α-Cation equivalents of amino acids

PATRICK D. BAILEY, JOANNE CLAYSON,

Department of Chemistry, Heriot-Watt University, Riccarton, Edinburgh, EH14 4AS, UK

and ANDREW N. BOA

*School of Chemistry, University of Leeds, Leeds LS2 9JT, UK*

Reviewing the literature published up to the end of 1994

1 Introduction

Synthetic equivalents of amino acid α-cation synthons have enormous potential in the synthesis of a wide range of amino acids, peptides, and many other nitrogen-containing compounds. The synthetic equivalents are the α-substituted amino acid derivatives 1 and the imines/iminium ions 2/3.
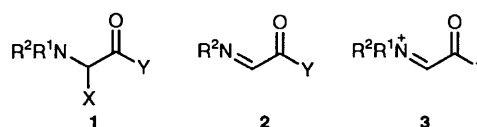
Glycine derivatives **1** possessing an additional heteroatom at the α-position are not only of value as synthetic intermediates, but they are also important compounds in their own right:

- They are amino acid derivatives that might be incorporated into biologically active peptides, to generate new analogues with enhanced medicinal properties.

- Some α-hetero-substituted α-amino acids are natural products, *e.g.* bicyclomycin **4** and aranotin **5**.

- The poly-functionalized α-carbon possesses unusual chemical properties that can be studied and exploited.

Many peptide analogues have been prepared in which residues have been modified by the incorporation of heteroatom groups into the side-chains. In contrast, there are relatively few examples of such modification at the α-positions of peptides. This is almost certainly because of the inherent instability of the corresponding free α-amino acid, in which the nitrogen lone pair displaces the hetero-atom leaving group (**Scheme 1**). When the nitrogen lone pair is not fully available to displace X (*e.g.*
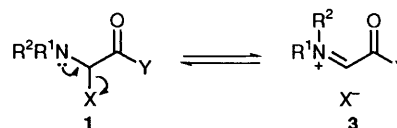
X = F, Cl, Br, SR, OR, OCOR
Y = OR, NHR
R¹ and/or R² = electron-withdrawing groups such as MeCO, PhCO, Bu^{t}OCO, PhCH$_2$OCO, phthaloyl.

Scheme 1

when R^1 or R^2 exert a -M effect), the α-substituted α-amino acid derivatives can be moderately stable. However, in most cases the nitrogen lone pair can still assist in the displacement of X, either through the anomeric effect or by generating imine/iminium ion intermediates.

In nucleophilic displacement reactions of X from compounds such as 1, it is often unclear whether the reaction is accelerated simply by the anomeric effect from the nitrogen lone pair, or whether full displacement of X occurs before attack by the nucleophile. Whichever mechanism does operate, the enhanced electrophilic reactivity of α-substituted peptides affects their medicinal potential, and allows them to be exploited very successfully in further synthetic transformations.

Whether they are the ultimate target or synthetic intermediates, it is difficult to obtain or exploit the chirality that most α-substituted α-amino acids should possess — again, the reversible formation of imines is the culprit, usually causing racemization at the α-centre. The stability of an α-substituted α-amino acid is also affected by the leaving group ability of X. Although this can be influenced strongly by the reaction conditions, the following order of reactivity is a useful guide:

$$F < OR < SR < Cl < Br$$

(R = alkyl or acyl; where R = H, the derivatives are usually unstable). Looking at this approximate order of reactivity, it is perhaps not surprising that the more stable derivatives are often targets in their own right, whilst the relatively reactive α-bromo derivatives have dominated work on the use of α-substituted α-amino acids as synthetic intermediates.

Work on compounds that were effectively glycine α-cation equivalents began in the mid-1970s, but significant developments have taken place over the past 5–10 years which have really opened up their potential in synthesis.[1] This article gives an overview of the field, and includes references up to the end of 1994. Although this review primarily concerns α-substituted glycine derivatives, other α-substituted amino acids are discussed wherever this is appropriate. Throughout this review, α-substituents refer to *heteroatom* groups on the α-carbon (*i.e.* substituent X in 1).

2 Methods for preparing α-substituted α-amino acid derivatives
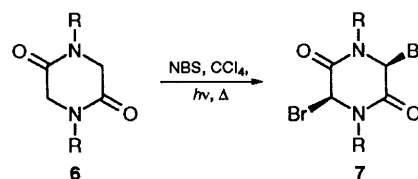
2.1 Bromination of glycine derivatives

This is the commonest route to α-substituted amino acids, and is normally carried out under free radical conditions using N-bromosuccinimide. It gives easy access to α-bromoglycine derivatives, for use either directly, or after conversion into other α-substituted analogues. One of the earliest research groups to develop this chemistry was that of Steglich,[2,3] for which the following transformation is illustrative (**Scheme 2**).


4

5
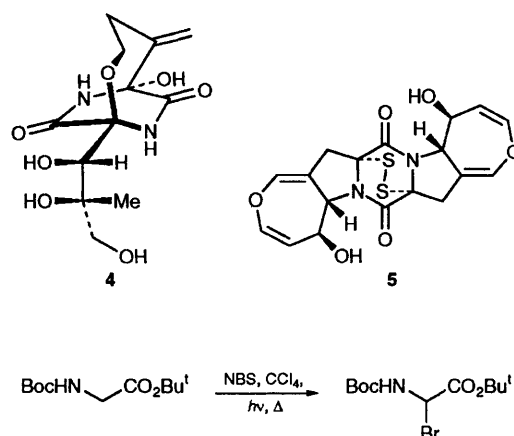
Scheme 2

Other simple, protected glycine derivatives have also been brominated using this method and a wide range of N-protecting groups is compatible with the transformation; for example, benzoyl,[2–4] acetyl,[2,3] bromoacetyl[2,3] or chloroacetyl,[5,6] trifluoroacetyl,[2,3] trichloroethoxycarbonyl,[2,3] and the benzophenone imine,[7] and also Boc as illustrated in **Scheme 2**.[2,3,8–12] The carboxyl function is invariably protected as an ester, from the simple (m)ethyl[2–5,7] and t-butyl[2,3,11] to the chiral menthyl[6] and 8-phenylmenthyl groups.[8–11] Williams has shown that the diketopiperazine derivative of *cyclo*-glycylglycine **6** is brominated under free radical conditions to produce the diastereoisomerically pure racemic *syn* dibromide derivative **7** (**Scheme 3**).[13] Selective bromination at the glycine α-position is also possible in *cyclo*-glycylvaline, and further asymmetric transformations are possible under the stereocontrol of the isopropyl group.[14]


6   **7**

Scheme 3

As time has progressed, it has become apparent that the α-bromination of quite complex glycine derivatives can be highly regioselective. The extensive investigations of Easton have shown that glycine derivatives are brominated at significantly faster rates than other residues. Initial work showed that in the case of N-benzoyl valine derivatives[15,16] the amido-carboxy substituted radical (α-radical) was considerably more stable than the tertiary radical produced at the β-centre, but that subsequent hydrogen abstraction by this radical led to mixtures of products being isolated. Lidert and Gronowitz[5] also reported mixtures of products from the bromination of the alanine derivative **8** (**Scheme**
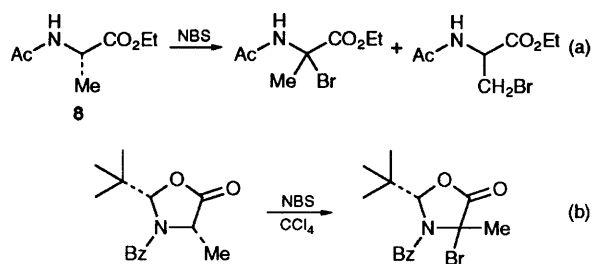
Scheme 4

4a), but, in contrast, Seebach et al.[18] reported regiospecific bromination of a cyclic oxazolidinone derivative of alanine, (**Scheme 4b**).

Easton has put forward evidence[15-17] that the intermediate α-centered radical produced by H-atom abstraction is planar, and therefore there are significant non-bonding interactions between the amino acid side-chain and the carbonyl group of the N-acyl function, and this explains the preferential reactivity of glycine derivatives (no side-chain) over those of other amino acids. He proposed that cyclic amino acid derivatives should be brominated selectively at the α-centre and this was duly illustrated with the pyroglutamate derivative **9** (**Scheme 5**).
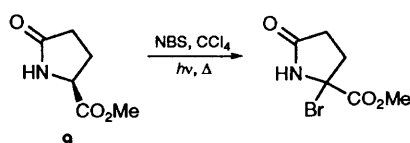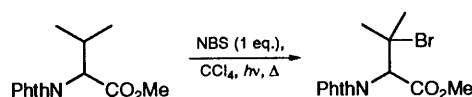

Scheme 5

The observed preferential α-bromination of N-benzoyl glycine derivatives means that selective α-functionalization of the glycyl moiety can be achieved in the presence of other residues, for example in di- and tri-peptides.[19] Interestingly, reactivity can be further modified if the N-terminal residue is N-phthaloylated.[20,21] This protecting group prevents α-bromination of the N-terminal residue and directs functionalization away from the phthaloylated residue (**Scheme 6**).

The site-specificity of the free radical bromination is again demonstrated in the work of Williams, which (most unusually) leads to stereochemically pure α-bromoglycine derivatives (**Scheme 7**).[22,23] The formation of the bromoglycine derivative **10** was essentially quantitative and, although NMR data were broad and relatively uninformative, single crystal X-ray diffraction studies led to an unambiguous structural assignment. It is interesting that neither of the benzylic positions underwent bromination, and that 100% asymmetric induction was observed. In further transformations, the displacement of bromide was found to take place with overall retention of stereochemistry, thereby giving access to optically active amino acid derivatives — see Section 3.

