Stoichiometric asymmetric processes

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1. Introduction

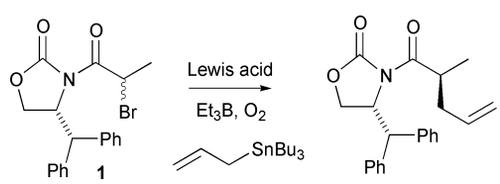
When reading and abstracting this 'millennium' edition of *Stoichiometric Asymmetric Processes* it was immediately apparent that oxazolidinone and chiral hydrazone auxiliaries are the most widely used in asymmetric synthesis and in many places their use has become so routine and commonplace that synthetic procedures are cited rather than given explicitly. However, aside from chiral borane reagents, there are significantly fewer chiral reagents used routinely, which may perhaps be attributed to the cost of such reagents. As advances in the preparation and uses of polymer supported reagents are made this may well change in the near future.

The topic *Stoichiometric Asymmetric Processes* covers a huge range of chemical transformations when one considers that all diastereoselective reactions of non-racemic substrates containing a stereogenic centre fall under this heading, including areas as diverse as rearrangements and glycosylation reactions. Thus, following the lead of Peter O'Brien's contribution last year, I have decided to concentrate on those transformations whereby the stereodirecting group is or has the potential to be removed at the end of the synthetic scheme. I have surveyed a majority of the primary chemical literature from 2000 but this review is far from comprehensive. I have decided to keep to a similar format to that introduced last year and have concentrated on the applications that auxiliaries have been used for in organic synthesis rather than the fine details regarding their reactivity and selectivity. However, some things have changed, and I have removed the section on the use of chiral reagents and auxiliaries in synthesis and incorporated this into the sections relating to transformations of that auxiliary. I have also added a few more subsections to help categorise the transformations.

2. Chiral auxiliaries

2.1 α-Alkylation

Asymmetric alkylation of lithium and sodium enolates of oxazolidinone and camphor sultam auxiliaries is one the most widely used transformations for the preparation of synthetic targets. Such reactions have been employed in many synthetic sequences including the synthesis of renin inhibitor BILA 2157 BS on a 0.6 kg scale,[1] both enantiomers of enterlactone,[2] isotopically ^{13}C and D labeled L-leucine and other α-amino acids,[3,4] β-amino acids through a subsequent Curtius rearrangement,[5] pitiamide A,[6] (−)-eburnamonine and (+)-epi-eburnamonine,[7] the sex pheromone of the sandfly *Lutzomyia longipalpis*,[8] α,α′-*cis* and *trans*-disubstituted medium ring ethers,[9] (*R*)-2-propyloctanoic acid,[10] orthogonally protected tricarballylic acid esters,[11] the terminal acid portion of zooxanthellatoxins,[12] epothilone B,[13] the C1–C25 domain of sanglifehrin A,[14] β²-amino acids[15] and (1*S*,3*S*,7*R*)-3-methyl-α-himachalene, the sex pheromone of the sandfly *Lutzomyia longipalpis*.[16] A few other interesting examples of oxazolidinone enolate alkylation stand out; alkylation of the lithium enolate of an oxazolidinone with a triflate electrophile gave a 3 : 1 mixture of *C*-alkyl and *O*-alkyl products, the former as a single diastereomer.[17] This was reported as the first example of *O*-alkylation in oxazolidinone enolate alkylation. Oxidative self coupling of lithium enolates of *N*-acyloxazolidin-2-ones with reagents such as $TiCl_4$ have been shown to occur with good yields and levels of selectivity.[18] Sibi and Rheault have investigated the stereoselectivity of the radical allylation of α-bromo-*N*-acyloxazolidinones **1** with allyltin reagents (Scheme 1).[19]



Scheme 1

Quite surprisingly, higher selectivities were obtained at higher temperatures and a working model was proposed based upon the rotational barriers of the chelated and non-chelated radical intermediates.

Although extensively used in synthesis, work is still carried out aimed at improving the efficiency and/or selectivity of oxazolidinone auxiliaries. Perhaps the most well known examples of these are the SuperQuat auxiliaries developed by Davies. Bull *et al.* have demonstrated that enhanced stereoselectivity in the alkylation of lithium enolates of the valine-derived SuperQuat chiral auxiliary is due to the geminal methyl groups controlling the conformation of the isopropyl stereodirecting group.[20] This in effect makes the isopropyl group behave like a *tert*-butyl group as far as controlling the diastereoselectivity of the alkylation step. Asymmetric alkylation of benzyl SuperQuat auxiliaries has been demonstrated for a number of substrates and electrophiles and the products were subsequently cleaved to the α-substituted aldehydes using DIBAL-H with no loss of stereochemical integrity.[21] The first

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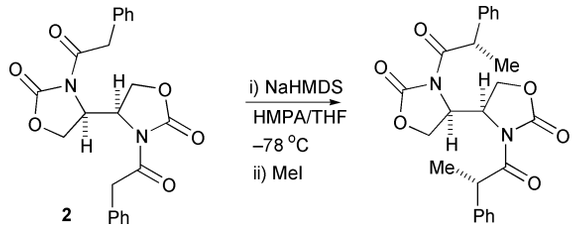
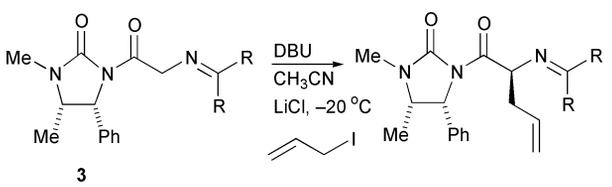
C_2 symmetric bis(oxazolidinone) auxiliary **2** has been prepared and undergoes asymmetric alkylations using methyl iodide with facial selectivities at each enolate of 95 : 5 (Scheme 2).[22] The



Scheme 2

auxiliary also has excellent water solubility making recycling through aqueous extraction a viable option.

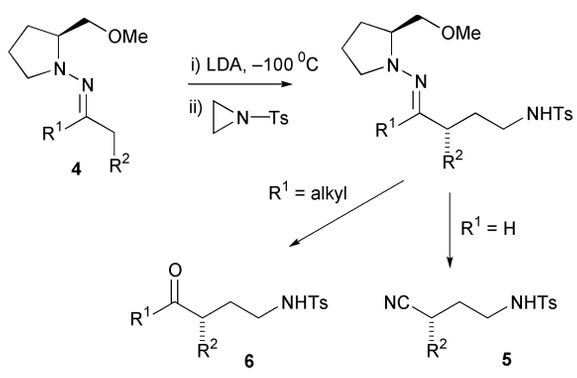
Other analogues of oxazolidinones have also been used but to a lesser extent. The diastereoselectivity of the alkylation of 2-imidazolidinone derivatives was found to be dependent upon the second nitrogen substituent,[23] while alkylation of the enolate of a glycinamide imidazolidinone **3** has been used in the diastereoselective synthesis of α-amino acids (Scheme 3).[24]



Scheme 3

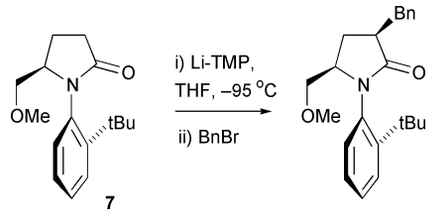
Asymmetric alkylation of a dienolate provides quick access to chiral α-substituted β-alkenes, although this methodology has not been used to as great an extent as enolate alkylation. Application of this methodology has been demonstrated in the synthesis of 1α-hydroxyvitamin D5[25] and in the synthesis of a fragment of madindolines[26] using oxazolidinones as the stereodirecting group.

Another preferred method for preparation of chiral α-substituted carbonyls is through the alkylation of aza-enolates of chiral hydrazone auxiliaries, which has been applied to the synthesis of (+)-maritimol,[27] stigmolone,[28] indolizidine alkaloids,[29] and components from crocodile exocrine secretion.[30] Ring opening reactions of *p*-tolylsulfonylaziridines with aza-enolates derived from the hydrazone **4** proceeded in excellent diastereoselectivity and have been used in the synthesis of γ-amino nitriles **5** and ketones **6** (Scheme 4).[31,32]



Scheme 4

The use of axially chiral reagents and catalysts continues to expand. Fujita *et al.* have reported in depth studies of the reaction of enolates derived from axially chiral pyrrolidinones **7** with a series of electrophiles (Scheme 5).[33] The pyrrolidinones were prepared in excellent yield and with apparent complete

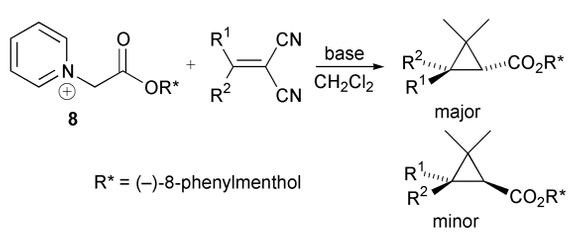


Scheme 5

chirality transfer and underwent reaction with electrophiles with excellent selectivity.

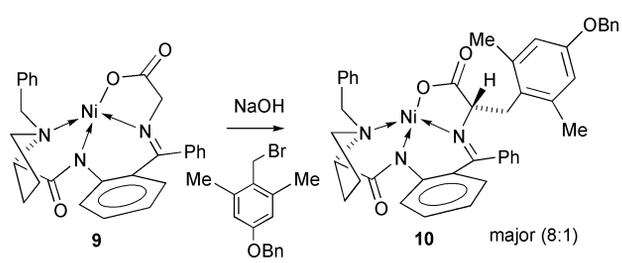
Clayden *et al.* have demonstrated that amides possessing axial chirality may be deprotonated and quenched with a variety of electrophiles giving good yields and reasonable selectivities (69% ee).[34] These compounds could be converted to chiral atropisomers bearing no stereogenic centers in a short synthetic sequence.

Terpenes have been used as a framework for chiral auxiliaries. A novel pinene-based auxiliary has been prepared and applied to asymmetric alkylations with poor to moderate diastereoselectivities,[35] while the diastereoselective ring opening of a chiral epoxide with the enolate of a hydroxypinanone auxiliary has been investigated using a variety of bases and additives.[36] Diastereoselective alkylation of a terpene-derived aza-enolate has been shown to proceed in excellent stereoselectivity and has been applied to the synthesis of 4,5-dihydroxypipecolinic acid.[37] A conformationally restricted metabotropic glutamate receptor agonist bearing a cyclopropyl group has been prepared by dialkylation of a bis(menthyl ester)[38] and asymmetric cyclopropanation has also been carried out by a tandem alkylation–Darzens reaction of a pyridinium salt **8** bearing the 8-phenylmenthyl auxiliary (Scheme 6).[39]



Scheme 6

The preparation of amino acid derivatives still continues to attract attention. One of the more widely used methods has been alkylation of Schöllkopf's bislactim ether template that has been used in the synthesis of 3-heteroaromatic substituted alanines,[40] tryptophan analogues,[41] silaproline,[42] (+)-deoxypyridinoline,[43] and α-methyl-α-substituted amino acids using mild phase transfer conditions.[44] Chiral nickel(II) complexes of Schiff bases **9** have been used for the preparation of amino acids by alkylation of alanine and glycine templates (Scheme 7),

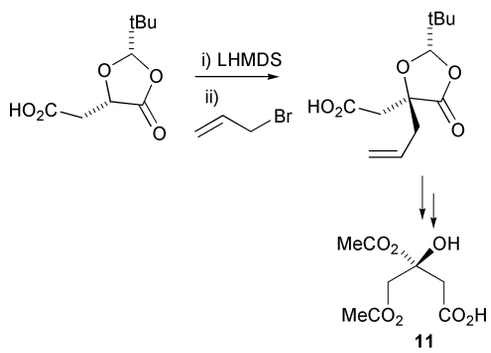


Scheme 7

which was amenable to large scale synthesis.[45] This methodology was applied to the synthesis of ω-borono-α-amino acids as active site probes of arginine NO synthase[46] and in the synthesis of 2′,6′-dimethyltyrosine *via* complex **10**.[47]

Stereoselective alkylation of aldimines using chiral *ansa* pyridoxyl derivatives proceeded in good enantiomeric excess, while introduction of a second stereogenic element allowed double asymmetric induction and greatly increased selectivities.[48] Other methods to prepare amino acids include the alkylation of Williams' glycine template to prepare (2*R*,5*R*)- and (2*S*,5*R*)-5-hydroxylysine,[49] alkylation of a chiral morpholinecarboxylate to prepare a non-proteinogenic fluorescent amino acid,[50] alkylation of a novel chiral oxazoline with a range of active electrophiles,[51] alkylation of a chiral aza-enolate with 1,2-fluorobromides,[52] and an alkylation–cyclisation procedure to prepare α,α′-diaminodicarboxylic acids.[53,54]

Many other chiral auxiliaries have been investigated in alkylation reactions. Some in particular merit further details. Denmark and Kim have reported good to excellent diastereoselectivities in the alkylation of phosphonamide auxiliaries based on a C_2 symmetric diamine.[55] Hanessian and Cantin have demonstrated that γ-chlorodienolates of similar chiral phosphonamides undergo a highly diastereoselective Darzens-like reaction with glyoxylaldehyde-derived oximes.[56] Seebach's self-replication of chirality is a useful procedure that has been used to prepare substrates for RCM reactions,[57] in the synthesis of both enantiomers of a neuroexcitant[58] and both enantiomers of the pheromone of the tropical wandering spider *Cupiennius salei* **11** (Scheme 8).[59]



Scheme 8

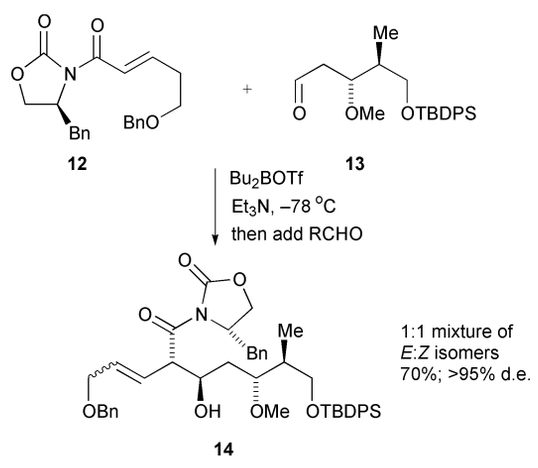
Diastereoselective alkylation of chiral oxazolidines has been used in the synthesis of the ladybird defence alkaloid (+)-calvine and (+)-2-epicalvine,[60] a compound from the pheromone gland of the stinkbug,[61] and 3-alkyl-3-arylpyrrolidines.[62] Alkylation of sodium enolates of sulfonamides with α-bromocarboxylates appeared to give single diastereomers of addition products that were subsequently reduced to diols.[63] This is interesting since the bromocarboxylates used were racemic implying that racemisation of such reagents is fast under these reaction conditions.

