Amines and amides

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Reviewing the literature published in 1995
Continuing the coverage in *Contemporary Organic Synthesis*, 1995, **2**, 269

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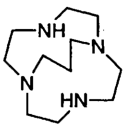
1 Introduction, scope and coverage

This review covers the literature published during 1995. Papers were selected from the online science citation index for 1995, so some papers published at the end of 1995 which are cited in the 1996 index have not been included, but will be covered in the next review of this topic. Some papers which were published at the end of 1994, or the beginning of 1996 and which are included in the 1995 citation index have however been included. This is not a comprehensive review of the literature, rather it is intended to highlight novel and potentially useful approaches to the synthesis of the title compounds. The review has the same format as that used last year,[1] and so is split into two main sections, amines and amides. The further subdivision of this review is somewhat arbitrary given the ease with which many of the derivatives (*e.g.* β-amino acids and β-lactams) can be easily interconverted.

2 Preparation of amines

2.1 Synthesis of achiral or racemic amines

One of the well known problems with preparing tertiary amines by the alkylation of secondary amines is overalkylation to give ammonium salts. A solution to this problem has been reported, in which a secondary amine is treated with potassium hydride in the presence of an excess of an alkyl halide and triethylamine. The role of the triethylamine is to scavenge excess alkyl halide.[2] Low valent titanium has been found to selectively cleave benzyl and allyl groups from tertiary amines, providing a convenient preparation of secondary amines.[3] A vinylogous Mannich reaction between an indole imine, acryloyl chloride and a 1-siloxybutadiene has been used to prepare a variety of alkaloids containing the tertiary amine group.[4] The synthesis and crystal structures of the tetra-amines **1** and **2** have been reported, both amines being found to act as proton sponges.[5]



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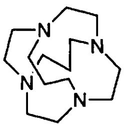
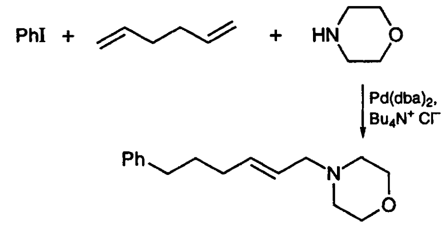


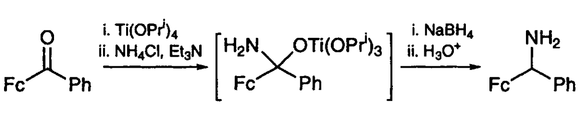
2

N-Benzyltriflamide (CF_3SO_2NHBn) has been introduced as an amine generating reagent for the Mitsunobu reaction. The reagent is an air-stable solid which is easily prepared from triflic anhydride and benzylamine, and can be used in conjunction with the standard Mitsunobu reagents triphenylphosphine and diethyl azodicarboxylate.[6] Also utilising a Mitsunobu reaction, a convenient procedure for the conversion of allyl alcohols into allylic primary amines which proceeds without allylic rearrangement has been reported. The allylic alcohol undergoes a Mitsunobu reaction (PPh_3–DIAD–phthalimide), following which treatment with hydrazine or methylamine cleaves the phthalimide group, giving the allylic amine.[7] A palladium catalysed process for the synthesis of allylic amines from non-conjugated dienes has been developed, an example of which is shown in **Scheme 1**. The reaction is compatible with a range of dienes (not just 1,5-dienes) and primary or secondary amines.[8] Simply heating a homoallylic mesylate with a primary amine in DMSO at 80 °C is sufficient to form a homoallylic amine.[9]



Scheme 1

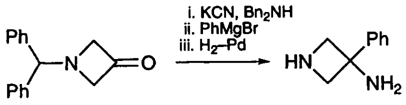
Reductive amination of an aldehyde is a well known and effective strategy for the synthesis of secondary amines. This approach has recently been utilised in the synthesis of a number of polyamine–polyamide derived toxins including philanthoxins, JSTX-toxins and argiotoxin-636.[10] A one-pot synthesis of 1-ferrocenylbenzylamine from ferrocenyl phenyl ketone and which proceeds *via* a reductive amination has been reported as shown in **Scheme 2**.[11] The reductive amination of paraformaldehyde has also been achieved by treatment with a secondary amine in the presence of zinc chloride followed by sodium borohydride–zinc chloride.[12] The reduction of aromatic oximes by borohydride exchange resin in the presence of nickel acetate has been used to prepare benzylic primary amines,[13] and the use of sodium borohydride and iodine to reduce oxime acetates to primary amines has been reported.[14]



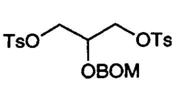
Fc = ferrocene

Scheme 2

A Strecker reaction, followed by cyanide displacement by phenylmagnesium bromide, is the key step in a synthesis of 3-amino-3-phenylazetidine as shown in **Scheme 3**.[15] In another synthesis of 3-substituted azetidines, treatment of ditosylate **3** with excess of a primary amine was found to give azetidines in high yield.[16]



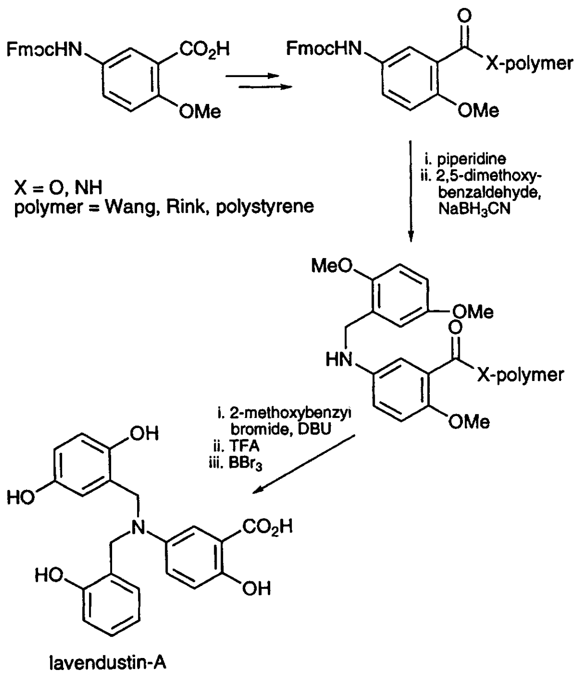
Scheme 3



3

Solid phase synthesis was once the preserve of biopolymer chemists, but the recent interest in combinatorial chemistry has resulted in a considerable increase in the scope of this methodology.

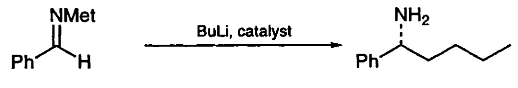
Total syntheses of the tertiary amine lavendustin-A have now been reported (**Scheme 4**), in which the use of a variety of polymeric supports was compared, and both alkylations and reductive alkylations were used to build up the tertiary amine.[17] In related work, polymer bound aldehydes were shown to undergo imine formation followed by either addition of Grignard reagents, or reduction followed by tosylation. In both cases, the product amines could be cleaved from the silicon based polymeric support by treatment with TFA.[18] Other authors, studying the solid phase reductive amination of aldehydes and acylation of amines, have shown that gel phase ^{13}C NMR can be used to monitor the progress of these reactions.[19] A solid phase synthesis of 1,2,3,4-tetrahydro-β-carbolines has also been reported, in which a Pictet–Spengler reaction is carried out on polymer bound tryptophan derivatives.[20]



Scheme 4

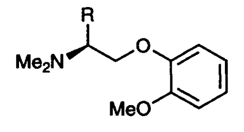
2.2 Synthesis of optically active amines

In last years review of this area,[1] considerable attention was paid to the asymmetric catalysis of the addition of organolithium reagents to imines. Work in this area has continued, and Itsuno *et al.* have studied the addition of butyllithium to a range of metallated imines as shown in **Scheme 5**. A number of catalysts were studied, including sparteine,

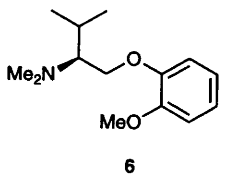


Scheme 5

proline derivatives and polymer supported proline derivatives. Enantiomeric excesses ranged from 1–52%, with the best results being obtained with sparteine as the catalyst and aluminium as the metal.[21] The asymmetric addition of methyllithium to *p*-methoxyphenyl benzyl imine has been further investigated this year, with a wide range of bi- and tri-dentate ligands being investigated as asymmetric catalysts for the reaction. In general, tridentate ligands (especially the amino acid derivatives **4** and **5**) were found to give better asymmetric induction than bidentate ligands.[22] Catalysts **4** and **5** both induce the formation of the (*R*)-enantiomer of the amine formed by the addition of organolithium reagents to imines. The related catalysts **6** and **7** have also been prepared, and whilst ligand **6** also gives the (*R*)-enantiomer of amines, catalyst **7** favours formation of the (*S*)-enantiomer.[23]



4 R = CH_2Ph
5 R = Ph



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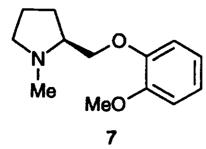
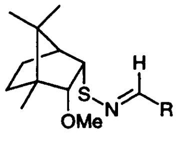


7

The addition of organometallic reagents to the chiral thioimines **8** has been studied: butyllithium and allylmagnesium bromide were found to give opposite senses of asymmetric induction, whilst diethylzinc gave a 1 : 1 mixture of diastereoisomers. Subsequent hydrolysis of the thio amines provided optically active amines.[24] The asymmetric addition of organometallic reagents to chiral imines and chiral oxazolidines was also used in a general synthesis of bis(1-arylethyl)amines (**Scheme 6**).[25] The asymmetric addition of an allyl cerium reagent to a chiral imine has been carried out as shown in **Scheme 7**. The initial adduct was transformed into a phenylogous amino acid.[26] The asymmetric addition of a wide variety of allyl metal reagents to valine derived imines has also been investigated (**Scheme 8**), the diastereoselectivity being dependent upon the metal used. Subsequent reduction and oxidative cleavage of the valine derived auxiliary provided an enantioselective synthesis of homoallylic amines.[27] Another application of the addition of organometallic reagents to imines is in the conversion of sugars to azasugars as shown in **Scheme 9**.[28]



