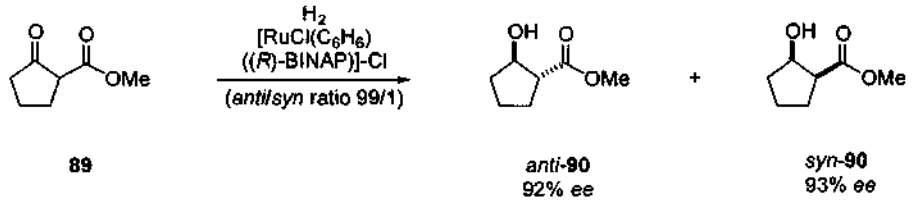
84 **85**
88% *ee* of product sign[65]

1.4.5.9 Hydrogenation via dynamic kinetic resolution

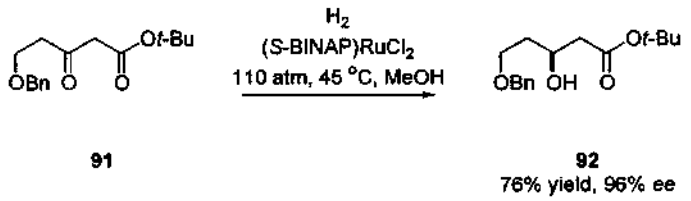
Many stereoselective reactions suffer from the disadvantage of producing the desired chiral product in 50% maximal yield. The lability of 2-substituted 3-oxo carboxylic esters to undergo facial epimerization, coupled with the high chiral recognition of the BINAP-Ru(II) complex, provides the possibility of stereoselective hydrogenation utilizing dynamic kinetic resolution.[66] If the racemization of enantiomers **86** and **87** is rapid with respect to hydrogenation, then the hydrogenation would form one isomer selectively among the four possible stereoisomeric hydroxyl esters (**88**).



The stereoselective transformation constitutes an ideal asymmetric catalysis, which is capable of converting racemic starting material to a single chiral product possessing stereodefined vicinal stereogenic centers in 100% yield. In dichloromethane containing a (*R*)-BINAP-Ru complex,[23] racemic ketone **89** is hydrogenated with high *anti* diastereoselectivity, to give a 99:1 mixture of the *trans*-hydroxyl ester *anti*-**90** (92% *ee*) quantitatively.[66]



1.4.6 Experimental



5-Benzyloxy-3-hydroxy-pentanoic acid *tert*-butyl ester (92)[67]

A sample of $[((S)\text{-BINAP})RuCl_2]_2{\cdot}NEt_3$ was prepared from $RuCl_2{\cdot}COD$ (0.020 g, 0.07 mmol) and (*S*)-BINAP as previously described.[68] A solution of **91** (10.06 g, 36 mmol) in methanol (20 mL) was degassed with N_2 and then added to a Schlenk vessel containing the catalyst. Stirring the mixture for 30 minutes gave a homogeneous orange solution. The mixture was acidified with 2 N HCl (0.24 mL), transferred by canula to a 125-mL pressure reaction vessel (Parr No. 4651), and heated to 45 °C. The vessel was pressurized to 110 atm with H_2, and the temperature was maintained for 24 hours. The mixture was concentrated and purified by SiO_2 chromatography (20% ethyl acetate/hexane) to give alcohol **92** (7.63 g, 76% yield, 96% *ee*) as a slightly yellow oil.

1.4.7 References

1. (a) [R] Chi, Y.; Tang, W.; Zhang, X. Rhodium-Catalyzed Asymmetric Hydrogenation. In *Modern Rhodium-Catalyzed Organic Reactions*, (Evans, P. A. Ed.), WILEY-VCH Verlag GmbH & Co. KgaA, Weinheim, 2005: pp 1–31. (b) [R] Zanotti-Gerosa, A.; Hems, W.; Groarke, M.; Hancock, F. *Platinum Metals Rev.* **2005**, *49*, 158–165. (c) [R] Ohkuma, T.; Noyori, R. In *Comprehensive Asymmetric Catalysis*, (Jacobsen, E. N.; Pfaltz, A.; Yamamoto, H. Eds.), Springer, Berlin, 1999, Vol. I, and 2004, Supplement I. (d) [R] Tang, W.; Zhang, X. *Chem. Rev.* **2003**, *103*, 3029–3069. (e) [R] Ager, D. J.; Laneman, S. A. *Tetrahedron: Asymmetry* **1997**, *8*, 3327–3355. (f) [R] Noyori, R.; Takaya, H. *Acc. Chem. Res.* **1990**, *23*, 345–350.
2. Rouhi, A. M. *Chem. Eng. News* **2003**, *81*, 45–55.
3. Noyori, R.; Kitamura, M.; Ohkuma, T. *PNAS* **2004**, *101*, 5356–5362.
4. (a) [R] Noyori, R.; Takaya, H. *Acc. Chem. Res.* **1990**, *23*, 345–350. (b) Ohta, T.; Takaya, H.; Noyori, R. *Inorg. Chem.* **1988**, *27*, 566–569. (c) Miyashita, A.; Yasuda, A.; Takaya, H.; Toriumi, K.; Ito, T.; Souchi, T.; Noyori, R. *J. Am. Chem. Soc.* **1980**, *102*, 7932–7934.
5. (a) [R] Sumi, K.; Kumobayashi, H. *Topics Organomet. Chem.* **2004**, *6*, 63–95. (b) [R] Takaya, H.; Ohta, T.; Noyori, R. Rhodium-Catalyzed Asymmetric Hydrogenation. In *Catalytic Asymmetric Synthesis*, (Ojima, I. Ed.), VCH: New York, 1993: pp 1–31.
6. Anderson, N. G. *Practical Process Research and Development*; Academic Press: London, 2000.
7. Knowles, W. S.; Sabacky, M. J. *Chem. Commun.* **1968**, 1445–1446.
8. Horner, L.; Siegel, H.; Büthe, H. *Angew. Chem. Int. Ed. Engl.* **1968**, *7*, 942.
9. (a) Korpium, O.; Lewis, R. A.; Chickos, J.; Mislow, K. *J. Am. Chem. Soc.* **1968**, *90*, 4842. (b) Horner, L. *Pure Appl. Chem.* **1964**, *9*, 225–244.
10. Dang, T. P.; Kagan, H. B. *J. Chem. Soc. Chem. Commun.* **1971**, 481.
11. (a) Knowles, W. S.; Sabacky, M. J.; Vineyard, B. D. *J. Chem. Soc. Chem. Commun.* **1972**, 10–11. (b) Vineyard, B. D.; Knowles, W. S.; Sabacky, M. J.; Bachman, G. L. Weinkauff, D. J. *J. Am. Chem. Soc.* **1977**, *99*, 5946–5952.
12. (a) Knowles, W. S. *Angew. Chem. Int. Ed. Engl.* **2002**, *41*, 1998–2007. (b) Noyori, R. *Angew. Chem. Int. Ed. Engl.* **2002**, *41*, 2008–2022.
13. (a) Tani, K.; Yamagata, T.; Otsuka, S.; Akutagawa, S. Kumobayashi, H.; Taketomi, T.; Takaya, H.; Miyashita, A.; Noyori, R. *J. Chem. Soc. Chem. Commun.* **1982**, 600. (b) Tani, K.; Yamagata, T.; Akutagawa, S.; Kumobayashi, H.; Taketomi, T.; Takaya, H.; Miyashita, A.; Noyori, R.; Otsuka, S. *J. Am. Chem. Soc.* **1984**, *106*, 5208–5217.
14. [R] Whitesell, J. K. *Chem. Rev.* **1989**, *89*, 1581–1590.
15. (a) Landis, C. R.; Halpern, J. *J. Am. Chem. Soc.* **1987**, *109*, 1746–1754. (b) Brown, J. M.; Chaloner, P. A. *J. Am. Chem. Soc.* **1980**, *102*, 3040–3048. (c) Chan, A. S.; Halpern, J. *J. Am. Chem. Soc.* **1980**, *102*, 838–840.
16. (a) Burk, M. J. *Acc. Chem. Res.* **2000**, *33*, 363–372. (b) van den Berg, M.; Minnaard, A. J.; Schudde, E. P.; van Esch, J.; de Vries, A. H. M.; de Vries, J. G.; Feringa, B. L. *J. Am. Chem. Soc.* **2000**, *122*, 11539–11540. (c) Claver, C.; Fernandez, E.; Gillon, A.; Heslop, K.; Hyett, D. J.; Martorell, A.; Orpen, A. G.; Pringle, P. G. *Chem. Commun.* **2000**, 961–962. (d) Reetz, M. T.; Mehler, G. *Angew. Chem. Int. Ed.* **2000**, *39*, 3889–3890.
17. Gridnev, I. D.; Higashi, N.; Asakura, K.; Imamoto, T. *J. Am. Chem. Soc.* **2000**, *122*, 7183–7194.
18. Kitamura, M.; Tokunaga, M.; Noyori, R. *J. Org. Chem.* **1992**, *57*, 4053–4054.
19. Kitamura, M.; Tsukamoto, M.; Bessho, Y.; Yoshimura, M.; Kobs, U.; Widhalm, M.; Noyori, R. *J. Am. Chem. Soc.* **2002**, *124*, 6649–6667.

