Amines and amides

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Reviewing the literature published between July 1992 and December 1993

1 Introduction, scope, and coverage

This review covers the literature published in the second half of 1992, and all of 1993. Papers were selected from the on-line science citation index for 1992 and 1993, so some papers published at the end of 1993 which are cited in the 1994 index have not been included but will be covered in the next review of this topic. This is not intended to be 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 is split into two main sections, dealing with amines and amides.

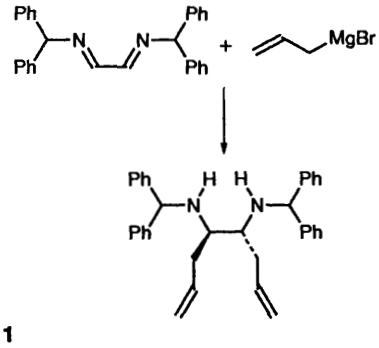
2 Preparation of amines

2.1 Synthesis of achiral and racemic amines

A number of reagents are known to reduce nitriles to amines, although there is still a need for reagents which can achieve this transformation chemoselectively. A recently reported method utilizing Raney cobalt, manganese, or nickel in the presence of methanol and potassium methoxide at high temperatures and pressures[1] may be of use in this respect. It has also been reported was that chromium or nickel promoted Raney cobalt in the presence of ammonia will catalyse the hydrogenation of polynitriles, to give polyamines.[2] Amines can also be prepared by the reduction of amides, and this can be accomplished by use of 10% Pd–C under H_2 (50 psi), in the presence of aqueous HCl.[3] A less obvious route to *N*-methyl secondary amines is the hydrogenation of tris-*N*-substituted triazines. However, this transformation can be achieved by using a CuO/Cr_2O_3 catalyst at 200°C under H_2 (850 psi).[4] A synthesis of primary amines by the reductive amination of an aromatic aldehyde, using tritylamine as a protected synthetic eqivalent to ammonia, in the presence of sodium cyanoborohydride, has been reported, and used to prepare the PAL handle for solid phase peptide synthesis.[5]

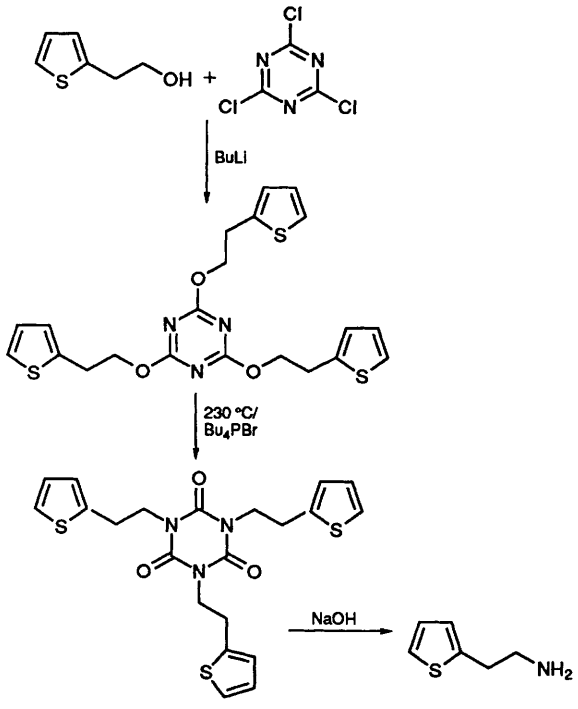
N-Methyl amines have been prepared from primary or secondary amines by reaction with diazomethane in the presence of $Co(BF_4)_2$.[6] A route to *N*-Boc protected amines has been developed by Genet *et al.*[7] Thus, reaction of *n*-Boc-*O*-tosyl hydroxylamine with BuLi or potassium hexamethyldisilazide results in the formation of a nitrogen anion which reacts with primary or secondary trialkylboranes to produce *N*-Boc amines. Propargyl amines can be prepared by the reaction of allenyl bromides with amines in the presence of a catalytic amount of copper(I) bromide.[8]

Addition of Grignard reagents to bis-imines is highly stereoselective,[9] giving mainly the *lk*-isomer of the diamine. Thus, addition of allylmagnesium bromide to bis-imine **1** gives the diamine shown in **Scheme 1** contaminated with < 5% of the *meso* isomer. 1,2-Diamines can also be prepared from oximes by α-bromination with NBS, bromide displacement with an amine or azide, and $LiAlH_4$ reduction.[10]



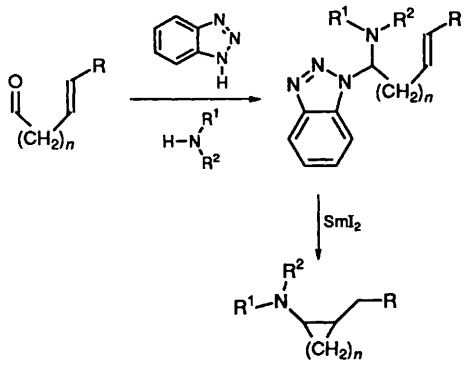
Scheme 1

A reported specific method for converting the readily available 2-(2-thienyl)ethanol into the corresponding amine is described in **Scheme 2**. Reaction of the alcohol with cyanuric chloride gives the tris-*O*-(2-thienyl)ethyl derivative which on heating in the presence of tetrabutylphosphonium bromide isomerizes to the tris-*N*-(2-thienyl)ethyl compound, and hydrolysis then provides 2-(2-thienyl) ethylamine.[11]



Scheme 2

A route to α-cyclic amines based on the radical cyclization of an α-amino radical has been developed (**Scheme 3**). Thus, treatment of an aldehyde with a secondary amine and benzotriazole results in formation of the corresponding α-amino-benzotriazole derivative from which the α-amino radical can be generated by treatment with samarium iodide. Best results are obtained with 5-*exo* and 6-*exo* cyclizations.[12] A synthesis of aminocyclopropanes from chloroenamines has also been reported,[13] and the synthesis of 1-amino-1-(aminomethyl)cyclopropane and its derivatives, by alkylation of the benzophenone imine of amino acetonitrile, has been described.[14] Piperidine derivatives can be prepared by the Diels–Alder reaction of imines with electron-rich dienes.[15]

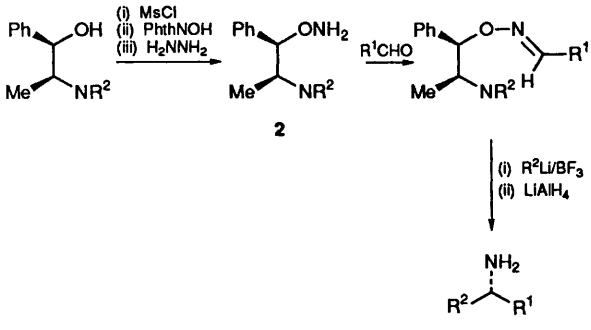


Scheme 3

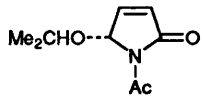
2.2 Synthesis of optically active amines

The preparation of racemic amines by the Gabriel synthesis (reaction of an alkyl bromide with potassium phthalimide) followed by their resolution by crystallization of the complex formed with (*S*,*S*)-1,6-(*o*-chlorophenyl)-1,6-diphenylhexa-2,4-diyne-1,6-diol or (−)-10,10′-dihydroxy-9,9′-biphenanthryl has been reported.[16] This may be of value when the more traditional resolution by salt formation with a chiral acid fails. Optically pure primary amines can be selectively monoalkylated with an alkyl halide using DMPU as the solvent, and sodium carbonate as base. Under these conditions, no over alkylation or racemization occurs.[17]

A general asymmetric synthesis of primary amines utilizing ephedrine derivatives as chiral auxiliaries has been described as illustrated in **Scheme 4**. Treatment of an *N*, *N*-dialkylephedrine with methanesulfonyl chloride followed by *N*-hydroxyphthalimide and removal of the phthalimide group with hydrazine gives the chiral auxiliary **2**. Reaction of **2** with an aldehyde produces the oxime ether to which organolithium reagents add stereospecifically. The oxime should be free to rotate about the N–O bond, but the stereochemistry of the resulting amines suggests that the organolithium reagents attack the least-hindered face of the conformer shown in **Scheme 4**. Presumably, the organolithium reagent coordinates to the tertiary amine and then delivers the alkyl group (R^2) intramolecularly to the less-hindered face; $LiAlH_4$ reduction then provides the chiral primary amines.[18] A route to chiral amines based on asymmetric conjugate addition of primary and secondary amines to the chiral pyrrolin-2-one **3** has also been reported; addition of the amine occurs on the face opposite the isopropoxy substituent.[19]



Scheme 4



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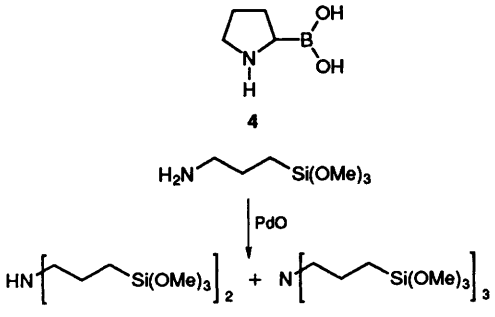
α-Amino acids have been converted into optically pure δ-amino allylsilanes, which reacted with aldehydes to give optically active piperidine derivatives, and with acid chlorides to give, after further manipulation, chiral pyrrolidines.[20] A synthesis of optically active 1,2-diamines from α-amino acids has been described.[21] Thus, reduction of an *N*-protected α-amino acid to the corresponding β-amino alcohol followed by activation of the alcohol by reaction with methanesulfonyl chloride and displacement with either an amine or azide and reduction, if necessary, gives optically active 1,2-diamines.

