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Syntheses and applications of C_2-symmetric chiral diols

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Abstract—Synthetic procedures for a large variety of C_2-symmetric chiral diols are reviewed. Prominent among these procedures are enantioselective reductions, epoxide-cleavages, dihydroxylation of olefins, and synthetic transformations. Applications of these diols as chiral auxiliaries/ligands for several important reactions are also highlighted.

Contents

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1. Introduction

The term pervasively associated with asymmetric synthesis is 'chiral inducer', that is a chiral auxiliary/ligand, which is the basis for asymmetric synthesis. Thus the synthesis of a variety of new chiral inducers and their structural optimization are of interest to synthetic chemists. Amongst these, molecules with a C_2-symmetry element provide higher levels of absolute stereochemical control compared to those lacking any symmetry.[1] The most significant advantage of using a C_2-symmetric molecule is to minimize the complexity of diastereodifferentiating events.

C_2-Symmetric diols, diamines, and diphosphines account for most of the chiral inducers. Amongst these, diols have constituted the major part not only because many of them can be derived from natural sources, but also for the fact that these prove to be synthons for diamines and diphosphines. Chiral diols thus remain the most sought after molecules in the area of asymmetric synthesis. In this report, we describe the syntheses and applications of enantiomerically pure C_2-symmetric diols, which are known to date.

2. Synthesis of C_2-symmetric chiral diols

A variety of C_2-symmetric chiral 1,2-, 1,3-, and 1,4-diols have been found to be excellent chiral inducers in different types of asymmetric transformations. A few long chain C_2-symmetric chiral diols also showed efficacy. The synthesis of the C_2-symmetric diols is conveniently accomplished by two basic synthetic strategies—chemical and enzymatic. Lack of stability, high cost, and narrow substrate specificity have been considered to be the most serious drawbacks of enzymes for use as synthetic catalysts. As a result, application of enzymes has been focused primarily on small-scale procedures yielding specific chemicals. Non-biochemical processes with wider applicability are therefore preferred alternatives to enzymatic processes.

2.1. Chemical methods

Various established chemical methods are available in the literature for the large-scale synthesis of C_2-symmetric diols. These methods include resolution, reduction, synthetic transformation, etc.

2.1.1. 1,2-Diols. C_2-symmetric 1,2-diols are the simplest variety of chiral diols. The most popular and useful C_2-symmetric chiral 1,2-diol has been tartaric acid and its derivatives, which are however outside the limits of the present article. Amongst synthetic diols, chiral hydrobenzoin **1**, 2,3-butanediol **2**, 1,2-cyclohexanediol **3**, 1,2-cyclopentanediol **4**, etc. have enriched this class of compounds (Fig. 1). Many chemical reactions have been invoked to access these diols. These include enantioselective reduction, epoxide ring-opening, dihydroxylation, and pinacol coupling reactions.

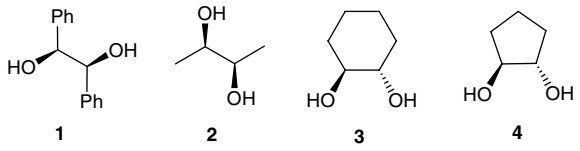
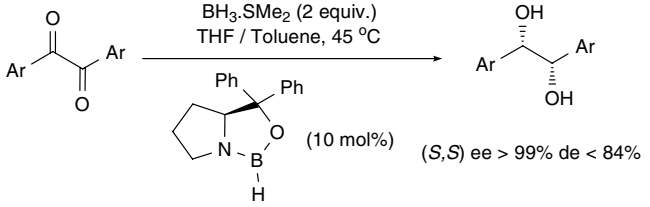


Figure 1. Representative examples of chiral 1,2-diols.

2.1.1.1. Enantioselective reduction. Borane reductions of benzils have an inherent preference for the *meso*-isomers.[2] However, oxazaborolidine-catalyzed reductions override this preference yielding chiral **1** as the major product with moderate enantioselectivity (Scheme 1).[3]

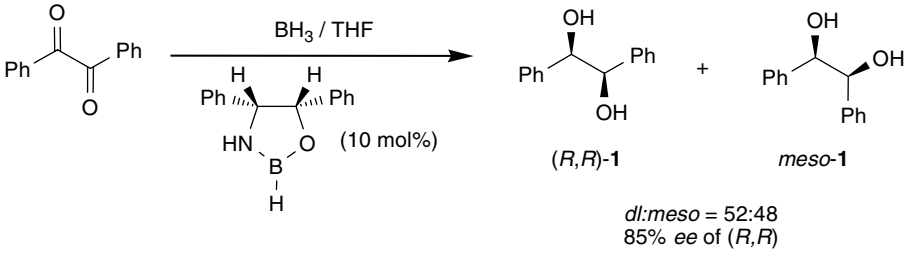
Our group established an efficient oxazaborolidine-catalyzed enantioselective route to enantiomerically pure (*S*,*S*)-hydrobenzoins.[4] Chiral products were obtained with high stereochemical control (Scheme 2).



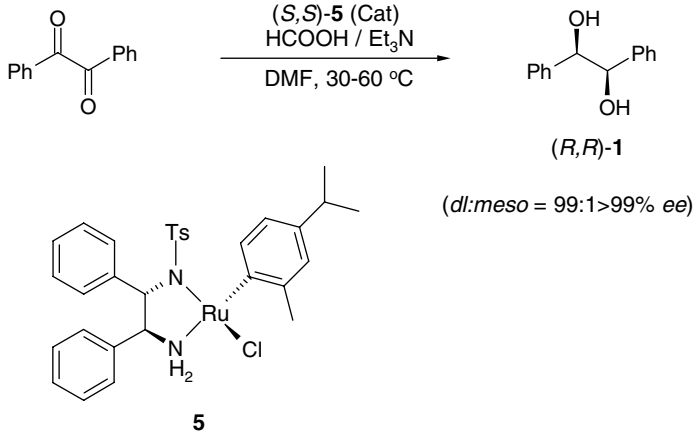
Scheme 2. Stereoselective reduction of benzils.

A breakthrough for the reduction protocol came from Noyori et al. They demonstrated a practical asymmetric reduction of benzil to chiral hydrobenzoins using a well-defined chiral Ru(II) catalyst **5** with a HCOOH/Et_3N mixture as the hydrogen source (Scheme 3).[5]

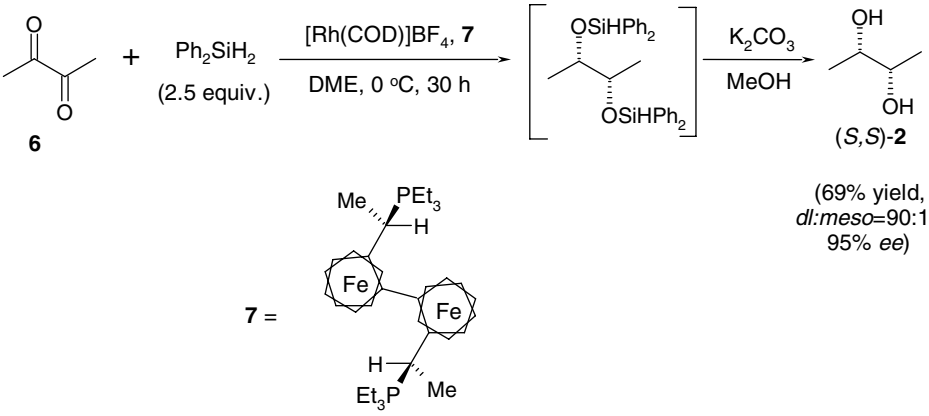
Enantioselective reduction through asymmetric hydrosilylation of symmetrical diketone **6** with diphenylsilane in the presence of a catalytic amount of Rh-complex **7** complexed with *trans*-chelating chiral phosphine ligand EtTRAP **7** gave diol **2** with high ee (Scheme 4).[6]



Scheme 1. Oxazaborolidine-catalyzed reduction.



Scheme 3. Rhodium-catalyzed transfer hydrogenation.



Scheme 4. Rhodium–EtTRAP catalyzed hydrosilylation.

2.1.1.2. Resolution. The first practical resolution of *rac*-**1** was reported by Dietl in 1982.[7] The diastereomeric bis-(−)-menthoxyacetates **8a** and **8b** were easily separated by fractional crystallization from ethanol (Fig. 2). Enantiomerically pure (*R*,*R*)- and (*S*,*S*)-**1** were obtained after saponification of the diesters **8a** and **8b**, respectively, in very high yield.

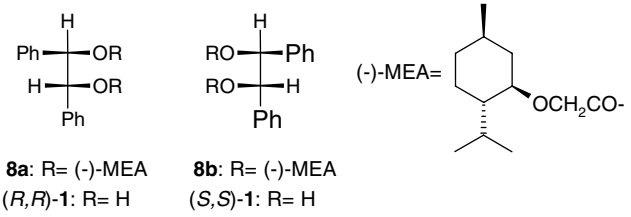


Figure 2. Chemical resolution of hydrobenzoin.

In another example, *rac*-**1** was resolved through an addition compound with (1*R*,2*R*)-cyclohexanediamine in 62% yield and 91% ee.[8] In the early 1930s, Read et al. resolved the two enantiomers of diol **3** using *l*-menthoxyacetic acid. The diastereomeric acetates (*R*,*R*)-**9** and (*S*,*S*)-**9** were separated by fractional crystallization from aqueous methanol (Fig. 3).[9] Saponification of separated monoesters provided enantiomerically pure (*R*,*R*)- and (*S*,*S*)-**3**.

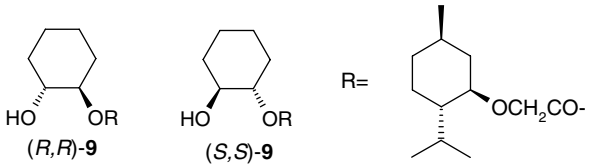
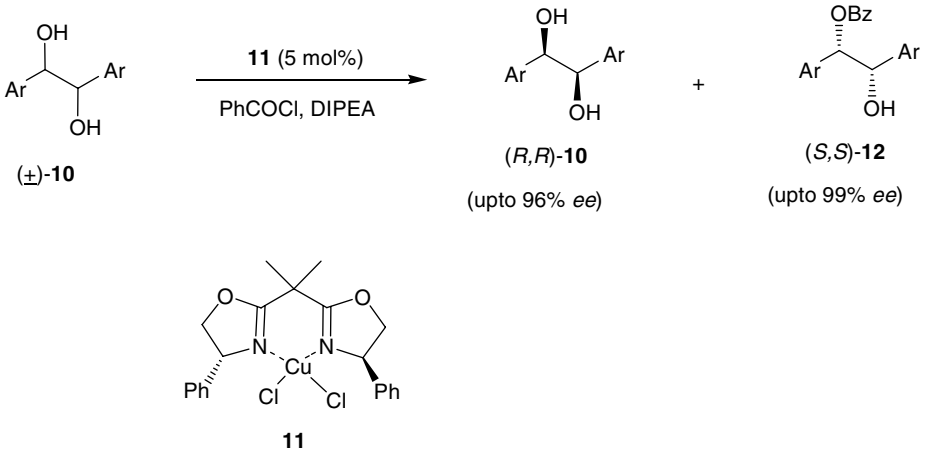


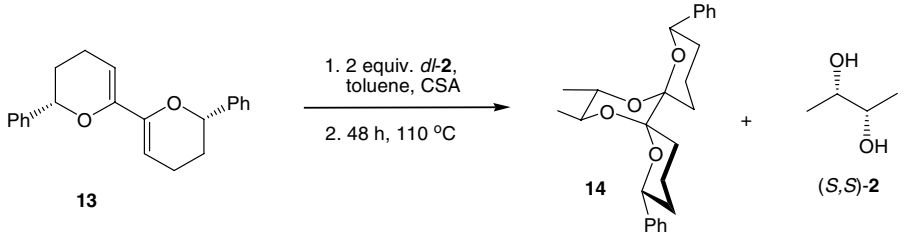
Figure 3. Chemical resolution of *trans*-1,2-cyclohexanediol.

Periasamy et al. resolved *rac*-**1** to obtain (*S*,*S*)-**1** in 99% ee through complexation with boric acid and (*S*)-proline.[10] The overall yield of pure (*S*,*S*)-**1** was poor. Matsumura et al. reported an excellent kinetic resolution of *rac*-**10** using catalytic amounts of chiral Cu(II) complex **11**. The monobenzoate (*S*,*S*)-**12** and unreacted diol (*R*,*R*)-**10** were obtained in very high enantiomeric excess (Scheme 5).[11]

Edwards et al. described a kinetic resolution of *rac*-**2** using (2*S*,2′*S*)-2,2′-diphenyl-3,3′,4,4′-tetrahydro-6,6′-bi-2*H*-pyran (PDHP, **13**).[12] The dispiroketal **14** was obtained as the



Scheme 5. Metal-catalyzed stereoselective esterification.



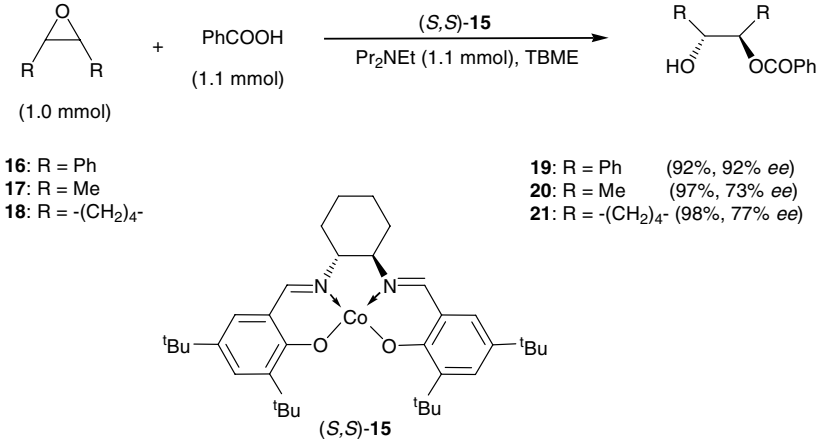
Scheme 6. Kinetic resolution through chiral derivatising agents.

single isomer in 91% yield, leaving (*S*,*S*)-**2** unreacted (Scheme 6).

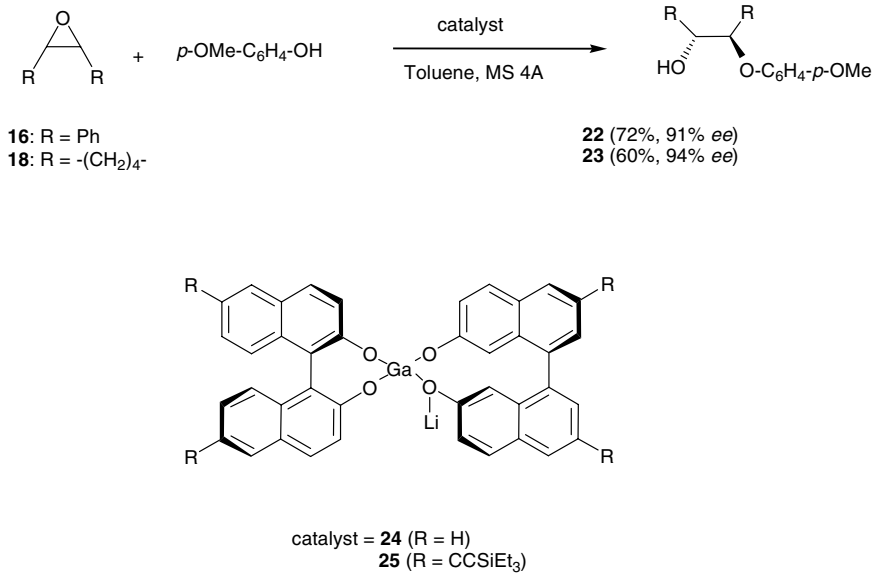
2.1.1.3. Epoxide ring opening. Jacobsen et al. demonstrated chiral Co–salen complex **15** as an effective catalyst for the enantioselective ring opening of several epoxides such as **16**, **17**, and **18** in the presence of benzoic acid as nucleophile.[13] The corresponding (*R*,*R*)-diols **19**, **20**, and **21** were obtained with very high yield and enantioselectivity (Scheme 7).