The chemistry of arene chromium tricarbonyls has been further expanded and the first example of the addition of the enolate of *tert*-butyl acetate to a chromium arene tricarbonyl complex to give a cyclohexadiene product has been reported with excellent levels stereoselectivity.[64] Huang and Comins achieved the highly diastereoselective addition (de >95%) of a zinc enolate equivalent to a *trans*-2-(α-cumyl)cyclohexanol pyridinium derivative, the key step in the synthesis of (+)-streptazolin.[65] Chiral alanine dianions have been shown to give excellent levels of selectivity in some alkylation reactions[66] and when employed with ethyl bromoacetate, a built-in 'auxiliary release' was used to free the chiral auxiliary. Chiral aldehydes have been used to prepare non-racemic aminals with good diastereoselection (84 : 16)[67] and *N*-acyl derivatives of these have subsequently been used in enolate alkylations giving diastereoselectivities of over 90%. The diastereoselectivity of the allylation of enolates of bicyclic oxazolidines was found to be dependent upon the nature of the protecting group of the amino alcohol.[68]

Other auxiliaries that have been used in asymmetric alkylations include a thiazolo[2,3-*a*]isoindolin-1-one,[69] α-methylbenzylamine[70] and phenylglycinol[71] in the synthesis of tetrahydroisoquinolines, an 8-phenylmenthyl ester in an intramolecular radical cyclisation,[72] a BINOL ester in the synthesis of (+)- and (−)-ferruginol,[73] 2-phenylcyclohexanol in the synthesis of (+)-huperzine A,[74] *N*-methylephedrine in the synthesis of the C14–C25 portion of amphidinolide B1,[75] and *O*-methyl phenylglycinol in the deprotonation–alkylation of oxazolidines[76] and aziridines.[77]

2.2 Aldol reactions and related processes

As with asymmetric alkylation, highly diastereoselective *syn*-aldol condensations using chiral boron enolates of oxazolidinones generated using dibutylboron triflate and an amine base are now used as a matter of routine in synthetic schemes. Although a robust model for the selectivity observed in this reaction is well established, the first report of the structure of a stable boron enolate of an oxazolidinone has been reported using 600 MHz 2D NOESY NMR and molecular modeling techniques.[78] Since the substitution pattern of the aldol product obtained closely matches that of many natural products, application of this methodology to total syntheses has been extensive. Successful uses include the synthesis of (+)-rajadone,[79] the C29–C51,[80] C29–C45[81] and C29–C44[82] fragments of spongistatin 1, the dihydrobenzofuran segment of ephedradine C,[83] a pyrrolidine α-glycosidase inhibitor,[84] antillatoxin,[85] the C1–C9 fragment of rhizoxin,[86] hapalosin,[87] (+)-madindoline A and (−)-mandinoline B,[88] (−)-CP-263,114,[89] and (+)-discodermolide.[90] Boron enolates of oxazolidinones have also been used to prepare substrates for stereoselective phenylsulfanyl rearrangements to provide spiro[4.5]decanes.[91] Reactions of boron dienolates are not as widespread as those of enolates. A boron dienolate of an oxazolidinone **12** has been shown to react with a chiral aldehyde **13** to give the desired aldol product **14** as a 1 : 1 mixture of *Z* and *E* isomers that was used in the synthesis of the tris(oxazole)

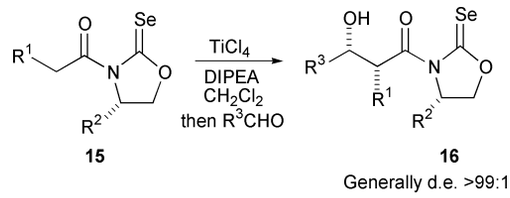


Scheme 9

macrolide ulapualide A[92] (Scheme 9) and similarly in the synthesis of polyene macrolides.[93]

One of the advantages of aldol reactions of oxazolidinones is that *syn*- and *anti*-aldol products may be selected by changing the reaction conditions and examples of this have been used in the synthesis of ribavirin[94] and phoboxazole B.[95]

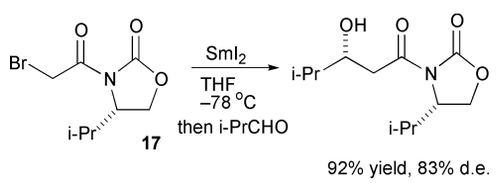
Although highly successful, aldol reactions are obviously not limited to boron enolates of oxazolidinones. Titanium(IV) enolates of *N*-acyloxazolidine-2-selones **15** give predominately 'non-Evans' *syn*-aldol products **16** with excellent diastereoselectivity,[96] and the selone was found to play a pivotal role in determining the stereoselectivity (Scheme 10).



Scheme 10

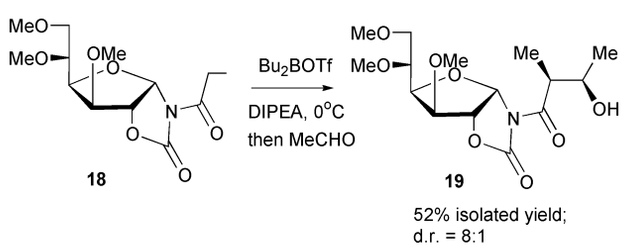
Titanium enolates have also been used with oxazolidinones and oxazolidinethiones that undergo *syn*-selective aldol reactions with the best selectivities observed for the oxazolidinethione[97] which was applied to the synthesis of (+)-prelaureatin and (+)-laurallene. Such enolates have also been shown to react in the presence of (−)-sparteine to give excellent diastereoselectivity in favour of the *syn*-aldol product and used in the synthesis of carbocyclic nucleosides.[98] Tin enolates have been used to mediate an aldol reaction of an α-hydroxyacyloxazolidinone giving the *anti*-aldol product in good diastereoselectivity when treated with a chiral aldehyde.[99]

Use of acetyl enolates in asymmetric aldol reactions is notoriously problematic and various methods have been employed to overcome this. A study of the use of a number of boron triflates and α-thioacetyl derivatives attempted to address this problem and was applied to the C1–C6 segment of epothilones.[100] Other types of enolate other than boron have also been investigated. An acetyl tin enolate of a thiazolidine-2-thione has been shown to give aldol products with excellent diastereomeric excess in the synthesis of (−)-teubrevin G,[101] while intermolecular SmI_2-promoted Reformatsky-type reactions of a number of acetyloxazolidin-2-one derivatives **17** has been investigated with good levels of diastereoselectivity (Scheme 11).[102]



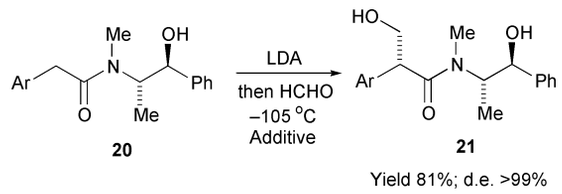
Scheme 11

Examples of transformations of new oxazolidinone auxiliaries continue to be developed. The asymmetric boron-mediated aldol reactions of a new glucose-derived oxazolidinone **18** have been described giving diastereomeric ratios from 3 : 1 to 16 : 1 in favor of the expected *syn*-product **19** depending upon the protecting groups of the carbohydrate and the aldehyde employed (Scheme 12).[103]



Scheme 12

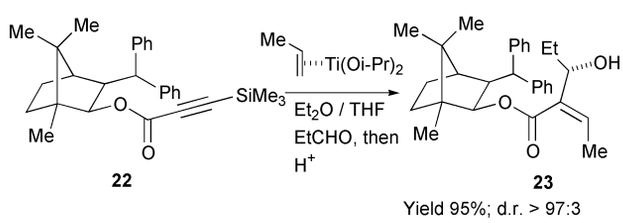
Asymmetric aldol reactions are not limited to employing oxazolidinones or thio-substituted analogues as chiral auxiliaries and many other examples exist that make use of the formation of an amide-type bond in the addition and cleavage steps. Boron enolates of imidazolidin-2-ones[104] and imidazolidinone glycine equivalents[105] undergo highly diastereoselective *syn*-selective aldol reactions with good to excellent diastereoselectivities. Sultams are often comparable in their chemistry to oxazolidinones and have been used in boron-mediated aldol reactions with chiral aldehydes and α-ketoesters.[106] Although the former proceeded with total diastereoselectivity in favour of the *syn*-product, the ketoester gave a 3 : 1 mixture to two diastereomers. Titanium enolates of sultams have also been employed giving the *anti*-aldol product in excellent yield (95%).[107] Amides derived from pseudoephedrine **20** have been used in asymmetric aldol reactions in the presence of different metal cations, in particular zirconocene dichloride gave selectivities of over 99 : 1 in favour of the *syn*-isomer **21** (Scheme 13),[108] and this auxiliary was used in the first asymmetric synthesis of isoflavanones.[109] The aldol reactions of *N*-propionylprolinol derivatives have also been investigated with and without the addition of Lewis acids.[110]



Scheme 13

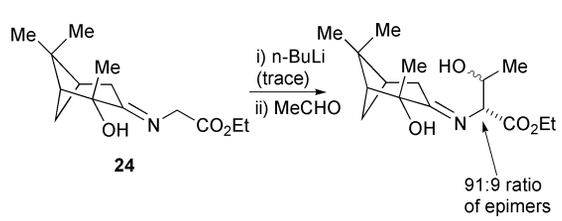
A number of auxiliaries make use of the formation of esters and acetals to facilitate the attachment or cleavage steps. Paterson *et al.* have made use of the excellent diastereoselective control in the aldol reaction of boron enolates derived from chiral ketones in an auxiliary type fashion.[111] Thus, after the desired aldol reaction had taken place, oxidative cleavage of the stereodirecting group was achieved, although this destroyed the stereochemistry of the attached chiral auxiliary.

Relatively few examples of aldol reactions with terpene-derived auxiliaries have been reported. Thus, menthol- and camphor-derived acetylenic esters **22** have been used in titanium-mediated additions giving Baylis–Hillman products **23** with good regioselectivities and varying diastereoselectivities (Scheme 14).[112] The best auxiliary was found to be the alcohol derived from D-camphor giving diastereoselectivities >97 : 3 for a range of structurally diverse aldehydes.



Scheme 14

Camphor derivatives have also been used as the stereodirecting group in a Darzens reaction of α-bromoacetyl substrates giving epoxides of >97 : 3 diastereoselectivity,[113] while a novel pinene-based auxiliary has been prepared and used in asymmetric aldol reactions with poor to moderate diastereoselectivities.[35] Aldol reactions of aza-enolates derived from the hydroxypinanone derivative **24** have been carried out using a catalytic quantity of base giving good diastereocontrol at the α-carbon but essentially no control at the β-centre (Scheme 15).[114]



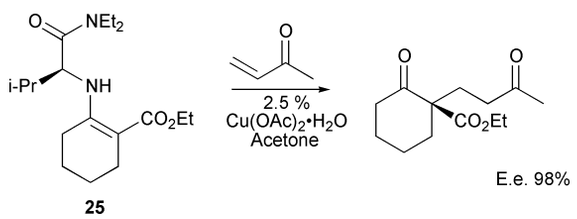
Scheme 15

Seebach's self-reproduction of chirality has been demonstrated on a 100 g scale in the synthesis of (*S*)-oxybutynin[115] and in the synthesis of a chiral spiro aminochromane,[116] the latter giving poor levels of stereocontrol at the newly formed stereogenic centre.

