Amines and amides

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Reviewing the literature published in 1994
Continuing the coverage in *Contempory Organic Synthesis*, 1994, 1, 475

1 Introduction, scope and coverage

This review covers the literature published during 1994. Papers were selected from the on-line science citation index for 1994, so some papers published at the end of 1994 which are cited in the 1995 index have not been included but will be covered in the next review of this topic. 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. However, the sections on 'Synthesis of γ- and higher amino acids' and 'Synthesis of α-amino aldehydes' have been omitted from this year's review due to lack of suitable material.

2 Preparation of amines

2.1 Synthesis of achiral and racemic amines

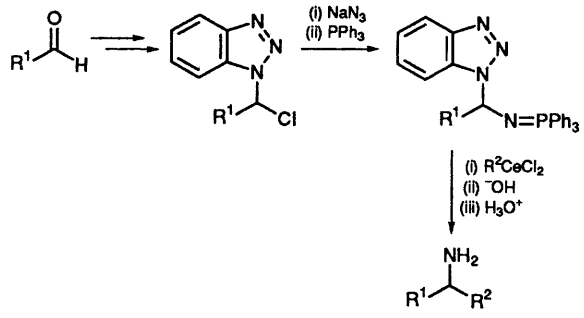
The Mitsunobu reaction is an extremely versatile method for the synthesis of alcohols and their derivatives, but attempts to extend this chemistry to the synthesis of amines have in the past been thwarted by the low acidity of amines. Edwards *et al.* have now shown that *p*-toluenesulfonamides and trifluoromethanesulfonamides are suitable substrates for use in the Mitsunobu reaction (using triphenylphosphine and diethyl azodicarboxylate), thus permitting the synthesis of a variety of amines from alcohol precursors.[2] Exactly the same results were obtained by Tsunoda *et al.*, using the more reactive Mitsunobu system composed of *N,N,N',N'*-tetramethylazodicarboxamide and tributylphosphine.[3]

Treatment of *N*-trityl-3-chloro, bromo, or tosyl propane with a base results in cyclization to *N*-trityl azetidine. The trityl group can then be removed by treatment with perchloric acid, providing a short, convenient synthesis of azetidine.[4] The ring-opening of azetidines by lithium has then been reported to be catalysed by 4,4' di-t-butylbiphenyl. The resulting *N,C*-dianion can be trapped with a wide range of electrophiles, including deuterated water, carbonyl compounds, imines, carbon dioxide, and alkyl halides, producing a variety of amines with remote functional groups.[5] Deprotonation of an *N*-Boc-methylalkylamine can also be achieved, and occurs regioselectively at the methyl group. The resulting carbanion can be trapped by a variety of electrophiles, including alkyl halides, aldehydes, silyl halides, tin halides, and deuterated water to provide a general synthesis of unsymmetrical secondary amines after cleavage of the Boc-group.[6]

A number of routes for the synthesis of amines which utilize organometallic chemistry have been reported. Thus, organozirconium chemistry has been used to prepare cyclopentylamines by the coupling of a diene and an isocyanide.[7] Both pyrrolidines and piperidines have been prepared by a palladium-catalysed process involving the coupling of a vinyl halide (or triflate) with an olefinic sulfonamide.[8] A synthesis of *N*-arylpiperidines using organobismuth chemistry has also been reported. Thus, reaction of a triaryl bismuth with piperidine derivatives in the presence of copper acetate results in formation of the aromatic-carbon to nitrogen bond, giving the N-aryl piperidines.[9]

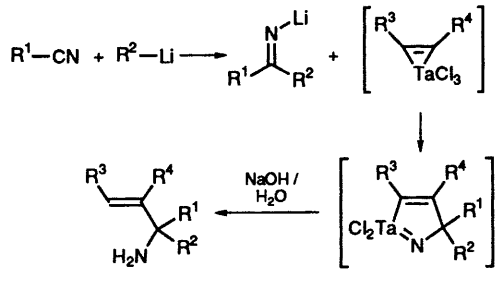
A synthetic route for the conversion of aldehydes into s-alkyl primary amines has been developed by Katritzky *et al.*, as shown in **Scheme 1**. Thus, the aldehyde can be converted into an α-iminophosphorane benzotriazole derivative, from which the benzotriazole group can be eliminated by treatment with an organocerium reagent. Subsequent hydrolysis then provides the primary amine.[10] Similar methodology has been reported by

Katritzky *et al.*, and simultaneously by Pearson and Stevens,[11] for the synthesis of β-hydroxyalkyl tertiary amines, and α-stannylamines. Hence, condensation of an aldehyde, a secondary amine, and benzotriazole gives an α-benzotriazole tertiary amine, which upon treatment with tributylstannyl lithium gives an α-stannyl amine. Transmetallation of the latter species with butyl lithium gives an α-amino anion which will react with ketones to give β-hydroxyalkyl tertiary amines.[11] Katritzky *et al.* have also shown that reaction of α-benzotriazole-tertiary amines with vinyl amides or vinyl amines provides a route for the synthesis of 1,3-diamines.[12]



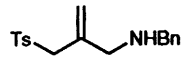
Scheme 1

The reaction between allyl chlorides and lithium hexamethyldisilazide is enhanced in the presence of silver iodide, providing a synthetic route to (*N,N,*-bis-trimethylsilyl)allyl amines.[13] A stereospecific synthesis of (*E*)-allylic amines utilizing tantalium chemistry has been reported as shown in **Scheme 2.** Thus, addition of an organolithium reagent to an imine gives a nitrogen anion which will insert into a tantalium-alkyne complex, giving an allylic amine after aqueous work-up.[14] Allylic amines can also be prepared stereoselectively from the corresponding bromides or mesylates by treatment with $(Boc)_2NH$ in the presence of caesium carbonate and lithium iodide followed by TFA to remove one or both of the Boc groups.[15] *N*-Benzyl-allylic amines have been prepared by the addition of vinylmagnesium bromide to an *N*-benzyl nitrone, followed by reduction of the resulting hydroxylamine with zinc in acetic acid.[16]



Scheme 2

Treatment of allyl amine **1** with two equivalents of BuLi followed by the addition of a bis-electrophile allows the preparation of a wide range of cyclic amines. The bis-electrophile can either be a dihalide or ethyl propynoate, in the latter case both the α-tosyl and N-anions undergo Michael additions onto the unsaturated ester.[17] Reaction of an allenic bromide with an amine results in the formation of a propargylic amine via an S_N2' reaction.[18] By contrast, treatment of a propargyl ester (acetate or phosphate) with a secondary amine in the presence of catalytic copper(I) chloride results in the formation of propargylic amines without allylic rearrangement.[19]



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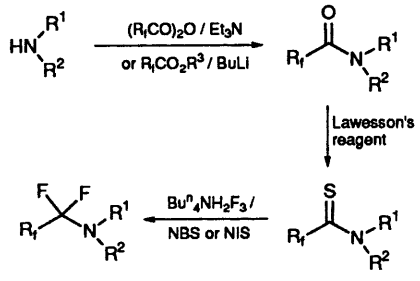
Synthesis of monoprotected ethylenediamine derivatives can be difficult due to lack of selectivity in reaction at the two amino groups. A synthesis of *N*-Boc-ethylenediamine which avoids this problem has been reported which utilizes readily available amino-acetonitrile as the starting material. Introduction of the Boc group followed by reduction of the nitrile (RaNi/EtOH/NH_3/50 p.s.i. H_2) gives the monoprotected ethylenediamine derivative.[20]

Photolysis of an *N*-phthaloyl α-amino acid in an acetone/D_2O mixture results in decarboxylation along with deuterium incorporation to give *N*-phthaloyl deuterated amines. Removal of the phthaloyl protecting group then gives α-deuterated amines.[21]

Reaction of an α-thio-tertiary amine ($R^1R^2NCH_2SR^3$) with an organolithium reagent results not in deprotonation, but in substitution of the thio-group, leaving a tertiary amine ($R^1R^2NCH_2R^3$).[22] The reaction is thought to proceed via an imine or carbene intermediate. A synthetic route for the synthesis of fluorinated tertiary amines has been reported as shown in **Scheme 3.** Thus treatment of a secondary amine with either a fluorinated anhydride or fluorinated ester in the presence of a suitable base gives the corresponding amide. Treatment with Lawesson's reagent then gives the thioamide which undergoes an oxidative desulfurization-fluorination upon treatment with tetrabutylammonium dihydrotrifluoride in the presence of NBS or NIS.[23]



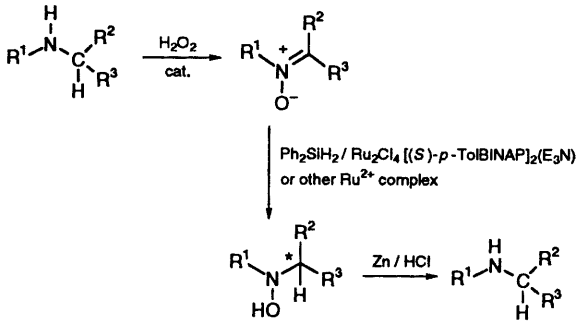
Scheme 3

Electron-rich arenes (at least *m*-xylene) react with di(2,2,2-trichloroethyl) azodicarboxylate in the presence of Lewis acids to give the *p*-substituted-bis-Troc hydrazine. Reduction with zinc in acetic acid

then removes both Troc groups and reduces the hydrazine, providing a useful synthesis of arylamines.[24]

2.2 Synthesis of optically active amines

A method for the deracemization of racemic amines has been reported, in which the amine is condensed with a polymeric, chiral ketone to give an imine.[25] Deprotonation of the imine with LDA followed by reprotonation with water and cleavage of the imine returns the amine in >75% e.e. In an alternative process, the racemic secondary amine is oxidized to the corresponding nitrone with hydrogen peroxide, this then undergoes asymmetric hydrosilylation upon treatment with diphenylsilane in the presence of catalytic $Ru_2Cl_4[(S)$-*p*-TolBINAP$]_2(Et_3N)$ or other chiral ruthenium catalysts, giving optically active hydroxylamines as shown in **Scheme 4**. Reduction with zinc in hydrochloric acid then produces the optically active secondary amine.[26]