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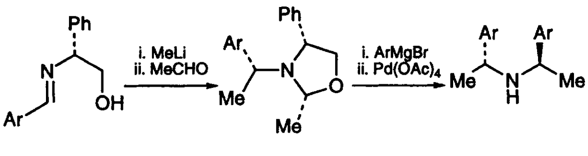
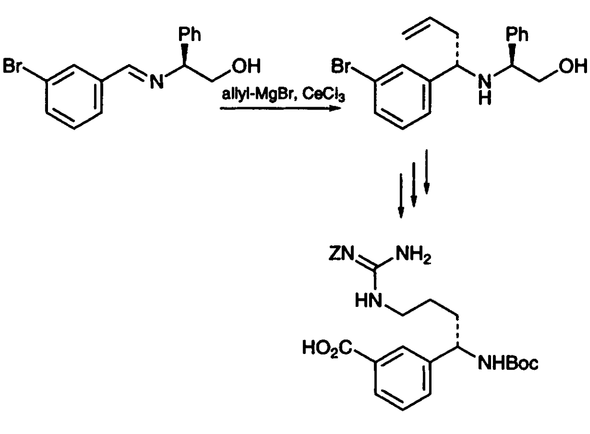
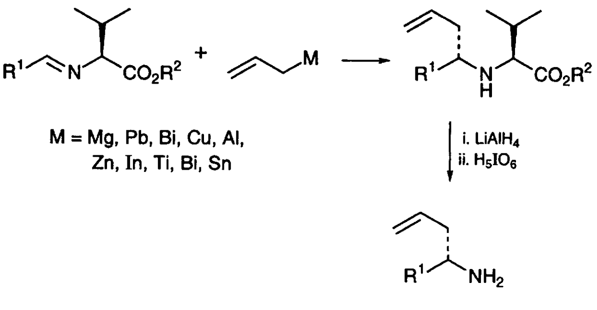


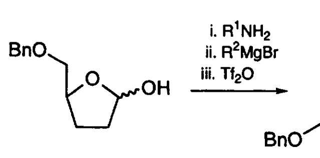
Scheme 6



Scheme 7

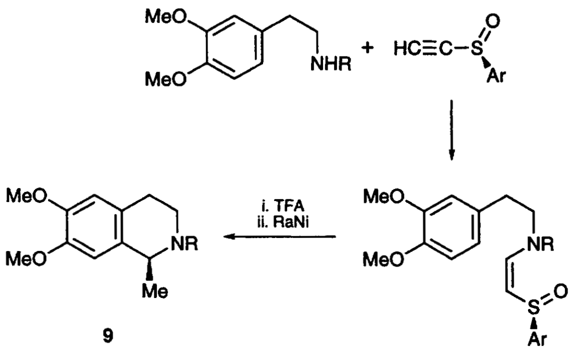


Scheme 8



Scheme 9

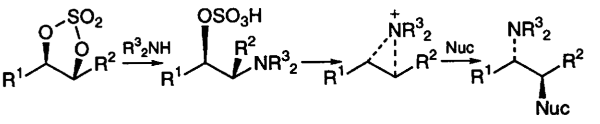
A total synthesis of (*S*)-carnegine and related compounds **9** has been reported this year, which employs a homochiral alkynyl sulfoxide as a chiral auxiliary in a Friedel–Crafts cyclisation of an iminium ion as shown in **Scheme 10**.[29] The asymmetric hydrogenation of imines using the Buchwald chiral titanocene catalyst has been discussed in previous reviews of this area.[1] Recently, the kinetics and mechanism of this reaction have been investigated.[30] A wide variety of chiral 1,2-diamines as well as related amides and ureas have been prepared from (*S*)-pyroglutamic acid.[31]



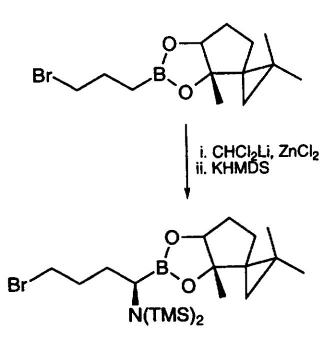
Scheme 10

2.3 Synthesis of amines bearing additional functional groups

In recent years, Katritzky and co-workers have been using benzotriazole chemistry to prepare a wide variety of functionalised amines as discussed in last years review.[1] Recent applications of this chemistry include the synthesis of *N*-alkyl prolines,[32] α-phosphoamides[33] and styrylamides.[34] Sharpless *et al.* have reported an asymmetric synthesis of a variety of β-heteroatom substituted amines starting from enantiomerically pure 1,2-diols. Thus conversion of the diol into a cyclic sulfonate, followed by reaction with a secondary amine gives an aziridinium salt which undergoes ring opening upon treatment with a second nucleophile as shown in **Scheme 11**.[35] As part of a synthesis of the thrombin inhibitor DUP-714, an asymmetric Matteson homologation was employed to prepare a homochiral α-amino borane (**Scheme 12**).[36]

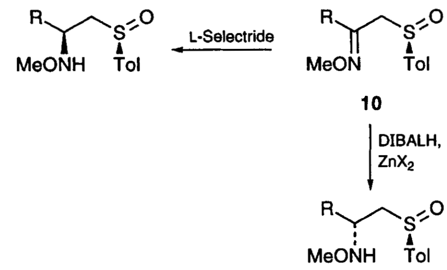


Scheme 11

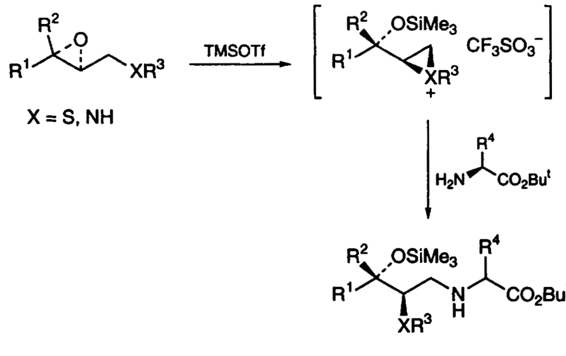


Scheme 12

Homochiral sulfoxides have been used in a synthesis of optically pure γ-fluoro-β-amino sulfoxides by the sodium borohydride induced reduction of γ-fluoro-β-enamino sulfoxides. Unfortunately, only a 3:1 ratio of stereoisomers was obtained at the newly formed chiral centre during the enamine reduction.[37] The reduction of sulfoxide containing oximes **10** was rather more diastereoselective. Reduction with DIBALH and zinc salts gave the β-amino sulfoxide resulting from chelation controlled reduction, whilst reduction with L-Selectride gave the diastereoisomeric β-amino sulfoxide *via* non chelation control (**Scheme 13**).[38] Treatment of a β-thioepoxide with trimethylsilyl triflate generates a β-trimethylsilyloxy thiiranium ion, which upon treatment with an α-amino ester undergoes ring opening to give a β-thio-γ-oxy-amino ester as shown in **Scheme 14**.[39] The same methodology can also be used starting with β-amino epoxides, thus producing β-amino-γ-oxy-amino esters *via* an aziridinium ion.[40]

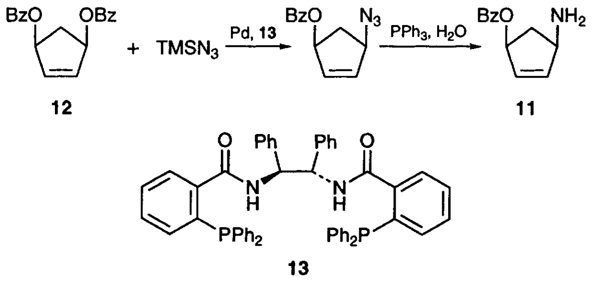


Scheme 13



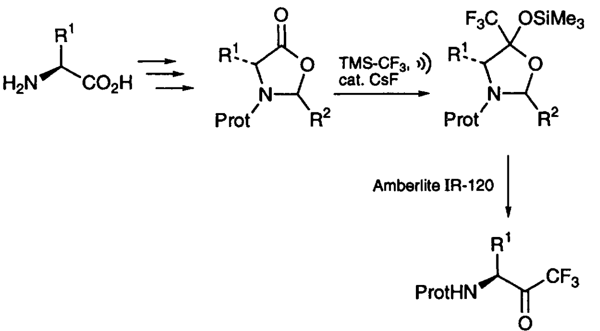
Scheme 14

The first synthesis of Amadori rearrangement products (α-amino keto tetraols, formed by the reaction of a sugar and an amino ester) to give pure products has been achieved by utilising protecting groups for all uninvolved functionalities. For the first time, the Amadori rearrangement product derived from a dipeptide has also been prepared.[41] In recent years, the acid chlorides of optically pure Fmoc-protected α-amino acids, and the corresponding acid fluorides of Boc and *Z*-protected amino acids have become readily available, and utilised as peptide coupling reagents. It has now been shown that reduction of any of these compounds by lithium tri(*tert*-butoxy)aluminium hydride provides an attractive route for the synthesis of homochiral α-amino aldehydes.[42] The Mannich reaction between an aldehyde, amine and enol ether has been found to be catalysed by Yb(OTF)$_3$ in a THF–water mixture, providing a convenient synthesis of β-amino ketones.[43] Trost *et al.* have reported an asymmetric synthesis of amine **11** from the *meso*-dibenzoate **12** as shown in **Scheme 15**. The key step is the enantioselective displacement of one of the two benzoate groups by a chiral palladium complex (derived from ligand **13**), forming a π-allyl complex. The latter species is displaced by TMS–N_3, giving the enantiomerically pure azide which can be reduced to the desired amine.[44]



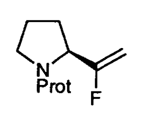
Scheme 15

A route for the conversion of α-amino acids into α-amino trifluoro ketones has also been developed as shown in **Scheme 16**. Thus the amino acids are first converted into *N*-protected oxazolidinones, and the latter react with trifluoromethyl trimethylsilane in the presence of sonication and a catalytic amount of caesium fluoride to give an adduct which upon treatment with Amberlite IR-120 ion exchange resin gives the desired *N*-protected α-amino trifluoro ketones. An alternative route is also available, in which the α-amino acid is first converted into an *N*-protected α-amino aldehyde. Reaction of the aldehyde with (trifluoromethyl)trimethylsilane gives the corresponding β-amino trifluoro alcohol, which can be oxidised to the corresponding ketone with the Dess–Martin perioindane reagent.[45] The vinyl fluoride derivatives **14** and **15** have been prepared from ethyl (*S*)-prolinate, and investigated as potential isosteres of the proline amide bond.[46]



Prot = protecting group

Scheme 16



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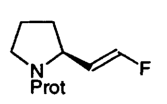
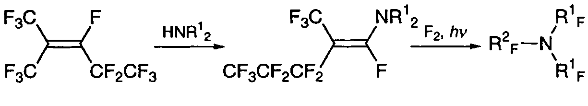


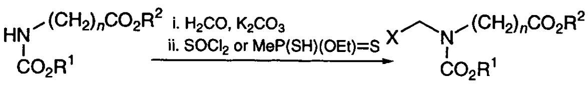
15

Prot = Boc, Z

A synthesis of perfluorotertiary amines (**Scheme 17**) has been reported, starting from a perfluoroalkene. Thus reaction with a non-fluorinated secondary amine followed by fluorination with elemental fluorine gives perfluorotertiary amines.[47] Treatment of a urethane protected ω-amino ester with formaldehyde, followed by trapping of the aminol with thionyl chloride gives α-chloro amines. Alternatively, the aminol can be trapped with dithiophosphinates to give α-amino dithiophosphinates as shown in **Scheme 18**.[48] Similarly, reaction of an α-amino ester with formaldehyde and an aryl amide provides a synthesis of *N*-acyl aminals (**Scheme 19**).[49] Treatment of either a *N*-methoxymethylarylamine or *N*,*N*,*N*-triaryl-1,3,5-triazine with titanium tetrachloride and TMS-azide provides a synthesis of *N*-azidomethylarylamines.[50]