20. Ikariya, T.; Ishii, Y.; Kawano, H.; Arai, T.; Saburi, M.; Yoshikawa, S.; Akutagawa, S. *J. Chem. Soc. Chem. Commun.* **1985**, 922–924.
21. Wiles, J. A.; Bergens, S. H.; Young, Y. G. *J. Am. Chem. Soc.* **1997**, *119*, 2940–2941.
22. (a) Noyori, R.; Ohkuma, T.; Kitamura, M.; Takaya, H.; Sayo, N.; Kumobayashi, H.; Akutagawa, S. *J. Am. Chem. Soc.* **1987**, *109*, 5856–5858. (b) Kitamura, M.; Ohkuma, T.; Inoue, S.; Sayo, N.; Kumobayashi, H.; Akutagawa, S.; Ohta, T.; Takaya, H.; Noyori, R. *J. Am. Chem. Soc.* **1988**, *110*, 629–631.
23. Mashima, K.; Kusano, K.; Ohta, T.; Noyori, R.; Takaya, H. *J. Chem. Soc. Chem. Commun.* **1989**, 1208–1210.
24. (a) King, S. A.; DiMichele, L. In *Catalysis of Organic Reactions*, (Scaros, M. G.; Prunier, M. L., Eds.), Dekker: New York, 1995: pp 157–166. (b) Ohta, T.; Tonomura, Y.; Nozaki, K.; Takaya, H.; Mashima, K. *Organometallics* **1996**, *15*, 1521–1523.
25. (a) Genet, J. P. In *Reduction in Organic Synthesis*, Abdel-Magit, A. F., Ed.; Am. Chem. Soc.: Washington, DC, 1996: pp 31–51. (b) Kumobayashi, H.; Miura, T.; Sayo, N.; Saito, T.; Zhang, X. *Synlett* **2001**, 1055–1064.
26. Noyori, R.; Ohkuma, T. *Angew. Chem. Int. Ed.* **2001**, *40*, 40–73.
27. (a) King, S. A.; Thompson, A. S.; King, A. O.; Verhoeven, T. R. *J. Org. Chem.* **1992**, *57*, 6689–6691. (b) Kitamura, M.; Yoshimura, M.; Kanda, N.; Noyori, R. *Tetrahedron* **1999**, *55*, 8769–8785.
28. (a) Ohkuma, T.; Noyori, R. In *Transition Metals for Organic Synthesis*, (Beller, M., Bolm, C., Eds.), Wiley: Weinheim, Germany, 1998: Vol. 2, pp. 25–69. (b) Ohkuma, T.; Kitamura, M.; Noyori, R. In *Catalytic Asymmetric Synthesis*, (Ojima, I., Ed.), Wiley: New York, 2000: 2nd Ed., pp. 1–110. (c) Noyori, R. *Science* **1990**, *248*, 1194–1199.
29. Tang, W.; Chi, Y.; Zhang, X. *Org. Lett.* **2002**, *4*, 1695–1698.
30. (a) Zhang, X.; Mashima, K.; Koyano, K.; Sayo, N.; Kumobayashi, H.; Akutagawa, S.; Takaya, H. *Tetrahedron Lett.* **1991**, *32*, 7283–7286. (b) Zhang, X.; Mashima, K.; Koyano, K.; Sayo, N.; Kumobayashi, H.; Akutagawa, S.; Takaya, H. *J. Chem. Soc., Perkin Trans. 1* **1994**, 2309–2322.
31. Wan, X.; Sun, Y.; Luo, Y.; Li, D.; Zhang, Z. *J. Org. Chem.* **2005**, *70*, 1070–1072.
32. Dai, Q.; Wang, C.-J.; Zhang, X. *Tetrahedron* **2006**, *62*, 868–871.
33. Li, W.; Waldkirch, J. P.; Zhang, X. *J. Org. Chem.* **2002**, *67*, 7618–7623.
34. Togni, A.; Breutel, C.; Schnyder, A.; Spindler, F.; Landert, H.; Tijani, A. *J. Am. Chem. Soc.* **1994**, *116*, 4062–4066.
35. (a) Ireland, T.; Grossheimann, G.; Wieser-Jeunesse, C.; Knochel, P. *Angew. Chem., Int. Ed. Engl.* **1999**, *38*, 3212–3215. (b) Ireland, T.; Tappe, K.; Grossheimann, G.; Knochel, P. *Chem. Eur. J.* **2002**, *8*, 843–852.
36. Lotz, M.; Polborn, K.; Knochel, P. *Angew. Chem. Int. Ed. Engl.* **2002**, *41*, 4708–4711.
37. (a) Pye, P. J.; Rossen, K.; Reamer, R. A.; Tsou, N. N.; Volante, R. P.; Reider, P. J. *J. Am. Chem. Soc.* **1997**, *119*, 6207–6208. (b) Pye, P. J.; Rossen, K.; Reamer, R. A.; Volante, R. P.; Reider, P. J. *Tetrahedron Lett.* **1998**, *39*, 4441–4444. (c) Burk, M. J.; Hems, W.; Herzberg, D.; Malan, C.; Zanotti-Gerosa, A. *Org. Lett.* **2000**, *2*, 4173–4176.
38. Zhou, Y.-G.; Zhang, X. *Chem. Commun.* **2002**, 1124–1125.
39. Zhou, Y.-G.; Tang, W.; Wang, W.-B.; Li, W.; Zhang, X. *J. Am. Chem. Soc.* **2002**, *124*, 4952–4953.
40. Agbossou, F.; Carpentier, J.-F.; Hapiot, F.; Suisse, I.; Mortreux, A. *Coord. Chem. Rev.* **1998**, *178–180*, 1615–1645.
41. (a) Scott, J. W.; Keith, D. D.; Nix, G., Jr.; Parrish, D. R.; Remington, S.; Roth, G. P.; Townsend, J. M.; Valentine, D., Jr.; Yang, R. *J. Org. Chem.* **1981**, *46*, 5086–5093. (b) Burk, M. J.; Feaster, J. E.; Nugent, W. A.; Harlow, R. L. **1993**, *115*, 10125–10138.
42. Burk, M. J.; Bedingfield, K. M.; Kiesman, W. F.; Allen, J. G. *Tetrahedron Lett.* **1999**, *40*, 3093–3096.
43. Robinson, A. J.; Stanislawski, P.; Mulholland, D.; He, L.; Li, H.-Y. *J. Org. Chem.* **2001**, *66*, 4148–4152.
44. (a) Noyori, R.; Ohta, M.; Hsiao, Y.; Kitamura, M.; Ohta, T.; Takaya, H. *J. Am. Chem. Soc.* **1986**, *108*, 7117–7119. (b) Kitamura, M.; Hsiao, Y.; Noyori, R.; Takaya, H. *Tetrahedron Lett.* **1987**, *28*, 4829–4832. (c) Kitamura, M.; Hsiao, Y.; Ohta, M.; Tsukamoto, M.; Ohta, T.; Takaya, H.; Noyori, R. *J. Org. Chem.* **1994**, *59*, 297–310.
45. Gridnev, I. D.; Yasutake, M.; Higashi, N.; Imamoto, T. *J. Am. Chem. Soc.* **2001**, *123*, 5268–5276.
46. (a) Tang, T.; Ellman, J. A. *J. Org. Chem.* **1999**, *64*, 12–13. (b) Hoekstra, W. J.; Maryanoff, B. E.; Damiano, B. P.; Andrade-Gordon, P.; Cohen, J. H.; Costanzo, M. J.; Haertlein, B. J.; Hecker, L. R.; Hulshizer, B. L.; Kauffman, J. A.; Keane, P.; McComsey, D. F.; Mitchell, J. A.; Scott, L.; Shah, R. D.; Yabut, S. C. *J. Med. Chem.* **1999**, *42*, 5254–5265.
47. Lubell, W. D.; Kitamura, M.; Noyori, R. *Tetrahedron: Asymmetry* **1991**, *2*, 543–554.
48. Heller, D.; Holz, J.; Drexler, H.-J.; Lang, J.; Drauz, K.; Krimmer, H.-P.; Börner, A. *J. Org. Chem.* **2001**, *66*, 6816–6817.

