Amines and amides

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Reviewing the literature published in 1996. Continuing the coverage in *Contemporary Organic Synthesis*, 1996, **3**, 323.

1 Introduction, scope and coverage

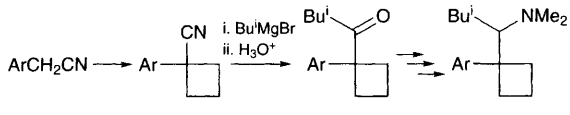
This review covers the literature published during 1996. References were obtained in the same way as in previous years, and the review has the same format as that used last year.[1] During the last twelve months, there has been an explosion of publications dealing with the related fields of solid supported synthesis and combinatorial synthesis. Most of these papers deal with the application of well developed solution phase methodology to solid state reactions, and this area has been extensively reviewed during 1996,[2–5] including a whole issue of *Accounts of Chemical Research*. In view of this, and to keep this report to a reasonable length, papers dealing just with solid phase or combinatorial synthesis have been omitted from this year's review unless they are of special importance, and the interested reader is referred to the reviews cited above.

2 Preparation of amines

2.1 Synthesis of achiral or racemic amines

A large number of reducing agents can be used during a reductive amination procedure to produce secondary amines, with sodium cyanoborohydride being the most common. However, the use of magnesium metal in methanol buffered with acetic acid and triethylamine has now been recommended. The reducing system is highly selective and produces no tertiary amines or alcohols as impurities.[6] The addition of allylic barium reagents to imines occurs with allylic rearrangement at −78 °C, whilst at 0 °C no allylic rearrangement occurs. It was shown that the former reaction occurs under kinetic control, whilst the latter gives the thermodynamically more stable product. The reaction was also extended to chiral imines, with asymmetric induction being observed in both cases, though the low temperature reaction gave the better diastereomeric excess.[7]

Sibutramine **1** is a potential drug for the treatment of obesity, and a synthesis of **1** along with a number of its metabolites has been reported. The synthesis starts from 4-chlorophenylacetonitrile which is first converted into cyclobutane **2**, subsequent addition of iso-butylmagnesium bromide to the nitrile, hydrolysis, reductive amination and methylation gives compound **1** as shown in **Scheme 1**.[8] The achiral amine **3** is an intermediate in the synthesis of the antibacterial agent trovafloxacin, and two syntheses of this amine have been reported. The two syntheses introduce the cyclopropylamine unit via a Curtius rearrangement or by reduction of the corresponding nitro compound respectively, with the latter synthesis being more suitable for the preparation of large quantities of **3**.[9]



2 **1**

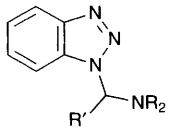
Ar = 4-chlorophenyl

Scheme 1

3

In previous reviews of this area, mention has been made of the α-aminobenzotriazole chemistry developed by Katritzky *et al.* It has now been shown

that in the presence of samarium(II) iodide, α-aminobenzotriazole derivatives **4** act as sources of α-amino-alkyl radicals which, depending upon the reaction conditions, can be reduced, dimerised to diamines, or intramolecularly cyclised onto suitably positioned alkenes, to produce pyrrolidines.[10] An unusual synthesis of *trans*-1,2-diaminocyclobutane by the borane induced ring expansion of an iminocyclopropyl nitrile derivative has been developed as shown in **Scheme 2**. The synthesis allows the preparation of derivatives of *trans*-1,2-diaminocyclobutane in which the two amino groups are differently protected.[11] A synthesis of 1,2-diamines by the diethylamine induced ring opening of 3,4-dinitrothiophene followed by Grignard addition and reduction has also been developed (**Scheme 3**).[12]



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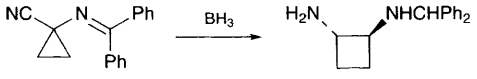
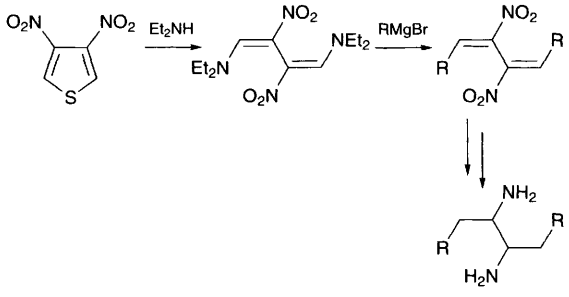


Scheme 2

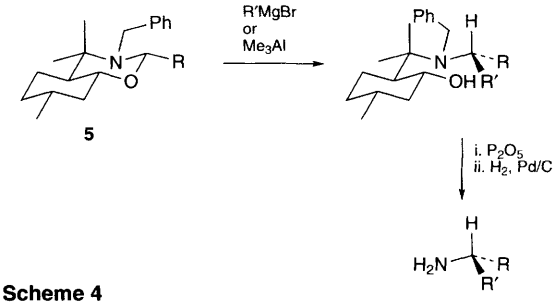


Scheme 3

One of the problems in the synthesis of derivatives of polyamines is to obtain selective reaction at just one of the number of primary and secondary amines present. It has long been known that trityl based protecting groups react selectively with primary amines, and Bycroft and co-workers have now reported that the 1-(4,4-dimethyl-2,6-dioxocyclohexylidene)ethyl group (DDE) also selectively reacts with primary amines. This has allowed the development of solid state methodology for the synthesis of derivatised polyamines.[13] An approach to selectively protected spermidine derivatives from amino alcohols has also been reported.[14]

2.2 Synthesis of optically active amines

Reaction of (*S*)-5-phenylmorpholin-2-one with an aldehyde leads to a chiral iminium salt which undergoes a diastereoselective Mannich reaction with 2-furylboronic acid to give chiral amine derivatives with excellent enantiomeric excesses.[15] The reaction of organometallic reagents with imines derived from (*S*)-1-phenylethylamine has also been studied. The addition of dimethylcuprate–boron trifluoride was shown always to occur on the *si*-face of the imine, whilst the diastereoselectivity of the addition of methyllithium was dependent upon the structure of the imine.[16] The reaction of Grignard reagents or trimethylaluminium reagents with oxazinane **5** occurs stereoselectively from the front face as shown in **Scheme 4**, providing after removal of the chiral auxiliary and benzyl groups a synthesis of enantiomerically pure primary amines.[17] The alkylation of the anions of camphor or pinone imines of 2-(aminomethyl)thiazole occurs diastereoselectively and provides access to chiral 2-(1-aminoalkyl)thiazoles.[18]



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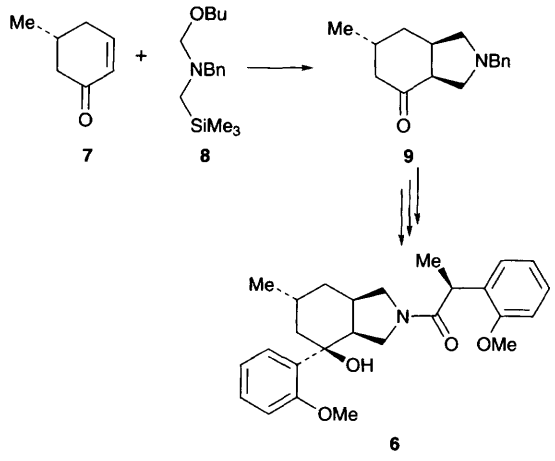
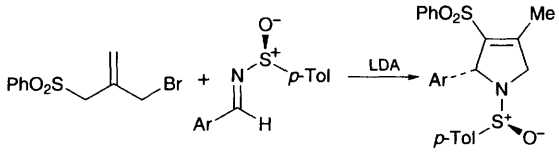
Scheme 4

RPR 107880 **6** is a non-peptidic Substance P antagonist, and a synthesis of enantiomerically pure RPR 107880 starting from (*R*)-pulegone has been reported as outlined in **Scheme 5**. The key step in the synthesis is a 1,3-dipolar cycloaddition reaction between enantiomerically pure enone **7** and aminol **8**, to form bicyclic amine **9** as a 9:1 mixture of diastereomers. The synthesis was completed by diastereoselective addition of *o*-anisyllithium to the less hindered face of the ketone of **9**, hydrogenation of the benzyl protecting group, and amide formation to give RPR 107880.[19] A 1,3-dipolar cycloaddition reaction was also utilised in a synthesis of chiral pyrrolidines as shown in **Scheme 6**. In this case, the 1,3-dipole is the anion of an allylic sulfone, and a chiral sulfinyl imine is the dipolarophile. The diastereomer shown in **Scheme 6** is the major product of the reaction, and subsequent manipulation allows removal of the sulfinyl imine and/or sulfone groups.[20]

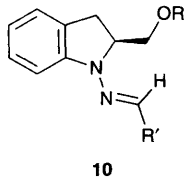


Scheme 5



Scheme 6

A synthesis of enantiomerically pure azetidines from β-amino ketones has been reported. The ketone is first reduced to the corresponding alcohol, either diastereomer of which can be obtained depending upon the choice of reducing agent. Cyclisation to an azetidine is then achieved by treatment with methanesulfonyl chloride.[21] A synthesis of chiral diamines has been developed, which utilises the asymmetric addition of trimethylsilyl cyanide to chiral hydrazones **10**. Subsequent hydrogenation of the α-cyano hydrazines produces the desired chiral diamines.[22] The same authors have also reported the addition of organolithium reagents to hydrazone **10**, producing chiral primary amines.[23] A synthesis of C_2-symmetric diamines from dialdehydes has also been reported, in which the key step is the diastereoselective addition of organocerium reagents to the *bis*-RAMP or SAMP [(*R*)- or (*S*)-1-amino-2-methoxymethylpyrrolidine] hydrazones of the dialdehyde.[24]



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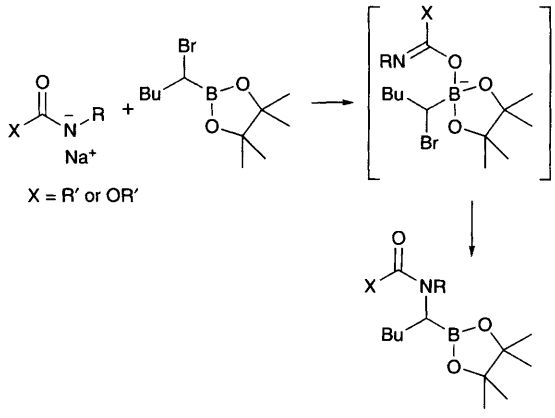
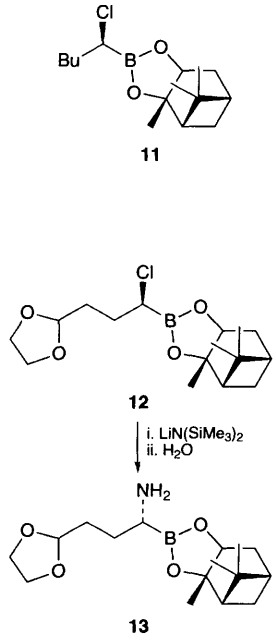
2.3 Synthesis of amines bearing additional functional groups

A versatile synthesis of α-amino boronates has been developed as shown in **Scheme 7**, starting from an amide or urethane and an α-halo boronate. In addition to the achiral case outlined in **Scheme 7**, the methodology is compatible with chiral, proline derived amides and chiral boronic esters. The α-chloro boronate **11** for example reacts with complete inversion of configuration to give enantiomerically pure α-amino boronates.[25] In virtually identical methodology, the reaction of enantiomerically pure α-chloro boronate **12** with lithium hexamethyldisilazide was used to prepare α-amino boronate **13** as shown in **Scheme 8**. Compound **13** was then used to prepare a range of α-amino boronic acid derivatives.[26] Similar chemistry was also employed in an asymmetric synthesis of the boronic acid analogue of ornithine.[27]



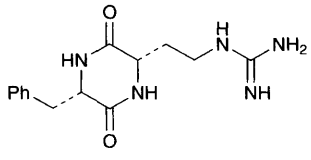
Scheme 7



Scheme 8

Chiral (*S*)-2-amino nitriles as well as the related (*S*)-2-azido nitriles and (*S*)-1,2-diamines have been prepared from chiral (*R*)-cyanohydrins which can be

prepared enzymatically. Thus tosylation of the cyanohydrin, substitution with azide and hydrogenation gives the 2-amino nitriles.[28] In an alternative and more direct synthesis of chiral amino nitriles, the diketopiperazine **14** has been reported by Lipton and co-workers to catalyse the asymmetric addition of HCN to imines, providing optically active amino nitriles. The addition of HCN to a range of aromatic and aliphatic imines was studied, with imines derived from aromatic aldehydes giving the best results (up to >99% ee), though imines derived from electron deficient aromatic aldehydes or from aliphatic aldehydes gave low levels of asymmetric induction. A benzhydryl group was found to be the ideal group to be present on nitrogen, as it could be removed by acidolysis without racemisation.[29] The unnatural guanidine containing amino acid contained in catalyst **14** is prepared from glutamine by a Hoffmann rearrangement, followed by guanylation. However, when carried out in solution these two reactions are low yielding, so the authors have developed a solid phase synthesis of the diketopiperazine catalyst which overcomes these difficulties.[30] The electrolysis of acetonitrile produces an anion which will add to imines producing β-amino nitriles.[31]