Boron and titanium enolates of chiral α-chloromethyleneoxazolines give oxazolinyl oxiranes when treated with ketones in excellent diastereoselectivity.[117] Other asymmetric aldol processes include the reaction of dienolates derived from chiral oxazolidines with aldehydes,[118] a diastereoselective Mukiyama aldol reaction of a chiral furyl sulfoxide,[119] the synthesis of enantiomerically pure mono- and bis-epoxides of isoprene using Ley's dispoke protected lactate,[120] and addition of (*E*)-enolates to chiral dithiane ketone equivalents.[121]

2.3 Michael additions

Michael additions are particularly important transformations as they facilitate bond formation β to a carbonyl centre and often allow construction of quaternary carbon centres. Examples of this include the use of a chiral aza-enolate in the first steps of the synthesis of some polycyclic diterpenes[122] and chiral enamines **25** derived from β-oxoesters that react under copper catalysis at ambient temperature and without an inert atmosphere (Scheme 16).[123]



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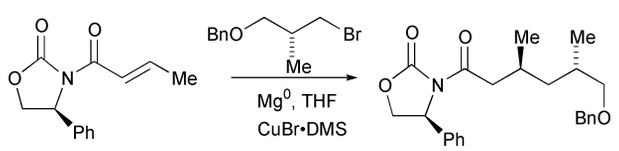
Scheme 16

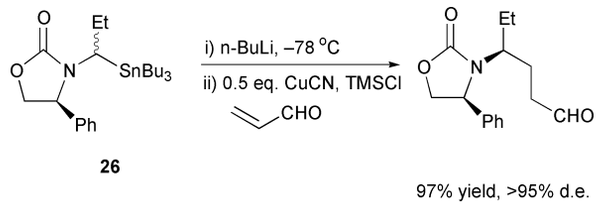
Addition of cuprate and organocopper reagents to chiral acceptors is a well used method for performing conjugate additions. Lithium alkyl cyanocuprates undergo highly diastereoselective conjugate addition from the least hindered *exo*-face to chiral bicyclic lactams and this has been applied to the synthesis of *trans*-3,4-disubstituted piperidines.[124] The addition of various cuprate and organocopper reagents to unsaturated *tert*-leucine oxazolidinone acceptors has been investigated with and without an added Lewis acid with excellent levels of diastereoselectivity.[125] Similar acceptors have been used in the synthesis of kalkitoxin,[126] an α,β-substituted histidine analogue[127] and 3′*O*,4′*O*-dimethylfuniculosin (Scheme 17).[128]



Scheme 17

Organocopper and organoaluminium reagents have also been used in domino Michael–aldol and Michael–Mannich reactions with chiral oxazolidinones to construct highly functionalised cyclohexane frameworks.[129] In an interesting switch, organolithium reagents based on chiral oxazolidinones **26** undergo copper-mediated Michael addition to an unsaturated aldehyde with excellent levels of diastereocontrol (Scheme 18).[130]

Addition of organocopper reagents to unsaturated chiral phosphonate derivatives gave good to poor levels of diastereoselectivity.[131] Under appropriate circumstances, organolithium



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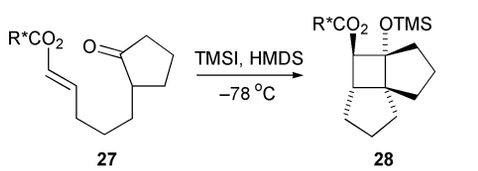
Scheme 18

and magnesium reagents can also add to chiral acceptors without the aid of copper additives. Diastereoselective Michael addition of MeLi to a vinyl selenide bearing a cyclohexanol auxiliary followed by quenching with an alkyl halide gave >15 : 1 diastereoselectivity.[132] Highly diastereoselective Grignard addition–alkylation to chiral aryloxazolines and imines have been shown to occur in good yield *via* an unusual Michael addition of the nucleophile directly to an aromatic ring.[133]

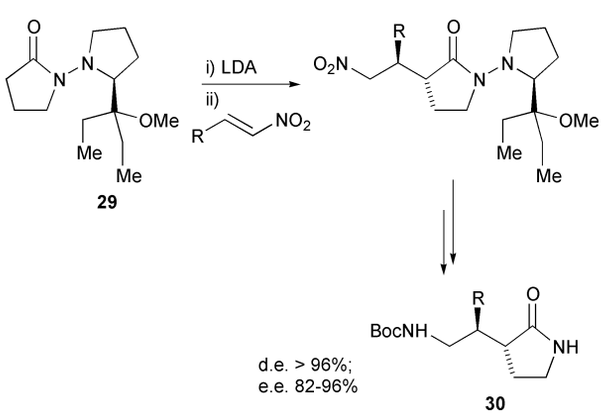
Carbon-based nucleophiles derived from enolates or enolate equivalents are generally more useful in Michael additions than alkyllithium and magnesium reagents since the conditions for their generation are invariably less harsh. Enolates themselves have been used in the synthesis of a key intermediate of a muscarinic M-3 receptor antagonist,[134] the novel H_3 agonist Sch 50971[135] and in the synthesis of pyroglutamates.[136] An interesting example of an asymmetric intramolecular tandem Michael–aldol reaction of an enolate with phenylmenthyl enoates **27** gave tricyclic structures **28** with excellent levels of diastereoselectivity (Scheme 19).[137]



27 **28**

Scheme 19

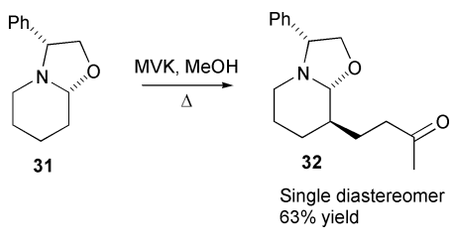
Glycine-derived enolates have been used in the synthesis of pyroglutamates,[138] and nickel(II) Schiff base complexes of such enolates found to react with α,β-unsaturated oxazolidin-2-one acceptors in excellent yield and diastereoselectivity.[139] The origin of the selectivity of this reaction was investigated in some detail and the stereochemical outcome was found to be independent of the stereochemistry of the Schiff base.[140] Aza-enolates generated from chiral imines have been shown to undergo Michael additions with excellent levels of diastereoselectivity[141] and used in the synthesis of (+)-α-vetivone.[142] α-Substituted δ-lactams **30** have been prepared *via* Michael addition of the enolate of a chiral hydrazone **29** to nitro alkenes with good to excellent levels of stereocontrol (Scheme 20).[143]



29 **30**

Scheme 20

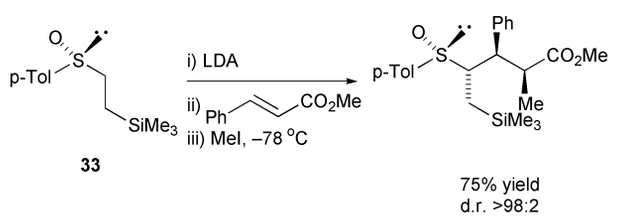
A study of the conjugate addition of an aza-enolate of Schöllkopf's bislactim ether to (*E*)- and (*Z*)-prop-1-enylphosphonates was found to occur with complete diastereoselectivity at the α-centre and excellent selectivity at the β-centre in all cases except when HMPA, $SnCl_2$ or $CuBr_2$ were used.[144] In a related reaction, Michael addition of a nitro enolate to a chiral chromium tricarbonyl Michael acceptor proceeded with excellent diastereocontrol.[145] Enolate equivalents are often prepared and reacted under milder conditions than enolates themselves and in this context enamines are very useful reagents as they can be prepared using chiral amines. A phenyloxazolopiperidine derivative **31** has been prepared and used as a latent enamine equivalent in an asymmetric Michael addition with methyl vinyl ketone giving the addition adduct **32** as a single diastereomer in reasonable yield (Scheme 21).[146]



Scheme 21

Enantioselective Michael additions of enamines to nitro olefins have been shown to occur with excellent yield and degrees of diastereoselectivity and the products from these reactions converted into non-racemic pyrrolidines.[147]

Other miscellaneous enolate equivalents have been used to perform carbon–carbon bond formation using Michael additions. 2,6-Dimethylmorpholine has been used as a chiral auxiliary in the Michael addition of Fischer carbene complexes to unsaturated nitro compounds in 75% de and 90% isolated yield.[148] Highly stereoselective conjugate additions of α-carbanions of chiral sulfoxides **33** to unsaturated esters followed by quenching with alkyl halides and aldehydes has been reported (Scheme 22),[149] while C_2 symmetric sulfoxides

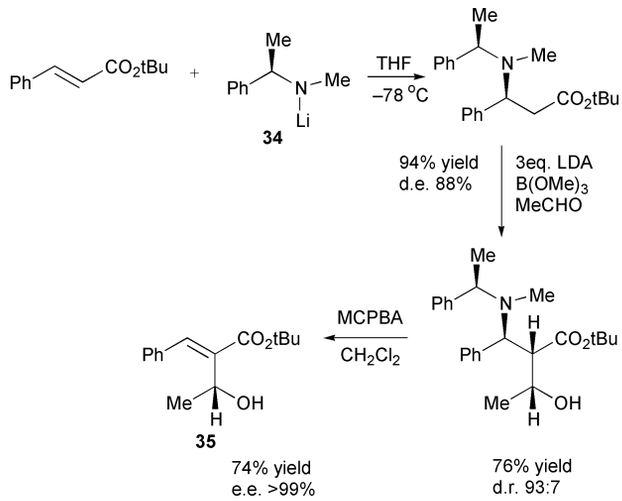


Scheme 22

have been shown to add to stabilised Michael acceptors giving a single diastereomer of addition product.[150]

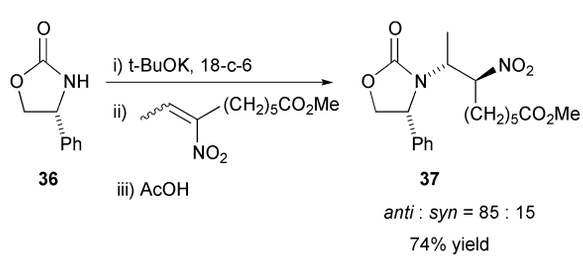
A diastereoselective Michael–Darzens-type addition of a sulfur ylide to an unsaturated chiral sultam has been used to prepare the pheromone of the pine sawfly.[151] Hanessian *et al.* have demonstrated phosphonamide dianions undergo highly diastereoselective Michael additions with ketones, lactones and lactams,[152] while phosphonamide anions have been used in a tandem Michael addition–Darzens-type type reaction to prepare cyclopropanes.[153] The asymmetric Michael addition of alkyl radicals has not received as much attention as other carbon–carbon bond forming processes, although a few reports have been made of addition to unsaturated chiral sulfoxides,[154] a crotonyl group tethered to a carbohydrate in the presence of diethylaluminium chloride[155] and of photosensitized radical addition to chiral fumaric acid derivatives[156] with good diastereoselectivities.

Michael additions are not limited to the formation of carbon–carbon bonds alone and additions of nitrogen nucleophiles are quite commonplace. One of the best-known examples of such reactions is the addition of homochiral ammonia equivalents developed by Davies. This work has been extended through the development of a new route towards chiral Baylis–Hillman products **35** by the diastereoselective Michael addition of a chiral lithium amide **34**, followed by subsequent stereoselective boron-mediated aldol reaction and finally Cope elimination (Scheme 23).[157]



Scheme 23

Bull *et al.* have provided further examples of chiral lithium amide additions to Michael acceptors in the preparation of substrates to demonstrate the debenzylation reactions of amines.[158] Other applications of this methodology have been reported including the synthesis of β-haloaryl β-amino acids,[159] cyclic β-amino acids,[160] β-homolysine,[161] plakoridine A,[162] trisubstituted piperidines[163] and the dihydrobenzofuran segment of ephedradine C.[83] Chiral hydrazines have also been used as ammonia equivalents and employed in the asymmetric synthesis of α-substituted β-amino sulfones[164] and in a stepwise Michael addition–α-alkylation of unsaturated lactones.[165] Michael addition of a chiral oxazolidinone **36** to a nitro olefin gave a good ratio of *anti* : *syn*-addition products **37** (85 : 15) that were used in the synthesis of dethiobiotin (Scheme 24).[166]

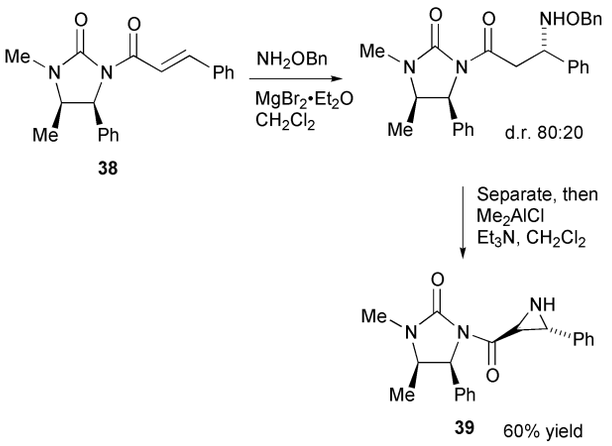


Scheme 24

Asymmetric Michael addition of amines has also been carried out using chiral acceptors. Addition of resin-bound amino acids to a chiral oxazolidinone acceptor proceeded in good to poor diastereoselectivity,[167] while the synthesis of enantiomerically pure aziridines **39** was accomplished by a fairly diastereoselective (80 : 20) addition of a hydroxylamine to a chiral imidazolidinone acceptor **38**, followed by separation and cyclisation (Scheme 25).[168]