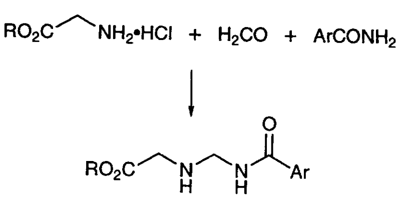


Scheme 17



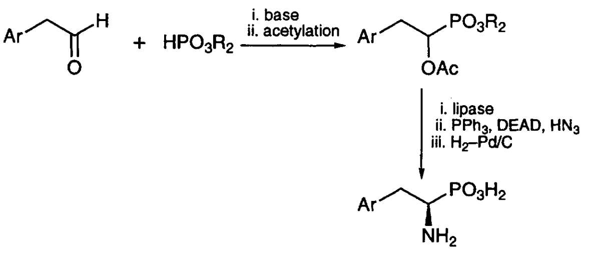
X = Cl or MeP(OEt)(=S)–S–

Scheme 18

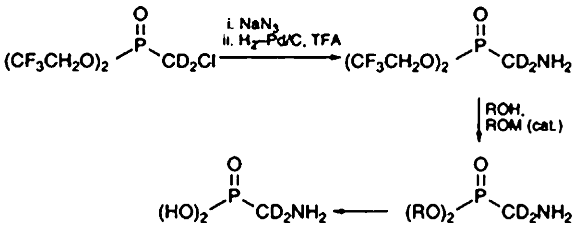


Scheme 19

An asymmetric synthesis of α-aminophosphonic acids from aldehydes, which incorporates an enzymatic resolution and a Mitsunobu reaction to introduce the nitrogen, has been reported, as outlined in **Scheme 20**.[51] Similar methodology has been used to prepare β-hydroxy-α-amino phosphonates starting from α,β-dihydroxy phosphonates.[52]



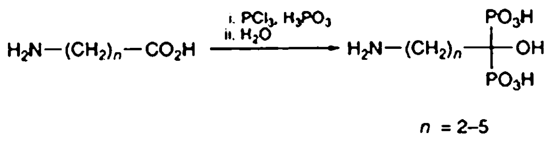
Scheme 20



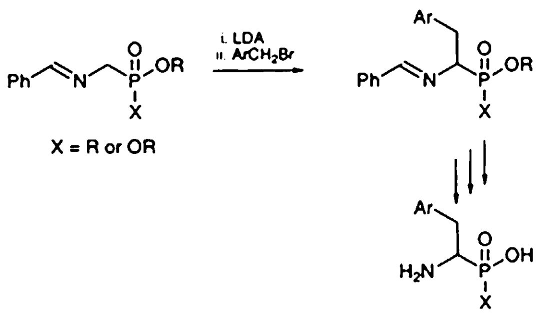
Scheme 21

The synthetic route shown in **Scheme 21** has been used to prepare α,α-dideutero α-amino phosphonic acid. The synthesis is based upon previous work by the same authors, but with the introduction of a transesterification step to circumvent the harsh conditions required for the direct removal of the β-trifluoroethyl esters.[53]

A synthesis of ω-amino α-hydroxy bisphosphonates from ω-amino acids has been reported as shown in **Scheme 22**.[54] This short synthesis has been adapted for large scale work by the inclusion of methanesulfonic acid as a solvent, to avoid problems associated with the reaction mixture solidifying and generating excess heat. The alkylation of the enolate of an imine of a glycine ester is a commonly used route for the synthesis of α-amino acids. This chemistry has now been adapted to allow the synthesis of α-amino phosphonic and phosphinic acids as shown in **Scheme 23**.[55]



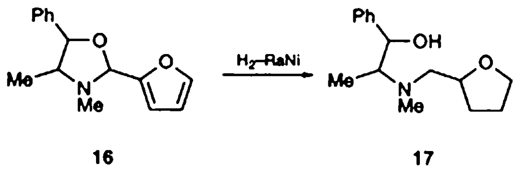
Scheme 22



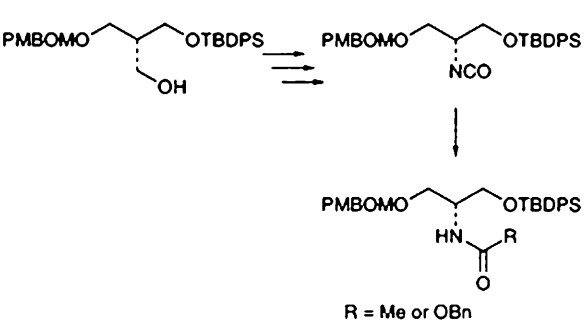
Scheme 23

2.3.1 Synthetic routes to β-hydroxyamines

The asymmetric reduction of α-amino phenyl ketones using a rhodium catalyst with chiral ligands has been used to prepare enantiomerically pure 2-hydroxy-2-phenylethylamines.[56] Hydrogenation of homochiral furan **16** using Raney Nickel proceeded chemoselectively, giving chiral amine **17**, as shown in **Scheme 24**.[57] Displacement of an α,α′-dibromoketone with potassium phthalimide or sodium azide followed by hydrolysis or reduction has been used to prepare a variety of C-2 symmetrical β-hydroxy diamines and α-keto diamines as potential anti-HIV-1 protease inhibitors.[58] A synthesis of β,β′-dihydroxyamines from an asymmetrised tris(hydroxymethyl)methane derivative has also been reported as shown in **Scheme 25**. Thus oxidation of the unprotected OH group followed by a Curtius rearrangement gives the corresponding isocyanate with retention of stereochemistry. The isocyanate can then be trapped with benzyl alcohol or methyllithium, giving the *N*-Z- and acetamide derivatives respectively.[59]

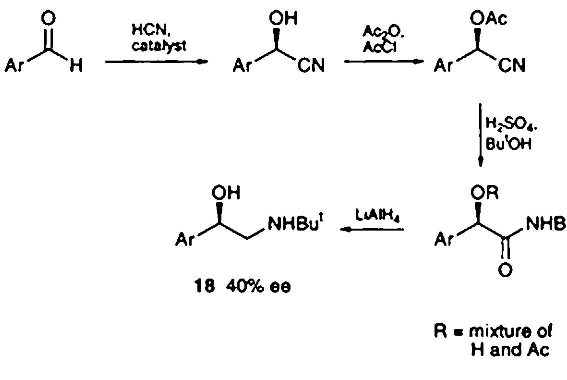


Scheme 24



Scheme 25

A synthesis of terbutaline **18** has been reported in which the cyclic dipeptide cyclo[-(*S*)-His-(*S*)-Phe-] is used to catalyse the asymmetric addition of HCN to an aldehyde, giving the derived cyanohydrin with very high enantiomeric excess (**Scheme 26**). The synthesis continued by protection of the alcohol, conversion of the nitrile to a *tert*-butyl amide, and finally reduction of the amide to the corresponding



Scheme 26

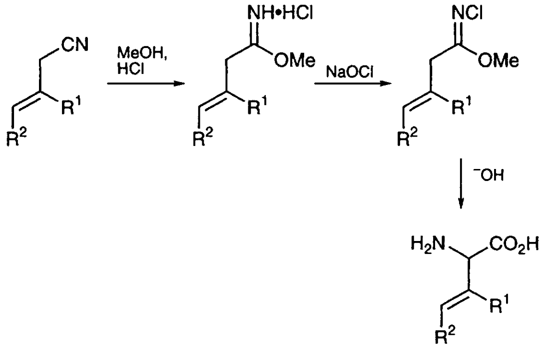
amine. However, the final reduction step using lithium aluminium hydride was found to cause extensive (60%) racemisation of the benzylic centre.[60] It is likely that the lithium aluminium hydride reduction of related systems will also have deleterious effects on stereochemical integrity.

2.3.2 Synthesis of α-amino acids

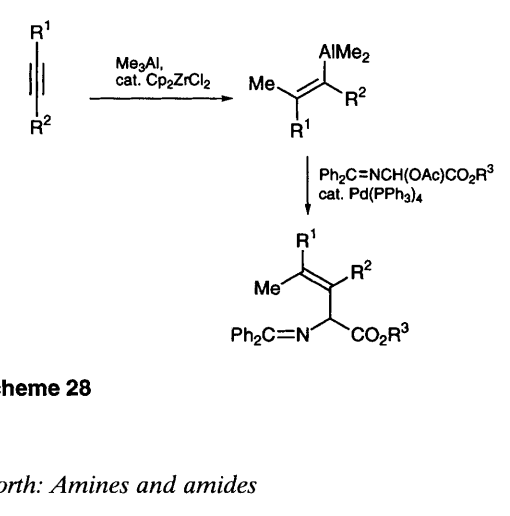
This remains an area of much synthetic interest, and as with the previous review of this area,[1] only those methods that result in the formation of the carbon–nitrogen bond, or in which the nitrogen atom plays a pivotal role in the chemistry have been included. The emphasis of this review has been placed on those methods that allow the stereocontrolled synthesis of amino acids, as most applications of amino acids require stereoisomerically pure compounds.

2.3.2.1 Racemic syntheses of α-amino acids

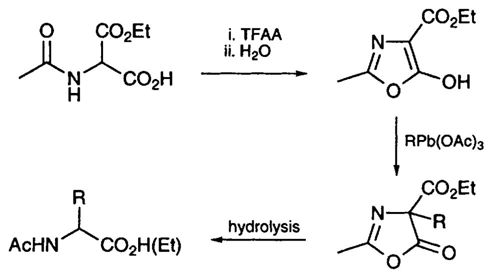
A synthesis of β,γ-unsaturated-α-amino acids starting from β,γ-unsaturated nitriles and incorporating a Neber rearrangement has been reported as shown in **Scheme 27**.[61] In a variation of well established glycine imine enolate alkylation reactions, O'Donnell *et al.* have also reported a synthesis of β,γ-unsaturated α-amino acids, using organometallic methodology (**Scheme 28**).[62] Also using organometallic reagents in a variation of well known chemistry, Maorgan and Pinhey have used organolead triacetates to alkylate ethyl acetamidomalonate as shown in **Scheme 29**.[63]



Scheme 27

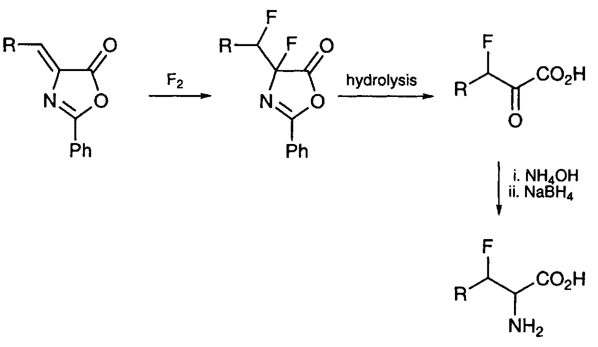


Scheme 28

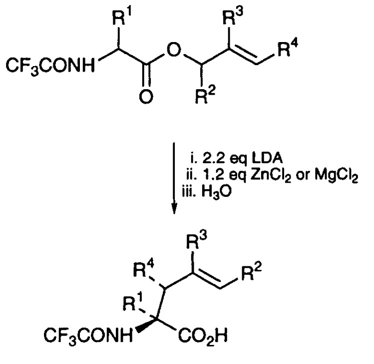


Scheme 29

A racemic, but erythro selective synthesis of β-fluoro α-amino acids has been reported (**Scheme 30**), in which the fluorine is introduced by the reaction of an azlactone with molecular fluorine. Subsequent ring opening and reductive amination gives the fluorinated amino acid.[64] Another stereoselective synthesis of amino acids utilises a Claisen rearrangement. This was discussed in the last review of this area,[1] and recent developments have allowed the synthesis of α-substituted γ,δ-unsaturated amino acids as shown in **Scheme 31**.[65]