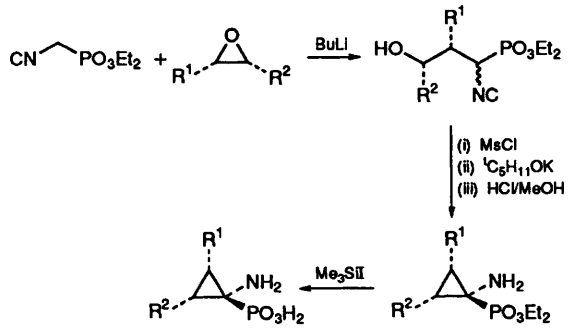
2.3 Synthesis of amines bearing additional functional groups

A racemic synthesis and resolution of proline boronic acid **4** derivatives by the lithiation of *N*-Boc-pyrrole, trapping with triethylborate, acid hydrolysis, and hydrogenation has been reported.[22] It is unfortunate that an asymmetric hydrogenation methodology could not be utilized to avoid the final resolution. Palladium oxide has been reported to catalyse the deamination of primary (silyloxy)alkylamines, giving the corresponding secondary and tertiary amines,[23] *e.g.* **Scheme 5**. A synthetic route to optically active γ-silyl-allylamines by the reaction of nitrogen nucleophiles with γ-silyl-π-palladium complexes has been described.[24] α-Amino isocyanides derived from morpholine have been prepared by dehydration of the corresponding formamides.[25]

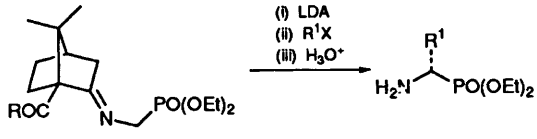


Scheme 5

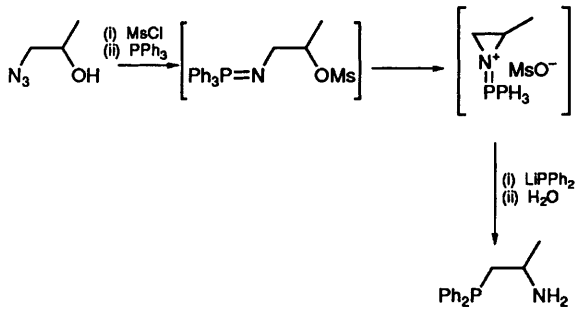
There is currently much interest in synthesizing α-amino phosphonates, as when incorporated into peptides these compounds function as transition state analogues of reactions involving nucleophilic attack onto the amide bond. Thus the synthesis of various cyclic and acyclic α-amino phosphonates by the addition of ammonia and diethyl phosphite to ketones has been described.[26] The diastereoselective synthesis of 1-aminocyclopropylphosphonic acids has been reported by Schöllkopf *et al.* as shown in **Scheme 6**.[27] The stereochemistry of the cyclopropane is determined by that of the epoxide. An asymmetric synthesis of α-amino phosphonates utilizing camphor-imine methodology initially developed for asymmetric amino acid synthesis has been described and is outlined in **Scheme 7**.[28] β-Amino phosphines can be prepared from β-hydroxyazides as shown in



Scheme 6



Scheme 7

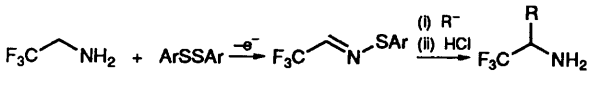


Scheme 8

Scheme 8.[29] The reaction involves migration of nitrogen *via* an aziridinium salt which lithium diphenylphosphine opens at the least-hindered end.

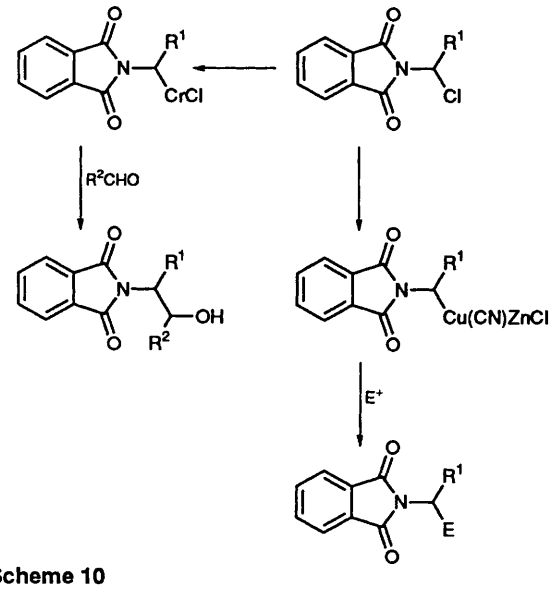
A synthetic equivalent to the β-trifluoroethylamine-α-cation has been prepared electrochemically from β-trifluoroethylamine and a diaryl disulfide, as shown in **Scheme 9**.[30] Reaction with a variety of carbanions, including enolates, then provides access to trifluoromethylamines.

Treatment of *N*-Boc cyclic amines with Bu^{s}Li results in α-deprotonation, and the resulting carbanion can be trapped with a wide variety of electrophiles, including aldehydes, amides, TMS-Cl, and tributyltin chloride, to give α-functionalized cyclic amines.[31]



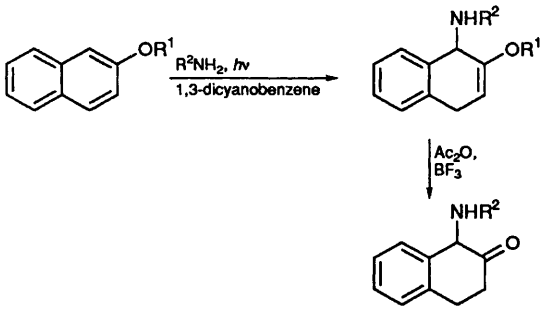
Scheme 9

α-Amino carbanion equivalents can also be prepared from α-chloro phthalimide derivatives (**Scheme 10**). The derived copper/zinc reagent undergoes Michael additions and displaces allylic, vinylic, and alkynic halides, whilst the chromium derivative reacts with aldehydes.[32]



Scheme 10

A number of routes have been developed for the synthesis of amines adjacent to aromatic or heteroaromatic rings. Thus, reaction of an optically active α-amino nitrile, derived from an α-amino acid, with acetylene and CpCo(COD) results in a [2 + 2 + 2] cycloaddition between the nitrile and acetylene to give 1-(2-pyridyl)alkylamines.[33] The synthesis of 1-amino-2-tetralones and the corresponding amides by the photolysis of 2-alkoxynaphthalenes has been reported (**Scheme 11**).[34] 2-Amino thiazoles and selenazoles can be prepared by the condensation of a β-diketone with thioureas or selenoureas, respectively, in the presence of [hydroxy(tosyloxy)iodo]benzene.[35]

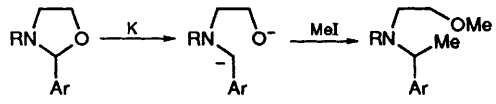


Scheme 11

2.3.1 Synthetic routes to β-hydroxyamines

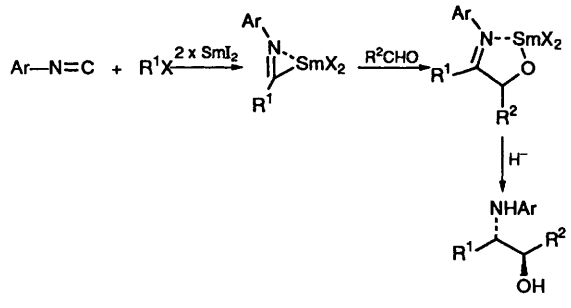
A bewildering array of methodologies for synthesizing β-hydroxyamines have been reported during the period under review. This interest in β-hydroxyamines reflects current interest in natural products which contain this fragment, and the versatility of β-hydroxyamines in the synthesis of other functionalities. Those methods which permit control of the diastereo- and/or enantio-selectivity are likely to prove the most useful, and this section will concentrate mainly on such routes.

Treatment of epoxides with amines,[36] or with reagents of the type $LiAl(NHR)_4$, which are derived from lithium aluminium hydride and four equivalents of an amine,[37] gives β-hydroxyamines. Reaction occurs at the least-hindered end of the epoxide. The ring-opening of oxazolidines by treatment with potassium has also been used to prepare β-alkoxyamines as shown in **Scheme 12**.[38]



Scheme 12

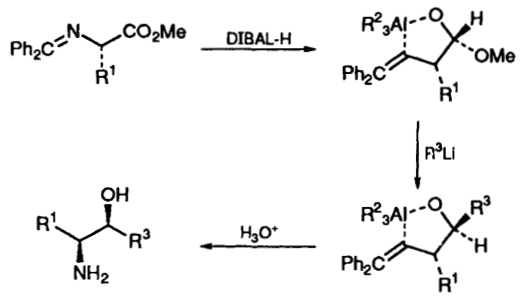
A diastereoselective approach to *syn*-β-hydroxyamines based on the reduction of β-hydroxy-oximino ethers by tetramethylammonium triacetoxyborohydride has been reported.[39] A complementary route, allowing the preparation of *anti*-β-hydroxyamines, was derived from the samarium iodide induced reaction between an isocyanide, an alkyl halide, and an aldehyde (**Scheme 13**). Hydride reduction of the resulting adduct furnishes predominantly the *anti*-isomer of the β-hydroxyamine.[40] The diastereoselective reduction of homochiral α-amino ketones derived from serine has also been investigated; most reducing agents gave mainly the *syn*-diastereomer of the β-hydroxyamine whilst DIBAL-H gave mainly the *anti*-diastereomer but in low yield.[41] Another reductive approach to β-hydroxyamines involves the reaction of an *O*-protected cyanohydrin with diisobutylaluminium hydride to give an *N*-diisobutylaluminium imine to which organometallic reagents add. The stereoselectivity of the addition of the organometallic derivative is variable, depending upon both the oxygen protecting group and the organometallic species.[42] The addition of organometallic reagents to *O*-protected α-hydroxyimines normally gives the *syn*-isomer of the β-hydroxyamine due to the formation of a chelated intermediate but Cainelli *et al.* have reported that addition of $RCuMgX_2.BF_3$ reagents to *O*-protected-*N*-TMS-α-hydroxyimines yields *anti*-β-hydroxyamines, usually with excellent diastereoselectivity.[43]



Scheme 13

Optically pure β-hydroxyamines have been prepared from α-amino acids either by reduction of the acid group or by the addition of Grignard reagents to the acid. This methodology was extended to *S*-alkylated cysteine derivatives, giving access to a new class of chiral ligands.[44] Similarly, treatment of the

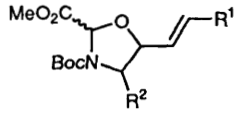
benzophenone imine of an amino acid methyl ester with DIBAL-H followed by addition of an organolithium reagent and hydrolysis gave *syn*-β-hydroxyamines as shown in **Scheme 14**.[45]



Scheme 14

Enamines have been converted into optically active β-hydroxyamines by hydroboration with diisopinocamphenylborane followed by treatment with hydrogen peroxide and sodium hydroxide.[46] Similarly, hydroboration of optically active allylic amine derivatives with borane gives, after a standard work-up, β-hydroxyamines with predominantly *anti*-configuration.[47]

A reported procedure for the conversion of *N*-Boc allylic amines into β-hydroxy-γ,δ-unsaturated amines involved treatment with methyl dimethoxyacetate followed by palladium-catalysed oxidative cyclization to give an oxazolidine **5** which could be further manipulated into β-hydroxyamines.[48]



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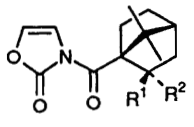
An asymmetric approach to β-hydroxyamines based upon the functionalization of the carbon–carbon double bond in oxazolones of type **6** has appeared.[49]



