Enantioselective desymmetrisation

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1 Introduction

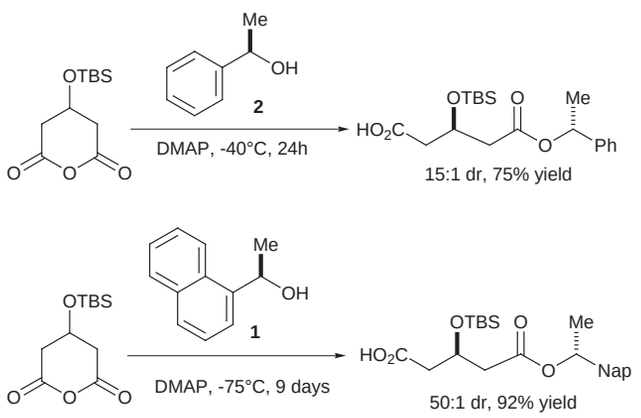
Desymmetrisation of an achiral or *meso* molecule to yield enantiomerically enriched products is proving to be a powerful synthetic tool. In general, to achieve an enantioselective symmetry breaking synthetic operation two enantiotopic functional groups must be differentiated; this can be achieved by the use of a chiral reagent or catalyst. The purpose of the following review is to collect together examples of the reactions, reagents and substrates that can be employed in such an approach. There are numerous examples of such reactions and this review cannot be fully comprehensive, rather, the aim is to highlight the range of transformations that are possible.[1] Where feasible, examples have been selected in which the reaction products are potentially useful synthetic units. Emphasis will be placed on more recent publications. The review will not cover termini differentiation of C_2-symmetric or non-symmetric compounds as this can be achieved by mono-functionalisation or diastereotopic group selection respectively.[2,3] Enzyme mediated desymmetrisations will also not be considered.[4]

2 Desymmetrisation by the formation of C–X bonds (X = O, N, S, Cl, Br)

By far the greatest number of enantioselective desymmetrisations involve the formation of a carbon–heteroatom bond. Perhaps not surprisingly the formation of a carbon–oxygen linkage is the most common bond construction. This section (and later ones) will be further divided according to the structure of the substrate to be desymmetrised.

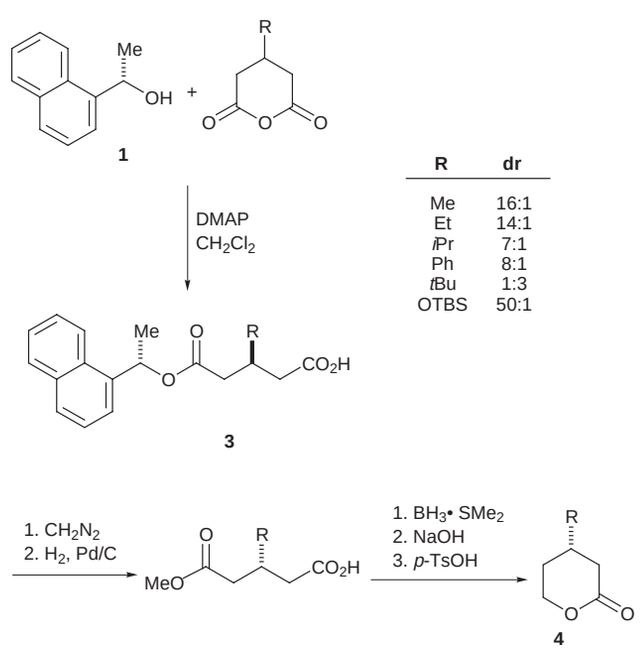
2.1 Anhydride substrates

There have been several reports of the addition of chiral alcohol nucleophiles to cyclic *meso*-anhydrides to deliver diastereomerically enriched mono-ester products.[5,6] One of the most successful systems, reported by Heathcock *et al.*, involves the addition of 1-(1′-naphthyl)ethanol **1** to 3-substituted glutaric anhydrides.[7] Early investigations revealed that far higher levels of diastereoselectivity were obtained using **1** as the nucleophile in preference to 1-(1′-phenyl)ethanol **2** (50:1 *versus* 15:1 diastereoselectivity) (Scheme 1).



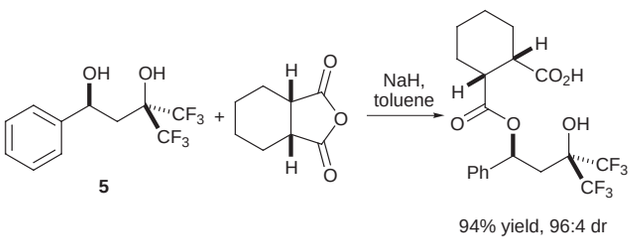
Scheme 1

The system proved to be fairly general and was successfully extended to include a variety of alkyl substituted anhydrides.[8] However, the more sterically encumbered anhydrides resulted in lower selectivities with the *tert*-butyl substituted example delivering the product in which the opposite diastereomer was produced as the major isomer (Scheme 2). The naphthyl esters **3** produced could be routinely converted to the corresponding δ-lactones **4** in an efficient five-step sequence.



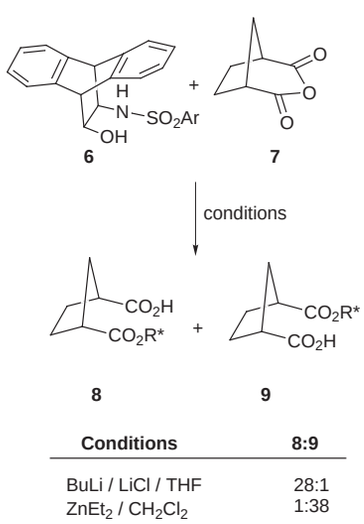
Scheme 2

Taguchi has also developed a system for the diastereoselective opening of *meso*-succinic anhydrides, in this case 1-phenyl-3,3-bis(trifluoromethyl)propane-1,3-diol **5** is used as the chiral nucleophile.[9] To achieve good levels of selectivity it was found necessary to use the sodium salt of the diol and to conduct the reactions in a non-polar solvent. Fused and bicyclic anhydrides are also suitable substrates for this system (Scheme 3).



Scheme 3

An interesting variation on this theme has been reported by Kunieda *et al.*[10] They were able to demonstrate that by using a single enantiomer of chiral amino-alcohol **6** they could selectively obtain either diastereomer of the ring-opened product. Treatment of anhydride **7** with amino-alcohol **6** in the presence of BuLi and LiCl delivered acid **8** as a 28 : 1 mixture of diastereomers (Scheme 4). Reaction of the same two components under the action of $ZnEt_2$ in CH_2Cl_2 delivered the opposite diastereomer **9** as a 38 : 1 mixture of isomers. A similar stereodivergence was observed in the opening of 4-substituted *meso*-glutaric anhydrides although with somewhat lower selectivity.

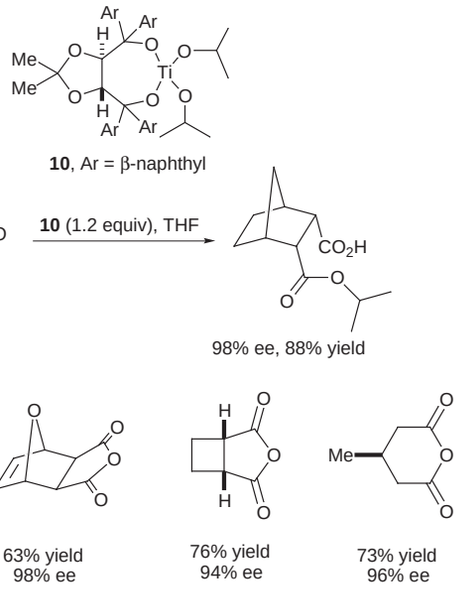


Conditions	8:9
BuLi / LiCl / THF	28:1
$ZnEt_2$ / CH_2Cl_2	1:38

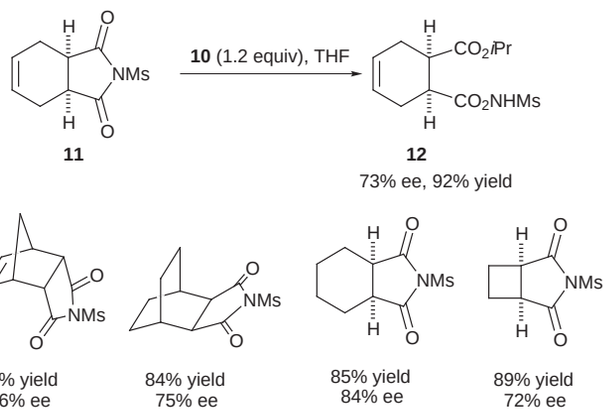
Scheme 4

Several publications dealing with the selective ring-opening of *meso*-anhydrides using chiral amines and amino-esters as nucleophiles have also appeared.[11–13] In a different approach Seebach has reported the enantioselective ring opening of cyclic *meso*-anhydrides using diisopropyloxytitanium TADDOLates (Scheme 5).[14] Unlike all of the previous examples we have considered in which the ring-opened products are obtained covalently linked to a chiral auxiliary, the products from the Seebach system are directly obtained enantiomerically enriched. Treatment of the *meso*-anhydrides with a slight excess of TADDOLate **10** delivered the ring-opened products in uniformly high ee and yield. The system was successfully applied to a range of bicyclic-anhydrides.

More recently Seebach has extended the methodology to include the enantioselective opening of dicarboximides **11** (Scheme 6).[15] The products of ring opening are now the synthetically useful ester-amides **12** although they are produced in



Scheme 5



Scheme 6

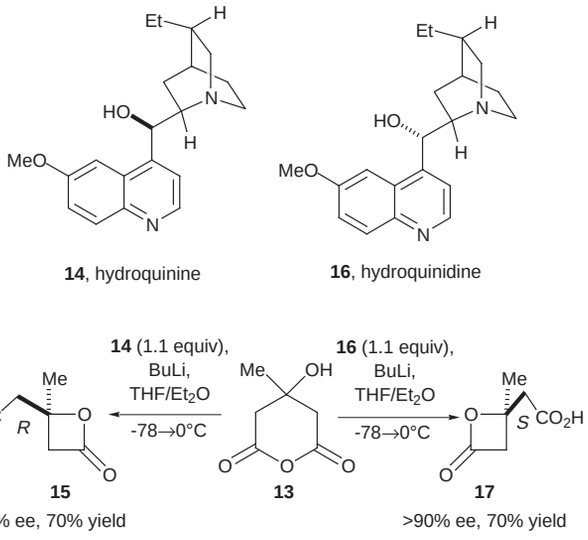
slightly lower ee's than for the corresponding anhydride substrates. However, in almost all cases the ee of the ester-amides could be increased to >99% by a single recrystallisation.

meso-Anhydrides that contain an internal nucleophile have also been investigated in enantioselective ring-opening reactions.[16] Shirahama found that treatment of 3-hydroxy-3-methylglutaric anhydride (HMGA) **13** with a mixture of hydroquinine **14** and butyllithium (1.1 equivalents each) delivered the *R* configured β-lactone **15** in 70% yield and in >90% ee (Scheme 7).[16] Conversely, replacing hydroquinine with hydroquinidine **16** resulted in production of the *S* configured lactone **17** with identical levels of selectivity.

The final example of *meso*-anhydride ring opening we will consider involves the use of *catalytic* amounts of Cinchona alkaloids to promote the addition of methanol to cyclic anhydrides.[17] Aitken *et al.* were able to demonstrate that by using 0.5 equivalents of quinine, the ester-acid **18** could be obtained in 58% ee (Scheme 8).[17] Use of the pseudo-enantiomeric quinidine as the catalyst provided ester-acid **19** of the opposite absolute configuration in 67% ee. Lowering the catalyst loading resulted in a decrease in the enantioselectivity.

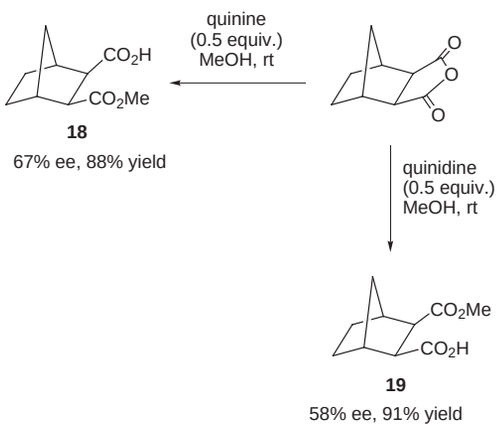
2.2 Epoxide and aziridine substrates

The ready availability of stereochemically defined epoxides from simple alkene precursors has resulted in their becoming a popular substrate for use in desymmetrisation chemistry. Epoxide desymmetrisation has been previously reviewed by Hodgson and readers are referred to this article for a more

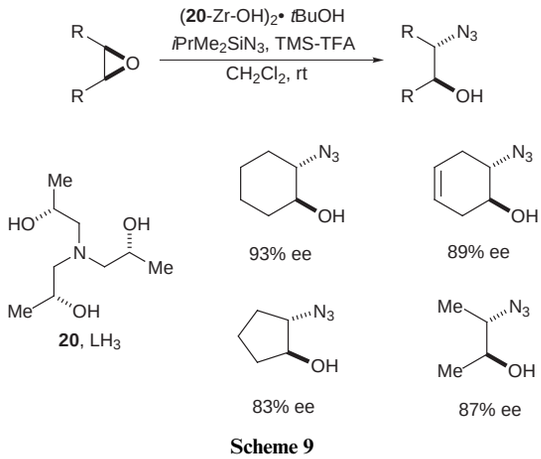


14, hydroquinine **16**, hydroquinidine

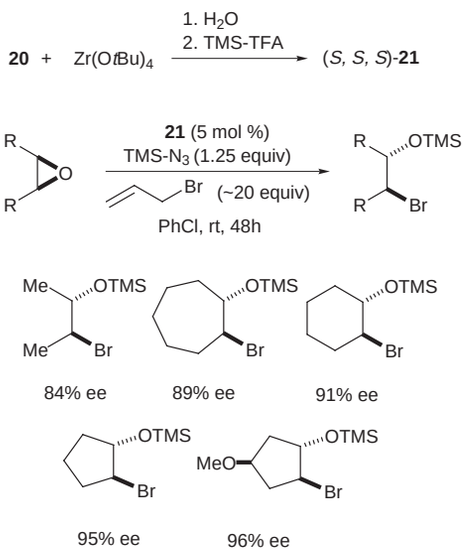
Scheme 7



Scheme 8



Scheme 9



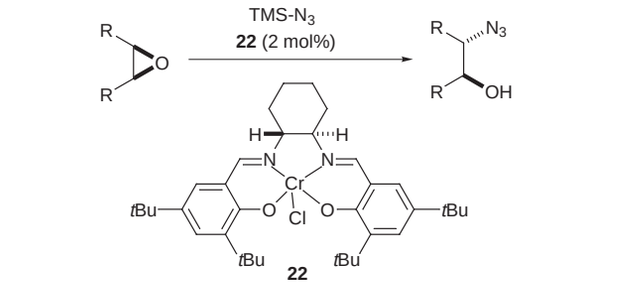
Scheme 10

comprehensive analysis of the subject.[18] The first enantioselective additions of non-carbon nucleophiles to *meso*-epoxides utilised various tartrate–transition metal complexes to catalyse the addition of trimethylsilyl azide ($TMSN_3$).[19,20] These early systems only delivered the ring-opened products with moderate levels of enantioselectivity. More recently Nugent has developed a range of chiral C_3-symmetric zirconium(IV) complexes to catalyse the addition of azide nucleophiles to *meso*-epoxides (Scheme 9).[21] Optimal enantioselectivity was obtained when the bulkier dimethylisopropylsilyl azide was employed as the nucleophile. The reaction could be extended from cyclohexene oxide to encompass a range of cyclic and acyclic epoxides with a particularly notable example being the use of but-2-ene oxide which provided the ring-opened product in an impressive 87% ee.