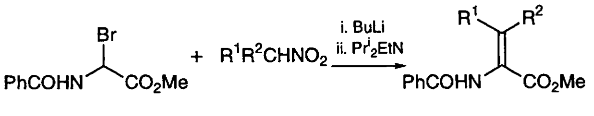
Scheme 30



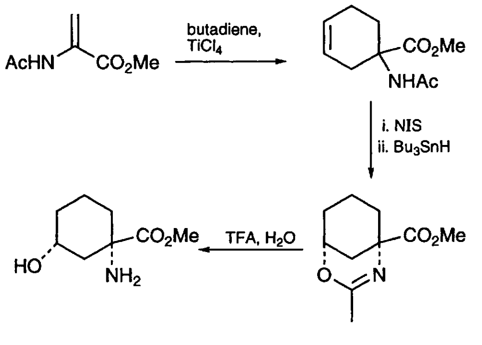
Scheme 31

Radiolabelled amino acids are important for a number of applications, and a synthesis of 2-amino-isobutyric acid specifically labelled with ^{11}C at the α-position has been reported. Thus addition of methyllithium to ^{11}C labelled CO_2 gives acetone with ^{11}C incorporated into the carbonyl group. A Strecker reaction and hydrolysis then gives the amino acid.[66]

A synthesis of α,β-unsaturated amino acids from an α-bromoglycinate has been reported as shown in **Scheme 32**. Thus condensation of the α-bromoglycinate with a nitro enolate followed by elimination of the nitro group gives the desired α,β-didehydro amino acids.[67] The Michael addition of secondary amines onto *N*-Z- or *N*-Ac-α,β-didehydro amino esters and amides has been used in the synthesis of racemic 2,3-diaminopropanoic acid derivatives.[68] α,β-Didehydro amino esters also undergo Diels–Alder and other cycloaddition reactions. This chemistry has been utilised in a synthesis of a conformationally constrained analogue of homoserine as shown in **Scheme 33**.[69]



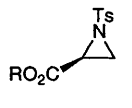
Scheme 32



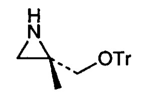
Scheme 33

2.3.2.2 Asymmetric syntheses of α-amino acids

Church and Young have developed a short asymmetric amino acid synthesis which proceeds *via* an alanine cation synthon.[70] Hence, ring opening of aziridine **19** by organocuprates occurs regiospecifically at the least hindered position. Subsequent removal of the *N*-tosyl group (HBr, AcOH) then provides the desired amino acids. The same methodology has been used by Solomon *et al.* to prepare *N*-β-alkylated-diaminopropionic acid derivatives by the ring opening of aziridine **20** by primary amines.[71] Similar methodology has also been used by Miller and co-workers in a synthesis of α-methyl serine derivatives. In this case, aziridine **21** was first protected with the β-trimethylsilylethylsulfonyl protecting group, then ring opened at the least hindered end by benzyl alcohol. Selective deprotection of one of the differentially protected alcohols followed by oxidation and final deprotection then gave the desired α-methyl serine.[72]

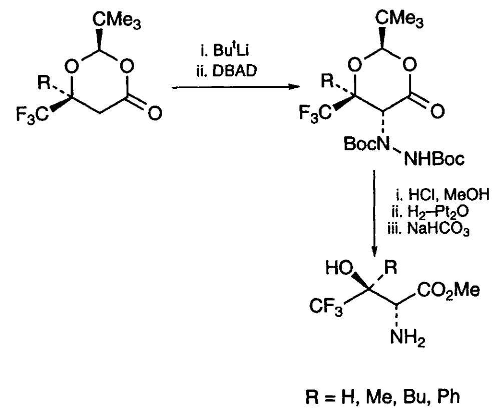


19 R = H
20 R = Bu^t



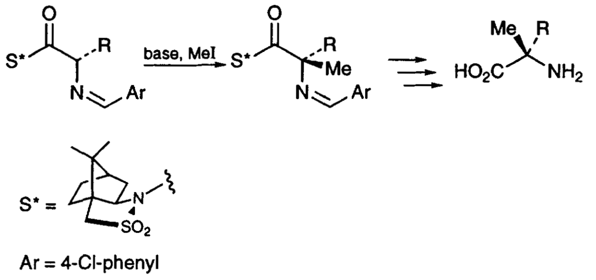
21

Seebach and co-workers have developed an effective methodology for the asymmetric synthesis of α,α-disubstituted amino acids using his transfer of chirality approach. Alonso and Davies have now optimised this approach by replacing the originally used pivaldehyde with ferrocene carboxaldehyde as the prochiral species to which the chirality is transferred.[73] The main limitation of the transfer of chirality approach to α-amino acid synthesis developed by Seebach *et al.* is the hydrolysis of the final adducts, especially with sterically hindered α,α-disubstituted amino acids. However, a new two stage hydrolysis procedure which first forms an *N*-benzoyl amino acid methylamide (by treatment with MeOH and HCl followed by PhCOCl and Et_3N), then hydrolyses this with anhydrous followed by aqueous HCl, should overcome these difficulties.[74] An asymmetric synthesis of fluorinated tyrosine and *meta*-tyrosines using Seebach's methodology has also been reported.[75] Seebach has modified his transfer of chirality methodology to provide an asymmetric synthesis of a variety of trifluorothreonine and allo-threonine analogues as shown in **Scheme 34**. For this synthesis, the cyclic template is formed between the acid and alcohol functionalities rather then between the acid and amino groups. Asymmetric induction is then achieved during the introduction of the α-amino group by reaction of the ester enolate with di-*tert*-butyl azodicarboxylate (DBAD).[76]

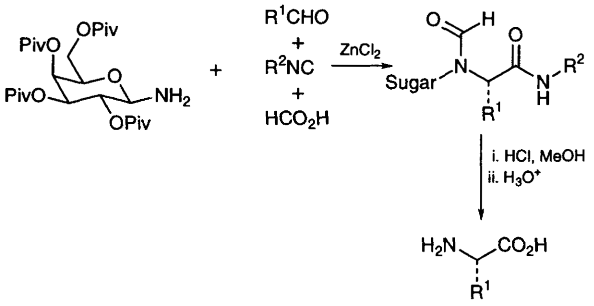


Scheme 34

The Oppolzer chiral sultam has been widely used in asymmetric amino acid synthesis over the last few years. In the latest application of this approach, Ayoub *et al.* have used the auxiliary to control the methylation of enolates of amino acid imines as shown in **Scheme 35**, leading to a synthesis of homochiral α-methyl amino acids.[77] An asymmetric variant of the Ugi condensation has also been developed (**Scheme 36**). Thus condensation of tetrapivaloylgalactosamine with an aldehyde, isocyanide and formic acid gives an adduct which on acid hydrolysis gives chiral amino acids.[78]

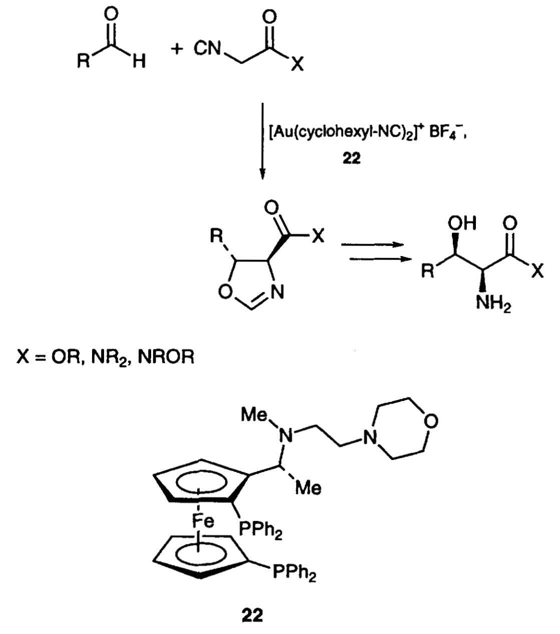


Scheme 35



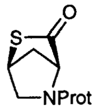
Scheme 36

Williams and co-workers have shown that treatment of a racemic allylic acetate with potassium phthalimide in the presence of a catalytic amount of a chiral palladium species gives optically active phthalimido protected allylic amines without allylic rearrangement. Subsequent oxidation of the alkene, and removal of the phthalimido protecting group leads to optically active amino acids.[79] A stereocontrolled, asymmetric synthesis of β-hydroxy α-amino acids, along with the corresponding aldehydes and ketones, has been reported by Sawamura *et al.* (**Scheme 37**). Thus the aldol reaction between an aldehyde and an α-isocyanocarbonyl derivative is catalysed by a gold catalyst in the presence of chiral ligand **22**.[80]



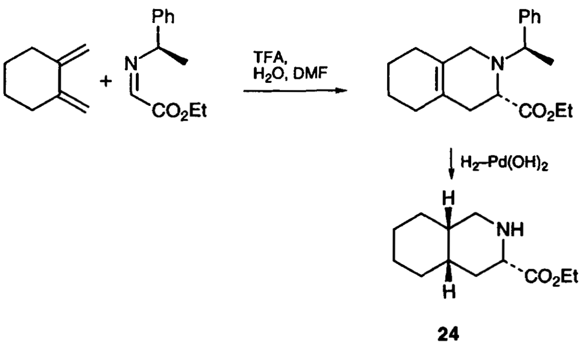
Scheme 37

As discussed in last years review of this topic,[1] there is currently much interest in the synthesis of ring substituted proline derivatives, due to their ability to function as conformationally constrained amino acids. Full experimental details of one of the syntheses of 3-carboxyproline mentioned last year have since been reported.[81] This year, an asymmetric synthesis of highly substituted prolines *via* a 1,3-dipolar cycloaddition between an azomethine ylid and a chiral α,β-didehydro amino acid has been reported.[82] A related field is the synthesis of 4-oxaprolines derived from serine or threonine, and synthetic methodology for the preparation of a range of such compounds including derivatives where the acid has been reduced to an aldehyde or alcohol has been reported.[83] *trans*-4-Hydroxyproline has been used as the starting material for a synthesis of *cis*-4-thioproline derivatives. The key intermediates in this synthesis are thiolactones **23** which undergo ring opening when treated with amines.[84]