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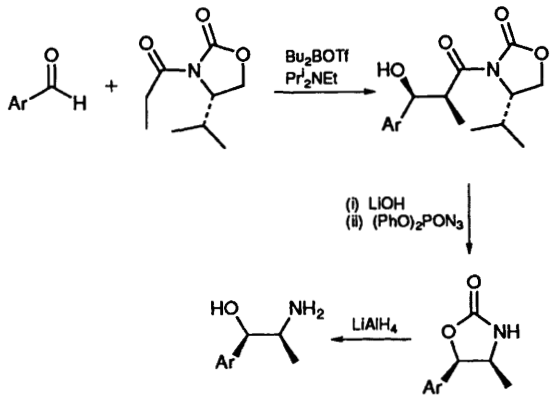
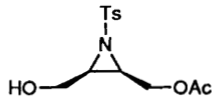
The same methodology can be used to prepare β-hydroxy-α-amino acids. Another diastereoselective chiral auxiliary approach to optically active β-hydroxyamines utilizes the Evans auxiliary (**Scheme 15**). Thus, aldol condensation of the Evans auxiliary derivative of propionic acid with an aromatic aldehyde gives α-methyl-β-hydroxy amides. Removal of the chiral auxiliary followed by a Curtius rearrangement gives cyclic carbamates which, on reduction, give α-methyl-β-aryl-β-hydroxyamines.[50]

Both enantiomers of 1-amino-2-propanol are readily available by the decarboxylation of threonine upon heating to 150°C in the presence of DMPU.[51] Since a number of methodologies for the asymmetric



Scheme 15

synthesis of β-hydroxy-α-amino acids exist, this decarboxylation may have more general applicability. Reduction of optically active 4-amino-2,3-epoxy-alcohols by DIBAL-H occurs exclusively at the 2-position, giving β-hydroxyamines. Using this methodology, the same starting materials can be used to prepare both β,γ,δ-trihydroxyamines and β,γ-dihydroxyaziridines stereoselectively.[52] A route to optically pure β- and γ-hydroxyamines from aspartic acid has been published, in which *N,N*-dibenzyl aspartate is reduced with $LiAlH_4$ to give the corresponding diol as the key intermediate. The two hydroxyl groups can then be regiospecifically protected, activated, and manipulated to give various hydroxyamines.[53] The synthesis of a range of β-hydroxyamines (and amino acids) based upon ring-opening of the readily prepared homochiral aziridine **7** has been described,[54] and a general synthesis of β-amino-γ-hydroxysulfoxides derived from the reaction of an oxazoline enolate with a chiral sulfinate was also reported.[55]



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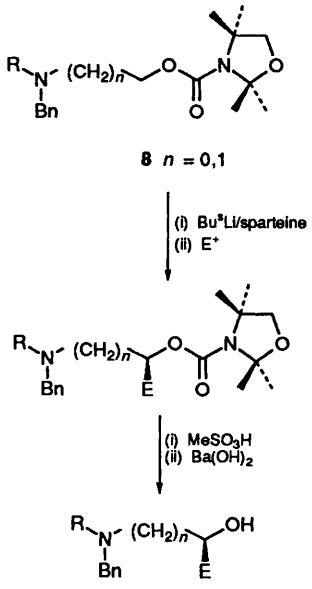
An asymmetric synthesis of β- or γ-amino alcohols *via* the formation of a carbanion adjacent to the protected alcohol has been published and is shown in **Scheme 16**.[56] Deprotonation of carbamates **8** by Bu^{s}Li in the presence of (−)-sparteine yields the configurationally stable carbanion adjacent to the masked alcohol which can be trapped by electrophiles giving, after removal of the carbamate group, γ-amino alcohols with 77 to > 98% e.e.

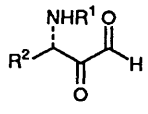
2.3.2 Synthesis of α-amino aldehydes

Reports of synthetic protocols which can be used to prepare either α-amino aldehydes or α-amino acids are described in the section on α-amino acids. α-Amino aldehydes are normally prepared by the reduction of α-amino acid derivatives. This is often not straightforward as it is frequently necessary to produce first the amino alcohol and then reoxidize this to the corresponding aldehyde. In this context, the



Scheme 16

Moffat–Swern reaction has been described as the method of choice for oxidizing the amino alcohol derived from *N*-Boc-cyclohexylalanine to the corresponding aldehyde.[57] A catalytic amount of TEMPO in the presence of bleach and sodium bromide has also been reported to oxidize a range of optically active *N*-protected amino alcohols to the corresponding aldehydes in good yield and without racemization.[58] The oxidation step has been avoided by converting an FMOC-amino acid into the corresponding benzylthio ester. Reduction of the thioester with triethylsilane in the presence of Pd–C then gave FMOC-α-amino aldehydes.[59] In a different approach, a synthesis of *N*-Boc-glycinal has been reported which used 2,3-dihydroxypropylamine as the starting material. Protection of the amine followed by oxidative cleavage of the 1,2-dihydroxy group with potassium periodate gave *N*-Boc glycidal which underwent reductive amination with glycine to give peptide analogues.[60] A route to both α-amino aldehydes and α-amino acetals based upon the asymmetric addition of organocerium reagents to the RAMP or SAMP hydrazones of glyoxal monoacetals has been described.[61] α-Amino glyoxals of general structure **9** are potentially versatile starting materials for the construction of a wide variety of amine derivatives, and an asymmetric synthesis of these compounds, by manipulation of α-amino acids, has been reported.[62]



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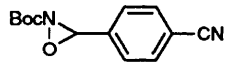
2.3.3 Synthesis of α-amino acids

Purely because of the extent of the publications in this area, no attempt is made here to cover all methods reported for the synthesis of α-amino acids. Only those methods involving formation of the C–N bond, or in which the amine functionality plays an important role in the chemistry, are included. Unfortunately, this meant excluding recent developments in a number of extremely useful and versatile amino acid syntheses. The same selectivity has been applied to the sections on β- and γ-amino acids.

2.3.3.1 Racemic syntheses of α-amino acids

Reaction of an α-bromo ester with an amine (or equivalent) is a classical method for the preparation of racemic amino acids. This has now been extended to the use of fluoroalkylamines by carrying out the reaction in acetonitrile with potassium carbonate as the base and benzyl triethylammonium chloride as a phase-transfer catalyst.[63] The use of trichloroacetamide as the amine component has also been reported,[64] as has the use of Boc_2N^- in the preparation of a range of ^{15}N and ^{13}C labelled glycine derivatives.[65]

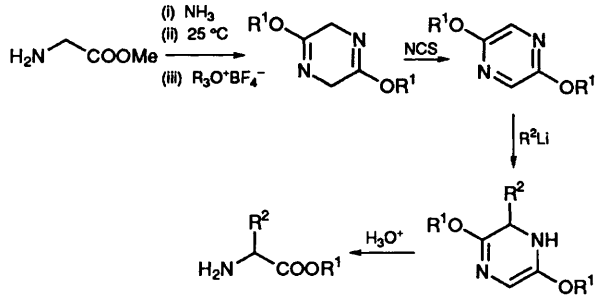
Amino acid imine chemistry was utilized in a synthesis of α-amino-β-keto esters by the reaction of the benzophenone imine of glycine methyl ester with an acid chloride in the presence of potassium t-butoxide.[66] Organozinc compounds add chemoselectively to the imine functionality of α-imino esters without affecting the ester, thus providing a racemic synthesis of α-amino acids.[67] The Strecker reaction, which was first reported in 1850, still provides convenient and simple access to a wide range of amino acids. It has been used in a synthesis of racemic α-monofluoromethyl amino acids from fluoromethyl ketones.[68] Oxaziridine **10** acts as a source of $BocN^+$, and reacts with ester enolates to give *N*-Boc-α-amino esters.[69] The same reagent reacts with ketone enolates to give *N*-Boc-α-amino ketones, and with amines to give *N*-Boc hydrazines.



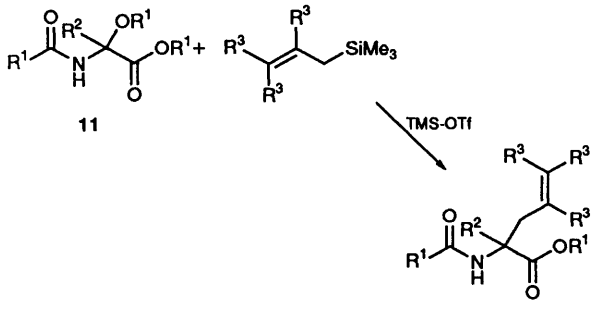
10

Over recent years, Schöllkopf *et al.* have developed a very successful asymmetric amino acid synthesis based on the formation of an enolate of a chiral bis-lactim ether. In an interesting continuation of this work, the authors have adapted the methodology to provide a racemic amino acid synthesis, as shown in **Scheme 17**. Thus the bis-lactim ether derived from glycine can be aromatized by treatment with *N*-chlorosuccinimide, and addition of organolithium reagents to the resulting pyrazine, followed by hydrolysis, provides racemic amino acids.[70] This methodology represents the *umpolung* of the authors' previous work.

α,α-Disubstituted amino acids can be prepared *via* α-alkoxyamino acid derivatives **11**, as shown in **Scheme 18**. Thus, compounds **11** (which can be prepared electrochemically from amino acid derivatives) react as α-cation synthons with allysilanes

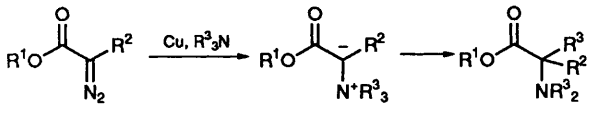


Scheme 17



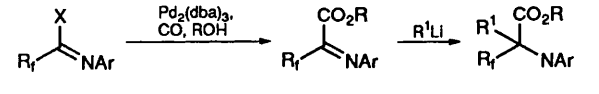
Scheme 18

in the presence of TMS-OTf to give α,α-disubstituted amino acid derivatives.[71] Another racemic synthesis of α,α-dialkylated amino acids starts from α-diazoesters (**Scheme 19**). Hence treatment of an α-diazoester with copper and a tertiary amine gives a nitrogen ylid, which undergoes an N–C migration of the most labile nitrogen substituent, giving α,α-disubstituted amino esters.[72] α-Amino ketones can be prepared in the same way, by starting with diazoketones.