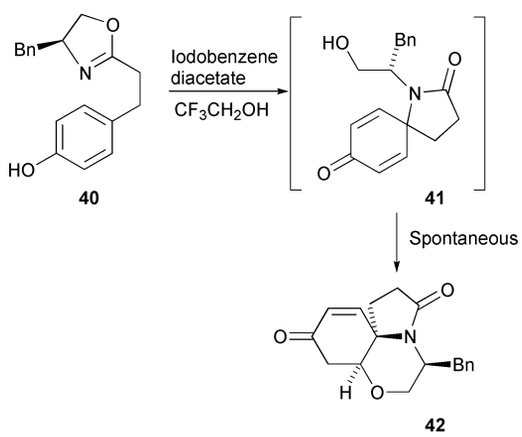
Addition of amine and alcohol nucleophiles to chiral α,β-unsaturated sulfamines has been shown to occur with good levels of diastereoselectivity, although this is limited in scope as the nucleophile must be used as the solvent.[169]

Oxygen-based nucleophiles have been used less often in such reactions. Two consecutive diastereoselective Michael additions of a propargylic (prop-2-ynyl) alcohol to a chiral unsaturated sulfoxide have been used in the synthesis of (+)-



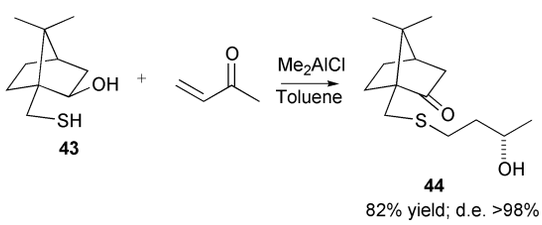
Scheme 25

asteriscanolide.[170] Oxidative cyclisation of chiral phenolic oxazolines **40** in the presence of iodobenzene diacetate gave an intermediate alkoxyspirolactam **41** that underwent spontaneous intramolecular Michael addition to give a single diastereomer of a tricyclic compound **42** (Scheme 26).[171]



Scheme 26

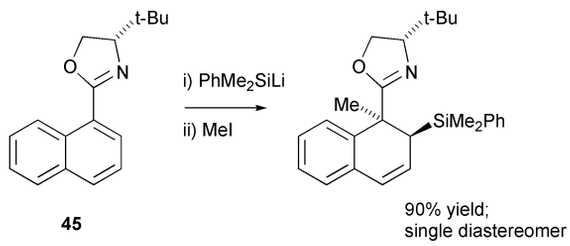
As with oxygen nucleophiles, relatively few examples of sulfur nucleophiles in Michael additions have been reported. Of particular interest is a novel tandem Michael addition and Meerwein–Ponndorf–Verley reduction which has been carried out using the 10-mercaptoisoborneol auxiliary **43** giving alcohols **44** in high yields and excellent levels of stereoselectivity (Scheme 27).[172,173]



Scheme 27

The diastereoselectivity of the addition of thiols to camphor-derived Michael acceptors has been investigated giving a wide range of selectivities and yields depending upon the reaction conditions.[174] Addition of a thiol to cyclic acceptors derived from 3-hydroxybutyric acid gave inseparable mixtures of diastereomers, the selectivity of which depended upon the exocyclic alkyl group.[175]

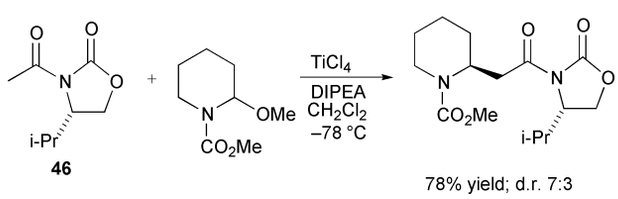
Two other unusual Michael additions warrant attention; Enders *et al.* have developed new methods for the synthesis of α-substituted β-nitrophosphonic acids using a chiral phosphite complex derived from 1,1,4,4-tetraphenyl-2,3-*O*-isopropylidene-L-threitol (TADDOL).[176] Reaction of such diethylzinc-activated complexes with a series of nitro alkenes afforded the desired products in good yield and diastereomeric excess with cleavage of the TADDOL auxiliary giving the nitrophosphonic acids. Degnan and Meyers have reported the only example in this survey of the highly diastereoselective conjugate addition–alkylation of silyl anions to naphthyloxazolines **45** and their application to the synthesis of aminotetralin (Scheme 28).[177]



Scheme 28

2.4 Addition to C=O and C=N bonds

Stereocontrolled addition to C=O and C=N bonds represents an easy route to the introduction of an additional stereogenic centre, and when using enolates or their equivalents as nucleophiles, the formation of a carbon–carbon bond. Oxazolidinone chiral auxiliaries have again been used extensively, primarily in the addition to C=N bonds. Various substitution of *N*-acyl groups has been investigated in some detail to study the addition of enolates of oxazolidinones to iminium ions generated from piperidines.[178] New methodology has also been reported for the synthesis of β-amino acids by the addition of enolates of *N*-acyloxazolidinones **46** to *N*-acyloxyiminium ions generated *in situ* (Scheme 29).[179] The reactions proceeded



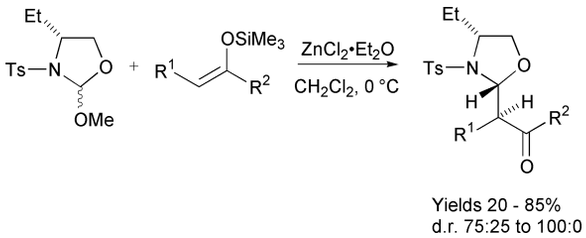
Scheme 29

with moderate levels of selectivity and the main advantage of this methodology is that chiral pyrrolidine and piperidine derivatives are easily prepared.

Other types of chiral auxiliary have also been used. Enantioselective reaction of lithium enolates of sultam chiral auxiliaries with diphenylphosphinyl imines gave excellent diastereo- and enantioselectivities.[180] A camphor-derived auxiliary has been used to demonstrate the versatility of an asymmetric Mannich-type reaction giving good to excellent yields and diastereoselectivity.[181] One report described the addition of an enolate to a chiral sulfinyl imine auxiliary in the synthesis of all four stereoisomers of 4-hydroxypipecolic acid.[182]

Enolate equivalents, in particular silyl enol ethers, have also been employed extensively. Addition of silyl enol ethers to chiral imines generated *in situ* gave good to excellent levels of diastereocontrol, the products of which could be transformed themselves into silyl enol ethers that underwent subsequent aldol reaction with excellent degrees of stereoselectivity.[183] Further applications of this methodology have also been reported (Scheme 30).[184]

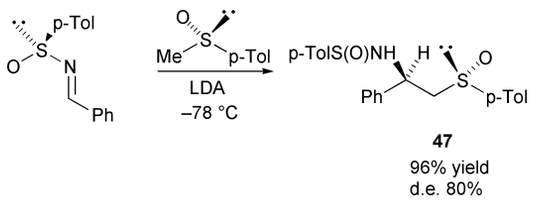
Ytterbium triflate has been used to catalyse the addition of chiral silyl ketene aminals to imines and the diastereomeric ratio was found to be dependent upon the structure of the imine.[185] A similar reaction has also been carried out under Mannich-type conditions.[186] Glycosyl bromides have been used to activate Schiff bases to nucleophilic attack of silylketene acetals.[187] Good yields were obtained but with moderate levels



Scheme 30

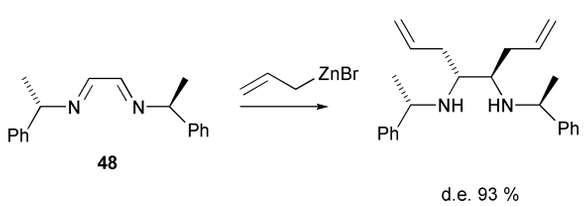
of diastereoselectivity (dr generally 3 : 1) which was shown to be due to *E* to *Z* isomerisation of the C=N bond after activation.

α-Carbanions of chiral sulfoxides have been used as chiral carbon nucleophiles. Thus, lithiation of the benzylic position of a chiral sulfoxide followed by quenching with a chloroformate, aldehyde or ketone gave the desired products in excellent diastereomeric excess.[188] In the case of prochiral ketones and aldehydes, good to poor ratios of epimeric alcohols were formed. Such carbanions have also been shown to add in a matched/mismatched fashion to chiral *N*-sulfimines **47** (Scheme 31).[189] In the matched case a diastereomeric excess of over 98% in 99% yield was observed.



Scheme 31

Although in general significantly more reactive, organometallic reagents undergo facile addition to C=O and C=N bonds, sometimes with the added benefit of chelation to improve stereochemical control. In particular, addition of Grignard reagents to chiral imines has been widely used, for example, in the synthesis of 4-hydroxypipecolic acid by addition to a chiral pyridinium salt,[190] in the preparation of chiral substituted piperidines,[191] and in the three step synthesis of an HIV non-nucleoside reverse transcriptase inhibitor.[192] An in depth study has been carried out using allylmagnesium and zinc reagents with bisimines **48** bearing the α-methylbenzylamine stereodirecting group (Scheme 32)[193] and independent studies have

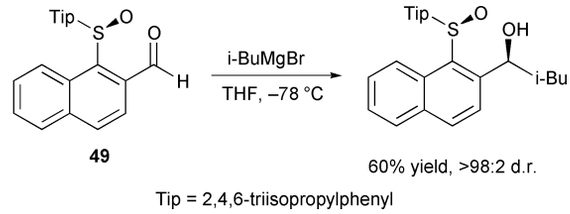


Scheme 32

shown that dynamic kinetic resolution may be observed with Grignard additions to such species.[194]

Grignard addition to chiral aza-acetals proceeded with reasonable levels of stereoselectivity dependent upon the Grignard reagent,[357] and reactions with related C_2 symmetric bisoxazolidines have also been investigated.[195] An in depth study of the enantioselectivity of the addition of Grignard reagents to chiral sulfinyl imines has also been carried out.[196] Nakamura *et al.* have investigated the diastereoselective addition of Grignard reagents to axially chiral aryl sulfoxide aldehydes **49**,[197,198] the selectivity of which was dependent upon the structure of the sulfoxide and any additive (Scheme 33). Attempted addition of silyl enol ethers gave poorer diastereoselectivities.

The only surveyed report of the asymmetric addition of

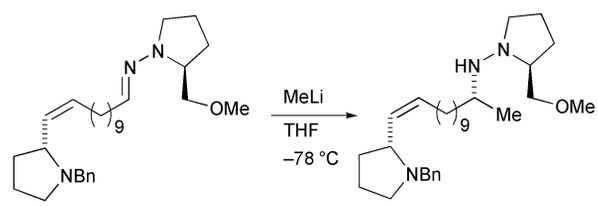


Tip = 2,4,6-triisopropylphenyl

Scheme 33

a Grignard reagent to a ketone has been the addition of 2-naphthylmagnesium bromide to a menthyl pyruvate ester with poor levels of diastereocontrol.[199]

Organolithium reagents have also been employed with good degrees of success. Studies of the addition of such reagents to chiral 1-ferrocenylalkanimines,[200] bisimines bearing the α-methylbenzylamine stereodirecting group,[201] chiral oxazolidines,[202] and aldehydes with axial chirality[203] have all been reported. Addition of organolithium reagents to chiral hydrazones provides excellent degrees of stereocontrol and has been used in the synthesis of a defence alkaloid of the Mexican bean beetle (Scheme 34)[204] and (+)-2-epideoxoprosopinine.[205]



Scheme 34

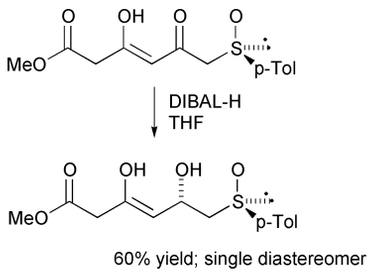
The application of heterosubstituted organolithium species has led to some success, for example, in the addition of lithium carbanions of chiral thiazolidines to aldehydes[206] and lithiated allyl sulfones to chiral *N*-sulfinylamines.[207]

Other organometallic species, primarily organozinc and titanium reagents have been used, presumably due to their availability. Alexakis *et al.* have prepared a new C_2 symmetric diamine in excellent enantiomeric excess by using a diastereoselective addition of allylzinc bromide to an α-methylbenzylamine-derived imine.[208] Reaction of chiral imines with alkenyltitanium[209] and allyltitanium alkoxides[210] have been shown to proceed with good levels of diastereoselectivity. Addition of an allylindium reagent generated *in situ* to an activated ketone bearing a chiral amine gave excellent levels of diastereoselectivity.[211]

Reduction of C=O and C=N bonds provides one of the easiest methods to install a new stereogenic centre. Reduction of chiral imines with zinc borohydride has been extensively studied,[212] and other borane- and alane-derived reducing agents have been used in the synthesis of chiral ferrocenyl amines,[213] 1,2-amino alcohols,[214] tetrahydroisoquinolines,[71] and piperidines.[215] Related hydrazones have been reduced with $LiAlH_4$ with varying levels of stereocontrol using 2-aminobutan-1-ol as an auxiliary.[216]