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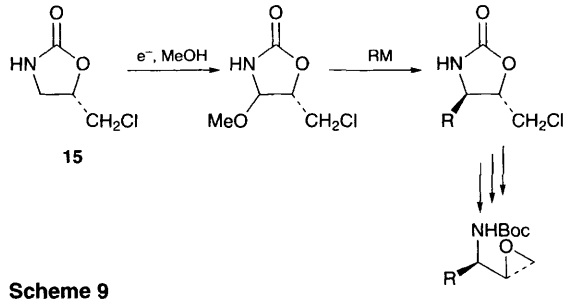
The synthesis of β-amino epoxides from L-malic acid has been reported in which the key steps are the electrolysis of cyclic carbamate **15** and the subsequent diastereoselective addition of organometallic reagents RM as shown in **Scheme 9**.[32] A novel synthesis of β-amino-tetrahydropyrans and -tetrahydrofurans based upon the Lewis acid induced cyclisation of a γ-alkoxyallylstannane onto an *N*-tosylhydrazone has been developed (**Scheme 10**). The reaction selectively produces the product with the α- and β-substituents *trans* to one another.[33] A synthesis of polyhydroxylated nortropane derivatives including the natural product calystegine has been reported, employing a hetero Diels–Alder reaction between a cycloheptadiene and a nitroso compound as the key step.[34] Condensation of 4-amino-1-azadienes with esters of glyoxylic acid produces 2*H*-1,3-oxazines which can be reduced by sodium cyanoborohydride to *syn,syn*-1,3-amino alcohols as shown in **Scheme 11**.[35] The synthesis of 3,6-dihydro-2*H*-1,3-oxazines and the conversion of this heterocyclic ring system into 1,3-amino alcohols has also been reported.[36] α-Hydroxyimines undergo a thermal rearrangement (1,2-carbon shift accompanied by simultaneous 1,4-hydrogen shift) to give α-amino ketones, an example being shown in **Scheme 12**. In those cases where the α-hydroxyimine is chiral, the rearrangement has been shown to occur with retention of stereochemistry.[37] Sharpless' *bis*-hydroxylation methodology was used in a synthesis of γ,δ-dihydroxyamines, by the hydroxylation of an enantiomerically pure allylic amine. By choice of the appropriate alkaloid derived ligands, either diastereomer of the γ,δ-dihydroxyamine could be obtained.[39] A synthesis of β-amino-α,α-difluoro ketones has been reported which employs the reaction between 1,1-difluorovinyl methyl ethers and *N*-acyl imines or their equivalents to construct the carbon–carbon bond between the amino and fluorine groups.[39]



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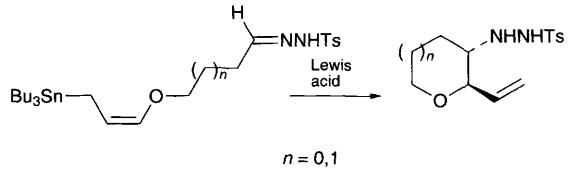
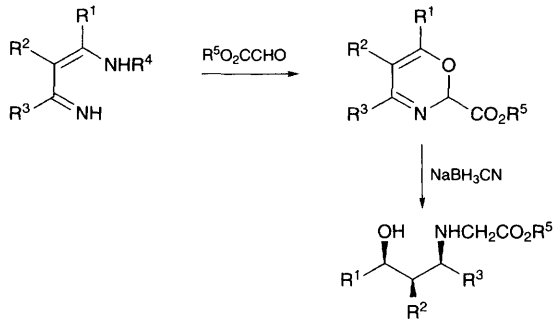
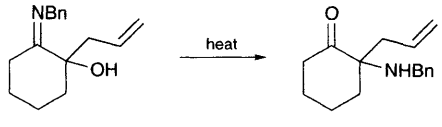
Scheme 9



Scheme 10



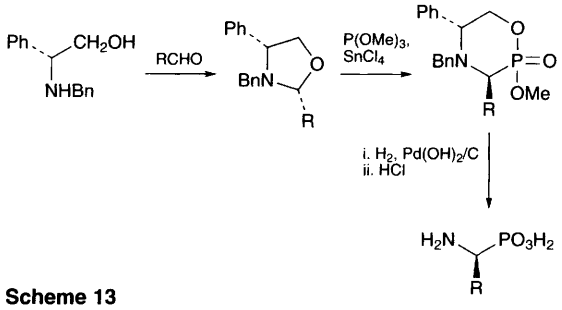
Scheme 11



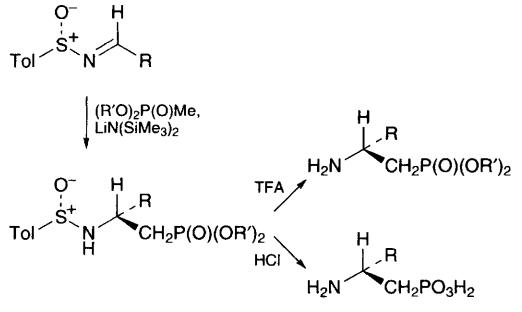
Scheme 12

An asymmetric synthesis of α-amino phosphonic acids has been developed in which the key step is

the diastereoselective insertion of trimethyl phosphite into an oxazolidine as shown in **Scheme 13**.[40] An asymmetric synthesis of β-amino phosphonic acids has also been reported (**Scheme 14**). The key step is the addition of an α-phosphonate carbanion to an enantiomerically pure sulfinyl imine. Subsequent acidolysis under anhydrous conditions led to methyl β-aminophosphonates, whilst acidolysis under aqueous conditions gave β-amino phosphonic acids.[41] Both racemic and enantiomerically pure 2-aminovinyl phosphonates have also been prepared, and can be reduced by sodium borohydride to β-amino phosphonates or converted into allylic amines by olefination followed by reduction.[42] The reaction of an alkene with diphenyl diselenide and sodium azide in the presence of $PhI(OAc)_2$ gives β-phenylseleno azides which can be reduced by triphenylphosphine to β-phenylseleno amines.[43]

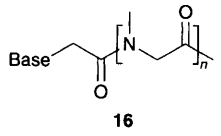


Scheme 13



Scheme 14

Recently, there has been much interest in the synthesis and applications of peptide nucleic acids (PNAs) of general structure **16** due to their ability to form a complex with strands of DNA or RNA. One of the limitations of this approach however, has been the lack of a negative charge within the PNA which adversely affects the solubility of the compounds. The synthesis of the phosphorus analogues **17** has now been reported as shown in **Scheme 15**, to overcome this problem. The key step in the synthesis is the nucleophilic addition of diphenyl phosphite to imine **18**, giving the α-amino phosphonate **19**.[44] An approach for the solid state synthesis of PNA oligomers has also been reported,[45] as has the synthesis of PNA–DNA hybrid polymers,[46] and a synthesis of conformationally constrained peptide nucleic acid derivatives derived from 4-hydroxyproline. For the latter synthesis, the hydroxy group is first substituted for a primary amino group, after which the nucleic acid bases are attached to the secondary amine within the pyrrolidine ring, giving monomers of structure **20**, which can be converted into peptide nucleic acids by standard peptide synthesis methodology.[47]



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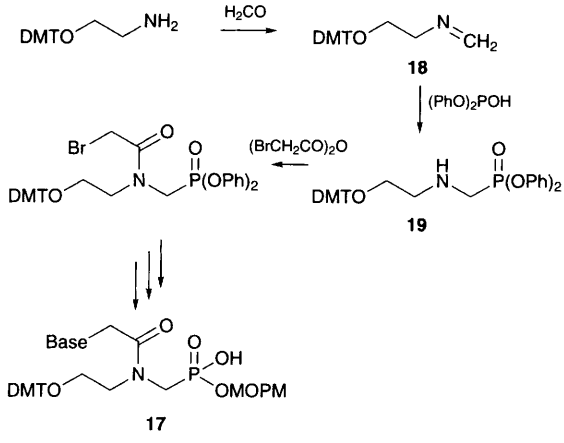
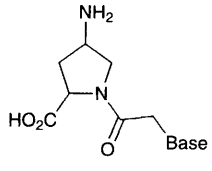


DMT = dimethoxytrityl
MOPM = methoxyphenylmethyl (*p*-methoxybenzyl)
Base = thymine or cytosine

Scheme 15



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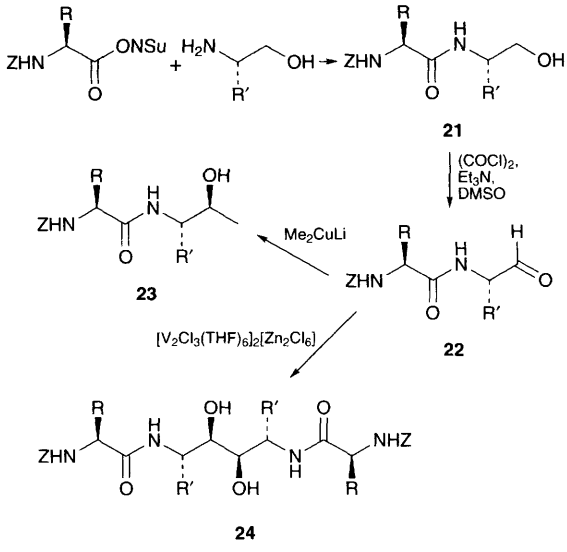
An asymmetric synthesis of both enantiomers of 2-aminopropane sulfonic acid (2-methyltaurine) from the corresponding 2-hydroxypropylamines has been reported. The amino group is first Boc-protected and the alcohol activated with a methanesulfonyl group. Deprotection of the amine followed be treatment with sodium sulfite results in the formation of an aziridine intermediate which the sulfite opens at the least hindered end to give the desired 2-aminopropanesulfonic acids.[48] *N*-Protected enantiomerically pure β-amino alcohols have also been used as the starting materials in a synthesis of β-amino sulfides and β-amino sulfoxides. The

sulfides are formed by displacement of the alcohol with diphenyl disulfide and tributylphosphine, and subsequent oxidation with sodium hypochlorite and catalytic TEMPO (2,2,6,6-tetramethylpiperidine-*N*-oxyl) gave predominantly the (*lk*)-diastereomer of the *β*-amino sulfoxides.[49]

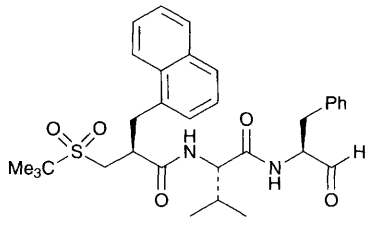
2.3.1 Synthetic routes to *β*-hydroxyamines

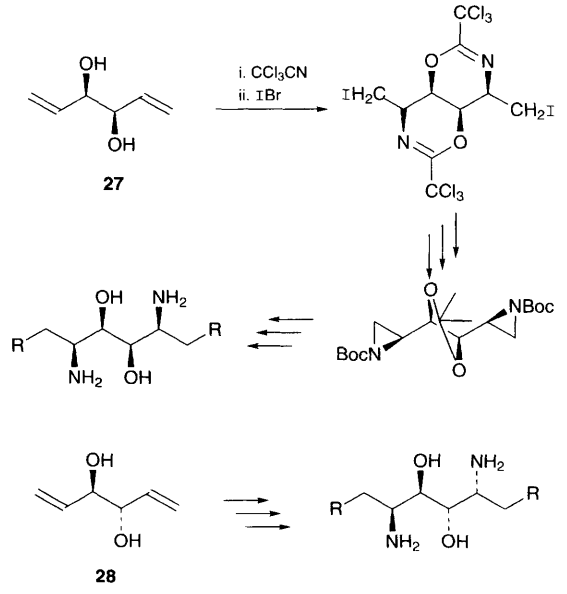
A synthetic route to amino acid derived *β*-hydroxy amines has been developed as shown in **Scheme 16**. Hence, reaction of an activated, *N*-protected amino acid with an amino acid derived amino alcohol formed an *N*-acyl-*β*-hydroxy amine **21**. Compound **21** could be oxidised under Swern conditions to the corresponding *N*-acyl-α-amino aldehyde **22**. Compounds **22** could be prepared without epimerisation of the stereocentre adjacent to the aldehyde, but on long term storage epimerisation did occur, with the (*R*,*S*)-diastereomers epimerising more rapidly than the (*S*,*S*)-diastereomers. Addition of organocopper reagents to aldehydes **22** occurred stereoselectively, giving *β*-hydroxy amines **23**. Aldehyde **22** also underwent a pinacol coupling, to give the dimeric *β*-hydroxy amines **24**, predominantly as the stereoisomer shown in **Scheme 16**.[50] The same pinacol coupling methodology has been used to prepare the C_2-symmetric HIV protease inhibitor **25** from aldehyde **26**.[51] Another synthesis of C_2-symmetric or meso-*β*-amino alcohols has been developed starting from diols **27** or **28** as shown in **Scheme 17**. The key steps are a stereospecific *bis*-iodoamination, followed by aziridine formation and ring opening of the aziridine rings at the least hindered end by Grignard reagents.[52] In this case, the two aziridines were found to react independently, but this is not always the case as the synthesis of pyrrolidine and piperidine derivatives by the ring opening of *bis*-aziridines has also been reported. The amine formed by the ring opening of the first aziridine acted as the nucleophile in the ring opening of the second aziridine ring, forming the five- or six-membered heterocyclic ring.[53]

As part of a synthesis of a conformationally constrained analogue of didemnin-B, the conversion of ketone **29** into amine **30** was investigated. A variety of reductive amination procedures were tried, along with oxime formation followed by hydrogenation but at best a 3:1 ratio of diastereomers was obtained.[54] The reduction of aziridinyl ketones **31** to hydroxyalkylaziridines with a variety of reducing agents has been investigated. The best diastereoselectivity (in favour of the *R*,*R*-diastereomer) was observed using L-Selectride.[55] A synthesis of enantiomerically pure *β*-hydroxymethylene-aziridines from amino acid derived *β*-amino alcohols has also been reported.[56] The stereoselective addition of organolithium reagents to enantiomerically pure aziridine **32**, followed by hydrogenation to ring open the aziridine and remove the chiral auxiliary, has been used to prepare *syn*-*β*-amino alcohols.[57] The Michael addition of enantiomerically pure hydroxide equivalent **33** to nitroalkenes followed by reduction of the nitro