Scheme 19

α-Fluoroalkyl amino acids have been prepared from perfluorohaloimidates, as shown in **Scheme 20**.[73] In a palladium-catalysed process, treatment of an allylic acetate with a dialkylamino anion gives the corresponding allylic amine without allylic transposition. Ozonolysis in the presence of sodium hydroxide and methanol then gives N,N-disubstituted amino acid methyl esters.[74] N-Arylidene imines of dehydroalanine esters undergo Diels–Alder reactions with themselves, giving adducts which can be further manipulated into a range of cyclic amino acids.[75]



X = Cl, Br

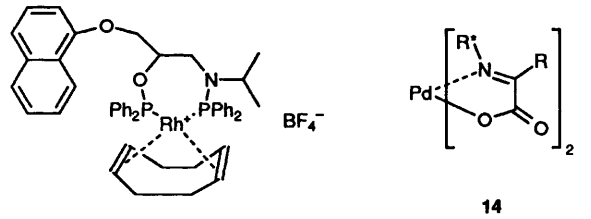
Scheme 20

2.3.3.2 Asymmetric syntheses of α-amino acids

Whilst many methods have been developed for the direct synthesis of a single enantiomer of amino acids, the use of enzymes to resolve racemic amino acid derivatives remains widely used for the preparation of homochiral amino acids. The continued popularity of what is often perceived to be out-dated technology is due to various factors: the simplicity of the methods for synthesizing racemic amino acids, the commercial availability of a large number of enzymes which will resolve amino acid derivatives (esterases, lipases, and acylases), the broad substrate specificity of these enzymes, and the generally excellent enantiomeric excesses that they produce. A number of recent developments in this field have been published. Treatment of an amino acid with deuterated acetic acid in the presence of a catalytic amount of benzaldehyde gives α-deuterated racemic amino acids, *via* formation of the N-benzylidene-amino acid and the corresponding oxazolone.[76] Esterification ($MeOH/SOCl_2$) followed by resolution with an acylase enzyme then gives homochiral α-deuterated amino acids. Racemic oxazolidinones are easily prepared, and treatment of them with a lipase enzyme results in the formation of optically active N-benzoyl amino acids.[77] Porcine pancreatic lipase gives (S)-amino acids whilst the lipase from *Aspergillus niger* results in the formation of (R)-amino acids. Treatment of an oxazolidinone with a lipase in methanol results in formation of the corresponding N-acyl amino acid methyl ester. This esterification is stereoselective for the (S)-enantiomer of the amino acid, and as the oxazolidinone can be racemized under the reaction conditions, a greater than 50% yield of the optically active methyl ester can be obtained. The optical purity of the product is then increased by hydrolysis of the methyl ester with a protease enzyme, giving an efficient two step enzymatic synthesis of N-acyl amino acids from racemic oxazolidinones.[78]

A well established approach to the asymmetric synthesis of α-amino acids is the hydrogenation of α,β-didehydroamino acids. This can be carried out either by using a chiral catalyst for the hydrogenation, or by the hydrogenation of a didehydroamino acid containing a chiral auxiliary. PROPRAPHOS (**12**) has been investigated as an asymmetric catalyst for the production of arylalanines from Z-α-N-benzoylamino-β-arylacrylic acids, and gave the amino acids with e.e.'s of 63–92%.[79] A methodology based on the latter approach has been reported by Cativiela *et al.* (**Scheme 21**).[80] Thus, condensation of the 2-hydroxypinan-3-one derivative **13** with an aldehyde gives a chiral didehydroamino acid derivative which can be hydrogenated and hydrolysed to give optically active α-amino acids. Alternatively, condensation of an α-keto-acid with a chiral amine in the presence of Na_2PdCl_4 gives complexes of the type **14**, which can be hydrogenated to give amino acids with up to 36% e.e.[81] Rhodium complexes can also be employed, as can hydroxylamines.

The addition of a homochiral bromovinyl anion to an N-sulfonylimine generates an allylic amine which on ozonolysis in the presence of methanol results in



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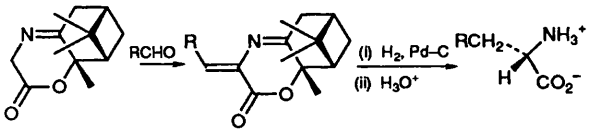
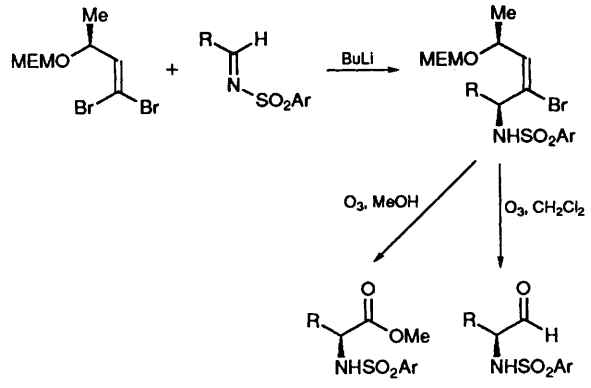
14



13

Scheme 21

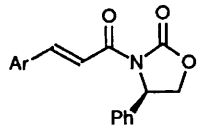
the formation of optically pure amino acid derivatives, as shown in **Scheme 22**. Ozonolysis in the absence of methanol provides the corresponding α-amino aldehydes.[82] Another synthetic route to both α-amino acids and α-amino aldehydes is the addition of organometallic reagents to RAMP or SAMP hydrazones. Thus addition of organocerium reagents to the SAMP hydrazone of diethoxyacetaldehyde followed by a hydrolytic procedure gives α-amino aldehydes, whilst an oxidative continuation gives α-amino acids.[83]



Scheme 22

Sharpless has developed two of the most useful, catalytic, asymmetric methodologies, namely his epoxidation and bishydroxylation protocols. Both have been utilized in the asymmetric synthesis of α-amino acids. Optically active epoxy alcohols are readily available *via* the Sharpless epoxidation of allylic alcohols, and this methodology has been applied to asymmetric amino acid synthesis. Reaction of an epoxy alcohol with benzhydrylamine results in ring-opening at the end of the epoxide remote from the alcohol, oxidative cleavage of the resulting 1,2-diol with ruthenium trichloride and sodium periodate then giving optically active amino acids.[84] A synthesis of *C*-α-D-glucosyl-α-amino acids from α-D-glucopyranoside has been reported, in which the Sharpless asymmetric dihydroxylation methodology is used to introduce the amino acid functionality onto the sugar.[85] A highly stereocontrolled synthesis of any of the four stereoisomers of a β,γ-unsaturated amino acid starting from the Sharpless epoxidation of an allylic alcohol has also been reported.[86]

Hruby *et al.* have developed an asymmetric synthesis of β-methyltyrosine and β-methyltryptophan derivatives based upon the asymmetric Michael addition of methyl cuprates to homochiral enones of structure **15**, followed by further manipulation to stereospecifically introduce the α-amino group *via* the enolate and α-azido compounds.[87] In the case of β-alkyl tryptophan derivatives, a more direct route is available by the addition of higher order organocuprates to homochiral indole derivatives of type **16**. Compound **16** can also be used to prepare 2,3-methanotryptophan derivatives by addition of trimethylsulfoxonium iodide to the C–C double bond.[88]



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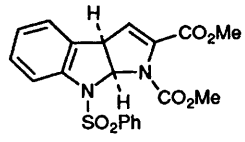
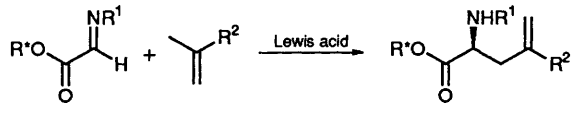


16

An asymmetric synthesis of either enantiomer of 2-amino-2-methylbutanoic acid based on the alkylation of an isobornyl sulfonamide derived chiral cyanoacetate followed by a Curtius rearrangement has been reported.[89] The same methodology should be suitable for the preparation of other α,α-disubstituted amino acids.

Concerted processes are a popular way of carrying out asymmetric synthesis, since they occur *via* transition states of well defined geometry, and hence usually result in excellent asymmetric transfer to the newly formed chiral centre(s). An asymmetric amino acid synthesis based on the ene reaction of an α-imino ester **17** has been reported (**Scheme 23**). Thus reaction of 8-phenylmenthyl glyoxylate imines with alkenes in the presence of a Lewis acid catalyst results in the formation of γ,δ-unsaturated amino acids.[90]

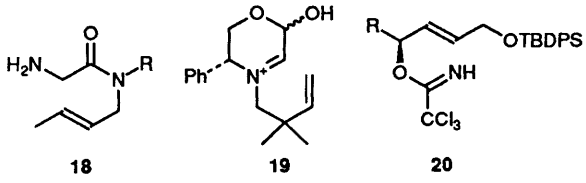


17

Scheme 23

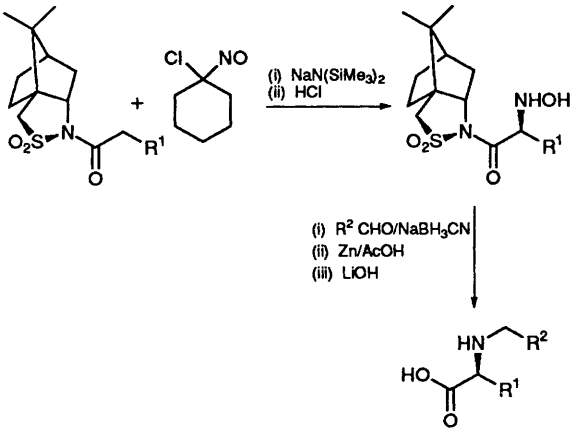
Grignard reagents also add stereospecifically to the imines (**17**, R^1 Boc), providing chiral amino acids after an acidic work-up.[91] The aza-Claisen rearrangement of glycinamide derivatives of type **18** also provides a route for the synthesis of γ,δ-unsaturated amino acids, and if chiral amides (R = 1-phenethyl) are used then asymmetric induction occurs during the rearrangement, giving optically active amino acids.[92] The aza-Cope rearrangement of chiral imine **19** can be followed by hydrolysis and a tandem ene-iminium ion

cyclization (or a Mannich cyclization) to provide access to various proline and homoserine derivatives.[71] Allyltrichloroacetimidates of type **20** undergo a palladium-catalysed [3,3]-sigmatropic shift to give after further manipulation the *E*-isomers of β,γ-unsaturated amino acids with high enantiomeric purity.[93]



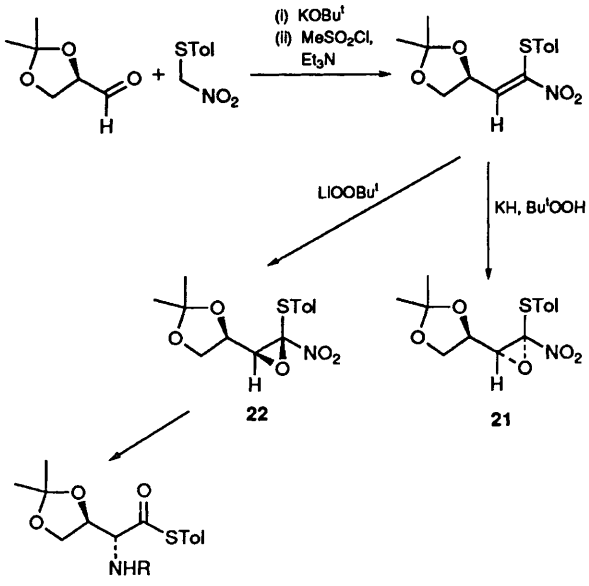
18 **19** **20**

In recent years, a number of groups have developed asymmetric amino acid syntheses based on formation of the C_α–N bond. Oppolzer *et al.* have utilized their sultam derived chiral acetate equivalent in a synthesis of *N*-alkyl-α-amino acids, as shown in **Scheme 24**. Enolate formation, and trapping with 1-chloro-1-nitrosocyclohexane results in stereospecific incorporation of an α-hydroxylamine group. Depending upon the subsequent steps, both α-amino acids and *N*-alkylated-α-amino acids can then be prepared.[94]