Scheme 6

10
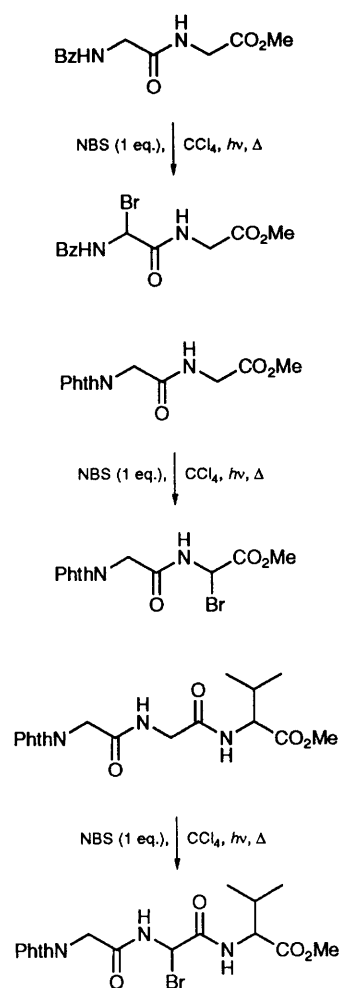
Scheme 7

There are very few examples of acyclic α-bromoglycine derivatives that are predominantly one stereoisomer. However, the (−)-8-phenylmenthyl ester of Boc-glycine **11** undergoes α-bromination with high diastereoselectivity when the reaction is carried out in refluxing CCl_4;[8] this is perhaps the thermodynamic product, since room temperature reaction conditions lead to a mixture of stereoisomers.[11] As in Williams' procedure, further transformations

proceed with overall retention of stereochemistry. For example, treatment with tributyltin deuteride, proceeding via a planar radical intermediate, produces the α-deuteroglycine derivative **12** in which the auxiliary has controlled the formation of the new chiral centre (**Scheme 8**).[8]
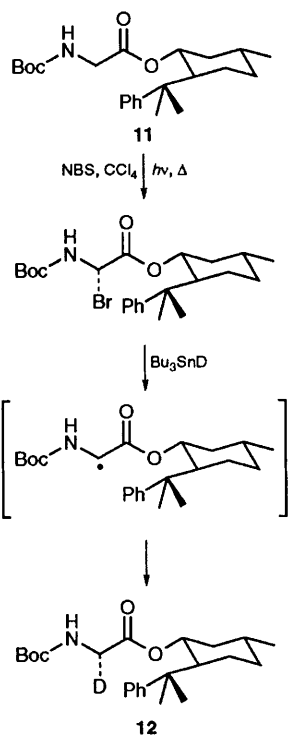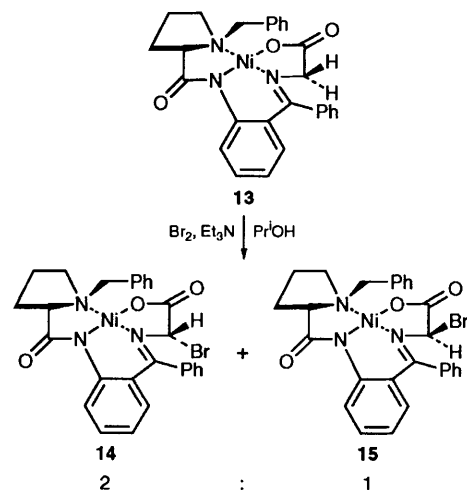

Scheme 8

Although the free radical procedures dominate the α-functionalization of glycine derivatives, Belokon[24-26] has shown how α-bromination of a glycine derivative can be achieved using bromine and base catalysis. Thus, the homochiral Ni[II]-Schiff base complex **13** derived from (S)-o-(N-benzyl-prolyl)aminobenzophenone and glycine reacts with bromine to produce a 2:1 mixture of the α-bromo derivative stereoisomers **14/15**; these can be separated by chromatography (**Scheme 9**).

Hence, the direct α-bromination of glycine derivatives is an efficient, and often chemoselective process, that readily gives access to α-bromoglycine derivatives. With suitable auxiliaries, this bromination can be stereospecific, but it is invariably the auxiliary that controls the stereochemistry of further transformations.

## 2.2 Direct routes to other α-substituted glycine derivatives

There are surprisingly few routes to α-substituted glycine derivatives (other than α-bromo) for which the glycine skeleton is intact in the starting material. There are, however, examples in which it is inferred that an α-bromo intermediate is trapped *in situ* by a suitable nucleophile (see Section 2.4). It would seem

Scheme 9

that free radical halogenation of glycine derivatives is not a viable method of α-chlorination; in general, α-chloroglycines are obtained by either quenching a glycine enol/enolate with a source of 'Cl⁺', or by replacing an α-hydroxy by an α-chloro group (see Section 2.4 for examples of the latter).
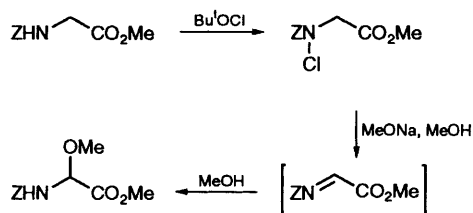
Williams[23] has made a chloro analogue of the chiral glycine cation equivalent shown in **Scheme 7** by treatment of an oxazinone with t-butyl hypochlorite (**Scheme 10**), and again the *trans*-product **16** is formed under the control of the auxiliary.
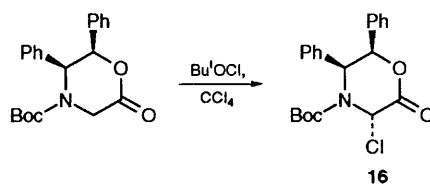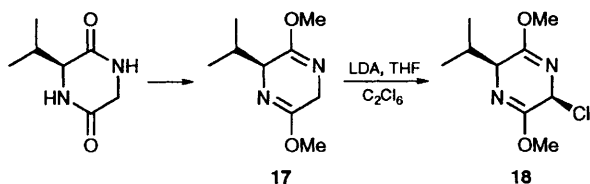

Scheme 10

It is important to note that on treatment with t-butyl hypochlorite and base, glycine derivatives[27-30] (and those of other amino acids,[29-31] including β-lactams[32,33]) possessing a free NH do not produce α-chloro derivatives as in the case reported above. In these examples N-chlorination is observed, but subsequent treatment with a suitable base (**Scheme 11**)[27,28] gives the same intermediate imine that an α-chloroglycine derivative would have generated.

The bis-lactim ether methodology developed by Schöllkopf for the asymmetric synthesis of amino acids usually employs the α-anion of a chiral glycine derivative (e.g. the anion of **17**), but he has extended the scope of this chemistry to a glycine α-cation equivalent via the α-chloro derivative **18** (**Scheme 12**).[34,35] Interestingly, the *cis*-chloro compound **18** is produced in this enolate reaction: the authors propose that the lithium cation co-ordinates *anti*- to the isopropyl group, so directing the chloro group
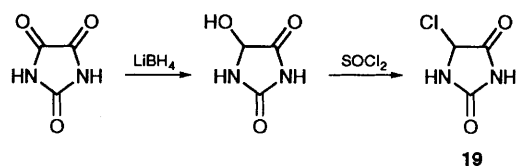
Scheme 11

ZHN~CO₂Me →[Bu^tOCl] ZN~CO₂Me
                                    |
                                    Cl

|MeONa, MeOH

OMe
ZHN~CO₂Me ←[MeOH] [ZN=CO₂Me]
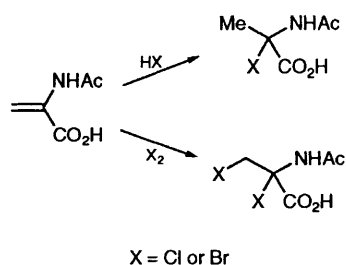
Scheme 12

17   18

LDA, THF
C₂Cl₆

syn- to the isopropyl group. Nevertheless, whether by a straight S_N2 mode or via elimination to an iminium ion, subsequent displacement of the chloride gives *anti*-products (see Section 3.1).

The use of α-unsaturated glycine derivatives is also possible. Thus, an α-hydroxy glycine hydantoin can be prepared by borohydride reduction of triketoimidazolidine (**Scheme 13**), treatment of which with thionyl chloride then gives the useful α-chloro derivative **19**.[36]
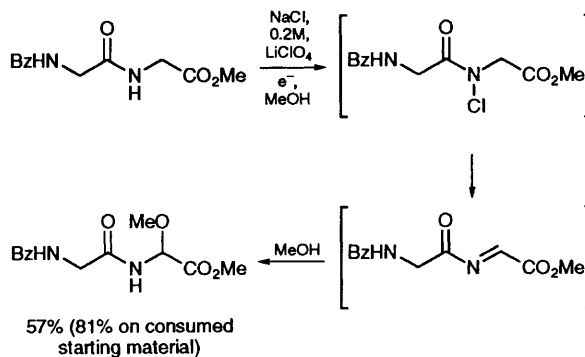
Scheme 13

LiBH₄   SOCl₂   19

A further example which exploits unsaturation, but yields α-haloalanine derivatives, is the addition of HX or X₂ to protected dehydroalanine (**Scheme 14**).[37-39]
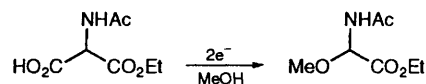
Scheme 14

X = Cl or Br

Electrochemical methods perhaps have limited appeal to many synthetic organic chemists, but they can be used very successfully for the direct α-derivatization of protected amino acids.[40] In cases

Scheme 15

NaCl, 0.2M, LiClO₄
e⁻, MeOH

MeOH

57% (81% on consumed starting material)

of dipeptides good regiocontrol can be achieved (**Scheme 15**).[41]

Finally, degradative procedures have been reported, though these are probably of limited practical value. Methods falling into this category include electrochemical decarboxylation[42-46] (**Scheme 16**) and chemical oxidative cleavage of serine and threonine side-chains[47-49] (**Scheme 17**).