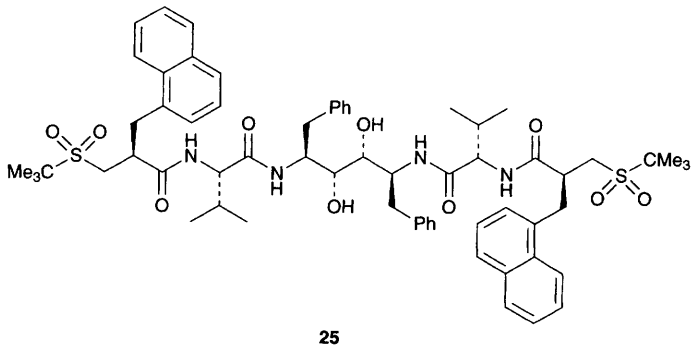


Scheme 16





Scheme 17



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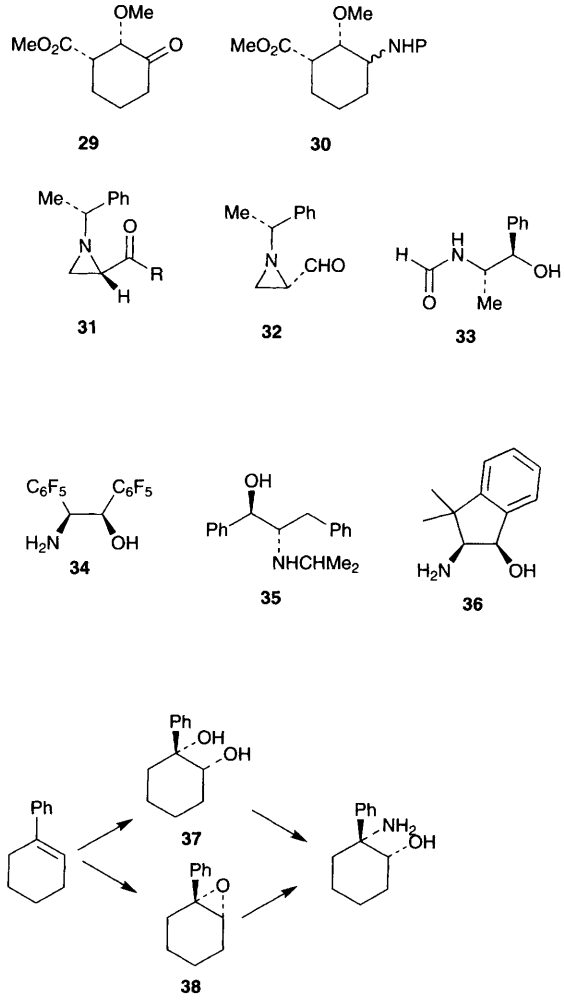
group and reductive cleavage of the chiral auxiliary has also been used in an enantioselective synthesis of β-amino alcohols.[58]

The two enantiomers of *cis*-2-amino-1,2-diphenylethanol have found a number of applications in asymmetric synthesis. A synthesis of the enantiomerically pure fluorinated analogue **34** has now been reported. The synthesis starts with the addition of cyanide to pentafluorobenzaldehyde, and the trapping of the resulting cyanohydrin as a silyl ether. Addition of pentafluorophenyllithium to the nitrile gives the corresponding imine which is diastereoselectively reduced and deprotected by treatment with sodium borohydride and tetrabutylammonium fluoride to give racemic **34**, which can be resolved with camphorsulfonic acid.[59] Since a number of catalysts are now available to induce the asymmetric addition of cyanide to aldehydes, it should be possible to prepare the cyanohydrin and hence β-amino alcohol **34** without the need for a resolution step. Indeed, just this approach was used in a synthesis of (1*R*,2*S*)-1,3-diphenyl-2(*N*-isopropylamino)propan-1-ol **35**. The synthesis started from enantiomerically pure mandelonitrile which was prepared enzymatically.[60] A synthesis of the related β-amino alcohol **36**, again employing a resolution step, has also been reported.[61]

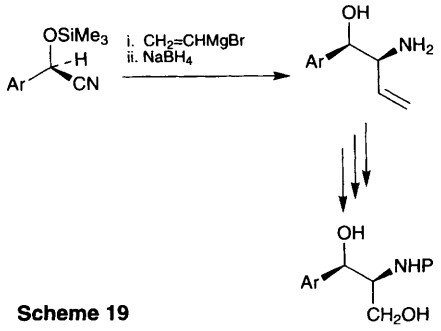
An asymmetric synthesis of *cis*-1-amino-1-phenylcyclohexan-2-ol has been reported as shown in **Scheme 18**. The starting material is 1-phenylcyclohexene which can be converted into either the enantiomerically pure diol **37** using Sharpless' *bis*-hydroxylation protocol, or epoxide **38** using Jacobsen's asymmetric epoxidation methodology. Either intermediate **37** or **38**, reacts with acetonitrile in the presence of trifluoromethanesulfonic acid to give after hydrolysis the desired β-amino alcohol.[62] Sharpless has also reported a synthesis of β-amino alcohols, based upon the ring opening of enantiomerically pure cyclic carbonates by azide followed by reduction. The cyclic carbonates are prepared from the corresponding diols which are available using the *bis*-hydroxylation methodology.[63] A conceptually similar approach based upon the opening of cyclic acetals has also been reported.[64]

The addition of vinylmagnesium bromide to enantiomerically pure cyanohydrin silyl ethers followed by sodium borohydride reduction of the intermediate imine leads to enantiomerically pure β-amino alcohols as shown in **Scheme 19**. Subsequent oxidative cleavage of the alkene and reduction leads to β,β'-dihydroxy amines.[65] The addition of organometallic reagents to imine **39** has also been studied as a route to β-amino alcohols. Organocopper based reagents (in the presence of boron trifluoride) gave predominantly the *anti*-diastereomer of the β-amino alcohol, whilst addition of organolithium reagents resulted in predominant formation of syn-β-amino alcohols.[66] These results

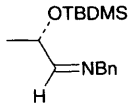


Scheme 18

can be compared with those of Alvaro *et al.* on similar chiral imines lacking the oxygen substituents reported in section 2.2.



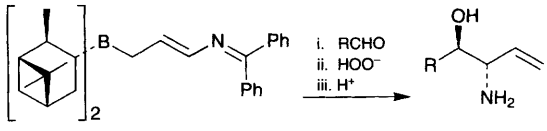
Scheme 19



39

One of the standard methods for the preparation of enantio- and diastereo-merically enriched β-amino alcohols involves the addition of organometallic reagents to amino acid derived α-amino aldehydes. The chromium(II) chloride mediated addition of allyl halides to such aldehydes has now been reported, and it was found that the structure of the α-amino aldehyde (side chain and *N*-protecting group) were important in determining both the diastereomeric excess, and which diastereomer was preferentially formed.[67] The addition of organocerium reagents to α-amino-β-hydroxy aldehydes in which the amine and alcohol are protected as a cyclic carbamate has also been investigated and was found to be highly selective in favour of a *syn*-relationship between the nitrogen and newly formed alcohol.[68] The synthesis of both α-amino ketones and β-amino alcohols by addition of organometallic reagents to *N*-9-phenylfluoren-9-yl protected alanine has also been reported.[69] The addition of Grignard reagents to serine derived oxazolidine aldehydes has been investigated as a route to the synthesis of β,β′-dihydroxyamines. The best asymmetric inductions were observed for oxazolidines derived from cyclohexanone.[70] The addition of diethylzinc to α-dibenzylamino aldehydes is chelation controlled, providing a synthesis of *syn*-β-amino alcohols.[71] Related chemistry involving a Wittig reaction on α-amino aldehydes and subsequent epoxidation and ring opening has also been reported as a route for the synthesis of β-amino alcohols.[72] The stereoselective synthesis of both β-amino alcohols and γ-amino alcohols from α- or β-amino-acylsilanes respectively has been reported.[73]

A synthesis of *anti*-β-amino alcohols based on the reaction of chiral allylic boranes with aldehydes has been developed as shown in **Scheme 20**.[74]



Scheme 20

The Payne rearrangement of α-hydroxy epoxides is a well known reaction which has gained considerable synthetic utility since the development of the Sharpless asymmetric epoxidation reaction; however the analogous rearrangement of α-hydroxy aziridines (the aza-Payne rearrangement) is less well known. It has now been shown that the treatment of α-hydroxy aziridines with nucleophiles such as organocuprates, thiols, or cyanide proceeds *via* an aza-Payne rearrangement and provides an approach to the synthesis of highly functionalised β-amino alcohols.[75]

2.3.2 Synthesis of α-amino acids

As with the previous reviews of this area,[1] only those methods that result in the formation of the carbon–nitrogen bond, or in which the nitrogen atom plays a pivotal role in the chemistry, have been included in this section. The emphasis has been placed on those methods that allow the stereocontrolled synthesis of amino acids.

2.3.2.1 Synthesis of racemic or achiral α-amino acids

The alkylation of glycine imines is a well established procedure for the preparation of racemic amino acids. O'Donnell *et al.* have now shown that this chemistry can be carried out whilst the glycine imine is attached to the Merrifield resin, thus permitting the synthesis of unnatural, racemic amino acids attached to an insoluble support ready for solid phase peptide synthesis.[76] Optimum conditions for the monoalkylation, dialkylation, and Michael addition to the enolate of ethyl *N*-(diphenylmethylene)glycinate under solid–liquid phase transfer catalysis have also been reported.[77] The use of this chemistry to prepare 3-trifluoromethylglutamic acid has also been described.[78]

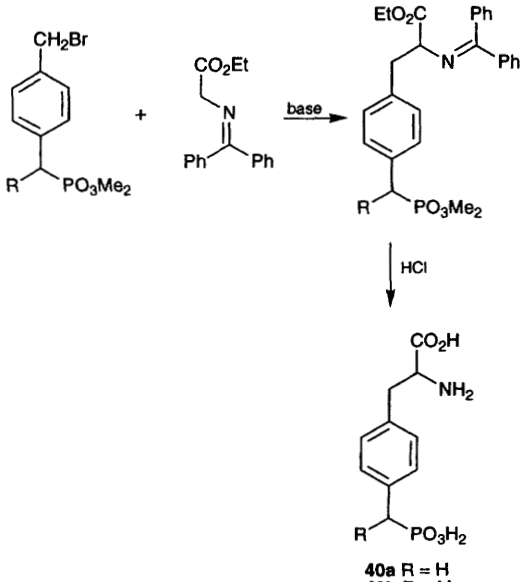
A number of methods have recently been developed for the synthesis of phosphorylated phenylalanine derivatives, for use in studies of protein phosphorylation and dephosphorylation. Glycine enolate alkylation methodology has been used to prepare 4-(phosphonomethyl)phenylalanine **40a** and 4-(1-phosphonoethyl)phenylalanine **40b** as shown in **Scheme 21**. The corresponding α-methyl, β-methyl, β,β-dimethyl, and α,β-methylene deriva-

tives were also prepared as conformationally constrained analogues of this amino acid.[79] The *N*-Fmoc-4-(dimethyl phosphonomethyl)phenylalanine ethyl ester could also be enzymatically resolved, and incorporated into a peptide sequence corresponding to a potentially phosphorylated site of phosphatase PTP 1C.[80] A synthesis of the conformationally constrained, cyclopropane containing amino acid α,β-methylene tryptophan has also been reported.[81]

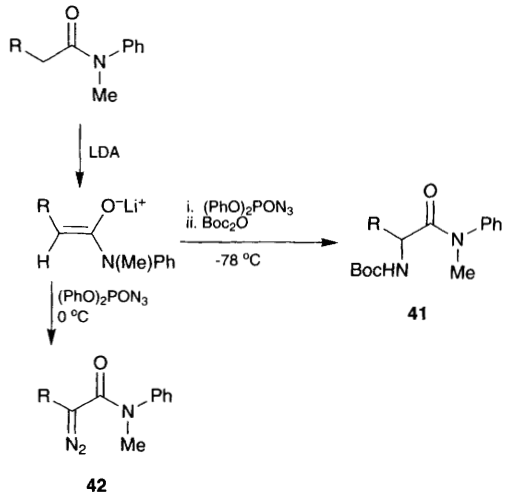
The reaction of a tertiary amide enolate with diphenylphosphoryl azide can be controlled to give either the α-amino amide **41** or α-diazo amide **42** depending upon the reaction conditions as shown in **Scheme 22**.[82] As part of a synthesis of microcystin-LA, the preparation of α-phosphono-α-amino acid **43** was reported (**Scheme 23**). Compound **43** could subsequently be employed as a Wadsworth–Emmons reagent for the synthesis of α,β-unsaturated α-amino acids.[83]

A procedure for the synthesis of racemic β-keto-α-amino acids from α-amino malonates has been developed. Thus treatment of *N*-Boc-malonic acid monoethyl ester with an acid chloride in the presence of magnesium chloride and triethylamine results in enolate formation, acylation and decarboxylation to give β-keto-α-amino acid ethyl esters. The products are substrates for BINAP catalysed hydrogenation with *in situ* racemisation to enantiomerically enriched β-hydroxy-α-amino acids.[84] Similar methodology has been used to prepare β-hydroxy-*m*-chlorotyrosine derivatives.[85] The hydrogenation of α,β-didehydroamino acid derivative **44** which is readily available from serine occurs diastereoselectively as shown in **Scheme 24**. Subsequent manipulation allows the synthesis of *meso*-2,4-diaminoglutaric acid **45**.[86]

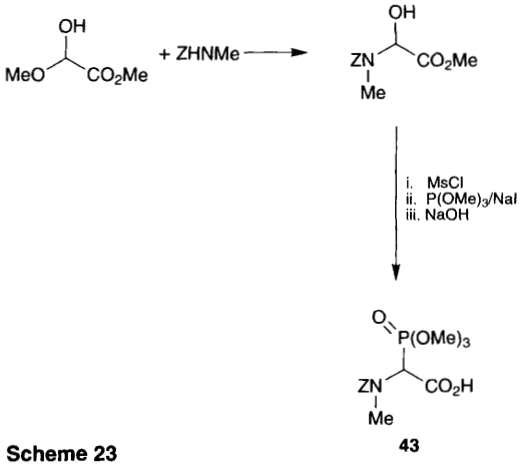
The addition of hydrazoic acid to γ-keto-α,β-unsaturated lactones gives enamines as shown in **Scheme 25**. Subsequent reduction of the enamine with zinc in acetic acid provides γ-keto-α-amino