Chiral keto sulfoxides have been used widely as substrates for asymmetric reductions. The reduction of such γ-keto sulfoxides with and without addition of Lewis acids has been investigated for a number of substrates giving excellent yields and levels of diastereoselectivity.[217] Reduction of a β-keto sulfoxide with DIBAL-H gave >95% diastereomeric excess that could be completely inverted by addition of ZnI_2 to the reaction.[218] Such reductions have been used in the synthesis of chiral 2-amino alcohols[219] and in the synthesis of colletol (Scheme 35).[220]

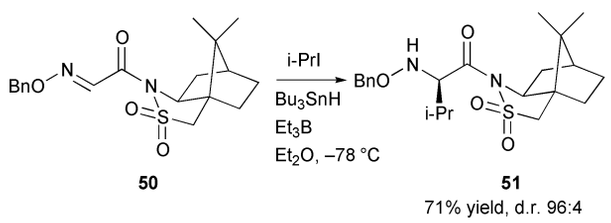
Fewer reports exist for the stereoselective reduction of ketones, presumably as there are now very efficient catalytic methods available for this transformation. The conditions for



Scheme 35

the stereocontrolled reduction of a chiral aziridinyl ketone have been optimised and used in the synthesis of *threo*-β-hydroxy-L-glutamic acid[221] and in the preparation of both enantiomers of 4-hydroxycyclohex-2-enone, an important chiral building block, achieved by using a 1,2-reduction of the chiral cyclohexenone acetal.[222]

Some reports have been made on diastereoselective radical or radical-type addition to chiral carbonyls and imines. *N*-Acylhydrazones based on oxazolidinones have been prepared and have been shown to undergo highly diastereoselective radical addition to give *N*-acylhydrazines[223] and sultam auxiliaries have been used to control the stereoselectivity of the carbon radical addition to oxime derivatives **50** (Scheme 36).[224] These reactions generally proceeded in good



Scheme 36

yield and selectivity (86 : 14 to 96 : 4) and the products **51** were easily converted to α-amino acids.

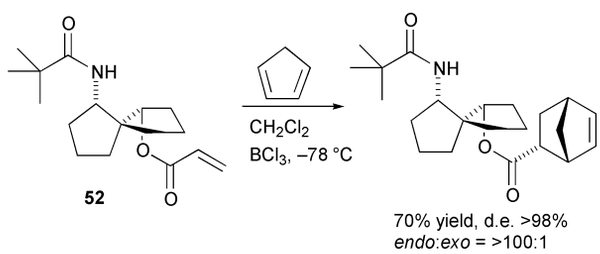
Triethylborane and diethylzinc-mediated radical additions to chiral glyoxylate and cyclic imines gave good selectivities with cyclic compounds and poorer selectivities with open chain substrates.[225] 2-Methoxymethylindolinone has been used as a chiral auxiliary in SmI_2-mediated pinacol couplings to give substituted tartrate derivatives of high enantiomeric purity,[226] while 8-phenylmenthol has been used as an auxiliary in normal and crossed pinacol couplings with reasonable levels of diastereoselectivity.[227]

The asymmetric Strecker reaction is a useful method to prepare chiral amino acids and several methods have been reported that employ this methodology, including the synthesis of the Corey precursor of lactacystin.[228] Use of chiral sulfimines as substrates for this reaction has been disclosed[229,230] and employed in the synthesis of diaminopimelic acids.[231] A number of carbohydrate derivatives have been examined in asymmetric Strecker reactions using α-methylbenzylamine as the stereodirecting group.[232] Diastereomeric ratios from 1 : 1 to 7 : 1 were obtained depending upon the substrate. An asymmetric Strecker reaction has been investigated in some detail with a series of chiral imines based on a racemic cyclopentane framework with varied levels of diastereoselection.[233]

Other miscellaneous additions to C=O and C=N bonds include the use of 1-phenylethylamine in the discrimination of enantiotopic symmetric bisketenes,[234] stereoselective acetal formation in the desymmetrisation of glycerol using camphor sulfamides[235] and in the synthesis of muricatetrocin C,[236] the stereoselective synthesis of *trans*-aryl vinyl epoxides using a chiral sulfur ylide,[237] an asymmetric Friedel–Crafts reaction of a menthyl pyruvate ester[238] and the first example of a highly diastereoselective hydrophosphorylation of a C=N bond.[239]

2.5 Cycloadditions

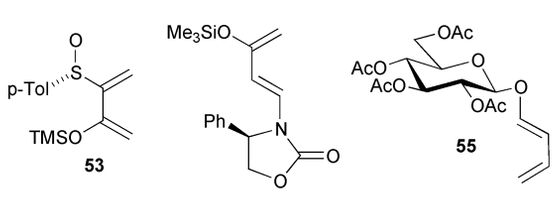
Asymmetric cycloadditions provide an excellent method for the generation of cyclic structures with a number of stereogenic centres. The classical [4 + 2] cycloaddition of a diene with a dienophile may be conducted in an asymmetric manner by installing a stereodirecting group in either of these components. However, the most used approach is to incorporate the chiral auxiliary into the dienophile and the diastereoselectivity of such substrates with classically used auxiliaries such as sultams and hydrazides has been investigated as a function of solvent polarity.[240] Applications of such reagents to synthesis include the use of chiral oxazolidinones in the preparation of the alkaloid (+)-gelsemine[241] and in the synthesis of ceralure B.[242] Extensive investigations of the asymmetric Diels–Alder additions of chiral sulfinyl benzoquinones with dienes have been carried out with and without added Lewis acid.[243–245] Chiral sulfoxides based on naphthoquinones,[246] sulfinyl and menthylsulfonyl furanones[247] have also been employed. Brimble *et al.* have shown that pantolactone or phenylmenthyl auxiliaries exert poor stereocontrol (1.4 : 1) on the cycloaddition of a naphthoquinone derivative and a diene.[248] These auxiliaries also required destructive removal after the reaction was complete. Carbohydrate-derived acrylates based on isomannide[249] and fructose[250] have been employed with good levels of diastereoselectivity, and the origins of the selectivity investigated with the former. Formation of each diastereomer from the Diels–Alder addition of a chiral oxazoline dienophile with cyclopentadiene can be achieved by using either Et_2AlCl or $EtAlCl_2$.[251] A chiral spirocyclic auxiliary **52** has been prepared *via* a lengthy procedure and used in asymmetric Diels–Alder reactions with excellent *endo* : *exo* ratios and enantiomeric excess (Scheme 37).[252]



Scheme 37

Diels–Alder additions of exocyclic methylenemorpholinones have been described including cyclopropanation and reduction, both with excellent levels of selectivity.[253] A new chiral glycine anion equivalent has been disclosed derived from α-amino-isovalerophenone and been used in the preparation of cyclopropyl and norbornane α-amino acids with excellent enantioselectivity.[254]

In contrast to employing a stereodirecting group in the dienophile, surprisingly few reports have been made that use a stereodirecting group in the diene. Those that have been used include a chiral sulfoxide butadiene derivative **53**[255] and oxazolidinyl **54**[256] and glycosyl **55**[257,258] dienes (Scheme 38).

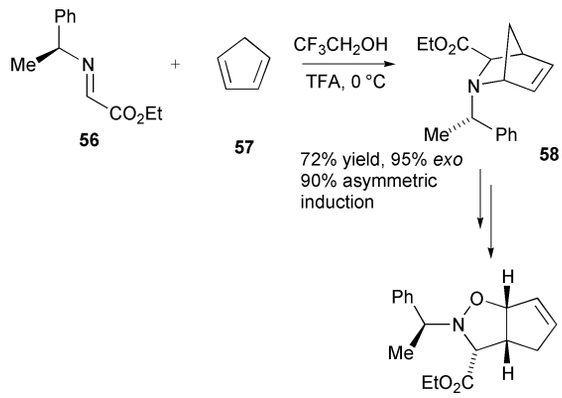


Scheme 38

A few examples also exist that use a tethered diene and dienophile or have used the auxiliary in both such components in the synthesis and include (−)-aminomenthol in the synthesis of

tetrahydroepoxyisolindolines,[259] (*R*)-2-phenylglycinol in the synthesis of solanoeclepin A,[260] and menthol in the synthesis of kuehneromycin A.[261]

Hetero-Diels–Alder reactions provide the added advantage of the introduction of a heteroatom into the reaction product and can often result in excellent stereoselectivities. Use of a chiral amine as the auxiliary in the imine component of an aza-Diels–Alder reaction is a strategy that has been employed successfully. Bailey *et al.* reported such an addition of cyclopentadiene **57** with an imine derived from ethyl glyoxylate **56** with 90% asymmetric induction (Scheme 39).[262] The [3.3.0] bicyclic systems **58** formed were subsequently converted to the *N*-oxides that spontaneously underwent a Meisenheimer-type rearrangement.



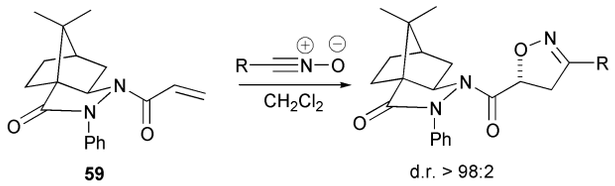
Scheme 39

A similar reaction has been performed with heterocyclic imines bearing the α-methylbenzylamine stereodirecting group in the presence of a Brønsted acid to give good yields and diastereoselectivity of the cycloadducts.[263] A Lewis acid-catalysed Diels–Alder addition of a chiral imine and a diene has been reported with varying degrees of diastereoselectivity.[264]

Hetero-Diels–Alder reactions have also been performed using highly reactive chiral nitroso species. Stereodirecting groups such as chiral *P*-nitrosophosphates,[265] carbohydrates,[266,267] and pyroglutamates[268] have been successfully used in this manner and, in the case of a nitroso sultam, employed in a formal synthesis of (−)-epibatidine.[269,270]

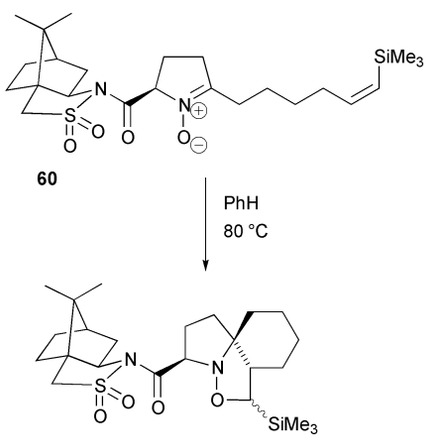
Several examples of an asymmetric Staudinger reaction have been reported that allow access to β-lactams, and auxiliaries that have been used in this reaction (with varying levels of stereocontrol) include chiral pyrrolidines,[271] a new class of D-xylose-derived oxazolidinones,[272] (+)-carene,[273] and 2-phenylcyclohexanol.[274] A double asymmetric [2 + 2] cycloaddition has also been carried out providing a single diastereomer in excellent yield.[275] Asymmetric nitrile oxide cycloadditions have attracted considerable attention and the stereoselectivities of such intramolecular cyclisations have been investigated with a range of chiral auxiliaries.[276] Only one report in this survey provided an example of chiral nitrile oxides from mannitol that reacted with 2-methylfuran with poor selectivity (3 : 2).[277] However, a number of examples where the chiral auxiliary has been installed in the acceptor have been reported. Magnesium ions were found to be essential for high diastereoselectivity in the nitrile oxide addition to chiral *N*-acryloyloxazolidinones[278] and reactions with polymer-bound acceptors of this type have been investigated both in solution and with Merrifield and Wang grafted auxiliary.[279] In general, the regio- and enantioselectivities were comparable but the solution yields were higher. Addition of nitrile oxides to camphor-derived auxiliaries **59** has been shown to occur with excellent diastereoselectivity in dichloromethane which dropped when THF was used as a solvent (Scheme 40).[280]

Moving down one oxidation state from nitrile oxides, a number of examples of asymmetric addition of olefins to



Scheme 40

nitrones have been reported including using camphor derivatives in a formal synthesis of a carbapenem,[281] the preparation of aza-2′,3′-dideoxynucleosides employing diastereoselective addition of a Vasella-type nitrone to vinyl acetate,[282] using new morpholinone nitrones in the synthesis of carbocyclic polyoxin C,[283] and in additions of furfural nitrones to an *N*-acryloyl chiral sultam.[284] A chiral nitrone **60**, itself prepared as a single diastereomer, has been used in intramolecular 1,3-dipolar cycloadditions with poor regioselectivity but excellent diastereoselectivity[285] and this methodology applied to the synthesis of cylindricine-type alkaloids (Scheme 41).[286]