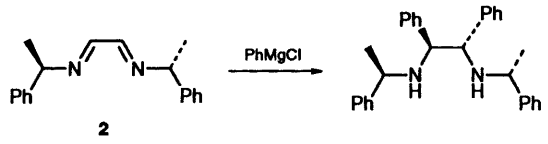


Scheme 4

Macrocyclic polyamines (aza-crown ethers) are currently attracting much attention as complexing agents, however, these compounds are quite difficult to synthesize via traditional routes, especially if highly functionalized derivatives are required. Cyclic peptides are, by contrast, relatively easily prepared, the group of Aston *et al.* have used lithium aluminium hydride to reduce a cyclic pentapeptide to the corresponding macrocyclic pentamine.[27] In a similar reaction, the reduction of serine derived diketopiperazines with lithium aluminium hydride, followed by oxidation of the serine alcohol to the corresponding carboxylic acid has been used to prepare 5-alkylpiperazine-2-carboxylic acids.[28]

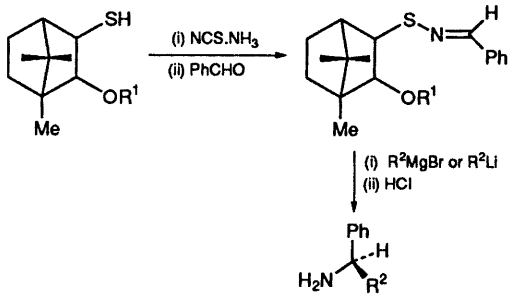
In the previous review of this area,[1] the highly diastereoselective addition of Grignard reagents to bis-imines was reported. Simpkins and co-workers have now extended this chemistry to the use of homochiral bis-imine **2** as shown in **Scheme 5**. The addition of phenylmagnesium bromide to compound **2** occurred with a diastereomeric ratio of 9:1, giving the isomer shown in **Scheme 5** as the major product as determined by *X*-ray crystallography.[29] The addition of methylmagnesium bromide was less diastereoselective (3:1).

Yang *et al.* have investigated the addition of Grignard and organolithium reagents to homochiral thio-imines derived from camphor and aromatic



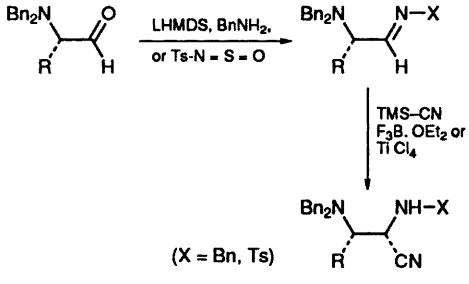
Scheme 5

aldehydes, producing optically active benzylamines as shown in **Scheme 6**. It was found that the corresponding sulfoxide and sulfone derivatives also gave good results, but attempts to extend the methodology to aliphatic aldehydes or ketones gave very low yields.[30]



Scheme 6

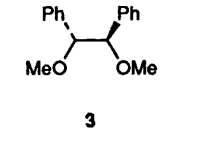
Also using imine chemistry, Reetz *et al.* have investigated the addition of TMS-CN to α-amino imines to produce α,β-diaminonitriles as shown in **Scheme 7**. Thus, condensation of readily available, optically pure *N*,*N*-dibenzyl-α-amino aldehydes with benzylamine, lithium hexamethyldisilazide, or Ts-N=S=O gave N-substituted imines, to which TMS-CN added diastereoselectively in the presence of a Lewis acid.[31] The best results were obtained using boron trifluoride or titanium tetrachloride as Lewis acids, and the diastereomeric ratio of the products ranged from 1:1 to >95:1. Enders *et al.* have shown that allyl cerium and allyl Grignard reagents will add to RAMP and SAMP hydrazones, leading eventually to β,γ-unsaturated amines with enantiomeric excesses of 90% or greater.[32]



Scheme 7

The asymmetric catalysis of the addition of organometallic reagents to carbonyl compounds has attracted considerable interest in recent years. By contrast, catalysis of the corresponding addition to imines has been rather neglected, though this is now starting to change. Hence, Inoue *et al.* reported that the dimethyl-dihydrobenzoin **3**, and the

phenylalanine derived ligand **4** both catalysed the asymmetric addition of organolithium reagents to aldehyde derived N-aryl-imines. It was necessary to use a full one equivalent of compound **3**, but only 0.3% of catalyst **4** was required.[33] Also in this area, the ephedrine derived polymer **5** has been found to catalyse the asymmetric addition of diethyl zinc to *N*-diphenylphosphinoylimines, giving optically active primary amines after an aqueous work-up. The best enantiomeric excesses were obtained in alkylbenzene solvents, which appears to be related to the swelling of the polymeric catalyst in these solvents.[34] An asymmetric catalyst for the hydrogenation of cyclic imines has also been reported. Thus titanocene **6** catalyses the asymmetric addition of hydrogen to prochiral cyclic imines, providing cyclic secondary amines with >95% enantiomeric excess.[35]



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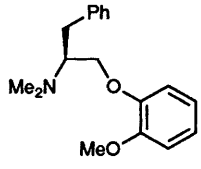

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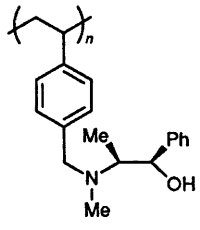

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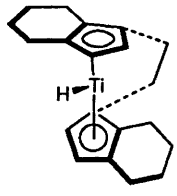
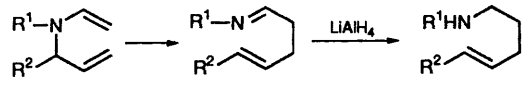


6

Reaction of a chiral allylsilane with the BF_3-complex of an *N*-carbomethoxyimine provides a synthetic route to homochiral γ,δ-unsaturated amines. The reaction occurs with allylic rearrangement, and asymmetric induction can be achieved at both the imine and alkene prochiral centres.[36] The Lewis acid promoted 3-aza-Cope rearrangement followed by reduction provides a convenient method for the synthesis of δ,ε-unsaturated amines (**Scheme 8**). Cook and Stille have investigated the stereochemical consequences of substituents at various positions of the N-allyl enamine, and concluded that only the nature of R^2 has a significant influence.[37] It appears that the R^2 substituent acts as a conformational anchor during the transition state, thus permitting the formation of products with diastereomeric ratios >95:5.



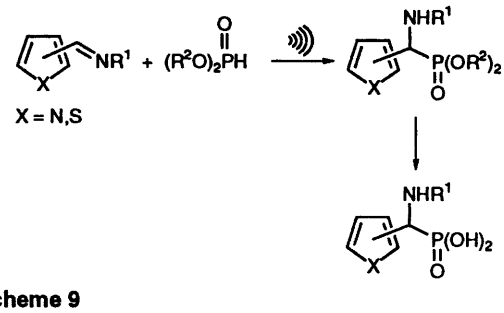
Scheme 8

In last year's review,[1] the thermal decarboxylation of threonine to optically active 2-hydroxy-propylamine was described, and it was suggested that the reaction should be of more general applicability. Indeed, it has now been shown that when a variety of α-amino acids containing two or more chiral centres are heated to 170°C in the presence of cyclohex-2-enone as a catalyst, smooth decarboxylation occurs to give optically active amines. Tetraethyleneglycol dimethyl ether is a convenient solvent for this reaction, as the amine products can then be distilled directly out of the reaction mixture as the free bases.[38]

Optically pure cyanohydrins can be prepared by a number of routes, and Chelucci *et al.* have shown that these compounds will undergo a cobalt(I)-catalysed [2+2+2] cycloaddition to give optically active α-hydroxymethyl pyridines from which α-aminomethyl pyridines can also be prepared.[39]

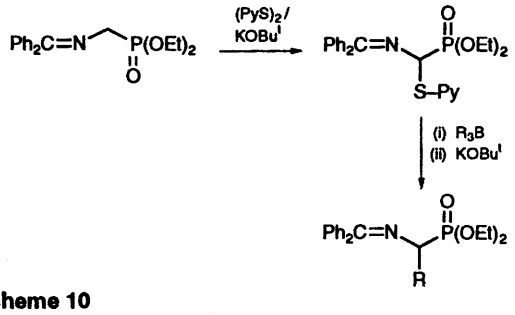
2.3 Synthesis of amines bearing additional functional groups

A variety of methods have recently been developed for the synthesis of α-amino phosphonic acid derivatives, for eventual use as transition state analogues of peptide bond hydrolysis. The addition of phosphinates to heteroaromatic imines, leading eventually to α-heteroaromatic-α-amino phosphinic acids, as shown in **Scheme 9**, has been shown to occur much more readily when the reaction mixture is sonicated than when it is heated.[40] *O*-Ethyl-1-hydroxyalkylphosphinates undergo a Mitsunobu reaction with hydrogen azide, giving *O*-ethyl-1-azidoalkylphosphinates which can be reduced with triphenylphosphine and water to *O*-ethyl-1-aminoalkylphosphinates.[41]