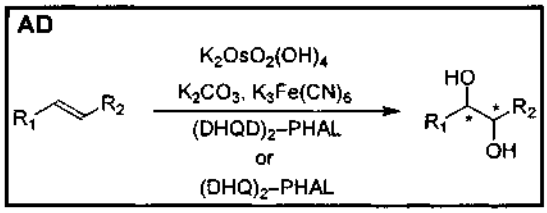
49. Zhu, G.; Chen, Z.; Zhang, X. *J. Org. Chem.* **1999**, *64*, 2127–2129.
50. Lee, S.-g.; Zhang, Y. J. *Org. Lett.* **2002**, *4*, 2429–2431.
51. Holz, J.; Monsees, A.; Jiao, H.; You, J.; Komarov, I. V.; Fischer, C.; Drauz, K.; Börner, A. *J. Org. Chem.* **2003**, *68*, 1701–1707.
52. (a) Tang, W.; Zhang, X. *Org. Lett.* **2002**, *4*, 4159–4161. (b) Tang, W.; Zhang, X. *Angew. Chem., Int. Ed. Engl.* **2002**, *41*, 1612–1614.
53. Burk, M. J. *J. Am. Chem. Soc.* **1991**, *113*, 8518–8519.
54. Wu, S.; Wang, W.; Tang, W.; Lin, M.; Zhang, X.; *Org. Lett.* **2002**, *4*, 4495–4497.
55. Crameri, T.; Foricher, J.; Scalone, M.; Schmid, R. *Tetrahedron: Asymmetry* **1997**, *8*, 3617–3623.
56. Ohta, T.; Miyake, T.; Seido, N.; Kumobayashi, H.; Takaya, H. *J. Org. Chem.* **1995**, *60*, 357–363.
57. Ohta, T.; Miyake, T.; Seido, N.; Kumobayashi, H.; Akutagawa, S.; Takaya, H. *Tetrahedron Lett.* **1992**, *33*, 635–638.
58. Schmid, R.; Broger, E. A.; Cereghetti, M.; Crameri, Y.; Foricher, J.; Lalonde, M.; Müller, R. K.; Scalone, M.; Schoettel, G.; Zutter, U. *Pure Appl. Chem.* **1996**, *68*, 131–138.
59. Takaya, H.; Ohta, T.; Sayo, N.; Kumobayashi, H.; Akutagawa, S.; Inoue, S.-i.; Kasahara, I.; Noyori, R.; *J. Am. Chem. Soc.* **1987**, *109*, 1596.
60. Inoguchi, K.; Sakuraba, S.; Achiwa, K. *Synlett* **1992**, 169–178.
61. Carpentier, J.-F.; Mortreux, A. *Tetrahedron: Asymmetry* **1997**, *8*, 1083–1099.
62. Boaz, N. W.; Debenham, S. D.; Mackenzie, E. B.; Large, S. E. *Org. Lett.* **2002**, *4*, 2421–2424.
63. Fehring, V.; Selke, R. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 1827–1830.
64. Ohkuma, T.; Koizumi, M.; Doucet, H.; Pham, T.; Kozawa, M.; Murata, K.; Katayama, E.; Yokozawa, T.; Ikariya, T.; Noyori, R. *J. Am. Chem. Soc.* **1998**, *120*, 13529–13530.
65. (a) Cobley, C. J.; Henschke, J. P.; *Adv. Synth. Catal.* **2003**, *345*, 195–201. (b) Abdur-Rashid, K.; Lough, A. J.; Morris, R. H.; *Organometallics* **2000**, *19*, 2655–2657.
66. Noyori, R.; Ikeda, T.; Ohkuma, T.; Widhalm, M.; Kitamura, M.; Takaya, H.; Akutagawa, S.; Sayo, N.; Saito, T.; Taketomi, T.; Kumobayashi, H. *J. Am. Chem. Soc.* **1989**, *111*, 9134–9135.
67. Rychnovsky, S. C.; Hoye, R.C. *J. Am. Chem. Soc.* **1994**, *116*, 1753–1765.
68. Ikariya, T.; Ishii, Y.; Kawano, H.; Aria, T.; Saburi, M.; Yoshikawa, S.; Akutagawa, S.; *J. Chem. Soc., Chem. Commun.* **1985**, 922–924.

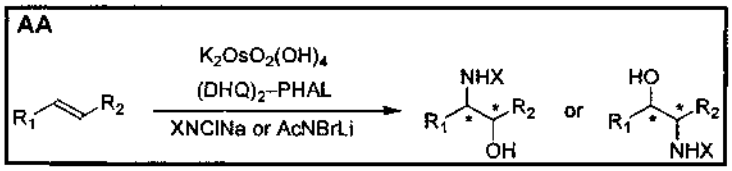
Manjinder S. Lall

1.5 Sharpless Asymmetric Hydroxylation Reactions

1.5.1 Description

The Sharpless asymmetric hydroxylation can take one of two forms, the initially developed asymmetric dihydroxylation (AD)[1] or the more recent variation, asymmetric aminohydroxylation (AA).[2] In the case of AD, the product is a 1,2-diol, whereas in the AA reaction, a 1,2-amino alcohol is the desired product. These reactions involve the asymmetric transformation of an alkene to a vicinally functionalized alcohol mediated by osmium tetraoxide in the presence of chiral ligands (e.g., $(DHQD)_2$–PHAL or $(DHQ)_2$–PHAL). A mixture of these reagents (ligand, osmium, base, and oxidant) is commercially available and is sold under the name of AD-mix β or AD-mix α (*vide infra*).





1.5.2 Historical Perspective

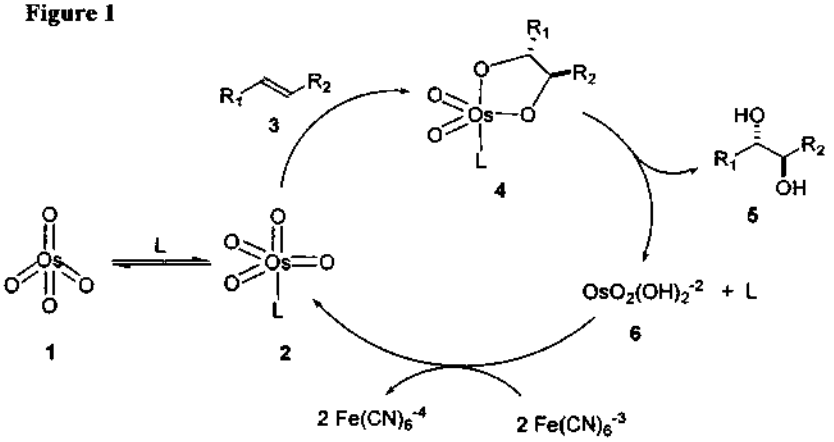
Makowka[3] first reported the use of osmium tetroxide for the dihydroxylation of alkenes. Later, Hofmann[4] showed this process could be made catalytic in osmium when conducted in the presence of chlorate. While both Milas[5] and Criegee[6] simultaneously reported that peroxides could be used to recycle the osmium, it was Criegee who reported the observation that amines, such as pyridine, dramatically accelerated the rate of the *cis*-hydroxylation reaction. The Criegee conditions became the standard method for osmium tetraoxide-catalyzed oxidation of alkenes until VanRheenen and co-workers[7] published improved conditions that employed tertiary amine oxides as oxidants. The first example that this dihydroxylation process could be carried out in an asymmetric fashion was reported in 1980, when Hentges and Sharpless[8] reported the chirality transfer from optically active cinchona alkaloids acting as chiral amine ligands. Refinements to this process ultimately led to the reaction conditions currently used and to reagents that are commercially available.[9] The AA was an offshoot of this work, when it was determined that imido analogs of osmium

tetraoxide could react with alkenes to produce amino alcohols by a *cis*-addition reaction.[10] In October of 2001, the Royal Swedish Academy of Sciences awarded the Nobel Prize in Chemistry for the development of catalytic asymmetric syntheses. K. Barry Sharpless was awarded half of the prize "for his work on chirally catalyzed oxidation reactions."[11]

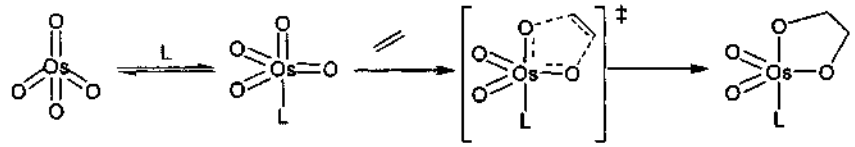
1.5.3 Mechanism

In general, the mechanism for the AD reaction is depicted in Figure 1. Coordination of a ligand to osmium tetraoxide **1** generates complex **2**. This species then reacts with alkene **3** producing osmium glycolate **4** that can then decompose to the desired 1,2-diols **5** and the reduced osmium species **6**. Catalytically active **2** can be regenerated from **6** by an external oxidant, such as ferricyanide.