In another catalytic enantioselective ring-opening approach, the *meso*-epoxides **16** and **18** were converted to **22** and **23**, respectively, with 4-methoxyphenol promoted by Ga–Li–BINOL complexes **24** and **25**, respectively (Scheme 8).[14]

2.1.1.4. Asymmetric dihydroxylation (ADH). Catalytic asymmetric dihydroxylation has proved to be the best procedure to produce enantiomerically pure 1,2-diols, particularly hydrobenzoins.[15,16] In 1994, Sharpless reviewed this useful reaction in detail.[15] In the years following this review, many new chiral ligands were unveiled for this synthetically useful reaction. Herein, we restrict our discussion on those articles, which appeared following Sharpless's review. To remove all ambiguities regarding



Scheme 7. Cobalt-catalyzed desymmetrization of *meso* epoxides.



Scheme 8. Gallium complex catalyzed desymmetrization of epoxides.

the efficiency of ADH, Sharpless demonstrated a process for the production of (*R*,*R*)-**1** (99% ee) from **26** on a kilogram scale. The reaction was performed at room temperature in a 5-L flask in the presence of the chiral ligand **27** and the insoluble solid diol product was isolated by simple filtration (Scheme 9).[17]

Osmium-catalyzed ADH of **26** using molecular oxygen as the stoichiometric oxidant was reported by Beller et al. providing (*R*,*R*)-**1** with 93% ee.[18] The use of both soluble polymer bound (SPB)[19,20] and insoluble polymer bound (IPB) cinchona alkaloids is a potential industrial process for the synthesis of enantiomerically pure diol **1**. A range of chiral polymeric systems were reported (Fig. 4).[20–22]

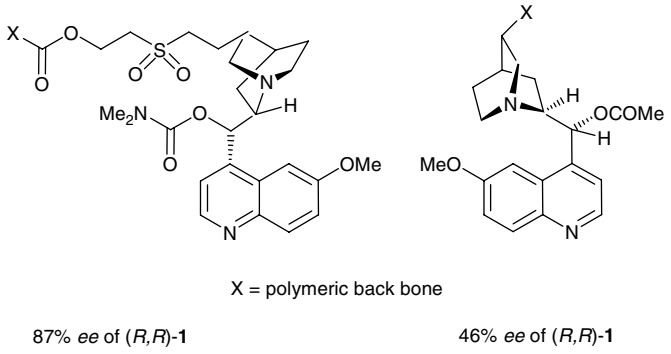
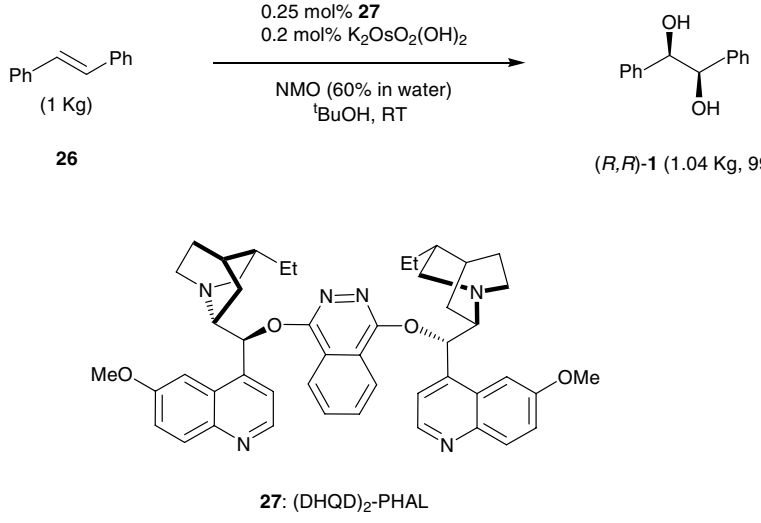
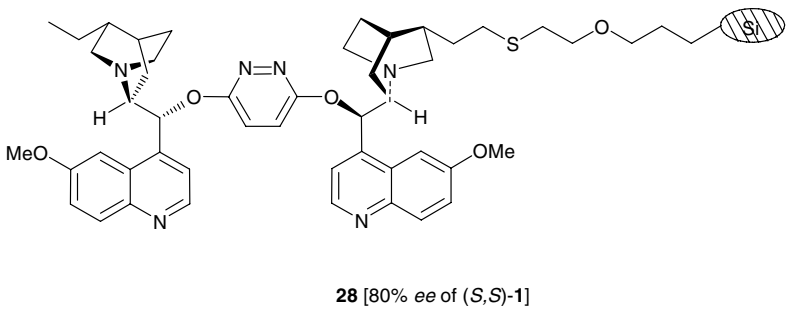


Figure 4. Polymer-bound cinchona alkaloids for ADH.

Recently, many groups have demonstrated very efficient catalytic ADH of **26** using immobilized chiral alkaloids on an inorganic support such as silica (e.g., **28**)[21] or modified resin.[22] A variety of catalytic systems of this type have shown their usefulness in ADH (Fig. 5).[23a]

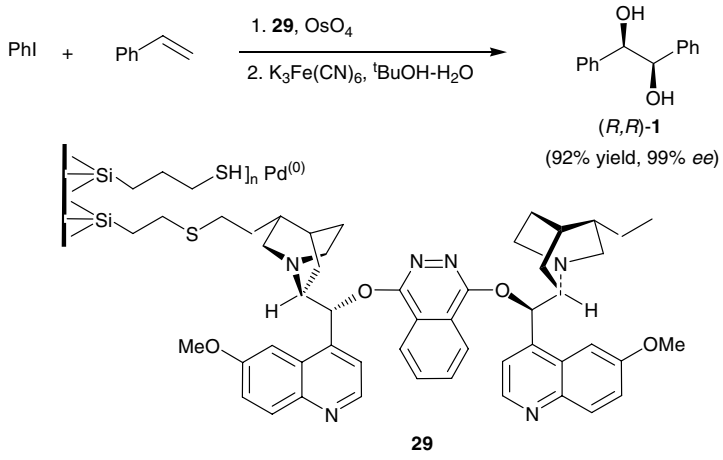


Scheme 9. Preparative procedure for asymmetric dihydroxylation.



28 [80% *ee* of (*S*,*S*)-**1**]

Figure 5. Ligand immobilized on silica.

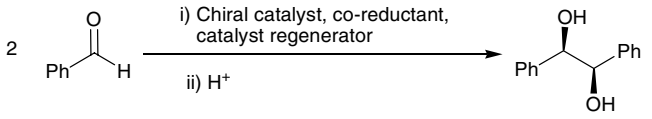


29

Scheme 10. Heterogeneous bifunctional ligand.

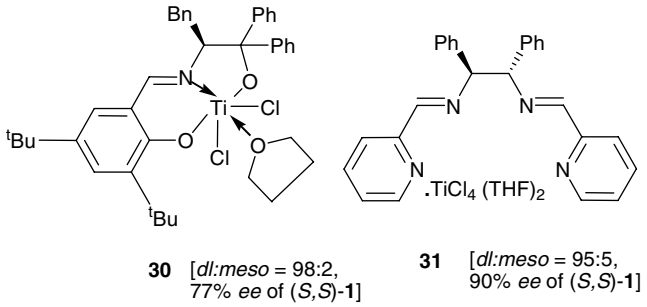
Choudhary et al. reported a new bifunctional heterogeneous system **29** as a highly effective catalyst for tandem Heck-AD of styrene to afford (*R*,*R*)-**1** with high yield and enantioselectivity (Scheme 10).[24]

2.1.1.5. Pinacol coupling. In addition to AD processes, pinacol coupling of benzaldehyde has been one of the most promising methods for preparing enantiomerically pure hydrobenzoin (Scheme 11).[25,26]



Scheme 11. Pinacol coupling for chiral hydrobenzoins.

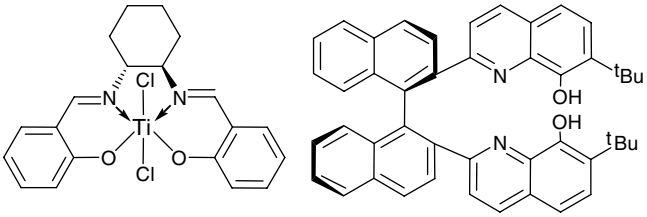
Earlier efforts relied on the stoichiometric use of chiral low-valent titanium complexes, for example, **30**,[26a] **31**[26b] (Fig. 6).



30 [*dl*:*meso* = 98:2, 77% *ee* of (*S*,*S*)-**1**]

31 [*dl*:*meso* = 95:5, 90% *ee* of (*S*,*S*)-**1**]

Figure 6. Chiral titanium complexes for pinacol coupling.



32

[*dl*:*meso* = 98:2, 95% *ee* of (*R*,*R*)-**1**]

33 (TBOXH)

[*dl*:*meso* = 98:2, 97% *ee* of (*R*,*R*)-**1**]

Figure 7. Very successful metal complexes for pinacol coupling.

Our group reported a catalytic protocol using titanium–Schiff base complex **32** (Fig. 7). A useful synthesis of (*R*,*R*)-**1** with very high diastereo- as well as enantioselectivity was accomplished.[27]

More recently, Yamamoto et al. developed a chromium complex tethered to the chiral bis(8-quinolinato)(TBOXH) ligand **33**, which represents the best catalyst reported so far in this reaction.[28]

2.1.1.6. Synthetic transformations. Read and Steele demonstrated the resolution of (±)-*erythro*-1,2-diphenyl-2-aminoethanol **34** by condensation with *d*-oxymethylene camphor. Upon treating the *N*-hydrochloride salt of D-(−)-**34** with nitrous acid, enantiomerically pure (*R*,*R*)-(+)-**1** was obtained in low yield (Scheme 12).[29] Berti and Bottari proposed a simple synthetic route to obtain (+)- or (−)-**1** starting from enantiomerically pure amino alcohol **34** via epoxide **16** and hydroxyester **35**. They also determined the configuration of (+)- and (−)-**1** (Scheme 12).[30]

There are many examples of the synthesis of enantiomerically pure diol **2** from diethyl tartarate **36** as the starting material. Simple chemical transformations have been designed to access diol **2** in high enantiomeric excess. Plattner et al. used the strategy described in Scheme 13.[31a]

Mori and Tamada demonstrated a similar approach to synthesize both enantiomers of **2** starting from the enantiomers of **36**.[31b] Cunningham and Kundig presented an efficient synthesis of enantiomerically pure (*S*,*S*)-**4** starting from (*R*,*R*)-**36** (Scheme 14).[32]

There are many other C_2-symmetric 1,2-diols known in the literature. The synthesis of diols, for example, **37**,[33,34] **38**,[35a] **39**,[11] **40**,[13,14] **41**,[13] **42**,[19,20h,36–38] **43**,[39] **44**,[14] **45**,[40] has been accomplished by several groups (Fig. 8).

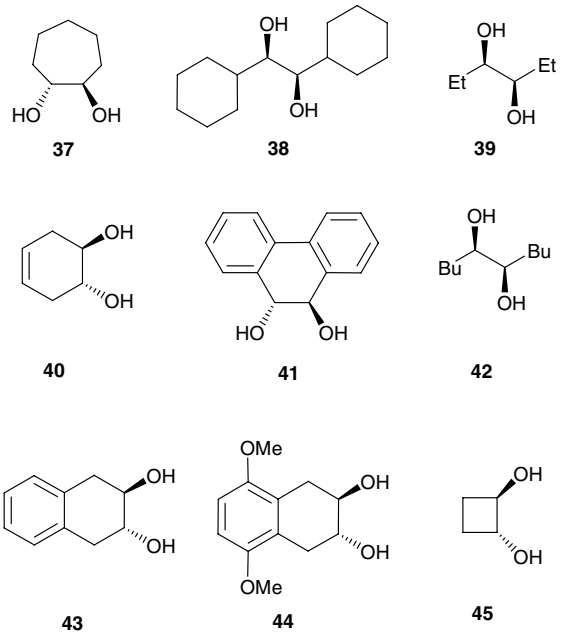
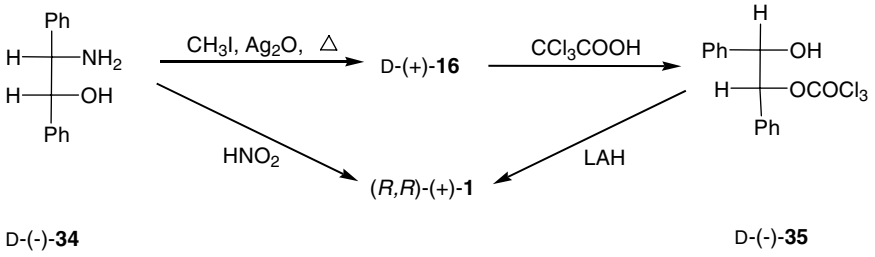
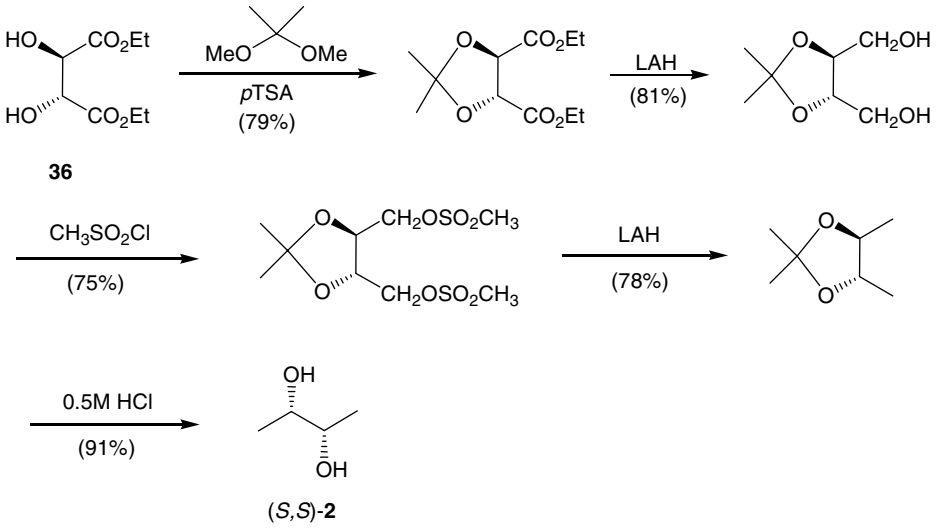


Figure 8. Miscellaneous C_2-symmetric chiral 1,2-diols.

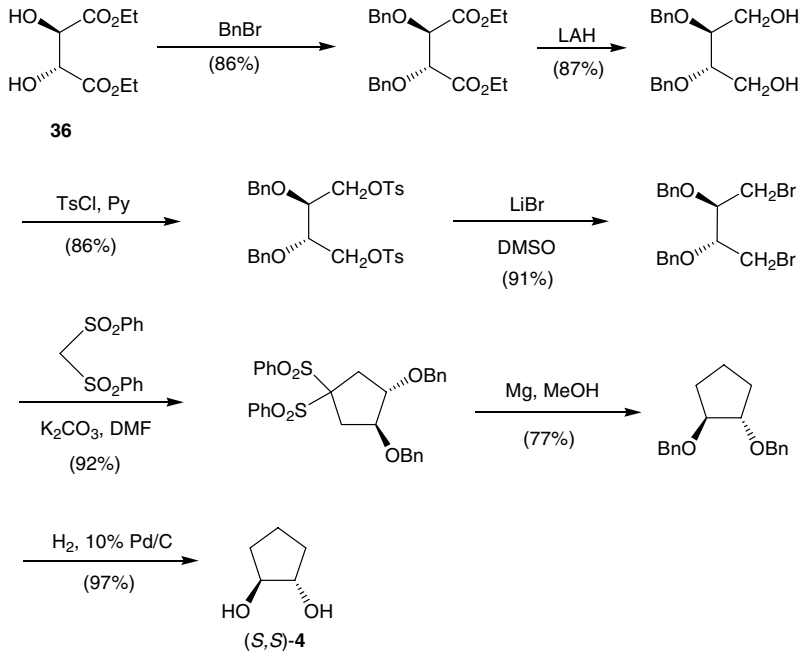
2.1.2. 1,3-Diols. Amongst C_2-symmetric 1,3-diols, 1,3-diphenylpropane-1,3-diol **46**, and 2,4-pentanediol **47** are popular representatives (Fig. 9).