Scheme 16

NHAc
HO₂C~CO₂Et →[2e⁻, MeOH] MeO~CO₂Et
                                            NHAc

Scheme 17

Pb(OAc)₄, PhH, Δ

Pb(OAc)₄, EtOAc, 4Å MS

R = H, Me
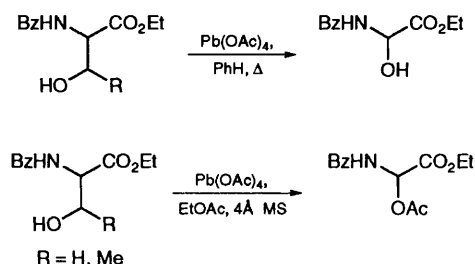
2.3 Routes that do not start from the glycyl skeleton

Most routes to α-hetero-substituted amino acid derivatives start with the amino acid skeleton intact. Of the routes to such compounds in which this is not the case, synthetic work has been dominated by the reaction of amides with glyoxylic acid or ester (**Scheme 18**).

R¹ = MeO, PhCH₂O, Ph;   R² = Me, Et

Scheme 18

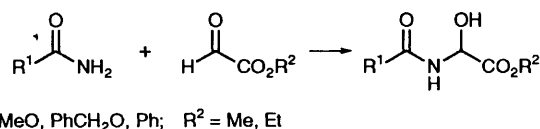This approach has been extensively studied by Ben-Ishai,[50-55] and developed subsequently by many research groups.[56-61] This tactic is an excellent general way of gaining access to substituted glycine derivatives, because of the ease with which the α-hydroxy function can be further derivatized (see Section 2.4). Amides are usually insufficiently nucleophilic to react with carbonyl electrophiles; it would seem that unhindered primary amides and highly electron-deficient aldehydes are prerequisites for the reaction to be successful. Glyoxylate esters are rather unstable, and the use of the hemiacetal,[62] although probably proceeding via the same aldehyde intermediate, is a useful practical alternative (Scheme 19). Alternatively, the equilibrium can be influenced by the use of TMS-triflate, forming α-silyloxy α-amino acids, and this approach has been used to generate α-oxygenated derivatives of amino acids other than glycine (i.e. α-alkyl-α-amino acids).[63]
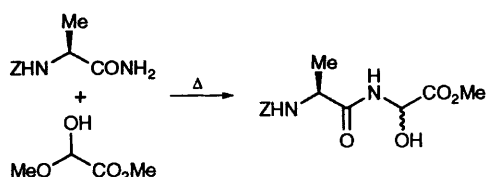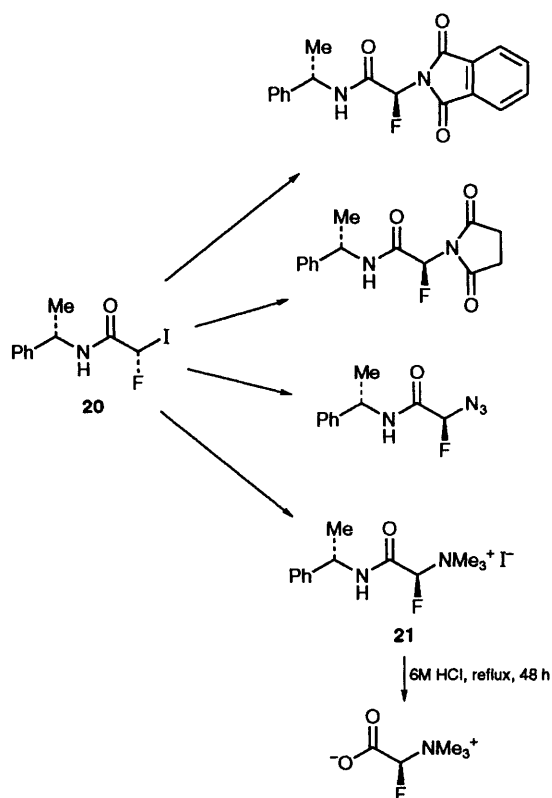

Scheme 19

A similar approach to the method described above is particularly effective when fluorine is the desired α-heteroatom, since its poor leaving group ability confers exceptional stability on α-fluoroglycine derivatives. Takeuchi et al.[64,65] have employed ethyl bromofluoroacetate as a key starting material; reaction with nitrogen nucleophiles [e.g. phthalimide, azide, KN(Boc)₂] can be controlled to give only displacement of bromide, allowing rapid access to α-fluoroglycine derivatives (Scheme 20). Using chiral esters of bromofluoroacetate, it has been possible to generate separable (and stable) diastereoisomers, which have found applications as chiral shift reagents, but the free amine (even in protonated form) has proved too unstable for detection or isolation.[64,65]
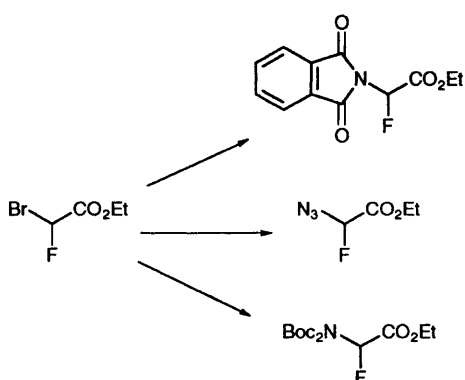
Scheme 20

In an alternative approach to α-fluoroglycine derivatives, Bailey et al.[66] have used chlorotrifluoroethene and (S)-α-methylbenzylamine to generate α-chlorofluoro- and α-fluoroiodo-ethanamide derivatives (e.g. 20). In these cases, not only are the diastereoisomers separable, but single crystal structure determinations have allowed assignment of the absolute stereochemistry at the α-centre. Subsequent displacement with nitrogen nucleophiles occurs with 85–100% inversion of stereochemistry, giving a range of protected α-fluoroglycine derivatives (Scheme 21). In the case of 21, standard peptide cleavage conditions result in the isolation of an α-fluorobetaine, the only reported example of a 'free' α-fluorinated α-amino acid.[67]

Scheme 21

2.4 Interconversion of α-substituents

Either through the anomeric effect, or via an imine/iminium ion intermediate, interconversion of heteroatoms α-to nitrogen is an easy process, even when the nitrogen is protected. Some of the major transformations are illustrated in Table 1.

## 2.5 Direct routes to the imines RN=CHCO—Y

Given that α-substituted glycines are usually in equilibrium with the corresponding imine, and that the imine is often the reactive component in subsequent transformations, it is pertinent to consider synthetic methods that lead directly to the imine. Perhaps the most obvious method is the

**Table 1** Interconversion of α-heteroatom substituted glycine derivatives

From	To	Ref.
Br	OR	15–17, 19–21, 24, 84, 90
Br	OAr	24
Br	SR	13, 37, 48, 90, 121
Br	SAr	23, 121
Br	OCOR	7, 90
Br	SCOR	5, 38
Br	P(O)(OR)$_2$	3, 48, 125
Br	NR$_2$	7, 24
Cl	OR	39
Cl	SR	37, 38
Cl	SH	38
Cl	SCOR	5, 38
Cl	SC(S)OEt	122
Cl	P(O)(OR)$_2$	48, 61
SR	OR	50
SR	Br	48
SR	Cl	48, 50
SCOR	OR	39
OH	Cl	36, 50, 57–60, 62
OH	OR	50, 61
OH	SR	50
OR	Cl	50, 61
OCOR	OR	7
OCOR	SR	7, 48, 90

direct condensation of glyoxylic acid or its ester with an amine (**Scheme 22**). Imine formation is reversible, and these highly electrophilic imines can be formed only if water is explicitly removed (*e.g.* azeotroping conditions or dehydrating agents).[68]
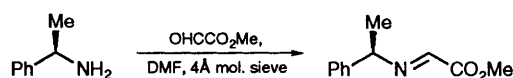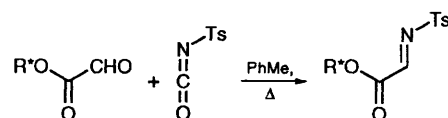

Scheme 22

In contrast, amides react with glyoxylate to give the hydrated product — *i.e.* the α-hydroxy glycine derivatives (**Scheme 18**).[50–61] When *N*-acyl-imines are required, a Wittig variation is a neat way to overcome this problem (**Scheme 23**).[69]
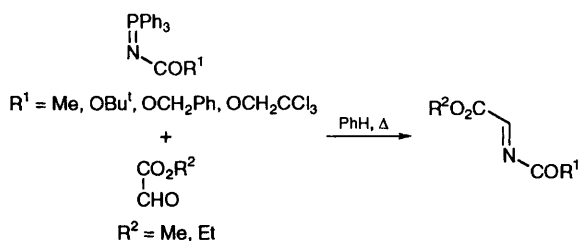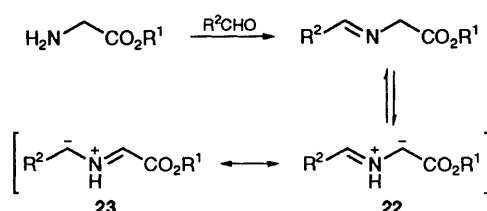

Scheme 23

If the tosyl rather than the carbonyl electron-withdrawing group is required on nitrogen, then these compounds are readily accessed using the procedure of Steglich,[2,3] Albrecht,[70,71] or Holmes[72] (**Scheme 24**).

Scheme 24

Finally, imines of glycine are being increasingly exploited as 1,3-dipoles,[73–75] by virtue of the equilibrium illustrated in **Scheme 25**. However, we will not discuss this valuable chemistry further in this review, as it is dominated by reactions implied by the mesomeric tautomer **22** rather than by **23** (formally an iminium ion **3**).