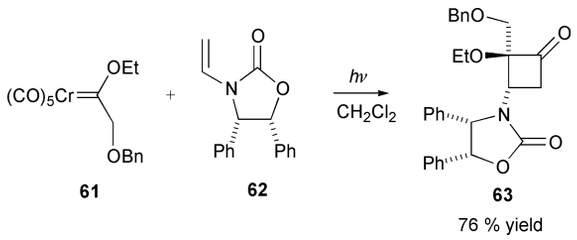
Scheme 41

Asymmetric nitrone cycloadditions have also been used in the synthesis of indolizidines using chiral nitrone[287] and olefin acceptors.[288] Denmark and co-workers described alternative routes to similar targets by making use of elegant tandem asymmetric [4 + 2]/[3 + 2] cyclisations giving products with good to excellent levels of diastereoselectivity that were used in the synthesis of (+)-casuarine, (−)-7-epiaustraline and (−)-1-epicastanospermine.[289,290]

Azomethine ylides have previously been used extensively in the facile preparation of polycyclic ring systems and novel amino acids. Intramolecular 1,3-dipolar cycloaddition of chiral morpholinone azomethine ylides with alkenes and alkynes has been investigated with semi-empirical calculations and the results agree with experimental observations.[291] Intermolecular variants of this methodology have been used in the synthesis of *syn*- and *anti*-β -substituted α-amino acids[292] and in the syntheses of (+)- and (−)-spirotryprostatin B.[293] Diastereoselective cycloadditions of novel chiral azomethine ylide templates bearing two electronically different nitrogen substituents have also been reported.[294] Finally, Carreira and co-workers have reported the asymmetric [3 + 2] cycloadditions of Me_3SiCHN_2 to unsaturated sultams in the synthesis of stelleamide A,[295] and in the preparation of pyrazolines and aspartic acid derivatives.[296]

A number of other miscellaneous types of asymmetric cycloadditions deserve mentioning. Photolysis of the chromium carbene complexes **61** with the chiral ene carbamate **62** gave a good yield of the cyclobutanone **63** as a single diastereomer which was used in the preparation of (+)-aristeromycin and (+)-carbovir (Scheme 42).[297]

In a similar manner, asymmetric [2 + 2] cycloaddition of a chiral chromium tricarbonyl imine with a ketene gave a

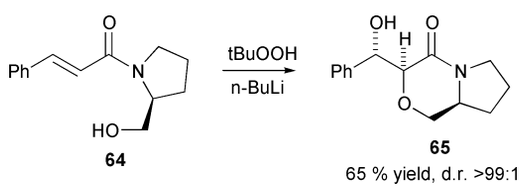


Scheme 42

β-lactam with excellent control of diastereoselectivity.[298] Highly diastereoselective [2 + 2] cycloadditions have been performed using a chiral carbinol enol ether and dichloroketene with total regioselectivity and used in the synthesis of (−)-slaframine.[299] β-Lactams have been prepared with complete diastereoselectivity by asymmetric [2 + 2] cycloaddition of a chiral oxazolidinone tethered ketene and subsequent asymmetric alkylation studies of the β-lactam investigated.[300] Finally, the cycloaddition of a chiral cyclopropyl vinyl sulfoxide with acrylonitrile has been studied giving cyclopentyl derivatives with moderate levels of diastereoselectivity.[301]

2.6 Oxidation

In contrast to many of the other types of stoichiometric asymmetric processes that have been reported, examples of asymmetric oxidation processes are surprisingly scarce. As with asymmetric reduction, this is undoubtedly due to the highly successful catalytic asymmetric processes that now exist developed in particular by Jacobsen and Sharpless. Asymmetric epoxidation of proline-derived cinnamides **64** unexpectedly gave pyrrolidinooxazinones **65** and piperazinediones as the major products in good yield with an excellent ratio of diastereomers (Scheme 43).[302]

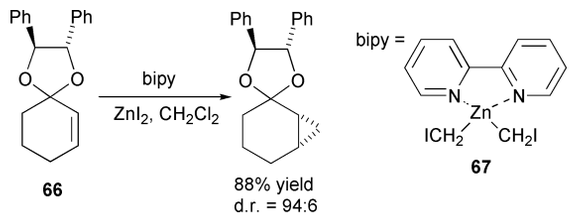


Scheme 43

Dihydroxylation of unsaturated sultams has been shown to proceed with excellent diastereoselectivity for α,β substrates but poor selectivity for the β,γ analogues,[303] while dihydroxylation of a chiral iron tricarbonyl compound has been used in the asymmetric synthesis of halicholactone.[304] Finally, high levels of regio- and diastereoselectivity have been observed in the photooxygenation of chiral vinyl oxazolidines.[305]

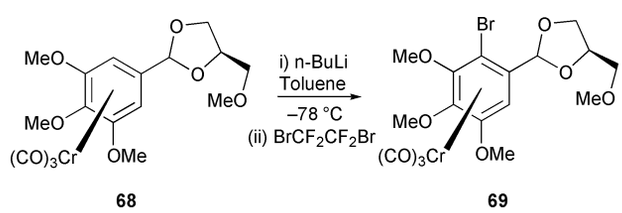
2.7 Miscellaneous uses of chiral auxiliaries

Many natural products contain a cyclopropyl functionality and several methods have been explored for the introduction of such a group in a stereoselective manner, as exemplified in the synthesis of the glycolipids plakoside A and B,[306] (−)-β-cuparenone and (−)-cuparane.[307] Several other methods for asymmetric cyclopropanation deserve attention. Unsaturated chiral oxazolidinones have been converted to cyclopropanes using sulfur ylides in the presence of a Lewis acid with good to poor diastereoselectivities observed.[308] The synthesis of enantiomerically pure *cis* configured cyclopropyl boronic esters has been achieved for the first time[309] and similar methodology used to investigate the asymmetric cyclopropanation of alkenes bearing a borate ester auxiliary and a chiral substrate. In this case, the diastereoselectivity of those reactions using diazomethane were found to be auxiliary-controlled while the selectivity of Simmons–Smith cyclopropanation was controlled by the substrate.[310] Bimetallic iron carbene–chromium tricarbonyl complexes have been used as substrates in the enantioselective synthesis of cyclopropanes giving enantioselectivities of >95% in some cases, the stereochemistry of which was controlled by the chromium moiety.[311] Asymmetric cyclopropanation controlled by a chiral acetal **66** has been carried out using stable haloalkylzinc bipyridine derivatives **67** with excellent diastereomeric ratios obtained (Scheme 44).[312]



Scheme 44

Asymmetric deprotonation, the stereochemistry of which is controlled by an adjacent stereodirecting group, is an excellent method for the selective remote introduction of functional groups. Asymmetric lithiation of an allyl carbamate induced by a complexing remote chiral group gave excellent diastereoselectivity after quenching with an electrophile, such as MeI.[313] Directed metallation of arene transition metal complexes has been used successfully in many applications. Ortholithiation of an arene chromium tricarbonyl complex bearing a tartrate ligand followed by quenching with DMF proceeded in excellent diastereoselectivity (de >94%).[314] Subsequent additions of organolithium and magnesium species to the aldehyde products of this reaction were investigated in some detail with diastereomeric excesses ranging from 82 to 94%. Directed metallation of a chromium tricarbonyl complex **68** and subsequent bromination controlled by an acetal stereodirecting group allowed the preparation of a key intermediate **69** in the synthesis of (−)-steganone (Scheme 45).[315] Similiar methodology was used



Scheme 45

in the synthesis of korupensamine A[316] and in an independent synthesis of (−)-steganone.[317]

The synthesis of planar chiral *ortho*-functionalised ferrocenyl ketones has been achieved in good enantioselectivity (71–96%) using asymmetric deprotonation mediated by chiral hydrazones[318] and *O*-methylephedrine.[319] Similar methodology was used to prepare ferrocenes with planar and central chirality.[320] Kagan has prepared enantiomerically pure ferrocene-based phosphines with only elements of planar chirality using asymmetric deprotonation mediated by chiral sulfoxides that can later be removed.[321]

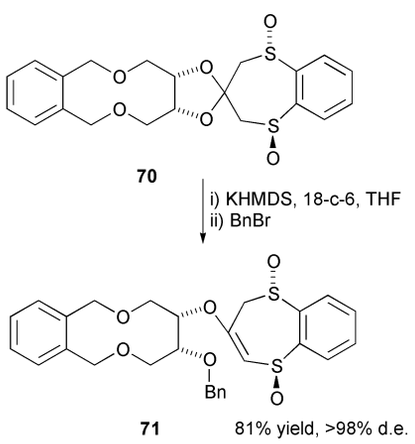
Chiral enolates have not just been used in asymmetric alkylation and aldol reactions. Asymmetric amination α to a carbonyl has generated significant interest for use in amino acid synthesis. Potassium enolates of chiral oxazolidinones have been used successfully when reacted with trisyl azide (trisyl = 2,4,6-triisopropylbenzenesulfonyl) in the synthesis of an α-azidophosphotyrosyl mimic[322] and in the synthesis of glycopeptide antibiotics related to teicoplanin.[323] Such enolates bearing a β-stereogenic centre undergo highly diastereoselective aziridination with complete control of stereochemistry from the oxazolidinone stereogenic centre only.[324] An interesting practical observation has been made in the quenching of such enolates with trisyl azide.[325,326] Reproducible yields (75–95%) of the

desired azides were obtained by addition of the solid trisyl azide in one portion at −78 °C. Electrophilic amination of enolates of chiral dithianes has been achieved with dibutyl azodicarboxylate giving relatively good levels of stereoselectivity, but with some loss of stereochemical integrity of the products that may have resulted during derivatisation procedures.[327]

Halogenation of chiral enolates is also of considerable synthetic importance. α-Fluoroalkylphosphonates have been prepared by quenching of the enolate of a chiral phosphonamide with *N*-fluorobenzenesulfonimide with poor selectivities.[328] Davis *et al.* have used a highly diastereoselective fluorination of a dienolate of a chiral oxazolidinone in the synthesis of fluorinated carbohydrates.[329] Other asymmetric halogenation reactions include stereoselective bromohydrin formation using glucose-derived auxiliaries to control the addition to a Michael acceptor,[330] asymmetric bromination of acetals derived from tartrate derivatives,[331] and an intramolecular bromoetherification of a chiral aldehyde to effect the kinetic resolution of norbornene-type substrates.[332,333] Radical bromination and subsequent alcoholysis have also been investigated using a glucose-derived stereodirecting group giving good to poor levels of regio- and stereocontrol.[334]

Asymmetric ring opening reactions of chiral acetals and azaacetals with nucleophiles has been performed with varying degrees of success. Allylsilanes have traditionally been used in nucleophilic additions to imines generated *in situ* and examples such as reaction with chiral bicyclic oxazolidines,[335] chiral α-sulfonylalkylimidazolidones,[336] and atropisomeric lactams[337] have been reported. They have also been used in an intramolecular route to prepare piperidines,[338] in the synthesis of (−)-coniceine[339] and pipecolic acids.[340] Lewis acid-mediated reaction of chiral silylketene and thioketene acetals with acetals and peroxyacetals has been studied with a number of auxiliaries, but poor selectivities have been observed.[341]

Enantiomerically pure C_2 symmetric keto sulfoxides have been used to prepare symmetrical acetals **70** that undergo base-promoted asymmetric ring opening reactions giving the benzyl ether **71** in excellent yield and diastereomeric excess (Scheme 46).[342,343]



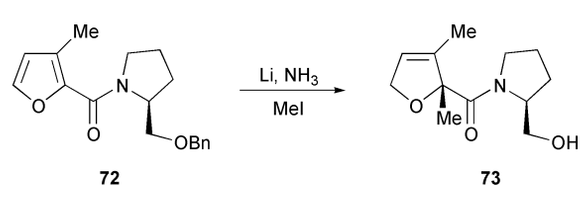
Scheme 46

Chiral oxazolidines derived from (*R*)-phenylglycinol react with dialkylalkynylalane–triethylamine complexes giving alkynylamines in excellent diastereomeric excess[344] while enantiopure substituted pyrrolidines may be prepared by the reduction of chiral bicyclic oxazolidines with $LiBHEt_3$.[345]

A number of miscellaneous reactions of organometallic reagents other than addition to carbonyl compounds have been reported. Cuprates have been shown to add to menthol derivatives in a highly diastereoselective S_N2' reaction, giving alkenes that can be cleaved by ozonolysis to chiral aldehydes.[346,347] Alcohols from *N*-Boc oxazolidines have also been used in S_N2' organocuprate displacements with good stereoselectivities.[348] Chiral α-chloro alkyl borates have been shown to undergo efficient S_N2 displacement with Grignard reagents giving products of >99% ee.[349] Chiral sulfoxides have been prepared by the sequential ring opening of chiral sulfites using organolithium and magnesium reagents.[350] Stereocontrolled addition of Grignard reagents to chiral pyridinium salts facilitated access to tetrahydropyridines but with only modest levels of diastereoselectivity.[351] Miscellaneous organometallic-based asymmetric transformations include the preparation of D-α-amino acids using a morpholinone template to control the stereochemistry of the condensation of a borate ester and aldehydes,[352] the use of 8-phenylmenthol in samarium iodide-mediated radical formation–reprotonation,[227] asymmetric Friedel–Crafts reaction,[353] and a route to the synthesis of ^{11}C enriched α-amino acids[354] using lithium oxazolidinyl-derived auxiliaries. Reactive intermediates such as radicals and carbenoids have been used to effect stereoselective cyclisations. Such reactions of the former include using a new cyclohexanol chiral auxiliary to prepare chiral cyclopentanes but with low diastereoselectivity,[355] in the asymmetric synthesis of (*S*)-pipecoline using reductive photocyclisation of dienamides controlled by a chiral amine,[356] photoinduced electron transfer in the diastereoselective cyclisation of a prolinol derivative[357] and in the synthesis of pyrrolidines.[358,359] One example of a carbenoid-initiated cyclisation has been reported in the copper(II)-catalysed decomposition of a chiral diazomorpholinone that gave a 1 : 2 mixture of diastereomeric bicyclic adducts.[360]

Stereoselective rearrangements provide an excellent method to introduce new stereogenic centres. Examples that have been reported include a highly diastereoselective thio-Claisen rearrangement using a C_2 symmetric pyrrolidine stereodirecting group,[361] desymmetrisation of a *meso*-*N*-hydroxyimide *via* a chiral Lossen rearrangement using a camphorsulfonyl auxiliary,[362] asymmetric Meisenheimer rearrangements,[363,364] an asymmetric Johnson ortho ester rearrangement of a chiral oxazolidine[365] and a diastereoselective aza-Claisen rearrangement used in the synthesis of (−)-antimycin A_{3b}.[366]

Stereoselective reductions of functional groups other than carbonyl groups have been carried out. Reduction of α,β-unsaturated sultams has been shown to give the highest levels of diastereoselectivity using hydrogenation conditions[367] while the diastereoselective hydrogenation of *ortho*-substituted benzoic acid derivatives has been shown to be most effective using a pyroglutamic acid derivative.[368] Asymmetric Birch reduction followed by quenching with methyl iodide has been optimised using proline-based auxiliaries **72** capable of controlling the intermediate enolate geometry by hindered rotation (Scheme 47).[369] Products **73** with diastereomeric ratios of 93 : 7 have been obtained in this way.