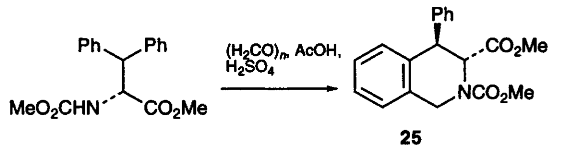


23
Prot = protecting group

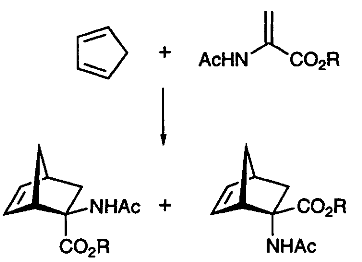
Over recent years,[1,85] Hruby and co-workers have been synthesizing topographically constrained phenylalanine derivatives by the incorporation of methyl groups either in the *ortho*-positions of the aromatic ring or on the β-carbon; full details of this work has now been published.[86] This methodology has now been extended to the synthesis of 2′,6′-dimethyl and β-methyltyrosines.[87] Another constrained amino acid is decahydroisoquinoline **24**, which has been synthesised by an asymmetric Diels–Alder reaction as shown in **Scheme 38**.[88] The related constrained amino acid **25** has been prepared from diphenylalanine by a route involving a Pictet–Spenger reaction as shown in **Scheme 39**. The key cyclisation proceeds with a 2.8 : 1 selectivity between the two phenyl rings.[89] The Diels–Alder reaction between cyclopentadiene and dehydro amino esters



Scheme 38



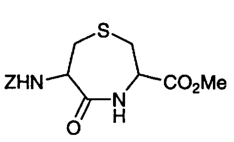
Scheme 39



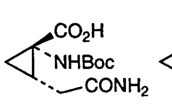
Scheme 40

(**Scheme 40**) is catalysed by a variety of silica based heterogeneous catalysts (using thermal or microwave activation), giving a mixture of the *endo* and *exo* isomers of the bicyclic amino acid. When a menthyl ester is used, asymmetric induction is observed, though this is greater in the case of the *endo* isomer (100:0) than in the *exo* isomer (best 4:1).[90]

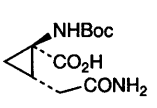
All four stereoisomers of the cyclic lanthionine derivative **26** have been prepared, and their conformations determined by X-ray and NMR techniques. Unlike the situation with the corresponding eight membered ring disulfides,[91] all four stereoisomers of compound **26** were found to possess a *cis* amide bond, indicating that an eight membered ring disulfide is the smallest such ring capable of accommodating a *trans* amide bond.[92] Stereoisomers **27** and **28** which are conformationally constrained glutamine analogues, have both been prepared by multistep procedures from D-manitol. The key step in these syntheses is the introduction of the amino group from a carboxylic acid with retention of stereochemistry, utilising a Hoffmann or Curtius rearrangement.[93]



26

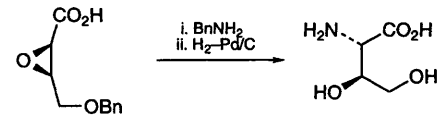


27



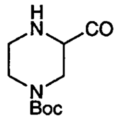
28

In the first review of this area,[85] the use of enantiomerically pure α-nitro vinyl sulfides as precursors to β-hydroxy α-amino acids reported by Jackson *et al.* was discussed. Full details of this chemistry have now been reported.[94] A synthesis of 4-hydroxy-(*S*)-threonine which can be used to incorporate ^{13}C labels at both C2 and C3 has also been reported (**Scheme 41**). The enantiomerically pure epoxide required for this synthesis is available by a Sharpless epoxidation.[95] Xue and Degrado have reported a short, regiospecific synthesis of *N*-α-methyl-arginine and -ornithine starting from *N*-α-Boc-glutamine.[96] Thus conversion of the amide to a nitrile (Ac_2O), followed by alkylation of the BocNH (NaH, MeI) and reduction of the nitrile (H_2–PtO_2), gives the desired ornithine derivative which can be further converted into the arginine derivative.



Scheme 41

The use of red yeast cells (in pH 10.5 aqueous buffer) to catalyse the addition of ammonia to ring substituted cinnamic acid derivatives, producing optically pure (*S*)-phenylalanine analogues, has been reported.[97] Enzymatic resolution can still be an effective methodology for the synthesis of optically pure amino acids, and Bruce *et al.* have shown that leucine aminopeptidase will resolve piperazine derivative **29**.[98] Similarly, amidase enzymes were utilised by Kaptein *et al.* to resolve α-methyl amino amides. The α-substituted amino acids prepared in this way were then used to prepare chiral ligands for Lewis acid catalysts of the trimethylsilylcyanation of aldehydes, to prepare optically active cyanohydrins.[99]



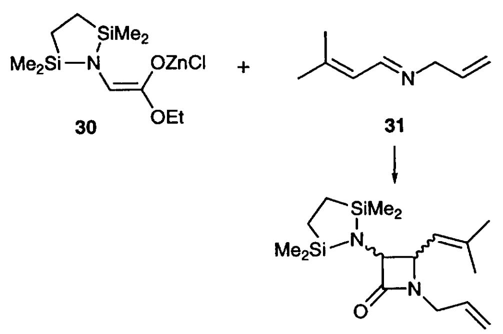
29

2.3.3 Synthesis of β-amino acids

2.3.3.1 Racemic syntheses of β-amino acids

Reaction of the lithium enolate of an α-alkoxy-*N*,*N*-dimethylacetamide with an α-methoxyurethane gives a racemic α-hydroxy β-amino acid derivative in which the *anti* diastereoisomer predominates (up to 90%) as shown in **Scheme 42**. However, if R′ is a TBDMS group and titanium tetraisopropoxide is added to transmetalate the lithium enolate, then the *syn* diastereomer is formed with up to 90% selectivity.[100] The stereochemistry of the reaction between zinc enolate **30** and imine **31** (**Scheme 43**) has been found to be solvent dependent. Usually, the *trans* diastereomer predominates, but in the presence of polar cosolvents (NMM, DMSO, NMP,

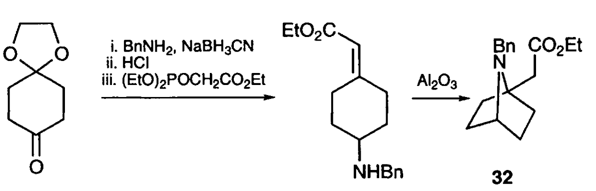
Scheme 42



Scheme 43

TMU, DMPU or optimally HMPA) the *cis* diastereoisomer becomes the major product.[101]

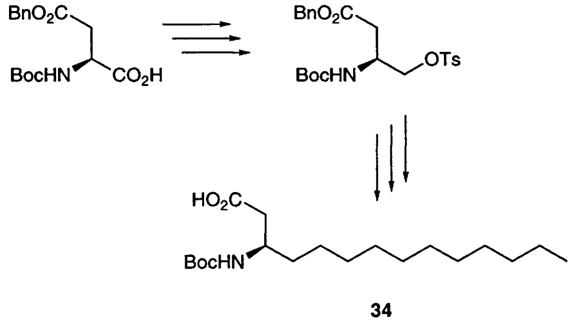
A one pot synthesis of β-amino esters (and β-lactams) from an aldehyde has also been reported. Thus addition of a lanthanide triflate catalysts to a mixture of an aldehyde, an amine and a silyl enolether gives β-amino esters.[102] The intramolecular Michael addition of an amine onto an α,β-unsaturated ester was employed in the synthesis of the bicyclic β-amino ester **32** as shown in **Scheme 44.**[103]



Scheme 44

2.3.3.2 Asymmetric syntheses of β-amino acids

An asymmetric synthesis of β-amino acids starting from aspartic acid has been reported, in which the α-acid group of the aspartic acid becomes the acid of the β-amino acid.[104] Thus aspartic acid is converted into the *N*,*N*-dibenzyl diol **33** using known methodology; this is then mesylated, which results in the formation of a mesylate aziridinium ion as shown in **Scheme 45**. The latter reacts regiospecifically with cyanide at the least hindered end of the aziridinium ion, followed by displacement of the mesylate by an organocuprate. The resulting β-cyanoamines can then be hydrolysed and deprotected to give the desired β-amino acids. The same approach has been used to prepare 3,4-diaminobutanenitrile derivatives, starting from (*S*)-asparagine, the asparagine amide becoming the nitrile and the acid being converted into an amine.[105] The intuitively more obvious approach of using the β-acid of aspartic acid as a β-amino acid has been exploited in a synthesis of iturinic acid **34** as outlined in **Scheme 46.**[106]

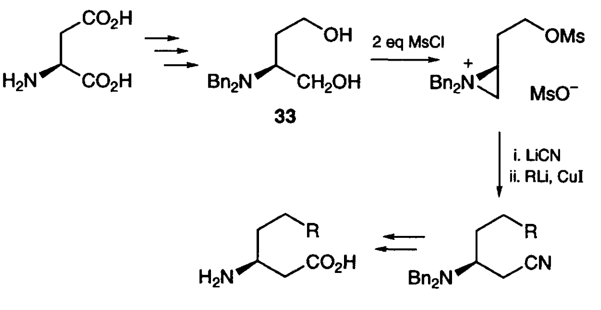


Scheme 46

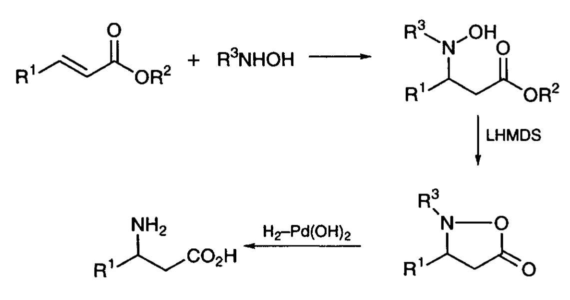
The asymmetric Michael addition approach to β-amino acids developed by Davies and his co-workers was discussed in last year's review of this area.[1] This year, the methodology has been used to prepare the natural product (2*S*,3*R*)-3-amino-2-hydroxydecanoic acid, as well as the 2-epimer and 2-deoxy derivative.[107] Davies *et al.* have also utilised this methodology [using (α-methylbenzyl)allylamine as the chiral amine] in a formal total synthesis of (+)-thienamycin.[108] Related methodology has now been reported by Enders *et al.* which uses TMS-SAMP as the chiral amine equivalent,[109] and by Sewald *et al.* using homochiral amidocuprates.[110]

Also using similar chemistry, the Michael addition of hydroxylamines to α,β-unsaturated esters has been investigated as a route to asymmetric β-amino acid synthesis as shown in **Scheme 47**. Subsequent cyclisation of the hydroxylamine adduct to give an isoxazolidinone followed by hydrogenation gives the β-amino acids. The influence of chiral esters (R^2) and chiral hydroxylamines (R^3) on the stereochemistry of the reaction was investigated.[111]