Scheme 25

3 α-Substituted glycines in synthesis

The use of α-glycine cations in synthesis has been reviewed by Williams,[1] and the versatility of this chemistry is summarized in the next section of this review — reactions with carbon nucleophiles, aza-Diels–Alder cycloadditions, radical chemistry, reductions, Wittig chemistry, and dipolar cycloadditions all feature in this rich area of chemistry.

It is worth re-stating the observation that the chemistry of α-substituted α-amino acid derivatives appears to take place via imine/iminium ion intermediates (**Scheme 26**).
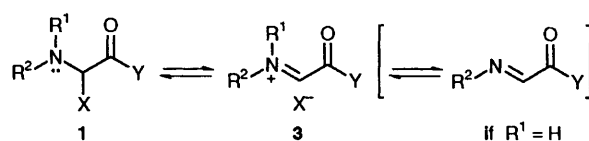
Scheme 26

It is not clear whether it is the completely free imine that is always involved, or whether it is an extremely powerful anomeric effect in some cases. Nevertheless, asymmetric variations of these reactions have proved extremely important for the synthesis of optically active compounds. The two main types of reaction with α-substituted glycine derivatives are:

● Attack by carbon nucleophiles, to give α-alkyl α-amino acid derivatives.
● Diels–Alder reactions, to give pipecolic acid derivatives.

Some additional reactions are discussed in a final section of this review (reductions, eliminations, free radical reactions).

3.1 Reactions with carbon nucleophiles

### 3.1.1 Grignard and related organometallic nucleophiles

3.1.1.1 Grignard reagents

α-Bromo- and α-chloro-glycine derivatives react with Grignard reagents to give α-substituted α-amino acids.[10,11,58,76,79] Two mole equivalents of reagent are needed; one to trigger elimination of HX, the second to add to the resulting imine at the α-carbon, so giving the new amino acid derivative (**Scheme 27**). This method has also been used successfully with alkenyl Grignards[58,59] to give α-vinyl glycine derivatives. If the Grignard reagent to be employed is valuable, a tertiary amine can be used to form the acyl imine,[76] before addition of just one equivalent of the Grignard reagent.
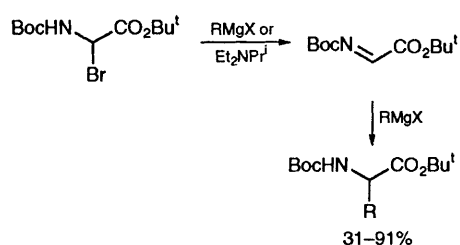
Scheme 27

With the 8-phenylmenthyl esters of α-halo glycines[10,11] the chiral group controls the face selectivity of the addition of the Grignard reagent to the acyl-imine, giving diastereoisomeric excesses of 51–98% in the products (**Scheme 28**). Careful acid hydrolysis[11] of the esters then gives the optically active amino acids, or reduction[10] yields the amino alcohols **24**, which can be re-oxidized to the amino acids **25**.
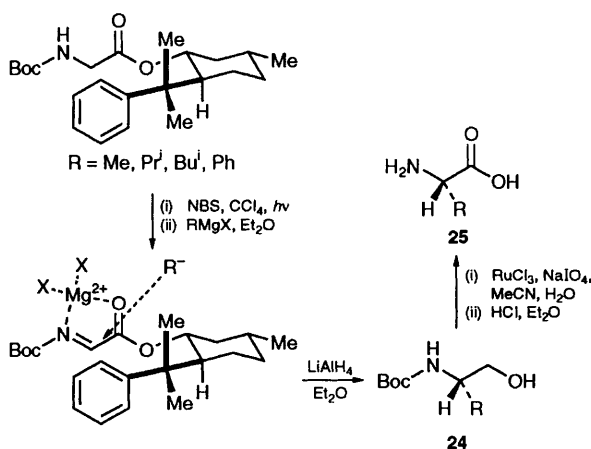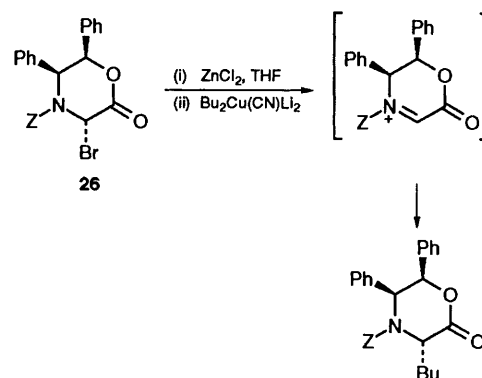

Scheme 28

3.1.1.2 Cuprates

In an analogous fashion to the organomagnesium nucleophiles, the α-halo glycine derivatives also react with higher order mixed cuprates.[22,23,77–79] Williams has shown that the homochiral α-bromo-oxazinone **26** can be treated with Lewis acid to produce the intermediate iminium species, to which the cuprate reagent adds from the least-hindered face (**Scheme 29**).[22,23] An extensive study of solvent and Lewis acid conditions[34] showed that hard Lewis acids and non-polar solvents favour an S_N2 mode (giving *syn* products) and soft Lewis acids and polar solvents lead to an elimination–addition mode (favouring *anti*-products).

Scheme 29

3.1.1.3 Alkyl zincs and alkyl lithiums

Examples of displacement reactions of α-hetero substituted glycines with alkyl lithiums are rare. In one case,[24] decomposition is reported; however, butyl-, phenyl-, and methyl-lithium add to *N*-acylimino malonates in good yields.[2,3] Reactions of α-bromo glycines with alkyl zinc halides are also known,[22–24,80] although yields are generally poor.

3.1.1.4 Tributyltin acetylides

Tin acetylides[81,82] may be used to generate α-alkynyl amino acid derivatives (**Scheme 30**). Subsequent deprotection via hydrogenation can be used to generate α-alkyl amino acids **27**[81] whereas dissolving metals[82] cause reduction of the triple bond to the *trans*-alkene **28**. This methodology gives an attractive approach to α-vinyl amino acids to augment methods using Grignards,[58] cuprates,[79] or amidoalkylation of alkenes.[53]

3.1.2 Enolate nucleophiles

3.1.2.1 Stabilized anions

α-Halo-glycine derivatives have been treated with a range of sodium and potassium enolates, especially those of malonic diesters.[23,24,34,36,57,62,83,84] Such reactions have been used to make the non-natural amino acid β-carboxyaspartic acid and its
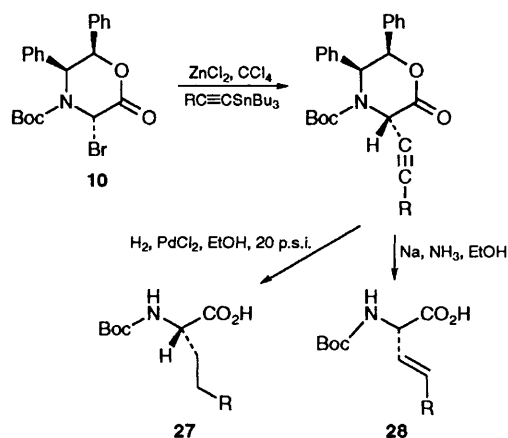
Scheme 30

Scheme 31

derivatives. This transformation has also been achieved with an α-haloglycine containing dipeptide (**Scheme 31**).[62,63]

The coupling of α-acetoxy glycines with the sodium enolate of malonic dialkyl esters has been reported using Pd(PPh₃)₄ catalysis (**Scheme 32**).[85] Other enolates react in a similar fashion,[6] as do the enols of 1,3-dicarbonyl compounds under acidic conditions (**Scheme 33**).[55,79]
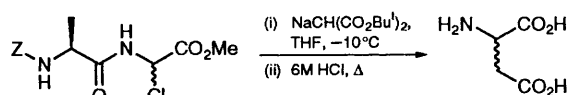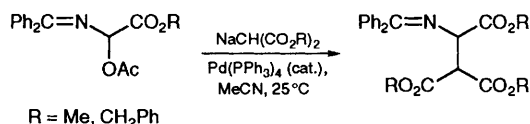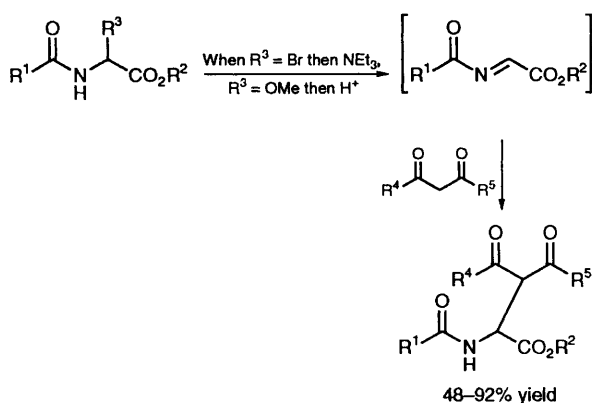

R = Me, CH₂Ph

Scheme 32

48–92% yield

Scheme 33

3.1.2.2 Silyl enol ethers

α-Bromo-glycines react in the presence of Lewis acids and silyl enol ethers to produce β-keto amino acids.[13,22,23,79] O'Donnell[86] has also performed this type of reaction with other α-hetero substituted glycines (*e.g.* α-methoxy and α-acetoxy glycines). Yet again, if Williams' oxazinone template is employed as the α-bromo glycine derivative, impressive diastereoisomeric excesses are obtained in the final product (**Scheme 34**).[13,22,23]
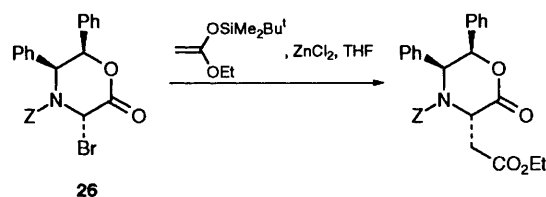
Scheme 34