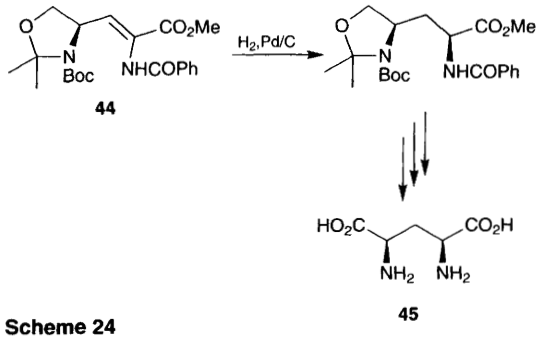
Scheme 21



Scheme 22

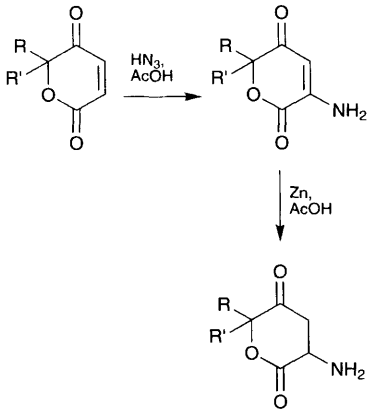


Scheme 23



Scheme 24

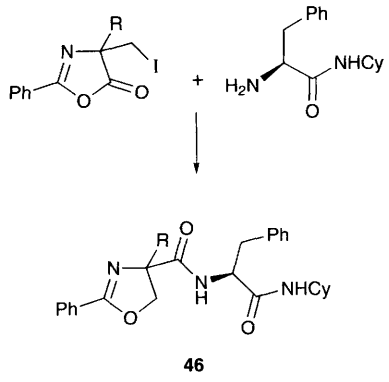
lactones.[87] The ring opening of 3-fluoroalkyl-2,3-epoxypropanoates by primary amines occurs regiospecifically at C2, leading to fluorinated β-hydroxy-α-amino esters. No reaction occurs with secondary amines, and using azide as a nucleophile gives a mixture of products resulting from reaction at C2 and C3, though the α-azido ester resulting from reaction at C2 is again the major product.[88] The amidocarbonylation of benzyl chloride using $Co_2(CO)_8$–CO–H_2–CH_3CONH_2 has been shown to provide a one step synthesis of racemic *N*-acetylphenylalanine.[89]



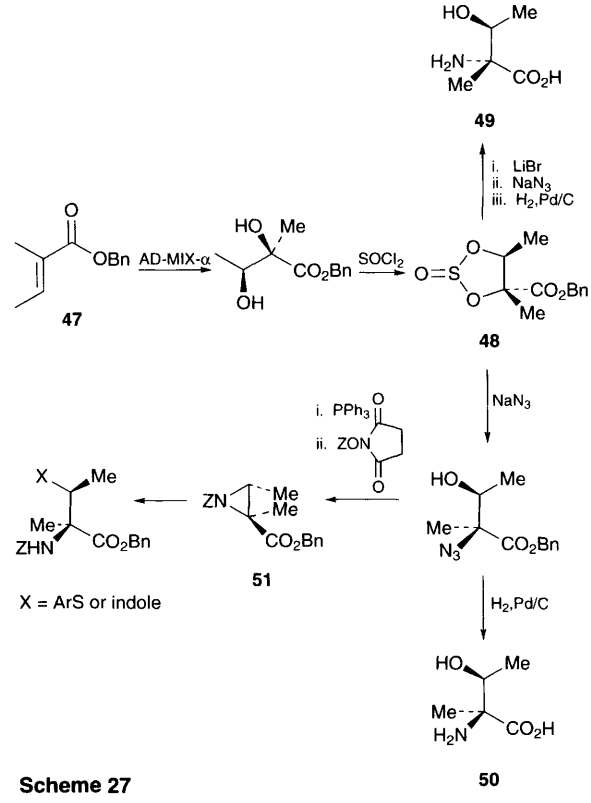
Scheme 25

2.3.2.2 Asymmetric syntheses of α-amino acids

A synthesis of α,α-disubstituted amino acids has been developed as shown in **Scheme 26**. (*S*)-Phenylalanine cyclohexylamide was used to ring open racemic 1,3-oxazol-5(4*H*)-ones, the intermediate dipeptide derivatives undergoing ring closure to give diastereomeric oxazolines **46**. The oxazoline diastereomers could be separated, and hydrolysis gave the α,α-disubstituted, enantiomerically pure amino acids.[90] Another synthesis of α,α-disubstituted α-amino acids uses the Sharpless bis-hydroxylation reaction to prepare α-methyl α-amino acids as shown in **Scheme 27**. The synthesis starts from α,β-unsaturated ester **47**, which is converted in two steps into cyclic sulfinate **48**. Ring opening of sulfinate **48** with azide can be carried out to give either diastereomer of the azido alcohol, and subsequent hydrogenation gives the α-methylthreonine derivatives **49** and **50**. Alternatively, the azido alcohols can be cyclised to aziridine **51** which undergoes ring opening with thiols or indoles to give α,β-dimethylcysteine and tryptophan derivatives. The same methodology can be used to prepare *allo*-threonine derivatives.[91] A synthesis of enantiomerically pure α-fluoroalkyl-α-amino acids has been reported in which the asymmetric Michael addition of cyanide onto a chiral α,β-unsaturated sulfoxide is employed as the key step.[92]



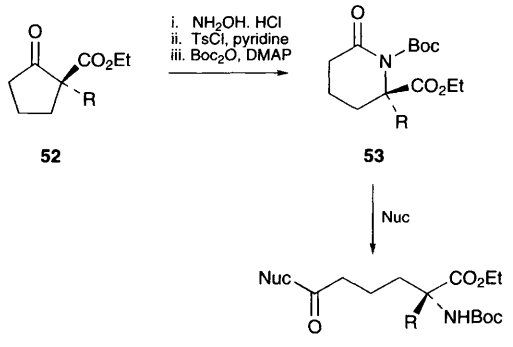
Scheme 26



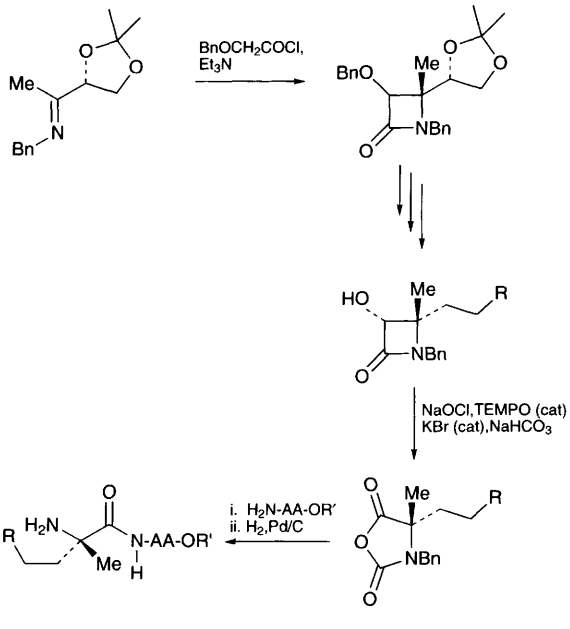
Scheme 27

Enantiomerically pure cyclopentane derived α-substituted β-keto esters **52** are readily available *via* a pig liver esterase catalysed kinetic resolution. These keto esters have been used in a short synthesis of enantiomerically pure α-substituted α-amino acids as shown in **Scheme 28**. Thus Beckmann rearrangement followed by the introduction of a Boc-protecting group gave lactam **53**, which underwent ring opening on treatment with oxygen or carbon based nucleophiles to give α-substituted α-amino acids.[93] An asymmetric Strecker reaction has been used in a synthesis of the four stereoisomers of 1-amino-2-methylcyclohexanecarboxylic acid. Cyclohexanone is first condensed with α-methylbenzylamine, and the subsequent chiral imine reacted with cyanide from trimethylsilyl or sodium cyanide. The stereochemistry of the

addition is determined by the cyanide source and the nature of any Lewis acid catalyst.[94] Palomo *et al.* have been developing a novel synthesis of enantiomerically pure amino acids based upon the oxidative conversion of β-lactams into *N*-carboxy anhydrides and subsequent manipulation. The most recent applications of this methodology have been to the preparation of α-substituted α-amino acids and peptides containing α-substituted α-amino acids (**Scheme 29**) as well as the synthesis of the tripeptide component of the antibiotic lysobactin.[96] The [3,3]-allylic trichloroacetamidate rearrangement has been widely used for the synthesis of amino acids, and the extension of this methodology to α,α-disubstituted amino acids has now been reported.[97]

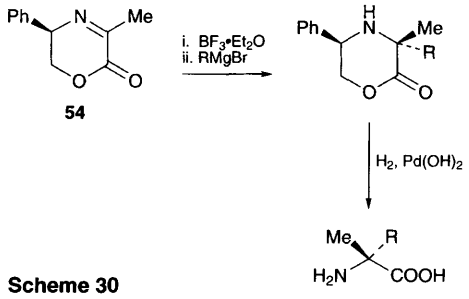


Scheme 28

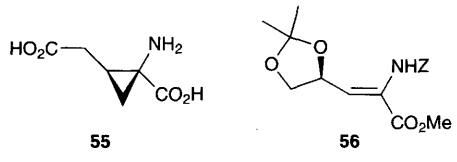


Scheme 29

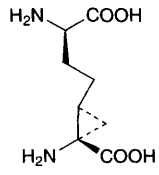
An approach to α-substituted alanine derivatives has been developed by Harwood *et al.* as shown in **Scheme 30**. Thus the addition of Grignard reagents to imine **54** occurs diastereoselectively, giving the desired α-substituted alanine derivatives after subsequent hydrogenation.[98] Another approach to α-methyl-α-amino acids employs the hydrogenation of 2-methylaziridine-2-carboxylates which can be prepared from chiral sulfinyl imines by a Darzens type condensation. The hydrogenation occurs selectively across the N–C3 bond, providing the α-methyl-α-amino acids.[99] A synthesis of the conformationally constrained glutamic acid analogue **55** in which the key step is the diastereoselective cyclopropanation of α,β-didehydroamino acid **56** has also been reported.[100] Diphenylmethanimines of glycine are widely used for the preparation of racemic amino acids, however it has now been shown that the methodology can be adapted to prepare enantio- and diastereo-merically pure β-substituted α-amino-cyclopropanecarboxylic acids. The key step in the synthesis is the reaction of the anion of the diphenylmethanimine of aminoacetonitrile with an enantiomerically pure allylic chloride bearing an ester in the β′-position, followed by palladium(0) catalysed cyclisation to give β-alkylidene amino-cyclopropane derivatives.[101]



Scheme 30



Corey's sulfoxonium ylide has been used to cyclopropanate α,β-didehydroamino acid derivatives bearing a 2-hydroxypinan-3-one chiral auxiliary, to prepare enantio- and diastereo-merically pure β-substituted α-amino-cyclopropanecarboxylic acids.[102] A related synthesis of β-substituted α-aminocyclopropanecarboxylic acids by the cyclopropanation of α,β-didehydroamino acids bearing a chiral unit in the β-position has also been reported.[103] β-Substituted-α-amino-cyclopropane carboxylic acids have also been prepared by Wittig olefination of a β-formyl-α-amino-cyclopropane carboxylic acid.[104] In yet another approach to α,β-cyclopropylamino acids, Williams and co-workers have used his template for asymmetric



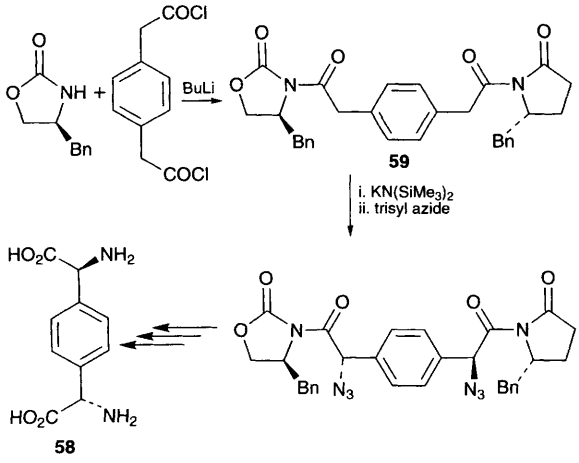
57

amino acid synthesis to prepare diamino diacid **57** along with its C6 epimer.[105]

The Evans chiral auxiliary has been used in a synthesis of both the *para*- and *meta*-isomers of (*S*,*S*)-phenylenebis(glycine) **58**, which can be considered a conformationally constrained cystine analogue. The synthesis of the *para*-isomer is shown in **Scheme 31**. Thus reaction of the diacid chloride with the Evans auxiliary gives precursor **59**. Formation of the *bis*-potassium enolate of compound **59** and trapping with trisyl azide gave the *bis*-azide in which both new stereocentres possessed the (*S*)-configuration. Reduction of the azides and cleavage of the chiral auxiliaries could be carried out in either order to give (*S*,*S*)-*p*-phenylenebis(glycine) **58** and a variety of partially protected derivatives suitable for peptide synthesis.[106] The same methodology has been used in a synthesis of *N*-Boc- and *N*-Fmoc-(dicyclohexylphosphino)serine **60**. The unnatural amino acid was subsequently incorporated into a decapeptide and its coordination to rhodium investigated.[107] Both enantiomers of carboranylalanine have been prepared using the same chemistry.[108] The Evans auxiliary was also used in an asymmetric synthesis of 3-substituted prolines, the key step being the hydroboration induced cyclisation of an α-azido β-vinyl ester as shown in **Scheme 32**.[109] A different approach to the synthesis of amino acids employing the Evans auxiliary has also been developed. Thus the cobalt(II) complex of the Evans imide of 3-oxobutyrate can be diastereoselectively alkylated, and the amino group introduced with retention of stereochemistry by a Schmidt rearrangement. Finally, hydrolysis provides the enantiomerically pure amino acids.[110]