Scheme 9

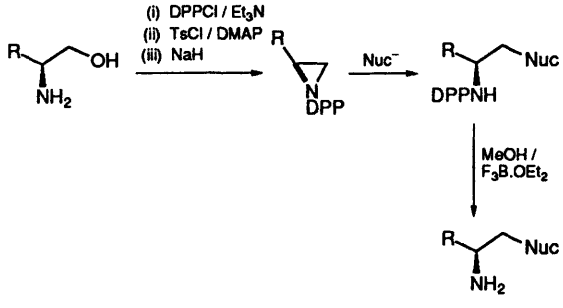
The enolate of a phosphonic diester can be trapped by di-t-butyl azodicarboxylate, giving initially an α-hydrazino phosphonic diester which can subsequently be converted into an α-amino phosphonic diester.[42] Another route to α-amino phosphonic acids has been developed by O'Donnell and co-workers[43] (**Scheme 10**) and is also based on methodology originally developed for amino acid synthesis. Thus, treatment of the benzophenone imine of diethyl aminomethylphosphonate with dipyridyldisulfide and potassium t-butoxide gives the α-pyridylthio derivative, which upon treatment with organoboranes, again in the presence of potassium t-butoxide, gives a variety of α-amino phosphonic acid precursors.[43]



Scheme 10

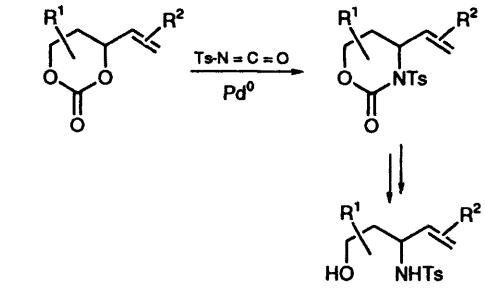
Also in an adaptation of work originally aimed at α-amino acid synthesis, it has been shown that treatment of an α-ketophosphonate with hydroxylamine followed by reduction with triactetoxyborohydride and titanium(III) chloride gives α-amino phosphonate esters.[44] Musiol *et al.* have investigated the incorporation of Z-protected α-amino-phosphonates into peptides. They report that the best procedure for formation of the phosphoramide bond involves formation of the α-amino phosphoroyl chloride with oxalyl chloride/DMF, followed by reaction with a peptide amine in the presence of either silver cyanide or HOAt.[45]

Sweeney and co-workers have investigated the ring-opening of optically pure *N*-diphenylphosphinyl aziridines which are readily prepared from β-amino alcohols (**Scheme 11**). Soft nucleophiles such as cuprates, cyanide, azide, thiols, and selinols all ring open the aziridine regiospecifically at the least-hindered end, providing a versatile approach to a variety of β-substituted amines after removal of the diphenylphosphinyl activating group by treatment with BF_3 in methanol.[46]

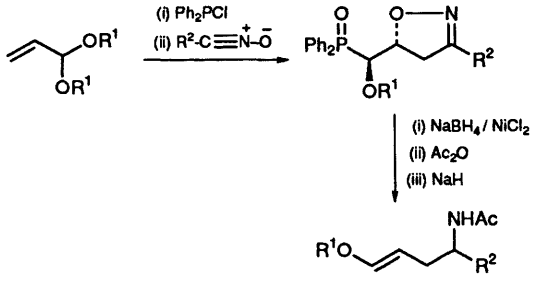


Scheme 11

A palladium-catalysed process for the synthesis of γ-hydroxy-amines from carbonates has been reported as shown in **Scheme 12**. The key step in this methodology is the insertion of tosyl isocyanate into a carbonate, and the stereochemistry of this process depends upon the stereochemistry of the substituents on the carbonate but is always highly stereoselective.[47] Warren and co-workers have described a diastereospecific synthesis of (*E*)-enol ethers of protected 4-amino aldehydes[48] in which the key step is a 1,3-dipolar cycloaddition reaction of a nitrile oxide as shown in **Scheme 13**.

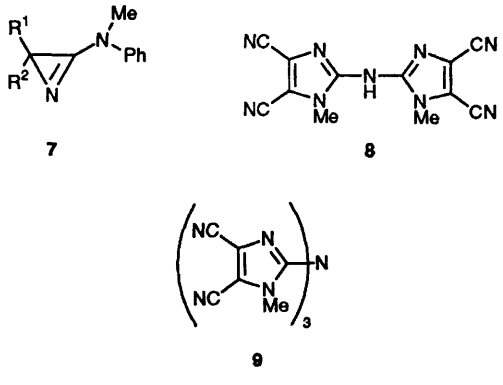


Scheme 12



Scheme 13

As discussed in the previous review of this area,[1] 3-amino-2*H*-azirines **7** can be used as activated amines for peptide synthesis. A new synthesis of these compounds by successive treatment of a tertiary amide with LDA, diphenylphosphoryl chloride, and sodium azide has now been reported.[49] The unusual heterocyclic secondary **8** and tertiary **9** amines have been prepared by reaction of the heterocyclic primary amine with the 2-fluoroimidazole derivative.[50] Compound **9** was found to be completely non-basic, whilst compound **8** is an acid with a pK_a of 4.2.



7 **8**

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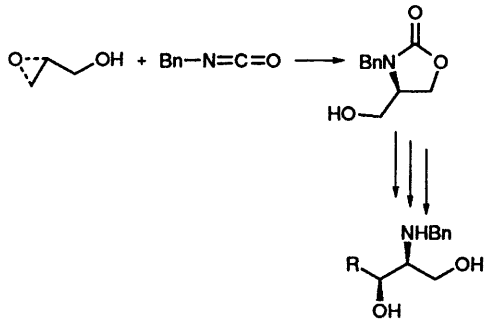
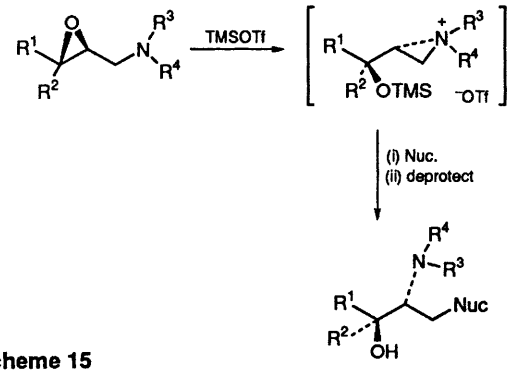
2.3.1 Synthetic routes to β-hydroxyamines

α-Amino acids have been quite widely used as synthetic precursors to optically active β-hydroxyamines. Usually, however, it is necessary to protect the amino group prior to reduction. Kamphuis and co-workers have now shown that sodium in propanol will reduce homochiral α,α-disubstituted-α-amino-amides to the corresponding enantiomerically pure β-hydroxyamines without the need to protect the amino group.[51]

Reaction of an optically pure β-hydroxy acid with diphenylphosphoryl azide results in formation of the corresponding oxazolidinone with retention of stereochemistry at both chiral centres. Subsequent manipulation gives enantiomerically and diastereomerically pure β-hydroxy amines, including the amino acid statine.[52] Reaction of optically pure glycidol with benzyl isocyanate has been shown to provide a diastereoselective synthesis of γ-hydroxy-β-amino alcohols[53] as shown in **Scheme 14**. Optically pure epoxy-amines, which are available via the Sharpless epoxidation, react with trimethylsilyl triflate to give an aziridinium ion as shown in **Scheme 15**. This undergoes regiospecific ring-opening with nitrogen nucleophiles, giving *anti*-β-hydroxy-diamines.[54]



Scheme 14



Scheme 15

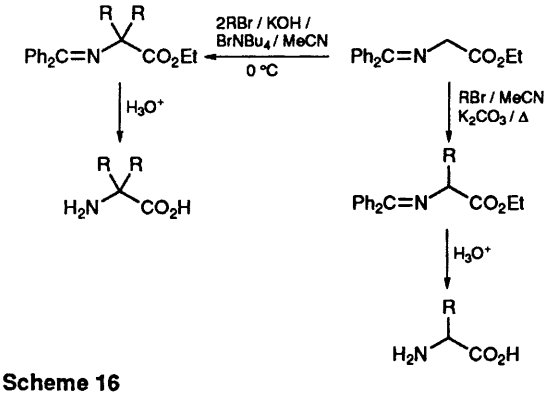
Photolysis of 2-alkoxynaphthalenes, in the presence of a primary amine and 1,3-dicyanobenzene, results in the formation of 1-alkylamino-2-alkoxy-1,4-dihydronaphthalenes.[55] Reaction of a racemic epoxide with 2-propylamine has been shown to be catalysed by lipases and subtilisin, to give optically active (*S*)-propanolamines.[56]

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. This unfortunately means that many excellent syntheses have had to be omitted from this review.

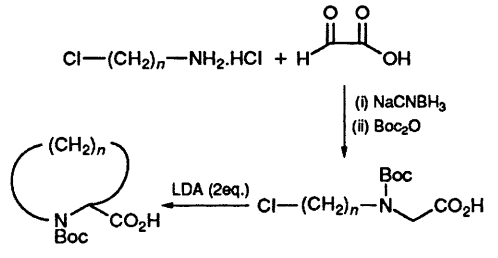
2.3.2.1 Racemic syntheses of α-amino acids

Alkylation of the enolate of an imine of a glycine ester is one of the standard methods for amino acid synthesis via a glycine-anion synthon. It had been thought that whilst imines derived from aldehydes often gave the dialkylated glycine derivative as the major product, imines derived from benzophenone gave only the mono-alkylated product. However, Ezquerra and co-workers[57] have shown that under appropriate reaction conditions (potassium hydroxide as base and a phase transfer catalyst), the benzophenone imine of glycine ethyl ester can be dialkylated as shown in **Scheme 16**.



Scheme 16

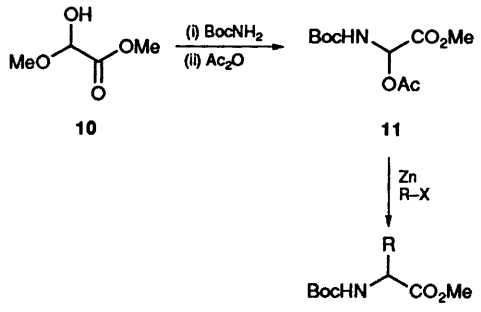
A synthesis of *N*-Boc-cyclic amino acids based upon the reductive amination of glyoxylic acid with an ω-halo-amine, followed by N-protection and intramolecular alkylation of the derived glycine anion[58] has been reported (**Scheme 17**).