3.1.3 Allylsilanes and allylstannanes

3.1.3.1 Allyl silanes

Allyl silanes react with α-hetero substituted glycines in the presence of Lewis acids to produce α-allyl amino acids.[22,23,85,86] Speckamp has shown how tin(IV) chloride (with α-chloroglycines) or boron trifluoride etherate (with α-methoxy glycines) generates an intermediate iminium species which reacts with allylsilanes to give the α-allyl amino acids in good to excellent yield (**Scheme 35**). Speckamp

73%
Isomer ratio 44 : 56
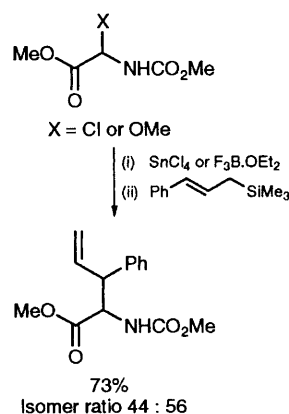
Scheme 35

has extended this chemistry to give access to α-allyl-alanine derivatives, via the α-trimethylsilyloxy derivative.[88] This use of protected α-chloroglycines has been further developed into an asymmetric version using the *N*-menthyl chiral auxiliary.[89]

3.1.3.2 Allylstannanes

Like allyl silanes, allyl stannanes react with α-bromo glycine derivatives to give γ,δ-unsaturated (α-allyl) amino acids, but evidence for the mechanism of

these reactions indicates that they proceed via radical pathways (see Section 3.3.1).[89,90] Easton has exploited this chemistry via the *N,N'*-diacetyl diketopiperazine of glycylvaline (the absence of NH-protons being essential); after introduction of bromine at the α position of glycine displacement by allylstannane is controlled by the isopropyl group (*c.f.* Schöllkopf chemistry).[14]

3.1.4 Other carbon nucleophiles

3.1.4.1 Alkyl boranes

O'Donnell has shown[77] that α-acetoxy glycine derivatives can react with alkyl boranes to give α-alkylated amino acids. This method can be used to generate quite sterically crowded amino acids such as α-cyclohexyl (90%) and α-t-butyl (57%) glycines in good yield (**Scheme 36**).
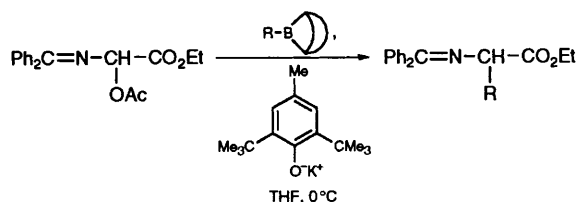
Scheme 36

3.1.4.2 Friedel–Crafts reactions

α-Heteroatom substituted glycines can be used successfully in Friedel–Crafts type reactions[23,51,56,86,92] with electron-rich aromatics such as anisoles, indoles, and furans. Both α-halo-[23,51,92] and α-alkoxy-/hydroxy-[51,56,86] glycines have been employed. Tin tetrachloride is the preferred Lewis acid for α-chloro glycines and Schöllkopf's bis-lactim ether methodology can be used to

generate optically active α-aryl amino acids (**Scheme 37**).[92] Ben-Ishai[53] has also shown that α-methoxy glycine derivatives react in a related fashion with alkenes under acid catalysis to produce α-vinyl amino acids.

3.1.4.3 Alkyl nitronates

N-Benzoyl α-bromo glycine methyl ester reacts with two equivalents of alkyl nitronates in a similar elimination/addition sequence to that for Grignard reagents.[93] The β-nitro functionalized amino acids **29** can then be modified in a range of interesting and useful ways (**Scheme 38**).

	R¹	R²	R³	R⁴
(a)	OEt	H	OEt	H
(b)	OMe	OMe	H	OMe
(c)	H	OMe	H	H
(d)	OMe	H	H	H

Scheme 37

R¹	R²
H	H
Me	Me
Me	H
Ph	H
CO₂Me	H
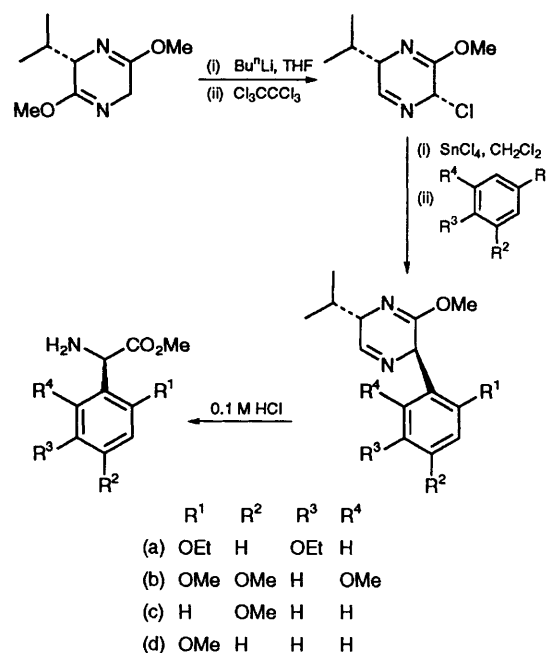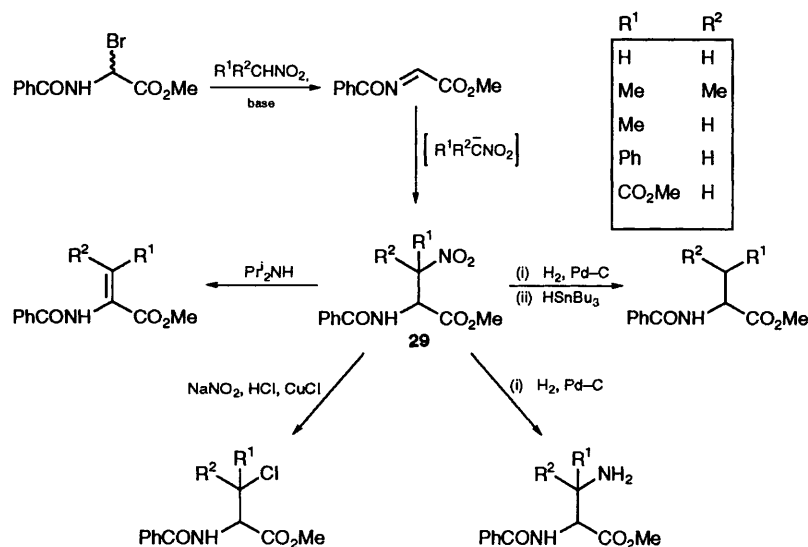
Scheme 38

3.1.4.4 Enamines

Steglich's group has reported the reaction of *N*-benzoyl α-bromo glycine menthyl and 8-phenylmenthyl esters with enamines.[76,94] The reaction with simple enamines proceeds with high diastereoselectivity, favouring *anti*-products, but with poor enantioselectivity (27–67%). Adding a second auxiliary to the enamine produces excellent diastereo- and enantio-selectivity (d.e. and e.e. > 99%) (**Scheme 39**).

Scheme 39

3.2 Diels–Alder reactions

Despite the obvious appeal of directly accessing the piperidine ring system via aza-Diels–Alder chemistry, imines have found only limited use as dienophile partners in $4\pi + 2\pi$ cycloadditions.[95,96] Extensive work by Grieco and others has indicated that imines derived from methanal will usually add to reactive dienes in aqueous solution, but that more hindered imines, less reactive dienes, or non-aqueous solvents often render the reaction useless.[97–1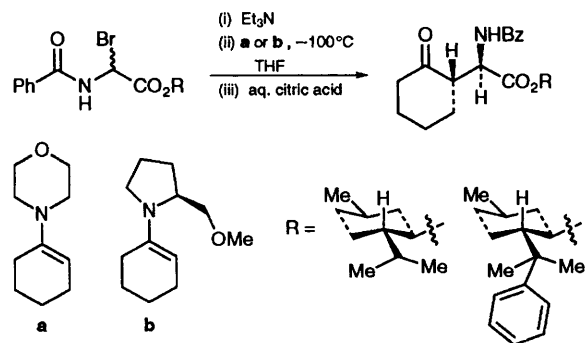03] One problem with imine dienophiles is the ease with which alternative reactions can often compete with cycloaddition.

However, strongly electron-deficient imines are more effective dienophiles, and imines of the type $R^1N{=}CHCO_2R^2$ are therefore potential 2π-partners in Diels–Alder chemistry. Moreover, their inability to tautomerize to the enamine reduces some of the potential side-reactions. This chemistry is particularly attractive because pipecolic acid derivatives can be accessed directly and they are a common structural unit in a wide range of important natural products (**Scheme 40**).
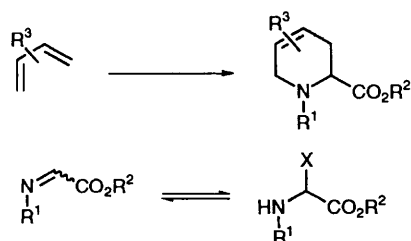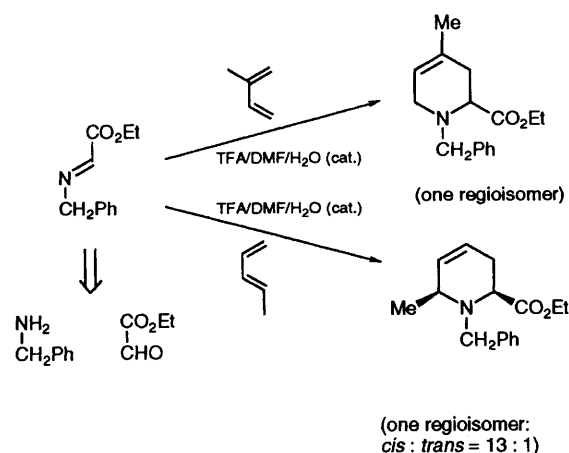

Scheme 40

Accordingly, there are several examples of α-hetero-substituted glycine derivatives for which, under suitable conditions, the corresponding imine can be trapped by a reactive diene.[104–106] Non-aqueous acidic conditions are the norm, to prevent hydrolysis of the iminium dienophile.