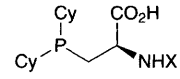
A synthesis of enantiomerically pure pipecolic acids as conformationally constrained lysine analogues has been reported as shown in **Scheme 33**. The synthesis started from (*S*)-lysine which was converted into the known lactam **61**. Alkylation of the amide enolate of the *N*-Boc lactam with iodoacetonitrile gave a 1:1 mixture of the diastereomeric nitriles **62**. These could be reduced first to the corresponding hemiacetals which could be separated, then further reduced and the protecting groups manipulated to give the desired *N*,*N*′-diprotected lysine analogues **63a,b**.[111] Another synthesis of conformationally constrained amino acid derivatives has been reported, which utilises an electrochemical cyclisation of a serine–proline dipeptide as shown in **Scheme 34**. The 6,5-bicyclic product was investigated as a reverse-turn peptidomimetic.[112]

Oppolzer's chiral bornane-10,2-sultam has previously been used in the asymmetric synthesis of



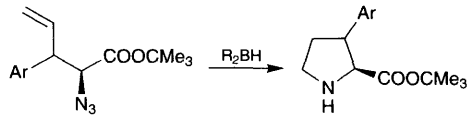
trisyl = 2,4,6-triisopropylsulfonyl

Scheme 31

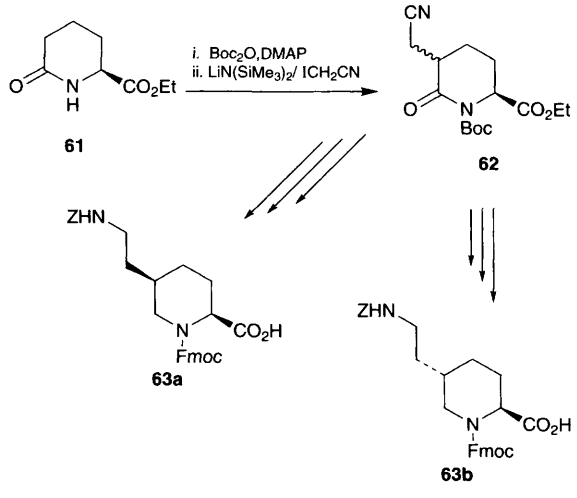


X = Boc or Fmoc (fluoren-9-ylmethoxycarbonyl)

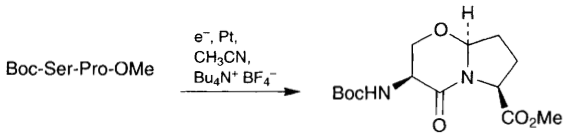
60



Scheme 32

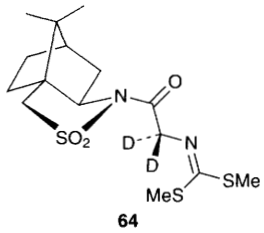


Scheme 33

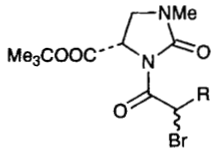


Scheme 34

α-amino acids. The same methodology has now been used in the asymmetric synthesis of α-deuterated α-amino acids, starting from the α,α-dideuterated derivative **64**. Alkylation of the enolate of compound **64** followed by hydrolysis of the chiral auxiliary and imine gave α-deuterated (*S*)-amino acids with high enantiomeric excesses and deuterium incorporations.[113] The same auxiliary has been used to control the addition of allylzinc reagents to α-oximo-esters, providing an asymmetric synthesis of allylglycine derivatives,[114] and in a synthesis of *o*- and *p*-carbornylalanine derivatives. In the latter case, the amine group was introduced using 1-chloro-1-nitrosocyclohexane.[115] An approach to enantiomerically pure α-hydroxyalkyl-α-amino esters from serine has been reported which is based upon Seebach's transfer of chirality approach.[116] α-Bromoamides **65** epimerise under basic conditions, which has allowed the development of an asymmetric amino acid synthesis employing a Gabriel reaction carried out under conditions where kinetic resolution can occur. Thus reaction of amides **65** with potassium phthalimide leads to the preferential formation of the (*S*,*S*)-diastereomer of the amino acid precursor. Subsequent removal of the chiral auxiliary and phthalimido groups provides (*S*)-α-amino acids.[117]



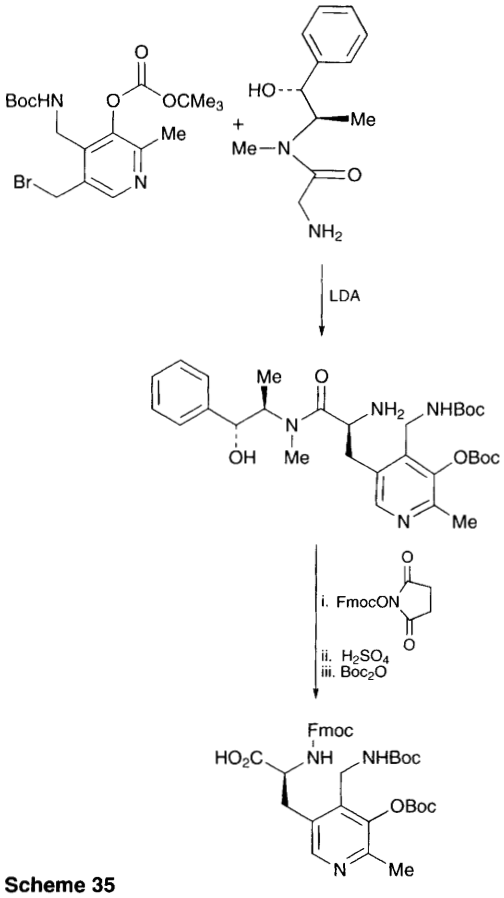
64



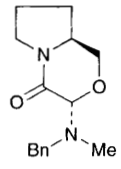
65

Myers has recently introduced (−)-pseudo-ephedrine glycinamide as an acyclic template for the asymmetric synthesis of α-amino acids. This methodology has been used by Roy and Imperiali in the synthesis of an unnatural amino acid with a pyridoxamine coenzyme containing side chain as shown in

Scheme 35. The key alkylation step proceeded with >10:1 diastereoselectivity in favour of the desired (*S*)-amino acid; however hydrolysis of the pseudo-ephedrine auxiliary could only be achieved (after Fmoc-protection of the amino group) under acidic conditions which also cleaved the Boc-groups, necessitating their reintroduction before the amino acid could be incorporated into a peptide.[118] Another new chiral template for amino acid synthesis is prolinol derivative **66**. The addition of Grignard reagents (and allyl silane) to this chiral, masked imine occurs selectively on the top face, allowing a synthesis of *N*-methyl (*S*)-amino acids after removal of the chiral auxiliary and *N*-benzyl group.[119]

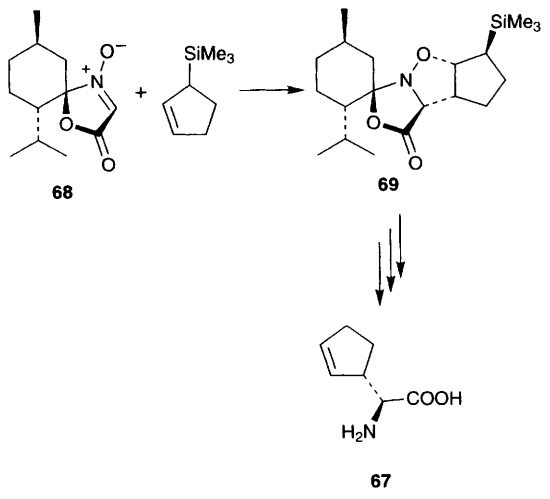


Scheme 35



66

The first enantio- and diastereo-merically pure synthesis of (2*S*,1′*S*)-(cyclopent-2-enyl)glycine **67**, a naturally occurring amino acid has been achieved as shown in **Scheme 36**. The key step is the diastereo-

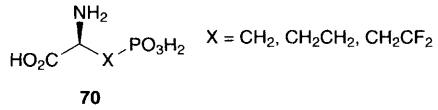


Scheme 36

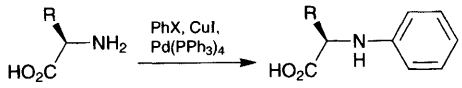
selective cycloaddition reaction between chiral nitrone **68** derived from (−)-menthone and 3-trimethylsilylcyclopentene giving adduct **69**.[120] In previous reviews, the use of the ester enolate Claisen rearrangement in the synthesis of racemic amino acids has been mentioned. It has now been shown that in the presence of $Al(OPr^i)_3$ and quinine, the rearrangement can be carried out enantiospecifically, providing a route to enantiomerically enriched γ,δ-unsaturated α-amino acids.[121]

The opening of the epoxide derived from diethyl tartarate by trimethylsilyl azide has been reported as an *Organic Syntheses* preparation for the synthesis of β-hydroxyaspartic acid.[122] The same methodology and related chemistry on the opening of cyclic sulfonates can also be adapted for the synthesis of both diastereomers of β-fluoroaspartic acid.[123] Many amino acids are biosynthesised from α-keto acids by reductive amination, and it has now been shown that, by attaching pyridoxamine cofactor to a protein known to bind lipids but with no reductive amination activity, a complex which is capable of reductively aminating keto acids to α-amino acids with enantiomeric excesses of up to 94% is obtained.[124] A synthesis of ω-phosphono-α-amino acids **70** has been reported, the key steps being an enzymatic desymmetrisation of a *meso*-diol, and Curtius rearrangement to introduce the amino group.[125] *N*-Phenyl-α-amino acids have been prepared by a palladium and copper catalysed coupling reaction between unprotected amino acids and a halobenzene as shown in **Scheme 37**.[126]

A number of papers this year could have been placed in either this or the following sections, as the compounds synthesised are both α- and β- or



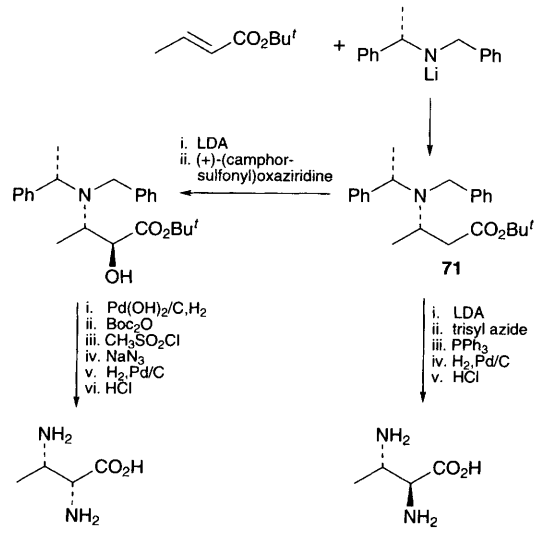
70



Scheme 37

γ-amino acids; however, they have all been included here. One of the approaches which has been developed for the asymmetric synthesis of β-amino acids is the conjugate addition of chiral amines to α,β-unsaturated esters developed by Davies *et al.* This methodology has now been utilised in the preparation of both diastereomers of α,β-diaminobutanoic acid. Thus addition of (*R*)-(α-methylbenzyl)benzylamine to *tert*-butyl crotonate gave β-amino acid **71** (**Scheme 38**). Subsequent enolate formation and reaction with trisyl azide led after subsequent manipulation to (2*S*,3*S*)-diaminobutanoic acid, whilst hydroxylation of the enolate followed by activation and S_N2 inversion with azide gave the (2*S*,3*R*)-diastereomer.[127] Conjugate addition methodology was also used in the preparation of benzyl *trans*-aziridine-2-carboxylates **72**, though in this case ammonia was added to a chiral α-bromo-α,β-unsaturated chiral amide.[128] Another synthesis of benzyl aziridine-2-carboxylates has been reported which employs the Lewis acid induced conjugate addition of *O*-benzylhydroxylamine to an α,β-unsaturated Evans imide. The stereochemistry of the addition was controlled by the structure of the Lewis acid, and subsequent manipulation gave the desired aziridine.[129] Another approach to the synthesis of α,β-diamino acids employs oxazolidinone **73**, both enantiomers of which are readily available using Sharpless asymmetric epoxidation methodology, as the starting material. Protocols were developed for substituting the hydroxy group of compound **73** by an amino group with and without inversion of configuration. Subsequent manipulation then provided α,β-diamino acids.[130] The asymmetric synthesis of both enantiomers of 2-aminonorbornane-2,3-dicarboxylic acid **74** has been reported by Cativiela *et al.* as conformationally constrained aspartic acid derivatives.[131] An asymmetric synthesis of α,γ-diamino acids and related species has also been developed, in which the key step is the diastereoselective Michael addition of organocuprates onto an α,β-unsaturated ester containing a chiral centre and nitrogen substituent at the γ-position. Subsequent enolate chemistry was used to introduce the α-amino group.[132]

Finally in this section, it has been shown that the ring opening of aziridine-2-carboxylates can be controlled to occur at either C2 or C3, providing a synthesis of α- and β-amino acids respectively. Most of the examples given by the authors were racemic, but one enantiomerically pure case, the synthesis of (*R*)-3-aminodecanoic acid, was also reported.[133]



Scheme 38

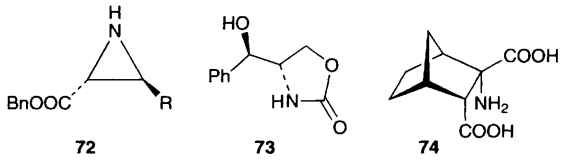
2.3.3 Synthesis of β-amino acids

2.3.3.1 Racemic syntheses of β-amino acids

A study of the factors that affect the conjugate addition of amines to α,β-unsaturated carbonyl compounds has been carried out. The author concluded that the use of high pressure conditions was the major activating factor, and that this could be used in conjunction with lanthanide catalysis. The addition of water to the reaction mixture was also found to have a favourable effect.[134] The use of catalytic titanium tetraiodide to induce the stereoselective *anti*-addition of silyl ketene acetals to imines has been reported as a route to α,β-substituted β-amino acids.[135]