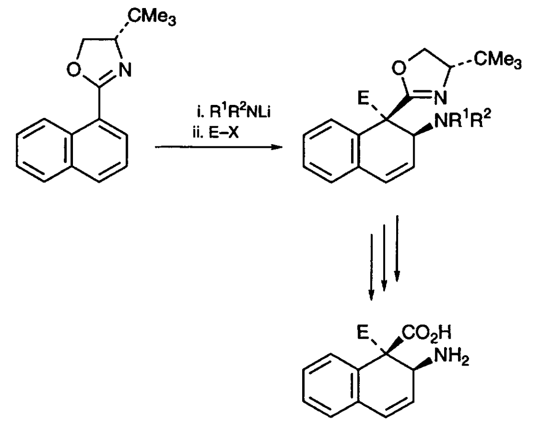
An alternative approach has been developed by Meyers *et al.* (**Scheme 48**), in which the Michael



Scheme 45



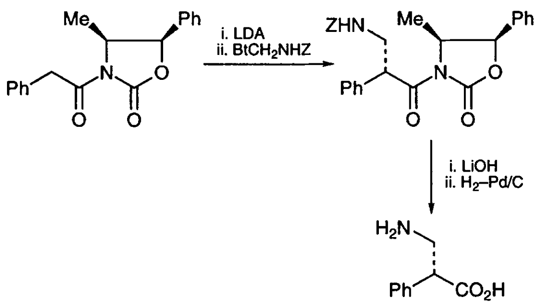
Scheme 47



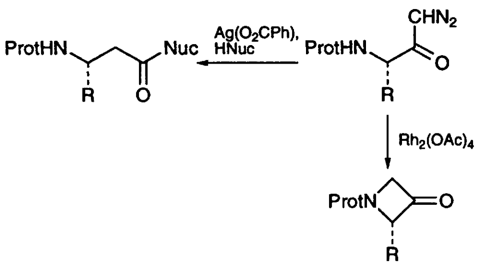
Scheme 48

addition of an achiral lithium amide to a chiral naphthyloxazoline is used to prepare cyclic β-amino acids.[112] The Michael addition of both chiral and achiral amines to homochiral α,β-unsaturated esters has also been investigated.[113] By the choice of a suitable pair of matched reagents, very high diastereoisomeric excesses could be obtained, and the adducts could be further manipulated by α-enolate formation (trapping with aldehydes) and cyclisation to β-lactams.

Wyatt and co-workers have exploited the leaving group abilities of a benzotriazole (Bt) group in an asymmetric synthesis of 3-amino-2-phenylpropanoic acid, in which the enolate of a chiral imide is allowed to react with $BtCH_2NHZ$ as shown in **Scheme 49**. As a result of this synthesis, the absolute configuration of this β-amino acid was revised.[114]



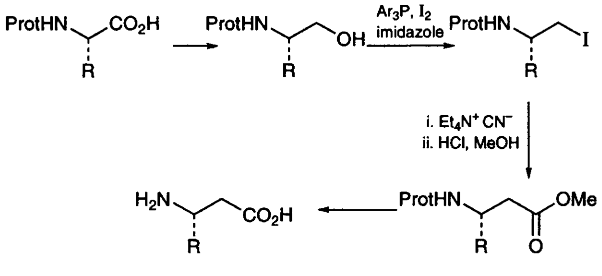
Scheme 49



Prot = protecting group

Scheme 50

Diazoketones derived from α-amino acids undergo a Arndt–Eistert rearrangement upon treatment with a catalytic amount of silver benzoate in the presence of a nucleophile (**Scheme 50**), giving β-amino acid derivatives. Alternatively, in the presence of rhodium acetate azetidin-3-ones are produced.[115] The Arndt–Eistert rearrangement has been shown not to cause any racemisation, except when the amino acid is phenylglycine, and it is possible to use the β-substituent to control the stereochemistry at the α-position during the alkylation of an enolate subsequently formed from the β-amino ester.[116] Alternative methodology for the homologation of α-amino acids into β-amino acids has also been reported as shown in **Scheme 51**. Thus reduction of an *N*-protected α-amino acid to the corresponding β-amino alcohol, conversion of the alcohol into an iodide, displacement with cyanide, hydrolysis and deprotection provides the desired β-amino acids.[117]

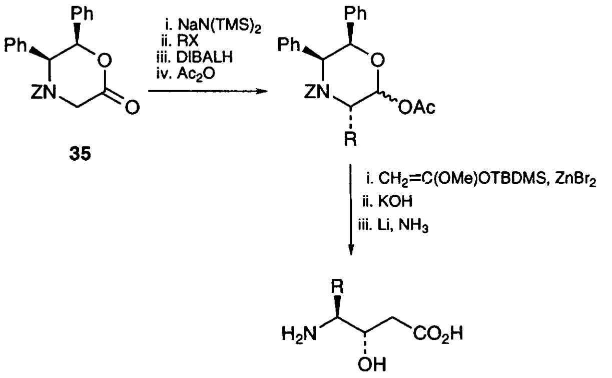


Prot = protecting group

Scheme 51

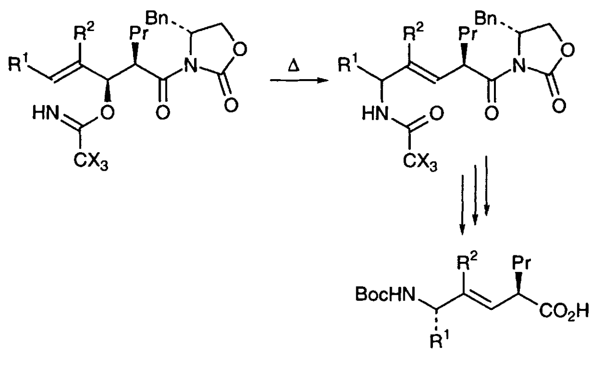
2.3.4 Synthesis of γ- and higher amino acids

In recent years, Williams and co-workers have developed an asymmetric synthesis of α-amino acids starting from the chiral template **35**. This has now been extended into a synthesis of β-hydroxy γ-amino acids (**Scheme 52**) which are of importance as hydroxymethylene peptide bond isosteres.[118] An asymmetric synthesis of the template **35** has also been developed, in which the key step is the oxynitrilase catalysed addition of HCN to benzaldehyde



35

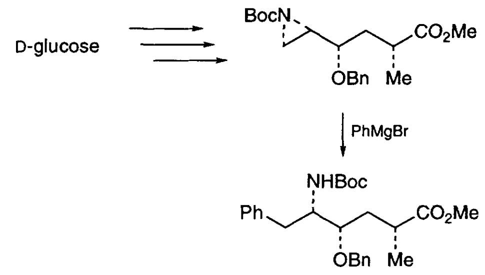
Scheme 52



Scheme 53

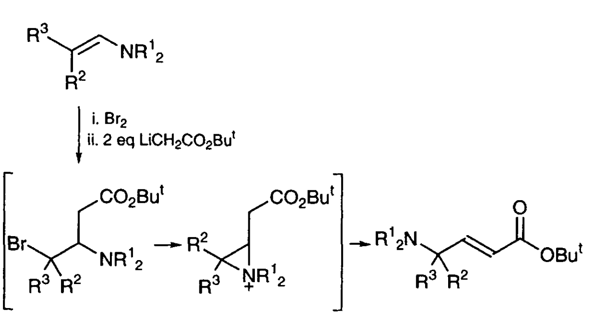
giving optically pure mandelonitrile.[119] This synthesis improves upon the previous synthesis of the template which involved a resolution step. Another synthesis of *β*-hydroxy-*γ*-aminobutanoic acid has also been reported, using malic acid as a chiral starting material.[120]

A [3,3]-sigmatropic shift has been used in a synthesis of *β*,*γ*-unsaturated *δ*-amino acids (**Scheme 53**) which are also used as peptide bond isosteres.[121] The ring opening of a glucose derived *N*-Boc aziridine by phenylmagnesium bromide has been used in the synthesis of the hydroxyethyl peptide bond isostere of the Phe-Ala dipeptide unit as shown in **Scheme 54**.[122]



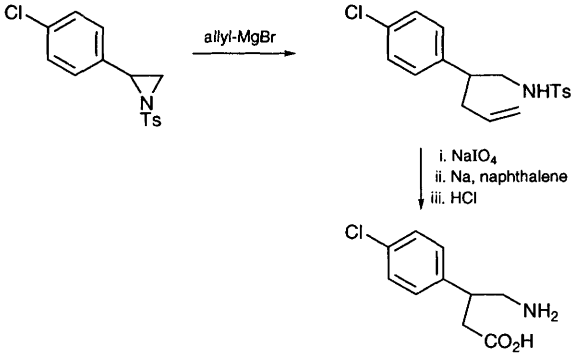
Scheme 54

A synthesis of *α*,*β*-unsaturated *γ*-aminobutyric acids has been reported (**Scheme 55**) which starts from enamines. Thus reaction of an enamine with bromine followed by lithium *tert*-butyl acetate gives a *β*-amino *γ*-bromo ester which undergoes elimination of HBr with rearrangement *via* an aziridinium ion to give *α*,*β*-unsaturated *γ*-aminobutyric acids.[123]

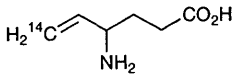


Scheme 55

A racemic synthesis of 4-amino-3-(4-chlorophenyl)-butyric acid has also been reported, which proceeds *via* the ring opening of an aziridine as shown in **Scheme 56**.[124] Unlike all of the other examples of aziridine ring-opening cited in this review, in this case the allyl group becomes attached to the more substituted carbon atom of the aziridine presumably due to its benzylic nature. A synthesis of the *γ*-amino acid vigabatrin **36** specifically labelled with ^{14}C in the terminal alkene position has also been reported.[125]



Scheme 56

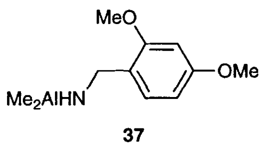


36

3 Preparation of amides

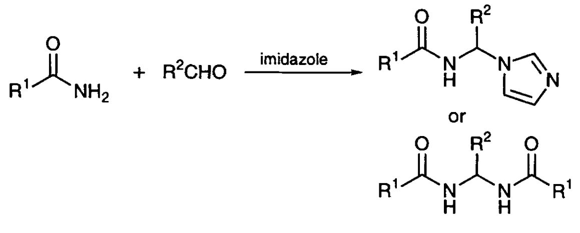
3.1 General methods, and the synthesis of acyclic amides

Reagent **37** has been used to convert a barrelene tetramethyl ester into the corresponding protected tetra-amide. Treatment with TFA subsequently removed the 2,4-dimethoxybenzyl protecting groups, giving the barrelene tetra-primary amide.[126] *p*-Nitrobenzenesulfonyl chloride has been used as a condensing agent for carboxylic acids and secondary amines,[127] and 2-chloro-1-methylpyridinium iodide has been used to prepare *N*-methoxyamides from carboxylic acids and *O*-methyl hydroxylamine.[128] 4′-Nitroanilides (4-nitrophenyl amides) are difficult to prepare, especially from amino acids as these cannot be highly activated due to the risk of racemisation. However, it has now been shown that *N*-Boc amino acids react with 4-nitrophenylisocyanate to give *N*-Boc amino anilides.[129] The same 4′-nitro anilides can also be prepared by treating an *N*-protected (protecting group = Alloc, Boc, Fmoc, Tr or Z) amino acid with 4-nitroaniline in the presence of phosphorus oxychloride and pyridine.[130]