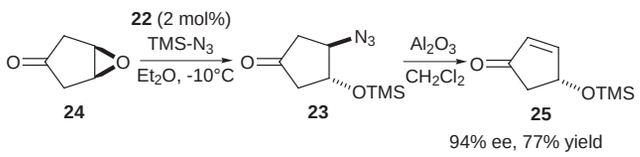
Detailed investigations into the mechanism of the process have recently been published and it has been proposed that a co-operative action of two zirconium centres, one each for the binding and the delivery of the azide to the epoxide, is operating.[22] A key intermediate in the proposed mechanism is a zirconium bound azide species that is responsible for the delivery of the azide nucleophile to the activated epoxide. It was proposed that if the metal-bound azide could be replaced by an alternative metal-bound nucleophile then this would be preferentially delivered to the epoxide. The successful realisation of this hypothesis resulted in the development of methodology for the enantioselective addition of the bromide ion to *meso*-epoxides.[23] The reaction conditions involve treating the relevant epoxide with the catalyst, $TMSN_3$ (1.25 equivalents) and an excess of allyl bromide (Scheme 10). The reaction is believed to proceed by the transformation of an initially formed azide–zirconium species in to a bromide–zirconium species, which is then delivered to the activated epoxide. The formation of an equivalent amount of allyl azide during the reaction supports this notion. These conditions were effective for the production of a range of highly enantiomerically enriched protected β-bromohydrins. The composition of the zirconium catalyst used in these studies varies slightly from the previous examples although tridentate ligand **20** is still employed.

Jacobsen and co-workers have also developed a highly selective system for the addition of azide nucleophiles to *meso*-epoxides.[24] The C_2-symmetric chromium(III) salen complex **22** catalyses the addition of $TMSN_3$ to *meso*-epoxides at room temperature and with catalyst loadings of only 2 mol% (Scheme 11). Significantly, the reaction can also be conducted in solvent free conditions without any deleterious effects upon the enantioselectivity of the process. The solvent free conditions were also used to demonstrate an efficient catalyst recycling procedure in which a single catalyst sample could be reused up to five times without significant variation in enantioselectivity or yield.

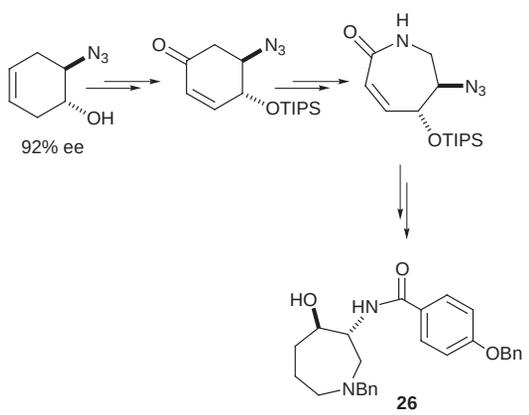
The azido protected alcohol **23** produced from the enantioselective ring opening of epoxide **24** has been converted in a single step to the key prostaglandin precursor **25** (Scheme 12).[25] Simply stirring the azido-alcohol with aluminium oxide in dichloromethane produced the enone **25** in 77% yield with a 94% enantiomeric excess. A second illustration of the synthetic utility of the chiral azido-alcohols produced in these ring-opening reactions is the facile preparation of cyclic amine **26**. The preparation of which represents a formal total synthesis of balanol (Scheme 13).[26] Similar azido-alcohols have



Scheme 11



Scheme 12



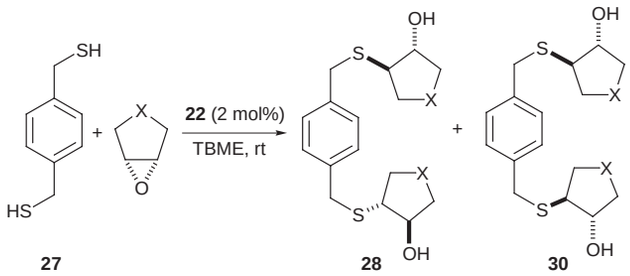
Scheme 13

been utilised in an enantioselective synthesis of carbocyclic nucleoside analogues.[27]

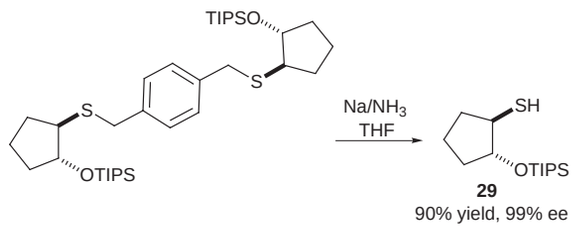
Mechanistic investigations by the Jacobsen group have also demonstrated that the reaction proceeds by activation of both the nucleophilic and electrophilic components in a bimetallic enantioselectivity-determining step.[28]

Jacobsen has employed the same chromium(III) salen complex to promote the addition of thio-nucleophiles to *meso*-epoxides.[29] However, the use of simple mono-thiols such as phenylmethanethiol resulted in desymmetrised products of only moderate ee. An ingenious solution was found in the use of dithiols as nucleophiles. Thus, treatment of a range of cyclic *meso*-epoxides with *p*-xylene-α,α′-dithiol **27** produced the ring-opened products **28** with excellent levels of selectivity (Scheme 14). The hydroxy-sulfide products could be reduced to the corresponding protected-hydroxy-thiols **29** under the action of sodium in ammonia. The high ee's obtained for the C_2-symmetric sulfides **28** is a consequence of the production of significant amounts of the *meso*-compounds **30**.

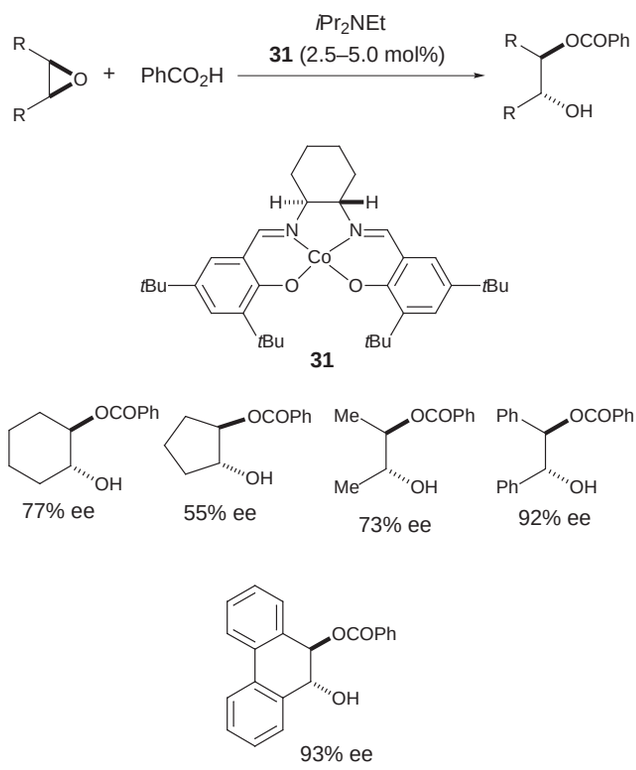
The related cobalt(II) salen complex **31** has been shown to be an effective catalyst for the enantioselective delivery of carboxylic acid nucleophiles to *meso*-epoxides.[30] The chromium(III) complex used to catalyse the addition of the azide and thiol nucleophiles yielded the ring opened products but with only moderate enantioselectivity. The reaction could be successfully applied to a range of epoxides to deliver the mono-protected diol products in good to excellent ee (Scheme 15). It has been



X	yield	28:30	28 ee (%)
CH_2CH_2	95	1.8:1	85
CH_2	95	2.8:1	93
N-BOC	84	2.1:1	89
O	69	2.2:1	91



Scheme 14

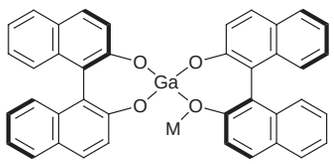


Scheme 15

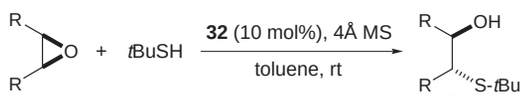
demonstrated that the Co(II) complex **31** acts as a precatalyst, with a Co(III) species being the true catalyst. The optimum reaction conditions involve preparing the Co(III) complex *in situ* by stirring the Co(II) complex with the carboxylic acid under an oxygen atmosphere for 30 minutes prior to addition of the base and epoxide.

Shibasaki has designed a range of heterobimetallic complexes that function as catalysts in the enantioselective ring-opening of *meso*-epoxides with non-silylated nucleophiles. The initial report focused on the enantioselective addition of thiols to *meso*-epoxides.[31] Reaction of cyclohexene oxide with 2-methylpropane-2-thiol in the presence of 10 mol% of the gallium·lithium·bis(binaphthoxide) complex **32** at room tem-

perature provides the hydroxy sulfide **34** in 80% yield and with an enantiomeric excess of 98% (Scheme 16). The presence of 20 mol% of 4 Å molecular sieves was found to be crucial to obtain good yields of the ring-opened products. The process proved to be applicable to a range of cyclic epoxides with the products being obtained with consistently high enantiomeric excesses. The one acyclic example reported provided the hydroxy sulfide in 82% ee.



32, M = Li
33, M = Na



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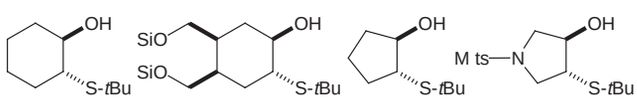
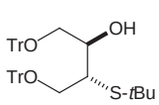


Si = Si*t*Bu(Ph)$_2$

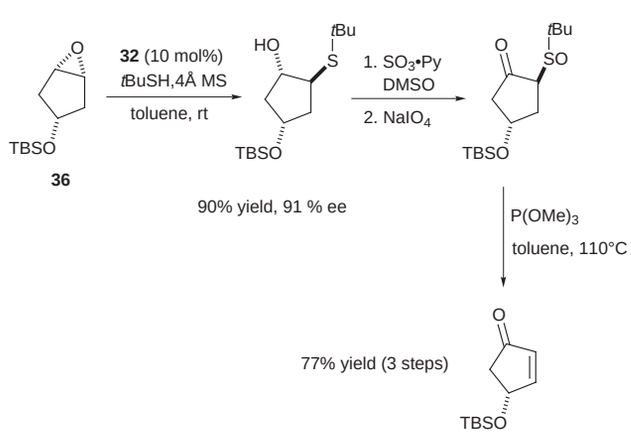
98% ee 96% ee 91% ee 89% ee



82% ee

Scheme 16

The mechanistic hypothesis for the reaction involves the gallium centre acting as a Lewis acid and activating the epoxide combined with lithium binaphthoxide functioning as a Lewis base and activating the thiol. The synthetic utility of Shibasaki's system has been demonstrated in a concise synthesis of the prostaglandin precursor **35** (Scheme 17). The crucial ring opening of substituted cyclopentene oxide **36** was achieved in 90% yield with 91% ee.



36

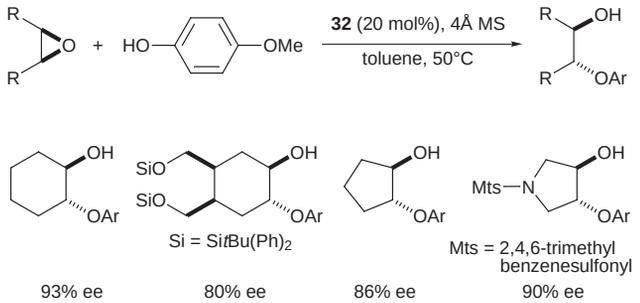
90% yield, 91 % ee

77% yield (3 steps)

35

Scheme 17

Shibasaki has also investigated the use of alcohol nucleophiles.[32] Addition of 4-methoxyphenol to cyclohexene oxide in the presence of 20 mol% of gallium complex **32** provided the mono-protected diol product in 93% ee (Scheme 18). Slightly higher temperatures (50 °C) were needed with the oxygen nucleophiles compared to the sulfur analogues.



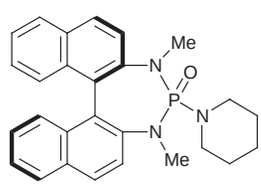
Si = Si*t*Bu(Ph)$_2$

Mts = 2,4,6-trimethyl benzenesulfonyl

93% ee 80% ee 86% ee 90% ee

Scheme 18

The examples of catalysed epoxide ring opening that we have so far considered have all involved some form of Lewis acidic activation of the epoxide. The final study we will examine involves the enantioselective addition of chloride ion to *meso*-epoxides catalysed by a formal Lewis base. The system, developed by Denmark, involves the reaction of silicon tetrachloride with a *meso*-epoxide in the presence of the chiral phosphoramide **37** (10 mol%) at −78 °C (Scheme 19).[33] The ring-opened chlorohydrin products **38** were obtained with moderate to good levels of enantioselectivity, with the acyclic substrates providing the highest levels of selectivity. Cyclohexene oxide was the only cyclic epoxide to display significant levels of enantioselectivity.



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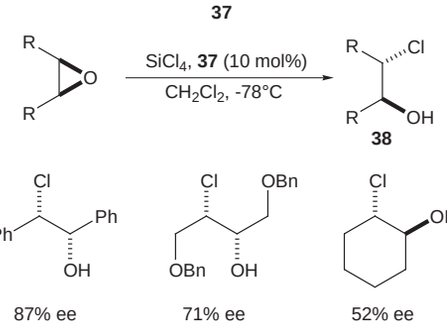


38

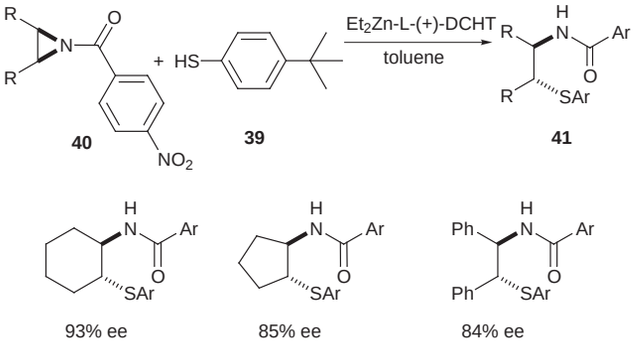
87% ee 71% ee 52% ee

Scheme 19

The enantioselective openings of *meso*-epoxides with stoichiometric amounts of *B*-halodiisopinocampheylboranes has been reported.[34] The 1,2-halohydrin products were obtained with moderate to good enantioselectivity. Chiral selenium nucleophiles have also been used in the asymmetric ring-opening of *meso*-epoxides.[35]

There are far fewer examples of the enantioselective ring-opening of *meso*-aziridines. Oguni has reported a system that allows the selective addition of *p*-*tert*-butylbenzenethiol **39** to *p*-nitrobenzoyl-protected *meso*-aziridines **40** in the presence of a Zn-dicyclohexyl tartrate complex to deliver enantiomerically enriched amino-sulfides **41** (Scheme 20).[36,37] A stoichiometric amount of the chiral complex is required to obtain high levels of enantioselectivity. The structure of the thiol and of the aziridine protecting group are both essential to obtain high enantioselectivity. The system as described was effective in the addition to cyclohexene oxide (93% ee) and cyclopentene oxide (83% ee) and to *cis*-styrene oxide (84% ee).