Nevertheless, the range of dienes has been very limited and it has been generally believed that aza-Diels–Alder reactions with less activated dienes require a second electron-withdrawing group on the imine; to this end, N-acyl[107] ($R^1CON{=}CHCO_2R^2$) and N-tosyl[108–112] ($TsN{=}CHCO_2R^2$) derivatives have been used with considerable success.

However, Bailey *et al.* found that N-alkyl imines of the type $R^1N{=}CHCO_2Et$ are effective dienophiles with a range of dienes provided that the solvent is carefully chosen – DMF yields the best results, with an equivalent of TFA (forming the electron-deficient iminium ion) and catalytic water being essential additives; yields are typically around 50% with acyclic dienes and display excellent regio- and diastereo-control (**Scheme 41**).[68]

(one regioisomer:
cis : *trans* = 13 : 1)

Scheme 41

In the chiral version of this reaction, using *N*-α-methylbenzyl as a chiral auxiliary, high asymmetric induction is observed for the 2-substituted dienes, and moreover the minor diastereoisomer can be removed by chromatography. Thus, after removal of the auxiliary, homochiral pipecolic acids derivatives can be formed.[113,114] Using slightly different conditions, Stella *et al.*[115,116] have also demonstrated the success of this auxiliary in this type of reaction. In a further development, asymmetric induction of > 95% can now be achieved using the double chiral auxiliary [(*R*)-*N*-α-methylbenzyl and 8-phenylmenthyl ester], and the use of trifluoroethanol as solvent enhances the yield and reproducibility of the cycloaddition.[117]

In general, the trapping of the imines derived from α-hetero-substituted glycine derivatives is often possible using reactive dienes, but more reliable procedures use preformed imines in which additional electron-withdrawing groups (acyl/tosyl) are present, or in which careful choice of conditions

favours the cycloadduct over alternative reactions. This constitutes a short, general, and efficient route to pipecolic acid derivatives.

3.3 Other reactions

3.3.1 Radical reactions

α-Substituted glycine derivatives undergo a wide range of free radical reactions.[8,84,90,118,119] α-Bromo substituents can be replaced with hydrogen, or more usefully deuterium, using tributyltin hydride or deuteride.[8,84,90] With the 8-phenylmenthyl esters of α-bromo glycine,[8] the reaction proceeds to give the deuterated product in 60–70% yield with diastereoisomeric excesses greater than 90%.[8,120] A similar deuteration procedure has been used to generate α-deutero glycine containing dipeptides (Scheme 42).[84]
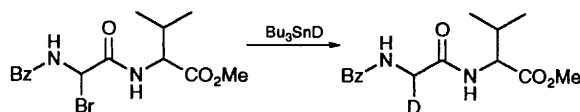

Scheme 42

α-Substituted glycine derivatives also react with allyl tin compounds[4,9,78,84] (with AIBN as initiator) to give the α-allyl glycine derivatives in good yield (see Section 3.1.3.2). α-Benzoyloxy and α-methoxy substituents with allyl tributyl tin[90] undergo a similar reaction giving α-allyl glycine in 47 and 31% yield, respectively (Scheme 43). Isomers of the glycine dimer 30 are also detected in this reaction, indicating a free radical mechanism. This dimer can be generated as the major product[118] by using N-benzoyl α-bromo glycine methyl ester and hexabutyl di-tin under rigorously dry conditions. In the presence of water the ether 31 can be isolated,[60,118] and this discovery prompted Easton to make a wide range of cross-linked peptides using α-bromo glycines and amino acids such as serine, lysine, and cysteine, though not via radical pathways.[119] Routes
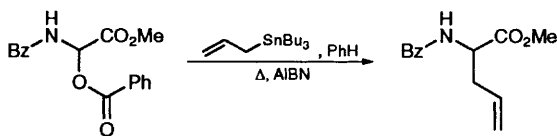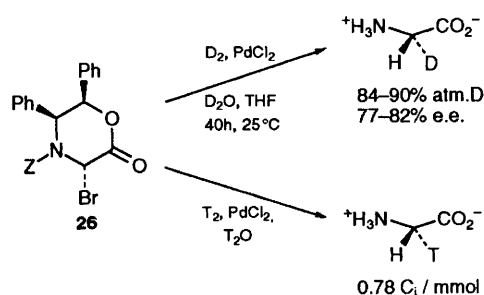

Scheme 43
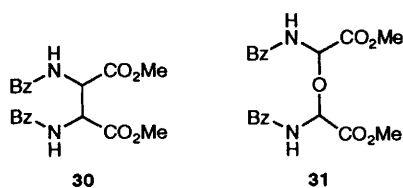
to glycine α-thio-ethers have also been developed by Easton, by the reaction of α-bromo glycine derivatives with Bu_3SnH in the presence of RSSR or ArSSAr.[121] Speckamp has accessed the related MeO_2C-NH-CH[SC(S)OEt]-CO_2Et using standard S_N2 chemistry, and has utilized this dithiocarbonate in some elegant free radical reactions with alkenes.[122]

3.3.2 Reductions

Heterogeneous reductions of homochiral α-bromo glycine derivatives can be performed using palladium-catalysed hydrogenation.[123,124] The α-bromo oxazinone of Williams has been reduced in the presence of both D_2 and T_2 to produce optically active α-deutero[123] and α-tritio[124] glycine for labelling experiments. The optical activity and label incorporation were excellent in both cases (Scheme 44). Reduction of α-bromo glycine derivatives is also possible using Bu_3SnH, as discussed in Section 3.3.1.

Scheme 44

3.3.3 Wittig-type reactions

α-Halo glycine derivatives react with trialkylphosphites in an Arbuzov-type reaction to yield phosphonates.[3,48,61,125] In fact, the Horner–Wadsworth–Emmons reagent Z-NH-CH[P(O)(OMe)$_2$]-CO_2Et is now commercially available; treatment of this with base, to form the ylid, followed by addition of an aldehyde gives α,β-dehydro amino acids via a short and flexible route.[126] When this method was applied to his oxazinone template, Williams showed[125] that a single geometric isomer of the alkene 32 was produced (Scheme 45). This could be converted with high diastereoselectivity into the cyclopropyl amino acid derivative 33, in which the auxiliary controlled the face of addition of the cyclopropanating reagent.

Another route to α,β-dehydroamino acids is by elimination from α-bromo substituted amino acids residues other than glycine (e.g. alanine in Scheme 46).[18] The N-chlorination of protected amino acids with t-butyl hypochlorite has already been described (see Section 2.2),[27–31] and, if these are derivatives of amino acids other than glycine,[29–31] the action of base first converts the N-chloro compound into the imine, which then isomerizes to the α,β-dehydro amino acid.
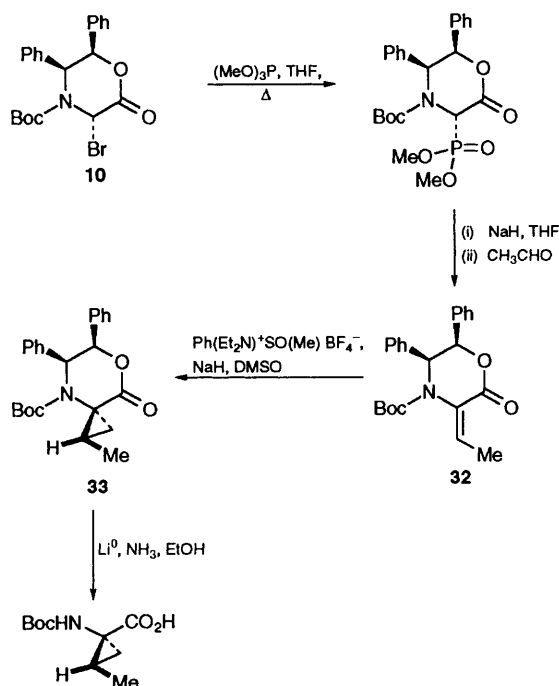
Scheme 45
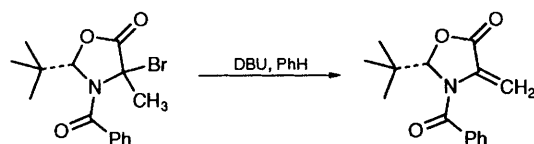
Scheme 46

3.3.4 Reaction with diazomethane

When *N*-acyl α-chloroglycine methyl ester is reacted with diazomethane, the imine is initially formed, which then reacts with excess diazomethane in a [3 + 2] cycloaddition to give the *N*-acyl triazoline **34**.[54] Upon warming, N_2 is extruded to give the aziridine **35** (**Scheme 47**), further demonstrating the versatility of glycine α-cation equivalents.
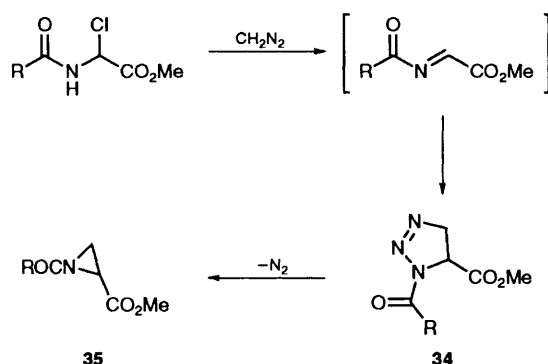

Scheme 47

4 Conclusions

With a range of reliable routes both to α-substituted glycine derivatives and to imino esters, synthetic equivalents of the glycine α-cation synthon are readily accessible. Moreover, their chemistry is more diverse and versatile than might have been imagined 10 years ago, and they can be converted into a wide range of compound classes with (perhaps unexpected) site-selectivity and stereo-control. If the chemistry of α-substituted α-amino acids can be harnessed successfully then such reactions allow access to a wide range of amino acids, N-heterocycles, and peptides with modified backbones. The use of α-substituted peptides for further functionalization is exemplified by the work of Steglich using α-chloro-,[127] α,α-dichloro-,[128] and α-acetoxy-glycine[129] derivatives, whilst Ramage[130] has indicated the future potential in this area by his use of α-methoxy-glycine derivatives in solid-phase peptide synthesis. The next stage of development will probably focus on 'α-cations' of α-amino acids other than glycine, and Speckamp[63] has already demonstrated the potential of such chemistry. Moreover, total syntheses exploiting glycine α-cation chemistry are becoming widespread, as exemplified by Williams' synthesis of the unusual diketopiperazine-derived natural product aspirochlorine.[131] It is clear that the chemistry of amino acid α-cations already plays a major role in synthetic methodology, and it will be developed and exploited substantially over the next few years.