Figure 1

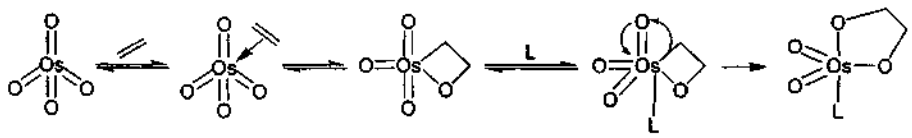


The specific details of how the transformation of **1** to **2** to **4** occurs still remain to be fully characterized. However, numerous studies have been reported in an attempt to provide the mechanistic details. The first rationalization, proposed by Boseken[12] and Criegee,[6,13] was based on the similarity between osmylation and permanganate oxidations of alkenes. A concerted [3 + 2] reaction of the osmium tetraoxide and the alkene could produce the observed product. It was proposed that the ligand acceleration of this reaction was related to the rehybridization from tetrahedral to trigonal bipyramidal at the osmium center upon ligand coordination (**1** to **2**). The decrease in the O–Os–O bond angle would reduce the strain in transition-state **7** on the way to formation of the five-membered ring intermediate **8**.



1 2 7 8

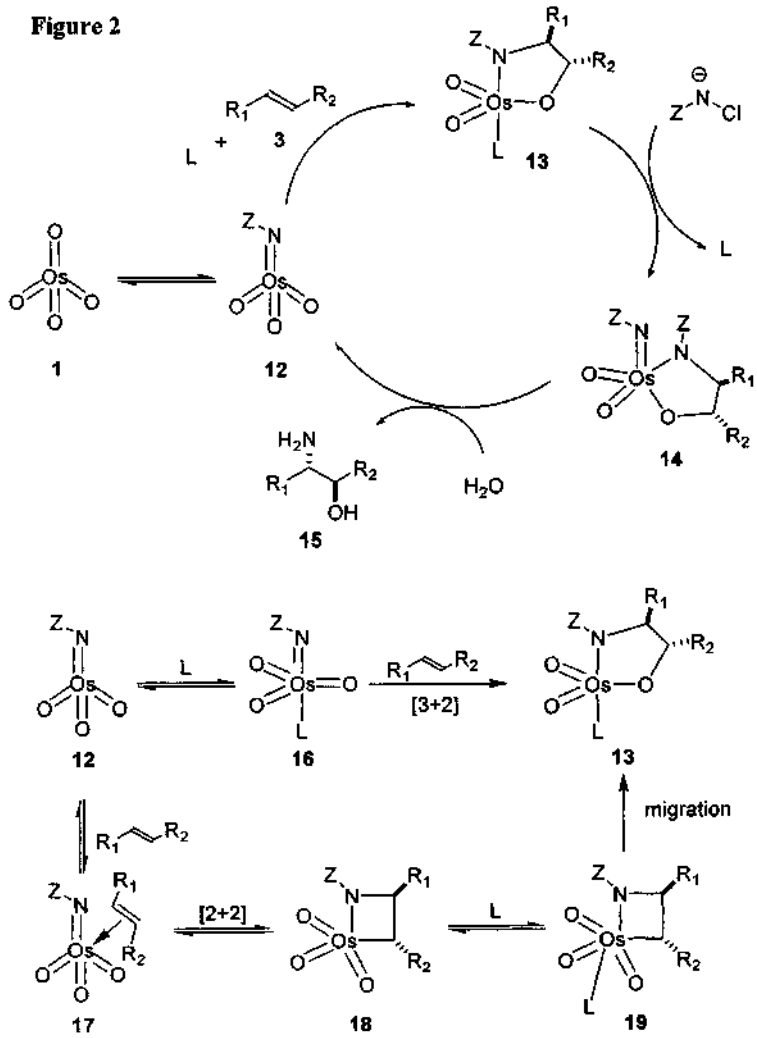
This mechanism fell out of favor with the observation of a nonlinear Eyring relationship between % *ee* and temperature.[14] As a result, this rationalization was replaced by a mechanism that required a stepwise pathway through an osmaoxetane **10**.[15] Ligand acceleration in the [2 + 2] mechanism could occur if rearrangement of osmaoxetane **10**, *via* intermediate **11**, to osmaglycolate **8** is facilitated by coordination of a ligand. The electrophilic nature of osmium in this species is also consistent with initial attack of the alkene at the metal center to form **9** and is inconsistent with an alkene π-bond attack of two partial negatively charged oxygen atoms in the [3 + 2] mechanism.



1 9 10 11 8

By direct analogy, the mechanism for the AA can be adapted from the work associated with the AD reaction.[2] The point of departure results from the change in the reagents required for the AA reaction. The catalytically active species is likely the imidotrioxoosmium (VIII) **12** (Figure 2). This complex is formed *in situ* from osmium tetraoxide and the stoichiometric nitrogen source (e.g., chloramines). Addition of alkene **3** produces complex **13**, the result of the asymmetric aminohydroxylation. The desired product **15** is released from the metallic center along with regeneration of the catalytic species by addition of another equivalent of the nitrogen source to convert **13** to **14** followed by hydrolysis of **14** to generate **15**.

Figure 2



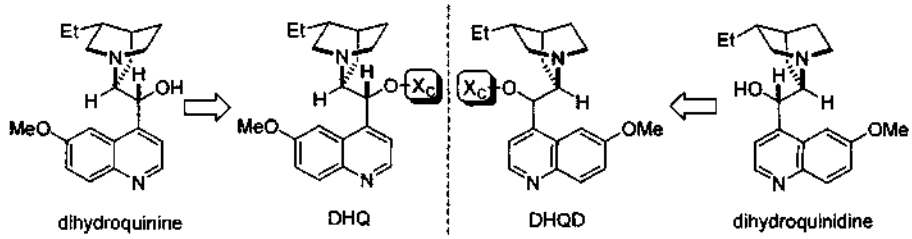
For the generation of **13**, all the uncertainty that was found in the AD reaction can also be translated to this variation of the reaction.[16] The dichotomy between a [2 + 2] and a [3 + 2] mechanistic process remains for the AA reaction. The formation of **13** can be

rationalized using a [3 + 2] mechanism in which **16** undergoes the cycloaddition after coordination of a ligand to **12**. Alternatively, the [2 + 2] pathway could proceed by π-bond complex **17** followed by the cycloaddition reaction to afford **18**. Ligand complexation then precedes bond migration to convert **19** to **13**.

Computational chemistry approaches aimed at resolving this mechanistic dichotomy have only made the situation less clear.[17] Furthermore, one cannot study this reaction using the standard principle of microscopic reversibility as these reactions are irreversible. Consequently, the chemistry of rhenium complexes has been applied to those of osmium to provide some insight as to what possibilities are accessible for this metal.[18]

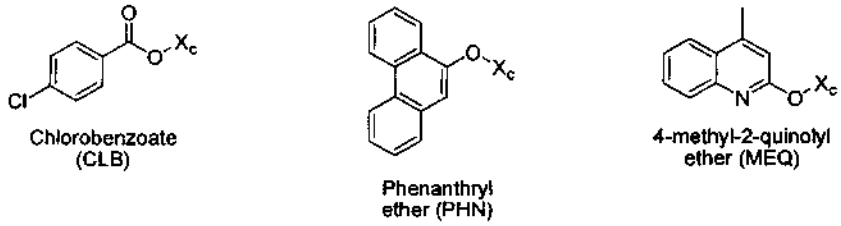
1.5.4 Variations and Improvements or Modifications

To improve the asymmetric induction in these reactions, numerous ligands were evaluated (over 500 have been tested in the Sharpless labs).[19] Within the cinchona alkaloid family, over 75 derivatives were screened. The best ligands have been found to be analogs of dihydroquinine **20** and dihydroquinidine **23**. The result of these studies are the DHQ **21** and DHQD **22** ligands, respectively.



20 **21** **22** **23**

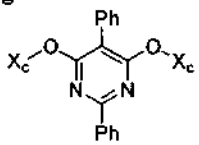
Figure 3



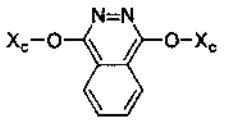
The nature of the chiral auxiliary has given rise to two generations of ligands. The first generation ligands consist of a single chiral auxiliary bonded to an aryl scaffold (Figure

3). The second generation ligands (Figure 4) consist of the aryl scaffold bonded to two chiral auxiliaries resulting in a C_2-symmetric system. These modifications were based on the desire to improve the chiral induction and broaden the scope of alkene substitution patterns that could be accommodated by these catalysts.