Scheme 24

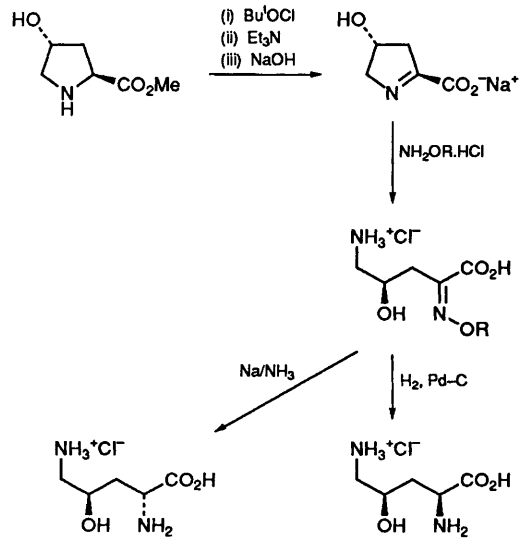
In an alternative methodology, pantolactone esters of α-bromoacids have been reported to react with amines to give α-amino esters with retention of configuration at the α-carbon.[95] Reaction of an α-bromo-ester with potassium phthalimide in the presence of *N*-benzyl-cinchonium (or quininium) chloride as phase-transfer catalysts also gives optically active amino acids (the enantiomeric excess being raised if an α-bromo-ester derived from bornyl alcohol is also used).[96] Evans's chiral auxiliary has been used to prepare optically active fluorinated amino acids, since bromination of an acyl group adjacent to the auxiliary followed displacement of bromide by azide occurs stereoselectively.[97] Jackson *et al.* have developed a synthesis of hydroxy amino acids from glyceraldehyde (**Scheme 25**). Thus, reaction of isopropylidene glyceraldehyde with (*p*-tolyl)nitromethane gives a 1-tolylthio-1-nitroalkene which undergoes a stereoselective epoxidation to give **21** or **22** depending upon the epoxidation reagent.



Scheme 25

Ring-opening of the epoxide with amines occurs regiospecifically to give thioesters of protected amino acids which can then be deprotected to provide an asymmetric synthesis of α-amino acids.[98]

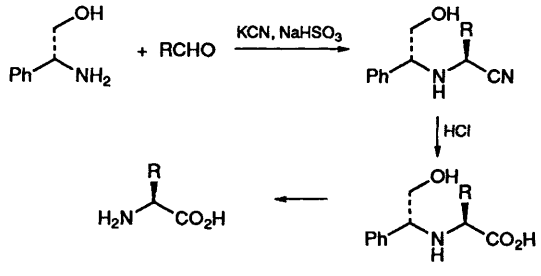
^{15}N-Labelled phenylalanine and leucine have been prepared from the unlabelled amino acids by a route involving diazotization of the amino acid to the corresponding hydroxy acid with retention of configuration, followed by esterification. Conversion of the alcohol into the corresponding triflate followed by displacement with $(Boc)_2{}^{15}N^-$ and deprotection gives the labelled amino acids with overall inversion of configuration.[99] A synthesis of ornithine derivatives based on the ring-opening of 1,2-didehydroprolines has been reported. This provides an asymmetric approach to ornithine derivatives only if an additional chiral centre is present in the proline starting material as in the case of 4-hydroxyproline (**Scheme 26**).



Scheme 26

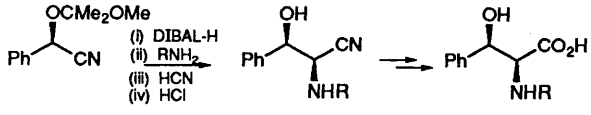
The final hydrogenation reaction can be carried out to give either stereoisomer of the ornithine derivative depending upon the reagent used.[100]

The formation of the α-C–CO_2 bond is at the heart of the classical Strecker amino acid synthesis, and a number of chiral versions of this reaction using chiral auxiliaries on the amine have been developed. In the latest example, phenylglycidol is used as the chiral auxiliary as shown in **Scheme 27**. (*R*)-Phenylglycidol induces predominant formation of the (*S*)-isomer at the new chiral centre, and the auxiliary can be cleaved either by reduction or oxidation, allowing a wide range of amino acids to be prepared in this way.[101]



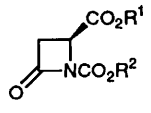
Scheme 27

A stereoselective synthesis of β-hydroxy-α-amino acids based on the Strecker reaction has also been reported (**Scheme 28**). Thus *O*-protected optically pure cyanohydrins, which are readily available,[102] are reduced by DIBAL-H to the corresponding imines. The latter compounds undergo imine exchange when treated with an amine, followed by stereoselective addition of hydrogen cyanide giving β-hydroxy-α-amino acids after further manipulation.[103]



Scheme 28

Baldwin *et al.* have shown that aspartic acid derived β-lactams **23** react with both organocuprates and sulfur stabilized carbanions to give γ-keto-α-amino acids by nucleophile induced ring-opening of the β-lactam ring.[104]

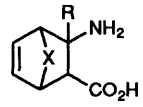


23

2.3.4 Synthesis of β-amino acids

2.3.4.1 Racemic syntheses of β-amino acids

Reaction of diethylenetriamine with $ReNCl_2(PPh_3)_2$ results in oxidative cleavage of the C–N bonds to give β-alanine.[105] A racemic synthesis of norbornane-containing β-amino acids of type **24** and their derivatives by the Diels–Alder reaction of maleic acid derivatives followed by a Curtius rearrangement has been reported.[106] The use of penicillin acylase to resolve the *N*-phenylacetyl derivatives of a variety of β-amino acids has been reported, and enantiomeric excesses of > 99% were obtained.[107]

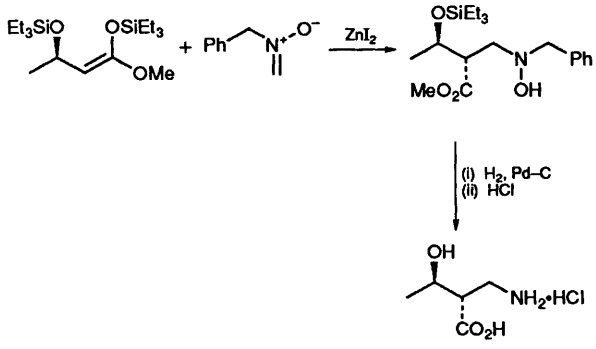


24 X = O, CH_2

An attractive approach for the synthesis of β-amino acids involves the addition of an ester or acid enolate to an imine. However, this reaction is more difficult than the corresponding enolate addition to carbonyl compounds due mainly to the lower electrophilicity of the C=N double bond compared to C=O. The introduction of sulfonyl groups onto the imine nitrogen raises the electrophilicity of the imine, and reaction with Reformatsky reagents then provides a route to β-amino esters and acids.[108] An asymmetric version of this reaction has also been published[109] (see Section 2.3.4.2). In an alternative approach, lithium perchlorate[110] or zinc bromide[111] can be used to catalyse the addition of silylketene acetals to aldimines, giving β-amino esters.

2.3.4.2 Asymmetric syntheses of β-amino acids

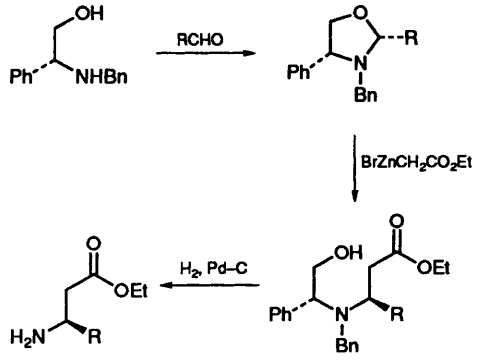
A synthesis of β-amino acids and β-hydroxylamino acids based on the Lewis acid catalysed reaction of a silylketene acetal with a nitrone has been developed by Murahashi and Otake.[112] An asymmetric example of this reaction is shown in **Scheme 29**.



Scheme 29

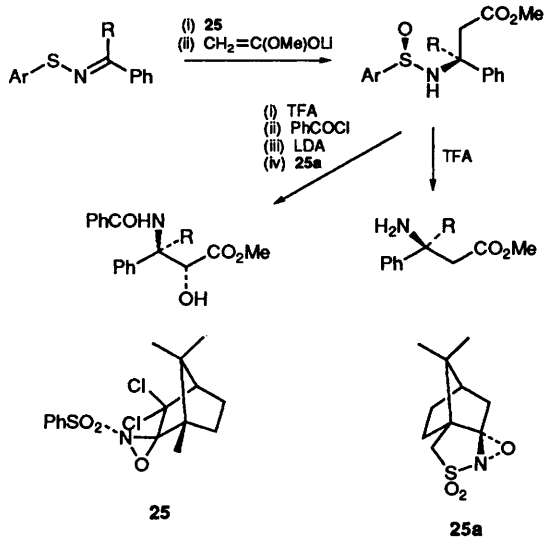
An asymmetric β-amino acid synthesis based on the stereoselective ring opening of chiral oxazolidines by Reformatsky reagents has been developed by Pedrosa *et al.*[113] (**Scheme 30**). The degree of asymmetric induction depends upon the size of the R group. An almost identical approach to these compounds uses ethyl tributylstannylacetate in the presence of $ZnCl_2$ and $F_3B.OEt_2$.[114]

The addition of organocerium reagents to the RAMP or SAMP hydrazones of 3,3-ethylene-



Scheme 30

dioxypropanal, followed by ozonolysis of the acetal and removal of the RAMP/SAMP auxiliary gives β-amino acids in greater than 80% e.e.[115] An asymmetric β-amino acid synthesis derived from the addition of an ester enolate to a chiral sulfinimine has been described as shown in **Scheme 31**. Thus, asymmetric oxidation of a sulfenimine with chiral oxaziridine **25** gives the corresponding chiral sulfinimine which reacts with the lithium enolate of methyl acetate to give a β-amino acid precursor. The resulting steps can be varied to allow access to either α-unsubstituted or α-hydroxy-β-amino acids.[108]

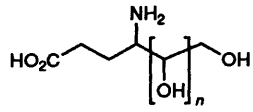


Scheme 31

β-Amino acids can also be prepared by the ring-opening of β-lactams, since nucleophiles such as alcohols attack *N*-acyl-β-lactams at the ring carbonyl,[116] and this approach has been used to prepare analogues of the phenylisoserine (norstatine) side-chain found in taxol.[117] The same approach has been used to prepare β-hydroxyaspartates and β-hydroxymethylserines.[118] The ring-opening of optically active *cis*-2-benzyloxy-3-alkoxyalkyl-β-lactams by chlorotrimethylsilane and methanol has been used to prepare α-benzyloxy-β-amino-γ-alkoxy-acids.[119]