Scheme 17

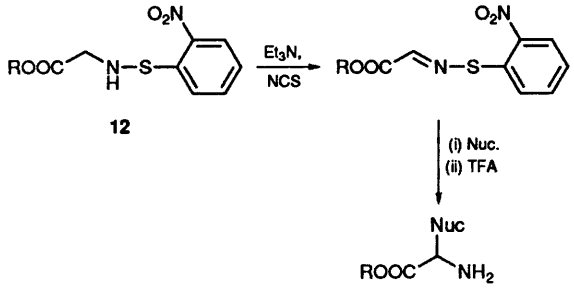
A reductive amination protocol was also utilized in a synthesis of N-Boc-N-alkyl glycines, which are building blocks for peptoid synthesis. Three separate synthetic routes were investigated: formation of an imine between glycine and an aldehyde, or imine formation between an α-ketoacid and an amine, followed in both cases by reduction and introduction of the Boc-group. The third approach involved alkylation of *N*-Boc glycine, with no one method being advantageous in all cases.[59]

A racemic synthesis of α-amino acids via a glycine cation synthon has been reported starting from the glyoxylic acid derivative **10** as shown in **Scheme 18**. Thus, consecutive treatment of compound **10** with $BocNH_2$ and acetic anhydride gave the α-acyloxy

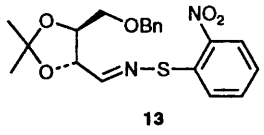


Scheme 18

glycine derivative **11**. In the presence of zinc metal, reactive alkyl halides such as allyl, benzyl, and propargyl halides displaced the acetoxy group from aminol **11**, giving racemic amino acids.[60] An alternative glycine cation synthon utilizes readily available *N*-(*o*-nitrophenylsulfenamine)glycine esters **12** as starting materials (**Scheme 19**). Hence, treatment with triethylamine and *N*-chloro-succinimide forms the sulfenimine, to which either enolates or Grignard reagents add, giving α-amino acids after acidic deprotection.[61] An asymmetric version of this reaction was also reported, using imine **13**.

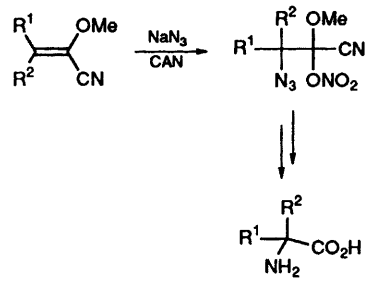


Scheme 19



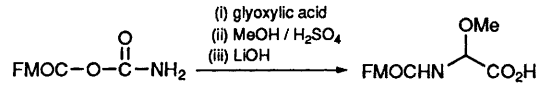
Glycine t-butyl ester is usually prepared by a multi-step procedure, however, it has now been shown that reaction of t-butyl bromoacetate with excess ammonia in ether gives the t-butyl ester of glycine directly. The same approach can be used to prepare *N*-methyl-glycine t-butyl ester.[62] Benzenediazonium tetrafluoroborate can react as an electrophilic nitrogen source, and treatment with silyl enol ethers gives either the derived imine or azo-compound. In either case hydrogenation provides α-amino esters.[63]

There are relatively few synthetic approaches to α-amino acids which utilize radical chemistry. In this regard, Clive and Etkin have reported that α-methoxy-α,β-dehydro-nitriles (readily prepared by the Wittig reaction between a ketone and the phosphorane derived from methoxyacetonitrile) will undergo addition to azide radicals generated from sodium azide and ceric ammonium nitrate as shown in **Scheme 20**. Hydrolysis and hydrogenation of the products then completes a synthesis of α-amino acids.[64]



Scheme 20

α-Hydroxyglycine is the biological precursor of peptide amides, and Brown and Ramage have reported the synthesis of a protected derivative of this amino acid suitable for use in FMOC-peptide synthesis as shown in **Scheme 21**.

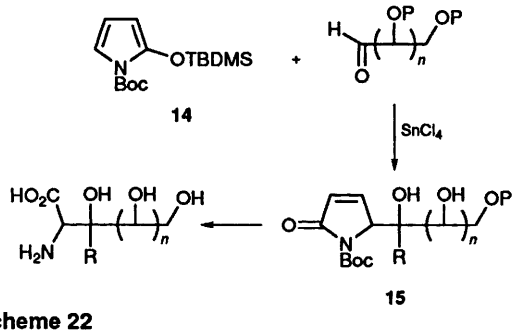


Scheme 21

The methyl ether is converted into the corresponding alcohol under the standard acidolysis conditions used to cleave the final peptide from the resin. However, coupling of other amino acids to the *O*-methyl-hydroxyglycine derivative was reported to occur only in low yield due to side-reactions.[65] Schmidt *et al.* have used protected α-hydroxyglycine derivatives as starting materials in a synthesis of differentially protected α-amino glycines. Thus, treatment of an *N*-urethane protected α-hydroxyglycine ester with diphenylphosphoryl azide substitutes an azido group for the alcohol, and subsequent reduction followed by N-protection with a second urethane group gives the desired derivatives. These manipulations can be carried out either at the amino acid or dipeptide stage, and the resulting α-amino glycine derivatives can be used in peptide synthesis.[66]

Compound **14** has been utilized in a racemic synthesis of polyhydroxy-α-amino acids. Hence, condensation of pyrrole **14** with a polyhydroxylated

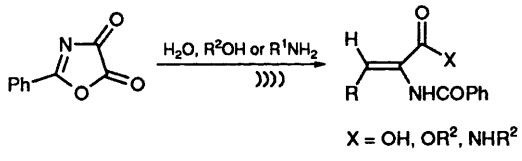
aldehyde in the presence of tin tetrachloride results in condensation adjacent to the nitrogen, giving adducts **15** as shown in **Scheme 22**. Oxidative cleavage of the alkene in compounds **15**, then leads to amino acids.[67]



Scheme 22

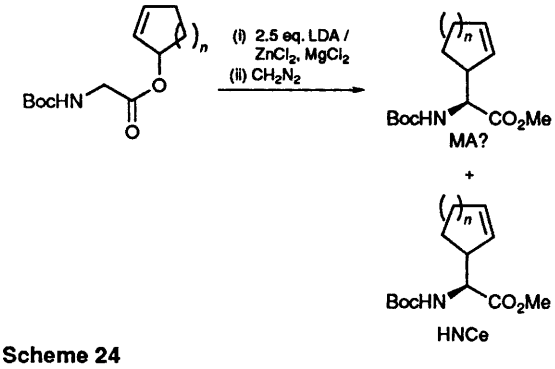
A synthesis of *o*-methyl and *o,o*-dimethyl-phenylalanine derivatives based upon the Pictet–Spengler condensation of a phenylalanine derivative and formaldehyde followed by hydrogenolysis has been reported. Unfortunately, whilst conditions were found under which the Pictet–Spengler reaction proceeded with retention of configuration at the amino acid α-centre, the hydrogenolysis was found to cause complete racemization, thus preventing the synthesis of optically active substituted phenylalanines using this methodology.[68]

A novel approach to the synthesis of α,β-didehydroamino acids has been developed by Effenberger *et al.* Thus, treatment of an α-azido ester with $NaReO_4$ in the presence of an acid chloride (which can be an *N*-phthaloylamino acid chloride) gives *N*-acyl α,β-didehydroamino esters or dipeptides incorporating an α,β-didehydroamino acid residue.[69] A variety of *N*-benzoyl-α,β-didehydroamino acids, esters, and amides have also been prepared from readily available azlactones[70] by sonication in the presence of water, alcohols, or amines as shown in **Scheme 23**. α,β-Didehydroamino acids, when incorporated into peptides, act as conformational constraints, for example α,β-didehydrolysine units have been incorporated into analogues of tuftsin.[71]



Scheme 23

A diastereoselective synthesis of cyclic, β,γ-unsaturated α-amino acids using the Lewis acid catalysed [3,3] sigmatropic rearrangement of β,γ-unsaturated esters of *N*-Boc glycine has been reported by Kazmaier as shown in **Scheme 24**. The best results were obtained with zinc chloride or magnesium chloride as Lewis acids.[72] For an



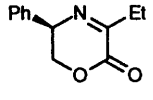
Scheme 24

asymmetric version of this reaction see Section 2.3.2.2.