Scheme 12. Synthesis and determination of absolute configuration.



Scheme 13. Synthesis of homochiral butane diol.



Scheme 14. Synthesis of homochiral 1,2-cyclopentane diol.

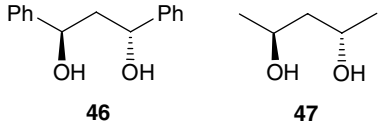
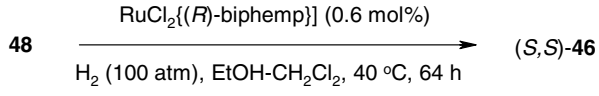


Figure 9. Common examples of chiral 1,3-diols.

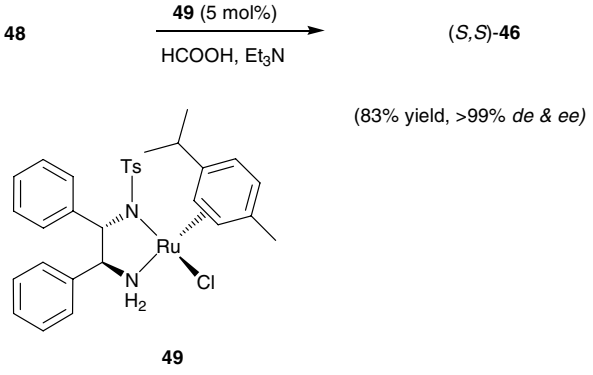
2.1.2.1. Enantioselective reduction. Ito et al. presented the first synthesis of enantiomerically pure diol **46** from the corresponding β-diketone **48**.[41] Hydrogenation of **48** over a Raney-Ni catalyst modified with a mixture of tartaric acid and NaBr (TA–NaBr–MRNi) gave (*R*,*R*)-**46**. After three consecutive recrystallizations from an ether/ethyl acetate mixture, enantiomerically pure (*R*,*R*)-**46** was obtained in 20% overall yield (Scheme 15).

A highly stereoselective hydrogenation of **48** in the presence of [$RuCl_2${(*R*)-biphemp}][biphemp = 2,2′-bis(diphenylphosphino)-6,6′-dimethyl-1,1′-biphenyl] was reported by Salvadori et al. (Scheme 16).[42]



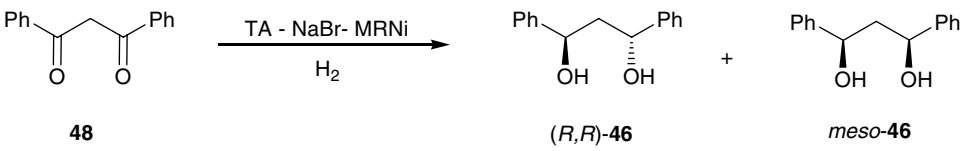
Scheme 16. Hydrogenation using chiral ruthenium complex.

Recently, Cossy et al. reduced **48** using the chiral diamine-based Ru(II) catalyst **49** furnishing enantiomerically pure (*S*,*S*)-**46** (Scheme 17).[43] This is the best method reported so far for the synthesis of this diol.



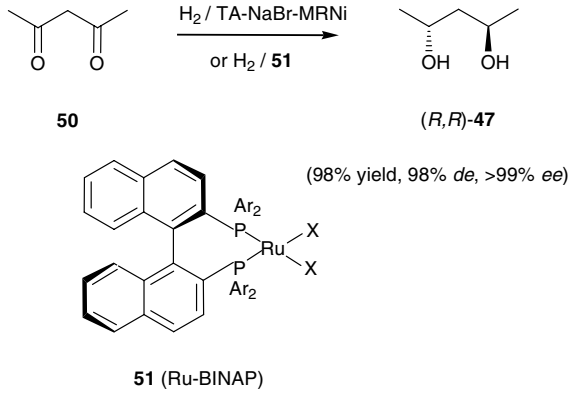
Scheme 17. Asymmetric transfer hydrogenation using ruthenium catalyst.

A facile method for the preparation of enantiomerically pure (*R*,*R*)- and (*S*,*S*)-**47** was described by Ito et al.[44] Their method involved asymmetric hydrogenation of dione **50** on TA–NaBr–MRNi, followed by recrystallization of the resulting product from ether. The same hydrogenation



Scheme 15. Modified Raney-Ni for enantioselective hydrogenation.

was carried out by Kawano et al. using Ru(II)–BINAP **51** as the catalyst (Scheme 18).[45]



Scheme 18. Stereoselective hydrogenation of 1,3-diketones.

Noyori et al. simultaneously reported the use of a Ru(II)–BINAP complex for the enantioselective hydrogenation of 1,3-diketones.[46] Complete stereoselection was observed for the reduction process. Two important catalysts developed later are **52**[47] and **53**[48] (Fig. 10).

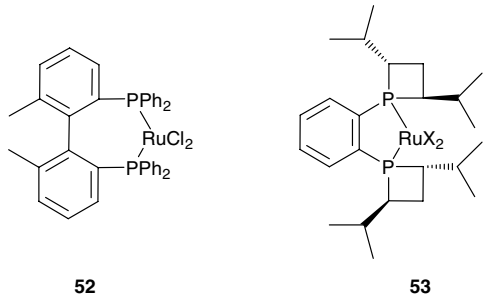


Figure 10.

Quallich's oxazaborolidine catalyst reduced diketone **50** to produce (*S*,*S*)-**47** with high enantioselectivity (92%).[3]

2.1.2.2. Resolution. Fry and Britton resolved *rac*-**47** by repeated fractional crystallization of the diastereomeric salt prepared from the racemic boronic ester **54** and brucine (Scheme 19).[49]

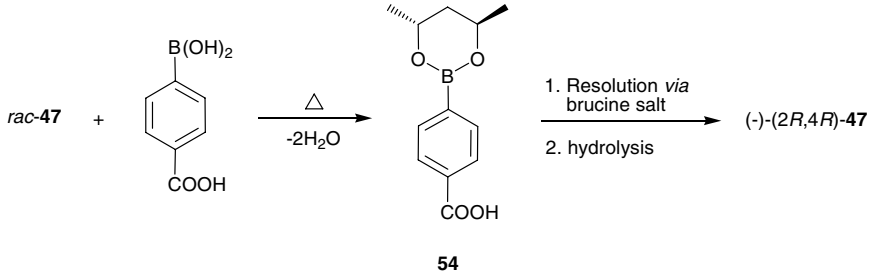
Two resolution procedures are available for the synthesis of enantiomerically pure spiro[4.4]nonane-1,6-diol **55**, a conformationally rigid molecule. Gerlach resolved (*trans*,*trans*)-**55** by preparing its diastereomeric esters **56** from (−)-camphanic acid followed by separation on silica gel (Scheme 20).[50]

Diol (*cis*,*cis*)-**55** was resolved through diastereomeric ketals with (+)-camphor (Scheme 21).[51]

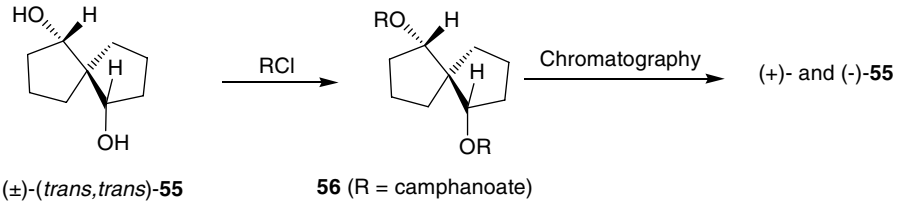
We synthesized a new chiral 1,3-diol **57** through diastereoselective reduction followed by resolution (Fig. 11).[52] Two multigram scale resolution procedures were reported for the resolution of *rac*-**57**. The diastereomeric diesters **58a** and **58b** were separated by fractional crystallization, whereas diesters **59a** and **59b** were separated by column chromatography. The separated diesters were saponified to obtain homochiral diol **57**.

2.1.2.3. Synthetic transformation. Corey and Chan have described a synthetic route to obtain (*R*,*R*)-**46**.[53] Racemic α-silyl-organolithium reagent **60** reacted with (*R*)-styrene oxide to produce chiral γ-hydroxysilane **61**, which gave (*R*,*R*)-**46** after mercuric acetate treatment (Scheme 22).

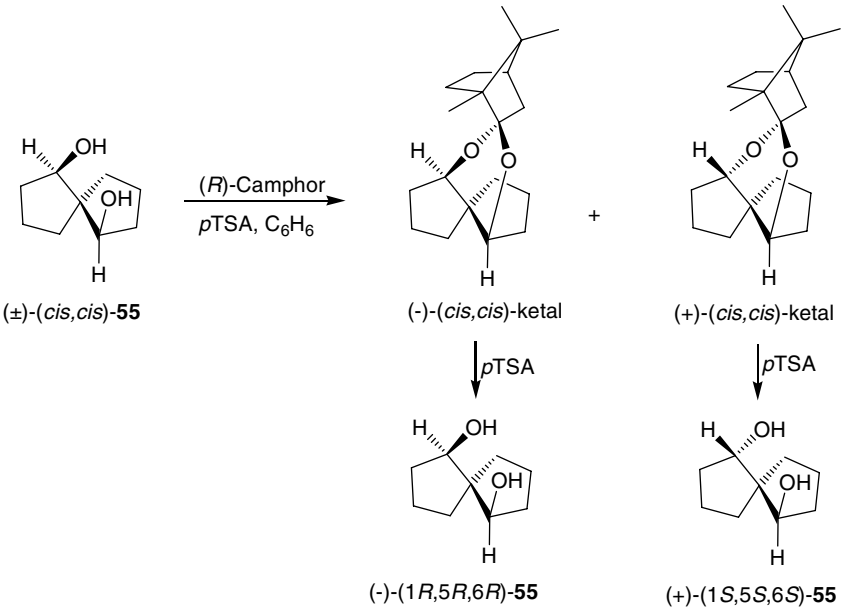
Stereoselective generation of 1,3-carbanions by sparteine-assisted deprotonation of 1,3-propane diol **62** is a novel method for the synthesis of (*S*,*S*)-**47** (Scheme 23).[54]



Scheme 19. Resolution through boronate ester derivative.



Scheme 20. Resolution through camphanoate ester.



Scheme 21. Resolution through camphor ketal.

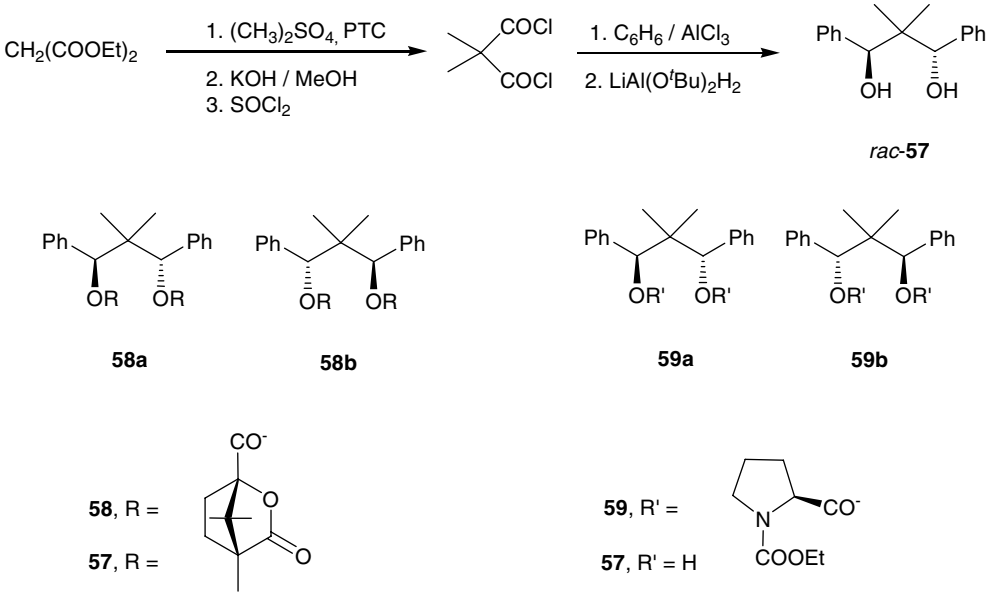


Figure 11. Synthesis and resolution of a new 1,3-diol.

There are several other useful C_2-symmetric 1,3-diols known in the literature, for example, **63**,[55,56,57b] **64**,[6] **65**,[62a] and **66**[57a] (Fig. 12).

2.1.3. 1,4-Diols. There are not many C_2-symmetric 1,4-diols, which have been used as chiral auxiliary/ligands in asymmetric synthesis. The most disadvantageous factor for this class of compounds as 'chiral inducer' is the conformational flexibility of the molecule. Seebach for the first time solved this problem with the C_2-symmetric 1,4-diol TADDOL **67**. It is a sterically hindered, conformationally rigid, and extraordinarily versatile chiral inducer. It has been prepared from tartaric acid using simple sequence of reactions as shown in Scheme 24.[58–60]

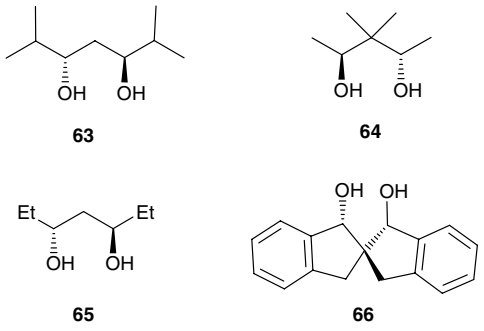
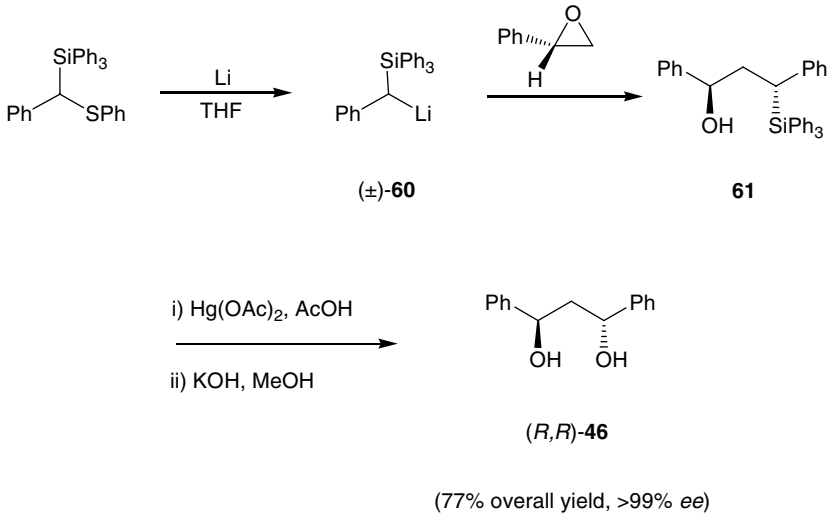
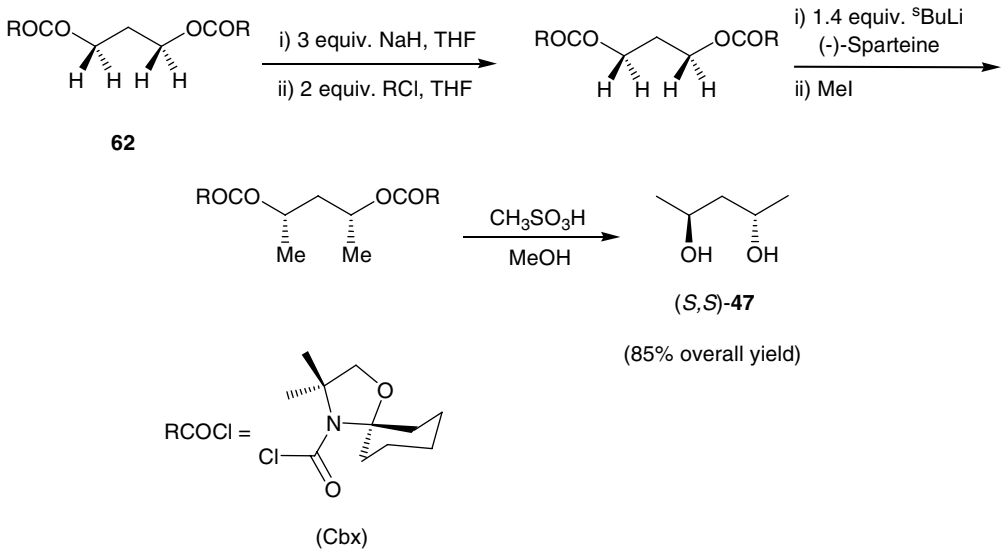


Figure 12. Miscellaneous C_2-symmetric 1,3-diols.