The reaction of *meso*-cyclic epoxides with a strong base can lead to the formation of two distinct rearrangement products. β-Deprotonation leads to the formation of allylic alcohols, while α-deprotonation of medium ring derived epoxides generally provides bicyclic alcohols. Section 5 briefly documents

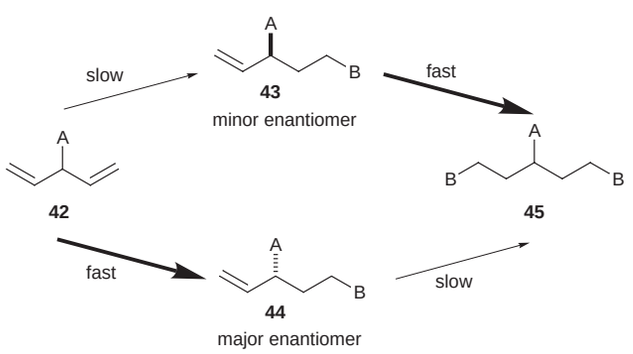


Scheme 20

these areas. The vitamin B_{12} catalysed rearrangement of *meso*-epoxides and aziridines leading to enantio-enriched products has also been reported.[38,39]

2.3 Alkene and diene substrates

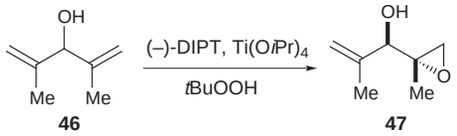
The desymmetrisation of *meso*-dienes by enantioselective epoxidation has received considerable attention.[40,41] One attractive feature of such an approach is the possibility of combining an initial enantioselective reaction with a subsequent kinetic resolution leading to the formation of products with extremely high enantiomeric excess. The basic concept is illustrated graphically, for a hypothetical reaction of an alkene, in Scheme 21. The *meso*-diene **42** is subjected to an enantioselective reaction leading to the production of the two enantiomers of the product **43** and **44**. The rate of formation of the major enantiomer will be greater than the minor (if any is produced). Both enantiomers **43** and **44** contain a second alkene unit that is capable of further reaction. If this second reaction occurs then the alkene of the minor enantiomer **43** is the favoured alkene and as such will be transformed into the double reaction product **45** at a rate faster than the initially formed major enantiomer. The longer the reaction is allowed to continue the higher the ee of the remaining mono-reaction product will be. This selective destruction of the minor enantiomer has been shown to allow the production of materials with extremely high ee.[42,43]



Scheme 21

Schreiber has been instrumental in utilising the Sharpless asymmetric epoxidation to desymmetrise *meso*-dienes. Such a system allows for the selective destruction of the minor enantiomer *via* a kinetic resolution, however, in the case of the Sharpless epoxidation the system is more complex as the reaction leads to the formation of new stereogenic centres (the epoxide bearing atoms). Mathematical models have been formulated to account for the exceptional selectivity that can be obtained in such a system.[44]

Subjection of the simple diene **46** to standard Sharpless conditions leads to the formation of enantiomerically enriched epoxide **47** (Scheme 22). Schreiber illustrated that as the reaction time increases so does the amount of di-epoxides

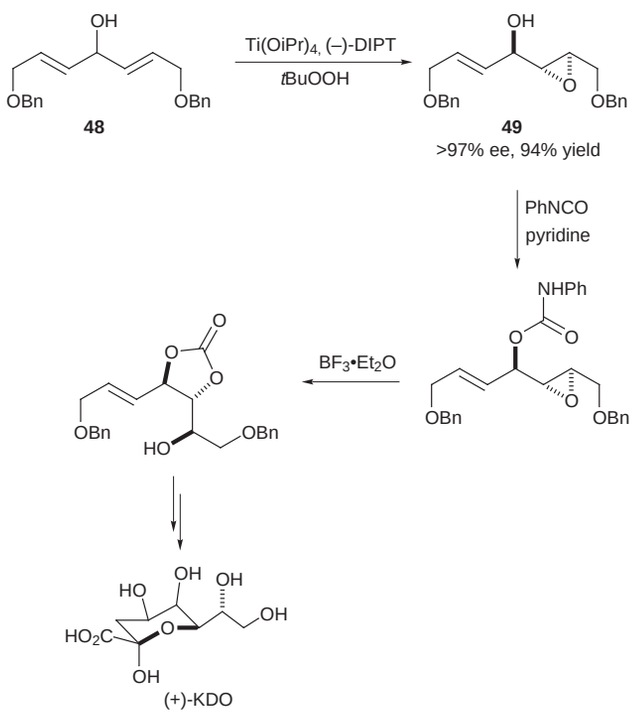


Time (h)	ee (%)	de (%)
0.5	88	99
1.0	94	99
1.5	99.3	99

Scheme 22

produced with the consequence that the ee of mono-epoxide **47** increases.

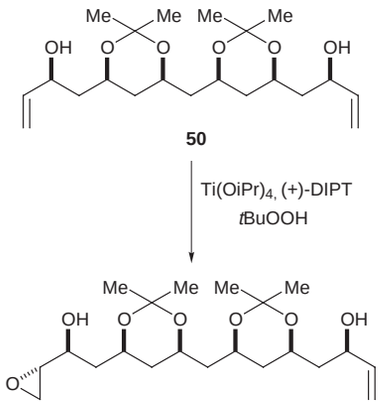
This approach has been applied to a wide range of diene substrates and the synthetic utility of the epoxides produced amply demonstrated. For example, desymmetrisation of diene **48** produced the required mono-epoxide **49** in 94% yield and >98% ee (Scheme 23). Mono-epoxide **49** was advanced through several steps to complete an enantioselective synthesis of KDO (2-deoxy-D-*manno*-2-octulosonic acid).[40]



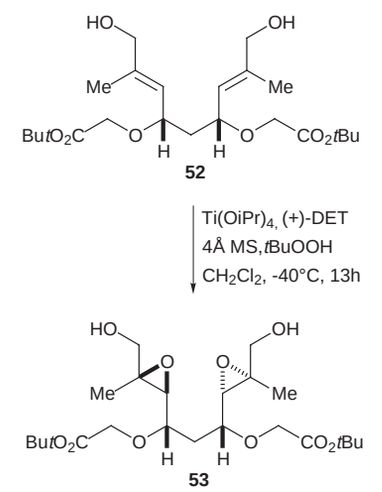
Scheme 23

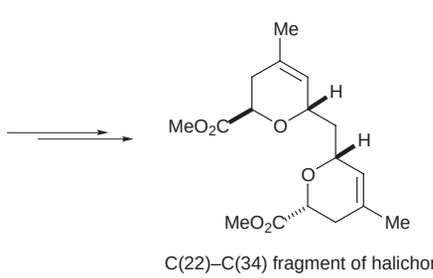
The key desymmetrisation in the synthesis of KDO established the absolute configuration of two stereocentres in a single step. The enantioselective epoxidation strategy can also be applied to significantly more complex dienes leading to the production of multiple stereocentres. The selective epoxidation of diene **50** is an example of such a case; treatment of **50** under standard Sharpless conditions leads to the production of mono-epoxide **51** in which the configuration of seven stereocentres are established in 81% yield and >98% ee (Scheme 24). Similar desymmetrisation strategies have been applied in the synthesis of several natural products, including citreoviridin,[45] FK506[46] and prostaglandin intermediates.[47]

Burke has also employed a Sharpless epoxidation in the desymmetrisation of an advanced synthetic intermediate, although in this example the double epoxidation product was required.[48] Treatment of *meso*-diene **52** with the Sharpless reagents provided the desymmetrised bis-epoxide **53** in 81% yield with "high diastereo- and enantiomeric purity" (Scheme 25). The bis-epoxide was advanced to a C(22)–C(34) fragment of halichondrin.



Scheme 24

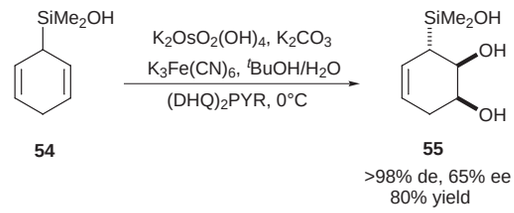




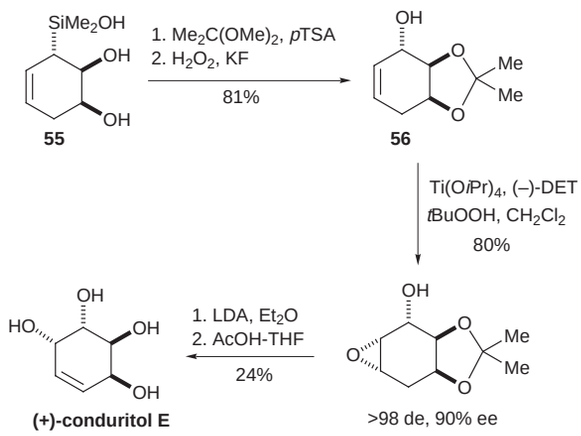
Scheme 25

The use of the Sharpless asymmetric dihydroxylation (AD) to effect the desymmetrisation of a *meso*-diene intermediate in a synthesis of (+)-conduritol E has recently been reported.[49] Landais has pioneered the use of the AD reaction to selectively produce enantiomerically enriched diols from silyl-substituted cyclohexadienes **54** (Scheme 26).[49] Treatment of diene **54** under modified AD conditions provided diol **55** in good yield with 65% enantiomeric excess and excellent diastereoselectivity. The authors found that the use of the $(DHQ)_2PYR$ (DHQ = dihydroquinone, PYR = diphenylpyrimidine) ligand was necessary to obtain these levels of enantioselectivity; this correlates well with reported oxidations of closely related substrates.

The enantiomerically enriched diol **55** was advanced through five steps to provide (+)-conduritol E (Scheme 27). The enantiomeric excess was increased from the 65% realised after the initial desymmetrising AD by the use of a Sharpless asymmetric epoxidation of allylic alcohol **56**. The natural product was eventually produced with >99% ee.

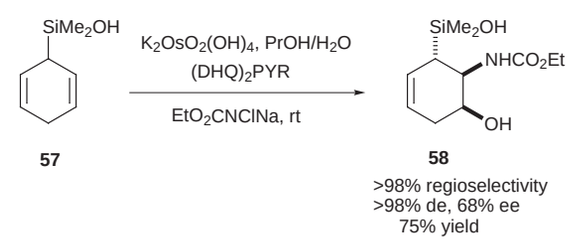


Scheme 26



Scheme 27

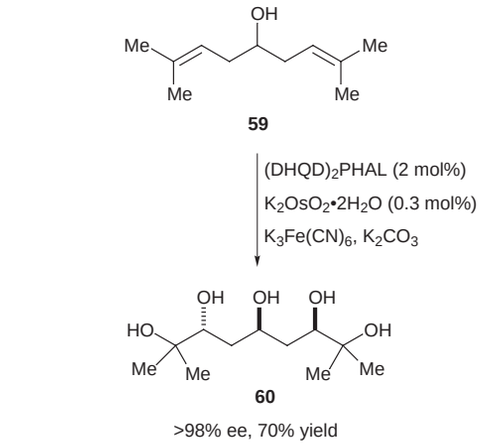
Related approaches have utilised the AD desymmetrisation of dienes similar to **54** in the synthesis of carba-sugars and palitantin.[50] Landais has also developed the Sharpless asymmetric aminohydroxylation (AA) as a desymmetrising tool. Reaction of dienylsilane **57** under the AA conditions provided amino alcohol **58** with excellent levels of regio- and diastereoselectivity and in reasonable ee (69%) (Scheme 28).[51] Amino alcohol **58** has been utilised in the synthesis of a fortamine precursor and in the synthesis of amino-carba-sugars. In both cases the enantiomeric excess of the synthetic material could be increased to "enantiomeric purity" by a single recrystallisation of a later intermediate.

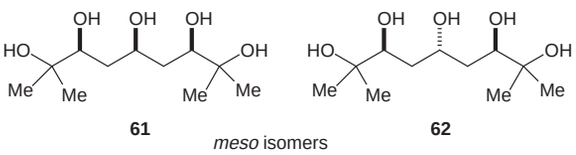


Scheme 28

The use of a desymmetrising Sharpless AD reaction to provide access to polyols has also been explored. Belley has shown that application of the AD reaction to substituted dienes such as **59** can provide enantiomerically enriched pentols *via* two selective dihydroxylation reactions (Scheme 29).[52] The required pentol **60** is produced in good yield (70%) and selectivity (>98% ee) along with the two possible *meso* isomers **61** and **62**. The selectivity of the process proved to be highly substrate dependent, in particular the presence of substitution β to the initial hydroxy group led to low selectivity.

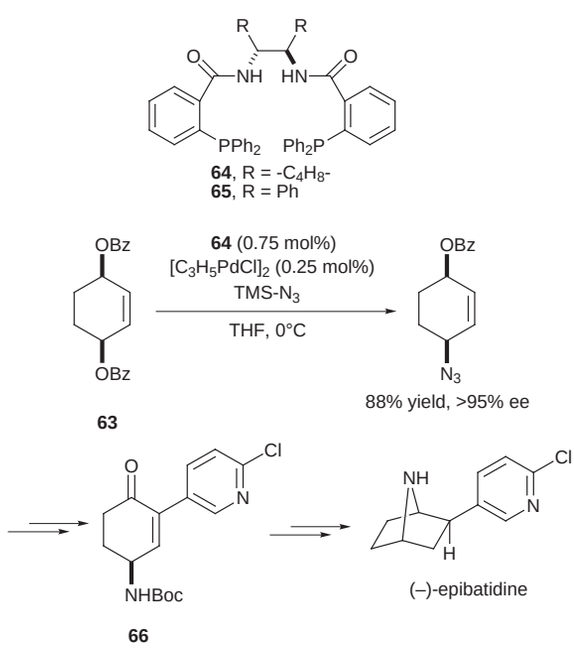
There is a considerable body of work dealing with the desymmetrisation of *meso*-2-ene-1,4-diols *via* π-allyl palladium intermediates. Trost and his group have been pioneers in this field and two excellent examples of the power of such a strategy are their syntheses of (−)-epibatidine and (−)-neplanocin. Treatment of *meso*-dibenzoate **63** with TMS-N_3 and the catalyst derived from diphosphine **64** and allyl palladium chloride dimer provides the mono-substituted product in 88% yield and >95% ee (Scheme 30).[53] The azide containing product is