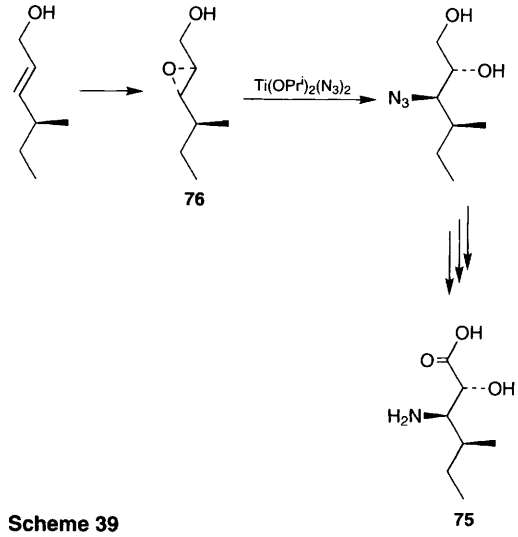
2.3.3.2 Asymmetric syntheses of β-amino acids

The α-hydroxy-β-amino acid isostatine **75** continues to attract synthetic attention, and an asymmetric synthesis of this β-amino acid utilising a Sharpless epoxidation has been reported as shown in **Scheme 39**. The key step in the synthesis is the regiospecific ring opening of the epoxy alcohol **76**. The reagent $Ti(OPr^i)_2(N_3)_2$ was found to add azide to the end of the epoxide further from the alcohol, and not to cause any Payne rearrangement.[136] A general synthesis has been reported of enantiomerically pure both *syn*- and *anti*-α-hydroxy-β-amino acids, including **75**, by the manipulation of β,γ-dihydroxyamines, which are themselves available from allylic alcohols *via* the Sharpless epoxidation.[137] Yet another synthesis of α-hydroxy-β-amino acids including **75** starts from enantiomerically pure imine

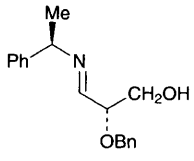


72 **73** **74**

77. It has previously been shown that the stereochemistry of the addition of Grignard reagents to imine **77** can be controlled to give either diastereomer of the resulting β-amino alcohol, and subsequent manipulation has now been shown to produce α-hydroxy-β-amino acids, β-hydroxy-γ-amino acids, or γ-hydroxy-δ-amino acids.[138] The trapping of the enolate of a β-amino acid with MoOPH has also been used to prepare syn-α-hydroxy-β-amino acids.[139]



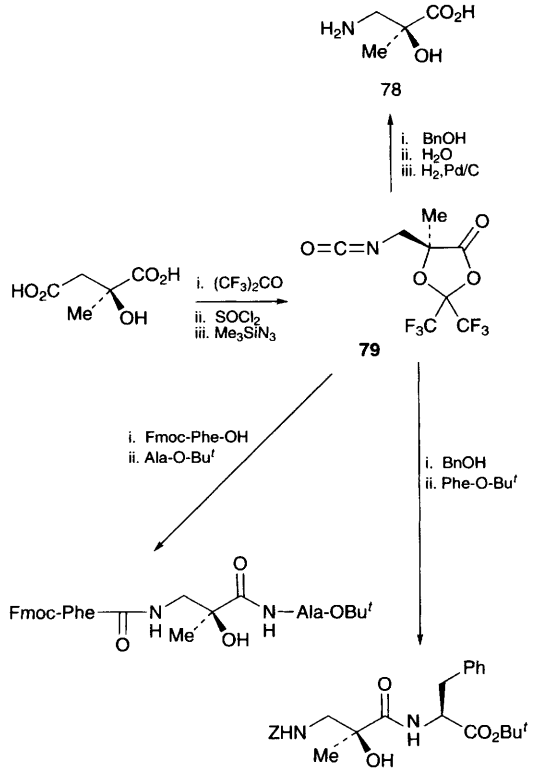
Scheme 39



77

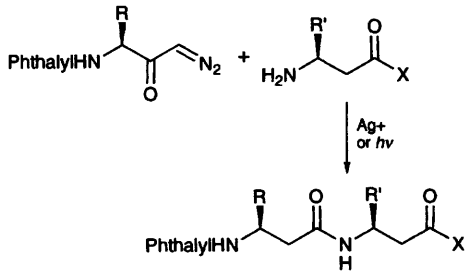
A general synthesis of α-hydroxy-β-amino acids from (*R*,*E*)-2-hydroxypent-3-enitrile has also been reported. The hydroxy group is silylated and the nitrile subjected to Grignard addition or reduction to produce an imine, which is transaminated with benzylamine and further reduced diastereoselectively to form a β-amino alcohol after deprotection of the silyl ether. Subsequent protection of the amino and hydroxy groups as a cyclic urea and oxidation of the alkene by ozone and Jones' reagent, followed by deprotection, provides α-hydroxy-β-amino acids. The cyanohydrin used as the starting material is available by the enzymatic addition of HCN to but-2-enal.[140] Yet another synthesis of *syn*- or *anti*-α-hydroxy-β-amino esters has been developed which starts from enantiomerically pure α-keto epoxides. Reductive amination of the ketone

occurs diastereoselectively to give the *anti*-amino epoxide, and subsequent manipulation provides α-hydroxy-β-amino esters.[141] A synthesis of (*S*)-α-methylisoserine **78** has been reported as shown in **Scheme 40**. The key step was a Curtius rearrangement to give hexafluoroacetonide **79**, which could also be directly employed in the synthesis of peptides incorporating this α-hydroxy-β-amino acid.[142] A synthesis of (*S*)-isoserinal from D-glyceraldehyde acetonide has also been reported.[143]



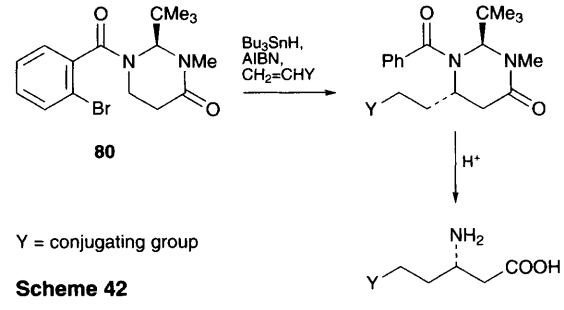
Scheme 40

In last year's review, Seebach's synthesis of β-amino acids using an Arndt–Eistert reaction to homologate α-amino acids was discussed. It has now been shown that this methodology can be extended to the synthesis of peptides derived from β-amino acids as shown in **Scheme 41**.[144] The enzymatic resolution (by lipase) of cyclopentane and norbornane derived β-lactams has been reported. Subsequent opening of the β-lactam ring provides a route to both enantiomers of *cis*-2-aminocyclopentanecarboxylic acid and *cis*-3-amino-2-carboxynorbornane.[145] Fluorinated β-keto esters have been converted into fluorinated β-amino acids by a route involving imine formation with benzylamine, base catalysed [1,3]-proton shift to form a benzylimine and hydrolysis. It was found that the use of cinchonidine as a chiral base gave the β-amino acids in 15–36% ee.[146] The stereoselective reduction of enantiomerically pure β-enamino esters (bearing an α-methylbenzyl group on nitrogen) has been achieved by sodium triacetoxyborohydride, producing enantiomerically and diastereomerically pure α,β-substituted β-amino acids.[147]



Scheme 41

An approach to the asymmetric synthesis of β-amino acids which employs radical chemistry has been developed as shown in **Scheme 42**. The synthesis starts from chiral template **80**, which when treated with tributyltin hydride generates an aryl radical. This undergoes a 1,5-hydrogen shift to form an α-amino radical, which then reacts stereoselectively with conjugated alkenes. Subsequent acid hydrolysis liberates enantiomerically pure β-substituted β-amino acids.[148]

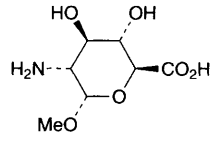


Scheme 42

The addition of silyl enol ethers to chiral imines derived from valine has been shown to be catalysed by $Yb(OTf)_3$, and provides an approach to the synthesis of enantiomerically pure β-amino acids.[149] Addition of ester enolates to enantiomerically pure sulfinyl imines has also been used to prepare enantiomerically pure β-amino acids.[150] A synthesis of β-amino acids from (*S*)-homoserine lactone has also been reported, the methodology involves carbon–carbon bond formation using the lactone carbonyl, and subsequent oxidation of the masked alcohol to give the β-amino acid.[151] The use of penicillin-G acylase to resolve racemic *anti*-α,β-substituted β-amino acids has been reported.[152]

2.3.4 Synthesis of γ- and higher amino acids

The introduction of amino and acid groups onto a monosaccharide skeleton provides access to a variety of conformationally constrained amino acids. Five such amino acids **81–85** have been prepared from the corresponding sugars. Compounds **81** and **82** contain a δ-amino acid unit and impose a linear conformation on peptides into which they are incorporated. Compounds **83** and **84** which contain a γ-amino acid unit possess the correct geometry for the formation of β-turns, whilst compound **85** which contains a β-amino acid unit was designed to mimic a γ-turn. The amino acids **81–85** were incorporated into biologically active peptides using solution or solid state peptide synthesis, and the conformations of the resulting peptide analogues determined by NMR techniques to confirm the formation of the desired conformational constraints.[153]



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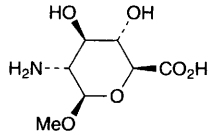

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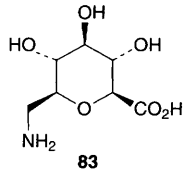

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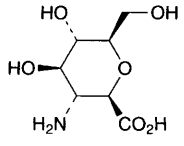

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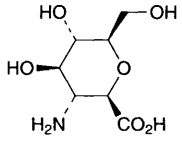

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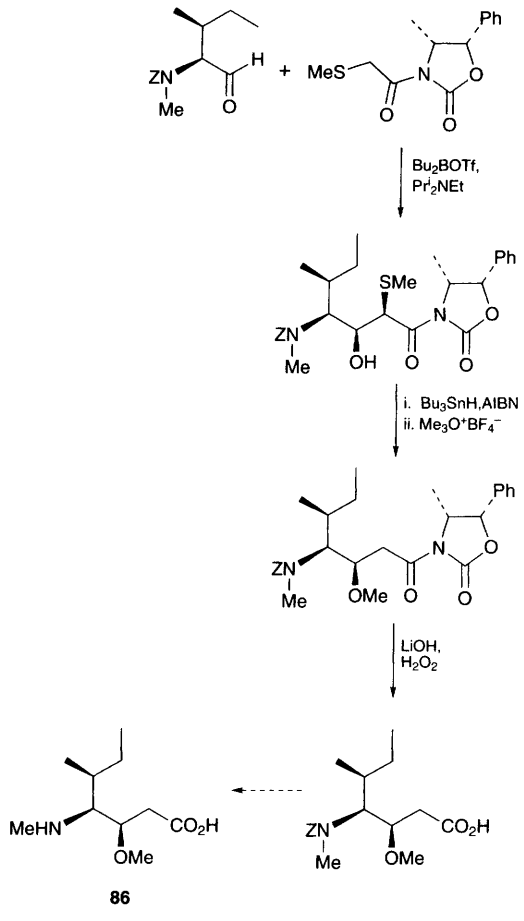
Pettit *et al.* have reported an asymmetric synthesis of the β-methoxy γ-amino acid dolaisoleucine **86**, a component of the antineoplastic peptide dolastatin 10. The synthesis employs an asymmetric aldol reaction between an Evans chiral enolate and *N*-benzyloxycarbonyl-*N*-methyl-(2*S*,3*S*)-isoleucinal as shown in **Scheme 43**. The presence of the thiomethyl group in the enolate was necessary to provide the desired asymmetric induction, as in its absence a 1:1 mixture of diastereomers was formed. By employing the corresponding Evans auxiliary derived from (*S*)-valine, it was also possible to prepare selectively the (3*R*,4*S*,5*S*)-diastereomer of dolaisoleucine.[154] Similar methodology was used to prepare dolaproline **87**, which is also found in dolastatin 10.[155] The authors subsequently utilised the (3*S*,4*S*,5*S*)-dolaisoleucine and dolaproline in a total synthesis of dolastatin 10 **88**.[156]



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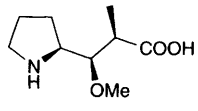
Scheme 43



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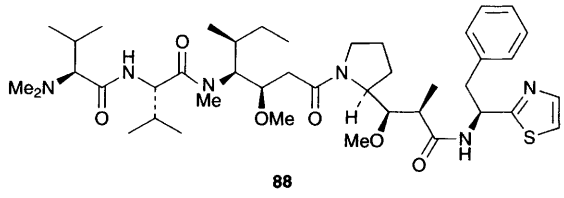
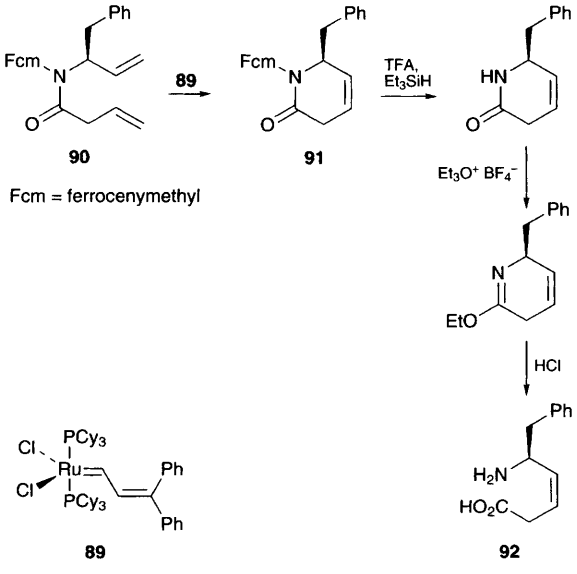