Cativiela *et al.* have developed a synthesis of 1-aminocyclopropane-carboxylic acids based upon the addition of a carbene or carbenoid to an imine of dehydroalanine methyl ester. Diazo-compounds used as carbene precursors gave very poor diastereoselectivity, whilst sulfoxonium salts gave a >9:1 diastereomeric ratio in favour of the (*Z*)-isomer of the cyclopropane.[73] An asymmetric variant of this reaction has also been reported.[74]

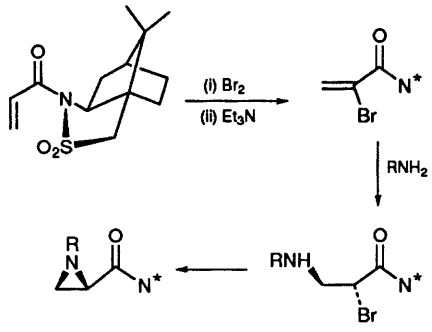
2.3.2.2. Asymmetric syntheses of α-amino acids

For an asymmetric synthesis of 5-alkylpiperazine-2-carboxylic acids see Section 2.2. Cox and Harwood have prepared the homochiral α-amino-propanoic acid precursor **16** from an α-ketoacid and phenylglycinol. Hydrogenation of the imine (H_2/PtO_2) occurs from the less-hindered face, following which hydrogenolysis under more forcing conditions [H_2/$Pd(OH)_2$, 6 atm.] gives the amino acid. The scope of this methodology is currently being further investigated.[75] Also using methodology originally developed by Harwood *et al.*, Baldwin *et al.* have used a [3+2] cycloaddition between an (*S*)-phenylglycinol derived azomethine ylid and a variety of dipolarophiles to prepare highly functionalized proline derivatives.[76]



16

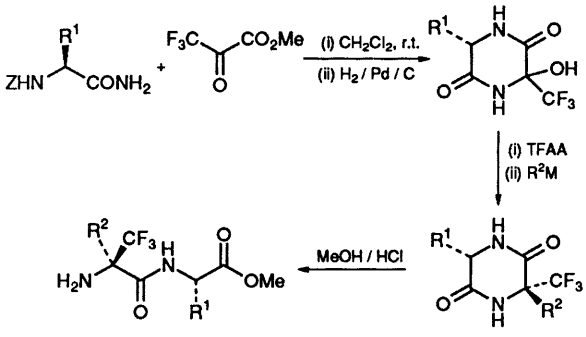
Oppolzer's chiral sultam approach has previously been shown to be a versatile method for the asymmetric synthesis of α-amino acids. This methodology has now been used in an asymmetric synthesis of aziridine-2-carboxylic acid derivatives as shown in **Scheme 25**. However, starting from the corresponding crotonate derivative, a mixture of stereoisomers at the 3-position of 3-methyl-aziridine-2-carboxylic acid were obtained.[77] Cativiela *et al.* have used a closely related chiral auxiliary in an asymmetric synthesis of α-methyl-β-phenyl-



Scheme 25

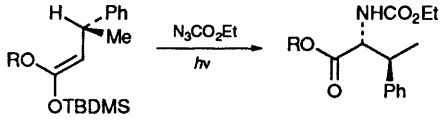
phenylalanine, an unusual amino acid which may be of some interest as a phenylalanine analogue.[78]

An asymmetric synthesis of α-trifluoromethyl amino acids which uses another amino acid as a chiral auxiliary and proceeds via a glycine-cation synthon has been described (**Scheme 26**). The key step in the synthesis (the addition of the organometallic reagent to the putative imine intermediate) proceeds with very variable d.e. (5 to >99%) depending upon the structure of the organometallic reagent.[79] Another synthetic equivalent to a glycine-cation synthon was discussed in Section 2.3.2.1.



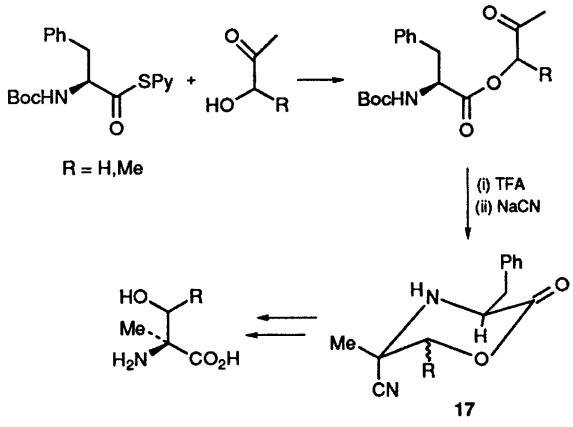
Scheme 26

An asymmetric synthesis of β-methylphenylalanine derivatives has been described based upon the addition of a nitrene to a chiral silyl ketene acetal (**Scheme 27**). The best asymmetric induction was obtained when a chiral group (camphor sulfonamide derived) was attached to the ketene acetal, in addition to the chiral centre adjacent to the phenyl group.[80]



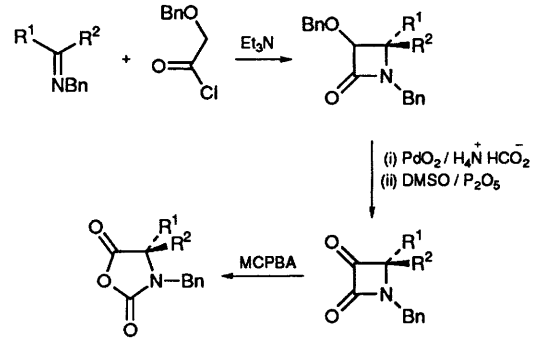
Scheme 27

Full details of the synthesis of all four stereoisomers of β-methyl-tryptophan described in last year's review[1] have now been reported by Hruby and co-workers,[81] as has the synthesis of all four stereoisomers of β-methyl-phenylalanine.[82] A synthetic route to all four stereoisomers of α-methyl-threonine, and both enantiomers of α-methyl-serine which uses phenylalanine as a chiral auxiliary has been developed as shown in **Scheme 28**. Thus, condensation of *N*-Boc phenylalanine with an α-hydroxyketone followed by removal of the Boc protecting group gives a cyclic imine to which cyanide adds stereospecifically, giving intermediate **17**. In the case where R = Me, compound **17** is formed as an equilibrating mixture, thus allowing subsequent hydrolysis to furnish either diastereomer of α-methyl-threonine.[83]

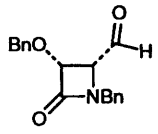


Scheme 28

N-Carboxyanhydrides are usually prepared from amino acids by treatment with phosgene or an equivalent reagent. Palomo *et al.*, however, have now reported the alternative synthesis shown in **Scheme 29**. Thus the [2+2] cycloaddition of a homochiral imine with a benzyloxyketene gives a β-lactam. Hydrogenolysis of the benzyl protecting group followed by Swern oxidation gives the corresponding α-keto-β-lactam, which upon further oxidation with MCPBA gives an *N*-carboxy-anhydride.[84] The authors have also shown that the β-lactam **18** will undergo Wittig reactions and Grignard additions prior to oxidation, thus providing access to a variety of amino acids and β-hydroxy-amino acids via a synthetic equivalent to an alanine di-cation.[85]

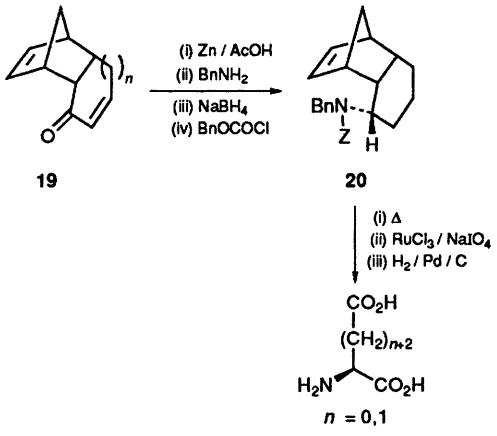


Scheme 29



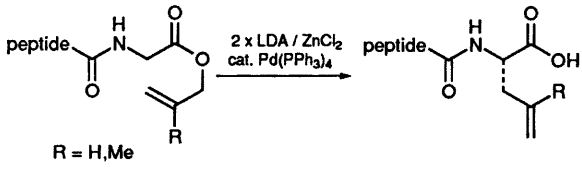
18

Takano *et al.*[86] have developed a method for obtaining optically pure enones **19**, and have used these compounds as the starting materials in an ingenious asymmetric synthesis of glutamic and aminoadipic acids as shown in **Scheme 30**. Hence, selective reduction of the conjugated alkene, followed by imine formation, reduction from the outside face, and protection gives the chiral tricyclic amine **20**. A retro-Diels–Alder reaction followed by oxidative cleavage of the newly formed alkene, and reductive deprotection of the amine protecting groups, then gives the amino acids.[86]



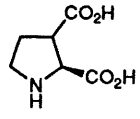
Scheme 30

Kazmaier has investigated the synthesis of peptides containing C-terminal amino acids with allylic side-chains by a palladium-catalysed ester enolate Claisen rearrangement as shown in **Scheme 31**. It was found that this methodology caused no racemization at chiral centres elsewhere in the peptide, but the diastereomeric induction at the C-terminal amino acid was variable.[87] A racemic version of this reaction was mentioned in Section 2.3.2.1.



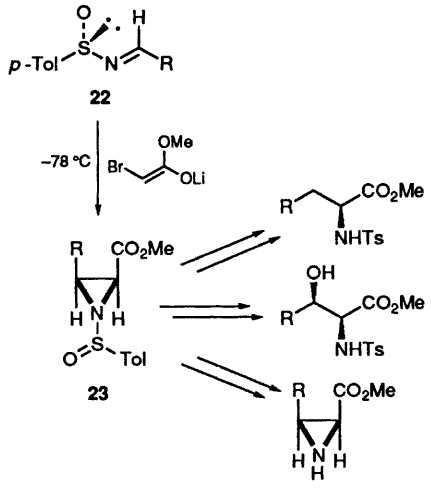
Scheme 31

The conformationally constrained aspartic acid analogue 3-carboxy-proline **21** has attracted considerable attention this year, with four independent asymmetric syntheses being reported. Three of these syntheses involve the generation of an aspartic acid β-enolate equivalent, reaction of this with a suitable bis-electrophile, and finally cyclization onto nitrogen to give the five-membered ring. The syntheses developed by North and co-workers,[88] and by Chamberlin and co-workers[89] both employ suitably protected aspartic acid derivatives as the β-enolate equivalent, whilst that of Potier and co-workers[90] starts from a serine derivative. Of these three syntheses, that of Chamberlin gives best control over the stereochemistry at the new chiral centre, and allows both diastereomers of 3-carboxy-proline to be prepared, whilst the methodology of North also allows the preparation of 5-substituted analogues of *trans*-3-carboxy-proline in addition to the parent molecule. The methodology of Potier produces only the *trans*-diastereomer of 3-carboxy-proline. The final asymmetric synthesis of 3-carboxy-proline reported this year,[91] uses a none-(amino acid) precursor, and can be controlled to give either diastereomer of 3-carboxy-proline. Regiospecific enolate formation was also utilized in a synthesis of γ-amino glutamic acid derivatives which involved the generation of the γ-enolate of a glutamate derivative and its trapping with 2,4,6-triisopropyl-benzenesulfonyl azide.[92]