Scheme 22. Synthesis of a 1,3-diol through a chiral epoxide.



Scheme 23. Stereoselective deprotonation–alkylation route to a diol.

Some other examples of chiral 1,4-diols are **68**,[56,61,62] **69**,[63] and **70**[3,63d] (Fig. 13).

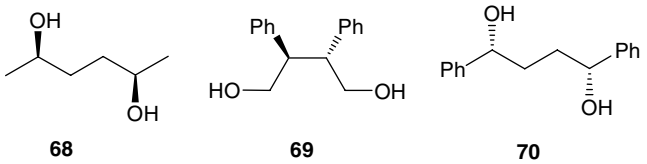
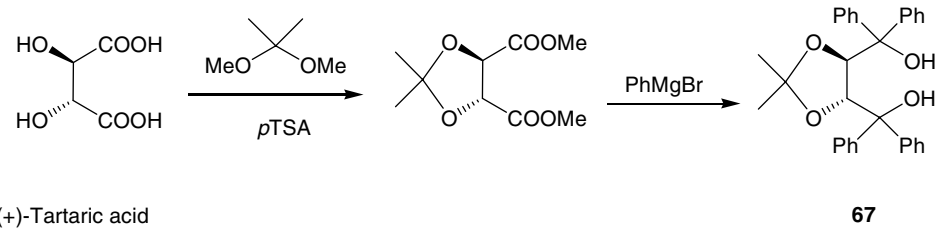
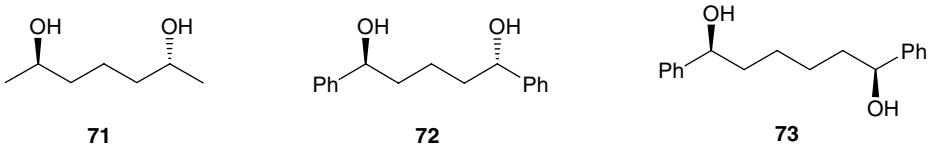


Figure 13. Miscellaneous C_2-symmetric 1,4-diols.

2.1.4. Other diols. A few C_2-symmetric long chain chiral diols are also known in the literature. These include **71**,[62g] **72**,[3,64,65] and **73**[63,65] (Fig. 14).



Scheme 24. Synthesis of TADDOL.



71 72 73

Figure 14. Some long chain chiral diols.

2.2. Enzymatic methods

Parallel to chemical processes, enzymatic methods have also evolved for many transformations. Active sites of enzymes are substrate specific as well as chiral, and hence can show high degrees of enantiodifferentiation. Moreover, enzymes are intrinsically environmentally friendly materials that operate best in water. Therefore, enzymatic methods have been explored to obtain enantiomerically pure compounds, including several C_2-symmetric chiral diols.

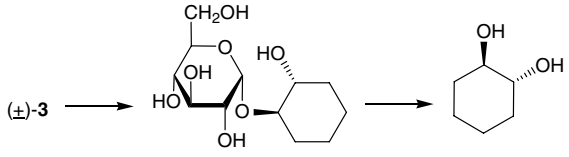
2.2.1. 1,2-Diols. Since the early 20th century, several enzymatic approaches have been directed to access these diols in enantiomerically pure form.

2.2.1.1. Enantioselective reduction. A series of *para*-substituted symmetrical benzils and benzoins were reduced using *C. macerans* to yield (*R*,*R*)-hydrobenzoins of high enantiomeric excess, albeit in modest yield.[66] Buisson et al. reported double reduction of benzils by different yeast strains with varying enantio- and diastereoselectivities.[67] With *S. uvarum* and *S. montanus*, it was possible to obtain nearly homochiral (*R*,*R*)- and (*S*,*S*)-hydrobenzoins in good yields.

2.2.1.2. Resolution. Basavaiah and Krishna obtained (*R*,*R*)-**1** in 98% ee via resolution of the corresponding racemic diacetates using chicken liver acetone powder (CLAP).[68] Parmar et al. reported an efficient enzymatic kinetic resolution to obtain diacetate (2*R*,3*R*)-**74** with high enantiomeric excess from a commercial mixture of *meso*- and *rac*-**1**.[69] Monoacetate **75** of chiral diol **1** was shown to be (2*S*,3*S*)-enantiomer (Scheme 25).

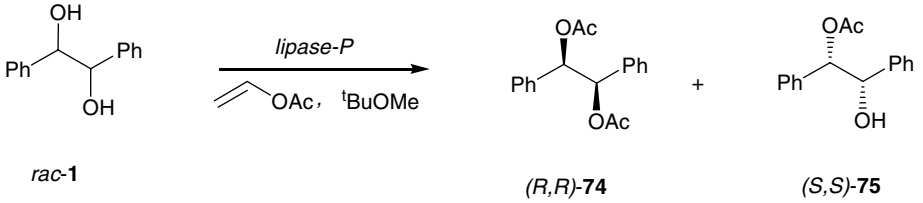
Similarly, lipase from *Pseudomonas cepacia* (PCL, Amano PS) catalyzed the enantioselective diacetylation of *rac*-**2** in vinylacetate.[70] This synthetic scale sequential kinetic resolution of *rac*-**2** provided the corresponding diacetate with 96% ee (30% yield) and (2*S*,3*S*)-**2** with 99% ee (23% yield). Recently, Matsumoto et al. demonstrated the first example of a highly enantioselective preparation of (*R*,*R*)- and (*S*,*S*)-**2** via microbial hydrolysis of the corresponding racemic cyclic carbonates **76** (Scheme 26).[71]

Itano et al. demonstrated a kinetic resolution process to separate the two enantiomers of *rac*-**3** (Scheme 27).[72] A racemic mixture of **3** was incubated with *Takadiastase* and maltose (donor), to give exclusively one D-glucoside **77**. Acid hydrolysis of **77** yielded (*R*,*R*)-**3** with >99% ee.



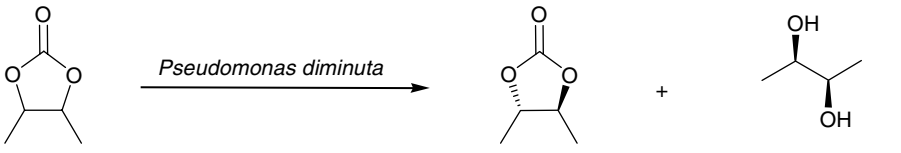
77

Scheme 27. Enantioselective kinetic glycosidation.



rac-**1** (*R*,*R*)-**74** (*S*,*S*)-**75**

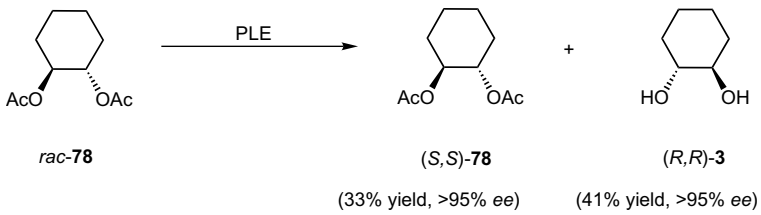
Scheme 25. Lipase-catalyzed resolution of hydrobenzoin.



rac-**76** (*S*,*S*)-**76** (*R*,*R*)-**2**

(43% yield, 95% *ee*) (42% yield, 93% *ee*)

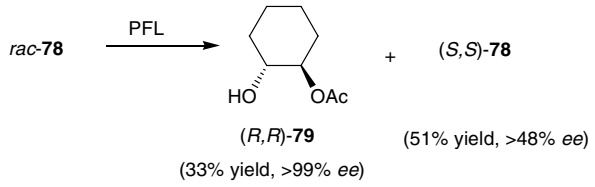
Scheme 26. Enantioselective microbial hydrolysis of a cyclic carbonate.



Scheme 28. Enzymatic hydrolysis for the resolution of diacetates.

The enzymatic hydrolysis of racemic diacetate **78** in the presence of porcine liver esterase (PLE) was reported by Crout et al. (Scheme 28).[40]

Sakai et al. described an enzymatic kinetic resolution where *Pseudomonus fluorescens* lipase (PFL) hydrolyzed *rac*-**78** selectively to monoacetate (*R*,*R*)-**79** in 33% yield (Scheme 29).[33]

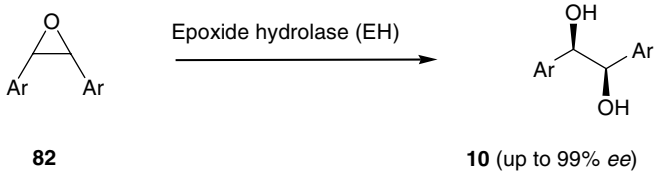


Scheme 29. Enzymatic kinetic resolution through diacetate.

1,2-Cyclopentanediol **4** is another useful chiral ligand/auxiliary in asymmetric synthesis. Derx initiated the preparation of **4** in enantiomerically pure form by resolving the strychnine salt of bis-hydrogensulfate of *rac*-**4**.[73] Later the racemic diacetates **80** of *rac*-**4** were successfully resolved into the optically active alcohols with high enantiomeric excesses by PFL. Sakai et al. obtained monoacetate (*R*,*R*)-**81** in >99% ee (Scheme 30).[74]

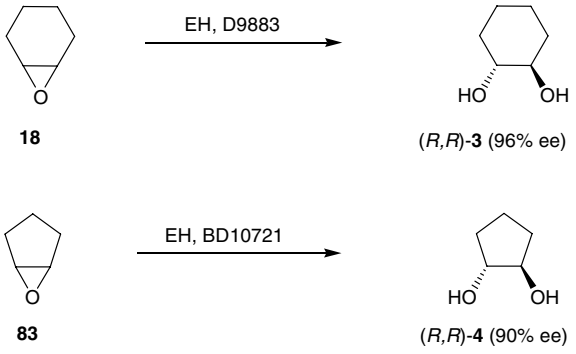
Schneider and Seemayer also demonstrated an efficient method where (*R*,*R*)-**80** and (*S*,*S*)-**81** with 97% ee and ⩾98% ee were prepared, respectively, by enzymatic kinetic hydrolysis of (±)-**80**.[34]

2.2.1.3. Epoxide ring opening. Simultaneous construction of two contiguous stereogenic centers via desymmetrization of *meso*-epoxides is an attractive route for catalytic production of chiral 1,2-diol derivatives with 100% theoretical yield. Bellucci et al. reported microsomal epoxide hydrolase catalyzed ring opening of *meso*-stilbene oxide to furnish (*R*,*R*)-**1** with 87% enantiomeric excess.[75] They also reported enantioselective ring opening by both the microsomal and the cytosolic epoxides hydrolase of rabbit liver.[76] The former enzyme provided higher enantioselectivity (88% ee). Very recently, Zhao et al. identified certain epoxide hydrolases (EHs), which provide access to both substituted (*R*,*R*)- and (*S*,*S*)-hydrobenzoins **10** with high enantioselectivity from epoxides **82** (Scheme 31).[35b]

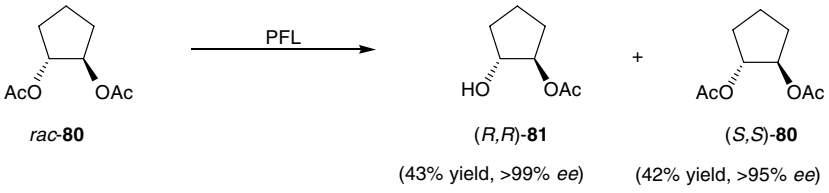


Scheme 31. Enzymatic desymmetrization of stilbene oxides.

Jerina et al. reported a moderate enantioselective process where epoxide hydrolase converted *meso*-cyclohexene oxide **18** to (*R*,*R*)-**3** with 70% ee.[77] Recently, Chang et al. demonstrated an efficient hydrolysis of **18** with epoxide hydrolase HXN-200 giving diol (*R*,*R*)-**3** in 99% yield and 87% ee.[78] According to Zhao et al., (*R*,*R*)-**3** was synthesized in very high enantioselectivity from **18**.[35b] Diol (*R*,*R*)-**4** was also synthesized from epoxide **83** using this method (Scheme 32).

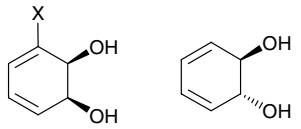


Scheme 32. Enzymatic desymmetrization of acyclic epoxides.



Scheme 30. Very efficient enzymatic resolutions.

2.2.1.4. Dihydroxylation of aromatics. Enzymatic dihydroxylation of aromatics (with *Pseudomona putida*) is an unusual reaction exploited by Hudlicky et al.[79] Enzymatically derived *cis*-diols **84** are good precursors for homochiral diol **85** through a sequence of dehalogenation and inversion (Fig. 15).[80]

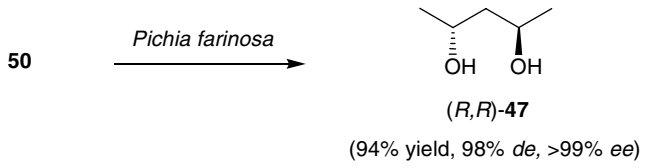


84 (X = Cl, Br) **85**

Figure 15. Enzymatic dihydroxylation of aromatics.

2.2.2. 1,3-Diols. Several enzymatic methods have been reported for the synthesis of this class of compounds.

2.2.2.1. Enantioselective reduction. Diol (*R*,*R*)-**47** was obtained by enantioselective reduction of acetylacetone **50** with the yeast *Candida boidinii* KK 912 (IFO 10574).[81] A practical synthesis of enantiomerically pure diol **47** was reported by Ikeda et al.[61] This highly efficient preparative method for (*R*,*R*)-**47** was based on the reduction of ketone **50** by *Pichia farinosa* IAM 4682 (Scheme 33).



Scheme 33. Enzymatic reduction of 1,3-diketones.