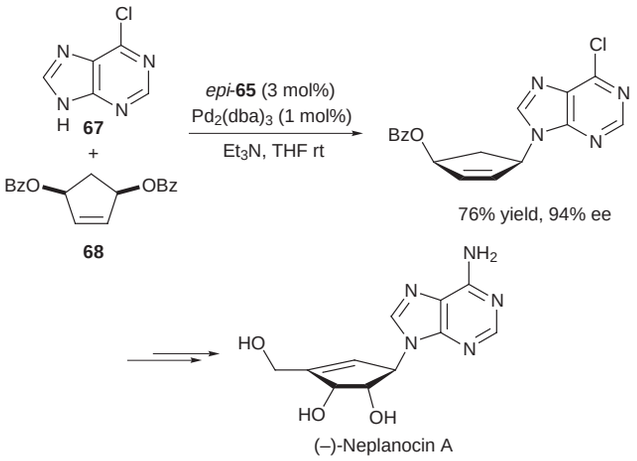


60:**61**:**62**, 53:16:1

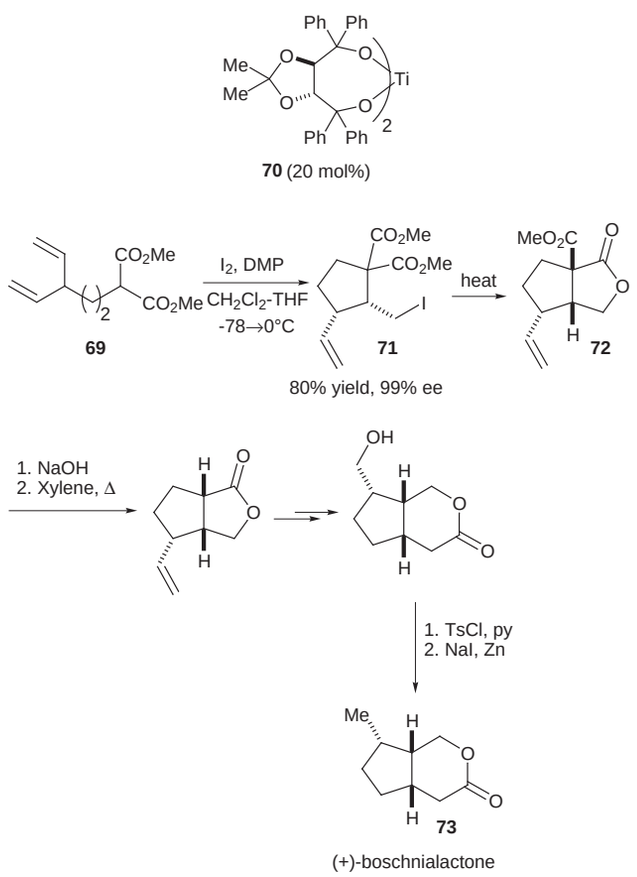
Scheme 29



Scheme 30



Scheme 31



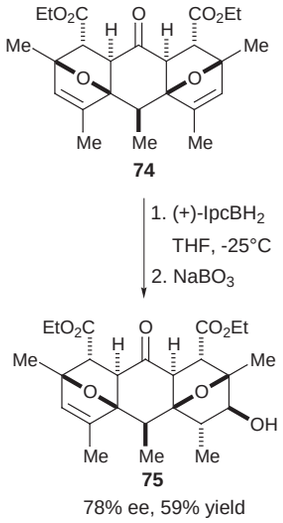
Scheme 32

converted first into ketone **66** and ultimately to (−)-epibatidine. The nitrogen nucleophile is not restricted to azide; use of 6-chloro-9*H*-purine **67** as the nucleophilic component has been exploited in a synthesis of (−)-neplanocin. Thus, treatment of cyclopentene-dibenzoate **68** with the heterocyclic nucleophile in the presence of ligand **65** and $Pd_2(dba)_3$ provides the mono-substituted product in excellent yield and enantioselectivity (76% yield, 94% ee) (Scheme 31).[54] Conversion to the natural product is accomplished in short order. *meso*-Biscarbamates are also excellent substrates for similar desymmetrisations.[55]

Taguchi and co-workers have developed a desymmetrising iodocarbocyclisation of bisalkenylated malonates.[56] Treatment of *meso*-malonate **69** with 20 mol% of Ti-TADDOLate **70**, iodine and 2,6-dimethoxypyridine yields cyclopentane **71** in 80% yield and in an excellent 99% ee (Scheme 32). Heating **71** causes displacement of the iodide to provide lactone **72** in excellent yield. The methodology was successfully extended to provide products in which the alkene substituent is situated in the remaining two positions of the cyclopentane ring. Lactone **72** was used in a short synthesis of (+)-boschnialactone **73**.

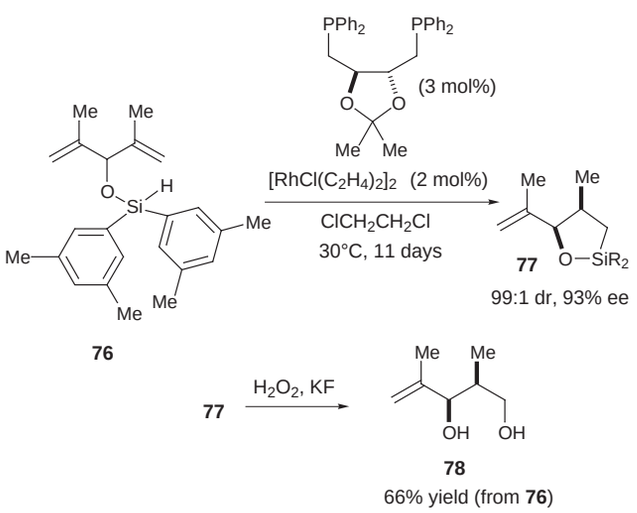
The use of chiral alkyl boranes to desymmetrise *meso*-dienes has been known for some time.[57] Vogel utilised a selective mono-hydroboration of *meso*-diene **74** in his approach towards the preparation of long-chain polypropionate fragments (Scheme 33).[58] Treatment of **74** with (+)-$IpcBH_2$ (isopinocampheylborane) followed by oxidative work-up provided alcohol **75** in 59% yield with 78% ee. Hodgson has recently reported a carbamate-directed enantioselective hydroboration *en-route* to the synthesis of 1-aminocyclopentane-1,3-dicarboxylic acid.[59]

A catalysed intramolecular hydrosilylation of achiral dienes using a Rh(I)-DIOP {4,5-bis[(diphenylphosphino)methyl]-2,2-dimethyl-1,3-dioxolane} complex followed by oxidative work-up has been used to prepare enantiomerically enriched diols.[60] For the desymmetrisation of protected di(prop-2-enyl)meth-



Scheme 33

anol **76** the optimum conditions involved reaction with the Rh(I) complex (2 mol%) in DCE at 30 °C for 11 days. Using such a procedure delivered cyclic silane **77** in 93% ee and 98% de (Scheme 34). Treatment with hydrogen peroxide provided diol **78** in 66% yield over the two steps. The use of the bulky bis(3,5-dimethylphenyl) substituted silane was crucial in achieving this high selectivity as less sterically demanding silanes delivered material of significantly lower ee. A similar procedure was also applied to a derivative in which the Me substituents of **76** were replaced with OMEM groups; in this case use of a Rh(I)-BINAP complex delivered the desymmetrised product in 70% ee.

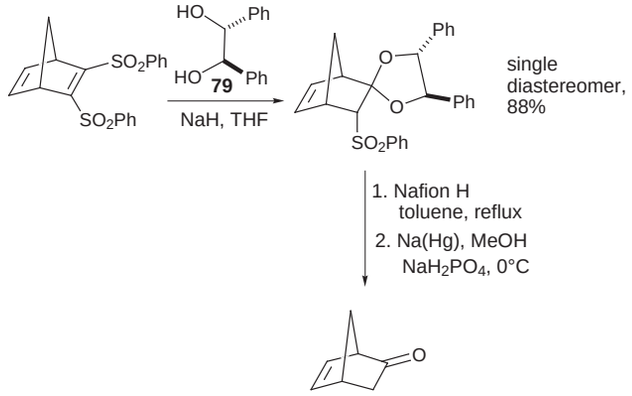


Scheme 34

The base promoted addition of a C_2-symmetric diol has been employed to effectively desymmetrise 1,2-disulfonyl substituted alkenes.[61] Optimum selectivity was obtained when (1*R*,2*R*)-1,2-diphenylethane-1,2-diol **79** was employed as the chiral diol delivering the acetal products as single isomers in good yields (Scheme 35). Acetal cleavage followed by desulfonylation allows access to bicyclic ketones.

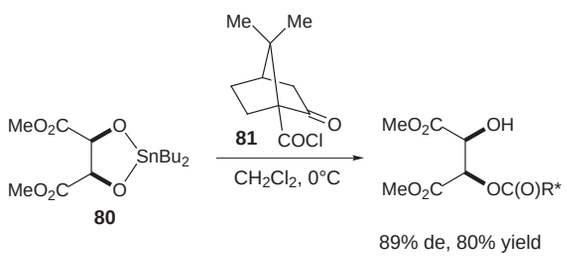
2.4 Diol and polyol substrates

The ready availability of *meso*-diols by the *cis*-dihydroxylation of suitable alkenes has established them as popular substrates for enantioselective desymmetrisation studies. In an early report Mukaiyama disclosed the enantioselective acylation of *meso*-diols *via* the formation of tin acetals.[62] For example, reac-



Scheme 35

tion of the tartrate-derived *meso*-tin acetal **80** with d-ketopinic acid chloride **81** in methylene chloride at 0 °C provided the mono-acylated product in good yield and an impressive 89% de (Scheme 36). Unfortunately the system proved to be highly substrate dependent and high ee's were only obtained with a limited number of substrates.

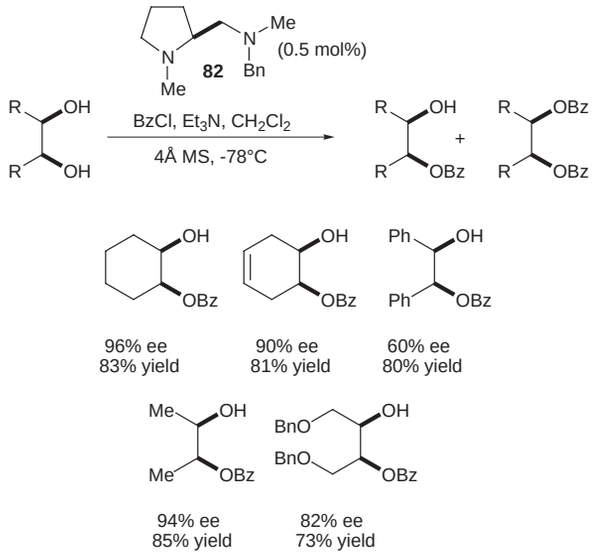


Scheme 36

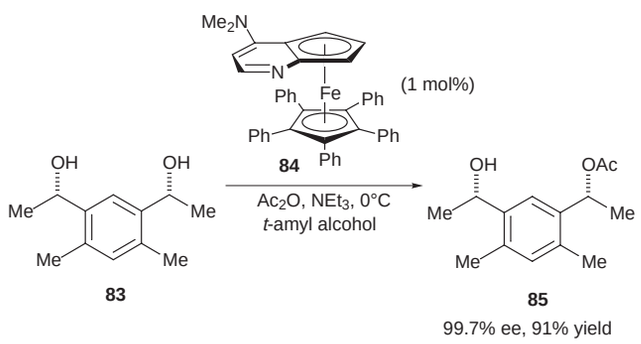
The Oriyama group have recently disclosed a *catalytic* asymmetric acylation of *meso*-diols.[63,64] The optimised system involves reacting the *meso*-diol with benzoyl chloride and a chiral diamine **82** (0.5 mol%) in the presence of an equivalent of triethylamine (Scheme 37). The reaction is conducted in methylene chloride at −78 °C and the presence of 4 Å MS was found to be crucial to reduce reaction times. The mono-acylated diols are produced in excellent yields and enantioselectivities, for example, *cis*-cyclohexanediol provides the mono-acylated product in 83% yield with 96% ee. The reaction could be extended to a variety of diols, of particular note is the acylation of *cis*-butane-2,3-diol which yields the mono-acylated product in 85% yield with 94% ee. The reaction is proposed to proceed *via* activation of the acid chloride by the chiral diamine.

Fu has also recently reported a catalytic enantioselective acylation of *meso*-diols.[65] The Fu system employs a chiral nucleophilic catalyst to facilitate the acylation. Reaction of diol **83** with acetic anhydride and triethylamine in the presence of only 1 mol% of the planar-chiral derivative of DMAP **84** provides the mono-acylated diol **85** in good yield (91%) and an excellent 99.7% ee (Scheme 38). The chiral DMAP derivative **84** has also been successfully used as an acylation catalyst in kinetic resolution of secondary alcohols.

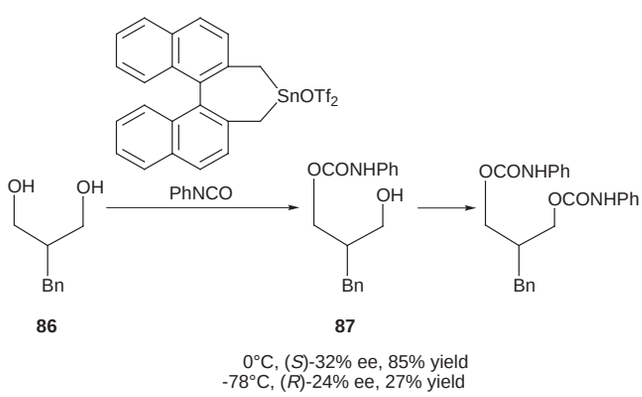
An enantioselective carbamate synthesis resulting from the desymmetrisation of an achiral diol has recently been reported. The sense of absolute asymmetric induction has been shown to be temperature dependent.[66] The system under study was the Sn-BINOL catalysed addition of phenyl isocyanate to diol **86** (Scheme 39). When the reaction is performed at 0 °C the (*S*)-configured mono-carbamate **87** was produced in 85% yield and 32% ee. Lowering the reaction temperature to −78 °C produced the (*R*)-carbamate in 24% ee. If the reaction was performed at −47 °C racemic mono-carbamate was produced. The enantioselectivity–temperature dependence was shown to exhibit a



Scheme 37



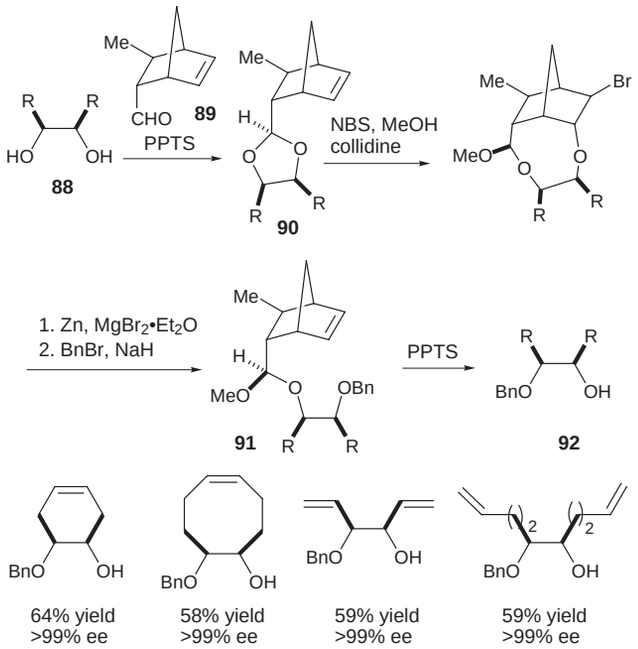
Scheme 38



Scheme 39

linear relationship. The moderate yields are a consequence of the production of the dicarbamate product. Although the selectivities reported in this study are not high, it illustrates how both enantiomers of a product are accessible from a single enantiomer of catalyst simply by altering the reaction temperature.