21

The addition of the lithium enolate of methyl bromoacetate to homochiral *N*-sulfinylimines **22** results in the asymmetric, stereoselective formation of the *cis*-isomer of an aziridine-2-carboxylic acid derivative **23** as shown in **Scheme 32**. Subsequent manipulation of compounds **23** provides aziridine-2-carboxylic acids, α-amino acids, or β-hydroxy-α-amino acids.[93] Bravo *et al.* have reported a synthesis of optically pure α-trifluoromethyl-alanine



Scheme 32

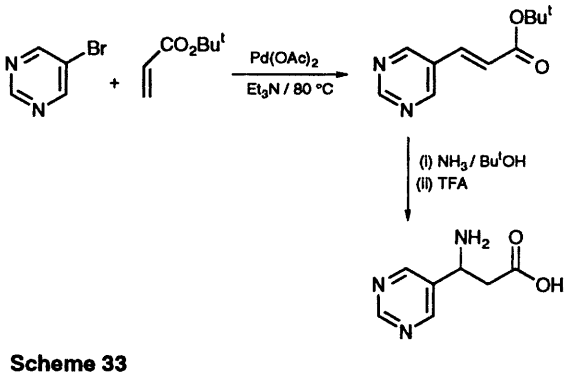
using the asymmetric addition of (*R*)-methyl-*p*-tolylsulfoxide to *N*-alkoxycarbonyl-trifluoropyruvate imines.[94]

Whilst a large number of enzymes are known which will resolve racemic amino acid derivatives, many of these will not tolerate secondary amino acids as substrates. However, it has now been found that partially purified lipase from *Aspergillus Niger* will resolve the n-octyl ester of pipecolic acid.[95] Chen *et al.* have shown that alcalase is very stable in supercritical carbon dioxide, and that N-protected amino acids can be resolved in this solvent in high yield and optical purity.[96] A chemoenzymatic synthesis of ^{15}N and ^{13}C labelled amino acids using an appropriate amino acid dehydrogenase enzyme coupled to formate dehydrogenase to catalyse the asymmetric reductive amination of a ketoacid with ammonium formate has been described.[97] The same approach has been used to prepare a variety of ^{15}N, ^{13}C, and ^{2}H labelled glutamic acid derivatives from α-keto glutaric acid, using glutamic acid dehydrogenase.[98] It has also been shown that an artificial bilayer membrane incorporating (*S*)-histidine units and copper ions can exhibit aminotransferase activity, converting α-ketoacids into (*R*)-α-amino acids but in poor yield and with low enantiomeric excesses.[99]

2.3.3 Synthesis of β-amino acids

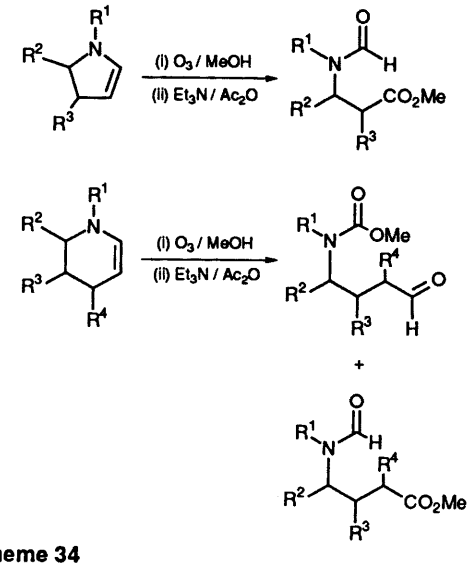
2.3.3.1 Racemic syntheses of β-amino acids

A racemic synthesis of β-amino-5-pyrimidinepropanoic acid by the Heck reaction of 5-bromopyrimidine and t-butyl acrylate followed by Michael addition of ammonia and deprotection has been reported[100] (**Scheme 33**). The Michael addition of lithium hexamethyldisilazide onto an α,β-unsaturated δ-lactone has also been used to prepare β-amino acid precursors.[101] For an asymmetric approach to β-amino acids using similar methodology, see the work of Davis *et al.* discussed in the next section.



Scheme 33

Ozonolysis of 2,3-dihydopyrroles has been shown to occur regiospecifically to give *N*-formyl-β-amino esters as shown in **Scheme 34**. Ozonolysis of 1,2,3,4-tetrahydropyridines was less selective however, giving a mixture of *N*-formyl-γ-amino

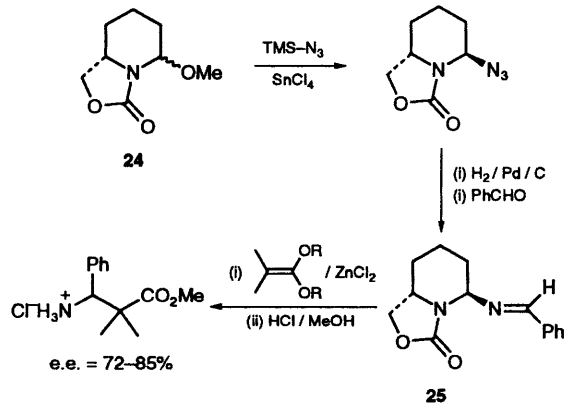


Scheme 34

esters and *N*-methyloxycarbonyl-γ-amino aldehydes.[102]

2.3.3.2 Asymmetric syntheses of β-amino acids

Perhaps the most obvious retro-synthesis of a β-amino acid involves cleavage of the central carbon–carbon bond, giving an imine and an acid enolate equivalent. However, synthetic approaches to this retrosynthesis are remarkably scarce, with the poor electrophilicity of an imine (compared to an aldehyde) being one contributing factor. Matsumura and Tomita[103] have now reported an asymmetric β-amino acid synthesis using this synthetic approach, and utilizing compound **24** as a chiral auxiliary as shown in **Scheme 35**. Thus, treatment of compound **24** with TMS-azide in the presence of tin tetrachloride gives the corresponding azide which can be reduced, and the amine condensed with benzaldehyde to give the homochiral imine **25**. Compound **25** reacts with a ketene acetal in the presence of zinc chloride to give, after an acidic work-up (MeOH/HCl), a β-amino ester (e.e. 72–85%), and recycled chiral auxiliary **24**.

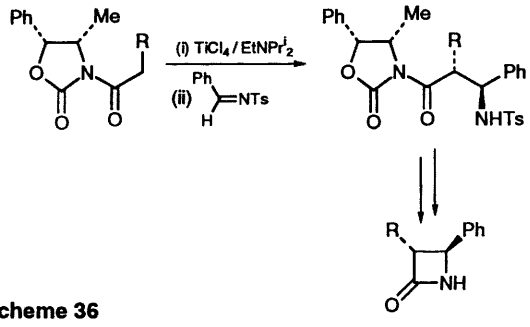


Scheme 35

An alternative solution to this problem has been developed by Jiang *et al.* starting from the optically pure sulfinate **26**. Hence, displacement of the menthoxide group from **26** using lithium hexamethyldisilazide followed by conversion of the bis-silylamine into the corresponding imine with benzaldehyde gives optically pure imine **27**. The sulfoxide group attached to the imine has an electron-withdrawing effect, increasing the susceptibility of the imine towards attack by nuclephiles, so that the sodium enolate of methyl acetate will add to the imine giving a β-amino acid after acidic work-up.[104] Unfortunately, unlike the method of Matsumura and Tomita, the chiral auxiliary cannot be recycled. Furthermore, use of the lithium enolate of methyl fluoroacetate in place of methyl acetate, gave the desired α-fluoro-β-amino acid but as an almost 1:1 ratio of diastereomers.[105] For an approach to aziridine-2-carboxylic acid and α-amino acids using the same retrosynthetic analysis as that discussed above, see Section 2.3.3.2.

26 **27**

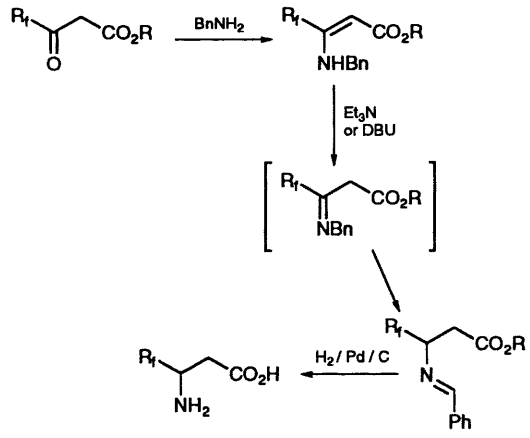
A related synthesis of β-amino acids has been developed by Wyatt *et al.* as shown in **Scheme 36**, though in this case the chiral auxiliary is attached to the ester component rather than to the imine. Again, it was found necessary to have a highly electron-withdrawing sulfonyl group in the imine to increase its susceptibility to nucleophilic attack.[106]



Scheme 36

A synthesis of fluorinated β-amino acids which incorporates an enzymatic resolution has been developed as shown in **Scheme 37**; condensation of a fluorinated β-keto-ester with benzylamine initially gives the α,β-unsaturated ester which can, however, be isomerized with base to the benzylidene imine. Hydrogenation of the latter gives a racemic β-amino acid which can be resolved by treatment of the N-phenacyl or N-benzoyl derivative with *Penicillin acylase*.[107]

Over the last few years, Davies and co-workers have developed a general, asymmetric synthesis of a variety of β-amino acids based on the asymmetric Michael addition of a homochiral nitrogen anion