88

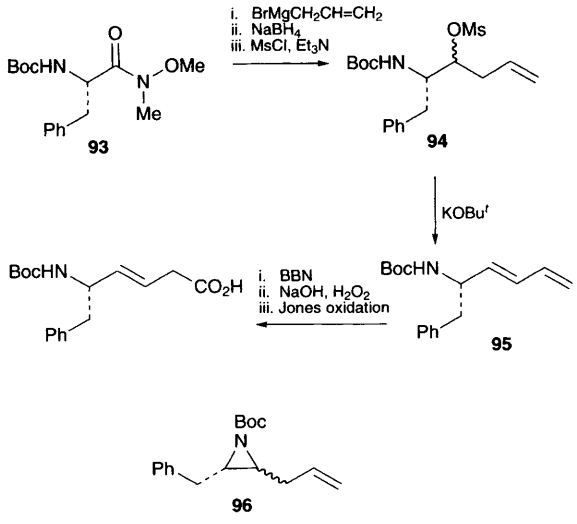
The reaction of *N*-protected *N*-carboxyanhydrides with the lithium enolate of ethyl acetate has been shown to result in addition of the enolate to the carbonyl of the *N*-protected *N*-carboxyanhydride, with ring opening followed by decarboxylation to give γ-amino-β-keto esters.[157] A synthesis of α,β-unsaturated γ-amino acids has been reported which employs the palladium catalysed [2,3]-rearrangement of allylic sulfoximines.[158] A route for the asymmetric synthesis of α,β-tetradehydro-γ-amino acids from α-amino acids based upon the Corey–Fuchs reaction of an *N*-Boc-α-amino aldehyde has also been developed.[159]

The recent development of highly selective new catalysts for alkene metathesis has led to a marked revival of interest in the applications of this chemistry. In one of the most recent applications, the Grubbs catalyst **89** was employed to catalyse the ring closing metathesis of amide **90** to lactam **91**. Subsequent acidolysis of the ferrocenylmethyl protecting group and hydrolytic ring opening of the lactam gave β,γ-unsaturated-δ-amino acid **92** (**Scheme 44**) which can be considered as a conformationally constrained pseudodipeptide. Unfortunately, the introduction of the rather unusual ferrocenylmethyl protecting group resulted in almost 40% racemisation. However, results from other groups suggest that it should be possible to employ more conventional protecting groups, or to leave the amide unprotected thus avoiding this problem.[160]

A more conventional synthesis of a β,γ-unsaturated δ-amino acid by the manipulation of the corresponding α-amino acid has also been reported (**Scheme 45**). Thus reaction of activated phenylalanine derivative **93** with allylmagnesium bromide followed by sodium borohydride reduction of the intermediate α-amino ketone gave a 7:1 mixture of diastereomeric β-amino alcohols which could be mesylated to give β-amino methanesulfonate **94**. Treatment of compound **94** with potassium *tert*-butoxide at -78 °C gave a 4:1 mixture of the desired amino diene **95** and the enamine resulting from elimination towards the nitrogen atom. Interestingly, the use of sodium methoxide as the base gave aziridine **96** in 90% yield and none of the elimination products. Hydroboration of diene **95** followed by oxidation gave the β,γ-unsaturated δ-amino acid.[161] A synthesis of β-hydroxy-γ-amino acids from allylic alcohols has also been reported. A Sharpless epoxidation was used to introduce the chirality, and the epoxide was ring opened with benzhydrylamine to provide β,γ-dihydroxyamines.



Scheme 44



Scheme 45

Subsequent manipulation of the hydroxy groups provided the targeted β-hydroxy-γ-amino acids.[162]

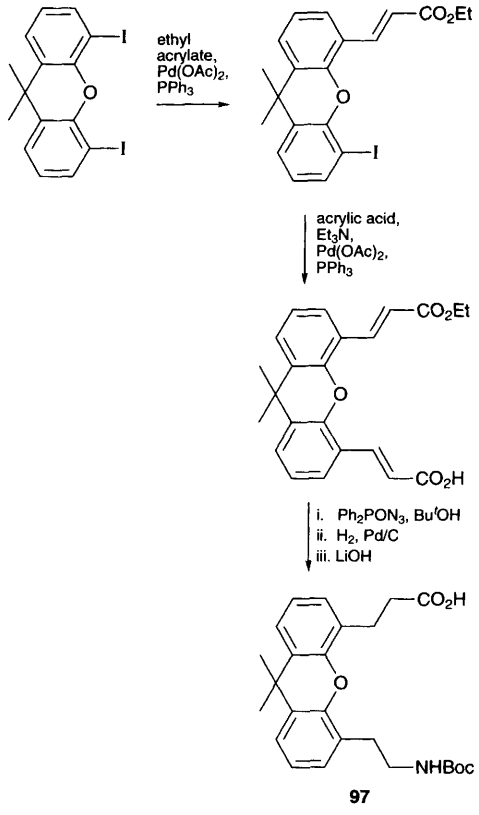
The achiral amino acid **97** has been prepared as a turn-inducer for antiparallel β-sheet forming peptides. The synthesis of compound **97** (**Scheme 46**) employs two consecutive palladium catalysed cross coupling reactions, followed by a Curtius rearrangement.[163] A synthesis of enantiomerically pure α-substituted ω-amino acids from the corresponding lactams lacking an α-substituent has been reported. The lactams are ring opened by a chiral β-amino alcohol, producing a chiral oxazoline the enolate of which is alkylated to produce the desired ω-amino acids after hydrolysis.[164]

A synthesis of enantiomerically pure [2.2]paracyclophane containing amino acids **98** and **99** has been reported, starting from enantiomerically pure methyl [2.2]paracyclophane carboxylate **100** as shown in **Scheme 47**. The nitration of ester **100** was non-regiospecific, giving a mixture of all four mononitrates in which the more electron rich aromatic ring was nitrated, from which isomers **101** and **102** could be separated. Subsequent hydrolysis of the ester and hydrogenation gave the enantiomerically pure amino acids **98** and **99** respectively.[165]

3 Preparation of amides

3.1 General methods, and the synthesis of acyclic amides

A very large number of reagents are known to induce the intermolecular dehydration of an acid and an amine, producing an amide. However, most of these reagents need to be handled under anhydrous conditions. Ito and co-workers have now reported that furanone **103** can be used to form an amide from an acid and amine in an aqueous solvent system, since neither the reagent nor any intermediates react with water at a significant rate. Compound **103** can also be used as a peptide coupling agent.[166]



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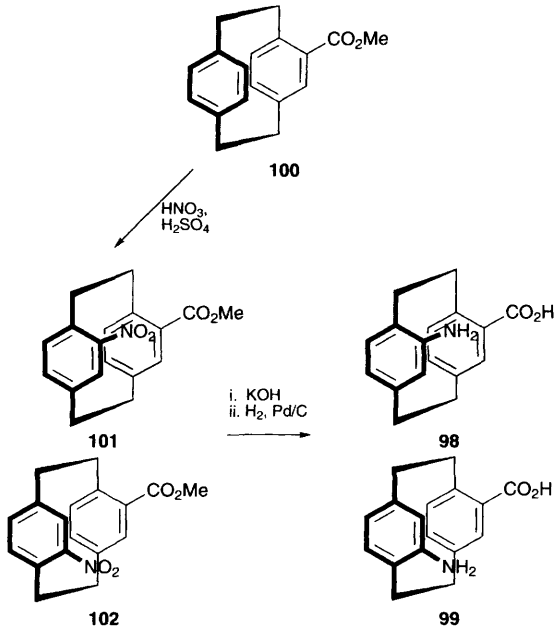
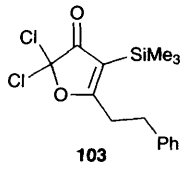
Scheme 46

N-Hydroxypyridine-2(1*H*)-thione esters of carboxylic acids have been widely used as radical precursors since their introduction by Barton and co-workers. Barton and Ferreira have now shown that the same esters can be used in non-radical chemistry to effect the conversion of an acid and



Scheme 47



103

amine (or sulfenamide) into the corresponding amide. In sterically demanding cases, the esters were more reactive towards sulfenamides than towards amines.[167] The *N*-hydroxypyridine-2(1*H*)-thione esters of protected amino acids also reacted with amino esters or the sulfenamides of amino esters, thus allowing the reagents to be used in peptide synthesis.[168]

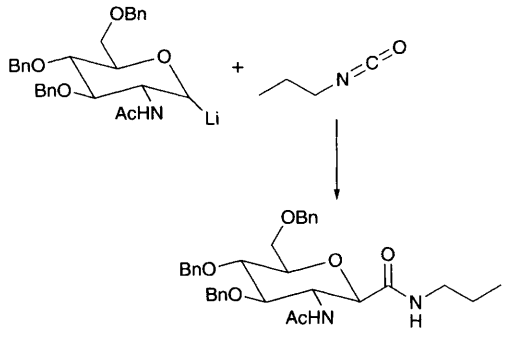
CLEC-Subtilisin has been found to catalyse the formation of amides from esters of amino acids or peptides and alkylamines in organic solvents such as acetonitrile or 3-methylpentan-3-ol. The enzyme was found to be highly enantiospecific, giving the amide derived from the (*S*)-enantiomer of the amino acid (or peptide) and the (*S*)-enantiomer of the alkylamine, but to accept a broad range of natural and unnatural substrates.[169]

The combination of diphenyl diselenide and tributylphosphine can be used to form an amide bond from a carboxylic acid and azides *via* a series of redox reactions as illustrated in **Scheme 48**. The methodology is also suitable for peptide synthesis, and has been applied to the synthesis of methionine enkephalin.[170] The use of aryllead triacetates in the *N*-arylation of amides catalysed by copper(II) has been reported.[171]

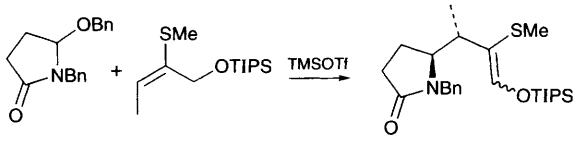
Scheme 48

One of the lesser used methods for amide synthesis involves the reaction of an organolithium reagent with an isocyanate. This chemistry has however been applied to the synthesis of sugar amides as shown in **Scheme 49**.[172] A different approach to sugar functionalised amides (and amines) has been reported, which involved reaction of the hydroxy groups with bromoacetonitrile followed by hydrolysis or reduction of the nitrile to produce amides or amines respectively.[173] A diastereoselective synthesis of amides by the ene reaction between cyclic *N*-acyliminium salts and vinyl sulfides has been achieved as shown in **Scheme 50**. If a chiral protecting group was used instead of benzyl for the nitrogen atom, then the reaction became enantioselective.[174] Another unusual approach to the synthesis of α-amino and α-hydroxy amides has also been reported. Thus reaction of a carbamoyl chloride ($ClCONR_2$) with lithium in the presence of a naphthalene catalyst generated an

acyllithium reagent which reacted with imines, aldehydes, and ketones to give the desired amides.[175]



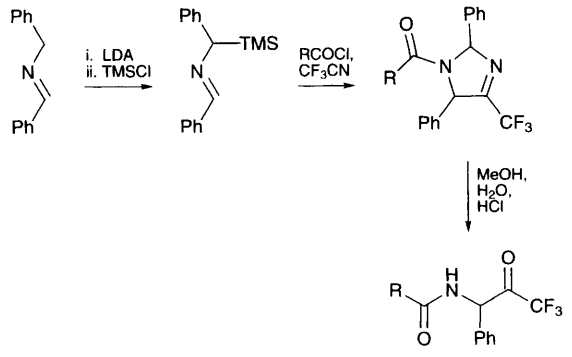
Scheme 49



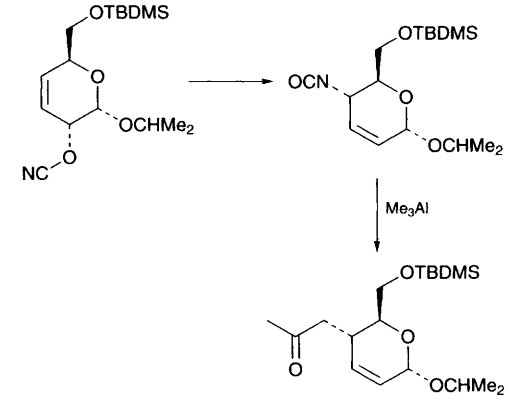
Scheme 50

The synthesis of trifluoromethyl ketone containing amides from imines has been reported as shown in **Scheme 51**. Deprotonation of the imine followed by silylation generates an α-silyl imine, a 1,3-dipole precursor. Addition of an acid chloride generates a 1,3-dipole, which undergoes a cycloaddition reaction with trifluoroacetonitrile to generate an imidazoline, which undergoes acid induced ring opening to generate the amide products. The acid chloride can be replaced with an *N*-Fmoc-amino acid fluoride to give peptide derived trifluoromethyl ketones, and the intermediate imidazolines are compatible with Fmoc-peptide synthesis, allowing the synthesis of larger peptides with a trifluoromethyl ketone end group.[176] Enantiomerically pure β-chloro amides or carbamates can be converted into the corresponding β-lithio amides or carbamates and trapped with a wide range of electrophiles (including D_2O, aldehydes, ketones, CO_2, and DCC) to produce β-functionalised amides and carbamates without any racemisation.[177] The reaction between an *N*-silylamide and an aldehyde has been shown to lead to the formation of *N*-(α-trimethylsilyloxyalkyl)amides.[178] An unusual approach to the synthesis of amides has been developed as shown in **Scheme 52**. An allylic cyanate undergoes thermal rearrangement to the corresponding isocyanante which can be trapped with trimethylaluminium to give an acetamide.[179]

A complementary approach to solid phase synthesis has been described by Kaldor *et al.* In this chemistry, a variety of organic reactions including the acylation and alkylation of amines were carried