5 References

1 R.M. Williams in 'Synthesis of Optically Active Amino Acids', Pergamon Press, 1993, pp. 95–133.
2 R. Kober, W. Hammes, and W. Steglich, *Angew. Chem., Int. Ed. Engl.*, 1982, **21**, 203.
3 R. Kober and W. Steglich, *Liebigs Ann. Chem.*, 1983, 599.
4 J.E. Baldwin, R.M. Adlington, C. Lowe, I.A. O'Neil, G.L. Sanders, C.J. Schofield, and J.B. Sweeney, *J. Chem. Soc., Chem. Commun.*, 1988, 1030.
5 Z. Lidert and S. Gronowitz, *Synthesis*, 1980, 322.
6 T. Allmendinger, G. Rihs, and H. Wetter, *Helv. Chim. Acta*, 1988, **71**, 395.
7 M.J. O'Donnell, W.D. Bennett, and R.L. Polt, *Tetrahedron Lett.*, 1985, **26**, 695.
8 D.P.G. Hamon, R.A. Massy-Westropp, and P. Razzino, *J. Chem. Soc., Chem. Commun.*, 1991, 332.
9 D.P.G. Hamon, P. Razzino, and R.A. Massy-Westropp, *J. Chem. Soc., Chem. Commun.*, 1991, 722.
10 D.P.G. Hamon, R.A. Massy-Westropp, and P. Razzino, *Tetrahedron*, 1992, **48**, 5163.
11 P. Ermert, J. Meyer, C. Stucki, J. Schneebeli, and J.P. Obrecht, *Tetrahedron Lett.*, 1988, **29**, 1265.
12 P. Hartmann and J.P. Obrecht, *Synth. Commun.*, 1988, **18**, 553.
13 R.M. Williams, R.W. Armstrong, L.K. Maruyama, J.S. Dung, and O.P. Anderson, *J. Am. Chem. Soc.*, 1985, **107**, 3246.
14 T.W. Badran, C.J. Easton, E. Horn, K. Kociuba, B.L. May, D.M. Schliebs, and E.R.T. Tiekink, *Tetrahedron: Asymm.*, 1993, **4**, 197.

15 C.J. Easton and M.P. Hay, *J. Chem. Soc., Chem. Commun.*, 1985, 425.

16 C.J. Easton, M.P. Hay, and S.G. Love, *J. Chem. Soc., Perkin Trans. 1*, 1988, 265.

17 V.A. Burgess, C.J. Easton, and M.P. Hay, *J. Am. Chem. Soc.*, 1989, **111**, 1047.

18 J. Zimmerman and D. Seebach, *Helv. Chim. Acta*, 1987, **70**, 1104.

19 C.J. Easton and M.P. Hay, *J. Chem. Soc., Chem. Commun.*, 1986, 55.

20 C.J. Easton, E. W. Tan, and M. P. Hay, *J. Chem. Soc., Chem. Commun.*, 1989, 385.

21 C.J. Easton, C. A. Hutton, G. Rositano, and E.W. Tan, *J. Org. Chem.*, 1991, **56**, 5614.

22 P.J. Sinclair, D. Zhai, J. Reibenspies, and R.M. Williams, *J. Am. Chem. Soc.*, 1986, **108**, 1103.

23 R.M. Williams, P.J. Sinclair, D. Zhai, and D. Chen, *J. Am. Chem. Soc.*, 1988, **110**, 1547.

24 Y.N. Belokon, A.N. Popkov, N.I. Chernoglazova, M.B. Saporovskaya, V.I. Bakhmutov, and V.M. Belikov, *J. Chem. Soc., Chem. Commun.*, 1988, 1336.

25 Y.N. Belokon, A.N. Popkov, N.I. Chernoglazova and V.I. Bakhmutov, *Bull. Acad. Sci. USSR, Div. Chem. Sci.*, 1989, **38**, 1744.

26 Y.N. Belokon, *Pure Appl. Chem.*, 1992, **64**, 1917.

27 M. Kawai, P. Neogi, P.S. Khattri, and Y. Butsugan, *Chem. Lett.*, 1990, 577.

28 M. Kawai, Y. Omori, H. Yamamura, and Y. Butsugan, *Tetrahedron Asymm.*, 1992, **3**, 1019.

29 U. Schmidt and H. Poisel, *Chem. Ber.*, 1975, **108**, 2547.

30 H. Poisel and U. Schmidt, *Angew. Chem., Int. Ed. Engl.*, 1976, **15**, 294.

31 J. Köppen, D. Matthies, and H. Schweim, *Liebigs Ann. Chem.*, 1985, 2383.

32 J.E. Baldwin, F.J. Urban, R.D.G. Cooper, and F.L. Jose, *J. Am. Chem. Soc.*, 1973, **95**, 2401.

33 R.A. Firestone and B.G. Christensen, *J. Org. Chem.*, 1973, **38**, 1436.

34 U. Schöllkopf, H.J. Neubauer, and M. Haputreif, *Angew. Chem., Int. Ed. Engl.*, 1985, **24**, 1066.

35 U. Groth, T. Huhn, B. Porsch, C. Schmeck, and U. Schöllkopf, *Liebigs Ann. Chem.*, 1993, 715.

36 E.B. Henson, P.M. Gallop, and P.V. Hauschka, *Tetrahedron*, 1981, **37**, 2561.

37 A.L. Love and R.K. Olsen, *J. Org. Chem.*, 1972, **37**, 3431.

38 S.M. Patel, J.O. Currie Jr., and R.K. Olsen, *J. Org. Chem.*, 1973, **38**, 126.

39 R.K. Olsen and A.J. Kolar, *Tetrahedron Lett.*, 1975, **16**, 3579.

40 K.D. Ginzel, P. Brungs, and E. Steckhan, *Tetrahedron*, 1989, **45**, 1691.

41 A. Papadopoulos, J. Heyer, K.D. Ginzel, and E. Steckhan, *Chem. Ber.*, 1989, **122**, 2159.

42 H. Horikawa, T. Iwasaki, K. Matsumoto, and M. Miyoshi, *Tetrahedron Lett.*, 1976, **17**, 191.

43 T. Iwasaki, H. Horikawa, K. Matsumoto, and M. Miyoshi, *J. Org. Chem.*, 1977, **42**, 2419.

44 Y. Ozaki, T. Iwasaki, H. Horikawa, M. Miyoshi, and K. Matsumoto, *J. Org. Chem.*, 1979, **44**, 391.

45 Y. Ozaki, T. Iwasaki, M. Miyoshi, and K. Matsumoto, *J. Org. Chem.*, 1979, **44**, 1714.

46 T. Iwasaki, H. Horikawa, K. Matsumoto, and M. Miyoshi, *Bull. Chem. Soc. Jap.*, 1979, **52**, 826.

47 W. Oettmeier, *Chem. Ber.*, 1970, **103**, 2314.

48 G. Apitz and W. Steglich, *Tetrahedron Lett.*, 1991, **32**, 3163.

49 D. Ranganathan and S. Saini, *J. Am. Chem. Soc.*, 1991, **113**, 1042.

50 U. Zoller and D. Ben-Ishai, *Tetrahedron*, 1975, **31**, 863.

51 D. Ben-Ishai, I. Sataty, and Z. Bernstein, *Tetrahedron*, 1976, **32**, 1571.

52 D. Ben-Ishai, J. Altman, and N. Peled, *Tetrahedron*, 1977, **33**, 2715.

53 D. Ben-Ishai, R. Moshenberg, and J. Altman, *Tetrahedron*, 1977, **33**, 1533.

54 Z. Bernstein and D. Ben-Ishai, *Tetrahedron*, 1977, **33**, 881.

55 D. Ben-Ishai, J. Altman, Z. Bernstein, and N. Peled, *Tetrahedron*, 1978, **34**, 467.

56 K.E. Harding and C.S. Davis, *Tetrahedron Lett.*, 1988, **29**, 1891.

57 D.H. Rich and M.K. Dhaon, *Tetrahedron Lett.*, 1983, **24**, 1671.

58 A.L. Castelhano, S. Horne, R. Billedeau, and A. Krantz, *Tetrahedron Lett.*, 1986, **27**, 2435.

59 A.L. Castelhano, S. Horne, G.J. Taylor, R. Billedeau, and A. Krantz, *Tetrahedron*, 1988, **44**, 5451.

60 I. Malassa and P. Mathies, *Liebigs Ann. Chem.*, 1986, 1133.

61 U. Schmidt, A. Lieberknecht, and J. Wild, *Synthesis*, 1984, 53.

62 S. Shiono and K. Harada, *Bull. Chem. Soc. Jpn.*, 1985, **58**, 1061.

63 E.C. Roos, M.C. Lopez, M.A. Brook, H. Hiemstra, W.N. Speckamp, B. Kaptein, J. Kamphuis, and H.E. Schoemaker, *J. Org. Chem.*, 1993, **58**, 3259.