Scheme 37

lithium benzyl(α-methylbenzyl)amine to an α,β-unsaturated ester. This approach has been taken up by Rico *et al.* in an asymmetric synthesis of β-3-pyridyl-β-alanine, in this case using trimethylsily(α-methylbenzyl)amine as the chiral amine.[108] If the α,β-unsaturated ester contains substituents at both the α- and β-positions then excellent asymmetric induction can be obtained at both new chiral centres, with the *syn*-diastereomer being formed diastereoselectively provided 2,6-di-t-butylphenol is used as the proton source to quench the reaction.[109] The corresponding *anti*-α,β-disubstituted β-amino acids are available by deprotonation of α-unsubstituted β-amino esters (prepared as described above) with LDA and reaction of the resulting enolate with an alkyl halide.[110] β-Lactams can also be prepared using this methodology. Attempts to carry out a tandem Michael addition of the homochiral amine, followed by enolate trapping with an electrophile, resulted in much lower diastereomeric excesses than obtained in the two-step process described above. The enolate (generated either by the conjugate addition of a homochiral amine to an α,β unsaturated ester, or by deprotonation of a β-amino ester) can also be trapped with an electrophilic oxygen source, providing a synthesis of *anti*-β-amino-α-hydroxy acids.[111] The authors have used this methodology in a synthesis of the taxol side-chain.[112]

A related procedure for the synthesis of both β-amino acids and β-lactams has been reported by Asao *et al.* Thus, Michael addition of achiral lithium *N*-TMS-benzylamine to γ-trityloxy α,β-unsaturated esters gives β-amino acids with excellent asymmetric induction. The presence of a trityl or other bulky group on the γ-hydroxy group is essential for good asymmetric induction.[113]

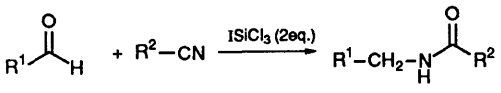
3 Preparation of amides

3.1 General methods, and the synthesis of acyclic amides

Whilst a large number of reagents are known to be suitable for activating carboxylic acids for subsequent reaction with amines, the recently

reported reagent phenyl dichlorophosphite has the advantage of being compatible with aqueous solvent systems.[114] Alternatively, electron-rich triarylbismuthanes $(MeOC_6H_4)_3Bi$ have been shown to promote the direct reaction between primary carboxylic acids and amines.[115] Secondary, tertiary, and aromatic carboxylic acids are, however, inert to this reagent. Sodium diethyldiamidoaluminate has been used to convert esters into amides.[116]

A general procedure for the synthesis of secondary amides by the iodotrichlorosilane-catalysed condensation of an aldehyde with a nitrile has been reported[117] as shown in **Scheme 38**. It has been stated that condensation of an α-amino ester hydrochloride salt with trimethyl- or triethyl-orthoformate results in the racemization free formation of N-formyl amino esters.[118]

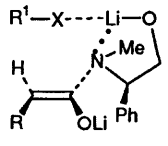


Scheme 38

Amides are often used as synthetic precursors to thioamides. The reverse reaction is less commonly encountered, but thioamides can be converted into amides by treatment with a silver carboxylate.[119]

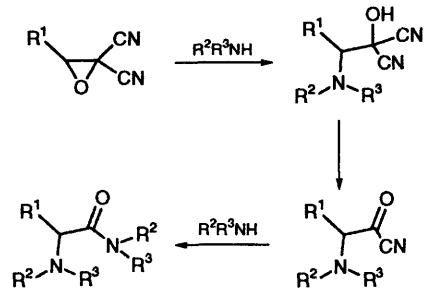
Given the current degree of interest in fullerene chemistry it is not surprising that a method has been developed for attaching amides and amino acids onto C_{60}. Thus, heating a toluene solution of C_{60} with a diazo derivative of the form $R^1R^2NCOCHN_2$ (where R^1 and R^2 can be amino acid derived) results in the formation of fullerene derivatives attached to an amide via a cyclopropane.[120]

A synthetic route for the diastereoselective alkylation of N,N-disubstituted amide enolates has been developed which uses phenylglycinol as a chiral auxiliary.[121] The asymmetric induction is thought to proceed through a chelated intermediate of type **28**. Reaction of a ketenimine with a sulfenyl or selenyl chloride gives, after an aqueous work-up, α-sulfenyl or selenyl amides.[122]

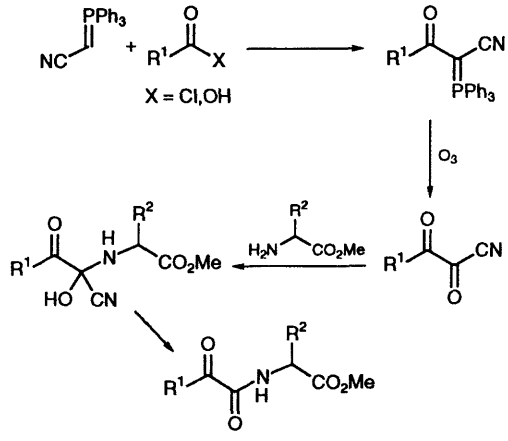


28

Two approaches have been developed for the synthesis of amides via acyl cyanide intermediates. In the first of these (**Scheme 39**), reaction of an α,α-dicyano epoxide with a secondary amine results in regiospecific ring-opening and elimination of HCN to give an α-amino acyl cyanide, which reacts with a second equivalent of the secondary amine to give an α-amino amide.[123] The second route involves reaction of a (cyanomethylene)phosphorane with a carboxylic acid or acid chloride, followed by ozonolysis of the resulting phosphorane to give an α-ketoacyl cyanide as shown in **Scheme 40**. Reaction with an amino ester then leads to *N*-α-ketoamide-α-amino esters.[124]

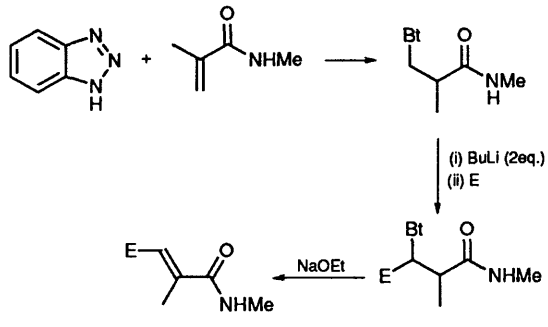


Scheme 39



Scheme 40

Benzotriazole will undergo a Michael addition to α,β-unsaturated amides, and then has an acidifying effect on the β-carbon. Thus, deprotonation with butyllithium followed by addition of an electrophile gives the β-substituted-β-benzotriazole-amide as shown in **Scheme 41**. The benzotriazole group can then be eliminated by treatment with sodium ethoxide, leaving a β-substituted-α,β-unsaturated amide.[125]



Scheme 41

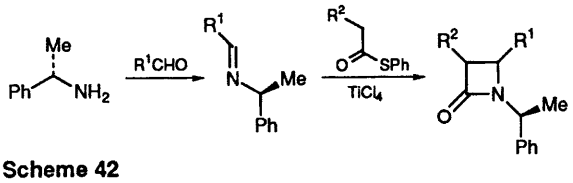
Treatment of an allylic amine with carbon monoxide in the presence of a palladium catalyst results in carbon monoxide insertion into the carbon–nitrogen

bond, providing a convenient synthesis of β,γ-unsaturated amides.[126] Pattenden and co-workers[127] have been investigating the chemistry of acyl radicals generated from acyl cobalt species, and this has resulted in a synthesis of α,β-unsaturated amides: thermolysis of *N,N*-dialkylcarbamoyl cobalt(salophen) complexes in the presence of styrene gives an (*E*/*Z*)-mixture of β-phenyl acrylamides. The acyl radical can also be trapped intramolecularly, providing a route to 4–6 membered ring lactams.[127] The lipase enzyme *Candida antartica* has been used to condense a variety of β-ketoesters with amines, giving optically active β-ketoamides.[128]

3.2 Synthesis of lactams

3.2.1 Synthesis of β-lactams

One of the standard methods for the synthesis of β-lactams is the [2+2] cycloaddition of an imine and a ketene usually derived from a thioester. The stereoselectivity of this process using *N*-α-methylbenzyl imines has been investigated (**Scheme 42**).[129] In general, the *trans*:*cis* ratio is greater than 9:1 unless R^1 or R^2 is oxygenated, in which case the diastereomeric ratio is lowered. The asymmetric induction from the α-methylbenzyl group is, however, highly variable, with the diastereomeric excess ranging from 0 to >80%. The use of β-tosylethyl imines in the synthesis of β-lactams has also been investigated, as the β-tosylethyl protecting group can subsequently be cleaved from the β-lactam by treatment with potassium t-butoxide.[130] The zinc enolate of an α-amino ester can also be condensed with an imine to give β-lactams, and the stereochemistry of this condensation can be controlled by using appropriate groups attached to the ester and imine.[131]

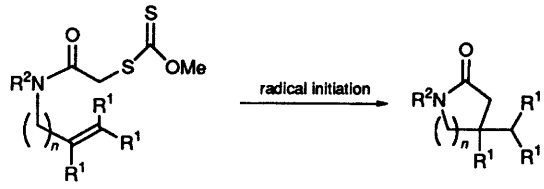


Scheme 42

Another established method for the synthesis of β-lactams is the cyclization of β-amino acids (see Section 2.3.3), and *N*-(chlorosulfinyloxy)-*N*-methylmethanaminium chloride has been reported to be an effective condensing reagent for this transformation. The same reagent also allows the synthesis of β-lactams from unsaturated amides.[132] A rhodium(II)-catalysed synthesis of β-lactams from diazoacetoacetamides and diazoacetamides has also been described.[133]

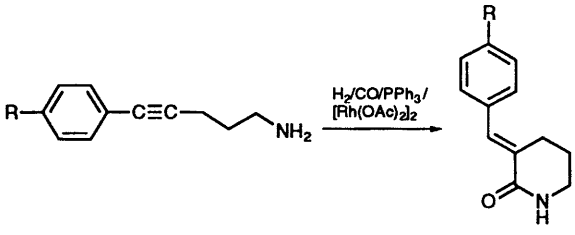
3.2.2 Synthesis of other lactams

A radical synthesis of lactams using xanthate chemistry has been reported[134] as shown in **Scheme 43**, and a synthesis of γ-lactams using the nickel induced radical cyclization of α-carbamoyl radicals onto an N-allyl substituent has been reported.[135] Similar methodology but utilizing tin chemistry has also been described,[136] and cobalt based radical cyclizations were mentioned in Section 3.1. Cationic cyclizations have also been used to prepare lactams, with γ- and δ-lactams being synthesized by the *endo* cyclization of β,γ- and γ,δ-unsaturated amides respectively.[137]