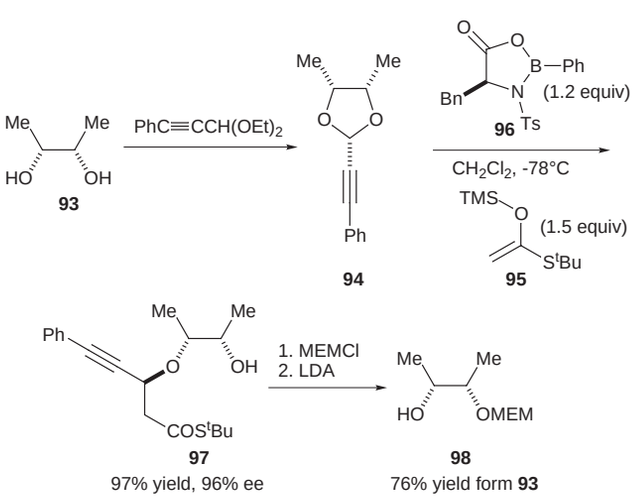
The Fujioka group utilise the selective formation of an ene-acetal to achieve an efficient reaction cycle equivalent to the mono-alkylation of a *meso*-diol.[67] The multi-reaction system is illustrated in Scheme 40 with the overall transformation being represented by diol **88**→alcohol **92**. Reaction of *meso*-diols with aldehyde **89** leads to the formation of ene-acetal **90** as "essentially a single isomer". Bromination followed by elimination and alkylation provides acetal **91** which is cleaved under the action of PPTS to yield the free alcohol **92**. The system tolerates saturated and unsaturated diols and despite being a



Scheme 40

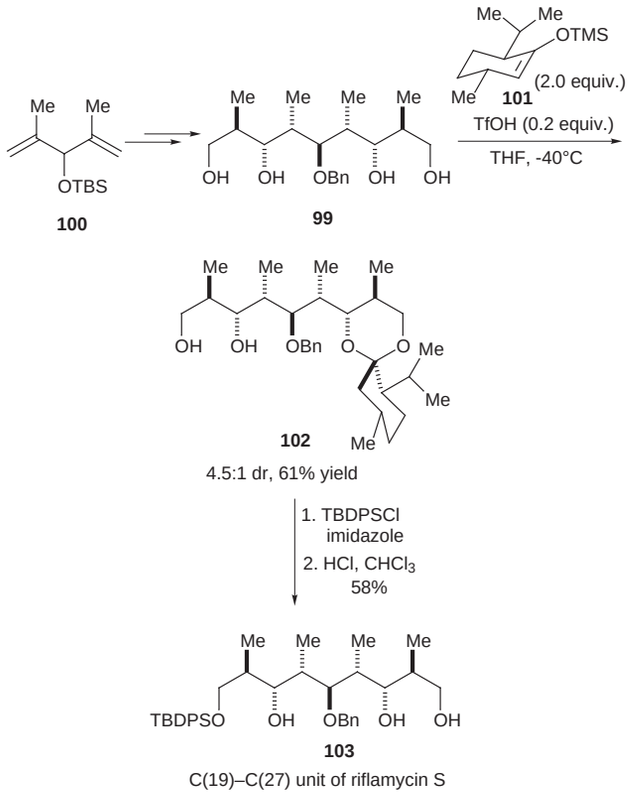
multi-step procedure provides the desymmetrised products in reasonable yield with excellent enantioselectivity.[68]

Harada has also developed an efficient multi-step procedure for the production of enantiomerically enriched mono-protected diols. The *meso*-diols **93** are initially converted to the corresponding *meso*-acetals **94** which are then treated with thio silyl ketene acetal **95** in the presence of a stoichiometric amount of chiral boron Lewis acid **96** (Scheme 41).[69,70] For the butane-1,2-diol-derived acetal the ring-cleavage product **97** is isolated in 97% yield and 96% enantioselectivity. MEM protection of the free hydroxy group followed by deprotection of the alternative hydroxy group, *via* β-elimination, delivers the mono-MEM-protected diol **98** in 76% yield from the starting diol. The process is general for a range of diols including cyclic and acyclic examples. The process has also been extended to include the desymmetrisation of *meso*-tetraols.[71]



Scheme 41

The Harada group have also pioneered the use of menthone in selective acetal and ketal formation from *meso*-diols.[72,73] A particularly impressive example is the enantioselective desymmetrisation of *meso*-tetraol **99** (Scheme 42).[74] The tetraol was prepared using a two-directional strategy starting from diene **100**. Reaction of **99** with menthone TMS enol silane **101** in the presence of triflic acid provides ketal **102** in 61% yield with



Scheme 42

good diastereoselectivity. Silylation of the terminal hydroxy group followed by HCl mediated ketal cleavage provided triol **103** which corresponds to the C(19)–C(27) unit of riflamycin S.

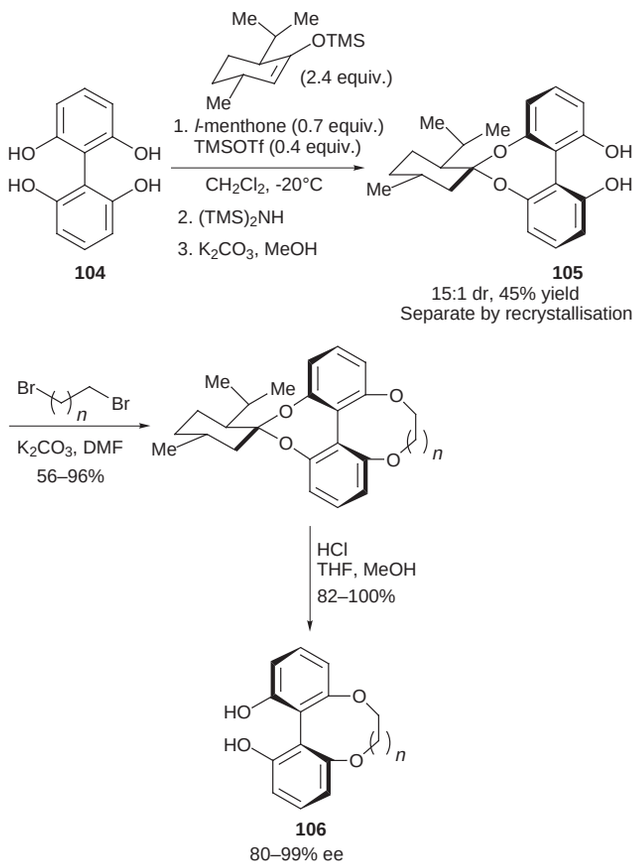
Menthone has also been applied to the desymmetrisation of axially chiral compounds.[75] For example, reaction of achiral bis-catechol **104** with menthone TMS enol silane and TMSOTf followed by silylation, separation of the diastereomers and desilylation provides axially chiral diol **105** in 45% yield as a single diastereomer (Scheme 43). The ketalisation reaction provides a 15 : 1 mixture of diastereomers before purification. Diol **105** is advanced *via* cyclic ether formation and ketal hydrolysis to provide the chiral cyclic ethers **106** in high ee.

The enantioselective desymmetrisation of glycerol by the formation of a chiral dispiroketal derivative has been reported by Ley.[76] Reaction of glycerol with the C_2-symmetric dimethyl bis-dihydropyran derivative **107** with a catalytic amount of CSA in toluene provided dispiroketal **108** as a single isomer in 96% yield (Scheme 44). The selective formation of **108** is accounted for by multiple anomeric effects and the absolute configuration of the methyl groups on the pyran rings which adopt equatorial arrangements. Benzyl protection of the free hydroxy group of **108** provides benzyl ether **109**, which, when treated with glycerol and CSA liberates mono-protected glycerol **110** and regenerates dispiroketal **108**. Thus completing an efficient glycerol desymmetrisation cycle.

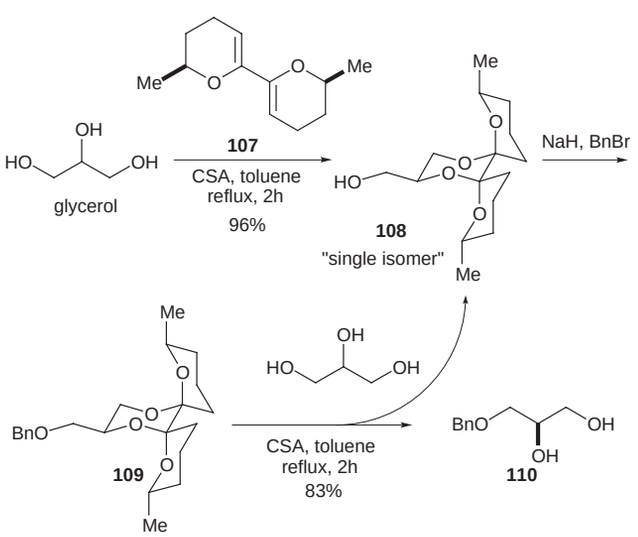
Chiral bis-dihydropyran derivatives have also been employed in the desymmetrisation of more complex polyols.[77] For example, treatment of bis-silyl protected pentol **111** with tetrahydrobipyran **107** and CSA in chloroform yields dispiroketal **112** as a single isomer in good yield (Scheme 45). Desilylation, perbenzylation and dispiroketal cleavage (TFA–H_2O) provided the protected desymmetrised pentol **113** in good yield and high enantiomeric purity (>95% ee).

2.5 Miscellaneous substrates

An asymmetric version of the Beckmann rearrangement has been developed by Aubé and co-workers and applied to the desymmetrisation of a range of prochiral ketones.[78] Such an approach was applied to the enantioselective synthesis of



Scheme 43



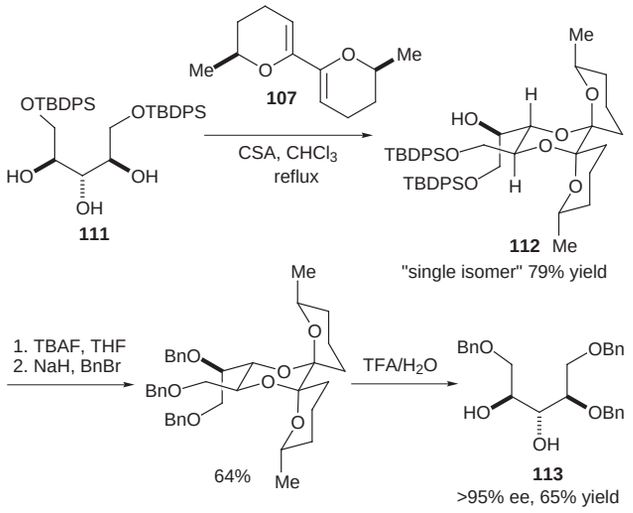
Scheme 44

several indole alkaloids.[79] As an advancement of this system Aubé has investigated the use of asymmetric Schmidt rearrangements as desymmetrising tools.[80] For example, treatment of 4-*tert*-butylcyclohexanone **114** with chiral azido alcohol **115** in the presence of $BF_3{\cdot}OEt_2$ followed by treatment with $NaHCO_3$ provided the seven-membered lactam **116** as a single diastereomer (Scheme 46). A two step oxidation (PCC) and β-elimination sequence (NaH) yielded the enantiomerically enriched lactam **117**. This represented the first example of an asymmetric Schmidt reaction.

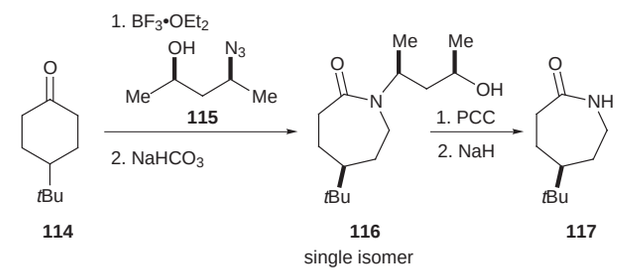
3 Desymmetrisation by the formation of C–C bonds

3.1 Alkene and diene substrates

An early example of enantioselective desymmetrisation involving the formation of a C–C bond was reported by Whitesell.[81]

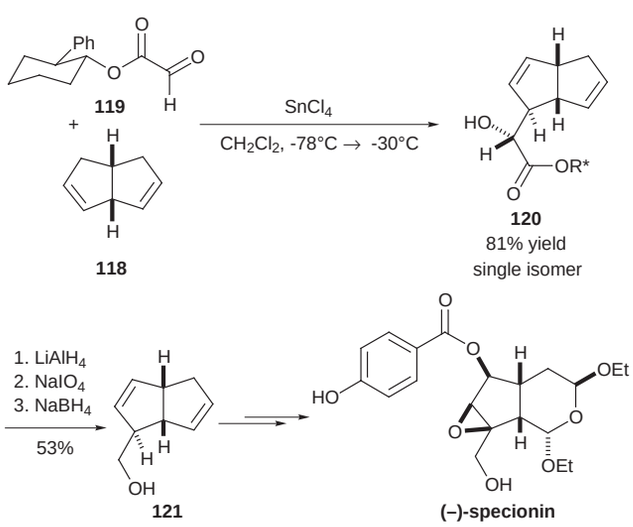


Scheme 45



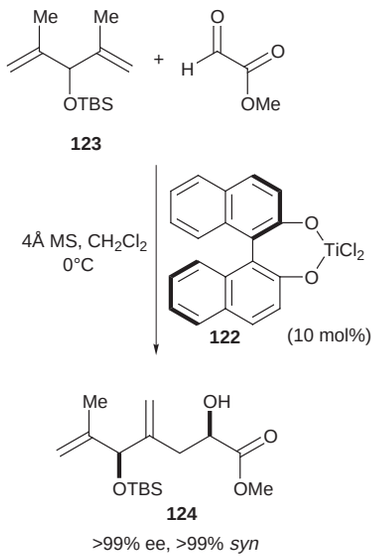
Scheme 46

He pioneered the use of chiral glyoxylate esters as enophiles in the intermolecular ene reaction. Reaction of cyclic diene **118** with the glyoxylate ester **119** derived from *trans*-2-phenylcyclohexanol in the presence of $SnCl_4$ in methylene chloride at −78 °C provided the ene adduct **120** in 81% yield (Scheme 47).[82] Reductive removal of the chiral auxiliary followed by oxidative cleavage provided allylic alcohol **121**. An eight step sequence commencing from **121** was used to prepare (−)-specionin in optically pure form.



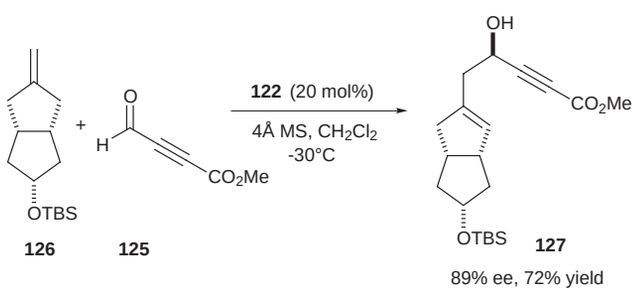
Scheme 47

More recently Mikami has reported a catalytic enantioselective glyoxylate-ene reaction that can be employed in diene desymmetrisation.[83] The BINOL derived chiral Ti(IV) Lewis acid **122** was used to catalyse the reactions between methyl glyoxylate and bis-allylic silyl ether **123** (Scheme 48). The use of 10 mol% of complex **122** in methylene chloride in the presence of 4 Å molecular sieves delivered alcohol **124** with excellent levels of diastereo- and enantioselectivity (>99% *syn*, >99% ee).