Scheme 51



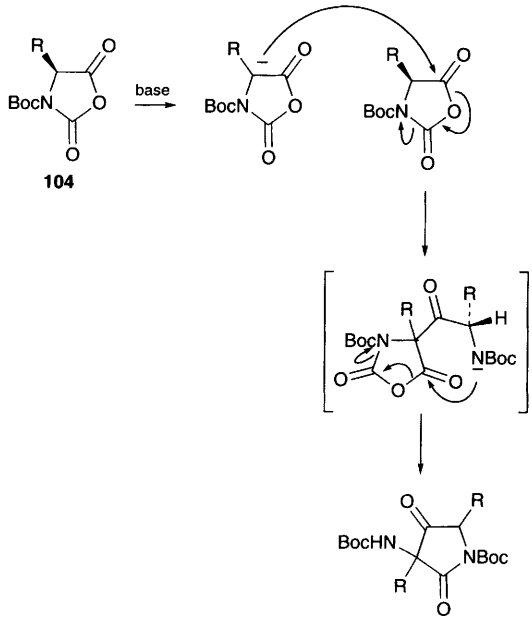
Scheme 52

out in solution, with one of the reagents present in excess. A solid supported scavenger was then added to remove the excess of reagent, thus simplifying the work-up. For example, the acylation of an amine could be carried out using an excess of an acid chloride and a solid supported amine to remove the excess acid chloride.[180]

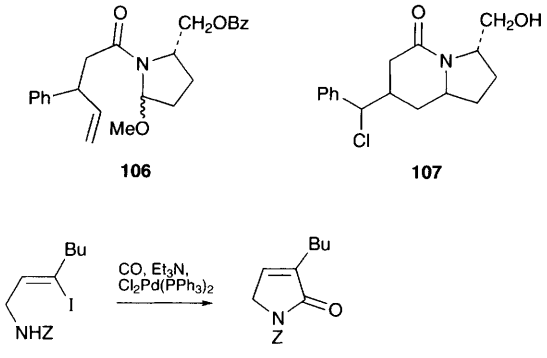
3.2 Synthesis of lactams

N-Urethane protected *N*-carboxyanhydrides **104** are being increasingly used in peptide synthesis. However, it has now been shown independently by two research groups that, in the presence of bases such as triethylamine, these compounds undergo rearrangement to give pyrrolidine-2,4-diones **105** as shown in **Scheme 53**.[181] In last year's review of this area,[1] the titanium tetrachloride induced rearrangement and cyclisation of methoxyamides **106** to 6,5-bicyclic lactams **107** was reported. Full details of this work have now been reported, along with the application of the products in the preparation of conformationally constrained TRH analogues.[182]

Treatment of a vinyl iodide containing a protected amine in the allylic position with carbon monoxide in the presence of a palladium catalyst has been shown to lead to the formation of γ-lactams. A simple example is shown in **Scheme 54**, though with suitable systems a series of tandem cyclisations culminating in lactam formation can



Scheme 53

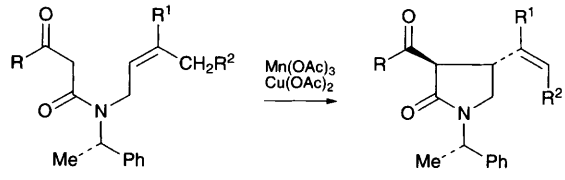


Scheme 54

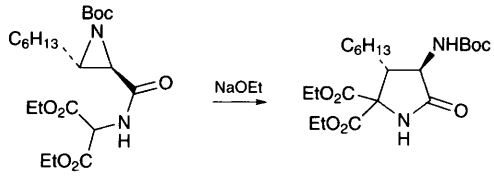
occur.[183] A radical synthesis of γ-lactams based upon the manganese(III) acetate–copper(II) acetate mediated cyclisation of *N*-allyl amides also bearing a chiral auxiliary on nitrogen has been developed (**Scheme 55**). The lactams are obtained as a 2:1 ratio of *trans*:*cis* isomers.[184] A synthesis of 3-amino-pyrrolidin-2-ones by the intramolecular ring opening of aziridines has also been reported, an example being shown in **Scheme 56**.[185] A synthesis of enantiomerically pure γ-lactams in which a Beckmann rearrangement is used for the ring expansion of chiral α,α-dichloro cyclobutanones has also been described.[186]

3.2.1 Synthesis of β-lactams

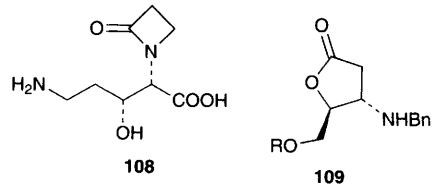
Proclavaminic acid **108** is a biosynthetic precursor to clavulanic acid. A synthesis of this β-lactam from (*S*)-serine has been reported in which 2-chloro-*N*-methylpyridinium iodide was used to form the β-lactam ring from the corresponding β-amino acid.[187] β-Amino lactone **109** has been prepared by the asymmetric Michael addition of benzylamine



Scheme 55



Scheme 56



onto the corresponding α,β-unsaturated lactone which is available from D-mannitol. The alkylation of the enolate of lactone **109** can be controlled to provide either diastereomer of the product, and subsequent manipulation gives a stereodivergent synthesis of both *cis*- and *trans*-3,4-disubstituted β-lactams as well as the corresponding β-amino esters.[188]

The reaction between an imine and a ketene is one of the standard methods for the preparation of β-lactams (the Staudinger reaction). This reaction has now been used to prepare *trans*-3-amino-4-substituted β-lactams by the reaction between a chiral *N*-trimethylsilyl-imine, and a chiral ketene.[189] The importance of the size of the chiral auxiliary attached to the imine in determining the diastereoselection observed in Staudinger reactions has also been studied. It was found that for good levels of selectivity in favour of the *cis*-β-lactam, a large chiral auxiliary should be present at the β-position of the imine.[190] A procedure for the preparation of α-amino-β-lactams *via* the Staudinger reaction has also been reported. The synthesis starts from glycine which is protected as its tetrachlorophthaloyl derivative before formation of the acid chloride and ketene in the presence of an imine, to form the β-lactam. Both the glycine protection and imine formation are carried out in a microwave oven, and under these conditions the β-lactam formation is highly *trans*-selective. The amine protecting group can then be removed by treatment with ethylene diamine giving the desired α-amino-β-lactams.[191]

The use of chiral, protected α-amino-β-hydroxyimines in the Staudinger reaction producing *cis*-β-lactams has also been described, and the products were found to undergo an acid catalysed rearrangement to pyrrolidines.[192] A synthesis of fused bi- and tri-cyclic β-lactams by a procedure which involves a Staudinger reaction followed by an intramolecular aldol condensation has been reported.[193]

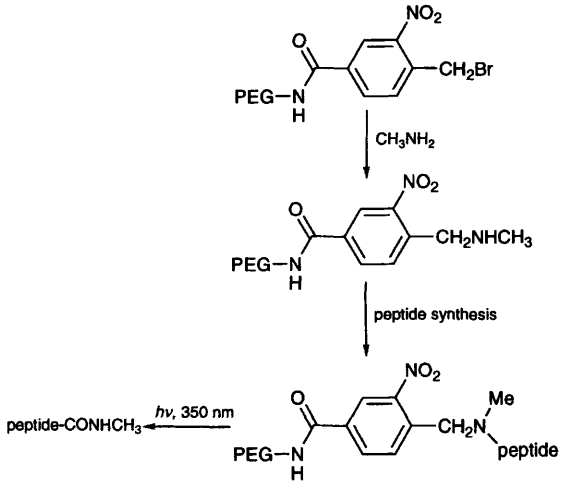
A reaction closely related to the Staudinger reaction is the formation of β-lactams by the Lewis acid induced reaction between imines and silylketene thioacetals. It has been shown that such reactions generally favour the formation of *trans*-substituted β-lactams, and that if a Lewis acid containing chiral ligands is employed, then a non-racemic β-lactam is produced.[194]

3.3 Synthesis of peptides

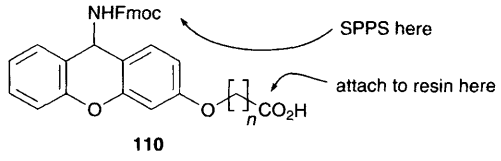
1-(2-Naphthylsulfonyloxy)-6-nitrobenzotriazole has been developed as a coupling reagent for use in solid phase peptide synthesis, giving yields which are comparable to or better than those obtained with other coupling reagents.[195] Fmoc-Amino acid fluorides are also showing significant promise as peptide coupling agents, and the application of these activated acid derivatives to couplings involving highly sterically hindered residues has been investigated. It was found advantageous to pretreat the amino component with *bis*-trimethylsilylacetamide prior to addition of the Fmoc-amino acid fluoride. Under these conditions, high yields (> 80%) could be obtained even for couplings between two very hindered residues such as Fmoc-Val-F and MeHN-Aib-OMe.[196] The benefits of silylation on the yields of peptide couplings involving sterically hindered residues (α-methyl amino acids) have also been reported by Lavielle and co-workers, for reactions carried out on a solid support using DCC, DCC–HOBt, or HATU [*O*-7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate as coupling reagents.[197] A quantitative study of the many pathways leading to epimerisation during carbodiimide induced peptide synthesis has been reported.[198] The uses of amino acid chlorides and amino acid fluorides in peptide synthesis have been reviewed.[199]

One of the most problematical steps in solid phase peptide synthesis can be the coupling between the second and third amino acids, since diketopiperazine formation can be a serious competing reaction. A protocol for avoiding this problem has been reported by Albericio *et al.* The authors recommend the use of *N*-trityl protection for the second amino acid. This protecting group can be removed under mildly acidic conditions, allowing subsequent coupling to the third amino acid to be carried out with PyAOP [7-azabenzotriazol-1-yloxy-tris(pyrrolidino)phosphonium hexafluorophosphate] without prior neutralisation.[200] It has also been shown that Fmoc-Cys(Tr) is particularly prone to racemisation by the diisopropylethylamine used in solid phase peptide synthesis. The recommended solution to this problem is to use the preformed symmetrical anhydride of Fmoc-Cys(Tr) for the coupling reaction in the absence of any base.[201]

A number of developments have taken place in the design of new linkers for polymer supported peptide synthesis. An *o*-nitrobenzyl based linker has been designed to allow the synthesis of *N*-methyl-peptide amides with photolytic cleavage of the peptide from a poly(ethylene glycol) soluble polymeric support. The key steps in the synthesis are shown in **Scheme 57**.[202] Similarly, the xanthenyl-amide linker **110** has been developed to allow the synthesis of peptide amides on an insoluble polymeric support. The linker is compatible with Fmoc-methodology, and the peptide amide is released from the solid support by acidolysis.[203]



Scheme 57

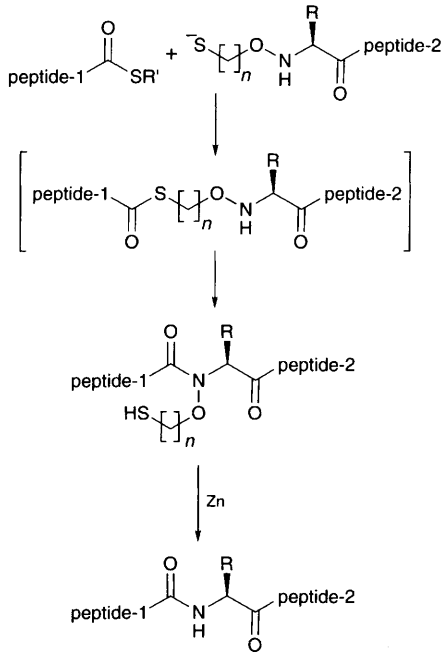


110

Enzyme catalysed peptide synthesis continues to attract much interest. Ullmann *et al.* have shown that the protease enzymes α-chymotrypsin, trypsin, and papain can be used to catalyse peptide bond formation between *N*-protected amino acid ethyl esters and amino acid or dipeptide esters in a frozen aqueous solvent system at −15 to −25°C.[204] Under these conditions, α-chymotrypsin was also found to tolerate unnatural phenylalanine derivatives as the acyl donor.[205] Papain has also been used to catalyse amide bond formation with racemic *N*-benzyloxycarbonyl-γ,γ′-di-*tert*-butyl-α-methyl-γ-carboxyglutamic acid as the acyl donor. For this study, the papain was supported on Celite, and organic solvents such as acetonitrile were utilised.

The enzyme was shown to react enantioselectively, as only the (*S*)-enantiomer of the γ-carboxyglutamic acid was incorporated into the peptides.[206] Papain catalysed tripeptide synthesis has also been shown to tolerate the presence of α,β-didehydroamino acids within dipeptide acyl donors.[207] The kinetics of thermolysin catalysed peptide synthesis have been investigated, and it was found that the rate of reaction was not significantly changed by the addition of organic solvents.[208] The effect of pressure on subtilisin catalysed peptide synthesis has been investigated, and it was found that increasing the pressure increased the rate of reaction.[209]

A chemical synthesis of peptides based upon the use of thioesters of unprotected peptide fragments has been developed as shown in **Scheme 58**. A peptide thioester is allowed to react with another peptide fragment in which the *N*-terminus has been modified to an ω-thiohydroxylamine. The initially formed thioester rearranges to a hydroxamate which can be reduced with zinc to an amide.[210]



Scheme 58

4 Summary

This continues to be a healthy area for research into new synthetic methods. Particular emphasis is currently being placed on the synthesis of enantiomerically enriched amines and amides, with a wide range of synthetic approaches being investigated. In previous summaries I have commented on the rapid developments in imine and aziridine chemistry which are being used to prepare amines, and this continues to be an area which attracts much interest. A review of this size cannot possibly do justice to the field of peptide synthesis, and this area of the review has had to be highly selective, though throughout the entire review, far more papers which could have been cited have had to be omitted this year, particularly those dealing with the total synthesis of natural products containing amines and amides. Indeed, the initial computerised literature search for this review produced twice as many references (>5000) this year as in previous years.

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