2.2.2.2. Resolution. An efficient microbial synthesis of homochiral **46** has been achieved by exposing the corresponding racemic diacetate **86** to *Trichoderma viride*. (*R*,*R*)-**86** and monoacetate (*S*,*S*)-**87** were obtained along with diol (*S*,*S*)-**46** (Scheme 34).[82]

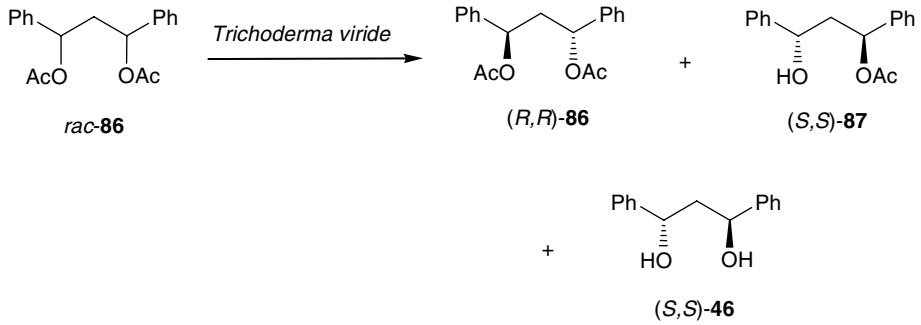
Guo et al. prepared enantiomerically pure (*R*,*R*)- and (*S*,*S*)-**47** by biocatalytic sequential enantioselective esterification.[83] Recently, Matsumoto et al. demonstrated the first example of highly enantioselective preparation of optically active **47** via microbial hydrolysis of the corresponding racemic cyclic carbonates (Scheme 35).[71]

3. Applications of C_2-symmetric chiral diols

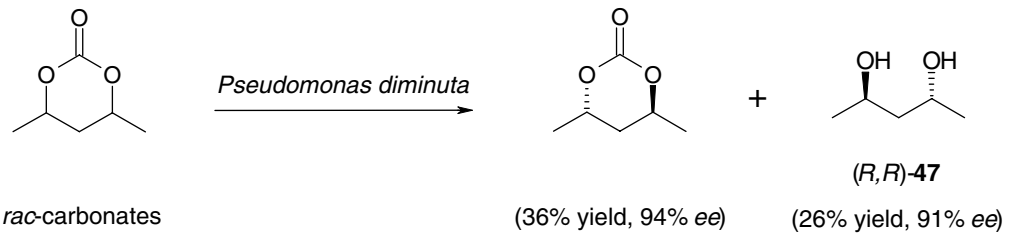
Enantiomerically pure C_2-symmetric chiral 1,2-, 1,3-, 1,4-, and some long chain diols have found a variety of uses in asymmetric synthesis as chiral ligands, as auxiliaries and as chiral building blocks. The presence of C_2-symmetry and appropriate steric and tunable electronic properties have widened their application. Easy availability of these chiral diols according to the methods discussed in this report is another advantage. Herein, the applications of various C_2-symmetric chiral diols are discussed with special emphasis on **1** (a 1,2-diol), **47** (a 1,3-diol), and **67** (a 1, 4-diol) in different asymmetric transformations. These include stereoselective addition to carbonyls or imines, protonation, Michael addition reactions, nucleophilic substitutions, Diels–Alder reactions, etc.

3.1. As chiral auxiliary

Much attention has been paid to different types of diastereo-differentiating reactions of prochiral substrates carrying C_2-symmetric chiral diols as an auxiliary.[87]



Scheme 34. Enzymatic kinetic resolution of a 1,3-diacetate.



Scheme 35. Microbial enantioselective hydrogenation of cyclic carbonates.

3.1.1. Stereoselective addition to C=O or C=N. α-Keto-ester **88** prepared in three steps from (*R*,*R*)-**1** was reduced with L-Selectride providing the corresponding α-hydroxy-ester **89** with diastereoselectivities up to 56% (Scheme 36).[85]

This selectivity has been interpretated as due to carbonyl face-shielding by the stacked –O–CH_2–Ph moiety of **88** (Fig. 16).

The use of chiral **1** for the preparation of chiral acetals has been investigated in several laboratories.[86] Myles's group described a highly diastereoselective addition reaction to chiral α-ketoacetals **90** (Scheme 37).[87]

The same group also provided an explanation for the asymmetric induction. As depicted in Figure 17, addition reactions to the carbonyl should occur from *exo* face of the chelated bicyclic intermediate. Increasing steric hindrance to the trajectory for *endo* addition can therefore maximize the selectivity.

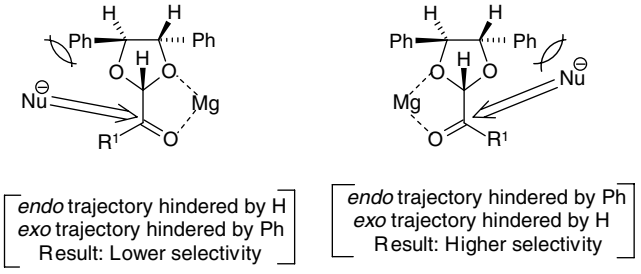
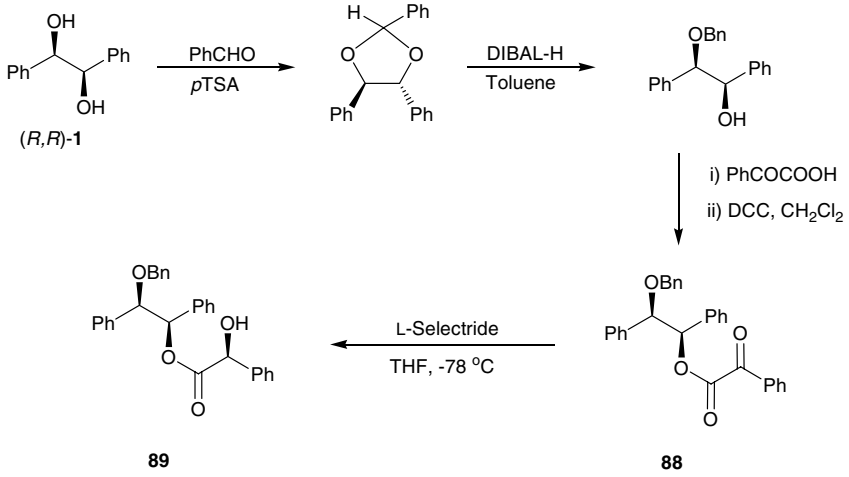


Figure 17. Trajectory of the nucleophile directed by chelated intermediate.



Scheme 36. Auxiliary-directed asymmetric reduction of α-keto acids.

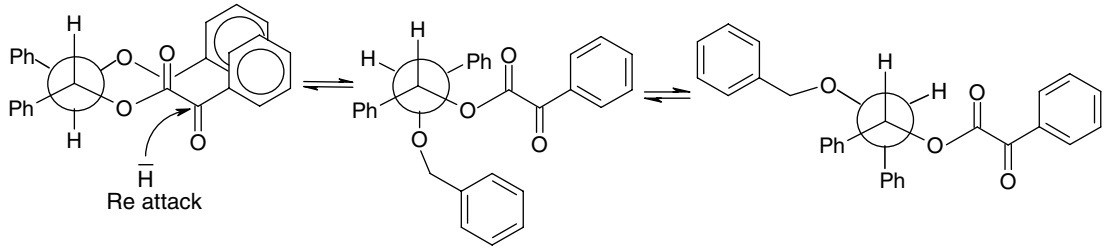
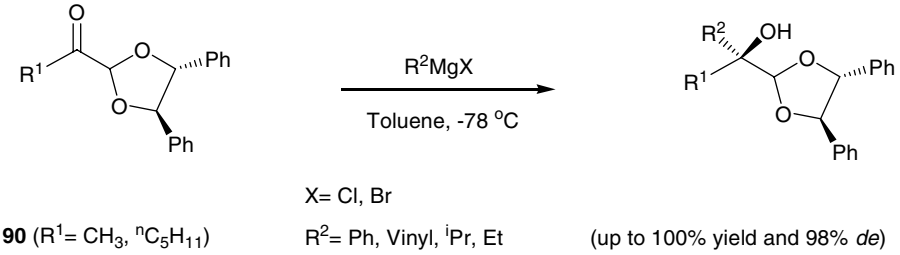


Figure 16. Mechanism for facial selective reduction.

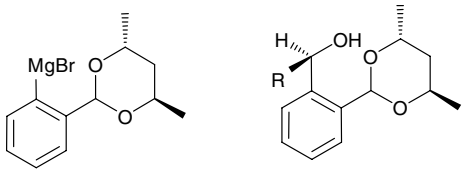


Scheme 37. Auxiliary-directed addition of Grignard reagent.

Very recently, Boezio et al. studied a novel class of chiral auxiliaries **91** derived from (*R*,*R*)-**1** for nucleophilic addition to imines.[88] The main advantage of their method was the ease of recovery of the chiral auxiliary (Scheme 38).

Aube et al. prepared (2*R*,3*R*,5*S*)- and (2*R*,3*R*,5*R*)-5-carboxaldehyde-2,3-diphenyl-1,4-dioxane **92** from (*R*,*R*)-**1** as surrogates for enantiomerically pure 2,3-*O*-isopropylidene glyceraldehydes used in asymmetric synthesis.[89] Several organometallic reagents were added to **92** and the resulting adducts **93** were treated with TBSOTf followed by hydrogenolysis to give diastereo- and enantiomerically enriched 1,2,3-triol **94** (Scheme 39).

Chiral aryl Grignard reagents **95** derived from (*R*,*R*)-**47** were added to aldehydes to provide product **96** with high diastereoselectivity (Fig. 18).[90]



95 **96** (R= Ph, ^{t}Bu, *c*-Hex)

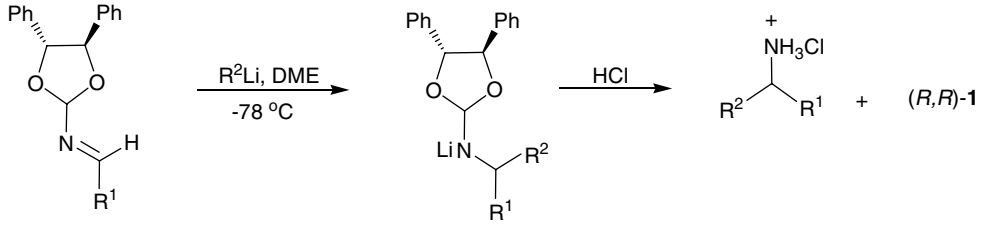
(up to 88% *de*)

Figure 18. Stereodifferentiating intramolecular chelation of a Grignard reagent.

3.1.2. Michael addition reactions. A series of enantiomerically pure 2-(2-bromobenzyl)-1,3-dioxolanes **98** have been prepared by transacetalization of enol ether **97** with enantiomerically pure (*R*,*R*)-**2**. The ability of the chiral 1,3-dioxolane moiety to control the diastereoselectivity during the 1,4-addition of aryllithium intermediate **99** to the acylimines was investigated (Scheme 40).[84c]

Chiral diol **43** was examined in the conjugate addition of lithium dibutylcuprate to monocrotonate **100** to give product **101** with 86% de (Scheme 41).[39]

3.1.3. Cyclopropanation. Application of the asymmetric Simmons–Smith cyclopropanation reaction is an attractive procedure to prepare optically active cyclopropane derivatives from prochiral alkenes. Highly diastereoselective cyclopropanation of α,β-unsaturated homochiral ketals derived from (*S*,*S*)-**1** was reported by Mash and Torok (Fig. 19).[91]

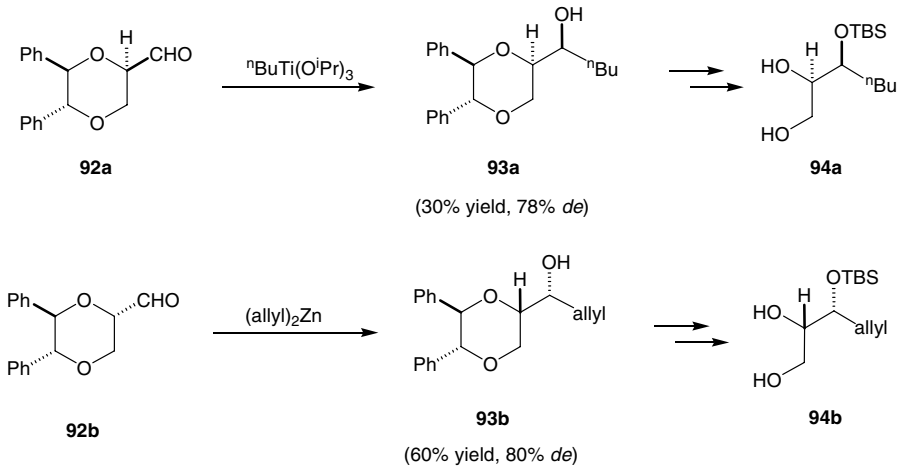


91

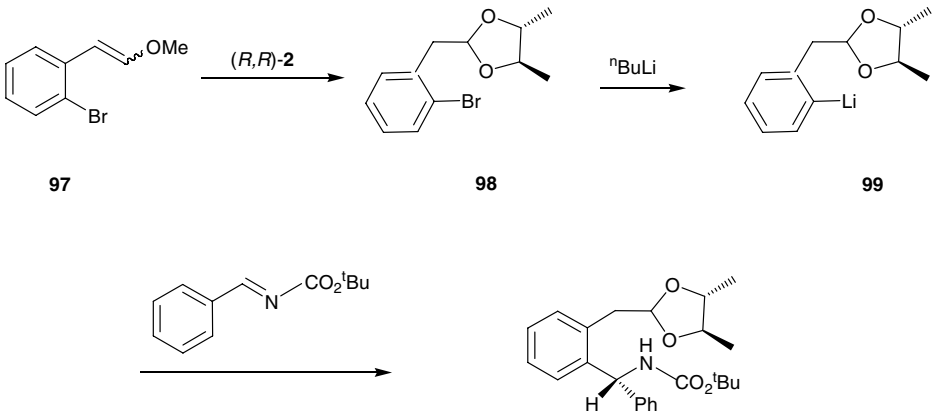
R^1= Ph, ^{t}Bu, Furan; R^2= Me, Ph, nBu

(up to >98% yield and 98% *ee*)

Scheme 38. Auxiliary-directed addition of alkyl lithium to imines.



Scheme 39. Auxiliary-directed addition of organometals to aldehydes.



Scheme 40. Stereodifferentiating intramolecular chelation of organolithium.

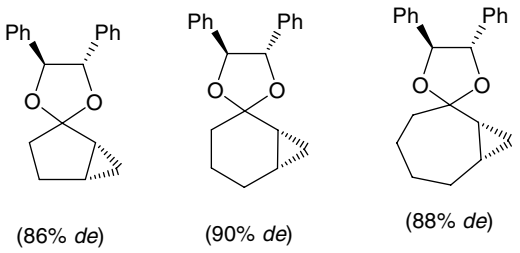
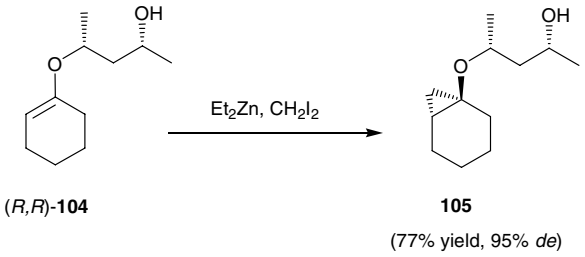


Figure 19. Cyclopropane derivatives from α,β-unsaturated ketones.



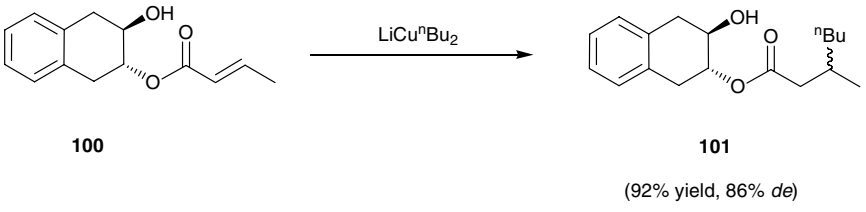
Scheme 43. Chiral auxiliary directed Simmons–Smith reaction.