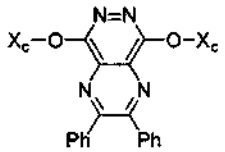
Figure 4



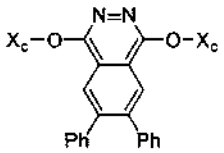
diphenylpyrimidine
(PYR)



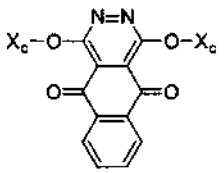
Phthalazine
(PHAL)



diphenyl pyrazinopyridazine
(DPP)

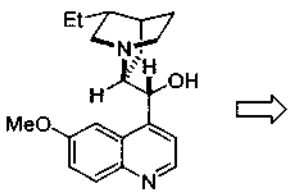


diphenyl phthalazine
(DP-PHAL)



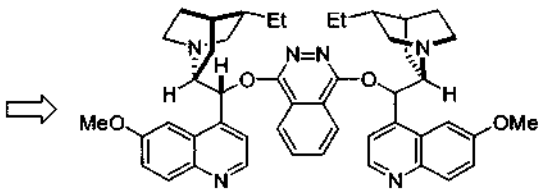
anthraquinone
(AQN)

The most common and commercially available variation of this reaction makes use of the PHAL-based ligands, **24** (AD-mix β) and **25** (AD-mix α). Both reagents are a mix of an osmium source ($K_2OsO_2(OH)_4$), an oxidant ($K_3Fe(CN)_6$),[20] and a base (K_2CO_3) in combination with the chiral ligand. For AD-mix β this ligand is $(DHQD)_2$–PHAL **24** and for AD-mix α this ligand is $(DHQ)_2$–PHAL **25**.



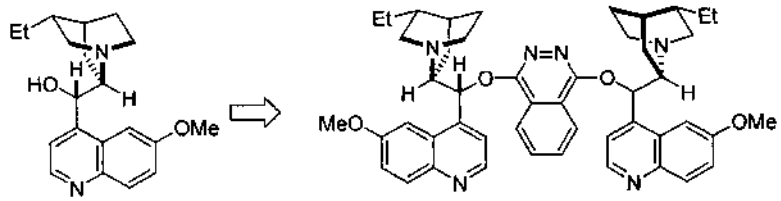
dihydroquinine

20



$(DHQD)_2$–PHAL

24



dihydroquinidine

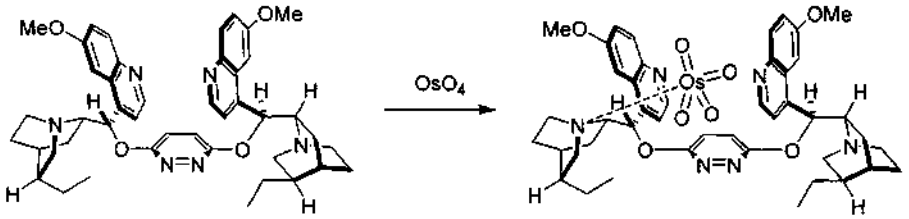
23

(DHQ)$_2$–PHAL

25

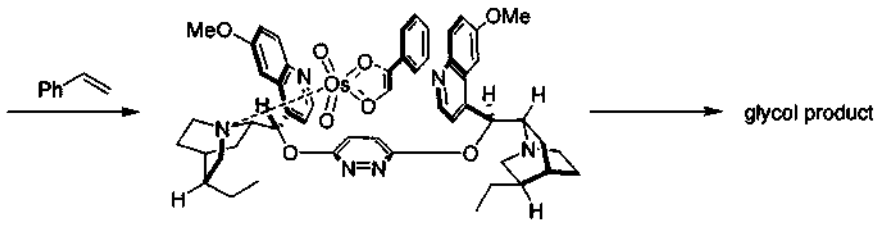
The lack of resolution by which mechanism the osmylation proceeds has resulted in two models to rationalize the face selectivity of the AD reaction. The commonality of these two predictive models resides in the basic principle that a chiral binding pocket is formed from the ligand's aromatic groups. However, the shape and location of this pocket in the complex is not identical.

The Corey group at Harvard, based on a [3+2] mechanistic pathway, has proposed a U-shaped binding pocket constructed from two parallel methoxyquinoline moieties contained in the second generation Sharpless ligands (*vide supra*).[21] Thus, chiral ligand **26** coordinates an osmium center through one of the bicyclo[2.2.2]octane moieties. This places the oxidant in close proximity to the bound substrate as depicted in **27**. The chiral volume generated by complex **26** permits the alkene substrate to come in contact in only one possible orientation **28**, thereby inducing chirality in the product.



26

27



28

The Sharpless group has proposed a more L-shaped conformation for the methoxyquinoline moieties of the ligand.[22] Coordination of the osmium tetraoxide and binding of the alkene then generates complex **29**. As before, the chiral environment in which the alkene is held results in the asymmetry imparted during the course of this transformation.

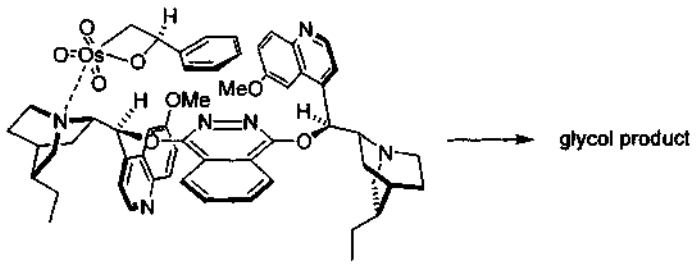


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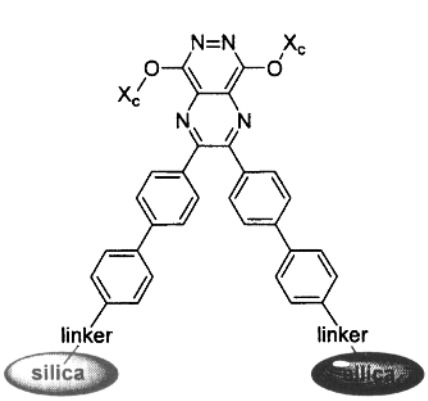
Table 1.

alkene class	R_1	R_1 R_2	R_1 R_2	R_1 R_2	R_1 R_2 R_3	R_1 R_2 R_3 R_4
preferred ligand	R_1 = aromatic DPP, PHAL	R_1, R_2 = aromatic DPP, PHAL	Acyclic IND	R_1, R_2 = aromatic DPP, PHAL	PHAL, DPP, AQN	PYR, PHAL
	R_1 = aliphatic AQN	R_1, R_2 = aliphatic AQN	Cyclic PYR, DPP, AQN	R_1, R_2 = aliphatic AQN		
	R_1 = branched PYR					

The utility of the ligands for inducing asymmetry for different alkene substitution patterns has been explored. Since the binding pocket will vary in size and preference for which substituents it will best interact, a systematic analysis of this relationship has been conducted. There are six possible substitution patterns that can be found for an alkene and the best combination of substitution pattern and ligand for maximizing asymmetric induction is shown in Table 1. While there are specific ligands that are best for certain alkene substitution patterns, the PHAL ligand is the one that appears to have the best selectivity, in general.

Conducting the AD reaction at pH 12 was found to improve the reaction rates for internal alkenes.[23] Additionally, the need for hydrolysis adjuvants, such as methanesulfonamide, could be omitted.

Additional modifications include the immobilization of the catalyst on an insoluble surface. Silica-anchored ligands have been reported based on the DPP **33** and PYR **34** cores.[24] Their use in AD reactions were comparable to the untethered versions of the chiral ligands. Alkenes substituted with alkyl or aryl groups and with internal and terminal double bonds gave diol products with yields ranging 51–93% and optical purities of 61–99% *ee*. The differentiation between **33** or **34** was the ability to readily recover and recycle the chiral ligands.



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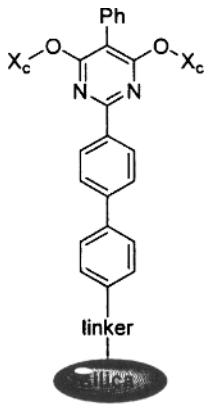
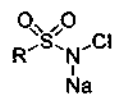
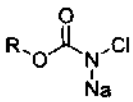


34

For the AA reaction, the smaller the substituent on the nitrogen source, the more efficient the reaction became. Thus, there are three variations of this reaction based on the nitrogen source, sulfonamide **30**, carbamate **31**, or amide **32**.