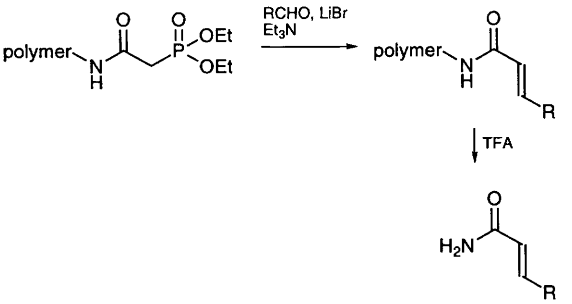


37

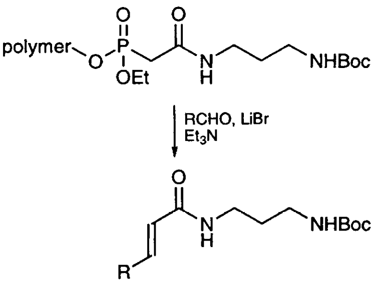
Reaction of a primary amide with an aldehyde in the presence of imidazole results in the formation of either an *N*-[(imidazol-1-yl)alkyl] amide or alkyl bridged bis-amide depending upon the structures of the amide and aldehyde as shown in **Scheme 57**.[131]



Scheme 57



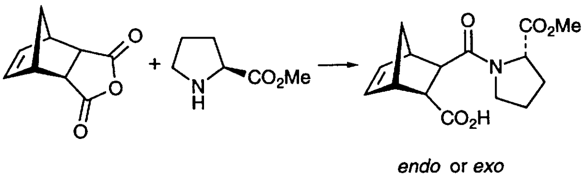
Scheme 58



Scheme 59

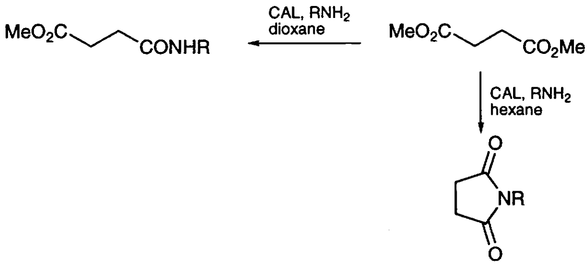
A solid state synthesis of α,β-unsaturated amides *via* a Wadsworth–Emmons reaction has been described (**Schemes 58** and **59**). The phosphonate amide can be attached to the solid support either through the phosphonate esters or *via* the amide, and the reaction can be monitored by gel phase ^{13}C NMR.[132]

The desymmetrisation of *meso*-anhydrides by homochiral amines is an attractive approach to the synthesis of enantiomerically pure compounds, as the adducts contain two versatile functional groups, an acid and an amide. The use of proline methyl ester as a cheap, readily available and efficient reagent to desymmetrise norbornene derived anhydrides (**Scheme 60**) has been reported.[133] The absolute stereochemistry of the amido acids was determined both by X-ray crystallography, and by conversion to the known corresponding lactones. A related approach has also been used by Ward *et al.* to synthesise a lignan lactone utilising α-methylbenzylamine as the chiral amine.[134]



Scheme 60

The use of the enzyme *Candida antartica lipase* (CAL) to catalyse the formation of amides from esters and amines has been investigated. In studies using dimethyl succinate, the product of the reaction was found to be solvent dependent (**Scheme 61**); the amido ester being formed in dioxane whilst the cyclic imide was produced in hexane. The reaction could also be used to resolve racemic amines, and was found to be regio- and stereo-specific when applied to dimethyl 2-methylbutanedioate. The latter reaction does not require a chiral amine, and gives predominantly the product of attack at the least hindered carbonyl.[135] The use of the same enzyme (in diisopropyl ether at elevated temperature) to catalyse the formation of amides from *N*-Z-glutamate derivatives has also been investigated. With diesters (ethyl or benzyl) of (*S*)-glutamic acid, reaction with amines occurred regiospecifically at the α-carbonyl, whilst with diethyl *N*-Z-(*R*)-glutamate amidation occurred regioselectively at the γ-carbonyl. This reaction was also found to be enantioselective when α-methylbenzylamine was used as the amine.[136]



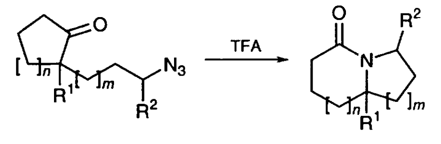
Scheme 61

Both lipase and protease enzymes have been investigated for the ammonation of methyl *N*-Z-α-amino esters. Whilst many amino acids were substrates for this reaction, most amino acid–enzyme combinations gave low to moderate enantiomeric excesses when the enzymes were used to resolve racemic amino esters. An exception was the resolution of methyl *N*-Z-phenylglycinate which when treated with lipase gave the amino amide with 91% ee.[137]

3.2 Synthesis of lactams

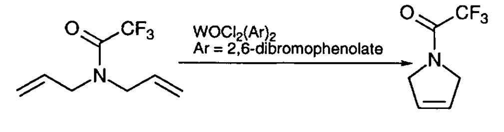
A simple approach to the synthesis of macrocyclic diamides, by the condensation of a diacid chloride and a diamine which does not need to be carried out under high dilution conditions, has been reported.[138] However, a similar cyclisation using *meta*-benzoic diacid chloride and *para*-di(aminomethyl)benzene lead to a catenane composed of the macrocyclic dimer.[139]

A general procedure for the conversion of cyclic ketones into lactams *via* the Beckmann rearrangement which employs microwave irradiation of a mixture of the ketone, hydroxylamine sulfate and silica in the absence of any solvent has been reported.[140] An intramolecular Schmidt reaction can also be used to prepare bicyclic lactams as shown in **Scheme 62**. The regio- and stereo-chemistry of this reaction has been studied using a wide range of substrates.[141]



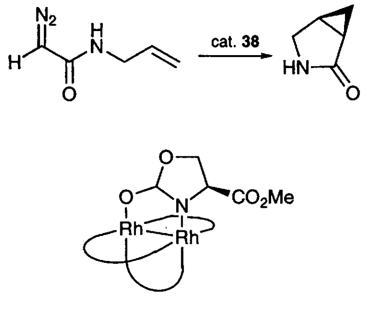
Scheme 62

Olefin metathesis is enjoying a revival of interest at present, with particular interest being shown in both ring opening and ring closing metathesis. This activity has been largely stimulated by new catalysts which are tolerant of a wide range of functional groups. Nugent *et al.* have developed a tungsten based catalyst for ring closing metathesis which will tolerate amides; the catalyst was used to prepare nitrogen heterocycles as shown in **Scheme 63**.[142] A synthesis of the *N*-norbornenyl derivatives of amino acids and their esters has been reported. These compounds undergo ring opening metathesis polymerisation to give polymers which are analogues of peptides and proteins.[143]



Scheme 63

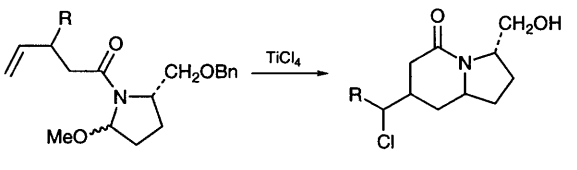
Reaction of an *N*-allyl diazoamide with rhodium catalyst **38** results in asymmetric addition of the carbenoid onto the alkene, giving cyclopropyl γ-lactams with up to 98% enantiomeric excess as shown in **Scheme 64**.[144] During the synthesis of 6,5-bicyclic lactams as peptide mimetics, the Lewis acid induced cyclisation of compound **39** was investigated. It was found that cyclisation occurred with rearrangement and concomitant removal of the benzyl protecting group (**Scheme 65**), giving lactam **40** as the product.[145]



38

each bridge is as shown for the top bridge

Scheme 64



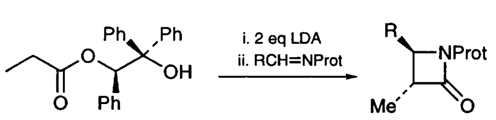
39 **40**

Scheme 65

The use of polymer bound HOBt (1-hydroxybenzotriazole) in lactam synthesis has also been investigated. Thus reaction of an ω-*N*-Boc amino acid with DCC and polymer bound HOBt results in the formation of a polymer bound ω-*N*-Boc amino activated ester. The *N*-Boc group can then be removed with TFA. Subsequent treatment with triethylamine results in cyclisation to give the macrocyclic lactam with concomitant cleavage of the lactam from the polymer support and regeneration of the polymer bound HOBt. The method has been used to prepare 7–13 membered rings.[146]

3.2.1 Synthesis of β-lactams

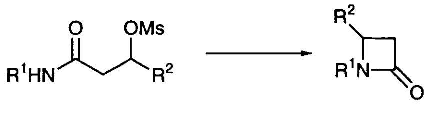
An asymmetric synthesis of either diastereomer of β-lactams has been reported which utilises 1,2,2-triphenylethane-1,2-diol as a chiral auxiliary in a condensation between an ester enolate and an imine as shown in **Scheme 66**. Interestingly, whilst normally the *trans* isomer of the β-lactam is obtained, simply protecting the alcohol as a methyl or silyl ether results in the formation of the *cis* diastereoisomer instead.[147]



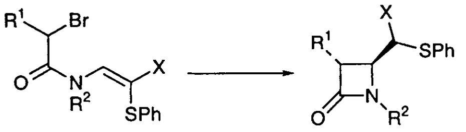
Prot = protecting group

Scheme 66

Perhaps the least utilised approach to β-lactam synthesis is formation of the N–C3 bond. However it has now been reported that β-mesyloxy amides can be cyclised to give β-lactams as shown in **Scheme 67**.[148] Another approach to β-lactam synthesis uses a 4-*exo-trig* radical cyclisation to form the C2–C3 bond as outlined in **Scheme 68**. A variety



Scheme 67

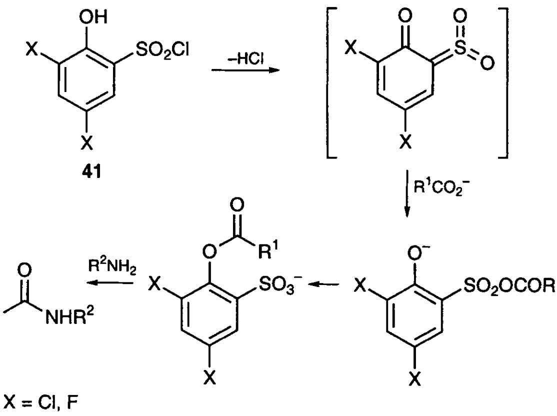


Scheme 68

of racemic and optically active β-lactams have been prepared using this methodology, utilising chiral auxiliaries within R^1 and R^2 where appropriate.[149]