Scheme 43

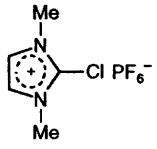
The rhodium-catalysed insertion of carbon monoxide into a γ-alkynyl amine provides a short approach to the synthesis of α-methylene δ-lactams as shown in **Scheme 44**. When the same reaction is carried out on a β-alkynyl amine, however, a mixture of γ- and δ-lactams are obtained.[138] Treatment of FMOC-glutamic acid with thionyl chloride and a catalytic amount of DMF results in formation of FMOC-pyroglutamic acid chloride, which on reaction with HONSu gives the corresponding active ester.[139]



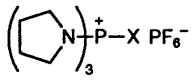
Scheme 44

3.3 Synthesis of peptides

Whilst a whole armoury of reagents are now available for the coupling of amino acids, the formation of peptide bonds to sterically hindered α,α-disubstituted amino acids can still be problematical. In this respect the chloroimidazolium reagent **29** may be of use, since it has been reported[140] that in the presence of a suitable additive (HOAt = HODhbt > DMAP > HOBt) this compound will form peptide bonds in good yields when amino isobutyric acid is either the amino or acid component. Alternatively, the *m*-trifluoromethyl analogues of BOP, pyBOP, and HBTU have been found to be especially good coupling reagents for reactions involving α-aminoisobutyric acid.[141] The halogenophosphonium salts PyBrOP (**30**) and PyClPO (**31**) have been reported to be good coupling reagents for reactions involving *N*-methyl amino esters.[142]



29



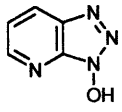
30 X = Br
31 X = Cl

4-Methylthiophenyl esters provide a 'safety-catch' type activating group for peptide synthesis. Hence, whilst 4-methylthiophenolate is not a particularly good leaving group, electrolysis in acetonitrile/water in the presence of potassium chloride results in oxidation of the sulfide to the corresponding sulfone, and reaction with an amino acid then gives peptides by displacement of 4-methylsulfonylphenolate.[143] Pyrocarbonates are normally utilized in the preparation of the urethane protected amino acids needed for peptide synthesis, however, Pozdnev has shown that in the presence of base, pyrocarbonates can also function as coupling reagents.[144]

Despite the plethora of alternative reagents, DCC is still by far the most widely used activating reagent for carboxylic acids, and the mechanism of this reaction, including racemization and by-product formation, has been investigated by a kinetics study.[145] The new water soluble analogue **32** of DCC has been introduced by Rapoport and co-workers, and has been shown to couple amino acids with similar yields and degrees of racemization to other carbodiimides.[146]

32

HOBt and derived reagents are probably the most widely used active esters/coupling reagents in peptide chemistry. In most cases, HOBt derived esters undergo peptide couplings in high yield and with very little racemization. However, in difficult cases both the chemical and optical yields can be lower than desired. Recently, therefore, Carpino *et al.* have been developing the azo analogue of HOBt (HOAt, **33**). This active ester (and derived coupling agents) has been shown to cause significantly less racemization than HOBt and to be better for the synthesis of difficult sequences.[147] This comparison has also been extended to solid-phase peptide synthesis, and again HOAt and derived coupling reagents were found to give superior results to HOBt (including for the coupling of *N*-methyl amino acids[148]), with the additional advantage that the HOAt reagents change colour from yellow to colourless when the coupling reaction is complete, thus providing an *in situ* monitor for the progress of the coupling reaction. Peptide synthesis using either HOBt or HOAt usually requires the addition of a tertiary amine base. However, Indian workers have shown that for peptide synthesis using FMOC-amino acid chlorides, the potassium salt of HOBt can be used as both active ester forming reagent and base, and that the resulting peptide synthesis is racemization-free.[149]

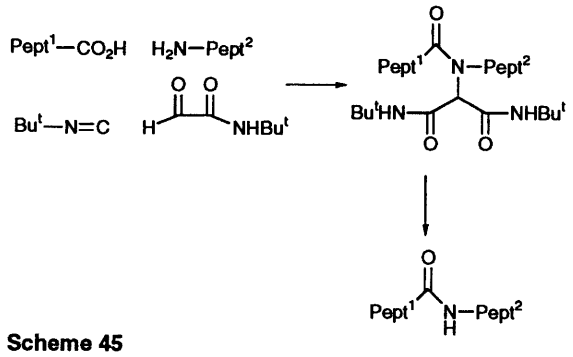


33

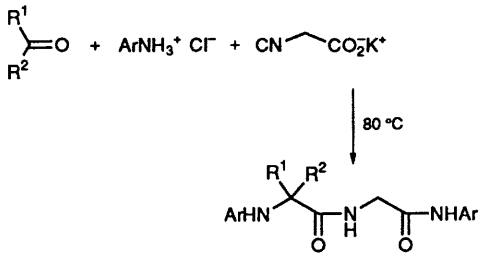
Recently, there has been much interest in *N,N*-diurethane derivatives of amino acids, following the discovery that these compounds are relatively easily prepared. However, most activated *N,N*-diurethane protected amino acids racemize too readily to be utilized in peptide synthesis, in marked contrast to the *N*-monourethane protected amino acid derivatives. The acid fluorides appear to be an exception to this rule, and methods for preparing these compounds and their use in peptide synthesis have been reported, along with further studies on urethane protected N-carboxyanhydrides.[150] N-Carboxyanhydrides have also been used in a synthesis of peptides containing *N*-alkyl-α-trifluoromethyl group.[151]

The use of enzymes to catalyse peptide synthesis is still being developed, and the enzyme *Prolyl endopeptidase* has been used to prepare peptides with C-terminal proline residues.[152] Chen *et al.* have reported the synthesis of a variety of proline-containing peptides using alcalase in anhydrous t-butanol to catalyse formation of the Xxx-Pro amide bond. The chemical yield was found to be dependent on the structure of the acyl donor, and on the amount of water present, though interestingly both L- and D-proline derivatives could be utilized.[153] The use of immobilized pepsin to catalyse the formation of Z-Phe-Phe-OMe in solvent systems containing up to 5% water has been studied, and an attempt made to correlate the enzyme activity with factors such as solvent, concentration, and amino acid side-chain *etc.*[154]

Ugi and co-workers have adapted his well known four component amino acid synthesis for the coupling of peptide fragments as shown in **Scheme 45**. Thus, treatment of two partially protected peptide fragments, one with a free acid and the other with a free amine, with t-butylisocyanide and *N*-t-butyl glyoxamide gives an intermediate which can be decomposed to the coupled peptide.[155] An unusual synthesis of N,N'-diaryldipeptide amides using an Ugi-type condensation between a carbonyl compound, an arylamine, and an isocyanide has been developed[156] as shown in **Scheme 46**.



Scheme 45



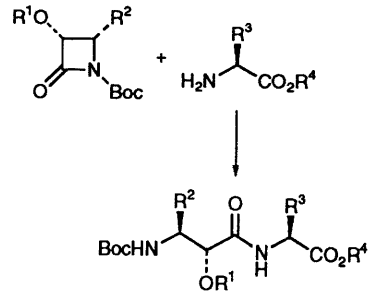
Scheme 46

The oxime resin is amongst the most versatile resins for solid-phase peptide synthesis, as a wide range of cleavage conditions can be utilized to produce a variety of peptide derivatives. Voyer *et al.* have shown that peptide amides can be prepared directly from a peptide attached to an oxime resin by treatment with a variety of aliphatic or aromatic amines, provided only that the amine is not sterically hindered.[157]

Whilst *N*-Z protecting groups are widely used in solution-phase peptide synthesis they are rarely used in solid phase work due to the lack of a suitable method of cleaving the protecting group from a peptide attached to a resin. The recent discovery that iodotrichlorosilane rapidly cleaves Z-groups under anhydrous conditions that are compatible with solid-phase peptide synthesis may change this situation.[158]

In the previous review of this topic,[1] the 2-hydroxy-4-methoxybenzyl amide protecting group developed by Sheppard *et al.* was discussed as a method for preventing the formation of β-sheeted networks during FMOC solid-phase peptide synthesis. Johnson and Quibell have now shown that the 2-hydroxybenzyl protecting group can serve the same purpose during solid-phase peptide synthesis using Boc methodology.[159] The 2-hydroxybenzyl protecting group is more acid stable than the 2-hydroxy-4-methoxybenzyl group, and is not affected by TFA used to cleave the Boc groups. It is, however, cleaved by trifluoromethane sulfonic acid.

A novel method for the synthesis of peptides incorporating β-amino acids has been reported which uses β-lactams as 'activated' β-amino acid derivatives for the coupling reaction as shown in **Scheme 47**. This chemistry can be used in both solution- and solid-state peptide synthesis methodologies.[160]



Scheme 47

4 Summary

Probably the most striking feature of this review is the current prominence of imine chemistry in just about every section. This may reflect the transfer of methodologies developed initially for carbonyl compounds to this rather more demanding area; however, many of the results disclosed so far, especially concerning the asymmetric catalysis of the addition of nucleophiles to imines, have significant synthetic potential.

Comparison of this review with the previous one shows that a number of areas have undergone a dramatic decrease in activity; this is especially apparent in the β-hydroxy-amine, α-amino aldehyde, β-lactam, and γ-amino acid fields. Whether this is just a temporary glitch in the publication rate, or reflects the previous saturation of synthetic approaches to these compounds remains to be seen.

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