Scheme 47

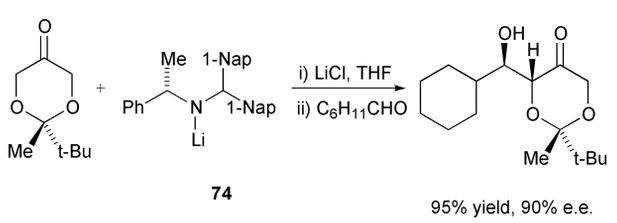
A number of axially chiral biaryls have been prepared using a chiral template based upon L-threitol.[370] BINOL has also been used as chiral tether for $TiCl_4$-mediated oxidative coupling reactions giving chiral 2,3-diarylbutane-1,4-diols as single diastereomers.[371] Axially chiral biaryls have also been prepared using diastereoselective cross coupling reactions and a series of such reactions have been carried out using chiral oxazolines.[372] The selectivity was found to be dependent upon the structure of the substrate and selectivities of up to 8.5 : 1 were obtained.

A number of other asymmetric transformations have been reported that cannot easily be grouped together. An asymmetric variant of a four component coupling of a silyl enol ether, chiral 1-alkoxy-1,3-diene, SO_2 and an alkyl halide has been shown to occur with good to excellent diastereomeric excess, making use of a (*S*)-1-(2,4,6-triisopropylphenyl)ethyl stereodirecting group.[373] A new chiral sulfenylating agent has been prepared and used in the sulfenylation of keto esters with good levels of enantioselectivity dependent upon the substrate structure[374] and chiral diselenides have been used in the methoxy and hydroxyselenenylation of styrene giving good to excellent levels of diastereoselectivity.[375] Chiral nucleophiles have been used in the asymmetric synthesis of β^2-homoglycines by reaction of aryl ketenes with chiral alcohols, giving selectivities of greater than 90 : 10[376] and a similar transformation used in the first stages of a formal synthesis of roseophilin using menthol as the nucleophile, giving selectivities of 5 : 1.[377] Highly enantioselective propenoylation of lithium enolates of oxazolidinones has been carried out in the synthesis of the C13–C19 fragment of sanglifehrin A.[378] Finally, diastereoselective ring opening reactions of *gem*-dibromocyclopropanes controlled by cyclohexyl and menthol derived auxiliaries have been used to prepare the core structures of epibatidine and anatoxin A.[379]

3. Chiral reagents

3.1 Chiral amine and lithium amide bases

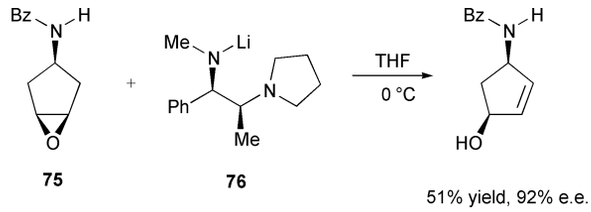
Desymmetrisation of *meso*-ketones using chiral amines or lithium amide bases is now growing more widespread in use in organic synthesis. For example, the first step in the synthesis of the C38–C44 segment of altohyrtin A was asymmetric deprotonation with a chiral lithium amide, followed by silyl enol ether formation that proceeded in 95% enantiomeric excess.[380] This methodology has been further extended by the use of new chiral lithium amides,[381] chiral magnesium amides,[382] in the synthesis of the pseudoguaiane framework,[383] and chiral amine–silyl triflate complexes to generate chiral silyl enol ethers for a subsequent asymmetric tandem Michael–aldol reaction.[384] Asymmetric deprotonation using chiral lithium amides **74** has provided substrates for subsequent asymmetric aldol reactions with good levels of diastereoselectivity (Scheme 48).[385,386]



Scheme 48

Asymmetric deprotonation of epoxides can lead to unexpected rearrangement products and Kee *et al.* have disclosed preliminary observations of such reactions with cyclohexene epoxides.[387] Attempted kinetic resolution of racemic epoxides with a chiral lithium amide base gave the product allylic alcohol (32% yield, 63% ee) and recovered starting material (51% yield, 44% ee). This method forms an excellent route for the preparation of highly functionalised cyclohexyl ring systems. Enantioselective deprotonation–rearrangement of *meso*-amino epoxides **75** gave good levels of stereoselectivity with a number of diamine-derived lithium amides **76** (Scheme 49).[388]

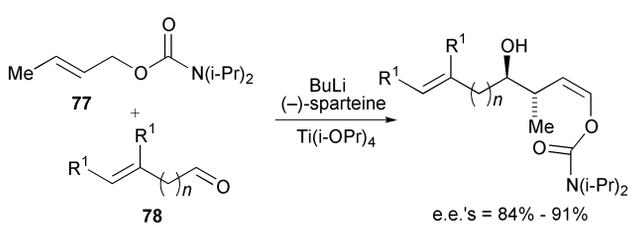
The asymmetric deprotonation and subsequent quenching of substituted arene chromium tricarbonyl derivatives has been extensively studied with a variety of lithium amide bases and aryl directing groups.[389] Axially chiral anilides have also been prepared with varying degrees of enantioselectivity by employing this methodology.[390]



Scheme 49

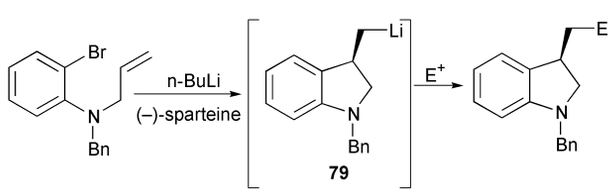
3.2 Sparteine-mediated reactions and related processes

Interest in using sparteine and other chiral amines in mediating asymmetric deprotonation has been gaining momentum and this methodology appears to deliver excellent levels of stereoselectivity in many of the reactions studied. Beak *et al.* have reviewed similar chemistry to this, in particular, the use of dynamic thermodynamic resolution in achieving high levels of stereocontrol with particular emphasis on the use of chiral amines and organolithium species.[391] Several interesting observations have been made in the area of (−)-sparteine-mediated deprotonation–alkylation, including those made by Deiters *et al.*[392] Intramolecular trapping of an allylic anion in the presence of (−)-sparteine with an allylic chloride gave cyclonona-1,5-dienes in excellent enantiomeric excess. Introduction of an additional stereogenic centre in the substrate was found to only affect the diastereoselectivity of the reaction, not the enantioselectivity. A highly enantioselective anionic oxy-Cope rearrangement of the products was also shown to occur. A carbamate protecting group was used in this chemistry to direct metallation and a similar directed asymmetric deprotonation of a carbamate **77** in the presence of (−)-sparteine was followed by quenching with a variety of aldehydes **78**. Excellent enantioselectivities were observed and the products used to make 5- to 8-membered ring unsaturated oxacycles (Scheme 50).[393]



Scheme 50

Wiberg and Bailey have used molecular modeling to propose a transition state for the related enantioselective deprotonation of *N*-Boc pyrrolidine with isopropyllithium–(−)-sparteine.[394] Carbamate groups are not essential for the directed metallation step and other methods have been used to generate the alkyllithium species. Addition of (−)-sparteine to aryllithiums prepared by lithium–halogen exchange facilitated the carbocyclic ring closure with a pendant allyl group giving selectivities of >86 : 14 except when using THF as solvent.[395] Identical work has also been reported with the additional feature that the resultant alkyllithium species **79** was trapped with a number of electrophiles (Scheme 51).[396]

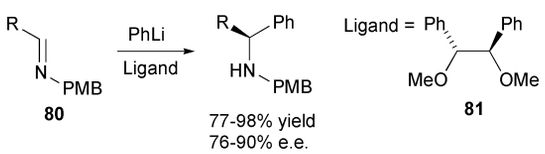


Scheme 51

Nakamura *et al.* have demonstrated that α-thiobenzyllithium reagents react with aldehydes and ketones in the presence of chiral diamine ligands giving good yields and excellent levels of enantioselectivity.[397] Of the diamines studied, bisoxazolines proved to be the most successful, while (−)-sparteine gave the worst results. Optically active phosphine–borane complexes have been prepared using (−)-sparteine–*s*-BuLi deprotonation followed by oxidation.[398] The enantiomeric excess varied with the choice of alkyl group and with 1-adamantyl 93% was obtained. Sparteine-mediated deprotonation of medium ring epoxides has been investigated and gives different products with moderate to good levels of stereoselectivity depending upon the substrate structure and whether $BF_3{\cdot}Et_2O$ is added or not.[399]

Other chiral amines have also been used in similar reactions; chiral bisoxazolines have been used to induce chirality in the reaction of benzylic lithium reagents with benzophenone with good to excellent enantioselectivities.[400] Similar studies have also been reported for methylation reactions.[401] In a study of the catalytic use of a chiral amine in the asymmetric alkylation of achiral lithium enolates, stoichiometric use of these additives gave excellent yields and enantioselectivities using DME as solvent.[402]

Amine and amino alcohol additives have also been used successfully to control the stereochemistry of addition to carbonyl compounds. Diastereoselective additions of monosubstituted acetylenes to aldehydes have been shown to proceed in excellent enantioselectivity using *N*-methylephedrine and zinc triflate.[403] These reactions have the advantage over similar dialkylzinc additions in that the reactions can be conducted in air. The asymmetric synthesis of (+)-salsolidine has been accomplished using the enantioselective addition of an alkyllithium to an imine in the presence of a chiral amino alcohol[404] and a chiral C_2 symmetric methyl ether **81** used to control the stereoselectivity of the addition of organolithium reagents to imines **80** with good to excellent enantioselectivities (Scheme 52).[405]

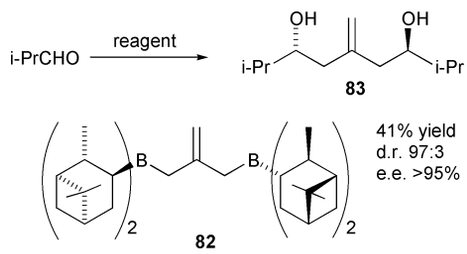


Scheme 52

Similar reactions have also been shown to occur in the presence of stoichiometric quantities of bisoxazoline ligands with different bite angles.[406] Slight variations in enantioselectivities were observed with each of these ligands. The mechanism and structure of the intermediates used in the highly successful addition of lithium acetylides to an aryl trifluoromethyl ketone used in the asymmetric synthesis of efavirnez have been reported.[407]

3.3 Addition to C=O, C=N and C=C bonds

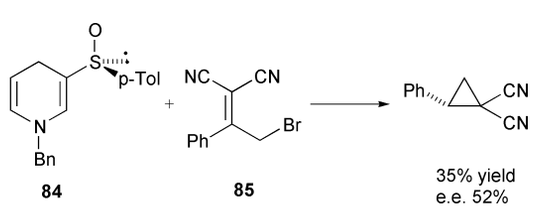
Perhaps one of the most used chiral reagents for addition to C=O bonds are the terpene-derived borane reagents originally developed by Brown and the origins of the stereoselectivity of *β*-chlorodiisopinocamphenylborane [$(Ipc)_2BCl$] reagents have been investigated using molecular modeling.[408] These reagents have been used to introduce the allyl functionality in a stereoselective manner and have been used in the total synthesis of many natural products including the macrocyclic core of apoptolidin,[409] salicylihalamide A,[107] epothilone analogues,[410] lankacyclinol,[411] lamoxirene,[412] cryptophycin-24,[413] the C29–C45 fragment of spongistatin 1,[81] sanglifehrin A,[414] δ-lactones,[415] polyenes based upon (−)-stipiamide,[416] nicotine analogues,[417] and glycosphingolipids.[418] Development of new methodology and applicability is still carried out in this field and Brown himself has reported application of this chemistry in the synthesis of both enantiomeric forms of perfluoroalkyl and aryl homoallylic alcohols.[419] A new method for the preparation of chiral allylsilanes has also been reported using modified chiral allylborane reagents.[420] Barrett *et al.* have described the synthesis of asymmetric bidirectional allylboration reagents **82** and their use in the preparation of C_2 symmetric 1,5-diols **83** in excellent enantiomeric excess (Scheme 53).[421] These diols were used to prepare enantiomerically pure spiroketals.