Scheme 48

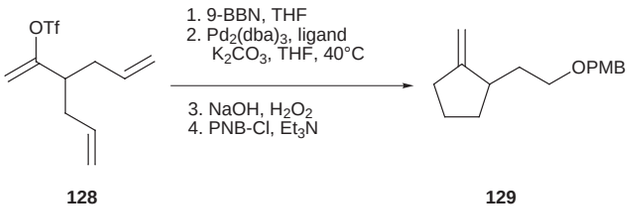
Mikami has adapted the system to encompass the use of vinylogous glyoxylate esters as substrates; reaction of aldehyde **125** with *exo*-cyclic alkene **126** under the previously reported conditions provided ene-adduct **127** in 72% yield and with 89% ee (Scheme 49).[84] The methodology was subsequently applied to a synthesis of isocarbacyclin. A related reaction has been employed by Daniewski to desymmetrise 1-alkyl-4-methylenecyclohexanes, the products of which were used to achieve the first total synthesis of pravastatin.[85]



Scheme 49

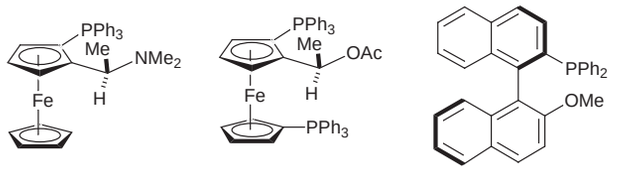
Shibasaki has reported an asymmetric cyclopentane synthesis based on the enantioselective cyclisation of prochiral dialkyl boranes.[86] Treatment of dienes such as **128** with 9-BBN produces the corresponding dialkyl boranes which are not isolated but treated directly with a chiral palladium(0) complex to effect an intramoleular Suzuki reaction. Oxidative work-up with basic hydrogen peroxide provides cyclopentane alcohols **129**. A range of chiral phosphine ligands were investigated and a selection of the results are presented below (Scheme 50). The highest selectivity was obtained by using the catalyst derived from (*S*)-(*R*)-BPPFOAc **131** which provided the product with 28% ee. The methodology was also extended to substrates containing quaternary carbon atoms; similar levels of enantioselectivity were obtained.

A palladium(II) catalysed oxidative cyclisation of *cis*-1,2-divinylcyclohexane **133** leading to the production of a bicyclo-[4.3.0] ring system has been reported by Moberg.[87,88] By employing chiral carboxylic acids as the nucleophiles, diastereomerically enriched products are produced (Scheme 51). The highest levels of diastereoselectivity were obtained when the lactic acid derived acid **134** was used in combination with non-dried molecular sieves.



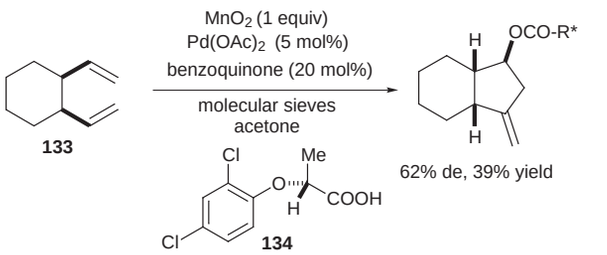
128 **129**

Ligand	yield	ee
132	67	14(*S*)
130	48	20(*S*)
131	58	28(*R*)



130 (*S*)-(*R*)-PPFA **131** (*S*)-(*R*)-BPPFOAc **132** (*R*)-MOP(OMe)

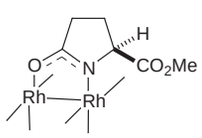
Scheme 50



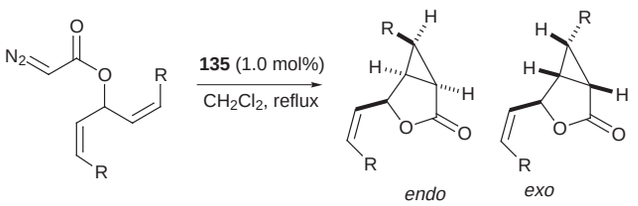
133 **134** 62% de, 39% yield

Scheme 51

An enantioselective intramolecular cyclopropanation has been employed by Martin to provide access to fused cyclopropane-δ-lactones (Scheme 52).[89] The optimal catalyst proved to be the rhodium(II) carboximide **135** which delivered the cyclopropane products in excellent ee although the diastereoselectivity of the process was shown to be heavily substrate dependent.



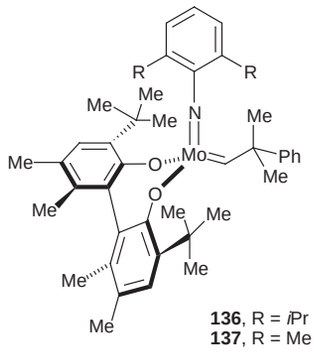
135 Rh_2(5*S*-MEPY)$_4$



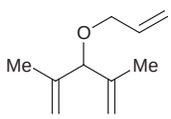
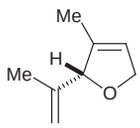
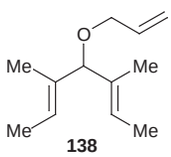
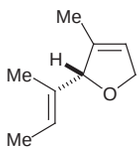
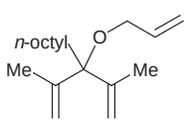
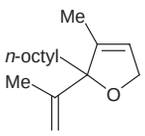
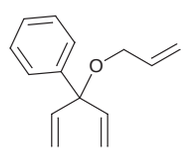
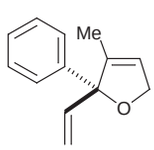
R = H, 20:1 *endo:exo*, 94% ee (*endo*), 75% yield
R = Me, 1:1.2 *endo:exo*, 92% ee (*endo*), 91% ee (*exo*), 73% yield

Scheme 52

Schrock and Hoveyda have recently reported the application of chiral biphenol molybdenum alkylidene complexes **136** and **137** to the desymmetrisation of prochiral trienes (Scheme 53).[90] Treatment of a range of trienes with 5 mol% of **136** or **137** effected ring closing metathesis to deliver enantiomerically enriched dihydrofuran products in good to excellent ee. Significantly the methodology can be used to create stereochemically defined quaternary chiral centres with high ee. The system could also be conducted in the absence of solvent; for example, reaction of substrate **138** using only 1–2 mol% of complex **137** to deliver the cyclised product in 93% yield and in 99% ee.



136, R = *i*Pr
137, R = Me

Substrate	Catalyst (5 mol%)	Temp.	Product	Yield	ee
	**136**	22°C		86	93
 **138**	**137**	22°C		83	99
	**137**	22°C		28	50
	**137**	-20°C		91	82

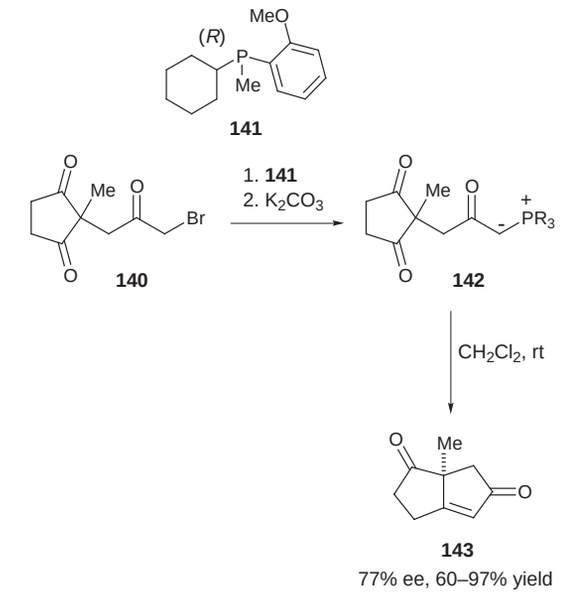
Scheme 53

Grubbs has also reported the preparation and application of chiral molybdenum alkylidene complexes for ring closing metathesis; the one example of the desymmetrisation of an achiral triene delivered the cyclised product with 15% ee.[91]

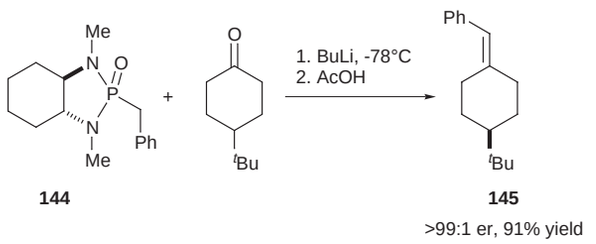
3.2 Ketone substrates

There is a considerable body of work detailing the preparation of chiral Wittig or Wittig "type" reagents. An early example, reported by Trost and Curran, used a chiral phosphine in an enantioselective synthesis of the Wieland–Miescher ketone.[92] Treatment of α-bromo ketone **140** with the chiral phosphine **141** and then base-generated phosphorus ylide **142** followed by simple stirring in dichloromethane at room temperature effected the intramolecular olefination to provide ketone **143** in 60–97% yield and 77% ee (Scheme 54). The ee reported has been corrected to take into account the 88% ee of the starting chiral phosphine. A selection of chiral phosphines were surveyed, including diphosphines, but all were inferior to **141**.

Several groups have reported the preparation of chiral phosphonates or phosphonamides for use in chiral Horner or Wadsworth–Emmons reactions.[93,94] Hanessian has employed the phosphonamide **144**, derived from *trans*-cyclohexane-1,2-diamine, to desymmetrise a range of achiral ketones (Scheme 55).[95,96] For example, treatment of phosphonamide **144** with butyllithium at −78 °C then reaction with 4-*tert*-butylcyclohexanone followed by acid treatment provides *exo*-alkene **145**



Scheme 54



Scheme 55

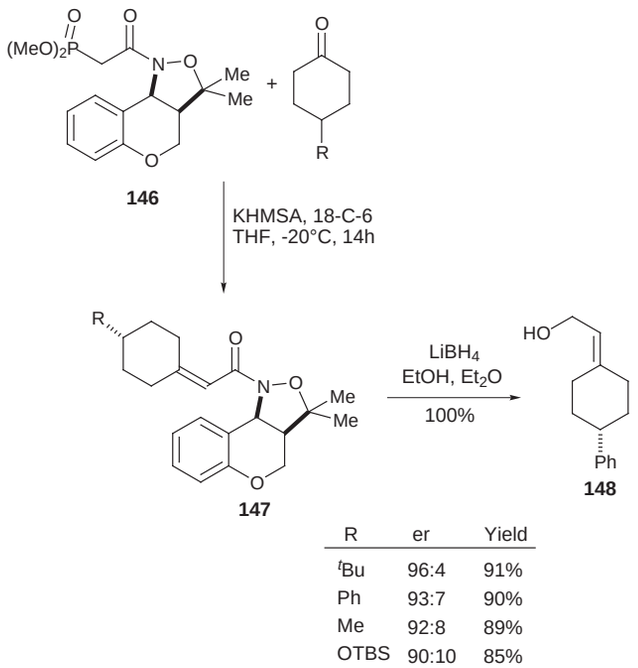
in 91% yield and 98% ee. The allyl (as opposed to benzyl) substituted phosphonamide was also successfully employed to provide enantiomerically pure allylidene alkylcyclohexanes.

Masamune and Abiko adopted an alternative approach to desymmetrise 4-alkylcyclohexanes. They prepared chiral phosphonate **146** in which the chiral auxiliary is attached *via* the amide unit (Scheme 56).[97] Deprotonation of **146** with KHMSA (potassium hexamethyldisilazanide) in the presence of 18-crown-6 and reaction with ketones at −78 °C delivers the alkene products **147** in good yield. Cleavage of the benzopyran-isoxazoline unit was effected by treatment with lithium borohydride to provide the chiral allylic alcohols **148** with good to excellent ee's. Before arriving at the KHMSA conditions a range of reaction conditions were investigated including Lewis acid activation.

Very recently a *catalytic* asymmetric Horner–Wadsworth–Emmons reaction conducted under phase-transfer conditions was reported by Arai and Shioiri.[98] Quaternary ammonium salt **149**, derived from cinchonine, in combination with phosphonate **150** and rubidium hydroxide was found to effectively desymmetrise 4-*tert*-butylcyclohexane (Scheme 57). These optimal conditions (employing 20 mol% of **149**) delivered the product α,β-unsaturated ester **151** in 69% yield and 57% ee. A range of counterions and different alkyl substituted catalysts were investigated, however all were found to be inferior to **149**.

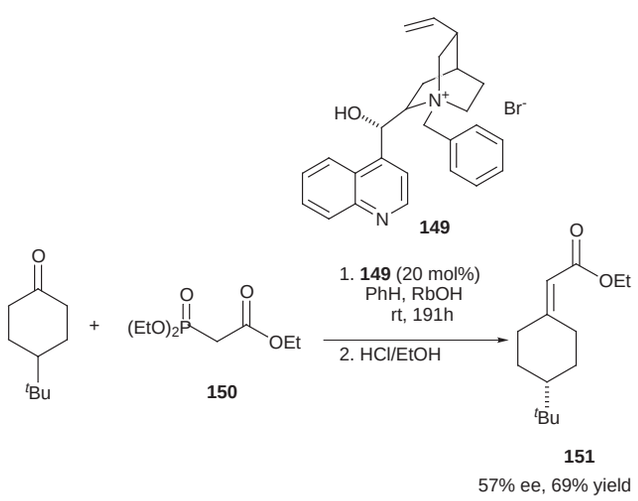
3.3 Dialdehyde substrates

meso-Dialdehydes have proved to be popular desymmetrisation substrates; Rein *et al*. have investigated the desymmetrisation of such a substrate using a chiral Horner–Wadsworth–Emmons reaction.[99] Treatment of dialdehyde **152** with menthol derived chiral phosphonate **153** and KHMSA and 18-crown-6 at −100 °C in THF delivers the corresponding alkene **154** (Scheme 58). Product analysis was performed on the derived alcohol obtained by simply treating with $NaBH_4$. The α,β-



R	er	Yield
^{t}Bu	96:4	91%
Ph	93:7	90%
Me	92:8	89%
OTBS	90:10	85%

Scheme 56

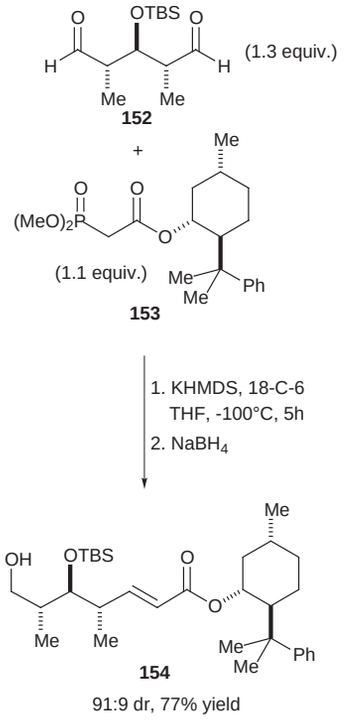


Scheme 57

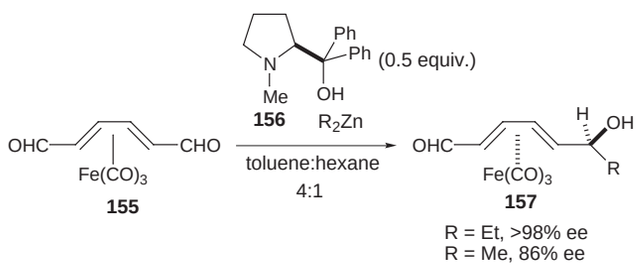
unsaturated ester was obtained in 77% yield as a 91 : 9 mixture of diastereomers. The diastereomeric ratio could be improved by increasing the number of equivalents of the phosphonate from 1.3 to 2.0. These modified conditions delivered the α,β-unsaturated ester in a lower yield (36%) but as an improved 97 : 3 mixture of diastereomers, along with 48% of the symmetrical dienone product. *meso*-α-Diketones have also been desymmetrised by a similar strategy.[100]

The enantioselective addition of dialkylzinc reagents to *meso*-dialdehydes has also been employed as a desymmetrising tool. Takemoto has developed methodology to exploit the chirality inherent in (diene)$Fe(CO)_3$ complexes. This can be extended to include enantioselective additions to *meso*-dialdehyde **155** (Scheme 59).[101,102] For example, addition of diethylzinc and 0.5 equivalents of diphenylprolinol {*N*-methyl-[2-(diphenyl)hydroxymethyl]pyrrolidine} **156** to dialdehyde **155** results in the production of the mono-addition product **157** in an excellent 98% ee. Use of the less bulky dimethylzinc reagent resulted in an alcohol of lower enantioselectivity (86%). The methodology could also be applied to the kinetic resolution of (sorbic† aldehyde)$Fe(CO)_3$ complexes.[103]

† IUPAC nomenclature for sorbic acid is hexa-2,4-dienoic acid.