30



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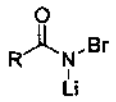
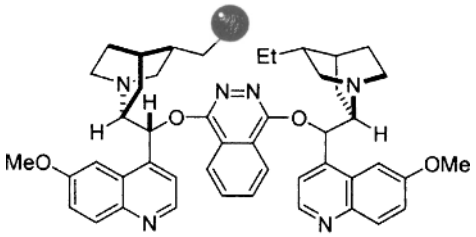


32

Polymer-based derivatives of PHAL **35** have been investigated in the AA reaction.[25] The utility of this ligand was evaluated relative to the free form using the reaction of cinnamate **36** to amino alcohol **37**. This conversion, using the chiral ligand **28**, afforded **37** in 96% yield and 96% *ee*, while **35** effected this transformation in 91% yield and 87% *ee*.



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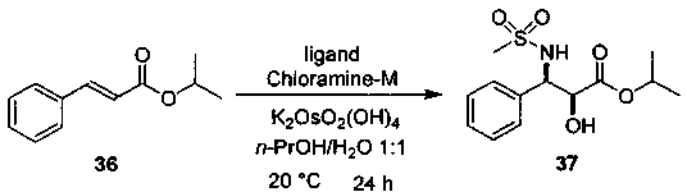
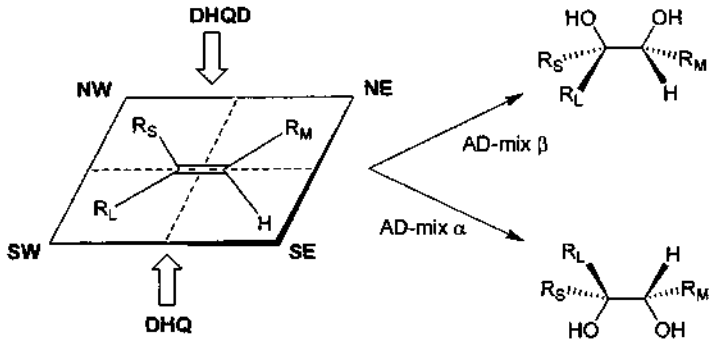


36 37

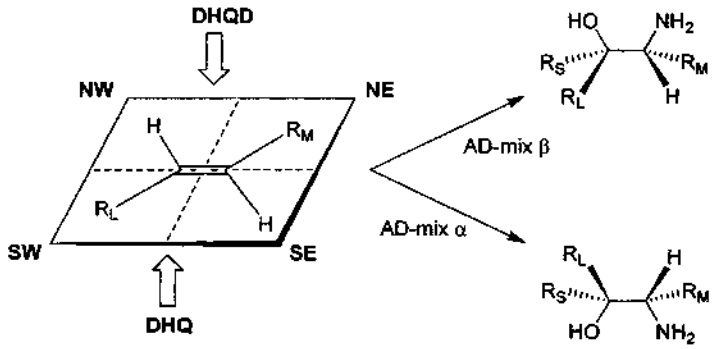
Despite the uncertainty in the exact mechanism for the AD reaction, a useful mnemonic to predict the direction of asymmetric dihydroxylation has been established.[19] If one places the carbon–carbon double bond of the alkene along the east–west axis of a compass, the substituents on the alkene point to the off-directional positions into the four quadrants shown in Figure 5. The SE quadrant is sterically most demanding, so there is sufficient room for only a hydrogen substituent. The diagonal position, NW, is slightly more accessible and can accept small substituents. The NW quadrant is more accommodating and will fit medium-sized groups. The largest groups are typically placed into the SW quadrant, but the nature of the substituent that can be accommodated is ligand dependent. For example, aromatic groups are favored at this position when employing PHAL ligands, whereas PYR ligands show a preference for aliphatic groups at this position (*vide supra*).

Figure 5



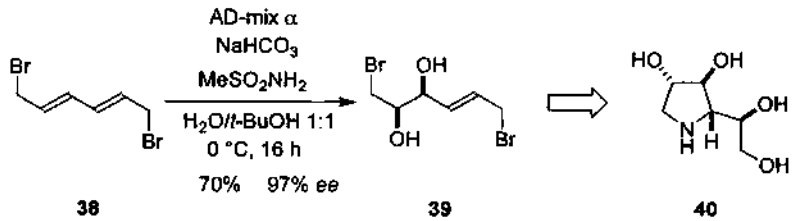
Just as with the AD reaction, a mnemonic for the AA reaction has also been put forward (Figure 6). The same model predicts the identical sense of enantiofacial selectivity indicating the chiral ligands are behaving in a similar manner.

Figure 6

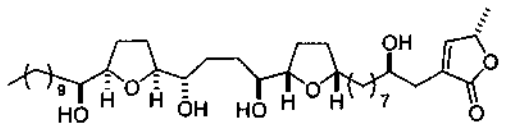


1.5.5 Synthetic Utility

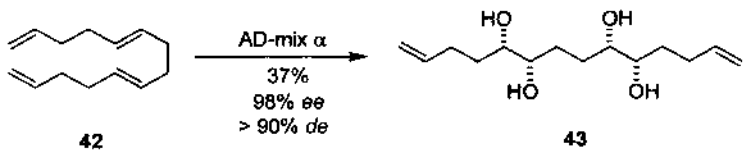
Azasugars, in general, have shown promise as anti-cancer and anti-viral agents. The preparation of pyrrolidine azasugar **40** took advantage of the AD reaction.[26] Diene **38** could be mono-dihydroxylated using the AD-mix α system to produce **39** in excellent optical purity. This compound was then taken on in three steps to **40** in an overall yield of 60%.



The AD reaction was central in the preparation of (+)-*cis*-sylvaticin **41**,[27] a natural product found to have potent anti-tumor activity. The ability of this compound to inhibit ATP production by blockade of the mitochondrial complex I was thought to be the origin of this biological outcome. The AD reaction, in this example, exploited the preference of this reaction for the oxidation of 1,2-*trans*-alkenes over monosubstituted alkenes. The *E,E*-isomer of tetradecatetraene **42** could be chemoselectively dihydroxylated at both internal alkenes, while the terminal alkenes remained untouched. Thus, **43** was generated in excellent chemical yield.

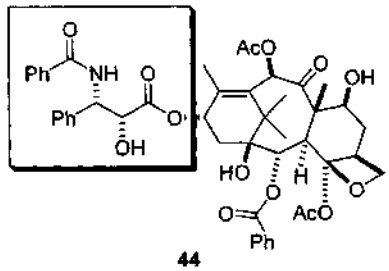


41

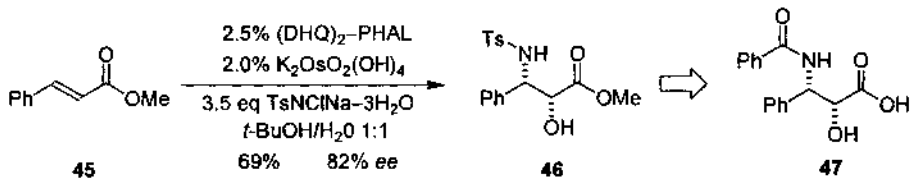


42 **43**

The AA reaction has been used in the preparation of the paclitaxel **44** side-chain **47**.[28] The structure activity relationship (SAR) associated with the anti-cancer activity of the scaffold embedded in this substituent is wellknown. Starting with the commercially available methyl cinnamate **45**, on a one-third mole scale, the advanced intermediate **46** could be prepared in one step with essentially no workup. The ready access to **46** enabled the preparation of **47** which could be used in the semi-synthesis of **44**.

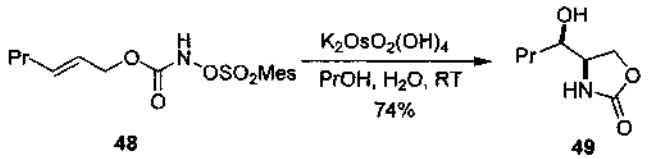


44

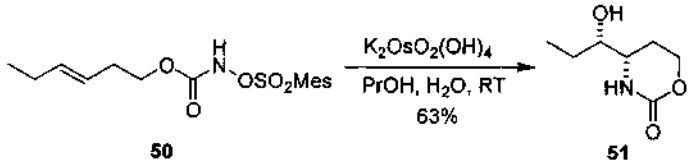


45 46 47

A tethered aminohydroxylation (TA) reaction extends the utility of carbamate versions of the nitrogen source.[29] Combining the nitrogen source with allylic or homoallylic alcohols enabled formation of products not previously accessible. Thus, exposure of **48** to the osmium reagent, in the absence of a chlorinating agent and base, led to cyclized amino alcohol **49**. A similar result was observed for homoallylic alcohol derivative **50**.