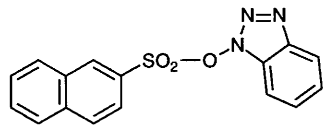
3.3 Synthesis of peptides

Cabaret and Wakselman have introduced sulfonyl chloride **41** as a coupling reagent for peptide synthesis. The reagent is proposed to act through initial elimination of HCl, producing a sulfene which reacts with the carboxylic acid component to give initially a carboxylic–sulfonic mixed anhydride. This then undergoes an intramolecular rearrangement to give an aryl ester which reacts with the amine component to give the desired peptide bond as shown in **Scheme 69**.[150]



Scheme 69

Sulfonyloxybenzotriazole **42** has also been investigated as a coupling reagent in solid phase peptide synthesis.[151] As an alternative to solid phase peptide synthesis, polymer supported triphenylphosphine has been used as a peptide coupling reagent in the presence of iodine and imidazole.[152] Carpino and Elfaham have introduced (*N*,*N*,*N*′,*N*′-tetramethyl) fluoroformamidinium hexafluorophosphate **43** as a convenient reagent for converting Fmoc amino acids into acid fluorides, which can be isolated or used *in situ*.[153] Pentafluorophenyl diphenylphosphate has been introduced as a reagent for the *in situ* formation of pentafluorophenyl active esters for peptide synthesis, and is reported to give superior results to other reagents.[154]



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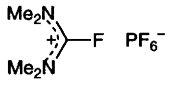
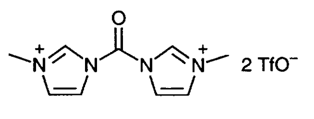


43

The use of water soluble carbodiimide in a two phase water–dichloromethane solvent system was found to give peptides in high yield and with low racemisation provided an additive was added. The best additives were HOBt, HOAt (1-hydroxy-7-azabenzotriazole) and HOPO (2-hydroxypyridine-*N*-oxide), whilst NHS (*N*-hydroxysuccinimide) was less effective.[155] Gibson and Rapoport have introduced CBMIT [1,1′-carbonylbis(3-methylimidazolium) triflate] **44** as a coupling reagent for peptide synthesis, and have shown that in the presence of copper(II) salts it can be used for fragment condensations without causing significant racemisation.[156] The chloro imidazolidinium salt **45** has been used as a coupling reagent (in the presence of HOAt or HODhbt) during the synthesis of Alamethicin-F30, a peptide which contains many Aib (α-aminoisobutyric acid) and other hindered residues.[157] A theoretical study of peptide coupling *via* mixed anhydrides has been conducted using semiempirical methods, in an attempt to assess the importance of the various possible side reactions during this process.[158]



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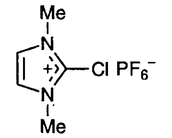
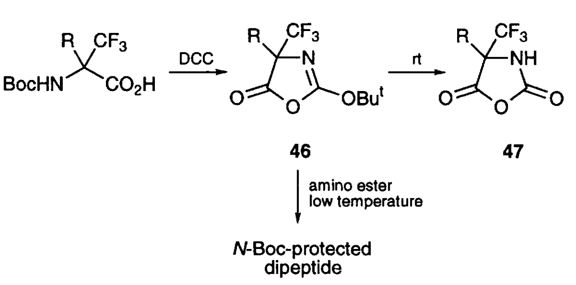


45

Peptide synthesis with α-trifluoromethyl amino acids is prone to numerous side reactions. However, the reaction of *N*-Boc α-trifluoromethyl amino acids with DCC has now been investigated in detail (**Scheme 70**). The initial product is a 4,5-dihydrooxazol-5-one **46**, which at room temperature eliminates isobutene giving Leuch's anhydride **47**. However, at lower temperatures the formation of **47** is inhibited and peptide synthesis can successfully be carried out.[159] In the last review of this area, a novel synthesis of α,α-disubstituted enantiomerically pure Leuch's anhydrides was discussed.[1] It has now been

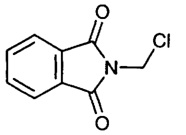


Scheme 70

reported, that these Leuch's anhydrides react with a variety of amino esters (including other α,α-disubstituted amino esters) to give dipeptides incorporating an (*R*)-α-methyl-β-alkylserine residue.[160]

Deprotection and coupling are usually carried out in two separate steps during peptide synthesis. However, Roos *et al.* have shown that the Alloc group can be removed [Bu_3SnH, cat. $Pd(PPh_3)_4$] from a protected amino acid in the presence of a second activated amino acid, giving dipeptides directly.[161]

Aminomethyl-polystyrene resins are widely used in solid phase peptide synthesis, and a synthesis of high capacity resins has recently been reported. Thus an $FeCl_3$ catalysed Friedel–Crafts reaction between polystyrene and phthalimidomethyl chloride **48** followed by hydrazinolysis gave the desired resin.[162] A general procedure for the synthesis of *N*-alkylamido peptides (H_2N-peptide-C(O)NHR where R = alkyl) has been reported, in which an amine resin is first reductively aminated to give an *N*-alkylamino resin. Subsequent solid phase peptide synthesis, and cleavage of the peptide from the resin gives the desired *N*-alkylamido peptides.[163] The solid phase synthesis of peptide aldehydes has also been reported, using linker **49** between the resin and peptide chain. This methodology is compatible with either Boc or Fmoc protecting groups, and after the desired peptide has been assembled treatment with $LiAlH_4$ cleaves the linker producing the peptide aldehyde.[164]



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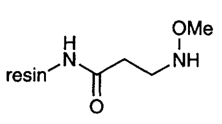

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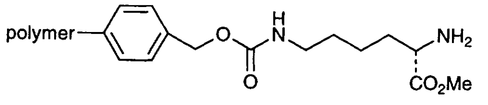
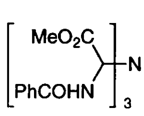


50

A hydrogenolysable solid support–linker **50** for solid phase peptide synthesis has also been reported. At the completion of peptide synthesis, hydrogenolysis produces a peptide with a *C*-terminal lysine methyl ester.[165] One of the most problematical steps in solid phase peptide synthesis is the attachment of the first amino acid to the resin. The use of Fmoc amino acid fluorides in the presence of DMAP [(4-dimethylamino)pyridine] has now been recommended for attaching amino acids to the acid labile Wang resin.[166] An alternative procedure involving the reaction of Fmoc amino acids with the Wang resin in the presence of $(Boc)_2O$, pyridine and DMAP has also been reported.[167]

Treatment of methyl (*N*-benzoyl)bromoglycine with ammonia gives the tertiary amine derivative **51** predominantly as the *RRR*/*SSS* stereoisomer.[168] Saponification of the methyl esters from compound **51** followed by peptide synthesis provides a method for the synthesis of peptides with three chains constrained to close proximity. Hegedus *et al.* have reported that photolysis of a chiral chromium amino carbene in the presence of an amino ester and carbon monoxide leads to the formation of a dipeptide as shown in **Scheme 71**. The methodology can also be used to prepare dipeptides incorporating α,α-disubstituted amino acids.[169]



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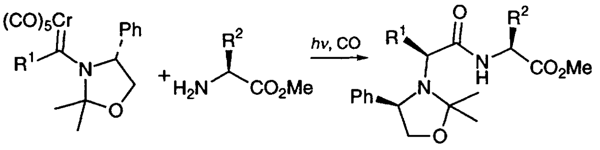
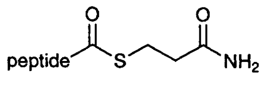


Scheme 71

Peptide nucleic acids (PNAs) are compounds which consist of nucleic acid bases attached to a peptidic backbone, and have potential pharmaceutical applications as they have greater *in vivo* stability than nucleic acids. Methodology has now been developed for the solid phase synthesis of PNA–DNA hybrids.[170]

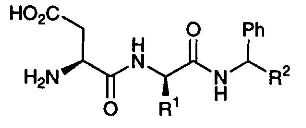
Enzyme catalysed peptide synthesis continues to attract much research. Hence, trypsin has been used in a semisynthesis of salmon calcitonin, the enzyme being used to form the amide bond between amino acids 24 and 25, thus joining the two fragments of the peptide together.[171] The use of α-chymotrypsin immobilised on graft copolymers has also been investigated for peptide synthesis in organic solvents.[172] Thiolsubtilisin has been used in peptide fragment condensation, with the *N*-terminal peptide activated as a thioester of type **52**.[173] The enzyme subtiligase has been used to cyclise linear peptides, forming macrocyclic peptides containing between 12 and 16 amino acids. The main side reactions in this process are hydrolysis and dimerisation.[174] The kinetics of thermolysin catalysed peptide synthesis in a homogeneous aqueous–organic solvent system have been studied.[175] Alcalase or subtilisin Carlsberg have been used to form peptide bonds between proline or pyroglutamate derivatives (methyl or benzyl ester or amide), and the methyl esters of other Z-protected amino acids or peptides.[176] One of the problems in enzyme catalysed peptide synthesis has been the specificity of the enzymes, resulting in couplings occurring slowly or not at all. This selectivity has now been turned to advantage in a synthesis of an octapeptide in which five different



52

enzymes were used to selectively form the desired amide bond and avoid the use of protecting groups.[177]

Standard peptide chemistry has been used to prepare peptides **53**, which are of interest as they taste sweet, but are more stable than aspartame.[178]



53

Solid phase peptide synthesis has been used to prepare both enantiomers of an enzyme (4-oxalocrotonate tautomerase). Predictably, the two enantiomeric enzymes showed enantiomeric stereochemical preferences, but otherwise had identical properties.[179] The 2-hydroxy-4-methoxybenzyl group has previously been shown to act as an amide protecting group for use in solid phase peptide synthesis using Fmoc amino acids. It was introduced to disrupt the formation of secondary structure whilst the peptide was attached to the solid support. It has now been shown that use of this amide protecting group also prevents aspartimide formation and the subsequent rearrangement to a β-aspartate residue when used on sequences which are prone to this cyclisation–rearrangement.[180]

4 Summary

In last year's review, I commented on the increased prominence of imine chemistry; this has continued during the last twelve months. This year, however, an enormous expansion in the use of aziridines in synthesis is evident: there is hardly a section of this review where the chemistry of this functional group is not exploited. There appears to be a general realisation amongst the organic chemical community that chemistry developed for use with oxygen containing functional groups can be adapted to work with the corresponding nitrogen analogues. The main difference is that a protecting group will usually be required for the nitrogen atom due to its higher valence than oxygen. In view of the wide variety of different protecting groups used in the work reported in this review, I would suggest that the ideal nitrogen protecting group (except for amines during peptide synthesis) has yet to be developed.

The other notable feature of this year's review is the explosion of interest in solid phase synthesis. For the last thirty years, this area has been utilised only by biopolymer chemists. However, the recent interest in the preparation of compound libraries has resulted in a realisation that a far wider range of chemical reactions can be carried out on polymeric supports. Almost certainly, this activity will increase further in the coming years, and it may be that in the near future total syntheses of fairly complex natural products (other than biopolymers) will be conducted entirely on a polymeric support.

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