Scheme 53

Only one example of an asymmetric alkyl transfer reagent that uses a non-terpene stereodirecting group has been reported using the addition of an alkynyl BINOL borate to an unsaturated ketone with high regio- and stereoselectivities.[422]

Use of stoichiometric reducing agents is limited, undoubtedly for similar reasons as covered in Section 2.4. Binaphthol aluminium hydride complex (BINAL) has been used successfully to perform enantioselective reductions in the synthesis of (*S*)-coriolic acid[423] and in the desymmetrisation of thioanhydrides used in the synthesis of *d*-biotin.[424] Biomimetic NADH reagents have attracted some attention and macrocyclic analogues have been evaluated in the reduction of carbonyl compounds[425] while chiral-bridged models have been used in the reduction of pyruvate analogues both with excellent enantioselectivities.[426] Use of chiral dihydropyridine sulfoxides **84** in this sense has facilitated the asymmetric reduction–cyclisation of the ethylidenemalononitrile **85** with low levels of enantioselectivity (Scheme 54).[427] Only one example in this

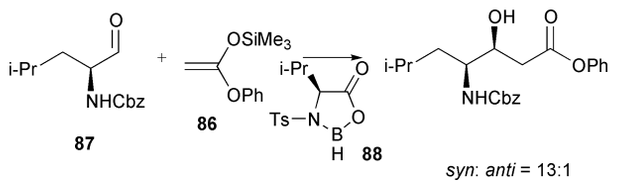


Scheme 54

survey of asymmetric hydroboration has been reported in the reduction of (*E*)- and (*Z*)-2-methoxybut-2-enes.[428]

Chiral organometallic-based reagents have not been widely used, probably due to the difficulty in their preparation and/or expense. Of those described, chiral organotitanium reagents have been studied the most. The total synthesis of (+)-sedamine has been carried out using the key step of the enantioselective allylation of an aldehyde using a chiral titanium complex,[429] methodology that has also been used in the synthesis of the lactone units of compactin and mevinolin.[430] Allylation of acetylenic aldehydes with excellent enantiomeric excess has also been reported with this reagent.[431] Chiral cyclopentadienyltitanium complexes based upon carbohydrates have been used in asymmetric aldol reactions giving the desired aldol products in good yield and enantiomeric excess (>90%).[432] In the only example of a chiral allyltin reagent in this survey, addition of these reagents to *N*-acyliminium ions generated *in situ* proceeded with excellent levels of enantio- and diastereoselectivity.[433] The matched/mismatching characteristics of this reaction were also evaluated.

Enantioselective aldol reactions have been carried out with chiral reagents, the most used of which appear to be chiral oxazaborolidine-mediated condensations with silyl ketene acetals and aldehydes[434,435] and applied in the synthesis of amamistatin A[436] and of a filipin III polyacetate unit.[437] In the specific case of the addition of the silyl ketene acetal **86** to chiral aldehyde **87** in the presence of oxazaborolidine **88**, excellent stereoselectivity was observed for the matched case and inverted stereoselection for the mismatched one (Scheme 55).[438]



Scheme 55

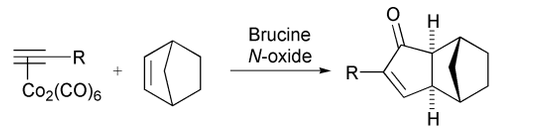
Corey and Choi have examined the use of chiral diazaboroli-dines in asymmetric aldol reactions and applied them to the synthesis of chloramphenicol.[439,440] Chiral boron enolates have been prepared using (+)-$(Ipc)_2BCl$ and used to override the stereocontrolling elements of existing stereogenic centres in the synthesis of (+)-discodermolide.[441]

Several other transformations have been carried out on C=O and C=N bonds. Preparation of a cyclopropylstannane as a key intermediate in the synthesis of dictyopterene A was achieved in excellent enantioselectivity using the Charette asymmetric cycloprotonation methodology.[442] Five molar equivalents of $Zn(CH_2I)_2$ were essential for high enantioselectivities. Chiral nucleophiles can be useful in deracemisation and desymmetrisation reactions. Thus, pantolactone has been used as a chiral nucleophile in the diastereoselective synthesis of α-phenyl δ-amino valeric acid with excellent diastereoselectivity by deracemisation of a ketene intermediate,[443] while ring opening of *meso*-anhydrides with chiral carbinols gave good levels of diastereoselectivity but took 5 days for reaction to occur.[444] Finally, chiral zirconium alkoxides have been used to effect the enantioselective Meerwein–Ponndorf–Verley cyanation of aldehydes giving enantioselectivities of 61–91%.[445]

3.4 Miscellaneous uses of chiral reagents

A number of stoichiometric chiral agents have been used to promote cycloaddition reactions. Diels–Alder addition of butadiene to *N*-acryloyloxazolidinones proceeded in 85% yield and >92% ee in the presence of stoichiometric quantities of TADDOL ligands, products of which were used to prepare δ-peptide analogues of pyranosyl RNA.[446] Significant improvements have been made in the selectivity of such reactions by addition of 4 Å molecular sieves.[447] Chiral titanium(IV) complexes have also been used to promote Diels–Alder reactions of cyclohexa-1,3-diene and *N*-sulfinylbenzoyl carbamate with poor to good enantioselectivities.[448] Other cycloadditions that have been carried out include a photochemical [2 + 2] cyclisation in the presence of a 'chiral host', the purpose of which was to participate in hydrogen bonding and transmit stereochemical information during the reaction, [449] and the use of chiral dioxazaborocines in nitrile oxide and nitrone cycloadditions.[450]

The asymmetric Pauson–Khand reaction has attracted much attention and excellent selectivities have been obtained by preparing and using chiral dicobalt carbonyl reagents based on chiral propargylic alcohols.[451] Chiral dicobalt carbonyl complexes bearing chiral ligands such as phosphines,[452,453] and bidentate (*P*,*S*) ligands[454] have also been employed generally with good selectivities. Optically pure heterobimetallic alkyne–cobalt complexes have also been used with excellent levels of enantioselectivity[455] and brucine *N*-oxide has been employed as an 'external' source of chirality with encouraging enantioselectivities (Scheme 56).[456]



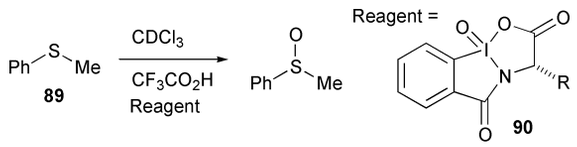
e.r. from 22:78 to 48:52

Scheme 56

A number of reactions involving organometallic species deserve attention; Coldham and Vennall have shown that the rate of cyclisation of chiral organolithium species is considerably slower for the formation of six-membered rings than for five-membered analogues.[457] In the former case, this led to predominant racemisation giving products of low enantiomeric excess. Using a more reactive alkene acceptor increased the rate of the cyclisation giving improved enantiomeric excesses. The synthesis of a chiral secondary Grignard reagent has been achieved by making use of a carbenoid homologation procedure.[458] Once prepared the reagent was found to be configurationally stable at −78 °C, racemising at higher temperatures. Addition of this reagent to phenyl isothiocyanate gave the addition product in excellent enantioselectivity, while oxidation gave secondary alcohols with varying degrees of selectivity. Copper-catalysed Grignard addition to alkene acceptors has been carried out using chiral dioxazaborocines as acceptors.[459]

Chiral organoaluminium reagents have been used to effect the stereoselective displacement of α-bromo amino acids using stoichiometric quantities of BINOL and trialkylaluminiums giving *N*-sulfonyl amino acids with moderate levels of enantioselectivity,[460] while chiral aluminium trinaphthoxide derivatives have been used to effect a regio- and enantioselective siloxybutylation at the more hindered α-site of unsymmetrical ketones.[461] Miscellaneous uses of organometallic reagents include addition of a Reformatsky-type reagent to a nitrone using a tartrate-derived additive[462] and one example of a titanium-mediated dihydrodimerisation of dihydrotetrahydrofurans in good enantiomeric excess using titanium TADDOLates.[463]

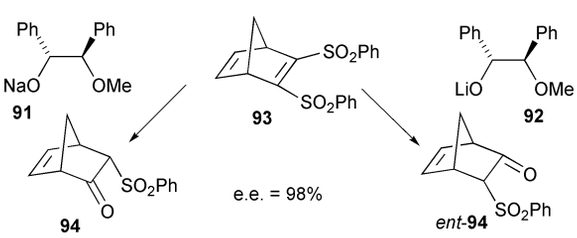
Asymmetric protonation of prochiral enolates has attracted much attention and the use of a wide range of chiral auxiliaries in enantioselective protonation has been studied.[464] Lewis acid-assisted chiral Brønsted acids, such as those derived from BINOL and $SnCl_4$, have been used successfully in enantioselective protonations of silyl enol ether and silyl ketene acetals both stoichiometrically and catalytically.[465] Seebach and coworkers have reported the highly enantioselective protonation (>99% ee) of lithium enolates using TADDOL derivatives[466] and a fluorous chiral proton source gave higher enantioselectivies than a non-fluorous analogue in the asymmetric protonation of a samarium enolate.[467] Enantioselective protonation of an organolithium species was carried out using chiral amines with good degrees of selectivity (83–86% ee) and applied to the synthesis of salsolidine.[468] Chiral bisphosphonates have been shown to adopt linear or cyclic macrocyclic structures when treated with HBF_4.[469] The former gave good levels of enantioselectivity when used in asymmetric protonation, while the latter demonstrated essentially no selectivity. Reasonable levels of enantioselectivity have also been observed by using chiral diamines.[470] Enolates or their equivalents have also been shown to undergo asymmetric fluorination using chiral spirocyclic *N*-fluorosulfonamides[471] and alkylation using a chiral alkylating agent used in the synthesis of (+)-chimonanthine.[472] Several examples of asymmetric oxidants have been reported. Dichlorocamphorsulfonyloxaziridine has been shown to give significantly increased levels of diastereoselectivity (80 : 20) compared to the parent oxaziridine in the asymmetric oxidation of an aromatic sulfide.[473] Chiral hypervalent iodine oxidants **90** have been used in the oxidation of sulfides **91** with poor levels of enantioselectivity (Scheme 57).[474]



Scheme 57

Very few examples of cyclisation reactions that proceed under the influence of a chiral additive have been reported. Lewis acid-assisted chiral Brønsted acids, such as those derived from BINOL and $SnCl_4$, have been used and have also been employed in enantioselective biomimetic cyclisations of isoprenoids with good to moderate levels of selectivity.[475]

Finally in this survey are a group of miscellaneous transformations that cannot easily be categorised elsewhere. A few examples of chiral organophosphorus chemistry have been reported. α-Methylbenzyl- and naphthylamines have been used in lanthanide three component couplings to prepare amino phosphonic acids with moderate diastereoselectivity.[476] Enantioselective ring opening of *meso*-disulfides has been carried out using chiral phosphinamides with low levels of enantioselectivity.[477] Phosphorothiolates containing a stereogenic phosphorus atom have been prepared with good selectivities (20 : 1) using phosphorylating reagents derived from indole.[478] Another asymmetric heteroatom involves the asymmetric amidoselenenylation of alkenes using a camphor-derived selenenylation reagent.[479] Several radical or radical-type reactions have been performed. Inter- and intramolecular asymmetric radical carbon–carbon bond formation of sulfonamides has been studied using chiral diamine or TADDOL ligands with allyltributyltin reagents,[480] while asymmetric pinacol coupling of aromatic aldehydes has been carried out in the presence of chiral amines and hydrazines giving diols with varying degrees of enantioselectivities.[481] Chiral nucleophiles have been used in several applications. Use of either the sodium **91** or lithium alkoxide **92** of a chiral alcohol in the alcoholysis of a bis(vinyl sulfoxide) **93** leads to formation of either enantiomer of product **94** (Scheme 58).[482]



Scheme 58

Desymmetisation of *meso*-norbornadiene diesters with chiral alcohols and thiols gave poor to moderate degrees of diastereoselectivity,[483] while an intramolecular oxy-Michael addition mediated by a carbohydrate derivative gave good levels of stereocontrol.[484]

Finally, an enantioselective Prins reaction has been developed using chiral tin BINOL derivatives that gives reasonable levels of enantioselectivity,[485] and enantioselective acylating agents for amines have been described that perform excellently in kinetic resolutions of racemic piperidines.[486]

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