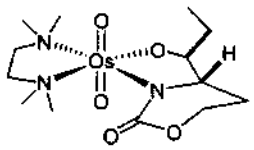
48 49



50 51

If the reaction was conducted with 1 equivalent of osmium and in the presence of TMEDA, then the intermediate osmium azaglycolate **52** could be isolated. The structure of **52** was confirmed by single crystal X-ray analysis. This observation demonstrated that the

reaction does indeed occur by *syn*-addition across the alkene and provides strong evidence that the Os(VI) species is oxidized by a *N*-sulfonyl derivative.

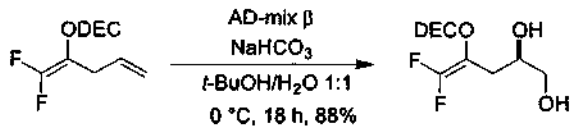


52

1.5.6 Experimental

The two examples below provide representative experimental protocols for the AD[11] and AA reactions, respectively. There are several confirmed methods that have been reported in *Organic Syntheses*.[30]

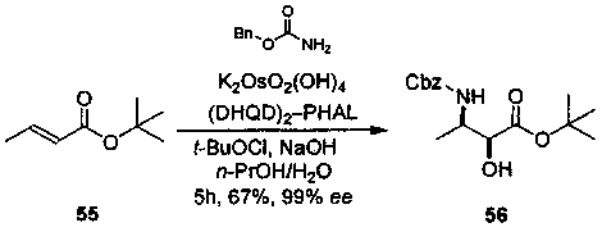
(2*R*)-4-(*N*,*N*-Diethylcarbamoyloxy)-5,5-difluoropent-4-en-1,2-diol (54)[31]



53 **54**

A mixture of AD-mix β (11.7 g, 1.41g/mol) and $NaHCO_3$ (1.8 g, 21.4 mmol) in *t*-BuOH/H_2O (82 mL, 1:1 v/v) at room temperature was stirred vigorously until a solution was obtained. The reaction was cooled to 0 °C and diene **53** (1.82 g, 8.32 mmol) was added. Once the reaction was complete, as judged by TLC, the yellow mixture was quenched with NaS_2O_3 (12 g) and stirred an additional 30 min to produce a grey solution. This was diluted with DCM (5 mL) and the phases were separated. The aqueous layer was back extracted with DCM (3 × 20 mL) and the combined organic phases were dried and concentrated *in vacuo*. The crude product was purified by silica gel chromatography to afford **54** (1.85 g, 88%) as a colorless oil.

(2*S*,3*R*)-*tert*-Butyl-2-hydroxy-3-(*N*-benzyloxycarbonyl)-aminobutanoate 56.[32]



55 **56**

To a solution of benzyl carbamate (6.6 g, 43.6 mmol) in *n*-propanol (56 mL) was added a solution of NaOH (1.71 g, 42.9 mmol) in 105 mL of water followed by freshly prepared *tert*-butyl hypochlorite (4.7 mL, 43.9 mmol). To this mixture was then added a solution of $(DHQD)_2$–PHAL (0.54 g, 0.56 mmol) in 49 mL of *n*-propanol. Finally, **55** (2.0 g, 14.1 mmol) and $K_2OsO_2(OH)_4$ (0.20 g, 0.56 mmol) were added. Once the reaction was completed, partially judged by the change in colour from the initially light green coloured reaction to a light yellow colour, the mixture was diluted with 30 mL of ethyl acetate. The aqueous phase was extracted with ethyl acetate (4 × 60 mL) and the combined organic phases were washed with brine, dried (Na_2SO_4), and concentrated. The crude product was purified by flash chromatography to afford **56** (2.92 g, 67%) as a white solid.

1.5.7 References

1. [R] (a) Schroder, M. *Chem. Rev.* **1980**, *80*, 187–213. [R] (b) Lohray, B. B. *Tetrahedron: Asymm.* **1992**, *3*, 1317–1349. [R] (c) Johnson, R. A.; Sharpless, K. B. *Catal. Asymmetric Synth.* **1993**, *227*, 227–272. [R] (d) Kolb, H. C.; VanNieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483–2547. [R] e) Berrisford, D. J.; Bolm, C.; Sharpless, K. B. *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 1059–1070. [R] (f) Beller, M.; Sharpless, K. B. *Appl. Homogen. Catal. Organomet. Compounds* **1996**, *2*, 1009–1024. [R] (g) Becker, H.; Sharpless, K. B. *Asymm. Oxid. Reac.* **2001**, 81–104. [R] (h) Kolb, H. C.; Sharpless, K. B. in *Transition Metals for Organic Synthesis*, eds Beller, M.; Bolm, C. 2nd Ed., **2004**, Wiley-VCH, pp 275-298. [R] (i) Noe, M. C.; Letavic, M. A.; Snow S. I *Org. React.* **2005**, *66*, 109–625.
2. [R] (a) Reiser, O. *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 1308–1309. [R] (b) O'Brien, P. *Angew. Chem. Int. Ed.* **1999**, *38*, 326–329. [R] (c) Schlingloff, G.; Sharpless, K. B. *Asymm. Oxid. Reac.* **2001**, 104-114. [R] (d) Bodkin, J. A.; McLeod, M. D. *J. Chem. Soc., Perkin Trans. 1* **2002**, 2733–2746. [R] (e) Nilov, D.; Reiser, O. *Adv. Synth. Catal.* **2002**, *344*, 1169–1173. [R] (f) Nilov, D.; Reiser, O. *Org. Synth. Highlights V* **2003**, *118*, 118–124. [R] (g) Kolb, H. C.; Sharpless, K. B. in *Transition Metals for Organic Synthesis*, eds Beller, M.; Bolm, C. 2nd Ed., **2004**, Wiley-VCH, pp 309-326.
3. Makowka, O. *Chem. Ber.* **1908**, *41*, 943–944.
4. (a) Hofmann, K. A. *Chem. Ber.* **1913**, *45*, 3329–3336. (b) Hofmann, K. A.; Ehrhart, O.; Schnieder, O. *Chem. Ber.* **1913**, *46*, 1657–1668.
5. (a) Milas, N. A., Sussman, *S. J. Am. Chem. Soc.* **1936**, *58*, 1302–1304. (b) Milas, N. A.; Sussman, S. *J. Am. Chem. Soc.***1937**, *59*, 2345–2347.
6. (a) Criegee, R. *Ann.* **1936**, *522*, 75–96. (b) Criegee, R.; Marchand, B.; Wannowius, H. *Ann.* **1942**, *550*, 99–133.
7. VanRheenen, V.; Kelly, R. C.; Cha, D. Y. *Tetrahedron Lett.* **1976**, 1973–1976.
8. Hentges, S. G.; Sharpless, K. B. *J. Am. Chem. Soc.* **1980**, *102*, 4263–4265.
9. Aldrich