Since hydrobenzoin is available in both enantiomeric forms, either enantiomer of a particular cyclopropyl ketone can be prepared via this methodology. Mash et al. again reported the effect of cyclohexane ring conformation on the diastereoselectivity observed for Simmons–Smith cyclopropanation of **102** using (*R*,*R*)-**2** as chiral auxiliary. The cyclopropanated product **103** was obtained with high diastereoselectivity (Scheme 42).[84b]

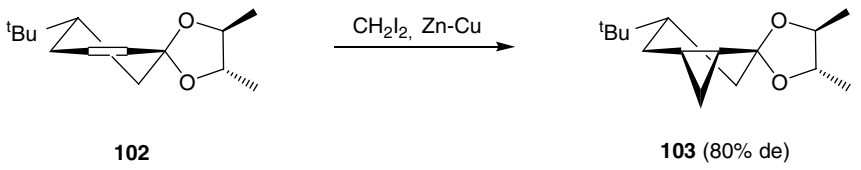
Sugimura et al. reported a highly effective diastereo-differentiating Simmons–Smith reaction on **104** employing (*R*,*R*)-**47** as auxiliary. Product **105** was obtained with very high diastereoselectivity (Scheme 43).[92]

Enol ether carrying (*R*,*R*)-**47** as the chiral auxiliary was subjected to cyclopropanation with methyl carbenoid too.[93]

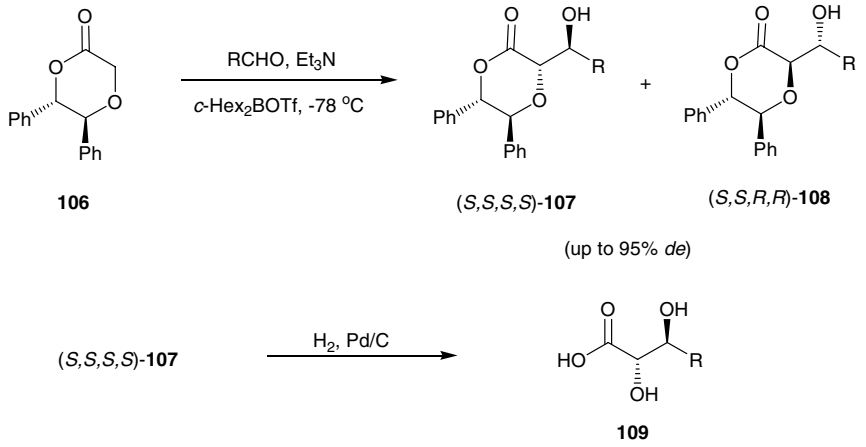
3.1.4. Aldol reaction. The boron enolate of pyrone **106** undergoes asymmetric aldol reactions with aldehydes to give protected *anti*-1,2-diols **107** and **108**. Pyrone **106** was readily obtained from *trans*-stilbene in two steps. Yields for the aldol reaction ranged 62–92% and the stereoselectivities 70–90% for the *anti*-isomers.[94] Product **107** was subjected to hydrogenolysis to give enantiomerically enriched α,β-dihydroxy acids **109** (Scheme 44).



Scheme 41. Chelation-controlled addition of cuprates.



Scheme 42. Control of ring-conformation through chiral auxiliary.



Scheme 44. Stereoselective aldol reaction through a chiral pyrone.

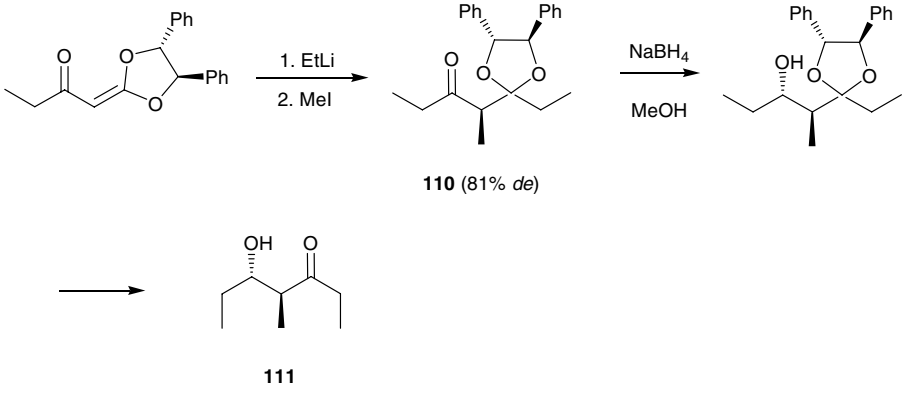
3.1.5. Reaction via acyl ketene acetal. Enantiomerically pure acylketene acetals derived from (*R*,*R*)-**1** were employed to generate homochiral β-ketoketal **110** through a highly diastereoselective lithium enolate quench. β-Ketoketal **110**, which was also prepared through desymmetrization–ketalization reaction on a *meso*-dione, was employed in the synthesis of the insect pheromone Sitophilure, **111** (Scheme 45).[95,96]

Enantiomerically pure vinylketene acetals **112** derived from enantiomerically pure (*R*,*R*)-**1** were employed in asymmetric Diels–Alder reaction (Scheme 46).[97]

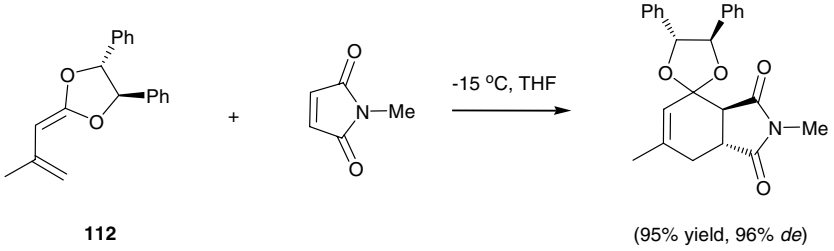
Heterodiene cycloaddition of (*S*,*S*)-4,5-bis(*p*-tolyl)-2-methylene-1,3-dioxolane **113** with a series of substituted β-amido-α,β-unsaturated carbonyl compounds **114** has been found to be diastereoselective (Scheme 47).[98]

3.1.6. α-Chloro boronic ester. (*R*,*R*)-2,3-Butane diol **2** was used as chiral directing group in the synthesis of (α*S*)-α-chloroboronic esters **115** providing 91–96% de.[99a] Esters **115** were easily hydrolyzed to crystalline boronic acids **116**. Highly stereoselective boronic ester chemistry has been used to synthesize the drugstore beetle pheromone Stegobiol **117** and Stegobinone **118** (Fig. 20).[99b] Hoffman et al. synthesized Denticulatins A and B[99c] and Mycinolide V[99d] using same boronic ester chemistry.

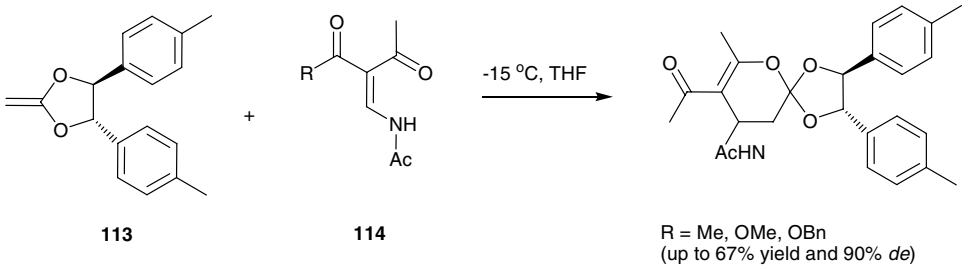
The generation of enantiomerically pure homoallyl alcohols by allylmetalation of aldehydes using chiral reagents



Scheme 45. Acylketenes as the precursors for β-hydroxyketones.



Scheme 46. Vinyl ketene acetals as dienes for Diels–Alder reaction.



Scheme 47. Chiral 2-methylene-1,3-dioxalone as dienophile.

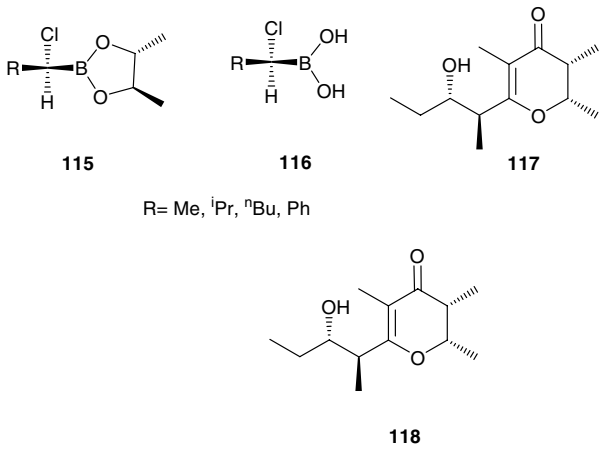
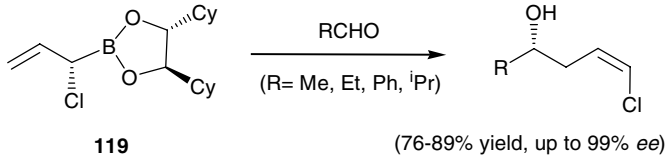


Figure 20. Chiral boronic acids for the synthesis of pheromones.

has been in constant development over the last two decades. In continuation of the effort, a highly enantioselective allylboration of aldehydes with **119** was accomplished by Hoffmann's group (Scheme 48).[99e]



Scheme 48. Allylboration using chiral boronate esters.

Recently, Shreeve et al. reported a highly stereocontrolled boronic ester chemistry to prepare several fluorinated aryl alcohols, **120** (Scheme 49).[99f]

3.1.7. Miscellaneous reactions. $TiCl_4$ catalyzed the coupling of chiral acetals **121** with silyl enol ether **122** providing excellent diastereoselection for product **123** (Scheme 50).[100] This procedure was followed toward the synthesis of (*R*)-(+)-α-lipoic acid **124** (Fig. 21).

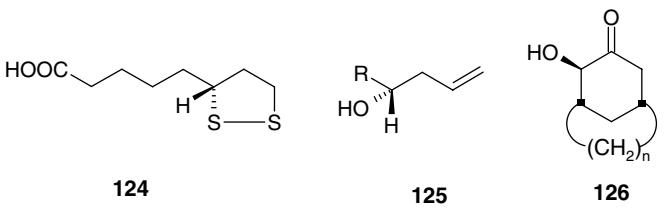
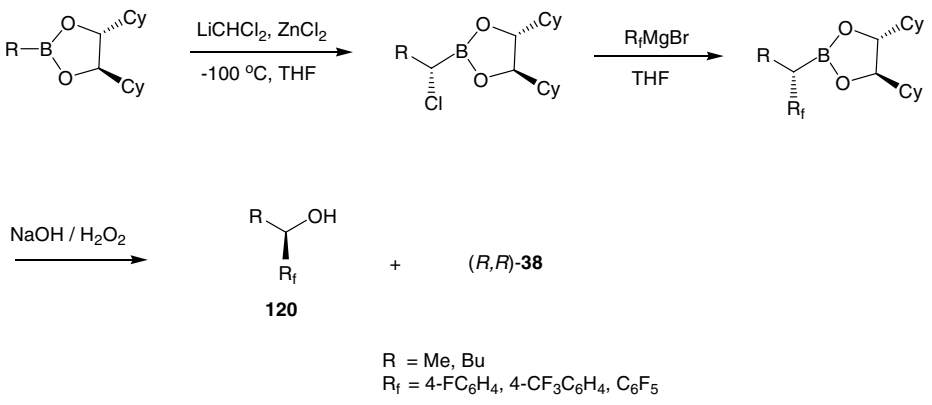


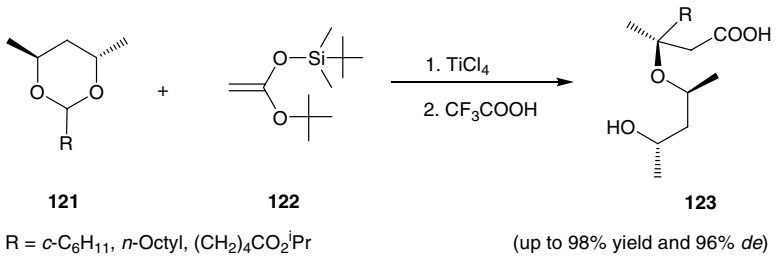
Figure 21. Miscellaneous molecules through auxiliary-directed functionalization.

Homoallylic alcohols **125** were also synthesized from chiral acetal templates derived from (*R*,*R*)-**61**.[101] A tandem acetal cleavage–epoxidation reaction providing **126** with 100% diastereoselectivity using (*R*,*R*)-**46** as auxiliary was reported by Paquette and Underiner (Fig. 21).[102]

Direct asymmetric carboxylation of the α-position of an amine with an optically active CO_2-equivalent **127** derived from (*R*,*R*)-**1** was demonstrated by Tunge et al.[103] α-Amine



Scheme 49. Chloroboronate esters for the preparation of fluoro alcohols.



Scheme 50. Cleavage of chiral acetals with a silyl enol ether.

esters **129** (up to 99%) were obtained through a dynamic kinetic resolution of **128** (Scheme 51). The rate of equilibration of zirconium aziridine and the rate of insertion of the carbonate determines the stereochemical outcome.

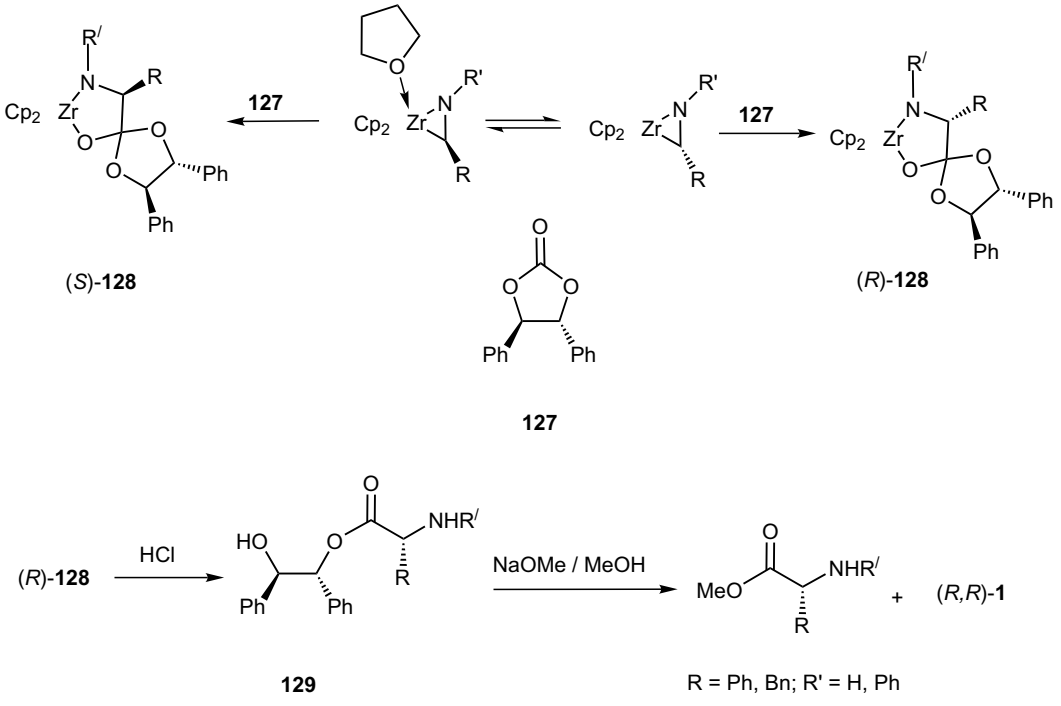
Halterman used (*R*,*R*)-**1** as a resolving reagent for the separation of racemic aromatic aldehyde **130** via formation of acetal **131** (Scheme 52).[104]

Epoxidation of **104**,[105] ene reaction of **132**,[106] and stereoselective cleavage of acetal **133**[107] provided the corresponding products **134**, **135** and **136**, respectively, with very high enantioselectivities (Fig. 22).