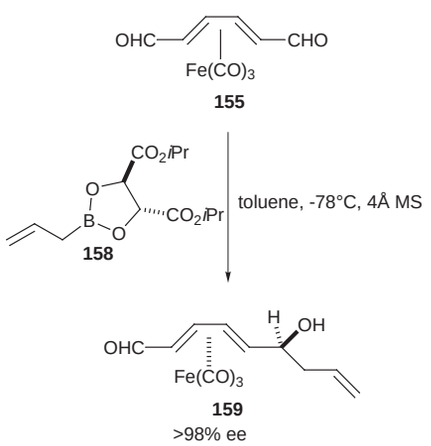


Scheme 58



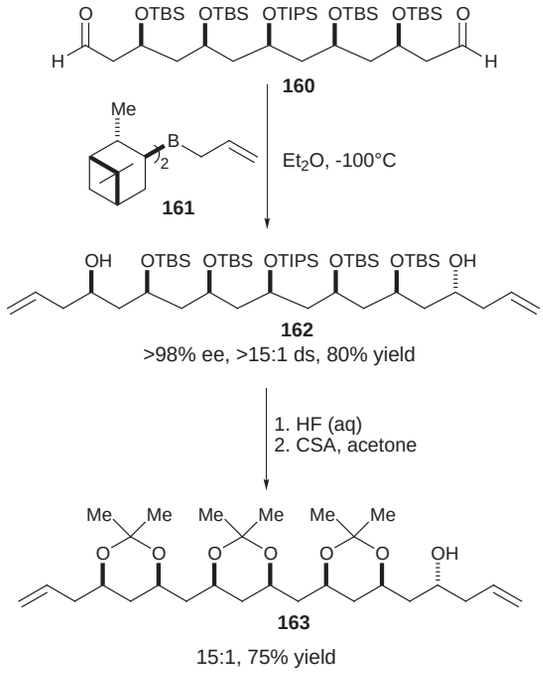
Scheme 59

Roush has utilised the same dialdehyde as a substrate for enantioselective allylation.[104] Treatment of **155** with the tartrate derived chiral allyl borane **158** delivers the chiral allyl alcohol product **159** in excellent ee (Scheme 60). Again, the methodology has also been applied to the kinetic resolution of various (diene)$Fe(CO)_3$ complexes.



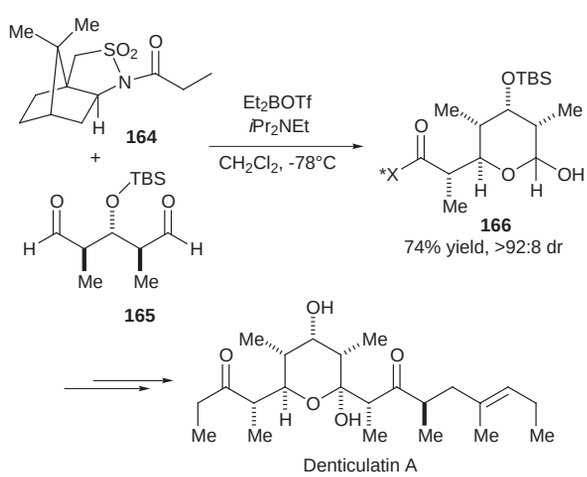
Scheme 60

The more complex *meso*-dialdehyde **160** was also effectively desymmetrised by enantioselective allylation (Scheme 61).[105] Wang combined **160** with diisopinocampheyl(allyl)borane **161** in ether at −78 °C and obtained the double addition product **162** in >98% ee in 80% yield. This single operation has established the absolute configurations of seven stereocentres with excellent control. The two termini of **162** now have a diastereotopic relationship and can thus be differentiated by a diastereotopic-group selective, as opposed to an enantiotopic-group selective, reaction. Thus, treatment of diol **162** with aqueous HF followed by acetone–CSA delivered the tris(acetonide) **163** as a 15 : 1 mixture of diastereomers.



Scheme 61

An auxiliary controlled diastereoselective aldol addition reaction has been used to desymmetrise *meso*-dialdehydes. Oppolzer utilised a boron enolate of his chiral sultam **164** to effectively desymmetrise dialdehyde **165** (Scheme 62).[106] Enolisation of **164** with Et_2BOTf and Hünig's base followed by the addition of **165** provided the lactols **166** in good yield (74%) and excellent diastereoselectivity (>92 : 8). The lactol mixture has been utilised in a total synthesis of denitculatin A. Oppolzer has also used a similar strategy for the synthesis of the Prelog–Djerassi lactone.[107]

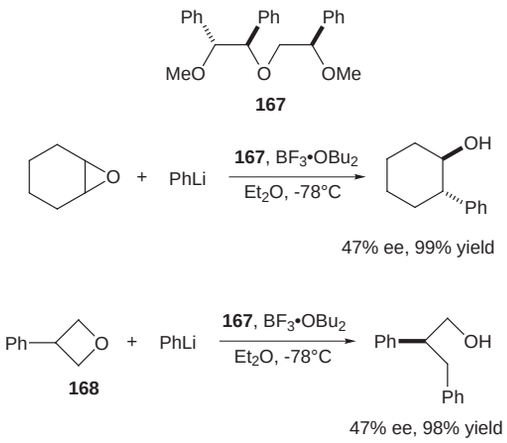


Scheme 62

3.4 Miscellaneous substrates and reactions

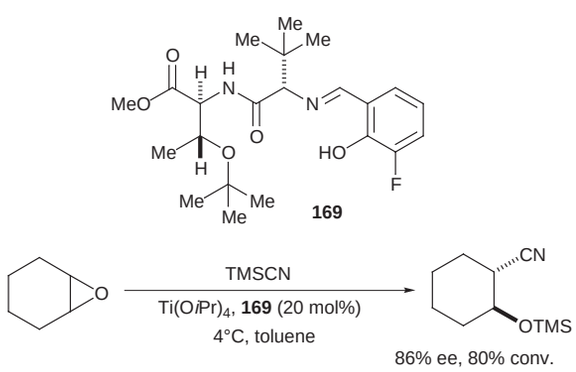
The enantioselective addition of carbon nucleophiles to achiral or *meso*-epoxides has been used to obtain enantiomerically enriched alcohols. Addition of phenyllithium in combination with a stoichiometric amount of the chiral tridentate ether **167**

and $BF_3{\cdot}OBu_2$ to cyclohexene oxide provided the corresponding alcohol in 47% ee (Scheme 63).[108] Reaction of the phenyl-substituted oxetane **168** under the same conditions also yielded the ring opened product in 47% ee. Suprisingly, the use of non-coordinating solvents such as toluene led to a dramatic reduction in the enantioselectivity of the process.



Scheme 63

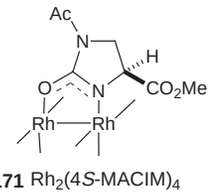
Hoveyda and Snapper have developed a catalytic enantioselective addition of TMSCN to *meso*-epoxides.[109,110] Dipeptide-Schiff base **169** in combination with $Ti(iOPr)_4$ was found to catalyse the addition of TMSCN to cyclohexene oxide to provide the cyanohydrin product in 80% yield and 88% ee (Scheme 64). The ligand was identified using solid phase combinatorial methods and was found to be highly substrate specific. The same approach identified related ligands that were optimal for TMSCN additions to cyclopentene, cyclohexa-1,4-diene and cycloheptene oxides.

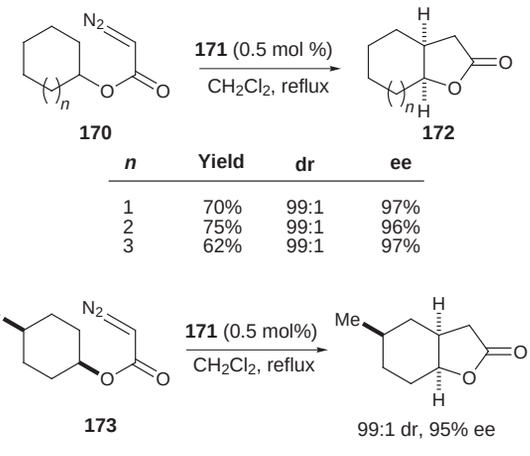


Scheme 64

Chiral rhodium(II) catalysts have been used to promote desymmetrising carbon–hydrogen insertions. Doyle demonstrated that treatment of cyclic α-diazo ester substituted alkanes such as **170** with 0.5 mol% of chiral Rh(II) complex **171** in refluxing methylene chloride provides the fused ring lactones **172** in excellent yield, diastereo- and enantioselectivity (Scheme 65).[111] Disubstituted cyclic alkanes such as **173** could also be successfully employed, however the diastereoselectivity of these systems was shown to be dependent on the stereochemistry of the 4-alkyl substituent.

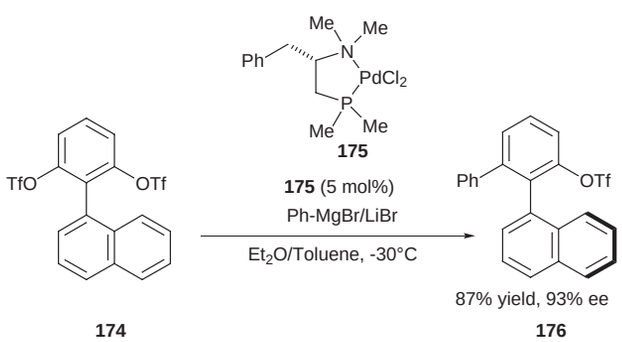
A palladium-catalysed cross-coupling reaction between an aromatic ditriflate and an aromatic Grignard reagent has been used by Hayashi to access axially chiral biaryls.[112,113] Reaction of triflate **174** with phenylmagnesium bromide in the presence of chiral palladium catalyst **175** (5 mol%) and LiBr provided the mono-coupled biaryl **176** in 87% yield and 93% ee (Scheme 66). The enantioselectivity could be increased to even higher levels if the reaction time was increased, however, significant





n	Yield	dr	ee
1	70%	99:1	97%
2	75%	99:1	96%
3	62%	99:1	97%

Scheme 65



Scheme 66

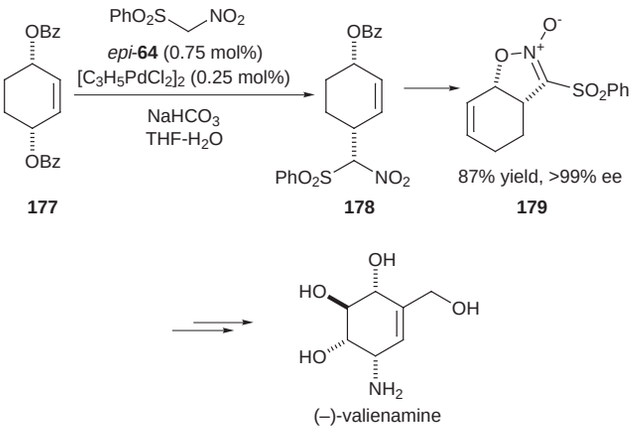
amounts of the di-coupled product are then produced. The LiBr was found to be essential for high catalytic activity as well as enantioselectivity. Hayashi has also reported a similar approach to the production of chiral arene–$Cr(CO)_3$ complexes, however in this case the enantioselectivities obtained were not as impressive.[114]

In section 2.3 on the formation of C–X bonds we have already seen examples of Trost's work employing chiral Pd(0) complexes to effect the desymmetrisation of *meso*-allyl dibenzoates by the selective addition of nitrogen based nucleophiles. A similar approach can also be adopted involving the enantioselective formation of C–C bonds. For example, treatment of dibenzoate **177** with (phenylsulfonyl)nitromethane, allylpalladium chloride dimer and 0.75 mol% of diphosphine **64** yields mono-benzoate **178** which is cyclised to form isoxazoline *N*-oxide **179** in 87% yield and 99% ee (Scheme 67).[115] Isoxazoline **179** was utilised in a synthesis of (+)-valienamine. Malonates are also useful nucleophiles for use in similar systems.[116]

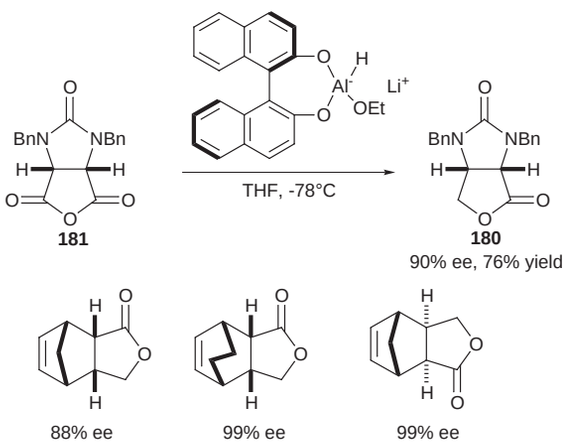
4 Desymmetrisation by oxidative and reductive processes

4.1 Reduction reactions

The enantioselective reduction of *meso*-anhydrides has been employed as a route to chiral lactones. Matsuki used Noyori's BINOL-H reagent to effect the selective reduction of a range of symmetrical anhydrides (Scheme 68).[117] Reactions were performed in THF at −78 °C and routinely provided the lactones in good yield and with high ee. Lactone **180**, a key intermediate in the synthesis of (+)-biotin, was prepared by the enantioselective reduction of carbamate-anhydride **181**. The crude



Scheme 67



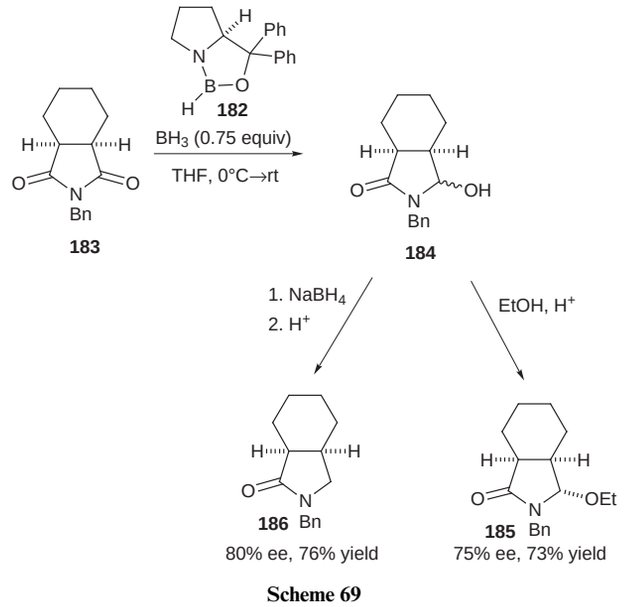
Scheme 68

reaction product was produced with 90% enantiomeric excess, which could be raised to 99% by a single recrystallisation from benzene–cyclohexane. The methodology was successfully applied to a range of bicyclic anhydrides.