10. (a) Sharpless, K. B.; Patrick, D. W.; Truesdale, L. K.; Biller, S. A. *J. Am. Chem. Soc.* **1975**, *97*, 2305–2307. (b) Herranz, E.; Biller, S. A.; Sharpless, K. B. *J. Am. Chem. Soc.* **1978**, *100*, 3596–3598. (c) Herranz, E.; Sharpless, K. B. *J. Org. Chem.* **1978**, *43*, 2544–2548. (d) Patrick, D. W.; Truesdale, L. K.; Biller, S. A.; Sharpless, K. B. *J. Org. Chem.* **1978**, *43*, 2628–2638.
11. Sharpless, K. B. *Angew. Chem. Int. Ed.* **2002**, *41*, 2024–2032.
12. Boseken, J.; de Graff, C. *Rec. Trav. Chim.* **1922**, *41*, 199–207.
13. (a) Criegee, R. *Angew. Chem.* **1937**, *50*, 153–155. (b) Criegee, R. *Angew. Chem.* **1938**, *51*, 519–520.
14. Gobel, T.; Sharpless, K. B. *Angew. Chem. Int. Ed. Engl.* **1993**, *32*, 1329–1331.
15. (a) Sharpless, K. B.; Teranishi, A. Y.; Backvall, J.-E. *J. Am. Chem. Soc.* **1977**, *99*, 3120–3128. (b) Nelson, D. W.; Gypser, A.; Ho, P. T.; Kolb, H. C.; Kondo, T.; Kwong, H.-L. McGrath, D. V.; Rubin, A. E.; Norrby, P.-O.; Gable, K. P.; Sharpless, K. B. *J. Am. Chem. Soc.* **1997**, *119*, 1840–1858. [R] (c) Jorgensen, K. A.; Schiott, B. *Chem. Rev.* **1990**, *90*, 1483–1506.
16. (a) Sharpless, K. B.; Patrick, D. W.; Truesdale, L. K.; Biller, S. A. *J. Am. Chem. Soc.* **1975**, *97*, 2305–2307. (b) Sharpless, K. B.; Chong, A. O.; Oshima, K. *J. Org. Chem.* **1976**, *41*, 177–179. (c) Sharpless, K. B.; Teranishi, A. Y.; Backvall, J.-E. *J. Am. Chem. Soc.* **1977**, *99*, 3120–3128. (d) Chong, A. O.; Oshima, K.; Sharpless, K. B. *J. Am. Chem. Soc.* **1977**, *99*, 3420–3426. (e) Herranz, E.; Sharpless, K. B. *J. Org. Chem.* **1978**, *43*, 2544–2548. (f) Herranz, E.; Biller, S. A.; Sharpless, K. B. *J. Am. Chem. Soc.* **1978**, *100*, 3596–3598. (g) Patrick, D. W.; Truesdale, L. K.; Biller, S. A.; Sharpless, K. B. *J. Org. Chem.* **1978**, *43*, 2628–2638. (h) Herranz, E.; Sharpless, K. B. *J. Org. Chem.* **1980**, *45*, 2710–2713. (i) Hentges, S. G.; Sharpless, K. B. *J. Org. Chem.* **1980**, *45*, 2257–2259. (j) Li, G.; Chang, H.-T.; Sharpless, K. B. *Angew. Chem. Intl. Ed. Engl.* **1996**, *35*, 451–454.
17. (a) Veldkamp, A.; Frenking, G. *J. Am. Chem. Soc.* **1994**, *116*, 4937–4946. (b) Norrby, P.-O.; Kolb, H. C.; Sharpless, K. B. *J. Am. Chem. Soc.* **1994**, *116*, 8470–8478. (c) Norrby, P.-O.; Becker, H.; Sharpless, K. B. *J. Am. Chem. Soc.* **1996**, *118*, 35–42. (d) Dapprich, S.; Ujaque, G.; Maseras, F.; Lledos, A.; Musaev, D. G.; Morokuma, K. *J. Am. Chem. Soc.* **1996**, *118*, 11660–11661. (e) DelMonte, A. J.; Haller, J.; Houk, K. N.; Sharpless, K. B.; Singleton, D. A.; Strassner, T.; Thomas, A. A. *J. Am. Chem. Soc.* **1997**, *119*, 9907–9908.
18. (a) Gable, K. P.; Juliette, J. J. J. *J. Am. Chem. Soc.* **1995**, *117*, 955–962. (b) Gable, K. P.; Juliette, J. J. J. *J. Am. Chem. Soc.* **1996**, *118*, 2625–2633.
19. (a) Jacobsen, E. N.; Marko, I.; Mungall, W. S.; Schroder, G.; Sharpless, K. B. *J. Am. Chem. Soc.* **1988**, *110*, 1968–1970. (b) Sharpless, K. B.; Amberg, W.; Beller, M.; Chen, H.; Hartung, J.; Kawanami, Y.; Lubben, D.; Manoury, E.; Ogino, Y.; Shibata, T.; Ukita, T. *J. Org. Chem.* **1991**, *56*, 4585–4588. (c) Sharpless, K. B.; Amberg, W.; Bennani, Y. L.; Crispino, G. A.; Hartung, Y.; Jeong, K.-S.; Kwong, H.-L.; Morikawa, K.; Wang, Z.-M.; Xu, D.; Zhang, X.-L. *J. Org. Chem.* **1992**, *57*, 2768–2771. d) Crispino, G. A.; Jeong, K.-S.; Kolb, H. C.; Wang, Z.-M.; Xu, D.; Sharpless, K. B. *J. Org. Chem.* **1993**, *58*, 3785–3786. (e) Kolb, H. C.; Andersson, P. G.; Bennani, Y. L.; Crispino, G. A.; Jeong, K.-S.; Kwong, H.-L.; Sharpless, K. B. *J. Am. Chem. Soc.* **1993**, *115*, 12226–12227. (f) Becker, H.; King, S. B.; Taniguchi, M.; Vanhessche, K. P. M.; Sharpless, K. B. *J. Org. Chem.* **1995**, *60*, 3940–3941. (g) Iwahima, M.; Kinsho, T.; Smith, A. B., III *Tetrahedron Lett.* **1995**, *36*, 2199–2202. (h) Becker, H.; Sharpless, K. B. *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 448–451. (i) Vanhessche, K. P. M.; Sharpless, K. B. *J. Org. Chem.* **1996**, *61*, 7978–7979.
20. Minato, M.; Yamamoto, K.; Tsuji, J. *J. Org. Chem.* **1990**, *55*, 766–768.
21. (a) Corey, E. J.; Noe, M. C.; Sarshar, S. *Tetrahedron Lett.* **1994**, *35*, 2861–2864. (b) Corey, E. J.; Noe, M. C.; Grogan, M. J.; *Tetrahedron Let.* **1994**, *35*, 6427–6430. (c) Corey, E. J.; Guzman-Perez, A.; Noe, M. C. *J. Am. Chem. Soc.* **1994**, *116*, 12109–12110. (d) Corey, E. J.; Guzman-Perez, A.; Noe, M. C. *J. Am. Chem. Soc.* **1995**, *117*, 10805-10816. (e) Corey, E. J.; Noe, M. C. *J. Am. Chem. Soc.* **1996**, *118*, 319–329. (f) Corey, E. J.; Noe, M. C.; Ting, A. Y. *Tetrahedron Lett.* **1996**, *37*, 1735–1738. (g) Corey, E. J.; Noe, M. C.; Grogan, M. J. *Tetrahedron Lett.* **1996**, *37*, 4899–4902.
22. (a) Kolb, H. C.; Andersson, P. G.; Bennani, Y. L.; Crispino, G. A.; Jeong, K.-S.; Kwon, H.-L.; Sharpless, K. B. *J. Am. Chem. Soc.* **1993**, *115*, 12226–12227. (b) Becker, H.; Ho, P. T.; Kolb, H. C.; Loren, S.; Norrby, P.-O.; Sharpless, K. B. *Tetrahedron Lett.* **1994**, *35*, 7315–7318. (c) Kolb, H. C.; Andersson, P. G.; Sharpless, K. B. *J. Am. Chem. Soc.* **1994**, *116*, 1278–1291. (d) Norrby, P.-O.; Kolb, H. C.; Sharpless, K. B. *J. Am. Chem. Soc.* **1994**, *116*, 8470–8478. (e) Norrby, P.-O.; Becker, H.; Sharpless, K. B. *J. Am. Chem. Soc.* **1996**, *118*, 35–42.
23. Mehltretter, G. M. Dobler, C.; Sundermeier, U.; Beller, M. *Tetrahedron Lett.* **2000**, *41*, 8083–8087.
24. Bolm, C.; Maischak, A.; Gerlach, A. *Chem. Commun.* **1997**, 2353–2354.

25. Mandoli, A.; Pini, D.; Agostini, A.; Savadori, P. *Tetrahedron: Asymm.* **2000**, *11*, 4039–4042.
26. Lindstrom, U. M.; Ding, R.; Hidestal, O. *Chem. Commun.* **2005**, 1773–1774.
27 Donohoe, T. J.; Harris, R. M.; Burrows, J.; Parker, J. *J. Am. Chem. Soc.* **2006**, *128*, 13704–13705.
28. Li, G.; Sharpless, K. B. *Acta Chem. Scand.* **1996**, *50*, 649–651.
29. Donohoe, T. J.; Chughtai, M. J.; Klauber, D. J.; Griffin, D.; Campbell, A. D. *J. Am. Chem. Soc.* **2006**, *128*, 2514–2515.
30. (a) McKee, B. H.; Gilheany, D. G.; Sharpless, K. B. *Org. Synth.* **1992**, *70*, 47–53. (b) Oi, R.; Sharpless, K. B. *Org. Synth.* **1996**, *73*, 1–12. (c) Gonzalez, J.; Aurigemma, C.; Truesdale, L. *Org. Synth.* **2002**, *79*, 93–102.
31. Cox, L. R.; DeBoos, G. A.; Fullbrook, J. J.; Percy, J. M.; Spencer, N. *Tetrahedron: Asymm.* **2005**, *16*, 347–359.
32. Kandula, S. R. V.; Kumar, P. *Tetrahedron* **2006**, *62*, 9942–9948.

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