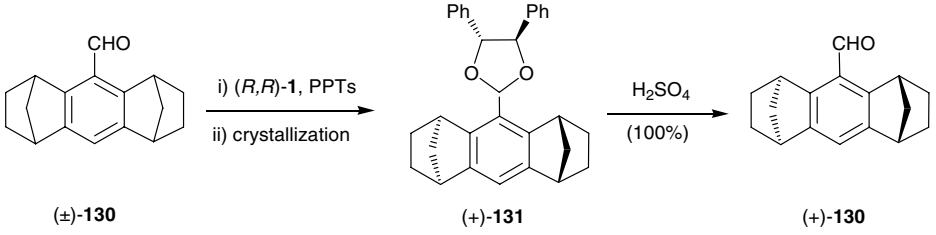
3.2. As chiral ligand

Excellent results have been demonstrated by several groups for the application of chiral C_2-symmetric diols as ligands in various asymmetric transformations.

3.2.1. Nucleophilic addition. Enantioselective addition of diethylzinc to aldehydes has emerged as an important



Scheme 51. Enantioselective α-carboxylation of an amine.



Scheme 52. Resolution of an aldehyde through diastereomeric ketal.

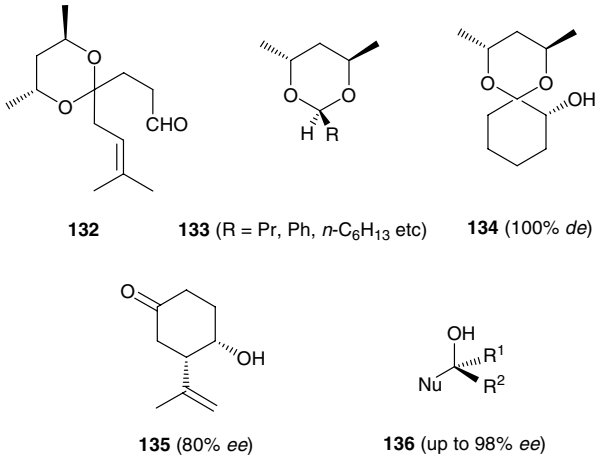
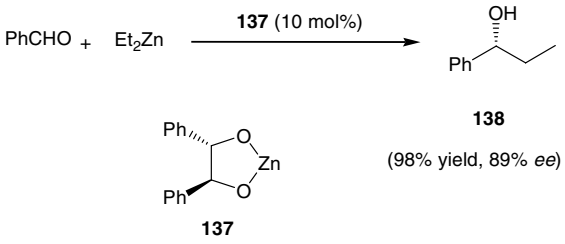


Figure 22. Miscellaneous diastereoselective functionalization.

reaction in recent times.[108] The majority of the catalysts employed for this reaction were based on amino alcohols. Rosini et al. for the first time used a C_2-symmetric diol ligand (*S*,*S*)-**1** for this reaction, though their procedure involved long reaction times and a large excess of diethylzinc.[109] Our group examined various dialkoxides derived from zinc/magnesium/boron and (*S*,*S*)-**1**. It was found that chiral zinc-dialkoxide **137** proved to be the best catalyst providing 89% ee of product **138** (Scheme 53).[110]



Scheme 53. Zinc-dialkoxide catalyzed addition of diethylzinc.

Dialkoxide **139** derived from new 1,3-diol **57** was found to catalyze the addition of diethylzinc to benzaldehyde with good yield but low enantioselectivity (25%). Catalyst **140** derived from monoethyl derivative of (*R*,*R*)-**72** improved the reactivity as well as selectivity (72% ee). These results were inferior to those obtained using **137**, but much better than that with **141** (Fig. 23).[111]

Diol (*S*,*S*)-**3** was identified as an effective ligand for titanium alkoxide catalyzed asymmetric phosphonylation of aldehydes **142** (Scheme 54).[112]

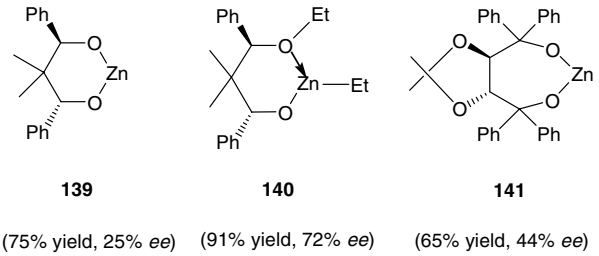
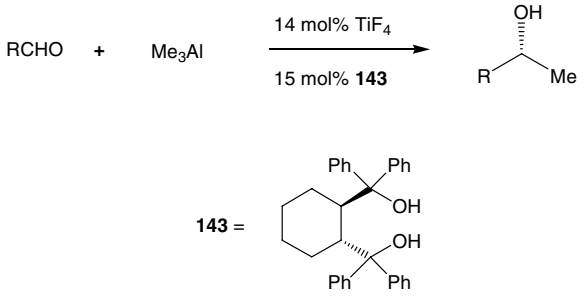


Figure 23. Representative chiral zinc-dialkoxides as catalysts.

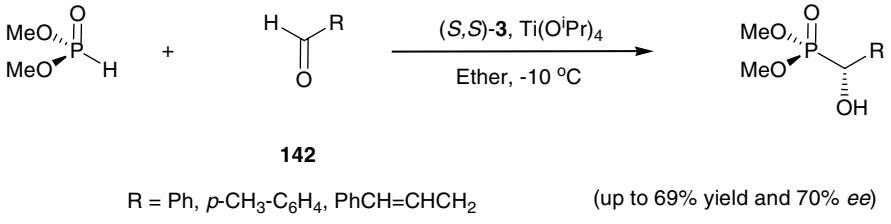
1,4-Diol **143**, a structural analogue of TADDOL, has also been used as a ligand for the addition of Me_3Al to aldehydes (Scheme 55).[113]



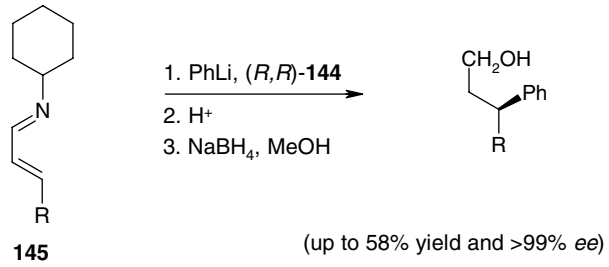
Scheme 55. Catalyzed asymmetric alkylation with trimethyl aluminum.

3.2.2. 1,4-Conjugate addition reaction. Application of this process to asymmetric synthesis is a focused and exciting area of current investigations. A variety of chiral ligands have made extraordinary contributions to generate chiral adducts with moderate to very high asymmetric induction.[114] Tomioka et al. extensively explored the chiral diether ligand **144** derived from (*R*,*R*)-**1** for Michael reaction.[115] The group reported a prototype of enantioselective conjugate addition of an organolithium to achiral α,β-unsaturated aldimine **145** using C_2-symmetric (*R*,*R*)-**144** as a stereocontrolling catalyst (Scheme 56).[115a]

The same authors described a process wherein the reaction of naphthyllithium **146** with naphthylamine **147** containing a leaving group at C-1 was catalyzed by (*R*,*R*)-**144** leading to the corresponding chiral binaphthyl imine **148**, which upon acid treatment provided binaphthaldehyde **149** in high enantiomeric excess (Scheme 57).[115b]



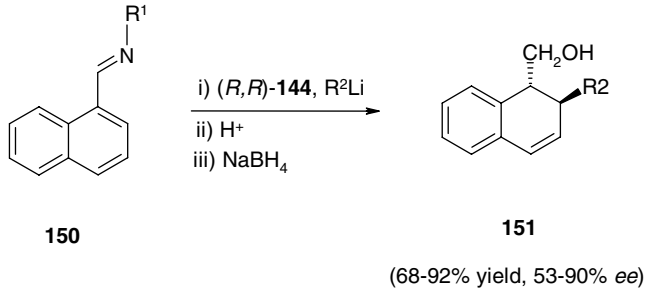
Scheme 54. Titanium alkoxide catalyzed asymmetric phosphonylation.



Scheme 56. Catalyzed enantioselective conjugate addition to aldimines.

Mediated by chiral diether **144**, high enantioselectivities for products **151** were achieved in conjugate addition of organolithiums to naphthaldehyde imine **150** (Scheme 58).[116]

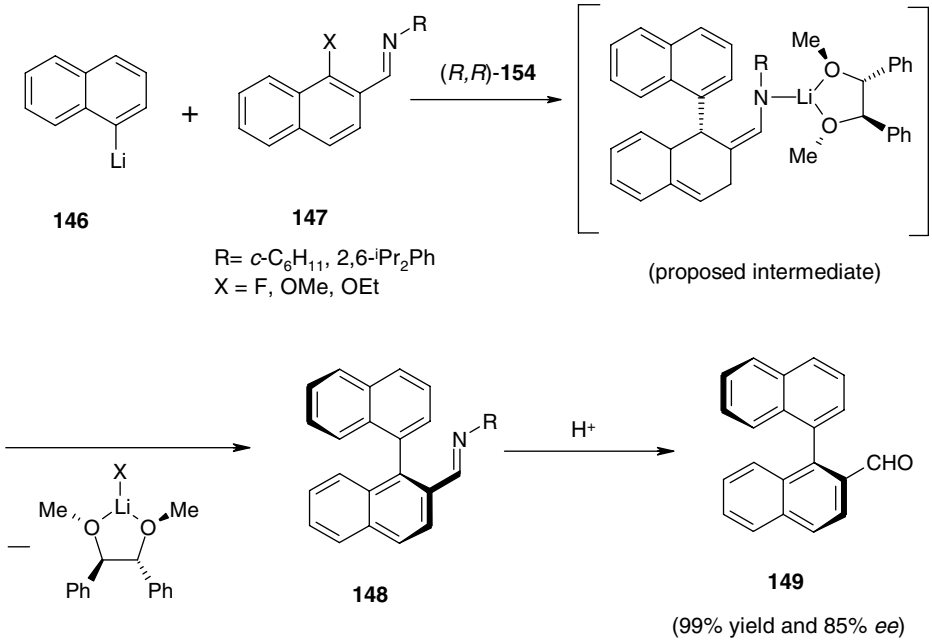
Catalytic asymmetric addition of aryllithiums to naphthalene 2,6-di-*tert*-butyl-4-methoxyphenyl (BHA)-esters **152** using the chiral mediator (*R*,*R*)-**144** was also demonstrated.[115c] Product **153** was obtained with 95% ee (Scheme 59).



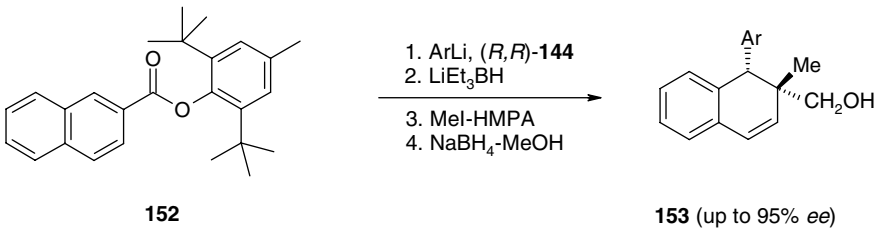
Scheme 58. Enantioselective conjugate addition of aryllithiums to aldimines.

Crosby et al. synthesized various chiral crown ethers (CCE), for example, **154**, **155**, and **156** from (*R*,*R*)-**1** (Fig. 24). These were used as chiral solid–liquid phase transfer catalysts for asymmetric Michael addition reaction (Scheme 60).[117]

Transformation of benzene and substituted benzenes to chiral non-racemic alicyclic compounds is an interesting methodology.[118] Kundig et al. studied this methodology in detail to understand both the regio- and enantioselective outcome of this reaction. They reported the addition of



Scheme 57. Synthesis of an optically active biaryl through conjugate addition.



Scheme 59. Addition of aryllithium complexed with a chiral 1,2-diether.

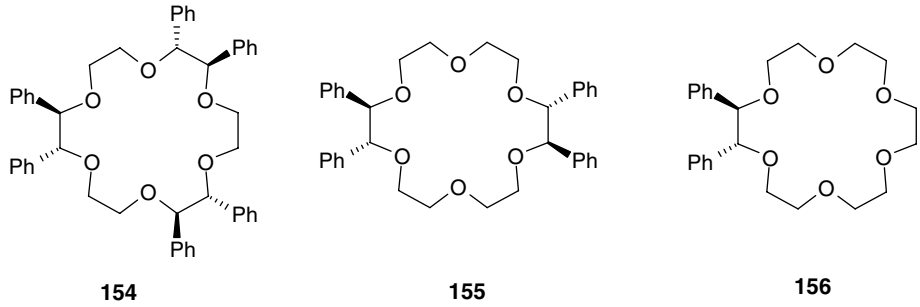
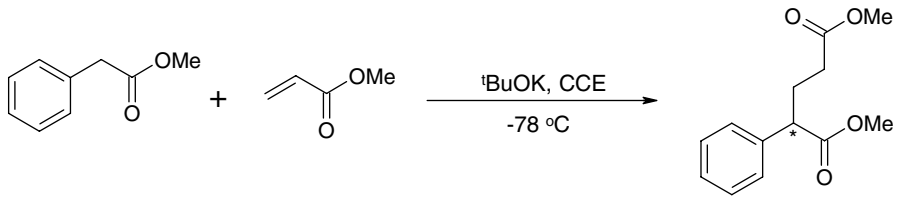


Figure 24. Crown ethers from chiral hydrobenzoin.