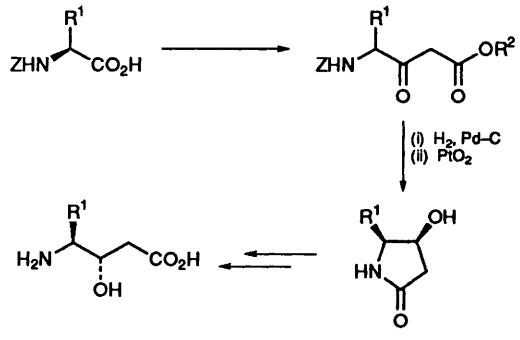
2.3.5 Synthesis of γ- and higher amino acids

γ-Aminobutyric acid (GABA) is an important neurotransmitter, and a large number of analogues of this amino acid have been synthesized.
An asymmetric synthesis of compounds of type **26** has been reported in which *N*-Boc-2-TBDMSO-pyrrole is used as a precursor to the γ-aminobutyric acid unit.[120]



26

An asymmetric synthesis of β-hydroxy-γ-amino acids which utilizes α-amino acids as chiral starting materials has been described as shown in **Scheme 32**. Thus, *N*-*Z* α-amino acids can be converted into β-keto esters by a number of routes; hydrogenation of these results in cyclization to tetramic acids which can be further reduced and ring-opened to β-hydroxy-γ-amino acids.[121] A process for removing the hydroxyl group from the intermediates, thus providing γ-amino acids has also been described. Optically active α,β-unsaturated-γ-amino esters can be prepared from α,β-unsaturated-γ-benzyloxyesters by treatment with $Fe_2(CO)_9$ to form an iron allyl species, followed by addition of an amine and oxidative removal of the iron group.[122] An asymmetric route to various β-hydroxy-ω-carboxy-amines, based upon the enzymatic resolution of cyanohydrin acetates or the derived β-amino acetates, has been reported.[123]



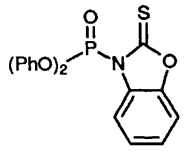
Scheme 32

3 Preparation of amides

3.1 General methods, and the synthesis of acyclic amides

There are many well established methods for coupling an acid and an amine to produce an amide. However, new reagents for this transformation are still being developed which are more tolerant of other functional groups, and allow the reaction to be conducted under milder conditions. In this context, the controlled reaction of phosphoryl chloride with one equivalent of ethanol gives a reagent, $EtOPOCl_2$, which has been reported to be useful for the coupling of amines and acids to give amides.[124] Reagent **27** has also been considered useful for this reaction, and in addition to

simple amines, α-amino esters can be used as the amine component, or if the acid contains a β-amino group then β-lactams can be formed.[125] The oxadiazaphosphole **28** acted as a condensing agent for acids and amines, and was reported to give good results even in sterically hindered cases.[126] For the conversion of acids containing very sensitive functional groups, such as β-lactams into amides, a two-step process involving treatment first with di-2-pyridyldisulfide and triphenylphosphine (or tributylphosphine or triethylphosphite) to form the 2-thiopyridyl ester followed by reaction with an *N*-silylamine has been developed.[127] The use of polymer supported EDC to couple acids and amines has also been investigated.[128]



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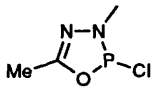
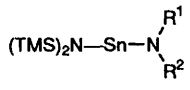


28

The tin reagent **29** converts esters into amides.[129] The bis-trimethylsilylamine group is not transferred, and best results are obtained with methyl esters. The same transformation can be achieved with reagents of the type $LiAl(NHR)_4$ which are derived from lithium aluminium hydride and four equivalents of an amine. Reaction occurs with both ethyl esters and lactones.[37] Primary and secondary amides can be converted into the *N*-*p*-tolyl derivatives by treatment with *p*-tolyl-lead triacetate.[130]



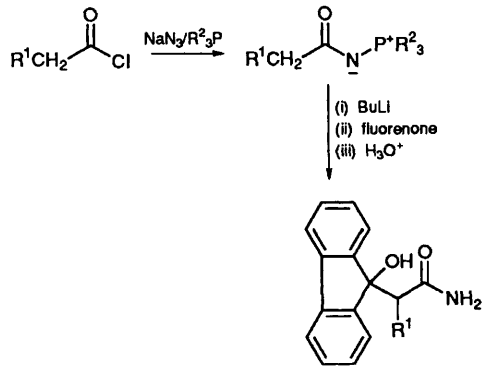
29

Given the recent level of interest in the use of enzymes to catalyse organic reactions, it is not surprising that enzymatic routes to the synthesis of amides have been developed. Two main approaches have been investigated: the use of enzymes to catalyse condensation of an amine and an acid, and the enzymatic hydrolysis of a nitrile. The use of papain to catalyse the formation of various amides derived from *N*-(*Z*)-glycine methyl ester and amides has been reported,[131] and provides a route to a variety of peptide bond isosteres. Lipases have also been used to convert α,β-unsaturated esters into the corresponding amides, and the kinetic resolution of racemic amines giving optically active amides has been achieved in this way.[132] The use of *Candida antartica* lipase to catalyse the preparation of optically active β-hydroxy and β-epoxyamides from racemic esters and amines has also been published.[133]

An increasingly popular route to amides involves the use of enzymes to effect the hydrolysis of nitriles. This has been used to prepare a variety of achiral,[134] and optically active amides.[135] A non-enzymatic method of achieving this transformation in the case of α-amino amides has also been reported.[136] Thus, treatment of a racemic α-amino nitrile with a chiral, polymeric ketone in the presence of hydroxide results in formation of the (*S*)-α-amino amide. The unreacted (*R*)-α-amino nitrile is racemized under the reaction conditions, and then converted into the (*S*)-α-amino amide.

An asymmetric synthesis of amides *via* the Favorskii rearrangement of chiral α-chloro-α-sulfonyl ketones has been reported, an amine being used as the nucleophile to ring-open the intermediate cyclopropanone.[137] Carbamates are widely used protecting groups for amines, and the conversion of carbamate to amine to amide can be carried out in one step by treatment of a carbamate and an acid chloride and sodium iodide.[138] Cyanohydrins can be oxidized to acylcyanides by treatment with t-butyl hydroperoxide in the presence of $RuCl_2(PPh_3)_2$. The resulting acylcyanides are good acylating agents and treatment with an amine gives the corresponding amide.[139] Overall this is a method for converting aldehydes into amides. A synthetic route to *N*-fluoroalkyl malonamides began with a fluoroalkyl isothiocyanate. Reaction with a stabilized phosphorane gives an iminoketene which on acidification yields the corresponding malonamide.[140]

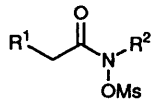
The enolate of a tertiary amide is easily formed, but the corresponding enolate of a primary or secondary amide is not so readily accessible owing to the presence of acidic hydrogens on the nitrogen. A way of generating the enolate of a primary amide which uses an iminophosphorane group to protect the nitrogen atom has been reported, as shown in **Scheme 33**. Thus, treatment of an acid chloride with sodium azide followed by a trialkylphosphine gives the iminophosphorane. Enolate formation can then be achieved with BuLi, and after the enolate is trapped with a ketone the iminophosphorane group is cleaved by treatment with acid.[141]



Scheme 33

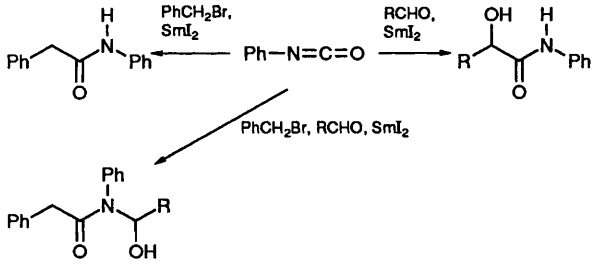
Whilst a carbanion adjacent to a tertiary amide can easily be formed, the corresponding carbocation is less accessible. Hoffman *et al.* have reported that *O*-mesyl hydroxamic acids **30** react with triethylamine to give a synthetic equivalent of this carbocation which can be reacted with nucleophiles such as halide, hydroxide, azide, or amines to give α-substituted amides.[142]

The reaction of phenylisocyanate with benzyl bromide and/or aldehydes in the presence of samarium iodide has been reported to form amides



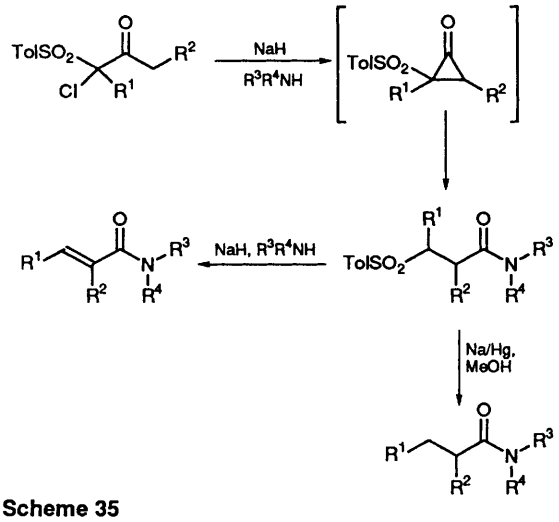
30

(**Scheme 34**).[143] Hence, reaction of phenylisocyanate with benzyl bromide gives *N*-phenyl-phenylacetamide whilst reaction with an aldehyde gives an *N*-phenyl-α-hydroxyamide. Reaction with both an aldehyde and benzyl bromide gives an *N*-phenyl-*N*-hydroxyalkyl-phenylacetamide.



Scheme 34

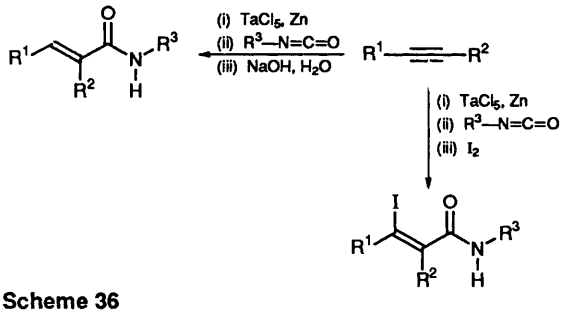
A route to both saturated and α,β-unsaturated amides based on the Favorski rearrangement of α-chloro-α-sulfonyl ketones has been developed (**Scheme 35**).[144] α,β-Unsaturated nitriles can also be prepared from aldehydes by reaction with a tertiary amide of bromoacetic acid in the presence of zinc and tributylphosphine.[145]



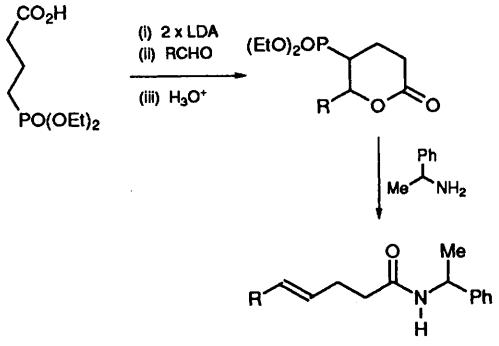
Scheme 35

An alternative route to α,β-unsaturated nitriles (including β-iodo-α,β-unsaturated nitriles) based on tantalum chemistry is shown in **Scheme 36**.[146]

A synthesis of γ-δ-unsaturated amides has also been described (**Scheme 37**).[147] Thus, treatment of a γ-diethylphosphonyl carboxylic acid with LDA and an aldehyde results in formation of a lactone which on treatment with α-methylbenzylamine undergoes ring-opening and elimination of diethyl phosphonate to give the γ,δ-unsaturated amide. *N*-Allyl acetamides can be prepared from allylic alcohols by reaction with



Scheme 36

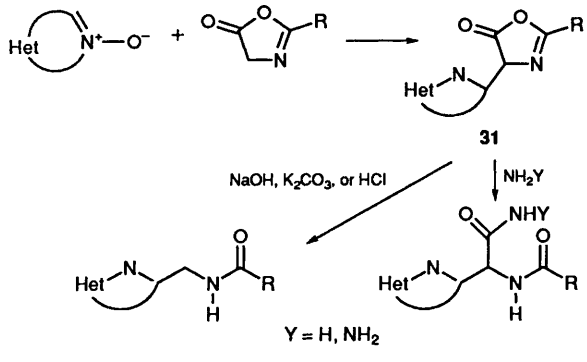


Scheme 37

acetonitrile in the presence of catalytic amounts of cobalt(II) chloride and acetic acid.[148] The reaction proceeds with allylic rearrangement.