64 Y. Takeuchi, M. Nabetani, K. Takagi, T. Hagi, and T. Koizumi, *J. Chem. Soc., Perkin Trans 1*, 1991, 49.

65 Y. Takeuchi, K. Takagi, K. Nakata, and T. Koizumi, *Chem. Pharm. Bull.*, 1991, **39**, 3120.

66 P.D. Bailey, A.N. Boa, G.A. Crofts, M. Van-diepen, M. Helliwell, R.E. Gammon, and M.J. Harrison, *Tetrahedron Lett.*, 1989, **30**, 7457.

67 P.D. Bailey, A.N. Boa, and D.J. Londesbrough, *Amino Acids*, 1993, **5**, 442.

68 P.D. Bailey, R.D. Wilson, and G.R. Brown, *Tetrahedron Lett.*, 1989, **30**, 6781.

69 M.E. Jung, K. Shishido, L. Light, and L. Davis, *Tetrahedron Lett.*, 1981, **22**, 4607.

70 R. Albrecht, G. Kresze, and B. Mlakar, *Chem. Ber.*, 1964, **97**, 483.

71 R. Albrecht and G. Kresze, *Chem. Ber.*, 1965, **98**, 1431.

72 P. Hamley, A.B. Holmes, A. Kee, T. Laduwahetty, and F.F. Smith, *Synlett*, 1991, 29.

73 R. Grigg, Z. Rankovic, M. Thornton-Pett, and A. Somasunderam, *Tetrahedron*, 1993, **49**, 8679.

74 L.M. Harwood and L.C. Kitchen, *Tetrahedron Lett.*, 1993, **34**, 6603.

75 R.M. Williams, W. Zhai, D.J. Aldous, and S.C. Aldous, *J. Org. Chem.*, 1992, **57**, 6527.

76 P. Münster and W. Steglich, *Synthesis*, 1987, 223.

77 M.J. O'Donnell and J.B. Falmagne, *Tetrahedron Lett.*, 1985, **26**, 699.

78 M.J. O'Donnell and J.B. Falmagne, *J. Chem. Soc., Chem. Commun.*, 1985, 1168.

79 T. Bretschneider, W. Miltz, P. Münster, and W. Steglich, *Tetrahedron*, 1988, **44**, 5403.

80 N.A. Abood and R. Nosal, *Tetrahedron Lett.*, 1994, **35**, 3669.

81 D.G. Zhai, W. Zhai, and R.M. Williams, *J. Am. Chem. Soc.*, 1988, **110**, 2501.

82 R.M. Williams and W. Zhai, *Tetrahedron*, 1988, **44**, 5425.

83 R.M. Williams, P.J. Sinclair, and W. Zhai, *J. Am. Chem. Soc.*, 1988, **110**, 482.

84 C.J. Easton, I.M. Scharfbillig, and E. W. Tan, *Tetrahedron Lett.*, 1988, **29**, 1565.

85 M.J. O'Donnell, X. Yang, and M. Li, *Tetrahedron Lett.*, 1990, **31**, 5135.

86 M.J. O'Donnell and W.D. Bennett, *Tetrahedron*, 1988, **44**, 5389.

87 H.H. Mooiweer, H. Hiemstra, and W.N. Speckamp, *Tetrahedron*, 1989, **45**, 4627.

88 E.C. Roos, H. Hiemstra, W.N. Speckamp, B. Kaptein, J. Kamphuis, and H.E. Schoemaker, *Synlett.*, 1992, **5**, 451.

89 S.C. Ebeling, *J. Prakt. Chem.*, 1994, **336**, 330.

90 C.J. Easton and S.C. Peters, *Tetrahedron Lett.*, 1992, **33**, 5581.

91 C.J. Easton and I.M. Scharfbillig, *J. Org. Chem.*, 1990, **55**, 384.

92 U. Schöllkopf, S. Grüttner, R. Anderskewitz, E. Egert, and M. Dyrbusch, *Angew. Chem., Int. Ed. Engl.*, 1987, **26**, 683.

93 V.A. Burgess and C.J. Easton, *Aust. J. Chem.*, 1988, **41**, 1063.

94 R. Kober, K. Papadopoulos, W. Miltz, D. Enders, W. Steglich, H. Reuter, and H. Puff, *Tetrahedron*, 1985, **41**, 1693.

95 D.L. Boger and S.M. Weinreb, *Hetero-Diels–Alder Methodology in Organic Synthesis*, Academic Press, Orlando, 1987.

96 H. Waldmann, *Synthesis*, 1994, 535.

97 S.D. Larsen and P.A. Grieco, *J. Am. Chem. Soc.*, 1985, **107**, 1768.

98 P.A. Grieco and S.D. Larsen, *J. Org. Chem.*, 1986, **51**, 3553.

99 P.A. Grieco, S.D. Larsen, and W.F. Fobare, *Tetrahedron Lett.*, **27**, 1986, 1975.

100 P.A. Grieco and A. Bahsas, *J. Org. Chem.*, 1987, **52**, 5746.

101 P.A. Grieco and D.T. Parker, *J. Org. Chem.*, 1988, **53**, 3658.

102 H. Waldmann, *Angew. Chem., Int. Ed. Engl.*, 1988, **27**, 274.

103 H. Waldmann, *Liebigs Ann. Chem.*, 1989, 231.

104 D. Ben-Ishai, I. Sataty, N. Peled, and R. Goldshare, *Tetrahedron*, 1987, **43**, 439.

105 D. Ben-Ishai and S. Hirsch, *Tetrahedron Lett.*, 1983, **24**, 955.

106 D. Ben-Ishai and S. Hirsch, *Tetrahedron*, 1988, **44**, 5441.

107 S.M. Weinreb, *Acc. Chem. Res.*, 1985, **18**, 16.

108 W.A. Zunnebeld and W.N. Speckamp, *Tetrahedron*, 1975, **31**, 1717.

109 A.B. Holmes, J. Thompson, A.J.G. Baxter, and J. Dixon, *J. Chem. Soc., Chem. Commun.*, 1985, 37.

110 T.N. Birkinshaw, A.B. Tabor, A.B. Holmes, P. Kaye, P.M. Mayne, and P.R. Raithby, *J. Chem. Soc., Chem. Commun.*, 1988, 1599.

111 T.N. Birkinshaw, A.B. Tabor, A.B. Holmes, and P.R. Raithby, *J. Chem. Soc., Chem. Commun.*, 1988, 1601.

112 J. Sisko and S.M. Weinreb, *Tetrahedron Lett.*, 1989, **30**, 3037.

113 P.D. Bailey, R.D. Wilson, and G.R. Brown, *J. Chem. Soc., Perkin Trans. 1*, 1991, 1337.

114 P.D. Bailey, G.R. Brown, F. Korber, A. Reid, and R.D. Wilson, *Tetrahedron Asymmetry*, 1991, **2**, 1263.

115 L. Stella, H. Abraham, J. Feneau-Dupont, B. Tinant, and J.P. Declercq, *Tetrahedron Lett.*, 1990, **31**, 2603.

116 H. Abraham and L. Stella, *Tetrahedron*, 1992, **48**, 9707.

117 P.D. Bailey, D.J. Londesbrough, T.C. Hancox, J.D. Heffernan, and A.B. Holmes, *J. Chem. Soc., Chem. Commun.*, 1994, 2543.

118 V.A. Burgess, C.J. Easton, M.P. Hay, and P.J. Steel, *Aust. J. Chem.*, 1988, **41**, 701.

119 C.J. Easton and S.C. Peters, *Aust. J. Chem.*, 1990, **43**, 87.

120 D.P.G. Hamon, R.A. Massy-Westropp, and P. Razzino, *Tetrahedron*, 1993, **49**, 6419.

121 C.J. Easton and S.C. Peters, *Aust. J. Chem.*, 1994, **47**, 859.

122 J.H. Udding, H. Hiemstra, and W.N. Speckamp, *J. Org. Chem.*, 1994, **59**, 3721.

123 R.M. Williams, D. Zhai, and P.J. Sinclair, *J. Org. Chem.*, 1986, **51**, 5021.

124 S.E. Ramer, H. Cheng, M.M. Palcic, and J.C. Vederas, *J. Am. Chem. Soc.*, 1988, **110**, 8526.

125 R.M. Williams and G.J. Fegley, *J. Am. Chem. Soc.*, 1991, **113**, 8796.

126 T. Masquelin, E. Broger, K. Müller, R. Schmid, and D. Obrecht, *Helv. Chim. Acta*, 1994, **77**, 1395.

127 W. Steglich, M. Jäger, S. Jaroch, and P. Zistler, *Pure Appl. Chem.*, 1994, **66**, 2167.

128 S. Jaroch, T. Schwarz, W. Steglich, and P. Zistler, *Angew. Chem., Int. Ed. Engl.*, 1993, **32**, 1771.

129 G. Apitz, M. Jäger, S. Jaroch, M. Kratzel, L. Schäffeler, and W. Steglich, *Tetrahedron*, 1993, **49**, 8223.

130 A.R. Brown and R. Ramage, *Tetrahedron Lett.*, 1994, **35**, 789.

131 G.F. Miknis and R.M. Williams, *J. Am. Chem. Soc.*, 1993, **115**, 536.