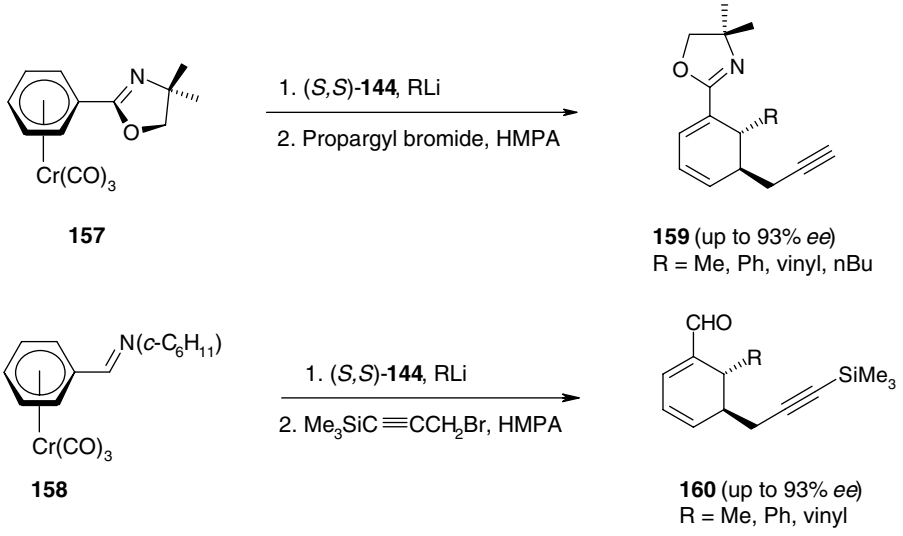
Scheme 60. Michael addition mediated by chiral crown ethers.

various nucleophiles, for example, alkyl-, vinyl-, and aryllithiums, to two different prochiral arene–$Cr(CO)_3$ complexes **157** and **158** in the presence of an external chiral ligand (*S*,*S*)-**144**, to provide **159** and **160**, respectively (Scheme 61).[119]

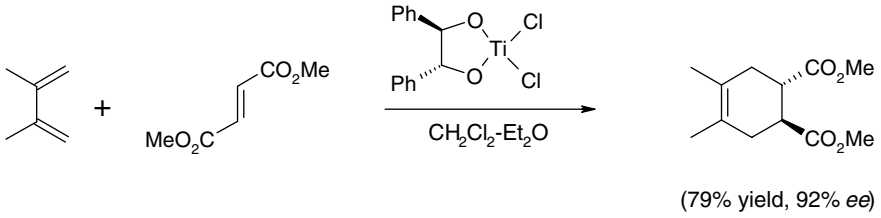
3.2.3. Diels–Alder reaction. Chiral Lewis acids are excellent catalysts for asymmetric Diels–Alder reactions. A variety of chiral ligands are known to induce absolute stereoselectivity in this concerted six-membered ring-forming reaction. Homochiral diol **1** has also been used as a chiral inducer in this reaction with particular success. Devine et al. showed that chiral titanium Lewis acid derived from (*R*,*R*)-**1** and $TiCl_4$ effectively promotes Diels–Alder reaction of less reactive carboxylic ester dienophiles (Scheme 62).[120]

Diol **47** has not been used much as chiral ligand. An asymmetric Diels–Alder reaction was performed to furnish product **161** using (*R*,*R*)-**47** as chiral ligand (Fig. 25).[121]

3.2.4. Aldol reaction. Few novel cationic Lewis acid complexes were generated by the addition of silver hexafluoroantimonate to titanium complexes **162**. Asymmetric Mukaiyama aldol reaction of benzaldehyde with silyl enol ether **163** was conducted using the in situ generated Lewis acid complexes with moderate enantioselectivity (Scheme 63).[122]



Scheme 61. Diastereoselective dearomatization of metal–arene complex.



Scheme 62. Chiral titanium complex as Diels–Alder catalyst.

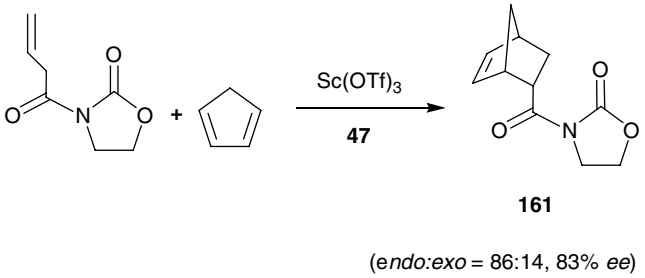
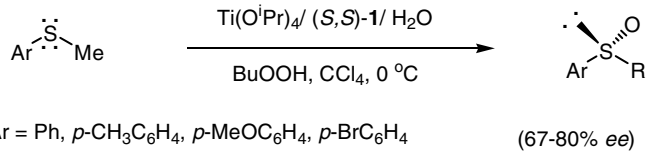


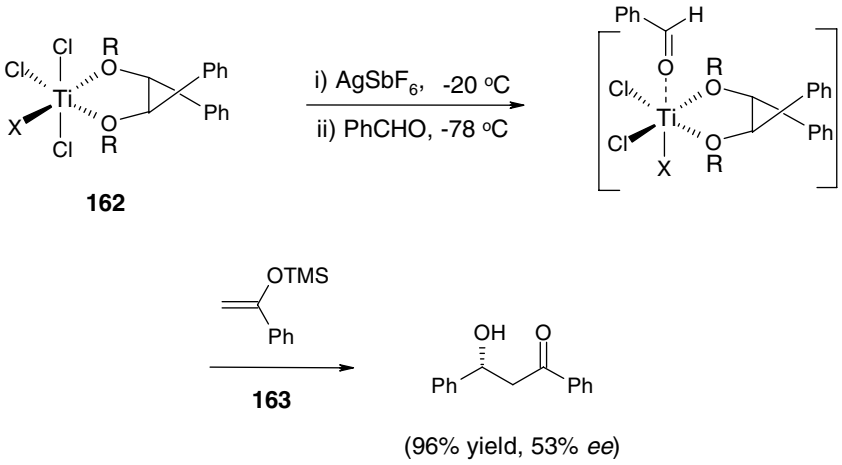
Figure 25. Chiral ligand modified scandium triflate catalyst.

3.2.5. Enantioselective protonation. The control of enantioselectivity in the protonation of silyl enol ethers with Bronsted acids is difficult, mainly due to bond flexibility between the proton and its chiral connection. Also, the proton sources available are limited to acidic compounds such as carboxylic acids. Yamamoto et al. developed a Lewis acid-assisted chiral Bronsted acid (LBA) system to overcome these difficulties.[123] Very recently, the author described (*R*,*R*)-**1**·$SnCl_4$ complex **164** as a new type of LBA for the enantioselective protonation of silyl enol ethers (Scheme 64).[124] Few other derivatives of (*R*,*R*)-**1** provided enantioselectivities up to 96% for the same reaction.

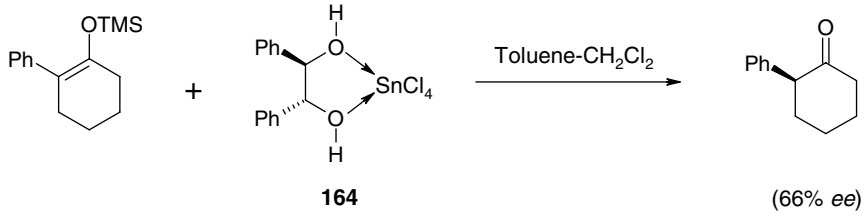
3.2.6. Oxidation of sulfides. Asymmetric oxidation of aryl methyl sulfides with hydroperoxides has been achieved using catalytic amounts of $Ti(O^iPr)_4$, (*S*,*S*)-**1** complex and water. Sulfoxides were thus obtained in 67–80% ee by Superchi et al. (Scheme 65).[125a]



Scheme 65. Asymmetric oxidation of sulfides with a chiral titanium complex.



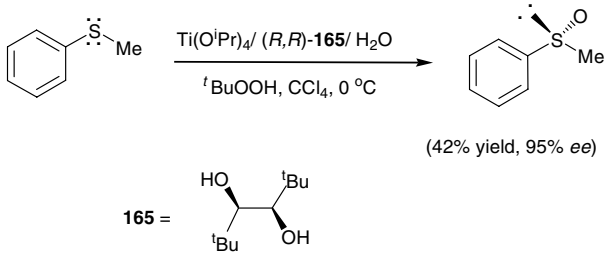
Scheme 63. Chiral titanium complex for Mukaiyama aldol reaction.



Scheme 64. Lewis acid-assisted chiral Bronsted acid as a catalyst.

The same group also optimized the reaction conditions in order to attain higher enantioselectivity and avoid the intervention of a kinetic resolution process.[125b] The oxidation protocol described was quite versatile. The chemical yields (60–73%) and enantioselectivities (70–80%) achieved for aryl alkyl sulfides were almost independent of the nature of the aryl substituent and the size of alkyl group. Notably, aryl benzyl sulfides, which were poor substrates for the titanium/diethyl tartarate catalyzed oxidation,[126] afforded very high ees (92–99%) with this oxidizing system.

Inamoto and Yamanoi reported a new preparation of enantiopure diol **165** and its application as a chiral ligand in Ti(IV)-catalyzed enantioselective oxidation of sulfides (Scheme 66).[127]

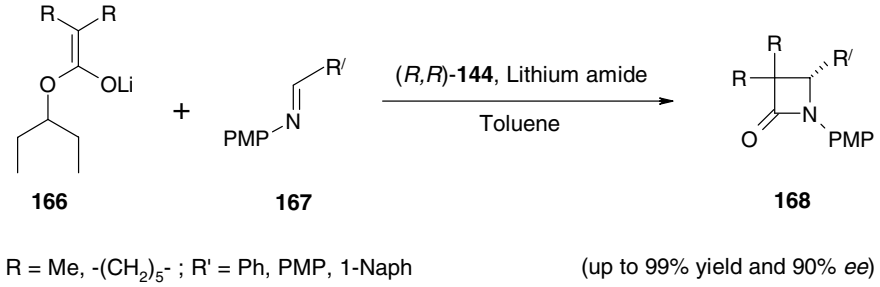


Scheme 66. Asymmetric oxidation of a prochiral sulfide.

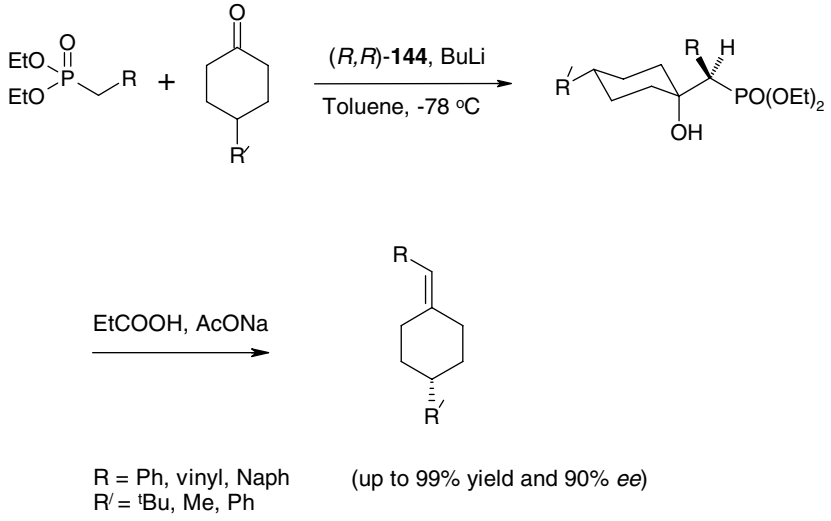
3.2.7. Miscellaneous reactions. Chiral ligand **144** has found its application in several asymmetric transformations.[115] Asymmetric addition of a lithium ester enolate to an azomethine group in the presence of an external chiral ligand has not been much studied. Tomioka et al. described the stoichiometric as well as catalytic asymmetric reactions of lithium ester enolates **166** with imines **167** based on a ternary complex. The reagent comprised three compounds: a chiral ether ligand (*R*,*R*)-**144**, an achiral lithium amide, and **166** giving the corresponding lactams **168** in high ee (Scheme 67).[128]

Tomioka et al. also presented an asymmetric Horner–Wadsworth–Emmons reaction mediated by (*R*,*R*)-**144** (Scheme 68).[129]

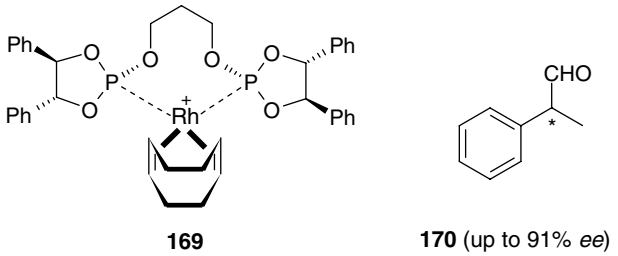
A chiral Rh-complex **169** was synthesized from (*R*,*R*)-**1** for asymmetric hydrogenation and hydroformylation reaction (Fig. 28).[130] The hydroformylated product **170** was obtained with very high enantioselectivity using (*R*,*R*)-**47** as the chiral ligand (Fig. 26).[131]



Scheme 67. Addition of lithium ester enolate to azomethines.



Scheme 68. Asymmetric Horner–Wadsworth–Emmons reaction.

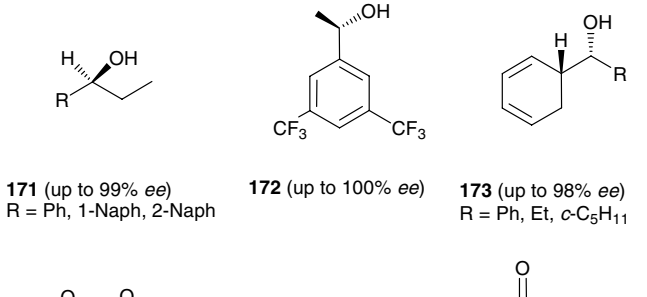


169 **170** (up to 91% *ee*)

Figure 26. Enantioselective hydroformylation.

Several other 1,3-diols, for example, **46**,[82,86] **55**,[132] and **63**,[93a,133] have also been used as effective chiral ligands in a variety of asymmetric reactions.

Application of TADDOL **67** as a chiral ligand in asymmetric synthesis is extraordinarily broad. A detailed review on the synthesis and applications of TADDOL and its structural analogues have been discussed recently by Seebach.[60] In the years following this review, TADDOL has been employed in enantioselective additions of $AlEt_3$ to aldehydes,[134] methylation of aldehydes,[135] cyclohexadienyl addition to aldehydes,[136] asymmetric fluorination reaction,[137] asymmetric phospha-analogous Michael addition reaction,[138] and asymmetric Heck reaction[139] providing a variety of chiral products such as **171**–**176**, respectively, with very high asymmetric inductions (Fig. 27).



171 (up to 99% *ee*)
R = Ph, 1-Naph, 2-Naph

172 (up to 100% *ee*)

173 (up to 98% *ee*)
R = Ph, Et, *c*-C_5H_{11}

174 (81%*ee*)

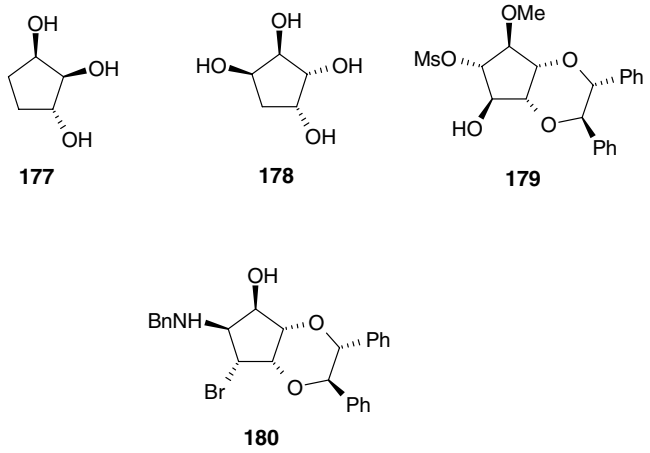
175 (up to 95% *ee*)
R = Ph, Me

176 (up to 96% *ee*)

Figure 27. Various chiral molecules obtained through reactions mediated by TADDOL.

3.3. As chiral building blocks

Use of enantiomerically pure C_2-symmetric chiral diols as chiral building blocks is not much explored, but opportunities exist. Kim et al. synthesized several enantiopure cyclopentitols **177**, **178**, and **179** and amino cyclopentitol **180** employing oxyselenenylation of cyclopentene with (*R*,*R*)-**1** (Fig. 28).[140]



177 **178** **179** **180**

Figure 28. Representative cyclopentitol derivatives.

4. Concluding remarks

Considerable attention has been focused on the synthesis of a broad range of homochiral C_2-symmetric diols. The syntheses include both chemical and enzymatic strategies. An ideal classical resolution is always a desirable method, since both the enantiomers are made available in multigram quantities. Other synthetic procedures, for example, enantioselective reduction, asymmetric epoxidation, and dihydroxylation, etc. are adopted considering the structure of the diol ligand to be prepared. The ligands having generic structure to a naturally occurring and inexpensive chiral source are very much sought after, for example, TADDOL, which is synthesized by only two steps from tartaric acid. 'Synthesis' and 'Application' of a ligand are symbiotically related terms. Simple and cost effective synthesis enhances the application opportunities of a chiral ligand in asymmetric synthesis. There has been no study that would provide a rationale for the design of a particular chiral diol needed for a given application. The search therefore continues for more diverse structures.

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