Lactams can be converted into ω-amino amides in a two step process.[149] Thus conversion of a lactam into the *N*-Boc derivative followed by reaction with an amine under high pressure (10 kbar) gives ω-*N*-Boc-amino amides. A synthesis of all four stereoisomers of a β-hydroxy-γ-amino amide related to statine has been reported, starting from optically pure epoxy-alcohols and involving a Mitsunobu reaction to convert the alcohol into an azide, regioselective ring-opening of the epoxide by cyanide at the less-hindered end, hydrolysis, and finally reduction.[150]

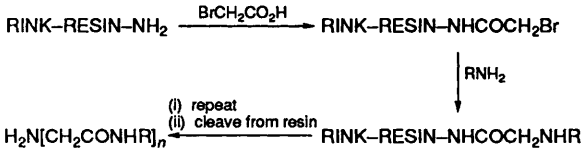
A synthesis of amidomethylphosphine oxides from secondary amides has been described.[151] Thus, reaction of a secondary amide with paraformaldehyde and TMS-Cl gives *N*-chloromethyl-amides which react with ethyl diphenylphosphinite to give amidomethylphosphine oxides. A versatile synthesis of heterocycle-containing amides as well as related amino acid derivatives has been reported (**Scheme 38**).[152]



Scheme 38

Hence, treatment of a heterocyclic nitrile oxide with an oxazolidinone gives the key intermediate **31** which reacts with acid or base to give amides, or with ammonia or hydrazine to give amino acid derivatives.

Peptoids are defined as poly-*N*-alkylated glycine derivatives, and as such they are polyamides. A solid synthesis of these peptide analogues has been developed, as shown in **Scheme 39**. Thus, treatment of a RINK-amine resin with bromoacetic acid in the presence of diisopropylcarbodiimide gives the bromoacetylated derivative, which reacts with a primary amine to give the first peptoid residue. This process can then be repeated with different amines, to give peptoids of any length.[153]

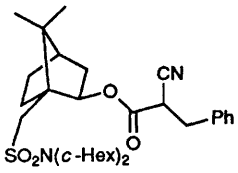


Scheme 39

3.2 Synthesis of lactams

3.2.1 Synthesis of β-lactams

Microwave irradiation of a solid mixture of a silylketene acetal and an aldimine in the presence of montmorillonite clay or *p*-toluenesulfonic acid results in the formation of β-amino esters, whilst replacement of the acid catalyst with KF/18-crown-6 results in the synthesis of β-lactams.[154] β-Amino esters can be converted into β-lactams by treatment with $Sn[N(TMS)_2]_2$, and in difficult cases pivalic acid can be added to displace one of the TMS groups from the tin reagent, resulting in a more reactive species.[155] An asymmetric synthesis of 3-alkyl-3-benzyl-β-lactams starting from the chiral ester **32** has been reported.[156] Thus, alkylation of the enolate of **32**, followed by reduction of the nitrile to an amine and cyclization, gives β-lactams. A synthesis of optically active 3-amino-β-lactams by the addition of the zinc enolate of an *N,N*-bis-silyl-glycine ester to an imine derived from phenylglycine has also been described.[157] Routes to chiral β-lactams based upon the condensation of the titanium enolate of a thiopyridyl ester with chiral imines derived either from the condensation of 1-phenylethylamine with an achiral aldehyde[158] or condensation of benzylamine with a chiral α-hydroxyaldehyde[159] have also been reported. Simple esters can also be used in this reaction, and the effect of introducing chiral groups at various sites on the ester or imine component has been investigated.[160] β-Lactams can also be prepared by the reaction of an imine with an acid chloride in the presence of triethylamine, a reaction considered to proceed *via* the [2 + 2] cycloaddition of the imine and the ketene derived from the acid chloride. Application of this methodology to optically active α-alkoxyaldimines and α-alkoxy acid chlorides gives optically active *cis*-2,3-disubstituted β-lactams,[119] whilst the use of a bis-imine can give either a bis-β-lactam or a 4-formyl-β-lactam.[161]



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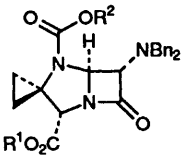
In recent years, Hegedus *et al.* have reported a novel synthesis of both amino acids and β-lactams utilizing chromium carbene complexes. This methodology has been used by de-Meijere *et al.* to prepare a novel class of cyclopropane-containing β-lactams represented by structure **33**.[162] A novel synthesis of 1,3,4-tris-(trimethylsilyl)azetidine-2-one (**34**) by the ring-expansion of a silylated cyclopropanone has been described as outlined in **Scheme 40**. Compound **34** can then be converted into a variety of other β-lactams.[163]



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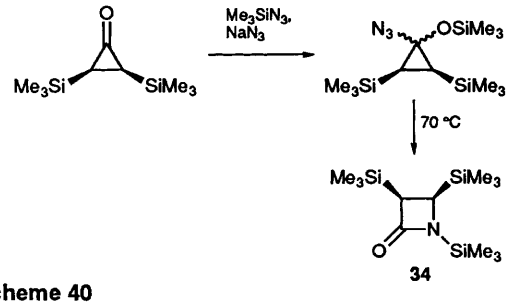
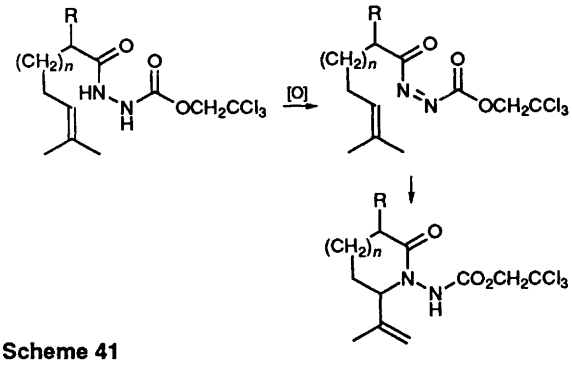


34

Scheme 40

3.2.2 Synthesis of other lactams

γ-Lactams can be prepared from allyl or propargyl amides of bromoacetic acid by nickel-catalysed electro-reductive cyclization.[164] The reaction can also be applied to the cyclization of *o*-bromophenylamides of propenoic acid. A route to both γ- and δ-lactams by the intramolecular ene reaction of azo compounds has been also developed (**Scheme 41**).[165]



Scheme 41

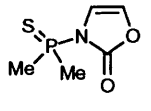
3.3 Synthesis of peptides

Only the development of new methodologies for peptide bond formation is discussed here. Unfortunately, lack of space prevents discussion of new protecting groups and methods for their removal, new resins for solid phase peptide synthesis, peptide conformation, or the synthesis and incorporation of conformationally-constrained peptides or amide bond surrogates.

Whilst DCC and other carbodiimides are still by far the most popular coupling reagents for peptide synthesis, a number of alternatives are available which avoid the production of ureas as side-products. Acid chlorides were amongst the first peptide coupling reagents to be investigated, but their use rapidly diminished when it was realized that they caused extensive racemization. They are now enjoying something of a resurgence in popularity, since FMOC-amino acid chlorides have been found not to be significantly susceptible to racemization. Much interest has been expressed in the use of acid fluorides in peptide synthesis, as they have greater stability than acid chlorides so all three main amine protecting groups (FMOC, Boc, and Z) can be utilized. The preparation of both α- and side-chain acid fluorides of aspartic and glutamic acid derivatives has been reported.[166]

Active esters of amino acids are normally prepared using DCC activation, but this method suffers from the various disadvantages associated with DCC, and a route to active esters from mixed anhydrides has been reported which avoids these problems.[167] Nagase *et al.* have described the synthesis of tripeptides from an *N*-Boc-dipeptide azide and the tetrabutylammonium salt of an amino acid, thus avoiding the need to deprotect the *C*-terminal amino acid.[168] In a comparative study of coupling reagents, BOP was found to give the best yields and least racemization.[169] However, the generality of such studies is questionable as previous investigations usually gave contradictory results. The efficiency of coupling reactions during solid phase peptide synthesis can be enhanced by microwave irradiation of the resin.[170]

Amongst the many new peptide coupling agents investigated during the period of this review, the synthesis of 6-nitro-β-naphthalenesulfonyl-oxybenzotriazole and its use to produce 6-nitrohydroxybenzotriazole active esters for peptide synthesis has been described.[171] 3-Dimethylphosphinothioyl-2(3*H*)-oxazolone MPTO (**35**) has been recommended for the racemization-free coupling of amino acids,[172] and the saccharin derivative **36** has also been used as a coupling reagent for the synthesis of dipeptides.[173] *p*-Nitrobenzophenone oxime was used as an active ester coupling reagent in the synthesis of tetrapeptides.[174]



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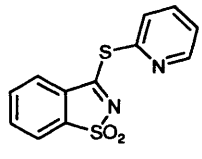
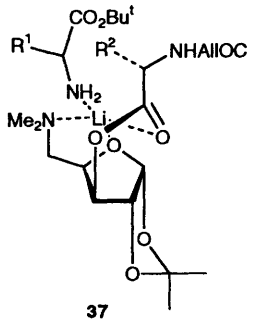


36

Treatment of a carboxylic acid (including *N*-protected amino acids) with diphenyldiselenide in the presence of tributylphosphine and *N*-methyl-morpholine-*N*-oxide results in the formation of an acyl selenide which will react with amino acids to give peptides, without the need to protect the carboxyl group of the second amino acid.[175] The use of polymer supported *o*-nitrophenol as an active ester for peptide synthesis has been reported,[176] as has the use of polymer bound 4-dimethylamino pyridine as a coupling agent in the presence of DCC.[177] The use of carbohydrate derived esters for peptide synthesis has been investigated as they are activated by lithium bromide and a complex of type **37** is thought to be formed in which the amino group of a second amino acid can be delivered intramolecularly.[178]



37

There is still scope for the development of new coupling reagents for peptide synthesis, especially for use in fragment condensation reactions where traditional methods often result in significant racemization. In this respect, the reported use of a combination of 2-thiopyridyl trifluoroacetate and the sodium salt of HOBt for peptide synthesis appears to hold much promise, as both urethane and benzoyl protected amino acids were coupled to amino esters (including *N*-methylamino esters) with very low degrees of racemization.[179] Another area which still causes problems is the cyclization of linear peptides through their terminal amine and carboxyl groups to give cyclic peptides, although in the case of tetrapeptides molecular mechanics calculations have been used to predict the best linear precursor.[180] In a study of a number of coupling reagents for formation of a cyclic hexapeptide, the combination of TBTU/HOBt/DIEA was found to give the best results,[181] although again this may not be a generally applicable conclusion.