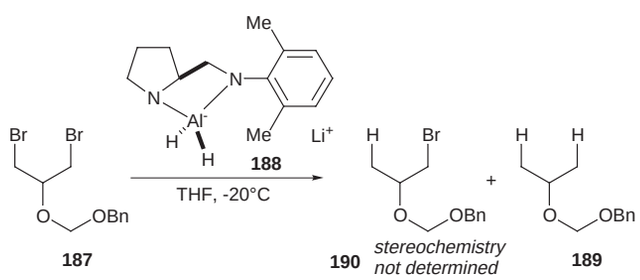
Speckamp and co-workers have reported a catalytic enantioselective reduction of cyclic *meso*-imides.[118] Chiral oxazaborolidine **182** was employed as the chiral catalyst with borane as the stoichiometric reductant (Scheme 69). Reaction of imide **183** with 0.5 equivalents of **182** and borane in THF provided a mixture of the *cis* and *trans* isomers of 2-hydroxypyrrolidinone **184**. Treatment of the crude reaction product with acidic ethanol produced *trans* ethoxy lactam **185** in 73% overall yield and in 75% ee. Conversely, treatment of **184** with sodium borohydride followed by sulfuric acid provided lactam **186** in 76% yield and 80% ee. The system could be applied to a range of bicyclic imides with the reduction products being readily isolated with ee's in the range 75–89%. A rhodium catalysed enantioselective hydrogenolysis of a *meso*-epoxide has been reported; enantioselectivities from 6% to 62% were obtained.[119]

The enantioselective desymmetrisation of *meso*-1,3-dihalides has been studied by Chong and Sokoll.[120] Dihalides such as **187** could be reduced with the chiral aluminium hydride reagent **188** to provide enantiomerically enriched mono-halides (Scheme 70). The enantiomeric purity of the mono-halide was found to increase as the reaction progresses and as the amount of the doubly reduced product **189** increases, suggesting that although the initial enantiotopic-group selective reaction occurs with only modest selectivity, the subsequent kinetic resolution of **190** increases its enantiomeric purity. At extended reaction times the mono-halide can be obtained in reasonable enantiomeric purity albeit in low yield.

Lautens has developed a nickel-catalysed enantioselective reductive ring-opening of oxabicyclic alkenes.[121] For example, the reaction of *meso*-bicyclo[2.2.1] alkene **191** with DIBAL-H



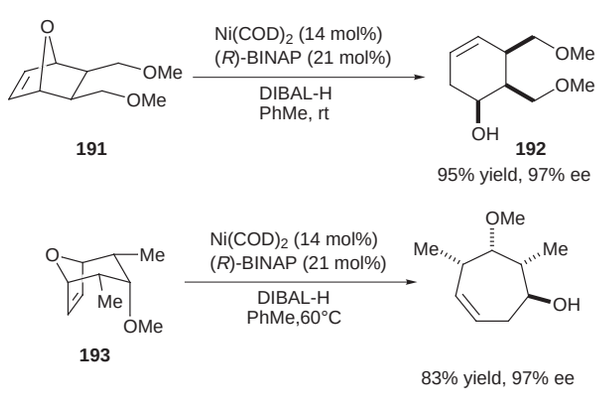
Scheme 69



Time (min)	187:190:189	Yield of 190 (%)	ee of 190 (%)
50	10:86:4	69	42
90	0:77:23	62	60
130	0:60:40	48	74
240	0:18:82	17	87

Scheme 70

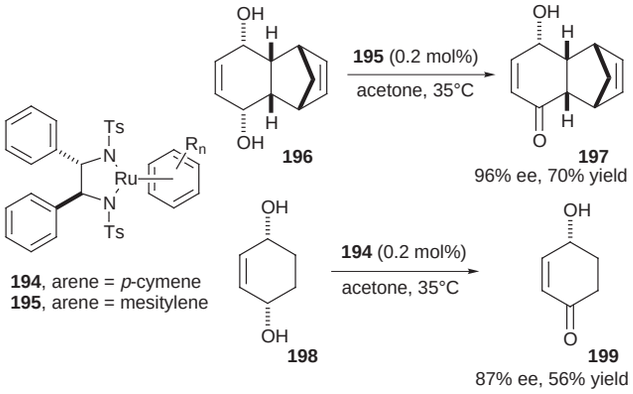
in the presence of Ni(COD)$_2$/(*R*)-BINAP provides the corresponding cyclohexene **192** in 95% yield and 97% ee (Scheme 71). The methodology can also be applied to the formation of cycloheptenol products. Thus, reaction of bicyclo[3.2.1] alkene **193** under similar conditions yielded the seven membered ring product with equally good selectivity. The strategy has been successfully employed in a synthesis of the antidepressant sertraline.[122]



Scheme 71

4.2 Oxidation reactions

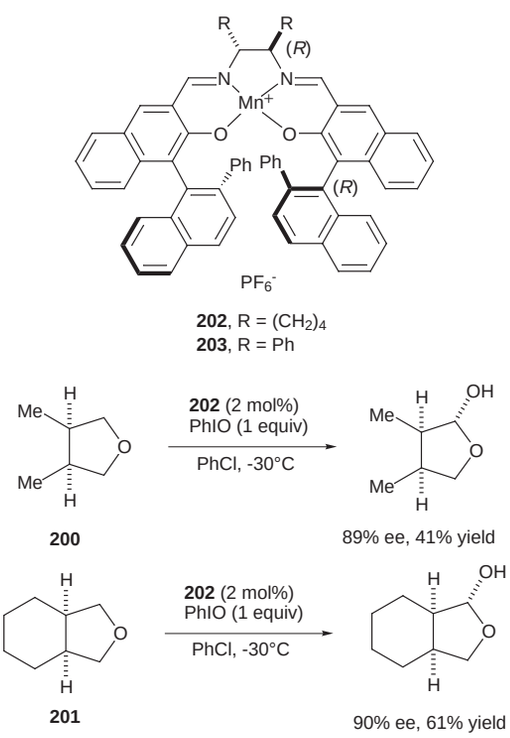
The Ru(II)-diamine complexes **194** and **195** have been employed by Noyori as efficient catalysts for the enantioselective oxidation of *meso*-diols (Scheme 72).[123] Treatment of diol **196** with



Scheme 72

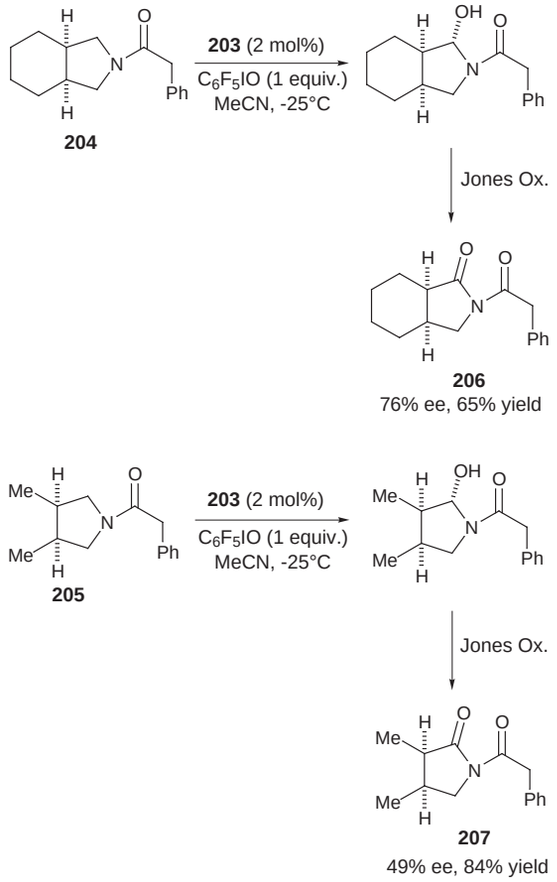
complex **194** (0.2 mol%) in acetone at room temperature provided the hydroxy ketone **197** in 70% yield and 96% ee. Diol **198** was oxidised in the presence of catalyst **195** to provide the ketone **199** with 87% ee. These two examples are remarkable for the excellent enantioselectivities that are obtained with such a low catalyst loading.

The enantioselective oxidation of C–H bonds in tetrahydrofurans and pyrrolidines has been investigated by Katsuki. The Mn(III) complexes **202** and **203** were employed to successfully desymmetrise cyclic ethers such as **200** and **201** by an enantioselective C–H oxidation (Scheme 73).[124,125] The product lactols were obtained in moderate yields with excellent enantioselectivity (89–90% ee). The optimum reaction conditions involve the use of 0.02 equivalents of complex **202** with chlorobenzene as solvent and iodosylbenzene as the stoichiometric oxidant.



Scheme 73

By using complex **203** the system could be extended to include pyrrolidines.[126] Treatment of the phenylacetamide protected pyrrolidines **204** and **205** provided the corresponding aminols that were immediately oxidised to lactams **206** and **207** to aid in the determination of their ee's (Scheme 74). The enantioselectivity in these oxidations (76–84% ee) was found to be generally lower than in the tetrahydrofuran series.



Scheme 74

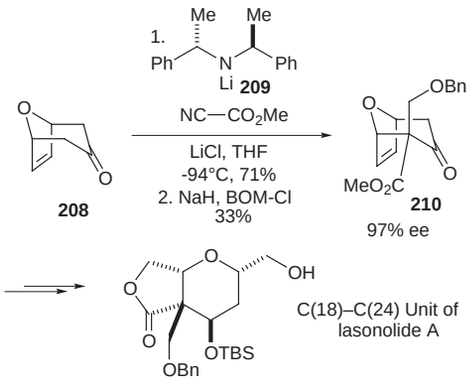
5 Desymmetrisation by enantioselective deprotonation

Chiral bases are arguably the largest single reagent class to be employed in enantioselective desymmetrisation reactions. Because of this it is not possible in this review to consider in detail the impact that these important reagents have had in this area. Readers are referred to recent reviews by O'Brien,[127] Beak[128] and Hoppe[129] for comprehensive accounts of this subject. Chiral bases have proved to be successful in many different desymmetrising reactions; four different reaction types are illustrated below. The most common use is in the enantioselective deprotonation of *meso* or achiral ketones. Hoffmann has utilised such a strategy in his synthesis of the C(18)–C(24) fragment of lasonolide A (Scheme 75).[130] Deprotonation of bicyclic ketone **208** with chiral lithium amide base **209** and quenching with methyl cyanoformate followed by a further deprotonation with NaH and quenching with benzyloxymethyl chloride (BOM-Cl) delivered the α-alkylated ketone **210** in reasonable yield and excellent enantioselectivity (97%).

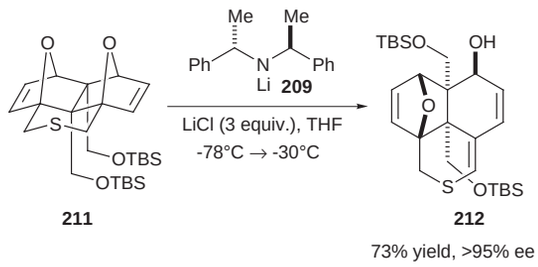
Lautens uses the same chiral lithium amide to desymmetrise dioxacyclic alkene **211**.[131] Treatment with **209** and LiCl in THF results in ring opening to provide *cis*-decalin **212**, formed by selective deprotonation of the methylene hydrogen adjacent to the sulfur atom followed by fragmentation (Scheme 76). The decalin was obtained in 95% ee. Careful control of the reaction conditions was found to be crucial as over-reaction resulted in a second deprotonation and formation of the doubly ring opened *meso*-product.

Chiral bases have also been used extensively in the desymmetrisation of *meso* or achiral epoxides. For example, treatment of disubstituted cyclohexene oxide **213** with chiral lithium amide **214** resulted in formation of allylic alcohol **215** in 93% yield and 76% ee (Scheme 77).[132] The allyl alcohol is formed *via* selective deprotonation β to the epoxide.

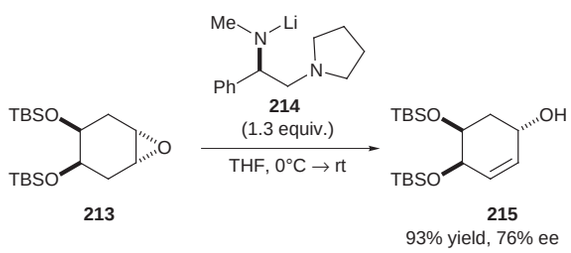
Deprotonation of the methine carbon α to the epoxide is also possible. Hodgson has utilised such an approach to effect the



Scheme 75

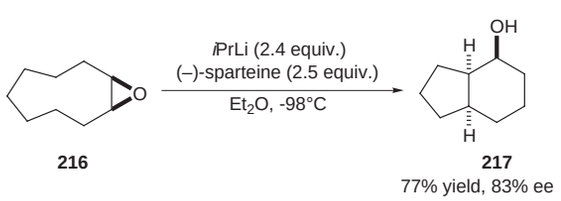


Scheme 76



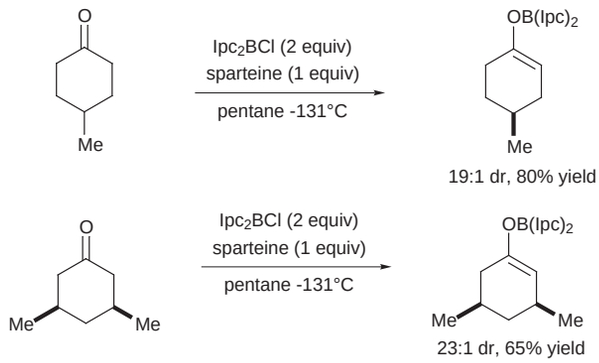
Scheme 77

desymmetrisation of epoxide **216** (Scheme 78).[133] Treatment of the epoxide with *i*PrLi complexed with (−)-sparteine results in the formation of the alcohol **217** in 77% yield and 83% ee. The rearrangement is believed to proceed *via* the formation of a carbenoid intermediate which facilitates transannular C–H insertion. The reader is again referred to the review by Hodgson for a comprehensive account of epoxide desymmetrisation.[18]



Scheme 78

A recent report by Ward documents the desymmetrisation of *meso* and achiral ketones by enantioselective enolborination.[134] Treatment of the requisite ketones with $(Ipc)_2BCl$ and sparteine in pentane at −131 °C delivers the desymmetrised boron-enolates in good yield and diastereoselectivity (Scheme 79).



Scheme 79

6 Conclusion

The last few years have seen many impressive advances in the field of enantioselective desymmetrisation and many varied bond-constructions can be successfully employed. One area where examples of desymmetrisation reactions are scarce is in the catalytic enantioselective construction of C–C bonds. Given the strategic importance of this bond construction, this is sure to be a topic of interest in the coming years.

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