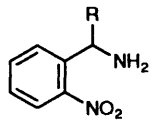
The formation of cyclic peptides on a solid support is an area that is attracting much interest at present, as generally higher yields are obtained than if the cyclization was carried out in solution (due to the effective high dilution conditions present within the polymer matrix). Albericio *et al.* have described a method of preparing cyclic peptides in this way in which the peptide is bound to the resin *via* the side-chains of aspartic or glutamic acids, and a triply orthogonal protecting group strategy (FMOC, t-butyl, allyl) is applied.[182] A similar approach but with the peptide attached to the resin through an α-carboxyl

group has been used by Bloomberg *et al.* to prepare branched cyclic peptides in which the side-chains of lysine and glutamic acid residues are connected *via* a peptide sequence.[183]

The formation of peptides containing multiple sterically hindered residues such as α-methylalanine (Aib) can be difficult, requiring the use of highly activated carboxylic acid derivatives. Both urethane protected *N*-carboxyanhydrides and the use of PyBroP as a coupling reagent gave good results with Aib-containing peptides.[184] In the case of α,α-diphenylglycine, it was found that the optimum choice of coupling agent depended upon whether the diphenylglycine residue was the amine or acid component.[185] In the former case, EEDQ gave the best results and water soluble carbodiimide the worst, whilst in the latter case the order of efficiency of the coupling reagents was reversed. Methodology for the incorporation of β-trifluoroalanine residues into a preformed peptide amide has been developed. Thus, treatment of the peptide amide with methyl trifluoropyruvate followed by dehydration with TFAA gives an imine which is reduced by sodium borohydride to give the chain-extended peptide with a β-trifluoroalanine residue at the *C*-terminus.[186]

The choice of solvent can also be important for peptide synthesis, as many protected oligopeptides are highly insoluble in common organic solvents. 1,1,1,3,3,3-Hexafluoro-2-propanol is a good solvent for protected peptides but not suitable for use in peptide synthesis; however, by adding a proton accepting solvent (DMF, DMSO, pyridine) an excellent solvent mixture for peptide synthesis is obtained.[187] Solid phase fragment condensation is becoming a popular strategy for the preparation of large peptides, but unfortunately the method suffers from the disadvantage that extensive racemization can occur at the *C*-terminal amino acid residue of the activated fragment. The effect of solvent on this racemization has been investigated, and it was found that for diisopropylcarbodiimide mediated couplings, racemization was minimized in DMF/DCM and NMP/DCM solvent systems provided HOBt was also added.[188]

Enzyme-catalysed peptide synthesis continues to attract much attention. Kawashiro *et al.* have optimized the preparation of *Z*-Phe-Phe-NH_2 from *Z*-Phe-OEt and Phe-NH_2 using porcine pancreatic lipase in water/water miscible solvent systems.[189] The use of chymotrypsin to catalyse the formation of a dipeptide in frozen, aqueous solution has been reported.[190] Freezing the reaction mixture appears to improve the yield of both kinetically and thermodynamically controlled enzymatic peptide synthesis. Protease enzymes have been used to couple *N*-*Z*-α,β-dehydroglutamic acid derivatives to α-amino amides.[191] Pepsin has been used in the synthesis of tetrapeptide *p*-nitroanilides. The enzyme was used to catalyse the coupling of *N*-*Z*-tripeptides with amino acid *p*-nitroanilides.[192] An enzymatic route to peptide amides utilizing *o*-nitrobenzylamine derivatives of type **38** has been developed in which the enzyme is used to convert a peptide into its *o*-nitrobenzylamine derivative, and the *o*-nitrobenzyl



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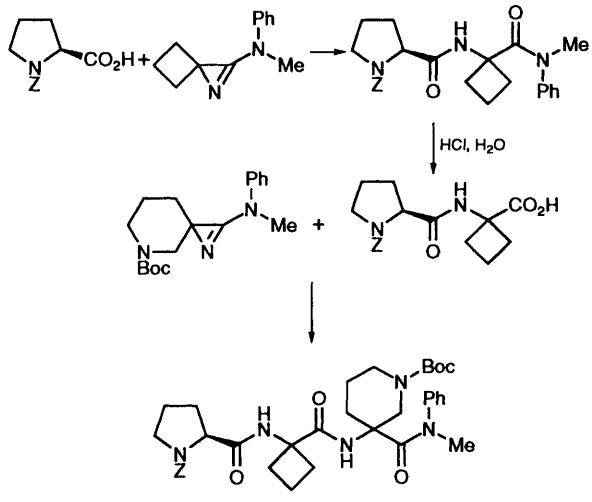
group is then cleaved by photolysis.[193] A similar approach using 2,4,6-trimethoxybenzylamine has been reported in which papain or subtilisin is used to transform a protected peptide ester into the amide, the trimethoxybenzyl protecting group then being cleaved with TFA.[194]

Peptide synthesis is almost universally carried out by reacting an activated carboxyl group with an amine. However, over the last few years Heimgartner has investigated the alternative approach, namely that of reacting an activated amine with an unactivated carboxylic acid. The activated amine takes the form of a 2*H*-azirine (which can be prepared from the enolate of a tertiary amide by reaction with diphenyl chlorophosphate followed by sodium azide) which on reaction with an amino acid or peptide gives rise to a peptide containing an α,α-disubstituted amino acid. Such peptides can be difficult to prepare by more traditional methods as α,α-disubstituted amino acids are sterically hindered and so react with carboxylic acid derivatives only slowly. In the latest example of this work,[195] a tripeptide containing two adjacent α,α-disubstituted amino acids is constructed as illustrated in **Scheme 42**.

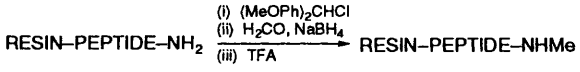


Scheme 42

Another occasional problem in solid phase peptide synthesis is the double incorporation of serine residues if the OH group is left unprotected, due to *O*-acylation followed by a facile *O*–*N* acyl migration. This problem is traditionally circumvented by the use of *O*-benzyl serine, but the benzyl group requires HF for its deprotection. Thus the use of *O*-t-butyl-*N*-Boc serine has been recommended, as the t-butyl group temporarily protects the alcohol during acylation but is cleaved concomitantly with the Boc group.[196]

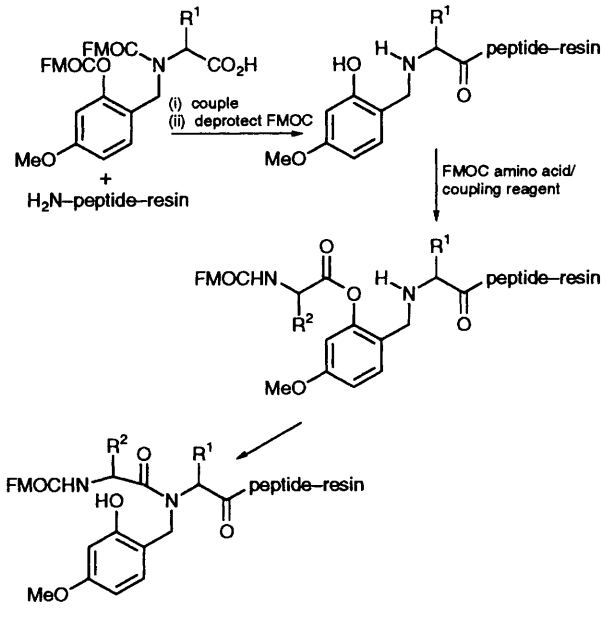
The incorporation of *N*-methyl amino acids into peptides is a popular way of investigating the

conformational and H-bonding requirements of a peptide, and methodology to convert amino acids into *N*-methylamino acids whilst they are attached to peptide synthesis resin has been developed, as shown in **Scheme 43**. Thus, treatment of an *N*-deprotected peptide-resin adduct with dimethoxylbenzhydryl chloride followed by reductive amination with formaldehyde/$NaBH_4$ and deprotection of the dimethoxybenzhydryl group gives a terminal *N*-methyl amino acid, and peptide synthesis can then be continued.[197]



Scheme 43

Whilst the standard conditions of solid state peptide synthesis have been optimized to give excellent yields of small model peptides, problems are often encountered in the synthesis of larger peptides which are thought to be due to the formation of extensively hydrogen bonded networks (β-sheets) within the peptide whilst it is attached to the resin. The obvious way to prevent this problem is to use an additional protecting group for the primary amide bonds during the synthesis. Unfortunately, *N*-alkyl amino acid derivatives are sterically-hindered which again reduces yields and causes problems during solid phase peptide synthesis. However, Sheppard *et al.* have devised a novel solution to this problem, by use of *N*,*O*-bis-FMOC derivatives of (2-hydroxy-4-methoxybenzyl)amino acids as shown in **Scheme 44**.



Scheme 44

The substituted benzyl group protects the primary amide bond of subsequently formed peptides, and the next amino acid residue is coupled first to the phenol-OH and then transferred intramolecularly to the secondary amine, thus avoiding problems due to steric hindrance. The 2-hydroxy-4-methoxybenzyl protecting group is cleaved by TFA under the conditions normally used to cleave the peptide from the resin.[198] An alternative solution to this problem, also due to Sheppard, is the use of DMSO as solvent during solid phase peptide synthesis, as this solvent strongly disrupts hydrogen bonds.[199] A set of aggregation parameters which can be used to predict problem sequences during solid state peptide synthesis have been derived,[200] as have a set of parameters based on the ability of amino acid residues to stabilize β-sheets.[201]

4 Summary

In writing this review, a number of trends became apparent, some of which have been alluded to within the main text. As expected, the emphasis in amino acid synthesis (and to a lesser extent in amine synthesis) seems to be on the development of new asymmetric methodology, though a major change of direction from α- to β-amino acids is apparent. This probably reflects the saturation of α-amino acid methodology and the realization that much of the same chemistry can be modified for β-amino acid synthesis, along with the biological properties of β-amino acids.

Work in the amide area seems to be far more diverse, though β-lactams remain attractive synthetic targets. The development of new methods for peptide synthesis continues to occupy many research groups, with increasing interest being exhibited in the use of enzymes. Future, annual reviews of amines and amides will follow developments in these areas with interest.

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